



US009688627B2

(12) **United States Patent**
Barrett et al.

(10) **Patent No.:** **US 9,688,627 B2**
(45) **Date of Patent:** **Jun. 27, 2017**

(54) **LACTAM COMPOUNDS AS EP₄ RECEPTOR-SELECTIVE AGONISTS FOR USE IN THE TREATMENT OF EP4-MEDIATED DISEASES AND CONDITIONS**

(71) Applicants: **Cayman Chemical Company, Inc.**, Ann Arbor, MI (US); **Myometrics, LLC**, New London, CT (US)

(72) Inventors: **Stephen Douglas Barrett**, Hartland, MI (US); **Joseph Michael Colombo**, Ann Arbor, MI (US); **Bradlee David Germain**, Ann Arbor, MI (US); **Gregory William Endres**, Saline, MI (US); **Andriy Komilov**, Ypsilanti, MI (US); **James Bernard Kramer**, Sylvania, OH (US); **Adam Uzieblo**, Farmington Hills, MI (US); **Fred Lawrence Ciske**, Dexter, MI (US); **Kirk M. Maxey**, Ann Arbor, MI (US); **James Paul O'Malley**, Dunedin (NZ); **Thomas Allen Owen**, Pompton Plains, NJ (US)

(73) Assignee: **CAYMAN CHEMICAL COMPANY, INC.**, Ann Arbor, MI (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/775,427**

(22) PCT Filed: **Mar. 14, 2014**

(86) PCT No.: **PCT/US2014/029057**

§ 371 (c)(1),
(2) Date: **Sep. 11, 2015**

(87) PCT Pub. No.: **WO2014/144584**

PCT Pub. Date: **Sep. 18, 2014**

(65) **Prior Publication Data**

US 2016/0060216 A1 Mar. 3, 2016

Related U.S. Application Data

(60) Provisional application No. 61/793,736, filed on Mar. 15, 2013.

(51) **Int. Cl.**
C07D 417/06 (2006.01)
C07D 207/26 (2006.01)
C07D 409/06 (2006.01)
C07D 207/12 (2006.01)

(52) **U.S. Cl.**
CPC **C07D 207/12** (2013.01); **C07D 207/26** (2013.01); **C07D 409/06** (2013.01); **C07D 417/06** (2013.01)

(58) **Field of Classification Search**
CPC C07D 207/263
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,975,399 A	8/1976	DeFranco et al.
4,073,934 A	2/1978	Skuballa et al.
4,268,522 A	5/1981	Eggler et al.
6,043,275 A	3/2000	Maruyama et al.
6,573,294 B1	6/2003	Old et al.
6,849,657 B2	2/2005	Elworthy et al.
6,891,062 B2	5/2005	Oida et al.
6,894,175 B1	5/2005	DeLong
7,169,807 B2	1/2007	Donde

(Continued)

FOREIGN PATENT DOCUMENTS

CA	1085859	9/1980
EP	0046082 B1	6/1985

(Continued)

OTHER PUBLICATIONS

Billot, X. et al. "Discovery of a Potent and Selective Agonist of the Prostaglandin EP₄ Receptor," *Biorganic & Medicinal Chemistry Letters*, 2003, 13, 1129-1132.

Brochure: "Comprehensive Bone Regeneration Solutions," *BioHorizons Science Innovation Service*, 2009, www.biohorizons.com, 12 pgs.

Brochure: "JRF STIMUBLAST™ Demineralized Bone Matrix," *Arthrex Inc.*, 2011, http://biologics.arthrex.com, 6 pgs.

Cameron, K.O. et al. "Discovery of Highly Selective EP₄ Receptor Agonists That Stimulate New Bone Formation and Restore Bone Mass in Ovariectomized Rats," *Biorganic & Medicinal Chemistry Letters*, 2006, 16, 1799-1802.

Dorozhkin, S.V. et al. "Calcium Orthophosphate Cements and Concretes," *Materials*, 2009, 2, 221-291.

(Continued)

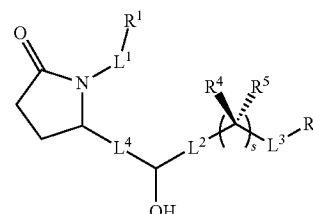
Primary Examiner — Rebecca Anderson

Assistant Examiner — Karen Cheng

(74) *Attorney, Agent, or Firm* — Brinks Gilson & Lione

(57) **ABSTRACT**

Disclosed herein are compounds of formula (I)



wherein L¹, L², L³, L⁴, R¹, R⁴, R⁵, R⁶, and s are as defined in the specification. Compounds of formula (I) are EP₄ agonists useful in the treatment of glaucoma, osteoporosis, bone fracture, periodontal bone loss, orthopedic implant, alopecia, neuropathic pain, and related disorders. Pharmaceutical compositions and methods of treating conditions or disorders are also described.

24 Claims, 1 Drawing Sheet

(56)

References Cited

U.S. PATENT DOCUMENTS

7,256,211	B1	8/2007	Kambe et al.
7,402,605	B2	7/2008	Tani et al.
7,410,991	B2	8/2008	Araldi et al.
7,419,999	B2	9/2008	Araldi et al.
7,683,094	B2	3/2010	Tani et al.
9,180,116	B2	11/2010	Barrett et al.
2003/0176479	A1	9/2003	Cameron et al.
2005/0020686	A1	1/2005	Maruyama et al.
2005/0124577	A1	6/2005	Tani et al.
2005/0288357	A1*	12/2005	Araldi et al. 514/424
2006/0167081	A1	7/2006	Billot et al.
2008/0021021	A1	1/2008	Okada et al.
2008/0234337	A1	9/2008	Kuwahara et al.
2010/0216689	A1	8/2010	Takigawa et al.
2010/0280250	A1	11/2010	Im et al.
2012/0283293	A1	11/2012	Andreasson
2014/0179606	A1	6/2014	Kanaji et al.
2015/0174099	A1	6/2015	Barrett et al.
2015/0175538	A1	6/2015	Barrett et al.

FOREIGN PATENT DOCUMENTS

EP	1121939	A2	8/2001
GB	1553595	A1	10/1979
GB	1583163	A1	1/1981
WO	WO 01/46140	A1	6/2001
WO	WO 02/24647	A1	3/2002
WO	WO 02/42268	A2	5/2002
WO	WO 03/007941	A1	1/2003
WO	WO 03/008377	A1	1/2003
WO	WO 03/047417	A2	6/2003
WO	WO 03/047513	A2	6/2003
WO	WO 03/077910	A1	9/2003
WO	WO 03/103604	A2	12/2003
WO	WO 2004/037786	A2	5/2004
WO	WO 2009/055289	A2	4/2009
WO	WO 2011/003058	A1	1/2011
WO	WO 2012/063207	A1	5/2012
WO	WO 2013/018837	A1	2/2013
WO	WO 2014/015246	A1	1/2014
WO	WO 2014/015247	A1	1/2014

OTHER PUBLICATIONS

Elworthy, T.R. et al. "Lactams as EP₄ Prostanoid Receptor Agonists. 3. Discovery of N-Ethylbenzoic Acid 2-Pyrrolidinones as Subtype Selective Agents," *J. Med. Chem.*, 2004, 20, 6124-6127.

Elworthy, T.R. et al. "Lactams as EP₄ Prostanoid Receptor Subtype Selective Agonists. Part 1: 2-Pyrrolidinones-Stereochemical and Lower Side-Chain Optimization," *Bioorganic & Medicinal Chemistry Letters*, 2004, 14, 1655-1659.

Elworthy, T.R. et al. "Lactams as Prostanoid Receptor Ligands. Part 4: 2-Piperidones as Selective EP₄ Receptor Agonists," *Bioorganic & Medicinal Chemistry Letters*, 2005, 15, 2523-2526.

Espanol, M. et al. "Intrinsic Porosity of Calcium Phosphate Cements and Its Significance for Drug Delivery and Tissue Engineering Applications," *Acta Biomaterialia*, 2009, 5, 2752-2762.

Ginebra, M.P. et al. "Calcium Phosphate Cements as Bone Drug Delivery Systems: A Review," *J. Controlled Release*, 2006, 113, 102-110.

Ginebra, M-P. et al. "Calcium Phosphate Cements: Competitive Drug Carriers for the Musculoskeletal System?" *Biomaterials*, 2006, 27, 2171-2177.

Hayashi, K. et al. "Effect of a Prostaglandin EP₄ Receptor Agonist on Early Fixation of Hydroxyapatite/Titanium Composite- and Titanium-Coated Rough-Surfaced Implants in Ovariectomized Rats," *J. Biomedical Materials Research Part A*, 2009, 1202-1209.

Hayashi, K. et al. "Prostaglandin EP₄ Receptor Agonist Augments Fixation of Hydroxyapatite-Coated Implants in a Rat Model of Osteoporosis," *J. Bone and Joint Surgery*, 2005, 87-8, 1150-1156.

International Search Report and Written Opinion for corresponding International Patent Application No. PCT/US2013/051263 dated Jul. 19, 2013.

International Search Report and Written Opinion for International Patent Application No. PCT/US2014/029057, dated Sep. 17, 2014 (9 pages).

Iwaniec, U.T. et al. "A Comparative Study of the Bone-Restorative Efficacy of Anabolic Agents in Aged Ovariectomized Rats," *Osteoporos. Int.*, 2007, 18, 351-362.

Kambe, T. et al. "Synthesis and Evaluation of γ -lactam Analogs of PGE₂ as EP₄ and EP₂/EP₄ Agonists," *Bioorganic & Medicinal Chemistry*, 2012, 20, 3502-3522.

Li, M. et al. "Prostaglandin E₂ Receptors in Bone Formation," *International Orthopaedics*, 2007, 31, 767-772.

Maruyama, T. et al. "Design and Synthesis of a Selective EP₄-Receptor Agonist. Part 1: Discovery of 3,7-DithiaPGE₁ Derivatives and Identification of Their ω Chains," *Bioorganic & Medicinal Chemistry*, 2002, 10, 975-988.

Maruyama, T. et al. "Design and Synthesis of a Selective EP₄-Receptor Agonist. Part 2: 3,7-DithiaPGE₁ Derivatives With High Selectivity," *Bioorganic & Medicinal Chemistry*, 2002, 10, 989-1008.

Nakagawa, K. et al. "Prostaglandin E₂ EP₄ Agonist (ONO-4819) Accelerates BMP-induced Osteoblastic Differentiation," *Bone*, 2007, 41, 543-548.

Orlovskii, V.P. et al. "Hydroxyapatite and Hydroxyapatite-Based Ceramics," *Inorganic Materials*, 2002, 38, 973-984.

Partial Translation of International Publication No. WO 2002/024647 A1.

Saeki, T. et al. "Effects of Prostanoid EP Agonists on Mouse Intraocular Pressure," *IOVS*, 2009, 50, 2201-2208.

Smith, R.L. et al. "Prostaglandin Isosteres. I. (8-Aza-, 8,10-Diaza-, and 8-Aza-11-thia)-9-oxoprostanic Acids and Their Derivatives," *J. Med. Chem.*, 1977, 20, 1292-1299.

Toyoda, H. et al. "Augmentation of Bone Morphogenetic Protein-Induced Bone Mass by Local Delivery of a Prostaglandin E EP₄ Receptor Agonist," *Bone*, 2005, 555-562.

Wang, C-L.J. et al. "Azaprostanoids I. Synthesis of (RAC)-8-Aza-11-Deoxy-15-Deoxy-16-Hydroxy-16-Methylprostaglandins," *Tetrahedron Letters*, 1982, 10, 1067-1070.

Xiao, Y. et al. "Discovery of Novel Prostaglandin Analogs of PGE₂ as Potent and Selective EP₂ and EP₄ Receptor Agonists," *Bioorganic & Medicinal Chemistry Letters*, 2007, 17, 4323-4327.

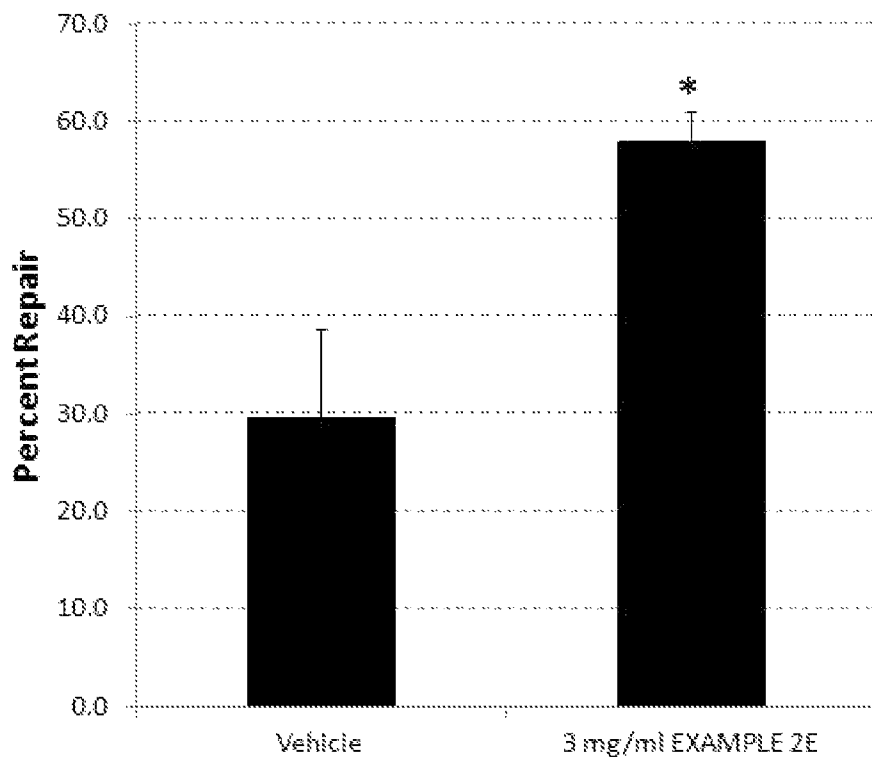
Xiao, Y. et al. "Synthesis and Evaluation of a γ -lactam as a Highly Selective EP₂ and EP₄ Receptor Agonist," *Bioorganic & Medicinal Chemistry Letters*, 2008, 18, 821-824.

Yokoyama, U. et al. "Chronic Activation of the Prostaglandin Receptor EP₄ Promotes Hyaluronan-Medicated Neointimal Formation in the Ductus Arteriosus," *J. Clin. Invest.*, 2006, 116, 3026-3034.

Yoshida, K. et al., "Stimulation of bone formation and prevention of bone loss by prostaglandin E EP₄ receptor activation," *PNAS*, 2002, 99(7), 4580-4585.

* cited by examiner

Calvarial Defect Repair 8 weeks



* p < 0.05 vs Vehicle

1

**LACTAM COMPOUNDS AS EP₄
RECEPTOR-SELECTIVE AGONISTS FOR
USE IN THE TREATMENT OF
EP4-MEDIATED DISEASES AND
CONDITIONS**

RELATED APPLICATIONS

This application is the U.S. National Phase under 35 U.S.C. §371 of International Patent Application No. PCT/US2014/029057, filed Mar. 14, 2014, which claims priority to and the benefit of U.S. Provisional Application Ser. No. 61/793,736, filed Mar. 15, 2013.

FIELD OF THE INVENTION

The subject matter disclosed and claimed herein centers on novel EP₄ receptor-selective pyrrolidin-2-one (γ -lactam) derivatives and their uses as therapies for EP₄ receptor-mediated diseases and conditions.

BACKGROUND OF THE INVENTION

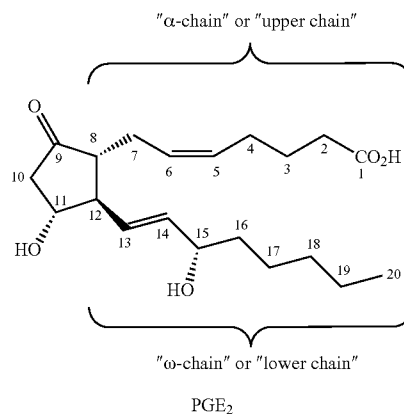
All references, including patents and patent applications, are hereby incorporated by reference in their entireties.

Arachidonic acid (abbreviated as AA herein) is a ubiquitous polyunsaturated fatty acid (PUFA) that is found esterified to phospholipids at the secondary alcohol of glycerol in all mammalian cellular membranes. Enzymatic hydrolysis of esterified AA by calcium (Ca²⁺)-induced cytosolic phospholipase 2 (cPLA2) releases free AA, which may be further catalytically converted by the cyclooxygenase (COX) into the intermediate prostaglandin H₂ followed by subsequent enzymatic isomerization into the naturally occurring prostaglandins (PGs) and thromboxanes. The five primary prostanooids include prostaglandin F_{2 α} (PGF_{2 α}), prostaglandin D₂ (PGD₂), prostaglandin I₂ (PGI₂), thromboxane A₂ (TxA₂), and prostaglandin E₂ (PGE₂), (Jahn, U. et al., *Angew. Chem. Int. Ed.* 2008, 47, 5894-5955; Wymann, M. P. et al., *Nat. Rev. Mol. Cell. Biol.* 2008, 9, 162-176; Samuelsson, B. et al., *Ann. Rev. Biochem.* 1978, 47, 997-1029). These five prostaglandins are lipid mediators that interact with nine specific members of a distinct prostanoid subfamily of G-protein-coupled receptors (GPCRs), designated FP, DP₁₋₂, IP, TP, and EP₁₋₄, respectively (Breyer, R. M. et al., *Annu. Rev. Pharmacol. Toxicol.* 2001, 41, 661-690). Prostaglandin and PG receptor pharmacology, signaling, and physiology have been studied and well documented (Hata, A. N. et al., *Pharmacol. Ther.* 2004, 103(2), 147-166; ElAttar, T. M. A., *J. Oral Pathol. Med.* 1978, 7(5), 239-252; Poyser, N. L., *Clinics in Endocrinology and Metabolism* 1973, 2(3), 393-410). Prostaglandins are short-lived local signaling molecules that are not stored in cells or tissues but are produced as needed by specific cells of virtually all body tissues. Their target cells reside in the immediate vicinity of their secretion sites. Well-known PG functions include regulation of cell stimulation, growth, and differentiation, immune response and inflammation, allergy, asthma, pain, vasomotor action, neuromodulation, intraocular pressure, and platelet aggregation, as well as mediation of fever, managing of renal blood flow, and induction of labor (Negishi, M. et al., *Prog. Lipid Res.* 1993, 32(4), 417-434).

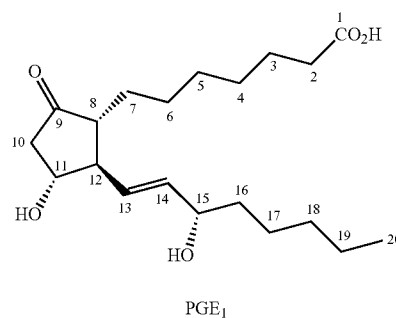
As is the case for most prostaglandins, the biosynthesis of PGE₂ commences with liberation of free AA from its esterified form in the cell membrane. One key enzyme involved in PGE₂ biosynthesis is prostaglandin H synthase (PGHS). PGHS possesses both a COX and a peroxidase function. The

2

COX activity promotes conversion of free AA to the unstable endoperoxide prostaglandin G₂ (PGG₂) via double oxygen insertion. One inserted oxygen molecule is subsequently reduced by the peroxidase activity of PGHS to provide the versatile biosynthetic cascade intermediate PGH₂. The glutathione-dependent enzyme prostaglandin E synthase (PGES) promotes isomerization of PGH₂ to PGE₂ via peroxide ring opening of PGH₂ to provide the highly functionalized hydroxypentanone scaffold of PGE₂.



The physiology of PGE₂ and the pharmacology of its four known complementary receptor subtypes designated EP₁, EP₂, EP₃, and EP₄ are among the most widely studied and published fields of PG research (Sugimoto, Y. et al., *J. Biol. Chem.* 2007, 282(16), 11613-11617; Suzuki, J. et al., *Prostaglandins* 2010, 127-133; Regan, J. et al., *Life Sciences* 2003, 74(2-3), 143-153; Bouayad, A. et al., *Current Ther. Res.* 2002, 63(10), 669-681; Breyer, M. et al., *Kidney Int., Suppl.* 1998, 67, S88-S94; Breyer, M. et al., *Amer. J. Physiol.* 2000, 279(1, Part 2), F12-F23; Negishi, M. et al., *Recent Res. Dev. Endocrinol.* 2000, 1(1), 133-143; Ma, W. et al., *Prog. Inflamm. Res.* 2006, 39-93; Mutoh, M. et al., *Current Pharmaceutical Design* 2006, 12(19), 2375-2382; Hebert, R. et al., *Current Topics in Pharmacology* 2002, 6, 129-137; Coleman, R. et al., *Pharm. Rev.* 1994, 46(2), 205-229). PGE₂ binds to each of the four EP receptors with high affinity (Anderson, L. et al., *Journal of Reproduction and Fertility*, 1999, 116, 133-141). The prostaglandin PGE₁ (saturated α -chain analog of PGE₂), the major eicosanoid synthesized biologically from dihomo- γ -linolenic acid (DGLA) in response to various stimuli, also binds efficiently to all four EP receptor subtypes.



3

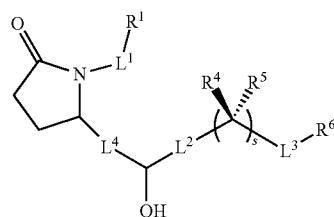
The EP₄ receptor is expressed in a wide variety of tissues including those of the skeletal, muscular, central and peripheral nervous, immune, respiratory, cardiovascular, digestive, excretory, and reproductive tissues and is known to be involved in such processes and conditions as bone growth and remodeling, osteoporosis, relaxation of smooth muscle, neuroprotection, ocular inflammation, immune response, and cancer. Modulation of the EP₄ receptor may also be involved in the neonatal development of the circulatory system (Fan, F. et al., *Clinical and Experimental Pharmacology and Physiology*, 2010, 37, 574-580; Bouayad, A. et al., *Current Ther. Res.* 2002, 63(10), 669-681; Bouayad, A. et al., *Am. J. Physiol. Heart Circ. Physiol.* 2001, 280, H2342-H2349). Activation of the EP₄ receptor by PGE₂ increases intracellular cAMP levels, leading to downstream effects associated with antiapoptotic activity and cytoprotection (Fujino, H. and Regan, J., *Trends in Pharmacological Sciences*, 2003, 24(7), 335-340; Hoshino, T. et al., *J. Biol. Chem.*, 2003, 278(15), 12752-12758; Takahashi, S. et al., *Biochem. Pharmacol.*, 1999, 58(12), 1997-2002; Quiroga, J. et al., *Pharmacol. Ther.*, 1993, 58(1), 67-91).

EP₄ receptor agonists are reported to be useful in lowering intraocular pressure and to have application in treating glaucoma. Prasanna, G. et al., *Exp. Eye Res.*, 2009, 89 (5), 608-17; Luu, K. et al., *J. Pharmacol. Exp. Ther.* 2009, 331(2), 627-635; Saeki, T. et al., *Invest. Ophthalmol. Vis. Sci.*, 2009, 50 (5) 2201-2208.

EP₄ receptor agonists are also reported to induce bone remodeling and to have use in the treatment of osteoporosis. Iwaniec, U. et al., *Osteoporosis International*, 2007, 18 (3), 351-362; Aguirre, J. et al., *J. Bone and Min. Res.*, 2007, 22(6), 877-888; Yoshida, K. et al., *Proc. Natl. Acad. Sci. USA*, 2002, 99 (7), 4580-4585. Hayashi, K. et al., *J. Bone Joint Surg. Br.*, 2005, 87-B (8), 1150-6.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

L¹ is

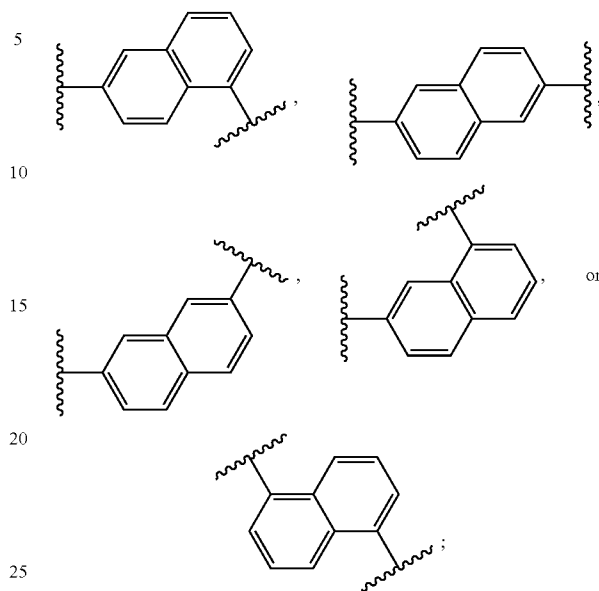
a) C₃-C₇alkylene, C₃-C₇alkenylene, or C₃-C₇alkynylene, wherein the C₃-C₇alkylene, C₃-C₇alkenylene, or C₃-C₇alkynylene are each optionally substituted with 1, 2, 3, or 4 fluoro substituents;

b) —(CH₂)_t-G-(CH₂)_p—; wherein t is 0, 1, or 2, p is 0, 1, 2, or 3, and t+p=0, 1, 2, 3, or 4; or

c) —(CH₂)_n-G¹-(CH₂)_p—, —(CH₂)_n-G²-(CH₂)_p—, —(CH₂)_n-C≡C-G²—, or —(CH₂)_n-C(R¹²)=C(R¹²)-G²—, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and n+p=1, 2, 3, 4, 5, or 6;

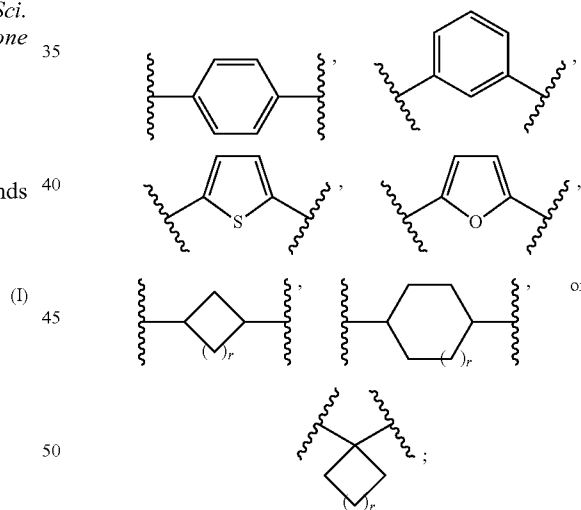
4

G is



G¹ is O, C(O), S, S(O), S(O)₂, or NR⁷; wherein R⁷ is H, C₁-C₄ alkyl, or C₁-C₄alkylcarbonyl;

G² is



wherein G² is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₄alkyl, C₁-C₃haloalkyl, cyano, halogen, C₁-C₃alkoxy, and C₁-C₃haloalkoxy;

R¹ is COOR⁹, CONR⁹R¹⁰, CH₂OR⁹, SO₃R⁹, SO₂NR⁹R¹⁰, PO(OR⁹)₂, or tetrazol-5-yl;

R⁹ is H, C₁-C₄ alkyl, or aryl;

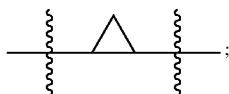
R¹⁰ is H, C₁-C₄ alkyl, COR¹¹, OR⁹, or SO₂R¹¹;

R¹¹ is C₁-C₄ alkyl;

R¹², at each occurrence, is independently H or C₁-C₄alkyl;

5

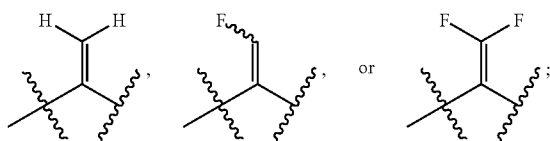
L^4 is $-C(R^2)_2-C(R^3)_2-$, $-C(R^2)=C(R^3)-$,
 $-C=C-$, or



wherein R^2 and R^3 are each H, CH_3 , fluoro, or chloro;

L^2 is $-CH_2-$ or a bond;

R^4 and R^5 are each independently H, F, CF_3 , or C_1-C_4 alkyl; or R^4 and R^5 together with the carbon to which they are attached form a C_3-C_5 cycloalkyl,



L^3 is C_2-C_6 alkynylene, wherein the C_2-C_6 alkynylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents;

R^6 is aryl, heteroaryl, heterocyclyl, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_8 halocycloalkyl, C_2-C_{10} haloalkenyl, or C_2-C_{10} haloalkynyl; wherein the aryl and heteroaryl are optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_3 haloalkyl, cyano, halogen, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy; and $-C_1-C_3$ alkylene- C_1-C_3 alkoxy; and wherein the C_1-C_{10} alkyl, C_3-C_8 alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_8 halocycloalkyl, C_2-C_{10} haloalkenyl, and C_2-C_{10} haloalkynyl are optionally substituted with a substituent selected from the group consisting of $COOR^9$, $CONR^9R^{10}$, CH_2OR^9 , SO_3R^9 , $SO_2NR^9R^{10}$, $PO(OR^9)_2$, and tetrazol-5-yl;

R^9 is H, C_1-C_4 alkyl, or aryl;

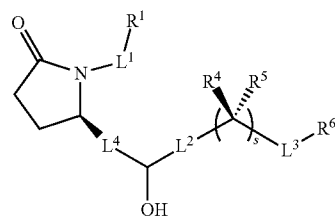
R^{10} is H, C_1-C_4 alkyl, COR^{11} , OR^9 , or SO_2R^{11} ;

R^{11} is C_1-C_4 alkyl;

r is 0 or 1; and

s is 0 or 1.

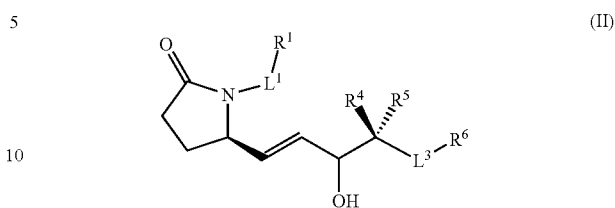
In another aspect, the present invention provides compounds of formula (Ia)



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^4 , R^5 , R^6 , L^1 , L^2 , L^3 , L^4 , and s are as defined herein.

6

In another aspect of the invention are compounds of formula (II)



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^4 , R^5 , R^6 , L^1 , and L^3 , are as defined herein.

Another aspect of the present invention relates to pharmaceutical compositions comprising therapeutically effective amounts of a compound described herein or a pharmaceutically acceptable salt, solvate, salt of a solvate, or solvate of a salt thereof, in combination with a pharmaceutically acceptable carrier.

In another aspect, the invention provides compounds that bind to the EP_4 receptor with high affinity and agonist activity. In certain embodiments, compounds of the invention may possess selectivity for the EP_4 receptor over other EP receptors. In other certain embodiments, compounds of the invention may possess selectivity for the EP_4 receptor versus other EP receptors and other prostaglandin receptors.

In another aspect, the present invention provides a method of treating a disease or disorder related to the EP_4 receptor by administering to a patient a therapeutically effective amount of a compound or composition of formula (I), (Ia), or (II). Such diseases or disorders include those related to elevated intraocular pressure such as glaucoma. Other diseases or conditions treatable by the compounds and compositions of the invention include those associated with excessive bone loss, such as osteoporosis.

The present invention also provides methods of preparing compounds of formula (I), (Ia), (II).

In another aspect, the invention provides intermediates useful in the preparation of EP_4 agonists. In still another aspect, the invention provides methods of preparing the intermediates.

Further provided herein are the use of the present compounds or pharmaceutically acceptable salts, solvates, salts of solvates, or solvates of salts thereof, in the manufacture of a medicament for the treatment of the diseases or conditions described herein, alone or in combination with one or more pharmaceutically acceptable carrier(s).

BRIEF DESCRIPTION OF THE DRAWINGS

(Ia) FIG. 1 depicts data showing the effect of Compound 2E on stimulation of bone growth in the rat calvarial defect model.

DETAILED DESCRIPTION

Definition of Terms

The term "agonist" as used herein refers to a compound, the biological effect of which is to mimic the action of the natural agonist PGE_2 . An agonist may have full efficacy (i.e., equivalent to PGE_2), partial efficacy (lower maximal efficacy compared to PGE_2), or super maximal efficacy (higher maximal efficacy compared to PGE_2). An agonist with

partial efficacy is referred to as a “partial agonist.” An agonist with super maximal efficacy is referred to as a “super agonist.”

The term “alkyl” as used herein, means a straight or branched chain saturated hydrocarbon. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term “alkenyl” as used herein, means a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-deceny.

The term “alkynyl,” as used herein, means a straight or branched chain hydrocarbon containing at least one carbon-carbon triple bond. Representative examples include propynyl, butynyl, pentynyl, and the like.

The term “alkylene,” as used herein, means a divalent group derived from a straight or branched chain saturated hydrocarbon. Representative examples of alkylene include, but are not limited to, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, and $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2-$.

The term “alkenylene,” as used herein, means a divalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Representative examples of alkenylene include, but are not limited to $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CH}-$, and $-\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)-$.

The term “alkynylene,” as used herein, means a divalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon triple bond. Representative examples of alkynylene include, but are not limited to $-\text{CH}_2-\text{C}\equiv\text{C}-$, $-\text{CH}_2\text{CH}_2-\text{C}\equiv\text{C}-$, and $-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$.

The term “alkoxy” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term “alkylcarbonyl” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a C(O) group.

The terms “haloalkyl,” “haloalkenyl,” and “haloalkynyl” as used herein, mean, respectively an alkyl, alkenyl, or alkynyl group, as defined herein, in which one, two, three, four, five, six, or seven hydrogen atoms are replaced by halogen. For example, representative examples of haloalkyl include, but are not limited to, 2-fluoroethyl, 2,2-difluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1,1-dimethylethyl, and the like.

The term “haloalkoxy,” as used herein, means an alkoxy group, as defined herein, in which one, two, three, four, five, or six hydrogen atoms are replaced by halogen. Representative examples of haloalkoxy include, but are not limited to, trifluoromethoxy, difluoromethoxy, 2,2,2-trifluoroethoxy, 2,2-difluoroethoxy, 2-fluoroethoxy, and pentafluoroethoxy.

The term “aryl,” as used herein, means phenyl or a bicyclic aryl. The bicyclic aryl is naphthyl, dihydronaphthalenyl, tetrahydronaphthalenyl, indenyl, or indenyl. The phenyl and bicyclic aryls are attached to the parent molecular moiety through any carbon atom contained within the phenyl or bicyclic aryl.

The term “heteroaryl,” as used herein, means a monocyclic heteroaryl or a fused bicyclic heteroaryl. The monocyclic heteroaryl is a 5 or 6 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The 5-membered ring contains two double bonds, and one, two, three, or four heteroatoms as ring atoms. The 6-membered ring contains three double bonds, and one, two, three or four heteroatoms as ring atoms. Representative examples of monocyclic heteroaryl include, but are not limited to, furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl is an 8- to 12-membered ring system having a monocyclic heteroaryl fused to an additional ring; wherein the additional ring may be aromatic or partially saturated, and may contain additional heteroatoms. Representative examples of bicyclic heteroaryl include, but are not limited to, benzofuranyl, benzoxadiazolyl, 1,3-benzothiazolyl, benzimidazolyl, benzodioxolyl, benzothienyl, chromenyl, furo-pyridinyl, indolyl, indazolyl, isoquinolinyl, naphthyridinyl, oxazolopyridine, quinolinyl, thienopyridinyl, 5,6,7,8-tetrahydroquinolinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, and 2,3-dihydrofuro[3,2-b]pyridinyl. The monocyclic and the bicyclic heteroaryl groups are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the monocyclic and the bicyclic heteroaryl groups.

The term “cycloalkyl” as used herein, means a carbocyclic ring system containing 3, 4, 5, 6, 7, or 8 carbon atoms and zero heteroatoms as ring atoms, and zero double bonds. Examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The cycloalkyl groups of the present invention may contain an alkylene bridge of 1, 2, 3, or 4 carbon atoms, linking two non adjacent carbon atoms of the group. Examples of such bridged systems include, but are not limited to, bicyclo[2.2.1]heptanyl and bicyclo[2.2.2]octanyl. The cycloalkyl groups described herein can be appended to the parent molecular moiety through any substitutable carbon atom.

The term “heterocycle” or “heterocyclic” as used herein, refers to a monocyclic heterocycle, a bicyclic heterocycle, or a spirocyclic heterocycle. The monocyclic heterocycle is a 3, 4, 5, 6, 7, or 8-membered ring containing at least one heteroatom selected from O, N, or S. The 3 or 4 membered ring contains one heteroatom and optionally one double bond. The 5-membered ring contains zero or one double bond and one, two or three heteroatoms. The 6, 7, or 8-membered ring contains zero, one, or two double bonds, and one, two, or three heteroatoms. Representative examples of monocyclic heterocycle include, but are not limited to, azetidiny, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, 4,5-dihydroisoxazol-5-yl, 3,4-dihydropyranyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazoliny, imidazolidinyl, isothiazoliny, isothiazolidinyl, isoxazoliny, isoxazolidinyl, morpholinyl, oxadiazoliny, oxadiazolidinyl, oxazoliny, oxazolidinyl, oxetanyl, piperazinyl, piperidinyl, pyranyl, pyrazoliny, pyrazolidinyl, pyrroliny, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, thiazoliny, thiazolidinyl, thiadiazoliny, thiadiazolidinyl, thiazoliny, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, thiopyranyl, and trithianyl. The bicyclic heterocycle is a 5-12-membered ring system having a monocyclic heterocycle fused to a phenyl, a saturated or partially saturated carbocyclic ring, or another monocyclic heterocyclic ring. Representative examples of bicyclic heterocycle include, but are not limited

9

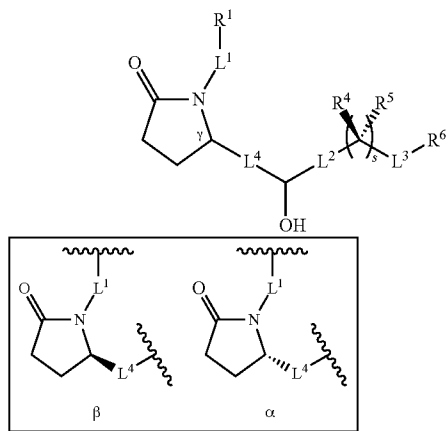
to, 1,3-benzodioxol-4-yl, 1,3-benzodithioly, 3-azabicyclo [3.1.0]hexanyl, hexahydro-1H-furo[3,4-c]pyrrolyl, 2,3-dihydro-1,4-benzodioxinyl, 2,3-dihydro-1-benzofuranyl, 2,3-dihydro-1-benzothieryl, 2,3-dihydro-1H-indolyl, and 1,2,3,4-tetrahydroquinoliny. Spirocyclic heterocycle means a 4, 5-, 6-, 7-, or 8-membered monocyclic heterocycle ring wherein two of the substituents on the same carbon atom form a 3-, 4-, 5-, or 6-membered monocyclic ring selected from the group consisting of cycloalkyl and heterocycle, each of which is optionally substituted with 1, 2, 3, 4, or 5 alkyl groups. Examples of a spiroheterocycle include, but are not limited to, 5-oxaspiro[3,4]octane and 8-azaspiro[4,5]decane. The monocyclic and bicyclic heterocycle groups of the present invention may contain an alkylene bridge of 1, 2, 3, or 4 carbon atoms, linking two non-adjacent atoms of the group. Examples of such a bridged heterocycle include, but are not limited to, 2-azabicyclo[2.2.1]heptanyl, 2-azabicyclo[2.2.2]octanyl, 1,2,3,4-tetrahydro-1,4-methanoisoquinoliny, and oxabicyclo[2.2.1]heptanyl. The monocyclic, bicyclic, and spirocyclic heterocycle groups are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the monocyclic, bicyclic, and spirocyclic heterocycle groups.

Terms such as "alkyl," "cycloalkyl," "alkylene," etc. may be preceded by a designation indicating the number of atoms present in the group in a particular instance (e.g., "C₃-C₁₀alkyl," "C₃-C₁₀cycloalkyl," "C₂-C₆alkynylene," "C₂-C₆alkenylene"). These designations are used as generally understood by those skilled in the art. For example, the representation "C" followed by a subscripted number indicates the number of carbon atoms present in the group that follows. Thus, "C₃alkyl" is an alkyl group with three carbon atoms (i.e., n-propyl, isopropyl). Where a range is given, as in "C₃-C₁₀," the members of the group that follows may have any number of carbon atoms falling within the recited range. A "C₃-C₁₀alkyl," for example, is an alkyl group having from 3 to 10 carbon atoms, however arranged.

A "patient" as used herein refers to a mammal (e.g., a human) or a bird having a condition that may be treated with compounds of the invention.

Compounds

According to a general aspect of the present invention, there are provided compounds useful as EP₄ receptor agonists, as well as compositions and methods relating thereto. Compounds of the invention have the structure set forth in formula (I), (Ia), (II).



10

Formula (I) refers to compounds having either β stereochemistry or a substantially equal mixture of β and α stereochemistries at the γ -position of the lactam ring. Excluded are compounds having pure or substantially pure a stereochemistry at the γ -position.

In some embodiments of the invention, L¹ is C₃-C₇alkylene, C₃-C₇alkenylene, or C₃-C₇alkynylene, wherein the C₃-C₇alkylene, C₃-C₇alkenylene, or C₃-C₇alkynylene are each optionally substituted with 1, 2, 3, or 4 fluoro substituents. In other embodiments, L¹ is C₃-C₇alkylene, optionally substituted. In some groups of compounds, L¹ is n-pentylene, n-hexylene, or n-heptylene each optionally substituted with 1, 2, 3, or 4 fluoro substituents. In subgroups of compounds, L¹ is n-hexylene.

In other embodiments, L¹ is $-(CH_2)_t-G-(CH_2)_p-$; wherein t, p, and G are as defined herein. In some groups of compounds, t and p are both 0. In other groups of compounds, t is 0 and p is 0, 1, 2, or 3. In still other groups of compounds, p is 0 and t is 0, 1, or 2.

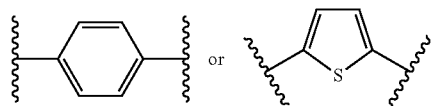
In other embodiments, L¹ is $-(CH_2)_n-G^1-(CH_2)_p-$, wherein G¹ is as defined herein, n is 1, 2, 3, 4, or 5 and p is 1, 2, or 3.

In still other embodiments, L¹ is $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$, or $-(CH_2)_n-C(H)=C(H)-G^2-$ wherein G², n and p are as defined herein.

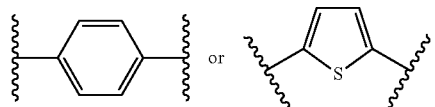
In still other embodiments, L¹ is $-(CH_2)_3-G^2-(CH_2)_p-$, $-CH_2-C\equiv C-G^2-$, or $-CH_2-C(H)=C(H)-G^2-$.

In still other embodiments, L¹ is $-(CH_2)_3-G^2-$, $-CH_2-C\equiv C-G^2-$, or $-CH_2-C(H)=C(H)-G^2-$.

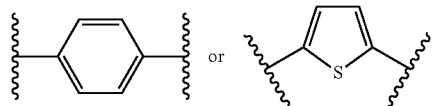
In some embodiments L¹ is $-(CH_2)_n-G^2-(CH_2)_p-$. For example, in some groups of compounds, G² is



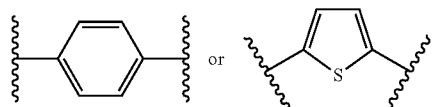
n is 2 and p is 0. In other groups, G² is



(I) n is 3 and p is 0. In still other groups, G² is

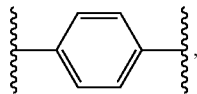


n is 2 and p is 0, 1, 2, or 3. In yet other groups, G² is

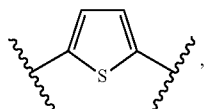


11

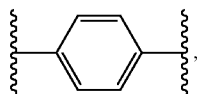
p is 0, and n is 2, 3, 4, or 5. In some subgroups, G² is



n is 2 and p is 0. In other subgroups, G² is

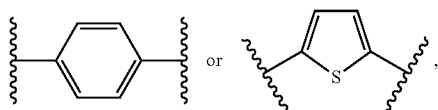


n is 3 and p is 0. In other subgroups, G² is

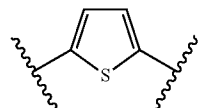


n is 1 and p is 1.

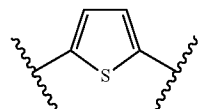
In still other embodiments, L¹ is $-(CH_2)_n-C\equiv C-G^2-$ or $-(CH_2)_n-C(H)=C(H)-G^2-$. For example, in some groups of compounds G² is



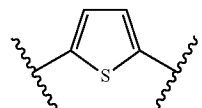
and n is 1. In certain subgroups of compounds G² is



and n is 1. In other subgroups, L¹ is $-(CH_2)_n-C\equiv C-G^2-$, G² is



and n is 1. In still other subgroups, L¹ is $-(CH_2)_n-C(H)=C(H)-G^2-$, G² is



and n is 1.

In compounds of formula (I), (Ia), or (II), R¹ is COOR⁹, CONR⁹R¹⁰, CH₂OR⁹, SO₃R⁹, SO₂NR⁹R¹⁰, PO(OR⁹)₂, or

12

tetrazol-5-yl; wherein R⁹ is H, C₁-C₄ alkyl (e.g., methyl, ethyl) or aryl (e.g., phenyl) and R¹⁰ is H, C₁-C₄ alkyl (e.g., methyl, ethyl), COR¹¹, OR⁹, or SO₂R¹¹; wherein R¹¹ is C₁-C₄ alkyl (e.g., methyl, ethyl). In one group of compounds, R¹ is COOH or COOCH₃. In another group of compounds, R¹ is COOH.

In compounds of formula (I) or (Ia), L⁴ is $-C(R^2)_2-C(R^3)_2-$, $-C(R^2)=C(R^3)-$, $-C\equiv C-$, or

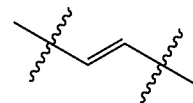
10



15

wherein R² and R³ are each H, CH₃, fluoro, or chloro. In some embodiments, L⁴ is $-C(R^2)_2-C(R^3)_2-$ and R² and R³ are each hydrogen. In other embodiments, L⁴ is $-C(R^2)=C(R^3)-$ and R² and R³ are each independently H, CH₃, fluoro or chloro. In some groups of compounds, L⁴ is $-C(R^2)=C(R^3)-$ and R² and R³ are hydrogen. In certain subgroups, L⁴ is

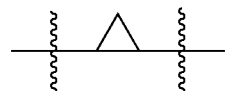
25



30

In other embodiments, L⁴ is $-C\equiv C-$. In yet other embodiments, L⁴ is

35



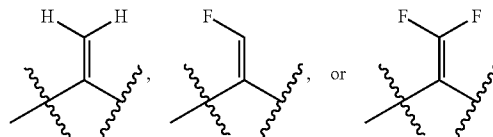
40

In compounds of formula (I) or (Ia), L² is $-CH_2-$ or a bond. In some embodiments, L² is a bond.

45

In compounds of formula (I), (Ia), or (II), R⁴ and R⁵ are each independently H, F, CF₃, or C₁-C₄ alkyl (e.g., methyl, ethyl, etc.); or R⁴ and R⁵ together with the carbon to which they are attached form a C₃-C₅ cycloalkyl (e.g., cyclopropyl),

50



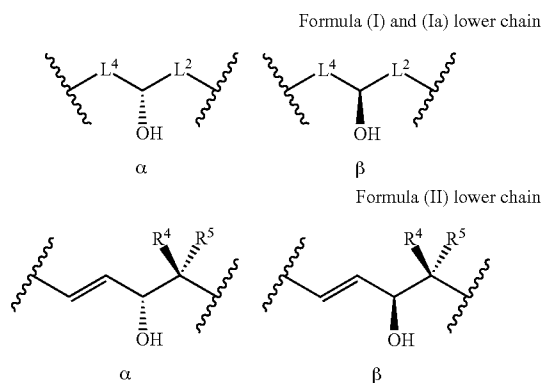
55

In some embodiments, R⁴ and R⁵ are each independently hydrogen or CH₃. In other embodiments R⁴ is C₁-C₄ alkyl (e.g., methyl, ethyl, etc.) and R⁵ is hydrogen. In yet other embodiments, R⁴ is hydrogen and R⁵ is C₁-C₄ alkyl (e.g., methyl, ethyl, etc.). In still other embodiments, R⁴ and R⁵ are fluoro. In some embodiments, R⁴ is methyl and R⁵ is hydrogen. In other embodiments, R⁴ is hydrogen and R⁵ is methyl.

65

In the compounds of formula (I), (Ia), or (II), the stereochemistry of the hydroxyl group on the lower chain may be either α or β or a mixture of α and β.

13

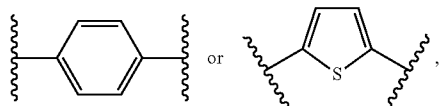


In some embodiments, L^3 is C_2 - C_6 alkynylene, wherein the C_2 - C_6 alkynylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents. In other embodiments, L^3 is C_2 - C_6 alkynylene. For example, in some groups of compounds, L^3 is ethynylene, propynylene, or butynylene. In some subgroups of compounds, L^3 is $-C\equiv C-$ or $-\text{CH}_2-\text{C}\equiv\text{C}-$. In other subgroups, L^3 is $-C\equiv C-$. In other subgroups, L^3 is $-\text{CH}_2-\text{C}\equiv\text{C}-$.

In some embodiments of the invention, R^6 is aryl or C_1 - C_{10} alkyl, wherein the aryl is optionally substituted as described herein. In other embodiments, R^6 is aryl, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} haloalkyl, C_3 - C_8 halocycloalkyl, C_2 - C_{10} haloalkenyl, or C_2 - C_{10} haloalkynyl, wherein the aryl is optionally substituted as described herein. In one group of compounds, R^6 is phenyl or C_1 - C_6 alkyl, wherein the phenyl is optionally substituted as described herein. In certain subgroups, R^6 is phenyl, methyl, ethyl, or propyl.

In some embodiments of the invention, R^6 is aryl or heteroaryl, each optionally substituted as described herein. In some groups of compounds, R^6 is aryl, optionally substituted as described herein. In some groups of compounds, R^6 is phenyl optionally substituted with halogen (e.g., fluoro, chloro), C_1 - C_3 haloalkyl (e.g., CF_3), or $-\text{C}_1$ - C_3 alkylene- C_1 - C_3 alkoxy (e.g., CH_2OCH_3). In other embodiments of the invention, R^6 is heterocyclyl, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} haloalkyl, C_3 - C_8 halocycloalkyl, C_2 - C_{10} haloalkenyl, or C_2 - C_{10} haloalkynyl, each optionally substituted as described herein. In other embodiments, R^6 is C_1 - C_{10} alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, octyl, etc.). In some groups of compounds, R^6 is methyl, ethyl, n-propyl, n-butyl, or n-pentyl. In a particular subgroups of compounds, R^6 is methyl, ethyl, or n-propyl.

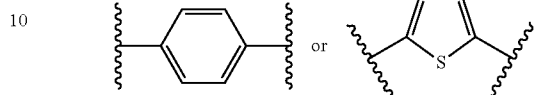
In one aspect of the invention are compounds of formula (I), or (II), wherein L^1 - R^1 is C_3 - C_7 alkylene- R^1 , wherein the C_3 - C_7 alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents; or L^1 - R^1 is $-(\text{CH}_2)_n$ - G^2 - $(\text{CH}_2)_p$ - R^1 , $-(\text{CH}_2)_n$ - $\text{C}\equiv\text{C}$ - G^2 - R^1 , or $-(\text{CH}_2)_n$ - $\text{C}(\text{H})=\text{C}(\text{H})$ - G^2 - R^1 , wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1$, 2, 3, 4, 5, or 6; G^2 is



wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_4 alkyl,

14

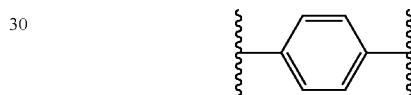
C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, and C_1 - C_3 haloalkoxy; R^1 is COOR^9 ; and R^9 is H or C_1 - C_4 alkyl. In one embodiment of this aspect of the invention L^1 - R^1 is n-hexylene- COOR^9 , $-(\text{CH}_2)_n$ - G^2 - $(\text{CH}_2)_p$ - COOR^9 , $-(\text{CH}_2)_n$ - $\text{C}\equiv\text{C}$ - G^2 - COOR^9 , or $-(\text{CH}_2)_n$ - $\text{C}(\text{H})=\text{C}(\text{H})$ - G^2 - COOR^9 ; wherein n is 1, 2 or 3, p is 0 or 1; G^2 is



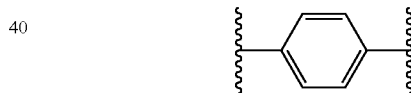
15 and R^9 is H or CH_3 .

In another embodiment of this aspect of the invention, L^1 - R^1 is C_3 - C_7 alkylene- R^1 and the C_3 - C_7 alkylene is optionally substituted with 1-4 fluoro substituents. In one group of compounds, for example, L^1 - R^1 is n-pentylene- COOR^9 , n-hexylene- COOR^9 , n-heptylene- COOR^9 , etc., and R^9 is H, CH_3 , or $-\text{CH}_2\text{CH}_3$. In one embodiment, L^1 - R^1 is n-hexylene- COOH , n-hexylene- COOCH_3 , or n-hexylene- $\text{COOCH}_2\text{CH}_3$.

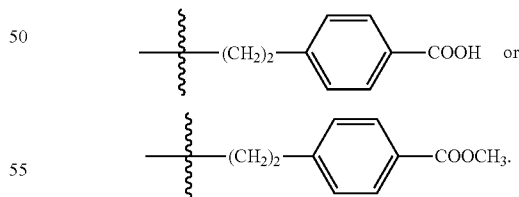
25 In another embodiment of this aspect of the invention, L^1 - R^1 is $-(\text{CH}_2)_n$ - G^2 - $(\text{CH}_2)_p$ - R^1 ; and G^2 is



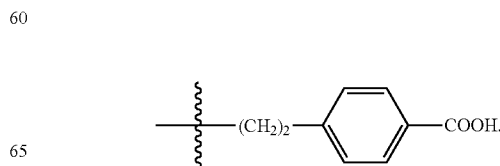
35 In another embodiment, L^1 - R^1 is $-(\text{CH}_2)_n$ - G^2 - COOR^9 (i.e., p is 0), G^2 is



45 n is 2 or 3, and R^9 is H or CH_3 . In one embodiment, L^1 - R^1 is

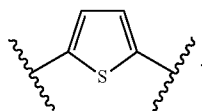


In another embodiment, L^1 - R^1 is

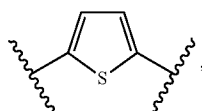


15

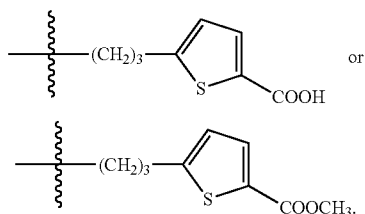
In another embodiment of this aspect of the invention L^1-R^1 is $-(CH_2)_n-G^2-(CH_2)_p-R^1$ and G^2 is



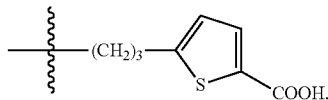
In another embodiment, L^1-R^1 is $-(CH_2)_n-G^2-COOR^9$ (i.e., p is 0), G^2 is



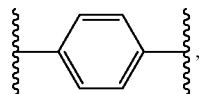
n is 2 or 3; and R^9 is H or CH_3 . In still another embodiment, L^1-R^1 is



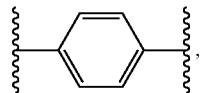
In yet another embodiment, L^1-R^1 is



In another embodiment, L^1-R^1 is $-CH_2-G^2-CH_2-$ 45
 $COOR^9$, G^2 is



and R^9 is H or CH_3 . In another embodiment, L^1-R^1 is 55
 $-CH_2-G^2-CH_2-COOR^9$, G^2 is

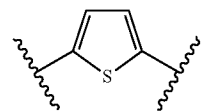


and R^9 is H.

16

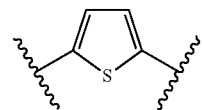
In still another embodiment of this aspect of the invention, L^1-R^1 is $-(CH_2)_n-C\equiv C-G^2-COOR^9$ and G^2 is

5



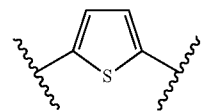
In yet another embodiment, L^1-R^1 is $-(CH_2)_n-C\equiv C-G^2-$
 $COOR^9$, G^2 is

15



n is 1, and R^9 is H or CH_3 . In another embodiment, L^1-R^1 is $-(CH_2)_n-C\equiv C-G^2-COOR^9$, G^2 is

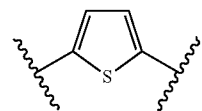
25



n is 1, and R^9 is H.

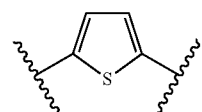
In another embodiment of this aspect of the invention, L^1-R^1 is $-(CH_2)_n-C(H)=C(H)-G^2-COOR^9$ and G^2 is

35



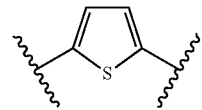
In another embodiment, L^1-R^1 is $-(CH_2)_n-C(H)=C(H)-$
 G^2-COOR^9 , G^2 is

40



n is 1, and R^9 is H or CH_3 . In another embodiment, L^1-R^1 is $-(CH_2)-C(H)=C(H)-G^2-COOR^9$, G^2 is

55

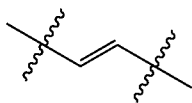


n is 1, and R^9 is H.

In another aspect of the invention are compounds of formula (I) or (Ia), wherein L^2 is a bond, L^4 is $-C(R^2)=C(R^3)-$, R^2 and R^3 are each hydrogen, R^4 and R^5 are independently H or C_1-C_4 alkyl, L^3 is C_2-C_6 alkenylene; wherein the C_2-C_6 alkenylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents; and R^6 is aryl or C_1-C_{10} alkyl, wherein the aryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_3 haloalkyl, cyano, halogen, C_1-C_3 alkoxy,

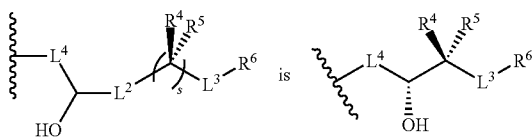
17

C₁-C₃haloalkoxy; and —C₁-C₃alkylene-C₁-C₃alkoxy. In a first embodiment of this aspect, L⁴ is

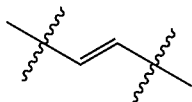


and R⁴ and R⁵ are independently H or CH₃. In one group of compounds according to the first embodiment, L³ is ethynylene, propynylene, or butynylene. In a subgroup of compounds R⁶ is aryl optionally substituted as described herein. In another subgroup, R⁶ is phenyl optionally substituted as described herein. In another subgroup, R⁴ is methyl and R⁵ is hydrogen. In a subgroup of compounds, L³ is —CH₂—C≡C— or —C≡C—. In another group of compounds of this embodiment, R⁶ is C₁-C₁₀alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, octyl, etc.). In a subgroup of compounds, R⁶ is methyl, ethyl, n-propyl, or n-butyl.

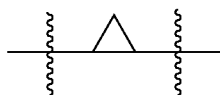
In another aspect of the invention are compounds of formula (I) or (Ia), wherein



(i.e., the hydroxyl group stereochemistry is α, L² is a bond and s is 1), R⁶ is aryl, heteroaryl, heterocyclyl, C₁-C₁₀alkyl, C₃-C₈cycloalkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₁-C₁₀haloalkyl, C₃-C₈halocycloalkyl, C₂-C₁₀haloalkenyl, or C₂-C₁₀haloalkynyl, (each optionally substituted as described herein) and L³, L⁴, R⁴, and R⁵ are as defined herein. In a first embodiment of this aspect of the invention, L⁴ is



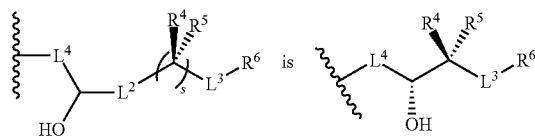
and R⁴ and R⁵ are independently H or CH₃. In one group of compounds according to the first embodiment, L³ is ethynylene, propynylene, or butynylene. In another group, R⁶ is phenyl optionally substituted as described herein. In another group, R⁴ is methyl and R⁵ is hydrogen. In a subgroup of compounds, L³ is —CH₂—C≡C— or —C≡C—. In another group of compounds of this embodiment, R⁶ is C₁-C₁₀alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, octyl, etc.). In a subgroup of compounds, R⁶ is methyl, ethyl, n-propyl, or n-butyl. In a second embodiment of this aspect of the invention, L⁴ is —CH₂—CH₂— and R⁴ and R⁵ are independently H or CH₃. In a third embodiment of this aspect of the invention L⁴ is —C≡C— and R⁴ and R⁵ are independently H or CH₃. In a fourth embodiment of this aspect of the invention, L⁴ is



18

and R⁴ and R⁵ are independently H or CH₃. Groups of compounds according to the second, third, and fourth embodiments include those where L³ is ethynylene, propynylene, or butynylene and R⁶ is C₁-C₁₀alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, octyl, etc.) or phenyl optionally substituted as described herein.

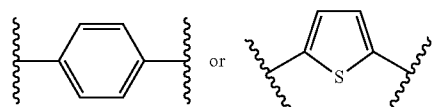
In another aspect of the invention are compounds of formula (I) or (Ia), wherein



L⁴ is —C(R²)=C(R³)—; R² and R³ are each hydrogen; and R⁴ and R⁵ are independently H or C₁-C₄ alkyl. In a first embodiment according to this aspect of the invention, L³ is C₂-C₆alkynylene; wherein the C₂-C₆alkynylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents; and R⁶ is aryl, heteroaryl, heterocyclyl, C₁-C₁₀alkyl, C₃-C₈cycloalkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₁-C₁₀haloalkyl, C₃-C₈halocycloalkyl, C₂-C₁₀haloalkenyl, or C₂-C₁₀haloalkynyl, (each optionally substituted as described herein).

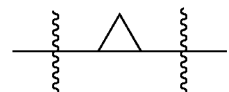
In another aspect of the invention are compounds of formula (I) or (Ia) wherein:

L¹-R¹ is C₃-C₇alkylene-R¹, wherein the C₃-C₇alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents; or L¹-R¹ is —(CH₂)—G²—(CH₂)_p—R¹, —(CH₂)_n—C≡C—G²—R¹, or —(CH₂)_n—C(H)=C(H)—G²—R¹, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and n+p=1, 2, 3, 4, 5, or 6; G² is



wherein G² is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₄alkyl, C₁-C₃haloalkyl, cyano, halogen, C₁-C₃alkoxy, and C₁-C₃haloalkoxy; R¹ is COOR⁹; R⁹ is H or C₁-C₄ alkyl;

L² is a bond;
L⁴ is —C(R²)₂—C(R³)₂—, —C(R²)=C(R³)—, —C≡C—, or



wherein R² and R³ are each H, CH₃, fluoro, or chloro;

R⁴ and R⁵ are each independently H, F, CF₃, or C₁-C₄ alkyl; or R⁴ and R⁵ together with the carbon to which they are attached form a C₃-C₅ cycloalkyl;

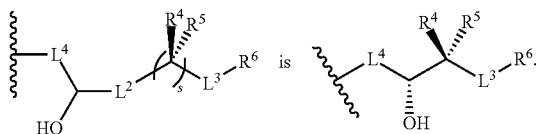
L³ is C₂-C₆alkynylene; wherein the C₂-C₆alkynylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents;

R⁶ is aryl, C₁-C₁₀alkyl, C₃-C₈cycloalkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₁-C₁₀haloalkyl, C₃-C₈halocycloalkyl, C₂-C₁₀haloalkenyl, or C₂-C₁₀haloalkynyl, wherein the aryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₄alkyl,

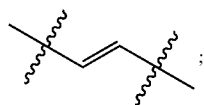
19

C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy; and $-C_1$ - C_3 alkylene- C_1 - C_3 alkoxy; and s is 0 or 1.

In one embodiment of the foregoing aspect,

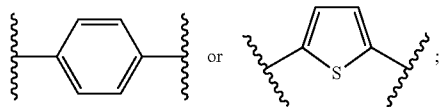


In another embodiment according to the foregoing aspect of the invention, L^4 is



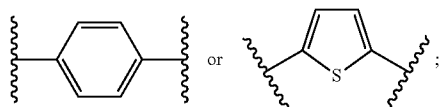
R^4 and R^5 are independently H or C_1 - C_4 alkyl; L^3 is C_2 - C_6 alkynylene; and R^6 is aryl or C_1 - C_{10} alkyl; wherein the aryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy, and $-C_1$ - C_3 alkylene- C_1 - C_3 alkoxy.

In one group of compounds according to the foregoing embodiment, L^1 - R^1 is C_3 - C_7 alkylene- R^1 ; or L^1 - R^1 is $-(CH_2)_n-G^2-(CH_2)_p-R^1$, $-(CH_2)_n-C\equiv C-G^2-R^1$, or $-(CH_2)_n-C(H)=C(H)-G^2-R^1$, wherein n is 1, 2 or 3, p is 0, 1, or 2, and $n+p=1, 2, 3$ or 4; G^2 is



R^1 is $COOR^9$; R^9 is H or C_1 - C_4 alkyl; R^4 and R^5 are independently H or CH_3 ; L^3 is ethynylene, propynylene, or butynylene; and R^6 is phenyl or C_1 - C_6 alkyl, wherein the phenyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy; and $-C_1$ - C_3 alkylene- C_1 - C_3 alkoxy.

In one subgroup of compounds according to the foregoing embodiment, L^1 is n -hexylene, $-(CH_2)_n-G^2-(CH_2)_p$, $-CH_2-C\equiv C-G^2$, or $-CH_2-C(H)=C(H)-G^2$, wherein n is 1, 2 or 3; p is 0 or 1, and $n+p=2$ or 3; G^2 is



R^1 is $COOR^9$; R^9 is H or CH_3 ; L^3 is $-C\equiv C-$ or $-CH_2-C\equiv C-$; and R^6 is phenyl, methyl, ethyl, or propyl. For example, in certain compounds of this subgroup, L^3 is $-CH_2-C\equiv C-$ and s is 1. In yet other compounds of this subgroup L^3 is $-C\equiv C-$ and s is 0.

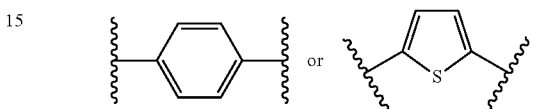
In another subgroup of compounds according to the foregoing embodiment L^3 is $-CH_2-C\equiv C-$ and s is 1.

20

In another subgroup of compounds according to the foregoing embodiment L^3 is $-C\equiv C-$ and s is 0.

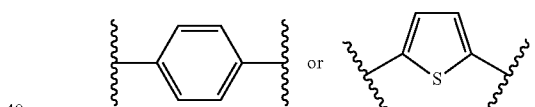
In another group of compounds according to the foregoing embodiment L^1 is C_3 - C_7 alkylene, wherein the C_3 - C_7 alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents.

In another group of compounds according to the foregoing embodiment L^1 is $-(CH_2)_n-G^2-(CH_2)_p$, $-(CH_2)_n-C\equiv C-G^2$, or $-(CH_2)_n-C(H)=C(H)-G^2$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5$, or 6; and G^2 is



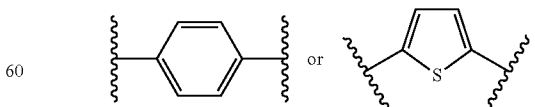
wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, and C_1 - C_3 haloalkoxy.

In another subgroup of compounds according to the foregoing embodiment L^3 is $-CH_2-C\equiv C-$; s is 1; and L^1 is C_3 - C_7 alkylene, wherein the C_3 - C_7 alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents. In another subgroup of compounds according to the foregoing embodiment L^3 is $-CH_2-C\equiv C-$; s is 1; L^1 is $-(CH_2)_n-G^2-(CH_2)_p$, $-(CH_2)_n-C\equiv C-G^2$, or $-(CH_2)_n-C(H)=C(H)-G^2$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5$, or 6; and G^2 is



wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, and C_1 - C_3 haloalkoxy.

In another subgroup of compounds according to the foregoing embodiment L^3 is $-C\equiv C-$; s is 0; and L^1 is C_3 - C_7 alkylene, wherein the C_3 - C_7 alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents. In another subgroup of compounds according to the foregoing embodiment L^3 is $-C\equiv C-$; s is 0; and L^1 is $-(CH_2)_n-G^2-(CH_2)_p$, $-(CH_2)_n-C\equiv C-G^2$, or $-(CH_2)_n-C(H)=C(H)-G^2$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5$, or 6; and G^2 is



wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, cyano, halogen, C_1 - C_3 alkoxy, and C_1 - C_3 haloalkoxy.

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylic acid;

5-((Z)-3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid;

4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid;

3-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)benzoic acid;

methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

(Z)-methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-enoate;

methyl 4-((2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)thio)butanoate;

methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;

methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;

methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate;

methyl 5-((Z)-3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate;

methyl 4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate;

methyl 3-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)benzoate;

7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

(Z)-7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-enoic acid;

4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)thio)butanoic acid;

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;

5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylic acid;

5-((Z)-3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid;

4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid;

3-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)benzoic acid;

methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((3R,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

5 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((3R,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

10 methyl 7-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((S)-2-((3S,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

15 methyl 7-((S)-2-((3S,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

7-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((S)-2-((3S,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

20 7-((S)-2-((3S,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

ethyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

25 isopropyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

N-ethyl-7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanamide;

7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)-N-(methylsulfonyl)heptanamide;

30 (R)-1-(6-(1H-tetrazol-5-yl)hexyl)-5-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)pyrrolidin-2-one;

(R)-5-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-1-(7-hydroxyheptyl)pyrrolidin-2-one;

35 methyl 7-((R)-2-((3S,4S,E)-4-ethyl-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((3R,4R,E)-3-hydroxy-4-isopropylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

40 methyl 7-((R)-2-((R,E)-3-hydroxy-4,4-dimethylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclopropyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

45 methyl 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclobutyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((R,E)-4,4-difluoro-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

50 methyl 7-((R)-2-((S,E)-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

7-((R)-2-((3S,4S,E)-4-ethyl-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((3R,4R,E)-3-hydroxy-4-isopropylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

55 7-((R)-2-((R,E)-3-hydroxy-4,4-dimethylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclopropyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

60 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclobutyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((R,E)-4,4-difluoro-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((S,E)-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

65 methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenylloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 methyl 5-(3-((S)-2-((3R,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 methyl 5-(3-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 5-(3-((S)-2-((3R,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 5-(3-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-ynoate; and
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-ynoic acid; or a pharmaceutically acceptable salt thereof.

Compounds described herein may exist as stereoisomers wherein asymmetric (or chiral) centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The terms "R" and "S" used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., 1976, 45: 13-30.

The various stereoisomers (including enantiomers and diastereomers) and mixtures thereof of the compounds described are also contemplated. Individual stereoisomers of compounds described may be prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution of the individual stereoisomer

using methods that are known to those of ordinary skill in the art. Examples of resolution are, for example, (i) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography, followed by liberation of the optically pure product; or (ii) separation of the mixture of enantiomers or diastereomers on chiral chromatographic columns.

Geometric isomers may exist in the present compounds. All various geometric isomers and mixtures thereof resulting from the disposition of substituents around a carbon-carbon double bond, a carbon-nitrogen double bond, a cycloalkyl group, or a heterocycle group are contemplated. Substituents around a carbon-carbon double bond or a carbon-nitrogen bond are designated as being of Z or E configuration and substituents around a cycloalkyl or a heterocycle are designated as being of cis or trans configuration.

It is to be understood that compounds disclosed herein may exhibit the phenomenon of tautomerism.

Thus, the formulae within this specification can represent only one of the possible tautomeric forms. It is to be understood that encompassed herein are any tautomeric form, and mixtures thereof, and is not to be limited merely to any one tautomeric form utilized within the naming of the compounds or formulae.

Additionally, unless otherwise stated, the structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, probes in a biological assay, or as EP₄ receptor agonists.

Also contemplated as part of the invention are compounds formed by synthetic means or formed in vivo by biotransformation or by chemical means. For example, certain compounds of the invention may function as prodrugs that are converted to other compounds of the invention upon administration to a subject.

Methods of Treatment

The compounds of the invention are EP₄ receptor agonists and are useful in treating or preventing conditions or diseases responsive to an EP₄ receptor agonist. Conditions or diseases treatable with compounds of the invention include elevated intraocular pressure, glaucoma, ocular hypertension, dry eye, macular edema, macular degeneration, alopecia (alone or in combination with, for example, an L-PGDS inhibitor or an H-PGDS inhibitor or in combination with both an L-PGDS inhibitor and H-PGDS inhibitor; Garza, L. A. et al, *Science Translational Medicine*, 2012, 4(126), 126ra34), cerebralvascular accident (Liang, X. et al, *Journal of Clinical Investigation*, 2011, 121(11), 4362-4371), brain damage due to trauma, neuropathic pain (e.g., diabetic neuropathy, sciatica, post-herpetic neuralgia, HIV-related neuropathy, trigeminal neuralgia, ductus arteriosus, chemotherapy-induced pain), low bone density due to osteoporosis (Cameron, K. O. et al, *Bioorganic and Medicinal Chemistry Letters*, 2006, 16, 1799-1802) or glucocorticoid treatment, bone fracture, and bone loss due to periodontal disease, surgical procedures, cancer, or trauma. Further uses of the compounds of the invention include use in increasing bone density in preparation of bone for receiving dental or ortho-

pedic implants, coating of implants for enhanced osseointegration, and use in all forms of spinal fusion.

The present invention provides methods of treatment comprising administering to a patient in need thereof: (i) a therapeutically effective amount of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, or a solvate of either; or (ii) a composition comprising any of the foregoing compound, salt, or solvate and a pharmaceutically acceptable carrier.

In one aspect, the invention provides a method of treating glaucoma, osteoporosis, bone fracture, bone loss or low bone density due to periodontal disease, alopecia, a tooth socket having undergone implantation, a joint that is to undergo or that has undergone orthopedic implantation, vertebrae that have undergone spinal fusion, or neuropathic pain.

In another aspect, the invention provides a method of stimulating bone formation. According to this aspect of the invention, one embodiment provides a method of treating osteoporosis, bone fracture, and periodontal disease. In another embodiment, the compound or composition of the invention is administered alone. In still another embodiment, the compound or composition is administered in combination with one or more additional therapeutic agents to treat bone loss or osteoporosis. Compounds of the invention can be used in combination other agents useful in treating or preventing bone loss such as an organic bisphosphonate (e.g., alendronic acid or sodium alendronate); a cathepsin K inhibitor; an estrogen or an estrogen receptor modulator; calcitonin; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; a RANKL inhibitor such as denosumab; a bone anabolic agent, such as PTH; a bone morphogenetic agent such as BMP-2, BMP-4, and BMP-7; Vitamin D or a synthetic Vitamin D analogue such as ED-70; an androgen or an androgen receptor modulator; a SOST inhibitor; and the pharmaceutically acceptable salts and mixtures thereof. A preferred combination is a compound of the present invention and an organic bisphosphonate.

In another aspect, the invention provides a method of lowering intraocular pressure. According to this aspect of the invention, one embodiment provides a method of treating glaucoma. In another embodiment, the compound or composition of the invention is administered alone. In still another embodiment, the compound or composition is administered in combination with one or more additional therapeutic agents that lower intraocular pressure such as a β -adrenergic blocking agent such as timolol, betaxolol, levobetaxolol, carteolol, levobunolol, a parasympathomimetic agent such as pilocarpine, a sympathomimetic agents such as epinephrine, iopidine, brimonidine, clonidine, or para-aminoclonidine, a carbonic anhydrase inhibitor such as dorzolamide, acetazolamide, metazolamide or brinzolamide; and a prostaglandin such as latanoprost, travaprost, or unoprostone, and the pharmaceutically acceptable salts and mixtures thereof.

In still another aspect, the invention provides a method of treating neuropathic pain. According to this aspect of the invention, one embodiment provides a method of treating diabetic neuropathy, sciatica, post-herpetic neuralgia, HIV-related neuropathy, trigeminal neuralgia, or chemotherapy-induced pain. In another embodiment, the compound or composition of the invention is administered alone. In still another embodiment, the compound or composition is administered in combination with one or more additional therapeutic agents that treat neuropathic pain such as gaba-

entin, pregabalin, duloxetine, and lamotrigine, and the pharmaceutically acceptable salts and mixtures thereof.

Compounds described herein can be administered as a pharmaceutical composition comprising the compounds of interest in combination with one or more pharmaceutically acceptable carriers. The phrase "therapeutically effective amount" of the present compounds means sufficient amounts of the compounds to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It is understood, however, that the total daily dosage of the compounds and compositions can be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient can depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health and prior medical history, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well-known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Actual dosage levels of active ingredients in the pharmaceutical compositions can be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient and a particular mode of administration. In the treatment of certain medical conditions, repeated or chronic administration of compounds can be required to achieve the desired therapeutic response. "Repeated or chronic administration" refers to the administration of compounds daily (i.e., every day) or intermittently (i.e., not every day) over a period of days, weeks, months, or longer. In particular, the treatment of chronic painful conditions may require such repeated or chronic administration of the compounds. Compounds described herein may become more effective upon repeated or chronic administration such that the therapeutically effective doses on repeated or chronic administration can be lower than the therapeutically effective dose from a single administration.

Combination therapy includes administration of a single pharmaceutical dosage formulation containing one or more of the compounds described herein and one or more additional pharmaceutical agents, as well as administration of the compounds and each additional pharmaceutical agent, in its own separate pharmaceutical dosage formulation. For example, a compound described herein and one or more additional pharmaceutical agents, can be administered to the patient together, in a single oral dosage composition having a fixed ratio of each active ingredient, such as a tablet or capsule; or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, the present compounds and one or more additional pharmaceutical agents can be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

In one aspect of the invention, compounds of the invention, or a pharmaceutically acceptable salt thereof, or a solvate of either; or (ii) a composition comprising any of the foregoing compound, salt, or solvate and a pharmaceutically acceptable carrier are administered as the active pharmaceutical agent. In another aspect, compounds of the invention or a pharmaceutically acceptable salt thereof, or a

solvate of either; or (ii) a composition comprising any of the foregoing compound, salt, or solvate and a pharmaceutically acceptable carrier are administered to a subject and the administered compounds are converted to the active pharmaceutical agent in the subject by chemical or biotransformation.

Ophthalmic formulations of this compound may contain from 0.001 to 5% and especially 0.001 to 0.1% of active agent. Higher dosages as, for example, up to about 10% or lower dosages can be employed provided the dose is effective in reducing intraocular pressure, treating glaucoma, increasing blood flow velocity or oxygen tension. For a single dose, from between 0.001 to 5.0 mg, preferably 0.005 to 2.0 mg, and especially 0.005 to 1.0 mg of the compound can be applied to the human eye.

Compounds may be administered orally once or several times per day each in an amount of from 0.001 mg to 100 mg per adult, preferably about 0.01 to about 10 mg per adult. Compounds may also be administered parenterally once or several times per day each in an amount of from 0.1 ng to 10 mg per adult or continuously administered into a vein for 1 hour to 24 hours per day. Compounds may also be administered locally to stimulate bone formation in an amount from 0.0001 µg to 500 µg.

Pharmaceutical Compositions

Pharmaceutical compositions comprise compounds described herein, pharmaceutically acceptable salts thereof, or solvates of either. The pharmaceutical compositions comprising the compound, salt, or solvate described herein can be formulated together with one or more non-toxic pharmaceutically acceptable carriers, either alone or in combination with one or more other medicaments as described herein-above.

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The pharmaceutical compositions can be administered to humans, other mammals, and birds orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), buccally or as an oral or nasal spray. The term "parenterally" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The pharmaceutical compositions can further be administered to humans, other mammals, and birds locally to the desired site of action; for example, into a bone void such as a tooth socket defect, adjacent to an alveolar bone, or a bone defect caused by surgery, trauma, or disease.

The term "pharmaceutically acceptable carrier" as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters

such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, can depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, cement, putty, and granules. In such solid dosage forms, the active compound can be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as

paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form can also comprise buffering agents.

Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such carriers as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They can optionally contain opacifying agents and can also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned carriers.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms can contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, can contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, poly(lactic-co-glycolic acid), microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, collagen sponge, demineralized bone matrix, and mixtures thereof.

The compounds can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to compounds described herein, stabilizers, preservatives, excipients and the like. The preferred lipids are natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used separately or together. Methods to form liposomes are known in the art. See, for example, Prescott,

Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of compounds described herein include powders, sprays, ointments and inhalants. The active compounds can be mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope.

The compounds can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in (*J. Pharmaceutical Sciences*, 1977, 66: 1 et seq). The salts can be prepared in situ during the final isolation and purification of the compounds or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate (isothionate), lactate, malate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as, but not limited to, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as, but not limited to, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid and such organic acids as acetic acid, fumaric acid, maleic acid, 4-methylbenzenesulfonic acid, succinic acid and citric acid.

Basic addition salts can be prepared in situ during the final isolation and purification of compounds by reacting a carboxylic acid-containing moiety with a suitable base such as, but not limited to, the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as, but not limited to, lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methyl-

amine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Compounds described herein can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol, among others, are equivalent to the unsolvated forms.

Chemistry and Examples

Unless otherwise defined herein, scientific and technical terms used in connection with the exemplary embodiments shall have the meanings that are commonly understood by those of ordinary skill in the art.

Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclature used in connection with, and techniques of chemistry and molecular biology described herein are those well-known and commonly used in the art.

It will be appreciated that the synthetic schemes and specific examples are illustrative and are not to be read as limiting the scope of the invention. Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed and substituents present in the reactants used. Unless otherwise specified, solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art. The skilled artisan will also appreciate that not all of the substituents in the compounds of formula (I) or (Ia) will tolerate certain reaction conditions employed to synthesize the compounds. Routine experimentation, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection and deprotection may be required in the case of particular compounds. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts,

Protecting Groups in Chemical Synthesis (3 d ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety.

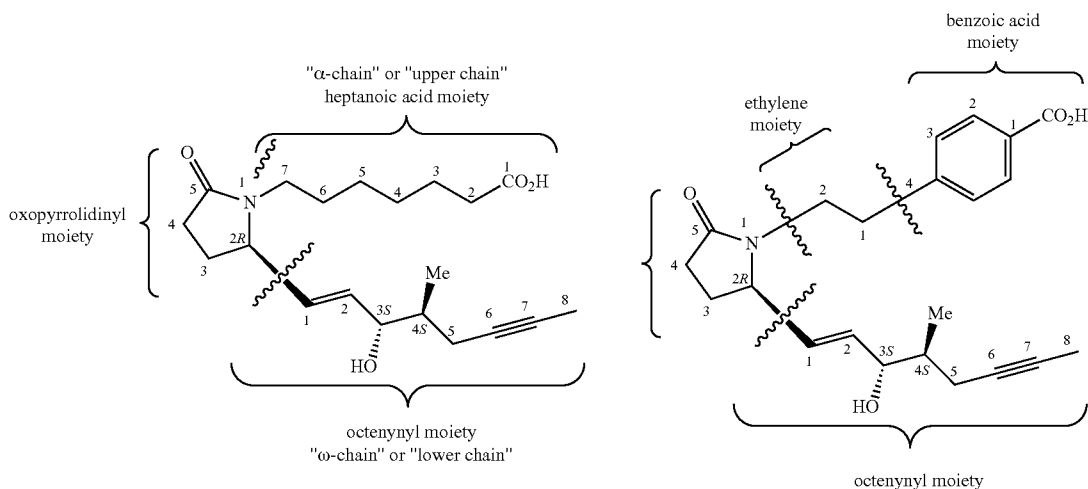
Furthermore, the skilled artisan will appreciate that in some cases, the order in which moieties are introduced may vary. The particular order of steps required to produce the compounds of formula (I) or (Ia) is dependent upon the particular compounds being synthesized, the starting compound, and the relative stability of the substituted moieties. Thus, synthesis of the present compounds may be accomplished by methods analogous to those described in the synthetic schemes described herein and in the specific examples, with routine experimentation (e.g., manipulation of the reaction conditions, reagents, and sequence of the synthetic steps).

Starting materials, if not commercially available, may be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

When an optically active form of a compound is required, it may be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound is required, it may be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

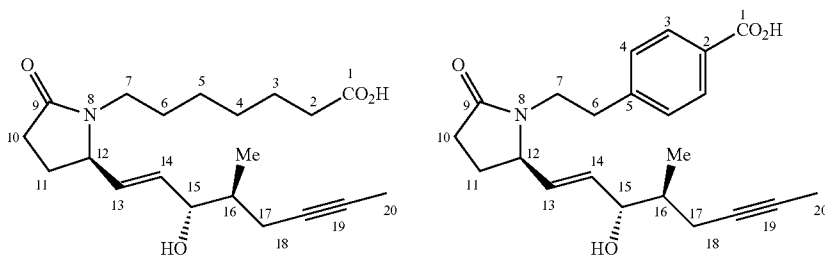
Systematic names of compound structures have been generated by the Convert-Structure-to-Name function of Chem & Bio Draw 12.0 Ultra by CambridgeSoft®, which uses the Cahn-Ingold-Prelog rules for stereochemistry. When discussing individual atomic positions of compound structures, an alternative continuous numbering scheme for the lactams as described below may be used.



Systematic name:
7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid

4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid

-continued



Alternative atom-position numbering schemes
for γ -lactams (also known as oxopyrrolidines or pyrrolidinones)

Liquid chromatography-mass spectra (LC/MS) were obtained using an Agilent LC/MSD G1946D or an Agilent 1100 Series LC/MSD Trap G2435A. Quantifications were obtained on a Cary 50 Bio UV-visible spectrophotometer.

^1H , ^{13}C , and ^{19}F Nuclear magnetic resonance (NMR) spectra were obtained using a Varian INOVA nuclear magnetic resonance spectrometer at 400, 100, and 376 MHz, respectively.

High performance liquid chromatography (HPLC) analytical separations were performed on an Agilent 1100 or Agilent 1200 HPLC analytical system and followed by an Agilent Technologies G1315B Diode Array Detector set at or near the UV_{max} 260 nm.

High performance liquid chromatography (HPLC) preparatory separations were performed on a Gilson preparative HPLC system or an Agilent 1100 preparative HPLC system and followed by an Agilent Technologies G1315B Diode Array Detector set at or near the UV_{max} 260 nm.

Analytical chiral HPLC separations were performed on an Agilent 1100 analytical system and followed by an Agilent Technologies G1315B Diode Array Detector set at or near the UV_{max} 260 nm.

Thin layer chromatography (TLC) analyses were performed on UniplatTM 250 μ , silica gel plates (Analtech, Inc. Catalog No. 02521) and were typically developed for visualization using a diluted sulfuric acid spray like 50 volume % in water or 10 volume % in methanol.

When used in the present application, the following abbreviations have the meaning set out below:

Ac is acetyl;
ACN is acetonitrile;
BBr₃ is boron tribromide;
Bn is benzyl;
BnNH₂ is benzylamine;
BSA is bovine serum albumin;
CH₂Cl₂ is dichloromethane;
CHCl₃ is chloroform;
CDCl₃ is deuteriochloroform;
CSA is camphorsulfonic acid;
DCC is N,N'-dicyclohexylcarbodiimide;
DME is 1,2-dimethoxyethane;
DMF is N,N-dimethylformamide;
DMSO is dimethyl sulfoxide;
DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene;
DIA is diisopropylamine;

DMAP is 4-dimethylaminopyridine;

EDC/EDAC is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride;

EDTA is ethylenediaminetetraacetic acid;

EE is ethoxyeth-1-yl;

ee is enantiomeric excess;

EIA is enzyme immunoassay;

Et is ethyl;

EtOAc is ethyl acetate;

EtOH is ethanol;

Et₃N is triethylamine;

HCl is hydrogen chloride;

HOBt is 1-hydroxybenzotriazole;

Me is methyl;

MeOH is methanol;

MTBE is methyl tert-butyl ether;

NaOMe is sodium methoxide;

nBuLi or n-BuLi is n-butyllithium;

NHS is N-hydroxysuccinimide;

NMP is 1-methyl-2-pyrrolidinone;

PG is a protecting group;

Ph is phenyl;

Pd(PPh₃)₄ is tetrakis(triphenylphosphine)palladium;

PhMe is toluene;

rt is room temperature;

TBAF is tetrabutylammonium fluoride;

TBS or TBDMS is tert-butyldimethylsilyl;

tBu or t-Bu is tert-butyl;

TEA is triethylamine;

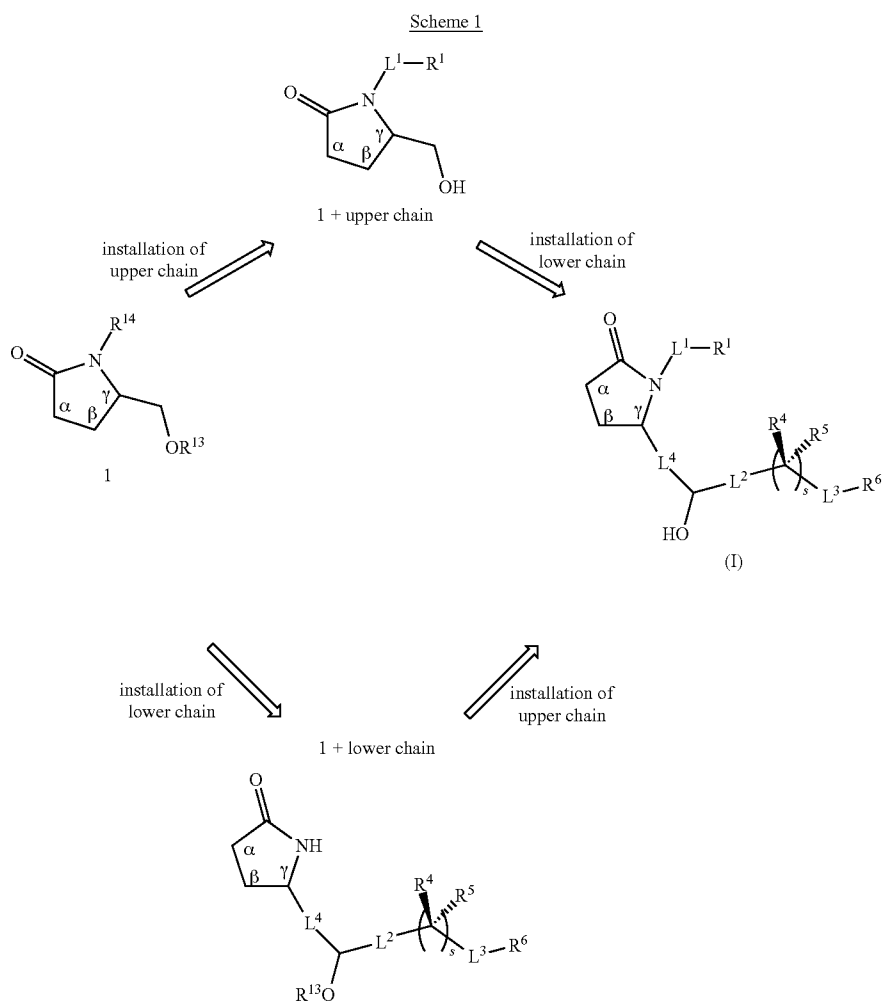
TFA is trifluoroacetic acid;

THF is tetrahydrofuran;

TMS is trimethylsilyl; and

Tris-HCl is 2-amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride.

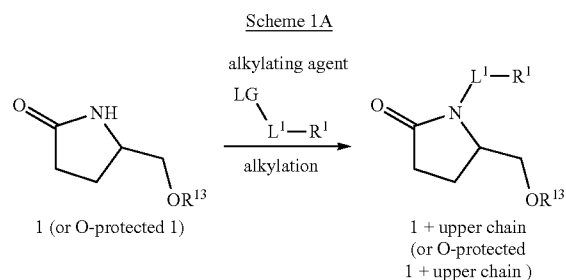
Compounds of the present invention may be prepared from commercially available 5-(hydroxymethyl)pyrrolidin-2-one (pyroglutaminol) (1) by general routes illustrated in Scheme 1.



R^{13} is hydrogen or an oxygen protecting group.

R^{14} is hydrogen or a nitrogen protecting group.

Compounds of the present invention, (I), may be prepared from 1, for example, by a process that comprises first installing the upper chain with a nitrogen-carbon bond forming reaction, wherein the nitrogen atom of the γ -lactam ring of 1 forms a covalent bond with the appropriate upper chain carbon atom to provide the corresponding 1+upper chain intermediate shown in Scheme 1. In some aspects of the present invention, the nitrogen-carbon forming reaction comprises an alkylation reaction between 1 or an oxygen-protected analog of 1 and an alkylating agent comprising the upper chain moiety and a leaving group as illustrated in Scheme 1A. In some aspects of the present invention, the alkylating agent is an alkyl halide such as an alkyl iodide, alkyl bromide, or alkyl triflate. In other aspects of the present invention, the alkylating agent is an allyl bromide. In other aspects of the present invention, the alkylating agent is a propargyl halide such as a propargyl bromide.



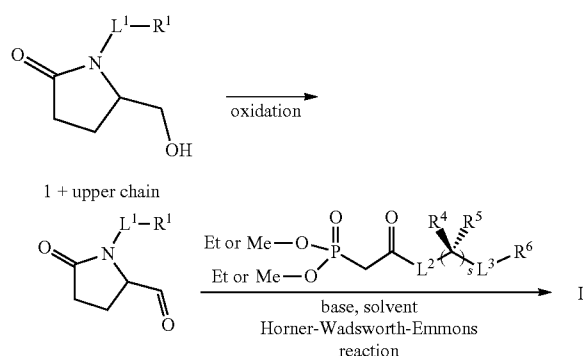
Leaving group "LG" is, for example, iodo, bromo, chloro, trifluoromethanesulfonyl, methanesulfonylate toluenesulfonylate, or 4-nitrobenzenesulfonylate. R^{13} is hydrogen or an oxygen protecting group.

The installation of the upper chain may be followed by a process that comprises installation of the lower chain by way of a carbon-carbon bond forming reaction, wherein the

39

hydroxymethyl group carbon atom attached to the γ -position of the lactam ring of intermediate 1+upper chain forms a covalent bond (carbon-carbon single, double, or triple bond) with the appropriate lower chain carbon atom to provide the corresponding compound (I). In some aspects of the present invention, the intermediate 1+upper chain (directly from the alkylation reaction or its O-protected analog having undergone subsequent deprotection) is oxidized to the corresponding aldehyde intermediate, which may be subsequently subjected to Horner-Wadsworth-Emmons reaction conditions in the presence as a phosphonate ester coupling partner to provide compounds (I) of the present invention, wherein L^4 is a carbon-carbon double bond, as illustrated in Scheme 1B.

Scheme 1B



Alternatively, compounds of the present invention, (I), may be prepared from 1, for example, by a process that comprises first installing the lower chain with a carbon-carbon bond forming reaction, wherein the hydroxymethyl group carbon atom attached to the γ -position of the lactam ring of starting material 1 forms a covalent bond (carbon-carbon single, double, or triple bond) with the appropriate lower chain carbon atom to provide the corresponding 1+lower chain intermediate shown in Scheme 1. The installation of the lower chain may be followed by a process that comprises installation of the upper chain by way of nitrogen-carbon bond forming reaction, wherein the nitrogen atom of the γ -lactam ring of 1+lower chain forms a covalent bond with the appropriate upper chain carbon atom to provide the corresponding compound (I).

In some aspects of the present invention, the synthetic route to a compound (I) comprises a process wherein certain intermediates 1+upper chain may undergo chemical reaction or a series of chemical reactions, which are known in the art or disclosed herein, that chemically modify the upper chain such that chemical installation and/or modification of the lower chain is facilitated.

In further aspects of the present invention, the synthetic route to a compound (I) comprises a process wherein a certain intermediate 1+upper chain may undergo chemical reaction or a series of chemical reactions, which are known in the art or disclosed herein, that chemically modify the upper chain such that at least one particular functional group or other structural feature not incorporated into said intermediate is incorporated into the structure of invention compound (I).

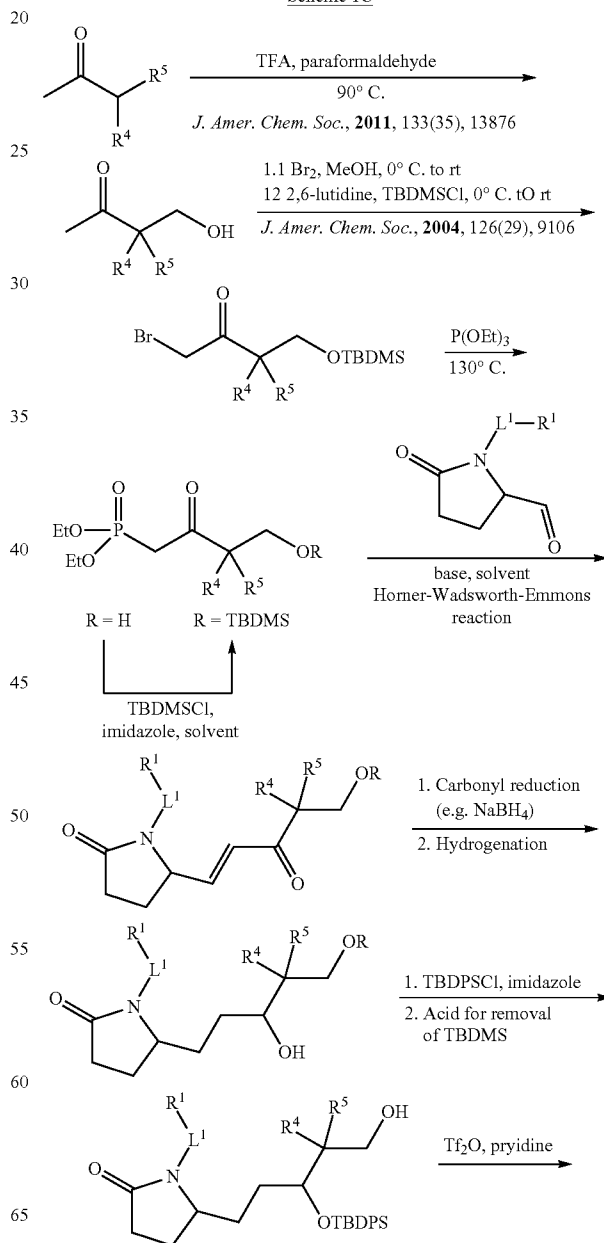
In some aspects of the present invention, the synthetic route to a compound (I) comprises a process wherein certain intermediates 1+lower chain may undergo chemical reaction

40

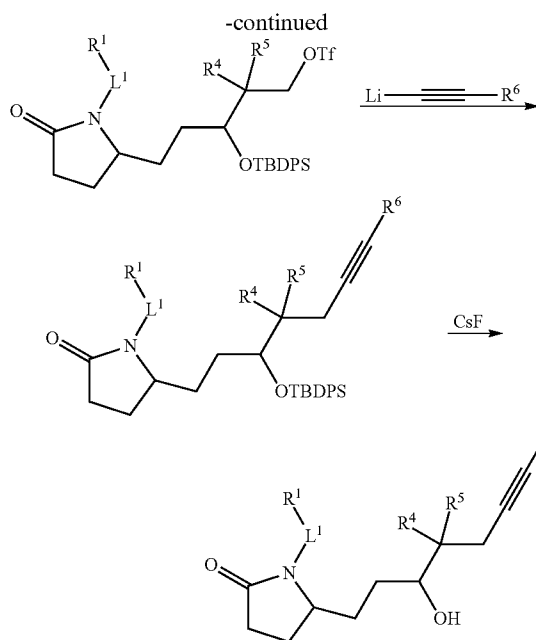
or a series of chemical reactions, which are known in the art or disclosed herein, that chemically modify the lower chain such that chemical installation and/or modification of the upper chain is facilitated.

In further aspects of the present invention, the synthetic route to a compound (I) comprises a process wherein a certain intermediate 1+lower chain may undergo chemical reaction or a series of chemical reactions, which are known in the art or disclosed herein, that chemically modify the lower chain such that at least one particular functional group or other structural feature not incorporated into said intermediate is incorporated into the structure of invention compound (I). For some embodiments of compound (I) wherein L^4 is a carbon-carbon single bond, the synthesis may comprise a sequence of steps as shown in Scheme 1C.

Scheme 1C



41



Omission of the hydrogenation step of Scheme 1C may provide compounds of Formula (I) wherein L^4 is a carbon-carbon double bond and wherein various R^4 and R^5 may be incorporated. In some aspects, R^4 and R^5 are determined by the starting ketone used in the chemical route sequence. Some ketones that may be utilized for this purpose and are commercially available include butan-2-one, pentan-2-one, 3-methyl-2-butanone (Aldrich), cyclopropyl methyl ketone (Aldrich), cyclobutyl methyl ketone (Aldrich), and 1-cyclopentyl-ethanone (Aldrich). Starting ketones and substituted acetylenes may also be available according to published procedures or methods well known to those skilled in the art.

Synthetic routes utilized to prepare compounds of the present invention typically proceed through a carbon-carbon double bond formation (olefination) step to install the compound's lower chain. The olefination may be accomplished by the interaction of an appropriate aldehyde intermediate with an appropriate nucleophilic carbanion species. Such methods may include Wittig reactions, wherein the nucleophilic carbanion species is an appropriate organic phosphonium ylide. Another carbon-carbon bond forming reaction that may be employed is a Horner-Wadsworth-Emmons reaction, wherein the coupling partner with the aldehyde is an appropriate organic phosphonate carbanion. Published reviews describing the general scope and mechanism along with various protocols for these types of olefination reactions include the following:

Boutagy, J. and Thomas, R. *Chemical Reviews*, 1974, 74, 87-99.

Wadsworth, W. S., Jr. *Organic Reactions*, 1977, 25, 73-253.

Walker, B. J. in *Organophosphorous Reagents in Organic Synthesis*, Cadogan, J. I. G., Ed.; Academic Press: New York, 1979, pp. 155-205.

Schlosser, M. et al., *Phosphorous and Sulfur and the Related Elements*, 1983, 18(2-3), 171-174.

Maryanoff, B. E. and Reitz, A. B. *Chemical Reviews*, 1989, 89(4), 863-927.

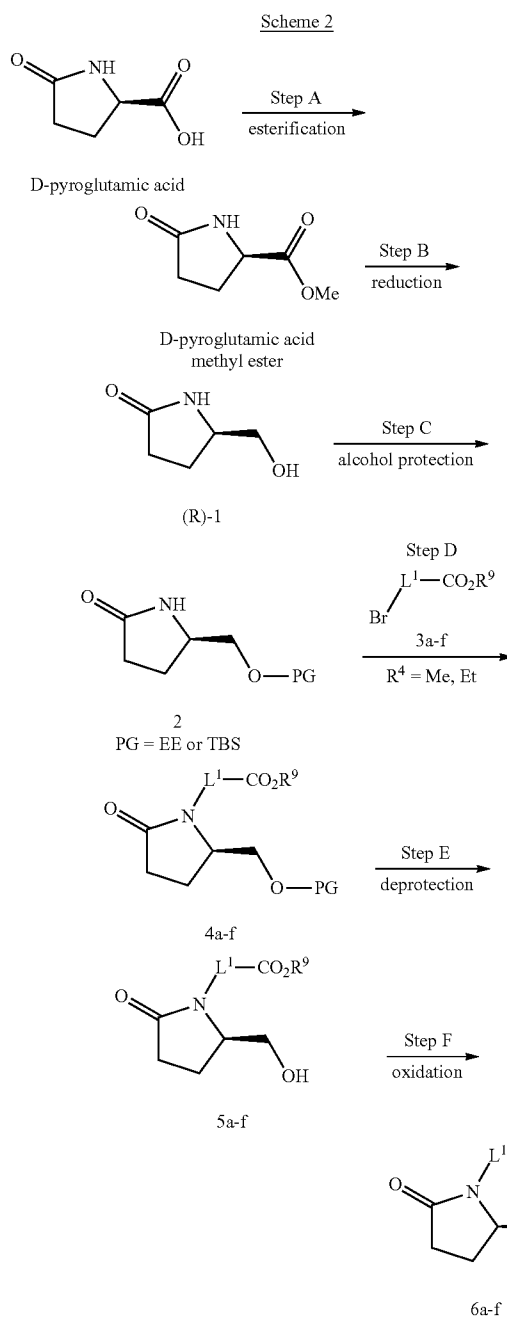
Kelly, S. E. in *Comprehensive Organic Synthesis*, Trost, B. M. and Fleming, I. Ed.; Pergamon: Oxford, 1991, Vol. 1, pp. 729-817.

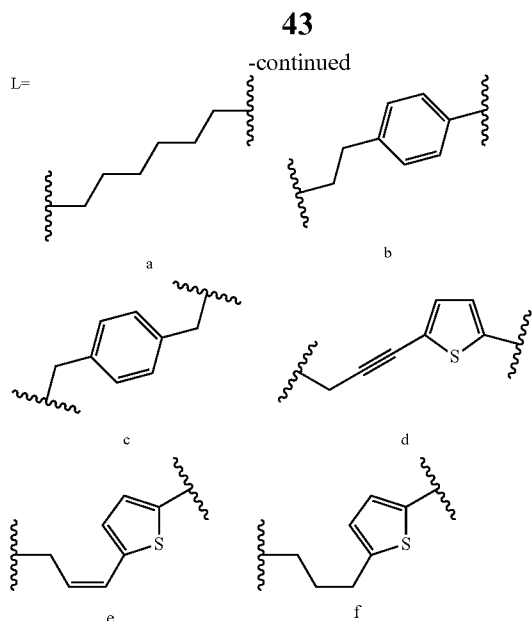
42

Kolodiazhnyi, O. I., *Phosphorus Ylides, Chemistry and Application in Organic Synthesis*; Wiley-VCH: New York, 1999.

Another carbon-carbon bond forming reaction that may be used to install the lower chain is the Peterson olefination reaction, which is reviewed by Ager, D. J. *Organic Reactions*, 1990, 38, 1-223.

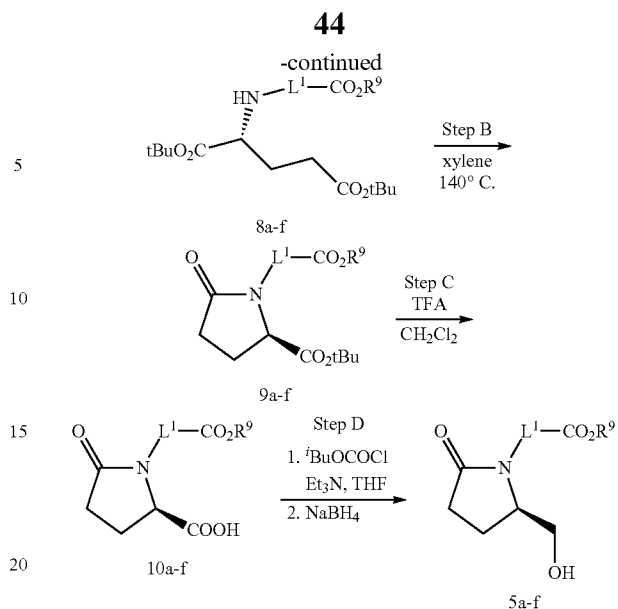
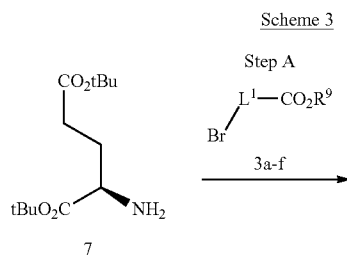
Aldehydes that may be used in the olefination step involved in preparation of compounds of the present invention include, but are not limited to, intermediates 6a-f, which can be generally prepared from (R)-(+)-5-oxopyrrolidine-2-carboxylic acid (D-pyroglytamic acid) as shown in Scheme 2.



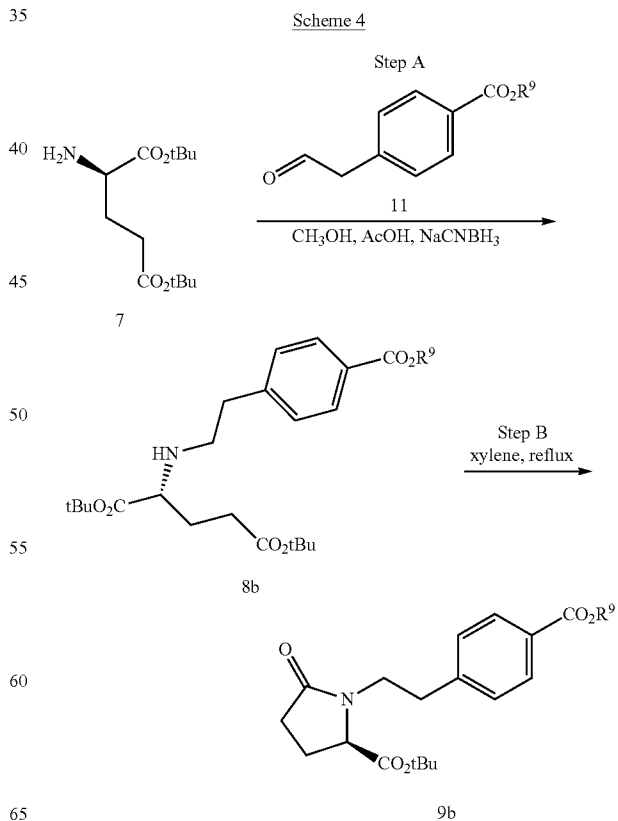


D-pyroglytamic acid may be esterified (Step A) and subsequently reduced (Step B) by known methods, including those described herein, to provide the resulting alcohol intermediate (R)-1. The hydroxyl moiety of intermediate (R)-1 may be protected (Step C) by reacting with ethyl vinyl ether (EVE) in the presence of TFA or tert-butyldimethylsilyl chloride (TBDMSCl or TBSCl) in the presence of a base, such as imidazole, to provide the EE-protected or TBS-protected species (2), respectively. N-alkylation of one of the protected pyrrolidone intermediates (2) with an alkylating agent, such as one of 3a-f, affords the corresponding intermediate 4a-f (Step D). Alcohol deprotection (Step E) and subsequent controlled alcohol oxidation (Step F) provides the corresponding aldehyde intermediates 6a-f that may be employed in the subsequent olefination step.

The aldehydes 6a-f may also be prepared from commercially available (R)-di-tert-butyl 2-aminopentanedioate 7 according to the route illustrated in Scheme 3. Condensation of 7 with bromides 3a-f provides 8a-f, respectively (Step A). Subsequent ring closure provides pyrrolidinone intermediates 9a-f (Step B). Removal of the tert-butyl group with TFA (Step C) unmasks the carboxylic acid moiety of intermediates 10a-f. Mixed anhydride formation by reacting these carboxylic acids with isobutyl chloroformate and subsequent reduction of the mixed anhydride with sodium borohydride (Step D) provides alcohol intermediates 5a-f. Controlled oxidation of the alcohol group of each of the compounds 5a-f provides aldehydes 6a-f as illustrated in Scheme 2, Step F.

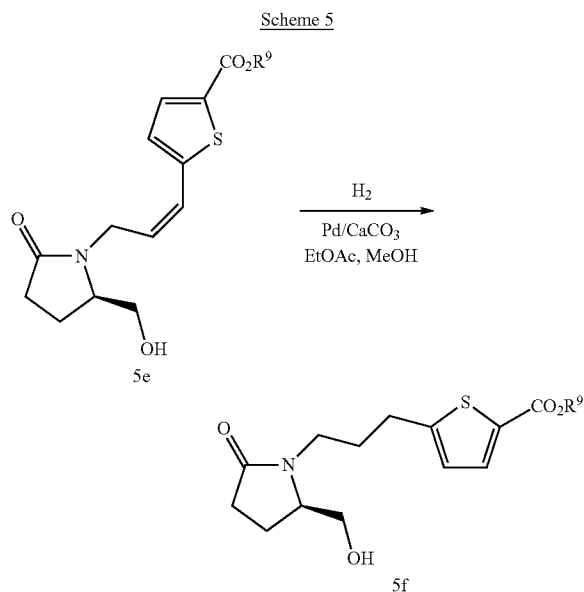


The aldehyde (R)-methyl 4-(2-(2-formyl-5-oxopyrrolidin-1-yl)ethyl)benzoate (6b) may be prepared from commercially available (R)-di-tert-butyl 2-aminopentanedioate (7) and aldehyde 11 according to the method described by Yufang X. et al. in *Bioorganic and Medicinal Chemistry Letters*, 2008, 18, 821-824, where the key reductive alkylation step is shown below in Scheme 4. Condensation of 7 with methyl 4-(2-oxoethyl)benzoate (11) accompanied with subsequent ring closure provides pyrrolidinone intermediate 9b (Step A and B). Deesterification of 9b, as shown generally in Scheme 3, Step C, followed by reduction (Scheme 3, Step D) and subsequent controlled oxidation as generally shown in Scheme 2, Step F produces aldehyde 6b.



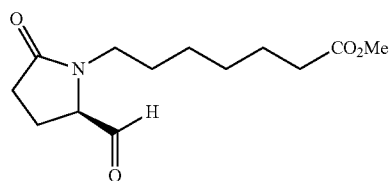
45

Aldehyde intermediate 6f may alternatively be acquired by the hydrogenation of protected alcohol intermediates 4d or 4e to 4f or the unprotected alcohol intermediates 5d or 5e to 5f, followed by the subsequent deprotection (for 4f) and controlled oxidation to 6f. One hydrogenation reaction example is illustrated in Scheme 5. Palladium-catalyzed reduction of the internal carbon-carbon double bond of intermediate 5e (Scheme 5) to provide alcohol intermediate 5f followed by the controlled oxidation of the alcohol affords aldehyde intermediate 6f as illustrated in Scheme 2, Step F.

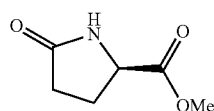


Detailed procedures for preparing the aldehyde intermediates is described below.

Preparation of (R)-methyl 7-(3,3-difluoro-5-formyl-2-oxopyrrolidin-1-yl)heptanoate (6a)



Scheme 2, Step A: Preparation of (R)-methyl 5-oxopyrrolidine-2-carboxylate (D-pyroglutamic acid methyl ester) from (R)-5-oxopyrrolidine-2-carboxylic acid (D-pyroglutamic acid)

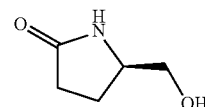


To a solution consisting of (R)-5-oxopyrrolidine-2-carboxylic acid (D-pyroglutamic acid from Chem-Impex International, 12.6 g, 97.4 mmol) in methanol (100 mL) was added sulfuric acid (1 mL) and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated

46

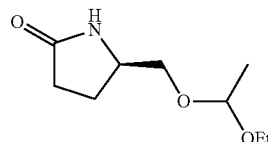
from the mixture, and the residue was purified by silica gel chromatography. Elution with acetone-dichloromethane (3:7 v/v) afforded the title intermediate (13.3 g, 95%) as a clear oil; TLC R_f 0.42 (solvent system: 3:7 v/v acetone-dichloromethane); $^1\text{H-NMR}$ (CDCl_3) δ 4.25 (t, 1H), 3.73 (s, 3H), 2.5-2.2 (m, 4H).

Scheme 2, Step B: Preparation of (R)-5-(hydroxymethyl)pyrrolidin-2-one ((R)-1)



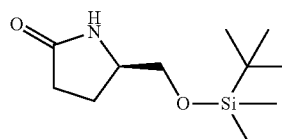
To a solution consisting of (R)-methyl 5-oxopyrrolidine-2-carboxylate (D-pyroglutamic acid methyl ester, 13.2 g, 115 mmol) in methanol (100 mL) at 0°C . was added sodium borohydride (10.5 g, 278 mmol) in portions. The reaction mixture was stirred at 0°C . until completion, at which time, acetic acid (3 mL) was added. The reaction mixture was concentrated and the residue was purified on silica gel, eluting with methanol-chloroform (1:9 v/v) to afford the title intermediate (12.9 g, 97%) as a colorless solid; TLC R_f 0.33 (solvent system: 1:9 v/v methanol-chloroform); $^1\text{H-NMR}$ (CDCl_3) δ 7.17 (s, 1H), 3.92 (s, 1H), 3.85-3.75 (m, 1H), 3.64-3.40 (m, 2H), 2.42-2.35 (m, 2H), 2.2-2.05 (m, 1H), 1.88-1.7 (m, 1H).

Scheme 2, Step C: Preparation of (5R)-5-((1-ethoxyethoxy)methyl)pyrrolidin-2-one (2/EE)



To a solution consisting of (R)-5-(hydroxymethyl)pyrrolidin-2-one (intermediate (R)-1, 21.7 g, 188 mmol) in dichloromethane (250 mL) was added ethyl vinyl ether (36.2 mL, 376 mmol) followed by trichloroacetic acid (0.878 g, 5.37 mmol). The reaction mixture was stirred at room temperature for 16 hours. To the reaction mixture was added a saturated solution of sodium bicarbonate (400 mL) and the organic phase was separated. The organic phase was subsequently washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with methanol-chloroform (1:9 v/v) to afford the title intermediate (13.0 g, 37%) as a clear oil; TLC R_f 0.56 (solvent system: 1:9 v/v methanol-chloroform); $^1\text{H-NMR}$ (CDCl_3) δ 4.69 (quartet, 1H), 3.83-3.2 (m, 5H), 2.35 (t, 2H), 2.25-2.19 (m, 1H), 1.8-1.7 (m, 1H), 1.38 (d, 3H), 1.21 (t, 3H).

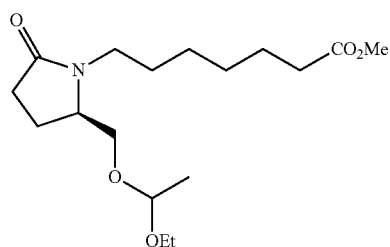
Scheme 2, Step C: Preparation of (R)-5-(((tert-butyl)dimethylsilyloxy)methyl)pyrrolidin-2-one (2/TBS)



47

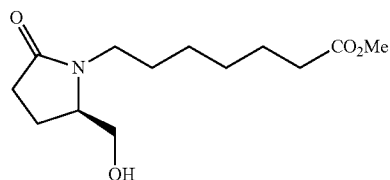
To a solution consisting of (R)-5-(hydroxymethyl)pyrrolidin-2-one (intermediate (R)-1, 5.7 g, 50 mmol) in dimethylsulfoxide (50 mL) was added tert-butyldimethylchlorosilane (9.71 g, 64.5 mmol) followed by imidazole (4.39 g, 64.5 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3×100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with methanol-chloroform (5:95 v/v) to afford the title intermediate (10.0 g, 85%) as a clear oil; TLC R_f 0.37 (solvent system: 5:95 v/v methanol-chloroform).

Scheme 2, Step D: Preparation of methyl 7-((2R)-2-((1-ethoxyethoxy)methyl)-5-oxopyrrolidin-1-yl)heptanoate (4a)



To an ice-chilled suspension consisting of sodium hydride (60% in mineral oil, 1.07 g, 26.7 mmol) and sodium iodide (4.40 g, 29.4 mmol) in hexamethylphosphoramide (30 mL) was added dropwise a solution consisting of (5R)-5-((1-ethoxyethoxy)methyl)-pyrrolidin-2-one (intermediate 2/EE, 5.00 g, 26.7 mmol) in hexamethylphosphoramide (20 mL). The mixture was stirred at room temperature for two hours followed by 50° C. for 20 minutes. To the reaction mixture was added dropwise methyl 7-bromoheptanoate (commercially available from Alfa Aesar, 7.15 g, 32.0 mmol) and stirred overnight at 50° C. The mixture was diluted with ethyl acetate (300 mL). Concentrated aqueous hydrochloric acid (10 mL) was subsequently added followed by water (50 mL). The aqueous phase was separated and the organic layer was washed with 5% aqueous sodium thiosulfate (100 mL), water (200 mL), and brine (300 mL), and was dried over anhydrous sodium sulfate, filtered and evaporated to provide the crude title intermediate, which was carried on to the next step without further purification or characterization.

Scheme 2, Step E: Preparation of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate (5a)

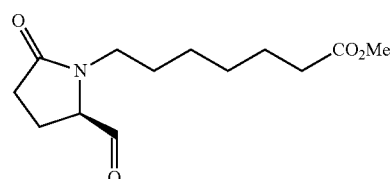


To a solution consisting of the crude methyl 7-((2R)-2-((1-ethoxyethoxy)methyl)-5-oxopyrrolidin-1-yl)heptanoate (4a) in methanol (50 mL) was added p-toluenesulfonic acid monohydrate (10 mg) and the mixture was stirred at room temperature for 18 hours. To the reaction mixture was added a saturated aqueous solution of sodium bicarbonate and the organic material was extracted with ethyl acetate. The organic phase was separated and washed with brine, dried

48

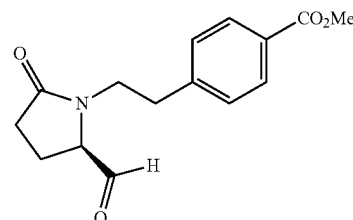
over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with methanol-ethyl acetate (3:97 v/v) to afford the title intermediate (1.24 g, 18% over two steps) as a pale yellow oil; TLC R_f 0.24 (solvent system: 3:97 v/v methanol-ethyl acetate); MS (APCI⁺) m/z 258 (M+1).

Scheme 2, Step F: Preparation of (R)-methyl 7-(2-formyl-5-oxopyrrolidin-1-yl)heptanoate (6a)

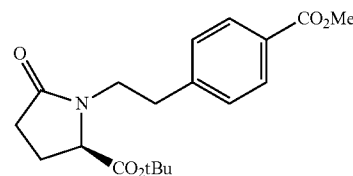


To a solution consisting of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate (intermediate 5a, 1.24 g, 4.82 mmol) in dichloromethane (25 mL) was added Dess-Martin periodinane (2.04 g, 4.82 mmol) in portions and the mixture was stirred at room temperature until completion as monitored by TLC. The volatiles were evaporated, and to the residual mixture was added diethyl ether (50 mL). The solid material was filtered through a thin pad of Celite and the filtrate was concentrated. The residue was purified on silica gel eluting with methanol-ethyl acetate (3:97 v/v) to afford the title intermediate (1.1 g, 89%) as a pale yellow oil; TLC R_f 0.33 (solvent system: 3:97 v/v methanol-ethyl acetate).

Preparation of (R)-methyl 4-(2-(2-formyl-5-oxopyrrolidin-1-yl)ethyl)benzoate (6b)



Scheme 4, Steps A and B: Preparation of (R)-tert-butyl 1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylate (9b)



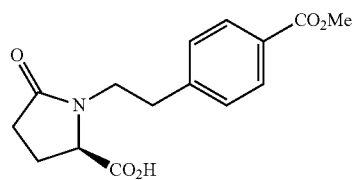
Step A: To a solution consisting of (R)-di-tert-butyl 2-aminopentanedioate (reagent 7, H-D-Glu(OtBu)-OtBu, commercially available from Life ProTein (3.50 g, 15.6 mmol) in methanol (100 mL) was added methyl 4-(2-oxoethyl)benzoate (synonym: 4-carbomethoxyphenylacetaldehyde, reagent 11; obtained from methyl 4-formyl benzoate as described in Nair et al., *J. Med. Chem.*, 1989, 32, 1277-1283; 2.80 g, 15.6 mmol), acetic acid (1.05 mL, 2.67 mmol), and sodium cyanoborohydride (1.45 g, 23.1 mmol),

49

and the mixture was stirred at room temperature for three hours. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

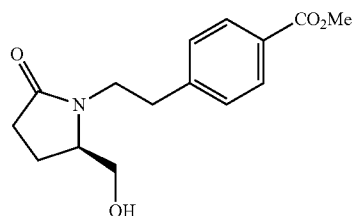
Step B: The residue (crude intermediate 8b) was diluted with xylene and the solution refluxed for 5 hours and concentrated. The residue was purified by silica gel chromatography eluting with ethyl acetate-heptane (1:1) to afford the title compound (2.0 g, 37%) as a white solid; TLC R_f 0.45 (solvent system 1:1 v/v ethyl acetate-heptane).

Scheme 3, Step C: Preparation of (R)-1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylic acid (10b)



A mixture consisting of (R)-tert-butyl 1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylate (intermediate 9b, 2.0 g, 5.7 mmol), trifluoroacetic acid (25 mL), and water (0.125 mL) was stirred for three hours at room temperature and was subsequently concentrated in vacuo to afford the crude title intermediate (2.26 g) as a yellow oil, which was used in the next step without purification.

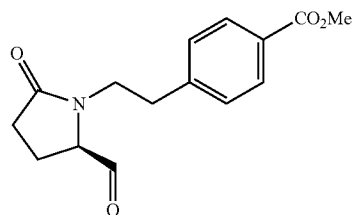
Scheme 3, Step D: Preparation of (R)-methyl 4-(2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (5b)



To a stirring mixture consisting of crude (R)-1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylic acid (intermediate 10b, 2.26 g, 8.14 mmol) in THF (40 mL) at -10°C . was added N-methylmorpholine (0.9 mL, 8 mmol). After stirring for five minutes, isobutyl chloroformate (1.08 mL, 8.25 mmol) was added dropwise and the reaction mixture was stirred for an additional thirty minutes and was subsequently filtered through a pad of Celite. The filtrate was cooled to -10°C ., and a solution consisting of sodium borohydride (0.434 g, 11.5 mmol) predissolved in water (15 mL) was added. The resulting mixture was stirred at 0°C . for one hour and then at room temperature for one hour. The mixture was poured into a separatory funnel and diluted with ethyl acetate (200 mL). The organic layer was washed sequentially with 1N hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, was dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with methanol-ethyl acetate (3:97 v/v) to afford the title compound as an off white solid; TLC R_f 0.19 (solvent system 3:97 v/v methanol-ethyl acetate); MS (APCI⁺) m/z 278 (M+1).

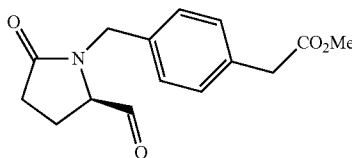
50

Scheme 2, Step F: Preparation of (R)-methyl 4-(2-(2-formyl-5-oxopyrrolidin-1-yl)ethyl)benzoate (6b)

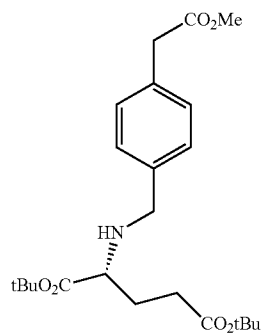


(R)-Methyl 4-(2-(2-formyl-5-oxopyrrolidin-1-yl)ethyl)benzoate (0.246 g, 62.5% yield from 5b, a colorless oil) was prepared by the method described in Scheme 2, Step F for the preparation of aldehyde intermediate 6a except that (R)-methyl 4-(2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (5b) was used instead of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate; TLC R_f 0.29 (solvent system 3:97 v/v methanol-ethyl acetate).

Preparation of (R)-methyl 2-(4-((2-formyl-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (6c)



Scheme 3, Step A: Preparation of (R)-di-tert-butyl 2-((4-(2-methoxy-2-oxoethyl)benzyl)amino)pentanedioate (8c)

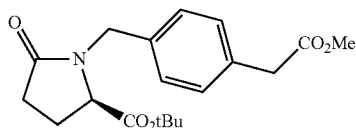


A stirring mixture consisting of (R)-di-tert-butyl 2-amino-pentanedioate (reagent 7, H-D-Glu(OtBu)-OtBu, 5.0 g, 16.9 mmol), methyl 2-(4-(bromomethyl)phenyl)acetate (reagent 3c, 4.52 g, 18.6 mmol; prepared in 99% yield from the corresponding carboxylic acid and trimethylsilyldiazomethane according to known methods such as those described in Leggio, A. et al., *Chemical Biology & Drug Design*, 2009, 73(3), 287-291), diisopropylethylamine (8.83 mL, 50.7 mmol), and sodium iodide (2.53 g, 16.9 mmol) in dry hexamethylphosphoramide (50 mL) was heated at 55°C . for 15 hours. The reaction mixture was cooled, diluted with ethyl acetate (1.5 L), and washed sequentially with an aqueous solution of ammonium chloride and a saturated aqueous solution of sodium chloride. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography eluting

51

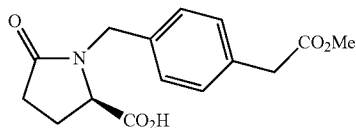
with a gradient of ethyl acetate-heptane (1:20 to 1:5 v/v) to afford the title intermediate (5.78 g, 81%) as a colorless oil; TLC R_f 0.45 (solvent system 1:3 v/v ethyl acetate-heptane); MS (APCI⁺) m/z 422 (M+1).

Scheme 3, Step B: Preparation of (R)-tert-butyl 1-(4-(2-methoxy-2-oxoethyl)benzyl)-5-oxopyrrolidine-2-carboxylate (9c)



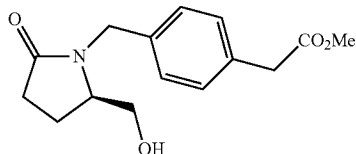
A stirring mixture consisting of (R)-di-tert-butyl 2-((4-(2-methoxy-2-oxoethyl)benzyl)amino)pentanedioate (intermediate 8c, 5.75 g, 13.6 mmol) in *o*-xylene (40 mL) was heated at 100° C. for three days. The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography eluting with a gradient of ethyl acetate-heptane (1:20 to 1:1 v/v) to afford the title intermediate (3.09 g, 65.2%) as a colorless oil; TLC R_f 0.6 (solvent system 4:6 v/v ethyl acetate-heptane); MS (APCI⁺) m/z 370 (M+23, Na⁺).

Scheme 3, Step C: Preparation of (R)-1-(4-(2-methoxy-2-oxoethyl)benzyl)-5-oxopyrrolidine-2-carboxylic acid (10c)



A stirring mixture consisting of (R)-tert-butyl 1-(4-(2-methoxy-2-oxoethyl)benzyl)-5-oxopyrrolidine-2-carboxylate (intermediate 9c, 2.93 g, 8.43 mmol) and trifluoroacetic acid (4.55 mL, 59.0 mmol) in dichloromethane (30 mL) was heated at 45° C. for seven hours with subsequent stirring at room temperature overnight. The reaction mixture was diluted with ethanol and evaporated under reduced pressure. The crude residue (2.44 g) was carried onto the next step (Step D) without purification.

Scheme 3, Step D: Preparation of (R)-methyl 2-(4-((2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (5c)

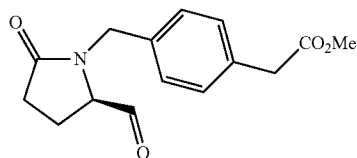


(R)-Methyl 2-(4-((2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (1.6 g, 65%, as a colorless oil) was prepared in the same manner as compound 5b in Scheme 3, Step D except that (R)-1-(4-(2-methoxy-2-oxoethyl)benzyl)-5-oxopyrrolidine-2-carboxylic acid (10c) was used instead of (R)-1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylic acid; TLC R_f 0.5 (solvent system 5:95 v/v methanol-dichloromethane); ¹H-NMR (CDCl₃) δ 7.3-

52

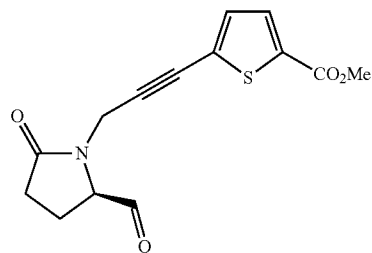
7.2 (m, 4H), 4.9 (d, 1H), 4.2 (d, 1H), 3.8-3.7 (m, 1H), 3.7 (s, 3H), 3.6 (s, 2H), 3.6-3.4 (m, 2H), 2.6-2.4 (m, 2H), 2.1-1.9 (m, 2H).

Scheme 2, Step F: Preparation of (R)-methyl 2-(4-((2-formyl-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (6c)

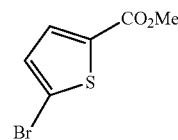


(R)-Methyl 2-(4-((2-formyl-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (0.2 g, 90%) was prepared in the same manner as compound 6a in Scheme 2, Step F except that (R)-methyl 2-(4-((2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (5c) was used instead of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate; MS (ESI⁻) m/z 274 (M-1); ¹H-NMR (CDCl₃) δ 9.4 (d, 1H), 7.3-7.1 (m, 4H), 5.0-4.8 (m, 2H), 4.2-4.0 (m, 1H), 3.7 (s, 3H), 3.6 (s, 2H), 2.6-1.9 (m, 4H).

Preparation of (R)-methyl 5-((2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)ethynyl)thiophene-2-carboxylate (6d)



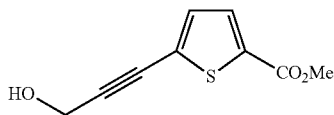
Step 1: Preparation of methyl 5-bromo-2-thiophene carboxylate



To an ice-cooled mixture consisting of 5-bromo-2-thiophene carboxylic acid (5.25 g, 25.4 mmol) in ethyl acetate (200 mL) and methanol (20 mL) was added trimethylsilyldiazomethane (2M in diethyl ether, 20 mL, 40 mmol) over 20 minutes. The reaction mixture was stirred for 24 hours. The solvent was removed and the residue was purified by silica gel chromatography eluting with ethyl acetate-heptanes (1:50 v/v) to afford the title intermediate (5.5 g, 98%) as a white solid; TLC R_f 0.60 (solvent system 1:9 v/v ethyl acetate-heptanes); ¹H-NMR (CDCl₃) δ 7.5 (d, 1H), 7.1 (d, 1H), 4.9 (s, 3H).

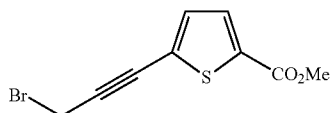
53

Step 2: Preparation of methyl 5-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylate



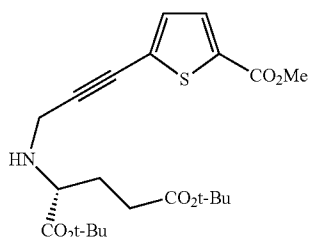
To a covered mixture consisting of methyl 5-bromo-2-thiophene carboxylate (5.6 g, 25 mmol) in benzene (60 mL) was added a suspension consisting of tetrakis(triphenylphosphine)palladium (0) (1.4 g, 1.3 mmol) in benzene (10 mL), and the reaction mixture was stirred for 30 minutes. To the reaction mixture was then added copper(I) iodide (480 mg, 2.52 mmol) and n-butylamine (5 mL, 50 mmol) in one portion each, followed by propargyl alcohol (2.2 mL, 38 mmol) in benzene (30 mL) over 15 minutes, and the reaction was stirred for 24 hours. To the reaction mixture was added a saturated solution of ammonium chloride (200 mL) and the organic material was extracted with ethyl acetate. The organic phase was washed with water, then brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with ethyl acetate:heptanes (1:10 v/v) to afford the title intermediate (3.8 g, 78%); TLC R_f 0.7 (solvent system 1:1 v/v ethyl acetate:heptanes); $^1\text{H-NMR}$ (CDCl_3) δ 7.6 (d, 1H), 7.1 (d, 1H), 4.5 (s, 2H), 3.9 (s, 3H), 2.0 (br s, 1H).

Step 3: Preparation of methyl 5-(3-bromoprop-1-yn-1-yl)thiophene-2-carboxylate (3d)



To an ice cooled solution of methyl 5-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylate (1.32 g, 6.73 mmol) in dichloromethane (25 mL) was added carbon tetrabromide (3.1 g, 9.42 mmol) and triphenylphosphine (2.5 g, 9.42 mmol) and the mixture stirred for 4 hours. The solvent was removed and the residue was purified by silica gel chromatography eluting with ethyl acetate:heptanes (1:25 v/v) to afford the title compound (1.5 g). TLC R_f 0.65 (solvent system 80:20 v/v heptanes:ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.6 (d, 1H), 7.1 (d, 1H), 4.1 (s, 2H), 3.9 (s, 3H).

Scheme 3, Step A: Preparation of (R)-di-tert-butyl 2-((3-(5-(methoxycarbonyl)-thiophen-2-yl)prop-2-yn-1-yl)amino)pentanedioate (8d)

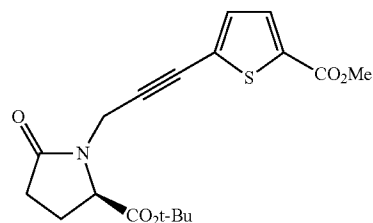


(R)-Di-tert-butyl 2-((3-(5-(methoxycarbonyl)thiophen-2-yl)prop-2-yn-1-yl)amino)pentanedioate was prepared in the same manner as compound 8c in Scheme 3, Step A except

54

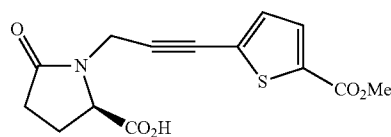
that methyl 5-(3-bromoprop-1-yn-1-yl)thiophene-2-carboxylate (3d) was used instead of methyl 2-(4-(bromomethyl)phenyl)acetate; TLC R_f 0.45 (solvent system 80:20 v/v heptanes:ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H), 6.9 (d, 1H), 3.9 (s, 3H), 3.3-3.2 (m, 1H), 3.2 (s, 2H), 2.4 (t, 2H), 2.0-1.8 (m, 2H), 1.45 (d, 18H).

Scheme 3, Step B: Preparation of (R)-tert-butyl 1-(3-(5-(methoxycarbonyl)-thiophen-2-yl)prop-2-yn-1-yl)-5-oxopyrrolidine-2-carboxylate (9d)



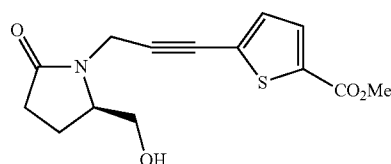
(R)-Tert-butyl 1-(3-(5-(methoxycarbonyl)thiophen-2-yl)prop-2-yn-1-yl)-5-oxopyrrolidine-2-carboxylate was prepared in the same manner as compound 9c in Scheme 3, Step B except that (R)-di-tert-butyl 2-((3-(5-(methoxycarbonyl)thiophen-2-yl)prop-2-yn-1-yl)amino)pentanedioate (8d) was used instead of (R)-di-tert-butyl 2-((4-(2-methoxy-2-oxoethyl)benzyl)amino)pentanedioate; TLC R_f 0.25 (solvent system 60:40 v/v heptanes:ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H), 6.9 (d, 1H), 4.5-4.4 (m, 1H), 4.2-4.0 (m, 2H), 3.85 (s, 3H), 2.6-2.5 (m, 1H), 2.4-2.2 (m, 2H), 2.1-2.0 (m, 1H), 1.4 (s, 9H).

Scheme 3, Step C: Preparation of (R)-1-(3-(5-(methoxycarbonyl)thiophen-2-yl)prop-2-yn-1-yl)-5-oxopyrrolidine-2-carboxylic acid (10d)



A solution of (R)-tert-butyl 1-(3-(5-(methoxycarbonyl)thiophen-2-yl)prop-2-yn-1-yl)-5-oxopyrrolidine-2-carboxylate (1.1 g, 3.03 mmol) and trifluoroacetic acid (4 mL, 51.9 mmol) in dichloromethane (45 mL) was heated at 50° C. overnight. The reaction mixture was diluted with ethanol and toluene and evaporated under reduced pressure to produce a residue that was used in the next step (Step D) with no further purification; TLC R_f 0.10 (solvent system 60:40 v/v heptanes:ethyl acetate).

Scheme 3, Step D: Preparation of (R)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate (5d)

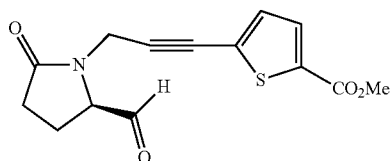


(R)-Methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate was prepared in

55

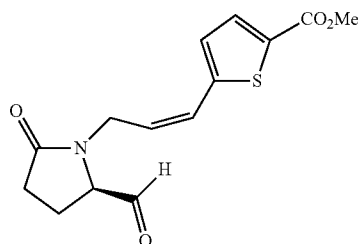
the same manner as compound 5b in Scheme 3, Step D except that (R)-1-(3-(5-(methoxycarbonyl)thiophen-2-yl)prop-2-yn-1-yl)-5-oxopyrrolidine-2-carboxylic acid (10d) was used instead of (R)-1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylic acid and triethylamine was used instead of N-methylmorpholine; TLC R_f 0.30 (solvent system 95:5 v/v dichloromethane:methanol); $^1\text{H-NMR}$ (CDCl_3); δ 7.6 (d, 1H), 6.9 (d, 1H), 4.1-4.0 (m, 1H), 3.85 (s, 3H), 3.8 (s, 2H) 3.6-3.5 (s, 1H), 3.2-3.0 (br s, 1H), 2.6-2.4 (m, 1H), 2.4-2.3 (m, 1H), 2.2-2.0 (m, 1H), 2.0-1.9 (m, 1H); MS (ESI^+) m/z 294.0 ($\text{M}+1$), (ESI^-) m/z 292.0 ($\text{M}-1$).

Scheme 2, Step F: Preparation of (R)-methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate (6d)

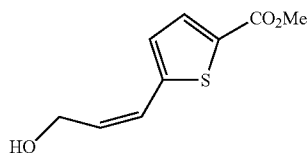


(R)-Methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate was prepared in the same manner as compound 6a in Scheme 2, Step F except that (R)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate (5d) was used instead of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate; TLC R_f 0.30 (solvent system 95:5 v/v dichloromethane:methanol).

Preparation of (R,Z)-methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (6e)



Step 1: Preparation of (Z)-methyl 5-(3-hydroxyprop-1-en-1-yl)thiophene-2-carboxylate

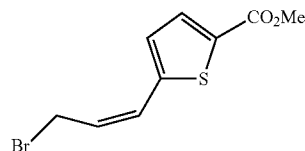


To a mixture consisting of methyl 5-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylate (1.9 g, 9.7 mmol) in ethyl acetate (50 mL) and methanol (5 mL) was added palladium on calcium carbonate (5%, 1.5 g). The reaction flask was evacuated and backfilled with hydrogen gas and the reaction mixture was subsequently stirred for 2 hours while maintaining a hydrogen atmosphere. The mixture was then filtered through Celite and the solvent removed. The residue was purified by silica gel chromatography eluting with ethyl acetate-heptanes (1:10 v/v) to afford the title intermediate

56

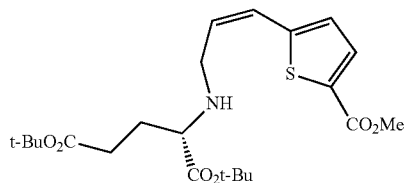
(1.5 g); TLC R_f 0.65 (solvent system 1:1 v/v ethyl acetate-heptanes); MS (ESI^+) m/z 221 ($\text{M}+\text{Na}^+$); $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H), 6.9 (d, 1H), 6.6 (d, 1H), 6.0-5.9 (m, 1H), 4.6 (d, 2H), 3.9 (s, 3H), 1.9 (br s, 1H).

Step 2: Preparation of (Z)-methyl 5-(3-bromoprop-1-en-1-yl)thiophene-2-carboxylate (3e)



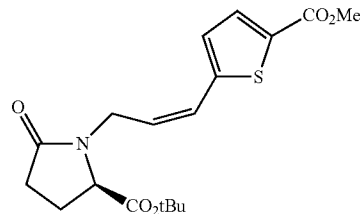
(Z)-Methyl 5-(3-bromoprop-1-en-1-yl)thiophene-2-carboxylate (2.56 g) was prepared in the same manner as compound 3d except that (Z)-methyl 5-(3-hydroxyprop-1-en-1-yl)thiophene-2-carboxylate was used instead of 5-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylate; TLC R_f 0.60 (solvent system 20:80 v/v ethyl acetate-heptanes); MS (ESI^+) m/z 261 ($\text{M}+1$); $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H), 7.2 (d, 1H), 6.6 (d, 1H), 6.2-6.0 (m, 1H), 4.3 (d, 2H), 3.9 (s, 3H).

Scheme 3, Step A: Preparation of (R,Z)-di-tert-butyl 2-((3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)amino)pentanedioate (8e)



(R,Z)-Di-tert-butyl 2-((3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)amino)pentanedioate was prepared in the same manner as compound 8c in Scheme 3, Step A, except that (Z)-methyl 5-(3-bromoprop-1-en-1-yl)thiophene-2-carboxylate (3e) was used instead of methyl 2-(4-(bromomethyl)phenyl)acetate; TLC R_f 0.30 (solvent system 1:4 v/v ethyl acetate-heptanes); MS (ESI^+) m/z 440 ($\text{M}+1$); $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H), 6.9 (d, 1H), 6.6 (d, 1H), 5.9-5.8 (m, 1H), 3.9 (s, 3H), 3.7-3.5 (s, 2H), 3.3-3.2 (m, 1H), 2.4 (t, 2H), 2.0-1.8 (m, 2H), 1.5 (s, 9H), 1.4 (s, 9H).

Scheme 3, Step B: Preparation of (R,Z)-tert-butyl 1-(3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)-5-oxopyrrolidine-2-carboxylate (9e)

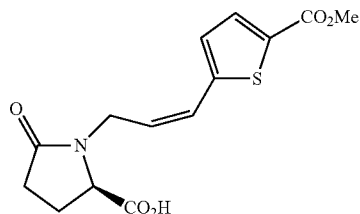


(R,Z)-tert-Butyl 1-(3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)-5-oxopyrrolidine-2-carboxylate was prepared in the same manner as compound 9c in Scheme 3, Step B except that (R,Z)-di-tert-butyl 2-((3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)amino)pentanedioate (8e) was used instead of (R)-di-tert-butyl 2-((4-(2-methoxy-2-oxoethyl)

57

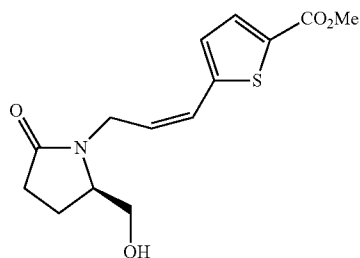
benzyl)amino)-pentanedioate; TLC R_f 0.20 (solvent system 2:3 v/v ethyl acetate-heptanes); MS (ESI⁺) m/z 366 (M+1), 388 (M+Na⁺); ¹H-NMR (CDCl₃) δ 7.7 (d, 1H), 6.9 (d, 1H), 6.6 (d, 1H), 5.7-5.6 (m, 1H), 4.5-4.4 (m, 1H), 4.2-4.0 (m, 2H), 3.85 (s, 3H), 2.6-2.5 (m, 1H), 2.4-2.2 (m, 2H), 2.1-2.0 (m, 1H), 1.4 (s, 9H).

Scheme 3, Step C: Preparation of (R,Z)-1-(3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)-5-oxopyrrolidine-2-carboxylic acid (10e)



A stirring mixture consisting of (R,Z)-tert-butyl 1-(3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)-5-oxopyrrolidine-2-carboxylate (intermediate 9e, 2.05 g, 5.61 mmol) and trifluoroacetic acid (5.0 mL, 65 mmol) in dichloromethane (40 mL) was heated at 45° C. overnight. The reaction mixture was diluted with ethanol and evaporated under reduced pressure to provide a residue (2.44 g) that was used in the next step (Step D) without further purification; TLC R_f 0.25 (solvent system 50:50:1 v/v ethyl acetate-heptanes-acetic acid).

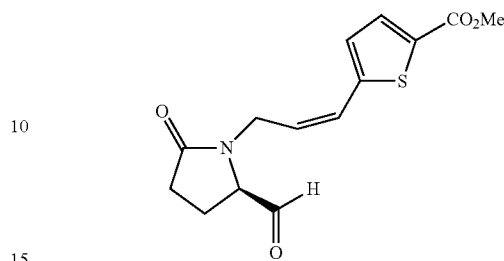
Scheme 3, Step D: Preparation of (R,Z)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (5e)



(R,Z)-Methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate was prepared in the same manner as compound 5b in Scheme 3, Step D except that (R,Z)-1-(3-(5-(methoxycarbonyl)thiophen-2-yl)allyl)-5-oxopyrrolidine-2-carboxylic acid (10e) was used instead of (R)-1-(4-(methoxycarbonyl)phenethyl)-5-oxopyrrolidine-2-carboxylic acid and triethylamine was used instead of N-methylmorpholine; TLC R_f 0.20 (solvent system 50:50:1 v/v ethyl acetate-heptanes-acetic acid); MS (ESI⁺) m/z 296 (M+1), 318 (M+Na⁺); ¹H-NMR (CDCl₃) δ 7.6 (d, 1H), 6.9 (d, 1H), 6.6 (d, 1H), 6.1-5.6 (m, 1H), 4.5-4.3 (m, 1H), 4.1-4.0 (m, 1H), 3.85 (s, 3H), 3.7 (s, 2H), 3.6-3.5 (m, 1H), 3.2-3.0 (br s, 1H), 2.6-2.4 (m, 1H), 2.4-2.3 (m, 1H), 2.2-2.0 (m, 1H), 2.0-1.9 (m, 1H).

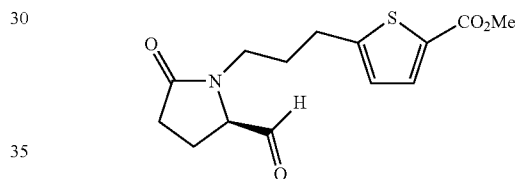
58

Scheme 2, Step F: Preparation of (R,Z)-methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (6e)

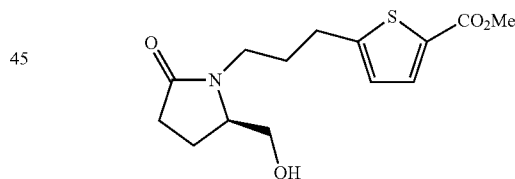


(R,Z)-Methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate was prepared in the same manner as compound 6a in Scheme 2, Step F except that (R,Z)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (5e) was used instead of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate; TLC R_f 0.40 (solvent system 1:1 v/v ethyl acetate-heptanes).

Preparation of (R)-methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (6f)



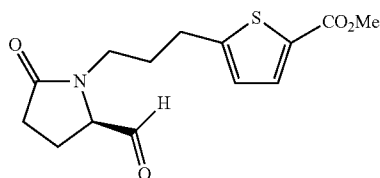
Scheme 5: Preparation of (R)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (50)



To a solution of (R,Z)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (5e, 496 mg) in ethyl acetate (40 mL) and methanol (4 mL) was added palladium on carbon (10%, 40 mg) and the flask evacuated and exposed to hydrogen for 4 hours. The mixture was then filtered through Celite and the solvent removed to afford the title intermediate in a quantitative yield, which was used without purification; TLC R_f 0.25 (solvent system 95:5 v/v dichloromethane:methanol); ¹H-NMR (CDCl₃) δ 7.6 (d, 1H), 6.6 (d, 1H), 3.85 (s, 3H), 3.8 (dd, 1H), 3.75-3.65 (m, 2H), 3.6 (dd, 1H), 3.1 (m, 1H), 2.85 (t, 2H), 2.7-2.4 (br s, 1H), 2.5-2.4 (m, 1H), 2.35-2.25 (m, 1H), 2.1-1.8 (m, 4H); MS (ESI⁺) m/z 298.0 (M+1), 320.0 (M+Na⁺).

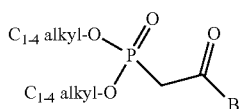
59

Scheme 2, Step F: Preparation of (R)-methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (6f)

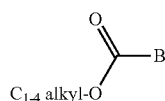


(R)-Methyl 5-(3-(2-formyl-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate was prepared in the same manner as compound 6a in Scheme 2, Step F except that (R)-methyl 5-(3-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (5f) was used instead of (R)-methyl 7-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)heptanoate; TLC R_f 0.25 (solvent system 95:5 v/v dichloromethane:methanol).

Organic β -keto phosphonate esters such as

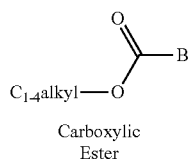


may be used as reaction coupling partners with aldehydes such as 6a-f in a Horner-Emmons-Wadsworth-type process to install the lactam lower-chain scaffold. Such β -keto phosphonate esters may be prepared by coupling an appropriate carboxylic ester



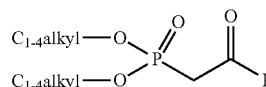
with lithiated/deprotonated dialkyl methylphosphonate according to the general reaction illustrated in Scheme 6 and variations thereof. Tables A-G/H of Lower Chains (below) describe various lower-chain components B of the exemplary embodiments.

Carboxylic esters 12 may be commercially available or prepared from commercially-available starting materials as shown in Schemes 7a-g. The numbering system, comprising various numerical, lower-case alphabetical, and lower-case Roman numeral descriptors, for intermediates comprising component B, such as carboxylic esters 12, β -keto phosphonate esters 13, NHS esters 16, amides 17, carboxylic acids 18, and (S)-3-(B-carbonyl)-4-benzyloxazolidin-2-ones 19 found in Schemes, Tables, and Examples herein in the following manner. Intermediates comprising component B, such as in the formulae shown below,

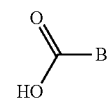


60

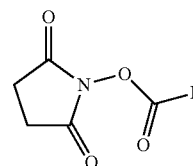
-continued



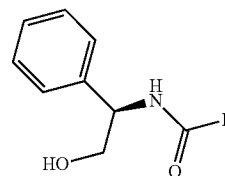
β -Keto
Phosphonate
Esters



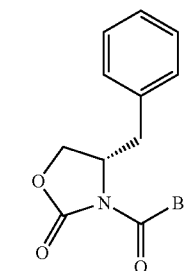
Carboxylic
Acids



NHS
Esters

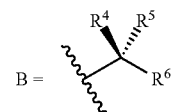


Amides



(S)-3-(B-Carbonyl)-
4-benzyloxazolidin-2-ones

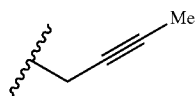
wherein:



shall be expressed as a formula having three or four moieties which define the functionality of the intermediate and the R^4 , R^5 and R^6 substituents of B comprising the intermediate. The first moiety is expressed as an Arabic numeral which represents the type of intermediate with its compound structure in accordance with the descriptions herein (e.g., 12 is a carboxylic ester; 13 is a β -keto phosphonate ester; 16 is an NHS ester; 17 is an amide; 18 is a carboxylic acid, etc.). The second moiety is expressed as a lower case letter that represents the structure of the R^6 group in accordance with

61

the descriptions herein. A particular genus of intermediates having a range of R^6 substituents is shown by replacing the first moiety by a letter range enclosed within parentheses (e.g., (a-f)). The third moiety is expressed as a lower case letter that represents the nature of the R^4 and R^5 substitutions as follows: a (wherein both R^4 and R^5 are hydrogen); b (wherein R^4 is C_1 - C_4 alkyl, R^5 is hydrogen); c (wherein R^4 is hydrogen, R^5 is C_1 - C_4 alkyl); d (wherein both R^4 and R^5 are C_1 - C_4 alkyl); and e (wherein R^4 and R^5 with the carbon to which they are bound form a C_3 - C_5 cycloalkyl). In addition, a third moiety designation of "b/c" represents a mixture of the b and c stereoisomers. The fourth moiety is expressed as a lower-case Roman numeral in parentheses that represents the size and structure of the R^4 and/or R^5 C_1 - C_4 alkyl group or groups, if present, or the size of the C_3 - C_5 cycloalkyl ring, if present, in accordance with the descriptions herein. In the case where both R^4 and R^5 are hydrogen (e.g. 12aa), no lower-case Roman numeral in parentheses is present. This descriptor only takes into account embodiments for which only one of R^4 and R^5 is C_1 - C_4 alkyl, both R^4 and R^5 are identical C_1 - C_4 alkyl, or R^4 and R^5 with the carbon to which they are bound form a C_3 - C_5 cycloalkyl, and does not take into account embodiments for which both R^4 and R^5 are C_1 - C_4 alkyl that are different one from another. However, R^4 and R^5 may both be C_1 - C_4 alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope. Table A lists some intermediates with defined B substituents (R^4 , R^5 and R^6) as well as indicating the partial formulae notations for each listed combination of R^4 , R^5 and R^6 . By way of example, a carboxylic ester of formula 12 with R^4 as H, R^5 as Me and R^6 as



is expressed as 12ac(i) when the hereinabove defined notations are used. Similarly, a genus of carboxylic esters wherein R^4 and R^5 are each H and R^6 is varied can be envisaged when expressed by the formula 12(a-f)a in view of Tables A through F as provided herein.

A carboxylic ester, 12(a-f)a or 12(a-f)b/c(i-viii), may be prepared in two steps from commercially available diethyl malonate or an appropriate commercially available diethyl 2-(C_1 - C_4 alkyl) malonate starting material. Reaction of the malonate starting material with an appropriate lithium amide base, such as LDA or LiHMDS, followed with an appropriate alkylating agent R^6 - L^3 - X^1 , as illustrated in Scheme 7a, Step A, affords the corresponding 2-(R^6 - L^3 -)-substituted diethyl malonate 14a-f. Subsequent decarboxylation (Step B) provides the corresponding carboxylic ester intermediate 12, wherein both R^4 and R^5 are hydrogen, or wherein one of R^4 and R^5 is a C_1 - C_4 alkyl group (alkyl groups (i) through (viii) represent methyl, ethyl, n-propyl, 2-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl, respectively) and the other is a hydrogen. Examples of commercially available diethyl (C_1 - C_4 alkyl) malonates include diethyl methyl malonate, diethyl ethyl malonate, diethyl isopropyl malonate, diethyl n-propyl malonate, diethyl n-butyl malonate (all from Sigma-Aldrich, Acros Organics, or Alfa Aesar), diethyl isobutyl malonate, and diethyl sec-butyl malonate (both from Alfa Aesar). Methods for preparing the starting diethyl (C_1 - C_4 alkyl) malonates are known in the art; for example, diethyl malonate may be combined with a base

62

such as potassium carbonate and an appropriate alkylating agent such as methyl iodide, ethyl iodide, n-propyl bromide, or n-butyl bromide under microwave irradiation in the method described by Keglevich et al. in *Letters in Organic Chemistry*, 2008, 5(3), 224-228 and in *Green Chemistry*, 2006, 8(12), 1073-1075. Other methods that may be used to prepare the diethyl (C_1 - C_4 alkyl) malonates include the reaction of diethyl malonate with an appropriate alkylating agent such as ethyl iodide, isopropyl bromide, isobutyl bromide, or sec-butyl bromide in the presence of a base such as sodium ethoxide in an organic solvent such as ethanol as described in Patel and Ryono in *Bioorganic and Medicinal Chemistry Letters*, 1992, 2(9), 1089-1092 and elsewhere.

Carboxylic ester intermediates 12 possessing a gem-dimethyl substitution at the carbon atom α to the ester carbonyl group (both R^4 and R^5 are methyl), such as 12(a-f)d(i), may be prepared by the methylation of the corresponding mono- α -methyl ester intermediate (stereochemical mixture) 12(a-f)b/c(j) as shown in Scheme 7b and reported in Shibasaki, M. et al, in *Chemical and Pharmaceutical Bulletin*, 1989, 37(6), 1647-1649.

Scheme 7c illustrates mono-alkylations of commercially available or prepared carboxylic esters 12(a-f)a with an alkylating agent R^4/R^5 - X^1 , wherein the R^4/R^5 group is a C_1 - C_4 alkyl group and X^1 is a leaving group such as iodide or bromide to provide the corresponding mono-alkylated analogs 12(a-f)b/c, respectively. The mono-alkylated carboxylic ester analogs may be alkylated a second time; for example, mono-methylated carboxylic acid esters (stereochemical mixture) 12(a-f)b/c(i) may be methylated a second time to provide the corresponding gem-dimethyl substituted esters 12(a-f)d(i), as illustrated in Scheme 7d.

Scheme 7e illustrates the preparation of 1-(R^6 - L^3 -)-substituted C_3 - C_5 cycloalkylcarboxylic acids and their C_1 - C_4 alkyl esters 12(a-f)e(ix-xi). Similar transformations are described in Yang, D. et. al. in *Journal of Organic Chemistry*, 2009, 74(22), 8726-8732; Cowling, S. J. and Goodby, J. W. in *Chemical Communications* (Cambridge, United Kingdom), 2006, 39, 4107-4709; Araldi, G. L. et. al. in WO 2003/103604; and others.

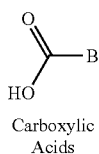
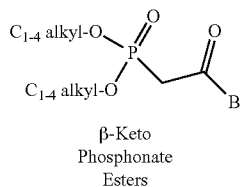
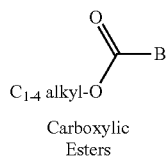
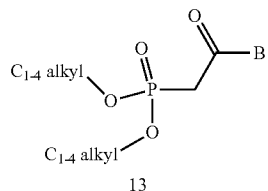
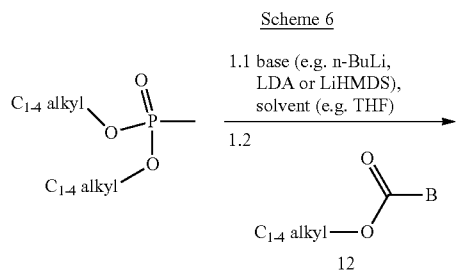
Stereopure carboxylic esters 12(a-f)b(i-viii) and their stereoisomers, 12(a-f)c(i-viii) may be prepared according to the route illustrated in Scheme 7f. Alkylation of an appropriately-substituted carboxylic acid starting material, such as propionic acid (R^4/R^5 is a methyl group), at the carbon position alpha to the acid carbonyl group by treatment of the acid with an appropriate base, such as lithium diisopropylamide (about two molar equivalents) in the presence of a suitable solvent, such as THF, with an alkylating agent R^6 - L^3 - X^1 (Step A) provides the corresponding carboxylic acid intermediates 18(a-f)b/c(i-viii). Subsequent coupling of the carboxylic acid intermediate with N-hydroxysuccinimide (NHS) forms the corresponding NHS ester (an activated ester) stereoisomeric mixture 16(a-f)b/c(i-viii) (Step B). Treatment of the activated ester stereoisomeric mixture 16(a-f)b/c(i-viii) with (R)-2-amino-2-phenylethanol in THF results in the mixture of two amide diastereomers 17(a-f)b(i-viii) and 17(a-f)c(i-viii) (Step C), which may be separated by chromatography to provide each pure diastereomer (Step D). Amide hydrolysis of each diastereomer to its corresponding carboxylic acid 18(a-f)b(i-viii) and 18(a-f)c(i-viii), respectively (Step E), and subsequent esterification (Step F) provides corresponding individual carboxylic ester stereoisomers 12(a-f)b(i-viii) and 12(a-f)(i-viii), respectively.

Scheme 7g shows a synthetic pathway to stereopure carboxylic esters 12(a-f)b(i-vii) (R^5 is hydrogen) employing the use of the chiral auxiliary to generate "(S)-3-(B-carbo-

63

nyl)-4-benzyloxazolidin-2-ones” 19(a-f)a (both R⁴ and R⁵ are hydrogen) for more-efficient (asymmetric) alkylation in Step C to provide the corresponding alkylated. “(S)-3-(B-carbonyl)-4-benzyloxazolidin-2-ones” analogs enriched in the 19(a-f)b(i-vii) stereoisomer over the 19(a-f)c(i-vii) stereoisomer. Removal of the chiral auxiliary (Step D) following alkylation and subsequent chiral amide derivatization (Steps E and F) provides the diastereomers 17(a-f)b(i-vii) separable by chromatography and further purified by crystallization (Step G). Acid-catalyzed amide hydrolysis (Step H) to the corresponding stereopure carboxylic acid 18(a-f) b(i-vii) and subsequent esterification (Step I) provide the desired stereopure carboxylic ester intermediates 12(a-f)b(i-vii), which can be carried onto their corresponding stereopure β-keto phosphonate esters 13(a-f)b(i-vii).

Scheme 8 particularly illustrates the conversions of acetylenic carboxylic esters 12(a-f)a and 12(a-f)(b-e)(i-xi) to the corresponding β-keto phosphonates by the previously-described general manner.



64

-continued

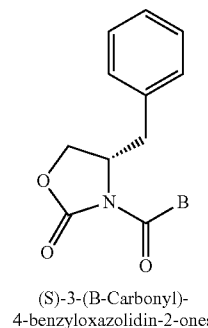
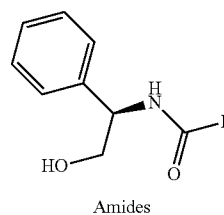
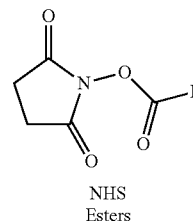
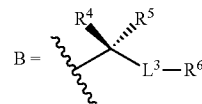


TABLE A

of Lower Chains



	B	R ⁴	R ⁵	L ³ -R ⁶
12	aa	H	H	
	ab(i)	Me	H	
	ac(i)	H	Me	
	ad(i)	Me	Me	
	ab(ii)	Et	H	
50	ac(ii)	H	Et	
	ad(ii)	Et	Et	
	ab(iii)	n-Pr	H	
13	ac(iii)	H	n-Pr	
	ad(iii)	n-Pr	n-Pr	
	ab(iv)	i-Pr	H	
55	ac(iv)	H	i-Pr	
	ad(iv)	i-Pr	i-Pr	
	ab(v)	n-Bu	H	
	ac(v)	H	n-Bu	
	ad(v)	n-Bu	n-Bu	
	ab(vi)	i-Bu	H	
	ac(vi)	H	i-Bu	
18	ad(vi)	i-Bu	i-Bu	
	ab(vii)	sec-Bu	H	
	ac(vii)	H	sec-Bu	
	ad(vii)	sec-Bu	sec-Bu	
	ab(viii)	tert-Bu	H	
	ac(viii)	H	tert-Bu	
65	ad(viii)	tert-Bu	tert-Bu	

65

TABLE A-continued

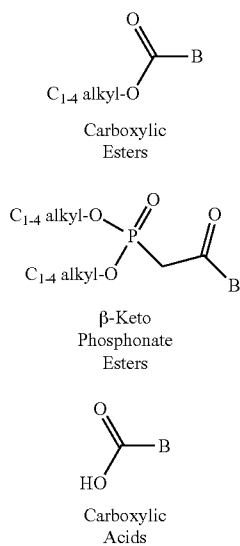
of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
ae(ix)			
ae(x)			
ae(xi)			

R⁴ and/or R⁵ = C₁-C₄ alkyl*

- (i) Me
- (ii) Et
- (iii) n-Pr
- (iv) i-Pr
- (v) n-Bu
- (vi) i-Bu
- (vii) sec-Bu
- (viii) tert-Bu

C ₃ -C ₅ cycloalkyl	
(ix)	cyclopropyl
(x)	cyclobutyl
(xi)	cyclopentyl

*R⁴ and R⁵ may both be C₁-C₄ alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope.



66

-continued

5		16
10	NHS Esters	
15		17
20	Amides	
25		19
30	(S)-3-(B-Carbonyl)-4-benzyloxazolidin-2-ones	
35		

TABLE B

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
12	ba	H	
	bb(i)	Me	
	bc(i)	H	
	bd(i)	Me	
50	bb(ii)	Et	
	bc(ii)	H	
	bd(ii)	Et	
	bb(iii)	n-Pr	
13	bc(iii)	H	
	bd(iii)	n-Pr	
	bb(iv)	i-Pr	
55	bc(iv)	H	
	bd(iv)	i-Pr	
	bb(v)	n-Bu	
	bc(v)	H	
	bd(v)	n-Bu	
	bb(vi)	i-Bu	
	bc(vi)	H	
18	bd(vi)	i-Bu	
	bb(vii)	sec-Bu	
	bc(vii)	H	
	bd(vii)	sec-Bu	
	bb(viii)	tert-Bu	
	bc(viii)	H	
65	bd(viii)	tert-Bu	

67

TABLE B-continued

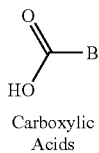
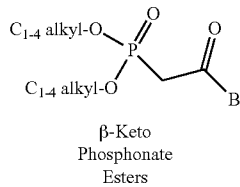
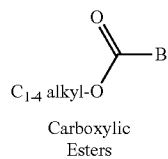
of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
be(ix)		-CH ₂ -CH ₂ -	
be(x)		-(CH ₂) ₂ -CH ₂ -	
be(xi)		-(CH ₂) ₃ -CH ₂ -	

R⁴ and/or R⁵ = C₁-C₄ alkyl*

- (i) Me
- (ii) Et
- (iii) n-Pr
- (iv) i-Pr
- (v) n-Bu
- (vi) i-Bu
- (vii) sec-Bu
- (viii) tert-Bu

(ix)	cyclopropyl
(x)	cyclobutyl
(xi)	cyclopentyl

*R⁴ and R⁵ may both be C₁-C₄ alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope.



68

-continued

5		16
10	NHS Esters	
15		17
20	Amides	
25		19
30	(S)-3-(B-Carbonyl)-4-benzyloxazolidin-2-ones	
35		

TABLE C

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
12	ca	H	H
	cb(i)	Me	H
	cc(i)	H	Me
	cd(i)	Me	Me
50	cb(ii)	Et	H
	cc(ii)	H	Et
	cd(ii)	Et	Et
13	cb(iii)	n-Pr	H
	cc(iii)	H	n-Pr
	cd(iii)	n-Pr	n-Pr
	cb(iv)	i-Pr	H
55	cc(iv)	H	i-Pr
	cd(iv)	i-Pr	i-Pr
	cb(v)	n-Bu	H
	cc(v)	H	n-Bu
	cd(v)	n-Bu	n-Bu
	cb(vi)	i-Bu	H
	cc(vi)	H	i-Bu
18	60	cd(vi)	i-Bu
	cb(vii)	sec-Bu	H
	cc(vii)	H	sec-Bu
	cd(vii)	sec-Bu	sec-Bu
	cb(viii)	tert-Bu	H
	cc(viii)	H	tert-Bu
65	65	cd(viii)	tert-Bu



69

TABLE C-continued

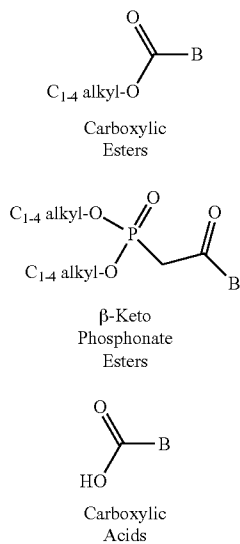
of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
ce(ix)		-CH ₂ -CH ₂ -	
ce(x)		-(CH ₂) ₂ -CH ₂ -	
ce(xi)		-(CH ₂) ₃ -CH ₂ -	

R⁴ and/or R⁵ = C₁-C₄ alkyl*

- (i) Me
- (ii) Et
- (iii) n-Pr
- (iv) i-Pr
- (v) n-Bu
- (vi) i-Bu
- (vii) sec-Bu
- (viii) tert-Bu

C ₃ -C ₅ cycloalkyl	
(ix)	cyclopropyl
(x)	cyclobutyl
(xi)	cyclopentyl

*R⁴ and R⁵ may both be C₁-C₄ alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope.



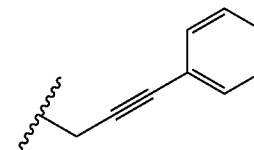
70

-continued

5		16
10	<p>NHS Esters</p>	
15		17
20	<p>Amides</p>	
25		19
30	<p>(S)-3-(B-Carbonyl)-4-benzyloxazolidin-2-ones</p>	
35		

TABLE D

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
12	da	H	H
	db(i)	Me	H
	dc(i)	H	Me
	dd(i)	Me	Me
50	db(ii)	Et	H
	dc(ii)	H	Et
	dd(ii)	Et	Et
13	db(iii)	n-Pr	H
	dc(iii)	H	n-Pr
	dd(iii)	n-Pr	n-Pr
	db(iv)	i-Pr	H
55	dc(iv)	H	i-Pr
	dd(iv)	i-Pr	i-Pr
	db(v)	n-Bu	H
	dc(v)	H	n-Bu
	dd(v)	n-Bu	n-Bu
	db(vi)	i-Bu	H
	dc(vi)	H	i-Bu
18	dd(vi)	i-Bu	i-Bu
	db(vii)	sec-Bu	H
	dc(vii)	H	sec-Bu
	dd(vii)	sec-Bu	sec-Bu
	db(viii)	tert-Bu	H
	dc(viii)	H	tert-Bu
65	dd(viii)	tert-Bu	tert-Bu



71
TABLE D-continued

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
de(ix)		-CH ₂ -CH ₂ -	
de(x)		-(CH ₂) ₂ -CH ₂ -	
de(xi)		-(CH ₂) ₃ -CH ₂ -	

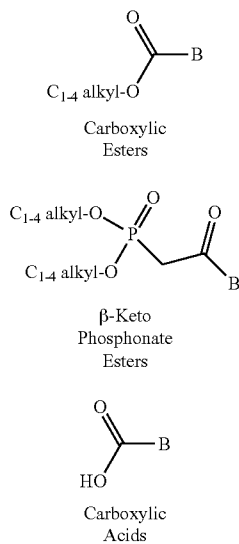
R⁴ and/or R⁵ =

C ₁ -C ₄ alkyl*	
(i)	Me
(ii)	Et
(iii)	n-Pr
(iv)	i-Pr
(v)	n-Bu
(vi)	i-Bu
(vii)	sec-Bu
(viii)	tert-Bu

=

C ₃ -C ₅ cycloalkyl	
(ix)	cyclopropyl
(x)	cyclobutyl
(xi)	cyclopentyl

*R⁴ and R⁵ may both be C₁-C₄ alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope.

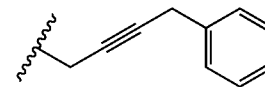


72
-continued

5		16
10	NHS Esters	
15		17
20	Amides	
25		19
30	(S)-3-(B-Carbonyl)-4-benzyloxazolidin-2-ones	
35		

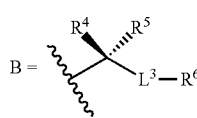
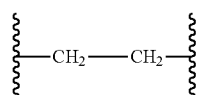
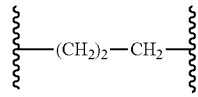
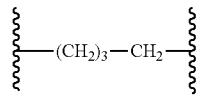
TABLE E

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
12	ea	H	H
	eb(i)	Me	H
	ec(i)	H	Me
	ed(i)	Me	Me
50	eb(ii)	Et	H
	ec(ii)	H	Et
	ed(ii)	Et	Et
13	eb(iii)	n-Pr	H
	ec(iii)	H	n-Pr
	ed(iii)	n-Pr	n-Pr
	eb(iv)	i-Pr	H
55	ec(iv)	H	i-Pr
	ed(iv)	i-Pr	i-Pr
	eb(v)	n-Bu	H
	ec(v)	H	n-Bu
	ed(v)	n-Bu	n-Bu
	eb(vi)	i-Bu	H
	ec(vi)	H	i-Bu
18	ed(vi)	i-Bu	i-Bu
	eb(vii)	sec-Bu	H
	ec(vii)	H	sec-Bu
	ed(vii)	sec-Bu	sec-Bu
	eb(viii)	tert-Bu	H
	ec(viii)	H	tert-Bu
65	ed(viii)	tert-Bu	tert-Bu



73

TABLE E-continued

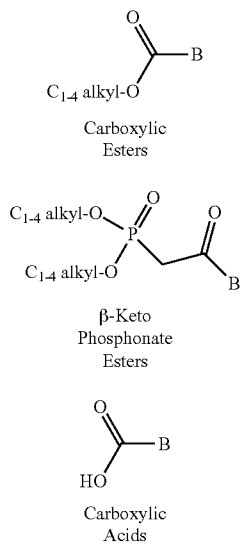
of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
			
ee(ix)			
ee(x)			
ee(xi)			

R⁴ and/or R⁵ = C₁-C₄ alkyl*

- (i) Me
- (ii) Et
- (iii) n-Pr
- (iv) i-Pr
- (v) n-Bu
- (vi) i-Bu
- (vii) sec-Bu
- (viii) tert-Bu

C ₃ -C ₅ cycloalkyl	
(ix)	cyclopropyl
(x)	cyclobutyl
(xi)	cyclopentyl

*R⁴ and R⁵ may both be C₁-C₄ alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope.



74

-continued

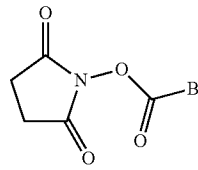
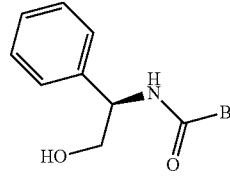
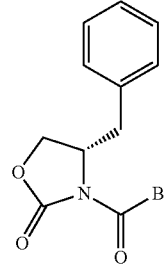
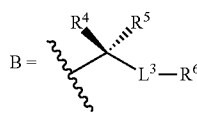
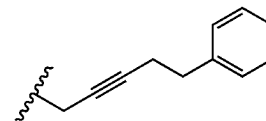
5		16
10	NHS Esters	
15		17
20	Amides	
25		19
30	(S)-3-(B-Carbonyl)-4-benzylloxazolidin-2-ones	
35		

TABLE F

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
40			
45			
12	fa	H	H
	fb(i)	Me	H
	fc(i)	H	Me
	fd(i)	Me	Me
50	fb(ii)	Et	H
	fc(ii)	H	Et
	fd(ii)	Et	Et
13	fb(iii)	n-Pr	H
	fc(iii)	H	n-Pr
	fd(iii)	n-Pr	n-Pr
	fb(iv)	i-Pr	H
55	fc(iv)	H	i-Pr
	fd(iv)	i-Pr	i-Pr
	fb(v)	n-Bu	H
	fc(v)	H	n-Bu
	fd(v)	n-Bu	n-Bu
	fb(vi)	i-Bu	H
	fc(vi)	H	i-Bu
18	fd(vi)	i-Bu	i-Bu
	fb(vii)	sec-Bu	H
	fc(vii)	H	sec-Bu
	fd(vii)	sec-Bu	sec-Bu
	fb(viii)	tert-Bu	H
	fc(viii)	H	tert-Bu
65	fd(viii)	tert-Bu	tert-Bu



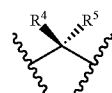
75

TABLE F-continued

of Lower Chains			
B	R ⁴	R ⁵	L ³ -R ⁶
fe(ix)			
fe(x)			
fe(xi)			

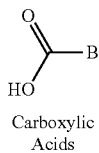
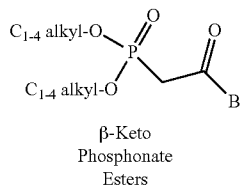
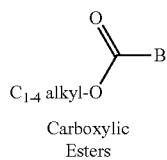
R⁴ and/or R⁵ = C₁-C₄ alkyl*

- (i) Me
- (ii) Et
- (iii) n-Pr
- (iv) i-Pr
- (v) n-Bu
- (vi) i-Bu
- (vii) sec-Bu
- (viii) tert-Bu



- = C₃-C₅ cycloalkyl
- (ix) cyclopropyl
 - (x) cyclobutyl
 - (xi) cyclopentyl

*R⁴ and R⁵ may both be C₁-C₄ alkyl groups that are not the same. Although no examples of these embodiments are represented in these tables, their absence infers no limitation in scope.



76

TABLE G/H

of Lower Chains		
5	B	
10	g	
15	h	
20		
25		
30	12	
35	13	
40	18	
45		
50	TABLE P/Q	
55	of Lower Chains	
60	B	
65	P	
	q	

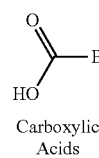
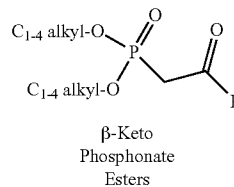
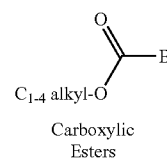
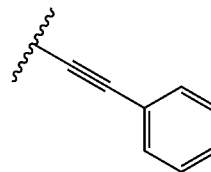
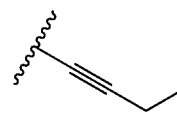
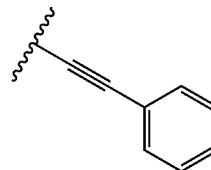
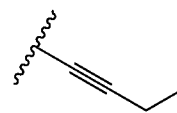


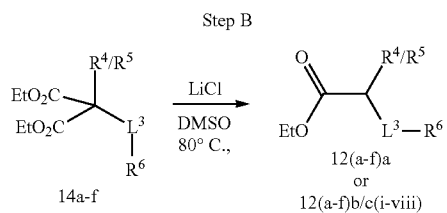
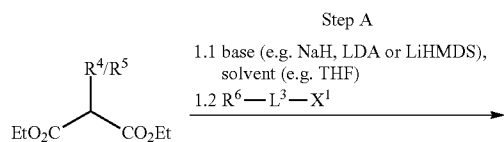
TABLE P/Q

of Lower Chains



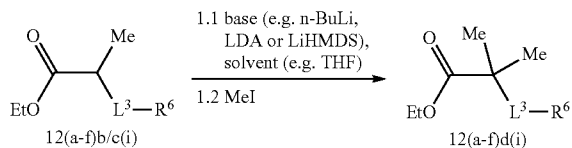
77

Scheme 7a

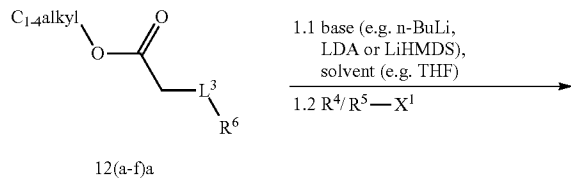


X¹ = leaving group
(e.g. iodide, bromide, or triflate)

Scheme 7b

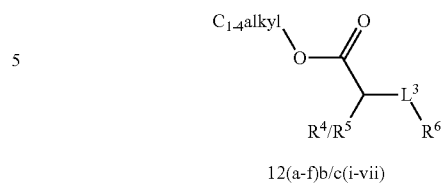


Scheme 7c



78

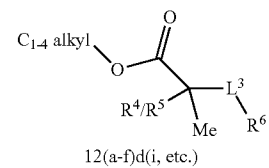
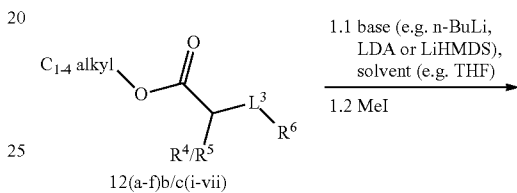
-continued



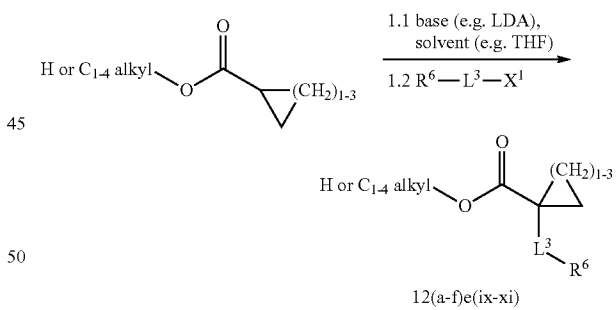
X¹ = leaving group
(e.g. bromide, iodine, or triflate)

15

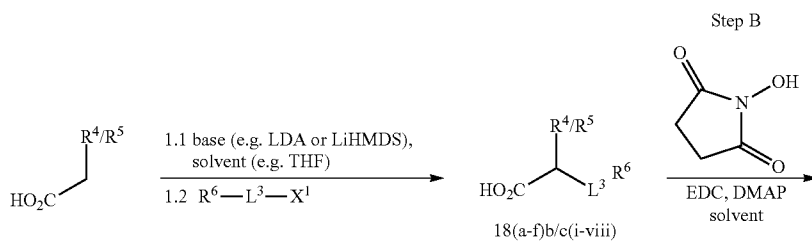
Scheme 7d



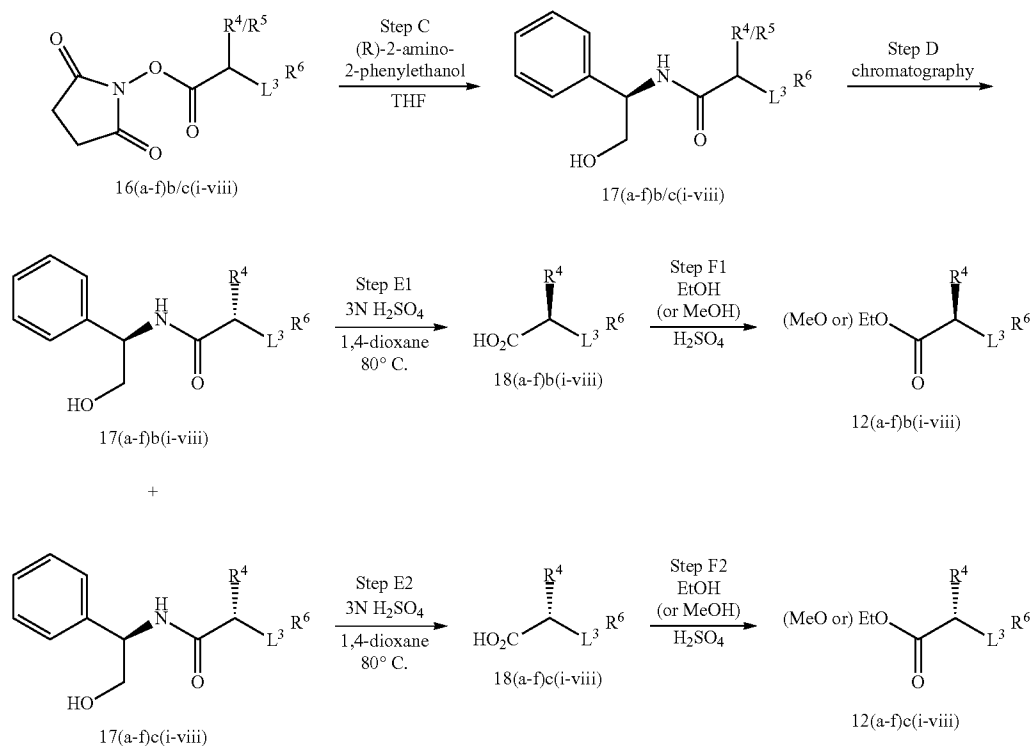
Scheme 7e



Scheme 7f

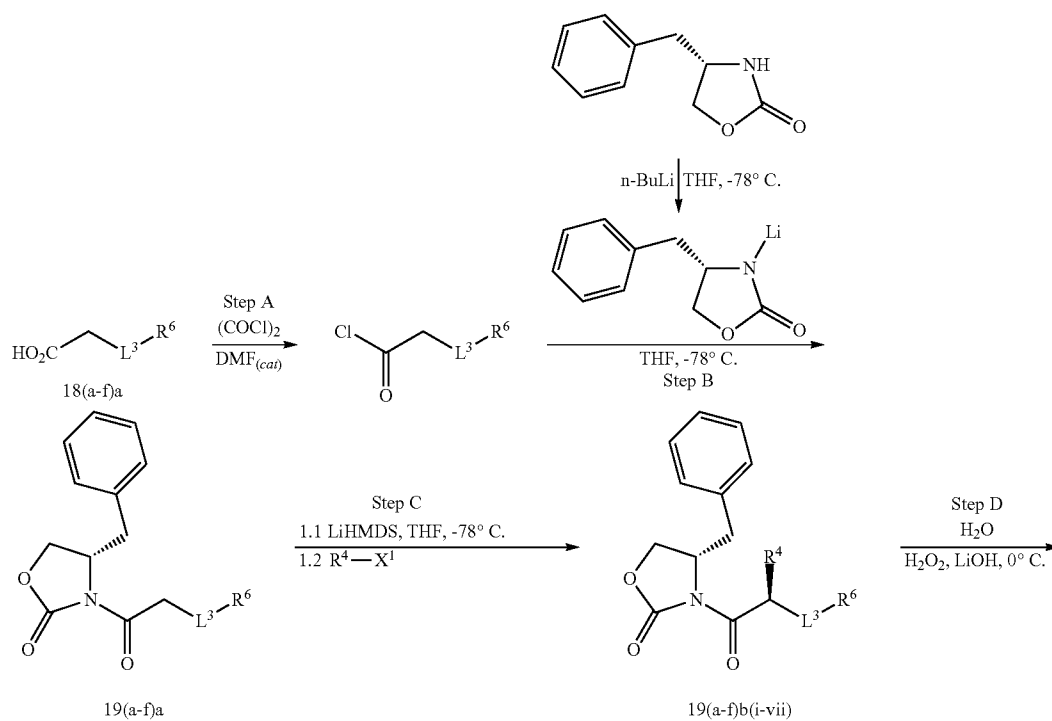


-continued



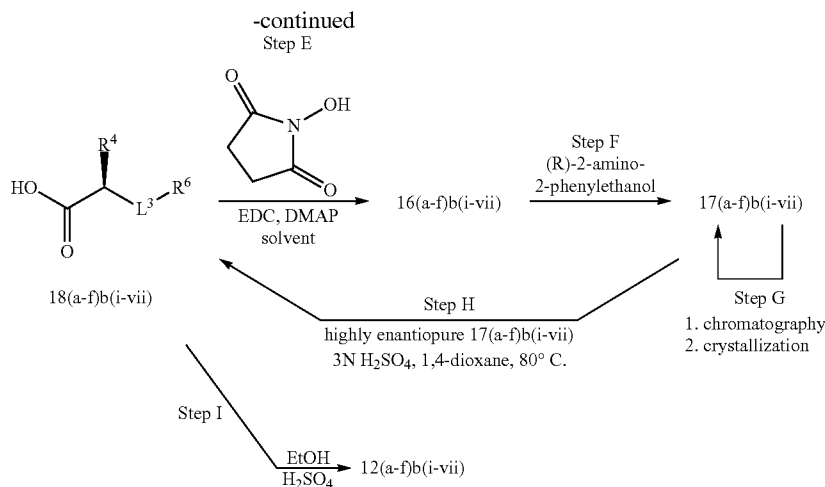
X^1 = leaving group
 (e.g. bromide, iodine, or triflate)

Scheme 7g

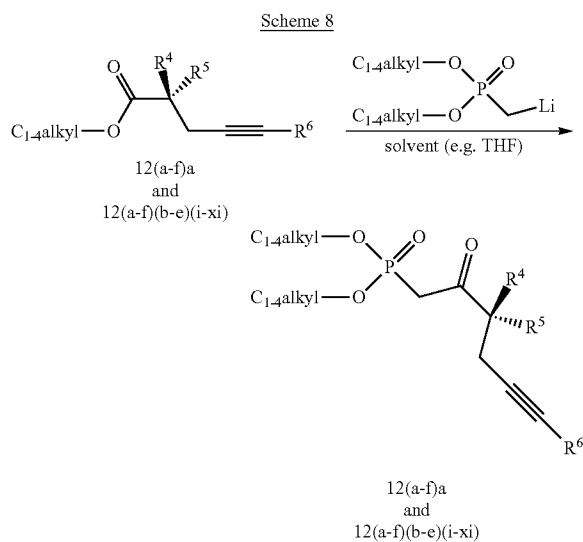


81

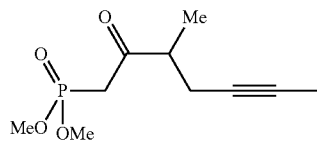
82



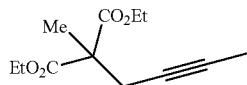
X¹ = leaving group
(e.g. bromide, iodine, or triflate)



(±)-Dimethyl (3-methyl-2-oxohept-5-yn-1-yl)phosphonate (13ab(i)/13ac(i))



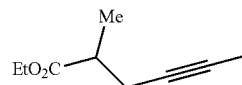
Scheme 7a, Step A: Preparation of diethyl 2-(but-2-yn-1-yl)-2-methylmalonate (14a)



To a stirring mixture consisting of diethyl 2-methylmalonate (Sigma-Aldrich, 34.8 g, 200 mmol) in THF (50 mL) at -78°C . was added lithium bis-(trimethylsilyl)amide (1M in THF, 200 mL, 200 mmol) and the resulting reaction mixture was stirred at -78°C . for 30 minutes. To the

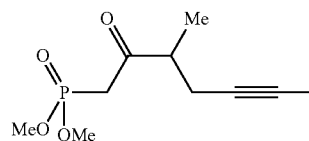
reaction mixture was added a mixture consisting of 1-bromobut-2-yne (GFS, 25 g, 190 mmol) in THF (50 mL), and the mixture was stirred for another hour at -78°C ., and was then allowed to warm to room temperature. The mixture was treated with 10% aqueous sodium hydrogen sulfate, diluted with brine (800 mL), and extracted with ethyl acetate (300 mL). The organic phase was washed with brine (2x250 mL), dried over sodium sulfate, filtered, and concentrated. The residue (brown oil) was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:9 v/v) to afford the title intermediate (41.5 g, 97.6%); TLC R_f 0.52 (solvent system: 1:9 v/v ethyl acetate-hexane).

Scheme 7a, Step B: Preparation of (±)-ethyl 2-methylhex-4-ynoate (12ab(i)/12ac(i))



To a mixture consisting of diethyl-2-(but-2-yn-1-yl)-methylmalonate (intermediate 14a, 41.5 g, 184 mmol) in DMSO (150 mL) was added lithium chloride (8.05 g, 190 mmol) and water (6.2 mL), and the stirring mixture was heated at 160°C . overnight. The reaction mixture was cooled and diluted with brine, and the organic material was extracted with ethyl acetate (250 mL). The organic phase was washed with brine (2x200 mL), dried over sodium sulfate, filtered, and concentrated. The residue (dark brown oil) was filtered through a pad of silica gel, using ethyl acetate-hexane (1:4 v/v) to flush the column. The filtrate was concentrated to give the title intermediate (22.3 g, 78.9%) as a colorless oil; TLC R_f 0.37 (solvent system: 1:4 v/v ethyl acetate-hexane).

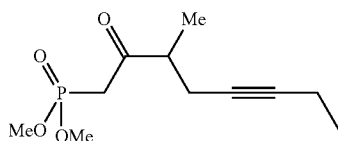
Scheme 8: Preparation of (±)-dimethyl (3-methyl-2-oxohept-5-yn-1-yl)phosphonate (13ab(i)/13ac(i))



83

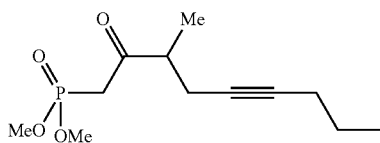
To a stirring mixture consisting of dimethyl methylphosphonate (21.7 g, 175 mmol) in THF (200 mL) at -78°C . was added *n*-butyllithium (1.6M in hexanes, 106.2 mL, 169.9 mmol) and the mixture was allowed to continue stirring at -78°C . for one hour. To the reaction mixture was added dropwise (\pm)-ethyl 2-methylhex-4-ynoate (intermediate 15, 22.3 g, 145 mmol) and the resulting mixture was stirred at -78°C . for three hours. The reaction mixture was treated with 10% sodium hydrogen sulfate to achieve pH 4, diluted with brine (800 mL), and extracted with ethyl acetate (250 mL). The organic phase was washed with brine (2 \times 150 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with ethyl acetate to afford the title intermediate (24.12 g, 71.6%) as a colorless oil; TLC R_f 0.31 (solvent system: ethyl acetate); MS (ESI⁺) m/z 233 (M+1).

Preparation of (\pm)-dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bb(i)/13bc(i))



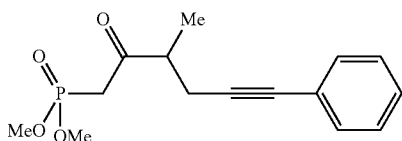
(\pm)-Dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate was prepared in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Schemes 7a and 8 except that 1-bromopent-2-yne was used instead of 1-bromobut-2-yne in Scheme 7a, Step A; MS (ESI⁺) m/z 247.1 (M+1).

Preparation of (\pm)-dimethyl (3-methyl-2-oxonon-5-yn-1-yl)phosphonate (13cb(i)/13cc(i))



(\pm)-Dimethyl (3-methyl-2-oxonon-5-yn-1-yl)phosphonate was prepared in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Schemes 7a and 8 except that 1-bromohex-2-yne (prepared from the corresponding commercially available alcohol using PBr_3 /pyridine) was used instead of 1-bromobut-2-yne in Scheme 7a, Step A; MS (ESI⁺) m/z 261 (M+1).

Preparation of (\pm)-dimethyl (3-methyl-2-oxo-6-phenylhex-5-yn-1-yl)phosphonate (13db(i)/13dc(i))

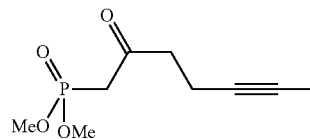


(\pm)-Dimethyl (3-methyl-2-oxo-6-phenylhex-5-yn-1-yl)phosphonate was prepared in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Schemes 7a and 8 except that (3-bromoprop-1-yn-1-yl)benzene (prepared from the correspond-

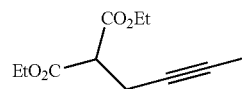
84

ing commercially available alcohol using PBr_3 /pyridine) was used instead of 1-bromobut-2-yne in Scheme 7a, Step A to afford 2.4 g of a clear oil; $^1\text{H-NMR}$ (CDCl_3) δ 7.35-7.45 (m, 2H), 7.2-7.3 (m, 3H), 3.85-3.75 (m, 6H), 3.25 (d, 2H), 3.0-3.2 (m, 1H), 2.5-2.7 (m, 2H), 1.25 (d, 3H); MS (ESI⁺) m/z 295.1 (M+1).

Dimethyl (2-oxohept-5-yn-1-yl)phosphonate (13aa)

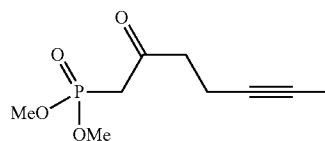


Scheme 7a, Step A: Preparation of diethyl 2-(but-2-yn-1-yl)malonate (14a)



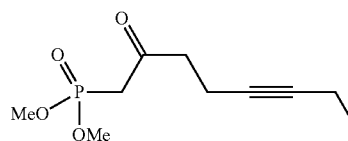
To a stirring mixture consisting of diethyl malonate (24.3 g, 141 mmol) in THF (140 mL) was added sodium hydride (60% disp. in oil, 2.8 g, 70 mmol) and the resulting reaction mixture was stirred for 50 minutes. To the reaction mixture was added 1-bromobut-2-yne (GFS, 6.2 g, 47 mmol), and the mixture was stirred for two hours. The reaction mixture was treated carefully with 0.5N HCl and extracted with ethyl acetate. The organic phase was washed with water, then brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with ethyl acetate-heptane (5:95 to 15:85 v/v) to afford the title intermediate (11.5 g, quantitative yield) as a clear oil.

Scheme 7a, Step B, subsequently, Scheme 8: Preparation of dimethyl (2-oxohept-5-yn-1-yl)phosphonate (13aa)



Dimethyl (2-oxohept-5-yn-1-yl)phosphonate was prepared in two steps from diethyl 2-(but-2-yn-1-yl)malonate (14a), above, in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Scheme 7a, Step B and Scheme 8, to afford 2.5 g as a clear oil; $^1\text{H-NMR}$ (CDCl_3) δ 3.78 (d, 6H, $J=11.5$ Hz), 3.1 (d, 2H, $J=22.5$ Hz), 2.80 (t, 2H), 2.42-2.35 (m, 2H), 1.73 (t, 3H).

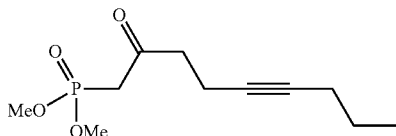
Preparation of dimethyl (2-oxooct-5-yn-1-yl)phosphonate (13ba)



85

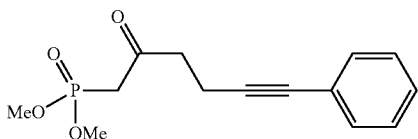
Dimethyl (2-oxooct-5-yn-1-yl)phosphonate was prepared in the same manner as that of compound intermediate 13aa as described above and illustrated in Scheme 7a and 8, except that 1-bromopent-2-yne (GFS, 6.9 g, 47 mmol) was used instead of 1-bromobut-2-yne to afford 2.5 g as a clear oil; $^1\text{H-NMR}$ (CDCl_3) δ 3.78 (d, 6H, $J=11.1$ Hz), 3.11 (d, 2H, $J=22.8$ Hz), 2.81 (t, 2H), 2.45-2.38 (m, 2H), 2.28-2.36 (m, 2H), 1.08 (t, 3H).

Preparation of dimethyl (2-oxonon-5-yn-1-yl)phosphonate (13ca)

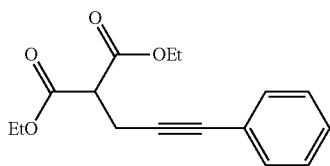


Dimethyl (2-oxonon-5-yn-1-yl)phosphonate is prepared in the same manner as that of compound intermediate 13aa as described above and illustrated in Scheme 7a and 8, except that 1-bromohex-2-yne is used instead of 1-bromobut-2-yne.

Preparation of dimethyl (2-oxo-6-phenylhex-5-yn-1-yl)phosphonate (13da)



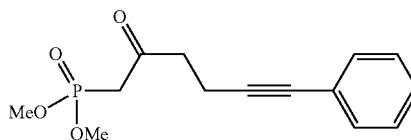
Scheme 7a, Step A: Preparation of diethyl 2-(hex-2-yn-1-yl)malonate (14d)



To a 0°C . stirring suspension consisting of sodium hydride (1.22 g, 51.3 mmol) in THF (100 mL) was added dropwise a solution of diethyl malonate (12.3 g, 76.9 mmol) in THF (20 mL) and the reaction mixture was stirred for 30 minutes. To the 0°C . reaction mixture was added a solution of (4-bromobut-1-yn-1-yl)benzene (5.0 g, 25.6 mmol, prepared from the corresponding commercially available alcohol using PBr_3 /pyridine) in THF (30 mL) and the mixture was allowed to warm to room temperature for one hour. The reaction mixture was quenched with an aqueous solution of sodium chloride (500 mL) and extracted with diethyl ether (500 mL). The organic phase was washed with brine (300 mL), dried over sodium sulfate, filtered, and concentrated to afford the title intermediate (10.6 g) which was used as is in the following reaction; TLC R_f 0.47 (solvent system: 1:5 v/v ethyl acetate-heptane).

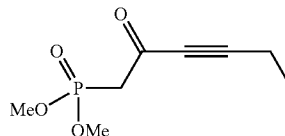
86

Preparation of dimethyl (2-oxo-6-phenylhex-5-yn-1-yl)phosphonate (13da)



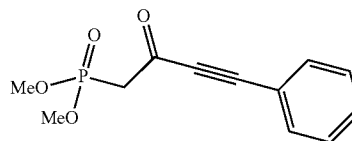
Dimethyl (2-oxo-6-phenylhex-5-yn-1-yl)phosphonate was prepared in two steps from diethyl 2-(hex-2-yn-1-yl)malonate, above, in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Scheme 7a, Step B and Scheme 8 to afford 2.12 g; TLC R_f 0.20 (solvent system: 4:1 v/v ethyl acetate-heptane); MS (ESI^+) m/z 281 ($M+1$).

Preparation of dimethyl (2-oxohex-3-yn-1-yl)phosphonate (13g)



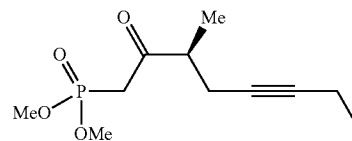
Dimethyl (2-oxohex-3-yn-1-yl)phosphonate was prepared in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Scheme 8 except that ethyl pent-2-ynoate was used instead of (\pm)-ethyl 2-methylhex-4-ynoate; MS (ESI^+) m/z 205 ($M+1$).

Preparation of dimethyl (2-oxo-4-phenylbut-3-yn-1-yl)phosphonate (13h)



Dimethyl (2-oxo-4-phenylbut-3-yn-1-yl)phosphonate was prepared in the same manner as that of compound intermediate 13ab(i)/13ac(i) as described above and illustrated in Scheme 8 except that ethyl 3-phenylpropionate was used instead of (\pm)-ethyl 2-methylhex-4-ynoate; MS (ESI^+) m/z 253 ($M+1$).

Preparation of (S)-(+)-dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bb(i))



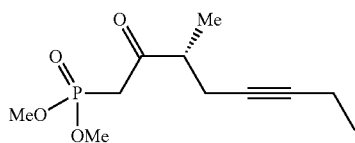
(S)-(+)-Dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bb(i)) was prepared by following the sequence of reaction steps described in Scheme 7b and Scheme 8. The intermediate 2-methylhept-4-ynoic acid was prepared according to a method described in WO 2011/003058 A1. (S)-(+)-Dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phospho-

87

nate was prepared according to the method described in the *Journal of Medicinal Chemistry*, 1986, 29(3), 313-315, except that 2,5-dioxopyrrolidin-1-yl 2-methylhept-4-ynoate (N-hydroxysuccinimide 2-methylhept-4-ynoate) was prepared as an activated acyl species (activated ester) instead of 2-methylhept-4-ynoyl chloride to make the diastereomeric pair (S)-N-((R)-2-hydroxy-1-phenylethyl)-2-methylhept-4-ynamide (17bb(i)) and (R)-N-((R)-2-hydroxy-1-phenylethyl)-2-methylhept-4-ynamide (17bc(i)) described in general terms in Scheme 7f. The diastereomers were separated by silica gel chromatography and 17bb(i) was subsequently manipulated as described to afford the title intermediate as a clear oil. The absolute stereochemistry of the title intermediate was proven by determination of its specific rotation: $[\alpha]_D^{25} = +45.92^\circ$ (c=2.5, CHCl₃); literature-reported specific rotation for (S)-(+)-diethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate from *Liebigs Annalen der Chemie*, 1989, 11, 1081-1083; $[\alpha]_D^{20} = +37.7^\circ$ (c=1, CHCl₃); chiral analytical HPLC (stationary phase: Chiralcel OJ-H normal phase 250×4.6 mm; mobile phase: 85:15 hexane/1-propanol; flow rate: 1 mL/min) retention time 6.4 min, 100% purity; TLC R_f 0.32 (solvent system: 4:1 v/v ethyl acetate-hexane); ¹H-NMR (CDCl₃) δ 3.76-3.80 (m, 6H), 3.11-3.29 (m, 2H), 2.86-2.95 (m, 1H), 2.36-2.44 (m, 1H), 2.26-2.33 (m, 1H), 2.09-2.16 (m, 2H), 1.16-1.20 (m, 3H), 1.06-1.11 (m, 3H); MS (ESI⁺) m/z 247 (M+H)⁺.

A second preparation of the title intermediate by the same process described above afforded the title intermediate wherein the specific rotation (c=1, CHCl₃) is +49°.

Preparation of (R)-(-)-dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bc(i))



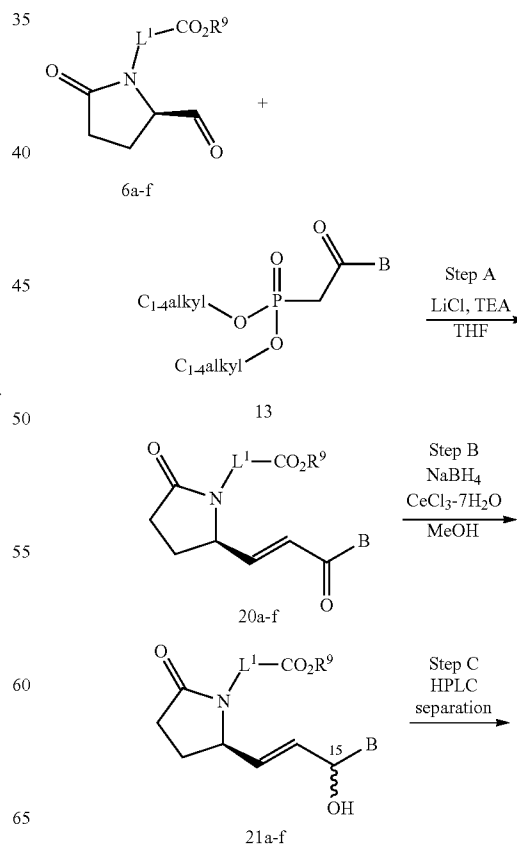
(R)-(-)-Dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bc(i)) was prepared by the same method described for the preparation of 13fbb(i) above, except that the (R)-N-((R)-2-hydroxy-1-phenylethyl)-2-methylhept-4-ynamide (17bc(i)) diastereomer collected from the silica gel chromatography was taken on to afford the title phosphonate intermediate; $[\alpha]_D^{25} = -47.69^\circ$ (c=1.28, CHCl₃); TLC R_f 0.347 (solvent system: 85:15 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 247 (M+H)⁺.

Exemplary embodiments may be prepared utilizing a Horner-Emmons-Wadsworth-type procedure, according to the route described below in Schemes 9 and 10 by the coupling of an aldehyde intermediate, such as those for which their preparations are described and illustrated above (6a-f), with an organic β-keto phosphonate ester, such as those that are commercially available or for which their preparations are described and illustrated above (13), to provide an α,β-unsaturated ketone compound intermediate (20a-f). In some applications, the Horner-Emmons-Wadsworth reaction comprises contacting the aldehyde with the β-keto phosphonate in the presence of lithium chloride, a trialkylamine base, such as triethylamine or diisopropylethylamine, and a suitable solvent such as THF. A reduction of the C15-oxo group to the corresponding C15-hydroxyl group may be carried out with a reducing agent to provide

88

stereoisomeric mixtures of the corresponding C15-alcohol 21a-f (Scheme 9, Step B). In some applications, the reducing agent comprises sodium borohydride. In some applications, the reduction is a stereoselective reduction such as a Corey-Bakshi-Shibata (CBS) reduction. These mixtures may be separated into their C15-stereoisomer components 22a-f and 23a-f by HPLC (Step C) to provide the C15α-hydroxy (22a-f) and C15β-hydroxy (23a-f) diastereomers. The ester intermediates 22a-f and 23a-f may subsequently be hydrolyzed to carboxylic acid embodiments 24a-f (Step D1) and 25a-f (Step D2), respectively. Organic β-keto phosphonate esters 13 bearing a single chiral center, such as 13(a-f)b(i-viii), where R⁴ is a C₁-C₄ alkyl group and R⁵ is hydrogen, or such as 13(a-f)c(i-viii), where R⁴ is a hydrogen and R⁵ is a C₁-C₄ alkyl group, when coupled with aldehydes like 6a-f in Scheme 9, Step A and subsequently reduced as in Step B, form a mixture (26a-f) comprising four diastereomers. The mixture may be separated into its isolated diastereomers 27-30a-f using preparatory HPLC as illustrated in Scheme 10, Step A. The corresponding carboxylic acids 31-34a-f may be obtained by basic aqueous hydrolysis of the esters using equimolar or excess (about 1-10 molar equivalents) hydroxide base, such as lithium hydroxide, potassium hydroxide, or sodium hydroxide, at about 1-3 M in hydroxide base. The basic aqueous hydrolysis reaction mixture may further comprise at least one solvent that is miscible with water, such as methanol, ethanol, THF, 1,4-dioxane, or DMF. Detailed procedures for preparing these compounds are described below.

Scheme 9

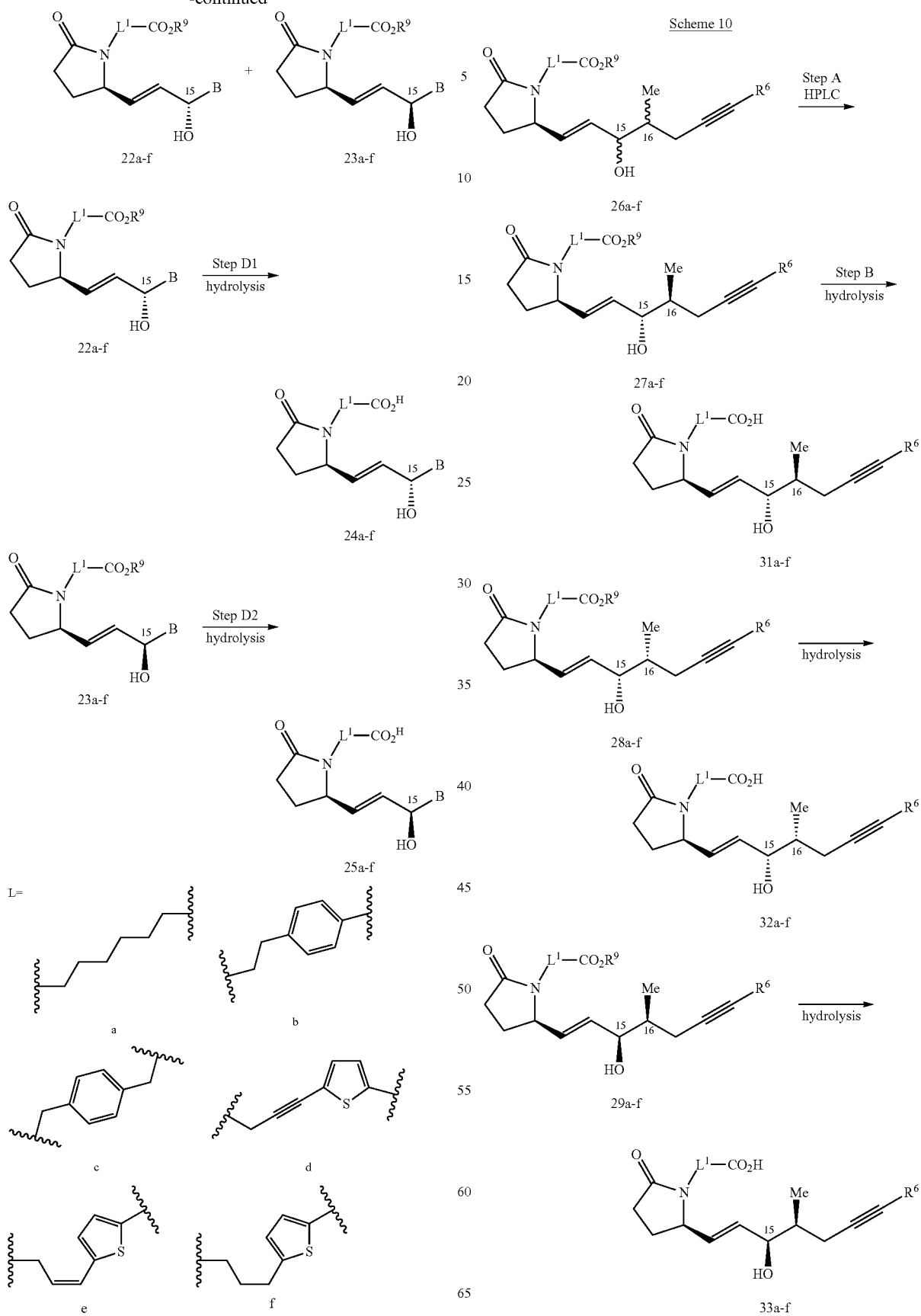


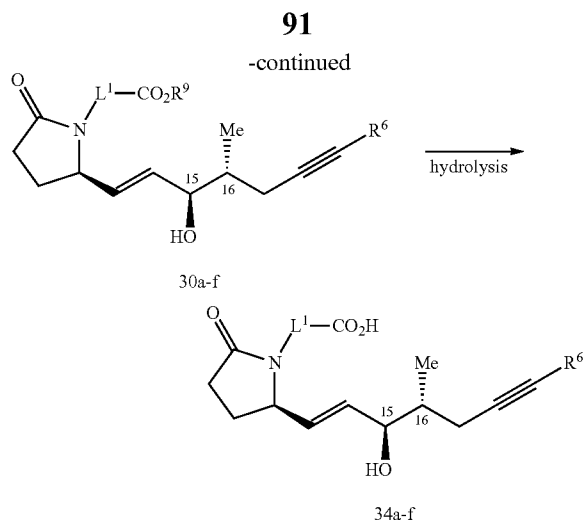
89

90

-continued

Scheme 10

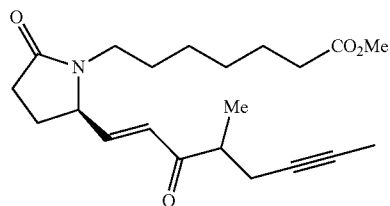




EXAMPLES

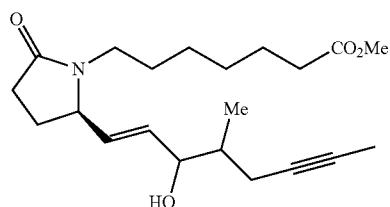
Examples 1A-1F

Scheme 9, Step A: Preparation of methyl 7-((2R)-2-((4R/S,E)-4-methyl-3-oxooct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate



To a stirring mixture consisting of (R)-methyl 7-(2-formyl-5-oxopyrrolidin-1-yl)heptanoate (6a, 0.500 g, 1.96 mmol) and (±)-dimethyl (3-methyl-2-oxohept-5-yn-1-yl)phosphonate (13ab(i)/13ac(i)), 0.438 g, 1.89 mmol) in THF (40 mL) at 0° C. was added lithium chloride (280 mg, 6.61 mmol) and triethylamine (0.30 g, 3.0 mmol). The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added a saturated solution of ammonium chloride (30 mL) and organic material was extracted with ethyl acetate (100 mL). The organic layer was separated, washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with ethyl acetate-heptane (7:3 v/v) to afford the title compound (360 mg, 51%); TLC R_f 0.44 (solvent system: ethyl acetate); MS (APCI⁺) m/z 362 (M+1).

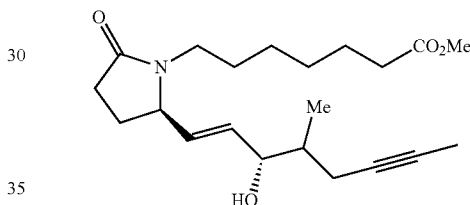
Scheme 9, Step B: Preparation of four-diastereomer mixture methyl 7-((2R)-2-((E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate

**92**

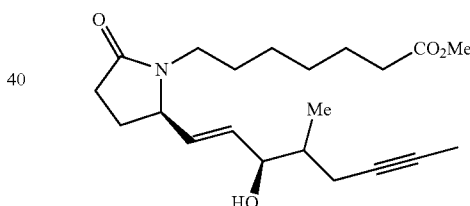
To a mixture consisting of methyl 7-((2R)-2-((4R/S,E)-4-methyl-3-oxooct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (0.36 g, 1.0 mmol) in methanol (10 mL) at -40° C. was added cerium (III) chloride heptahydrate (0.373 g, 1.00 mmol). The reaction mixture was cooled to -78° C. and stirred for one hour. To the reaction mixture was added sodium borohydride (0.076 g, 2.0 mmol), and the reaction mixture stirred for two hours. Acetone was added and the mixture was stirred for 15 minutes at -78° C., after which time the mixture was elevated to room temperature. To the room temperature reaction mixture was added a saturated aqueous solution of ammonium chloride (30 mL) and the organic material was extracted with ethyl acetate (100 mL). The organic layer was separated and washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with ethyl acetate-heptanes (7:3 v/v) to afford the title compound (450 mg) as a stereoisomeric mixture of four diastereomeric components with regard to the configurations of the C15-OH and C16-Me positions.

Scheme 9, Step C: Preparation of methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 1A) and methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 1B)

Example 1A



Example 1B



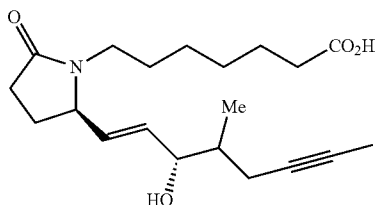
From the stereoisomeric mixture comprising the four methyl 7-((2R)-2-((3R/S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate diastereomers (450 mg, prepared in Step B of this Example above) were separated the methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate diastereomeric pair from the methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate diastereomeric pair by prep HPLC. The separations were performed on an Agilent Semi-Prep instrument equipped with an ultraviolet detector at 210 nm and using a Chiralpak IA 250 mm×20 mm column eluting with a mobile phase of heptanes-ethanol (90:10 v/v) at a flow rate of 18 mL/min. Each of the two diastereomeric mixtures, Examples 1A and 1B, was isolated as a clear oil.

Example 1A (89 mg); prep HPLC retention time 22-25 minutes; TLC R_f 0.20 (solvent system: ethyl acetate); MS (APCI⁺) m/z 364 (M+1).

Example 1B (191 mg); prep HPLC retention time 16-19 minutes; TLC R_f 0.27 (solvent system: ethyl acetate); MS (APCI⁺) m/z 364 (M+1).

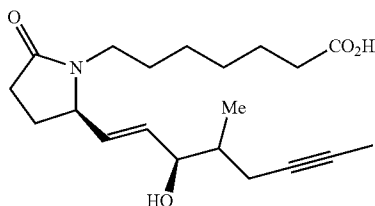
93

Scheme 9, Step D1: Preparation of 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1C)



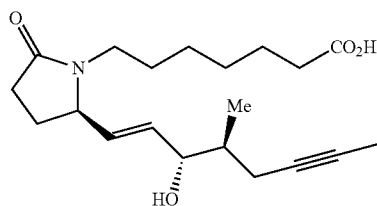
To a mixture consisting of methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (0.089 g, 0.24 mmol, prepared as Example 1A above) in methanol (3 mL) was added 2N sodium hydroxide (6 drops). The reaction mixture was stirred at room temperature for three hours. To the reaction mixture was added a solution of 5% potassium hydrogen sulfate-brine (1:1) to achieve an acidic pH, and the organic material was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel eluting with ethyl acetate-acetic acid (100:0.4 v/v) to afford the title compound (62 mg, 75%) as a nearly colorless solid; TLC R_f 0.27 (solvent system: 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 348 (M-1); ¹H-NMR (CDCl₃) δ 5.7 (dd, 1H), 5.5 (dd, 1H), 4.25 (t, 1H), 3.6-3.5 (m, 1H), 2.9-2.8 (m, 1H), 2.5-1.2 (m, 20H), 0.95 (dd, 3H).

Scheme 9, Step D2: Preparation of 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1D)



The title compound was prepared from methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (0.191 g, 0.525 mmol) according to the procedure described in Step D1 for the preparation of Example 1C. The title compound was obtained (146 mg, 79.6%) as a yellow oil; TLC R_f 0.31 (solvent system: 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 348 (M-1).

Step E: Preparation of 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1E) and 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1F)

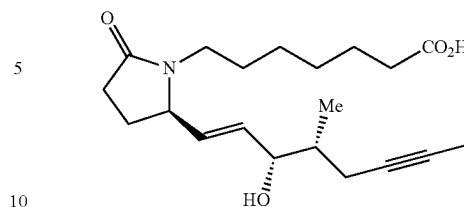


Example 1E

94

-continued

Example 1F



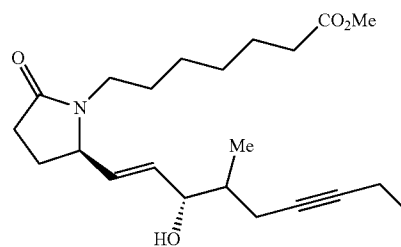
From the stereoisomer mixture comprising 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1C, 35 mg) were separated the pure stereoisomers 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1E) and 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 1F) by prep HPLC. Each pure stereoisomer was isolated as a colorless solid. The separation was performed on a Gilson Semi-Prep instrument equipped with an ultraviolet detector at 205 nm and using a Luna Silica 5μ 250 mm×10 mm column eluting with a mobile phase of heptane-ethanol (92:8 v/v).

Example 1E (5 mg); a colorless solid; HPLC retention time 52 minutes; TLC R_f 0.31 (solvent system: 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 348 (M-1); melting point 113-114° C.

Example 1F (9 mg); a colorless solid; HPLC retention time 49 minutes; TLC R_f 0.31 (solvent system: 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 348 (M-1); melting point 100-101° C.

Examples 2A-2F

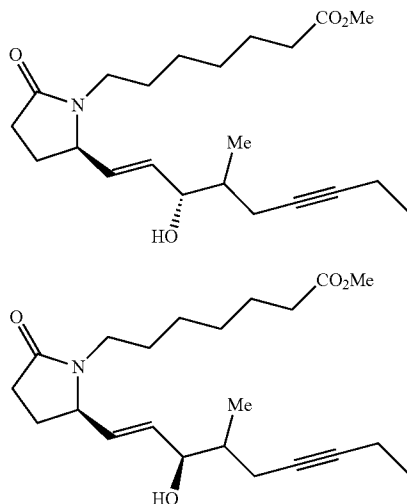
Scheme 9, Step A: Preparation of methyl 7-((2R)-2-((4R/S,E)-4-methyl-3-oxonon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate



Methyl 7-((2R)-2-((4R/S,E)-4-methyl-3-oxonon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (648 mg) was prepared by the method described in Examples 1A-1F section, Step A above except that (±)-dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bb(i)/13bc(i)) was used instead of dimethyl (3-methyl-2-oxohept-5-yn-1-yl)phosphonate; TLC R_f 0.33 (solvent system: 4:1 v/v ethyl acetate-heptane).

Scheme 9, Steps B and C: Preparation of methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2A) and methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2B)

95

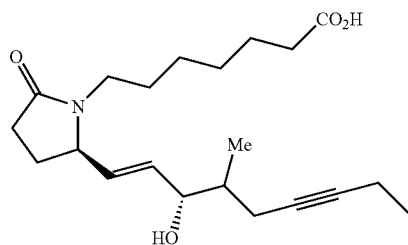


Mixture methyl 7-((2R)-2-((E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (570 mg), consisting of the four diastereomers, was prepared by the method described in Examples 1A-1F, Steps B and C. Both diastereomeric pairs methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2A) and methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2B) were isolated following separation by prep HPLC. The separation was performed on a Gilson Prep instrument equipped with an ultraviolet detector at 210 nm and using a Luna Silica 250x42.5 mm column eluting with a mobile phase of 9:1 v/v heptane-n-propanol.

Example 2A (70 mg); a clear oil; HPLC retention time of 7 min; TLC R_f 0.35 (solvent system: ethyl acetate); MS (ESI⁺) m/z 378 (M+1).

Example 2B (240 mg); a clear oil; HPLC retention time of 6 min; TLC R_f 0.44 (solvent system: ethyl acetate); MS (ESI⁺) m/z 378 (M+1).

Scheme 9, Step D1: Preparation of 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2C)

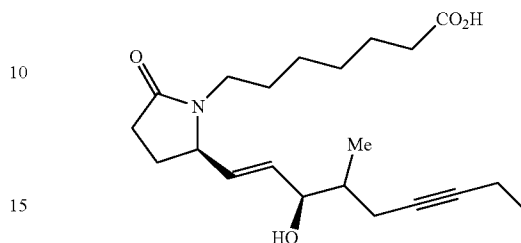


7-((2R)-2-((3S,4R/S,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2C) was prepared from methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2A) by the method described in Step D1 for the preparation of Example 1C, to obtain the title compound (58 mg, 91%) as a nearly colorless solid; melting point 123-124° C.; MS (ESI⁻) m/z 362 (M-1); ¹H-NMR (CDCl₃) δ 5.76 (dd, 1H), 5.64 (dd, 1H), 4.25 (t, 1H), 4.2-4.0

96

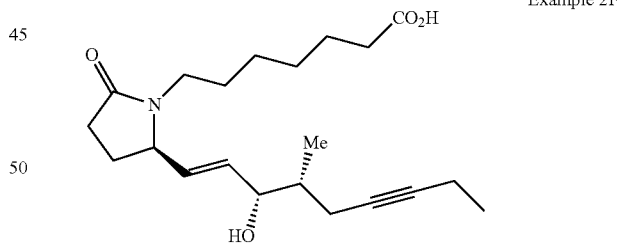
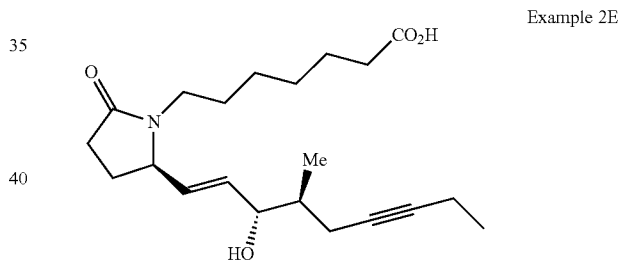
(m, 1H), 3.6-3.4 (m, 1H), 3.0-2.9 (m, 1H), 2.5-1.15 (m, 19H), 1.15 (t, 3H), 0.9 (dd, 3H).

Example 2A
Scheme 9, Step D2: Preparation of 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2D)



7-((2R)-2-((3R,4R/S,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2D) was prepared from methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2B) by the method described in Step D1 for the preparation of Example 1C, to obtain the title compound (223 mg) as a nearly colorless solid; MS (ESI⁻) m/z 362 (M-1); melting point 56-57° C.

Step E: Preparation of 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2E) and 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2F)



From the stereoisomer mixture comprising 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2C, 143 mg) were separated the pure stereoisomers 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2E) and 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2F) by prep HPLC. Each pure stereoisomer was isolated as a colorless solid. The separation was performed on an Agilent 1200 Prep instrument equipped with an ultraviolet detector at 210 nm and using a Luna Silica 21.2x250 mm column eluting with a mobile phase of heptanes-ethanol (95:5 v/v).

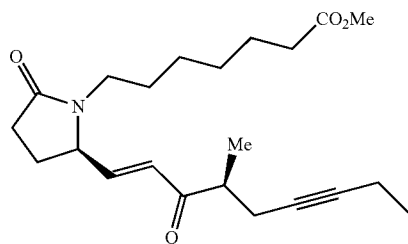
97

Example 2E (24 mg); white solid; prep HPLC retention time 67 minutes; MS (ESI⁻) m/z 362 (M-1); melting point 138-139° C.

Example 2F (30 mg); white solid; prep HPLC retention time 62 minutes; MS (ESI⁻) m/z 362 (M-1); melting point 112-113° C.

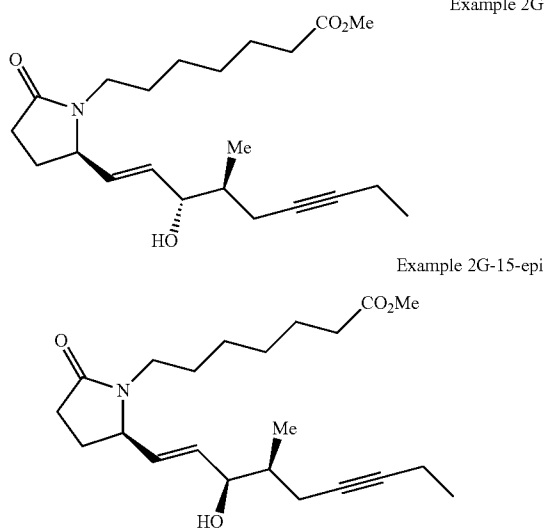
Example 2E, Alternate Route

Step A: Preparation of methyl 7-((2R)-2-((S,E)-4-methyl-3-oxonon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate



Methyl 7-((2R)-2-((S,E)-4-methyl-3-oxonon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate was prepared by the method described for Examples 1A-1F, Step A, except that (S)-(+)-dimethyl (3-methyl-2-oxooct-5-yn-1-yl)phosphonate (13bb(i); prepared above) was used instead of (±)-dimethyl (3-methyl-2-oxohept-5-yn-1-yl)phosphonate (13bb(i)/13bc(i)); TLC R_f 0.33 (solvent system: 4:1 v/v ethyl acetate-heptane).

Steps B and C: Preparation of diastereomeric mixture methyl 7-((2R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2G) and methyl 7-((2R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2G-15-epi)



To a room temperature solution consisting of methyl 7-((2R)-2-((S,E)-4-methyl-3-oxonon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (695 mg, 1.85 mmol) was treated with (R)-(+)-2-methyl-CBS-oxazaborolidine (1.85 mL, 1.85 mmol, 1M solution in toluene). The reaction

98

mixture was cooled to -40° C. and to the mixture was added catecholborane (6.1 mL, 6.1 mmol, 1M solution in THF). The reaction mixture was allowed to warm to room temperature and stirred for one hour followed by the addition of 1 mL of 1N HCl and stirring over night. To the reaction mixture was added methanol and the organic material was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was chromatographed on a silica gel column eluted with 80:20 ethyl acetate-heptane to afford (280 mg) the diastereomeric mixture of alcohols; TLC R_f 0.17 (solvent system: 4:1 v/v ethyl acetate-heptane).

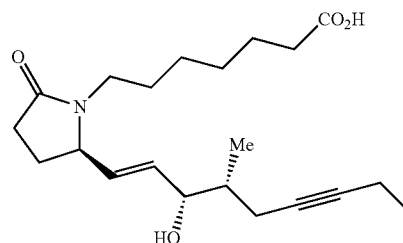
From the diastereomeric mixture of methyl 7-((2R)-2-((4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (approximately 95:5 ratio of Example 2G to Example 2G-15-epi) were separated the pure stereoisomers methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2G) and methyl 7-((R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2G-15-epi) by prep HPLC. The separation was performed on an Agilent 1200 Prep instrument equipped with an ultraviolet detector at 210 nm and using a CN 5μ250x21.2 mm column eluting with a mobile phase of heptanes-ethanol (92:8 v/v).

Example 2G (57 mg); a clear oil; prep HPLC retention time 19 minutes; TLC R_f 0.35 (solvent system: ethyl acetate); MS (ESI⁺) m/z 378 (M+1).

Scheme 9, Step D1: Preparation of 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2E)

7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2E) was prepared from methyl 7-((2R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 2G) by the method described in Step D1 for the preparation of Example 1C, to obtain the title compound MS (ESI⁻) m/z 362 (M-1); ¹H-NMR (MeOD-d₄) δ 5.76 (dd, 1H), 5.55 (dd, 1H), 4.17-4.23 (m, 1H), 4.02 (t, 1H), 3.43-3.51 (m, 1H), 2.95 (ddd, 1H), 2.21-2.41 (m, 6H), 2.08-2.18 (m, 3H), 1.68-1.82 (m, 2H), 1.43-1.64 (m, 4H), 1.25-1.4 (m, 5H), 1.1 (t, 3H), 0.96 (d, 3H).

Example 2F, Alternate Route



7-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 2F) is prepared according to the alternative route to Example 2E presented immediately above, except that 13bc(i) is used instead of 13bb(i).

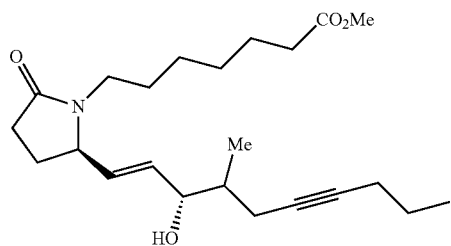
The following Examples were prepared by the method described in Example 1A-1F, Steps A through D1/2 (Scheme 9), using the appropriate aldehyde (6a-f) and the appropriate β-keto phosphonate ester (13) as described above followed

99

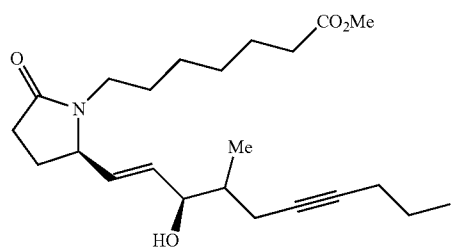
by selective reduction of the α,β -unsaturated ketone. The isomers were isolated by the use of HPLC and the esters were hydrolyzed using aqueous base such as lithium, potassium or sodium hydroxide.

Examples 3A-3D

Scheme 9, Steps A, B and C: Preparation of methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 3A) and methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 3B)



Example 3A



Example 3B

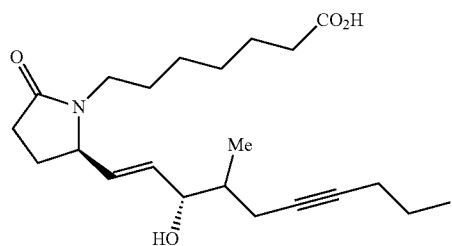
The diastereomeric mixtures of Example 3A and Example 3B were isolated following separation by prep HPLC.

Gilson Prep instrument; ultraviolet detector at 210 nm; Luna 5 μ Silica 250 \times 21.2 mm column; mobile phase of heptane-ethanol (9:1 v/v) with a flow rate of 21 mL/min.

Example 3A (80 mg); a clear oil; HPLC retention time 19 min; TLC R_f 0.69 (solvent system: ethyl acetate); MS (ESI⁺) m/z 392 (M+1).

Example 3B (180 mg); a colorless solid; HPLC retention time 14.5 min; TLC R_f 0.74 (solvent system: ethyl acetate); MS (ESI⁺) m/z 392 (M+1).

Scheme 9, Step D1: Preparation of 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 3C)

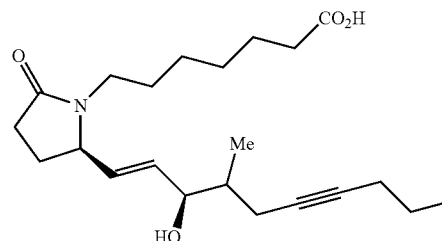


71 mg (92%) as a white solid; melting point 104-105 $^\circ$ C.; TLC R_f 0.22 (solvent system: 85:15:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁺) m/z 376.2 (M-1); ¹H-NMR

100

(CDCl₃) δ 5.76 (dd, 2H), 4.26 (t, 1H), 4.1-4.15 (m, 1H), 3.4-3.5 (m, 1H), 2.9-2.98 (m, 1H), 2.1-2.5 (m, 9H), 1.75-1.84 (m, 2H), 1.25-1.66 (m, 10H), 0.92-1.1 (m, 6H).

Scheme 9, Step D2: Preparation of 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 3D)



10

15

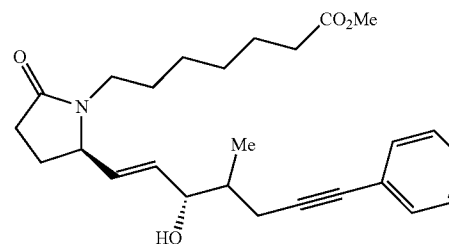
20

87 mg (91%) as a clear oil; TLC R_f 0.28 (solvent system: 85:15:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 376 (M-1).

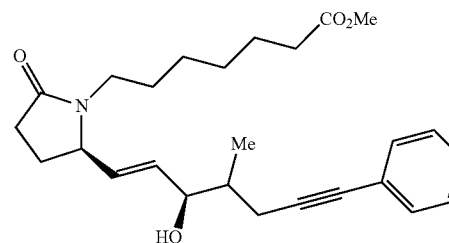
Examples 4A-4D

25

Scheme 9, Steps A, B, and C: Preparation of methyl 7-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 4A) and methyl 7-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 4B)



Example 4A



Example 4B

35

40

45

50

55

The diastereomeric mixtures of Example 4A and Example 4B were isolated following separation by prep HPLC.

Agilent Prep 1100 instrument; ultraviolet detector at 233 nm; Chiralpak IA 250 \times 20 mm column; mobile phase of heptane-ethanol (88:12 v/v) with a flow rate of 18 mL/min.

Example 4A (100 mg); a clear oil; HPLC retention time 28 min; TLC R_f 0.30 (solvent system: 9:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 426 (M+1).

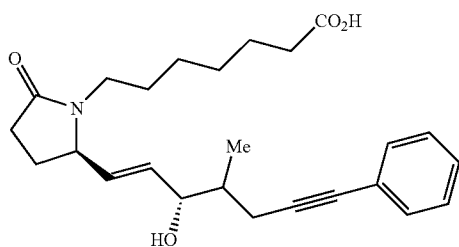
Example 4B (195 mg); a clear oil; HPLC retention time 20 min; TLC R_f 0.36 (solvent system: 9:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 426 (M+1).

60

65

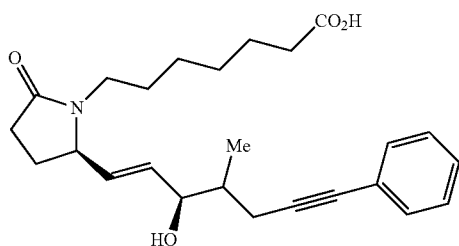
101

Scheme 9, Step D1: Preparation of 7-((2R)-2-((3S,4R/S, E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 4C)



95 mg (100%) as a pale yellow oil; TLC R_f 0.28 (solvent system: 50:50:1 v/v acetone-heptane-acetic acid); MS (ESI⁺) m/z 412 (M+1).

Scheme 9, Step D2: Preparation of 7-((2R)-2-((3R,4R/S, E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 4D)

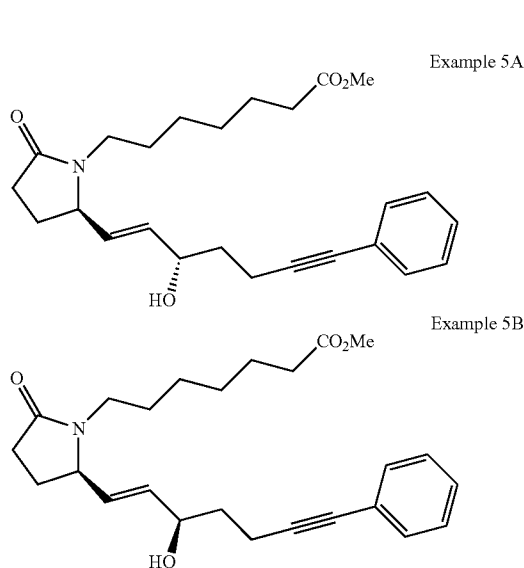


175 mg (93%) as a pale yellow oil; TLC R_f 0.32 (solvent system: 50:50:1 v/v acetone-heptane-acetic acid); MS (ESI⁺) m/z 412 (M+1).

Examples 5A-5D

Scheme 9, Steps A, B, and C: Preparation of methyl 7-((2R)-2-((3S,E)-3-hydroxy-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 5A) and methyl 7-((2R)-2-((3R,E)-3-hydroxy-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate

Example 5B



102

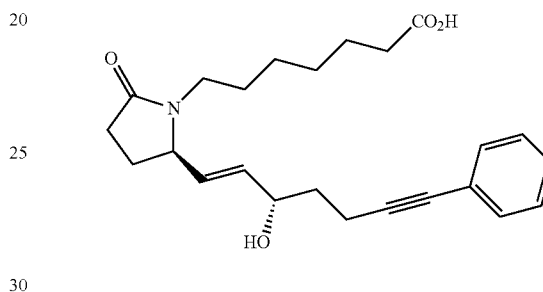
The single diastereomers of Example 5A and Example 5B were isolated following separation by prep HPLC.

5 Gilson Prep instrument; ultraviolet detector at 210 nm; Luna 5 μ Silica 250 \times 21.2 mm column; mobile phase of heptanes-ethanol (90:10 v/v) with a flow rate of 21.2 mL/min.

10 Example 5A (47 mg): a clear oil; HPLC retention time 27 min; TLC R_f 0.36 (solvent system: 8:2 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 412 (M+1).

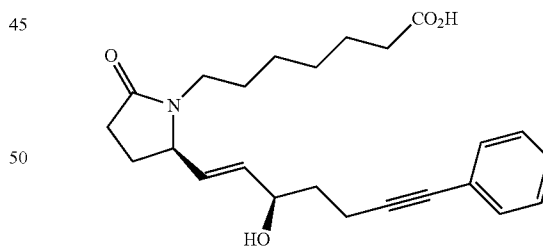
Example 5B (67 mg): a clear oil; HPLC retention time 21 min; TLC R_f 0.41 (solvent system: 8:2 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 412 (M+1).

15 Scheme 9, Step D1: Preparation of 7-((R)-2-((3S,E)-3-hydroxy-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 5C)



20 37 mg (100%); clear oil; TLC R_f 0.25 (solvent system: 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 397 (M-1); ¹H-NMR (MeOH-d₄) δ 7.26-7.36 (m, 5H), 5.81 (dd, 1H), 5.6 (dd, 1H), 4.3 (q, 1H), 4.07-4.22 (m, 2H), 3.4-3.49 (m, 1H), 2.97 (ddd, 1H), 2.34-2.53 (m, 4H), 2.21-2.33 (m, 3H), 1.73-1.84 (m, 3H), 1.5-1.62 (m, 3H), 1.21-1.38 (m, 5H)

25 30 Scheme 9, Step D2: Preparation of 7-((R)-2-((3R,E)-3-hydroxy-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 5D)

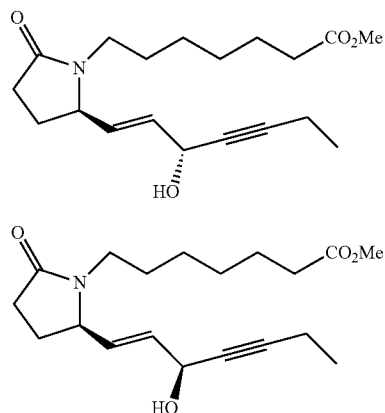


35 40 55 55 mg (100%); clear oil; TLC R_f 0.33 (solvent system: 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 397 (M-1).

Examples 6A-6D

60 65 Steps A and B: Preparation of methyl 7-((R)-2-((R,E)-3-hydroxyhept-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 6A) and methyl 7-((R)-2-((S,E)-3-hydroxyhept-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 6B)

103



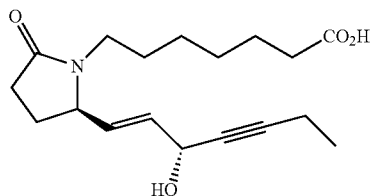
From the diastereomeric mixture (404 mg), the single diastereomers Example 6A and Example 6B were isolated following separation by prep HPLC.

Agilent 1100 Prep instrument; ultraviolet detector at 210 nm; Luna 5 μ Silica 250 \times 21.2 mm column; mobile phase of heptanes-ethanol (92:8 v/v) with a flow rate of 21.2 mL/min.

Example 6A (40 mg); a clear oil; HPLC retention time 26 min; TLC R_f 0.34 (solvent system 4:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 336 (M+1);

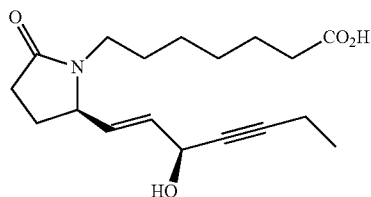
Example 6B (90 mg); a clear oil; HPLC retention time 24 min; TLC R_f 0.39 (solvent system 4:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 336 (M+1).

Scheme 9, Step D1: Preparation of 7-((R)-2-((R,E)-3-hydroxyhept-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 6C)



27 mg (70%) as a clear oil; TLC R_f 0.22 (solvent system 85:15:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁺) m/z 322 (M+1); ¹H-NMR (CDCl₃) δ 5.8 (dd, 2H), 4.90 (d, 1H), 4.12 (t, 1H), 1.2-2.58 (m, 18H), 1.08 (t, 3H).

Scheme 9, Step D2: Preparation of 7-((R)-2-((S,E)-3-hydroxyhept-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 6D)



40 mg (46%) as a clear oil; TLC R_f 0.25 (solvent system 85:15:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁺) m/z 322 (M+1).

Examples 7A-7D

Scheme 9, Steps A, B, and C: Preparation of methyl 7-((R)-2-((R,E)-3-hydroxy-5-phenylpent-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 7A) and methyl 7-((R)-2-((S,E)-3-hydroxy-5-phenylpent-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 7B)

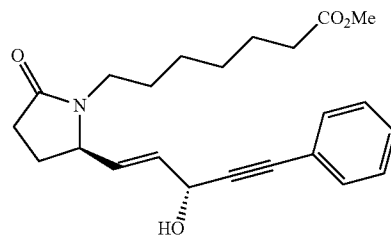
104

Example 6A

5-oxopyrrolidin-1-yl)heptanoate (Example 7A) and methyl 7-((R)-2-((S,E)-3-hydroxy-5-phenylpent-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate (Example 7B)

5

Example 7A

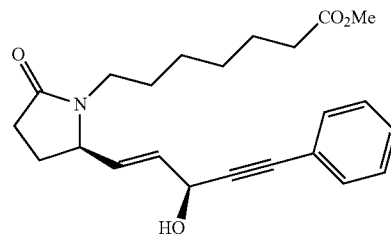


Example 6B

10

15

Example 7B



20

25

The single diastereomers Example 7A and Example 7B were isolated following separation by prep HPLC.

Agilent 1100 Prep instrument; ultraviolet detector at 210 nm; Luna Silica 250 \times 21.2 mm column; mobile phase of heptanes-ethanol (92:8 v/v) with a flow rate of 21.2 mL/min.

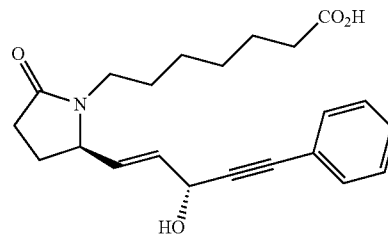
Example 7A (40 mg); a clear oil; HPLC retention time 20.9 min;

Example 7B (90 mg); a yellow oil; HPLC retention time 19.4 min.

35

Scheme 9, Step D1: Preparation of 7-((R)-2-((R,E)-3-hydroxy-5-phenylpent-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 7C)

40



45

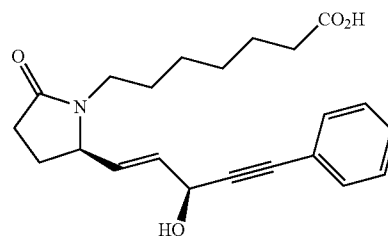
27 mg (71%) as a yellow solid; MS (ESI⁻) m/z 368 (M-1); ¹H-NMR (CDCl₃) δ 7.5-7.2 (m, 5H), 5.9 (dd, 1H), 5.8 (dd, 1H), 5.19 (d, 1H), 4.1-4.0 (m, 1H), 3.6-3.4 (m, 1H), 3.0-2.9 (m, 1H), 2.45-1.2 (m, 14H).

50

Step D2: Preparation of 7-((R)-2-((S,E)-3-hydroxy-5-phenylpent-1-en-4-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid (Example 7D)

55

60



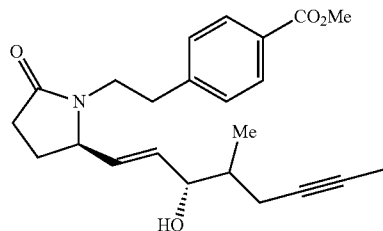
65

105

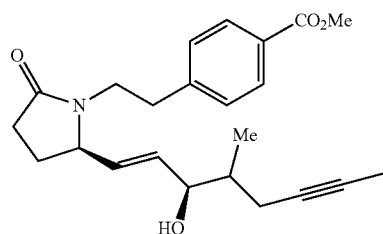
40 mg (47%) as a yellow oil; TLC R_f 0.22 (solvent system 90:10:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 368 (M-1).

Examples 8A-8D

Scheme 9, Steps A, B, and C: Preparation of methyl 4-(2-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 8A) and methyl 4-(2-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 8B)



Example 8A



Example 8B

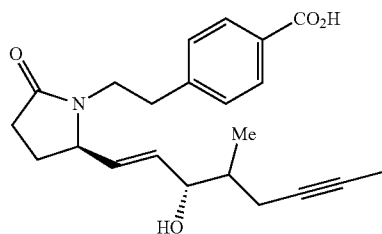
The diastereomeric mixtures of Example 8A and Example 8B were isolated following separation by prep HPLC.

Agilent Semi-Prep instrument; ultraviolet detector at 210 nm; Chiralpak IA 250 mm×10 mm column; mobile phase of heptanes-ethanol (9:1 v/v) with a flow rate of 5 mL/min.

Example 8A (30 mg of a clear oil); prep HPLC retention time 19.3-21.1 minutes; TLC R_f 0.69 (solvent system: ethyl acetate); MS (ESI⁺) m/z 406 (M+23);

Example 8B (40 mg of a colorless solid); prep HPLC retention time 14.9-16.1 minutes; TLC R_f 0.72 (solvent system: ethyl acetate); MS (ESI⁺) m/z 406 (M+23).

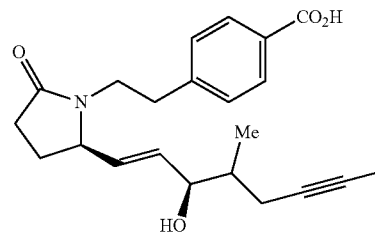
Scheme 9, Step D1: Preparation of 4-(2-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 8C)



16.5 mg (59%) as a colorless solid; TLC R_f 0.28 (solvent system 90:10:1 v/v ethyl acetate-heptane-acetic acid); melting point 183-185° C.; MS (ESI⁻) m/z 368 (M-1); ¹H-MNR (CDCl₃) δ 8.0 (d, 2H), 7.2 (d, 2H), 5.6 (dd, 2H), 5.4 (dd, 2H) 4.2 (t, 1H), 4.1-4.0 (m, 1H), 3.85-3.75 (m, 1H), 3.2-3.1 (m, 1H), 2.4-1.2 (m, 12H), 0.9 (dd, 3H).

106

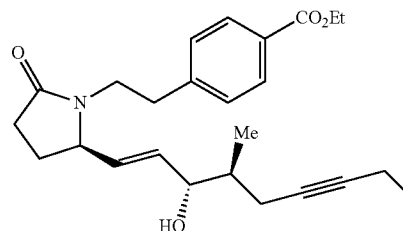
Scheme 9, Step D2: Preparation of 4-(2-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 8D)



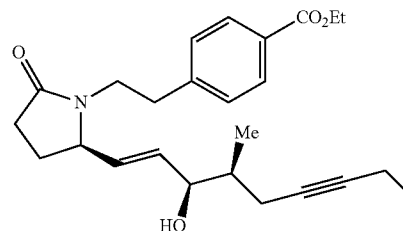
10 mg (26%) as an off-white solid; TLC R_f 0.29 (solvent system 90:10:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 368 (M-1).

Examples 9A-9D

Scheme 9, Steps A, B, and C: Preparation of ethyl 4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 9A) and ethyl 4-(2-((R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 9B)



Example 9A



Example 9B

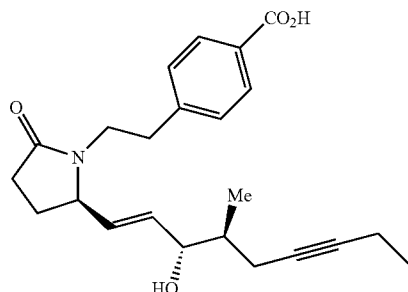
Mixture ethyl 4-(2-((2R)-2-((4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (217 mg), consisting of the two diastereomers, was prepared by the method described in Example 2E, Steps A, and B (Scheme 9) utilizing the appropriate aldehyde (6b) and β-keto phosphonate ester (13bb(i)). Both C15-hydroxy diastereomers ethyl 4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 9A) and ethyl 4-(2-((R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 9B) were isolated following separation by prep HPLC. The separation was performed on an Agilent Semi-Prep instrument; ultraviolet detector at 210 nm; Luna Silica 250 mm×10 mm column; mobile phase of heptane-ethanol-acetic acid (93:7:0.1 v/v) with a flow rate of 5 mL/min.

Example 9A; a clear oil, HPLC retention time 26 minutes; TLC R_f 0.39 (solvent system: 3:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 434 (M+23(Na⁺));

107

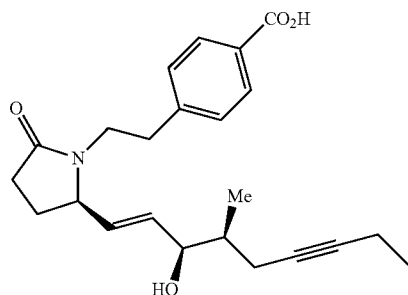
Example 9B; a clear oil, HPLC retention time 18 minutes; TLC R_f 0.45 (solvent system: 3:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 434 (M+23(Na⁺)).

Scheme 9, Step D1: 4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 9C)



42 mg (100%) as a colorless solid; TLC R_f 0.31 (solvent system 100:1 v/v ethyl acetate-acetic acid); melting point 173-174° C.; MS (ESI⁻) m/z 382 (M-1); ¹H-NMR (MeOH-*d*₄) δ 7.94-7.96 (d, 2H), 7.32-7.34 (d, 2H), 5.66-5.71 (dd, 1H), 5.46-5.52 (dd, 1H), 3.98-4.09 (m, 2H), 3.71-3.8 (m, 1H), 3.14-3.29 (m, 1H), 2.8-2.98 (m, 2H), 2.3-2.39 (m, 2H), 2.09-2.29 (m, 6H), 1.67-1.79 (m, 2H), 1.09 (t, 3H), 0.91-1.03 (m, 3H)

Scheme 9, Step D2: 4-(2-((R)-2-((3R,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 9D)

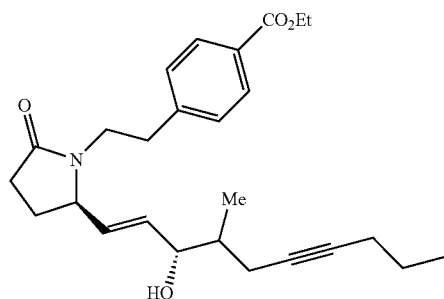


111 mg (100%) as a colorless solid; TLC R_f 0.42 (solvent system 100:1 v/v ethyl acetate-acetic acid); MS (ESI⁻) m/z 382 (M-1).

Examples 10A-10D

Scheme 9, Steps A, B, and C: Preparation of ethyl 4-(2-((R)-2-((3S,4R/S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 10A) and ethyl 4-(2-((R)-2-((3R,4R/S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 10B)

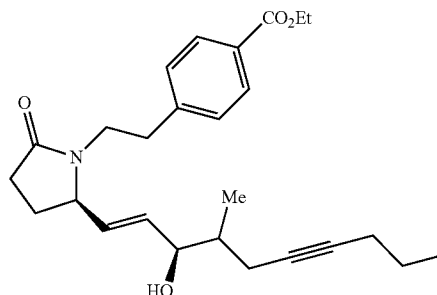
Example 10A



108

-continued

Example 10B



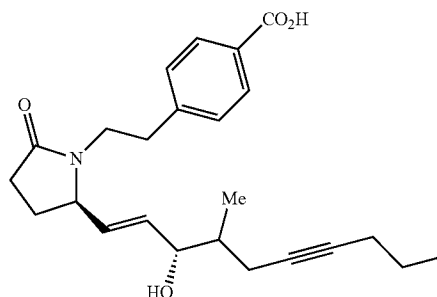
The diastereomeric mixtures of Example 10A and Example 10B were isolated following separation by prep HPLC.

Gilson Semi-Prep instrument; ultraviolet detector at 210 nm; Luna Silica 250 mm×21.2 mm column; mobile phase of heptane-ethanol (94:6 v/v) with a flow rate of 21.2 mL/min.

Example 10A (161 mg); a clear oil; HPLC retention time 24 minutes; TLC R_f 0.36 (solvent system: 3:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 448 (M+23(Na⁺));

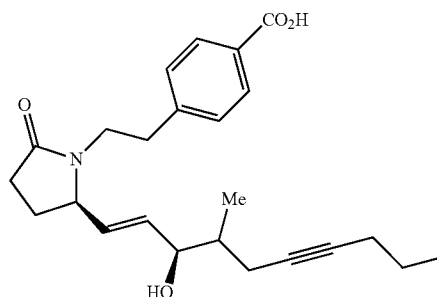
Example 10B (97 mg); a clear oil; HPLC retention time 39 minutes; TLC R_f 0.43 (solvent system: 3:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 448 (M+23(Na⁺)).

Scheme 9, Step D1: 4-(2-((2R)-2-((3S,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 10C)



61 mg (96%) as a colorless solid; TLC R_f 0.47 (solvent system 80:20:1 v/v ethyl acetate-heptane-acetic acid); melting point 109-111° C.; MS (ESI⁻) m/z 396 (M-1); ¹H-NMR (MeOH-*d*₄) δ 7.94-7.96 (d, 2H), 7.32-7.34 (dd, 2H), 5.66-5.73 (m, 1H), 5.45-5.54 (m, 1H), 4.-4.09 (m, 2H), 3.71-3.79 (m, 1H), 3.14-3.29 (m, 1H), 2.8-2.98 (m, 2H), 2.09-2.38 (m, 7H), 1.66-1.79 (m, 2H), 1.48 (m, 2H), 0.93-1.04 (m, 6H).

Scheme 9, Step D2: 4-(2-((2R)-2-((3R,E)-3-hydroxy-4-methyldec-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 10D)

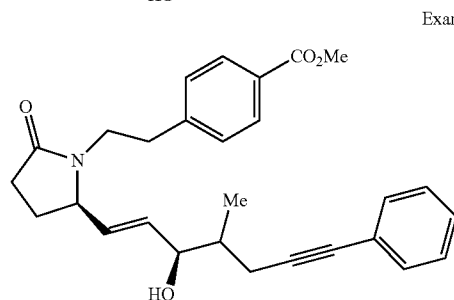
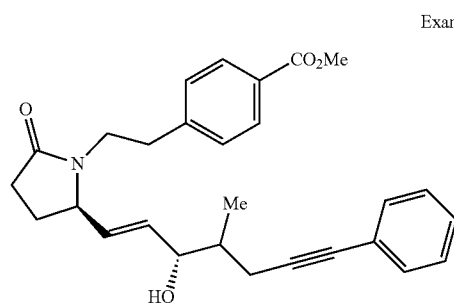


109

113 mg (75%) as a colorless solid; TLC R_f 0.51 (solvent system 80:20:1 v/v ethyl acetate-heptane-acetic acid); MS (ESI⁻) m/z 396 (M-1).

Examples 11A-11D

Scheme 9, Step A, B, and C: Preparation of methyl 4-(2-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 11A) and methyl 4-(2-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate (Example 11B)



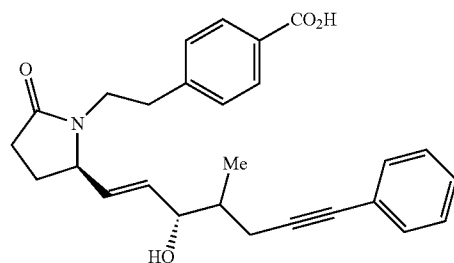
The diastereomeric mixtures of Example 11A and Example 11B were isolated following separation by prep HPLC.

Gilson Semi-Prep instrument; ultraviolet detector at 240 nm; Luna Silica 5 μ 250 mm \times 10 mm column; mobile phase of heptane-ethanol (9:1 v/v) with a flow rate of 5 mL/min.

Example 11A (64 mg); HPLC retention time 18 minutes; TLC R_f 0.15 (solvent system: 4:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 446 (M+1);

Example 11B (90 mg); HPLC retention time 15.5 minutes; TLC R_f 0.18 (solvent system: 4:1 v/v ethyl acetate-heptane); MS (ESI⁺) m/z 446 (M+1).

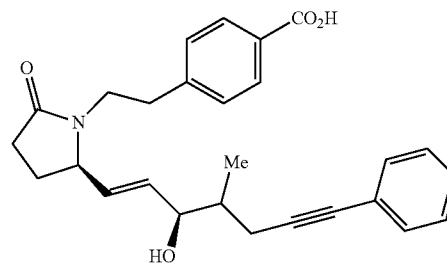
Scheme 9, Step D1: Preparation of 4-(2-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 11C)



110

60 mg (100%) as a clear oil; TLC R_f 0.31 (solvent system 50:50:1 v/v acetone-heptane-acetic acid); MS (ESI⁻) m/z 430 (M-1); ¹H-NMR (400 MHz, CDCl₃) δ 8.0 (d, 2H), 7.35-7.45 (m, 2H), 7.25-7.32 (m, 5H), 5.6 (dd, 2H), 4.3 (t, 1H), 4.15-4.2 (m, 2H), 3.2-3.1 (m, 2H) 2.6-1.3 (m, 9H) 1.1 (dd, 3H); ¹³CNMR (100 MHz, CDCl₃) δ 175.18, 170.16, 145.05, 134.89, 134.70, 130.84, 130.35, 128.88, 128.26, 127.82, 123.44, 87.91, 87.80, 82.43, 74.94, 74.15, 60.92, 50.81, 41.82, 38.29, 33.83, 29.96, 25.88, 23.27, 22.64, 15.81, 14.30.

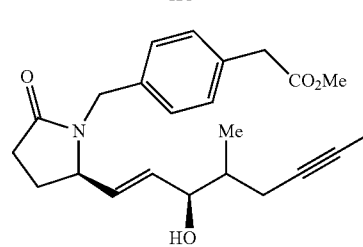
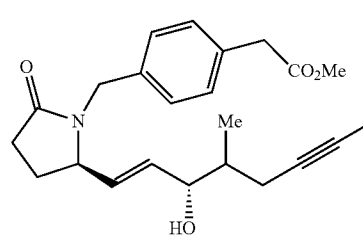
Scheme 9, Step D2: Preparation of 4-(2-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid (Example 11D)



45 mg (51%) as a clear oil; TLC R_f 0.36 (solvent system: 50:50:1 v/v acetone-heptane-acetic acid); MS (ESI⁻) m/z 430 (M-1).

Examples 12A-12D

Scheme 9, Step A, B, and C: Preparation of methyl 2-(4-(((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (Example 12A) and methyl 2-(4-(((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetate (Example 12B)



The diastereomeric mixtures of Example 12A and Example 12B were isolated following separation by prep HPLC.

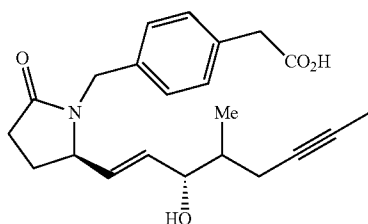
Agilent Semi-Prep instrument; ultraviolet detector at 210 nm; Chiralpak IA 250 mm \times 10 mm column; mobile phase of heptane-ethanol (9:1 v/v).

111

Example 12A (11.2 mg); prep HPLC retention time 18.1-19.5 minutes; TLC R_f 0.5 (solvent system 5:95:1 v/v methanol-dichloromethane-acetic acid);

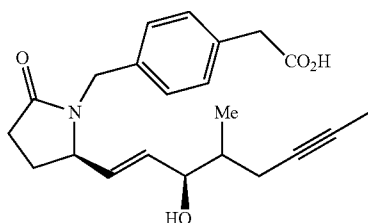
Example 12B (7.3 mg); prep HPLC retention time 15.0-16.0 minutes; TLC R_f 0.45 (solvent system 5:95:1 v/v methanol-dichloromethane-acetic acid).

Scheme 9, Step D1: Preparation of 2-(4-(((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid (Example 12C)



3.5 mg as an oil; TLC R_f 0.25 (solvent system: 5:95:1 v/v methanol-dichloromethane-acetic acid); MS (ESI⁻) m/z 368 (M-1); ¹H-NMR (400 MHz, CDCl₃) δ 7.2 (quartet, 4H), 5.6-5.4 (m, 2H), 4.8 (t, 1H), 4.2 (t, 1H), 4.0-3.9 (m, 2H), 3.7 (s, 2H), 2.6-2.3 (m, 2H), 2.3-2.1 (m, 2H), 2.1-2.0 (m, 2H), 1.8-1.7 (m, 5H), 0.9 (t, 3H).

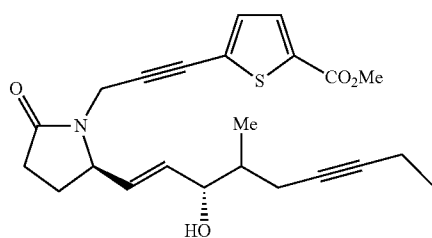
Scheme 9, Step D2: Preparation of 2-(4-(((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid (Example 12D)



8.4 mg as an oil; TLC R_f 0.2 (solvent system: 5:95:1 v/v methanol-dichloromethane-acetic acid); ¹H-NMR (400 MHz, CDCl₃) δ 7.2 (quartet, 4H), 5.6-5.4 (m, 2H), 4.8 (t, 1H), 4.2 (t, 1H), 4.0-3.9 (m, 2H), 3.7 (s, 2H), 2.6-2.3 (m, 2H), 2.3-2.1 (m, 2H), 2.1-2.0 (m, 2H), 1.8-1.7 (m, 5H), 0.9 (t, 3H).

Examples 13A-13D

Scheme 9, Steps A, B, and C: Preparation of methyl 5-(3-((2R)-2-((3S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate (Example 13A) and methyl 5-(3-((2R)-2-((3R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate (Example 13B)

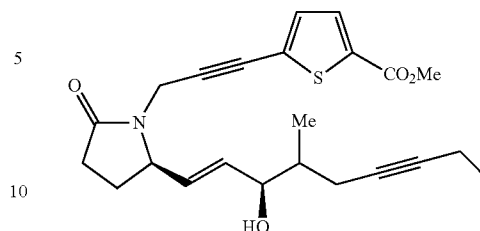


Example 13A

112

-continued

Example 13B



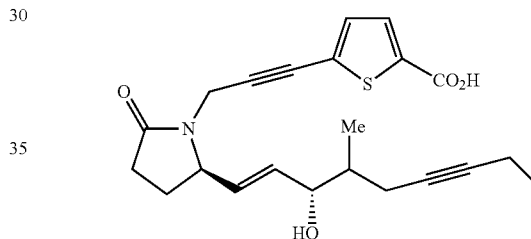
From the diastereomeric mixture of four isomers (76 mg), the diastereomeric mixtures of Example 13A and Example 13B were isolated following separation by prep HPLC.

Agilent Semi-Prep instrument; ultraviolet detector at 205 nm; Luna Silica 5μ 250 mm×10 mm column; mobile phase of 9:1 v/v heptane: ethanol.

Example 13A (18.7 mg); as a clear oil; HPLC retention time of 16.1-18.1 minutes; MS (APCI⁺) m/z 436.1 (M+23 (Na⁺))

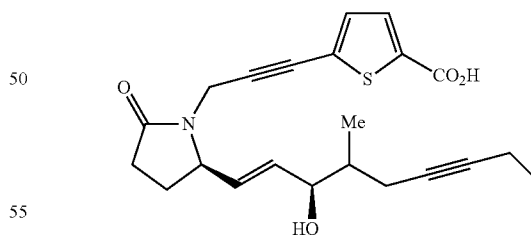
Example 13B (46.6 mg); as a clear oil; HPLC retention time of 13.4-15.1 minutes; MS (APCI⁺) m/z 436.1 (M+23 (Na⁺))

Scheme 9, Step D1: Preparation of 5-(3-((2R)-2-((3S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylic acid (Example 13C)



10.7 mg as an oil; TLC R_f 0.35 (solvent system 96:4:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 400.1 (M+1) (ESI⁻) m/z 398.0 (M-1)

Scheme 9, Step D2: Preparation of 5-(3-((2R)-2-((3R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylic acid (Example 13D)



35.6 mg as an oil; TLC R_f 0.35 (solvent system 96:4:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 400.1 (M+1) (ESI⁻) m/z 398.1 (M-1)

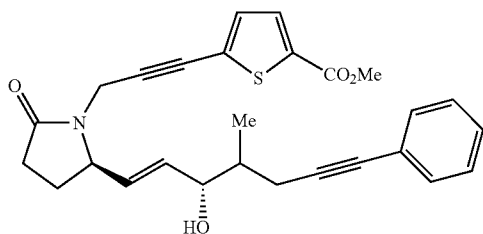
Example 14A-14D

Scheme 9, Steps A, B, and C: Preparation of methyl 5-(3-((2R)-2-((3S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate (14A) and methyl 5-(3-((2R)-2-((3R,

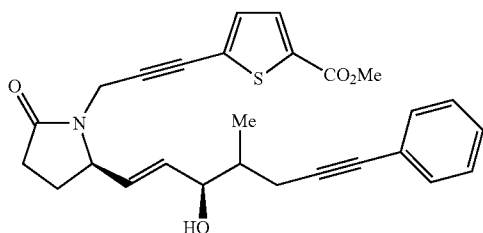
113

E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (14B)

Example 14A



Example 14B



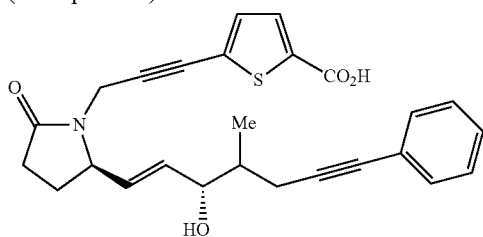
The diastereomeric mixtures of Example 14A and Example 14B were isolated following separation by prep HPLC.

Agilent Semi-Prep instrument; ultraviolet detector at 205 nm; Luna Silica 5 μ 250 mm \times 10 mm column; mobile phase of 9:1 v/v heptane: ethanol.

Example 14A (18.7 mg); as a clear oil; HPLC retention time of 16.1-18.1 minutes; MS (APCI⁺) m/z 436.1 (M+23 (Na⁺))

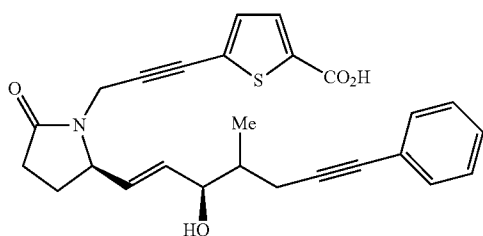
Example 14B (50.1 mg); as a clear oil; HPLC retention time of 13.4-15.1 minutes; MS (APCI⁺) m/z 436.1 (M+23 (Na⁺))

Scheme 9, Step D1: Preparation of 5-((Z)-3-((2R)-2-((3S, E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid (Example 14C)



14.4 mg as an oil; TLC R_f 0.35 (solvent system 96:4:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 400.1 (M+1) (ESI⁻) m/z 398.0 (M-1)

Scheme 9, Step D2: Preparation of 5-((Z)-3-((2R)-2-((3R, E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid (Example 14D)



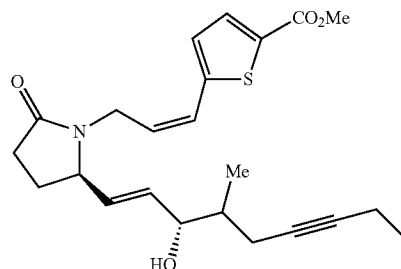
114

36.1 mg as an oil; TLC R_f 0.35 (solvent system 96:4:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 400.1 (M+1) (ESI⁻) m/z 398.1 (M-1)

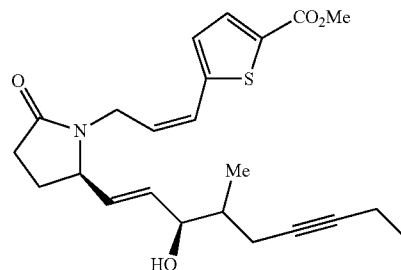
Examples 15A-15D

Scheme 9, Step A, B, and C: Preparation of methyl 5-((Z)-3-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (Example 15A) and methyl 5-((Z)-3-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (Example 15B)

Example 15A



Example 15B



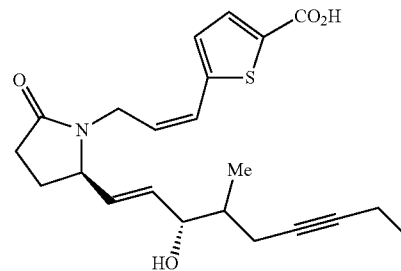
The diastereomeric mixtures of Example 15A and Example 15B were isolated following separation by prep HPLC.

Agilent Semi-Prep instrument; ultraviolet detector at 205 nm; Luna Silica 5 μ 250 mm \times 10 mm column; mobile phase of heptane-ethanol (93:7 v/v).

Example 15A (6.3 mg); as a clear oil; prep HPLC retention time 27-29.8 minutes; MS (APCI⁺) m/z 438 (M+23(Na⁺));

Example 15B (2.7 mg); as a clear oil; prep HPLC retention time 23.5-24.8 minutes; MS (APCI⁺) m/z 438 (M+23(Na⁺)).

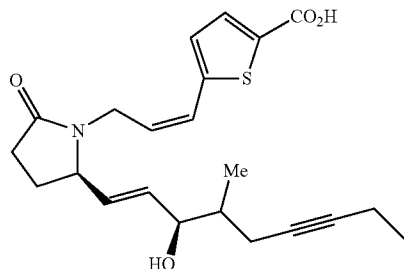
Scheme 9, Step D1: Preparation of 5-((Z)-3-((2R)-2-((3S, 4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid (Example 15C)



3.0 mg as a colorless oil; TLC R_f 0.30 (solvent system: 95:5:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 424 (M+Na).

115

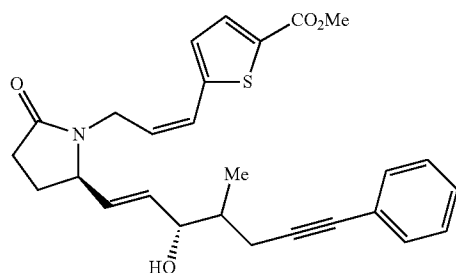
Scheme 9, Step D2: Preparation of 5-((Z)-3-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid (Example 15D)



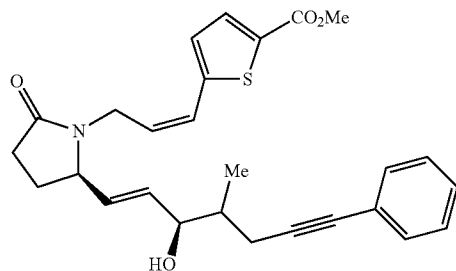
2.5 mg as a colorless oil; TLC R_f 0.30 (solvent system: 95:5:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 424 (M+23(Na⁺)).

Examples 16A-16D

Scheme 9, Step A, B, and C: Preparation of methyl 5-((Z)-3-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (Example 16A) and methyl 5-((Z)-3-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate (Example 16B)



Example 16A



Example 16B

The diastereomeric mixtures of Example 16A and Example 16B were isolated following separation by prep HPLC.

Agilent Semi-Prep instrument; ultraviolet detector at 205 nm; Luna Silica 5 μ 250 mm \times 10 mm column; mobile phase of heptane-ethanol (93:7 v/v).

Example 16A (23 mg); a clear oil; prep HPLC retention time 26.5-28.2 minutes; MS (APCI⁺) m/z 464 (M+1);

Example 16B (7.5 mg); a clear oil; prep HPLC retention time 23-24.8 minutes; MS (APCI⁺) m/z 464 (M+1).

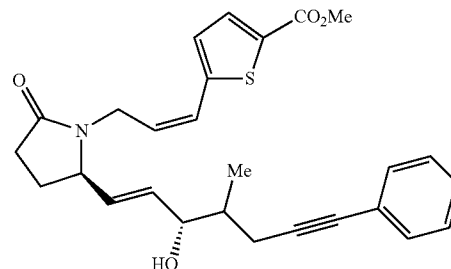
116

Scheme 9, Step D1: Preparation of 5-((Z)-3-((2R)-2-((3S,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid (Example 16C)

5

10

15

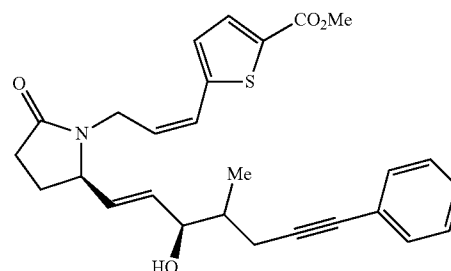


3.0 mg as a colorless oil; TLC R_f 0.35 (solvent system: 95:5:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁺) m/z 472 (M+23(Na⁺)).

20

25

Scheme 9, Step D2: Preparation of 5-((Z)-3-((2R)-2-((3R,4R/S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid (Example 16D)



30

35

40

2.5 mg as a colorless oil; TLC R_f 0.35 (solvent system: 95:5:1 v/v dichloromethane-methanol-acetic acid); MS (ESI⁻) m/z 448 (M-1).

Examples 17A-17E

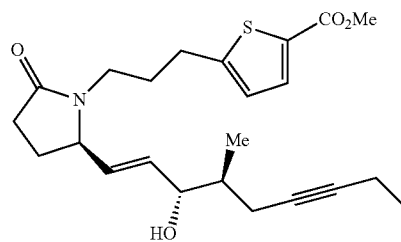
Scheme 9, Step A, B, and C: Preparation of methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 17A) and methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 17B) and

50

methyl 5-(3-((2R)-2-((3R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 17C)

55

Example 17A

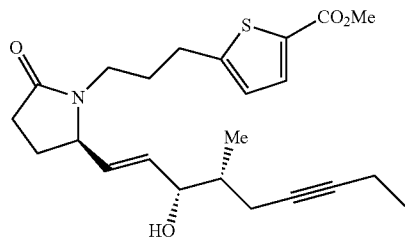


60

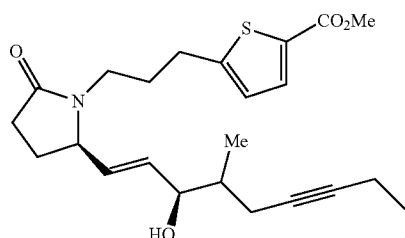
65

117

-continued



Example 17B



Example 17C

The stereoisomeric mixtures of Examples 17A, 17B, and 17C were isolated from the diastereomeric mixture of methyl 5-(3-((2R)-2-((E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)propyl)thiophene-2-carboxylate following separation by prep HPLC.

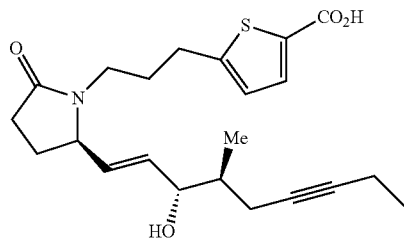
Agilent Semi-Prep instrument; ultraviolet detector at 205 nm; Luna Silica 5 μ 250 mm \times 10 mm column; mobile phase of heptane-ethanol (95:5 v/v).

Example 17A (4.9 mg); a clear oil; HPLC retention time 48.8-51.8 minutes; $^1\text{H-NMR}$ (CDCl_3) δ 7.6 (d, 1H), 6.8 (d, 1H), 5.7-5.6 (m, 1H), 5.6-5.5 (m, 1H), 4.2-4.1 (m, 2H), 3.85 (s, 3H), 3.7-3.5 (m, 1H), 3.0-2.9 (m, 1H), 2.9-2.8 (t, 2H), 2.5-2.1 (m, 6H), 2.0-1.7 (m, 5H), 1.1 (t, 3H), 0.95 (d, 3H); MS (ESI^+) m/z 418.1 (M+1), 440.1 (M+23(Na^+)).

Example 17B (7.2 mg); a clear oil; HPLC retention time 45.9-48.4 minutes; $^1\text{H-NMR}$ (CDCl_3) δ 7.6 (d, 1H), 6.8 (d, 1H), 5.7-5.6 (m, 1H), 5.6-5.5 (m, 1H), 4.3-4.2 (m, 1H), 4.1-4.2 (m, 1H), 3.85 (s, 3H), 3.7-3.5 (m, 1H), 3.0-2.9 (m, 1H), 2.9-2.8 (t, 2H), 2.5-2.1 (m, 6H), 2.0-1.7 (m, 5H), 1.1 (t, 3H), 0.95 (d, 3H); MS (ESI^+) m/z 418.1 (M+1), 440.1 (M+23 (Na^+)).

Example 17C (26.7 mg); a clear oil; HPLC retention time 34.1-36.9 minutes; $^1\text{H-NMR}$ (CDCl_3) δ 7.6 (d, 1H), 6.8 (d, 1H), 5.7-5.6 (m, 1H), 5.6-5.5 (m, 1H), 4.3-4.2 (m, 0.5H), 4.1-4.2 (m, 1.5H), 3.85 (s, 3H), 3.7-3.5 (m, 1H), 3.0-2.9 (m, 1H), 2.9-2.8 (t, 2H), 2.5-2.1 (m, 6H), 2.0-1.7 (m, 5H), 1.1 (t, 3H), 0.95 (d, 3H); MS (ESI^+) m/z 418.1 (M+1), 440.1 (M+23(Na^+)).

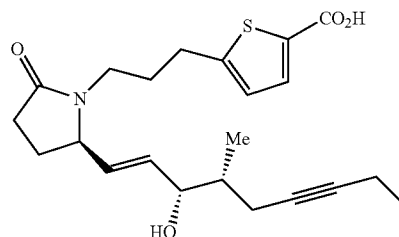
Scheme 9, Step D1: Preparation of 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)propyl)thiophene-2-carboxylic acid (Example 17D)



118

5-(3-((R)-2-((3S,4S,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17D) was prepared from methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 17A) by the method described in Step D1 for the preparation of Example 1C, to obtain the title compound (3.7 mg) as a colorless oil; TLC R_f 0.35 (solvent system: 96:4:1 v/v dichloromethane-methanol-acetic acid); $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H, $J=3.6$ Hz), 6.8 (d, 1H, $J=3.6$ Hz), 5.8-5.7 (m, 1H), 5.6-5.5 (m, 1H), 4.3-4.2 (m, 0.5H), 4.2-4.0 (m, 1.5H), 3.7-3.5 (m, 1H), 3.1-3.0 (m, 1H), 2.9-2.8 (m, 2H), 2.6-2.3 (m, 2H), 2.3-2.1 (m, 5H), 2.0-1.7 (m, 4H), 1.2-1.0 (m, 3H), 1.0-0.9 (m, 3H); MS (ESI^+) m/z 404.1 (M+1), (ESI^-) m/z 402.1 (M-1).

Scheme 9, Step D1: Preparation of 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17E)



20

25

30

35

40

45

50

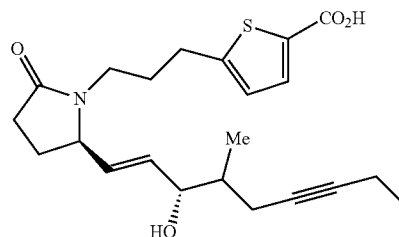
55

60

65

5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17E) is prepared from methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 17B) by the method described in Step D1 for the preparation of Example 1C.

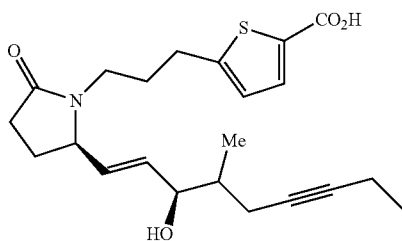
Scheme 9, Step D1: Preparation of 5-(3-((R)-2-((3S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17F)



5-(3-((R)-2-((3S,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17F) was prepared from methyl 5-(3-((R)-2-((3S,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate by the method described in Step D1 for the preparation of Example 1C, to obtain the title compound as a colorless oil; $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H, $J=3.6$ Hz), 6.8 (d, 1H, $J=3.6$ Hz), 5.8-5.7 (m, 1H), 5.6-5.5 (m, 1H), 4.3-4.2 (m, 0.5H), 4.2-4.0 (m, 1.5H), 3.7-3.5 (m, 1H), 3.1-3.0 (m, 1H), 2.9-2.8 (m, 2H), 2.6-2.3 (m, 2H), 2.3-2.1 (m, 5H), 2.0-1.7 (m, 4H), 1.2-1.0 (m, 3H), 1.0-0.9 (m, 3H); MS (ESI^-) m/z 402.1 (M-1).

Scheme 9, Step D2: Preparation of 5-(3-((R)-2-((3R,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17G)

119

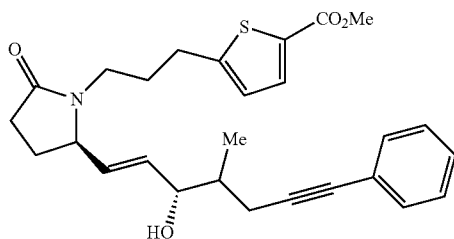


5-(3-((R)-2-((3R,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 17G) was prepared from methyl 5-(3-((R)-2-((3R,E)-3-Hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 17C) by the method described in Step D1 for the preparation of Example 1C, to obtain the title compound as a colorless oil; $^1\text{H-NMR}$ (CDCl_3) δ 7.7 (d, 1H, $J=3.6$ Hz), 6.8 (d, 1H, $J=3.6$ Hz), 5.8-5.7 (m, 1H), 5.6-5.5 (m, 1H), 4.2-4.0 (m, 2H), 3.7-3.5 (m, 1H), 3.1-3.0 (m, 1H), 2.9-2.8 (m, 2H), 2.6-2.3 (m, 2H), 2.3-2.1 (m, 5H), 2.0-1.7 (m, 4H), 1.2-1.0 (m, 3H), 1.0-0.9 (m, 3H); MS (ESI^-) m/z 402.1 ($M-1$).

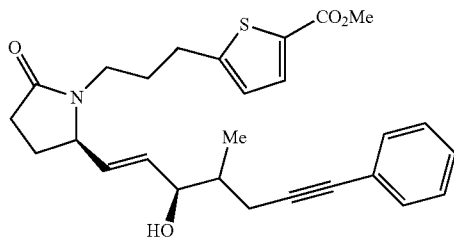
Examples 18A-18D

Scheme 9, Steps A, B, and C: Preparation of methyl 5-(3-((2R)-2-((3S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 18A) and methyl 5-(3-((2R)-2-((3R,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate (Example 18B)

Example 18A



Example 18B



The diastereomeric mixtures of Example 18A and Example 18B were isolated following separation by prep HPLC.

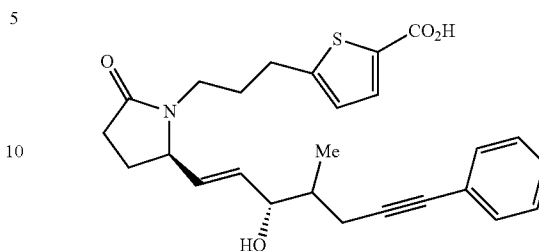
Agilent Semi-Prep instrument; ultraviolet detector at 205 nm; Luna Silica 5μ 250 mm \times 10 mm column; mobile phase of heptane-ethanol (90:10 v/v).

Example 18A (15.4 mg); a clear oil; prep HPLC retention time 21.5-24.5 minutes; MS (ESI^+) m/z 466.1 ($M+1$), 488.1 ($M+23(\text{Na}^+)$)

Example 18B (38.2 mg); a clear oil; prep HPLC retention time 17.1-20.2 minutes; MS (ESI^+) m/z 466.1 ($M+1$), 488.1 ($M+23(\text{Na}^+)$)

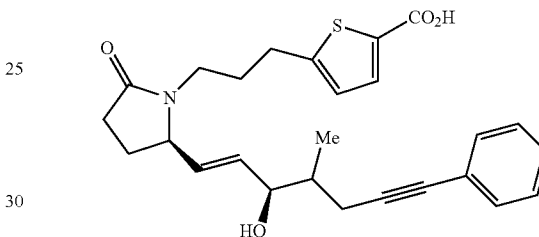
120

Scheme 9, Step D1: 5-(3-((2R)-2-((3S,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 18C)



9.8 mg as a colorless oil; TLC R_f 0.35 (solvent system: 96:4:1 v/v dichloromethane-methanol-acetic acid); MS (ESI^-) m/z 450.1 ($M-1$).

Scheme 9, Step D2: 5-(3-((2R)-2-((3R,E)-3-hydroxy-4-methyl-7-phenylhept-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid (Example 18D)



28.9 mg as a colorless oil; TLC R_f 0.35 (solvent system: 96:4:1 v/v dichloromethane-methanol-acetic acid); MS (ESI^-) m/z 450.1 ($M-1$).

Example 19

Radioligand Binding Assay for the Evaluation of the Affinity of Compounds for the Agonist Site of the Human Prostanoid EP_4 Receptor in Transfected HEK-293 Cells

Assay Volume and Format:

200 μl in 96-well plate

Cell membrane homogenates (20 μg protein) are incubated for 120 min at 22 $^\circ$ C. with 0.5 nM [^3H]PGE $_2$ in the absence or presence of the test compound in a buffer containing 10 mM MES/KOH (pH 6.0), 10 mM MgCl_2 and 1 mM EDTA.

Nonspecific binding is determined in the presence of 10 μM PGE $_2$.

Following incubation, the samples are filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters are dried then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard).

The standard reference compound is PGE $_2$, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} is calculated.

Example 20

Functional Cellular Assays (STEP Plate Format)

Both SEAP activity assay and cAMP level assay for EP_2 or EP_4 agonist were performed on EP_2/EP_4 STEP (Surface

121

Transfection and Expression Protocol) plates (from Origimus®) which are coated with both rat EP₂ or EP₄ receptor and secreted alkaline phosphatase (SEAP) reporter constructs. Cells grown on the STEP complex will express EP₂ or EP₄ at the cell surface. Binding of agonists to EP₂ or EP₄ initiates a signal transduction cascade results in a transient increase in cAMP and an increase in expression of SEAP which is secreted into the cell culture media. cAMP levels were then measured with an ELISA assay and SEAP activity was measured with a luminescence-based alkaline phosphatase substrate.

Procedure of SEAP Activity Assay for EP₂/EP₄ Agonist

1. Seed cells on an EP₂ or EP₄ STEP plate at a density of 40,000-80,000 cells/well in 200 μ l of reduced serum medium containing 0.5% FBS. Place the plate in a 37° C. incubator with 5% CO₂ and incubate overnight.

2. After 16-18 hours of incubation, aspirate the culture media from each well.

3. Add 200 μ l of culture medium containing different concentration of test compounds to the assigned wells. For each test compound, at least 8 concentrations starting at highest 10 μ M and lowest 0.01 pM were tested. In addition each concentration had triplicates. A PGE₂ curve (concentrations from lowest to highest, 0 pM, 0.384 pM, 1.92 pM, 9.6 pM, 48 pM, 240 pM, 1200 pM, and 6000 pM) was always run in parallel with test compounds.

4. After 6-8 hours of stimulation with test compounds and PGE₂, 10 μ l of culture media from each well was transferred to a corresponding well of a 96-well solid black plate. Cover the plate with the lid.

5. Inactivate the endogenous alkaline phosphatase by heating the samples at 65° C. for 30 minutes.

6. Add 50 μ l of luminescence-based alkaline phosphatase substrate (Michigan Diagnostics, LLC, Cat#SAP450101) to each well.

7. Measure the SEAP (secreted alkaline phosphatase) activity by reading the luminescent signal from each well with a TeCan Safire² microplate detection system (measures fluorescence) to measure activity.

8. The data was analyzed and the EC₅₀ for PGE₂ and each test compound was calculated using GraphPad Prism 5.

122

Procedure of cAMP Assay for EP₂/EP₄ Agonist

1. Seed cells on an EP₂ or EP₄ STEP plate at a density of 40,000-80,000 cells/well in 200 μ L of reduced serum medium containing 0.5% FBE. Place the plate in a 37° C. incubator with 5% CO₂ and incubate overnight.

2. After 16-18 hours of incubation, aspirate the culture media from each well.

3. Add 200 μ l of culture medium containing 500 μ M IBMX (an inhibitor of cAMP phosphodiesterase) and different concentration of test compounds to the assigned wells. For each test compound, at least 8 concentrations starting at highest 10 μ M and lowest 0.01 pM were tested. In addition each concentration had triplicates. A PGE₂ curve (concentrations from lowest to highest, 0 pM, 0.384 pM, 1.92 pM, 9.6 pM, 48 pM, 240 pM, 1200 pM, and 6000 pM) was always run in parallel with test compounds.

4. Incubate the cells in a cell culture incubator for 30 minutes.

5. Centrifuge the plate at 1,000 \times rpm for 10 minutes.

6. Aspirate the supernatant.

7. Add 100 μ L of EIA assay buffer to each well and put the plate with the lid in a -80° C. freezer. Freeze the sample in the -80° C. for at least one hour.

8. Take the plate out from the -80° C. freezer and leave it at room temperature to thaw completely.

9. Centrifuge the plate at 1,000 \times rpm for 10 minutes.

10. Pick up 50 μ l of supernatant from each well for cAMP level measurement, using an ELISA assay kit from Cayman chemical, Item #581001.

11. The data was analyzed and the EC₅₀ for PGE₂ and each test compound was calculated using GraphPad Prism 5.

Specificity of EP₂/EP₄ Agonist on the Receptors

Compounds demonstrating potency in SEAP or cAMP functional assays were confirmed for receptor agonist specificity by incubation of the cells with the compound together with an EP₂ specific antagonist AH-6809 or an EP₄ specific antagonist L-161,982. Compounds that showed agonist activity for either EP₂ or EP₄ are specific if the stimulation effect was diminished when incubated together with their receptor specific antagonist.

TABLE 1

Example No.	Absolute Configuration		R ⁹	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
PGE ₂				0.38 \pm 0.07 (N = 10)	0.14 \pm 0.02 (N = 10)	0.48 \pm 0.36 (N = 22)	0.05 \pm 0.03 (N = 38)	59 \pm 17 (N = 15)
PGE ₁						0.22 \pm 0.04 (N = 5)		16.5

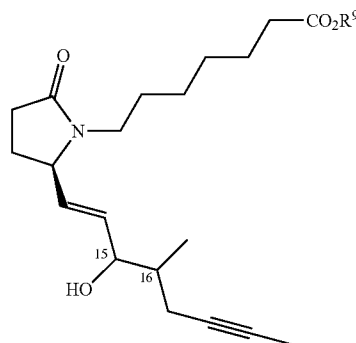
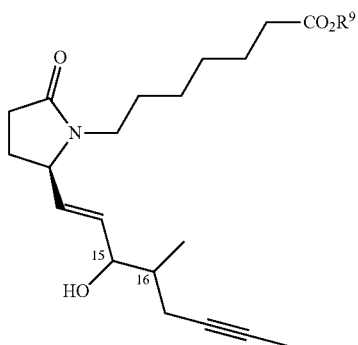


TABLE 1-continued

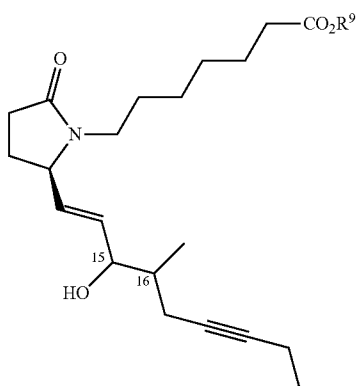


Example No.	Absolute Configuration		R ⁹	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
1A	α	α/β	Me					
1B	β	α/β	Me					
1C	α	α/β	H	86% @ 100 nM			0.67	760
1D	β	α/β	H	11% @ 100 nM			4.82	>10,000
1E	α	β	H	3.9	1.5	2.98	0.57 ± 0.00 (N = 2)	800
1F	α	α	H	18	6.9		5.79	184

α = or

β = or

TABLE 2

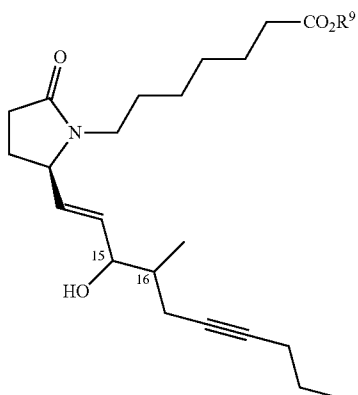


Example No.	Absolute Configuration		R ⁹	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
2A	α	α/β	Me					
2B	β	α/β	Me					
2C	α	α/β	H	4.0	1.5		0.064	905
2D	β	α/β	H				0.145	1,420
2E	α	β	H	3.0	1.1	0.96 ± 0.46 (N = 5)	0.19 ± 0.07 (N = 10)	>1,000
2F	α	α	H				1.06 ± 0.11 (N = 2)	

α = or

β = or

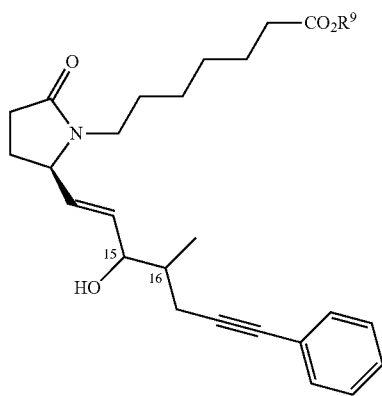
TABLE 3



Example No.	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
3A	α	α/β	Me				8.64	2,485
3B	β	α/β	Me				223.1	>10,000
3C	α	α/β	H				0.085	2,260
3D	β	α/β	H				29.03	>10,000

α = / or /
β = / or /

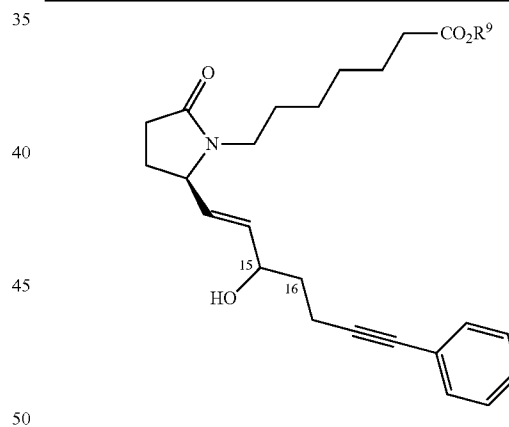
TABLE 4



Example No.	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
4A	α	α/β	Me					
4B	β	α/β	Me					
4C	α	α/β	H				2.49	830
4D	β	α/β	H					

α = / or /
β = / or /

TABLE 5



Example No.	Absolute Configuration		R ⁹	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
5A	α	Me					77.7	>10,000
5B	β	Me					41.5	>5,000
5C	α	H					110.9	>1,000
5D	β	H					46.8	>5,000

α = / or /
β = / or /

127
TABLE 6

Example No.	Configuration	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
6A	α	Me			6.71	>3,000
6B	β	Me				>2,000
6C	α	H			4.73	>1,000
6D	β	H			4.79	>1,000

α = / or /
β = / or /

TABLE 7

Example No.	Configuration	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
7A	α	Me				
7B	β	Me				
7C	α	H			22.3	>10,000
7D	β	H				

α = / or /
β = / or /

128
TABLE 8

Example No.	Configuration	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
8A	α	α/β	Me			6.74 364
8B	β	α/β	Me			1,640
8C	α	α/β	H	1.3	0.47	0.19 120
8D	β	α/β	H			13.4 1,130

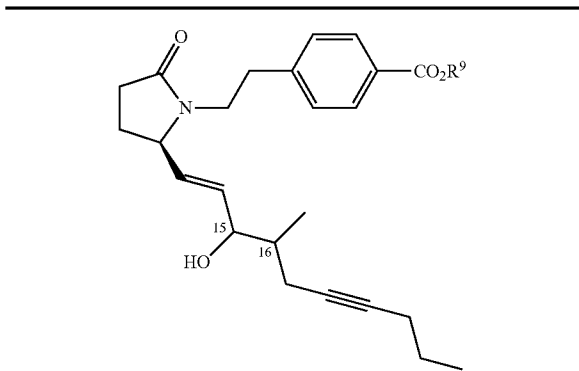
α = / or /
β = / or /

TABLE 9

Example No.	Configuration	hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
9A	α	β	Et			
9B	β	β	Et			
9C	α	β	H	0.67	0.25	0.31 0.020 ± 0.017 >1,000 (N = 4)
9D	β	β	H			

α = / or /
β = / or /

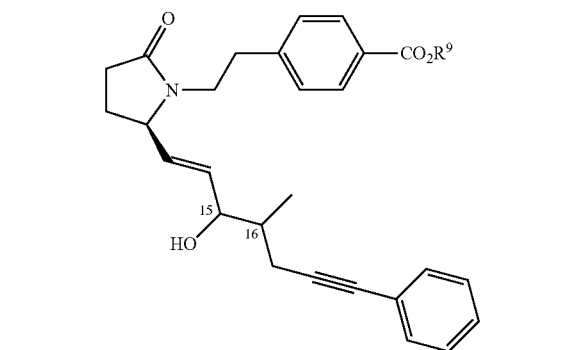
129
TABLE 10



Example	Configuration	Absolute		hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		C-15	C-16	IC ₅₀	K _i	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
No.	C-15	C-16	R ⁹	(nM)	(nM)	EP ₄	EP ₄	EP ₂
10A	α	α/β	Et					
10B	β	α/β	Et					
100	α	α/β	H					
10D	β	α/β	H					

α = / or /
β = / or /

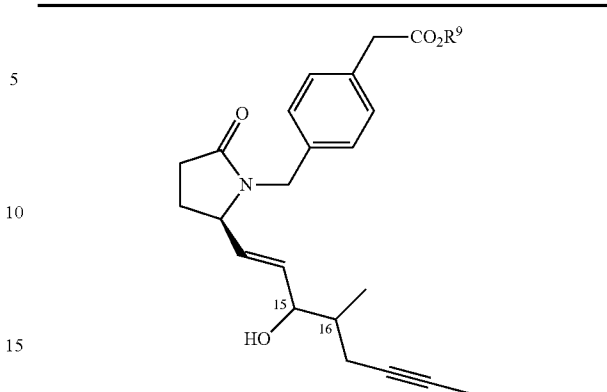
TABLE 11



Example	Configuration	Absolute		hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		C-15	C-16	IC ₅₀	K _i	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
No.	C-15	C-16	R ⁹	(nM)	(nM)	EP ₄	EP ₄	EP ₂
11A	α	α/β	Me					
11B	β	α/β	Me					
11C	α	α/β	H			0.054	2,960	
11D	β	α/β	H			3.51	1,750	

α = / or /
β = / or /

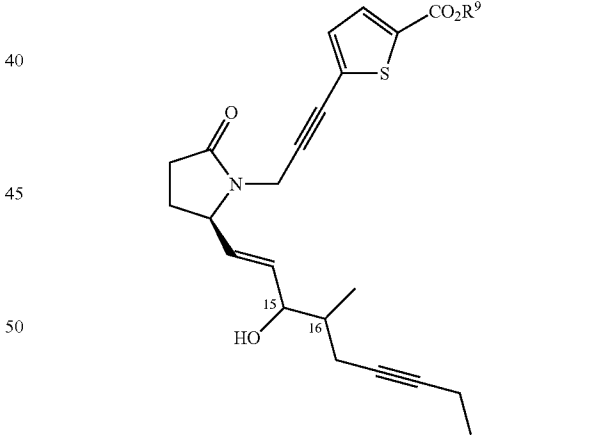
130
TABLE 12



Example	Configuration	Absolute		hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		C-15	C-16	IC ₅₀	K _i	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
No.	C-15	C-16	R ⁹	(nM)	(nM)	EP ₄	EP ₄	EP ₂
12A	α	α/β	Me					
12B	β	α/β	Me					
12C	α	α/β	H				2,290	>10,000
12D	β	α/β	H				>10,000	>10,000

α = / or /
β = / or /

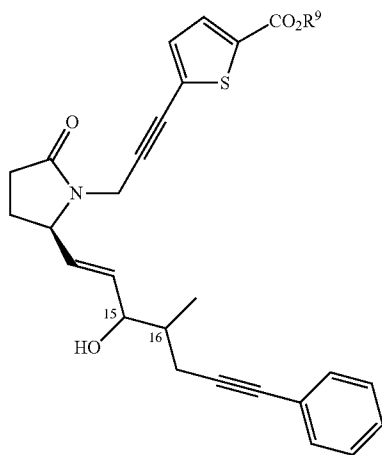
TABLE 13



Example	Configuration	Absolute		hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
		C-15	C-16	IC ₅₀	K _i	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
No.	C-15	C-16	R ⁹	(nM)	(nM)	EP ₄	EP ₄	EP ₂
13A	α	α/β	Me					
13B	β	α/β	Me					
13C	α	α/β	H				18.3	>10,000
13D	β	α/β	H					>10,000

α = / or /
β = / or /

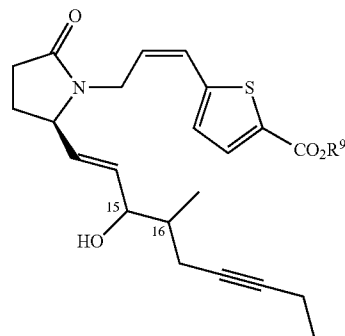
131
TABLE 14



Example	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)			
	No.	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
14A		α	α/β	Me					
14B		β	α/β	Me					
14C		α	α/β	H			>100	>10,000	
14D		β	α/β	H				>10,000	

α = / or //
β = / or //

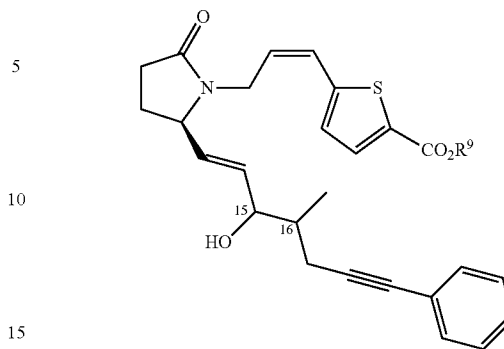
TABLE 15



Example	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)			
	No.	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
15A		α	α/β	Me					
15B		β	α/β	Me					
15C		α	α/β	H			947	>10,000	
15D		β	α/β	H			1,600	>10,000	

α = / or //
β = / or //

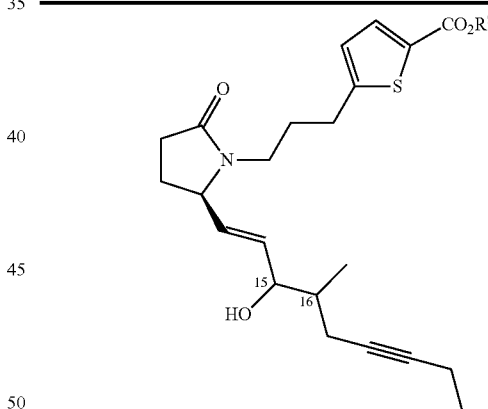
132
TABLE 16



Example	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)			
	No.	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
25	16A	α	α/β	Me					
	16B	β	α/β	Me					
	16C	α	α/β	H				67.2	>10,000
	16D	β	α/β	H				1,200	>10,000

30 α = / or //
β = / or //

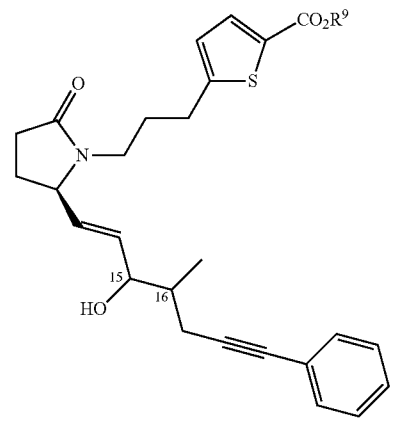
TABLE 17



Example	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)			
	No.	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
55	17A	α	β	Me					
	17B	α	α	Me					
	17C	β	α/β	Me					
60	17D	α	β	H	6.1	2.3	1.54	0.32	5,300
	17E	α	α	H					
	17F	α	α/β	H				0.091	>10,000
	17G	β	α/β	H				18.4	>10,000

65 α = / or //
β = / or //

TABLE 18



Example No.	Absolute Configuration			hEP ₄ receptor binding		STEP cell functional assay EC ₅₀ s (nM)		
	C-15	C-16	R ⁹	IC ₅₀ (nM)	K _i (nM)	cAMP/EP ₄	SEAP/EP ₄	SEAP/EP ₂
18A	α	α/β	Me					
18B	β	α/β	Me					
18C	α	α/β	H				<0.01	>10,000
							(75% agonist response vs PGE ₂)	
18D	β	α/β	H				2.03	>10,000
18E	α	β	H					
18F	α	α	H					

α = / or /
β = \ or \

Example 21

Accelerated Healing of a Calvarial Bone Defect by Example 2E

The rat calvarial defect model is a widely used model through which the ability of a treatment agent to induce bone formation is assessed (Aghaloo et al., The effect of NELL1 and bone morphogenetic protein-2 on calvarial bone regeneration, *J. Oral Maxillofac. Surg.*, 2010, 68, 300-308; Mark et al., Repair of calvarial nonunions by osteogenin, a bone-inductive protein, *Plast. Reconstr. Surg.*, 1990, 86, 623-30).

Bone defects are created by removal of bone from the cranium of female Sprague Dawley rats by a bone trephine (cranial defect). Cranial defects are 2.6 mm in diameter and the cranium approximately 1 mm thick. A matrix of approximately 2 mm thickness is applied to the defect. Thus the dosing volume for each defect is calculated as $\pi r^2 \times \text{matrix thickness} = 3.14 \times 1.3^2 \times 2 = 10.61 \mu\text{l}$ and rounded to 11 μl for purposes of dose calculation.

Example 2E is delivered set inside calcium phosphate cement that, after loading with drug and setting, is ground to a fine powder and suspended in demineralized bone matrix at a ratio of 1:8 (weight/volume). Example 2E is tested at one dose of 3 mg/ml with five rats in the test group. A negative control group treated with dosing matrix containing no drug (Vehicle) is also included in the study.

Calcium Phosphate cement powders may be combinations of α -tri-calcium phosphate, β -tri-calcium phosphate and hydroxyapatite; combinations of Dicalcium Phosphate and Tetracalcium Phosphate; or a commercially available calcium phosphate cement. Commercially available Human demineralized bone matrix, Puros Demineralized Bone Matrix Bone Putty manufactured by RTI Biologics (Ala-

chua, Fla.) using the Urist & Dowell method, is used in the studies described. Demineralized bone matrix can also be made by the method described by Urist & Dowell (Inductive Substratum for Osteogenesis in Pellets of Particulate Bone Matrix, *Clin. Orthop. Relat. Res.*, 1968, 61, 61-78.)

Dosing solutions are made from a 10 mg/ml Example 2E stock which is made by dissolving 2.07 mg of neat Example 2E in 207 μl of 100% ethanol.

The dosing volume of a single defect is 11 μl . Thus for each group of five rats the total treatment volume is 55 μl . The ratio of calcium phosphate cement to volume is 1:8 thus for each group of five rats 6.8 mg of calcium phosphate cement was used.

The dosing solution for Example 2E was made by adding 18 μl of the 5 mg/ml stock to 6.8 mg of calcium phosphate cement powder. The Vehicle dosing solution was made by adding 18 μl of ethanol containing no Example 2E to 6.8 mg of calcium phosphate cement powder.

After the ethanol had been vented off, the cement was wetted with a setting solution and mixed thoroughly for 1 minute as the cement begins to set. The cement was allowed to set overnight at room temperature before being ground to a fine powder in a mortar and pestle.

Following grinding the cement was added to 55 μl of demineralized bone matrix (DBM) and thoroughly mixed using two spatulas. The cement-DBM mix was rolled into a single length of material of equal thickness and using a ruler as a guide cut into five equal length pieces. The dosing matrix was placed in a test subject within four hours of mixing the cement with the DBM.

Immediately after creation the bone defect was filled with dosing matrix containing no drug (Vehicle) or 3 mg/ml of Example 2E. The operation area was closed and sutured and the animal was allowed to recover. Eight weeks after the beginning of treatment each rat was anaesthetized with isoflurane and the defect area was imaged using a cone beam dental CT scanner (Vatech Pax-Duo3D).

The area measured at eight weeks was compared to the area of the original defect and the degree of repair calculated by the following formula:

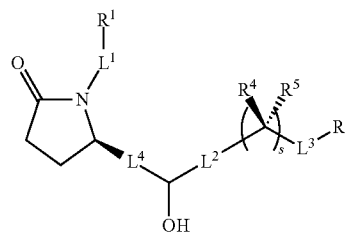
$$(\text{original area} - \text{current area}) / \text{original area} * 100$$

The mean repair for each group after eight weeks of treatment is shown in the FIG. 1.

The above description of the examples and embodiments of the invention is merely exemplary in nature and, thus, variations thereof are not to be regarded as a departure from the spirit and scope of the invention.

We claim:

1. A compound of formula (Ia)



or a pharmaceutically acceptable salt thereof, wherein:

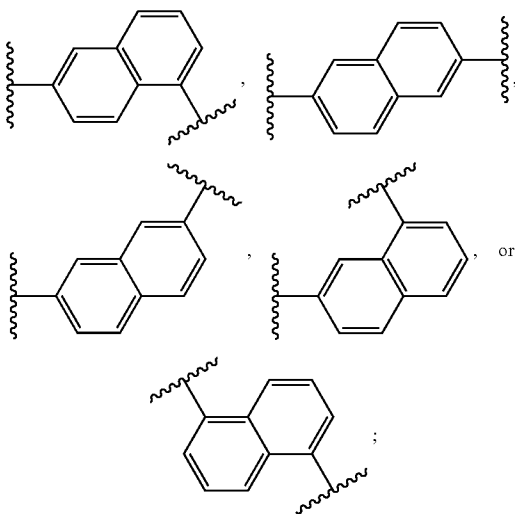
L¹ is

a) C₃-C₇alkylene, C₃-C₇alkenylene, or C₃-C₇alkynylene, wherein the C₃-C₇alkylene, C₃-C₇alkenylene, or C₃-C₇alkynylene are each optionally substituted with 1, 2, 3, or 4 fluoro substituents;

135

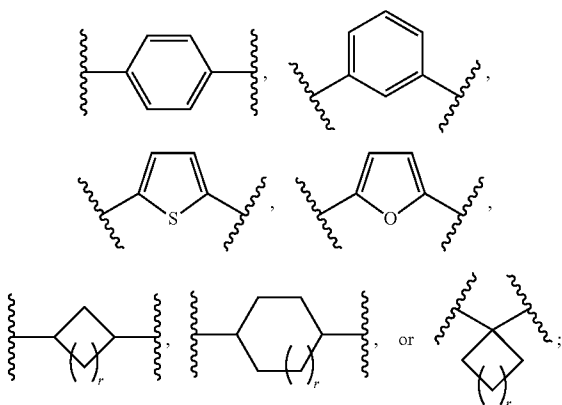
- b) $-(CH_2)_t-G-(CH_2)_p-$; wherein t is 0, 1, or 2, p is 0, 1, 2, or 3, and $t+p=0, 1, 2, 3, \text{ or } 4$; or
 c) $-(CH_2)_n-G^1-(CH_2)_p-$, $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$, or $-(CH_2)_n-C(R^{12})=C(R^{12})-G^2-$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5, \text{ or } 6$;

G is



G^1 is O, C(O), S, S(O), S(O)₂, or NR⁷; wherein R⁷ is H, C₁-C₄ alkyl, or C₁-C₄alkylcarbonyl;

G^2 is



wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₄alkyl, C₁-C₃haloalkyl, cyano, halogen, C₁-C₃alkoxy, and C₁-C₃haloalkoxy;

R¹ is COOR⁹, CONR⁹R¹⁰, CH₂OR⁹, SO₃R⁹, SO₂NR⁹R¹⁰, PO(OR⁹)₂, or tetrazol-5-yl;

R⁹ is H, C₁-C₄ alkyl, or aryl;

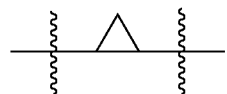
R¹⁰ is H, C₁-C₄ alkyl, COR¹¹, OR⁹, or SO₂R¹¹;

R¹¹ is C₁-C₄ alkyl;

R¹², at each occurrence, is independently H or C₁-C₄alkyl;

136

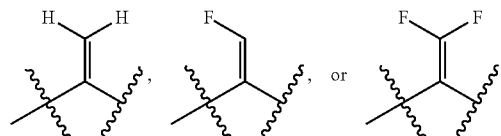
L⁴ is C(R²)₂-C(R³)₂-, -C(R²)=C(R³)-, -C≡C-, or



10 wherein R² and R³ are each H, CH₃, fluoro, or chloro; L² is a bond;

R⁴ and R⁵ are each independently H, F, CF₃, or C₁-C₄ alkyl; or R⁴ and R⁵ together with the carbon to which they are attached form a C₃-C₅ cycloalkyl,

15



20

L³ is -C≡C- or -CH₂-C≡C-;

25 R⁶ is aryl, heteroaryl, heterocyclyl, C₁-C₁₀alkyl, C₃-C₈cycloalkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₁-C₁₀haloalkyl, C₃-C₈halocycloalkyl, C₂-C₁₀haloalkenyl, or C₂-C₁₀haloalkynyl; wherein the aryl and heteroaryl are optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of C₁-C₄alkyl, C₁-C₃haloalkyl, cyano, halogen, C₁-C₃alkoxy, C₁-C₃haloalkoxy; and -C₁-C₃alkylene-C₁-C₃alkoxy; and wherein the C₁-C₁₀alkyl, C₃-C₈alkenyl, C₂-C₁₀alkynyl, C₁-C₁₀haloalkyl, C₃-C₈halocycloalkyl, C₂-C₁₀haloalkenyl, and C₂-C₁₀haloalkynyl are optionally substituted with a substituent selected from the group consisting of COOR⁹, CONR⁹R¹⁰, CH₂OR⁹, SO₃R⁹, SO₂NR⁹R¹⁰, PO(OR⁹)₂, and tetrazol-5-yl;

30

R⁹ is H, C₁-C₄ alkyl, or aryl;

R¹⁰ is H, C₁-C₄ alkyl, COR¹¹, OR⁹, or SO₂R¹¹;

R¹¹ is C₁-C₄ alkyl;

r is 0 or 1; and

s is 0 or 1.

35

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

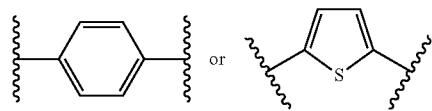
L¹ is

a) C₃-C₇alkylene, wherein the C₃-C₇alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents; or

40

c) $-(CH_2)_n-G^2-(CH_2)_p-$, $-(CH_2)_n-C\equiv C-G^2-$, or $-(CH_2)_n-C(H)=C(H)-G^2-$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5, \text{ or } 6$;

G^2 is



wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₄alkyl, C₁-C₃haloalkyl, cyano, halogen, C₁-C₃alkoxy, and C₁-C₃haloalkoxy;

65

R¹ is COOR⁹; and

R⁹ is H or C₁-C₄ alkyl.

137

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

L^4 is $-\text{C}(\text{R}^2)=\text{C}(\text{R}^3)-$;

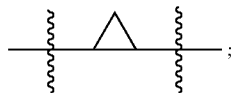
R^2 and R^3 are each hydrogen;

R^4 and R^5 are independently H or $\text{C}_1\text{-C}_4$ alkyl;

and R^6 is aryl or $\text{C}_1\text{-C}_{10}$ alkyl, wherein the aryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, cyano, halogen, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy; and $-\text{C}_1\text{-C}_3$ alkylene- $\text{C}_1\text{-C}_3$ alkoxy.

4. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein:

L^4 is $-\text{C}(\text{R}^2)_2-\text{C}(\text{R}^3)_2-$, $-\text{C}(\text{R}^2)=\text{C}(\text{R}^3)-$, $-\text{C}\equiv\text{C}-$, or



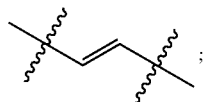
wherein R^2 and R^3 are each H, CH_3 , fluoro, or chloro;

R^4 and R^5 are each independently H, F, CF_3 , or $\text{C}_1\text{-C}_4$ alkyl; or R^4 and R^5 together with the carbon to which they are attached form a $\text{C}_3\text{-C}_5$ cycloalkyl; and

R^6 is aryl, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, $\text{C}_1\text{-C}_{10}$ haloalkyl, $\text{C}_3\text{-C}_8$ halocycloalkyl, $\text{C}_2\text{-C}_{10}$ haloalkenyl, or $\text{C}_2\text{-C}_{10}$ haloalkynyl, wherein the aryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, cyano, halogen, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy; and $-\text{C}_1\text{-C}_3$ alkylene- $\text{C}_1\text{-C}_3$ alkoxy.

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein:

L^4 is



R^4 and R^5 are independently H or $\text{C}_1\text{-C}_4$ alkyl;

R^6 is aryl or $\text{C}_1\text{-C}_{10}$ alkyl, wherein the aryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, cyano, halogen, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy; and $-\text{C}_1\text{-C}_3$ alkylene- $\text{C}_1\text{-C}_3$ alkoxy.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein:

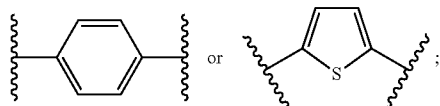
R^4 and R^5 are independently H or CH_3 ;

L^1 is

a) $\text{C}_3\text{-C}_7$ alkylene; or

c) $-(\text{CH}_2)_n\text{-G}^2\text{-(CH}_2)_p-$, $-(\text{CH}_2)_n\text{-C}\equiv\text{C-G}^2-$, or $-(\text{CH}_2)_n\text{-C(H)=C(H)-G}^2-$, wherein n is 1, 2 or 3; p is 0, 1, or 2, and $n+p=1, 2, 3$, or 4;

G^2 is



R^6 is phenyl or $\text{C}_1\text{-C}_6$ alkyl, wherein the phenyl is optionally substituted with 1, 2, 3, or 4 substituents selected

138

from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, cyano, halogen, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ haloalkoxy; and $-\text{C}_1\text{-C}_3$ alkylene- $\text{C}_1\text{-C}_3$ alkoxy.

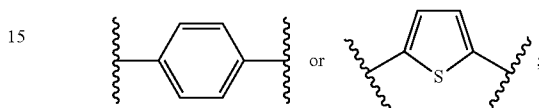
7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is

a) n-hexylene; or

c) $-(\text{CH}_2)_n\text{-G}^2\text{-(CH}_2)_p-$, $-\text{CH}_2\text{-C}\equiv\text{C-G}^2-$, or $-\text{CH}_2\text{-C(H)=C(H)-G}^2-$, wherein n is 1, 2 or 3; p is 0 or 1, and $n+p=2$ or 3;

G^2 is



R^1 is COOR^9 ;

R^9 is H or CH_3 ;

and

R^6 is phenyl, methyl, ethyl, or propyl.

8. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein:

L^3 is $-\text{CH}_2\text{-C}\equiv\text{C}-$; and

s is 1.

9. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein:

L^3 is $-\text{C}\equiv\text{C}-$; and

s is 0.

10. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein:

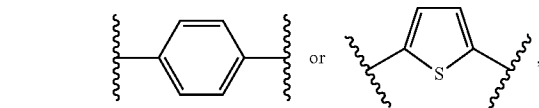
L^1 is $\text{C}_3\text{-C}_7$ alkylene, wherein the $\text{C}_3\text{-C}_7$ alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents.

11. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is

c) $-(\text{CH}_2)_n\text{-G}^2\text{-(CH}_2)_p-$, $-(\text{CH}_2)_n\text{-C}\equiv\text{C-G}^2-$, or $-(\text{CH}_2)_n\text{-C(H)=C(H)-G}^2-$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5$, or 6;

G^2 is



wherein G^2 is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ haloalkyl, cyano, halogen, $\text{C}_1\text{-C}_3$ alkoxy, and $\text{C}_1\text{-C}_3$ haloalkoxy; and

R^4 is $\text{C}_1\text{-C}_4$ alkyl and R^5 is H, or R^4 is H and R^5 is $\text{C}_1\text{-C}_4$ alkyl.

12. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein:

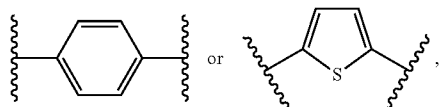
L^1 is $\text{C}_3\text{-C}_7$ alkylene, wherein the $\text{C}_3\text{-C}_7$ alkylene is optionally substituted with 1, 2, 3, or 4 fluoro substituents.

13. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein:

L^1 is

c) $-(\text{CH}_2)_n\text{-G}^2\text{-(CH}_2)_p-$, $-(\text{CH}_2)_n\text{-C}\equiv\text{C-G}^2-$, or $-(\text{CH}_2)_n\text{-C(H)=C(H)-G}^2-$, wherein n is 1, 2, 3, 4, or 5, p is 0, 1, 2, or 3, and $n+p=1, 2, 3, 4, 5$, or 6;

139

G² is

wherein G² is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C₁-C₄alkyl, C₁-C₃haloalkyl, cyano, halogen, C₁-C₃alkoxy, and C₁-C₃haloalkoxy; and

R⁴ is C₁-C₄ alkyl and R⁵ is H, or R⁴ is H and R⁵ is C₁-C₄ alkyl.

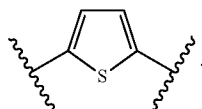
14. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein:

L¹ is C₃-C₇alkylene; and

R⁴ is C₁-C₄ alkyl and R⁵ is H, or R⁴ is H and R⁵ is C₁-C₄ alkyl.

15. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:

G² is



16. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein:

L³ is —CH₂—C≡C—;

R⁴ is methyl and R⁵ is H, or R⁴ is H and R⁵ is methyl; and s is 1.

17. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein:

L³ is —C≡C—;

R⁴ is methyl and R⁵ is H, or R⁴ is H and R⁵ is methyl; and s is 0.

18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

(Z)-methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-enoate;

methyl 4-((2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)thio)butanoate;

methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;

methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;

methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate;

methyl 5-((Z)-3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate;

methyl 4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate;

140

methyl 3-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)benzoate;

7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

(Z)-7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-enoic acid;

4-((2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)thio)butanoic acid;

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;

5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylic acid;

5-((Z)-3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylic acid;

4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoic acid;

3-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)benzoic acid;

methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

(Z)-methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-enoate;

methyl 4-((2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)thio)butanoate;

methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;

methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;

methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylate;

methyl 5-((Z)-3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-en-1-yl)thiophene-2-carboxylate;

methyl 4-(2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)benzoate;

methyl 3-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)benzoate;

7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;

(Z)-7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-enoic acid;

4-((2-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)ethyl)thio)butanoic acid;

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;

5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;

5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)prop-1-yn-1-yl)thiophene-2-carboxylic acid;

7-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((S)-2-((3S,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((S)-2-((3S,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 ethyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 isopropyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 N-ethyl-7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanamide;
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)-N-(methylsulfonyl)heptanamide;
 (R)-1-(6-(1H-tetrazol-5-yl)hexyl)-5-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)pyrrolidin-2-one;
 (R)-5-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-1-(7-hydroxyheptyl)pyrrolidin-2-one;
 methyl 7-((R)-2-((3S,4S,E)-4-ethyl-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((3R,4R,E)-3-hydroxy-4-isopropylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((R,E)-3-hydroxy-4,4-dimethylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclopropyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclobutyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((R,E)-4,4-difluoro-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((S,E)-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 7-((R)-2-((3S,4S,E)-4-ethyl-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((3R,4R,E)-3-hydroxy-4-isopropylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((R,E)-3-hydroxy-4,4-dimethylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclopropyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((R,E)-3-hydroxy-3-(1-(pent-2-yn-1-yl)cyclobutyl)prop-1-en-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-24R,E)-4,4-difluoro-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((S,E)-3-hydroxynon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyl oct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyl oct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyl oct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;
 methyl 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoate;

7-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 7-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid;
 methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-8-phenyloct-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 methyl 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 methyl 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 5-(3-((R)-2-((3S,4R,E)-3-hydroxy-4-methyl-9-phenylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 methyl 5-(3-((S)-2-((3R,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 methyl 5-(3-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylate;
 5-(3-((S)-2-((3R,4S)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 5-(3-((S)-2-((3R,4R)-3-hydroxy-4-methylnon-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid;
 methyl 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-ynoate; and
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)hept-5-ynoic acid.
19. A pharmaceutical composition comprising the compound of claim 1, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.
20. A method of treating osteoporosis, bone fracture, or bone loss due to periodontal disease, comprising administering a therapeutically effective amount of the compound of claim 1 to a patient in need thereof.
21. A method of stimulating bone formation in a tooth socket having undergone implantation, a joint that is to undergo or that has undergone orthopedic implantation, or vertebrae that have undergone spinal fusion comprising administering a therapeutically effective amount of the compound of claim 1 to a patient in need thereof.
22. A method of treating glaucoma, alopecia, or neuropathic pain comprising administering a therapeutically effective amount of the compound of claim 1 to a patient in need thereof.
23. The compound of claim 18 selected from:
 7-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)heptanoic acid, or a pharmaceutically acceptable salt thereof.

145

24. The compound of claim **18** selected from:
5-(3-((R)-2-((3S,4S,E)-3-hydroxy-4-methylnon-1-en-6-yn-1-yl)-5-oxopyrrolidin-1-yl)propyl)thiophene-2-carboxylic acid, or a pharmaceutically acceptable salt thereof.

5

* * * * *

146