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Synthesis of the methylene bis-tetrahydropyran motif of (−)-exiguolide

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ABSTRACT

A chiral-pool approach for the construction of methylene bis-tetrahydropyran subunit, C_1–C_{16} fragment, of (−)-exiguolide is described. The synthesis was efficiently accomplished starting from L-glutamic acid and L-aspartic acid involving *oxa*-Michael reaction and an aldol-driven-reductive etherification as key steps for the formation of tetrahydropyran ring.

(−)-Exiguolide (1) is a 20-membered macrolide isolated from the methanol extract of the marine sponge *Geodia exigua* Thiele (order Astrophorida, Family Geodiidae) by Ohta and co-workers.[1] The macrolide **1** prevents the fertilization of the sea urchin (*Hemicentrotus pulcherrimus*) gametes. Structurally, exiguolide consists of a methylene bis-tetrahydropyran (THP) subunit, five C–C double bonds, and seven asymmetric carbons. Further, one of the THP rings contains methoxycarbonyl methylidene group, a less commonly found structural feature.[2] The biological activity and complex structure of **1** are features that make it a fascinating target. In 2008, Lee and co-workers have reported the total synthesis of (+)-exiguolide, enantiomer of **1**, and unambiguously determined the absolute stereochemistry.[3] Recently, the total syntheses of (−)-exiguolide (**1**) were reported by Roulland and Fuwa research groups, independently.[4] In continuation of our interest in synthesis of macrolides and THP-containing molecules,[5] herein, we report the synthesis of methylene bis-tetrahydropyran subunit (C_1–C_{16} fragment) of (−)-exiguolide. Our retrosynthetic analysis of **1** simplified the structure into two major subunits by the disconnection of lactone bond and C_{16}–C_{17} bond. The lactone can be formed using Yamaguchi conditions and C_{16}–C_{17} double bond can be achieved either by ring-closing metathesis or by Julia olefination. In this Letter, we describe the synthesis of bis-THP subunit **2**, which was envisioned from the THP–ketone **3** and aldehyde **4** via an aldol-driven-reductive etherification. Further, ketone **3** can be derived from L-glutamic acid using *oxa*-Michael reaction and aldehyde **4** can be obtained from L-aspartic acid (Scheme 1).

The synthesis of THP-ketone **3** (Scheme 2) was began with the known protected (4*S*)-hydroxymethyl-4-butanolide **5**, obtained from L-glutamic acid.[6] In the first step, stereoselective methylation of **5** was carried out with the use of LDA/MeI at −78 °C to afford **6** in 78% yield that established the C-15 methyl stereo center.[7] The reduction of lactone **6** using $LiBH_4$ provided the 1,4-diol **7** in 99% yield, which was protected as a seven-membered acetonide **8** under 2,2-DMP/CSA reaction conditions (90% yield). Then, *tert*-butyldiphenylsilyl group of **8** was deprotected to alcohol **9** using TBAF (91% yield) and subsequent tosylation of **9** (TsCl/Py) provided the tosylate **10** in 96% yield. The next step involved the four-carbon chain extension by employing Schlosser copper-catalyzed Grignard coupling reaction[8] on tosylate **10**. In the presence of dilithium tetrachloro cuprate, compound **10** was readily reacted with 3-butenyl magnesium bromide to give **11** in 88% yield. The compound **11** was further used for the pyran ring formation. Hence, olefin **11** was subjected to ozonolysis followed by a Wittig olefination (PPh_3=CHCOMe) to provide enone **12** in 84% yield (over two steps). Hydrolysis of acetonide **12** and consequent *oxa*-Michael addition were accomplished through a *p*-TSA-catalyzed one-pot reaction to afford pyran **13** in 89% yield.[9] The relative *syn*-relationship of 2,6-disubstituted tetrahydropyran **13** was confirmed by NOE effect between H-9 and H-13 (2D NOESY). The protection of free-hydroxyl group of **13** as TBS ether (TBSCl/imidazole, 95% yield) provided the THP–ketone fragment **3**.

In the approach to aldehyde **4** (Scheme 3), epoxide **14** was prepared in three steps from commercially available L-aspartic acid using literature methods.[10] Ring opening of epoxide **14** with vinyl magnesium bromide afforded the homoallylic alcohol **15** in 89% yield.[11] Protection of the alcohol **15** as TBS ether **16** with TBSCl/

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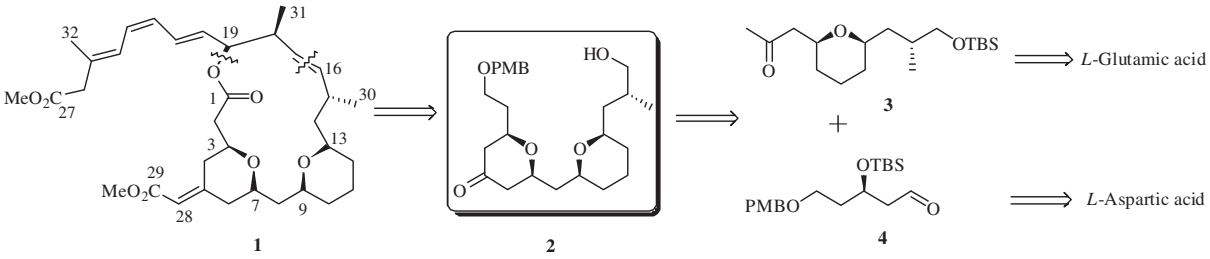
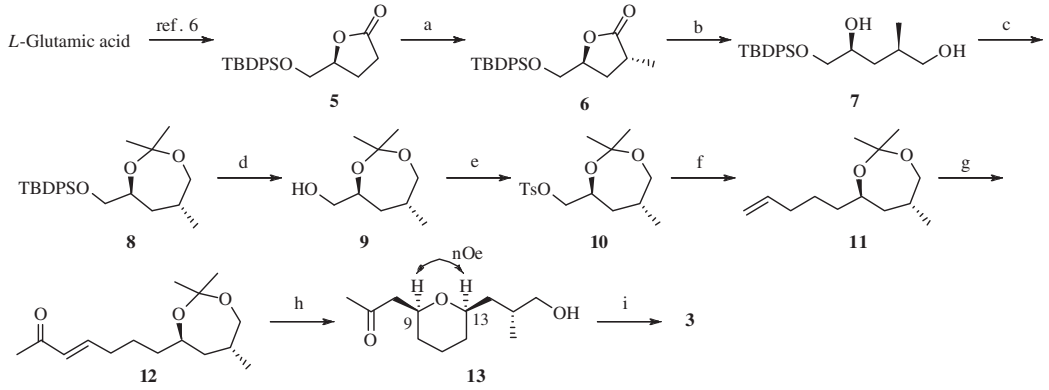
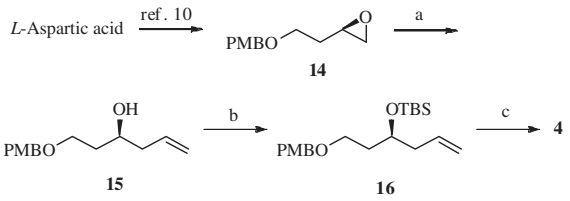


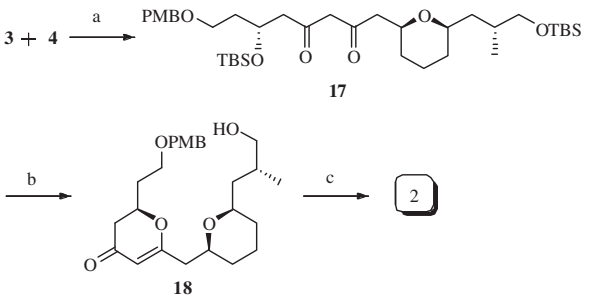
Scheme 1. Retrosynthetic analysis of (−)-exiguolide.



Scheme 2. Reagents and conditions: (a) LDA, MeI, THF, −78 °C, 1 h, 78%; (b) $LiBH_4$, THF, MeOH, 0 °C, 1 h, 99%; (c) 2,2-DMP, CSA (cat.), CH_2Cl_2, 0 °C to rt, 30 min, 90%; (d) TBAF (1 M in THF), THF, 0 °C to rt, 1 h, 91%; (e) TsCl, Py, 0 °C, 12 h, 96%; (f) *n*-C_4H_7MgBr, Li_2CuCl_4, THF, −30 °C to rt, 12 h, 88%; (g) (i) O_3, CH_2Cl_2, $NaHCO_3$, −78 °C, 30 min, (ii) Ph_3P=CHCOMe, THF, reflux, 10 h, 84% (over two steps); (h) *p*-TsOH·H_2O, CH_2Cl_2, 0 °C to rt, 3 h, 89%; (i) TBDMSCl, DMF, 0 °C to rt, 1 h, 95%.



Scheme 3. Reagents and conditions: (a) vinyl magnesium bromide, CuI, THF, 0 °C, 2 h, 89%; (b) TBDMSCl, imidazole, CH2Cl_2, 0 °C to rt, 24 h, 95%; (c) (i) OsO_4, NMO, acetone–H_2O (3:1), rt, 4 h, (ii) $NaIO_4$, $NaHCO_3$, THF–H_2O (4:1), 0 °C, 1 h, 84%.



Scheme 4. Reagents and conditions: (a) (i) LDA, THF, −78 °C, 1 h; (ii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 30 min (71% over two steps); (b) HF (40% aq), CH_3CN, 0 °C to rt, 4 h, 86%; (c) H_2, 10% Pd/C, Na_2CO_3, EtOAC, rt, 10 h, 91%.

imidazole (95% yield) followed by oxidative cleavage of terminal olefin afforded the aldehyde **4** in 84% yield.[12]

Having both the fragments **3** and **4** in hand, we next proceeded for the synthesis of methylene bis-tetrahydropyran subunit **2**, using an aldol-driven-reductive etherification strategy (Scheme 4), which was successfully employed in our previous Letter.[5e] Thus, treatment of aldehyde **4** with the lithiated enolate, derived from **3** using LDA, produced an aldol product as a inseparable mixture of diastereomers. This mixture was treated with Dess–Martin periodinane to give β-diketone **17** (71% yield over two steps), which entirely existed as the enol form (confirmed by ^1H NMR). The exposure **17** to HF (40% aq solution) in CH_3CN led to the formation of cyclodehydrated product **18** in 86% yield.[13] Finally, hydrogenation of **18** was proceeded (91% yield) with the exclusive formation of a tetrahydropyranone ring[14,5e] that completed the synthesis of **2**.[15] Compound **2** was fully characterized by IR, ^1H, ^{13}C NMR, MS, and the *syn*-relationship of both the THP rings was confirmed by 2D NOESY experiments.[16]

In summary, we have successfully demonstrated the synthesis of methylene bis-THP motif of (−)-exiguolide using a chiral-pool-based approach. The strategy used is efficient and scalable from commercially available natural amino acids. The present route exhibits the applicability of *oxa*-Michael reaction and an aldol-driven-reductive etherification in the synthesis of THP-containing targets. Ongoing efforts toward the completion of (−)-exiguolide are currently underway and will be reported in due course.

Acknowledgment

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15. *Spectroscopic data for representative compounds: (E)-7-((4R,6R)-2,2,6-Trimethyl-1,3-dioxepan-4-yl)hept-3-en-2-one* (**12**): R_f = 0.50 (20% EtOAc in Hexanes); Optical Rotation: $[\alpha]_D^{26}$ +2.6 (c = 1.05, $CHCl_3$); IR (KBr): υ_{max} 2931, 2864, 1712, 1673, 1358, 1218, 1072, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.74 (dt, J = 15.8, 6.8 Hz, 1H), 6.03 (dt, J = 15.8, 1.4 Hz, 1H), 3.85 (dd, J = 12.0, 1.5 Hz, 1H), 3.82–3.72 (m, 1H), 3.31 (dt, J = 12.0, 2.3 Hz, 1H), 2.28–2.17 (m, 2H), 2.22 (s, 3H), 1.83–1.70 (m, 1H), 1.71–1.32 (m, 6H), 1.30 (s, 3H), 1.27 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6, 148.2, 131.3, 100.3, 67.6, 65.7, 41.7, 36.2, 32.4, 31.1, 26.8, 25.1, 25.0, 24.9, 17.1; HRMS: calcd for $C_{15}H_{26}O_3Na$ $(M+Na)^+$ 277.1774; found 277.1776.
1-((2S,6R)-6-((R)-3-Hydroxy-2-methylpropyl)tetrahydro-2H-pyran-2-yl)propan-2-one (**13**): R_f = 0.40 (40% EtOAc in Hexanes); Optical Rotation: $[\alpha]_D^{28}$ −3.3 (c = 0.90, $CHCl_3$); IR (KBr): υ_{max} 3433, 2927, 1709, 1361, 1195, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.85–3.74 (m, 1H), 3.57–3.48 (m, 1H), 3.46 (dd, J = 10.5, 5.3 Hz, 1H), 3.34 (dd, J = 10.5, 6.8 Hz, 1H), 2.67 (dd, J = 15.8, 7.5 Hz, 1H), 2.39 (dd, J = 15.8, 5.3 Hz, 1H), 2.15 (s, 3H), 1.93–1.78 (m, 2H), 1.65–1.37 (m, 5H), 1.31–1.12 (m, 3H), 0.9 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 75.5, 73.9, 67.6, 49.8, 40.1, 32.0, 31.1, 31.0, 30.9, 23.3, 17.2; HRMS: calcd for $C_{12}H_{22}O_3Na$ $(M+Na)^+$ 237.1461; found 237.1463.
1-((2S,6R)-6-((R)-3-(tert-Butyldimethylsilyloxy)-2-methylpropyl)tetrahydro-2H-pyran-2-yl)propan-2-one (**3**): R_f = 0.50 (20% EtOAc in Hexanes); Optical Rotation: $[\alpha]_D^{27}$ −3.2 (c = 1.20, $CHCl_3$); IR (KBr): υ_{max} 2930, 2856, 1717, 1360, 1252, 1086, 839, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.77–3.65 (m, 1H), 3.44–3.30 (m, 3H), 2.64 (dd, J = 15.1, 7.8 Hz, 1H), 2.35 (dd, J = 15.1, 4.8 Hz, 1H), 2.15 (s, 3H), 1.88–1.65 (m, 2H), 1.64–1.49 (m, 2H), 1.47–1.37 (m, 1H), 1.33–1.06 (m, 4H), 0.9 (m, 12H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 76.4, 74.3, 67.7, 50.3, 39.8, 32.3, 31.9, 31.5, 31.4, 31.0, 25.9, 23.5, 17.5; HRMS: calcd for $C_{18}H_{36}O_3SiNa$ $(M+Na)^+$ 351.2326; found 351.2325.
(R)-6-(tert-Butyldimethylsilyloxy)-1-((2S,6S)-6-((R)-3-(tert-butyldimethylsilyloxy)-2-methylpropyl)tetrahydro-2H-pyran-2-yl)-8-(4-methoxybenzyloxy)octane-2,4-dione (**17**): R_f = 0.40 (10% EtOAc in Hexanes); IR (KBr): υ_{max} 2928, 2855, 1729, 1612, 1513, 1462, 1248, 1089, 834, 774 cm^{-1}; Optical Rotation: $[\alpha]_D^{28}$ −7.7 (c = 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.55 (s, 1H), 4.41 (AB, J = 11.3 Hz, 1H, B of AB), 4.35 (AB, J = 11.3 Hz, 1H, A of AB), 4.30–4.20 (m, 1H), 3.80 (s, 3H), 3.72–3.62 (m, 1H), 3.47 (t, J = 6.8 Hz, 2H), 3.39 (d, J = 6.0 Hz, 2H), 3.38–3.29 (m, 1H), 2.48 (dd, J = 14.3, 6.7 Hz, 1H), 2.38 (d, J = 6.8 Hz, 2H), 2.28 (dd, J = 14.3, 6.0 Hz, 1H), 1.88–1.67 (m, 4H), 1.64–1.36 (m, 4H), 1.30–1.06 (m, 3H), 0.9 (s, 9H), 0.85 (m, 12H), 0.04 (s, 3H), 0.02 (s, 6H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.6, 190.6, 159.1, 130.4, 129.2, 113.7, 102.1, 76.6, 74.6, 72.6, 67.8, 67.2, 66.2, 55.2, 46.5, 45.7, 39.7, 37.4, 32.4, 31.5, 31.4, 25.9, 25.8, 23.5, 17.4, −4.7, −5.3; HRMS: calcd for $C_{37}H_{66}O_7Si_2Na$ $(M+Na)^+$ 701.4239; found 701.4234.
(2S,6R)-2-(((2S,6S)-6-((R)-3-Hydroxy-2-methylpropyl) tetrahydro-2H-pyran-2-yl)methyl)-6-(2-(4-methoxy-benzyloxy)ethyl)dihydro-2H-pyran-4(3H)-one (**2**): R_f = 0.40 (50% EtOAc in Hexanes); IR (KBr): υ_{max} 3433, 2931, 2859, 1716, 1606, 1512, 1253, 1088, 1033, 751 cm^{-1}; Optical Rotation: $[\alpha]_D^{28}$ + 8.9 (c = 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.78–3.68 (m, 2H), 3.57–3.37 (m, 6H), 2.36 (t, J = 13.1 Hz, 2H), 2.21 (td, J = 13.1, 5.4 Hz, 2H), 1.99–1.72 (m, 5H), 1.60–1.35 (m, 5H), 1.31–1.16 (m, 3H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 159.3, 130.4, 129.3, 113.9, 75.7, 74.5, 74.3, 74.0, 72.9, 67.7, 66.0, 55.4, 48.0, 47.7, 42.4, 40.5, 36.5, 32.3, 31.5, 31.2, 29.8, 23.7, 17.6; HRMS: calcd for $C_{25}H_{38}O_6Na$ $(M+Na)^+$ 457.2561; found 457.2571.
16. The NOE effect between H3–H7 and H9–H13 confirmed the cis-relationship in both the 2,6-disubstituted THP rings.