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Total synthesis of hyptolide

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ABSTRACT

The total synthesis of hyptolide, a naturally occurring α,β-unsaturated six-membered δ-lactone substituted with a polyoxygenated chain, is described. Sharpless kinetic resolution and opening of two different epoxy alcohols under two different conditions—Swern oxidation conditions and a radical reaction using Cp_2TiCl—fixed the stereocenters at C-9, C-11, and C-12, respectively. Brown's asymmetric allylation reaction installed the remaining stereocenter at C-6. A RCM protocol was used for construction of the α,β-unsaturated six-membered δ-lactone moiety of the molecule.

In recent years, naturally occurring six-membered α,β-unsaturated δ-lactones substituted with a polyoxygenated chain have attracted considerable attention from synthetic as well as bioorganic chemists, because of their interesting structures and important biological activities.[1,2] Representative examples of this class of molecules are hyptolide (**1**),[3] spicigerolide (**2**),[4] anamarine (**3**)[5] and synrotolide (**4**)[6] (Fig. 1).

These compounds were isolated from species of *Hyptis*, *Syncolostemon*, and related genera of the family *Lamiaceae*, and show interesting pharmacological properties.[3–6] As a result, many synthetic approaches have been reported for their syntheses, where mostly carbohydrates were used as chiral pool starting materials.[7]

Recently, we developed an efficient methodology by which a chiral 4-hydroxy-2,3-unsaturated carbonyl compound **C** (Scheme 1) could be obtained via opening of a 3,4-epoxy alcohol **A** under Swern oxidation conditions.[8] We have also demonstrated another method for the synthesis of chiral 1,3-diols,[9] such as **D**, via a radical-mediated opening of a 2,3-epoxy alcohol **B** using Cp_2TiCl[10] as shown in Scheme 1. In this Letter, we report the total synthesis of hyptolide (**1**)[11] to demonstrate the practical utilities of these two methodologies developed by us (see Scheme 2).

Our synthesis started from compound **6**, which was prepared from alcohol **5** according to the reported procedure[8] involving Sharpless asymmetric kinetic resolution,[12] followed by protective group manipulations. With chiral epoxy alcohol **6** in hand, it was subjected to oxidation under Swern conditions[13] to afford exclusively the *trans* enal, (4*R*,5*S*,*E*)-5-(*tert*-butyl-dimethylsilyloxy)-4-hydroxy-hex-2-en-1-al (**7**) in 90% yield. Reduction of the aldehyde functionality with DIBAL-H followed by selective protection of the resultant primary alcohol as a TBDPS-ether furnished compound **8** in 81% yield in two steps. Stereoselective epoxidation of **8** with *m*CPBA afforded the epoxide **9** (90%, 2:1 in favor of the required isomer). The stage was now set to carry out the crucial radical-mediated epoxide opening from the hydroxy side to give the requisite 1,3-diol. Accordingly, when compound **9** was treated with Cp_2TiCl, generated in situ from Cp_2TiCl_2 and Zn dust,[9,10] diol **10** was obtained in 85% yield. Acetonide protection of the 1,3-diol of **10** gave **11**. The ^{13}C NMR spectrum of **11** showed the chemical shifts of the methyl carbons of the acetonide function at 19.82 and 29.9 ppm and that of the ketal carbon at 98.28 ppm, thereby confirming it to be a '1,3-syn' acetonide.[14] This, in turn, proved that the major epoxide obtained during the *m*CPBA epoxidation of **8** was indeed the syn-epoxy alcohol **9**. Chemoselective deprotection of the TBDPS-ether using TBAF in THF afforded the primary alcohol **11a**, which was converted to alkene **12** in two steps. Oxidation of **11a** was followed by selective *Z*-olefination following Still's protocol,[15] using the ketophosphonate $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, to give **12** as the major product in a *Z*:*E* ratio of 95:5. The minor

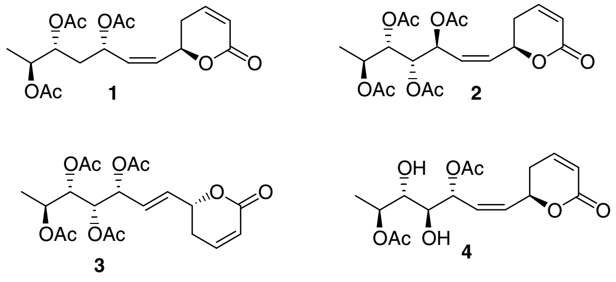

Figure 1.

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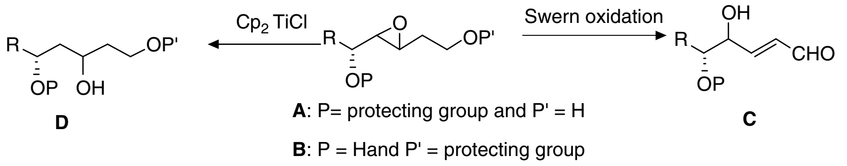
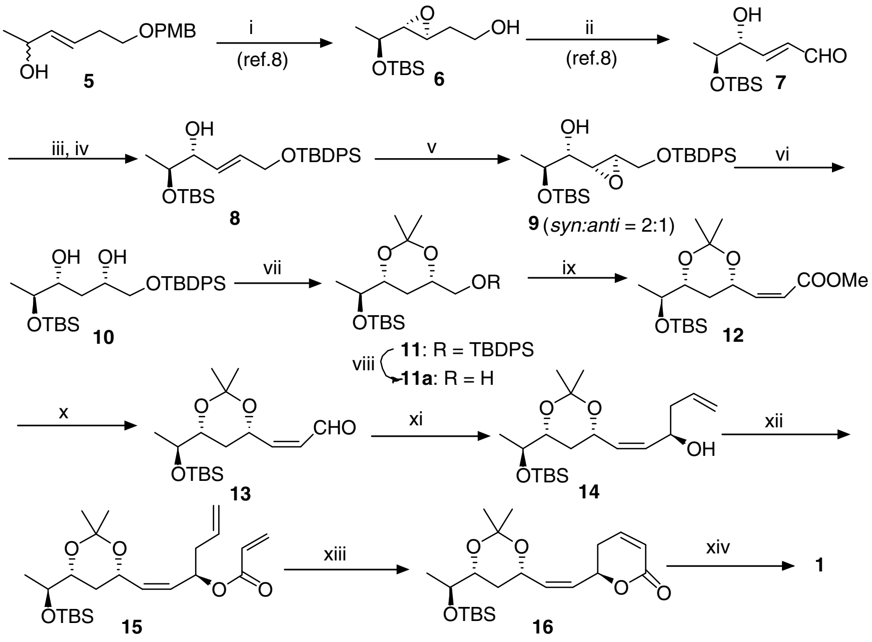


Scheme 1.



Scheme 2. Reagents and conditions: (i) Ref. 88; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 90%; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h; (iv) TBDPSCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt, 3 h, 81% over two steps; (v) *m*CPBA, CH_2Cl_2, 0 °C, 12 h, 90% (2:1 in favor of the required isomer); (vi) Cp_2TiCl_2, Zn, $ZnCl_2$, THF, −20 °C to rt, 12 h, 85%; (vii) 2,2-dimethoxypropane, CSA (cat), CH_2Cl_2, rt, 1 h; (viii) TBAF, THF, 0 °C to rt, 1 h, 85%, over two steps; (ix) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (b) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, −78 °C to 0 °C, 1.5 h, 80% (*Z*:*E* = 95:5) over two steps; (x) (a) step iii; (b) DMP, CH_2Cl_2, 0 °C to rt, 0.5 h, 85% over two steps; (xi) (+)-$Ipc_2B(allyl)$, Et_2O, −78 °C, 1 h, 70%; (xii) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C; 15 min, 70%; (xiii) Grubbs' 1st generation catalyst, CH_2Cl_2, 42 °C, 5 h, 85%; (xiv) (a) PPTS, MeOH, rt, 24 h; (b) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt, 0.5 h, 80% over two steps.

isomer could be removed chromatographically after the reduction step. The α,β-unsaturated aldehyde **13** was obtained from **12** in two steps. DIBAL-H reduction of **12** afforded the corresponding primary alcohol, which on oxidation with Dess Martin periodinane (DMP)[16] furnished aldehyde **13**. Asymmetric allylation of **13** using Brown's protocol[17] afforded the secondary alcohol **14** as the only diastereomer as determined by ^1H NMR. Alcohol **14** on acylation with acryloyl chloride afforded *bis*-olefinic compound **15** in 49% yield over the two steps.

Ring-closing metathesis (RCM) of **15** using Grubbs' 1st generation catalyst[18] furnished the α,β-unsaturated δ-lactone **16** in 85% yield, which was converted to hyptolide **1** in two steps—global deprotection followed by acetylation of the resulting triol to afford **1** in 80% yield. The spectral and analytical data of **1**[19] were in good agreement with those reported in the literature.

In conclusion, we have shown the utility of 2,3-epoxide opening reactions under two different conditions for the total synthesis of hyptolide. Further applications of these methodologies to the synthesis of other natural products are in progress, and the results will be reported in due course.

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19. (a) *Analytical and spectral data of compound* **11**: $[\alpha]_D^{27}$ +3.09 (c 1.06, $CHCl_3$); IR (neat): ν_{max} 3069, 2931, 2860, 1742, 1592, 1466, 1430, 1378, 1254, 1201, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.65 (m, 4H, Ar-*H*), 7.45–7.33 (m, 6H, Ar-*H*), 3.96 (m, 1H), 3.72 (dd, 1H, $J = 9.8$, 5.3 Hz), 3.66–3.50 (m, 3H), 1.91 (dt, 1H, $J = 12.8$, 2.26 Hz), 1.63 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.16 (d, 3H, $J = 6.0$ Hz), 1.05 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.64, 133.69, 129.54, 127.55, 98.28, 73.61, 71.41, 69.77, 67.55, 30.23, 29.90, 26.81, 25.86, 20.46, 19.82, 18.15, 18.05, −4.36, −4.64; MS (ESIMS): *m*/*z*: 565 $[M+Na]^+$; (b) *Analytical and spectral data of compound* **16**: $[\alpha]_D^{27}$ +13.17 (c 1.05, $CHCl_3$); IR (neat): ν_{max} 2929, 2857, 1724, 1465, 1380, 1248, 1200, 1150, 1102, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.86 (m, 1H), 6.04 (dd, 1H, $J = 9.8$, 1.5 Hz), 5.64–5.61 (m, 2H), 5.39 (ddd, 1H, $J = 12.0$, 6.8, 5.3 Hz), 4.60 (dq, 1H, $J = 12.0$, 7.5 Hz), 3.65–3.52 (m, 2H), 2.48–2.28 (m, 2H), 1.58 (dt, 1H, $J = 12.8$, 5.2 Hz), 1.42 (s, 3H), 1.36 (s, 3H), 1.35 (m, 1H), 1.13 (d, 3H, $J = 6.0$ Hz), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.69, 144.53, 134.01, 127.81, 121.57, 98.59, 74.41, 73.27, 71.08, 66.64, 33.01, 30.12, 29.96, 25.79, 20.28, 19.63, 18.02, −4.39, −4.67; MS (ESIMS): *m*/*z*: 419 $[M+Na]^+$; (c) *Analytical and spectral data of hyptolide* (**1**): $[\alpha]_D^{27}$ +11.2 (c 0.58, $CHCl_3$), reported +12.1 (c 0.68, $CHCl_3$);[11b] IR (neat): ν_{max} 2926, 2854, 1728, 1427, 1372, 1226, 1152, 1020 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 6.87 (ddd, 1H, $J = 9.8$, 5.5, 3.1 Hz), 6.03 (ddd, 1H, $J = 9.8$, 2.6, 1 Hz), 5.77 (dd, 1H, $J = 10.4$, 8.3 Hz), 5.56–5.50 (m, 2H), 5.28 (ddd, 1H, $J = 10.9$, 8.8, 4.6 Hz), 4.98 (dq, 1H, $J = 9.8$, 6.2 Hz), 4.92 (dt, 1H, $J = 9.3$, 3.1 Hz), 2.49–2.35 (m, 2H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.97 (m, 1H), 1.83 (m, 1H), 1.20 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.65, 170.34, 169.76, 163.46, 144.65, 131.32, 130.71, 121.48, 73.79, 70.90, 70.45, 66.48, 34.73, 29.47, 21.12, 21.10, 21.06, 14.69; MS (ESIMS): *m*/*z*: 391 $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{24}O_8Na$ $[M+Na]^+$ 391.1368. Found 391.1362.