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Stereoselective total syntheses of α,β-unsaturated δ-lactones having a 1,3-*syn*-polyol moiety, isolated from *Cryptocarya latifolia*

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Abstract

The first total syntheses of two α,β-unsaturated δ-lactones having a 1,3-*syn*-polyol moiety, isolated from *Cryptocarya latifolia*, were achieved. The key reactions include the Sharpless asymmetric epoxidation of the allyl alcohol, stereoselective addition of an allyl group to the epoxy aldehyde, regioselective reduction of the epoxy ring, and formation of the α,β-unsaturated δ-lactone. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Sharpless asymmetric epoxidation; 1,3-polyol; lactone; allylation; reduction.

Recently, two natural products **1** and **2**, isolated from *Cryptocarya latifolia* indigenous to South Africa, were reported to be α,β-unsaturated δ-lactones having a 1,3-*syn*-polyol moiety on the side chain, without stereochemistry, as shown in Fig. 1.[1] The absolute stereochemistry of **2** was then unequivocally determined to be 5*R*,7*R*,9*S*,11*S* based on Mosher's method[2] using the ^{1}H NMR of the MTPA ester and Rychnovsky's method[3] using the ^{13}C NMR of the acetonide.[4] Although the stereochemistry of the 5*R* and 7,9-*syn* configuration of **1** was also determined, the absolute stereochemistry at C7 and C9 remains unknown; however, because of the proven stereochemistry of **2**, it was reported that the δ-lactone **1** probably possesses a 7*S*,9*S*-configuration.[4] We have already reported that the relative stereochemistry at C5 and C7 in these types of α,β-unsaturated δ-lactones can be determined by the ^{1}H NMR splitting pattern of the C4-methylene protons;[5] i.e. a separated pattern of the C4-methylene protons means a 5,7-*syn*-configuration and an overlapped pattern means a 5,7-*anti*-configuration. Since the reported ^{1}H NMR data[1] of **1** showed a separated pattern at δ 2.29 and 2.42, the relative stereochemistry should be 5,7-*syn*; i.e. the absolute stereochemistry of **1** is 5*R*,7*S*,9*S*. It is very interesting that the same type of α,β-unsaturated δ-lactone **3** (Fig. 1), isolated from *Eupatorium pilosum*,[6] has the opposite absolute stereochemistry of the 5,7,9,11-all-*syn*-hydroxyl groups, which was determined through synthesis by us.[7]

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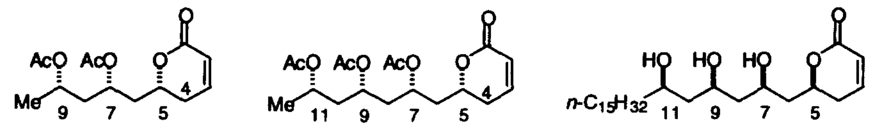
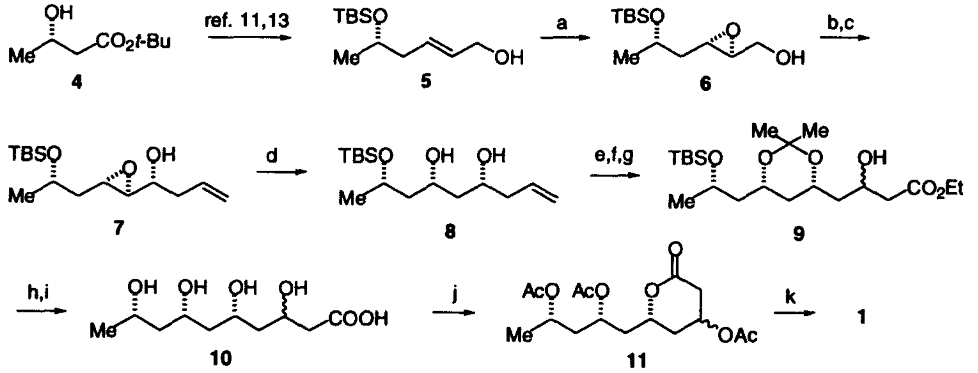


1 2 3

Figure 1.

In connection with our studies on natural products having a 1,3-polyol moiety, we have focused our attention on the synthesis of **1** and **2** and the confirmation of the stereochemistry through synthesis. We have already developed two efficient synthetic methods for 1,3-polyols based on iterative and convergent strategies[8,9] and accomplished the total syntheses of several natural products having a 1,3-polyol moiety, including the α,β-unsaturated δ-lactone **3**.[10] We now report the first total synthesis of **1** and **2** by a new synthetic method for a 1,3-polyols based on the stereoselective epoxidation of an allyl alcohol, stereoselective allylation to an epoxy aldehyde, and regioselective reduction of an epoxy ring.

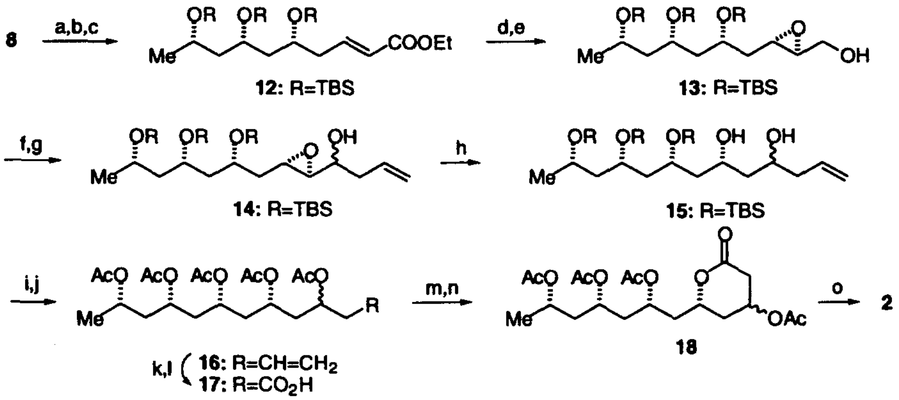
First, we investigated the synthesis of the α,β-unsaturated δ-lactone **1** having a diacetate (Scheme 1). The synthesis began with the allyl alcohol **5**,[11] which was prepared from commercially available (*S*)-*t*-butyl 3-hydroxybutyrate (**4**). The Sharpless asymmetric epoxidation[12] of **5** with *t*-BuOOH in the presence of (+)-diethyl tartrate (DET) and Ti(O*i*-Pr)$_4$ exclusively gave the α-epoxide **6**.[13,14] After the Swern oxidation of **6**, the stereoselective addition of an allyl group to the resulting epoxy aldehyde was examined. After several attempts, we found that the $LiClO_4$-mediated reaction with allyltributyltin[15] gave good results; upon treatment of the resulting epoxy aldehyde with allyltributyltin in the presence of $LiClO_4$ in ether, the chelate-controlled diastereoselective allylation took place to give the desired α-alcohol **7** and its diastereomer in 60% and 11% yields, respectively. The reductive opening of the epoxy ring in **7** was then examined. The usual procedure for the regioselective ring-opening of the 2,3-epoxy-1-ol to the 1,3-diol using $NaAlH_2(OCH_2CH_2OMe)_2$[16] was first applied to the epoxy alcohol **7**; however, there was almost no reaction in this case. Alternatively, treatment of **7** with Cp_2TiCl and *t*-BuSH in THF[17] produced the regioselective and reductive ring-opening of the epoxide **7** to give the 1,3-*syn*-diol **8** exclusively in 78% yield. After protection of the diol **8** as the acetonide, the olefin was oxidatively cleaved by OsO_4 followed by $NaIO_4$ treatment to an aldehyde, which was subjected to aldol condensation with the lithium enolate of ethyl acetate to give a mixture of hydroxy esters **9**. The treatment of **9**



Scheme 1. Reagents and conditions: (a) *t*-BuOOH, (+)-DET, Ti(O*i*-Pr)$_4$, 4A-MS, CH_2Cl_2, −21°C (80%); (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N, −78°C–rt; (c) allylSnBu$_3$, 5 M $LiClO_4$, ether, rt (60% from **6**); (d) Cp_2TiCl, *t*-BuSH, THF, rt (78%); (e) $Me_2C(OMe)_2$, CSA, acetone, rt (97%); (f) OsO_4–*t*-BuOH, NMO, acetone–H_2O, rt; $NaIO_4$, THF–H_2O, rt (92%); (g) LDA, EtOAc, THF, −78°C (90%); (h) Dowex® 50W-X2, MeOH–H_2O, rt; (i) LiOH, THF–H_2O, rt; Dowex® 50W-X2; (j) Ac_2O, DMAP, pyridine, rt; (k) DBU, toluene, rt (59% from **9**)

with Dowex® 50W-X2 in MeOH–H_2O simultaneously provided deprotection of the TBS and acenonide groups and subsequent hydrolysis with LiOH in THF–H_2O afforded the tetrahydroxy carboxylic acid **10**. The treatment of **10** with acetic anhydride gave the triacetoxy-δ-lactone **11**, which was finally treated with DBU in toluene to give the α,β-unsaturated lactone **1**. The NMR data and $[\alpha]_D$ of the synthetic **1**[18] were in good accordance with those of the natural product **1**.[1]

Next, the synthesis of the α,β-unsaturated δ-lactone **2** having a triacetate was accomplished from **8** (Scheme 2). Protection of the diol **8** as the TBS ether, oxidative cleavage of the olefin, and the Horner–Wadsworth–Emmons reaction afforded the α,β-unsaturated ester **12**. The DIBAH reduction followed by the Sharpless asymmetric epoxidation using L-(+)-DET stereoselectively gave the α-epoxide **13** and its β-isomer in a ratio of ca. 11:1. The Swern oxidation of **13** produced an aldehyde which was treated with allylMgCl to give a mixture of the α- and β-allyl alcohols **14**. The reductive cleavage of the epoxide **14** was also achieved by treatment with Cp_2TiCl and *t*-BuSH in THF to give the 1,3-diol **15** exclusively in 67% yield along with the recovered **14** (17%). Deprotection of the silyl group in **15** with Dowex® 50W-X2 in MeOH followed by acetylation with Ac_2O afforded the pentaacetate **16**. Ozonolysis followed by $KMnO_4$ oxidation produced the carboxylic acid **17**. Finally, methanolysis of the acetates, lactonization–acetylation, and DBU treatment furnished the α,β-unsaturated δ-lactone **2**. The NMR data and $[\alpha]_D$ of the synthetic **2**[19] were in good accordance with those of the natural product **2**.[1]



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) OsO_4–*t*-BuOH, acetone–H_2O, rt, $NaIO_4$, THF–H_2O, rt; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0°C (85% from **8**); (d) DIBAH, toluene, 0°C; (e) *t*-BuOOH, (+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, 4A-MS, CH_2Cl_2, −23°C (84% from **12**); (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N −78°C–rt; (g) allylMgCl, ether, −78°C (73% from **13**); (h) Cp_2TiCl, *t*-BuSH, THF, rt (67%); (i) Dowex® 50W-X2, MeOH, rt; (j) Ac_2O, DMAP, pyridine, rt (90% from **15**); (k) O_3, MeOH–CH_2Cl_2, −78°C; Me_2S, −78°C–rt; (l) $KMnO_4$, phosphate buffer, *t*-BuOH, rt (92% from **16**); (m) K_2CO_3, MeOH, rt; (n) Ac_2O, DMAP, pyridine, rt; (o) DBU, benzene, rt (38% from **17**)

In summary, α,β-unsaturated-δ-lactones **1** and **2** having a 1,3-*syn*-polyol moiety on the side chain were stereoselectively synthesized. The key reactions involve the Sharpless asymmetric epoxidation of an allyl alcohol, $LiClO_4$-mediated stereoselective addition of an allyl group to the epoxy aldehyde, regioselective and reductive ring-opening of the epoxy alcohol by Cp_2TiCl-*t*-BuSH, and formation of the α,β-unsaturated-δ-lactone. The absolute structures of **1** and **2** were thus confirmed through the total syntheses. The new procedure could be widely applicable to the synthesis of natural compounds having a 1,3-polyol moiety.

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11. The allyl alcohol **5** was prepared from **4** in four steps: (1) silylation by TBSCl, (2) DIBAH reduction, (3) the Horner–Wadsworth–Emmons reaction, and (4) DIBAH reduction (83% overall yield).
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18. Data for synthetic **1**: $[\alpha]_D^{29}$ +45.4 (c 0.33, $CHCl_3$); lit[1] $[\alpha]_D^{22}$ +55.8 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, d, *J*=6.4 Hz), 1.79 (1H, ddd, *J*=14.3, 5.8, 5.8 Hz), 1.95 (1H, ddd, *J*=14.6, 6.6, 3.8 Hz), 2.00 (1H, ddd, *J*=14.3, 7.2, 7.2 Hz), 2.04 (3H, s), 2.07 (3H, s), 2.16 (1H, ddd, *J*=14.6, 8.2, 6.4 Hz), 2.31 (1H, dddd, *J*=18.3, 11.6, 2.8, 2.4 Hz), 2.45 (1H, dddd, *J*=18.3, 6.1, 4.2, 0.9 Hz), 4.50 (1H, dddd, *J*=11.6, 6.6, 6.4, 4.2 Hz), 4.98 (1H, ddq, *J*=7.2, 5.8, 6.4 Hz), 5.10 (1H, dddd, *J*=8.2, 7.2, 5.8, 3.8 Hz), 6.02 (1H, ddd, *J*=9.8, 2.8, 0.9 Hz), 6.87 (1H, ddd, *J*=9.8, 6.1, 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 21.1, 21.3, 29.2, 39.1, 40.4, 67.7, 67.7, 74.9, 121.4, 144.7, 163.7, 170.5, 170.6.
19. Data for synthetic **2**: $[\alpha]_D^{25}$ +45.6 (*c* 0.46, $CHCl_3$); lit[1] $[\alpha]_D^{25}$ +43.8 (*c* 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, d, *J*=6.2 Hz), 1.75 (1H, ddd, *J*=11.3, 6.3, 5.0 Hz), 1.8–2.1 (4H, m), 2.03 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 2.16 (1H, ddd, *J*=14.7, 8.4, 6.4 Hz), 2.32 (1H, dddd, *J*=18.4, 11.4, 2.6, 2.6 Hz), 2.43 (1H, dddd, *J*=18.4, 5.7, 4.4, 1.1 Hz), 4.48 (1H, dddd, *J*=11.1, 6.5, 6.5, 4.3 Hz), 4.9–5.1 (3H, m), 6.01 (1H, ddd, *J*=9.7, 2.6, 1.1 Hz), 6.87 (1H, ddd, *J*=9.7, 5.7, 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 21.1, 21.1, 21.3, 29.1, 39.0, 40.0, 40.1, 67.6, 67.7, 68.1, 74.8, 121.3, 144.7, 163.7, 170.4, 170.5, 170.6.