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Stereoselective Synthesis of a Marine Natural Product, (±)-6β-Isovaleroxylabda-8,13-diene-7α,15-diol

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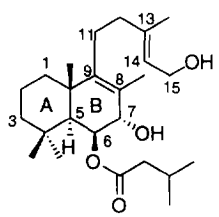
Abstract: The first synthesis of a marine natural product, (±)-6β-isovaleroxylabda-8,13-diene-7α,15-diol (**1**), has been accomplished starting from an octalone derivative **2**. Copyright © 1996 Elsevier Science Ltd

6β-Isovaleroxylabda-8,13-diene-7α,15-diol (**1**), a diterpene diol isolated from the marine pulmonate limpet *Trimusculus reticulatus*, exhibits potent repellent activity against predatory starfish.[1] From the structural point of view, the compound has a labdane carbon framework possessing four contiguous asymmetric carbon centers on the B-ring and two allylic alcohols. We wish to report herein the stereoselective synthesis of (±)-**1** from (±)-9-methoxycarbonyl-4,4,10-trimethyl-Δ^6-8-octalone (**2**), readily prepared from β-ionone.[2] The key feature of the present synthesis is characterized by the stereocontrolled construction of the B-ring of **1**, which involved sequential 1,4-addition to a diene (**8**→**9**), intramolecular S_N2' epoxide formation (**9**→**10**),[3] and S_N2' alkylative epoxide cleavage (**10**→**11**).



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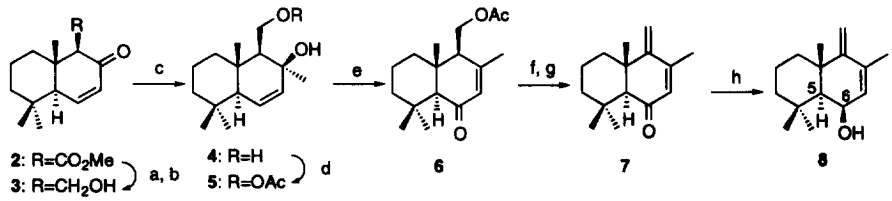
Thus, the synthesis began with readily available **2**, which was converted into the diol **4** using standard procedures (Scheme 1). After selective protection of the primary hydroxyl group, oxidative rearrangement of the allylic alcohol **5** with pyridinium chlorochromate (PCC) afforded the desired enone **6**, exclusively.[4] Sequential treatment of **6** with (1) K_2CO_3 in MeOH and (2) *p*-toluenesulfonic acid (*p*-TsOH) in benzene gave the dienone **7**. Reduction of **7** with diisobutylaluminum hydride (DIBAH) yielded the 6β-hydroxyl compound **8**,[4c,5] the configuration of which was assigned by its ^{1}H NMR data (δ and J values of the key protones).[6]

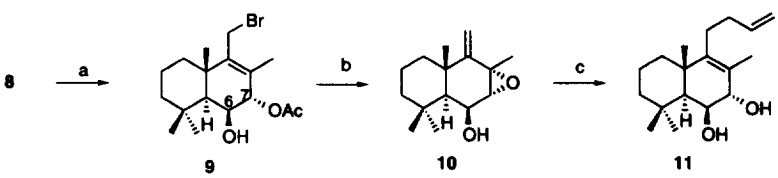


a) $LiAlH_4$, Et_2O, 0 °C, 2.5 h. b) $BaMnO_4$, CH_2Cl_2, room temperature, 24 h (92 % from **2**). c) MeLi, Et_2O, -78 °C, 3 h (91%). d) Ac_2O, Py, DMAP, room temperature, 24 h (97 %). e) PCC, CH_2Cl_2, room temperature, 3 h (92 %). f) K_2CO_3, MeOH, room temperature, 5 h. g) *p*-TsOH, C_6H_6, reflux, 6 h (82 % from **6**). h) DIBAH, CH_2Cl_2, -78 °C, 3 h.

Scheme 1

The crucial introduction of the 7α-hydroxyl group into **8** was examined using 1,4-addition to its diene moiety. Thus, treatment of **8** with *N*-bromosuccinimide (NBS) in AcOH effected a stereospecific acetoxyl attack to C7 to give in 85% yield the allylic acetate **9** as the sole product (Scheme 2).[7,8] The structure of the product was determined by its ^1H NMR data in which the dihedral angles of H-C(5)-C(6)-H and H-C(6)-C(7)-H were almost 90°. Therefore, the configuration of the C7 acetoxyl group of **9** was assigned as depicted in Fig. 1. The stereochemical outcome of the present transformation would be explained as an attack of the acetoxyl group from the sterically less hindered α-face, although neighboring group participation of the C6 hydroxyl group can not be eliminated.

Methanolysis of **9** resulted in an initial removal of the acetoxyl group and subsequent intramolecular S_N2' epoxide formation to give the desired allylic epoxide **10**.[9] Treatment of **10** with an allylic Grignard reagent in the presence of catalytic amounts of $CuBr{\cdot}SMe_2$ proceeded in an S_N2' manner involving an epoxide cleavage to give the diol **11**.[10,11] Thus, a series of S_N2' substitution reactions resulted in the stereospecific functionalization of the B-ring including the tetrasubstituted olefin.



a) NBS (1 eq), AcOH, room temperature, 1 h (85 % from **7**). b) K_2CO_3, MeOH, room temperature, 2 h (85 %). c) $CH_2{=}CH{-}CH_2MgBr$, $CuBr{\cdot}SMe_2$ (cat), LiBr (cat), Et_2O, -78 °C, 2 h (83 %).

Scheme 2

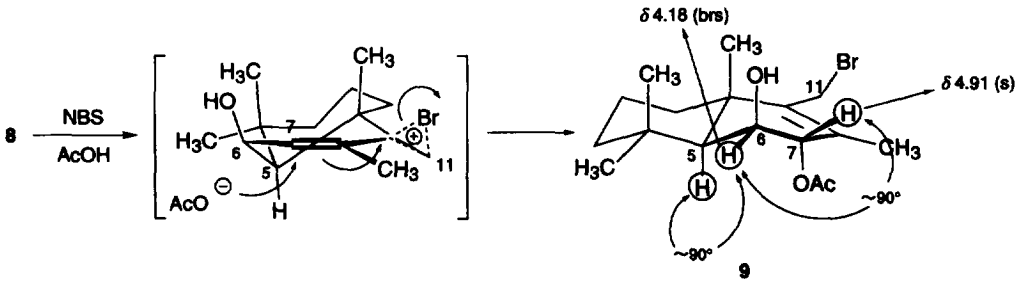
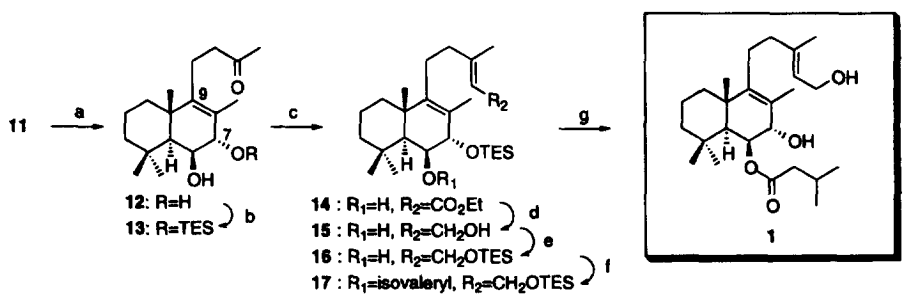


Figure 1

We next examined the construction of the C9 side chain. Wacker oxidation of **11** yielded the methyl ketone **12**. Prior to introducing a C2 unit to **12**, the 7α-hydroxyl group was protected with a triethylsilyl (TES) group. This reaction was highly chemoselective and only the C7 hydroxyl group was silylated to give **13**. Horner-Emons reaction of **13** gave the ester **14** which consisted of the desired *E*-isomer as the major product (*E*/*Z* = 20 : 1). Finally, the conversion of **14** to **1** was accomplished by the following sequence of reactions: (1) reduction of the ester group with DIBAH, (2) protection of the resulting alcohol by a TES group, (3) esterification of the secondary alcohol with isovaleric acid, and (4) removal of the TES groups. The yield of each synthetic process was excellent (>80%). Synthetic **1** was completely identical with the natural product in all respects (^{1}H NMR, ^{13}C NMR, and IR).[12]

Thus, we succeeded in the synthesis of (±)-**1** from (±) -**2** in 18 steps (22% overall yield).



a) $PdCl_2$, CuCl, DMF-H_2O, O_2, room temperature, 1 h (80%). b) TESCl, Py, 0 °C, 30 min (99 %). c) $(C_2H_5O)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C to room temperature, 6 h (97 % (*E* : *Z* = 20 : 1)). d) DIBAH, CH_2Cl_2, -78 °C, 3 h (88 %). e) TESCl, Py, 0 °C to room temperature, 30 min (99 %). f) isovaleric acid, DCC, DMAP, CH_2Cl_2, room temperature, 24 h. g) TBAF, THF, room temperature, 6 h (90% from16).

Scheme 3

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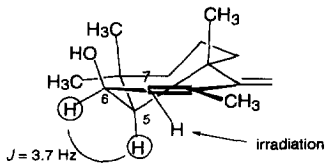
6. **8**: Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, 1 H, J = 5.1 Hz), 4.98 (d, 2 H, J = 6.6 Hz), 4.50 (br m, 1 H), 1.85 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.05 (s, 3 H), 2.00 - 0.98 (8 H). The small J value (3.7 Hz) between C5-H and C6-H, which was obtained by irradiation of the C7-H, suggested that the C6 hydroxyl group possesses β configuration. This was confirmed by the completion of the present synthesis.



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8. **9**: Colorless crystals, mp 125.5 - 126.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (s, 1 H), 4.18 (br m, 1 H), 4.09 (d, 1 H, J = 10.3 Hz), 3.98 (d, 1 H, J = 10.3 Hz), 2.09 (s, 3 H), 1.83 (m, 1 H), 1.77 (s, 3 H), 1.80 - 1.40 (5 H), 1.36 (s, 3 H), 1.30 (s, 1 H), 1.22 (m, 1 H), 1.19 (s, 3 H), 0.93 (s, 3 H).
9. **10**: Colorless crystals, mp 76.0 - 77.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (s, 1 H), 5.22 (s, 1 H), 4.60 (m, 1 H), 3.15 (m, 1 H), 1.54 (s, 3 H), 1.28 (m, 6 H), 1.00 (s, 3 H), 1.90-1.05 (8 H).
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11. **11**: Colorless crystals, mp 121.0 - 121.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1 H), 5.04 (dd, 1 H, J = 17.1, 1.7 Hz), 4.96 (dd, 1 H, J = 10.1, 1.9 Hz), 4.25 (m, 1 H), 3.71 (dd, 1 H, J = 6.6, 1.8 Hz), 2.22 - 2.00 (4 H), 1.79 (s, 3 H), 1.80 - 1.40 (5 H), 1.35 - 1.05 (4 H), 1.31 (s, 3 H), 1.22 (s, 3 H), 1.01 (s, 3 H).
12. Synthetic **1**: Colorless crystals, mp 89.0 - 90.0 °C; TLC R_f 0.20 (hexane : ethyl acetate = 3 : 2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (br t, 1 H, J = 6.4 Hz), 5.27 (brs, 1 H), 4.17 (t, 2 H, J = 6.1 Hz), 3.67 (br d, 1 H, J = 4.2 Hz), 2.30 - 2.04 (6 H), 2.00 (d, 1 H, J = 4.8 Hz), 1.80 (m, 1 H), 1.75 (s, 3 H), 1.72 (s, 3 H), 1.68 (m, 1 H), 1.60 - 1.50 (3 H), 1.43 (m, 1 H), 1.27 (s, 3 H), 1.30 - 1.14 (3 H), 1.00 (s, 3 H), 1.00 (s, 3 H), 0.94 (d, 6 H, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 145.6, 140.0, 124.1, 122.9, 73.2, 72.6, 59.3, 47.9, 43.9, 42.8, 39.5, 39.3, 38.9, 33.4, 33.1, 26.8, 25.5, 23.4, 22.4, 22.3, 21.1, 18.9, 17.5, 16.3; IR ($CHCl_3$) 3620, 3450, 2970, 2950, 2880, 1730, 1670, 1475, 1390, 1300, 1230, 1110, 990, 915 cm^{-1}.

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