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Enantioselective Total Synthesis of (+)-Labd-8(17)-ene-3β,15-diol and (-)-Labd-8(17)-ene-3β,7α,15-triol

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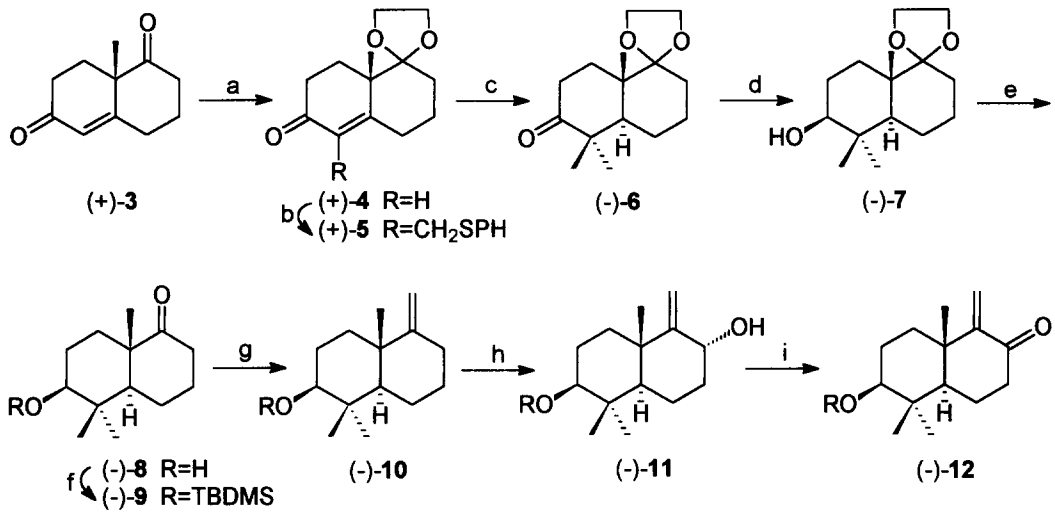
Abstract: Enantioselective total synthesis of the labdane diterpenes (+)-labd-8(17)-ene-3β,15-diol ((+)-**1**) and (-)-labd-8(17)-ene-3β,7α,15-triol ((-)-**2**) was achieved starting from the (*S*)-(+)-enantiomer of the Wieland-Miescher ketone (+)-**3** and the (*R*)-(+)-enantiomer of lactone (+)-**13**. These results established that the natural compounds (+)-**1** and (-)-**2** possess the (13*S*) absolute configuration.

Bicyclic diterpenes of the labdane-type belong to a class of compounds with increasing pharmacological interest. Antibacterial[1], cytotoxic as well as fungitoxic[2], and blood coagulation influencing effects[3,4] are reported.

The investigation of structure-activity relationships is often limited due to the insufficient availability of 3-functionalized labdane compounds isolated from marine or plant sources. While in position 3 unsubstituted labdanes can readily be prepared by partial syntheses starting from other natural compounds, for example abietic acid or manool[5,6], 3-functionalized labdanes are only available by a total synthetic approach.

Herein we wish to report the first enantioselective total synthesis of (13*S*)-labd-8(17)-ene-3β,15-diol ((+)-**1**), a diterpene isolated by Chandra et al.[7] from the bark of the Australian coniferous tree *Araucaria imbricata* and of (13*S*)-labd-8(17)-ene-3β,7α,15-triol ((-)-**2**), another labdane diterpene isolated by de Pascual Teresa et al. from the neutral fraction of the hexane extract of *Halimium viscosum*[8].

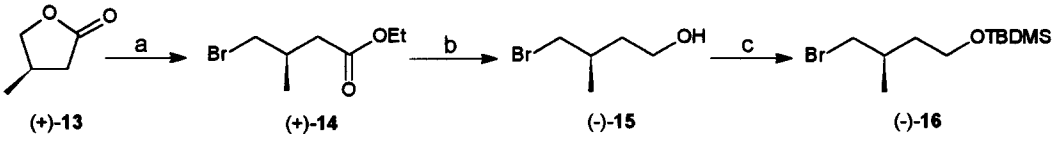
The starting material for our synthesis was the Wieland Miescher ketone (*S*)-(+)-**3** chosen because of its availability in high chemical yield and high enantiomeric excess (ee > 98 %) using the Buchschacher method[9]. After regioselective transketalization of (+)-**3** to the monoketal (+)-**4** we adopted a convenient method for constructing the trans-decalone skeleton involving phenylthiomethylation of (+)-**4** by means of a thioanalogous Mannich reaction[10]. Stork's reductive methylation[11,12] of (+)-**5** led then to the 4,4-dimethyl-trans-decalone derivative (-)-**6**. $NaBH_4$ reduction of (-)-**6**[13], deketalization of (-)-**7** and protection of the hydroxyl group of (-)-**8** with TBDMS triflate[14] afforded the protected ketone (-)-**9**. Wittig reaction of ketone (-)-**9** gave the exo-methylene compound (-)-**10**[15]. Allylic oxidation of (-)-**10** with catalytic amounts of selenium dioxide and tert. butylhydroperoxide[16] led to alcohol (-)-**11** which finally yielded the bicyclic exo-enone (-)-**12** by means of a Swern oxidation with trifluoroacetic anhydride/DMSO[17] (Scheme 1).



a) 2-ethyl-2-methyl-1,3-dioxolane, p-TsOH, ethylene glycol, room temperature, 30 h (79 %). b) n-propanol, Et_3N, PhSH, formaldehyde 37 %, potassium formate, 100 °C, 1 d (87 %). c) Li/NH_3, MeI, THF, -78 °C, 90 min (74 %). d) $NaBH_4$, EtOH, -40° C, 2 h (98 %). e) 5 % aq. hydrochloric acid, room temperature, 2 h (97 %). f) TBDMS triflate, Et_3N, CH_2Cl_2, 0° C, 1 h (97 %). g) $Ph_3P{=}CH_2$, NaH, DMSO, 60° C, 6 h (88 %). h) SeO_2 (cat), 70% tert. butylhydroperoxide, CH_2Cl_2, room temperature, 14 h (59 %). i) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, -78° C followed by Et_3N, room temperature, 1 h (88 %).

Scheme 1

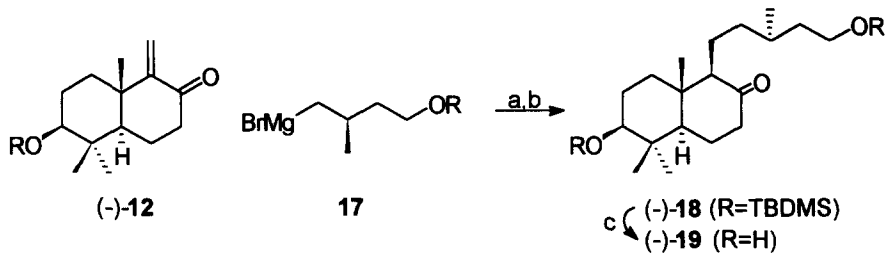
Next we carried out the formation of the optically active saturated isoprene side-chain building block (-)-**16**. Adopting a convenient method developed by Schmid and Barner[18] compound (-)-**16** was available from the chiral lactone (+)-**13**[19] (Scheme 2). Transesterification of lactone (+)-**13** with ethanolic HBr led to the γ-bromoester (+)-**14**. DIBAH reduction of (+)-**14** and protection of the bromoalcohol (-)-**15** as TBDMS ether afforded the chain building block (-)-**16**, synthesized for the first time and in high overall yield from lactone (+)-**13**[19,20].



a) 8M HBr/EtOH, room temperature, 16 h (96 %). b) DIBAH, hexane, 0° C, 12 h (96 %). c) TBDMS triflate, Et_3N, CH_2Cl_2, 0° C, 12 h (95 %).

Scheme 2

Subsequently we examined the crucial connection of the bicyclic building block (-)-**12** with the optically active saturated isoprene unit (-)-**16**[21] (Scheme 3). The connection of (-)-**12** and (-)-**16** was accomplished by cuprate-catalyzed conjugated 1,4-addition of the Grignard reagent **17**, derived from (-)-**16**, to the enone (-)-**12**, followed by enolate anion trapping with freshly distilled acetic anhydride. Treatment of the resulting crude enolacetate with potassium hydroxide in methanol afforded ketone (-)-**18** as the sole product in 65% overall yield from enone (-)-**12**.

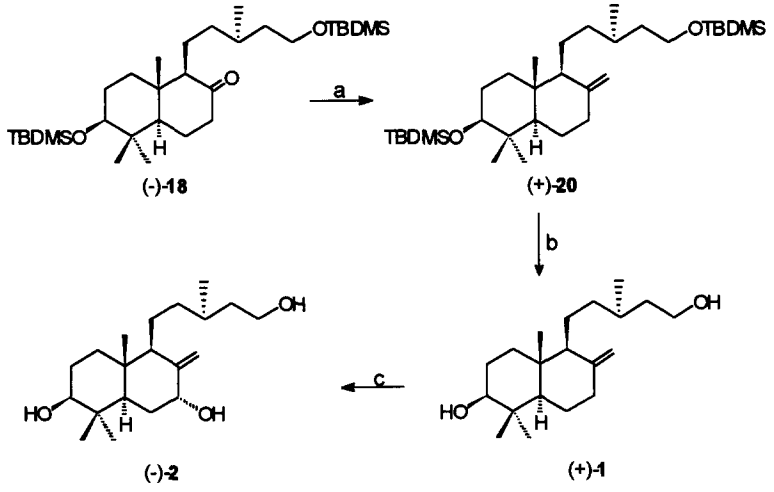


a) i) CuI (cat), ether, -10° C to room temperature, 30 min, ii) acetic anhydride, -10° C, 2 h. b) 10 % KOH in MeOH, room temperature, 12 h (65 % from (-)-**12**). c) HF (40%)/ MeCN (5:95), room temperature, 4 h (97 %).

Scheme 3

Based on the high stereoselectivity of the protonation in position 9α of the enolate, the syn-connection (syn to the methyl group 20) of the bicyclic skeleton (-)-**12** and the side-chain building block, according to labdane (+)-**1**, was achieved. The application of this connection method led to the 8-oxo-17-norlabdane (-)-**19**.

The introduction of the exo-methylene group in position 8 of compound (-)-**18**, a characteristic function in labdanes, was carried out by the Lombardo olefination using zinc, titanium tetrachloride and dibromomethane[22]. Deprotection of compound (+)-**20** with HF in MeCN yielded the natural compound (+)-**1**[23]. The total synthesis of the natural triol (-)-**2** was achieved by allylic oxidation of (+)-**1** with selenium dioxide and tert. butylhydroperoxide[16] (Scheme 4).



a) Zn dust, $TiCl_4$, dibromomethane, CH_2Cl_2, room temperature, 4 h (86 %). b) HF (40%)/MeCN (5:95), room temperature, 4 h (99 %). c) SeO_2 (cat), 70% tert. butylhydroperoxide, CH_2Cl_2, room temperature, 14 h (61 %).

Scheme 4

The structures of all compounds have been determined by means of mass spectra[24,25] and one- and two-dimensional NMR techniques. For the first time the ^1H- and ^{13}C-resonances of (+)-**1** and (-)-**2** have been assigned[26]. Comparison of the optical rotations of synthetic (+)-**1**[24] with the natural product (+)-**1**[7] shows that both values

are very similar. The still unknown configuration at C-13 of the naturally occurring labdane (+)-**1** can unambiguously be determined as (13*S*). The absolute configuration in position 13 of the natural compound **2** remained unclear since different literature values referring to the optical rotation have been reported[8,27]. Due to the determination of the optical rotation of the synthesized compound (-)-**2** the (13*S*) configuration of the natural labdane (-)-**2** can now be attributed.

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24. (+)-**1**: Colourless crystals, mp 112.0-113.0° C; $[\alpha]_D^{25}$+27.7° (c 0.63, $CHCl_3$) (Lit.[7] $[\alpha]_D$+29°); MS: 308 (8, $M^{+\cdot}$), 293 (6, $M^{+\cdot}$-15), 290 (29, $M^{+\cdot}$-18), 275 (18), 247 (6), 207 (17), 189 (16), 175 (21), 135 (100), 121 (12), 107 (14), 93 (10), 43 (4); HRMS calcd for $C_{20}H_{36}O_2$ 308.2715, found 308.2715.
25. (-)-**2**: Colourless oil; $[\alpha]_D^{19}$-12.7° (c 0.224, $CHCl_3$) (Lit.[8] $[\alpha]_D$-16.9°, Lit.[27] $[\alpha]_D$+19°); MS: 324 (8, $M^{+\cdot}$), 306 (47, $M^{+\cdot}$-18), 288 (17, $M^{+\cdot}$-18-18), 273 (17, $M^{+\cdot}$-18-18-15), 262 (8), 223 (46), 210 (22), 189 (14), 187 (30), 173 (28), 136 (53), 121 (100), 109 (21), 107 (26), 95 (37), 93 (17), 43 (14); HRMS calcd for $C_{20}H_{36}O_3$ 324.2664, found 324.2665.
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