Stereoselective Entry to the Bicycle [4.3.0] Skeleton of Oplopanes Using a Transannular Cyclization Strategy

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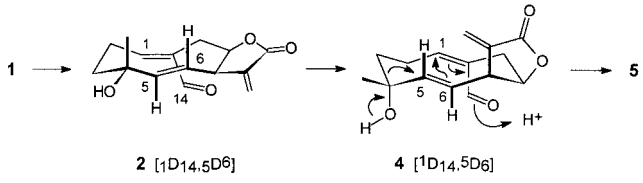
Abstract: Treatment of budlein B with acid gave a H-4β,H-9α-oplopane via lactone cleavage, allylic rearrangement, transannular cyclization and pinacol-type rearrangement. This transformation is stereochemically complementary to that of schkuhriolide, which produces a H-4α,H-9β-oplopane.

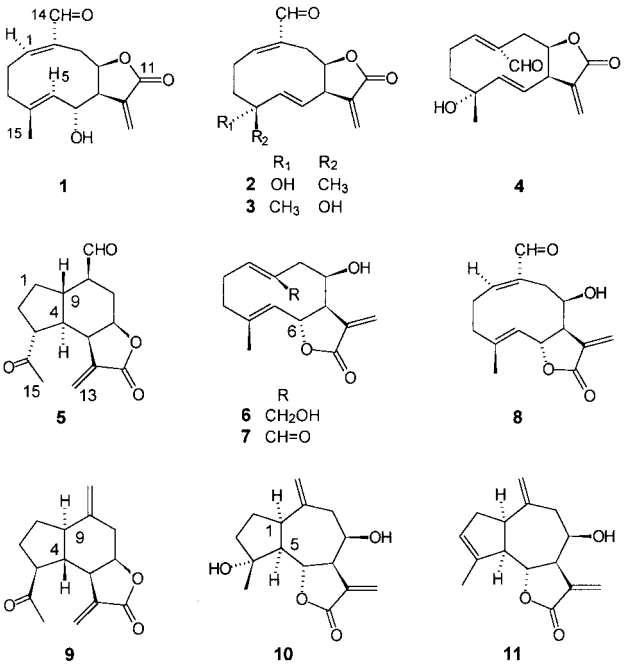
Key words: oplopanes, sesquiterpenes, cyclization, rearrangement, stereoselectivity

The generation of carbocyclic compounds from *trans,trans*-1(10),4-germacradienolides (germacrolides) via acid catalyzed reactions has been topic of several studies.[1] Such cyclizations can be utilized for the preparation of elemanolides,[2] eudesmanolides,[3] guaianolides,[4] xanthanolides[5] and cyclobutane[6] derivatives as the main products, and these transformations are significantly giving support to the proposed biogenetic schemes.[7] However, the acid catalyzed transformations of melampolides,[8] heliangolides[9] and *cis,cis*-1(10),4-germacradienolides were less studied compared with those of *trans,trans*-1(10),4-germacradienolides,[10] and their roles in the biogenesis of polycyclic terpenoids remain uncertain.

We previously reported[11] that acid treatment of the natural melampolide schkuhriolide (**1**)[12] gave mainly the epimers **2** and **3**, **4**,[10] and the tricyclic compound **5**. The formation of the H-4α,H-9β-oplopanolide **5** can be rationalized via an initial allylic rearrangement of **1** (to afford **2** and **3**), isomerization of the C(1)-C(10) double bond (to produce **4**), transannular Michael type reaction and pinacol rearrangement, to afford the bicycle [4.3.0] nonane (Scheme 1). The yield of **5** was optimized to 85% from **1**, and represents an alternative entry to H-4α,H-9β-oplopanolides.[13]

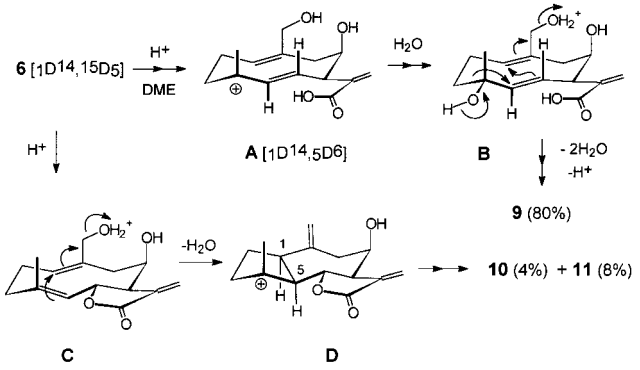


Scheme 1



Since the configuration of the bicycle [4.3.0] nonane depends on the conformation adopted by the cyclodecadiene precursor during the transition state of the cyclization (Scheme 1), it was decided to explore the scope of this reaction with the isomers of the cyclodecadiene, and here we report the results. Manganese dioxide oxidation of the natural *trans,trans*-1(10),4-germacradienolide budlein B (**6**)[14] afforded the aldehyde **7**,[15] which adopts a [$_1$D^{14},^{15}D$_5$] conformation[16] both in the crystal and in solution. Acid treatment of **7** (TFA in acetone) afforded *allo*-schkuhriolide (**8**),[17] previously obtained as natural product. **8** remained unaffected in trifluoroacetic acid. Attempts to relactonize budlein B (**6**) or the aldehyde **7** could not be achieved, presumably by the preferential lactonization to C-6 of the *trans,trans*-1(10),4-germacradienolides with oxygens at C-6α and C-8β.[18] When budlein B (**6**) was treated with perchloric acid in acetone, a mixture of products was obtained, but using DME as solvent, the same mixture was obtained with a major product (80%) which was characterized as the H-4β,H-9α-oplopanolide **9**.[19] Additional products of the transformation were the H-1α,H-5α-guaianolides vestenolide (**10**,[20] 4%), and ligustrin (**11**,[21] 8%). The formation of compound **9** can be ra-

tionalized as arising from cleavage of the γ-lactone and allylic rearrangement, to afford the cationic intermediate at C(4) (intermediate **A**, Scheme 2), which is stabilized by the addition of water to give the allylic tertiary alcohol (intermediate **B**, Scheme 2); protonation of the primary alcohol triggered the transannular cyclization and pinacol rearrangement to produce the oplopane **9**. At the same time, protonation of the primary alcohol of **6** (intermediate **C**), followed by dehydration, allows the transannular cyclization, which produces the C(1)-C(5) σ bond, and the cationic center at C(4) (intermediate **D**) is stabilized by the addition of water (to form **10**) or by loss of a proton (to produce **11**). The pseudoenantiomeric relationship of the endocyclic double bonds in the key intermediates (**4** in Scheme 1 and **B** in Scheme 2) is reflected in the enantiomeric fusion in the bicycle [4.3.0] nonane of the products (**5** and **9**).



Scheme 2

The results show that the tertiary alcohol at C-4 and the 1(10)-*trans*,5(6)-*trans*- double bonds in the intermediate cyclodecadiene are the structural requirements for the oplopane formation, and that the functionalities at C-8 and C-14 determine the preferred conformations of the intermediates, to produce diastereomeric products. In summary, transannular cyclizations of germacradienes provide alternative, efficient synthetic entries to diastereomeric (H-4α,H-9β and H-4β,H-9α) oplopanes.

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(15) **7**: White solid mp > 275 °C, UV λ_{max} 205 (ε 28419); IR ($CHCl_3$) ν_{max} 3453, 2980, 1759, 1658, 1412, 1355, 1286, 1142, 1090, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.89 (1H, br s, H-14), 6.40 (1H, br dd, J = 12 and 4 Hz, H-1), 6.33 (1H, d, J = 3 Hz, H-13 *cis*), 5.60 (1H, d, J = 3 Hz, H-13 *trans*), 5.03 (1H, t, J = 10 Hz, H-6), 5.05 (1H, br d, J = 10 Hz, H-5), 4.56 (1H, br d, J = 6 Hz, H-8), 1.50 (3H, br s, H-15). ^{13}C NMR ($CDCl_3$, 50 MHz, APT):192.9 (C-14), 169.9 (C-12), 156.6 (C-1), 141.5 (C-10), 138.3 (C-4 (C-11)), 138.2 (C-11 (C-4)), 127.7 (C-5), 120.3 (C-13), 74.5 (C-6), 69.8 (C-8), 53.1 (C-7), 39.2 (C-2 (C-3)), 38.5 (C-3 (C-2)), 25.0 (C-9), 16.9 (C-15); EIMS m/z (%) 262 (M^+, 25), 244 (41), 215 (61), 137 (100), 105 (92), 81 (90), 41 (80); HRMS Calculated for: $C_{15}H_{18}O_4$: 262.1205; Found: 262.1208.

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(19) To a stirred solution containing 25 mg (0.09 mmol) of budlein B (**6**) in DME (20 mL) under N_2 was slowly added $HClO_4$ (Aldrich, 0.3 mL). The solution was stirred for 20 min at 55 °C. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc and washed exhaustively with satd. aq. Na_2CO_3 and then with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil obtained from six runs was subjected to column chromatography and then to prep. TLC (mixtures of *n*-hexane-EtOAc as elution system) to give, in order of increasing polariry: ligustrin (**11**,[21] 8%), H-4β,H-9α-oplopanolide (**9,** 80%), vestenolide (**10**,[20] 4%). Minor additional products were not characterized. **9**: white solid: mp 132-134 °C; $[\alpha]_D$+205 (MeOH, *c* 0.102); UV λ_{max} 208 (ε 12150); IR ($CHCl_3$) ν_{max} 2951, 1764, 1697, 1658, 1413, 1357, 1265, 1142, 1011, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, COSY): δ 6.09 (1H, d, J = 1 Hz, H-13 *cis*), 5.45 (1H, d, J = 1 Hz, H-13 *trans*), 4.92 (1H, br s, H-10a), 4.83 (1H, br s, H-10b), 4.57 (1H, ddd, J = 5,5,3 Hz, H-6), 2.91 (1H, dddd, J = 10, 5, 1, 1, H-5), 2.87 (1H, dd, J = 16, 3, H-7a), 2.75 (1H, ddd, J = 11, 10, 6, H-9), 2.48 (1H, dd, J = 16, 5, H-7b), 2.10-2.14 (1H, m. H-1a), 2.07 (3H, s, H-15), 2.01-2.05 (1H, m, H-3), 1.85 (1H, ddd, J = 12, 10, 10, H-4); 1.77-1.66 (3H, m, H-1b, H-2a,b); ^{13}C NMR ($CDCl_3$, 125 MHz, HMQC, HMBC): 210.3 (C-14), 169.7 (C-12), 143.1 (C-8), 139.5 (C-11), 121.8 (C-13), 108.7 (C-10), 78.0 (C-6), 57.4 (C-9), 48.2 (C-4), 47.7 (C-3), 47.1 (C-5), 36.6 (C-7), 21.9 (C-1), 27.7 (C-15), 26.4 (C-2); EIMS m/z (%) 246 (M^+, 9), 203 (48), 150 (35), 91 (44), 69 (55), 46 (100), 45 (60); HRMS Calculated for: $C_{15}H_{18}O_3$ 246.1256, Found: 246.1252; Anal. Calcd for $C_{15}H_{18}O_3$: C 73.14, H 7.36, Found: C 73.04, H 7.51; X-Ray analysis of **9** (to be published) confirmed the structure.

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