Pergamon

Tetrahedron, Vol. 52, No. 5, pp. 1549-1556, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01000-9

A Highly Stereoselective in vitro Cyclization of Dolabellatriene Diterpenes into Novel Dolastadienes

Luzi Jenny, Hans-Jürg Borschberg*

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule,
ETH Zentrum, Universitätstrasse 16, CH – 8092 Zürich, Switzerland

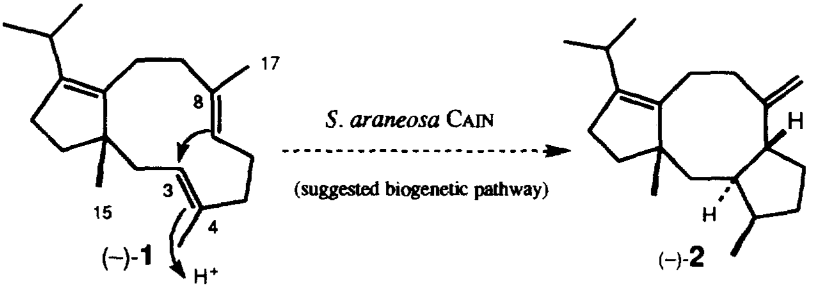
and Pierre Acklin[1]

Ciba-Geigy AG, K-136.5.82, CH – 4002 Basel, Switzerland

Abstract: Natural (–)-δ-araneosene ((–)-1) was shown to undergo an acid-catalyzed, kinetically controlled cyclization to the exomethylene dolastadiene (–)-3, which isomerized rapidly to the thermodynamically more stable *endo*-isomer (+)-4. A synthetically prepared 15-silyloxy derivative of 1 behaved in an analogous fashion, furnishing the two functionalized dolastadiene isomers 8 and 9. Force-field calculations suggest that the most stable conformation of 1 be represented by the unusual *C-syn* arrangement type 1A, and the stereochemistry of the cyclization products obtained points to a Markownikow-type protonation of the $\Delta^{7,8}$-double bond in the calculated ground state conformation, followed by an intramolecular cyclization without prior conformational change.

Introduction

The diterpene hydrocarbon (–)-δ-araneosene ((–)-1), most likely the immediate biogenetic precursor of (–)-cycloaraneosene ((–)-2)[2] (Scheme1), was synthesized recently and subsequently shown to be present in significant amounts in the neutral extracts of the mold *Sordaria araneosa* CAIN.[3] The biogenetic transformation of 1 to the fusicoccane-type diterpene 2 is probably initiated by protonation of the $\Delta^{3,4}$-double bond in an anti-Markownikow sense, and followed by a transannular cyclization[4] to give a tertiary carbenium ion at C(8) which leads to the end product by proton loss from C(17). As the acid-catalyzed cyclization of 1,5-cycloundecadienes has been little studied, and since we had sufficient starting material (–)-1, we decided to investigate its fate when exposed to various acids.

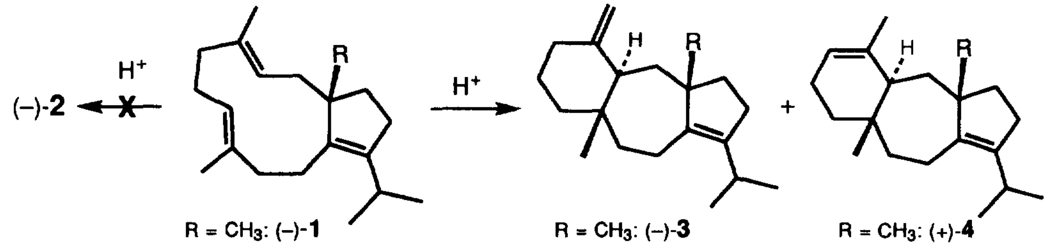


Scheme 1.

Results

A capillary GLC system allowing us detection of as little as 0.5% of (–)-**2** in a mixture of isomeric diterpene hydrocarbons was established. Natural δ-araneosene ((–)-**1**) was treated with various acids in organic solvents, however, no cycloaraneosene (**2**) was detected in the resulting reaction mixtures. In all cases two predominant products were discernible, these were virtually the only compounds formed by treatment with conc. HCl in $CHCl_3$ (2 h at – 45°). The two products were separated by chromatography on argentated silica gel and shown by combustion analysis and MS to be isomeric with the starting material **1**. Both compounds contain only 4 olefinic C-atoms and must, therefore, be tricyclic. The presence of an additional angular methyl group pointed to a skeleton of the dolastane type, but surprisingly, our major product was clearly different from (5*S**,12*R**,14*R**)-dolasta-1(15),8-diene (**5**) (Scheme 2), a synthetic intermediate prepared by Majetich et al.[5] on their route to (±)-14-deoxyisoamijiol (**6**)[6] (see Table 2).[7]

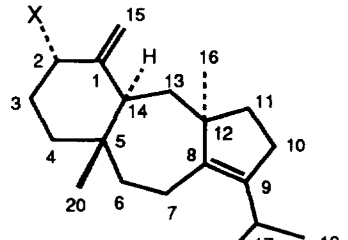
The conclusion that the relative configuration of our cyclization products is different from all presently known natural dolastanes[6,8] was verified after the functionalized derivatives **8** and **9** were analyzed by spectroscopic means. These compounds were prepared by an analogous reaction to that above, starting from synthetic (±)-**7**.[3] Their ^1H NMR spectra were simpler and easier to interpret than the ones obtained from **3** and **4**. An analysis of the $^1H/^1H$-COSY spectrum of a 7:3-mixture of (±)-**8** and (±)-**9** led to the assignment of all signals, as shown in Table 2, and the critical configuration at the asymmetric centers C(5) and C(14) could be determined by means of difference NOE experiments, carried out with purified (±)-**8**. As H_{ax}-C(7) and H_{ax}-C(13) displayed positive nuclear Overhauser effects when the angular methyl group, and when the silyloxy methylene group were irradiated, the latter two substituents must then be located on the same side of the 7-membered ring (see Figure 1). Accordingly, the aromatic protons of the protecting group also showed a positive NOE upon irradiation of H_3-C(20). The *trans*-fusion of the 7- and 6-membered rings followed from the observed coupling constant between H_{ax}-C(13) and H-C(14) that is 9.7 Hz. Taking these assignments as a guide, an unambiguous interpretation of the spectra of the parent hydrocarbons (–)-**3** and (+)-**4** became feasible, and from the data it follows that they must have the same relative configuration as (±)-**8** and (±)-**9**, respectively (see Table 2).



R = CH_3: (–)-**1**
R = $CH_2OSi(t\text{-}Bu)Ph_2$: (±)-**7**

R = CH_3: (–)-**3**
R = $CH_2OSi(t\text{-}Bu)Ph_2$: (±)-**8**

R = CH_3: (+)-**4**
R = $CH_2OSi(t\text{-}Bu)Ph_2$: (±)-**9**



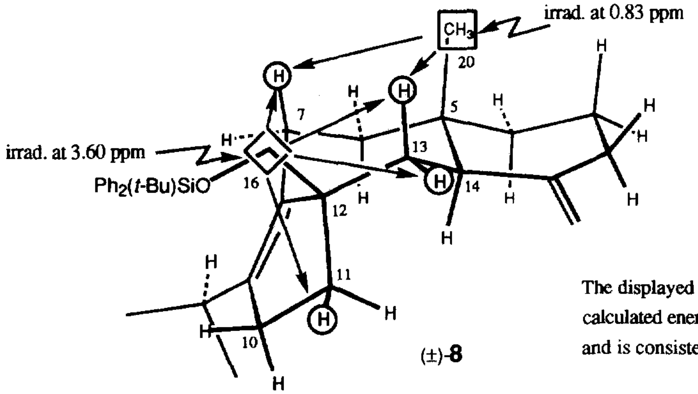
X = H: (±)-**5**
X = OH: (–)-**6**

Scheme 2.

Table 1. Cyclization (conc. HCl in $CDCl_3$) of **1** to **3** and **4**.

Entry	Time [h]	T [°C]	**3** [%]	**4** [%]
1	2	– 45	69	31
2	12	25	29	67
3	33	25	2	89
4	69	25	1	88
5	140	25	1	83
$\Delta H_f°$ [kcal/mol]	AM1[9]		-27.04	-29.02
$\Delta\Delta H_f°$ [kcal/mol]	6–31G[10]		1.94	0.00

Further investigation of the acid-catalyzed cyclization of (–)-**1** revealed that with increasing reaction time and at higher temperatures the former major product **3** was transformed almost completely into the thermodynamically more stable endocyclic isomer **4** (see Table 1 in Scheme 2). The fact that the combined yield of **3** and **4** slowly decreased can be ascribed to a slow formation of additional, as yet unidentified, products which arise from consecutive reactions. However, if **4** represents the desired target, the cyclization of **1** is remarkably efficient, producing (+)-(5*S*,12*S*,14*R*)-dolasta-1,8-diene in almost 90% yield, uncontaminated by epimeric byproducts (Table 1, entry 4).



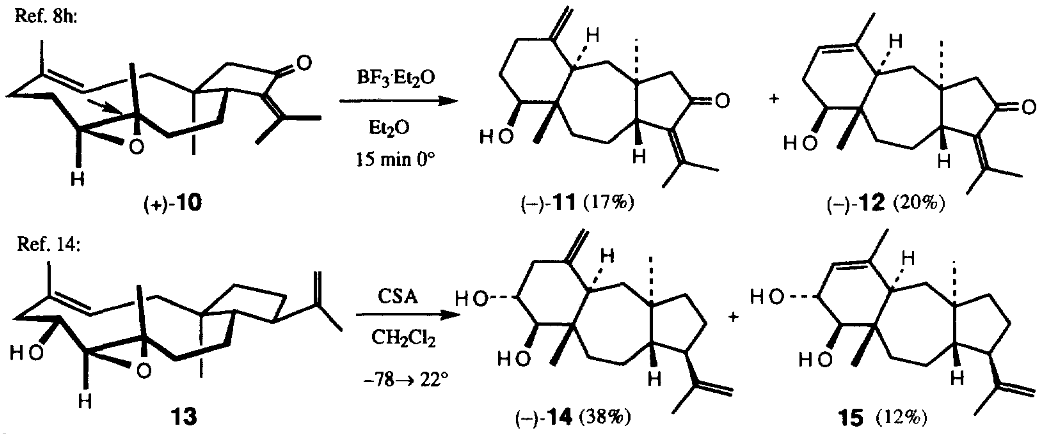
(±)-**8**

The displayed conformation corresponds to the calculated energy minimum (force field Amber)[11] and is consistent with the observed coupling constants.

Figure 1. Observed NOEs for Compound (±)-**8** (300 MHz, C_6D_6).

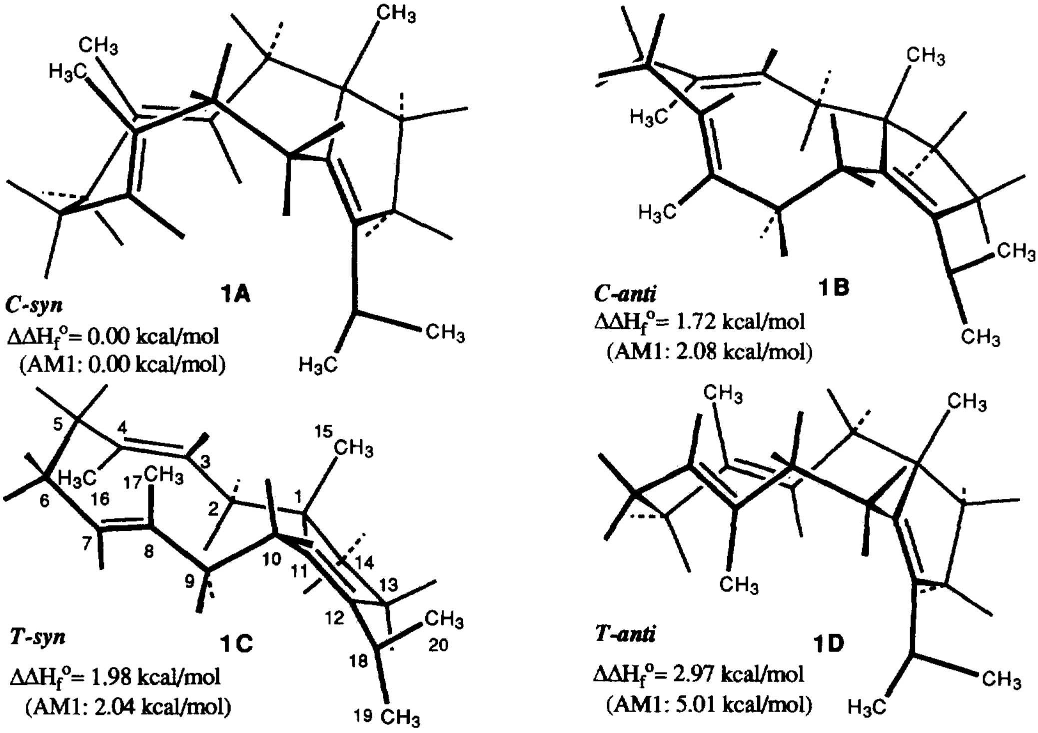
Discussion

Whereas within the bicyclic dolabellane precursors members of both antipodal series have been shown to occur naturally, those natural tricyclic dolastanes, whose absolute configuration has been determined so far, are all endowed with the (5*S*,12*R*)-configuration.[8h-k,8m,12] In those cases where only their relative configuration could be determined, the two angular methyl groups are almost invariably oriented *trans* to each other with respect to the 7-membered ring.[13] In an investigation dealing with a biomimetic cyclization of a dolabellane precursor, Look and Fenical isolated the two *trans*-dolastanes (–)-**11** and (–)-**12** upon treatment of the naturally occurring epoxide (+)-**10** with BF_3 (Scheme 3).[8h] They showed by means of NOE experiments that the most stable conformation of the bicyclic precursor **10** corresponded to the *C-anti* type (see below) which is required for the observed stereochemistry of the products. An analogous result was reported by Williams et al. in the last step of their synthesis of (–)-**14**,[14] and by Matsuo et al. in the transannular bromohydrin formation upon exposure of a natural 3,7-dolabelladiene to NBS.[15]



Scheme 3.

Evidently, in the case of **1** and **7** the conformation of the molecules undergoing an acid-catalyzed cyclization must differ from those of **10** displayed above. As our substrates were not amenable to an unambiguous conformational analysis by experimental methods, we took recourse to a force-field calculation[16] of the lowest energy conformations of **1** with the result shown in Figure 2. To describe the 4 conformations of lowest energy, the following convention is utilized: *C* or *T* are used in the sense proposed by Sutherland,[4] i.e. *C* defines conformations were the double bonds are crossed and were the ensuing cyclohexane ring is formed in a chair conformation (**1A** and **1B**), whereas in *T*-arrangements the double bonds are roughly parallel to each other and lead to cyclohexane derivatives in a twist conformation (**1C** and **1D**). In the case of (*E*,*E*)-configured double bonds (or epoxides) *C*-conformations lead to *trans*-fused rings and *T* to their *cis*-fused counterparts.[4] The second parameter describes the spatial relationship between the angular methyl group $H_3C(15)$ and $H_3C(17)$ (*syn*, if on the same side of the crown-shaped 11-membered ring, leading to dolastanes where the two angular methyl groups of the 7-membered ring end up *cis*, and *anti*, if otherwise).



C-syn **1A**
$\Delta\Delta H_f^{\circ}$= 0.00 kcal/mol
(AM1: 0.00 kcal/mol)

C-anti **1B**
$\Delta\Delta H_f^{\circ}$= 1.72 kcal/mol
(AM1: 2.08 kcal/mol)

T-syn **1C**
$\Delta\Delta H_f^{\circ}$= 1.98 kcal/mol
(AM1: 2.04 kcal/mol)

T-anti **1D**
$\Delta\Delta H_f^{\circ}$= 2.97 kcal/mol
(AM1: 5.01 kcal/mol)

Figure 2. The Calculated 4 Lowest Energy Conformations of **1** (Macro Model 4.0;[11] unlabelled substituents are H's).

In the case of **1** the most stable conformation corresponds to the *C-syn* type **1A**, calculated to be favored over the next higher energy conformation *C-anti* (**1B**) by 1.72 kcal/mol at 25°. Gratifyingly, **1A** represents the conformation which is expected to lead to formation of the experimentally observed cyclization products **3** and **4**. Furthermore, AM1 calculations of the protonated lowest energy conformers **1A-C**, with a proton placed 2Å above the $\Delta^{7,8}$ double bond,[17] reveiled a significant increase in the respective energy gaps (from 2.08 to 2.30 kcal/mol between **1A** and **1B**, and from 2.04 to 2.73 kcal/mol between **1A** and **1C**; on the other hand, the difference between **1A** and **1D**, the conformation that is required for the production of (–)-**2**, is lowered from 5.01 kcal/mol in their ground states to 3.74 kcal/mol for the respective protonated species.

In contrast to these findings, all other naturally occurring (*E*,*E*)-dolabella-3,7-dienes, as well as the corresponding epoxides with established conformation, determined either by *X*-ray crystallography[18] or NOE experiments,[19] prefer the *C-anti* type conformation[20] which eventually produces the (5*S**,12*R**)-dolastanes, as shown in Scheme 3.[21] The reason why δ-araneosene (**1**) adopts a ground state conformation which is different from all other related dolabellanes may lie in the altered state of hybridization at C(11) (sp^2, vs. sp^3 with *trans*-fused 5- and 11-membered rings, as in structures **10** and **13**).[22]

Conclusion

The presented results and research reported by others[8h,14,15] have demonstrated that in vitro transannular cyclizations can be highly stereoselective and the configuration of the products predicted with confidence – even if the medium ring system is very flexible – provided that the calculated or experimentally determined energy gap between the two lowest conformation types is sufficiently wide (≥ 1.5 kcal/mol).[23]

Table 2. ^{1}H NMR Chemical Shift Values (400 MHz, [ppm] vs. TMS).

Cpd.:	**8**	**3**	**9**	**4**	**3**	**5**[a)]	**6**[b)]	Typical Multiplicity
Solv.:	C_6D_6	C_6D_6	C_6D_6	C_6D_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	
2_{ax}	1.90	1.86	5.53 (*m*)	5.51 (*m*)	1.91		–	(*td* / 12.5, 4.5)
2_{eq}	2.29	2.24			2.29		4.28[c)]	(*ddt* / 12.5, 4, 2.5)
3_{ax}	1.47	1.45	2.10	2.09	1.43		1.75	(*m*)
3_{eq}	1.47	1.45	1.85	1.85	1.43		1.75	(*m*)
4_{ax}	1.23	1.25	1.30	1.30	1.25		1.91	(br.*td* / 13.5, 4.0)
4_{eq}	1.39	1.39	1.30	1.30	1.43		1.08	(br.*dq* / 13.5, ca.2.5)
6_{ax}	1.18	1.18	1.09	1.09	1.09		1.86	(br.*td* / 13.1, 2.1)
6_{eq}	1.58	1.57	1.44	1.43	1.58		1.33	(*ddd* / 13.1, 5.1, 2.1)
7_{ax}	2.00	1.82	2.10	1.88	1.75		2.40	(*tt* / 13.4, 1.7)
7_{eq}	2.29	2.24	2.34	2.29	2.19		2.13	(*m*)
10_{endo}	2.12	2.12	2.14	2.14	2.10		2.17	(*dd* / 15.3, 9.2)
10_{exo}	2.29	2.24	2.29	2.29	2.19		2.17	(*m*)
11_{endo}	1.59	1.64	1.64	1.69	1.52		1.58	(*dt* / 12.5, ca. 9)
11_{exo}	1.90	1.50	1.90	1.52	1.42		1.58	(*dd* / 12.5, 6.9)
13_{ax}	1.76	1.52	1.64	1.40	1.52		1.54	(*dd* / 14.7, 9.7)
13_{eq}	1.83	1.78	1.75	1.69	1.60		1.45	(br.*d* / 14.7)
14	2.09	2.02	2.02	2.02	1.88		2.69[d)]	(br.*d* / 9.7)
15	4.79 (br.*s*)	4.76 (br.*s*)	1.70 (br. *s*)	1.69 (br. *s*)	4.59 (br.*s*)	4.53	4.67	
15'	4.92 (*q* /1.2)	4.91 (*q* /1.4)			4.78 (*q* /1.4)	4.76	4.97	
16	3.62 (*d* / 9.5)	1.00	3.62 (*d* / 9.6)	0.99	0.90	1.04	1.11	(*s*)
16'	3.59 (*d* / 9.5)		3.59 (*d* / 9.6)					
17	2.73	2.65	2.73	2.65	2.65	2.61	2.61	(*sept.* / 6.8)
18	1.06	1.06	1.04	1.03	1.03	0.95	0.93	(*d* / 6.8)
19	0.97	0.94	0.98	0.95	0.92	0.94	0.94	(*d* / 6.8)
20	0.83	0.83	0.90	0.90	0.77	0.67	0.64	(*s*)

[a)] Values taken from ref. 5. [b)] Values taken from ref. 6. [c)] (*t* / 2.8). [d)] (*dddd* / 11.5, 2.8, 1.5, 1.3).

EXPERIMENTAL PART

General. All solvents employed as reaction media were reagent grade (Fluka, puriss.) and were stored over molecular sieves (4Å). M.p. (not corrected): Tottoli apparatus, sealed evacuated capillaries, unless mentioned otherwise. Optical rotations: Perkin-Elmer 241 at 25° and 589 nm (Na_D). IR spectra: Perkin-Elmer 781, ν_{max} in cm^{-1}. ^1H NMR spectra (δ [ppm] from TMS, apparent coupling constants *J* [Hz]): 400 MHz: Bruker AMX 400. ^{13}C NMR spectra (δ [ppm] from TMS, multiplicities as determined from DEPT spectra): 75 MHz: Varian Gemini 300; 100 MHz: Bruker AMX 400. NOE: Bruker WM 300 (300 MHz); irradiated proton → affected signal(s). Mass spectra (m/z [amu] (% base peak)): Hitachi-Perkin-Elmer, VG TRIBRID (EI at 70 eV). GC: HP 5890 or Carlo Erba HRGC 5300. FID; carrier H_2 at 0.45 m/s; capillary tubes, internal diameter 0.25-0.32 mm (glass or fused silica). All calculations were performed on an SGI Onyx.

(5*R*,12*S*,14*R*)-Dolasta-1(15),8-diene ((–)-3) and (5*R*,12*S*,14*R*)-dolasta-1(2),8-diene ((+)-4). A soln. of 123 mg (0.45 mmol) of natural (–)-δ-araneosene (= (1*S*, 3*E*, 7*E*)-3,7,11-dolabellatriene) ((–)-1) from *Sordaria araneosa* CAIN[3] in 38 ml of $CHCl_3$ was cooled to - 45° and treated with 0.01 ml of 38% aq. HCl. After stirring at – 45° for 8 h, 0.25 ml of pyridine were added and the mixture poured onto 100 ml of satd. aq. KH_2PO_4 soln. Workup with CH_2Cl_2 furnished 122 mg (99%) of crude material which was homogeneous on TLC (silica gel, hexane), but shown by GLC (OV 1701) to consist of a 7:3-mixture of **3** and **4**. Repeated chromatography (argentated silica gel (10% $AgNO_3$); hexane/ether, gradient ranging from 98:2 to 95:5) yielded 48 mg (39%) of (–)-**3**, 24 mg (20%) of (+)-**4**, and 34 mg (26%) of a mixture of the two compounds. (–)-**3**: M.p. 54°, sintering at 52° (hexane). $[\alpha]_D$ –115.2 (c = 2.40, hexane). Anal.: Calc. for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.18; H, 12.00%. IR (KBr): 3080, 2980, 2930, 2860, 2840, 1638, 1460, 1452, 1440, 1378, 1360, 1340, 1330, 1098, 1025, 965, 890, 885. ^1H NMR (400 MHz, $CDCl_3$): 4.78 (*q*, *J*= 1.4, 1H); 4.59 (br. *s*, 1H); 2.64 (*sept.*, *J*= 6.8, 1H); 2.28 (*m*, 1H); 2.24-2.16 (*m*, 2H); 2.09 (*dd*, *J*= 15.3, 9.2, 1H); 1.91 (*m*, 1H); 1.88 (br. *d*, *J*= 9.7, 1H); 1.74 (*tt*, *J*= 13.4, 1.7, 1H); 1.61-1.53 (*m*, 3H); 1.50-1.37 (*m*, 5H); 1.23 (*m*, 1H); 1.08 (*td J*= 12.7, 1.7, 1H); 1.03 (*d*, *J*= 6.8, 3H); 0.92 (*d*, *J*= 6.8, 3H); 0.90 (*s*, 3H); 0.77 (*s*, 3H). ^1H NMR (400 MHz, C_6D_6): 4.91 (*q*, *J*= 1.2, 1H); 4.76 (br.*s*, 1H); 2.65 (*sept.*, *J*= 6.8, 1H); 2.30-2.20 (*m*, 3H); 2.12 (*dd*, *J*= 15.3, 9.2, 1H); 2.02 (br. *d*, *J*= 10.0, 1H); 1.90-1.75 (*m*, 3H); 1.68-1.42 (*m*, 6H); 1.38 (*m*, 1H); 1.25-1.14 (*m*, 2H); 1.06 (*d*, *J*= 6.8, 3H); 1.00 (*s*, 3H); 0.94 (*d*, *J*= 6.8, 3H); 0.83 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.4 *(s)*, 142.4 *(s)*, 138.8 *(s)*, 107.5 *(t)*, 48.8 *(s)*, 47.5 *(t)*, 45.4 *(d)*, 44.4 *(t)*, 39.2 *(s)*, 38.6 *(t)*, 37.4 *(t)*, 36.6 *(t)*, 27.2 *(t)*, 28.8 *(d)*; 26.1 *(q)*, 24.5 *(t)*, 21.9 *(q)*, 21.3 *(q)*, 20.3 *(t)*, 17.9 *(q)*. MS (EI): 272 (60, M$^+$), 257 (23), 229 (100), 161 (12), 147 (15), 135 (16), 133 (30), 123 (58), 122 (64), 121 (42), 119 (16), 107 (48), 105 (24), 95 (31), 93 (33), 91 (38), 81 (24), 79 (34), 77 (27), 55 (36), 43 (23), 41 (51). (+)-**4**: Colorless oil. $[\alpha]_D$ +30.8 (c = 1.04, hexane). Anal.: Calc. for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 87.99; H, 12.07%. IR (CCl_4): 3020, 2960, 2920, 2860, 2840, 1660, 1465, 1450, 1435, 1378, 1360, 1012. ^1H NMR (400 MHz, $CDCl_3$): 5.43 (*m*, 1H); 2.65 (*sept.*, *J*= 6.8, 1H); 2.26-2.17 (*m*, 2H); 2.11 (*dd*, *J*= 15.3, 9.2, 1H); 2.03 (*m*, 1H); 1.87-1.78 (*m*, 3H); 1.66-1.59 (*m*, 2H); 1.64 (br. *s*, 3H); 1.48 (*dd*, *J*= 12.5, 6.9, 1H); 1.44 (*m*, 1H); 1.34-1.18 (*m*, 3H); 1.00 (*td*, *J*= 12.7, 2.5, 1 H); 1.00 (*d*, *J*= 6.8, 3H); 0.91 (*d*, *J*= 6.8, 3H); 0.90 (*s*, 3H); 0.84 (*s*, 3H). ^1H NMR (400 MHz, C_6D_6): 5.51 (*m*, 1H); 2.65 (*sept.*, *J*= 6.8, 1H); 2.31-2.23 (*m*, 2H); 2.10 (*m*, 1H); 2.14 (*dd*, *J*= 15.3, 9.2, 1H); 1.93 (br.*d*, *J*= 9.5, 1H); 1.88 (*tt*, *J*= 13.4, 1.7, 1H); 1.85 (*m*, 1H); 1.68 (*m*, 1H); 1.68 (br. *s*, 3H); 1.52 (*dd*, *J*= 12.5, 6.9, 1H); 1.43 (*m*, 1H); 1.40 (*dd*, *J*= 14.9, 9.5, 1H); 1.25-1.14 (*m*, 2H); 1.30-1.26 (*m*, 2H); 1.07 (*td*, *J*= 12.7, 2.5, 1H); 1.03 (*d*, *J*= 6.8, 3H); 0.99 (*s*, 3H); 0.95 (*d*, *J*= 6.8, 3H); 0.90 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 141.8 *(s)*, 139.9 *(s)*, 136.5 *(s)*, 122.7 *(d)*, 49.6 *(s)*, 46.4 *(t)*, 43.7 *(d)*, 39.8 *(t)*, 36.2 *(t)*, 35.4 *(s)*, 34.5 *(t)*, 27.4 *(t)*, 26.9 *(d)*, 25.5 *(q)*; 23.2 *(q)*, 22.5 *(t)*, 22.0 *(q)*, 21.2 *(q)*, 20.5 *(t)*, 18.5 *(q)*. MS (EI): 272 (11, M$^+$), 257 (1), 229 (12), 147 (8), 123 (19), 122 (100), 121 (42), 107 (20), 95 (14), 93 (12), 91 (13), 81 (11), 41 (12).

(5*R,12*S**,14*R**)-16-(*t*-Butyl-diphenylsilyl)oxy-dolasta-1(15),8-diene ((±)-8) and (5*R**,12*S**,14*R**)-16-(*t*-butyl-diphenylsilyl)oxy-dolasta-1(2),8-diene ((±)-9).** A soln. of 17.4 mg (0.031 mmol) of synthetic (±)-16-(*t*-butyl-diphenylsilyl)oxy-δ-araneosene (**7**)[3] in 2 ml of $CHCl_3$ was treated with 0.01 ml of 38% aq. HCl at 25°. After stirring at 25° for 1 h, 0.1 ml of pyridine were added and the mixture poured onto 30 ml of satd. aq. KH_2PO_4 soln. Workup with ether furnished 17 mg (98%) of crude material which was homogeneous on TLC (silica gel, hexane), but shown by GLC (SE 54) to consist of a 2.6:1-mixture of **8** and **9**. This mixture was analyzed by means of a DQF-^1H-COSY experiment (400 MHz, C_6D_6) with the results presented in Table 2). Repeated chromatography (argentated silica gel (10% $AgNO_3$); hexane/ether, gradient ranging from 97:3 to 1:1) yielded 11.1 mg (64%) of the more polar (±)-**8** and 4 mg (23%) of (±)-**9**. (±)-**8**: Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): 7.69-7.65 (*m*, 4H); 7.44-7.34 (*m*, 6H); 4.79 (*q*, *J*= 1.3, 1H); 4.58 (br. *s*, 1H); 3.40 (*d*, *J*= 9.5, 1H); 3.36 (*d*, *J*= 9.5, 1H); 2.71 (*sept.*, *J*= 6.8, 1H); 2.30 (*m*, 1H); 2.24-2.15 (*m*, 2H); 2.08 (*dd*, *J*= 15.3, 9.2, 1H); 1.96-1.90 (*m*, 2H); 1.87 (*tt*, *J*= 13.4, 1.7, 1H); 1.75 (*dd*, *J*= 12.5, 6.9, 1H); 1.60-1.53 (*m*, 4H); 1.49-1.37 (*m*, 3H); 1.24 (*m*, 1H); 1.08 (*td*, *J*= 12.7, 2.5, 1H); 1.05 (*s*, 9H); 1.04 (*d*, *J*= 6.8, 3H); 0.92 (*d*, *J*= 6.8, 3H); 0.73 (*s*, 3H). ^1H NMR (400 MHz, C_6D_6): 7.84-7.80 (*m*, 4H); 7.28-7.20 (*m*, 6H); 4.92 (*q*, *J*= 1.2, 1H); 4.79 (br. *s*, 1H); 3.62 (*d*, *J*= 9.5, 1H); 3.59 (*d*, *J*= 9.5, 1H); 2.73 (*sept.*, *J*= 6.8, 1H); 2.33-2.25 (*m*, 3H); 2.12 (*dd*, *J*= 15.3, 9.2, 1H); 2.09 (br. *d*, *J*= 9.7, 1H); 2.00 (*tt*, *J*= 13.4, 1.7, 1H); 1.90 (*dd*, *J*= 12.5, 6.9, 1H); 1.88 (*m*, 1H); 1.83 (br. *d*, *J*= 14.7, 1H); 1.76 (*dd*, *J*= 14.7, 9.7, 1H); 1.61-1.53 (*m*, 2H); 1.50-1.43 (*m*, 2H); 1.39 (*m*, 1H); 1.23 (*m*, 1H); 1.21 (*s*, 9H); 1.18 (*td*, *J*= 12.7, 2.5, 1H); 1.06 (*d*, *J*= 6.8, 3H); 0.97 (*d*, *J*= 6.8, 3H); 0.83 (*s*, 3H). NOE (300 MHz, C_6D_6): a) Irrad. at 0.83 ppm (H_3-C(20)) → 7.82 (ar. H's); 2.00 (7_{ax}); 1.76 (13_{ax}); 1.58 (6_{eq}); 1.47 (3_{ax}); 1.39 (4_{eq}). b) Irrad. at 3.60 ppm (H_2-C(16)) → 7.82 (ar. H's); 2.00 (7_{ax}); 1.90 (11_{exo}); 1.83 (13_{eq}); 1.76 (13_{ax}); 1.21 (*t*-Bu). MS (EI): 526 (4, M$^+$), 469 (12), 257 (100), 256 (25), 199 (45), 161 (15), 135 (15), 121 (10), 105 (11), 95 (14), 91 (11). (±)-**9**: Colorless oil. ^{1}H NMR (400 MHz, C_6D_6): 7.83-7.79 (*m*, 4H); 7.28-7.21 (*m*, 6H); 5.53 (*m*, 1H); 3.61 (*d*, *J*= 9.6, 1H); 3.59 (*d*, *J*= 9.6, 1H); 2.73 (*sept.*, *J*= 6.8, 1H); 2.36-2.25 (*m*, 2H); 2.13 (*dd*, *J*= 15.3, 9.2, 1H); 2.10 (*tt*, *J*= 13.4, 1.7, 1H); 2.10 (*m*, 1H); 2.02 (br. *d*, *J*= 9.7, 1H); 1.90 (*dd*, *J*= 12.5, 6.9, 1H); 1.85 (*m*, 1H); 1.75 (*d*, *J*= 14.9, 1H); 1.70 (br. *s*, 3H); 1.64 (*dd*, *J*= 14.9, 9.7, 1H); 1.64 (*m*, 1H); 1.43 (*m*, 1H); 1.29 (*dd*, *J*= 8.9, 3.5, 1H); 1.20 (*s*, 9H); 1.08 (*td*, *J*= 12.7, 2.5, 1H); 1.04 (*d*, *J*= 6.8, 3H); 0.98 (*d*, *J*= 6.8, 3H); 0.90 (*s*, 3H).

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(*Received in Germany* 2 *October* 1995; *accepted* 13 *November* 1995)