Synthesis of (1α,7α,8β)-(±)-8-Methyl-2-methylenebicyclo[5.3.0]dec-5-en-8-ol. Structure Revision of Natural Dictamnol

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The total synthesis of the title compound (±)-1 is described. The key step in the synthesis of this *cis*-fused trinor-guaiane is the base-induced and -directed rearrangement of the tosylate ester 4. Because of differences in the spectral data of synthetic (±)-1 and natural dictamnol, a trinor-guaiane isolated from *Dictamnus dasycarpus* TURCZ., a revised structure for the natural product is proposed. Nuclear Overhauser effect (NOE) difference experiments and a detailed investigation of the air-induced cyclization reaction of pregeijerene, isolated from *Amyris diatrypa* SPRENGEL, support the structure revision of natural dictamnol.

Key words *Dictamnus dasycarpus*; dictamnol; structure revision; pregeijerene; cyclization

Recently, the isolation of a trinor-guaiane sesquiterpene from the roots of *Dictamnus dasycarpus* TURCZ. has been reported.[1] Based on information obtained by spectroscopic techniques, it has been proposed that this natural product, named dictamnol, possesses a *cis*-fused hydroazulene skeleton and a tertiary β-hydroxyl group at C-4 as shown in structure **1** (Fig. 1).[2] In the present paper the total synthesis of (±)-**1** is described and a revision of the structure of natural dictamnol is proposed.

From our previous work on the total synthesis of sesquiterpenes,[3] it is known that stereochemically rigid *trans*-perhydronaphthalene-1,4-diol monosulfonate esters rearrange smoothly upon treatment with sodium *tert*-amylate in refluxing apolar solvents to *cis*-perhydroazulene systems with an exocyclic methylene unit. It was recognized that this intramolecular base-induced and -directed rearrangement could also be used for the synthesis of the cis-fused trinor-guaiane **1**.

Our synthetic route to **1**, shown in Chart 1, was straightforward and started from the readily available monoprotected olefinic 1,4-diol **2**, previously used in the total synthesis of alloaromadendrane-4,10-diols.[3b] Cleavage of the *tert*-butyldimethylsilyl (TBDMS) protecting group with 40% aqueous hydrogen fluoride (**2**→**3**) followed by tosylation of the secondary alcohol (**3**→**4**) could be achieved in 67% overall yield. A short treatment (15 min) of **4** with five equivalents of sodium *tert*-amylate in refluxing toluene gave, after chromatographic separation, **1** (60% yield) together with the cyclic ether **5** (21%).

The formation of **1** and **5** proceeds *via* initial heterolysis of the tosylate ester bond, intramolecularly induced by the deprotonated hydroxyl group.[3,4] The resulting dipolar intermediate A rapidly rearranges to the thermodynamically more stable *cis*-fused tertiary carbocation B (Chart 2). In B, the original angular methyl group and the alkoxide substituent are close together which explains the formation of **1** by selective deprotonation and of **5** by direct trapping of the positive charge by the alkoxide group.

The 1,5-*cis*-hydroazulene structure of (±)-**1** and its stereochemistry around C-4 were ascertained by nuclear Overhauser effect (NOE) difference experiments.[5] Irradiation of the H-1 signal at δ 3.05 lead to NOEs with H-5 and

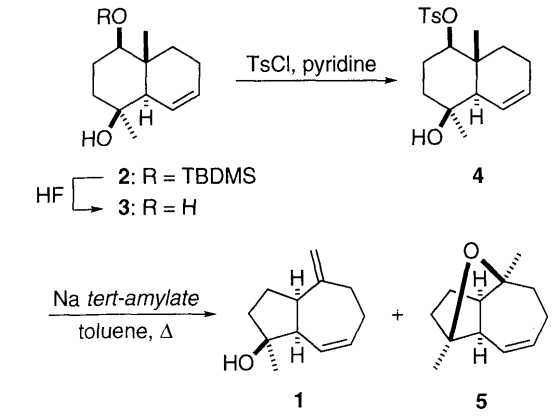

Chart 1

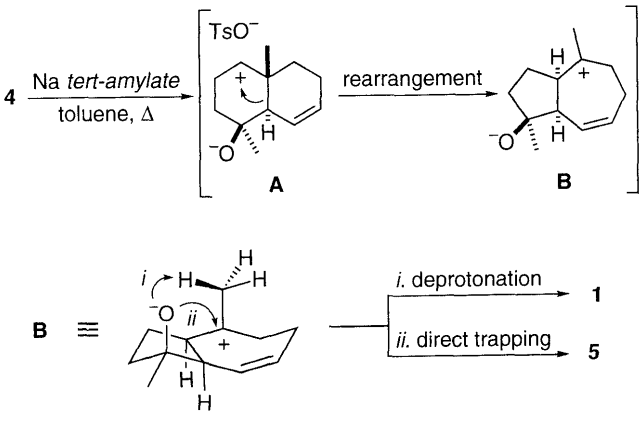

Chart 2

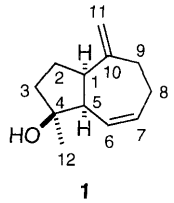

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Fig. 1. Proposed Structure for Natural Dictamnol

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Table 1. ^{1}H-NMR Spectral Data for Natural Dictamnol and (±)-**1**

H	Natural dictamnol[a]	(±)-**1**[b]
	δ, multiplicity (J in Hz)	δ, multiplicity (J in Hz)
1	2.46 m	3.05 ddd (10.6, 7.7, 7.7)
2	1.92 m	1.98 m
2′		1.79 m
3	1.75—1.87 m	1.90 ddd (12.6, 7.4, 2.1)
3′		1.65 ddd (12.6, 11.0, 8.0)
5	2.40 ddq (11.8, 2.4, 2.4)	2.66 ddq (10.6, 5.7, 1.7)
6	5.80 ddt (11.2, 2.4, 1.2)	5.55 ddt (12.0, 5.7, 1.5)
7	5.89 dddd (11.2, 5.3, 5.3, 2.4)	5.83 dddd (12.0, 5.2, 5.2, 1.7)
8	2.31 m	
8′	2.13 m	2.14—2.29 m
9	2.22 m	
9′	2.58 m	2.51 m
11	4.76 br s	4.73 br s
11′	4.84 br s	4.79 br s
12	1.25 s	1.27 s
4OH	1.44 br s	1.70 br s

a) Measured in $CDCl_3$ at 400 MHz. b) Measured in $CDCl_3$ at 200 MHz.

Table 2. ^{13}C-NMR Spectral Data for Natural Dictamnol and (±)-**1**

C	Natural dictamnol[a]	(±)-**1**[b]
	δ[c]	δ[c]
1	47.46 d	48.99 d
2	25.71 t	29.27 t
3	40.50 t	40.33 t
4	80.78 s	80.44 s
5	55.86 d	53.21 d
6	130.16 d	125.68 d
7	132.06 d	132.32 d
8	29.17 t	30.38 t
9	37.17 t	32.68 t
10	153.80 s	152.56 s
11	107.57 t	109.99 t
12	24.56 q	27.04 q

a) Measured in $CDCl_3$ at 100 MHz. b) Measured in $CDCl_3$ at 50 MHz. c) Multiplicities were determined by DEPT.

the C-11 proton at δ 4.79. Irradiation of the methyl singlet at δ 1.27 gave clear NOEs with H-5 and H-6. These NOEs show the close proximity of H-1 and H-5, and of H-5 and the methyl protons, indicating that these protons are positioned on the same side of the molecule. In addition, the concomitant formation of the cyclic 4,10-ether **5** also indicates a *cis*-fused ring junction of the 5,7-ring system. As the NMR spectral data of our synthetic (±)-**1** were clearly different from those of a pure sample of natural dictamnol[6] (Tables 1 and 2), we had reasons to assume that the natural compound has a different stereochemistry as proposed in the literature.[1]

NOE difference measurements[5] on natural dictamnol revealed the presence of a *trans*-fused ring junction. On irradiation of the methyl singlet at δ 1.25, no NOE with H-5 was observed, while a NOE was present between this methyl group and H-1. This observation led us to conclude that H-1 and the methyl group are situated on one side of the molecule and H-5 on the opposite side.

Detailed analysis of the ^{1}H-NMR data for natural dictamnol and synthetic (±)-**1** also revealed different ring

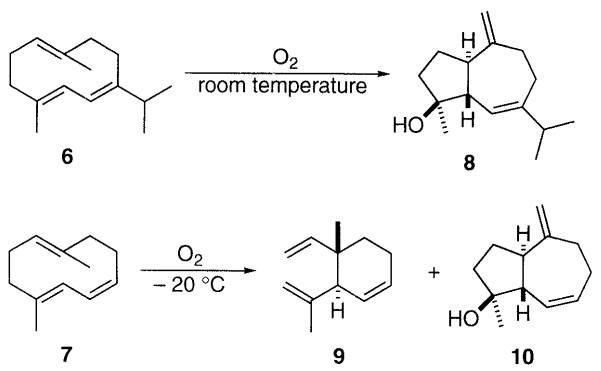

Chart 3

junctions in the two compounds. From the spectral data collected in Table 1, we concluded that the coupling constant between H-5 and H-6 ($J_{5,6}$) amounts to 2.4 Hz for natural dictamnol and 5.7 Hz for synthetic (±)-**1**. The $J_{5,6}$ values for the 1,5-*trans*-guaiane sesquiterpene alismol (**8**) and structurally related 1,5-*trans*-guaianes, given in the literature,[7-9] range from 2.5 to 3.1 Hz. These values are similar to the $J_{5,6}$ value found for natural dictamnol, and from this similarity one may conclude that these compounds all possess a common structural characteristic, *i.e.*, a *trans*-fused ring junction.

Additional support for the *trans*-fused structure of dictamnol was obtained from comparison of the chemical behavior of germacrene C (**6**)[10] and pregeijerene (**7**).[11] The latter compound is the major constituent of the essential oil of the leaves of *Amyris diatrypa* SPRENGEL.[12] It is known[13] that germacrene C cyclizes to **8** under the influence of air at room temperature (Chart 3).

A similar cyclization reaction was accomplished for pregeijerene. After being in contact with air for one week at −20 °C, a sample of **7**[14] was completely converted into a mixture of two major and several minor compounds. According to GC-MS analysis, the two main components of the mixture were geijerene (**9**) (45%) and compound **10** (20%) which exhibits exactly the same retention time and mass spectrum as natural dictamnol, isolated from *D. dasycarpus*. A Cope rearrangement of **7** explains the formation of **9**,[11] whereas air-oxidation must be responsible for the formation of **10** which is, most likely, (±)-dictamnol.[15] Because, as mentioned above, air-oxidation of **6** gives exclusively a 1,5-*trans*-guaiane, it is to be expected that air-oxidation of the structurally related **7** will also result in a *trans*-fused ring junction as is illustrated in structure **10**.

Summarizing the results described above, we propose that dictamnol isolated from *D. dasycarpus* possesses the *trans* stereochemistry as shown in structure **10**, and not the one proposed in structure **1**. In addition, it seems likely that pregeijerene (**7**), present in *ca.* 2% in *D. dasycarpus*,[16] is the natural precursor of dictamnol.

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The ^{1}H- and ^{13}C-NMR spectra were obtained with a Bruker AC-E 200 or a Bruker DPX 400 spectrometer. Chemical shifts are given relative to tetramethylsilane (δ 0.00), with $CHCl_3$ as an internal standard (δ_H 7.23 and δ_C 76.90). ^{13}C-NMR multiplicities were determined by using a DEPT pulse sequence. NOE

difference experiments were performed at 200 or 400 MHz, using a τ_m of 2—4 s. MS data were determined at 70 eV on either an Finigan EI-MAT95 spectrometer or a Hewlett Packard 5890B series Mass Selective Detector, coupled with a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 mm. He was used as the carrier gas. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. Flash chromatography was performed on Silica gel 60 (Merck, 230—400 mesh).

Solvents were dried and freshly distilled by common practice. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent.

(1α,4α,4aα,8aβ)-(±)-1,2,3,4,4a,5,6,8a-Octahydro-1,4a-dimethylnaphthalene-1,4-diol (3) A solution of **2**[3b] (2.00 g, 6.45 mmol) in acetonitrile (50 ml) was treated with 40% aqueous hydrogen fluoride (2 ml) and the mixture was stirred at room temperature for 1.5 h. After this time, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (150 ml) and extracted with EtOAc. The EtOAc extract was washed with brine and dried. After removal of the solvent from the EtOAc extract under reduced pressure, the remaining residue (1.28 g) was purified by crystallization from petroleum ether (bp 60—80 °C)–EtOAc to furnish **3** (0.94 g, 74%).

(±)-**3**: White crystals, mp 122—122.5 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.97 (s, 3H, C4a-CH_3), 1.16 (s, 3H, C1-CH_3), 1.19—2.07 (m, 11H), 3.26 (dd, 1H, J=11.4, 4.1 Hz, C4-H), 5.62—5.77 (m, 2H, C7, C8-H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 11.7 (q), 22.9 (t), 27.0 (t), 29.3 (q), 34.7 (t), 37.9 (s), 38.8 (t), 49.9 (d), 71.0 (s), 78.2 (d), 124.0 (d), 129.4 (d). HR-MS m/z: 196.1463 [Calcd for $C_{12}H_{20}O_2$ (M^+): 196.1463]. MS m/z (rel. int. %): 196 (M^+, 0.1), 181 (1), 178 (16), 163 (12), 160 (9), 145 (20), 120 (100), 118 (33), 107 (69), 105 (39). *Anal.* Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 72.84; H, 10.30.

(1α,4α,4aα,8aβ)-(±)-1,2,3,4,4a,5,6,8a-Octahydro-1,4a-dimethylnaphthalene-1,4-diol 4-(4′-Methyl-benzenesulfonate) (4) A solution of **3** (0.90 g, 4.58 mmol) and TsCl (1.75 g, 9.15 mmol) in dry pyridine (50 ml) was stirred at room temperature and the reaction progress was followed by TLC. At completion, pyridine was removed under reduced pressure and the residue was taken up in EtOAc. The EtOAc solution was washed successively with 10% aqueous H_2SO_4, saturated aqueous $NaHCO_3$, and brine, then dried. After removal of the solvent from the EtOAc solution under reduced pressure, the remaining residue (1.70 g) was crystallized from petroleum (bp 60—80 °C)–EtOAc to afford **4** (1.45 g, 91%).

(±)-**4**: White crystals, mp 120—121 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.04 (s, 3H, C4a-CH_3), 1.09—2.36 (m, 10H), 1.17 (s, 3H, C1-CH_3), 2.41 (s, 3H, C4′-CH_3), 4.27 (dd, 1H, J=11.9, 4.3 Hz, C4-H), 5.60—5.76 (m, 2H, C7, C8-H), 7.30 (d, 2H, J=8.2 Hz, C3′, C5′-H), 7.76 (d, 2H, J=8.2 Hz, C2′, C6′-H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 12.3 (q), 21.6 (q), 22.7 (t), 24.5 (t), 29.1 (q), 34.2 (t), 37.6 (s), 38.5 (t), 50.1 (d), 70.3 (s), 89.3 (d), 123.1 (d), 127.6 (2d), 129.7 (3d), 134.6 (s), 144.4 (s). HR-MS m/z: 178.1357 [Calcd for $C_{12}H_{18}O$ ($M^+ - 172$): 178.1357]. MS m/z (rel. int. %): 178 ($M^+ - 172$, 43), 172 (17), 163 (18), 160 (22), 145 (32), 120 (100), 118 (36), 107 (25). *Anal.* Calcd for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48. Found: C, 64.80; H, 7.46.

Rearrangement of Tosylate 4 A solution of **4** (0.35 g, 1.0 mmol) in dry toluene (11 ml) was degassed and refluxed under an Ar atmosphere. To the refluxing solution was added 2.2 M sodium *tert*-amylate in toluene[17] (2.5 ml) at once. The reaction mixture was refluxed for an additional 10 min, quenched with precooled saturated aqueous NH_4Cl (15 ml), and then quickly cooled to 0 °C. The mixture was vigorously stirred for 20 min and extracted with petroleum ether (bp 40—60 °C). The extract was washed with brine, dried, and concentrated under reduced pressure. The remaining product mixture was separated by flash chromatography [petroleum ether (bp 40—60 °C)–EtOAc (25 : 1)] to afford, in order of elution, the cyclic ether **5** (26 mg, 21%) and **1** (107 mg, 60%).

(1α,7α,8β)-(±)-8-Methyl-2-methylenebicyclo[5.3.0]dec-5-en-8-ol (1) Colorless oil. ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2. HR-MS m/z: 178.1352 [Calcd for $C_{12}H_{18}O$ (M^+): 178.1358]. MS m/z (rel. int. %): 178 (M^+, 2), 160 (17), 145 (38), 131 (15), 120 (60), 118 (26), 105 (79), 91 (79), 79 (61), 71 (28), 43 (100).

(1α,2β,7α,8β)-(±)-2,8-Dimethyl-2,8-epoxybicyclo[5.3.0]dec-5-ene (5) Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.22, 1.26 (both s, 3H each, C4-CH_3, C10-CH_3), 1.45—1.73 (m, 4H), 1.83—1.92 (m, 2H), 2.13—2.29 (m, 3H), 2.41 (br d, 1H, J=3.3 Hz, C1-H), 5.55 (ddt, 1H, J=11.5, 7.1, 1.5 Hz, C6-H), 5.88 (dt, 1H, J=11.5, 5.4 Hz, C7-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.1 (q), 25.0 (t), 25.2 (t), 28.3 (q), 35.6 (t), 41.9 (t), 50.0 (d), 55.2 (d), 82.2 (s), 87.8 (s), 127.5 (d), 131.9 (d). HR-MS m/z: 178.1353 [Calcd for $C_{12}H_{18}O$ (M^+): 178.1358]. MS m/z (rel. int. %): 178 (M^+, 16), 145 (29), 120 (88), 118 (27), 107 (31), 105 (94), 93 (41), 92 (55), 91 (84), 79 (69), 43 (100).

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Added in Proof (June 21, 1996) In a very recent paper, Koike *et al.* [*Chem. Pharm. Bull.*, **44**, 646—652 (1996)) claim to have synthesized natural dictamnol, having a *cis*-fused hydroazulene skeleton. As we have pointed out in the current paper, natural dictamnol possesses a *trans*- and not a *cis*-fused hydroazulene system. In the synthetic sequence of Koike *et al.*, epimerization at the bridgehead carbon atom next to the keto function of compound **30** under the influence of the strongly acidic Jones' reagent has not been recognized. Co-injection of our synthetic *cis*-dictamnol (**1**) and natural dictamnol (**10**) on capillary GC (SGE-BP5, 25 m × 0.25 mm, d_f=0.25 μm, 60°→260°, 3°/min) reveals that these compounds are different (Kováts indices of **1** and **10** are 1382 and 1429, respectively). Furthermore, the stereochemistry of compound **20** (and **21**) in Koike's article is incorrect. Inversion of the hydroxyl group during the rearrangement **19**→**20** as proposed has never been observed in similar rearrangement reactions studied by us and is mechanistically unlikely. In fact, Koike's compound **20** is identical to *cis*-dictamnol **1** in the current paper, as is proved by the identity of the ^{1}H- and ^{13}C-NMR-spectra of these compounds.

References and Notes

1) Takeuchi N., Fujita T., Goto K., Morisaki N., Osone N., Tobinaga S., *Chem. Pharm. Bull.*, **41**, 923—925 (1993).
2) The numbering system for azulenic compounds follows the numbering as given in structure **1**.
3) *a*) Wijnberg J. B. P. A., Jenniskens L. H. D., Brunekreef G. A., de Groot A., *J. Org. Chem.*, **55**, 941—948 (1990); *b*) Jenniskens L. H. D., Wijnberg J. B. P. A., de Groot A., *ibid.*, **56**, 6585—6591 (1991).
4) *a*) Orrū R. V. A., Wijnberg J. B. P. A., Jenniskens L. H. D., de Groot A., *J. Org. Chem.*, **58**, 1199—1206 (1993); *b*) Orrū R. V. A., Wijnberg J. B. P. A., Bouwman C. T., de Groot A., *ibid.*, **59**, 374—382 (1994); *c*) Orrū R. V. A., Wijnberg J. B. P. A., de Groot A., *ibid.*, **60**, 4233—4239 (1995).
5) The small positive NOEs found in most small and medium-sized molecules are difficult to detect reliably by nuclear Overhauser and exchange spectroscopy (NOESY), partly because of sensitivity problems exacerbated by long relaxation delays needed between experiments: Morris G. A., *Magn. Reson. Chem.*, **24**, 371—403 (1986). Therefore, NOE difference spectroscopy instead of NOESY was used to determine NOEs in synthetic (±)-**1** and natural dictamnol.
6) Following the isolation procedure described in the literature,[1] 1 kg of commercially available *Dictamnus dasycarpus* TURCZ. (Uchida Wakanyaku Company, Ltd.) provided 96 mg of dictamnol. This compound was reported to have a specific optical rotation of $[\alpha]_D$+55° (c=0.1, MeOH).[1] In this investigation, we have found that dictamnol isolated from *D. dasycarpus* showed no significant optical activity: $[\alpha]_D$±0° (c=0.1, MeOH; c=0.9, $CHCl_3$). In contrast to the $[\alpha]_D$ data, the NMR spectral data of dictamnol determined in this study (Tables 1 and 2) were found to be the same as those reported.[1]
7) *a*) Yoshikawa M., Yamaguchi S., Matsuda H., Kohda Y., Ishikawa H., Tanaka N., Yamahara J., Murakami N., *Chem. Pharm. Bull.*, **42**, 1813—1816 (1994); *b*) Yoshikawa M., Yamaguchi S., Matsuda H., Tanaka N., Yamahara J., Murakami N., *ibid.*, **42**, 2430—2435 (1994).
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13) Kitagawa I., Kobayashi M., Cui Z., Kiyota Y., Ohnishi M., *Chem. Pharm. Bull.*, **34**, 4590—4596 (1986).
14) Preparative GC at 120 °C of the essential oil of the leaves of *Amyris diatrypa* SPRENGEL provided an almost pure sample of pregeijerene (**7**). At temperatures > 120 °C Cope rearrangement to geijerene (**9**) took place. For example, see: Kubeczka K.-H., *Phytochemistry*, **13**, 2017—2018 (1974).
15) Because air-oxidation of **6** resulted in the formation of (±)-**8**,[13] it was assumed that air-induced cyclization of **7** also led to a racemic mixture, in this case (±)-dictamnol.
16) GC-MS analysis of the essential oil of the leaves of *Amyris diatrypa* SPRENGEL also revealed the presence of both pregeijerene and dictamnol.[12]
17) Sodium *tert*-amylate (2.2 M in toluene) was prepared as described: Conia M. J.-M., *Bull. Soc. Chim.*, **17**, 537—541 (1950).