The Formation of 8-Epipodocarp-9(11)en-12-one in the Course of the Preparation of Podocarp-9(11)-en-12-one from *O*-Methylpodocarpane and Related Studies[1])

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The preparation of podocarp-9(11)-en-12-one (**1a**) from *O*-methylpodocarpane (**2**) was investigated with the aim of clarifying whether 8-epipodocarp-9(11)-en-12-one (**1b**) is formed to any extent during the early stages of the process. This study, supported by molecular-mechanics calculations, resulted in the preparation, along with **1a**, of the previously undescribed **1b**, which could be fully characterized by means of 2D-NMR experiments. Significant differences recorded in the NMR and NOESY spectra of **1a** and **1b** were of diagnostic value in establishing the relative configuration at C(8) and possibly might be helpful to solve similar problems on podocarp-9(11)-en-12-one derivatives.

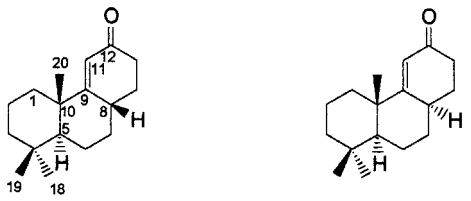
1. Introduction. – Podocarp-9(11)-en-12-one (**1a**) and derivatives [1][2] are key intermediates in the synthesis of several polycyclic diterpenes such as podocarpic acid [1e], methyl vinhaticoate [1c], nagilactone F [1l], maritimol [1i][2b], aphidicolin [1n][2c] and related isosters [1p], stemarin [1h], stemar-13-ene [2e], phytocassane D [1q]. They have been obtained either by *Birch* reduction of an *O*-methylpodocarpane, followed by acidic cleavage of the resulting dienol ether, or from a 5,5,8a-trimethyloctahydronaphthalene-1-one by *Robinson* annulation with but-3-en-2-one.

Though these processes could, in principle, lead to two epimers at C(8), apparently a single epimer was always obtained. Thus, the H–C(8) was assigned the β-configuration, which corresponds to the most stable structure on molecular-model inspections [1a]. This conclusion, supported by chemical evidence [1b] but not clarified by ^{1}H-NMR experiments [1e] or by a theoretical or experimental evaluation of stability difference between the two C(8) epimers, was eventually confirmed through the established configuration of the final products. To the best of our knowledge, the corresponding H_α–C(8) epimers were never observed. It is not known whether this is because the H_α–C(8) epimers were not formed at all, owing to a steric preference for protonation of the dienol intermediate at C(8) from the β face, or to a very large

[1]) A preliminary report of this work was presented at the 'XXVII Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana', Trieste, Sept. 3.–7., 2001, Atti P124.

stability difference and to the harsh experimental conditions adopted in the preparation, or because they were inadvertently removed during the purification step.

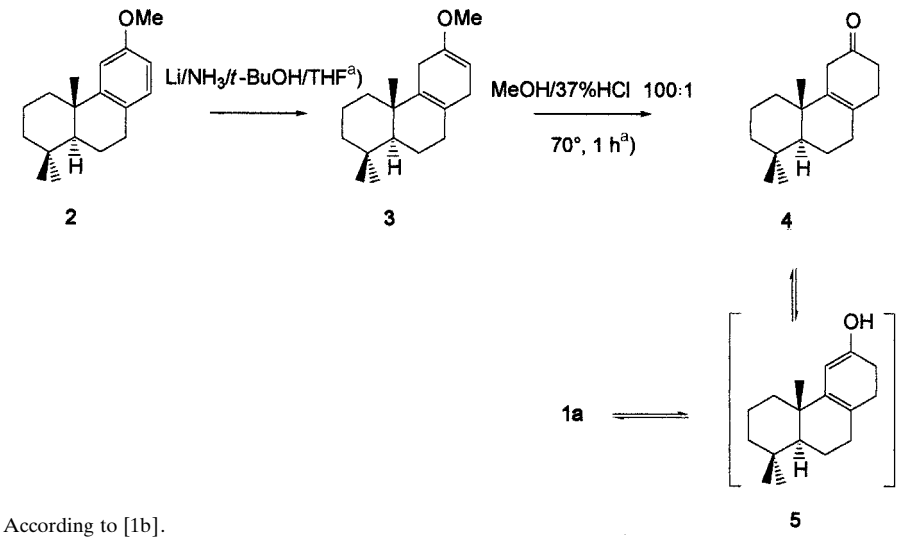
Thus, as a part of our investigation on the synthesis of natural products *via* podocarp-9(11)-en-12-ones and with respect to the general interest in this class of compounds, we decided to evaluate, by molecular-mechanics (MM) calculations, the stability difference between **1a** and **1b**, the parent members of this class, to investigate



1a **1b**

whether **1b** is formed in the course of the preparation of **1a**[2]), and to find ways to establish directly the relative configuration at C(8) without the need of a chemical correlation. Between the two processes (see above) leading to **1a**, we chose the one starting from *O*-methylpodocarpane (**2**) and proceeding *via* **3**, **4**, and **5** (*Scheme*) [3]. This route seemed more suitable than that based on the *Robinson* annulation, since it can be carried out more easily in two steps, the second of which is executable under mild acidic conditions.

Scheme



[a]) According to [1b].

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[2]) One of us (*R. M. B.*) recalls Prof. *Sándor Antus* asking him this question after a seminar given in the fall of 1993 at the Institute of Organic Chemistry of the *L. Kossuth* University, Debrecen.

2. Results and Discussion. – 2.1. *Molecular-Mechanics* (MM) *Calculations and Geometric Analysis.* MM Calculations were performed with MM2*, MM3*, and MMFF force fields (see *Exper. Part*). As can be observed (*Table 1*), depending on the force field used, the differences in steric energy between **1a** and **1b** vary from 1.2 to 4.2 kcal/mol.

Table 1. *Steric Energies* [kcal/mol] *Obtained from MM2*, MM3*, and MMFF Force Fields Implemented in MacroModel 6.0*

	MM3*	MM2*	MMFF
1a	35.8	34.8	57.2
1b	40.0	36.0	59.4
ΔE(**1b** – **1a**)	4.2	1.2	2.2

Though calculated steric-energy values should be regarded as merely qualitative, their trend is in agreement with the fact that 8-epipodocarp-9(11)-en-12-ones were not detected among the products at the end of the vigorous preparation process to obtain podocarp-9(11)-en-12-ones.

The structures of the most stable conformer of **1a** and **1b** are shown in *Fig. 1*. Their inspection reveals that, in **1a**, ring B is in a chair conformation, while, in **1b**, the same ring is constrained in a twist-boat conformation.

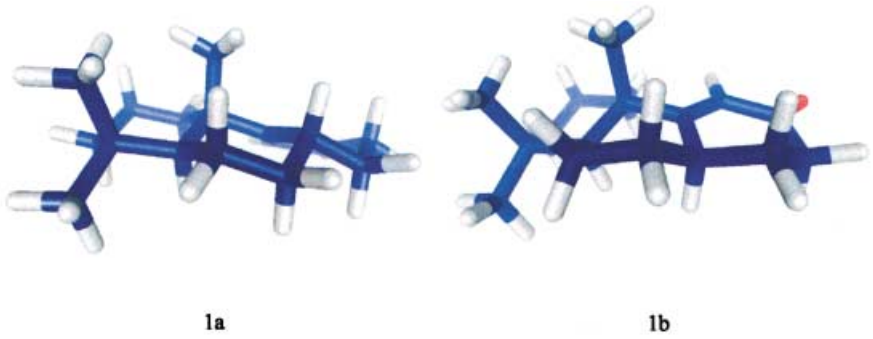


Fig. 1. *Structures of the most stable conformer of* **1a** *and* **1b**

The diastereotopic faces of the dienol system in the optimized structure of intermediate **5** (*Fig. 2*)[3]) apparently do not show any major steric preference for protonation at C(8) (arrows in *Fig. 2*). It cannot be excluded, therefore, that, provided that the reaction medium does not play a significant role, **1b** might be formed along with **1a** under proper conditions.

2.2. *Preparation and Characterization of* **1a** *and* **1b**. Optically active **1a** was prepared, according to the literature, by *Birch* reduction of podocarpic acid derivative *O*-methylpodocarpane (**2**), followed by acidic cleavage of the resulting dienol ether **3** [1a].

^{1}H- and ^{13}C-NMR, DEPT, HETCOR, and 2D-COSY-45 on **1a** allowed us to assign all resonances (*Table 2*), confirming the assignments previously given by *Enzell* and co-workers [4].

[3]) The calculation was performed with MM3* force field.

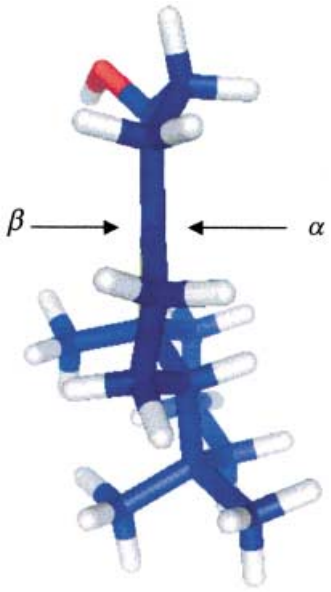


Fig. 2. *Optimized structure of* **5**[3])

Table 2. *[13]C-NMR and [1]H-NMR Chemical Shifts* ($CDCl_3$) *for* **1a** *and* **1b**

C-Atom	^{13}C [ppm]		$\Delta\delta$(**1a** – **1b**)	^{1}H [ppm]		H-Atom
	1a	**1b**		**1a**	**1b**	
C(1)	36.8	39.6	– 2.8	1.40; 1.66	1.92; 1.23	CH_2(1)
C(2)	18.7	18.4	0.3	1.57	1.58; 1.87	CH_2(2)
C(3)	41.7	42.0	– 0.3	1.18; 1.40	1.12; 1.41	CH_2(3)
C(4)	34.0	33.8	0.2	–	–	–
C(5)	53.1	44.2	8.9	1.03	1.37	H–C(5)
C(6)	21.5	19.1	2.4	1.7; (1.57)	1.52	CH_2(6)
C(7)	35.2	25.8	9.4	1.22; 2.01	1.38; 1.80	CH_2(7)
C(8)	34.3	34.2	0.1	2.55	2.50	H–C(8)
C(9)	176.6	181.4	– 4.8	–	–	–
C(10)	41.1	39.5	1.6	–	–	–
C(11)	119.6	122.8	– 3.8	5.81 ($d, J = 1.9$)	5.93 ($d, J = 2.2$)	H–C(11)
C(12)	201.5	201.0	0.5	–	–	–
C(13)	35.9	37.3	– 1.4	2.21; 2.39	2.25; 2.38	CH_2(13)
C(14)	29.4	31.0	– 1.6	1.59; 2.07	1.52; 2.02	CH_2(14)
C(18)	33.3	32.8	0.5	0.87	0.91	Me(18)
C(19)	22.0	21.7	0.3	0.86	0.88	Me(19)
C(20)	21.2	23.7	– 2.5	1.09	1.12	Me(20)

We then turned to verify the hypothesis, put forward in the *Introduction*, of the preparation of **1b** by mild acidic cleavage of the dienol ether **3**. To find the best conditions before moving to a preparative scale, the reaction was monitored by ^{1}H-NMR by dissolving **4** (20 mg, 0.081 mmol) in (D_4)THF/2N HCl 4 : 1 (0.5 ml) and recording a spectrum every 15 min (*Fig. 3*).

From *Fig. 4*, in which the concentrations of **1a** and **1b** are reported as a function of time, it can be observed that the concentration of **1b** increases during the first 115 min

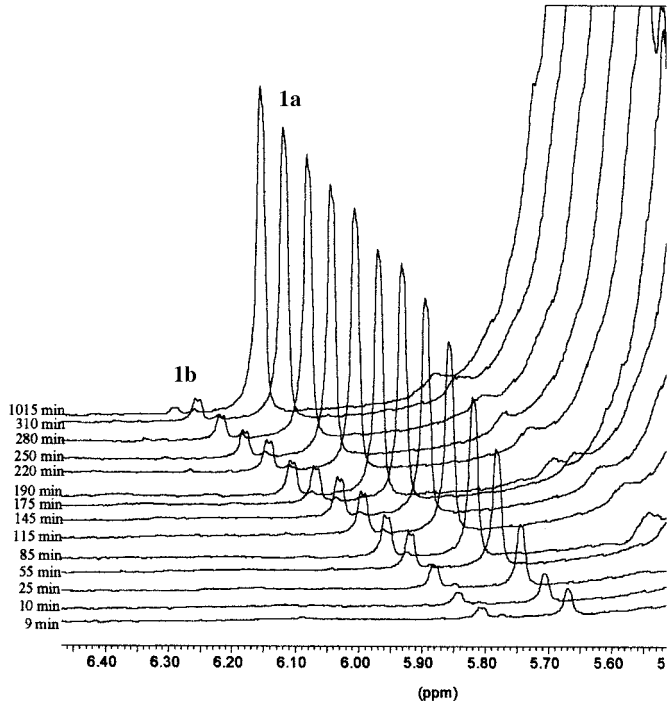


Fig. 3. *Olefinic region of ^{1}H-NMR spectra at different times showing the formation of* **1a** *and* **1b** *by mild acid cleavage of* **4** (300-MHz ^{1}H-NMR at 25°; [**4**] = 0.16M, $[C_6H_6] = 1.34 \cdot 10^{-2}$ M as reference standard)

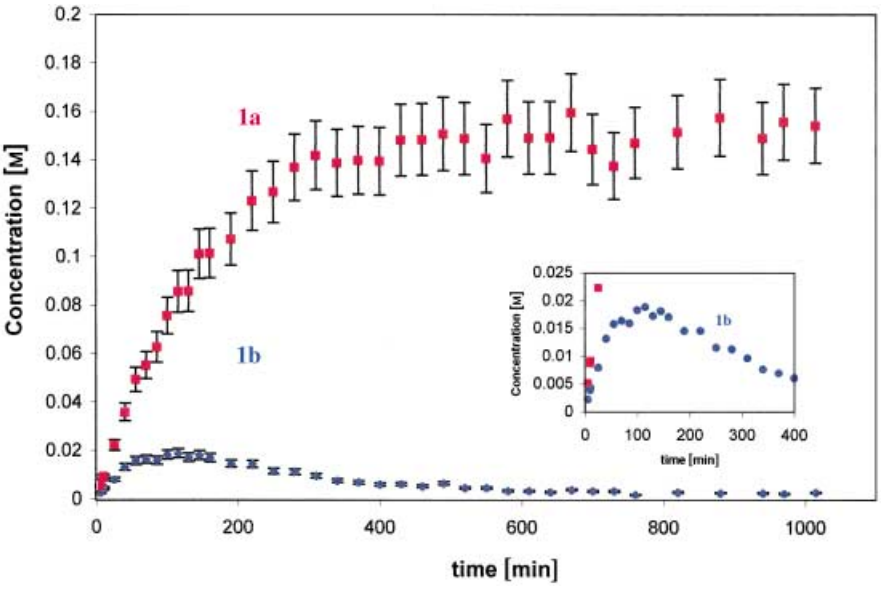


Fig. 4. *Concentration of* **1a** *and* **1b** *as a function of time*

and then decreases slowly, owing to the simultaneous presence of the process leading from **4** to **1a** and **1b**, and of the equilibration of **1a** and **1b**. In the first 115 min, the first process is dominant, while, after that time, the equilibration process becomes overwhelming.

On the basis of these experiments, we were able to prepare **1b** in an amount sufficient to characterize it. Compound **1b**, which shows on TLC an R_f value very close to that of **1a** (AcOEt/hexane 3:7, 3 developments, $R_f(\mathbf{1a}) > R_f(\mathbf{1b})$), could then be separated from **1a** either by PTLC or by semipreparative HPLC.

^{1}H-NMR, ^{13}C-NMR, DEPT, HETCOR, 2D-COSY-45, 2D-NOESY of **1b**, in conjunction with the data available for **1a** [4], allowed also the complete assignment of all resonances, thus bringing significant differences to light, as reported in *Table 2*. The two epimers can be distinguished in the ^{1}H-NMR spectrum (*Fig. 5*) on the basis of the chemical shift of H–C(11), the $\Delta\delta$ being $\approx$0.1 ppm, and on the basis of the ^{13}C-NMR spectrum, the $\Delta\delta$ of C(5), C(7), C(9), C(11), C(13), and C(14) being 8.9, 9.4, −4.8, −3.8, −1.4, and −1.6 ppm, respectively.

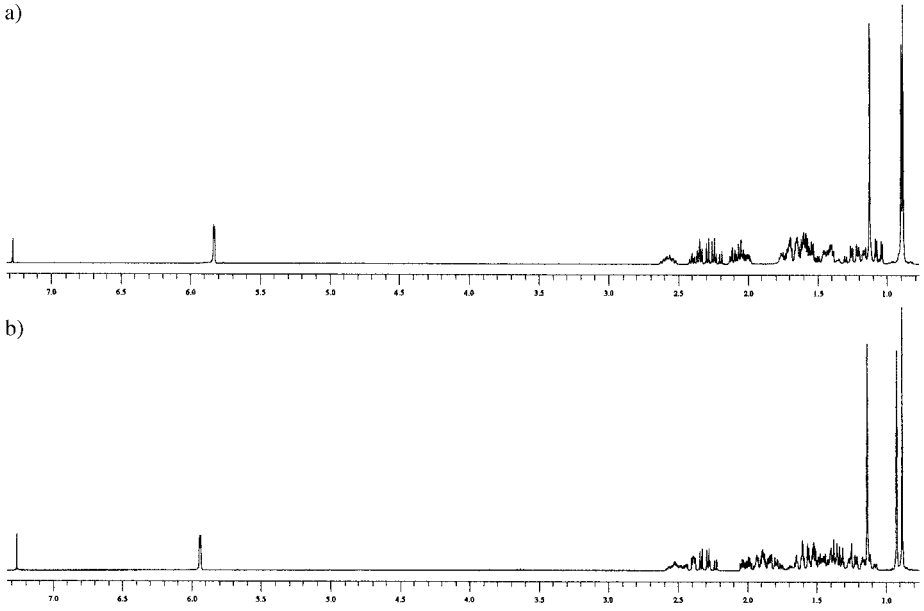


Fig. 5. a) *300-MHz ^{1}H-NMR Spectrum* ($CDCl_3$) *of* **1a**; b) *300-MHz ^{1}H-NMR spectrum* ($CDCl_3$) *of* **1b**

The twist-boat conformation of ring B in **1b** affects particularly C(5) and C(7), which are strongly shielded, and on C(9) and C(11) whose signals are deshielded in comparison to **1a**. From *Table 2* it appears also that the ^4J(H–C(11), H–C(8)) in **1a** and **1b** differ by 0.33 Hz.

2D-NOESY Experiments carried out on **1a** and **1b** showed a cross-peak between H–C(8) and Me(20) only in the case of the former compound (*Fig. 6*).

The data presented above are in good agreement (*Table 3*) with those previously recorded for the same C-atoms of *ent*-pimaradiene derivative **6** [5a], and for C(5) of

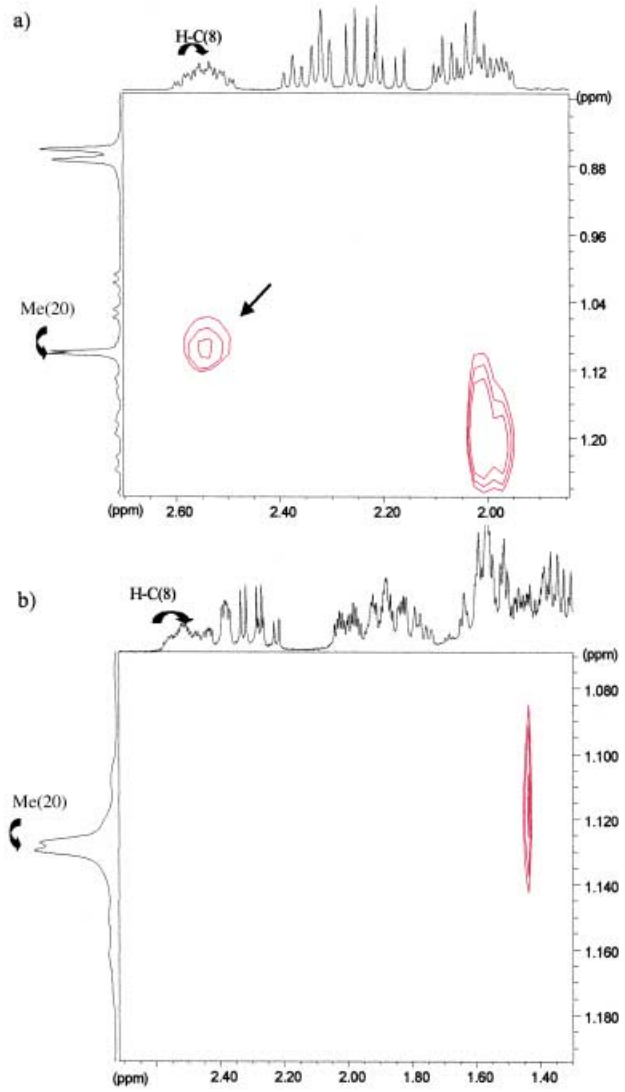


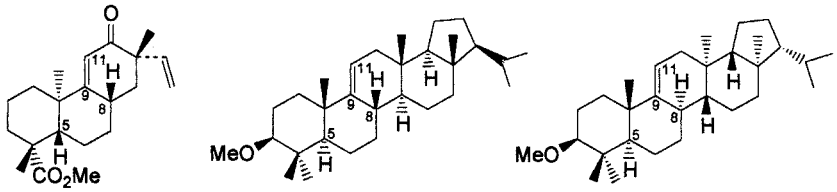
Fig. 6. a) *Portion of the 2D-NOESY spectrum* ($CDCl_3$) *of* **1a**; b) *Portion of the 2D-NOESY spectrum* ($CDCl_3$) *of* **1b**

cylindrin **7** and arundoin **8** [5b]. Additionally, the $\Delta\delta$ trend of C(5), C(7), C(9), and C(11) of **7** and **8** is similar to that displayed by the same C-atoms of **1a** and **1b**.

3. Conclusions. – The studies presented above showed that the higher stability of podocarp-9(11)-en-12-one (**1a**) over 8-epipodocarp-9(11)-en-12-one (**1b**) ranges from 1.2 to 4.2 kcal/mol depending on the force field used. They also showed that **1b** is formed along with podocarp-9(11)-en-12-one (**1a**) in the course of its preparation from

Table 3. *Diagnostic ^{13}C- and ^{1}H-NMR Chemical Shifts* ($CDCl_3$) *for* **6**, **7**, *and* **8**

C-Atom	^{13}C [ppm]			$\Delta\delta$(**7**–**8**)	^{1}H [ppm]			H-Atom
	6	**7**	**8**		**6**	**7**	**8**	
C(5)	46.7	52.9	44.8	8.1	–	–	–	–
C(7)	26.6	28.3	19.0	9.3	–	–	–	–
C(8)	30.1	41.1	40.1	1.0	–	–	–	–
C(9)	177.4	149.1	151.3	−2.2	–	–	–	–
C(11)	121.9	114.2	116.1	−1.9	5.92(*d*)	–	–	H–C(11)



6 **7** **8**

O-methylpodocarpane (**2**). If vigorous experimental conditions and sufficient reaction time are adopted, **1b** equilibrates to the more stable **1a**. The significant differences in the NMR and NOESY spectra of **1a** and **1b** are diagnostic for establishing the relative configuration at C(8), and possibly might constitute useful guidelines to solve similar problems on podocarp-9(11)-en-12-one derivatives. Finally, the studies described by us might have general interest, since they could be applied *in toto* or in part to cyclic α,β-unsaturated carbonyl compounds having a stereogenic vinylogous H-atom.

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Experimental Part

General. All solns. were evaporated to dryness under vacuum. All solvents were of anal. grade. TLC: *Merck* silica gel *60* F_{254}. PTLC: silica gel *60* F_{254} 2 mm. CC: silica gel *60*, 70–230 mesh ASTM. HPLC Analysis: *Shimadzu LC-10AD*; RID detector. M.p.: *Mettler FP-61* apparatus (uncorrected). UV/VIS Spectra: *Perkin-Elmer λ18* spectrometer equipped with a thermostated cell holder. IR Spectra: *Shimadzu 470* scanning IR spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR: *Bruker AC-300-P* at 300.13 and 75.48 MHz respectively; δ in ppm rel. to internal Me_4Si (= 0 ppm), *J* in Hz. DEPT, HETCOR, 2D-COSY-45 and 2D-NOESY (mixing time 800 ms) experiments were the standard sequences from the *Bruker* Library. ^{1}H-NMR chemical shifts of **1a** and **1b** (except for the olefinic H-atoms and Me groups) were obtained from the HETCOR spectra.

1. Theoretical Calculations. The force fields employed for MM calculations were the MacroModel [6] variants (MM2* and MM3*) of the authentic Allinger MM2 and MM3 force fields [7], and MMFF [8].

Owing to the rigidity of our tricyclic systems, a systematic conformational search varying the C(1)–C(2)–C(3)–C(4) and C(9)–C(8)–C(14)–C(13) dihedral angles was carried out.

The energy of the structures obtained was minimized *in vacuo* by means of the conjugate gradient algorithm (*Polak-Ribiere* method, gradient 0.001 kcal A^{-1} mol^{-1}). Four conformations corresponding to steric-energy minima were found for **1a** and **1b**. The energy found for **1a** and **1b** (*Table 1*) was expressed as $E = \Sigma_i \chi_i E_i$, where χ_i is the molecular fraction for each conformation, obtained by the *Boltzmann* law of distribution at 298 K, and E_i is the conformer steric energy. To evaluate the relative stabilities of **1a** and **1b**, steric-energy differences were considered assuming for the two epimers $\Delta G \approx \Delta H \approx \Delta E$.

2. *Preparation of the 1,2,3,4,4a,5,8,9,10,10a-Decahydro-6-methoxy-1,1-dimethylphenanthrene* (**3**). Anh. NH_3 (20 ml) was condensed into a three-necked flask equipped with a mechanical stirrer and cooled to $-78°$ by means of a dry-ice/acetone bath. THF (20 ml) and *t*-BuOH (0.5 ml) were then added dropwise while stirring, followed by Li in pieces (50 mg). After 20 min a THF soln. (2 ml) of O-*methylpodocarpane* (**2**; 500 mg, 1.94 mmoles) was added, followed, after further 25 min, by additional *t*-BuOH (0.25 ml). The mixture was stirred until decolorization occurred (*ca*. 3 h 30 min); during this period Li and *t*-BuOH were added in small portions, until the TLC (petroleum ether (40–70°)/Et_2O 9.75 : 0.25 R_f(**3**) > R_f(**2**), 2 developments) indicated the almost complete disappearance of **2**. H_2O (20 ml) was then cautiously added, and NH_3 was allowed to evaporate. The soln. was neutralized with sat. NH_4Cl soln. and thoroughly extracted with Et_2O. The combined org. layers were then washed with H_2O, brine, dried (Na_2SO_4), and evaporated to give the crude diene **3** (500 mg).

2.2. *Hydrolysis of* **3**. Crude **3** (70 mg) dissolved in THF/2N HCl 4 : 1 (2 ml) was stirred under Ar at r.t. for 115 min. Then, the mixture was neutralized with a 8N aq. $NaHCO_3$ soln. and extracted 3 times with Et_2O (4 ml). Combined org. layers were then washed with H_2O, brine, dried (Na_2SO_4), and evaporated. The HPLC analysis of the crude mixture revealed that **1a**, **1b**, and **4** were formed in a 4.2 : 1.0 : 3.1 ratio (eluting mixture: H_2O/MeCN 20 : 80; flow rate: 1 ml/min; detection: RID; column: *EC 250/4 Nucleosil 100-5 C18*, *Macherey-Nagel*). The residue was purified by CC (SiO_2; hexane/Et_2O 9 : 1) to give in 4 : 1 ratio **4**, as an oil [9], and a mixture of **1a**/**1b**, resp. (85% overall yield). Compounds **1a** and **1b** were separated by PTLC (hexane/AcOEt 7 : 3; 8 developments; R_f(**1a**) > R_f(**1b**)). Compound **1b** is an oil that solidifies at $-25°$.

Data of Podocarp-9(11)-en-12-one (**1a**): m.p. (EtOH/H_2O 1 : 1) 53.0–54.5° ([1b]: 56.0–57.5° (aq. DMF)). UV (EtOH 96%): λ_{max} 240 nm (ε = 20440 l mol^{-1} cm^{-1}). IR (CCl_4): 1677. ^{1}H- and ^{13}C-NMR: see *Table 2*. Anal. calc. for $C_{17}H_{26}O$ (246.39): C 82.87; H 10.64; found: C 82.51, H 11.03.

Data of 8-Epipodocarp-9(11)-en-12-one (**1b**): UV (96% EtOH): λ_{max} 245 nm (ε = 11390 l mol^{-1} cm^{-1}). IR (CCl_4): 1674. ^{1}H- and ^{13}C-NMR: see *Table 2*. Anal. calc. for $C_{17}H_{26}O$ (246.39): C 82.87, H 10.64; found: C 82.49, H 10.98.

Data of Podocarp-8(9)-en-12-one (**4**): IR (CCl_4): 1717. ^{1}H-NMR ($CDCl_3$): 2.83 (*A* of *AB*, *J* = 20.6, 1 H); 2.71 (*B* of *AB*, *J* = 20.6, 1 H); 2.62–2.12 (*m*, 4 H); 2.12–1.92 (*m*, 2 H); 1.92–1.36 (*m*, 7 H); 1.36–1.01 (*m*, 2 H); 0.95 (*d*, *J* = 0.5, 3 H); 0.90 (*s*, 3 H); 0.84 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 212.4; 136.0; 127.1; 51.4; 41.7; 38.5; 38.3; 37.5; 36.6; 33.3; 33.2; 31.8; 30.6; 21.6; 19.4; 18.9; 18.7. DEPT ($CDCl_3$): CH_2: 41.7; 38.5; 38.3; 36.6; 31.8; 30.6; 18.9; 18.7; CH, Me: 51.4; 33.2; 21.6; 19.4. Anal. calc. for $C_{17}H_{26}O$ (246.39): C 82.87, H 10.64; found: C 83.27, H 10.95.

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