Formal Total Synthesis of (+)-Dihydromevinolin *via* a Chelate-Controlled Intramolecular *Diels-Alder* Reaction as the Key Step[1])

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Dedicated to Prof. *Armin de Meijere* on the occasion of his 60th birthday

Compound **3** was synthesized efficiently from enone **4** *via* (silyloxy)cyclopropanecarboxylate intermediates **6** and **7**. A chelate-controlled intramolecular *Diels-Alder* reaction of **3** afforded the octahydronaphthalene-2-carboxylate isomer *trans*-**2b** as the main product. This compound was stereoselectively converted into the known dihydromevinolin precursor **1**, thus providing a formal total synthesis of this natural product.

Introduction. – Compactin, mevinolin (also known as lovastatin, monacolin K), and their dihydro analoga are natural products of high pharmaceutical interest[3]). They are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoA reductase) [3], an enzyme which controls the rate-determining step in cholesterol biosynthesis. Since the discovery of these compounds, numerous structural modifications have been accomplished, leading to a number of novel HMG-CoA reductase inhibitors[4]). Three inhibitors of natural origin, mevinolin, pravastatin, and simvastatin[5]), are marketed as therapeutics for treating hypercholesterolemia. The significance of this family of compounds is also reflected in the number of total syntheses (for reviews, see [6])[6]) [8]. For the construction of the fused bicyclic core of these compounds, several synthetic routes have employed an intramolecular *Diels-Alder* reaction [6a][7]). Here, we report the efficient synthesis[8]) of an advanced intermediate **1** towards dihydromevinolin *via* a chelate-controlled intramolecular *Diels-Alder* reaction, developed by our group [13], to install the correct configuration of the bicyclo[4.4.0]decene framework. Since (racemic) **1** was converted into (+)-dihydro-

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1) Part 4 of 'Intramolecular *Diels-Alder* Reactions'. Part 3: [13].

2) Part of the Ph. D. thesis [1].

3) For isolation of compactin, see [2a]; for isolation of mevinolin, see [2b]; for isolation of dihydrocompactin, see [2c]; for isolation of dihydromevinolin, see [2d].

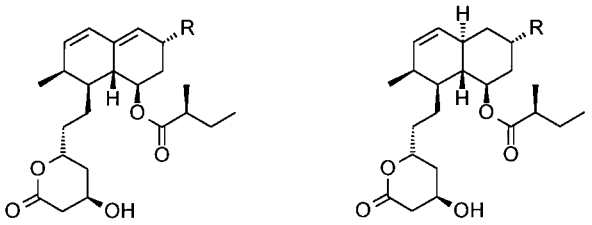
4) For recent synthetic work on decalin derivatives of mevinic acids, see [4a]; for recent work on novel synthetic HMG-CoA reductase inhibitors, see [4b].

5) For isolation of pravastatin, see [5a]; for partial synthesis of simvastatin from mevinolin, see [5b].

6) Recent synthetic work on naturally occurring HMG-CoA-reductase inhibitors: for total synthesis of (+)-compactin, see [7a]; for total synthesis of (+)-mevinolin, see [7b]; for total synthesis of dihydrocompactin, see [7c]; for total synthesis of dihydromevinolin, see [7d].

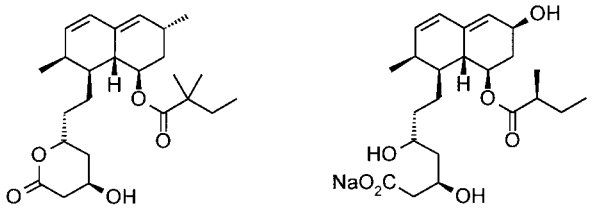
7) For total syntheses of mevinic acids involving an intramolecular *Diels-Alder* reaction of the decalin framework, see [9]. For the intramolecular *Diels-Alder* reaction approach for construction of the decalin framework of mevinic acids, see [10]. For reviews about the intramolecular *Diels-Alder* reaction, see [11].

8) For a preliminary report, see [12].



Compactin R = H Dihydrocompactin

Mevinolin R = Me Dihydromevinolin



Simvastatin Pravastatin sodium

mevinolin by *Heathcock* and co-workers [9a][9b], our approach comprises a formal total synthesis of this target compound.

Results and Discussion. – A retrosynthetic analysis suggested that the decalin derivative **1** should be available from octahydronaphthalene **2**, which was expected to form in a stereocontrolled intramolecular *Diels-Alder* reaction of the ester **3** (*Scheme 1*). Compound **3** should be assembled in a few steps from the three known precursors (*E*,*E*)-1-bromohexa-2,4-diene[9]), enone **4** [15], and methyl diazoacetate [16].

Actually, ester **3** was synthesized efficiently in a four-step process starting with $BnOCH_2$-substituted enone **4**, which was first transformed into silyl enol ether **5** by a standard protocol [17] (*Scheme 2*). The [2 + 1] cycloaddition of **5** with methyl diazoacetate under $Rh_2(OAc)_4$ catalysis afforded cyclopropane **6** in 75% yield (*cis*/*trans*-mixture 30 : 70). Stereoselective alkylation [18] of **6** with sorbyl bromide [14] provided a 4 : 1 mixture of the tetrasubstituted cyclopropane **7** and its ring-opened product **3**. This instability of a tetrasubstituted cyclopropane under the conditions of alkylation has not been seen before, even in compounds with very similar structure to **7** [18]. However, this did not present a problem, as **3** was the desired product of the

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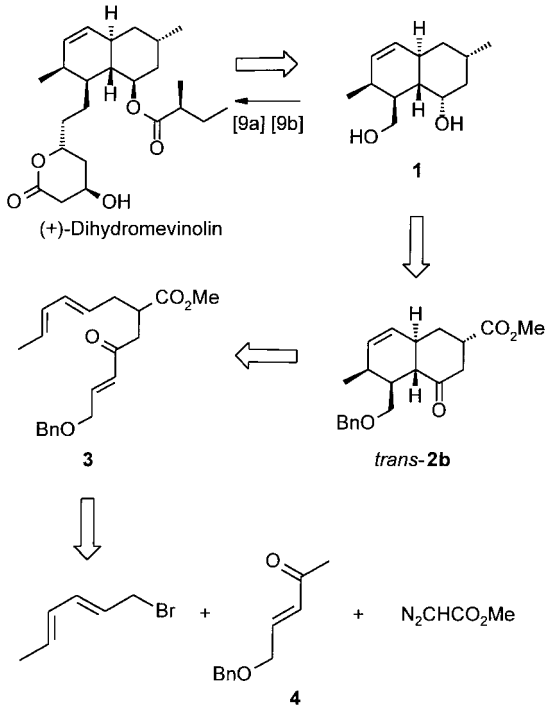
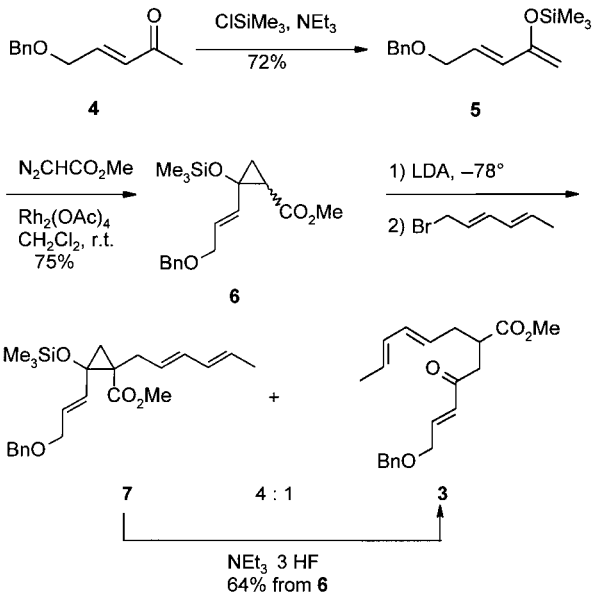
[9]) Following the procedure in [14], we obtained the desired (2*E*,4*E*)-1-bromohexa-2,4-diene in only 80–85% purity, along with 15–20% of the (2*E*,4*Z*)- and (2*Z*,4*E*)-isomers. As this inseparable mixture was employed in the alkylation of **6**, intermediates **7** and **3** consisted of the corresponding three isomers in approximately the above-mentioned ratio. However, only the (*E*,*E*)-form undergoes the intramolecular *Diels-Alder* reaction, and the isomers with one (*Z*)-configured C=C bond could be completely separated from **2** at this stage.

Scheme 1



Scheme 2



subsequent step. The completion of the ring opening of cyclopropane **7** was achieved by treatment of the mixture with $NEt_3 \cdot 3$ HF [19] to afford **3** in 64% yield in two steps from **6**.

Our earlier investigations on the intramolecular *Diels-Alder* reaction of related trienones ($BnOCH_2$ replaced by Me or (*t*-Bu)Me_2SiOCH_2) showed that the thermal cycloaddition reactions furnish a mixture of all four possible diastereoisomers [20]. Catalysis by monocoordinating *Lewis* acids, however, enhanced the *endo*-selectivity of the reaction markedly, and provided the *cis*-fused isomers in high yields [1][13]. Good *exo*-selectivities could be achieved by application of strong *Lewis* acids with two free coordination sites, such as $TiCl_4$, $TiBr_4$, and $SnCl_4$ [13][21]. These promoters afforded the desired *trans*-fused products in good yields, and have found application in the total synthesis of the sesquiterpene α-eudesmol [13][21]. *Yamamoto* and co-workers could increase the *trans*-selectivity of a simple deca-1,7,9-trien-3-one remarkably by using the bulky *Lewis* acid ATPH (aluminium tris(2,6-diphenylphenoxide)) [22]. They also observed high preferences for the otherwise unfavorable *exo*-transition states in bimolecular *Diels-Alder* reactions [22]. The authors assumed that the secondary orbital interactions, which are responsible for the *endo*-preference of activated dienophiles, are effectively diminished by the complexation of the dienophile-activating group with ATPH.

We employed both types of *Lewis* acids, the biscoordinating $SnCl_4$ and the bulky ATPH, in the intramolecular *Diels-Alder* reactions of trienone **3**[10]). It was found that the desired isomer *trans*-**2b** was formed preferentially and with similar ratios (60 and 56%, resp.) with both promoters (*Scheme 3*). The only other isomer, formed in the $SnCl_4$-mediated reaction, was *cis*-**2a** (40%), whereas *cis*-**2a** and *trans*-**2a** were found in the ATPH-promoted cycloaddition in 32 and 12% overall yield, respectively. Based on earlier work on *Lewis*-acid-promoted intramolecular *Diels-Alder* reactions [13][21], we attributed the *exo*-product *trans*-**2b** to an *exo*-chelate transition state **8** as depicted in *Scheme 3*. The *Lewis* acid thereby forces the MeOCO group of **3** into the otherwise unfavored axial position on the folded chain. It is unclear, however, whether *cis*-**2a** results from an *endo*-chelate transition state **9** or from a ($SnCl_4 \cdot 2$ trienone) complex, in which $SnCl_4$ coordinates the C=O groups of two trienone molecules in boat-like transition conformations [20]. The high *trans*-selectivity of ATPH was, based on *Yamamoto*'s results [22], as expected. We see no obvious reason, however, why in this case the diastereoisomer *trans*-**2b** is favored so significantly over isomer *trans*-**2a**. In the thermal intramolecular *Diels-Alder* reactions of related trienones, and in the reactions that were promoted by monocoordinating *Lewis* acids, *trans*-**b** did not appear as a product, or it was formed in very minor amounts [13][21][11]).

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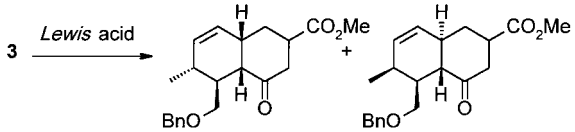
[10]) For other decatrienones, the highest *trans*-selectivities had been recorded with $TiCl_4$ or $TiBr_4$ as promoters (see [20][21]). However, since attempts to use these very strong *Lewis* acids for the cycloaddition of a precursor similar to **3** (Me instead of $BnOCH_2$) lead to decomposition of the substrate, we did not try these promoters with our valuable compound **3**.

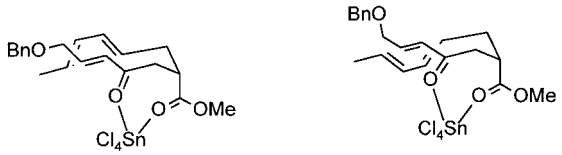
[11]) It is possible that formation of *trans*-**2b** with usually unfavorable axial orientation of the MeOCO group might be attributed to a repulsive interaction of this substituent in an equatorial position (leading to *trans*-**2a**). Here, complexation with ATPH might force the MeO group into a conformation where strong repulsions with adjacent H-atoms at the dienophile and diene come into play.

Scheme 3



	····CO$_2$Me *cis*-**2a**	—CO$_2$Me *cis*-**2b**	—CO$_2$Me *trans*-**2a**	····CO$_2$Me *trans*-**2b**
1.3 equiv. $SnCl_4$ –78 to –40°, 85%	40 :	0 :	0 :	60
1.5 equiv. ATPH[a]) –10° to r.t., 61%	32 :	0 :	12 :	56

[a]) ATPH = aluminium tris(2,6-diphenylphenoxide)

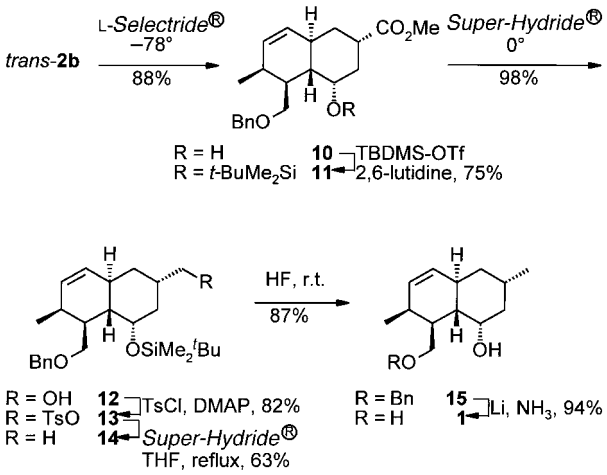


exo-chelate **8** *endo*-chelate **9**

Octahydronaphthalene-carboxylate *trans*-**2b** could be obtained in pure form, after flash chromatography (45% overall yield from **3**), of the $SnCl_4$-promoted cycloaddition reaction. Subsequent conversion of *trans*-**2b** into the known dihydromevinolin precursor **1** was achieved by a series of standard steps analogous to a related compound (*Scheme 4*). Stereoselective reduction of the ketone moiety with L-*Selectride*® [9d] furnished the alcohol **10**, which was subsequently protected as the silyl ether **11** [9e]. The MeOCO group was transformed into a Me group [9e] by reduction with *Super-Hydride*®, and subsequent tosylation of the formed alcohol **12**, followed by a second reduction with *Super-Hydride*®, providing intermediate **14** in satisfactory yields. Finally, cleavage of the silyl ether to alcohol **15**, and reductive deprotection of the BnO group proceeded smoothly to afford target compound **1**. All spectroscopic data of **1** were in accordance with those reported in [9a][9b], thus confirming the relative configuration of this compound and of the crucial intermediate *trans*-**2b**.

The overall yield of **1** over 11 steps from enone **4** was 4%; the crucial intermediate *trans*-**2b** was synthesized in 14% overall yield. Although these yields seem to be rather low, the efficiency of our route to (+)-dihydromevinolin compares very well with other known syntheses [8][9]. A shortcoming of our approach is the fact that three steps alone were devoted to the conversion of the MeOCO function into a Me group (**11** → **14**). On the other hand, the ester function served as a second ligating group in the chelate-controlled intramolecular *Diels-Alder* reaction of **3**, thereby enabling the formation of the otherwise unfavored *trans*-**b** isomer. Moreover, the MeOCO group can serve as a tool for introducing other substituents and functional groups for the synthesis of analogs of dihydromevinolin [9e].

Scheme 4



Conclusion. – Our approach to the mevinolin core demonstrates that the correct relative configuration of five of the six stereogenic centres can be established in a single step by the appropriate *Diels-Alder* conditions. A chelate-controlled intramolecular *Diels-Alder* reaction, which had been employed successfully in earlier examples [19][20], provided the otherwise unfavored isomer *trans*-**2b**. This intermediate should also provide a versatile precursor for the syntheses of other known or new mevinic-acid analogs [9e][9f][12]).

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Experimental Part

General. NMR Spectra (^{1}H: 500 MHz, ^{13}C: 125.8 MHz) of **10** were recorded on a *Bruker AM 500*. All other instrumentation and general conditions have been described previously [18].

*(*E*)-5-(Benzyloxy)-2-(trimethylsilyloxy)penta-1,3-diene* (**5**). To a soln. of *(*E*)-5-(benzyloxy)pent-3-en-2-one* (**4**; 7.50 g, 39.5 mmol) and NEt_3 (6.38 g, 63.1 mmol) in MeCN (40 mL) at 0° was added dropwise over a period of 0.5 h a soln. of Me_3SiCl (6.85 g, 63.1 mmol) in MeCN (20 ml), followed by a soln. of dry NaI (7.50 g, 49.7 mmol) in MeCN (70 ml). The mixture was refluxed for 20 h, cooled to r.t., and poured into a mixture of ice-water (100 ml) and pentane (100 ml). After separation of the top (pentane) layer, the two bottom layers were extracted with pentane (2×50 ml), and the combined org. phases were washed with H_2O (50 ml), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation of the residue (110–150°/0.06 Torr) yielded **5** (7.49 g, 72%). Pale-yellow oil. IR (neat): 3125, 3100, 3075, 3050 (=C–H); 2975–2850 (C–H); 1625, 1595 (C=C); 1250 (Si–C). ^{1}H-NMR (200 MHz): 7.36 (*m*, 5 arom. H); 6.13–6.07 (*m*, H–C(3), H–C(4)); 4.54, 4.35 (2*s*, 2 H each, H–C(1), PhCH_2); 4.12 (*d*, $J = 4.5$, 2 H–C(5)); 0.26 (*s*, Me_3Si). ^{13}C-NMR (50.3 MHz): 154.3 (*s*, C(2)); 138.3 (*s*, arom. *ipso*-C); 130.3, 128.3, 127.7, 127.4, 126.9 (5*d*, C(3), C(4), arom. C); 95.9 (*t*, C(1)); 72.9, 69.8 (2*t*, C(5), PhCH_2); –0.1 (*q*, Me_3Si). Anal. calc. for $C_{15}H_{22}O_2Si$ (262.4): C 68.65, H 8.45; found: C 68.98, H 8.53.

trans/cis-*Methyl 2-[(*E*)-3-(Benzyloxy)prop-1-enyl]-2-(trimethylsilyloxy)cyclopropanecarboxylate* (**6**). To a mixture of **5** (7.40 g, 28.2 mmol) and $Rh_2(OAc)_4$ (175 mg, 0.396 mmol) in CH_2Cl_2 (20 ml), a soln. of methyl

[12]) For synthesis of octahydrobenzocycloheptenone derivatives employing a chelate-controlled intramolecular *Diels-Alder* reaction, see [23].

diazoacetate (4.55 g, 45.1 mmol) in CH_2Cl_2 (40 ml) was added over a period of 4 h. The mixture was concentrated and filtered through alumina (pentane). The filtrate was concentrated, and the crude product (8.71 g) was distilled (bulb-to-bulb; 150°/0.02 Torr) to give **6** (*trans*/*cis* 70:30) (7.05 g, 75%). Colorless oil. IR (neat): 3100–3050, 2950–2850 (C−H); 1730 (CO_2Me); 1675, 1500, 1450 (C=C); 1250 (Si−C).

Data of trans-**6**: ^{1}H-NMR (200 MHz): 7.32 (m_c, 5 arom. H); 5.83 (*td*, J = 5, 15, H−C(2′)); 5.46 (*td*, J = 1.5, 15 Hz, H−C(1′)); 4.48 (*s*, PhCH_2); 4.08–4.00 (obscured *m*, 2 H−C(3′)); 3.65 (*s*, MeOCO); 2.17 (*dd*, J = 8, 9 Hz, H−C(1)); 1.58–1.41, 1.34–1.19 (2 obscured *m*, 1 H each, H−C(3)); 0.18 (*s*, Me_3Si). ^{13}C-NMR (50.3 MHz): 170.3 (*s*, MeO*C*O); 138.3 (*s*, arom. *ipso*-C); 131.4, 128.2, 127.9, 127.7, 127.0 (5*d*, C(1′), C(2′), arom. C); 71.6 (*t*, Ph*C*H$_2$); 69.9 (*t*, C(3′)); 62.6 (*s*, C(2)); 51.7 (*q*, *Me*OCO); 30.2 (*d*, C(1)); 22.0 (*t*, C(3)); −0.9 (*q*, Me_3Si).

Data of cis-**6**: ^{1}H-NMR (200 MHz): 7.32 (m_c, 5 arom. H); 5.94 (*td*, J = 5, 15, H−C(2′)); 5.19 (*td*, J = 1.5, 15, H−C(1′)); 4.50 (*s*, PhCH_2); 4.08–4.00 (obscured *m*, 2 H−C(3′)); 3.67 (*s*, MeOCO); 1.86 (*dd*, J = 8, 10, H−C(1)); 1.58–1.41, 1.34–1.19 (2 obscured *m*, 1 H each, H−C(3)); 0.18 (*s*, Me_3Si). ^{13}C-NMR (50.3 MHz): 169.1 (*s*, MeO*C*O); 138.1 (*s*, arom. *ipso*-C); 135.3, 128.3, 128.0, 127.6, 125.5 (5*d*, C(1′), C(2′), arom. C); 72.0 (*t*, Ph*C*H$_2$); 69.6 (*t*, C(3′)); 62.0 (*s*, C(2)); 51.5 (*q*, *Me*OCO); 28.5 (*d*, C(1)); 20.7 (*t*, C(3)); −0.85 (*q*, Me_3Si). Anal. calc. for $C_{18}H_{26}O_4Si$ (334.5): C 64.64, H 7.83; found: C 64.71, H 7.83.

Methyl c-*2-[(*E*)-3-(Benzyloxy)prop-1-enyl]-1-[(2*E*,4*E*)-hexa-2,4-dienyl]*-t-*2-(trimethylsilyloxy)cyclopropane*-r-*1-carboxylate* (**7**). To a soln. of (i-Pr)$_2$NLi (8.97 mmol; generated from (i-Pr)$_2$NH and BuLi at −78°, 20 min reaction time) in THF (90 ml) at −78°, the methyl cyclopropanecarboxylate **6** (2.00 g, 5.98 mmol) was added. After stirring for 2 h at −78°, 1-bromohexa-2,4-diene (1.44 g, 8.97 mmol) was added, and stirring was continued at −78° for 16 h. The reaction was quenched with sat. aq. NH_4Cl soln. (90 ml) and extracted with AcOEt (3 × 180 ml). The combined org. extracts were washed with H_2O (500 ml), dried ($MgSO_4$), and concentrated. The excess of 1-bromohexa-2,4-diene was removed by bulb-to-bulb distillation (60°/0.02 Torr), and the residue (2.00 g) was filtered through alumina with Et_2O to provide a mixture of **7** and **3** (4:1; 1.62 g, 65%). The products contain 15–20% of the corresponding (2*E*,4*Z*)- and (2*Z*,4*E*)-hexa-2,4-dienyl isomers, which could not be separated from the desired (2*E*,4*E*)-isomers. IR (neat): 3100–3050 (=C−H); 2950, 2850 (C−H); 1725 (CO_2Me); 1625, 1500, 1450 (C=C); 1255 (Si−C).

Data of Compound **7**: ^{1}H-NMR (200 MHz): 7.14 (m_c, 5 arom. H); 5.95–5.25 (*m*, 6 olef. H); 4.28 (*s*, PhCH_2); 3.84 (*d*, J = 5.5, 2 H−C(3′)); 3.44 (*s*, MeOCO); 2.77 (*dd*, J = 6, 16, H−C(1″)); 2.10–1.91 (partially obscured *m*, H−C(1″)); 1.64 (*dd*, J = 1.5, 6.5, H_{cis}−C(3)); 1.56 (*d*, J = 6, 3 H−C(6″)); 0.92 (*d*, J = 6.5, H_{trans}−C(3)); 0.04 (*s*, Me_3Si). ^{13}C-NMR (50.3 MHz): 172.2 (*s*, MeO*C*O); 138.4 (*s*, arom. *ipso*-C); 132.2, 131.7, 131.5, 128.5, 128.3, 127.8, 127.7, 127.5, 127.2 (9*d*, arom. C, olef. C); 71.6 (*t*, Ph*C*H$_2$); 69.9 (*t*, C(3′)); 64.7 (*s*, C(2)); 51.9 (*q*, *Me*OCO); 37.1 (*s*, C(1)); 31.9 (*t*, C(1″)); 24.8 (*t*, C(3)); 17.9 (*q*, C(6″)); 0.93 (*q*, Me_3Si).

*Methyl (4*E*,6*E*)-2-[(*E*)-5-(Benzyloxy)-2-oxopent-3-enyl]octa-4,6-dienoate* (**3**). To a soln. of **7** (*ca.* 1.79 g, 4.27 mmol; mixed with **3**, *ca.* 0.366 g, 1.07 mmol) in CH_2Cl_2 (50 ml) at −25°, $NEt_3 \cdot 3$ HF (2.76 g, 17.1 mmol) was added. After stirring for 2 h at −25°, the reaction was stopped by the addition of H_2O (80 ml). The aq. layer was extracted with CH_2Cl_2 (3 × 40 ml), the combined org. phases were washed with H_2O (100 ml), dried (Na_2SO_4), and concentrated. The crude material was filtered through silica gel (hexane/AcOEt 2:1), and the resulting product **3** was obtained as a yellow oil (1.80 g, 98%; purity *ca.* 85% due to the presence of (2*E*,4*Z*)- and (2*Z*,4*E*)-hexa-2,4-dienyl isomers) and used without further purification. IR (neat): 3100–3050 (=C−H); 2950, 2850 (C−H); 1735 (CO_2Me); 1700 (C=O); 1640 (C=C). ^{1}H-NMR (200 MHz): 7.25 (m_c, 5 arom. H); 6.76 (*td*, J = 4, 16, H−C(4′)); 6.28 (*td*, J = 2, 16, H−C(3′)); 6.01–5.82 (*m*, H−C(5), H−C(6)); 5.61–5.42, 5.40–5.20 (2*m*, 1 H each, H−C(7), H−C(4)); 4.47 (*s*, PhCH_2); 4.09 (*dd*, J = 2, 4, 2 H−C(5′)); 3.57 (*s*, MeOCO); 2.98–2.81, 2.65–2.11 (2*m*, H−C(2), 2 H−C(3), 2 H−C(1′)); 1.63 (*d*, J = 6, 3 H−C(8)). ^{13}C-NMR (50.3 MHz): 197.7 (*s*, C=O); 175.0 (*s*, MeO*C*O); 142.4 (*d*, C(4′)); 137.6 (*s*, arom. *ipso*-C); 133.2, 131.0, 128.8, 128.3, 128.2, 127.8, 127.6, 126.4 (8*d*, C(4), C(5), C(6), C(7), C(3′), arom. C); 72.8 (*t*, Ph*C*H$_2$); 68.7 (*t*, C(5′)); 41.1 (*t*, C(1′)); 40.1 (*d*, C(2)); 34.7 (*t*, C(3)); 17.9 (*q*, C(8)). Anal. calc. for $C_{21}H_{26}O_4$ (342.4): C 73.66, H 7.65; found: C 73.52, H 7.73.

Intramolecular Diels-Alder *Reaction of* **3** *to* **2** *Promoted by* $SnCl_4$. To a soln. of $SnCl_4$ (228 mg, 0.876 mmol) in CH_2Cl_2 (45 ml) at −78°, **3** (200 mg, 0.584 mmol) was added. The mixture was stirred at −78° for 12 h, then warmed to −40°, and stirred at this temp. for 9 h. After addition of H_2O (45 ml), the aq. phase was extracted with CH_2Cl_2 (3 × 45 ml), the combined org. layers were washed with H_2O (180 ml), dried (Na_2SO_4), and concentrated. The residue (180 mg) was filtered through a plug of silica gel with Et_2O. The diastereoisomer ratio of the crude product (180 mg) was determined by ^{1}H-NMR as *cis*-**2a**/*trans*-**2b** 40:60. Separation by flash chromatography (hexane/AcOEt 10:1) yielded pure *cis*-**2a** (80 mg, 40%) and *trans*-**2b** (90 mg, 45%) as colorless oils.

Intramolecular Diels-Alder *Reaction of* **3** *to* **2** *Promoted by ATPH*. To a soln. of 2,6-diphenylphenol (485 mg, 1.97 mmol) in CH_2Cl_2 (30 ml), 2.0M Me_3Al in hexane (0.328 ml, 0.66 mmol) was added. The mixture

Table 1. *^{1}H-NMR* (300 MHz) *Data of Octahydronaphthalene-carboxylate* **2**

H-Atom[a])	*cis*-**2a**	*trans*-**2a**	*trans*-**2b**
H–C(7)	5.50 (*d*, *J* = 10)	5.72 (*ddd*, *J* = 2, 5, 10)	5.70 (*ddd*, *J* = 2.5, 5, 10)
H–C(8)	5.65 (*ddd*, *J* = 2, 4.5, 10)	5.41 (*td*, *J* = 1.5, 10)	5.40 (*td*, *J* = 1.5, 10)
MeOCO	3.67 (*s*)	3.70 (*s*)	3.68 (*s*)
H–C(2)	2.66 (*tt*, *J* = 3.5, 12.5)	2.83 (*tt*, *J* = 4.5, 12.5)	3.16 (m_c)
H_{ax}–C(3)	2.83 (*t*, *J* = 13)	2.66 (*t*, *J* = 12.5)	2.54 (*dd*, *J* = 7, 13)
H_{eq}–C(3)	2.50–2.35 (*m*)	2.52 (*ddd*, *J* = 1.5, 5, 12.5)	2.70 (*td*, *J* = 2, 13)
H–C(8a)	2.50–2.35 (*m*)	2.24–2.12 (*m*)	2.50–2.23 (*m*)
H–C(4a)	2.50–2.35 (*m*)	2.42–2.25 (*m*)	2.50–2.23 (*m*)
H_{eq}–C(1)	2.06 (br. *d*, *J* = 13)	2.24–2.12 (*m*)	2.50–2.23 (*m*)
H–C(5)	1.90–1.75 (*m*)	2.42–2.25 (*m*)	2.50–2.23 (*m*)
H–C(6)	1.90–1.75 (*m*)	2.57–2.45 (*m*)	2.50–2.23 (*m*)
H_{ax}–C(1)	1.70 (br. *t*, *J* = 13)	1.66 (*q*, *J* = 13)	1.72 (*ddd*, *J* = 6, 12, 14)
Me–C(6)	1.05 (*d*, *J* = 7)	0.94 (*d*, *J* = 7)	0.95 (*d*, *J* = 7)
2 H–C(5)	3.63 (*dd*, *J* = 2, 9)	3.96 (*dd*, *J* = 3, 9)	4.03 (*dd*, *J* = 3, 9)
	3.25 (*dd*, *J* = 8, 9)	3.48 (*t*, *J* = 9)	3.50 (*t*, *J* = 9)
PhCH_2	4.37, 4.28 (2*d*, *J* = 11.5 each)	4.50, 4.39 (2*d*, *J* = 12 each)	4.49, 4.39 (2*d*, *J* = 12 each)
Ph	7.31 (m_c)	7.31 (m_c)	7.33–7.20 (*m*)

[a]) Integrals are in accordance with the expected values.

Table 2. *^{13}C-NMR* (75.5 MHz) *Data of Octahydronaphthalene-carboxylate* **2**

C-Atom	*cis*-**2a**	*trans*-**2a**	*trans*-**2b**
C(4) (*s*)	211.7	209.9	208.8
MeO*C*O (*s*)	173.8	173.6	174.0
Arom. *ipso*-C (*s*)	137.9	138.7	138.8
C(7), C(8), arom. C (5*d*)	133.3, 128.2, 127.92, 127.86, 127.5	134.4, 128.2, 127.5, 127.4, 127.0	134.1, 128.2, 127.5, 127.4, 127.2
Ph*C*H_2 (*t*)	73.2	73.0	72.9
CH_2–C(5) (*t*)	71.7	68.8	69.0
C(4a) (*d*)	54.7	49.0	49.3
*Me*OCO (*q*)	51.9	52.1	52.0
C(3) (*t*)	41.3	44.5	43.0
C(2) (*d*)	42.9	44.1	41.8
C(8a) (*d*)	38.1	43.3	40.6
C(5) (*d*)	40.4	35.8	36.0
C(6) (*d*)	32.7	31.2	31.2
C(1) (*t*)	31.5	35.4	36.0
Me–C(6) (*q*)	20.1	16.2	16.2

was stirred for 0.5 h at r.t., then cooled to $-10°$ and treated with **3** (147 mg, 0.429 mmol). The mixture was warmed slowly to r.t., and then left for a period of 21 h. The reaction was then quenched with 2N HCl (30 ml), and the aq. layer was extracted with CH_2Cl_2 (30 ml). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (2 × 60 ml), dried (Na_2SO_4), and concentrated. The residue was subjected to gradient elution chromatography on silica gel (first hexane/AcOEt 10 : 1, to elute the 2,6-diphenylphenol, followed by Et_2O) to afford **2** (90 mg, 61%, *cis*-**2a**/*trans*-**2a**/*trans*-**2b** 32 : 12 : 56) as a yellow oil.

Data of Methyl 5-[(Benzyloxy)methyl]-1,2,3,4,4a,5,6,8a-octahydro-4-oxo-6-methylnaphthalene-2-carboxylate (**2**): IR (neat): 3100–3075 (=C–H); 2950–2850 (C–H); 1735 (CO_2Me); 1710 (C=O); 1650 (C=C). ^{1}H-NMR: See *Table 1*. ^{13}C-NMR: See *Table 2*. Anal. calc. for $C_{21}H_{26}O_4$ (342.4): C 73.66, H 7.65; found: C 73.83, H 7.90.

Methyl (2α,4α,4aβ,5β,6β,8aα)-5-[(Benzyloxy)methyl]-1,2,3,4,4a,5,6,8a-octahydro-4-hydroxy-6-methylnaphthalene-2-carboxylate (**10**). To a soln. of *trans*-**2b** (200 mg, 0.584 mmol) in THF (30 ml) at −78°, L-*Selectride*® (1.0M in THF; 0.640 ml, 0.64 mmol) was added. The mixture was stirred at −78° for 10 min, and then quenched by the addition of sat. aq. NH_4Cl soln. (20 ml) and Et_2O (20 ml). The aq. layer was extracted with Et_2O (2 × 15 ml), the combined org. layers were dried (Na_2SO_4), and concentrated. The residue (264 mg) was chromatographed on silica gel (hexane/AcOEt 5:1) to provide **10** (177 mg, 88%) as a colorless oil that contained small amounts of tri-*s*-butylborane. ^{1}H-NMR (500 MHz): 7.35–7.26 (*m*, 5 arom. H); 5.54 (*ddd*, *J* = 2.5, 5, 10, H−C(7)); 5.43 (br. *d*, *J* = 10, H−C(8)); 4.55, 4.46 (2*d*, *J* = 12, 12, 1 H each, PhC*H*$_2$); 4.00 (m_c, H−C(4)); 3.71 (*s*, MeOCO); 3.55 (*t*, *J* = 9, 1 H, BnOC*H*$_2$); 3.43 (*dd*, *J* = 4.5, 9, 1 H, BnOC*H*$_2$); 3.41 (m_c, OH); 2.68 (m_c, H−C(2)); 2.57 (*tdd*, *J* = 5, 10.5, 13, H−C(8a)); 2.51 (*ddd*, *J* = 2, 5, 14.5, H_{eq}−C(3)); 2.37 (m_c, H−C(6)); 2.18 (*ddd*, *J* = 2, 5.5, 13, H_{eq}−C(1)); 2.09 (*dddd*, *J* = 4.5, 6, 9, 11, H−C(5)); 1.74 (*ddd*, *J* = 3, 6, 14.5, H_{ax}−C(3)); 1.20 (*dt*, *J* = 5, 13, H_{ax}−C(1)); 1.16 (*dt*, *J* = 2, 11, H−C(4a)); 0.86 (*d*, *J* = 7, Me−C(6)). ^{13}C-NMR (125.8 MHz): 175.2 (*s*, MeO*C*O); 132.1 (*d*, C(7)); 131.1 (*d*, C(8)); 138.9 (*s*, arom. *ipso*-C); 128.4, 127.8, 127.7 (3*d*, arom. C); 73.5 (*t*, Ph*C*H$_2$); 72.2 (*t*, BnO*C*H$_2$); 65.8 (*d*, C(4)); 51.7 (*q*, *Me*OCO); 42.6 (*d*, C(4a)); 38.7 (*d*, C(5)); 36.9 (*d*, C(2)); 33.8 (*t*, C(3)); 33.2 (*d*, C(6)); 33.1 (*t*, C(1)); 31.9 (*d*, C(8a)); 15.8 (*q*, Me−C(6)).

*Methyl (2α,4α,4aβ,5β,6β,8aα)-5-[(Benzyloxy)methyl]-4-{[(*tert*-butyl)dimethylsilyl]oxy}-1,2,3,4,4a,5,6,8a-octahydro-6-methylnaphthalene-2-carboxylate* (**11**). A soln. of **10** (150 mg, 0.436 mmol) in CH_2Cl_2 (10 ml) was treated with 2,6-lutidine (117 mg, 1.09 mmol) and [(*tert*-butyl)dimethylsilyl] trifluoromethanesulfonate (196 mg, 0.741 mmol). After stirring at r.t. for 1.5 h, the mixture was hydrolyzed with 2N HCl (25 ml). The org. layer was washed with 2N HCl (20 ml), sat. aq. NH_4Cl soln. (20 ml), and brine (20 ml), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane/AcOEt 20:1) to provide **11** (150 mg, 75%). Colorless oil. IR (neat): 3100–3025 (=C−H); 2955–2855 (C−H); 1735 (CO_2Me); 1650, 1475 (C=C); 1260 (Si−C). ^{1}H-NMR (200 MHz): 7.35–7.25 (*m*, 5 arom. H); 5.57 (*ddd*, *J* = 2.5, 5, 10, H−C(7)); 5.38 (br. *d*, *J* = 10, H−C(8)); 4.42 (m_c, PhC*H*$_2$); 3.92 (m_c, H−C(4)); 3.61 (*s*, MeOCO); 3.62–3.54 (*m*, 1 H, BnOC*H*$_2$); 3.23 (*dd*, *J* = 4, 10.5, 1 H, BnOC*H*$_2$); 2.72–2.01 (*m*, H−C(2), H−C(8a), H_{eq}−C(3), H−C(6), H_{eq}−C(1), H−C(5)); 1.68 (*ddd*, *J* = 3, 7, 14.5, H_{ax}−C(3)); 1.23–0.93 (*m*, H_{ax}−C(1), H−C(4a)); 0.84 (*d*, *J* = 7, Me−C(6)); 0.80 (*s*, *t*-Bu); −0.05, −0.06 (2*s*, Me_2Si). ^{13}C-NMR (50.3 MHz): 175.3 (*s*, MeO*C*O); 132.2 (*d*, C(7)); 130.6 (*d*, C(8)); 138.7 (*s*, arom. *ipso*-C); 128.3, 127.7, 127.5 (3*d*, arom. C); 73.2 (*t*, Ph*C*H$_2$); 69.3 (*t*, BnO*C*H$_2$); 66.9 (*d*, C(4)); 51.4 (*q*, *Me*OCO); 41.9 (*d*, C(4a)); 36.6, 36.5 (2*d*, C(2), C(5)); 35.4, 33.4 (2*t*, C(1), C(3)); 31.2, 30.5 (2*d*, C(6), C(8a)); 25.9, 18.2 (*q*, *s*, Me_3C); 15.9 (*q*, Me−C(6)); −3.3, −5.0 (2*q*, Me_2Si). Anal. calc. for $C_{27}H_{42}O_4Si$ (458.7): C 70.70, H 9.23; found: C 70.15, H 9.32.

*(2α,4α,4aβ,5β,6β,8aα)-5-[(Benzyloxy)methyl]-4-{[(*tert*-butyl)dimethylsilyl]oxy}-1,2,3,4,4a,5,6,8a-octahydro-2-(hydroxymethyl)-6-methylnaphthalene* (**12**). A soln. of **11** (125 mg, 0.272 mmol) in THF (10 ml) at 0° was treated dropwise with *Super-Hydride*® (1.0M in THF; 0.680 ml, 0.68 mmol) and stirred at this temp. for 2 h. The reaction was stopped by successive addition of H_2O (0.5 ml), 2N NaOH (0.34 ml), and 30% H_2O_2 soln. (0.24 ml). The mixture was concentrated to *ca.* 1/3 of its volume, diluted with brine (20 ml), and extracted with Et_2O (3 × 10 ml). The combined org. extracts were washed with brine (3 × 20 ml), dried (Na_2SO_4), and concentrated. Crude alcohol **12** (115 mg, 98%) was used without further purification. ^{1}H-NMR (200 MHz): 7.22 (m_c, 5 arom. H); 5.52 (*ddd*, *J* = 2.5, 5, 10, H−C(7)); 5.27 (br. *d*, *J* = 10, H−C(8)); 4.37 (m_c, PhC*H*$_2$); 3.84 (m_c, H−C(4)); 3.80–3.11 (*m*, BnOC*H*$_2$, C*H*$_2$OH); 2.49–1.57 (*m*, H_{eq}−C(1), H−C(2), 2 H−C(3), H−C(5), H−C(6), H−C(8a), OH); 1.25–0.97 (*m*, H_{ax}−C(1), H−C(4a)); 0.82 (*d*, *J* = 7, Me−C(6)); 0.79 (*s*, *t*-Bu); −0.01, −0.07 (2*s*, Me_2Si). ^{13}C-NMR (50.3 MHz): 132.4 (*d*, C(7)); 130.8 (*d*, C(8)); 138.7 (*s*, arom. *ipso*-C); 128.3, 127.7, 127.5 (3*d*, arom. C); 73.3 (*t*, Ph*C*H$_2$); 69.4 (*t*, BnO*C*H$_2$); 67.6 (*d*, C(4)); 67.0 (*t*, CH$_2$OH); 41.9 (*d*, C(4a)); 37.0, 35.6 (2*d*, C(2), C(5)); 36.1, 34.2 (2*t*, C(1), C(3)); 31.2, 30.1 (2*d*, C(6), C(8a)); 26.0, 18.2 (*q*, *s*, Me_3C); 15.8 (*q*, Me−C(6)); −2.5, −5.5 (2 *q*, $SiMe_2$).

*(2α,4α,4aβ,5β,6β,8aα)-5-[(Benzyloxy)methyl]-4-{[(*tert*-butyl)dimethylsilyl]oxy}-1,2,3,4,4a,5,6,8a-octahydro-6-methyl-2-{[(4-methylphenyl)sulfonyloxy]methyl}naphthalene* (**13**). To a soln. of **12** (97 mg, 0.23 mmol), 4-(dimethylamino)pyridine (10 mg, 0.082 mmol), and pyridine (1 ml) in CH_2Cl_2 (5 ml) freshly recrystallized TsCl (47 mg, 0.25 mmol) was added. The mixture was stirred at r.t. for 90 h. After this period, the mixture was washed with 2N HCl (2 × 10 ml), 2N NaOH (10 ml), and brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Crude **13** (108 mg, 82%) was used without further purification. ^{1}H-NMR (200 MHz): 7.80 (*d*, *J* = 8, H_o of Ts); 7.39–7.28 (*m*, Ph, H_m of Ts); 5.60 (*ddd*, *J* = 2, 5, 10, H−C(7)); 5.16 (br. *d*, *J* = 10, H−C(8)); 4.46 (m_c, PhC*H*$_2$); 4.35 (m_c, 1 H, TsOC*H*$_2$); 3.99 (m_c, H−C(4)); 3.90 (*dd*, *J* = 4, 9, 1 H, TsOC*H*$_2$); 3.58 (*dd*, *J* = 4, 9, 1 H, BnOC*H*$_2$); 3.26 (*dd*, *J* = 9, 10, 1 H, BnOC*H*$_2$); 2.45 (*s*, *Me*Ar); 2.42–1.62 (*m*, H_{eq}−C(1), H−C(2), 2 H−C(3), H−C(5), H−C(6), H−C(8a)); 1.29–1.01 (*m*, H_{ax}−C(1), H−C(4a)); 0.88 (*d*, *J* = 7, Me−C(6)); 0.85 (*s*, *t*-Bu); 0.02,

– 0.05 (2*s*, Me_2Si). ^{13}C-NMR (50.3 MHz): 144.6, 138.5, 133.2 (3*s*, arom. *ipso*-C); 132.6, 130.2, 130.0, 129.7, 128.3, 127.7, 127.5 (7*d*, C(7), C(8), 5 arom. C); 73.5, 73.3 (2*t*, Ph*C*H$_2$, TsO*C*H$_2$); 69.1 (*t*, BnO*C*H$_2$); 67.2 (*d*, C(4)); 67.0 (*t*, CH_2OH); 41.9 (*d*, C(4a)); 36.8, 32.6 (2*d*, C(2), C(5)); 35.6, 32.8 (2*t*, C(1), C(3)); 31.1, 28.9 (2*d*, C(6), C(8a)); 25.9, 18.1 (*q*, *s*, Me_3C); 21.9 (*Me*Ar); 15.7 (*q*, *Me*–C(6)); – 2.3, – 5.7 (2*q*, Me_2Si).

*(2α,4α,4aβ,5β,6β,8aα)-5-[(Benzyloxy)methyl]-4-[[(*tert*-butyl)dimethylsilyl]oxy}-1,2,3,4,4a,5,6,8a-octahydro-2,6-dimethylnaphthalene* (**14**). To a soln. of **13** (100 mg, 0.171 mmol) in THF (5 ml) was added *Super-Hydride*® (1.0M in THF; 0.430 ml, 0.43 mmol). The mixture was refluxed for 3 h, then treated with a second batch of *Super-Hydride*® (1.0M in THF; 1.3 ml, 1.3 mmol), and refluxed for further 3 h. After cooling to 0°, the reaction was quenched by successive addition of H_2O (2 ml), 2N NaOH (1 ml), and 30% H_2O_2 soln. (1 ml). The mixture was stirred for 1.5 h at this temp., then diluted with brine (10 ml) and extracted with Et_2O (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The crude product (60 mg) was purified on silica gel (hexane/AcOEt 10:1) to yield **14** (45 mg, 63%). Colorless oil. IR (neat): 3075–3025 (=C–H); 2960–2860 (C–H); 1650, 1475 (C=C); 1250 (Si–C). ^{1}H-NMR (200 MHz): 7.32 (m_c, 5 arom. H); 5.63 (*ddd*, *J* = 2.5, 5, 10, H–C(7)); 5.34 (br. *d*, *J* = 10, H–C(8)); 4.46 (m_c, PhCH_2); 3.93 (m_c, H–C(4)); 3.64 (*dd*, *J* = 4, 9, 1 H, BnOCH_2); 3.28 (*dd*, *J* = 9, 11, 1 H, BnOCH_2); 2.63–1.05 (*m*, 2 H–C(1), H–C(2), 2 H–C(3), H–C(4a), H–C(5), H–C(6), H–C(8a)); 1.16 (*d*, *J* = 7.5, Me–C(2)); 0.89 (*d*, *J* = 7, Me–C(6)); 0.88 (*s*, *t*-Bu); 0.09, – 0.01 (2*s*, Me_2Si). ^{13}C-NMR (50.3 MHz): 132.4 (*d*, C(7)); 131.4 (*d*, C(8)); 138.9 (*s*, arom. *ipso*-C); 128.3, 127.7, 127.4 (3*d*, arom. C); 73.3 (*t*, Ph*C*H$_2$); 69.4 (*t*, BnO*C*H$_2$); 68.3 (*d*, C(4)); 42.2 (*d*, C(4a)); 39.9, 38.6 (2*t*, C(1), C(3)); 37.0, 31.2, 29.3, 27.5 (4*d*, C(2), C(5), C(6), C(8a)); 26.0, 18.2 (*q*, *s*, Me_3C); 22.1 (*q*, *Me*–C(2)); 15.8 (*q*, Me–C(6)); – 2.5, – 5.6 (2*q*, Me_2Si). Anal. calc. for $C_{26}H_{42}O_2Si$ (414.7): C 75.30, H 10.21; found: C 75.35, H 10.39.

(2α,4α,4aβ,5β,6β,8aα)-5-[(Benzyloxy)methyl]-1,2,3,4,4a,5,6,8,8a-octahydro-2,6-dimethylnaphthalen-4-ol (**15**). A soln. of **14** (40 mg, 0.096 mmol) in MeCN (10.5 ml) was treated with 40% aq. HF (0.5 ml) and stirred for 21 h at r.t. The mixture was then neutralized with solid $NaHCO_3$ and concentrated. The residue was suspended in H_2O (10 ml) and extracted with CH_2Cl_2 (4 × 10 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated. The residue (30 mg) was purified by chromatography (hexane/AcOEt 10:1) to provide **15** (25 mg, 87%). Colorless oil. IR (neat): 3500–3400 (O–H); 3030 (=C–H); 2960–2880 (C–H); 1600, 1460 (C=C). ^{1}H-NMR (200 MHz): 7.26 (m_c, 5 arom. H); 5.46 (*ddd*, *J* = 2.5, 5, 10, H–C(7)); 5.32 (br. *d*, *J* = 10, H–C(8)); 4.45 (m_c, PhCH_2); 3.97 (m_c, H–C(4)); 3.43, 3.33 (2m_c, 1 H each, BnOCH_2); 2.55–1.20 (*m*, 2 H–C(1), H–C(2), 2 H–C(3), H–C(4a), H–C(5), H–C(6), H–C(8a), OH); 1.13 (*d*, *J* = 7.5, Me–C(2)); 0.73 (*d*, *J* = 7, Me–C(6)). ^{13}C-NMR (50.3 MHz): 132.4 (*d*, C(7)); 131.6 (*d*, C(8)); 137.5 (*s*, arom. *ipso*-C); 128.5, 127.89, 127.86 (3*d*, arom. C); 73.8, 73.6 (2*t*, Ph*C*H$_2$, BnO*C*H$_2$); 67.4 (*d*, C(4)); 43.6 (*d*, C(4a)); 39.2, 37.6 (2*t*, C(1), C(3)); 38.9, 33.9, 30.2, 27.3 (4*d*, C(2), C(5), C(6), C(8a)); 21.2 (*q*, Me–C(2)); 15.8 (*q*, Me–C(6)). Anal. calc. for $C_{20}H_{28}O_2$ (300.4): C 79.97, H 9.39; found: C 80.15, H 9.56.

(2α,4α,4aβ,5β,6β,8aα)-1,2,3,4,4a,5,6,8a-Octahydro-5-(hydroxymethyl)-2,6-dimethylnaphthalen-4-ol (**1**). To a soln. of Li (5 mg, 0.7 mmol) in liq. NH_3 (2 ml) at – 78°, a soln. of **15** (20 mg, 0.066 mmol) in THF (5 ml) was added. After stirring at – 78° for 2 h, the mixture was treated with solid NH_4Cl and warmed to r.t. The residue was extracted with Et_2O (4 × 5 ml), the combined org. extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated. The crude product was purified on silica gel (hexane/AcOEt 4:1) to yield **1** (12 mg, 94%). Colorless solid. M.p. 119–121° ([9d]: 118–120°). All spectroscopic data correspond to those reported in [9a][9b][9d]. IR (neat): 3550–3150 (O–H); 3050 (=C–H); 2950–2850 (C–H); 1460 (C=C). ^{1}H-NMR (300 MHz): 5.55 (*ddd*, *J* = 3, 5, 10, H–C(7)); 5.39 (br. *d*, *J* = 10, H–C(8)); 4.21 (*q*, *J* = 3, H–C(4)); 3.75 (*t*, *J* = 10, 1 H, CH_2OH); 3.65 (*dd*, *J* = 3, 10, 1 H, CH_2OH); 2.90 (br. *s*, 2 OH); 2.56–2.45 (*m*, H–C(8a)); 2.43–2.34 (*m*, H–C(6)); 2.10–1.95 (*m*, H–C(2), H–C(5)); 1.88–1.70 (*m*, 2 H–C(3)); 1.63–1.53 (*m*, H_{eq}–C(1)); 1.30 (*td*, *J* = 5, 13, H_{ax}–C(1)); 1.24–1.15 (partially obscured *m*, H–C(4a)); 1.21 (*d*, *J* = 7.5, Me–C(2)); 0.81 (*d*, *J* = 7, Me–C(6)). ^{13}C-NMR (75.5 MHz): 132.1 (*d*, C(7)); 132.0 (*d*, C(8)); 67.9 (*d*, C(4)); 65.3 (*t*, CH_2OH); 43.1 (*d*, C(4a)); 41.0 (*d*, C(2)); 38.9 (*t*, C(1)); 38.1 (*t*, C(3)); 33.8 (*d*, C(6)); 30.3 (*d*, C(8a)); 27.1 (*d*, C(5)); 21.2 (*q*, *Me*–C(2)); 15.7 (*q*, *Me*–C(6)). Anal. calc. for $C_{13}H_{22}O_2$ (192.2): C 74.25, H 10.54; found: C 74.33, H 10.67.

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