7. Angular Alkylation of *cis*-Decalin Epoxides with C-Nucleophiles: Mechanism, Scope, and Limitations of a Novel Bridgehead Functionalisation

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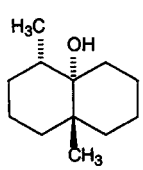
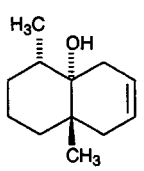
The angular alkylation of *cis*-decalin epoxides like **5** or **7** can be achieved at C(8a)[1]) in good yield by using CuI and a large excess of *Grignard* reagents without an sp^3 centre at C(2). The reaction proceeds *via* a carbenium-ion intermediate which is stabilised by homoconjugative interaction with the adjacent double bond. Due to 1,3-diaxial strain in the alkoxides resulting from alkylation or reduction at C(4a) of the epoxides **5** or **7**, the nucleophile is delivered selectively to C(8a). *Grignard* reagents possessing H-atoms at C(β), transfer a hydride to the epoxide yielding the *trans*-decalol **11** (*Grignard* reduction). The angular alkylation of **5** with allylic and benzylic *Grignard* reagents proceeds with good yield.

Introduction. – Terpenoids possessing a bis-angularly substituted structural element like **1** are quite common in nature. Some typical representatives are the bacterial metabolite geosmin (**1**) [1], the strongly odoriferous dehydrogeosmin (**2**) from flowers of cactaceae [2], cybullol (**3**) from birds nest fungi [3], and the selinenol **4** from the red alga *Laurencia nipponica* [4]. The previously known synthetic routes towards compounds possessing this structural feature utilise a sequence of an intermolecular *Michael* addition between an α,β-unsaturated ketone and an appropriately activated cyclohexanone followed by an intramolecular aldol reaction yielding an unsaturated octalone skeleton [5]. Subsequent functional-group manipulations are required to establish all centres of, *e.g.*, **1** and **3** [6]. The sequence is, however, of limited use, if functionalised substituents in the products or unsymmetrically 2,6-substituted cyclohexanone educts are required.

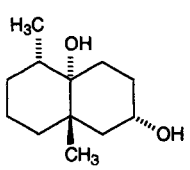
A recently developed, chiral approach towards (+)- and (−)-dehydrogeosmin (**2**) starts from readily available aromatic precursors. The key reaction of the novel sequence relies on the ring-opening reaction of the angular *cis*-decaline epoxide **5** with MeMgI and Cu^I as depicted in *Scheme 1* [7]. The reaction deserves special attention, since tetrasubstituted oxiranes like **5** generally fail to react with C-nucleophiles. In the transformations



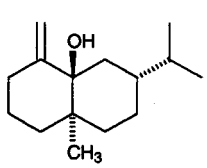
1 (−)-geosmin



2 (+)-dehydro-geosmin



3 (−)-cybullol

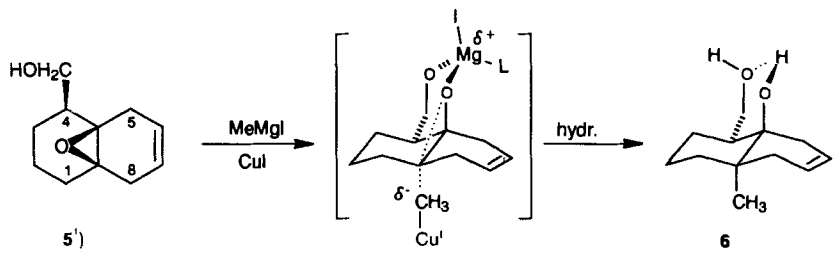


4 (+)-selinenol

[1]) For convenience, the arbitrary numbering given for **5** (*Scheme 1*) is used throughout the *General Part*; for systematic names, see *Exper. Part.*

5 → **6**, the ease of the reaction is facilitated by the presence of the CH_2OH group allowing the formation of a metallacycle between the two O-atoms. The ongoing reaction is believed to labilise one of the two C–O single bonds of the adjacent oxirane generating a carbenium ion which rapidly reacts with the C-nucleophile. Furthermore, the reaction profits from the push-pull character of the reagent combination of a *Lewis* acid (ROMg-Hal) with a strong nucleophile like RCuI or R_2Cu. Interestingly, the alkylation occurs exclusively at C(8a)[1]). We speculated that the observed regiospecificity could be due to the greater ease of the formation and the enhanced thermodynamic stability of the six-membered metallacycle instead of a seven-membered system [7].

Scheme 1

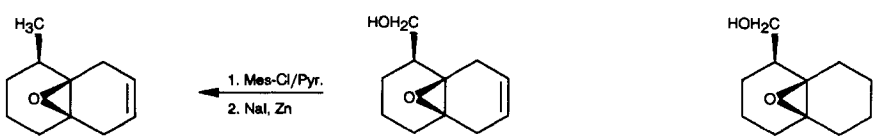


5[1]) 6

Up to now, only a few related transformations using *Grignard* reagents [8] [9] or $LiAlMe_4$ [10] and some steroidal expoxides have been described. To gain more insight into the mechanistic aspects and to explore the structural requirements of this versatile bridgehead functionalisation, we continued our studies and tested other *Grignard* reagents and other organometallic alkylation systems along with some modified decalins of the structural type **5**. The results of these studies and the synthesis of some novel, angularly substituted decalins are reported.

Results. – *Synthesis of* cis-*Decaline Epoxides.* To check whether or not the formation of the dioxametallacycle of *Scheme 1* is essential for the success of the reaction, the CH_2OH substituent of **5** is reduced to a non-coordinating Me group. This is readily achieved by mesylation and *in-situ* reduction with iodide/Zn metal yielding **7** [2]. The oxirane moiety is not affected (*Scheme 2*).

Scheme 2



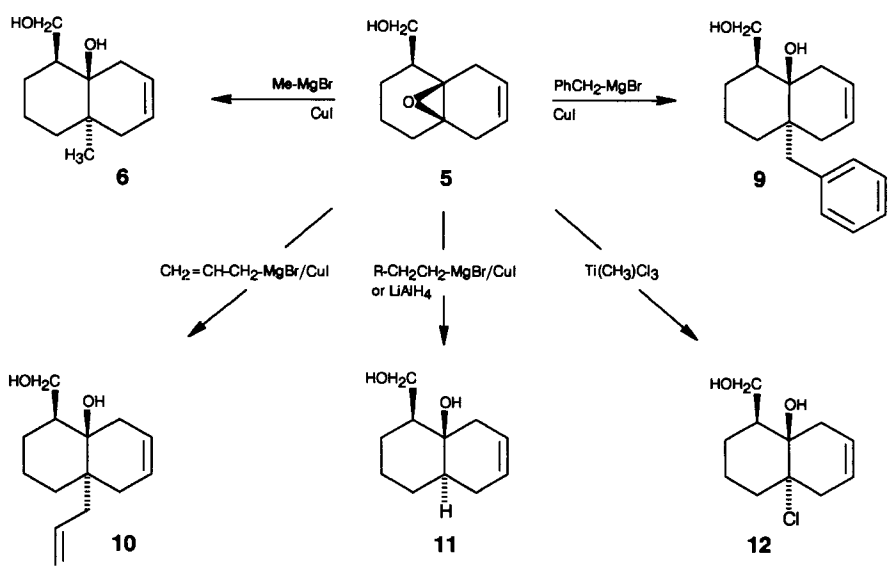
7 **5** **8**

The saturated epoxy alcohol **8** is obtained from a hexahydronaphthalene precursor by selective hydrogenation of the disubstituted double bond and epoxidation of the central, tetrasubstituted double bond as described [7].

Alkylation Experiments with Grignard *Reagents.* Best results for the angular alkylation of **5** are obtained by using 1 equiv. of Cu^I and a 40- to 70-fold excess of the corresponding *Grignard* reagent in refluxing Et_2O [7] [11]. The formation of by-products is minimal (< 5%). According to GLC and ^{1}H-NMR, the alkylation product is isolated with high purity (≥ 98% d.e.) in 50–80% yield after chromatography on SiO_2. The reaction is very slow at room temperature (*ca.* 2 d); slightly enhanced temperatures (Et_2O reflux) strongly accelerate the reaction (2 h). Since organocopper nucleophiles are generally unstable above 0° [12], other reagent pairs were tested. The combinations of MeMgBr or MeLi with *Lewis* acids like $BF_3 \cdot Et_2O$, $AlCl_3$, $Ti(i\text{-}PrO)_4$, or $TiCl_4$ is ineffective [13]. The strongly nucleophilic $LiCuMe_2$ and the reagent pair $LiCuMe_2/BF_3$ [14] also fail to react and, thereby, indicate that only certain combinations of a *Lewis* acid with a nucleophile can be applied. Since already MeMgI without additives affords **6**, albeit in low yield (10% according to GLC), the combination of MeMgI with a weak *Lewis* acid like $ZnCl_2$ was tried. As a matter of fact, this reagent pair is able to achieve the angular alkylation, but the formation of by-products is considerable.

Higher alkyl-*Grignard* reagents cannot be used for the angular alkylation, since these reagents transfer a hydride instead of the alkyl moiety. The regioselectivity and the stereochemical course of the reductive ring opening of tetrasubstituted epoxides with *Grignard* reagents is identical with that of the Me group transfer **5** → **6**. The hydride is exclusively delivered to C(8a)[1]) yielding **11**. Pure **11** is also available by reduction of **5** with $LiAlH_4$ in THF (*Scheme 3*). The angular alkylation can be extended to *Grignard* reagents without an sp^3 centre at C(2). *E.g.*, the angular alkylations of **5** with benzylmagnesium bromide and allylmagnesium bromide proceed smoothly and furnish the *trans*-decalins **9** and **10** in 44 and 78% yield, respectively. Analogous reactions with phenyl- and vinylmagnesium bromide fail.

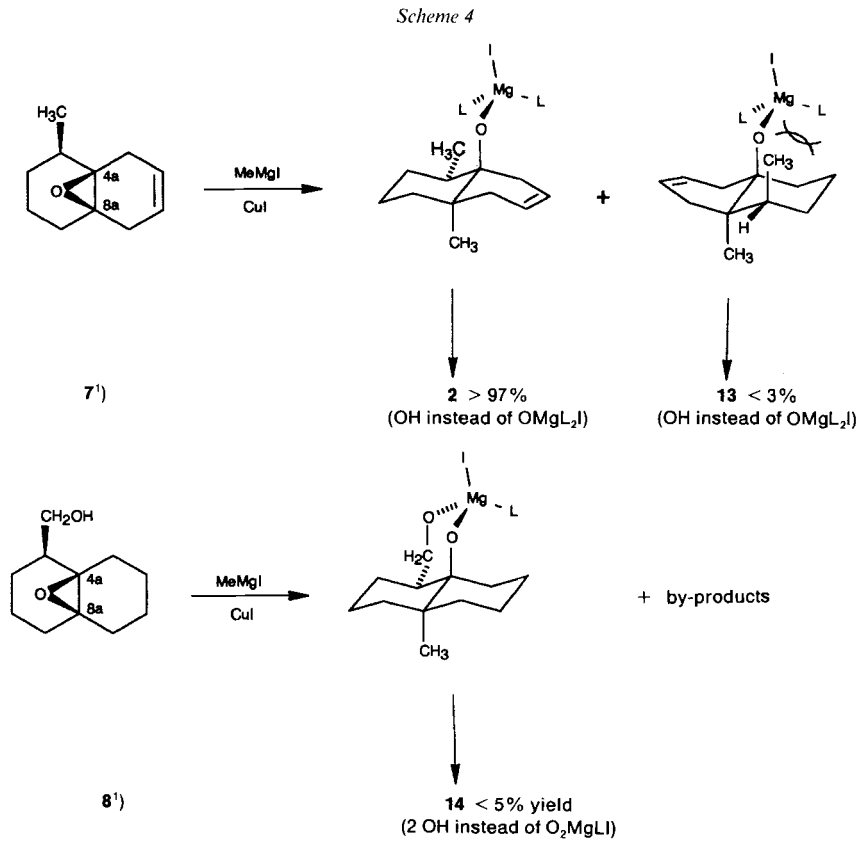
Scheme 3



Treatment of **5** with $MeTiCl_3$ [15] or Me_2TiCl_2 [16] affords an unexpected product. Instead of the Me group, both reagents transfer the Cl^- ion to C(8a), yielding the moderately stable chlorodiol **12** in 63% yield. The preferred transfer of the halide ion instead of the more nucleophilic Me group is remarkable and may reflect the peculiar stereochemical constraints of this reaction.

Structural Aspects of the cis-*Decalin Epoxides.* The reaction of the standard system MeMgI/CuI with the two *cis*-decalin epoxides **7** and **8** provides important informations about the structural prerequisites of the oxirane moiety. Not unexpected, the deoxy compound **7** reacts very slowly. However, according to GLC and ^1H- and ^{13}C-NMR, didehydrogeosmin (**2**) is formed as the major product (> 97%). The amount of the regioisomer **13** is not significant (< 3% according to GLC/MS). Owing to a key fragment of *m/z* 126, corresponding to a *retro-Diels-Alder* cleavage, both products of the angular alkylation are readily identified by GLC/MS.

Scheme 4



Although the coordinating CH_2OH group is present in **8**, the standard reagent pair MeMgI/CuI fails to react with the saturated epoxide ($\leq$ 5% yield of **14** according to GLC; standard reaction conditions).

Discussion. – The angular alkylation of tetrasubstituted epoxides like **5** or **7** is a valuable method for the angular functionalisation of the decalin system 'en route' to natural products and other synthetic targets. The reaction proceeds most readily with an unsaturated oxirane of type **5**. The ease of this reaction can be rationalised by the formation of the magnesium alkoxide placing a weak *Lewis* acid into the vicinity of the epoxide O-atom [7]. The transition-state structure shown in *Scheme 1* illustrates the push-pull character of the reaction and accounts at the same time for the exclusive production of the regioisomer **6**. However, considering the very high degree of the regioselectivity (> 97%) of the transformation **7** → **2**, this explanation is clearly insufficient, since the formation of a dioxametalla cycle is not possible in this case. Furthermore, owing to the *cis*-orientation of the epoxy moiety and the Me group in **7**, there is no substantial difference for the approaching reagent to attack either C(4a) or C(8a)[1]). However, as depicted in *Scheme 4*, the attack onto C(4a) leads to **13** which lets expect a significant 1,3-diaxial interaction between the Me group at C(4) and the angular magnesium alkoxide at C(8a). If the nucleophile is delivered to C(8a), the resulting alkoxide at C(4a) experiences no unfavourable steric interactions. Since the transition state of the reaction **7** → **2** can be considered as a species with partial positive charges at both C(4a) and C(8a) (similar to the transition state of *Scheme 1*), the nucleophile will, thus, selectively add to C(4a) yielding the least hindered alkoxide with high preference.

Comparative MM2 calculations of **5** and **8** indicate similar strain energies for both molecules and show no significant differences in the backside approach to either C(8a) or C(4a), respectively. Therefore, the complete fail of the angular alkylation of **8** with MeMgI/Cu[I] is unexpected and cannot be attributed to conformational constraints. To account for this result, we assume that the angular alkylation of the decalin epoxides proceeds *via* a carbenium-ion intermediate which profits from a substantial homoconjugative stabilisation owing to which the developing π-orbital of the ionising epoxide finds itself in a favourable position for overlapping with the π-electrons of the adjacent double bond [17]. A cationic intermediate is also in agreement with the observed hydride transfer from higher *Grignard* reagents which are known to deliver a hydride to non-enolisable ketones [18] and other electrophiles (*Grignard* reduction) [19]. In conclusion, the combination of a weak *Lewis* acid with a strong, but nonbasic nucleophile like R–Cu[I] as depicted in *Scheme 1* is essential for the success of the angular alkylation of the *cis*-decalin epoxides. Within the above limits, the method appears to be of general applicability and has been already extended to the field of steroids.

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Experimental Part

General. See [7]. Moreover: Column chromatography: silica gel *Si 60* (0.040–0.063 mm; *E. Merck*, Darmstadt, Germany). Anal. GLC: *Carlo-Erba* gas chromatograph, *GC 6000, Vega* series *2*; fused-silica capillary *SE 30* (10 m × 0.32 mm); N_2 at 30 cm^3/s as carrier. Melting points: not corrected. ^{1}H- and ^{13}C-NMR: *Bruker Cryospec WM 250* and *Bruker WM 400*. MS: *Finnigan-MAT-90* GLC/MS system and *Finnigan ITD 800* combined with a *Carlo-Erba* gas chromatograph, model *Vega*, equipped with a fused-silica capillary *SE 30* (10 m × 0.32 mm); carrier gas, He at 30 cm^3/s; scan range: 35–350 Dalton/s.

(±)-4aβ,8aβ-Epoxy-1,2,3,4,5,8-hexahydro-1β-methylnaphthalene (**7**). A chilled soln. of the epoxyalcohol **5** (0.30 g, 1.66 mmol) and pyridine (6.0 ml) in CH_2Cl_2 (24 ml) is treated with stirring with $MeSO_2Cl$ (0.39 g, 2.62 mmol). After 24 h at r.t., the soln. is poured into cold 2N HCl (60 ml). The mesylate is extracted with AcOEt (4 × 75 ml). The combined org. layers are washed with brine, dried, and evaporated. The residue is dissolved in THF (75 ml). Zn Dust (2.55 g, 39 mmol) and NaI (2.55 g, 16.95 mmol) are added, and the suspension is refluxed for 12 h. The solids are removed by filtration. Extractive workup (Et_2O) and chromatography on SiO_2 (pentane/Et_2O 7:3) afford **7** (0.169 g, 62%; > 96% according to GLC). Colourless liquid. IR (KBr, neat): 3031, 2960, 2933, 2819, 1670, 1458, 1422, 1374, 1362, 1120, 1088, 881, 869, 842, 793, 661. ^{1}H-NMR ($CDCl_3$): 5.45 (*s*, H–C(6), H–C(7)); 2.74–2.12 (*m*, 2 H–C(5), 2 H–C(8)); 1.98–1.13 (*m*, H–C(1), 2 H–C(2), 2 H–C(3), 2 H–C(4)); 1.06 (*d*, Me). ^{13}C-NMR ($CDCl_3$): 122.7 (C(6)); 122.5 (C(7)); 63.8 (C(4a)); 61.9 (C(8a)); 33.5 (C(1)); 32.2 (C(4)); 30.3 (C(5)); 29.8 (C(8)); 29.0 (C(2)); 19.2 (C(3)); 16.0 (Me). MS (70 eV): 164 (75, $M^{+\cdot}$), 149 (100), 136 (18), 131 (41), 121 (52), 110 (33), 106 (51), 95 (47), 93 (57), 91 (47), 82 (45), 80 (46), 79 (77), 77 (35), 67 (45), 55 (24), 53 (14). HR-MS: 164.1172 ($C_{11}H_{16}O^+$, $M^{+\cdot}$, calc. 164.1201).

(±)-4aβ,8aβ-Epoxyperhydronaphthalene-1-methanol (**8**). IR (KBr): 3422*s*, 2936, 2863, 1448, 1436, 1068, 1039, 1020, 993, 875, 837. ^{1}H-NMR ($CDCl_3$): 3.93–3.70 (*m*, CH_2OH); 2.18–1.77 (*m*, 15 H). ^{13}C-NMR ($CDCl_3$): 64.4 (CH_2OH); 63.8 (C(8a)); 61.5 (C(4a)); 40.9 (C(1)); 31.1 (C(8)); 31.0 (C(4)); 30.2 (C(5)); 24.0 (C(2)); 20.8 (C(7)); 20.1 (C(3)); 18.7 (C(6)). MS (70 eV): 182 (3, $M^{+\cdot}$), 164 (8), 152 (22), 151 (100), 135 (22), 134 (57), 133 (32), 123 (23), 111 (19), 95 (21), 91 (35), 81 (38), 79 (29), 67 (45), 55 (24). HR-MS: 182.1291 ($C_{11}H_{18}O_2^+$, $M^{+\cdot}$, calc. 182.1307).

Angular Alkylation of **5** *with* Grignard *Reagents and Cu^I: General Procedure.* A suspension of Cu^I (0.107 g, 0.56 mmol) is treated at r.t. with the corresponding 1M *Grignard* reagent in Et_2O (41 ml). The soln. turns black while stirring is continued for 15 min. Then, **5** (0.10 g, 0.56 mmol in Et_2O (5.0 ml)) is added to the cooled (0°) soln. of the organometallic reagent. The reaction is usually completed within 2 h at reflux. The excess of the *Grignard* reagent is destroyed by pouring the soln. into ice/H_2O. After extraction with Et_2O (4 × 75 ml), the org. layer is washed with brine, dried, and evaporated. Chromatography (SiO_2, pentane/Et_2O 1:1 (*v*/*v*)) yields the angularly alkylated *trans*-decalin. Careful control of the reaction parameters and pure CuI (no photodecomposition) are essential to warrant high yields.

(±)-8aα-Benzyl-1,3,4,5,8,8a-hexahydro-4aβ(2H)-ol (**9**). Prepared from **5** (0.1 g, 0.56 mmol) and benzylmagnesium bromide: 0.066 g (44%; > 98% according to GLC). Colourless solid. M.p. 130°. IR (KBr): 3297*s*, 3028, 2931, 2883, 2859, 1657, 1603, 1496, 1455, 1424, 883, 707, 659. ^{1}H-NMR ($CDCl_3$): 7.33–7.06 (*m*, 5 arom. H); 5.78 (*m*, H–C(6), H–C(7)); 4.14 (*dd*, 1 H, CH_2OH); 3.63 (*dd*, 1 H, CH_2OH); 3.16 (*s*, OH); 2.87 (*d*, 1 H–C(5)); 2.69 (*s*, OH); 2.50 (*d*, 1 H–C(8)); 2.39 (*m*, 1 H–C(5), 1 H–C(8)); 2.32–1.17 (*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3), H–C(4), $PhCH_2$). ^{13}C-NMR ($CDCl_3$): 138.7 (arom. C); 130.7 (2 arom. C); 127.8 (2 arom. C); 126.4 (C(6)); 126.0 (arom. C); 123.9 (C(7)); 75.9 (C(4a)); 64.4 (CH_2OH); 40.4 (C(4)); 40.2 ($PhCH_2$); 34.8 (C(8a)); 34.7 (C(5)); 31.0 (C(8)); 28.7 (C(3)); 25.0 (C(1)); 21.0 (C(2)). MS (70 eV): 254 (1, $[M - H_2O]^{+\cdot}$), 218 (18), 162 (19), 146 (12), 145 (100), 131 (21), 117 (10), 115 (5), 91 (64), 81 (8), 79 (10), 77 (8), 67 (10), 55 (8). HR-MS: 254.1688 ($C_{18}H_{22}O^+$, $[M - H_2O]^{+\cdot}$, calc. 254.1671).

(±)-8aβ-Allyl-1,3,4,5,8,8a-hexahydro-4aβ(2H)-ol (**10**). Prepared from **5** (0.1 g, 0.56 mmol) and allylmagnesium bromide: 0.09 g (73%; > 90% according to GLC). Colourless solid. M.p. 114°. IR (KBr): 3387*s*, 3072, 3023, 2927, 2865, 1657, 1638, 1458, 1431, 1391, 1280, 1057, 1043, 1018, 988, 970, 914, 903, 882. ^{1}H-NMR ($CDCl_3$): 5.86–5.58 (*m*, H–C(6), H–C(7), $CH_2{=}CHCH_2$); 5.07 (*m*, $CH_2{=}CHCH_2$); 4.10 (*dd*, 1 H, CH_2OH); 3.59 (*dd*, 1 H, CH_2OH); 3.12 (*s*, 1 OH); 2.58 (*s*, 1 OH); 2.43–1.18 (*m*, $CH_2{=}CHCH_2$, 2 H–C(1), 2 H–C(2), 2 H–C(3), H–C(4), 2 H–C(5), 2 H–C(8)). ^{13}C-NMR ($CDCl_3$): 134.5 ($CH_2{=}CHCH_2$); 126.3 (C(6)); 123.6 (C(7)); 117.4 ($CH_2{=}CHCH_2$); 75.6 (C(4a)); 64.3 (CH_2OH); 40.1 (C(4)); 39.4 (C(8a)); 34.4 (C(5)); 34.2 (C(8)); 31.7 ($CH_2{=}CHCH_2$); 29.6 (C(3)); 25.0 (C(1)); 20.4 (C(2)). MS (70 eV): 222 (2, $M^{+\cdot}$), 204 (10), 179 (6), 168 (30), 145 (100), 136 (15), 117 (8), 107 (8), 93 (8), 91 (18), 81 (9), 79 (12), 67 (10), 55 (7). HR-MS: 222.1605 ($C_{14}H_{22}O_2^+$, $M^{+\cdot}$, calc. 222.1620).

(±)-8aα-Chloro-1,3,4,5,8,8a-hexahydro-4aβ(2H)-ol (**12**). Into a cold (–78°) soln. of $TiCl_4$ (0.52 g, 2.74 mmol) in Et_2O (15 ml) is injected with stirring 1.6M MeLi in Et_2O (1.7 ml, 2.72 mmol).

After 15 min, a soln. of **5** (0.10 g, 0.56 mmol) in Et_2O (1.0 ml) is added gradually, and stirring is continued for 5 h at −78°. The mixture is hydrolysed by addition of sat. aq. NH_4Cl soln. (10 ml) and allowed to come to r.t. Extractive workup with Et_2O and chromatography (SiO_2, pentane/Et_2O 1:4) afford unstable **12** (0.076 g, 63%; > 89% according to GLC). Colourless solid. M.p. 141°. The compound decomposes within several days at −20°. IR (KBr): 3409*s*, 3033, 2939, 2910, 2869, 1659, 1432, 1395, 1125, 1061, 1041, 996, 884, 771, 676, 608. ^{1}H-NMR ($CDCl_3$): 5.71 (*m*, H–C(6), H–C(7)); 4.11 (*dd*, 1 H, C*H*$_2$OH); 3.63 (*dd*, 1 H, C*H*$_2$OH); 3.30 (*s*, 2 OH); 2.72–2.30 (*m*, H–C(4), 2 H–C(5), 2 H–C(8)); 2.11–1.47 (*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3)). ^{13}C-NMR ($CDCl_3$): 123.7 (C(7)); 123.6 (C(6)); 74.7 (C(8a)); 72.4 (C(4a)); 64.3 (CH_2OH); 40.3 (C(4)); 38.2 (C(8)); 35.9 (C(5)); 35.1 (C(3)); 24.4 (C(1)); 20.9 (C(2)). MS (70 eV): 200 (0.06), 198 (2, $[M - H_2O]^{+\cdot}$), 164 (22), 162 (77), 146 (12), 145 (100), 131 (19), 117 (5), 107 (7), 91 (14), 79 (10), 77 (8), 67 (7), 55 (7). HR-MS: 198.0831 ($C_{11}H_{15}ClO^+$, $[M - H_2O]^{+\cdot}$, calc. 198.0811).

(±)-1,3,4,5,8,8aα-Hexahydro-4β-(hydroxymethyl)naphthalen-4aβ(2H)-ol (**11**). A well stirred and chilled suspension of $LiAlH_4$ (0.150 g, 3.95 mmol) in THF (15 ml) is gradually treated with a soln. of **5** (0.10 g, 0.56 mmol) in THF (3.0 ml). Stirring is continued for 30 h at r.t. Then, the excess of $LiAlH_4$ is destroyed by slow addition of a sat. aq. NH_4Cl soln. Extractive workup and chromatography on SiO_2 (pentane/Et_2O 1:4) yield **11** (0.067 g, 66%; > 98% according to GLC). Colourless solid. IR (KBr): 3354*s*, 3022, 2915, 2854, 1448, 1395, 1661, 1635, 1276, 1128, 1109, 1059, 1042, 1019, 1001, 989, 887. ^{1}H-NMR ($CDCl_3$): 5.73 (*m*, H–C(6)); 5.62 (*m*, H–C(7)); 4.16 (*dd*, 1 H, C*H*$_2$OH); 3.57 (*dd*, 1 H, C*H*$_2$OH); 2.99 (*s*, OH); 2.50–2.33 (*m*, 1 H–C(5), 1 H–C(8)); 2.17–1.72 (*m*, H–C(4), 1 H–C(5), 1 H–C(8), H–C(8a), OH); 1.57–1.20 (*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3)). ^{13}C-NMR ($CDCl_3$): 126.9 (C(6)); 123.7 (C(7)); 72.6 (C(4a)); 64.1 (CH_2OH); 46.7 (C(8a)); 39.8 (C(4)); 37.8 (C(5)); 28.8 (C(8)); 28.7 (C(3)); 25.5 (C(1)); 25.4 (C(2)). MS (70 eV): 182 (6, $M^{+\cdot}$), 164 (7), 133 (3), 128 (100), 110 (17), 97 (9), 95 (11), 91 (8), 79 (7), 67 (9), 55 (6). HR-MS: 182.1300 ($C_{11}H_{18}O_2^+$, $M^{+\cdot}$, calc. 182.1307).

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