189. A Total Synthesis of Aphidicolin: Stereospecific Synthesis of (±)-3α,18-Dihydroxy-17-noraphidicolan-16-one

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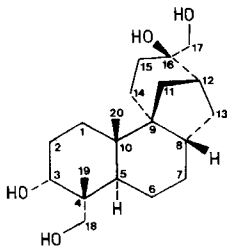
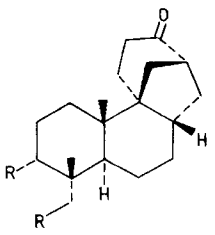
Summary

A simple, efficient, and stereospecific total synthesis of (±)-3α,18-dihydroxy-17-noraphidicolan-16-one (**2**), by solvolytic rearrangement of the *endo*-bicyclo-[2.2.2]oct-5-en-2-yl methanesulfonate **16**, is described. Since aphidicolin (**1**) has already been obtained from **2**, the preparation of the latter formally constitutes a new total synthesis of **1**.

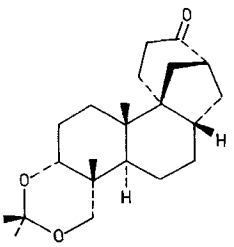
The diterpenic tetrol aphidicolin (=aphidicolane-3α,16,17,18-tetrol; **1**) [1] doubtless represents, because of its biological properties and unique C/D ring system, an interesting and challenging synthetic target. Many syntheses of **1** were planned *via* 3α,18-isopropylidenedioxy-17-noraphidicolan-16-one (**3**) [2–4] or other derivatives of 3α,18-dihydroxy-17-noraphidicolan-16-one (**2**) [5], since **1**, in the course of its structure elucidation, has been degraded to **2** and the latter reconverted to **1** *via* **3**[1][2].



1



2 R = OH
4 R = H



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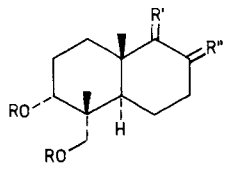
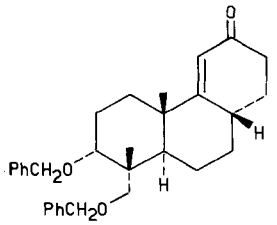
[1] For another synthesis of **1**, see [6].
[2] For synthetic approaches to **1**, see [7].

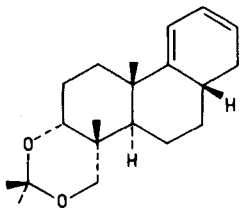
We have already described the preparation of 17-noraphidicolan-16-one (**4**) [8], a model for compound **2**, by solvolytic rearrangement of a suitable bicyclo[2.2.2]-oct-5-en-2-yl methanesulfonate [9], applying a strategy first used by *Wiesner et al.* for the synthesis of the diterpene alkaloid napelline [10][3]). We wish now to implement our model work with a stereospecific total synthesis of (±)-**2**, confirming that the simplicity and efficiency of a synthetic route depends, to a great extent, on the stereochemical strategy chosen.



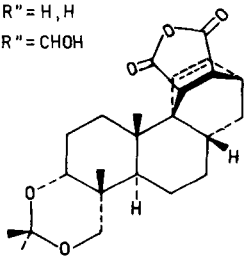
5 R = H, R' = OCH_2CH_2O R" = H,H
6 R = CH_2Ph, R' = O, R" = H,H
7 R = CH_2Ph, R' = O, R" = CHOH



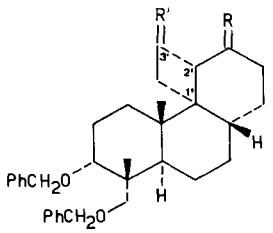
8a



8b



9b



9a R = O, R' = CH_2
10 R = OCH_2CH_2O, R' = CH_2
11 R = OCH_2CH_2O, R' = OH,H

Our starting material was the known diol **5** [2] [3] which was dibenzylated by standard procedure; acidic workup gave the ketone **6**[4]). The latter was then converted *via* the hydroxymethylidene derivative **7** into the enone **8a**[5]) by *Robinson* annellation with 3-buten-2-one.

The α,β-unsaturated carbonyl function present in **8a** was the necessary 'handle' for the preparation, by the *Wiesner* photochemical method [13], of the alcohol **15**, needed for the rearrangement to the aphidicolin system. This sequence appeared, in fact, more favorable to this purpose than a *Diels-Alder* approach, used by another group, without comparable efficiency, for the above mentioned synthesis of **3** [4][6]).

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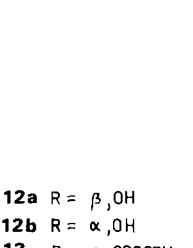
[3]) The same basic strategy has been adopted for the synthesis reported in [4].

[4]) Considering that the present work parallels in part our recent synthesis of the diterpenoid maritimol [11], the discussion is extended only to the new aspects.

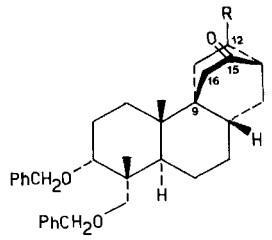
[5]) For a discussion on the configuration at C(8) see [12]; for examples see [8] [11].

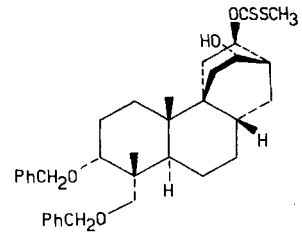
[6]) Some interesting considerations may be done observing the opposite stereochemical outcome of the allene *cis*-photoaddition to **8a** and of the *Diels-Alder* addition of maleic anhydride to **8b** [4] to give the adducts **9a** and **9b**, respectively. Since from a steric point of view the C-ring moieties of **8a** and **8b** are comparable, the opposite outcome of the two reactions further proofs that the *cis*-photoaddition of olefins to α,β-unsaturated carbonyl compounds is governed by other principles than steric hindrance (see also [13b]), to which, on the contrary, the *Diels-Alder* addition is well-known to be very sensitive.

Thus, photoaddition of allene to **8a** at $-78°$ gave regio- and stereospecifically the adduct **9a** which was converted *via* the acetal **10** and the cyclobutanol **11** into the aldol **12a** [14][7])[8]). The next operations were the protection of HO–C(12), the reduction of the C(15) ketone to the corresponding 15α-alcohol, and then the introduction of the double bond at C(11) in order to make quantitative the key rearrangement itself. Therefore, compound **12a** was transformed into the dithio-



12a R = β,OH
12b R = α,OH
13 R = β,OCSSCH$_3$





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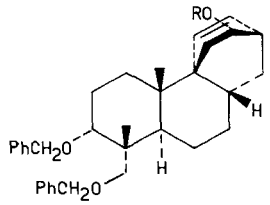
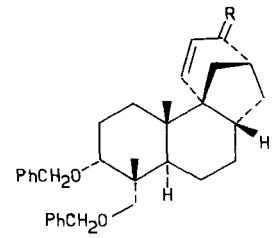


15 R = H
16 R = Ms



17 R = OH,H
18 R = O

carbonate **13** which, upon $NaBH_4$ reduction in Et_2O/MeOH at $-20°$, gave stereospecifically the secondary alcohol **14**. The latter, at reflux in *o*-xylene, underwent a *Chugaev* reaction giving the unsaturated alcohol **15**. The corresponding methanesulfonate **16** was then rearranged at 70° in acetone/water 2:1 affording, stereospecifically and quantitatively, the allylic alcohol **17**[9]).

Oxidation of **17** with pyridinium dichromate in CH_2Cl_2 yielded the α,β-unsaturated ketone **18** proving, beyond any doubt, that the rearrangement had proceeded successfully. Li/NH_3 reduction of **18** gave, finally, (±)-**2**, identical by TLC, IR, ^{1}H-NMR and MS with a sample obtained from natural **1**[10]) [1]. Since **1** has already been obtained from **2** [1] [5], the total synthesis of aphidicolin (**1**) is formally complete.

We wish to thank *Simonetta Antonaroli, Patrizia Gioia* and *Claudio Pastori* for carrying out some of the experiments described above. We wish to thank also *Anna Brugnoli, Romano Amore* and *Adalberto Santi* for technical assistance. High resolution MS is due to the courtesy of Prof. *Pierluigi*

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[7]) The minor epimer **12b** (7%), also formed in the reaction, can be reequilibrated in dilute NaOH to give additional **12a**.

[8]) For examples of the configuration at C(12) of **12a** see [8] [11] [15].

[9]) For the configuration at C(16) of **17** see footnote 6 in [11].

[10]) For another synthesis of (±)-**2** see [5].

Giacomello (Istituto di Chimica Farmaceutica, Facoltà di Farmacia, Università degli Studi «La Sapienza», Roma). We are finally indebted to Dr. *Barrie Hesp* (*Stuart Pharmaceuticals*, Wilmington, DE, USA) and to Dr. *Alexander H. Todd* (*ICI, PLC*, Macclesfield, Chesire, England) for kindly providing us with a sample of **1**.

Experimental Part

General Remarks. S. [11]. Differing of that: Mass spectra: *AEI MS 12* spectrometer (70 eV), electron impact. High-resolution MS: *VG-Micromass ZAB-2f* double focussing MS. R.P. > 10.000, $T = 220°$, E.E. = 70 eV.

6α-Benzyloxy-5α-benzyloxymethyl-5β, 8aβ-dimethyl-trans-*3, 4, 4a, 5, 6, 7, 8, 8a-octahydronaphthalen-1(2H)-one* (**6**). To a stirred solution of **5** (1.1 g, 4.1 mmol) in anh. THF (15 ml), NaH (60% in white oil, 0.9 g, 22.5 mmol) was added portionwise under N_2. After refluxing for 1 h, benzyl bromide (1.1 ml, 9.3 mmol) was added and boiling at reflux continued for 3 h. The mixture was then cooled with an ice bath, excess NaH quenched with MeOH (5 ml), and HCl (6N, 2 ml) added. The mixture was refluxed for 30 min, cooled to r.t. and thoroughly extracted with Et_2O. The combined extracts were then washed with $NaHCO_3$, H_2O and brine and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was chromatographed on a SiO_2 column (petroleum ether (40–70°)/Et_2O 7:3) yielding **6** (1.5 g, 90%). Crystallization (hexane) afforded an anal. sample, m.p. 86–87°. IR (CCl_4): 1709. ^{1}H-NMR ($CDCl_3$): 1.08, 1.16 (2 *s*, 3 H each, 2 CH_3); 3.34 (*AB*, $J_{AB} = 8$, 2 H, CH_2–C(5)); 4.33 (*s*, 2 H, $C_6H_5CH_2$); 4.37 (*AB*, $J_{AB} = 12$, 2 H, $C_6H_5CH_2$); 7.10 (*s*, 10 H, 2 C_6H_5). MS: 395 (10, $M^+ - 91$), 300 (10), 182 (32), 91 (100).

$C_{27}H_{34}O_3$ (406.25) Calc. C 79.75 H 8.43% Found C 79.69 H 8.48%

3α, 18-Bis(benzyloxy)-9(11)-podocarpen-12-one (**8a**). Anh. HCO_2Et (8.0 ml, 99.1 mmol) was added to a stirred suspension of MeONa (3.0 g, 55.5 mmol) in anh. C_6H_6 (30 ml). After 30 min, the mixture was cooled with an ice bath, and a solution of **6** (2.6 g, 6.4 mmol) in anh. C_6H_6 (30 ml) was added dropwise under N_2 while stirring. The mixture was allowed to warm up to r.t. overnight, diluted with Et_2O, and acidified with 2N H_2SO_4. The org. layer was separated, washed with H_2O and brine, and dried (Na_2SO_4). Evaporation of the solvent gave **7** which was pure enough to be used in the next reaction without purification. To an ice-bath cooled mixture of **7** and 3-buten-2-one (1.9 ml, 23.1 mmol), Et_3N (1.6 ml, 11.5 mmol) was added under N_2 while stirring. After 2 h, the ice bath was removed and stirring continued at r.t. overnight. The solution was then diluted with Et_2O, repeatedly washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was taken up with MeOH (90 ml) and cooled in an ice bath. MeONa (2.0 g, 37.0 mmol) was subsequently added while stirring under N_2, and the mixture was allowed to warm up to r.t. overnight. The solution was then refluxed for 3 h, cooled to r.t., diluted with H_2O, neutralized with 5% HCl, and concentrated. The residue was thoroughly extracted with $CHCl_3$, and the combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (petroleum ether (40–70°)/Et_2O 6:4) to afford **8a** (2.2 g, 75%). Crystallization (Et_2O/hexane) gave an anal. sample, m.p. 95.5–96.5°. UV (EtOH): 238 (14827). IR (CCl_4): 1675. ^{1}H-NMR ($CDCl_3$): 1.03, 1.10 (2 *s*, 3 H each, 2 CH_3); 3.33 (*AB*, $J_{AB} = 8$, 2 H, 2 H–C(18)); 4.34 (*s*, 2 H, $C_6H_5CH_2$); 4.36 (*AB*, $J_{AB} = 12$, 2 H, $C_6H_5CH_2$); 5.76 (*d*, 1 H, H–C(11)); 7.10 (*s*, 10 H, 2 C_6H_5). MS: 367 (9, $M^+ - 91$), 352 (6), 244 (10), 91 (100).

$C_{31}H_{38}O_3$ (458.28) Calc. C 81.17 H 8.36% Found C 81.13 H 8.44%

3α, 18-Bis(benzyloxy)-3′-methylidene-9, 11β, 3′, 4′-tetrahydrocyclobuta[1′, 2′: 9a, 11]podocarpan-12-one (**9a**). The enone **8a** (1.7 g, 3.7 mmol) was dissolved in freshly distilled THF (30 ml) and poured into a gas-washing bottle *(Pyrex)*. After cooling to −78°, allene was added in excess (about 40-fold). Then, the stirred mixture was irradiated at −78° under N_2 by an *Italquartz UV 13F W* lamp, until TLC monitoring indicated the end of the reaction (about 8 h). The cooling bath was removed and the excess allene allowed to evolve at r.t. overnight. Then, the solution was evaporated and the residue purified by CC (petroleum ether (40–70°)/Et_2O 8:2) affording **9a** (1.6 g, 86%). Crystallization (Et_2O/hexane) gave an anal. sample, m.p. 118–119°. IR (CCl_4): 1685. ^{1}H-NMR ($CDCl_3$): 0.87, 0.96 (2 *s*, 3 H each, 2 CH_3); 4.33 (*s*, 2 H, $C_6H_5CH_2$); 4.40 (*AB*, $J_{AB} = 12$, 2 H, $C_6H_5CH_2$); 4.79 (*m*, 2 H, CH_2=C(3′)); 7.10, 7.13 (2 *s*, 5 H each, 2 C_6H_5). MS: 498 (0.6, M^+), 407 (7), 284 (25), 91 (100).

$C_{34}H_{42}O_3$ (498.31) Calc. C 81.87 H 8.49% Found C 81.76 H 8.41%

3α,18-Bis(benzyloxy)-3'-methylidene-9,11β,3',4'-tetrahydrocyclobuta[1',2':9α,11]podocarpan-12-one Ethylene Acetal (**10**). To **9a** (1.5 g, 3.0 mmol) dissolved in anh. C_6H_6 (25 ml) ethylene glycol (1.0 ml, 17.9 mmol) and *p*-TsOH (40 mg, 0.21 mmol) were added. The mixture was refluxed under N_2 for 3 h with a *Dean-Stark* apparatus. After cooling to r.t., the mixture was diluted with Et_2O, washed with $NaHCO_3$, H_2O, and brine, and dried (Na_2SO_4). Evaporation gave a residue which was purified by CC (petroleum ether (40–70°)/Et_2O 9:1) affording **10** (1.3 g, 80%). Crystallization (pentane) gave an anal. sample, m.p. 98.5–99.5°. IR ($CHCl_3$): 1452. ^{1}H-NMR (CCl_4): 0.97 (*s*, 6 H, 2 CH_3); 3.83 (*s*, 4 H, OCH_2CH_2O); 4.34 (*s*, 2 H, $C_6H_5CH_2$); 4.40 (*AB*, J_{AB} = 12, 2 H, $C_6H_5CH_2$); 4.82 (*m*, 2 H, CH_2=C(3')); 7.18, 7.21 (2 *s*, 5 H each, 2 C_6H_5). MS: 542 (24, M^+), 451 (3), 330 (6), 99 (58), 91 (100).

$C_{36}H_{46}O_4$ (542.34) Calc. C 79.65 H 8.55% Found C 79.56 H 8.52%

3α,18-Bis(benzyloxy)-12β-hydroxy-9β,13β-ethano-9β-podocarpan-15-one (**12a**). Compound **10** (0.60 g, 1.11 mmol) was dissolved in abs. EtOH/CH_2Cl_2 1:1 (60 ml) and cooled to −78°; a stream of O_3 was then slowly passed through the stirred solution until a faint blue color persisted. $NaBH_4$ (0.60 g, 15.85 mmol) was then added portionwise and the mixture stirred for additional 4 h at −78°. After evaporation of the solvent, the residue was taken up with H_2O, neutralized with 5% HCl, and thoroughly extracted with CH_2Cl_2. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. To the residue in THF (15 ml), 1N HCl (6 ml) was added and the solution stirred under N_2 at r.t. overnight. Then, 1N NaOH (12 ml) was added dropwise, followed by MeOH (12 ml) and THF (12 ml); stirring at r.t. under N_2 was continued for 24 h. After neutralization with 5% HCl and evaporation of the org. solvents, the residue was diluted with H_2O and thoroughly extracted with CH_2Cl_2. The combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by SiO_2 CC (petroleum ether (40–70°)/Et_2O 8:2) affording first **12b** (40 mg, 7%) and then its epimer **12a** (425 mg, 76%). The latter was crystallized (Et_2O/CH_2Cl_2) to give an anal. sample, m.p. 165–166.5°. IR ($CHCl_3$): 3590, 3390, 1705. ^{1}H-NMR ($CDCl_3$): 1.03 (*s*, 6 H, 2 CH_3); 4.43 (*s*, 2 H, $C_6H_5CH_2$); 4.45 (*AB*, J_{AB} = 12, 2 H, $C_6H_5CH_2$); 7.30, 7.32 (2 *s*, 5 H each, 2 C_6H_5). MS: 411 (15, $M^+ - 91$), 289 (43), 247 (30), 229 (23), 91 (100).

$C_{33}H_{42}O_4$ (502.31) Calc. C 78.84 H 8.43% Found C 78.94 H 8.55%

O-[3α,18-Bis(benzyloxy)-15-oxo-9β,13β-ethano-9β-podocarpan-12-yl] S-Methyl Dithiocarbonate (**13**). To a solution of **12a** (0.60 g, 1.19 mmol) in anh. THF (24 ml), NaH (80% in white oil, 90 mg, 3.00 mmol) was added while stirring under N_2. After refluxing for 1 h, CS_2 (3.0 ml, 49.64 mmol) was added to the cooled mixture, and boiling continued for additional 2.5 h. The mixture was then cooled to r.t. and CH_3I (0.6 ml, 9.64 mmol) added. After refluxing for 1.5 h and cooling to r.t., excess NaH was quenched with MeOH (1 ml) and the org. solvent evaporated; after addition of H_2O, the mixture was thoroughly extracted with CH_2Cl_2. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 CC (petroleum ether (40–70°)/Et_2O 8:2) afforded **13** (0.51 g, 72%). Crystallization (MeOH) gave an anal. sample, m.p. 56.5–58°. IR ($CHCl_3$): 1720, 1185. ^{1}H-NMR (CCl_4): 1.00, 1.03 (2 *s*, 3 H each, 2 CH_3); 2.46 (*s*, 3 H, SCH_3); 4.33 (*s*, 2 H, $C_6H_5CH_2$); 4.40 (*AB*, J_{AB} = 12, 2 H, $C_6H_5CH_2$); 7.16, 7.19 (2 *s*, 5 H each, 2 C_6H_5). MS: 501 (0.2, $M^+ - 91$), 486 (0.2), 395 (7), 229 (40), 91 (100).

$C_{35}H_{44}O_4S_2$ (591.94) Calc. C 70.95 H 7.49 S 10.75% Found C 70.86 H 7.45 S 10.82%

O-[3α,18-Bis(benzyloxy)-15α-hydroxy-9β,13β-ethano-9β-podocarpan-12-yl] S-Methyl Dithiocarbonate (**14**). To a cooled (−20°) solution of **13** (0.40 g, 0.68 mmol) in Et_2O/MeOH 1:1 (80 ml), $NaBH_4$ (0.40 g, 10.57 mmol) was added portionwise while stirring. After 30 min, the mixture was concentrated, taken up with a NH_4Cl solution, and thoroughly extracted with $CHCl_3$. The combined extracts were washed with H_2O and brine, dried (Na_2SO_4) and evaporated. Purification of the residue by SiO_2 CC (petroleum ether (40–70°)/Et_2O 6:4) afforded **14** (0.37 g, 91%) as an oil homogeneous in TLC. IR ($CHCl_3$): 3600, 3450, 1195. ^{1}H-NMR (CCl_4): 1.00 (*s*, 6 H, 2 CH_3); 2.56 (*s*, 3 H, SCH_3); 4.34 (*s*, 2 H, $C_6H_5CH_2$); 4.43 (*AB*, J_{AB} = 12, 2 H, $C_6H_5CH_2$); 7.20, 7.23 (2 *s*, 5 H each, 2 C_6H_5). MS (HR): 442.29559 (1.62, $C_{31}H_{38}O_2$, $M^+ - 108 - 42 - 2$; calc. 442.28698), 395.26398 (1.56, $C_{26}H_{35}O_3$, $M^+ - 108 - 91$; calc. 395.25843), 319.20645 (1.53), 228.18664 (21.54), 186.14213 (10.00), 105.07622 (11.72), 91.05733 (100.00).

3a,18-Bis(benzyloxy)-9a,13a-vinylene-9β-podocarpan-15-ol (**15**). A solution of **14** (385 mg, 0.65 mmol) in *o*-xylene (6 ml) was heated at reflux under N_2 for 2.5 h. After evaporation of the solvent, the residue was chromatographed on a SiO_2 column (petroleum ether (40–70°)/Et_2O 6:4) yielding **15** (285 mg, 90%). Crystallization (pentane) gave an anal. sample, m.p. 121–122.5°. IR ($CHCl_3$): 3570, 3430. ^{1}H-NMR (CCl_4): 1.03 (*s*, 6 H, 2 CH_3); 4.36 (*s*, 2 H, $C_6H_5CH_2$); 4.43 (*AB*, J_{AB} = 12, 2 H, $C_6H_5CH_2$); 6.03, 6.40 (*B* and *A* of *ABX*, J_{AB} = 9, J_{BX} = 6, 1 H each, H–C(11), H–C(12)); 7.20, 7.23 (2 *s*, 5 H each, 2 C_6H_5). MS: 395 (0.04, $M^+ - 91$), 272 (21), 230 (11), 91 (100).

$C_{33}H_{42}O_3$ (486.31) Calc. C 81.43 H 8.70% Found C 81.39 H 8.75%

3a,18-Bis(benzyloxy)-17-nor-14-aphidicolen-16-ol (**17**). A stirred solution of **15** (285 mg, 0.59 mmol) and Et_3N (0.6 ml, 4.31 mmol) in anh. CH_2Cl_2 (7 ml) was cooled to 0° and treated with MsCl (0.3 ml, 3.86 mmol). After 30 min, the solution was diluted with CH_2Cl_2, washed with 3% H_2SO_4, H_2O until neutrality, and brine, dried (Na_2SO_4), and evaporated. The residue (**16**) was dissolved in acetone/H_2O 2:1 (30 ml) and stirred at 70° for 5 h under N_2. After evaporation of the acetone, the aq. layer was thoroughly extracted with $CHCl_3$. The combined org. extracts were washed with $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by SiO_2 CC (petroleum ether (40–70°)/Et_2O 1:1) affording **17** (280 mg, 97%). Crystallization (benzene/hexane) gave an anal. sample, m.p. 123–124.5°. IR ($CHCl_3$): 3595, 3430. ^{1}H-NMR (CCl_4): 1.01 (*s*, 6 H, 2 CH_3); 4.36 (*s*, 2 H, $C_6H_5CH_2$); 4.43 (*AB*, J_{AB} = 12, 2 H, $C_6H_5CH_2$); 5.53 (*B* of *ABX*, J_{AB} = 9, 1 H, H–C(14)); 6.13 (*A* of *ABX*, J_{AB} = 9, 1 H, H–C(15)); 7.20, 7.23 (2 *s*, 5 H each, 2 C_6H_5). MS: 486 (0.08, M^+), 442 (0.20), 395 (0.19), 228 (32), 91 (100).

$C_{33}H_{42}O_3$ (486.31) Calc. C 81.43 H 8.70% Found C 81.32 H 8.75%

3a,18-Bis(benzyloxy)-17-nor-14-aphidicolen-16-one (**18**). To a stirred solution of **17** (310 mg, 0.64 mmol) in anh. CH_2Cl_2 (10 ml), pyridinium dichromate (300 mg, 0.80 mmol) was added portionwise during 30 min. After 6 h, the mixture was diluted with Et_2O and filtered through a *Celite* pad; the resulting solution was evaporated and the residue chromatographed on a SiO_2 column (petroleum ether (40–70°)/Et_2O 7:3) affording **18** (250 mg, 81%). Crystallization (hexane) gave an anal. sample, m.p. 120.5–121.5°. UV (EtOH): 235 (10000). IR ($CHCl_3$); 1675. ^{1}H-NMR (CCl_4): 1.03 (*s*, 6 H, 2 CH_3); 4.40 (*s*, 2 H, $C_6H_5CH_2$); 4.43 (*AB*, 2 H, $C_6H_5CH_2$); 5.82 (*dd*, *J* = 12, 2, 1 H, H–C(15)); 7.15 (*d*, *J* = 12, 1 H, H–C(14)); 7.23 (*s*, 10 H, 2 C_6H_5). MS: 484 (0.08, M^+), 393 (29), 270 (58), 228 (44), 91 (100).

$C_{33}H_{40}O_3$ (484.30) Calc. C 81.77 H 8.32% Found C 81.71 H 8.35%

(±)-3a,18-Dihydroxy-17-noraphidicolan-16-one (**2**). A solution of **18** (25 mg, 0.052 mmol) and *t*-BuOH (3.3 mg, 0.045 mmol) in anh. THF (1 ml) was added to a stirred solution of Li (30 mg, 4.32 mmol) in liq. NH_3 (30 ml), at –78°. After stirring for 30 min at –78°, isoprene was added dropwise until the blue color fainted, and the solution was left at r.t. to allow NH_3 to evaporate. Et_2O was then added followed by little H_2O, the org. layer separated, and the aq. one thoroughly extracted with Et_2O. The combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated; the residue was purified by SiO_2 CC (Et_2O/petroleum ether (40–70°) 8:2) affording **2** (11 mg, 69%) which was crystallized (EtOAc/hexane), m.p. 144.5–145.5°.

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