98. A Total Synthesis of (±)-Aphidicolin: Regio- and Stereoselective Conversion of 3α,18-Di-*O*-benzyl-17-nor-14-aphidicolen-16-one into (±)-Aphidicolin[1])

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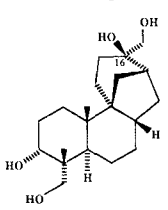
A regio- and stereoselective conversion of the totally synthetic 3α,18-di-*O*-benzyl-17-nor-14-aphidicolen-16-one (**5**), into (±)-aphidicolin **1**, by hydroxylation of the 2-methylidenebicyclo[3.2.1]oct-3-ene derivative **6** is described. Compound **5** was a key intermediate in our previously described total synthesis of **2**, which represented a formal synthesis of **1**.

Introduction. – Although the diterpenic tetraol aphidicolin (**1**)[2]) [1] attracted the attention of many synthetic chemists, only one stereoselective total synthesis of this interesting, biologically active [2] compound has been reported so far [3].

Since 17-noraphidicolan-16-one (**2**), a degradation product of **1**, has been reconverted *via* the acetonide **3** into the natural product, albeit with poor stereoselectivity [1b], **2** [4b] or protected derivatives thereof, **3** [5–7] and **4** [8] [9], have been the targets of most synthetic plans. While such achievements constitute formal total syntheses of **1**, they do not address the problem of introducing the chiral centre at C(16), a hurdle by no means trivial [3] [6b] [8].

Other ingenious approaches to **1** [10] also do not avoid this difficulty. When the conversion of **2**, **3**, or **4** into **1** was accomplished, the lack of stereochemical control, necessitated a difficult separation of **1** from its C(16)-epimer [1b] [6b] [8].



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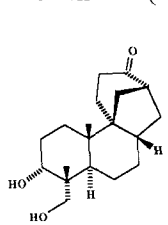
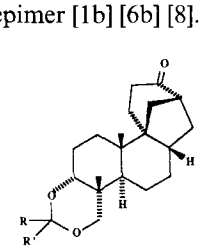


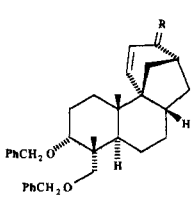
2



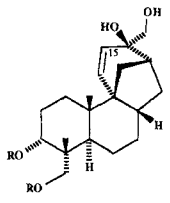
3 R = CH_2, R' = CH_3
4 R = H, R' = *t*-Bu

[1]) This work was presented at the IASOC II Meeting, Ischia, May 1986.

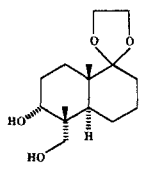
[2]) Systematic name: *tetradecahydro-3,9-dihydroxy-4,11b-dimethyl-8,11a-methano-11a*H*-cyclohepta[a]naphthalene-4,9-dimethanol*.



5 R = O
6 R = CH_2



7 R = CH_2Ph
8 R = H



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The absence of stereoselectivity may be attributed in large part to the conformational mobility of the bicyclo[3.2.1]octan-2-one[3]) system, which constitutes the C/D ring moiety of these intermediates.

During the total synthesis of **2**, which we described some years ago [4b], we observed that the C/D ring system of the diene **6**, readily prepared from the enone **5**, has a rigid norcamphor-like conformation which, restricting the approach of reagents from the *exo*-side, should allow its stereoselective conversion to **1**.

The documented *exo*-reactivity of geometrically related systems [14] supported this hypothesis. In this paper, we report the successful implementation of this strategy in the conversion of intermediate **5** to (±)-aphidicolin[2]).

Results and Discussion. – Compound **5** was converted quantitatively into the diene **6**, by reaction with MeLi in THF at 0°, followed by dehydration with TsOH in refluxing benzene. Compound **6** was then hydroxylated with OsO_4 and the osmate cleaved *in situ* with $NaHSO_3$ to give, as the only detectable reaction product, regio- and stereoselectively the diol **7**[4]).

The configuration at C(16) of **7**, predictable on the basis of the precedents mentioned above [14], followed from its conversion into (±)-**1**. Compound **7** was then debenzylated by catalytic hydrogenation in the presence of 10% Pd(C) yielding quantitatively the unsaturated tetraol **8**.

The C(14)=C(15) double bond, which also previously played a key role in our synthesis by steering the rearrangement [4b], was finally reduced under pressure in the presence of 5% Rh/Al_2O_3 [16] to give (±)-aphidicolin indistinguishable from an authentic sample on the basis of chromatographic as well as spectroscopic comparisons. The described reaction sequence from **5** to **1** can be carried out without any chromatographic separation.

Conclusions. – The synthesis of **5** reported previously [4b], in connection with the work described herein, constitutes an efficient total synthesis of racemic (±)-**1** in which complete regio- and stereocontrol are maintained throughout.

The availability of the known precursor diol **9** [5] [6] in optically active form [17] makes this an attractive route for enantioselective synthesis of aphidicolin.

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[3]) Notwithstanding many attempts [6b] [8] [11] [12], the direct stereoselective nucleophilic addition to a bicyclo-[3.2.1]octan-2-one system has been accomplished, to our knowledge, only in the synthesis of cedrol, where one side of the CO group was hindered [13]. A related strategy, exploiting steric encumbrance, was used to prepare (±)-**1** stereoselectively from a 2-methylidenebicyclo[3.2.1]octane [3].

[4]) An analogous reaction was performed in the course of the total synthesis of maritimol [15].

Experimental Part

General. See [2] [3]. UV: *Varian 634.* ^{1}H-NMR: *Varian XL-300* spectrometer. HR-MS: *Kratos MS 80* RF. R.P. > 7500, T = 190°, E.E. 70 eV. ψ = pseudo.

3α,18-Di-O-benzyl-16-methylidene-14-aphidicolene (**6**). To a stirred soln. of the enone **5** (25 mg, 0.05 mmol) in anh. Et_2O (5 ml), cooled in an ice-bath, was added dropwise a 1.6M soln. (0.1 ml, 3 times excess) of CH_3Li in Et_2O under N_2. When TLC monitoring (Et_2O/petroleum ether (40–70°) 1:1; R_f (product) < R_f (**5**)) indicated completion of the reaction, H_2O (1 ml) was added dropwise and the whole thoroughly extracted with Et_2O. Combined org. extracts were then washed with H_2O until neutral, with brine, dried (Na_2SO_4), and evaporated. The residue, dissolved in dry benzene (15 ml), was then refluxed for 1 h in the presence of a catalytic amount of TsOH. When TLC monitoring indicated the disappearance of the starting material, the mixture was cooled to r.t., diluted with Et_2O, poured into a separatory funnel, and washed with an aq. $NaHCO_3$ soln., H_2O, brine, dried (Na_2SO_4), and evaporated affording, in an overall yield of 95% from **3**, the diene **6** (TLC: Et_2O/petroleum ether (40–70°) 5:95, R_f (**6**) > R_f (start. mat.)). Compound **6** was sufficiently pure to be used in the next reaction without purification. For anal. purposes, a sample was crystallized from Et_2O/CH_3OH. M.p. 89–90°. UV (EtOH): 237 (1.76×10^4). IR (CCl_4): 2930, 2860, 1635, 1452, 1095. ^{1}H-NMR ($CDCl_3$): 1.03 (*s*, 3H); 1.05 (*s*, 3H); 2.75 (ψt, 1H); 3.28 (*d*, *J* = 7.9, 1H); 3.55 (ψt, 1H); 3.56 (*d*, *J* = 7.8, 1H); 4.38 (*B* of *AB*, J_{AB} = 11.7, 1H); 4.44 (*B* of *AB*, J_{AB} = 12.3, 1H); 4.45 (*d*, *J* = 1.90, 1H); 4.47 (*A* of *AB*, J_{AB} = 12.2, 1H); 4.58 (*d*, *J* = 1.8, 1H); 4.60 (*A* of *AB*, J_{AB} = 11.9, 1H); 5.99 (*dd*, *J* = 9.9, 1.5, 1H); 6.20 (*d*, *J* = 9.9, 1H); 7.20–7.50 (*m*, 10H). MS: 91 (100), 188 (7), 226 (8), 268 (26), 390 (4), 482 (0.15). MS (HR): 482.3193 ($C_{34}H_{42}O_2$, $M^{+\cdot}$; calc. 482.3184).

3α,18-Di-O-benzyl-14-aphidicolene (**7**). To a soln. (1.5 ml) of **6** (14 mg, 0.03 mmol) in pyridine/Et_2O (1.5 ml/50 ml) cooled to −20°, was added a soln. (1.6 ml) of OsO_4 in Et_2O (100 mg/20 ml) precooled to the same temp. The whole was kept at −20° in the dark (freezer) and stirred from time to time for 2 days, till TLC monitoring (petroleum ether (40–70°)/Et_2O 95:5) indicated the disappearance of the starting material. The org. solvent was then evaporated, the residue taken up with 95% EtOH (3 ml), and a 0.3M aq. soln. (2 ml) of $Na_2S_2O_5$ was added. The brown mixture was stirred at r.t. for 2 h. The whole was then thoroughly extracted with $CHCl_3$. Colorless combined org. extracts were then washed with H_2O, brine, dried (Na_2SO_4), and evaporated to give crude **7**. For anal. purposes, a sample was crystallized from Et_2O/hexane. M.p. 99–100°. The yield was 83%. IR (CCl_4): 3630, 3590, 3410, 2950, 2870, 1620, 1455, 1100. ^{1}H-NMR ($CDCl_3$): 1.04 (*s*, 3H); 1.05 (*s*, 3H); 3.26 (*d*, *J* = 7.8, 1H); 3.54 (*d*, *J* = 7.3, 1H); 3.56 (*B* of *AB*, J_{AB} = 11.0, 1H); 3.63 (*d*, *J* = 11.2, 1H); 4.38 (*d*, *J* = 11.5, 1H); 4.44 (*B* of *AB*, J_{AB} = 12.2, 1H); 4.47 (*A* of *AB*, J_{AB} = 12.2, 1H); 4.58 (*A* of *AB*, J_{AB} = 11.5, 1H); 5.50 (*dd*, *J* = 10.3, 1.5, 1H); 6.25 (*dd*, *J* = 8.8, 1.5, 1H); 7.1–7.5 (*m*, 10H). MS: 91 (100), 255 (9), 271 (4), 284 (5), 498 (1). HR-MS: 498.3127 ($C_{34}H_{42}O_3$, $M^{+\cdot}$ − 18; calc. 498.3127).

14-Aphidicolene (**8**). A soln. of **7** (5 mg, 0.015 mmol) in 95% EtOH (3 ml) was hydrogenated, at atmospheric pressure and r.t., in the presence of a catalytic amount of 10% Pd/C *(Fluka AG)*. When TLC monitoring (Et_2O/petroleum ether (40–70°)/CH_3OH 7.5:2:0.6) indicated the disappearance of the starting material, the catalyst was removed by filtration through a *Celite* pad, which was thoroughly washed with 95% EtOH. Evaporation of the solvent afforded quantitatively **8**, which was crystallized from $CHCl_3/Et_2O$. M.p. of 148–150°. IR ($CHCl_3$): 3420, 2940, 1605, 1090. ^{1}H-NMR ($CDCl_3$): 0.73 (*s*, 3H); 1.03 (*s*, 3H); 3.15 (ψs, 1H); 3.30–3.80 (*m*, 6H); 5.54 (*dd*, *J* = 10.0, 1, 1H); 6.31 (*dd*, *J* = 10.1, 1, 1H); MS: 79 (22), 91 (29), 105 (20), 107 (20), 145 (11), 147 (10), 187 (19), 305 (100), 318 (0.5). HR-MS: 305.2117 ($C_{19}H_{29}O_3$, $M^{+\cdot}$ − 31; calc. 305.2117).

(±)-*Aphidicolin* (**1**). A stirred soln. of **8** (5 mg, 0.014 mmol) in abs. EtOH (4 ml) was hydrogenated in the presence of a catalytic amount of 5% Rh/Al_2O_3 *(Engelhard Industries Inc.)* for 24 h at 1000 psi and at r.t. in a steel *Parr* apparatus. The catalyst was then removed by filtration through a *Celite* pad, which was thoroughly washed with 95% EtOH. Evaporation of the solvent and purification by SiO_2-CC afforded in 73% (±)-**1** which was indistinguishable from an authentic sample by TLC (Et_2O/petroleum ether (40–70°)/CH_3OH 8:2:0.6, 3 developments, R_f (**8**) > R_f (**1**) [6b][5]). ^{1}H-NMR ($CDCl_3$): 0.71 (*s*, 3H); 0.99 (*s*, 3H); 3.38 (*B* of *AB*, J_{AB} = 11.4, 2H); 3.47 (*A* of *AB*, J_{AB} = 11.2, 2H); 3.69 (ψs, 1H). MS: 180 (29), 181 (9), 217 (7), 231 (6), 259 (8), 271 (7), 275 (8), 289 (4), 290 (4), 307 (100), 308 (15), 320 (0.1). HR-MS: 307.2271 ($C_{19}H_{31}O_3$, $M^{+\cdot}$ − 31; calc. 307.2273).

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[5]) Under these chromatographic conditions, C(16)-epi-aphidicolin displays an R_f value < **1** [6b].

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