37. On the Construction of the C/D-Ring Systems of Aphidicolin and Stemodin: a Regio- and Stereospecific Synthesis of 17-Noraphidicolan-16-one and 17-Norstemodan-16-one

Preliminary Communication

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(29.X.81)

Summary

A very simple regio- and stereospecific synthesis of 17-noraphidicolan-16-one and 17-norstemodan-16-one by solvolytic rearrangement of suitable bicyclo[2.2.2]-octenyl methanesulfonate is described.

The biogenetically related systems of aphidicolin (**1**) [1], stemodin (**2a**) [2], its isomer maritimol (**2b**) [3], and stemarin (**3**) [4], have been recently the object of several synthetic studies.

Besides the stereoselective total synthesis of **1** by *Ireland et al.* [5] and other interesting approaches [6], syntheses of **1** have been announced by the groups of *Trost et al.* [7] and *McMurry et al.* [8]. Moreover *Corey et al.* [9] have synthesized **1**, *via* the ketone **4b**, and the structurally related tetracyclic diterpene stemodin (**2a**) – which differs from **1** mainly in the stereorelationship of the C/D-rings [10] – through the intermediate **5**.

Very recently *van Tamelen et al.* [11] published a synthesis of **2b** by skeletal rearrangement in base of a suitable bicyclooctane from [2.2.2]- to [3.2.1]-system, adopting the same strategy introduced by *Wiesner* [12] for the synthesis of some delphinine-type alkaloids and later applied by *Kelly et al.* [13] to a total synthesis of **3**.

Considering the simplicity of the functional groups present, the above mentioned syntheses of compounds **2**, **3**, and **4** are either unnecessarily complicated or suffering from some low-yield steps or not stereospecific.

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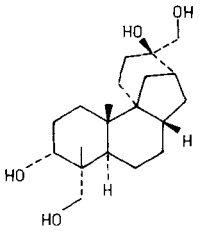

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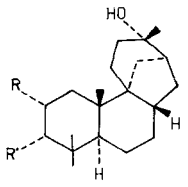
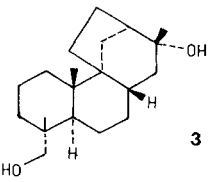


2a R = OH, R' = H
2b R = H, R' = OH



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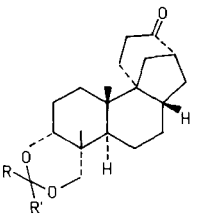
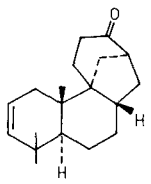


4a R = R' = CH_3
4b R = t-Bu, R' = H



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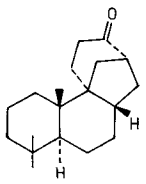
In the present communication we report the regio- and stereospecific synthesis of the ketones **6** [1] and **7**, model compounds for **4** and **5** respectively, demonstrating that the choice of the proper stereochemical strategy can enable a very efficient and simple synthesis.

We describe herein our approach to the construction of the bicyclo[3.2.1]octane parts of **1**, **2a**, **2b**, based on the solvolytic rearrangement of bicyclo[2.2.2]-5-octen-2-yl methanesulfonates represented in the present study respectively by the model compounds **8** and **9** which are simply and stereospecifically obtainable from the same intermediate **10**. A related rearrangement was first used as a key step in a stereospecific total synthesis of the diterpene alkaloid napelline by *Wiesner et al.* [14].

Our starting material was the easily available enone **11** [15]; photoaddition of allene to **11** in THF at $-78°$ gave a quantitative yield of the adduct **12**, m.p. 85–86°[2]) [IR. (CCl_4): 1680, 1710. – ^{1}H-NMR. (CCl_4/TMS): 0.80 (*s*, 3 H); 0.83 (*s*, 6 H); 4.80 (*m*, 2 H)]. The configuration of **12** was anticipated on the basis of the *Wiesner* rule [16] and confirmed by the configuration of the products in each synthetic sequence *(vide infra)*.

The acetal **13**, m.p. 103–104° [IR. (CCl_4): 1680. – ^{1}H-NMR. (CCl_4/TMS): 0.84 (*s*, 6 H); 0.93 (*s*, 3 H); 2.45 (p.*t*, 2 H); 2.69 (br. *s*, 1 H); 3.85 (*s*, 4 H); 4.75 (*m*c., 1 H); 4.97 (*m*c., 1 H)], obtained by standard procedures from **12**, was ozonized at $-78°$ in a (1:1)-mixture of EtOH/CH_2Cl_2 and the subsequent $NaBH_4$-reduction afforded the

[2]) The elemental compositions of all compounds described in this communication have been determined by high resolution mass spectrometry and/or elementary analysis. Melting points are uncorrected. – IR. values in cm^{-1}; ^{1}H-NMR. values in δ; br. = broad; p = pseudo; * with long-range coupling.



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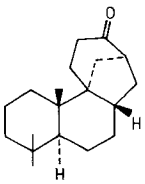

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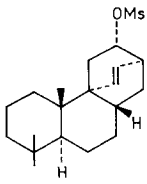

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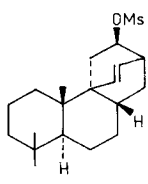

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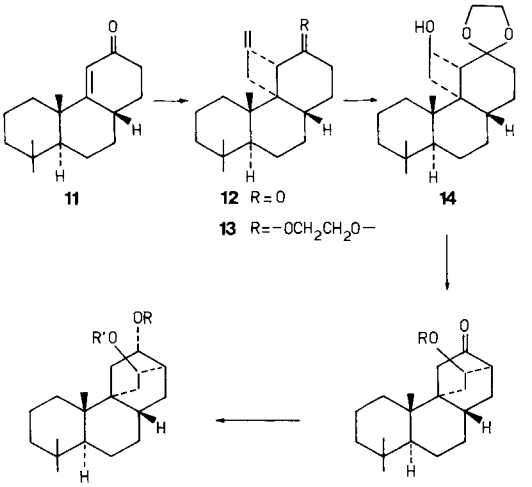
secondary alcohol **14**, used without purification in the next step. Treatment of **14** with 1 N HCl in THF removed the acetal group and effected opening of the cyclobutanol by a *retro*-aldol reaction; subsequent addition of MeOH and 1 N NaOH afforded the hydroxy-ketone **10**, m.p. 229–230° (70% overall yield from **13**)[3]) [IR. ($CHCl_3$): 1725, 3360, 3560; ^{1}H-NMR. ($CDCl_3$/TMS); 0.89 (*s*, 3 H); 0.90 (*s*, 3 H); 1.00 (*s*, 3 H); 2.15 (p.*s*, 2 H); 4.15 (br. *s*, 1 H)].

In accord with precedent results [12], the hydroxyl group of **10** was assigned the β-configuration which is stabilized by intramolecular H-bonding; this assignment was indicated by the successful rearrangement of **9** to the stemodin system **7**.

Compound **10**, the common synthon for ketones **6** and **7**, was treated successively in boiling THF with NaH, CS_2 and CH_3I, to give the dithiocarbonate **15**, m.p. 136–137° (80%) [IR. ($CHCl_3$): 1720. – ^{1}H-NMR. (CCl_4/TMS): 0.90 (*s*, 6 H); 1.00 (*s*, 3 H); 2.50 (*s*, 3 H); 5.72 (*m*c., 1 H)]. Subsequent reduction of the ketone with $NaBH_4$ in MeOH/Et_2O 1:1 at −10° could be achieved stereospecifically as a con-



11 **12** R = O

13 R = $-OCH_2CH_2O-$

14

16 R = H, R' = $CS-SCH_3$

19 R = Ms, R' = CH_2Ph

23 R = H, R' = THP

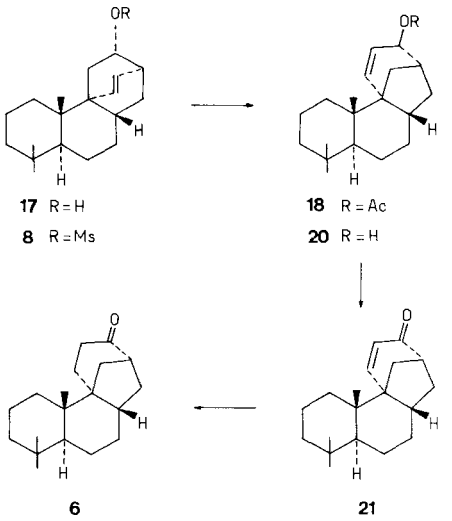
24 R = $CS-SCH_3$, R' = THP

10 R = H

15 R = $CS-SCH_3$

22 R = THP

[3]) The minor epimer at C(12), m.p. 198–199°, obtained from this reaction sequence in 14% yield can be reconverted to **10** by treatment with dil. NaOH-solution improving therefore the overall yield of the transformation of **13** to **10**.



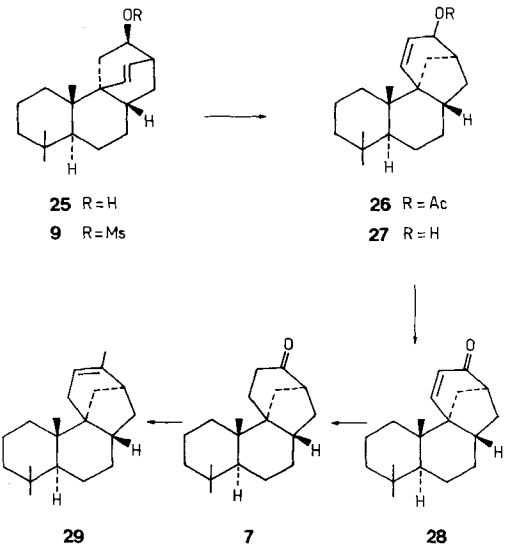
sequence of the bulky dithiocarbonate group, to give the alcohol **16**, m.p. 41–43° (95%) [IR. ($CHCl_3$): 3450, 3600. – ^{1}H-NMR. (CCl_4/TMS): 0.85 (*s*, 6 H); 0.94 (*s*, 3 H); 2.55 (*s*, 3 H); 3.78 (br. *s*, 1 H); 5.66 (br. *s*, 1 H)]. The configuration of the hydroxyl group of **16** is confirmed by the subsequent rearrangement of the methanesulfonate **8** to the aphidicolin system **6**.

Compound **16**, treated in *o*-xylene at 190° for 4 h, underwent *Chugaev* reaction to give the unsaturated alcohol **17**, m.p. 105–107° (90%) [IR. (CCl_4): 3590. – ^{1}H-NMR. (CCl_4/TMS): 0.87 (*s*, 6 H); 0.97 (*s*, 3 H); 2.47 (br. *s*, 1 H); 3.77 (p. *d*, 1 H); 5.95 and 6.33 (*AB* of *ABX*, $J_{AB}=9$, $J_{BX}=5$, 2 H)]. The latter, on treatment with mesyl chloride in pyridine at 0°, afforded the methanesulfonate **8**, m.p. 80–81° (dec.) (95%) [IR. (CCl_4): 1350. – ^{1}H-NMR. ($CDCl_3$/TMS): 0.90 (*s*, 6 H); 1.00 (*s*, 3 H); 2.80 (*s*, 3 H); 4.81 (br. *s*, 1 H); 6.05 and 6.36 (*AB* of *ABX*, $J_{AB}=9$, $J_{BX}=6$, 2 H)], which, in glacial acetic acid at 50° rearranged to the acetate **18**, m.p. 108–110° (95%), homogeneous on silica gel TLC. using several solvent systems [IR. (CCl_4): 1730. – ^{1}H-NMR. (CCl_4/TMS): 0.91 (*s*, 6 H); 1.10 (*s*, 3 H); 1.14 (*s*, 3 H); 4.66 (p. *t*, 1 H); 5.52* and 6.21 (*AB* of *ABX*, $J_{AB}=10$, $J_{BX}=4.5$, 2 H)][4]).

In our earlier attempted solvolysis of the methanesulfonate **19**, substitution predominated twofold over rearrangement in accord with the results of *Walborski et al.* [17]. This suggests that the stabilizing effect of the double bond on the developing positive charge at the (original) bridgehead C-atom is an important factor in the rearrangement.

Saponification of **18** with 5% methanolic KOH-solution [**20** (oil): IR. (CCl_4): 3450, 3560. – ^{1}H-NMR. (CCl_4/TMS): 0.88 (*s*, 3 H); 0.90 (*s*, 3 H); 1.00 (*s*, 3 H); 3.58 (*t*, 1 H); 5.56* and 6.08 (*AB* of *ABX*, $J_{AB}=10$, $J_{BX}=4.5$, 2 H)], followed by oxidation with PCC/Al_2O_3 [18] in CH_2Cl_2 afforded the enone **21**, m.p. 110–111° (80%) [IR. (CCl_4): 1685. – ^{1}H-NMR. (CCl_4/TMS): 0.91 (*s*, 3 H); 0.96 (*s*, 3 H); 1.04

[4]) We are investigating at present the stereochemistry of the nucleophilic attack which, occurring from the β-side, would allow a stereospecific synthesis of **2** and **4**.



25 R = H
9 R = Ms

26 R = Ac
27 R = H

29 **7** **28**

(*s*, 3 H); 5.77 and 7.12 (*AB*, J_{AB} = 12, 2 H)]; hydrogenation of the latter over 10% Pd (C) in dry dioxane yielded the target ketone **6** (95%), identical with an authentic sample (mixed m.p., TLC. in several solvent systems, IR., ^{1}H-NMR., MS.).

The versatility of this strategy was confirmed by the cognate conversion of the hydroxy-ketone **10** to the stemodin-type ketone **7**.

The tetrahydropyranyl derivative **22**, m.p. 130–131°, obtained (95%) [IR. ($CHCl_3$): 1715. – ^{1}H-NMR. (CCl_4/TMS): 0.87 (*s*, 6 H); 0.97 (*s*, 3 H)] from **10** by standard procedures, was reduced with $NaBH_4$ in a (1:1)-mixture of MeOH/Et_2O to give the oily alcohol **23** in quantitative yield [IR. ($CHCl_3$): 3505. – ^{1}H-NMR. (CCl_4/TMS): 0.70 (*s*, 6 H); 0.76 (*s*, 3 H)]: the latter in Et_2O was transformed to the dithiocarbonate **24**, m.p. 47–49° (80%) [^{1}H-NMR. (CCl_4/TMS): 0.83 (*s*, 6 H); 0.93 (*s*, 3 H); 2.50 (*s*, 3 H)] using the procedure described above.

Pyrolysis of **24** afforded the unsaturated alcohol **25** directly, m.p. 128–129° (85%) [IR. ($CHCl_3$): 3435, 3595. – ^{1}H-NMR. (CCl_4/TMS): 0.80 (*s*, 6 H); 0.97 (*s*, 3 H); 5.92 and 6.26 (*AB* of *ABX*, J_{AB} = 9, J_{BX} = 6, 2 H)].

Using a reaction sequence analogous to that for the transformation of **17** to **21**, the alcohol **25** was converted [the intermediate methanesulfonate **9** (oil): IR. (CCl_4): 1350. – ^{1}H-NMR. (CCl_4/TMS): 0.80 (*s*, 6 H); 0.93 (*s*, 3 H); 2.73 (*s*, 3 H); 4.47 (br. *s*, 1 H); 5.94 and 6.23 (*AB* of *ABX*, J_{AB} = 8, J_{BX} = 5.5, 2 H)] in 73% overall yield – *via* the acetate **26** (oil) [IR. ($CHCl_3$): 1725. – ^{1}H-NMR. (CCl_4/TMS): 0.74 (*s*, 6 H); 0.98 (*s*, 3 H); 1.83 (*s*, 3 H); 4.53 (p.*t*, 1 H); 5.33* and 6.06 (*AB* of *ABX*, J_{AB} = 10, J_{BX} = 4, 2 H] [12] and the saponification product **27**, m.p. 109–110° [IR. ($CHCl_3$): 3440, 3610. – ^{1}H-NMR. (CCl_4/TMS): 0.87 (*s*, 6 H); 1.10 (*s*, 3 H); 3.56 (p.*t*, 1 H); 5.47* and 6.03 (*AB* of *ABX*, J_{AB} = 10, J_{BX} = 4, 2 H)] – into the enone **28**, m.p. 75–76° [IR. ($CHCl_3$): 1675. – ^{1}H-NMR. (CCl_4/TMS): 0.90 (*s*, 6 H); 1.20 (*s*, 3 H); 5.66* and 7.10 (*AB*, J_{AB} = 10, 2 H)].

Finally, hydrogenation of **28** over 10% Pd (C) in dry dioxane gave the desired ketone **7**, m.p. 68–69° (95%) [IR. ($CHCl_3$): 1705. – ^{1}H-NMR. ($CHCl_3$/TMS): 0.90 (*s*, 6 H); 1.02 (*s*, 3 H)], confirmed as 17-norstemodan-16-one by its conversion, using CH_3MgI in Et_2O, followed by dehydration with $POCl_3$ in pyridine into the olefin **29** [2] which was identical with an authentic sample by the same criteria adopted for the ketone **6**.

In conclusion we believe to have shown that the choice of the proper stereochemical strategy leads to a highly efficient and stereospecific synthesis.

At present syntheses of aphidicolin, stemodin and maritimol are in progress in our laboratories along the above described simple lines.

We wish to thank *Anna Brugnoli, Romano Amore,* and *Francesco Piccioni* for technical assistance.

We are also indebted to Dr. *Barrie Hesp (ICI Americas Inc.)* and Dr. *A.H. Ratcliffe (ICI Ltd.)* for generously donating a sample of the ketone **6**, and to Dr. *Percy S. Manchand (Hoffmann-La Roche Inc.)* for kindly sending us a sample of **29**.

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