Tetrahedron Letters, Vol. 34, No. 7, pp. 1141-1144, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Diels-Alder Approaches to Pentacyclic Triterpenes of the Arborane and the Fernane Families

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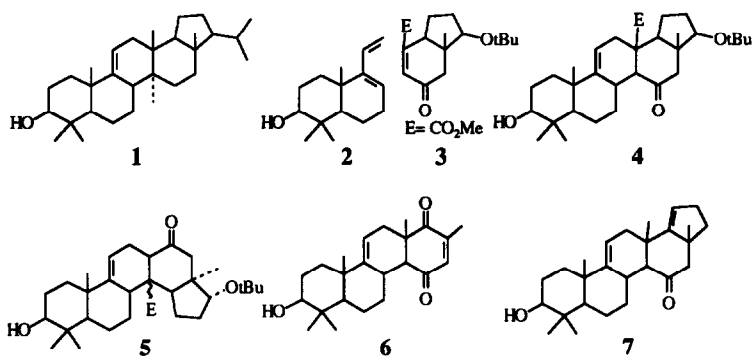
Abstract: *The high pressure Diels-Alder reaction of diene 2 and ene-dione 3 does not lead to the arborane skeleton but to angular isomers 5. The AB + D synthesis of tetracyclic ene-dione 6, followed by construction of the E-ring by a double alkylation, yields the isoarborinol precursor 7; the fernane series is similarly accessed.*

Isoarborinol **1**, a pentacyclic analogue of lanosterol found several times in sediments has been postulated to be a bacterial membrane constituent,[1] but does not display the expected reinforcing properties on model phospholipid membranes. Hence, our interest in developing syntheses for **1** making it possible to obtain also some of its analogues, in particular partially demethylated ones. We have previously paved the way for these syntheses by describing the synthesis of bicyclic precursors of rings A+B, **2** and of rings D+E[2], **3**.



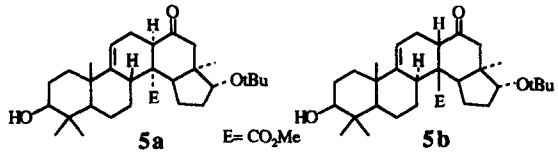
1 **2** **3** **4**

5 **6** **7**

We now show that the AB + DE route does not lead to the arborane arrangement of rings **4**, but to the isomeric system **5**; we show however that it is possible to use a double alkylation of the tetracyclic ene-dione **6** to obtain the desired arborane skeleton pruned of several appendices, like in **7**, in a form suitable for further elaboration.

The AB + DE route: All attempts to condense the intermediates **2** and **3** in a thermal or a Lewis acid-catalyzed Diels-Alder reaction have failed. However, when diene **2** (2 mmol) and dienophile **3** (2 mmol) were heated at 45°C under a pressure of 13 kbar in dry CH_2Cl_2 (2 ml) for 60 h, silica gel chromatography afforded 68% of a mixture of two products in a ratio of 1 (first eluted) to 1.2; structures **5a** (first eluted) and **5b** were assigned to these adducts on the basis of the NMR spectra of their corresponding 3β-acetate derivatives (**5a**, 3β-OAc: mp : 278°C, pentane, $[\alpha]_D$: -119, c=1.3; **5b**, 3β-OAc: mp :125-127°C, pentane; $[\alpha]_D$: -43, c=0.9).

These showed all the signals expected for the AB and DE moieties; however, a COSY ^1H-^1H showed conclusively that the vinylic portion at C-11 was the X part of an ABCX system, not the ABX system



5a **5b**

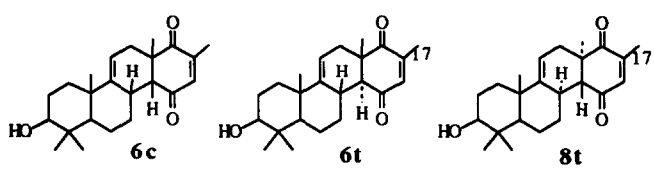
expected for **4**. Also 2D homo- and heteronuclear analyses established conclusively the presence of a spin system H-5, H-6, H-7, H-8, not extended to C-14 as would have been the case for **4**. A nuclear Overhauser effect between the signals of the angular methyl group at C-10 and of H-8 was observed for the isomer first eluted, in agreement with structure **5a** (10-Me and H-8 β-1,3 diaxial), but not for **5b**, which is compatible with the structure proposed. Fortunately, a crystal of the 3β-acetate of **5a** was found to be amenable to X-ray crystallographic structure determination, and this confirmed definitively the structure proposed.[3]

It is of interest that the keto group of the dienophile prefers the *exo* orientation, thus leading to the unwanted skeleton **5**. The formation of the two diastereomers **5a** and **5b** results from the top (β) and bottom (α) face attacks of the dienophile to the diene **2**; we had expected the α approach of the dienophile, *anti* to the β C-10 angular methyl group of the diene, to be much preferred, and therefore **5a** to be predominant. That the α and β approaches are essentially equivalent may be due to the high pressure conditions.

We have also attempted to condense diene **2** with the *cis* isomer of the bicyclic DE moiety; but no reaction occured, and the enone ester was recovered unchanged.

In short, this approach could not be used for our synthetic goal; its structural and stereochemical features can be explained by a more detailed analysis, which will be presented in the final paper.

The AB + D + E route: We had shown earlier[4] that the Lewis acid-catalyzed Diels-Alder addition of 2,6-dimethyl-benzoquinone to the diene **2** gave two tetracyclic ene-diones,in good yield and in proportions depending on the nature of the Lewis acid: the *cis* ene-dione **6c**, easily epimerizable into its *trans* isomer **6t**, and its isomer **8c**, itself epimerizable into the trans isomer **8t**.

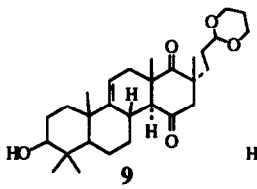


6c **6t** **8t**

These can be used to add 1,4 to C-17 a C_3-chain due to build ring E, with a Grignard reagent functionalized at the γ-position by a group able to react with the 17α carbonyl (steroid numbering). To succeed, the reaction used must be specific in many ways: 1,4 rather than 1,2, and at C-17, not C-16. We shall describe in the final paper the successful results obtained with the four starting materials **6c**, **6t**, **8c**, and **8t**, but restrict ourselves here to the trans substrates **6t** and **8t**, which give access to pentacyclic systems related to isoarborinol and to fernenol, an isomeric fern triterpene. In every case, all the structures described below have been fully established by extensive 1D and 2D NMR studies; the stereostructures have been unambiguously shown to correspond to the lowest energy conformations deduced by MM2 calculations. We have also shown that the regiospecificity observed is in agreement with MINDO/3 calculations. All the details will be given in the full paper.

In the 13β, 14α-series (**6t**), addition of the Grignard or the organolithium derivative of 2-(2-bromo-ethyl)-1,3-dioxane in THF at -78°C went 1,4. It proceeded exclusively from the less hindered α

side, to give dione **9** (mp : 158-160°C, ether-heptane, $[\alpha]_D$: 27, c=0.9). The addition of the CuBr-Me_2S complex led to lower yields, whereas the addition of Ce(III) chloride led to a dramatic acceleration: in 10 min at -78°C, the reaction was terminated, and gave an 85% yield of isolated product **9**; a trace of the product of 1,2-addition on the 18-carbonyl group was isolated. The synthesis was pursued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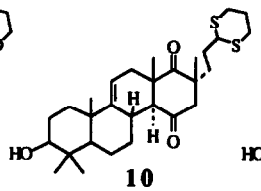
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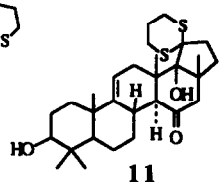
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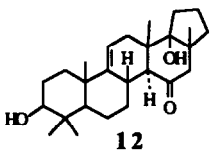
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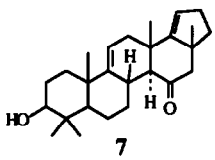
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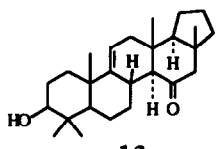
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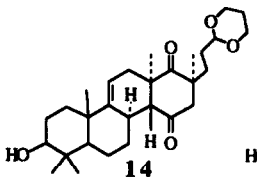
first by BF_3-catalyzed ketal exchange with 1,3-propanedithiol at room temperature, to obtain the dithioketal **10** (mp : 116-118°C, methanol, $[\alpha]_D$: 22, c=1.0), converted with t-BuLi in THF, with 10% HMPA at -78°C, into the first pentacyclic product, **11** (mp : 238-240°C, $[\alpha]_D$: -92, c=0.8,THF), obtained in 73% yield. Raney-nickel desulfurization of **11** proved troublesome, as it was initially accompanied by some hydrogenolysis of the tertiary alcohol **12**, a complication already reported sometimes.[5] Ultimately, an 85% yield of **12** (mp : 122-125°C, methanol, $[\alpha]_D$: -79, c=0.7, THF) was obtained under very mild conditions (10 min reflux in ethanol). This tertiary alcohol was easily dehydrated with p-toluenesulfonic acid in refluxing toluene to the diene **7** (mp : 205-207°C, heptane, $[\alpha]_D$: -63, c=1.1), the E-ring double bond of which could be remarkably selectively hydrogenated over Pd/C in acetic acid to give 9(11)-ene **13** (mp : 145-148°C, heptane-EtOAc, $[\alpha]_D$: -27, c=1.3, THF).
In the 13α, 14β-series, exactly the same series of reactions led from the enedione **8t** to the pentacyclic derivatives indicated.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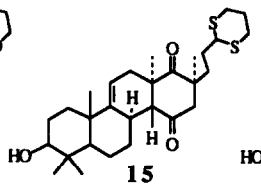
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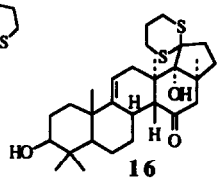
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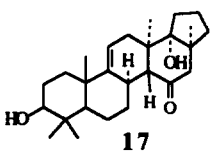
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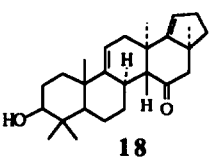
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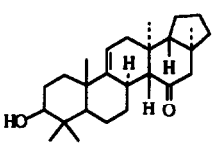
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The pentacyclic products **7**[6] and **18** (mp :195°C, pentane, $[\alpha]_D$: 22, c=1.1) could be used to effect methylation at C-14 and/or elaborations of the ring E; alternately, the synthetic strategy could be altered to provide directly the proper substitution pattern in ring E; both routes are presently explored[7].

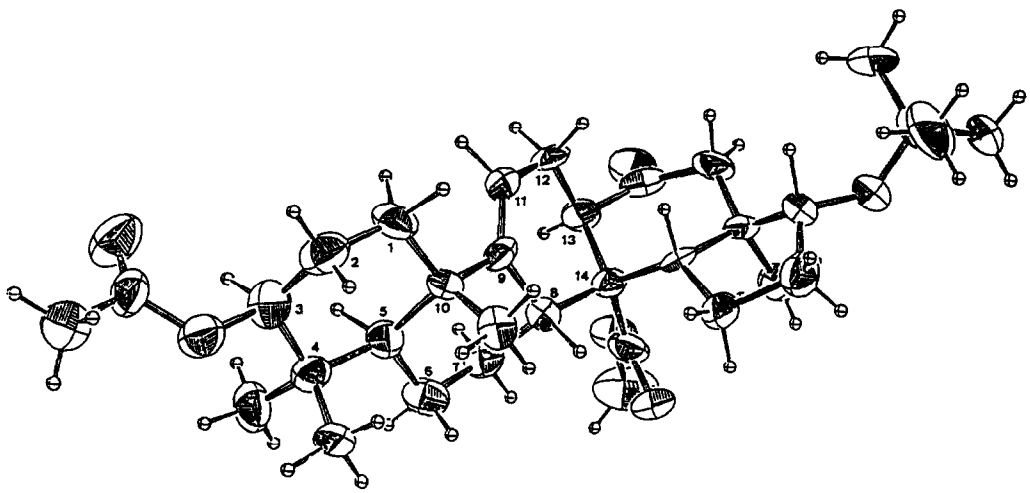
Acknowledgement: We thank Prof. Guy Ourisson (Strasbourg) for having suggested and followed this project, and for help with the preparation of the manuscript. We are also grateful to Dr André Guingant (ESPCI, Paris) for having kindly helped us to perform the high pressure experiments on his equipment.

References and Notes:

1-Albrecht, P. and Ourisson, G., *Science*, **1969**, 163, 1192; Dastillung, M., Albrecht, P. and Ourisson, G., *J.Chem.Res.*, **1980**,(S) 168, (N) 2353; Ourisson, G., Albrecht, P. and Rohmer, M., *Trends in Biochem. Sci.*, 1982, **6**, 236; Ourisson, G. and Rohmer, M., *Acc. Chem. Res.* 1992, **25**, 403-408.

2-Arséniyadis, S., Rodriguez, R., Cabrera, E., Thompson, A. and Ourisson, G., *Tetrahedron*, 1991, **47**, 7045-7058.

3-Computer generated drawing of **5a**-3b-OAc derived from X-ray coordinates:



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5- Krafft, M.E., Crooks, W.J., *J.Org.Chem.*, 1988, **53**, 432-434.

6- **IR**: 3385, 2935, 2957, 1711, 1654, 1597, 1376, 1281, 1277, 1185, 1085, 1056, 1044, 984, 755. **^{1}H-NMR** (400MHz, $CDCl_3$): 0.999 (1H, m, H-7ax), 1.167 (3H,s,Me-4ax), 1.206 (3H,s, Me-13), 1.25 (1H,m, H-5), 1.298 (3H,s, Me-4eq), 1.403 (3H, s, Me-10), 1.488 (3H, s, Me-17), 1.85-2.02 (5H,m), 2.21 (1H,m, H-21), 2.359 (1H,ddd, J=2.2, 7.2, 12.2, H-7eq), 2.47 (1H, dd, J=6.3, 16.6, H-12eq), 2.51 (1H,d,J=8.5, H-14), 2.65 (1H,m),2.70(1H,m, H-12ax), 2.78 (2H,AB quartet, J=12, H-16), 2.95(1H, m, H-8), 3.553 (1H,dd, J=4.4, 11.1, H-3), 5.579 (1H, d, J=6.3, H-11), 5.798 (1H, t, J=1.9, H-19). **^{13}C-NMR** (62.5MHz, $CDCl_3$): 15.4, 20.5, 20.8, 21.5, 26.4, 27.8, 28.1, 29.8, 30.2, 34.2, 35.7, 38.9, 39.2, 39.3, 44.6, 52.1, 53.0, 57.4, 60.0, 78.9, 111.6, 121.5, 148.6, 155.1, 211.6. **EIMS**: 382($M^{+\cdot}$, 100), 367 (45), 364 (56), 349 (52), 105 (59), 91 (58), 69 (44), 55 (72). **CIMS**: 383 (M+H). **HREIMS**: calcd for $C_{26}H_{38}O_2$: m/z 382.2871, fd: 382.2865.

7- Satisfactory spectroscopic and analytical data have been obtained for all new compounds. Optical rotations were measured in chloroform, unless otherwise noted.

(Received in France 30 November 1992)