discussions, and to Professor H. J. T. Bos (University of Utrecht) for access to unpublished results.

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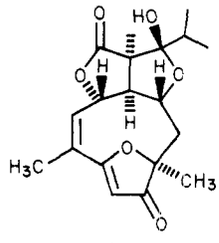
Chiral Models of the Furenone Moiety of Germacranolide Sesquiterpenes

Summary: A procedure is outlined for converting 2,3:5,6-di-*O*-isopropylidene-D-mannose (**4**, diacetone mannose), by a series of simple, efficient steps, into the unsaturated hydroxy esters **14** and **15**, which are then oxidized by Fetizon's reagent to afford the dienones **3a** and **3b**, these being analogues of the furenone system found in many germacranolide sesquiterpenes.

Sir: The plant metabolites known as the germacranolide sesquiterpenes are among some of the most intriguing natural products.[1] Many are of special interest because of their biological[2] and specifically antitumor[3] activity, and the majority possess structures which pose daunting challenges to the synthetic organic chemist. Eremanotholide A[3a] (**1**) and ciliarin[1e] (**2a**) and its recently isolated



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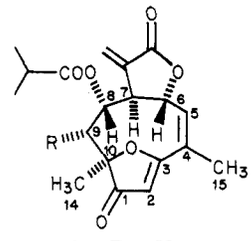


2a, R = H
b, R = OH

congener[1a] **2b** typically exemplify their structural complexity. The origin of their biological activity is still a matter of speculation. This is particularly so in relation to antitumor activity, since most members of the family possess α-methylene lactone and dienone functionalities, each[4] of which could conceivably act as an alkylating agent for terminating DNA synthesis, in the context of Kupchan's hypothesis.[5]

In spite of the foregoing there have been very few[6] reported synthetic ventures related to these substances. In order to acquaint ourselves with the idiosyncracies of such complex molecules, we have divided the molecules into upper and lower halves, noting that we thereby separate the two alkylating moieties. In this communication we describe the synthesis of a model of the lower half by a route which gives the material **3** in the chiral form that is congruent with most germacranolides.[7] Interestingly, the procedure can be adapted for preparing the enantiomer of **3** corresponding to the unnatural series.

For our approach the furenone **3** was viewed as a highly modified *C*-glycofuranoside, a class of sugar derivatives that has received much attention recently since they provide ready access to the pharmacologically important *C*-nucleosides.[8] It would obviously be judicious to introduce the angular methyl group at an early stage so as to avoid aromatization of the furan ring.

The model substance **3** is seen to have a two-carbon fragment at each end, one (C_8–C_9) being saturated and the other (C_4–C_{15}) unsaturated. One of these could conceivably be derived from the C_5–C_6 moiety of a hexofuranose, while the other could be elaborated from the anomeric center. For the latter objective 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**4**, diacetone mannose) seemed a logical choice since the anomeric center is not protected.

We therefore had two alternatives for proceeding from **4** to **3** (Scheme I). In pathway a, **4** → **5** → **6** → **3**, the anomeric center of **4** becomes the unsaturated "end" (C_3–C_4–C_{15}) of **3**, while the C_5–C_6 unit of **4** ends up as C_8–C_9 of **3**. In pathway b, **4** → **7** → **3**, the C_{10}–C_9–C_8 moiety of **3** is elaborated from the anomeric center of **4**, while the unsaturated "end" is derived from C_5–C_6. In either pathway, the addition of the two-carbon unit at the anomeric center could be carried out by means of tandem Wittig and Michael reactions developed by Moffatt and co-workers.[9] Actually these investigators had examined only aldoses, e.g., **4**, and an attractive feature is that the C_3 epimers of **5** produced could both be utilized since H-3 of **6** would be lost in going to **3**. These considerations would seem to recommend pathway a, but a further requirement would be the attachment of a methyl group at C_{10} of **5**. Although this has in fact been done by us in another study,[10] the difficulties encountered caused us to explore pathway b as shown in Scheme II.

Diacetone mannose **4** was oxidized with Collins reagent to the known[11] lactone **8** which upon treatment with methyllithium gave the β-D-ketose **9** as the exclusive product.[12,13] Attempts to react **9** with methyl (triphenyl-

(1) (a) W. Herz and J. F. Blount, *J. Org. Chem.*, **43**, 1268 (1978); (b) F. Bohlmann and J. Jakupovic, *Phytochemistry*, **18**, 119 (1979); (c) P. S. Marchand and J. F. Blount, *J. Org. Chem.*, **43**, 4352 (1978); (d) A. R. de Vivar, C. Guerro, E. Diaz, E. A. Bratoeff, and L. Jimenez, *Phytochemistry*, **15**, 525 (1976); (e) A. Ortega, A. R. de Vivar, E. Diaz, and J. Romo, *Rev. Latinoam. Quim.*, **3**, 81 (1970).

(2) W. Vichnewski, S. J. Sarti, B. Gilbert, and W. Herz, *Phytochemistry*, **15**, 191 (1976).

(3) (a) R. F. Raffauf, P. C. Huang, P. W. LeQuesne, S. B. Levery, and T. F. Brennan, *J. Am. Chem. Soc.*, **97**, 6884 (1975); (b) S. M. Kupchan, V. H. Davies, T. Fujita, M. R. Cox, R. J. Restivo, and R. F. Bryan, *J. Org. Chem.*, **38**, 1853 (1973); (c) S. M. Kupchan, V. H. Davies, T. Fujita, M. R. Cox, and R. F. Bryan, *J. Am. Chem. Soc.*, **93**, 4916 (1971); (d) S. M. Kupchan, M. Maruyama, R. J. Hemingway, J. C. Hemingway, S. Shibuya, T. Fujita, P. D. Cradwick, A. D. V. Hardy, and G. A. Sine, *ibid.*, **93**, 4914 (1971); (e) Y. Aynchihi, J. M. Cassady, A. T. McPhail, G. A. Sims, H. K. Schnoes, S. M. Kupchan, and A. L. Burlingame, *ibid.*, **88**, 3674 (1966).

(4) Le Quesne has found, for example, that isopropyl mercaptan adds at the δ-position of **1**; presumably cysteine would do the same. P. Le Quesne, 7th Natural Products Symposium, University of the West Indies, Kingston, Jamaica, 1978.

(5) S. M. Kupchan, M. F. Eakin, and A. M. Thomas *J. Med. Chem.*, **14**(12), 1147 (1971).

(6) (a) A. B. Smith III and P. J. Jervis, *Synth. Commun.*, **8**(7), 421 (1978); (b) A. W. McCulloch and A. G. McInnes, Abstracts, CIC Conference, Winnipeg, Manitoba, Canada, 1978, No. OR-68.

(7) With the exception of liatrin, the absolute configuration of these compounds is not known. For a hypothesis on defining the stereochemistry of germacranolide sesquiterpenes, see S. M. Kupchan, J. E. Kelsey, and G. A. Sim, *Tetrahedron Lett.*, 2863 (1967).

(8) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111 (1976).

(9) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975).

(10) T. F. Tam and B. Fraser-Reid, *Can. J. Chem.*, **57**, 2818 (1979).

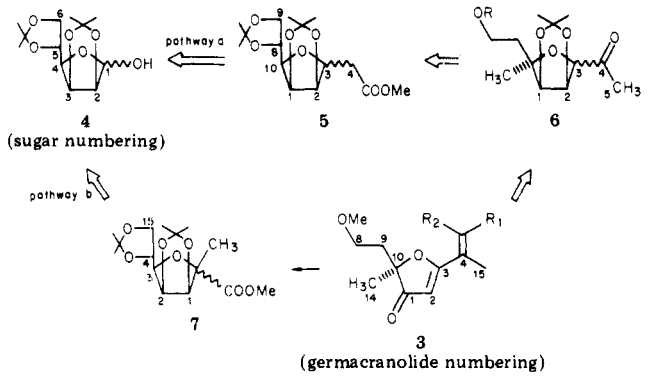
(11) E. H. Goodyear and W. H. Haworth, *J. Chem. Soc.*, 3126 (1927); H. Ohle and G. Berend, *Chem. Ber.*, **58**, 2590 (1925).

(12) This compound gave satisfactory elemental analysis or mass, NMR, and IR spectroscopic data.

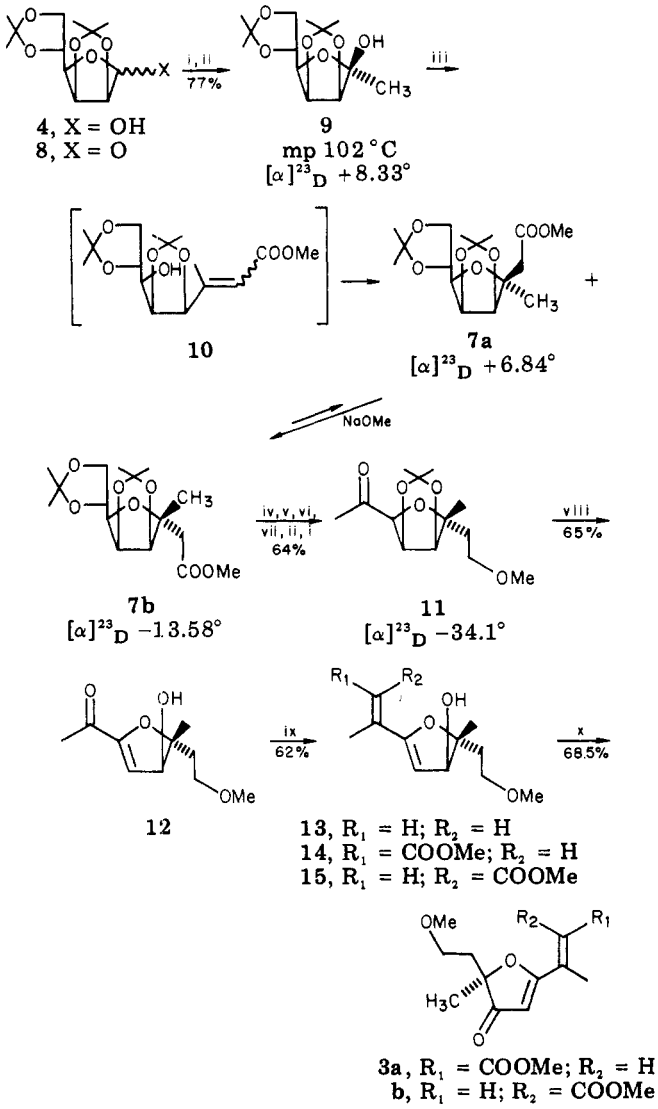
(13) The configuration at the anomeric center of **9** was established by observing hydrogen bonding of the hydroxyl proton to the vicinal oxygen atom.

0022-3263/80/1945-1344$01.00/0

Scheme I



Scheme II[a]



[a] i, Collins reagent, CH_2Cl_2; ii, MeLi, THF, −78 °C; iii, Ph_3P=CHCOOMe, MeCN, 125 psi, 160 °C; iv, $LiAlH_4$, ether; v, MeI, NaH, THF, *n*-Bu_4NI; vi, 70% HOAc/H_2O; vii, $NaIO_4$, MeOH, H_2O; viii, NaOMe, MeOH; ix, Ph_3P=CHCOOMe, MeCN, reflux; x, Ag_2CO_3, Celite, C_6H_6, reflux.

phosporanylidene)acetate in refluxing benzene or acetonitrile, conditions which had succeeded with aldoses (e.g., **4** → **5**),[9] led to complete recovery of the starting material, and although the Wadsworth–Emmons–Horner procedure did succeed somewhat, the product, **10**, was irretrievably contaminated with several byproducts.

However, it was found that the Wittig reaction could be successfully carried out in acetonitrile in a glass-lined pressure vessel at 160 °C, the internal pressure attained being 125 psi.[15] Under these conditions the acyclic intermediate **10** was bypassed, and a 2.2:1 mixture of **7a** and **7b** was obtained in 52% yield.[12] These isomers could be separated chromatographically, and the structures were assigned (see Scheme II) on the basis of comparisons with the stereochemically related compounds **5** prepared from diacetone mannose **4** by Moffatt and co-workers.[9] Accordingly, the AB quartet for the methylene protons of **7a** appears at higher field (2.73 ppm) than that of **7b** (2.50 ppm). Upon equilibration of the minor isomer **7a** with sodium methoxide in methanol, a 2.5:1 mixture of **7b** and **7a** was obtained. Thus the major isomer **7b** can be accumulated by sequential equilibration and fractionation, and this is considered advantageous since in this isomer the angular methyl group is chirally congruent with the corresponding center in the germacranolides.[7]

Compound **7b** was converted into the methyl ketone **11** by six simple, standard procedures in excellent overall yield. Elimination to the enone **12** was effected smoothly by using sodium methoxide in methanol for 30 min.

Reaction of **12** with methylenetriphenylphosphorane gave the dienol **13** which proved to be unstable, and attempts at oxidation with a variety of reagents led to complete degradation.[16] In order to obtain a more stable diene system, we used a stabilized Wittig reagent, whereupon the *E* and *Z* esters **14** and **15** were isolated as an inseparable mixture.

The oxidation of this mixture proved to be surprisingly troublesome. Manganese dioxide and chromium(VI) reagents led to massive decomposition. However, Fetizon's reagent[17] was found to be successful if a generous excess of the carefully dried oxidant was added in portions to a solution of the mixture of **14** and **15** in dry refluxing benzene over 8 h. The yield was 68.5%, and the isomers **3a** and **3b** were separated by preparative layer chromatography. The ratio of **3a** to **3b** was 8:1, and their spectroscopic data[18] are entirely consistent with the assigned structures.

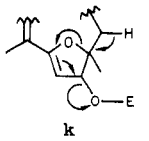
The fact that the minor anomer **7b** can also be obtained in pure form means that the enantiomer of **3** may also be prepared by a route identical with that outlined in Scheme II for **7a**.

Compounds **14** and **15** are currently undergoing tests for biological activity and the results will be disclosed in due course.

(14) W. S. Wadsworth, Jr., and W. D. Emmons, "Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 547.

(15) We have found that this procedure is very effective for standard Wittig reactions which do not go at ordinary refluxing temperatures.

(16) It is conceivable that the instability of **13** and the oxidative decomposition of **13**, **14**, and **15** could be explained by the mechanism expressed in k, where E is an oxidizing agent or electrophile. We are grateful to Professor Amos Smith for helpful discussions on this aspect.



k

(17) M. Fetizon and M. Golfier, *C. R. Hebd. Seances Acad. Sci.*, **267**, 900 (1968).

(18) **3a**: $C_{13}H_{18}O_5$ requires 254.1154, found 254.1141; $[\alpha]^{23}_D$ −7.77; λ_{max} 257 nm (ϵ 7936); NMR 3.36 (m, H-1), 2.06 (m, H-2), 5.76 (s, H-5), 6.60 (m, H-8), 2.36 (d, H-10), 1.56 (s, CCH_3), 3.21 (s, OCH_3), 3.76 ppm (s, $COOCH_3$); R_f (ether) 0.67. **3b**: $[\alpha]^{23}_D$ −1.87; NMR 3.40 (m, H-1), 2.03 (m, H-2), 5.60 (s, H-5), 5.93 (m, H-8), 2.13 (s, H-10), 1.40 (s, CCH_3); R_f (ether) 0.53.

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Registry No. 3a, 72926-52-4; **3b**, 72938-25-1; **7a**, 72926-53-5; **7b**, 72926-54-6; **9**, 72926-55-7; 11, 72926-56-8.

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