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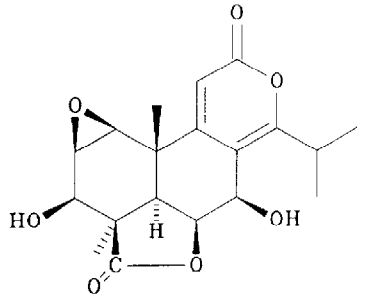
A NOVEL STEREOSELECTIVE SYNTHESIS OF THE RING AB PODOCARPATE SYSTEM

Ling Lu, Richard K. Shoemaker and Desmond M.S. Wheeler*
Department of Chemistry, University of Nebraska-Lincoln
Lincoln, Nebraska 68588-0304, U. S. A.

Abstract: A new way of stereoselectively synthesizing rings A and B of podocarpate has been developed; the correct stereochemistry at C_4 is obtained during a cyclization linking C_2 to C_3.

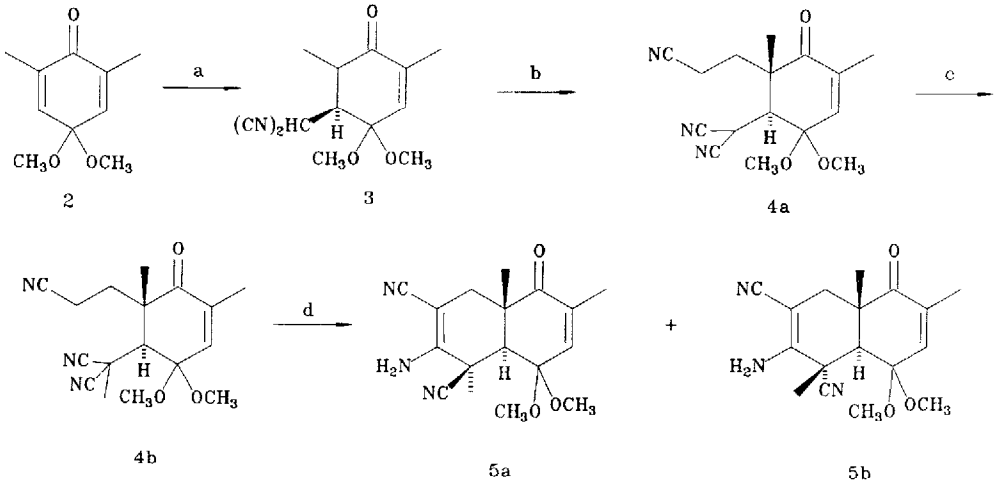
Although members of the family of norditerpenoid dilactones that includes inumakilactones, podolactones, nagilactones, podolide, and the sellowins,[1] (e.g.1), show interesting biological activities,[2] they have attracted little attention from synthetic chemists.[3] Apparently only four syntheses have been completed: that of nagilactone F from podocarpic acid[3a] and three syntheses of the related mold metabolite LL-Z1271α[4].



Nagilactone C

1

In earlier studies[5] we devised an approach to diterpenoid acids in which ring A was fused to ring B by constructing the C_4-C_5 bond. This led to a *cis* fusion of the rings, thus necessitating an inversion at C_5. We now describe a novel way of obtaining the correct stereochemistry at C_4, C_5 and C_{10}. The key step in this work is the completion of ring A by joining C_2 to C_3. Addition of malononitrile to the 4-dimethylketal of 2,6-dimethylbenzoquinone (**2**),[6] gave **3**.[8,9] A subsequent Michael addition of **3** to acrylonitrile yielded the trinitrile **4a** [8,9]. Methylation of this compound gave **4b** [8]. Both **3** and **4**[10] were obtained as single stereoisomers. The stereochemistry of **4** was assigned on the view that attack of the acrylonitrile on the enolate of **3** should occur from the less hindered side.



(a) $CH_2(CN)_2$, $NaOC_2H_5$, C_2H_5OH, 90%; (b) NaH (2eq), CH_2=CHCN, THF, 54%;
(c) NaH, CH_3I, DMSO; 70%; (d) NaH, THF, 67%(5a), 4%(5b)
All reactions were run at room temperature

Cyclization of **4b** was effected under basic condition to give two products **5a** (67%)[8,9] and **5b**(4%)[8]. The assignments of these structures, which were made on the basis that the less hindered product would predominate (see Figure 1), was confirmed by a study of the relaxation times T_1 of C_4 and the NOE interactions between the protons on the two methyl groups and that on C_5 in **5a** and **5b**[11]. (See Tables 1 and 2). The T_1 of the protons of the C_4-methyl and the C_5-hydrogen of **5b** is greater than those in **5a**. This is probably due to a dampening of the efficient dipolar relaxation between the C_4 methyl and the C_5 proton because of their decreased proximity in the *trans* configuration. This conclusion is confirmed by the Nuclear Overhauser Enhancement studies, a large NOE effect (14.6%) is observed between the C_4 methyl and C_5-**H** in **5a**, while the effect between the similar groups in **5b** is quite small (3.1%). One must be extremely careful in interpreting NOE results on diastereomers such as these, where multiple relaxation processes are taking place, and correlation times might vary between the two isomers. In this case, however, the results are conclusive: the similar T_1 values of the C_1 hydrogens provide a benchmark which indicates that the overall correlation times of the two ring systems are similar. In addition, the **5-H** in the **5a** isomer, which shows the larger NOE effect, has the smaller

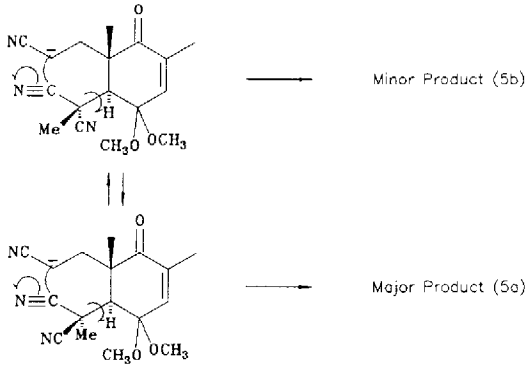


Figure 1

T_1. This clearly shows that the C_5-hydrogen and C_4-methyl in **5a** is much closer than in **5b**. When structures were minimized using a simplex algorithm the RMS distance between the C_5-hydrogen and the C_4-methyl is 2.4 Å in **5a** and 3.8 Å in **5b**. These distances are consistent with the relative enhancements observed. The NOE enhancements between the C_{10}-methyl to the C_5-hydrogen, and the C_{10}-methyl to each of the C_1-hydrogens were all small.

The NOE results (Table 2) clearly establish that **C_5-H** is *trans* to the **C_{10}** methyl group in both compounds and the **C_4**-methyl in **5b** and *cis* to the **C_4** methyl in **5a.** Thus our assignments of stereochemistry at **C_4**, **C_5** and **C_{10}** in **5a** and **5b** are secure.

Relaxation Data:

	Major Product T1	Minor Product T1
4-Methyl	0.25 Sec	0.5 Sec
5-Hydrogen	0.69 Sec	1.25 Sec
10-Methyl	0.35 Sec	0.35 Sec
1-Hydrogens	0.42 Sec	0.32 Sec

Table 1, T_1 relaxation time constants for each of the diastereomers studied.

NOE Data:

	Major Product	Minor Product
4-Me -> 5-H	14.6%	3.1%
10-Me -> 5-H	2.0%	3.2%
10-Me -> 1ß-H	9.4%	9.3%
10-Me -> 1α-H	-3.4%	-1.1%

Table 2, NOE enhancements for the two isomers. The group listed first is the irradiated resonance, and the latter is the functionality producing the enhanced signal.

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6. Prepared from 2,6-dimethylphenol by oxidation with iodobenzenediacetate.[7]

7. cf. Pelter, A; Elgendy, S. *Tetrahedron Lett.* 1988, **29**, 677.

8. Spectral data are in accord with the structure.

9. CHN analyses confirm composition.

10. A polymer is also produced in the reaction leading to **4**. No epimer of **4** was detected.

11. ^{1}H NMR (ω_o=361.04 MHz) δ($CDCl_3$): **5a**, 6.65 (d, 1H, =CH), 4.57 (s, 2H, NH_2) 3.50 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 2.49 (d, AB J=16.5 Hz, 1H, CH_2) 2.30 (s, 1H, CH), 2.26 (d, AB J=16.5 Hz, 1H, CH_2), 1.90 (d, 3H, $=CCH_3$), 1.87 (s, 3H, CH_3CCN), 1.33 (s, 3H, CH_3); **5b**, 6.92 (d, 1H, =CH), 4.55 (s, 2H, NH_2), 3.43 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 2.80 (s, 1H, CH), 2.49 (d, AB J=16.3 Hz, 1H, CH_2), 2.30 (d, AB J=16.3 Hz, 1H, CH_2), 1.91 (s, 3H, CH_3CCN), 1.89 (d, $=CCH_3$), 1.36 (s, 3H, CH_3).

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