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"ACCORDION" REARRANGEMENTS OF CYCLOBUTANE α-SULFONYL LACTONES

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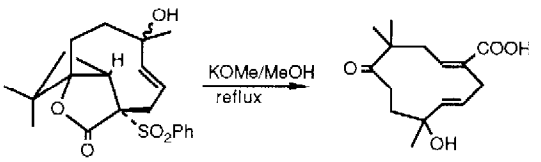
SUMMARY: The tricyclic α-sulfonyl lactone **4** is converted by alkoxides to bicyclic acids **5,6**; the homologous α-sulfonyl lactone **8** yields bicyclic acid **10** or the cyclononene ketoacid **9**. These products arise from a common Grob fragmentation mechanism (Scheme 3), in which the fate of the medium-ring trans-cycloalkene intermediates **12** is determined by ring size and by the nature of the nucleophilic base used.

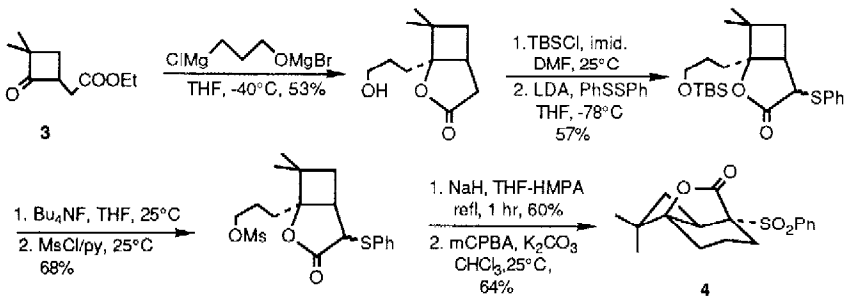
During recent studies culminating in our total synthesis of the fungal metabolite (±)-Punctaporonin B[1] we noted an unusual rearrangement of the diastereomeric mixture of α-sulfonyl lactones **1** by KOMe in MeOH to a cycloundecadiene keto acid having spectroscopic properties consistent with structure **2**[2]. We tentatively rationalized this transformation as a multistep Grob fragmentation sequence, and on this basis we assumed the stereochemistry of the conjugated double bond in **2** to be trans on the basis of the antiperiplanar stereoelectronic requirement of the postulated Grob fragmentation step (vide infra).



1 **2**

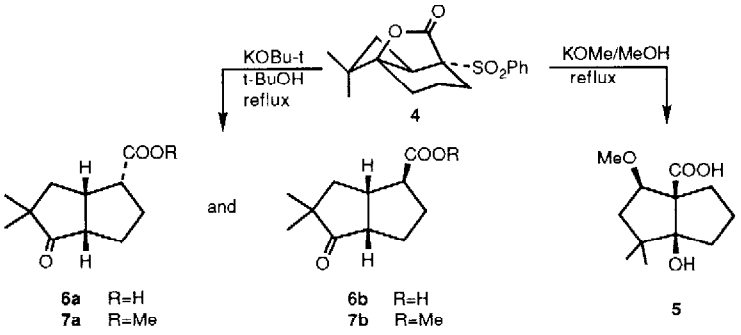
To confirm the mechanism and to determine whether the above rearrangement could serve as a general method for alicyclic ring expansion by two ring carbons, we undertook the study of a simpler model, namely the 6-4 fused γ-lactone **4**. Lactone **4**, mp 108-110°C, was synthesized from keto ester **3**[1] by the reactions in Scheme 1.

Scheme 1.



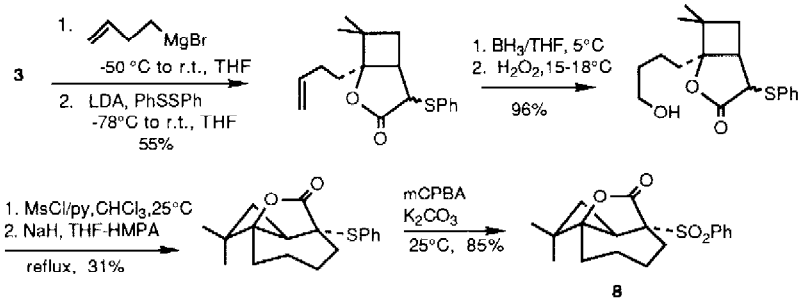
3 **4**

When lactone **4**[3] was reacted with KOMe in dry MeOH at reflux, workup after 2 hrs. produced a single $C_{12}H_{20}O_4$ carboxylic acid,[4] mp 125-126°C, in 85-90% yield. The presence of a new OCH_3 group was indicated by a 3H singlet at δ 3.37. The nature of this methoxy acid was shown by detailed spectroscopic characterization of the acid (and its methyl ester), and its structure and stereochemistry were established as **5** by single crystal X-ray analysis.[5] In contrast, when the lactone **4** was refluxed in t-BuOH containing KOt-Bu, workup produced in 65% overall yield a 3:1 mixture of epimeric keto acids **6a** and **6b**. Esterification with CH_2N_2, followed by silica gel chromatography produced the mixture of keto esters **7a** and **7b**.[6] The stereochemistry at the epimeric carbon was assigned by the observation that exposure of the 3:1 mixture of esters **7a** and **7b** to KOMe in MeOH at room temperature for 3 days gave a high yield of the same two esters in a new 1:3 ratio, identifying **7b** as the thermodynamically more stable exo isomer.



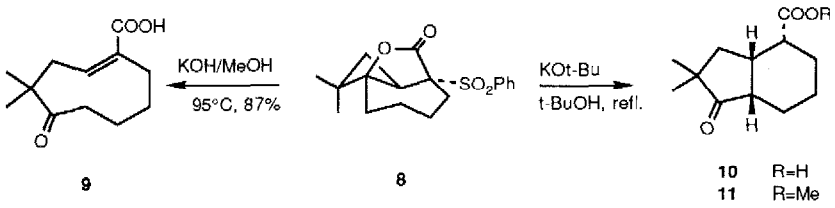
In order to establish the reason for our failure to observe the anticipated medium-ring Grob fragmentation product from lactone **4**, we extended our survey to the homologous 7-4 fused γ-lactone **8**, synthesized as shown in Scheme 2.

Scheme 2.



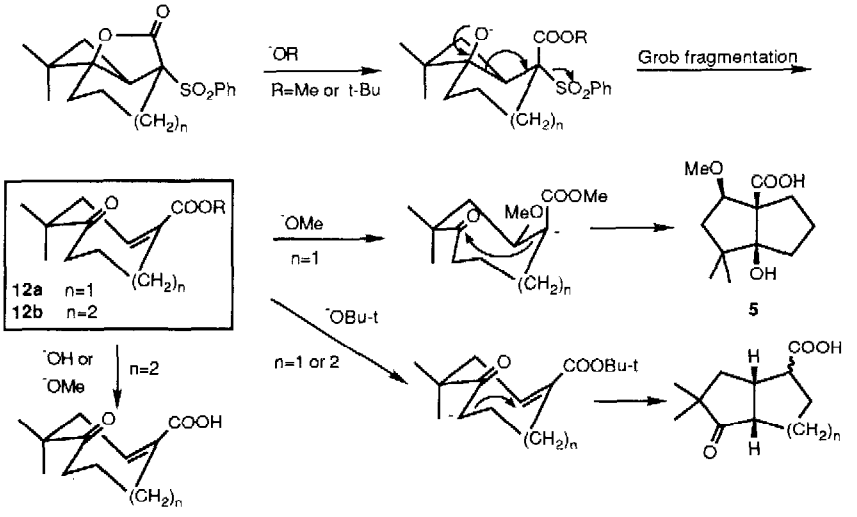
When lactone **8**, mp 149-150°C,[7] was reacted with KOMe in MeOH at 95°C for 2 hrs, **8** was largely recovered. However, powdered KOH in MeOH at 95°C for 40 min. produced the single crystalline keto acid **9**, mp 113-114°C in 87% yield.[8] The trans stereochemistry of the cyclononene double bond was dictated by the chemical shift of the lone vinyl proton at δ 6.09 (dd, J=13,5 Hz), in good agreement with the literature values of δ 6.17-6.23 for trans isomers (vs. δ 6.8-7.0 for the cis isomers) of related esters and acids.[9] Once again the use of KOt-Bu in

t-BuOH at 100°C produced a bicyclic keto acid, in this case mainly **10**, which was converted to its methyl ester **11** using CH_2N_2 in 45% overall yield.[10]



We conclude that these "accordion" rearrangements[11] proceed by the postulated Grob fragmentations to yield as typical primary intermediates the corresponding trans-cycloalkene ester **12** (Scheme 3). In the case of the 6-4 lactone precursor **4**, the ester **12a** has the high strain energy characteristic of trans-cyclooctenes,[12] and should undergo rapid conjugate addition of the nucleophile MeO^- to give, upon subsequent intramolecular aldol cyclization, the ester of acid **5**. On the other hand, $t\text{-}BuO^-$ is a larger and more basic species, permitting competitive deprotonation of **12a** α-to the ketone, leading by intramolecular Michael cyclization to the t-butyl esters of **6a/6b**. In the reaction of the 7-4 lactone precursor **8** with KOH/MeOH, the primary intermediate will be the relatively unstrained cyclononene acid **9**, which can be isolated.[13]

Scheme 3.



Even with substrate **8**, however, t-butoxide is a sufficiently strong base to generate an enolate α-to the ketone in **12b**, producing ultimately bicyclic acid **10**. Control experiments show that cyclononene acid **9** does not undergo further cyclization with KOt-Bu in t-BuOH. These data demand that the secondary Michael cyclizations proceed on the medium-ring esters rather than on the acids, and that the ultimate formation of acids probably results from alkoxide cleavage[14] or adventitious hydrolysis of their ester precusors.

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References and Notes

1. Kende, A. S.; Kaldor, I.; Aslanian, R. *J. Am. Chem. Soc.* **1988**, *110*, 6525.

2. Acid **2**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.98-5.88 (2H, m), 5.26 (1H, d, J=16), 2.96 (1H, dd, J=13,6), 2.83-2.61 (4H, m), 2.22-2.02 (3H, m), 1.67 (1H, dd, J=13,10), 1.31 (3H, s), 1.25 (3H, s), 1.15 (3H, s). **^{13}C NMR** (300 MHz, $CDCl_3$): δ 216.7, 172.1, 146.6, 137.6, 134.4, 130.5, 73.5, 49.4, 42.6, 33.8, 34.5, 34.3, 29.5, 27.7, 24.0. **MS**: m/e 266 (M^+). Examination of purified **2** shows by ^{1}H and ^{13}C-NMR the presence of a single atropisomer only.

3. Lactone **4**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.99 (2H, d, J=7), 7.68 (1H, t, J=7), 7.56 (2H, t, J=7), 2.67 (1H, t, J=8), 2.14 (1H, dd, J=5,13), 2.03-1.60 (7H, m), 1.19 (3H, s), 1.04 (3H, s). **Anal**. Calcd. for $C_{17}H_{20}O_4S$: C, 63.75; H, 6.25. Found: C, 63.73; H, 6.21.

4. Acid **5**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.1 (1H, s(br)), 3.58 (1H, dd, J=5,6Hz), 3.37 (3H, s), 2.45-2.52 (1H, m), 1.93-1.64 (8H, m), 1.09 (3H, s), 1.00 (3H, s). **Anal**. Calcd. for $C_{12}H_{20}O_4$: C, 63.15; H, 8.77. Found: C, 63.03; H, 8.41.

5. Crystal data for acid **5**: monoclinic, space group $P2_1/n$, a=9.213 (2) Å, b=12.377 (3) Å, c=11.187 (4) Å, β=102.16 (2)°, V=1247 (1) Å^3, Z=4. Data collected on Enraf-Nonius CAD-4 diffractometer, with use of 942 unique data ($4° \leq 2\theta \leq 48°$, $I \geq 3\sigma(I)$). The structure was refined to $R(R_w)$=5.2 (6.0)%. We thank Professor W. D. Jones for his guidance in the X-ray analysis.

6. Ester mixture of **7a** and **7b**: **^{13}C NMR** (300 MHz, $CDCl_3$): major: δ 223.25, 173.42, 51.35, 49.51, 48.55, 47.17, 38.68, 38.54, 27.90, 26.30, 24.67, 22.59. minor: 223.37, 175.53, 51.67, 51.24, 50.38, 47.43, 42.99, 40.48, 29.71, 27.80, 25.23, 23.49. **HRMS** Calcd. for $C_{12}H_{18}O_3$: 210.1255. Found: 210.1279.

7. Lactone **8**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.08 (2H, d, J=8), 7.69 (1H, t, J=8), 7.58 (2H, t, J=8), 3.16 (1H, t, J=8), 2.72 (1H, dd, J=8,12), 2.06 (2H, dd, J=8,13), 1.80-1.40 (7H, m), 1.19 (3H, s), 1.10 (3H, s). **Anal**. Calcd. for $C_{18}H_{22}O_4S$: C, 64.67; H, 6.58. Found: C, 64.83; H, 6.46.

8. Keto acid **9**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.99 (1H, dd, J=5,13), 3.47 (1H, t, J=12), 2.72 (1H, m), 2.40 (2H, m), 2.15 (1H, dd, J=5,12), 2.10-1.95 (2H, m), 1.80-1.65 (3H, m), 1.32 (3H, s), 1.25 (3H, s). **Anal**. Calcd. for $C_{12}H_{18}O_3$: C,68.57; H,8.57. Found: C,68.57; H,8.67.

9. Silveira, A.; Mehra, Y.R.; Atwell, W.A. *J.Org.Chem.* **1977**, *42*, 3892, and related references therein.

10. Keto ester **11**: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.72 (3H, s), 2.80-2.70 (2H, m), 2.37 (1H, ddd, J=6,6,7), 1.91 (1H, d, J=12), 1.87-1.80 (2H, m), 1.75-1.65 (1H, m), 1.63-1.55 (2H, m), 1.35-1.2 (2H, m), 1.16 (3H, s), 1.05 (3H, s). **HRMS** Calcd. for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1423.

11. We define an "accordion" rearrangement as one in which a given bicyclic ring system undergoes cleavage of a bond common to both rings, thereby expanding to a larger ring, followed by recyclization to a new bicyclic ring system. Diverse examples can be found in: (a) Baldwin, J. E.; Kaplan, M. S.; *J. Am. Chem. Soc.* **1972**, *94*, 4696. (b) Vogel, E.; Meckel, W.; Grimme, W. *Angew. Chem.* ***1964***, *76*, 786. (c) Boekelheide, V.; Anderson, A. E.; Sauvage, G. L. *J. Am. Chem. Soc.* **1953**, *75*, 2558. (d) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099.

12. Marshall, J.A., *Acc. Chem. Res.* **1980**, *13*, 213, and references therein.

13. Attempts to obtain the cyclooctene acid corresponding to **12a** (R=H), by treating the 6-4 fused γ-lactone **4** with KOH/MeOH/H_2O led only to decomposition.

14. E.g., Bunnett, J. F.; Robinson, M. M.; Pennington, F. C., *J. Am. Chem. Soc.* **1950**, *72*, 2378.

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