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A Short Synthesis of the Tricyclo[3.3.2^{1,4}.0]decane Ring System

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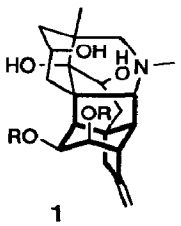
Abstract: An approach to the tricyclo[3.3.2^{1,4}.0]decane ring system has been demonstrated. Acyloin ring closure gives a 1,2-disilyloxy alkene product of surprising stability.

Anopterine (**1**, R = tigloyl),[1b] delnudine (**2**),[1c] ryanodine (**3**),[2a] and related structures[1,2] are diterpene alkaloids found in higher plants. The alkaloids of *Anopterus* species, of which **1** is the major constituent, are associated with a high level of antitumor activity.[3] Ryanodine (**3**) exhibits potent insecticidal activity, an effect due to binding at a calcium channel receptor of skeletal muscle.[4,5]



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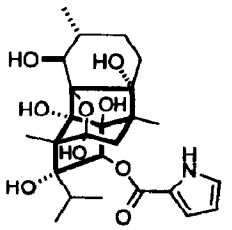

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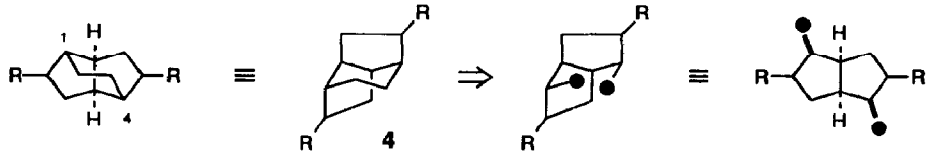
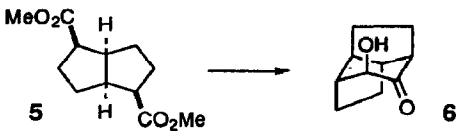
A unifying substructure of these molecules is tricyclo[3.3.2^{1,4}.0]decane (**4**). This ring system has been of interest as an isomer of adamantane[6] and as the structure lumibullvalene[7] but has most often been prepared fortuitously.[8] As part of a program directed at these alkaloids, we have explored the use of the acyloin condensation for closure of the indicated two-carbon bridge, a previously untested disconnection. This coupling reaction would bridge the two five-membered rings with the necessary oxidation (e.g., **6**) for natural products **1–3**, but would require an endo, endo diester substrate such as **5**.

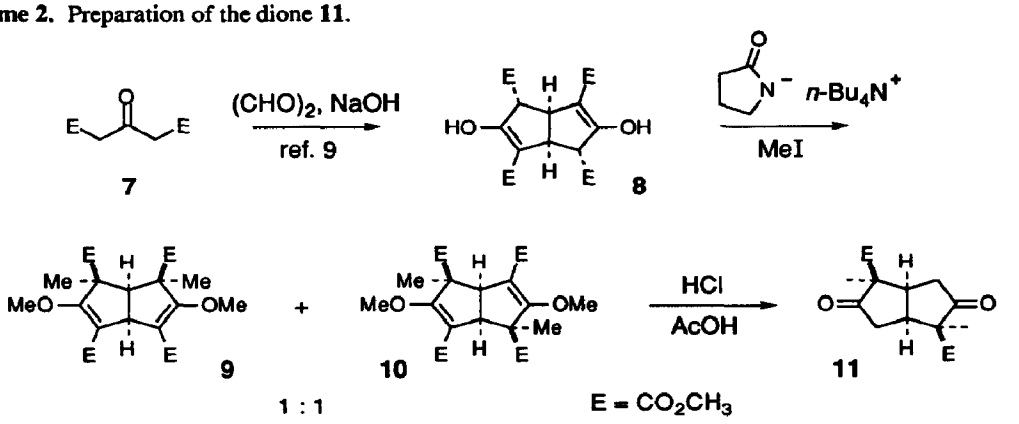
Scheme 1. Retrosynthetic approach to the [3.3.2^{1,4}.0] framework.





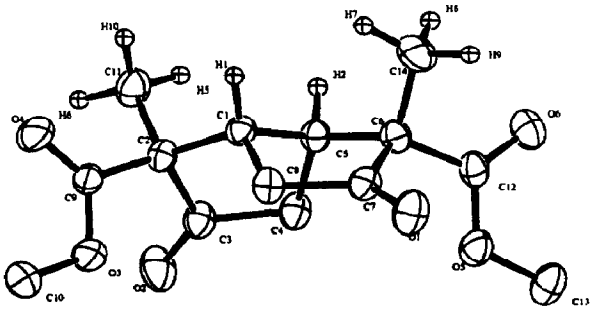
A suitable diester with the necessary stereochemistry for this transformation was readily prepared utilizing the Weiss-Cook reaction of glyoxal and dimethyl acetonedicarboxylate (7).[9] Alkylation of the product **8** by the method of Shono[10] gave a highly reproducible yield (75%) of tetramethylated **9** and **10**,[11] that were readily separable by flash chromatography. The C_2 symmetric **10** was then hydrolyzed and decarboxylated following the conditions reported by Cook and Weiss[11] to give **11** (75%) retaining the more hindered, and less readily hydrolyzed, endo esters.[12]

Scheme 2. Preparation of the dione **11**.

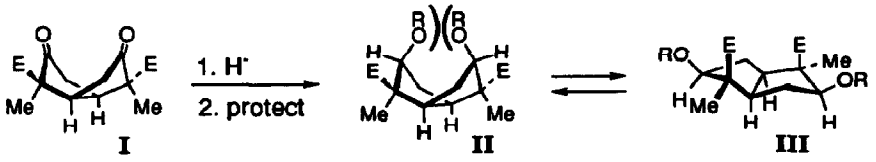


X-ray crystallography confirmed the structural assignment of dione **11**[13] and gave some insight into the preferred conformation (Figure 1). Of particular concern, in view of the proposed acyloin reaction, was the distance between the two ester groups that we hoped to couple (6.1 Å). Nevertheless, we anticipated that the esters would be brought into proximity by reduction of the ketones and protection of the resulting alcohols.

Figure 1. Crystal structure of **11**.



The desired conformational change was anticipated based on hydride reduction from the convex face of the molecule and the resulting steric interaction that would result (see **II**).

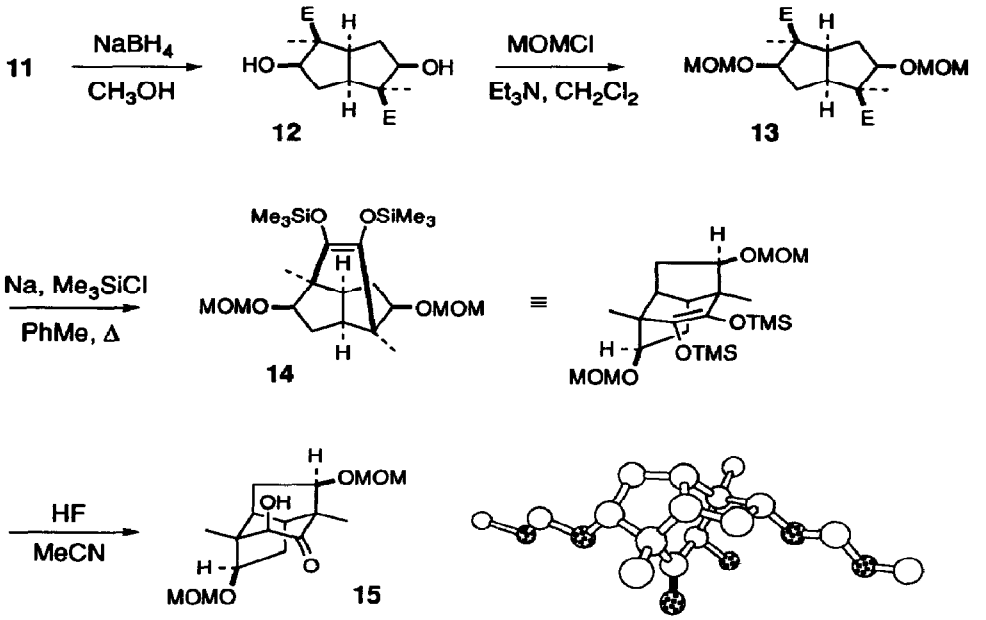


I **II** **III**

In the event, reduction of **11** gave diol **12** as the sole reaction product (90%) and protection of the alcohols as methoxymethyl ethers proceeded smoothly in methylene chloride to give **13** (80%). The key acyloin reaction was then performed using the standard conditions of sodium and chlorotrimethylsilane in

toluene at reflux under argon.[14] Careful workup of the reaction mixture by addition of degassed methanol gave a quantitative yield, not of the expected α-hydroxy ketone product **15**, but the bis-trimethylsilyloxy alkene **14**. The steric environment of flanking MOM ethers on either side of the enediol disilyl ether apparently provides a tremendous stabilizing effect. Not only could **14** be chromatographed on silica gel without special precautions (90% isolated yield from **13**), but even 24 h in refluxing methanol led to a quantitative recovery of **14**! Treatment with dilute mineral acid gave rapid decomposition of **14** to a complex, polar mixture of products, presumably by simultaneous deprotection of the MOM groups. Hydrofluoric acid in acetonitrile, however, smoothly transforms **14** into the anticipated acyloin product **15**.[12]

Scheme 3. Sequence leading to acyloin product **15** and Chem3D representation of **15**.



Acyloin product **15** contains strategic oxidation on all three bridges of the tricyclic system. In this example, the carbon skeleton contains methyl groups only found in **3** and related structures.[2] Structures **1** or **2** would require starting with an α-oxo aldehyde other than glyoxal.[15] The successful preparation of **15** using this approach to the [3.3.2^{1,4}.0] ring system provides a foundation for further work on these complex natural products.

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12 All new compounds were characterized by NMR, IR, MS, and HRMS or combustion analysis. Selected ^{1}H and ^{13}C data ($CDCl_3$): **10:** ^{1}H δ 3.97 (s, 6 H), 3.71 (s, 6 H), 3.61 (s, 6 H), 3.48 (s, 2 H), 1.49 (s, 6 H); ^{13}C δ 172.6, 170.6, 164.3, 108.3, 62.8, 60.6, 52.4, 51.7, 51.0, 24.3. **11:** ^{1}H δ 3.71 (s, 6 H), 2.86 (s, 2 H), 2.54 (d, 4 H, J = 7.5 Hz), 1.42 (s, 6 H),; ^{13}C δ 211.3, 171.2, 59.1, 52.4, 45.2, 39.6, 20.8. **12:** ^{1}H δ 4.50 (bs, 2 H), 4.16 (d, 2 H, J = 6.4 Hz), 3.76 (s, 6 H), 2.70 (s, 2 H), 2.50 (s, 2 H), 1.98 (dd, 2 H, J = 3.6, 16.2 Hz), 1.20 (s, 6 H); ^{13}C δ 171.2, 80.1, 59.5, 51.2, 49.4, 36.2, 24.8. **13:** ^{1}H δ 4.53 (d, 2 H, J = 6.8 Hz), 4.44 (d, 2 H, J = 6.8 Hz), 4.00 (dd, 2 H, J = 3.2, 5.5 Hz), 3.67 (s, 6 H), 3.29 (s, 6 H), 2.47 (s, 2 H), 2.33 (s, 4 H), 1.23 (s, 6 H); ^{13}C δ 174.8, 94.8, 84.6, 57.8, 55.3, 51.2, 49.9, 33.1, 25.3. **14:** ^{1}H δ 4.66 (d, 2 H, J = 6.7 Hz), 4.55 (d, 2 H, J = 6.7 Hz), 3.65 (t, 2 H, J = 8.1 Hz), 3.34 (s, 6 H), 2.01 (m, 2 H), 1.79 (d, 2 H, J = 7.1 Hz), 1.50 (dd, 2 H, J = 7.9, 12.9 Hz), 1.00 (s, 6 H), 0.21 (s, 18 H); ^{13}C δ 132.9, 95.4, 87.8, 55.5, 50.7, 45.9, 28.8, 17.1, 1.8. **15:** ^{1}H δ 4.55 (m, 4 H), 4.18 (d, 1 H, J = 10.6 Hz), 4.08 (m, 1 H), 3.99 (m, 1 H), 3.65 (d, 1 H, J = 10.7 Hz), 3.31 (s, 3 H), 3.29 (s, 3 H), 2.36 (m, 1 H), 2.17 (d, 1 H, J = 4.4 Hz), 2.12 (m, 2 H), 1.80 (dd, 1 H, J = 4.2, 4.4 Hz), 1.30 (s, 3 H), 1.25 (m, 1H), 1.14 (s, 3H).

13 Compound **11** crystallizes from acetone in the monoclinic space group $P2_1/n$ with a = 9.5309 (7) Å, b = 11.8448 (6) Å, c = 12.1641 (8) Å, β = 97.369 (3)°, V = 1361.9 (1) Å^3, and Z = 4. Final least squares refinement using 1868 unique reflections with $I > 3\sigma(I)$ gave $R(R_w)$ = 0.044 (0.051).

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