Cobalt-Mediated Total Synthesis of (+)-Epoxydictymene

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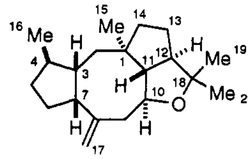
Epoxydictymene[1] (**1**) is a diterpene natural product of the brown alga *Dictyota dichotoma*. It features a 5–8–5–5[2] tetracyclic skeleton containing a strained *trans*-3-oxabicyclo[3.3.0]octane ("*trans*-5–5").[3] Previous studies from our laboratory illustrated an efficient method of preparing 8–5-5 fused ring systems using dicobalt hexacarbonyl complexes of alkynes.[4,5] We now report an application of this methodology to the total synthesis of (+)-epoxydictymene.

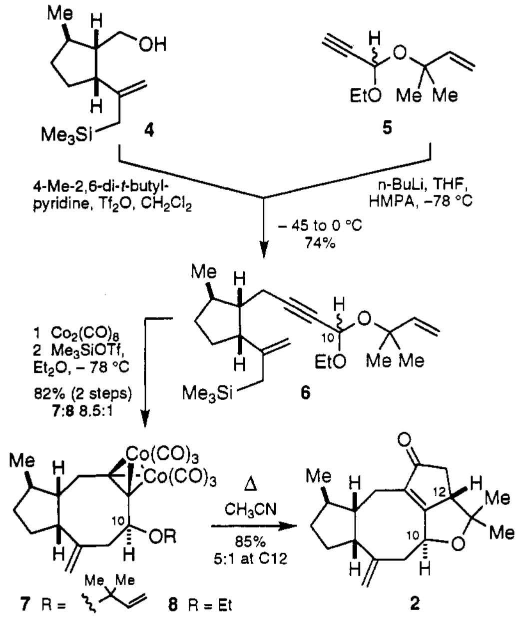


1 (+)-epoxydictymene

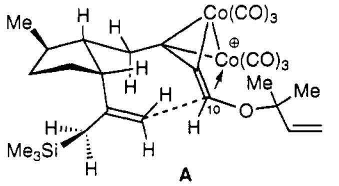
We began the retrosynthesis of **1** with tetracyclic enone **2** (Scheme 1) as it possessed the skeletal and functional assembly typical of the end products of our cobalt chemistry. Further retrosynthetic analysis provided two pieces for the construction of **2**: allylsilane **4**, corresponding to the left portion of **2**, and propargylic mixed acetal **5**, corresponding to the right portion of **2**. Both **4**[6,7] (optically active) and **5**[8] (racemic) were readily prepared from commercially available starting materials using known procedures.

The pieces were then joined through a displacement of a triflate ester derived from alcohol **4** by the lithium anion of **5** under carefully controlled conditions, giving alkyne **6** in 74% yield as a 1:1 mixture of diastereomers at the acetal carbon, corresponding to C10 of epoxydictymene. Treatment of **6** with $Co_2(CO)_8$ gave the desired organometallic cluster, which underwent facile Lewis acid cyclization[4a,b] (1.1 equiv of Me_3SiOTf, Et_2O, −78 °C, 15 min) to afford an 8.5:1 mixture of diastereomerically pure ethers **7** and **8** in 82% overall yield.

Scheme 1



It is noteworthy that this reaction behaves selectively in three respects. First, it is group selective. Ether **7** is formed predominantly, probably due to preferential complexation of the Lewis acid with the less hindered oxygen of the acetal.[9] Second, the cyclization is stereoselective. Within the limits of 500-MHz ^1H NMR spectroscopy, the ether linkage at C10 occupies exclusively a β-configuration in both **7** and **8**. This observation can be rationalized by invoking the transition structure **A** wherein g^+/g^- interactions are minimized, and the ether substituent at C10 is placed outside the incipient eight-membered ring. Finally, the fact that the yield of the reaction (82% for two steps) is greater than 50% reveals that equilibration of the stereochemistry at the propargylic center (C10) is faster than cyclization. Equilibration is envisioned as occurring *via* a fluxional cationic intermediate. A central assumption in this analysis is one of mechanistic uniformity between this intramolecular process and related intermolecular Lewis acid mediated Nicholas reactions.[4b]



The cobalt cluster served a second purpose in the subsequent Pauson–Khand reaction. Thus, heating an acetonitrile solution of **7** and **8** at 82 °C in air for 15 min afforded tetracyclic enone **2** in 85% yield (5:1 mixture of diastereomers at C12).[10] Single crystal X-ray diffraction of the major diastereomer of **2** confirmed the stereochemical assignment shown.

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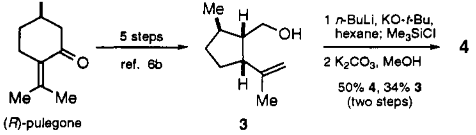
(6) (a) Prepared (*vide infra*) by a double deprotonation reaction (ref 7) and careful silylation of a dianion of alcohol **3**, followed by selective *O*-desilylation, giving **4** in 50% overall yield with 34% recovered **3**. (b) Alcohol **3** was prepared from (*R*)-pulegone according to Wolinsky *et al.*: Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247.



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(8) Prepared from commercially available propiolaldehyde diethyl acetal in 54% yield by the Me_2BBr method of Guindon: Morton, H. E.; Guindon, Y. *J. Org. Chem.* **1985**, *50*, 5379.

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(10) The *N*-oxide promoted Pauson–Khand procedure (ref 4c) affords **2** in 65% yield as an 11:1 mixture of diastereomers.

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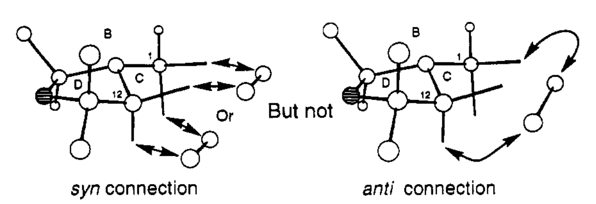
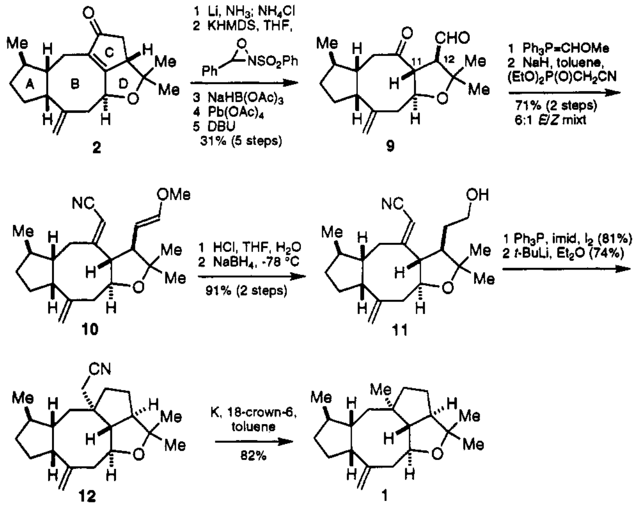


Figure 1. The predicted spatial relationship of C1 and C12 in the ABD ring system of **1**, and two modes (*syn* and *anti*) of connecting them (shown in part for clarity).

Scheme 2



Completion of the synthesis required elaboration of the enone ring of **2** to the C ring of epoxydictymene. Unfortunately, neither reductive nor deconjugative alkylation procedures proved fruitful. While the latter consistently produced complex mixtures of products, the former provided only products with the incorrect stereochemistry at the quaternary C1. These reactions suggested, both directly and through inference, that alkylation at C1 with the desired stereochemistry could be achieved only after inversion of the C12 stereocenter in **2**. This proposition was also supported by exercises in molecular modeling which revealed (Figure 1) that a two-atom bridge between C1 and C12 is more easily accommodated in a *syn* rather than an *anti* fashion.

In order to correct the stereochemistry at C12, the enone ring of **2** was unraveled through a four step sequence (Scheme 2, 54% overall yield) to give the appropriate functionality at an adjacent site. Base treatment (DBU) accomplished the desired epimerization to give a 3:1 mixture of keto aldehydes **9** (major) and a minor diastereomer (not shown). One recycling of the latter afforded a 57% yield of **9**, in which the correct configurations at both C11 and C12 had been established. Selective functional group manipulation of **9** provided, without any further epimerization, primary alcohol **11** in good yield.[11]

In order to reclose ring C, we used an anionic cyclization.[12] Transmetalation (2.2 equiv of *t*-BuLi, Et_2O, −78 °C) of the iodide derived from alcohol **11** gave a 74% yield of nitrile **12** having the complete skeletal and stereochemical arrangement of the natural product. Reductive decyanation[13] completed the synthesis, giving epoxydictymene (**1**) in 82% yield.[14]

Deriving all asymmetry from (*R*)-pulegone and utilizing no protecting groups, the synthesis of (+)-epoxydictymene illustrates the potential of reactions involving alkyne–dicobalt hexacarbonyl complexes for the stereoselective construction of polycyclic ring systems. Also noteworthy was the anionic intramolecular cyclization reaction in the formation of the *trans*-fused 5–5 ring system. To the best of our knowledge, this is the first total synthesis of a *trans*-5–5 containing natural product.

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Supplementary Material Available: Complete physical and spectral data for compounds **1**, **2**, **4–7**, and **9–12** and a ^1H NMR spectrum of the crude product mixture of **7** and **8** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) NOE experiments on derivatives of **9** and on **10** confirmed the stereochemical assignments shown.

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(14) Identical in all respects to the physical and spectral data reported for natural epoxydictymene (ref 1 and the additional data provided to us by Drs. Fuyuhiko Matsuda and Mikiko Sodeoka).