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HIGHLY ENANTIOSELECTIVE TOTAL SYNTHESIS OF NATURAL EPOXYDICTYMENE. AN ALKOXY-DIRECTED CYCLIZATION ROUTE TO HIGHLY STRAINED *trans*-OXABICYCLO[3.3.0]OCTANES

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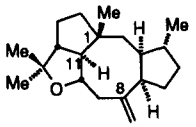
Abstract: An enantioselective synthesis of (+)-epoxydictymene, which involves efficient construction of the strained oxabicyclo[3.3.0]octane subunit by irradiation with iodosobenzene diacetate and iodine in cyclohexane solution, is reported.

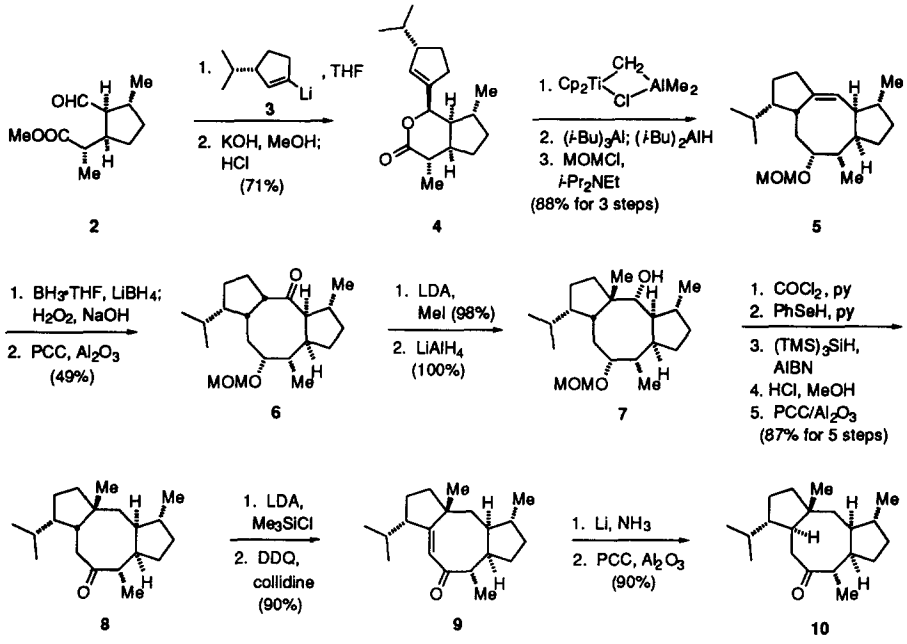
(+)-Epoxydictymene (**1**), a metabolite of the brown algae *Dictyota dichotoma*, is perhaps the structurally most complex member of the fusicoccin diterpenes. The tetracyclic nature of **1** and its absolute configuration were elucidated by Matsumoto and co-workers by means of X-ray crystallographic analysis.[1] Attention is called in par-ticular to the considerable increase in strain energy introduced by the presence of a *trans*-oxa-bicyclo[3.3.0]octane subunit in the western sector. In the only reported synthesis of **1** to date, Schreiber *et al.* utilized a Pauson-Khand reaction to elaborate a dehydro derivative, from which **1** was ultimately produced in 12 additional steps.[2] The successful exploitation of an alkoxy-directed cyclization for accomplishing the same goal with enhanced expediency and versatility is reported here.



1

Our approach began by diastereofacially selective[3] addition of (*S*)-**3**[4] to enantiomerically pure aldehydo ester **2**,[5] so as to provide a 14:86 diastereomeric mixture rich in **4** (Scheme 1). The latter was subjected sequentially to Tebbe olefination,[6] triisobutylaluminum-catalyzed Claisen rearrangement (with ensuing carbonyl reduction),[7] and hydroxyl protection to afford the tricyclic olefin **5**. The task of introducing the remaining C-1 angular methyl group was next pursued. Although we had earlier developed a means for accomplishing this objective by intramolecular syn delivery of a functionalized carbon,[8] it ultimately proved more expedient to prepare ketone **6** and to take advantage of its unidirectional enolization capability. Further, methylation of **6** proceeded ex-

Scheme 1

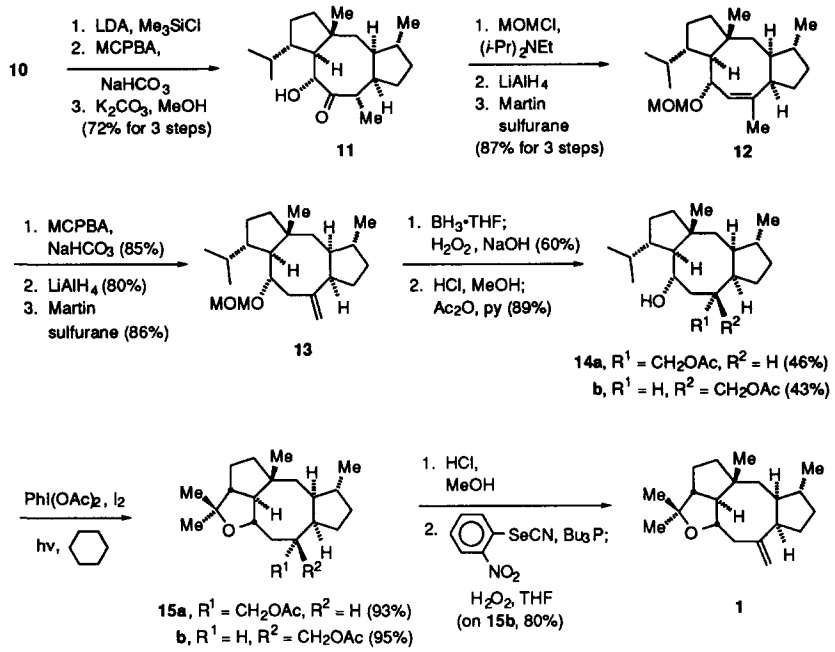


clusively from the β-face as desired. Once assembly of the diterpenoid framework had been completed in this fashion, the superfluous carbonyl was removed by free radical reduction of the derived selenocarbonate,[9] the transannular hydroxyl group was unmasked, and the resulting alcohol was oxidized. The efficiency of the **6** → **8** conversion was exceptionally high.

The overall strategy next called for the specific epimerization of C-11, one of the four carbons commonly shared by a 5- and an 8-membered ring. To this end, **8** was transformed under kinetically controlled conditions into the less substituted silyl enol ether, DDQ oxidation of which[10] led efficiently to **9**. In line with MM2 calculations which showed **10** and several analogs to be invariably more thermodynamically stable than their cis isomers, **9** underwent smooth dissolving metal reduction to deliver **10** in 90% yield.

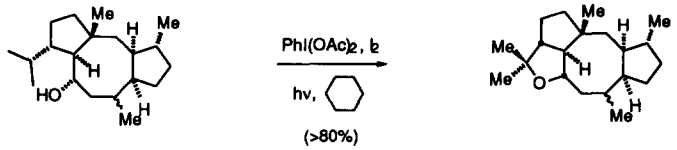
As depicted in Scheme 2, Rubottom oxidation[11] of **10** proceeded with high levels of regio- and stereoselectivity to furnish **11**. In order to set the stage for the projected alkoxy radical cyclization, the MOM derivative of **11** was prepared, subjected to hydride reduction, and dehydrated with the Martin sulfurane reagent,[12] whereupon **12** was isolated in 87% overall yield. The decisive experiment could not yet be performed because of the susceptibility of isolated double bonds to the requisite reagents. Therefore, we next opted to relocate the double bond of **12** by epoxidation, epoxide reduction and dehydration to form **13**, and temporarily mask the exocyclic double bond of

Scheme 2



13 via hydroboration and acetylation to form **14a** and **14b**. Since these epimers were easily separated on silica gel, it proved possible to subject them individually to irradiation in cyclohexane solution containing iodosobenzene diacetate and iodine.[13] Both substrates underwent intramolecular abstraction of the tertiary isopropyl hydrogen and subsequent cyclization to generate the highly strained *trans*-oxabicyclo[3.3.0]octanes **15a** and **15b** with remarkable facility. A main strength of this process is its allowance for the ready assembly of thermodynamically disadvantaged heterocyclic diquinane structural elements in a single step. In order to gauge the generality of this reaction, an inseparable mixture of **16a** and **16b** (ratio 4:1) was also subjected to the same photochemical ring closure conditions. The anticipated dihydro epoxydictymenes **17a** and **17b** were formed in a combined yield exceeding 80% as before.[14] Accordingly, recourse to alkoxy radical intermediates in this manner constitutes a powerful strategy for the elaboration of products closely related in structure to epoxydictymene.

The target molecule was secured by sequential acetate hydrolysis and dehydration via the *o*-nitrophenylselenide derivative.[15] While **15b** was converted to **1** in 80% yield under these conditions, **15a** proved unreactive, presumably as a result of the highly hindered nature of its primary hydroxyl substituent. In the first instance, synthetic (+)-epoxydictymene was obtained



16a, α-methyl
b, β-methyl

17a, α-Me (4:1)
b, β-Me

whose spectroscopic and physical properties (^1H and ^{13}C NMR, MS, $[\alpha]_D$) were identical in all respects with those reported previously.

The ability to carry out the effective closure of the oxabicyclooctane ring in such complicated settings could not have been anticipated in advance and nicely underscores how readily a strained strategic bond can be constructed intramolecularly under the proper conditions. This strategy should lend itself nicely to further exploitation.

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