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ENANTIOSELECTIVE SYNTHESIS OF (+)-CLEOMEOLIDE, THE STRUCTURALLY UNIQUE DITERPENE LACTONE CONSTITUENT OF *CLEOME VISCOSA*

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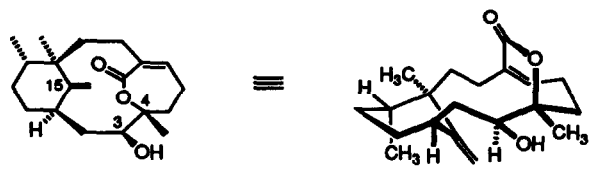
Abstract: The first total synthesis of (+)-cleomeolide has been accomplished in enantioselective fashion from optically pure Wieland-Miescher ketone.

Cleomeolide (**1**) is a cembranoid lactone produced by *Cleome viscosa* Linn,[1,2] a widely distributed Indian herb reputed to possess rubefaciant, vesicant, and anthelmintic properties.[3] The unprecedented structural features of **1**, unambiguously defined by NMR, X-ray, and CD methods,[4] have prompted us to undertake its stereocontrolled construction. The first successful total synthesis of **1**, accomplished in enantiospecific fashion, is herein described.



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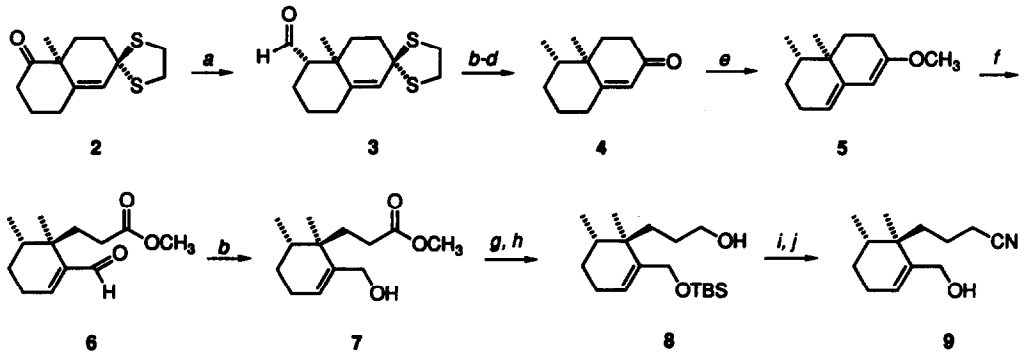
Since the 3-methoxy-3,5-diene **5** was viewed as a key early intermediate in our conceptual retrosynthesis, optically pure Wieland-Miescher ketone[5] was first transformed into **5** as detailed in Scheme I. Differentiation of the two carbonyls was achieved quantitatively by selective dithioketalization[6] to give **2** whose homologation to **3** resulted from condensation with methoxymethylenetriphenylphosphorane[7] and ensuing acid hydrolysis (82%). Following sodium borohydride reduction, the major carbinol (α/β = 7:1) was chromatographically separated from the minor diastereomer and reduced to the dimethyl level in 76% yield by exposing the mesylate to $LiBHEt_3$ in order to maintain stereochemical integrity. With the acquisition of **4** (90-94%) by hydrolysis with thallium trinitrate trihydrate,[8] a new and efficient route to this octalone, $[\alpha]_D^{25}$ +185.6° (*c* 1.63, $CHCl_3$), had been developed.[9,10]

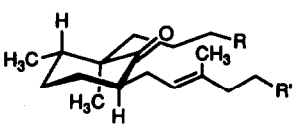
Acid-catalyzed condensation of **4** with trimethyl orthoformate in a methanol-DMF solvent system gave **5** (89%), the vinyl ether linkage in which was cleaved upon oxidation with *m*-chloroperbenzoic acid and subsequent silica gel chromatography.[11] Direct chemoselective reduction of this aldehydo ester furnished **7** in 59% overall yield. A series of four conventional transformations then gave rise very efficiently to the cyano alcohol **9**.

Scheme I



[a] $Ph_3\overset{+}{P}CH_2OCH_3\ Cl^-$, $KN(SiMe_3)_2$, THF, 0 °C → rt; 10% HCl. [b] $NaBH_4$, MeOH. [c] CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; $LiBHEt_3$, THF, rt. [d] $Tl(NO_3)_3 \cdot 3H_2O$, MeOH-THF. [e] $HC(OCH_3)_3$, (TsOH), MeOH, DMF. [f] MCPBA, benzene-hexanes, 0 °C → rt; silica gel. [g] TBSCl, imid, DMF. [h] $LiAlH_4$, THF, 0 °C. [i] CH_3SO_2Cl, Et_3N, CH_2Cl_2; KCN, 18-crown-6, DMF. [j] Py·HF, CH_3CN, H_2O.

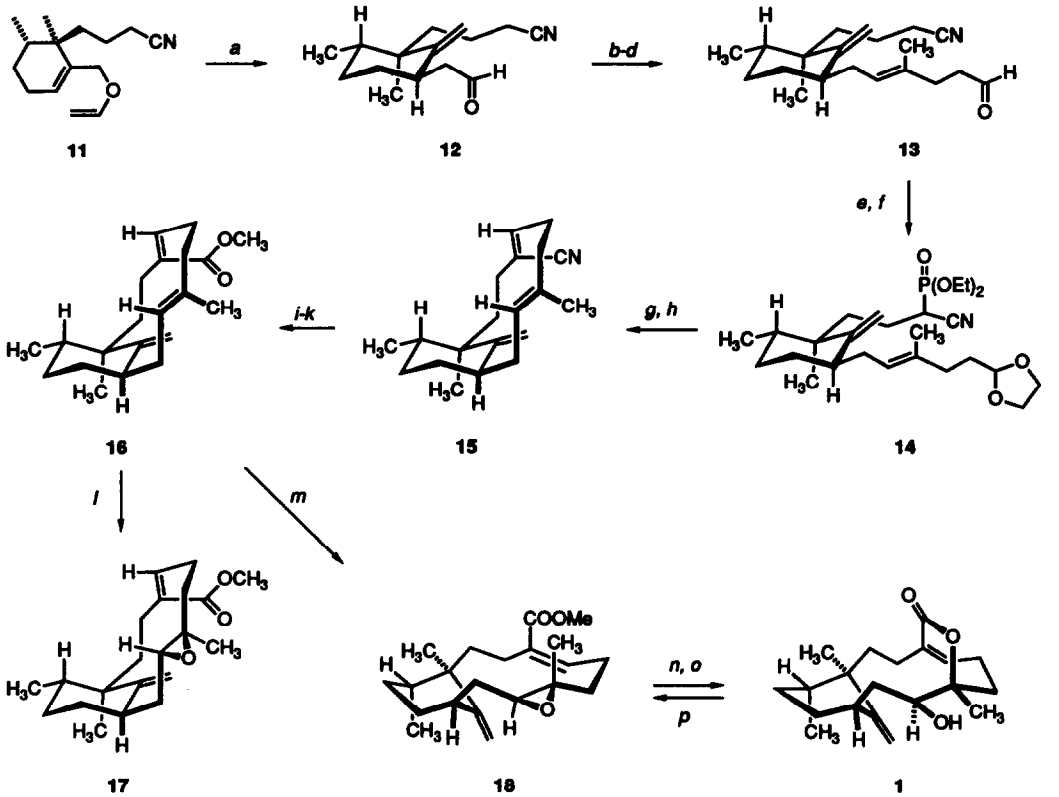
The involvement of **9** was predicated on our awareness[12] that ketones of the general type depicted by **10** possess carbonyl functionality too sterically hindered to be attacked by such nucleophiles as $Ph_3P{=}CH_2$, CH_3CeCl_2, and Me_3SiCN/KCN/18-crown-6/100,000 psi,[13] as well as the Lombardo[14] and Tebbe reagents.[15] The expectation was that the requisite C-15 methylene group could be alternatively installed by preincorporation of an allylic carbinol as in **9** as a prelude to Claisen rearrangement. Accordingly, **11** was prepared in 73% yield by mercuric(II) trifluoroacetate-promoted transetherification[16] with ethyl vinyl ether and heated to 200 °C in xylene solution (sealed tube). While the desired [3,3] sigmatropic reaction is notably efficient (95%), steric factors introduced by the other cyclohexyl substituents cause **12** to be less prevalent than its epimer (ratio 1:2.7). This disadvantage is partially offset by the remarkable ease with which these isomers can be chromatographically separated. The structural assignments rest firmly on combined 2-D COSY and nOe measurements.



10

Elaboration of the "lower" sidechain was achieved next by implementation of a second Claisen sequence. Notably, both alcohols formed upon addition of 2-propenylmagnesium bromide to **12** were smoothly transformed into **13** (92%).[17] In preparation for the requisite macrocyclization, **13** was converted into its acetal under the Noyori conditions[18] and the α-cyano carbanion was condensed with diethyl chlorophosphate[19] (86%). Once deprotection had been completed, reaction of the aldehyde with K_2CO_3 and 18-crown-6 in toluene at rt[20] afforded **15** (38%). This ring closure presumably occurs while both functionalized sidechains are equatorially disposed since the cyano triene was found to adopt the somewhat coiled conformation shown (nOe).

Scheme II



[a] Xylene, 200 °C, sealed tube. [b] CH_2=C(MgBr)CH_3, THF, -78 °C; H_2O. [c] CH_2=$CHOC_2H_5$, $Hg(OCOCF_3)_2$. [d] Benzene, 170 °C, sealed tube. [e] $(Me_3SiOCH_2)_2$ TMSOTf, CH_2Cl_2, -78 °C. [f] LDA, THF, -78 °C; ClP(O)$(OC_2H_5)_2$. [g] TsOH, H_2O, acetone. [h] K_2CO_3, 18-crown-6, toluene, 20 °C. [i] Dibal-H, toluene, ether, -78 °C → 0 °C; silica gel. [j] $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, t-BuOH. [k] CH_2N_2, ether. [l] MCPBA, $NaHCO_3$, CH_2Cl_2 [m] I_2, Ag_2O, H_2O, dioxane. [n] 3.5% KOH in MeOH, reflux. [o] 5% HCl, THF. [p] 3.5% KOH in MeOH, Δ; H_3O^+; CH_2N_2.

Since the transformation of **15** to ester **16** was expectedly not accompanied by a meaningful topographical change, a fascinating tactical issue now had to be addressed. As a consequence of preexisting crystallographic data,[1,2] the macrocyclic ring of cleomeolide was recognized to be projected quasi-axially from the methylenecyclohexane subunit (see **1**). However, variable-temperature NMR studies performed on **15** and **16** suggested that neither was prone to reside preferentially in the alternative six-ring chair conformation related to that adopted by **1**.[21] As a consequence, the direct capture by **16** of electrophilic reagents, as in the conversion to **17** by peracid oxidation, proceeds from the wrong face of the trialkyl-substituted double bond to be serviceable.

We hypothesized that proper conformational realignment might well accompany the repositioning of the oxirane ring on the sterically more hindered inner surface of this center of unsaturation. After some experimentation, it was found that iodine and silver(I) oxide in aqueous dioxane[22] combine to provide the desired diastereofacial outcome, although in modest yield (28%).

Relevantly, a remarkable three-dimensional realignment operates within **18**, $[\alpha]_D^{20}$ -67.4° (*c* 0.27, $CHCl_3$), that features adoption of a geometry akin to that of cleomeolide. This outcome was evidenced not only on the basis of nOe studies, but also by conversion of **1** to the identical epoxy center, $[\alpha]_D^{20}$ -71.6° (*c* 0.55, $CHCl_3$), through saponification, acidification, and esterification with diazomethane.[2] Most important to our current concerns, alkaline hydrolysis of **18** made available the carboxylic acid, which cyclized to **1** with 30% efficiency under acidic conditions. Since spectroscopic comparisons showed our product to be identical to **1**, the total synthesis of (+)-cleomeolide was thereby completed.

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