

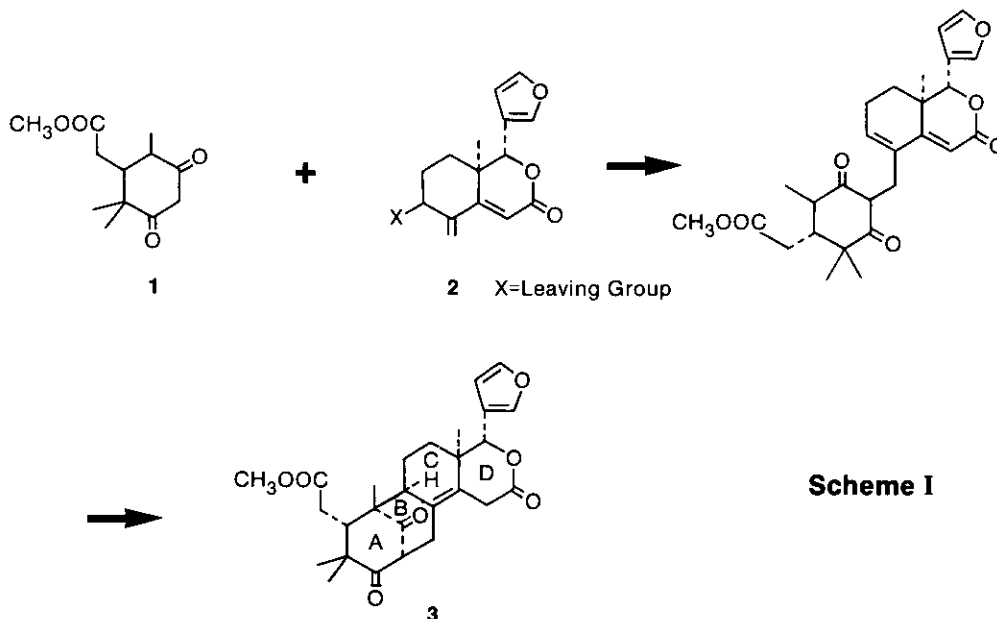
STUDIES TOWARDS THE TOTAL SYNTHESIS OF MEXICANOLIDE.
 STEREOSELECTIVE CONSTRUCTION OF THE CD RING SEGMENT FOR A
 CONVERGENT APPROACH¹

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Abstract — The CD ring segment **18** required for a convergent approach towards the total synthesis of the limonoid mexicanolide (**3**) has been prepared in a highly stereoselective manner.

As illustrated in Scheme I, the double Michael addition of diketo acid **1** (ring A) to diene lactone **2** (rings C and D) presents itself as an attractive approach towards the total synthesis of mexicanolide (**3**),² a limonoid found in the species *Cedrela odorata* and in plants of the genera *Khaya* and *Xylocarpus*. We have been pursuing this convergent synthetic approach to the modified triterpenoid and now wish to describe an efficient synthesis of a CD ring segment of the type **2**.

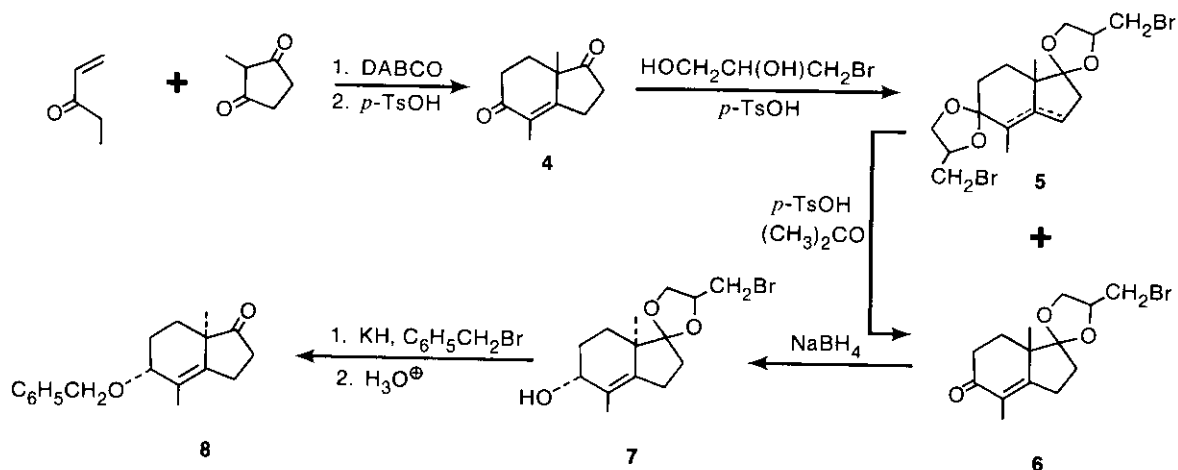


Scheme I

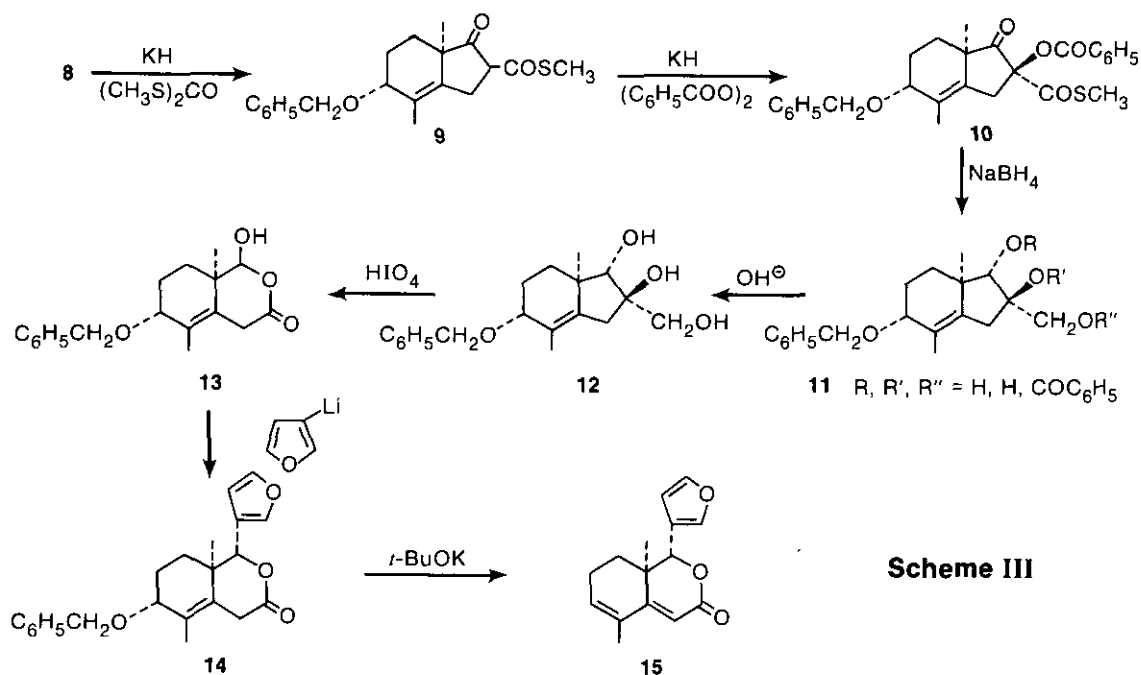
Our synthetic plan called for the modification of the Wieland-Mischner ketone analog **4** to assemble the bicyclo[4.4.0]decanolide ring system present in the target molecule. For this purpose, 2-methylcyclopentane-1,3-dione³ was subjected to Michael reaction with ethyl vinyl ketone in 1,2-dimethoxyethane (DME) in the presence of 1,4-diazabicyclo[2.2.2]octane⁴ at room temperature and the Michael adduct thus obtained was treated with *p*-toluenesulfonic acid in refluxing toluene to give enedione **4** (Scheme II) in 98% yield.⁵ The saturated five-membered ketone was selectively protected in the form of bromomethylethylene ketal as follows. Treatment of **4** with 3-bromo-1,2-propanediol and *p*-toluenesulfonic acid in refluxing benzene resulted in the formation of an equimolar mixture of ketals **5** and **6** which, without separation, was exposed to *p*-toluenesulfonic acid in acetone at room temperature. Under these conditions, selective cleavage of the allylic ketal present in **5** occurred and the desired monoketal **6** was isolated in 74% yield. Subsequent reduction of ketal **6** with sodium borohydride in methanol gave an 83% yield of the corresponding alcohol **7**.⁸ Only the *cis*-isomer was formed presumably as a result of hydride attack from the less hindered side of the molecule.

Williamson reaction of alcohol **7** with benzyl bromide and potassium hydride in DME gave the corresponding benzyl ether. The crude material was immediately subjected to hydrolysis under carefully controlled conditions (hydrochloric acid in aqueous acetone, $-70^{\circ}\rightarrow 0^{\circ}\text{C}$, 3 h) to furnish ketone **8** in 72% yield.

Scheme II

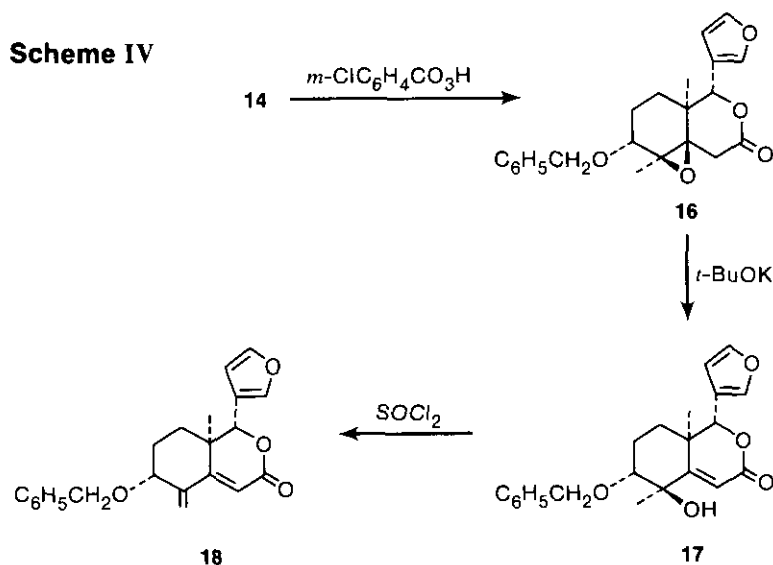


The formation of the bicyclo[4.4.0]decanolide portion of **2** was accomplished in the following manner. Ketone **8** was treated with *S,S'*-dimethyl dithiocarbonate⁹ and potassium hydride in hexamethylphosphoramide (HMPA) at room temperature to give β -keto thiolester **9**. Further treatment of the potassium salt, generated from **9** with potassium hydride, with benzoyl peroxide in DME at ambient temperature gave rise to keto benzoate **10** as a single diastereomer.¹⁰ Reduction of both the ketone carbonyl and the thiolester group¹¹ was effected by sodium borohydride in ethanol. During the reduction, partial migration of the benzoyl group also occurred resulting in a mixture of three dihydroxy benzoate **11** which gave, in 25% overall yield, crystalline triol **12** (mp 129.5°C) upon heating with lithium hydroxide in aqueous methanol. The oxidative cleavage of **12** proceeded readily when exposed to periodic acid in acetone-water. The epimeric lactones **13** (5:1), thus formed in 60% yield, were found to undergo addition with β -lithiofuran in ether in the presence of HMPA at room temperature. Acidic workup (hydrochloric acid) gave, interestingly, the desired lactone **14** as the sole diastereomer in 43% yield. The stereochemistry of this compound was confirmed by conversion into the known diene lactone **15**¹² by brief treatment with potassium *t*-butoxide in DME.



To complete the synthesis of the required CD ring segment of type **2**, it remained to modify the β,γ -unsaturated lactone moiety present in compound **14**. Towards this end, lactone **14** was subjected to epoxidation with *m*-chloroperbenzoic acid in chloroform at room temperature. Epoxide **16**, which was formed as the only stereoisomer¹⁰ in 50% yield, was subsequently treated with potassium *t*-butoxide in DME at 0°C to give alcohol **17** (65% yield). Finally, exposure of a pyridine solution of alcohol **17** to thionyl chloride at 0°C provided two principal products, identified as the desired diene lactone **18** (30% yield) and the corresponding endo-double bond isomer (16% yield).

Studies on the outlined convergent approach towards the total synthesis of mexicanolide are being continued.



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REFERENCES AND NOTES

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