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EFFICIENT APPROACH TO THE OPPOLZER-KAMETANI INTERMEDIATE FOR ESTRONE METHYL ETHER USING THE CONJUGATE ADDITION-ENOLATE METHYLATION OF THE CYCLOPENTENONE CONTAINING AN α-APPENDED BENZOCYCLOBUTANE MOIETY

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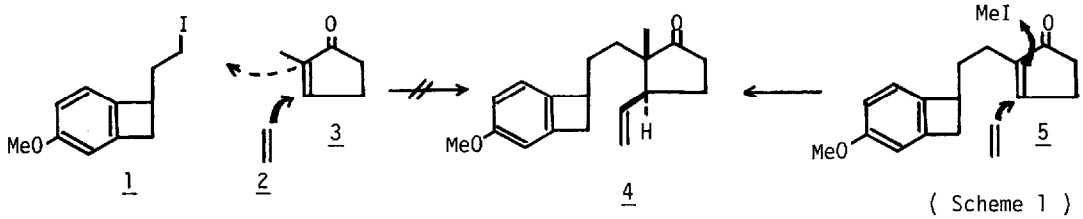
Summary: Simple synthesis of (±)-estrone methyl ether by the conjugate addition-enolate methylation of the 2-alkylcyclopentenone followed by the intramolecular Diels-Alder reaction of the o-quinodimethane, and discussions for the diastereoselectivity in the enolate-methylation based on the MM2 transition structure model are presented.

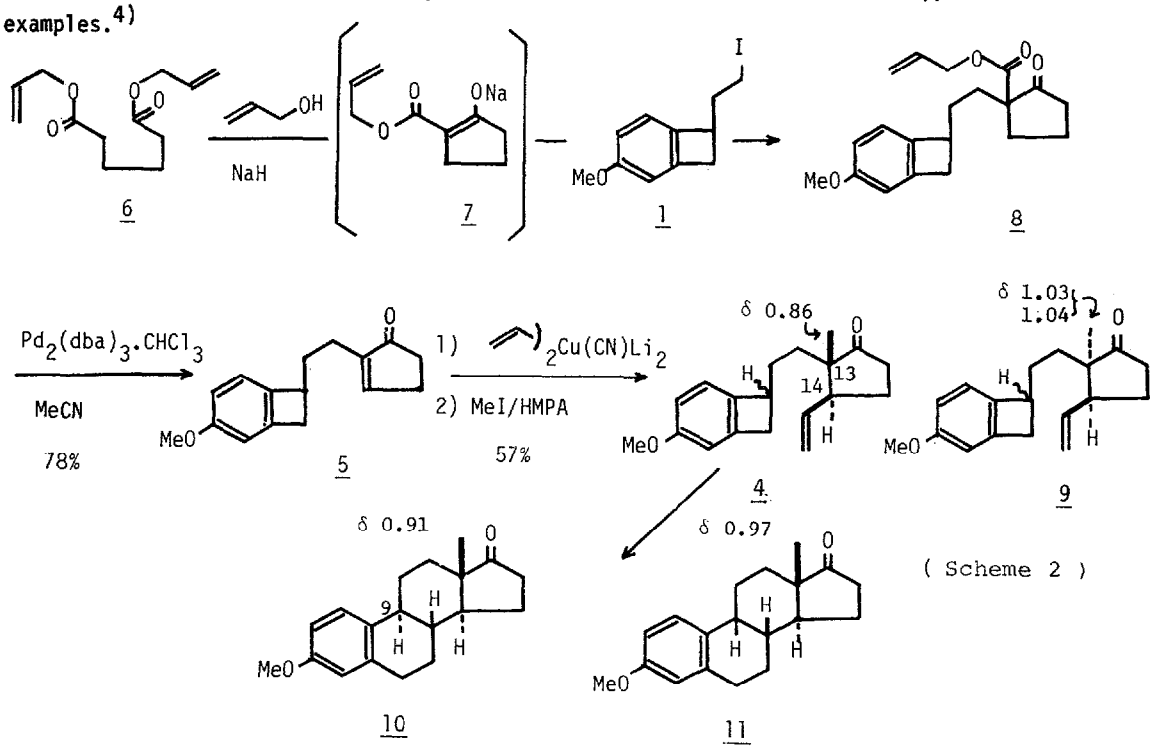
The conjugate addition-enolate alkylation is one of the ideal approaches to 2,2,3-trialkylcyclopentanones; e.g. **1**,**2**,**3** - **4**.[1)] This approach, however, involves two problems; regio- and stereoselectivities. With the less reactive alkylating reagent such as **1**, the enolate exchange promoted by the rapid proton transfer competes with the alkylation and regioselectivities and chemical yields are generally low.[2)] Indeed, in syntheses of **4**,[3)] an intermediate for the Oppolzer-Kametani reaction, this difficulty was avoided by the use of "reactive" alkyl α-haloacetate[4)] but a number of steps were then required to convert the added ester group into the desired alkylbenzocyclobutene moiety in **4**. On the other hand, stereoselectivities are influenced by the structure of 2,3-dialkylcyclopentanone enolate. Most reported results suggest that the stereochemistry of the enolate alkylation is controlled by the steric approach factor (less hindered side attack).[1b)] We recently reported the diastereoselective methylation of 2,3-dialkylcyclopentanone enolate having two bulky chains, and in this reaction, the major product was formed by the "cis methylation" to the alkyl group at 3-position.[5)] We report here the simple synthesis of estrone methyl ether (**10**) by the conjugate addition-enolate methylation using the enone **5** (Scheme 1) followed by the intramolecular Diels-Alder reaction of the benzocyclobutane **4**.



(Scheme 1)

At first, we examined the regio- and stereoselectivities in the conjugate addition-enolate methylation. The enone **5** was synthesized by our procedures.[6)] The Dieckmann condensation of the diallyl adipate (**6**) (allyl alcohol/NaH/benzene reflux) followed by alkylation of the resulting β-keto ester **7** with the iodide **1** gave the alkylated product **8** in 66% overall yield. The palladium-catalyzed decarboxylation-dehydrogenation[6a)] of the β-keto ester **8** using $Pd_2(dba)_3.CHCl_3$ at MeCN reflux gave the enone **5** in 78% yield and its exocyclic

isomer was also formed in 19% yield. The conjugate addition of $(CH_2=CH)_2Cu(CN)Li_2$[7] to the enone **5** at -70°C in ether, followed by addition of an excess HMPA at -30 °C and methylation with MeI at -40 °C gave a 70:30 mixture of **4** and **9** in 57% combined yield[8] (Scheme 2). Moreover stereoselectivities in the enolate-methylation were examined using the enone **12** and various organocuprates (55-65% yield) (Table 1). In all cases, the major isomer was formed by the cis methylation to the nucleophile.[9] These stereoselections were opposite to earlier examples.[4]



(Scheme 2)

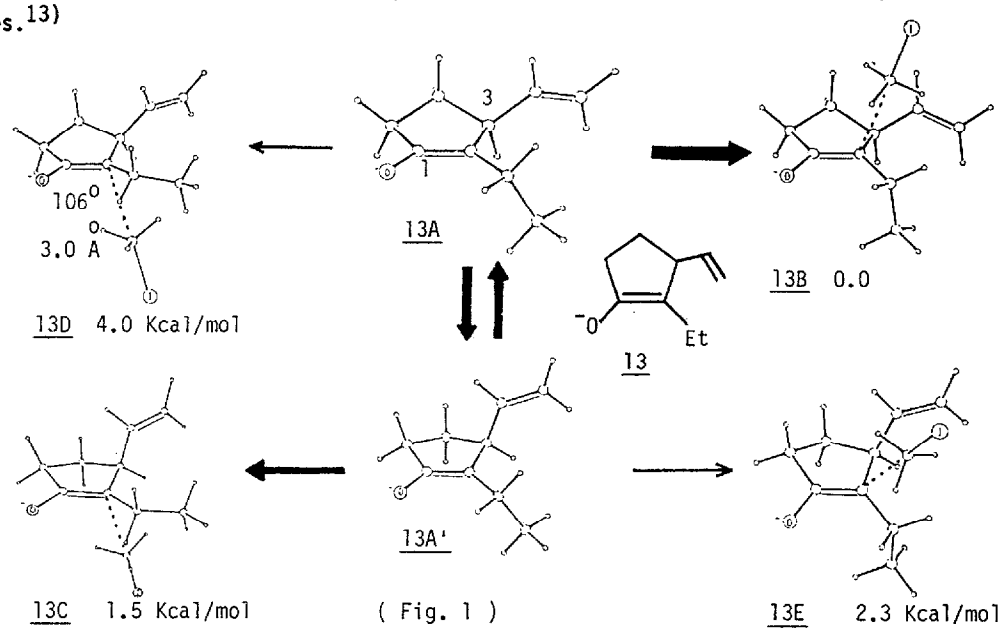
Table 1. Diastereoselectivites in the conjugate addition-enolate methylation of the enone 12.

12		C(13β)-Me		C(13α)-Me
$(CH_2=CH)_2CuLi$	78 [a]	δ 0.83 [b]	22 [a]	δ 1.01 [b]
$(\quad)_2CuLi$	76 [a]	δ 0.87 [b]	24 [a]	δ 1.01 [b]
Bu_2CuLi	88 [c]	-	12 [c]	-

a) The ratio of β- and α-Me, determined by ^{1}H-NMR spectrum.
b) The characteristic ^{1}H-NMR spectrum peaks of the C(13β)- and C(13α)-Me.
c) The ratio of β- and α-Me, determined by HPLC.

In order to analyze the preferential formation of C(13) β-Me isomer in the enolate methylation, the MM2 calculations on the α- and β-methylation of the 2-ethyl-3-vinylcyclopentanone enolate (**13**), as a simplified model, were performed[10] (Fig. 1). Based on the assumption that the kinetic enolate methylation can be controlled by an early reactant-like transition state, first, the stable conformations of the enolate **13** were created. The MM2

calculations indicated that the enolates **13A** and **13A'** were the two lowest energy conformers. In these conformers the C-H bond at the exo-allylic position is coplanar with the enolate π-system due to the allylic strain, and the methyl group at the exo-allylic position is opposite to the vinyl group at C(3)-position, to minimize steric interactions. Then the transition state energies in the α- and β-methylations of the enolate **13A, 13A'** were calculated, respectively. In these calculations the distance (3.0 Å)[11] and the attacking angle (106°)[12] of the methyl iodide to the C(2)-carbon, and the two sp^2 hybridized carbons of the enolate were fixed and the geometry for the rest of system was optimized. The structures and strain energies of likely intermediates in the kinetic enolate methylation are shown in Fig. 1. It is clear that the energy difference of the enolates **13B** and **13C** having the relatively lower energies could be used to rationalize the observed preferential β-methylation, although the calculated energy difference (1.47 Kcal/mol) was rather larger than the experimental results. Our modeling described here is, of course, quite crude since the complexity of aggregated metal enolate structures was neglected. These considerations based on calculations, however, would be sufficient to analyze (or predict) the stereoselectivity in organic synthetic studies.[13]



(Fig. 1)

The relative stereochemistry between C(13) and C(14) in the major isomer **4**, separated from the minor isomer **9**, was confirmed by the conversion of **4** to the (±)-estrone methyl ether (**10**). Diels-Alder reaction of **4** in o-dichlorobenzene at 180 °C gave a 90 : 10 mixture of (±)-estrone methyl ether (**10**)(m.p. 141-142 °C; lit[14] 143-144 °C) and its C(9)-epimer **11** in 85% yield. The ^{1}H-NMR, IR, MS spectral properties of the synthetic **10** were identical with the reported spectral data.[15] Thus the short approach (4 steps from **6**; Dieckmann condensation-alkylation, Pd-catalyzed enone formation, conjugate addition-enolate methylation, and Diels-Alder reaction) reported herein provides an eminently practical route for the total synthesis of (±)-estrone and congener steroids.[16] Development of this methodology combined with the enantioselective conjugate addition for the construction of chiral steroid skelton is in progress.

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