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Studies on Intramolecular Cr(0)-Promoted [6π+2π] Cycloaddition Reactions. Synthesis of β-Cedrene

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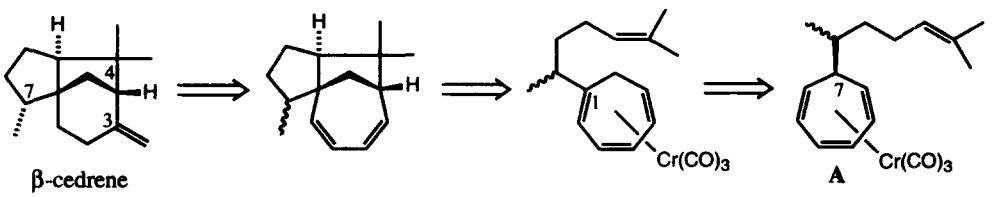
Abstract: Intramolecular metal-promoted [6π+2π] cycloaddition followed by Tl(III)-mediated oxidative ring contraction affords β-cedrene.

Metal-promoted higher-order cycloaddition reactions have recently emerged as powerful methods for the rapid assembly of functionally elaborate bicyclic systems.[1] In general, these pericyclic processes can be effected by either photochemical or thermal activation and are characterized by their high chemical efficiencies and significant levels of stereoselectivity. The intramolecular versions of these transformations are capable of delivering polycyclic systems suitable for subsequent conversion into a variety of natural product targets.[2] In this paper, a synthesis of β-cedrene[3,4] featuring a chromium(0)-promoted, intramolecular [6π+2π] cycloaddition as the key ring forming process is described.[5] The basic strategy for this synthesis is depicted in Scheme I. Keys to the success of this endeavor include the ability to rapidly isomerize the readily available 7-substituted cycloheptatriene complex (**A**) to the more reactive 1-substituted isomer as well as achieving regioselective contraction of the seven-membered ring portion of the initially formed cycloadduct to the six-membered carbocycle required in the target molecule. The strategic bond formations projected for this approach to the cedrane ring system, while tactically distinct, are reminiscent of the Fallis intramolecular Diels-Alder-based synthesis reported previously.[5e] Rapid access to the building blocks for complex (**A**) was also an important consideration during the planning stages of the current synthesis work.

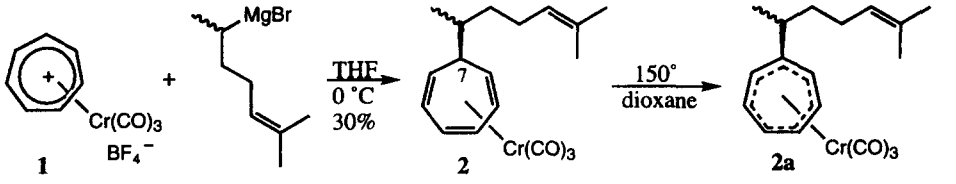
Scheme I



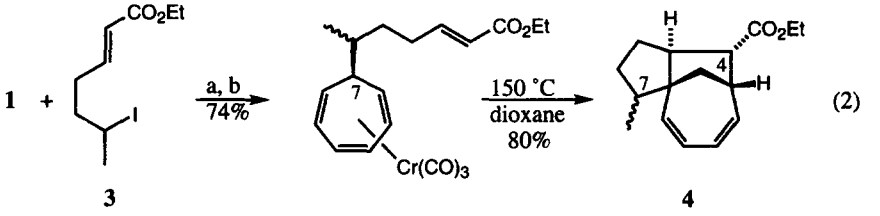
β-cedrene **A**

Assembly of the cycloaddition substrate by addition of the Grignard reagent derived from 6-bromo-2-methyl-2-heptene[6] to the tropylium cation complex (**1**)[7] proceeded relatively smoothly (Eq. (1)). Consistent with ample literature precedent,[8] the *exo*-isomer at C7 was produced exclusively in this reaction. In earlier studies, it was noted that the 1-substituted cycloheptatriene isomer underwent cycloaddition in preference to the other triene isomers.[9] Consequently, it was envisioned that, in a single operation, a series of Cr(0)-facilitated 1,5-hydrogen shifts[10] would be brought about by heating substrate **2**[11] at an appropriate temperature, while throughout the

isomerization event, cycloaddition of the 1-isomer would occur in preference to other competitive pathways to deliver the desired tricyclic adduct. In the event, none of the anticipated product was observed after heating **2** at 150 °C for 2 days in a sealed tube, instead only a mixture of all possible isomeric cycloheptatriene complexes **2a** was isolated. Since unactivated alkenes have previously been shown to be viable 2π partners in intramolecular, metal-promoted [6π+2π] cycloadditions,[2] it was assumed that steric hindrance played a significant role in the failure of the current reaction to proceed as expected. In an effort to overcome these problems a more reactive and less hindered 2π partner was examined within the cycloaddition substrate.

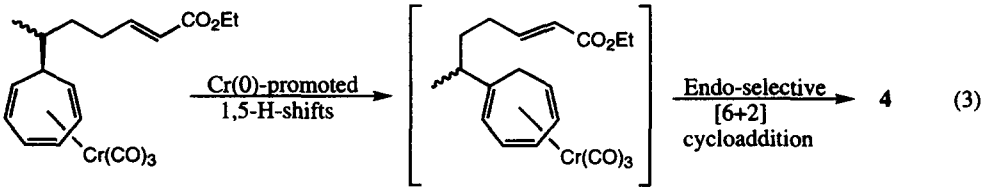


The more functionalized cycloaddition substrate was prepared in good yield by treating tropylium cation complex (**1**) with the mixed copper-zinc reagent derived from iodide **3**.[12] To our delight, heating this material in dioxane (sealed tube, 150 °C) afforded the key tricycle **4**[11] as a 1 : 1 mixture of epimers at C7 (cedrene numbering) in excellent yield.[13] As suggested above this reaction was presumed to proceed via a series of rapid Cr(0)-promoted 1,5-H shifts of the *endo*-proton at C7 in the starting triene complex followed by selective cycloaddition of the corresponding C1 isomer (Eq. (3)). The relative stereochemistry of the two incipient bridgehead protons in **4** stems from the *endo* nature of the cycloaddition process.[2]

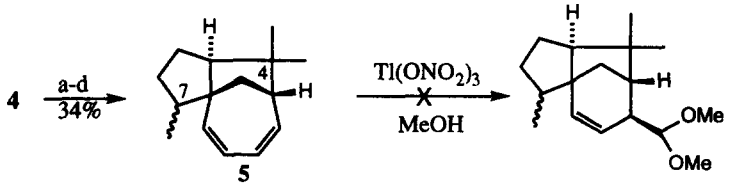


3 4

a) Zn, THF, TMSCl, rt b) CuCN, LiCl, 0 ° to -78 to 0 °C



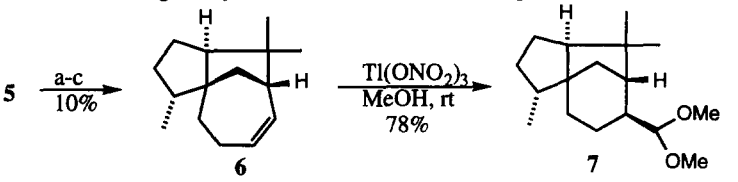
Routine processing of the C4 position in **4** afforded the requisite gem-dimethyl intermediate **5**,[11] and at this juncture direct conversion of the conjugated diene system into the requisite ring contracted species became the focal point of the synthesis. In light of the success of the so-called Taylor-McKillop oxidative rearrangement protocol[14] for effecting similar ring contractions in related bicyclic substrates,[15] compound **5** was exposed to excess $Tl(ONO_2)_3$/MeOH at 0 °C. Unfortunately, multiple products were isolated from this reaction with only insignificant quantities of the desired tricycle being produced.



(4)

a) LDA, THF-HMPA, MeI; b) DIBALH, THF, 0 °C; c) TsCl, py, 0 °C, d) $LiEt_3BH$, THF, 0°C

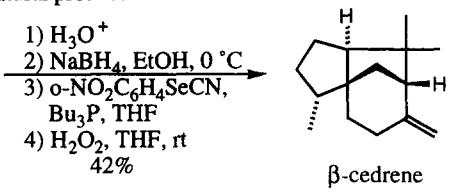
An alternative substrate that was expected to be more amenable to undergoing the rearrangement was prepared in routine fashion by regioselective epoxidation of the less hindered double bond of the cycloheptadiene system followed by catalytic hydrogenation that gave the corresponding saturated alcohol. The sequence was completed by effecting dehydration to the alkene **6**[11] with the Burgess reagent.[16] It is noteworthy that the mixture of C7 epimers could be conveniently separated at the alcohol stage, and consequently, only the compound exhibiting the correct C7 stereogenicity was carried forward in the sequence.



(5)

a) mClPBA, CH_2Cl_2, 0 °C, b) H_2, Pd/C, MeOH; c) $MeO_2CNSO_2NEt_3$, PhH, 60 °C

In contrast to the results with diene **5**, treatment of alkene **6** under the Tl(III) conditions now proceeded smoothly to deliver the desired tricycle **7**[11] as a single regio- and stereoisomer in 78% yield. Hydrolysis of the acetal function followed by carbonyl group reduction and elimination of the resultant primary alcohol using the Grieco protocol[17] afforded β-cedrene, which was shown to be identical (^1H NMR, ^{13}C NMR, IR, HRMS) to a commercial sample of the natural product.



(6)

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13. *Typical cycloaddition conditions:* A solution of the chromium complex (1.277 g, 3.34 mmol) in freshly distilled 1,4-dioxane (120 mL) was added to a Carius tube. The mixture was freeze-pump-thaw-degassed and sealed under vacuum, and then heated at 150-155 °C for 36 h in a silicone oil bath. The reaction mixture was cooled, filtered through Celite, and the solvent removed *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, EtOAc/hexanes 3 : 97) to give 658 mg (80%) of cycloadduct **4** as a 1 : 1 mixture of diastereomers: colorless oil; IR (neat) ν 3016, 2954, 2871, 1730, 1455, 1374 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 1.5H), 1.03 (d, J = 7.1 Hz, 1.5H), 1.15 (m, 1H) 1.25 (t, J = 7.1 Hz, 3H), 1.43 (m, 0.5H), 1.62 (m, 1H), 1.67-1.98 (m, 4 H), 2.14 (d, J = 11.9 Hz, 0.5H), 2.59 (dd, J = 9.1, 6.1 Hz, 0.5H), 2.77 (dd, J = 9.2, 6.1 Hz, 0.5H), 2.93-3.04 (m, 2H), 4.09-4.20 (m, 2H), 5.62 (dd, J = 11.4, 7.1 Hz, 1H), 5.72-5.83 (m, 2H), 5.88 (d, J = 10.9 Hz, 0.5H), 6.16 (d, J = 11.2, 0.5H). Anal. calcd. for $C_{16}H_{22}O_2$; C, 78.01; H, 9.00. Found: C, 78.14; H, 9.06.
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