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Formal Substitution at Both Bridgeheads of a Bicyclo[2.2.2]oct-5-en-2-one and its Application to a Synthesis of (±)-Modhephene

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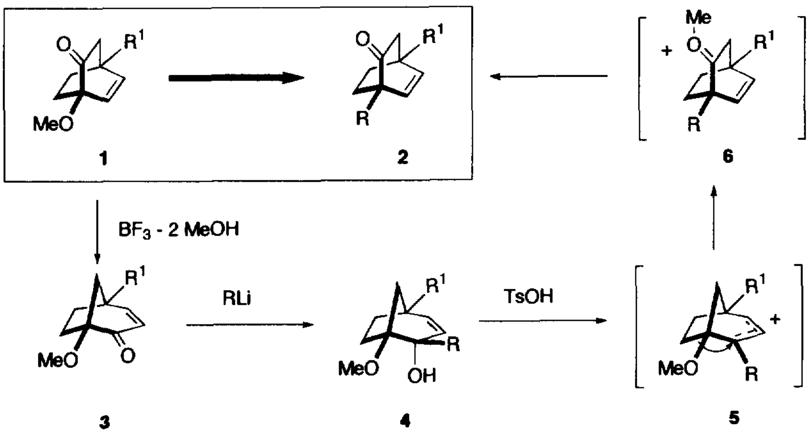
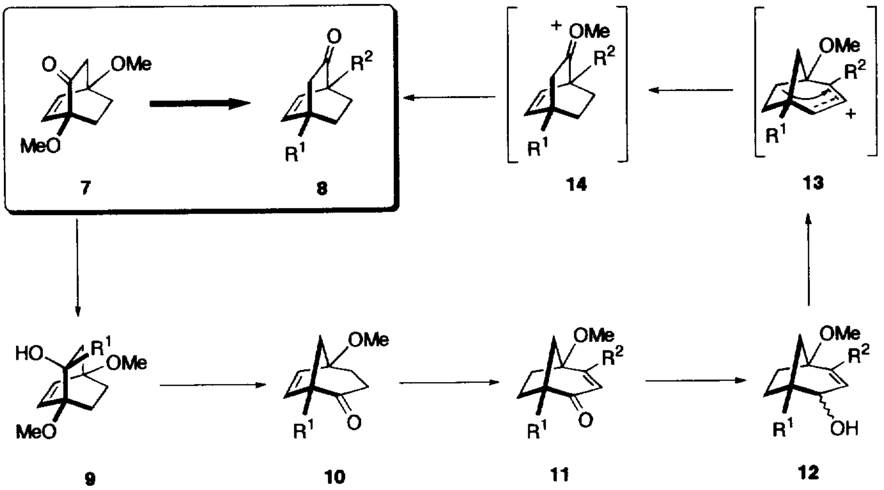
Abstract: Synthesis of a propellane sesquiterpene (±)-modhephene (**23**) was achieved on the basis of a novel procedure to introduce the desired alkyl groups at both bridgeheads of a bicyclo[2.2.2]oct-5-en-2-one. Copyright © 1996 Elsevier Science Ltd

Bicyclo[2.2.2]oct-5-en-2-ones are potential bridged compounds that are convertible into [m-n] fused-ring products by means of oxy-Cope rearrangement[1] and photochemical [1,2]-acyl migration (oxa-di-π methane rearrangement).[2] We have reported the formal bridgehead substitution of 1-methoxybicyclo[2.2.2]oct-5-en-2-ones (**1**), outlined in Scheme 1, in connection with our studies on rearrangement approaches to cyclic skeletons.[3] This procedure facilitates the tedious route for preparation of a polysubstituted 1,3-cyclohexadiene for a Diels-Alder reaction with a ketene equivalent and/or the regioselectivity of the Diels-Alder reaction governing the mode of substituents of the bicyclic ketone. However, the handling of the C-4 substituent (R^1) had uninvestigated. We wish to report herein a method to introduce the desired substituents at both C-1 and

Scheme1



Scheme 2



C-4 bridgeheads of a bicyclo[2.2.2]oct-5-en-2-one as shown in Scheme 2.

The successful conversion of allyl alcohols **4** into ketones **2** in Scheme 1 seemed to suggest the possibility of the transformation of allyl alcohols **12** into a ketone **8** by a pinacol-type rearrangement through an allyl cation **13**. The allyl alcohols **12** would be derived from an α, β-unsaturated ketone **11** ($R^2 = H$) via a 1,4-addition reaction of an organometallic reagent, such as $(R^2)_2CuLi$, followed by conversion into the α, β-unsaturated ketone **11** ($R^2 \neq H$) and then the reduction of the carbonyl. A precursor of the conjugated ketone **11** ($R^2 = H$) would be a ketone **10**, a predominant product of the pinacol-type rearrangement of an alcohol **9**.[4] The alcohol **9** should be the major product derived from a reaction of the ketone **7** with an organometallic reagent (R^1M). This overall transformation means the desired substitution of both bridgehead methoxyl groups of **7** is feasible.

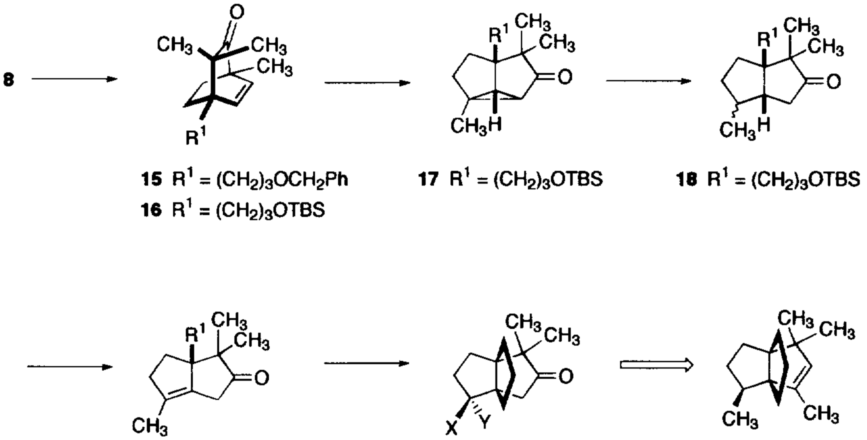
The conversion of **7** into **8** ($R^1 = (CH_2)_3OBn$, $R^2 = CH_3$) was carried out as follows. The addition of 3-benzyloxypropylmagnesium bromide to **7**[5] at room temperature gave the exo alcohol **9** ($R^1 = (CH_2)_3OBn$) in 61% yield along with the endo isomer in 37% yield.[6] The alcohol **9** was converted into the ketone **10** ($R^1 = (CH_2)_3OBn$) in 87% yield by treating with TsOH (10 mol %) in boiling benzene for 15 min. Sequential treatment of **10** with hydrogen and 5% Pt-C, potassium *t*-butoxide and then allyl chloroformate in THF, and palladium acetate in boiling acetonitrile[7] for 1 h gave the α, β-unsaturated ketone **11** ($R^1 = (CH_2)_3OBn$, $R^2 = H$) in 79% overall yield. A conjugate addition reaction of $(CH_3)_2CuLi$ to **11** ($R^1 = (CH_2)_3OBn$, $R^2 = H$) in ether followed by an α-bromination (LDA, TMSCl, and NBS) and then the dehydrobromination (Li_2CO_3 in DMF) formed **11** ($R^1 = (CH_2)_3OBn$, $R^2 = CH_3$) in 79% overall yield. Reduction of the latter with DIBALH to yield **12** ($R^1 = (CH_2)_3OBn$, $R^2 = CH_3$) followed by treatment with an equimolar amount of TsOH in boiling benzene for 30 min gave the ketone **8** ($R^1 = (CH_2)_3OBn$, $R^2 = CH_3$) in 95% overall yield.

Scheme 3 shows transformation of the ketone **8** into a propellane **21**,[8l] a key intermediate of (±)-modhephene (**23**).[8] The ketone **8** was led to **15** in 99% yield, by treatment with potassium *t*-butoxide (4 equiv) and iodomethane (5 equiv) in a mixture of THF and DMF. Since the benzyl protecting group of **15** was somewhat labile to photochemical reaction conditions, the ether bond was cleaved by treatment with BBr_3 in CH_2Cl_2 at -78 °C and the resulting alcohol was converted into a *t*-butyldimethylsilyl (TBS) ether **16** in 92% overall yield by using TBSCl and imidazole. A tricyclic ketone **17** was derived in 90% yield from the β, γ-unsaturated ketone **16** by irradiation in acetone through a Pyrex filter with a 100-W Ushio Hg lamp under argon for 2 h.

The dissolved metal reduction of **17** with Li and *t*-BuOH in liquid ammonia-ether followed by PCC oxidation gave a mixture of ketones **18** in 92% yield. The ketones **18** were converted into the α,β-unsaturated ketones in 76% yield by a method similar to the preparation of **11** from **10**. The β,γ-unsaturated ketone **19** was derived from the enones in 92% yield, by treatment with LDA in THF-HMPA followed by protonation with aqueous ammonium chloride and chromatographic purification on silica gel. The TBS ether of **19** was cleaved without migration of the double bond by treatment with acetic acid in THF-H_2O.[9] The bromination of the resulting alcohol with CBr_4-PPh_3 and triethylamine in CH_3CN led to **20** in 87% yield. A radical cyclization reaction of **20** using Bu_3SnH (1.6 equiv) and AIBN (0.1 equiv) in benzene gave a 1.7 : 1 mixture of propellanes **21** and **22** in 67% yield after 2 h heating under reflux. The stereostructures of these products were elucidated on the basis of difference NOE experiments.[10]

Thus, we have successfully replaced both bridgehead-substituents of 1,4-dimethoxybicyclo[2.2.2]oct-5-en-2-one (**7**) by the desired alkyl groups.

Scheme 3



15 $R^1 = (CH_2)_3OCH_2Ph$
16 $R^1 = (CH_2)_3OTBS$

17 $R^1 = (CH_2)_3OTBS$

18 $R^1 = (CH_2)_3OTBS$

19 $R^1 = (CH_2)_3OTBS$
20 $R^1 = (CH_2)_3Br$

21 X = CH_3, Y = H
22 X = H, Y = CH_3

23

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5. Compound **7** was derived from 1,4-dimethoxy-1,3-cyclohexadiene by sequential treatment with 1) acrylonitrile, 2) LDA, 3) oxygen, and 4) Na_2SO_3.
6. All new compounds reported here exhibit satisfactory spectral and analytical and/or HRMS characteristics.
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10. Compound **21**: Colorless oil, IR (neat) 1740 cm^{-1}, ^1H NMR ($CDCl_3$) δ = 0.98 (3H, d, J = 6.5 Hz, 8-exo-CH_3), 1.01 (3H, s), 1.03 (3H, s, 4-endo-CH_3), 1.24-1.32 (1H, m, H-exo-6), 1.32-1.45 (4H, m), 1.58-1.77 (5H, m), 1.88 (1H, dddd, J = 12.9, 6.3, 5.3, and 1.0 Hz, H-endo-6), 2.19 (1H, d, J =17.7 Hz) and 2.39 (1H, d, J =17.7 Hz); positive NOEDS between [4-endo-CH_3 and H-endo-2] and [4-endo-CH_3 and H-endo-6]. Compound **22**: Colorless oil, IR (neat) 1740 cm^{-1}, ^1H NMR ($CDCl_3$) δ = 0.96 (3H, d, J = 6.5 Hz, 8-endo-CH_3), 0.99 (3H, s, 4-exo-CH_3), 1.05 (3H, s, 4-endo-CH_3), 1.09-1.17 (2H, m), 1.25 (1H, dddd, J = 13.5, 12.5, and 6.4 Hz, H-exo-6), 1.41-1.45 (1H, m), 1.50-1.62 (3H, m), 1.71-1.77 (1H, m, H-8), 1.76-1.82 (2H, m), 1.93 (1H, d, J =17.1 Hz, H-exo-2), 1.95 (1H, ddd, J =13.5, 6.7, and 1.6 Hz, H-endo-6), and 2.51 (1H, d, J =17.1 Hz, H-endo-2); positive NOEDS between [8-endo-CH_3 and H-endo-2], [4-endo-CH_3 and H-endo-2], and [4-endo-CH_3 and H-endo-6].

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