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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  $(\pm)$ -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<sup>1</sup> and photochemical [1,2]-acyl migration (oxa-di- $\pi$  methane rearrangement).<sup>2</sup> We have reported the formal bridgehead substitution of l-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.<sup>3</sup> 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<sup>1</sup>) had uninvestigated. We wish to report herein a method to introduce the desired substituents at both C-1 and

Scheme1





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  $\alpha$ ,  $\beta$ -unsaturated ketone 11 ( $\mathbb{R}^2 = H$ ) via a 1,4-addition reaction of an organometallic reagent, such as ( $\mathbb{R}^2$ )<sub>2</sub>CuLi, followed by conversion into the  $\alpha$ ,  $\beta$ -unsaturated ketone 11 ( $\mathbb{R}^2 \neq H$ ) and then the reduction of the carbonyl. A precursor of the conjugated ketone 11 ( $\mathbb{R}^2 = H$ ) would be a ketone 10, a predominant product of the pinacol-type rearrangement of an alcohol 9.<sup>4</sup> The alcohol 9 should be the major product derived from a reaction of the ketone 7 with an organometallic reagent ( $\mathbb{R}^1M$ ). This overall transformation means the desired substitution of both bridgehead methoxyl groups of 7 is feasible.

The conversion of 7 into 8 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn, R<sup>2</sup> = CH<sub>3</sub>) was carried out as follows. The addition of 3-benzyloxypropylmagnesium bromide to 7<sup>5</sup> at room temperature gave the exo alcohol 9 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn) in 61% yield along with the endo isomer in 37% yield.<sup>6</sup> The alcohol 9 was converted into the ketone 10 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn) 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<sup>7</sup> for 1 h gave the  $\alpha$ ,  $\beta$ -unsaturated ketone 11 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn, R<sup>2</sup> = H) in 79% overall yield. A conjugate addition reaction of (CH<sub>3</sub>)<sub>2</sub>CuLi to 11 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn, R<sup>2</sup> = H) in ether followed by an  $\alpha$ -bromination (LDA, TMSCl, and NBS) and then the dehydrobromination (Li<sub>2</sub>CO<sub>3</sub> in DMF) formed 11 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn, R<sup>2</sup> = CH<sub>3</sub>) in 79% overall yield. Reduction of the latter with DIBALH to yield 12 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn, R<sup>2</sup> = CH<sub>3</sub>) followed by treatment with an equimolar amount of TsOH in boiling benzene for 30 min gave the ketone 8 (R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>OBn, R<sup>2</sup> = CH<sub>3</sub>) in 95% overall yield.

Scheme 3 shows transformation of the ketone 8 into a propellane 21,<sup>81</sup> a key intermediate of (±)modhephene (23).<sup>8</sup> 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 BBr3 in CH<sub>2</sub>Cl<sub>2</sub> 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  $\beta$ ,  $\gamma$ -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  $\alpha,\beta$ -unsaturated ketones in 76% yield by a method similar to the preparation of 11 from 10. The  $\beta,\gamma$ -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-H2O.<sup>9</sup> The bromination of the resulting alcohol with CBr4-PPh3 and triethylamine in CH3CN led to 20 in 87% yield. A radical cyclization reaction of 20 using Bu3SnH (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.<sup>10</sup>

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

Scheme 3



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- Compound 21: Colorless oil, IR (neat) 1740 cm<sup>-1</sup>, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 0.98 (3H, d, J = 6.5 Hz, 8 exo-CH<sub>3</sub>), 1.01 (3H, s), 1.03 (3H, s, 4-endo-CH<sub>3</sub>), 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<sub>3</sub> and H-endo-2] and [4-endo-CH<sub>3</sub> and H-endo-6]. Compound 22: Colorless oil, IR (neat) 1740 cm<sup>-1</sup>, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 0.96 (3H, d, J = 6.5 Hz, 8-endo-CH<sub>3</sub>), 0.99 (3H, s, 4-exo-CH<sub>3</sub>), 1.05 (3H, s, 4-endo-CH<sub>3</sub>), 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<sub>3</sub> and H-endo-6].

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