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A sequential stereocontrolled cyclopropane ring formation and semi-pinacol rearrangement

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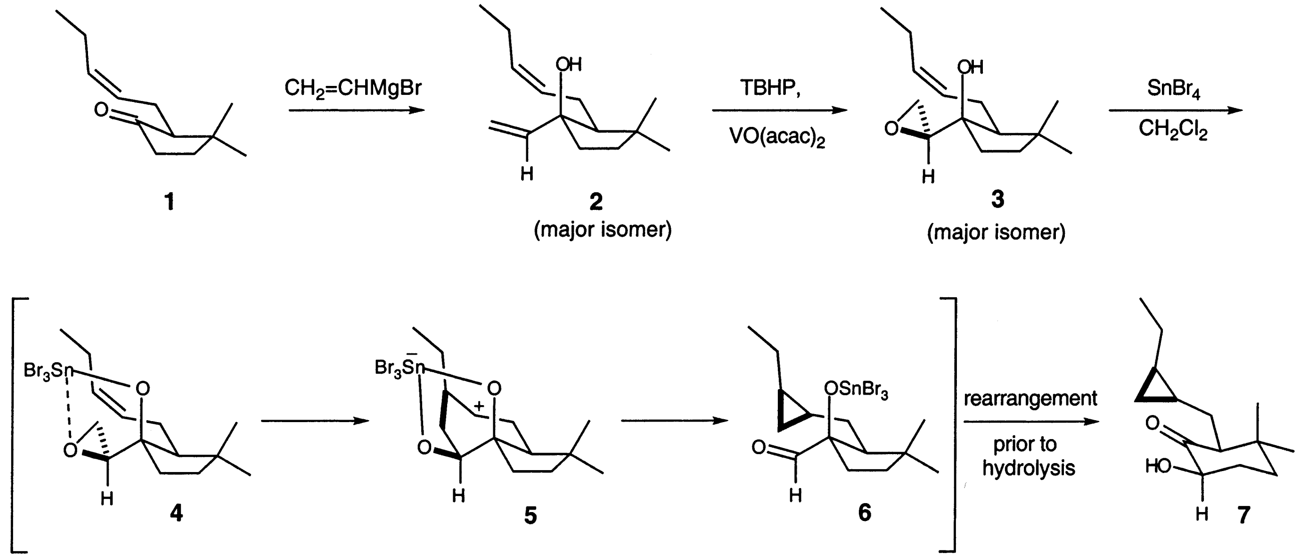
Abstract—Treatment of an unsaturated 2,3-epoxy alcohol with $SnBr_4$ leads to a stereoselective formation of a cyclopropane ring, and an α-ketol unit as part of a subsequent ring expansion. © 2002 Elsevier Science Ltd. All rights reserved.

The reaction of a 2,3-epoxy alcohol with a π-nucleophile is a powerful means of creating a new carbon–carbon bond, frequently with high stereocontrol.[1] A common mode is for the π-nucleophile to attack the epoxide, held in a chelation-controlled conformation by a Lewis acid, often a tin(IV) reagent. The size of ring formed depends on the structure of the 2,3-epoxy alcohol, and the nature and alignment of the π-nucleophile, amongst other factors. Recently, we reported that such cyclizations could result in seven-membered rings, by the presentation of the epoxide terminus to the π-nucleophile.[2,3] We now disclose a new outcome of the intramolecular attack of an alkene unit upon a 2,3-epoxy alcohol that leads to a stereoselective formation of a cyclopropane ring, followed by a ring expansion of the semi-pinacol type (Scheme 1).



Scheme 1. Formation of a cyclopropane ring followed by a semi-pinacol ring expansion.

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Reaction of *cis*-jasmone with dimethylcopperlithium in diethyl ether, generated from methyllithium (2.0 equiv.) and CuI (1.0 equiv.) at 0°C, and $BF_3 \cdot OEt_2$ (1.78 equiv.) at −78°C with subsequent warming to 20°C over 4 h afforded the *gem*-dimethyl ketone **1** in 63% yield.[4] Addition of vinylmagnesium bromide (1.3 equiv.) in THF to **1** in THF at −78°C with subsequent warming to 20°C over 20 h afforded **2** as the major diastereoisomer (15:1; total yield 98%). Reaction of the epimeric mixture of **2** with *tert*-butyl hydroperoxide[5] (1.4 equiv., 70% aqueous solution, **CAUTION**) and $VO(acac)_2$ (0.5 mol%) in benzene at reflux for 24 h gave the 2,3-epoxy alcohol **3** as the major diastereoisomer (6:1, total yield 74%). Treatment of this epimeric mixture **3** with $SnBr_4$ (2.0 mol. equiv.) in dichloromethane at 0°C for 1 h afforded, after column chromatography, the cyclopropyl α-ketol **7** (65%), isolated as a single diastereoisomer.[6] The structure of **7** was confirmed by X-ray crystallography (Fig. 1) on a single crystal of the *p*-bromobenzenesulfonate derivative **8**, mp 96°C[7] (obtained in 75% yield by reaction of **7** with *p*-bromobenzenesulfonyl chloride in pyridine at 0°C).

The transformation of **3** into **7** demonstrates that a 2,3-epoxy alcohol can undergo the formalism of cyclopropanation of an alkene; we are aware of one other formation of a cyclopropane ring from a 2,3-epoxy alcohol.[8] Consistent with Sharpless' observations[8] and our previous work on cyclizations to give seven-membered rings,[1–3] an indirect route seems likely, probably via a chelation-controlled conversion of **4** into a seven-membered ring intermediate such as **5** that subsequently undergoes collapse, with formation of the cyclopropane ring.[9] Ring expansions of 1-hydroxycyclopentanecarboxaldehyde systems to α-ketols under Brønsted–Lowry or Lewis acidic conditions are known in both steroidal[10–12] and non-steroidal[13–15] cases. The observed migration often proceeds through a chair transition state,[13,16] and can involve migration of a group that is either the more substituted[13] or the less substituted[14] at the α-position. Migration involving the less substituted (methylene) α-carbon atom of **6** can proceed through a chair transition state, leading to the α-ketol **7**, after hydrolytic work-up. A more detailed study of such processes and the scope of related reactions is warranted.

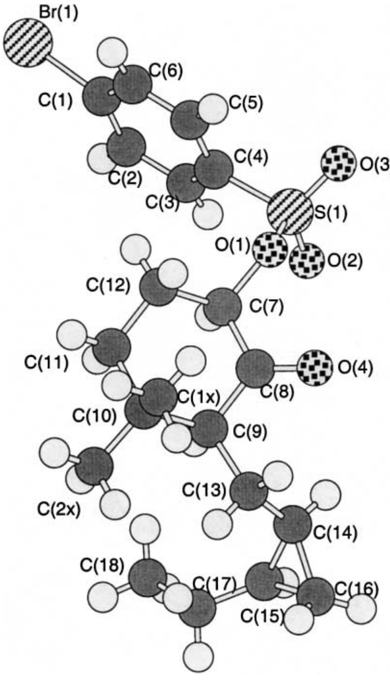

Figure 1. ORTEP representation of **8**.

Acknowledgements

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6. Spectral data for **7**: IR: λ_{max} 3435 (OH), 1710 (C=O) cm^{-1}; ^1H NMR δ_H (250 MHz, $CDCl_3$) 4.20 (1H, t, $J=3.5$, 11.0 Hz, C*H*OH), 3.68 (1H, d, $J=3.5$ Hz, CHO*H*), 2.30 (1H, m, $C(CH_3)_2CHC{=}O$), 2.10–0.80 (8H, m, $O{=}CCHCH_2$, $CH(OH)(CH_2)_2$, CH_2CH_3), 1.18 (3H, s, $C(CH_3)CH_3$), 1.00 (3H, t, $J=7.5$ Hz, CH_2CH_3), 0.71 (3H, s, $CCH_3(CH_3)$), 0.70–0.50 (2H, cyclopropyl-C*H*), 0.25 (2H, m, cyclopropyl-CH_2); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 212.5 (s), 75.1 (d), 59.3 (d), 40.9 (s), 38.0 (t), 33.0 (t), 29.7 (d), 22.2 (t), 21.6 (t), 20.3 (d), 17.8 (q), 15.2 (q), 14.6 (q), 10.9 (t); EI (*m*/*z*, %) 224 (5, M^+), 209 (40), 127 (40), 109 (30), 95 (30), 81 (35), 60 (40), 55 (90), 41 (100). HRMS found 224.1783, $C_{14}H_{24}O_2$ requires 224.1776.
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