

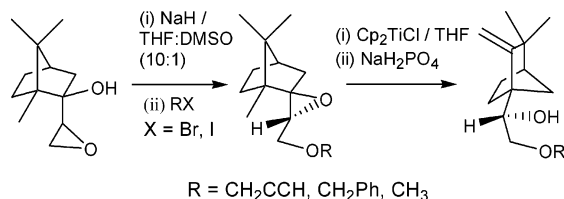
Radical Promoted Wagner–Meerwein-Type Rearrangement of Epoxides in Camphoric Systems Using a Ti(III) Radical Source

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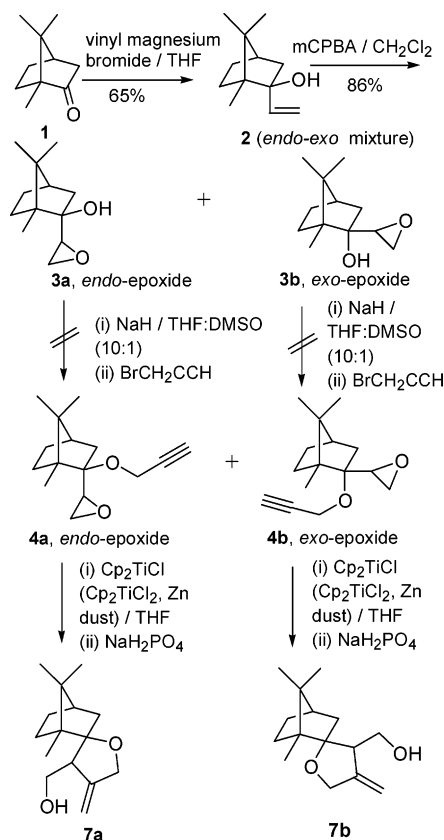
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A radical based Wagner–Meerwein-type rearrangement has been observed in camphoric systems. The radical was generated from the epoxide using Cp₂TiCl as the radical source. The radical initiator Cp₂TiCl was prepared in situ from commercially available Cp₂TiCl₂ and Zn dust in THF under argon.

The tremendous growth in free radical cyclization reactions in recent years proves their significance as a powerful tool in modern synthetic chemistry leading to the complex carbocyclic as well as heterocyclic natural products.¹ Epoxides are vastly used as building blocks for organic synthesis due to their ready availability and facile substitution reactions with predictable stereochemistry.² In continuation of our study³ toward the synthesis of natural products through radical cyclization of epoxides using a Ti(III) species as the radical initiator, we noticed a Wagner–Meerwein-type molecular rearrangement in camphoric systems promoted by a free radical⁴ generated from an epoxide. The radical initiator titanocene(III) chloride (Cp₂TiCl) was generated⁵ in situ

SCHEME 1



from commercially available Cp₂TiCl₂ and Zn dust in THF under argon.

In relation to our efforts for the synthesis of spirocyclic natural compounds,^{3c} we intended to prepare the spiroethers **7** by radical cyclization of the epoxides **4** using titanocene(III) chloride (Cp₂TiCl) as the radical initiator as depicted in Scheme 1.

Thus, commercially available camphor **1** on treatment with vinylmagnesium bromide following the standard procedure⁶ afforded compound **2** as an inseparable mixture of two isomers, *endo*-vinyl and *exo*-vinyl adducts, in a ratio of 1.4:1 (GC, detector-FID, column: OB17, column temperature: 100 °C) along with a trace of unreacted camphor. Since there was not any distinguishable peak for the isomers of the crude **2**, the ratio could not be determined from the ¹H NMR spectra. It is noteworthy that the energy difference between these two isomers is about 2.5 kcal/mol (MOPAC, AM1) and *endo*-vinyl adduct is more favored than the *exo* one. The formation of *endo* adduct is preferred probably due to the easier approach of the vinyl moiety from the less hindered *endo*-face compared to the *exo*-face where two methyl groups as well as the bridge restrict the approach of the vinyl moiety.⁷ This was further confirmed when the crude **2** was subjected to epoxidation with mCPBA to furnish **3** in 86%

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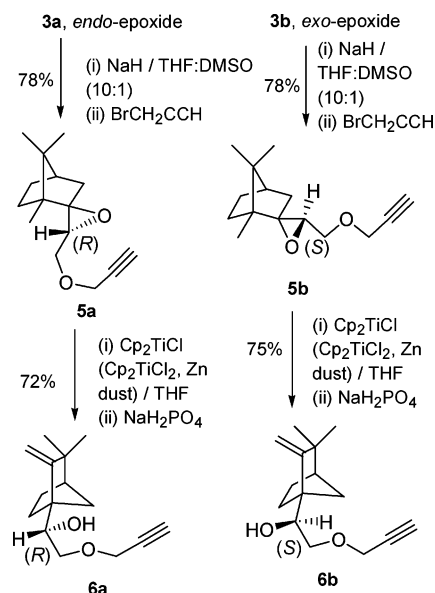
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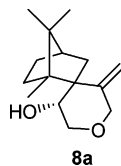
SCHEME 2



yield as a mixture of two isomers in a ratio of 1.4:1 (Scheme 1). It is well established⁸ that during the epoxidation of allylic alcohols the incoming oxygen from the peroxy acid undergoes *syn*-addition with respect to the OH group due to the hydrogen bonding between the OH group and the peroxy acid in the transition state. Therefore, each isomer of **2** furnished only one corresponding isomer of the epoxide. It is obvious that the major *endo*-vinyl adduct afforded the *endo*-epoxide **3a** and the minor *exo*-vinyl adduct afforded the *exo*-epoxide **3b**, respectively. The isomers **3a** and **3b** were separated by column chromatography in 50 and 36% yields, respectively.

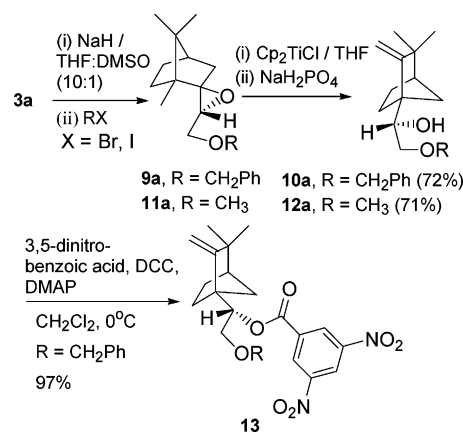
The isomers **3a** and **3b** on separate treatment with propargyl bromide in the presence of NaH did not afford the epoxy ethers **4a** and **4b**, but rather furnished the rearranged epoxides **5a** and **5b**, respectively, in good yields (Scheme 2) by Payne's rearrangement.⁹ The pure epoxide **5a** on treatment with Cp₂TiCl in THF under argon at room temperature underwent a radical based Wagner–Meerwein-type ring rearrangement to furnish **6a** as the only isolated product in 72% yield.

No trace of the radical cyclization product **8a** was detected. Similarly, the pure epoxide **5b** on treatment



with Cp₂TiCl under identical reaction conditions furnished solely the rearranged product **6b** in 75% yield. To observe any influence of the *O*-alkyl group on the

SCHEME 3



radical rearrangement process, epoxides **9a** and **11a** were also subjected separately to the radical cyclization reaction with Cp₂TiCl in THF under identical reaction conditions and furnished the rearranged products **10a** (72%) and **12a** (71%), respectively (Scheme 3).

The compounds **6a**, **6b**, **10a**, and **12a** were isolated as viscous liquids. Although the structures of the rearranged products were in good agreement with the NMR and analytical data, the structural connectivity and relative stereochemistry was finally established using X-ray analysis of the 3,5-dinitrobenzoate ester derivative **13** (Figure 1) (colorless crystals, mp 104–106 °C) prepared from the alcohol **10a**.

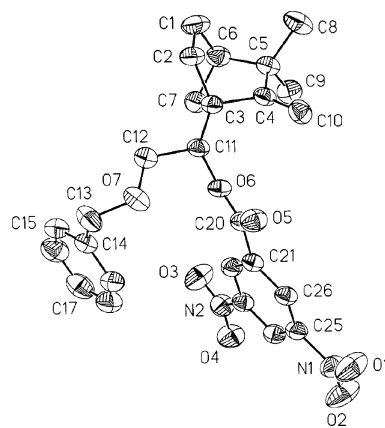


FIGURE 1. X-ray of **13**.

The proposed mechanism of the ring rearrangement is depicted in Scheme 4.

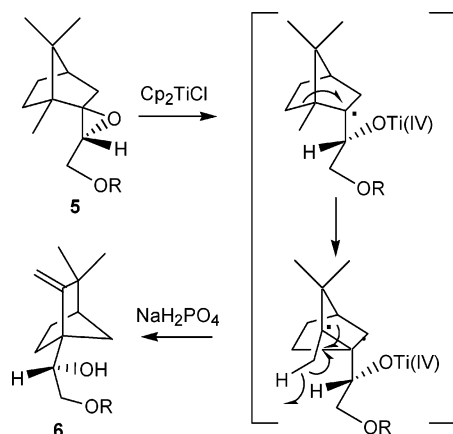
The last step of the reaction may not be a H-atom loss, but is a Ti(III) trapping of the radical followed by β -elimination.¹⁰

In support of the radical-promoted molecular rearrangement, two separate experiments were done with the epoxide **9a** under the same reaction conditions as described for the rearrangement reaction (i) without zinc dust and (ii) with ZnCl₂ in the absence of Cp₂TiCl₂. In both cases, no rearrangement was found to get **10a**, only the unreacted starting material was isolated in quantitative yield. This observation proved that Cp₂TiCl₂ or ZnCl₂ (generated in situ in the reaction mixture from zinc dust and Cp₂TiCl₂) did not take part in any cationic rearrangement to obtain the rearranged product **10a**.

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SCHEME 4



In conclusion, a radical-induced Wagner–Meerwein-type rearrangement has been observed in camphoric systems. The radical was generated from the epoxide using titanocene(III) chloride as the radical initiator.

Experimental Section

Preparation of (1*R*)-1-(2,2-Dimethyl-3-methylenebicyclo[2.2.1]hept-1-yl)-2-(prop-2-ynyloxy)ethanol (6a) by Radical Rearrangement of the Epoxide 5a. Representative Procedure. A solution of Cp_2TiCl_2 (225 mg, 0.9 mmol) in THF (5 mL) (dried over Na) was stirred with activated zinc dust (195 mg, 2.99 mmol) for 1 h under argon (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl, thorough washing with water until the washings became neutral, and finally washing with dry acetone and then drying in vacuo). The resulting green solution was then added dropwise to a stirred solution of the epoxide **5a** (100 mg, 0.43 mmol) in dry THF (12 mL) at room temperature under argon. It was stirred for an additional 1 h and decomposed with saturated sodium dihydrogen phosphate (10 mL). After removal of most of the THF under reduced pressure, the crude material obtained was purified by column chromatography over silica gel (5% ethyl acetate in light petroleum) to furnish **6a** (72 mg, 72%) as a colorless liquid. IR (neat) ν 3463, 3307, 2931, 2873, 1739,

1654, 1456, 1388, 1369, 1261 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.03 (s, 3H), 1.08 (s, 3H), 1.21–1.89 (m, 7H), 2.45 (t, $J = 2.4$ Hz, 1H), 3.59 (dd, $J = 9.6, 8.4$ Hz, 1H), 3.83 (dd, $J = 9.6, 2.4$ Hz, 1H), 4.14–4.30 (m, 3H), 4.72 (s, 1H), 4.85 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.9, 26.3, 29.7, 31.2, 38.5, 43.7, 47.1, 57.1, 58.9, 71.4, 72.2, 75.1, 80.0, 100.4, 165.4; Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88; H, 9.46. Found: C, 76.26; H, 9.50.

(1*S*)-1-(2,2-Dimethyl-3-methylenebicyclo[2.2.1]hept-1-yl)-2-(prop-2-ynyloxy)ethanol (6b): colorless oil; 75% yield; IR (neat) ν 3477, 3307, 2958, 2875, 2115, 1652, 1461, 1361 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.99 (s, 3H), 1.07 (s, 3H), 1.09–2.00 (m, 7H), 2.44 (t, $J = 2.4$ Hz, 1H), 3.46 (t, $J = 9.0$ Hz, 1H), 3.78 (dd, $J = 9.3, 2.6$ Hz, 1H), 4.16 (dd, $J = 8.7, 2.5$ Hz, 1H), 4.19 (d, $J = 2.4$ Hz, 2H), 4.65 (s, 1H), 4.74 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 23.94, 25.8, 29.1, 29.8, 37.2, 43.1, 46.9, 55.7, 58.3, 70.4, 72.0, 74.5, 79.4, 99.3, 165.7; Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88; H, 9.46. Found: C, 76.16; H, 9.26.

(1*R*)-2-(Benzyloxy)-1-(2,2-dimethyl-3-methylenebicyclo[2.2.1]hept-1-yl)ethanol (10a): colorless oil; 74% yield; IR (neat) ν 3444, 3064, 3030, 2950, 2871, 1722, 1651, 1494, 1454, 1386, 1361, 1315, 1274, 1201 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.02 (s, 3H), 1.07 (s, 3H), 1.20–1.85 (m, 7H), 3.57 (dd, $J = 9.4, 8.4$ Hz, 1H), 3.73 (dd, $J = 9.6, 2.7$ Hz, 1H), 4.18 (dd, $J = 8.4, 2.5$ Hz, 1H), 4.60 (d, $J = 2.9$ Hz, 2H), 4.69 (s, 1H), 4.82 (s, 1H), 7.25–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 24.9, 26.3, 29.7, 31.1, 38.5, 43.7, 47.1, 57.0, 71.5, 72.5, 73.7, 100.3, 128.1, 128.5, 130.0, 130.1, 133.5, 138.5, 165.5; Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_2$: C, 79.68; H, 9.15. Found: C, 79.58; H, 9.16.

(1*R*)-1-(2,2-Dimethyl-3-methylenebicyclo[2.2.1]hept-1-yl)-2-methoxyethanol (12a): colorless liquid; 71% yield; IR (neat) ν 3465, 2956, 2927, 2879, 1651, 1458, 1361, 1195, 1124 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.03 (s, 3H), 1.08 (s, 3H), 1.16–1.88 (m, 7H), 2.35 (brs, OH), 3.42 (s, 3H), 3.47 (dd, $J = 9.6, 8.6$ Hz, 1H), 3.63 (dd, $J = 9.7, 2.6$ Hz, 1H), 4.14 (dd, $J = 8.5, 2.5$ Hz, 1H), 4.71 (s, 1H), 4.85 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.9, 26.3, 29.6, 31.1, 38.4, 43.7, 47.1, 57.0, 59.4, 71.3, 74.8, 100.3, 165.4; Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.24; H, 10.54. Found: C, 74.18; H, 10.55.

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Supporting Information Available: General experimental details and spectral and analytical data of compounds **3a**, **3b**, **5a**, **5b**, **6a**, **6b**, **9a**, **10a**, **11a**, **12a**, and **13**. Copies of ^1H NMR spectra of **3a**, **3b**, **5a**, **5b**, **6a**, **6b**, **10a**, and **12a**. Copies of ^{13}C NMR spectra of **6a**, **6b**, **10a**, and **12a**. X-ray crystallographic data for **13** (CIF) and copy of the X-ray of **13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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