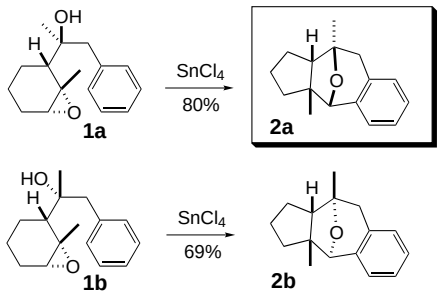
Stereocontrolled Routes to Bridged Ethers by Tandem Cyclizations

Charles M. Marson,* Jon Campbell, Michael B. Hursthouse, and K. M. Abdul Malik

The construction of carbocyclic seven-membered rings continues to present an appreciable challenge, particularly when stereocontrolled placement of multiple chiral centers is required.[1, 2] The 8-oxabicyclo[3.2.1]octane system and its fused analogues form a fundamental class of compounds which include hydroazulenoid diterpene natural products.[3] Currently, the most general methods of access to the oxabicyclo[3.2.1]octane system are by [3+4] cycloadditions[4] and annulations.[5] Herein we report the first examples of cyclizations involving 3,4-epoxy alcohols, and disclose a new tandem contraction–lactolization–cyclization sequence (Scheme 1). This reaction sequence has led to the development of lactol cyclizations and hence a general route to bridged bicyclo ethers.



Scheme 1. Cyclizations giving bis-fused 8-oxabicyclo[3.2.1]octane systems.

Epoxides are powerful initiators in cyclizations involving π nucleophiles, particularly when activated by a Lewis acid.[6] The stereochemical control of an epoxide can be further enhanced by the presence of an hydroxyl group adjacent to the epoxide;[2] such 2,3-epoxy alcohols can participate in bidentate chelation, which usually leads to high regio- and stereocontrol during cyclization.[2] In contrast, cyclizations involving epoxides derived from homoallylic alcohols (3,4-epoxy alcohols) appear to be without precedent. Since the epoxidation of acyclic homoallylic alcohols is not usually diastereoselective,[7] advantage was taken of a cycloalkenyl unit in which epoxidation could be face-selective on account of conformational restriction to a ring. This proved to be the case, and 3,4-epoxy alcohols **1a** and **1b** were the only isomers resulting from the epoxidation of 2-(2-methylcyclohex-2-enyl)-1-phenylpropan-2-ol with *tert*-butyl hydroperoxide in the presence of $[VO(acac)_2]$ (acac = acetylacetonate). Epoxides **1a** and **1b** were separated by chromatography and independently treated with $SnCl_4$ (2.0 equiv) in CH_2Cl_2 at $-78\,^{\circ}C$. Each underwent a remarkable skeletal rearrangement to give **2a** and **2b**, respectively, as the result of rearrangement followed by consecutive cyclizations. An X-ray crystal structure determination[8] of **1a** disclosed the relative configuration shown in Figure 1, in which the ether bridge is *trans* to the cyclopentane ring. Epoxy alcohol **1b**, being epimeric with **1a**, gave **2b** in which the epimeric configuration at the carbinol center results in the ether bridge that is *syn* to the cyclopentane ring. In each case, **2a** and **2b** were the only cyclized products isolated.

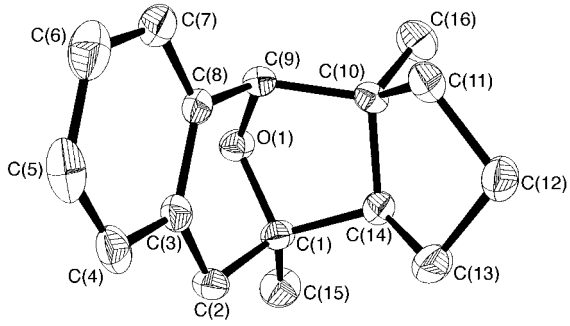
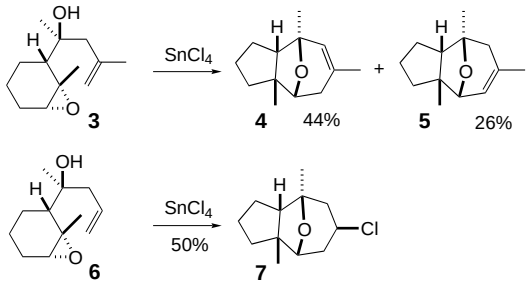


Figure 1. Crystal structure of **2a**.

The novel tandem cyclization was explored with other π nucleophiles as terminating groups. Reaction of 1-acetyl-2-methylcyclohex-2-ene with 2-methyl-2-propenylmagnesium chloride in place of a benzyl Grignard reagent in the above sequence afforded a 1:1 mixture of homoallylic alcohols, which was epoxidized with *m*-chloroperbenzoic acid and then separated by chromatography. Treatment of epoxy alcohol **3** with $SnCl_4$ (2.0 equiv) in CH_2Cl_2 ($-78\,^{\circ}C$, 20 min) gave the bicyclic ethers **4** and **5** (Scheme 2). Constitutional isomerism had arisen as a consequence of lack of control during deprotonation of the presumed tertiary carbocation. The carbinol epimer of **3** did not afford any identifiable cyclized products.



Scheme 2. Cyclizations with alkenes.

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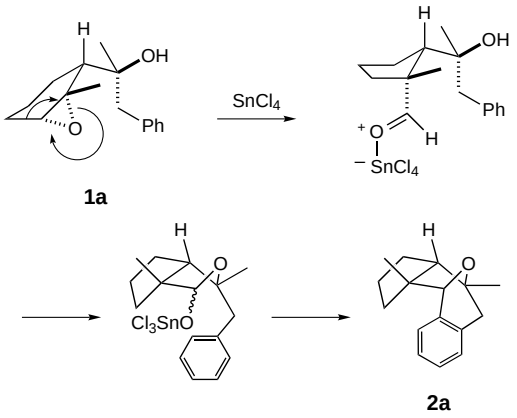
The less substituted alkenyl substrate **6** was prepared by addition of allylmagnesium chloride to 1-acetyl-2-methylcyclohex-2-ene to give a 1:1 mixture of 2-(2-methylcyclohex-2-enyl)-pent-4-en-2-ols (67%), which was epoxidized; the epoxy alcohols were then separated by chromatography. Treatment of **6** with $SnCl_4$ (2.0 equiv) in CH_2Cl_2 ($-78\,^\circ C$, 15 min) gave **7** (50%). Instead of a cycloalkene ring being formed, chloride trapping occurred, a phenomenon consistent with the reactivity of the developing secondary carbocation leading to rapid nucleophilic quenching. The trajectory of approach is consistent with a chairlike transition state in which the C–C bond of the newly forming ring is parallel with the equatorially forming C–Cl bond (the α-chloro epimer of **7** would require a boatlike transition state); chloro ether **7** was the only cyclized product isolated. The CHCl unit of **7** ($\delta = 4.38$) exhibits a triplet of triplets ($J = 11.5$ and 5.5 Hz) in the ^{1}H NMR spectrum, consistent only with *trans*-diaxial coupling and an equatorially disposed chloro substituent. As in the case of **3**, the carbinol epimer of **6** did not afford any identifiable cyclized products.

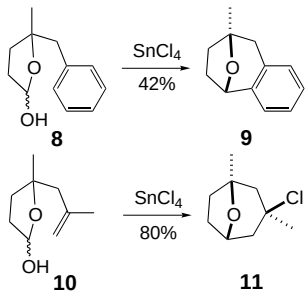
The above cyclizations can be understood in terms of the following sequence of events: First, epoxide ring opening and ring contraction[9] take place, mediated by the Lewis acid (Scheme 3). The configurations of the final products imply that



Scheme 3. Possible mechanism for the formation of **2a**.

the contraction is stereoselective and proceeds with inversion at the new quaternary center. The carbinol oxygen atom then participates in an intramolecular attack upon the activated carbonylic electrophile, resulting in a fused lactol intermediate. Lastly, the effect of $SnCl_4$ upon the lactol intermediate leads to an electrophile presumed to be the oxonium cation, which undergoes attack by the aryl or alkenyl π nucleophile.

The above rationale suggested that independently prepared lactol intermediates could be expected to undergo cyclization to give related bridged ethers. This was demonstrated for the two lactols **8** and **10** (Scheme 4), which were prepared as follows: Addition of benzylmagnesium chloride and 2-methyl-2-propenylmagnesium chloride, respectively, to ethyl levulinate followed by hydrolysis of the hydroxy esters with aqueous NaOH and acidification gave the γ-hydroxy acids, which were cyclodehydrated to the γ-lactones by heating in benzene at reflux. The lactones were reduced with diisobutylaluminum hydride (1.5 equiv) in toluene at $-78\,^\circ C$ to give the lactols **8** and **10**. Treatment at $-78\,^\circ C$ in CH_2Cl_2 with $SnCl_4$ (2.8 equiv, 1 h for **8**; 2.0 equiv, 2 h for **10**) gave bridged ethers **9** and **11**, respectively, as single diastereomers. The stereoelectronic preference resulting in the *syn* relation of chloro substituent to ether bridge can be explained on the basis of a chairlike transition state prior to chloride trapping, as for the formation of **7**.



Scheme 4. Cyclizations to give mono- and bicyclic bridged ethers.

In conclusion, bridged ethers incorporating stereocontrolled placement of functionality can be prepared by Lewis acid induced cyclizations. A reaction sequence with a ring contraction and a tandem cyclization allows the 8-oxabicyclo[3.2.1]octane system to be constructed with one or two additional fused rings from unfunctionalized alkenes or arenes. Cleavage of the 8-oxabicyclo[3.2.1]octane system affords a stereoselective synthesis of *cis*-2,5-disubstituted tetrahydrofurans,[5b] which are useful precursors of ionophore antibiotics. The potential of the new ring-construction processes in total synthesis is currently being explored.

Experimental Section

2-(2-Methylcyclohex-2-enyl)-1-phenylpropan-2-ol: A solution of 1-acetyl-(2-methylcyclohex-2-ene)[10] (6.0 g, 43.0 mmol) in dry THF (100 mL) was treated with benzylmagnesium chloride (32.6 mL, 2.5 M in THF) under nitrogen at 0 °C. The mixture was stirred at 20 °C for 16 h, and the reaction quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was then extracted with Et_2O (2×150 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 95/5) to give a 1:1 mixture of the two epimers of 2-(2-methylcyclohex-2-enyl)-1-phenylpropan-2-ol as a colorless oil (6.0 g, 60%); IR (KBr): $\tilde{\nu} = 3400, 2900, 1600, 1500\ cm^{-1}$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.40-7.15$ (5H, m), 5.60 (1H, m), 2.80 (1H, m), 1.10–2.40 (15H, m); ^{13}C NMR (68.8 MHz, $CDCl_3$): $\delta = 137.9$ (s), 137.5 (s), 135.1 (s), 135.0 (s), 131.0 (d), 131.0 (d), 128.2 (d), 128.2 (d), 127.1 (d), 127.0 (d), 126.5 (d), 126.4 (d), 75.4 (s), 49.3 (d), 48.4 (d), 47.5 (t), 43.1 (t), 27.8 (q), 26.8 (t), 26.6 (t), 26.4 (q), 26.3 (q), 25.6 (t), 25.5 (t), 23.2 (q), 21.5 (t), 21.0 (t); MS (EI 70 eV): *m/z* (%): 213 (9), 181 (10), 135 (65), 123 (35), 95 (100), 81 (20), 43 (30); HR-MS calcd for $C_{16}H_{22}O$: 230.1671; found: 230.1669.

2-(2-Methyl-2,3-epoxycyclohexyl)-1-phenylpropan-2-ol (**1a** and **1b**): A solution of 2-(2-methylcyclohex-2-enyl)-1-phenylpropan-2-ol (5.5 g, 0.024 mol) in benzene (150 mL) was treated with $[VO(acac)_2]$ (10 mg) and aqueous *tert*-butyl hydroperoxide (4.0 g, 70%), and then heated at reflux for 3 h. The mixture was allowed to cool, and was then poured onto saturated aqueous Na_2SO_3. The organic extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatogaphy (silica gel, petroleum ether/ethyl acetate 94/6) to give **1a** (1.65 g, 29%) as microprisms and **1b** (1.65 g, 29%) as an oil; **1a**: M.p. 76.5 °C; IR (KBr): $\tilde{\nu} = 3480, 2950, 1600, 1500\ cm^{-1}$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.40-7.15$ (5H, m), 3.05–2.80 (2H, AB q, $J = 18$ Hz), 2.85 (1H, m), 2.10–1.00 (14H, m); ^{13}C NMR (68.8 MHz, $CDCl_3$): $\delta = 138.0$ (s), 130.7 (d), 128.1 (d), 126.3 (d), 77.1 (s), 60.2 (t), 59.9 (q), 45.5 (t), 43.7 (d), 28.4 (q), 26.5 (q), 24.4 (t), 23.0 (t), 18.2(t); elemental analysis calcd for $C_{16}H_{22}O_2$: C 78.01, H 9.00; found C 77.96, H 9.02; **1b**: IR (KBr): $\tilde{\nu} = 3500, 2950, 1500\ cm^{-1}$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.40-7.20$ (5H, m), 3.10–2.70 (2H, AB q, $J = 18$ Hz), 2.80 (1H, m), 2.30 (1H, s), 2.00–1.10 (13H, m); ^{13}C NMR (68.8 MHz, $CDCl_3$): $\delta = 137.5$ (s), 131.0 (d), 128.0 (d), 126.4 (d), 76.7 (s), 60.3 (d), 59.6 (s), 48.2 (t),

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46.4 (d), 26.5 (q), 25.6 (t), 24.4 (q), 22.9 (t), 18.9 (t); MS (EI 70 eV): *m/z* (%): 246 (3), 228 (20), 185 (10), 155 (36), 135 (28), 112 (29), 95 (100), 91 (52); HR-MS calcd for $C_{16}H_{20}O_2$: 246.1620; found: 246.1621.

1,2,3,3a,4,9,10,10a-Octahydro-3a,10-dimethyl-4,10-epoxybenz[*f*]azulene (**2a**): A solution of **1a** (0.30 g, 1.22 mmol) in CH_2Cl_2 (50 mL) at $-78\,^\circ C$ was treated with $SnCl_4$ (0.29 mL, 2.44 mmol) and then stirred at that temperature for 105 min. The mixture was poured onto ice (10 g), and the solution extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation gave an oil, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 94/6) to give **2a** (0.22 g, 80%) as a white solid. M.p. 37 °C. IR (KBr): $\tilde{\nu}=3950$, 1450, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta=7.18-7.07$ (2H, m), 7.02 (1H, t, $J=8$ Hz), 6.92 (1H, d, $J=8$ Hz), 4.46 (1H, s), 2.93 (1H, d, $J=17$ Hz), 2.78 (1H, d, $J=17$ Hz), 2.10 (1H, m), 1.65–0.90 (6H, m), 1.48 (3H, s), 1.38 (3H, s); ^{13}C NMR (68.8 MHz, $CDCl_3$): $\delta=138.5$ (s), 134.2 (s), 127.9 (d), 127.0 (d), 126.1 (d), 125.0 (d), 86.6 (d), 83.0 (s), 63.8 (d), 59.7 (s), 36.9 (t), 35.5 (t), 30.8 (q), 29.0 (t), 29.0 (q), 27.9 (t); MS (EI 70 eV): *m/z* (%): 228 (M, 10), 145 (100), 131 (27), 109 (55); HR-MS calcd for $C_{16}H_{20}O$: 228.3370; found: 228.3365.

1,2,3,3a,4,9,10,10a-Octahydro-3a,10-dimethyl-4,10-epoxybenz[*f*]azulene (**2b**): A solution of **1b** (0.30 g, 1.22 mmol) in CH_2Cl_2 (50 mL) at $-78\,^\circ C$ was treated with $SnCl_4$ (0.29 mL, 2.44 mmol) and then stirred at that temperature for 75 min. The mixture was poured onto ice (10 g), and the solution extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation gave an oil, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 94/6) to give **2b** (0.19 g, 69%) as an oil; IR (KBr): $\tilde{\nu}=3950$, 1450, 1370, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta=7.15-7.05$ (2H, m), 7.00 (1H, t, $J=8$ Hz), 6.88 (1H, d, $J=8$ Hz), 4.47 (1H, s), 2.96 (1H, d, $J=17$ Hz), 2.54 (1H, d, $J=17$ Hz), 1.90–1.45 (7H, m), 1.32 (3H, s), 0.63 (3H, s); ^{13}C NMR (68.8 MHz, $CDCl_3$): $\delta=138.9$ (s), 132.6 (s), 128.8 (d), 126.8 (d), 125.6 (d), 125.0 (d), 86.2 (d), 81.6 (s), 59.3 (s), 58.5 (d), 43.7 (t), 41.7 (t), 29.7 (t), 27.3 (t), 24.6 (q), 23.0 (q); HR-MS calcd for $C_{16}H_{20}O$: 228.3370; found: 228.3377.

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Ruthenium Trichloride, Tricyclohexylphosphane, 1-Alkynes, Magnesium, Hydrogen, and Water—Ingredients of an Efficient One-Pot Synthesis of Ruthenium Catalysts for Olefin Metathesis

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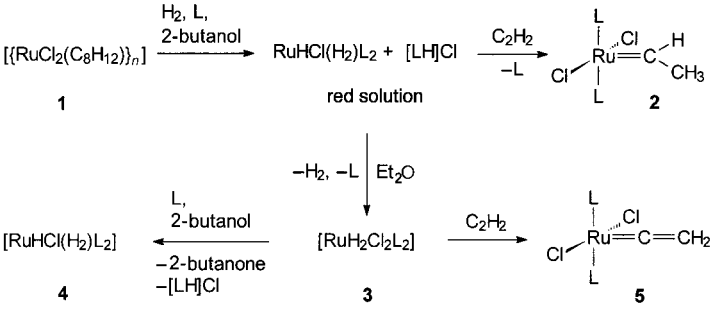
Ruthenium carbene complexes of the type $[RuCl_2(=CHR)(PR'_3)_2]$, are highly efficient catalysts for olefin metathesis. On account of their unique properties, for example, their stability to oxygen and their tolerance of diverse functional groups, they have been increasingly used in organic synthesis, since their discovery by Grubbs and coworkers.[1] The extreme demand and the manifold applications of these catalysts have inevitably initiated the search for alternative synthetic routes that avoid the use of carbene precursors such as diphenylcyclopropenes or diazoalkanes utilized in the established routes. These carbene precursors are either difficult to access or problematic in their handling.[2] The goal set by these demands is fulfilled by a synthetic route recently established in our laboratory that starts from hydrido complexes of ruthenium and 1-alkynes.[3] We found that on reaction of $[\{RuCl_2(C_8H_{12})\}_n]$ (**1**) with hydrogen and P*i*Pr$_3$ in 2-butanol at 80 °C a red solution is formed, which reacts with ethyne (at 25 °C) to afford the carbene complex $[RuCl_2(=CHCH_3)(PiPr_3)_2]$ (**2**). After workup of the red solution with ether, the dihydridoruthenium(IV) compound **3** is obtained in nearly quantitative yield (based on **1**). Complex **3**, however, does not give the carbene complex **2** on reaction with ethyne but rather the vinylidene complex **5** (see Scheme 1).[3, 4]



Scheme 1. L = P*i*Pr$_3$.

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