Highly selective synthesis of oxabicycloalkanes by indium tribromide-mediated cyclization reactions of epoxyalkenes

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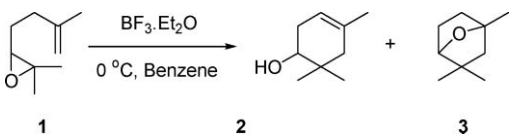
The cyclization of epoxyalkenes to oxabicycloalkanes is catalyzed by stoichiometric quantities of indium tribromide which exhibits excellent selectivity giving the oxabicyclic product in high yield in preference to other cyclized or rearrangement products.

Introduction

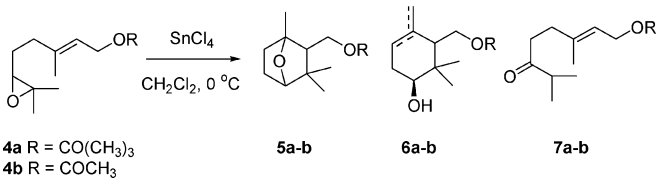
The details of enzymatic cyclizations involved in the biosynthesis of steroids and terpenoids continue to be of both mechanistic and synthetic interest.[1] In particular, the enzyme-mediated cyclization of epoxyalkenes has attracted considerable attention, as has its analogous acid-catalyzed reaction which has been shown to occur under a variety of non-enzymatic conditions.[2] Goldsmith demonstrated that geraniolene oxide **1** gives equal amounts of the cyclized materials **2** and **3**, in addition to the carbonyl product, on treatment with boron trifluoride diethyl etherate (Scheme 1).[3] Subsequent work utilizing a range of Lewis acids has demonstrated the value of mastering biomimetic cyclization routes for the preparation of both natural and unnatural steroid and polycyclic materials.[4,5]



Scheme 1 Boron trifluoride diethyl etherate mediated cyclization of geraniolene oxide.

While there is a wealth of information concerned with the production of cyclic alcohols, the synthesis of bridged oxabicyclic ethers using this approach is less well developed.[6] These materials are usually observed as minor products in cyclization reactions and there have been few studies designed to exploit this approach as a viable entry point for their synthesis. Vidari recently demonstrated that **5a** is produced in moderate yields in iron(III) chloride-mediated cyclization reactions of 6,7-epoxygeranyl pivalate **4a**.[6f] Similarly, Barrero has demonstrated that tin(IV) chloride selectively catalyzes the cyclization of 6,7-epoxygeranyl acetate **4b** producing the bicyclic ether **5b**, however, careful control of the reaction temperature is required to achieve good selectivity[6e] (Scheme 2).

There has been considerable recent interest in the synthesis of oxabicycloalkanes due to the occurrence of this structural motif in a number of natural products displaying potentially beneficial cytotoxic and protein phosphatase inhibitory activity.[7] The development of efficient epoxyalkene cyclization routes to oxabicycloalkanes will potentially allow access to analogues that are inaccessible by current methodologies, however, this goal is constrained by the lack of suitable Lewis acid catalysts. The outcome of the cyclization reaction is highly dependant on the Lewis acid used, and poor catalyst selectivity for the bicyclic material results in low yields of the desired materials. Furthermore, the catalysts typically employed are highly corrosive and difficult to handle. Mohan recently reported that a range of metal triflates are efficient catalysts for the cyclization of geraniolene oxide with the product ratio being dependant on solvent and substrate concentration.[8] However, all of the catalysts studied displayed poor selectivity for the bicyclic ether product and difficulties in separating this product from the reaction mixture led to low isolated yields.



Scheme 2 Lewis acid mediated cyclization reactions of 6,7-epoxygeranyl esters.

Results and discussion

Recent studies have disclosed that a range of metal salts, such as rare-earth triflates,[9] are effective Lewis acid catalysts in a range of organic transformations such as the rearrangement of epoxides to carbonyl compounds displaying high catalytic activity and good selectivity.[10] The formation of carbonyl compounds is a side-reaction frequently observed in epoxyalkene cyclization reactions which may arise through an intermediate common to both reaction pathways. As part of a programme investigating new routes to bicyclic ethers, we investigated the ability of a series of Lewis acid catalysts to cyclize 6,7-epoxygeranyl pivalate **4a** to determine their activity and, more importantly, their selectivity for the bicyclic ether **5a** (Table 1).

It can be seen that while all of the catalysts studied displayed good activity, the selectivity for the bicyclic ether is poor, the notable exception being in the case of indium salts. Our initial studies with stoichiometric quantities of indium triflate produced the bicyclic ether as the major product, however, these reactions also contained considerable quantities of degradation products.

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Table 1 Lewis acid mediated cyclization reactions of 6,7-epoxygeranyl pivalate ester[a]

Entry	Catalyst	Mol%	Ratio of Products[b] 5a	6a	7a	Conversion[c] (%)
1	$ZnCl_2$	100	15	11	74	100
2	$BiCl_3$	100	14	21	59	100[d]
3	$BiOClO_4 \cdot nH_2O$	100	22	7	0	100[d,e]
4	$Gd(OTf)_3$	100	10	6	84	100
5	$Yb(OTf)_3$	100	12	9	79	100
6	$Cu(OTf)_3$	100	33	0	56	100[e]
7	$Cu(BF_4)_2 \cdot nH_2O$	100	19	0	17	85[f,g]
8	$In(OTf)_3$	100	75	25	0	100[e]
9	$In(OTf)_3$	10	13	11	76	100
10	$InCl_3$	100	23	33	44	100
11	$InCl_3$	10	8	15	77	100
12	$InBr_3$	100	>95	<5	0	100[h]
13	$InBr_3$	50	84	16	0	100
14	$InBr_3$	20	80	0	20	100
15	$InBr_3$	10	32	0	68	100

[a] All reactions were carried out in dichloromethane at room temperature under a nitrogen atmosphere for 4 hours. [b] Determined by ^{1}H NMR and GC analysis. [c] Determined by ^{1}H NMR. [d] Contains furane product. [e] Contains unidentified products. [f] Reaction over 18 hours. [g] Contains addition products. [h] 89% isolated yield.

Interestingly, the use of catalytic quantities of this salt led to a reversal in selectivity in which the ketone was observed as the major product. Encouraged by this observation we studied other commercially available indium salts and were gratified to observe that stoichiometric quantities of indium tribromide produced the bicyclic ether with excellent selectivity. Furthermore, the product is easily isolated in high yield simply by passing the crude reaction mixture through a silica plug to remove the catalyst. It has been suggested that the nature of the alcohol substituent plays a significant role in determining the product distribution,[6e,f] however, we noted no significant differences in product ratios in reactions of the 6,7-epoxides derived from either geranyl acetate or geranyl benzoate or which contained silyl protecting groups. Reactions involving sub-stoichiometric quantities of indium tribromide showed a similar reversal in selectivity to that observed with the triflate. The reason for this reversal is unclear at the moment although co-ordination of the catalyst to the bicyclic ether has been proposed as a mechanism for the formation of the allylic alcohol product.[6f] In our case, this co-ordination may have a beneficial effect preventing subsequent degradation.

We also took the opportunity to investigate the ability of indium tribromide to catalyze the cyclization reaction of the regioisomeric 2,3-epoxide. Previously, it has been demonstrated that boron trifluoride diethyl etherate catalyzes this cyclization to produce the diol **9** in poor yields through a 6-*endo* cyclization pathway.[6d] The formation of 6-membered ring cyclization products derived from a concerted, S_N2-like cyclization pathway have been reported and has been the subject of considerable interest in steroid synthesis.[11] Recently, indium tribromide has been shown to promote the highly regio- and stereoselective alkylation of indoles with enantiomerically pure epoxides through an S_N2-type pathway to produce β-3-indolyl alcohols.[12] It has been proposed that it is the electronic features of the Lewis acid which are important in preventing the formation of carbocation intermediates and in this context, the mild Lewis acidity of indium(III) salts and their relatively low oxophilicity make them suitable candidates for the promotion of these S_N2-type reactions.[13] Thus, 2,3-epoxygeranyl acetate **8** was synthesized using literature procedures[14] (Scheme 3), and the indium tribromide-promoted cyclization was studied under our standard conditions using a stoichiometric quantity of catalyst. Gratifyingly, the cyclic diol **9** was produced in high yield and with excellent selectivity.

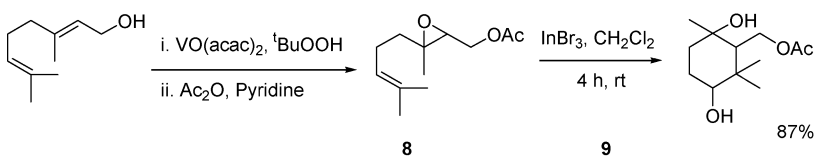
Conclusions

In summary, the indium tribromide mediated cyclization reactions of 6,7-epoxygeranyl esters proceed with excellent selectivity to produce the bicyclic ether product in high yield using stoichiometric quantities of the catalyst. The use of sub-stoichiometric quantities of indium tribromide leads to a reversal of selectivity giving carbonyl compounds produced by a Meinwald-type rearrangement process. Reaction of the isomeric 2,3-epoxide gives the cyclic diol produced through a 6-*endo* cyclization in high yield and with excellent selectivity.

Experimental

General experimental

Commercially available reagents were used without further purification; anhydrous solvents were obtained from the Aldrich Chemical Company. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 and/or 360 nm) or using potassium permanganate solution (1% in water) followed by charring. Infrared (IR) spectra were recorded in the range 4000–600 cm^{-1} as neat oils or solids and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ at 25 °C unless stated otherwise and are reported in ppm; *J* values are recorded in Hz and multiplicities are expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using the ionization technique stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron impact ionization. High resolution mass spectra (HRMS) were obtained courtesy of the



Scheme 3 Synthesis and cyclization reactions of 2,3-epoxygeranyl acetate.

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EPSRC Mass Spectrometry Service University of Wales Swansea, UK using the ionization method specified. Removal of solvent refers to evaporation at reduced pressure using a rotary evaporator followed by the removal of trace volatiles using a vacuum pump.

Geranyl pivalate

To a solution of geraniol (4.00 g, 25.9 mmol) in pyridine (10 ml) was added trimethylacetyl chloride (3.52 g, 29.2 mmol) and a catalytic quantity of 4-dimethylaminopyridine (158.4 mg, 1.30 mmol) and the reaction mixture was left to stir at room temperature for 6 hours. Dichloromethane (40 ml) was added and the organic phase washed with water (2 × 50 ml), hydrochloric acid (2 × 20 ml, 1 M solution) and sodium hydrogen carbonate solution (4 × 20 ml, 10% solution). The organic phase was then dried over magnesium sulfate and the solvent removed under reduced pressure to give a yellow oil which was purified by column chromatography (hexane → 10% ethyl acetate : hexane) to give the product *geranyl pivalate* as a colourless oil (5.86 g, 95%); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 1.12$ (9H, s), 1.53 (3H, s), 1.61 (3H, s), 1.63 (3H, s), 1.94–2.08 (4H, m), 4.50 (2H, d, $J = 7$ Hz), 5.00 (1H, t, $J = 7$ Hz), 5.25 (1H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta =$ 179.0, 142.0, 132.1, 124.2, 119.1, 61.7, 39.9, 39.1, 27.6, 26.7, 26.1, 18.1, 16.8; ν_{max} (film)/cm^{-1} (neat) 2970, 2931, 1727, 1480, 1397, 1281, 1147, 939 and 771; MS (EI) *m/z* 238, (M)$^+$; HRMS (EI) calculated for $C_{15}H_{26}O_2$ (M)$^+$ 238.1927, found (M)$^+$ 238.1926.

Geranyl acetate

(99% yield); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 1.61$ (3H, s), 1.69 (3H, s), 1.71 (3H, s), 2.07 (3H, s), 2.08–2.15 (4H, m), 4.60 (2H, d, $J = 7$ Hz), 5.09 (1H, t, $J = 7$ Hz), 5.35 (1H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 171.5$, 142.6, 132.2, 124.5, 118.6, 61.8, 39.9, 26.7, 26.1, 21.4, 18.1, 16.8; ν_{max} (film)/cm^{-1} (neat) 2968, 2919, 2857, 1739, 1443, 1365, 1227, 1021, 953 and 607; MS (EI) *m/z* 196 (M)$^+$; HRMS (ES, NH_3) calculated for $C_{12}H_{24}NO_2$ (M + NH_4)$^+$ 214.1802, found (M + NH_4)$^+$ 214.1802.

6,7-Epoxygeranyl pivalate 4a

To a solution of geranyl pivalate (1.63 g, 6.85 mmol) in dichloromethane (75 ml) at room temperature was added 3-chloroperoxybenzoic acid (77%, 1.25 g, 7.24 mmol) and sodium hydrogen carbonate (608 mg, 7.24 mmol) and the reaction mixture was left to stir at room temperature for 48 hours. The reaction mixture was then washed with sodium metabisulfite solution (2 × 50 ml, 10% solution) and sodium hydrogen carbonate solution (4 × 50 ml, 10% solution). The organic phase was then dried over magnesium sulfate and the solvent removed under reduced pressure to give a yellow oil which was purified by column chromatography (hexane → 10% ethyl acetate : hexane) to give the product *6,7-epoxygeranyl pivalate* **4a** as a colourless oil (1.14 g, 66%); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 1.12$ (9H, s), 1.19 (3H, s), 1.23 (3H, s), 1.55–1.63 (2H, m), 1.65 (3H, s), 2.02–2.20 (2H, m), 2.63 (1H, t, $J = 7$ Hz), 4.50 (2H, d, $J = 7$ Hz), 5.30 (1H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 138.7$, 130.7, 122.9, 122.3, 60.2, 58.4, 38.5, 26.2, 25.4, 24.7, 16.7, 15.2; ν_{max} (film)/cm^{-1} (neat) 2962, 2933, 1726, 1481, 1459, 1281, 1148, 939 and 771; MS (EI) *m/z* 254 (M)$^+$; HRMS (ES, NH_3) calculated for $C_{15}H_{27}O_3$ (M + H)$^+$ 255.1955, found (M + H)$^+$ 255.1957.

6,7-Epoxygeranyl acetate 4b

(71% yield); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 1.19$ (3H, s), 1.24 (3H, s), 1.56–1.63 (2H, m), 1.66 (3H, s), 1.98 (3H, s), 2.03–2.21 (2H, m), 2.63 (1H, t, $J = 7$ Hz), 4.52 (2H, d, $J = 7$ Hz), 5.32 (1H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 171.5$, 141.6, 119.3, 64.3, 61.6, 58.8, 36.6, 27.5, 25.2, 21.4, 19.1, 16.9; ν_{max} (film)/cm^{-1} (neat) 2962, 2926, 1736, 1448, 1378, 1228, 1121, 1022, 954 and 679; MS (EI) *m/z* 212 (M)$^+$; HRMS (ES, NH_3) calculated for $C_{12}H_{24}NO_3$ (M + NH_4)$^+$ 230.1751, found (M + NH_4)$^+$ 230.1748.

Typical experimental procedure for the indium tribromide-mediated cyclization of 6,7-epoxygeranyl pivalate

To a solution of 6,7-epoxygeranyl pivalate (115 mg, 0.45 mmol) in anhydrous dichloromethane (10 ml) under a nitrogen atmosphere was added indium tribromide (161 mg, 0.45 mmol) and the reaction stirred at room temperature for 4 hours. The solvent was then removed under reduced pressure and the crude reaction mixture passed through a short plug of silica which was washed with 10% ethyl acetate : hexane. Removal of the solvent under reduced pressure gave the product *2,2-dimethylpropionic acid 1,3,3-trimethyl-7-oxa-bicyclo[2.2.1] hept-2-ylmethyl ester* **5a** (102 mg, 89%); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 0.98$ (3H, s), 1.03 (3H, s), 1.13 (9H, s), 1.29 (3H, s), 1.36–1.69 (5H, m), 3.71 (1H, d, $J = 5$ Hz), 3.91 (1H, dd, $J = 11$ and 7 Hz), 4.06 (1H, dd, $J = 11$ and 7 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 177.4$, 85.0, 84.7, 62.5, 53.3, 43.9, 37.6, 37.4, 26.2, 24.9, 24.8, 22.2, 17.3; ν_{max} (film)/cm^{-1} (neat) 2964, 2876, 2256, 1720, 1458, 1384, 1287, 1167, 1075 and 919; MS (EI) *m/z* 254 (M)$^+$; HRMS (ES, NH_3) calculated for $C_{15}H_{27}O_3$ (M + H)$^+$ 255.1955, found (M + H)$^+$ 255.1958.

2,3-Epoxygeranyl acetate 8

To a solution of geraniol (6.22 g, 40.3 mmol) and vanadyl acetylacetonate (149.3 mg, 0.56 mmol) in chloroform (50 ml) was added an anhydrous solution of *tert*-butyl hydroperoxide (5–6 M solution in decane, 8 ml, 44.4 mmol) dissolved in chloroform (2 ml) drop-wise over 20 minutes and the reaction heated to reflux for 6 hours. The reaction mixture was then washed with sodium metabisulfite solution (2 × 40 ml, 10% solution), the organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product obtained was then stirred at room temperature with acetic anhydride (20 ml) and pyridine (25 ml) for 18 hours. Dichloromethane was then added (40 ml) and the reaction mixture washed with water (2 × 50 ml), hydrochloric acid (2 × 20 ml, 1 M solution) and sodium hydrogen carbonate solution (4 × 25 ml, 10% solution). The organic phase was then dried over magnesium sulfate and the solvent removed under reduced pressure to give a yellow oil which was purified by column chromatography (hexane → 10% ethyl acetate : hexane) to give the product *2,3-epoxygeranyl acetate* **8** as a colourless oil (5.75 g, 67%); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 1.30$ (3H, s), 1.42–1.51 (2H, m), 1.60 (3H, s), 1.68 (3H, s), 2.04–2.08 (2H, m), 2.09 (3H, s), 2.98 (1H, dd, $J = 4$ and 7 Hz), 4.02 (1H, dd, $J = 7$ and 12 Hz), 4.30 (1H, dd, $J = 4$ and 12 Hz), 5.07 (1H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 171.3$, 132.6, 123.6, 63.8, 61.0, 60.0, 38.7, 26.1, 24.0, 21.2, 18.1, 17.2; ν_{max} (film)/cm^{-1} (neat) 2978, 2928, 2251, 1714, 1651, 1445, 1378, 1219, 1146, 1037, 914, 870

and 731; MS (EI) m/z 212 $(M)^+$; HRMS (ES, NH_3) calculated for $C_{12}H_{21}O_3$ $(M + H)^+$ 213.1485, found $(M + H)^+$ 213.1484.

Typical experimental procedure for the cyclization of 2,3-epoxygeranyl acetate

To a solution of 2,3-epoxygeranyl acetate (110 mg, 0.52 mmol) in anhydrous dichloromethane (10 ml) under a nitrogen atmosphere was added indium tribromide (184 mg, 0.52 mmol) and the reaction stirred at room temperature for 4 hours. The solvent was then removed under reduced pressure and the crude reaction mixture passed through a short plug of silica which was washed with 10% ethyl acetate : hexane. Removal of the solvent under reduced pressure gave the product *(2′,5′-dihydroxy-2′,6′,6′-trimethyl)cyclohexylmethyl acetate* **9** (104 mg, 87%); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 1.11$ (3H, s), 1.19 (6H, s), 1.44–1.73 (5H, m), 2.03 (3H, s), 3.50 (1H, dd, $J = 8$ and 3 Hz), 3.89 (1H, dd, $J = 12$ and 3 Hz), 4.22 (1H, dd, $J = 12$ and 3 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 171.9$, 75.1, 72.7, 65.7, 53.8, 36.8, 33.5, 29.0, 27.9, 23.2, 21.6, 16.1; ν_{max} (film)/cm^{-1} (neat) 3466, 2936, 1737, 1371, 1234, 1036; MS (EI) m/z 230 $(M)^+$; HRMS (ES, NH_3) calculated for $C_{12}H_{23}O_4$ $(M + H)^+$ 231.1591, found $(M + H)^+$ 231.1589.

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