A stereospecific one-pot synthesis of β-chloro esters *via* the $BiCl_3$ catalysed *O*-acylative cleavage of crowded epoxides

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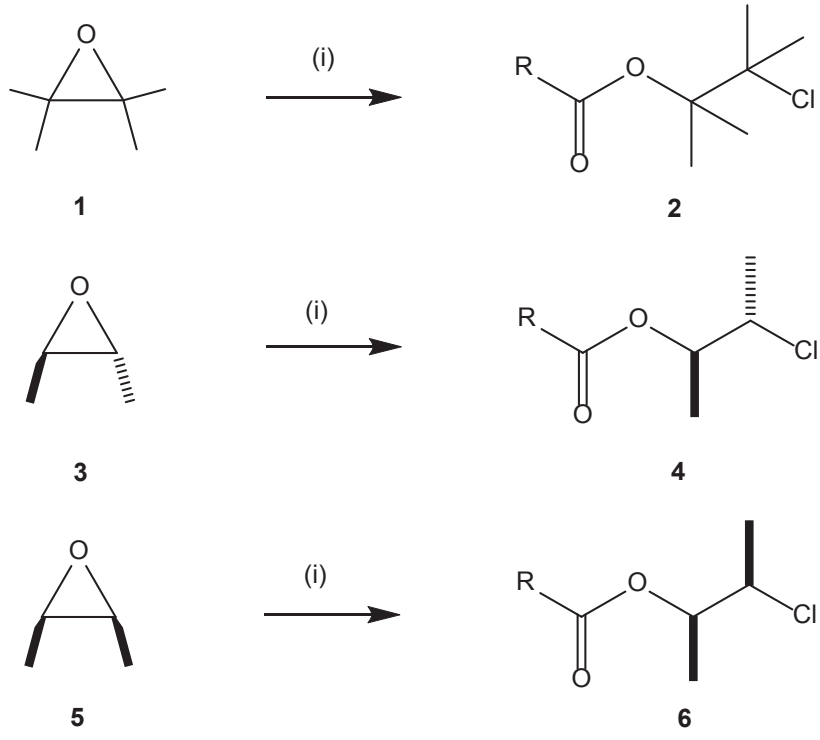
A simple, one-pot procedure is described for the stereospecific preparation of β-chloro esters from the corresponding crowded epoxide.

Keywords: epoxides, β-chloro esters, stereospecific synthesis

The cleavage of cyclic ethers using Lewis acids is, in principle, an attractive synthetic route to stereochemically defined halo-alkanes.[1] However, the cleavage of furans for example, has failed to attain any prominence in organic synthesis perhaps because both stoichiometric amounts of Lewis acid, and extended periods of heating are often required for ring fission to occur (*i.e.,* $ZnCl_2$[2] $FeCl_3$[3] $MgBr_2$[4] $AlCl_3$[5]). To address these limitations, we developed previously a mild (DCM/20°C), stereospecific, high yielding, Bi(III) catalysed (5%) *O*-acylative cleavage approach using acid halides, to afford γ-haloesters starting from the corresponding five-membered furan.[6,7] Our interest in the development of Fuel Dehydrating Icing Inhibitors (FDII)[8] based upon crowded 1,3-dioxolan-2-ylium cations for applications in the aeronautical industry, stimulated our approach to seeking high-yielding and efficient routes to a range of substituted and stereochemically defined β-halo esters. Stereospecific, yet experimentally arduous routes to β-halo esters *via* the chlorination of *E*/*Z* butenes have been known for some time.[9] The cleavage of epoxides in the presence of an activated acyl equivalent to afford the corresponding β-chloro ester has been achieved using air sensitive ($TiCl_4$),[10] expensive (Eu),[11] or toxic (Hg/Al)[12] Lewis acids. A "one-pot" approach has been reported which requires a Cu catalyst along with a stoichiometric quantity of *tert*-butyldimethylsilyl chloride to generate the intermediate silyl ether; however this must then be transformed to the desired β-chloro ester *in situ*.[13] We report here the extension of our Bi(III) catalysed *O*-acylative cleavage methodology to include epoxides, which in turn furnishes a high-yielding, efficient, one-pot, stereospecific route to stereochemically defined β-chloro esters (Scheme 1).

Results and discussion

The hitherto unreported 2,2,3,3-tetramethyl β-chloro ester **2** was prepared in excellent yield (85%) by treating a mixture of epoxide **1** and $^tBuCH_2COCl$, with $BiCl_3$ (5%). It should be pointed out that the corresponding β-bromo ester may, in principle, be prepared using a catalyst/electrophile combination of $^tBuCH_2COBr$ and $BiBr_3$.[6] Importantly, the *trans* (±)-**3**, and *cis* (±)-**5** epoxides were converted in near quantitative chemical yield to the similarly novel *erythro* (±)-**4** and *threo* (±)-**6** diastereoisomers with excellent stereocontrol (*i.e.,* diastereoisomer excess > 97% as determined *via* gas chromatography). The relative stereochemistries of **4** and **6** were assigned on the basis of the similarity of their NMR data with respect to closely related diastereoisomerically pure compounds (*i.e.,* 3-chloro-2-butyl acetate,[9] 3-bromo-2-



Scheme 1 Synthesis of **2**, **4**, and **6** from the corresponding epoxide. Reagents: R = $^tBuCH_2$- (i) $BiCl_3$ (5%), ($^tBuCH_2COCl$).

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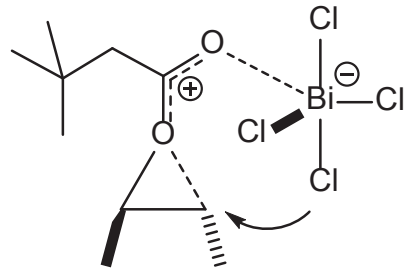

Fig. 1 Proposed acyloxy:$BiCl_4^-$ ion pair intermediate consistent with *O*-acylative cleavage of epoxides (reaction of **3** shown).

butyl acetate,[14] 3-hydroxy-2-butyl acetate[15]). The implication of the observed stereospecificity is that the Bi(III) catalysed *O*-acylative cleavage of epoxides **3** and **5** is consistent with a concerted S_N2 process, wherein the ethereal C—O bond of the intermediate acyloxy:$BiCl_4^-$ ion pair[7] becomes significantly polarised without actual cleavage prior to attack by the chloride anion (Fig. 1).

In conclusion, we have developed a mild, high yielding, stereospecific, one-pot route to β-chloro esters, thereby extending the utility of Bi(III) catalysed *O*-acylative cleavage for the elaboration of cyclic ethers in organic synthesis.

Experimental

^{1}H NMR spectra were determined in $CDCl_3$ at 400 MHz on a Variant instrument at the University of Bristol. HRMS were also determined at the University of Bristol. GC analyses were performed using an Agilent 6890N GC system. {HP-5MS (30 m x 0.25 mm) He = 1 mL min^{-1}, T^o (inj) = 280°, T^o(oven) = 40° (3 min) → 240° /10°C min^{-1}].

Conversion of epoxides into β*-chloro esters; general procedure*

(2'-Chloro-1',1',2'-trimethylpropyl)-3,3-dimethylbutanoate (**2**): The ester **2** was prepared *via* a modification of the method reported by Costello *et al*.[6] To a mixture of 3,3-dimethyl-butanoyl chloride (1.65 g, 12 mmol) and epoxide **1** (1.54 g, 15 mmol) in DCM (30 mL) was added $BiCl_3$ (0.3 g, 0.9 mmol) under an atmosphere of dry nitrogen. The solution was stirred at room temperature for 12 h, after which time water (30 mL) was added to afford a suspension which was extracted with DCM (3 x 15 mL). The combined extracts were dried (K_2CO_3), filtered, concentrated *in vacuo* and distilled (50°C, 8 mmHg) to afford an oil characterised as **2** (2.39 g, 85%); δ_H (400 MHz, $CDCl_3$) 1.03 (s, 9H), 1.63 (s, 6H), 1.68 (s, 6H), 2.13 (s, 2H); δ_C (100 MHz, $CDCl_3$) 21.1, 28.1, 29.9, 31.2, 49.5, 75.0, 85.8, 171.5. HR-MS(CI) calcd for $[M+H]^+$ 235.1465; found 235.1463.

[1'(RS),2'(SR),2'-Chloro-1'-methylpropyl]-3,3-dimethylbutanoate (**4**): Yield 87%; δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9H), 1.29 (d, 3H, *J* 6.4Hz), 1.48 (d, 3H, *J* 6.8Hz), 2.22 (s, 2H), 4.12 (dq, 1H, *J* 6.8, 4.2Hz), 4.99 (dq, 1H, *J* 6.4, 4.2Hz). δ_C (100 MHz, $CDCl_3$) 15.6, 20.8, 29.8, 31.0, 48.2, 59.5, 72.9, 171.8. HR-MS(CI) calcd for $[M+H]^+$ 207.1152; found 207.1149. GC retention times 12.44 min (**4**) and 12.56 min (**6**); 37:1 respectively, d.e. > 97%.

[1'(RS),2'(RS),2'-Chloro-1'-methylpropyl]-3,3-dimethylbutanoate (**6**): Yield 90%; δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9H), 1.30 (d, 3H, *J* 6.4Hz), 1.49 (d, 3H, *J* 6.8Hz), 2.23 (s, 2H), 4.05 (dq, 1H, *J* 6.8, 4.5Hz), 5.04 (dq, 1H, *J* 6.4, 4.6Hz); δ_C (100 MHz, $CDCl_3$) 16.6, 20.7, 29.8, 31.0, 48.2, 58.9, 72.6, 171.7. HR-MS(CI) calcd for $[M+H]^+$ 207.1152, found 207.1145. GC retention times 12.44 min (**4**) and 12.56 min (**6**); 1:44, respectively, d.e. > 98%.

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