Pergamon

Tetrahedron Letters 43 (2002) 4111–4114

TETRAHEDRON LETTERS

Cesium propionate as an epoxide cleavage and inversion reagent

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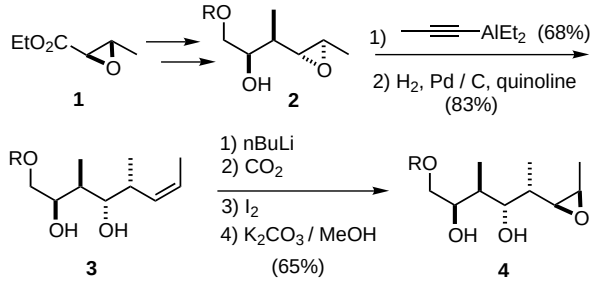
Received 12 February 2002; accepted 20 March 2002

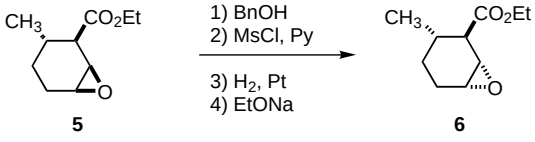
Abstract—A new epoxide inversion method, based on cesium propionate as the epoxide-cleaving agent, was developed. The initial epoxide-cleavage reaction produced a pair of regioisomeric propionates that were mesylated and methanolyzed to produce the inverted epoxide. Several new epoxides were prepared by this method, including 3,4-epoxy alcohols, which are important precursors for polypropionate synthesis. © 2002 Elsevier Science Ltd. All rights reserved.

Epoxides are versatile and useful intermediates for organic synthesis that have been prepared stereoselectively from a variety of starting materials and by different strategies.[1] For some time, our group has been interested in the application of epoxide chemistry to the preparation of polypropionates (Scheme 1).[2] This approach provides a route for the preparation of polypropionate units where the stereochemistry of the resulting hydroxyl and methyl groups rely on the configuration and the *cis*/*trans* geometry of the epoxide precursors (**1**, **2** and **4**). The crucial stereoselective epoxidations in the sequence were attained by iodocyclization reactions, where the configuration of the resulting epoxide depends on the configuration of the preexisting hydroxyl and methyl groups.[2,3] Although this approach provides a series of highly substituted diastereomeric 3,4-epoxy alcohols, the complementary epoxide stereoisomers (*anti* versus *syn* or vice versa) cannot be obtained. To make our strategy general, a method that could produce the elusive 3,4-epoxy alcohol diastereomers was required. Therefore, an epoxide inversion strategy was explored as a possible solution to this problem.



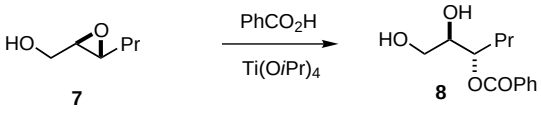
Scheme 1.

Epoxide inversion procedures are usually based on cleavage by a masked hydroxyl nucleophile, conversion of the resulting alcohol to a suitable leaving group and ring closure under basic conditions.[4] For example, in a study related to the synthesis of the Mediterranean fruit fly attractant **6**, benzyl alcohol was used as the oxirane-cleaving agent (Eq. (1)).[4b] Mesylation, followed by hydrogenolysis and ethanolysis afforded the inverted *endo* epoxide **6**, which was previously available only as a mixture with **5**.



(1)

Carboxylic acids and carbonates have also been used as epoxide cleaving agents. Sharpless and co-workers showed that 2,3-epoxy alcohol **7** can be opened regioselectively with benzoic acid and titanium tetraisopropoxide (Eq. (2)).[5] Other examples include the work of Kishi and collaborators, where the 2,3-epoxy alcohol **9** was cleaved intermolecularly by a carbonate with the aid of a Lewis acid (Eq. (3)).[6] This neighboring group assisted (α)-ring cleavage of 2,3-epoxy alcohols has been similarly applied to other systems.[7]



(2)

Keywords: epoxide inversion; oxirane inversion; cesium propionate; 3,4-epoxy alcohols.

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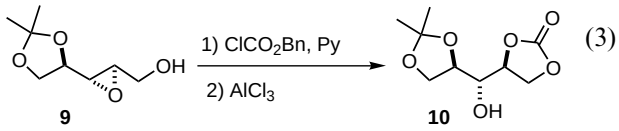
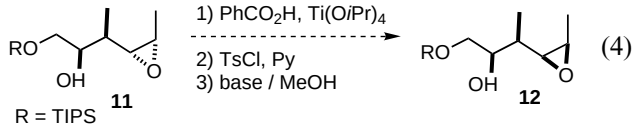
PII: S0040-4039(02)00739-6



(3)

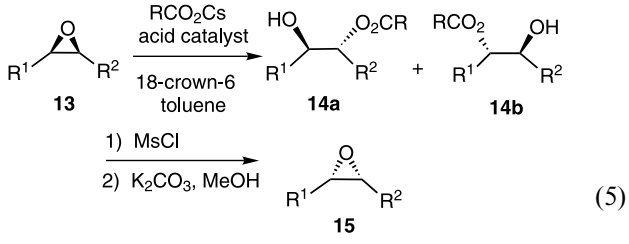
We herein describe a new epoxide inversion strategy based on cesium propionate as the oxirane-cleaving agent. This strategy is amenable to highly hindered oxirane systems and does not require the assistance of a neighboring group.

For our systematic polypropionate synthesis studies (vide supra), we envisaged an adaptation of the Sharpless procedure as a way to access the complementary epoxides. Consequently, in an attempt to prepare epoxide **12** (which cannot be prepared via the carbonate extension procedure), the hindered 3,4-epoxy alcohol **11** was reacted with benzoic acid in the presence of $Ti(OiPr)_4$ (Eq. (4)). Interestingly, no epoxide cleavage product was obtained even after 30 h and 5 equiv. of benzoic acid. The Kishi carbonate approach was also tried, but again, only starting material was recovered. In these instances, the chemistry of 3,4-epoxy alcohols did not resemble that of their 2,3-analogues.



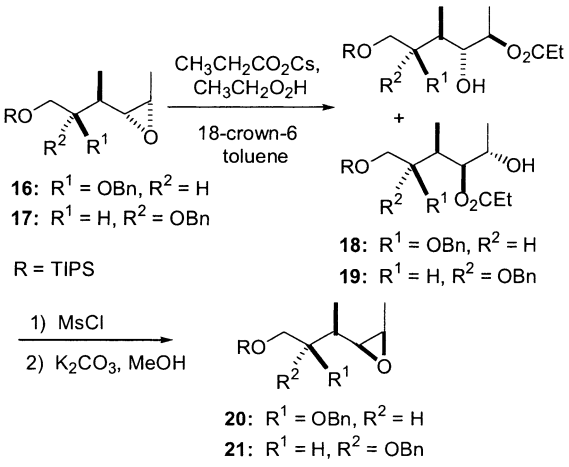
(4)

Parallel to these studies, we were independently exploring a hydroxyl inversion strategy on a related system using cesium acetate.[8] This prompted us to explore the possibility of using cesium carboxylates as oxirane-cleaving agents for an epoxide inversion sequence. Cesium salts are known to enhance nucleophilic substitution reactions by what has been termed 'the cesium effect'.[9] Our approach is illustrated in Eq. (5). Although a mixture of regioisomeric hydroxy esters (**14a**,**b**) can be produced, this is of no consequence as both products would be converted to the same inverted epoxide **15**.



(5)

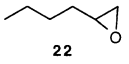
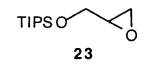
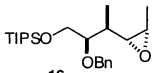
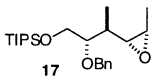
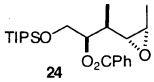
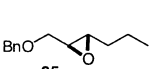
We began our investigation with epoxy alcohol **16** as the test substrate since this compound was essential to our ongoing polypropionate synthesis studies (Eq. (6)). Cesium acetate, commonly used for hydroxyl inversion, was not effective as an oxirane cleaving agent. However, commercially available cesium propionate, which contains 2% propionic acid, allowed the propionate to attack the epoxide carbons in **16**. To expand upon this finding, several acid catalysts were examined. Propionic acid, acetic acid, $HClO_4$, PTSA and NH_4Cl were shown to catalyze the reaction. Other acids such as $SnCl_4$ and CSA were less effective. Among these, acetic acid was the most effective and was selected for the remainder of the study. Interestingly, cesium acetate was not effective even after the addition of acetic acid. Thus, a mixture of cesium propionate/2% propionic acid (5 equiv.), 18-crown-6 (1 equiv.), acetic acid (1 equiv.) and epoxide **16** in toluene produced, after 120 h, a 5:1 mixture of regioisomeric propionates (**18**) in 62% yield. Lower cesium propionate and catalyst loads could be used at the expense of longer reaction times.



(6)

This study was then extended to other epoxide substrates. The results are summarized in Table 1. The epoxide cleavage reaction was slow, in accordance to

Table 1. Acid-catalyzed epoxide cleavage with cesium propionate

entry	epoxide	time (h)[a]	product (ratio)[b]	yield (%)[c]
1	 22	36	**26** (2:1)	87
2	 23	80	**27** (2:1)	98
3	 16	120	**18** (5:1)	62[d]
4	 17	120	**19** (5:1)	68[d]
5	 24	120	**28** (1:0)	45[d]
6	 25	160	**29** (4:1)	59[d]

[a] The reaction time was monitored by TLC.

[b] Mixture of regioisomeric carboxylates. The ratio was determined by NMR.[11]

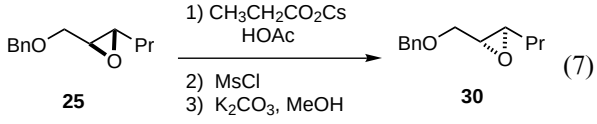
[c] Isolated yield (mixture of regioisomers).

[d] The remainder was recovered unreacted starting material for a close to quantitative material balance.

other epoxide cleavage methods, and a mixture of regioisomers was produced. As expected, for the less hindered epoxides **22** and **23** (entries 1 and 2), the reaction was faster and proceeded with higher yields. In each case, a 2:1 regioselectivity favoring attack on the less hindered epoxide carbon was observed.[10,11] The more hindered polypropionate precursor **17** (as well as **16**) exhibited longer reaction times with improved regioselectivity in 68% yield (entry 4). In each instance, the carboxylate product mixtures were easily separated from the unreacted starting epoxides by flash chromatography for a close to quantitative material balance. In order to gain some insight into the effects of the electronic properties of the adjacent protecting groups, the benzoylated epoxide **24** was prepared (entry 5). This time, only one regioisomer was detected but the epoxide was less reactive. Most S_N2 reactions on epoxides are retarded by the presence of inductive electron-withdrawing groups, as was the case for **24**.[12]

Since the diastereomeric 3,4-epoxy alcohols **16** and **17** were racemic, an optically active system was included in this study. Thus, commercially available (2*S*,3*S*)-(−)-3-propyloxiranemethanol was benzylated to produce **25** in 88% yield. This *trans*-disubstituted protected 2,3-epoxy alcohol ($[\alpha]_D^{23} = -26.6°$) was used to verify the stereochemical outcome of our epoxide inversion protocol. This epoxide reacted more slowly and exhibited a somewhat lower regioselectivity (entry 6).

In order to complete the epoxide inversion sequence, hydroxy esters **18**, **19** and **29** were efficiently mesylated and methanolyzed (>90% yield) to the inverted epoxides **20**, **21** and **30**, respectively (Eqs. (6) and (7)).[10] It is noteworthy that epoxides **20** and **21** cannot be prepared diastereoselectively by standard epoxidation procedures.[2]



(7)

A side-by-side comparison of the ^{13}C NMR spectra of starting epoxides **16** and **17** with those of the inverted epoxides **20** and **21** clearly established their diastereomeric relationship. The epoxide carbons chemical shifts, shown in Table 2, were used to aid in establishing their relative stereochemistry.[13] A close examination of the ^{13}C NMR spectra of a series of diastereomeric 2-methyl-3,4-epoxy alcohols collected from our previous polypropionate synthetic studies[2] reveals that their relative configuration can be established from the ^{13}C NMR resonances of the epoxide bearing carbons. When the relative configuration between the methyl and epoxide moiety is *syn*, chemical shifts ranging from 60–62 and 54–55 ppm are observed for C-4 and C-5, respectively. Similarly, the series having the *anti* relative configuration show chemical shifts between 57–59 and 51–53 ppm for C-4 and C-5, respectively. These trends allowed the confirmation of the proposed relative stereochemistry for the new epoxides **20** and **21**. In addition, the optically active epoxide **30** confirmed that epoxide inversion had indeed occurred; the specific rotation changed from $[\alpha]_D^{23} = -26.6°$ for compound **25** to $[\alpha]_D^{21} = +25.0°$ for epoxide **30**.[14]

Table 2. ^{13}C NMR chemical shifts for the C-4, C-5 carbons and epoxide configuration

Epoxide	C-4 (ppm)	C-5 (ppm)	Configuration[a]
16	58.8	52.8	*anti*
17	57.4	51.1	*anti*
20	60.4	53.6	*syn*
21	60.1	55.0	*syn*

[a] Relative configuration between the C-3 methyl and the epoxide.

In conclusion, this study represents a novel solution to the problem of inversion of configuration encountered in sterically hindered epoxides. This strategy is based on the acid-catalyzed cleavage of the oxirane ring with cesium propionate and represents a new tool for the preparation of new diastereomeric epoxides unattainable through other means. This route improves the scope for the application of epoxide-based approaches to polypropionate synthesis.

Acknowledgements

This work was supported by grants from the NIH RISE (1R25-GM-61151-01A1) and SCORE (2S06GM-08102-29) programs. Partial support for the NMR facility was provided by the NIH-RCMI program (RR03641). The authors also thank Dr. Abimael D. Rodríguez for many helpful discussions and for proofreading this manuscript.

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10. All products in this study were characterized by 1D/2D ^{1}H and ^{13}C NMR methods.
11. The regiochemistry for each system was established by 1D and 2D NMR. For example, the major regioisomer **18**, arising from attack of the propionate nucleophile at C-5 (epoxide **16**), produced a correlation in the COSY spectra between the resonance at 5.09 ppm (dq, $J=6.4$, 2.9 Hz) for the proton at the carboxylate bearing carbon and the terminal methyl at 1.29 ppm (d, $J=6.4$ Hz). Similar analyses allowed easy discrimination among each pair of regioisomers.
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13. For the application of ^{13}C NMR spectroscopy for stereochemical analysis in acyclic highly substituted alcohol, see: (a) Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *J. Org. Chem*. **1996**, *61*, 4975; (b) Whitesell, J. K.; Hildebrandt, B. *J. Org. Chem*. **1985**, *50*, 4975.
14. (a) General procedure for epoxide cleavage with cesium propionate: **(2*S*,3*S*)-3-(1-benzyloxy-2-hydroxyhexyl) propanoate (29)**. Cesium propionate/2% propionic acid (1.17 g, 4.17 mmol, 5 equiv.) and 18-crown-6 (1.10 g, 0.834 mmol, 1 equiv.) were added to the reaction flask. The flask was flame-dried under nitrogen while stirring to remove moisture from the solids. Dry toluene (15 mL) and 0.05 mL (0.834 mmol, 1 equiv.) of acetic acid were added and the mixture was vigorously stirred. When the solids dispersed, 0.17 g (0.83 mmol) of epoxide **25** $[\alpha]_D^{22}=-26.6°$ (*c* 0.03, ether) was added. The system was heated to reflux for 160 h (monitored by TLC). Work-up and solvent evaporation yielded the crude product mixture. The unreacted starting material and ester regioisomers were separated by flash chromatography (4:1 hexane/ethyl acetate) yielding 0.13 g (57%) of a 4:1 mixture of regioisomers **29**; (b) General procedure for the mesylation of alcohols: **3-[(2S,3S)-1-benzyloxy-2-methanesufonyloxyhexyl] propionate (31)**. To the reaction flask was added 0.03 g (0.1 mmol) of the corresponding hydroxy ester mixture **29**, 5 mL of CH_2Cl_2, 0.2 g (0.2 mmol) of DMAP and 0.05 mL (0.28 mmol) of *N*,*N*-diisopropylethylamine. The reaction mixture was cooled to −10°C with a water/NaCl/ice bath. After 30 min, 0.02 mL (0.19 mmol) of mesyl chloride was added dropwise via syringe. The reaction was completed in 30 min (TLC) at which time, water (1 mL) was added dropwise while keeping the system cold. Work-up and solvent evaporation yielded the crude regioisomeric mesylate mixture, which could be used without further purification; (c) General procedure for the methanolysis of propionates: **(+)-(2*R*,3*S*)-1-benzyloxy-2,3-epoxyhexane (30)**. The mesylate mixture (0.03 g, 0.1 mmol), 5 mL of MeOH and 0.01 g (0.04 mmol) of K_2CO_3 were added to the reaction flask and stirred for 3 h (TLC). Work-up and solvent evaporation yielded a crude oil, which was purified by column chromatography (29:1 hexane/ethyl acetate) yielding 0.018 g (90%) of epoxide product **30**. ^{1}H NMR ($CDCl_3$): δ 7.30 (m, 5H), 4.57 (d, $J=12.0$ Hz, 1H), 4.55 (d, $J=12.0$ Hz, 1H), 3.72 (dd, $J=11.4$, 3.3 Hz, 1H), 3.47 (dd, $J=11.4$, 5.6 Hz, 1H), 2.95 (m, 1H), 2.83 (m, 1H), 1.55 (m, 4H), 0.98 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 138.0, 128.4, 127.7, 127.7, 73.3, 70.5, 57.0, 56.0, 33.7, 19.3, 13.9; HREIMS for $C_{13}H_{18}O_2$ [M^+]; calcd 206.1306, found 206.1306; $[\alpha]_D^{23}=+25.0°$ (*c* 0.02, ether).