A Highly Diastereoselective Synthesis of trans-para-Menthanic Epoxyesters

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Abstract: A highly diastereoselective two-step synthesis of trans-para-menthanic epoxyesters from parent para-menthenic esters is presented. Among bromolactones or bromohydrines obtained with NBS in the first step, only those, which afforded trans-epoxides, reacted.

Key words: para-menthanic epoxyesters, highly diastereoselective epoxidation, highly diastereoselective synthesis

The ease of preparation of epoxides and their facile ring opening make them important intermediates in organic synthesis. Many reactions show a chemo-, regio-, diastereo- and enantioselective character: for example, the enantioselective epoxidation of prochiral allylic alcohols by Sharpless, or the highly diastereoselective one of unsaturated chiral alcohols with m-chloroperoxybenzoic acid or tert-butyl hydroperoxide and salts of transition metals.

With simple alkenes, the results are less selective. Using carboxylic peroxy acids, the reaction occurs on the less-hindered side of the double bond: for instance, cis-3-methyl-4-tert-butyl cyclopentene yields both cis/trans-isomers in the ratio 12:88. We tried to use peroxyacetic acid to obtain epoxides from unsaturated esters 1a–d (Figure): the isomeric cis/trans ratio (CH2= with respect to the substituent i-Pr) was approximately 47:53. This result is consistent with epoxidation of limonene which furnishes an approximately 50:50 mixture of isomers: the reaction is not stereoselective since there are no axially oriented bulky groups to selectively shield one face.

In order to obtain non-stoichiometric mixtures enriched in one of the isomers, we tested a two-step procedure via the bromohydrine.

Treatment of methyl 2(R,S)-methyl-3-[4(S)-iso-propylcyclohexenyl] propanoate (1a) with N-bromosuccinimide (NBS) in a water/acetone mixture afforded in quantitative yield the four diastereoisomeric bromolactones 3a (Scheme 1), according to the mechanism proposed by Bartlett. The cis/trans isomeric ratio was about 10:90, hence, the approach of bromine on the double bond of 1a is much more stereoselective than that of oxygen from peracid. It may be that the i-Pr substituent hinders the access of NBS to the shielded face of the cycle, whereas the peracid is small enough to be able to access even the sterically hindered alkene. When the crude mixture of bromolactones was treated with a methanolic sodium hydroxide solution, only the trans-isomers 3a reacted (trans-esterification followed by intramolecular nucleophilic substitution), affording exclusively both epoxides trans-2a (isomeric ratio ~68:32) in a 75% yield, isomers cis-3a remaining unchanged.

The different behaviour of isomers cis-3a and trans-3a is easily understood by examination of molecular models (Scheme 2). In the trans-3a isomers, both chair-chair conformations coexist, one of them offering the trans-coplanar relation between substituents Br and O- essential for the intramolecular nucleophilic substitution. On the other hand, in the cis-3a isomers, the conformer allowing the reaction would require three bulky substituents in the axial position: its presence is hence most unlikely in the equilibrium. Thus, the epoxides trans-2a were stereospecifically synthesised from the parent unsaturated esters in 75% yield.

Among the four bromolactones 3a, one of them could be isolated by recrystallisation: the action of methanolic sodium hydroxide gave only one of the trans-2a isomers. Therefore, it was possible to unambiguously assign the spectroscopic characteristics of each of the trans-2a isomers. Those of cis-isomers were obtained by comparison...
with the mixture of epoxides afforded by peroxyacetic acid.

In the same way, dimethyl (4S)-iso-propylcyclohexenyl methyl malonate (1b), when treated as its homologue 1a, gave exclusively the epoxide trans-2b via both bromolactones trans-3b with an overall yield of 78% (Scheme 1).

The stereospecific epoxidation of methyl (4S)-iso-propylcyclohexenyl acetate (1c), and methyl 4(R,S)-tert-butylcyclohexenyl acetate (1d) to yield trans- (2c) and trans- (2d), respectively, was also possible. The action of NBS upon 1c or 1d in the former conditions afforded a mixture of the expected bromohydrine trans-4c or trans-4d, and the bromolactone cis-5c or cis-5d (the latter resulting from intramolecular opening of the intermediate bromonium ion) in the relative ratios ~80:20 and 66:33, respectively (Scheme 3). No isomeric compounds were found. When treated with DBU,13 these mixtures gave only the trans-epoxide with an overall yield of ~75% and ~60%, respectively (the unsaturated lactone 6 resulting from the bromolactone 5 can be easily removed).

Correlations can be established between the configuration of diastereoisomeric p-menthanic epoxides (trans-isomers afforded in two steps / mixtures cis-trans resulting from the action of peroxyacetic acid) and their NMR characteristics. Systematic differences appear in the 1H and 13C spectra of the isomers. They are collected in the Table.

It appears that the proton bonded to the epoxidic carbon 2¢ is more shielded in the trans-isomers than in cis ones (~−0.04 ppm), which agrees with the observations of Sallees regarding limonene oxide.14 The 13C spectrum shows important differences for carbons 2¢, 5¢ and the exocyclic carbon bound to carbon 1¢, which are more shielded in the trans-isomers than in cis ones (~−1.5, −2.8 and −1.0 ppm, respectively). On the contrary, carbon 4¢ is less shielded in the trans-isomers (~+3.6 ppm). These differences allow differentiation and identification of diastereoisomeric isomers.

In conclusion, a highly diastereoselective synthesis of trans-diastereoisomers of para-menthanic epoxyesters has been presented. The method is both easy and efficient, and the yields are good. 1H and 13C NMR spectra of each isomer (trans and cis) were well defined and therefore permit an easy determination of the configuration of these compounds.

NMR spectra were measured on a Bruker AC 250 spectrometer operating at 250 MHz (1H) or 62.9 MHz (13C); δ (ppm) and J (Hz). 1H shifts were referenced to residual CHCl3 (δ = 7.26 ppm) as internal standard, and 13C shifts to internal standard CDCl3 (δ = 77.0 ppm). Mass spectra were recorded on a Fisons Autospec-EQ instrument with electron impact (70 eV). The exact molecular weights were determined by high-resolution analysis. Capillary GC analyses were run on a Delsi Di200 with a CP Sil-8 column (length 25 m, i.d. 0.25 mm, film thickness 0.25 μm).

Methyl 2(R,S)-methyl-3-[4(S)-iso-propylcyclohexenyl] propanoate (1a), dimethyl (4S)-iso-propylcyclohexenyl methyl malonate (1b), and methyl (4S)-iso-propylcyclohexenyl acetate (1c), were ob-
Table NMR Characteristics of cis/trans-Epoxides

<table>
<thead>
<tr>
<th>Epoxide 2</th>
<th>$^1$H NMR δ, $J$ (Hz)</th>
<th>$^{13}$C NMR δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H-2'</td>
<td>C-1'</td>
</tr>
<tr>
<td>cis-2a*</td>
<td>2.95–2.92 (m)</td>
<td>58.6</td>
</tr>
<tr>
<td>trans-2a*</td>
<td>2.89 (d, $J = 5.2$)</td>
<td>58.9</td>
</tr>
<tr>
<td></td>
<td>2.91 (d, $J = 5.5$)</td>
<td>58.8</td>
</tr>
<tr>
<td>cis-2b</td>
<td>2.94 (br)</td>
<td>57.7</td>
</tr>
<tr>
<td>trans-2b</td>
<td>2.89 (d, $J = 5.2$)</td>
<td>58.1</td>
</tr>
<tr>
<td>cis-2c</td>
<td>3.09 (br)</td>
<td>56.8</td>
</tr>
<tr>
<td>trans-2c</td>
<td>3.07 (d, $J = 5.8$)</td>
<td>57.3</td>
</tr>
<tr>
<td>cis-2d</td>
<td>3.08 (br)</td>
<td>56.7</td>
</tr>
<tr>
<td>trans-2d</td>
<td>3.04 (d, $J = 5.5$)</td>
<td>57.1</td>
</tr>
</tbody>
</table>

*Two diastereoisomers.

Note: crystallization of the mixture resulting from step A in a petroleum ether–Et$_2$O solution gave one of the four bromolactones (mp 138 °C). The reaction of NaOH in MeOH with bromolactone thus afforded only one of the trans-2a isomers.

trans-2a Isomer: 2(R or S)-(1S)-(4S)-(4R)-iso-propylcyclohexyl-1-yl)propanoate (2a); Typical Procedure

Step A:

To a well-stirred solution of unsaturated ester 1a (2.24 g, 10 mmol), and H$_2$O (0.45 g, 25 mmol) in acetic (15 mL) kept below 20 °C under Ar, NBS was added in small portions (1.78 g, 10 mmol). The solution was stirred for 30 min. The mixture was poured into H$_2$O and extracted with Et$_2$O, and the extracts were washed with H$_2$O and dried. The solvent was removed to yield the four isomers of bromolactone 3a (quantitative crude yield).

Step B:

A solution of bromolactones (crude mixture) (2.31 g, 8 mmol) and NaOH (0.64 g, 16 mmol) in MeOH (100 mL) was stirred at r.t. for 2 h. The solvent was removed and replaced with Et$_2$O, and the ether layer was washed, dried, and concentrated. The residue was subjected to HPLC (petroleum ether–Et$_2$O, 80:20) to remove unreacted bromolactones cis-3a and to afford pure epoxides trans-2a (isomeric ratio ~ 68:32).

Note: Synthesis of cis-3a was purified by HPLC (petroleum ether–Et$_2$O, 80:20). The mixture was stirred for 30 min. The mixture was poured into H$_2$O under Ar, NBS was added in small portions (1.78 g, 10 mmol). The reaction of NaOH in MeOH with bromolactone thus afforded one of the four isomers of bromolactone 3a (quantitative crude yield).

trans-2a: Other Isomer 2(S or R)-(1S)-(4S)-(4R)-iso-propylcyclohexyl-1-yl)propanoate

Synthesized by the two-step reaction and obtained from trans-2a mixture

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Synthesized by the two-step reaction and obtained from trans-2a mixture
Dimethyl[1(R,2S)-2-Epoxy-(4S)-iso-propylcyclohex-1-yl]methyl Malonate (2b)  
Same procedure as for 2a.

Trans-2b Isomer: (1S)-(4S)  
Synthesized by the two-step reaction.

1H NMR (250 MHz, CDCl₃): δ = 3.665 and 3.659 (2 × s, 6H, 20Me), 3.39 (t, 1H, J = 7.3 Hz, H-2), 2.94 (br, 1H, H-2'), 2.12 (d, 2H, J = 7.3 Hz, H-3), 0.75 (d, 6H, J = 6.7 Hz, H-8', -9').

13C NMR (62.9 MHz, CDCl₃); δ = 169.37 (C-1), 58.1 (C-1'), 57.8 (C-2'), 52.48 and 52.60 (OMe), 47.39 (C-2), 38.9 (C-4'), 34.8 (C-3), 32.0 (C-7'), 28.0 (C-6'), 27.3 (C-3'), 22.0 (C-5'), 19.4 and 19.1 (C-8' and C-9').

EIMS: m/z (%) = 284 (M⁺, 20), 152 (87), 137 (35), 135 (38), 133 (40), 132 (99), 113 (44), 111 (39), 109 (49), 81 (38), 69 (52), 59 (36), 55 (100), 43 (44).


cis-2b Isomer: (1R)-(4S)  
Obtained from cis/trans mixture.

1H NMR (250 MHz, CDCl₃) (only characteristic signals displayed): δ = 3.662 and 3.657 (2 × s, 6H, 20Me), 3.39 (t, 1H, J = 7.3 Hz, H-2), 2.94 (br, 1H, H-2'), 2.12 (d, 2H, J = 7.3 Hz, H-3), 0.75 (d, 6H, J = 6.7 Hz, H-8', -9').

13C NMR (62.9 MHz, CDCl₃); δ = 169.43 (C-1), 59.2 (C-1'), 57.7 (C-2'), 52.4 (OMe), 47.33 (C-2), 36.3 (C-3), 35.1 (C-4'), 31.4 (C-7'), 28.7 (C-6'), 27.5 (C-3'), 24.6 (C-5'), 19.5 and 19.4 (C-8' and C-9').

Methyl [1,2-Epoxy-4-tert-butylcyclohex-1-yl] Acetate (2d)  
(2c); Typical Procedure

Step A:  
To a well-stirred solution of an unsaturated ester 1e (0.49 g, 2.5 mmol) and H₂O (0.11 g, 6.25 mmol) in DMSO (12.5 mL) kept below 20°C under Ar, NBS was added in small portions (0.89 g, 5 mmol). The solution was stirred for 15 min. The mixture was poured into H₂O, extracted with Et₂O, and the extracts were washed with H₂O and dried. The solvent was removed to yield the bromohydryne trans-4c and the bromolactone cis-5e (relative yield ~ 80:20, quantitative crude yield).

Step B:  
A solution of the mixture from step A (0.586 g, 2 mmol) and DBU (360 µL, 2.4 mmol) in CH₂Cl₂ (20 mL) was stirred at r.t. for 5 min under Ar. The solvent was removed and replaced with Et₂O. The ethereal layer was washed with 0.5 M HCl, sat. Na₂CO₃, and water, dried and concentrated. The residue was chromatographed on alumina to afford pure trans-epoxide 2c.

Trans-2c Isomer: (1S)-(4S)  
Synthesized by the two-step reaction.

1H NMR (250 MHz, CDCl₃): δ = 3.66 (s, 3H, OMe), 3.07 (d, 1H, J = 5.8 Hz, H-2'), 2.67 and 2.40 (2 × d, 2H, J = 15.3 Hz, H-2), 2.20–0.90 (m, other H's), 0.79 (d, 6H, J = 6.7 Hz, H-8', -9').

13C NMR (62.9 MHz, CDCl₃); δ = 170.7 (C-1), 58.4 (C-2'), 57.3 (C-1'), 51.6 (OMe), 42.3 (C-2), 38.7 (C-4'), 32.0 (C-7'), 28.8 and 27.4 (C-3'- and C-6'), 22.1 (C-5'), 19.4 and 19.1 (C-8' and C-9').

EIMS: m/z (%) = 212 (1), 169 (81), 168 (25), 137 (38), 129 (26), 110 (25), 109 (51), 108 (38), 101 (49), 97 (42), 95 (63), 91 (36), 83 (43), 82 (36), 81 (48), 79 (27), 74 (44), 69 (73), 68 (28), 67 (46), 59 (51), 56 (33), 55 (75), 53 (27), 43 (68), 41 (100).


References

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