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A simple and efficient synthesis of optically pure 4-alkylisoxazolidin-4-ols

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Abstract—The reaction between *N*-hydroxyphthalimide and optically pure epichlorohydrin followed by addition of methanol represents a straightforward procedure for the synthesis of isoxazolidin-4-ols in high enantiomeric purity. Under the same conditions, the reaction of glycidyl arenesulfonates can lead to different products depending on the nature of the sulfonate. This property allowed the synthesis of both enantiomers of 4-methylisoxazolidin-4-ol from the same chiral epoxide starting material.

Small hydrophilic heterocycles are often the key constituents in biologically interesting compounds. Furthermore, the introduction of polar substituents and small alkyl groups to improve potency and aid metabolic stability are strategies often employed in the drug discovery process. Therefore, short asymmetric syntheses of such compounds, in high enantiomeric purity, are of great importance to the medicinal chemist. During our research we became interested in heterocycles such as isoxazolidine and of particular interest were those containing sterically hindered hydroxyl groups. Very few syntheses of these interesting fragments have been reported. We now report the asymmetric syntheses of both optically pure enantiomers of 4-methylisoxazolidin-4-ol, *S*-**1** and *R*-**1** (Fig. 1).

It has been demonstrated that alkylation of *N*-hydroxyphthalimide (NHP) with racemic epibromohydrin

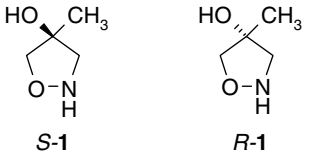
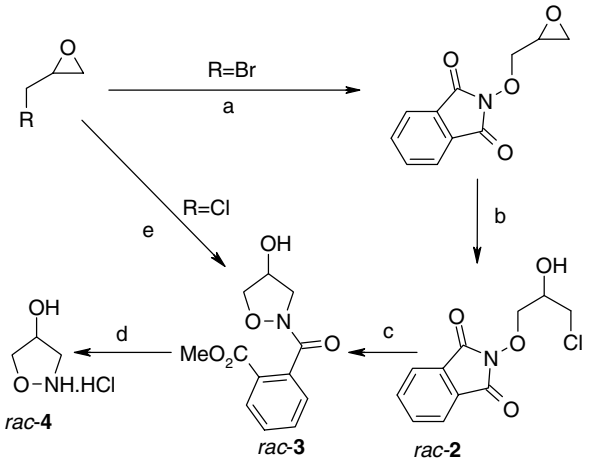


Figure 1. 4-Methylisoxazolidin-4-ols.

followed by opening of the oxirane ring with hydrochloric acid affords chlorohydrin *rac*-**2**. Treatment of *rac*-**2** with *t*-butylamine in methanol furnishes methyl 2-[(4-hydroxyisoxazolidin-2-yl)carbonyl]benzoate, *rac*-**3** via nucleophilic attack of methoxide on the phthalimide carbonyl followed by intramolecular *N*-alkylation. The desired heterocycle, *rac*-**4**, can then be isolated as the hydrochloride salt by acidic hydrolysis of the amide (Scheme 1).[1,2]

Buchalska and Plenkiewicz, as well as reporting the first chiral resolution of this system via a lipase catalysed



Scheme 1. Reagents and conditions: (a) NHP, DMF, Et_3N, 35%; (b) HCl, $CHCl_3$, 100%; (c) *t*-$BuNH_2$, MeOH, 100%; (d) HCl, H_2O, 100%; (e) NHP, MeOH, Et_3N, 80%.

Keywords: Isoxazolidin-4-ol; 4-Methylisoxazolidin-4-ol; Asymmetric synthesis; Epoxide.
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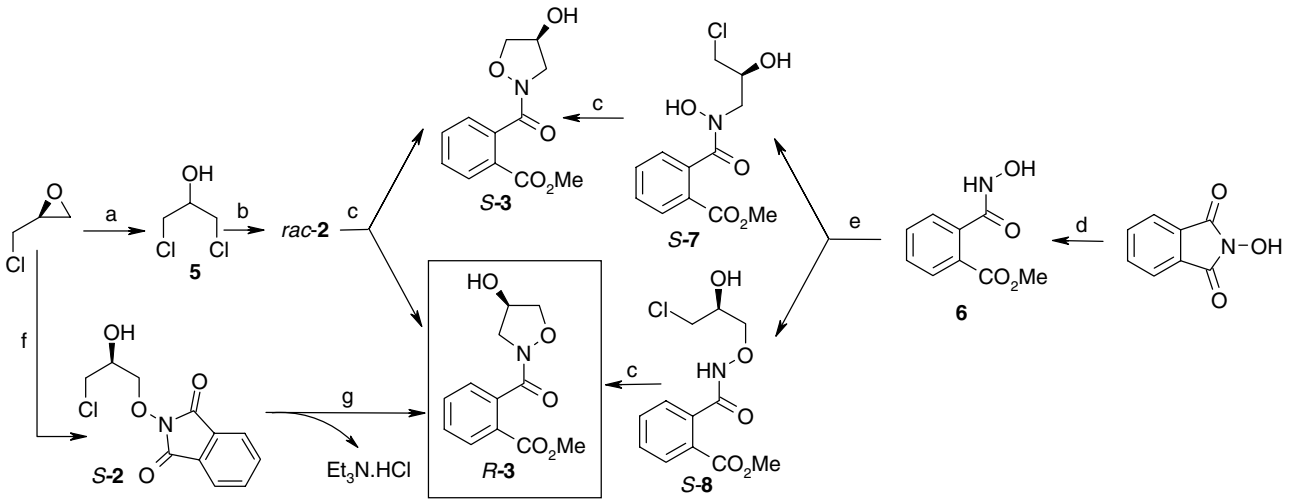


Scheme 2. Reagents and conditions: (a) $Et_3N{\cdot}HCl$; (b) NHP, Et_3N; (c) Et_3N; (d) MeOH, Et_3N; (e) (*S*)-epichlorohydrin, Et_3N; (f) NHP, Et_3N, 1,4-dioxane, 50 °C, 48 h; (g) MeOH, Et_3N, 50 °C, 2 h, 44%.

acetylation of both *rac*-**2** and *rac*-**3**, were also able significantly to shorten the synthesis. They demonstrated that the preparation of *rac*-**3** could be achieved in a one-pot process by reaction of NHP with racemic epichlorohydrin and triethylamine in methanol (Scheme 1).[3,4] We believed that this short synthetic route could be exploited in the asymmetric synthesis of 4-methylisoxazolidin-4-ol stereoisomers by making use of suitably substituted optically pure epoxides.

For our initial investigations we elected to focus on the synthesis of isoxazolidines containing a secondary hydroxyl group by employing optically pure epichlorohydrin, expecting to produce optically pure **3** in a single step (cf. Scheme 1). Unfortunately, these experiments gave disappointing results. For example, reaction of NHP with (*S*)-epichlorohydrin and triethylamine in methanol afforded *R*-**3** in good yield but with an enantiomeric excess of only 74% (as determined by chiral HPLC).[‡] This level of enantiomeric purity could not be significantly improved by recrystallisation and only moderate improvements were achieved with alternative bases.

We considered a number of possible side reactions to explain these unsatisfactory results. For example the known reaction between tertiary or quaternary ammonium salts and epoxides would result in the formation of a symmetrical alkylating agent **5**.[5] The consequence of reaction of **5** with NHP would be the generation of *rac*-**2** and subsequently *rac*-**3** (Scheme 2). Another possibility is the premature reaction between NHP and methoxide to reveal hydroxamic acid **6**. Subsequent alkylation of this ambident species with (*S*)-epichlorohydrin could then result in a mixture of *N*- and *O*-alkyl hydroxamates *S*-**7** and *S*-**8**.[6] Although one would expect *N*-alkylation to be the minor reaction pathway, the consequence of ring closure of *S*-**7** would be the formation of enantiomer *S*-**3**. Although no experimental attempt was made to determine which hypothesis was correct, we reasoned that only in the presence of methanol could either side reaction occur leading to an overall reduction in the enantiomeric excess of *R*-**3**. Thus, we elected to explore an alternative procedure employing an aprotic, nonnucleophilic solvent.

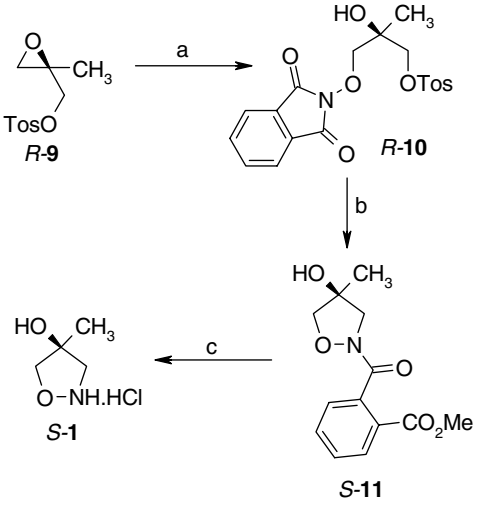
Using 1,4-dioxane as solvent, reaction of NHP with (*S*)-epichlorohydrin and triethylamine proceeded smoothly to furnish *S*-**2**. Upon addition of methanol to the reaction mixture, *R*-**3** was formed quickly (Scheme 2). Following the isolation of this product we were gratified to find that chiral HPLC analysis revealed excellent optical purity with an ee of >99%. The expected absolute stereochemistry was confirmed by NMR analysis of the (*S*)-α-methoxyphenylacetate.[7] Acidic hydrolysis yielded the hydrochloride salt of (4*R*)-isoxazolidin-4-ol (*R*-**4**) with no loss of enantiomeric purity.[8]

Encouraged by this success we turned our attention to the synthesis of 4-methylisoxazolidin-4-ols *S*-**1** and *R*-**1**. We hoped that a similar approach could be employed, however, the lack of commercial availability or suitable routes to enantiomerically pure 2-(chloromethyl)-2-methyloxirane precluded this. We believed that glycidyl arenesulfonates, readily available via Sharpless asymmetric epoxidation of allylic alcohols followed by in situ derivatisation, would provide an alternative strategy.[9] Nucleophilic substitution of compounds of this type can result in displacement of the sulfonate or opening of the oxirane ring with high selectivity. Thus, reaction of glycidyl tosylate with a variety of nucleophiles leads to selective epoxide opening, while direct displacement of the arenesulfonate moiety can be attained with glycidyl 3-nitrobenzenesulfonate.[10] We recognised that good C-1 versus C-3 selectivity offered a possible method for the preparation of *S*-**1** and *R*-**1** from a single enantiomer of (2-methyloxiran-2-yl)methanol.

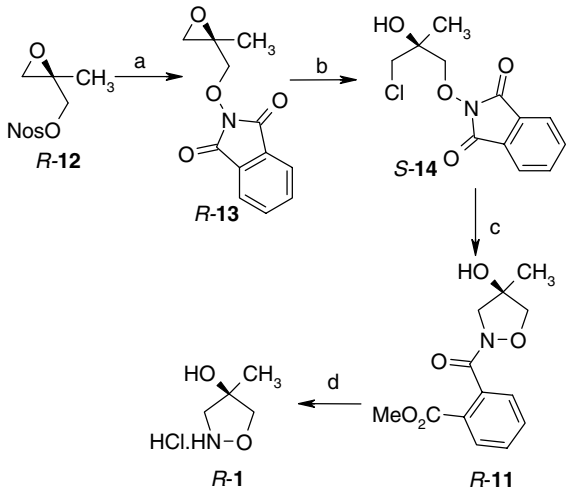
[‡]Although IUPAC nomenclature rules require a change in stereochemical descriptor no inversion of chiral centre had occurred.

Reaction between [(2*R*)-2-methyloxiran-2-yl]methyl 4-methylbenzenesulfonate (*R*-**9**) and NHP formed tosylate *R*-**10**. Subsequent addition of methanol and triethylamine furnished isoxazolidine *S*-**11** in good yield and high enantiomeric excess (ee >99%). The formation of *R*-**10** as a single enantiomer must occur as a consequence of selective nucleophilic attack on the oxirane ring. Therefore the absolute stereochemistry of *R*-**10** can be assigned. Acidic hydrolysis completed the synthesis of target heterocycle *S*-**1** (Scheme 3).

Under similar conditions, the reaction between [(2*R*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (*R*-**12**) and NHP afforded epoxyphthalimide *R*-**13** in accordance with direct displacement of the arenesulfonate (Scheme 4). Conversion of *R*-**13** to chlorohydrin *S*-**14** was achieved by the action of concentrated hydrochloric acid. Chlorohydrin *S*-**14** then underwent cyclisation with triethylamine in methanol to furnish the desired 4-methylisoxazolidin-4-ol, *R*-**11**, again in excellent enantiomeric excess (ee >99%). Chiral HPLC confirmed this product, *R*-**11**, to be the enantiomer of that obtained from tosylate *R*-**9** (i.e., *S*-**11**) thus selective displacement of the nosylate rather than an epoxide opening-Payne rearrangement sequence had occurred.



Scheme 3. Reagents and conditions: (a) NHP, Et_3N, 1,4-dioxane, 50 °C, 48 h; (b) MeOH, Et_3N, 50 °C, 2 h, 41%; (c) HCl, H_2O, 95 °C, 4 h, 72%.



Scheme 4. Reagents and conditions: (a) NHP, Et_3N, CH_2Cl_2, 24 h, 62%; (b) concd HCl, 1 h, 95%; (c) MeOH, Et_3N, 50 °C, 2 h, 59%; (d) HCl, H_2O, 95 °C, 3 h, 75%.

In summary, our investigations into the reaction between NHP and optically pure epichlorohydrin have led to the development of a short synthetic route to isoxazolidin-4-ols **3** with excellent enantiomeric excess. Furthermore, exploitation of the differences in the mode of reaction of different glycidyl arenesulfonates led to the synthesis of both stereoisomers of 4-methylisoxazolidin-4-ol (**1**), again in excellent enantiomeric excess. Both stereoisomers were derived from a single enantiomer of (2-methyloxiran-2-yl)methanol. This procedure has been successfully employed in the synthesis of other 4-alkylisoxazolidin-4-ols.

General procedure for the synthesis of {[4-hydroxyisoxazolidin-2-yl]carbonyl}benzoates from epichlorohydrins or glycidyl tosylates

Methyl 2-{[(4*R*)-4-hydroxyisoxazolidin-2-yl]carbonyl}-benzoate (*R*-3)

Triethylamine (0.56 ml, 4.0 mmol) was added to a solution of *N*-hydroxyphthalimide (5.0 g, 31 mmol) and (*S*)-epichlorohydrin (2.6 ml, 34 mmol) in anhydrous 1,4-dioxane (10 ml) under nitrogen and the mixture stirred at 50 °C for 48 h. Methanol (10 ml) and triethylamine (4.3 ml, 31 mmol) were then added to the reaction mixture and stirring at 50 °C was continued for a further 2 h. The mixture was evaporated under reduced pressure, and partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organics were dried and the residue recrystallised from ethyl acetate to give *R*-**3** as a white solid (3.4 g, 44%).

δ ^{1}H ($CDCl_3$) 3.66 (1H, d, $J = 6$ Hz), 3.79 (1H, d, $J = 6$ Hz), 3.89–3.99 (4H, m), 3.99–4.10 (2H, m), 4.74–4.81 (1H, m), 7.46 (1H, d, $J = 7$ Hz), 7.49 (1H, t, $J = 7$ Hz), 7.62 (1H, t, $J = 7$ Hz), 7.99 (1H, d, $J = 7$ Hz). $[\alpha]_D^{21}$ +28.73 (*c* 0.1, CH_3OH). Chiral HPLC rt = 12.71 min, ee >99%.[11]

Methyl 2-{[(4*S*)-4-hydroxyisoxazolidin-2-yl]carbonyl}-benzoate (*S*-3)

Prepared using (*R*)-epichlorohydrin in 44% yield.

δ ^{1}H ($CDCl_3$) 3.66 (1H, d, $J = 6$ Hz), 3.79 (1H, d, $J = 6$ Hz), 3.89–3.99 (4H, m), 3.99–4.10 (2H, m), 4.74–4.81 (1H, m), 7.46 (1H, d, $J = 7$ Hz), 7.49 (1H, t, $J = 7$ Hz), 7.62 (1H, t, $J = 7$ Hz), 7.99 (1H, d, $J = 7$ Hz). $[\alpha]_D^{21}$ −30.24 (*c* 0.1, CH_3OH). Chiral HPLC rt = 12.89 min, ee >99%.[11]

Methyl 2-{[(4*S*)-4-hydroxy-4-methylisoxazolidin-2-yl]-carbonyl}benzoate (*S*-11)

Prepared using [(2*R*)-2-methyloxiran-2-yl]methyl 4-methylbenzenesulfonate (*R*-**9**) in 41% yield.

δ ^{1}H ($CDCl_3$) 1.52 (3H, s), 3.59 (1H, d, $J = 11$ Hz), 3.81 (1H, d, $J = 8$ Hz), 3.88 (1H, d, $J = 8$ Hz), 3.92 (3H, s), 4.03 (1H, s), 4.35 (1H, d, $J = 11$ Hz), 7.45 (1H, d, $J = 8$ Hz), 7.49 (1H, dt, $J = 8$, 1 Hz), 7.62 (1H, t, $J = 7$ Hz), 8.00 (1H, d, $J = 8$ Hz). $[\alpha]_D^{25}$ −7.23 (*c* 0.1, $CHCl_3$). Chiral HPLC rt = 4.97 min, ee >99%.[12]

General procedure for the synthesis of {[4-hydroxy-isoxazolidin-2-yl]carbonyl}benzoates from glycidyl nosylates

2-{[(2*R*)-2-Methyloxiran-2-yl]methoxy}-1*H*-iso-indole-1, 3(2*H*)-dione (*R*-13)

A solution of *R*-**12** (5.9 g, 22 mmol), *N*-hydroxyphthalimide (5.3 g, 33 mmol) and triethylamine (10.6 ml, 76 mmol) in dichloromethane (15 ml) was stirred at ambient temperature for 24 h. The mixture was then concentrated to dryness and the residue purified by SiO_2 chromatography, eluting with dichloromethane to yield *R*-**13** as a white solid (3.1 g, 62%).

δ ^{1}H ($CDCl_3$) 1.03 (3H, s), 2.63 (1H, d, $J = 5$ Hz), 2.77 (1H, d, $J = 5$ Hz), 4.17 (1H, d, $J = 11$ Hz), 4.21 (1H, d, $J = 11$ Hz), 7.73–7.78 (2H, m), 7.82–7.87 (2H, m).

2-{[(2*S*)-3-Chloro-2-hydroxy-2-methylpropyl]oxy}-1*H*-isoindole-1,3(2*H*)-dione (*S*-14)

Compound *R*-**13** (3.1 g, 13 mmol) was treated with concd hydrochloric acid (12 ml) and the resulting solution stirred at ambient temperature for 1 h. The reaction mixture was partitioned between water and dichloromethane, the organics were washed with saturated sodium bicarbonate solution then dried over magnesium sulfate, filtered and concentrated to dryness. The residue was purified by SiO_2 chromatography, eluting with ethyl acetate to afford *S*-**14** as a white solid (3.3 g, 95%).

δ ^{1}H ($CDCl_3$) 1.39 (3H, s), 3.01 (1H, s), 3.67 (1H, d, $J = 11$ Hz), 3.76 (1H, d, $J = 11$ Hz), 4.09 (1H, d, $J = 11$ Hz), 4.47 (1H, d, $J = 11$ Hz), 7.77–7.80 (2H, m), 7.84–7.87 (2H, m).

Methyl 2-{[(4*R*)-4-hydroxy-4-methylisoxazolidin-2-yl]-carbonyl}benzoate (*R*-11)

A solution of *S*-**14** (3.3 g, 12 mmol) in methanol (25 ml) was treated with triethylamine (3.4 ml, 24 mmol) and the mixture heated at reflux for 2 h. The reaction mixture was then concentrated to dryness and purified by SiO_2 chromatography, eluting with 95:5 dichloromethane: methanol and then recrystallised from acetonitrile to give *R*-**11** as a white solid (1.92 g, 59%).

δ ^{1}H ($CDCl_3$) 1.52 (3H, s), 3.59 (1H, d, $J = 11$ Hz), 3.81 (1H, d, $J = 8$ Hz), 3.88 (1H, d, $J = 8$ Hz), 3.92 (3H, s), 4.03 (1H, s), 4.35 (1H, d, $J = 11$ Hz), 7.45 (1H, d, $J = 8$ Hz), 7.49 (1H, dt, $J = 8$, 1 Hz), 7.62 (1H, t, $J = 7$ Hz), 8.00 (1H, d, $J = 8$ Hz). $[\alpha]_D^{21}$ +2.88 (*c* 0.12, $CHCl_3$). Chiral HPLC rt = 6.48 min, ee >99%.[12]

General procedure for the hydrolysis of {[4-hydroxy-isoxazolidin-2-yl]carbonyl}benzoates

(4*R*)-Isoxazolidin-4-ol (*R*-4)

A solution of *R*-**3** (1.9 g, 7.4 mmol) in 4 M hydrochloric acid (15 ml) was heated at reflux for 3 h. The mixture was filtered and the filtrate concentrated to dryness. The residue was recrystallised from propan-2-ol to give *R*-**4** as a colourless solid (0.78 g, 84%).

δ ^{1}H (DMSO-d_6) 3.35 (1H, d, $J = 11$ Hz), 3.47 (1H, dd, $J = 11.5$ Hz), 4.03 (1H, dd, $J = 9$, 4 Hz), 4.07 (1H, d, $J = 9$ Hz), 4.78–4.81 (1H, m). $[\alpha]_D^{21}$ −29.29 (*c* 0.15, CH_3OH).

(4*S*)-Isoxazolidin-4-ol (*S*-4)

Prepared using methyl 2-{[(4*S*)-4-hydroxyisoxazolidin-2-yl]carbonyl}benzoate (*S*-**3**) in 80% yield.

δ ^{1}H (DMSO-d_6) 3.35 (1H, d, $J = 11$ Hz), 3.47 (1H, dd, $J = 11$, 5 Hz), 4.03 (1H, dd, $J = 9$, 4 Hz), 4.07 (1H, d, $J = 9$ Hz), 4.78–4.81 (1H, m). $[\alpha]_D^{21}$ +21.11 (*c* 0.22, CH_3OH).

(4*S*)-4-Methylisoxazolidin-4-ol (*S*-1)

Prepared from methyl 2-{[(4*R*)-4-hydroxy-4-methylisoxazolidin-2-yl]carbonyl}benzoate (*S*-**11**) in 72% yield.

δ ^{1}H (DMSO-d_6) 1.42 (3H, s), 3.29 (1H, d, $J = 11$ Hz), 3.41 (1H, dd, $J = 11$, 0.3 Hz), 3.87 (1H, d, $J = 8$ Hz), 4.05 (1H, dd, $J = 8$, 0.5 Hz). $[\alpha]_D^{25}$ +5.20 (*c* 0.31, H_2O).

(4*R*)-4-Methylisoxazolidin-4-ol (*R*-1)

Prepared from methyl 2-{[(4*R*)-4-hydroxy-4-methylisoxazolidin-2-yl]carbonyl}benzoate (*R*-**11**) in 75% yield.

δ ^{1}H (DMSO-d_6) 1.42 (3H, s), 3.29 (1H, d, $J = 11$ Hz), 3.41 (1H, dd, $J = 11$, 0.3 Hz), 3.87 (1H, d, $J = 8$ Hz), 4.05 (1H, dd, $J = 8$, 0.5 Hz). $[\alpha]_D^{25}$ −10.64 (*c* 0.30, H_2O).

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11. Chiralpack AD 4.6×50 mm, 90:10 isohexane/EtOH, 1 ml/min, 220 ± 10 nm over 15 min at 10 °C.
12. Chiralpack AD 4.6×50 mm, 90:10 isohexane/2-propanol, 1 ml/min, 220 ± 10 nm over 10 min at 10 °C.