



Synthesis of enantiomerically pure 2,3-disubstituted oxirane-2-carboxamides

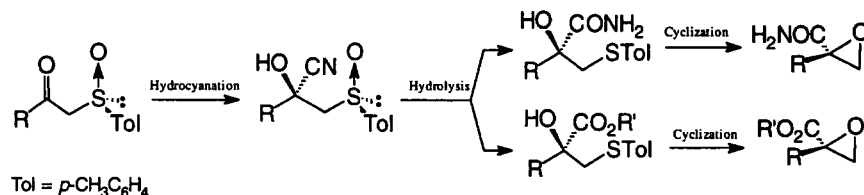
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Abstract: The title compounds were efficiently prepared from 1-alkyl(or phenyl)-2-methyl-2-(tolylsulfinyl)ethanone through a simple four-step sequence: highly stereoselective hydrocyanation with Et_2AlCN (key step to control the stereochemistry); hydrolysis to sulfinylamides and separation of epimers; reduction of the sulfur functionality; and final cyclization to enantiopure oxirane derivatives. © 1997 Elsevier Science Ltd

The easy transformation of oxiranes into biologically interesting organic moieties, such as vicinal diols,¹ ethanolamines,² etc, converts these compounds into versatile starting materials in organic synthesis. Among them, special attention has to be paid to 2-alkyl and 2,3-dialkylglycidic acid derivatives,³ not only for being building blocks of naturally occurring or pharmacologically active compounds (e.g. hypoglycemic agent methyl (*R*)-(+)-palmoxirate,⁴ or antibiotics methylenomycin A and B⁵), but also for being potential starting materials for the synthesis of chiral β -substituted α -alkyl- α -hydroxycarboxylic acids by nucleophilic opening of the oxirane ring.⁶

Recently we have reported a simple method to obtain enantiomerically pure 2-alkylglycidic acid derivatives⁴ (Scheme 1) by a sequence consisting of a highly stereoselective hydrocyanation of chiral α -sulfinyl ketones with Et_2AlCN ,⁷ hydrolysis of the obtained sulfinylcyanohydrins into sulfenylamides or sulfenylesters, and subsequent cyclization by treatment of these compounds with Me_3OBF_4 and K_2CO_3 . The hydrolysis of the cyano group takes place with concomitant reduction of the sulfoxide. Further studies enabled us to propose a mechanistic pathway for this hydrolysis involving the anchimeric assistance of the sulfinyl group.⁸



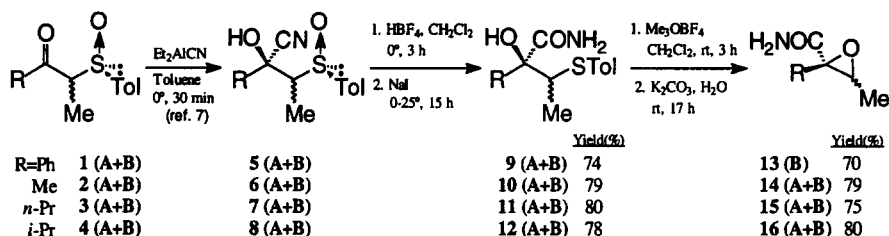
Scheme 1.

In order to prepare 2,3-dialkylglycidic acid derivatives from the above sequence, it was necessary to study the evolution of the α -alkyl α -sulfinylketones under the conditions used for the α -unsubstituted sulfinylketones. In this paper we report the synthesis of enantiomerically pure 2-alkyl- (or aryl-) -3-methyloxirane-2-carboxamides.

The syntheses of glycidic amides **13–16** (Scheme 2) were initially tried by hydrolysis of cyanohydrins **5–8** (obtained in a completely stereoselective manner as a mixture **A**(*S*₂,*R*₃,*R*₅)+**B**(*S*₂,*S*₃,*R*₅) of epimers at C- α from the corresponding epimers of chiral α -sulfinyl ketones **1–4**)⁷ into sulfenylamides **9–12**. These hydrolysis reactions were accomplished by treatment with HBF_4 followed by NaI .⁹ The

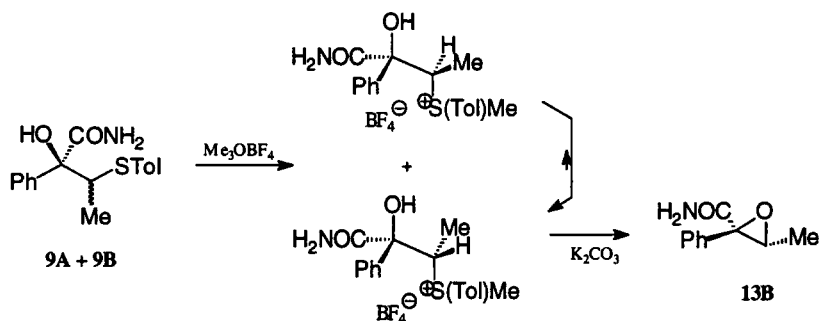
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formation of the corresponding oxiranes **13–16** was achieved in high yields (one-pot procedure) by treatment of the sulfides with Me_3OBF_4 followed by K_2CO_3 .⁴



Scheme 2.

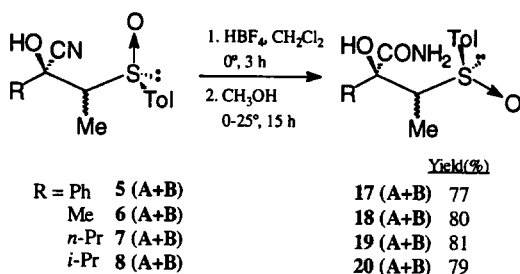
Starting from a **9A+9B** mixture, only one epoxide **13B** was obtained in 70% yield. This result indicates that epimerization at the stereogenic carbon vicinal to the sulfur moiety had taken place, probably at the sulfonium salt stage, in the presence of K_2CO_3 (Scheme 3). The higher steric hindrance of the transition state derived from the epimer **9A**, with a Ph/Me interaction, could justify its slower evolution to the oxirane derivative, which would explain the direction of the epimerization.



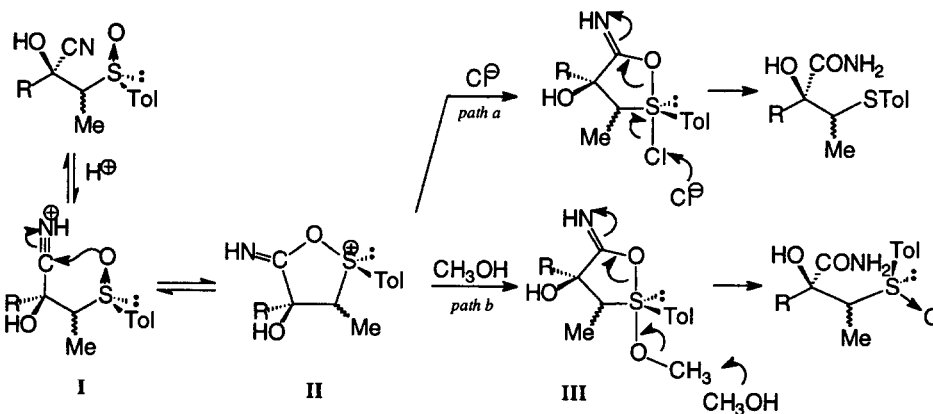
Scheme 3.

The reactions of **A+B** mixtures of hydroxyamides **10–12** led to mixtures of epoxides **14–16**, the proportion of the epimers of the products being similar to those of the starting acyclic compounds. All the attempts to separate the mixtures of epimers of epoxides **14–16** proved to be unsuccessful, which prompted us to study the reactions affording oxiranes starting from diastereomerically pure sulfenyl hydroxyamides. Unfortunately, the separation of the **A+B** mixtures of hydroxysulfides **10–12** was not possible in our hands, neither by chromatographic techniques nor by crystallization.¹⁰ We did not try the separation of the mixture of cyanohydrins **5–8** because of their known easy decomposition into the starting ketones **1–4**.

Our previous experience with epimeric β -hydroxysulfoxides¹¹ suggested to us that these substrates would be more easily separated than their corresponding sulfides and thus, the syntheses of sulfinylhydroxyamides **17–20** were undertaken (Scheme 4). With this aim, and after some unsuccessful trials to obtain them by stereoselective oxidation of the corresponding sulfides, bearing in mind the stereochemical course proposed for the hydrolysis of the cyano group (Scheme 5, path a),⁸ we reasoned that the use of oxygenated nucleophiles such as methanol (path b), would yield **A+B** mixtures of sulfinylamides, which means that cyclic oxosulfonium species **II**, resulting from the nucleophilic intramolecular attack of the sulfinylic oxygen on the protonated cyano group, reacts with methanol, leading to a sulfurane intermediate **III**. Further attack of a second molecule of methanol would give rise to the sulfinyl derivatives, with inversion of the sulfur configuration.¹²



Scheme 4.



Scheme 5.

As expected, the addition of methanol¹³ to the reaction mixtures of cyanohydrins and fluoboric acid (or $\text{BF}_3 \cdot \text{OEt}_2$) afforded epimeric **A+B** mixtures of β -sulfinyl α -hydroxyamides **17–20** in good yields, which could be easily separated by flash chromatography.

Once we had isolated compounds **17A–20A** and **17B–20B**, both diastereoisomers were treated separately with $\text{BF}_3 \cdot \text{OEt}_2$ and NaI in CH_3CN ,¹⁴ to yield the corresponding β -sulfinyl α -hydroxyamides **9A–12A** and **9B–12B** (Scheme 6). Further treatment of both epimers of compounds **10–12** in the previously described epoxidation conditions⁴ (Me_3OBF_4 and K_2CO_3) led to the enantiomerically pure epoxides **14–16** (**A** and **B**, respectively) in high yields, with a complete absence of epimerization. On the other hand, the same epoxide **13B** was achieved starting from **9A** as well as from **9B**.

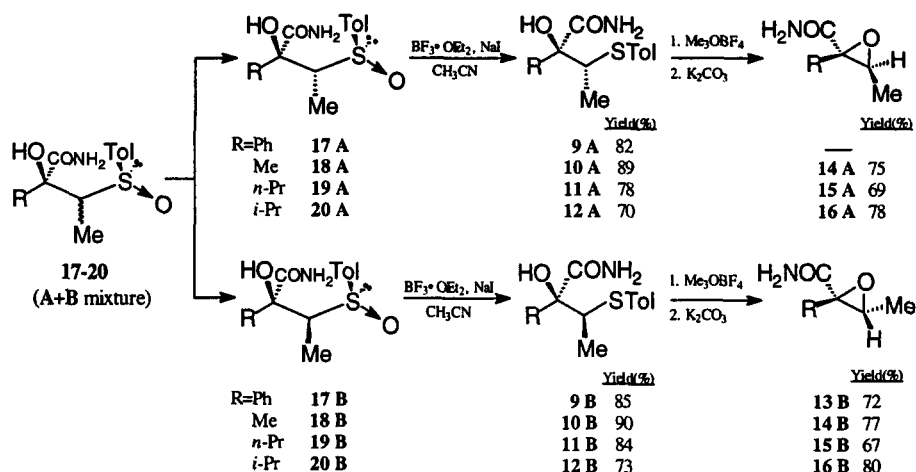
From the NMR data of the cases where both isomers were available (**14–16**), we could state that epoxides **A** exhibit a higher chemical shift for the methinic proton than that of epimers **B** in proton spectra and a lower one for the carbons in $\text{CH}_3\text{—CH}$ grouping (where the influence of the substituent **R** is weaker) in carbon spectra.

In summary, we have reported a stereoselective synthesis of 2,3-disubstituted glycidic amides by means of hydrocyanation of α -sulfinyl ketones, hydrolysis of sulfinyl cyanohydrins and suitable transformation of the resulting products. This four-step sequence leads to enantiomerically pure epoxides, bearing two chiral centres and one tertiary carbon, not easily available by other methods, starting from commercially available reagents.

Experimental

General methods

All reactions were carried out in flame-dried glassware under an argon atmosphere. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM). Melting points were



Scheme 6.

determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). The ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively in a Bruker AC-200 spectrometer using CDCl_3 solutions; δ chemical shifts refer to TMS (^1H) or deuterated chloroform (^{13}C) signals. Multiplicities in proton spectra are indicated as s (singlet), d (doublet), t (triplet), q (quartet), sept (septuplet), m (multiplet), and bs (broad singlet). Elemental analyses were performed with a Perkin–Elmer 2400 CHN analyser.

The synthesis of compounds 1–8 has been previously described.⁷

Hydrolysis of sulfinyl cyanohydrins into sulfenyl or sulfinyl hydroxyamides with HBF_4

To a cold (0°C) solution of 1.5 mmol of cyanohydrin in 5 mL of anhydrous CH_2Cl_2 , 2 mL of fluoboric acid was added. The temperature was then allowed to rise to rt and the mixture was stirred for 3 h. Then 600 mg (4.0 mmol) of NaI (to obtain the sulfenyl derivative) or 320 mg (10 mmol) of MeOH (to obtain the sulfinyl derivative) was added. After 15 or 3 h, respectively, the mixture was treated with 10 mL of water and extracted with CH_2Cl_2 . The extracts were washed with aqueous NaHSO_3 in the first case, dried (Na_2SO_4) and evaporated. Epimers A and B of sulfinyl hydroxyamides 17–20 were separated by flash chromatography using ethyl acetate–hexane (1:1) as eluent. Yields are indicated in Schemes 2 and 4.

(S_2, R_3, S_5) and (S_2, S_3, S_5)-2-Hydroxy-2-phenyl-3-(p-tolylsulfinyl)butanamide 17A and 17B

17A and 17B were obtained from a 5A+5B mixture.

Isomer (S_2, R_3, S_5) 17A After chromatography 17A was crystallised from ethyl acetate–hexane (3:2), mp 75–76°C (white solid); $[\alpha]_D -97.6$ (c 0.5 chloroform); δ_{H} 7.69 (m, 2H, Ph), 7.35–7.20 (m, 7H, Ph and Tol), 7.10 (bs, 1H, NH), 5.60 (bs, 1H, NH), 3.71 (q, 1H, J 7.0 Hz, CHCH_3), 2.43 (s, 3H, CH_3Ar), 0.74 (d, 3H, J 7.0 Hz, CH_3CH); δ_{C} 175.9 (CONH_2), 141.2 (C-4 Tol), 139.7 (C-1 Ph), 136.9 (C-1 Tol), 129.9 (C-3 Tol), 128.4 and 128.0 (C-2 and C-4 Ph), 124.7 and 124.0 (C-3 Ph and C-2 Tol), 81.4 (COH), 62.0 (CHCH_3), 21.4 (CH_3Ar), 3.2 (CH_3CH).

Isomer (S_2, S_3, S_5) 17B After chromatography 17B was crystallised from ethyl acetate–hexane (2:1), mp 83–84°C (white solid); $[\alpha]_D -110$ (c 0.66 chloroform); δ_{H} 7.87 (m, 2H, Ph), 7.50–7.30 (m, 7H, Ph and Tol), 6.90 (bs, 1H, NH), 5.43 (bs, 1H, NH), 3.69 (q, 1H, J 6.9 Hz, CHCH_3), 2.41 (s, 3H,

CH_3Ar), 1.07 (d, 3H, J 6.9 Hz, CH_3CH); δ_{C} 174.2 (CONH_2), 141.5 (C-4 Tol), 139.7 (C-1 Ph), 137.0 (C-1 Tol), 129.7 (C-3 Tol), 128.6 and 128.4 (C-4 and C-2 Ph), 124.0 and 123.8 (C-3 Ph and C-2 Tol), 86.6 (COH), 68.5 (CHCH_3), 29.8 (CH_3Ar), 1.2 ($\dot{\text{C}}\text{H}_3\text{CH}$).

(S₂,R₃,S₅) and (S₂,S₃,S₅)-2-Hydroxy-2-methyl-3-(p-tolylsulfinyl)butanamide 18A and 18B

18A and **18B** were obtained from a **6A**+**6B** mixture.

Isomer (S₂,R₃,S₅) 18A After chromatography **18A** was crystallised from ethyl acetate–hexane (2:1), mp 77–78°C (white solid); $[\alpha]_{\text{D}}$ –58.3 (c 0.7 chloroform); δ_{H} 7.54 and 7.33 (AA'BB' system, 4H, C_6H_4), 6.75 (bs, 1H, NH), 5.76 (bs, 1H, NH), 3.60 (q, 1H, J 7.2 Hz, CHCH_3), 3.15 (bs, 1H, OH), 2.35 (s, 3H, CH_3Ar), 1.45 (s, 3H, CH_3C), 1.35 (d, 3H, J 7.2 Hz, CH_3CH); δ_{C} 177.8 (CONH_2), 141.3 (C-4 Tol), 136.5 (C-1 Tol), 129.9 (C-3 Tol), 124.0 (C-2 Tol), 78.1 (COH), 61.5 (CHCH_3), 28.7 (CH_3Ar), 26.1 (CH_3C), 4.7 (CH_3CH).

Isomer (S₂,S₃,S₅) 18B After chromatography **18B** was crystallised from ethyl acetate–hexane (3:2), mp 84–85°C (white solid); $[\alpha]_{\text{D}}$ –87.4 (c 0.75 chloroform); δ_{H} 7.60 and 7.35 (AA'BB' system, 4H, C_6H_4), 6.40 (bs, 1H, NH), 5.75 (bs, 1H, NH), 3.70 (q, 1H, J 7.1 Hz, CHCH_3), 3.56 (bs, 1H, OH), 2.40 (s, 3H, CH_3Ar), 1.85 (s, 3H, CH_3C), 1.05 (d, 3H, J 7.1 Hz, CH_3CH); δ_{C} 176.2 (CONH_2), 141.3 (C-4 Tol), 136.5 (C-1 Tol), 129.9 (C-3 Tol), 124.2 (C-2 Tol), 67.0 (COH), 61.1 (CHCH_3), 21.3 (CH_3Ar), 25.9 (CH_3C), 3.0 (CH_3CH).

(S₂,R₃,S₅) and (S₂,S₃,S₅)-2-Hydroxy-2-n-propyl-3-(p-tolylsulfinyl)butanamide 19A and 19B

19A and **19B** were obtained from a **7A**+**7B** mixture.

Isomer (S₂,R₃,S₅) 19A After chromatography **19A** was crystallised from ethyl acetate–hexane (2:1), mp 86–87°C (white solid); $[\alpha]_{\text{D}}$ –78 (c 0.66 chloroform); δ_{H} 7.55 and 7.35 (AA'BB' system, 4H, C_6H_4), 6.90 (bs, 1H, NH), 5.70 (bs, 1H, NH), 3.55 (q, 1H, J 7.1 Hz, CHCH_3), 2.39 (s, 3H, CH_3Ar), 1.70–1.50 (m, 4H, CH_2CH_2), 1.37 (d, 3H, J 7.1 Hz, CH_3CH), 0.90 (t, 3H, J 7.0 Hz, CH_3CH_2); δ_{C} 173.2 (CONH_2), 140.2 (C-1 Tol), 136.5 (C-4 Tol), 129.9 (C-3 Tol), 125.2 (C-2 Tol), 83.5 (COH), 56.7 (CHCH_3), 39.4 (CH_2C), 21.4 (CH_3Ar), 18.3 (CH_2CH_3), 15.8 (CH_3CH), 13.2 (CH_3CH_2).

Isomer (S₂,S₃,S₅) 19B After chromatography **19B** was crystallised from ethyl acetate–hexane (2:1), mp 76–77°C (white solid); $[\alpha]_{\text{D}}$ –36.8 (c 0.66 chloroform); δ_{H} 7.49 and 7.30 (AA'BB' system, 4H, C_6H_4), 6.70 (bs, 1H, NH), 5.77 (bs, 1H, NH), 3.70 (q, 1H, J 7.2 Hz, CHCH_3), 2.35 (s, 3H, CH_3Ar), 1.54–1.40 (m, 4H, CH_2CH_2), 1.20 (d, 3H, J 7.2 Hz, CH_3CH), 0.85 (t, 3H, J 7.0 Hz, CH_3CH_2); δ_{C} 172.9 (CONH_2), 141.2 (C-1 Tol), 137.4 (C-4 Tol), 129.9 (C-3 Tol), 124.2 (C-2 Tol), 86.2 (COH), 54.8 (CHCH_3), 40.1 (CH_2C), 21.3 (CH_3Ar), 18.3 (CH_2CH_3), 16.2 (CH_3CH), 12.3 (CH_3CH_2).

(S₂,R₃,S₅) and (S₂,S₃,S₅)-2-Hydroxy-2-i-propyl-3-(p-tolylsulfinyl)butanamide 20A and 20B

20A and **20B** were obtained from a **8A**+**8B** mixture.

Isomer (S₂,R₃,S₅) 20A After chromatography **20A** was crystallised from hexane–acetone (3:2), mp 144–145°C (white solid); $[\alpha]_{\text{D}}$ –123.0 (c 0.25 methanol); δ_{H} 7.41–7.33 (m, 4H, C_6H_4), 6.80 (bs, 1H, NH), 5.50 (bs, 1H, NH), 3.50 (bs, 1H, OH), 3.35 (q, 1H, J 6.8 Hz, SCHCH_3), 2.63 (sept, 1H, J 6.8 Hz, $\text{CH}(\text{CH}_3)_2$), 2.43 (s, 3H, CH_3Ar), 1.34 (d, 3H, J 6.8 Hz, CH_3CHS), 1.15 (d, 3H, J 6.8 Hz, CH_3CHCH_3), 0.94 (d, 3H, J 6.8 Hz, CH_3CHCH_3); δ_{C} 173.7 (CONH_2), 141.4 (C-1 Tol), 135.9 (C-4 Tol), 130.0 (C-3 Tol), 124.0 (C-2 Tol), 82.7 (COH), 57.6 (CHS), 36.5 ($\text{CH}(\text{CH}_3)_2$), 21.4 (CH_3Ar), 17.5 and 16.9 ($(\text{CH}_3)_2\text{CH}$), 5.3 (CH_3CHS).

Isomer (S₂,S₃,S₅) 20B After chromatography **20B** was crystallised from hexane–acetone (3:2), mp 182–183°C (white solid); [α]_D –82.3 (c 0.2 methanol); δ_{H} 7.61 and 7.31 (AA'BB' system, 4H, C₆H₄), 7.15 (bs, 1H, NH), 5.70 (bs, 1H, NH), 3.38 (q, 1H, J 7.2 Hz, SCHCH₃), 2.43 (s, 3H, CH₃Ar), 2.34 (sept, 1H, J 6.8 Hz, CH(CH₃)₂), 1.29 (d, 3H, J 7.2 Hz, CH₃CHS), 1.05 (d, 3H, J 6.8 Hz, CH₃CHCH₃), 0.94 (d, 3H, J 6.8 Hz, CH₃CHCH₃); δ_{C} 175.3 (CONH₂), 142.3 (C-1 Tol), 138.6 (C-4 Tol), 129.5 (C-3 Tol), 125.6 (C-2 Tol), 82.2 (COH), 61.7 (CHS), 33.4 (CH(CH₃)₂), 21.3 (CH₃Ar), 17.2 and 16.5 ((CH₃)₂CH), 10.2 (CH₃CHS).

Reduction of sulfinyl hydroxyamides into sulfenyl hydroxyamides

Reduction was accomplished following the procedure described by Vankar *et al.*¹³ Yields are shown in Scheme 6.

(S₂,R₃) and (S₂,S₃)-2-Hydroxy-2-phenyl-3-(p-tolylsulfenyl)butanamide 9A and 9B

Isomer (S₂,R₃) 9A **9A** was obtained from **17A**. It was crystallised from hexane–acetone (1:3), mp 81–82°C (white solid); [α]_D –12.6 (c 0.7, chloroform); δ_{H} 7.57 (m, 2H, Ph), 7.38 and 7.15 (AA'BB' system, 4H, C₆H₄), 7.30 (m, 3H, Ph), 7.00 (bs, 1H, NH), 5.20 (bs, 1H, NH), 4.03 (q, 1H, J 7.1 Hz, CHCH₃), 3.58 (bs, 1H, OH), 2.32 (s, 3H, CH₃Ar), 1.82 (d, 3H, J 7.1 Hz, CH₃CH); δ_{C} 175.9 (CONH₂), 144.8 (C-1 Ph), 135.3 (C-1 Tol), 130.0, 129.8, 128.9, 128.5, 127.5, 127.1 (aromatic carbons), 75.7 (COH), 63.0 (CHCH₃), 21.3 (CH₃Ar), 12.7 (CH₃CH). Anal. Calcd. for C₁₇H₁₉NO₃S: C 64.36, H 6.00, N 4.43, S 10.09. Found: C 64.28, H 6.29, N 4.64, S 9.67.

Isomer (S₂,S₃) 9B **9B** was obtained from **17B**. Physical and data are coincident with those previously described.⁷

(S₂,R₃) and (S₂,S₃)-2-Hydroxy-2-methyl-3-(p-tolylsulfenyl)butanamide 10A and 10B

10A and **10B** were obtained from **18A** and **18B**, respectively. Physical and spectroscopic data are coincident with those previously described.⁷

(S₂,R₃) and (S₂,S₃)-2-Hydroxy-2-n-propyl-3-(p-tolylsulfenyl)butanamide 11A and 11B

Isomer (S₂,R₃) 11A **11A** was obtained from **19A**. It was crystallised from dichloromethane, mp 90–91°C (white solid); [α]_D –15.6 (c 0.63, chloroform); δ_{H} 7.35 and 7.12 (AA'BB' system, 4H, C₆H₄), 6.90 (bs, 1H, NH), 6.06 (bs, 1H, NH), 3.70 (bs, 1H, OH), 3.55 (q, 1H, J 6.9 Hz, CHCH₃), 2.35 (s, 3H, CH₃Ar), 1.75–1.65 (m, 2H, CH₂C), 1.55–1.46 (m, 2H, CH₂CH₃), 1.35 (d, 3H, J 6.9 Hz, CH₃CH), 0.90 (t, 3H, J 7.1 Hz, CH₃CH₂); δ_{C} 176.5 (CONH₂), 137.5 (C-1 Tol), 132.8 and 132.4 (C-3 and C-4 Tol), 129.8 (C-2 Tol), 81.3 (COH), 53.1 (CHCH₃), 40.4 (CH₂C), 21.2 (CH₃Ar), 17.3 (CH₂CH₃), 16.3 (CH₃CH), 13.8 (CH₃CH₂). Anal. Calcd. for C₁₃H₁₉NO₂S: C 61.66, H 7.50, N 5.55, S 12.60. Found: C 61.46, H 7.61, N 5.78, S 12.46.

Isomer (S₂,S₃) 11B **11B** was obtained from **19B**. It was crystallised from dichloromethane–hexane (9:1), mp 88–89°C (white solid); [α]_D –4.6 (c 0.52, chloroform); δ_{H} 7.40 and 7.19 (AA'BB' system, 4H, C₆H₄), 6.65 (bs, 1H, NH), 5.75 (bs, 1H, NH), 3.35 (q, 3H, J 7.1 Hz, CHCH₃), 2.33 (s, 3H, CH₃Ar), 1.60–1.45 (m, 4H, CH₂CH₂), 1.37 (d, 3H, J 7.1 Hz, CH₃CH), 0.90 (t, 3H, J 7.3 Hz, CH₃CH₂); δ_{C} 175.8 (CONH₂), 137.8 (C-1 Tol), 133.1 (C-3 Tol), 130.1 and 129.7 (C-2 and C-4 Tol), 80.1 (COH), 52.9 (CHCH₃), 39.0 (CH₂C), 21.2 (CH₃Ar), 16.7 (CH₂CH₃), 16.3 (CH₃CH), 14.2 (CH₃CH₂). Anal. Calcd. for C₁₃H₁₉NO₂S: C 61.66, H 7.50, N 5.55, S 12.60. Found: C 61.56, H 7.51, N 5.65, S 12.59.

(S₂,R₃) and (S₂,S₃)-2-Hydroxy-2-i-propyl-3-p-tolylsulfenylbutanamide 12A and 12B

Isomer (S₂,R₃) 12A **12A** was obtained from **20A**. It was crystallised from hexane–acetone (3:2), mp 85–86°C (white solid); [α]_D –24.1 (c 0.50, chloroform); δ_{H} 7.35 and 7.19 (AA'BB' system, 4H,

C₆H₄), 6.95 (bs, 1H, NH), 6.30 (bs, 1H, NH), 3.25 (q, 1H, J 6.8 Hz, CHCH₃), 2.56 (sept, 1H, J 6.7 Hz, CH(CH₃)₂), 1.25 (d, 3H, J 6.8 Hz, CH₃CH), 1.10 (d, 3H, J 6.7 Hz, CH₃CHCH₃), 0.90 (d, 3H, J 6.7 Hz, CH₃CHCH₃); δ_{C} 177.5 (CONH₂), 137.9 (C-1 Tol), 133.5 (C-3 Tol), 130.0 (C-4 Tol), 129.9 (C-2 Tol), 82.3 (COH), 51.2 (CHCH₃), 34.5 (CH(CH₃)₂), 21.1 (CH₃Ar), 17.5 and 17.3 ((CH₃)₂CH), 15.9 (CH₃CH).

Isomer (S₂,S₃) 12B **12B** was obtained from **20B**. It was crystallised from hexane–acetone (3:1), mp 93–94°C (white solid); $[\alpha]_{\text{D}}$ –15.2 (c 0.50, chloroform); δ_{H} 7.35 and 7.12 (AA'BB' system, 4H, C₆H₄), 6.80 (bs, 1H, NH), 5.32 (bs, 1H, NH), 3.60 (q, 1H, J 7.0 Hz, CHCH₃), 3.59 (bs, 1H, OH), 2.40 (s, 3H, CH₃Ar), 2.15 (sept, 1H, J 6.8 Hz, CH(CH₃)₂), 1.30 (d, 3H, J 7.0 Hz, CH₃CH), 0.90 (d, 6H, J 6.8 Hz, (CH₃)₂CH); δ_{C} 177.5 (CONH₂), 138.3 (C-1 Tol), 133.5 (C-3 Tol), 130.1 (C-4 Tol), 129.9 (C-2 Tol), 81.5 (COH), 49.8 (CHCH₃), 33.7 (CH(CH₃)₂), 21.1 (CH₃Ar), 17.3 and 17.1 ((CH₃)₂CH), 15.9 (CH₃CH).

Synthesis of oxirane carboxamides from sulfenyl hydroxyamides

The synthesis of oxirane carboxamides was accomplished following the procedure previously described.⁴ Yields are shown in Scheme 6.

(R₂,R₃)-3-Methyl-2-phenyloxirane-2-carboxamide 13B

13B was obtained from **9A** (68%) or **9B** (70%) and purified by flash chromatography (ethyl acetate–hexane 1:1 as the eluent). It was crystallised from hexane, mp 135–136°C (white solid); $[\alpha]_{\text{D}}$ –5.3 (c 0.2, chloroform); δ_{H} 7.65–7.60 (m, 2H, Ph), 7.45 (m, 3H, Ph), 6.40 (bs, 1H, NH), 5.65 (bs, 1H, NH), 3.27 (q, 1H, J 5.3 Hz, CHCH₃), 1.50 (d, 3H, J 5.3 Hz, CH₃CH); δ_{C} 170.0 (CONH₂), 134.8 (C-1 Ph), 129.6 (C-4 Ph), 128.0 (C-2 Ph), 126.1 (C-3 Ph), 62.9 (CPh), 29.5 (CHCH₃), 14.1 (CH₃).

(R₂,S₃)-2,3-Dimethyloxirane-2-carboxamide 14A

It was obtained from **10A**, purified by flash chromatography (ethyl acetate–hexane 1:1 as the eluent), and crystallised from ethyl acetate–hexane 4:1, mp 88–89°C (white solid); $[\alpha]_{\text{D}}$ –13.6 (c 0.33, chloroform); δ_{H} 6.80 (bs, 1H, NH), 5.92 (bs, 1H, NH), 3.70 (q, 1H, J 8.0 Hz, CH), 1.70 (s, 3H, CH₃C), 1.40 (d, 3H, J 8.0 Hz, CH₃CH); δ_{C} 172.3 (CONH₂), 62.3 (C), 38.6 (CH₃C), 28.8 (CH), 13.5 (CH₃CH). Anal. Calcd. for C₅H₉NO₂: C 52.16, H 7.88, N 12.17. Found: C 52.10, H 7.85, N 12.22.

(R₂,R₃)-2,3-Dimethyloxirane-2-carboxamide 14B

14B was obtained from **10B**, purified by flash chromatography (ethyl acetate–hexane 1:1 as the eluent), and crystallised from ethyl acetate–hexane 4:1, mp 92–93°C (white solid); $[\alpha]_{\text{D}}$ –5.89 (c 0.4, chloroform); δ_{H} 6.75 (bs, 1H, NH), 5.50 (bs, 1H, NH), 3.30 (q, 1H, J 7.9 Hz, CH), 1.40 (s, 3H, CH₃C), 1.20 (d, 3H, J 7.9 Hz, CH₃CH); δ_{C} 175.4 (CONH₂), 63.2 (C), 35.4 (CH₃C), 28.2 (CH), 12.8 (CH₃CH). Anal. Calcd. for C₅H₉NO₂: C 52.16, H 7.88, N 12.17. Found: C 52.20, H 7.73, N 12.24.

(R₂,S₃)-3-Methyl-2-n-propyloxirane-2-carboxamide 15A

15A was obtained from **11A**, purified by flash chromatography (ethyl acetate–hexane 2:1 as the eluent), and crystallised from ethyl acetate–hexane 3:1, mp 90–91°C (white solid); $[\alpha]_{\text{D}}$ –15.25 (c 0.25, chloroform); δ_{H} 6.50 (bs, 1H, NH), 5.60 (bs, 1H, NH), 3.75 (q, 1H, J 6.0 Hz, CH), 1.80–1.51 (m, 4H, CH₂CH₂), 1.40 (d, 3H, J 6.0 Hz, CH₃CH), 0.90 (t, 3H, J 7.0 Hz CH₃CH₂); δ_{C} 174.3 (CONH₂), 64.8 (C), 45.2 (CH₂C), 28.2 (CH), 15.8 (CH₂CH₃), 13.3 (CH₃CH₂), 12.8 (CH₃CH). Anal. Calcd. for C₇H₁₃NO₂: C 58.72, H 9.15, N 9.78. Found: C 59.07, H 8.82, N 9.60.

(R₂,R₃)-3-Methyl-2-n-propyloxirane-2-carboxamide 15B

15B was obtained from **11B**, purified by flash chromatography (ethyl acetate–hexane 2:1 as the eluent), and crystallised from ethyl acetate–hexane 3:1, mp 85–86°C (white solid); $[\alpha]_{\text{D}}$ –11.43 (c

0.1, chloroform); δ_{H} 6.60 (bs, 1H, NH), 5.45 (bs, 1H, NH), 3.71 (q, 1H, J 5.9 Hz, CH), 1.70–1.20 (m, 4H, CH_2CH_2), 1.20 (d, 3H, J 5.9 Hz, CH_3CH), 0.80 (t, 3H, J 7.1 Hz CH_3CH_2); δ_{C} 173.3 (CONH_2), 62.5 (C), 43.1 (CH_2C), 27.5 (CH), 14.2 (CH_2CH_3), 13.6 (CH_3CH_2), 12.2 (CH_3CH). Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{NO}_2$: C 58.72, H 9.15, N 9.78. Found: C 59.29, H 8.78, N 9.56

(R₂,S₃)-3-Methyl-2-i-propyloxirane-2-carboxamide 16A

16A was obtained from **12A**, purified by flash chromatography (ethyl acetate–hexane 2:1 as the eluent), and crystallised from ethyl acetate–hexane 2:1, mp 100–101°C (white solid); $[\alpha]_{\text{D}} -32.8$ (c 0.14, chloroform); δ_{H} 6.30 (bs, 1H, NH), 6.10 (bs, 1H, NH), 3.10 (q, 1H, J 5.8 Hz, CH), 2.10 (sept, 1H, J 7.1 Hz, $\text{CH}(\text{CH}_3)_2$), 1.35 (d, 3H, J 5.8 Hz, CH_3CH), 0.92 (d, 3H, J 7.1 Hz, CH_3CHCH_3) 0.81 (d, 3H, J 7.1 Hz, CH_3CHCH_3); δ_{C} 174.3 (CONH_2), 61.9 (C), 47.5 ($\text{CH}(\text{CH}_3)_2$), 28.5 (CHCH_3), 13.2 (CH_3CH), 9.9 and 9.3 ($\text{CH}(\text{CH}_3)_2$); Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{NO}_2$: C 58.72, H 9.15, N 9.78. Found: C 58.95, H 8.75, N 9.93.

(R₂,R₃)-3-Methyl-2-i-propyloxirane-2-carboxamide 16B

16B was obtained from **12B**, purified by flash chromatography (ethyl acetate–hexane 2:1 as the eluent), and crystallised from ethyl acetate–hexane 2:1, mp 89–90°C (white solid); $[\alpha]_{\text{D}} -15.7$ (c 0.12, chloroform); δ_{H} 6.00 (bs, 1H, NH), 5.58 (bs, 1H, NH), 3.72 (q, 1H, J 5.8 Hz, CH), 2.02 (sept, 1H, J 7.1 Hz, $\text{CH}(\text{CH}_3)_2$), 1.19 (d, 3H, J 5.8 Hz, CH_3CH), 0.95 (d, 3H, J 7.1 Hz, CH_3CHCH_3) 0.90 (d, 3H, J 7.1 Hz, CH_3CHCH_3); δ_{C} 174.3 (CONH_2), 61.9 (C), 46.8 ($\text{CH}(\text{CH}_3)_2$), 27.5 (CHCH_3), 12.9 (CH_3CH), 9.7 and 9.3 ($\text{CH}(\text{CH}_3)_2$); Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{NO}_2$: C 58.72, H 9.15, N 9.78. Found: C 59.10, H 8.71, N 9.82.

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9. Although the yields of this reaction are slightly lower than those obtained with HCl(g) /diethyl ether previously reported,⁷ the thus obtained products are pure enough to be used after the usual workup without additional purification.
10. Compounds **9B**, **10A** and **10B** could be isolated diastereomerically pure by flash chromatography, but in small quantities, just to be individually characterized.
11. See J. C. Carretero, J. L. García Ruano, J. H. Rodríguez, *Tetrahedron*. **1985**, *41*, 2433; M. C. Carreño, J. C. Carretero, J. L. García Ruano, J. H. Rodríguez *Tetrahedron*. **1990**, *46*, 5649 and references therein.

12. Different experimental evidence supporting this mechanistic proposal implying inversion at the sulfur configuration will be published in due course.
13. The use of water gave similar results but the reactions were not so clean as with methanol.
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