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

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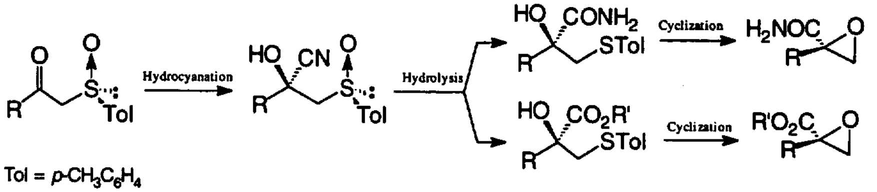
Abstract: The title compounds were efficiently prepared from 1-alkyl(or phenyl)-2-methyl-2-(tolylsulfinyl)ethanone through a simple four-step sequence: highly stereoselective hydrocyanation with Et_2AlCN (key step to control the stereochemistry); hydrolysis to sulfinylamides and separation of epimers; 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 B[5]), 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 derivatives[4] (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_S)+**B**(S_2,S_3,R_S) 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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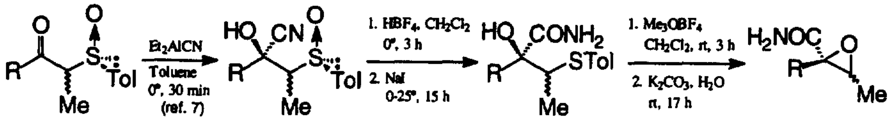
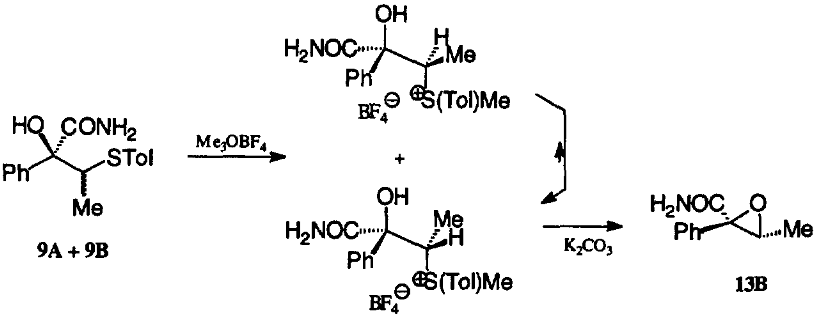
formation of the corresponding oxiranes **13–16** was achieved in high yields (one-pot procedure) by treatment of the sulfides with Me_3OBF_4 followed by K_2CO_3.[4]



R=				Yield(%)		Yield(%)
Ph	1 (A+B)	5 (A+B)	9 (A+B)	74	13 (B)	70
Me	2 (A+B)	6 (A+B)	10 (A+B)	79	14 (A+B)	79
n-Pr	3 (A+B)	7 (A+B)	11 (A+B)	80	15 (A+B)	75
i-Pr	4 (A+B)	8 (A+B)	12 (A+B)	78	16 (A+B)	80

Scheme 2.

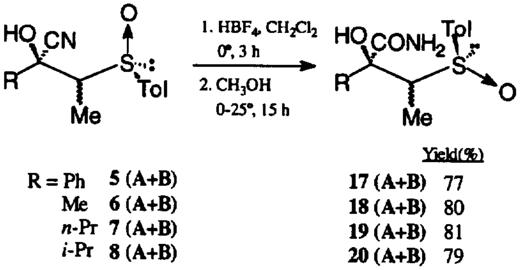
Starting from a **9A+9B** mixture, only one epoxide **13B** was obtained in 70% yield. This result indicates that epimerization at the stereogenic carbon vicinal to the sulfur moiety had taken place, probably at the sulfonium salt stage, in the presence of K_2CO_3 (Scheme 3). The higher steric hindrance 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.



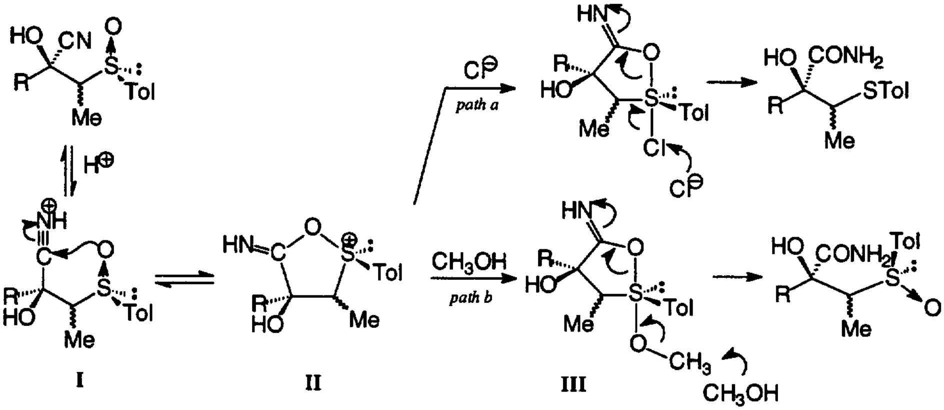
Scheme 3.

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-hydroxysulfoxides[11] 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 methanol[13] to the reaction mixtures of cyanohydrins and fluoboric acid (or $BF_3 \cdot OEt_2$) 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 $BF_3 \cdot OEt_2$ and NaI in CH_3CN,[14] to yield the corresponding β-sulfenyl α-hydroxyamides **9A–12A** and **9B–12B** (Scheme 6). Further treatment of both epimers of compounds **10–12** in the previously described epoxidation conditions[4] (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**.

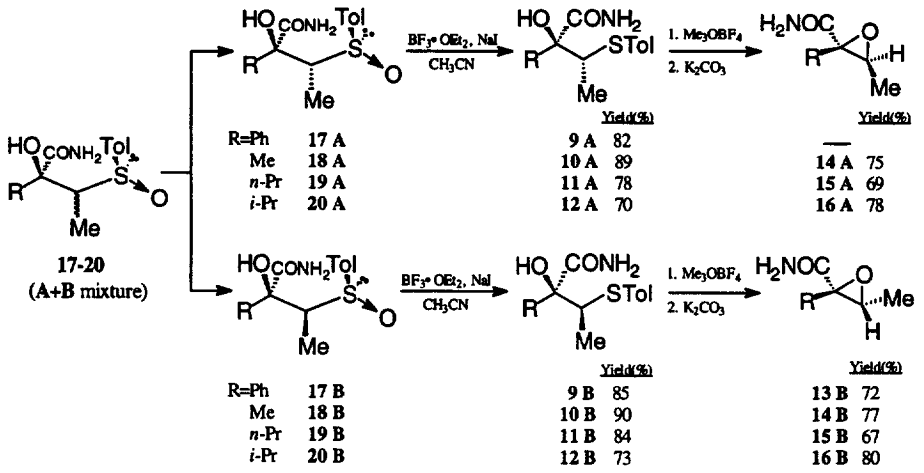
From the NMR data of the cases where both isomers were available (**14–16**), we could state that epoxides **A** exhibit a higher chemical shift for the methinic proton than that of epimers **B** in proton spectra and a lower one for the carbons in CH_3–CH grouping (where the influence of the substituent 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 ^{1}H 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 (^{1}H) 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 hydroxiamides **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_S) and (S_2,S_3,S_S)-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_S) **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, C*H*CH$_3$), 2.43 (s, 3H, CH_3Ar), 0.74 (d, 3H, J 7.0 Hz, C*H*$_3$CH); 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 (*C*HCH$_3$), 21.4 (CH_3Ar), 3.2 (*C*H$_3$CH).

*Isomer (S_2,S_3,S_S) **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, C*H*CH$_3$), 2.41 (s, 3H,

CH_3Ar), 1.07 (d, 3H, J 6.9 Hz, $C\mathit{H}_3CH$); 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 ($\mathit{C}HCH_3$), 29.8 (CH_3Ar), 1.2 ($\mathit{C}H_3CH$).

*(S_2,R_3,S_S) and (S_2,S_3,S_S)-2-Hydroxy-2-methyl-3-(*p*-tolylsulfinyl)butanamide 18A and 18B*
18A and **18B** were obtained from a **6A+6B** mixture.

Isomer (S_2,R_3,S_S) 18A After chromatography **18A** was crystallised from ethyl acetate–hexane (2:1), mp 77–78°C (white solid); $[\alpha]_D$ −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, $C\mathit{H}CH_3$), 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, $C\mathit{H}_3CH$); 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 ($\mathit{C}HCH_3$), 28.7 (CH_3Ar), 26.1 ($\mathit{C}H_3C$), 4.7 ($\mathit{C}H_3CH$).

Isomer (S_2,S_3,S_S) 18B After chromatography **18B** was crystallised from ethyl acetate–hexane (3:2), mp 84–85°C (white solid); $[\alpha]_D$ −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, $C\mathit{H}CH_3$), 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, $C\mathit{H}_3CH$): 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 ($\mathit{C}HCH_3$), 21.3 (CH_3Ar), 25.9 ($\mathit{C}H_3C$), 3.0 ($\mathit{C}H_3CH$).

*(S_2,R_3,S_S) and (S_2,S_3,S_S)-2-Hydroxy-2-*n*-propyl-3-(*p*-tolylsulfinyl)butanamide 19A and 19B*
19A and **19B** were obtained from a **7A+7B** mixture.

Isomer (S_2,R_3,S_S) 19A After chromatography **19A** was crystallised from ethyl acetate–hexane (2:1), mp 86–87°C (white solid); $[\alpha]_D$ −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, $C\mathit{H}CH_3$), 2.39 (s, 3H, CH_3Ar), 1.70–1.50 (m, 4H, CH_2CH_2), 1.37 (d, 3H, J 7.1 Hz, $C\mathit{H}_3CH$), 0.90 (t, 3H, J 7.0 Hz, $C\mathit{H}_3CH_2$); 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 ($\mathit{C}HCH_3$), 39.4 ($\mathit{C}H_2C$), 21.4 (CH_3Ar), 18.3 ($\mathit{C}H_2CH_3$), 15.8 ($\mathit{C}H_3CH$), 13.2 ($\mathit{C}H_3CH_2$).

Isomer (S_2,S_3,S_S) 19B After chromatography **19B** was crystallised from ethyl acetate–hexane (2:1), mp 76–77°C (white solid); $[\alpha]_D$ −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, $C\mathit{H}CH_3$), 2.35 (s, 3H, CH_3Ar), 1.54–1.40 (m, 4H, CH_2CH_2), 1.20 (d, 3H, J 7.2 Hz, $C\mathit{H}_3CH$), 0.85 (t, 3H, J 7.0 Hz, $C\mathit{H}_3CH_2$); 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 ($\mathit{C}HCH_3$), 40.1 ($\mathit{C}H_2C$), 21.3 (CH_3Ar), 18.3 ($\mathit{C}H_2CH_3$), 16.2 ($\mathit{C}H_3CH$), 12.3 ($\mathit{C}H_3CH_2$).

*(S_2,R_3,S_S) and (S_2,S_3,S_S)-2-Hydroxy-2-*i*-propyl-3-(*p*-tolylsulfinyl)butanamide 20A and 20B*
20A and **20B** were obtained from a **8A+8B** mixture.

Isomer (S_2,R_3,S_S) 20A After chromatography **20A** was crystallised from hexane–acetone (3:2), mp 144–145°C (white solid); $[\alpha]_D$ −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, $SC\mathit{H}CH_3$), 2.63 (sept, 1H, J 6.8 Hz, $C\mathit{H}(CH_3)_2$), 2.43 (s, 3H, CH_3Ar), 1.34 (d, 3H, J 6.8 Hz, $C\mathit{H}_3CHS$), 1.15 (d, 3H, J 6.8 Hz, $C\mathit{H}_3CHCH_3$) 0.94 (d, 3H, J 6.8 Hz, $CH_3CHC\mathit{H}_3$); 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 ($\mathit{C}H(CH_3)_2$), 21.4 (CH_3Ar), 17.5 and 16.9 ($(\mathit{C}H_3)_2CH$), 5.3 ($\mathit{C}H_3CHS$).

Isomer (S_2,S_3,S_S) ***20B*** After chromatography **20B** was crystallised from hexane–acetone (3:2), mp 182–183°C (white solid); $[\alpha]_D$ −82.3 (c 0.2 methanol); δ_H 7.61 and 7.31 (AA′BB′ system, 4H, C_6H_4), 7.15 (bs, 1H, NH), 5.70 (bs, 1H, NH), 3.38 (q, 1H, J 7.2 Hz, $SC\mathit{H}CH_3$), 2.43 (s, 3H, CH_3Ar), 2.34 (sept, 1H, J 6.8 Hz, $C\mathit{H}(CH_3)_2$), 1.29 (d, 3H, J 7.2 Hz, $C\mathit{H}_3CHS$), 1.05 (d, 3H, J 6.8 Hz, $C\mathit{H}_3CHCH_3$), 0.94 (d, 3H, J 6.8 Hz, $CH_3CHC\mathit{H}_3$); δ_C 175.3 ($CONH_2$), 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 ($\mathit{C}H(CH_3)_2$), 21.3 (CH_3Ar), 17.2 and 16.5 ($(CH_3)_2CH$), 10.2 ($\mathit{C}H_3CHS$).

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.

*(S_2,R_3) and (S_2,S_3)-2-Hydroxy-2-phenyl -3-(*p*-tolylsulfenyl)butanamide* ***9A*** *and* ***9B***

Isomer (S_2,R_3) ***9A*** **9A** was obtained from **17A**. It was crystallised from hexane–acetone (1:3), mp 81–82°C (white solid); $[\alpha]_D$ −12.6 (c 0.7, chloroform); δ_H 7.57 (m, 2H, Ph), 7.38 and 7.15 (AA′BB′ system, 4H, C_6H_4), 7.30 (m, 3H, Ph), 7.00 (bs, 1H, NH), 5.20 (bs, 1H, NH), 4.03 (q, 1H, J 7.1 Hz, $C\mathit{H}CH_3$), 3.58 (bs, 1H, OH), 2.32 (s, 3H, CH_3Ar), 1.82 (d, 3H, J 7.1 Hz, $C\mathit{H}_3CH$); δ_C 175.9 ($CONH_2$), 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 ($\mathit{C}HCH_3$), 21.3 (CH_3Ar), 12.7 ($\mathit{C}H_3CH$). Anal. Calcd. for $C_{17}H_{19}NO_3S$: 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 (S_2,S_3) ***9B*** **9B** was obtained from **17B**. Physical and data are coincident with those previously described.[7]

*(S_2,R_3) and (S_2,S_3)-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]

*(S_2,R_3) and (S_2,S_3)-2-Hydroxy-2-*n*-propyl-3-(*p*-tolylsulfenyl)butanamide* ***11A*** *and* ***11B***

Isomer (S_2,R_3) ***11A*** **11A** was obtained from **19A**. It was crystallised from dichloromethane, mp 90–91°C (white solid); $[\alpha]_D$ −15.6 (c 0.63, chloroform); δ_H 7.35 and 7.12 (AA′BB′ system, 4H, C_6H_4), 6.90 (bs, 1H, NH), 6.06 (bs, 1H, NH), 3.70 (bs, 1H, OH), 3.55 (q, 1H, J 6.9 Hz, $C\mathit{H}CH_3$), 2.35 (s, 3H, CH_3Ar), 1.75–1.65 (m, 2H, CH_2C), 1.55–1.46 (m, 2H, $C\mathit{H}_2CH_3$), 1.35 (d, 3H, J 6.9 Hz, $C\mathit{H}_3CH$), 0.90 (t, 3H, J 7.1 Hz, $C\mathit{H}_3CH_2$); δ_C 176.5 ($CONH_2$), 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 ($\mathit{C}HCH_3$), 40.4 ($\mathit{C}H_2C$), 21.2 (CH_3Ar), 17.3 ($\mathit{C}H_2CH_3$), 16.3 ($\mathit{C}H_3CH$), 13.8 ($\mathit{C}H_3CH_2$). Anal. Cald. for $C_{13}H_{19}NO_2S$: 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 (S_2,S_3) ***11B*** **11B** was obtained from **19B**. It was crystallised from dichloromethane–hexane (9:1), mp 88–89°C (white solid); $[\alpha]_D$ −4.6 (c 0.52, chloroform); δ_H 7.40 and 7.19 (AA′BB′ system, 4H, C_6H_4), 6.65 (bs, 1H, NH), 5.75 (bs, 1H, NH), 3.35 (q, 3H, J 7.1 Hz, $C\mathit{H}CH_3$), 2.33 (s, 3H, CH_3Ar), 1.60–1.45 (m, 4H, CH_2CH_2), 1.37 (d, 3H, J 7.1 Hz, $C\mathit{H}_3CH$), 0.90 (t, 3H, J 7.3 Hz, $C\mathit{H}_3CH_2$); δ_C 175.8 ($CONH_2$), 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 ($\mathit{C}HCH_3$), 39.0 ($\mathit{C}H_2C$), 21.2 (CH_3Ar), 16.7 ($\mathit{C}H_2\ CH_3$), 16.3 ($\mathit{C}H_3CH$), 14.2 ($\mathit{C}H_3CH_2$). Anal. Calcd. for $C_{13}H_{19}NO_2S$: 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.

*(S_2,R_3) and (S_2,S_3)-2-Hydroxy-2-*i*-propyl-3-*p*-tolylsulfenylbutanamide* ***12A*** *and* ***12B***

Isomer (S_2,R_3) ***12A*** **12A** was obtained from **20A**. It was crystallised from hexane–acetone (3:2), mp 85–86°C (white solid); $[\alpha]_D$ −24.1 (c 0.50, chloroform); δ_H 7.35 and 7.19 (AA′BB′ system, 4H, C$_6$H$_4$), 6.95 (bs, 1H, NH), 6.30 (bs, 1H, NH), 3.25 (q, 1H, J 6.8 Hz, C*H*CH$_3$), 2.56 (sept, 1H, J 6.7 Hz, C*H*(CH$_3$)$_2$), 1.25 (d, 3H, J 6.8 Hz, C*H*$_3$CH), 1.10 (d, 3H, J 6.7 Hz, C*H*$_3$CHCH$_3$), 0.90 (d, 3H, J 6.7 Hz, CH$_3$CHC*H*$_3$); δ_C 177.5 (CONH$_2$), 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 (*C*HCH$_3$), 34.5 (*C*H(CH$_3$)$_2$), 21.1 (CH$_3$Ar), 17.5 and 17.3 ((*C*H$_3$)$_2$CH), 15.9 (*C*H$_3$CH).

Isomer (S$_2$,S$_3$) 12B **12B** was obtained from **20B**. It was crystallised from hexane–acetone (3:1), mp 93–94°C (white solid); $[\alpha]_D$ −15.2 (c 0.50, chloroform); δ_H 7.35 and 7.12 (AA′BB′ system, 4H, C$_6$H$_4$), 6.80 (bs, 1H, NH), 5.32 (bs, 1H, NH), 3.60 (q, 1H, J 7.0 Hz, C*H*CH$_3$), 3.59 (bs, 1H, OH), 2.40 (s, 3H, CH$_3$Ar), 2.15 (sept, 1H, J 6.8 Hz, C*H*(CH$_3$)$_2$), 1.30 (d, 3H, J 7.0 Hz, C*H*$_3$CH), 0.90 (d, 6H, J 6.8 Hz, (C*H*$_3$)$_2$CH); δ_C 177.5 (CONH$_2$), 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 (CHCH$_3$), 33.7 (*C*H(CH$_3$)$_2$), 21.1 (CH$_3$Ar), 17.3 and 17.1 ((*C*H$_3$)$_2$CH), 15.9 (*C*H$_3$CH).

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.

(R$_2$,R$_3$)-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); $[\alpha]_D$ −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, C*H*CH$_3$), 1.50 (d, 3H, J 5.3 Hz, C*H*$_3$CH); δ_C 170.0 (CONH$_2$), 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 (*C*HCH$_3$), 14.1 (CH$_3$).

(R$_2$,S$_3$)-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); $[\alpha]_D$ −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, CH$_3$C), 1.40 (d, 3H, J 8.0 Hz, C*H*$_3$CH); δ_C 172.3 (CONH$_2$), 62.3 (C), 38.6 (*C*H$_3$C), 28.8 (CH), 13.5 (*C*H$_3$CH). Anal. Calcd. for $C_5H_9NO_2$: C 52.16, H 7.88, N 12.17. Found: C 52.10, H 7.85, N 12.22.

(R$_2$,R$_3$)-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); $[\alpha]_D$ −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, CH$_3$C), 1.20 (d, 3H, J 7.9 Hz, C*H*$_3$CH); δ_C 175.4 (CONH$_2$), 63.2 (C), 35.4 (*C*H$_3$C), 28.2 (CH), 12.8 (*C*H$_3$CH). Anal. Calcd. for $C_5H_9NO_2$: C 52.16, H 7.88, N 12.17. Found: C 52.20, H 7.73, N 12.24.

*(R$_2$,S$_3$)-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); $[\alpha]_D$ −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, CH$_2$CH$_2$), 1.40 (d, 3H, J 6.0 Hz, C*H*$_3$CH), 0.90 (t, 3H, J 7.0 Hz C*H*$_3$CH$_2$); δ_C 174.3 (CONH$_2$), 64.8 (C), 45.2 (*C*H$_2$C), 28.2 (CH), 15.8 (*C*H$_2$CH$_3$), 13.3 (*C*H$_3$CH$_2$), 12.8 (*C*H$_3$CH). Anal. Calcd. for $C_7H_{13}NO_2$: C 58.72, H 9.15, N 9.78. Found: C 59.07, H 8.82, N 9.60.

*(R$_2$,R$_3$)-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); $[\alpha]_D$ −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 $C_7H_{13}NO_2$: C 58.72, H 9.15, N 9.78. Found: C 59.29, H 8.78, N 9.56

(R_2,S_3)-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); $[\alpha]_D$ −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, $CH(CH_3)_2$), 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 ($CH(CH_3)_2$), 28.5 ($CHCH_3$), 13.2 (CH_3CH), 9.9 and 9.3 ($CH(CH_3)_2$); Anal. Calcd. for $C_7H_{13}NO_2$: C 58.72, H 9.15, N 9.78. Found: C 58.95, H 8.75, N 9.93.

(R_2,R_3)-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); $[\alpha]_D$ −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, $CH(CH_3)_2$), 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 ($CH(CH_3)_2$), 27.5 ($CHCH_3$), 12.9 (CH_3CH), 9.7 and 9.3 ($CH(CH_3)_2$); Anal. Calcd. for $C_7H_{13}NO_2$: 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.
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