Diastereoselectivity and assignment of absolute stereochemistry in the aza-Diels–Alder reaction of a sulfonylimino acetate with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene

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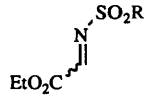
N-[(1*R*)-(−)-camphor-10-ylsulfonyl]imine **1b** generated *in situ* from the corresponding brominated glycinate **4b** reacts with Danishefsky's diene under thermal conditions to give a high yield of diastereoisomeric Diels–Alder adducts **7b** and **6b** in a 2.04:1 ratio. Under Lewis acid catalysis at −78 °C the diastereoselectivity improves slightly to 2.30:1 using titanium tetraisopropoxide. However, the sense of asymmetric induction is reversed when using diethylaluminium chloride as the catalyst. Determination of the absolute stereochemistry of the adducts **6b** and **7b** was achieved by comparison with pipecolic acid derivatives **10b** and **12b** and showed that **7b** had the (2*R*)-configuration at the newly formed chiral centre and **6b** the (2*S*)-configuration.

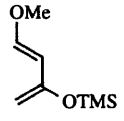
Introduction

Asymmetric aza-Diels–Alder reactions[1] offer significant potential for the enantioselective synthesis of N-heterocycles containing a six-membered ring. Most of the recent advances in developing these reactions have come from the use of imines with a chiral auxiliary attached to nitrogen.[2–7] The most reliable and efficient imino dienophiles[8] are those with electron withdrawing groups attached to both nitrogen and carbon and in particular those where the nitrogen substituent is a sulfonyl group. However, this type of imino dienophile has found limited use in asymmetric aza-Diels–Alder reactions. Maggini *et al.*[9] reported that *N*-phenylsulfonylimino acetates substituted with a chiral ester show little diastereoselectivity in reaction with cyclopentadiene, however Hamley *et al.*[10] have shown that using lactate or pantolactone derived *N*-toluenesulfonylimino acetates in conjunction with Lewis acid catalysis improved the diastereoselectivity to synthetically useful levels. Recently, we reported[11] preliminary results of a study of the aza-Diels–Alder reactions of *N*-sulfonylimino acetates **1** with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene **2**. In this paper, we report the full details of this work and the methods used to determine the absolute stereochemistry of the adducts obtained.



1

a R = Ph
b R = (1*R*)-(−)-camphor-10-yl

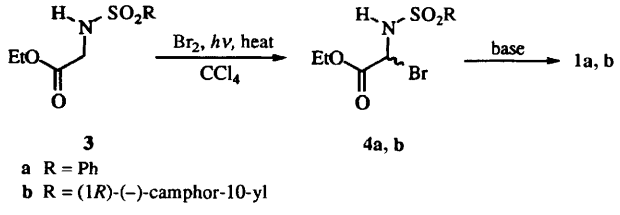


2

Results and discussion

Using a method analogous to that of Maggini *et al.*,[9] photochemical bromination of *N*-sulfonylglycinates **3** gave the highly moisture sensitive bromides **4** (as a 1:1 mixture of diastereoisomers in the case of **4b**), from which *in situ* elimination of HBr with various bases gives access to non-isolable imines **1** (Scheme 1).

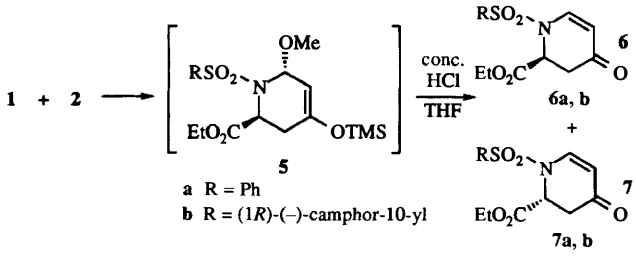
Thus, a trial reaction of bromide **4a** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in dichloromethane gave imine **1a** which in turn reacted with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene **2** (Scheme 2) to give a non-isolable (due to hydrolytic instability) intermediate adduct, presumably possessing structure **5a**. Treatment of the crude reaction mixture with acid gave a racemic mixture of the readily purified tetrahydropyridinones **6a** and **7a** in 76% yield after chromatography. The proposed assignment of the relative stereochemistry of the intermediate **5** was based on the following evidence; (*a*) the corresponding Diels–Alder reaction of **1a** or **1b** with cyclopentadiene gives solely the *exo*-ethyl 2-sulfonyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates **8**[9,10] and (*b*) **5a** shows only a single methoxy resonance at δ 3.40 in the crude ^{1}H NMR spectrum.



3 **4a, b**

a R = Ph
b R = (1*R*)-(−)-camphor-10-yl

Scheme 1



5

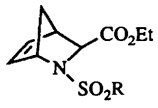
a R = Ph
b R = (1*R*)-(−)-camphor-10-yl

6a, b + **7a, b**

Scheme 2

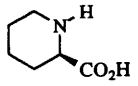
Accordingly, *N*-[(1*R*)-(−)-camphor-10-ylsulfonyl]imine **1b**, generated from **4b** by triethylamine mediated elimination (DBU was ineffective) of HBr, also reacted with **2** to give an intermediate adduct (presumably with relative stereochemistry **5b**) as a mixture of two diastereoisomers, as demonstrated by only two methoxy peaks at δ 3.66 and 3.70 in the crude ^{1}H NMR spectrum. Again isolation of these adducts was not possible and hydrolysis of **5b** with conc. HCl in tetrahydrofuran gave a 58% yield of the pure tetrahydropyridines **6b** and **7b** as an

inseparable 1 : 1.86 (relative amounts estimated by the ratio of the two olefinic ^{1}H NMR signals at δ 7.71–7.73 and 7.59–7.62, each a 1 H doublet of doublets respectively for each diastereoisomer) mixture of diastereoisomers. The rather disappointing level of asymmetric induction led us to examine the reaction conditions to see if any improvement was possible.



8

a R = Ph
b R = (1*R*)-(–)-camphor-10-yl



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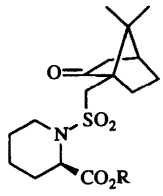


10

a R = H
b R = Et

Examination of the effect of varying the polarity of the reaction solvent on the diastereoisomeric ratio of **6b** to **7b** showed that solvent polarity played only a minor part on the stereoselectivity of the reaction. However, there was a general trend in that the more stereoselective reactions occurred in less polar solvents. For example, the highest diastereoisomeric excess (de) (1 : 1.83) was obtained in carbon tetrachloride at room temperature. Dropping the reaction temperature to −15 °C improved the de, but only to 1 : 2.04. The lack of major solvent effects on the diastereoselectivity of the aza-Diels–Alder reaction indicates that the reaction mechanism involves relatively little charge separation, pointing to a relatively concerted [4 + 2] cycloaddition process. Although the stereoselectivity was only moderate, it was encouraging to observe that lowering the temperature of the reaction could improve the stereoselectivity, which prompted an investigation into whether it was possible to improve the stereoselectivity further by using Lewis acid catalysis and lowering the temperature.

By using butyllithium as the base for the formation of the imine **1b**, catalysis of the aza-Diels–Alder reaction at −78 °C was successful with a variety of Lewis acids. In a control experiment with no Lewis acid catalyst carried out at −78 °C there was no reaction. However, addition of catalytic amounts (generally 25 mol%) of various Lewis acids [*e.g.* Et_2AlCl, $TiCl_4$, Cp_2TiCl_2, $Ti(OPr^i)_4$, $ZnCl_2$ and $BF_3{\cdot}Et_2O$] did catalyse the reaction at −78 °C, with the highest de being observed with titanium(IV) isopropoxide (de 1 : 2.33) but with only 25% conversion after 4 h. The yield of the Diels–Alder adducts generally decreased with increasing the amount of the catalyst; becoming zero when using stoichiometric quantities of the Lewis acids. It is noteworthy that boron, zinc and titanium Lewis acids gave the same diastereoisomer as the major product obtained from the thermal cycloaddition reaction. However, diethylaluminium chloride showed a reversal in selectivity compared to the thermal reaction (de 1.44 : 1), which suggests that aluminium may activate imine **1b** in a different manner to the other Lewis acids.

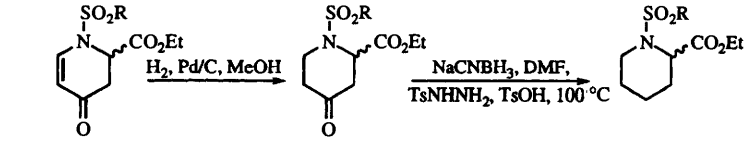
Having isolated a mixture of diastereoisomeric adducts **6b** and **7b**, methods were required for determining the absolute stereochemistry of each adduct. This was achieved by preparation of the *N*-camphorsulfonamide derivatives of ethyl pipecolates (ethyl piperidine-2-carboxylates) (*i.e.* **12b**) from the aza-Diels–Alder adduct mixture **6b**/**7b** and comparing this sample with that derived from resolved (2*R*)-pipecolic acid **9**.

Initially employing the racemic aza-Diels–Alder adduct **6a**/**7a** to develop the conditions for removal of the double bond and ketone functions, reduction of the double bond of **6a**/**7a** by catalytic hydrogenation (Scheme 3) gave piperidone **11a** in 86% yield. Subsequent one pot [12] deoxygenation of the ketone function of **11a** using a sodium cyanoboranuide–toluene-4-sulfonylhydrazine mediated reduction in DMF–sulfolane (tetrathiophene 1,1-dioxide) gave racemic ethyl *N*-phenylsulfonylpiperidine-2-carboxylate **12a**, albeit in only 2% isolated yield. This procedure suffered from problems due to the difficulty of removing sulfolane from the product. However, sulfolane was not critical for the success of the reaction; when conducted in *N*,*N*-dimethylformamide alone, the desired product **12a** was obtained in 37% yield.

To aid structure determination of the *N*-[(1*R*)-(−)-camphor-10-ylsulfonyl]imine derived adducts **6b** and **7b**, gradient elution chromatography of a crude 1 : 2 mixture of these diastereoisomers provided a diastereoisomerically enriched (1 : 7 in favour of the major diastereoisomer) sample, which was suitable for conversion into **12b**. Hydrogenation, followed by deoxygenation of the 1 : 7 mixture of **6b** and **7b** gave the expected 1 : 7 mixture of the corresponding camphorylsulfonyl pipecolates **11b** and **12b** in 82% and 58% yields, respectively. For determination of the stereochemical outcome of the aza-Diels–Alder reactions, a diastereoisomerically pure sample of **10b** was required for comparison.

The synthesis of pure **10b** was achieved from racemic pipecolic acid, *via* (1) resolution of racemic pipecolic acid to give **9** as the tartrate salt using a literature procedure;[13] (2) *N*-sulfonylation of the tartrate salt of **9** with (1*R*)-(−)-camphor-10-sulfonyl chloride to give the corresponding sulfonylated pipecolic acid **10a**, albeit in poor yield (10%) (attempts to improve the yield of the sulfonylation reaction by using diisopropylethylamine, as recently reported for the *N*-tosylation of amino acids,[14] were unsuccessful); and (3) treatment of **10a** with ethanol–hydrogen chloride gave the corresponding ethyl ester **10b** in 45% yield. A 1 : 1 mixture of camphor-10-ylsulfonylpiperidine-2-carboxylates **10b** and **14** was also prepared from (1*R*)-(−)-camphor-10-sulfonyl chloride and racemic pipecolic acid as shown in Scheme 4.

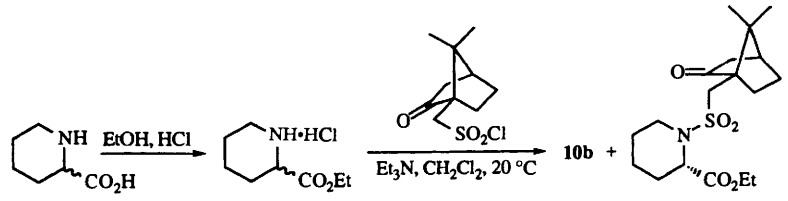
Comparison of the ^{1}H NMR spectra of the enantiomerically pure (1*R*)-(−)-camphor-10-ylsulfonyl derivative **10b** and that of the 1 : 7 diastereoisomerically enriched **12b** showed that the major diastereoisomer formed in the aza-Diels–Alder reaction in the absence of any catalyst was **7b**, *i.e.* with the (*R*)-configuration in the piperidine ring. This assignment was based upon the following evidence; (*a*) two singlets due to two CH_3 groups at δ 0.86 and 1.09, respectively were present in both the unambiguously prepared **10b** and the major diastereoisomer present in **12b** derived from the thermal aza-Diels–Alder adduct; (*b*) an AB quartet due to the CH_2SO_2 group was observed at δ 3.24 in both the unambiguously prepared **10b** and the major diastereoisomer present in **12b** from the aza-Diels–Alder adduct; (*c*) the 1 : 1 mixture of **10b** and **14** showed pairs of methyl signals at δ 0.86 and 1.09, and at 0.88 and 1.12, and AB quartets at δ 3.24 and 3.28; and (*d*) the minor diastereoisomer



6/7 11a, b 12a, b

a R = Ph
b R = (1*R*)-(−)-camphor-10-yl

Scheme 3



13 14

Scheme 4

derived from the thermal aza-Diels–Alder reaction, showed methyl signals at δ 0.88 and 1.12, respectively, and an AB quartet at 3.28 for CH_2SO_2 group. Therefore, the minor diastereoisomer from the aza-Diels–Alder reaction possesed structure **6b**.

In conclusion, we have demonstrated that the *N*-(1*R*)-(−)-camphor-10-ylsulfonylimine **1b** reacts with diene **2** with moderate diastereoselectivity under both thermal and Lewis acid catalysed conditions. Determination of the absolute stereochemistry of adducts **6b** and **7b** shows that the major adduct (generally **7b**, except when catalysed by diethylaluminium chloride) has the (*R*)-configuration at the newly formed chiral centre.

Experimental

Dichloromethane, chloroform, carbon tetrachloride and toluene were distilled from calcium hydride. *N*,*N*-Dimethylformamide was distilled from calcium hydride at reduced pressure (20 mmHg). Triethylamine was purchased from Aldrich or Acros and stored over KOH pellets. DBU was purchased from Aldrich and stored over KOH pellets. (1*R*)-(−)-Camphor-10-sulfonyl chloride was prepared from (1*R*)-(−)-camphor-10-sulfonic acid by refluxing with thionyl chloride in toluene solution. Methanol, ethanol, hexane, sodium hydrogen carbonate, sodium hydroxide and 36% hydrochloric acid were purchased from Vickers and used without further purification. All other reagents were purchased from Aldrich or Acros and used directly. Column chromatography was achieved under gravity using Crosfield Silica Gel Type 60.

All anhydrous, low temperature reactions were carried out in glassware which was dried prior to use in an oven at 140 °C and cooled under a stream of argon. All ultraviolet irradiations were carried out in quartz glassware with a Hanovia 4781 medium pressure mercury vapour lamp. All organic extractions were dried with magnesium sulfate. Evaporations were carried out using a Büchi rotary evaporator, followed by evaporation under high vacuum (typically at approximately 2 mmHg).

Optical rotations were measured using Perkin-Elmer model 241 and Optical Activity model A4000 polarimeters and are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined using Büchi or Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200, 300 or 400 MHz on Bruker AC200, AC300 and AC400 spectrometers, respectively, using residual incompletely deuteriated solvent as internal standard. *J* Values are given in Hz. ^{13}C NMR spectra were recorded at 75 or 100 MHz on Bruker AC300 and AC400 spectrometers respectively, using deuteriated solvent as internal standard. IR spectra were recorded using Nicolet 520 FT-IR or Perkin-Elmer 783 (with PE600 datastation) spectrometers. UV spectra were recorded on Kontron Uvikon 820 or Perkin-Elmer 115 spectrometers. ε Values are given in units of dm^3 mol^{-1} cm^{-1}. Fast atom bombardment (FAB) mass spectra were obtained from Finnegan MAT 8430 or Kratos MS50 spectrometers, using *m*-nitrobenzyl alcohol or thioglycolic acid–glycolic acid matrices. Electron impact (EI) (70 ev) and chemical ionisation (CI) using ammonia gas mass spectra were obtained from Finnegan MAT 8430 or Kratos MS25 spectrometers. High resolution mass spectrometry was carried out using a Kratos Concept IS spectrometer. Combustion analysis was carried out on Perkin-Elmer 240C or Carlo-Erba 1106 elemental analysers.

Ethyl *N*-phenylsulfonylglycinate 3a

To a stirred slurry of ethyl glycinate hydrochloride (87.24 g, 0.62 mol) in dichloromethane (500 cm^3) was added benzenesulfonyl chloride (88.31 g, 0.50 mol) and the mixture cooled to 0–5 °C. Triethylamine (126.25 g, 1.25 mol) was then added dropwise, whilst maintaining the temperature of the reaction mixture below 10 °C (vigorous stirring is required as the reaction mixture becomes very thick). After stirring for 12 h at room temperature the reaction mixture was washed with water (3 × 500 cm^3). The organic layer was then dried and evaporated. Recrystallisation of the crude material from hexane gave the title compound **3a** (114.84 g, 95%), mp 62 °C; ν_{max}(KBr disc)/cm^{-1} *inter alia* 3239 (N–H) and 1701 (C=O); λ_{max} (EtOH)/nm 221 (ε 8311) and 204 (6540); δ_H(400 MHz; $CDCl_3$), 1.18 (3 H, t, *J* 7.1, CH_2CH_3), 3.80 (2 H, d, *J* 5.5, NCH_2, collapses to a singlet on addition of D_2O), 4.08 (2 H, q, *J* 7.1, OCH_2), 5.23 (1 H, t, *J* 5.5, NH, disappears on addition of D_2O), 7.52 (2 H, m, *m*-ArH), 7.60 (1 H, m, *p*-ArH) and 7.88 (2 H, m, *o*-ArH); δ_C(100 MHz; $CDCl_3$) 13.9 (CH_3), 44.1 (CH_2CO_2Et), 61.8 (OCH_2), 127.1 (*o*-ArC), 129.0 (*m*-ArC), 132.8 (*p*-ArC), 139.2 ($ArCSO_2$) and 168.7 (CO_2); *m*/*z* (FAB) 244 (M^+ + H, base peak), 170 ($M^+ - C_3H_5O_2$) and 141 ($M^+ - C_4H_8NO_2$) [Found: C, 49.1; H, 5.4; N, 5.9%; M (EI), 243.0562. Calc. for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.38; N, 5.76%; *M*, 243.0565].

Ethyl 2-bromo-*N*-phenylsulfonylglycinate 4a

To a slurry of ethyl *N*-phenylsulfonylglycinate **3a** (5.0 g, 20.5 mmol) in carbon tetrachloride (100 cm^3) under an argon atmosphere was added bromine (1.0 cm^3, 19.4 mmol). The

mixture was then heated at reflux and irradiated with UV light for 2 h or until the solution decolourised. The resulting solution was then reduced to about $\frac{1}{3}$ of its original volume by distillation in a stream of argon. The precipitated product was then rapidly filtered under an argon atmosphere and dried over P_2O_5 to give the title compound **4a** (4.75 g, 72%), mp 116.5–117 °C; ν_{max}(KBr disc)/cm^{-1} *inter alia* 3280 (N–H) and 1740 (C=O); λ_{max}(MeCN)/nm 220 (ε 10 650); δ_H(300 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.1, CH_2CH_3), 4.29 (2 H, q, *J* 7.1, CH_2CH_3), 6.16 (1 H, d, *J* 11.2, CHBr), 6.27 (1 H, d, *J* 11.2, NH, addition of D_2O causes hydrolysis to form benzenesulfonamide and ethyl glyoxylate), 7.54 (2 H, m, *m*-ArH), 7.64 (1 H, m, *p*-ArH) and 7.95 (2 H, m, *o*-ArH); δ_C(75 MHz; $CDCl_3$) 13.7 (CH_3), 53.9 (CHBr), 63.4 (CH_2), 127.8 (*o*-ArC), 129.2 (*m*-ArC), 133.8 (*p*-ArC), 138.7 ($ArCSO_2$) and 165.4 (CO_2); *m*/*z* (EI) 323 and 321 (M^+), 242 (M^+ – Br, base peak) and 141 (SO_2Ph) (Found: C, 37.6; H, 4.0; N, 4.6; S, 9.6. Calc. for $C_{10}H_{12}BrNO_4S$: C, 37.3; H, 3.8; N, 4.4; S, 10.0%).

Ethyl 4-oxo-2-phenylsulfonyl-1,2,3,4-tetrahydropyridine-2-carboxylate 6a/7a

To a solution of ethyl 2-bromo-*N*-phenylsulfonylglycinate **4a** (1.0 g, 3.10 mmol) in dichloromethane (40 cm^3) under an argon atmosphere at room temperature was added DBU (480 mm^3, 3.15 mmol) followed by 1-methoxy-3-trimethylsilyloxybuta-1,3-diene **2** (840 mm^3, 3.88 mmol). The reaction mixture was stirred at room temperature for 12 h and then conc. HCl–THF (1:19, 20 cm^3) was added and the mixture stirred at room temperature for 1 h. The mixture was then diluted with water (20 cm^3) and the organic layer separated, dried and evaporated. Flash silica chromatography (1:1, ethyl acetate–hexanes) of the crude oil (dissolved in a little dichloromethane) gave the title compound **6a/7a** (730 mg, 76%) as a pale green oil; ν_{max}(neat)/cm^{-1} *inter alia* 1740 (C=O), 1673 (C=O) and 1599 (C=C); λ_{max}(EtOH)/nm 287 (ε 13 767); δ_H(300 MHz; $CDCl_3$) 1.13 (3 H, t, *J* 7.1, CH_2CH_3), 2.74 (1 H, asymmetric dd, *J* 6.9 and 17.0, O=C–CHH), 2.85 (1 H, asymmetric dd, *J* 3.0 and 16.5, O=C–CHH), 4.02 (2 H, qABq, *J* 7.1 and 17, sep. 35.6 Hz, OCH_2), 4.99 (1 H, dt, *J* 6.8 and 3.0, $CHCO_2Et$), 5.38 (1 H, d, *J* 8.3, O=C–CH=), 7.58 (2 H, m, *m*-ArH), 7.69 (1 H, m, *p*-ArH), 7.73 (1 H, dd, *J* 1.3 and 8.4, =CHN) and 7.87 (2 H, m, *o*-ArH); δ_C(75 MHz; $CDCl_3$) 13.8 (CH_3), 38.1 (CH_2–C=O), 56.3 ($CHCO_2$), 62.5 (OCH_2), 107.9 (O=C–CH=), 127.4 (*o*-ArC), 129.6 (*m*-ArC), 134.2 (*p*-ArC), 137.9 ($ArCSO_2$), 142.4 (=CHN), 167.8 (CO_2) and 189.2 (C=O); *m*/*z* (FAB) 310 (M^+ + H, base peak), 236 (M^+ – CO_2Et), 168 (M^+ – SO_2Ph) and 141 (SO_2Ph) (Found: C, 54.1; H, 5.2; N, 4.4; S, 10.8. Calc. for $C_{14}H_{15}NO_4S$: C, 54.4; H, 4.9; N, 4.5; S, 10.4%).

(–)-Ethyl *N*-[(1*R*)-camphor-10-ylsulfonyl]glycinate 3b

To a cooled (0 to 5 °C), stirred, slurry of (1*R*)-(–)-camphor-10-sulfonyl chloride (17.76 g, 70 mmol) and ethyl glycinate hydrochloride (12.36 g, 88 mmol) in dichloromethane (100 cm^3) was added triethylamine (17.88 g, 175 mmol) dropwise over 30 min. The mixture was stirred at room temperature for 12 h and then washed successively with (100 cm^3 each) water, hydrochloric acid (0.5 mol dm^{-3}; ×2), aqueous sodium hydrogen carbonate (0.5 mol dm^{-3}; ×3) and water. The organic layer was then dried and evaporated. The resulting oil was purified by flash silica chromatography (dichloromethane) to give the title compound **3b** (14.55 g, 65%), as a colourless oil which slowly crystallised on standing, mp 42 °C; $[\alpha]_D^{20}$ –22.3 (*c* 1.06, EtOH); ν_{max}(neat)/cm^{-1} *inter alia* 3304 (NH) and 1746 (C=O); λ_{max}(EtOH)/nm 206 (ε 727); δ_H(400 MHz; $CDCl_3$) 0.88 (3 H, s, CCH_3), 0.96 (3 H, s, CCH_3), 1.22 (3 H, t, *J* 7.2, CH_2CH_3), 1.43 (1 H, m), 1.94 (2 H, m), 2.07 (1 H, t, *J* 4.3), 2.16 (1 H, m), 2.36 (1 H, m), 3.28 (2 H, ABq, *J* 15.0, sep. 256 Hz, CH_2SO_2), 3.96 (2 H, asymmetric dABq, *J* 5.1 and 18.0, 6.6 and 18.1, sep. 66.0 Hz, NCH_2, collapses to ABq, *J* 15.0, sep. 26.0 Hz, on addition of D_2O), 4.16 (2 H, q, *J* 7.1, OCH_2) and 6.02 (1 H, br t, *J* 5.8, NH, disappears on addition of D_2O); δ_C(100 MHz; $CDCl_3$) 14.0 (CH_2CH_3), 19.4 (CCH_3), 19.8 (CCH_3), 26.5 (CH_2CH_2), 26.9 (CH_2CH_2), 42.7 (CH_2CHCH_2), 42.8 (CH_2CO), 44.6 (CH_2SO_2), 48.6 [$C(CH_3)_2$], 51.2 (NCH_2), 59.1 (CH_2CCO), 61.5 (OCH_2), 169.7 (CO_2Et) and 216.3 (C=O); *m*/*z* (FAB) 318 (M^+ + H), 215 (M^+ – $C_4H_8NO_2$, base peak) and 151 (M^+ – $C_4H_8NSO_4$) [Found: C, 52.9; H, 7.2; N, 4.24%; M (FAB), 318.1391. Calc. for $C_{14}H_{23}NO_5S$: C, 52.98; H, 7.30; N, 4.41%; *M*, 318.1375].

Ethyl 2-bromo-*N*-[(1*R*)-camphor-10-ylsulfonyl]glycinate 4b

To a solution of (–)-ethyl *N*-[(1R)-camphor-10-ylsulfonyl]glycinate **3b** (6.15 g, 19.33 mmol) in carbon tetrachloride (450 cm^3) under an argon atmosphere was added bromine (1.0 cm^3, 19.33 mmol). The mixture was then heated at reflux and irradiated with ultraviolet light for 2 h to give an essentially quantitative yield of the title compound **4b** as a 1:1 mixture of diastereoisomers. The resulting solution was then stored under argon, ν_{max}(neat)/cm^{-1} *inter alia* 3264 (NH) and 1745 (C=O); δ_H(400 MHz; $CDCl_3$) 0.97 (3 H, s, CCH_3), 1.0 (3 H, s, CCH_3), 1.36 (3 H, t, *J* 7.1, CH_2CH_3), 1.49 (1 H, m), 2.07 (5 H, m), 4.94 (1 H, m), 3.43 (2 H, ABq, *J* 15.4, sep. 344.0 Hz, CH_2SO_2), 4.33 and 4.34 (1 H + 1 H, 2 × q, *J* 7.1, two overlapping quartets corresponding to OCH_2 for each of the two diastereoisomers in 1:1 ratio), 6.19 (1 H, d, *J* 11.8, CHBr), 7.87 (1 H, d, *J* 11.8, NH, addition of D_2O causes hydrolysis to camphorsulfonamide and ethyl glyoxylate); *m*/*z* (FAB) 316 (M^+ – Br), 215 ($C_{10}H_{15}SO_3$, base peak) and 151 ($C_{10}H_{15}O$).

Example procedure for the preparation of ethyl 1-[(1*R*)-camphor-10-ylsulfonyl]-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate 6b/7b

To a solution of compound **4b** (320 mg, 0.81 mmol) in carbon tetrachloride (20 cm^3) under an argon atmosphere at room temperature was added triethylamine (115 mm^3, 0.83 mmol) and then 1-methoxy-3-trimethylsilyloxybuta-1,3-diene **2** (400 mm^3, 1.85 mmol). The reaction mixture was stirred at room temperature for 12 h and then conc. HCl–THF (1:19, 20 cm^3) was added and the mixture stirred at room temperature for 1 h. The mixture was then diluted with water (20 cm^3) and the organic layer separated, dried and evaporated. Purification by silica gel chromatography (2:1, ethyl acetate–hexane as eluent) of the crude oil gave a mixture of the title compounds **6b** and **7b** (178 mg, 58%) as a pale brown oil. The 35:65 diastereoisomeric mixture of **6b** and **7b** was characterised as such, ν_{max}(neat)/cm^{-1} *inter alia* 2967 (C–H), 1746 (C=O), 1674 (C=O) and 1601 (C=C); λ_{max}(EtOH)/nm 280 (ε 10 923); δ_H(400 MHz; $CDCl_3$) 0.9 (3 H, s, CCH_3), 1.10 (1.8 H, s, CH_3C, major diastereoisomer), 1.11 (1.2 H, s, CH_3C, minor diastereoisomer), 1.28 (3 H, t, *J* 7.1, CH_2CH_3), 1.50 (1 H, m), 1.72 (0.4 H, ddd, *J* 4.7, 9.3 and 14.0, minor diastereoisomer), 1.85 (0.6 H, ddd, *J* 4.7, 9.3 and 14.0, major diastereoisomer), 1.96 (0.4 H, asymmetric d, *J* 6.0, minor diastereoisomer), 2.00 (0.6 H, asymmetric d, *J* 6.0, major diastereoisomer), 2.09 (1 H, m), 2.16 (1 H, t, *J* 4.5), 2.39 (2 H, m), 3.06 (2 H, m, CH_2CHCO_2Et), 3.50 (0.8 H, ABq, *J* 15, sep. 277.0, CH_2SO_2, minor diastereoisomer), 3.55 (1.2 H, ABq, *J* 14.9, CH_2SO_2, sep. 160.0, major diastereoisomer), 4.24 (2 H, m, OCH_2), 5.17 (1 H, m, $CHCO_2Et$), 5.39 (0.4 H, dd, *J* 1.1 and 8.4, O=C–CH=, minor diastereoisomer), 5.43 (0.6 H, d, *J* 8.4, O=C–CH=, major diastereoisomer), 7.61 (0.4 H, dd, *J* 1.5 and 8.4, =CHN, minor diastereoisomer) and 7.72 (0.6 H, dd, *J* 1.5 and 8.4, =CHN, major diastereoisomer); δ_C(100 MHz; $CDCl_3$) major diastereoisomer: 14.0 (CH_2CH_3), 19.8 (2 × CH_3), 25.4 (CH_2CH_2), 27.0 (CH_2CH_2), 38.4 ($NCHCH_2$), 42.5 (CH_2CO), 42.7 (CH_2CHCH_2), 48.3 [$C(CH_3)_2$], 51.4 (CH_2SO_2), 57.0 ($NCHCH_2$), 58.6 (CH_2CCO), 62.8 (OCH_2), 107.7 (O=C–CH=),

142.9 (=CHN), 169.0 (CO_2Et), 189.5 (C=C–C=O) and 214.1 (C=O); minor diastereoisomer: 14.0 (CH_2CH_3), 19.7 (2 × CH_3), 25.4 (CH_2CH_2), 26.9 (CH_2CH_2), 38.4 (NCHCH$_2$), 42.4 (CH_2CO), 42.8 (CH_2CHCH_2), 48.3 [$C(CH_3)_2$], 51.4 (CH_2SO_2), 57.0 (NCHCH$_2$), 58.5 (CH_2CCO), 62.7 (OCH_2), 107.5 (O=C–CH=), 142.7 (=CHN), 168.8 (CO_2Et), 189.6 (C=C–C=O) and 214.0 (C=O); *m/z* (FAB) 384 ($M^+ + H$), 215 ($M^+ + H - C_8H_{10}NO_3$), 170 ($M^+ + 2\ H - C_{10}H_{12}SO_3$, base peak) (Found: C, 56.1; H, 6.5; N, 3.6. Calc. for $C_{18}H_{25}NO_6S$: C, 56.38; H, 6.57; N, 3.65%).

Example procedure for the Lewis acid catalysed preparation of ethyl 1-[(1*R*)-camphor-10-ylsulfonyl]-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate 6b/7b

To a solution of compound **4b** (346 mg, 0.870 mmol) in toluene (20 cm^3) under argon at 0 °C was added butyllithium (2.5 mol dm^{-3} in hexanes, 0.350 cm^3, 0.875 mmol). The mixture was cooled to −78 °C and diethylaluminium chloride (56 mm^3, 0.435 mmol) and then 1-methoxy-3-trimethylsilyloxybuta-1,3-diene **2** (0.400 cm^3, 1.850 mmol) were added to it. The reaction mixture was stirred at −78 °C for 8 h and then conc. HCl–THF (1:19, 20 cm^3) was added and the mixture allowed to warm to room temperature. After 1 h, the mixture was diluted with water (20 cm^3) and the organic layer separated, dried and evaporated. The residue was purified by silica gel chromatography (1:1, ethyl acetate–hexane as eluent) to give the title compounds **6b** and **7b** (153 mg, 45%) in a 59:41 ratio as a pale brown oil. All analytical and spectroscopic data were identical to those in the preceding experiment.

General procedure for the catalytic hydrogenation of ethyl 4-oxo-1-sulfonyl-1,2,3,4-tetrahydropyridine-2-carboxylates 6/7

To a stirred solution of the ethyl 1-sulfonyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate **6/7** (0.65 mmol) in methanol (20 cm^3) was added 3% palladium on charcoal (0.25 g, 0.07 mmol of palladium) and the mixture was then placed under a hydrogen atmosphere for 1 h at room temperature. After hydrogen uptake was complete, the mixture was filtered through Celite and evaporated to give compounds **11a** and **11b**.

Ethyl 4-oxo-1-phenylsulfonylpiperidine-2-carboxylate 11a. The residue was purified by silica gel chromatography (1:1, ethyl acetate–hexanes) to give the title compound **11a** (0.174 g, 86%) as a colourless oil; ν_{max}(neat)/cm^{-1} *inter alia* 2980 (C–H) and 1740 (C=O); λ_{max}(EtOH)/nm 202 (ε 11 615) and 225 (ε 8500); δ_H(300 MHz; $CDCl_3$) 1.12 (3 H, t, *J* 7.1, CH_2CH_3), 2.43 (1 H, m), 2.59 (1 H, ddd, *J* 7.1 and 11.3 and 15.3), 2.73 (2 H, m, CH_2CH), 3.53 (1 H, ddd, *J* 4.0, 11.3 and 13.0), 3.97 (2 H, q, *J* 7.1, CH_2CH_3), 4.10 (1 H, m), 5.08 (1 H, ddd, *J* 1.7, 2.9 and 5.5, CH_2CH), 7.52 (2 H, m, *m*-ArH), 7.61 (1 H, m, *p*-ArH) and 7.85 (2 H, m, *o*-ArH); δ_C(75 MHz; $CDCl_3$) 13.7 (CH_3), 39.8 (CH_2), 41.8 (CH_2), 42.3 (CH_2), 55.7 ($CHCO_2Et$), 61.7 (OCH_2), 127.1 (*o*-ArC), 129.0 (*m*-ArC), 133.0 (*p*-ArC), 138.9 (SO_2ArC), 169.1 (CO_2Et) and 203.7 (C=O); *m/z* (FAB) 312 ($M^+ + H$), 238 (base peak, $M^+ - CO_2Et$), 170 ($M^+ - SO_2Ph$), 141 (SO_2Ph) and 77 (C_6H_5) (Found: C, 54.3; H, 5.8; N, 4.3; S, 10.6. Calc. for $C_{14}H_{17}NO_5S$: C, 54.0; H, 5.5; N, 4.5; S, 10.3%).

Ethyl 1-[(1*R*)-camphor-10-ylsulfonyl]-4-oxopiperidine-2-carboxylate 11b. No further purification needed, the title compound (205 mg, 82%) was isolated as a colourless oil.

General procedure for the reduction of the ethyl 4-oxo-1-sulfonylpiperidine-2-carboxylates 11

To a solution of the ethyl 4-oxo-1-sulfonylpiperidine-2-carboxylate (0.32 mmol), toluene-4-sulfonohydrazide (75 mg, 0.40 mmol) and toluene-4-sulfonic acid (5 mg) in dry *N*,*N*-dimethylformamide (0.9 cm^3) at 100 °C under an argon atmosphere was added sodium cyanoboranuide ($NaBH_3CN$) (70 mg, 1.06 mmol). Heating was maintained at 100 °C for 2 h and the reaction mixture then cooled to room temperature and diluted with toluene (35 cm^3). The resulting solution was then washed successively with water (50 cm^3), saturated aqueous sodium hydrogen carbonate (50 cm^3) and then water (50 cm^3). The organic layer was then dried and evaporated to give the ethyl 1-sulfonylpiperidine-2-carboxylates.

Ethyl 1-phenylsulfonylpiperidine-2-carboxylate 12a. (35 mg, 37%), $[\alpha]_D^{24}$ +40.6 (*c* 1.0, EtOH); ν_{max}(neat)/cm^{-1} *inter alia* 2940 (C–H) and 1740 (C=O); λ_{max}(EtOH)/nm 203 (ε 10 140) and 226 (ε 6810); δ_H(300 MHz; $CDCl_3$) 1.13 (3 H, t, *J* 7.1, CH_3), 1.27 (1 H, m), 1.56 (1 H, m), 1.72 (3 H, m), 2.14 (1 H, m), 3.22 (1 H, dt, *J* 2.9 and 12.6), 3.79 (1 H, m), 3.98 (2 H, qABq, *J* 7.1 and 10.9, sep. 33.8 Hz, OCH_2), 4.74 (1 H, d, *J* 5.2, CH), 7.52 (3 H, m, *m*- and *p*-ArH) and 7.79 (2 H, m, *o*-ArH); δ_C(75 MHz; $CDCl_3$) 14.1 (CH_3), 20.1 (CH_2), 24.8 (CH_2), 27.9 (CH_2), 42.7 (CH_2N), 54.9 (CH), 61.1 (OCH_2), 127.2 (*o*-ArC), 128.9 (*m*-ArC), 132.5 (*p*-ArC), 140.2 ($ArCSO_2$) and 170.7 (CO_2Et), *m/z* (FAB) 298 ($M^+ + H$), 224 ($M^+ - CO_2Et$, base peak) and 156 ($M^+ - SO_2Ph$) (Found; C, 56.5; H, 6.7; N, 4.7; S, 11.2. Calc. for $C_{14}H_{19}NO_4$: C, 56.5; H, 6.4; N, 4.7; S, 10.8%).

Ethyl 1-(1*R*)-camphor-10-ylsulfonyl]piperidine-2-carboxylate 12b. (58 mg, 58%).

(2*R*)-1-[(1*R*)-camphor-10-ylsulfonyl]piperidine-2-carboxylic acid 10a. To a vigorously stirred solution of (2*R*)-(+)-pipecolic acid (2*R*,3*R*)-(+)-tartrate salt (500 mg, 1.79 mmol) in aqueous sodium hydroxide (2 mol dm^{-3}; 3.60 cm^3, 7.20 mmol) at 0 °C was added (1*R*)-(−)-camphor-10-sulfonyl chloride (455 mg, 1.81 mmol). After 30 min a further portion of aqueous sodium hydroxide (2 mol dm^{-3}; 125 mm^3, 0.25 mmol) was added and the mixture stirred for 24 h at room temperature. The now homogeneous solution was acidified to pH < 1 with concentrated hydrochloric acid and the solution diluted to 50 cm^3 with water and then extracted with dichloromethane (3 × 50 cm^3). The extracts were combined, dried and evaporated to give the title compound **10a** (60 mg, 10%), mp 157.5 °C (decomp.); $[\alpha]_D^{22}$ +7.8 (*c* 1.0, EtOH); ν(KBr disc)/cm^{-1} *inter alia* 2950 (br, O–H) and 1740 and 1705 (C=O); λ_{max}(EtOH)/nm 201 (ε 690); δ_H(300 MHz; $CDCl_3$) 0.85 (3 H, s, CH_3), 1.10 (3 H, s, CH_3), 1.42 (2 H, m), 1.72 (6 H, m), 2.05 (2 H, m), 2.40 (3 H, m), 3.21 (1 H, dt, *J* 2.8 and 12.5), 3.23 (2 H, ABq, *J* 15, sep. 168.0 Hz, CH_2SO_2), 3.81 (1 H, br d, *J* 11.5), 4.80 (1 H, d, *J* 4.6, $CHCO_2H$) and 5.4–6.6 (1 H, vbr s, CO_2H, disappears on addition of D_2O); δ_C(75 MHz; $CDCl_3$) 19.1, 20.0, 25.0, 25.1, 27.0, 27.9, 29.7, 42.6, 42.7, 42.9, 48.0, 48.6, 55.3, 58.4, 176.2 and 215.3; *m/z* (FAB) 344 ($M^+ + H$, base peak), 298 ($M^+ - CO_2H$) and 215 ($M^+ - C_6H_{10}NO_2$) (Found: C, 55.7; H, 7.3; N, 4.2; S, 9.7. Calc. for $C_{16}H_{25}NO_5S$: C, 56.0; H, 7.3; N, 4.1; S, 9.3%).

Ethyl (2*R*)-1-[(1*R*)-camphor-10-ylsulfonyl]piperidine-2-carboxylate 10b. A solution of (2*R*)-1-[(1*R*)-camphor-10-ylsulfonyl]piperidine-2-carboxylic acid **10a** (120 mg, 0.35 mmol) in ethanol (20 cm^3) was saturated with hydrogen chloride gas at room temperature (a cooling bath was employed to moderate the exothermic dissolution of the hydrogen chloride). After 24 h at room temperature the solvent was evaporated and the residue taken up in dichloromethane (50 cm^3) and the solution washed with water (3 × 50 cm^3), then dried and evaporated to give the title compound **10b** (58 mg, 45%) as a colourless oil, $[\alpha]_D^{23}$ +14.8 (*c* 1.0, EtOH); ν_{max}(neat)/cm^{-1} *inter alia* 2950 (C–H) and 1745 (C=O); λ_{max}(EtOH)/nm <200; δ_H(300 MHz; $CDCl_3$) 0.86 (3 H, s, CCH_3), 1.09 (3 H, s, CCH_3), 1.29 (3 H, t, *J* 7.1, CH_2CH_3), 1.35 (2 H, m), 1.68 (6 H, m), 2.03 (2 H, m), 2.24 (1 H, m), 2.36 (1 H, m), 2.50 (1 H, m), 3.20 (1 H, dt, *J* 3.2 and 12.5), 3.24 (2 H, ABq, *J* 15.0, sep. 168.0 Hz, SO_2CH_2), 3.80 (1 H, br d, *J* 12.0), 4.21 (2 H, dq, *J* 1.2 and 7.1, CH_2CH_3) and 4.72 (1 H, d, *J* 4.7, $CHCO_2Et$); δ_C(75 MHz; $CDCl_3$) 14.2, 19.8, 20.0, 20.4, 24.9, 25.0, 26.9, 28.0, 42.6, 42.7, 47.8, 48.1, 55.5, 58.3, 61.3, 171.4 and

215.0; *m/z* (FAB) 372 ($M^+ + H$), 298 ($M^+ - CO_2Et$), 215 ($M^+ - C_8H_{14}NO_2$) and 158 ($C_8H_{16}NO_2^+$, base peak) (Found: C, 58.0; H, 7.6; N, 3.7; S, 9.0. Calc. for $C_{18}H_{29}NO_5S$; C, 58.2; H, 7.9; N, 3.8; S, 8.6%).

(±)-Ethyl piperidine-2-carboxylate hydrochloride 13

A solution of (±)-pipecolic acid (7.5 g, 0.058 mol) in ethanol (550 cm^3) was saturated with hydrogen chloride gas at room temperature (a cooling bath was employed to moderate the exothermic dissolution of the hydrogen chloride). After 24 h at room temperature the solvent was evaporated and the residue triturated with diethyl ether (250 cm^3) to give a white crystalline precipitate that was filtered by suction and dried under reduced pressure at 45 °C to give the title compound **13** (11.12 g, 99%), mp 192 °C; ν_{max}(KBr disc)/cm^{-1} *inter alia* 3000–2400 (complex multiplet N–H and C–H) and 1745 (C=O); λ_{max}(EtOH)/nm <200; δ_H(300 MHz; [$^2H_6$]DMSO) 1.34 (3 H, t, *J* 7.1, CH_3), 1.73 (5 H, m), 2.16 (1 H, d, *J* 12.6), 2.97 (1 H, m), 3.33 (1 H, d, *J* 12.7), 4.14 (1 H, dd, *J* 3.2 and 11.0), 4.32 (2 H, q, *J* 7.1, OCH_2) and 9.41 (2 H, br s, disappears on addition of D_2O, NH_2); δ_C(75 MHz; $CDCl_3$) 17.5 (CH_3), 24.5 (CH_2), 24.6 (CH_2), 29.1 (CH_2), 46.9 (CH_2N), 58.3 (CH), 65.7 (OCH_2) and 172.3 (CO_2Et); *m/z* (EI) 158 (M^+ – Cl, base peak) and 84 ($C_5H_{10}N$) (Found: C, 49.4; H, 8.2; N, 7.3; Cl, 18.5. Calc. for $C_8H_{16}ClNO_2$: C, 49.6; H, 8.3; N, 7.2; Cl, 18.3%).

Ethyl (2*R*/*S*)-1-[(1*R*)-camphor-10-ylsulfonyl]piperidine-2-carboxylate 10b/14

To a stirred mixture of (±)-ethyl pipecolate hydrochloride (100 mg, 0.52 mmol) and (1*R*)-(–)-camphor-10-sulfonyl chloride (130 mg, 0.52 mmol) in dichloromethane (10 cm^3) was added triethylamine (145 mm^3, 1.07 mmol) at < 30 °C. The resulting solution was then stirred for 18 h at room temperature, diluted with dichloromethane (40 cm^3) and then washed successively with hydrochloric acid (1 mol dm^{-3}; 50 cm^3) and water (50 cm^3). The dichloromethane layer was then dried and evaporated to give a 1 : 1 mixture of the title compounds **10b** and **14** (120 mg, 66%) as a colourless oil. Analytical data identical to that found for **10b** alone. Spectroscopic data were also identical to that reported for **10b** alone, except for δ_H(200 MHz; $CDCl_3$) 0.86 (3 H, s), 0.88 (3 H, s), 1.12 (3 H, s), 1.09 (3 H, s), 1.28 (3 H, t, *J* 7.1, CH_2CH_3), 1.29 (3 H, t, *J* 7.1, CH_2CH_3), 1.35 (4 H, m), 1.68 (12 H, m), 2.03 (4 H, m), 2.24 (2 H, m), 2.36 (2 H, m), 2.50 (2 H, m), 3.20 (2 H, m), 3.24 (2 H, ABq, *J* 15.0, sep. 168 Hz, SO_2CH_2), 3.28 (2 H, ABq, *J* 15.0, sep. 159 Hz, SO_2CH_2), 3.80 (2 H, m), 4.21 (4 H, m, 2 × CH_2CH_3) and 4.72 (2 H, m).

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