Asymmetric Synthesis of Thiadecalins via an Organocatalytic Triple Cascade/ Sulfa-Michael Sequence

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Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

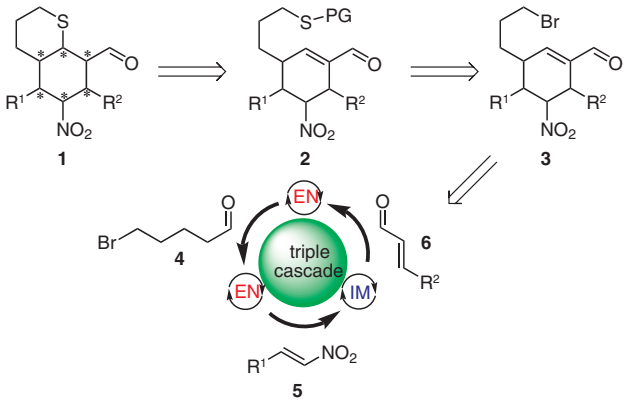
Abstract: An efficient two-step asymmetric synthesis of highly substituted *cis*-configured thiadecalins and the corresponding hexahydrobenzothiophene core is described. Thiadecalin derivatives are known for their widespread biological activities, such as antimicrobial and neurotropic properties. The procedure is based on an organocatalytic triple cascade reaction followed by an intramolecular sulfa-Michael addition. In this manner six consecutive stereocentres are controlled and the target molecules are obtained in moderate yields, with virtually complete enantioselectivitiy (ee >99%) and after recystallisation in diastereomeric ratios of >97:3. The relative and absolute configuration was determined by NMR spectroscopy and X-ray structure analysis.

Key words: organocatalysis, asymmetric synthesis, Michael addition, thiadecalins, domino reaction

The research field of organocatalysis[1] has developed rapidly since about the turn of the millennium and can now be seen as a third pillar of asymmetric catalysis beside metal and biocatalysis. Numerous basic organocatalytic protocols for very efficient and highly stereoselective carbon–carbon and carbon–heteroatom bond formations are now part of the strategic arsenal of synthetic chemistry and can be used in the asymmetric total synthesis of natural products and bioactive compounds in general.

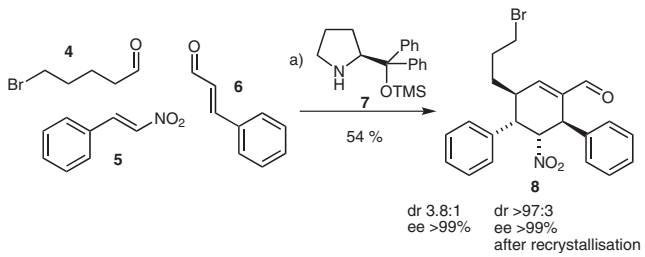
Thiadecalin derivatives have been studied intensively with regard to their antimicrobial and antiphage properties including the treatment of infected wounds.[2] It has also been shown that thiadecalins exhibit neutrotropic activity.[3] The corresponding thiadecalin sulfonium salts showed sedative properties during hexenal-induced sleep. In addition, other thiadecalin derivatives are known to be antigestagens and antiglucocorticoids.[4] These compounds are also mentioned in combination with the treatment of psychosis and addictive behaviour. The antiglucocorticoids can be used to treat spontaneous or narcotic-induced withdrawals, especially from heroin, morphine, methadone, cocaine, and their mixtures.[5]

Among the various subdisciplines of organocatalysis, domino reactions[6] enabling the highly stereoselective construction of complex molecules in a single operation have been studied intensively in the last few years.[7] In 2006, our group reported an efficient three-component domino reaction leading to tetrasubstituted cyclohexenecarbaldehydes.[8] In order to synthesize the potentially bioactive thiadecalins **1** we envisaged extending the triple cascade method by a subsequent intramolecular sulfa-Michael addition[9] via nucleophilic displacement of bromide **3** to form the sulfa-Michael precursor **2** (Scheme 1).



Scheme 1 Retrosynthetic analysis of the asymmetric thiadecalin synthesis

Employing 5-bromopentanal (**4**), readily available through DIBAL-H reduction of the commercially available bromo ester, in the cascade reaction with nitrostyrene (**5**) and cinnamaldehyde (**6**) under diphenylprolinol TMS-ether catalysis **7** gave the desired domino product **8** as a 3.8:1 diastereometric mixture of the α-nitro epimers and with practically complete enantiomeric excess (ee >99%) in 68% yield. The major diastereomer shown could be obtained as a pure stereoisomer (dr >97:3, ee >99%) after recrystallisation in 54% yield (Scheme 2).



Scheme 2 Triple domino reaction with 5-bromopentanal (**4**). *Reagents and conditions*: a) 0.2 M toluene, 20 mol% **7**, 24 h 0 °C, then 48 h, r.t.

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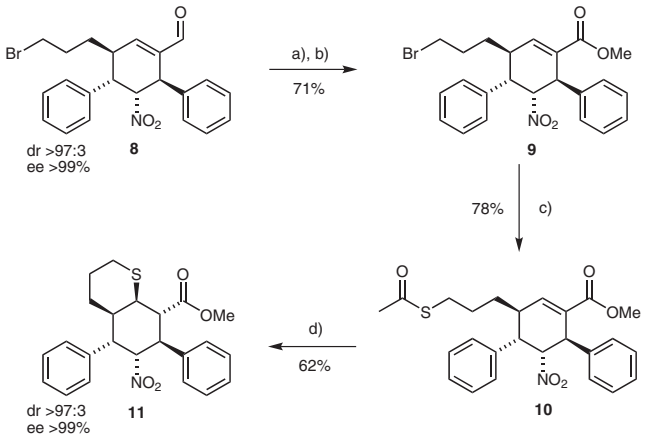
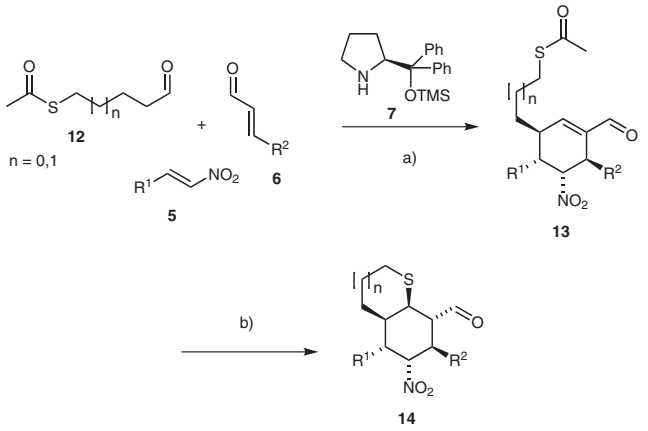
The cyclohexenecarbaldehyde **8** thus obtained was then converted into the more stable methyl ester **9** by Pinnick oxidation followed by esterification with HCl/methanol. The displacement of the bromide with potassium thioacetate in DMF proceeded smoothly, affording an 8.5:1 diastereomeric mixture of the corresponding thioester **10**. The minor diastereomer could be easily removed by column chromatography. Deprotection of the thiol with potassium carbonate in anhyd methanol provided the *cis*-thiadecalin **11** via intramolecular sulfa-Michael addition as a single stereoisomer in 62% yield after recrystallisation (Scheme 3).



Scheme 3 First route to thiadecalin **11**. *Reagents and conditions*: a) $NaClO_2$, 2-methylbut-2-ene, buffer; b) $SOCl_2$, MeOH; c) KSAc, DMF; d) K_2CO_3, MeOH; recrystallisation.

With the first route to the thiadecalin **11** in hand, we then shortened the protocol to a two-step version by employing the thioester containing aldehyde **12** as a substrate in the triple cascade. After optimisation, we were able to carry out the sulfa-Michael addition with the enal domino products **13**. The thiadecalins **14** were obtained with complete enantioselectivity and in diastereomeric ratios ranging from 85:15 to >97:3. To our delight, one recrystallisation gave the virtually pure stereoisomers in moderate yields (Scheme 4).



Scheme 4 Optimised two-step route. *Reagents and conditions*: a) 20 mol% **7**, toluene, 24 h, 0 °C, 48 h r.t.; b) K_2CO_3, MeOH.

The scope of the novel asymmetric thiadecalin synthesis was demonstrated by variation of the substituents R^1 and R^2 (Tables 1 and 2). In addition, by shortening the chain length (n = 0) of the aldehyde **12** opened an entry to the corresponding hexahydrobenzothiophene system as was exemplified in the case of **14e**.

Table 1 Scope of the Domino Reaction

13	R^1	R^2	n	Yield dr[b] (%)[a]		ee (%)[c]
a	Ph	Ph	1	51	>97:3 (80:20)	>99
b	4-ClC_6H_4	Ph	1	45	>97:3 (95:5)	>99
c	4-$MeOC_6H_4$	Ph	1	43	>97:3 (85:15)	>99
d	4-methylfuran-2-yl	Ph	1	60	>97:3	>99
e	Ph	Ph	0	57	>97:3 (80:20)	>99
f	Ph	H	1	32	>97:3 (80:20)	>99

[a] Yield after recrystallisation.
[b] Diastereomeric ratio determined by NMR spectroscopy; dr of the crude product is given in parentheses.
[c] The percentage of ee was determined by chiral stationary phase HPLC.

Table 2 Scope of the Thiadecalin Synthesis

14	R^1	R^2	n	Yield dr[b] (%)[a]		ee (%)
a	Ph	Ph	1	57	>97:3 (90:10)	>99
b	4-ClC_6H_4	Ph	1	40	>97:3 (60:40)	>99
c	4-$MeOC_6H_4$	Ph	1	52	>97:3 (88:12)	>99
d	4-methylfuran-2-yl	Ph	1	50	>97:3	>99
e	Ph	Ph	0	57	>97:3 (80:20)	>99
f	Ph	H	1	40	85:15 (70:30)	>99

[a] Yield after recrystallisation.
[b] Diastereomeric ratio determined by NMR; dr of the crude product is given in parentheses.

The methylfuranyl group as R^1 gave the best results for the triple cascade reaction in terms of both yield and diastereoselectivity. The yield for the subsequent sulfa-Michael reaction was moderate, yet the diasteromeric ratio was better than 97:3, even before recrystallisation. In comparing the electron-donating and -withdrawing groups at the phenyl ring of R^1, no overall tendencies were observed. For n = 0, the reaction proceeded smoothly with 57% yield for the triple cascade and the sulfa-Michael addition, respectively. Further variation on R^2 was possible, but led to lower yields and diastereomeric ratios. Although a one-pot procedure for the two steps was feasible and led to good overall yields, the main drawback was the lack of diastereomeric excess obtained. For this reason the two-step procedure with purification of the intermediates **13** was preferred.

The relative and absolute configuration of the thiadecalin **14b** and the hexahydrobenzothiophene **14e** was determined by ^{1}H NMR spectroscopy (coupling constants) and X-ray crystallography (Figures 1 and 2).

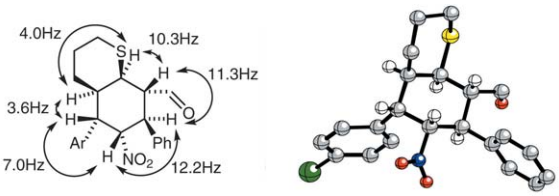


Figure 1 Determination of the relative and absolute configuration of **14b** (Ar = 4-ClC$_6$H$_4$) by ^{1}H NMR and X-ray analysis

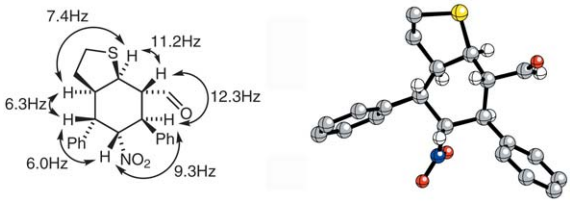


Figure 2 Determination of the relative and absolute configuration of **14e** by ^{1}H NMR and X-ray analysis

As shown in Figure 1, the ^{1}H NMR coupling constants indicate a chair conformation of the hexa-substituted cyclohexane ring of the *cis*-thiadecalin **14b**. This is also confirmed for the crystalline stage by the corresponding Röntgen structure. In the *cis*-configured hexahydrobenzothiophene derivative **14e**, however, the ^{1}H NMR and Röntgen data indicate a twist-boat conformation of the cyclohexane moiety (Figure 2).

In summary, we have developed a two-step organocatalytic asymmetric synthesis of functionalised, highly substituted *cis*-thiadecalins and the corresponding hexahydrobenzothiophene core. The novel entry is based on our diphenylprolinol TMS-ether catalysed triple cascade followed by an intramolecular sulfa-Michael addition. The target molecules are of pharmaceutical and medicinal interest and bear six consecutive stereocentres as part of a fully substituted cyclohexane ring. Besides moderate overall yields, virtually complete enantiomeric excesses (ee >99%) and after crystallisation, with one exception, diastereomeric ratios of >97:3 are obtained.

All reactions were carried out under argon in flame-dried glassware. Unless otherwise noted, all commercially available compounds were used without further purification. Toluene was freshly distilled under argon from Solvona® (Na on Celite). MeOH was freshly distilled under argon over Mg and I_2. The catalyst was prepared according to the previously described procedure.[10] For the protocol to prepare 5-bromopentanal (**4**), see ref.[11] For preparative column chromatography SIL G-25 UV$_{254}$ from Macherey-Nagel, particle size 0.040–0.063 mm (230–240 mesh, flash) was used. Visualisation of the developed TLC plates was performed with ultraviolet irradiation (254 nm) or by staining with a $KMnO_4$ solution. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed with a Vario EL element analyser. Mass spectra were measured on a Finnigan SSQ7000 (EI 70 eV) spectrometer and high-resolution mass spectra on a Thermo Fisher Scientific Orbitrap XL. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 using an ATR-Unit. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on Varian Mercury 300 or Inova 400 spectrometers with TMS as an internal standard. Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument using chiral stationary phases (Chiralcel OD, Chiralcel OJ, Chiralpak AD, Chiralpak AS, Chiralcel IA).

Organocatalytic Domino Reaction; General Procedure (GP 1)

Catalyst **7** (0.2 equiv) and nitroalkene **5** (1.0 equiv) were dissolved in toluene (0.5 M with respect to **12**) and cooled to 0 °C. Aldehyde **12** (1.0 equiv) was slowly added followed by a slow addition of the α,β-unsaturated aldehyde **6** (1.0 equiv). The reaction was kept at 0 °C until TLC showed complete consumption of **12** (usually 24 h) and then allowed to warm to r.t. The stirring was continued for 48 h. The domino product **13** was purified by column chromatography and recrystallisation.

Sulfa-Michael Addition; General Procedure (GP 2)

The domino product **13** (1 equiv) was dissolved in anhyd MeOH (0.02 M). Anhyd K_2CO_3 (1 equiv) was added and the suspension stirred at r.t. until **13** was consumed (usually 20 min). Brine (1 mL per 10 mg of **13**) was added, followed by H_2O (1 mL per 10 mg of **13**), and the product was extracted with CH_2Cl_2 (3 × 1 mL per 10 mg of **13**). The solvent was evaporated and the residue was recrystallised.

Bromocarbaldehyde 8

The synthesis of **8** following GP 1 yielded 4.2 g (54%) of the main diastereomer as colourless crystals; mp 122 °C; ee >99%; R_f = 0.38 (pentane–Et$_2$O, 1:1); $[\alpha]_D^{23}$ –1.1 (*c* 1, CHCl$_3$).

IR (film): 1648, 1546, 1451, 1401, 1366, 1285, 1240, 1166, 887, 772, 754, 699, 614, 552 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.62 (m, 1 H), 1.79 (m, 1 H), 1.95 (m, 1 H), 2.08 (m, 1 H), 3.01 (dd, *J* = 10.6, 3.4 Hz, 1 H), 3.36 (m, 2 H), 3.41 (m, 1 H), 4.47 (s, 1 H), 4.87 (dd, *J* = 3.4, 1.6 Hz, 1 H), 6.99 (m, 2 H), 7.20 (m, 2 H), 7.42–7.27 (m, 7 H), 9.61 (s, 1 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.6, 30.9, 32.7, 36.4, 42.9, 43.2, 92.3, 127.6, 127.7, 127.8, 128.1, 129.0, 129.1, 136.7, 137.6, 138.3, 153.0, 191.5.

MS (EI): *m*/*z* = 427.0 (M$^+$).

Anal. Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.86; H, 4.76; N, 3.35.

Bromomethyl Ester 9

Compound **8** (4.0 g, 9.4 mmol) was dissolved in acetone (50 mL) and cooled to 0 °C. After the addition of 2-methylbut-2-ene (6.60 g, 10 equiv), a solution of $NaClO_2$ (2.13 g, 2.0 equiv) in H_3PO_4–aq $NaHCO_3$ buffer (15 mL, 1.25 M, pH 3.5) was added dropwise. The reaction mixture was allowed to warm to r.t. and stirred until completion of the reaction (TLC). Acetone was evaporated and the residue was treated with brine (40 mL). After extraction with EtOAc (3 × 50 mL), the combined organic phases were evaporated and the crude product was purified by flash chromatography (Et$_2$O) yielding the carboxylic acid in 3.38 g (81%) as a pale-brown solid. Most of the carboxylic acid (3.24 g) was redissolved in MeOH (70 mL) at 0 °C to obtain a 0.1 M solution. After the dropwise addition of $SOCl_2$ (3.47 g, 4.0 equiv), the solution was refluxed at 75 °C until completion of the reaction (4 h). MeOH was evaporated, the residue was treated with H_2O (30 mL) and the product was extracted with EtOAc (3 × 30 mL). The crude product was purified by flash chromatography yielding 2.94 g (88%) of yellow crystals; mp 137 °C;

ee >99%; dr >97:3; R_f = 0.58 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –20.1 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2950, 1717, 1550, 1448, 1368, 1272, 758, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.54 (m, 1 H), 1.73 (m, 1 H), 1.91 (m, 1 H), 2.97 (m, 1 H), 2.94 (dd, *J* = 10.4, 3.5 Hz, 1 H), 3.28 (m, 1 H), 3.35 (m, 2 H), 3.65 (s, 3 H), 4.52 (s, 1 H), 4.88 (dd, *J* = 3.5, 2.0 Hz, 1 H), 6.99 (m, 2 H), 7.23–7.42 (m, 8 H), 7.46 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 31.2, 32.9, 35.8, 42.5, 44.8, 52.0, 92.6, 127.4, 127.6, 127.7, 127.9, 128.9, 129.0, 137.0, 139.4, 143.2, 165.8.

MS (EI): *m*/*z* = 457.1 (M^+).

HRMS: *m*/*z* calcd for $C_{23}H_{24}BrNO_4$: 457.0889; found: 457.0885.

Methyl Ester 10

To a solution of **9** (0.50 g, 1.1 mmol) in DMF (6 mL) was added KSAc (0.37 g, 3.3 mmol) in portions. After stirring for 2 h at r.t., brine (10 mL) was added, followed by H_2O (300 mL). The product was extracted with EtOAc (3 × 40 mL). Evaporation of the solvent yielded a mixture of 2 diastereomers (dr = 8.5:1). Purification by flash chromatography (pentane–Et_2O, 2:1) yielded 0.39 g (78%) of the major diastereomer as colourless crystals; mp 117 °C; R_f = 0.30 (pentane–Et_2O, 2:1).

IR ($CHCl_3$): 3027, 2919, 2852, 1717, 1691, 1549, 1452, 1437, 1366, 1272, 1232, 1133, 1110, 756, 702, 626 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (m, 1 H), 1.65 (m, 2 H), 1.80 (m, 1 H), 2.29 (s, 3 H), 2.82 (m, 2 H), 2.93 (dd, *J* = 10.3, 3.4 Hz, 1 H), 3.33 (m, 1 H), 3.64 (s, 3 H), 4.51 (s, 1 H), 4.87 (dd, *J* = 3.4, 2.2 Hz, 1 H), 6.98 (m, 2 H), 7.22–7.41 (m, 8 H), 7.45 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5, 28.8, 30.6, 31.6, 36.1, 42.5, 44.8, 51.9, 92.6, 127.2, 127.6, 127.7, 127.8, 128.8, 129.0, 137.1, 139.5, 143.4, 165.8, 195.3.

MS (EI): *m*/*z* = 453.1 (M^+).

Anal. Calcd for $C_{25}H_{27}NO_5S$: C, 66.20; H, 6.00; N, 3.09. Found: C, 65.87; H, 6.06; N, 3.02.

Thiadecaline Methyl Ester 11

The synthesis of **11** following GP 2 yielded 0.12 g (62%) of colourless crystals; mp 244 °C; R_f = 0.16 (pentane–Et_2O, 3:1).

IR ($CHCl_3$): 1726, 1548, 1453, 1436, 1366, 1279, 1237, 1197, 1171, 909, 831, 760, 733, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.82 (m, 1 H), 1.93 (m, 2 H), 2.2 (m, 1 H), 2.36 (m, 1 H), 2.61 (m, 1 H), 2.79 (m, 1 H), 3.33 (dd, *J* = 12.1, 11.9 Hz, 1 H), 3.46 (s, 3 H), 3.59 (dd, *J* = 6.4, 1.5 Hz, 1 H), 3.69 (dd, *J* = 11.9, 4.3 Hz, 1 H), 4.13 (dd, *J* = 12.3, 12.1 Hz, 1 H), 5.33 (dd, *J* = 12.3, 6.3 Hz, 1 H), 7.20–7.46 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 28.0, 28.3, 37.7, 43.1, 45.7, 50.4, 51.9, 53.0, 87.3, 127.5, 128.0, 128.1, 128.9, 129.0, 138.0, 138.3, 172.7.

MS (CI): *m*/*z* = 440.1 (M + $C_2H_5^+$), 412.1 (M + H^+).

Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 66.89; H, 6.12; N, 3.27.

***S*-(5-Oxopentyl) Ethanthioate 12 (n = 1)**

Compound **4** (2.7 g, 16 mmol) was dissolved in DMF (30 mL) at 0 °C. After the addition of KSAc (4.5 g, 39 mmol), the solution was stirred for 30 min. H_2O (500 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The solvent was evaporated and the crude **12** (n = 1) was purified by flash chromatography (pentane–Et_2O, 3:1) to give 1.76 g (67%) of a colourless oil; R_f = 0.32 (pentane–Et_2O, 2:1).

IR ($CHCl_3$): 2934, 2861, 1723, 1690, 1355, 1134, 958, 627 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (m, 4 H), 2.33 (s, 3 H), 2.47 (ddd, *J* = 7.2, 7.2, 1.5 Hz, 2 H), 2.88 (dd, *J* = 6.9, 6.9 Hz, 2 H), 9.77 (dd, *J* = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 28.6, 29.0, 30.6, 43.3, 195.7, 201.9.

Anal. Calcd for $C_7H_{12}OS$: C, 52.47; H, 7.55. Found: C, 52.20; H, 7.56.

Carbaldehyde 13a

The synthesis of **13a** following GP 1 yielded 0.44 g (51%) of a colourless solid; mp 163 °C; ee >99%; R_f = 0.40 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –9.9 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 1681, 1654, 1451, 1359, 1163, 1139, 1110, 953, 774, 754, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (m, 1 H), 1.70 (m, 2 H), 1.82 (m, 1 H), 2.31 (s, 3 H), 2.82 (m, 2 H), 3.00 (dd, *J* = 10.6, 3.4 Hz, 1 H), 3.37 (m, 1 H), 4.46 (s, 1 H), 4.87 (dd, *J* = 3.4, 1.8 Hz, 1 H), 6.98 (m, 2 H), 7.19 (m, 2 H), 7.41–7.26 (m, 7 H), 9.60 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6, 28.7, 30.6, 31.3, 36.7, 42.9, 43.2, 92.3, 127.6, 127.7, 127.8, 128.0, 129.0, 136.8, 137.5, 138.4, 153.3, 191.6, 195.3.

MS (EI): *m*/*z* = 423.4 (M^+).

Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.15; H, 5.97; N, 3.29.

Carbaldehyde 13b

The synthesis of **13b** following GP 1 yielded 0.935 g (45%) of a yellow solid; mp 132 °C; ee >99%; R_f = 0.45 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –13.6 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2947, 1677, 1544, 1362, 1136, 706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (ddt, *J* = 4.2, 6.7, 9.6 Hz, 1 H) 1.68 (m, 2 H), 1.81 (m, 1 H), 2.32 (m, 3 H), 2.83 (m, 2 H), 2.98 (dd, *J* = 3.4, 10.5 Hz, 1 H), 3.32 (m, 1 H), 4.46 (m, 1 H), 4.82 (dd, *J* = 1.8 Hz, 3.4 Hz, 1 H), 7.19 (m, 10 H), 9.59 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.63, 28.77, 30.67, 31.34, 36.77, 42.83, 42.90, 92.11, 127.76–129.16, 133.99, 135.41, 137.55, 138.29, 152.85, 191.48, 195.37.

MS (CI): *m*/*z* = 458.2.

Anal. Calcd for $C_{24}H_{24}ClNO_4S$: C, 62.94; H, 5.28; N, 3.06. Found: C, 63.04; H, 5.25; N, 3.06.

Carbaldehyde 13c

The synthesis of **13c** following GP 1 yielded 4.28 g (43%) of the major diastereomer as a yellow solid; ee >99%; R_f = 0.27 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –4.5 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 1684, 1546, 1512, 1452, 1362, 1305, 1250, 1181, 1132, 1109, 1031, 954, 837, 759, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (m, 1 H), 1.69 (m, 2 H), 1.82 (m, 1 H), 2.32 (s, 3 H), 2.83 (m, 2 H), 2.95 (dd, *J* = 10.4, 3.5 Hz, 1 H), 3.30 (m, 1 H), 3.77 (s, 3 H), 4.44 (s, 1 H), 4.84 (dd, *J* = 3.5, 1.8 Hz, 1 H), 6.80 (m, 2 H), 6.90 (m, 2 H), 7.18 (m, 2 H), 7.40–7.27 (m, 4 H), 9.59 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6, 28.8, 30.6, 31.4, 37.0, 42.5, 42.8, 55.1, 92.4, 114.3, 127.6, 127.7, 128.8, 129.0, 137.5, 138.5, 153.4, 159.1, 191.6, 195.3.

MS (EI): *m*/*z* = 453.3 (M^+).

Anal. Calcd for $C_{25}H_{27}NO_5S$: C, 66.20; H, 6.00; N, 3.09. Found: C, 66.01; H, 5.96; N, 3.07.

Carbaldehyde 13d

The synthesis of **13d** following GP 1 yielded 2.49 g (60%) of a pale-red oil; ee >99%; R_f = 0.35 (pentane–Et_2O, 2:1); $[\alpha]_D^{23}$ 24.1 (*c* 1, $CHCl_3$).

IR (film): 3360, 2920, 1689, 1551, 1451, 1362, 1218, 1135, 757, 625 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (m, 1 H) 1.72 (m, 1 H), 1.85 (m, 2 H), 2.19 (m, 3 H), 2.34 (m, 3 H), 2.90 (m, 2 H), 3.09 (dd, *J* = 3.5, 10.1 Hz, 1 H), 3.20 (m, 1 H), 4.49 (s, 1 H), 5.01 (dd, *J* = 2.2, 3.4 Hz, 1 H), 5.86 (dd, *J* = 1.0, 3.1 Hz, 1 H), 5.98 (m, 1 H), 7.28 (m, 5 H), 9.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 26.9, 28.9, 30.8, 32.0, 36.9, 37.6, 42.5, 89.8, 106.4, 108.4, 127.9, 128.0, 129.2, 137.5, 138.2, 148.2, 152.0, 152.7, 191.6, 195.5.

MS (CI): *m*/*z* = 428 ($M + H^+$).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{25}NO_5S$: 427.1453. Found: 427.1436.

Carbaldehyde 13e

The synthesis of **13e** following GP 1 yielded 2.40 g (57%) of the major diastereomer as a yellow solid; mp 42 °C; ee >99%; R_f = 0.29 (pentane–Et_2O, 2:1); $[\alpha]_D^{23}$ –5.0 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 1684, 1546, 1365, 1131, 767, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.74 (m, 1 H), 1.87 (m, 1 H), 2.33 (s, 3 H), 3.01 (m, 3 H), 3.47 (m, 1 H), 4.48 (s, 1 H), 4.87 (dd, *J* = 1.7, 3.3 Hz, 1 H), 7.21 (m, 11 H), 9.63 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 30.6, 32.4, 36.3, 43.2, 43.0, 92.4, 127.8–129.2, 136.7, 137.7, 138.5, 152.8, 191.8, 195.2.

Anal. Calcd for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42. Found: C, 67.31; H, 5.87; N, 3.24.

Carbaldehyde 13f

The synthesis of **13f** following GP 1 yielded 1.45 g (32%) of the major diastereomer as a colourless oil; ee >99%; R_f = 0.27 (pentane–Et_2O, 2:1); $[\alpha]_D^{23}$ –156.0 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 3025, 2921, 2852, 1682, 1548, 1371, 1134, 757, 627 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.57 (m, 2 H), 1.73 (m, 2 H), 2.32 (m, 3 H), 2.82 (m, 4 H), 3.12 (m, 1 H), 3.32 (dd, *J* = 4.0, 6.3 Hz, 1 H), 4.89 (dt, *J* = 4.0, 5.8 Hz, 1 H), 6.99 (td, *J* = 1.6, 3.2 Hz, 1 H), 7.06 (m, 2 H), 7.32 (m, 3 H), 9.59 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 26.9, 28.9, 30.6, 32.6, 39.1, 47.2, 83.4, 127.5, 128.1, 128.9, 136.6, 137.0, 151.5, 192.0, 195.4.

MS (EI): *m*/*z* = 347 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{21}NO_4S$: 347.1191; found: 347.1187.

Thiadecaline 14a

The synthesis of **14a** following GP 2 yielded 0.05 g (57%) of colourless needles; mp 251 °C; ee >99%; R_f = 0.42 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –151.1 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2930, 1720, 1544, 1496, 1452, 1367, 1333, 913, 828, 758, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.82 (m, 1 H), 1.92 (m, 2 H), 2.19 (m, 1 H), 2.48 (m, 1 H), 2.56 (m, 1 H), 2.83 (m, 1 H), 3.42 (ddd, *J* = 11.5, 10.8, 2.5 Hz, 1 H), 3.64 (dd, *J* = 10.8, 3.9 Hz, 1 H), 3.70 (dd, *J* = 6.9, 3.0 Hz, 1 H), 4.18 (dd, *J* = 12.1, 11.5 Hz, 1 H), 5.41 (dd, *J* = 12.1, 6.9 Hz, 1 H), 7.40–7.21 (m, 10 H), 9.68 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 26.8, 28.2, 36.1, 42.2, 42.8, 51.4, 53.4, 87.8, 127.8, 127.9, 128.0, 128.7, 128.8, 128.9, 137.7, 200.5.

MS (EI): *m*/*z* = 382.2 (M^+).

Anal. Calcd for $C_{22}H_{23}NO_3S$: C, 69.26; H, 6.08; N, 3.67. Found: C, 69.50; H, 5.98; N, 3.66.

Thiadecaline 14b

The synthesis of **14b** following GP 2 yielded 0.04 g (40%) of colourless crystals, mp 126 °C; ee >99%; R_f = 0,40 (pentane–Et_2O 1:1); $[\alpha]_D^{23}$ –55.0 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2926, 1720, 1546, 1369, 912, 835, 728, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.88 (m, 3 H), 2.17 (m, 1 H), 2.52 (m, 2 H), 2.82 (ddd, *J* = 3.0, 10.3, 13.5 Hz, 1 H), 3.39 (ddd, *J* = 2.4, 11.3, 10.3 Hz, 1 H), 3.58 (dd, *J* = 4.0, 10.3 Hz, 1 H), 3.70 (dd, *J* = 3.6, 7.0 Hz, 1 H), 4.11 (dd, *J* = 12.2, 11.3 Hz, 1 H), 5.41 (dd, *J* = 7.0, 12.2 Hz, 1 H), 7.29 (m, 9 H), 9.68 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 26.5, 28.2, 36.2, 41.9, 42.6, 50.4, 53.5, 87.8, 128.0–130.2, 134.2, 136.3, 137.8, 200.8.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{22}ClNO_3S$: 369.1080 ($M^+ - NO_2$); found: 369.1065 ($M^+ - NO_2$).

Thiadecaline 14c

The synthesis of **14c** following GP 2 yielded 0.51 g (52%) of the major diastereomer as colourless needles; mp 156 °C; ee >99%; R_f = 0.29 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –130.7 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2917, 1717, 1609, 1548, 1511, 1455, 1368, 1250, 1180, 1109, 1032, 835, 812, 762, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.81 (m, 1 H), 1.89 (m, 2 H), 2.17 (m, 1 H), 2.48 (m, 1 H), 2.52 (m, 1 H), 2.81 (ddd, *J* = 13.7, 11.3, 3.0 Hz, 1 H), 3.4 (ddd, *J* = 12.0, 11.0, 2.6 Hz, 1 H), 3.62 (m, 1 H), 3.64 (m, 1 H), 3.79 (s, 3 H), 4.13 (dd, *J* = 12.2, 12.0 Hz, 1 H), 5.38 (dd, *J* = 12.2, 6.9 Hz, 1 H), 6.87 (m, 2 H), 7.32–7.20 (m, 7 H), 9.66 (d, *J* = 2.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 26.8, 28.1, 36.2, 42.3, 42.7, 50.7, 53.4, 55.1, 87.9, 114.1, 127.9, 128.9, 129.7, 129.8, 137.8, 159.0, 200.6.

MS (EI): *m*/*z* = 411.2 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{25}NO_4S$: 411.1499, found: 411.1506.

Thiadecaline 14d

The synthesis of **14d** following GP 2 yielded 0.045 g (50%) of a colourless solid; mp 140 °C; ee >99%; R_f = 0.31 (pentane–Et_2O, 2:1); $[\alpha]_D^{23}$ –153.0 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 2931, 1719, 1548, 1367, 1031, 791, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.88 (m, 3 H), 2.22 (m, 1 H), 2.33 (s, 3 H), 2.40 (m, 1 H), 2.66 (m, 1 H), 2.81 (m, 1 H), 3.37 (dt, *J* = 3.5, 12.0 Hz, 1 H), 3.58 (m, 1 H), 3.80 (dd, *J* = 4.2, 12.2 Hz, 1 H), 4.04 (t, *J* = 12.0 Hz, 1 H), 5.21 (dd, *J* = 5.6, 12.3 Hz, 1 H), 5.90 (m, 1 H), 6.07 (d, *J* = 3.1 Hz, 1 H), 7.25 (m, 5 H), 9.56 (d, *J* = 3.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 23.3, 27.3, 27.4, 35.9, 42.1, 43.7, 46.3, 52.9, 87.2, 106.3, 110.2, 128.0, 128.3, 129.0, 137.3, 149.2, 152.8, 200.4.

MS (CI): *m*/*z* = 386 ($M + H^+$).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}NO_4S$: 339.1419 ($M - NO_2^+$); found: 339.1417 ($M - NO_2^+$).

Hexahydrobenzothiophene Derivative 14e

The synthesis of **14e** following GP 2 yielded 0.055 g (57%) of the major diastereomer as a yellow solid; mp 166 °C; ee >99%; R_f = 0.3 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –139.0 (*c* 1, $CHCl_3$).

IR ($CHCl_3$): 1722, 1542, 1372, 767, 746, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.46 (s, 1 H, *J* = 1.9 Hz), 7.29 (m, 10 H), 5.25 (dd, *J* = 6.0, 9.3 Hz, 1 H), 4.13 (dd, *J* = 7.4, 11.2 Hz, 1 H), 3.74 (dd, *J* = 9.3, 12.3 Hz, 1 H), 3.69 (t, *J* = 6.3, 6.0 Hz, 1 H), 3.22 (ddd, *J* = 1.9, 11.2, 12.3 Hz, 1 H), 3.09 (m, 1 H), 2.94 (ddd, *J* = 3.6, 7.1, 10.7 Hz, 1 H), 2.86 (m, 1 H), 2.37 (dtd, *J* = 3.7, 6.1, 9.7 Hz, 1 H), 2.10 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9, 35.8, 43.9, 44.6, 45.0, 46.6, 57.9, 92.2, 127.6, 128.2, 128.3, 129.0, 129.3, 137.2, 137.4, 201.1.

MS (EI): *m*/*z* = 367 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{21}NO_3S$: 321.1313 (M – NO_2^+), found: 321.1297(M – NO_2^+).

Thiadecaline 14f

The synthesis of **14f** following GP 2 yielded 0.032 g (40%) of the major diastereomer as a colourless oil; ee >99%; R_f = 0.31 (pentane–Et_2O, 1:1); $[\alpha]_D^{23}$ –178.0 (*c* 1, $CHCl_3$).

IR (film): 2935, 2854, 1724, 1684, 1547, 1448, 1375, 910, 763, 731, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (m, 2 H), 1.59 (m, 2 H), 2.23 (m, 1 H), 2.52 (m, 2 H), 2.73 (m, 2 H), 2.87 (m, 1 H), 3.84 (m, 1 H), 4.20 (dd, *J* = 11.5, 11.5 Hz, 1 H), 4.74 (dt, *J* = 4.7, 11.5 Hz, 1 H), 7.30 (m, 5 H), 9.70 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 25.9, 28.2, 29.5, 39.6, 42.2, 43.9, 51.6, 91.0, 127.7, 128.9, 137.0, 198.5.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{19}NO_3S$: 305.1086; found: 305.1087.

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