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Synthesis of two (*S*)-indoline-based chiral auxiliaries and their use in diastereoselective alkylation reactions

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Abstract—Two chiral auxiliaries, 2-[(*S*)-indolin-2-yl]propan-2-ol **1a** and (*S*)-2-(2-methoxypropan-2-yl)indoline **1b**, were synthesised from enantiomerically pure (*S*)-indoline-2-carboxylic acid **3**. High diastereoselectivities in alkylations of enolates of the propanoylamides derived from the two auxiliaries are presented. Surprisingly, both auxiliaries induced the same selectivity at the newly created stereogenic centre. The benzyl bromide and *n*-butyl iodide alkylation reactions showed diastereomeric ratios that were moderate (81:19) to very good (96:4) and with very good yields (86–98%). When LiCl was used as an enolate coordinating agent, in the benzylation of the enolate from propanoylated auxiliary **1a**, a very high crude diastereomeric ratio was obtained (99.7:0.3).

1. Introduction

The need for stereoisomerically pure compounds and building blocks in today's modern chemistry presents an increasingly demanding task for organic chemists to improve the efficiency of asymmetric reactions. The use of chiral building blocks from stereoselective alkylation reactions has had many applications, for example, in insect pheromone synthesis[1] as well as other natural products.[2] Over the last few decades, a large number of chiral auxiliaries, reagents and organo catalysts have been developed and evaluated as asymmetric tools in a wide variety of reactions.[3] Some indoline derivatives have previously been used in asymmetric reaction sequences as catalysts or auxiliaries, for example, in α-amino acid syntheses,[4] reductions of prochiral ketones[5] and organolithium additions to hydrazones.[6] In previous reports, we have presented some results concerning aldol and alkylation reactions, using prolinol derivatives as chiral auxiliaries.[7] Herein, we report the synthesis of the two enantiomerically pure auxiliaries 2-[(*S*)-indolin-2-yl]propan-2-ol **1a** and (*S*)-2-(2-methoxypropan-2-yl)indoline **1b**, derived from enantiomerically pure (*S*)-indoline-2-carboxylic acid and diastereoselective alkylation reactions using 1-[(*S*)-2-(2-hydroxypropan-2-yl)indolin-1-yl]- propan-1-one **2a** and 1-[(*S*)-2-(2-methoxypropan-2-yl)indolin-1-yl]propan-1-one **2b**.

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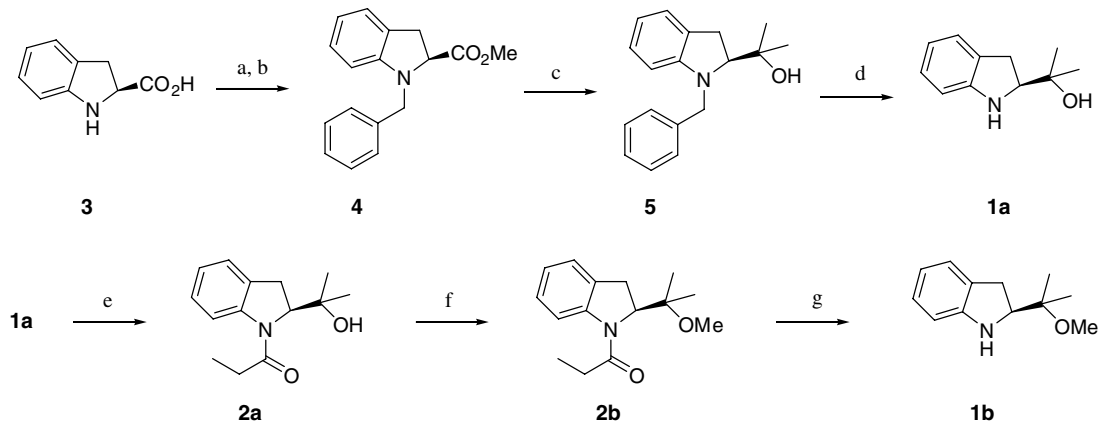
2. Results and discussion

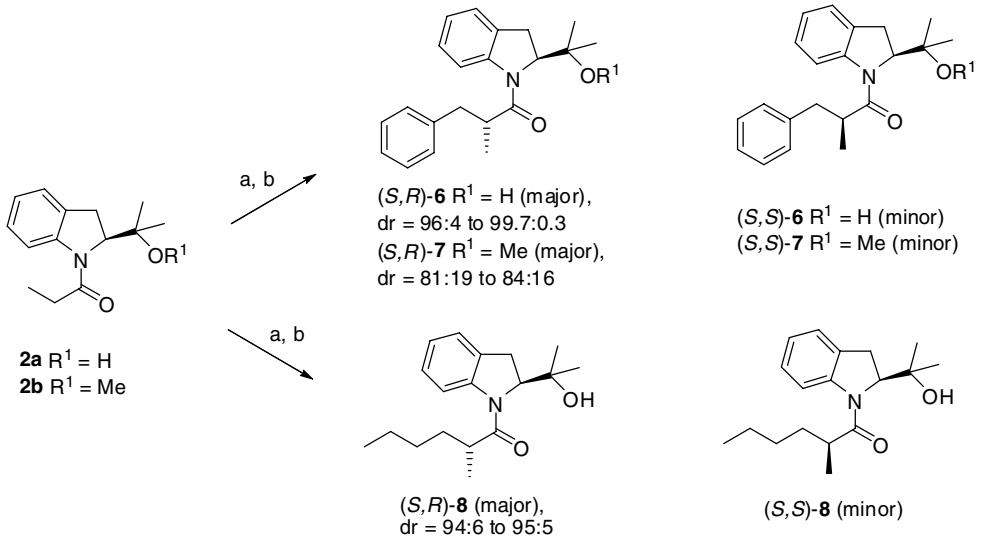
The two propanoylated auxiliaries **2a** and **2b** were prepared in total yields of 27% and 23%, respectively, from (*S*)-indoline-2-carboxylic acid **3** (see Scheme 1), principally following our procedure previously reported for the synthesis of some proline derivatives.[7a]

The enantiomeric excesses of **2a** and **2b** were >99%, based on GC analyses of the corresponding (*R*)- and (*S*)-MTPA amides, respectively, of auxiliary **1a**. The general procedure for the alkylation of the propanoylated auxiliaries **1a** and **1b** was first to generate the *Z*-metal amide enolates[8] of these amides by adding to freshly prepared LDA. Then, either benzyl bromide or *n*-butyl iodide was added to the amide enolate, or when LiCl was used, it was added before the addition of the electrophile (see Scheme 2).

Our first attempt (Table 1, entry 1) when using benzyl bromide in the alkylation of **2a** resulted in a high conversion and high diastereomeric ratio of 96:4. We learned from our earlier results on the alkylation of proline based auxiliaries that when using LiCl as additive, the diastereoselectivity was improved.[7b] Thus, we added 6.5 equiv of LiCl (entry 2) and the diastereoselectivity of the reaction was excellent (99.7:0.3). Addition of LiCl has been used to improve conversions and in some cases has resulted in higher diastereomeric ratios in other additions[9] and even in our reaction the conversion was somewhat improved to near quantitative. The excellent diastereoselectivity when using



Scheme 1. Synthetic route to enantiomerically pure chiral auxiliaries **1a** and **1b** from (*S*)-indoline-2-carboxylic acid **3**. Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C to rt, 100%; (b) (i) Et_3N, MeOH, Et_2O, 0 °C, (ii) K_2CO_3, benzyl bromide, toluene, reflux, 50%; (c) MeMgI, Et_2O, 0 °C and then reflux, 83%; (d) 10% Pd/C, H_2, EtOH, rt, 73%; (e) propanoic anhydride, 70–75 °C, 88%; (f) NaH, THF, MeI, rt, 88%; (g) (i) 3 M HCl (aq) 1,4-dioxan, 90–95 °C, (ii) 6 M NaOH (aq), 84%.



Scheme 2. General procedure for the alkylation of the propanoylated auxiliaries **1a** and **1b**. Reagents and conditions: (a) LDA (2.25 or 1.25 equiv), THF, 0 °C and then up to rt; (b) benzyl bromide or *n*-butyl iodide (2.50 equiv), different reaction temperatures, see Table 1. When LiCl was used, it was added before the LDA preparation.

Table 1. Alkylations of amides **2a** and **2b**, favouring an (*R*)-configuration at the newly created stereogenic centre

Entry	Amide[a] [additive (equiv)]	Electrophile	Reaction conditions	Conv.[b] (%)	Diastereomeric ratio[c] (*S*,*R*):(*S*,*S*)
1	**2a**	BnBr	−78 °C (3 h)→rt, overnight	94	96:4[d]
2	**2a** [LiCl (6.50)]	BnBr	−78 °C (2 h)→rt, overnight	98	99.7:0.3[d]
3	**2a**	*n*-BuI	0 °C (4.5 h)→rt, overnight	98	95:5[e]
4	**2a** [LiCl (6.50)]	*n*-BuI	0 °C (4.5 h)→rt, overnight	95	94:6[e]
5	**2b**	BnBr	−78 °C (2 h)–2 h→−30 °C	91	84:16[f]
6	**2b** [LiCl (6.50)]	BnBr	−78 °C (2 h)–2 h→−30 °C	86	81:19[f]

[a] Enolisation with LDA.
[b] Determined by GC (EC-1 capillary column) of the crude product.
[c] Determined by GC.
[d] Determined on an EC-5 capillary column of the crude product.
[e] Determined on a β-dex 225 chiral phase capillary column, as the enantiomeric ratio of 2-methylhexanoic acid.
[f] Determined on a VF-23ms capillary column of the crude product.

this new auxiliary is in comparison with other highly efficient auxiliaries such as pseudoephedrine derivatives.[9] We then used *n*-butyl iodide as the electrophile (entry 3) and the diastereoselectivity was once again high (95:5) as

well as the conversion however, when adding LiCl this time, the diastereoselectivity and the conversion were practically unchanged (entry 4). When we used a methyl ether derivative of a proline based auxiliary, we observed an excellent and reversed diastereoselectivety in the alkylation reactions.[7b] Thus, we turned our attention to using the same strategy to obtain both diastereomers as products just by a minor change of the structure of the auxiliary. However, when using the new methyl derived propanoylated auxiliary **2b**, the diastereoselectivity was not so high. What was surprising was that the diastereomer obtained was the same as that observed when **2a** was used (entry 5). An explanation for this result might be that a chelated enolate[8] of **2a** probably attacks the electrophile from the *Si*-face, since the *Re*-face is rather crowded for attack due to hindrance from another enolate moiety in a dimeric species of the enolate (Fig. 1). In the case of **2b**, we have suggested a *C*–*N*-rotated and dimeric non-chelated enolate as the reactive species (Fig. 1), since the chelation properties of monoanionic enolates should be weaker or even absent in comparison with dianionic ones.[8b,c] The enolate should react from the *Si*-face, due to the steric hindrance exerted by the substituent on the indoline ring. We have chosen to illustrate the enolate structures of **2a** and **2b** as dimeric species, since it is most likely that the enolates exist as dimers or even as higher aggregates.[10]

We then added LiCl but both the diastereoselectivity and the conversion dropped to somewhat lower values (entry 6). The observed different behaviour when LiCl was added in the alkylation of **2a** and **2b** is difficult to explain. Most likely, several parameters such as the interactions of the enolates with the added LiCl, the amine from the base used in the enolisation, the solvent, and the temperature influence the structure of the lithium enolate aggregates and also the conformation of the reactive enolate species.[10]

Removal of the chiral auxiliary from alkylated **2a** by acid hydrolysis[11] furnished non-racemic 2-benzylpropanoic acid or 2-methylhexanoic acid (Scheme 3). The negative sign of the optical rotation of the obtained 2-benzylpropanoic acid verified the (*R*)-configuration [(*R*)-2-benzylpropanoic acid lit.[11] $[\alpha]_D^{20} = -22.1$ (neat)] and consequently (*S*,*R*)-**6** is the major diastereomer produced in the alkylation reaction. The retention time on chiral GC-column for the obtained non-racemic 2-methylhexanoic acid was compared with samples of (*R*)- and (*S*)-2-methylhexanoic acid of known stereochemistry.[7b] The peak coincided with the (*R*)-2-methylhexanoic acid peak and this verified (*S*,*R*)-**8** as the major diastereomer produced in the alkylation reaction. The major diastereoisomer of benzylated **2b** was determined to be (*S*,*R*)-**7**, by comparing GC retention times of (*S*,*R*)- and (*S*,*S*)-**7** with the corresponding Me-ether derivative of (*S*,*R*)- and (*S*,*S*)-**6**. Auxiliary **1a** was recovered from the above hydrolysis with the same enantiomeric excess (analysed as MTPA-amide) as before the propanoylation step.

3. Conclusion

We have synthesised two indoline-based chiral auxiliaries which in one case has proven to be highly efficient in benzyl bromide alkylation reaction of its propanoylated enolate derivative. The diastereomeric ratio of the crude alkylated

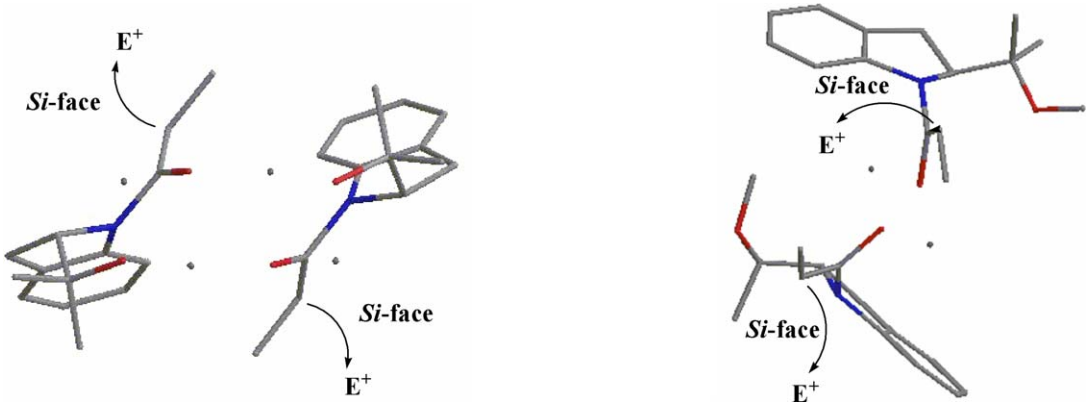
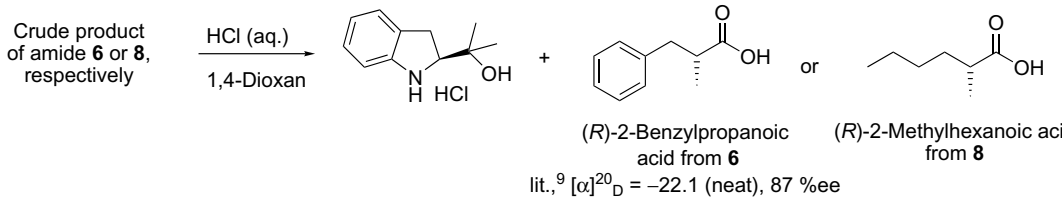


Figure 1. 3D representations of low-energy conformations under simplifying assumption of dimeric Li-enolates of **2a** (left) and **2b** (right), by using minimum energy in the Chem 3D software (Chemd 3D® Ultra, CambridgeSoft).



Scheme 3. Determination of the absolute configuration of the produced enantiomerically enriched carboxylic acids obtained after hydrolysis of the alkylated amide mixtures **6** and **8**.

amide (*S*,*R*)-**6** was excellent (99.7:0.3) and now the scope and use of the chiral auxiliaries **1a** and **1b** including some derivatives thereof, and also as organo catalysts, are under investigation.

4. Experimental

Unless otherwise stated, starting materials and solvents were used as received from commercial suppliers. Dry THF (benzophenone and potassium), diisopropylamine (CaH_2), benzyl bromide ($CaCl_2$) and *n*-butyl iodide (K_2CO_3) were distilled from the indicated drying agents and either used immediately or stored under argon. NMR spectra were recorded on a Bruker 500 or DMX 250 instrument at 298 K or at the indicated temperature and all shifts are reported in parts per million. GC analyses were carried out using an EC-1 capillary column (Alltech), 30 m × 0.32 mm id, $d_f = 0.25$ μm, carrier gas: N_2 (3 ml/min), split ratio: 1/50, an EC-5 capillary column (Alltech), 30 m × 0.32 mm id, $d_f = 0.25$ μm, carrier gas: N_2 (1.2 ml/min), split ratio: 1/20, a VF-23ms capillary column (Varian), 30 m × 0.32 mm id, $d_f = 0.25$ μm, carrier gas: N_2 (1.5 ml/min), split ratio: 1/20 or a β-dex 225 capillary column (Supelco), 30 m × 0.25 mm id, $d_f = 0.25$ μm, carrier gas: He (1.7 ml/min), split ratio: 1/10. Mass spectra were recorded on a Varian SATURN 2000 GC/MS instrument. Optical rotations were carried out on a Perkin–Elmer 341 Polarimeter in a 1 dm cell and are reported in units of 10^{-1} deg cm^2 g^{-1}. Fluka Silica gel 60 (0.040–0.063 mm) was used in preparative liquid chromatography (LC) using distilled EtOAc in distilled cyclohexane as eluent, unless otherwise stated. Thin-layer chromatography (TLC) was performed on silica gel plates (Fluka, pre-coated aluminium foil) eluted with EtOAc (100%), developed in UV-light and then sprayed with vanillin in sulfuric acid followed by heating with a heat gun. Melting and boiling points are uncorrected, and boiling points are given as air-bath temperatures in a bulb-to-bulb (Büchi-GKR-51) apparatus. Elemental analyses were performed by Mikrokemi AB, Uppsala, Sweden. HRMS analyses were performed by STFI (Swedish Pulp and Paper Research Institute), Stockholm, Sweden.

4.1. (*S*)-Methyl 1-benzylindoline-2-carboxylate 4

Thionyl chloride (2.36 ml, 32.3 mmol) was added dropwise to a suspension of (*S*)-indoline-2-carboxylic acid **3** (5.05 g, 30.9 mmol) in MeOH (40 ml) at 0 °C under an argon atmosphere. The light brownish clear solution was then allowed to stir at room temperature for 3.5 h. The reaction mixture was then concentrated under reduced pressure and the final traces of thionyl chloride were evaporated by co-evaporation with CH_2Cl_2 (3 × 50 ml) which yielded 6.70 g (quantitative) of white hygroscopic crystals. The ester hydrochloric salt was used in the next step without further purification.

Et_3N (4.31 ml, 30.9 mmol) was added to a solution of the ester hydrochloride (6.60 g, 30.9 mmol) in MeOH (10 ml) at 0 °C, followed by the addition of Et_2O (50 ml). After 0.75 h, $Et_3N{\cdot}HCl$ was removed by filtration. The free amine was isolated and dissolved in toluene (100 ml), followed by addition of K_2CO_3 (4.70, 34.0 mmol) and benzyl bromide (3.68 ml, 30.9 mmol). The reaction mixture was refluxed for 2 h. After cooling, H_2O (50 ml) was added and the organic phase separated. The aqueous phase was extracted with cyclohexane (3 × 50 ml), and the combined extracts washed with H_2O (50 ml), brine (50 ml) and dried over $MgSO_4$. Concentration under reduced pressure resulted in a brownish oil. After LC (CH_2Cl_2/cyclohexane) and bulb-to-bulb distillation, the title compound was isolated as a light yellow viscous oil (4.10 g, 15.3 mmol, 50%) with 98.8% purity according to GC. Bp 185 °C/0.7 mbar; $[\alpha]_D^{20} = +5.4$ (*c* 2.90, MeOH); ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ 3.19 (1H, dd, $J = 8.0$, 15.9 Hz), 3.37 (1H, dd, $J = 10.3$, 15.9 Hz), 3.66 (3H, s), 4.25 (1H, dd, $J = 8.0$, 10.3 Hz), 4.31 (1H, d, $J = 15.4$ Hz), 4.50 (1H, d, $J = 15.4$ Hz), 6.46 (1H, d, $J = 7.7$ Hz), 6.68 (1H, t, $J = 7.4$ Hz), 7.02–7.06 (2H, m), 7.23–7.37 (5H, m); ^{13}C NMR (125.8 MHz; $CDCl_3$; Me_4Si): δ 33.52, 52.06, 52.18, 65.30, 107.36, 118.29, 124.21, 126.91, 127.26, 127.80, 127.91 (2C), 128.51 (2C), 128.56, 137.68, 151.23, 173.32; MS (EI) *m*/*z* (relative intensity): 267 (M^+, 44%), 208 (100), 91 (85). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4; N, 5.2. Found: C, 76.2; H, 6.4; N, 5.2.

4.2. 2-((*S*)-1-Benzylindolin-2-yl)propan-2-ol 5

MeMgI (3 M in Et_2O, 17.7 ml, 52.9 mmol) was added to a solution of methyl ester **4** (3.93 g, 14.7 mmol) in Et_2O (50 ml) at 0 °C. The resulting thick slurry was refluxed for 5.5 h under an argon atmosphere. The reaction was quenched with aqueous saturated NH_4Cl (25 ml) and filtered through Celite. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 50 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give a viscous brownish oil. This oil was purified by LC, bulb-to-bulb distillation (190–195 °C/1 mbar) and this yielded the title compound as a viscous light yellow oil (3.25 g, 12.2 mmol, 83%) with >99% purity according to GC. $[\alpha]_D^{20} = -10.1$ (*c* 0.80, MeOH); ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ 1.18 (3H, s), 1.21 (3H, s), 1.64 (1H, s), 2.90 (1H, dd, $J = 7.8$, 16.4 Hz), 3.21 (1H, dd, 10.3, 16.4 Hz), 3.66 (1H, dd, $J = 7.8$, 10.3 Hz), 4.43 (1H, d, $J = 16.6$ Hz), 4.59 (1H, d, $J = 16.6$ Hz), 6.46 (1H, d, $J = 7.8$ Hz), 6.71 (1H, t, $J = 7.3$ Hz), 7.01–7.06 (2H, m), 7.23–7.36 (2H, m); ^{13}C NMR (125.8 MHz; $CDCl_3$; Me_4Si): δ 24.19, 27.58, 32.21, 57.40, 73.87, 108.64, 118.58, 124.00, 126.90, 127.01, 127.52, 128.67, 139.81, 154.25; MS (EI) *m*/*z* (relative intensity): 267 (M^+, 70%), 250 (14), 208 (100), 91 (28). Anal. Calcd for $C_{18}H_{21}NO$: C 80.9; H, 7.9; N, 5.2. Found: C, 80.8; H, 8.0; N, 5.1.

4.3. 2-((*S*)-Indolin-2-yl)propan-2-ol 1a

Pd/C (10%, 0.97 g), benzylamine **5** (3.08 g, 11.5 mmol) and EtOH (100 ml absolute) were stirred at room temperature for 28 h under 1 atm of hydrogen. The catalyst was then filtered off and washed with several portions of MeOH. The solvent was removed under reduced pressure and the resulting viscous oil purified by LC and bulb-to-bulb distillation (100–185 °C/3 mbar) which yielded the title

compound as a viscous colourless oil (1.49 g, 8.36 mmol, 73%) with >99% purity according to GC. The oil crystallised upon standing. Mp = 77–78 °C; $[\alpha]_D^{20} = -56.4$ (*c* 0.61, $CHCl_3$), {lit.[12] $[\alpha]_D^{20} = -53.5$ (*c* 0.60, $CHCl_3$)}; ^1H NMR and ^{13}C NMR spectral data were similar to data previously reported;[12] MS (EI) *m*/*z* (relative intensity): 178 (MH^+, 100 %), 177 (M^+, 70), 160 (10), 118 (22).

(*R*)- and (*S*)-MTPA-amides of amino alcohol **1a** were prepared from (*S*)- and (*R*)-MTPA-Cl, as described in the literature.[13] The enantiomeric excess of the amino alcohol **1a** was determined to be >99% according to GC analyses of the diastereomeric ratio of the MTPA-amides. The auxiliary **1a** was also recovered from the hydrolysis and showed no loss in enantiomeric purity when analysed as MTPA-amide.

[VF-23ms capillary column. 180 °C, 2 min, then programmed 0.5 °C/min up to 210 °C. Retention times: (*S*,*R*)*-amide 43.66 min and *S*,*S**-amide 44.97 min. Asterisk denotes configuration of the MTPA moiety.]

4.4. 1-((*S*)-2-(2-Hydroxypropan-2-yl)indolin-1-yl)propan-1-one 2a

Propanoic anhydride (1.08 ml, 8.39 mmol) was added to amino alcohol **1a** (1.36 g, 7.63 mmol) under an argon atmosphere and stirred for 1.5 h at 70–75 °C. After cooling to room temperature, 6 M aqueous NaOH was added and the reaction mixture stirred for an additional 2.5 h. The mixture was then extracted with Et_2O (4 × 15 ml). The combined extracts were washed with 2 M aqueous HCl (10 ml), brine (20 ml) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by LC and bulb-to-bulb distillation at 180–185 °C/0.6 mbar (1.56 g, >99% according to GC). The resulting viscous colourless oil crystallised upon standing. Mp = 114–115 °C; $[\alpha]_D^{20} = -129.5$ (*c* 1.53, MeOH); ^1H NMR (500 MHz; DMSO-d_6; Me_4Si, 343 K): δ 0.85 (3H, s), 1.03 (3H, s), 1.07 (3H, t, $J = 7.4$ Hz), 2.61 (1H, dq, $J = 16.0$, 7.4 Hz), 2.75 (1H, dq, $J = 16.0$, 7.4 Hz), 2.87 (1H, d, $J = 16.4$ Hz), 3.22 (1H, dd, $J = 16.4$, 9.3 Hz), 4.42 (1H, br d, $J = 1.9$ Hz), 4.48 (1H, d, $J = 9.2$ Hz), 6.95 (1H, t, $J = 7.4$ Hz), 7.11 (1H, t, $J = 7.7$ Hz), 7.16 (1H, d, $J = 7.3$ Hz), 7.68 (1H, br d, $J = 7.7$ Hz); ^{13}C NMR (125.8 MHz; DMSO-d_6; Me_4Si, 343 K): δ 9.21, 24.82, 26.26, 27.82, 30.69, 67.08, 72.58, 116.78, 123.11, 123.94, 126.38, 133.08, 143.73, 173.55; MS (EI) *m*/*z* (relative intensity): 234 (MH^+, 100%), 216 (13), 175 (3), 118 (22). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.0; H, 8.4; N, 5.9.

4.5. 1-((*S*)-2-(2-Methoxypropan-2-yl)indolin-1-yl)propan-1-one 2b

Hydroxyamide **1a** (330 mg, 1.41 mmol) was added to a suspension of 95% NaH (56 mg, 2.22 mmol) in THF (10 ml), followed by the addition of MeI (0.28 ml, 4.44 mmol). The reaction mixture was stirred under an argon atmosphere overnight, and then quenched with H_2O (5 ml). Extraction with Et_2O (3 × 15 ml), washing of the combined extracts with brine (10 ml) followed by drying over $MgSO_4$, resulted in a yellow viscous oil (344 mg with 93% purity according to GC) after evaporation of the solvent. The crude product was purified by LC and bulb-to-bulb distillation (180 °C/1.1 mbar) which gave the title compound as a colourless viscous oil (307 mg, 1.24 mmol, 88%) with 98.6% purity according to GC. $[\alpha]_D^{20} = -94.3$ (*c* 1.51, MeOH); ^1H NMR (500 MHz; DMSO-d_6; Me_4Si, 343 K): δ 0.90 (3H, s), 0.97 (3H, s), 1.07 (3H, t, $J = 7.3$ Hz), 2.57–2.69 (2H, m), 2.91 (1H, d, $J = 16.5$ Hz), 3.10 (3H, s), 3.22 (1H, dd, $J = 16.5$, 9.4 Hz), 4.61 (1H, d, $J = 9.1$ Hz), 6.96 (1H, t, $J = 7.4$ Hz), 7.12 (1H, t, $J = 7.7$ Hz), 7.18 (1H, d, $J = 7.3$ Hz), 7.66 (1H, d, $J = 7.9$ Hz); ^{13}C NMR (125.8 MHz; DMSO-d_6; Me_4Si, 343 K): δ 9.28, 19.82, 20.83, 27.75, 30.32, 48.92, 65.69, 77.71, 116.85, 123.29, 123.96, 126.48, 133.18, 143.82, 173.47; MS (EI) *m*/*z* (relative intensity): 248 (MH^+, 50%), 247 (M^+, 21), 233 (2), 216 (7), 175 (42), 118 (100), 73 (50), 57 (6). HRMS (70 eV): 247.15716 (M^+). $C_{15}H_{21}NO_2$ require 247.15723.

4.6. (*S*)-2-(2-Methoxypropan-2-yl)indoline 1b

Methyletheramide **2b** (88 mg, 0.36 mmol) was dissolved in 3 M aqueous HCl/1,4-dioxan (4 ml/4 ml) and refluxed for 2.5 h. The reaction mixture was extracted several times with small portions of Et_2O. The aqueous phase was basified with 6 M aqueous NaOH, extracted with small portions of Et_2O and the combined extracts dried over $MgSO_4$. Evaporation of solvent resulted in a brown oil, 58 mg (97.8% purity according to GC), which was subjected to LC (Et_2O/*n*-pentane) for further purification. The title compound was isolated as a colourless oil (44 mg, 0.23 mmol, 64%) with 100% purity according to GC. $[\alpha]_D^{20} = +182.3$ (*c* 0.62, MeOH); ^1H NMR (500 MHz; $CDCl_3$; Me_4Si): δ 1.13 (3H, s), 1.21 (3H, s), 2.88 (1H, dd, $J = 8.4$, 16.0 Hz), 3.08 (1H, dd, $J = 9.6$, 16.0 Hz), 3.27 (3H, s), 3.96 (1H, dd, $J = 8.6$, 9.4 Hz), 6.69–6.77 (2H, m), 7.03 (1H, t, $J = 7.6$ Hz), 7.07 (1H, d, $J = 7.2$ Hz); ^{13}C NMR (125.8 MHz; DMSO-d_6; Me_4Si): δ 19.97, 20.56, 30.84, 48.67, 65.29, 76.45, 107.71, 116.28, 123.86, 126.73, 127.82, 151.95; MS (EI) *m*/*z* (relative intensity): 192 (MH^+, 10 %), 191 (M^+, 20), 160 (5), 118 (100), 91 (18), 73 (8). Anal. Calcd for $C_{12}H_{17}NO$: C 75.4; H, 9.0; N, 7.3. Found: C, 75.3; H, 8.7; N, 7.4.

4.7. Alkylation of amide 2a and 2b. General procedure

Amide **2a** or **2b** (153 mg, 0.66 mmol or 100 mg, 0.40 mmol) dissolved in THF (1.0 ml) was added to freshly prepared LDA in THF [prepared from a THF (2.0 ml) solution of diisopropylamine (for **2a**: 0.21 ml, 1.47 mmol or for **2b**: 74 μl, 0.53 mmol) and 1.6 M *n*-butyllithium in hexane (for **2a**: 0.90 ml, 1.44 mmol or for **2b**: 0.32 ml, 0.51 mmol) at 0 °C]. After 30 min, the reaction solution was cooled to the indicated temperature (see Table 1) and the electrophile [benzylbromide (for **2a**: 0.19 ml, 1.60 mmol or for **2b**: 0.12 ml, 1.01 mmol) or *n*-butyliodide (for **2a**: 0.18 ml, 1.60 mmol)] dissolved in THF (0.75 ml) was added (when LiCl was used it was added from the beginning and dried with a heat gun in the reaction vessel before use). After the indicated reaction time and temperature (Table 1), the reaction was quenched with diluted hydrochloric acid.

Extraction of the aqueous phase with Et_2O (4 × 10 ml) was followed by drying over $MgSO_4$ of the combined organic extracts. Concentration by evaporation of the solvent afforded the crude alkylation products. Conversions and diastereomeric ratios were determined by GC as below.

GC retention times (EC-5 capillary column; isothermal 200 °C): $t_R(S,R)$-**6** 20.06 min and $t_R(S,S)$-**6** 21.12 min, (VF-23ms capillary column; 200 °C, 5 min, then programmed 2 °C/min up to 220 °C, 15 min): $t_R(S,R)$-**7** 21.18 min and $t_R(S,S)$-**7** 21.77 min and (EC-1 capillary column; 100 °C, 2 min, then programmed 10 °C/min up to 250 °C, 5 min): $t_R(SR)$-**8** and (*S*,*S*)-**8** 13.75 min.

4.8. Determination of the configuration at the newly created stereogenic centre of amides 6, 7 and 8

The diastereomeric amide mixtures **6** [(*S*,*R*):(*S*,*S*) = 84.4:15.6] and **8** [(*S*,*R*):(*S*,*S*) = unknown] were hydrolysed to the corresponding enantiomerically enriched 2-benzylpropanoic acid and 2-methylhexanoic acid, respectively, following the procedure of Lin et al.[11]

The negative sign of the specific rotation of the obtained 2-benzylpropanoic acid {(*R*)-2-benzylpropanoic acid lit.[11] $[\alpha]_D^{20} = -22.1$ (neat)} verified (*S*,*R*)-**6** as the major diastereomer produced in the alkylation reaction. The acid was reduced to the corresponding 2-benzylpropanol. The ^{1}H NMR spectrum of this alcohol is in agreement with literature data[14] and the enantiomeric ratio (*R*:*S*) was analysed by GC of the corresponding trifluoroacetate (β-dex 225 capillary column; 70 °C, 1 min, then programmed 0.5 °C/min up to 110 °C): $t_R(S)$ 66.50 min and $t_R(R)$ 67.05 min.

The enantiomerically enriched 2-methylhexanoic acid obtained from amide mixture **8** was analysed on a β-dex 225 GC column and compared with non-racemic samples of (*R*)- and (*S*)-2-methylhexanoic acids.[7b] This verified (*S*,*R*)-**8** as the major diastereomer produced in the alkylation reaction (β-dex 225 capillary column; 80 °C, 10 min, then programmed 0.2 °C/min up to 90 °C): $t_R(S)$ 43.98 min and $t_R(R)$ 44.87 min.

After etherification of the hydroxyamide mixture **6** of known diastereomeric composition (84.4:15.6) with MeI, following the procedure described above, the major diastereomer of the corresponding amide mixture **7** was verified as (*S*,*R*)-**7** according to GC analysis on a VF-23ms column as above.

4.9. (*R*)-2-Benzyl-1-((*S*)-2-(2-hydroxypropan-2-yl)indolin-1-yl)propan-1-one (*S*,*R*)-6

(*S*,*R*)-**6** (major isomer): 98.5% chemical purity and dr = 99.7:0.3; $[\alpha]_D^{20} = -170.2$ (*c* 0.60, MeOH); ^{1}H NMR (500 MHz; DMSO-d_6; Me_4Si, 363 K): δ 0.87 (3H, s), 0.98 (3H, s), 1.10 (3H, d, $J = 6.7$ Hz), 2.62 (1H, dd, $J = 13.5$, 8.0 Hz), 2.86 (1H, d, $J = 16.4$ Hz), 3.01 (1H, dd, $J = 13.5$, 6.1 Hz), 3.05–3.10 (1H, m), 3.53 (1H, sextett, $J = 7.0$ Hz), 4.33 (1H, s), 4.43 (1H, d, $J = 9.0$ Hz), 6.95 (1H, t, $J = 7.4$ Hz), 7.10–7.21 (7H, m), 7.61 (1H, br s); MS (EI) *m*/*z* (relative intensity): 324 (MH^+, 13%), 306 (8), 265 (72), 195 (7), 174 (7), 119 (60), 118 (100), 91 (62), 77 (4), 59 (12). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.0; H, 7.8; N, 4.3. Found: C, 77.8; H, 7.8; N, 4.4.

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