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Application of *meso*-hydrobenzoin-derived chiral auxiliaries for the stereoselective synthesis of highly substituted pyrrolidines by 1,3-dipolar cycloaddition of azomethine ylides

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Dedicated to Professor Dr. Peter Stanetty on the occasion of his 65th birthday

ABSTRACT

The metal-catalyzed stereoselective 1,3-dipolar cycloaddition of azomethine ylides and acrylates using recyclable meso-hydrobenzoin-derived chiral auxiliaries is described. Cleavage of the auxiliary leads to highly substituted pyrrolidines in up to 87% enantiomeric excess.

1. Introduction

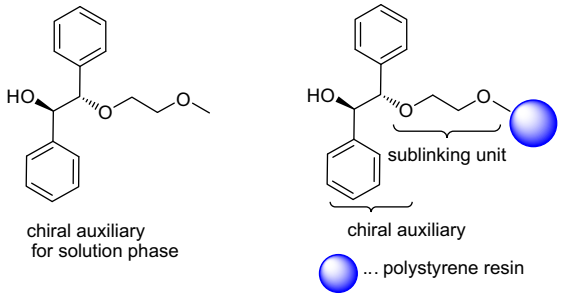
Enantiopure substituted pyrrolidines are widely found as building blocks in alkaloids and have recently attracted considerable interest as therapeutically interesting compounds, for example, potent inhibitors of glucosidase[1] and angiotensin-converting enzyme (ACE) inhibitors.[2] The possibility to form up to four new stereogenic centers in a single step makes the 1,3-dipolar cycloaddition of azomethine ylides and α,β-unsaturated carbonyl compounds one of the most potent methods for the stereoselective synthesis of substituted pyrrolidines and some syntheses using chiral auxiliaries have been published so far.[3]

Hydrobenzoins and similar structures containing a 1,2-diol moiety are already known as chiral auxiliaries for the α-alkylation of esters,[4] reduction of α-ketoesters,[5] aldol addition reactions,[6] ring-opening reactions of oxirans,[7] and oxidation reactions of sulfides,[8] respectively. In our recent studies we have designed novel chiral hydrobenzoin ethers derived from *meso*-hydrobenzoin which have been successfully applied as recyclable dual chiral auxiliaries and linkers for solid-phase organic synthesis (Scheme 1).[4a,9]

Herein, we report the highly regio- and stereoselective 1,3-dipolar cycloaddition of a N-lithiated azomethine ylide and an auxiliary-bound acrylic ester for the preparation of highly substituted pyrrolidines with the possibility for stereoselective solid-phase synthesis.

2. Results and discussion

Our synthesis of the auxiliary-bound dipolarophile started from the *meso*-hydrobenzoin derivative **4a** whose preparation in both (*R*)- and (*S*)-substituted form via desymmetrization of *meso*-hydrobenzoin with either *exo*- or *endo*-anhydro lactol **2** or **2′** has already been described earlier and was performed analogously.[10,11] The reaction with acrylic acid chloride in the presence of triethylamine and a catalytic amount of hydroquinone to prevent polymerization led to the chiral acrylic ester **5a** in 86% yield (Scheme 2).[12,13]



Scheme 1. *meso*-Hydrobenzoin derivatives as chiral auxiliaries for solid-phase synthesis.

The in situ preparation of the N-lithiated azomethine ylide **7** was achieved by deprotonation of the Schiff base **6** with DBU in the presence of a stoichiometric amount of anhydrous LiBr as a Lewis acid (Scheme 3).

The resulting 1,3-dipole reacted with the auxiliary-bound acrylic ester **5a** at room temperature using CH_3CN/CH_2Cl_2 as solvent and yielded the pyrrolidine **8a** as a single regioisomer in a yield of 67%, but low *endo*/*exo* selectivity and negligible diastereofacial selectivity were observed (Table 1).

Nevertheless, a change of the solvent to anhydrous THF led to complete *endo*/*exo* selectivity and enhanced the yield to 85%. Variation of the Lewis acid was unsuccessful: the use of AgOAc

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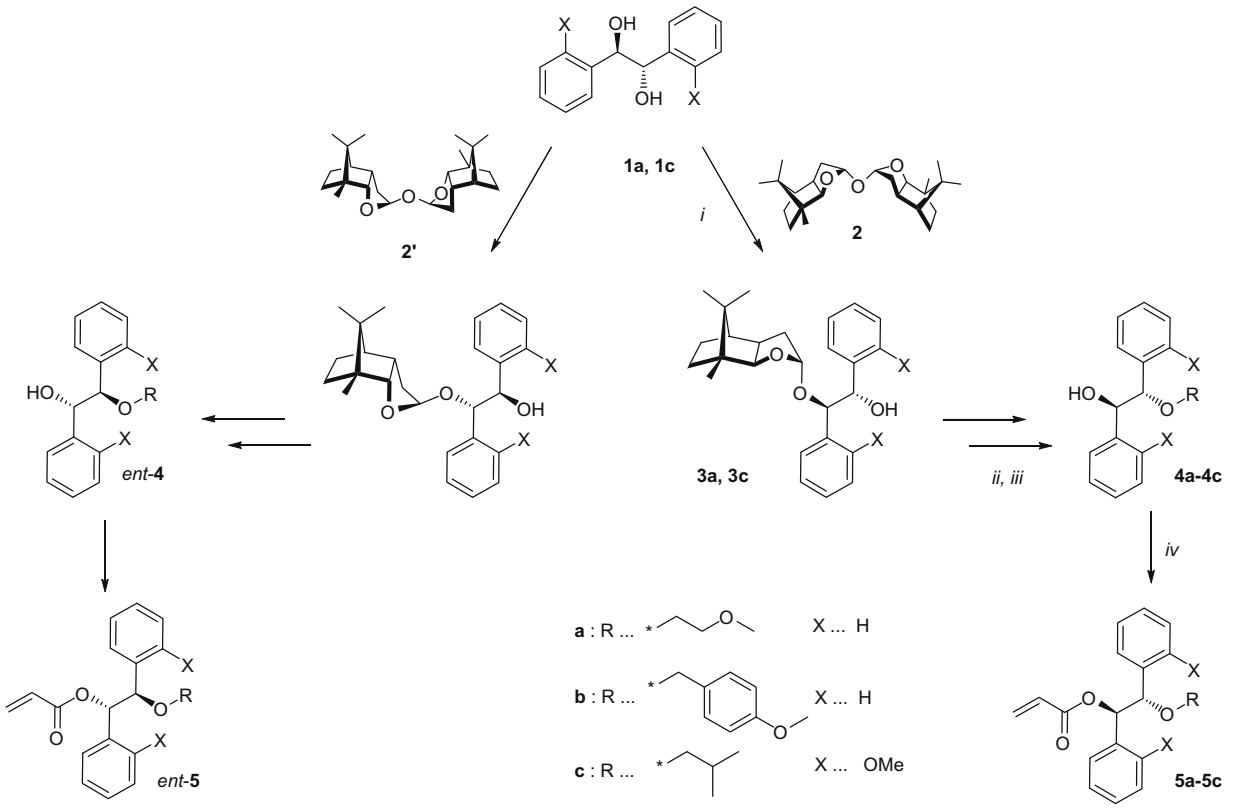
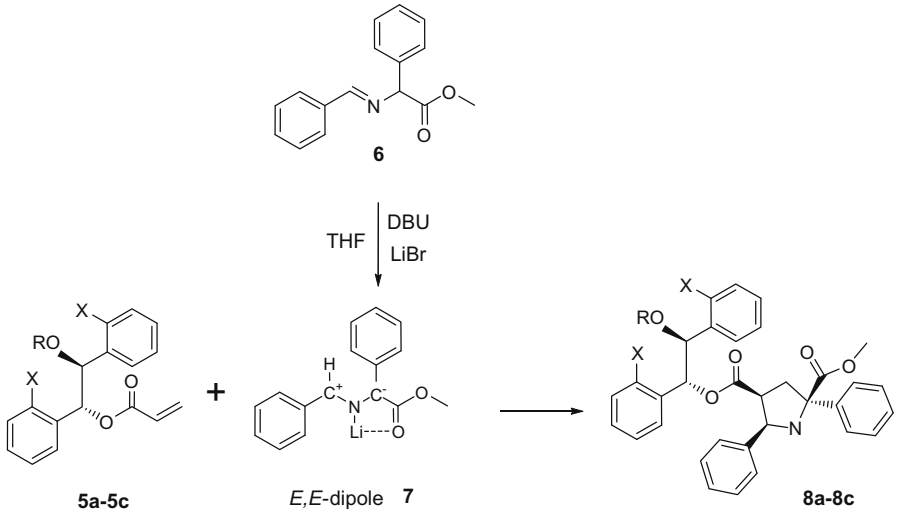


Scheme 2. Reagents and conditions: (i) *p*-TsOH, CH_2Cl_2; (ii) for **4a**: (a) (1) **3a**, NaH, (2) $BrCH_2COO$-*t*-Bu, HMPA, THF; (b) $LiAlH_4$, THF; (c) (1) NaH, (2) CH_3I, DMF; for **4b**: (1) **3a**, NaH, (2) NaI (cat.), $BrCH_2PhOMe$, DMF; for **4c**: (1) **3c**, NaH, (2) 4-toluenesulfonic acid *i*-butylester, DMF; (iii) *p*-TsOH, MeOH, CH_2Cl_2; (iv) acrylic acid chloride, Et_3N, hydroquinone monomethyl ether, CH_2Cl_2.



Scheme 3.

resulted in a complete loss of diastereofacial selectivity, while no cycloaddition was observed in the presence of $Ti(OiPr)_3Cl$. The best results were achieved at low temperature: by running the cycloaddition with LiBr as a Lewis acid at −80 °C, the product was isolated in 78% yield as a single regioisomer with complete *endo*/*exo* selectivity and a diastereofacial selectivity of 87% de.

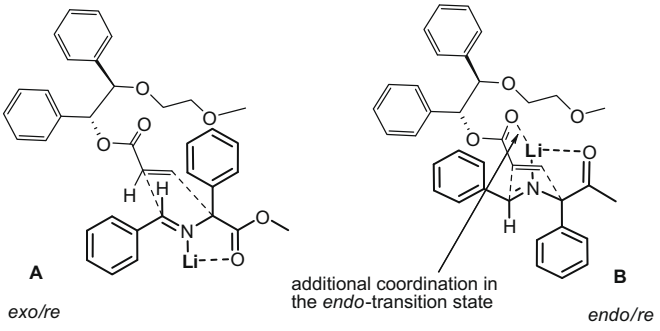
For further studies in selectivity, we synthesized different *meso*-hydrobenzoin-derived auxiliaries with a *p*-methoxybenzyl ether moiety **5b** as well as a substituted hydrobenzoin system with a bulky *sec*-butyl ether moiety **5c**.[12,13] We expected additional π–π stacking between the electron-rich *p*-methoxybenzyl ether and the acrylate in auxiliary **5b** to force a conformation with an effective shielding of the acrylate *si* face and thus improve the selectivity. On the other hand, we introduced onto auxiliary **5c** the non-π–π-stacking but sterically demanding *sec*-butyl group as well as increasing the electron density in the aromatic rings of the hydrobenzoin by introduction of methoxy substituents to achieve stronger π–π-interactions in the hydrobenzoin skeleton. A significant decrease in the diastereoselectivity and, in the case of auxiliary **5b**, the yield occurred. This led us to the conclusion that coordina-

Table 1
Results of cycloaddition

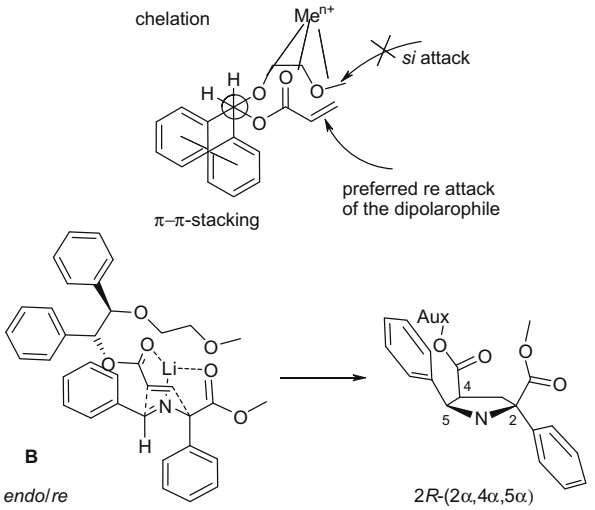
Entry	Product	Substrate	Lewis acid Temperature (°C)	*endo*:*exo*[a]	Diastereofacial selectivity[b] (%ee)	Yield[c] (%)
1[d]	**8a**	X···H R···$CH_2CH_2OCH_3$	LiBr rt	3.9:1	6[e]	67
2	**8a**	X···H R···$CH_2CH_2OCH_3$	LiBr rt	>99:1	53	85
3	**8a**	X···H R···$CH_2CH_2OCH_3$	AgOAc rt	>99:1	<1	73
4	**8a**	X···H R···$CH_2CH_2OCH_3$	$Ti(OiPr)_3Cl$ rt	—	—	0
5	**8a**	X···H R···$CH_2CH_2OCH_3$	LiBr −80	>99:1	87	78
6	**8b**	X···H R···CH_2Ph-4-OCH_3	LiBr rt	>99:1	35[e]	46
7	**8c**	X···OMe R···$CH_2CH(CH_3)_2$	LiBr −80	>99:1	25	80

[a] *endo*:*exo* ratios were determined by ^{13}C NMR integration on crude reaction mixtures.
[b] Diastereofacial selectivity was determined by HPLC analyses (Chiralcel® OD-H) of the pyrrolidines after reductive cleavage. It was ensured that no enrichment of any diastereomer occurred during this process.
[c] Isolated yield after flash column chromatography.
[d] In this case, CH_3CN/CH_2Cl_2 was used as a solvent.
[e] In these cases, the diastereofacial selectivity was determined by ^{13}C NMR integration on crude reaction mixtures of diastereomeric **8a** and **8b**.

tion of the oxygens in the ethylene glycol–ether chain in auxiliary **1a** is necessary to obtain satisfactory selectivity. Complete *endo*/*exo*-selectivity can be explained by the preferable *endo* transition state **B**, in which coordination of the dipolarophile oxygen with the Li^+ cation of the dipole occurs, which is not possible in the *exo* transition state **A** (Scheme 4).



Scheme 4. *endo*/*exo*-Transition state.



Scheme 5. Diastereofacial selectivity.

We assumed that additional coordination to both the oxygens of the carbonyl and the ethylene glycol moiety thus resulting in an effective shielding of the acrylates' *si* side: the favored attack occurs via an *endo*/*re* transition state to form the [2*R*-(2α,4α,5β)] pyrrolidine (Scheme 5).

The cleavage of the pyrrolidine **8a** and recovery of the auxiliary were best achieved under reductive conditions, since basic LiOH-mediated saponification at room temperature cleaved only the methyl ester whereas harsher reaction conditions could lead to racemization. Reductive cleavage of the auxiliary-bound pyrrolidine **8a** with $LiAlH_4$ in THF proceeded instantaneously to afford the pyrrolidinediol **9** after extractive work-up in an excellent yield of 98% (Scheme 6).

Isolation of the hydrobenzoin auxiliary could be achieved by simple extraction of the acidic phase and gave pure **4a** according to ^1H NMR in 96% yield.

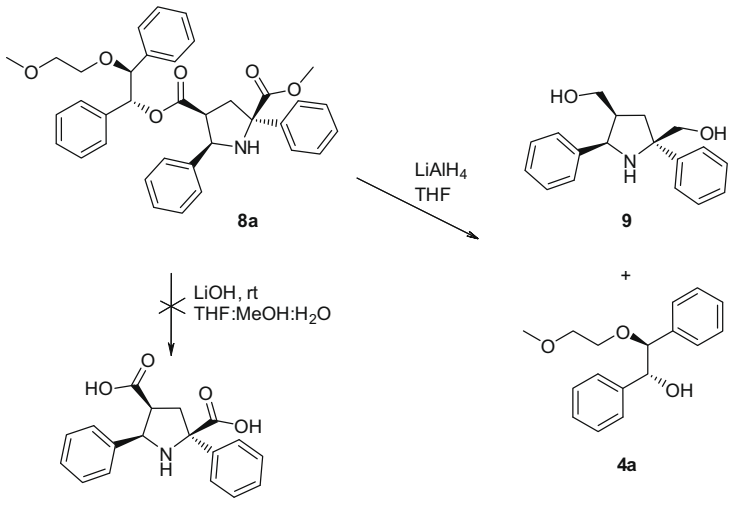
To confirm the configuration of the pyrrolidine diol **9** NOE correlations were carried out: a strong NOE between H-4 and H-5 was observed proving the suspected *syn*-conformation of the protons at C-4 and C-5 (Scheme 7).

Additional NOE signals between H_a-3 and H-6 and H-7 indicated a *syn*-orientation of the hydroxylmethyl substituents at the 2- and 4-positions. Together with the *syn*-conformation of H-4 and H-5, these results are in accordance with the *E*,*E*-structure of the *N*-lithiated azomethine ylide suggested by Grigg which yields an *anti*-relationship between both phenyl substituents in product **8a** (Scheme 8).[3]

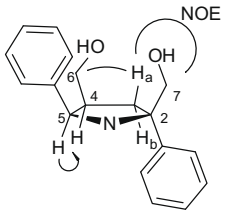
Consequently, NOE measurements confirm the (2α,4α,5β) relative configuration of **8a** which was proposed based on theoretical considerations about the most likely *endo*/*re*-transition state and thus support our model.

3. Conclusion

In conclusion, we have proved the efficiency of novel *meso*-hydrobenzoin-derived chiral auxiliaries for the facile stereoselective synthesis of highly substituted pyrrolidines, as well as the easy cleavage of the heterocycle and recovery of the auxiliary. Furthermore, the ability to use an analogous *meso*-hydrobenzoin system attached to a solid support[4a,9] may make our method a useful tool for the stereoselective preparation of heterocyclic compound assemblies for drug development programs.



Scheme 6. Cleavage of the auxiliary.



Scheme 7. NOE-spectroscopy

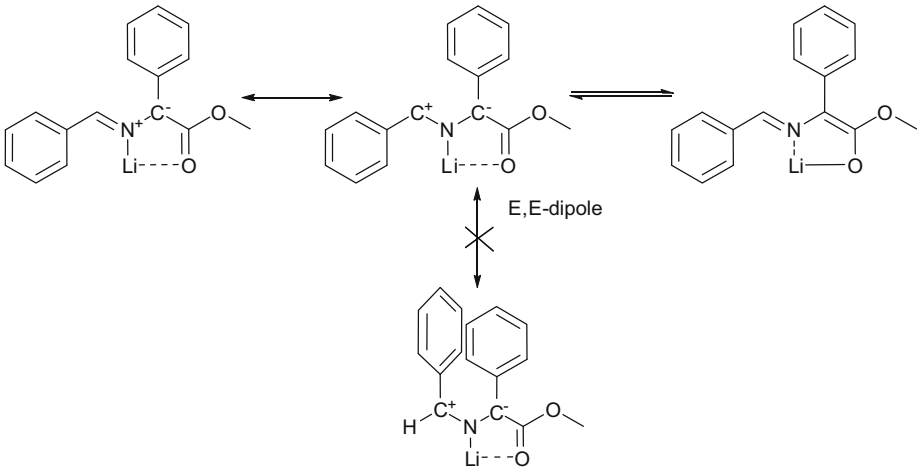
4. Experimental

4.1. General

Commercially available reagents and solvents were used as received from the supplier unless otherwise specified. Diethyl ether (E), petroleum ether (PE; 60–80 °C fraction), ethyl acetate (EE), and dichloromethane (DCM) were distilled prior to use. Dry diethyl ether and tetrahydrofuran (THF) were predried over KOH and distilled from Na/benzophenone. Dry dichloromethane was distilled from P_2O_5. Compounds LiBr and AgOAc were dried by heating to 150–300 °C in high vacuo for 60 min prior to use. All moisture-sensitive reactions were carried out under a nitrogen atmosphere. For TLC-analysis precoated aluminum-backed plates (Silica Gel 60 F_{254}, Merck) were used. Compounds were visualized by spraying with 5% phosphomolybdic acid hydrate in ethanol and heating. Column chromatography was carried out with Silica Gel Merck 60. All fractions of products containing NOE's acetal-protecting group together with a free hydroxy group were concentrated immediately after chromatography together with a few drops of NEt_3. Melting points were determined with a Kofler hot-stage apparatus. Specific rotations were measured on a Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 in $CDCl_3$ at 200 and 50 MHz, respectively, using TMS or the solvent peak as the reference. HPLC analysis of pyrrolidines was carried out with a SHIMADZU LC-10AD (SHIMADZU SPD-10AV UV/VIS detector; Chiralcel® OD-H; *n*-hexane/*i*-PrOH 80:20; 0.80 mL/min; t_{R1} = 36.3 min, t_{R2} = 39.6 min). Elemental analysis was carried out at Vienna University, Department of Physicochemistry—Laboratory for Microanalysis, Währinger Str. 42, A-1090 Vienna.

4.2. (*R*)-(1*R**,2*S**)-2-(4-Methoxybenzyloxy)-1,2-diphenylethanol 4b

A solution of alcohol **3a**[11] (1.46 g, 3.72 mmol) in dry DMF (5 mL) was added slowly to a suspension of freshly washed NaH (0.18 g, 7.5 mmol) in dry DMF (5 mL) and the mixture was stirred for 2 h at room temperature. Then a catalytic amount of NaI and 4-MeO-BnCl (1.02 g, 6.54 mmol) was added and stirring was continued for 30 min at room temperature. Unreacted NaH was then carefully



Scheme 8. Conformation of the 1,3-dipole.

hydrolyzed by adding water (60 mL) while cooling on an ice bath, until the reaction ceased. The resulting mixture was extracted six times with ether. The combined ether extracts were washed four times with brine, dried over Na_2SO_4, filtered, and evaporated. Short column chromatography on silica gel (100 g, PE/E 15:1) yielded 1.68 g of a colorless oil (88%), R_f = 0.64 (PE/E 3:1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.47–7.28 (m, 10H, H-aromatic), 6.79 (d, J = 8.80 Hz, 2H, H-aromatic), 6.70 (d, J = 8.80 Hz, 2H, H-aromatic), 4.82 (d, 2H, J = 3.91 Hz, 1H, H-2), 4.68/4.25 (2d, J = 8.41 Hz, 2H, Ph–CH–O), 4.34/4.02 (2d, J = 11.93 Hz, 2H, Ph–CH_2–), 2.37 (d, J = 6.65 Hz, 1H, H-7a), 1.94–0.46 (m, 17H, MBE-aliph.-H, therein 0.78 (2s, 6H, 2 MBE-CH_3), 0.69 (s, 3H, MBE-CH_3)) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 158.8 (s, C-17), 140.8/140.3 (2s, C-11, C-12), 130.4 (s, C-14), 128.9–127.4 (m, 10-Ph–C), 100.8 (d, C-2), 89.9 (d, C-7a), 83.6/78.6 (2d, C-9, C-10), 70.0 (t, C-13), 55.21 (q, C-18), 48.1 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.8 (d, C-3a), 38.3 (t, C-3), 32.1 (t, C-6), 28.8 (t, C-5), 22.8/20.5/11.4 (3q, 3 MBE-CH_3) ppm. Anal. Calcd for $C_{35}H_{42}O_3\times0.9H_2O$: C, 79.78; H, 8.38. Found: C, 79.64; H, 8.02.

This oil (1.66 g, 3.25 mmol) was dissolved in methanol (25 mL), *p*-toluenesulfonic acid monohydrate (0.11 g, 0.58 mmol) was added, and the reaction mixture was stirred for 12 h. Then saturated $NaHCO_3$ solution (50 mL) was added to the mixture, and the aqueous phase was extracted several times with CH_2Cl_2. The combined extracts were dried with Na_2SO_4, filtered, and evaporated to dryness, yielding 1.75 g of a colorless oil which was purified via chromatography (PE/E 10:1 → 4:1) to give 0.92 g **4b** (85%) and 0.68 g octahydro-2-methoxy-7,8,8-trimethyl-4,7-methanobenzofuran (88%) which was used for the recyclization of NOE's chiral protecting group.[10]

Compound **4b**: R_f = 0.39 (PE/E 3:1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.43–7.20 (m, 4H, Ar–H), 7.09 (d, J = 8.6 Hz, 2H,), 6.87 (d, J = 8.6 Hz, Ar-), 4.93 (d, J = 5.7 Hz, 1H, Ph–CH–O), 4.52 (d, 5.7 Hz, 1H, Ph–CH–O), 4.49 (d, J = 11.4 Hz, 1H, Ph–CH_2–O), 4.21 (d, J = 11.5 Hz, 1H, Ph–CH_2–O), 3.83 (s, 3H, OCH_3), 2.53 (s, 1H, OH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 159.0 (s, Ph–C–OCH_3), 140.5/137.7 (2s, 2Ph–C-1), 129.9 (s, CH_3O–Ph–C-1), 129.2–127.0 (9d, 9Ph–C), 113.6 (d, Ph–C), 84.6/76.9 (2d, Ph–CH–O), 70.2 (t, Ph–CH_2–O), 55.1 (q, OCH_3) ppm. Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.74; H, 6.77.

4.3. General procedure for the preparation of acrylic acid esters 5a–5c

Acrylic acid chloride (2.0 equiv) was added dropwise to a solution of auxiliary **4a**–**4c** (1.0 equiv) and triethylamine (2.0 equiv) in dry DCM while cooling on a NaCl/ice bath. The mixture was stirred for 2 h at room temperature until TLC control indicated complete conversion. Then the suspension was diluted with H_2O and extracted with DCM. The organic phases were washed successively with 5% $KHSO_4$ solution, a saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, a catalytic amount of hydroquinone monomethyl ether added, and evaporated. The crude product was purified by flash column chromatography on silica gel, eluting with PE/E (15:1).

Acrylic acid esters **5a** and **5c** were identical to the material described in the literature.[13]

4.4. Propenoic acid, *R*-(1*R**,2*S**)-[2-(4-methoxybenzyloxy)-1,2-diphenylethyl]ester 5b

Yield 76%, viscous oil, R_f = 0.45 (PE/EE 4:1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.37–7.04 (m, 10H, aromatic), 7.00/6.80 (2d, 4H, *p*-Ph–H, J = 8.6 Hz), 6.31 (dd, 1H, –C*H*=CH_2, J_1 = 17.2 Hz, J_2 = 1.6 Hz), 6.03/5.75 (2dd, 2H, –CH=C*H*$_2$, J_1 = 16.9 Hz, J_2 = 10.7 Hz/ J_1 = 10.2 Hz, J_2 = 1.6 Hz), 6.00/4.64 (2d, 2H, Ph–C*H*–O, J = 6.4 Hz), 4.47/4.18 (2d, 2H, –OC*H*$_2$–Ph), 3.81 (s, 3H, CH_3O–) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 164.6 (s, CO), 159.0 (s, CH_3O–*C*), 137.9/137.4 (s, Ph–C-1), 130.7 (d, –*C*H=CH_2–), 130.0 (s, CH_3O–Ph–C1), 130.8 (d, –*C*H=CH_2–) 129.0–127.6 (d, Ph–C and –*C*H=CH_2–), 82.3/77.9 (2d, Ph–*C*H–O), 70.2 (t, Ph–*C*H$_2$–O), 55.2 (q, CH_3O–) ppm. Anal. Calcd for $C_{29}H_{24}O_4$: C, 77.30; H, 6.23. Found C, 77.18; H, 6.46.

4.5. Preparation of the Schiff base phenyl[(1-phenylmethyliden)-amino]acetic acid, methyl ester 6

rac-Phenylglycine, methylester hydrochloride, and triethylamine were dissolved in 250 mL of dry DCM and stirred in the presence of $MgSO_4$ for 60 min. Freshly distilled benzaldehyde was added and the mixture was refluxed for 42 h. After cooling to room temperature, the resulting suspension was filtered and washed twice with brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by bulb to bulb distillation (100 °C/ 0.02 mm Hg) to obtain 8.49 g (yield 81%) of a yellow oil, R_f = 0.24 (PE/E 4:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 8.36 (s, 1H, –CH=N), 7.90–7.78 (m, 2H, aromatic), 7.60–7.31 (m, 8H, aromatic), 5.23 (s, 1H, C*H*NH_2), 3.76 (s, 3H, CH_3O) ppm.[14]

4.6. General procedure for the cycloaddition

A solution of the Schiff base **6** (1.0 equiv) in dry THF was added to a solution of acrylic acid esters **5a**–**5c** followed by a solution of freshly dried LiBr in THF. After cooling to −80 °C DBU was added dropwise and stirred for 2 h. Additional Schiff base and DBU were added and stirred for 1 h at −80 °C until TLC control indicated total conversion. The solution was allowed to reach room temperature, diluted with 10% NH_4Cl solution, and extracted with DCM. The organic phases were washed twice with brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel, eluting with PE/E (10:1). By quantitative comparison of NMR spectra before and after flash chromatography it was verified that no separation of the diastereomers had occurred during this process. Only the NMR signals of major diastereomers are given below.

4.7. [(2*R*)-(2α,4α(1′*R**,2′*S**),5α)]-2,5-Diphenylpyrrolidine-2,4-dicarboxylic acid, 4-[2-(2-methoxyethoxy)-1,2-diphenylethyl]-ester, 2-methylester 8a (contains as minor component [2*S*-(2α,4α(1′*S**,2′*R**),5α)])

Yield 67–85%, yellow oil, R_f = 0.21 (PE/EE 5:1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.90–6.92 (m, 20H, aromatic), 5.53/4.64 (2d, 2H, Ph–C*H*–O, J = 7.4 Hz), 5.30 (br s, 1H, NH), 4.52 (d, 1H, PhC*H*–N, J = 6.3 Hz), 3.80 (s, 3H, CH_3OCO–), 3.55–3.40 (m, 5H, O–C*H*$_2$–C*H*$_2$–O– and –C*H*COO–), 3.38 (s, 3H, C*H*$_3$OCH$_2$–), 3.11/2.75 (2dd, 2H, –COCH–C*H*$_2$–CPh, J_1 = 13.5 Hz, J_2 = 6.3 Hz/J_1 = 13.3 Hz, J_2 = 7.4 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 174.2 (s, –*C*OOCH$_3$), 171.1 (s, –CH–*C*OO–), 142.8/139.3/137.9/137.3 (4s, Ph–C-1), 128.3–126.4 (20d, Ph–C), 83.4/78.6 (2d, Ph–*C*H–O), 71.6/68.8 (2t, O–C*H*$_2$–C*H*$_2$–O–), 71.5 (s, N–*C*–Ph), 64.5 (d, PhCH–N), 58.8 (q, *C*H$_3$OCH$_2$–), 52.7 (q, *C*H$_3$OCO–), 50.0 (d, –*C*H–COO–), 40.8 (t, –CH–*C*H$_2$–CPh) ppm. Anal. Calcd for $C_{36}H_{37}NO_6\times1H_2O$: C, 72.34; H, 6.58; N, 2.34. Found: C, 72.35; H, 6.54; N, 2.33.

4.8. [(2*R*)-(2α,4α(1′*R**,2′*S**),5α)]-2,5-Diphenylpyrrolidine-2,4-dicarboxylic acid, 4-[2-(4-methoxybenzyloxy)-1,2-diphenylethyl]ester, 2-methylester 8b (contains as minor component [2*S*-(2α,4α(1′*S**,2′*R**),5α)])

Yield 46%, yellow oil, R_f = 0.32 (PE/EE 5:1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.68–6.62 (m, 24H, aromatic), 5.50 (d, 1H, Ph–C*H*–O, J = 5.1 Hz), 5.30 (br s, 1H, NH), 4.44–4.15 (m, 2H, Ph–C*H*–O

and OCH_2–Ph), 4.07–3.90 (m, 2H, PhC*H*–N and OCH_2–Ph), 3.70 (s, 3H, CH_3OCO–), 3.57 (s, 3H, CH_3O–), 3.10 (m, 1H, –*CH*COO–), 2.86/2.46 (2dd, 2H, –COCH–CH_2–CPh, J_1 = 13.5 Hz, J_2 = 6.5 Hz/J_1 = 13.5 Hz, J_2 = 7.4 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 174.3 (s, –*C*OOCH$_3$), 171.0 (s, –CH–*C*OO–), 159.0 (s, CHO_3–C–), 142.8/139.3/137.9/136.3 (4s, Ph–C-1), 130.3 (s, CH_3O–Ph–C1), 129.0–113.5 (22d, Ph–C), 82.0/78.3 (2d, Ph–*C*H–O), 71.5 (s, N–*C*–Ph), 70.2 (t, Ph–*C*H_2–O), 64.4 (d, PhCH–N), 55.2 (q, *C*H_3OPh–), 52.7 (q, *C*H_3OCO–), 50.0 (d, –C*H*–COO–), 40.8 (t, –CH–*C*H_2–CPh) ppm. Anal. Calcd for $C_{41}H_{39}NO_6\times1.4H_2O$: C, 73.83; H, 6.32; N, 2.10. Found: C, 73.88; H, 6.19; N, 1.95.

4.9. [(2*R*)-(2α,4α(1′*R**,2′*S**),5α)]-2,5-Diphenylpyrrolidine-2,4-dicarboxylic acid, 4-[1,2-di(2-methoxyphenyl)-2-(2-methylpropoxy)ethyl]ester, 2-methylester 8c (contains as minor component [2*S*-(2α,4α(1′*S**,2′*R**),5α)])

Yield 80%, yellow oil, R_f = 0.17 (PE/EE 4:1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.84–6.43 (m, 18H, aromatic), 6.14 (d, J = 3.1 Hz, 1H, OCHPh), 4.63–4.49 (m, 2H, OCHPh and PhC*H*–N), 4.15–3.12 (m, 10H, 3 × CH_3O– and –*CH*COO–), 3.19–2.94 (m, 3H, O–CH_2CH(CH_3)$_2$ and –CH–*C*H_2–CPh), 2.71 (dd, 1H, J_1 = 13.4 Hz, J_2 = 6.2 Hz, –CH–*C*H_2–CPh) 1.96–1.71 (m, 1H, O–CH_2C*H*(CH_3)$_2$), 0.92/0.91 (2d, J = 6.6 Hz, 6H, O–CH_2CH(C*H*$_3$)$_2$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 174.2 (s, –*C*OOCH$_3$), 171.4 (s, –CH–*C*OO–), 157.1/156.4 (2s, Ph–C-2), 142.9/139.5 (4s, Ph–C-1), 128.7–109.3 (18d, Ph–C), 126.3/125.0 (2s, CH_3O–Ph–C1), 76.1 (t, O–*C*H_2–CH(CH_3)$_2$), 75.9/75.6 (2d, Ph–*C*H–O), 71.5 (s, N–*C*–Ph), 64.5 (d, PhCH–N), 55.0/54.9 (2q, Ph–O*C*H$_3$), 52.6 (q, *C*H_3OCO–), 50.0 (d, –C*H*–COO–), 41.1 (t, –CH–*C*H_2–CPh) 28.6 (d, O–CH_2–*C*H(CH_3)$_2$), 19.4/19.3 (2q, O–CH_2–CH(*C*H_3)$_2$) ppm. Anal. Calcd for $C_{39}H_{43}NO_7$: C, 73.45; H, 6.80; N, 2.20. Found: C, 73.21; H, 6.88; N, 2.15.

4.10. Reductive cleavage of pyrrolidine ester 8a; [(2*R*)-(2α,4α,5α)]-2,5-diphenylpyrrolidine-2,4-dimethanol 9

To an ice-cooled solution of $LiAlH_4$ (1.286 mmol/48 mg) in dry THF (20 mL) was added a solution of ester **8a** (0.643 mmol) in dry THF (10 mL) and the reaction mixture was stirred for 1 h at ambient temperature. Next, H_2O (0.5 mL) and 40% NaOH (0.1 mL) were added while cooling on an ice bath and the mixture was stirred at ambient temperature until a white solid had precipitated. A small portion of Mg_2SO_4 was added and the mixture was filtered over a pad of silica. The solvent was evaporated and the crude product was dissolved in 10 mL CH_2Cl_2 and extracted five times with 2 N HCl. For recovery of the auxiliary **5a** the organic phase was washed with brine, dried with Na_2SO_4, filtered, evaporated, and, if necessary purified via flash column chromatography. Thereby all auxiliaries **5a**–**5c** could be recovered almost quantitatively without any loss of enantiomeric purity. To the acidic aqueous phase was carefully added 40% NaOH while cooling on an ice bath. The basic aqueous phase was extracted four times with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and evaporated to yield 56 mg of pyrrolidinediol **9** (98%) as a colorless oil, R_f = 0.31 ($CHCl_3$/MeOH 20/1); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ_H = 7.47–7.25 (m, 10H, aromatic), 4.52 (d, 1H, Ph–C*H*–N, J = 8.2 Hz), 3.77/3.56 (2d, 2H, HO–CH_2–CH–, J = 11.0 Hz), 3.32/3.25 (2dd, 2H, HO–CH_2–C–, J_1 = 11.1 Hz, J_2 = 6.0 Hz), 2.66–2.44 (br s, 4H, Ph–CH–C*H*–CH_2–, NH and 2OH), 2.39/2.31 (2dd, 2H, –CH–C*H*$_2$–C–Ph, J_1 = 12.9 Hz, J_2 = 8.2 Hz/J_1 = 13.0 Hz, J_2 = 7.2 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 144.7/140.5 (2s, Ph–C-1), 128.7–125.2 (d, Ph–C), 68.6 (s, N–*C*–Ph), 68.0 (t, HO–*C*H_2–CH), 66.8 (t, HO–*C*H_2–C), 62.0 (d, N–*C*H–Ph), 44,1 (d, CH_2OH–*C*H–CH_2) ppm. Anal. Calcd for $C_{18}H_{21}NO_2\times0.5H_2O$: C, 73.94; H, 7.58; N, 4.79. Found: C, 73.98; H, 7.27; N, 4.72.

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