Asymmetric Synthesis via Heterocyclic Intermediates; XXXVII[1] Asymmetric Synthesis of Dimethyl (R)-2-Amino-(*E*)-hept-4-enedioates by the Bislactim Ether Method

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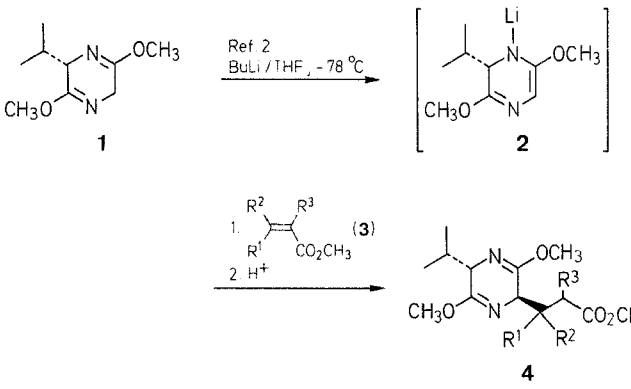
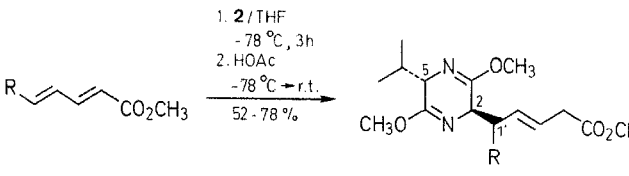
An asymmetric synthesis of (virtually enantiomerically and diastereomerically pure) dimethyl (2*R*, 3?)-2-amino-(*E*)-heptene-1,7-dioates of type **9** is described.

As reported recently,[2,3] the Michael addition of the lithiated bislactim ether **2** of cyclo-(L-Val-Gly) to methyl acrylates **3** proceeds with an exceptionally high degree of asymmetric induction [(2*R*,5*S*):(2*S*,5*S*) > 150:1] to give good yields of Michael adducts **4**, which are precursors of dimethyl (*R*)-glutamates.



1 2 4

Methyl 2,4-pentadienoates **5** react with **2** regioselectively in an 1,6-addition and again with an outstanding degree of diastereoselectivity. Out of four possible diastereomers of **6** virtually only one is formed (Table 1). In the ^{1}H-NMR and ^{13}C-NMR spectra only one isomer is detectable. The *trans* relation of the substituents at the heterocyclic ring, i.e., the (2*R*,5*S*)-configuration of **6**, follows from $^5J_{H\text{-}2/H\text{-}5}$ of ca. 3.5 Hz in the ^{1}H-NMR spectrum (typical for the *trans* relation between H-2 and H-5 in the bislactim ether system). Likewise, the *trans* configuration of the double bond was deduced from $^3J_{H\text{-}2'/H\text{-}3'}$ of ca. 15.5 Hz. Unfortunately, the configuration of the 1'-ste reocenter has not yet been established.[4]



5 a-d 6 a-d

5, 6	a	b[a]	c	d
R	H	CH_3	C_6H_5	4-pyridyl

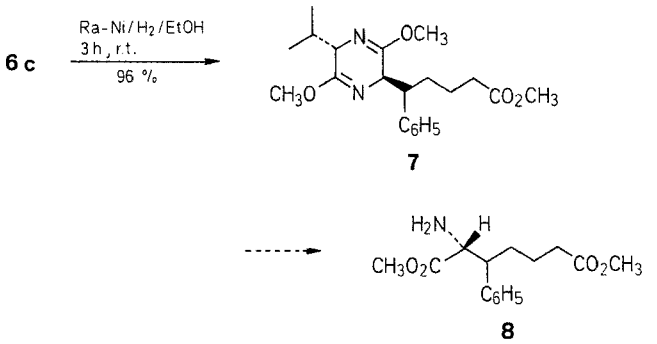
[a] ethyl ester

Table 1. Methyl 5-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl)-3-pentenoates **6** Prepared

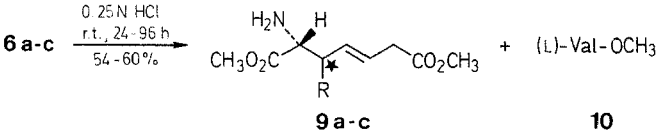
6	Yield (%)	Molecular Formula[a]	de (C-2)	(2*R*,1'?) : (2*R*,1'?)
a	52	$C_{15}H_{24}N_2O_4$ (296.4)	>98[b]	–
b	78	$C_{17}H_{28}N_2O_4$ (324.2)	>98[b]	98.2 : 1.8
c	70	$C_{21}H_{28}N_2O_4$ (372.5)	>98[b]	>99 : 1[b]
d	68	$C_{20}H_{27}N_3O_4$ (373.5)	>98[b]	>99 : 1[b]

[a] Satisfactory microanalyses obtained: C ±0.20, H ±0.09; except for **6d**.
[b] Only one diastereomer detectable by GC/MS and ^{13}C-NMR.

The side chain of **6** can be subjected to various transformations due to the presence of a double bond or an ester group. In one case, namely **6c**, the double bond was hydrogenated using Raney nickel/hydrogen to give the bislactim ether **7** with the saturated side chain. This is the precursor of dimethyl (2*R*,3?)-2-amino-3-phenyl-1,7-heptanedioate **8**.



7 8



9 a-c 10

Table 2. Dimethyl (*R*)-2-Amino-(*E*)-4-heptene-1,7-dioates **9** Prepared

Product	R	Hydrolysis Time (h)	Yield (%)	bp (°C)/ Torr[a]	Molecular Formula[b]	de (C-3)
9a	H	24	60	130/0.01	$C_9H_{15}NO_4$ (201.2)	–[c]
9b[d]	CH_3	48	54	130/0.01	$C_{11}H_{19}NO_4$ (229.3)	>95
9c	C_6H_5	96	58	150/0.01	$C_{15}H_{19}NO_4$ (277.3)	>95

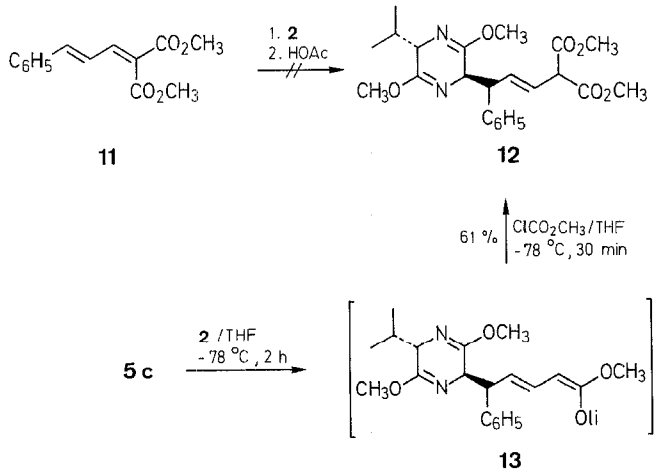
[a] Bulb-to-bulb distillation.
[b] Satisfactory microanalyses obtained: C +0.17, H +0.11.
[c] ee > 95%. $[\alpha]_D^{20}$ – 4.5 (*c* = 2, H_2O).
[d] 7-Ethyl ester.

Table 3. Characteristic Spectral Data for Compounds **6** and **9**

Product	^{1}H-NMR ($CDCl_3$/TMS)[a], δ (J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[b], δ
6a	0.67, 1.03 [2d, 6H, $^3J = 7$, $(CH_3)_2CH$]; 2.16–2.36 [m, 1H, $(CH_3)_2CH$]; 2.52 (ddd, 2H, $^3J = 7$, $^3J = 5$, $^4J = 1$, 1′-CH_2); 3.02 (dd, 2H, $^3J = 7$, $^4J = 1$, 4′-CH_2); 3.66, 3.68, 3.69 (3s, 9H, 3- and 6-OCH_3, CO_2CH_3); 3.88 (dd, 1H, $^3J = 3.5$, $^5J = 3.5$, H-5); 4.10 (dt, 1H, $^3J = 5$, $^5J = 3.5$, 2-H); 5.45, 5.60 (2dtt, 2H, $^3J = 15.5$, $^3J = 7$, $^4J = 1$, 2′-H, 3′-H)	16.53, 19.09 [$(CH_3)_2CH$]; 31.58 [$(CH_3)_2CH$]; 37.20 (1′-CH_2); 38.10 (4′-CH_2); 51.71, 52.32, 52.43 (3- and 6-OCH_3, CO_2CH_3); 55.37, 60.67 (2- and 5-CH); 125.18, 129.44 (2′- and 3′-CH); 163.02, 163.88 (C-3, C-6); 172.24 (CO_2CH_3)
6b	0.65, 1.03 [2d, 6H, $^3J = 7$, $(CH_3)_2CH$]; 1.16 (d, 3H, $^3J = 7.5$, 1″-CH_3); 1.24 (t, 3H, $^3J = 7$, CH_3CH_2); 2.14–2.34 [m, 1H, $(CH_3)_2CH$]; 2.83 (ddq, 1H, $^3J = 3$, $^4J = 1$, $^3J = 7.5$, 1′-CH); 2.96 (dd, 2H, $^3J = 7$, $^4J = 1$, 4′-CH_2); 3.68, 3.69 (2s, 6H, 3- and 6-OCH_3); 3.84 (dd, 1H, $^3J = 3.5$, $^5J = 3.5$, H-5); 3.97 (dd, 1H, $^3J = 3$, $^5J = 3.5$, H-2); 4.12 (q, 2H, $^3J = 7$, CH_3CH_2); 5.31 (ddt, 1H, $^3J = 15.5$, $^3J = 7.5$, $^4J = 1$, 2′-CH); 5.52 (dtd, 1H, $^3J = 15.5$, $^3J = 7$, $^4J = 1$, 3′-CH)	14.03, 16.33, 16.55 [$(CH_3)_2CH$, 1″-CH_3]; 18.91 (CH_3CH_2O); 31.33 [$(CH_3)_2CH$]; 38.20 (4′-CH_2); 40.09 (1′-CH); 52.03, 52.17 (3- and 6-OCH_3); 60.19, 60.23 (2- and 5-CH); 60.31 (CH_3CH_2O); 122.72, 134.73 (2′- and 3′-CH); 162.62, 163.69 (C-3, C-6); 171.61 (CO)
6c	0.62, 0.99 [2d, 6H, $^3J = 7$, $(CH_3)_2CH$]; 2.12–2.30 [m, 1H, $(CH_3)_2CH$]; 3.04 (dd, 2H, $^3J = 7$, $^4J = 1$, 4′-CH_2); 3.66, 3.70, 3.73 (3s, 9H, 3- and 6-OCH_3, CO_2CH_3); 3.99 (dd, 1H, $^3J = 8.5$, $^3J = 3$, 1′-CH); 4.30 (dd, 1H, $^3J = 3.5$, $^5J = 3.5$, H-5); 5.64 (dtt, 1H, $^3J = 15.5$, $^3J = 7$, $^4J = 1$, 3′-CH); 5.82 (ddd, 1H, $^3J = 15.5$, $^3J = 8.5$, $^4J = 1$, 2′-CH); 7.2–7.46 (m, $5H_{arom}$)	16.49, 19.07 [$(CH_3)_2CH$]; 31.43 [$(CH_3)_2CH$]; 38.03 (4′-CH_2); 51.67, 52.31, 52.48 (3- and 6-OCH_3, 1′-CH); 60.26, 60.97 (2- and 5-CH); 124.53, 132.46 (2′- and 3′-CH); 126.49, 128.03, 128.71, 141.53 (C_6H_5); 161.96, 164.17 (C-3, C-6); 171.93 (CO)
6d	0.64, 1.02 [2d, 6H, $^3J = 7$, $(CH_3)_2CH$]; 2.14–2.32 [m, 1H, $(CH_3)_2CH$]; 3.06 (dd, 2H, $^3J = 4.5$, $^4J = 1$, 4′-CH_2); 3.67, 3.74 (2s, 9H, 3- and 6-OCH_3, CO_2CH_3); 3.83 (dd, 1H, $^3J = 3.5$, $^4J = 1$, H-5); 3.96–4.05 (m, 1H, 1′-CH); 4.31 (dd, 1H, $^3J = 3$, $^5J = 3.5$, H-2); 5.64–5.71 (m, 2H, 2′- and 3′-CH); 7.36 (dd, 2H, $^3J = 5$, $^4J = 1.5$, 2″- and 6″-CH); 8.55 (dd, 2H, $^3J = 5$, $^4J = 1.5$, 3″- and 5″-CH)	16.53, 19.01 [$(CH_3)_2CH$]; 31.66 [$(CH_3)_2CH$]; 37.87 (4′-CH_2); 50.57, 51.71, 52.41, 52.48 (3- and 6-OCH_3, CO_2CH_3, 1′-CH); 59.92, 60.42 (2′- and 5′-CH); 123.87 (2″- and 6″-CH); 125.94, 130.53 (2′- and 3′-CH); 149.31 (3″- and 5″-CH); 150.58 (C-1″); 161.20, 164.37 (C-7, C-6); 171.51 (CO)
9a	1.68 (s, 2H, NH_2); 2.30–2.60 (m, 2H, 3-CH_2); 3.09 (dd, 2H, $^3J = 7$, $^4J = 1$, 6-CH_2); 3.56 (dd, 1H, $^3J = 7$, $^3J = 5$, 2-CH); 3.69, 3.72 (2s, 6H, 1- and 7-CO_2CH_3); 5.53, 5.71 (2dtt, 2H, $^3J = 15.5$, $^3J = 7$, $^4J = 1$, 4- and 5-CH)	37.75, 37.80 (2- and 6-CH_2); 51.85, 52.03, 53.99 (2-CH, 1- and 7-CO_2CH_3); 126.00, 129.15 (4- and 5-CH); 172.13, 175.51 (1- and 7-CO)
9b	1.09 (d, 3H, $^3J = 7$, CH_3CH); 1.26 (t, 3H, $^3J = 7$, 3H, CH_3CH_2O); 1.7 (s, 2H, NH_2); 2.54–2.70 (m, 1H, 3-CH); 3.05 (dd, 2H, $^3J = 6.5$, $^4J = 1$, 6-CH_2); 3.32 (d, $^3J = 8.5$, 1H, 2-CH); 3.73 (s, 3H, CO_2CH_3); 4.14 (q, 2H, $^3J = 7$, CH_3CH_2O–); 5.47 (ddt, 1H, $^3J = 15.5$, $^3J = 7.5$, $^4J = 1$, 4-CH); 5.67 (dtd, 1H, $^3J = 15.5$, $^3J = 6.5$, $^4J = 1$, 5-CH)	14.20 (CH_3CH_2O); 16.97 (CH_3CH); 38.04 (6-CH_2); 41.00 (3-CH); 51.90 (2-CH); 59.25 (CO_2CH_3); 60.66 (CH_3CH_2O); 124.18, 134.38 (4- and 5-CH); 171.78, 175.24 (1- and 7-CH)
9c	1.64 (s, 2H, NH_2); 3.11 (dd, $^3J = 6.5$, $^4J = 1$, 2H, 6-CH_2); 3.56, 3.69 (2s, 6H, 1- and 7-CO_2CH_3); 3.66 (d, 1H, $^3J = 6.5$, 2-CH); 5.62 (dtd, 1H, $^3J = 15.5$, $^3J = 6.5$, $^4J = 1$, 4-CH); 7.18–7.40 (m, $5H_{arom}$)	37.72 (6-CH_2); 51.81 (1- and 7-CO_2CH_3); 53.51 (2-CH); 59.69 (3-CH); 125.76, 132.02 (4- and 5-CH); 126.93, 127.93, 128.56, 140.44 (C_6H_5); 171.87, 174.22 (1- and 7-CO)

[a] Recorded on a XL 200 spectrometer.
[b] Recorded on a XL 200 spectrometer.

Upon hydrolysis, the bislactim ethers **6** furnish the dimethyl (*R*)-2-amino-(*E*)-4-heptene-1,7-dioates **9**, that are enantiomerically and diastereomerically pure (determined with Eu(TFC)$_3$ in the ^{1}H-NMR spectrum and by ^{13}C-NMR spectroscopy).



The bislactim ether adduct **12** could not be prepared by 1,6-addition of **2** to dimethyl 3-phenylpropenylidenemalonate (**11**). It was obtained by trapping the enolate **13** with methyl carbonochloridate **14** to give the dicarboxylate **12** in 61% yield (after purification by chromatography). As expected, only one diastereomer of **12** was detectable in the NMR spectra.

The bislactim ether **1** was prepared according to the literature[5] or purchased from Merck-Schuchardt.[6] All distillations were performed on a Kugelrohr apparatus. Flash chromatography was performed with ca. 80 g of silica gel (E. Merck, 0.040–0.063 mm, 230–400 mesh ASTM).

Methyl 5-[2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl)-(*E*)-3-pentenoates 6; General Procedure:

A 1.6 M solution of BuLi in hexane (2.5 mL, 4.0 mmol) is added by syringe at −78 °C to a solution of (*S*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (**1**; 0.736 g, 4.0 mmol) in THF (10 mL). Stirring is continued at −78 °C for 10 min (formation of **2**). Then a solution of the appropriate methyl 2,4-pentadienoate **5** (4.0 mmol) in THF (5 mmol) is added dropwise at −78 °C. The mixture is stirred for an additional 3 h at −78 °C and then AcOH (0.240 g, 4.0 mmol) is added at the same temperature. The mixture is allowed to warm to room temperature, the solvent is removed *in vacuo*, and the residue dissolved in ether (10 mL). The ether solution is shaken with water (5 mL) and the aqueous layer is

extracted with ether (3 × 10 mL). The organic solution is dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The crude compounds **6** were purified by flash-chromatography: for **6a** ($R_f = 0.3$) and **6c** ($R_f = 0.27$) ether/petroleum ether, 1:3; for **6d** ($R_f = 0.15$) EtOAc/petroleum ether, 2:3 or by distillation (**6b**, bp 130 °C/0.01 Torr). With **6a**, the bis addition product of **5a** to the enolate of **6a** is formed as by-product [$R_f = 0.20$ (ether/petroleum ether)]. Amounts of **5** used: **5a:** 0.448 g, **5b:** 0.560 g, **5c:** 0.752 g, **5d:** 0.756 g.

Methyl 5-[(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]-5-phenylpentanoate 7:

A solution of **6c** (0.745 g; 2.0 mmol) in dry EtOH (5 mL) is added to a suspension of neutral (pH 7–8) Raney Ni (2 g) in EtOH (20 mL), and the resultant mixture is stirred for 3 h at room temperature. The metal powder is filtered, and the solvent removed *in vacuo*. To remove traces of metal powder, the crude product is filtered through silica gel with ether (250 mL) as eluent. The solvent is evaporated *in vacuo* to give **7** as an oil; yield: 0.718 g (96%).

$C_{21}H_{30}N_2O_4$	calc.	C 67.36	H 8.07
(374.5)	found	67.21	8.16

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 0.60$, 0.97 (2 d, 6 H, $^3J = 7$ Hz, $(C\underline{H}_3)_2CH$); 1.38–2.40 (m, 7 H, 2'-, 3'- and 4'-CH_2, $(CH_3)_2C\underline{H}$); 3.25 (ddd, 1 H, $^3J = 10.5$, 3.5, 3.5 Hz, 1'-CH); 3.51 (dd, 1 H, $^3J = 3.5$ Hz, $^5J = 3.5$ Hz, H-5); 3.62, 3.72, 3.74 (3 s, 9 H, 3- and 6-OCH_3, CO_2CH_3); 4.17 (dd, 1 H, $^3J = 3.5$ Hz, $^5J = 3.5$ Hz, H-2); 7.14–7.44 (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 16.48$, 19.06 ($(\underline{C}H_3)_2CH$); 23.07 (3'-CH_2); 31.36 ($(CH_3)_2\underline{C}H$); 29.49, 33.98 (2'- and 4'-CH_2); 48.62, 51.39, 52.38, 52.46 (1'-CH, 3- and 6-OCH_3, $CO_2\underline{C}H_3$); 60.28, 60.67 (2'- and 5'-CH); 126.59, 127.94, 129.07, 141.39 (C_6H_5); 162.51, 164.02 (C-3, C-6); 173.87 (CO).

Dimethyl (2*R*,3?)-2-Amino-(*E*)-4-heptene-1,7-dioates 9: General Procedure:

A suspension of **6** (3.0 mmol) in 0.25 N HCl (24 mL, 6.0 mmol) is vigorously stirred for 24–96 h at room temperature. The solvent is evaporated *in vacuo* at room temperature, and the residue dissolved in water (≈ 5 mL). The water solution is extracted with ether (2 × 10 mL), which is discarded. Ether (20 mL) is added to the water solution, and then conc. ammonia is added with shaking until pH 9–10 is reached. The aqueous layer is extracted with ether (2 × 20 mL). The combined ether solution is dried ($MgSO_4$), and the solvent evaporated *in vacuo*. Then, methyl L-valinate is removed by bulb-to-bulb distillation (50 °C/0.01 Torr), and product **9** is distilled (bp see Table 2).

Dimethyl 3-{[(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]-3-phenyl-(*E*)-1-propenyl}malonate (12):

A 1.6 M solution of BuLi in hexane (3.44 mL, 5.5 mmol) is added by syringe at −78 °C to a solution of **1** (1.012 g, 5.5 mmol) in THF (10 mL). Stirring is continued at −78 °C for 10 min. Then a solution of **5c** (1.035 g, 5.5 mmol) in THF (5 mL) is added dropwise at −78 °C. After 2 h at −78 °C, a solution of $ClCO_2Me$ (1.04 g, 11.0 mmol) in THF (5 mL) is added at −78 °C. Stirring is continued at the same temperature for another 30 min, then an aqueous solution of phosphate buffer (pH 7; 15 mL) is added and the mixture allowed to warm to room temperature. The solvent is evaporated *in vacuo* and the residue shaken with water/ether (1:2, 30 mL). The aqueous layer is extracted with ether (3 × 20 mL). The organic layer is dried ($MgSO_4$) and the ether removed *in vacuo*. The crude product is purified by chromatography (EtOAc/petroleum ether, 1:6) to give 12 as an oil; yield: 1.44 g (61%) (only one diastereomer detectable by ^{1}H- and ^{13}NMR-spectroscopy).

$C_{23}H_{30}N_2O_6$	calc.	C 64.17	H 7.02
(430.5)	found	64.33	7.17

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 0.62$, 1.00 (2 d, 6 H, $^3J = 7$ Hz, $(C\underline{H}_3)_2CH$); 2.10–2.34 (m, 1 H, $(CH_3)_2C\underline{H}$); 3.69, 3.72, 3.74 (3 s, 12 H, 3- and 6-OCH_3, $(CO_2C\underline{H}_3)_2CH$); 4.03 (d, 1 H, $^3J = 8.5$ Hz, 4'-CH); 4.31 (dd, 1 H, $^3J = 3.5$ Hz, $^5J = 3.5$ Hz, H-2); 5.74, 5.90 (2 dd, 2 H, $^3J = 15.5$, 8.5 Hz, 2'- and 3'-C$\underline{H}$); 7.18–7.41 (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 16.48$, 19.08 [$(\underline{C}H_3)_2CH$]; 31.40 ($(CH_3)_2\underline{C}H$); 51.46, 52.30, 52.49, 52.53, 52.63 (3- and 6-OCH_3, $(CO_2\underline{C}H_3)_2CH$, 1'-CH); 55.36 (4'-CH); 60.21, 60.91 (2- and 5-CH); 124.01, 134.70 (2'- and 3'-CH); 126.62, 128.08, 128.72, 140.85 (C_6H_5); 161.58, 164.30 (C-3, C-6); 168.25, 168.33 ($\underline{C}O_2CH_3)_2CH$).

Dedicateded to Professor H. Dörfel on the occasion of his 60th birthday.

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(1) Part XXXVI: Schöllkopf, U., Schröder, J. *Liebigs Ann. Chem.* **1988**, 87.

(2) Schöllkopf, U., Pettig, D., Busse, U., Egert, E., Dyrbusch, M. *Synthesis* **1986**, 737.
Hartwig, W., Born, L. *J. Org. Chem.* **1987**, *52*, 4352.
Hartwig, W., *Ger. Offen. Appl.* 3616989 (1986).

(3) For reviews on the bislactimether method for the asymmetric synthesis of amino acids, see:
Schöllkopf, U. *Pure Appl. Chem.* **1983**, 55, 1799; *Chem Scripta* **1985**, *25*, 105.

(4) The configuration will be determined by X-ray analysis as soon as a crystalline compound **9** is available.

(5) Schöllkopf, U., Groth, U., Deng, C. *Angew. Chem.* **1981**, *93*, 793; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798.

(6) Compounds **1** and *ent*-**1** are available from Merck-Schuchardt, D-8011 Hohenbrunn.
Cf. *MS-Info* 85/14.