Efficient Entry to Amino Sugars and Derivatives via Asymmetric Organocatalytic Mannich Reactions

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Dedicated to Professor Martin F. Semmelhack on the occasion of his 65th birthday

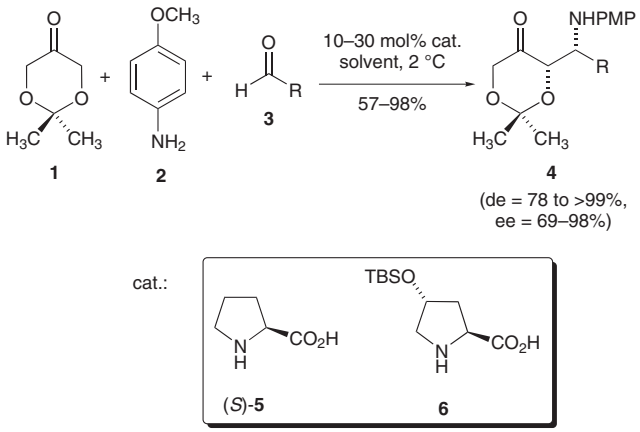
Abstract: An efficient biomimetic C_3+C_n entry to amino sugars and derivatives via a direct asymmetric organocatalytic Mannich methodology employing 2,2-dimethyl-1,3-dioxan-5-one as a dihydroxyacetone phosphate equivalent and *N*-PMP or *N*-Boc protected imines has been developed. The Mannich bases were obtained in high diastereo- and enantiomeric excesses (78% to >99% de, 81–98% ee) and were further elaborated using diastereoselective reduction protocols, as well as via diastereoselective direct reductive amination reactions.

Key words: organocatalysis, Mannich reaction, amino sugars, asymmetric synthesis, reductive amination

The rapidly developing area of organocatalysis has attracted much attention during the past few years and in particular the development of asymmetric reactions catalyzed by proline.[1] The Mannich reaction represents a powerful tool of organic synthetic chemistry and has found broad application in the preparation of synthetic building blocks, especially aimed towards the synthesis of natural products and biologically active compounds.[2,3] The direct proline-catalyzed asymmetric three-component Mannich reaction was first reported by List[4] and Barbas.[5,6] Although proline has been used as an efficient organocatalyst,[1,7] its derivatives have also been studied and successfully employed in a number of cases.[8] Amino sugars comprise a class of carbohydrates where one or more hydroxyl groups have been replaced by amino groups. They are found as components of glycoproteins, glycolipids, aminoglycosides, as well as numerous biologically active secondary metabolites.[9] They play important physiological roles and are of potential interest for the development of novel drugs.[10] As a result, there is a wide range of approaches for the preparation of amino sugars. The major part of these use naturally occurring carbohydrates and involve several protecting group manipulations, as well as oxidation–reduction steps.[11] Alternatively, a linear sequence is employed, which generally requires numerous reaction steps.[12] We recently reported the development of a diastereo- and enantioselective organocatalytic Mannich reaction which paves the way to selectively protected amino sugars and their unnatural derivatives in one step[13,14] and the current article is aimed at enlarging the scope of this methodology. Thus, the existing methodology has been broadened to incorporate an organocatalytic Mannich reaction employing *N*-Boc imines, as well as further elaboration of the resulting Mannich bases via diastereoselective reduction and direct reductive amination reactions.

Initially, the three-component organocatalytic Mannich reaction between the dihydroxyacetone equivalent 2,2-dimethyl-1,3-dioxan-5-one (**1**),[15] *p*-anisidine (**2**) and various aldehydes **3** was investigated (Scheme 1). The observed *syn* configuration of the products **4** has been previously confirmed.[13a]

A wide range of aldehydes was screened and to our delight the corresponding Mannich bases were obtained in moderate to excellent yields and with good to excellent diastereo- and enantioselectivities employing proline (*S*)-**5** and the TBS-protected hydroxy proline **6** as catalysts. We could show that **6** is often the catalyst of choice regarding stereoselectivity and yield (Table 1).



Scheme 1 Direct organocatalytic Mannich reactions via *N*-*p*-methoxyphenyl imines

In the case of α-substituted aldehydes bearing a stereogenic center (**4d**–**h**), (*S*)-proline was found to be the appropriate catalyst for *R*-configured substrates, whereas (*R*)-proline was employed in the case of *S*-configured compounds.

In several cases, the organocatalysis was also performed at different temperatures in an attempt to optimize the selectivities observed. Despite the fact that initially there seemed to be a trend of decreasing selectivity at lower

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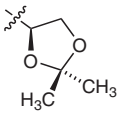
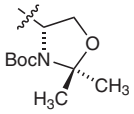
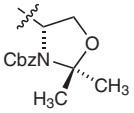
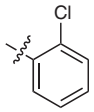
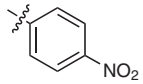
Table 1 Catalytic Asymmetric Three-Component Mannich Reaction of Dioxanone **1** with *p*-Anisidine (**2**) and Aldehydes **3** To Give the Corresponding β-Aminoketones **4**[a]

4	R	Cat. (mol%)	Yield (%)[b]	Solvent	Water (equiv)	de (%)[c]	ee (%)[d]
a[e]	$CH(OCH_3)_3$	(*S*)-**5** (30)	91	DMF	4	>99[d]	98
a[e]	$CH(OCH_3)_3$	**6** (20)	98	DMF	4	>99[d]	93
b	CO_2Et	(*S*)-**5** (10)	91	DMF	3	96	98
b	CO_2Et	**6** (20)	94	DMF	–	96	95
c	CO_2Bn	(*S*)-**5** (30)	68	NMP	–	96	96
c	CO_2Et	**6** (20)	70	NMP	3	96	93
d	CH_2OBn	(*S*)-**5** (30)	94	NMP	3	60[d]	82
d	CH_2OBn	**6** (20)	69	MeCN	5	88[d]	96
e		(*S*)-**5** (30)	57	DMF	–	80 (≥96)[f]	98[g]
f		(*R*)-**5** (30)	67	DMF	–	96	96[g]
g		(*R*)-**5** (30)	63	DMF	–	96	96[g]
h		(*S*)-**5** (30) **6** (20)	83 85	MeCN MeCN	– –	86 96	96[g] 96[g]
i		(*S*)-**5** (10) **6** (20)	67 70	NMP NMP	– 3	96 96	51 81
j		(*S*)-**5** (30) **6** (20)	75 96	DMF MeCN	2 5	60 78	67 87
k		**6** (20)	96	MeCN	5	78[d]	78

[a] General reaction conditions: dioxanone **1** (0.77 mmol), *p*-anisidine (**2**; 0.42 mmol), aldehyde **3** (0.38 mmol), catalyst (10−30 mol%), solvent (1 mL), 2 °C, 25 d.
[b] Yields of **4** after flash chromatography on silica gel.
[c] Determined by ^1H NMR and ^{13}C NMR spectroscopy.
[d] Determined by HPLC on chiral stationary phases (Daicel Chiralpak AD, Daicel Chiralcel OD).
[e] Full characterization of **4a** was previously reported.[13a,]
[f] After flash chromatography on silica gel.
[g] Based on the ee value of the corresponding aldehydes **3**.

temperatures,[13a] following further investigation, the variation of selectivity with temperature seems to be substrate-dependent (Table 2).

In the case of **4d**, for instance, the results collected from performing the reaction in NMP at three different temperatures support a downward trend with decreasing temperature, whereas in the case of **4k**, the data obtained from carrying out the reaction in two different solvents (DMF and NMP) and at three different temperatures support the opposite.

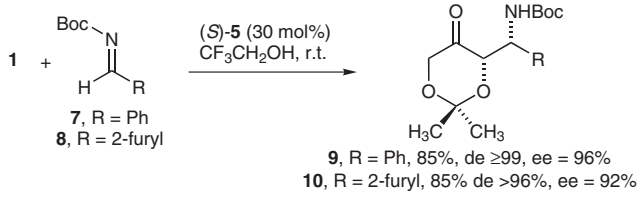
Due to their reactivity and pure *E* geometry, PMP imines have so far dominated this area of research. The use of differently protected imines, however, would also be of interest and we are pleased to report that equally satisfactory

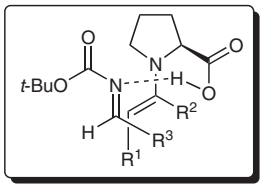
Table 2 Variation of Diastereomeric and Enantiomeric Excess Values with Increasing Temperature

4[a]	Solvent	–10 °C	2 °C	25 °C
		de, ee (%)	de, ee (%)	de, ee (%)
d	NMP	46, 49	76, 80	55, 81
k	DMF	66, 29	60, 15	70, 12
k	NMP	71, 60	72, 60	76, 45

[a] Compound (*S*)-**5** was used as organocatalyst.

results were obtained in the case of (*E*)-Boc imines **7** and **8**[16] (Scheme 2). To the best of our knowledge this is the first example of an organocatalytic Mannich reaction employing Boc imines. We recently reported a concise synthesis of (+)-polyoxamic acid starting from the Mannich base **10**.[13b] The use of Boc imines complements that of PMP imines since the Boc group can be easily removed under acidic instead of oxidative conditions. To our delight the stereoselectivities are nearly perfect and we obtained only the *syn*-Mannich product. We therefore propose the transition state which is depicted in Scheme 2 and is based on List's model.[4]

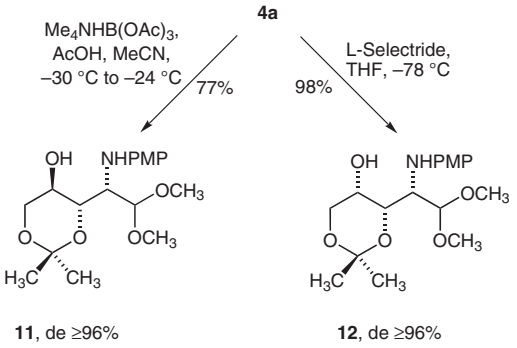




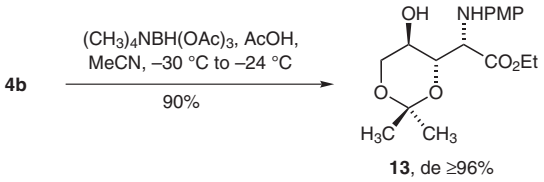
Scheme 2 Organocatalytic Mannich reaction using Boc imines

Further elaboration of the Mannich products into the corresponding β-amino alcohols is also possible as exemplified for **4a**, **4b** and **9**. In the case of **4a** (Scheme 3) it was possible to access both diastereoisomers (*syn*[17] and *anti*) with high selectivities, whereas with **4b** only the *anti* isomer could be selectively obtained (Scheme 4). These β-aminoalcohols **11** and **12** represent the selectively and orthogonal protected 2-amino-2-deoxyaldopentoses 2-amino-2-deoxy-D-arabinose (**11**) and 2-amino-2-deoxy-L-xylose (**12**), whereas **13** constitutes a protected 4-*epi*-(+)-polyoxamic acid.

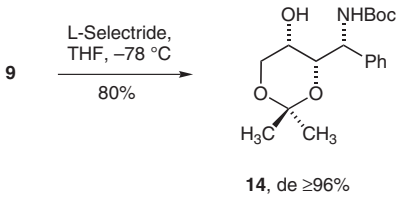
In addition, we have also carried out the diastereoselective reduction of the Mannich base **9**. The *syn* β-aminoalcohol **14** was also obtained with high diastereoselectivity (Scheme 5). All attempts for an *anti* selective reduction of



Scheme 3 Diastereoselective *syn*- and *anti*-reduction of **4a**



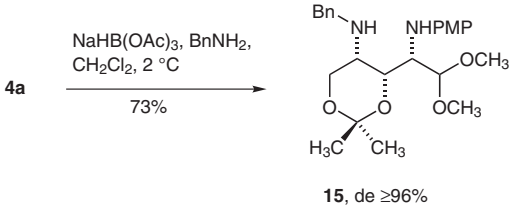
Scheme 4 Diastereoselective *anti*-reduction of **4b**



Scheme 5 Diastereoselective *syn*-reduction of **9**

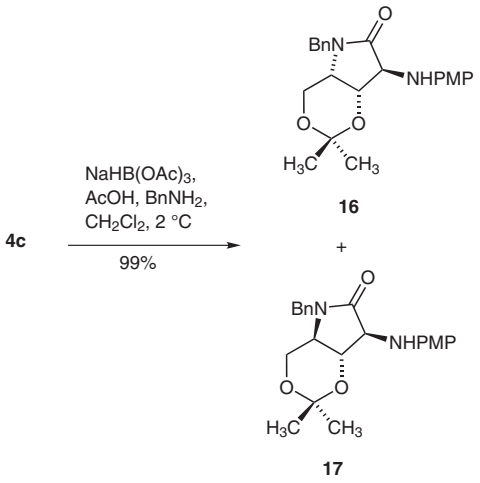
9 using $Me_4NHB(OAc_3)$ failed and resulted in quantitative recovery of the starting material.

Alternatively, the derivatization of the Mannich products is possible, e.g. via diastereoselective direct reductive amination, as illustrated for **4a** and **4c** (Schemes 6 and 7). The direct reductive amination was carried out using $NaHB(OAc)_3$, $BnNH_2$ and acetic acid. This protocol includes an in situ imine formation, followed by a highly chemo- and diastereoselective reduction of the imine.[18] The diamine **15** also represents a protected aminosugar, in this case the protected 2,4-diamino-2,4-dideoxy-L-xylose.



Scheme 6 *syn*-Selective direct reductive amination of **4a**

Interestingly, the direct reductive amination of the **4c** was followed by in situ cyclization to afford a 10:1 mixture of **16** and **17**, which can be easily separated by column chromatography.



Scheme 7 Diastereoselective direct reductive amination of **4c**, followed by in situ lactamization

In conclusion, the scope of a direct asymmetric organocatalytic Mannich reaction using 2,2-dimethyl-1,3-dioxan-5-one as a dihydroxyacetone equivalent and PMP-imines derived from structurally diverse aldehydes has been successfully enlarged via diastereoselective reduction and direct reductive amination reactions. Furthermore, initial examples of this methodology adapted to Boc imines have also given excellent results. Overall, this biomimetic C_3+C_n methodology represents a concise and efficient way to access amino sugars and derivatives of this important class of biomolecules.

All solvents were dried by conventional methods. Starting materials and reagents were purchased from commercial suppliers and were used without further purification unless otherwise stated. THF was freshly distilled from Na-Pb alloy under Ar. CH_2Cl_2 and MeCN were freshly distilled from CaH_2 under Ar. AcOH was distilled from CrO_3 under Ar. Preparative column chromatography was performed using silica gel 60, particle size 0.040−0.063 mm (230−240 mesh, flash). Analytical TLC was carried out employing silica gel 60 F254 plates. Visualization of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or staining using acidic ammonium molybdate. Optical rotation values were measured on a Perkin−Elmer P241 polarimeter. Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were recorded on a Finnigan SSQ7000 spectrometer. High-resolution mass spectra were recorded on a Finnigan MAT95 spectrometer. IR spectra were measured on a Perkin−Elmer FT-IR 1760 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury 300, Inova 400 or Unity 500 spectrometers with tetramethylsilane as the internal standard and at ambient temperature unless otherwise stated. Analytical HPLC and GC analyses were performed on Hewlett-Packard 1100 Series and Varian CP 3800 Series chromatographs, respectively. All racemic samples were obtained according to GP 1 using equal amounts of (*S*)- and (*R*)-proline. Compounds **4e**,[19] **4f**,[20] **4g**,[21] **4h**[22] and **6**[23] were synthesized by standard procedures.

Organocatalytic Mannich Reaction (4b); General Procedure (GP 1)

To a mixture of ethyl glyoxylate (**3b**; 2.00 mL, 13.50 mmol, 50% solution in toluene) and *p*-anisidine (**2**; 1.66 g, 13.5 mmol) in DMF (135 mL) at 0 °C was added (*S*)-**5** (155 mg, 1.35 mmol), followed by dioxanone **1** (1.76 g, 13.50 mmol). The reaction mixture was stored for 5 d at 2 °C before quenching with a pH 7 phosphate buffer (200 mL). The resulting biphasic mixture was stirred for an additional 15 min at r.t. before addition of Et_2O (200 mL) and separation of the phases. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined extracts were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure, followed by flash chromatography (silica gel, *n*-pentane−Et_2O, 2:1), afforded the desired product **4b** as a slightly yellow oil (4.14 g, 91%); ee = 98% [HPLC analysis: Daicel OD at r.t., *n*-heptane−*i*-PrOH = 80:20 (0.5 mL/min), t_1 = 10.5 min (minor), t_2 = 13.3 min (major)]; $[\alpha]_D^{24}$ –88.0 (*c* = 1.00, $CHCl_3$).

IR ($CHCl_3$): 3395, 2990, 2940, 2838, 1845, 1798, 1744, 1714, 1652, 1620, 1575, 1513, 1463, 1367, 1280, 1231, 1158, 1096, 1032, 968, 906, 828, 667, 613, 530 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.84 (t, *J* = 7.1 Hz, 3 H), 1.16 (s, 3 H), 1.22 (s, 3 H), 3.31 (s, 3 H), 3.71−3.83 (m, 2 H), 3.92−4.00 (m, 2 H), 4.67 (app t, *J* = 1.8 Hz, 1 H), 4.80 (d, *J* = 2.5 Hz, 1 H), 6.70−6.74 (m, 2 H), 6.76−6.80 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.1 (CH_3), 23.1 (CH_3), 24.3 (CH_3), 55.0 (CH_3), 59.7 (CH), 61.1 (CH_2), 67.1 (CH_2), 77.0 (CH), 100.5 (C), 114.9 (CH), 117.3 (CH), 141.4 (C), 154.1 (C), 171.0 (C), 205.3 (C).

MS (CI, methane): *m*/*z* = 338 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.37; H, 6.75; N, 4.24.

4d

According to GP 1, dioxanone **1** (200 mg, 1.54 mmol), benzoyloxyacetaldehyde (**3d**; 114 mg, 0.77 mmol), *p*-anisidine (**2**; 102 mg, 0.84 mmol) and (*S*)-**6** (36 mg, 0.16 mmol) were reacted in MeCN containing H_2O (8 mL, 5 equiv) for 40 h. After purification by column chromatography (silica gel, *n*-pentane−Et_2O = 2:1), **4d** was obtained as a colorless solid (226 mg, 77%); mp 51−52 °C; ee = 96% [HPLC analysis: Daicel OD at r.t., *n*-heptane−*i*-PrOH = 80:20 (0.8 mL/min); t_1 = 10.6 min (major), t_2 = 13.5 min (minor)]; $[\alpha]_D^{22}$ –94.3 (*c* = 0.95, $CHCl_3$).

IR ($CHCl_3$): 3380, 3030, 2989, 2937, 2897, 2864, 1514, 1455, 1377, 1234, 1097, 1035, 860, 823, 749, 699 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6): δ = 1.45 (s, 3 H), 1.50 (s, 3 H), 3.50 (t, *J* = 9.0 Hz, 1 H), 3.61 (dd, *J* = 4.3, 9.0 Hz, 1 H), 3.74 (s, 3 H), 3.97 (d, *J* = 16.8 Hz, 1 H), 4.21 (dd, *J* = 1.5, 16.8 Hz, 1 H), 4.46 (d, *J* = 11.9 Hz, 1 H), 4.56 (d, *J* = 11.9 Hz, 1 H), 4.62 (app s, 1 H), 6,63 (d, *J* = 8.9 Hz, 2 H), 6.74 (d, *J* = 8.9 Hz, 2 H), 7.25−7.35 (m, 5 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 23.2, 24.8 (CH_3), 53.9 (CH), 55.7 (CH_3), 67.3, 67.8, 73.2 (CH_2), 74.2 (CH), 100.4 (C), 114.9 (CH), 115.8 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 137.9 (C), 140.6 (C), 152.7 (C), 208.2 (C).

MS (EI): *m*/*z* = 385 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.48; H, 6.97; N, 3.79.

4e

According to GP 1, dioxanone **1** (400 mg, 3.08 mmol), (*R*)-2,3-*O*-(isopropylidene)-D-glyceraldehyde (**3e**; 300 mg, 2.31 mmol), *p*-anisidine (**2**; 314 mg, 2.54 mmol) and (*S*)-**5** (81 mg, 0.70 mmol) were reacted in DMF (23 mL) for 5 d. After purification by column chromatography (silica gel, *n*-pentane−Et_2O = 2:1), **4e** was obtained as a pale yellow oil (274 mg, 96%); ee = 98% (based on the ee of the starting aldehyde); $[\alpha]_D^{21}$ +3.1 (*c* = 0.79, C_6H_6).

IR ($CHCl_3$): 3380, 2989, 2938, 2894, 2835, 1747, 1514, 1461, 1378, 1229, 1154, 1070, 1041, 896, 826, 758 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.23 (s, 3 H), 1.27 (6 H), 1.43 (3 H), 3.34 (s, 3 H), 3.51 (d, *J* = 10.2 Hz, 1 H), 3.68 (d, *J* = 16.7 Hz, 1 H),

3.82 (dd, *J* = 1.7, 16.7 Hz, 1 H), 3.85 (dd, *J* = 4.9, 8.9 Hz, 1 H), 3.90 (dd, *J* = 4.9, 8.9 Hz, 1 H), 4.00 (m, 1 H), 4.28 (t, *J* = 10.2 Hz, 1 H), 4.75 (s, 1 H), 6.60 (d, *J* = 9.1 Hz, 2 H), 6.69 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 23.0 (CH_3), 24.9 (CH_3), 26.1 (CH_3), 27.3 (CH_3), 55.0 (CH_3), 57.9 (CH), 67.2 (CH_2), 67.3 (CH_2), 75.7 (CH), 75.9 (CH), 100.1 (C), 109.3 (C), 115.0 (CH), 116.2 (CH), 141.0 (C), 153.4 (C), 207.1 (C).

MS (EI, 70 eV): *m*/*z* = 365 $[M]^+$.

Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.82; H, 7.41; N, 3.84.

4f

According to GP 1, dioxanone **1** (600 mg, 4.62 mmol), *N*-Boc-protected (*S*)-Garner aldehyde **3f** (530 mg, 2.31 mmol), *p*-anisidine (**2**; 310 mg, 2.50 mmol) and (*R*)-**5** (81 mg, 0.70 mmol) were reacted in DMF (23 mL) for 5 d. After purification by column chromatography (silica gel, *n*-pentane–Et_2O = 2:1), **4f** was obtained as a pale yellow oil (718 mg, 67%); ee >96% (based on the ee of the starting aldehyde); $[\alpha]_D^{24}$ –4.7 (*c* = 1.35, $CHCl_3$).

IR ($CHCl_3$): 3397, 2980, 2937, 2835, 1748, 1692, 1515, 1463, 1375, 1241, 1172, 1097, 1045, 849, 822, 758 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6, 70 °C): δ = 1.29 (s, 6 H), 1.45 (s, 9 H), 1.48 (s, 3 H), 1.58 (s, 3 H), 3.39 (s, 3 H), 3.70 (dd, *J* = 1.3, 16.8 Hz, 1 H), 3.74 (m, 1 H), 3.87 (d, *J* = 16.8 Hz, 1 H), 4.05 (br, 2 H), 4.26 (d, *J* = 9.3 Hz, 1 H), 4.36 (br, 1 H), 4.83 (d, *J* = 5.2 Hz, 1 H), 6.73 (m, 4 H).

^{13}C NMR (100 MHz, C_6D_6, 70 °C): δ = 23.4 (CH_3), 24.6 (CH_3), 25.2 (CH_3), 27.2 (CH_3), 28.5 (CH_3), 55.3 (CH_3), 55.4 (CH), 60.6 (CH), 64.8 (CH_2), 67.3 (CH_2), 77.2 (CH), 79.9 (C), 94.1 (C), 100.3 (C), 115.3 (CH), 115.5 (CH), 142.2 (C), 152.6 (C), 153.2 (C), 206.1 (C).

MS (EI, 70 eV): *m*/*z* = 464 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{36}N_2O_7$: C, 62.05; H, 7.81; N, 6.03. Found: C, 62.07; H, 7.80; N, 5.84.

4g

According to GP 1, dioxanone **1** (600 mg, 4.62 mmol), (*S*)-Cbz-protected Garner aldehyde **3g** (607 mg, 2.31 mmol), *p*-anisidine (**2**; 314 mg, 2.54 mmol) and (*R*)-**5** (81 mg, 0.70 mmol) were reacted in DMF (23 mL) for 5 d. After purification by column chromatography (silica gel, *n*-pentane–Et_2O = 1:1), **4g** was obtained as a pale yellow oil (725 mg, 63%); ee ≥96% (based on the ee of starting aldehyde); $[\alpha]_D^{24}$ = +31.8 (*c* = 0.79, C_6H_6).

IR ($CHCl_3$): 3396, 2988, 2940, 2882, 2832, 2362, 2335, 1747, 1701, 1515, 1460, 1408, 1378, 1350, 1241, 1158, 1094, 1049, 904, 825, 757, 700 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6, 70 °C): δ = 1.22 (s, 3 H), 1.28 (s, 3 H), 1.46 (s, 3 H), 1.60 (s, 3 H), 3.39 (s, 3 H), 3.67–3.74 (m, 2 H), 3.89 (d, *J* = 16.5 Hz, 1 H), 4.10 (br, 2 H), 4.18 (dd, *J* = 1.7, 9.3 Hz, 1 H), 4.33 (br, 1 H), 4.72 (d, *J* = 5.0 Hz, 1 H), 5.14 (s, 2 H), 6.58–6.69 (m, 4 H), 7.05–7.35 (m, 5 H).

^{13}C NMR (100 MHz, C_6D_6, 70 °C): δ = 22.8 (CH_3), 24.1 (CH_3), 24.8 (CH_3), 26.2 (CH_3), 55.1 (CH_3), 55.2 (CH), 60.3 (CH), 64.7 (CH_2), 66.8 (CH_2), 67.0 (CH_2), 76.5 (CH), 94.2 (C), 99.9 (C), 115.0 (CH), 115.1 (CH), 127.5 (C), 127.8 (CH), 128.1 (CH), 128.3 (CH), 136.6 (C), 141.5 (C), 152.9 (C), 205.8 (C).

MS (EI, 70 eV): *m*/*z* = 498 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{34}N_2O_7$: C, 65.04; H, 6.87; N, 5.62. Found: C, 65.33; H, 7.17; N, 5.94.

4h

According to GP 1, dioxanone **1** (558 mg, 4.29 mmol), (*S*)-2-formylpyrrolidine-1-carboxylic acid benzyl ester (**3h**; 1.00 g, 4.29 mmol) and *p*-anisidine (**2**; 528 mg, 4.29 mmol) were reacted in MeCN (43 mL) in the presence of (*S*)-**6** (210 mg, 0.86 mmol) for 5 d. Purification by flash chromatography (silica gel, *n*-pentane–EtOAc = 85:15) afforded **4h** as a pale yellow oil (1.67 g, 83%); ee ≥96% (based on the ee of the starting aldehyde); $[\alpha]_D^{22}$ +33.5 (*c* = 1.64, $CHCl_3$).

IR ($CHCl_3$): 3389, 2989, 2953, 2885, 2834, 1747, 1695, 1617, 1588, 1513, 1452, 1416, 1377, 1355, 1231, 1098, 1039, 974, 902, 824, 757, 700, 667, 610, 582, 520 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6, 70 °C): δ = 1.28 (s, 7 H), 1.43–1.60 (m, 2 H), 1.81–1.87 (m, 2 H), 3.00–3.06 (m, 1 H), 3.36–3.38 (m, 2 H), 3.39 (s, 3 H), 3.71 (d, *J* = 16.5 Hz, 1 H), 3.91 (d, *J* = 16.5 Hz, 1 H), 4.13 (br, 1 H), 4.34 (br, 1 H), 4.64 (app d, *J* = 4.1 Hz, 1 H), 5.16 (br, 1 H), 6.65 (d, *J* = 8.5 Hz, 2 H), 6.69 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 7.0 Hz, 1 H), 7.16 (br, 2 H), 7.32 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, C_6D_6, 70 °C): δ = 23.4 (CH_3), 24.4 (CH_2), 25.0 (CH_3), 27.8 (CH_2), 46.8 (CH_2), 55.4 (CH_3), 56.4 (CH), 60.9 (CH), 67.0 (CH_2), 67.3 (CH_2), 100.3 (C), 115.3 (CH), 115.8 (CH), 128.3 (CH), 128.5 (CH), 137.6 (C), 142.1 (C), 153.2 (C), 155.2 (C), 206.5 (C).

MS (EI, 70 eV): *m*/*z* = 468 $[M]^+$, 469 $[M + H]^+$.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{26}H_{32}N_2O_6$: 468.2260; found: 468.2260.

4i

According to GP 1, dioxanone **1** (1.21 g, 9.34 mmol), freshly distilled pyridine-2-carbaldehyde (**3i**; 1.00 g, 9.34 mmol) and *p*-anisidine (**2**; 1.15 mmol, 9.34 mmol) were reacted in NMP containing H_2O (3 equiv, 93 mL) in the presence of (*S*)-**6** (458 mg, 1.87 mmol) for 5 d. Purification by flash chromatography (silica gel, *n*-pentane–EtOAc = 80:20) afforded **4i** as a pale yellow solid (2.14 g, 67%); ee = 81% [HPLC analysis: Daicel AD, r.t., *n*-heptane–*i*-PrOH = 90:10 (1 mL/min), t_1 = 16.9 min (minor), t_2 = 25.6 min (major)]; mp 95–98 °C; $[\alpha]_D^{22}$ = –102.4 (*c* = 1.64, $CHCl_3$).

IR (KBr): 3424, 3367, 3057, 2991, 2937, 2866, 2834, 2367, 2344, 1747, 1593, 1513, 1438, 1378, 1328, 1241, 1177, 1098, 1039, 981, 894, 828, 763, 707, 665, 621, 582, 526, 490 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6): δ = 1.03 (s, 3 H), 1.20 (s, 3 H), 3.30 (s, 3 H), 3.82 (d, *J* = 16.8 Hz, 1 H), 4.05 (dd, *J* = 1.5, 16.8 Hz, 1 H), 4.76 (br, 1 H), 5.16 (app t, *J* = 1.7 Hz, 1 H), 5.53 (d, *J* = 1.9 Hz, 1 H), 6.53–6.56 (m, 2 H) 6.57 (d, *J* = 9.1 Hz, 2 H), 6.67 (d, *J* = 9.1 Hz, 2 H), 6.98 (dt, *J* = 1.9, 7.5 Hz, 1 H), 8.42–8.45 (m, 1 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 22.4 (CH_3), 24.4 (CH_3), 54.8 (CH_3), 59.1 (CH), 67.2 (CH_2), 78.5 (CH), 100.1 (C), 114.9 (CH), 115.2 (CH), 121.6 (CH), 121.7 (CH), 135.7 (CH), 140.9 (C), 148.9 (CH), 152.9 (C), 159.9 (C), 206.0 (C).

MS (CI, methane): *m*/*z* = 343 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.33; H, 6.38; N, 8.20.

4j

According to GP 1, dioxanone **1** (200 mg, 1.54 mmol), *o*-chlorobenzaldehyde (**3j**; 108 mg, 0.77 mmol), *p*-anisidine (**2**; 102 mg, 0.84 mmol) and (*S*)-**5** (36 mg, 0.16 mmol) were reacted in DMF containing H_2O (8 mL, 2 equiv) for 40 h. After purification by column chromatography (silica gel, *n*-pentane–Et_2O = 2:1) **4j** was obtained as a pale yellow oil (274 mg, 96%); ee = 87% [HPLC analysis: Daicel OD at r.t., *n*-heptane–*i*-PrOH = 95:5 (0.8 mL/min); t_1 = 9.9 min (major), t_2 = 8.3 min (minor)]; $[\alpha]_D^{21}$ –3.1 (*c* = 0.99, $CHCl_3$).

IR ($CHCl_3$): 3399, 2992, 2937, 2834, 1751, 1514, 1468, 1443, 1379, 1238, 1092, 1039, 823, 757 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.89 (s, 3 H), 1.28 (s, 3 H), 3.25 (s, 3 H), 3.81 (d, *J* = 17.1 Hz, 1 H), 4.02 (dd, *J* = 1.4, 17.1 Hz, 1 H),

4.64 (s, 1 H), 4.75 (s, 1 H), 6.01 (s, 1 H), 5.51−6.62 (m, 4 H), 6.72 (dt, *J* = 1.4, 8.0 Hz, 1 H), 6.85 (dt, *J* = 1.1, 8.0 Hz, 1 H), 7.15 (dd, *J* = 1.1, 8.0 Hz, 1 H), 7.39 (dd, *J* = 1.4, 7.7 Hz, 1 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.3 (CH_3), 24.9 (CH_3), 54.1 (CH_3), 55.0 (CH), 67.4 (CH_2), 78.0 (CH), 100.3 (C), 115.1 (CH), 115.5 (CH), 126.7 (CH), 128.6 (CH), 129.0 (CH), 129.6 (CH), 133.2 (C), 137.3 (C), 139.0 (C), 153.1 (C), 204.7 (C).

MS (EI, 70 eV): *m*/*z* = 375 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{22}ClNO_4$: C, 63.91; H, 5.90; N, 3.73. Found: C, 64.20; H, 6.00; N, 3.89.

4k

According to GP 1, dioxanone **1** (861 mg, 6.62 mmol), *p*-nitrobenzaldehyde (**3k**; 1.00 g, 6.62 mmol) and *p*-anisidine (**2**; 815 mg, 6.62 mmol) were reacted in MeCN containing H_2O (5 equiv, 66 mL) in the presence of (*S*)-**6** (325 mg, 1.32 mmol) for 5 d. Purification by flash chromatography (silica gel, *n*-pentane−EtOAc = 85:15) afforded **4k** as a bright orange solid (2.45 g, 96%); mp 55−58 °C; ee = 87% [HPLC analysis: Daicel AD at r.t., *n*-heptane−*i*-PrOH = 90:10 (0.7 mL/min); t_1 = 26.8 min (minor), t_2 = 32.0 min (major)]; $[\alpha]_D^{23}$ +5.7 (*c* = 5.27, $CHCl_3$).

IR (KBr): 3389, 2993, 2939, 2835, 2453, 2279, 1929, 1750, 1673, 1603, 1517, 1464, 1380, 1346, 1237, 1177, 1107, 1040, 982, 907, 852, 824, 757, 695, 668, 624, 525 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6): δ = 0.93 (d, *J* = 1.4 Hz, 3 H), 1.76 (d, *J* = 1.4 Hz, 3 H), 3.29 (d, *J* = 0.8 Hz, 3 H), 3.73 (dd, *J* = 2.1, 16.9 Hz, 1 H), 3.85 (dt, *J* = 1.4, 16.9 Hz, 1 H), 4.13 (br, 1 H), 5.03 (br, 1 H), 6.41 (dd, *J* = 1.6, 8.8 Hz, 2 H), 6.69 (d, *J* = 8.8 Hz, 2 H), 6.97 (dd, *J* = 3.0, 8.7 Hz, 2 H), 7.78 (dd, *J* = 1.4, 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 22.7 (CH_3), 24.4 (CH_3), 55.2 (CH_3), 57.3 (CH), 67.2 (CH_2), 100.7 (C), 115.2 (CH), 116.0 (CH), 123.5 (CH), 128.1 (CH), 140.0 (C), 147.5 (C), 147.6 (C), 153.7 (C), 205.4 (C).

MS (CI, methane): *m*/*z* = 387 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.04; H, 5.80; N, 7.01.

9

To a solution of **7** (1.00 g, 4.87 mmol) in CF_3CH_2OH (49 mL) at ambient temperature was added (*S*)-**5** (168 mg, 1.46 mmol), followed by dioxanone **1** (634 mg, 4.87 mmol) and the mixture was stirred for an additional 5 d. Upon reaction completion a pH 7 phosphate buffer (50 mL) was added and the mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, *n*-pentane−Et_2O = 2:1) afforded the desired product **9** as a colorless solid (1.39 g, 85%); mp 60−63 °C; ee = 96% [chiral GC analysis: CP Chirasil-DEX CB, 140-10iso-1-160-3-180-50iso; t_1 = 42.7 min (minor), t_2 = 43.3 min (major)]; $[\alpha]_D^{23}$ –137.0 (*c* = 1.73, $CHCl_3$).

IR (KBr): 3425, 3066, 3031, 2981, 2936, 2866, 2381, 1755, 1719, 1499, 1375, 1328, 1228, 1172, 1099, 1053, 979, 889, 849, 800, 754, 702, 567, 528 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6, 70 °C): δ = 1.01 (s, 3 H), 1.11 (s, 3 H), 1.39 (s, 9 H), 3.69 (d, *J* = 16.9 Hz, 1 H), 3.83 (d, *J* = 16.9 Hz, 1 H), 4.28 (br, 1 H), 5.56 (br, 2 H), 7.03−7.18 (m, 3 H), 7.31 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (100 MHz, C_6D_6, 70 °C): δ = 22.8 (CH_3), 23.8 (CH_3), 28.1 (CH_3), 53.5 (CH), 66.8 (CH_2), 77.8 (CH), 79.1 (C), 100.4 (C), 126.9 (CH), 127.0 (CH), 127.9 (CH), 140.3 (C), 154.5 (C), 205.1 (C). MS (CI, methane): *m*/*z* = 336 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.24; H, 7.73; N, 4.14.

Diastereoselective Reduction with $Me_4NHB(OAc)_3$ (Amino Alcohol 11); General Procedure (GP 2)

$(CH_3)_4NBH(OAc)_3$ (1.16 g, 4.40 mmol) was dissolved in MeCN (9 mL) and AcOH (0.51 mL, 8.80 mmol) and cooled to –30 °C. Then ketone **4a** (300 mg, 0.88 mmol, dissolved in 0.5 mL MeCN) was added and stored for 2 d at –24 °C in a freezer. The reaction was quenched with 0.5 N sodium tatrate solution (4 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by flash chromatography (silica gel, *n*-pentane−Et_2O, 1:2) to afford the product **11** as a yellow oil (230 mg, 77%); $[\alpha]_D^{21}$ –15.4 (*c* = 0.99, $CHCl_3$).

IR ($CHCl_3$): 3404, 2992, 2939, 2834, 1516, 1461, 1379, 1236, 1201, 1124, 1073, 980, 888, 823, 756 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 1.34 (s, 3 H), 1.46 (3 H), 3.17 (s, 3 H), 3.24 (s, 3 H), 3.39 (s, 3 H), 3.52 (m, 1 H), 3.70 (m, 2 H), 4.01 (dd, *J* = 1.5, 7.3 Hz, 1 H), 4.16 (dd, *J* = 1.5, 9.1 Hz, 1 H), 4.48 (d, *J* = 7.3 Hz, 1 H), 6.68 (dt, *J* = 2.6, 8.9 Hz, 2 H), 6.79 (dt, *J* = 2.6, 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 19.5 (CH_3), 28.9 (CH_3), 54.2 (CH_3), 54.9 (CH_3), 55.4 (CH_3), 56.0 (CH), 62.9 (CH), 65.2 (CH_2), 74.0 (CH), 98.8 (C), 105.5 (CH), 114.9 (CH), 115.3 (CH), 143.5 (C), 152.6 (C).

MS (EI, 70 eV): *m*/*z* = 341 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.31; H, 8.01; N, 3.89.

Diastereoselective Reduction with L-Selectride (Amino Alcohol 12); General Procedure (GP 3)

To a solution of **4a** (180 mg, 0.53 mmol) in THF (4 mL) was added dropwise a 1 M solution of L-Selectride in THF (0.69 mL, 0.69 mmol) at –78 °C. After 2 h the reaction mixture was warmed to r.t., then Et_2O (8 mL) and sat. NH_4Cl solution (4 mL) were added and stirring was continued for an additional 10 min. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, *n*-pentane−Et_2O, 1:4) to afford the product **12** as a colorless solid (178 mg, >98%); mp 51−52 °C; $[\alpha]_D^{22}$ –14.9 (*c* = 0.90, $CHCl_3$).

IR ($CHCl_3$): 3370, 2998, 2940, 2834, 1513, 1462, 1380, 1240, 1199, 1121, 1082, 1043, 978, 857, 827, 757 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 1.26 (s, 3 H), 1.48 (s, 3 H), 3.03 (s, 3 H), 3.14 (s, 3 H), 3.38 (s, 3 H), 3.50 (q, *J* = 1.8 Hz, 1 H), 3.67 (dd, *J* = 1.9, 12.2 Hz, 1 H), 3.75 (app t, *J* = 4.6 Hz, 1 H), 3.82 (dd, *J* = 2.5, 12.2 Hz, 1 H), 4.12 (dd, *J* = 2.5, 4.6 Hz, 1 H), 4.43 (d, *J* = 4.9 Hz, 1 H), 6.68 (dt, *J* = 2.4, 9.1 Hz, 2 H), 6.77 (dt, *J* = 2.4, 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 18.9 (CH_3), 29.6 (CH_3), 54.8 (CH_3), 55.2(CH_3), 55.6 (CH_3), 59.8 (CH), 66.0 (CH_2), 66.3 (CH), 70.7 (CH), 99.1 (C), 105.5 (CH), 115.0 (CH), 116.9 (CH), 142.6 (C), 153.6 (C).

MS (EI): *m*/*z* = 341 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.31; H, 8.01; N, 3.89.

Amino Alcohol 13

According to GP 2, **4b** (337 mg, 1.00 mmol) was treated with $Me_4NHB(OAc)_3$ (1.32 g, 5.00 mmol) in MeCN (10 mL) in the presence of AcOH (0.58 mL, 10.00 mmol) overnight. Following flash chromatography (silica gel, *n*-pentane−EtOAc = 7:3) **13** was col-

lected as a colorless oil (305 mg, 90%); $[\alpha]_D^{23}$ –27.4 (*c* = 3.12, $CHCl_3$).

IR ($CHCl_3$): 3715, 3421, 2990, 2944, 2392, 2295, 1736, 1608, 1516, 1465, 2295, 1736, 1608, 1516, 1465, 1377, 1238, 1162, 1074, 960, 917, 827, 756, 671, 517 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.89 (t, *J* = 7.0 Hz, 3 H), 1.25 (s, 3 H), 1.43 (s, 3 H), 3.34 (s, 3 H), 3.48 (dd, *J* = 9.5, 11.1 Hz, 1 H), 3.68 (dd, *J* = 5.6, 11.1 Hz, 1 H), 3.83–3.94 (m, 2 H), 4.03 (dq, *J* = 3.8, 7.0 Hz, 1 H), 4.29 (dd, *J* = 1.6, 9.3 Hz, 1 H), 4.46 (br, 1 H), 4.57 (br, 1 H), 6.58 (d, *J* = 8.9 Hz, 2 H), 6.75 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 14.3 (CH_3), 19.2, (CH_3), 28.7 (CH_3), 55.2 (CH_3), 58.0 (CH), 60.9 (CH_2), 62.9 (CH), 65.0 (CH_2), 75.8 (CH), 99.1 (C), 115.2 (CH), 115.8 (CH), 142.4 (C), 153.5 (C), 172.3 (C).

MS (CI, methane): *m*/*z* = 340 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 59.76; H, 7.69; N, 4.35.

Amino Alcohol 14

According to GP 3, **9** (1.00 g, 2.98 mmol) was treated with L-Selectride (3.58 mL, 3.58 mmol) in THF (26 mL) for 5 h. Purification by flash chromatography (silica gel, *n*-pentane–EtOAc = 7:3) afforded **14** as a colorless solid (804 mg, 80%); mp 185–187 °C; $[\alpha]^{23}_D$ +0.5 (*c* = 2.96, $CHCl_3$).

IR (KBr): 3481, 3410, 2977, 2922, 2364, 2344, 1690, 1520, 1458, 1376, 1288, 1252, 1169, 1117, 1073, 1020, 980, 954, 912, 859, 828, 747, 700, 620, 577, 535, 474 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (br, 9 H), 1.46 (s, 3 H), 1.49 (s, 3 H), 2.79 (app d, *J* = 11.3 Hz, 1 H), 3.05 (app d, *J* = 10.7 Hz, 1 H), 3.73 (dd, *J* = 1.9, 12.4 Hz, 1 H), 3.77 (app d, *J* = 8.8 Hz, 1 H), 3.87 (dd, *J* = 1.4, 12.4 Hz, 1 H), 4.70 (br, 1 H), 5.12 (d, *J* = 4.1 Hz, 1 H), 7.23–7.28 (m, 1 H), 7.30–7.35 (m, 2 H), 7.37–7.40 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH_3), 28.2 (CH_3), 29.6 (CH_3), 56.4 (CH), 62.5 (CH), 65.9 (CH_2), 74.8 (CH), 79.5 (C), 99.7 (C), 127.4 (CH), 127.5 (CH), 128.4 (CH), 139.4 (C), 155.9 (C).

MS (CI, methane): *m*/*z* = 338 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.82; H, 8.01; N, 3.94.

Diastereoselective Reductive Amination with $Me_4NHB(OAc)_3$ (Diamine 15); General Procedure (GP 4)

To a solution of the β-aminoketone **4a** (103 mg, 0.30 mmol) and $BnNH_2$ (0.076 mL, 0.70 mmol) in CH_2Cl_2 (2 mL) at 2 °C were added $Me_4NHB(OAc)_3$ (184 mg, 0.43 mmol) and AcOH (0.017 mL, 0.30 mmol) and the reaction mixture was stored at this temperature for 2 d. The reaction was quenched with 0.5 N sodium tartrate solution (4 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and purified by flash chromatography (silica gel, *n*-pentane–Et_2O = 1:2) to afford product **15** as a yellow oil (97 mg, 73%); $[\alpha]_D^{21}$ +14.4 (*c* = 0.99, $CHCl_3$).

IR ($CHCl_3$): 3398, 2998, 2934, 2834, 1616, 1514, 1454, 1379, 1237, 1147, 1078, 1043, 977, 822, 757, 702, 668 cm^{-1}.

^1H NMR (300 MHz, C_6D_6): δ = 1.31 (s, 3 H), 1.43 (s, 3 H), 2.24 (d, *J* = 1.7 Hz, 1 H), 3.13 (s, 3 H, CH_3), 3.17 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 3.44 (d, *J* = 13.1 Hz, 1 H), 3.51 (dd, *J* = 1.5, 12.1 Hz, 1 H), 3.73 (d, *J* = 13.1 Hz, 1 H), 3.88 (dd, *J* = 1.5, 12.1 Hz, 1 H), 3.98 (dd, *J* = 3.2, 6.7 Hz, 1 H), 4.17 (dd, *J* = 2.1, 6.8 Hz, 1 H), 4.30 (d, *J* = 3.2 Hz, 1 H), 6.82–6.89 (m, 4 H), 7.10–7.25 (m, 5 H).

^{13}C NMR (75 MHz, C_6D_6): δ = 18.7 (CH_3), 30.0 (CH_3), 50.6 (CH_2), 52.0 (CH), 55.3 (CH_3), 55.9 (CH_3), 58.9 (CH), 60.4 (CH_2), 73.8 (CH), 99.2 (C), 105.4 (CH), 115.0 (CH), 115.7 (CH), 127.2 (CH), 128.5 (CH), 129.1 (CH), 140.9 (C), 144.9 (C), 152.8 (C).

MS (EI): *m*/*z* = 430 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{34}N_2O_5$: C, 66.95; H, 7.96; N, 6.51. Found: C, 66.94; H, 7.46; N, 6.30.

Diamines 16 and 17

According to GP 4, β-aminoketone **4c** (250 mg, 0.63 mmol) and $BnNH_2$ (0.28 mL, 2.60 mmol) in CH_2Cl_2 (4 mL) were treated with $NMe_4HB(OAc)_3$ (533 mg, 2.50 mmol) and AcOH (0.145 ml, 2.50 mmol) for 4 d. The crude mixture was purified by flash chromatography (silica gel, *n*-pentane–Et_2O = 1:2) to afford the major diastereoisomer **16** as a cream-colored foam (213 mg, 89%) and the minor diastereoisomer **17** as a yellow oil (25 mg, 10%).

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Mp 47–48 °C; $[\alpha]_D^{21}$ –27.1 (*c* = 1.04, $CHCl_3$).

IR ($CHCl_3$): 3346, 2991, 2932, 1693, 1514, 1439, 1242, 1106, 1037, 824, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 6 H), 3.66 (m, 3 H), 3.75 (s, 3 H), 3.78 (dd, *J* = 1.8, 6.1 Hz, 1 H), 3.95 (s, 1 H), 4.16 (d, *J* = 15.0 Hz, 1 H), 4.28 (d, *J* = 4.5 Hz, 1 H), 4.86 (d, *J* = 15.0 Hz, 1 H), 6.82 (dd, *J* = 2.1, 9.1 Hz, 2 H), 7.25 (dd, *J* = 2.1, 9.1 Hz, 2 H), 7.28–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 (CH_3), 26.4 (CH_3), 45.0 (CH_2), 54.5 (CH), 55.7 (CH_3), 59.0 (CH_2), 62.6 (CH), 68.9 (CH), 99.7 (CH_3), 114.9 (CH), 115.2 (CH), 127.9 (CH), 128.0 (CH), 128.9 (CH), 135.4 (C), 140.9 (C), 153.2 (C), 173.9 (C).

MS (EI): *m*/*z* = 382 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.62; H, 6.96; N, 7.09.

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$[\alpha]_D^{21}$ = +32.8 (*c* = 0.95, $CHCl_3$).

IR ($CHCl_3$): 3346, 2991, 2932, 1693, 1514, 1439, 1242, 1106, 1037, 824, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.33 (s, 3 H), 3.64 (dd, *J* = 9.3, 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.87 (dd, *J* = 5.5, 11.3 Hz, 1 H), 3.98 (m, 1 H), 4.15 (dd, *J* = 2.2, 9.1 Hz, 1 H), 4.43 (d, *J* = 2.2 Hz, 1 H), 5.06 (d, *J* = 12.1 Hz, 1 H), 5.26 (d, *J* = 12.1 Hz, 1 H), 6.68 (m, 2 H), 6.79 (m, 2 H), 7.26–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (CH_3), 28.2 (CH_3), 55.6 (CH_3), 57.5 (CH), 62.9 (CH), 64.5 (CH_2), 66.8 (CH_2), 74.9 (CH), 99.0 (C), 114.7 (CH), 115.2 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 135.5 (C), 140.8 (C), 153.4 (C), 173.5 (C).

MS (EI, 70 eV): *m*/*z* = 382 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.75; H, 6.71; N, 7.05.

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