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Enantioselective Synthesis of α,α-Disubstituted-α-Amino Acids by a Sequential Nucleophilic Addition to Nitriles

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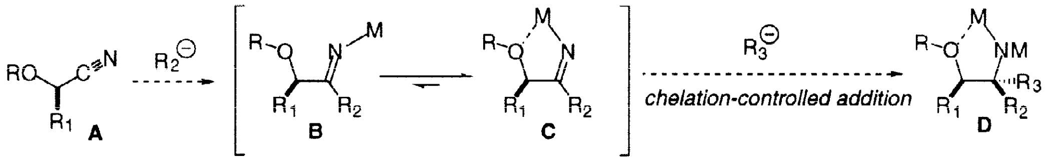
Abstract: The sequential addition of two different nucleophiles to a tartaric acid-derived nitrile produced carbinamines. The adducts from chelation-controlled addition which are obtained in high diastereoselectivities and yields, were easily converted to α,α-disubstituted-α-amino acids.

The interest for unnatural α-amino acids has increased significantly in the last few decades.[1] Among these derivatives, α,α-disubstituted-α-amino acids represent powerful starting materials for further derivatization in medicinal chemistry. These derivatives generally induce strong conformational preferences when they are incorporated into peptides.[2] Furthermore, the amide linkage formed is extremely resistant to both chemical and enzymatic hydrolyses.[3] Despite their tremendous potential, access to this class of compounds is impeded by the notoriously difficult task of constructing a quaternary asymmetric center. The most general methods developed for the preparation of optically active α,α-disubstituted-α-amino acids relied mainly on enolate alkylation with highly reactive electrophiles.[4] Among the methods involving the nucleophilic addition to a C=N bond is the asymmetric Strecker reaction.[1b] However, in many instances, the ketimine which is initially formed consists of a mixture of the carbon-nitrogen double bond isomers, except for some methyl ketones.[5] The mixture of geometrical isomers generally translates into poor diastereoselectivities.[6] Herein, we report a chelation strategy that avoids the carbon-nitrogen double bond geometry issue by using a nucleophilic addition to α-alkoxynitrile **A** (Scheme 1).[7] The α-oxygen group should complex the metal of the imine anion (**B**) generated by the attack of a first nucleophile onto the nitrile. A subsequent chelation-controlled addition to the more reactive bidentate intermediate **C** should provide the adduct **D**. Although sequential additions of different alkyl and/or aryl nucleophiles to a nitrile have been reported sporadically, none of those were designed to access optically active amines.[8]

Scheme 1



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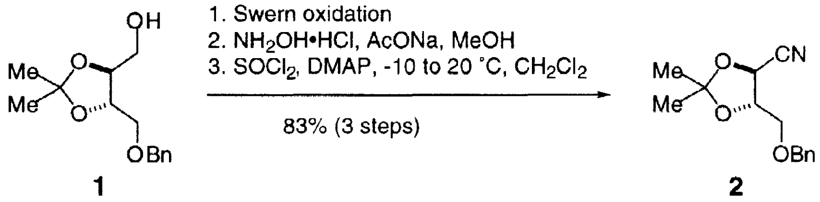
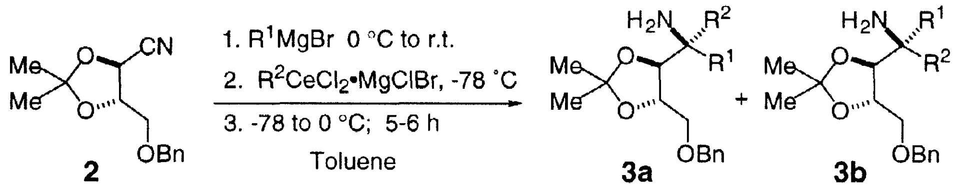
The optimal chiral template we found was readily synthesized in five steps from threitol (eq 1). Monobenzylation of threitol acetonide according to Seebach's procedure[9] produced **1**. Oxidation,[10] oxime formation and dehydration proceeded smoothly to afford nitrile **2** in 83% overall yield for the three-step process.



(1)

The optimal conditions for the first step of our chelation-controlled sequence involved the addition of the Grignard reagent in THF or ether to a solution of the nitrile in toluene at 0 °C. Grignard and organolithium reagents are unreactive as second nucleophiles. The sequential addition could be successfully accomplished when the imine anion resulting from the first addition was cannulated into a suspension of the previously prepared organocerium reagent at -78 °C (Table 1).

Table 1. Diastereoselective sequential nucleophilic addition to nitrile 2.[a]



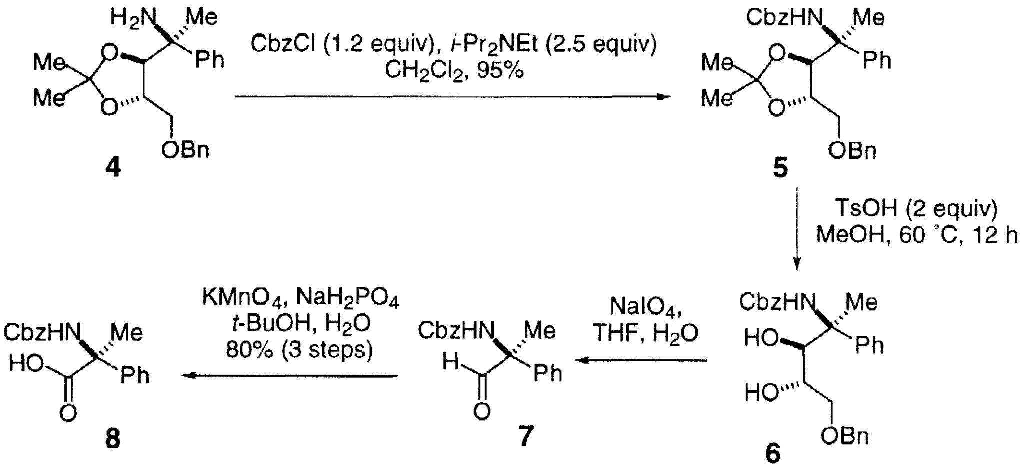
Entry	R_1	R_2	Yield[b]	ds (**3a**:**3b**)[c]
1	Me	Et	44%	24 : 1
2	Et	Me	63%	32 : 1
3	Me	Ph	75%	21 : 1
4	Ph	Me	89%	>40 : 1
5	Me	c-C_6H_{11}	62%	14 : 1
6	*n*-Pr	Ph	44%	>40 : 1
7	Ph	*n*-Pr	71%	>40 : 1
8	Ph	Allyl[d]	66%	39 : 1
9	Et	$PhCH_2CH_2$	87%	>40 : 1
10	$PhCH_2CH_2$	Et	72%	>40 : 1
11[e]	$PhCH_2CH_2$	Et	50%[f]	39 : 1

[a] All the reactions were carried out by adding 1.05 equiv of the first Grignard reagent to a solution of the nitrile in toluene followed by the addition of 3.3 equiv of the organocerium reagent. [b] Isolated yields after column chromatography. [c] Diastereomeric excesses were determined by capillary GC (DB-1) of the crude trifluoroacetamide derivatives. The sense of induction was established by conversion to the known amino acid (entries 3 and 4) or by X-Ray crystallography of the trifluoroacetamide (entry 6). [d] Allylcerium formed at -78 °C. [e] Second addition performed at 0 °C for 3 h with only 1.3 equiv of organocerium reagent. [f] Conversion determined by ^1H NMR analysis.

Good to excellent diastereoselectivities were observed with a variety of Grignard reagents. Both isomers were readily accessible by inverting the order of addition. In all the cases studied, the configuration of the newly formed stereogenic center is in agreement with a chelation-controlled nucleophilic addition from the least hindered face of the iminate complex.

Conversion of the adducts to the amino acid could be easily and efficiently accomplished as shown in Scheme 2. Protection of the amino group as a Cbz derivative followed by removal of the acetal produced diol **6**. Oxidative cleavage of the diol and oxidation of the aldehyde using Masamune's conditions[11] afforded the *N*-protected amino acid **8** in 80% yield for the last three steps.

Scheme 2



In summary, chelation could be used efficiently for controlling the carbon-nitrogen geometry in the sequential addition of two different alkyl- or aryl nucleophiles onto a nitrile. The approach is very flexible allowing access to a variety of quaternary carbon centers with high diastereoselectivities. Both enantiomeric forms of the heterocyclic chiral template are readily available and easily prepared from tartaric acid. Finally, we have demonstrated that the double addition product can be converted to the corresponding α,α-disubstituted-α-amino acid in high yield and under mild conditions.

Experimental Section

General. All non-aqueous reactions are carried out under argon with exclusion of moisture and air. Toluene is dried over sodium, dichloromethane is dried over calcium hydride and tetrahydrofuran is dried over sodium benzophenone ketyl. Anhydrous acetonitrile, dimethylformamide and dimethylsulfoxide were purchased from Aldrich Chemical Co., Inc. Threitol was prepared from natural tartaric acid.[12] Cerium chloride heptahydrate 99% was obtained from Aldrich Chemical Co., Inc. and dried as described below. Allylmagnesium bromide (1.0 M), methylmagnesium bromide (3.0 M) and cyclohexylmagnesium chloride (2.0 M) were bought from Aldrich Chemical Co., Inc. Other Grignard reagents were prepared as 2M or 3M solutions from the corresponding bromide in ether.

(2*S*,3*S*)-4-Benzyloxy-2,3-dihydroxybutyronitrile Acetonide (2). The Swern oxidation on the monoprotected diol (6.3 g, 24.97 mmoles) was carried out as reported[13]. The crude aldehyde was dissolved in methanol (55 mL). Sodium acetate (3.78 g, 1.84 equiv) and hydroxylamine hydrochloride (2.95 g, 1.7 equiv) were added simultaneously. After 16 h of stirring at room temperature, the reaction was then diluted with ether (300 mL) and sat. aq. $NaHCO_3$ (50 mL) and the layers were separated. The organic phase was washed with sat. aq. $NaHCO_3$ (50 mL), with brine (50 mL), dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude oxime was dissolved in dichloromethane (15 mL) at -10 °C. This solution was then cannulated into a mixture of DMAP (3.66 g, 1.2 equiv) and thionyl chloride (2.00 mL, 1.1 equiv) in dichloromethane (100 mL) at -10 °C. The reaction was stirred for 10 min and DMAP (3.05 g, 1.0 equiv) was added. After 10 min, the cooling bath was removed. After another 10 minutes, the TLC showed consumption of the starting material and the reaction was diluted with water (75 mL). The phases were separated and the organic layer was dried over Na_2SO_4. After concentration under reduced vacuum, the nitrile was purified by chromatography on silica gel (20% EtOAc:hexanes) to produce the pure nitrile as a colorless liquid (5.55 g, 83%, 3 steps): R_f 0.52 (20% EtOAc:hexanes); $[\alpha]_D^{24}$ -19.3° (*c* 2.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H, Ph), 4.64 (d, *J* = 5.8 Hz, 1H, **CH**CN), 4.61 (s, 2H, O**CH**$_2$Ph), 4.57 (ddd, *J* = 5.8, 5.5, 4.4 Hz, 1H, **CH**(OR)CH_2), 3.67 (dd, *J* = 10.4, 4.4 Hz, 1H, **CH**$_2$OBn), 3.59 (dd, *J* = 10.4, 5.5 Hz, 1H, CH_2OBn), 1.54 (s, 3H, **CH**$_3$), 1.48 (s, 3H, **CH**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.25, 128.46, 127.91, 127.61, 117.88, 113.07, 78.98, 73.62, 68.54, 65.15, 26.63, 25.02; IR (neat) 3680, 3660, 3480, 3010, 2880, 2260(vw), 1615, 1505, 1460, 1395, 1385, 1225, 1105, 855, 750, 705 cm^{-1}; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.17; H, 7.17; N, 5.66.

General Procedure for Preparation of the Organocerium Reagent: $CeCl_3 \cdot 7H_2O$ was dried at 145 °C for 24 h under high vacuum (0.05 mmHg). The lumps were broken with a spatula after 2 h and 6 h to generate a powder. The amount of anhydrous $CeCl_3$ corresponding to approximately 3.3 equiv of the nitrile to be used was weighed in a flask and further dried with stirring for 2 h at 145 °C under high vacuum (0.05 mmHg). Next, the flask was filled with argon and cooled to room temperature. The flask was then put into an ice-water bath and dry THF (to make a 0.35 M suspension) was added. After 5 min of stirring at 0 °C, the ice bath was removed and the white milky suspension was stirred overnight. The suspension was cooled to 0 °C (-78 °C in the case of allylmagnesium bromide) and the Grignard reagent (3.3 equiv with respect to the nitrile) was added dropwise. The reaction mixture turned yellow (brown in the case of allyl and phenylmagnesium bromide). The mixture was stirred for 2 h at 0 °C and then cooled to -78 °C.

General Procedure for the Nucleophilic Additions: To a solution of nitrile **2** in toluene (0.1 M) at 0 °C was added 1.05 equiv of the Grignard reagent. After 5 min of stirring at 0 °C, the bath was removed and the mixture was stirred at room temperature until TLC analysis showed complete consumption of the starting nitrile (20-60 min). The reaction was cooled to -78 °C and then it was cannulated into the previously prepared organocerium solution at -78 °C. The resulting mixture was warmed to 0 °C over 5 or 6 h and poured into a mixture of concentrated aqueous NH_4OH and ether and stirred for an additional 2 h. The cerium-containing sludge was filtered on celite. The layers from the clear solutions were separated and the aqueous phase was washed twice with ether. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. An aliquot was trifluoroacetylated (2:1 pyridine:TFAA, overnight) for G.C. analysis. The crude amine was purified by chromatography on silica gel. When small nucleophiles were used, it was possible to purify the amine by acid-base extraction, but the more lipophilic substrates were not efficiently extracted from ether by 10% aqueous HCl.

(4*S*,5*S*)-4-[(*R*)-(1-Amino-1-methyl)propyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1, entry 1). The title compound was prepared by the procedure described above on 0.598 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 157 °C for 30 min then 0.1 °C/min, R_t: 29.9 min (major), 29.5 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (100:25:5:1 hexanes:EtOAc:*i*-PrOH:Et_3N) to afford the desired compound (77.6 mg, 44%) as a colorless liquid: R_f 0.24 (100:25:5:1 hexanes:EtOAc:*i*-PrOH:Et_3N); $[\alpha]_D^{20}$ -16.3° (*c* 1.54, $CHCl_3$); ^1H NMR (300 MHz, CDCl3) δ 7.35-7.25 (m, 5H, Ph), 4.60 (s, 2H, OCH_2Ph), 4.17-4.11 (m, 1H, $CH(OR)CH_2$), 3.74 (d, *J* = 7.8 Hz, 1H, **CH**(OR)), 3.60 (dd, *J* = 10.6, 3.1 Hz, 1H, $\mathbf{CH_2}OBn$), 3.55 (dd, *J* = 10.6, 5.9 Hz, 1H, $\mathbf{CH_2}OBn$), 1.50-1.35 (m, 4H, $\mathbf{CH_2}CH_3$ and $\mathbf{NH_2}$), 1.43 (s, 3H, CH_3CCH_3), 1.40 (s, 3H, CH_3CCH_3), 0.91 (s, 3H, $\mathbf{CH_3}$), 0.88 (t, *J* = 7.6 Hz, 3H, $CH_2\mathbf{CH_3}$); ^{13}C NMR (100 MHz, CDCl3) δ 137.96, 128.24, 127.56, 127.51, 108.70, 83.06, 76.59, 73.27, 72.18, 52.22, 33.21, 27.16, 26.98, 22.03, 7.82; IR (neat) 3390, 3320, 2990, 2880, 1590, 1500, 1455, 1380, 1250, 1065, 860, 735, 690 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{28}NO_3$ (M+H) 294.2069, found 294.2056; Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.66; H, 9.50; N, 4.78.

(4*S*,5*S*)-4-[(*S*)-(1-Amino-1-methyl)propyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 2). The title compound was prepared by the procedure described above on 0.604 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 157 °C for 30 min then 0.1 °C/min, R_t: 29.5 min (major), 29.9 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (100:25:5:1 hexanes:EtOAc:*i*-PrOH:Et_3N) to afford the desired compound (111.8 mg, 63%) as a colorless liquid: R_f 0.24 (100:25:5:1 hexanes:EtOAc:*i*-PrOH:Et_3N); $[\alpha]_D^{20}$ -17.4° (*c* 1.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H, Ph), 4.59 (s, 2H, OCH_2Ph), 4.14-4.09 (m, 1H, $CH(OR)CH_2$), 3.71 (d, *J* = 7.8 Hz, 1H, CH(OR)), 3.65 (dd, *J* = 10.5, 3.3 Hz, 1H, $\mathbf{CH_2}OBn$), 3.57 (dd, *J* = 10.5, 5.8 Hz, 1H, $\mathbf{CH_2}OBn$), 1.42 (s, 3H, CH_3CCH_3), 1.39 (s, 3H, $\mathbf{CH_3}CCH_3$), 1.39-1.27 (m, 2H, CH_2CH_3), 1.25 (s(br), 2H, $\mathbf{NH_2}$), 1.04 (s, 3H, $\mathbf{CH_3}$), 0.88 (t, 3H, *J* = 7.5 Hz, $CH_2\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.95, 128.23, 127.59, 127.51, 108.57, 83.74, 76.53, 73.30, 72.16, 52.35, 31.55, 27.16, 26.97, 23.74, 7.38; IR (neat) 3380, 3320, 2990, 2860, 1610, 1590, 1500, 1455, 1380, 1250, 1070, 860, 730, 690 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{28}NO_3$ (M+H) 294.2069, found 294.2078; Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.77. Found: C, 69.30; H, 9.67; N, 4.85.

(4*S*,5*S*)-4-[(*R*)-(1-Amino-1-phenyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1, entry 3). The title compound was prepared by the procedure described above on 0.534 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 15.6 min (major), 15.1 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (55:40:4:1 hexanes:EtOAc:*i*-PrOH:Et_3N) to afford the desired compound (137 mg, 75%) as a colorless liquid: R_f 0.39 (55:40:4:1 hexanes:EtOAc:*i*-PrOH:Et_3N); $[\alpha]_D^{20}$ -22.4° (*c* 1.58,

$CHCl_3$); ^{1}H NMR (300 MHz, CDC13) δ 7.52-7.20 (m, 10H, Ph), 4.42 (s, 2H, OCH_2Ph), 4.04 (d, *J* = 8.1 Hz, 1H, CH(OR)), 3.96-3.90 (m, 1H, **CH**(OR)CH_2), 3.16 (dd, *J* = 10.5, 5.9 Hz, 1H, $\mathbf{CH_2}$OBn), 3.05 (dd, *J* = 10.5, 2.9 Hz, 1H, $\mathbf{CH_2}$OBn), 1.82 (br, 2H, NH_2), 1.52 (s, 3H, CH_3), 1.40 (s, 3H, $\mathbf{CH_3}CCH_3$), 1.38 (s, 3H, CH_3CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.95, 137.97, 128.24, 128.02, 127.60, 127.49, 126.95, 126.19, 109.00, 84.66, 77.27, 73.19, 71.55, 55.68, 27.08, 27.05, 25.44; IR (neat) 3380, 3320, 3060, 2990, 2870, 1605, 1500, 1455, 1380, 1060, 855, 795 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{28}NO_3$ (M+H) 342.2069, found 342.2060; Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.82; H, 8.16; N, 4.17.

(4*S*,5*S*)-4-[(*S*)-(1-Amino-1-phenyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (4) (Table 1, entry 4). The title compound was prepared by the procedure described above on 0.517 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 15.1 min (major), 15.6 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (55:40:4:1 hexanes:EtOAc:*i*-PrOH:Et_3N) to afford the desired compound (156 mg, 89%) as a colorless liquid: R_f 0.43 (55:40:4:1 hexanes:EtOAc:*i*-PrOH:Et_3N); $[\alpha]_D^{20}$ -24.2° (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, CDC13) δ 7.49-7.13 (m, 10H, Ph), 4.28 (d, *J* = 12.3 Hz, 1H, $O\mathbf{CH_2}Ph$), 4.22 (d, *J* = 12.3 Hz, 1H, $O\mathbf{CH_2}Ph$), 4.09-4.04 (m, 2H, CH_2OBn), 2.66 (d, *J* = 10.5 Hz, 1H, **CH**(OR)), 2.59 (ddd, *J* = 10.5, 2.7, 2.1 Hz, 1H, **CH**(OR)CH_2), 1.62 (s(br), 5H, CH_3, $\mathbf{NH_2}$), 1.49 (s, 3H, $\mathbf{CH_3}CCH_3$), 1.47 (s, 3H, CH_3CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.92, 138.13, 128.19, 128.13, 127.45, 127.30, 126.92, 125.57, 108.87, 83.41, 76.62, 72.96, 70.85, 54.88, 30.45, 27.20, 27.16; IR (neat) 3390, 3320, 3070, 2990, 2860, 1605, 1575, 1500, 1455, 1420, 1055, 690 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{28}NO_3$ (M+H) 342.2069, found 342.2063; Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.72; H, 8.27; N, 4.16.

(4*S*,5*S*)-4-[(*R*)-(1-Amino-1-methyl)-2-cyclohexylmethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 5). The title compound was prepared by the procedure described above on 0.533 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 16.3 min (major), 15.3 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (55:40:4:1 hexanes:EtOAc:*i*-PrOH:Et_3N) to afford the desired compound (114 mg, 62%) as a colorless liquid: R_f 0.41 (55:40:4:1 hexanes:EtOAc:*i*-PrOH:Et_3N); $[\alpha]_D^{20}$ -8.7° (*c* 1.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H, Ph), 4.59 (s, 2H, $O\mathbf{CH_2}Ph$), 4.22-4.17 (m, 1H, **CH**(OR)CH2), 3.96 (d, *J* = 7.7 Hz, 1H, **CH**(OR)), 3.59 (dd, *J* = 10.7, 2.9 Hz, 1H, $\mathbf{CH_2}$OBn), 3.52 (dd, J = 10.7, 5.8 Hz, 1H, $\mathbf{CH_2}$OBn), 1.79-0.93 (m, 13H, *c*-C_6H_{11}, NH_2), 1.43 (s, 3H, $\mathbf{CH_3}CCH_3$), 1.39 (s, 3H, CH_3CCH_3), 0.78 (s, 3H, $\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.03, 128.23, 127.54, 127.47, 108.54, 80.40, 76.70, 73.20, 72.22, 54.12, 45.91, 27.68, 27.20, 26.95, 26.77, 26.68, 26.53, 19.16; IR (neat) 3380, 2930, 2850, 1580, 1495, 1450, 1380, 1250, 1060, 860, 730, 690 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{34}NO_3$ (M+H) 348.2539, found 348.2532; Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.59; H, 9.57; N, 4.03. Found: C, 72.66; H, 9.90; N, 4.11.

(4*S*,5*S*)-4-[(*S*)-(1-Amino-1-phenyl)butyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 6). The title compound was prepared by the procedure described above on 0.638 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude trifluoroacetamide derivative (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 18.8 min (major), 18.3 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (33% EtOAc/hexanes) to afford the desired compound (103.8 mg, 44%) as a colorless liquid: R_f 0.57 (33% EtOAc/hexanes); $[\alpha]_D^{20}$ -20.9° (*c* 1.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.20 (m, 10H, Ph), 4.54 (s, 2H, OCH_2Ph), 4.08 (d, *J* = 8.0 Hz, 1H, CH(OR)), 3.99-3.93 (m, 1H, $CH(OR)CH_2$), 3.46-3.44 (m, 2H, CH_2OBn), 2.02-1.90 (m, 1H, $CH_2CH_2CH_3$), 1.75 (s(br), 2H, NH_2), 1.69-1.59 (m, 1H, $CH_2CH_2CH_3$), 1.37 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.29-1.22 (m, 1H, CH_2CH_3), 1.03-0.90 (m, 1H, CH_2CH_3), 0.85 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.57, 138.03, 128.25, 127.73, 127.62, 127.51, 126.79, 126.45, 108.62, 84.69, 77.28, 73.27, 71.81, 58.59, 41.18, 26.95, 26.91, 16.28, 14.31; IR (neat) 3380, 3320, 3020, 2960, 2860, 1600, 1595, 1450, 1415, 1365, 1245, 1205, 1070, 805, 690 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{32}NO_3$ (M+H) 370.2382, found 370.2375; Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.70; H, 8.46; N, 3.82.

(4*S*,5*S*)-4-[(*S*)-(1-Amino-1-phenyl)butyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 7). The title compound was prepared by the procedure described above on 0.676 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude trifluoroacetamide derivative (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 18.3 min (major), 18.8 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (33% EtOAc/hexanes) to afford the desired compound (177.8 mg, 71%) as a colorless liquid: R_f 0.59 (33% AcOEt/hexanes); $[\alpha]_D^{20}$ -23.0° (*c* 1.08, $CHCl_3$); IR (neat) 3390, 3320, 3020, 2930, 2860, 1605, 1495, 1450, 1365, 1245, 1060, 820, 790 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 7.42-7.15 (m, 10H, Ph), 4.25 (d, *J* = 12.3 Hz, 1H, OCH_2Ph), 4.18 (d, *J* = 12.3 Hz, 1H, OCH_2Ph), 4.08 (s, 1H, CH(OR)), 4.07 (s, 1H, CH(OR)), 2.57 (d, *J* = 10.6 Hz, 1H, CH_2OBn), 2.50-2.44 (m, 1H, CH_2OBn), 2.01-1.93 (m, 1H, $CH_2CH_2CH_3$), 1.58 (s(br) 2H, NH_2), 1.49 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.69-1.59 (m, 1H, $CH_2CH_2CH_3$), 1.31-1.23 (m, 1H, CH_2CH_3), 1.00-0.90 (m, 1H, CH_2CH_3), 0.90-0.85 (m, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.86, 138.23, 128.17, 128.07, 127.39, 127.21, 126.71, 125.98, 108.80, 83.78, 76.50, 72.90, 70.81, 57.98, 43.88, 27.19, 27.14, 16.35, 14.35; HRMS (FAB) calcd for $C_{23}H_{32}NO_3$ (M+H) 370.2382, found 370.2374; Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.69; H, 8.59; N, 3.78.

(4*S*,5*S*)-4-[(*S*)-(1-Amino-1-phenyl)buten-3-yl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 8). The title compound was prepared by the procedure described above on 1.122 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 18.6 min (major), 19.2 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (17% EtOAc/toluene) to afford the desired compound (292.3 mg, 66%) as a colorless liquid: R_f 0.28 (17% AcOEt/toluene); $[\alpha]_D^{20}$ -74.9° (*c* 1.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.17 (m, 10H, Ph), 5.45-5.34 (m, 1H, $CH{=}CH_2$), 5.12-5.01 (m, 2H, $CH{=}CH_2$), 4.25 (d, *J* = 12.3 Hz, 1H, OCH_2Ph), 4.17 (d, *J* = 12.4 Hz, 1H, OCH_2Ph), 4.15-4.13 (m, 2H, CH(OR)), 2.92 (dd, *J* = 13.8, 5.2 Hz, 1H, $CH_2CH{=}$), 2.66-2.58 (m, 2H, CH_2OBn), 2.46-2.41 (m, 1H, $CH_2CH{=}$), 1.67 (s(br), 2H, NH_2), 1.50 (s, 3H, CH_3), 1.46 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.48, 138.20, 133.44, 128.22, 128.07, 127.38, 127.22, 126.91, 126.17, 118.87, 108.85, 82.96, 76.54, 72.90, 70.53, 57.48, 46.48, 27.15, 27.11; IR (neat) 3380, 3310, 3060, 2980, 2860, 1640, 1600, 1570, 1490, 1445, 1360, 1250, 1070, 910, 790 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{30}NO_3$ (M+H) 368.2226, found 368.2214; Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.25; H, 8.14; N, 3.86.

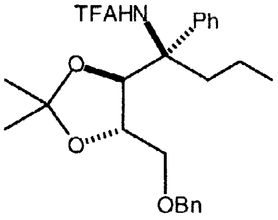
(4*S*,5*S*)-4-[(*R*)-(1-Amino-1-ethyl)-3-phenylpropyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 9). The title compound was prepared by the procedure described above on 0.532 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 27.0 min (major), 26.0 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (55:40:4:1 hexanes/EtOAc/*i*-PrOH/Et_3N) to afford the desired compound (178.0 mg, 87%) as a colorless liquid: R_f 0.46 (55:40:4:1 hexanes/EtOAc/*i*-PrOH/Et_3N); $[\alpha]_D^{20}$ -10.2° (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, CDCl3) δ 7.37-7.16 (m, 10H, Ph), 4.62 (s, 2H, OCH_2Ph), 4.24-4.19 (m, 1H, **C*H***(OR)CH2), 3.94 (d, *J* = 7.8 Hz, 1H, **C*H***(OR)), 3.68 (dd, *J* = 10.6, 3.0 Hz, 1H, CH_2OBn), 3.58 (dd, *J* = 10.6, 5.5 Hz, 1H, CH_2OBn), 2.62 (t, *J* = 8.7 Hz, 2H, $PhCH_2CH_2$), 1.91-1.71 (m, 2H, $PhCH_2CH_2$), 1.50 (s(br), 2H, NH_2), 1.45 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.39-1.31 (m, 2H, CH_2CH_3), 0.91 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 142.64, 137.99, 128.35, 128.27, 128.24, 127.63, 127.55, 125.61, 108.43, 81.54, 76.19, 73.36, 71.93, 54.27, 39.03, 29.87, 27.83, 27.21, 26.83, 7.42; IR (neat) 3380, 3320, 2990, 2930, 2850, 1605, 1500, 1455, 1070, 860, 730, 690 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{34}NO$ (M+H) 384.2539, found 384.2550. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 9.27; N, 3.65. Found: C, 75.40; H, 9.01; N, 3.72.

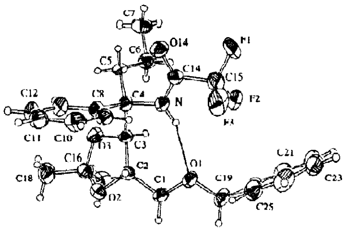
(4*S*,5*S*)-4-[(*S*)-(1-Amino-1-ethyl)-3-phenylpropyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (Table 1. entry 10). The title compound was prepared by the procedure described above on 0.541 mmol-scale. The diastereomeric ratio was determined by capillary GC analysis of the crude product (DB-1 at 200 °C for 1 min then 1 °C/min, R_t: 26.0 min (major), 27.0 min (minor)). The crude reaction mixture was purified by chromatography on silica gel (55:40:4:1 hexanes/EtOAc/*i*-PrOH/Et_3N) to afford the desired compound (149 mg, 72%) as a colorless liquid: R_f 0.54 (55:40:4:1 hexanes/EtOAc/*i*-PrOH/Et_3N); $[\alpha]_D^{20}$ -23.3° (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, CDCl3) δ 7.31-7.11 (m, 10H, Ph), 4.60 (s, 2H, OCH_2Ph), 4.26-4.21 (m, 1H, **C*H***(OR)CH2), 3.95 (d, *J* = 7.7 Hz, 1H, CH(OR)), 3.66 (dd, *J* = 10.6, 3.0 Hz, 1H, CH_2OBn), 3.57 (dd, *J* = 10.6, 5.6 Hz, 1H, CH_2OBn), 2.70-2.55 (m, 2H, $PhCH_2CH_2$), 1.72-1.60 (m, 2H, CH_2CH_3), 1.60 (s(br), 2H, NH_2), 1.53 (t, 2H, *J* = 8.8 Hz, $PhCH_2CH_2$), 1.47 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 0.94 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 142.24, 137.89, 128.34, 128.27, 128.12, 127.57, 127.53, 125.72, 108.47, 81.34, 76.15, 73.32, 71.93, 54.37, 36.82, 29.61, 29.28, 27.20, 26.89, 7.83; IR (neat) 3390, 3320, 3020, 2960, 2860, 1600, 1495, 1450, 1060, 860, 690 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{34}NO_3$: (M+H) 384.2539, found 384.2523. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 9.27; N, 3.65. Found: C, 75.35; H, 8.95; N, 3.71.

(4*S*,5*S*)-4-[(*S*)-(1-*N*-(Benzyloxycarbonyl)amino-1-phenyl)ethyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (5). To a solution of primary amine **4** (414.4 mg, 1.21 mmol) and diisopropylethylamine (0.53 mL, 2.5 equiv) in acetonitrile (10 mL) was added CBzCl (0.22 mL, 1.2 equiv) over 1 min. The reaction was stirred until TLC shows disappearance of starting material (24 h). H_2O (20 mL) and ether (60 mL) were added and the layers were separated. The organic layer was washed twice with 10% aqueous HCl (2 x 20 mL) and then with a saturated solution of brine (20 mL) containing saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by chromatography (15% EtOAc/hexanes) to yield the protected amine **5** as a colorless oil (551 mg, 95%): R_f 0.46 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ -18.2° (*c* 1.74, $CHCl_3$); ^1H NMR (300 MHz, CDC13) δ 7.42-7.25 (m, 15H, Ph), **5.89 (s(br), 1H, NH)**, 5.14-5.08 (m(br), 2H, $C(O)OCH_2Ph$), 4.38 (d, *J* = 12.2 Hz, 1H, CH_2OCH_2Ph), 4.34 (d, *J* = 12.2 Hz, 1H, CH_2OCH_2Ph), 4.12 (d, *J* = 7.7 Hz, 1H, CH(OR)), 4.06-4.02 (m, 1H, $CH(OR)CH_2$), 2.88 (dd, 1H, *J* = 10.4, 3.2 Hz, CH_2OBn), 2.80 (dd, *J* = 10.4, 5.3 Hz, 1H, CH_2OBn), 1.92 (s(br), 3H, CH_3), 1.48 (s, 3H, CH_3CCH_3), 1.44 (s, 3H, CH_3CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.01, 140.96, 137.76, 136.68, 128.41, 128.27, 128.17, 128.08, 127.98, 127.64, 127.59, 127.20, 126.10, 109.41, 83.43, 76.37, 73.28, 70.77, 66.34, 58.47, 27.2, 26.80, 22.69; IR (neat) 3420, 3340, 3060, 3030, 2980, 2930, 2860, 1740, 1490, 1450, 1245, 1080, 1040, 905, 730, 690 cm^{-1}. Anal. Calcd for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95. Found: C, 73.53; H, 7.21; N, 3.04.

(*S*)-2-*N*-(Benzyloxycarbonyl)amino-2-methyl-2-benzeneacetic Acid (8). A solution of the protected amine **5** (236 mg, 0.495 mmoles) in methanol (5 mL) containing $TsOH{\bullet}H_2O$ (198 mg, 1.04 mmol) was stirred at 60 °C for 13 h. The reaction mixture was diluted with water (20 mL) and ether (60 mL). The organic layer was washed with a mixture of saturated aqueous $NaHCO_3$ (5 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The diol obtained (218.2 mg) was then dissolved in a 4:1 mixture of THF:H_2O (10 mL) and sodium periodate (325 mg, 1.52 mmol) was added. After 8 h of stirring at room temperature, the reaction mixture was quenched with saturated aqueous $NaHSO_3$ (5 mL) and diluted with ether (50 mL) and H_2O (20 mL). The layers were separated and the organic layer was washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Benzyloxyacetaldehyde was removed by pumping under high vacuum (0.01 mm Hg) for 12 hours. The remaining aldehyde was dissolved in *t*-BuOH (3 mL) and 5% aqueous NaH_2PO_4 (2 mL) was added followed by a 1.0 M aqueous solution of $KMnO_4$ (3 mL). The oxidation was complete after 5-10 min. The reaction was then immediately quenched with saturated aqueous $NaHSO_3$ and the brown thick suspension was treated with 10% aqueous HCl until the solution became clear. The mixture was then extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography (57:38:5 hexanes/EtOAc/AcOH) to produce the desired acid as pasty white solid (116.0 mg, 80% 3 steps): R_f 0.50 (57:38:5 hexanes/EtOAc/AcOH); $[\alpha]_D^{20}$ +35.5° (*c* 2.83, MeOH), (lit.$[\alpha]_D$ +38.5° (*c* 0.2, MeOH);[14] ^1H NMR (300 MHz, CDC13) δ 11.9 (br, 1H, COOH), 8.31 (br, 0.5H, NH), 7.51-7.29 (m, 8H, Ph), 7.20 (br, 1H, Ph), 6.74 (br, 1H, Ph), 6.14 (br, 0.5H, NH), 5.05 (br, 1H, OCH_2Ph), 4.90 (br, 1H, OCH_2Ph), 2.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ Two rotamers: 176.74, 176.06, 156.98, 154.87, 140.93, 139.75, 135.98, 135.27, 128.95, 128.48, 128.40, 128.26, 128.14, 128.10, 128.01, 127.95, 125.90, 67.29, 67.12, 61.94, 22.91. IR (neat) 3420, 3400, 3030, 3000 (v br), 2610, 2510, 1700 (br), 1500, 1450, 1390, 1265, 1055, 940, 910, 750, 690 cm^{-1}.

(4*S*,5*S*)-4-[(S)-(1-N-(Trifluoroacetyl)amino-1-phenyl)butyl]-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (X-ray). To a solution of the amine (97.0 mg, 0.262 mmol) (obtained in Table 1, entry 6) in dichloromethane (5 mL) was added pyridine (63 µL, 0.78 mmol) and trifluoroacetic anhydride (56 µL, 0.39 mmol). The mixture was stirred until tlc analysis showed complete consumption of starting material (2 h). The mixture was then diluted with H_2O (15 mL) and ether (40 mL) and the layers were separated. The organic layer was washed with 10% aqueous HCl (2 x 10 mL) and with a mixture of brine (15 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (12% EtOAc/hexanes) to afford the desired protected amine (109.5 mg, 90%) as a white solid suitable for X-ray crystallographic analysis: mp 101 °C; R_f 0.38 (10% EtOAc/hexanes), $[\alpha]_D^{21}$ -40.6° (*c* 1.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 8.35 (br, 1H, **NH**), 7.44-7.26 (m, 10H, Ph), 4.66-4.64 (m, 2H, $OC\mathbf{H}_2Ph$), 4.21 (d, *J* = 6.9 Hz, 1H, **CH**(OR)), 3.81 (ddd, *J* = 9.0, 6.9, 4.5 Hz, 1H, C**H**(OR)CH_2); 3.55 (dd, *J* = 8.8, 4.5 Hz, 1H, $\mathbf{CH_2}OBn$), 3.28 (t, *J* = 8.9 Hz, 1H, $\mathbf{CH_2}OBn$), 2.66-2.55 (m, 1H, $\mathbf{CH_2}CH_2CH_3$), 2.51-2.43 (m, 1H, $\mathbf{CH_2}CH_2CH_3$), 1.52-1.45 (m, 1H, $\mathbf{CH_2}CH_3$), 1.36-1.30 (m, 1H, $\mathbf{CH_2}CH_3$), 1.26 (s, 3H, $\mathbf{CH_3}$), 1.02 (s, 3H, $\mathbf{CH_3}$), 1.01 (t, *J* = 7.2 Hz, 3H, $CH_2\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.90 (q, *J* = 36 Hz), 138.56, 136.24, 128.60, 128.33, 128.18, 127.78, 127.41, 127.01, 115.90 (q, *J* = 290 Hz), 109.69, 81.73, 74.41, 73.56, 70.06, 63.31, 35.59, 26.90, 26.21, 16.65, 14.15; IR (neat) 3400, 3090, 2970, 1730, 1565, 1380, 1210, 1140, 1070, 860, 745, 690 cm^{-1}.





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