Synthesis of Adamantylglycine Using a Diastereoselective Grignard-to-Nitrone Addition

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Dedicated to Professor Dr. Franz X. Effenberger on the occasion of his 80th birthday

Abstract: In contrast to amino acids with a bulky substituent like *tert*-leucine, adamantylglycine has so far received little attention. Here, a new, practical synthesis of adamantylglycine is described. This is based on a highly diastereoselective addition of adamantyl Grignard reagent to 2,3-*O*-cyclohexylideneglyceraldehyde *N*-benzylnitrone, mediated by the Lewis acid diethylaluminum chloride. Adamantylglycine is obtained from the nitrone in 6 steps and 28% yield as a crystalline hydrochloride with 0.5 methanol incorporated.

Key words: glyceraldehyde, chiral nitrone, Grignard addition, electrophilic glycine equivalent, crystal structure

Amino acids, respective amino alcohols, and their derivatives have played a major role in stereoselective organic chemistry[1] as enantiomerically pure building blocks,[2] auxiliaries,[3] ligands,[3a,4] or organocatalysts.[5] Of particular interest in this respect are α-amino acids with bulky substituents, such as *tert*-leucine ('α-*tert*-butylglycine') or the derived *tert*-leucinol.[6,7]

In contrast to this, the related adamantylglycine (AdGly, **1**, Figure 1) and -glycinol are much less known[8,9] and have rarely been employed in synthesis.[8f,10] Notably, enantiomerically pure adamantylglycine has been secured by separation of racemic or diastereomeric precursors.[8] The seemingly most efficient (6 steps, '44%' overall yield) approach to *N*-Boc-adamantylglycine has been developed in the course of a synthesis of saxagliptin (**A**), an efficient dipeptidylpeptidase inhibitior (DPP-IV) applied for the treatment of type 2 diabetes mellitus.[8f] This was based on an asymmetric variant of the Strecker synthesis, using (*R*)-phenylglycinol as a chiral adjuvant. In this paper, however, intermediates and adamantylglycine were only characterized by ^{1}H NMR and low-resolution MS; other spectroscopic data, optical rotations or elemental analyses, were not given.[8f] However, an interesting ligand-mediated addition of phenyllithium to the *N*-anisylimine of 1-adamantane carboxaldehyde, high induction (89% ee) was achieved, with low overall efficiency.[9]

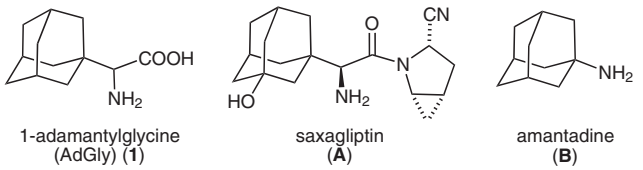

Figure 1 Adamantylglycine (**1**), saxagliptin (**A**), and amantadine (**B**)

Amino derivatives with the adamantane framework have also found attention in medicinal chemistry, for example, memantine (Alzheimer's desease),[11] amantadine (**B**), rimantadine (influenza virus A in adults),[12] and tromantadine (herpes simplex).[13]

In order to elaborate a practical synthesis of adamantylglycine enantiomers, we considered to extend the earlier, related work in our group concerning approaches to various amino acids, amino- and iminopolyols. Thus, additions of C-nucleophiles to imines derived from optically active α-oxyaldehydes (e.g., glyceraldehyde, lactaldehyde, threose, erythrose) had been used.[14–19] Due to the 1,2-asymmetric induction, mostly highly diastereoselective additions were found. If less so, additional diastereoselection was achieved by applying (*R*)- or (*S*)-1-phenethylamine-derived imines as match/mismatch-effecting substrates.[17] When the imine approach proved less satisfactory, recourse to respective nitrones often rectified this situation.[20,21] Now N-derivatives of 1,2-*O*-alkylidene glyceraldehyde like **C** or **D** were considered: They would constitute chiral electrophilic equivalents of glycine,[22] since the diol part after addition to the C=N bond and deprotection can then be converted to a carboxy group[14,16,17,19,20b,e,h,23] (see Figure 2). A closely related sequence has also been applied with nitrile oxides **D** such as glyceronitrile oxide,[24] or with respective imines **C** for [2+2] cycloadditions towards β-lactams.[25]

The addition of adamantyl Grignard reagent[26] was first studied with *N*-benzylimines of 2-*O*-benzyl- and 2,3-*O*-

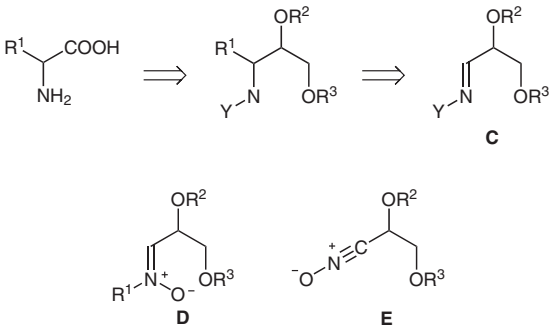

Figure 2 Electrophilic glycine equivalents

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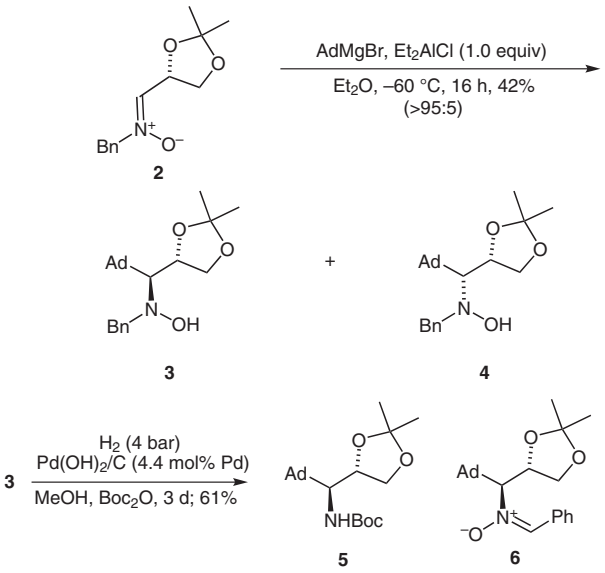
isopropylideneglyceraldehyde. Both reactions led to moderate yields with side-products difficult to remove; it had been registered earlier that such additions proceeded rather sluggishly with voluminous Grignard reagents like *tert*-butylmagnesium chloride, where an aziridine had been identified as one of the by-products.[17] In some cases, Grignard additions even had not occurred at room temperature, and high pressure of 12 kbar at 50–54 °C had to be applied.[17]

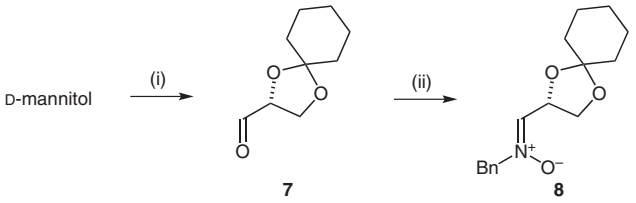
We therefore turned to the *N*-benzylnitrone of glyceraldehyde acetonide **2**;[20,27] this indeed gave a product from which the required adduct was readily isolated, albeit in 51% yield and as a 42:58 mixture of diastereomers **3** and **4**. Similar additions to this nitrone had been reported earlier by Dondoni et al. and Merino et al., who also had shown that distinct variations of diastereoselectivity could be effected by adding Lewis acids.[20a,b,d] For example, the reaction of **2** with phenylmagnesium bromide in diethyl ether alone afforded a 65:35 mixture of *threo*/*erythro* isomers, which then changed to 78:22 ($ZnBr_2$, 1.1 equiv) or 15:85 (Et_2AlCl, 1.1 equiv).[20b] Indeed, upon addition of an equimolar amount of diethylaluminum chloride in our case the adamantyl product **3** was obtained as the sole isomer (dr >95:5), in a moderate 42–48% yield (Scheme 1).



Scheme 1

The next step of the planned synthesis involved the removal of the *N*-benzyl and *N*-hydroxy groups by catalytic hydrogenation. This also proved a rather slow process; with Pearlman's catalyst $Pd(OH)_2$ on carbon,[28] ca. 4 mol% of Pd, at a pressure of 4 bar in the presence of di-*tert*-butyl dicarbonate (Boc_2O) after 3 days the *N*-Boc-protected amine **5** was isolated in pure form in 61% yield. In earlier experiments using less Pd catalyst (1.8 mol%), the reduction had been incomplete, and after workup and chromatography on silica gel, the nitrone **6** had also been obtained (23%). Formation of this nitrone is probably due to oxidation of the starting compound, in accord with the well-known sensitivity of N,N-disubstituted hydroxylamines towards aerial oxygen.[29] The structure of this unusual nitrone, which also formed when the hydroxylamine **3** was kept in solution ($CDCl_3$, NMR), became evident after crystal structure analysis.[30]

As seen, for example, from the above-mentioned moderate yields, the acetonide group may have caused problems during workup and chromatographic separations, due to its lability towards even mildly acidic conditions. Cyclohexylidene acetals,[24d,31] with diminished water solubility and higher stability,[32] were employed therefore, starting from D-mannitol via the 2,3-*O*-cyclohexylideneglyceraldehyde (**7**)[31a] as the new key substrate. Adopting the procedure given by Dondoni et al.,[27] the nitrone **8** was obtained in 74% yield in pure form as the *Z*-isomer[31b,33] (Scheme 2).



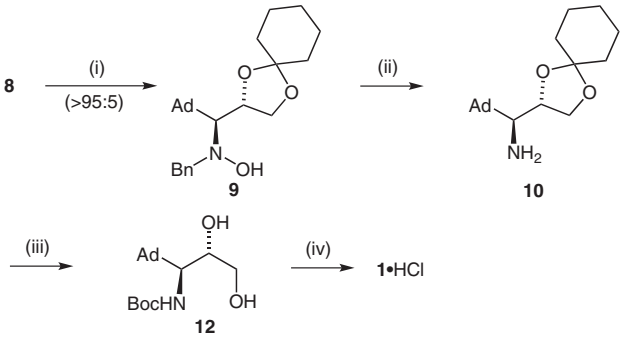
Scheme 2 *Reagents and conditions:* (i) Ref. 31; (ii) BnNHOH, $MgSO_4$, CH_2Cl_2, r.t., 17 h, 74%.

The Grignard addition to yield **9** was carried out as above and proceeded with better yield, again with *erythro*/*threo* >95:5. Catalytic hydrogenation of the hydroxylamine **9** led to the diol-protected amine **10** and on further acid-catalyzed acetal cleavage to the free aminodiol hydrochloride **11**·HCl. This salt crystallized as a monohydrate suitable for crystal structure determination, which also permitted to ascertain the relative and absolute configurations (anomalous dispersion method).[34]

The diol part of **12**, the *N*-Boc derivative, was converted to the carboxy function according to standard procedures, that is, sodium periodate cleavage followed by sodium chlorite oxidation[35] of the intermediate aldehyde. This furnished the crystalline hydrochloride of 1-adamantylglycine **1**·HCl (with 0.5 MeOH) in pure form and somewhat higher optical rotation than reported before (see experimental section) (Scheme 3).

The crystal structure of **1**·HCl depicted below (Figure 3) shows methanol (one half equivalent!) in between two sheets of organic molecules exhibiting three hydrogen bonds, while chloride acts to fix the protonated amino acids with the respective sheet.[36,37]

In conclusion, we have outlined a convenient route to (*S*)-1-adamantylglycine **1**·HCl from the known nitrone **8** (6 steps, 28% yield), amenable to access the *R*-enantiomer likewise (from L-gulose via the respective L-glyceraldehyde). In addition, the intermediate aminodiol **11** and its N- or O-protected derivatives should be interesting ligands for applications in metal-catalyzed catalytic processes.



Scheme 3 *Reagents and conditions:* (i) AdMgBr, Et_2AlCl (1.0 equiv), Et_2O, –60 °C, 16 h, 61%; (ii) H_2 (4 bar), $Pd(OH)_2/C$ (4.1 mol% Pd), MeOH–THF (4:1), Et_3N, 3 d, 87%; (iii) 1. aq 12 N HCl, THF, 16 h, 82% of **11**·HCl; 2. Boc_2O, Et_3N, 16 h, 79%; (iv) 1. $NaIO_4$ (1.2 equiv), MeOH–H_2O (1:1), then $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, 82% of *N*-Boc-AdGly **13**; 2. aq 12 N HCl, THF, 21 h, 94% of **1**·HCl·(0.5 MeOH).

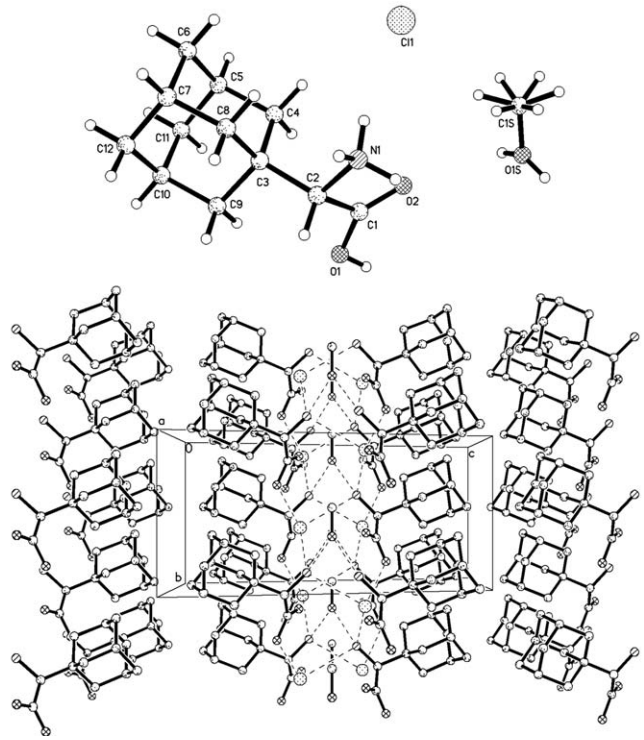


Figure 3 Crystal structure of **1**·HCl·(0.5MeOH) as a single species and orientation in the unit cell[36]

Benzaldehyde oxime[38] and *N*-benzylhydroxylamine were obtained in accordance with the literature[39] [*N*-benzylhydroxylamine: 72% yield; mp 49–52 °C (Lit.[39] 79%; mp 58–59 °C)]. 1,2:5,6-Diisopropylidene-D-mannitol was prepared according to the literature[40] in 49% yield; mp 117–119 °C (Lit.[40] 54%; mp 121.8–123.4 °C). 2,3-*O*-Isopropylidene-D-glyceraldehyde *N*-benzylnitrone (**2**) was synthesized according to a known procedure;[27] yield: 68%; mp 85–87 °C; $[\alpha]_D^{20}$ +92 (c = 0.6, $CHCl_3$) {Lit.[27] yield: 86%; mp 88 °C; $[\alpha]_D^{20}$ +96.7 (c = 0.5, $CHCl_3$)}. 2,3-*O*-Cyclohexylidene-D-glyceraldehyde was prepared as described from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol by periodate cleavage;[31] the crude product (yield ca. 90%) was used directly. AdBr was purchased from Aldrich and Et_2AlCl (ca. 1 M *n*-hexane solution) from Fluka. Petroleum ether (PE) refers to the fraction boiling in the range 40–60 °C.

^1H and ^{13}C NMR spectra were recorded on Bruker ARX 300 or Bruker ARX 500 spectrometers with TMS as internal standard. Peak assignments are based on DEPT and 2D NMR studies. All dr values were determined from ^{13}C NMR spectra. IR spectra were recorded on a Bruker IFS 28 spectrophotometer. The optical rotations were measured on a Perkin-Elmer 241 MC polarimeter using the Drude method to calculate $[\alpha]_D^{20}$ from the values found at 546 and 579 nm. Crystal structure analysis: Nicolet P3 diffractometer with graphite monochromator, Mo-K_α radiation, calculation of structures according to programs of Sheldrick.[41]

(2*S*,3*RS*)-3-(1-Adamantyl)-3-(*N*-benzylhydroxylamino)-1,2-*O*-isopropylidene-1,2-propanediol (3/4)

Preparation of the ethereal solution of 1-adamantylmagnesium bromide:[26,42] A 50 mL two-necked flask was equipped with a condenser, connected to the vacuum line, and charged with Mg turnings (23.3 mmol, 0.56 g). The flask was preheated to 150 °C for 10 min under reduced pressure, cooled under N_2, and absolute Et_2O (4 mL) was added followed by the addition of dibromoethane (3 drops). To this suspension, a solution of 1-bromoadamantane (4.66 mmol, 1.00 g) in absolute Et_2O (6 mL) was carefully added within 20–30 min, keeping the temperature below the boiling point of Et_2O. The suspension was stirred for 30 min at r.t. and heated under reflux for 1 h. After cooling to r.t., the solution of 1-adamantylmagnesium bromide was used immediately in the next step.

According to literature procedures,[20b,d] a well-stirred solution of the *N*-benzylnitrone **2** (0.55 g, 2.3 mmol) in absolute Et_2O (40 mL) was cooled to –60 °C, treated with previously prepared AdMgBr, and stirred for 17 h at this temperature. The reaction was quenched by the addition of sat. aq NH_4Cl (10 mL) and allowed to stir for 20 min. The aqueous layer was separated and extracted with Et_2O (3 × 15 mL). The combined ethereal layers were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo (40 °C/15 mbar, then 0.05 mbar) to afford a yellow solid (0.92 g, '106%'). This was purified by flash chromatography on silica gel (60 g, column 18 cm × 3 cm), eluting first with PE and then with EtOAc–PE (15:85, v/v) to yield 0.44 g (51%) of a colorless solid consisting of **3/4** with dr = 58:42.

Major Diastereomer (*erythro*-3)

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.7 and 27.00 [2 q, C(CH_3)$_2$], 28.8 (d, C-3′, C-5′, C-7′), 37.2 (t, C-4′, C-6′, C-9′), 38.1 (s, C-1′), 40.4 (t, C-2′, C-8′, C-10′), 64.7 (t, $CH_2C_6H_5$), 68.2 (t, C-1), 74.9 (d, C-3), 75.0 (d, C-2), 107.2 [s, $C(CH_3)_2$], 127.2 (d, *p*-C of C_6H_5), 128.3 and 129.0 (2 d, *o*-, *m*-C of C_6H_5), 139.4 (s, *i*-C of C_6H_5).

Minor Diastereomer (*threo*-4)

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.4 and 26.6 [2 q, C(CH_3)$_2$], 28.6 (d, C-3′, C-5′, C-7′), 36.7 (t, C-4′, C-6′, C-9′), 36.8 (t, C-2′, C-8′, C-10′), 39.9 (s, C-1′), 65.6 (t, $CH_2C_6H_5$), 70.1 (t, C-1), 75.0 (d, C-3), 108.0 [s, $C(CH_3)_2$], 127.1 (d, *p*-C of C_6H_5), 128.2 and 128.2 (2 d, *o*-, *m*-C of C_6H_5), 139.1 (s, *i*-C of C_6H_5).

(2*S*,3*S*)-3-(1-Adamantyl)-3-(*N*-benzylhydroxylamino)-1,2-*O*-isopropylidene-1,2-propanediol (3)

1-Adamantylmagnesium bromide was prepared as described above. In accordance with literature reports,[20b,d,e] to a well-stirred solution of the *N*-benzylnitrone **2** (1.00 g, 4.3 mmol) in absolute Et_2O (50 mL) was added Et_2AlCl (ca. 4.3 mmol) in one portion at r.t. The resulting mixture was stirred for 15 min under N_2, cooled to –60 °C, treated with a solution of 1-adamantylmagnesium bromide (ca. 8.5 mmol), and stirred for 16 h at this temperature. The reaction was quenched by the addition of 2.5% aq NaOH (20 mL) and allowed to stir for additional 20 min. The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined ethereal layers were washed with brine (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo (40 °C/15 mbar, then 0.05 mbar) to give 1.23 g (89%) of a

yellow solid. This was purified by flash chromatography on silica gel (60 g, column 18 cm × 3 cm); elution with EtOAc–PE (20:80, v/v) yielded 0.67 g ('42%') of a spectroscopically pure colorless solid; mp 131–132 °C. According to the ^{13}C NMR spectra, the ratio **3/4** (*erythro*/*threo*) was >95:5; $[\alpha]_D^{20}$ +31 (*c* = 0.67, $CHCl_3$).

IR (neat): 3417 (w, OH), 2899 (s), 2843 (s, NH_2), 1447 (m), 1113 (vs, C–O), 1008 (s), 909 (s), 695 cm^{-1} (s).

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.39 and 1.48 [2 s, 3 H each, $C(CH_3)_2$], 1.68 (m, 6 H, 4′-H, 6′-H, 9-H), 1.78 (m, 6 H, 2′-H, 8′-H, 10′-H), 1.98 (m, 3 H, 3′-H, 5′-H, 7′-H), 2.58 ('d', $^3J_{2,3}$ = 5.6 Hz, 1 H, 3-H), 3.96 (A of AB, $^2J_{A,B}$ = 13.7 Hz, 1 H, $CH_AH_BC_6H_5$), 4.20 ('dd', $^2J_{1a,2}$ = 6.4 Hz, $^3J_{1b,2}$ = 8.1 Hz, 2 H, 1-H_a, 1-H_b), 4.24 (B of AB, ^2J = 13.7 Hz, 1 H, $CH_AH_BC_6H_5$), 4.39 (br s, 1 H, NOH), 4.46 ('ddd', $^2J_{1a,2}$ = 6.4 Hz, $^3J_{1b,2}$ = 8.1 Hz, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 7.24–7.40 (m, 5 H, *o*-, *m*-, *p*-H of C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.7 and 26.9 [2 q, $C(CH_3)_2$], 28.7 (d, C-3′, C-5′, C-7′), 37.1 (t, C-4′, C-6′, C-9′), 40.4 (t, C-2′, C-8′, C-10′), 38.0 (s, C-1′), 64.6 (t, $CH_2C_6H_5$), 68.1 (t, C-1), 74.8 (d, C-3), 75.0 (d, C-2), 107.1 [s, $C(CH_3)_2$], 127.1 (d, *p*-C of C_6H_5), 128.3 and 128.9 (2 d, *o*-, *m*-C of C_6H_5), 139.3 (s, *i*-C of C_6H_5).

Anal. Calcd for $C_{23}H_{33}NO_3$ (371.5): C, 74.36; H, 8.95; N, 3.77. Found: C, 74.54; H, 8.99; N, 3.63.

(2*S*,3*S*)-3-(1-Adamantyl)-3-(*tert*-butoxycarbonylamino)-1,2-*O*-isopropylidene-1,2-propanediol (5)

Diastereomerically pure *N*-benzylhydroxylamine **3** (320 mg, 0.86 mmol) was dissolved in anhyd MeOH (10 mL), then di-*tert*-butyl dicarbonate (282 mg, 11.5 mmol) was added, and the resulting solution was transferred into a hydrogenation vessel. This was flushed with N_2 and $Pd(OH)_2$/C (40 mg) was added. The reaction was carried out under H_2 pressure (4.8 bar) for 3 days. The resulting suspension was filtered through a pad of Celite/silica gel (ca. 1 cm, Celite on top) and the adsorbent was washed with EtOAc (2 × 10 mL). The filtrate was concentrated in vacuo (40 °C/15 mbar) to give a colorless semi-solid, which was purified by column chromatography on silica gel (10 g, column 1 cm × 4 cm), eluting with EtOAc–PE–Et_3N (50:50:2, v/v/v). From this, 192 mg (61%) of **5** was isolated as an analytically pure, colorless solid; mp 109–114 °C; $[\alpha]_D^{20}$ +20 (*c* = 1.54, MeOH).

IR (neat): 2902 (vs, b), 2849 (vs), 1678 (vs, amide I), 1525 (s, amide II), 1452 (m), 1365 (s), 1242 (s), 1161 (vs), 1049 (vs, b, C-O), 1011 (vs, C–O), 940 (s), 827 cm^{-1} (s).

^1H NMR (500.2 MHz, $CDCl_3$): δ = 1.34 and 1.38 [2 s, 3 H each, $C(CH_3)_2$], 1.44 [s, 9 H, $C(CH_3)_3$], 1.51–1.71 (m, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 9′-H, 10′-H), 1.98 (br s, 3 H, 3′-H, 5′-H, 7′-H), 3.55 ('dd', $^3J_{2,3}$ = 6.2 Hz, $^3J_{2,NH}$ = 10.8 Hz, 1 H, 3-H), 3.67 ('dd', $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1a,2}$ = 7.7 Hz, 1 H, 1-H_a), 3.98 ('dd', $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1b,2}$ = 6.4 Hz, 1 H, 1-H_b), 4.23 ('dt', $^3J_{1a,2}$ = 7.5 Hz, $^3J_{1b,2}$ = $^3J_{2,3}$ = 6.3 Hz, 1 H, 2-H), 4.45 (d, $^3J_{3,NH}$ = 10.8 Hz, 1 H, NH).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.7 and 26.4 [2 q, $C(CH_3)_2$], 28.3 [q, $C(CH_3)_3$], 28.4 (d, C-3′, C-5′, C-7′), 35.9 (s, C-1′), 36.9 (t, C-4′, C-6′, C-9′), 39.1 (t, C-2′, C-8′, C-10′), 58.1 (d, C-3), 66.8 (t, C-1), 74.7 (d, C-2), 79.2 [s, $C(CH_3)_3$], 108.8 [s, $C(CH_3)_2$], 156.2 (C=O).

Anal. Calcd for $C_{21}H_{35}NO_4$ (365.5): C, 69.01; H, 9.65; N, 3.83. Found: C, 68.77; H, 9.58; N, 3.57.

2,3-*O*-Cyclohexylidene-D-glyceraldehyde *N*-Benzylnitrone (8)

According to Dondoni's procedure,[27] 2,3-*O*-cyclohexylidene-D-glyceraldehyde (**7**; 1.38 g, 8.1 mmol) and *N*-benzylhydroxylamine[39] (1.00 g, 8.1 mmol) were dissolved in anhyd CH_2Cl_2 (20 mL), and $MgSO_4$ (ca. 2 g) was added. The suspension was stirred overnight (17 h) at r.t., and the solid was filtered off. The filtrate was evaporated and the residue recrystallized from EtOAc–PE to give the nitrone product **8** as a spectroscopically and analytically pure solid (1.65 g, 74%); mp 97–100 °C (Lit.[31] mp 88–89 °C); $[\alpha]_D^{20}$ +79 (*c* = 1.28, EtOH) {Lit.[31] $[\alpha]_D^{20}$ +82.5 (*c* = 1.00, EtOH)}.

IR (neat): 2929 (s), 2852 (m, C = N–O), 1443 (s), 1273 (s, N–O), 1198 (s), 1168 (s), 1102 (vs, C–O), 1024 (s), 927 (vs, N–O), 706 (vs), 664 (s), 589 cm^{-1} (s).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.40 (m, 2 H, 4′-H), 1.58 (m, 8 H, 2′-H, 3′-H, 5′-H, 6′-H), 3.88 ('dd', $^3J_{2,3a}$ = 5.7 Hz, $^2J_{3a,3b}$ = 8.6 Hz, 1 H, 3-H_a), 4.38 ('dd', $^3J_{2,3b}$ = 7.0 Hz, $^2J_{3a,3b}$ = 8.6 Hz, 1 H, 3-H_b), 4.87 ('s', 2 H, A, B of $CH_AH_BC_6H_5$), 5.15 ('ddd', $^3J_{1,2}$ = 4.2 Hz, $^3J_{2,3a}$ = 5.7 Hz, $^3J_{2,3b}$ = 7.0 Hz, 1 H, 2-H), 6.86 ('d', $^3J_{1,2}$ = 4.2 Hz, 1 H, 1-H), 7.39–7.41 (m, 5 H, *o*-, *m*-, *p*-H of C_6H_5).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.7 (t, C-4′), 23.9 and 25.0 (2 t, C-3′ and C-5′), 34.3 and 35.9 (2 t, C-2′, C-6′), 67.5 (t, C-3), 69.0 (t, $CH_2C_6H_5$), 71.7 (d, C-2), 110.6 (s, C-1′), 129.2 (d, *p*-C of C_6H_5), 129.0 and 129.4 (2 d, *o*-, *m*-C of C_6H_5), 132.1 (s, *i*-C of C_6H_5), 139.4 (d, C-1).

Anal. Calcd for $C_{16}H_{21}NO_3$ (275.3): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.75; H, 7.72; N, 5.05.

(2*S*,3*S*)-3-(1-Adamantyl)-3-(*N*-benzylhydroxylamino)-1,2-*O*-cyclohexylidene-1,2-propanediol (9)

1-Adamantylmagnesium bromide was prepared as described above. In analogy to literature reports,[20b,d,e] to a well-stirred solution of the *N*-benzylnitrone **8** (1.42 g, 5.2 mmol) in absolute Et_2O (60 mL) was added Et_2AlCl (ca. 5.2 mmol) in one portion at r.t. The resulting mixture was stirred for 15 min under N_2, cooled to –60 °C, treated with adamantylmagnesium bromide (ca. 10.4 mmol), and stirred for 17 h at this temperature. The reaction was quenched by the addition of sat. aq NH_4Cl (ca. 40 mL) and allowed to stir for 20 min. The aqueous layer was then separated and extracted with Et_2O (3 × 20 mL). The combined ethereal layers were washed with brine (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo (40 °C/15 mbar, then 0.05 mbar) to give the crude product as a yellowish semi-solid, 2.50 g ('117%'). Only one diastereomer of **9** was detected according to the ^{13}C NMR spectrum, as well as 10–15% of the starting nitrone **8**. The crude material was purified by flash chromatography on silica gel (40 g, column 14 cm × 3 cm), eluting with PE (ca. 100 mL) followed by PE–EtOAc (80:20, v/v). The product **9** was isolated as a colorless, analytically pure solid; mp 129–132 °C (1.29 g, 61%); $[\alpha]_D^{20}$ +21 (*c* = 1.00, $CHCl_3$).

IR (neat): 3417 (w, OH), 2899 (s), 2843 (s, NH_2), 1447 (m), 1113 (vs, C–O), 1008 (s), 909 (s), 695 cm^{-1} (s).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.41 (m, 2 H, 4″), 1.55–1.70 (m, 14 H, 4′-H, 6′-H, 9′-H, 2″-H, 3″-H, 5″-H, 6″-H), 1.80 (br s, 6 H, 2′-H, 8′-H, 10′-H), 1.99 (br s, 3 H, 3′-H, 5′-H 7′-H), 2.57 ('d', $^3J_{2,3}$ = 6.3 Hz, 1 H, 3-H), 3.95 (A of AB, $^2J_{A,B}$ = 13.7 Hz, 1 H, $CH_AH_BC_6H_5$), 4.14 (dd, $^2J_{1a,1b}$ = 8.1 Hz, $^3J_{1a,2}$ = 8.8 Hz, 1 H, 1-H_a), 4.21 (B of AB, $^2J_{A,B}$ = 13.8 Hz, 1 H, $CH_AH_BC_6H_5$), 4.22 ('dd', $^2J_{1a,1b}$ = 8.1 Hz, $^3J_{1b,2}$ = 5.7 Hz, 1 H, 1-H_b), 4.45 ('ddd', $^3J_{1a,2}$ = 8.8 Hz, $^3J_{1b,2}$ = 5.7 Hz, $^3J_{2,3}$ = 6.3 Hz, 1 H, 2-H), 7.24–7.36 (m, 5 H, *o*-, *m*-, *p*-H of C_6H_5).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.1 (t, C-3″, C-5″), 25.3 (t, C-4″), 28.8 (d, C-3′, C-5′, C-7′), 35.1 and 36.6 (2 t, C-2″, C-6″), 37.2 (t, C-4 ′, C-6′, C-9′), 38.0 (s, C-1′), 40.4 (t, C-2′, C-8′, C-10′), 64.6 (t, $CH_2C_6H_5$), 68.1 (t, C-1), 74.4 (d, C-3), 75.0 (d, C-2), 107.8 (s, C-1″), 127.1 (d, *p*-C of C_6H_5), 128.3 and 128.9 (2 d, *o*-, *m*-C of C_6H_5), 139.4 (s, *i*-C of C_6H_5).

Anal. Calcd for $C_{26}H_{37}NO_3$ (411.6): C, 75.87; H, 9.06; N, 3.40. Found: C, 75.41; H, 9.35; N, 3.31.

(2*S*,3*S*)-3-(1-Adamantyl)-3-amino-1,2-*O*-cyclohexylidene-1,2-propanediol (10)

Diastereomerically pure *N*-benzylhydroxylamine **9** (1.52 g, 3.7 mmol) was dissolved in THF–MeOH (10 mL:40 mL), and the resulting solution was transferred into a hydrogenation vessel. This was flushed with N_2, and $Pd(OH)_2/C$ (160 mg) was added. The reaction was carried out under H_2 pressure (4.8 bar) for 3 days. Then the suspension was filtered through a pad of Celite/silica gel (ca. 1 cm, Celite on top) and the adsorbent was washed with EtOAc (3 × 30 mL). The filtrate was concentrated in vacuo (40 °C/15 mbar, then 0.05 mbar). The crude product, a colorless semi-solid (1.13 g, '100%'), was chromatographed on silica gel (40 g, column 4 cm × 5 cm), eluting with EtOAc–PE–Et_3N (50:50:2, v/v/v). From this, 0.99 g (87%) of the amine **10** was isolated as an analytically pure, colorless solid; mp 94–95 °C; $[\alpha]_D^{20}$ +21 (*c* = 1.2, $CHCl_3$).

IR (neat): 2901 (vs, b, NH_2), 2846 (vs, NH_2), 1446 (s), 1362 (s), 1165 (s), 1097 (vs, b, C-O), 1032 (vs, C–O), 940 (s,), 827 cm^{-1} (s).

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.15 (br s, 2 H, NH_2), 1.40 (br s, 2 H, 4″-H), 1.49–1.74 (m, 20 H, 2′-H, 4′-H, 6′-H, 8′-H, 9′-H, 10′-H, 2″-H, 3″-H, 5″-H, 6″-H),1.98 (br s, 3 H, 3′-H, 5′-H, 7′-H), 2.70 ('d', $^3J_{2,3}$ = 3.6 Hz, 1 H, 3-H), 3.83 ('dd', $^2J_{1a,1b} = {}^3J_{1a,2}$ = 8.0 Hz, 1 H, 1-H_a), 3.92 ('dd', $^2J_{1a,1b}$ = 7.9 Hz, $^3J_{1b,2}$ = 6.9 Hz, 1 H, 1-H_b), 4.26 ('ddd', $^3J_{1a,2}$ = 7.8 Hz, $^3J_{1b,2}$ = 6.9 Hz, $^3J_{2,3}$ = 3.7 Hz, 1 H, 2-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.8 and 24.0 (2 t, C-3″, C-5″), 25.2 (t, C-4″), 28.4 (d, C-3′, C-5′, C-7′), 34.7 and 36.2 (2 t, C-2″, C-6″), 35.1 (s, C-1′), 37.1 (t, C-4′, C-6′, C-9′), 39.2 (t, C-2′, C-8′, C-10′), 61.4 (d, C-3), 64.4 (t, C-1), 75.6 (d, C-2), 107.8 (s, C-1″).

Anal. Calcd for $C_{19}H_{31}NO_2$ (305.5): C, 74.71; H, 10.23; N, 4.59. Found: C, 74.64; H, 10.11; N, 4.57.

(2*S*,3*S*)-3-(1-Adamantyl)-3-aminopropane-1,2-diol Hydrochloride (11·HCl)

According to a known procedure,[43] (2*S*,3*S*)-3-(1-adamantyl)-3-amino-1,2-*O*-cyclohexylidene-1,2-propanediol (**10**; 200 mg, 0.65 mmol) was dissolved in THF (2 mL), treated with concd HCl (2 mL), and stirred for 16 h at r.t. Then the solvents were removed in vacuo (40 °C/15 mbar) to give a colorless solid, which after recrystallization from MeOH–Et_2O gave 606 mg (82%) of the title 3-aminodiol **11**·HCl as a colorless, analytically pure solid; mp 235 °C (dec.); $[\alpha]_D^{20}$ +13 (*c* = 0.91, MeOH).

IR (neat): 3052 (bm, OH), 2998 (vs), 2846 (s), 1602 (m), 1505 (s), 1029 cm^{-1} (s).

^{1}H NMR (300.1 MHz, MeOD): δ = 1.70–1.81 (m, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 10′-H), 2.05 (br s, 3 H, 3′-H, 5′-H, 7′-H), 2.98 ('d', $^3J_{2,3}$ = 3.9 Hz, 1 H, 3-H), 3.86 ('d', $^3J_{1,2}$ = 3.5 Hz, 2 H, 1-H), 3.94 ('dd', $^3J_{1,2} = {}^3J_{2,3}$ = 3.7 Hz, 1 H, 2-H).

^{13}C NMR (75.5 MHz, MeOD): δ = 29.5 (d, C-3′, C-5′, C-7′), 35.5 (s, C-1′), 37.5 (t, C-4′, C-6′, C-9′), 39.5 (t, C-2′, C-8′, C-10′), 65.2 (t, C-1), 67.2 (d, C-2), 68.5 (d, C-3).

Anal. Calcd for $C_{13}H_{24}ClNO_2$ (261.8): C, 59.64; H, 9.24; N, 5.35; Cl, 13.54. Found: C, 59.35; H, 9.31; N, 5.22; Cl, 13.38.

(2*S*,3*S*)-3-(1-Adamantyl)-3-(*tert*-butoxycarbonylamino)-1,2-*O*-cyclohexylidenepropane-1,2-diol (12)

In analogy to a literature procedure,[44] the amine hydrochloride **11**·HCl (100 mg, 0.38 mmol) was suspended in MeCN (3 mL) and treated with Et_3N (ca. 20 μL). After stirring for 1 h, the pH of the solution became ca. 9. Then, di-*tert*-butyl dicarbonate (83 mg, 0.38 mmol) was added, and the mixture was left with stirring for 21 h. The solvent was removed in vacuo (40 °C/15 mbar), and the colorless solid was purified by filtration through silica gel (2.5 g, column 5 cm × 1.5 cm), eluting with EtOAc–PE (50:50, v/v). The diol **12** was isolated as an analytically pure, colorless solid (98 mg, 79%); mp 147–151 °C; $[\alpha]_D^{20}$ –5.9 (*c* = 0.56, $CHCl_3$).

IR (neat): 2900 (m), 2886 (m) and 2846 (m) (OH, NH), 1694 (s), 1671 (vs, amide I), 1507 (s, NH), 1366 (s), 1158 (s), 1041 (s), 1012 cm^{-1} (vs) .

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.45 [s, 3 H, $C(CH_3)_3$], 1.66–1.72 (br m, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 10′-H), 2.00 (br s, 3 H, 3′-H, 5′-H, 7′-H), 3.17 ('dd', $^3J_{1a,OH}$ = 3.9 Hz, $^3J_{1b,OH}$ = 9.6 Hz, 1 H, 1-OH), 3.20 ('d', $^3J_{2,OH}$ = 8.9 Hz, 1 H, 2-OH), 3.27 ('dd', $^3J_{2,3}$ = 6.7 Hz, $^3J_{3,NH}$ = 9.3 Hz, 1 H, 3-H), 3.58 (m, 1 H, 1-H_a), 3.65 ('ddd', $^3J_{1b,OH}$ = 3.8 Hz, $^2J_{1a,1b}$ = 11.9 Hz, $^3J_{1b,2}$ = 4.2 Hz, 1 H, 1-H_b), 3.72 (m, 1 H, 2-H), 4.69 (d, $^3J_{3,NH}$ = 9.3 Hz, 1 H, NH).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 28.4 [q, $C(CH_3)_3$], 28.4 (d, C-3′, C-5′, C-7′), 35.5 (s, C-1′), 36.8 (t, C-4′, C-6′, C-9′), 39.6 (t, C-2′, C-8′, C-10′), 61.8 (d, C-3), 64.7 (t, C-1), 71.1 (d, C-2), 80.3 [s, $C(CH_3)_3$], 157.8 (s, C=O).

^{1}H NMR (500.1 MHz, DMSO-d_6): δ = 1.38 [s, 3 H, $C(CH_3)_3$], 1.50–1.69 (br m, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 9′-H, 10′-H), 1.90 (br s, 3 H, 3′-H, 5′-H, 7′-H), 3.11 ('dd', $^3J_{2,3}$ = 3.2 Hz, $^3J_{3,NH}$ = 7.2 Hz, 1 H, 3-H), 3.20 ('ddd', *J* = 1.3, 2.3, 5.0 Hz, 1 H, 1-H_a), 3.42–3.46 ('ddd', *J* = 1.5, 2.8, 3.4 Hz, 1 H, 1-H_b), 3.53–3.58 (m, 1 H, 2-H), 4.38 (m, 2 H, 1-OH and 2-OH), 6.40 (d, $^3J_{3,NH}$ = 10.3 Hz, 1 H, NH).

^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 27.9 [q, $C(CH_3)_3$], 28.3 (d, C-3′, C-5′, C-7′), 36.0 (s, C-1′), 36.7 (t, C-4′, C-6′, C-9′), 38.5 (t, C-2′, C-8′, C-10′), 61.0 (d, C-3), 62.5 (t, C-1), 70.5 (d, C-2), 77.2 [s, $C(CH_3)_3$], 156.0 (s, C=O).

Anal. Calcd for $C_{18}H_{31}NO_4$ (325.4): C, 66.43; H, 9.60; N, 4.30. Found: C, 66.25; H, 9.61; N, 4.13.

(*S*)-*N*-(*tert*-Butoxycarbonylamino)-1-adamantylglycine [(*S*)-13]

In analogy to the literature,[24,35] the diol **12** (370 mg,1.14 mmol) was dissolved in THF–H_2O (60:40, 10 mL) and cooled to 0 °C. $NaIO_4$ (365 mg, 1.71 mmol) was added with vigorous stirring. The reacting suspension was left with stirring at 0–5 °C for 45 min, then it was filtered off and the solid was washed with Et_2O (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo (cold water bath/200 mbar). The residual colorless solid was dissolved in a mixture of *t*-BuOH (3 mL) and 2-methylbut-2-ene (5 mL). To this, an aq solution of $NaClO_2$ (154 mg, 1.71 mmol) and KH_2PO_4 (236 mg, 1.71 mmol) was added dropwise within 10 min at 0–10 °C. The resulting suspension was stirred for 1.5 h, followed by the addition of the same amount of $NaClO_2$ and KH_2PO_4 at 0 °C. After stirring overnight (18 h), aq 3 N NaOH (ca. 5 mL) was added and volatiles were removed in vacuo (40 °C/15 mbar). The residue was diluted with H_2O (ca. 10 mL) and acidified by the addition of aq 6 N HCl (ca. 3 mL) to reach pH 3–4 (with cooling in an ice-bath). The solid formed was extracted with EtOAc (5 × 80 mL). The combined organic layers were washed with sat. aq Na_2SO_3 (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo (40 °C/15 mbar) to give 357 mg (quant) of a colorless solid. Recrystallization from EtOAc–PE gave 291 mg (82%) of the spectroscopically and analytically pure *N*-Boc-protected amino acid (*S*)-**13**; mp >300 °C (dec.) (Lit.[8f] 'white foam'); $[\alpha]_D^{20}$ +22.6 (*c* = 1.13, $CHCl_3$).

IR (neat): 2972 (w), 2924 (m), 2901 (s), 2851 (m), 1713 (s, C=O of Boc), 1686 (s, amide I), 1645(s), 1506 (s, amide II), 1396 (m), 1153 (vs), 1041 (s), 1023 cm^{-1} (m) .

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 1.60–1.72 (bm, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 9′-H, 10′-H), 2.01 (br s, 3 H, 3′-H, 5′-H, 7′-H), 3.99 and 5.08 (2 d, $^3J_{2,NH}$ = 9.3 Hz, together 1 H, 2-H, rotamers). The ^{1}H NMR spectrum corresponds to that of the *S*-enantiomer of *N*-(*tert*-butoxycarbonylamino)-1-adamantylglycine reported.[8f]

^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 28.2 [q, $C(CH_3)_3$], 28.3 (d, C-3′, C-5′, C-7′), 36.1 (s, C-1′), 36.6 (t, C-4′, C-6′, C-9′), 38.5 (t, C-2′, C-

8′, C-10′), 62.4 (d, C-2), 79.9 [s, *C*(CH_3)$_3$], 155.7 (s, C=O of Boc), 176.3 (s, C=O).

At r.t. (295 K) the signals show satellite peaks at 64.5, 81.5 and 156.8 ppm, probably due to the presence of two rotamers. Recording the NMR spectra at 375 K (102 °C) using DMSO-d_6 as a solvent led to a coalescence of signals, which resulted in clear ^{1}H and ^{13}C NMR spectra.

^{1}H NMR (500.1 MHz, DMSO-d_6, 375 K): δ = 1.42 [s, 9 H, C(CH_3)$_3$], 1.60–1.71 (br m, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 9′-H, 10′-H), 1.98 (br s, 3 H, 3′-H, 5′-H, 7′-H), 3.72 (d, $^3J_{2,NH}$ = 9.2 Hz, 1 H, 2-H), 5.96 (d, $^3J_{2,NH}$ = 8.2 Hz, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6, 375 K): δ = 28.0 [q, C(*C*H_3)$_3$], 28.2 (d, C-3′, C-5′, C-7′), 35.1 (s, C-1′), 36.5 (t, C-4′, C-6′, C-9′), 38.5 (t, C-2′, C-8′, C-10′), 63.2 (d, C-2), 78.4 (s, [q, *C*(CH_3)$_3$], 155.4 (s, C=O of Boc), 171.8 (s, CO_2H).

Anal. Calcd for $C_{17}H_{27}NO_4$ (309.4): C, 65.99; H, 8.80; N, 4.53. Found: C, 66.05; H, 8.66; N, 4.51.

(*S*)-1-Adamantylglycine Hydrochloride [(*S*)-1·HCl]

The *N*-Boc-protected amino acid (*S*)-**13** (50 mg, 0.16 mmol) was dissolved in THF (1 mL) and treated with aq 12 N HCl (1 mL). After stirring for 1 h, a colorless solid was formed. Stirring was continued for ca. 20 h, and the solvents were removed in vacuo (40 °C/15 mbar, then 0.05 mbar) to give 40 mg (94%) of the title compound as an analytically almost pure (vide supra) colorless solid with a melting/decomposition range of 247–292 °C (Lit.[8c] mp 236–240 °C; Lit.[9] mp 236–241 °C); $[\alpha]_D^{20}$ +20.9 (*c* = 0.93, MeOH) {Lit.[8c] $[\alpha]_D$ +16 (*c* = 0.50, MeOH); Lit.[9] $[\alpha]_D$ +18.0 (*c* = 0.50, MeOH)}. The hydrochloride of **1** crystallized with 0.5 MeOH.[37]

IR (neat): 3019 (m, NH_2), 2902 (vs, OH), 2848 (s), 2597 (m), 1507 (s, C=O), 1219 (s), 1030 cm^{-1} (s).

^{1}H NMR (300.1 MHz, MeOD): δ = 1.63–1.84 (m, 12 H, 2′-H, 4′-H, 6′-H, 8′-H, 9′-H, 10′-H), 2.06 (br s, 3 H, 3′-H, 5′-H, 7′-H), 3.52 (s, 1 H, 2-H).

^{13}C NMR (75.1 MHz, MeOD): δ = 29.3 (d, C-3′, C-5′, C-7′), 35.4 (s, C-3), 37.1 (t, C-4′, C-6′, C-9′), 39.0 (t, C-2′, C-8′, C-10′), 63.3 (d, C-2), 170.2 (C=O).

Anal. Calcd for $C_{12}H_{20}ClNO_2$ (245.7): C, 58.65; H, 8.20; N, 5.70; Cl, 14.43; Anal. Calcd for $C_{12}H_{20}ClNO_2$·0.5MeOH (261.6): C, 57.35; H, 8.47; N, 5.35; Cl, 13.54. Found: C, 57.91; H, 8.47; N, 5.35; Cl, 13.54.

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