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SYNTHESIS OF ORTHOGONALLY PROTECTED ENANTIOPURE 2,9-DIAMINODECANEDIOIC ACID: A MODEL FOR A NEW GENERAL METHOD FOR THE SYNTHESIS OF ORTHOGONALLY PROTECTED α,α'-DIAMINODICARBOXYLIC ACIDS[#]

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Abstract – A new method for the synthesis of orthogonally protected enantiopure α,α'-diaminodicarboxylic acids is described. A key step involves the Julia olefination of an aldehyde and a sulfone, both of which are derived from an optically pure dicarboxylic amino acid such as aspartic and glutamic acid. Straightforward synthesis of orthogonally protected 2,9-diaminodecanedioic acid is chosen to demonstrate the conciseness of this new versatile approach.

INTRODUCTION

Synthesis of α,α'-diaminodicarboxylic acids has been a subject of considerable interest. 2,6-Diaminopimelic acid, a biosynthetic precursor of L-lysine in most bacteria, is a key amino acid component in the cell wall peptidoglycan layer of many Gram-negative organisms.[1] Moreover, 2,7-diaminosuberic acid has been used as a dicarba analogue of cystine to enhance metabolic and chemical stability of biologically active cystine peptides such as oxytocin[2], calcitonin[3] and somatostatin.[4] Recently, higher homologues of these α,α'-diaminodicarboxylic acids have been used to provide peptidomimetics that favor a β-turn conformation[5] or stabilize an α-helical conformation.[6]

Application of Kolbe electrolysis is one of the shortest methods for this synthesis though yields are low and problems of product separation exist.[7] Vederas and co-workers reported the use of Schöllkopf's bis-lactam ether and of Evans' bis(oxazoline)-copper complex for stereoselective synthesis of *meso*-2,6-diaminopimelic acid.[8] Combination of the Schöllkopf's bis-lactam ether and the Evans auxiliary provides an efficient approach to the synthesis of orthogonally protected (2*S*,9*R*)-2,9-diaminodecanedioic acid

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[#] Dedicated to Professor Pierre Potier on the occasion of his 70th birthday and in recognition of his outstanding contributions to medicinal chemistry.

derivative as demonstrated by Andrews and Tabor.[6a] L-Aspartic and glutamic acids have proved to be valuable starting materials for the synthesis of 2,6-diaminopimelic and 2,7-diaminosuberic acids, respectively. In this approach, their side-chain carboxylic groups are transformed into chiral 2,3-epoxy alcohols by the Katsuki-Sharpless asymmetric epoxidation protocol.[9] Since the first report by Grubbs and co-workers,[10] ring-closing metathesis (RCM) has become an important method for the synthesis of 2,6-diaminopimelic and 2,7-diaminosuberic acids, rigidified amino acids and peptides.[5,11] Although RCM is generally quite efficient in preparing cyclic peptidomimetics of dipeptides,[5,11d,11e] tripeptides[11b] and tetrapeptides,[10] this protocol completely failed to provide cyclic peptidomimetics of pentapeptides and octapeptides with 6 and 8 cross-linking carbons, respectively.[6c] Therefore, we deemed it still desirable to develop a practical method for asymmetric synthesis of this class of compounds.

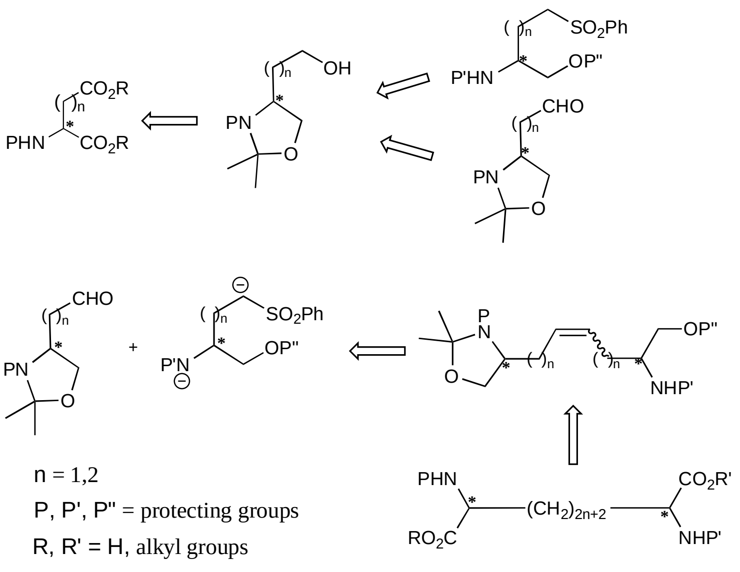
There are three criteria to be taken into account. Firstly, the two stereogenic centers must be enantiopure. Secondly, the choice of the number of cross-linking methylene units between α- and α'-carbons should be feasible. Thirdly, at least three of the four amino acid functionalities must be differentially protected if further manipulation of such an amino acid or its incorporation into peptides are needed.

In this report, we describe a new versatile general method that fulfills all these three conditions for the synthesis of orthogonally protected α,α'-diaminodicarboxylic acids. In order to demonstrate this methodology, we synthesized enantiopure orthogonally protected 2,9-diaminodecanedioic acid, an α,α'-diaminodicarboxylic acid potentially interesting for the reinforcement of the α-helical conformation of peptides and proteins.

RESULTS AND DISCUSSION

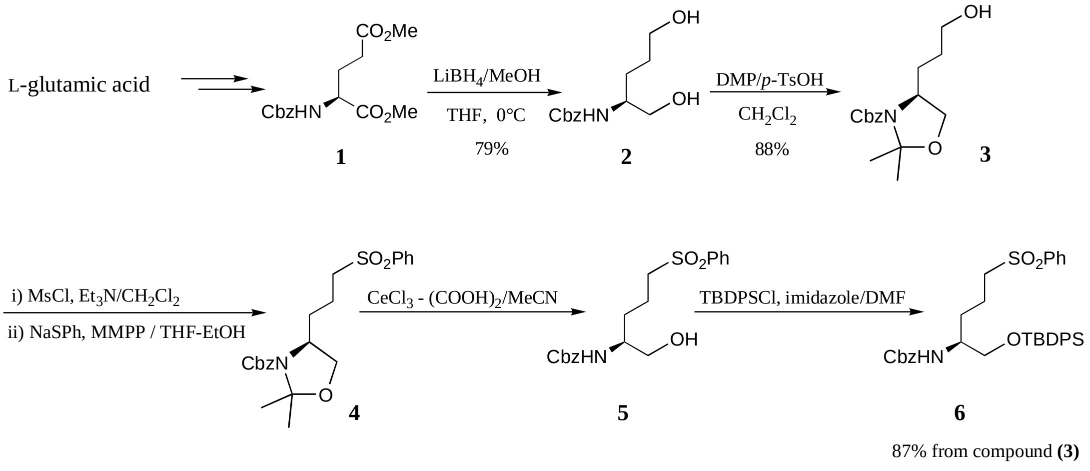
Instead of using chiral auxiliaries for creating a specific configuration at the α- and α'-stereocenters, we envisaged C-C bond formation on the cross-linking hydrocarbon chain by reacting an electrophile with a nucleophile both of which are derived from readily available optically pure amino acids with the desired configuration. Our new approach is demonstrated in the retrosynthetic analysis shown in Scheme 1.

Thus, *N*-protected dicarboxylic amino acids, such as aspartic acid and glutamic acid, can be transformed into aldehydes and aminosulfones in manners analogous to those described for the preparation of Garner's aldehyde[12] and aminosulfone developed by us.[13] Julia olefination[14] using these two electrophiles and nucleophiles followed by differential oxidation of each hydroxyl functionality can afford the desired α,α'-diaminodicarboxylic acids. Furthermore, random combination of electrophiles and nucleophiles derived from dicarboxylic amino acids, provides *a priori* α,α'-diaminodicarboxylic acids with various lengths of cross-linking hydrocarbons. For the evaluation of this new protocol, we have chosen 2,9-diaminodecanedioic acid as a model compound.



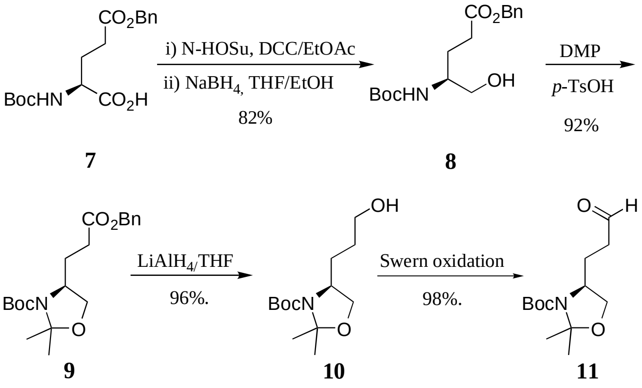
Scheme 1

Our initial endeavors commenced with the preparation of the sulfone **(6)** (Scheme 2). *N*-Cbz protected L-glutamic acid was converted in 98% yield to its dimethyl ester **(1)** using the procedure described by Watanabe *et al.*[15] (BF_3.etherate in MeOH) followed by reduction with $LiBH_4$ and 3 eq. of methanol in THF to afford **2** in 79% yield. The diol **(2)** was then transformed into oxazolidine **(3)** in 88% yield using dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in dichloromethane. The monoalcohol **(3)** was then treated with mesyl chloride in the presence of triethylamine in dichloromethane. The thus-obtained crude mesylate was converted to the sulfone **(4)** in one-pot. Thus, the mesylate was first converted to its phenyl sulfide by treatment with sodium thiophenolate in THF followed by addition of magnesium monoperoxy phthalate (MMPP) to afford **4**. Cleavage of the oxazolidine ring of crude **4** and subsequent treatment of the resulting alcohol **(5)** with TBDPSCl provided *tert*-butyldiphenylsilyloxy derivative **(6)** (in 87% yield from **3**).



Scheme 2

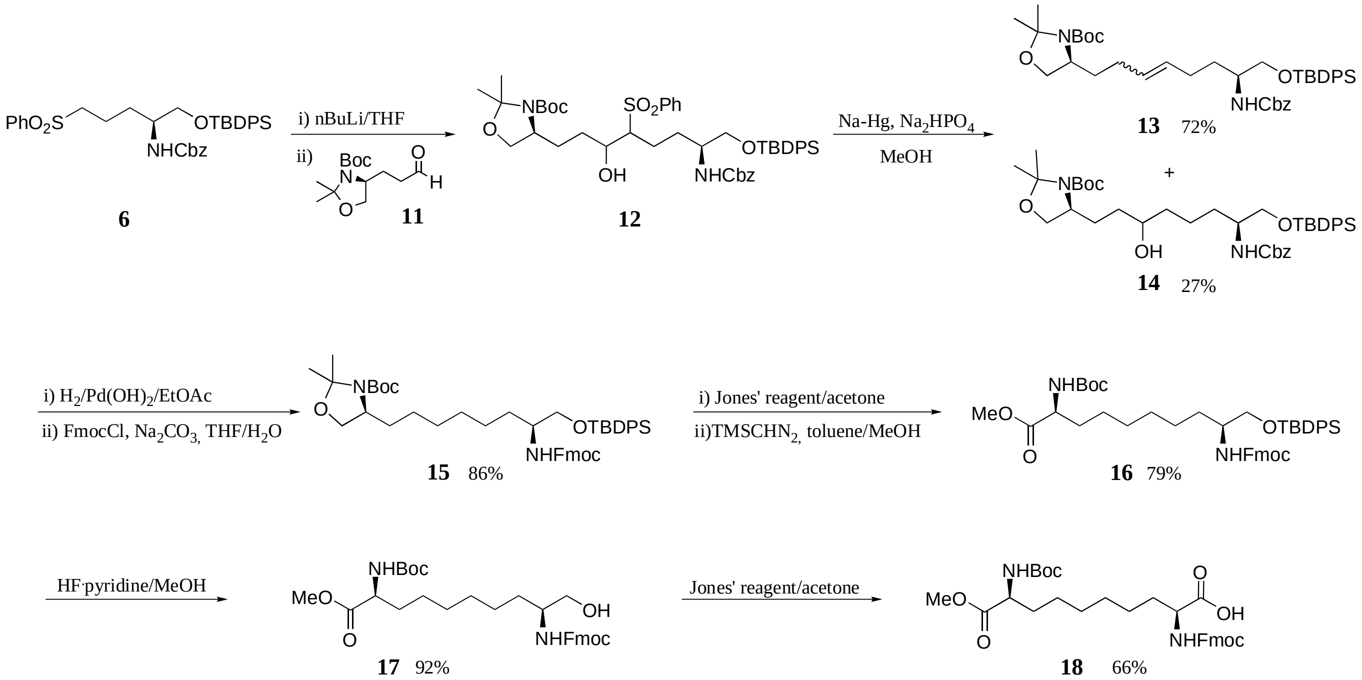
Commercially available compound **(7)** was submitted to regioselective reduction of the α-carboxylic acid moiety using the procedure described by Ohfune *et al.*[16] to afford **8** in 82% yield (Scheme 3). This alcohol was subsequently protected as the oxazolidine **(9)** in 92% yield in the same manner described for the preparation of **3**. Compound **(9)** was reduced to **10** in 96% yield by treatment with $LiAlH_4$ in THF. The resulting alcohol was finally submitted to Swern oxidation to give the desired aldehyde **(11)** in 98% yield.



Scheme 3

Next, the sulfone **(6)** and the aldehyde **(11)** were used for the construction of 2,9-diaminodicarboxylic acid as follows (Scheme 4). To the dianion of sulfone **(6)**, generated by *n*-BuLi in THF at –78°C, was added aldehyde **(11)** to form the hydroxysulfone adduct **(12)** in 85% yield. Treatment of **12** with Na-Hg afforded the olefin **(13)** in 72% yield together with the undesired alcohol **(14)** (27%), easily separated by column chromatography. The olefin **(13)** was obtained as a mixture of *E* and *Z* diastereomers. Although the *E* isomer was supposed to be the major component of the mixture, we did not get unambiguous ^1H NMR spectra supporting this point due to the presence of the *N*-Boc-rotamers. The olefin **(13)** was submitted to hydrogenolysis allowing simultaneous reduction of the double bond and removal of the *N*-Cbz protecting group. The resulting amine was converted to its Fmoc derivative **(15)** in 86% yield. Transformation of the oxazolidine to alcohol and oxidation of the latter were carried out in one-pot using Jones' reagent. The resulting carboxylic acid was converted to its methyl ester **(16)** in 79% yield by treatment with (trimethylsilyl)diazomethane ($TMSCHN_2$).[17] The *tert*-butyldiphenylsilyl ether was easily cleaved under mild conditions using HF-pyridine in MeOH at 0°C to afford the desired alcohol **(17)** in 92% yield. The final compound **(18)** was obtained by treatment of **17** with Jones' reagent in 66% yield. Although it was not rigorously demonstrated by synthesizing its enantiomer and carrying out subsequent HPLC analysis, this orthogonally protected 2,9-diaminodecanedioic acid is assumed to be optically pure. Indeed, **18** was synthesized *via* the coupling of two chiral units, sulfone **(6)** and aldehyde **(11)**, both of which have been proven to be enantiopure in our recent studies.[18] Moreover, all compounds derived from the adduct **(12)** are considered not to be prone to epimerization under the reaction conditions employed in this work.

In conclusion, we have developed a new method allowing synthesis of enantiopure orthogonally protected α,α'-diaminodicarboxylic acids with the desired configuration at the stereogenic centers. The key intermediates, sulfone **(6)**[19] and aldehyde **(11)**, are easily available from L-glutamic acid on a large scale. It should be noted that both of these compounds can also be converted to olefinic amino acids suitable for the RCM protocol. We are currently applying this strategy to the synthesis of other α,α'-diaminodicarboxylic acids.



Scheme 4

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium benzophenone ketyl, and dichloromethane from P_2O_5 immediately prior to use. All reagents obtained from commercial sources were used without purification, unless otherwise specified. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck). Melting points were determined on a Büchi B-540 and are uncorrected. Optical rotations were recorded on a JASCO P-1010 polarimeter, and IR spectra on a Perkin Elmer Spectrum BX spectrometer. HRMS spectra were run on Waters Micromass LCT with an electrospray source (ZQ) in positive mode ionization (ESI). ^1H NMR and ^{13}C NMR spectra were recorded on Brucker AM-300 with chemical shifts reported in ppm relative to the central line of the solvent residual peak : 7.26 ppm in $CDCl_3$, 1.94 ppm in CD_3CN, 3.31 ppm in MeOD for ^1H, and 77.16 ppm in $CDCl_3$, 1.32 in CD_3CN, 49.00

in MeOD for ^{13}C. Some spectra were recorded preferentially in CD_3CN because of the significal improvement of their readability in that solvent (presence of rotamers).

(2*S*)-Dimethyl 2-(benzyloxycarbonylamino)pentanedioate (1): Commercially available N-Cbz-L-glutamic acid (1.33 g, 4.73 mmol) was converted to **1** (1.43 g, 98 %) using the procedure described by Watanabe.[15] $[\alpha]_D^{25}$ –26° (c 1.0, MeOH) (lit.,[15] –23° (c 1.0, MeOH)); spectral data were found to be in agreement with those reported in the literature. [20]

(2*S*)-Benzyl 1,5-dihydroxypentan-2-ylcarbamate (2): To a solution of **1** (1.11 g, 3.59 mmol) in THF (20 mL) were added successively $LiBH_4$ (247 mg, 10.8 mmol) and MeOH (0.44 mL, 10.8 mmol) at 0°C. The reaction mixture was stirred for 4 h at 0°C and then was quenched by addition of 1 M HCl. The reaction mixture was stirred for 20 min and then extracted with dichloromethane. The organic extracts were dried over Na_2SO_4 and filtered on Celite. The solvents were removed in vacuo to afford crude **2** (768 mg), that was purified by flash chromatography on silica gel (dichloromethane/MeOH = 95/5) to yield 718 mg of pure **2** (79%) as a white solid. mp 103-105°C; $[\alpha]_D^{25}$ –16° (c 1.0, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 7.39-7.23 (5H, m), 5.07 (2H, s), 3.67-3.46 (5H, m), 1.73-1.28 (4H, m); ^{13}C NMR (75.5 MHz, MeOD) δ 158.7, 138.4, 129.4, 128.9, 128.7, 67.3, 65.4, 62.7, 54.2, 30.0, 28.6; IR ($CHCl_3$) ν 3436, 3024, 3009, 2947, 2881, 1708, 1511, 1226, 1069 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{13}H_{19}NO_4Na$ 276.1212, obsd 276.1213.

(4*S*)-Benzyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (3): To a solution of **2** (170 mg, 0.67 mmol) in dichloromethane (3 mL) were added *p*-TsOH (13 mg, 0.07 mmol) and dimethoxypropane (0.85 mL, 6.72 mmol) at rt. The reaction mixture was stirred for 24 h at rt. Et_3N (10 μL) was added and the solvents were evaporated in vacuo. Ethyl acetate and 1 M HCl were added to the residue, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed successively with 1M HCl, water, saturated aqueous $NaHCO_3$, water and brine. The solvents were removed in vacuo to afford crude **3** (182 mg), which was purified by flash chromatography on silica gel (heptane/EtOAc = 1/1) to yield 174 mg of pure **3** (88%) as a colorless oil. $[\alpha]_D^{25}$ +27° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (5H, m), 5.14 (2H, m), 4.06-3.87 (2H, m), 3.78 (1H, m), 3.66 (1H, m), 3.56 (1H, m), 2.73 (0.5H, br), 2.08 (0.5H, br), 1.95-1.39 (10H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.1, 152.3, 136.6, 136.3, 128.6, 128.1, 128.0, 128.0, 94.1, 93.7, 67.2, 66.6, 62.3, 57.8, 57.1, 30.0, 29.5, 29.2, 29.0, 27.6, 26.6, 24.6, 23.2; IR ($CHCl_3$) ν 3456, 3026, 3013, 2941, 2881, 1694, 1412, 1352, 1255, 1090 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{16}H_{23}NO_4Na$ 316.1525 obsd 316.1522.

(4*S*)-Benzyl 2,2-dimethyl-4-(3-phenylsulfonylpropyl)oxazolidine-3-carboxylate (4): To a solution of **3** (21.6 g, 74 mmol) in dichloromethane (400 mL) at –20°C was added triethylamine (11.4 mL, 81 mmol). Mesyl chloride (6.0 mL, 77 mmol) was then added dropwise over 10 min, and the reaction was stirred at –20°C for 30 min. The mixture was then washed with 1N HCl, H_2O, saturated aqueous $NaHCO_3$, H_2O, brine, filtered through Celite, dried over Na_2SO_4, and evaporated in vacuo to give 27.4 g of a colorless oil. The crude mesylate (27.4 g) was dissolved in THF (450 mL) and NaSPh (10.7 g, 77 mmol) was added carefully at 0°C. The cooling bath was removed and the reaction mixture was stirred for 1 h. Magnesium monoperoxy phthalate (MMPP) (50.0 g, 81 mmol) in 135 mL of ethanol was then added at 0°C. The bath was removed and the reaction mixture was stirred overnight. The solvents were removed in vacuo, the residue was diluted in EtOAc, and filtered. The solid was washed with EtOAc, and the filtrates were combined and washed with water. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and filtered through Celite,. The solvents were removed in vacuo to afford 31.4 g of crude **4**. For characterization purposes, a sample was purified by flash chromatography on silica (heptane/EtOAc = 3/7) to give pure **4** as a colorless oil as two rotamers. $[\alpha]_D^{25}$ +20° (c 4.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (2H, m) , 7.72 (1H, t, *J* = 7.2 Hz) , 7.62 (2H, t, *J* = 7.7 Hz) , 7.39 (5H, m), 5.16 (2H, s), 4.05-3.85 (2H, m), 3.76 (1H, m), 3.20 (1H, m), 3.05 (1H, m), 1.90-1.67 (4H, m), 1.67-1.45 (6H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.9, 152.1, 139.0, 136.4, 136.2, 133.8, 129.3, 128.6, 128.2, 128.0, 94.2, 93.7, 67.1, 67.0, 66.7, 57.3, 56.4, 55.8, 32.2, 31.4, 27.5, 26.6, 24.5, 23.0, 19.4, 19.3; IR ($CHCl_3$) ν 3028, 3011, 2941, 2881, 1697, 1448, 1410, 1352, 1148, 1087, 837 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{22}H_{27}NO_5NaS$ 440.1508, obsd 440.1479.

(2*S*)-Benzyl 1-hydroxy-5-phenylsulfonylpentan-2-ylcarbamate (5): To a solution of crude **4** (31.4 g) in acetonitrile (350 mL) was added $CeCl_3.7H_20$ (34.0 g, 90 mmol) and oxalic acid (346 mg, 3.8 mmol) at rt, and the reaction mixture was stirred overnight. The mixture was neutralized with solid $NaHCO_3$, and concentrated in vacuo. The residue was dissolved in EtOAc, filtered through Celite, dried over Na_2SO_4, and the solvent was removed in vacuo to give 24.1 g of a pale yellow oil. For characterization purposes, a sample was purified by flash chromatography on silica gel (heptane/EtOAc = 2/3) to give pure **5** as a colorless oil. $[\alpha]_D^{25}$ –21° (c 5.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (2H, d, J = 7.5 Hz), 7.48 (1H, t, J = 7.3 Hz), 7.38 (2H, t, J = 7.5 Hz), 7.17 (5H, m), 5.48 (1H, d, J = 8.5 Hz), 4.90 (2H, s), 3.55-3.25 (3H, m), 2.96 (2H, m), 1.75-1.30 (4H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.5, 138.6, 136.3, 133.6, 129.2, 128.4, 127.9, 127.8, 66.5, 64.2, 55.4, 52.1, 29.6, 19.1; IR ($CHCl_3$) ν 3435, 3024, 2955, 1712, 1508, 1306, 1228, 1148, 1087 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{19}H_{23}NO_5NaS$ 400.1195, obsd 400.1205.

(2*S*)-Benzyl 1-*tert*-butyldiphenylsilyloxy-5-phenylsulfonylpentan-2-ylcarbamate (6): To a solution of crude **5** (23.8 g) in DMF (80 mL) was added imidazole (10.9 g, 158 mmol) and *tert*-butyldiphenylsilyl chloride (17.5 mL, 66 mmol). The reaction mixture was stirred for 2 h at rt and quenched with saturated $NaHCO_3$ solution. The mixture was stirred for 30 min and the aqueous phase was extracted with EtOAc; the extracts were washed with brine, dried over Na_2SO_4 and filtered through Celite. The solvents were removed in vacuo and the residue was purified by flash chromatography on silica gel (heptane/EtOAc = 1/5) to give pure **6** (38.6 g, 87% from 73 mmol of **3**) as a white solid. mp 89-91°C; $[\alpha]_D^{25}$ –16° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (2H, m), 7.61-7.49 (7H, m), 7.42-7.34 (11H, m), 5.04 (2H, s), 4.87 (1H, d, J = 8.3 Hz), 3.66-3.54 (3H, m), 3.20-2.99 (2H, m), 1.82-1.60 (4H, m), 1.03 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.1, 139.1, 136.5, 135.6, 134.9, 133.7, 133.0, 133.0, 130.0, 130.0, 129.3, 128.6, 128.2, 128.1, 127.9, 66.8, 65.5, 55.7, 51.7, 30.4, 26.9, 19.4, 19.3; IR ($CHCl_3$) ν 3440, 3020, 2932, 2860, 1717, 1507, 1306, 1219, 1208, 1148, 1113, 1086, 823 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{35}H_{41}NO_5NaSSi$ 638.2372, obsd 638.2335.

(4*S*)-Benzyl 4-*tert*-butoxycarbonylamino-5-hydroxypentanoate (8): To a solution of **7** (22.7 g, 67.1 mmol) and *N*-hydroxysuccinimide (9.5 g, 80.6 mmol, 1.2 eq) in EtOAc (220 mL, HPLC grade) was added DCC (16.8 g, 80.6 mmol, 1.2 eq) at 0°C. The reaction mixture was warmed to rt and stirred overnight. The mixture was then filtered and the filtrate was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo to give 32 g of crude ester. To a solution of the residue (32 g) in THF (180 mL) was added $NaBH_4$ (2.8 g, 70.5 mmol, 1.05 eq) at 0°C. Dry EtOH (60 mL) was then added and the suspension was stirred at 0°C for 30 min. The reaction was quenched with aqueous NH_4Cl and the mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated to give 25 g of crude **8**, which was purified by flash chromatography on silica gel (heptane/EtOAc = 65/35) to yield 17.7 g of pure **8** (81%) as a white solid. Mp 75-76°C (lit.,[21] 76-77°C); $[\alpha]_D^{25}$ –10° (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m), 5.10 (2H, s), 5.04 (1H, br d, *J* = 8.1 Hz), 3.57 (3H, m), 3.26 (1H, m), 2.44 (2H, t, *J* = 7.8 Hz), 1.96-1.66 (2H, m), 1.41 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6, 156.3, 135.8, 128.6, 128.3, 79.6, 66.5, 64.9, 52.1, 30.9, 28.4, 26.4; IR ($CHCl_3$) ν 3439, 3009, 2981, 2935, 1707, 1501, 1368, 1167 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{17}H_{25}NO_5Na$ 346.1630, obsd 346.1620.

(4*S*)-*tert*-Butyl 4-(3-benzyloxy-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate (9): To a solution of **8** (17.7 g, 54.8 mmol) in dimethoxypropane (180 mL) was added *p*-TsOH (208 mg 0.02 eq) at rt. The reaction mixture was stirred at room temperature for 48 h. Et_3N (160 μL) was added and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to give 18.7 g of crude **9**, which was purified by flash chromatography on silica gel (heptane/EtOAc = 85/15) to afford 18.3 g of pure **9** (92%) as a colorless oil (two rotamers). $[\alpha]_D^{25}$ +20° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m), 5.10 (2H, m), 4.03-3.78 (2H, m), 3.69 (1H, d, J = 8.2 Hz), 2.38 (2H, m), 2.12-1.82 (2H, m), 1.58 (1.5H, br s), 1.54 (1.5H, br s), 1.45 (12H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 152.4, 151.9, 136.0, 135.9, 128.6, 128.3, 93.9, 93.4, 80.1, 79.8, 66.9, 66.3, 56.7, 56.5, 31.0, 28.9, 28.5, 27.6, 26.8, 24.4, 23.1; IR ($CHCl_3$) ν 2978, 2936, 2876, 1738, 1694, 1390, 1376, 1365, 1258, 1166 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{20}H_{29}NO_5Na$ 386.1943, obsd 346.1944.

(4*S*)-*tert*-Butyl 4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (10): To a solution of **9** (18.20 g, 50.1 mmol) in THF (400 mL) was added $LiAlH_4$ (2.35 g, 60.2 mmol, 1.2 eq) at 0°C, and the reaction mixture was stirred for 15 min at 0°C. Water (2.4 mL) was then added dropwise at 0°C, followed by 15% aqueous NaOH (2.4 mL) and water (7.2 mL). The cooling bath was removed and the reaction mixture was stirred for 45 min at rt. The precipitate was filtered off and the solvents were removed in vacuo to afford crude **10** (18.25 g), which was purified by flash chromatography on silica gel (heptane/EtOAc = 65/35) to give 12.52 g of pure **10** (96%) as colorless oil (two rotamers). $[\alpha]_D^{25}$ +31° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01-3.59 (5H, m), 2.74 (0.5H, br), 2.12 (0.5H, br), 1.92-1.36 (19H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.5, 151.9, 93.8, 93.4, 80.4, 79.6, 67.1, 62.6, 62.4, 57.2, 30.1, 29.7, 29.5, 29.1, 28.5, 27.7, 26.9, 24.6, 23.3; IR ($CHCl_3$) ν 3444, 2979, 2936, 2871, 1694, 1478, 1455, 1392, 1257, 1174, 1086 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{13}H_{25}NO_4Na$ 282.1681, obsd 282.1684.

(4*S*)-*tert*-Butyl 2,2-dimethyl-4-(3-oxopropyl)oxazolidine-3-carboxylate (11): To a solution of oxalyl chloride (4.60 mL, 52.2 mmol) in dichloromethane (180 mL) was added a solution of DMSO (8.20 mL, 114.6 mmol) in dichloromethane (30 mL) at –78°C. The reaction mixture was stirred for 15 min at –78°C, and a solution of **10** (9.05 g, 34.9 mmol) in dichloromethane (30 mL) was added. The reaction mixture was stirred for 45 min at –78°C. Et_3N (33.2 mL, 236.4 mmol, 6.8 eq) was then added at –78°C, the cooling bath removed, and the reaction mixture was stirred for 1 h at rt. The reaction was quenched by addition of water, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed successively with 1M HCl, water, satrated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered on Celite and the solvent was removed in vacuo to give 8.80 g of crude **11** (98%). This aldehyde was used without any purification for the next step. For characterization purposes, a sample (235 mg) was purified by flash chromatography on silica gel (heptane/EtOAc = 5/1) to provide 232 mg of pure **11** as a colorless oil. $[\alpha]_D^{25}$ +26° (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3CN) δ 9.69 (1H, s), 3.96-

3.77 (2H, m), 3.68 (1H, m), 2.52-2.24 (2H, m), 1.92-1.72 (2H, m), 1.52 (3H, s), 1.43 (12H, m); ^{13}C NMR (75.5 MHz, CD_3CN) δ 203.0, 174.7, 153.2, 152.8, 94.2, 80.5, 80.2, 67.6, 57.4, 40.8, 31.0, 29.4, 28.6, 28.0, 27.2, 26.8, 26.4, 24.8, 23.3; IR ($CHCl_3$) ν 2979, 2937, 2876, 1725, 1694, 1390, 1367, 1257, 1173, 1084 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{13}H_{23}NO_4Na$ 280.1525 obsd 280.1531.

(4*S*)-*tert*-Butyl 4-(7*S*)-7-benzyloxycarbonylamino-8-*tert*-butyldiphenylsilyloxy-3-hydroxy-4-phenylsulfonyloctyl-2,2-dimethyloxazolidine-3-carboxylate (12): To a solution of **6** (8.84 g, 14.4 mmol) in THF (140 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (20 mL, 32.0 mmol) at –78°C. After stirring for 20 min, a solution of **11** (4.15 g, 16.2 mmol) in THF (10 mL) was added dropwise. The reaction was stirred for 1.5 h at –78°C, the bath was then removed and the mixture was stirred for an additional 30 min. The reaction was then quenched with a saturated solution of NH_4Cl and stirred for 10 min. The aqueous phase was extracted with EtOAc and the extracts were washed with water and brine. The organic phase was dried over Na_2SO_4, filtered through Celite, concentrated in vacuo to afford 13.10 g of crude product, which was then purified by flash chromatography on silica gel (dichloromethane/EtOAc = 97/3 then 9/1) to give1.06 g (12%) of unreacted starting sulfone **(6)**, and pure **12** (10.70 g, 85%) as a white foam (mixture of diastereomers and rotamers). ^{1}H NMR (300 MHz, CD_3CN) δ 7.89 (2H, m), 7.74-7.51 (7H, m), 7.51-7.25 (11H, m), 5.55 (1H, m), 5.07 (2H, m), 4.26-3.04 (9H, m), 2.00-1.36 (23H, m), 1.03 (9H, s); ^{13}C NMR (75.5 MHz, CD_3CN) δ 157.2, 157.1, 152.9, 152.8, 152.7, 140.7, 139.5, 138.3, 136.4, 134.6, 134.2, 130.8, 130.2, 129.6, 129.4, 129.3, 128.8, 128.6, 94.0, 80.4, 79.8, 70.4, 69.8, 69.3, 67.6, 66.8, 58.1, 57.8, 53.9, 53.7, 32.6, 31.7, 31.1, 30.9, 30.3, 30.2, 28.7, 28.0, 27.8, 27.3, 24.9, 23.5, 22.3, 20.7, 19.8; IR ($CHCl_3$) ν 3437, 3019, 2933, 2860, 1709, 1689, 1511, 1394, 1367, 1212, 1145, 1111, 823 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{48}H_{64}N_2O_9NaSSi$ 895.4000, obsd 895.3974.

(4*S*)-*tert*-Butyl 4-(7*S*)-7-benzyloxycarbonylamino-8-*tert*-butyldiphenylsilyloxyoct-3-enyl-2,2-dimethyloxazolidine-3-carboxylate (13): To a solution of hydroxysulfone **(12)** (9.77 g, 11.2 mmol) in MeOH (HPLC grade, 112 mL) was added Na_2HPO_4 (19.3 g, 134.4 mmol) followed by 6% sodium amalgam (38.6 g, 100.7 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 min, then 3 h at rt. The mercury residue was removed by decantation, and the solvent was evaporated in vacuo. Water and EtOAc were added and the aqueous layer was extracted with EtOAc. The organic extracts were combined and washed with brine, dried over Na_2SO_4, filtered on Celite, and finally concentrated to give a crude mixture of **13** and **14** (8.52 g). The two compounds were easily separated by flash chromatography on silica gel (heptane/EtOAC = 85/15 then 1/3) to give pure **13** (5.80 g, 72%) as a white solid (mixture of *E*/*Z* diastereomers and rotamers) and pure **14** (2.25 g, 27%) as a colorless oil. ^{1}H NMR (300 MHz,

CD_3CN) δ 7.67 (4H, m), 7.26-7.48 (11H, m), 5.59 (1H, m), 5.41 (2H, m), 5.05 (2H, s), 3.55-3.93 (6H, m), 1.87-2.12 (4H, m), 1.38-1.79 (19H, m), 1.04 (9H, s); ^{13}C NMR (75.5 MHz, CD_3CN) δ 157.0, 152.7, 138.5, 136.4, 134.4, 131.0, 130.8, 130.4, 129.4, 128.8, 128.6, 94.0, 80.3, 80.0, 79.8, 67.6, 67.3, 67.0, 67.0, 66.7, 58.0, 57.8, 57.7, 53.5, 53.3, 34.2, 33.5, 31.8, 30.4, 30.0, 29.8, 29.6, 28.7, 28.3, 28.1, 27.8, 27.3, 25.0, 24.7, 24.4, 23.6, 19.9; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{42}H_{58}N_2O_6NaSi$ 737.3962, obsd 737.4002.

(4*S*)-*tert*-Butyl 4-(7*S*)-7-benzyloxycarbonylamino-8-*tert*-butyldiphenylsilyloxy-3-hydroxyoctyl-2,2-dimethyloxazolidine-3-carboxylate (14): Obtained as a colorless oil, mixture of diastereomers and rotamers. ^1H NMR (300 MHz, CD_3CN) δ 7.67 (4H, m), 7.48-7.25 (11H, m), 5.62 (1H, br d, *J* = 8.3 Hz), 5.06 (2H, s), 3.95-3.35 (8H, m), 1.87-1.27 (25H, m), 1.04 (9H, s); ^{13}C NMR (75.5 MHz, CD_3CN) δ 157.1, 152.7, 138.4, 136.4, 134.4, 130.8, 129.4, 128.7, 128.6, 94.0, 93.9, 80.4, 79.8, 71.6, 71.2, 67.8, 67.5, 66.8, 66.7, 62.4, 58.4, 58.1, 53.9, 53.8, 38.0, 34.7, 32.0, 30.7, 30.6, 30.4, 30.2, 28.7, 28.1, 27.3, 24.9, 23.5, 23.0, 22.8, 19.9; IR ($CHCl_3$) ν 3445, 2931, 2858, 1695, 1391, 1375, 1105 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{42}H_{60}N_2O_7NaSi$ 755.4062, obsd 755.4068.

(4*S*)-*tert*-Butyl 4-(7*S*)-7-9*H*-fluoren-9-ylmethoxycarbonylamino-8-*tert*-butyldiphenylsilyloxyoctyl-2,2-dimethyloxazolidine-3-carboxylate (15): A suspension of **13** (5.60 g, 7.83 mmol) and $Pd(OH)_2$ on charcoal (1.40g, 0.78 mmol) in EtOAc (80 mL) was hydrogenated at rt for 24 h. The reaction mixture was then filtered on Celite, and the solvent was removed in vacuo to give the crude amine as an oil (5.70 g). This amine was dissolved in a mixture of THF and water (200 mL, 3:1), and a 0.5 M solution of Na_2CO_3 in water (31 mL) was added. Fmoc-Cl (2.13 g, 7.99 mmol) was added at 0°C, and the reaction mixture was stirred for 1 h at rt. The reaction was quenched by addition of water, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered on Celite and the solvents were removed in vacuo to give 6.61 g of crude **15** which was purified by flash chromatography on silica gel (heptane/EtOAc = 85/15) to afford 5.44 g of pure **15** (86%) as a colorless oil (two rotamers). $[\alpha]_D^{25}$ +4° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, CD_3CN) δ 7.81 (2H, d, *J* = 7.5 Hz), 7.64 (6H, m), 7.47-7.22 (10H, m), 5.57 (1H, br d, *J* = 7.6 Hz), 4.37-4.15 (3H, m), 3.92-3.25 (6H, m), 1.75-1.13 (27H, m), 1.03 (9H, s); ^{13}C NMR (75.5 MHz, CD_3CN) δ 157.0, 152.6, 145.1, 142.1, 136.4, 134.4, 130.7, 128.7, 128.6, 128.0, 126.1, 120.9, 118.1, 94.0, 93.9, 80.1, 79.7, 67.7, 67.4, 66.9, 66.8, 58.2, 53.7, 48.1, 34.5, 33.7, 32.6, 31.8, 30.4, 30.1, 28.8, 28.4, 28.1, 27.9, 27.4, 26.8, 26.6, 25.1, 23.6, 23.4, 19.9; IR ($CHCl_3$) ν 3442, 3019, 3015, 2931; 2858; 1714, 1685, 1509, 1394, 1105 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{49}H_{64}N_2O_6NaSi$ 827.4431, obsd 827.4476.

(2*S*,9*S*)-Methyl 9-9*H*-fluoren-9-ylmethoxycarbonylamino-2-*tert*-butoxycarbonylamino-10-*tert*-butyldiphenylsilyloxydecanoate (16): To a solution of **15** (4.40 g, 5.47 mmol) in acetone (110 mL) was added Jones' reagent (3 mL, 1.5 eq) at 0°C. After 6 h of stirring at 0°C, the reaction was quenched by addition of 2-propanol, and the pH was adjusted to 6 by addition of a saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine. The resulting solution was dried over Na_2SO_4 and the solvents were removed in vacuo. The crude acid thus obtained (4.62 g) was dissolved in a mixture of toluene and methanol (50 mL, 4/1) and a solution of $TMSCHN_2$ in hexane (2.8 mL, 5.6 mmol) was added at rt. The reaction was stirred 1 h and the solvents were evaporated. The crude ester (4.96 g) was purified by flash chromatography on silica gel (heptane/EtOAC = 3/1) to yield 3.42 g of pure **16** (79%) as a yellow oil. $[\alpha]_D^{25}$ –3° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 7.4 Hz), 7.66 (6H, m), 7.51-7.27 (10H, m), 5.07 (1H, br d, *J* = 7.9 Hz), 4.98 (1H, br d, *J* = 8.3 Hz), 4.42 (2H, d, *J* = 7.0 Hz), 4.34 (1H, m), 4.26 (1H, t, *J* = 7.1 Hz), 3.76 (3H, s), 3.75-3.62 (3H, m), 1.90-1.53 (3H, m), 1.49 (9H, s), 1.32 (9H, m), 1.13 (9H, s); ^{13}C NMR (75.5 MHz, CDCl3) δ 173.5, 156.1, 155.5, 144.1, 141.4, 135.7, 133.3, 129.9, 127.9, 127.7, 127.1, 125.2, 120.0, 79.9, 66.7, 65.6, 53.5, 52.6, 52.2, 47.4, 32.8, 31.8, 29.4, 29.2, 28.4, 27.0, 25.9, 25.4, 19.4; IR ($CHCl_3$) ν 3442, 3020, 2931, 2859, 1711, 1503, 1367, 1112 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{47}H_{60}N_2O_7NaSi$ 815.4068, obsd 815.4037.

(2*S*,9*S*)-Methyl 9-9*H*-fluoren-9-ylmethoxycarbonylamino-2-*tert*-butoxycarbonylamino-10-hydroxydecanoate (17): To a solution of **16** (455 mg, 0.57 mmol) in methanol (11 mL, HPLC grade) was added a 65-70% solution of HF-pyridine (2.3 mL) at 0°C. After 8 h of stirring at 0°C, the reaction was quenched by addition of a saturated $NaHCO_3$ solution, and an excess of that solution was added to adjust the pH to 7-8. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with a 1 M solution of HCl, water, a saturated $NaHCO_3$ solution, water and brine. The organic phase was dried over Na_2SO_4 and the solvents were removed in vacuo. The crude oil (447 mg) was purified by flash chromatography on silica gel (heptane/EtOAc = 7/3) to provide 293 mg of pure **17** (92%) as a colorless oil. $[\alpha]_D^{25}$ +0.1° (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 7.5 Hz), 7.60 (2H, d, *J* = 7.4 Hz), 7.40 (2H, t, *J* = 7.4 Hz), 7.31 (2H, t, *J* = 7.4 Hz), 5.12 (2H, br d, *J* = 5.1 Hz), 4.42 (2H, m), 4.30 (1H, m), 4.21 (1H, t, *J* = 6.7 Hz), 3.73 (3H, s), 3.71-3.48 (3H, m), 1.76 (1H, m), 1.68-1.50 (2H, m), 1.46 (9H, s), 1.29 (9H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6, 156.8, 155.5, 144.0, 141.4, 127.7, 127.1, 125.1, 120.0, 80.0, 66.7, 65.2, 53.5, 53.2, 52.3, 47.4, 32.7, 31.4, 29.2, 29.0, 28.4, 25.9, 25.3; IR ($CHCl_3$) ν 3440, 3020, 2933, 2860, 1710, 1508, 1212, 1164 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{31}H_{42}N_2O_7Na$ 577.2890, obsd 577.2896.

(2*S*,9*S*)-2-9*H*-Fluoren-9-ylmethoxycarbonylamino-9-*tert*-butoxycarbonylamino-10-methoxy-10-oxodecanoic acid (18): To a solution of **17** (135 mg, 0.24 mmol) in acetone (5 mL) was added Jones' reagent (180 μL, 2 eq) at 0°C. After 4 h of stirring at rt, the reaction was quenched by addition of 2-propanol, and the pH was adjusted to 6 by addition of a saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine. The resulting solution was dried over Na_2SO_4 and the solvents were removed in vacuo. The residue (134 mg) was purified by flash chromatography on silica gel (heptane/EtOAc = 3/1 then 1/3) to yield 91 mg of pure **18** (66%) as an opaline oil (two rotamers). $[\alpha]_D^{25}$ +16° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, CD_3CN) δ 7.83 (2H, d, *J* = 7.5 Hz), 7.67 (2H, m), 7.41 (2H, t, *J* = 7.4 Hz), 7.33 (2H, t, *J* = 7.4 Hz), 6.00 (1H, br d, *J* = 7.8 Hz), 5.59 (1H, br d, *J* = 7.6 Hz), 4.33 (2H, d, *J* = 7.1 Hz), 4.23 (1H, t, *J* = 6.9 Hz), 4.09 (2H, m), 3.65 3H, s), 1.81-1.47 (4H, m), 1.39 (9H, s), 1.35-1.24 (8H, m); ^{13}C NMR (75.5 MHz, CD_3CN) δ 174.4, 157.2, 156.6, 145.1, 145.0, 142.1, 128.7, 128.1, 126.2, 121.0, 79.9, 79.1, 67.3, 54.8, 54.6, 52.6, 48.0, 32.4, 32.2, 29.5, 28.5, 26.2; IR ($CHCl_3$) ν 3686, 3438, 3022, 2935, 2861, 1714, 1507, 1226, 1166, 1049 cm^{-1}; HRMS (ESI) $(M+Na)^+$: m/z calculated for $C_{31}H_{40}N_2O_8Na$ 591.2682, obsd 591.2684.

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