Convenient and Efficient Preparation of N-Protected (α-Aminoacyl)oxy-Substituted Terpenes and Alkanes

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Abstract: Chiral N-protected (α-aminoacyl)oxy-substituted terpenes and alkanes, including diastereomeric analogues, are conveniently and efficiently prepared from the corresponding readily available chiral and racemic 1-[(benzyloxycarbonyl)aminoacyl]benzotriazoles under microwave irradiation with naturally occurring terpene alcohols or alkanols.

Key words: N-protected [(α-aminoacyl)oxy]benzotriazoles, alcohols, O-acylation, chirality, microwave

Amino acid esters of hydroxylic terpenes are effective medicinal agents for, for example, atherosclerosis.1 N-Protected [(α-aminoacyl)oxy]alkanes derived from long-chain alkanols containing 12–22 carbon atoms and α-amino acids (Gly, Ala, Phe, Leu, Val, Tyr, Lys, Pro) or peptides (Gly–Gly, Phe–His, Val–His, Phe–Val–His) possess medicinal, nutritional, and industrial utility,2 including as immunoadjuvants for vaccine production3a and in allergic desensitization therapy.3b

We have worked extensively on N-acylbenzotriazoles for N-acylation,4 C-acylation,5 and O-acylation,6 as summarized in Scheme 1. Herein, we present the extension of our methodology7 for the convenient and efficient formation of α-amino ester conjugates from N-protected (α-amino-acyl)benzotriazoles8 and alcohols from naturally occurring terpenes and aliphatic alcohols under microwave irradiation. Microwave irradiation is well known to facilitate a variety of reactions.9

N-Protected [(α-aminoacyl)oxy]terpenes were prepared by coupling N-protected (α-aminoacyl)benzotriazoles 2a–d and 2a/2a’ (diastereomeric mixture of 2a and 2a’) with hydroxyterpenes 3a–d. In the presence of a catalytic amount of 4-(N,N-dimethylamino)pyridine (0.1 equiv) under microwave irradiation at 65 °C and 100 W irradiation power for 15 minutes, the acylating reagents 2a–d and 2a/2a’ were completely consumed (Schemes 2–6, Tables 1–3). However, for the preparation of 4h, 0.2 equivalent 4-(N,N-dimethylamino)pyridine were utilized (Scheme 6). The crude products 4a–h and the corresponding diastereomeric mixtures 4d/4d’ and 4f/4f’, obtained after basic workup (saturated sodium carbonate), were subjected to silica-gel column chromatography using ethyl acetate–hexane (2:1) as eluent. With or without catalytic amounts of 4-(N,N-dimethylamino)pyridine (0.1 equiv), no reaction was observed either at room temperature or under refluxing conditions for up to two days in the absence of microwave irradiation.

Scheme 1 N-, C-, and O-Acylation by N-acylbenzotriazoles

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The desired chiral compounds 4a–h and their corresponding diastereomeric mixtures 4d/4d' and 4f/4f' were obtained in yields ranging from 78–98% and were characterized by 1H and 13C NMR spectroscopy, elemental analysis, their melting points, and optical rotation measurements. TLC analysis showed the absence of starting materials 2a–d, 2a/2a′ and side products. This result suggests that microwave irradiation facilitates coupling reactions efficiently over short periods, preserving chirality in compounds such as L-menthol (3c).

NMR analysis detected no racemization (<5%) for 4d and 4f. Thus, the 1H NMR spectra (CDCl3) of 4d and 4f contained clear doublets for the α-NH protons of the amino acid fragments at δ 5.31 and 5.28, respectively. The isopropenyl group of the citronellol moiety of 4d appeared as two separate methyl singlets, and the methyl group in the citronellol fragment of 4d also gave a clear doublet, as expected. Similarly, the L-menthol fragment of 4f appeared as a doublet for all the methyl protons present. No signals of the methyl protons of the corresponding diastereomers were observed in the NMR spectra of 4d and 4f. The 13C NMR spectra of 4d and 4f displayed a singlet for each carbonyl carbon, whereas for the corresponding diastereomer pairs 4d/4d' and 4f/4f' the carbonyl carbons were each present as two singlets, supporting the enantiopurity of 4d and 4f (see Tables 4 and 5).
The 13C NMR spectrum of the 4f/4f¢ mixture displayed doublets for most aliphatic and carbonyl carbons, although no significant difference was observed for the aromatic carbons. For example, the methyl carbon peaks of 4f appeared at δ 16.4, 20.8, and 22.1, whereas those of the diastereomeric pair 4f/4f¢ each appeared as two singlets (see Table 5); this suggests that the peaks of the LL-configuration appear further downfield than those of the LD-configuration (see Tables 4 and 5).

The enantiopurities of the N-protected [(α-aminoacyl)oxy]terpenes were further supported by HPLC analysis. These HPLC results showed a single peak for 4d at 6.3 minutes. By contrast, two peaks (6.3, 6.9 min) were observed for the corresponding diastereomeric mixture 4d/4d¢ prepared from Cbz-DL-Phe-Bt and citronellol by the same procedures, thus confirming the enantiopurity of 4d. Similar results also observed for 4f (6.2 min) and 4f/4f¢ (6.2, 6.8 min) confirmed the enantiopurity of 4f (see Table 6). These results also indicated shorter retention times for 4d and 4f compared to their corresponding diastereomeric mixtures 4d/4d¢ and 4f/4f¢ (Table 6).

N-Protected [(α-aminoacyl)oxy]thymols 4i,j were prepared by coupling of N-protected (α-aminoacyl)benzotriazoles 2a,b with thymol (3e). In the presence of 4-(N,N-

<table>
<thead>
<tr>
<th>R</th>
<th>2</th>
<th>Product</th>
<th>4</th>
<th>Yield*(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>2a</td>
<td>Cbz-L-Phe-O-menthol</td>
<td>4f</td>
<td>89</td>
</tr>
<tr>
<td>Bn</td>
<td>2a/2a¢</td>
<td>Cbz-DL-Phe-O-menthol</td>
<td>4f/4f¢</td>
<td>83</td>
</tr>
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</table>

* Isolated yield.

**Diastereomeric mixture.

<table>
<thead>
<tr>
<th>Compound</th>
<th>13C NMR, δ (CO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4d</td>
<td>171.7</td>
</tr>
<tr>
<td>4d/4d¢</td>
<td>171.5, 171.6</td>
</tr>
</tbody>
</table>

* Diastereomeric mixture.

<table>
<thead>
<tr>
<th>NMR</th>
<th>Assignment</th>
<th>δ (4f)</th>
<th>δ (4f/4f¢)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NH</td>
<td>5.28</td>
<td>5.25, 5.31</td>
<td></td>
</tr>
<tr>
<td>13C CO</td>
<td>171.2</td>
<td>170.9, 171.2</td>
<td></td>
</tr>
<tr>
<td>13C CH₃</td>
<td>16.4</td>
<td>15.8, 16.2</td>
<td></td>
</tr>
<tr>
<td>13C CH₃</td>
<td>20.8</td>
<td>20.6, 20.8</td>
<td></td>
</tr>
<tr>
<td>13C CH₃</td>
<td>22.1</td>
<td>21.9, 22.0</td>
<td></td>
</tr>
</tbody>
</table>

* Diastereomeric mixture.

**Scheme 5** Preparation of N-protected [(α-aminoacyl)oxy]terpene 4g

**Scheme 6** Preparation of N-protected [(α-aminoacyl)oxy]terpene 4h

**Table 5** Comparison of NMR Data of 4f and 4f/4f¢

**Table 6** HPLC Data of 4d, 4d/4d¢, 4f, and 4f/4f¢

<table>
<thead>
<tr>
<th>Compound</th>
<th>tR (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4d</td>
<td>6.3</td>
</tr>
<tr>
<td>4d/4d¢</td>
<td>6.3, 6.9</td>
</tr>
<tr>
<td>4f</td>
<td>6.2</td>
</tr>
<tr>
<td>4f/4f¢</td>
<td>6.2, 6.8</td>
</tr>
</tbody>
</table>

* HPLC analysis was carried out using a Chirobiotic T column (detection at λ = 254 nm, flow rate 0.5 mL·min⁻¹, EtOAc as solvent).
the following methods: (i) An amino acid (L-Phe, L-Pro) or its corresponding hydrochloride salt (Gly, L-, D-, DL-Ala, L-, D-, DL-Val, L-, D-, DL-Leu, L-, DL-Phe, L-, D-Met, L-, DL-Pro, DL-PheGly, L-Ser) is directly esterified with the terpene (menthol, 1-borneol, thymol) in benzene–toluene, with p-toluensulfonic acid as catalyst, and by azeotropic distillation in a Dean–Stark apparatus. However, these literature reaction conditions cause decomposition of sensitive amino acids such as serine and loss of chirality, e.g., in α-phenylglycine. (ii) α-Amino carboxy anhydride derivatives of L-, D-Ala, L-, D-Phe, L-Val, L, DL-PheGly, L-, and DL-Ser and terpenes (menthol) are used. This significantly reduces racemization, but requires longer reaction times (2–4 days). (iii) N-Aminoacyl anhydrides (L-Glu and L-Asp) are refluxed with terpene (menthol) for two hours in toluene and p-toluensulfonic acid; this gives the desired compounds in yields of 68–79%. (iv) Coupling reagents such as 1,1′-carbonyl bis(3-methylimidazolium triflate), N,N′-dicyclohexylcarbodiimide, and N,N′-dicyclohexylcarbodiimide/4-(N,N-dimethylamino)pyridine are used for esterification. Acetic anhydride is used with catalytic amounts of niobium(V) chloride or other additives. (v) N-Methylimidazole in the presence of p-toluensulfonyl chloride gives esters from equimolar amounts of the carboxylic acid and alcohol. However, major drawbacks for such methodology is lack of generality, as a large excess of reagents sometimes have to be employed to achieve completion.

The procedure developed for the synthesis of N-protected [(α-aminoacyl)oxy]terpenes 4a–l was successfully applied for the preparation of N-protected [(α-aminoacyloxy)alkanes 4k,l].

### Table 7 Preparation of N-Protected [(α-Aminoacyl)oxy]thymols 4i,j

<table>
<thead>
<tr>
<th>R</th>
<th>2</th>
<th>Product</th>
<th>4</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>2a</td>
<td>Cbz-L-Phe-O-thymol</td>
<td>4i</td>
<td>89</td>
</tr>
<tr>
<td>CH2-3-indolyl</td>
<td>2b</td>
<td>Cbz-L-Trp-O-thymol</td>
<td>4j</td>
<td>78</td>
</tr>
</tbody>
</table>

* Isolated yield.

### Table 8 Preparation of N-Protected [(α-Aminoacyl)oxy]alkanes 4k,l

<table>
<thead>
<tr>
<th>R</th>
<th>2</th>
<th>Product</th>
<th>4</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>2a</td>
<td>Cbz-L-Phe-O-octadecanol</td>
<td>4k</td>
<td>98</td>
</tr>
<tr>
<td>CH2-3-indolyl</td>
<td>2b</td>
<td>Cbz-L-Trp-O-octadecanol</td>
<td>4l</td>
<td>95</td>
</tr>
</tbody>
</table>

* Isolated yield.

Terpene α-amino esters have been prepared previously by the following methods: (i) An amino acid (L-Phe, L-Pro) or its corresponding hydrochloride salt (Gly, L-, D-, DL-Ala, L-, D-, DL-Val, L-, D-, DL-Leu, L-, DL-Phe, L-, D-Met,
Preparation of N-Protected (α-Aminoacyl)oxy-Substituted Terpenes and Alkanes

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cyl)oxy]alkanes 4k–m derived from linear alcohols 3f and 3g (Schemes 8 and 9, Table 8). Compounds 4k–m were obtained in yields of 91–98% and were characterized by 1H and 13C NMR spectroscopy, elemental analysis, and optical rotation measurements. TLC and NMR analysis showed the absence of starting materials 2a, b, d and any side products.

For the preparation of 4n, the same conditions as before were employed, with the exception that 2.5 equivalents 2c, one equivalent 3h, and 0.2 equivalents N-(benzyloxy carbonyl)-protected amino acids were used (Scheme 10). When the usual conditions were employed for coupling 2c and 3h, both the mono- and disubstituted ester derivatives formed. Both of these derivatives were easily isolated by column chromatography and were characterized by NMR and CHN analysis.

NMR analysis showed no detectable racemization (<5%) for 4k–n. 1H NMR analysis of 4k in CDCl3 revealed a doublet for the α-NH proton of the amino acid fragment at δ 5.31 and the same for 4l in DMSO-d6 at δ 7.49. 13C NMR analysis of 4k,l displayed a singlet for each carbon-yl carbon.

Previous preparations were by the following methods: (i) The N-protected amino acid and long-chain alkyl alcohol were heated in the presence of methanesulfonic acid as a catalyst; however, the reaction takes 18–24 hours for completion.2c,11a (ii) The N-protected amino acid, long-chain alkyl alcohol, and p-toluenesulfonic acid were refluxed overnight; the desired compounds were obtained in average yields. In the abovementioned methods, the compounds were characterized by NMR spectroscopy, but control of chirality was not specified.11b,c (iii) Acetic anhydride was used in conjunction with catalytic amounts of niobium(V) chloride and/or other catalysts; however, this method has been reported for acetylations only.10h (iv) N-Methylimidazole in the presence of p-toluenesulfonyl chloride with equimolar amounts of the carboxylic acid and alcohol afforded the products in high yields and enantiomeric excesses; however, the only amino acid derivatives reported were of L-alanine (2 examples) and L-proline (1 example).10i

In conclusion, we have demonstrated a convenient and efficient preparation of chirally pure N-protected [(α-aminoacyl)oxy]terpenes 4a–j, 4d/4d', and 4f/4f' and N-protected [(α-aminoacyl)oxy]alkanes 4k–n in average yields of 78–98%. The chirality of the starting material was preserved in >97% ee in the products, as evidenced by NMR and HPLC methods. These advantages also establish N-protected (α-aminoacyl)benzotriazoles as a potential candidate for the esterification reaction between N-protected amino acids and naturally occurring hydroxyterpenes and alkanols.

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. 1H (300 MHz) and 13C (75 MHz) NMR spectra were recorded of samples in CDCl3 or DMSO-d6 with TMS as internal reference. Amino acids and N-(benzyloxy-carbonyl)-protected amino acids were purchased from Fluka and Acros, and were used without further purification. All the reactions were carried out under microwave irradiation with a single-mode cavity Discover Microwave Synthesizer (CEM Corporation, NC) producing continuous irradiation at 2450 MHz. Elemental analyses were performed on a Carlo Erba-1106 instrument. Optical rotation

Scheme 9 Preparation of N-protected [(α-aminoacyl)oxy]alkane 4m

Scheme 10 Preparation of N-protected [(α-aminoacyl)oxy]alkane 4n
values were measured with the use of the sodium D line. Column chromatography was performed on silica gel (200–425 mesh).

**N-Protected ([α-Aminoacyloxy]terpenes 4a–h, 4d/4d′, and 4f/4f′; General Procedure**

A dried, heavy-walled Pyrex tube containing a small stirring bar was charged with a benzotriazole 2a–d or 2a′/2a″ (1.0 mmol), a terpene 3a–d (1.2 mmol), DMAP (0.1 mmol), and dry THF (0.5 mL). For the preparation of 4f, 2h (1.0 equiv), 3a (2.5 equiv), and DMAP (0.2 equiv) in dry THF (0.5 mL) were utilized. The reaction mixture was exposed to microwave irradiation (100 W) for 15 min at 65 °C. After the irradiation, the mixture was allowed to cool down through an inbuilt system in the instrument until the temperature had fallen below 30 °C (ca. 10 min). The mixture was diluted with EtOAc (100 mL) and the soln was washed with sat. aq Na2CO3 (3 × 50 mL) and sat. NaCl soln (50 mL) and dried (MgSO4). Removal of the solvents under reduced pressure gave the crude products 4a–h, 4d/4d′, and 4f/4f′, which were purified by column chromatography (silica gel, EtOAc–hexanes, 2:1); this afforded 4a–e.g.h., 4d′/4d″, and 4f′/4f″ as colorless oils and 4f as microcrystals, recrystallized from CHCl3–hexanes.

**3-(1H-indol-3-yl)propanoate (Cbz-L-Trp-O-Citronellol, 4e)**

Colorless oil; yield: 86%; [α]23° +0.3 (c 0.28, CH2Cl2).

**3-[(1,5,5)-2-Isopropyl-5-methylcyclohexyl (4f)]-O-[Benzoyl]oxy]-4-(methylsulfanyl)butanoate (Cbz-L-Met-thol, 4f)**

White microcrystals; yield: 89%; mp 64–65 °C; [α]23° +16.2 (c 4.42, CH2Cl2).

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(1R,2R,5R)-2-Isopropyl-5-methylcyclohexyl 2-[[Benzyloxycarbonyl]amino]-3-phenylpropanoate (Cbz-Ot-Phe-Ot-Menthyl, 4f/4f)

Colorless oil; yield: 83%; \([\text{Cbz}]^{[3]}_{23} -26.0^\circ (c 1.67, \text{CH}_2\text{Cl}_2).\)

1H NMR (300 MHz, CDCl3): \(\delta = 0.71 (d, J = 6.6 \text{ Hz}, 3 \text{ H}), 0.85 (d, J = 7.1 \text{ Hz}, 3 \text{ H}), 0.89 (d, J = 6.3 \text{ Hz}, 1.5 \text{ H}), 0.90 (d, J = 6.1 \text{ Hz}, 1.5 \text{ H}), 0.93–1.07 (m, 3 \text{ H}), 1.26–1.50 (m, 2 \text{ H}), 1.64–1.78 (m, 3 \text{ H}), 1.93 (d, J = 11.5 \text{ Hz}, 0.5 \text{ H}), 1.99 (d, J = 11.8 \text{ Hz}, 0.5 \text{ H}), 2.98–3.18 (m, 2 \text{ H}), 4.59–4.74 (m, 2 \text{ H}), 5.01–5.11 (m, 2 \text{ H}), 5.25 (d, J = 8.2 \text{ Hz}, 0.5 \text{ H}), 5.31 (d, J = 8.2 \text{ Hz}, 0.5 \text{ H}), 7.11–7.14 (m, 2 \text{ H}), 7.21–7.36 (m, 8 \text{ H}).

13C NMR (75 MHz, CDCl3): \(\delta = 15.8, 16.1, 20.6, 20.8, 21.9, 21.9, 22.8, 23.2, 25.7, 25.9, 31.2, 34.0, 38.0, 38.1, 40.5, 40.5, 46.6, 46.7, 54.7, 54.9, 66.7, 75.6, 75.8, 126.9, 126.9, 127.9, 128.0, 128.0, 128.3, 128.4, 129.2, 129.4, 135.6, 135.7, 135.7, 136.2, 136.2, 155.5, 155.5, 170.9, 171.2.

Anal. Calcd for C35H53NO4: C, 76.18; H, 9.68; N, 2.54. Found: C, 73.98; H, 6.48; N, 5.72.

N-Protected [(a-Aminoacyloxy)alkanes 4k–n; General Procedure

Compounds 4a–n were prepared by the procedure described above for 4a–h, 4d/4d’, and 4f/4f’. However, for the preparation of 4n, 2c (2.5 equiv), 3h (1.0 equiv), and DMAP (0.2 equiv) in dry THF (0.5 ml) were utilized.

Octadecyl S-2-[[Benzyloxycarbonyl]amino]-3-phenylpropanoate (Cbz-Ot-Phe-octadecanol, 4k)

White microcrystals; yield: 98%; mp 61–62 °C; \([\text{Cbz}]^{[3]}_{23} +16.7^\circ (c 2.17, \text{CH}_2\text{Cl}_2).\)

1H NMR (300 MHz, CDCl3): \(\delta = 0.88 (t, J = 6.6 \text{ Hz}, 3 \text{ H}), 1.26 (s, 30 \text{ H}), 1.55–1.57 (m, 2 \text{ H}), 3.09 (t, J = 5.1 \text{ Hz}, 2 \text{ H}), 4.07 (t, J = 4.9 \text{ Hz}, 2 \text{ H}), 4.61 (m, 1 \text{ H}), 5.08 (s, 2 \text{ H}), 5.31 (d, J = 8.3 \text{ Hz}, 1 \text{ H}), 7.08–7.10 (m, 2 \text{ H}), 7.20–7.25 (m, 3 \text{ H}), 7.31 (s, 5 \text{ H}).

13C NMR (75 MHz, CDCl3): \(\delta = 4.0, 22.6, 25.7, 28.3, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 31.8, 32.8, 54.2, 65.6, 66.8, 127.0, 128.0, 128.1, 128.4, 128.5, 129.2, 129.3, 135.7, 136.2, 155.6, 171.5.

Anal. Calcd for C35H53NO4: C, 76.18; H, 9.68; N, 2.54. Found: C, 76.44; H, 9.75; N, 2.56.

Octadecyl (S)-2-[[Benzyloxycarbonyl]amino]-3-(1H-indol-3-yl)propanoate (Cbz-Ot-Trp-Ot-octadecanol, 4i)

Yellow microcrystals; yield: 95%; mp 60–61 °C; \([\text{Cbz}]^{[3]}_{23} +15.9^\circ (c 1.92, \text{CH}_2\text{Cl}_2).\)

1H NMR (300 MHz, CDCl3): \(\delta = 0.85 (t, J = 6.6 \text{ Hz}, 3 \text{ H}), 1.12–1.30 (m, 30 \text{ H}), 1.38–1.50 (m, 2 \text{ H}), 3.02 (dd, J = 14.2, 9.2 \text{ Hz}, 1 \text{ H}), 3.14 (dd, J = 14.2, 5.5 \text{ Hz}, 1 \text{ H}), 3.98 (t, J = 6.1 \text{ Hz}, 2 \text{ H}), 4.23–4.30 (m, 1 \text{ H}), 4.95 (d, J = 12.6 \text{ Hz}, 1 \text{ H}, B part of AB system), 5.01 (d, J = 12.6 \text{ Hz}, 1 \text{ H}, A part of AB system), 6.97 (t, J = 7.3 \text{ Hz}, 1 \text{ H}), 7.06 (t, J = 7.1 \text{ Hz}, 1 \text{ H}), 7.15 (d, J = 1.8 \text{ Hz}, 1 \text{ H}), 7.28–7.36 (m, 6 \text{ H}), 7.49 (d, J = 7.7 \text{ Hz}, 1 \text{ H}), 7.79 (d, J = 7.6 \text{ Hz}, 1 \text{ H}), 10.87 (s, 1 \text{ H}).

13C NMR (75 MHz, CDCl3): \(\delta = 13.9, 22.1, 25.2, 26.9, 28.0, 28.6, 28.7, 30.0, 31.3, 51.1, 64.4, 64.5, 109.6, 111.4, 117.9, 118.3, 120.9, 123.8, 127.0 (2 \text{ C}), 127.8, 128.3, 136.1, 136.6, 155.9, 172.3.

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Anal. Calcd for C_{20}H_{30}N_{2}O_{8}: C, 75.72; H, 9.01; N, 4.77. Found: C, 75.50; H, 9.12; N, 4.68.

Dodecyl (S)-2-[(Benzyloxy-carbonyl)amino]-3-[(S)-2-[(benzyloxy-carbonyl)amino]-3-(dodecyl-oxy)-3-oxopropyl]disulfanylpropanoate (Cbz-1-Cys-S-O-di-dodecanol, 4n)

Colorless oil; yield: 91%; mp 77–78 °C.

1H NMR (300 MHz, CDCl_{3}): δ = 0.88 (t, J = 6.6 Hz, 6 H), 1.18–1.37 (m, 36 H), 1.54–1.64 (m, 4 H), 3.07–3.16 (m, 4 H), 4.12 (t, J = 6.3 Hz, 4 H), 4.60–4.68 (m, 2 H), 5.10 (s, 2 H), 5.11 (s, 2 H), 5.78–5.86 (m, 2 H), 7.28–7.32 (m, 10 H).

13C NMR (75 MHz, CDCl_{3}): δ = 14.0, 22.6, 25.7, 26.1, 28.3, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 31.8, 41.1, 53.3, 66.0, 66.9, 127.9, 128.0, 128.4, 136.0, 155.6, 170.2.

Anal. Calcd for C_{46}H_{72}N_{2}O_{8}S_{2}: C, 65.37; H, 8.59; N, 3.31. Found: C, 65.56; H, 8.90; N, 3.29.

Ethylene Bis(S)-(2-[(Benzyloxy-carbonyl)amino]-4-(methylsulfonyl)butanoate) (Cbz-1-Met-di-O-Glyceryl, 4n)

White microcrystals; yield: 89%; mp 80–81 °C.

1H NMR (300 MHz, CDCl_{3}): δ = 1.90–2.00 (m, 2 H), 2.07 (s, 3 H), 2.12–2.21 (m, 2 H), 2.53 (t, J = 7.3 Hz, 4 H), 4.32–4.41 (m, 4 H), 4.50 (q, J = 8.1 Hz, 2 H), 5.07 (d, J = 12.6 Hz, 6 H), 5.60 (d, J = 8.2 Hz, 2 H), 7.33 (s, 10 H).

13C NMR (75 MHz, CDCl_{3}): δ = 15.4, 29.8, 31.4, 53.1, 62.7, 67.1, 128.2, 128.3, 136.5, 150.6, 171.7.

Anal. Calcd for C_{37}H_{54}N_{2}O_{4}: C, 75.21; H, 9.21; N, 4.74. Found: C, 75.50; H, 9.39; N, 4.60.

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