Synthesis of (2S,3R,4S)-Isonorstatine Using a Solvent-Induced Highly Stereoselective 3-Butenyl Addition to L-Threose Imines

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Abstract: Isonorstatine was obtained in an 11-step sequence starting from L-tartaric acid, based on a highly stereoselective addition of 1-butene-3-yl to a threose imine. The orientation of the methyl group at C-4 of isonorstatine was determined by transformation of the key α-xylo adduct into a δ-lactone. This also shows that both termini of the key adduct, the diol acetonide and vinyl moiety, can be elaborated selectively into an acid function leading to both amino-hydroxymethyl acid and diacid derivatives.

Key words: threose imines, allyl/1-butene-3-yl addition, aminohydroxymethyl acid, solvent effect, N-(1-phenylethyl) auxiliary

The stereoselective synthesis of β-amino acids and their derivatives has been an active area of research, due to the importance of β-amino acids in various fields. In particular, non-proteinogenic β-amino-α-hydroxy acids are found in many natural products and drugs, for example, as a central moiety of oligopeptide-related structures such as pepstatin. Thus, norstatine A [(2S,3R)-3-amino-2-hydroxy-4-methylhexanoic acid] is part of amastatin, an inhibitor of leucine aminopeptidase. On the other hand, the enantiomer of A has been found in human renin inhibitors KRI-1230 and KRI-1314. Isonorstatine B [(2R,3S,4S)-3-amino-2-hydroxy-4-methylhexanoic acid] and other analogues of cyclohexylstatine (cf. C) have been used as the terminal amino acid part of such renin inhibitors.

The synthesis of (2R,3S,4S)-isonorstatine isopropyl ester by Kiso et al. was based on (2S,3S)-isoleucine, using a poorly selective cyanide addition to leucinal. (2R,3S,4S)-Isonorstatine was finally obtained by separation of a diastereomeric mixture, but there were no details given for the intermediates. In our group, several approaches to variously substituted 1,2-amino alcohols have been developed, such as diastereoselective nitroaldol additions of a series of chiral aldehydes and nitro compounds. In a complementary way, highly stereoselective additions to α-alkoxyimines have provided an efficient and versatile access to aminopolys, 1,4-iminopolypol derivatives such as anisomycin, and to the statine family.

The addition of Grignard and lithium reagents to the C=N bond of the N,O-dibenzythreose derivative 1 had been found to proceed with high 3,4-threo selectivity. We then began to wonder if an α-branched alkyl chain, introducing a new vicinal stereocentre, could be connected likewise. Indeed, the addition of sec-butyl-lithium proved highly threo-selective with respect to C-3/C-4; however, both C-5 diastereomers 2 were formed non-selectively (Scheme 1).

In order to overcome this lack of selectivity, we then examined allyl additions to the imine 1 and to the auxiliary-adorned N-(1-phenylethyl)imines 3 [N-(S)] and 4 [N-(R)], allyl, methallyl, and crotyl/3-butene-1-yl Grignard reagents were used (Table 1).

The addition of allylmagnesium bromide to the N-benzylimine led to an 85:15 ratio of D-threo/xylo isomers 5a/6a, which is somewhat lower than that obtained with the vinyl derivative. With N-(1-phenylethyl)imines 3 and 4, due to the additional induction from the auxiliary, the isomer ratio changed to 92:8 and 77:23, respectively.

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Table 1 Allyl Additions to Imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>R1</th>
<th>Solvent</th>
<th>Product</th>
<th>dr* [(D-xylo)/(L-arabino)]</th>
<th>Yieldb (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Allyl</td>
<td></td>
<td>Et2O</td>
<td>5a/6a</td>
<td>85:15</td>
<td>64</td>
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<tr>
<td>2</td>
<td>Allyl</td>
<td></td>
<td>Et2O</td>
<td>5b/6b</td>
<td>92:8</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>Allyl</td>
<td></td>
<td>Et2O</td>
<td>5c/6c</td>
<td>77:23</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Methallyl&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Et2O</td>
<td>7a/8a</td>
<td>66:34</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Methallyl&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Et2O</td>
<td>7b/8b</td>
<td>94:6</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>Methallyl&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Et2O</td>
<td>7c/8c</td>
<td>22:78</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>3-Butenyl/Crotyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Et2O</td>
<td>9a,10a/11a</td>
<td>(42:51):(7:&lt;5)</td>
<td>79</td>
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<tr>
<td>8</td>
<td>3-Butenyl/Crotyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Et2O</td>
<td>9b,10b&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(42:58):(5:&lt;5)</td>
<td>77</td>
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<tr>
<td>9</td>
<td>3-Butenyl/Crotyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Et2O</td>
<td>9c,10c/11c.12c</td>
<td>(57:18):(25:5)</td>
<td>82</td>
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<tr>
<td>10</td>
<td>3-Butenyl/Crotyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>THF</td>
<td>9a,10a/11a</td>
<td>(67:28):(5:&lt;5)</td>
<td>71</td>
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<tr>
<td>11</td>
<td>3-Butenyl/Crotyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>THF</td>
<td>9b,10b&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(92:8):(5:&lt;5)</td>
<td>81</td>
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<tr>
<td>12</td>
<td>3-Butenyl/Crotyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>THF</td>
<td>9c</td>
<td>(&gt;95:&lt;5):(5:&lt;5)</td>
<td>85</td>
</tr>
</tbody>
</table>

**a** Determined from analyses of the 13C NMR spectra of crude addition products; estimated limit of detection 5%.

**b** Yield based on imine, after chromatography on basic alumina.

**c** Incomplete after addition of 2 equiv; 4 equiv required.

**d** Reagent prepared from crotyl bromide.

A dramatic, unexpected improvement was found when the solvent was changed from diethyl ether to tetrahydrofuran. With the ‘parent’ imine 1, the D-xylo 9a and 10a isomers were favoured and formed in a ratio of 67:28; this rose to 92:8 with the (S)-imine 3 and, fortunately, to >95:5 for 9c with the (R)-imine 4, where none of the other three diastereomers could be detected by NMR analyses of the crude reaction product.

Consequently, the initial objective of finding a method to access methyl-branched aminohydroxy acids of the iso-norstatine type B, which had failed by direct sec-butyl addition, could now be reconsidered and extended. The amino-heptenetriol 9 constitutes an advanced intermediate with orthogonally structured termini capable of undergoing further transformations to carboxyl groups. Either end would be amenable to regioselective oxidative degradation, eventually leading to β-amino-α-hydroxy-γ-methyl acids D (norisostatine type B), to β-amino-γ-hydroxy-α-methyl acids E, or to β-amino-α-hydroxy-γ-methyl diacids F (Figure 2). A remaining problem, however, concerned the configuration at the methyl-bearing stereocentre, which had to be elucidated later on.

(Table 1, entries 2 and 3), which is in line with our earlier results concerning the imines of 2-O-benzylglyceraldelyde. The methallyl case showed a similar tendency concerning diastereomeric ratio changes, but now the opposite mismatching effect of the N-[(R)-1-phenylethyl] substituent was more pronounced, leading to the L-arabino isomer 8c predominantly (Table 1, entry 6).

Since we intended to add a 2-butyl group, the results with the crotyl/3-butenyl Grignard derivative were of particular relevance. Our first attempts paralleled those with sec-butyl (vide supra) though (Table 1, entries 7–9); the best result was obtained with the (S)-imine 3 which furnished a mixture of 5-epimers of the xylo compounds 9b/10b only. With the (R)-imine 4 a third diastereomer 11c was formed. The latter was assigned the L-arabino configuration, based on the coupling constant $J_{3,4} = 5.2$ Hz. Earlier, the coupling constant $J_{3,4}$ had proved diagnostic for all simple addition products from 1, while the D-xylo-aminotriol derivatives consistently showed a small coupling of $J_{3,4} = 1.4–1.8$ Hz. Similar values of ca. 1.2 Hz were found with all the diastereomers designated as D-xylo (3,4-threo) which are described here.10,13

With the key intermediate 9c in hand, the synthesis of isonorstatine 17 was accomplished in a straightforward manner. The aminotriol 13 was obtained pure and in high yield by hydrolysis of the acetal group under acidic conditions. The olefinic double bond was then reduced by catalytic hydrogenation (H2, 1 bar, 5% Pd/BaSO4) at room temperature in good yield without loss of the benzyl protecting group. Next, the free diol 14 was cleaved by means of sodium periodate to give the aldehyde 15, which was oxidised to the carboxylic acid 16. Finally, the N,O-protected amino acid 16, upon catalytic hydrogenation, was converted into free, analytically pure isonorstatine 17 in 93% yield (Scheme 2).

We then turned to the elaboration of the olefinic terminus, with two objectives – assignment of the configuration at C-5 in 9c (C-4 in 17), combined with finding a method to access the second type of C-methyl-branched β-amino acids E – in mind. Dihydroxylation of the key intermediate 9c according to Sharpless’ procedure provided the 6,7-diol 18. The diol 18 was cleaved by sodium periodate to furnish the aldehyde 19, which was directly oxidised to the acid 20. On treatment of the latter with excess diazomethane the corresponding ester 21 was isolated. Hydrolysis of the acetonide ester 21 was now expected to lead to a δ-lactone, with the methyl group positioned within the ring, which should allow to determine its orientation. Indeed, on acid-mediated hydrolysis the ester and the acetal group were cleaved, but this was accompanied by partial loss of the O-benzyl group. Anyway, the lactones 22 and 23 were readily separable by flash column chromatography leading to the analytically pure γ-benzylxoy-δ-lactone 22 (40%) and to the γ-hydroxy-δ-lactone 23 (26%).

The lactone 22 now permitted to assign the configuration at C-2, since the proton signals appeared well separated in the 1H NMR spectrum. From this, coupling constants J2,3 = 0.7 Hz, J3,4 = 7.3 Hz, and J4,5 = 5.2 Hz were derived. This information was complemented by NOE measurements, which showed enhancement of 2-CH3/3-H and 2-H/4-H. In summary, the 2-methyl and the 3-amino group are situated trans, as are 3-amino/4-benzyloxy; for 4-BnO/5-CH2OH the cis-arrangement as present in the starting material L-threose was confirmed. From these cou-

Scheme 2 Reagents and conditions: (i) HCl, dioxane–H2O (1:1), 50 °C, 18 h, 90%; (ii) H2, 1 bar, 5% Pd/BaSO4, MeOH, r.t., 3 h, 90%; (iii) NaIO4, MeOH–H2O–THF (4:2:1), 0 °C, 2 h, 97%; (iv) NaClO2, NaH2PO4, t-BuOH, r.t., 3 h, 90%; For assignment of configuration at C-5 in 9c (C-4 in 17) vide infra.

Scheme 3 Reagents and conditions: (i) K3[Fe(CN)6], K2CO3, K3OsO2(OH)3(DHQD)PHAL, t-BuOH–H2O (1:1), r.t., 6 h, 78%, dr 82:18; (ii) NaIO4, MeOH–H2O–THF (4:2:1), 0 °C, 3 h, 99%; (iii) NaClO2, NaH2PO4, t-BuOH, r.t., 3 h, 90%; (iv) CH2N2, r.t., 10 min, 86%; (v) HCl, dioxane–H2O (1:1), 50 °C, 18 h, 40% + 26%.
plings, the S4 conformation of the δ-lactone is most likely, where the trans-oriented 2-H/3-H enclose an angle of ca. 90° (Scheme 3).

Finally, a method to access an aminohydroxymethyl diacid (type F in Figure 2) remained to be demonstrated, by twofold oxidative conversion of the diol-acetonide, and the olefinic double bond into carboxyl groups, as had been effected individually with the approaches to D and E, respectively. To this purpose, the ester 21 with the acetal-protected 5,6-diol was treated with orthoperiodic acid, which caused both diol protection and cleavage. The resulting aldehyde 24 without purification was oxidised with sodium chlorite as above to afford the glutaric acid and 25% overall yield. (ii) NaH2PO4, Et2O, r.t., 6 h, quant.; (iii) CH2N2, Et2O, 72%.

In conclusion, a new route to methyl-branched β-aminohydroxy acids of types D, E and F has been outlined, based on the highly stereoselective reaction of 3-butenyl Grignard with the threose-derived imine 4. In particular, the (2S,3R,4S)-isomer 17 of isonostatine was obtained via the threose imine 4 from diethyl L-tartrate in 11 steps and 25% overall yield.

For general experimental details, see ref. 10b. 2-O-Benzyl-3,4-O-isopropylidene-L-threonol was prepared in four steps from diethyl L-tartrate according to known procedures;[10,12–14] [α]D20 +35.9 (c 1.50, CHCl3), [α]D20 +54.6 (c 1.51, CHCl3). N-Benzyl-lactimine (1)10 and N-(S)-1-phenethyl-lactimine (3)10 were prepared according to known procedures.

Allylamine oxide bromide was purchased from Aldrich and Pf/NaH2PO4, t-BuOH, r.t., 3 h, 86%; (iii) CH3N2, Et2O, 72%.

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Scheme 4 Reactants and conditions: (i) H2IO6, Et2O, r.t., 6 h, quant.; (ii) NaH2PO4, t-BuOH, r.t., 3 h, 86%; (iii) CH3N2, Et2O, 72%.

In [1H NMR (250.1 MHz, CDCl3): δ = 0.90 (m, CH2SH, 6 H, 7-CH2), 1.14 (m, 1 H, 6-H), 3.17, 3.22 (2 s, 6 H, C(CH3)2), 1.49 (m, 1 H, 6-H), 1.67 (s, 1 H, NH), 1.72 (m, 1 H, 5-H), 2.20 (dd, J2,4a = 5.7 Hz, J3,4a = 1.7 Hz, 1 H, 4-H), 3.50 (m, 1 H, 3-H), 3.52 (app dd, J2,4a = 8.1 Hz, J3,4a = 8.0 Hz, 1 H, 1-H), 3.73–3.91 (m, 3 H, 1-H, NCH2Ph), 4.51 (m, 1 H, 2-H), 4.58, 4.96 (AB’ system, J = 11.5 Hz, 2 H, OCH2Ph), 7.20–7.36 (m, 10 H, 2 Ph).

13C NMR (62.9 MHz, CDCl3): δ = 12.14 (q, C-7), 15.8 (q, C-1’), 26.5 (t, C-6), 26.8 (q, C(CH3)2), 26.75 (dd, c-5), 51.6 (t, NCH2Ph), 60.7 (d, C-4), 66.5 (t, C-1), 73.5 (t, OCH2Ph), 79.3 (d, C-2), 80.5 (d, C-3), 109.1 (s, O2C(C2H5)2), 126.8, 127.3, 127.8, 128.1, 128.2, 128.3 [6 d, 2 Ph (α-, α-, p-C)], 139.0, 141.0 (2 s, 2 Ph(α-C)).

Minor Isomer
[1H NMR (250.1 MHz, CDCl3): δ = 1.37, 1.44 (2 s, 6 H, C(CH3)2), 2.24 (dd, J2,4a = 5.4 Hz, J3,4a = 2.2 Hz, 1 H, 4-H), 3.50 (app dd, J2,4a = 8.1 Hz, J3,4a = 8.0 Hz, 1 H, 1-H), 4.55, 4.98 (AB’ system, J = 11.4 Hz, 2 H, OCH2Ph); the other signals overlapped with those of the main isomer.

13C NMR (62.9 MHz, CDCl3): δ = 12.04 (q, C-7), 15.9 (q, C-1’), 25.6 (q, C(CH3)2), 26.0 (t, C-6), 35.7 (d, C-5), 52.4 (t, NCH2Ph), 61.4 (d, C-4), 73.3 (t, OCH2Ph), 81.1 (d, C-3); the other signals coincided with those of the main isomers.

N-{[(S)-1-Phenethyl]liminyl} 3
Prepared according to the method described for 4, from 2-O-benzyl-3,4-O-isopropylidene-L-threonol (1.00 g, 4.00 mmol), Al2O3 (1.02 g, 10.0 mmol), and (S)-1-phenethyl-lactimine (484 mg, 4.00 mmol) to give 1.39 g (98%) of 3 as a colourless, spectroscopically pure oil; [α]D20 +2.72 (c 1.30, CHCl3).

1H NMR (250.1 MHz, CDCl3): δ = 1.38, 1.42 (2 s, 6 H, C(CH3)2), 1.48 (d, J = 6.6 Hz, 3 H, NCH2CH3), 3.91 (dd, J2,4a = 8.6 Hz, J3,4a = 6.6 Hz, 1 H, 4-H), 3.98 (dd, J2,4a = 6.0 Hz, J3,4a = 5.6 Hz, 1 H, 2-H), 4.03 (dd, J2,4a = 8.6 Hz, J3,4a = 6.7 Hz, 1 H, 4-H), 4.34 (m, 3-H), 4.35 (q, J = 6.6 Hz, NCH2CH3) together 2 H, 4.54, 4.61 (AB system, J = 12.1 Hz, 2 H, OCH2Ph), 7.21–7.41 (m, 10 H, 2 Ph), 7.68 (d, J2,4a = 5.6 Hz, 1 H, 1-H).
1H NMR of (250.1 MHz, CDCl 3): δ = 1.38, 1.41 [2 s, 6 H, (C(CH3)2)], 2.31–2.37 (m, 2 H, 5-H), 2.45 (app dd, J1a,b = 7.8 Hz, J1a,2 = 5.3 Hz, J1a,1b = 2.4 Hz, 1 H, 4-H), 3.42 (dd, J1a,1b = 7.5 Hz, J1a,4 = 2.4 Hz, 1 H, 3-H), 3.48 (app dd, J1a,4 = 8.2 Hz, J1a,1b = 8.1 Hz, 1 H, 1-H), 3.65 (A of AB, J = 13.1 Hz, 1 H, NCH2CH3Ph), 3.82 (app dd, J1a,1b = 8.1 Hz, J1a,2 = 6.3 Hz, 1 H, 1-H), 3.85 (B of AB, J = 13.1 Hz, 1 H, NCH2CH3Ph), 4.50 (app dd, J2a,b = 8.2 Hz, J2a,3 = 7.5 Hz, J2a,1a = 6.3 Hz, 1 H, 2-H), 4.60, 49.1 (A’B’ system, J = 11.7 Hz, 2 H, OCH2Ph), 4.94–5.04 (m, 2 H, 7-H), 5.65 (m, 1 H, 6-H), 7.20–7.38 (m, 10 H, 2 Ph).

13C NMR (62.9 MHz, CDCl 3): δ = 24.3 (q, NCH(CH3)2), 25.3, 26.3 [2 q, C(CH3)2], 65.6 (t, C-4), 69.6 (d, NCH2CH3Ph), 71.7 (t, OCH3Ph), 76.5 (d, C-3), 80.6 (d, C-2), 109.6 [s, C(CH2)2], 126.4, 126.9, 127.6, 127.9, 128.4 [6 d, 2 Ph o-, m-, p-]], 137.7 [s, OCH2Ph(1-C), 144.3 [s, NCH2CH3Ph(1-C)], 161.0 (d, C-1).
1H NMR (500.1 MHz, CDCl 3); δ = 0.87 (d, J\textsubscript{1,2} = 6.9 Hz, 5-H\textsubscript{CH\textsubscript{3}}), 1.19 (d, J\textsubscript{1,2} = 6.5 Hz, NCH\textsubscript{CH\textsubscript{3}}\textsubscript{3}), 1.33, 1.37 [2 s, C(\textsubscript{CH\textsubscript{3}})\textsubscript{2}], 1.74 (s, NH), 2.14 (dd, J\textsubscript{1,2} = 6.1 Hz, J\textsubscript{1,2} = 1.6 Hz, 4-H), 2.30 (m, 5-H), 3.47 (dd, J\textsubscript{1,2} = 8.1 Hz, J\textsubscript{1,2} = 3.6 Hz, 3-H), 3.49 (dd, J\textsubscript{1,2} = 8.1 Hz, J\textsubscript{1,2} = 8.0 Hz, 1-H\textsubscript{1}), 3.83 (q, J\textsubscript{1,2} = 6.4 Hz, NCH\textsubscript{CH\textsubscript{3}}\textsubscript{3}), 3.90 (dd, J\textsubscript{1,2} = 8.1 Hz, J\textsubscript{1,2} = 6.4 Hz, 1-H\textsubscript{1}), 4.48 (m, 2-H), 4.49 (AB system, J\textsubscript{1,2} = 11.5 Hz, OCH\textsubscript{H\textsubscript{2}Ph}), 4.80 (dd, J\textsubscript{1,2} = 17.2 Hz, J\textsubscript{1,2} = 19.9 Hz, 7-H), 4.83 (dd, J\textsubscript{1,2} = 10.3 Hz, J\textsubscript{1,2} = 9.7 Hz, OCH\textsubscript{H\textsubscript{2}Ph}), 4.88 (AB system, J\textsubscript{1,2} = 11.5 Hz, OCH\textsubscript{H\textsubscript{2}Ph}), 5.62 (dd, J\textsubscript{1,2} = 17.2 Hz, J\textsubscript{1,2} = 10.3 Hz, J\textsubscript{1,2} = 8.0 Hz, 6-H), 7.15–7.28 (m, 2 Ph).

13C NMR (125.8 MHz, CDCl 3); δ = 17.3 (q, 5-CH\textsubscript{3}), 24.15 (q, NCH\textsubscript{CH\textsubscript{3}}\textsubscript{3}), 25.68, 26.76 [2 q, C(\textsubscript{CH\textsubscript{3}})\textsubscript{2}], 40.75 (d, C-5), 55.8 (d, NCH\textsubscript{CH\textsubscript{3}}\textsubscript{3}), 59.4 (d, C-4), 66.43 (t, C-1), 73.3 (t, OCH\textsubscript{H\textsubscript{2}Ph}), 79.3 (d, C-2), 80.5 (d, C-3), 109.2 [s, C(\textsubscript{CH\textsubscript{3}})\textsubscript{2}], 114.15 (t, C-7), 126.88, 127.04, 127.25, 127.72, 128.09, 128.21 [6 d, 2 Ph (m, o–p, C–C)], 139.00 [s, OCH\textsubscript{H\textsubscript{2}Ph}], 142.03 (d, C-6), 146.15 [s, NCH\textsubscript{CH\textsubscript{3}}\textsubscript{3}](C–C)].

9c from a mixture of 9c/10c = 76:24

10c from a mixture of 9c/10c = 76:24

IR (neat): 3348 (NH), 1638, 1494, 1453, 1369, 1252, 1211, 1156, 1069, 697 cm\(^{-1}\).

Amino heptenetriol 9c (1.80 g, 4.40 mmol) was dissolved in dio xo–H\textsubscript{2}O (1: 1; 16 mL) and conc HCl (0.4 mL) was added. The reaction mixture was kept at 50 °C for 18 h. The resulting solution was concentrated (40 °C/200 mbar) and then dissolved in a sat. solution of NaHCO\textsubscript{3} (20 mL). The mixture was extracted with Et\textsubscript{2}O (4 × 40 mL). The combined organic phases were washed with a sat. aq solution of NH\textsubscript{4}Cl (4 mL) and extracted with Et\textsubscript{2}O (4 × 40 mL). The combined organic phases were washed with a sat. aq solution of Na\textsubscript{2}CO\textsubscript{3} (50 mL) and dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure and the crude reaction mixture was heated to reflux for 30 min. The mixture was allowed to warm to r.t. and stirred for 3 h. The reaction was quenched with a sat. aq solution of NaHCO\textsubscript{3} (50 mL) and dried over MgSO\textsubscript{4}.

The reaction was carried out as described above for 9c.

Found: C, 76.36; H, 8.72; N, 3.39.

A two-necked 50 mL flask was charged with Mg (314 mg, 13.1 mmol), Et\textsubscript{2}O (4 × 40 mL). The combined organic phases were washed with Et\textsubscript{2}O (4 × 40 mL). The combined organic phases were washed with a sat. aq solution of NH\textsubscript{4}Cl (4 mL) and extracted with Et\textsubscript{2}O (4 × 40 mL). The combined organic phases were washed with a sat. aq solution of Na\textsubscript{2}CO\textsubscript{3} (50 mL) and dried over MgSO\textsubscript{4}.

The solvent was removed under reduced pressure and the crude product was purified by chromatography (silica gel; 25 g, 8 cm × 3 cm, PE–EtOAc, 10:1, 1% Et\textsubscript{3}N) to give 1.46 g (90%) of the free diol 9c as an analytically pure, colourless oil; [\(\alpha\)]\textsubscript{D}\textsuperscript{20} +15.6 (c 2, CHCl\textsubscript{3}).
13C NMR (75.5 MHz, CDCl3); δ = 17.8 (q, 5-CH3), 20.8 (q, NCH3H), 37.0 (d, C-5), 53.4 (d, NCH3CH3), 57.3 (d, C-4), 61.5 (t, C-1), 71.4 (d, C-2), 73.2 (t, OCH2Ph), 78.1 (d, C-3), 115.2 (t, C-7), 127.1, 128.0, 128.2, 128.9, 129.2 (5 d, 2 Ph), 138.2 [s, OCH2Ph(i-C)], 140.4 (d, C-6), 145.2 [s, NCH(2)Ph(i-C)].

Anal. Calc'd for C31H41NO3 (467.6): C, 75.76; H, 8.90; N, 3.94. Found: C, 75.65; H, 8.89; N, 3.91.

(2S,3S,4R,5S,6R,1'R)-4-Amino-3-o-benzyl-5-methyl-N-(1'-phenyl-ethyl)-1,2,3-heptanetriol (14)
A 25 mL flask was charged with Pd/BaSO4 (5%, 35 mg); MeOH (2.0 mL) and the diol 13 (350 mg, 0.95 mmol) were added. The mixture was hydrogenated for 4 h at normal pressure. After centrifugation of the solids the filtrate was concentrated (40 °C/300 mbar) to give 21 mg (93%) of the free hexanoic acid 17 as a light-yellow, analytically pure powder; mp 204–205 °C; [α]D20 –20.8 (c 0.36, MeOH).

IR (solid): 3500–2500, 1733, 1599, 1511, 1461, 1377, 1281, 1228, 1143, 1073, 1024, 823, 694 cm–1.

1H NMR (300.1 MHz, D2O): δ = 0.78 (t, J3,6 = 7.4 Hz, 3 H, 3-H, H2), 0.89 (d, J3,6 = 6.5 Hz, 3 H, 6-CH3), 1.08 (m, 1 H, 5-H), 1.15 (d, J1,2 = 6.7 Hz, 3 H, NCH3H), 1.28 (m, 1 H, 5-H), 1.29 (m, 1 H, 3-H), 1.38 (m, 1 H, 2-H), 1.48 (m, 1 H, 3-H), 1.55 (m, 1 H, 2-H), 1.71 (m, 1 H, 3-H), 1.74 (dd, J1,2 = 4.8 Hz, 1 H, 1-H), 4.31 (d, J3,6 = 4.3 Hz, 1 H, 2-H).

13C NMR (75.5 MHz, D2O): δ = 10.7 (q, C-6, 14.1 (q, C-4), 25.7 (t, C-5), 34.4 (d, C-4), 58.0 (d, C-3), 70.1 (d, C-2), 177.2 (s, C-1). Anal. Calc'd for C11H25NO3HC1 (161.2); C, 42.53; H, 8.16; N, 7.09. Found: C, 42.21; H, 8.72; N, 6.75.

(2R,3S,4R,5R,6R,1'R)-2-Amino-2-benzyl-1,2-3-isoarylprolidene-5-methyl-N-(1'-phenyl-ethyl)heptane-1,2,3,6,7-pentol (18)
A 50 mL round-bottom flask, equipped with a magnetic stirrer, was charged with t-BuOH–H2O (1:1, 8.0 mL). To the mixture were added K2OsO3(OH)4 (5.4 mg, 0.015 mmol) and hydroquinidine 1,4-chloro-2,6-cresol (4.0 mmol) to give 21 mg (93%) of the free hexanoic acid 17 as a light-yellow, analytically pure powder; mp 204–205 °C; [α]D20 –20.8 (c 0.36, MeOH).

IR (solid): 3500–2500, 1733, 1599, 1511, 1461, 1377, 1281, 1228, 1143, 1073, 1024, 823, 694 cm–1.

1H NMR (300.1 MHz, D2O): δ = 0.78 (t, J3,6 = 7.4 Hz, 3 H, 3-H, H2), 0.89 (d, J3,6 = 6.5 Hz, 3 H, 6-CH3), 1.08 (m, 1 H, 5-H), 1.15 (d, J1,2 = 6.7 Hz, 3 H, NCH3H), 1.28 (m, 1 H, 5-H), 1.29 (m, 1 H, 3-H), 1.38 (m, 1 H, 2-H), 1.48 (m, 1 H, 3-H), 1.55 (m, 1 H, 2-H), 1.71 (m, 1 H, 3-H), 1.74 (dd, J1,2 = 4.8 Hz, 1 H, 1-H), 4.31 (d, J3,6 = 4.3 Hz, 1 H, 2-H).

13C NMR (75.5 MHz, D2O): δ = 10.7 (q, C-6), 14.1 (q, C-4), 25.7 (t, C-5), 34.4 (d, C-4), 58.0 (d, C-3), 70.1 (d, C-2), 177.2 (s, C-1). Anal. Calc'd for C32H53NO5 (595.6): C, 72.81; H, 8.61; N, 3.59. Found: C, 72.85; H, 8.66; N, 3.51.
(2R,3R,4S,1R)-3-Amino-4-O-benzyl-5,6-O-isopropylidene-2-methyl-3-[(1-phényl)ethyl]hexanoic acid (20)

To a solution of the diol 12 (253 mg, 0.57 mmol) in MeOH–THF–H2O (4:2:1, 10 mL) was added NaIO4 (428 mg, 2.0 mmol) at 0 °C. The reaction mixture was stirred for 3 h at the same temperature, then quenched with a sat. solution of NaHCO3 (10 mL) and extracted with CH2Cl2 (4 × 30 mL). The combined organic phases were dried (MgSO4) and concentrated to give 234 mg (99%) of the aldhyde 19 as a colourless oil which was used directly in the next step.

The aldehyde 19 was dissolved in t-BuOH (5.0 mL) and 2-methyl-2-butene (2.5 mL). To the mixture was added a solution of ethereal NaH2PO4 (78 mg, 0.86 mmol) and NaClO2 (104 mg, 0.86 mmol) in H2O (1.0 mL). After stirring for 90 min the same amounts of NaClO2 and NaHPO4 were added again. After further stirring for 1 h, the NaOH solution (8 M, 0.5 mL) was added. The solvent was removed under reduced pressure and the resulting residue was dissolved in H2O (6.0 mL). The pH was adjusted to 3–4 by dropwise addition of 6 M HCl. The mixture was extracted with EtOAc (5 × 40 mL), the combined organic phase was dried (MgSO4) and concentrated to give 219 mg (90%) of the carboxylic acid 20 as a colourless oil.

1H NMR (300.1 MHz, CDCl3): δ = 0.99 (d, J1/CH3 = 7.2 Hz, 3 H, 2-CH3), 1.40, 1.42 [2 s, 6 H, (CH2)3], 1.47 (d, Jq = 6.6 Hz, 3 H, H3, NCHCH3), 1.94 (m, 1 H, 2-H), 2.84 (dd, Jd, J5 = 5.7 Hz, Jq = 13.1 Hz, 1 H, 3-H), 3.59 (dd, Jq = 4.0 Hz, Jd, J5 = 12.1 Hz, 1 H, 4-H), 3.74 (dd, Jq, Jd = 8.2 Hz, J5, Jd = 7.6 Hz, 1 H, 1-H; 6-H), 3.91 (q, Jq = 6.6 Hz, 1 H, NCHCH3), 4.01 (dd, J1/CH3 = 8.3 Hz, J5 = 6.5 Hz, 1 H, 1-H; 6-H), 4.21 (m, 1 H, 5-H), 4.51, 4.61 (AB system, J = 10.4 Hz, 2 H, OCH2Ph), 7.29–7.41 (m, 10 H, 2 Ph).

13C NMR (75.5 MHz, CDCl3): δ = 12.5 (q, 2-CH3), 23.1 (q, NCHCH3), 25.7, 26.3 [2 q, C(CH3)2], 39.0 (d, C-2), 59.0 (d, NCHCH3), 61.6 (d, C-3), 66.0 (t, C-6), 74.7 (t, OCH2Ph), 75.1 (d, C-5), 79.1 (d, C-4), 110.0 [2 s, (CH2)3], 125.9, 127.1, 128.0, 128.32, 128.38, 128.7, 129.0 (7 t, 2 Ph), 137.1 [s, OCH2Ph(2-C)], 141.9 [s, NCH(CH3)Ph(3-C)], 176.0 (s, C-1).

Methyl (2R,3R,4S,1R)-3-Amino-4-O-benzyl-5,6-O-isopropylidene-2-methyl-3-[(1-phényl)ethyl]hexanoate (21)

Acid 20 (219 mg, 0.51 mmol) was treated with a solution of ethereal CH2N2 (excess). After 20 min the solvent was evaporated and the residue was purified by flash column chromatography (silica gel; PE–EtOAc, 6:1) to afford 195 mg (86%) of the methyl ester 21 as a colourless, analytically pure oil; [α]D20 = +4.08 (c 1.45, CHCl3).

IR (neat): 3320, 1729 (C=O), 1453, 1369, 1247, 1193, 1113, 1054, 975, 761, 689 cm–1.

1H NMR (300.1 MHz, CDCl3): δ = 1.12 (d, J1/CH3 = 7.1 Hz, 3 H, 2-CH3), 1.25 (d, Jq = 6.4 Hz, 3 H, 3, NCHCH3), 1.41, 1.44 [2 s, 6 H, (CH2)3], 2.66 (m, 2 H, 2-H, NCHCH3), 3.34 (s, 3 H, OCH3), 3.49 (dd, Jq = 7.7 Hz, J1/CH3 = 0.9 Hz, 1 H, 4-H), 3.69 (app t, J1/CH3 = Jq = 8.1 Hz, 1 H, 6-H), 3.91 (q, Jq = 6.5 Hz, 1 H, NCHCH3), 4.09 (dd, Jq = Jd = 8.1 Hz, 1 H, 1-H; 6-H), 4.47, 4.94 (AB system, J = 11.2 Hz, 2 H, OCH2Ph), 4.51 (m, 1 H, 5-H), 7.22–7.27 (m, 10 H, 2 Ph).

13C NMR (75.5 MHz, CDCl3): δ = 14.7 (q, 2-CH3), 23.6 (q, NCHCH3), 26.2, 27.2 [2 q, C(CH3)2], 40.3 (d, C-2), 51.7 (q, OCH3), 55.7 (d, NCHCH3), 59.0 (d, C-3), 66.8 (t, C-6), 74.0 (t, OCH2Ph), 79.5 (d, C-5), 81.3 (d, C-4), 109.7 [s, C(CH3)2], 127.5, 127.8, 128.5, 128.7 (4 d, 2 C(CH3), 139.1 [s, OCH2Ph(2-C)], 146.4 [s, NCH(CH3)Ph(3-C)], 175.9 (s, C-1).


(2R,3R,4S,1R)-3-Amino-4-O-benzyl-4,6-dihydroxy-3-[(1-phényl)ethyl]pentanedioate (26)

H2O (159.6 mg, 0.70 mmol) was added to a solution of the acetaldehyde 21 (123 mg, 0.28 mmol) in EtOH (6.0 mL) and the reaction mixture was stirred under N2 for 6 h. A solution of Na2S2O3 (2 ml, 1.5 mmol) was added; the mixture was extracted with EtOAc (3 × 15 mL)
The aldehyde was dissolved in t-BuOH (4.0 mL) and 2-methyl-2-butenone (1.5 mL), then NaClO3 (38 mg, 0.42 mmol) and NaH2PO4 (50.4 mg, 0.42 mmol) were added. After stirring for 90 min, the same amounts of NaClO3 and NaH2PO4 were added again. After 1 h, NaOH solution (4 M, 2.0 mL) was added and the solvent was removed under reduced pressure (40 °C, 60 mbar). The residue, a colourless powder, was dissolved in H2O (4.0 mL), then the pH was adjusted to 3–4 by dropwise addition of 6 M HCl. The mixture was extracted with EtOAc (5 × 30 mL) and dried (MgSO4). The solvent was removed to give 80 mg (72%) of the diester 26 as a spectroscopically pure, colourless oil.

Without purification, this acid 25 was treated with a solution of ethereal CH2N2 (excess). After stirring for 10 min, the solvent was evaporated and the light-yellow oil was purified by flash column chromatography (silica gel, 8 g; 2 cm × 5 cm; PE–EtOAc, 4:1) to give 80 mg (72%) of the diester 26 as a spectroscopically pure, colourless oil; [αi]D20 –8.7 (c 1.02, CHCl3).

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References


