Development of an Amino Acid/Hydroxy Oxime Dual Catalyst System for Highly Stereoselective Direct Asymmetric Aldol Reactions in the Presence of Water

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Dedicated to Prof. Dieter Enders on the occasion of his 70th birthday

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Abstract
An eco-friendly dual catalyst system for stereoselective aldol reactions in the presence of water is described. It is based on the cooperative action of acyclic amino acids and H-bond donating hydroxy oxime catalysts. The synthetic utility of this dual catalyst system was further demonstrated by applying it as the key step in the expeditious and highly stereoselective total synthesis of D-lyxo-phytosphingosine (29\% overall yield). Here the amino acid/hydroxy oxime system significantly accelerated the direct aldol reactions in the presence of water as compared to organic solvents. The stereo- and chemoselectivity were also significantly increased.

Key words
aldol reaction, total synthesis, phytosphingosine, stereoselectivity, dual catalysis

The direct asymmetric aldol reaction is one of the most powerful transformations for achieving stereoselective C–C bond-formation both in nature and synthetic chemistry.\textsuperscript{1} In biosynthesis, Type I and Type II aldolase enzymes perform this transformation with excellent chemo-, regio-, and enantioselectivity. Type I aldolases use the primary amine functionality of a lysine residue in their active site for the covalent activation of a carbonyl donor. Type II aldolases employ a metal co-factor (Zn) for Lewis acid activation of a carbonyl donor.\textsuperscript{2} Inspired by the high selectivity of these enzymes, chemists started to design small organometallic and organic molecule catalysts for the direct asymmetric aldol reaction. The development of catalytic methods for the enantioselective aldol reaction is a highly fruitful research area.\textsuperscript{3} In particular, the employment of organocatalysis has progressed at an astonishing pace.\textsuperscript{3a,b,k} In this regard, the proline-catalyzed enantioselective aldol reaction was first disclosed by Hajos and Parrish in the beginning of the 1970s.\textsuperscript{4a} This powerful protocol was applied frequently for total synthesis of steroids and used by the pharmaceutical industry. In 2000, List, Barbas and Lerner disclosed that proline also catalyzed the direct intermolecular asymmetric aldol reaction.\textsuperscript{4d} These works ignited a spark in the field of asymmetric catalysis and a range of proline derivatives and cyclic-five membered small organic amine molecules were investigated as catalysts for the asymmetric aldol reaction.\textsuperscript{3} We later demonstrated that acyclic amino acids and small non-proline derived peptides could also catalyze the intermolecular asymmetric aldol reaction with high enantioselectivity in organic solvents.\textsuperscript{5} Here, the presence of water accelerated these amino acid and peptide catalyzed C–C bond-forming reactions. Several groups disclosed the use of a hydrogen bond donor to improve the stereoselectivity of the catalytic aldol reaction.\textsuperscript{6} Proline-catalyzed aldol reactions are known to be anti-selective. However, the use of acyclic amino acids can switch the diastereoselectivity of this reaction to be syn-selective when acyclic donors are used.\textsuperscript{7} On this subject, the group of Lu reported that O-protected threonine derivatives were able to catalyze highly syn- and enantioselective aldol reactions of protected hydroxycetone.\textsuperscript{7a} Barbas and coworkers also reported that O-Bu protected threonine was a highly syn-selective organocatalyst for the direct asymmetric aldol reaction.\textsuperscript{7b} In 2011, Li et al. reported a large-scale asymmetric direct aldol reaction in water using threonine derivatives as recoverable organocatalysts.\textsuperscript{7c} Nowadays, the employment of supramolecular interactions such as H-bonding is a powerful activation mode in asymmetric catalysis using small molecule catalysts.\textsuperscript{8} The groups of Demir, Rios, and Moyano independently demonstrated that proline in combination with thiourea derivatives such as Schreiner’s thiourea 6b can co-catalyze highly stereoselective aldol reactions.\textsuperscript{8} We found that the
hydroxy oxime 6a can participate as a H-bond donating co-catalyst in chiral amine-catalyzed dynamic one-pot three-component enantioselective [2+3] cycloaddition reactions.10 Recently, our group reported a highly efficient asymmetric aldol reaction using a hydrogen bonding donor as a co-catalyst along with acyclic amino acid derivatives in organic solvents.11 However, the use of water is a highly attractive alternative for developing sustainable synthetic chemical process and is considered a 'green' solvent. Water can also accelerate chemical reactions involving hydrophobic substrates12 as well as improve the stereoselectivity of amino acid and peptide-catalyzed direct aldol reactions.5c,13,14

Phytosphingosines are one of the principal structural backbones of sphingolipids typically possessing a 2-amino-1,3-diol functionality, which are among the major membrane constituents and play a significant role in cell regulation as well as signal transduction.15 In 1911, the phytosphingosine was first isolated from mushrooms16a and then the structure was elucidated by the groups of Oda16b and Carter.16c Now, studies have revealed that the phytosphingosines are widely distributed in the plants,17a marine organisms,17b fungi,17b yeasts, even mammalian tissues of kidney,17d brain, liver,17e uterus,17f intestine,17g skin, and in blood plasma.17h In addition to being base components of sphingolipids in membranes, phytosphingosines themselves are found to be bioactive lipids.17i For example, ribophytosphingosine is a potential heat stress signal in yeast cells, and some of its derivatives, α- and β-galactosyl and glucosylphytoceramids are highly potent against tumors (Figure 1).17j

The four naturally occurring stereoisomers of phytosphingosine are depicted in Figure 2.18–20 Due to its promising biological findings, there has been considerable importance in the synthesis of 1 and its stereoisomers. Therefore, the construction of the three contiguous stereogenic centers has become an interesting and synthetic challenge. So far, a broad spectrum of different approaches has been described for the synthesis of the target phytosphingosine 1 and its stereoisomers, but most of the methods require multistep reactions, expensive starting materials, and extensive manipulation of protecting group.18–20 Moreover, these strategies sometimes suffer from low stereo- and regioselectivity. Therefore, practical, concise, expeditious, stereoselective, and high yield synthesis of the target stereoisomers are still desirable.

The approach of using protected dihydroxyacetone in stereoselective aldol reactions was pioneered by the research group of Enders.21,22 Recently, Enders and coworkers demonstrated an elegant approach for the synthesis of arabino- and ribo-phytosphingosine stereoisomers based on the proline-catalyzed anti-selective aldol reaction.23 Furthermore, the group of Jørgensen also disclosed an elegant catalytic one-pot approach to the synthesis of these compounds.24 However, to the best of our knowledge the total synthesis of the lyxo-phytosphingosine stereoisomer by a dual catalysis has not been disclosed.25 The retrosynthetic plan, depicted in Scheme 1, involves the construction of C3–C4 bond of lyxo-phytosphingosine by a co-catalytic stereo-selective syn-selective aldol reaction. Next, a highly diastereoselective reductive amination followed by deprotection will provide the desired d-lyxo phytosphingosine (1).

Herein we disclose the development of the amino acid/hydroxy oxime dual catalyst system for stereoselective and asymmetric aldol reactions in the presence of water. The development and short total synthesis of d-lyxo-phytosphingosine (1) is also described.
Catalyst Screening for Aldol Reaction

The direct co-catalytic intermolecular aldol reaction of cyclohexanone (2) and p-nitrobenzaldehyde (3) was carried out in the presence of different chiral primary amino acid catalysts 5 and hydrogen-bond donating catalysts 6 in the presence of water (Table 1). Key results are summarized in Table 1. We found that the hydrophobic amino acids 5c, 5d, 5e, 5f, 5g, and 5h were able to catalyze the reaction in water. The highest stereoselectivity was observed when the protected threonine derivatives 5g and 5h were used as the amino acid catalyst, respectively. It is important to note that significant rate acceleration was observed when the reactions were performed in the presence of hydrogen-bond donating catalyst 6a and 6d, respectively. For example, the employment of 5g gave corresponding aldol product 4 in 93% yield with 18:1 dr and 98% ee after 4 hours (Table 1, entry 9). Adding 6a as the co-catalyst gave 4 in 92% yield with 19:1 dr (anti/syn) and 98% ee after 2 hours (entry 11). Furthermore, catalyst loadings could be decreased to 2 mol%, which increased the stereoselectivity of the transformation (entries 20–22). Moreover, a dramatic increase in the reaction rate was observed when a dual catalyst system comprising of co-catalyst 6a or 6d was employed for the direct asymmetric aldol reaction. Here, the use of 6d as the co-catalyst decreased the enantioselectivity as compared to the employment of 6a (entries 14, 19, and 21). Out of the investigated co-catalytic systems, catalyst 5g or 5h in combination with H-donating hydroxyl oxime 6a exhibited the best performance with respect to efficiency, diastereoselectivity and enantioselectivity for the stereoselective aldol reaction in the presence of water. To demonstrate the synthetic utility of this aqueous amino acid/hydroxyl oxime system we decided to apply it to the total synthesis of d-lyxo-phytosphingosine (1) (Scheme 1).

Synthesis of d-lyxo-Phytosphingosine

Our novel synthetic approach to the targeted d-lyxo-phytosphingosine (1) commences with a direct co-catalytic syn-selective aldol reaction of the readily available TBS-protected dihydroxyacetone 8 as the donor and pentadecan-1-ol 7 as the acceptor using the catalysts 5g combined with hydroxyl oxime 6a in the presence of water (Table 2). The direct aldol reaction proceeded with high diastereoselectivity and syn-aldol product 9 was formed with 19:1 dr (syn/anti, 55% yield, Table 2, entry 1). Based on our previous research on co-catalytic direct aldol reaction,11 we also attempted the combination of catalyst 5g with hydrogen bond donor 6b in toluene. However, satisfactory result was not observed as both the reaction rate and diastereoselectivity were decreased. Here aldol product 9 was isolated in 43% yield with 12:1 dr after 48 hours (entry 2). Performing the

Table 1 Catalyst Screening for the aldol reaction between 2 and 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>5 (mol%)</th>
<th>6 (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>dr (anti/syn)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a (20)</td>
<td>–</td>
<td>144</td>
<td>20</td>
<td>0.85:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>5b (20)</td>
<td>–</td>
<td>72</td>
<td>–</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>5c (20)</td>
<td>–</td>
<td>120</td>
<td>53</td>
<td>2:1</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>5d (20)</td>
<td>–</td>
<td>120</td>
<td>93</td>
<td>4:1</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>5e (20)</td>
<td>–</td>
<td>22</td>
<td>95</td>
<td>7:1</td>
<td>82</td>
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<tr>
<td>6</td>
<td>5e (20)</td>
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<td>22</td>
<td>92</td>
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<td>80</td>
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<tr>
<td>7</td>
<td>5f (20)</td>
<td>–</td>
<td>3</td>
<td>85</td>
<td>14:1</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>5f (20)</td>
<td>6b (20)</td>
<td>5</td>
<td>82</td>
<td>9:1</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>5g (20)</td>
<td>–</td>
<td>4</td>
<td>93</td>
<td>18:1</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>5g (20)</td>
<td>–</td>
<td>4</td>
<td>85</td>
<td>12:1</td>
<td>98</td>
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<tr>
<td>11</td>
<td>5g (20)</td>
<td>6a (20)</td>
<td>2</td>
<td>92</td>
<td>19:1</td>
<td>98</td>
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<tr>
<td>12</td>
<td>5g (20)</td>
<td>6b (20)</td>
<td>5</td>
<td>83</td>
<td>17:1</td>
<td>98</td>
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<tr>
<td>13</td>
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<td>6c (20)</td>
<td>6</td>
<td>90</td>
<td>15:1</td>
<td>98</td>
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<tr>
<td>14</td>
<td>5g (20)</td>
<td>6d (20)</td>
<td>2</td>
<td>90</td>
<td>18:1</td>
<td>90</td>
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<tr>
<td>15</td>
<td>5h (20)</td>
<td>–</td>
<td>144</td>
<td>53</td>
<td>3:1</td>
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<td>16</td>
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<td>6a (20)</td>
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<td>17</td>
<td>5g (10)</td>
<td>–</td>
<td>8</td>
<td>92</td>
<td>19:1</td>
<td>99</td>
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<tr>
<td>18</td>
<td>5g (5)</td>
<td>–</td>
<td>24</td>
<td>85</td>
<td>20:1</td>
<td>98</td>
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<tr>
<td>20</td>
<td>5h (2)</td>
<td>–</td>
<td>120</td>
<td>90</td>
<td>21:1</td>
<td>98</td>
</tr>
<tr>
<td>21</td>
<td>5h (2)</td>
<td>6d (2)</td>
<td>20</td>
<td>90</td>
<td>13:1</td>
<td>90</td>
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<tr>
<td>22</td>
<td>5h (2)</td>
<td>6a (2)</td>
<td>12</td>
<td>92</td>
<td>19:1</td>
<td>99</td>
</tr>
</tbody>
</table>

* Reaction conditions: 5 (0.025 mmol), 6 (0.025 mmol), 2 (0.125 mmol), 3 (1.25 mmol) in H2O (0.128 mL).
* Yield of isolated 4 after column chromatography on silica gel.
* Determined by H NMR analysis of the crude reaction mixture; n.d.: not determined.
* Determined by chiral HPLC analysis; n.d.: not determined.
* Neat reaction.
reaction in the presence of water without the addition of co-catalyst 6a slightly decreased the reaction rate without significantly affecting the stereoselectivity of the transformation.

Thus, the presence of water had a remarkable beneficial effect on the reaction rate and stereoselectivity. In addition, the chemoselectivity was improved since less self-aldol condensation product 13 was formed. The lower yield of 9 in toluene may also be contributed by the fact that the linear aldehydes undergo self-aldol condensation, which has indirect competition with the cross-aldol reaction, at higher level in this solvent. Having the syn-aldol 9 in hand, we next investigated the diastereoselective reductive amination route to obtain the target compound 1 (Scheme 2). In this respect, Enders and coworkers have previously shown in their arabinino-phytosphingosine synthesis that it is important to protect the hydroxyl group of an acetal-protected aldol product with anti-configuration in order to obtain a high diastereoselectivity during the reductive amination step.23 Thus, protection by treatment with TBSOTf in the presence of 2,6-lutidine in dichloromethane at –15 °C gave the corresponding TBS-ether 10 in 90% yield. Then the synthesis of the corresponding amine 11 was carried out by diastereoselective reductive amination with sodium cyanoborohydride as the reducing agent and benzylamine as the amino donor together with acetic acid in dichloromethane at –15 °C. We found that the direct reductive amination of 10 gave the protected amine 11 in 90% yield with excellent dr (anti/syn 26:1, determined from 1H NMR spectroscopy). Thus, the nucleophilic addition of the hydride to the Re-face of the in situ generated N-benzyl-protected imine leading to the anti-configuration at C2–C3 is more favored by installing a bulky group at the hydroxyl functionality of 9. Next, sequential deprotection of 11b gave D-lyxo-phytosphinganine (1) in 25% overall yield ([α]D20 = –9.5 (c = 0.96, pyridine)) (Lit.18a [α]D20 = –6.4 (c = 1.0, pyridine)).

The formation of the highly anti-aldol product 4 and syn-aldol product 9 is in accordance with the literature of acyclic amino acid catalyzed transformations and can be explained by transition states I and II, which involves cyclic and acyclic donors, respectively (Scheme 3).5,7a–f,11,26 In TS I,26 the nucleophilic enamine has an anti-configuration whereas in TS II2–11 it has a syn-configuration providing the corresponding aldol products with anti- and syn-configuration, respectively. Installing a bulky protective group on the alcohol moiety of threonine significantly improved the stereoselectivity by efficient shielding of the Re-phase of the chiral enamine. The H-bond donating hydroxy oxime co-catalyst is proposed to accelerate the enamine formation by enhancing the rate of condensation between the ketone donor and the amino acid catalyst. This is also the case for thiourea 6b and p-nitrophenol 6d.27 However, when using 6d as an additive the enantioslectivity was decreased.

**Table 2 Primary Amino Acid Co-Catalyzed Stereoselective syn-aldol Reaction between 7 and 8 Delivering the Aldol Product 9**

<table>
<thead>
<tr>
<th>Entry</th>
<th>5 (mol%)</th>
<th>6 (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>dr (anti/syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5g (10)</td>
<td>6a (10)</td>
<td>H2O</td>
<td>24</td>
<td>55c</td>
<td>19:1</td>
</tr>
<tr>
<td>2</td>
<td>5g (10)</td>
<td>6b (10)</td>
<td>toluene</td>
<td>48</td>
<td>43d</td>
<td>12:1</td>
</tr>
</tbody>
</table>

a Yield of isolated 9 after column chromatography (SiO2, PE/EtOAc).

b The dr was determined by 1H NMR analysis of the crude reaction mixture.

c Self aldol condensation product 13 was isolated in 10% yield.

d Self aldol condensation product 13 was isolated in 22% yield.

**Scheme 2 Reagents and conditions: a) O-(TBS)-l-threonine (5g), hydroxy oxime 6a, H2O, r.t., 24 h; b) TBSOTf, 2,6-lutidine, CH2Cl2, –15 °C to r.t.; c) BnNH2, AcOH, MS 4Å, NaBH4CN, CH2Cl2, –15 °C to r.t., 24 h; d) Pd/C, H2 (1 atm), MeOH, r.t., 24 h; e) TBAF, THF, r.t., 24 h.**
In summary, we have successfully developed an efficient and eco-friendly amino acid/hydroxy oxime catalyst system for highly chemoselective and stereoselective direct aldol reaction in water. The cooperation of the H-bonding hydroxy oxime co-catalyst has a dramatic effect on the reaction rate of the amino acid-catalyzed direct asymmetric aldol reaction. Moreover, the reaction was significantly accelerated in water as compared to the use of organic solvent. For example, when a protected dihydroxy-acetone derivative was reacted with a linear aldehyde using water as the solvent system, the cross-aldol reaction was completed within 24 hours in H₂O as compared to 48 hours in toluene. The synthetic utility of the amino acid/hydroxy oxime catalyst system in water was also demonstrated by the to date shortest total synthesis of D-lyxo-phosphoglucone (1) (29% overall yield). Further investigation and applications of combined amino acid derivative and hydroxy oxime H-bond donating catalysts for asymmetric synthesis are ongoing and will be reported in due course.

IR spectra were recorded on a Termo Fisher Nicolet 6700 FT-IR spectrometer in cm⁻¹. Melting Points were measured on a Stuart SMP, Melting Point Apparatus and are uncorrected. ¹H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from TMS with the solvent resonance resulting from incomplete deuteration incorporation as the internal standard (CDCl₃: δ = 7.26). Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant (Hz), and integration. ¹³C NMR spectra were recorded on a Bruker Avance 500 (125.8 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from TMS with the solvent resonance as the internal standard (CDCl₃: δ = 77.16). High-resolution mass spectrometry was performed on an Agilent 6520 Accurate-Mass Q-TOF LC/MS (positive mode). Optical rotations were measured on a PerkinElmer 341 Polariometer (n = 546 nm, Hg lamp, 1 dm cell). The enantiomeric excess was determined by Agilent 1260 infinity series HPLC (Chiral Technologies Chiralpak AS-H column (4.6 mm × 250 mm)) in comparison with authentic racemic materials. All the reactions were carried out under an atmosphere of air in a closed system. Chemicals and solvents were either purchased puriss p. a. from commercial suppliers or were purified by standard techniques. Aluminum sheet silica gel plates (Fluka 60 F254) were used for TLC, and the compounds were visualized by irradiation with UV light (254 nm) or by treatment with a solution of phosphomolybdic acid (25 g, Ce(SO₄)₂·H₂O (10 g), concd H₂SO₄ (60 mL), and H₂O (940 mL), followed by heating. Purification of the product was carried out by flash column chromatography using silica gel (Fluka 60, particle size 0.040–0.063 mm).

Asymmetric Aldol Reaction for Screening; (2S)-2-{[(R)-Hydroxy-(4-nitrophenyl)methyl]cylohexanone (4):¹⁰ Typical Procedure
To a mixture of catalyst O-(tert-butyl dimethylsilyloxy)-l-threonine (5g; 5.83 mg, 0.025 mmol, 20 mol%, 0.2 equiv), methyl (Z)-2-cyano-2-(hydroxyiminio)acetate (6a; 3.2 mg, 0.025 mmol, 20 mol%, 0.2 equiv), and cyclohexanone (2; 0.128 mL, 1.25 mmol, 10 equiv) were added 4-nitrobenzaldehyde (3; 18.87 mg, 0.125 mmol, 1 equiv) and H₂O (0.128 mL). The mixture was vigorously stirred at r.t. until completion of the reaction (monitored by NMR analysis). Diastereoselectivity and conversion were determined from the ¹H NMR analysis of the crude. The product was purified by silica gel column chromatography (PE/EtOAc, 2:1) to give the pure aldol product 4 as a colorless oil (28.5 mg, 92%). The enantiomeric excess was determined by chiral-phase HPLC analysis.

¹H NMR (500 MHz, CDCl₃): δ = 8.21 (m, 2 H), 7.50 (m, 2 H), 4.89 (dd, J = 8.4, 3.1 Hz, 1 H), 4.07 (d, J = 3.1 Hz, 1 H), 2.59 (m, 1 H), 2.47 (m, 1 H), 2.37 (m, 1 H), 2.12 (m, 1 H), 1.83 (m, 1 H), 1.67 (m, 1 H), 1.56 (m, 2 H), 1.38 (m, 1 H).

¹³C NMR (125.8 MHz, CDCl₃): δ = 214.7, 148.5, 147.5, 127.9, 123.5, 73.9, 57.2, 42.7, 30.8, 27.7, 24.7.

[x]D₂⁰ = +12.6 (c = 1.00, CHCl₃) for an enantiomer enriched sample (98% ee). From HPLC analysis enantiomeric purity was determined in comparison with authentic racemic material (AS column, 90:10 hexanes/i-PrOH, 1.0 mL/min, 254 nm): tᵣ (major enantiomer) = 46.34 min, tᵣ (minor enantiomer) = 56.53 min.

(3R,4S)-1,3-Bis[[(tert-butyl(dimethyl)silyloxy)]-4-hydroxyoctadecan-2-one (9)
To a mixture of O-(tert-butyl dimethylsilyloxy)-l-threonine (5g; 11 mg, 0.044 mmol, 10 mol%), (Z)-methyl 2-cyano-2-(hydroxyiminio)acetate (6a; 5.63 mg, 0.044 mmol, 10 mol%) and TBS protected 1,3-dihydroxypropan-2-one (8; 280 mg, 0.88 mmol, 2.0 equiv) were added pentacontane (7; 100 mg, 0.44 mmol, 1.0 equiv) and H₂O (8 µl, 0.044 mmol). The mixture was stirred at r.t. for 24 h. Reaction progress was monitored by NMR analysis of the crude. After completion of the reaction, the product was directly purified by flash column chromatography (PE/EtOAc, 15:1 to 10:1) to afford the pure compound 9 (132 mg, 55%) as a colorless oil; dr (syn/anti) = 19:1; [α]D₂⁰ = +3.1 (c = 1.0, CHCl₃); Rₛ = 0.41 (PE/EtOAc, 10:1).

IR (neat): 2924 (s), 2853 (s), 1734 (C=O), 1463 (m), 1388 (w), 1361 (w), 1252 (m), 1096 (m), 1005 (w), 938 (w), 834 (s), 776 (s), 733 (w), 674 cm⁻¹ (w).

¹H NMR (500 MHz, CDCl₃): δ = 4.50 (d, J = 18.4 Hz, 1 H), 4.45 (d, J = 18.4 Hz, 1 H), 4.30 (d, J = 2.8 Hz, 1 H), 3.77 (m, 1 H), 2.16 (d, J = 9.8 Hz, 1 H), 1.47 (m, 2 H), 1.35–1.20 (m, 24 H), 0.94 (s, 9 H), 0.90 (s, 9 H), 0.86 (t, J = 7.0 Hz, 3 H), 0.09 (s, 9 H), 0.06 (s, 3 H).

¹³C NMR (125.8 MHz, CDCl₃): δ = 210.5, 79.2, 73.2, 68.6, 34.1, 32.1, 29.85, 29.84, 29.82, 29.79, 29.71, 29.6, 29.5, 26.0, 25.96, 25.89, 22.85, 18.6, 18.3, 14.2, –4.6, –4.9, –5.2, –5.3.

HRMS (ESI+): m/z [M + H]⁺ calcd for C₃₀H₆₅O₇Si₂: 545.4416; found: 545.4420.
The ee of 9 could not be determined either by chiral-phase HPLC analysis or using chiral shift reagents and NMR analysis.

(3R,4S)-1,3,4-Tris[tert-butyl(dimethyl)silyloxy]octadecan-2-one (10)

To a solution of 9 (108 mg, 0.20 mmol) and 2,6-lutidine (93 μL, 0.80 mmol) in CH₂Cl₂ (1 mL) was added dropwise TBSOTf (68 μL, 0.33 mmol) at −15 °C. After 4 h, sat. aq NaHCO₃ (1 mL) was added, extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic layers were dried (Na₂SO₄). The crude product was purified by column chromatography on silica gel (PE/EtOAc, 23:1 to 15:1) to afford 10 (118 mg, 90%) as a colorless oil; [α]D²⁰ −2.8 (c = 0.59, CHCl₃); Rf = 0.43 (PE/EtOAc, 15:1).

IR (neat): 3346 (br s), 2922 (s), 2852 (m), 2360 (m), 2341 (w), 1733 (s). 1H NMR (500 MHz, CDCl₃): δ = 4.61 (d, J = 18.9 Hz, 1 H), 4.46 (d, J = 18.9 Hz, 1 H), 4.17 (d, J = 3.3 Hz, 1 H), 3.80 (m, 1 H), 1.67 (m, 1 H), 1.43–1.19 (m, 25 H), 0.95 (s, 3 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.89 (t, J = 6.7 Hz, 3 H), 0.15 (s, 3 H), 0.09 (m, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H). 13C NMR (125.8 MHz, CDCl₃): δ = 74.4, 72.0, 64.2, 56.7, 34.6, 32.1, 30.2, 30.1, 30.0, 29.9, 29.6, 26.7, 22.9, 14.3. HRMS (ESI+): m/z [M + H]+ calcd for C₃₀H₅₀NO₃Si: 569.5281; found: 569.5283.

(2S,3S,5S)-N-Benzyl-1,3,4-{tris[tert-butyl(dimethyl)silyloxy]}octadecan-2-amine (11)

To a solution of 10 (105 mg, 0.16 mmol) in CH₂Cl₂ placed in a vial were added benzylamine (35 μL, 0.32 mmol) and AcOH (17 μL, 0.30 mmol), and MS 4Å (240 mg). After stirring the resulting mixture at r.t. for 1 h, the vial was merged in an ice-acetone bath (−15 °C) and the reaction mixture was treated with NaBH₃CN (26 mg, 0.40 mmol). The mixture was partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na₂SO₄), filtered, and evaporated. The residue was purified by flash chromatography on silica gel (CHCl₃/MeOH/NH₄OH, 40:10:1) to afford the pure α-lyxo-phytosphinogine (1) as a white solid (37 mg, 68%); mp 106–107 °C (Lit. 18a mp 104–105 °C; Lit. 18b mp 103–104 °C): [α]D²⁰ −9.5 (c = 0.69, pyridine); Rf = 0.17 (CHCl₃/MeOH/NH₄OH, 30:10:1).

IR (neat): 3346 (br s), 2922 (s), 2852 (m), 2360 (m), 2341 (w), 1733 (s), 1586 (w), 1464 (m), 1102 cm⁻¹ (s).

1H NMR (500 MHz, CDCl₃): δ = 4.43 (m, 2 H), 4.24 (m, 1 H), 4.10 (m, 1 H), 3.73 (m, 1 H), 2.02 (m, 1 H), 1.88 (m, 1 H), 1.72 (m, 1 H), 1.56 (m, 1 H), 1.45–1.15 (m, 22 H), 0.85 (t, J = 6.3 Hz, 3 H).

13C NMR (125.8 MHz, CDCl₃): δ = 74.4, 72.0, 64.2, 56.7, 34.6, 32.1, 30.2, 30.1, 30.0, 29.9, 29.6, 26.7, 22.9, 14.3. HRMS (ESI+): m/z [M + H]+ calcd for C₃₄H₅₀NO₃Si: 581.3303; found: 581.3305.

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Supporting Information

Supporting information for this article is available at http://dx.doi.org/10.1055/s-0036-1588089.

References


(13) For reviews discussing factors required to make a reaction in water environmentally benign, see: (a) Chanda, A.; Fokin, V. V. Chem. Rev. 2009, 109, 725. (b) Blackmond, D. G.; Armstrong, A.; Coombes, V.; Wells, A. Angew. Chem. Int. Ed. 2007, 46, 3798.


