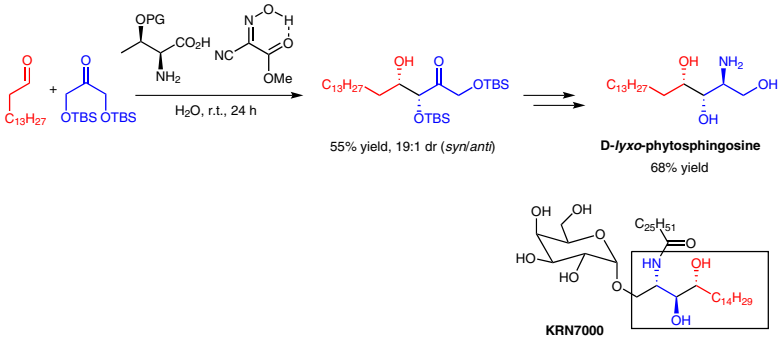
Synthesis M. Mridha et al. Paper

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

**Moniruzzaman Mridha**[a,b]
**Guangning Ma**[a]
**Carlos Palo-Nieto**[a]
**Samson Afewerki**[a,c]
**Armando Cordova***[a,c]

[a] Department of Natural Sciences, Holmgatan 10, Mid Sweden University, 851 70 Sundsvall, Sweden
[b] Department of Chemistry – BMC, Uppsala University, 751 23 Uppsala, Sweden
[c] Berzelii Center EXSELENT, The Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden
armando.cordova@miun.se
acordova@organ.su.se

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




Received: 30.08.2016
Accepted after revision: 11.10.2016
Published online: 04.11.2016
DOI: 10.1055/s-0036-1588089; Art ID: ss-2015-z0592_op

**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.[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.[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.[3] In particular, the employment of organocatalysis has progressed at an astonishing pace.[3a,b,4] In this regard, the proline-catalyzed enantioselective aldol reaction was first disclosed by Hajos and Parrish in the beginning of the 1970s.[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.[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.[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.[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.[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.[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 hydroxyacetone.[7a] Barbas and coworkers also reported that O-*t*Bu protected threonine was a highly *syn*-selective organocatalyst for the direct asymmetric aldol reaction.[7i] In 2011, Li et al. reported a large-scale asymmetric direct aldol reaction in water using threonine derivatives as recoverable organocatalysts.[7f] Nowadays, the employment of supramolecular interactions such as H-bonding is a powerful activation mode in asymmetric catalysis using small molecule catalysts.[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.[9] 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 substrates[12] 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 mushrooms[16a] and then the structure was elucidated by the groups of Oda[16b] and Carter.[16c] Now, studies have revealed that the phytosphingosines are widely distributed in the plants,[17a] marine organisms,[17b,c] 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, *ribo*-phytosphingosine 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]

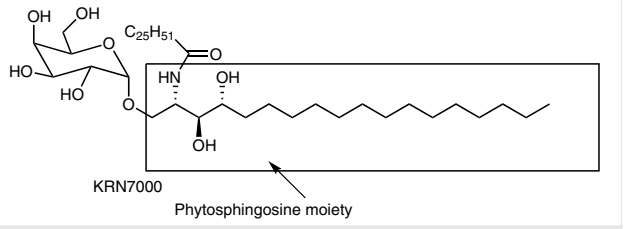



**Figure 1** α-Galactosylphytoceramide KRN7000

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.

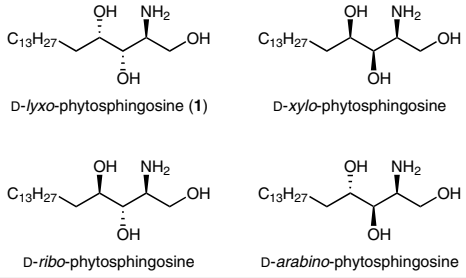
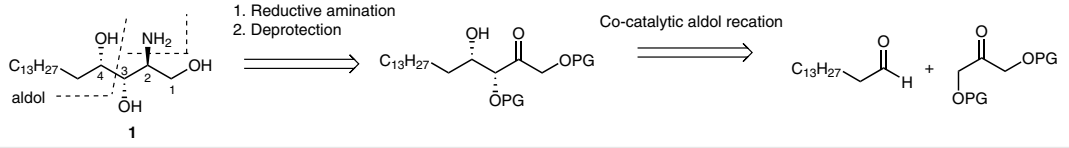



**Figure 2** D-*lyxo*-Phytosphingosine and its stereoisomers

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 stereosisomers 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 $C_3$–$C_4$ bond of *lyxo*-phytosphingosine by a co-catalytic stereoselective *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.




**Scheme 1** Retrosynthesis of D-*lyxo*-[2*S*,3*S*,4*S*]-phytosphingosine (**1**); PG = protective group

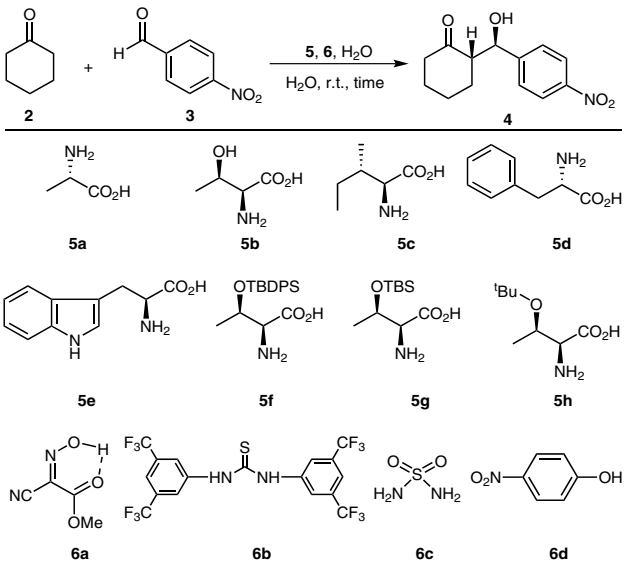
## Catalyst Screening for Aldol Reaction

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 hydroxy oxime **6a** exhibited the best performance with respect to efficiency, diastereo- 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 pentadecanal **7** as the acceptor using the catalysts **5g** combined with hydroxy 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

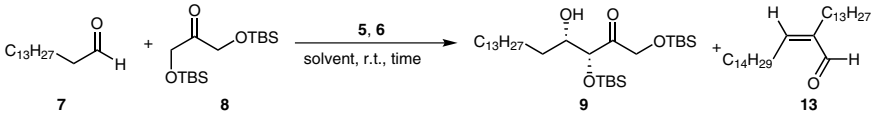
**Table 1** Catalyst Screening for the Aldol Reaction between **2** and **3**[a]




| Entry | **5** (mol%) | **6** (mol%) | Time (h) | Yield (%)[b] | dr (*anti*/*syn*)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | **5a** (20) | – | 144 | 20 | 0.85:1 | n.d. |
| 2 | **5b** (20) | – | 72 | – | n.d. | n.d. |
| 3 | **5c** (20) | – | 120 | 53 | 2:1 | 70 |
| 4 | **5d** (20) | – | 120 | 93 | 4:1 | 68 |
| 5 | **5e** (20) | – | 22 | 95 | 7:1 | 82 |
| 6 | **5e** (20) | **6a** (20) | 22 | 92 | 5:1 | 80 |
| 7 | **5f** (20) | – | 3 | 85 | 14:1 | 78 |
| 8 | **5f** (20) | **6b** (20) | 5 | 82 | 9:1 | 74 |
| 9 | **5g** (20) | – | 4 | 93 | 18:1 | 98 |
| 10[e] | **5g** (20) | – | 4 | 85 | 12:1 | 98 |
| 11 | **5g** (20) | **6a** (20) | 2 | 92 | 19:1 | 98 |
| 12 | **5g** (20) | **6b** (20) | 5 | 83 | 17:1 | 98 |
| 13 | **5g** (20) | **6c** (20) | 6 | 90 | 15:1 | 98 |
| 14 | **5g** (20) | **6d** (20) | 2 | 90 | 18:1 | 90 |
| 15 | **5h** (20) | – | 144 | 53 | 3:1 | 71 |
| 16 | **5h** (20) | **6a** (20) | 20 | 96 | 17:1 | 96 |
| 17 | **5g** (10) | – | 8 | 92 | 19:1 | 99 |
| 18 | **5g** (5) | – | 24 | 85 | 20:1 | 98 |
| 19 | **5g** (5) | **6d** (5) | 24 | 90 | 19:1 | 90 |
| 20 | **5h** (2) | – | 120 | 90 | 21:1 | 98 |
| 21 | **5h** (2) | **6d** (2) | 20 | 90 | 13:1 | 90 |
| 22 | **5h** (2) | **6a** (2) | 12 | 92 | 19:1 | 99 |

[a] Reaction conditions: **5** (0.025 mmol), **6** (0.025 mmol), **2** (0.125 mmol), **3** (1.25 mmol) in $H_2O$ (0.128 mL).
[b] Yield of isolated **4** after column chromatography on silica gel.
[c] Determined by $^1H$ NMR analysis of the crude reaction mixture; n.d.: not determined.
[d] Determined by chiral HPLC analysis; n.d.: not determined.
[e] Neat reaction.

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




| Entry | **5** (mol%) | **6** (mol%) | Solvent | Time (h) | Yield (%)[a] | dr (*anti*/*syn*)[b] |
|---|---|---|---|---|---|---|
| 1 | **5g** (10) | **6a** (10) | $H_2O$ | 24 | 55[c] | 19:1 |
| 2 | **5g** (10) | **6b** (10) | toluene | 48 | 43[d] | 12:1 |

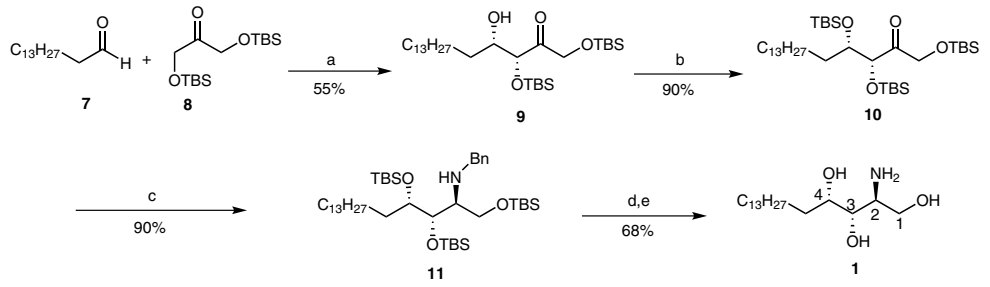
[a] Yield of isolated **9** after column chromatography ($SiO_2$, PE/EtOAc).
[b] The dr was determined by $^1H$ NMR analysis of the crude reaction mixture.
[c] Self aldol condensation product **13** was isolated in 19% yield.
[d] Self aldol condensation product **13** was isolated in 22% yield.

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.

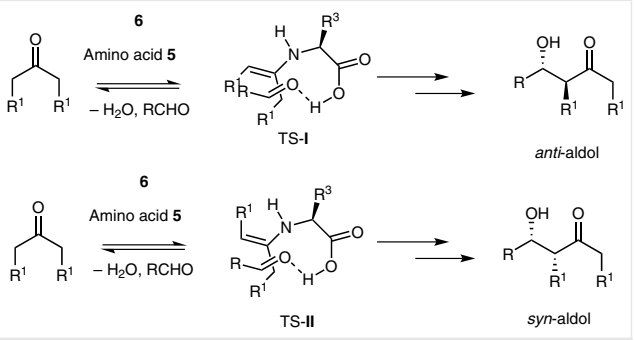
Thus, the presence of water had a remarkable beneficial effect on the reaction rate and stereoselectivity. In addition, the chemoselectivity was improved since less self-aldol condensation product **13** was formed. The lower yield of **9** in toluene may also be contributed by the fact that the linear 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 *arabino*-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 $C_2$–$C_3$ is more favored by installing a bulky group at the hydroxyl functionality of **9**. Next, sequential deprotection of **11b** gave D-*lyxo*-phytosphingonine (**1**) in 29% overall yield {$[\alpha]_D^{20}$ –9.5 (*c* = 0.96, pyridine) (Lit.[18a] $[\alpha]_D^{20}$ –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 II[7,11] 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 enantioselectivity was decreased.




**Scheme 2** *Reagents and conditions:* a) *O*-(TBS)-L-threonine (**5g**), hydroxy oxime **6a**, $H_2O$, r.t., 24 h; b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, –15 °C to r.t.; c) $BnNH_2$, AcOH, MS 4Å, $NaBH_3CN$, $CH_2Cl_2$, –15 °C to r.t., 24 h; d) Pd/C, $H_2$ (1 atm), MeOH, r.t., 24 h; e) TBAF, THF, r.t., 24 h.




**Scheme 3** Transition states for the acyclic amino acid catalyzed aldol reactions and enamine formation[26]

In summary, we have successfully developed an efficient and eco-friendly amino acid/hydroxy oxime catalyst system for highly chemo- and stereoselective direct aldol reaction in the presence of water. The cooperative action 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 dihydroxyacetone derivative was reacted with a linear aldehyde using this catalyst system the cross-aldol reaction was completed within 24 hours in $H_2O$ 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*-phytosphingosine (**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 Stuart $SMP_3$ 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 deuterium incorporation as the internal standard ($CDCl_3$: δ = 7.26). Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant (Hz), and integration. $^{13}C$ 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 ($CDCl_3$: 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 Polarimeter (D = 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), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), concd $H_2SO_4$ (60 mL), and $H_2O$ (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; (2*S*)-2-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]cyclohexanone (4);[10] Typical Procedure

To a mixture of catalyst *O*-(*tert*-butyldimethylsiloxy)-L-threonine (**5g**; 5.83 mg, 0.025 mmol, 20 mol%, 0.2 equiv), methyl (*Z*)-2-cyano-2-(hydroxyimino) 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 $H_2O$ (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, $CDCl_3$): 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).

$^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ = 214.7, 148.5, 147.5, 127.9, 123.5, 73.9, 57.2, 42.7, 30.8, 27.7, 24.7.

$[\alpha]_D^{20}$ +12.6 (*c* = 1.00, $CHCl_3$) for an enantiomeric 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); $t_R$ (major enantiomer) = 46.34 min, $t_R$ (minor enantiomer) = 56.53.

### (3*R*,4*S*)-1,3-Bis{[(*tert*-butyl(dimethyl)silyl]oxy}-4-hydroxyoctadecan-2-one (9)

To a mixture of *O*-(*tert*-butyldimethylsiloxy)-L-threonine (**5g**; 11 mg, 0.044 mmol, 10 mol%), (*Z*)-methyl 2-cyano-2-(hydroxyimino)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 pentadecanal (**7**; 100 mg, 0.44 mmol, 1.0 equiv) and $H_2O$ (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; $[\alpha]_D^{20}$ +3.1 (*c* = 1.0, $CHCl_3$); $R_f$ = 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, $CDCl_3$): 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).

$^{13}C$ NMR (125.8 MHz, $CDCl_3$): 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 $C_{30}H_{65}O_4Si_2$: 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.

**(3*R*,4*S*)-1,3,4-Tris{[*tert*-butyl(dimethyl)silyl]oxy}octadecan-2-one (10)**

To a solution of **9** (108 mg, 0.20 mmol) and 2,6-lutidine (93 µL, 0.80 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise TBSOTf (68 µL, 0.3 mmol) at –15 °C. After 4 h, sat. aq $NaHCO_3$ (1 mL) was added, extracted with $CH_2Cl_2$ (3 × 5 mL), and the combined organic layers were dried ($Na_2SO_4$). The crude product was purified by column chromatography on silica gel (PE/EtOAc, 25:1 to 15:1) to give **10** (118 mg, 90%) as a colorless oil; $[\alpha]_D^{20}$ –2.8 (*c* = 0.59, $CHCl_3$); $R_f$ = 0.43 (PE/EtOAc, 15:1).

IR (neat): 2925 (s), 2854 (s), 1736 (C=O), 1471 (m), 1462 (m), 1361 (w), 1252 (m), 1111 (m), 1004 (w), 938 (w), 833 (s), 773 (s), 673 $cm^{-1}$ (w).

$^1H$ NMR (500 MHz, $CDCl_3$): 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, 9 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).

$^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ = 208.7, 79.1, 75.0, 69.1, 34.3, 32.89, 32.09, 29.86, 29.84, 29.82, 29.80, 29.72, 29.71, 29.69, 29.5, 26.1, 26.04, 26.0, 25.90, 25.85, 22.8, 18.7, 18.3, 14.3, –4.2, –4.4, –4.5, –4.9, –5.0, –5.2.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{79}O_4Si_3$: 659.5281; found: 659.5283.

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

To a solution of **10** (105 mg, 0.16 mmol) in $CH_2Cl_2$ placed in a vial were added benzylamine (35 µL, 0.32 mmol), 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 $NaBH_3CN$ (26 mg, 0.40 mmol). The mixture was allowed to warm to r.t. and stirred for an additional 24 h. The reaction was monitored by NMR analysis of the crude. After completion of the reaction, the mixture was filtered through a short Celite pad. The reaction was quenched with sat. aq $NaHCO_3$ (1 mL) and extracted with $CH_2Cl_2$ (4 × 5 mL). The combined organic layers were dried ($Na_2SO_4$), evaporated, and the residue was purified by flash chromatography on silica gel (PE/EtOAc, 40:1 to 30:1) to afford **11** (108 mg, 90%) as a colorless oil; $[\alpha]_D^{20}$ –7.6 (*c* = 1.35, $CHCl_3$); $R_f$ = 0.22 (PE/EtOAc, 30:1).

IR (neat): 3346 (br s), 2952 (m), 2925 (s), 2853 (s), 1462 (m), 1388 (w), 1360 (w), 1250 (s), 1089 (s), 1005 (w), 937 (w), 831 (s), 811 (m), 773 (s), 730 (w), 696 (w), 669 $cm^{-1}$ (w).

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 2 H), 7.29 (m, 2 H), 7.20 (m, 1 H), 3.88 (d, *J* = 12.7 Hz, 1 H), 3.84 (m, 1 H), 3.73 (d, *J* = 12.6 Hz, 1 H), 3.69 (m, 1 H), 3.62 (m, 2 H), 2.81 (td, *J* = 13.2, 6.6, 2.2 Hz, 1 H), 1.61 (m, 1 H), 1.41 (m, 1 H), 1.35–1.20 (m, 25 H), 0.90 (s, 9 H), 0.88 (m, 12 H), 0.80 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H), 0.06 (m, 6 H), 0.05 (s, 3 H), 0.03 (s, 3 H).

$^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ = 141.4, 128.7, 128.3, 126.7, 76.3, 73.5, 64.5, 61.6, 53.4, 32.1, 31.5, 29.9, 29.86, 29.83, 29.76, 29.71, 29.5, 26.8, 26.2, 26.0, 25.9, 22.85, 18.5, 18.2, 18.0, 14.3, –3.7, –4.2, –4.4, –4.6, –4.9, –5.1.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{43}H_{88}NO_3Si_3$: 750.6067; found: 750.6070.

**(2*S*,3*S*,4*S*)-2-Aminooctadecane-1,3,4-triol [D-*lyxo*-Phytosphingosine (1)][18a]**

Under a $H_2$ atmosphere, **11** (134 mg, 0.178 mmol) and 5% Pd/C (20 mg) were stirred vigorously in MeOH (1 mL). After 12 h, the reaction mixture was filtered through a Celite pad and concentrated in vacuum to give a colorless oil (114 mg, 98%). This was dissolved in THF (2 mL) and added dropwise to a 1 M solution of TBAF (0.73 mL, 0.310 mmol) at r.t. After stirring for 24 h at r.t., the mixture was partitioned between EtOAc and $H_2O$. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and evaporated. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH/$NH_4OH$, 40:10:1) to afford the pure D-*lyxo*-phytosphingosine (**1**) as a white solid (37 mg, 68%); mp 106–107 °C (Lit.[18d] mp 104–105 °C, Lit.[18a] mp 104.5–105.5 °C); $[\alpha]_D^{20}$ –9.5 (*c* = 0.96, pyridine) {Lit.[18a] $[\alpha]_D^{20}$ –6.4 (*c* = 1.0, pyridine)}; $R_f$ = 0.17 ($CHCl_3$/MeOH/$NH_4OH$, 30:10:1).

IR (neat): 3346 (br s), 2922 (s), 2852 (m), 2360 (m), 2341 (w), 1733 (w), 1586 (w), 1464 (m), 1102 $cm^{-1}$ (s).

$^1H$ NMR (500 MHz, pyridine-$d_5$): δ = 4.33 (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).

$^{13}C$ NMR (125.28 MHz, pyridine-$d_5$): 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 $C_{18}H_{40}NO_3$: 318.3003; found: 318.3005.

## Acknowledgment

Financial support was provided by Mid Sweden University and the Swedish National Research Council (VR).

## Supporting Information

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

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