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A direct organocatalytic entry to sphingoids: asymmetric synthesis of D-*arabino*- and L-*ribo*-phytosphingosine

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The organocatalytic asymmetric synthesis of D-*arabino*- and L-*ribo*-phytosphingosine is described employing a diastereo- and enantioselective (*S*)-proline-catalyzed aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one and pentadecanal as the key step.

Sphingoids are long-chain amino-diol and -triol bases that form the backbone and the characteristic structural unit of sphingolipids, which are important membrane constituents and play vital roles in cell regulation as well as signal transduction.[1] Furthermore, glycosphingolipids show important biological activities, *e.g.* antitumor,[2a] antiviral,[2b] antifungal[2c] or cytotoxic properties.[2d] Phytosphingosines, one of the major classes of sphingoids, have been isolated and identified either separately or as parts of sphingolipids found in plants,[3a] marine organisms,[3b–c] fungi,[3d] yeasts[3e] and even mammalian tissues,[3f–l] for instance in the kidney,[3g] liver,[3h] uterus,[3i] intestine,[3j] skin[3k] and blood plasma.[3l] Due to the physiological importance of these compounds a large number of syntheses have been reported, which usually involve many steps and extensive protecting group strategies.[4]

We now wish to report a direct and flexible organocatalytic approach to sphingoids demonstrated with the efficient asymmetric synthesis of D-*arabino*- (**1**) and L-*ribo*-phytosphingosine (**2**) (Fig. 1). Our novel approach to the title compounds **1** and **2** commences with a diastereo- and enantioselective (*S*)-proline-catalyzed aldol reaction[5] of the readily available dihydroxy acetone equivalent 2,2-dimethyl-1,3-dioxan-5-one (**3**, dioxanone) and pentadecanal (**4**) (Scheme 1).[6–8]

After extensive optimization of the reaction conditions regarding to yield as well as diastereo- and enantioselectivity (Table 1), we were able to obtain the aldol product **5** with 49% yield and

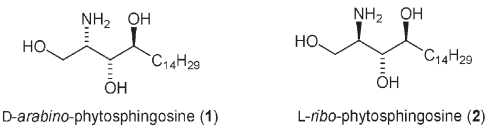
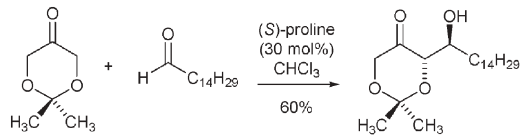
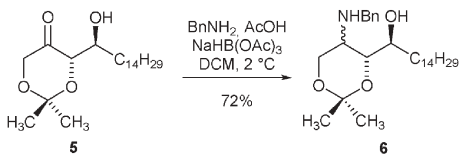


Fig. 1 Structures of the title phytosphingosines **1** and **2**.



Scheme 1 (*S*)-proline catalyzed aldol reaction as key step to sphingoids.



Scheme 2 Direct reductive amination of **5**.

Table 1 Optimization of the (*S*)-proline-catalyzed asymmetric aldol reaction of dioxanone **3** with pentadecanal (**4**) to afford **5**

Entry	Temp	Time/d	Ratio **3** : **4**	(*S*)-proline (mol%)	Solvent	Yield (%)[a]	de (%)[b]	ee (%)[c]
1	rt	4	1 : 1	30	DMSO	6	>99	94
2	rt	4	1 : 1	30	DMF	28	>99	92
3	rt	4	1 : 1	30	CH_3CN	25	>99	89
4	rt	4	1 : 1	30	THF	38	>99	81
5	rt	4	1 : 1	30	H_2O	no reaction	—	—
6	rt	4	1 : 1	30	neat	36	>99	91
7	rt	4	1 : 1	30	CH_2Cl_2	40	>99	81
8	rt	4	1 : 1	30	Pentane	28	>99	94
9	rt	4	1 : 1	30	$CHCl_3$	49 (60)[d]	>99	95
10	2 °C	20	1 : 1	30	$CHCl_3$	no reaction	—	—
11	rt	4	1 : 1	10	$CHCl_3$	37	>99	82
12	rt	4	2 : 1	30	$CHCl_3$	49	>99	94
13	rt	4	2 : 1	60	$CHCl_3$	50	>99	94
14	rt	4	5 : 1	30	$CHCl_3$	53	>99	88

[a] Yield of **5** isolated after flash chromatography on silica gel. [b] Determined on crude **5** by ^{1}H-NMR, ^{13}C-NMR, GC and HPLC. [c] Determined by HPLC on a chiral stationary phase (Daicel IA, *n*-heptane : isopropanol 95 : 5, major isomer 11.2 min, minor isomer 10.7 min). [d] Yield of 8 mmol experiment (see text).

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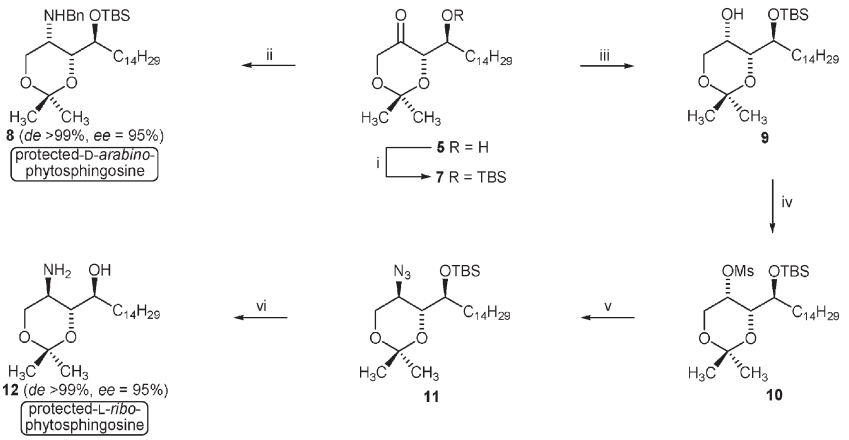


Scheme 3 Diastereoselective reductive amination and ketone–amine conversion. *Reagents and conditions*: i, TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 95%, de > 99%; ii, $BnNH_2$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 2 °C, 94%, de > 99%; iii, L-Selectride, THF, −78 °C, 93%, de > 99%; iv, MsCl, DMAP, CH_2Cl_2, −10 to 0 °C, 91%, de > 99%; v, NaN_3, 18-crown-6, DMF, 100 °C, 80%, de > 99%; vi, LAH, THF, 0 °C, 98%, de > 99%.

excellent diastereo- and enantiomeric excesses (entry 9). The optimization process was performed on small scale (1 mmol). To our delight, after carrying out the optimized reaction conditions on larger scale (8 mmol) we were able to obtain **5** with an increased yield of 60% and identical diastereo- and enantioselectivity.†

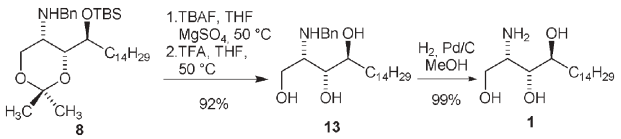
Thus, the simple (*S*)-proline catalyzed aldol reaction of the dioxanone **3** with pentadecanal directly delivered gram amounts of the selectively acetonide protected ketotriol precursor of the core unit of phytosphingosines in excellent stereoisomeric purity. In order to create stereoselectively the *syn*- and the *anti*-1,3-aminoalcohol function of the stereotriad, we first envisaged a diastereoselective reductive amination of **5**.

Initially, we investigated this reductive amination of **5** with $BnNH_2$ and $NaHB(OAc)_3$ in the presence of AcOH, but unfortunately we obtained only a 1 : 1 epimeric mixture of the corresponding 1,3-aminoalcohol **6** in 72% yield (Scheme 2).

Therefore we attempted the reductive amination with the corresponding TBS-protected aldol derivative **7**, which can be easily obtained in excellent yield (95%) using TBSOTf and 2,6-lutidine.[8b] The *anti*-1,3-aminoalcohol **8** was obtained in almost quantitative yield (94%) and virtually complete diastereoselectivity (de > 99%). Thus, our 3-step organocatalytic protocol affords orthogonality and selectively protected D-*arabino*-phytosphingosine of high diastereo- and enantiomeric purity. Needless to say, that the corresponding enantiomer can be obtained using (*R*)-proline instead of (*S*)-proline as the organocatalyst.

Because the direct and stereoselective reductive amination of **5** or **7** to afford the corresponding *syn*-1,3-aminoalcohol was not possible, we decided to synthesize the *syn*-isomer *via* a substitution reaction by inversion of the stereogenic centre. Therefore **7** was first transformed to the corresponding *anti*-1,3-diol **9** by a highly diastereoselective reduction with L-Selectride. The newly generated secondary alcohol was then converted into the mesylate **10** (91%) and subsequently into azide **11** (80%). The substitution of the mesylate **10** by NaN_3 in the presence of a crown ether (18-c-6) proceeded with complete inversion of the stereogenic centre (>99 : 1, determined by GC).

Subsequent reduction of the azide **11** with LAH afforded the *syn*-1,3-aminoalcohol **12** in virtually quantitative yield (Scheme 3).[9]



Scheme 4 Deprotection of **8** to D-*arabino*-phytosphingosine **1**.

The deprotection of the orthogonally triple protected phytosphingosine **8** could be achieved by removal of the silyl- and acetonide group in the presence of TBAF and TFA in THF. The remaining benzyl group was cleaved by hydrogenation on Pd/C to afford the title D-*arabino*-phytosphingosine (**1**) in 99% yield (Scheme 4).[10]

In summary, we have developed a direct and flexible entry to phytosphingosines by an asymmetric organocatalytic aldol reaction and subsequent diastereoselective ketone–amine conversion. Our modular [C_3 + C_n]-concept for the key aldol reaction should enable the introduction of different sidechains, which will greatly expand the potential of this strategy to sphingoids. For example, the class of sphingofungines[11] should be directly accessible employing long chain α-oxygenated aldehydes, and this is currently being investigated in our laboratory.

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Notes and references

† Unless otherwise stated, all chemicals are commercially available and were used without further purification with the exception of pentadecanal (**4**).[6] All new compounds were fully characterized (IR, NMR, MS, elemental analysis, optical rotation). **5**: In a 25 mL round-bottomed flask the dioxanone **3** (1 g, 7.7 mmol) and 30 mol% (*S*)-proline (0.27 g, 2.3 mmol) were dissolved in chloroform (4 mL). The solution was stirred for 30 min before **4** (1.7 g, 7.7 mmol) was added in one portion. The flask was flushed with argon and stirred for 4 d. The reaction mixture was quenched with sat. ammonium chloride solution (10 mL), extracted with diethyl ether (3 × 20 mL) and the combined organic phases were dried over $MgSO_4$, concentrated and purified by column chromatography (silica gel, methylene chloride : diethyl ether, 9 : 1). The aldol product **5** was obtained as

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colourless oil (1.64 g, 60%). $[\alpha]_D^{26} = -111.8$ (c = 1.1, $CHCl_3$); Found: C, 71.0; H, 11.4. Calc. for $C_{21}H_{40}O_4$: C, 70.7; H, 11.3.; IR ($CHCl_3$) ν_{max}/cm^{-1} 3540, 2925, 2855, 1741, 1463, 1378, 1223, 1092, 722; ^{1}H-NMR δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, J 6.9 Hz, CH_3), 1.28 (26H, m, 13 × CH_2), 1.44 (3H, s, CH_3), 1.48 (3H, s, CH_3), 2.97 (1H, br s, OH), 3.89 (1H, m, CH), 4.02 (1H, d, J 17.3 Hz, CH_2), 4.09 (1H, dd, J 6.9 and 1.4 Hz, CH), 4.27 (1H, dd, J 17.3 and 1.4 Hz, CH_2); δ_C(100 MHz, $CDCl_3$, Me_4Si) 14.1 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 23.9 (CH_3), 25.0 (CH_2), 29.4 (CH_2), 29.6 (3 × CH_2), 29.7 (2 × CH_2), 29.8 (3 × CH_2), 31.9 (CH_2), 32.3 (CH_2), 66.7 (CH_2), 70.6 (CH), 76.0 (CH), 100.9 (C), 211.2 (CO); m/z (CI, isobutane) 340 ($M^+ - 16$, 22), 339 ($M^+ - 17$, 100), 338 (8).

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