Recent Progress in Chemical Syntheses of Sphingosines and Phytosphingosines

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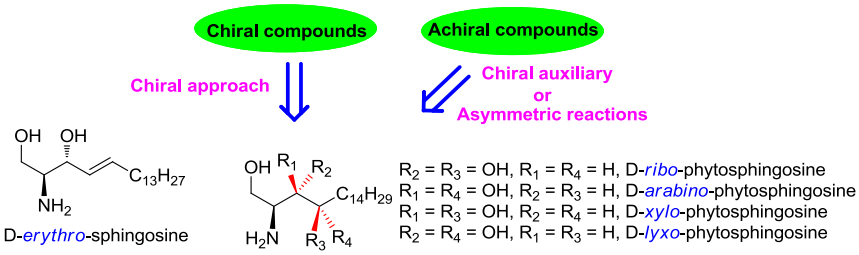

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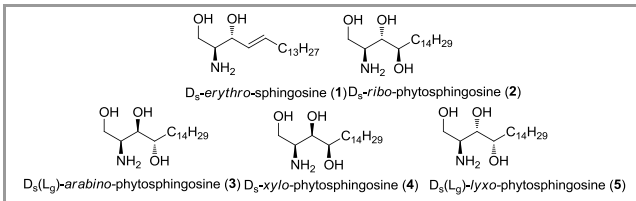
Abstract Sphingolipids and their derivatives such as glycosphingolipids and sphingomyelins exist ubiquitously in biomembrane of all eukaryotic cells, which play pivotal roles in cell proliferation, recognition, adhesion, and signal transduction. Sphingosine is shown to be the important lipid moiety in the large majority of glycosphingolipids and sphingomyelins, while phytosphingosine is one of the major long-chain moieties of glycosphingolipids. Due to the significance of the two bioactive lipids, tremendous efforts have been made to synthesize sphingosine or phytosphingosine using chiral pool approaches, chiral auxiliary and asymmetric reactions to construct the continuous stereogenic centers in them. This review covers the synthetic literatures published in the year after 2000.

Key words sphingosine, phytospingosine, synthesis, chiral pool, auxiliary, epoxidation

1 Introduction

Sphingolipids and glycosphingolipids are expressed on the surface of cell membrane and distributed throughout all eukaryotic cells, which are of physiological importance for cell growth, recognition, adhesion, neuronal repair, and signal transduction.[1] Sphingonsine, an amino alcohol, assigned as [(2*S*, 3*R*, 4*E*)-2-amino-3-hydroxyoctadec-4-en-1-ol)](Scheme 1), which is major lipid moiety of various sphingolipids, has itself displayed potent inhibitory activity against protein kinase C and plays key roles in cell signaling. [2] Study on sphingosine has underwent a long time since its first isolation by Thudichum from human brain in 1884,[3] the correct relative structural confirmation of the key functional groups by Carter in 1947, [4] and first total synthesis by Shapro and Segal in 1954. [5] Phytosphingosine, one of the major backbone of glycosphingolipids found in higher plants, protozoa, yeast and fungi,[6-9] is a sphingoid base incorprating a long aliphatic chain and a polar 2-amino-1,3-diol group at head end. The fixed amino function and variation in hydroxyl stereogenic centers of phytosphingosine leads to four diastereomers, which exhibit different activities and metabolisms. Phytosphingosine is also a bioactive lipid, and its glycosylated derivatives display hopeful antitumor and antivirus activity. [10-11] For example, D-*ribo*-phytosphingosine can work as a cytotoxic agent against human leukemic cell lines. [12] In addition, D-*ribo*-phytosphingosine acts as hopeful heat stress signaling molecule in yeast. [13]

To note, there is an underlying disorder related to D/L descriptors since two nomenclatures (i.e. amino-acid nomenclature and carbohydrate nomenclature) are employed for phytosphingosines.[14] For the sake of consistency, a traditional carbohydrate nomenclature in the amino-acid sense is used in this review unless otherwise stated.



Scheme 1 Structures of sphigosine and phytosphigosines. Note: the subscript s is for serine, g is for glyceraldehyde.

Because of the diverse biological activies and novel structural characters of sphingosines and phytosphingosines mentioned above, much attention has been drawn from biological and chemical community, especially from chemical community due to the scarcity of the two lipids in nature. To date, several reviews have been present in literatures. [15] Herein, we would like to introduce some recent advance in chemical syntheses of sphingosines and phytosphingosines published from 2000 to 2015, the synthetic procedures would be discussed together based upon their structural similarity.

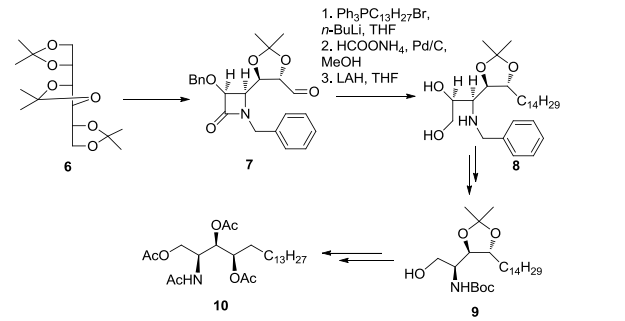
2 Chiral Approach

2.1 Chirality from sugar

2.1.1 Chirality from mannose or mannitol

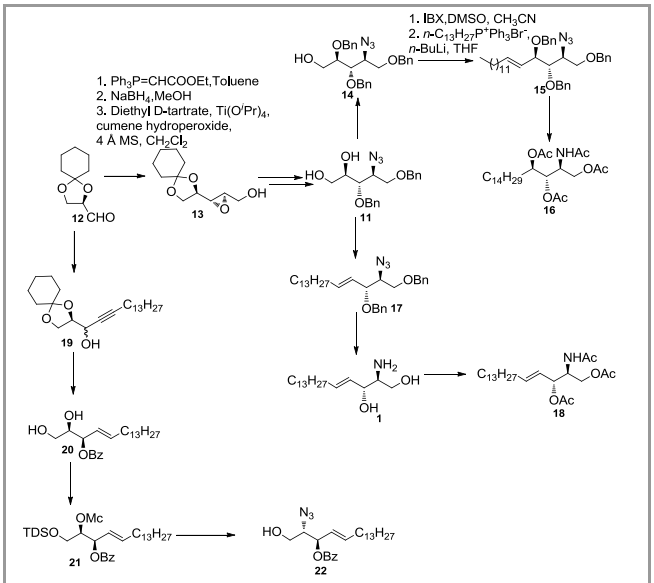
Pandey has reported an enantioselective and concise synthesis of (2*S*,3*R*,4*R*)-D-*xylo*-phytosphingosine with 7 steps in 36% overall yield utilizing D-mannitol triacetonide as chiral pool (Scheme 2).[16] In his scheme, D-mannitol triacetonide was converted into β-lactam **7** according to literature's procedure [17] to install all of the required stereogenic centers. Wittig olefination was employed for chain elongation followed by two-step reduction to give compound **8**. Finally, full deprotection under acidic condition, then, peracetylation with acetic anhydride/pyridene gave *N,O,O,O*-tetraacetyl-D-*xylo*-phytosphingosine (**10**) in a good yield.

Mettu has accomplished the syntheses of tetraacetyl-D-*ribo*-phytosphingosine (**16**) and triacetyl-D-*erythro*-sphingosine (**18**) using a common intermediate **11** obtained from cyclohexylidene protected D-glyceraldehyde (**12**), which was readily prepared from D-mannitol (Scheme 3).[18a] The key steps included high diastereo-selective Sharpless asymmetric epoxidation, regioselective epoxide-opening reaction by azide nucleophile, and Wittig olefination. Panza also adopted compound **12** as chiral pool to synthesize 3-*O*-benzoyl azidosphingosine **22**.[18b] Nucleophilic addition of the Grignard reagent to D-glyceraldehyde gave the propargylic alcohol **19** with low diastereoselectivity (*syn*/*anti* = 4:6). The undesired *anti* addition product was recycled through deacetylation followed by Mitsunobu inversion. Different from triflate or mesylate as leaving group in literatures, chloromesylate



Scheme 2 Synthesis of *N,O,O,O*-tetraacetyl-D-*xylo*-phytosphingosine (**10**) from D-mannitol triacetonide (**6**).

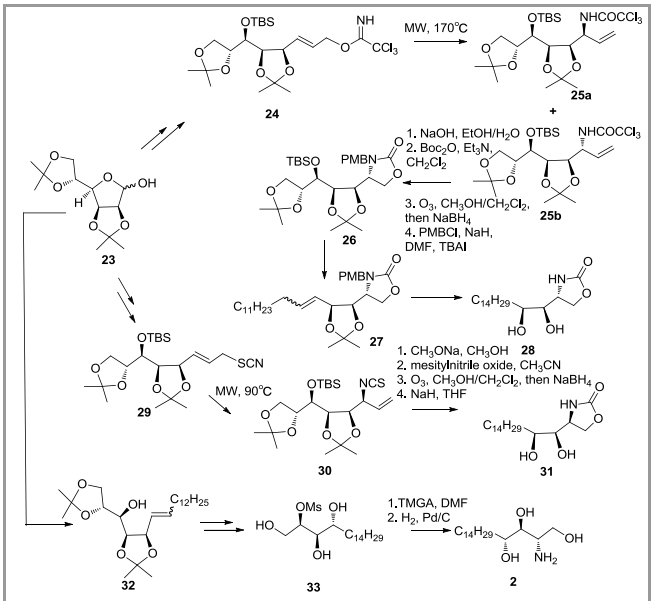
was utilized as leaving group which was subjected to displacement by azide nucleophile to afford azidosphingosine in a very satisfactory yield.



Scheme 3 Syntheses of tetraacetyl-D-*ribo*-phytosphingosine (**16**), triacetyl-D-*erythro*-sphingosine (**18**), and 3-*O*-benzoyl azidosphingosine (**22**) from cyclohexylidene protected D-glyceraldehyde (**12**).

Recently, Martinkov described the total synthesis of protected L$_g$-*arabino*-phytosphingosine (**31**), L-*ribo*-phytosphingosine (**28**) from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (Scheme 4)(g means for glyceraldehyde).[19] The pivotal reactions involved [3,3]-sigmatropic rearrangement to introduce the desired amino functionality, and chain elongation through Wittig olefination. Notably, thermal Overman rearrangement of **24** furnished inseperable rearranged products in a low yield and pool diastereoselectivity, while the use of microwave heating afforded high-yielding of rearranged products and greatly shortened reaction time. The protected L-*ribo*-phytosphingosine (**28**) could be accessible from rearranged product **25b** through several manipulations. Utilizing the same procedure as described for the preparation of protected L-*ribo*-phytosphingosine (**28**), synthesis of compound **31** was achieved from compound **25a**. An alternative route for preparation of **31** was commenced with allylic thiocyanate **29** according to the similar procedure for synthesis of compound **28**. Though aza-Claisen rearrangement of **29** was carried out in modest yield, displayed better stereoselectivities than those observed for the Overman rearrangement of trichloroacetimidate **24**.

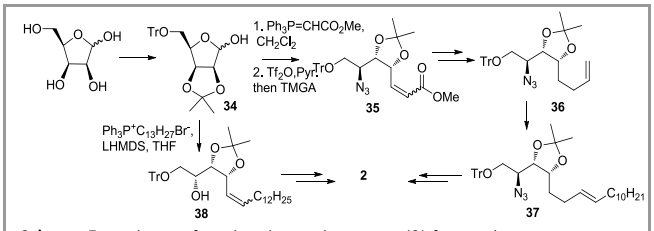
Also from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose, Lin reported a concise and efficient synthesis of D-*ribo*-phytosphingosine (**2**), which employed eight-step conventional manipulation in 57% overall yield using Wittig olefination and azide nucleophilic replacement as key reactions (Scheme 4).[20]



Scheme 4 Syntheses of compound **28**, **31** and **2** from compound **23**.

2.1.2 Chirality from D-lyxose

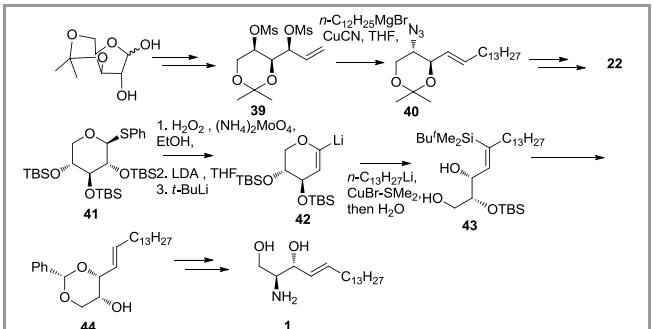
A short and very efficient route for synthesis of D-*ribo*-phytosphingosine from D-lyxose was reported by Lin group in 2003 (Scheme 5). [21] In his work, D-*ribo*-phytosphingosine (**2**) was prepared from D-lyxose over 6 steps in 28% overall yield using Wittig olefination and substitution by tetramethylguanidinium azide (TMGA) as crucial steps. A similar synthesis of D-*ribo*-phytosphingosine was also achieved by Lin group, in which both Wittig olefination and olefin cross-metathesis (CM) were adequately employed to extend carbon chain. [22] The later strategy seemed not to be concise compared to the former; however, it afforded rapid access to syntheses of the phytosphingosine derivatives.



Scheme 5 Synthesis of D-*ribo*-phytosphingosine (**2**) from D-lyxose.

2.1.3 Chirality from D-xylose

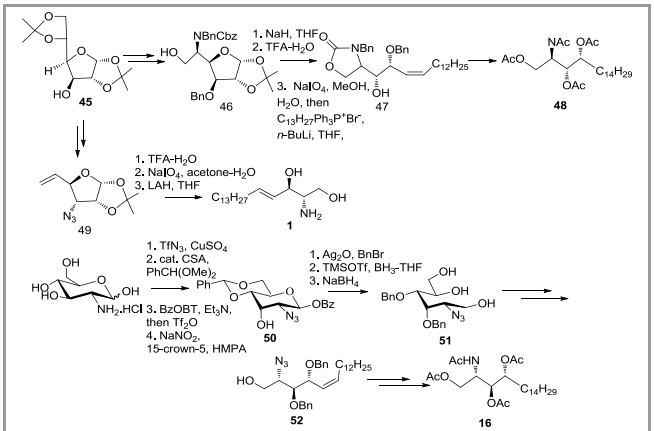
Panza has reported the synthesis of 3-*O*-benzoylazido-sphingosine (**22**) from 3,5-*O*-isopropylidene-D-xylofuranose using Peterson olefination and allylic displacement by Grignard reagent as key steps (Scheme 6). [23] The deficiency of the strategy was low *trans* selectivity (*E*/*Z*=2/1) in allylic displacement. Still from cheap D-xylose, Kocienski has reported a twelve-step synthesis of the D-*erythro*-sphingosine utilizing a 1,2-metallate rearrangement as the key step. In addition, Brook rearrangement and substitution by diphenylphosphoryl azide (DPPA) *via* Mitsunobu reaction were equally indispensable for the synthesis. [24] This synthesis provided a novel strategy for effective construction of *trans* double bond.



Scheme 6 Synthesis of D-*erythro*-sphingosine (**1**) and its derivative compound **22** .

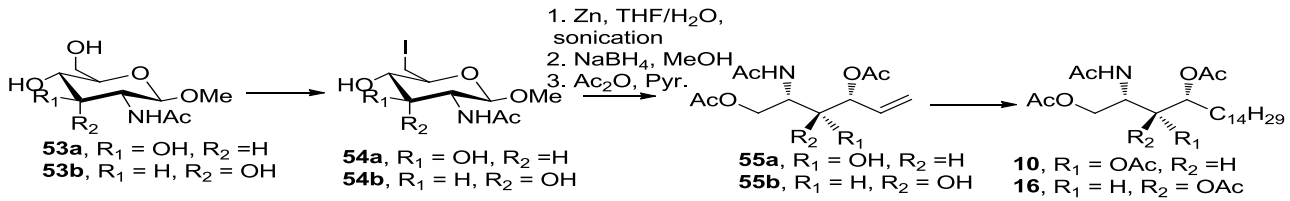
2.1.4 Chirality from D-glucose and its derivatives

In 2012, Rao has accomplished the synthesis of acetyl derivative of L_g-*lyxo*-phytosphingosine (**48**) commencing with known 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose derived from D-glucose (Scheme 7). [25] In this work, *Z*-selectivity Wittig olefination was employed as key step to elongate carbon chain though stereochemistry of the double bond was unnecessary because of the subsequent hydrogenation. As shown in Schme 7, the important intermediate **49** was also prepared from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose over 4 steps. Synthesis of D-*erythro*-sphingosine (**1**) was achieved by Dhavale *via* *E*-selective olefin cross-metathesis between compound **49** and long-chain terminal alkene in 65.4% overall yield. [26] A direct synthesis of **16** from D-glucosamine hydrochloride *via* the D-allosamine derivative **50** as key intermediate has been reported by Hung in 2002.[27] Similar to the synthesis of acetyl derivative of L_g-*lyxo*-phytosphingosine (**48**), *Z*-selectivity Wittig olefination was employed as well for extension chain to synthesize tetraacetyl-D-*ribo*-phytosphingosine (**16**). Besides, amino–azido conversion and highly regioselective benzoylation were also essential to this work.



Scheme 7 Syntheses of compound **1**, **16** and **48** from D-glucose and its derivatives.

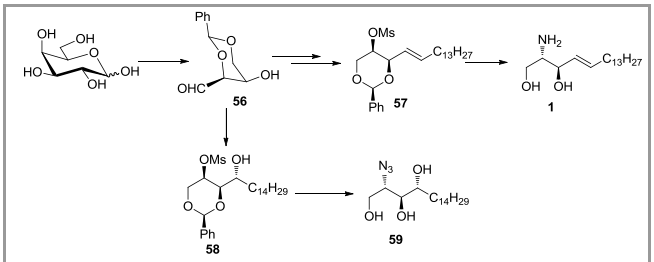
Bundle has utilized selective iodination, zinc-mediated reductive ring-opening reaction and olefin cross-metathesis as crucial steps to prepare tetraacetyl-D-*xylo*- and D-*ribo*-phytosphingosine (**10** and **16**) starting from the methyl β-glycosides of D-GlcNAc (**53a**) and D-AllNAc (**53b**), respectively (Scheme 8). [28] The spotlight of the synthesis was excellent *E*/*Z* selectivity (*E*/*Z* = 19:1 for **55a**, only *E* for **55b**) of olefin cross-metathesis (OCM), and the OCM could be applied to synthesize phytosphingosine derivatives with desired alkyl chains length.



Scheme 8 Syntheses of tetraacetyl-D-*xylo*- and D-*ribo*-phytosphingosine (**10** and **16**) starting from the methyl β-glycosides of D-GlcNAc (**53a**) and D-AllNAc (**53b**), respectively.

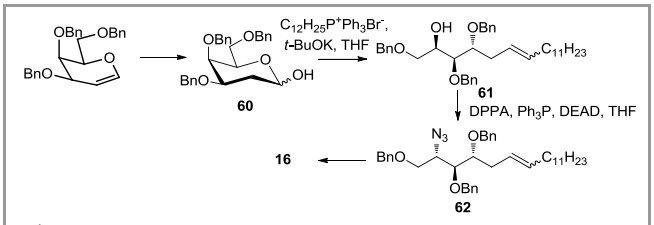
2.1.5 Chirality from D-galactose and its derivatives

Duclos Jr reported a concise and conventional synthesis of D-*erythro*-sphingosine (**1**) starting from D-galactose over 7 steps in 2001 (Scheme 9), [29a] which was based on the previous protocol adopted by Schmidt in 1988.[30] The key step was Wittig olefination between 1,3-*O*-benzylidene-D-threose (**56**) and *n*-tetradecyl ylide to exclusively form *trans* double bond. The same protocol was utilized by Demchenko to synthesize L-*erythro*-sphingosine (***ent*-1**) from 1,3-*O*-benzylidene-L-threose (prepared from L-arabitol) in 2010. [29b] In 2000, Schmidt also utilized 1,3-*O*-benzylidene-D-threose for preparing D-*ribo*-azidophyto-sphingosine (**59**).[31] Highlight of this work involved stereoselective addition of 1,3-*O*-benzylidene-D-threose by *n*-tetradecyl magnesium chloride to exclusively produce chiral hydroxyl at C4 position, and regioselective mesylation at C2 position.



Scheme 9 Syntheses of D-*erythro*-sphingosine (**1**) and D-*ribo*-azidophyto-sphingosine (**59**) from 1,3-*O*-benzylidene-D-threose.

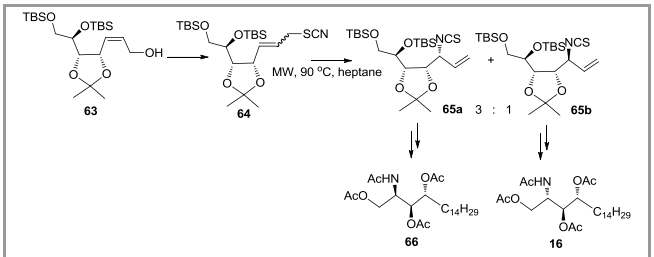
In 2008, Ye group accomplished a facile synthesis of tetraacetyl-D-*ribo*-phytosphingosine (**16**) over 5 steps in 74% overall yield from 3,4,6-tri-*O*-benzyl-D-galactal (Scheme 10). [32] Spotlight of this synthesis included a high-yielding Wittig olefination of lactol **60** and one-step azide substitution *via* Mitsunobu reaction.



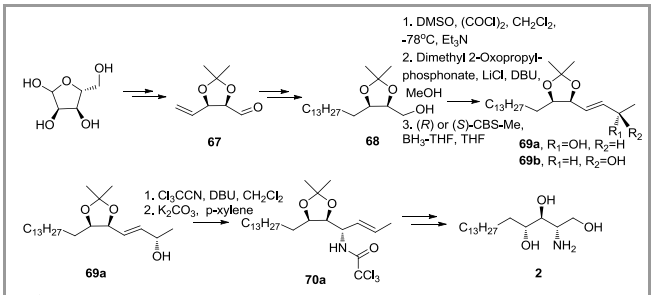
Scheme 10 Synthesis of tetraacetyl-D-*ribo*-phytosphingosine (**16**) from 3,4,6-tri-*O*-benzyl-D-galactal.

2.1.6 Chirality from D-ribose

Very recently, Martinková [33] accomplished the syntheses of tetraacetyl-D-*arabino*-phytosphingosine (**66**), tetraacetyl-D-*ribo*-phytosphingosine (**16**) starting from D-ribose on the basis of the same procedures as described for preparation of their enantiomers in 2011 (Scheme 11). [34] The key step involved aza-Claisen rearrangement of allylic thiocyanate **64** to afford rearranged products **65a**, **65b** in an approximate ratio of 3:1 with 50% yield, which was further used to synthesize compound **66** and **16**, respectively. Unlike Martinková's protocol, Sutherland employed Overman rearrangement of allylic trichloroacetimidate to install the chiral amino group of compound **70a** as a single diastereomer in a satisfactory yield (72%) (Scheme 12). [35] While the other two stereogenic centers of phytospingosines were also derived from D-ribose. Thus, a new access to D-*ribo*-phytosphingosine (**2**) was achieved using Overman rearrangement, *trans*-selective CM reaction, and stereoselective reduction of unsaturated ketone *via* CBS-reduction as key steps. The synthesis of L-*arabino*-phytosphingosine (***ent*-3**) was prepared from **69b** according to the same preceduce as decribed for **2**.



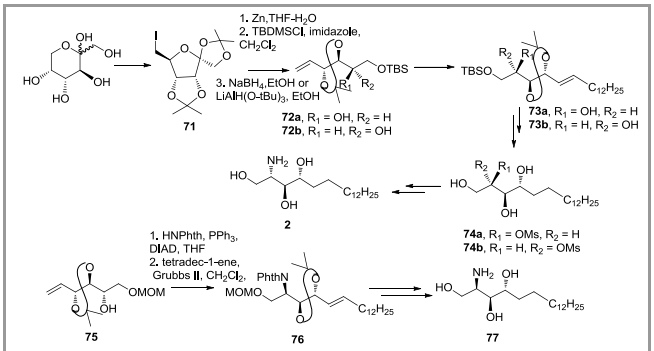
Scheme 11 Syntheses of tetraacetyl-D-*arabino*-phytosphingosine (**66**) and tetraacetyl-D-*ribo*-phytosphingosine (**16**) from D-ribose.



Scheme 12 Synthesis of D-*ribo*-phytosphingosine (**2**) from D-ribose.

2.1.7 Chirality from D-fructose

In 2011, a new methodology for synthses of D-*ribo*-phytosphingosine (**2**) and L-*arabino*-phytosphingosine (**77**) from D-fructose was developed by Perali (Scheme 13). [36] In this scheme, zinc-mediated fragmentation of **71** was used as key step to give the cerresponding ketone. Interestingly, subsequent reduction by $NaBH_4$ almost yielded **72b**, corresponding to **72a** as major product (**72a** : **72b** = 7 : 3) *via* reduction by $LiAlH(O\text{-}^tBu)_3$. Both **72a** and **72b** were subjected to crucial olefin cross-metathesis for chain extention, azido substitution, and other simple conversions to successfully afford **2**. To note, the reason for retention of configuration at C2 position from **74b** to **2** was that substitution of **74b** by NaN_3 underwent S_N1 type substitution. To invert this configuration, Mitsunobu reaction was finally utilized, thus, L-*arabino*-phytosphingosine (**77**) was obtained from compound **75**.

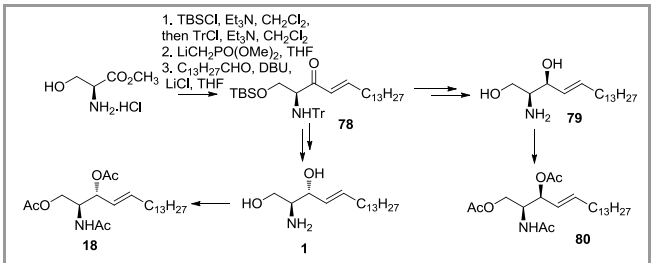


Scheme 13 Syntheses of D-*ribo*-phytosphingosine (**2**) and L-*arabino*-phytosphingosine (**77**) starting from D-fructose.

2.2 Chirality from serine and its derivatives

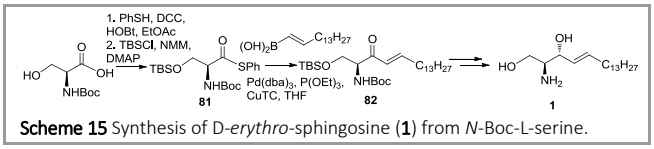
2.2.1 Chirality from serine ester

In 2002, Chuang group presented a short and efficient route for synthesis of all four stereomers of sphingosine from serine (Scheme 14). [37] The authors employed HWE olefination to form *trans* double bond in high yield. Treatment of 3-ketosphingosine derivative **78** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ afforded *syn* reduction product, which leaded to further prepare L-*threo*-sphingosine (**79**) and its acetyl derivative (**80**). However, reduction of deprotection product of **78** by $Zn(BH_4)_2$ gave *anti* reduction product, which was subjected to further conversion to D-*erythro*-sphingosine (**1**) and its acetyl derivative (**18**). According to the same procedure, L-*erythro*-sphingosine and D-*threo*-sphingosine were easily prepared from D-serine methyl ester HCl. The similar stereoselective reduction protocol was also employed by Katsumura and Bittman to synthesize D-*erythro*-sphingosine (**1**) from L-serine or *N*-Boc-L-serine methyl ester. [38] Olefin cross-metathesis and elimination of sulfoxide intermediate was respectively utilized by Katsumura and Bittman to construct *trans* double bond.



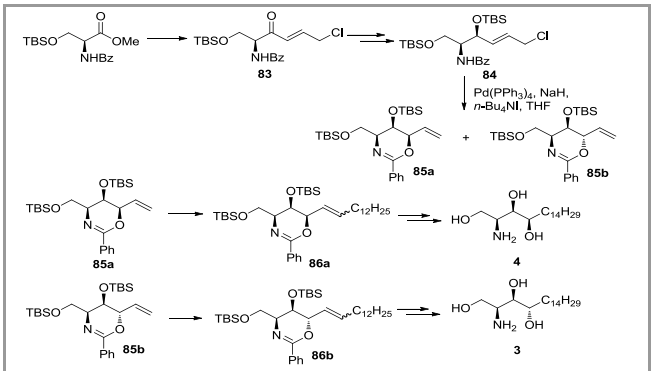
Scheme 14 Syntheses of compound **1**, **18**, **79** and **80** from L-serine methyl ester HCl.

Liebeskind reported a concise and very efficient synthesis of D-*erythro*-sphingosine (**1**) from *N*-Boc-L-serine over 6 steps in 72% overall yield in 2007 (Scheme 15). [39] In this work, new methodology for cross-coupling between thiol ester **81** and vinyl boronic has been developed to construct the classic alkenyl ketone intermediate **82**, which was further subjected to stereoselective reduction mentioned above to give the target compound **1**.



Scheme 15 Synthesis of D-*erythro*-sphingosine (**1**) from *N*-Boc-L-serine.

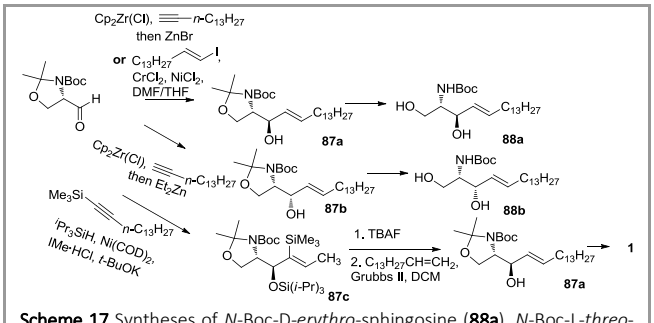
An efficient, stereocontrolled synthetic method for the preparation of D-*xylo*-phytosphingosine (**4**) and D-*arabino*-phytosphingsine (**3**) was reported by Ham *et al* in 2012 starting from L-serine methyl ester *via* chiral 1,3-oxazines intermediate (Scheme 16). [40] The crucial reactions involved stereoselective intramolecular oxazine formation catalyzed by palladium (0) and CM reaction for chain extention. Notably, both **85a** and **85b** could be separately obtained as major products by changing the reaction temperature. **85a** leaded to give D-*xylo*-phytosphingosine (**4**), however, **85b** leaded to give D-*arabino*-phytosphingosine (**3**) in the same manner.



Scheme 16 Syntheses of D-*xylo*- (**4**) and D-*arabino*-phytosphingsine (**3**) from L-serine methyl ester.

2.2.2 Chirality from Garner's aldehyde

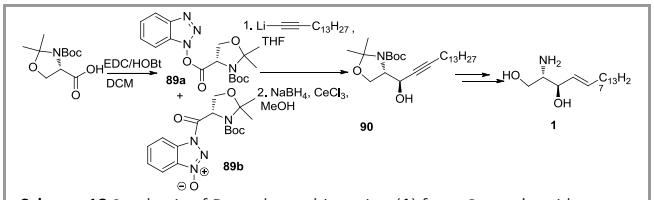
In 2002, Murakami [41a] achieved efficient and high diastereoselective syntheses of *N*-Boc-D-*erythro*-sphingosine (**88a**) and *N*-Boc-L-*threo*-sphingosine (**88b**) using addition of 1-alkenyl nucleophiles to Garner's aldehyde as pivotal steps (Scheme 17). Notably, addition of 1-alkenylzirconocene chloride to Garner's aldehyde in the presence of $ZnBr_2$ gave *anti*-isomer, conversely, addition of 1-alkenyl-ethyl-zinc to Garner's aldehyde afforded *syn*-isomer. An alternative synthesis of intermediate **87a** was reported by Arenz through addition of Garner's aldehyde by vinylmagnesium bromide and subsequent CM reaction in 37% yield. [41b] The similar addition of 1-alkenyl nucleophile to Garner's aldehyde to prepare D-*erythro*-sphingosine was also employed by Ferjančić in 2014 using alkenylchromium (III) reagent instead, however, with a lower diastereoselectivity (7:1) and yield (46%) compared with Murakami's protocol. [42a] In contrast, Montgomery took advantage of nickel-catalyzed reductive coupling of Garner's aldehyde with silyl alkyne to give compound **87c** with good yield (78%) and satisfactory diastereoselectivity (>95:5), which easily converted into **87a** over 2 steps. [42b]



Scheme 17 Syntheses of *N*-Boc-D-*erythro*-sphingosine (**88a**), *N*-Boc-L-*threo*-sphingosine (**88b**) and D-*erythro*-sphingosine (**1**) from Garner's aldehyde.

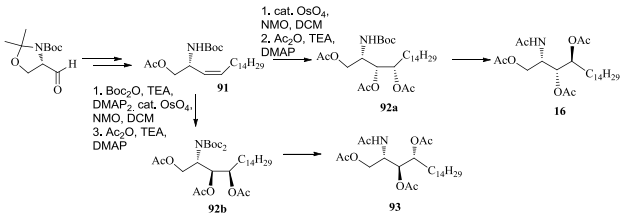
A short and convenient synthesis of D-*erythro*-sphingosine (**1**) was accomplished by Cárdennas's group over 4 steps in 33%

overall yield from Garner's acid in 2013 (Scheme 18). [43] Key steps included efficient addition of terminal alkyne to benzotriazole esters (**89a**, **89b**) and stereoselective reduction.



Scheme 18 Synthesis of D-*erythro*-sphingosine (**1**) from Garner's acid.

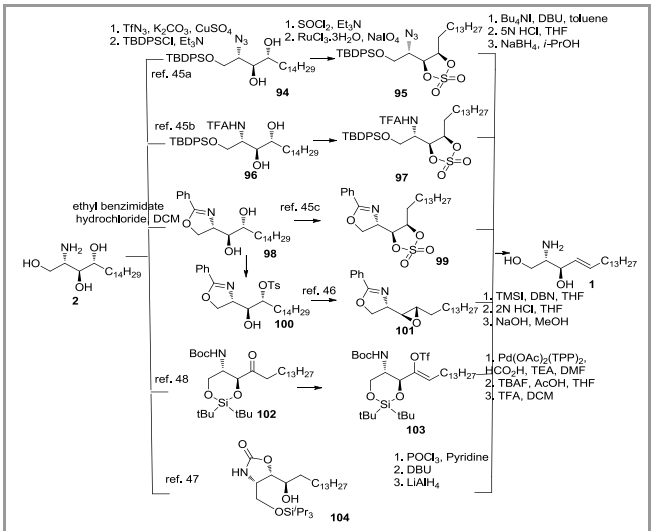
Unlike Lomobardo's strategy, Kim *et al* employed OsO_4-catalyzed dihydroxylation reactions of (*Z*)-allylic amines derived from (*Z*)-selective Wittig olefination of Garner's aldehyde to set the stereochemistry at C3, C4 positions. [44] As shown in Scheme 19, dihydroxylation of (*Z*)-allylic amine with *N*,*N*-diBoc groups gave *anti*-selective isomer **92a**, however, dihydroxylation of *N*-Boc-(*Z*)-allylic amine (**91**) gave *syn*-selective isomer **92b**. This can be explained by severe 1,2-allylic strain between the *N*,*N*-diBoc groups and the vinylic hydrogen atom. The stereocontrolled dihydroxylation of (*Z*)-allylic amines was better than Sharpless dihydroxylation to some degree, upon which syntheses of both tetraacetyl derivatives of D-*ribo*-phytosphingosine (**16**) and L-*arabino*-phytosphingosine (**93**) were achieved.



Scheme 19 Syntheses of both tetraacetyl derivatives of D-*ribo*-phytosphingosine (**16**) and L-*arabino*-phytosphingosine (**93**) from Garner's aldehyde.

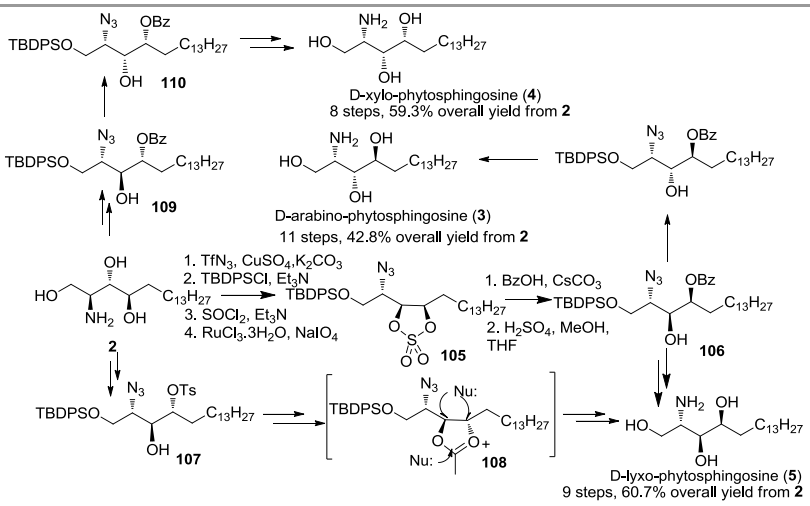
2.3 Chirality from D-*ribo*-phytosphingosine

Since D-*ribo*-phytosphingosine is easily accessible from a yeast fermentation process, it has been used as chiral pool to prepare sphingosine and other phytosphingosines. Several syntheses of D-*erythro*-sphingosine from D-*ribo*-phytosphingosine have been achieved in a concise manner (Scheme 20). [45] The common point of these syntheses was selective protection of C1-hydroxy and C2-amine groups followed by elimination of a cyclic sulfate intermediate (**95**, **97** and **99**) to exclusively construct *trans* olefin. Aside from elimination of a cyclic sulfate intermediate, epoxide (**101**) [46] and alcohol (**104**) [47] were also eliminated to give *trans* olefin. Different from the above protocols, van Boom [48] has employed stereoselective transformation of **102** into the corresponding (*Z*)-enol triflate (**103**) followed by a regiospecific reduction to install *trans* double bond. Among these syntheses, Overkleeft [45c] has provided a short synthetic route with highest overall yield (67%) to date.



Scheme 20 Synthesis of D-*erythro*-sphingosine (**1**) from D-*ribo*-phytosphingosine (**2**) through different routes.

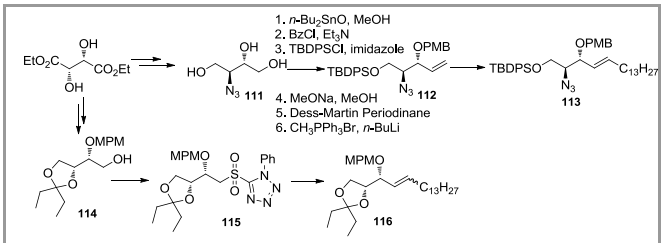
D-*ribo*-phytosphingosine works as important chiral pool, it was also used to prepare other phytosphingosines. Kim reported high-yielding and concise syntheses of D-*arabino*-(**3**), D-*lyxo*-(**5**), and D-*xylo*-phytosphingosine (**4**) from D-*ribo*-phytosphingosine (**2**) (Scheme 21). [49] The configurational inversion of C-4 of compound **2** which leaded to afford D-*lyxo*-phytosphingosine (**5**) was carried out *via* cyclic sulfate intermediate **105** or oxonium ion intermediate **108** attacked by nucleophiles. On the other hand, inversion of C-3 and C4 leaded to D-*arabino*-phytosphingosine (**3**), and inversion of C-3 leaded to D-*xylo*-phytosphingosine (**4**). Both were carried out *via* mesylate intermediate attacked by nucleophiles (H_2O).



Scheme 21 Syntheses of D-*arabino*-phytosphingosine (**3**), D-*lyxo*-phytosphingosine (**5**), and D-*xylo*-phytosphingosine (**4**) from D-*ribo*-phytosphingosine (**2**).

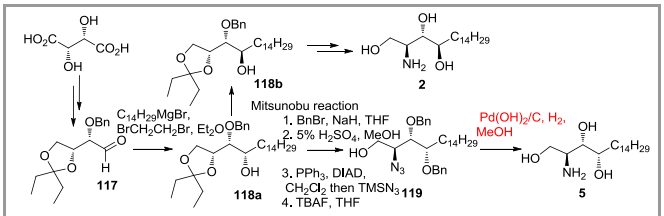
2.4 Chirality from D-tartric acid and its diester

In 2004, Basu [50] employed two contiguous hydroxyl groups of D-tartrate diester as chiral template to accomplish the synthesis of protected D-*erythro*-azidosphingosine (**113**) (Scheme 22). The highlight of this work was selective benzoylation of azidotriol **111** and exclusive formation of *trans* olefin *via* cross metathesis. However, compound **113** was obtained in a low yield (36%). Another formal synthesis of D-*erythro*-azidosphingosine from D-tartrate diester was reported by Panza [51] in 2002 taking advantage of Julia olefination of sulfone **115** to construct *trans* olefin in a *E/Z* ratio of 5:1 in 53% yield.



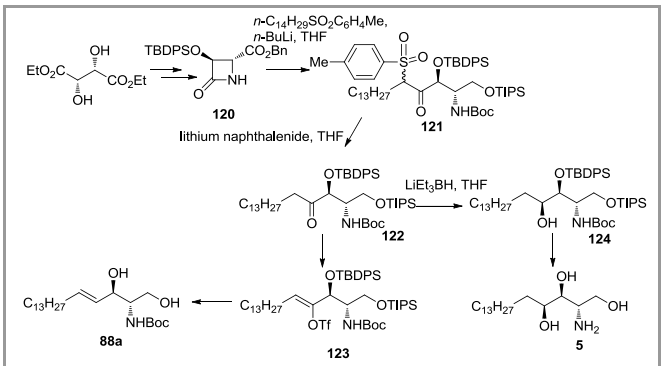
Scheme 22 Syntheses of compound **113** and **116** from D-tartrate diester.

Bittman [52] has achieved the synthesis of L$_g$-*lyxo*-phytosphingosine (**5**) employing diastereoselective addition of the Grignard reagent to aldehyde **117** derived from D-tartric acid to give a mixture of **118a** and **118b** in a ratio of 9:1 (Schem 23). Another crucial step was convertion of diol to azido **119** by Mitsunobu's procedure. According to the same synthetic procedure for **5**, D-*ribo*-phytosphingosine (**2**) was also prepared from compound **118b** which was obtained from **118a** *via* Mitsubobu reaction.



Scheme 23 Syntheses of L$_g$-*lyxo*-phytosphingosine (**5**) and D-*ribo*-phytosphingosine (**2**) from D-tartric acid.

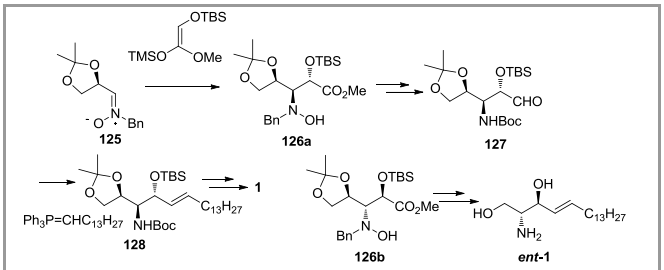
Shiozaki [53] has provided an alternative access to D-*erythro*-sphingosine (**1**) and L$_g$-*lyxo*-phytosphingosine (**5**) using chiral β-lactam **120** derived from D-tartrate diester as chiral template (Scheme 24). Ring-opening reaction of β-lactam **120** by 4-tolyltetrade-cylsulfone followed by elimination afforded key ketone **122** in a satisfactory yield (93%). Isomerization of ketone **122** to enol triflate **123**, then reductive elimination and deprotection yielded *N*-Boc-D-*erythro*-sphingosine (**88a**) in a moderate yield. On the other hand, diastereoselective reduction of **122** by LiEt$_3$BH gave protected aminotriol **124** in good yield and stereoselectivity, which further converted into **5** in an excellent yield (96%).



Scheme 24 Syntheses of L$_g$-*lyxo*-phytosphingosine (**5**) and *N*-Boc-D-*erythro*-sphingosine (**88a**) from D-tartrate diester.

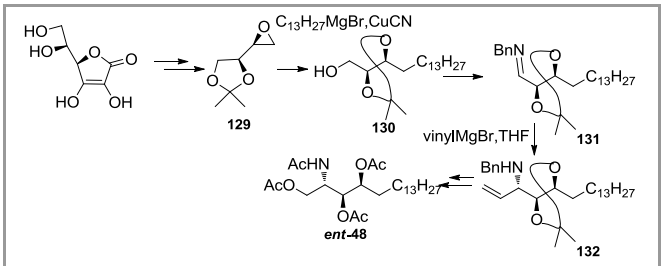
2.5 Chirality from other chiral precursors

Concise, efficient and enantiodivergent syntheses of D- and L-*erythro*-sphingosine (**1** and ***ent*-1**) were achieved by Merino *et al* in 2006.[54] As shown in scheme 25, the key steps involved a stereocontrolled Mannich-type reaction between D-glyceraldehyde nitrone **125** and 2-silyloxy silylketene acetal, and a *trans*-selective Wittig olefination. Interestingly, Mannich-type reaction conducted in the presence of $SnCl_2$, $Yb(OTf)_3$, or $Zn(OTf)_2$ gave compound **126a** as major product , on the other hand, when using $SnCl_4$ as promoter gave compound **126b** as major product. L-*erythro*-sphingosine (***ent*-1**) was prepared according to the same procedure as described for **1** from **126a**.



Scheme 25 Syntheses of D- and L-*erythro*-sphingosine (**1** and ***ent*-1**) from D-glyceraldehyde nitrone.

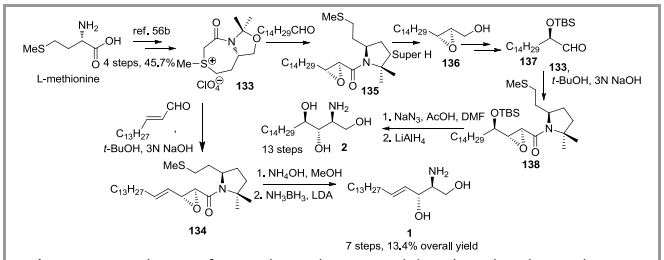
Rao's group [55a] has reported a stereoselective synthesis of *N*,*O*,*O*,*O*-tetraacetyl D-*lyxo*-phytosphingosine (***ent*-48**) over 10 steps from a known intermediate [55b] derived from L-ascorbic acid. The crucial reactions involved Grignard addition on epoxide **129** and stereoselective addition of chiral imine **131** by vinylmagnesium bromide (Scheme 26).



Scheme 26 Synthesis of *N*,*O*,*O*,*O*-tetraacetyl D-*lyxo*-phytosphingosine (***ent*-48**) from L-ascorbic acid.

Aside from the above chiral precursors, Sarabia and his co-authors employed L-methionine as chiral pool to synthesize cyclic sulfonium salt **133**, which was successfully applied to synthesize D-*erythro*-sphingosine (**1**) and D-*ribo*-phytosphingosine (**2**) over 7 steps, 13 steps, respectively (Scheme 27). [56] Highlight of this work was stereoselective formation of epoxide amide (**134**, **135** or **138**)

and regioselective epoxide-opening reaction by amino or azide nucleophile at C2 position.

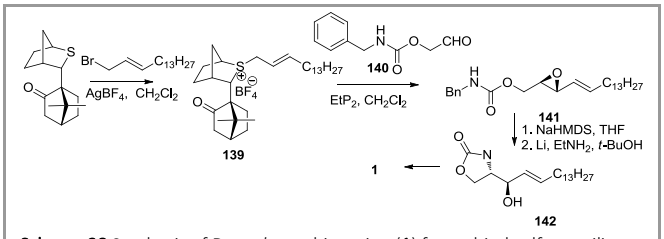


Scheme 27 Syntheses of D-*erythro*-sphingosine (**1**) and D-*ribo*-phytosphingosine (**2**) from L-methionine.

3 Chiral auxiliary

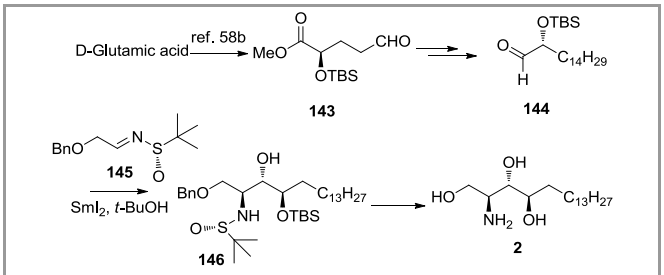
3.1 Chiral sulfur auxiliary

A high-yielding and facile synthesis of D-*erythro*-sphingosine (**1**) was achieved by Castillón *et al* in 2008 in 42% overall isolated yield with 6 steps (Scheme 27).[56] The success of this work was employing asymmetric sulfur ylide reaction between the sulfonium salt **139** and the aldehyde **140** to construct the epoxide **141** with the desired configuration. In addition, *E*-selective CM for chain extension and a regio-, stereoselective intramolecular epoxide-opening reaction to form oxazolidinone **142** were also crucial for the synthesis.



Scheme 28 Synthesis of D-*erythro*-sphingosine (**1**) from chiral sulfur auxiliary.

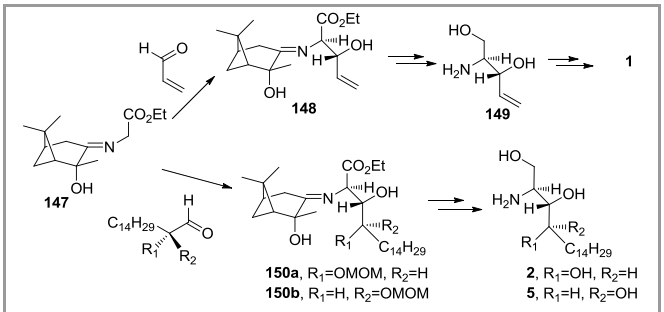
Aside from the above sulfur auxiliary, Wei *et al* [58a] has introduced a novel chiral *N*-*tert*-butanesulfinamide **145** for cross-coupling with bulky long-chain aliphatic aldehydes **144** derived from D-glutamic acid to stereoselectively install amino functionality at C2 position and hydroxyl functionality at C3 position, thus, an efficient synthesis of D-*ribo*-phytosphingosine (**2**) was accomplished (Scheme 29) over 5 steps in 27% overall yield from known compound **143**.[58b]



Scheme 29 Synthesis of D-*ribo*-phytosphingosine (**2**) from D-glutamic acid.

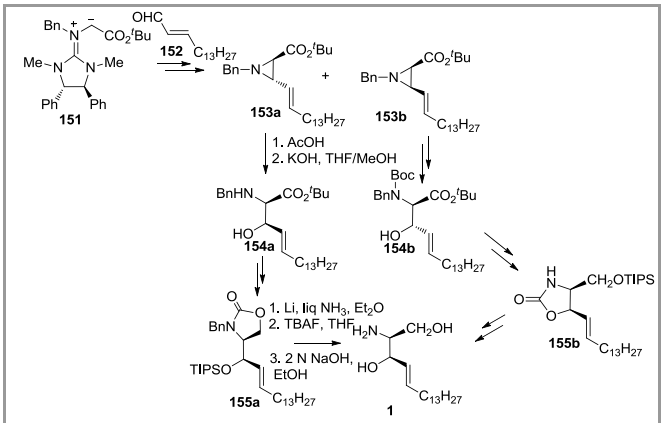
3.2 Chiral N-containing auxiliary

Similar to Wei's protocol,[58a] chiral iminoglycinate **147** was used by Bundle *et al* [59] to condense with alehyde to build amino group at C2 position and hydroxyl group at C3 postion, therefore, iminoglycinate condensed with acrolein to give truncated sphingosine **149** in a concise manner. On the other hand, iminoglycinate condensed with aldehyde containing a *R* or *S*-configuration hydroxyl group to give D-*ribo*-phytosphingosine (**2**) and L-*lyxo*-phytosphingosine (**5**) in more than 45% overall yield in both cases (Scheme 30).



Scheme 30 Syntheses of truncated sphingosine (**149**), D-*ribo*-phytosphingosine (**2**) and L-*lyxo*-phytosphingosine (**5**) from chiral iminoglycinate (**147**).

Ishikawa [60] has reported a synthesis of D-*erythro*-sphingosine (**1**) using chirality transfer from chiral guanidinium ylide **151** to 3-alkenyl aziridine-2-carboxylate (**153a** and **153b**) to build chiral amino alcohol unit in **1** (Scheme 31). In this work, chiral guanidinium ylide **151** reacted with α,β-unsaturated aldehyde **152** to give a mixture of *cis*/*trans* (ca. 1:1) aziridine-2-carboxylate without diastereoselectivity. However, both diastereoisomers can be further converted into compound **1** *via* oxazolidinone intermediates (**155a** or **155b**). To note, *cis*-aziridine-2-carboxylate (**153b**) was subjected to ring-opening reaction followed by S_N2 type substitution to invert the hydroxyl configuration at the C3 position.



Scheme 31 Synthesis of D-*erythro*-sphingosine (**1**) from chiral guanidinium ylide **151**.

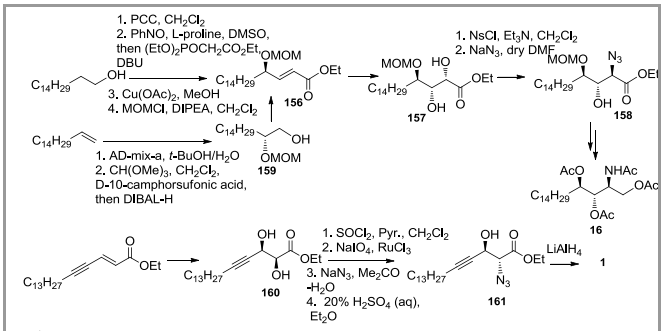
4 Asymmetric reactions

A number of syntheses of sphingosines and phytosphingosines have been accomplished from achiral starting materials using asymmetric reactions to set chiral hydroxyl groups, or chiral amino groups, or both. The extensive literatures searching revealed they could be classified into five categories: Sharpless dihydroxylation, Sharpless epoxidation and Shi's epoxidation, catalytic asymmetric aldol reaction, Sharpless kinetic resolution, asymmetric aminohydroxylation and amination.

4.1 Sharpless dihydroxylation reaction

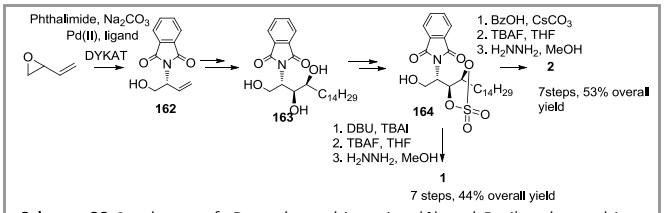
Very recently, Sudalai *et al* [61] has reported an enantioselective synthesis of tetraacetyl-D-*ribo*-phytosphingosine (**16**) starting from 1-hexadecanol taking advantage of L-proline-catalyzed α-amino-

oxylation, Horner–Wardsworth–Emmons olefination for *E*-selective olefin and Sharpless asymmetric dihydroxylation as the pivotal reactions (Scheme 32). Besides, regioselective sulfonylation of diol **157** at the α-position of the ester was also necessary for the synthesis. Prior to Sudalai's synthesis, Bittman [62] employed a similar synthesis of **16** *via* the common intermediate **156** from 1-hexadecene. Sharpless dihydroxylation reaction was utilized twice by Bittman to install the three continous stereogenic centers in **16**. Minor difference from Sudalai's strategy was that the synthesis of α-aizdoester **158** was carried out through regioselective α-azidation of the cyclic sulfate of dihydroxyl ester **157**. This strategy was also sucessfully employed by Bittman to synthesize D-*erythro*-sphingosine (**1**) commencing with 1-pentadecyne.



Scheme 32 Syntheses of tetraacetyl-D-*ribo*-phytosphingosine (**16**) and D-*erythro*-sphingosine (**1**).

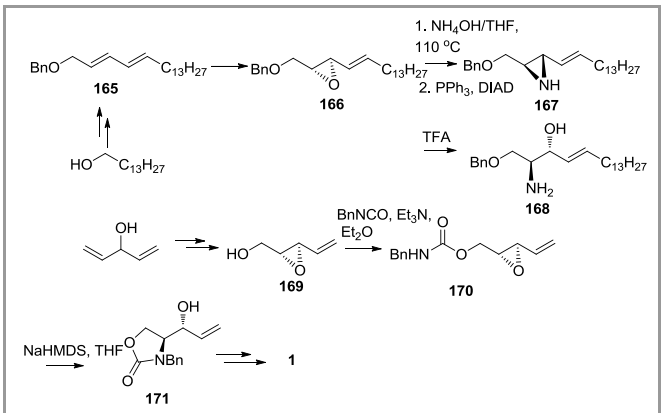
Matheu has reported efficient and high-yielding syntheses of D-*erythro*-sphingosine (**1**) and D-*ribo*-phytosphingosine (**2**) *via* common cyclic sulfate intermediate **164** over 7 steps in 44%, 53% overall yield, respectively (Scheme 33). [64] The desired chirality was obtained by dynamic kinetic resolution of butene epoxide and sequential Sharpless hydroxylation. Elimination of compound **164** gave compound **1**, on the other hand, ring-opening by BzOH, $CsCO_3$ further provided compound **2**.



Scheme 33 Syntheses of D-*erythro*-sphingosine (**1**) and D-*ribo*-phytosphingosine (**2**) from butadiene monoepoxide.

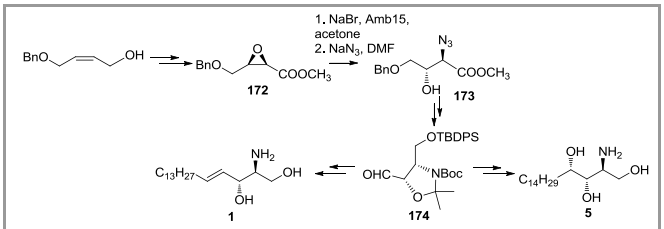
4.2 Sharpless epoxidation and Shi's epoxidation reaction

Somfai *et al* [65] has reported the synthesis of Bn-protected D-*erythro*-sphingosine (**168**) utilizing Shi's epoxidation, regioselective opening reactions of vinyl epoxide **166** and vinylaziridine **167** in the allylic position as crucial steps (Scheme 34). Notably, no regioseletivity was observed during Shi's epoxidation of diene **165** so as to give a mixture of 2,3-epoxy olefin **166** and 4,5-epoxy olefin. Later, Somfai *et al* described an improved strategy to synthesize D-*erythro*-sphingosine (**1**) from divinylcarbinol over 5 steps in 51% overall yield. Highlight of the strategy was Sharpless epoxidation, subsequent Payne rearrangement, a regioselective ring-opening reaction and *E*-selective cross-metathesis for chain extension.



Scheme 34 Syntheses of Bn-protected D-*erythro*-sphingosine (**168**) and D-*erythro*-sphingosine (**1**).

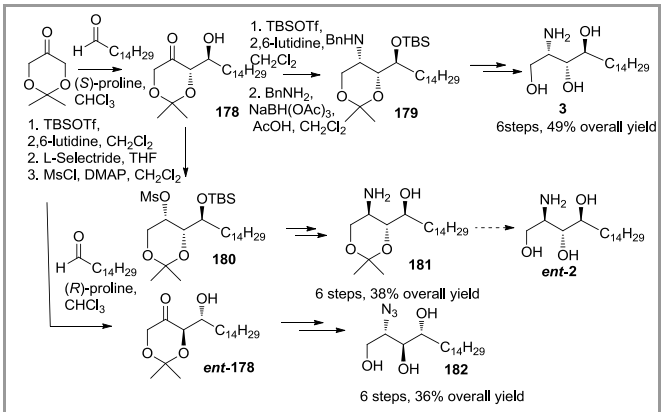
Righi *et al* [66] has described an efficient approach to synthsize D-*erythro*-sphingosine (**1**) and D-*lyxo*-phytosphingosine (**5**) based on Wittig olefination, stereoselective addition of the common aldehyde **174**, respectively (Scheme 35). The aldehyde **174** was derived from (*Z*)-4-benzyloxy-2-buten-1-ol employing Sharpless epoxidation and following regioselective ring-opening reactions as key steps. Notably, Wittig olefination of **174** didn't gave *trans* olefin in a satisfactory selectivity (*E*/*Z*=7/3).



Scheme 35 Syntheses of D-*erythro*-sphingosine (**1**) and D-*lyxo*-phytosphingosine (**5**) from (*Z*)-4-benzyloxy-2-buten-1-ol.

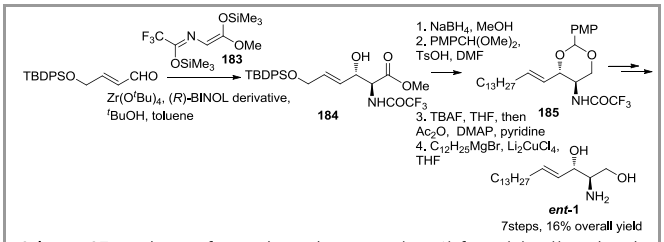
4.3 Asymmetric aldol reaction

In 2006, Enders's group [67a] reported concise and straightforward syntheses of D-*arabino*-phytosphingosine (**3**) and protected L-*ribo*-phytosphingosine (**181**) *via* the common ketone **178** with 6 steps in 49%, 38% overall yield, respectively (Scheme 36). The stereogenic centers at C3, C4 positions were introduced by (*S*)-proline-catalyzed aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one and pentadecanal with excellent diastereo- and enantiomeric excess (>99%, 95% respectively). While the configuration at C2 position was installed by stereoselective reduction of ketone. To improve the diastereoselectivity during the reduction, hydroxyl group at C4 position was protected as its silyl ether. On the other hand, the adol reaction was catalyzed by (*R*)-proline giving compound ***ent*-178** with 59% yield and good diastereo-and enantioselectivity (>99%, 95% respectively), and compound ***ent*-178** further converted into D-*ribo*-azidophytosphingosine (**182**).[67b]



Scheme 36 Syntheses of D-*arabino*-phytosphingosine (**3**), protected L-*ribo*-phytosphingosine (**181**) and D-*ribo*-azidophytosphingosine (**182**) from 2,2-dimethyl-1,3-dioxan-5-one.

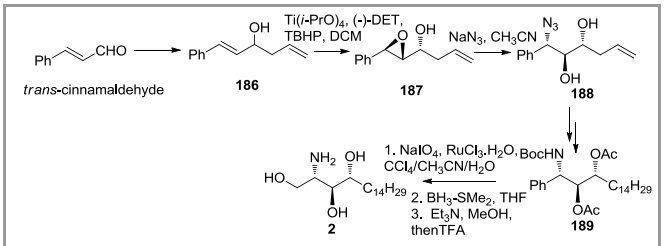
Kobayashi [68] has reported an efficient synthesis of L-*erythro*-sphingosine (***ent*-1**) from (*E*)-4-((tert-butyldiphenylsilyl)oxy)but-2-enal over 7 steps with 16% overall yield. The key steps involve a chiral zirconium complex catalyzed aldol reaction of aldehyde by silicon enolate **183** and cross coupling of acetate with Grignard reagent (Scheme 37). Notably, the aldol reaction successfully introduced the desired chiral hydroxyl and amino groups of compound **184** in a high yield (95%) and moderate stereoselectivity (*anti*/*syn*=8/2).



Scheme 37 Synthesis of L-*erythro*-sphingosine (***ent*-1**) from (*E*)-4-((tert-butyldiphenylsilyl)oxy)but-2-enal.

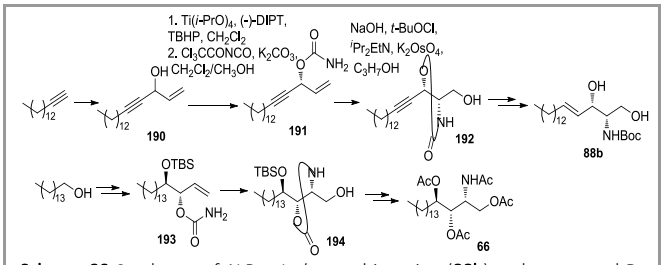
4.4 Sharpless kinetic resolution

Barua [69] has reported a facile and flexible synthesis of D-*ribo*-phytosphingosine (**2**) from achiral *trans*-cinnamaldehyde over 13 steps in 15.6% overall yield (Scheme 38). The stereocenters at C3, C4 positions were obtained by Sharpless kinetic resolution of homoallylic alcohol **186**, while the stereocenter at C2 postion was obtained by a regioselective epoxide-opening reaction. Another highlight of the synthesis was oxidative cleavage of phenyl ring by $NaIO_4$/ $RuCl_3{\cdot}H_2O$.



Scheme 38 Synthesis of D-*ribo*-phytosphingosine (**2**) from *trans* cinnamaldehyde.

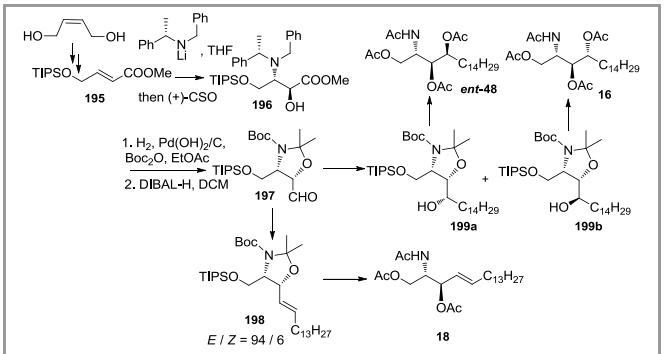
Like Barua's protocol, Kumar [70] has also employed Sharpless kinetic resolution to introduce the stereocenter at C3 postion in the syntheses of *N*-Boc-L-*threo*-sphingosine (**88b**) and tetraacetyl-D-*arabino*-phytosphingosine (**66**) (Scheme 39). And the *syn* stereochemistry of amino group at C2 position was installed by a tethered aminohydroxylation in a moderate yield (65-66%). Both compound **88b** and **66** were synthesized over 8 steps in 8%, 11% overall yield, respectively.



Scheme 39 Syntheses of *N*-Boc-L-*threo*-sphingosine (**88b**) and tetraacetyl-D-*arabino*-phytosphingosine (**66**) from 1-pentadecyne and 1-pentadecanol, respectively.

4.5 Asymmetric aminohydroxylation and amination

In 2008, Davies *et al* reported divergent and efficient syntheses of *N*,*O*,*O*-triacetyl-D-*erythro*-sphingosine (**18**), tetraacetyl-D-*lyxo*-phytosphingosine (***ent*-48**) and tetraacetyl-D-*ribo*-phytosphingosine (**16**) from the common intermediate oxazolidine aldehyde **197** (Scheme 40). [71] Wittig olefination of oxazolidine aldehyde **197** leaded to give compound **18**, and the *E*-selectivity (*E*/*Z*=94/6) was carried out by quenching the reaction with methanol. On the other hand, addition of compound **197** by Grignard reagent gave a 90:10 mixture of alcohol **199a** and **199b**, which further converted into compound ***ent*-48** and **16**, respectively. Highlight of the protocol was highly diastereoselective conjugate addition of unsaturated ester **195** followed by *in situ* enolate oxidation with (camphorsulfonyl)oxaziridine (CSO).

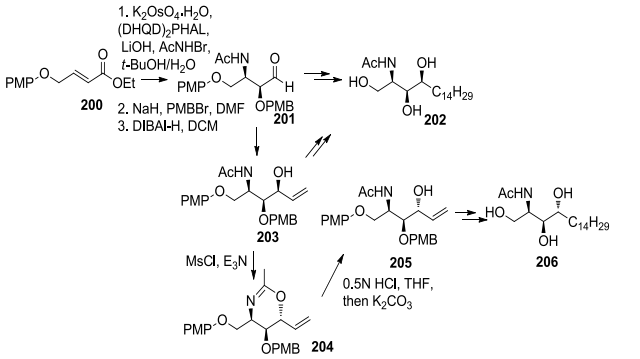


Scheme 40 Syntheses of *N*,*O*,*O*-triacetyl-D-*erythro*-sphingosine (**18**), tetraacetyl-D-*lyxo*-phytosphingosine (***ent*-48**) and tetraacetyl-D-*ribo*-phytosphingosine (**16**) from *cis*-but-2-ene-1,4-diol.

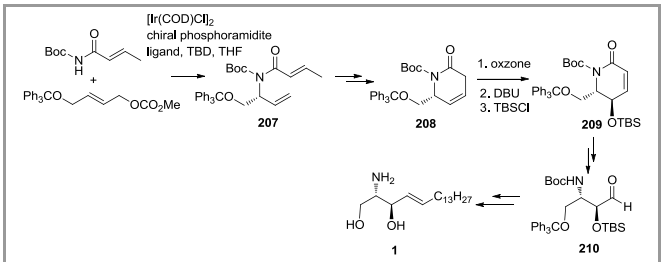
Same as Davies's protocol, Han [72] also employed an asymmetric aminohydroxylation reaction of α,β-unsaturated ester **200** to introduce the stereocenters at C2, C3 postions with high regioselectivity (>20:1) and enantioselectivity (>99%). While the stereochemistry at C4 position was set by a high diastereoselective (>10:1) addition of aldehyde **201** by Grignard reagent. Thus, *N*-acetyl L-*xylo*-phytosphingosine (**202**) was obtained with 5 steps in 22% overall yield (Scheme 41). An alternative synthesis of **202** could also be achieved through a two-step manipulation on compound **203**. On the other hand, the stereochemical interconversion of the hydroxyl group at C4 postion was carried out by treatment of compound **203** with MsCl/Et_3N *via* oxazine intermediate **204**, which further converted into *N*-acetyl L-*arabino*-phytosphingosine (**206**).

In 2013, Helmchen [73] reported a novel synthesis of D-*erythro*-sphingosine (**1**) in 9 linear steps and 5% overall yield (scheme 42).

Highlight of the scheme was a chiral iridium-catalyzed allylic amination to set the chiral carbamate **207** in a high yield (87%) and enantioselectivity (98%). The other pivotal reactions involved ring-closing metathesis (RCM) and stereoselective epoxidation-regioselective elimination reaction.



Scheme 41 Syntheses of *N*-acetyl L-*xylo*-phytosphingosine (**202**) and *N*-acetyl L-*arabino*-phytospchingosine (**206**) from α,β-unsaturated ester **200**.



Scheme 42 Synthesis of D-*erythro*-sphingosine (**1**) from *N*,*N*-diacylamine.

5 Conclusions

Sphingosines and phytosphingosines have drawn increased attention from the synthetic chemists' community in recent years because of their various physiological activities. Two key points of theses syntheses were introduction of stereochemistry and extension of a long aliphatic chain. Chiral pool approaches, chiral auxiliary and asymmetric reactions are the three main strategies to set stereogenic centers. Among them, chiral pool strategy which was concise and efficient with short synthetic route, high yield, and high optical purity usually seemed to be more acceptable. Meanwhile, chiral auxiliary and asymmetric reactions provided candidate strategies to synthesize sphingosines and phytosphingosines from various starting materials, which could be more flexible and straightforward in some cases. And the protocol for chain elongation often employed Wittig olefination, olefin cross metathesis and nucleophilic addition by Grignard reagent. The protocols with higher yield, shorter synthetic route, higher enantioselectivity, higher diastereoselective, and better versatility for the syntheses of the library of sphingosines and phytosphingosines are still expected in future.

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