A New Strategy for the Synthesis of Sphingosine Analogues. Sphingofungin F

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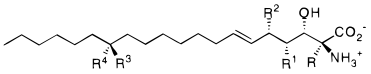
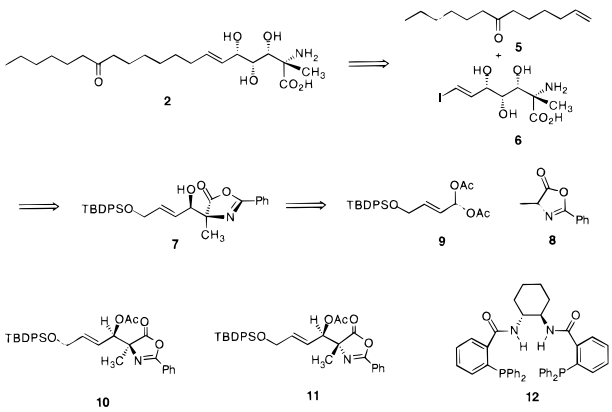
Sphingosines, compounds consisting of polar polyhydroxyl amino head groups and long lipid chains, are membrane constituents involved in a number of cellular events including protein binding (GPI anchors) and transmembrane signaling.[1] A related series of compounds wherein the primary alcohol is oxidized to a carboxylic acid such as sphingofungin B (**1**)[2] or possesses a



1 R=H, R^1=R^2=R^3=OH, R^4=H
2 R=CH_3, R^1=R^2=OH, R^3=R^4=O
3 R=CH_2OH, R^1=OH, R^2=H, R^3=R^4=O
4 R=CH_2OH, R^1=R^2=H, R^3=R^4=O

quaternary center such as sphingofungin F (**2**)[3] were found to inhibit the biosynthesis of sphingolipids due to their activity as serinepalmitoyl transferase inhibitors.[4] These compounds are also strikingly similar to myriocin (**3**),[5] a compound shown to be 10−100 times more potent than cyclosporin A.[6] Mycestericin D (**4**), a deoxy analogue, and its dihydro and 3-*epi* isomer have also been isolated.[7] The biological importance of these compounds stimulated a number of synthetic efforts largely making use of the "chiral pool".[8] The difficulties of creating quaternary centers asymmetrically in catalytic procedures and the noted biological activity of these analogues led us to develop a general strategy to this series. We now report the successful realization of a concise synthesis of sphingofungin F in which all stereochemistry emanates from a new asymmetric alkylation in which an asymmetric palladium complex differentiates between enantiotopic leaving groups of a *gem*-diacetate and enantiotopic faces of an azlactone enolate.

Scheme 1. Retrosynthetic Analysis



Scheme 1 illustrates the retrosynthetic analysis whereby the major disconnection splits the molecule into the lipid tail **5** and the polar head **6**, the latter being the challenging fragment. If two of the hydroxyl groups derive from a distereoselective *cis*-dihydroxylation, the serine analogue **7** becomes a precursor. The stereochemistry of the C-3 hydroxyl group was inverted from the natural product to address the known effects of such allylic functionality on the diastereoselectivity of the osmium catalyzed dihydroxylation.[9] Such quaternary serine analogues **7** may derive from our newly developed asymmetric alkylation of azlactones with *gem*-diacetates, in this case requiring **8** and **9**, respectively.[10,11]

The *gem*-diacetate **9**, derived from the corresponding known aldehyde,[12] is available in two steps from commercially available *cis*-2-butene-1,4-diol, in quantitative yield by ferric chloride (0.1 mol%) catalyzed addition of acetic anhydride.[11] The Pd catalyzed alkylation must control both relative and absolute stereochemistry. For example, by using triphenylphosphine as the ligand, the two diastereomers **10** and **11** (as their racemates) are formed in a 1:1.6 ratio at room temperature. Thus, the chiral ligand must override the intrinsic bias of the substrates to provide **7**.

Performing the alkylation of the sodium salt of the azlactone **8** (NaH, THF) and *gem*-diacetate **9** with the catalyst derived from π-allylpalladium chloride dimer (0.5%) and ligand **12**[13] (1.5%)

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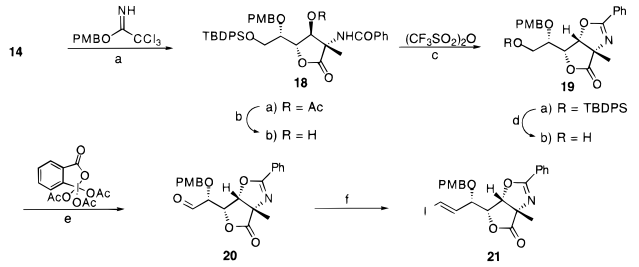
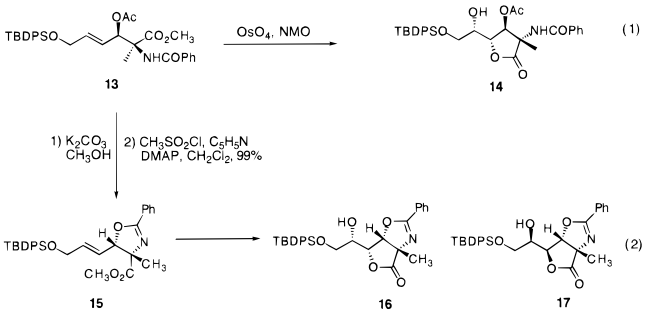
Scheme 2. Asymmetric Synthesis of Polar Head Group from **14**



a) CSA, CH_2Cl_2, rt, 96%. b) K_2CO_3, CH_3OH, 0°C, 93%. c) C_5H_5N, DMAP, DCE, 83°C, 96%. d) TBAF, THF, rt, 99%. e) $NaHCO_3$, CH_2Cl_2, 0°C. f) $CrCl_2$, CHI_3, THF, 0°C, 68% overall from **19b**.

at −5 °C in THF gave a 10.5:1 ratio of **10** and **11**, isolated in 70% and 5% yields respectively. Both diastereomers have an ee of 89% as determined by chiral HPLC. Methanolysis (1% CSA or *p*-TsOH, CH_3OH, room temperature) of **10** gave a quantitative yield of the protected amino acid **13**. Dihydroxylation of alkene **13** (eq 1, 2% OsO_4, NMO)[14] proceeded best in moist methylene chloride to give a single product **14** in which the initial diol spontaneously lactonized. In contrast to the excellent diastereo-

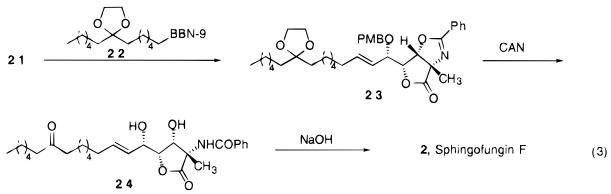


selectivity in the dihydroxylation of **13** to give **14**, inverting the C-3 hydroxyl group first to form **15** and then performing the dihydroxylation (eq 2) gave a 1:5 ratio of **16** and **17** in 95% yield. Asymmetric dihydroxylation (AD-mix-α)[15] was unable to overcome this latter substrate controlled diastereoselectivity (1:2.3, 100% yield).

The relative stereochemistry of **17** was established by X-ray crystallography and therefore allows the assignment of the minor lactone as shown in **16**. Correlation of **14** with **16** therefore establishes the relative configuration of **14**.[16] The absolute configuration for asymmetric alkylations of **9** was established by the *O*-methyl mandelate method[17] and, in this case, was ultimately verified by correlation of our synthetic product to the natural material.

Scheme 2 outlines the synthesis of the fully elaborated head fragment. Setting the proper configuration at C-3 was achieved by inversion with neighboring group participation by simple activation of the hydroxyl group of **18b**, which directly formed oxazoline **19a**. The aldehyde **20** underwent the iodomethylenation with low valent chromium to generate the *E*-alkene **21** exclusively.[18]

The final stage of the synthesis (eq 3) added all of the remaining carbon atoms by Suzuki cross-coupling (5% (dppf)$PdCl_2$, 5% Ph_3As, Cs_2CO_3, DMF−THF−H_2O, room temperature)[19] with the organoborane **22** formed *in situ* by hydroboration of the ethylene ketal of alkene **5** (derived in 3 steps from commercially available heptanoyl chloride)[20] to give alkene **23** in 94% yield. Oxidative



cleavage of the PMB group (CAN, CH_3CN, H_2O, room temperature, 93% yield) effected simultaneous hydrolyses of the ketal and the oxazoline to give keto alkene **24**. Base hydrolysis (1 N NaOH, reflux) and neutralization with Amberlite IRC-76 produced sphingofungin F, mp 143−5 °C (lit. mp 142−4 °C), identical spectroscopically to the natural product. Our $[\alpha]_D$ of +0.99 (*c* 0.25, CH_3OH) compared to the reported $[\alpha]_D$ +0.8 (*c* 0.33, CH_3OH) confirms the identity of the absolute configuration.

The efficiency of this synthesis is noted in that it requires only 15 linear steps from commerically available *cis*-2-butene-1,4-diol and proceeds in 17% overall yield. All the stereochemistry derives from that established in the asymmetric palladium catalyzed alkylation. It is noteworthy that the route provides ready access to a number of diastereomers. For example, the epimer at C-3 would derive by taking **14** through the synthesis without inversion. Access to **17** provides the epimers at C-4 and C-5. Variation of the azlactone would also allow variation of the alkyl substituent. Finally, the lipid tail can readily be varied in the cross-coupling reaction. The success of the palladium-catalyzed alkylation demonstrates a high level of catalyst control of diastereoselectivity, further demonstrating the potential selectivity that the complexes bearing these bidentate ligands like **12** may exert beyond enantioselectivity.

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Supporting Information Available: Experimental procedures and characterization data for **10**, **11**, **13**−**19**, **21**, **23**, **24**, and **2** (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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