An Improved, Versatile and Easily Scalable Synthesis of Sphingomyelins: Application to Stable Isotope Labelling

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$^1$H NMR Spectrum of 3
(500 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^{13}$C NMR Spectrum of 3

(125 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^1$H NMR Spectrum of 4

(500 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^{13}$C NMR Spectrum of 4

(125 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^1$H NMR Spectrum of 5

(500 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^{13}$C NMR Spectrum of 5  

(125 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^1$H NMR Spectrum of 6

(500 MHz, CDCl$_3$)
$^{13}$C NMR Spectrum of 6

(125 MHz, CDCl$_3$)
$^1$H NMR Spectrum of 7

(500 MHz, CDCl$_3$)
$^{13}$C NMR Spectrum of 7

(125 MHz, CDCl$_3$)
$^1$H NMR Spectrum of 8

(500 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^{13}$C NMR Spectrum of 8

$(125 \text{ MHz}, \text{CDCl}_3 / \text{CD}_3\text{OD 50:50})$
$^1$H NMR Spectrum of 9

(500 MHz, CDCl$_3$ / CD$_3$OD 50:50)
$^{13}$C NMR Spectrum of 9

(125 MHz, CDCl$_3$ / CD$_3$OD 50:50)
IR Spectrum of 8 ATR Diamond
Specific correlations between *cis* protons (green arrows: H1b with H2, H2 with H3) support the erythro configuration of compound 9.
Synthesis of azidosphingosine 1

The starting material 1 was synthesised according to published procedures as presented below.

D-galactose 11 was first converted into the acetal 12 (yield: 52%) by using camphor sulfonic acid\(^1\) as a more efficient catalyst than zinc chloride (yield: 13%)\(^2\).

The acetal 12, purified by crystallisation, was oxidized quantitatively to aldehyde 13 (in equilibrium with the dimeric form 14) as described.\(^2,3\)

Olefination of mixture 13/14 was achieved using phenyl lithium (2 eq.) generated from bromobenzene and metallic lithium prior to the addition of solid lithium bromide (4 eq.). This solution was added at -30°C in 15 minutes to a suspension of the phosphonium in toluene, then stirred for 45 minutes before letting the mixture warm between -10/-20°C. A solution of 13/14 in THF was then added slowly (30 minutes) at -15°C. The temperature was kept at this value in order to obtain a high E isomeric excess of the Wittig product. The reaction was then stirred under these conditions for 2h30 and quenched with methanol before usual work-up to give olefin 15 as a mixture of E/Z diastereomers.\(^2,3\) Finally, this mixture was subjected to two chromatographic steps on standard silica gel: the first (pentane/diethyl ether...
8:2) was designed to isolate the mixture of diastereomers and the second (toluene/diethyl ether 9:1) to obtain pure 15 (E/Z ratio : 98:2).

The subsequent steps leading to azidosphingosine 17 were carried out as described.³ Finally, the TBDPS protecting group proved to be a better choice than the more popular trityl³ to get the final 4-O-benzyl derivative 1 as its removal proceeded under smoother conditions. However, the last step must be performed at -25°C to avoid benzyl group migration from the secondary to the primary alcohol function.⁴

The overall yield over nine synthetic steps was 15%.

References: