Serinal-derived vinyl oxiranes as novel and versatile building blocks for the stereoselective synthesis of D- and L-*erythro*-sphingosines

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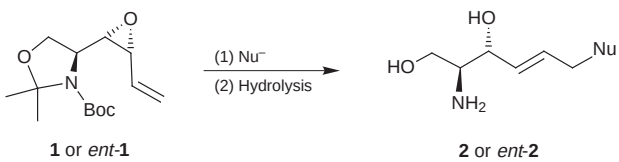
Oxazolidine vinyl oxirane 1, a novel and highly versatile building block for the preparation of enantiopure D-(+)-*erythro*-sphingosine and analogues, has been prepared by chloroallylboration of the Garner aldehyde with absolute stereocontrol and in good yield.

Over the last decade, interest in the biological functions of sphingosine, and its derivatives, has increased dramatically. While ceramide has been shown to be an important regulatory component of programmed cell death,[1] sphingosine-1-phosphate (SPP) has been implicated as a secondary messenger in cell proliferation and survival.[2] In addition, sphingosine and its N-methylated derivatives were found to be involved in cell signalling,[3] the induction of cancer cell apoptosis[4] and in the regulation of inflammatory processes.[5] Since the biological activity of these molecules varies substantially with structural modifications of the alkyl side chain,[6] unnatural and functionalized sphingosines are an inviting target for synthesis.

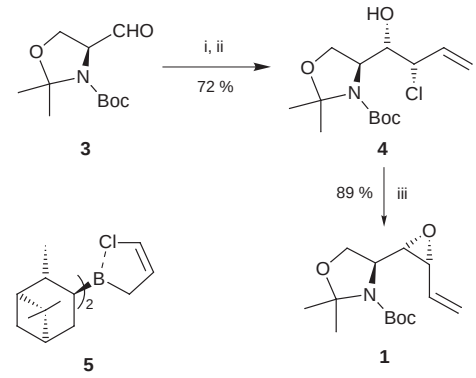
Many protocols for sphingoid base synthesis have been reported.[7] However, a versatile building block, easily accessible in high optical purity, that may be linked to a large variety of functionalized residues has not been available to date. Here, we report the synthesis of such a precursor, vinyl oxirane **1**, that leads directly to isomerically pure protected sphingoid bases, without the need for further synthetic manipulations of the side chain (Scheme 1).

Following the protocol of Oehlschlager, readily available and configurationally stable L-Garner aldehyde **3**[8] was alkylated with an *in situ* formed γ-(*Z*)-chloroallyl-(+)-diisopinocampheylborane **5**[9] to give chlorohydrin **4** in good yield (72% after cleavage of the borinic ester with 8-hydroxyquinoline,[10] 68% after buffered oxidative work-up[11]) (Scheme 2). Subsequent treatment of **4** with a sterically hindered base (DBU) provided vinyl oxirane **1** in high yield under mild conditions.[12] Analyses of ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showed the relative diastereoselectivity to be higher than 97:3 (*anti*:*syn*), which clearly resulted from matched stereochemical bias of the double diastereoselection. With achiral γ-chloroallyl-BBN,[9] similar diastereospecificity was observed, resulting from substrate controlled *si*-facial attack of the allylation reagent. Thus, use of 9-MeO-9-BBN is an inexpensive alternative to the pinene-based borane, provided that a slightly lower degree of diastereoselection (*anti*:*syn* = 95:5), and the formation of *trans*-**1** (4%) as a by-product, is acceptable. Irrespective of the borane used, the entire sequence could be conducted as a 'one-pot' synthesis with an overall yield of 48–57% starting from **3**. Moreover, the protocol does not require tedious purification of any of the intermediates between commercially available serine and the vinyl oxirane building block **1**, and is suitable for multigram synthesis.[8] Upon recrystallisation of the crude product, colourless needles [mp 49–50.5 °C (pentane–Et_2O = 1:1 v/v)]; $[\alpha]_D^{25}$ +40.37 (*c* 1.08, $CHCl_3$)] were obtained and, in all cases, only a single isomer could be detected by NMR spectroscopy. The ORTEP plot (Fig. 1) shows the X-ray structure‡ of vinyl oxirane **1**. The crystal structure shown and semiempirical calculations of the energy minimised conformation of **1** (data not shown) proved to be in good agreement. Both the ORTEP and energy minimised plots



1 or *ent*-**1** **2** or *ent*-**2**

Scheme 1



Scheme 2 *Reagents and conditions*: i, (+)-Ipc_2BOMe (or 9-MeO-9-BBN), allyl chloride, Et_2O, Cy_2NLi, THF, $BF_3{\cdot}OEt_2$, −100 °C; ii, 8-hydroxyquinoline, MeOH or H_2O_2, $NaHCO_3$ buffer; iii, DBU, CH_2Cl_2, 0 °C

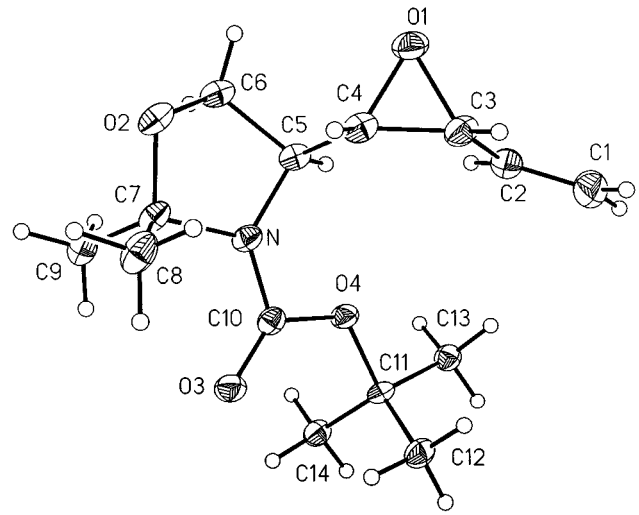


Fig. 1 The molecular structure of vinyl oxirane **1** (ORTEP plot) showing the absolute stereochemistry. Selected bond lengths (Å) and angles (°): C(2)–C(3) 1.472(3), C(3)–C(4) 1.478(3), O(1)–C(4) 1.444(2), O(1)–C(3) 1.461(2); C(4)–O(1)–C(3) 61.1(1), O(1)–C(3)–C(2) 116.0(2), O(1)–C(3)–C(4) 58.8(1), O(1)–C(4)–C(3) 60.0(1), O(1)–C(4)–C(5) 115.3(2); C(1)–C(2)–C(3)–C(4) −159.2(1).

demonstrated that the vinyl oxirane moiety is exposed in such a fashion that nucleophiles, for example lower order or hetero-cuprate reagents, would be predicted to react preferentially *via* a S_N2' type nucleophilic substitution. Electronic and steric factors are expected to determine the initial cuprate–olefin complex, leading to an *anti*-γ σ-allyl cuprate intermediate that suffers reductive elimination to yield the desired S_N2' *E*-configured product.[13]

In fact, excellent selectivity was observed upon treatment of **1** with an *in situ* prepared organocuprate as depicted in general in Scheme 1. Introduction of the alkyl side chain occurred smoothly and proceeded with exclusive formation of the (*E*)-double bond according to ^{13}C and ^{1}H NMR analysis. For the synthesis of native C_{18}-sphingosine,[7] dodecyl bromide was subjected to Br–Li exchange with Bu^{t}Li in Et_2O at −100 °C, followed by transmetallation with CuCN. Coupling of the resulting cuprate with vinyl oxirane **1** provided the protected sphingosine as a single diastereomer in high yield (82%).[14] The free sphingoid base was liberated by mild acid hydrolysis.§ Since cuprates containing sensitive functional groups are readily available by transmetallation of organozinc precursors, this approach promises to be a particularly simple route to a wide range of native and modified sphingosines, under exceptionally mild conditions (*e.g.* for the introduction of isotopes or their attachment on stationary phases for affinity chromatography).

In conclusion, the isomerically pure key intermediate **1** (or *ent*-**1**) is readily available from D- or L-serine on a large scale. This versatile reagent should find general use in the stereoselective synthesis of natural products with special emphasis on D- and L- sphingoid bases and nitrogen heterocycles,[15] which are often difficult and time-consuming to prepare *via* published protocols. Methods for the *syn*-selective chloroallylation of **3** are also under investigation with a view to making the *threo*-series of sphingoid bases equally accessible.

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Notes and References

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‡ *Crystal Data* for **1**: $C_{14}H_{23}NO_4$, M = 269.33 g mol^{-1}, colourless prism, size 0.30 × 0.28 × 0.24 mm^3, orthorhombic, space group $P2_12_12_1$, a = 5.7136(2), b = 9.9806(5), c = 26.526(1) Å, V = 1512.6(1) Å^3, T = −90 °C, Z = 4, ρ_{calc} = 1.183 g cm^{-3}, μ(Mo-Kα) = .86 cm^{-1}, F(000) = 584, 4084 reflections in h (−6/6), k (−11/11), l (−29/29), measured in the range $2.18 \leqslant \theta \leqslant 23.25°$, 2136 independent reflections, R_{int} = 0.0347, 2004 reflections with $F_o > 4\sigma(F_o)$, 265 parameters, R_{obs} = 0.0315, wR^2_{obs} = 0.0785, GOOF = 1.043, Flack-parameter 2(1), largest difference peak and hole: 0.123/−0.143 e Å^{-3}. For the data collection, a Nonius KappaCCD using graphite-monochromated Mo-Kα radiation was used. Data were corrected for Lorentz and polarisation effects. The structure was solved by direct methods (SHELXS) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-93). All hydrogen atoms were located by difference Fourier synthesis and refined isotropically. The non-hydrogen atoms were refined anisotropically. XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations. The absolute stereochemistry was not determined crystallographically. CCDC 182/961.

§ *Reagents and conditions*: i, $C_{12}H_{25}Br$, Et_2O, Bu^{t}Li, −100 °C, then CuCN, −40 °C; ii, 1 M HCl, THF, room temperature.

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