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Synthesis of (2*S*,3*R*,4*E*,8*E*)-9-methyl-4,8-sphingadienine via a novel S_N2' type reaction mediated by a thioether carbanion

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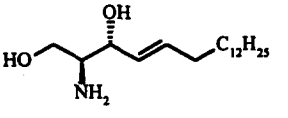
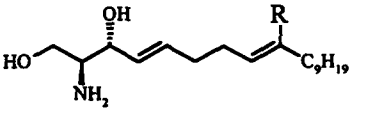
Abstract

A stereoselective synthesis of sphingadienine **3** as a new analogue of sphingosine has been achieved by a novel copper-catalyzed S_N2' type homoallylic coupling reaction between an allylic mesylate and a thioether-stabilized allylic carbanion.

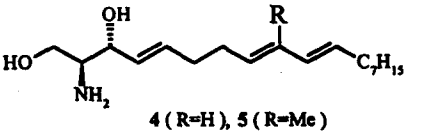
Sphingosine **1** and its analogues are the backbone components of ceramides, constituents of the cell membrane. Ceramides play a key role as secondary messengers in many biological processes such as cellular defense/repair mechanisms and apoptosis.[1] Since the discovery of sphingosine as a potent inhibitor of protein kinase C (PKC) both in vivo and in vitro,[2] its synthesis has been widely reported.[3] However, the syntheses of the diene and triene analogues (**2–5**) which were also isolated from natural sources have received very little attention.[4,5] Owing to the ever increasing importance of sphingolipids and their metabolites in cell membrane research, we have focused our efforts on the synthesis of these sphingosine analogues. In this communication, we report the synthesis of sphingadienine **3** via a novel homoallylic coupling reaction of allylic mesylate **6**[6a] with an allylic metal reagent (Scheme 1).



Sphingosine **1**



2 (R=H), **3** (R=Me)



4 (R=H), **5** (R=Me)

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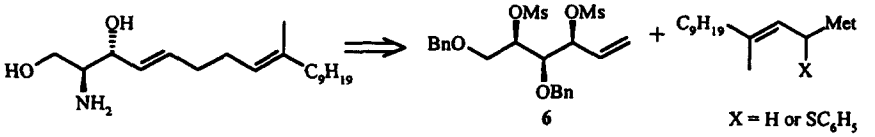
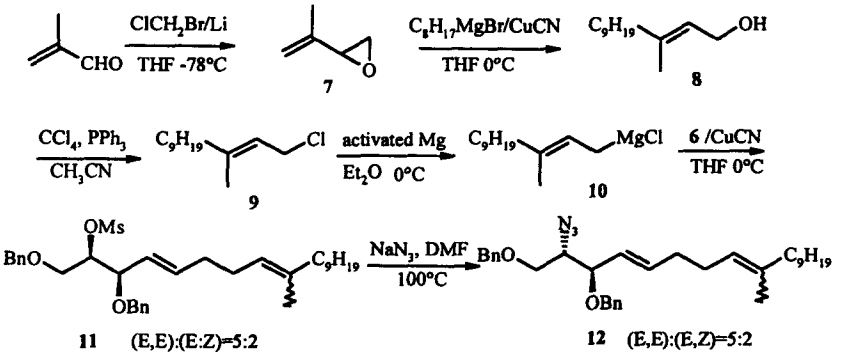


Scheme 1.

During the last decade, copper-catalyzed S_N2 and S_N2' reactions between Grignard reagents and allylic substrates have been extensively studied and widely used in the syntheses of sphingosines.[6] However, application of the copper-mediated homoallylic coupling reaction between allylic substrates in stereoselective synthesis is complicated by rapid isomerization of the allylic carbanion, even at low temperature. The key to the successful application of this homoallylic coupling reaction to the synthesis of sphingadienine **3** was to retain the configuration of the allyl anion during the reaction.

Stereoselective introduction of the *E*-configuration of the double bond in allylic alcohol **8** was readily achieved by a copper-catalyzed S_N2' type reaction of a Grignard reagent with the oxirane **7**[7] which was prepared using a modified procedure by reacting methacrolein with a halomethyllithium.[8] Reaction of the crude oxirane **7** with octylmagnesium bromide in the presence of CuCN (5 mol%) gave almost exclusively the desired alcohol **8** in 88% yield with only traces of the *Z*-isomer.[7b] The (*E*)-alcohol **8** was converted to (*E*)-chloride **9** in high yield (97%) by treatment with triphenylphosphine and carbon tetrachloride in acetonitrile. The crude product was purified by Kugelrohr distillation because of its instability on a silica gel column.

The Grignard reagent **10**, prepared from activated magnesium[9] and allylic chloride **9**, was added to a solution of allylic mesylate **6** in THF at 0°C in the presence of 5 mol% CuCN to afford the homoallylic coupling product **11** in 84% yield. Thus, the generally required 4,5-*trans* C=C bond was constructed with concomitant chain extension in one step. However, ^{1}H NMR showed the diene **11** to be a 5:2 mixture of the *E*- and *Z*-isomers due to the difference of the configuration at the C-8,9 C=C bond (based on the integration of the 9-CH_3 signal appearing at δ 1.58 for the *E*-form and δ 1.67 ppm for the *Z*-form). This mixture of isomers, which resulted from isomerization of the allylic carbanion during the reaction, proved to be difficult to separate by flash chromatography and was therefore treated with sodium azide to give compound **12**, which again turned out to be an inseparable mixture of isomers (Scheme 2).

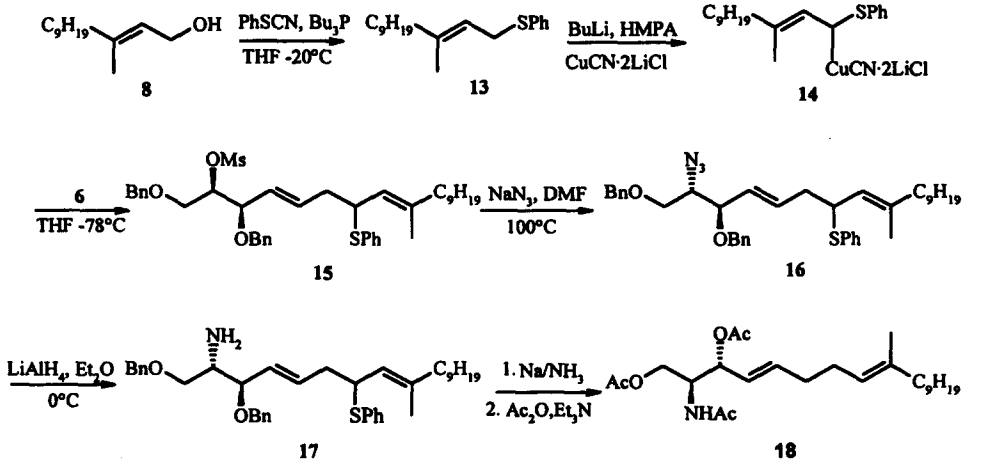


Scheme 2.

In order to minimize or eliminate isomerization of the allylic carbanion during the coupling reaction we then considered the use of allylic carbanion derived from an allylic thioether. Literature studies indicated that thioether-stabilized allylic carbanions have less tendency to interconvert between the *E*- and *Z*-forms at −78°C and this has already found application in terpene chemistry.[10] Although the organocopper reagent is known to be softer than the lithium reagent, the use of heteroatom-substituted

allylic copper reagents in S_N2' type reactions has not been fully exploited.[11] In our synthesis, the alcohol **8** was treated with PhSCN and Bu_3P in THF to give the thioether **13** (98%), which was then deprotonated with butyllithium and converted to the corresponding allylic copper reagent **14** via transmetalation with CuCN·2LiCl or CuI·2LiCl. After examining various reaction conditions, it was found that compound **15** could be readily obtained in excellent yield (89% yield) by adding a solution of **6** to the copper reagent **14** at −78°C. The structure of diene **15** was confirmed by its ^1H NMR and NOESY spectra, where the *trans* C=C bond at C-4,5 was confirmed ($J_{4,5}$=15.4 Hz) while the configuration of the *E*-C=C bond at C-8,9 was retained.

With the key intermediate **15** in hand, it was converted to compound **16** in 78% yield by an S_N2 replacement of the mesylate group with sodium azide. Lithium aluminium hydride reduction of the azide group in **16** quantitatively afforded the corresponding amine **17**, and it was then treated with sodium in liquid ammonia to finish the debenzylation and desulfurization in one step to furnish the final sphingadienine **3**, which was subsequently acetylated to yield the triacetate **18** (84%) for further characterization.[12] We later found that the azide reduction, debenzylation and desulfurization of azide **16** could be accomplished with sodium in liquid ammonia in one step, although with a slightly lower yield (43%) (Scheme 3).



Scheme 3.

In conclusion, sphingadienine **3** has been successfully prepared via a novel S_N2' type homoallylic coupling reaction during which the thioether-stabilized allylic copper reagent retained the configuration of its double bond.

Acknowledgements

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12. Properties of compound **18**: mp 62–63°C. $[\alpha]_D$=–13.8 (*c* 1.13, $CHCl_3$). IR(KBr)ν_{max}: 3290, 2922, 2852, 1736, 1656, 1553, 1375, 1270 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=5.80 (dt, *J*=15.2, 6.4 Hz, 1H, H_5), 5.65 (d, *J*=9.1 Hz, 1H, -NHAc), 5.42 (dd, *J*=15.2, 7.4 Hz, 1H, H_4), 5.30 (dd, *J*=7.0, 5.8 Hz, 1H, H_3), 5.08 (br, 1H, H_8), 4.45 (m, 1H, H_2), 4.30 (dd, *J*=11.6, 6.2 Hz, 1H, H_1), 4.05 (dd, *J*=11.6, 4.1 Hz, 1H, H_1), 2.10 (s, 2×3H, -$OCOCH_3$), 2.0 (s, 3H, -$NHCOCH_3$), 2.15–1.95 (m, 6H), 1.55 (s, 3H, 9-CH_3), 1.25 (br, 14H), 0.90 (t, *J*=6.9 Hz, 3H). MS(EI) *m/z*: 438 (M^++1), 378 (M^+–CH_3CO_2), 318, 102, 84. Anal. calcd for $C_{25}H_{43}NO_5$: C, 68.61; H, 9.90; N, 3.20. Found: C, 68.59; H, 9.96; N, 3.35.