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# A formal synthesis of 3-*O*-(4-methoxybenzyl)-azidosphingosine by a modified Julia olefination

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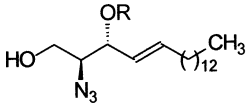
**Abstract**—The stereoselective construction of the D-*erythro*-azidosphingosine characteristic *trans* double bond was accomplished by condensation between tetradecanal and a heterocyclic sulfone derived from diethyl-D-tartrate, following the Kocienski modification of the Julia olefination. 

## 1. Introduction

Glycosphingolipids (GSLs) are characteristic membrane components of eukaryotic cells and they serve a variety of functions either taking part in cell type-specific adhesion processes or acting as binding sites for certain virus or bacterial toxin.[1] Each GLS carries a hydrophobic ceramide moiety and a hydrophilic oligosaccharide chain. Among the synthetic procedures for the coupling of the oligosaccharide part of GSLs to the sphingosine moiety the 'azidosphingosine glycosylation procedure'[2] has been by far preferred over the direct attachment to the oligosaccharide of the preformed ceramide unit or of the sphingosine moiety followed by *N*-acetylation. This strategy, in fact, minimizes the formation of by-products, moreover azidosphingosine is an excellent precursor of sphingosine. A number of syntheses of D-*erythro*-azidosphingosine (**1**), mainly by the asymmetric induction or the 'ex chiral pool' approaches, have been reported.[3] When chiral substrates are used as starting material, the characteristic *trans* double bond is generally generated via Wittig related reactions; unfortunately some preliminary attempts revealed that even the simplest synthetic pathways are not free from problems. A critical revision of the different approaches for the formation of *E* double bond, evidenced the Kocienski modification of the olefination procedure developed by Sylvester Julia as useful for this purpose.[4] During the last years, this methodology has been successfully applied to the synthesis of natural product.[5–10] The original Julia procedure consists in the one-pot formation of alkenes by addition of α-lithiated benzothiazol-2-yl sulfones to aldehydes, but suffers from the fact that stereoselectivities are often low.[11–13] Kocienski found that the replacement of the benzothiazol-2-yl group by a 1-phenyl-1*H*-tetrazol-5-yl moiety leads, in the case of aliphatic aldehydes and sulfones, to *E* alkenes with high selectivities. Furthermore, the stereochemistry of the reaction is influenced by the choice of base and solvent, DME as solvent, and potassium hexamethyldisilazide (KHMDS) as base being the better combination for high *trans* selectivity.[4]

Herein the construction of the 4*E* double bond present in 3-*O*-(4-methoxybenzyl) azidosphingosine (**2**), a coupling partner in GSLs synthesis, using the Kocienski modification of the Julia protocol is reported.




**1.** R = H
**2.** R = MPM

## 2. Results and discussion

Known alcohol **3**,[14] derived from diethyl D-tartrate, was chosen as starting material owing to its D-*threo*-diol structure, suitable to obtain, after nitrogen introduction with inversion of configuration, the natural sphingosine geometry.

In the first attempt, the two partners of the Julia coupling were aldehyde **4**, derived from alcohol **3** by Swern oxidation,[14] and sulfone **5**. Compound **5** was obtained by

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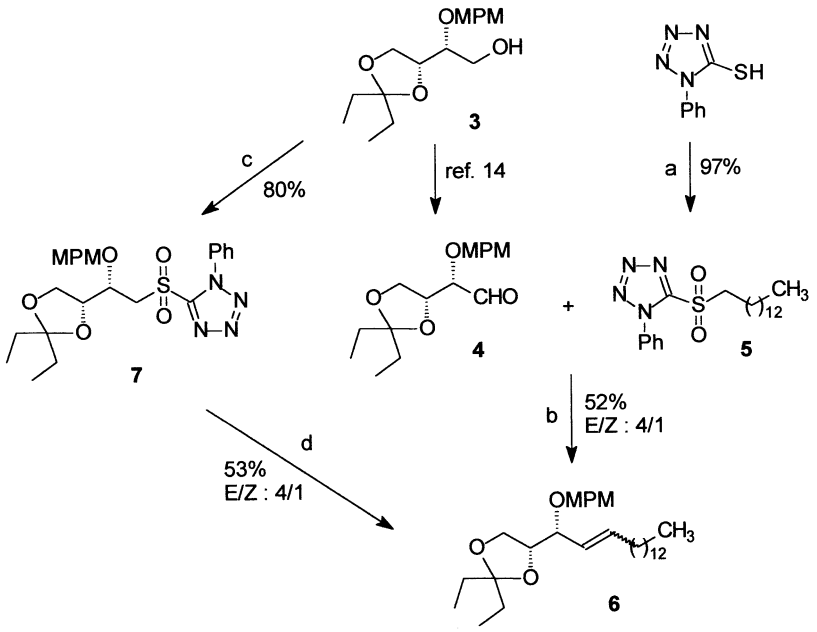


**Scheme 1.** (a) (i) $CH_3(CH_2)_{12}CH_2Br$, $Et_3N$, THF, rt→60°C. (ii) MCPBA, $CH_2Cl_2$. (b) KHMDS, DME, −55°C. (c) (i) 1-phenyl-1*H*-tetrazole-5-thiol, $PPh_3$, DEAD, THF, 40°C. (ii) MCPBA, $CH_2Cl_2$. (d) $CH_3(CH_2)_{12}CHO$, KHMDS, DME, −55°C.

reaction of the commercially available 1-phenyl-1*H*-tetrazole-5-thiol with 1-bromotetradecane, $Et_3N$ in THF to afford the thioether, which was in turn treated with MCPBA in $CH_2Cl_2$ to give the corresponding sulfone **5** in 97% overall yield (Scheme 1). The reaction of metalated tetradecyl sulfone **5** with aldehyde **4** (see Section 4, procedure A), carried out in DME at −55°C by adding the base to a mixture of sulfone and aldehyde, resulted in the stereoselective formation of the desired 4*E* olefin **6** in a reasonable yield (52%, *E*/*Z*, 4:1), but in the complete decomposition of the unreacted starting materials; moreover, a serious drawback of the reaction was the low solubility of sulfone **5** at the reaction temperature. An attempt to carry out the condensation in THF instead of DME, lead on one side to a slight increase of the sulfone solubility, but on the other to lower yields and selectivities.

The good results in term of stereoselectivity stimulated the planning of an alternative pathway ensuring a better solubility of the reaction partners. The switch between sulfone and aldehyde functional groups of the two synthons of the above procedure was devised, leading to a new approach to compound **6**: the coupling between sulfone **7** and commercially available tetradecanal. The synthesis of compound **7** was accomplished as shown in Scheme 1. Alcohol **3** was first converted into the 1-phenyl-1*H*-tetrazole-5-yl thioether under Mitsunobu conditions, and then oxidized to **7** in 75% overall yields. A solution of sulfone **7** in DME at −55°C was treated with KHMDS (1 equiv.) to prove both the complete solubility of **7** and its stability despite the presence of the *p*-methoxybenzyl group in β to the sulfone: the anion of compound **7** was efficiently stabilized by the sulfone group, so that no β-elimination product was formed.[15] Thus compound **7** is a good candidate for the coupling.

After a preliminary screening, the standard Julia procedure was in this second approach preferred over the Barbier-type fashion, that consists in the addition of the base to a mixture of the aldehyde and the sulfone. So, KHMDS (0.5 M in toluene) was added to a solution of sulfone **7** in dry DME at −55°C, followed by the addition of tetradecanal in DME (see Section 4, procedure B). The coupling was carried out different times by varying the equivalents of base (from 1 to 1.5 equiv.) and/or aldehyde (from 1 to 3 equiv.), and the following considerations emerge. First of all, all the tests confirm the good stereoselection of the reaction with these substrates: olefin **6** was always recovered in a *E*/*Z* ratio of 4:1. As far as the reaction yields are concerned, compound **6** was obtained in only acceptable yields (45–53%), but it is worth noting that it has always been possible to completely recover the unreacted sulfone **7**, resulting in nearly quantitative yield based on conversion. The best result (53%) was obtained when 1 equiv. of both the aldehyde and the base were used; in any case the general trend is that it is better to use a stoichiometric quantity of the base, since the only low yield (36%) has been obtained when 1.5 base equivalents were used. The reason why the reaction is not quantitative might be due to a competitive α-deprotonation of the aldehyde by the sulfone anion; in fact, an increase of the aldehyde/sulfone ratio resulted in a decrease of the yield. In order to augment the nucleophilicity of the anion, a more coordinating solvent was tried, but the reaction carried out in THF/DMPU at −70°C resulted in low yields and decomposition of the starting material.

While this work was in progress a relevant publication by Jacobsen[10] appeared; he attained, during a fragment coupling by means of a Kocienski–Julia olefination with a sulfone of the phenyltetrazole series, an high *E*-selectivity with LiHMDS in DMF/DMPU mixture. However, when the Jacobsen's conditions were applied to sulfone **7** and tetradecanal, great solubility problems arose; product **6** was recovered in very low yield (5%), even if a slight increase in the *E*/*Z* ratio was observed (*E*/*Z*, 8.3:1.7). Once again this result shows that is very difficult to generalize the conditions

of Julia olefination leading to high stereoselectivities, since the outcome of the reaction is strictly dependent on the features of the substrates.

Lastly, compound **6** can be efficiently transformed into the target 3-*O*-(4-methoxybenzyl) azidosphingosine (**2**) with the procedure described by Somfai and Olsson.[8]

## 3. Conclusion

A further example of the versatility of the Kocienski modification of the Julia protocol applied, in this paper, to the construction of the *trans* double bond of D-*erythro*-azidosphingosine skeleton has been described. This represents a good alternative to other methods, since it allows the generation of the double bond in high selectivities and permits to recover and recycle all the expensive material of the reaction.

## 4. Experimental

### 4.1. General

Optical rotations were determined on a Perkin–Elmer 241 polarimeter in a 1 dm cell at 20°C. Mass experiments were performed through chemical ionization mass spectrometry (CI-MS) as described in Ref. 16. All NMR spectra were recorded at 303 K with a Bruker AM-500 spectrometer equipped with an Aspect-3000 computer, a process controller, and an array processor in $CDCl_3$ solutions; chemical shifts of NMR spectra are reported as $\delta$ (ppm) relative to tetramethylsilane as internal standard. All reactions were monitored by TLC on Silica Gel 60 F-254 plates (Merck) with detection by dipping in an ammonium molybdate solution followed by heating. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). All evaporations were carried out under reduced pressure at 40°C. Potassium bis(trimethylsilyl)amide (0.5 M in toluene) and tetradecanal were purchased from Fluka; 1-phenyl-1*H*-tetrazole-5-thiol was purchased from Aldrich. Compounds **3** and **4** were obtained as described in Ref. 14.

**4.1.1. 1-Phenyl-5-tetradecylsulfonyl-1*H*-tetrazole (5).** To a solution of 1-phenyl-1*H*-tetrazole-5-thiol (1.25 g, 7.01 mmol) in dry THF (25 mL), $Et_3N$ (1.17 mL, 8.41 mmol) was added, and the mixture stirred at room temperature. After 40 min, 1-bromotetradecane (2.29 mL, 8.41 mmol) was added and the reaction refluxed for 6 h, then diluted with water (40 mL), and extracted with $Et_2O$ (3×40 mL). The combined organic layers were dried and evaporated at reduced pressure to give the crude thioether. MCPBA (55%) (7.70 g, 24.53 mmol) was added in small portions to a solution of the crude thioether in $CH_2Cl_2$ (46 mL) at 0°C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was washed with $NaHSO_3$ (40 mL), and saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried, and the solvent removed by evaporation. The residue was submitted to flash-chromatography (hexane/AcOEt, 95:5) to afford compound **5** (2.76 g, 97%) as a sticky white solid. Mp 55.5–56.5 (from diisopropyl ether). $^1$H NMR: $\delta$ 0.90 (t, 3H, $J$=7.5 Hz, $CH_3$); 1.20–1.40 (m, 20H, $CH_2$); 1.51 (quint, 2H, $J$=7.5 Hz, $CH_2$); 1.96 (m, 2H, $CH_2$); 3.74 (m, 2H, $CH_2$); 7.56–7.74 (m, 5H, arom). $^{13}$C NMR: $\delta$ 14.8; 22.6; 23.4; 28.8; 29.5–30.3 (8C); 32.6; 56.7; 125.8 (2C); 130.4 (2C); 132.1; 133.7; 154.2. MS: $m/z$ 424 $[M+NH_4]^+$. IR (nujol) $\nu_{max}$ 1160, 1340 $cm^{-1}$. $C_{21}H_{34}N_4O_2S$: calcd C 62.04, H 8.43, N 13.78; found C 62.22, H 8.31, N 13.65.

**4.1.2. (2*R*,3*R*)-1,2-*O*-Pentylidene-3-(4-methoxybenzyl)-4-octadecen-1,2,3-triol (6).** *Procedure A*: A 0.5 M solution of KHMDS in toluene (1.55 mL, 0.77 mmol) was slowly added to a mixture of aldehyde **4** (0.13 g, 0.43 mmol) and sulfone **5** (0.23 g, 0.56 mmol) in dry DME (4 mL) at −55°C. The reaction mixture was stirred at −55°C for 30 min, then slowly warmed to room temperature. Water (5 mL) was added, and stirring continued for 30 min. The resulting mixture was extracted with $Et_2O$ (3×5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The crude product was purified by flash-chromatography (hexane/AcOEt, 95:5) to afford **6** (0.11 g, 52%, *E*/*Z*, 8:2) as an oil.

*Procedure B*: A 0.5 M solution of KHMDS in toluene (0.80 mL, 0.40 mmol) was slowly added to a solution of sulfone **7** (0.20 g, 0.40 mmol) in dry DME (2 mL) under argon at −55°C. The solution was stirred for 30 min during which time the color turned yellow. A solution of tetradecanal (0.086 g, 0.40 mmol) in DME (1.6 mL) was added via cannula; the mixture was stirred at −55°C for 15 min, and then quenched by the addition of water and warmed to room temperature. After stirring for 30 min, the mixture was extracted with $Et_2O$. The combined organic layers were washed with brine, dried, and concentrated. Purification by flash chromatography (hexane/AcOEt, 95:5, then 1:1) gave **6** (0.104 g, 53%, *E*/*Z*, 8:2), and sulfone **7** (0.094 g).

Compound **6** was recovered as *E*/*Z* mixture by flash-chromatography (hexane/AcOEt, 95:5). The *E*/*Z* ratio was established through $^1$H NMR analysis by integration of the two doublets centered at 4.38 and 4.39 ppm due to the $OCH_aH_bPh$–OMe proton. The two diastereoisomers were separated by flash-chromatography (toluene/AcOEt, 40:0.5). Elution gave first *E*-**6**: physical data were all in agreement with those reported in Ref. 14, and then *Z*-**6**: $[\alpha]_D$=−14 (*c* 0.3, $CHCl_3$). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 0.80–0.96 (m, 9H, $3CH_3$); 1.15–1.42 (m, 22H, $11CH_2$); 1.55–1.67 (m, 4H, $2CH_2$); 1.96 (m, 2H, $2H_6$); 3.54 (dd, 1H, $J_{1a,1b}$=8.4 Hz, $J_{1a,2}$=7.0 Hz, $H_{1a}$); 3.78 (s, 3H, $OCH_3$); 3.90 (dd, 1H, $J_{1a,1b}$=8.4 Hz, $J_{1b,2}$=6.5 Hz, $H_{1b}$); 4.11–4.19 (m, 2H, $H_2$ and $H_3$); 4.38 (d, 1H, $J$=12.0 Hz, $OCH_aH_bPh$–OMe); 4.58 (d, 1H, $J$=12.0 Hz, $OCH_aH_bPh$–OMe); 5.22 (ddt, 1H, $J_{4,5}$=11.0 Hz, $J_{3,4}$=9.0 Hz, $J_{all}$=1.0 Hz, $H_4$); 5.68 (dt, $J_{4,5}$=11.0 Hz, $J_{5,6}$=7.5 Hz, $H_5$); 6.84 (d, 2H, $J$=8.4 Hz, arom.); 7.25 (d, 2H, $J$=8.4 Hz, arom.). $^{13}$C NMR: $\delta$ 8.8; 8.9; 14.8; 23.4; 28.9; 30.0–30.4 (11C); 32.6; 55.9; 67.2; 70.1; 75.5; 79.3; 114.3 (3C); 126.2; 129.9 (2C); 131.6; 137.4; 159.7. MS: $m/z$ 506 $[M+NH_4]^+$. IR (neat) $\nu_{max}$ 3045, 2920, 1620 $cm^{-1}$. $C_{31}H_{52}O_4$: calcd C 76.18, H 10.72; found C 76.40 H 10.55.

**4.1.3. (2*R*,3*S*)-3-*O*-(4-Methoxybenzyl)-1,2-*O*-(3-pentylidene)-4-(1-phenyl-1*H*-tetrazol-5-sulfonyl)-1,2,3-butantriol (7).** To a solution of 1-phenyl-1*H*-tetrazole-5-thiol

(0.69 g, 3.89 mmol), alcohol **3** (1.10 g, 3.54 mmol), and $Ph_3P$ (1.21 g, 4.60 mmol) in dry THF (50 mL), DEAD (0.66 mL, 4.24 mmol) was added dropwise at room temperature. The reaction was stirred at 40°C for 1 h, then the solvent was evaporated at reduced pressure. Purification by flash-chromatography (hexane/AcOEt, 8:2) afforded the thioether (1.57 g, 94%). MCPBA (55%) (3.67 g, 11.69 mmol) was added in small portions to a solution of the thioether in $CH_2Cl_2$ (43 mL) at 0°C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was washed with $NaHSO_3$ (40 mL), and saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried, and the solvent removed by evaporation. The residue was submitted to flash-chromatography (hexane/EtOAc, 8:2) to afford compound **7** (1.35 g, 80%) as a sticky white solid. Mp 59.0–60.4 (from diisopropyl ether). $[\alpha]_D=+14$ (*c* 1 in $CHCl_3$). $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.84 (t, 3H, $J$=7.5 Hz, $CH_3$); 0.88 (t, 3H, $J$=7.5 Hz, $CH_3$); 1.55 (m, 2H, $CH_2$); 1.63 (m, 2H, $CH_2$); 3.70 (dd, $J_{4a,4b}$=8.5 Hz, $J_{4a,3}$=6.5 Hz, $H_{4a}$); 3.78 (s, 3H, $OCH_3$); 3.85–3.89 (m, 2H, $2H_1$); 3.93 (dd, $J_{4a,4b}$=8.5 Hz, $J_{4b,3}$=6.5 Hz, $H_{4b}$); 4.22–4.28 (m, 2H, $H_2$ and $H_3$); 4.43 (d, 1H, $J$=11.0 Hz, $OCH_aH_bPh$–OMe); 4.51 (d, 1H, $J$=11.0 Hz, $OCH_aH_bPh$–OMe); 6.82 (m, 2H, arom.); 7.05 (m, 2H, arom.); 7.45–7.62 (m, 5H, arom.). $^{13}C$ NMR: $\delta$ 8.9 (2C); 28.8; 29.8; 56.0; 57.5; 65.8; 73.6; 74.1; 76.1; 114.5 (2C), 114.8; 126.2 (2C); 129.7; 130.0 (2C); 130.3 (2C); 132.2; 133.6; 154.9; 160.2. MS: *m/z* 520 $[M+NH_4]^+$, 503 $[M+H]^+$. IR (nujol) $\nu_{max}$ 1150, 1170, 1350, 1460, 1510, 1610 $cm^{-1}$. $C_{24}H_{30}N_4O_6S$: calcd C 57.36, H 6.02, N 11.15; found C 57.51, H 5.95, N 10.97.

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