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ORIGINAL PAPER

Total synthesis of *N*,*O*,*O*,*O*-tetraacetyl-D-*ribo*-phytosphingosine and its 2-*epi*-congener

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Dedicated to Professor Štefan Toma on the occasion of his 75th birthday

Total synthesis of the natural D-*ribo*-phytosphingosine *I* and its 2-epimer *III* in the protected form was achieved through a common strategy. The aza-Claisen rearrangement of allylic thiocyanate (*Z*)-*V* incorporated the new stereogenic centre with nitrogen and the subsequent Wittig olefination constructed a non-polar side chain. Hydrogenation, followed by removal of protecting groups, completed the syntheses of *I* and *III*.

Keywords: phytosphingosine, aza-Claisen rearrangement, microwave irradiation, isothiocyanates

Introduction

(2*S*,3*S*,4*R*)-D-*ribo*-Phytosphingosine *I* (PHS, Fig. 1), the most abundant member of the phytosphingosine family, is a structural component of the cell membranes of plants, fungi, bacteria, marine organisms, and some mammalian tissues (Holst, 2001; Karlsson & Mårtensson, 1968). From a structural perspective, *I* possesses a saturated lipid chain linked to a polar 2-amino-1,3,4-triol head group bearing three stereogenic centres. PHS is a characteristic sphingoid base of the epidermal lipid architecture in human skin that contributes to production of the water permeability barrier (Kolter & Sandhoff, 1999). In addition to its structural functions, *I* has been shown to play a key role in the heat stress response of yeast cells (Wells et al., 1998; Chung et al., 2000). Furthermore, D-*ribo*-phytosphingosine *I* is an essential scaffold of some bioactive lipid molecules such as KRN7000 (*II*, also known as AGL-582 or α-GalCer, Fig. 1), which exhibits potent immunostimulatory and antitumour activities (Motoki et al., 1995) due to its ability to activate NKT-cells (natural killer cells).

The remarkable spectrum of the biological activity of *I* has prompted a number of groups to synthesise *I* as well as its stereoisomers or their analogues with other alkyl chain lengths using different approaches commencing from the various starting materials, especially from carbohydrates (Howell & Ndakala, 2002, see also references herein; Luo et al., 2002; Naidu & Kumar, 2003; Raghavan et al., 2003; Lu et al., 2004; Singh et al., 2004; Lu & Bittman, 2005; Righi et al., 2006; Lombardo et al., 2006; Kumar & Rode, 2007; Abraham et al., 2007, 2008; Jeon et al., 2007; Chang et al., 2007; Kim et al., 2008; Niu et al., 2008; Pandey & Tiwari, 2009; Dubey & Kumar, 2009; Cai et al., 2009; Llaveria et al., 2009; Liu et al., 2010; Kumar et al., 2010; Morales-Serna et al., 2010, see also references herein; Rao & Rao, 2011a, 2011b; Perali et al., 2011).

We were recently engaged in the synthesis of phytosphingosines and reported the ready preparation of D-*ribo*-C_{20}-phytosphingosine and its 2-*epi*-congener (Martinková et al., 2011) from D-ribose, employing the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates as the key reaction. In tandem with our

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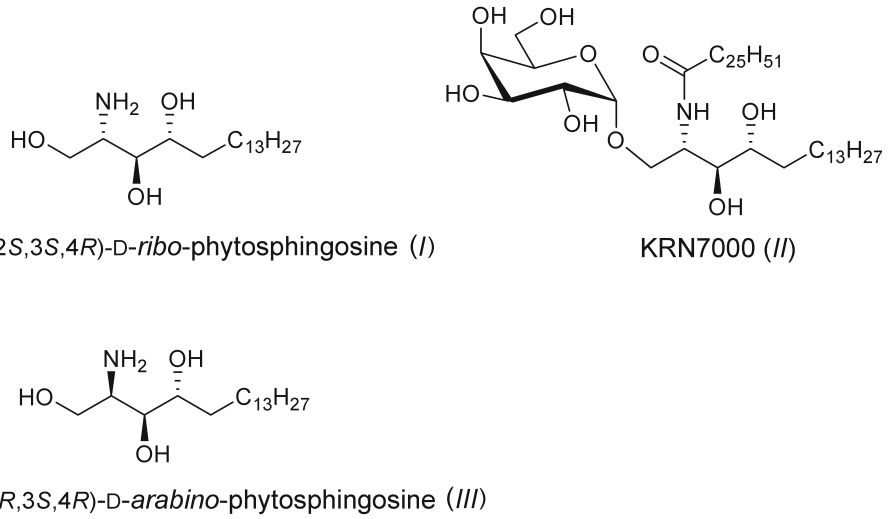

Fig. 1. D-*ribo*-Phytosphingosine *I* and its analogues.

Table 1. aza-Claisen rearrangement of thiocyanates (*Z*)-*V* and (*E*)-*V*

Entry	Thiocyanates	Conditions	Time	Molar ratio[a]	Yield[b]
			h	*VIa* : *VIb*	%
1	(*Z*)-*V*	MW, 90 °C, heptane	7	75 : 25	51
2	(*Z*)-*V*	MW, 150 °C, heptane	4	68 : 32	49
3	(*Z*)-*V*	Δ, 90 °C, heptane	15	73 : 27	60
4	(*Z*)-*V*	MW, 90 °C, *o*-xylene	5	74 : 26	30
5	(*Z*)-*V*	MW, 150 °C, *o*-xylene	3	68 : 32	30
6	(*E*)-*V*	Δ, 90 °C, heptane	16	71 : 29	53

a) Ratio in the crude reaction mixture; *b*) isolated combined yields of *VIa* and *VIb*.

interest in the total synthesis of natural phytosphingosines and their related compounds, we describe here an extension of the above methodology to allylic thiocyanates (Gonda et al., 2011; Martinková et al., 2010) derived from the same starting molecules and illustrate its use in construction of the predominant member in the class of phytosphingosines (D-*ribo*-phytosphingosine *I*) and its C(2)-epimer *III*.

Results and discussion

As shown in Fig. 2, our synthesis commenced with the known (4*S*,5*S*,6*R*,2*Z*)-6,7-bis[(*tert*-butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)hept-2-en-1-ol *IV* readily obtained from D-ribose on a multi-gram scale (Martinková et al., 2011). Exposure of *IV* to methanesulphonyl chloride (MsCl) in the presence of Et_3N in CH_2Cl_2 produced a crude mesylate, treatment of which with KSCN in CH_3CN provided the corresponding thiocyanate (*Z*)-*V* (J_{cis} = 11.0 Hz) in 89 % yield after two reaction steps (Fig. 2); its structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy including 2D experiments.

Having produced allylic thiocyanate (*Z*)-*V*, we then explored the thermal aza-Claisen rearrangement which was carried out in heptane at 90 °C under a nitrogen atmosphere and afforded the rearranged products *VIa* and *VIb* with overall yield of 60 % (Table 1, entry 3) as an inseparable mixture of diastereoisomers. By contrast, the microwave-mediated thermal [3,3]-sigmatropic rearrangement led to considerably shorter reaction times (Table 1, entries 1 and 2), with isolated yields similar to those observed for the thermally driven reaction (Table 1, entries 3 and 6).

In the course of this reaction, in all cases, we also recovered the isomerised thiocyanate (*E*)-*V* with approximately 30–40 % yield; the coupling constant observed in (*E*)-*V* (J_{trans} = 15.2 Hz) proved the *trans*-configuration of the double bond. Its rearrangement, performed in heptane at 90 °C, gave the rearranged products *VIa* and *VIb* with 53 % yield (Table 1, entry 6). The extended reaction time or higher temperature had almost no influence on the yield of isothiocanates *VIa* and *VIb*. Table 1 (entries 4 and 5) shows that realization of the rearrangement in *o*-xylene exhibited an equilibrium shifted towards thiocyanate (*E*)-*V*, hence these conditions could not be utilised preparatively.

Although the diastereoselectivity observed in the [3,3]-sigmatropic rearrangement of thiocyanate (*Z*)-*V* was moderate (*VIa* : *VIb* ≈ 3 : 1 molar ratio, see

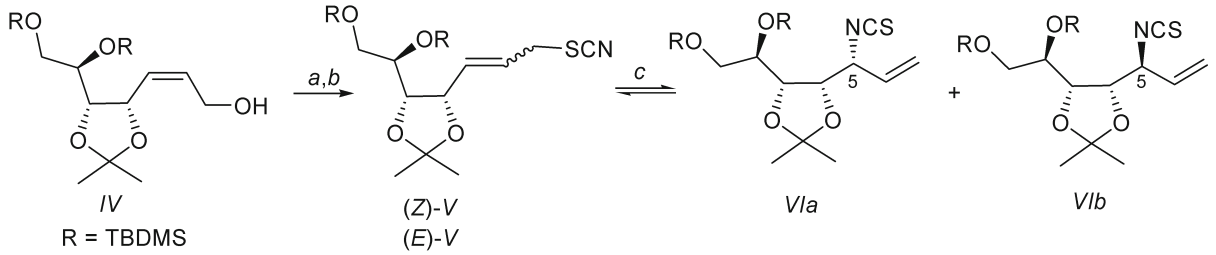

Fig. 2. Synthesis of isothiocyanates *VIa* and *VIb*. Reagents and conditions: (*a*) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t.; (*b*) KSCN, CH_3CN, 0 °C to r.t., 89 % after two steps; (*c*) Δ or MW, see Table 1. TBDMS = *tert*-butyldimethylsilyl.

Table 1, entries 1 and 3) and the yield of isolated isothiocyanates *VIa* and *VIb* was lower (60 %, see Table 1, entry 3), the relatively short synthetic pathway to these rearranged products along with their interesting structure prompted us to use these compounds for the construction of D-*ribo*-phytosphingosine *I* and its 2-*epi*-congener *III*.

The stereochemistry of the newly installed stereogenic centre with an isothiocyanate group was assigned by conversion of a mixture of the rearranged products *VIa* and *VIb* into the known compounds *XVII* and *XVIII* (Martinková et al., 2011). The crucial structures of alcohols *XVII* and *XVIII*, prepared by the sequence of reaction steps outlined in Fig. 3 (vide infra), clearly showed that the major isomer of the aza-Claisen rearrangement *VIa* possessed (5*R*)-configuration (Fig. 2). As an additional confirmation of configuration, we converted the known trichloroacetamide *XXIX* (Martinková et al., 2011) to cyclic carbamate *XIII* in two steps: (*a*) ozonolysis of *XXIX* and the subsequent reduction ($NaBH_4$) afforded alcohol *XXX* (66 %) and (*b*) DBU-mediated cyclisation produced compound *XIII* with 96 % yield (Fig. 3). The same compound with identical spectroscopic data and optical rotation was obtained from the major thiocarbamate *VII* (Fig. 3).

Thus, exposure of a mixture of isothiocyanates *VIa* and *VIb* to sodium methoxide in CH_3OH afforded the corresponding thiocarbamates *VII* and *VIII* as an readily separable mixture of diastereoisomers with 81 % overall yield. Replacement of the sulphur atom by oxygen in both derivatives *VII* and *VIII* was achieved under very mild conditions by the action of mesitylnitrile oxide (Kniežo et al., 1994) in CH_3CN to give the corresponding carbamates *IX* and *X* with 82 % and 53 % isolated yields, respectively (Fig. 3). The lower yield of 53 % for the isolated compound *X* was due to generation of further unidentified (probably decomposition) products. Their ozonolysis in a mixture of CH_3OH/CH_2Cl_2 (φ_r = 5 : 1) at –78 °C, followed by $NaBH_4$ reduction, successfully afforded primary alcohols *XI* and *XII* with 90 % and 82 % yields from *IX* and *X*, respectively. Treatment of *XI* and *XII* with sodium hydride in THF at 0 °C induced intramolecular cyclisation to produce the corresponding oxazolidinones *XIII* and *XIV* with 95 % and 94 % yields, respectively (Fig. 3). Protection of the carbamate nitrogen atom with a Boc group in *XIII* and *XIV* (Bo_2O, DMAP, CH_3CN) (Hansen et al., 1995) resulted in formation of the fully protected compounds *XV* and *XVI* in 96 % and 97 % isolated yields, respectively (Fig. 3).

In order to modify the protected oxazilidinones *XV* and *XVI* into suitable compounds (aldehydes) for the final coupling reaction with hydrophobic C_{13} counterpart (vide infra), deprotection of TBDMS groups was required. As exposure of *XV* and *XVI* to tetrabutylammonium fluoride resulted in cleavage of the *tert*-butyldimethylsilyl and also *tert*-butoxycarbonyl groups, we selected formation of the oxazolidine ring as the protecting group for both amino and alcohol functions. Thus, basic hydrolysis of the protected oxazolidinone ring in *XV* and *XVI* was achieved by employing Cs_2CO_3 in CH_3OH at room temperature to give the known compounds *XVII* and *XVIII* (Martinková, et al., 2011) with 90 % and 91 % yields, respectively (Fig. 5). Their treatment with 2,2-DMP and catalytic amounts of CSA in benzene followed by deprotection with TBAF provided the known derivatives *XXI and XXII* (Martinková et al., 2011) with 88 % and 93 % isolated yields (Fig. 4). Having established the procedure for the preparation of molecules *XXI* and *XXII*, we were able to complete our synthesis. Oxidative cleavage of diols *XXI* and *XXII* with sodium metaperiodate ($NaIO_4$) in CH_3OH/H_2O afforded aldehydes, which were immediately used in the next step without purification to avoid any problems associated with their possible instability. Their Wittig olefination with the destabilised ylide derived from tridecyltriphenylphosphonium bromide ($C_{13}H_{27}PPh_3Br$; prepared from the commercial undecanal in five reaction steps with 53 % overall yield, Fig. 5), using LHMDS (freshly prepared from *n*-BuLi and $NH(SiMe_3)_2$) as a base (Azuma et al., 2000), resulted in the formation of barely separable mixtures of olefins *XXIII* and *XXIV* (*Z* : *E* = 94 : 6 ratio for both cases, determined by ^{1}H NMR spectroscopic analysis) with 86 % and 68 % isolated yields, respectively. Small amounts of the mixtures of *XXIII* and *XXIV* were separable by column chromatography to afford only (*Z*)-isomers of *XXIII* and *XXIV* in pure forms; the geometries of their double bonds were as-

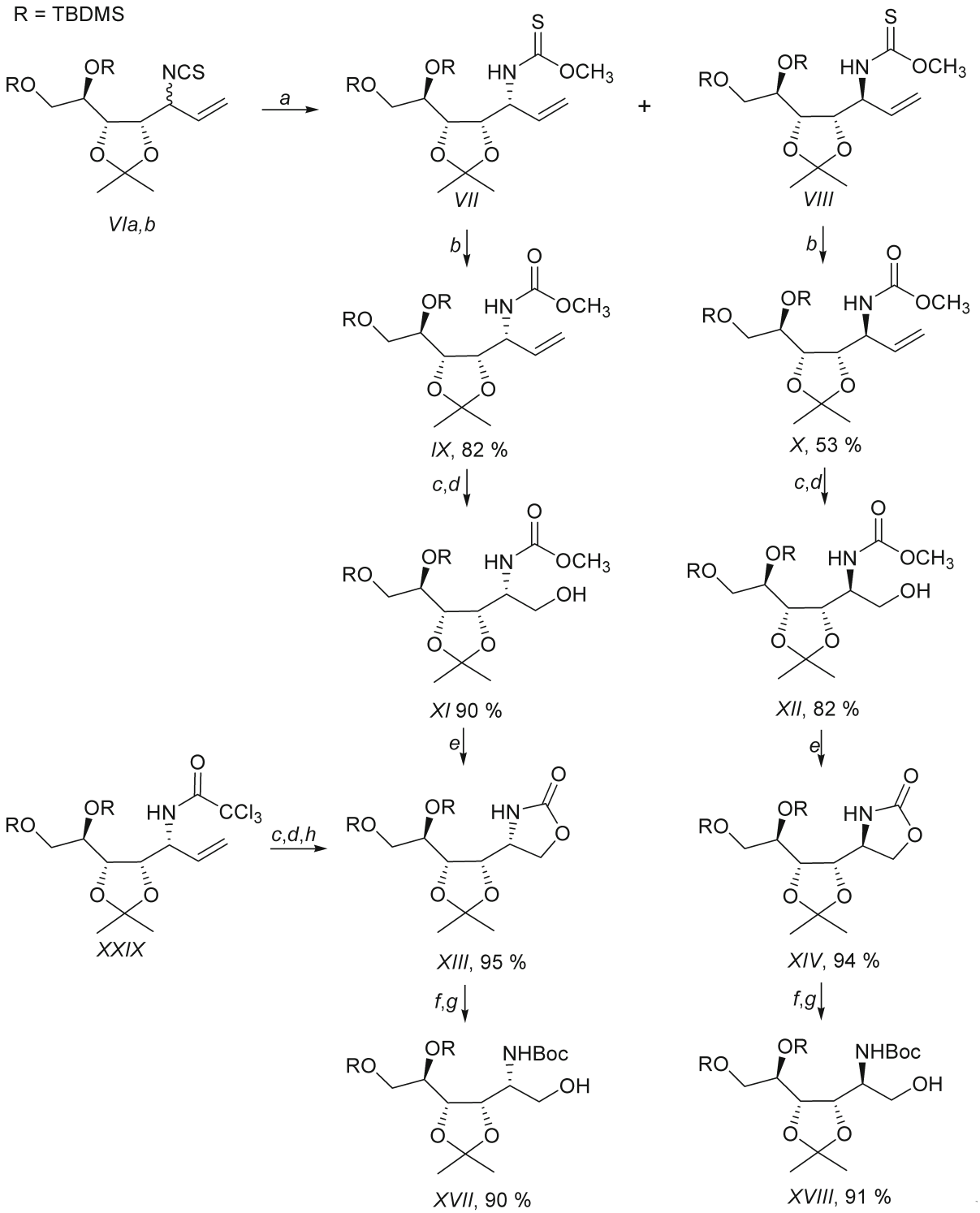

Fig. 3. Synthesis of alcohols *VII* and *VIII*. Reagents and conditions: (*a*) CH_3ONa, CH_3OH, 0 °C to r.t., 81 %; (*b*) MNO, CH_3CN, r.t.; (*c*) O_3, CH_3OH/CH_2Cl_2 (φ_r = 5 : 1), –78 °C; (*d*) $NaBH_4$, –78 °C to r.t., *XXX*, 66 % after two steps; (*e*) NaH, THF, 0 °C to r.t.; (*f*) Boc_2O, CH_3CN, DMAP, r.t., *XV*, 96 %, *XVI*, 97 %; (*g*) Cs_2CO_3, CH_3OH, r.t.; (*h*) DBU, CH_2Cl_2, 0 °C to r.t. TBDMS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

signed through the vinyl proton coupling constant values (J_{cis} = 10.4 Hz for (*Z*)-*XXIII* and J_{cis} = 10.6 Hz for (*Z*)-*XXIV*). Both mixtures of the corresponding alkenes *XXIII* and *XXIV* were hydrogenated at ambient temperature under atmospheric pressure using 10 % Pd/C to provide saturated derivatives *XXV* and *XXVI* with 93 % and 90 % yields. Finally, global deprotection in *XXV* and *XXVI* was achieved by acid

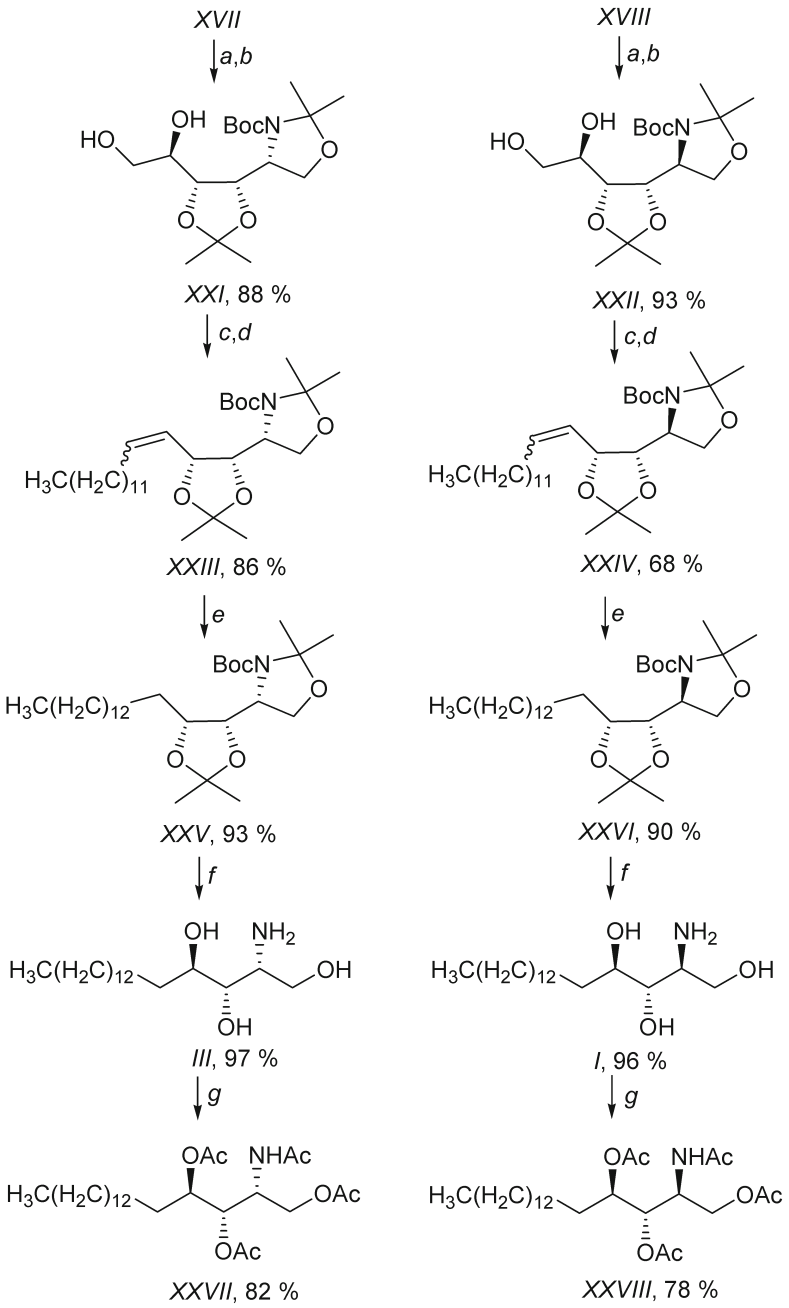

Fig. 4. Synthesis of acelytated derivatives *XXVII* and *XXVIII*. Reagents and conditions: (*a*) 2,2-DMP, CSA, benzene, reflux, *IX*, 80 %, *XX*, 93 %; (*b*) TBAF, THF, 0 °C to r.t.; (*c*) $NaIO_4$, CH_3OH/H_2O, r.t.; (*d*) LHMDS, $C_{13}H_{27}PPh_3Br$, THF, r.t.; (*e*) 10 % Pd/C, EtOH, r.t.; (*f*) TFA/H_2O, r.t.; 1 % NaOH, CH_3OH, r.t.; (*g*) Ac_2O, pyridine, DMAP, r.t. Ac = acetyl, Boc = *tert*-butoxycarbonyl.

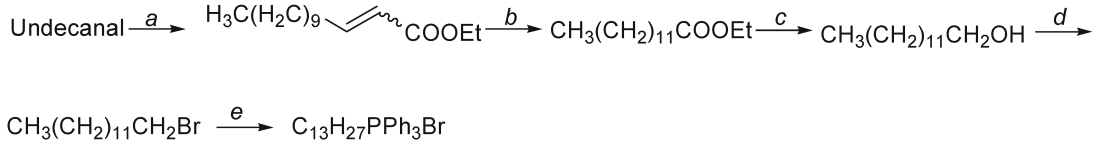

Fig. 5. Synthesis of $C_{13}H_{27}PPh_3Br$. Reagents and conditions: (*a*) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, r.t., 92 %; (*b*) H_2, 10 % Pd/C, EtOH, r.t., 97 %; (*c*) $LiAlH_4$, Et_2O, 0 °C to r.t., 79 %; (*d*) CBr_4, CH_2Cl_2, –30 °C to r.t., 88 %; (*e*) Ph_3P, toluene, reflux, 85 %.

hydrolysis (TFA/H_2O) followed by treatment with a 1 % solution of NaOH in CH_3OH to give the desired D-*ribo*-phytosphingosine *I* and its 2-*epi*-congener *III* [(2*R*,3*S*,4*R*)-D-*arabino*-phytosphingosine)] with 96 % and 97 % yields, respectively. The structures of isolated phytosphingosines *I* and *III* were confirmed by conversion to their tetraacetyl derivatives (Ac_2O, pyridine, DMAP, Fig. 4) *XXVII* (82 %, m.p. 49.5–51 °C, $[\alpha]_D^{22} = +27.9°$, $c = 6.8$ g L^{-1}, $CHCl_3$. IR (KBr), $\tilde{\nu}/cm^{-1}$: 3391, 2958, 2917, 2851, 1748, 1683. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.88 (t, 3H, $J = 6.8$ Hz, CH_3), 1.25 (br s, 24H, 12 × CH_2), 1.56 (m, 2H, 2 × H_5), 1.99 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.99–4.01 (m, 2H, 2 × H_1), 4.57–4.63 (m, 1H, H_2), 4.98–5.02 (m, 1H, H_4), 5.19 (dd, 1H, $J = 6.6$ Hz, $J = 3.3$ Hz, H_3), 5.62 (d, 1H, $J = 9.5$ Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.1 (CH_3), 20.7 (2 × CH_3), 20.9 (CH_3), 22.6 (CH_2), 23.2 (CH_3), 25.0 (CH_2), 29.3 (CH_2) 29.4 (2 × CH_2), 29.5 (CH_2), 29.6 (5 × CH_2), 30.2 (C_5), 31.9 (CH_2), 47.0 (C_2), 63.0 (C_1), 70.9 (C_4), 71.9 (C_3), 169.6 (CO), 169.8 (CO), 170.2 (CO), 170.6 (CO). For $C_{26}H_{47}NO_7$ ($M_r = 485.65$) w_i/mass % calc.: C, 64.30; H, 9.75; N, 2.88; found: C, 64.37; H, 9.68; N, 2.81) and *XXVIII* (78 %, amorphous compound, $[\alpha]_D^{24} = +29.8°$, $c = 6.0$ g L^{-1}, $CHCl_3$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.88 (t, 3H, $J = 6.8$ Hz, CH_3), 1.25 (br s, 24H, 12 × CH_2), 1.57–1.70 (m, 2H, 2 × H_5), 2.03 (s, 3H, CH_3), 2.05 (s, 6H, 2 × CH_3), 2.08 (s, 3H, CH_3), 4.00 (dd, 1H, $J = 11.7$ Hz, $J = 3.1$ Hz, H_1) 4.29 (dd, 1H, $J = 11.7$ Hz, $J = 4.9$ Hz, H_1), 4.44–4.51 (m, 1H, H_2), 4.94 (dt, 1H, $J = 9.8$ Hz, $J = 3.2$ Hz, $J = 3.2$ Hz, H_4), 5.11 (dd, 1H, $J = 8.3$ Hz, $J = 3.1$ Hz, H_3), 6.02 (d, 1H, $J = 9.4$ Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.1 (CH_3), 20.7 (2 × CH_3), 21.0 (CH_3), 22.7 (CH_2), 23.3 (CH_2), 25.5 (CH_2), 28.1 (C_5), 29.3 (2 × CH_2), 29.5 (2 × CH_2), 29.6 (5 × CH_2), 31.9 (CH_2), 47.6 (C_2), 62.8 (C_1), 71.9 (C_3), 72.9 (C_4), 169.7 (CO), 170.0 (CO), 170.8 (CO), 171.1 (CO). For $C_{26}H_{47}NO_7$ ($M_r = 485.65$) w_i/mass % calc.: C, 64.30; H, 9.75; N, 2.88; found: C, 64.25; H, 9.81; N, 2.94). The spectroscopic data and optical rotation for *XXVIII* were in accord with those reported (Azuma et al. (2000); $[\alpha]_D^{25} = +26.2°$, $c = 20.0$ g L^{-1}, $CHCl_3$; He et al. (2000); $[\alpha]_D^{25} = +27.8°$, $c = 8.0$ g L^{-1}, $CHCl_3$; Cai et al. (2009); $[\alpha]_D = +25.8°$, $c = 14.0$ g L^{-1}, $CHCl_3$; Liu et al. (2010); $[\alpha]_D^{25} = +22.6°$, $c = 7.0$ g L^{-1}, $CHCl_3$). ^{1}H and ^{13}C NMR data for derivative *XXVII* matched the known values for *ent-XXVII* (Azuma et al. (2000) for ^{1}H NMR; Shirota et al. (1999) for ^{1}H and ^{13}C NMR). The magnitude of optical rotation was in good agreement with that reported for *ent-XXVII* and was opposite in sign (Azuma et al. (2000) for *ent-XXVII*, $[\alpha]_D^{25} = -25.1°$, $c = 15.0$ g L^{-1}, $CHCl_3$). Surprisingly, the optical data published for compound *XXVII* (Kumar et al. (2010) and Dubey and Kumar (2009); $[\alpha]_D^{25} = -25.95°$, $c = 15.0$ g L^{-1}, $CHCl_3$) have comparable magnitude and the same sign of rotation as those for *ent-XXVII* (Azuma et al., 2000).

In addition, optical rotation values were only reported for *ent-III* (Mulzer and Brand (1986); $[\alpha]_D^{20} = -12.3°$, $c = 6.0$ g L^{-1}, pyridine; Imashiro et al. (1998); $[\alpha]_D^{26} = -3.7°$, $c = 10.0$ g L^{-1}, pyridine; Shirota et al. (1999); $[\alpha]_D^{23} = -4.5°$, $c = 5.8$ g L^{-1}, pyridine; Kim et al. (2008); $[\alpha]_D^{23} = -2.76°$, $c = 10.0$ g L^{-1}, pyridine) and are considerably different. Prompted by these findings, we prepared compound *III* in the pure form and fully characterised by spectroscopic means (97 %, m. p. 83–85 °C, $[\alpha]_D^{23} = +14.7°$, $c = 3.4$ g L^{-1}, pyridine. IR (KBr), $\tilde{\nu}/cm^{-1}$: 3357, 2918, 2850, 1578, 1468, 1059. ^{1}H NMR (400 MHz, CD_3OD), δ: 0.88 (t, 3H, $J = 6.7$ Hz, CH_3), 1.27 (br s, 24H, 11 × CH_2, H_5, H_6), 1.53–1.55 (m, 1H, H_6), 1.62–1.67 (m, 1H, H_5), 3.03–3.06 (m, 1H, H_2), 3.37 (dd, 1H, $J = 7.0$ Hz, $J = 2.1$ Hz, H_3), 3.48–3.60 (m, 3H, 2 × H_1, H_4). ^{13}C NMR (100 MHz, CD_3OD), δ: 14.5 (CH_3), 23.8 (CH_2), 26.9 (C_6), 30.5 (CH_2), 30.8 (CH_2), 30.9 (6 × CH_2), 31.0 (CH_2), 33.1 (CH_2), 35.0 (C_5), 54.1 (C_2), 65.4 (C_1), 73.5 (C_4), 74.4 (C_3). For $C_{18}H_{39}NO_3$ ($M_r = 317.51$) w_i/mass % calc.: C, 68.09; H, 12.38; N, 4.41; found: C, 68.14; H, 12.30; N, 4.36).

Conclusions

We have developed a synthetic strategy for preparation of D-*ribo*-phytosphingosine *I* and its 2-*epi*-congener *III* in the protected form. The key transformations were aza-Claisen rearrangement of the allylic thiocyanate (*Z*)-*V* which installed the new asymmetric centre with nitrogen and the Wittig reaction of the corresponding aldehydes generated in situ to establish the non-polar side-chain. To prove the configuration at the stereogenic centre incorporated in both isomers *VIa* and *VIb*, chemical correlations of these compounds to known diastereoisomers *XVII* and *XVIII* were performed. On the basis of our recent and present results, we conclude that the diastereoslectity observed in both the Overman rearrangement of trichloroacetimidates (Martinková et al., 2011) and aza-Claisen rearrangement of allylic thiocyantes (*Z*)-*V* and (*E*)-*V* (Table 1) was moderate (Overman ≈ 2 : 1, Martinková et al. (2011), aza-Claisen *VIa* : *VIb* ≈ 3 : 1) and the resultant rearranged products were obtained with 65 % (Martinková et al., 2011) and 60 % yields. To compare both synthetic routes leading to the final sfingofungins *I* and *III*, the "Overman approach" (Martinková et al., 2011) appears to be more practical and also affords a greater amount of the natural product *I* (aza-Claisen rearrangement of (*Z*)-*V* produced a reversal diastereoselectivity (5*R*)-*VIa* : (5*S*)-*VIb* ≈ 3 : 1).

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