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Synthesis of (2*S*,3*R*,11*S*,12*R*,2‴*R*,11‴*S*,12‴*R*)-plakoside A, a prenylated and immunosuppressive marine galactosphingolipid with cyclopropane-containing alkyl chains

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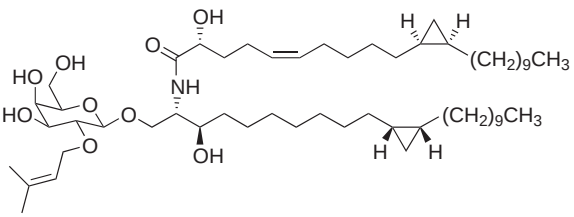
Abstract—Plakoside A (**1**) is a prenylated galactosphingolipid isolated from the marine sponge *Plakortis simplex* and is strongly immunosuppressive without cytotoxicity. (2*S*,3*R*,11*S*,12*R*,2‴*R*,11‴*S*,12‴*R*)-plakoside A (**1**) was synthesized by combining sphingosine part **16**, α-hydroxy acid part **24** and prenylated sugar part **29**. © 2001 Elsevier Science Ltd. All rights reserved.

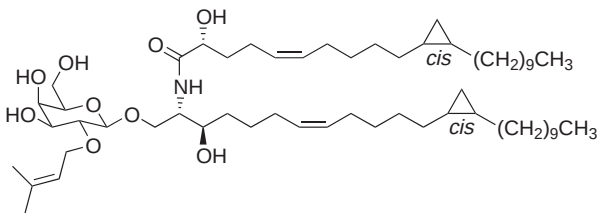
Plakosides A [(2*S*,3*R*,11*R**,12*S**)-1-*O*-{2′-*O*-(3″-methyl-2″-butenyl)-β-D-galactopyranosyl}-2-{(2‴*R*,5‴*Z*,11‴*R**,12‴*S**}-2‴-hydroxy-11‴,12‴-methylene-5‴-docosenamido}-11,12-methylene-1,3-docosanediol, **1**] and B were isolated in 1997 by Fattorusso and coworkers as the metabolites of the Caribbean sponge *Plakortis simplex*.[1] Their unique structures (Fig. 1) as glycosphingolipid with a prenylated D-galactose and cyclopropane-containing alkyl chains, together with its strong immunosuppressive activity without cytotoxicity, have made their synthesis very attractive. Indeed, in addition to the further isolation work by Fatturusso to identify plakosides C and D,[2] an attempt was made by Li et al. to synthesize analogs of **1**.[3] The fact that only 5 mg of **1** could be secured from 57 g (dry weight) of the sponge[1] also encouraged us to explore a synthetic route leading to **1**.

Since the absolute configuration of the stereogenic centers of the two cyclopropane moieties was unknown except that they are *cis*-disubstituted cyclopropanes, we took the liberty of synthesizing (2*S*,3*R*,11*S*,12*R*,2‴*R*,11‴*S*,12‴*R*)-plakoside A (**1**), because of the availability of (1*S*,2*R*)-1-acetoxymethyl-2-hydroxymethylcyclopropane (**3**) using an enzymatic method.[4–6] Obviously, plakoside A (**1**) can be synthesized by connecting three building blocks, the sphingosine part, the α-hydroxy acid part and the sugar part. In late 2000, Nicolaou et al. reported a synthesis of (2*S*,3*R*,11*R*,12*S*,2‴*R*,11‴*R*,12‴*S*)-plakoside A, a diastereomer of our target **1**, by constructing the cyclopropane moieties via a Charette reaction.[7]

Scheme 1 summarizes the synthesis of the sphingosine part **16**. Enzymatic acetylation of *meso*-diol **2** with vinyl acetate in the presence of lipase AK (Amano) gave monoacetate (1*S*,2*R*)-**3**, $[\alpha]_D^{21}$ −19.9 ($c=1.65$, $CHCl_3$), whose enantiomeric purity was >99.9% ee as



(2*S*,3*R*,11*S*,12*R*,11‴*S*,12‴*R*)-Plakoside A (**1**)



Plakoside B

Figure 1. Structures of plakosides A and B.

Keywords: immunosuppressive compounds; marine metabolites; sphingolipids; sponges.

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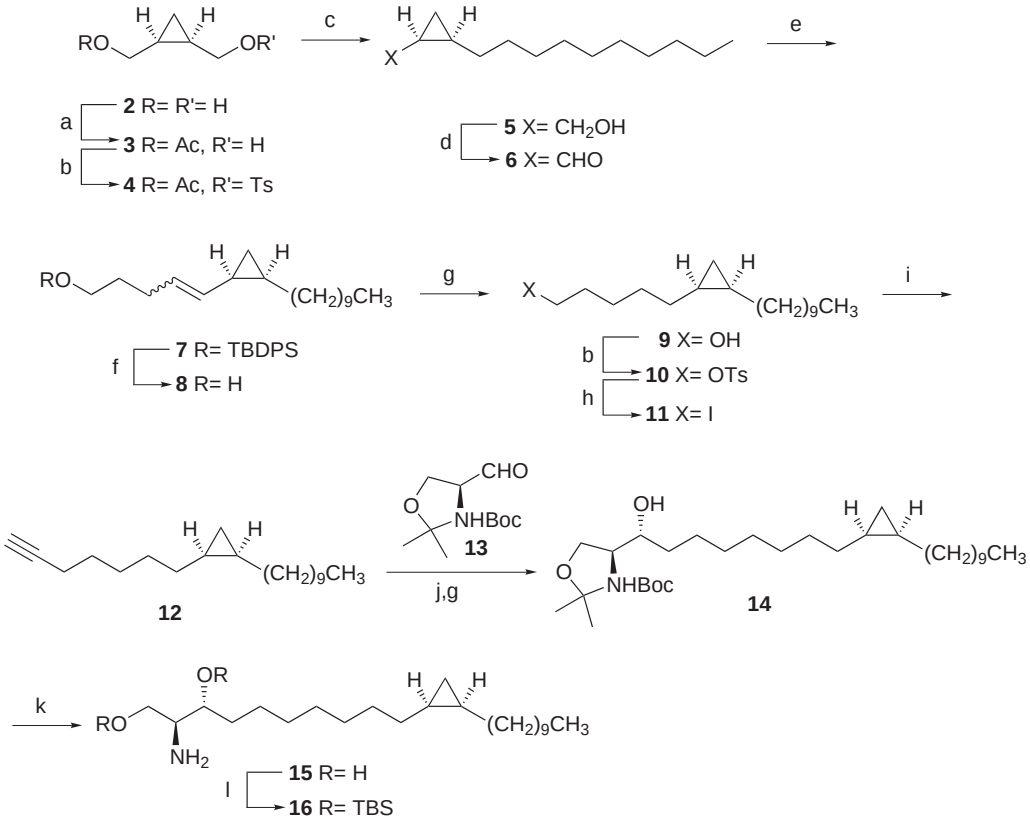


Scheme 1. Synthesis of the sphingosine part **16**. Reagents: (a) vinyl acetate, lipase AK, THF (86%); (b) TsCl, C_5H_5N, CH_2Cl_2; (c) $Me(CH_2)_8MgBr$, Li_2CuCl_4, THF (85%, two steps); (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (e) $TBDPSO(CH_2)_4PPh_3Br$, *n*-BuLi, THF (98%, two steps); (f) TBAF, THF (98%); (g) N_2H_4, H_2O_2, EtOH, H_2O (94% for **9**; 85% for **14**); (h) NaI, DMF (90%, two steps); (i) $LiC{\equiv}CH{\cdot}H_2N(CH_2)_2NH_2$, DMSO (88%); (j) **13**, *n*-BuLi, THF, HMPA (75%); (k) dil. HCl, MeOH (quant.); (l) TBSOTf, 2,6-lutidine, CH_2Cl_2 (91%).

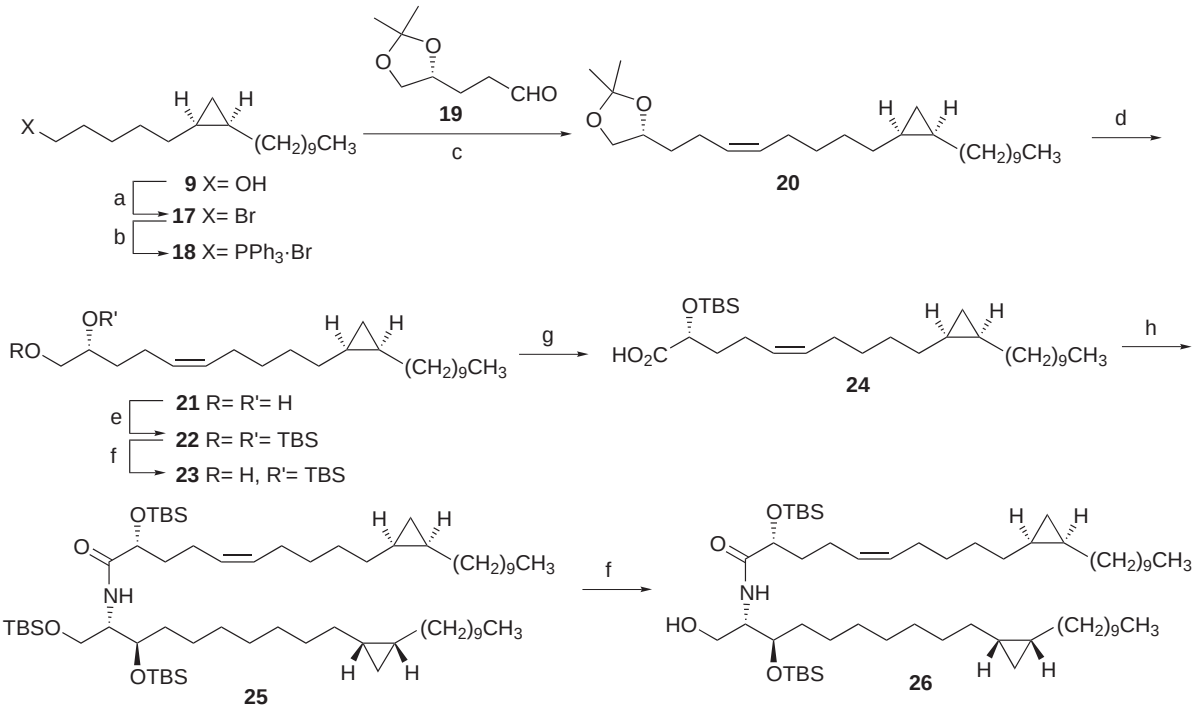
determined by HPLC analysis (Chiralcel® OD-H).[4–6,8] Tosylation of **3** afforded **4**, which was treated with nonylmagnesium bromide under Schlosser conditions[9] to furnish alcohol **5**, $[\alpha]_D^{19}$ −20.7 ($c=1.04$, $CHCl_3$). Swern oxidation of **5** to give aldehyde **6** was followed by Wittig reaction, yielding **7**. Removal of the TBDPS protective group of **7** afforded olefinic alcohol **8**, whose diimide reduction provided alcohol **9**, $[\alpha]_D^{20}$ −5.5 ($c=1.81$, $CHCl_3$). Iodide **11** was derived from **9** via the corresponding tosylate **10**, which was treated with a lithium acetylide–ethylenediamine complex to give alkyne **12**, $[\alpha]_D^{21}$ +0.65 ($c=1.33$, $CHCl_3$). Coupling of **12** with Garner aldehyde **13** derived from (*S*)-serine[10] was executed under standard conditions[11] to afford **14**, $[\alpha]_D^{25}$ −34.2 ($c=1.11$, $CHCl_3$), as the sole product after diimide reduction and chromatographic purification.

Treatment of **14** with dilute hydrochloric acid yielded sphingosine **15** as its hydrochloride, whose hydroxy groups were protected as TBS ethers to furnish **16**, one of the three building blocks for **1**.

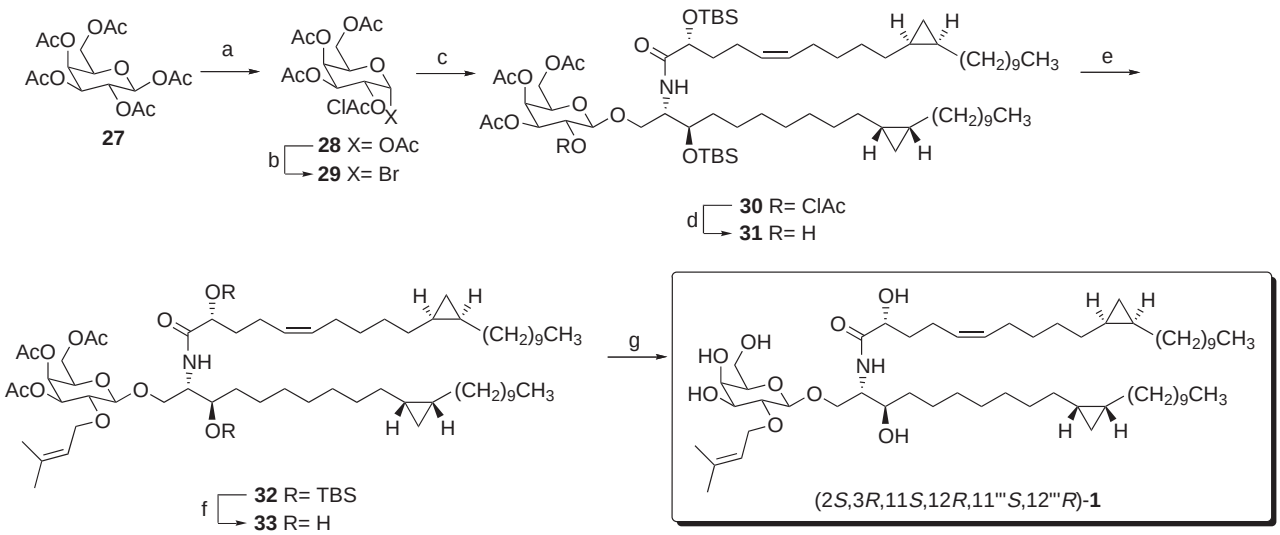
Synthesis of the α-hydroxy acid part **24** and its coupling with the sphingosine part **16** to give the ceramide part **26** are summarized in Scheme 2. Alcohol **9** was converted to phosphonium salt **18** via bromide **17**. The Wittig reagent generated from **18** reacted with aldehyde **19** (prepared from D-glutamic acid in four steps)[12] to give (*Z*)-alkene **20**, $[\alpha]_D^{23}$ −8.9 ($c=1.44$, $CHCl_3$), as the only product as determined by ^{13}C NMR analysis. Removal of the acetonide protective group of **20** was followed by silylation of the resulting diol **21** to give **22**, $[\alpha]_D^{22}$ +10.7 ($c=0.86$, $CHCl_3$).

Treatment of **22** with trifluoroacetic acid afforded a mixture of **21**–**23** from which **23** could be separated by silica gel chromatography. Two-step oxidation of **23** with Dess–Martin periodinane and sodium chlorite yielded acid **24**. Acylation of **16** with **24** proceeded in the presence of DCC and DMAP to furnish tris-TBS protected ceramide **25**, $[\alpha]_D^{23}$ +7.5 ($c=0.17$, $CHCl_3$). Mono-deprotection of the TBS protective group of **25** under acidic conditions afforded **26**, the protected ceramide part.

Scheme 3 summarizes the preparation of the galactosyl donor **29** and completion of the synthesis of (2*S*,3*R*,11*S*,12*R*,2‴*R*,11‴*S*,12‴*R*)-plakoside A (**1**). Pentaacetyl β-D-galactopyranose (**27**) was converted to the known C-2′ monochloroacetyl-protected bromide **29** via **28**.[13] Glycosidation of ceramide **26** with **29** under conventional Königs–Knorr conditions was followed by selective removal of the chloroacetyl group at C-2′ of **30** to give **31**. Prenylation of **31** with 1-(1-imino-2,2,2-trichloroethoxy)-3-methyl-2-butene in the presence of boron trifluoride etherate[3] gave bis-TBS and triacetyl-protected compound **32**.



Scheme 2. Synthesis of the ceramide part **26**. Reagents: (a) CBr_4, PPh_3, CH_2Cl_2 (quant.); PPh_3, MeCN (99%); (c) *n*-BuLi, THF (57%); (d) dil. HCl, THF (quant.); (e) TBSCl, imidazole, DMF (95%); (f) 10% TFA, THF (46% for **22** with 43% of **23** and 10% recovery of **21**; 45% for **26** and 33% recovery of **25**); (g) (i) Dess–Martin periodinane; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O (69%, two steps); (h) **16**, DCC, DMAP, CH_2Cl_2 (55%).



Scheme 3. Synthesis of (2*S*,3*R*,11*S*,12*R*,11‴*S*,12‴*R*)-plakoside A (**1**). Reagents: (a) (i) TFA, H_2O (70%); (ii) $(ClCH_2CO)_2O$, C_5H_5N, CH_2Cl_2 (86%); (b) HBr, AcOH, CH_2Cl_2 (98%); (c) **26**, $Hg(CN)_2$, $MeNO_2$, C_6H_6 (59%); (d) N_2H_4, AcOH, AcOEt, MeOH (73%); (e) $Me_2C{=}CHCH_2OC(=NH)CCl_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (87%); (f) TBAF, THF (87%); (g) NaOMe, MeOH (81%).

Two-step removal of the protective groups of **32** under conventional conditions gave **1** via **33**. Synthetic (2*S*,3*R*,11*S*,12*R*,2‴*R*,11‴*S*,12‴*R*)-plakoside A (**1**), $[\alpha]_D^{22}$ +8.9 ($c=0.065$, MeOH), showed spectral properties[14] in agreement with those reported for the natural product.[1,15] The overall yield of **1** was 3.0% (**2**→**16**→**1**; 21 steps) or 2.4% (**2**→**9**→**24**→**1**; 20 steps) based on **2**.

In conclusion, (2*S*,3*R*,11*S*,12*R*,2‴*R*,11‴*S*,12‴*R*)-plakoside A (**1**) was synthesized from (1*S*,2*R*)-1-acetoxymethyl-2-hydroxymethylcyclopropane (**3**), L-serine, D-glutamic acid and D-galactose. We are currently synthesizing (2*S*,3*R*,11*R*,12*S*,2‴*R*,11‴*R*,12‴*S*)-plakoside A in order to determine both the absolute configuration of the cyclopropane moieties and the influence of stereo-

chemistry on the immunosuppressive activity of plakoside A.[20]

Acknowledgements

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14. Properties of synthetic (+)-**1**: $[\alpha]_D^{22}=+8.9$ ($c=0.065$, MeOH) {natural product:[1] $[\alpha]_D^{25}=+7$ ($c=0.5$, MeOH); Nicolaou's isomer:[7] $[\alpha]_D=+10.4$ ($c=1.6$, MeOH)}; FABMS (negative-ion mode): m/z 946, 878, 716; HR-FABMS (negative-ion mode) obsd: 946.7692, calcd for $C_{57}H_{104}NO_9$: 946.7684; ^{1}H NMR (500 MHz, C_5D_5N): $\delta=-0.25$ to -0.20 (2H, m, 23-,23‴-H), 0.62–0.68 (2H, m, 23-,23‴-H), 0.68–0.75 (4H, m, 11-,12-,11‴-,12‴-H), 0.86 (6H, t, $J=7.0$, 22-,22‴-Me), 1.15–1.50 (56H, m, 5-,6-,7-,8-,9-,10-,13-,14-,15-,16-,17-,18-,19-,20-,21-,8′-,9′-,10′-,13′-,14′-,15′-,16′-,17′-,18′-,19′-,20′-,21′-H), 1.58 (6H, s, 4″-,5″-Me), 1.57–1.65 (1H, m, 5-H), 1.85–1.97 (3H, m, 4-,5-H), 2.13–2.13 (3H, m, 3‴-,7‴-H), 2.30–2.38 (1H, m, 3‴-H), 2.55–2.65 (2H, m, 4‴-H), 3.94 (1H, t, $J=6.0$, 5′-H), 4.02–4.10 (3H, m, 1-,2′-,3′-H), 4.18–4.23 (1H, m, 3-H), 4.35–4.43 (2H, m, 6′-H), 4.48 (1H, d, $J=3.0$, 4′-H), 4.58 (1H, dd, $J=11.9$, 7.3, 1″-H), 4.60–4.64 (1H, m, 2‴-H), 4.70–4.76 (2H, m, 1″-,2-H), 4.74 (1H, $J=7.4$, 1′-H), 4.81 (1H, dd, $J=10.1$, 4.9, 1-H), 5.48–5.55 (1H, m, 6‴-H), 5.58–5.63 (1H, m, 5‴-H), 5.67–5.71 (1H, m, 2″-H), 6.50–6.70 (3H, m, 4×OH), 7.80 (1H, m, OH), 8.27 (1H, d, $J=9.5$, NH); ^{13}C NMR (126 MHz, C_5D_5N): $\delta=11.4$, 14.4, 16.2, 18.2, 23.0, 23.8, 25.8, 26.6, 27.7, 29.1, 29.9–30.1, 32.2, 34.8, 35.7, 54.3, 62.2, 69.5, 69.8, 70.2, 71.1, 71.8, 74.3, 76.8, 79.6, 105.4, 123.1, 129.6, 130.8, 135.2, 175.0.
15. Nicolaou's synthetic **1** also exhibited spectroscopic data identical to those reported for natural plakoside A.[7] There are a number of reported examples wherein two diastereomers with separated stereogenic centers show identical spectroscopic data such as in the cases of penazetidine A,[16,17] penaresidin A,[17,18] and sphingofungin D[19] (Fig. 2). In these cases, derivatization or degradation of the natural or synthetic products was necessary to completely solve the stereochemical problems.[18,19] In the present case of plakoside A, our endeavor in this direction will be reported later in a full paper.

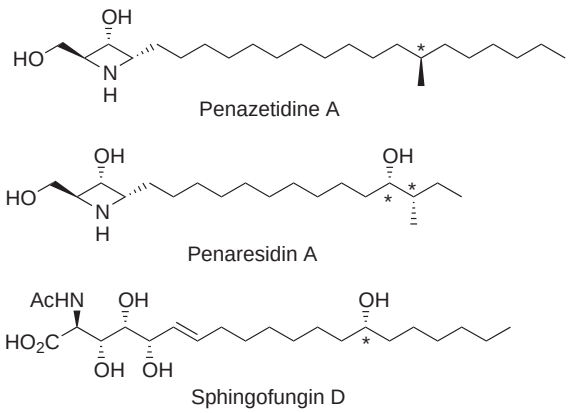

Figure 2. Examples of related natural products with asterisked remote stereogenic center(s).

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20. Nicolaou reported their synthetic plakoside A to be only a modest immunosuppressive agent.[7]