Tetrahedron: *Asymmetry* 21 (2010) 1983–1987

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Nitrolaldol reaction of (*R*)-2,3-cyclohexylideneglyceraldehyde: a simple and stereoselective synthesis of the cytotoxic Pachastrissamine (Jaspine B)

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ARTICLE INFO

Article history:
Received 4 May 2010
Accepted 17 June 2010

ABSTRACT

(*R*)-2,3-Cyclohexylideneglyceraldehyde **1** has been found to be a good substrate for nitroaldol reaction both in anhydrous and aqueous conditions. In both cases, the reaction took place with good substrate-controlled *anti*-selectivity. The major nitroaldol product **2b** has been exploited to develop a simple and stereoselective synthesis of jaspine B **X**. Also, beginning with nitroaldol reaction of **1**, this route presents a simple approach for the stereoselective preparation of (*anti*–*anti*-**5**,**7**)- and (*syn*–*syn*-**9**, **11**, **12**)-1,2,3,4-alkanetetrols, each possessing three contiguous oxygenated stereocenters.

1. Introduction

The stereoselective construction of molecules containing sequences of contiguous heterosubstituted stereocenters is a challenging task in organic synthesis. An easy and direct approach consists of the nucleophilic addition of various nucleophiles to α- and/or β-heterosubstituted chiral aldehydes possessing a chiral auxiliary that governs the degree of stereocontrol.[1] In this context, the reactions of many differently protected α-amino and α-alkoxy aldehydes with different nucleophiles have been studied showing varied levels of diastereoselections.[2] The Henry nitroaldol reaction is an efficient and powerful method for nucleophilic addition to carbonyls, which has attained considerable popularity in order to prepare various synthetic intermediates.[3] Considerable attention has been directed toward developing asymmetric nitroaldol reactions of prochiral aldehydes in the presence of a chiral metal catalyst[4] or organocatalyst.[5] However, similar to the cases of other nucleophilic reactions, a good substrate-controlled stereoselective nitroaldol reaction of a chiral aldehyde in the absence of any chiral additives is always worthwhile in asymmetric synthesis as this makes the overall procedure simpler and more straightforward. This depends on the structure of the aldehyde and the chiral auxiliary present in it.

2. Results and discussion

In our ongoing program in bioorganic research, we have been exploiting several stereoselective reactions of easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde **1**[6a] for the synthesis of different classes of bio-molecules.[6] Compound **1** has several operational advantages due to its easy accessibility,[6a] low cost, good stability, and good reactivity with different nucleophiles both in anhydrous[6a,e,f] and in aqueous media.[6b,c,h–l] So far, it has been found to be a very good substrate for several nucleophilic addition reactions such as alkylations,[6a] allylation/crotylation,[6a–c,i–k] Reformatsky reaction,[6l] amongst others. We next turned our attention to study the reactivity of **1** in the nitroaldol reaction in both anhydrous and wet conditions and also to investigate the unsuring stereoselectivity.

Firstly, **1** was subjected to the simplest nitroaldol reaction in anhydrous THF by treating it with nitromethane in the presence of tetrabutylammonium fluoride as a base. The reaction took place with the formation of the nitroaldol product **2** in good yield (89%) and with *anti*-selectivity (*syn* **2a**:*anti* **2b**::30:70). The diastereoisomers **2a** and **2b** were easily separable by column chromatography. The same nitroaldol reaction of **1** when performed in aqueous medium using K_2CO_3 as a base took place producing **2** in good yield (91%). Interestingly the aqueous nitroaldol reaction showed a large improvement of *anti*-selectivity [**2a**:**2b**::2:98]. Thus, **1** was found to be a good substrate for the nitroaldol reaction in both aqueous and anhydrous media and has the potential to impart good substrate-controlled selectivity for this reaction in both the media. Having obtained a substantial amount of **2b** in homochiral form, especially from the reaction in aqueous medium, our next objective was to exploit it in different synthetic programs. Herein we report its utility as a chiral template for the synthesis of Pachastrissamine **X**.

Pachastrissamine **X** (Fig. 1) was first discovered by Higa et al.[7] from the marine sponge *Pachastrissa* sp. in 2002 in Okinawa, Japan

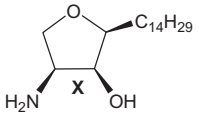

Figure 1.

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doi:10.1016/j.tetasy.2010.06.024

and was shown to exhibit significant cytotoxicity against P388, A549, HT29, and MEL 28 cancer cell lines with an IC50 value of 10 mg/mL. Later, Debitus et al.[8] isolated the same compound together with another anhydrophytisphingosine derivative from the marine sponge *Jaspis* sp. and named them Jaspine B **(X)** and Jaspine A; the hydrochloride of **X** was shown to display marked cytotoxicity (IC_{50} = 0.24 μM) against the A549 human lung carcinoma cell lines. In addition to its high biological activity, it possesses a unique structural feature due to the presence of contiguous stereocentres and an all *cis*-2,3,4-trisubstituted tetrahydrofuran. This made **X** a thoroughly reviewed[9a] synthetic target over the ages using various strategies[9] and exploiting varied sources of chirality such as; (a) the use of chiral pool materials (L-serine, carbohydrates, Garner's aldehyde, and tartaric acids);[9b–j] (b) the use of commercially available D-*ribo* phytosphingosine;[9n,o] (c) asymmetric conjugate additions of chiral amides;[9p,q] (d) asymmetric epoxidation/dihydroxylations;[9r–v] (e) asymmetric aldol reactions.[9w]

Our approach to the synthesis of **X** started with the Nef reaction of the silylether **3** of **2b** following a known procedure[10] to produce aldehyde **4**. This was found to be highly unstable on standing and hence was immediately treated with the Grignard reagent from *n*-tetradecylbromide at −50 °C. The reaction took place with absolute 1,2-*anti*-selectivity producing only **5** in good yield. The formation of the other possible diastereomer was not observed within the detectable limit of NMR of the crude product. Benzoylation of compound **5** afforded **6**, which on desilylation gave **7** in good yield. The hydroxyl at C-3 of **7** was subjected to stereochemical inversion following an oxidation–reduction protocol.[11] Accordingly, **7** was oxidized with PCC[12] to produce **8** which was reduced with K-selectride[11] to afford **9** in good yield and with absolute stereoselectivity. Benzoylation of **9** and deketalization of the resulting **10** on treatment with aqueous CF_3COOH afforded diol **11** in good yield. Regioselective monobenzoylation of **11** at its primary hydroxyl produced **12**. The other hydroxyl was subjected to azidation to obtain **14** in two steps; (a) mesylation, and (b) azidation of the mesylate **13** which took place along with stereochemical inversion at C-2 (via S_N2 substitution). The latter on treatment with excess methanolic K_2CO_3 was hydrolyzed exhaustively to afford triol **15**. This was converted into a trisubstituted tetrahydrofuran **17**[9k,m] in two simple steps with good overall yield, viz., (a) monotosylation at its primary hydroxyl and (b) intramolecular cyclization of the resulting tosylate **16** on treatment with a base. As usual, cyclization of **16** took place with absolute regioselectivity to produce tetrahydrofuran **17** through intramolecular attack at the O-Tos at C-1 from a C-4 hydroxyl. Finally, catalytic hydrogenation of **17** produced Jaspine B **X** in high yield. The physical, optical, and the spectroscopic data of our synthesized compound **X** were found to be in accordance with the reported ones.[9m,r]

3. Conclusion

In conclusion, the nitroaldol reaction of **1** has been exploited to develop a simple and stereoselective synthesis of Jaspine B **X**. Despite the route being somewhat lengthy for the synthesis of **X**, the easy accessibility of **1** on a large scale,[6a] the operational simplicity, and the practical viability of all the reactions involved herein should make it efficiently scaleable. Also, by beginning with the nitroaldol reaction of **1**, we are able to obtain two series of chiral 1,2,3,4-alkanetetrols in enantiomerically pure form, (*anti*–*anti*-**5**,**7**) and (*syn*–*syn*-**9**, **11**, **12**), each of which has three contiguous oxygenated stereocenters at C-2, C-3, and C-4. As evident from Scheme 1, one of them (C-2) was inherited from **1** while the other two (C-3 and C-4) could be generated stepwise through varied combinations among three reactions viz., (a) *anti* nitroaldol reaction of **1** under aqueous conditions (step ib); (b) 1,2-*anti*-Grignard addition to **4** (step iv); and (c) *syn* reduction[11] of ketone **8** with K-selectride (step viii). Among the aforementioned tetrols, three **5**, **7**, and **9** have all their four hydroxyls differently protected that are amenable for selective manipulation independent of the others. Presumably, following the same reactions protocol and employing other alkylations of aldehyde **4** would give a different series of tetrols, which could be exploited for the synthesis of other complex molecules possessing multiple stereocenters.

4. Experimental

Chemicals used as starting materials are commercially available and were used without further purification. All solvents used for extraction and chromatography were distilled twice at atmospheric pressure prior to use. The ^1H and ^{13}C NMR spectra were scanned with a Brucker Ac-200 (200 MHz) instrument in $CDCl_3$. The organic extracts were desiccated over dry Na_2SO_4.

4.1. (2*R*,3*R*)-1,2-*O*-Cyclohexylidene-3-nitromethyl propane-1,2,3-triol 2a and (2*R*,3*S*)-1,2-*O*-cyclohexylidene-3-nitromethyl propane-1,2,3-triol 2b

4.1.1. Using TBAF as base

To a stirred solution of **1** (6.8 g, 0.04 mol) and nitromethane (5 mL, 0.104 mol) in THF (25 mL) was added tetrabutylaammonium fluoride (TBAF) (41 mL of 1 M solution in THF, 0.041 mol) at room temperature. The resulting yellow solution was stirred for an additional 5 h at room temperature till the total disappearance of the starting material (TLC). It was then treated with water and extracted with EtOAc. The combined organic extract was washed with water, brine, and then dried. Solvent removal and column chromatography of the residue (silica gel; 0–20% EtOAc in petroleum ether) afforded **2a** (2.25 g, 24.3%) and **2b** (5.25 g, 56.8%).

4.1.2. Using K_2CO_3 as base

To a stirred mixture of **1** (6.8 g, 0.04 mol) and nitromethane (5 mL, 0.104 mol) in THF (40 mL) was added an aqueous solution (30 mL) of K_2CO_3 (7.5 g, 0.054 mol) at room temperature. The mixture was stirred at room temperature overnight and then treated with water. Usual extraction with EtOAc as done in the previous procedure and purification of the product by column chromatography afforded **2a** (170 mg, 1.8%) and **2b** (8.25 g, 89.3%).

4.1.3. Minor (2*R*,3*R*)-2a

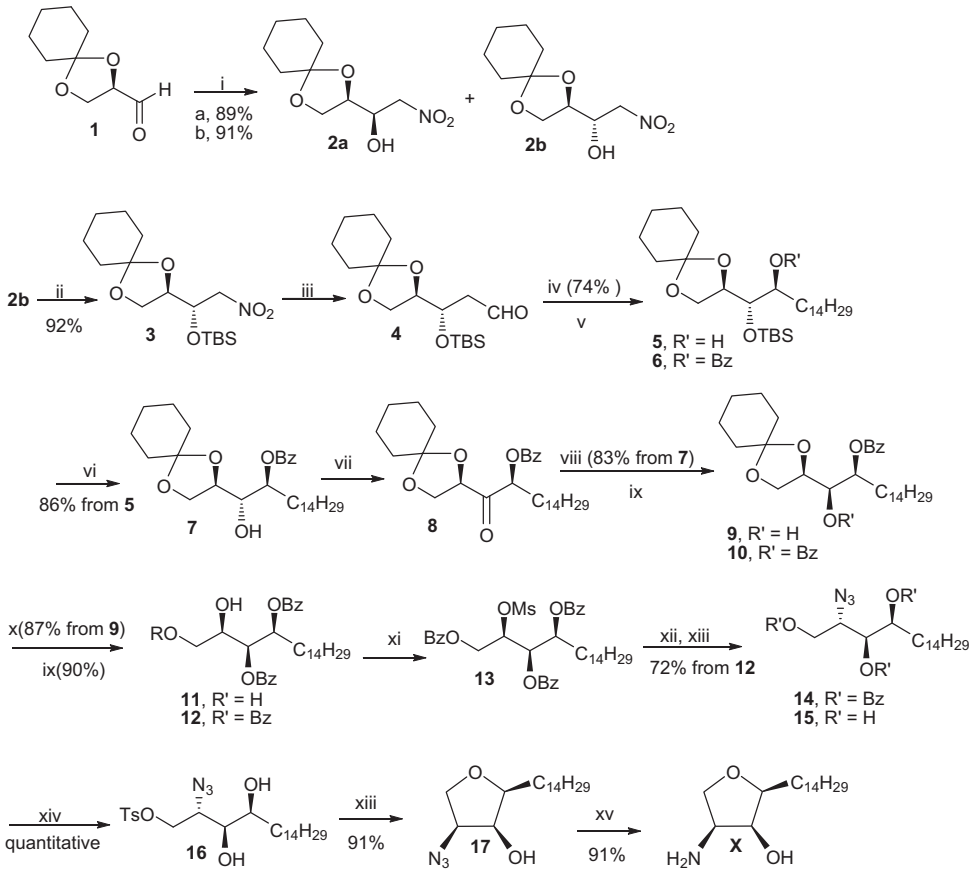
R_f: 0.68 (20% EtOAc in hexane); $[\alpha]_D^{25} = +9.0$ (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.2–1.6 (m, 10H), 3.11 (br s, D_2O exchangeable, 1H), 3.74 (dd, *J* = 8, 4.6 Hz, 1H), 4.0–4.2 (m, 2H), 4.48–4.72 (m, 3H). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.93; H, 7.40; N, 6.05. Found: C, 51.72; H, 7.59; N, 6.19.

4.1.4. Major (2*R*,3*S*)-2b

R_f: 0.61 (20% EtOAc in hexane); $[\alpha]_D^{25} = +20.7$ (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.2–1.6 (m, 10H), 2.62 (br s, D_2O exchangeable, 1H), 3.9–4.2 (m, 4H), 4.39–4.75 (m, 2H). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.93; H, 7.40; N, 6.05. Found: C, 51.81; H, 7.29; N, 6.22.

4.2. (2*R*,3*S*)-1,2-*O*-Cyclohexylidene-3-*O*-*tert*-butysimethylsilyl 3-nitromethyl-propane-1,2,3-triol 3

To a stirred solution containing **2b** (4.6 g, 0.02 mol) and *tert*-butyldimethylsillyl chloride (3.05 g, 0.02 mol) in CH_2Cl_2 (50 mL) was added imidazole (2 g, 0.03 mol). The mixture was stirred for a further 10 h and then treated with water. The organic layer



Scheme 1. Reagents and conditions: (i) (a) CH_3NO_2, TBAF, THF, rt (**2a**:**2b**::30:70) or (b) CH_3NO_2, K_2CO_3 (aq), rt (**2a**:**2b**:: 2:98); (ii) TBDMSCl, TEA, CH_2Cl_2, rt; (iii) K_2CO_3, $KMnO_4$ (aq), $MgSO_4$, 0 °C; (iv) $C_{14}H_{29}MgBr$, −50 °C, THF; (v) BzCl, Py, DMAP, 0 °C; (vi) TBAF, THF, rt; (vii) PCC, CH_2Cl_2; (viii) K-selectride, THF, −78 °C; (ix) BzCN, TEA, CH_2Cl_2; (x) CF_3COOH (aq), CH_2Cl_2, 0 °C; (xi) MsCl, TEA, DMAP, CH_2Cl_2, 0 °C; (xii) NaN_3, DMF, 100 °C; (xiii) K_2CO_3, MeOH, rt; (xiv) TsCl, Py, 0 °C; (xv) H_2, 10% Pd–C, MeOH, CH_2Cl_2.

was separated and washed with water, brine, and dried. Solvent removal at reduced pressure afforded the residue which was purified by column chromatography (silica gel; 0–10% ethyl acetate in petroleum ether, v/v) to afford **3** (6.36 mg, 92.1%). $[\alpha]_D^{25} = +26.2$ (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.02, 0.09 (2s, 6H), 0.84 (s, 9H), 1.2–1.6 (m, 10H), 3.83 (dd, *J* = 7.8 & 4.6 Hz, 1H), 3.9–4.0 (m, 2H), 4.25–4.3 (m, 1H), 4.39–4.5 (m, 1H), 4.64 (dd, *J* = 9.6, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): −4.9, 17.8, 23.6, 23.8, 24.9, 25.5, 34.4. 36.3, 66.7, 71.9, 75.9, 79.2, 110.5. Anal. Calcd for $C_{16}H_{31}NO_5Si$: C, 55.62; H, 9.04; N, 4.05. Found: C, 55.47; H, 9.30; N, 4.19.

4.3. (2R,3*R*)-2-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2,3,4-trihydroxybutanal 4

To a stirred solution of **3** (3.45 g, 0.01 mol) in MeOH (70 mL) kept at 0 °C under an atmosphere of argon was added dropwise over a period of 45 min a freshly prepared methanolic (100 mL) solution of K_2CO_3 (2.07 g, 0.015 mol) After stirring for an additional 1 h, a freshly prepared aqueous solution of $KMnO_4$ (1.1 g, 0.0068 mol) and $MgSO_4$ (0.90 g, 0.0074 mol) was added dropwise with vigorous stirring while the temperature outside the reaction flask was maintained at 0 °C. The reaction mixture was stirred for 1 h more at 0 °C and filtered through a short pad of silica gel, followed by washing several times with EtOAc. The combined filtrate and washings were concentrated by removing the solvent under reduced pressure. The residue was taken in EtOAc. The organic layer was washed with water until neutral, and then with brine, and then dried. Solvent removal under reduced pressure afforded the crude residue (2.9 g) of aldehyde **4**, which was found to be unstable on standing. Thus the residue was used as such for the next step without further purification. A small part of the residue was purified by column chromatography (silica gel; 0–10% EtOAc in hexane) for its characterization. IR (film): 2934, 2894, 2857, 2711, 1737, 1472, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.3–1.6 (m, 10H), 3.89–3.98 (m, 1H), 4.02–4.05 (m, 2H), 4.19–4.22 (m, 1H), 9.65 (d, *J* = 1.36 Hz, 1H).

4.4. (2*R*,3*S*,4*S*)-1,2-Cyclohexylidene-3-*O*-*tert*-butyldimethylsilyl-octadecan-1,2,3,4-tetrol 5

To a cooled (−50 °C) suspension of the Grignard reagent prepared from *n*-bromotetradecane (9.7 g, 0.035 mole) and magnesium (912 mg, 0.038 g-atom) in THF (60 mL) was added a solution of the crude aldehyde **4** (5.6 g) in THF (40 mL) dropwise over a period of 1 h. The mixture was stirred for an additional 2 h at −50 °C and stirred for 3 h more at room temperature. It was then treated with saturated aqueous NH_4Cl and extracted with EtOAc. Usual work up, followed by solvent removal under reduced pressure afforded a residue. This was chromatographed (silica gel; 0–20% EtOAc in hexane, v/v) to obtain **5** as a single diastereoisomer (6.8 g, 74.4%). $[\alpha]_D^{25} = +5.3$ (*c* 1.55, $CHCl_3$); ^{1}H NMR: δ 0.10 (s, 6H), 0.88 (br t, 3H, overlapped with a s, 9H), 1.25–1.56 (m, 36H), 2.4 (br s, 1H), 3.54 (br m, 1H), 3.6–3.8 (m, 2H), 3.9–4.2 (m, 2H). ^{13}C NMR ($CDCl_3$): −4.43, −4.39, −4.23, 14.1, 18.0, 22.7, 23.8, 23.9, 25.2, 25.5, 25.8, 26.0, 26.1, 29.3, 29.6, 30.3, 31.9, 32.0, 35.1, 36.2, 66.1, 74.2, 74.5, 75.2, 108.9. Anal. Calcd for $C_{30}H_{60}O_4Si$: C, 70.26; H, 11.79. Found: C, 70.53; H, 11.59.

4.5. (2*R*,3*S*,4*S*)-1,2-Cyclohexylidene-4-*O*-benzoyl-octadecan-1,2,3,4-tetrol 7

To a cooled (0 °C) solution of **5** (2.56 g, 0.005 mol) in dichloromethane (30 mL) containing pyridine (5 mL) and DMAP (100 mg) was added benzoyl chloride (844 mg, 0.006 mol). The mixture was stirred at that temperature for 30 min, at room temperature for 1 h, and then the reaction was quenched with water. The organic layer was washed successively with 5% aqueous HCl, water, and brine, and then dried. The solvent was removed and the residue containing the benzoate **6** was taken in dry THF (50 ml). To it was added TBAF (3 ml). After stirring the mixture at room temperature for 1 h, the reaction was quenched with water and the reaction mixture was extracted with EtOAc. The combined extract was washed with water, brine, and dried. Solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford **7** (2.16 g, 86.4%). $[\alpha]_D^{25} = -1.9$ (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (br t, 3H), 1.23 (m, 26H), 1.4–1.8 (m, 10H.), 2.5 (br s, 1H), 3.95–4.04 (m, 3H), 4.08–4.17 (m, 1H), 5.25 (m, 1H), 7.2–7.6 (m, 3H), 8.04 (d, *J* = 7.6 Hz, 2H) ^{13}C NMR ($CDCl_3$): 13.9, 22.5, 23.6, 23.8, 24.9, 25.2, 29.3, 29.5, 31.7, 34.6, 36.0, 65.4, 72.4, 75.2, 75.6, 109.5, 128.2, 129.5, 129.9, 132.9, 166.2. Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 73.83; H, 9.77.

4.6. (2*R*,3*R*,4*S*)-1,2-Cyclohexylidene-4-*O*-benzoyl-octadecan-1,2,3,4-tetrol 9

Following the usual procedure, **7** (1.506 g, 0.003 mol) was oxidized by stirring its solution in CH_2Cl_2 (50 mL) with PCC (1 g, 0.00464 mol) for 1 h. After the usual work up, crude ketone **8** produced was taken up in dry THF (50 ml). The solution was cooled (−78 °C) under an argon atmosphere. To it was added K-selectride (3.5 mL, 1 molar solution in THF, 0.0035 mol) over a period of 45 min. The mixture was stirred at −78 °C for 1 h, the reaction quenched by the dropwise addition of water, and the mixture extracted with EtOAc. The combined extract was washed with water, brine, and dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford **9** (1.25 g, 83.3%). Data for **9**: $[\alpha]_D^{25} = -12.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (br t, 3H), 1.2–1.8 (m, 36H), 2.38 (br s, 1H), 3.61 (m, 1H), 3.82 (distorted t, 1H), 4.0–4.2 (m, 2H), 5.21 (m, 1H), 7.3–7.6 (m, 3H), 8.06 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 14.0, 22.6, 23.4, 23.7, 24.9, 25.5, 29.3, 29.4, 29.6, 30.7, 31.8, 34.7, 36.0, 65.9, 72.1, 74.9, 75.9, 110.0, 122.0, 129.7, 130.2, 132.9, 166.3. Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 74.23; H, 10.25.

4.7. (2*R*,3*R*,4*S*)-3,4-*O*-Dibenzoyl-octadecan-1,2,3,4-tetrol 11

To a cooled (0 °C) solution of **9** (1.0 g, 0.002 mol) in dichloromethane (25 mL) containing pyridine (3 mL) and DMAP (100 mg) was added benzoyl chloride (295 mg, 0.0021 mol). The mixture was stirred at that temperature for 30 min, then at room temperature for 1 h, and then the reaction was quenched with water. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried. Solvent was removed and the residue containing the dibenzoate **10** obtained in quantitative crude yield was taken in CH_2Cl_2 (50 ml). The solution was cooled (0 °C) and treated with 90% aqueous trifluoroacetic acid (10 mL). The mixture was stirred with at 0 °C for 1.5 h until the total disappearance of **10** (vide TLC). It was then extracted with $CHCl_3$. The combined organic extract was washed successively with 5% KOH, water until neutral, and then with brine. Solvent removal under reduced pressure and column chromatography of the residue (0–5% MeOH in $CHCl_3$) afforded pure diol **11** (911 mg, 86.6%). $[\alpha]_D^{25} = -6.6$ (*c* 1.25, $CHCl_3$); ^{1}H NMR: δ 0.87 (br t, 3H), 1.2–1.8 (m, 26H), 2.86 (br s, 2H), 3.67 (m, 2H), 4.03 (m, 1H), 5.47 (m, 1H), 5.66 (m, 1H), 7.2–7.5 (m, 6H), 7.9–8.0 (m, 4H). ^{13}C NMR: δ 14.1, 22.7, 25.2, 29.3, 29.6, 30.6, 31.9. 63.4, 71.8, 72.2, 74.9, 128.4, 129.3, 129.7, 133.1, 133.3, 166.1, 166.6. Anal. Calcd for C_{32} H_{46} O_6: C, 72.97; H, 8.80. Found: C, 73.24; H, 8.60.

4.8. (2*R*,3*R*,4*S*)-1,3,4-*O*-Tribenzoyl-octadecan-1,2,3,4-tetrol 12

To a cooled (0 °C) solution of **11** (736 mg, 0.0014 mol) in dichloromethane (25 mL) containing triethylamine (3 mL) and DMAP (100 mg) was added benzoyl cyanide (183 mg, 0.0014 mol). The mixture was stirred at that temperature for 1 h, then at room temperature for 2 h, and then the reaction was quenched with water. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried. Solvent removal under reduced pressure and column chromatography of the residue (0–15% EtOAc in hexane) afforded pure **12** (795 mg, 90.1%). $[\alpha]_D^{25} = -8.3$ (*c* 1.4, $CHCl_3$); ^{1}H NMR: δ 0.87 (br t, 3H), 1.2–1.3 (m, 24H), 1.83 (m, 2H), 2.0 (br s, 1H), 4.0–4.2 (m, 1H), 4.6–4.8 (m, 2H), 5.42 (m, 1H), 5.64 (m, 1H), 7.2–7.5 (m, 9H), 7.9–8.0 (m, 6H). ^{13}C NMR: δ 13.9, 22.5, 25.0, 29.1, 29.4, 30.4, 31.7. 63.2, 71.5, 72.0, 74.6, 128.1, 129.1, 129.4, 129.5, 132.9, 133.0, 165.7, 165.9, 166.4. Anal. Calcd for $C_{39}H_{50}O_7$: C, 74.26; H, 7.99. Found: C, 73.98; H, 8.24.

4.9. (2*S*,3*S*,4*S*)-2-Azido-octadecan-1,3,4-triol 15

To a cooled (0 °C) solution of **12** (504 mg, 0.0008 mol) in dichloromethane (25 mL) containing triethylamine (2 mL) and DMAP (50 mg) was slowly added a solution of methane sulfonylchloride (0.07 mL, 0.0009 mol) in dichloromethane (15 mL) over a period of 30 min. The mixture was stirred at that temperature for 1 h, then at room temperature for 1 h, and then the reaction was quenched with water. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried. Solvent removal under reduced pressure gave a residue containing **13** that was produced in quantitative crude yield. This was taken up in DMF (20 mL) and treated with NaN_3 (52 mg, 0.0008 mol). The mixture was heated at 100 °C for 2 h, mixed with water, and extracted with EtOAc. The solvent was removed under reduced pressure and the residue containing **14** was dissolved in MeOH (25 mL). To it solid K_2CO_3 (4 g) was added and the mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed successively with water, 5% aqueous HCl, again with water, brine, and then dried. Solvent removal under reduced pressure and column chromatography of the residue (0–7% MeOH in $CHCl_3$) afforded pure **15** (199 mg, 72.5% from **12**). $[\alpha]_D^{25} = +8.6$ (*c* 1.22, $CHCl_3$); ^{1}H NMR: δ 0.87 (br t, 3H), 1.2–1.7 (m, 26H), 3.3–3.9 (m, 5H, overlapped with a br s, 3H at 3.32). ^{13}C NMR: δ 13.9, 22.5, 25.3, 25.7, 29.3, 29.6, 31.8, 33.7, 33.8, 63.5, 66.8, 72.9, 73.1. Anal. Calcd for $C_{18}H_{37}O_3N_3$: C, 62.92; H, 10.85; N, 12.26. Found: C, 63.19; H, 10.61; N, 12.51.

4.10. (2*S*,3*S*,4*S*)-2-Azido-1,4-anhydro octadecan-1,3,4-triol 17

To a cooled (0 °C) solution of **15** (137 mg, 0.0004 mol) in pyridine (4 mL) containing DMAP (50 mg) was slowly added *p*-toluenesulfonylchloride (133 mg, 0.0007 mol). The mixture was stirred at 0 °C for 6 h. After the reaction was complete (monitored with TLC), it was quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine, and then dried. The solvent was removed under reduced pressure to obtain the crude residue which was quickly purified by passing through a short silica gel and eluting first with 5% EtOAc in hexane to remove little *p*-toluenesulfonylchloride that

was used in excess and then with 5% MeOH in $CHCl_3$ to obtain **16** in quantitative yield. This was immediately dissolved in MeOH (20 mL) and mixed with solid K_2CO_3 (2 g). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed successively with water, 5% aqueous HCl, again water, brine, and then dried. The solvent was removed under reduced pressure and column chromatography of the residue (0–5% MeOH in $CHCl_3$) afforded pure **17** as a white solid substance (119 mg, 91.5% from **15**). $[\alpha]_D^{25} = +16.6$ (*c* 1.04, $CHCl_3$); lit[9m] $[\alpha]_D^{24} = +16.7$ (*c* 1.0, $CHCl_3$); mp 99.6–100.2 °C (lit[9m] mp 99.4–100.1 °C) ^{1}H NMR: δ 0.87 (br t, 3H), 1.24 (m, 23H), 1.62 (m, 3H), 2.0 (br s 1H), 3.7–3.8 (m, 1H), 3.85 (dd, *J* = 3.6, 6.6 Hz, 1H), 3.97 (dd, *J* = 7.0, 9.0 Hz, 1H), 4.1 (m, 1H), 4.2 (dd, *J* = 3.4, 4.6 Hz, 1H). ^{13}C NMR: δ 14.1, 22.7, 26.0, 28.8, 29.3, 29.7, 31.9, 63.7, 68.4, 72.5, 82.1.

4.11. (2*S*,3*S*,4*S*)-4-Amino-2-tetradecyl-tetrahydrofuran-3-ol X (Jaspine B)

A solution of **17** (75 mg, 0.0023 mol) in a solvent mixture of MeOH (4 mL) and CH_2Cl_2 (3 mL) was stirred with 10% Pd/C (42 mg, 50 wt %) for 6 h under hydrogen atmosphere at room temperature. It was then diluted with CH_2Cl_2 and filtered through a pad of Celite and repeatedly washed with 5% MeOH in CH_2Cl_2. The solvent was removed under reduced pressure and column chromatography of the crude residue (0–5% MeOH in $CHCl_3$) afforded pure **A** as a white solid (63 mg, 91.4%) whose physical (mp 95.9–97.1 °C), specific rotation {$[\alpha]_D^{25} = +17.7$ (*c* 0.38, EtOH)} and spectroscopic data were in accordance with the reported ones {mp 96.6–97.2 °C;[9m] $[\alpha]_D^{24} = +17.5$ (*c* 0.3, EtOH)[9r]}.

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