Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1820

www.rsc.org/obc

PAPER

Organocatalytic stereoselective synthesis of passifloricin A†

Pradeep Kumar,*[a] Menaka Pandey,[a] Priti Gupta[a] and Dilip D. Dhavale[b]

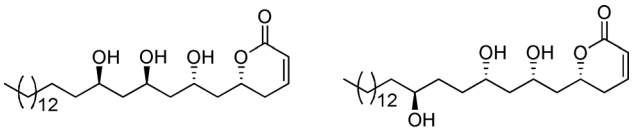
Received 10th October 2011, Accepted 1st December 2011
DOI: 10.1039/c2ob06711k

The enantioselective synthesis of passifloricin A has been achieved in high diastereomeric excess. The 1,3-polyol moiety was constructed by iterative proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehydes while the synthesis of lactone moiety was achieved by ring-closing metathesis (RCM).

Optically active *syn*-and *anti*-1,3-polyols/5,6-dihydropyran-2-ones are common structural motifs in various biologically active compounds.[1] The lactone ring constitutes an important structural feature of many natural products, particularly those that are Michael acceptors (α,β-unsaturated). They possess interesting pharmacological properties, such as plant growth inhibition, as well as antifeedant, antifungal, antibacterial and antitumor properties.[2,3] α-Pyrones possessing polyhydroxy or polyacetoxy side chains have attracted much attention from synthetic and medicinal chemists due to their broad range of biological activities. One such polyketide type 6-substituted 5,6-dihydropyran-2-one, passifloricin A, was isolated by Echeverri *et al.*[4] from the resin of *Passiflora foetida* var. *hispida*, a species from the family *Passifloraceae* that grows in tropical zones of America.

Passifloricin A was found to display interesting antifungal and antiprotozoal properties.[5] The structure and relative configuration of passifloricin A was assigned as **1a** on the basis of spectroscopic findings, but on that basis absolute configuration could not be determined. Several syntheses of the proposed structure of passifloricin **1a** were reported in the literature.[6] Later Murga *et al.*[7] found a discrepancy in the NMR data of synthetic passifloricin from those of the natural product. In order to correct the proposed structure **1a** and establish the absolute configuration, these authors synthesized several isomers of this compound and after systematic and careful study of their NMR spectra, they revised the structure of passifloricin as **1** (Fig. 1). Subsequently Chandrasekhar *et al.*[8] accomplished the total synthesis of **1** using Jacobsen epoxidation and Evans intramolecular oxa-Michael reaction[9] as key transformations, while Sabitha *et al.*[10] described its synthesis by employing Prins cyclization as the key step.

During the last decade it has been established that small organic molecules can be highly selective and efficient catalysts.



Proposed structure **1a** Revised structure **1**

Fig. 1 Structure of passifloricin A.

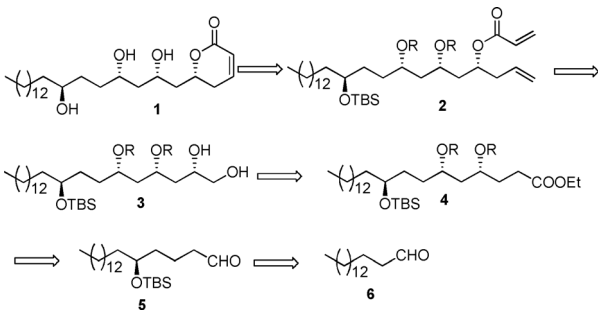
As a result, the area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[11] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[12] Proline, in the recent past has been defined as a 'universal catalyst' because of its utility in different reactions providing rapid, catalytic, atom-economical access to enantiomerically pure products.[13] Similarly, organocatalytic tandem processes provide efficient means to construct complex target molecules in an environmentally friendly and rapid way from simple and readily available precursors, while minimizing time and energy losses.[14]

Recently, we have developed an iterative approach to the enantiopure synthesis of *syn*/*anti*-1,3-polyols, which is based on proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehydes.[15] The interesting moiety of passifloricin combined with the biological activity drew our attention and, as a part of our research program aimed at developing enantioselective syntheses of biologically active natural products,[16] we became interested in devising a simple and concise route to passifloricin *via* our recently developed organocatalytic methodology.[15] Herein we report our successful endeavours towards the total synthesis of **1** employing proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehyde as the key step.

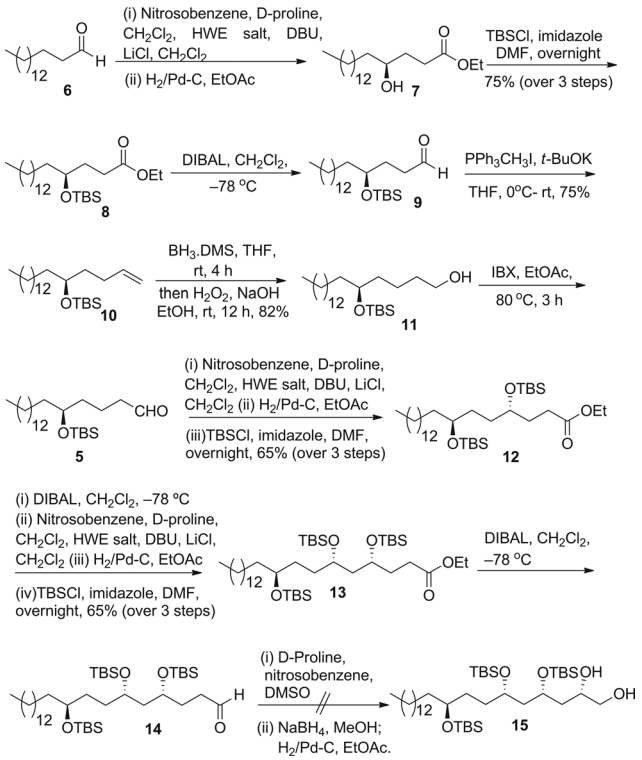
Our synthetic strategy for the synthesis of **1** is outlined in Scheme 1. We envisioned that the lactone ring could be constructed by the ring-closing metathesis of an acrylate ester **2**, which in turn could be derived from the diol **3**. Diol **3** could be obtained by using proline catalyzed α-aminoxylation and reduction of ester **4**, which in turn could be obtained from iterative sequential α-aminoxylation and Horner–Wadsworth–Emmons

[a]*Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune, 411 008, India*
[b]*Chemistry Department, University of Pune, Pune, 411007, India*

†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c2ob06711k



Scheme 1 Retrosynthetic analysis of passifloricin A.



Scheme 2

olefination of aldehyde **5**. The aldehyde **5** could be obtained from the palmitaldehyde **6** *via* α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination followed by one-carbon homologation and oxidation.

Thus as shown in Scheme 2, synthesis of passifloricin A **1** started from the commercially available palmitaldehyde **6**, which was subjected to sequential α-aminoxylation using D-proline as catalyst followed by a HWE-olefination reaction to furnish the *O*-amino-substituted allylic alcohol. The crude product was directly subjected to hydrogenation conditions using catalytic amount of Pd/C to furnish the γ-hydroxy ester **7**. The ester **7** was obtained only in 15% yield when reaction was performed in DMSO presumably because of the formation of self-aldol (homodimerized) as a major side product. To overcome the problem of low yield, we performed the reaction by varying the reaction conditions using different solvents and temperatures; the results obtained are summarized in Table 1. With the use of acetonitrile as solvent either there was no reaction or it did not

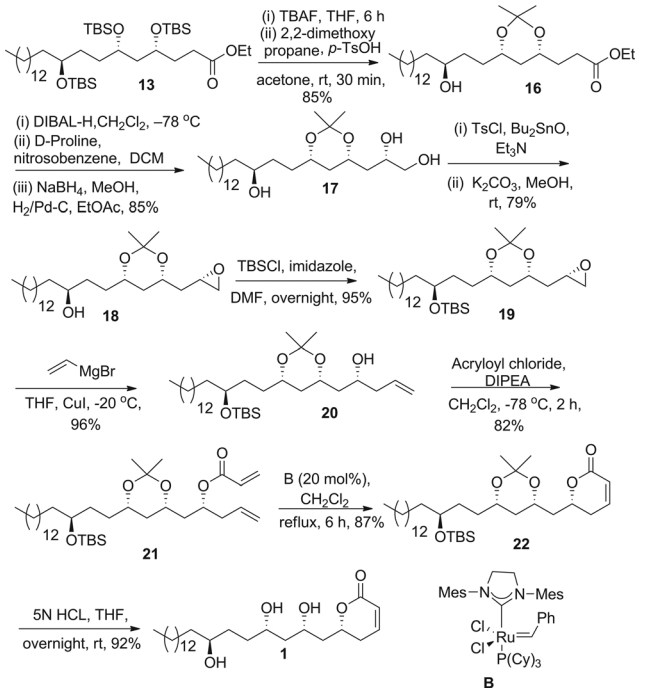
Table 1 Optimization of reaction conditions for α-aminoxylation of aldehyde **6**

Entry	Solvent	Temperature	Yield of **7**
1.	DMSO	rt	15%
2.	ACN	0 °C	No reaction
3.	ACN	rt	Slow reaction
4.	DCM	0 °C	75%

go to completion. This may probably be attributed to the inhomogeneous solution formed in acetonitrile due to the poor solubility of reactants. Interestingly when we used CH_2Cl_2 as solvent at 0 °C, the reaction proceeded cleanly, however facile lactonization of γ-hydroxy ester was observed during the process of purification and storage of compound at room temperature for long time. Hence to avoid lactonization, the crude γ-hydroxy ester **7** was subsequently converted into the corresponding TBS ether **8** in 75% yield (over three steps) and >93% ee.[17]

The DIBAL-*H* reduction of ester **8** in CH_2Cl_2 at −78 °C furnished γ-silyloxy aldehyde **9**, which was subjected to one-carbon Wittig olefination[18] using methyl triphenylphosphonium iodide and *t*-BuOK as a base to give the terminal olefin **10**. The hydroboration-oxidation of olefin **10** gave the alcohol **11**. Compound **11** was oxidized by using IBX to furnish aldehyde **5**, which was directly subjected to sequential α-aminoxylation using D-proline as a catalyst followed by a HWE-olefination reaction to furnish the *O*-amino-substituted allylic alcohol. Hydrogenation of the crude product with catalytic amount of Pd/C, followed by TBS protection of the resultant hydroxy group using TBSCl in DMF afforded the TBS protected γ-hydroxy ester **12** in 65% yield and in 92% de (as determined from ^{1}H and ^{13}C NMR spectroscopy).

With a substantial amount of the TBS protected γ-hydroxy ester **12** in hand, we then proceeded towards another cycle of iteration (Scheme 2) which consists of the same reaction sequences *i.e.* DIBAL-*H* reduction of ester to aldehyde at −78 °C, sequential α-aminoxylation, HWE olefination and H_2-Pd/C reduction followed by TBS protection of the hydroxy group to eventually furnish the *syn* TBS protected γ-hydroxy ester **13** in 65% yield and in 92% de (determined from the ^{1}H and ^{13}C NMR spectral analysis). These findings could probably be attributed to match/mismatch effect of the TBS group, without any appreciable change in yield of the reaction. After generating three stereogenic centers, our next task was to generate the fourth and final stereogenic centers *via* aminoxylation of the aldehyde and subsequent reduction. Towards this end, the ester **13** was subjected to DIBAL-*H* reduction in CH_2Cl_2 at −78 °C to furnish aldehyde **14** which was subjected to α-aminoxylation catalyzed by D-proline, followed by *in situ* reduction using $NaBH_4$, but to our surprise the reaction did not lead to the desired product. We made several attempts to synthesize the diol by changing the reaction conditions, however the required product could not be obtained. This could probably be attributed to the steric crowding around reactive sites because of the TBS groups. The carbonyl group and its α-position is completely shielded due to the steric crowding of the three umbrella-like TBS groups, therefore the access of these active sites is blocked for further reaction. Taking into consideration this observation we considered it worthwhile to change the protecting group and reduce the bulk around the reactive sites of aldehyde **14**. Thus,



Scheme 3

the TBS groups in compound **13** were deprotected followed by hydroxyl group protection as an acetonide to yield **16** in 85% yield (Scheme 3). Ester **16** was then reduced with DIBAL-*H* at −78 °C to furnish the aldehyde, which was subjected to α-aminoxylation catalyzed by D-proline, followed by *in situ* reduction using $NaBH_4$ to give the required *O*-amino-substituted diol, which on reductive hydrogenation afforded the diol **17** in 85% yield. Diol **17** on selective monotosylation and base treatment afforded epoxide **18** in 79% yield, which on TBS protection gave compound **19**. Epoxide **19** was opened with vinylmagnesium bromide to get the homoallylic alcohol **20** in 96% yield.

With the desired allylic alcohol **20** in hand, our next task was to construct the pyranone moiety by ring-closing metathesis. Thus, alcohol **20** was esterified with acryloyl chloride in the presence of iPr_2EtN in CH_2Cl_2 at −78 °C to afford the acryloyl ester **21** in 82% yield. Subsequent ring-closing metathesis[19] of ester **21** with commercially available Grubbs 2nd generation catalyst **B** in refluxing CH_2Cl_2 for 6 h afforded the α,β-unsaturated δ-lactone **22** in 87% yield. Finally global deprotection of TBS and the acetonide group was achieved by treatment of lactone **22** with 5 M hydrochloric acid in tetrahydrofuran to give the target molecule passifloricin A **1** in 92% yield. Our synthetic approach afforded the target compound **1** in a linear sequence of 16 steps with an overall yields of 4.7% in comparison with the most efficient literature synthesis by Murga *et al.*[7] providing an overall 5.6% yields in 14 steps.

Conclusions

In summary, a stereoselective total synthesis of passifloricin A was accomplished *via* an organocatalytic approach employing easily accessible starting materials. The strategy used is amenable to both the *syn* and *anti*-1,3-diol with a high degree of enantio- and diastereoselectivities. The desired stereocenters can be achieved by simply changing the catalyst. We believe that this new approach would permit maximum variability in product structure with regard to stereochemical diversity which is particularly important for making various synthetic analogues required for screening of biological activity.

Experimental

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)octadecanoate (8)

To a solution of palmitaldehyde **6** (2.0 g, 8.3 mmol) and nitroso benzene (0.89 g, 8.3 mmol) in anhydrous CH_2Cl_2 (29 mL) was added D-proline (0.38 g, 3.2 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (4.9 mL, 24.9 mmol), DBU (3.7 mL, 24.9 mmol) and LiCl (1.05 g, 24.9 mmol) in CH_2Cl_2 (29 mL) was added quickly (1–2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The CH_2Cl_2 was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5 × 100 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo* to give crude product which was directly subjected to the next step without purification. To the crude allylic alcohol in ethyl acetate Pd–C (10%) was added under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of the reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of Celite® and concentrated *in vacuo* to give the γ-alcohol. The crude product was then directly subjected to the next step without purification. To an ice-cold stirred solution of γ-hydroxy ester in CH_2Cl_2 (10 mL) imidazole (0.82 g, 12.17 mmol) was added followed by TBSCl (1.37 g, 9.13 mmol) at 0 °C. The resulting mixture was stirred overnight at rt before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether: ethyl acetate (99 : 1) gave the TBS ether **8** (1.76 g, 75% over three step) as a colorless liquid. $[\alpha]_D^{25}$: +4.73 (*c* 0.64, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3011, 1730, 1602, 1491, 1023, 703; ^1H NMR (200 MHz, $CDCl_3$): δ 4.06–4.16 (q, J = 7.07 Hz, 2H), 3.60–3.72 (m, 1H), 2.23–2.38 (m, 2H), 1.60–1.64 (m, 5H), 1.21–1.28 (m, 26H), 0.83–0.9 (m, 12H), 0.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 174.1, 71.1, 60.2, 37.0, 31.9, 31.7, 30.1, 29.7, 29.4, 25.9, 25.2, 22.7, 18.1, 14.2, 14.1, −4.4, −4.6; HRMS (ESI) for $C_{26}H_{54}O_3Si$ $(M + Na)^+$ found 465.3752, calcd 465.3740.

(*S*)-*tert*-Butyldimethyl(oct-7-en-4-yloxy)silane (10)

To a solution of ester **8** (0.5 g, 1.12 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C DIBAL-*H* (1.12 mL, 1.12 mmol, 1 M in toluene) was added dropwise through a syringe. The reaction mixture was stirred for 1 h until the disappearance of the starting material as indicated by TLC and then quenched with saturated sodium potassium tartrate. The precipitate obtained was filtered

off and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude aldehyde, which was used for the next step without purification. To a suspension of methyl triphenylphosphonium iodide (1.36 g, 3.38 mmol) in dry THF (30 mL) *t*-BuOK (0.38 mg, 3.38 mmol) was added. The reaction mixture was stirred for 1 h and allowed to settle. The yellow supernatant liquid was added *via* a syringe to a solution of the crude aldehyde (1 g, 2.25 mmol) in THF (15 mL). The reaction mixture was stirred for 12 h at room temperature and then quenched with 5% aq. NH_4Cl solution. The organic layer was separated and aq. layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether: EtOAc (49 : 1) as eluent to give **10** as a colorless oil (0.34 g, 75%). $[\alpha]_D^{25}$: +0.05 (*c* 0.9, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3008, 1520, 1491, 1023, 703; ^1H NMR (200 MHz): δ 5.91–5.71 (m, 1H), 5.05 4.89 (m, 2H), 3.69–3.98 (m, 1H), 2.17–2.00 (m, 2H), 1.57–1.47 (m, 4H), 1.24–1.16 (m, 24H), 0.88–0.87 (m, 12H), 0.06–0.02 (m, 6H); ^{13}C NMR (50 MHz): δ 139.1, 114.1, 71.8, 37.1, 36.3, 31.5, 29.7, 25.9, 25.3, 22.7, 14.1, −4.4, −4.4.

(*S*)-5-(*tert*-Butyldimethylsilyloxy)nonadecan-1-ol (11)

A solution of olefin **10** (0.982 g, 2.5 mmol) in dry THF (10 mL) was treated under N_2 with BH_3.DMS (1.23 mL of a 2 M THF solution, 2.47 mmol). The reaction mixture was stirred for 4 h at room temperature and then quenched by addition of MeOH (8 mL), 6 M aqueous NaOH (3 mL), and 30% H_2O_2 (5 mL) and stirred for additional 12 h. The resulting mixture was then stirred for 1 h and worked up (extraction with EtOAc). Column chromatography on silica gel (hexane : EtOAc, 19 : 1) afforded **11** (0.84 g, 82%) as a light yellow colored oil. $[\alpha]_D^{25}$ +3.0 (*c* 1.4, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3340 (br, OH) cm^1;^1H NMR (200 MHz) δ 3.64–3.57 (m, 3H), 1.55–1.49 (m, 6H), 1.42–1.36 (m, 4H), 1.22–1.14 (m, 22H), 0.86–0.84 (m, 12H), 0.03 (s, 6H); ^{13}C NMR (50 MHz): δ 72.2, 62.8, 37.1, 36.8, 32.9, 31.9, 29.7, 29.3, 25.9, 25.3, 22.7, 21.4, 18.1, 14.1, −4.5, −5.5; HRMS (ESI) for $C_{25}H_{54}O_2Si$ $(M + Na)^+$ found 437.3793, calcd 437.3791.

(4*S*, 7*S*)-Ethyl 4,7-bis(*tert*-butyldimethylsilyloxy)decanoate (12)

To a solution of **11** (2 g, 4.8 mmol) in 10 mL EtOAc was added IBX (4.05 g,14.4 mmol) and it was heated to 80 °C for 3 h. It was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated and the crude aldehyde was used for the next step without purification. Compound **12** was prepared from the above aldehyde by using the same procedure as described for compound **8** (D-proline as a catalyst) and was purified by flash column chromatography using petroleum ether : ethyl acetate (90 : 10) to furnish pure TBS-ether **12** as a colorless liquid (1.92 g, 65%). $[\alpha]_D^{25}$: +5.44 (*c* 0.28, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 2964, 1730, 1602, 1495, 1020, 703. ^1H NMR (200 MHz, $CDCl_3$): δ 4.16–4.06 (q, *J* = 7.20 Hz, 2H), 3.69–3.58 (m, 2H), 2.41–2.24 (m, 2H), 1.60 (m, 7H), 1.28–1.21 (m, 28H), 0.87–0.83 (m, 21H), 0.02 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 174.0, 72.4, 71.4, 60.2, 37.0, 32.4, 32.3, 31.9, 29.7, 29.4, 25.9, 25.3, 22.7, 14.2, 14.1, −4.4, −4.5, −4.6; HRMS (ESI) for $C_{35}H_{74}O_4Si_2$ $(M + Na)^+$ found 637.5023, calcd 637.5023.

(4*R*, 6*S*, 9*S*)-Ethyl 4,6,9-tris(*tert*-butyldimethylsilyloxy) dodecanoate (13)

Following the same procedure as for compound **8** using D-proline as a catalyst, compound **13** was obtained from compound **12** as a crude product (>92% diastereomeric excess) and was purified by flash column chromatography using petroleum ether : ethyl acetate (90 : 10) to furnish pure TBS-ether **13** (65%) as a colorless liquid. $[\alpha]_D^{25}$: +0.41 (*c* 3.3, $CHCl_3$). IR (neat, cm^{-1}): ν_{max}3011, 1730, 1602, 1495, 1023, 703. ^1H NMR (200 MHz, $CDCl_3$): δ 4.16–4.06 (q, *J* = 7.20 Hz, 2H), 3.80–3.60 (m, 3H), 2.38–2.24 (m, 2H), 1.39–1.21 (m, 37H), 0.91–0.83 (m, 30H), 0.02 (s, 6H), 0.03 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 173.9, 72.5, 69.6, 69.1, 68.5, 60.3, 45.1, 44.5, 37.0, 32.2, 31.9, 29.7, 29.4, 25.9, 25.3, 22.7, 18.0, 14.1, −4.3, −4.4, −4.5; HRMS (ESI) for $C_{43}H_{92}O_5Si_3$ $(M + H\text{-}C_6H_{13}Si_1)^+$ found 659.5462, calcd 659.5466.

Ethyl 3-((4*R*,6*S*)-6-((*S*)-3-hydroxyheptadecyl)-2,2-dimethyl-1,3-dioxan-4-yl)propanoate (16)

To a solution of **13** (0.05 g, 0.06 mmol) in THF (10 mL) TBAF (0.161 mL, 0.16 mmol, 1.0 M solution in THF) was added at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (7 : 3) as eluent gave the alcohol, which was used for the next step without purification. To a solution of the alcohol (0.03 g, 0.08 mmol) in dry acetone (10 mL) 2,2-dimethoxypropane (0.014 mL, 0.12 mmol) and a catalytic amount of *p*-TSA was added. The reaction mixture was then stirred at room temperature for 30 min after which a pinch of solid sodium bicarbonate was added to it and the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography using petroleum ether : ethyl acetate (3 : 2) as eluent to give pure **16** (0.25 g, 85%) as a colorless liquid. $[\alpha]_D^{25}$: +1.11 (*c* 0.18, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3486, 1720, 1605, 1491, 1023, 704. ^1H NMR (200 MHz, $CDCl_3$): δ 5.36–5.31 (m, 1H), 4.68–4.57 (q, *J* = 6.06 Hz, 2H), 4.09–3.89 (m, 2H), 3.74–3.71 (m, 1H), 2.53–2.52 (m, 2H), 1.73–1.61 (m, 8H), 1.37–1.30 (m, 33H), 0.82–0.81 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 174.4, 98.5, 74.3, 72.1, 70.6, 65.5, 40.6, 39.3, 37.3, 35.9, 34.3, 32.3, 31.9, 29.7, 27.0, 25.9, 22.7, 14.11; LC–MS: *m*/*z* = 493 $[M + Na]^+$.

(*S*)-3-((4*R*,6*S*)-6-((*S*)-3-Hydroxyheptadecyl)-2,2-dimethyl-1,3-dioxan-4-yl)propane-1,2-diol (17)

To a solution of ester **16** (0.110 g, 0.23 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C DIBAL-*H* (0.23 mL, 0.23 mmol, 1 M in toluene) was added dropwise through a syringe. The reaction mixture was stirred for 1 h until the disappearance of the starting material as indicated by TLC and then quenched with saturated sodium potassium tartrate. The precipitate obtained was filtered off and the combined organic layers were dried over Na_2SO_4 and

concentrated to give the crude aldehyde, which was used for the next step without purification. To a stirred solution of aldehyde (100 mg, 0.23 mmol) and nitrosobenzene (0.025 g, 0.23 mmol) in $CHCl_3$ (9 mL) D-proline (0.010 g, 0.093 mmol, 20 mol%) was added in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with THF : H_2O (9 : 1) and careful addition of excess $NaBH_4$ (0.031 g, 8.2 mmol). The reaction was quenched after 10 min by sat. NH_4Cl. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc : petroleum ether (40 : 60) as eluent to give the pure aminoxy alcohol. The aminoxy alcohol was dissolved in EtOAc (10 mL), 10% Pd/C (0.010 g) was added to the solution and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography using petroleum ether : ethyl acetate (3 : 2) as eluent to give the pure diol **17** (0.088 g, 85%) as a colorless liquid. $[\alpha]_D^{25}$: +1.11 (*c* 0.18, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3412, 3018, 2938, 1612, 703. ^1H NMR (200 MHz, $CDCl_3$): δ 4.20–4.13 (m, 1H), 3.92–3.86 (m, 2H), 3.58–3.40 (m, 3H), 1.68–1.24 (m, 43H), 0.89–0.85 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 98.8, 71.9, 71.5, 71.4, 69.4, 69.3, 66.5, 39.3, 37.6, 37.4, 37.1, 37.0, 33.5, 33.1, 33.0, 32.2, 31.9, 30.1, 29.7, 25.7, 22.7, 19.9, 19.7, 14.1; HRMS (ESI) for $C_{26}H_{52}O_5$(M + Na)+ found 467.3716, calcd 467.3712.

tert-Butyl((*S*)-1-((4*S*,6*S*)-2,2-dimethyl-6-((*S*)-oxiran-2-yl-methyl)-1,3-dioxan-4-yl)heptadecan-3-yloxy) dimethylsilanebutyldimethyl((*S*)-1-((*R*)-oxiran-2-yl)-4-phenylbutan-2-yloxy)silane (19)

To a mixture of diol **17** (0.26 g, 0.04 mmol), in dry CH_2Cl_2 (5 mL) dibutyltin oxide (catalytic) was added followed by the addition of *p*-toluenesulfonyl chloride (0.008 g, 0.04 mmol) and triethylamine (0.006 mL, 0.04 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with CH_2Cl_2 (3 × 10 ml) and then the combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C K_2CO_3 (18 mg, 0.13 mmol) was added and the resultant mixture was allowed to stir for 1 h at same temperature. After completion of reaction (as indicated by TLC) the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 × 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether : ethyl acetate (19 : 1) gave the epoxide **18** (0.20 g, 79%) as a colorless liquid.

To the ice cold stirred solution of epoxide **18** (0.115 g, 0.28 mmol) in DMF (0.5 mL) imidazole (0.038 g, 0.56 mmol) and TBSCl (0.06 g, 0.42 mmol) was added at 0 °C. The resulting mixture was stirred for overnight at rt before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The column chromatography of crude product using petroleum ether : ethyl acetate (19 : 1) gave the TBS protected epoxide **19** (0.30 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$: +1.01 (*c* 1.65, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3012, 2988, 1612, 1581, 1463, 703. ^1H NMR (200 MHz, $CDCl_3$): δ 3.81–3.76 (m, 1H), 3.52–3.49 (dd, *J* = 5.8 Hz, *J* = 9.76 Hz, 1H), 3.33–3.30 (dd, *J* = 6.41 Hz, *J* = 9.77 Hz, 1H), 2.30–2.27 (m, 1H), 2.04–1.98 (m, 1H), 1.78–166 (m, 1H), 1.42–1.24 (m, 30H), 0.89–0.87 (m, 22H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 98.4, 72.1, 69.4, 68.9, 65.4, 62.9, 51.5, 49.2, 37.2, 36.5, 34.1, 32.3, 31.9, 29.7, 29.4, 25.9, 25.7, 24.9, 22.7, 20.6, 18.4, 14.1, −2.9; HRMS (ESI) for $C_{32}H_{64}O_4Si$ $(M + H)^+$ found 541.4653, calcd 541.4652.

(*R*)-1-((4*R*,6*S*)-6-((*S*)-3-(*tert*-Butyldimethylsilyloxy)heptadecyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol (20)

A round bottom flask was charged with copper(I) iodide (57 mg, 0.30 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to −20 °C, vigorously stirred and vinylmagnesium bromide (1 M in THF, 15.9 mL, 1.21 mmol) was injected to it. A solution of **19** (164 mg, 1.21 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at −20 °C for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : EtOAc (19 : 2) as eluent provided **20** (0.165 g, 96%) as a colorless liquid. $[\alpha]_D^{25}$: +2.02 (*c* 1.12, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 3448, 2929, 2855, 1612, 1580, 1381, 1103, 703. ^1H NMR (200 MHz, $CDCl_3$): δ 5.87–5.74 (m, 1H), 5.15–5.02 (m, 2H), 4.15–4.03 (m, 2H), 3.66–3.60 (m, 2H), 2.65–2.58 (m, 2H), 1.28–1.23 (m, 40H), 0.88–0.86 (m, 12H), −0.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 135.0, 134.8, 129.0, 129.2, 125.3, 98.6, 72.1, 71.7, 64. 7, 60.4, 51.3, 44.9, 44.7, 38.9, 34.3, 31.9, 29.7, 29.4, 26.9, 25.9, 22.7, 21.9, 16.8, 14.1, −4.4; LC–MS: *m*/*z* = 591 $[M + Na]^+$.

(*R*)-1-((4*S*,6*S*)-6-((*S*)-3-(*tert*-Butyldimethylsilyloxy)heptadecyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-yl acrylate (21)

Alcohol **20** (50 mg, 0.087 mmol) was dissolved in dry CH_2Cl_2 (10 mL) at −78 °C and treated sequentially with ethyl diisopropyl amine (0.17 g, 0.2 mL, 13.18 mmol) and acryloyl chloride (0.079 g, 0.071 mL, 0.878 mmol). The reaction mixture was stirred for 2 h at −78 °C. The resulting mixture was filtered through a pad of Celite, poured into water and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (19 : 1) as eluent afforded **21** (44 mg, 82%) as an amorphous solid. $[\alpha]_D^{25}$: +0.18 (*c* 1.65, $CHCl_3$). IR (neat, cm^{-1}): ν_{max} 2886, 1730, 1644, 1491, 1140, 731; ^1H NMR (500 MHz, $CDCl_3$): δ 6.42–6.36 (m, 1H), 6.18–6.04 (m, 1H), 5.83–5.71 (m, 2H), 5.38–5.20 (m, 1H), 5.11–5.04 (m, 2H), 3.86–3.70 (m, 1H), 3.65–3.58 (m, 2H), 2.06–1.98 (m, 2H),

1.29–1.19 (m, 40H), 0.88–0.85 (m, 12H), 0.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 165.6, 133.4, 128.1, 127.7, 117.9, 98.2, 74.3, 72.2, 70.0, 69.2, 40.6, 38.9, 37.1, 34.1, 29.7, 27.0, 25.9, 24.9, 22.7, 18.1, 16.8, 14.1, −4.4; HRMS (ESI) for $C_{37}H_{70}O_5Si$ $(M + Na)^+$ found 645.4893, calcd 645.4890.

(*R*)-6-(((4*S*,6*S*)-6-((*S*)-3-(*tert*-Butyldimethylsilyloxy)heptadecyl)-2,2-dimethyl-1,3- dioxan-4-yl)methyl)-5,6-dihydro-2*H*-pyran-2-one (22)

Grubbs' catalyst **B** (33 mg, 0.004 mmol) dissolved in CH_2Cl_2 (10 mL) was added drop wise to a refluxing solution of acrylate **21** (25 mg, 0.040 mmol) in dry CH_2Cl_2 (60 mL). Refluxing was continued for 6 h by which time all the starting material was consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using petroleum ether : EtOAc (19 : 1) as eluent to afford **22** (27 mg, 87%) as an amorphous solid. $[\alpha]_D^{25}$: +0.41 (*c* 1.35, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν_{max} 2925, 2855, 1725, 1459, 1385, 1100, 1052, 705. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91–6.83 (m, 1H), 6.03–6.00 (d, J = 9.8 Hz, 1H), 5.15–5.06 (m, 1H), 4.23–4.15 (m, 1H), 3.63–3.60 (m, 2H), 2.50–2.37 (m, 2H), 1.29–1.21 (m, 40H), 0.88–0.85 (m, 12H), 0.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 174.4, 146.5, 133.4, 128.8, 128.1, 127.7, 118.1, 98.5, 74.3, 72.1, 70.1, 70.6, 69.0, 65.5, 41.2, 39.3, 38.9, 35.9, 32.3, 30.2, 29.4, 25.9, 23.8, 21.9, 19.5, 18.1, 16.8, 14.1, −4.4; LC–MS: m/z = 617 $[M + Na]^+$.

(*R*)-6-((2*S*,4*S*,7*S*)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydro-2*H*-pyran-2-one (1)

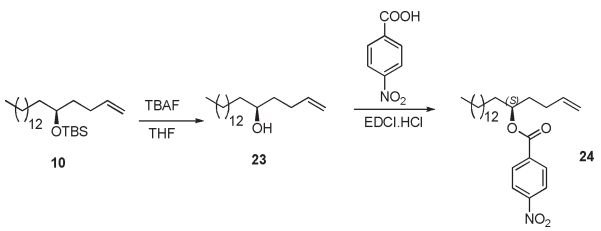
To a solution of compound **22** (0.033 g, 0.05 mmol) in THF (2 mL) 5 M aq HCl (1 mL) was added, and the mixture was stirred at r.t. for overnight. After completion of the reaction, the reaction mixture was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with H_2O (5 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography to afford compound **1** (0.022 g, 92%) as a colorless solid. mp 102–105 °C (lit[7] mp 103–106 °C).; $[\alpha]_D^{25}$ +34.3 (*c* 1.0, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +33.3 (*c* 0.8, $CHCl_3$)}; IR (KBr): 3325, 2917, 1707, 1530, 1251, 1027, 740 cm^1; ^{1}H NMR (200 MHz, $CDCl_3$):δ 6.90–6.89 (m,1H), 6.03(d, J = 9.8 Hz, 1 H), 4.68–4.33 (m, 1H), 4.02–3.86 (m, 4H), 2.54–2.51 (m, 2H), 1.84–1.81 (m, 8H), 1.24 (br, m, 28H), 0.90–0.89 (m, 3H).

Acknowledgements

M. P. and P. G. thank DST, New Delhi and CSIR New Delhi respectively for financial assistance. Financial support from DST, New Delhi (Grant No. SR/S1/OC-44/2009) is gratefully acknowledged. The authors also thank Prof. M. K. Ghorai, from Indian Institute of Technology, Kanpur, for HRMS analysis.

Notes and references

1 S. D. Rychnovsky, *Chem. Rev.*, 1995, **95**, 2021.
2 J. Jodynis-Liebert, M. Murias and E. Bloszyk, *Planta Med.*, 2000, **66**, 199.
3 S. E. Drewes, B. M. Schlapelo, Horn, R. Scott-Shaw and O. Sandor, *Phytochemistry*, 1995, **38**, 1427.
4 F. Echeverri, V. Arango, W. Quiñones, F. Torres, G. Escobar, Y. Rosero and R. Archbold, *Phytochemistry*, 2001, **56**, 881.
5 W. Cardona, W. Quinones and F. Echeverri, *Molecules*, 2004, **9**, 666.
6 (*a*) J. Murga, J. Garcia-Fortanet, M. Carda and J. A. Marco, *Tetrahedron Lett.*, 2003, **44**, 7909; (*b*) J. Garcia-Fortanet, J. Murga, M. Carda and J. A. Marco, *Org. Lett.*, 2003, **5**, 1447; (*c*) J. Cossy, S. BouzBouz and M. C. R. Popkin, *C. R. Chim.*, 2003, **6**, 547; (*d*) S. BouzBouz and J. Cossy, *Tetrahedron Lett.*, 2003, **44**, 4471.
7 J. Murga, J. García-Fortanet, M. Carda and J. A. Marco, *J. Org. Chem.*, 2004, **69**, 7277 and references cited therein.
8 S. Chandrasekhar, C. H. Rambabu and A. S. Reddy, *Tetrahedron Lett.*, 2008, **49**, 4476.
9 (*a*) D. A. Evans and J. A. Gauchet-Prunet, *J. Org. Chem.*, 1993, **58**, 2446. For its use in 1,3-polyol synthesis, see: (*b*) T. J. Hunter and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 1049; (*c*) Y. Wang, Y. Xing, Q. Zhang and G. A. O'Doherty, *Chem. Commun.*, 2011, **47**, 8493.
10 G. Sabitha, M. N. Prasad, K. Shankaraiah, M. N. Reddy and J. S. Yadav, *Synthesis*, 2010, **22**, 3891.
11 (*a*) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures* Wiley, Weinheim, 2007; (*b*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638.
12 D. W. C. MacMillian, *Nature*, 2008, **455**, 304.
13 (*a*) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak and A. Cordova, *Angew. Chem., Int. Ed.*, 2005, **44**, 1343; (*b*) D. B. Ramachary, N. S. Chowdari and C. F. Barbas, *Synlett*, 2003, 1910; (*c*) M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 3958; . For α-functionalization reviews, see: (*d*) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 18296; . For a comprehensive review on α-aminoxylation, see: (*e*) P. Merino and T. Tejero, *Angew. Chem., Int. Ed.*, 2004, **43**, 2995 and references cited therein (*f*) B. List, *J. Am. Chem. Soc.*, 2002, **124**, 5656; (*g*) G. Zhong and Y. Yu, *Org. Lett.*, 2004, **6**, 1637; (*h*) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan and G. Zhong, *Angew. Chem., Int. Ed.*, 2008, **47**, 10187; . For a review on proline-catalyzed asymmetric reactions, see: (*i*) B. List, *Tetrahedron*, 2002, **58**, 5573.
14 For reviews on organocatalytic tandem reactions, see: (*a*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*b*) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037; (*c*) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477.
15 N. B. Kondekar and P. Kumar, *Org. Lett.*, 2009, **11**, 2611.
16 (*a*) P. Kumar, S. V. Naidu and P. Gupta, *J. Org. Chem.*, 2005, **70**, 2843; (*b*) P. Kumar and S. V. Naidu, *J. Org. Chem.*, 2005, **70**, 4207; (*c*) P. Gupta, S. V. Naidu and P. Kumar, *Tetrahedron Lett.*, 2005, **46**, 6571; (*d*) P. Kumar, P. Gupta and S. V. Naidu, *Chem.–Eur. J.*, 2006, **12**, 1397; (*e*) P. Kumar and S. V. Naidu, *J. Org. Chem.*, 2006, **71**, 3935; (*f*) P. Gupta and P. Kumar, *Eur. J. Org. Chem.*, 2008, 1195; (*g*) S. K Pandey, M. Pandey and P. Kumar, *Tetrahedron Lett.*, 2008, **49**, 3297; (*h*) P. S. Chowdhury, P. Gupta and P. Kumar, *Tetrahedron Lett.*, 2009, **50**, 7018; (*i*) P. Kumar, M. Pandey, P. Gupta, S. V. Naidu and D. D. Dhavale, *Eur. J. Org. Chem.*, 2010, **36**, 6993.
17 The enantioselectivity of compound **8** was determined as 93% ee using chiral HPLC by converting compound **10** (derived from **8**, Scheme 2) into compound **24** through the following sequence of reaction. Compound **10** was subjected to TBS deprotection followed by hydroxyl group conversion into its 4-nitrobenzoate ester **24**. {Chiralcel OD-H, iPrOH/hexane (1 : 99), flow rate 0.4 ml min^{-1}, tR = 11.35(major), tR = 12.31(minor)}



18 L. Fitjer and U. Quabeck, *Synth. Commun.*, 1985, **15**, 855.
19 For reviews on ring-closing metathesis, see: (*a*) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; (*b*) J. Prunet, *Angew. Chem., Int. Ed.*, 2003, **42**, 2826.