An asymmetric route to the construction of the bicyclic framework of marine eicosanoids Bacillariolides

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Dedicated to Professor S. Swaminathan on the occasion of his 80th birthday
(received 31 Aug 04; accepted 14 Oct 04; published on the web 02 Nov 04)

Abstract
A stereoselective route to the synthesis of γ-lactone fused cyclopentenes, the core structure of the marine eicosanoids bacillariolides, is described. The key step involves ring closing metathesis of 1,6-diene built from D-mannitol to construct the cyclopentene unit in enantiomerically pure form.

Keywords: Asymmetric synthesis, eicosanoids, butanolides, olefin metathesis

Introduction
Bacillariolides 1-3 are structurally unique eicosanoids possessing a γ-lactone fused cyclopentanol framework with four contiguous stereocenters. Bacillariolide I 1 and bacillariolide II 2 were isolated from the marine diatom, pseudonitzscha multiseries, while bacillariolide III 3 was isolated from the culture medium of the same marine diatom and is considered a metabolite obtained from oxidative cleavage of the side chain. The natural product 1 was reported as an inhibitor of phospholipase A2 (PLA2) while the biological functions of bacillariolides 2 and 3 are under investigation. PLA2 is one of the enzymes that metabolize lipids liberating fatty acids which through a cyclooxygenase pathway leads to the formation of prostaglandins and leukotrienes, which are known to be potent mediators of inflammation. Thus, inhibition of PLA2 is considered to be an attractive target for the design of antiinflammatory drugs. Due to the biological potential and stereochemically accessible structure, bacillariolides have become the target of synthetic investigations.3 We herein report an asymmetric approach for the synthesis of bacillariolides starting from D-mannitol.
Results and Discussion

The key concept employed in this approach relies on the construction of the cyclopentane ring of bacillariolides through ring closing metathesis (RCM) of a diene built from a carbohydrate derivative. The carbohydrate derivative is chosen in a way so as to provide the lactone unit. RCM of dienes derived from carbohydrates has been shown to be an efficient approach for the synthesis of enantio-pure cyclic systems of various ring size. This concept has recently been employed by us to construct substituted cyclopentenols, the core structural unit of the carbocyclic nucleosides carbovir and abacavir. We envisaged that the cyclopentene derivative would be an ideal intermediate for the synthesis of bacillariolides (Scheme 1) as hydroxyl group can be introduced through intramolecular hydroboration by alkoxyborane generated in situ from the hydroxymethyl group in (R=H) during reaction with borane. A sequence of RCM followed by lactonisation in the diene will provide this bicyclic intermediate. The diene may be expected to be available from the known unsaturated ester which in turn is available from D-mannitol.

The unsaturated ester along with its diastereoisomer was obtained from D-mannitol derivative following the procedure developed by us as depicted in Scheme 2. Wittig-Horner reaction of the aldehyde generated in situ from periodate cleavage of the diol afforded the unsaturated ester. The ester was reduced with LiAlH₄ at –60 °C to afford the allyl alcohol.

![Diagram](image)

**Scheme 1**

Ortho-ester Claisen rearrangement of this allylic alcohol produced a mixture of chromatographically separable unsaturated esters 6 and 10.
In connection to a different project, alkylation of the enolate generated from the unsaturated ester 6 was investigated. It was found that such alkylation results in the synthesis of products in which the incoming electrophile occupies a position anti to the vinyl group. Thus alkylation of the enolate of the ester 6 was unlikely to provide the required cis-diene 5. To circumvent this problem we decided to use the malonate derivative 11. The malonate derivative 11 was prepared in 75% yield from the lithium enolate of the unsaturated ester 6 with ethyl chloroformate (Scheme 3). Allylation of the malonate derivative 11 with allyl bromide afforded the diene 12 in 78% yield. Ring closure of 12 proceeded smoothly when treated with the Grubbs’ catalyst $(PCy_3)_2Cl_2Ru=CHPh$ 13 in benzene at 60°C to produce the cyclopentene 14 in 83% yield. Treatment of 14 with 80% aqueous acetic acid at 80-85°C led to deketalisation with concomitant lactonisation to produce the bicyclic lactone 15 in 83% yield.

Scheme 3
The unsaturated ester 10 was similarly converted to the bicyclic lactone 19 through the malonate derivative 16 (Scheme 4). The synthesis of the diene 17 through allylation of 16 followed by its RCM to produce the cyclopentene 18 was straightforward. The cyclopentene latter underwent smooth lactonisation when treated with 80% aqueous acetic acid to produce the lactone 19 in excellent yield.

Scheme 4

The stereochemical assignment to the lactones 15 and 19 relies on comparison of the chemical shifts and coupling constants of Hₐ. Typically vicinal protons on a five-membered ring exhibit a coupling constant of at least 8 Hz when they are in a syn configuration, whereas the vicinal protons in an anti configuration normally exhibit a coupling constant close to zero. In the lactone 19, Hₐ appears at δ 4.85 as a dd (J = 6.12 and 12.18 Hz). Coupling of Hₐ with Hₐ gives rise to a doublet with a coupling constant of 12.18 Hz indicating a syn configuration. A second coupling (J = 6.12 Hz) with the CH₂ protons of CH₂OH group leads to a dd (formed by merger of two triplets). On the other hand in 15, Hₐ appears at δ 4.40 as a dt (J = 1.95 and 4.5 Hz). The smaller value of coupling constant (J = 1.95 Hz) between Hₐ and Hₐ in 15 indicates an anti relationship between them. This is further supported by the shielding of Hₐ proton in 15 by 0.45 ppm over 19. This indicates that Hₐ lies in the shielding zone of the alkene unit in the cyclopentene ring which requires Hₐ and cyclopentene ring to be on the same side in 15. The transformation of the esters 6 and 10 to the lactones 15 and 19 respectively also confirms the stereochemical assignment to the esters 6 and 10. The bicyclic lactones 15 and 19 represent the core structural units with the desired relative stereochemistry present in 1 and 2 respectively. Transformation of these lactones to the desired intermediate 4 requires removal of the carbethoxy group. Disappointingly, the carbethoxy group present in them could not be removed as both the lactones 15 and 19 were found to be resistant to hydrolysis or decarbethoxylation by
Krapcho’s method. The failure of 15 and 19 to undergo hydrolysis may be attributed to increase in steric crowding due to change in hybridisation state from sp$^2$ to sp$^3$ during hydrolysis.

In conclusion we have developed an asymmetric route for access to bacillariolides using RCM of 1, 6 -dienes built from D-mannitol as the key step. This investigation has resulted in the synthesis of bicyclic core structure of bacillariolides with correct stereochemistry.

**Experimental Section**

**General Procedures.** All reactions were carried out under an atmosphere of N$_2$. A usual work up involves extraction of the reaction mixture with diethyl ether, washing of organic extracts with brine, drying over anhydrous Na$_2$SO$_4$ and removal of solvent at reduced pressure. Column chromatography was performed on silica gel (60-120 mesh). Petroleum refers to the fraction of petroleum ether bp 60-80 °C. IR spectra were recorded in thin film. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ solution at 300 MHz and 75 MHz respectively in Bruker DPX 300. Elemental analyses were carried out at the microanalytical laboratory of this department.

**Diethyl[(1R)-1-(1,4-dioxaspiro[4.5]dec-2-yl)prop-2-enyl]malonate (11).** A solution of the ester 6 (870 mg, 3.25 mmol) in THF (8 mL) was added dropwise to a magnetically stirred solution of LDA [prepared from diisopropylamine (0.91 mL, 8.12 mmol) in anhydrous THF (3 mL) and nBuLi (4.8 mL, 6.5 mmol, 1.35 M in hexane)] at -78 °C. The reaction mixture was then slowly warmed to –30 °C and stirred at that temperature for 1h. The reaction mixture was again cooled to –78 °C and to it HMPA (0.5 mL) followed by ethyl chloroformate (0.37 mL, 3.9 mmol) was added dropwise. The reaction mixture was allowed to attain –30 °C and stirred for 2 h. After quenching with saturated aqueous ammonium chloride solution (1mL), the reaction mixture was worked up in the usual way. The crude product was purified by column chromatography using n-hexanes-ether (19:1) as eluent to afford the malonate derivative 11 (830 mg, 75%) as a colourless liquid; [$\alpha$]$_D^{25}$ $^{+}$13.8 (c 0.95, CHCl$_3$); IR $\nu_{max}$ 1736.25 cm$^{-1}$; $^1$H NMR $\delta$ 1.23 (3H, t, $J$ = 7 Hz), 1.25 (3H, t, $J$ = 7 Hz), 1.30 (2H, br s), 1.50 (4H, s), 1.56 (4H, s), 2.78-2.87 (1H, m), 3.61 (1H, dd, $J$ = 8.0, 6.7 Hz), 3.76 (1H, d, $J$ = 5.9 Hz), 3.89 (1H, d, $J$ = 8.2, 6.0 Hz), 4.06-4.24 (5H, m), 5.08-5.16 (2H, m), 5.77-5.89 (1H, m); $^{13}$C NMR $\delta$ 14.5 (CH$_3$), 24.1 (CH$_2$), 24.3 (CH$_2$), 25.5 (CH$_2$), 35.3 (CH$_2$), 36.8 (CH$_2$), 49.3 (CH), 53.8 (CH), 61.5 (CH$_2$), 61.7 (CH$_2$), 68.3 (CH$_2$), 75.7 (CH), 110.6 (C), 120.1 (CH$_2$), 134.3 (CH), 169.0 (CO). Anal. Caled for C$_{18}$H$_{28}$O$_6$: C, 63.49; H, 8.30. Found : C, 63.77; H, 8.89.

**Diethyl [(1S)-1-(1,4-dioxaspiro[4.5]dec-2-yl)prop-2-enyl]malonate (16).** Following the above procedure, the malonate derivative 16 (690 mg, 78%) was prepared from the ester 10 (640 mg, 2.39 mmol); [$\alpha$]$_D^{25}$ $^{+}$17.0 (c, 0.975, CHCl$_3$); IR $\nu_{max}$ 1749.3, 1732.0 cm$^{-1}$; $^1$H NMR $\delta$ 1.19 (3H, t, $J$ = 7.1 Hz), 1.22 (3H, t, $J$ = 7.1 Hz), 1.34 (2H, br s), 1.49 (4H, s), 1.62 (4H, s), 2.89 (1H, dt, $J$ = 9.9, 2.6 Hz), 3.61 (2H, m), 3.94 (1H, t, $J$ = 7.8 Hz), 4.06-4.26 (5H, m), 5.08-5.18 (2H, m), 5.68-5.81 (1H, m); $^{13}$C NMR $\delta$ 14.40 (CH$_3$), 14.43 (CH$_3$), 24.1 (CH$_2$), 24.3 (CH$_2$), 25.5 (CH$_2$), 34.8
(CH2), 36.0 (CH2), 46.4 (CH), 54.3 (CH), 61.7 (CH2), 61.9 (CH2), 66.8 (CH2), 74.9 (CH), 110.0 (C), 120.4 (CH2), 133.3 (CH), 168.4 (CO), 168.5 (CO). Anal. Calcd for C18H28O6 : C, 63.49; H, 8.30 Found : C, 63.82; H, 8.48.

**Diethyl allyl [(1R)-1-(1,4-dioxaspiro[4.5]dec-2-yl)prop-2-enyl]malonate (12).** To a magnetically stirred suspension of NaH (116 mg, 2.43 mmol, 50% in oil) [de-greased by repeated washing with petroleum] in THF (2 mL) was added dropwise a solution of the substituted malonate 11 (550 mg, 1.62 mmol) in THF (5 mL). The mixture was stirred for 2 h and then HMPA (0.3 mL) followed by allyl bromide (0.21 mL, 2.43 mmol) was added at rt. After refluxing for 2 h, the reaction mixture was cooled to rt and quenched by adding saturated aqueous NH4Cl solution (1 mL). A usual work-up of the reaction mixture followed by column chromatography using n–hexanes-ether (19:1) as eluent afforded the diene 12 (510 mg, 83%) as colorless viscous liquid; [α]D25 +4.4 (c 0.9, CHCl3); IR: νmax 1732.0, 1737.8 cm-1; 1H NMR δ 1.23 (6H, t, J = 7 Hz), 1.32 (2H, br s), 1.50 (4H, s), 1.52 (4H, s), 2.63-2.67 (2H, m), 2.89 (1H, dd, J = 10, 7.6 Hz), 3.47 (1H, t, J = 8 Hz), 3.84 (1H, dd, J = 8.2, 6.0 Hz), 4.18-4.3 (4H, m), 4.97-5.19 (4H, m), 5.55-5.67 (1H, m), 5.80-5.90 (1H, m); 13C NMR δ 14.4 (CH3), 24.2 (CH2), 24.26 (CH2), 24.3 (CH2), 24.3 (CH2), 25.6 (CH2), 35.4 (CH2), 36.8 (CH2), 40.2 (CH2), 60.4 (C), 53.2 (CH), 61.4 (CH2), 61.5 (CH2), 68.4 (CH2), 75.1 (CH), 109.9 (C), 118.0 (CH2), 118.6 (CH2), 133.4 (CH), 134.4 (CH), 170.3 (CO). Anal. Calcd for C21H32O6 : C, 66.29; H, 8.48. Found : C, 66.34; H, 8.88.

**Diethyl allyl[(1S)-1-(1,4-dioxaspiro[4.5]dec-2-yl)prop-2-enyl]malonate (17).** Following the above procedure, the diene 17 (340 mg, 86%) was prepared from 16 (350 mg, 1.03 mmol); IR: νmax 1732.0 cm-1; 1H NMR δ 1.8 (6H, t, J = 7 Hz), 1.27 (2H, br s), 1.44 (8H, br s), 2.56 (1H, dd, J = 7.8, 18 Hz), 2.67 (2H, m), 3.50 (1H, t, J = 8.1 Hz), 3.94-4.20 (5H, m), 4.45 (1H, m), 4.95-5.04 (3H, m), 5.18 (1H, dd, J = 10.2, 2.0 Hz), 5.57-5.60 (1H, m), 5.76-5.89 (1H, m); 13C NMR δ 14.2 (CH3), 14.4 (CH3), 24.2 (CH2), 24.2 (CH2), 25.5 (CH2), 35.8 (CH2), 35.9 (CH2), 28.2 (CH2), 48.8 (CH), 59.5 (C), 61.4 (CH2), 61.8 (CH2), 67.8 (CH2), 74.7 (CH), 110.0 (C), 119.3 (CH2), 120.3 (CH2), 132.6 (CH), 133.1 (CH), 170.5 (CO), 170.9 (CO).

**Diethyl (2R)-2-(1,4-dioxaspiro[4.5]dec-2-yl)cyclopent-3-ene-1,1-dicarboxylate (14).** A solution of the diene 12 (500 mg, 1.33 mmol) in anhydrous benzene (20 mL) was degassed by bubbling argon gas through it. To it was added Grubbs’ catalyst 13 (42 mg, 4 mole%) in one portion. The resulting pink solution was stirred at 60 °C for 36 h. The solvent was removed under reduced pressure, and the dark residue was purified by column chromatography using n-hexanes-ether (19:1) as eluent to afford the cyclopentene derivative 14 (400 mg, 83%); [α]D25 +5.8 (c 1.07, CHCl3); IR: νmax 1731.7 cm-1; 1H NMR δ 1.23 (3H, t, J = 7 Hz), 1.25 (3H, t, J = 7 Hz), 1.34 (2H, br s), 1.49 (4H, s), 1.63 (4H, s), 2.85 (1H, d, J = 17.3 Hz), 3.57 (1H, d, J = 17.5 Hz), 3.52(1H, t, J = 7.5 Hz), 3.79 (1H, m), 3.85-3.90 (1H, m), 3.99-4.24 (5H, m), 5.45 (1H, br s), 5.73 (1H, br s); 13C NMR δ 14.3 (CH3), 14.4 (CH3), 24.2 (CH2), 24.3 (CH2), 25.2 (CH2), 35.3 (CH2), 36.6 (CH2), 40.2 (CH2), 54.7 (CH), 61.9 (CH2), 61.9 (CH2), 62.2 (C), 67.2 (CH2), 75.4 (CH), 109.8 (C), 128.6 (CH), 133.3 (CH), 170.6 (CO), 172.2 (CO). Anal. Calcd for C19H28O6: C, 64.75; H, 8.00. Found : C, 64.98; H, 7.61.
Diethyl (2S)-2-(1,4-dioxaspiro[4.5]dec-2-yl)cyclopent-3-ene-1,1-dicarboxylate (18). Following the above procedure, the cyclopentene 18 (250 mg, 90%) was prepared from the diene 17 (300 mg, 0.79 mmol); IR: $\nu_{\text{max}}$ 1736 cm$^{-1}$; $^1$H NMR $\delta$ 1.21 (3H, t, $J = 7.1$ Hz), 1.23 (3H, t, $J = 7$ Hz), 1.36 (2H, br s), 1.50 (4H, br s), 1.56 (4H, m), 2.70 (1H, dd, $J = 16.9, 1.6$ Hz), 3.28 (1H, dd, $J = 16.9, 1.5$ Hz), 3.62 (1H, m), 3.77 (1H, dd, $J = 8.2, 6.3$ Hz), 3.99 (1H, dd, $J = 8.3, 6.2$ Hz), 4.09-4.25 (5H, m), 5.73 (2H, s); $^{13}$C NMR $\delta$ 14.3 (CH$_3$), 14.4 (CH$_3$), 24.2 (CH$_2$), 24.4 (CH$_2$), 25.6 (CH$_2$), 35.2 (CH$_2$), 36.5 (CH$_2$), 41.5 (CH$_2$), 54.7 (CH), 61.9 (CH$_2$), 61.9 (CH$_2$), 62.1 (C), 68.1 (CH$_2$), 75.5 (CH), 109.8 (C), 129.3 (CH), 129.7 (CH), 170.4 (CO), 172.3 (CO). Anal. Calcd for C$_{19}$H$_{28}$O$_6$: C, 64.75; H, 8.00. Found: C, 64.47; H, 8.12.

Ethyl (1S, 3a$S$, 6a$R$)-1-(hydroxymethyl)-3-oxo-4,6a-dihydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate (15). A solution of the cyclopentene derivative 14 (150 mg, 0.43 mmol) in aqueous acetic acid (80%, 1.5 mL) was stirred at 80 °C for 4h. The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated NaHCO$_3$ solution (3x2 mL) to make it alkaline (pH paper). The organic layer was separated and dried (Na$_2$SO$_4$). Evaporation of the solvent under vacuum afforded a liquid which was chromatographed using n-hexanes-ether (7:3) as eluent to afford the lactone 15 (80 mg, 83%); $[\alpha]_{D}^{25}$ +14.6 (c 0.5, CHCl$_3$); IR: $\nu_{\text{max}}$ 3504.4, 1774.4, 1735.8 cm$^{-1}$; $^1$H NMR $\delta$ 1.26 (3H, t, $J = 7.1$ Hz), 2.56 (1H, br s), 3.09 (2H, d, $J = 4.3$ Hz), 3.84 (2H, d, $J = 4.2$ Hz), 4.20 (2H, q, $J = 7.0$ Hz), 4.40 (1H, dt, $J = 1.95, 4.5$ Hz), 5.60 (1H, m), 5.76 (1H, m); $^{13}$C NMR $\delta$ 14.4 (CH$_3$), 42.7 (CH$_2$), 54.7 (CH), 60.2 (C), 62.6 (CH$_2$), 64.5 (CH$_2$), 84.5 (CH), 131.0 (CH), 129.6 (CH), 170.5 (CO), 176.4 (CO). Anal. Calcd for C$_{11}$H$_{14}$O$_5$: C, 58.40; H, 6.24. Found : C, 58.55; H, 6.17.

Ethyl (1S, 3a$R$, 6a$S$)-1-(hydroxymethyl)-3-oxo-4,6a-dihydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate (19). Following the above procedure, the cyclopentene derivative 18 (250 mg, 0.71 mmol) was treated with 80% aqueous acetic acid to afford the lactone 19 (130 mg, 81%) as a colorless oil; $[\alpha]_{D}^{25}$ +61 (c 0.15, CHCl$_3$); IR: $\nu_{\text{max}}$ 3438.8, 1776.3, 1737.7 cm$^{-1}$; $^1$H NMR $\delta$ 1.28 (3H, t, $J = 7$ Hz), 2.47 (1H, br s), 3.04 (2H, ddd, $J = 17.5, 4.4, 2.1$ Hz), 3.75-3.80 (1H, m), 3.83 (2H, d, $J = 6$ Hz), 4.26 (2H, q, $J = 7$ Hz), 4.85 (1H, dd, $J = 6.12, 12.18$ Hz), 5.51-5.55 (1H, m), 5.83-5.87 (1H, m); $^{13}$C NMR $\delta$ 14.4 (CH$_3$), 40.0 (CH$_2$), 54.7 (CH), 61.7 (C), 62.8 (CH$_2$), 62.8 (CH$_2$), 82.5 (CH), 125.4 (CH), 133.3 (CH), 169.1 (CO). Anal. Calcd for C$_{11}$H$_{14}$O$_5$: C, 58.40; H, 6.24. Found : C, 58.69; H, 6.43.

Acknowledgements

Financial support from the Department of Science and Technology, Government of India is gratefully acknowledged. SS and TB thank Council of Scientific and Industrial Research, New Delhi for research fellowships.
References


