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

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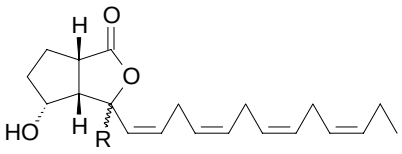
Abstract

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.

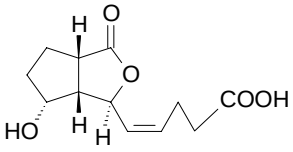
Keywords: Asymmetric synthesis, eicosanoids, butanolides, olefin metathesis

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 (PLA_2) while the biological functions of bacillariolides **2** and **3** are under investigation. PLA_2 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 PLA_2 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.



1, R = α - H
2, R = β - H



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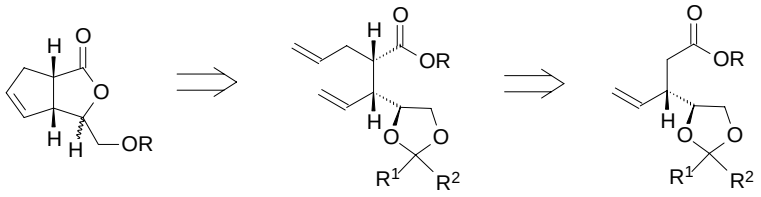
Results and Discussion

The key concept employed in this approach relies on the construction of the cyclopentane ring of bacillariolides through ring closing metathesis (RCM)[4] 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[4-6] for the synthesis of enantio-pure cyclic systems of various ring size. This concept has recently been employed by us[6] to construct substituted cyclopentenols, the core structural unit of the carbocyclic nucleosides carbovir and abacavir. We envisaged that the cyclopentene derivative **4** 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 **4** (R=H) during reaction with borane. A sequence of RCM followed by lactonisation in the diene **5** will provide this bicyclic intermediate **4**. The diene **5** may be expected to be available from the known unsaturated ester **6** which in turn is available from D-mannitol.

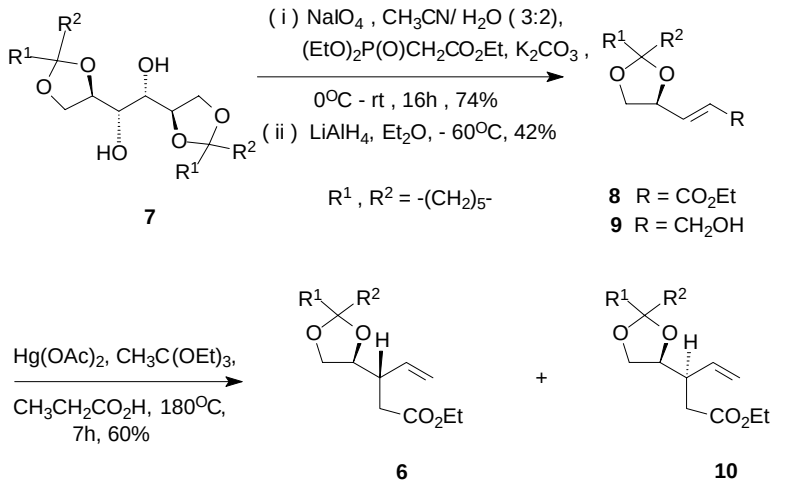
The unsaturated ester **6** along with its diastereoisomer **10** was obtained from D-mannitol derivative **7**[7] following the procedure developed by us[8] as depicted in Scheme 2. Wittig-Horner reaction of the aldehyde generated *in situ* from periodate cleavage of the diol **7** afforded the unsaturated ester **8**. The ester **8** was reduced with $LiAlH_4$ at –60 °C to afford the allyl alcohol **9**.



4 **5** **6**

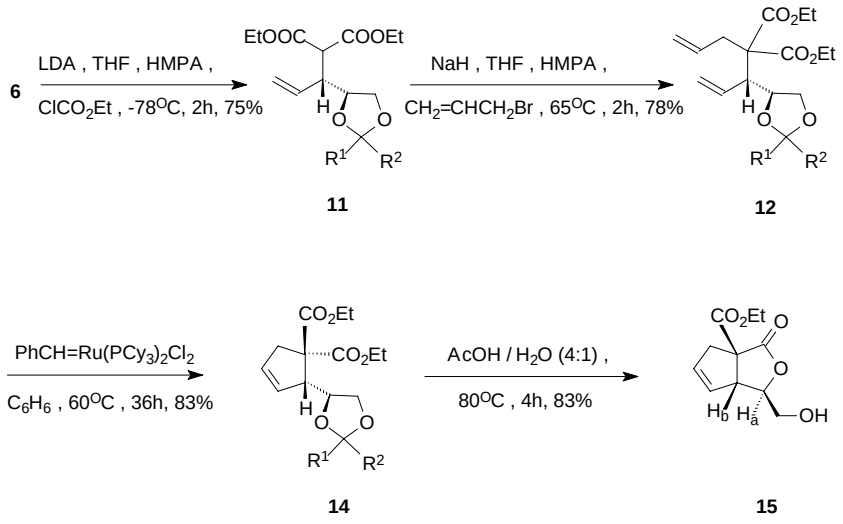
Scheme 1

Ortho-ester Claisen rearrangement of this allylic alcohol produced a mixture of chromatographically separable unsaturated esters **6** and **10**.



Scheme 2

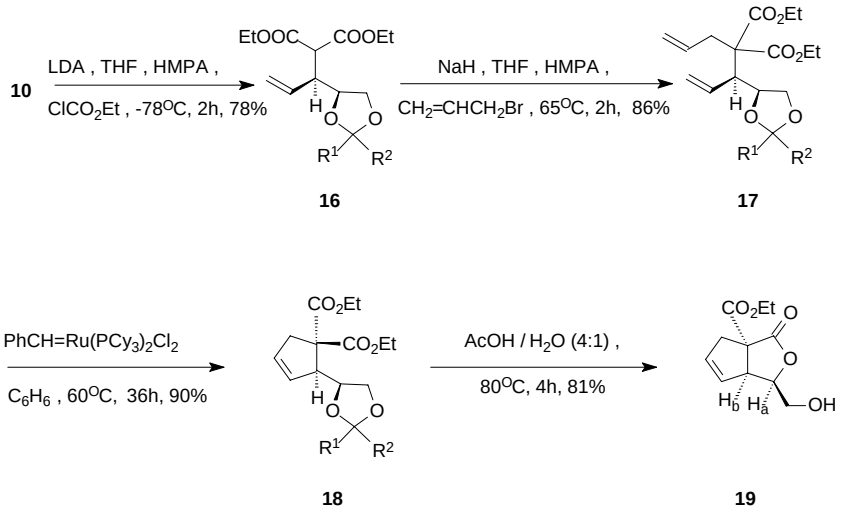
In connection to a different project,[9] alkylation of the enolate generated from the unsaturated ester **6** was investigated. It was found that such alkylation results in the synthesis of products in which the incoming electrophile occupies a position anti to the vinyl group. Thus allylation of the 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.



For structures **11** - **14** , R^1 , R^2 = -($CH_2)_5$ -

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 H_a. 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,** H_a appears at δ 4.85 as a dd (J = 6.12 and 12.18 Hz). Coupling of H_a with H_b 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 CH_2 protons of CH_2OH group leads to a dd (formed by merger of two triplets). On the other hand in **15,** H_a 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 H_a and H_b in **15** indicates an anti relationship between them. This is further supported by the shielding of H_a proton in **15** by 0.45 ppm over **19**. This indicates that H_a lies in the shielding zone of the alkene unit in the cyclopentene ring which requires H_a 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_2SO_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. ^1H 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[(1*R*)-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 ν_{max} 1736.25 cm^{-1}; ^1H NMR δ 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, dd, *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 δ 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. Calcd for $C_{18}H_{28}O_6$: C, 63.49; H, 8.30. Found : C, 63.77; H, 8.89.

Diethyl [(1*S*)-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 ν_{max} 1749.3, 1732.0 cm^{-1}; ^1H NMR δ 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 δ 14.40 (CH_3), 14.43 (CH_3), 24.1 (CH_2), 24.3 (CH_2), 25.5 (CH_2), 34.8

(CH_2), 36.0 (CH_2), 46.4 (CH), 54.3 (CH), 61.7 (CH_2), 61.9 (CH_2), 66.8 (CH_2), 74.9 (CH), 110.0 (C), 120.4 (CH_2), 133.3 (CH), 168.4 (CO), 168.5 (CO). Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.49; H, 8.30 Found : C, 63.82; H, 8.48.

Diethyl allyl [(1*R*)-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 NH_4Cl 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; $[\alpha]_D^{25}$ +4.4 (*c* 0.9, $CHCl_3$); IR: ν_{max} 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); ^{13}C NMR δ 14.4 (CH_3), 24.2 (CH_2), 24.26 (CH_2), 24.3 (CH_2), 24.3 (CH_2), 25.6 (CH_2), 35.4 (CH_2), 36.8 (CH_2), 40.2 (CH_2), 60.4 (C), 53.2 (CH), 61.4 (CH_2), 61.5 (CH_2), 68.4 (CH_2), 75.1 (CH), 109.9 (C), 118.0 (CH_2), 118.6 (CH_2), 133.4 (CH), 134.4 (CH), 170.3 (CO). Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found : C, 66.34; H, 8.88.

Diethyl allyl[(1*S*)-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: ν_{max} 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); ^{13}C NMR δ 14.2 (CH_3), 14.4 (CH_3), 24.2 (CH_2), 24.2 (CH_2), 25.5 (CH_2), 35.8 (CH_2), 35.9 (CH_2), 28.2 (CH_2), 48.8 (CH), 59.5 (C), 61.4 (CH_2), 61.8 (CH_2), 67.8 (CH_2), 74.7 (CH), 110.0 (C), 119.3 (CH_2), 120.3 (CH_2), 132.6 (CH), 133.1 (CH), 170.5 (CO), 170.9 (CO).

Diethyl (2*R*)-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%); $[\alpha]_D^{25}$ +5.8 (*c* 1.07, $CHCl_3$); IR: ν_{max} 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); ^{13}C NMR δ 14.3 (CH_3), 14.4 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 25.2 (CH_2), 35.3 (CH_2), 36.6 (CH_2), 40.2 (CH_2), 54.7 (CH), 61.9 (CH_2), 61.9 (CH_2), 62.2 (C), 67.2 (CH_2), 75.4 (CH), 109.8 (C), 128.6 (CH), 133.3 (CH), 170.6 (CO), 172.2 (CO). Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.00. Found : C, 64.98; H, 7.61.

Diethyl (2*S*)-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 : ν_{max} 1736 cm^{-1}; ^{1}H NMR δ 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 δ 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 (1*S*, 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_2SO_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: ν_{max} 3504.4, 1774.4, 1735.8 cm^{-1}; ^{1}H NMR δ 1.26 (3H, t, J = 7.1 Hz), 2.56 (1H, br s), 3.09 (2H, q, *J* = 17.5 Hz), 3.70 (1H, dd, *J* = 2.1, 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 δ 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 (1*S*, 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: ν_{max} 3438.8, 1776.3, 1737.7 cm^{-1}; ^{1}H NMR δ 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 δ 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.

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References

1. (a) Wang, R.; Shimizu, Y. *J. Chem. Soc., Chem. Commun*. **1990**, 413. (b) Wang, R.; Shimizu, Y.; Steiner, J.R.; Clardy, J. *J. Chem. Soc., Chem. Commun*. **1993**, 379.
2. Zheng, N.; Shimizu, Y. *J. Chem. Soc., Chem. Commun*. **1997**, 399.
3. (a) Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron Lett*. **1988**, *39*, 621. (b) Seo, S.Y.; Jung, J.K.; Paek, S.M.; Lee, Y.S.; Kim, S.H.; Lee, K.O.; Suh, Y.G. *Organic Lett*. **2004**, *6*, 429.
4. (a) For reviews on the RCM reaction see : Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed*. **1997**, *36*, 2036. (b) Grubbs, R.H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Pariya, C.; Jayaprakash, K.N.; Frustner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012. (e) Trnka, T.M.; Grubbs, R.H. *Acc. Chem. Res*. **2001**, *34*, 18. (f) Kotha, S.; Sreenivasachary, N. *Indian J. Chem*. **2001**, *40B*, 763.
5. (a) Holt, D.J.; Barker, W.D.; Jenkins, P.R.; Davies, D.L.; Garratt, S.; Fawcett, J.; Russell, D.R.; Ghosh, S. *Angew. Chem., Int. Ed*. **1998**, *37*, 3298. (b) Haque, A.; Panda, J.; Ghosh, S. *Indian J. Chem*. **1999**, *38B*, 8. (c) Holt, D.J.; Barker, W.D.; Jenkins, P.R.; Panda, J.; Ghosh, S. *J. Org. Chem*. **2000**, *65*, 482.
6. Nayek, A.; Banerjee, S.; Sinha, S.; Ghosh, S. *Tetrahedron Lett*. **2004**, *45*, 6457.
7. Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585.
8. Sarkar, N.; Nayek, A.; Ghosh, S. *Organic Lett*. **2004**, *6*, 1903.
9. Banerjee, S.; Ghosh, S. unpublished work from this laboratory.