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Total Synthesis of *R*-(+)-Patulolide A and *R*-(-)-Patulolide B : The Macrolides Isolated from *Penicillium urticae* Mutant

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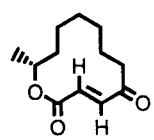
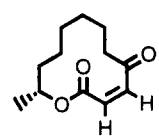
Abstract : *The title compounds (2E,11R)-4-oxo-2-dodecen-11-olide, 1 and (2Z,11R)-4-oxo-2-dodecen-11-olide, 2 were synthesised in optically pure forms from a nitroalkane synthon involving a chiral resolution step using goat liver lipase.*

In recent years, chemistry of medium and large size ring lactones has attracted considerable attention because many of the molecules belonging to this group have revealed diverse and significant biological activities.[1-3] The macrocyclic lactones, namely macrolides, describe a class of antibiotics derived from species of streptomyces. Medium-sized lactones of this type constitute an important class of compounds which occur naturally as the aglycons in the macrolide antibiotics. The macrolide (2*E*,11*R*)-4-oxo-2-dodecen-11-olide, **1** commonly known as Patulolide A; (2Z,11*R*)-4-oxo-2-dodecan-11-olide **2**, known as Patulolide B have been isolated by Yamada *et al.* from the culture broth of *Penicillium urticae* mutant, S11R59 and clarified their structures as depicted in formula **1** and **2** respectively.[4,5] Patulolide A & B are twelve membered macrolides which have a double bond flanked with a lactone carbonyl group and a keto group, which is common among some antifungal metabolites such as pyrenophorin,[6] pyranolides,[7,8] vermiculin.[2]



(*R*)-Patulolide A (**1**)



(*R*)-Patulolide B (**2**)

Both patulolide A and B showed antifungal, antibacterial and antiinflammatory activities.[4,5,9] Recent reports indicate that the *R*-antipode of Patulolide A inhibits IgE induced release of histamine for human leucocytes better than the degeneration inhibitor, theophylin.[10] The reported antifungal, antimicrobial, anti-inflammatory activities and the interesting 'ene dione' system of Patulolide A and B led to several syntheses, mainly as racemates.[9,11-12] More recently a few asymmetric synthesis have also been reported.[10,13-16]

In continuation of our interest on the application of nitroaliphatics in the synthesis of bioactive natural products,[17] we recently reported an efficient Nef procedure for converting a nitro group in the γ-position of an α,β-unsaturated ester system into a carbonyl group involving the use of buffered titanium trichloride and maintaining the pH at 5.3.[18] It may be noted that conversion of a nitro group in the γ-position of an α,β-unsaturated ester is very difficult as most of the reported Nef procedures involving either strong acidic or

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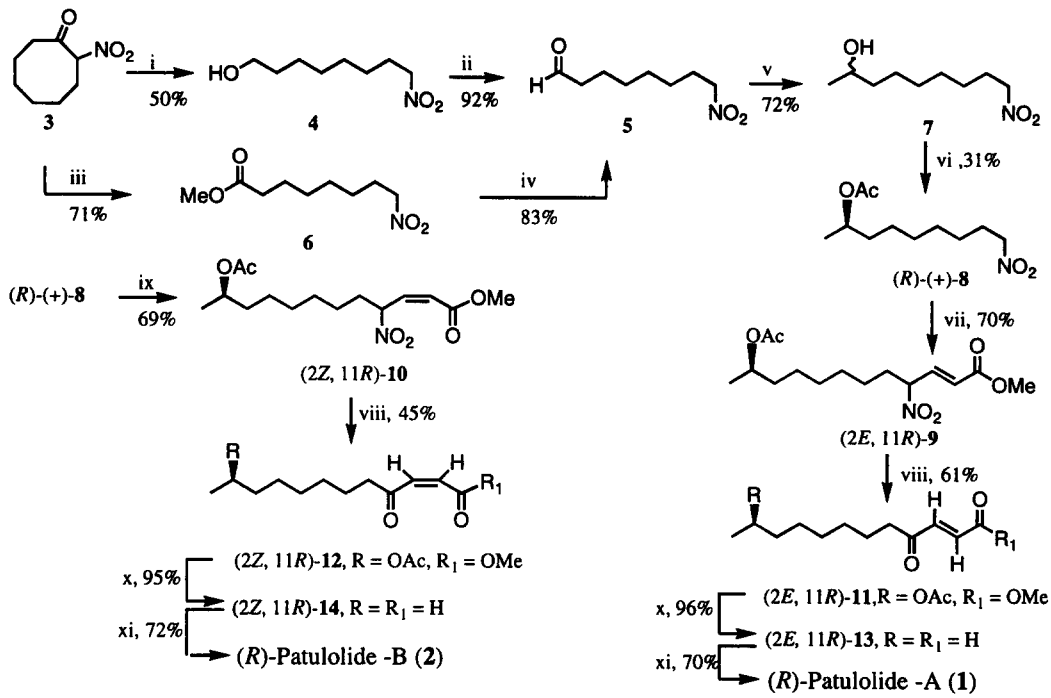
basic conditions result in either hydrolysis of the ester function or reduction of the α,β-unsaturated double bond. In order to establish the general applicability of this procedure, we investigated the synthesis of **1** & **2** and conceived **scheme I** for their synthesis.



Scheme I

i) $NaBH_4/CH_3CN$-H_2O; ii) PCC/CH_2Cl_2; iii) KF/MeOH, reflux; iv) DIBAL-H/CH_2Cl_2; v) MeMgI/Et_2O, 0°C vi) goat liver lipase, vinyl acetate; vii) KF/Bu_4NBr/methyl propiolate/ DMSO;viii) $TiCl_3$/THF,NH_4OAc, pH 5.1; ix) Et_3N/CH_3CN; x) LiOH, THF-H_2O; xi) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, reflux.

Our first attempt was to synthesise the bifunctional nitroalkane synthon R-(+)-**8** in substantial amount. Treatment of 2-nitrocyclohexanone **3** with $NaBH_4$ in CH_3CN-H_2O mixture and subsequent acidification with 2M HCl as per procedure reported by Ballini *et al.*[19] gave 8-nitrooctan-1-ol **4** in 50% yield which on PCC oxidation gave nitro aldehyde **5** in 92% yield as a gum. The compound **5** was also obtained from 2-nitrocyclooctanone first by treating **3** with KF in dry methanol to afford nitro ester **6** in 71% yield[20] which on subsequent DIBAL-H reduction at -72°C in CH_2Cl_2 gave aldehyde **5** in 83% yield. Scrutiny of the existing literature reveals that DIBAL-H reduction of the ester in presence of nitro functionality has not been reported so far. Treatment of nitroaldehyde **5** with one equivalent of MeMgI in dry ether at 0°C gave alcohol **7** in 72% yield. Recently, we have established a procedure for enantioselective *trans*-esterification of a variety of secondary nitroalcohols by goat liver lipase[21] using vinyl acetate as acyl donor. Treatment of this alcohol with this lipase in hexane gave *R*-(+)-**8** in 31% yield, $[\alpha]^{27}_D$= +92.5 (c 0.8, $CHCl_3$) with 91% ee as determined by using Mosher's reagent[22] on the corresponding alcohol obtained after hydrolysis of the acetate, *R*-(+)-**8**. Our next attempt was to prepare the basic carbon chain of the Patulolide molecule for which we performed a

Michael type coupling of (2*R*)-2-acetoxy-9-nitro nonane, *R*-(+)-**8**, with methyl propiolate, however the main problem in this case was the maintenance of the *trans* geometry of the newly formed double bond. Treatment of the nitronate dianion generated by treating *R*-(+)-**8** with a variety of bases viz Et_3N, DBU, DBN, amberlyst A-21 resin with methyl propiolate led to the formation of an *E/Z* mixture of the newly formed double bond. However, exclusive formation of the *trans*-adduct (2*E*,11*R*)-**9** was achieved by treatment of *R*-(+)-**8** with methyl propiolate, KF and Bu_4NBr in DMSO under nitrogen in 70% yield. Treatment of (2*E*,11*R*)-**9** with buffered 15% titanium trichloride and maintaining the pH at 5.1 using ammonium acetate gave (2*E*,11*R*)-**11** in 61% yield {$[\alpha]_D^{25}$= -3.4 (lit[10] $[\alpha]_D^{25}$= -3.1). Hydrolysis of (2*E*,11*R*)-**11**, with LiOH in THF-H_2O followed by macrolactonisation according to Yamaguchi's macrolactonisation procedure[23] gave *R*-(+)-Patulolide A, **1** in 70% yield (overall yield 9% from **7**). When the nitronate dianion generated from *R*-(+)-**8** by using triethylamine as a base in acetonitrile was coupled with methyl propiolate under a nitrogen atmosphere, compound (2*Z*,11*R*)-**10** was obtained in 69% yield along with a minor amount of (2*E*,11*R*)-**9**. Treatment of (2*Z*,11*R*)-**10** with buffered 15% $TiCl_3$ solution at pH 4.8 using ammonium acetate gave (2Z,11*R*)-**12** in 45% yield. Hydrolysis of (2Z,11*R*)-**12** with LiOH in THF-H_2O gave (2Z,11*R*)-**14** in 95% yield which on Yamaguchi macrolactonisation yielded Patulolide B, **2** in 72% yield (overall yield 7% from **7**). Although conversion of (2*E*,11*R*)-**11** to Patulolide A has been reported,[10,14] it is the first synthesis of Patulolide B from (2*Z*,11*R*)-**10** by this macrolactonisation procedure. Thus, it has been demonstrated that the yields of the Patulolide A, **1** and Patulolide B, **2** in our procedure are quite comparable with those reported by Mori *et al.*[13] (overall yield 10% of **1** and 9% of **2** in 14 steps), Bestmann *et al.*[15] (9.4% of **1** in 8 steps) and is better than that reported by Chattopadhyay *et al.*[10] (2.18 % of **1** in 10 steps).

Experimental section :

^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz (Bruker DPX-300) unless otherwise stated using TMS as the internal standard and chemial shift values are expressed in δ, ppm. IR spectra were recorded as thin flims and mass spectra were recorded on a INCOS 50 GC-MS instrument. Elemental analyses were performed using a Perkin Elmer C, H, N analyser model 2400. Optical rotation measurements were done in a polarimeter, model AA-1000 (M/S optical activity, UK) All chemicals were purified before use and literature procedures were followed for the synthesis of 2-nitro cyclooctanone.[20]

8-Nitrooctan-1-ol (4)

To a solution of 2-nitrocyclooctanone (8.55g, 50 mmol) in acetonitrilile/water (60 ml, 3;2) at 0°C was added sodium borohydride (1.9g, 50 mmol) and stirred for 2h. The solution was then acidified with2N HCl and extracted with ethyl acetate (4x40 ml). The organic layer was dried over Na_2SO_4 and evaporated in a rotavapor to yield a gummy residue which was purified by column chromatography using ethyl acetate-hexane (1:1) as eluent. Yield 50%; $b.p._{(0.03\ mm\ Hg)}$ 190°C; [Found C, 54.87; H, 9.82; N, 7.89. $C_8H_{17}O_3N$ requires C, 54.83; H, 9.78; N, 7.99%]; ν_{max}(neat) 1550 (NO_2), 3370 (OH) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.3-1.4 (m, 8H, -C<u>H</u>$_2$-), 1.51-1.6 (m, 2H, -C<u>H</u>$_2$-), 1.9-2.1 (m, 2H, -C<u>H</u>$_2$-), 3.6 (t, 2H, *J* 6.4 Hz, -C<u>H</u>$_2$OH), 4.37 (t, 2H, *J* 7.0 Hz, -C<u>H</u>$_2$$NO_2$); m/z (EI) 176 ($MH^+$).

Methyl 8-nitrooctanoate (6)

To a solution of 2-nitro cyclooctanone **3** (5.1g, 30.0 mmol) in absolute methanol (100 ml) was added potassium flouride dihydrate (2g, 21.2 mmol) at room temperature and was allowed to reflux for 48h. Then the solvent was evaporated and the residue was dissolved in water. The reaction mixture was extracted with ether (3x30ml), dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography (50% ethyl acetate/hexane) gave the title compound **6** (4.36g, 21.2 mmol, 71%) as an oil. [Found C, 53.08; H, 8.50; N, 6.77. $C_9H_{17}O_4N$ requires C, 53.19; H, 8.43; N, 6.89%]; ν_{max}(neat) 1550 (NO_2), 1735 (CO) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.2-2.2 (m, 10H, -C<u>H</u>$_2$-), 2.3 (t, 2H, *J* 6.8 Hz, -COC<u>H</u>$_2$-), 3.7 (s, 3H, -COOC<u>H</u>$_3$-), 4.37 (t, 2H, *J* 7.0 Hz, -C<u>H</u>$_2$$NO_2$).

8-Nitrooctan-1-al (5)

To a stirred solution of 0.52 g (3.4 mmol) of 8-nitrooctan-2-ol **4** in 20 ml of anhydrous dichloromethane was added PCC (1.51 g, 6.0 mmol) at room temperature. After 2 h, dry diethyl ether (50 ml) was added and the resulting mixture was passed through a silica gel (60-120 mesh) pad and the solvent was removed by distillation. The resulting crude gummy product was purified by column chromatography using hexane : ethyl acetate (3:1) as eluent to afford 8-nitrooctan-1-al **5** as an oil in 92% (0.480 g, 2.78 mmol) yield. [Found C, 54.33; H, 8.82; N, 7.92. $C_8H_{15}NO_3$ requires C, 54.49; H, 8.86; N 8.1]. ν_{max}(neat) 1545 (NO_2), 1715 (CO) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.40 (br s, 10H, -C<u>H</u>$_2$-), 2.19 (t, 2H, J= 6.0 Hz, -C<u>H</u>$_2$CO-), 4.37 (t, 2H, J= 7.0 Hz, -C<u>H</u>$_2$$NO_2$), 9.77 (t, 1H, J= 1.0 Hz, -C<u>H</u>O) ppm ; m/z (EI) 174 (MH^+), 103, 75.

Reduction of methyl 8-nitrooctanoate (6) with DIBAL-H

To a stirred solution of methyl-8-nitrooctanoate **6** (1.11 g, 5.46 mmol) in anhydrous dichloromethane (25 ml) at -72°C was added DIBAL-H (4 ml) and the reaction was monitored by TLC. After 1 h, the reaction mixture was quenched by adding one drop of methanol and the entire mixture was brought to the room temperature. The mixture was then diluted with 100 ml of CH_2Cl_2 and poured into 100 ml cold water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuuo to yield a crude which was purified by column chromatography (silica gel, hexane : ethyl acetate; 3 : 1) to yield 8-nitrooctan-1-al **5** (0.78 g, 4.5 m mol, 83%) as an oil. [Found C, 54.39; H, 8.80; N, 8.2. $C_8H_{15}NO_3$ requires C, 54.49; H, 8.86; N 8.1]; ν_{max}(neat) 1545 (NO_2), 1715 (CO) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.40 (br s, 10H, -C<u>H</u>$_2$-), 2.19 (t, 2H, J= 6.0 Hz, -C<u>H</u>$_2$CO-), 4.37 (t, 2H, J= 7.0 Hz, -C<u>H</u>$_2$$NO_2$), 9.77 (t, 1H, J= 1.0 Hz, -C<u>H</u>O) ppm ; m/z (EI) 174 (MH^+), 103, 75.

(±)-9-Nitrononan-2-ol (7)

To a stirred solution of freshly prepared methyl magnesium iodide (1.85 mmol) in 10 ml of anhydrous ether was added an ethereal solution of 8-nitrooctan-1-al **5** (0.160 g, 0.924 mmol) dropwise at 0°C. The mixture was stirred for 30 minutes at 0°C, after which the temperature was raised to room temperature and stirring continued for an additional 30 minutes. The mixture was then quenched by adding saturated aqueous ammonium chloride solution, extracted with ether (3 x 20 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain an oily product which was subjected to purification by preparative TLC using ethyl acetate : hexane (1:3) as eluent to afford (±)-9-nitrononan-2-ol **7** in 72% (0.135 g, 0.78 m mol) yield as a gum; [Found C, 57.28; H, 9.9; N, 7.38. $C_9H_{19}NO_3$ requires C, 57.12; H, 10.12; N,

7.40]; $\nu_{max}(CHCl_3)$ 1550 (NO_2), 3370 (OH) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.1 (d, 3H, J= 6.0 Hz, CH_3), 1.29 (br s, 12H, $-CH_2-$), 3.67 (br s, 1H, OH), 4.27 (t, 2H, J= 6.0 Hz, $-CH_2NO_2$).

Isolation of goat liver lipase[21]

Fresh goat liver was cut into small pieces and washed thoroughly with distilled water. The washed liver pieces were dipped in distilled acetone and stirred vigorously with a mechanical stirrer fitted with a sharp steel blade for 4-5 h. On standing, the fine powdered liver settled down in the bottom of the container which was seperated by filtration. The powder was washed several times with acetone till the acetone become colourless. Finally, the powder was dried under vacuum at room temperature and stored in the fridge.

2*R*-(+)-Acetoxy-9-nitrononane (8)

A mixture of (±)-9-nitrononan-2-ol **7** (0.090 g, 0.42 mmol), vinyl acetate (0.5 ml) and goat liver lipase (0.5 g) in dry hexane (5 ml) was stirred for 48 h. The mixture was then filtered to remove the solid enzyme and the filtrate was concentrated in a rotavapor. The residue was chromatographed over silica gel (ethyl acetate : hexane, 1:3) to furnish the polar starting alcohol **7** (0.04 g, 50%) and the title less polar product **8** (0.030 g, 31% yield); [Found C, 57.36; H, 8.9; N, 6.18. $C_{11}H_{21}NO_4$ requires C, 57.12; H, 9.1; N, 6.06] ; $[\alpha]_D^{27}$ +92.5 (c 0.8, $CHCl_3$), 91% ee; ν_{max}(neat) 1550 (NO_2), 1730 (CO) cm^{-1}; δH (60 MHz, $CDCl_3$] 1.14 (d, 3H, *J* 6.2 Hz, $-C\underline{H}_3$), 1.18-1.3 (br s, m, 12H), 1.95 (s, 3H, $OCOC\underline{H}_3$), 4.27 (t, 2H, *J* 6.9 Hz, $-C\underline{H}_2NO_2$), 4.75-4.81 (m, 1H, -C<u>H</u>-OAc); m/z (EI) 232 (M^++1).

Methyl (2*E*,11*R*)-11-acetoxy-4-nitrododec-2-enoate (9)

A mixture of 2*R*-(+)-acetoxy-9-nitrononane **8** (0.199g, 0.86 mmol), potassium fluoride (0.1 g, 1.72 mmol), tetrabutyl ammonium bromide (0.28 g, 0.861 mmol) and DMSO (2 ml) was stirred at room temperature for 30 min. Methyl propiolate (0.072 g, 0.86 mmol) was added over a period of 1 h in portions and stirring was continued for an additional hour.The reaction mixture was poured into water (30 ml) and extracted with ethyl acetate (3 x 20 ml). The extract was dried over Na_2SO_4 and evaporated to yield a gum which was subjected to chromatographic purification over silica gel (60-120 mesh) using hexane : ethyl acetate (3 : 1) giving the Michael adduct **9** (0.140 g, 70%, 0.44 mmol) as a gum; [Found C, 56.92; H, 7.69; N, 4.23. $C_{15}H_{25}NO_6$ requires C, 57.13; H, 7.99; N, 4.44%]; ν_{max}(neat) 1550 (NO_2), 1715 (CO) cm^{-1} ; δ_H (60 MHz, $CDCl_3$) 1.14 (d, 3H, *J* 6.2 Hz, $C\underline{H}_3$), 1.25 (br s, 12H, $-C\underline{H}_2-$), 1.95 (s, 3H, $-OCOC\underline{H}_3$), 3.73 (s, 3H, $-OC\underline{H}_3$), 4.74-4.78 (m, 1H, -C<u>H</u>OAc), 6.0 (d, 1H, *J* 16 Hz, -C<u>H</u>=), 7.2 (dd, 1H, *J* 16 & 8 Hz, =C<u>H</u>-) ppm.

Methyl (2*Z*,11*R*)-11-acetoxy-4-nitrododec-2-enoate (10)

In a 25 ml round bottom flask, a mixture of 2*R*-(+)-acetoxy-9-nitrononane **8** (0.22 g, (0.95 mmol, 0.32 ml) of triethylamine (dried over CaH_2) and 10 ml of dry acetonitrile was stirred at room temperature for 30 min under nitrogen atmosphere. To this solution was added 0.08 g (0.95 mmol) of methyl propiolate and the resulting mixture was stirred at r.t. for 24 h. Then it was quenched by adding water and extracted with ethyl acetate (3 x 10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The product was purified by preparative TLC using 1:20 mixture of acetone and toluene to give methyl (2Z,11R)-11-acetoxy-4-nitrododec-2-enoate **10** as a colourless liquid in 69% (0.206 g, 0.66 mmol) yield; [Found C, 56.90; H, 7.7; N, 4.26. $C_{15}H_{25}NO_6$ requires C, 57.14; H, 7.94; N 4.44%];

ν_{max}(neat) 1550 (NO_2), 1710 (CO) cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.20 (d, 3H, *J* 6.0 Hz, -C<u>H</u>$_3$), 1.30 (br s, 12H, -C<u>H</u>$_2$-), 1.90 (s, 3H, -OCOC<u>H</u>$_3$), 3.60 (s, 3H, -OC<u>H</u>$_3$), 4.74-4.8 (m, 1H, -C<u>H</u>OAc), 5.45 (d, 1H, *J* 12.0 Hz, -C<u>H</u>=), 7.4 (dd, 1H, *J* 12.0 & 8.9 Hz, =C<u>H</u>-) ppm.

Methyl (2*E*,11*R*)-11-acetoxy-4-oxododec-2-enoate (11)

To a NH_4OAc buffered $TiCl_3$ solution (30 ml) at pH 4.8 (prepared by mixing ammonium acetate (15 g) in water (40 ml) and 7.5 ml of 15% $TiCl_3$ solution in HCl), methyl 11*R*-acetoxy-4-nitrododec-2-enoate **9** (0.2 g, 0.63 mmol) in THF (15 ml) was rapidly added and the reaction mixture was stirred at room temperature for 2h under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethyl acetate (3 x 10 ml) and the organic layer was successively washed with water (50 ml), 5% $NaHCO_3$ solution (50 ml), and finally with brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to yield a crude product which was purified by preparative TLC (EtOAc : hexane, 1:3) to obtain methyl 11-acetoxy-4-oxododec-2-enoate **11** as a gum in 61% (0.110 g, 0.39 mmol) yield. [Found C, 63.48; H, 8.77. $C_{15}H_{24}O_5$ requires C, 63.36; H, 8.51%]; $[\alpha]_D^{27}$ = -3.4 (c 1.2, $CHCl_3$){lit [10] $[\alpha]_D^{25}$ = -3.1 (c 2.1, $CHCl_3$); ν_{max}(neat) 1710 (CO), 1730 (CO), 1650 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 1.14 (d, 3H, *J* 6.2 Hz, -C<u>H</u>$_3$), 1.25 -1.45 (br s+m, 10H, -C<u>H</u>$_2$-), 2.0 (s, 3H, -OCO-C<u>H</u>$_3$), 2.5 (t, 2H, *J* 6.0 Hz, -COC<u>H</u>$_2$), 3.8 (s, 3H, -COOC<u>H</u>$_3$), 4.74-4.78 (m, 1H, -C<u>H</u>OAc), 6.5 (d, 1H, *J* 16.1 Hz, -C<u>H</u>=CH-), 7.2 (d,1H, *J* 16.1, -CH=C<u>H</u>-COOCH$_3$) ppm.

Methyl-(2*Z*,11*R*)-11-acetoxy-4-oxododec-2-enoate (12)

The procedure was similar to the preparation of **11**, described as above. Yield 45%, oil ; [Found C, 63.51; H, 8.67. $C_{15}H_{24}O_5$ requires C, 63.36; H, 8.51%]; $[\alpha]_D^{27}$ = +6.2 (c 1.2, $CHCl_3$) ; ν_{max}(neat) 1710 (CO), 1725 (CO); δ_H (300 MHz, $CDCl_3$) 1.25 (d, 3H, *J* 6.0 Hz, -C<u>H</u>$_3$), 1.35 (br s, 10H, -C<u>H</u>$_2$-), 2.05 (s, 3H, -OCOC<u>H</u>$_3$), 2.4 (t, 2H, *J* 6.0 Hz, -COC<u>H</u>$_2$), 3.6 (s, 3H, -COOC<u>H</u>$_3$), 4.4-4.8 (m, 1H, -C<u>H</u>OAc), 5.5 (d, 1H, *J* 12.0 Hz, -C<u>H</u>=CH-COOCH$_3$), 7.4 (d, 1H, *J* 12.0, -CH=C<u>H</u>-COOCH$_3$) ppm.

Saponification of compound (2*E*,11*R*)-11 with LiOH

LiOH (0.120 g, 0.498 mmol) was added to a stirred solution of (2*E*,11*R*)-**11** (0.180 g, 0.66 mmol) in THF (12 ml) and H_2O (12 ml). The solution was heated at 50°C for 6 h and the progress of the reaction was monitored by TLC. The reaction mixture was acidified with tartaric acid to pH 4.0 and extracted with EtOAc (3 x 30 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and distilled off in a rotavapour to get (2*Z*,11*R*)-**13** as an oil in 95% (0.108 g, 0.473 mmol) yield. [Found C, 63.11; H, 8.77. $C_{12}H_{20}O_4$ requires C, 63.14; H, 8.83%]; $[\alpha]_D^{25}$ -4.0 (c 1.2, CH_3OH){Lit[10] $[\alpha]^{25}$= 4.3 (c 1.2, CH_3OH)}; ν_{max}(neat) 3700-3500, 1710, 1650 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.14 (d, 3H, *J* 6.2 Hz, -C<u>H</u>$_3$), 1.25 -1.45(br s + m, 10H, -C<u>H</u>$_2$-), 1.9 (s, 1H), 2.4 (t, 2H, *J* 6.0 Hz, -COC<u>H</u>$_2$-), 3.8 (m, 1H), 6.5 (d, 1H, *J* 16.1 Hz, -C<u>H</u>=CH-COOCH$_3$), 7.2 (d, 1H, *J* 16.1, -CH=C<u>H</u>-COOCH$_3$), 8.9 (s, 1H) ppm.

Saponification of compound (2*Z*,11*R*)-12 with LiOH

The procedure was similar to the preparation of **13**, described as above.Yield 81%, oil ; [Found C, 63.09; H, 8.78. $C_{12}H_{20}O_4$ requires C, 63.14; H 8.83%]; ν_{max}(neat) 3450, 1710 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25

(d, 3H, *J* 6.0 Hz, -CH_3); 1.3 (br s, 10H, -CH_2-); 1.9 (s, 1H); 2.39 (t, 2H, *J* 6.0 Hz, -$COCH_2$-); 5.5 (d, 1H, *J* 12.0 Hz, -CH=CH-$COOCH_3$); 7.4 (d, 1H, *J* 12.0 Hz, C=CH-$COOCH_3$) ppm.

Macrolactonisation of compound (2*E*,11*R*)-13

A mixture of compound (2*E*,11*R*)-13 (0.108 g, 0.473 mmol), triethylamine (90 μL) and 2,4,6-trichlorobenzoyl chloride (0.100 g, 0.476 mmol) in THF (40 ml) was stirred for 6 h at room temperature. The solution was filtered under argon and the filtrate diluted to 250 ml with anhydrous toluene and introduced into a refluxing solution of DMAP (0.400 g) in toluene (50 ml) over a period of 3 h. After being refluxed for an additional period of 3 h, the resultant solution was brought to room temperature, washed with aqueous 10% $NaHCO_3$ (20 ml), water (20 ml) and brine (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by chromatographic purification over silica gel (EtOAc : Hexane ; 1:20) gave the required macrolide, Patulolide A **1** in 64 % (0.061 g, 0.3 mmol) yield. M.p. 81-83°C (Lit[15] 81°C); [Found C, 68.42; H, 8.61. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%]; $[\alpha]_D^{25}$ +24.1 (c 1.2, EtOH) {Lit[15], [α] +28.5 (c 0.83, EtOH)}; ν_{max}(neat) 3400, 1710, 1680 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.21 (d, *J* 7.0 Hz, 3H) ; 1.45-1.8 (m, 8H); 1.85-1.92 (m, 2H); 2.42-2.5 (m, 1H); 2.7-2.8 (m, 1H); 4.84 (s,1H); 6.7 (d, *J* 16.1 Hz, 1H); 7.2(d, *J* 16.1 Hz, 1H) ppm.

Macrolactonisation of compound (2*Z*,11*R*)-14

The procedure was similar to the preparation of **1**, described as above. Yield 60% ; m.p. 63-65°C (Lit[5] 66-67°C); [Found C, 68.49; H, 8.60. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%]; $[\alpha]_D^{25}$ -41.3 (c 1.2, EtOH) {Lit[5], $[\alpha]_D^{25}$ -42 (c 2, EtOH); ν_{max}(neat) 3400, 1710, 1680 cm^{-1}; δ_H(300 MHz, $CDCl_3$) 1.24 (d, *J* 6.2 Hz, 3H); 1.3-1.9 (m, 10H); 2.4-2.5 (m, 2H); 4.8 (m,1H); 6.1 (d, *J* 12.1 Hz, 1H); 7.2 (d, *J* 12.1 Hz, 1H) ppm.

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