Expedient Synthesis of (*R*)-Patulolide A

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An efficient derivation of the title compound has been formulated from easily accessible 10-undecenoic acid (**1**). Thus, dodec-11-en-2-ol (**3**), prepared from **1**, was pyranylated and subjected to bromination with NBS followed by acetolysis to furnish (2*E*)-1-acetoxy-11-(tetrahydropyranyloxy)-dodec-2-ene **(5)**. Its hydrolysis, oxidation, and depyranylation afforded the (2*E*)-hydroxy ester (**9**). This, on *Candida rugosa* lipase-catalyzed acetylation, SeO_2 oxidation, hydrolysis, and Yamaguchi macrolactonization, led to (*R*)-patulolide A (**I**) with 67.1% ee. The enantiomeric excess was improved to 97% by first resolving the alcohol **3** *via* porcine pancreatic lipase catalyzed acetylation and converting the corresponding (*R*)-acetate (**13**) to **I** as done above.

Construction of macrocyclic lactones is an arduous task in organic synthesis. However, these are widely distributed[1] in nature and often possess chiral centers. This in turn offers a challenge for their synthesis. Recently, we have devised chemoenzymatic routes for two such compounds, one with a skipped methylenic group[2] and the other possessing a chiral center.[3] The macrolide, (2*E*)-4-oxo-2-dodecen-11-olide (**I**), commonly known as patulolide A, has been isolated[4] from *Penicillium urticae*. Its (*R*)-antipode inhibits IgE-induced release of histamine for human leukocytes better than the degranulation inhibitor, theophyline. The reported antifungal, antimicrobial, and antiinflammatory activities of **I** have led to its several syntheses mainly as a racemate.[5−7] More recently, a few asymmetric syntheses have also been reported.[8−11] However, poor enantiocontrol, multiple steps, and use of inaccessible materials are some of the limitations in the existing asymmetric routes. We, therefore, formulated an expedient synthesis of (*R*)-**I** starting from commercially available 10-undecenoic acid (**1**), wherein the asymmetry was induced by a lipase-catalyzed acetylation.

The aldehyde **2**, prepared from the acid **1**, was reacted with methylmagnesium iodide to furnish the alcohol **3** in excellent yield. It was pyranylated to compound **4** which was then subjected to allylic bromination with NBS. The resultant bromide on reaction with AcONa furnished the (*E*)-acetate **5** exclusively *via* concomitant rearrangement.[12] Its alkaline hydrolysis to the alcohol **6** followed by oxidation with PDC in MeOH led to a complex mixture of products which was not identified. Subsequently, the alcohol was oxidized with MnO_2 to furnish the aldehyde **7**. This was then subjected to Corey's oxidation[13] to furnish the ester **8** directly. Its (*E*)-geometry was easily established from the coupling constant (16 Hz) of its olefinic protons. Compound **8** was subsequently depyranylated to the hydroxy ester **9**. For the resolution, we attempted its *trans*-acetylation with vinyl acetate using lipase from *Candida rugosa* (CRL) as the catalyst. However, this proceeded with disappointing enantioselection. Best results were obtained in diisopropyl ether where, at 30% conversion, the (*R*)-acetate **10** and the resolved (*S*)-**9** were obtained with 68% and 61% ee's, respectively. Allylic oxidation of **10** with SeO_2 gave the keto ester **11** which was hydrolyzed to the desired acid **12**. This was then cyclized following Yamaguchi's method[14] to obtain the target compound (*R*)-**I** with 67.1% ee. The % ee was ascertained by comparing its $[\alpha]_D$ value with the reported one.[11] Since the enantiomeric purity of the synthetic sample was not satisfactory, we explored another strategy (Scheme 1).

Recently, we have extensively studied[15] the porcine pancreatic lipase (PPL)-catalyzed acylation of 2-alkanols with different acyl donors in various solvents. On this basis, kinetic resolution of **3** itself seemed more appealing for the enantiomeric synthesis of (*R*)-**I**. This seems all the more reasonable as the resolution step could then be incorporated at the initial stage of the synthesis. Hence, following the above protocol, we first prepared the acetate (*R*)-**13** (97% ee) and (*S*)-**3** (96% ee). The % ee of both these compounds were determined by GLC analyses of their respective MTPA esters. The positive optical rotation of the resolved alcohol indicated its (*S*)-configuration by analogy with the sign of $[\alpha]_D$ of 2-alkanols.[15] This was also confirmed by its hydrogenation to the known compound 2-dodecanol and comparison of its chiroptical data with those reported.[16] Compound (*R*)-**13** was then converted to the macrolide (*R*)-**I** following a procedure identical to that described earlier.

Experimental Section

All anhydrous reactions were carried out under Ar using freshly distilled solvents. For enzymatic reactions, solvents

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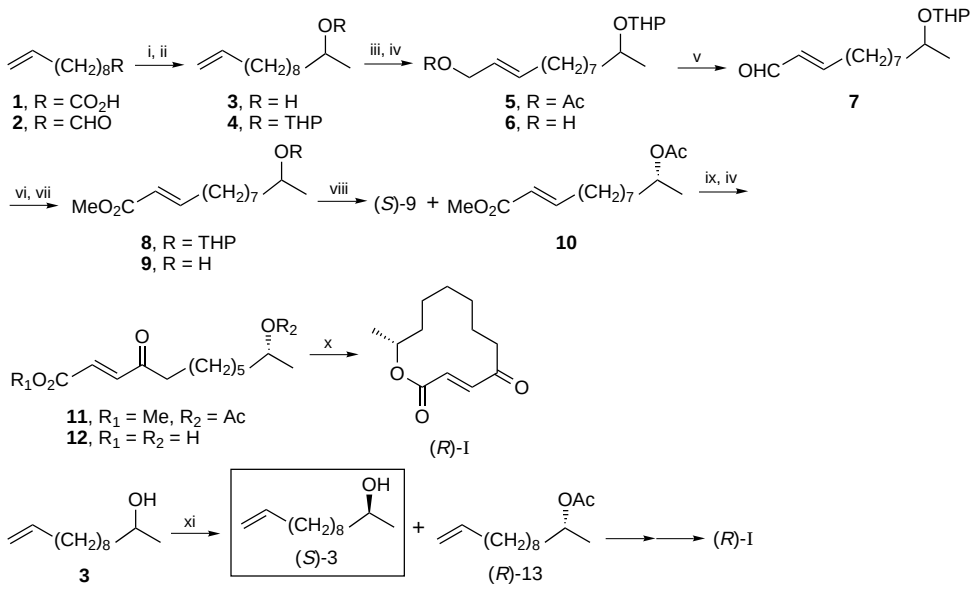
Scheme 1[a]



[a] Key: (i) MeMgI/ether; (ii) DHP/PPTS/CH_2Cl_2; (iii) NBS/AIBN/CCl_4/Δ, NaOAc/DMF; (iv) alcoholic KOH; (v) MnO_2/hexane; (vi) MnO_2/MeOH/NaCN/AcOH; (vii) MeOH/PTS/Δ; (viii) vinyl acetate/CRL/diisopropyl ether; (ix) SeO_2/dioxane; (x) Yamaguchi's procedure; (xi) vinyl acetate/PPL/diisopropyl ether.

were dried by standard procedures and then desiccated over molecular sieves (4 Å, Linde) for at least 72 h. CRL (Sigma, specific activity 941 units/mg) and PPL (Sigma, specific activity 54 units/mg) were used as obtained. SeO_2 (Fluka) was recrystallized prior to use. The ^{1}H NMR spectra were recorded in $CDCl_3$ solvent.

10-Undecenal (2). To a stirred suspension of LAH (3.8 g, 0.1 mol) in anhydrous ether (300 mL) was added dropwise the acid **1** (18.4 g, 0.1 mol) in ether (100 mL). After the initial reaction subsided, the mixture was gently heated to reflux for 3 h when the reaction was complete (*cf*. TLC). The reaction mixture was cooled by ice−water and the excess hydride decomposed with aqueous saturated Na_2SO_4 solution to get a crystalline white precipitate. The supernatant was decanted and the precipitate thoroughly washed with ether. Concentration of the ether extract followed by distillation gave pure 10-undecenol (16.3 g, 96%): bp 125−127 °C/10 mm; IR 3360, 3090, 1640, 990, 910 cm^{-1}; ^{1}H NMR δ 1.32 (br s, 14H), 1.9−2.1 (m, 2H), 2.8 (br s, D_2O exchangeable, 1H), 3.68 (t, J = 6 Hz, 2H), 4.8−6.2 (m, 3H).

To a stirred and cooled (0 °C) suspension of PCC (15.2 g, 0.07 mol) in CH_2Cl_2 (70 mL) was added the above alcohol (8.0 g, 0.047 mol) in one lot. After 3 h, the reaction mixture was diluted with dry ether (100 mL) and the supernatant passed through a pad (6 in.) of silica gel. The brown residue was repeatedly extracted with ether and passed through the above pad. The combined organic layer was concentrated under vacuum and the residue distilled to get the pure aldehyde **2** (5.8 g, 73%): bp 100−102 °C/0.1 mm; IR 2720, 1640, 990, 910 cm^{-1}; ^{1}H NMR δ 1.3 (br s, 12H), 2.0−2.1 (m, 2H), 2.34 (t, J = 7 Hz, 2H), 4.8−6.2 (m, 3H), 9.78 (t, J = 1.5 Hz, 1H).

Dodec-11-en-2-ol (3). To a stirred and cooled (0 °C) solution of MeMgI [prepared from MeI (5.3 g, 0.037 mol) and Mg (0.826 g, 0.034 mol)] in ether (100 mL) was added dropwise the aldehyde **2** (4.36 g, 0.026 mol) in ether (25 mL). After 3 h, the reaction was quenched with aqueous saturated NH_4Cl, the ether layer separated, and the aqueous portion extracted with ether. The combined ether extract was washed with water and brine and finally dried. Removal of solvent followed by column chromatography of the residue over silica gel (0−15% EtOAc/hexane) gave pure **3** (4.3 g, 90%): IR 3360, 3090, 1640, 990, 910 cm^{-1}; ^{1}H NMR δ 1.16 (d, J = 6 Hz, 3H), 1.29 (br s, 14H), 2.1 (br s, D_2O exchangeable, 1H), 2.2−2.4 (m, 2H), 3.7−3.9 (m, 1H), 4.8−6.2 (m, 3H). Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.12. Found: C, 78.38; H, 13.01.

2-(Tetrahydropyranyloxy)dodec-11-ene (4). A solution of **3** (4.3 g, 0.023 mol), dihydropyran (DHP) (2.2 g, 0.026 mol), and PPTS (0.2 g) in CH_2Cl_2 (60 mL) was stirred at room temperature for 12 h. It was poured into 10% aqueous $NaHCO_3$ (30 mL), the organic layer separated, and the aqueous part reextracted with $CHCl_3$. The entire organic extract was washed with water and brine, dried, and concentrated in vacuo. The residue was chromatographed over a silica gel column (0−10% ether/hexane) to furnish pure **4** (5.85 g, 95%): IR 3090, 1640, 990, 910, 870, 810 cm^{-1}; ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3H), 1.3 (br s, 14H), 1.5−1.7 (m, 6H), 2.1−2.3 (m, 2H), 3.5-3.9 (m, 3H), 4.6 (br s, 1H), 4.8−6.2 (m, 3H). Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 75.86; H, 12.17.

(2*E*)-1-Acetoxy-11-(tetrahydropyranyloxy)dodec-2-ene (5). A mixture of compound **4** (5.8 g, 0.022 mol), NBS (4.63 g, 0.026 mol), and AIBN (24 mg) in CCl_4 (60 mL) was refluxed for 1 h. It was poured into ice-cold water, the precipitated solid removed by filtration, and the filtrate extracted with *n*-pentane. The organic layer was washed with water and brine and dried. Removal of solvent gave a mixture containing isomeric bromides along with some unreacted **4** which was directly used in the next step.

Thus, a mixture of the above product and anhydrous NaOAc (7.4 g, 0.09 mol) in DMF (20 mL) was stirred at room temperature for 20 h. Then it was poured into excess ice−water and the aqueous layer extracted with ether. The ethereal solution was repeatedly washed with water followed by brine and dried. After concentration, the residue was chromatographed over silica gel (0−15% EtOAc/hexane) to get unreacted **4** (38%) and pure **5** (2.2 g, 49.4% based on conversion): IR 1760, 1650, 1385, 980, 870, 810 cm^{-1}; ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3H), 1.3 (br s, 12H), 1.5−1.7 (m, 6H), 2.1−2.3 (m containing a s at 2.1, 5H), 3.5−3.9 (m, 3H), 4.4 (d, J = 6 Hz, 2H), 4.6 (br s, 1H), 5.3−5.5 (m, 2H). Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.72; H, 10.26.

(2*E*)-11-(Tetrahydropyranyloxy)dodec-2-en-1-ol (6). A solution of compound **5** (2.0 g, 6.1 mmol) in alcoholic KOH (20 mL, 25%) was stirred for 4 h. Most of the solvent was removed in vacuo, the mixture diluted with water, and the aqueous layer extracted with EtOAc. The organic layer was washed with water and brine and dried. Removal of solvent followed by column chromatography (silica gel, 0−20% EtOAc/hexane) gave the alcohol **6** (1.65 g, 95%): IR 3360, 1640, 980, 910, 870, 810 cm^{-1}; ^{1}H NMR δ 1.18 (d, J = 6 Hz, 3H), 1.29 (br s, 12H), 1.5−1.7 (m, 6H), 2.0−2.3 (m, 2H), 3.5-3.8 (m, 3H), 3.9−4.0 (m partially D_2O exchangeable, 3H), 4.6 (br s, 1H), 5.5−5.8 (m, 2H). Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 72.02; H, 11.26.

Methyl (2*E*)-11-(Tetrahydropyranyloxy)dodec-2-enoate (8). A mixture of **6** (1.65 g, 5.8 mmol) and MnO_2 (10.08 g, 0.116 mol) in hexane (30 mL) was stirred at room temperature for 12 h. The black precipitate was filtered off and the filtrate concentrated under reduced pressure to afford the pure (cf. TLC) aldehyde **7** (1.38 g, 84.4%): IR 2700, 1720, 1640, 980, 910, 870, 810 cm^{-1}.

To a stirred solution of **7** (1.6 g, 5.7 mmol) in MeOH (25 mL) was successively added MnO_2 (9.91 g, 0.114 mol), NaCN (1.4 g, 0.029 mol), and AcOH (0.7 g). After being stirred for 16 h at room temperature, the mixture was concentrated in vacuo and the residue diluted with EtOAc. The organic layer was filtered and the filtrate washed with water and brine and dried. Removal of the solvent and column chromatography (silica gel, 0−20% EtOAc/hexane) of the residue gave the ester **8** (1.08 g, 61%): IR 1720, 1640, 980, 910, 870, 810 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.29 (br s, 12H), 1.5−1.7 (m, 6H), 2.0−2.3 (m, 2H), 3.5-3.9 (m containing a s at δ 3.62, 6H), 4.6 (br s, 1H), 5.8 (d, J = 16 Hz, 1H), 6.91 (dt, J = 16 Hz, 5.4 Hz, 1H). Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.36; H, 10.17.

Methyl (2*E*)-11-Hydroxydodec-2-enoate (9). A solution of **8** (1.08 g, 3.46 mmol) and PTS (0.1 g) in MeOH (20 mL) was refluxed for 4 h. The usual isolation gave pure **9** (0.71 g, 90%) after column chromatography (silica gel, 0−20% EtOAc/hexane): IR 3360, 1720, 1640, 980 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.32 (br s, 12H), 2.1−2.3 (m, 2H), 3.5−3.9 (m containing a s at δ 3.7, 4H), 4.0 (s, D_2O exchangeable, 1H), 5.81 (d, J = 16 Hz, 1H), 6.91 (dt, J = 16 Hz, 5.5 Hz, 1H). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.56; H, 10.83.

Methyl (11*R*,2*E*)-11-Acetoxydodec-2-enoate (10). A solution of **9** (0.7 g, 3.07 mmol), vinyl acetate (0.6 mL, 6.2 mmol), and CRL (1.0 g) in diisopropyl ether (20 mL) was stirred at room temperature until 30% conversion was reached (6 h). The mixture was filtered, the organic extract was concentrated, and the products *viz*. (*R*)-**10** (0.21 g, 25.3%) and (*S*)-**9** (0.31 g, 44%) were isolated by preparative thin layer chromatography. The spectral data of (*S*)-**9** were identical with those of the racemic sample.

(*S*)-**9**: $[\alpha]^{25}$ +1.48° (*c* 6.2, $CHCl_3$).

(*R*)-**10**: $[\alpha]^{25}$ −2.86° (*c* 4.2, $CHCl_3$); IR 1730, 1720, 1640, 1260, 980 cm^{-1}; ^1H NMR δ 1.18 (d, J = 6 Hz, 3H), 1.32 (br s, 12H), 2.0 (s, 3H), 2.1−2.3 (m, 2H), 3.6 (s, 3H), 4.4−4.6 (m, 1H), 5.82 (d, J = 16 Hz, 1H), 6.91 (dt, J = 16 Hz, 5.4 Hz, 1H). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.36; H, 9.87.

Methyl (11*R*,2*E*)-11-Acetoxy-4-oxododec-2-enoate (11). A solution of **10** (0.4 g, 1.5 mmol) and SeO_2 (0.23 g, 2.07 mmol) in dioxane (25 mL) was refluxed for 48 h. Then, the mixture was filtered and the filtrate concentrated. The residue was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue obtained was chromatographed over silica gel (0−15% EtOAc/hexane) to get **11** (0.298 g, 71%): $[\alpha]^{25}$ −3.1° (*c* 2.1, $CHCl_3$); IR 1750, 1720, 1640, 1260, 980 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.25−1.45 (m, 10H), 2.1 (s, 3H), 2.5 (t, J = 6 Hz, 2H), 3.83 (s, 3H), 4.4−4.7 (m, 1H), 6.54 (d, J = 16 Hz, 1H), 7.1 (d, J = 16 Hz, 1H). Anal. Calcd for $C_{18}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.48; H, 8.77.

(11*R*,2*E*)-4-Oxo-2-dodecen-11-olide (I). A solution of **11** (0.284 g, 1.0 mmol) in alcoholic KOH (20 mL, 25%) was stirred for 6 h. The usual isolation gave the hydroxy acid **12** (0.212 g, 93%): $[\alpha]^{25}$ −4.31 (*c* 1.2, CH_3OH); IR 3700−3500, 1710, 1640, 1060, 980 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.25−1.4 (m, 10H), 1.8 (s, D_2O exchangeable, 1H), 2.34 (t, J = 6 Hz, 2H), 3.6−3.9 (m, 1H), 6.61 (d, J = 16 Hz, 1H), 7.2 (d, J = 16 Hz, 1H), 8.71 (s, D_2O exchangeable, 1H).

A mixture of the above compound (41 mg, 0.18 mmol), TEA (34 μL), and 2,4,6-trichlorobenzoyl chloride (50 mg) in THF (15 mL) was stirred for 4 h at room temperature. The solution was filtered under Ar and the filtrate diluted to 100 mL with toluene and introduced into a refluxing solution of DMAP (150 mg) in toluene (20 mL) over a period of 3 h. After being refluxed for an additional period of 3 h, it was brought to room temperature, washed with aqueous 10% $NaHCO_3$, water, and brine and dried. Solvent removal followed by preparative TLC gave pure (*R*)-**I** (23.0 mg, 61%): mp 83 °C (lit.[11] mp 81 °C); $[\alpha]^{22}$ +21.4° (*c* 1.14, EtOH) (lit.[11] [α] +28.5° (*c* 0.83, EtOH)); IR 3400, 1710, 1680, 1620, 980 cm^{-1}; ^1H NMR δ 1.22 (d, J = 7 Hz, 3H), 1.4−1.7 (m, 8H), 1.8−1.9 (m, 2H), 2.4−2.5 (m, 1H), 2.7−2.8 (m, 1H), 4.88 (s, 1H), 6.71 (d, J = 16 Hz, 1H), 7.21 (d, J = 16 Hz, 1H).

(2*R*)-2-Acetoxydodec-11-ene (13). A mixture of (±)-**3** (7.7 g, 0.042 mol), vinyl acetate (5.8 mL, 0.063 mol), and PPL (5.0 g) in diisopropyl ether (50 mL) was stirred for 48 h. At that time, 34% conversion was noticed by GLC. The mixture was then filtered to remove the solid enzyme and the filtrate concentrated in vacuo. The residue was chromatographed over silica gel (0−15% EtOAc/hexane) to furnish pure (*S*)-**3** (4.85 g, 63%) and (*R*)-**13** (2.65 g, 28%). The spectral data of (*S*)-**3** and all the subsequent chiral intermediates were identical to those of their respective (±)-samples.

(*S*)-**3**: $[\alpha]^{25}$ +5.88° (*c* 1.24, EtOH).

(*R*)-**13**: $[\alpha]^{25}$ −4.18° (*c* 1.4, Hexane); IR 1730, 1640, 1230, 990, 910 cm^{-1}; ^1H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.29 (br s, 14H), 2.1 (s, 3H), 2.2−2.4 (m, 2H), 4.1−4.4 (m, 1H), 4.8−6.2 (m, 3H). Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.14; H, 11.52.

Patulolide A from 13: $[\alpha]^{22}$ +28.1° (*c* 1.14, EtOH) (lit.[11] [α] +28.5° (*c* 0.83, EtOH)).

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