# THE TOTAL SYNTHESIS OF (±)-PATULOLIDE A

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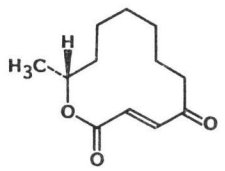
(+)-Patulolide A, a new macrolide isolated from a *Penicillium urticae* mutant, was synthesized from 12-hydroxydodecanoic acid.

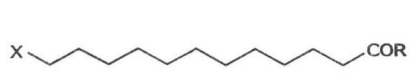
A new 12-membered macrolide, (+)-patulolide A (**1**), was isolated from the culture broth of *Penicillium urticae* S11R59[1] which is a patulin-minus mutant of *P. urticae* NRRL 2159A[2]. Patulolide A shows weak antibacterial activities and relatively high antifungal activities[3]. The structure of patulolide A is rather simple but it has a characteristic structural feature, one double bond flanked with lactone carbonyl and ketone group, which is common with some antifungal metabolites such as pyrenophorin[4], pyrenolides[5,6], vermiculine[7] and A26771B[8]. Thus it is interesting to synthesize this new 12-membered macrolide in order to provide some knowledge of the chemistry of these compounds.



(+)-Patulolide A (**1**)

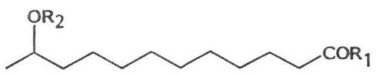
In this report we describe the total synthesis of (±)-patulolide A from 12-hydroxydodecanoic acid (**2**).

The hydroxy acid (**2**) was converted to 12-bromododecanoic acid (**3**) by refluxing in hydrobromic acid solution[9]. The bromo acid (**3**) was transformed to methyl ester (**4**) by refluxing with hydrochloric acid in methanol. Overall yield of **4** from **2** was 63.4%. The ester (**4**) was dehydrobrominated by heating with sodium iodide (1 equiv) in hexamethylphosphoramide (HMPA)[10] at 170°C for 3 hours to give methyl dodecenoate (**5**) and dimethylamide (**6**) in 26.3 and 50.8% yield respectively. Methyl dodecenoate (**5**) was treated with $Hg(OAc)_2$ (1.03 equiv) in THF - $H_2O$ (1 : 1) at room temperature for 0.5 hour and then $NaBH_4$ (1.9 equiv) to give 11-hydroxydodecanoic acid (**7**) in 97.2% yield[11]. The hydroxy acid (**7**) was methylated to **8** with methanol-hydrochloric acid which was transformed to *tert*-butyldimethylsilyl ether (**9**)[12] in 84.7% overall yield from **7**. The amide (**6**) was converted to 11-hydroxydodecanamide (**10**) by the same procedure as the ester (**5**). The amide (**10**) was hydrolyzed to the hydroxy acid (**7**) by refluxing in 3 N-HCl solution. The ester (**9**) was converted to $\alpha,\beta$-unsaturated ester (**11**) by treating with lithium diisopropylamine (LDA) (1.2 equiv) in tetrahydrofuran (THF) at −78°C for 1 hour and then with benzeneselenenyl bromide (1.2 equiv) at −78 ~ −40°C for 2 hours and hydrogen peroxide solution (30%) and acetic acid at 0°C in 62.6% yield[13]. As *tert*-butyldimethylsilyl ether did not resist the next oxidation step, this protective group was replaced with an acetyl group in 89.9% yield by treating **11** with anhydrous $FeCl_3$ (0.15 equiv) in acetic anhydride at 5°C for 20 minutes[14]. The acetate (**12**) thus obtained was oxidized to the ketone (**13**) with $CrO_3$ (5

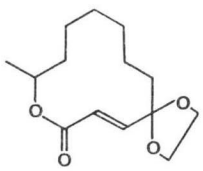


**2** R = OH, X = OH
**3** R = OH, X = Br
**4** R = $OCH_3$, X = Br

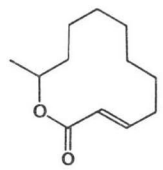
**5** R = $OCH_3$
**6** R = $N(CH_3)_2$



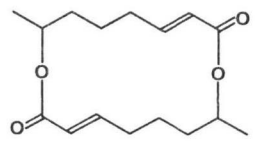
**7** $R_1$ = OH, $R_2$ = H
**8** $R_1$ = $OCH_3$, $R_2$ = H
**9** $R_1$ = $OCH_3$
$R_2$ = $Si(CH_3)_2{}^tBu$
**10** $R_1$ = $N(CH_3)_2$
$R_2$ = H



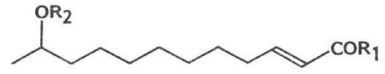
**16**



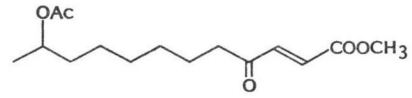
**17**



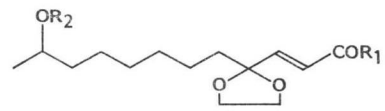
**18**



**11** $R_1$ = $OCH_3$
$R_2$ = $Si(CH_3)_2{}^tBu$
**12** $R_1$ = $OCH_3$, $R_2$ = Ac



**13**



**14** $R_1$ = $OCH_3$, $R_2$ = Ac
**15** $R_1$ = OH, $R_2$ = H

equiv) in acetic anhydride - acetic acid - benzene (1 : 1 : 2) at 20°C for 1 hour in 42.4% yield[15]. It is noteworthy that application of the chromic anhydride oxidation to 12-membered $\alpha,\beta$-unsaturated macrolide (**17**) to give patulolide A was unsuccessful whereas SEEBACH *et al.* successfully oxidized 16-membered $\alpha,\beta$-unsaturated diolide (**18**) to pyrenophorin[16]. The carbonyl group of **13** was protected as an ethylene ketal to give **14** by treating with ethylene glycol (1.5 equiv), triethyl orthoformate (1.03 equiv) and trace boron trifluoride etherate in boiling benzene for 24 hours in 90.6% yield[17]. The ketal ester was quantitatively hydrolyzed to hydroxy acid (**15**) in 2 N-KOH - methanol at room temperature for 5 hours. The hydroxy acid (**15**) was cyclized to the lactone (**16**) by reaction with trichlorobenzoyl chloride (1 equiv) and triethylamine (1.1 equiv) in THF at room temperature for 2 hours then after the removal of triethylamine hydrochloride and THF, the resulting mixed anhydride in toluene was added to refluxing toluene by high dilution method[18]. The cleavage of cyclic ketal to patulolide A in acetone with *p*-toluenesulfonic acid was failed although this procedure was successful in pyrenophorin synthesis[19]. Deprotection of ketal group was successfully carried out by BARTON's method[20] using trityl fluoroborate (1.1 equiv) in dichloromethane in 32%. The synthesized (±)-patulolide A showed mp 78~79°C; MS *m/z* 210 ($M^+$); $^1H$ NMR ($CCl_4$) $\delta$ 7.25, 6.45 (1H, d, $J$=16 Hz), 4.91 (1H, m), 2.44 (2H, t, $J$=6 Hz), 1.8~1.2 (10H, m), 1.35 (3H, d, $J$=6 Hz). The spectroscopy and Rf values on TLC of syn-

thetic patulolide A were identified with those of the natural product.

## Experimentals

Methyl 12-Bromododecanoate (**4**)

12-Hydroxydodecanoic acid (25 g, 0.116 mol, Aldrich) was refluxed with 6.3 ml of sulfuric in 24.7 ml of hydrobromic acid solution (47%) at 160°C for 7.5 hours with stirring. The reaction product was extracted with $CH_2Cl_2$ and dried over anhydrous sodium sulfate and the solvent was evaporated to give a crude brownish oil. This crude oil was dissolve in 300 ml of MeOH and dry HCl gas (15 g) was introduced into the solution. The solution was refluxed at 80°C for 1.5 hours. The reaction mixture was poured in to 300 ml of $H_2O$ and extracted with $CH_2Cl_2$. The extract was dried over anhydrous sodium sulfate and concd to give 30.8 g of crude oil. The product was purified on silica gel column (Kieselgel 60, Merck 70~230 mesh) using *n*-hexane - EtOAc as solvent system. Yield 21.4 g: $^1$H NMR ($CDCl_3$) $\delta$ 3.65 (3H, s), 3.38 (2H, t, $J$=6 Hz), 2.1~2.7 (2H, m); IR $\nu_{max}^{film}$ cm$^{-1}$ 1740.

Methyl 11-Dodecenoate (**5**) and *N*,*N*-Dimethyl 11-Dodecenamide (**6**)

The bromo ester (**4**) (21 g, 71.7 mmol) was heated with sodium iodide (10.75 g) in 50 ml of HMPA at 170°C for 3 hours. To the reaction mixture 200 ml of $H_2O$ was added and was extracted with *n*-hexane. The extract was washed with sodium thiosulfate solution, HCl solution and $H_2O$. After drying over anhydrous sodium sulfate the solvent was evaporated to give 12.3 g of crude oil. The crude product was purified by silica gel column chromatography (Kieselgel 60, Merck 70~230 mesh) using *n*-hexane - EtOAc (10: 1). The first fraction was the ester (**5**) (4.0 g) and the second fraction was the amide (**6**) (8.2 g).

**5**: IR $\nu_{max}^{film}$ cm$^{-1}$ 1740, 1650; MS *m/z* 212 ($M^+$), 180; $^1$H NMR ($CDCl_3$) $\delta$ 5.6~6.0 (1H, m), 4.8~5.1 (2H, m), 3.62 (3H, s), 2.29 (2H, t), 1.85~2.15 (2H, m).

*Anal* Calcd for $C_{13}H_{24}O_2$: C 73.52, H 11.40.
Found: C 73.21, H 11.56.

**6**: MS *m/z* 225 ($M^+$); $^1$H NMR ($CDCl_3$) $\delta$ 5.6~5.95 (1H, m), 4.8~5.1 (2H, m), 3.0 and 2.95 (3H, s, $CH_3N$), 2.28 (2H, t), 1.8~2.2 (2H, m).

*Anal* Calcd for $C_{14}H_{27}ON$: C 73.76, H 12.33, N 6.09.
Found: C 74.60, H 12.09, N 6.22.

11-Hydroxydodecanoic acid (**7**)

To the THF solution of methyl dodecenoate (**5**) (1 g in 10 ml), 1.56 g of $Hg(OAc)_2$ in 20 ml of $H_2O$ - THF (1: 1) was added in one portion and the mixture was stirred for 30 minutes. Then 20 ml of 3 N NaOH solution was added to the reaction mixture and stirred for 30 minutes. $NaBH_4$ (0.36 g) was added portionwise and after 1 hour the reaction mixture was acidified with 6 N HCl solution. THF was evaporated and the solution was extracted with EtOAc. The extract was dried over anhydrous sodium sulfate and evaporated to give white crystals (mp 39~41°C). Yield 0.99 g: MS *m/z* 216 ($M^+$), 198, 183, 172, 129; $^1$H NMR ($CDCl_3$) $\delta$ 3.1~4.1 (1H, m), 2.35 (2H, t), 2.20 (3H, d).

*N*,*N*-Dimethyl 11-Hydroxydodecanamide (**10**)

The amide (**6**) (1 g) was treated with $Hg(OAc)_2$ and $NaBH_4$ in THF and $H_2O$ according to the same procedure with that of the ester (**5**). The hydroxy amide (**10**) was obtained quantitatively. Yield 1.08 g. White crystals: MP 48~49°C; MS *m/z* 243 ($M^+$), 225, 100, 88; $^1$H NMR ($CDCl_3$) $\delta$ 3.75 (1H, m), 3.01 and 2.91 (3H, s, $CH_3N$), 2.30 (2H, t), 1.18 (3H, d).

*Anal* Calcd for $C_{14}H_{29}O_2N$: C 69.07, H 12.02, N 5.76.
Found: C 68.51, H 11.94, N 5.52.

The hydroxy amide (**10**) was hydrolyzed in refluxing 3 N HCl solution to give the hydroxy acid (**7**).

Methyl 11-Hydroxydodecanoate (**8**)

Anhydrous HCl (5.7 g) was introduced into the MeOH solution of 11-hydroxydodecanoic acid (**7**) (3.0 g in 100 ml MeOH) and the solution was kept at room temp overnight. The reaction mixture was

poured into $H_2O$ and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and concd to give 3.0 g of crystalline methyl ester (**8**). Yield 93.9%: IR $\nu_{max}^{film}$ $cm^{-1}$ 3350, 1730; MS *m/z* 230 ($M^+$), 186, 143, 87, 74; $^1H$ NMR ($CDCl_3$) $\delta$ 3.8 (1H, m), 3.7 (3H, s), 2.4 (2H, t), 1.22 (3H, d).

*Anal* Calcd for $C_{13}H_{26}O_3$: C 67.77, H 11.39.
Found: C 67.64, H 11.27.

Methyl 11-*tert*-Butyldimethylsilyloxydodecanoate (**9**)

The hydroxy methyl ester (**8**) (5.31 g) was dissolved in 10.62 ml of DMF and *tert*-butyldimethylsilylchloride (4.19 g, 1.2 equiv) and imidazole (3.93 g, 2.5 equiv) was added. The reaction mixture was kept at room temp for overnight. $H_2O$ was added to the solution and it was extracted with EtOAc. The extract was dried over anhydrous sodium sulfate and concd to give 8.8 g of crude oil. The oil was distilled under reduced pressure and **8** was obtained in 90.2% yield. Yield 7.76 g (bp 147~148°C/2 mmHg): MS *m/z* 344 ($M^+$), 329, 314, 287, 256, 159, 107, 75; $^1H$ NMR ($CDCl_3$) $\delta$ 3.75 (1H, m), 3.68 (3H, s), 2.30 (2H, t), 1.10 (3H, d), 0.9 (9H, s).

*Anal* Calcd for $C_{19}H_{40}O_3Si$: C 66.22, H 11.71.
Found: C 66.09, H 11.76.

Methyl 11-*tert*-Butyldimethylsilyloxy-2-dodecenoate (**11**)

Lithium diisopropylamide (1.2 equiv) was prepared in 20 ml of THF from 0.56 ml of diisopropylamine and butyllithium (1.06 M in *n*-hexane, 3.85 ml) at −78°C for 20 minutes with stirring. The ester (**9**) (1.15 g, 3.4 mmol in 4.5 ml of THF) was added dropwise to the solution. Benzeneselenenyl bromide (4.08 mmol, in 4.5 ml of THF) which was freshly prepared from 0.63 g of diphenyldiselenide and 110 $\mu$l of $Br_2$, was added to the reaction mixture. It was stirred at −78°C for 1 hour and then at −40°C for 2 hours. The temperature of the solution was raised to 0°C and 2 ml of $H_2O$, 0.4 ml of acetic acid and 1.67 ml of $H_2O_2$ (30%) was added to it. After stirring for 30 minutes, the solution was neutralized with diluted $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The extract was washed with $H_2O$, 0.1 N HCl, and again $H_2O$ and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (Kieselgel 60, Merck 70~230 mesh) using *n*-hexane - EtOAc (500: 1). Yield 0.72 g (62.6%): IR $\nu_{max}^{film}$ $cm^{-1}$ 1730, 1660; MS *m/z* 342 ($M^+$), 327, 311, 295, 285, 254, 159, 75; $^1H$ NMR ($CDCl_3$) $\delta$ 6.9~7.2 (1H, m), 5.9 (1H, d, $J$=16 Hz), 2.25 (2H, m), 3.75 (3H, s), 1.12 (3H, d), 0.93 (9H, s).

*Anal* Calcd for $C_{19}H_{38}O_3Si$: C 66.61, H 11.19.
Found: C 65.72, H 11.17.

Methyl 11-Acetoxy-2-dodecenoate (**12**)

*tert*-Butyldimethylsilyloxy ester (**11**) (1.06 g, 3.1 mmol) was dissolved in 2 ml of acetic anhydride and stirred under argon with ice-bath cooling. To the solution 76 mg of anhydrous $FeCl_3$ was added and it was stirred for 20 minutes. $H_2O$ was added to the solution and it was extracted with *n*-hexane. After drying over anhydrous sodium sulfate and evaporation of the solvent, 0.99 g of crude oil was obtained. It was purified by middle pressure column chromatography (Licroprep Si 60) using *n*-hexane - EtOAc (20: 1). Yield 0.77 g (89.9%): IR $\nu_{max}^{film}$ $cm^{-1}$ 1740, 1735, 1660; MS *m/z* 270 ($M^+$), 238, 195, 177, 150, 136, 113, 105, 87; $^1H$ NMR ($CDCl_3$) $\delta$ 6.65~7.10 (1H, m), 5.79 (1H, d), 4.9 (1H, m), 3.72 (3H, s), 2.20 (2H, m), 2.0 (3H, s), 1.20 (3H, d).

Methyl 11-Acetoxy-4-oxo-2-dodecenoate (**13**)

To the mixture of acetic anhydride (11.12 ml) and acetic acid (22.25 ml) chromic anhydride (4.45 g, 5 equiv) was added portionwise with stirring under ice-cooling. After adding 22.25 ml of benzene to it, the acetoxy ester (**12**) (2.40 g, 8.9 mmol) in 4.45 ml of benzene was added dropwise to the reaction mixture keeping the temp under 20°C. After the addition, it was stirred for 1 hour at room temp. $H_2O$ was added to the reaction mixture and it was neutralized with 1 N NaOH solution and extracted with EtOAc. Evaporation of the solvent after drying over anhydrous sodium sulfate gave 2.60 g of crude oil. It was purified by silica gel column chromatography (Kieselgel 60, Merck 70~230 mesh) using *n*-hexane - EtOAc. Yield 1.07 g (42.4%): IR $\nu_{max}^{film}$ $cm^{-1}$ 1730, 1705, 1650; UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) 221 (11,000); MS *m/z* 284 ($M^+$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.08 and 6.65 (1H, d, $J$=16 Hz), 4.90 (1H, m), 3.82

(3H, s), 2.64 (2H, t), 2.04 (3H, s), 1.21 (3H, d).

*Anal* Calcd for $C_{15}H_{24}O_5$: C 63.34, H 8.51.
Found: C 63.11, H 8.85.

Ethylene Ketal of Methyl 11-Acetoxy-4-oxo-2-dodecenoate (**14**)

The keto ester (**13**) (1.07 g, 3.77 mmol) was refluxed with ethylene glycol (323 $\mu$l, 5.80 mmol), triethyl orthoformate (643 $\mu$l, 3.87 mmol) and trace amount of boron trifluoride etherate in 14.5 ml of benzene for 24 hours. $H_2O$ was added to the reaction mixture and it was extracted with EtOAc. The extract was dried and concd to give 1.12 g of pure ketal (**14**) (90.6%): MS *m/z* 328 ($M^+$), 297, 270, 243, 157, 113; $^1H$ NMR ($CDCl_3$) $\delta$ 6.75 and 6.04 (1H, d, $J$=16 Hz), 4.89 (1H, m), 3.86 (4H, m), 3.72 (3H, s), 2.0 (3H, s), 1.20 (3H, d).

Ethylene Ketal of 11-Hydroxy-4-oxo-2-dodecenoic Acid (**15**)

The ester (**14**) (1.13 g) was dissolved in 23.4 ml of MeOH and 11.7 ml of 2 N KOH solution was added to it. After 5 hours reaction at room temp, the reaction mixture was poured into the ice water and pH was adjusted to 3 with 1 N HCl. The solution was extracted with dichloromethane and it was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.95 g of crystals (mp 55~56°C): IR $\nu_{max}^{film}$ $cm^{-1}$ 1700, 1640; MS *m/z* 254, 239, 227, 201, 99; $^1H$ NMR ($CDCl_3$) $\delta$ 6.80 and 6.11 (1H, d, $J$=16 Hz), 3.9 (4H, m), 1.12 (3H, d).

*Anal* Calcd for $C_{14}H_{24}O_5$: C 61.74, H 8.87.
Found: C 61.12, H 8.90.

Ethylene Ketal of (±)-Patulolide A (**16**)

The hydroxy acid (**15**) (0.11 g, 0.4 mmol), triethylamine (0.44 mmol) and 2,4,6-trichlorobenzoyl chloride (0.1 g, 0.4 mmol) were dissolved in 4.4 ml of THF and stirred for 2 hours at room temp. The precipitate of triethylamine hydrochloride was removed by filtration and THF was evaporated by flushing with nitrogen gas. The residue was dissolved in 220 ml of toluene and it was added dropwise for 8 hours to the refluxing solution of 4-dimethylaminopyridine (0.27 g, 2.2 mmol) in 44 ml of toluene. The reaction mixture was diluted with ether and washed with 3% HCl, $H_2O$, $NaHCO_3$ solution and $H_2O$. The solvent layer was dried over anhydrous sodium sulfate and concd. The residue was purified by column chromatography (Kieselgel 60, Merck 70~230 mesh) and 70 mg of **16** was obtained (68.1%): MS *m/z* 254, 239, 210, 199, 182, 143, 125, 113, 98; $^1H$ NMR ($CDCl_3$) $\delta$ 6.72 and 6.10 (1H, d, $J$=16 Hz), 5.1 (1H, m) 3.9 (4H, m), 1.3 (3H, d).

(±)-Patulolide A (**1**)

The ketal (**16**) (37 mg) and 53 mg of $Ph_3CBF_4$ was dissolved in 6 ml of dichloromethane and the solution was stirred at room temp under nitrogen for 4 hours. $H_2O$ was added to the solution and it was extracted with dichloromethane. After drying over anhydrous sulfate, the extract was concd and the residue was purified on preparative TLC using dichloromethane.

Yield 12.6 mg: MP 78~79°C.

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