Highly Stereoselective Total Synthesis of Pikronolide, the Aglycon of the First Macrolide Antibiotic Pikromycin. Crucial Role of Benzyl-Type Protecting Groups Removable by 2,4-Dichloro-5,6-dicyanobenoquinone Oxidation¹,²)

NORIYUKI NAKAJIMA, TATSUYOSHI TANAKA, TATSUO HAMADA, YUJI OIKAWA, and OSAMU YONEMITSU*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

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The first total synthesis of pikronolide, the aglycon of pikromycin, isolated as the first macrolide antibiotic, is described. Two segments i (5: C-1–C-10) and ii (6: C-11–C-15) were synthesized highly stereoselectively from D-glucose and coupled by Yamaguchi's method to give the ester (17), which was subjected to macrocyclization by means of the intramolecular Wittig-Horner reaction developed by Nicolaou, and the 14-membered cyclic enone (18) was isolated in excellent yield. Removal of protecting groups and Swern oxidation gave pikronolide (2). In this synthesis, 3,4-dimethoxybenzyl, 4-methoxybenzyl, and benzyl protecting group for hydroxy function played a crucial role.

Keywords—macrolide antibiotic; pikromycin; aglycon; pikronolide; acyclic stereocontrol; protecting group; esterification; Wittig–Horner reaction; 2,4-dichloro-5,6-dicyanobenoquinone oxidation; stereoselective synthesis

In the preceding papers¹,²) we reported highly stereoselective syntheses of methynolide and tylonolide to exemplify some of the advantageous features of our synthetic methodology. In the present paper, we report the first total synthesis of pikronolide (2), the aglycon of the 14-membered macrolide antibiotic pikromycin (1), which was isolated from a strain of Streptomyces by Brockmann and Henkel as the first macrolide antibiotic in 1950.³) However, all attempts at the total synthesis of pikronolide (2)⁵) as well as pikromycin (1) itself during the past 35 years or more have been unsuccessful, because the construction of the 3β-hydroxyketone system at C-3—C-5⁶) of 1 is extremely difficult⁷) Even under very mild hydrolytic conditions (pH 6.5, 60°C), 1 readily gives the 4,5-anhydro compound, kromycin (3).⁷b,8) This facile elimination into the α,β-unsaturated ketone system was explained in terms of the anti-periplaner disposition of the C-4 hydrogen and the glycoside linkage.⁷b) For the total synthesis of 2, it is essential to avoid such a side reaction. Therefore, the C-3 ketone must be constructed in the final synthetic stage, and we decided to synthesize 4 as a final intermediate. Selection of protecting groups, R¹—R³, of 4 obviously holds the key to success in the total synthesis of 2. Differentiation among the three protecting groups and selective deprotection without any effect on the other functional groups and substituents are critical requirements. We chose 3,4-dimethoxybenzyl (DMPM)⁹,¹⁰) 4-methoxybenzyl (MPM)¹⁰,¹¹) and benzyl (Bn)¹⁰,¹²) as R¹, R², and R³, respectively. The utility of these protecting groups, removable by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), was shown by their use at crucial synthetic steps described in the preceding papers¹,²)

In the methynolide synthesis, the oxidative removal of Bn protection of a tertiary hydroxy function¹²a) was successfully applied at the final step.³c) In the tylonolide synthesis,
not only the selective oxidation of MPM and DMPM protecting groups, but also the selective removal of a Bn protecting group by hydrogenolysis with Raney nickel (Ni)\textsuperscript{10,12b}) was demonstrated.\textsuperscript{1,3d)}

In the present first total synthesis of 2, the selective removal of DMPM, MPM, and Bn protecting groups again played a decisive role. Segments i (5) and ii (6) were considered to be the most promising intermediates in the light of our synthetic methodology established in the syntheses of methynolide\textsuperscript{3a-c}) and tylonolide.\textsuperscript{1,3d) In the syntheses of 5 and 6, DMPM, MPM, and Bn protecting groups for the C-3, C-5 and C-12 hydroxy groups, respectively, were chosen. Segment ii (6) was readily synthesized from D-glucose as described in the previous paper,\textsuperscript{3c) but the synthesis of the more complex segment i (5) was somewhat tedious.

**Results and Discussion**

The Prelog–Djerassi lactone equivalent compound (7), derived from D-glucose as a chiral intermediate for the synthesis of methynolide,\textsuperscript{3d} already has four chiral centers corresponding to C-4, C-5, C-6, and C-8, and two additional chiral centers corresponding to C-2 and C-3 were introduced by an *erythro*-selective Cram addition of crotyl-tri-n-butyltin.\textsuperscript{13) Swern oxidation\textsuperscript{14) of the primary alcohol (7) readily gave the aldehyde, which was treated with excess boron trifluoride etherate (BF\textsubscript{3}·Et\textsubscript{2}O; 2.2. eq) and the tin reagent (2.4 eq)\textsuperscript{13) at −90 °C. The addition of the reagent proceeded quite smoothly to give the expected product (8) having all-\textit{syn} configurations of C-2, C-3, and C-4 with excellent yield and stereoselectivity (>30:1). The configuration of 8 was confirmed after conversion into the diacetate (9), which was also derived from 7 via another route involving the Sharpless asymmetric epoxidation.\textsuperscript{15)}

Oxidative cleavage of the double bond of 8 with ozone and reduction of the resulting aldehyde with sodium borohydride readily gave the diol, which was acetylated to give the diacetate (9). An authentic sample of 9 was synthesized as follows. The aldehyde, the Swern oxidation product of 7, was subjected to the Wittig reaction with a stable ylide, followed by lithium aluminium hydride reduction to give the allyl alcohol (10), which was treated with tert-butyl hydroperoxide, L-(-)-diethyltartrate, and titanium (IV) isopropoxide,\textsuperscript{15) and the expected epoxy alcohol (11) was isolated in excellent yield. Reductive ring opening of the epoxide (11) took place on treatment with sodium cyanoborohydride in the presence of boron
trifluoride etherate\textsuperscript{16)} to give mainly the expected 1,3-diol together with the 1,2-diol.\textsuperscript{17)  
Acetylation of the 1,3-diol gave the diacetate (9). Both samples of 9 were identical in terms of their nuclear magnetic resonance (NMR) spectra.

![Chemical structures and reactions](image-url)
The DMPM protection of the secondary alcohol of 8 was rather difficult. No reaction occurred under usual conditions with sodium hydride and DMPM chloride. Treatment of 8 with a large excess (10—20 eq) of potassium hydride and then DMPM chloride gave the expected DMPM ether (12), but the reproducibility of the reaction was poor. However, DMPM protection proceeded very rapidly upon reverse addition of the reagents (see below) to give 12 in excellent yield. The isopropyl protection of 12 was removed with 1 N hydrochloric acid, followed by reduction of the resulting hemiacetal with calcium borohydride to give the open-chain diol (13).

The primary alcohol of 13 was first protected as an acetal with the methoxyisopropyl group by treatment with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA), and then protection of the remaining secondary alcohol was examined. The MPM protection of the secondary alcohol at a sterically crowded position was quite difficult, and almost no reaction occurred under usual conditions. Treatment with a large excess of sodium hydride (or dimsyl sodium) and MPM chloride gave only a mixture of dienes, 21 and 22. However, when the chloride was first added to a dimethyl sulfoxide solution of the above acetal of 13 and then dimsyl potassium was added in two portions (reverse addition), the MPM protection proceeded quite rapidly to give the ether, which was treated with 0.1 N hydrochloric acid to remove the acetal protection, and the expected alcohol (14) was isolated in 50—60% yield.

Compound 14 was converted to segment i (5) in essentially the same way as described in the previous papers for the syntheses of methynolide and tylonolide. Oxidation of the primary alcohol of 14 by Swern’s method readily gave the aldehyde, which was treated with the lithio derivative of dimethyl methylphosphonate at −80 °C followed by oxidation with pyridinium dichromate (PDC) in dimethylformamide (DMF) to give the ketophosphonate (15). In order to convert 15 into 5 (segment i), the double bond of 15 was first oxidized directly to the carboxylic acid under Lemieux-von Rudloff’s conditions, which were successfully applied in the synthesis of tylonolide, but the yield of 5 was unfortunately less than 10%, because the benzylic positions of the MPM and DMPM protecting groups were not stable enough to this oxidation. Therefore, stepwise oxidation via the aldehyde (16) was next examined. Oxidation of 15 with osmium tetroxide (OsO₄) in the presence of N-methylmorpholine N-oxide (NMO) followed by oxidative cleavage of the resulting diol with sodium metaperiodate (NaIO₄) gave the aldehyde (16), which was oxidized with the Jones reagent at −20 °C for 5 min to give segment i (5) in good yield.

Coupling of the two segments i (5) and ii (6) proceeded smoothly by the Yamaguchi method using 2,4,6-trichlorobenzoyl chloride and 4-dimethylaminopyridine (DMAP) in toluene, and the expected ester (17) bearing both aldehyde and ketophosphonate functions was subjected to an intramolecular Wittig-Horner type macrocyclization by Nicolaou’s method using a large excess of powdered potassium carbonate and 18-crown-6 in toluene at 80 °C. The cyclization proceeded extremely smoothly and was completed within only 1 h to afford the expected 14-membered enone (18) in excellent yield.

For the purpose of conversion of 18 into pikronolide (2), it was necessary to remove selectively the DMPM protecting group at C-3 with minimum loss of the MPM and Bn protecting groups and other functional groups. Deprotection of DMPM groups with DDQ usually proceeds with excellent selectivity, but unfortunately, 18 gave unsatisfactory results with less than 4:1 selectivity, and the expected product (19) was isolated in poor yield. However, the isolated 19 was converted to 2 very smoothly. Swern oxidation of 19 readily gave the C-3 keto compound (20) in excellent yield. Finally, when 20 was further treated with a large excess of DDQ in dichloromethane containing a small amount of water at room temperature, the MPM protecting group at C-5 was removed quite rapidly within 5 min; the clean deprotection of the Bn group at the C-12 proceeded rather slowly and required 19 h to
complete. Surprisingly, during the reaction with DDQ, no trace of kromycin (3) was detected, and pikronolide (2) was isolated in high yield. The first total synthesis of 2 was thus achieved with a very high overall stereoselectivity (> 86%) for the construction of the new chiral centers at C-2, C-4, C-6, C-8, and C-12.26)

**Experimental**

Physical data were measured as described in the previous paper.3a) (3S,4R,5S)-4-Hydroxy-5-[2(S)-isopropyloxy-3(R),5(S)-dimethyl-6(S)-topanyl]-3-methylhexane (8) — Dry dimethyl sulfoxide (DMSO) (Me2SO, 1.23 ml, 1.73 mmol) in CH2Cl2 (7 ml) was added dropwise during 15 min to an efficiently stirred solution of oxalyl chloride (0.75 ml, 8.7 mmol) in dry CH2Cl2 (15 ml) cooled to below -65 C under an argon atmosphere. After 15 min at -70 C, a solution of 4 (1.0 g, 4.34 mmol) was added to the mixture during 10 min. Stirring was continued at -70 C for 30 min, then Et3N (4.8 ml, 34 mmol) was added dropwise, and after removal of the cooling bath, the reaction mixture was allowed to warm to room temperature (over ca. 1 h). Then H2O (20 ml) was added. The organic layer was separated, and the aqueous layer was extracted with ether (30 ml x 2), and the combined extracts were washed with brine, dried over MgSO4, and evaporated in vacuo. The residue was chromatographed on a silica gel column with hexane—EtOAc (9: 1) as the eluant to give the aldehyde (0.95 g, 95%) as a colorless oil. 1H-NMR (CDCl3) δ: 0.83 (3H, d, J=7 Hz), 0.85 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.23 (3H, d, J=7 Hz), 1.56-1.88 (2H, m), 1.92 (1H, ddq, J=2.5, 7 Hz), 4.05 (1H, dd, J=10, 2.5 Hz), 4.59 (1H, d, J=3.5 Hz), 9.68 (1H, s). A stirred solution of the above aldehyde (0.95 g, 4.16 mmol) in dry CH2Cl2 (60 ml), cooled at -93 C under nitrogen, was treated with BF3·Et2O (1.15 ml, 9.3 mmol) in CH2Cl2 (5 ml). After 10 min, crotyl-tri-n-butyltin (4 ml, 10 mmol) in CH2Cl2 (20 ml) was added to the mixture. The rate of addition of BF3·Et2O and crotyl-tri-n-butyltin was controlled to keep the temperature below -90 C. The mixture was stirred at below -90 C for 15 min, and the reaction was quenched with saturated NH4Cl (10 ml). The cooling bath was then removed and the reaction mixture was allowed to warm to room temperature, washed with brine, and dried over anhydrous MgSO4. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane—EtOAc (9:1) as the eluant to afford 8 as a colorless oil (1.1 g, 94%). 1H-NMR (CDCl3) δ: 0.76 (3H, d, J=7 Hz), 0.82 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.09 (3H, d, J=6 Hz), 1.10 (3H, d, J=7 Hz), 1.23 (3H, d, J=7 Hz), 1.56-1.88 (2H, m), 1.92 (1H, ddq, J=2.5, 7 Hz), 4.05 (1H, dd, J=10, 2.5 Hz), 4.59 (1H, d, J=3.5 Hz), 9.68 (1H, s).
2, 1.5, 7 Hz), 2.32 (1H, tq, J = 9, 7 Hz), 3.41 (1H, dd, J = 9, 1.5 Hz), 3.59 (1H, dd, J = 10, 2 Hz), 3.83 (1H, sept, J = 7 Hz), 4.67 (1H, d, J = 3 Hz), 4.97 (1H, d, J = 10, 2 Hz), 5.03 (1H, dd, J = 17, 2 Hz), 5.62 (1H, ddd, J = 17, 10, 9 Hz).

MS m/z (relative intensity): 267 (M+ - 17, 0.15), 225 (6), 169 (60), 100 (100). FD-MS m/z (relative intensity): 285 (M+ + 1, 28), 229 (100), 178 (17), 169 (15). Exact MS m/z Calcd for C12H14O2 (M+ + 1): 285.2340. Found: 285.2347. Calcd for C14H16O2 (M+ - 19): 229.1032. Found: 229.1051.

4S)-2(2S)-Isopropyl-3-(R,S)-dimethyl-6(S)-tetrahydropyranyl)-2-methyl-2(E)-pentenol (10)—A solution of the aldehyde (40 mg, 0.175 mmol), derived from 7, and Ph3P = C(Me)CO2Et (254 mg, 0.7 mmol) in CH2Cl2 (2 ml) was refluxed for 48 h. The Wittig reagent (254 mg, 0.7 mmol) was added again and refluxing was continued for an additional 24 h. After removal of the solvent in vacuo, the residue was purified on a silica gel column with hexane-EtOAc (50:1) as the eluant to give the oily x,6-unsaturated ester (51.4 mg, 94%).

A solution of the ester (33 mg, 0.105 mmol) in ether (0.2 ml) was added to a stirred solution of LiAlH4 (6 mg, 0.158 mmol) in ether (1 ml) at 0 °C under an argon atmosphere. After 50 min, H2O (6 μl), 15% NaOH (6 μl), and H2O (20 μl) were added successively, and the resulting precipitates were removed by filtration. After evaporation of the solvent, the residue was purified through a short silica gel column with hexane-EtOAc (3:1) to afford 10 as a colorless oil (27.3 mg, 91%).

H-NMR (CDCl3): δ: 0.82 (3H, d, J = 6 Hz), 0.84 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 1.07 (3H, d, J = 7 Hz), 1.12 (3H, d, J = 7 Hz), 1.69 (1H, m), 1.69 (3H, d, J = 1.5 Hz), 2.66 (1H, dq, J = 9, 3.5, 7 Hz), 3.37 (1H, dd, J = 8.5, 3.5 Hz), 3.80 (1H, sept, J = 7 Hz), 4.66 (1H, d, J = 2 Hz), 5.58 (1H, dq, J = 9, 1.5 Hz). IR vmax cm⁻¹: 3325. MS m/z (relative intensity): 211 (M+ - 75, 6), 171 (67.5), 129 (99), 100 (70), 71 (76), 58 (96), 43 (100).

[a]β = +146.2° (c = 1.07, CHCl3).

2(R,3R,4S)-1,3-Diacetoxy-4(2S)-isopropyl tartrate (31 mg, 0.15 mmol) in CH2Cl2 (0.4 ml) was added gradually via a syringe to a cold solution (−26 °C) of titanium (IV) isopropoxide (30 μl, 0.1 mmol) in CH2Cl2 (0.4 ml). After 10 min at −26 °C, 10 (27.3 mg, 0.09 mmol) in CH2Cl2 (0.4 ml) and 3 M tert-butyl hydroperoxide (63 μl, 0.21 mmol) in toluene were both added dropwise to the solution. The mixture was allowed to stand for 24 h at −23 °C and then saturated Na3SO3 (0.2 ml) was added. The reaction mixture was warmed to room temperature, then celite was filtered off, and the resulting precipitates were removed by filtration. The filtrate was concentrated in vacuo to give an oil, which was purified on a silica gel column with hexane-EtOAc (5 : 1) as the eluant to give 11 as a colorless oil (27.3 mg, 91%).

H-NMR (CDCl3): δ: 0.82 (3H, d, J = 7 Hz), 0.84 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 1.08 (3H, d, J = 6 Hz), 1.09 (3H, d, J = 7 Hz), 1.17 (3H, d, J = 7 Hz), 1.32 (3H, s), 1.22–1.50 (2H, m), 1.50–1.85 (4H, m), 3.16 (1H, dd, J = 9 Hz), 3.44 (1H, dd, J = 10, 2.5 Hz), 3.49 (1H, dd, J = 12, 8.5 Hz), 3.69 (1H, dd, J = 12, 5 Hz), 3.78 (1H, sept, J = 7 Hz), 4.64 (1H, d, J = 3.5 Hz). IR vmax cm⁻¹: 3400. MS m/z (relative intensity): 284 (M+ - 18, 0.3), 244 (5.5), 171 (8.8), 100 (100), 58 (89), 43 (81). [α]D +146.2° (c = 1.07, CHCl3).

25S,3R,4S)-1,3-Diacetoxy-4(2S)-isopropyl tartrate (31 mg, 0.15 mmol) in CH2Cl2 (0.4 ml) was added gradually via a syringe to a cold solution (−26 °C) of titanium (IV) isopropoxide (30 μl, 0.1 mmol) in CH2Cl2 (0.4 ml). After 10 min at −26 °C, 10 (27.3 mg, 0.09 mmol) in CH2Cl2 (0.4 ml) and 3 M tert-butyl hydroperoxide (63 μl, 0.21 mmol) in toluene were both added dropwise to the solution. The mixture was allowed to stand for 24 h at −23 °C and then saturated Na3SO3 (0.2 ml) was added. The reaction mixture was warmed to room temperature, then celite was filtered off, and the resulting precipitates were removed by filtration. The filtrate was concentrated in vacuo to give an oil, which was chromatographed on a silica gel column with hexane-EtOAc (5 : 1) as the eluant to give 11 as a colorless oil (27.3 mg, 91%).

H-NMR (CDCl3): δ: 0.82 (3H, d, J = 6 Hz), 0.84 (3H, d, J = 7 Hz), 0.93 (3H, d, J = 7 Hz), 1.08 (3H, d, J = 6 Hz), 1.15 (3H, d, J = 6 Hz), 1.21–1.44 (2H, m), 1.50–1.90 (2H, m), 1.90–2.10 (1H, m), 2.02 (3H, s), 2.06 (3H, s), 2.30 (1H, m), 3.43 (1H, dd, J = 10, 2 Hz), 3.81 (1H, dd, J = 11.5, 6.5 Hz), 3.83 (1H, sept, J = 7 Hz), 3.94 (1H, dd, J = 11.5, 8 Hz), 4.65 (1H, d, J = 3.5 Hz), 5.25 (1H, dd, J = 10, 2.5 Hz). IR vmax cm⁻¹: 1752, 1730. [α]D +47.6° (c = 0.42, CHCl3). MS m/z (relative intensity): 372 (M+ + 0.3), 330 (3.5), 131 (15), 122 (26), 100 (100), 58 (53), 43 (70). Exact MS m/z Calcd for C18H26O2 (M+ + 18): 327.2513. Found: 327.2486.

(b) NaBH4CN (24 mg, 0.384 mmol) and BF3·Et2O (31 mg, 0.15 mmol) were both added to a stirred solution of 11 (9.6 mg, 0.032 mmol) in tetrahydrofuran (THF) (2.5 ml) under reflux. The reaction mixture was cooled to room temperature, poured into ice-cooled saturated NaHCO3, and extracted with CH2Cl2. The extract was washed with brine, and dried over MgSO4. After removal of the solvent in vacuo, the residue was chromatographed on a silica gel column with hexane-EtOAc (10 : 1) as the eluant to give two oily fractions. The first fraction gave the 1,3-diol (3.4 mg, 35%), and the second fraction gave the 1,2-diol (2.0 mg, 21%). The 1,3-diol was readily converted to 9 in the usual way.

35S,4R,5S)-4(3,4-Dimethoxybenzyl)-5-(2S)-isopropyl-3-(R,S)-dimethyl-6(S)-tetrahydropyranyl)-3-methylhexene (12)—A 2.5 m potassium dimethyl amion solution [1 ml; prepared from KH (99 mg) and DMSO
tetramethy1-9-hexenal as a colorless oil (284 mg, 95%).

$^{1}$H-NMR (CDCl$_3$) $\delta$: 0.82 (3H, d, $J = 7$ Hz), 0.92 (3H, d, $J = 7$ Hz), 0.94 (3H, d, $J = 6$ Hz), 1.10 (3H, t, $J = 12$ Hz), 1.24 (1H, t, $J = 12$ Hz), 1.40 (1H, d, $J = 12$, 4 Hz), 1.54 – 1.58 (2H, m), 2.23 (1H, dq, $J = 8$, 7 Hz), 3.14 (1H, d, $J = 12$, 2 Hz). IR $v_{\text{max}}$ cm$^{-1}$: 3450, 1720. MS $m/z$ (relative intensity): 393 ($M^+$ 0.7), 374 ($M^+$ – 18, 1), 166 (5), 151 (100).

A solution of $\text{CaCl}_2$ (1 g, 8.8 mmol) in EtOH was cooled at –40 °C, and $\text{NaBH}_4$ (0.5 g, 13.3 mmol) in EtOH (20 ml) was added dropwise. The mixture was stirred at room temperature for 30 min, then excess $\text{CaCl}_2$ was filtered off and the filtrate was concentrated in vacuo. The residue was distilled under vacuum to give $\text{Ca(BH}_4)_2$ as a white solid (1.0 g, 100%).

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A 1.6 M n-BuLi solution in hexane (2.25 ml) was added to a stirred solution of dimethyl methylphosphonate (0.52 ml, 4.8 mmol) in THF at -90 °C. After 45 min, the above aldehyde (0.16 g, 1.2 mmol) in THF (3 ml) was added dropwise, and the reaction mixture was gradually warmed to -20 °C during 8 h. After the reaction had been quenched with saturated NH₄Cl solution, the whole mixture was extracted with ether, and the extract was washed with brine, dried over MgSO₄, and evaporated in vacuo to give the β-hydroxyphosphonate as an oil (0.69 g, 91%). MS m/z (relative intensity): 515 (M⁺ - 121, 2.4), 485 (M⁺ - 151, 0.5), 349 (4), 235 (16), 151 (100), 121 (69). Exact MS m/z Caled for C₂₃H₃₅O₅P (M⁺ - 121): 515.2775. Found: 515.2791.

PDC (2 g, 5.5 mmol) was added to a stirred solution of the β-hydroxyphosphonate (0.69 g, 1.1 mmol) in DMF (12 ml) at room temperature. After 5.5 h, the reaction mixture was poured into H₂O and then extracted with ether. The extract was washed with brine, dried (MgSO₄), and concentrated in vacuo to give the β-hydroxyphosphonate as an oil (0.52 ml, 4.8 mmol) in THF at -90 °C. After 45 min, the above aldehyde (0.16 g, 1.2 mmol) in THF (3 ml) was added.

The extract was washed with 0.1 N HC1 and brine, dried over MgSO₄, and evaporated in vacuo to leave an oil, which was used for the next reaction without further purification. 1H-NMR (CDCl₃) (δ): 0.96 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.12 (3H, d, J= 7 Hz), 1.15 (3H, d, J=7 Hz), 1.65–1.80 (1H, m), 1.90 (1H, dd, J=14, 10.5, 2.5 Hz), 2.04 (1H, ddq, J=7.5, 7, 3.5 Hz), 2.56 (1H, ddq, J=8–7.5, 7.5 Hz), 2.90 (1H, ddq, J=10.5, 7, 3.5 Hz), 3.09 (1H, dd, J=23, 14.5 Hz), 3.19 (1H, dd, J=23, 14.5 Hz), 3.19 (1H, dd, J=7, 3.5 Hz), 3.33 (1H, dd, J=7, 3.5 Hz), 3.77 (1H, d, J=11 Hz), 3.78 (1H, d, J=11 Hz), 3.80 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 4.40 (1H, d, J=11 Hz), 4.45 (1H, d, J=11 Hz), 4.50 (1H, d, J=11 Hz), 4.58 (1H, d, J=11 Hz), 4.99 (1H, dd, J=10.5, 2 Hz), 5.05 (1H, d, J=17.5, 2, 1 Hz), 5.91 (1H, d, J=17.5, 10.6, 8 Hz), 6.89–6.96 (5H, m), 7.1–7.3 (2H, m). IR νmax cm⁻¹: 1710. 1H + 15 (c =1.11, CHC1₃). MS m/z (relative intensity): 513 (M⁺ - 121, 1.9), 483 (4.4), 347 (6.6), 311 (5.2), 233 (7.7), 151 (100), 121 (60).

The reaction mixture was stirred for 30 min at room temperature, then diluted with water, and extracted with CH₂Cl₂. The extract was dried over MgSO₄, and concentrated in vacuo to give 5 (180 mg, 72.5%) as a colorless oil, which was used for the next reaction without further purification. 1H-NMR (CDCl₃) (δ): 0.96 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.17 (3H, d, J=7 Hz), 2.5–3.24 (4H, m), 2.98 (1H, dd, J=22.5, 14 Hz), 3.21 (1H, dd, J=22.5, 14.5 Hz), 3.75 (1H, d, J=11 Hz), 3.77 (1H, d, J=11 Hz), 3.80 (3H, s), 3.87 (3H, s), 4.32 (1H, d, J=11 Hz), 4.39 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.53 (1H, d, J=11 Hz), 6.83 (3H, s), 6.87 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz), 9.76 (1H, d, J=1 Hz). IR νmax cm⁻¹: 1715, 1710.

The diol was dissolved in MeOH (6 ml) and treated with NaI0₄ (282 mg, 1.32 mmol) in H₂O (3 ml) at 0 °C. The reaction mixture was stirred for 30 min at room temperature, then diluted with water, and extracted with CH₂Cl₂. The extract was dried over MgSO₄, and concentrated in vacuo to give 16 as an oil (447 mg, 100%). 1H-NMR (CDCl₃) (δ): 0.97 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.17 (3H, d, J=7 Hz), 2.5–3.24 (4H, m), 2.98 (1H, dd, J=22.5, 14 Hz), 3.21 (1H, dd, J=22.5, 14.5 Hz), 3.75 (1H, d, J=11 Hz), 3.77 (1H, d, J=11 Hz), 3.80 (3H, s), 3.87 (3H, s), 4.32 (1H, d, J=11 Hz), 4.39 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.53 (1H, d, J=11 Hz), 6.83 (3H, s), 6.87 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz), 9.76 (1H, d, J=1 Hz). IR νmax cm⁻¹: 1715, 1710.
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(3R,5R,6S,7S,9R,13R,14R)-13-Benzylxoy-4-(3,4-dimethoxybenzoyloxy)-14-ethyl-6-(4-methoxybenzoyloxy)-3,5,7,9,13-pentamethyl-1-oxacyclotetradec-11(E)-ene-2,10-dione (18) — A solution of 17 (2.9 mg) in toluene (1.5 ml) was added dropwise to a stirred suspension of K₂CO₃ (2.8 mg, 0.02 mmol) and 18-crown-6 (10.7 mg, 0.04 mmol) in toluene (2 ml) during 30 min at 80°C. After 1 h at 80°C, the reaction mixture was poured into ether (20 ml). This ether solution was washed with saturated NH₄Cl (5 ml), and poured into ether (20 ml). This ether solution was washed with saturated MgSO₄, and concentrated in vacuo. The residue was chromatographed on a silica gel column with hexane-EtOAc (3 : 1) as the eluent to afford 18 as a viscous oil (9.1 mg, 91%).

'H-NMR (CDCl₃) δ: 0.89 (3H, t, J=7.5 Hz), 1.01 (6H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.27 (1H, d, J=7 Hz), 1.38 (3H, s), 1.45-1.59 (1H, m), 1.50-1.60 (1H, m), 1.61 (2H, m), 1.77 (1H, m), 1.90-1.93 (1H, m), 2.69 (1H, dq, J=8.5, 7 Hz), 3.07 (1H, d, J=8 Hz), 3.15 (1H, dd, J=8, 7 Hz), 3.51 (1H, t, J=4.5 Hz), 3.75 (1H, d, J=8.5 Hz), 3.76 (3H, d, J=11.5 Hz), 4.30 (1H, d, J=11 Hz), 4.41 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.68 (1H, d, J=11 Hz), 5.01 (1H, d, J=11 Hz), 6.37 (1H, d, J=15.5 Hz), 6.80-6.90 (3H, m), 7.00 (1H, d, J=15.5 Hz), 7.19 (1H, d, J=9 Hz), 7.29 (1H, d, J=9 Hz), 7.29 (5H, m). IR νmax cm⁻¹: 3450, 1730, 1695. MS m/z (relative intensity): 730 (M⁺, 100), 580 (14), 136 (12). Exact MS m/z (relative intensity): 730 (M⁺, 100), 580 (14), 136 (12).

Fl-MS m/z (relative intensity): 472 (M⁺ - 108, 0.15), 401 (0.7), 336 (4.8), 121 (100), 91 (42).

(3R,5S,6S,7S,9R,13R,14R)-13-Benzylxoy-4-ethyl-4-hydroxy-6-(4-methoxybenzoyloxy)-3,5,7,9,13-pentamethyl-1-oxacyclotetradec-11(E)-ene-2,10-dione (19) — A solution of 17 (2.9 mg) in toluene (1.5 ml) was added to the reaction mixture. Stirring was continued for 30 min at -65°C, and then Et₃N (48 μl, 0.345 mmol) was added. After 70 min at -65°C, the reaction mixture was quenched with saturated NH₄Cl, then allowed to warm to room temperature during 1 h, and diluted with CH₂Cl₂. This CH₂Cl₂ solution was washed with brine, and dried over MgSO₄. After evaporation of the solvent, the residue was purified on a silica gel column with hexane-EtOAc (3 : 1) as the eluent to leave an oil, which was subjected to preparative thin layer chromatography (TLC) on silica gel (benzene : EtOAc = 15 : 1, three times development) to give 19 (6.4 mg, 33%, net 42%).

'H-NMR (CDCl₃) δ: 0.91 (3H, t, J=7 Hz), 0.92 (3H, d, J=6 Hz), 1.07 (3H, d, J=7 Hz), 1.16 (3H, d, J=7 Hz), 1.20-1.30 (1H, m), 1.30 (3H, d, J=7 Hz), 1.39 (3H, s), 1.45-1.60 (1H, m), 1.76 (1H, t, J=12 Hz), 2.02 (1H, ddq, J=14, 7.5, 2.5 Hz), 2.08 (1H, m), 2.50-2.65 (1H, m), 2.69 (1H, dq, J=6, 7 Hz), 3.07 (1H, d, J=8 Hz), 3.40 (1H, dd, J=6, 2.5 Hz), 3.79 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 4.30 (2H, d, J=11 Hz), 4.31 (1H, q, J=7 Hz), 4.41 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.68 (1H, d, J=11 Hz), 5.01 (1H, d, J=11 Hz), 6.37 (1H, d, J=15.5 Hz), 6.80-6.90 (3H, m), 7.00 (1H, d, J=15.5 Hz), 7.19 (1H, d, J=9 Hz), 7.29 (1H, d, J=9 Hz), 7.29 (5H, m). IR νmax cm⁻¹: 3450, 1730, 1695. MS m/z (relative intensity): 609 (M⁺ - 121, 3), 579 (1), 335 (4), 167 (7), 151 (100), 121 (86), 91 (42).

Fl-MS m/z (relative intensity): 472 (M⁺ - 108, 0.15), 401 (0.7), 336 (4.8), 121 (100), 91 (42).

MS m/z (relative intensity): 472 (M⁺ - 108, 100), 580 (14), 136 (12). Exact MS m/z (relative intensity): 472 (M⁺, 100), 580 (14), 136 (12).

Pikroonolide (2) — DDQ (22 mg, 0.097 mmol) was added to a stirred solution of 20 (5.4 mg, 0.0934 mmol) in a mixture of CH₂Cl₂ and H₂O (20:1, 0.5 ml) at room temperature. After 19 h, the reaction mixture was directly chromatographed on a silica gel column with hexane-EtOAc-hexane. 

"H-NMR (CDCl₃) δ: 0.91 (3H, t, J=7 Hz, C-15), 1.02 (3H, d, J=7 Hz, C-6), 1.11 (3H, d, J=6 Hz, C-8), 1.19-1.31 (1H, m, C-4'), 1.24 (3H, d, J=7 Hz, C-4'), 1.34 (3H, s, C-12'), 1.40-1.60 (1H, m, C-14), 1.44 (3H, d, J=7 Hz, C-2'), 1.45-1.59 (1H, m, C-7'), 1.79 (1H, ddq, J=14, 2.5, 7 Hz, C-14), 1.94 (1H, m, C-6), 1.95 (1H, d, J=4.5 Hz, C-5 OH), 2.83 (1H, dq, J=12, 6 Hz, C-8), 2.93 (1H, dq, J=5.5, 7 Hz,

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C-4), 2.94 (1H, s, C-12 OH), 3.79 (1H, q, J=7 Hz, C-2), 3.97 (1H, ddd, J=5.5, 4.5, 4 Hz, C-5), 5.00 (1H, dd, J=11, 2.5 Hz, C-13), 6.30 (1H, d, J=16 Hz, C-10), 6.71 (1H, d, J=16 Hz, C-11). IR νκς1 cm\(^{-1}\): 3550, 3450, 1740, 1695, 1635. [α]κ,8.5+ 66.3 (c = 0.187, MeOH). MS m/z (relative intensity): 368 (M\(^+\), 0.6), 350 (14), 310 (3.4), 292 (4.6), 267 (4.2), 254 (7.5), 178 (47), 122 (100), 109 (85). Exact MS m/z Calcd for C\(_{20}\)H\(_{32}\)O\(_6\) (M\(^+\): 368.2198. Found: 368.2196

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References and Notes


4) H. Brockmann and W. Henkel, Naturwissenschaften, 37, 138 (1950); idem, Chem. Ber., 84, 284 (1951).


6) Unless otherwise noted, the numberings are based on that of pikronolide (2).


17) Reduction with excess sodium bis(2-methoxyethoxy)aluminum hydride in refluxing xylene also gave the expected 1,3-diol, though the yield was very poor (6%).


22) Segment i (5) obtained by the Jones oxidation was contaminated with a small amount of a further oxidation product (3%) at the benzylic position of the DMPM group to the dimethoxybenzoyl group. Oxidation of 16 with other reagents such as PDC, RuO\(_2\), n-Bu\(_4\)N\(_2\)Mo\(_7\)O\(_{22}\), Pt-O\(_2\), etc. gave very poor results. Compound 5 was obtained in the pure state from 15 by the following five-step conversion: OsO\(_4\) oxidation to the diol, tert-butyldimethylsilyl protection of the primary alcohol, Swern oxidation (using trifluoroacetic anhydride) of the secondary alcohol, removal of the silyl protection, and finally oxidative cleavage of the keto-alcohol with NaIO\(_4\). However, the overall yield of 5 was less than 10%.


25) The DMPM protecting group of the acetate of 14 was also removed with excellent selectivity (22:1) by treatment with DDQ (1.2 eq) in toluene-H\(_2\)O (20:1) at -5°C.

26) The stereoselectivities at C-4, C-6, C-8, and C-12 were reported in the previous paper.\(^{31}\)