SYNTHESIS OF MACROLIDE ANTIBIOTICS.

18.* STEREOSPECIFIC BUILDING UP OF THE CARBON CHAIN OF ERYTHRONOLIDE B

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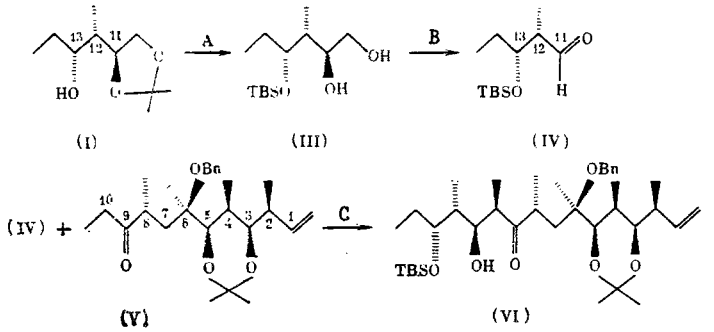
In the preceding article of this series [1], a synthesis of ketone (V) was described, which is a C^1-C^{10}-fragment common to erythronolides A and B. The subject of the present article is building up of the carbon chain of erythronolide B by coupling ketone (V) with the C^{11}-C^{13}-fragment, the aldehyde (IV).

The synthesis of aldehyde (IV) was carried out starting from the secondary alcohol (I), the synthesis of which from levoglucosan has already been described by us in [2]. The hydroxyl group in compound (I) was protected in the form of tert-butyldimethylsilyl (TBS) ether. Treatment of derivative (II) thus obtained with 1,3-propanedithiol in the presence of $BF_3 \cdot Et_2O$ at −78°C results in 1,2-diol (III) following a selective removal of the O-isopropylidene protecting grouping. The periodate splitting of the diol system in (III) gives the required aldehyde (IV) in good yield (Scheme 1).

As a result of the reaction of the Z(O)-lithium enolate of ketone (V) with aldehyde (IV), a single product of the aldol addition is formed in 65% yield, the β-hydroxyketone (VI), having a "natural" configuration of the C^{10} and C^{11} centers.†

Scheme 1



A. 1) $TBSOSO_2CF_3$, Et_3N—CH_2Cl_2, −7,8° → 20°; 2) $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$—CH_2Cl_2, −78°; B. $NaIO_4$—THF/H_2O; C. $LiN(SiMe_3)_2$—THF, −60°.

The reduction of β-hydroxy-ketone (VI) with $LiAlH(t\text{-}BuO)_3$ in ether results in a 12:1 mixture of the required anti-diol (VIII) and its isomeric syn-diol (VII), obtained in an almost quantitative yield. The high selectivity of the reaction is possibly the result of an intramolecular attack of a hydride ion on the carbonyl group in the intermediate (VIIIa), formed as a result of the initial reaction of (VI) with $LiAlH(t\text{-}BuO)_3$ (cf. [4]). It should be noted that the reduction of (VI) by $LiBHEt_3$ or $NaBHEt_3$ led to the selective formation of the syn-diol (VII), while the use of $NaAlH_2(OC_2H_4OCH_3)_2$ resulted in a mixture

*For previous communication, see [1].

†The "natural" configuration was assigned to the C^{10} and C^{11} centers on the basis of a literature analogy [3] and was later confirmed experimentally. The numbering of the carbon atoms in the compounds described in the present article corresponds to the numbering of the carbon chain in erythronolide B.

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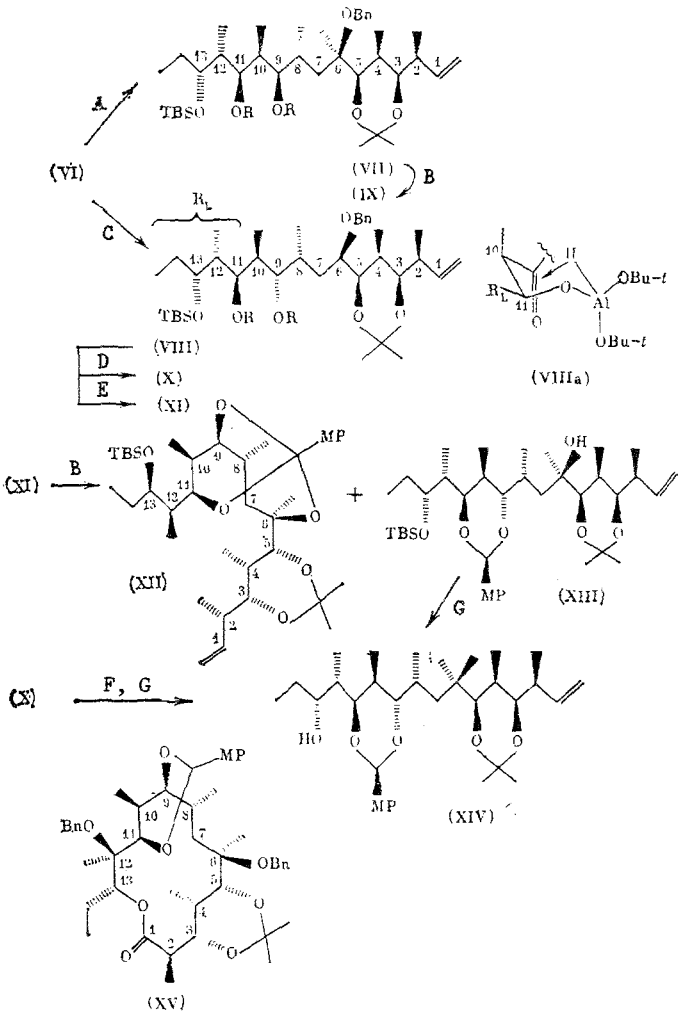
of (VII) and (VIII) with the former predominating. The relative configuration of the C^9, C^{10}, and C^{11} centers in compounds (VII) and (VIII) was established following the analysis of the PMR spectra of cyclic derivatives (IX) and (X) obtained from (VII) and (VIII), respectively (Scheme 2).

Scheme 2



R = H (VII); R = H, R′ = Bn (VIII); R = *p*-$MeOC_6H_4CH$ (IX); R = *p*-$MeOC_6H_4CH$, R′ = Bu (X); R = R′ = H (XI); MP = *p*-$MeOC_6H_4$.

A. $LiBHEt_3$—THF, —78°; B. *p*-$MeOC_6H_4CH_2OMe$, DDQ—CH_2Cl_2, MS 3A; C. $LiAlH$-(*t*-$BuO)_3$—Et_2O, —50°; D. *p*-$MeOC_6H_4CH(OMe)_2$TsOH—CH_2Cl_2; E. Na/NH_3, —78°; F. DQD—CH_2Cl_2-H_2O; G. *n*-Bu_4NF, THF, 80°.

The SSCC value $J_{10,11}$ = 2 Hz in compounds (IX) and (X) indicates a syn-orientation of the substituents at the C^{10} and C^{11} centers in the two compounds, and hence also in the initial ketone (VI). The SSCC value $J_{9,10}$ = 1.7 Hz in (IX), in turn, corresponds to the syn-configuration of the C^9 and C^{10} centers, while SSCC $J_{9,10}$ = 0 in (X) corresponds to the anti-orientation.

The transition from compound (VIII) to the desired compound (XIV) required the successive removal of the benzyl protecting group at O^6, setting up the 9,11-p-methoxybenzylidene protection and removal of TBS protecting group from the hydroxyl at C^{13}. The debenzylation of (VIII) by the action of sodium in liquid ammonia gives the triol (XI) in an unexpectedly low (50%) yield, and is accompanied by the formation of by-products. The reaction of (XI) with p-methoxybenzyl methyl ether and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone DDQ [5] leads to the preferential formation of a bicyclic ortho-benzoate (XII)

(50%). The yield of the required p-methoxybenzylideneacetal (XIII) is only 10%. The desilylation of (XIII) leads in quantitative yield to compound (XIV), which was found to be identical with the compound that we obtained by an alternative route (cf. compound (I) in [6]), which unequivocally establishes the absolute configuration of all the chiral centers in (XIV).

The low yield of the conversion of (VIII) into (XIV) compelled us to seek new paths for the synthesis of this compound. We have made use of an observation noted by us in the study of the removal of the 9,11-p-methoxybenzylidene group in the derivative of erythronolide A (XV). Treatment of compound (XV) with DDQ in wet CH_2Cl_2 (25°C, 1 h) leads to the debenzylation product at O^6 in a moderate yield (50%). The unusual chemoselectivity and high reaction rate (cf. [7]) are possibly due to the rigid conformation of the bicyclic derivative (XV), in which the axially positioned acetal proton in the p-methoxybenzylideneacetal ring and the benzyloxy group at O^6 sterically converge. This steric convergence possibly results in considerable hindrance to the attack by a molecule of water on the carbocation formed on the acetal center at the first stage of the reaction. Therefore, the hydride ion transfer from the neighboring benzyl group with the formation of a new benzyl cation at O^6 becomes the main process. The latter cation is also attacked by water, which leads subsequently to a debenzylation.

Compound (X) possibly has a fairly rigid conformation, similar to the conformation of (XV). We therefore studied the reaction of (X) with DDQ in wet CH_2Cl_2 and found that in this case the main path of the reaction is the removal of the benzyl protection at O^6. The yield of the debenzylated compound (XIII) is 50%. It was thus possible to considerably improve the yield on transition from (VIII) to (XIV). The conversion of compound (XIV) into erythronolide B was described by us previously in [8]. The use of ketone (V) in the synthesis of erythronolide A will be described in the succeeding articles in this series.

EXPERIMENTAL

The PMR spectra were taken in $CDCl_3$ solutions on a Bruker WM-250 spectrometer. The specific rotation was measured in $CHCl_3$ on a Perkin–Elmer M-141 polarimeter. The course of the reactions was monitored by TLC on plates with silica gel from E. Merck. The compounds were purified and the reaction mixtures were separated by high performance liquid chromatography (HPLC) in a column with Silpearl silica gel (20-40 μm).

Absolute solvents were obtained by distillation in argon atmosphere over the appropriate drying agents, directly before use. Benzene, pyridine, hexane, diisopropylamine, DMSO, and triethylamine were distilled over CaH_2. The ether and THF were held over an alkali and then distilled over $LiAlH_4$. Methylene chloride CH_2Cl_2 was distilled first over P_2O_5, and then over powdered CaH_2.

Compound (II). A 1.6 ml portion (11.5 mmoles) of Et_3N was added to a solution of 1.31 g (7.01 mmoles) of (I) [2] in 10 ml of CH_2Cl_2. The mixture was cooled to −78°C, and a 1.95 ml portion (8.4 mmoles) of $TBSOSO_2CF_3$ was added dropwise; the mixture was stirred for 20 min. It was then heated to ~20°C, decomposed with 5 ml saturated solution of $NaHCO_3$, and diluted with water, and extracted with ether. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ether (5%) system. Yield, 1.76 g (83%), syrup, $[\alpha]_D^{20}$ −0.6° (C 0.4). PMR spectrum (δ, ppm, J, Hz): 0.066 s [6H, Me_2(t-BuSiO)], 0.74 d (3H, $J_{Me,12}$ = 6.7, Me at C^{12}), 0.83 t (3H, CH_3CH_2), 0.89 s [9H, Me_2(t-BuSiO)], 1.34 s and 1.39 s (6H, Me_2C=), 1.47 m (2H, CH_3CH_2), 1.65 m (1H, H^{12}), 3.55 m and 4.0 m (3H, $H^{10'}$, H^{10}, H^{11}), 3.87 m (1H, H^{13}).

Compound (III). A 238 μliter portion (2.38 mmoles) of 1,3-propanedithiol was added to a solution of 0.36 g (1.19 mmoles) of (II) in 6 ml of CH_2Cl_2. The mixture was cooled to −78°C, and after adding 292 μliters (2.38 mmoles) of $BF_3 \cdot Et_2O$, was stirred for 1 h. The mixture was decomposed with 3 ml of a saturated solution of $NaHCO_3$, heated to 20°C, diluted with water, and extracted with $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ethyl acetate (EA) (30%) system. Yield, 0.24 g (77%), syrup, $[\alpha]_D^{20}$ +20.6° (C 1.0). PMR spectrum (δ, ppm, J, Hz): 0.1 s and 0.14 s [6H, Me_2(t-BuSiO)], 0.8 d (3H, $J_{Me,12}$ = 7, Me at C^{12}), 0.92 s [9H, Me_2(t-BuSiO)], 0.96 t (3H, CH_3CH_2), 1.57 br.d.q (2H, CH_3CH_2), 1.98 m (1H, H^{12}), 3.5 m and 3.7 m (4H, $H^{10'}$, H^{10}, H^{11}, H^{13}).

Compound (IV). A 228 mg portion (1.07 mmoles) of $NaIO_4$ was added to a solution of 140 mg (0.53 mmole) of (III) in 5 ml of a THF–H_2O (4:1) mixture. The mixture was stirred for 10 min, diluted with ether, and filtered through celite, and the precipitate was washed with ether. The filtrate was evaporated, and the residue was chromatographed in a hexane–ether (50:1) system. Yield, 103 mg (84%). PMR spectrum (δ, ppm, J, Hz): 0.05 s and 0.075 s [6H, $\underline{Me}_2$(t-BuSiO)], 0.88 t (3H, $\underline{CH_3}CH_2$), 0.875 s [9H, Me_2(t-$\underline{BuSi}$O)], 1.07 d (3H, $J_{Me,12}$ = 7, Me at C^{12}), 1.53 m (2H, $CH_3\underline{CH_2}$), 2.47 d.d.q (1H, $J_{12,13}$ = 3.5, H^{12}), 4.05 d.d.d (1H, $J_{13,14} = J_{13,14'}$ = 6.5, H^{13}), 9.77 d (H, $J_{11,12}$ = 0.75, H^{11}).

Compound (VI). A 675 μliter portion (1.17 mmoles) of a 1.74 *N* solution of n-BuLi in hexane was added at 0°C to a solution of 247 μliters (1.17 mmoles) of hexamethyldisilazane in 4 ml of THF. The mixture was stirred for 10 min, then cooled to −60°C, and a solution of 455 mg (1.06 mmoles) of (V) in 4.5 ml of THF was slowly added. The mixture was allowed to stand for 3 h, then was cooled to −75°C, a solution of 276 mg (1.2 mmoles) of (IV) in 2 ml of THF was added, and after stirring for 15 min, was decomposed with 2 ml of a saturated solution of NH_4Cl. The mixture was heated to 20°C, diluted with water, and extracted with $CHCl_3$. The extract was washed with water and saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ether (12%) system. Yield, 440 mg (65%), syrup, $[\alpha]_D^{19}$ = +13.3° (C 1.95). PMR spectrum (δ, ppm, J, Hz): 0.07 s [6H, $\underline{Me}_2$(t-BuSiO)], 0.57 d (3H, $J_{Me,10}$ = 6.7, Me at C^{10}), 0.6 d (3H, $J_{Me,12}$ = 7, Me at C^{12}), 0.875 s [9H, Me_2(t-$\underline{BuSi}$O)], 0.9 t (3H, Me at C^{14}), 0.91 d (3H, $J_{Me,4}$ = 7, Me at C^4), 1.02 d (3H, $J_{Me,2}$ = 6.5, Me at C^2), 1.13 d (3H, $J_{Me,8}$ = 7, Me at C^8), 1.31 s and 1.37 s (9H, Me at C^6, Me groups of isopropylidene residue), 1.27 d.d (1H, $J_{7',7}$ = 14.5, $J_{7,8}$ = 3.3, H^7), 1.49-1.68 m (4H, H^4, H^{12}, $CH_3\underline{CH_2}$), 2.27 d.d (1H, $J_{7',8}$ = 9, $H^{7'}$), 2.3 m (1H, H^2), 2.45 d.q (1H, $J_{10,11}$ = 1.7, H^{10}), 3.04 d.d.q (1H, H^8), 3.42 d.d (1H, $J_{3,4}$ = 2, $J_{3,2}$ = 10, H^3), 3.75 m (1H, H^{13}), 3.92 d (1H, $J_{4,5}$ = 2, H^5), 3.99 d.d.d (1H, $J_{11,12}$ = 10, H^{11}), 4.47 d and 4.6 d (2H, AB-spectrum, J_{gem} = 12, $Ph\underline{CH_2}O$), 5.04 d.d (1H, J_{cis} = 10, J_{gem} = 2, $H^{1°cis}$), 5.09 d.d (1H, J_{trans} = 17, $H^{1°trans}$), 5.58 d.d.d (1H, $J_{1,2}$ = 8.5, H^1).

Compound (VII). A 50 μliter portion of a 1 M solution of $LiBHEt_3$ in THF was added at −78°C to a solution of 28 mg (0.043 mmole) of (VI) in 0.7 ml of THF. The mixture was allowed to stand for 1 h, and was then heated to −5°C, and decomposed with 10 μliters of 15% NaOH and 10 μliters of 30% H_2O_2. It was then diluted with 5 ml of water, and extracted with $CHCl_3$ (2 × 10 ml). The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (7.5%) system. Yield, 27 mg (93%), syrup, $[\alpha]_D^{20}$ = +7.6° (C 3.1). PMR spectrum (δ, ppm, J, Hz): 0.05 s and 0.07 s [6H, $\underline{Me}_2$(t-BuSiO)], 0.69 d (6H, Me at C^{10}, C^{12}), 0.8-1.0 m [18H, Me_2(t-$\underline{BuSi}$O), Me at C^4, C^8, C^{14}), 1.05 d, (3H, $J_{Me,2}$ = 6.7, Me at C^2), 1.25 d.d (1H, $J_{7',7}$ = 14, $J_{7,8}$ = 3.5, H^7), 1.4 s, 1.45 s, 1.47 s (9H, Me at C^6, Me group of isopropylidene residue), 1.4-1.6 m (3H, H^{14}, $H^{14'}$, H^{12}), 1.64 m (2H, H^4, H^{10}), 1.86-2.04 m (2H, $H^{7'}$, H^8), 2.32 m (1H, H^2), 3.28 br.d (1H, H^9), 3.45 d.d (1H, $J_{3,4}$ = 1.7, $J_{2,3}$ = 10, H^3), 3.6 d (1H, H^{11}), 3.95 d.d.d (1H, $J_{13,14} = J_{13,14'}$ = 5.5, $J_{12,13}$ = 1.7, H^{13}), 4.03 d (1H, $J_{4,5}$ = 2, H^5), 4.6 d and 4.72 d (2H, AB-spectrum, $Ph\underline{CH_2}O$), 5.04 d.d (1H, J_{cis} = 10, J_{gem} = 2, $H^{1°cis}$), 5.1 d.d (1H, J_{trans} = 17, $H^{1°trans}$), 5.58 d.d.d (1H, $J_{1,2}$ = 8, H^1), 7.3 m (5H, $C_6\underline{H_5}CH_2O$).

Compound (VIII). A 320 μliter portion (3.4 mmoles) of t-BuOH was added to a suspension of 40 mg (1.05 mmoles) of $LiAlH_4$ in 5 ml of ether. The mixture was stirred for 20 min, cooled to −50°C, 288 mg (0.428 mmole) of (VI) in 2 ml of ether were added, and stirring was continued for 1 h, with the temperature being gradually raised to 20°C at the same time. An excess of $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was diluted with ether, filtered, and the precipitate was washed with ether. The filtrate was evaporated, and the residue was chromatographed in a hexane–ether (12%) system. Yield, 240 mg (86%), syrup, $[\alpha]_D^{23}$ = +22.9° (C 1.85). The yield of the 9(R)-isomer of (VII) was 22 mg (7.8%). PMR spectrum (δ, ppm, J, Hz): 0.1 two s [6H, $\underline{Me}_2$(t-BuOSiO)], 0.7 d, (3H, $J_{Me,10}$ = 7, Me at C^{10}), 0.77 d (3H, $J_{Me,12}$ = 6.7, Me at C^{12}), 0.91-0.97 m [18H, Me_2(t-BuSiO), Me at C^4, C^8, C^{14}), 1.04 d (3H, $J_{Me,2}$ = 6.2, Me at C^2), 1.36 s, 1.42 s, 1.46 s (9H, Me at C^6, Me groups of isopropylidene residue), 1.50-1.60 m (3H, H^{12}, H^{14}, $H^{14'}$), 1.39 d.d (1H, $J_{7',7}$ = 14, $J_{7,8}$ = 5.5, H^7), 1.68 d.d.q (1H, $J_{Me,4}$ = 6.5, H^4), 1.64 m (2H, $H^{7'}$, H^{10}), 1.98 m (1H, H^8), 2.38 m (1H, H^2), 3.43 d.d (1H, $J_{3,4}$ = 2, $J_{3,2}$ = 10, H^3), 3.7 m (2H, H^9, H^{13}), 3.92 d (1H, $J_{4,5}$ = 2, H^5),

4.3 br.d (1H, H^{11}), 4.6 s (2H, A_2-spectrum, $Ph\underline{CH_2}O$), 5.04 d.d (1H, J_{cis} = 10, J_{gem} = 2, $H^{1°}cis$), 5.1 d.d (1H, J_{trans} = 17, $H^{1°}trans$), 5.58 d.d.d (1H, $J_{1,2}$ = 8, H^1), 1.3 m (5H, $C_6\underline{H_5}CH_2O$).

Compound (IX). A 12 mg portion (0.08 mmole) of p-methoxybenzyl methyl ether, 100 mg of molecular sieves 3 Å, and 14 mg (0.06 mmole) of DDQ were added to a solution of 26 mg (0.04 mmole) of (VII) in 1 ml of CH_2Cl_2. The mixture was stirred for 20 min, then was decomposed by a $NaHCO_3$ solution, filtered through celite, and the precipitate was washed with $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ether (5%) system. Yield, 7 mg (23%), syrup, $[\alpha]_D^{20}$ = −21.2° (C 1.95). PMR spectrum (δ, ppm, J, Hz): 0.05 s [6H, $\underline{Me_2}$(t-BuSiO)], 0.75-0.9 m, (12H, Me at C^2, C^4, C^{10}, C^{14}), 0.9 s [9H, $Me_2(\underline{t\text{-}Bu}SiO)$], 1.01 d (3H, Me at C^8), 1.03 d (3H, Me at C^{12}), 1.15 d.d (1H, $J_{7',7}$ = 14, $J_{7,8}$ = 8.7, H^7), 1.3 s (3H, Me at C^6), 1.4 s and 1.47 s (6H, Me groups of the isopropylidene residue), 1.4-1.6 m (3H, H^{12}, H^{14}, $H^{14'}$), 1.73 m (2H, H^4, H^{10}), 2.04 m (1H, H^2), 2.3 m (1H, H^8), 2.58 d (1H, $H^{7'}$), 3.3 d.d (1H, $J_{9,10}$ = 1.7, $J_{8,9}$ = 10, H^9), 3.41 d.d (1H, $J_{3,4}$ = 2, $J_{2,3}$ = 10, H^3), 3.65 d.d (1H, $J_{10,11}$ = 2, $J_{11,12}$ = 10, H^{11}), 3.79 s (H, $\underline{Me}OPhCH$=), 3.86 d (1H, $J_{4,5}$ = 2, H^5), 4.06 d.d.d (1H, $J_{13,14}$ = $J_{13,14'}$ = 6, $J_{12,13}$ = 1, H^{13}), 4.55 d and 4.7 d (2H, AB-spectrum, $Ph\underline{CH_2}O$), 4.95 d.d (1H, J_{cis} = 10, J_{gem} = 2, $H^{1°}cis$), 5.05 d.d (1H, J_{trans} = 17, $H^{1°}trans$), 5.44 s (1H, $MeO\text{–}C_6H_4\underline{CH}$=), 5.55 d.d.d (1H, $J_{1,2}$ = 8, H^1), 6.8 m, 7.2 m, 7.36 m, (9H, aromatic protons).

Compound (X). A 55 mg portion (0.33 mmole) of p-methoxybenzaldehyde dimethylacetal and a catalytic amount of $TsOH\cdot H_2O$ were added to a solution of 95 mg (0.146 mmole) of (VIII) in 2 ml of CH_2Cl_2. The mixture was stirred for 30 min, and after adding 1 ml of a saturated solution of $NaHCO_3$, was diluted with water, and extracted with $CHCl_3$ (2 × 10 ml). The extract was dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ether (9:1) system. Yield, 60 mg (55%), syrup, $[\alpha]_D^{20}$ = −2.3° (C 1.0). PMR spectrum (δ, ppm, J, Hz): 0.00 s [6H, $\underline{Me_2}$(t-BuSiO)], 0.51 d (3H, $J_{Me,10}$ = 7, Me at C^{10}), 0.78 t (3H, Me at C^{14}), 0.86 s [9H, $Me_2(\underline{t\text{-}Bu}SiO)$], 1.0 d (3H, $J_{Me,4}$ = 6.7, Me at C^4), 1.03 d (3H, $J_{Me,2}$ = 6.5, Me at C^2), 1.13 d ($J_{Me,12}$ = 7, Me at C^{12}), 1.145 d (3H, $J_{Me,8}$ = 6.5, Me at C^8), 1.27 s (3H, Me at C^6), 1.35 s and 1.41 s (6H, Me groups of isopropylidene residue), 1.4-1.5 m (2H, H^{14}, $H^{14'}$), 1.58 d.d (1H, H^7), 1.64 d.d (1H, $H^{7'}$), 1.65 m (2H, H^4, H^{10}), 1.89 m (1H, H^{12}), 2.33 m (1H, H^2), 2.43 m (1H, H^8), 3.31 d (1H, $J_{8,9}$ = 10, H^9), 3.4 d.d (1H, $J_{3,4}$ = 2, $J_{2,3}$ = 10, H^3), 3.82 s (3H, $\underline{Me}OC_6H_4CH$=), 3.86 d (1H, $J_{4,5}$ = 2, H^5), 3.91 d.d (1H, $J_{10,11}$ = 2.2, $J_{10,12}$ = 10, H^{11}), 3.99 d.d.d (1H, $J_{13,14}$ = 8, $J_{13,14'}$ = 6, $J_{12,13}$ = 1.5, H^{13}), 4.66 d and 4.77 d (2H, AB-spectrum, $Ph\underline{CH_2}O$), 5.05 d.d (1H, J_{cis} = 10.5, J_{gem} = 2, $H^{1°}cis$), 5.11 d.d (1H, J_{trans} = 17, $H^{1°}trans$), 5.6 d.d.d (1H, $J_{1,2}$ = 8, H^1), 5.56 s (1H, $MeO\text{–}C_6H_4\underline{CH}$=), 6.9 m, 7.28 m, and 7.43 m (9H, aromatic protons).

Compound (XI). A 59 mg portion (0.09 mmole) of compound (VIII) in 1 ml of absolute ether was added at −78°C to a solution obtained from 115 mg (5 mmoles) of Na in 5 ml of liquid NH_3. The mixture was allowed to stand for 1 h, and was then decomposed by solid NH_4Cl. After the evaporation of ammonia, the residue was dissolved in a mixture of H_2O and $CHCl_3$, extracted with $CHCl_3$ (2 × 20 ml), and the extract was dried over Na_2SO_4. The chromatography was carried out in a hexane–ethyl acetate (20%) mixture. Yield of compound (XI), 22 mg (0.039 mmole, 43%), syrup, $[\alpha]_D^{22}$ = +29.3° (C 1.1). PMR spectrum, (δ, ppm, J, Hz): 0.09 and 0.12 s [6H, $\underline{Me_2}$(t-BuSiO)], 0.73 d (3H, $J_{Me,12}$ = 7, Me at C^{12}), 0.88 d (3H, $J_{Me,10}$ = 7.5, Me at C^{10}), 0.91 s [9H, $Me_2(\underline{t\text{-}Bu}SiO)$], 0.95 t (3H, $\underline{CH_3}CH_2$–), 0.96 d (3H, $J_{Me,8}$ = 6.5, Me at C^8), 0.98 d (3H, $J_{Me,4}$ = 6.5, Me at C^4), 1.03 d (3H, $J_{Me,2}$ = 6.5, Me at C^2), 1.33 d.d (1H, $J_{7',7}$ = 14.5, $J_{7,8}$ = 5.5, H^7), 1.17 s (3H, Me at C^6), 1.4 s and 1.44 s (6H, Me groups of isopropylidene residue), 1.5-1.7 m (4H, H^{10}, H^{11}, H^{14}, $H^{14'}$), 1.92 multiplet center (2H, H^7 and H^{12}), 2.0 m (1H, H^8), 2.32 m (1H, H^2), 3.4 d.d (1H, $J_{3,2}$ = 10, $J_{3,4}$ = 1.7, H^3), 3.5 d (1H, $J_{4,5}$ = 1.7, H^5), 3.59 d.d (1H, $J_{9,8}$ = 8, $J_{9,10}$ = 3.5, H^9), 3.68 d.d.d (1H, H^{13}), 4.13 d.d (1H, $J_{12,11}$ = 2, $J_{12,13}$ = 10, H^{12}), 5.03 d.d (1H, J_{cis} = 10.5, J_{gem} = 1.5, $H^{1°}cis$), 5.1 d.d (1H, J_{trans} = 17, $H^{1°}trans$), 5.6 d.d.d (1H, $J_{1,2}$ = 8, H^1).

Compounds (XII) and (XIII). a) a 147 mg portion (0.965 mmole) of p-methoxybenzyl methyl ether, 300 mg of molecular sieves 3 Å and 96 mg (0.425 mmole) of DDQ were added to a solution of 108 mg (0.192 mmole) of (XI) in 2 ml of CH_2Cl_2. The mixture was held for

20 min at 20°C, then was decomposed by a $NaHCO_3$ solution, and extracted with (2 × 25 ml) of $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, filtered through SiO_2, evaporated, and the residue was chromatographed in a hexane–EA (5%) system. Yield of (XIII) 16 mg (12%), syrup, $[\alpha]_D^{20} = -3.5°$ (C 1.0). Yield of (XII) 67 mg (51%), syrup, $[\alpha]_D^{25} = -22.4°$ (C 0.9).

b) DDQ (70 mg, 0.3 mmole) was added in portions in the course of 1 h to a solution of 60 mg (0.078 mmole) of (X) in 1 ml of wet CH_2Cl_2. The mixture was decomposed by a saturated solution of $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ether (9:1) system. Yield of (XIII) 25 mg (47%), syrup, $[\alpha]_D^{22} = -3.9°$ (C 1.25). PMR spectra of compounds obtained by the two methods are identical. PMR spectra of (XIII) (δ, ppm, J, Hz): 0.05 two s [6H, $\underline{Me}_2$(t-BuSiO)], 0.73 d (3H, $J_{Me,10} = 7$, Me at C^{10}), 0.82 t (3H, Me at C^{14}), 0.91 s [9H, Me_2(t-BuSiO)], 1.0 d (3H, $J_{Me,4} = 6.7$, Me at C^4), 1.05 d (3H, $J_{Me,2} = 6.5$, Me at C^2), 1.11 d ($J_{Me,8} = 6.5$, Me at C^8), 1.18 d (3H, $J_{Me,12} = 7$, Me at C^{12}), 1.17 s (3H, Me at C^6), 1.43 two s (6H, Me groups of isopropylidene residue), 1.41-1.72 m (6H, H^{14}, $H^{14'}$, H^7, $H^{7'}$, H^{12}, H^4), 1.86 d.q (1H, H^{10}), 2.34 m (1H, H^2), 2.53 m (1H, H^8), 3.31 d (1H, $J_{9,8} = 11$, H^9), 3.42 d.d (1H, $J_{3,4} = 2$, $J_{2,3} = 10$, H^3), 3.5 d (1H, $J_{4,5} = 2$, H^5), 3.71 s (3H, $\underline{Me}OC_6H_4CH=$), 4.02 d.d.d (1H, $J_{13,14} = J_{13,14'} = 6.2$, $J_{12,13} = 1.5$, H^{13}), 4.05 d.d (1H, $J_{11,12} = 10$, $J_{10,12} = 2$, H^{11}), 5.05 d.d (1H, $J_{cis} = 10$, $J_{gem} = 2$, $H^{1°cis}$), 5.13 d.d (1H, $J_{trans} = 17$, $H^{1°trans}$), 5.61 d.d.d (1H, $J_{1,2} = 8.5$, H^1), 6.9 m, 7.45 m (4H, $MeOC_6\underline{H}_4CH=$), 5.62 s (1H, $MeOC_6H_4CH=$). PMR spectrum of (XII) (δ, ppm, J, Hz): 0.00 two s [6H, $\underline{Me}_2$(t-BuSiO)], 0.9 m (12H, Me at C^4, Me at C^8, Me at C^{10}, Me at C^{14}; 9H, $Me_2(\underline{t\text{-}Bu}SiO)$), 1.03 d (3H, $J_{Me,2} = 6.7$, Me at C^2), 1.06 d (3H, $J_{Me,12} = 7$, Me at C^{12}), 1.08 s (3H, Me at C^6), 1.28 s and 1.36 s (3H + 3H, Me groups of isopropylidene residue), 1.5-1.8 m (5H, H^4, H^7, $H^{7'}$, H^{14}, and $H^{14'}$), 1.92 m (1H, H^8), 2.08 m (2H, H^{10}, H^{12}), 2.3 m (1H, H^2), 3.32 d.d (1H, $J_{3,2} = 10$, $J_{3,4} = 1.5$, H^3), 3.44 d (1H, $J_{5,4} = 2$, H^5), 3.62 d.d (1H, $J_{9,8} = 10$, $J_{9,10} = 2.5$, H^9), 3.66 d.d.d (1H, H^{13}), 3.88 s (3H, $\underline{Me}OPhC=$), 5.03 d.d (1H, $J_{cis} = 10$, $J_{gem} = 2$, $H^{1°cis}$), 5.11 d.d (1H, $J_{trans} = 17$, $H^{1°trans}$), 5.17 d.d (1H, $J_{11,10} = 3.5$, $J_{11,12} = 8$, H^{11}), 5.62 d.d.d (1H, $J_{1,2} = 8$, H^1), 6.91 t and 8.0 t (4H, aromatic protons).

Compound (XIV). A solution of 0.049 g (0.07 mmole) of (XIII) and 0.09 g (0.3 mmole) of Bu_4NF in 3 ml of THF was heated at 80°C for 20 h, then was evaporated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (3:1) system. Yield, 0.035 g (95%), syrup, $[\alpha]_D^{20} = +7.1°$ (C 1.2). The PMR spectrum was identical with the PMR spectrum of compound (I) in [6].

CONCLUSIONS

A stereodirected synthesis of erythronolide B carbon chain was carried out starting from from levoglucosan.

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