CONCLUSIONS

1. The general strategy for the synthesis of erythronolide B from levoglucosan was analyzed.

2. The stereochemistry of the hydrogenation of the double bond in certain $\Delta^{4,5}$-enopyranosides was investigated.

3. The synthesis of methyl-2,4,7-tridesoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-6-oxo-β-L-idoheptopyranoside, the C^1–C^6 fragment of erythronolides A and B, was carried out.

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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

12.* SYNTHESIS OF C^1–C^8 FRAGMENTS OF ERYTHRONOLIDES A AND B

A. F. Sviridov, M. S. Ermolenko, D. V. Yashunskii, V. S. Borodkin, and N. K. Kochetkov

UDC 542.91:547.455

We have already discussed [1] the possible scheme of preparation of erythronolide B from levoglucosan via seco-acid derivatives of erythronolide B (I) or (II), which were retrosynthetically reduced to fragments C^1–C^8 (IV) and (V) and C^9–C^{13} (III). Further retrosynthetic analysis of (IV) and (V) leads the C^1–C^6 fragments (VI) and (VII). We have already described the synthesis of fragments (III) [2] and (VII) [1]. In accordance with the accepted scheme [1], we describe in the present work the synthesis of the C^1–C^6 fragment in the acyclic form (VI) and two forms of the C^1–C^6 fragment (IV) and (V) (scheme 1).

The stereochemistry of the C^2–C^4 section of the chain of compound (VI) (scheme 2) coincides with that of the C^2–C^4 part of the 1,6-anhydro derivative (VIII) that we previously obtained from levoglucosan in five steps in an overall yield of 54% [3]. To pass from the bicyclic derivative (VIII) to the acyclic compound (VI), the C^1-center must be masked by a group which is relatively inert under the experimental conditions of subsequent synthesis, the chain at the C^6 atom must be extended by one carbon unit, and lastly, the configuration of the C^5-center has to be inverted (see top of following page).

The consecutive mercaptolysis of compound (VIII) [4], the selective acetylation of the primary hydroxyl in the triol formed (Ac_2O, Py) and setting up of the 3,5-O-isopropylidene protection carried out without separation of the intermediate products, resulted in the formation of derivative (IX) in 67% yield. The hydrolysis of (IX) under mild conditions [5] gives in a high yield aldehyde (X), which was entered into the reaction with Ph_3PCH_2. Thus,

*For previous communication, see [1].

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.

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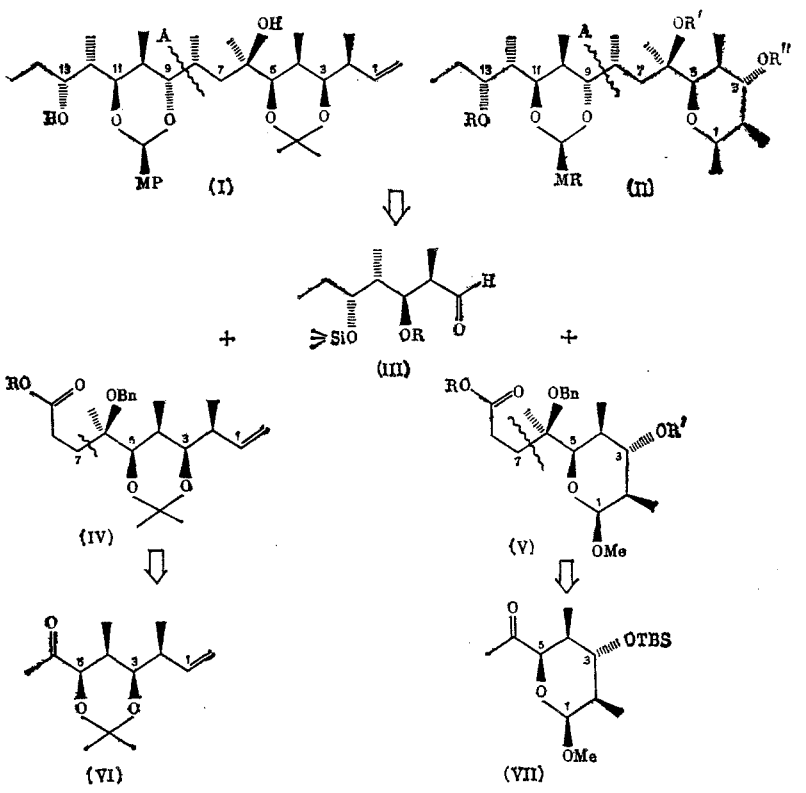
Scheme 1

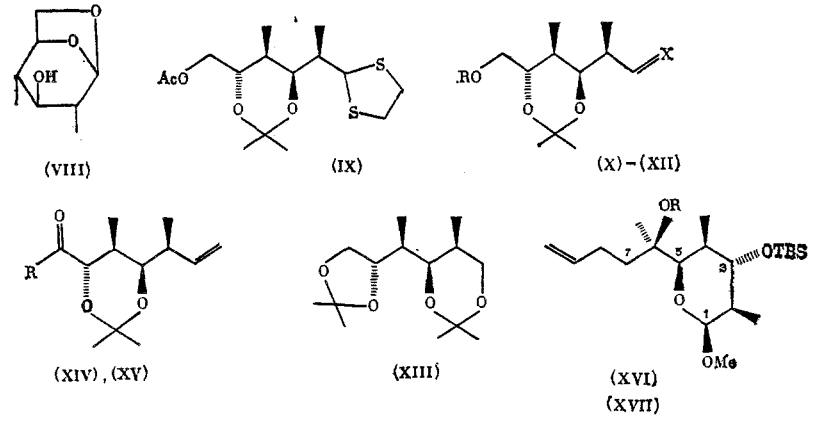


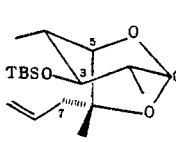
MP = p-$MeOC_6H_4$; Bn = $PhCH_2$; TBS = t-$BuMe_2Si$

together with olefin (XI), a product of its deacetylation (XII) is also formed and therefore, after the olefinization reaction, the reaction mixture was treated with MeONa/MeOH and derivative (XII) was isolated in 75% yield.

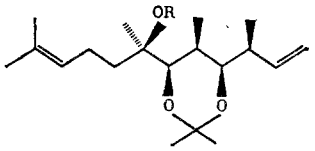
Since the stages of hydrolysis of dithiolane (IX) and olefinization of aldehyde (X) involve the participation of an α-configurated labile derivative (X), it was necessary to prove the invariability of the configuration at the C^2 atom during the (IX) → (XI) transition. To accomplish this, acetate (XI) was converted into derivative (XIII) by consecutive ozonolysis, reduction with $LiAlH_4$ and acetonylation; the yield of diacetonide (XIII) was 56%. The SSCC values in the PMR spectrum of (XIII) ($J_{2,3}$ = 2.3, $J_{1a,2}$ = 2.7, $J_{1e,2}$ = 1.7 Hz) indicate an equatorial disposition of the substituent at C^3 atom and an axial one at C^2, which, taking into account the lability of the configuration of the C^3 atom, confirms the invariability of the C^2 center on transition from dithiolane (IX) to olefin (XI).

Scheme 2

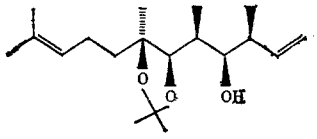




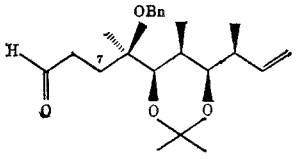
(XVIII)



(XIX)-(XX)



(XXI)



(XXII)

R = Ac, X = O (X); R = Ac, X = CH_2 (XI); R = H, X = CH_2 (XII); R = H (XIV), Me (XV); R = H (XVI), Bn (XVII); R = H (XIX), Bn (XX)

Olefin (XII) was then converted by conventional methods, i.e., oxidation according to Swern [6], reaction with MeMgCl, and repeated oxidation under the same conditions – into methyl ketone (XV) in 76% yield. The SSCC values in the PMR spectrum ($J_{3,4}$ = 4, $J_{4,5}$ = 7 Hz) in combination with the absence of nuclear electrostatic repulsion (NER) between the H^3 and H^5 protons, and the presence of NER for the protons of the axial methyl group of the isopropylidene residue and the H^3 proton, unequivocally indicate that compound (XV) is present in a distorted conformation. Therefore, a mild alkaline treatment of (XV) [7] causes the practically quantitative isomerization of the C^5 center and leads to methyl ketone (VI), in which the acetyl group occupies an equatorial position. This is confirmed by the SSCC values ($J_{3,4}$ = $J_{4,5}$ = 2.2 Hz) and by the presence of NER between the H^3, H^5 protons and the axial methyl group of the O-isopropylidene residue in the PMR spectrum of (VI). The derivative (VI) obtained is an acyclic form of the C^1–C^6 fragment of erythronolides A and B (VI).

By carrying out the synthesis of the C^1–C^6 fragments of erythronolides A and B (VI) and (VII) [1] it was possible to pass to the next stage of the total synthesis of the antibiotics, namely, grafting the C^7–C^8 chain section in the ketones obtained, i.e., to the synthesis of the C^1–C^8 fragments (IV) and (V).

Transition from methyl ketones (VI) and (VII) to esters (IV) and (V) (R = $MeOCH_2$) consists in constructing the configuration of the C^6 center and thus grafting a three-carbon fragment, the terminal group of which should be an ester group, while as the alcoholic component, we proposed to use the $MeOCH_2$ group, the presence of which should favor the syn-orientation of the substituents at the C^8 and C^9 atoms during the preparation of aldols (I) and (II) [8].

Transition from ketones (VI) and (VII) to compounds (IV) and (V) was accomplished as follows. The addition of a Grignard reagent, obtained from 4-bromobutene, to ketone (VII) proceeds stereospecifically and in a yield of 94% and leads to the only product, the tertiary alcohol (XVI) (scheme 2), having the configuration required for the new C^6 chiral center. This was proved by solvolysis of alcohol (XVI), which results in the 1,6-anhydro derivative (XVIII) in 61% yield. Measurement of the NER in the latter showed that a preirradiation of the methyl group at C^6 leads to a 3.5% increase in the integral intensity of the H^3 proton, and a 6.5% increase in the case of the methyl group at C^4, which unequivocally indicates the presence of a new chiral center in the above configuration.

The tertiary alcohol (XVI) was converted into benzyl ether (XVII) and subsequently into acid (V) (R = H, R^1 = TBS) by periodate splitting of the double bond in (XVII) in the presence of OSO_4 [9] to the corresponding aldehyde and its subsequent oxidation by m-chloroperbenzoic acid in THF [10]. The esterification of the acid obtained by a known method [11] led to the desired ester (V) (R = $MeOCH_2$, R^1 = TBS), the –C^1–C^8-fragment of erythronolides A and B in a pyranose form.

The same fragment in acyclic form (IV) (R = $MeOCH_2$) was obtained similarly, except that in this case it was necessary to ensure the regioselectivity of the cleavage of the double bonds in the derivative of type (XIX). The differentiation was achieved by using prenylmagnesium bromide for grafting the C^7–C^8 block to the ketone (VI). As in the case of (VII), the addition of a freshly prepared reagent to the keto group in (VI) proceeds stereospecifically and leads substantially to a single product, the tertiary alcohol (XIX).

In the last compound, the configuration of the C^6 center was determined by examining the spectral properties of the isomeric acetonide (XXI), obtained from (XIX) by acid isomerization in an acetone–dimethoxypropane medium. The investigation of NER of (XXI) showed that the H^5 and H^7 protons as well as H^7 and the methyl group at C^6 are sterically close to one another, which unequivocally confirms the structure of (XXI), and hence also that of (XIX).

The hydroxyl group in (XIX) is protected by benzylation and the more extensively substituted double bond in the ether (XX) obtained was selectively cleaved [12] by the action of one equivalent of ozone. As a result, aldehyde (XXII) was obtained in 62% yield (80% conversion), in the PMR spectrum of which there are signals of protons of an aldehyde group, and of a monosubstituted double bond.

The aldehyde group in (XXII) was oxidized under similar conditions as in the preceding case [see the (XVI) → (V) conversion] and the acid (IV) (R = H) obtained was converted, without isolation, into a methoxymethyl ester (IV) ($R = MeOCH_2$).

EXPERIMENTAL

General Methods, see [1].

1,2-Ethylenedithioacetal (IX). A 10.68 g portion (75.2 mmoles) of $BF_3 \cdot Et_2O$ was added to a solution of 3.97 g (25.1 mmoles) of (VIII) and 3.54 g (37.6 mmoles) of 1,2-ethanedithiol in 25 ml of CH_2Cl_2. The mixture was allowed to stand for 2 h at ~20°C, then was cooled to −40°C, and 23.8 g (301 mmoles) of pyridine and 12.8 g (125.4 mmoles) of Ac_2O were added. The mixture was left to stand for 2 h at −10°C, was then decomposed by 5 ml of MeOH, diluted with $CHCl_3$ and water, and extracted with $CHCl_3$. The extract was washed with 1 N HCl solution, saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, and evaporated. The residue was chromatographed in a benzene–ethyl acetate (EA) gradient (5 → 30%). The triol monoacetate that was isolated (R_f ~ 0.57 in EA) was dissolved in 20 ml of acetone and 20 ml of 2,2-dimethoxypropane and 0.5 g of $TsOH \cdot H_2O$ were added. The mixture was allowed to stand for 30 min at 20°C. then decomposed by solid $NaHCO_3$, and evaporated. The residue was dissolved in a $CHCl_3$–H_2O mixture, extracted with $CHCl_3$, and the extract was washed with a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–EA (4:1) system. The yield of (IX) was 4.75 g (56.6%), syrup, $[\alpha]_D^{23}$ −29° (C 1.0). PMR spectrum: 0.97 d (3H, $J_{CH_3,4}$ = 6.8 Hz, CH_3 at C^4), 1.12 d (3H, $J_{CH_3,2}$ = 6.5 Hz, CH_3 at C^2), 1.35 s and 1.37 s (6H, CH_3 of 3,5-O-acetal), 2.83 d.d.q (1H, $J_{4,3}$ = 4.4, $J_{4,5}$ = 7 Hz, H^4), 2.07 d.d.q (1H, $J_{2,1}$ = 3.3, $J_{2,3}$ = 9.5 Hz, H^2), 2.10 s (3H, $\underline{CH_3}C(O)O$ at C^6), 3.20 m (4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 3.50 d.d.d (1H, $J_{5,6}$ = 7, $J_{5,6}$ = 3 Hz, H^5), 3.58 d.d (1H, H^3), 4.07 d.d (1H, $J_{6,6}$ = 12 Hz, H^6), 4.17 d.d (1H, H^6), 4.68 d (1H, H^1).

Compound (X). A mixture of 4.81 g (14.28 mmoles) of (IX), 14.39 g (143.8 mmoles) of $CaCO_3$ and 19.52 g (71.9 mmoles) of $HgCl_2$ in 75 ml of a MeCN–H_2O (4:1) mixture was stirred for 84 h at 20°C. The precipitate was filtered through a Celite layer, and extracted with ether. The extract was washed with a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–EA (4:1) system. The yield of (IX) was 0.36 g (7.5%), and of (X) 2.8 g (77%, 83.4% based on (IX) that entered into the reaction), syrup, $[\alpha]_D^{23}$ +35.4° (C 1.0). PMR spectrum: 0.87 d (3H, $J_{CH_3,4}$ = 7 Hz, CH_3 at C^4), 1.16 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.35 s (6H, CH_3 of 3,5-O-acetal), 2.07 s (3H, $CH_3C(O)O$ at C^6), 1.90 d.d.q (1H, $J_{3,4}$ = 5, $J_{4,5}$ = 8 Hz, H^4), 2.62 d.d.q (1H, $J_{2,1}$ = 2, $J_{2,3}$ = 10 Hz, H^2), 3.50 d.d.d (1H, $J_{5,6}$ = 3 Hz, H^6), 4.16 d.d (1H, H^6), 9.68 d (1H, H^1).

Compounds (XI) and (XII). A 10.8 ml portion of 1.32 N solution of n-BuLi in hexane (14.2 mmoles) was added with stirring to a suspension of 6.43 g (19 mmoles) of Ph_3PCH_3Br in 35 ml of absolute benzene. The mixture was stirred for 10 min at ~20°C, heated to boiling, and a solution of 1.836 g (7.12 mmoles) of (X) in 10 ml of benzene was added. The mixture was boiled for 10 min and the excess phosphorane was decomposed with 0.5 ml of acetone. According to the TLC data, the mixture contained (XI) and (XII) in a 3:2 ratio. Then, 40 ml of MeOH and 0.5 ml of a 2N solution of MeONa/MeOH were added to the mixture. After 30 min, water was added, and the mixture was extracted with ether. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a pentane–ether (1:1) system. The yield of (XII) was 1.182 g (77.6%), syrup, $[\alpha]_D^{21}$ −17.2° (C 1.0). PMR spectrum: 0.92 d (3H, $J_{CH_3,4}$ = 7 Hz, CH_3 at C^4), 1.05 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.35 s and 1.38 s (6H, CH_3 of 3,5-O-acetal), 1.74 d.d.q (1H, $J_{4,5}$ = 7, $J_{4,3}$ = 4.6 Hz,

H^4), 1.98 m (1H, OH at C^6), 2.32 d.d.d.q (1H, $J_{2,3}$ = 10.7, $J_{2,1}$ = 8, $J_{2,1'trans}$ = 1 Hz, H^2), 3.42 d.d.d (1H, $J_{5,6}$ = 3, $J_{5,6}$ = $J_{5,4}$ = 7 Hz, H^5), 3.47 d.d (1H, H^3), 3.54 d.d (1H, $J_{6,6'}$ = 11.7 Hz, $H^{6'}$), 3.63 d.d (1H, $H^{6'}$) 5.03 d.d (1H, $J_{1'cis,1}$ = 10.7, $J_{1'cis,1'trans}$ = 2 Hz, $H^{1'cis}$), 5.11 d.d.d (1H, $J_{1'trans,1}$ = 17.5 Hz, $H^{1'trans}$), 5.65 d.d.d (1H, H^1).

From the reaction mixture after the Wittig reaction, compound (XI) can be isolated by chromatography, syrup, $[\alpha]_D^{21}$ 0° (C 1.0). PMR spectrum: 0.95 d (3H, J_{CH_3} = 6.8 Hz, CH_3 at C^4), 1.96 d (3H, $J_{CH_3,2}$ = 6.7 Hz, CH_3 at C^2), 1.36 s and 1.37 s (6H, CH_3 of 3,5-O-acetal), 1.71 d.d.q (1H, $J_{4,3}$ = 4.5, $J_{4,5}$ = 11 Hz, H^4), 2.08 s (3H, $CH_3C(O)O$ at C^6), 2.32 d.d.d.q (1H, $J_{2,1}$ = 8, $J_{2,1'trans}$ = 1.5, $J_{2,3}$ = 10.8 Hz, H^2), 3.50 d.d (1H, H^3), 3.52 d.d.d (1H, $J_{5,6}$ = 3 $J_{5,6}$ = 8 Hz, H^5), 4.02 d.d (1H, $J_{6,6'}$ = 12 Hz, H^6), 4.15 d.d (1H, H^6), 5.03 d.d (1H, $J_{1'cis}$ = 10.7, $J_{1'cis,1'trans}$ = 2 Hz, $H^{1'cis}$), 5.11 d.d.d (1H, $J_{1'trans,1}$ = 17.5 Hz, $H^{1'trans}$), 5.65 d.d.d (1H, H^1).

Compound (XV). An 8.5 ml portion of a 2.88 M solution of DMSO in CH_2Cl_2 (20.23 mmoles) was added at −60°C, with stirring, over a period of 10 min, to 17 ml of a 0.64 M solution of $(COCl)_2$ in CH_2Cl_2 (10.88 mmoles). The mixture was stirred at −60°C for 10 min, and then a solution of 1.82 g (8.5 mmoles) of (XII) in 15 ml of CH_2Cl_2 was added over a period of 5 min. The mixture was stirred for 15 min at −60°C, and then 4.36 g (43 mmoles) of triethylamine was added. The temperature was raised to −5°C, and 60 ml of an 1 N aqueous solution of HCl was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The extract was washed with water, saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated, and the residue of aldehyde (XIV) was dissolved in 10 ml of THF. The mixture was cooled to −70°C, and 6 ml of a 1.95 M solution of CH_3MgCl in THF (11.7 mmoles) was added. The mixture was heated to 20°C, and after 30 min was decomposed by a saturated NH_4Cl solution. The precipitate was separated, the solution was evaporated, and the residue of the secondary alcohols was oxidized according to the above-described procedure with the same quantities of the reagents. The ketone (XV) formed was chromatographed in a hexane–EA (11:1) system. Yield, 1.262 g (65.7%, 76% based on (XII) that entered into the reaction), syrup $[\alpha]_D^{20}$ −73.2° (C 1.0) PMR spectrum: 1.03 d (6H, $J_{CH_3,2}$ = $J_{CH_3,4}$ = 6.8 Hz, CH_3 at C^2 and C^4), 1.37 s and 1.39 d (6H, CH_3 of 3,5-O-acetal), 2.09 d.d.q (1H, $J_{4,5}$ = 7, $J_{4,3}$ = 4 Hz, H^4), 2.31 m (1H, $J_{2,3}$ = 10.5, $J_{2,1}$ = 8.2, $J_{2,1'trans}$ = 1 Hz, H^2), 2.23 s (3H, CH_3 at C^6), 3.50 d.d (1H, H^3), 3.71 d (1H, H^5) 5.03 d.d (1H, $J_{1'cis,1}$ = 10, $J_{1'cis,1'trans}$ = 2 Hz, $H^{1'cis}$), 5.11 d.d.d (1H, $J_{1'trans,1}$ = 17 Hz, $H^{1'trans}$), 5.63 d.d.d (1H, H^1).

In the spectral investigation of compound (XV), a NER was detected between the methyl group protons of the acetal (1.39 ppm), interacting in the space and the H^3 proton (3.71 ppm).

Compound (VI). A 0.2 g portion (1.45 mmole) of K_2CO_3 was added to a solution of 0.4955 g (0.508 mmole) of (XV) in 5 ml of MeOH. The mixture was stirred at 20°C for 1 h, diluted with water and extracted with CH_2Cl_2. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA system (11:1). Yield, 0.4707 g (95%), syrup, $[\alpha]_D^{20}$ +40.2° (C 1.0). PMR spectrum: 0.80 d (3H, $J_{CH_3,4}$ = 6.5 Hz, CH_3 at C^4), 1.03 d (3H, $J_{CH_3,2}$ = 6.5 Hz, CH_3 at C^2), 1.41 s (3H, axial CH_3 of 3,5-O-acetal), 1.49 s (3H, equatorial CH_3 of 3,5-O-acetal), 2.0 d.d.q (1H, $J_{4,3}$ = $J_{4,5}$ = 2.2 Hz, H^4), 2.18 s (3H, CH_3 at C^6), 2.28 d.d.d.q (1H, $J_{2,3}$ = 10, $J_{2,1}$ = 8.5, $J_{2,1'trans}$ = 0.5 Hz, H^2), 3.51 d.d (1H, H^3), 4.24 d (1H, H^5), 5.04 d.d (1H, $J_{1'cis,1}$ = 10, $J_{1'cis,1'trans}$ = 2 Hz, $H^{1'cis}$), 5.10 d.d.d (1H, $J_{1'trans,1}$ = 17 Hz, $H^{1'trans}$), 5.60 d.d.d (1H, H^1). NER for (VI): [H^5]; H^3 = 4.5%, [H^5]; H^4 = 6.8%, [H^5]; axial CH_3 of acetal = 5.3%.

Compound (XIII). A solution of 37 mg (0.144 mmole) of (XI), 0.3 ml of pyridine and 0.2 ml of a 0.05% solution of Sudan IV in CH_2Cl_2 (25 ml) was ozonized at −70°C to decoloration, the excess of ozone was removed by passing a current of argon for 5 min, 1 ml of dimethyl sulfide was added, and the mixture was heated to room temperature for a period of 1 h. The solution was evaporated, the residue was dissolved in a mixture of 5 ml of ether and 5 ml of CH_2Cl_2, and an excess of $LiAlH_4$ in THF was added. The mixture was stirred for 30 min and then decomposed by the successive addition of 0.25 ml of water, 0.25 ml of a 15% NaOH solution and 0.75 ml of water. The precipitate was separated by filtration through anhydrous Na_2SO_4, and the filtrate was evaporated. The residue was dissolved in a mixture of 3 ml of acetone and 0.5 ml of 2,2-dimethoxypropane, 2 mg of $TsOH \cdot H_2O$ were added, and the mixture was

allowed to stand for 30 min at ~20°C. An excess of Et_3N was added, the solution was evaporated and the residue was chromatographed in a heptane–EA system (4:1). Yield, 21 mg (56%), syrup, $[\alpha]_D^{23}$ +12° (C 1.0). PMR spectrum: 0.85 d (3H, $J_{CH_3,4}$ = 6.6 Hz, CH_3 at C^4), 1.14 d (3H, $J_{CH_3,2}$ = 6.9 Hz, CH_3 at C^2), 1.34 s, 1.38 s, 1.42 s (12H, CH_3 of 1.3- and 5,6-O-acetals), 1.73 d.d.d.q (1H, $J_{2,1a}$ = 2.7, $J_{2,1e}$ = 1.7, $J_{2,3}$ = 2.3 Hz, H^2), 1.91 d.d.q (1H, $J_{4,3}$ = 8.8, $J_{4,5}$ = 6.6 Hz, H^4), 3.58 d.d (1H, $J_{1e,1a}$ = 11.3 Hz, H^{1e}), 3.64, d.d (1H, H^3), 3.92 d.d.d and 3.95 d.d (2H, AB-system H^5 and H^6), 4.08 d.d (1H, H^{1a}), 3.60 d.d (1H, H^6).

Compound (XVI). A 4 ml portion of a 0.51 N solution of butenyl magnesium bromide in THF (2.04 mmoles) was added at −78°C with stirring, to a solution of 0.578 g (1.826 mmoles) of (VI) in 10 ml of THF. The mixture was stirred for 10 min and was then decomposed by a saturated NH_4Cl solution. The precipitate was separated, washed with ether, the organic solution was evaporated and the residue was chromatographed in a heptane–EA (19:1) system. Yield, 0.639 g (94%), syrup, $[\alpha]_D^{23}$ +55.2° (C 2.0). PMR spectrum: 0.05 and 0.07 s (6H, $OSi\underline{Me}_2Bu$-t, at C^3), 0.90 s (9H, $OSiMe_2\underline{Bu}$-t at C^3), 1.01 d and 1.13 d (6H, $J_{CH_3,2} = J_{CH_3,4}$ = 7.5 Hz, CH_3 at C^2 and C^4), 1.15 s (3H, CH_3 at C^6), 1.70 m, 1.87 m and 2.12 m (6H, H^2, H^4, H^7, $H^{7'}$, H^8, and $H^{8'}$), 3.52 s (3H, MeO at C^1), 3.54 s (1H, OH at C^6), 3.67 d.d (1H, $J_{2,3} = J_{3,4}$ = 2.5 Hz, H^3), 3.74 d (1H, $J_{4,5}$ = 2.5 Hz, H^5), 4.73 d (1H, $J_{1,2}$ = 3.7 Hz, H^1), 4.95 d.d.d.d (1H, $J_{10cis,10trans} = J_{10cis,8}$ = 1.9 Hz, $J_{10cis,9}$ = 10.2 Hz, H^{10cis}), 5.04 d.d.d.d (1H, $J_{10,trans9}$ = 17, $J_{10,trans8} = J_{10trans8'}$ = 1.9 Hz, $H^{10trans}$), 5.85 d.d.d.d (1H, $J_{9,8}$ = 6.5, $J_{9,8'}$ = 13.2 Hz, H^9).

Compound (XVIII). A 10 mg portion of $TsOH \cdot H_2O$ was added to a solution of 40 mg (0.107 mmole) of (XVI) in 1.2 ml of acetone. The mixture was decomposed by a $NaHCO_3$ solution, extracted with $CHCl_3$, the extract was washed with water and saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed in heptane. Yield, 23 mg (61%), syrup, $[\alpha]_D^{23}$ +50° (C 1.0). PMR spectrum: 0.08 s and 0.1 s (6H, $OSi\underline{Me}_2Bu$-t at C^3), 0.9 s (9H, $OSiMe_2\underline{Bu}$-t at C^3), 1.0 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.08 d (3H, $J_{CH_3,4}$ = 7.2 Hz, CH_3 at C^4), 1.37 s (3H, CH_3 at C^6), 1.63 m (3H, $J_{2,1}$ = 1.6, $J_{2,3}$ = 8 Hz, H^2, H^7, $H^{7'}$), 2.09 m (3H, $J_{4,3}$ = 10, $J_{4,5}$ = 3.5 Hz, H^4, H^8, $H^{8'}$), 3.64 d.d (1H, H^3), 3.82 d (1H, H^5), 4.92 d.d.d (1H, $J_{10,10'} = J_{10cis,8}$ = 1.7, $J_{9,10cis}$ = 10 Hz, H^{10cis}), 5.01 d.d.d (1H, $J_{10trans,8}$ = 1.7, $J_{9,10trans}$ = 17 Hz, $H^{10trans}$), 5.14 d (1H, H^1), 5.81 m (1H, H^9). NER: [CH_3 at C^6], CH_3 at C^4 = 6.5%; [CH_3 at C^6], H^3 = 3.5%.

Compound (XVII). A solution of 0.335 g (0.9 mmole) of (XVI) in 2 ml of DMF was added to a suspension of 0.1 g (3.33 mmoles) of NaOH in 3 ml DMF. The mixture was stirred for 30 min, cooled to 5°C, and 178 μliter (1.35 mmole) of benzyl bromide were added. The mixture was stirred at ~20°C for 30 min, and ws then decomposed by MeOH and water. It was extracted with ether, the extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was chromatographed in a heptane–EA (19:1) system. Yield 0.369 g (88.7%), syrup, $[\alpha]_D^{23}$ +68° (C 2.0).

Compound (V). A 32 mg portion (0.09 mmole) OsO_4 was added to a solution of 0.236 g (0.51 mmole) of (XVII) in 15 ml of a dioxane–water (3:1) mixture. The mixture was stirred for 5 min, an excess $NaIO_4$ was added, and after stirring for 15 h, it was diluted with $CHCl_3$ and water, and the aqueous layer was extracted with chloroform. The extract was washed with a saturated solution of $Na_2S_2O_3$, water, and a saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was dissolved in 2 ml of THF, 86 mg (0.5 mmole) of m-chloroperbenzoic acid were added, and after 30 min, the mixture was decomposed by saturated solutions of $NaHCO_3$ and Na_2SO_3, extracted with $CHCl_3$, the extract was washed with water, 1 M HCl, and a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was dried azeotropically by distillation with toluene. The material was dissolved in 5 ml of absolute MeCN, 150 μliter (1 mmole) of diazobicycloundecene were added and 150 μliter (2 mmoles) of methoxymethyl chloride. The mixture was stirred for 1 h at 20°C, was decomposed with water, and extracted with ether. The extract was washed with a 1 M HCl solution, saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated and the residue was chromatographed in a heptane–EA (9:1) system. Yield 0.226 g (84.5%), syrup, $[\alpha]_D^{23}$ +30.5° (C 0.5). PMR spectrum: 0.06 s and 0.08 s (6H, $OSi\underline{Me}_2Bu$-t at C^3), 0.9 s (9H, $OSiMe_2\underline{Bu}$-t at C^3), 1.02 d and 1.16 d (6H, $J_{CH_3,2} = J_{CH_3,4}$ = 7.5 Hz, CH_3 at C^2 and C^4), 1.76 m and 1.87 m (2H, $J_{2,3} = J_{4,3}$ = 2.4, $J_{1,2}$ = 2.5, $J_{4,5}$ = 2.5 Hz, H^2, H_4), 1.98 m and 2.19 m (2H, H^7, $H^{7'}$), 2.52 m (2H, H^8, $H^{8'}$), 3.42 s and 3.52 s (6H, MeO at C^1 and

MeOCH$_2$–OCH$_2$–O–), 3.67 d.d (1H, H^3), 4.02 d (1H, H^5), 4.62 d and 4.72 d (2H, AB system, J_{gem} = 11.5 Hz, OCH$_2$Ph at C^6); 4.70 d (1H, H^1), 5.18 d and 5.21 d (2H, AB system, J_{gem} = 5.8 Hz, MeOCH$_2$O–), 7.30- 7.40 m (5H, C$_6$H$_5$ at C^6).

Compound (XIX). A 10 ml portion of a freshly prepared 0.257 N solution of prenylmagnesium bromide in THF (2.57 mmoles) was added at −70°C to a solution of 0.471 g (2.08 mmoles) of (VI) in 3 ml of THF. The mixture was stirred for 10 min, heated to 20°C, and decomposed by a saturated NH_4Cl solution. The precipitate was separated by filtration through a layer of anhydrous Na_2SO_4, the filtrate was evaporated, and the residue was chromatographed in a heptane–ether (9:1) system. Yield, 0.55 g (85.2%), syrup, $[\alpha]_D^{21}$ +8.4° (C 1.0). PMR spectrum: 1.0 d and 1.05 d (6H, $J_{CH_3,2} = J_{CH_3,4}$ = 7 Hz, CH$_3$ at C^2 and C^4), 1.14 s CH$_3$ at C^6), 1.41 s and 1.44 s (6H, CH$_3$ of 3,5-O-acetal), 1.62 br. s and 1.69 br. s (6H (CH$_3$)$_2$C=CH– at C^8), 2.01 m (2H, H^4, H^8), 2.31 s (1H, OH at C^6), 2.33 d.d.q (1H, $J_{1,2}$ = 8.5, $J_{2,3}$ = 9.5 Hz, H^2), 3.41 d.d (1H, $J_{3,4}$ = 2 Hz, H^3), 3.56 d (1H, $J_{5,4}$ = 2 Hz, H^5), 5.03 d.d (1H, $J_{1'cis,1}$ = 10, $J_{1'cis,1'trans}$ = 2 Hz, H$^{1'cis}$), 5.12 d.d (1H, $J_{1'trans,1}$ = 17 Hz, H$^{1'trans}$), 5.13 m (1H, (CH$_3$)$_2$C=CH at C^8), 5.60 d.d.d (1H, H^1).

Compound (XXI). A 9.1 ml portion of 2,2-dimethoxypropene and 2 mg of TsOH·H$_2$O was added to a solution of 12.8 mg (0.0412 mmoles) of (XIX) in 0.5 ml of acetone. The mixture was allowed to stand at ~20°C for 2 h, decomposed by a saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed in a heptane–ether (9:1) system. Yield, 7 mg (54.6%), syrup, $[\alpha]_D^{22}$ +21.6° (C 0.5). PMR spectrum: 1.02 d (3H, $J_{CH_3,4}$ = 6.7 Hz, CH$_3$ at C^4) 1.11 d (3H, $J_{CH_3,2}$ = 6.6 Hz, CH$_3$ at C^2), 1.13 s (3H, CH$_3$ at C^6), 1.33 s and 1.42 s (6H, CH$_3$ of 3,5-O-acetal), 1.62 br. s (3H, CH$_3$-cis), 1.69 q (3H, $J_{CH_3,8}$ = 1.1 Hz, CH$_3$-trans), 1.96 d.d.q (1H, $J_{3,4}$ = 2, $J_{4,5}$ = 6.7 Hz, H^4), 2.15 m (2H, H^8), 2.34 d.d.q (1H, $J_{2,3} = J_{2,1}$ = 9 Hz, H^2), 3.34 d.d.d (1H, $J_{3,OH}$ = 5.4 Hz, H^3), 3.83 d (1H, H^5), 5.1 m and 5.58 d.d.d (4H, vinyl protons). NER: [H^5, CH$_3$ of acetal at 1.33 ppm = 5.5%; [CH$_3$ at C^4]. H^5 = 0.7%; [H^5], H^7 = 3%; [CH$_3$ at C^6], H^4 = 1.8%.

Compound (XX). A solution of 88 mg (283 μmole) of (XIX) in 2 ml of DMF was added with stirring to a suspension of 30 mg (1 mmole) of 80% NaH in 1.5 ml of DMF. The mixture was stirred at ~20°C for 30 min, and then 126.5 mg (736 μmoles) of benzyl bromide was added, and the mixture was further stirred at ~20°C for 4 h. It was decomposed with water, extracted with $CHCl_3$, and the extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, and evaporated. Yield, 101 mg, (89%), syrup, $[\alpha]_D^{21}$ −2.4° (C 1.25). PMR spectrum: 1.05 d and 1.07 d (6H, $J_{CH_3,2} = J_{CH_3,4}$ = 6.5 Hz, CH$_3$ at C^2 and C^4), 1.27 s (3H, CH$_3$ at C^8),1.42 s and 1.48 s (6H, CH$_3$ of 3,5-O-acetal), 1.62 br. s and 1.72 br. s (6H, (CH$_3$)$_2$C=CH at C^8), 2.35 d.d.q (1H, $J_{2,3}$ = 10, $J_{2,1}$ = 8.5 Hz, H^2), 3.43 d.d (1H, $J_{3,4}$ = 2 Hz, H^3), 3.84 d (1H, $J_{4,5}$ = 4 Hz, H^5), 4.57 d and 4.72 d (2H, J_{gem} = 11.5 Hz, AB system C$_6$H$_5$CH$_2$O at C^6), 5.04 d.d (1H, $J_{1'cis,1}$ = 10, $J_{1'cis,1'trans}$ = 2 Hz, H$^{1'cis}$), 5.10 d.d (1H, $J_{1'trans,1}$ = 17 Hz, H$^{1'trans}$), 5.13 m (1H, (CH$_3$)$_2$C=CH at C^8), 5.61 d.d.d (1H, H^1), 7.3 m (5H, C$_6$H$_5$).

Compound (XXII). A solution of 0.352 g (878 μmoles) of (XX) and 0.4 ml of pyridine in 40 ml of CH_2Cl_2 was ozonized at −70°C until 80-90% conversion was attained (a TLC control). The ozone was removed by passing an argon current for 5 min, 1 ml of dimethyl sulfide was added, and the mixture was heated at ~20°C for 1 h. The solution was evaporated several times with toluene and chromatographed in a heptane–ether (4:1) system. The yield of (XX) was 70.4 mg (20%); of (XXII) 204.5 mg (62%, 77.5% based on (XX) that entered into the reaction), syrup $[\alpha]_D^{21}$ +7.3° (C 1.0). PMR spectrum: 1.01 d and 1.06 d (6H, $J_{CH_3,2} = J_{CH_3,4}$ = 6.7 Hz, CH$_3$ at C^2 and C^4), 1.27 s (3H, CH$_3$ at C^6), 1.41 s and 1.47 s (6H, CH$_3$ of 3,5-O-acetal), 1.68 d.d.q (1H, $J_{3,4} = J_{4,5}$ = 2 Hz, H^4), 2.32 d.d.d.q (1H, $J_{2,1}$ = 8.5, $J_{2,1'trans}$ = 0.7, $J_{2,3}$ = 10 Hz, H^2), 2.55 d.d (1H, $J_{8,CHO}$ = 1.5, $J_{8,8'}$ = 7.5 Hz, H^8), 2.58 d.d.d (1H, $J_{8',CHO} = J_{8',7}$ = 1.5 Hz, H^8), 3.43 d (1H, H^3), 3.88 d (1H, H^5), 4.52 d and 4.65 d (2H, J_{gem} = 12 Hz, AB system C$_6$H$_5$·CH$_2$O at C^6), 5.03 d.d (1H, $J_{1'cis,1}$ = 10, $J_{1'cis,1'trans}$ = 2 Hz, H$^{1'cis}$), 5.11 d.d.d (1H, $J_{1'trans,1}$ = 17 Hz, H$^{1'trans}$), 5.59 d.d.d (1H, H^1), 7.30 m (5H, C$_5$H$_6$) 9.78 d.d (1H, CHO at C^8).

Compound (IV). A 0.134 g portion (0.777 mmole) of m-chloroperbenzoic acid was added to a solution of 0.224 g (0.598 mmoles) of (XXII) in 5 ml of THF–phosphate buffer mixture (pH 7.0) (9:1). The mixture was stirred at ~20°C for 5 min and then decomposed by a mixture of

saturated solutions of $NaHCO_3$ and $Na_2S_2O_3$, and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried over Na_2SO_4, evaporated and the residue was dissolved in 15 ml of absolute MeCN. A 0.457 g portion (3 mmoles) of 1,5-diazabicyclo[5.4.0]undec-5-ene and 0.24 g (3 mmoles) of methoxymethyl chloride were added. The mixture was allowed to stand at ~20°C for 30 min, was then decomposed with water, and extracted with ether. The extract was washed with 1 N HCl solution, saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–ether (5:1) system. Yield 0.24 g (92.3%), syrup $[\alpha]_D^{21}$ +1.5° (C 1.0). PMR spectrum: 1.0 d and 1.06 d (6H, $J_{CH_3,2} = J_{CH_3,4}$ = 7 Hz, CH_3 at C^2 and C^4), 1.27 s (3H, CH_3 at C^6), 1.41 s and 1.47 s (6H, CH_3 of 3,5-O-acetal), 1.69 d.d.q (1H, $J_{4,5} = J_{3,4}$ = 2 Hz, H^4), 1.79 d.d.d (1H, $J_{7,8} = J_{7,8'}$ = 8, $J_{7,7'}$ = 14 Hz, H^7), 2.20 d.d.d (1H, $H^{7'}$), 2.33 d.d.q (1H, $J_{2,3}$ = 10, $J_{2,1}$ = 8.5 Hz, H^2), 2.50 d.d (2H), $J_{8,8'}$ = 8 Hz, H^8, H^9, 3.43 d.d (1H, H^3), 3.43 s (3H, $\underline{C}H_3OCH_2OC(O)$ at C^8), 3.87 d (1H, H^5), 4.55 d and 4.68 d (2H, J_{gem} = 11.7 Hz, AB system $C_6C_5\underline{C}H_2O$ at C^6), 5.03 d.d (1H, $J_{1'cis,1}$ = 10, $J_{1'cis,1'trans}$ = 2 Hz, $H^{1'cis}$), 5.10 d.d (1H, $J_{1'trans,1}$ = 17 Hz, $H^{1'trans}$), 5.60 d.d.d (1H, H^1), 5.16 d and 5.19 d (2H, J_{gem} = 6 Hz, AB-system $CH_3OCH_2OC(O)$ at C^8), 7.30 m (5H, C_6H_5).

CONCLUSIONS

A stereodirected synthesis of the C^1–C^6- and C^1–C^8-fragments of erythronolides A and B was carried out.

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