SYNTHESIS OF MACROLIDE ANTIBIOTICS. COMMUNICATION 8. SYNTHESIS OF ACYCLIC FORMS OF C^9—C^{13} FRAGMENT OF ERYTHRONOLIDE B

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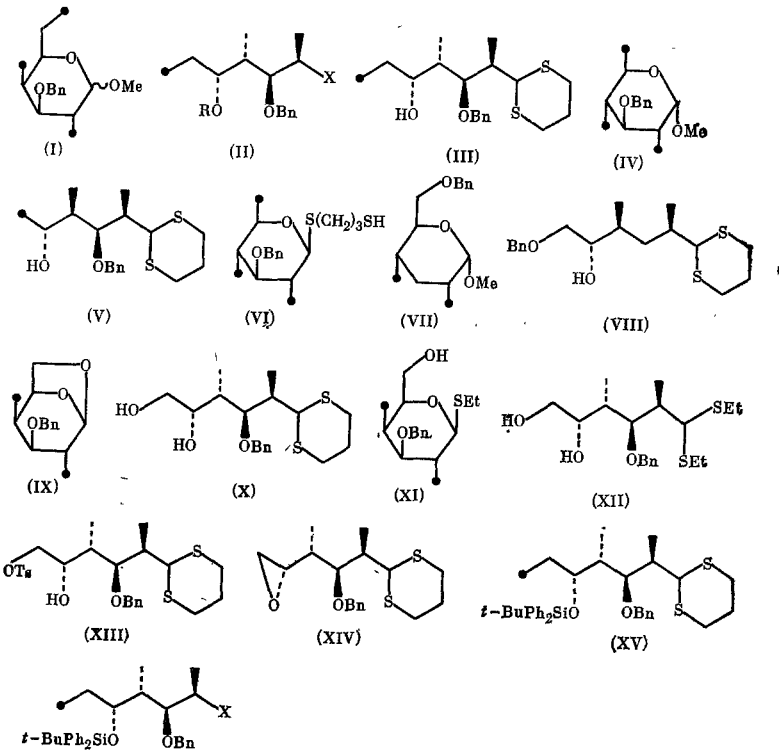
One of the stages in the total synthesis of macrolide antibodics from sugars, carried out in our laboratory [1], is linking the fragments already synthesized [1, 2]. It is first necessary to conver the C^9—C^{13} fragments (for example, erythronolide B (I) [2]) into an acyclic reactive form (II).

The most suitable method for this transformation is the mercaptolysis of (I) [3, 4], leading to dithioacetal (III), which, after protection of the hydroxyl at C^5, represents the nucleophilic component in the linking process.

However, the experiment showed that in the presence of strong Lewis acids ($BF_3 \cdot Et_2O$, $TiCl_4$), the mercaptolysis of (I) leads to debenzylation of the hydroxyl group at C^3, while the presence of weak Lewis acids or mineral acids ($ZnCl_2$, ZnI_2, $Me_3SiOSO_2CF_3$, CH_3COOH, HCl) stops the reaction at the stage of formation of the thioglycoside.

On the other hand, in the presence of boron trifluoride ethereate, model (IV), structurally similar to compound (I), is converted in a 40% yield into the corresponding dithiane (V) by the action of 1 equivalent of 1,3-propanedithiol (from the reaction mixture the thioglycoside (VI) was also isolated in a yield of 23%).



X = CHO (XVI), CH_2OH (XVII), CH_2SPh (XVIII), $CH_2S(O)Ph$ (XIX).

It was also found that in the presence of a donor substituent at the C^6 atom (compound (VII)), mercaptolysis proceeds smoothly, and the corresponding dithiane (VIII) can be isolated from the reaction mixture in a yield of 86%.

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Since the character of the protecting group for the hydroxyl at C^3 in (I), and the configuration of the C^2, C^3, C^4, and C^5 centers are determined by the strategy of the synthesis itself, we tried to introduce a compound similar to (I) with a different character of substitution at the C^6 atom into the mercaptolysis. The most suitable in this respect was the 1,6-anhydropyranose (IX), a synthetic predecessor of (I) [2]. In fact, it was found that by the action of 1,3-propanedithiol in the presence of $ZnCl_2$, dithiane (X) is formed in a 65% yield. It should be noted that the cyclic character of the dithioacetal formed appreciably influences the shift of the equilibrium in the direction of formation of the dithioacetal. When ethyl mercaptan is used under the same conditions, an equilibrium mixture of thioglycoside (XI) and diethyl dithioacetal (XII) is formed in the ratio of ∿2:1. The dithiane (X) formed was then selectively converted into monotosylate (XIII), and by the action of a base into the α-oxide (XIV). The reaction of the latter with methylmagnesium chloride (catalyzed by monovalent copper salt) led to dithiane (III) in an overall yield of 42%, based on dithiane (X) (because of their extraordinary lability, compounds (XIII) and (XIV) were not isolated).

The retention of the configuration of the asymmetric centers on transition from (IX) to (III) was proved by transforming dithiane (III) into a mixture of methylglycosides (I) under the conditions of a mercuric hydrolysis, and subsequent methanolysis (yield 88%).

The dithiane (III) was then transformed into silyl ether (XV) by the action of (tert-butyldiphenyl)silylium triflate. Attempts to silylate by the usual reagent (t-$BuPh_2SiCl$—imidazole—DMFA) were unsuccessful, because of the low reactivity of the hydroxyl in (III) (the same was observed on transition from diol (X) to monotosylate (XIII)).

For the dithiane (XV), we verified the possible formation of an anion by the action of different systems (n-BuLi; n-BuLi—tetramethylethylenediamine; t-BuLi; t-BuLi—HMPT). However, in these case, the data obtained in the deuterolysis of the reaction mixtures formed show the absence of formation of an anion at the C^1 atom in (XV). These results agree with recently published [5] results on attempts to obtain anions from polyfunctional dithianes. We therefore carried out a transition from the dithiane (XV) to sulfoxide (XIX), and thus could not only increase the acidity of the proton at C^1, but also markedly decrease steric hindrances at this center.

Mercuric hydrolysis of dithiane (V) under neutral conditions led to aldehyde (XVI) in a quantitative yield. Reduction of (XVI) by sodium borohydride gave the primary alcohol (XVII). The latter was coverted into phenyl sulfide (XVIII) by the action of a diphenyl disulfide—n-tributylphosphine system. Oxidation of (XVIII) by sodium periodate led to a mixture of two isomeric sulfoxides (XIX).

At present, we studying the possible utilization of sulfoxide (XIX) as an equivalent of acyl anion, and also of aldehyde (XVI) as the aldehyde component of the aldol condensation.

EXPERIMENTAL

The PMR and ^{13}C NMR spectra were run on a Bruker WM-250 spectrometer (solutions on $CDCl_3$, internal standard TMS). The specific rotation was measured on Perkin—Elmer-141 polarimeter in $CHCl_3$. The course of the reaction and the purity of the compounds obtained were controlled by TLC on plates with silica gel and by means of isocritical high-performance liquid chromatography. The mixtures were separated by column chromatography on Silpearl silica gel (25-40 m) in an isocratic regime, or by using a stepwise gradient.

Methyl-α-3-O-benzyl-2,4,6-tridesoxy-2,4-di-C-methyl-D-glucopyranoside (IV). A solution of 286 g (1.15 mmoles) of 1,6-anhydro-3-O-benzyl-2,4-didesoxy-2,4-di-C-methyl-β-D-glucopyranose [7] in 10 ml of a 10% methanolic solution of hydrogen chloride was held at ∿20°C for 4 h, then it was diluted by ether, cooled to −60°C, and saturated with NH_3 (gas). The precipitate was filtered, and the solution evaporated. The residue was chromatographed in a benzene—ether (3:1) system to yield 231 mg (71.8%) of methyl-α-3-O-benzyl-2,4-didesoxy-2,4-di-C-methyl-D-glucopyranoside, syrup, $[\alpha]_D^{+23}$ +109 (C 0.9). The product was dissolved in 5 ml of CH_2Cl_2 and 0.5 ml of Et_3N and 285 mg (1.6 mmoles) of TsCl were added. The mixture was stirred for 2 h, decomposed by water, and extracted by chloroform. The extract was washed with 1 N HCl, water and saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was dissolved in 5 ml of THF, and 2 ml of 0.9 N solution (1.8 mmoles) of lithium triethylborohydride in THF were added, with stirring. The mixture was held for 2 h, and then decomposed by water and extracted by chloroform. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel in a

heptane–ether (4:1) system. The yield of (IV) was 185 mg (85%), syrup, $[\alpha]_D^{+23}$ +84° (C 1.1). PMR spectrum (δ, ppm): 4.56 d (1H, H^1, $J_{1,2}$ = 3.4 Hz), 1.93 d.d.w (1H, H^2, J_2, CH_3-2 = 6.5, $J_{2,3}$ = 10 Hz), 3.21 d.d (1H, H^3, $J_{3,4}$ = 10 Hz), 1.5 d.d.q (1H, H^4, J_4, CH_3-4 = 6.5 Hz), 3.55 d.q (1H, H^5, $J_{4,5}$ 10, J_5, CH_3-5 = 6.3 Hz), 1.00 d (3H, CH_3 at C^4), 1.09 d (3H, CH_3 at C^2), 1.22 d (3H, CH_3 at C^5), 3.34 s (3H, OMe), 4.56 and 4.61 d (2H, $PhCH_2O$ at C^3, J_{gem} = 10 Hz).

1,1-Dimercaptopropylene-2,4,6-tridesoxy-2,4-di-C-methyl-3-O-benzyl-D-glucohaxaldose (V) and (3-Mercapto-1-propyl)-β-2,4,6-tridesoxy-2,4-di-C-methyl-D-glucothiopyranoside (VI). A 172-mg portion (1.59 mmoles) of 1,3-propanedithiol and 0.37 ml (3 mmoles) of $BF_3 \cdot Et_2O$ were added at −10°C to a solution of 400 mg (1.51 mmoles) of (IV) in 15 ml of CH_2Cl_2. The mixture was held at ∿20°C for 3 h, then diluted with CH_2Cl_2, cooled to −70°C, saturated with gaseous NH_3, and the precipitate was separated. The solution was evaporated, and the residue was chromatographed on silica gel in a benzene–ether gradient (from 0 to 30%). The yield of (V) was 208 mg (40%), syrup, $[\alpha]_D^{+23}$ +10° (C 1.0). PMR spectrum (δ, ppm): 4.05 d (1H, H^1, $J_{1,2}$ = 4.5 Hz), 2.10 m (1H, H^2, J_2, CH_3-2 = 7 Hz), 3.93 d.d (1H, H^3, $J_{2,3}$ = 4, $J_{3,4}$ = 3.5 Hz), 1.83 m (1H, H^4, J_4, CH_3-4 = 6.8 Hz), 3.75 d. q (1H, H^5, J_5, CH_3-5 = 6, $J_{4,5}$ = 8.5 Hz), 1.20 d (3H, CH_3 at C^5), 1.28 d (3H, CH_3 at C^2), 0.90 d (3H, CH_3 at C^4), 3.05 br s (1H, OH), 2.82 m (4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 2.10 m (2H, $SCH_2\underline{CH_2}CH_2S$), 4.62 and 4.72 d (2H, OCH_2Ph at C^3, J_{gem} = 11 Hz); (VI) — yield 123 mg (24), syrup $[\alpha]_D^{+23}$ +177° (C 0.98, PMR spectrum (δ, ppm): 5.18 d (1H, H^1, $J_{1,2}$ = 5 Hz), 2.24 d.d.q (1H, H^2, J_2, CH_3-2 = 7 Hz), 3.11 3.3 (1H, H^3, $J_{3,4}$ = 10 Hz), 1.50 m (1H, H^4, J_4, CH_3-4 = 7 Hz), 3.94 d.q (1H, H^5, $J_{4,5}$ = 10, J_5, CH_3-5 = 6 Hz), 1.10 d (3H, CH_3 at C^2), 1.02 d (3H, CH_3 at C^4), 1.22 d (3H, CH_3 at C^5), 1.92 m (2H, $SCH_2\underline{CH_2}CH_2SH$), 2.67 m (4H, $S\underline{CH_2}CH_2\underline{CH_2}SH$), 4.53 and 4.60 d (2H, OCH_2Ph at C^3, J_{gem} = 10.5 Hz).

Methyl-α-6-O-benzyl-2,3,4-tridesoxy-2,4-di-C-methyl-D-glucopyranoside (VII). A 5.1-g portion (170 mmoles) of sodium hydride and 30 mg of imidazole were added to a solution of 14.2 g (90 mmoles) of 1,6-anhydro-2,4-didesoxy-2,4-di-C-methyl-β-D-glucopyranose [7] in 350 ml of THF. The mixture was stirred for 30 min at ∿20°C, and then 18.2 ml (0.3 mmole) of carbo disulfide were added. The mixture was stirred for 1 h, and then 13 ml (0.2 mmole) of methyl iodide were added. The mixture was stirred for 1 h, decomposed by water, and extracted by ether. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated, and the residue was dissolved in 300 ml of toluene. To the solution, in an argon current, 400 mg of azoisobutyronitrile and 40 ml (0.15 mole) of tri-n-butylborohydride were added. The solution was boiled for 1 h, cooled, poured onto a layer of silica gel, and eluted by a pentane–ether gradient (0 to 100%). The solvent was distilled at atmospheric pressure, and the residue was distilled at 71.5°C (13 mm Hz) to yield 9.95 g of 1,6-anhydro-2,3,4-tridesoxy-2,4-di-C-methyl-β-D-glucopyranose (78%), syrup, $[\alpha]_D^{+23}$ −81° (C 0.84). PMR spectrum (δ, ppm): 5.22 br. s (1H, H^1), 1.70 m (2H, H^2 and H^4), 1.10 and 2.15 m (2H, $H^{3,3'}$), 4.23 m (1H, H^5), 3.82 m (2H, $H^{6,6'}$), 1.27 d (3H, CH_3 at C^2, J_2, CH_3-2 = 7 Hz), 1.12 d (3H, CH_3 at C^4, J_4, CH-4 = 7 Hz). ^{13}C NMR spectrum (δ, ppm): 105.7 (C^1), 33.9 and 32.4 (C^2 and C^4), 29.2 (C^3), 78.2 (C^5), 68.4 (C^6).

A 1-g portion of KU-23 (H^+) resin was added to a solution of 2.32 (16.3 mmoles) of the above 1,6-anhydro-2,3,4-tridesoxy-2,4-di-C-methyl-β-D-glucopyranose in 20 ml of absolute methanol. The mixture was stirred for 2 h, the resin was filtered, the solution was evaporated, and the residue was chromatographed in a benzene–ether (3:1) system. The yield of methyl-α-2,3,4-tridesoxy-2,4-di-C-methyl-D-glucopyranoside was 1.71 g (60%), syrup, $[\alpha]_D^{+23}$ +133° (C 1.05). PMR spectrum (δ, ppm): 4.5 d (1H, H^1, $J_{1,2}$ = 3.2 Hz), 1.54-1.90 m (2H, H^2 and H^4, J_2, CH_3-2 = 6, J_4, CH_3-4 = 6.7 Hz), 1.20-1.52 m (1H, H^3), 3.40 m (1H, H^5), 3.60 and 3.75 m (2H, H^6 and $H^{6'}$), 0.85 and 0.88 d (6H, CH_3 at C^2 and C^4), 3.45 br. s (1H, OH at C^3), 3.35 s (3H, OMe). ^{13}C NMR spectrum (δ, ppm): 101.55 (C^1), 35.0 (C^2 and C^3), 31.3 (C^4), 74.2 (C^5), 63.65 (C^6), 16.5 and 17.4 (CH_3 at C^2 and C^4), 54.8 (OMe).

A 135-g portion (6.8 mmoles) of sodium hydride (an 80% suspension in oil) was added, with stirring, to 788 mg (4.53 mmoles) of methyl-α-2,3,4-tridesoxy-2,4-di-C-methyl-D-glucopyranoside, obtained above, dissolved in 5 ml of DMFA, and then after 30 min, 0.81 ml (6.8 mmoles) of benzyl bromide were added. The mixture was stirred for 30 min, and after addition of water, it was extracted by chloroform. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated, and the residue was chromatographed on silica gel in a heptane–ether (4:1) system. The yield of (VII) was 800 mg (67%), syrup, $[\alpha]_D^{+23}$ +116 (C 1.2).

1,1-Dimercaptopropylene-2,3,4-tridesoxy-2,4-di-C-methyl-6-O-benzyl-D-riboaldohexose (VIII). A 57.5-mg portion (0.53 mmole). of 1,3-propanedithiol and 50 ml (0.4 mmole) of

$BF_3 \cdot Et_3O$ were added to a solution of 98 mg (0.37 mmole) of (VII) in 4 ml of CH_2Cl_2, cooled to −20°C. The mixture was held at ∿20°C for 30 min, then colled at −70°C, and saturated by gaseous ammonia. The precipitate was filtered, the solution was evaporated, and the residue was chromatographed on silica gel in a benzene–ether gradient (from 0 to 30%). The yield of (VIII) was 0.108 g (86%), syrup, $[\alpha]_D^{+23}$ −8° (C 1.1). ^{13}C NMR spectrum (δ, ppm): 54.8 (C^1), 37.3 (C^2), 36.3 (C^3), 33.8 (C^4), 74.2 (C^5), 72.3 (C^6), 16.0 (CH_3 at C^4), 18.0 (CH_3 at C^2), 26.5 ($\underline{CH_2}CH_2S$), 30.8 and 31.3 ($S\underline{CH_2}CH_2CH_2S$), 73.4 ($O\underline{CH_2}Ph$ and C^6).

1,1-Dimercaptopropylene-2,4-didesoxy-2,4-di-C-methyl-3-O-benzyl-D-galactoaldohexose (X). A 240-mg portion (1.7 mmoles) of $ZnCl_2$ was added at −10°C to a solution of 3.02 g (12.2 mmoles) of (IX) in 4 ml of 1.3-propanedithiol. The mixture was held at 0°C for 24 h and was then diluted with chloroform. The chloroform solution was saturated with gaseous ammonia, and the mixture was passed through a layer of silica gel. 1,3-Propanedithiol was isolated in chloroform, and the reaction product (X) was eluted in a chloroform–ethyl acetate (1:1) mixture. Repeated chromatography on silica gel in heptane–ethyl acetate (2:1) system gave pure (X) in a yield of 2.80 g (64.5%), syrup, $[\alpha]_D^{+23}$ +4° (C 0.95). PMR spectrum (δ, ppm): 4.08 d (1H, H^1, $J_{1,2}$ = 6 Hz), 2.21 d.d.q (1H, H_2, J_2, CH_3-2 = 7, $J_{2,3}$ = 5.2 Hz), 3.79 d.d. (1H, H^3, $J_{3,4}$ = 5.2 Hz), 1.89 m (1H, H^4, J_4, CH_3-4 = 7, $J_{4,5}$ = 1.5 Hz), 4.04 d.d.d (1H, H^5, $J_{5,6}$ = 4.3, $J_{5,6}$ = 7.9 Hz), 3.52 and 3.64 d.d (2H, $H^{6,6'}$ = 11 Hz), 1.00 d (3H, CH_3 at C^2), 1.22 d (3H, CH_3 at C^4), 2.12 m (2H, $SCH_2\underline{CH_2}CH_2S$), 2.82 m (4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 4.67 and 4.77 d (2H, OCH_2Ph at C^3, J_{gem} = 11 Hz). ^{13}C NMR spectrum (δ, ppm): 52.9 (C^1), 37.5 (C^2), 84.7 (C^3), 41.35 (C^4), 75.6 (C^5), 65.4 (C^6), 11.8 (CH_3 at C^2), 12.8 (CH_3 at C^4), 26.15 ($SCH_2\underline{CH_2}CH_2S$), 30.7 and 31.0 ($SCH_2CH_2CH_2S$), 71.5 ($OCH_2Ph$), at C^3.

Diethylmercaptal of 2,4-Didesoxy-2,4-di-C-methyl-3-O-benzyl-D-galactopyranose (XII) and Ethylmercaptal of β-2,4-Didesoxy-2,4-di-C-methyl-3-O-benzyl-D-galactiopyranose (XI). A 40-mg portion (0.3 mmole) of $ZnCl_2$ was added to a solution of 157 mg (0.63 mmole) of (IX) in 1 ml of ethyl mercaptan, at −10°C, and the mixture was left to stand at 0°C for 12 h. The mixture was diluted with ether and saturated with gaseous ammonia. The precipitate was filtered, the solution was evaporated, and the residue was chromatographed on silica gel in a petroleum ether–ethyl acetate (2:1) system. The yield of (XI) was 77.4 mg (40%). PMR spectrum (δ, ppm): 4.18 d (1H, H^1, $J_{1,2}$ = 10.5 Hz), 1.86 d.d.q (1H, H^2, $J_{2,3}$ = 10.5, J_2, CH_3-2 = 7 Hz), 3.20 d.d. (1H, H^3, $J_{3,4}$ = 4.5 Hz), 2.21 d.d.q (1H, H^4, J_4, CH_3-4 = 7, $J_{4,5}$ = 2 Hz), 3.79 m (1H, H^5), 3.52 m (2H, $H^{6,6'}$), 0.93 d (3H, CH_3 at C^2), 1.10 d (3H, CH_3 at C^4), 1.28 t (3H, $\underline{CH_3}CH_2S$, $J_{\underline{CH_3}CH_2S}$ = 7 Hz), 3.70 q (2H, $CH_3\underline{CH_2}S$), 4.37 and 4.65 d (2H, OCH_2Ph at C^3, J_{gem} = 11.5 Hz). The yield of (XII) was 59 mg (25%), $[\alpha]_D^{+23}$ −20° (C 1.0). PMR spectrum (δ, ppm): 3.91 d (1H, $H^{1,2}$, $J_{3,4}$ = 6 Hz), 2.27 m (1H, H^2, $J_{2,3}$ = J_2, CH_3-2 = 7 Hz), 3.87 d.d (1H, H^3, $J_{1,2}$ = 6 Hz), 1.88 m (1H, H^4, J_4, CH_3-4 = 7, $J_{4,5}$ = 1.5 Hz), 4.03 d.d.d (1H, H^5, $J_{5,6}$ = 4.5, $J_{5,6}$ = 7.8 Hz), 3.50 and 3.63 m (2H, $H^{6,6'}$, $J_{6,6'}$ = 10.7 Hz), 1.02 d (3H, CH_3 at C^2), 1.26 d (3H, CH_3 at C^4), 1.27 t (6H, CH_3CH_2S, $J_{\underline{CH_3}CH_2S}$ = 7.5 Hz), 2.63 m (4H, $CH_3\underline{CH_2}S$), 4.67 and 4.77 d (2H, OCH_2Ph at C^3, J_{gem} = 10 Hz). ^{13}C NMR spectrum: 55.4 (C^1), 41.5 (C^2), 75.9 (C^3), 37.0.5 (C^4), 86.0 (C^5), 65.2 (C^6), 12.0 (CH_3 at C^4), 12.9 at C^2), 14.5 ($\underline{CH_3}CH_2S$), 25.4 and 25.6 ($CH_3\underline{CH_2}S$), 71.5 ($\underline{CH_2}Ph$).

1,1-Dimercaptopropylene-2,4,6,7-tetradesozy-2,4-di-C-methyl-3-O-benzyl-D-galactoheto-aldose (III). A 2.76-g portion (14.5 mmoles, 1.05 equivalent) of TsCl was added, with stirring, to a solution of 4.9 g (13.8 mmoles) of (X) in 30 ml of absolute pyridine. The mixture was stirred at 20°C for 30 h, then diluted with chloroform, and poured into water. The mixture was extracted by chloroform, the extract was washed with 1 N HCl, water, and saturated solutions of $NaHCO_3$ and NaCl. It was dried over anhydrous Na_2SO_4, and evaporated. The residue (6.8 g) was dissolved in 50 ml of methanol and, with stirring at −20°C, 3.5 g (25 mmoles) of K_2CO_3 were added, and the mixture was stirred at −15°C for 1 h. The mixture was diluted with chloroform, poured into water, and extracted by chloroform. The extract was washed with water and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and evaporated. The residue (4.4 g), dissolved in 8 ml of THF at −40°C, was added to a suspension of 414 mg (2 mmoles) of $CuBr \cdot Me_2S$ in a mixture of 20 ml of THF and 10 ml of a 1.5 N solution of MeMgCl in ether.

The mixture was held at −40°C for 18 h, and then a saturated solution of NH_4Cl was added. The mixture was extracted by chloroform, the extract was washed with water and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and evaporated, and the reside was chromatographed on silica gel in a benzene–ether (4:1) mixture. The yield of (III) was 2.175 g (45), $[\alpha]_D^{+23}$ + 8.3° (C 1.05). PMR spectrum (δ, ppm): 4.05 d (1H, H^1, $J_{1,2}$ = 5.7), 2.22 d.d.d (2H, H^2, $J_{2,3}$ = 5.7, J_2, CH_3-2 = 7 Hz), 3.78 d.d (1H, H^3, $J_{3,4}$ = 5 Hz), 2.08 m (1H, H^4, J_4, CH_3-4 = 7 Hz), 3.86 d.d.d (1H, H^5, $J_{5,4}$ = 1.5, $J_{5,6}$ = 6, $J_{5,6'}$ = 7.5 Hz), 1.30-

1.60 m (2H, $\underline{CH_2}CH_3$), 0.94 t (3H, $\underline{CH_3}CH_2$, $J_{CH_3CH_2}$ = 7 Hz), 2.73 s (1H, OH at C^5), 4.67 and and 4.75 d (2H, OC_2Ph at C^3, J_{gem} = 11 Hz), 1.84 m (2H, $SCH_2\underline{CH_2}CH_2S$), 2.85 m $S\underline{CH_2}CH_2\underline{CH_2}S$). ^{13}C NMR spectrum (δ, ppm): 53.2 (C^1), 39.45 (C^2), 72.4 (C^3), 41.55 (C^4), 85.1 (C^5), 27.9 (C^6), 27.9 (C^6), 10.7 (CH_3 at C^6), 10.9 (CH_3 at C^2), 12.9 (CH_3 at C^4), 26.3 ($SCH_2\underline{CH_2}CH_2S$), 30.9 and 31.2 ($S\underline{CH_2}CH_2\underline{CH_2}S$), 75.8 ($O\underline{CH_2}Ph$ at C^3).

A mixture of 50 mg (0.141 mmole) of (III), 135 mg (0.5 mmole) of $HgCl_2$, and 108 mg (0.5 mmole) of HgO in 3 ml of a 10 aqueous solution of acetone was boiled for 3 h, filtered, and evaporated, and the residue was dissolved in 3 ml of absolute methanol. To the solution, one drop of acetyl chloride was added, and the mixture was held at ∿20°C for 2 h. The mixture was diluted with chloroform, the chloroform solution was washed with water, dried over sodium sulfate, and evaporated. According to PMR spectroscopy data (cf [2]), the residue, 34.6 mg (88%), was a mixture of α- and β-methylglycosides (I).

1,1-Dimercaptopropylene-2,4,6,7-tetradesoxy-2,4-di-C-methyl-3-O-benzyl-5-O-diphenyl-tert-butylsilyl-D-galactoaldoheptose (VS). A 9-ml portion of a 1 M solution (9 mmoles) of $t\text{-}BuPh_2SiO\text{-}SO_2CF_3$ was added to a solution of 1.76 g (4.96 mmoles) of (III) in 10 ml of CH_2Cl_2 and 2.8 ml of triethylamine, and the mixture was stirred for 30 min. The solution was diluted with hexane and a saturated solution of $NaHCO_3$, and extracted by hexane. The extract was washed with water and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified on silica gel in a hexane–ether (20:1) system. The yield of (XV) was 2.632 g (90%), syrup, $[\alpha]_D^{+23}$ −4° (C 1.1). PMR spectrum (δ, ppm): 4.00 d (1H, H^1, $J_{1,2}$ = 10 Hz), 2.10 m (1H, H^2, H_2, CH_3-2 = 7 Hz), 22 d.d. (1H, H^3, $J_{3,4}$ = 1.5, $J_{3,2}$ = 9 Hz), 1.80 m (1H, H^4, J_4, CH_3-4 = 7 Hz), 4.10 d.d.d (1H, H^5, $J_{5,4}$ = 1.5, $J_{5,6}$ = 5, $J_{5,6'}$ = 9 Hz), 1.30-1.65 m (2H, $\underline{CH_2}CH_3$), 0.61 t (3H, CH_3 at C^6, $J_{CH_3CH_2}$ = 7.5 Hz), 0.97 d (3H, CH_3 at C^2), 1.16 d (3H, CH_3 at C^4), 1.12 s (9H, t-Bu), 1.95 m (2H, $SCH_2\underline{CH_2}CH_2S$), 2.80 m (4H, $S\underline{CH_2}CH_2\underline{CH_2}S$), 4.44 and 4.68 d (2H, OCH_2Ph, at C^3, J_{gem} = 12 Hz). ^{13}C NMR spectrum (δ, ppm): 52.7 (C^1), 39.7 (C^2), 74.9 and 74.5 (C^3 and OCH_2Ph at C^3), 40.4 (C^4), 79.9 (C^5), 28.4 (C^6), 9.7 (CH_3 at C^6), 10.3 CH_3 at C^2), 11.1 (CH_3 at C^4), 19.9 ($C(\underline{CH_3})_3$), 26.3 ($SCH_2\cdot\underline{CH_2}CH_2S$), 27.4 ($C(CH_3)_3$), 30.3 and 30.4 ($S\underline{CH_2}CH_2\underline{CH_2}S$).

Al-2,4,6,7-tetradesoxy-2,4-di-C-methyl-3-O-benzyl-5-O-diphenyl-tert-butylsilyl-D-galacto-heptose (XVI). A 216-mg portion (1 mmole) of HgO was added to a solution of 180 mg (0.304 mmole) of (XV) in 7 ml of actone–water (4:1) mixture, and then, with stirring, a solution of 270 mg (1 mmole) of $HgCl_2$ in 2 ml of an acetone–water (4:1) mixture was added. The mixture was stirred at 60°C for 2 h, the precipitate was filtered, the solution was evaporated, and the residue was dissolved in chloroform. The chloroform solution was washed with water, dried over anhydrous Na_2SO_4, evaporated, and the residue was chromatographed in the heptane–ether (4:1) system. The yield of (XVI) was 151 mg (100%), syrup, $[\alpha]_D^{+23}$ −6.2° (C 1.51). PMR spectrum (δ, ppm): 9.83 s (1H, CHO), 2.56 d.q (1H, H^2, J_2, CH_3-2 = 7, $J_{2,3}$ = 1.5 Hz), 4.16 d.d (1H, H^3, $J_{3,4}$ = 9 Hz), 1.81 d.d.q (1H, H^4, $J_{4,5}$ = 1, J_4, CH_3-4 = 7 Hz), 4.12 m (1H, H^5), 1.40-1.60 m (2H, $H^{6,6'}$), 0.90 t (3H, $\underline{CH_3}CH_2$, $J_{CH_3CH_2}$ = 7.5 Hz), 1.00 d (3H, CH_3 at C^4), 1.13 d (3H, CH_3 at C^2), 1.08 s (9H, t-Bu), 3.96 and 4.15 d (2H, OCH_2Ph at C^3, J_{gem} = 11 Hz). ^{13}C NMR spectra (δ, ppm): 204.8 and 204.7 (C^1), 49.5 (C^2), 79.2 (C^3), 39.0 (C^4), 74.4 (C^5), 28.4 (C^6), 6.55 (CH_3 at C^5), 9.6 (CH_3 at C^4), 10.2 (CH_3 at C^2), 19.6 (C $\underline{CHC})_3$), 27.2 ($\underline{C}(CH_3)_3$), 72.9 (OCH_2Ph at C^3).

2,4,6,7-Tetradesoxy-2,4-di-C-methyl-3-O-benzyl-5-O-diphenyl-tert-butylsilyl-D-galactohep-tite (XVII). A 380-mg portion (10 mmoles) of $NaBH_4$ was added to a solution of 705 mg (1. mmoles) of (XVI) in 5 ml of EtOH, the mixture was stirred for 5 min, and 0.8 ml of acetic acid was added. The mixture was evaporated to dryness, and the residue was purified by ch chromatography on silica gel with a heptane–ethyl acetate (7:3) mixture. The yield of (XVII) was 645 mg (91%), mp 99.5-100°C (pentane), $[\alpha]_D^{+23}$ + 7.5° (C].46). PMR spectrum (δ, ppm): 3.62 br. d (2H, $\underline{CH_2}OH$), 1.80 m (1H, H^2, J_2, CH_3-2 = 7, $J_{3,2}$ = 9.5 Hz), 3.78 d.d. (1H, H^3, $J_{3,4}$ = 1.7 Hz), 1.97 d.d.q (1H, H^4, J_4, CH_3-4 = 7, $J_{4,5}$ = 7 Hz), 4.07 d.d.d (1H, H^5, $J_{5,6}$ = 4.5, $J_{5,6'}$ = 1 Hz), 1.52 m (2H, $H^{6,6'}$), 0.61 t (3H, CH_3, at C^6), $J_{CH_3CH_2}$ = 7.5 Hz), 0.90 d (3H, CH_3 at C^2), 0.97 d (3H, CH_3 at C^4), 1.10 s (9H, t-Bu), 1.66 m (1H, OH), 4.28 and 4.39 d (2H, OCH_2Ph at C^3), J_{gem} = 11 Hz).

1,2,4,6,7-Pentadesoxy-2,4-di-C-methyl-1-phenylmercapto-3-O-benzyl-5-O-diphenyl-tert-butylsilyl-D-galactoheptite (XVIII). A 546-mg portion (2.5 mmoles), of diphenyl disulfide and 0.75 ml (3 mmoles), of tri-n-butylphosphine were added to a solution of 420 mg (0.83 mmole) of (XVII) in 1.8 ml of pyridine. The mixture was held for 2 h, and was diluted wi chloroform. The chloroform solution was washed with water, 1N HCl, water, and saturated solutions of $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, and evaporated. The residue was

chromatographed on silica gel in heptane. The yield of (XVIII) was 433.4 mg (88%), syrup, $[\alpha]_D^{+23}$ +65.5° (C 2.04). PMR spectrum (, ppm): 2.88 d.d.d (2H, $H^{1,1'}$, $J_{1,2}$ = 8, $J_{1,2}$ = 6.5, $J_{1,1'}$ = 12.5 Hz), 1.65 d.d.d.q (1H, H^2, J_2, CH_3-2) = 7, $J_{2,3}$ = 10 Hz), 3.84 d.d. (1H, H^3, $J_{3,4}$ = 1.5 Hz), 1.92 d.d.q (1H, H^4, J_4, CH_3-4 = 7, $J_{4,5}$ = 5 Hz), 3.98 d.d.d (1H, H^5, $J_{5,6}$ = 1 Hz), 1.35-1.45 m (2H, $H^{6,6'}$), 0.50 t (3H, CH_3 at C^6), $J_{CH_3CH_2}$ = 7.5 Hz), 0.77 d (3H, CH_3 at C^4), 1.03 s (9H, t-Bu), 4.27 and 4.38 d (2H, OCH_2Ph at C^3, J_{gem} = 12.5 Hz).

1,2,4,6,7-Pentadesoxy-2,4-di-C-methyl-1-phenylsulfonyl-3-O-benzyl-5-O-diphenyl-tert-butylsilyl-D-galactoheptite (XIX). A 3-ml portion of THF was added (for homogenization) to a solution of 331.4 mg (0.56 mmoles) of (XVIII) in 5 ml of methanol and 2 ml of water, and then, with stirring, 1.42 g (7 mmoles) of $NaIO_4$ were added. Stirring was continued for 23 h at 20°C, the precipitate was filtered, and the solution was evaporated. The residue was dissolved in chloroform, and the chloroform solution was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel in a hexane—ethyl acetate (9:1) system. Two sulfoxides were isolated: 150 mg (44.5%) of (XIX) (A), syrup. $[\alpha]_D^{+23}$ −5° (C 1.0) and 170.5 mg (50.7%) of (XIX) (B), syrup, $[\alpha]_D^{+23}$ +92.4° (C 1.11). PMR spectrum for (XVIII) (A) (δ, ppm): 1.52 and 2.76 d.d (2H, H, $J_{1,2}$ = 11, $J_{1',2}$ = 3, $J_{1',1}$ = 12 Hz), 2.40 m (2H, H^2, J_2, CH_3-2 = 6.5 Hz), 3.44 d.d. (1H, H^3, $J_{2,3}$ = 10, $J_{3,4}$ = 1.5 Hz), 1.70 d.drg (1H, H^4, J_4,CH_3-4 = 7, $J_{4,5}$ = 5 Hz), 3.97 d.d.d (1H, H^5,$J_{5,6}$ = 9.5, $J_{5,6'}$ = 1Hz), 1.40 m (2H, $H^{6,6'}$), 0.50 t (3H, CH_3 at C^6, $J_{CH_3CH_2}$ = 7.5 Hz), 0.90 d (3H, CH_3 at C^4), 1.08 d (3H, CH_3 at C^2), 1.00 s (9H, t-Bu), 4.12 d and 4.28 (2H, OCH_2Ph at C^3, J_{gem} = 12 Hz), 7.00-760 m (20H, SPh, CH_2Ph, $SiPh_2$).

CONCLUSIONS

A synthesis of three acyclic forms of the C^9—C^{13} fragment of erythronolide B has been carried out.

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