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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

14.* SYNTHESIS OF 1-METHYLENE-3,5-O-ISOPROPYLIDENE-9,11-O-p-(METHOXYBENZYLIDENE)-9(S)-DIHYDRO DERIVATIVE OF SECO ACID OF 9(S)-DIHYDROERYTHRONOLIDE B

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UDC 542.91:547.455

In the preceding publications it was shown [1, 2] that a stereo-directed synthesis of a precursor of erythronolide B, compound (I) (Scheme 1), with the intention of coupling C^1-C^6 and C^9-C^{13} fragments, was unsuccessful because of the impossibility of building the correct stereochemistry of the C^8, C^9 atoms in the desired end product (I). Moreover, numerous attempts to carry out the macrolactonization of 9(R)-8-epidihydro derivatives of seco-acid of erythronolide B obtained by this scheme were not successful. We therefore resorted to an alternate path of synthesis of (I) based on the coupling of the C^1-C^6 and C^7-C^{13} fragments (Scheme 1). The present publication is devoted to the realization of this scheme.

The efficacy of using a seco-acid derivative obtained from (I) in the macrolactonization process was shown for the example of erythronolide A in [3, 4].

The synthesis of compound (I) can be carried out by adding compound (II) (the C^7-C^{13}-fragment), for example, in the form of anion generated from sulfoxide (II) (X = SOPh), to ketone (IV), which is a C^1-C^6 fragment (its synthesis, see [5]). With such a coupling of the fragments, the configuration of the C^6 center is produced at the final stage of building up the stereochemistry of (I). We have previously shown that the reaction of ketone (IV) with organomagnesium compounds leads to derivatives in which the configuration of the C^6 center corresponds to the "natural" configuration [5].

*For previous communication, see [1].

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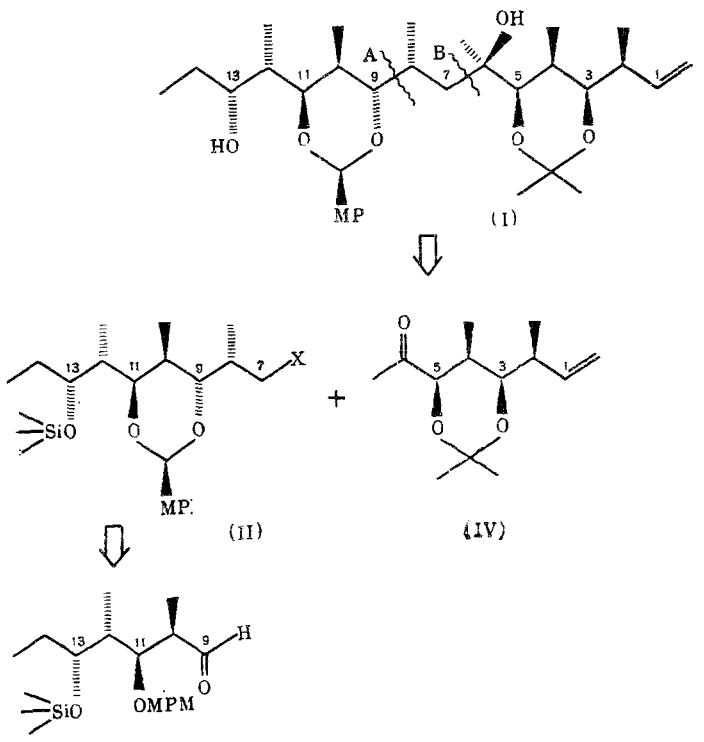
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 438-447, February, 1989. Original article submitted August 10, 1987.

 0568-5230/89/3802-0382 $12.50

Scheme 1



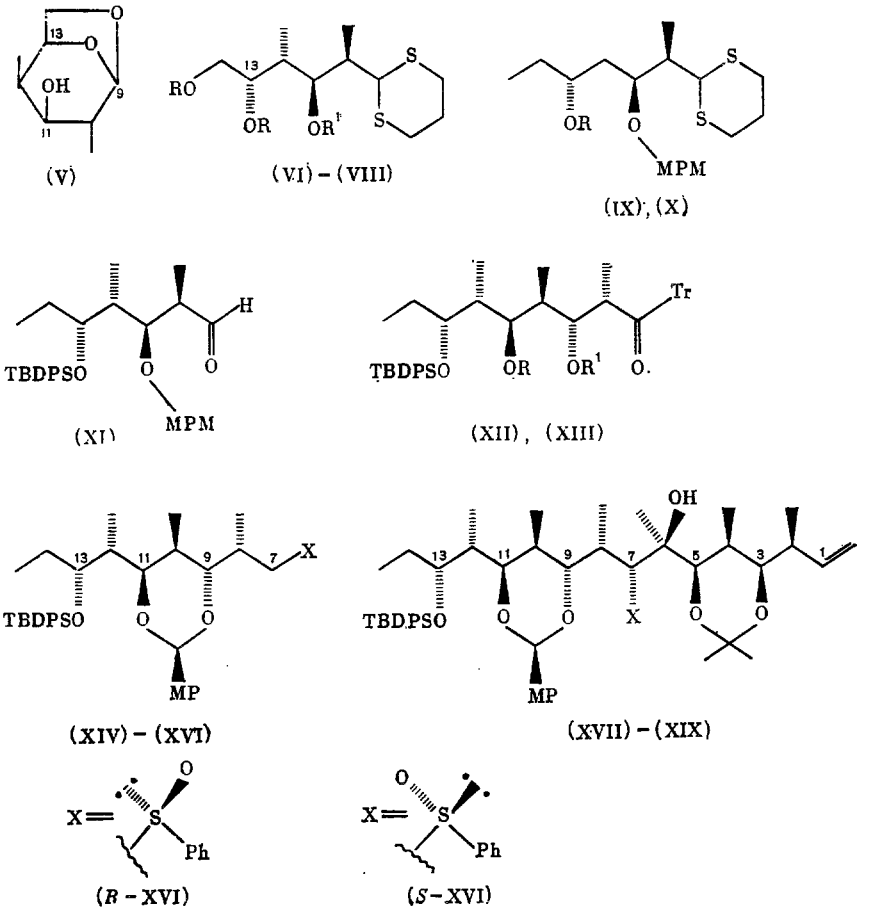
MP = p-$MeOC_6H_4$, MPM = p-$MeOC_6H_4CH_2$.

Likewise, a correct steeochemistry of the C^8, C^9 centers of fragment (II) can be obtained by a chelate-controlled syn-selective addition of the C^7-C^8 block to aldehyde (III), which is the C^9-C^{13} fragment, the synthesis of the 11-O-benzyl analog of which has been previously described by us in [6]. In this case, the p-methoxybenzyl (MPM) group was chosen to protect the hydroxyl group at C^{11} because at a certain stage the mono-O-substituted derivative can under neutral conditions be effectively converted into a cyclic 9,11-p-methoxybenzylideneacetal (MP) [7], thus ensuring the molecular protection of the hindered hydroxy group at C^9, which should impart the proper conformation to the seco-acid derivative and establish the prerequisites for its successful macrolactonization into 9(S)-dihydroerythronolide B.

The starting compound for the synthesis of the C^9-C^{13} fragment (aldehyde (XI)) was the bicyclic derivative (V) [8], the configuration of the chiral centers of which fully corresponds to the stereochemistry of the C^{10}-C^{13} section of the erythronolide B chain. To carry out the (V) → (XI) transition, it was necessary to transform the bicyclic form into an acyclic one, to differentiate the hydroxyl groups at C^{11} and C^{13}, and finally to extend the chain at C^{14} by one carbon unit.

The mercaptolysis of (V) and the subsequent acetonylation give preferentially the dioxolane derivative (VI), in which the free hydroxyl group at C^{11} was protected in the form of MPM ether. Acid hydrolysis of (VII) leads to diol (VIII), which through the stage of monotosylation, followed by closure of the corresponding 13,14-α-oxide, and reaction of the latter with a Grignard reagent [9], was converted into alcohol (IX), whereby, because of the extraordinary lability of the intermediate compounds, all the operations were carried out without their isolation. The hydroxyl group in (IX) was protected in the form of a tert-butyldimethyl- (TBS) or tert-butyldiphenylsilyl (TBDPS) ether (X) [10]. Subsequently it was found that the TBDPS group has clear advantages over the TBS group in view of the higher stability of the thioacetal at the hydrolysis stage (the yield of the aldehyde (XI) is 83% versus 60% in the case of the TBS derivative), and also ensures a higher selectivity at the key stage of coupling the fragments. Therefore we shall forthwith describe the experiments for this series only. The retention of the configuration of the C^{10} center in aldehyde (XI) in the course of the above-described series of (V) → (XI) transformations was previously confirmed in the synthesis of the 11-O-benzyl analog [6] (Scheme 2).

Scheme 2

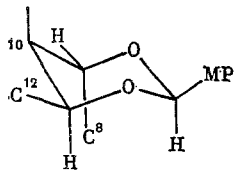


R, R = Me_2C, R^1 = H(VI); R, R = Me_2C, R^1 = MPM(VII); R = H, R^1 = MPM(VIII);
R = H(IX), TBDPS(X); R = MPM, R^1 = H(XII); R, R^1 = MP(XIII); X = OH(XIV);
X = SPh(XV); X = SOPh(XVII), SPh(XVIII), H(XIX) TBDPS = t-$BuPh_2S$.

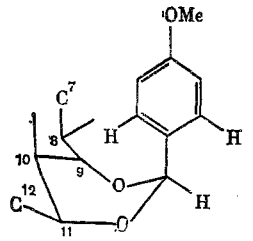
Furthermore, on using the stereoselective two-carbon block construction, the C^9-C^{13} aldehyde (XI) had to be converted to a C^7-C^{14} fragment of type (II), to ensure the suitability for the subsequent coupling. Study of a series of syn-selective aldol and crotyl reagents showed that this problem is most effectively solved by adding a lithium Z-enolate of ethyl trityl ketone [11], by the action of which the required (8,9-syn, 9,10-anti)aldol (XII) is obtained as the sole product isolated from aldehyde (XI) and then subsequently successfully transformed into the required derivative of type (II).

In the PMR spectrum of adduct (XII), the observed SSCC values ($J_{8,9}$ = 1 and $J_{9,10}$ = 10 Hz) characterize this compound as (8,9-syn, 9,10-anti)aldol, which fully agrees with the known results of the addition of lithium Z-enolates of ketones to β-alkoxy aldehydes [12]. This was also independently confirmed by the study of spectra of the cyclic derivative (XIII). The latter compound is obtained by treatment of the MPM-derivative (XII) with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone [7], whereby acetal (XIII) is formed in good yield in the form of a single equatorial isomer with respect to the acetal center, which should favor the subsequent stages of macrolactonization. The simplicity and selectivity of these transformations are among the merits of the MPM group which determine its use for the protection of the hydroxyl group at C^{11}.

In the PMR spectrum of (XIII), the observed SSCC ($J_{9,10}$ = 0.5 and $J_{10,11}$ = 2 Hz) and the nuclear electrostatic repulsion (NER) between the acetal proton and H^{11} indicate an axial configuration of the acetal proton and a somewhat distorted chair-like conformation of the 1,3-dioxolane ring.



(XIII)



(XIV)

The reductive splitting of trityl ketone (XIII) by the action of $LiBHEt_3$ [11] gives alcohol (XIV), whose PMR spectrum indicates a change in the conformation of the acetal ring. The study of NER showed a steric convergence of the ortho protons of the p-methoxyphenyl group, the Me group at C^{10}, and the H^9 proton, and also the absence of the effect between the acetal proton and H^{11}. In combination with the SSCC values ($J_{9,10}$ = 0.5 and $J_{10,11}$ = 2 Hz), this makes it possible to ascribe a distorted boat conformation to the acetal ring in (XIV). The spectral data obtained for (XIII) and (XIV) unequivocally confirm the absolute (S)-configuration of the C^9 center.

Alcohol (XIV) which was obtained was further converted by the action of Ph_2S_2–Bu_3P [13] into phenyl sulfide (XV), the oxidation of which by m-chloroperbenzoic acid gives a readily chromatographically separable mixture of sulfoxides (R)-(XV) and (S)-(XVI) in yields of 22 and 74%, respectively, in which the assignment of configurations of the chiral sulfur atom was accomplished polarimetrically (the (R)-isomers have a positive rotation sign [14]).

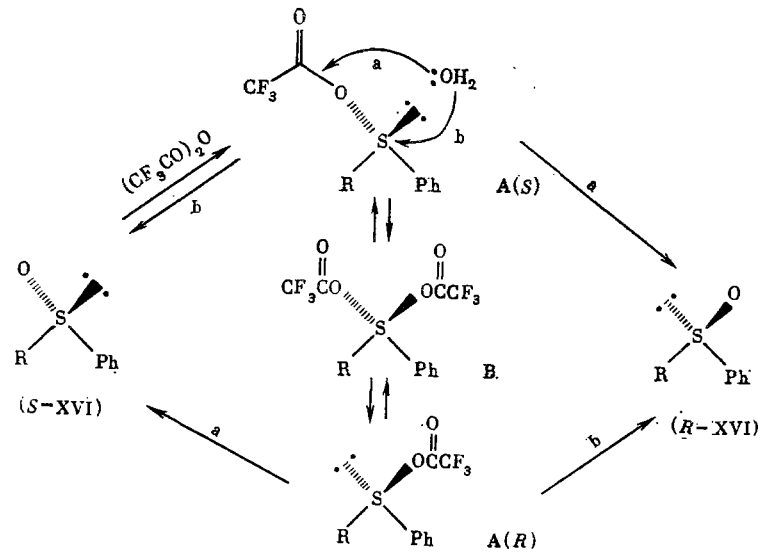
The (R)- and (S)-sulfoxides were introduced in the form of lithium derivatives into the reaction with the C^1-C^6 ketone (IV), which we have described previously in [5]. It was thus found that only the minor (R)-sulfoxide (XVI) enters into the reaction and gives a mixture of two products in a 7:1 ratio, while the main (S)-isomer (XVI) does not react.* Therefore, the necessity arose for a more selective synthesis of (R)-sulfoxide (XVI).

We attempted several oxidation methods, and as a consequence of not finding any significant differences in the ratio of the isomers of (XVI) formed, we developed a mild and conveient method for the isomerization of the stereoisomeric sulfoxides, which enables solving this problem. Thus, treatment of (S)-sulfoxide (XVI) with trifluoroacetic anhydride, followed by the addition of water leads to a mixture of (R)- and (S)-sulfoxides (XVI) in the ratio of 77:23. It is probable that this reaction proceeds via the formation of trifluoroacetoxysulfonium ion of type A, which is further attacked by water at the sulfur atom, giving the isomeric sulfoxide. The presence of the initial (S)-(XVI) in the reaction mixture is the result of attack by water at the trifluoroacetoxy group carbonyl, or the racemization of the sulfonium ion via the formation of a symmetrically tetracoordinated sulfurane B (see diagram on following page).

By using this method (oxidation of sulfide, separation of a mixture of isomeric sulfoxides, isomerization of (S)-sulfoxide (XVI)), sulfide (XV) was converted into the (R)-sulfoxide in a high overall yield. The main product of coupling of the latter with methyl ketone (IV), obtained in a yield of 88%, should have, in analogy with the reaction product of this ketone with Grignard reagents [5], the "natural" configuration of the C^6 center, which was later confirmed.

The sulfoxide (XVII) obtained was found to be a very labile compound, and therefore it was immediately converted into sulfide (XVIII) [16], the desulfuration of which completes the building up of the stereochemistry of the whole carbon chain of erythronolide B. The desulfuration process was complicated by the polyfunctionality of the molecule of (XVIII); the best results were obtained by the action of Na in liquid ammonia at −78°C, using ether as a cosolvent. Product (XIX), obtained in a high yield, was desilylated, which led to derivative (I), a key intermediate product in the synthesis of erythronolide B. The precursor of the seco-acid (I) obtained by this scheme has a rigorously proved configuration of nine out of eleven chiral centers in 9(S)-dihydroerythronolide B, C^2-C^5 and C^9-C^{13}. Comparison of

*Analysis of the literature data on the reactions of sulfoxides with a similar structure [15] did not make it possible to explain satisfactorily the reason for such a radical difference in the behavior of (R)- and (S)-sulfoxides (XVI).



(I) with the product of the same structure, obtained by an alternate scheme (see the following articles in this series) and having a known configuration of the C^6 and C^8 centers, proved their complete identity, and thus their stereochemical correspondence to 9(S)-dihydroerythronolide B. The completion of the synthesis of erythronolide B by this scheme is described in the following article.

EXPERIMENTAL

For general methods, see [2].

1,6-Anhydro-2,4-didesoxy-2,4-di-C-methyl-β-D-galactopyranose (V). A solution of 14 g (56.38 mmoles) of 3-O-benzyl derivative (V) [8] in 120 ml of MeOH was boiled over Ra/Ni for 5 h, and then stirred for another 45 h at 20°C. The catalyst was filtered, washed with MeOH, and the solution was evaporated at 30°C in vacuo. The residue was recrystallized twice from a pentane–ethyl acetate (EA) (9:1) mixture. The mother liquor was purified by chromatography in a hexane–EA (1:1) system. Yield 7.32 g (82%), mp 40.5-41°C (pentane), $[\alpha]_D^{25}$ −31° (C 1.09). PMR spectrum: 1.03 d (6H, $J_{CH_3,10} = J_{CH_3,12}$ = 7 Hz, CH_3 at C^{10} and C^{12}), 2.05 d.d.q (1H, $J_{9,10} = J_{10,11}$ = 1.8 Hz, H^{10}), 2.19 m (1H, $J_{12,14}$ = 1.2 Hz, H^{12}), 2.45 br.s (1H, OH at C^{11}), 3.45 m (1H, H^{11}), 3.57 d.d.d (1H, $J_{14,14'}$ = 7, $J_{14,13}$ = 4.9 Hz, H^{14}-exo), 4.21 m (2H, H^{13} and H^{14}-endo), 5.36 d.d (1H, $J_{9,11}$ = 1.8 Hz, H^9).

Compound (VI). A 19.7 g portion (138.8 mmoles) of $BF_3 \cdot Et_2O$ was added to a solution of 7.32 g (46.27 mmoles) of (V) and 7.51 g (69.4 mmoles) of 1.3-propanedithiol in 46 ml of CH_2Cl_2. The mixture was held at ~20°C for 12 h, cooled to −20°C and neutralized by NH_3 (gas) to a weakly alkaline value of pH. The mixture wass evaporated, the residue was dissolved in 50 ml of acetone, and 25 ml of 2,2-dimethoxypropane and 1 g of $TsOH \cdot H_2O$ were added (pH < 7). The mixture was held for 1 h, was then decomposed by a saturated solution of $NaHCO_3$, evaporated, and the residue was passed through a SiO_2 layer, using for eluting the compound a gradual benzene–EA gradient from 0 to 25% (at 5% spacings). Yield 9.34 g (66%), syrup, $[\alpha]_D^{23}$ −4.5° (C 2.0). PMR spectrum: 0.88 d and 1.10 d (6H, $J_{CH_3,10} = J_{CH_3,12}$ = 6.7 Hz, CH_3 at C^{10} and C^{12}), 1.34 s and 1.41 s (6H, CH_3 of 13,14-acetal), 1.82 d.d.q (1H, $J_{12,13}$ = 4.5, $J_{12,11}$ = 9 Hz, H^{12}), 2.0 d.d.q (1H, $J_{10,11}$ = 2.5, $J_{10,9}$ = 6.7 Hz, H^{10}), 2.05-2.18 m (2H, $SCH_2 \cdot C\underline{H_2}CH_2S$), 2.62 d (1H, $J_{11,OH}$ = 4 Hz, OH at C^{11}), 2.83-2.92 m (4H, $-S\underline{CH_2}CH_2C\underline{H_2}S-$), 3.71 d.d (1H, $J_{14,13} = J_{14,14'}$ = 7 Hz, H^{14}), 3.91 d.d.d (1H, H^{11}), 4.06 d.d (1H, $J_{14',13}$ = 6.7 Hz, $H^{14'}$) 4.17 d (1H, H^9), 4.31 d.d.d (1H, H^{13}).

Compound (VII). A solution of (VI) in 23 ml of DMF was added with stirring to a suspension of 1.1 g (4.6 mmoles) of NaH in 23 ml of DMF. The mixture was stirred at ~20°C for 5 min, and then 4.33 g (27.6 mmoles) of p-methoxybenzyl chloride (obtained by the reaction of p-methoxybenzyl alcohol and thionyl chloride in the presence of DMF) was added, and the mixture was stirred for 1 h. The excess NaH was decomposed with 2 ml of MeOH, poured into water and extracted with ether. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated and chromatographed in a heptane–ether (5:1) system.

Yield 8.55 g (87%), syrup, $[\alpha]_D^{21}$ −0.5° (C 2.0). PMR spectrum: 0.93 d and 1.12 d (6H, $J_{CH_3,10}$ = $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{10} and C^{12}), 1.35 s and 1.44 s (6H, CH_3 of 13,14-O-acetal), 1.70-1.90 m (2H, H^{10} and H^{12}), 2.08 m (2H, $SCH_2\underline{CH_2}CH_2S$), 3.65 d.d (1H, $J_{11,12}$ = $J_{11,10}$ = 7.6 Hz, H^{11}), 3.80 s (3H, $C\underline{H_3}OC_6H_4CH_2O$), 3.81 d.d (1H, H^{14}), 4.01 d.d (1H, $J_{14,14'}$ = 8, $J_{14',13}$ = 7 Hz, $H^{14'}$), 4.02 d (1H, $J_{9,10}$ = 8.5 Hz, H^9), 4.33 d.d.d (1H, $J_{13,14'}$ = 7, $J_{13,12}$ = 4 Hz, H^{13}), 4.62 d and 4.75 d (2H, J_{gem} = 11 Hz, AB system $CH_3OC_6H_4C\underline{H_2}O$), 6.90-7.30 m (4H, $CH_3OC_6\underline{H_4}CH_2O$).

Compound (VIII). A solution of 7.7 g (18 mmoles) of (VII) in 50 ml of 80% aqueous AcOH solution was heated at 60°C for 1.5 h, evaporated, and the residue was diluted with $CHCl_3$. The solution was washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, evaporated, and the residue was chromatographed in EA. Yield 5.25 g (75%), syrup, $[\alpha]_D^{21}$ +7.5° (C 2.0). PMR spectrum (D_2O was added to the solution of the sample in $CDCl_3$): 1.02 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 1.23 d (3H, $J_{CH_3,10}$ = 7 Hz, CH_3 at C^{10}), 1.88 d.d.q (1H, $J_{12,13}$ = 1.6, $J_{12,11}$ = 5 Hz, H^{12}), 2.10 m (2H, $SC\underline{H_2}C\underline{H_2}CH_2S$), 2.20 d.d.q (1H, $J_{10,11}$ = $J_{10,9}$ = 6 Hz, H^{10}), 2.86 m (4H, $SC\underline{H_2}CH_2C\underline{H_2}S$), 3.52 d.d (1H, $J_{14\ 13}$ = 4.3, $J_{14\ 14'}$ = 11.7 Hz, H^{14}), 3.65 d.d. (1H, $J_{14',13}$ = 8 Hz, $H^{14'}$), 3.74 d.d (1H, H^{11}), 3.80 s (3H, $C\underline{H_3}OC_6H_4CH_2O$), 4.04 d.d.d (1H, H^{13}), 4.08 d (1H, H^9), 4.58 d and 4.68 d (2H, J_{gem} = 10.5 Hz, AB-system $CH_3OC_6H_4C\underline{H_2}O$), 6.87-7.27 m (4H, $CH_3OC_6\underline{H_4}CH_2O$).

Compound (IX). A 2.72 g portion (14.26 mmoles, 1.05 equiv.) of TsCl was added to a solution of 5.25 g (13.58 mmoles) of (VIII) in 25 ml of pyridine, and the mixture was held at ~20°C for 5 h. The solution was diluted with $CHCl_3$, washed with 1 N HCl, water, a saturated solution of NaCl, dried over Na_2SO_4 and evaporated. The residue was dissolved in 50 ml of absolute MeOH, the solution was cooled to −15°C, and 2.82 g (20.37 mmoles) of K_2CO_3 were added. The mixture was stirred for 4 h, and then poured into water, and extracted with $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was dissolved in 20 ml of THF, and was added with stirring at −40°C to a suspension, obtained by adding 14 ml of 1.95 M solution of MeMgCl in THF (27.3 mmoles) to 438 mg (2.72 mmoles) of $CuCl\cdot Me_2S$ in 6 ml of THF. After 30 min, the mixture was heated to 0°C, decomposed with 3 ml of a saturated solution of NH_4Cl, and filtered. The filtrate was dried over Na_2SO_4, evaporated, and the residue was chromatographed in a benzene–ether (9:1) system. Yield 2.266 g (56.7%), syrup, $[\alpha]_D^{21}$ +8.5° (C 1.0). PMR spectrum: 0.95 t (3H, $J_{CH_3,14}$ = 7.3 Hz, CH_3 at C^{14}), 1.02 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 1.23 d (CH, $J_{CH_3,10}$ =7 Hz, CH_3 at C^{10}), 1.39 d.d.q (1H, $J_{14,13}$ = 5.5 Hz, $J_{14,14'}$ = 13 Hz, H^{14}), 1.58 d.d.q (1H, $J_{14',13}$ = 8 Hz, $H^{14'}$), 1.81 d.d.q (1H, $J_{12,13}$ = 1.6, $J_{12,11}$ = 4.5 Hz, H^{12}), 2.09 m (2H, $SCH_2C\underline{H_2}CH_2S$), 2.22 d.d.q (1H, $J_{10,11}$ = 6.5, $J_{10,9}$ = 5.5 Hz, H^{10}), 2.86 m (4H, $-SC\underline{H_2}CH_2C\underline{H_2}S-$), 2.98 m (1H, OH at C^{13}), 3.72 d.d (1H, H^{11}), 3.80 s (3H, $C\underline{H_3}OC_6H_4CH_2O$), 3.86 br.d.d (1H, H^{13}), 4.05 d, (1H, H^9), 4.58 d and 4.67 d (2H, J_{gem} = 10.5 Hz), AB system $CH_3\cdot OC_6H_4C\underline{H_2}O$), 6.86-7.28 m (4H, $CH_3OC_6\underline{H_4}CH_2O$).

Compound (X). A solution of 454 mg (1.888 mmoles) of tert-butyldiphenylsilane (obtained by reducing $t\text{-}BuPh_2SiCl$ by $LiAlH_4$) in 2 ml of CH_2Cl_2 was added at 0°C, with stirring, to a suspension of 603.9 mg (1.762 mmoles) of tritylium perchlorate [17] in 2 ml of CH_2Cl_2. The mixture was heated to ~20°C, and 382 mg (3.776 mmoles) of Et_3N were added, and then a solution of 484 mg (1.259 mmole) of (IX) in 4 ml of CH_2Cl_2. The mixture was stirred for 5 min, was then decomposed with a saturated solution of $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–EA (20:1) system. Yield 593 mg (75.6%), mp 118-118.5°C (hexane), $[\alpha]_D^{22}$ +53.2° (C 1.0). PMR spectrum: 0.58 t (3H, $J_{CH_3,14}$ = 7.5 Hz, CH_3 at C^{14}), 0.92 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 1.09 d (3H, $J_{CH_3,10}$ = 7 Hz, CH_3 at C^{10}), 1.10 s (9H, $t\text{-}\underline{Bu}Ph_2SiO$), 1.40-1.60 m (2H, H^{14}, $H^{14'}$), 1.74 d.d.q (1H, $J_{12,13}$ = 1, $J_{12,11}$ = 9.5 Hz, H^{12}), 1.89 d.d.q (1H, $J_{10,11}$ = 1.8, $J_{10,9}$ = 10 Hz, H^{10}), 2.08 m (2H, $SCH_2CH_2CH_2S$), 3.81 s (3H, $C\underline{H_3}OC_6H_4CH_2O$), 3.97 d (1H, H^9) 4.07 d.d.d (1H, $J_{CH_3,14}$= 5, $J_{13,14'}$ = 9 Hz, H^{13}), 4.19 d.d (1H, H^{11}), 4.32 d and 4.59 d (2H, J_{gem} = 12.5 Hz, AB-system $CH_3OC_6H_4C\underline{H_2}O$), 6.81 m, 7.02 m, 7.32 m, 7.62 m, 7.72 m (14H, $t\text{-}Bu(C_6\underline{H_5})_2SiO$, $CH_3OC_6\underline{H_4}CH_2O$).

Compound (XI). A 5.258 g portion (30.5 mmoles) of $CdCO_3$ and 4.968 g (18.3 mmoles) of $HgCl_2$ were added to a solution of 3.80 g (6.1 mmoles) of (X) in 40 ml of an acetone–water (9:1) mixture. The mixture was boiled for 6 h, the precipitate was filtered, and the solution was 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 heptane–ether (19:1) system. Yield 2.685 g (83%), mp 83-83.5°C (pentane), $[\alpha]_D^{22}$ −32.4° (C 1.0). PMR spectrum: 0.60 t (3H, $J_{CH_3,14}$ = 7.5 Hz, CH_3 at C^{14}), 1.0 d and 1.14 d (6H, $J_{CH_3,10}$ =

$J_{CH_3,12}$ = 7 Hz, CH_3 at C^{10} and C^{12}), 1.11 s (9H, t-$BuPh_2SiO$), 1.55 m (2H, H^{14} and $H^{14'}$), 1.79 d.d.q (1H, $J_{12,11}$ = 9.5, $J_{12,13}$ = 1 Hz, H^{12}), 2.56 d.q (1H, $J_{10,11}$ = 1.8 Hz, H^{10}), 3.80 s (3H, $C\underline{H}_3OC_6H_4CH_2O$), 3.94 d and 4.08 d (2H, J_{gem} = 10 Hz, AB-system $CH_3OC_6H_4C\underline{H}_2O$), 4.13 d.d (1H, H^{11}), 4.13 d.d.d (1H, $J_{13,14}$ = 5.5, $J_{13,14'}$ = 8.8 Hz, H^{13}), 6.75-7.75 (14H, t-$Bu(C_6\underline{H}_5)_2$·SiO, $CH_3OC_6\underline{H}_4CH_2O$), 9.85 s (1H, H^9).

Compound (XII). A 3.5 ml portion of a 1.79 N solution of n-BuLi in hexane (6.3 mmoles) was added at −78°C to a solution of 1.892 g (6.3 mmoles) of trityl ethyl ketone [11] in 30 ml of THF. The mixture was stirred for 1 h and a solution of 2.61 g (4.899 mmoles) of (XI) in 15 ml of THF was added. The mixture was stirred for 1 h, and then decomposed at −78°C with a saturated NH_4Cl solution, 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 heptane–ether (11:1) system. Yield 3.44 g (84.3%), mp 155.5-156°C (pentane), $[\alpha]_D^{22}$ −4.4° (C 1.0). PMR spectrum: 0.43 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 0.54 t (3H, $J_{CH_3,14}$ = 7.5 Hz, CH_3 at C^{14}), 0.71 d (3H, $J_{CH_3,10}$ = 7 Hz, CH_3 at C^{10}), 0.82 d (3H. $J_{CH_3,8}$ = 7 Hz, CH_3 at C^8), 1.07 s (9H, t-$BuPh_2SiO$), 1.20-1.70 m (4H, H^{10}, H^{12}, H^{14}, $H^{14'}$), 3.19 br.q (1H, $J_{8,9}$ = 1 Hz, H^8) 3.32 br. d (1H, $J_{9,10}$ = 10 Hz, H^9), 3.47 s (1H, OH at C^9), 3.79 s (3H, $C\underline{H}_3OC_6H_4CH_2O$), 4.0 br. d.d (1H, $J_{12,13}$ = 4, $J_{13,14}$ = 10 Hz, H^{13}), 4.10 d.d (1H, $J_{10,11}$ = 1, $J_{11,12}$ = 10 Hz, H^{11}), 6.80-7.70 m (29H, t-$Bu(C_6\underline{H}_5)_2SiO$, $CH_3OC_6\underline{H}_4CH_2O$, $(C_6\underline{H}_5)_3C(O)$.

Compound (XIII). A 2 g portion of 3 Å molecular sieves and 0.953 g (4.197 mmoles) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were added to a solution of 3.33 g (3.997 mmoles) of (XII) in 25 ml of CH_2Cl_2. The mixture was stirred for 1 min, and was then decomposed by a saturated solution of $NaHCO_3$. The precipitate was filtered through a celite layer, the filtrate was diluted with $CHCl_3$, washed with a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–ether (11:1) system. Yield 2.824 g (85%), mp 182-182.5°C (pentane), $[\alpha]_D^{20}$ −11.6° (C 1.0). PMR spectrum: 0.41 t (3H. $J_{CH_3,14}$ = 7.5 Hz, CH_3 at C^{14}), 0.54 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 0.81 d (3H, $J_{CH_3,8}$ = 6.5 Hz, CH_3 at C^8), 1.0 s (9H, t-$\underline{Bu}Ph_2SiO$), 1.18 d (3H, $J_{CH_3,10}$ = 6.7 Hz, CH_3 at C^{10}), 1.35 m (2H, H^{14}, $H^{14'}$), 1.53 d.q (1H, $J_{10,11}$ = 2 Hz, H^{10}), 1.68 d.d.q (1H, $J_{12,11}$ = 10, $J_{12,13}$ = 1.5 Hz, H^{12}), 3.80 s (3H, $C\underline{H}_3OC_6H_4$ of 9,11-O-acetal), 3.81 d.d (1H, H^{11}), 4.13 d.d.d (1H, $J_{13,14}$ = 4.5, $J_{13,14'}$ = 10 Hz, H^{13}), 4.22 d.q and 4.31 d (2H, AB system, $J_{9,8}$ = 10.5 Hz, H^8 and H^9, respectively), 5.18 s (1H, H of acetal), 6.80-7.60 m (29H, aromatic protons). The NER measurement showed a steric convergence of the acetal proton and the proton at C^{11} atom.

Compound (XIV). A 20 ml portion of 1 N solution of $NaBHEt_3$ in THF (20 mmoles) was added to a suspension of 1.924 g (22.2 mmoles) of LiBr and 2.99 g (3.597 mmoles) of (XIII) in 5 ml THF. The mixture was allowed to stand at 20°C for 120 h, and 72 ml of a 15% solution of NaOH, followed by 72 ml of a 30% solution of H_2O_2, were added. The mixture was stirred for 2 h, and then 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–EA (4:1) system. Yield 1.913 g (90%), syrup. PMR spectrum (after the addition of D_2O to the solution of a sample of (XIV) in $CDCl_3$): 0.55 t (3H, $J_{CH_3,14}$ = 7.4 Hz, CH_3 at C_{14}), 0.92 d (3H, $J_{CH_3,12}$ = 6.6 Hz, CH_3 at C^{12}), 1.06 d and 1.06 s (12H, $J_{CH_3,8}$ = 6.5 Hz, CH_3 at C^8 and t-$\underline{Bu}Ph_2SiO_2$), 1.18 d (CH, $J_{CH_3,10}$ = 6.5 Hz, CH_3 at C^{10}), 1.46 m (2H, H^{14} and $H^{14'}$), 1.72 d.d.q (1H, $J_{11,12}$ = 10, $J_{12,13}$ = 1 Hz, H^{12}), 1.86 br.d.q (1H, $J_{10,11}$ = 2 Hz, H^{10}), 2.36 m (1H, $J_{8,9}$ = 10, $J_{8,7}$ = 5, $J_{8,7'}$ = 4 Hz, H^8), 3.57 d.d (1H, $J_{7,7'}$ = 10.5 Hz, H^7), 3.56 br.d (1H, H^9), 3.67 d.d (1H, $H^{7'}$), 3.83 s (3H, $C\underline{H}_3OC_6H_4$, of 9,11-O-acetal), 4.05 d.d (1H, H^{11}), 4.14 d.d.d (1H, $J_{13,14}$ = 5, $J_{13,14}$ = 9 Hz, H^{13}), 5.12 s (1H, H of acetal), 6.84-7.70 m (14H, aromatic protons). The NER measurement showed a steric convergence of the aromatic ring o-protons of the acetal group, the H^9 proton and protons of the CH_3 groups at the C^8 and C^{10} atoms.

Compound (XV). A 1.279 g (5.856 mmoles) of Ph_2S and 1.394 g (6.889 mmoles) of Bu_3P were added to a solution of 1.73 g (2.928 mmoles) of (XIV) in 15 ml pyridine. The solution was held at ~20°C for 24 h, then was diluted with $CHCl_3$, washed with a 1 N HCl solution, 15% NaOH solution, and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (11:1) system. Yield 1.84 g (92%), mp 119.5-120°C (hexane), $[\alpha]_D^{21}$ +28° (C 1.0). PMR spectrum: 0.51 t (3H, $J_{CH_3,14}$ = 7 Hz, CH_3 at C^{14}), 0.90 d (3H, $J_{CH_3,12}$ = 6.9 Hz, CH_3 at C^{12}), 1.05 s (9H, t-$BuPh_2SiO$), 1.14 d (3H, $J_{CH_3,8}$ = 6.4 Hz, CH_3 at C^8), 1.16 d (3H, $J_{CH_3,10}$ = 6.5 Hz, CH_3 at C^{10}), 1.30-1.56 m (2H, $H^{14,14}$), 1.71 d.d.q (1H, $J_{12,11}$ = 10.4, $J_{12,13}$ = 1.6 Hz, H^{12}), 1.82 d.q (1H, $J_{10,11}$ = 2 Hz, H^{10}), 2.40 d.d.d.q (1H, $J_{8,9}$ = 11, $J_{8,7}$ = 8.5, $J_{8,7'}$ = 3.1 Hz, H^8), 2.68 d.d (1H, $J_{7,7'}$ = 13 Hz, H^7), 3.14 d.d

(1H, $H^{7'}$), 3.46 d (1H, H^9), 3.81 s (3H, $C\underline{H}_3OC_6H_4$, of 9,11-O-acetal), 3.95 d.d (1H, H^{11}), 4.07 d.d.d (1H, $J_{13,14} = 5.2$, $J_{13,14'} = 7$ Hz, H^{13}), 4.79 s (1H, H of acetal), 6.80-7.50 m (19H, aromatic protons).

Compound (XVI). A 0.446 g portion (2.583 mmoles) of m-chloroperbenzoic acid was added to a solution of 1.604 g (2.348 mmoles) of (XV) in 25 ml of EA, cooled to −40°C. The mixture was held for 10 min, and evaporated. The residue was dissolved in $CHCl_3$, the solution was washed with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (2:1) system. The yield of (R)-(XVI) was 358 mg (21.8%), mp 100.5-101°C (hexane), $[\alpha]_D^{25}$ +105.7° (C 1.0). (S)-(XVI): 1.215 g (74%), mp 106.5-107°C (hexane), $[\alpha]_D^{25}$ −24.5° (C 1.0). PMR spectrum (R)-(XVI): 0.50 t (3H, $J_{CH_3,14}$ = 7 Hz, CH_3 at C^{14}), 0.89 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 1.10 s (9H, t-$\underline{Bu}Ph_2SiO$), 1.12 d (3H, $J_{CH_3,8}$ = 6.5 Hz, CH_3 at C^8), 1.25 d (3H, $J_{CH_3,10}$ = 7 Hz, CH_3 at C^{10}), 1.25-1.70 m (4H, H^{10}, H^{12}, H^{14}, $H^{14'}$), 2.50 d.d (1H, $J_{7,8} = 10$, $J_{7,7'} = 13$ Hz, H^7), 2.80 d.d (1H, $J_{7',8} = 2.5$ Hz, $H^{7'}$), 2.91 m (1H, $J_{8,9} = 10.5$ Hz, H^8), 3.38 d (1H, H^9), 3.82 s (3H, $C\underline{H}_3OC_6H_4$ of 9, 11-O-acetal), 4.04 d.d (1H, $J_{10,11} = 2.5$, $J_{11,12} = 10$ Hz, H^{11}), 4.07 d.d.d (1H, $J_{13,12} = 1.2$, $J_{13,14} = 5$, $J_{13,14'} = 9$ Hz, H^{13}), 4.82 s (1H, H of acetal), 6.80-7.70 (19H, aromatic protons). PMR spectrum (S)-(XVI): 0.50 t (3H, $J_{CH_3,14} = 7$ Hz, CH_3 at C^{14}), 0.83 d (3H, $J_{CH_3,12} = 7$ Hz, CH_3 at C^{12}), 1.08 s (9H, t-$\underline{Bu}Ph_2SiO$), 1.16 t (6H, $J_{CH_3,10} = J_{CH_3,8} = 7$ Hz, CH_3 at C^8 and C^{10}), 1.20-1.80 m (4H, H^{10}, H^{12}, H^{14}, $H^{14'}$), 2.66 m (1H, H^8), 2.81 s, 2.82 s and 2.83 s (2H, H^7, $H^{7'}$), 3.52 br.d (1H, $J_{9,8} = 10$, $J_{9,10} = 1$ Hz, H^9), 3.82 s (3H, $C\underline{H}_3OC_6H_4$ of 9,11-O-acetal), 3.93 d.d (1H, $J_{11,10} = 2.5$, $J_{11,12} = 10.5$ Hz, H^{11}), 4.07 d.d.d (1H, $J_{13,12} = 1.5$, $J_{13,12} = 5$, $J_{13,14'} = 8$ Hz, H^{13}), 4.95 s (1H, H of acetal), 6.80-7.70 m (19H, aromatic protons).

Isomerization of Sulfoxide (S)-(XVI). A 0.589 g portion (4.944 mmoles) of 2,4,6-trimethylpyridine was added to a solution of 0.96 g (1.373 mmoles) of (S)-(XVI) in 5 ml of THF. The mixture was cooled to −60°C and after adding 0.346 g (1.648 mmoles) of $(CF_3CO)_2O$ and stirring for 20 min, a mixture of 820 μliter THF and 180 μliter water was added. The solution was heated to ~20°C, diluted with $CHCl_3$, washed with 1 N HCl solution, water, saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (2:1) system. The yield of (R)-(XVI) 0.734 g (76.5%), (S)-(XVI) was 0.226 g (23.5%).

Compound (XVII). A 300 μliter portion of a 1.72 N solution of n-BuLi in hexane (516 μmoles) was added at −78°C to a solution of 59 mg (583.3 μmoles) of diisopropylamine in 900 μliters of THF. The mixture was heated to −40°C in the course of 1 h and then cooled to −60°C. A solution of 339.7 mg (486 μmoles) of (R)-(XVI) in 1300 μliter of THF was added, and stirring was continued for 1 h. The solution was cooled to −78°C, and 107 mg (472.8 μmoles) of (IV) in 1200 μliter of THF were added. The mixture was held for 2 h, was then decomposed by a saturated solution of NH_4Cl, 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–EA (5:1) system. The yield of (XVII) was 283 mg (64.7%); the yield of the isomer at C^6 was 40 mg (8.9%). The compounds are unstable. PMR spectrum: 0.29 d (3H, $J_{CH_3,10} = 7$ Hz, CH_3 at C^{10}), 0.40 t (3H, $J_{CH_3,14} = 7$ Hz, CH_3 at C^{14}), 0.85 m (1H, H^{12}), 0.95 d (3H, $J_{CH_3,12} = 6.5$ Hz, CH_3 at C^{12}), 1.03 d (3H, $J_{CH_3,2} = 6.5$ Hz, CH_3 at C^2), 1.12 d (3H, $J_{CH_3,4} = 7$ Hz, CH_3 at C^4), 1.15 s (9H, t-$\underline{Bu}Ph_2SiO$), 1.17 d (3H, $J_{CH_3,14} = 7.3$ Hz, CH_3 at C^8), 1.22-1.48 m (2H, H^{14} and $H^{14'}$), 1.45 s and 1.46 s (6H, CH_3 of 3.5-O-acetal), 1.46 m (1H, H^{10}), 1.77 s (3H, CH_3 at C^6), 1.80 m (1H, H^4), 2.35 d.d.q (1H, H^2), 2.89 br.s (1H, H^7), 2.98 m (1H, H^8), 3.45 d.d (1H, $J_{2,3} = 10$, $J_{3,4} = 1.5$ Hz, H^3), 3.77 d (1H, $J_{9,8} = 10.5$ Hz, H^8), 3.82 s (3H, $C\underline{H}_3OC_6H_4$ of 9,11-O-acetal), 3.85 d.d (1H, $J_{11,10} = 2$, $J_{11,12} = 10$ Hz, H^{11}), 3.95 d.d.d (1H, $J_{13,12} = 1.4$, $J_{13,14} = 5$, $J_{13,14'} = 9$ Hz, H^{13}), 3.97 d (1H, $J_{5,4} = 2$ Hz, H^5), 4.80 s (1H, H of acetal), 5.07 d.d (1H, $J_{1'\text{-cis},1} = 10.5$, $J_{1'\text{-cis},1'\text{-trans}} = 2$ Hz, $H^{1'}$-cis), 5.13 d.d (1H, $J_{1'\text{-trans},1} = 17$ Hz, $H^{1'}$-trans), 5.58 d.d.d (1H, $J_{1,2} = 9$ Hz, H^1), 6.80-7.80 m (19H, aromatic protons).

Compound (XVIII). A 0.27 g portion (1.797 mmoles) of NaI was added to solution of 0.419 g (452.8 μmoles) of (XVII) in 4 ml of acetone, cooled to 0°C, and then a solution of 0.2853 g (1.358 mmoles) of $(CF_3CO)_2O$ in 0.5 ml of acetone was added. The mixture was held for 30 min, was then decomposed by a saturated solution of $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with saturated solutions of $Na_2S_2O_3$ and NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (11:1) system. Yield 0.371 g (90.1%), syrup, $[\alpha]_D^{21}$ +25.9° (C = 1.02). PMR spectrum: 0.49 t (3H, $J_{CH_3,14} = 7.3$ Hz, CH_3 at C^{14}), 0.92 d (3H, $J_{CH_3,12} = 7$ Hz, CH_3 at C^{12}), 0.97 d (3H, $J_{CH_3,4} = 6.5$ Hz, CH_3 at C^4),

1.0 d (3H, $J_{CH_3,2}$ = 6.5 Hz, CH_3 at C^2), 1.04 s (9H, t-$BuPh_2SiO$), 1.22 d (3H, $J_{CH_3,10}$ = 7 Hz, CH_3 at C^{10}), 1.25 d (3H, $J_{CH_3,8}$ = 7 Hz, CH_3 at C^8), 1.36 s (3H, CH_3 at C^6), 1.46 s and 151 s (6H, CH_3 of 3,5-O-ketal), 1.29 m and 1.47 m (2H, H^{14} and $H^{14'}$), 1.61 m (1H, H^4), 1.80 m (1H, H^{12}), 2.04 br.d.q (1H, $J_{10,11}$ = 2, $J_{9,10}$ = 0.5 Hz, H^{10}), 2.27 m (1H, H^2), 2.68 s (1H, OH at C^6), 2.79 m (1H, H^8), 3.40 d.d (1H, $J_{3,4}$ = 2, $J_{3,2}$ = 10 Hz, H^3), 3.45 d (1H, $J_{7,8}$ = 3 Hz, H^7), 3.83 s (3H, $C\underline{H}_3C_6H_4$ of 9,11-O-acetal), 4.10 d (1H, $J_{9,10}$ = 10.5 Hz, H^9), 4.20 d.d.d (1H, $J_{13,12}$ = 1.5, $J_{13,14}$ = 5, $J_{13,14'}$ = 9.5 Hz, H^{13}), 4.20 d (1H, $J_{5,4}$ = 2 Hz, H^5). 4.22 d.d (1H, $J_{11,12}$ = 10 Hz, H^{11}), 4.87 d.d (1H, $J_{1,1'\text{-cis}}$ = 10, $J_{1'\text{-cis},1'\text{-trans}}$ = 2 Hz, $H^{1'}$-cis), 5.02 d.d (1H, $J_{1,1'\text{-trans}}$ = 17 Hz, $H^{1'}$-trans), 5.30 d.d.d (1H, $J_{1,2}$ = 8.5 Hz, H^1), 5.32 s (1H, H of acetal), 6.80-7.70 m (19H, aromatic protons).

Compound (XIX). A 23 mg portion (1 mmole) of Na was added to a mixture of 3 ml of liquid NH_3 and 2 ml of ether cooled to −78°C. The mixture was stirred for 20 min, a solution of 0.371 g (408 μmoles) of (XVIII) in 2.5 ml of ether was added, and stirring was continued for 15 min. The mixture was decomposed by solid NH_4Cl, ammonia was evaporated, the residue was diluted with $CHCl_3$, and filtered. The filtrate was dried over Na_2SO_4, evaporated, and the residue was chromatographed in a hexane–EA (11:1) system. Yield 0.226 g (69.1%), syrup, $[\alpha]_D^{21}$ +14.2° (C = 1.0). PMR spectrum: 0.50 t (3H, $J_{CH_3,14}$ = 7.2 Hz, CH_3 at C^{14}), 0.90 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 1.03 d (3H, $J_{CH_3,4}$ = 7 Hz, CH_3 at C^4), 1.06 s (9H, t-$\underline{Bu}Ph_2$·SiO), 1.07 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.10 d (3H, $J_{CH_3,8}$ = 6.4 Hz, CH_3 at C^8), 1.17 d (3H, $J_{CH_3,10}$ = 7 Hz, CH_3 at C^{10}), 1.25 s (3H, CH_3 at C^6), 1.45 s and 1.47 s (6H, CH_3 of 3,5-O-ketal), 1.75 m (1H, H^{12}), 1.91 m (1H, H^{10}), 2.26 s (1H, OH at C^6), 2.36 m (1H, H^2), 2.56 m (1H, H^8), 3.28 br.d (1H, $J_{9,8}$ = 11 Hz, H^9), 3.45 d.d (1H, $J_{3,4}$ = 1.8, $J_{3,2}$ = 9.5 Hz, H^3), 3. 3.54 d (1H, $J_{5,4}$ = 2 Hz, H^5) 3.83 s (3H, $C\underline{H}_3OC_6H_4$ of 9,11-O-acetal), 4.16 d.d.d (1H, $J_{13,12}$ = 1.5 Hz, $J_{13,14}$ = 5, $J_{13,4'}$ = 9.5 Hz, H^{13}), 4.27 d.d (1H, $J_{11,10}$ = 2, $J_{11,12}$ = 10 Hz, H^{11}), 5.04 d.d (1H, $J_{1'\text{-cis},1}$ = 10, $J_{1'\text{-cis},1'\text{-trans}}$ = 2 Hz, $H^{1'}$-cis), 5.12 d.d (1H, $J_{1'\text{-trans},1}$ = 16.5 Hz, $H^{1'}$-trans), 5.61 d.d.d (1H, $J_{1,2}$ = 8.5 Hz, H^1), 6.80-7.70 m (14H, aromatic protons).

Compound (I). A solution of 0.264 g (329 μmoles) of (XIX) and 0.962 g (3.049 mmoles) of Bu_4NF in 3 ml of THF was heated at 80°C for 20 h, was then evaporated, and the residue was dissolved in $CHCl_3$. The 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 0.182 g (98%), syrup, $[\alpha]_D^{25}$ +7.2° (C = 1.0). PMR spectrum: 0.78 d (3H, $J_{CH_3,12}$ = 7 Hz, CH_3 at C^{12}), 1.0 t (1H, $J_{CH_3,14}$ = 7.3 Hz, CH_3 at C^{14}), 1.01 d (3H, $J_{CH_3,12}$ = 6.5 Hz, CH_3 at C^4), 1.05 d (3H, $J_{CH_3,2}$ = 6.3 Hz, CH_3 at C^2), 1.11 d (3H, $J_{CH_3,8}$ = 6.5 Hz, CH_3 at C^8), 1.20 s (3H, CH_3 at C^6), 1.21 d (3H, $J_{CH_3,10}$ = 6.5 Hz, CH_3 at C^{10}), 1.42 s and 1.43 s (6H, CH_3 of 3,5-O-ketal), 1.67 d.d.q (1H, $J_{4,5} = J_{4,3}$ = 2 Hz, H^4), 1.84 br.d.q (1H, $J_{10,11}$ = 2 Hz, H^{10}), 1.98 d.d.q (1H, $J_{12,11}$ = 10, $J_{12,13}$ = 2 Hz, H^{12}), 2.33 m (1H, $J_{2,3}$ = 9.5, $J_{2,1}$ = 8.2 Hz, H^2), 2.61 m (1H, $J_{8,9}$ = 10.5, $J_{8,7}$ = 1.5 Hz, H^8), 3.31 br.d (1H, H^9), 3.42 d.d (1H, H^3), 3.49 d (1H, H^5), 3.65 d.d.d (1H, $J_{13,14}$ = 5, $J_{13,14'}$ = 7.5 Hz, H^{13}), 4.17 d.d (1H, H^{11}), 5.05 d.d (1H, $J_{1'\text{-cis},1}$ = 10, $J_{1'\text{-cis},1'\text{-trans}}$ = 2 Hz, $H^{1'}$-cis), 5.12 br.d.d (1H, $J_{1'\text{-trans},1}$ = 16.8 Hz, $H^{1'}$-trans), 5.61 d.d.d (1H, H^1), 5.65 s (1H, H of acetal), 6.89 m, 7.41 m (4H, $CH_3OC_6\underline{H}_4$ of 9,11-O-acetal).

CONCLUSIONS

A directed synthesis of a seco-acid derivative of 9(S)-dihydroerythronolide B has been carried out.

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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

15.* STEREODIRECTED SYNTHESIS OF ERYTHRONOLIDE B ACCORDING TO THE COUPLING SCHEME OF THE (C^9-C^{13}) + (C^7-C^8) + (C^1-C^6) FRAGMENTS

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UDC 542.91:547.455

In the preceding publication of this series we have described a stereodirected synthesis of a precursor of a seco acid of 9(S)-dihydroerythronolide B (I). The configuration of nine out of eleven chiral centers in (I), C^2-C^5 and C^9-C^{13}, was rigorously proved from examination of the PMR spectra of a series of cyclic derivatives. Comparison of compound (I) with the product of the same structure obtained by an alternative scheme (see the following publications of this series) and having a known configuration of the C^6 and C^8 centers confirmed their complete identity, and thus their complete stereochemical correspondence to 9(S)-dihydroerythronolide B. The seco acid, which can be obtained from derivative (I), satisfies all the requirements necessary for the successful realization of the macrolactonization stage, formulated in [2, 3], in particular, the (S)-configuration of the C^9 center, the presence of 3,5- and 9,11-bis(cyclo)acetal system, the equatorial position of the p-methoxyphenyl group at the 9,11-acetal center. All the above enumerated factors made it possible to proceed to the concluding stage of a total stereodirected synthesis of erythronolide B from carbohydrates according to a (C^9-C^{13}) and (C^7-C^8) + (C^1-C^6) coupling scheme of fragments, i.e., a macrolactonization and direct comparison of the aglycones of synthetic and natural antibiotics and their derivatives, which is the subject of the present publication.

The double bond in compound (I) was subjected to ozonolysis, and the subsequent oxidation of the aldehyde formed by m-chloroperbenzoic acid in the presence of a phosphate buffer at pH 7.0 [4] leads to a hydroxy acid derivative of erythronolide B (II). This compound was converted into an activated thioether by reaction with bis(1-isopropyl-4-tert-butylimidazol-2-yl) disulfide and Ph_3P, and lactonized by boiling in toluene under highly dilute conditions ($C = 10^{-3}$ M) [5], which led to lactone (III) in a very high yield (72%). The structure of the product obtained was confirmed by the data of PMR spectroscopy and direct comparison of several derivatives obtained both from the macrolide (III) and from natural erythronolide B. The comparison was carried out on the basis of melting points, specific rotation and PMR spectra for macrolactones (III), (IV) and (VII). All the characteristics of the synthetic samples of the above lactones coincide exactly with those obtained from a natural erythronolide B (scheme).

Thus, macrolide (III) is converted by acid hydrolysis into 9(S)-dihydroerythronolide B (IV). The reduction of a sample of natural erythronolide B (VII) by sodium borohydride on

*For previous communication, see [1].

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 447-451, February, 1989. Original article submitted August 10, 1987.

0568-5230/89/3802-0391 $12.50