Synthetic study of hepoxilins 9.* Stereoselective total synthesis of trioxilin (10*S*,11*S*,12*S*)-B_3

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Total synthesis of trioxilin (10*S*,11*S*,12*S*)-B_3 was performed starting from a hepoxilin synthon, (2*S*,3*S*)-2,3-epoxyundec-5-yn-1-ol, available from the corresponding allylic alcohol by Sharpless enantiodirected epoxidation. The synthesis features stereoselective (*E*)-1,2-*syn*-addition of the acetylenide anion to the intermediate (2*S*,3*S*)-2,3-isopropylidenedioxyundec-5-yn-1-al and regioselective partial hydrogenation of a triacetylene trioxilin precursor, which allowed the preparation of 14,15-dehydro-(10*S*,11*S*,12*S*)-TrXB$_3$.

Key words: trioxilin (10*S*,11*S*,12*S*)-B_3, total synthesis; trioxilin 14,15-dehydro-(10*S*,11*S*,12*S*)-B_3, total synthesis; eicosanoids, total synthesis; hepoxilin synthon; triacetylene trioxilin precursor; regioselective partial hydrogenation.

The primary endogenous metabolites of arachidonic acid *via* the 12-lipoxygenase pathway are hepoxilins (Hx) A_3 and B_3 (Scheme 1), whose biological activity and role are already well known and continue to be under investigation.[2] The data available on trioxilins (TrX), the closest endogenic metabolites of hepoxilins, formed upon hydrolytic cleavage of the epoxide rings in these compounds, are actually limited to incomplete knowledge of their structures.[3,4] However, some trioxilins isolated from natural sources[5] and C_{18} analogs of trioxilins[6] are known to exhibit important biological functions. This situation has triggered interest in the total synthesis of both C_{18} analogs[7] and trioxilins themselves[8–12] as the only practicable source of these compounds for subsequent biological studies.

As a rule, the syntheses of trioxilins reported in the literature make use of natural chiral precursors, for example, carbohydrates,[8–10] D-tartaric acid,[11] or quinic acid,[12] whereas the syntheses of enantiomerically pure hepoxilins employ in addition enantiodirected Sharpless epoxidation,[1,13] which makes the synthetic schemes more flexible.[14] Formally, these syntheses are also ones of trioxilins because methods of chemical transformation of hepoxilins B_3 into trioxilins have recently been developed.[7e,15] However, for biological studies of trioxilins, it is expedient to find a more direct method for their preparative synthesis. The subject of this study has been to develop such a synthetic route.

Chiral (2*S*,3*S*)-epoxy alcohol **1**, used previously as a hepoxilin synthon was selected as the starting compound.[13] This epoxy alcohol was prepared by enantiodirected Sharpless epoxidation with an enantiomeric excess (*ee*) of 88%, which was improved up to 100% by low-temperature recrystallization. Alkaline hydrolysis of the epoxide ring in epoxy alcohol **1** afforded triol **2**. This hydrolysis is regiospecific and involves Walden inversion at C(2). The reaction mechanism includes reversible Payne rearrangement of 1-hydroxy-2,3-epoxide **1** with configuration inversion at C(2), yielding the corresponding 3-hydroxy-1,2-epoxide, and selective epoxide ring opening in this primary and secondary epoxide upon the attack by a hydroxide anion on the sterically unhindered C(1) center.[16] We were pleased to find that triol **2** with *ee* 100% was obtained from epoxy alcohol **1** with *ee* 88% after minimum purification. The enantiomeric purity of triol **2** was confirmed by performing a similar hydrolysis of a sample of epoxy alcohol **1** with *ee* 100%, which resulted in the formation of triol **2** with the same characteristics (and in a 10% higher yield) (Scheme 2).

A differentiating protection was introduced into triol **2** *via* a standard reaction sequence.[7a] Partial silylation proceeds selectively at the primary hydroxyl group and gives rise to monoether **3**. Acetonation of the α-glycol group and removal of the silyl protection on treatment with fluoride ion afford hydroxy acetonide **5** in a high yield.

The carbon chain was elongated according to a scheme developed previously[13] for the synthesis of hepoxilins. Oxidation of alcohol **5** gave rise to aldehyde **6**. The integral intensity of the signal of the aldehyde proton (a doublet at δ 9.78) in the ^{1}H NMR spectra of various samples of aldehyde **6** was often less than 1 H, simultaneously, a doublet of deficient intensity appeared

* For part 8, see Ref. 1

Translated from *Izvestiya Akademii Nauk, Seriya Khimicheskaya*, No. 3, pp. 545–551, March, 2000.

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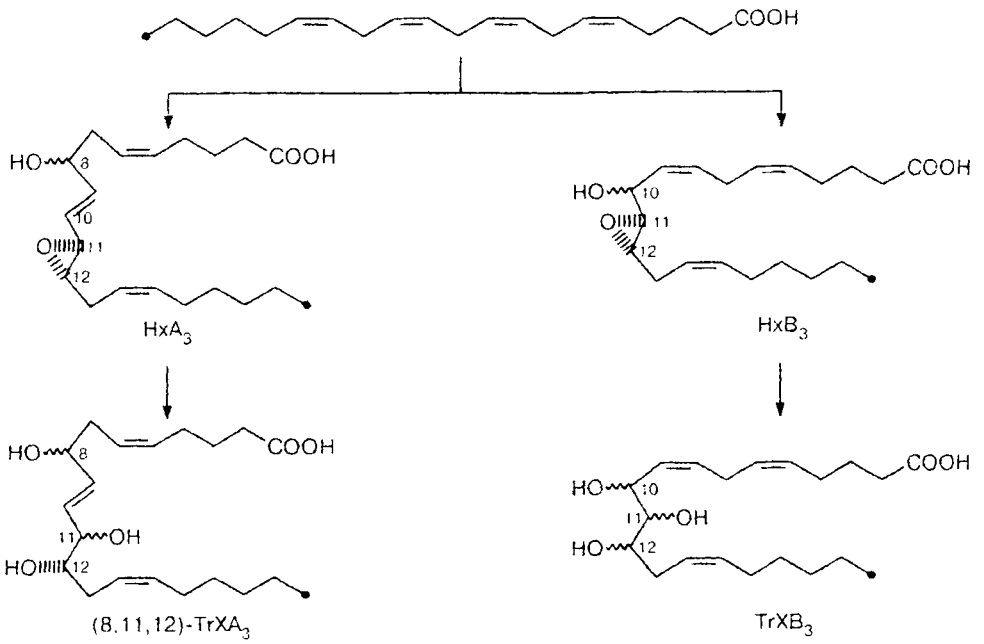
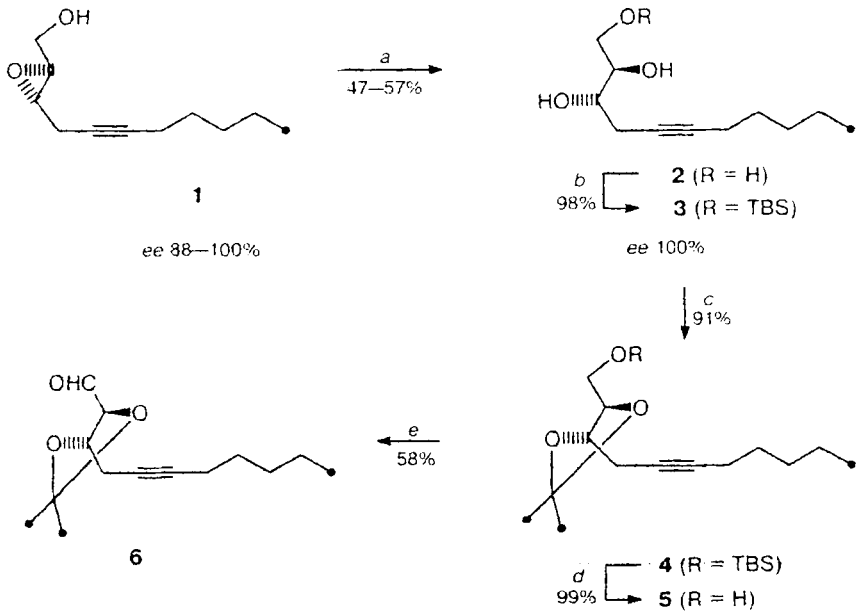
Scheme 1



Scheme 2



Reagents and conditions: *a*. NaOH, Bu^tOH-H_2O (1 : 5), 60—65 °C, 7 h; *b*. TBSCl—ImH—Py, 15 °C, 2 h; *c*. $Me_2C(OMe)_2$—CSA (CSA is ±-camphor-10-sulfonic acid), 0 °C, 4 h; *d*. Bu^n_4NF, THF, 20 °C, 1 h; *e*. PDC, AcOH, MS 3 Å (MS are molecular sieves), CH_2Cl_2, 20 °C, 30 min.

at δ 4.6, *i.e.*, in the region of protons of the $CH(OR)_2$ type. This indicates apparently the formation of a stable hydrate or hemiacetal of aldehyde **6**, which accounts for the incomplete conversion of the aldehyde in the next step.

The reaction of aldehyde **6** with $LiC{\equiv}CCH_2Cl$ gave propargyl chloride **7** and partial (10—20%) recovery of the starting aldehyde; nevertheless, the yield of **7** based on the unrecovered aldehyde **6** was ~90% (Scheme 3). It was difficult to check the selectivity of formation and

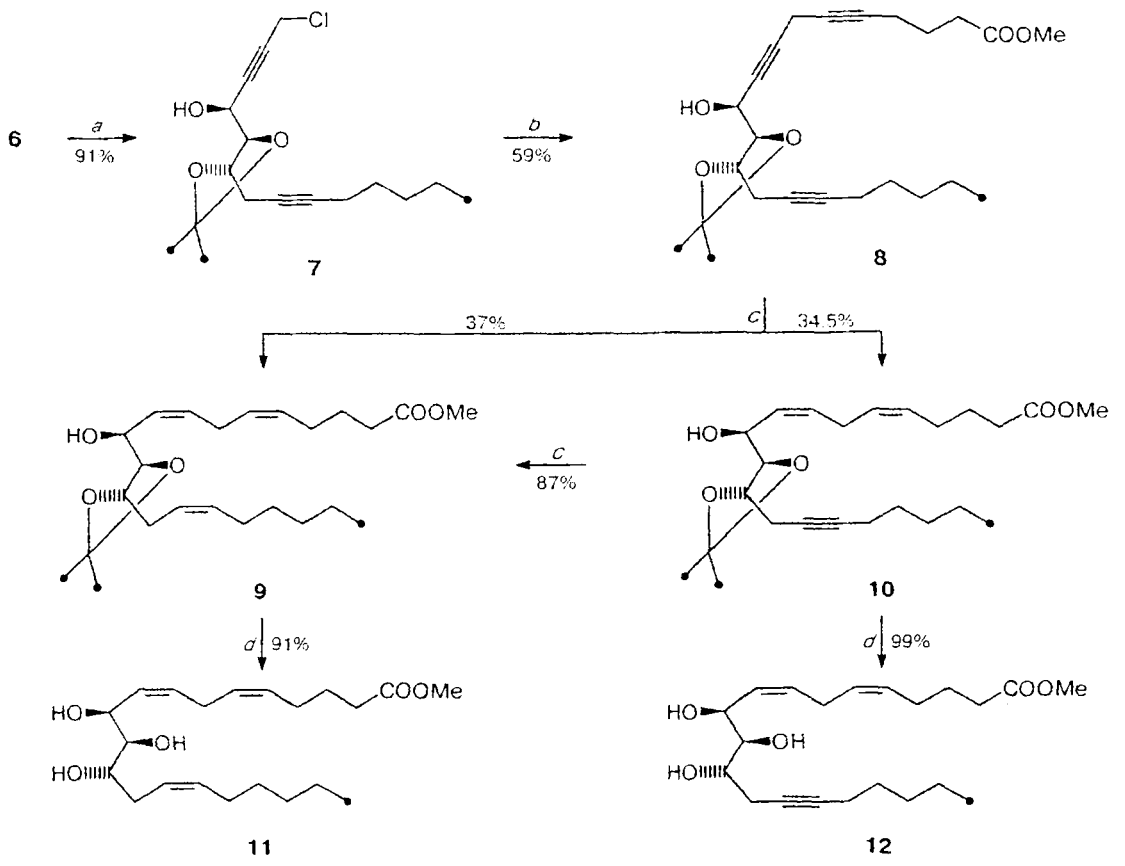
the configuration of the new asymmetric center at this step. This was done later (see below); it was found that the addition to the aldehyde group of dioxolanylaldehyde **6** proceeds with a substantial (7 : 1) *syn*-stereoselectivity, unlike analogous reactions of oxiranylaldehydes.[1,13,14,17,18]

Condensation of chloride **7** with methyl hex-5-ynoate under mild chemoselective conditions[19] resulted in a highly unstable triacetylene precursor of trioxilins **8**. Due to its instability and to the poisoning of hydrogenation catalysts by the impurities formed during storage, triyne **8** was subjected to hydrogenation over Lindlar catalyst for 24 h after the synthesis and immediately after purification by filtration through silica gel. When hydrogenation strongly slowed down or terminated, a portion of the catalyst was replaced by a fresh one and hydrogenation was continued until the starting and the intermediate di- and tetrahydrogenated products disappeared (TLC and ^{1}H NMR monitoring).

Despite this thoroughness in conducting the hydrogenation and six replacements of the catalyst, high performance flash chromatography (HPFC)[20] of the resulting mixture of hydrogenation products (whose subsequent hydrogenation proceeded very slowly) afforded only 37% of the desired hexahydro derivative, triene, as the single 10*S*-epimer **9**, together with a nearly equal amount (34.5%) of the corresponding tetrahydro derivative, dienyne **10**. The configurational similarity of products **9** and **10** was established by additional hydrogenation (under the same conditions) of tetrahydro derivative **10** to hexahydro derivative **9**, which can be readily carried out because this process is much less complicated. This almost doubled the total yield of the target triene **9**.

The configuration of triene **9** was established after the removal of the acetonide protection, giving rise to triol **11**, the methyl ester of trioxilin B_3. The resulting isomer was identical in chromatographic behavior (TLC) to a methylated sample of authentic (10*S*,11*S*,12*S*)-TrXB_3[15] when compared directly and exhibited a ^{1}H NMR spectrum virtually identical in positions and multiplicities of signals of characteristic protons ($C(7)H_2$, H(10–12)) to the spectra of the above-mentioned sample[15] and its enantiomer synthesized by a different method.[8,11] The absolute (10*S*,11*S*,12*S*)-configuration

Scheme 3



Reagents and conditions: *a*. HC≡CCH_2Cl–Bu^nLi, Et_2O, −78 °C, 15 min; *b*. HC≡$C(CH_2)_3COOMe$–CuI–NaI–K_2CO_3, DMF, 20 °C, 20 h; *c*. H_2–Pd/Pb/$CaCO_3$, C_6H_6, 5–8 °C, 6 h; *d*. AcOH–H_2O (4 : 1), 55 °C, 7 h.

of the sample of **11** synthesized follows from the configuration of the starting epoxy alcohol **1** and is confirmed by the (+) signs of the optical rotation of **11** and the same enantiomer of the corresponding free acid described in the literature,[15] as well as by the (−) sign published for the opposite enantiomer,[8,11] and by the fact that the absolute values of the optical rotations are close. Similar hydrolysis of dienyne acetonide **10** yielded the corresponding triol **12**, which has the same optical rotation sign as **11** and constitutes a dehydro analog of trioxilins.

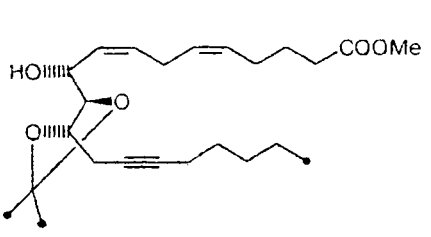
Thus, we identified two characteristic features of the synthetic scheme used. First, the addition of the acetylenide $LiC{\equiv}CCH_2Cl$ to aldehyde **6** occurs *syn*-stereoselectively (the content of 10*S*-products **9** + **10** in the mixture reaches 81%) and, second, the triple bonds in 5,8,14-triyne **8** are hydrogenated at substantially different rates, the 14,15-bond being the least reactive. In order to clarify these points, which present interest from the practical viewpoint for the use in other syntheses, we studied the structures of two minor products isolated upon the hydrogenation of triyne **8**, namely, dienyne **13** and enediyne **14** (yields 11 and 6%, respectively) (Scheme 4).

The structures of all hydrogenated products were mainly determined using ^{1}H NMR spectroscopy. The numbers of double bonds were found from the integral intensity of the signals corresponding to the vinylic protons, while the positions of double and triple bonds were identified from the characteristics of signals due to the allylic/propargylic methylene groups. The diagnostic signal for compounds with a triple 14,15-bond **10**, **13**, and **14** is the broad signal of the diastereotopic $C(13)H_2$ group centered at δ 2.56—2.62, which is the AB part of an $ABXY_2$ system (X = H(12), Y = $C(16)H_2$) with the characteristic spin—spin coupling constant $^5J_{H(13)-H(16)}$ = 2.3—2.4 Hz. This signal is also present in the spectrum of triyne **8** but not in the spectrum of triene **9**, in which the broad multiplet for $C(13)H_2$ is shifted upfield to δ 2.40. The simultaneous presence of multiple 4,5- and 8,9-bonds in molecules is proved by the position of the signal of the "separating" $C(7)H_2$ group at δ 2.90—2.98, while the nature of these multiple bonds is determined by the width of this multiplet, which is narrow ($W_{1/2}$ 0.05 ppm for enediyne **14** and 0.03 ppm for triyne **8**) if the 8,9-bond is a triple bond and broad ($W_{1/2}$ 0.21—0.36 ppm for compounds **9**, **10**, and **13**) for compounds with double 8,9(*Z*)-bonds, in which the difference between the chemical shifts of the protons of this methylene group increases substantially since the diastereotopic $C(7)H_2$ group is located close to the asymmetric centers of the molecule. Additional evidence for the presence of the triple 8,9-bond in enediyne **14** is provided by the fact that the position and the shape of the H(10) signal are the same as those for triyne **8**. The structures of compounds **9** and **10** derived from the ^{1}H NMR spectra are confirmed by mass spectral data. The spectra of both compounds exhibit intense peaks due to the C(1)...C(10) fragment with the same *m/z* 197, corresponding to the presence of two double bonds in this fragment. In addition, the C(11)...C(20) fragment ions have *m/z* 211 in the case of triene **9** and *m/z* 209 for dienyne **10**.

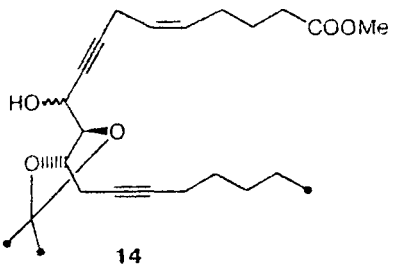
Thus, the molecules of dienynes (10*S*)-**10** and **13** are characterized by identical arrangements of the (*Z*)-double and triple bonds; hence, the 10*R* configuration was deduced for dienyne **13**. It should be mentioned that the 10*R*-triene corresponding to dienyne **13** cannot be detected in a noticeable amount (≥5%); thus, the triple 14,15-bond in the 10*R*-epimer, present as an impurity in triyne **8**, is even less reactive in the Lindlar hydrogenation. The isolation of epimer **13** makes it possible to estimate *syn*-stereoselectivity of the addition of $LiC{\equiv}CCH_2Cl$ to aldehyde **6** as about 7 : 1.

The structure of the second minor hydrogenation product, enediyne **14**, points to a substantial difference between the rates of hydrogenation of the triple bonds in triyne **8**; in terms of reactivity, they can be arranged in the sequence (5,6) > (8,9) >> (14,15). Whereas a possible reason for the different reactivities of the triple 5,6- and 8,9-bonds is obvious (different local environments), this is not so with the 5,6- and 14,15-bonds. A possible reason for the large difference between these two, seemingly similar bonds is suggested by the substantial high-field shift (Δδ −0.22) of the signal of H(10) in dienyne **10** (δ(H(10)) 4.70) observed upon hydrogenation of the triple 14,15-bond, far removed from this proton (by five bonds), to give triene **9** (δ(H(10)) 4.48).

Scheme 4



13



14

The conformational analysis (PM3 method) of the dienyne **10** molecule shows that in the stable conformation the H(10) proton is positioned close to the triple 14,15-bond (the distance from this proton to the center of this bond is 2.7 Å) due to the *cis*-arrangement of the substituents in the dioxolane ring. Hence, the H(10) proton is within the cone of anisotropy of the triple bond, in which the induced magnetic field is directed along the external field. This contribution to the external magnetic field switches to an opposite one or disappears when the 14,15-bond is converted into a double bond. This accounts for the observed changes in the chemical shift of H(10). However, the same close location of the C(9),C(10) fragment to the C(13)...C(15) fragment of the molecule provides steric shielding of the latter and hampers hydrogenation of the triple 14,15-bond. Conversely, the triple 5,6-bond is unshielded and retains the normal reactivity.

Similarly, the C(13)...C(15) fragment of the side chain in aldehyde **6** is located close to the aldehyde group and thus ensures enhanced stereoselectivity of its reactions. This mutual shielding of remote fragments of the molecule can also be observed in other compounds with a *cis*-substituted acetonide group: we now examine the possibility of using the selectivity thus induced for synthetic purposes.

The synthesis of enantiomerically pure methyl ester of trioxilin (10*S*,11*S*,12*S*)-B_3 is the first synthesis of trioxilins from achiral starting compounds. The chirality of the intermediate hepoxilin synthon **1** was attained using asymmetric Sharpless epoxidation,[13] which allows any enantiomer to be synthesized equally easily. The synthesis includes 9 or 10 steps (from synthon **1**) proceeding in an overall yield of 8—10%; it is characterized by stereoselective introduction of the additional asymmetric center and unexpectedly selective hydrogenation of the triple bonds in the intermediate triyne **8**, which allowed also the synthesis of the 14,15-dehydroanalog of the same trioxilin.

Experimental

Melting points were determined on a Kofler hot stage (Boetius). Optical rotation was measured on a DIP 360 polarimeter (Japan) in a 1-dm cell. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer (200.13 MHz), ^{13}C NMR spectra were run on a Bruker AM-300 instrument (75.47 MHz). Mass spectra were measured on a Kratos MS-890 mass spectrometer with direct introduction into the ion source at 150 °C. Analytical TLC was performed on Silufol UV_{254} plates (Czechoslovakia) in EtOAc (system A) and 8 : 2 (system B) and 7 : 3 (system C) hexane—EtOAc systems. The substances were visualized by spraying with a 5% solution of phosphomolybdic acid in ethanol followed by heating. Preparative separation was carried out by high performance flash chromatography (HPFC)[20] on a 2×24 cm column (2000 theoretical plates) with Kieselgel H silica gel (5—40 μm, Fluka) using gradient elution with 5 : 95 → 20 : 80 EtOAc—hexane mixtures. Primary purification of reaction mixtures was performed by filtration through Kieselgel 60 F_{254} silica gel (63—200 μm, Merck) in the specified solvents.

All the reactions were carried out under dry argon. The extracts were dried with calcined $MgSO_4$. The solvents were purified by distillation from appropriate drying agents (sodium for benzene and dimethoxypropane; sodium benzophenone ketyl for ether and THF; and CaH_2 for pyridine and CH_2Cl_2).

The following reagents were used: TBSCl, (±)-camphor-10-sulfonic acid (CSA), 2,2-dimethoxypropane, PDC, Lindlar catalyst (5% Pd—Pb/$CaCO_3$), a hexane solution of Bu^nLi (Fluka), and a 1 *M* solution of Bu^n_4NF in THF (Aldrich). Methyl hex-5-ynoate (b.p. 80—85 °C (15 Torr)) was synthsized by methylation of the corresponding acid, prepared as published previously,[21] with an ethereal solution of CH_2N_2.

(2*R*,3*S*)-Undec-5-yne-1,2,3-triol (2). ***A.*** An emulsion of crude (2*S*,3*S*)-2,3-epoxyundec-5-yn-1-ol (**1**) (1.59 g, 8.7 mmol) (m.p. 32.5—33.1 °C, $[\alpha]_D^{25}$ −11.1° (*c* 1.83, $CHCl_3$), *ee* 88% (according to the ^{1}H NMR data for the acetate with the addition of Eu(htfd)$_3$[13]) in a solution of NaOH (5.18 g, 130 mmol) in 320 mL of a 3.5 : 1 H_2O—Bu^tOH mixture was vigorously stirred for 7 h at 65 °C. The resulting dark yellow emulsion was partially evaporated *in vacuo* (to remove Bu^tOH), the product was extracted with EtOAc (5×50 mL), and the extract was washed with water (3×50 mL) to pH 7, dried, and concentrated to dryness. A solution of the remaining semicrystalline light brown material was filtered through 80 g of silica gel. Concentration of the filtrate gave 0.815 g (47%) of triol **2**, m.p. 59—61 °C, $[\alpha]_D^{25}$ 0° (*c* 1.77, $CHCl_3$). Two recrystallizations from a hexane—ether mixture afforded a sample with unchanging characteristics and *ee* 100% as snow-white needles, m.p. 61—61.5 °C, $[\alpha]_D^{25}$ −2.6° (*c* 2.13, $CHCl_3$), R_f 0.45 (system A; for starting epoxy alcohol **1**, R_f 0.50). ^{1}H NMR, δ: 0.91 (dist.t, 3 H, C(11)H_3, *J* = 7.0 Hz); 1.17—1.57 (m, 6 H, C(8—10)H_2); 1.61, 2.10, 2.42 (all br.s, 1 H each, 3 OH); 2.17 (tt, 2 H, C(7)H_2, *J* = 2.4 and 7.2 Hz); 2.52 (dt, 2 H, C(4)H_2, *J* = 2.4 and 5.5 Hz); 3.70—3.86 (m, 4 H, C(1)H_2 + H(2), H(3)).

B. The same treatment of a sample of epoxy alcohol **1** with *ee* > 98% (m.p. 34 °C, $[\alpha]_D^{25}$ −11.8° (*c* 1.14, $CHCl_3$)) gave triol **2** with the above-cited unchanging constants (m.p. 61—61.5 °C) (*i.e.*, with *ee* 100%) after concentration of the filtrate, trituration of the residue under a hexane—ether mixture, and separation of the crystals. The yield was 57%.

(2*R*,3*S*)-1-*tert*-Butyldimethylsilyloxyundec-5-yne-2,3-diol (3). A solution of triol **2** (550 mg, 2.75 mmol), TBSCl (539 mg, 3.6 mmol), and ImH (485 mg, 7.1 mmol) in 6 mL of anhydrous Py was kept for 2 h at 15 °C until the starting compound was completely consumed (TLC monitoring). The mixture was diluted with 5 mL of water, the product was extracted with EtOAc, and the extract was washed with water, dried, and concentrated. A solution of the oily residue in a 4 : 1 EtOAc—hexane mixture was filtered through 10 g of silica gel to give 850 mg (98%) of ether **3** as a colorless oil, $[\alpha]_D^{25}$ +7.8° (*c* 1.92, $CHCl_3$), R_f 0.24 (system B; for starting triol **2**, R_f ~0). The product was used in the next step without further purification or characterization.

(2*R*,3*S*)-1-*tert*-Butyldimethylsilyloxy-2,3-(isopropylidenedioxy)undec-5-yne (4). A solution of ether **3** (830 mg, 2.6 mmol) and CSA (30 mg, 0.13 mmol) in 10 mL of $Me_2C(OMe)_2$ was kept for 4 h at 0 °C until the starting compound was completely consumed (TLC monitoring). The mixture was diluted with 10 mL of ether and the solution was filtered through 5 g of Al_2O_3, which was additionally washed with ether. Concentration of the filtrate gave 853 mg (91%) of acetonide **4** (colorless oil, $[\alpha]_D^{25}$ 0° (*c* 2.11, $CHCl_3$), R_f 0.61 (system B)).

The product was used in the next step without further purification or characterization.

(2*R*,3*S*)-2,3-(Isopropylidenedioxy)undec-5-yn-1-ol (5). A mixture of a solution of acetonide **4** (845 mg, 2.38 mmol) in 10 mL of anhydrous THF and a 1 *M* solution of Bu^n_4NF in THF (9.9 mL, 9.9 mmol) was kept for 1 h at 20 °C until the starting compound was completely consumed (TLC monitoring). The mixture was diluted with 20 mL of water, the product was extracted with EtOAc, and the extract was washed with water, dried, and concentrated to a volume of 5 mL. The solution was filtered through 5 g of silica gel, which was additionally washed with EtOAc. The filtrate was concentrated and the oily residue was distilled to give 572 mg (99%) of alcohol **5** as a colorless oil, b.p. 150—165 °C (0.05 Torr), $[\alpha]_D^{25}$ −31.1° (*c* 2.69, $CHCl_3$), R_f 0.09 (system B). ^1H NMR, δ: 0.89 (dist.t, 3 H, C(11)H_3, J = 6.0 Hz); 1.16—1.53 (m, 6 H, C(8—10)H_2); 1.37, 1.47 (both s, each 3 H, CMe_2); 2.13 (tt, 2 H, C(7)H_2, J = 2.5 and 6.9 Hz); 2.34—2.61 (2 ddt, 2 H, C(4)H_2, AB part of ABXY$_2$ system, $\Delta\delta_{AB}$ = 0.033, $^2J_{AB}$ = 16.8 Hz, $^3J_{AX}$ = 8.2 Hz, $^3J_{BX}$ = 5.5 Hz, $^5J_{AY}$ = $^5J_{BY}$ = 2.5 Hz); 3.77—3.89 (both dd, 2 H, C(1)H_2, AB part of ABX system, $\Delta\delta_{AB}$ = 0.055, $^2J_{AB}$ = 11.5 Hz, $^3J_{AX}$ = 6.4 Hz, $^3J_{BX}$ = 4.4 Hz); 4.21—4.38 (m, 2 H, H(2, 3)).

(2*S*,3*S*)-2,3-(Isopropylidenedioxy)undec-5-yn-1-al (6). Acetic acid (79 μL) and a solution of alcohol **5** (518 mg, 2.16 mmol) in 5 mL of CH_2Cl_2 were added successively at 20 °C to a suspension of finely ground PDC (812 mg, 2.16 mmol) and 3 Å molecular sieves (1.1 g) in 15 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred for 30 min at 20 °C, finely powdered activated carbon (200 mg) was added, and the mixture was stirred for an additional 15 min and filtered through 10 g of silica gel, which was washed successively with CH_2Cl_2 and a 7 : 3 CH_2Cl_2—EtOAc mixture. After concentration of the filtrate, the oily residue was distilled to give 300 mg (58%) of aldehyde **6** as a colorless oil, b.p. 125—130 °C (1 Torr), $[\alpha]_D^{25}$ +13.1° (*c* 1.83, $CHCl_3$), R_f 0.55 (system B, two developments; for starting alcohol **5**, R_f 0.33). ^1H NMR, δ: 0.86 (dist.t, 3 H, C(11)H_3, J = 6.0 Hz); 1.20—1.54 (m, 6 H, C(8—10)H_2); 1.38, 1.58 (both s, each 3 H, CMe_2); 2.13 (tt, 2 H, C(7)H_2, J = 2.2 and 6.7 Hz); 2.50 (dt, 2 H, C(4)H_2, J = 5.6 and 2.2 Hz); 4.43 (dd, 1 H, H(2), J = 2.1 and 7.4 Hz); 4.52 (dd, 1 H, H(3), J = 2.1 and 7.4 Hz); 9.78 (d, 1 H, CHO, J = 2.1 Hz).

(4*S*,5*R*,6*S*)-1-Chloro-5,6-isopropylidenedioxytetradeca-2,8-diyn-4-ol (7). A 1.6 *M* solution of Bu^nLi (7.8 mL, 12.5 mmol) in hexane was added with stirring over a period of 5 min to a solution of $HC{\equiv}CCH_2Cl$ (952 mg, 12.9 mmol) in 4 mL of anhydrous ether cooled to −78 °C. The solution was kept for 15 min at −78 °C, then a solution of aldehyde **6** (374 mg, 1.56 mmol) in 5 mL of ether was added. After 15 min, the mixture was poured into 25 mL of a saturated solution of NH_4Cl. The organic layer was separated and washed with 5 mL of a solution of NH_4Cl, the aqueous layers were extracted with EtOAc, and the combined extracts were dried and concentrated. The residue dissolved in hexane was purified by chromatography on 15 g of silica gel using 1 : 10 → 2 : 8 EtOAc—hexane mixtures for elution. Concentration of initial fractions afforded 66 mg of starting aldehyde **6** (recovery 8%); concentration of later fractions gave a total of 410 mg (91% based on the unreacted aldehyde **6**) of chloride **7** with an admixture of aldehyde **6** (~10%), which was used in the next step without further purification. The fraction of pure chloride **7** used for analytical measurements was a colorless oil, $[\alpha]_D^{25}$ +21.9° (*c* 1.96, $CHCl_3$), R_f 0.37 (system B, two developments). ^1H NMR, δ: 0.91 (dist.t, 3 H, C(14)H_3, J = 6.9 Hz); 1.27—1.40 (m, 6 H, C(11—13)H_2); 1.28, 1.53 (both s, each 3 H, CMe_2); 2.10—2.22 (m, 2 H, C(10)H_2); 2.55 (d, 1 H, OH, J = 6.4 Hz); 2.64 (dt, 1 H, C(7)$\underline{H}_A H_B$, J = 7.5 and 2.8 Hz); 2.68 (dt, 1 H, C(7)$H_A\underline{H}_B$, J = 7.5 and 2.5 Hz); 4.19 (d, 2 H, C(1)H_2, J = 2.0 Hz); 4.23 (dd, 1 H, H(5), J = 5.4 and 6.4 Hz); 4.39 (q, 1 H, H(6), J = 6.4 Hz); 4.70 (ddt, 1 H, H(4), J = 5.4, 6.4, and 2.0 Hz).

Methyl (10*S*,11*R*,12*S*)-10-hydroxy-11,12-(isopropylidenedioxy)eicosa-5,8,14-triynoate (8). A mixture of methyl hex-5-ynoate (692 mg, 5.49 mmol), chloride **7** (570 mg, 1.83 mmol) (containing 10—20% aldehyde), and dry, finely ground CuI (349 mg, 1.83 mmol), NaI (550 mg, 3.66 mmol), and K_2CO_3 (505 mg, 3.66 mmol) in 12 mL of anhydrous DMF was stirred for 20 h at 20 °C. The suspension was poured into a mixture of a saturated aqueous solution of NH_4Cl (20 mL) and benzene (20 mL), the aqueous layer was additionally extracted with benzene, and the extracts were dried and concentrated. A benzene solution of the oily residue was filtered through 20 g of silica gel, which was additionally washed with 20 : 80 → 30 : 70 EtOAc—hexane mixtures. Concentration of the filtrate gave 430 mg (59%) of triyne **8**, which was immediately used in the next step (the product is oxidized in air to give more polar products, which hamper hydrogenation). Light yellow oil, $[\alpha]_D^{25}$ +12.9° (*c* 1.11, $CHCl_3$), R_f 0.26 (system B). ^1H NMR, δ: 0.91 (dist.t, 3 H, C(20)H_3, J = 7.0 Hz); 1.26—1.40 (m, 6 H, C(17—19)H_2); 1.40, 1.53 (both s, each 3 H, CMe_2); 1.84 (quint, C(3)H_2, J = 7.2 Hz); 2.08—2.30 (m, 4 H, C(4)H_2 + C(16)H_2); 2.46 (t, 2 H, C(2)H_2, J = 7.2 Hz); 2.44—2.79 (both ddt, 2 H, C(13)H_2, AB part of ABXY$_2$ system, $\Delta\delta_{AB}$ = 0.137, $^2J_{AB}$ = 16.5 Hz, $^3J_{AX}$ = $^3J_{BX}$ = 6.9 Hz, $^5J_{AY}$ = $^5J_{BY}$ = 2.3 Hz); 3.22 (m, 2 H, C(7)H_2); 3.70 (s, 3 H, OMe); 4.23 (dd, 1 H, H(11), J = 5.4 and 6.5 Hz); 4.38 (q, 1 H, H(12), J = 6.5 Hz); 4.61 (br.s, 1 H, H(10)).

Methyl (10*S*,11*R*,12*S*)-10-hydroxy-11,12-(isopropylidenedioxy)eicosa-5(*Z*),8(*Z*),14(*Z*)-trienoate (9), methyl (10*S*,11*R*,12*S*)- (10) and methyl (10*R*,11*R*,12*S*)-10-hydroxy-11,12-(isopropylidenedioxy)eicosa-5(*Z*),8(*Z*)-dien-14-ynoate (13), and methyl (10ξ,11*R*,12*S*)-10-hydroxy-11,12-(isopropylidenedioxy)eicos-5(*Z*)-en-8,14-diynoate (14). *A.* Freshly purified triyne **8** (420 mg, 1.04 mmol) was hydrogenated at 5—8 °C and at 1 atm in a solution of 1 g of quinoline in 14 mL of benzene over 700 mg of Lindlar catalyst pre-saturated with hydrogen. The course of the process was monitored by TLC. When the absorption of hydrogen substantially slowed down, the catalyst was replaced by an equal amount of fresh catalyst and hydrogenation was continued. When the starting compound and nonaccumulating intermediate compounds had disappeared and a mostly binary mixture had formed (six replacements of the catalyst; total duration of hydrogenation 6 h), the catalyst was filtered off. Quinoline was removed by passing the filtrate through a column with 50 g of Al_2O_3; the quinoline was eluted with a 5 : 95 EtOAc—hexane mixture (150 mL) and the products were eluted by a 1 : 1 EtOAc—hexane mixture (200 mL) to give 390 mg (91%) of an orange oil, a portion of which (110 mg) was separated by HPFC. Concentration of the corresponding fractions yielded 40.5 mg (37%) of triene **9**, R_f 0.42, 38 mg (34.5%) of dienyne **10**, R_f 0.45, 12 mg (11%) of dienyne **13**, R_f 0.46, and 6.5 mg (6%) of enediyne **14**, R_f 0.39 (always system A, five developments; for the starting triyne, R_f 0.34).

Triene 9 colorless oil, $[\alpha]_D^{24}$ −9.6° (*c* 1.33, $CHCl_3$). ^1H NMR, δ: 0.86 (dist.t, 3 H, C(20)H_3, J = 6.6 Hz); 1.22—1.34 (m, 6 H, C(17—19)H_2); 1.40, 1.53 (both s, each 3 H, CMe_2); 1.72 (quint, 2 H, C(3)H_2, J = 7.3 Hz); 1.96—2.19 (m, 4 H, C(4)H_2 + C(16)H_2); 2.34—2.45 (m, 2 H, C(13)H_2); 2.35 (t, 2 H, C(2)H_2, J = 7.3 Hz); 2.81, −2.98 (both dt, 2 H, C(7)H_2, AB part of ABXY system, $\Delta\delta_{AB}$ = 0.060, $^2J_{AB}$ =

15.8 Hz, $^3J_{AX} = {}^3J_{AY} = {}^3J_{BX} = {}^3J_{BY} = 7.5$ Hz); 3.68 (s, 3 H, OMe); 4.02 (t, 1 H, H(11), $J = 6.1$ Hz); 4.13 (ddd, 1 H, H(12), $J = 5.3$, 6.1, and 8.4 Hz); 4.48 (ddd, 1 H, H(10), $J = 2.6$, 6.1, and 8.7 Hz); 5.32–5.51 (m, 5 H, H(5), H(6), H(9), H(14), H(15)); 5.57 (dt, 1 H, H(8), $J = 10.7$ and 7.5 Hz). ^{13}C NMR, δ: 14.1 (Me); 22.6, 24.7, 25.4 (3 CH_2); 26.4, 26.6 ($C\underline{Me}_2$); 27.6, 27.9, 29.3, 29.8, 31.6, 33.4 (6 CH_2); 51.6 (OMe); 65.7, 77.2, 80.7 (3 CH–O); 108.3 ($\underline{C}Me_2$); 125.1, 127.8, 128.4, 129.8, 132.6, 133.0 (3 C=C); 174.1 (C=O). MS (EI, 30 eV), *m/z* (I_{rel} (%)): 408 $[M]^+$ (0.51), 393 $[M - Me]^+$ (7.4), 375 $[M - Me - H_2O]^+$ (0.43), 333 $[M - Me - AcOH]^+$ (2.8), 315 $[M - Me - AcOH - H_2O]^+$ (1.4), 239 $[C^{1-12} - Me_2CO]^+$ (7.9), 221 $[C^{1-12} - Me_2CO - H_2O]^+$ (9.6), 211 $[C^{17-20}]^+$ (32), 197 $[C^{1-10}]^+$ (23), 189 $[C^{1-12} - Me_2CO - MeOH - H_2O]^+$ (15), 179 $[C^{1-10} - H_2O]^+$ (25), 93 (100).

Dienyne 10, colorless oil, $[\alpha]_D^{24}$ +24.7° (*c* 1.75, $CHCl_3$). ^{1}H NMR, δ: 0.89 (dist.t, 3 H, C(20)H_3, $J = 7.1$ Hz); 1.23–1.50 (m, 6 H, C(17–19)H_2); 1.39, 1.54 (both s, each 3 H, CMe_2); 1.70 (quint, 2 H, C(3)H_2, $J = 7.3$ Hz); 2.04–2.20 (m, 4 H, C(4)H_2 + C(16)H_2); 2.34 (t, 2 H, C(2)H_2, $J = 7.3$); 2.45–2.67 (2 ddt, 2 H, C(13)H_2, AB part of $ABXY_2$ system, $\Delta\delta_{AB} = 0.044$, $^2J_{AB} = 15.8$ Hz, $^5J_{AX} = {}^3J_{BX} = 6.5$ Hz, $^5J_{AY} = {}^5J_{BY} = 2.3$ Hz); 2.78–3.05 (m, 2 H, C(7)H_2); 3.75 (s, 3 H, OMe); 4.08 (dd, 1 H, H(11), $J = 4.8$ and 6.5 Hz); 4.30 (q, 1 H, H(12), $J = 6.5$ Hz); 4.70 (dt, 1 H, H(10), $J = 7.3$ and 5.1 Hz); 5.39–5.64 (m, 4 H, H(5, 6, 8, 9)). ^{13}C NMR, δ: 14.04 (Me); 18.88, 20.62, 22.29, 24.86, 25.11 (5 CH_2); 26.39, 26.69 ($O_2C\underline{Me}_2$); 27.44, 28.74, 31.21, 33.52 (4 CH_2); 51.53 (OMe); 65.44, 76.08, 80.47 (3 CH–O); 77.31, 82.53 (C≡C); 108.49 ($O_2\underline{C}Me_2$); 127.95, 129.07, 129.77, 132.19 (2 C=C); 173.96 (C=O). MS (EI, 30 eV), *m/z* (I_{rel} (%)): 406 $[M]^+$ (0.38), 391 $[M - Me]^+$ (8.7), 373 $[M - Me - H_2O]^+$ (2.5), 331 $[M - Me - AcOH]^+$ (5.0), 313 $[M - Me - AcOH - H_2O]^+$ (3.8), 239 $[C^{1-12} - Me_2CO]^+$ (16), 221 $[C^{1-12} - Me_2CO - H_2O]^+$ (12), 209 $[C^{11-20}]^+$ (49), 197 $[C^{1-10}]^+$ (25), 189 $[C^{1-12} - Me_2CO - MeOH - H_2O]^+$ (23), 179 $[C^{1-10} - H_2O]^+$ (61), 81 (100).

Dienyne 13, colorless oil. ^{1}H NMR, δ: 0.90 (dist.t, 3 H, C(20)H_3, $J = 6.0$ Hz); 1.20–1.57 (m, 6 H, C$^{17-19}H_2$); 1.35, 1.45 (both s, each 3 H, CMe_2); 1.73 (quint, 2 H, C(3)H_2, $J = 7.4$ Hz); 1.93–2.20 (m, 4 H, C(4)H_2 + C(16)H_2); 2.31 (t, 2 H, C(2)H_2, $J = 7.4$ Hz); 2.50–2.62 (m, 2 H, C(13)H_2); 2.73–3.15 (m, 2 H, C(7)H_2); 3.66 (s, 3 H, OMe); 4.05 (t, 1 H, H(11), $J = 6.9$ Hz); 4.10–4.34 (m, 1 H, H(12)); 4.56 (t, 1 H, H(10), $J = 6.9$ Hz); 5.31–5.70 (m, 4 H, H(5), H(6), H(8), H(9)).

Enediyne 14, colorless oil. ^{1}H NMR, δ: 0.92 (dist.t, 3 H, C(20)H_3, $J = 6.5$ Hz); 1.25–1.50 (m, 6 H, C$^{17-19}H_2$); 1.40, 1.52 (both s, each 3 H, CMe_2); 1.74 (quint, 2 H, C(3)H_2, $J = 7.4$ Hz); 2.02–2.21 (m, 4 H, C(4)H_2 + C(16)H_2); 2.31 (t, 2 H, C(2)H_2, $J = 7.4$ Hz); 2.48–2.77 (2 ddt, 2 H, C(13)H_2, AB part of $ABXY_2$ system, $\Delta\delta_{AB} = 0.136$, $^2J_{AB} = 16.5$ Hz, $^5J_{AX} = {}^3J_{BX} = 6.4$ Hz, $^5J_{AY} = {}^5J_{BY} = 2.4$ Hz); 2.95–3.04 (m, 2 H, C(7)H_2); 3.68 (s, 3 H, OMe); 4.18 (t, 1 H, H(11), $J = 6.4$ Hz); 4.32 (q, 1 H, H(12), $J = 6.4$ Hz); 4.60 (br.s, 1 H, H(10)); 5.39–5.56 (m, 2 H, H(5), H(6)).

B. Hydrogenation of dienyne **10** (20 mg) under the conditions described above (without replacement of the catalyst; 2 h) gave 17.5 mg (87%) of triene **9** identical to the sample described above.

Methyl (10*S*,11*S*,12*S*)-10,11,12-trihydroxyeicosa-5(*Z*),8(*Z*)-dien-14-ynoate (12). A solution of dienyne acetonide **10** (25.5 mg) in 1 mL of 80% aqueous AcOH was kept for 7 h at 55 °C until the starting compound disappeared (TLC monitoring). The solution was concentrated *in vacuo* to dryness (20 °C, 1 Torr); the traces of AcOH were removed by co-evaporation with benzene. This gave 22.9 mg (99%) of triol **12** as a colorless oil, $[\alpha]_D^{23}$ +21.7° (*c* 1.12, $CHCl_3$), R_f 0.16 (system B; starting acetonide **10** R_f 0.61). ^{1}H NMR, δ: 0.89 (t, 3 H, C(20)H_3, $J = 6.5$ Hz); 1.23–1.57 (m, 6 H, C$^{17-19}H_2$); 1.69 (quint, 2 H, C(3)H_2, $J = 7.5$ Hz); 1.99–2.24 (m, 4 H, C(4)H_2 + C(16)H_2); 2.35 (t, 2 H, C(2)H_2, $J = 7.5$ Hz); 2.49–2.60 (m, 2 H, C(13)H_2); 2.84 (dt, 1 H, C(7)$\underline{H}_A H_B$, $J = 15.7$ and 5.7 Hz); 2.97 (dt, 1 H, C(7)$H_A\underline{H}_B$, $J = 15.7$ and 5.9 Hz); 3.51–3.60 (m, 1 H, H(11)); 3.69 (s, 3 H, OMe); 3.79–3.92 (m, 1 H, H(12)); 4.65–4.80 (m, 1 H, H(10)); 5.34–5.73 (m, 4 H, H(5), H(6), H(8), H(9)).

Methyl (10*S*,11*S*,12*S*)-10,11,12-trihydroxyeicosa-5(*Z*),8(*Z*),14(*Z*)-trienoate (trioxilin (10*S*,11*S*,12*S*)-B_3) (11) was prepared from 26 mg of triene acetonide **9** by the method described just above, yield 21 mg (91%). Preparative TLC afforded triol **11** as a colorless oil, $[\alpha]_D^{24}$ +9.5° (*c* 0.76, $CHCl_3$), +14.8° (*c* 0.79, acetone) (lit. data for the (10*R*,11*R*,12*R*)-enantiomer: $[\alpha]_D^{20}$ −16.1° (*c* 3.2, $CHCl_3$)[11]; $[\alpha]_D^{22}$ −16.4° (*c* 3.5, acetone)[8]), R_f 0.12 (system B; starting acetonide **9** R_f 0.68). ^{1}H NMR, δ: 0.89 (t, 3 H, C(20)H_3, $J = 6.7$ Hz); 1.19–1.45 (m, 6 H, C$^{17-19}H_2$); 1.69 (quint, 2 H, C(3)H_2, $J = 7.2$ Hz); 1.96–2.20 (m, 4 H, C(4)H_2 + C(16)H_2); 2.25–2.43 (m, 2 H, C(13)H_2); 2.33 (t, 2 H, C(2)H_2, $J = 7.2$ Hz); 2.80 (dt, 1 H, C(7)$\underline{H}_A H_B$, $J = 15.8$ and 5.1 Hz); 2.96 (dt, 1 H, C(7)$H_A\underline{H}_B$, $J = 15.8$ and 4.7 Hz); 3.48 (t, 1 H, H(11), $J = 4.3$ Hz); 3.68 (s, 3 H, OMe); 3.74 (dt, 1 H, H(12), $J = 8.0$ and 5.1 Hz); 4.70 (dd, 1 H, H(10), $J = 4.3$ and 7.1 Hz); 5.31–5.50 (m, 3 H, H(5), H(6), H(14)); 5.52–5.69 (m, 3 H, H(8), H(9), H(15)).

This work was financially supported by the Russian Foundation for Basic Research (Project Nos. 96-03-34439 and 98-03-32996) and by the Noncommercial Partnership program "ASGL — Development of New Biologically Active Compounds for Medical Purposes."

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Received November 17, 1999