Chemistry of Natural Compounds and Bioorganic Chemistry

Synthetic research on hepoxilins. 7.* Divergent total synthesis of hepoxilins and related eicosanoids

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A new synthetic strategy for hydroxy-epoxy eicosanoids formed through the lipoxygenase pathway is developed. It makes use of a single synthon of the central functionalized fragment of the target molecules, namely racemic (*E*)-$ClCH_2C{\equiv}CCHOHCH{=}CHCH_2OBz$. Elongation of the carbon chain of the synthon by successive condensations at both ends altenatively with hept-1-yne and hex-5-ynoic acid followed by enantioselective double bond epoxidation and partial hydrogenation of the triple bonds resulted in the syntheses of hepoxilins B_3, their potential 8-lipoxygenase analogs, or their enantiomers, depending on the sequence of carbon chain elongations and the chirality of the epoxidation controller used.

Key words: hepoxilins, total synthesis, analogs; eicosanoids, total synthesis; enantioselective epoxidation of olefin; kinetic resolution of racemates by enantioselective epoxidation.

Hepoxilins (Hx) and trioxilins, the endogenic metabolites of arachidonic acid, are produced in several human and animal organs through the 12-lipoxygenase metabolism pathway.[2] It was found that hepoxilins are able to control calcium transport, insulin secretion,[3,4] and other biological processes. Therefore, in recent years, chemical synthesis of hepoxilins, trioxilins, and their modified analogs has aroused increased interest (see a review[5]).

According to the biogenesis, hepoxilins contain functional groups in positions 8 or 10, 11, and 12 of the twenty-carbon molecule. In the case of hepoxilins B_3 (HxB_3), these are a hydroxyl group and an epoxide group. Unsaturated hydroxy epoxy acids of this type, incorporating a functionalized (and chiral) C(7)—C(13) fragment of the HxB_3 molecule, can be formed and are actually formed from arachidonic acid and other polyunsaturated fatty acids under the action of not only 12-lipoxygenase but also other lipoxygenases;[6] in addition, they are intermediate compounds in the syntheses of other types of hepoxilins[7–9] and various eicosanoids

* For Part 6, see Ref. 1.

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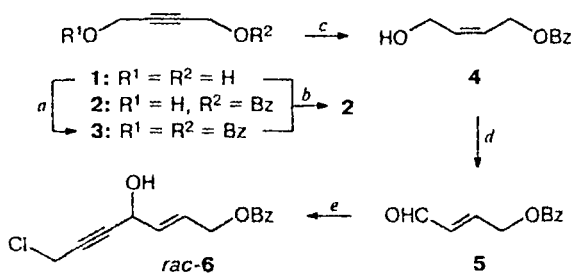
(trioxilins,[2] leukotrienes,[10,11] lipotrienes[12]). Although these metabolites differ only in the structure of the side chains attached to an identical chiral central fragment carrying functional groups, these eicosanoids are most commonly synthesized using an independent scheme in each particular case.[5]

The purpose of the present study is to develop a divergent scheme for the synthesis of eicosanoids, *i.e.*, a scheme based on a synthon that would serve as a common precursor for the central part of molecules of lipoxygenase eiconasoids, and to apply this scheme to the synthesis of eicosanoids of several types.

Polyfunctional compound *rac*-**6** (Scheme 1), in which each functional group is meant for a particular purpose, was deemed to be an appropriate synthon. The (*E*)-double bond serves for the introduction of a *trans*-epoxide group, while the triple bond is the precursor of a (*Z*)-double bond. Simultaneously, these multiple bonds could activate the differentiated terminal functions, which are meant for joining the synthon molecule consecutively with two side fragments, whose nature is determined by the structure of the eicosanoid being synthesized.

Scheme 1



Reagents and conditions: *a*. BzCl, Py, 20 °C, 14 h; *b*. K_2CO_3, 70 °C, 30 min; *c*. H_2, Pd—Pb/$CaCO_3$, quinoline, C_6H_6, 24 °C, 12 h; *d*. PDC, MS 3 Å, AcOH, CH_2Cl_2, 25 °C, 30 min; *e*. $HC{\equiv}CCH_2Cl$, Bu^nLi, Et_2O, −78 °C, 30 min.

The synthon *rac*-**6** was prepared in a straightforward manner. The starting compound, the monobenzoate of but-2-yn-1,4-diol **1** (**2**), is conveniently synthesized not only by the monobenzoylation of diol **1** described previously,[13] but also by the exchange* between diol **1** and dibenzoate **3** formed as a side product in the synthesis of monobenzoate **2**. Partial hydrogenation over Lindlar catalyst affords the corresponding (*Z*)-olefin **4**, whose hydroxyl group is oxidized by pyridinium dichromate (PDC) giving relatively unstable (*E*)-unsaturated aldehyde **5**. The intermediate (*Z*)-aldehyde, which can be detected by TLC, completely isomerizes into **5** during the oxidation (for analogies, see Refs. 14, 15). Condensation of aldehyde **5** with an excess of the Li derivative of propargyl chloride[16] smoothly gives the moderately stable synthon *rac*-**6** in an overall yield of 88% (based on benzoate **2**).

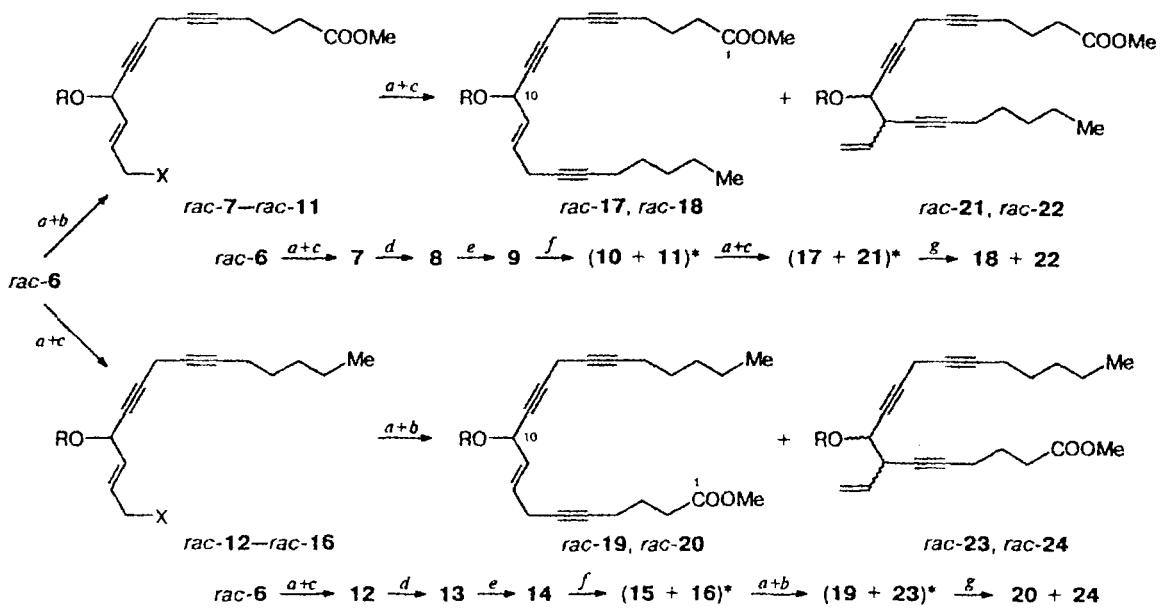
One of the termini of the *rac*-**6** molecule (the propargyl chloride group) is completely ready to be used for carbon chain elongation, as shown in Scheme 2. Condensation with methyl hex-5-ynoate under the conditions described for the chemoselective synthesis of skipped diacetylenes[17] gives the selectively protected diol *rac*-**7**. Successive tetrahydropyranylation and debenzoylation afford allylic alcohol *rac*-**9**. Tosylation of this alcohol with TsCl is performed optimally in the presence of a limited amount of collidine in order to prevent loss of the resulting tosylate *rac*-**10** due to secondary reaction with the base. However, even under these (and any other) conditions, a substantial quantity of the corresponding allylic chloride *rac*-**11** is formed together with *rac*-**10**. Fortunately, there is no need to separate this mixture, because both its components behave in the same way in the next step, in which the chain is extended by a second acetylenic component, by hept-1-yne in this particular case. The reaction is carried out under the same conditions[17] as the first extension. However, in this condensation the methylene components, *rac*-**10** and *rac*-**11**, are allylic; consequently, the linear product *rac*-**17** is contaminated by 10—15% of branched product *rac*-**21**, as has been observed previously in similar types of condensation.[18] Since each of products *rac*-**17** and *rac*-**21** (as well as their precursors *rac*-**8**—*rac*-**11**) is a mixture of epimers at the asymmetric center of the THP residue, this mixture can be more easily separated after the removal of the THP protection by chromatography of the simpler binary mixture of alcohols *rac*-**18** and *rac*-**22**. The twenty-carbon alcohol *rac*-**18** prepared in 59% yield (from synthon *rac*-**6**) can be regarded as an advanced precursor of 12-lipoxygenase eicosanoids, hepoxilins and trioxilins, because it contains in appropriate positions of the molecule only one double bond, which makes it possible to introduce selectively additional oxygen functions to positions 11 and 12, and also three triple bonds, which can be converted into (*Z*)-double bonds.

By the same sequence of reactions but with the two acetylenic components added in the opposite order, synthon *rac*-**6** was converted into alcohol *rac*-**20** having a similar structure; however, for the above-mentioned reasons, this product should be regarded as a precursor of 8-lipoxygenase eicosanoids belonging to a poorly studied class of metabolites of arachidonic acid.[3]

Enetriyne alcohols *rac*-**18** and *rac*-**20** are unstable compounds readily oxidized even by atmospheric oxygen. This oxidation involves not only triple bonds, which yield numerous polar products, but also the hydroxyl group resulting in the formation of the corresponding less polar 10-ketones. The structure of ketone **25**, formed

* The method was developed by T. A. Manukina (Institute of Experimental Endocrinology, National Endocrinology Scientific Center, Russian Academy of Medical Sciences).

Scheme 2



	7, 12	8, 13	9, 14	10, 15	11, 16	17, 19, 21, 23	18, 20, 22, 24
R	H	THP	THP	THP	THP	THP	H
X	OBz	OBz	OH	OTs	Cl	—	—

Reagents and conditions: *a*. K_2CO_3, CuI, NaI, DMF, 25 °C, 7 h; *b*. HC≡C$(CH_2)_3$COOMe; *c*. *n*-C_5H_{11}C≡CH; *d*. DHP, PPTS, CH_2Cl_2, 25 °C, 3 h; *e*. MeOH, K_2CO_3, 26 °C, 1 h; *f*. TsCl, 2,4,6-collidine, DMAP, $CHCl_3$, 25 °C, 24 h; *g*. EtOH, PPTS, 60 °C, 1.5 h.

from alcohol *rac*-**18**, can be easily derived from the data of UV and ^{1}H NMR spectra (see Experimental). The same ketone is formed as the major product in the attempted epoxidation of the double bond in alcohol *rac*-**18** by *m*-chloroperbenzoic acid.

The enantioselective epoxidation of alcohol *rac*-**18**, carried out using the Sharpless method with *L*-(+)-DET as the asymmetrizing reagent (further referred to as chiral controller) under conditions of kinetic resolution (up to a ~50% conversion), follows a normal pathway (Scheme 3) and yields a mixture consisting of chiral epoxy alcohol (10*S*,11*S*,12*S*)-**26** (44%) contaminated with epimer (10*R*,11*S*,12*S*)-**26** (8%), and the more slowly reacting enantiomer of the initial alcohol (10*S*)-**18** (35%).** Epoxy alcohols **26** are hexadehydro-analogs of HxB_3 **27** and have been previously converted into the latter compounds by partial Lindlar hydrogenation.[19]

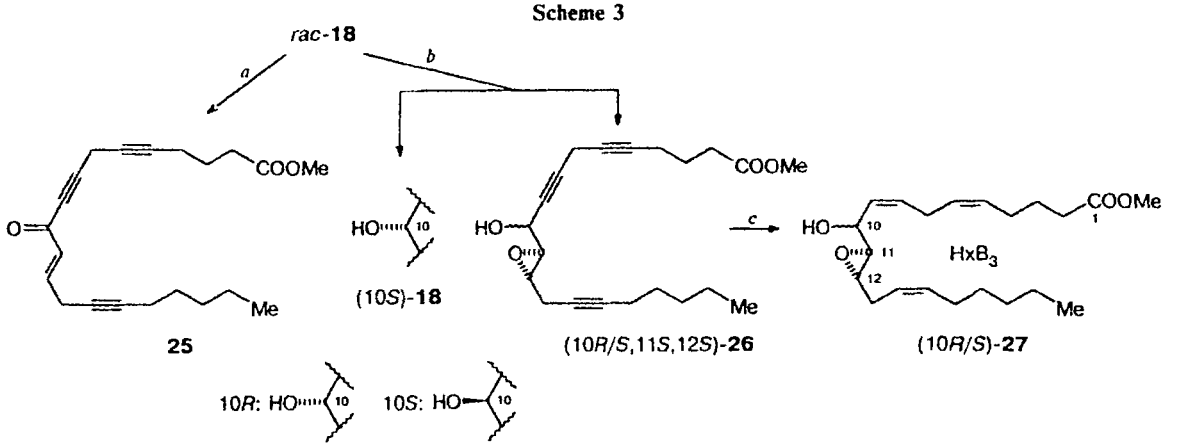
Hydrogenation of the mixture of epoxy alcohols (10*R*/*S*)-**26** according to this procedure gave (after chromatographic separation) the epimeric methyl esters of HxB_3: the major isomer (10*S*)-**27**,* $[\alpha]_D^{25}$ +60.1°, and the minor isomer (10*R*)-**27**, $[\alpha]_D^{25}$ −51.3°. Comparison of the optical rotation values given here with the published data[19] points to a high (>95%) enantiomeric excess (*ee*) in the major epimer (10*S*)-**27** and to a moderate excess (*ee* 82%) in the minor epimer (10*R*)-**27**. This finding will be discussed later. Determination of the *ee* in the recovered enantiomer of the starting (in relation to the epoxidation) alcohol (10*S*)-**18**, $[\alpha]_D^{25}$ +4.9°, is difficult because of its high lability and the absence of relevant published data. Nevertheless, the yields and enantiomeric purities of products **26** and **27**, produced from the reactive enantiomer (10*R*)-**18**, indicate that the degree of its conversion is no less than 85%, *i.e.*, that the recovered alcohol (10*S*)-**18** possesses a substantial enantiomeric excess. Thus, it could be an excellent starting material, better than *rac*-**18**, for preparation of "unnatural" hepoxilin enantiomers by a similar route (but using

* The product mixture was used in the next step without separation.

** Despite the identical stereochemical designation demanded by the IUPAC *R*,*S*-nomenclature, the C(10) asymmetric centers in alcohols (10*S*)-**18** and (10*S*,11*S*,12*S*)-**26** have the opposite absolute configurations (see Scheme 3). The same is true for the pairs of alcohols (10*R*)-**20** and (8*R*,9*R*,10*R*)-**28**, (10*S*)-**20** and (8*S*,9*S*,10*S*)-**28** (Scheme 4 and Table 1).

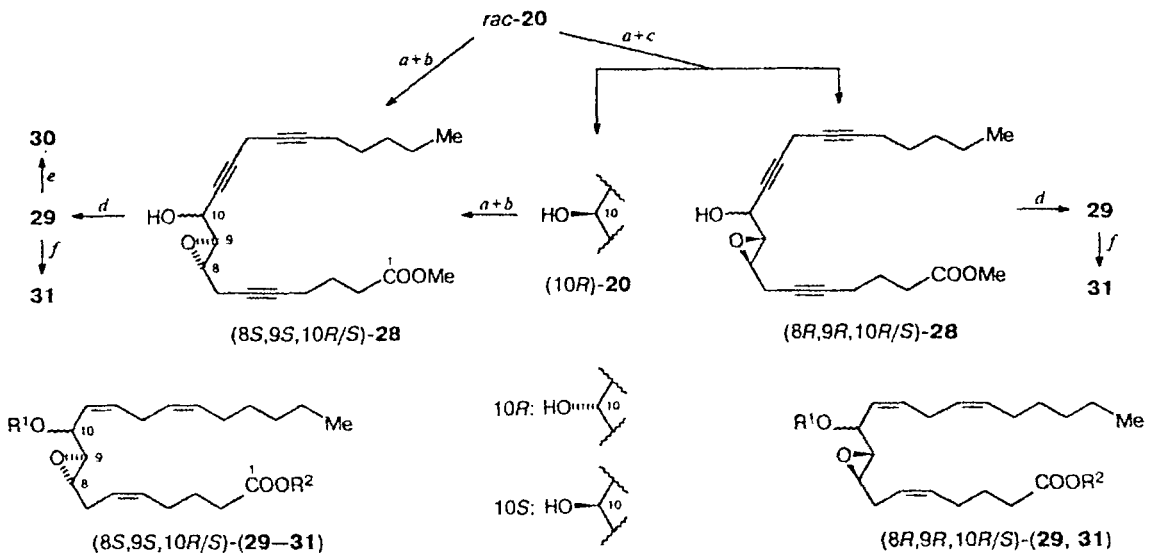
* In our previous publication,[19] we erroneously reported the (11*R*,12*S*)-configuration, instead of the correct (11*S*,12*S*) configuration, for hepoxilins B_3. We are grateful to M. Hamberg (Sweden), who attracted our attention to this mistake.

Scheme 3



Reagents and conditions: *a*. atmospheric O_2, C_6H_6, −20 °C, 4 months; *b*. Bu^{t}OOH, Ti(OPr^i)$_4$, *L*-(+)-DET, MS 4 Å, CH_2Cl_2, −20 °C, 2 h; *c*. H_2, Pd—Pb/$CaCO_3$, quinoline, C_6H_6, 0—10 °C.

Scheme 4



R^1 = H, R^2 = Me (**29**); R^1 = R^2 = H (**30**); R^1 = (*R*)-COCH(OMe)Ph, R^2 = Me (**31**)

Reagents and conditions: *a*. Bu^{t}OOH, Ti(OPr^i)$_4$, MS 3 Å, CH_2Cl_2, −20 °C, 2 h; *b*. *L*-(+)-DIPT; *c*. *D*-(−)-DIPT; *d*. H_2, Pd—Pb/$CaCO_3$, quinoline, C_6H_6, 0—10 °C; *e*. LiOH, Bu^{t}OH—H_2O, 25 °C, 1 h; *f*. (*R*)-PhCH(OMe)COOH, DCC, DMAP, CH_2Cl_2, 20 °C, 18 h.

D-(−)-DET). In addition, in this case both enantiomers of the initial racemic alcohol can be used in the synthesis. The synthesis of eicosanoids **29** and **30** described below was carried out using this scheme.

The same route, *viz.*, Sharpless epoxidation (using *L*-(+)-DIPT) and Lindlar hydrogenation, was used to convert the triacetylenic precursor *rac*-**20** of 8-lipoxygenase eicosanoids into two epimeric epoxy alcohols (8*S*,9*S*,10*R*/*S*)-**29** (Scheme 4). These compounds are regioisomers of the methyl esters HxB_3 (10*R*/*S*)-**27**, and the corresponding acids **30** are putative metabolites of arachidonic acid formed according to the 8-lipoxygenase pathway. Recently, the lactone of a stereoisomer of acid **30** has actually been found in the *Sarcodiotheca gaudichaudii* algae.[20] To study the biological properties of these eicosanoids, enantiomers (8*R*,9*R*,10*R*/*S*)-**29** were prepared in a similar way from the same initial *rac*-**20** but using *D*-(−)-DIPT.*

* Preliminary assays demonstrated the absence of insulin-secreting activity in the hepoxilin analog (8*S*,9*S*,10*S*)-**29** and the inhibitory (by 21—27%) activity of the hexadehydro-analog (8*S*,9*S*,10*S*)-**28**. We are grateful to Prof. V. P. Fedotov (Institute of Experimental Endocrinology of the National Endocrinology Scientific Center, Russian Academy of Medical Sciences) for informing us of the results of his research.

Table 1. Results of enantioselective epoxidation of enetriyne alcohol *rac*-**20** and subsequent hydrogenation of the resulting epoxides (reaction conditions are given in Experimental)

Epoxidation				Hydrogenation			
Chiral controller	Products	Yield[a] (%)	$[\alpha]_D^{25}$ (*c*)[b]	Products	Overall yield[a] (%)	$[\alpha]_D^{25}$ (*c*)[b]	*ee* (%)
L-(+)-DIPT	(10*S*)-**20**	40	+5.9° (2.15)				
	(8*S*,9*S*,10*S*)-**28**	41.5	−7.7° (2.00)	(8*S*,9*S*,10*S*)-**29**	31.0	+62.7° (1.32)	83
	(8*S*,9*S*,10*R*)-**28**	4.5		(8*S*,9*S*,10*R*)-**29**	1.53	−23.6° (0.52)	37
D-(−)-DIPT	(10*R*)-**20**	39	−2.9° (1.25)				
	(8*R*,9*R*,10*R*)-**28**	30.5	+7.7° (1.11)	(8*R*,9*R*,10*R*)-**29**	22.6	−62.2° (1.67)[c]	78
	(8*R*,9*R*,10*S*)-**28**	3.5		(8*R*,9*R*,10*S*)-**29**	2.59	+5.4° (0.86)	8.6
1) *D*-(−)-DIPT	(10*R*)-**20**[d]	57	−4.5° (1.62)				
	(8*R*,9*R*,10*R*)-**28**[e]	30	+4.8° (1.20)	(8*R*,9*R*,10*R*)-**29**	22.2	−66.1° (1.27)	93
2) *L*-(+)-DIPT	(10*S*)-**20**	19.4[f]	+3.5° (2.05)				
	(8*S*,9*S*,10*S*)-**28**[e]	30.2[f]	−10.1° (2.20)	(8*S*,9*S*,10*S*)-**29**	22.3	+65.6° (1.63)	94

[a] The yields are based on the amount of enetriyne alcohol *rac*-**20** used. The yields based on the reacting entantiomers of the initial racemic alcohol (*i.e.*, in relation to the theoretical yield) are twice as high.
[b] The optical rotations were measured for solutions in $CHCl_3$.
[c] $[\alpha]_D^{25}$ −27.5° (*c* 1.17, acetone). A similar influence of the solvent on the optical rotation value of *arabino*-isomers of HxB_3 **27** has already been noted in the literature (*cf.* Refs. 9, 19 and Ref. 21).
[d] Used as the starting compound in the second step of the process.
[e] Contains 10% of 10-epimers.
[f] The yields are based on alcohol *rac*-**20** used at the first step.

The enantiomeric purities of the resulting compounds were determined by HPLC of 10-*O*-esters **31** with (*R*)-(−)-α-methoxyphenylacetic acid,[22] which provides complete separation of the diastereomeric esters of the enantiomers. It was shown in separate experiments that the synthesis of esters **31** under standard conditions is not accompanied by the racemization of the acid residue, as warned by the authors of the method.[22] An attempt to use esters with non-racemizing (*R*)-MTPA (Mosher acid) in a similar way was unsuccessful (the experimental results are not presented). This method demonstrated that the major *arabino*-isomers (8*S*,9*S*,10*S*)-**29** and (8*R*,9*R*,10*R*)-**29** synthesized are characterized by a moderate enantiomeric excess, amounting to 78—83% (Table 1), despite the fact that the reaction was conducted with DIPT and an isooctane solution of Bu^tO_2H, *i.e.*, reagents that ensure the highest enatioselectivity of epoxidation.[23] The absolute configurations and *ee* values of the minor *xylo*-epimers (8*S*,9*S*,10*R*)-**29** and (8*R*,9*R*,10*S*)-**29**, equal to 9—37%, were found from a comparison of their optical rotation values with those published for compound (10*R*)-**27**,[19] because the structures of the molecules of HxB_3 **27** and their regioisomers **29** are very close. The corresponding stereoisomers incorporate identical 17-carbon C(2)—C(18) fragments, and the differences between these molecules start only at a distance of seven (or more) carbon—carbon bonds from the asymmetric centers. Therefore, as was to be expected, compounds (10*S*)-**27** and (8*S*,9*S*,10*S*)-**29**, for example, exhibit virtually identical ^1H NMR spectra and TLC and GLC mobilities and can hardly be distinguished by HPLC; the values of optical rotation of these compounds are also very close (see Experimental). The same should be expected for other similar pairs.

Among the results obtained, two findings deserve special attention. First, the differences between the *ee* values in the epoxidation of substrates *rac*-**18** and *rac*-**20** are apparently due to the experimental difficulties in the monitoring of the degree of conversion of the substrate during the kinetic resolution by enantioselective epoxidation of small amounts of substrates rather than due to special features of the substrate structure. A mathematical model of the process similar to that used in a previous study[24] indicates that the *ee* value of the epoxides being formed varies only slightly up to a 40% degree of conversion and much more significantly in the 40—60% range, *i.e.*, exactly in the range in which the reaction is quenched. Thus, the inevitable slight variation of the moment when the reaction is stopped can have a noticeable effect on the resulting *ee* values. Second, the configuration of the C(10) center in the minor *xylo*-isomers implies that they are mostly formed from the slowly reacting enantiomers of the substrates, which are accumulated in the reaction mixture. The slow reaction yielding the *xylo*-isomers can occur both with a chiral controller (tartrate) and without it;[24] the relative reaction rates of the substrate enantiomers in these two processes are different. The experimental variations of the ratio of the two processes should result in

even more poorly reproducible *ee* values in the resulting *xylo*-isomers, which is what we actually observe.

To achieve a higher and a more reproducible enantiomeric purity of the products, we used the strategy of two-step enantioselective epoxidation with kinetic resolution. The first step was carried out until the degree of conversion of the initial substrate *rac*-**20** was 35—40%. Since this degree of conversion is relatively low, an enantiomeric excess close to the highest possible (with allowance for the reagent enantioselectivity) should be retained in the resulting (with *D*-(−)-DIPT) epoxide (8*R*,9*R*,10*R*)-**28**, although the yield of the product decreases. The recovered (10*R*)-**20**, characterized by an *ee* of 40—50% according to calculations, served as the starting compound for the second step. This time, the reaction was carried out with the enantiomeric tartrate *L*-(+)-DIPT. Since the substrate has been enriched in the rapidly reacting enantiomer, the reaction can be conducted up to a degree of conversion of 60—70% without risking a decrease in the enantiomeric purity of the product (8*S*,9*S*,10*S*)-**28**. The real criterion for quenching the reaction at each of these steps is noticeable retardation of the conversion of the starting compound. It is clear that the order in which the enantiomers of the chiral controller are used is insignificant.

The results of this two-step process and subsequent hydrogenation of the resulting epoxides **28** are presented in Table 1. It can be seen from the table that this strategy actually does increase the *ee* for both enantiomeric epoxides **28** up to acceptable values of 93—94%. Moreover, each enantiomer was obtained in 22% yield (based on the racemic substrate, which makes 44% of the theoretical), so that the overall yield of the products is higher than the yields obtained in one-step processes. This strategy can also be used in other enantioselective reactions and is especially advantageous when (as in our work) both enantiomers of the product with high enantiomeric purities are required.

The results presented above demonstrate the advantages of using synthon *rac*-**6**, which is a common precursor for the central parts of the molecules, in the total synthesis of lipoxygenase eicosanoids. These advantages include the possibility of obtaining regioisomeric eicosanoids (regiodivergence) and both enantiomers of these eicosanoids (enantiodivergence) from the single synthon. Obviously, this synthon can also be used to synthesize other types of eicosanoids as well as eicosanoids with modified termini of molecules, analogs and metabolites.

Experimental

Melting points were determined using a Koffler hot-stage apparatus (Boetius). The optical rotation values were measured on a Polamat A polarimeter using a 1 dm cell and calculated, as recommended by the manufacturer, according to the formula $[\alpha]_D = 1.354 \cdot [\alpha]_{578} - 0.354 \cdot [\alpha]_{546}$. UV spectra were recorded in EtOH on a Unicam SP 800 spectrophotometer. IR spectra were measured on a Specord 75 IR instrument in CCl_4 solutions or in pellets with KBr for solids. ^{1}H NMR spectra were recorded in $CDCl_3$ on Tesla BS-587A (80 MHz) and Bruker WH-360 (360 MHz) instruments using $SiMe_4$ as the internal standard. The signals of the OH groups were identified by the exchange with D_2O. The signal multiplicities presented are based on the experimentally observed splitting. MS (EI, 22.5 eV) were obtained on an LKB-2091 GC/MS spectrometer with direct insertion into the ion source at the indicated rod temperatures. GLC analysis was performed on a Chrom 5 chromatograph with a fused silica capillary column (0.2 mm×50 m) with the OV-1 liquid phase at 264 °C using helium as the carrier gas (45 cm s^{-1}). Prior to the GLC analysis, hydroxyl-containing compounds were converted into Bu^tMe_2Si ethers by treating 0.3—0.5 mg of the sample with a solution of 1 mmol of Bu^tMe_2SiCl and 2 mmol of imidazole in 1 mL of DMF for 30 min at 65 °C. Analytical HPLC was performed on a Waters Millipore chromatograph with a 200×4 mm column (Silasorb SPH 300, 6 μm) at eluent flow rate of 2 mL min^{-1}, and with an UV detector operating at *indicated wavelengths.*

Analytical TLC was carried out on Silufol UV 254 plates, and preparative TLC was performed on Whatman plates (1 mm-thick sorbent layer) using the same solvent systems: hexane—EtOAc (6 : 4) (A), hexane—EtOAc (4 : 1) (B), CH_2Cl_2—hexane—Me_2CO (42 : 6 : 2) (C) (exceptions are indicated). The substances were detected by spraying the plates with a 5% EtOH solution of phosphomolybdic acid and subsequent heating. Preparative column chromatography was accomplished by high performance flash chromatography[25] (HPFC) on 18×3.5 or 16×2 cm columns (efficiency 2000 theoretical plates) with silica gel (SiO_2) Kieselgel H (Fluka).

The usual workup included washing of the extracts with brine and drying with $MgSO_4$, evaporation of the solvent *in vacuo* on a rotary evaporator at 40 °C, and drying of the residue in a vacuum of 0.05 Torr to a constant weight.

Commercial samples (Fluka) of the Lindlar catalyst (5% Pd—Pb/$CaCO_3$), molecular sieves (MS) 3 Å and 4 Å, PDC, a solution of Bu^nLi in hexane, quinoline, 2,4,6-collidine, propargyl chloride, TsOH, DHP, DMAP, PPTS, DCC, "ChiraSelect" (*R*)-(−)-α-methoxyphenylacetic acid (*ee* 99.5%), *L*-(+)-DET, *L*-(+)- and *D*-(−)-DIPT, and $Ti(OPr^i)_4$ were used. Solutions of Bu^tO_2H (Aldrich) in CH_2Cl_2 and isooctane were prepared according to previously described procedures[23] and titrated prior to use. Methyl hex-5-ynoate was prepared by methylation of the acid synthesized by a known procedure[26] with an ethereal solution of CH_2N_2. Dibenzoate **3**, m.p. 75—76 °C,[13] was prepared by standard exhaustive benzoylation of but-2-yne-1,4-diol **1**.

Prior to use, molecular sieves were finely powdered and activated by calcination at 200 °C; anhydrous finely powdered K_2CO_3, CuI, and NaI were dried at 60 °C in a vacuum of 0.05 Torr. All the solvents for the reactions were dried by standard procedures, and the reactions were carried out in an atmosphere of dry argon.

4-(Benzoyloxy)but-2-yn-1-ol (2).* *A.* A mixture of diol **1** (12.6 g, 0.146 mol), dibenzoate **3** (43 g, 0.146 mol), and anhydrous K_2CO_3 (400 mg, 2.89 mmol) was stirred for 30 min at 70 °C, and then the melt was cooled, dissolved in 100 mL of benzene, and washed with water (3×30 mL). The dried solution was concentrated, and the residual semicrystalline material was distilled ($6 \cdot 10^{-2}$ Torr) in a Kugelrohr apparatus at 125 °C in order to remove the more volatile component. This gave 23 g (53% recovery) of dibenzoate **3** (pot residue), which is recycled, and 23.2 g (42%, or 90% based on the consumed dibenzoate) of monobenzoate **2** (distillate) as white crystals, m.p. 31.5—32.5 °C

* The experiment was carried out by T. A. Manukina.

(Et_2O—hexane), R_f 0.36 (system A) (*cf.* lit:[13] oil). Found (%): C, 69.85; H, 5.23. $C_{11}H_{10}O_3$. Calculated (%): C, 69.46; H, 5.30. UV, λ_{max}/nm: 230 (log ε 4.19), 268 (inflection) (log ε 2.92), 274 (log ε 2.98), 280.5 (log ε 2.90). IR, ν/cm^{-1}: 3626 and 3510 (OH), 1733 (C=O), 1266 and 1103 (C—O), 715 (Ph). ^{1}H NMR, δ: 2.93 (br.s, 1 H, OH); 4.25 (m, 2 H, C(1)H_2); 4.88 (t, 2 H, C(4)H_2, J = 1.5 Hz); 7.42—7.58 (m, 3 H, 2 *m*-H + *p*-H); 7.92—8.18 (m, 2 H, 2 *o*-H).

B. Direct monobenzoylation of but-2-yne-1,4-diol **1** with 1 equiv. of BzCl according to the modified Schotten—Baumann method[27] gave 35% monobenzoate **2** and 22% dibenzoate **3**, while the reaction in pyridine[13] gave 49% monobenzoate **2** and 22% dibenzoate **3**.

4-(Benzoyloxy)but-2(*Z*)-en-1-ol (4). A solution of monobenzoate **2** (1.2 g, 5.40 mmol) in 40 mL of benzene containing quinoline (50 μL, 0.5 mmol) was hydrogenated with 100 mg of the Lindlar catalyst until hydrogen absorption ceased (24 °C, 1 atm, 12 h). The catalyst was filtered off and washed with benzene and EtOAc. The filtrate was washed with 5% HCl and then with water to neutral reaction. The usual workup gave 1.08 g (90%) of (*Z*)-hydroxy benzoate **4** as a colorless oil, R_f 0.30 (system A, double elution). UV, λ_{max}/nm: 229.5 (log ε 4.20), 267 (inflection) (log ε 2.92), 273 (log ε 2.98), 280 (log ε 2.89). IR, ν/cm^{-1}: 3633 and 3500 (OH), 1733 (C=O), 1270 and 1110 (C—O), 713 (Ph). ^{1}H NMR, δ: 3.75 (s, 1 H, OH); 4.32 (d, 2 H, C(1)H_2, J = 5.5 Hz); 4.89 (d, 2 H, C(4)H_2, J = 5.1 Hz); 5.66—5.96 (m, 2 H, CH=CH); 7.28—7.51 (m, 3 H, 2 *m*-H + *p*-H); 7.90—8.14 (m, 2 H, 2 *o*-H).

4-(Benzoyloxy)but-2(*E*)-enal (5). Acetic acid (0.6 mL, 11.6 mmol) was added over a period of 2 min at 15 °C to a stirred mixture of hydroxy benzoate **4** (2.6 g, 11.6 mmol), finely powdered PDC (3.8 g, 10.12 mmol), and MS 3 Å (5 g) in 85 mL of CH_2Cl_2. The mixture was stirred for 30 min at 25 °C with TLC monitoring (system A) of the formation and gradual disappearance of the corresponding (*Z*)-aldehyde with R_f 0.42 and the accumulation of (*E*)-aldehyde **5** with R_f 0.36. Celite (5 g) and Pr^{i}OH (0.5 mL) were added to the suspension, and after 15 min the mixture was filtered through 30 g of SiO_2, which was additionally washed with EtOAc. The eluate was concentrated *in vacuo* to 25—30 mL and again filtered through 10 g of SiO_2. Evaporation *in vacuo* (1 Torr) at 25 °C gave 2.56 g (100%) of aldehyde **5** as an unstable light-yellow oil, which tarred on attempted distillation. IR, ν/cm^{-1}: 2826 and 2743 (CHO), 1733 (C=O), 1703 (C=C), 1120 (C—O), 715 (Ph). ^{1}H NMR, δ: 5.06 (dd, 2 H, C(4)H_2, J = 4.1 and 1.8 Hz); 6.33 (ddt, 1 H, H(2), J = 15.5, 7.5, and 1.8 Hz); 6.92 (dt, 1 H, H(3), J = 15.5 and 4.1 Hz); 7.29—7.66 (m, 3 H, 2 *m*-H + *p*-H); 7.92—8.19 (m, 2 H, 2 *o*-H); 9.62 (d, 1 H, CHO, J = 7.5 Hz).

***rac*-1-Benzoyloxy-7-chlorohept-2(*E*)-en-5-yn-4-ol (*rac*-6).** A 1.52 *M* solution of Bu^{n}Li (23 mL, 34.96 mmol) in hexane was added at −78 °C over a period of 10 min to a stirred solution of propargyl chloride (2.72 mL, 37.73 mmol) in 30 mL of Et_2O, and 2 min later, a solution of aldehyde **5** (2.05 g, 10.78 mmol) in 10 mL of Et_2O was added. After 30 min, the reaction mixture was poured in 50 mL of a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The usual workup gave 2.80 g (98%) of chloride *rac*-**6** as a colorless oil, R_f 0.30 (system A). UV, λ_{max}/nm: 229 (log ε 4.21), 268 (inflection) (log ε 2.94), 273 (log ε 2.98), 280 (log ε 2.90). IR, ν/cm^{-1}: 3629 and 3470 (OH), 2230 (C≡C), 1725 (C=O), 1273 and 1113 (C—O), 709 (Ph). ^{1}H NMR, δ: 4.17 (d, 2 H, C(1)H_2, J = 1.9 Hz); 4.84 (dd, 2 H, C(7)H_2, J = 1.2 and 4.1 Hz); 4.99 (m, 1 H, H(4)); 5.89—6.21 (m, 2 H, CH=CH); 7.30—7.60 (m, 3 H, 2 *m*-H + *p*-H); 7.90—8.08 (m, 2 H, 2 *o*-H). MS (100 °C), *m*/*z* (I_{rel} (%)): 264 $[M]^+$ (0.06), 229 $[M-Cl]^+$ (3), 142 $[M-BzOH]^+$ (3), 105 $[Bz]^+$ (100), 77 $[Ph]^+$ (9.5).

Methyl *rac*-13-benzoyloxy-10-hydroxytridec-11(*E*)-ene-5,8-diynoate (*rac*-7). Chloride *rac*-**6** (2.75 g, 10.41 mmol) in 4 mL of DMF and then methyl hex-5-ynoate (2.06 g, 16.3 mmol) in 1 mL of DMF were added to a stirred suspension of K_2CO_3 (3.07 g, 22.24 mmol), NaI (3.56 g, 23.75 mmol), and CuI (2.04 g, 10.71 mmol) in 4 mL of DMF. After 7 h of stirring at 25 °C, the reaction mixture was poured in 200 mL of a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The usual workup gave 3.68 g (100%) of diacetylene *rac*-**7** as a yellow oil, R_f 0.19 (system A). IR, ν/cm^{-1}: 3606 and 3460 (OH), 2215 (C≡C), 1743 and 1733 (C=O), 1268 and 1115 (C—O), 713 (Ph). ^{1}H NMR, δ: 1.77 (m, 2 H, C(3)H_2); 2.07—2.23 (m, 2 H, C(4)H_2); 2.43 (t, 2 H, C(2)H_2, J = 7.0 Hz); 3.19 (q, 2 H, C(7)H_2, J = 2.1 Hz); 3.67 (s, 3 H, OMe); 4.73—4.97 (m, 3 H, H(10) + C(13)H_2); 5.88—6.11 (m, 2 H, CH=CH); 7.43—7.59 (m, 3 H, 2 *m*-H + *p*-H); 7.90—8.18 (m, 2 H, 2 *o*-H). MS (120 °C), *m*/*z* (I_{rel} (%)): 354 $[M]^+$ (0.13), 232 $[M-BzOH]^+$ (1.4), 117 (46), 105 $[Bz]^+$ (100), 77 $[Ph]^+$ (5).

Methyl *rac*-13-benzoyloxy-10-(tetrahydropyranyloxy)tridec-11(*E*)-ene-5,8-diynoate (*rac*-8). A solution of hydroxy benzoate *rac*-**7** (3.37 g, 9.52 mmol), DHP (1.74 mL, 19 mmol), and PPTS (358 mg, 1.42 mmol) in 70 mL of CH_2Cl_2 was kept for 3 h at 25 °C. Ether (250 mL) was added, and the usual workup gave 4.12 g (99%) of the THP ether *rac*-**8** as a brown oil, R_f 0.36 (system A). UV, λ_{max}/nm: 229.5 (log ε 4.08), 268 (log ε 3.25), 272.5 (log ε 3.26), 279 (log ε 3.21). IR, ν/cm^{-1}: 2220 (C≡C), 1750 and 1730 (C=O), 1270 and 1115 (C—O), 713 (Ph). ^{1}H NMR, δ: 1.58—1.84 (m, 8 H, C(3)H_2 +3 CH_2 in THP); 2.10—2.24 (m, 2 H, C(4)H_2); 2.43 (t, 2 H, C(2)H_2, J = 6.8 Hz); 3.21 (q, 2 H, C(7)H_2, J = 2.2 Hz); 3.52—4.00 (m, 2 H, H_2CO in THP); 3.66 (s, 3 H, OMe); 4.64—5.06 (m, 4 H, H(10) + C(13)H_2 + OCHO in THP); 5.79—6.08 (m, 2 H, CH=CH); 7.40—7.66 (m, 3 H, 2 *m*-H + *p*-H); 7.94—8.16 (m, 2 H, 2 *o*-H). MS (125 °C), *m*/*z* (I_{rel} (%)): 407 $[M-MeO]^+$ (4), 337 $[M-THPO]^+$ (100), 232 $[M-THPO-Bz]^+$ (30), 105 $[Bz]^+$ (60), 77 $[Ph]^+$ (8).

Methyl *rac*-13-hydroxy-10-(tetrahydropyranyloxy)tridec-11(*E*)-en-5,8-diynoate (*rac*-9). A suspension of K_2CO_3 (1.26 g, 9.13 mmol) in a solution of benzoate *rac*-**8** (4 g, 9.13 mmol) in 100 mL of MeOH was stirred for 1 h at 26 °C. Ether (250 mL) was added, and the reaction mixture was washed with a saturated aqueous solution of NH_4Cl and with brine. The aqueous solutions were additionally extracted with Et_2O. The usual workup gave 3.15 g of alcohol *rac*-**9** (as a mixture of two epimers) contaminated with BzOMe, which was used in the next step without purification. Brown oil, R_f 0.08 and 0.10 (two spots, system A). IR, ν/cm^{-1}: 3620 and 3463 (OH), 2257 (C≡C), 1740 (C=O), 1113 (C—O). ^{1}H NMR, δ: 1.36—1.86 (m, 8 H, C(3)H_2 + 3 CH_2 in THP); 2.12—2.26 (m, 2 H, C(4)H_2); 2.44 (t, 2 H, C(2)H_2, J = 7.0 Hz); 3.19 (q, 2 H, C(7)H_2, J = 2.2 Hz); 3.51—3.86 (m, 2 H, H_2CO in THP); 3.68 (s, 3 H, OMe); 4.14 (m, 2 H, C(13)H_2); 4.68—5.05 (m, 2 H, H(10) + OCHO in THP); 5.57—6.14 (m, 2 H, CH=CH).

Methyl *rac*-10-tetrahydropyranyloxy-13-(tosyloxy)tridec-11(*E*)-ene-5,8-diynoate (*rac*-10) and *rac*-10-tetrahydropyranyloxy-13-chlorotridec-11(*E*)-ene-5,8-diynoate (*rac*-11). A solution of crude alcohol *rac*-**9** (3.05 g, 8.84 mmol), collidine (3.32 g, 27.42 mmol), TsCl (2.61 g, 13.69 mmol), and DMAP (110 mg, 0.9 mmol) in 70 mL of $CHCl_3$ was kept for 24 h at 25 °C. The reaction mixture was diluted with 300 mL of Et_2O and washed with 5% HCl. The usual workup gave 4.22 g of a mixture of tosylate *rac*-**10** and chloride *rac*-**11** (~2 : 1), which was used in the next step without separation and purification. The individual samples for spectroscopy were obtained by preparative TLC. **Tosylate *rac*-10:** yellow oil, R_f 0.36

(system A). IR, ν/cm^{-1}: 2220 (C≡C), 1743 (C=O), 1125 (C—O), 1183 (SO_2), 673 (Ph). ^{1}H NMR, δ: 1.32—1.92 (m, 8 H, C(3)H_2 + 3 CH_2 in THP); 2.08—2.26 (m, 2 H, C(4)H_2); 2.36—2.50 (m, 2 H, C(2)H_2); 2.45 (s, 3 H, Me); 3.17 (q, 2 H, C(7)H_2, J = 2.2 Hz); 3.48—3.78 (m, 2 H, H_2CO in THP); 3.67 (s, 3 H, OMe); 4.57 (m, 2 H, C(13)H_2); 4.82—5.22 (m, 2 H, H(10) + OCHO in THP); 5.68—5.94 (m, 2 H, CH=CH); 7.34 (d, 2 H, 2 *m*-H, J = 8.0 Hz); 7.80 (dt, 2 H, 2 *o*-H, J = 8.0 and 1.6 Hz). **Chloride *rac*-11:** yellow oil, R_f 0.47 (system A). IR, ν/cm^{-1}: 2220 (C≡C), 1743 (C=O), 1125 (C—O). ^{1}H NMR, δ: 1.32—1.88 (m, 8 H, C(3)H_2 + 3 CH_2 in THP); 2.02—2.24 (m, 2 H, C(4)H_2); 2.44 (t, 2 H, C(2)H_2, J = 7.2 Hz); 3.19 (q, 2 H, C(7)H_2, J = 2.2 Hz); 3.42—3.87 (m, 2 H, H_2CO in THP); 3.67 (s, 3 H, OMe); 4.08 (dd, 2 H, C(13)H_2, J = 4.7 and 1.4 Hz); 4.60—5.00 (m, 2 H, H(10) + OCHO in THP); 5.56—6.14 (m, 2 H, CH=CH).

Compounds *rac*-**12**—*rac*-**16** were prepared under the conditions described for *rac*-**7**—*rac*-**11** but using hept-1-yne

***rac*-1-(Benzoyloxy)tetradec-2(*E*)-ene-5,8-diyn-4-ol (*rac*-12)**, yield 96%, yellow oil, R_f 0.43 (system A). UV, λ_{max}/nm: 229.5 (log ε 4.19), 268 (inflection) (log ε 3.07), 273 (log ε 3.11), 280 (log ε 3.04). IR, ν/cm^{-1}: 3623 and 3470 (OH), 2225 (C≡C), 1730 (C=O), 1115 (C—O), 710 (Ph). ^{1}H NMR, δ: 0.88 (t, 3 H, Me(14), J = 5.8 Hz); 1.38 (m, 6 H, C(11)H_2 + C(12)H_2 + C(13)H_2); 2.12 (m, 2 H, C(10)H_2); 2.74 (br.s, 1 H, OH); 3.22 (m, 2 H, C(7)H_2); 4.90—5.20 (m, 3 H, H(4) + C(1)H_2); 5.78—6.30 (m, 2 H, CH=CH); 7.30—7.68 (m, 3 H, 2 *m*-H + *p*-H); 8.00—8.20 (m, 2 H, 2 *o*-H).

***rac*-1-Benzoyloxy-4-(tetrahydropyranyloxy)tetradec-2(*E*)-ene-5,8-diyne (*rac*-13)**, yield 100%, a mixture of two epimers, brown oil, R_f 0.70 (system A), 0.46 and 0.50 (2 spots, system B). UV, λ_{max}/nm: 230 (log ε 4.14), 268 (inflection) (log ε 3.01), 273 (log ε 3.04), 280 (log ε 2.98). IR, ν/cm^{-1}: 2245 (C≡C), 1726 (C=O), 1270 and 1125 (C—O). ^{1}H NMR, δ: 0.88 (t, 3 H, Me(14), J = 5.9 Hz); 1.17—1.84 (m, 12 H, C(11)H_2 + C(12)H_2 + C(13)H_2 + 3 CH_2 in THP); 2.12 (m, 2 H, C(10)H_2); 3.24 (m, 2 H, C(7)H_2); 3.52—4.08 (m, 2 H, H_2CO in THP); 4.41—5.14 (m, 4 H, H(4) + C(1)H_2 + OCHO in THP); 6.14—6.60 (m, 2 H, CH=CH); 7.32—7.68 (m, 3 H, 2 *m*-H + *p*-H); 7.94—8.20 (m, 2 H, 2 *o*-H).

***rac*-4-(Tetrahydropyranyloxy)tetradec-2(*E*)-ene-5,8-diyn-1-ol (*rac*-14)**, a crude mixture of two epimers, brown oil, R_f 0.35 and 0.42 (two spots, system A). IR, ν/cm^{-1}: 3410 (OH), 2225 (C≡C), 1125 (C—O). ^{1}H NMR, δ: 0.89 (t, 3 H, Me(14), J = 5.7 Hz); 1.4—1.80 (m, 12 H, C(11)H_2 + C(12)H_2 + C(13)H_2 + 3 CH_2 in THP); 2.12 (m, 2 H, C(10)H_2); 3.19 (q, 2 H, C(7)H_2, J = 2.2 Hz); 3.40—3.90 (m, 2 H, H_2CO in THP); 4.16 (dd, 2 H, C(1)H_2, J = 4.4 and 1.2 Hz); 4.70—5.02 (m, 2 H, H(4) + OCHO in THP); 5.22—6.26 (m, 2 H, CH=CH).

***rac*-4-Tetrahydropyranyloxy-1-(tosyloxy)tetradec-2(*E*)-ene-5,8-diyne (*rac*-15) and *rac*-4-tetrahydropyranyloxy-1-chlorotetradec-2(*E*)-ene-5,8-diyne (*rac*-16)** (ratio ~2 : 1) were used in the next step without separation and purification. Individual samples for spectroscopy were obtained by preparative TLC. **Tosylate *rac*-15:** a mixture of two epimers, yellow oil, R_f 0.31 and 0.35 (two spots, system B). IR, ν/cm^{-1}: 1376 and 1176 (SO_2), 1120 (C—O), 675 (Ph). ^{1}H, δ: 0.89 (t, 3 H, Me(14), J = 5.7 Hz); 1.22—1.84 (m, 12 H, C(11)H_2 + C(12)H_2 + C(13)H_2 + 3 CH_2 in THP); 2.45 (s, 3 H, Me); 3.16 (q, 2 H, C(7)H_2, J = 2.0 Hz); 3.46—3.80 (m, 2 H, H_2CO in THP); 4.58 (dd, 2 H, C(1)H_2, J = 4.4 and 1.2 Hz); 4.84—5.00 (m, 2 H, H(4) + OCHO in THP); 5.77—5.94 (m, 2 H, CH=CH); 7.37 (d, 2 H, 2 *m*-H, J = 8.0 Hz); 7.84 (dt, 2 H, 2 *o*-H, J = 8.0 and 1.5 Hz). **Chloride *rac*-16:** a mixture of two epimers, yellow oil, R_f 0.57 and 0.62 (2 spot, system B). IR, ν/cm^{-1}: 2225 (C≡C), 1125 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(14), J = 5.7 Hz); 1.16—1.70 (m, 12 H, C(11)H_2 + C(12)H_2 + C(13)H_2 + 3 CH_2 in THP); 2.14 (m, 2 H, C(10)H_2); 3.22 (q, 2 H, C(7)H_2, J = 2.0 Hz); 3.46—3.90 (m, 2 H, H_2CO in THP); 4.12 (dd, 2 H, C(1)H_2, J = 4.4 and 1.2 Hz); 4.70—5.04 (m, 2 H, H(4) + OCHO in THP); 5.70—6.28 (m, 2 H, CH=CH).

Methyl *rac*-10-(tetrahydropyranyloxy)eicos-11(*E*)-ene-5,8,14-triynoate (*rac*-17) was prepared (together with branched isomer *rac*-**21** as an impurity) under the conditions described for the synthesis of *rac*-**7** from a 1.5-molar excess of hept-1-yne and a mixture of tosylate *rac*-**10** and chloride *rac*-**11** (3.63 g), yield 3.3 g, and used in the next step without separation and purification. Brown oil, R_f 0.56 (system A). IR, ν/cm^{-1}: 2230 (C≡C), 1743 (C=O), 1119 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(20), J = 5.9 Hz); 1.42—1.84 (m, 14 H, C(3)H_2 + C(17)H_2 + C(18)H_2 + C(19)H_2 + 3 CH_2 in THP); 2.02—2.16 (m, 4 H, C(4)H_2 + C(16)H_2); 2.44 (t, 2 H, C(2)H_2, J = 7.1 Hz); 2.98 (m, 2 H, C(13)H_2); 3.20 (m, 2 H, C(7)H_2); 3.50—4.02 (m, 2 H, H_2CO in THP); 3.68 (s, 3 H, OMe); 4.62—5.06 (m, 2 H, H(10) + OCHO in THP); 5.74—6.14 (m, 2 H, CH=CH).

Methyl *rac*-10-hydroxyeicos-11(*E*)-ene-5,8,14-triynoate (*rac*-18) and *rac*-11-vinyl-10-hydroxyoctadeca-5,8,12-triynoate (*rac*-22). A solution of a crude mixture of esters *rac*-**17** and *rac*-**21** (2.65 g) and PPTS (160 mg) in 90 mL of EtOH was kept for 1.5 h at 60 °C, cooled, diluted with 300 mL of Et_2O, and washed with water. The usual workup and HPFC (elution with hexane—EtOAc—Et_3N, 90 : 10 : 0.1) gave 1.21 g (60% from *rac*-**8**) of enetriyne alcohol *rac*-**18** and 84 mg (4.2% from *rac*-**8**) of olefin *rac*-**22**. **Alcohol *rac*-18**, yellow oil, R_f 0.38 (system A), 0.21 (system B). IR, ν/cm^{-1}: 3620 and 3470 (OH), 2225 (C≡C), 1743 (C=O), 1160 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(20), J = 6.1 Hz); 1.24—1.54 (m, 6 H, C(17)H_2 + C(18)H_2 + C(19)H_2); 1.80 (quint, 2 H, C(3)H_2, J = 6.4 Hz); 2.00—2.30 (m, 4 H, C(4)H_2 + C(16)H_2); 2.45 (t, 2 H, C(2)H_2, J = 7.0 Hz); 2.96 (m, 2 H, C(13)H_2); 3.18 (q, 2 H, C(7)H_2, J = 2.1 Hz); 3.68 (s, 3 H, OMe); 4.89 (br.s, 1 H, H(10)); 5.85 (dd, 2 H, CH=CH, J = 3.9 and 1.6 Hz). **Olefin *rac*-22**, yellow oil, R_f 0.45 (system A). IR, ν/cm^{-1}: 3475 (OH), 3095 (CH=CH_2), 2225 (C≡C), 1742 (C=O), 1170 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(18), J = 6.1 Hz); 1.23—1.53 (m, 6 H, C(15)H_2 + C(16)H_2 + C(17)H_2); 1.86 (quint, 2 H, C(3)H_2, J = 6.4 Hz); 2.02—2.30 (m, 4 H, C(4)H_2 + C(14)H_2); 2.44 (t, 2 H, C(2)H_2, J = 7.2 Hz); 3.18 (q, 2 H, C(7)H_2, J = 2.2 Hz); 3.34 (br.s, 1 H, H(11)); 3.68 (s, 3 H, OMe); 4.10—4.36 (m, 1 H, H(10)); 5.18—5.50 (m, 2 H) and 5.76—6.06 (m, 1 H) (CH=CH_2).

A similar procedure starting from methyl hex-5-ynoate and a mixture of tosylate *rac*-**15** and chloride *rac*-**16** gave successively *rac*-**19**, *rac*-**20**, *rac*-**23**, and *rac*-**24**.

Methyl *rac*-10-(tetrahydropyranyloxy)eicos-8(*E*)-ene-5,11,14-triynoate (*rac*-19), a mixture of two epimers (containing branched isomer *rac*-**23** as an impurity), brown oil, R_f 0.33 and 0.36 (two spots, system A). IR, ν/cm^{-1}: 2225 (C≡C), 1742 (C=O), 1120 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(20), J = 5.9 Hz); 1.20—1.86 (m, 14 H, C(3)H_2 + C(17)H_2 + C(18)H_2 + C(19)H_2 + 3 CH_2 in THP); 2.06—2.26 (m, 4 H, C(4)H_2 + C(16)H_2); 2.45 (t, 2 H, C(2)H_2, J = 7.1 Hz); 2.97 (m, 2 H, C(7)H_2); 3.22 (m, 2 H, C(13)H_2); 3.48—4.04 (m, 2 H, H_2CO in THP); 3.68 (s, 3 H, OMe); 4.70—5.04 (m, 2 H, H(10) + OCHO in THP); 5.78—6.00 (m, 2 H, CH=CH).

Methyl *rac*-10-hydroxyeicos-8(*E*)-ene-5,11,14-triynoate (*rac*-20), overall yield 48% (from *rac*-**13**), yellow oil, R_f 0.21 (system B). IR, ν/cm^{-1}: 3615 and 3430 (OH), 2225 (C≡C), 1742 (C=O), 1160 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(20), J = 5.9 Hz); 1.28—1.58 (m, 6 H, C(17)H_2 + C(18)H_2 + C(19)H_2); 1.88 (quint, 2 H, C(3)H_2, J = 7.0 Hz); 2.04—2.34

(m, 4 H, C(4)H_2 + C(16)H_2); 2.46 (t, 2 H, C(2)H_2, J = 7.0 Hz); 3.00 (m, 2 H, C(7)H_2); 3.26 (q, 2 H, C(13)H_2, J = 2.0 Hz); 3.68 (s, 3 H, OMe); 4.89 (br.s, 1 H, H(10)); 5.87—5.97 (m, 2 H, CH=CH).

Methyl *rac*-7-vinyl-8-hydroxyoctadeca-5,9,12-triynoate (*rac*-24), overall yield 8.8% (from *rac*-**13**), yellow oil, R_f 0.26 (system B). IR, ν/cm^{-1}: 3475 (OH), 3100 (CH=CH_2), 2225 (C≡C), 1742 (C=O), 1170 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(18), J = 6.4 Hz); 1.22—1.52 (m, 6 H, C(15)H_2 + C(16)H_2 + C(17)H_2); 1.90 (quint, 2 H, C(3)H_2, J = 6.4 Hz); 2.00—2.40 (m, 4 H, C(4)H_2 + C(14)H_2); 2.49 (t, 2 H, C(2)H_2, J = 7.1 Hz); 3.22 (q, 2 H, C(11)H_2, J = 2.1 Hz); 3.42 (br.s, 2 H, C(7)H_2); 3.68 (s, 3 H, OMe); 4.36 (br.s, 1 H, H(8)); 5.20—5.50 (m, 1 H) and 5.80—6.10 (m, 2 H) (CH=CH_2).

Methyl 10-oxoeicos-11(*E*)-en-5,8,14-triynoate (25). On storage for 4 months in a frozen benzene solution at −20 °C, samples of alcohol *rac*-**18** formed 20—40% ketone **25** (a less polar spot on a TLC plate), which was isolated by preparative TLC as a light yellow oil, R_f 0.26 (system B). UV, λ_{max}/nm: 239 (log ε 3.99), 284 (log ε 3.50). IR, ν/cm^{-1}: 2220 (C≡C), 1740 (C=O). ^{1}H NMR, δ: 0.89 (t, 3 H, Me(20), J = 6.8 Hz); 1.23—1.53 (m, 6 H, C(17)H_2 + C(18)H_2 + C(19)H_2); 1.84 (quint, 2 H, C(3)H_2, J = 7.2 Hz); 2.12—2.48 (m, 6 H, C(2)H_2 + C(4)H_2 + C(16)H_2); 3.16—3.26 (m, 2 H, C(13)H_2); 3.30—3.40 (m, 2 H, C(7)H_2); 3.68 (s, 3 H, OMe); 6.50 (dt, 1 H, H(11), J = 18.0 and 2.0 Hz); 7.15 (dt, 1 H, H(12), J = 18 and 6 Hz).

Methyl (10*S*,11*S*,12*S*)-10-hydroxy-11,12-epoxyeicosa-5,8,14-triynoate (10*S*,11*S*,12*S*)-26. Ti(OPr^i)$_4$ (261 mg, 0.92 mmol) and a 4.3 M solution of Bu^{t}O$_2$H (0.57 mL, 2.44 mmol) in CH_2Cl_2 were added successively at −20 °C to a stirred suspension of MS 4 Å (150 mg) in a solution of *L*-(+)-DET (234 mg, 1.13 mmol) in 5 mL of CH_2Cl_2. After 40 min, a solution of enetriyne alcohol *rac*-**18** (200 mg, 0.61 mmol) in 2 mL of CH_2Cl_2 was added. After 2 h of stirring at −20 °C, the reaction mixture contained (according to TLC) the initial compound and a more polar reaction product in a ratio of ~1 : 1. The mixture was poured in 30 mL of a saturated aqueous solution of $FeSO_4$ and extracted with Et_2O. The usual workup of the extract followed by HPFC (EtOAc—hexane, 15 : 85) gave 70 mg (35%) of alcohol (10*S*)-**18**, $[\alpha]_D^{25}$ +4.9° (*c* 1.15, $CHCl_3$) and 93 mg (44%) of epoxide (10*S*,11*S*,12*S*)-**26**, $[\alpha]_D^{25}$ −8.1° (*c* 1.32, $CHCl_3$) containing 8% epimer (10*R*,11*S*,12*S*)-**26** (according to GLC and ^{1}H NMR). According to TLC, GLC, and ^{1}H NMR, the resulting mixture of epoxides (10*R*/*S*)-**26** is practically identical (except for the ratio of the epimers) to that described previously;[19] the recovered alcohol (10*S*)-**18** was practically identical, according to TLC and ^{1}H NMR, to the sample of *rac*-**18**.

Methyl esters of hepoxilins (10*R*)-B$_3$ and (10*S*)-B$_3$, (10*R*)-27 and (10*S*)-27. A mixture of epoxides (10*R*/*S*)-**26** (8 : 92, 93 mg) was hydrogenated in benzene with the Lindlar catalyst in the presence of quinoline under the conditions described in a previous study.[19] Consecutive HPFC (EtOAc—hexane, 15 : 85) and preparative TLC (C_6H_6—Et_2O, 85 : 15, elution repeated 5—6 times) gave 67 mg (72%) of epimer (10*S*)-**27** as a colorless oil, $[\alpha]_D^{25}$ +60.1° (*c* 0.55, $CHCl_3$), *ee* >95% (calculated based on the published data:[19] $[\alpha]_D^{25}$ +61.9° for a sample with *ee* 100%). HPFC (Pr^{i}OH—hexane, 1.5 : 98.5, UV detector at 205 nm): retention time 4.7 min, and 6.7 mg (7%) of epimer (10*R*)-**27**, colorless oil, $[\alpha]_D^{25}$ −51.3° (*c* 0.67, $CHCl_3$), *ee* 82% (calculated based on the published data:[19] $[\alpha]_D^{25}$ −62.6°). The chromatographic (TLC and GLC) and spectral (IR, ^{1}H NMR) characteristics of the samples were practically identical to those reported previously.[19]

Methyl 10-hydroxy-8,9-epoxyeicosa-5,11,14-triynoates (28). *L*-(+)- or *D*-(−)-DIPT (360 mg, 1.54 mmol) in 1 mL of CH_2Cl_2 was added with stirring to a suspension of 3 Å sieves (800 mg) in 8 mL of CH_2Cl_2. After cooling to −20 °C, a 5.12 M solution of Bu^{t}O$_2$H (0.75 mL, 3.84 mmol) in isooctane and Ti(OPr^i)$_4$ (290 mg, 1.02 mmol) were added. After stirring at −20 °C for 40 min, enetriyne alcohol **20** (840 mg, 2.56 mmol) in 5 mL of CH_2Cl_2 was added, and the mixture was stirred for 2 h at −20 °C, poured in 250 mL of Et_2O, and washed with a saturated aqueous solution of $FeSO_4$ (3×75 mL) and with water. The usual workup and HPFC (system B + 0.1% Et_3N) gave the recovered alcohol **20** (a mixture of unequal amounts of enaniomers) and epoxides **28**. The yields and optical rotations of the products are listed in Table 1. Other properties: **alcohols (10*R*)-20** and **(10*S*)-20**: yellow oils, R_f 0.61 (system B, two elutions), practically identical to *rac*-**20** according to TLC and ^{1}H NMR. **Epoxides (8*S*,9*S*,10*R*/*S*)-28** (a 1 : 9 mixture of epimers; GLC data), yellow oils, R_f 0.45 (system B, two elutions). IR, ν/cm^{-1}: 3425 (OH), 2225 (C≡C), 1743 (C=O), 1166 (C—O). ^{1}H NMR, δ: 0.90 (t, 3 H, Me(20), J = 5.9 Hz); 1.20—1.44 (m, 6 H, C(17)H_2 + C(18)H_2 + C(19)H_2); 1.86 (quint, 2 H, C(3)H_2, J = 7.2 Hz); 2.04—2.34 (m, 6 H, C(4)H_2 + H(8) + H(9) + C(16)H_2); 2.44 (t, 2 H, C(2)H_2, J = 7.2 Hz); 2.53—2.63 (m, 2 H, C(7)H_2); 3.22 (q, 2 H, C(13)H_2, J = 2.2 Hz); 3.68 (s, 3 H, OMe); 4.37—4.47 (m, 0.1 H, H(10) in the 10*R*-epimer) and 4.57—4.67 (m, 0.9 H, H(10) in the 10*S*-epimer). **Compound (8*R*,9*R*,10*R*/*S*)-28** (a 9 : 1 mixture of epimers): chromatographic and spectral characteristics were almost identical to those presented above for the corresponding enantiomers.

Methyl 10-hydroxy-8,9-epoxyeicosa-5(*Z*),11(*Z*),14(*Z*)-trienoates (29) were prepared by hydrogenation of triacetylenic alcohols **28** under the conditions described for the synthesis of hepoxilins **27**. The yields, optical rotation values, and *ee* of the obtained compounds are presented in Table 1. Other properties: ***xylo*-isomer (8*S*,9*S*,10*S*)-29**, colorless oil, R_f 0.59 (system B, two elutions). HPLC (Pr^{i}OH—hexane, 1.5 : 98.5, UV detector at 205 nm): retention time 4.4 min. IR, ν/cm^{-1}: 3570 (OH), 1742 (C=O), 1162 (C—O). ^{1}H NMR, δ: 0.89 (t, 3 H, Me(20), J = 5.3 Hz); 1.13—1.43 (m, 6 H, C(17)H_2 + C(18)H_2 + C(19)H_2); 1.74 (quint, 2 H, C(3)H_2, J = 7.2 Hz); 1.95—2.15 (m, 4 H, C(4)H_2 + C(16)H_2); 2.29—2.39 (m, 4 H, C(2)H_2 + C(7)H_2); 2.83—2.93 (m, 3 H, H(9) + C(13)H_2); 3.06 (dt, 1 H, H(8), J = 2.4 and 5.3 Hz); 3.67 (s, 3 H, OMe); 4.67 (dd, 1 H, H(10), J = 7.8 and 3.0 Hz); 5.32—5.74 (m, 6 H, 3 CH=CH). ***arabino*-Isomer (8*S*,9*S*,10*R*)-29**, colorless oil, R_f 0.54 (system B, two elutions). ^{1}H NMR, δ: 0.89 (t, 3 H, Me(20), J = 5.6 Hz); 1.15—1.45 (m, 6 H, C(17)H_2 + C(18)H_2 + C(19)H_2); 1.74 (quint, 2 H, C(3)H_2, J = 7.2 Hz); 1.90—2.18 (m, 4 H, C(4)H_2 + C(16)H_2); 2.23—2.43 (m, 4 H, C(2)H_2 + C(7)H_2); 2.83—2.93 (m, 3 H, H(9) + C(13)H_2); 3.02 (dt, 1 H, H(8), J = 2.3 and 5.4 Hz); 3.67 (s, 3 H, OMe); 4.34 (dd, 1 H, H(10), J = 7.5 and 5.0 Hz); 5.22—5.74 (m, 6 H, 3 CH=CH). The chromatographic and spectral properties of (8*R*,9*R*,10*R*)-**29** and (8*R*,9*R*,10*S*)-**29** were virtually identical to the properties of the corresponding enantiomers presented above. The chromatographic mobility during TLC and GLC and the ^{1}H NMR spectra of triene alcohols **29** were virtually identical to the same characteristics of the corresponding epimers of hepoxilins **27**.

(8*R*,9*R*,10*S*)-10-Hydroxy-8,9-epoxyeicosa-5(*Z*),11(*Z*),14(*Z*)-trienoic acid, (8*S*,9*S*,10*S*)-30. A mixture of a solution of methyl ester (8*S*,9*S*,10*S*)-**29** (*ee* 94%) (26 mg) in 4.7 mL of Bu^{t}OH and 2 mL of a saturated aqueous solution of LiOH was stirred for 1 h at 25 °C. Then Et_2O (40 mL) and a phosphate buffer (pH 2) (15 mL) were added, and the mixture was extracted with Et_2O. The usual workup gave 24.6 mg (98%) of acid (8*S*,9*S*,10*S*)-**30** with a slight impurity of a less polar product. Chromatographic separation yielded a colorless

oil, R_f 0.16 (system A), $[\alpha]_D^{25}$ +56.5° (*c* 1.07, $CHCl_3$). IR, ν/cm^{-1}: 3400 (OH), 1710 (C=O). ^1H NMR, δ: 0.89 (t, 3 H, Me(20), J = 5.7 Hz); 1.15—1.45 (m, 6 H, $C(17)H_2$ + $C(18)H_2$ + $C(19)H_2$); 1.74 (quint, 2 H, $C(3)H_2$, J = 7.2 Hz); 2.02—2.12 (m, 4 H, $C(4)H_2$ + $C(16)H_2$); 2.30—2.40 (m, 4 H, $C(2)H_2$ + $C(7)H_2$); 2.81—2.91 (m, 3 H, H(9) + $C(13)H_2$); 3.06 (dt, 1 H, H(8), J = 2.4 and 5.5 Hz); 4.69 (dd, 1 H, H(10), J = 8.0 and 3.0 Hz); 5.22—5.82 (m, 6 H, 3 CH=CH).

10-(*R*)-α-Methoxyphenylacetate of methyl 10-hydroxy-8,9-epoxyeicosa-5(*Z*),11(*Z*),14(*Z*)-trienoate (31). (*R*)-(−)-α-methoxyphenylacetic acid (2.64 mg, 16.3 μmol) in 125 μL of CH_2Cl_2, a 0.33 *M* CH_2Cl_2 solution of DCC (50 μL, 16.3 μmol), and a 0.1 *M* solution of DMAP (16 μL, 1.63 μmol) in CH_2Cl_2 were added successively to a solution of one of the enantiomeric alcohols **29** (1.9 mg, 5.4 μmol) in 100 μL of CH_2Cl_2. After 18 h, the precipitated dicyclohexylurea was filtered off and washed with CH_2Cl_2, and the filtrate was diluted with 300 μL of CH_2Cl_2, and washed with 3% HCl and with a saturated aqueous solution of $NaHCO_3$. After the usual workup of the resulting semicrystalline material, the remaining urea was removed by redissolution in CH_2Cl_2. Evaporation of the filtrate gave 2.5 mg (93%) of a diastereomer of ester **31** containing an impurity of the enantiomeric 2'-diastereomer, whose quantity corresponded to the *ee* value of the initial alcohol **29**. **Diastereomer (2'*R*,8*S*,9*S*,10*S*)-31** (the data relating to the impurity were ignored): R_f 0.39 (Silufol, system B), 0.36 (DC-Alufolien Kieselgel 60, Merck, system B, two elutions). HPLC (Pr^iOH—hexane, 0.25 : 99.75, UV detector at 228 nm): retention time 8.2 min. IR, ν/cm^{-1}: 1740 (C=O), 1170 and 1115 (C—O), 695 (Ph). ^1H NMR spectrum of the ester, δ: 0.88 (t, 3 H, Me(20), J = 7.0 Hz); 1.13—1.43 (m, 6 H, $C(17)H_2$ + $C(18)H_2$ + $C(19)H_2$); 1.64—1.74 (m, 2 H, $C(3)H_2$); 1.97—2.07 (m, 4 H, $C(4)H_2$ + $C(16)H_2$); 2.25—2.35 (m, 4 H, $C(2)H_2$ + $C(7)H_2$); 2.71—2.81 (m, 2 H, $C(13)H_2$); 2.83 (dt, 1 H, H(8), J = 2.0 and 5.2 Hz); 2.91 (dd, 1 H, H(9), J = 3.7 and 2.0 Hz); 3.42 (s, 3 H, COMe); 3.66 (s, 3 H, CO_2Me); 4.77 (s, 1 H, HCOMe); 5.22—5.50 (m, 6 H, 3 CH=CH); 5.66 (dd, 1 H, H(10), J = 9.4 and 3.7 Hz); 7.32—7.52 (m, 5 H, Ph). **Diastereomer (2'*R*,8*R*,9*R*,10*R*)-31** (the data relating to the impurity were ignored): R_f 0.39 (Silufol, system B), 0.40 (DC-Alufolien Kieselgel 60, Merck, system B, two elutions). HPLC (Pr^iOH—hexane, 0.25 : 99.75, UV detector at 228 nm): retention time 5.8 min. The ^1H NMR spectrum was identical to the above-presented spectrum of the diastereomer except that the signal for HCOMe shifted to 4.75.

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