Enantioselective synthesis of methyl (5*Z*,8*S*)-8,9-epoxynon-5-enoate, an eicosanoid synthon*

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A six-step synthesis of methyl (5*Z*,8*S*)-8,9-epoxynon-5-enoate, a known synthon of constanolactones and hepoxilins, from 5-hexynoic ester was developed. The enantiomeric purity of the synthon was attained by *S*-enantiodirected dihydroxylation of a double bond in the intermediate methyl non-8-en-5-ynoate with subsequent enantioselective hydrolysis of the epoxide group in the admixture of the minor *R*-enantiomer.

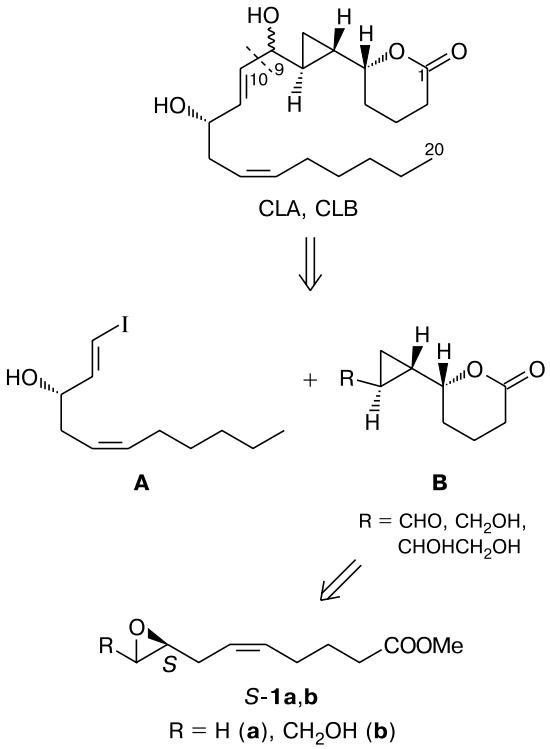
Key words: constanolactones, synthons, asymmetric catalysis, eicosanoids, enantioselective synthesis, oxiranes.

In the last 15—20 years, a new numerous family of oxidized arachidonic (and more polyunsaturated) acid metabolites, "marine" eicosanoids (ME) containing cyclopropane and lactone rings as typical structural elements, was isolated from sea algae (see a review, Ref. 1). Typical examples of the ME family include constanolactones CLA and CLB (Scheme 1) isolated from the algae *Constantinea simplex*.[2] The biological role and the activity of ME are unknown as yet but they are expected to be interesting by analogy with other endogenous cyclic (prostanoids) and aliphatic (leukotrienes, hepoxilins, *etc*.) metabolites of arachidonic acid including those of the "marine origin."

These circumstances stimulated considerable interest in the synthesis of ME (see Ref. 3 for the recent synthesis of CLA and CLB[4]). The total synthesis of ME is performed almost exclusively by the convergent synthon strategy. The most popular version of this strategy as applied to constanolactones includes retrosynthetic dissection of the "strategic" C(9)—C(10) bond, resulting in the synthons **A** and **B**. This pair of synthons can be efficiently coupled in one step by the Nozaki—Kishi reaction (for R = CHO in **A**).[4—6] Thus, the problem of CLA and CLB synthesis is mainly reduced to the synthesis of synthons **A** and **B**. Homoallylic epoxides (**1**) are among the best precursors of more complex cyclopropane synthons of type **B**, which are formed upon biomimetic homoallyl-cyclopropylcarbinyl rearrangement of the epoxides.[5,7]

Previously,[7] we used racemic epoxide (*rac*-**1a**) to obtain racemic synthon **B** (R = CH_2OH). The same epoxide was used as an early intermediate in the total synthesis of racemic hepoxilins A_3 (see Ref. 8). The enantioselective

Scheme 1



synthesis of CLA and CLB requires enantiomerically pure epoxide *S*-**1a**. In principle, this epoxide can be prepared from *rac*-**1a** by removing the *R*-enantiomer using enantioselective hydrolysis of terminal epoxides (EHTE).[9] However, the yield of epoxide *rac*-**1a** obtained from methyl 5-hexynoate (**2**) *via* esters of non-8-en-5-ynoic (**3**) and 8,9-epoxynon-5-ynoic (*rac*-**4**) acids (Scheme 2) does not

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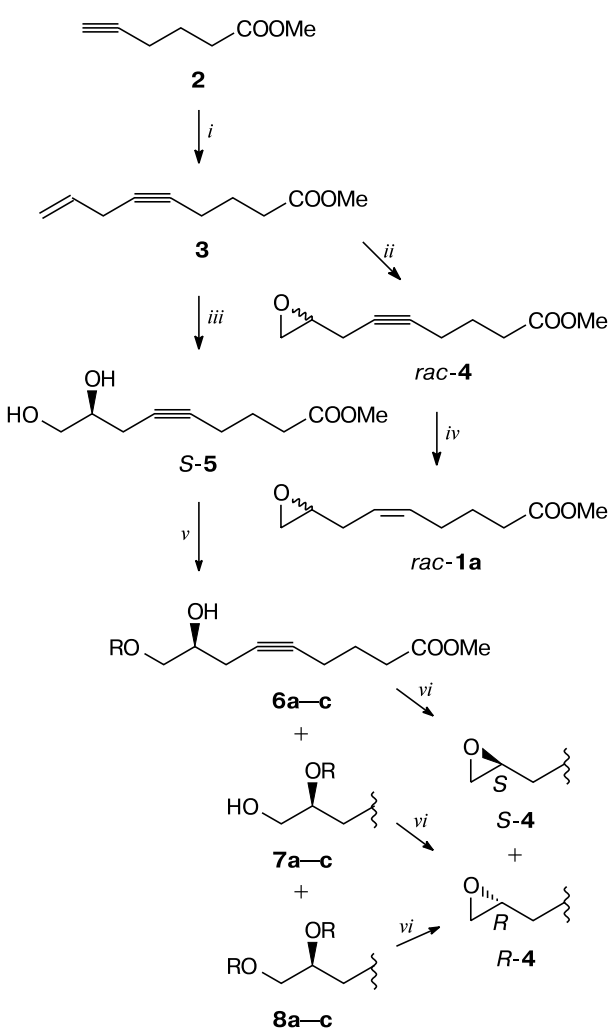
exceed 16% due to the low reactivity of the vinyl group of enyne **3** in *m*-chloroperoxybenzoic acid (MCPBA) epoxidation. This gives epoxide *rac*-**4** in a yield of not more than 50% due to the formation of by-products* and to the loss during the necessary chromatographic purification of the highly volatile product.[7] The epoxidation step was not improved by the use of dimethyldioxirane, as this potent oxidant affects also the triple bond of enyne **3** (see Ref. 10). The additional loss of a half of the poorly accessible product during deracemization appeared inadmissible.

An attempt at enantioselective epoxidation of enyne **3** with hydrogen peroxide, its urea complex, or HIO_4 catalyzed by (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(II) under previously described conditions[11] was unsuccessful, mainly giving, apart from traces of the epoxide, more polar products of an unidentified structure formed upon oxidation at the triple bond and/or the methylene bridge (no details are included here). In view of these facts and in order to decrease the volatility of the intermediate products, enantioselective dihydroxylation of olefins[12] (EDO) with the intention of subsequent transformation of the nonracemic diol thus obtained into epoxide *S*-**1a** was used.

Under standard EDO conditions[13] using dihydroquinine 1,4-phthalazinediyl ether [$(DHQ)_2PHAL$] as the chiral *S*-enantiodirecting catalyst, enyne **3** was smoothly converted into scalemic diol *S*-**5** but with *ee* of only ~60%. The *ee* value was determined at a later step, for epoxide *S*-**1a** obtained from this diol (see below); small optical rotations of terminal diols and epoxides are unsuitable for *ee* analysis. According to published data, $(DHQ)_2PHAL$-catalyzed EDO reaction transforms the aliphatic terminal $>C_6$ olefins into diols with *ee* 80—84%,[12] which changes little upon the variation of the structure of the catalyst.[14] Evidently, the lower enantioselectivity is due, in this case, to the presence of a triple bond, which decreases the effective volume of the single substituent at the reacting double bond.

A most popular method for the transformation of terminal diols into epoxides is sulfonation of the primary hydroxy group followed by treatment with a base. High regioselectivity of sulfonation is required in the case of nonracemic diols for retention of the enantiomeric purity. In view of moderate regioselectivity observed for primary-secondary diols,[15] this issue has been studied at this step of the synthesis using more readily accessible diol *S*-**5** as a model. With thorough control of the reaction conditions and performing the reaction to almost complete conversion of the diol, tosylation with TsCl in the presence of various co-reagents (pyridine, LiOH, Bu^n_2SnO) gave not only the primary monotosylate (**6a**) but also considerable amounts of the secondary monotosylate (**7a**) and ditosylate (**8a**) (overally up to 23%). The formation of tosylates **7a** and **8a** at the secondary hydroxy group is essential, since upon epoxide ring closure, both tosylates are converted into undesirable epoxide *R*-**4** with the op-

Scheme 2



	R	**6** : (**7** + **8**)
a	4-$MeC_6H_4SO_2$	77 : 23
b	2,4,6-$Me_3C_6H_2SO_2$	86 : 14
c	2,4,6-*i*-$Pr_3C_6H_2SO_2$	96 : 4

Reagents and conditions: *i*. $H_2C{=}CHCH_2I$, K_2CO_3, CuI, NaI, MeCN (60%); *ii*. MCPBA, $KHCO_3$ (57%); *iii*. $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $Bu^tOH{-}H_2O$ (85%); *iv*. H_2, $Pd{+}Pb/CaCO_3$, quinoline (48%); *v*. TsCl, Bu^n_2SnO (or Py, or $LiOH \cdot H_2O$) (91.5%); or MesCl, Py (57%); or TIPSCl, Py (57%); *vi*. DBU (43%).

* We were unable to reproduce the nearly quantitative yield described, without experimental details, for a closely similar epoxidation (MCPBA, CH_2Cl_2, 23 °C),[8] despite numerous repetitions of the epoxidation of enyne **3** with variable conditions and the use of two batches of MCPBA (commercial 85% and purified 100% ones).

posite configuration. As a result, treatment of the tosylate mixture formed with a base produces epoxide *S*-**4** with the enantiomeric purity sharply reduced to the unacceptable *ee* of 37%. Needless to note that fine chromatographic separation of the tosylate mixture is inconvenient from the preparative standpoint.

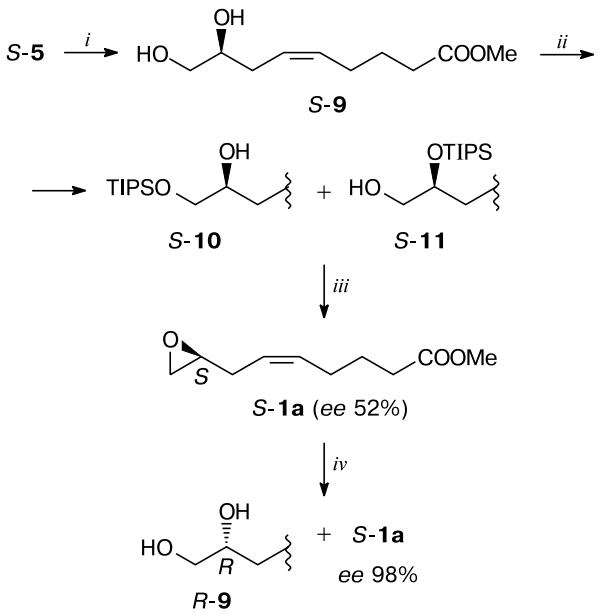
A decrease in the fraction of secondary sulfonyl derivatives **7** was attained by using more bulky arylsulfonyl groups. In the case of 2,4,6-trimethylbenzenesulfonyl (Mes) group, still too much of secondary derivative **7b** has been formed (14%), but the use of 2,4,6-triisopropylbenzenesulfonyl chloride (TIPSCl) decreased the content of secondary derivative **7c** to 4%. In both cases, primary sulfonates **6b**,**c** were formed as the major products, while bis-sulfonates **8b**,**c** were virtually missing. In the case of Ts and Mes derivatives, these results are consistent with the published data on the regioselectivity of sulfonation of other primary-secondary aliphatic diols, but much lower selectivity was reported for the synthesis of TIPS-derivatives (12% of the secondary and bis-TIPS-derivatives).[15]

The solution of the selectivity problem for sulfonation allowed us to continue the synthesis. The triple bond in diol *S*-**5** was converted into a Z-double bond of diol (*S*-**9**) by partial hydrogenation over the Lindlar catalyst. Unlike the two-step synthesis of epoxide *rac*-**1a** from enyne **3**, both steps of the preparation of diol *S*-**9** occur with high yields largely owing to low volatility of reaction products.

The reaction of diol *S*-**9** with sterically encumbered TIPSCl in the presence of pyridine to give primary sulfonate (*S*-**10**) proceeded very slowly and was not completed after 3 days; hence, the yield does not exceed 60%. On the contrary, *O*,*O*′-dibutylstannylidenic derivative of diol *S*-**9**, which is easily prepared *in situ*, reacted with TIPSCl over a period of several minutes giving rise to sulfonate *S*-**10** in 95% yield. In conformity with the results obtained for diol *S*-**5** (see above), in this case, too, the fraction of secondary TIPS ester (*S*-**11**) is not higher than 5%. A known difficulty faced in reactions involving organotin compounds is the removal of tin-containing secondary products.[16] We found that KF deposited on CaF_2 (KF/CaF_2) is a convenient reagent for this purpose. This easy-to-prepare reagent is stable (unlike KF/SiO_2) and readily available. In the presence of water in an equimolar amount with respect to KF, this reagent cleaves dibutylstannylidenic derivatives and removes Sn-containing components of reaction mixtures faster and more efficiently than crystalline KF or oxalic acid recommended for this purpose[17] or unstable KF/SiO_2, which we tested.

The transformation of sulfonate *S*-**10** into epoxide *S*-**1a** was complicated by a high reactivity of the latter. When DBU was used, the yield of epoxide was only 51% due to partial tarring, while on treatment with a suspension of K_2CO_3 in methanol, a considerable portion of the epoxide formed was converted into 1-*O*-methyl ether of diol *S*-**9**. The smooth transformation of sulfonate *S*-**10** into epoxide *S*-**1a** (yield 90%) was achieved by using an equimolar amount of a saturated solution of K_2CO_3 in methanol (0.225 mol L^{-1} of potassium carbonate) in which elimination occurs as a fast and controllable process due to the homogeneity (Scheme 3).

Scheme 3



TIPS = 2,4,6-$Pr^i_3C_6H_2SO_2$

Reagents and conditions: *i*. H_2, Pd+Pb/$CaCO_3$, quinoline (97%); *ii*. TIPSCl, Bu^n_2SnO, then KF/CaF_2 (95%); *iii*. K_2CO_3/MeOH (or DBU) (90% or 51%); *iv*. H_2O (0.35 mol-equiv.), Jacobsen-(*S*,*S*)-Co^{III}OAc-Salen (48% and 22% *R*-**9**).

For epoxide *S*-**1a** *ee* was measured to be 52%. Using this value and the ratio of sulfonates *S*-**10** and *S*-**11** equal to 95 : 5, the above *ee* for diol *S*-**5** can be easily calculated to be ~60% taking into account the measurement error.

The enantiomeric purity of scalemic epoxide *S*-**1a** obtained in a relatively high overall yield (42% from hexynoate **2**) is obviously too low for its use as a synthon. The *ee* was increased to an acceptable level of 98.4% by selective EHTE transformation of the minor *R*-component of this scalemic epoxide.[9] With the use of 1 mol % of *R*-selective precatalyst ((*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) = Jacobsen-(*S*,*S*)-Co^{II}-Salen) and 35 mol % of water, the *R*-**1a** impurity was hydrolyzed almost exclusively. After that, the enantiomer *S*-**1a**, which remained intact, was easily isolated owing to its volatility by distillation from the reaction mixture, and the minor amount of diol *R*-**9** formed was isolated from the nonvolatile residue.

The synthetic route to synthon *S*-**1a** that we developed includes six steps from methyl hex-5-ynoate **2**, which is relatively few. Moreover, this route illustrates the principle of synthesis of valuable terminal epoxides with high enantiomeric purity from achiral olefin precursors by means of successive use of two chiral metal complex catalysts with coordinated enantiodirectivity.

Experimental

^{1}H NMR spectra were recorded on Bruker VM-250 (250.13 MHz), Bruker AM-300 (300.13 MHz), and Bruker DRX-500 (500.13 MHz) spectrometers at 303 K using $SiMe_4$ (δ 0.00) as the internal standard. The optical rotations were measured on a PU-5 universal polarimeter (GNIIChNP, Russia). Analytical TLC was performed on Sorbfil silica gel plates (Sorbpolymer, Russia) and detection was done by spraying the plates with a solution of phosphomolybdic acid with subsequent heating. Column chromatography was carried out on Kieselgel 60 silica gel (Merck), 230—400 mesh activated at 150 °C/30 min or on neutral alumina (Merck), 70—230 mesh, activity I. Unless stated otherwise, the extracts were dried with anhydrous $MgSO_4$ and evaporated to dryness first on a rotary evaporator in vacuum of a water-jet pump and then at 3 Torr to a constant weight.

Commercial TsCl (Reachim), TIPSCl (Acros), Lindlar catalyst (10% Pd+Pb/$CaCO_3$) (Fluka), $(DHQ)_2PHAL$ (Fluka), and MesCl, DBU, $Bu^n{}_2SnO$, Jacobsen-(*S*,*S*)-Co^{II}-Salen, and MCPBA (85%) (all Aldrich) were used as received. *d*-Ephedrine free base was isolated from the hydrochloride (Aldrich) by a standard method. Methyl hex-5-ynoate **2** was synthesized by a known method.[18]

The reagent KF/CaF_2 was prepared by grinding a mixture of $KF\cdot 2H_2O$ (6.17 g), CaF_2 (24.68 g), and water (12 mL) in a mortar, drying of the resulting sticky material directly in the mortar, first at 25 Torr and then at 5 Torr and 24 °C, and finally at 100 °C, and repeated grinding of the solid material thus formed. The resulting dry loose white powder (30.51 g) contained 3.44 mmol of KF in 1 g.

Enantiomeric analysis of terminal epoxides (general procedure[19]). Samples of epoxides **1a** or **4** (5—20 mg) and *d*-ephedrine (1.02—1.05 mol-eq. of anhydrous base or its hemihydrate) were heated in a conical-bottom microvessel until *d*-ephedrine melted (m.p. 38 °C or 40 °C, anhydrous or hemihydrate), thoroughly stirred, and kept in the dark at room temperature for 3—5 days or heated for 1.5 h at 100 °C to complete epoxide conversion according to TLC. The reaction mixture (colorless transparent solid material) was dissolved in C_6D_6 (0.4 mL) and a ^{1}H NMR spectrum (500 MHz) was recorded. The enantiomer ratio was determined from the ratio of integral intensities of the proton signals for the C-methyl groups of the ephedrine residues in the diastereomer pairs of adducts, δ_H 0.97/1.00 (*R*/*S*) for the adducts from epoxides **1a** and 0.94/0.97 (*R*/*S*) for the adducts from epoxides **4**. The pairs of signals of other diastereomer protons can also be used for analysis (see Ref. 19).

Methyl non-8-en-5-ynoate (3) (for general method, see Ref. 20). Methyl 5-hexynoate **2** (7.2 g, 57.1 mmol) was added to a continuously stirred suspension of finely ground anhydrous K_2CO_3 (18.9 g, 137 mmol), CuI (9.16 g, 48 mmol), NaI (20.55 g, 137 mmol), and copper powder (10 mg) in anhydrous MeCN (100 mL), and the mixture was cooled in an ice bath. Freshly distilled allyl iodide (11.51 g, 68.5 mmol) was added in three portions over a period of 15 min and the cooling bath was removed. After 15 min, TLC analysis showed complete conversion of the starting acetylene **2**. Benzene (30 mL) and a saturated aqueous solution of NH_4Cl (30 mL) were added and the aqueous layer was separated and extracted with benzene (30 mL). The organic phases were combined, dried, and concentrated to 80 mL. The resulting solution was stirred for 10 min with 10% aqueous NH_4OH (10 mL) and a small amount of $Na_2S_2O_3$ (until the iodine color disappeared), the organic phase was separated and distilled first under atmospheric pressure and then *in vacuo* to give 5.69 g (60%) of enyne **3** as a colorless liquid, b.p. 87—89 °C (5 Torr), R_f 0.65 (hexane—EtOAc, 7 : 3; starting **2** R_f 0.35). ^{1}H NMR (300 MHz), $CDCl_3$, δ: 1.82 (tt, 2 H, C(3)H_2, $^3J_{2,3}$ = 7.3 Hz, $^3J_{3,4}$ = 7.1 Hz); 2.26 (tt, 2 H, C(4)H_2, $^5J_{4,7}$ = 2.2 Hz); 2.44 (t, 2 H, C(2)H_2); 2.92 (br.dt, 2 H, C(7)H_2, $^3J_{7,8}$ = 5.2 Hz, $^4J_{7,9c}$ = 1.7 Hz, $^4J_{7,9t}$ = 1.7 Hz); 3.66 (s, 3 H, OMe); 5.08 (dq, 1 H, H(9-*cis*), $^3J_{8,9c}$ = 9.9 Hz, $^2J_{9s,9t}$ = 1.7 Hz); 5.28 (dq, 1 H, *trans*-H(9), $^3J_{8,9t}$ = 17.0 Hz); 5.80 (ddt, 1 H, H(8)).

Racemic methyl 8,9-epoxynon-5-ynoate (*rac*-4). Portions of 85% MCPBA (4.87 g, 24 mmol) were added with stirring to a suspension of finely ground $KHCO_3$ (3.6 g, 36 mmol) in a solution of enyne **3** (2.0 g, 12 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at 24 °C with frequent TLC analysis; after 3 h, additional portions of $KHCO_3$ (0.9 g, 9 mmol) and MCPBA (2.22 g, 7.1 mmol) were added. Within 4.5 h after beginning of the reaction, about ~25% of the starting olefin remained in the thickened mixture, but the amount of polar products markedly increased. The mixture was filtered, the residue on the filter was washed with CH_2Cl_2, and the filtrate was washed with water, dried, and concentrated *in vacuo* to ~20 mL. The solution thus obtained was poured onto a column with alumina (50 g). Elution with CH_2Cl_2 gave successively (after careful evaporation) 1.0 g of a mixture of enyne **3** and epoxide (~6 : 4) and 1.0 g of epoxide *rac*-**4** containing up to 20% of enyne **3** and 3-ClC_6H_4COOH (NMR). Repeated epoxidtion of the first fraction gave additionally 250 mg of the product with the same purity. The overall yield of crude epoxide *rac*-**4** was 57% and the product was used without additional purification. Light-yellow volatile liquid, R_f 0.35 (hexane—EtOAc, 7 : 3; starting **3** R_f 0.55). ^{1}H NMR (500 MHz), $CDCl_3$, δ: 1.81 (quintet, 2 H, C(3)H_2, $^3J_{2,3}$ = $^3J_{3,4}$ = 7.2 Hz); 2.23 (tt, 2 H, C(4)H_2, $^5J_{4,7}$ = 2.2 Hz); 2.43 (t, 2 H, C(2)H_2); 2.43 + 2.56 (both ddt, 1 H each, C(7)H_2, $^2J_{7A,7B}$ = 17.2 Hz, $^3J_{7A,8}$ = 5.0 Hz, $^3J_{7B,8}$ = 4.4 Hz); 2.64 (dd, 1 H, H(9A), $^3J_{8,9A}$ = 2.6 Hz, $^2J_{9A,9B}$ = 5.0 Hz); 2.77 (dd, 1 H, H(9B), $^3J_{8,9B}$ = 3.8 Hz); 3.06 (m, 1 H, H(8)); 3.67 (s, 3 H, OMe).

Racemic methyl (*E*)-8,9-epoxynon-5-enoate (*rac*-1a). A solution of epoxide *rac*-**4** (1.0 g of 80% sample with enyne **3** and 3-ClC_6H_4COOH impurities) in a benzene—hexane solvent mixture (1 : 1, 10 mL) was added to a hydrogen-saturated (at +3—4 °C) suspension of the Lindlar catalyst (0.3 g) in a quinoline solution (0.6 mL) in the same solvent mixture (10 mL). The mixture was hydrogenated for 3 h at +5—7 °C under atmospheric pressure, 0.2-g portions of the catalyst being added every hour. During this period, about one-third of the theoretical amount of hydrogen (42 mL) was absorbed and hydrogenation ceased. The catalyst was filtered off, the filtrate was washed with 10% phosphoric acid (5, 2, and 2 mL) and water (3×2 mL) and passed through a column with alumina (3 g) with additional elution with benzene (10 mL). The catalyst (0.2 g) and quino-

line (0.1 mL) was added to the filtrate, and hydrogenation was continued under the same conditions with the addition of 0.25 g more of the catalyst after 2 h. During 3.5 h, 102 mL of hydrogen was absorbed and hydrogenation stopped. The catalyst was filtered off, and the filtrate was applied onto a column with silica gel (20 g) and eluted with mixtures of hexane with ethyl acetate (9 : 1, 8 : 2 and 7 : 3, 100 mL each). Careful concentration of the middle fractions gave 385 mg (48%) of epoxide *rac*-**1a** as a colorless volatile liquid with a strong fruit odor, R_f 0.40 (hexane—EtOAc, 8 : 2, double development, starting *rac*-**4** R_f 0.28). ^{1}H NMR (500 MHz), $CDCl_3$, δ: 1.70 (quintet, 2 H, C(3)H_2, $^3J_{2,3} = {}^3J_{3,4} = 7.3$ Hz); 2.09 (td, 2 H, C(4)H_2, $^3J_{4,5} = 6.5$ Hz); 2.23—2.42 (m, 2 H, C(7)H_2); 2.32 (t, 2 H, C(2)H_2); 2.50 (dd, 1 H, H(9A), $^3J_{8,9A} = 2.6$ Hz, $^2J_{9A,9B} = 5.0$ Hz); 2.73 (dd, 1 H, H(9B), $^3J_{8,9B} = 4.0$ Hz); 2.94 (tdd, 2 H, H(8), $^3J_{7,8} = 5.4$ Hz); 3.67 (s, 3 H, OMe); 5.40—5.55 (m, 2 H, HC(5)=C(6)H).

Methyl (*S*)-8,9-dihydroxynon-5-ynoate (*S*-5). The two-layer mixture of a solution of enyne **3** (4.38 g, 26.4 mmol) and $(DHQ)_2PHAL$ (103 mg, 0.13 mmol, 0.5 mol.% relative to the enyne) in *tert*-butanol (130 mL) and a solution of $K_3Fe(CN)_6$ (26.04 g, 79.1 mmol), K_2CO_3 (10.92 g, 79.1 mmol), and $K_2OsO_2(OH)_4$ (19.5 mg, 0.053 mmol, 0.2 mol % relative to the enyne) in water (130 mL) was stirred for 5 h at 24 °C until the starting **3** was completely converted (TLC monitoring). The mixture was filtered, the aqueous layer of the filtrate was extracted with EtOAc, and the combined organic layers were washed with 5% H_2SO_4 and then with water to a neutral reaction, dried, and concentrated to obtain an oily residue. The residue was dried by azeotropic distillation of benzene (50 °C (20 Torr) and concentrated to dryness at 60 °C (5 Torr)) to give 4.47 g (85%) of diol *S*-**5** as a light-yellow oil, R_f 0.33 (hexane—EtOAc, 3 : 7; starting enyne R_f 0.78), $[\alpha]_D^{20}$ +2.3° (*c* 3.13, EtOH), *ee* 55—60% (determined indirectly based on the subsequent transformation into epoxide *S*-**1a** with *ee* 52%, see below). ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.80 (tt, 2 H, C(3)H_2, $^3J_{2,3} = 7.3$ Hz, $^3J_{3,4} = 7.0$ Hz); 2.22 (tt, 2 H, C(4)H_2, $^5J_{4,7} = 2.2$ Hz); 2.37 (br.dt, 2 H, C(7)H_2, $^3J_{7,8} = 6.3$ Hz); 2.41 (t, 2 H, C(2)H_2); 3.55, 3.69 (both dt, 1 H each, C(9)H_2, $^3J_{8,9A} = 6.5$ Hz, $^3J_{8,9B} = 3.5$ Hz, $^2J_{9A,9B} = 11.3$ Hz); 3.66 (s, 3 H, OMe); 3.80 (dq, 1 H, H(8)).

Methyl (*S*)-9-(*p*-toluenesulfonyloxy)-8-hydroxynon-5-ynoate (6a) with impurities of isomeric 8-*O*-monosulfonate (7a) and 8,9-*O,O´*-bissulfonate (8a). Solution of diol *S*-**5** (146 mg, 0.73 mmol) in benzene (5.8 mL) was concentrated in a slight vacuum to a half of the volume, Bu^n_2SnO (272 mg, 1.09 mmol) was added to the remaining solution, and the suspension was refluxed until the precipitate dissolved almost completely (15 min). The solution was concentrated in a slight vacuum to dryness, the residue was dissolved in CH_2Cl_2 (1.5 mL), the resulting solution was cooled to 0 °C, and TsCl (132 mg, 0.69 mmol) was added with stirring. After 30 min, cooling was removed, and CH_2Cl_2 (7 mL) and finely ground $KF \cdot 2H_2O$* (424 mg, 7.3 mmol) were added (for destruction of the intermediate Sn alkoxides and removal of Sn-containing products). The suspension was stirred for 12 h and filtered, the filtrate was concentrated to 2 mL and passed through a column with 5 g of silica gel with CH_2Cl_2 as the eluent. Concentration of the filtrate gave a mixture of tosylates **6a** and **7a** (77 : 23, 236 mg, 91.5%) as a greenish-yellow oil, R_f 0.29 for **6a** and 0.34 for **7a** (hexane—EtOAc, 7 : 3, triple development). ^{1}H NMR (250 MHz), $CDCl_3$, δ **6a**: 1.78 (tt, 2 H, C(3)H_2, $^3J_{2,3} = 7.3$ Hz, $^3J_{3,4} = 6.9$ Hz); 2.18 (tt, 2 H, C(4)H_2, $^5J_{4,7} = 2.3$ Hz); 2.39 (t, 2 H, C(2)H_2); 2.38—2.43 (m, 2 H, C(7)H_2); 2.45 (s, 3 H, Me_{Ar}); 3.68 (s, 3 H, OMe); 3.94 (qd, 1 H, H(8), $^3J_{7,8} = 6.0$ Hz, $^3J_{8,9A} = 5.9$ Hz, $^3J_{8,9B} = 4.4$ Hz) 4.04 (dd, 1 H, H(9A), $^2J_{9A,9B} = 10.0$ Hz); 4.12 (dd, 1 H, H(9B)); 7.36 and 7.81 (both d, 2 H each, 4 H_{Ar}, $^3J = 8.0$ Hz); 4.58 (dtd, 0.30 H, H(8), $J = 7.5$ Hz, $J = 5.6$ Hz, $J = 3.5$ Hz). In an analogous experiment with 1.1 equiv. TsCl, 2.5% of bis-tosylate **8a** was identified; R_f 0.50, characteristic multiplet in the ^{1}H NMR spectrum with δ 4.62 ($\Sigma J = 22$ Hz).

Methyl (*S*)-9-(2,4,6-trimethylbenzenesulfonyloxy)-8-hydroxynon-5-ynoate (6b) with an impurity of isomeric 8-*O*-monosulfonate (7b). A solution of diol *S*-**5** (116.7 mg, 0.58 mmol), MesCl (140 mg, 0.64 mmol), and pyridine (92 mg, 1.17 mmol) in CH_2Cl_2 (1.2 mL) was stirred for 48 h at 24 °C (to almost complete conversion of the starting compound according to TLC). The reaction mixture was diluted with CH_2Cl_2 (6 mL), washed with 10% H_3PO_4 (2.5 mL) and water to a neutral reaction, dried, and concentrated to dryness. Chromatography of the residue on silica gel (5 g, elution with CH_2Cl_2) gave 126.5 mg (57%) of a sulfonate mixture **6b** and **7b** (86 : 14) as a light-yellow oil, R_f 0.62 (EtOAc, R_f of starting *S*-**5** 0.33). ^{1}H NMR (250 MHz), $CDCl_3$, δ **6b**: 1.77 (tt, 2 H, C(3)H_2, $^3J_{2,3} = 7.3$ Hz, $^3J_{3,4} = 7.0$ Hz); 2.18 (tt, 2 H, C(4)H_2, $^5J_{4,7} = 2.3$ Hz); 2.32 (s, 3 H, *p*-Me_{Ar}); 2.39 (t, 2 H, C(2)H_2); 2.44 (m, 2 H, C(7)H_2); 2.64 (s, 6 H, 2 *o*-Me_{Ar}); 3.67 (s, 3 H, OMe); 3.95—4.15 (m, 3 H, H(8) + C(9)H_2); 6.99 (br.s, 2 H, 2 H_{Ar}); **7b**: 4.58 (m, 0.14 H, H(8)).

Methyl (*S*)-9-(2,4,6-triisopropylbenzenesulfonyloxy)-8-hydroxynon-5-ynoate (6c) with an impurity of isomeric 8-*O*-monosulfonate (7c). A solution of diol *S*-**5** (122.6 mg, 0.61 mmol), TIPSCl (204 mg, 0.67 mmol), and pyridine (96.9 mg, 1.22 mmol) in CH_2Cl_2 (1.3 mL) was kept for 72 h at 24 °C (to ≥90% conversion of the starting compound according to TLC). The reaction mixture was diluted with CH_2Cl_2 (6 mL), washed with 10% H_3PO_4 (2.5 mL), and applied onto a column with silica gel (5 g). Elution with CH_2Cl_2 gave 162 mg (57%) of a sulfonate mixture **6c** and **7c** (96 : 4) as a light-yellow oil, R_f 0.58 (EtOAc). ^{1}H NMR (250 MHz), $CDCl_3$, δ **6c**: 1.26 (d, 6 H, *p*-$\underline{Me}_2CH$, $^3J = 6.9$Hz); 1.27 (d, 12 H, 2 *o*-$\underline{Me}_2CH$, $^3J = 6.7$Hz); 1.78 (tt, 2 H, C(3)H_2, $^3J_{2,3} = 7.4$ Hz, $^3J_{3,4} = 7.0$ Hz); 2.19 (tt, 2 H, C(4)H_2, $^5J_{4,7} = 2.3$ Hz); 2.39 (t, 2 H, C(2)H_2); 2.45 (m, 2 H, C(7)H_2); 2.92 (septet, 1 H, *p*-$Me_2C\underline{H}$, $^3J = 6.9$ Hz); 3.67 (s, 3 H, OMe); 3.95—4.20 (m, 5 H, H(8) + C(9)H_2 + 2 *o*-$Me_2C\underline{H}$); 7.20 (br.s, 2 H, 2 H_{Ar}); **7c**: 4.77 (m, 0.04 H, H(8)).

Methyl (*S*)-8,9-epoxynon-5-ynoate (*S*-4). A suspension of $LiOH \cdot H_2O$ (81.7 mg, 1.95 mmol) in a solution of diol *S*-**5** (120 mg, 0.60 mmol) and TsCl (148 mg, 0.78 mmol) in CH_2Cl_2 (1.5 mL) was stirred for 30 min at 24 °C. TLC analysis showed complete conversion of the starting diol *S*-**5** and the formation of tosylates **6a** and **7a** and a minor amount of epoxide *S*-**4** (hexane—EtOAc, 7 : 3, R_f 0.03, 0.24, 0.29, and 0.50, respectively). *N*-(2-Hydroxyethyl)pyrrolidine* (21 mg, 0.18 mmol) in CH_2Cl_2 and DBU (178 mg, 1.2 mmol) were added to the mixture and the mixture was stirred for 1.5 h at 24 °C. TLC analysis showed complete conversion of the tosylates and an increase in the epoxide content. The reaction mixture was combined with

* NaF is ineffective under these conditions.

* This amino alcohol serves for quenching of the excess of TsCl.

the reaction mixtures from experiments on DBU treatment of previously obtained sulfonyl derivatives **6a** (+ **7a**) and **6b** (+ **7b**), the total mixture was diluted with CH_2Cl_2 and washed with 10% H_3PO_4 and water. Chromatography on silica gel (hexane—EtOAc, 9 : 1 → 7 : 3) gave epoxide *S*-**4**, yield 43% (in relation to the total amount of the starting diol *S*-**5**) as a light yellow liquid, $[\alpha]_D^{24}$ +2.2° (*c* 1.54, EtOH), *ee* 37%. According to TLC and ^{1}H NMR spectrum, epoxide *S*-**4** was identical to the described *rac*-**4**.

Methyl (5*Z*,8*S*)-8,9-dihydroxynon-5-enoate (*S*-9). A suspension of the Lindlar catalyst (1.34 g) in a mixture of quinoline (1.46 g), benzene (67 mL), and hexane (31 mL) was saturated with hydrogen at 5—7 °C, and diol *S*-**5** (4.47 g) was added and hydrogenated at this temperature until hydrogen absorption ceased (2 h). The catalyst was filtered off and washed with benzene, and the filtrate was concentrated *in vacuo*. The main bulk of quinoline was removed by adding water (100 mL) to the residue followed by concentrating the mixture at 50—60 °C (20→5 Torr) (washing with dilute acids results in considerable loss of diol due to its high solubility in water) to give light-brown oil consisting of diol *S*-**9** (4.38 g, 97%) and quinoline (0.79 g) (according to NMR data) suitable for the use in the next step. For measurement of characteristics, a sample of diol *S*-**9** was purified by chromatography (according to TLC, it migrated similarly as the starting diol *S*-**5**) $[\alpha]_D^{24}$ −2.3° (*c* 1.28, EtOH). ^{1}H NMR (300 MHz), $CDCl_3$, δ: 1.70 (tt, 2 H, C(3)H$_2$, $^3J_{2,3}$ = 7.3 Hz, $^3J_{3,4}$ = 6.9 Hz); 2.10 (q, 2 H, C(4)H$_2$, $^3J_{4,5}$ = 6.9 Hz); 2.24 (q, 2 H, C(7)H$_2$, $^3J_{6,7}$ = 6.1 Hz, $^3J_{7,8}$ = 6.1 Hz); 2.32 (t, 2 H, C(2)H$_2$); 3.48, 3.65 (both dt, 1 H each, C(9)H$_2$, $^3J_{8,9A}$ = 7.0 Hz, $^3J_{8,9B}$ = 3.3 Hz, $^2J_{9A,9B}$ = 11.0 Hz); 3.67 (s, 3 H, OMe); 3.73 (br.qd, 1 H, H(8)); 5.41—5.56 (m, 2 H, HC(5)=C(6)H).

Methyl (5*Z*,8*S*)-9-(2,4,6-triisopropylbenzenesulfonyloxy)-8-hydroxynon-5-enoate (*S*-10). A suspension of Bu^n_2SnO (4.40 g, 17.6 mmol) in a solution of diol *S*-**9** (2.975 g, 14.71 mmol, with an impurity of 0.525 g of quinoline, see above) in benzene (119 mL) was slowly distilled under atmospheric pressure. After 30 min, half of the volume evaporated to give an opalescent solution. The solution was cooled, solid TIPSCl (4.90 g, 16.2 mmol) was added, the solution was stirred for 1 h at 24 °C and diluted with benzene (119 mL). The KF/CaF_2 reagent (21.9 g, 75 mmol KF) was added, water (1.35 g, 75 mmol) was added dropwise with stirring, and stirring was continued. The progress of removal of Sn-containing impurities was monitored as a decrease in the length of the "tail" starting at the site of sample application on the TLC plate. After 18 h, the suspension was filtered, the precipitate being washed on the filter with benzene. The filtrate was washed with 10% H_3PO_4 (19 mL) and water (10 mL), dried, and concentrated to dryness. The residue was chromatographed on silica gel (80 g), elution with CH_2Cl_2 (300 mL) and a hexane—EtOAc mixture (7 : 3, 400 mL). Concentrating the combined eluate to dryness gave 6.59 g (95%) of sulfonate *S*-**10** as a thick light-yellow oil, R_f 0.49 (hexane—EtOAc, 3 : 7; R_f 0.33 for the starting *S*-**9**), $[\alpha]_D^{24}$ −0.10° (*c* 2.59, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.26 (d, 6 H, *p*-Me$_2$CH, ^3J = 6.7 Hz); 1.27 (d, 12 H, 2 *o*-Me$_2$CH, ^3J = 6.7 Hz); 1.68 (tt, 2 H, C(3)H$_2$, $^3J_{2,3}$ = 7.2 Hz, $^3J_{3,4}$ = 7.3 Hz); 2.07 (q, 2 H, C(4)H$_2$, $^3J_{4,5}$ = 7.3 Hz); 2.27 (m, 2 H, C(7)H$_2$); 2.29 (t, 2 H, C(2)H$_2$); 2.91 (septet, 1 H, *p*-Me$_2$CH); 3.65 (s, 3 H, OMe); 3.92 (m, 1 H, H(8)); 3.98, 4.07 (both dt, 1 H each, C(9)H$_2$, $^3J_{8,9A}$ = 6.6 Hz, $^3J_{8,9B}$ = 3.5 Hz, $^2J_{9A,9B}$ 10.0); 4.14 (septet, 2 H, 2 *o*-Me$_2$CH, ^3J = 6.7 Hz); 5.42, 5.51 (both dt, 1 H each, HC(5)=C(6)H, $^3J_{6,7}$ = 7.2 Hz, $^3J_{5,6}$ = 11.1 Hz); 7.19 (br.s, 2 H, 2 H$_{Ar}$); impurity of 8-*O*-isomer *S*-**11**: 4.76 (m, 0.05 H, H(8)). The reaction of diol *S*-**9** with TIPSCl in the presence of pyridine was not completed in 3 days and afforded sulfonate *S*-**10** in 59% yield.

Methyl (5*Z*,8S)-8,9-epoxynon-5-enoate (*S*-1a). ***A.*** A mixture of TIPS-ester *S*-**10** (1.20 g, 2.56 mmol), DBU (0.78 g, 5.12 mmol), and CH_2Cl_2 (12 mL) was stirred for 80 min at 24 °C. The black solution was diluted with CH_2Cl_2 (5 mL), washed with water (5 mL), 10% H_3PO_4 (5 mL), and again water (5 mL), and filtered through silica gel (50 g). The pale yellow eluate was concentrated and the volatile fraction up to 170 °C (5 Torr) was collected to give 242 mg (51%) of epoxide *S*-**1a** as a colorless liquid, R_f 0.53 (hexane—EtOAc, 8 : 2; R_f 0.44 for the starting *S*-**10**), $[\alpha]_D^{24}$ +2.0° (*c* 1.10, EtOH), *ee* 52%. According to TLC and ^{1}H NMR, the product was identical to *rac*-**1a**.

B. A saturated (0.225 mol L^{-1}) solution of K_2CO_3 in methanol (68.4 mL, 15.4 mmol K_2CO_3) was added in portions with stirring over a period of 20 min to a cooled (0 °C) solution of TIPS ester *S*-**10** (6.59 g, 14.1 mmol) in methanol (26 mL), and the mixture was stirred for an additional 10 min. The light-yellow solution was diluted with water (140 mL) and extracted with CH_2Cl_2 (3×86 mL). The extract was dried and concentrated in a slight vacuum, the solvents were finally evaporated through a Vigreux column, and the residue was distilled to give 2.33 g (90%) of epoxide *S*-**1a**, b.p. 120—130 °C (0.1 Torr) identical to the product obtained by procedure ***A***.

C. A solution of the Jacobsen-(*S*,*S*)-Co^{II}-Salen precatalyst[9] (6.7 mg, 0.011 mmol) and AcOH (7 mg, 0.12 mmol) in toluene (134 μL) was stirred in air for 30 min until the solution color changed from red to dark-brown. The mixture was concentrated *in vacuo* to dryness to give a solid brown residue (Co^{III}OAc complex). Epoxide (*ee* 52%, 213 mg, 1.16 mmol) and Pr^iOH (41 μL) were added and then water (7.2 μL, 0.40 mmol, 0.35 equiv. with respect to the epoxide) was added with stirring and cooling to 0 °C. The homogeneous mixture was stirred for 22 h at 24 °C and the unreacted epoxide *S*-**1a** was distilled off *in vacuo* (0.12—0.15 Torr) at 107 °C (bath) (102 mg, 48%, 63% relative to the content of the *S*-enantiomer in the starting sample *S*-**1a**), *ee* 98.4%, $[\alpha]_D^{26}$ +1.85° (*c* 1.08, EtOH). The non-volatile residue left after distillation was dissolved in 50% aqueous methanol (2 mL), the red needle crystals of the precatalyst were filtered off, and the filtrate was concentrated to dryness. Chromatography of the residue on silica gel (2 mL, elution with a hexane—EtOAc mixture, 7 : 3) gave diol *R*-**9** (52 mg, 22%, 93% relative to the content of the *R*-enantiomer in the starting sample of *S*-**1a**), $[\alpha]_D^{22}$ +7.5° (*c* 2.05, EtOH), chromatographically identical to diol *S*-**9**.

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