77. Chiral [^{2}H]-Labelled Methylene Groups in Trienoic- and Dienoic Fatty Acids: a Facile Approach *via* Asymmetric Epoxidation of [^{2}H]Allyl Alcohols

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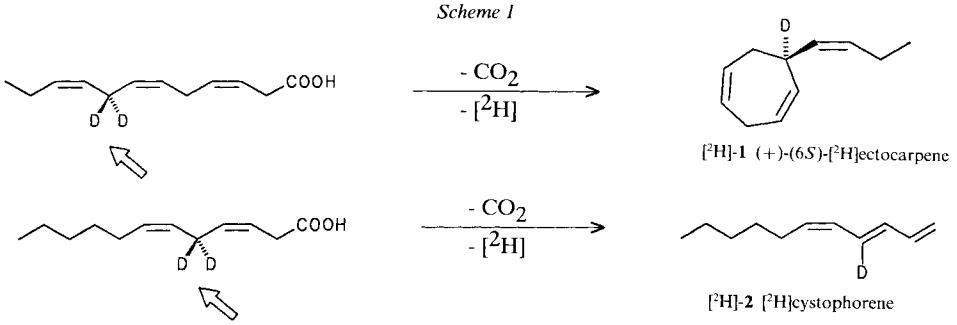
(28.II.90)

Chiral [^{2}H]-labelled methylene groups flanked by two double bonds within (poly)unsaturated fatty acids are readily available from *trans*-2,3-epoxy[2,3-$^2H_2$]alk-4-yn-1-ols, obtained in their turn by asymmetric epoxidation of the corresponding (*E*)-[2,3-$^2H_2$]alk-2-en-4-yn-1-ols (see *Scheme 3*). The procedure is exemplified for (8*S*,3*Z*,6*Z*,9*Z*)-[7,8-$^2H_2$]trideca-3,6,9-trienoic acid ((8*S*)-**11**) and (8*R*)-**11** *(Scheme 4)* as well as for (5*S*,3*Z*,6*Z*)-[4,5-$^2H_2$]deca-3,6-dienoic acid ((5*S*)-**13**) and (5*R*)-**13** *(Scheme 5)*.

1. Introduction. – Unsaturated fatty acids possessing a chiral methylene group (by isotopic substitution with ^{2}H or ^{3}H) have been successfully employed for many times to evaluate the stereochemical course of enzymatic reactions of the lipid metabolism. In particular, the unique physiological activities of the products of lipoxygenases and cyclooxygenases have given an enormous impact to follow their transformations with chirally labelled C_{18}- or C_{20}-fatty acids. Besides a deeper insight into the mechanistic precision work of enzymes, the stereochemical approach also provides a reliable basis for the classification of reaction types and the conceptual description of less well understood biosynthetic pathways.

In continuation of our studies on the biosynthesis of algal pheromones like, *e.g.*, ectocarpene **1** or cystophorene **2** from dodecatrienoic or dodecadienoic acid, such a stereochemical approach seemed to us particularly promising. In a previous model study with the flowering plant *Senecio isatideus*, we have already shown that the biosynthesis of **1** starts from (3*Z*,6*Z*,9*Z*)-dodeca-3,6,9-trienoic acid and proceeds *via* oxidative decarboxylation and loss of a single H-atom from C(8) of the precursor acid [1] *(Scheme 1)*. The linear hydrocarbon **2** is a metabolite of (3*Z*,6*Z*)-dodeca-3,6-dienoic acid, but besides

Scheme 1



decarboxylation, in this case, a single H-atom from the methlyene group at C(5) is involved [1]. To facilitate the mass-spectroscopic detection and analysis of the labelled metabolites, these studies have been carried out with [^{2}H]-labelled (3*Z*,6*Z*,(9*Z*))-undeca-3,6,(9)-di(tri)enoic acids or (3*Z*,6*Z*,(9*Z*))-trideca-3,6,(9)-di(tri)enoic acids. The unnatural acids are metabolized in the same way as the genuine precursors, but their metabolites can be easily analyzed by MS without being superimposed by the plant's own ^{1}H-compounds.

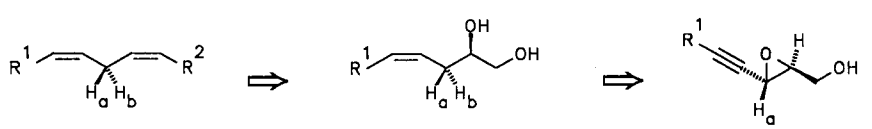
Using now chiral [^{2}H]-labelled (3*Z*,6*Z*,9*Z*)-trideca-3,6,9-trienoic acids (^{2}H at C(8)) or (3*Z*,6*Z*)-deca-3,6-dienoic acids (^{2}H at C(5)) of known absolute configuration and enantiomeric excess, the site specificity of the enzyme(s) (*viz* loss of the (*pro-S*)- or (*pro-R*) H-atom from the methylene groups at C(8) or C(5)) might be simply assessed by looking onto the metabolic fate of the individual hydrogen isotopes *via* MS analysis of the products. In conjunction with the already known absolute configuration of the major product, namely (6*S*)-ectocarpene (**1**) [1] [2], further information on the folding and cyclization of the fatty acid at the active center of the enzyme(s) may be also gained by this approach.

Various syntheses of chiral [^{2}H]- or [^{3}H]-labelled polyenoic fatty acids have appeared in the literature over the past ten years. Many of them make use of a final microbial desaturation of chiral [^{2}H]- or [^{3}H]-labelled stearic or icosanoic acids to α-linolenic or arachidonic acids, respectively [3]. Although this method is straightforward and effective, it is, of course, not applicable to the synthesis of unnatural and short-chain fatty acids. Thus, for the preparation of chiral (3*Z*,6*Z*,9*Z*)-[^{2}H]trideca-3,6,9-trienoic acids, only a highly flexible total synthesis, like *e.g. Corey*'s route towards (7*R*)-[7-^{2}H]arachidonic acid (*ex* tartaric acids [4]) can be successfully employed. However, the multitudiny of laborious steps leading to simple chiral intermediates has to be considered as a major drawback of this approach.

We, therefore, designed and elaborated a new route towards chiral [^{2}H]-labelled methylene groups of unsaturated fatty acids which combines the advantages and simplicity of the acetylenic chemistry and the procedural ease of the *Sharpless* asymmetric epoxidation with the general strategy of the *Corey* approach.

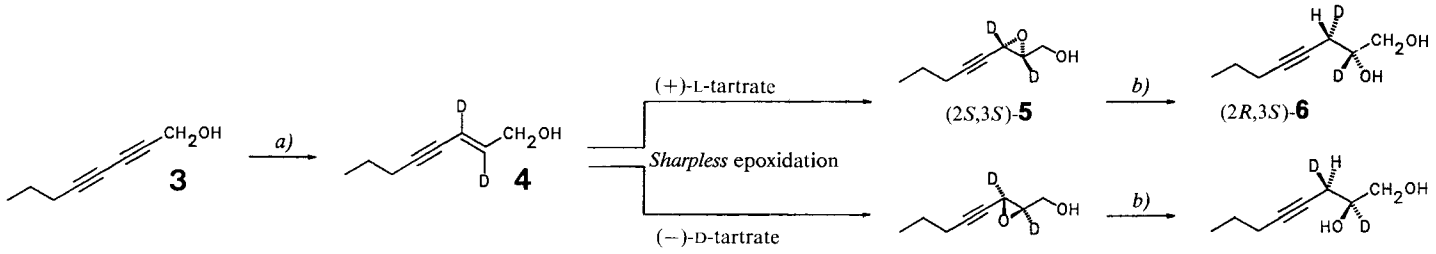
2. Highly Enantiomerically Pure (8*R*,3*Z*,6*Z*,9*Z*)- and (8*S*,3*Z*,6*Z*,9*Z*)-[7,8-^{2}H$_2$]-Trideca-3,6,9-trienoic Acids *via* Asymmetric Epoxidation. – According to the general concept outlined in *Scheme 2*, 2,3-epoxyalk-4-yn-1-ols are ideally suited for the construction of chiral methylene groups which are flanked by two double bonds. The 2,3-epoxy

Scheme 2



alcohols can be regioselectively reduced at C(3) at which a H-atom or one of its isotopes is introduced with inversion of the configuration at this chiral center. Subsequent cleavage of the resulting diol provides an aldehyde which in turn may be olefinated to give the C-backbone of the desired fatty acid. Since the starting alkynols as well as the *Wittig* reagents may contain various alkyl moieties, additional double or triple bonds, as well as

Scheme 3



a) 1. $LiAlD_4$ ($\geq$ 99% D); 2. D_2O ($\geq$ 99.75 D). *b*) 1. $Ti(i\text{-}PrO)_4$; 2. $LiBH_4$.

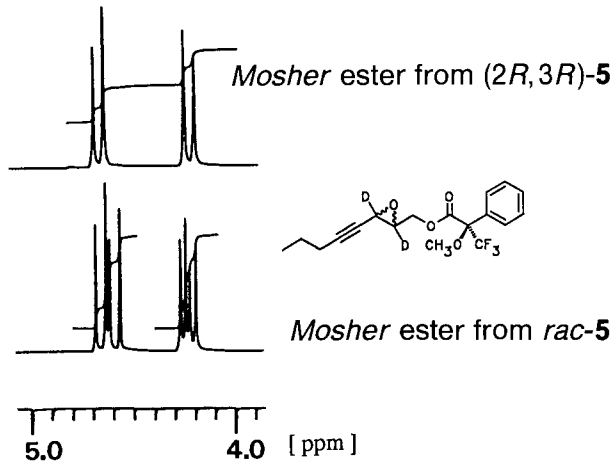
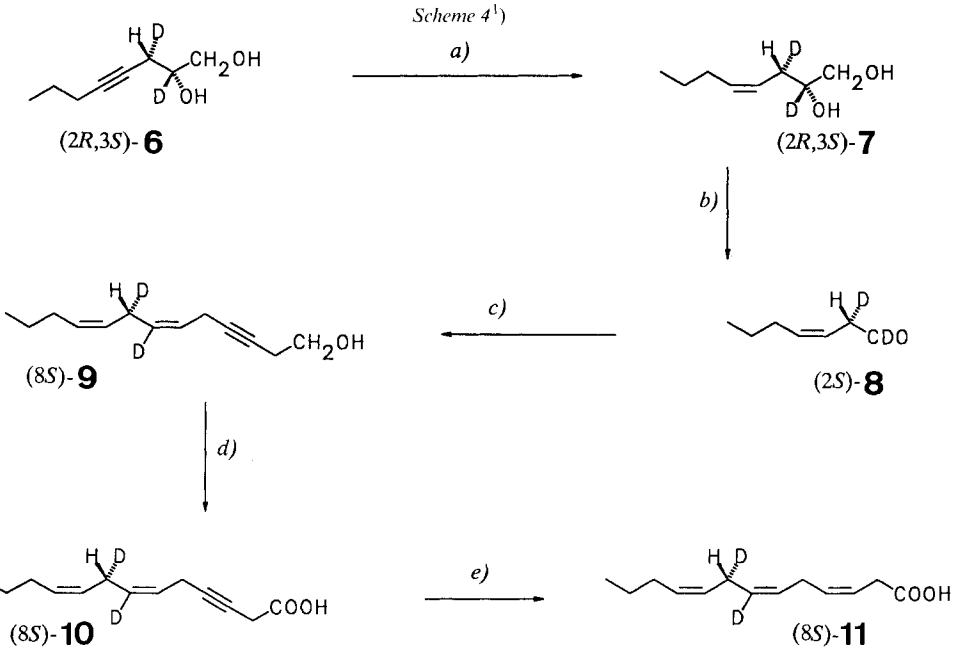


Figure. *250-MHz ^{1}H-NMR spectra ($CDCl_3$) of the methoxy(phenyl)(trifluoromethyl)acetates* (*Mosher* esters) *obtained from* rac-**5** *and* (2R,3R)-**5**. δ in ppm rel. to Me_4Si. Integration of the strongly enhanced signal of the respective contamination with the opposite enantiomer accounts for an ee $\geq$ 97% for (2*S*,3*S*)-**5** and (2*R*,3*R*)-**5**.

certain functional groups, the current concept can be easily extended to the synthesis of a wide range of chiral (^{2}H)polyenoic fatty acids.

For the synthesis of (3*Z*,6*Z*,9*Z*)-trideca-3,6,9-trienoic acid, labelled with ^{2}H at C(8), octa-2,4-diyn-1-ol (**3**) [5] is the most convenient starting material *(Scheme 3)*. Using the commercially available highly enriched $LiAl^2H_4$ ($\geq$ 99% ^{2}H), the required ^{2}H-atom can be introduced with stereospecific reduction of the first triple bond to give the (*E*)-alcohol **4**. The introduction of a second ^{2}H-atom by hydrolysis of the organoaluminum intermediate with ^2H_2O ($\geq$ 99% ^{2}H) is convenient, since it places a permanent ^{2}H-atom onto the C-backbone of the acid (8*S*)-**11** or (8*R*)-**11** (see below) which is not tackled by the enzymatic conversion of the precursor into ectocarpene **1** [1] (*cf. Scheme 1*). According to *Vasella* and coworkers, the asymmetric epoxidation of **4** is readily achieved with the system Ti(*t*-BuO)$_4$ and (−)-D- or (+)-L-diethyl tartrate in CH_2Cl_2 at −30° [6]. The use of Ti(*t*-BuO)$_4$ is essential, since the more commonly employed Ti(i-PrO)$_4$ effects nucleophilic ring opening of the very reactive acetylenic epoxides (2*S*,3*S*)- and (2*R*,3*R*)-**5**. As can be shown by ^{1}H-NMR analysis of their *Mosher* esters [7], both epoxides are of high enantiomeric purity ($\geq$ 97% ee; *Fig.*). Application of the more recently developed catalytical variant of the asymmetric epoxidation [8] is possible, but the ee of the product does not exceed 90% [9]. Following complexation of (2*S*,3*S*)- or (2*R*,3*R*)-**5** with Ti(i-PrO)$_4$, the epoxides are regioselectively reduced at C(3) using $LiBH_4$ [10] to give the two diols (2*R*,3*S*)- and (2*S*,3*R*)-**6**, respectively.

Scheme 4[1])



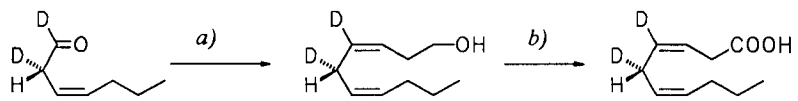
a) Nickel boride/H_2. *b*) $NaIO_4$. *c*) 1. $ThpOCH_2CH_2C{\equiv}CCH_2CH{=}PPh_3$ [4]; 2. pyridinium *p*-toluenesulfonate. *d*) CrO_3/H^+. *e*) *Lindlar*'s catalyst/H_2.

[1]) The same reactions were performed with the corresponding enantiomers (see *Exper. Part*).

Since β,γ-olefinic aldehydes are less prone to enolization (*viz* loss of ^2H and chirality) than their acetylenic analogoues, the triple bond of (2*R*,3*S*)-**6** is next reduced with nickel boride/H_2 [11] to yield the olefinic diol (2*R*,3*S*)-**7** (*Scheme 4*)[1]). Subsequent cleavage of the diol moiety with $NaIO_4$ proceeds under neutral conditions and affords the aldehyde (2*S*)-**8** as key intermediate for the synthesis of chiral (^2H)trienoic and (^2H)dienoic acids. To avoid racemization and isomerization of the sensitive β,γ-unsaturated (^2H)aldehyde (2*S*)-**8**, the crude product is immediately converted to (8*S*)-**9** by *Wittig* reaction and deblocking (Py/TsOH in MeOH), following the protocol of *Corey* and *Lansbury* [4]. Oxidation with CrO_3/H^+ furnishes the acetylenic acid (8*S*)-**10**, and a final hydrogenation with *Lindlar*'s catalyst/H_2 yields the chiral [^2H]acid (8*S*)-**11** without touching the chiral center C(8) ($\geq$ 97% ee; secured by exclusive loss of either ^1H or ^2H on administration of (8*S*)-**11** and (8*R*)-**11** to the flowering plant *Senecio isatideus* [12], *vide infra*).

3. (5*R*,3*Z*,6*Z*)- and (5*S*,3*Z*,6*Z*)-[4,5-$^2H_2$]Deca-3,6-dienoic Acids. – The (3*Z*,6*Z*)-[4,5-$^2H_2$]deca-3,6-dienoic acids, chirally labelled at C(5), are readily accessible from the aldehydes (2*S*)-**8** and (2*R*)-**8** by an analogous sequence. Treatment of (2*S*)-**8** with {3-[(tetrahydropyran-2-yl)oxy]propylidene}triphenylphosphorane affords the tetrahydropyranyl ether which is converted into the free alcohol (5*S*)-**12** on treatment with Py/TsOH in MeOH (*Scheme 5*)[1]). Final oxidation with CrO_3/H^+ gives the decadienoic acid (5*S*)-**13** in 37% overall yield from (2*S*)-**8**.

Scheme 5[1])



(2*S*)-**8** (5*S*)-**12** (5*S*)-**13**

a) 1. $ThpOCH_2CH_2CH{=}PPh_3$; 2. pyridinium *p*-toluenesulfonate. *b*) CrO_3/H^+.

Administration experiments with (8*S*)-**11** or (8*R*)-**11** and freshly disconnected sprouts of *Senecio isatideus* were already successful. Thus, (8*S*)-**11** is converted to ectocarpene **1** with retention of the ^2H-label, while (8*R*)-**11** is transformed into **1** with complete loss of the ^2H-atom from C(8) of the precursor acid. The detailed study is published elsewhere [12].

Financial support by the *Deutsche Forschungsgesellschaft* and the *Fonds der Chemischen Industrie*, Frankfurt am Main, is gratefully acknowledged. We also thank *Bayer AG*, Leverkusen, and *BASF*, Ludwigshafen, for generous supply with solvents and chemicals.

Experimental Part

General. Highly enriched $LiAl^2H_4$ ($\geq$ 99% ^2H) was from *Fluka*, Buchs, Switzerland, and ^2H_2O (99.75% ^2H) from *E. Merck*, Darmstadt, FRG. Reactions were performed under Ar. Solvents and reagents were purified and dried prior to use. Anh. $MgSO_4$ was used for drying operations. Solns. were usually concentrated by flash evaporation under reduced pressure. Anal. GLC: *Carlo Erba* gas chromatograph, *HRGC 5300, Mega* series, equipped with fused-silica capillaries, *SE 30* (10 m × 0.31 mm); H_2 at 30 ml/s served as carrier gas. Polarimetry: *Perkin-Elmer 141*, optical rotations at 21°. IR (cm^{-1}): *Perkin-Elmer-882* IR spectrophotometer. ^1H-NMR (250 or 400 MHz; $CDCl_3$, TMS as internal standard): *Bruker Cryospec WM 250* and *Bruker WM 400*. MS (*m/z*): *Finnigan MAT 90* GLC/MS system and *Finnigan ITD 800* combined with a *Carlo Erba* gas chromatograph, model *Vega*, equipped with a fused-silica capillary, *OV 101* (10 m × 0.32 mm); He at 30 ml/s as carrier gas.

(E)-[2,3-$^2H_2$]Oct-2-en-4-yn-1-ol (**4**). A soln. of **3** (1.23 g, 10.0 mmol) in dry THF (20 ml) is slowly added with cooling (0°) to a well-stirred suspension of $LiAl^2H_4$ ($\geq$ 99% ^2H; 0.355 g, 8 mmol) in THF (50 ml). After 4 h, the cold mixture is hydrolyzed by addition of ^2H_2O ($\geq$ 99% ^2H; 10 ml), and the product is extracted with Et_2O (5 × 50 ml). Pure **4** is obtained after drying, evaporation, and chromatography on silica gel (pentane, then pentane/Et_2O 4:1): 1.14 g (90%). Colorless oil. IR (film): 3337*s* (br.), 2967*s*, 2936*s*, 2876*s*, 2237*w*, 1604*w*, 1462*m*, 1431*m*, 1379*m*, 1338*m*, 1327*m*, 1227*w*, 1173*w*, 1095*s*, 1045*m*, 999*s*, 878*w*, 793*w*, 708*s*, 679*m*. ^1H-NMR ($CDCl_3$): 4.21 (*s*, 2 H–C(1)); 2.32 (*t*, 2 H–C(6)); 2.25 (br. *s*, OH); 1.49 (*sext.*, 2 H–C(7)); 0.92 (*t*, 3 H–C(8)). MS (70 eV): 109 (7, $M^{+\cdot}$ – OH), 97 (100), 83 (12), 80 (7), 69 (45), 55 (10), 40 (18). HR-MS: 126.1009 ($C_8H_{10}{}^2H_2O$, $M^{+\cdot}$, calc. 126.1013).

(2S,3S)-2,3-Epoxy[2,3-$^2H_2$]oct-4-yn-1-ol ((2*S*,3*S*)-**5**). A soln. of (+)-L-diethyl tartrate (6.4 g, 31 mmol) in CH_2Cl_2 (10 ml) is slowly added with stirring to a cold (–25°) soln. of Ti(*t*-BuO)$_4$ (10.3 g, 30.4 mmol) in CH_2Cl_2 (30 ml). The complex is aged for 30 min at –25°, before **4** (2.0 g, 16 mmol) in CH_2Cl_2 (60 ml) and *t*-BuOOH (12.2 ml, 26.4 mmol; 3M in 2,2,4-trimethylpentane) are sequentially added. The temp. is lowered to –30°, and after 5 h, the mixture is hydrolyzed by addition of aq. tartaric acid (150 ml of a 10% soln.). The product is extracted with Et_2O (5 × 100 ml), washed with aq. tartaric acid (10%) and brine, dried, and evaporated. Chromatography on silica gel (pentane/Et_2O 7:3) affords 1.1 g (55%) of a colorless oil. IR (film): 3429*s* (br.), 2967*s*, 2937*s*, 2876*s*, 2250*m*, 1461*m*, 1429*m*, 1381*m*, 1339*m*, 1276*w*, 1228*w*, 1164*w*, 1084*s*, 1030*s*, 964*m*, 940*m*, 895*m*, 871*m*, 800*m*, 769*m*, 759*m*, 745*m*. ^1H-NMR ($CDCl_3$/^2H_2O, 250 MHz): 3.95 (*d*, *J* = 12.5, 1 H–C(1)); 3.69 (*d*, *J* = 12.5, 1 H–C(1)); 2.19 (*t*, 2 H–C(6)); 1.55 (*sext.*, 2 H–C(7)); 0.99 (*t*, 3 H–C(8)). MS (70 eV): 112 (9 $M^{+\cdot}$ – CH_2O), 109 (10), 98 (50), 97 (70), 80 (100), 78 (42), 69 (71), 66 (50), 63 (18), 55 (72), 52 (66), 44 (66). HR-MS: 142.0962 ($C_8H_{10}{}^2H_2O_2$, $M^{+\cdot}$, calc. 142.0960).

(2R,3R)-2,3-Epoxy[2,3-$^2H_2$]oct-4-yn-1-ol ((2*R*,3*R*)-**5**). Prepared from **4** (2.0 g, 16 mmol) and (–)-D-diethyl tartrate as described for (2*S*,3*S*)-**5**. Yield: 1.1 g (55%). Spectroscopic data: identical with those of (2*S*,3*S*)-**5**.

Mosher *Esters of the 2,3-Epoxy Alcohols: General Procedure* [7]. A soln. of (2*S*,3*S*)-, (2*R*,3*R*)-, or (2*RS*,3*RS*)-**5** (20 µl, 0.20 mmol), (+)-(*S*)-methoxy(phenyl)(trifluoromethyl)acetyl chloride (60 µl, 0.24 mmol), and 4-(dimethylamino)pyridine (35 mg, 0.28 mmol) in CH_2Cl_2 (600 µl) is stirred for 30 min. The solvent is evaporated, the amine precipitated by pentane, and the pure *Mosher* ester (45 mg, 95%) obtained after chromatography on silica gel (pentane/Et_2O 9:1). IR (film; identical for both *Mosher* esters): 3072*w*, 2967*m*, 2853*w*, 2250*w*, 1757*s*, 1495*w*, 1451*m*, 1401*w*, 1381*w*, 1353*w*, 1324*w*, 1271*s*, 1239*s*, 1170*s*, 1123*s*, 1082*m*, 1017*s*, 973*m*, 914*w*, 886*w*, 797*w*, 764*m*, 718*s*, 697*m*, 641*m*. ^1H-NMR ($CDCl_3$, 400 MHz; *Mosher* ester of (2*R*,3*R*)-**5**): 7.46 (*m*, 5 arom. H); 4.68 (*d*, *J* = 12.2, 1 H–C(1)); 4.23 (*d*, *J* = 12.2, 1 H–C(1)); 3.56 (*d*, *J* = 1.1, MeO); 2.17 (*t*, 2 H–C(6)); 1.52 (*sext.*, 2 H–C(7)); 0.97 (*t*, 3 H–C(8)). ^1H-NMR (*Mosher* ester of (2*S*,3*S*)-**5**): identical with that of (2*R*,3*R*)-**5**, except for 4.61 (*d*, *J* = 12.2, 1 H–C(1)); 4.27 (*d*, *J* = 12.2, 1 H–C(1)).

(–)-(2R,3S)-[2,3-$^2H_2$]Oct-4-yne-1,2-diol ((2*R*,3*S*)-**6**). To a soln. of (2*S*,3*S*)-**5** (2.8 g, 19.7 mmol) in dry THF (200 ml) is slowly added with stirring at r.t. Ti(i-PrO)$_4$ (7.32 g, 29.5 mmol). After 5 min, $LiBH_4$ (1.64 g, 75.4 mmol) is added in three portions, and stirring is continued for 5 h at 30°. The mixture is hydrolyzed at 0° with H_2SO_4 (250 ml, 5% soln.), the product extracted with Et_2O (5 × 100 ml), and the combined org. layer washed with H_2O. After drying and evaporation, chromatography on silica gel (pentane/Et_2O 6:4) yields 1.5 g (53%) of (2*R*,3*S*)-**6**. Colorless viscous oil. $[\alpha]_D$ = –10.14 (CH_2Cl_2, *c* = 7.49). IR (film): 3371*s* (br.), 2964*s*, 2935*s*, 2875*m*, 2159*w*, 1632*w*, 1490*m*, 1438*s*, 1380*s*, 1338*s*, 1281*m*, 1167*w*, 1134*m*, 1109*m*, 1037*s*, 950*w*, 912*w*, 884*w*, 849*w*, 796*w*. ^1H-NMR ($CDCl_3$, 400 MHz): 3.73 (*d*, *J* = 11.2, 1 H–C(1)); 3.58 (*d*, *J* = 11.2, 1 H–C(1)); 2.46 (*s*, OH); 2.37 (*t*, *J* = 2.2, 1 H–C(3)); 2.2 (*s*, OH); 2.13 (*dt*, *J* = 7.3, 2.2, H–C(6)); 1.50 (*sext.*, *J* = 7.3, 2 H–C(7)); 0.96 (*t*, 3 H–C(8)). MS (70 eV): 126 (16, $M^{+\cdot}$ – H_2O), 115 (29), 113 (23), 101 (17), 97 (25), 83 (41), 82 (34), 68 (100), 67 (84), 62 (63), 55 (53). HR-MS: 126.1008 ($C_8H_{12}{}^2H_2O_2$, $M^{+\cdot}$ – H_2O, calc. 126.1013).

(+)-(2S,3R)-[2,3-$^2H_2$]Oct-4-yne-1,2-diol ((2*S*,3*R*)-**6**). Prepared from (2*R*,3*R*)-**5** (2.8 g, 19.7 mmol) as described for (2*R*,3*S*)-**6**. Yield: 1.5 g (53%). $[\alpha]_D$ = + 9.5 (CH_2Cl_2, *c* = 5.9). Spectroscopic data: identical with those of (2*R*,3*S*)-**5**. HR-MS: 126.1000 ($C_8H_{12}{}^2H_2O_2$, $M^{+\cdot}$ – H_2O, calc. 126.1013).

*(−)-(2*R*,3*S*,4*Z*)-[2,3-$^2H_2$]Oct-4-ene-1,2-diol* ((2*R*,3*S*)-**7**). A well stirred suspension of $Ni(AcO)_2$ (80.0 mg, 0.32 mmol) in EtOH (20.0 ml) is reduced in a closed system, connected to a gas burette and flushed with H_2, by slow injection of $NaBH_4$ (0.31 ml, 1M in EtOH). The active catalyst is poisoned by ethane-1,2-diamine (40 µl), and (2*R*,3*S*)-**6** (3.6 g, 25 mmol) is injected. When the H_2 uptake ceases, the catalyst is filtered off, and Et_2O (100 ml) is added. The org. layer is washed with 5% HCl soln. (2 × 10 ml) and H_2O (10 ml). After drying and evaporation, chromatography on silica gel (pentane/Et_2O 6:4) affords 3.5 g (95%) of (2*R*,3*S*)-**7**. Colorless viscous oil. $[\alpha]_D = -6.93$ ($c = 4.56$). IR (film): 3394*s* (br.), 3012*m*, 2961*s*, 2934*s*, 2874*s*, 2152*w*, 1657*w*, 1456*m*, 1402*m*, 1378*m*, 1337*w*, 1275*m*, 1153*m*, 1109*m*, 1041*s*, 982*w*, 950*m*, 880*w*, 849*m*, 796*w*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 5.36–5.59 (*m*, 2 olef. H); 3.65 (*d*, $J = 11.2$, 1 H–C(1)); 3.46 (*d*, $J = 11.2$, 1 H–C(1)); 2.42 (*s*, 1 OH); 2.17 (*d*, $J = 6.6$, 1 H–C(3)); 2.02 (*q*, 2 H–C(6)); 1.67 (*s*, 1 OH); 1.37 (*sext.*, 2 H–C(7)); 0.89 (*t*, 3 H–C(8)). MS (70 eV): 146 (2, $M^{+\cdot}$), 128 (36), 115 (16), 98 (12), 97 (78), 85 (79), 69 (43), 62 (100), 56 (60). HR-MS: 146.1255 ($C_8H_{14}{}^2H_2O_2$, $M^{+\cdot}$, calc. 1146.1275).

*(+)-(2*S*,3*R*,4*Z*)-[2,3-$^2H_2$]Oct-4-ene-1,2-diol* ((2*S*,3*R*)-**7**). Prepared from (2*S*,3*R*)-**6**. (2.8 g, 19.7 mmol) as described for (2*R*,3*S*)-**7**. Yield: 1.5 g (53%). $[\alpha]_D = +7.18$ (CH_2Cl_2, $c = 4.65$). Spectroscopic data: identical with those of (2*R*,3*S*)-**7**. HR-MS: 146.1239 ($C_8H_{14}{}^2H_2O_2$, $M^{+\cdot}$, calc. 1146.1275).

*(8*S*,6*Z*,9*Z*)-[7,8-$^2H_2$]Trideca-6,9-dien-3-yn-1-ol* ((8*S*)-**9**). At 0°, (2*R*,3*S*)-**7** (0.6 g, 4.0 mmol) is cleaved by stirring with $NaIO_4$ (0.97 g, 4.5 mmol) in H_2O (20 ml). After 1.5 h, the resulting (2*S*)-**8** is extracted with Et_2O (5 × 20 ml), and the combined org. layers are dried (Na_2SO_4). To avoid losses of the volatile (2*S*)-**8**, the bulk of solvent is removed at 200 Torr, and the crude aldehyde is then immediately transferred into a cold (−78°) soln. of {6-[(tetrahydro-2*H*-pyran-2-yl)oxy]hex-3-ynylidene}triphenylphosphorane (8.2 mmol; prepared from the corresponding phosphonium iodide by addition of 1.0 equiv. of BuLi) in dry THF (100 ml) [4]. The mixture is allowed to come to r.t. and hydrolyzed with sat. aq. NH_4Cl soln. (100 ml), and the product is extracted with pentane. The combined org. layers are washed with H_2O, dried, and evaporated, and the Thp ether is prepurified by chromatography on silica gel (pentane/Et_2O 9:1). The compound is deblocked in refluxing MeOH (150 ml) in the presence of pyridinium *p*-toluenesulfonate (100 mg). After 3 h, the alcohol is isolated as usual, and chromatography on silica gel (pentane/Et_2O 4:1) yields 0.5 g (63% overall) of (8*S*)-**9** as a colorless oil. IR (film): 3346*s* (br.), 3013*m*, 2962*s*, 2933*s*, 2874*s*, 2237*w*, 2156*w*, 1636*w*, 1607*w*, 1595*w*, 1465*m*, 1399*m*, 1377*m*, 1334*m*, 1276*m*, 1103*m*, 1046*s*, 928*w*, 880*w*, 848*w*. ^{1}H-NMR ($CDCl_3$, 400 MHz): 5.45–5.31 (*m*, 3 olef. H); 3.64 (*t*, 2 H–C(1)); 2.92 (*td*, $J = 6.5$, 2.4, 2 H–C(5)); 2.73 (br. *s*, 1 H–C(8)); 2.42 (*tt*, $J = 5$, 2.4, 2 H–C(2)); 2.03 (*q*, 2 H–C(11)); 1.58 (*s*, OH); 1.39 (*sext.*, 2 H–C(12)); 0.88 (*t*, 3 H–C(13)). MS (70 eV): 194 (0.5, $M^{+\cdot}$), 63 (5), 149 (9), 147 (11), 133 (15), 119 (53), 107 (52), 93 (100), 92 (84), 81 (78), 80 (65), 69 (61), 55 (45), 53 (28), 51 (32), 41 (92), 39 (82). HR-MS: 194.1591 ($C_{13}H_{18}{}^2H_2O$, $M^{+\cdot}$, calc. 194.1639).

*(8*R*,6*Z*,9*Z*)-[7,8-$^2H_2$]Trideca-6,9-dien-3-yn-1-ol* ((8*R*)-**9**). Prepared from (2*S*,3*R*)-**7** (0.6 g, 4.0 mmol) as described for (8*S*)-**9**. Yield: 0.5 g (63%). Spectroscopic data: identical with (8*S*)-**9**.

*(8*S*,6*Z*,9*Z*)-[7,8-$^2H_2$]Trideca-6,9-dien-3-ynoic Acid* ((8*S*)-**10**). A soln. of CrO_3 (0.74 g, 7.4 mmol) in H_2O (2.1 ml) and conc. H_2SO_4 soln. (0.675 ml) is added slowly with stirring at 0° to a soln. of (8*S*)-**9** (0.48 g, 2.5 mmol) in acetone (35 ml). When the red color of the oxidant persists, the soln. is stirred for 1.5 g at 0° without further addition of Cr(VI). H_2O (60 ml) is added, and the green soln. is extracted with Et_2O (5 × 50 ml). The combined org. layers are washed with brine, until the aq. phase remains colorless. After drying, evaporation and chromatography on silica gel (pentane/Et_2O 7:3), 0.322 g (64%) of (8*S*)-**10** are obtained. IR (film): 3600–3200*s* (br.), 3014*s*, 2963*s*, 2935*s*, 2876*s*, 2660*w*, 2558*w*, 2243*w*, 1720*s*, 1455*w*, 1421*m*, 1399*m*, 1284*m*, 1228*s*, 1178*m*, 1103*w*, 928*w*. ^{1}H-NMR ($CDCl_3/^2H_2O$, 400 MHz): 5.44–5.39 (*m*, 3 olef. H); 3.33 (*t*, $J = 2.4$, 2 H–C(2)); 2.99 (*td*, $J = 6.9$, 2.4, 2 H–C(5)); 2.78 (br. *s*, 1 H–C(8)); 2.03 (*q*, 2 H–C(11)); 1.37 (*sext.*, 2 H–C(12)); 0.91 (*t*, 3 H–C(13)). MS (methyl ester; 70 eV): 223 (5, $M^{+} + 1$), 195 (6), 181 (6), 165 (12), 163 (13), 149 (31), 148 (26), 147 (23), 133 (57), 123 (49), 120 (61), 119 (100), 107 (87), 106 (68), 94 (40), 93 (67), 92 (40), 82 (31), 81 (32), 69 (41), 67 (34), 59 (37), 55 (32), 41 (69), 39 (65). HR-MS: 208.1453 ($C_{13}H_{16}{}^2H_2O_2$, $M^{+\cdot}$, calc. 208.1432).

*(8*R*,6*Z*,9*Z*)-[7,8-$^2H_2$]Trideca-6,9-dien-3-ynoic Acid* ((8*R*)-**10**). Prepared from (8*R*)-**9** (0.48 g, 2.5 mmol) as described for (8*S*)-**10**. Yield: 0.32 g (64%). Spectroscopic data: identical with those of (8*S*)-**10**.

*(8*S*,3*Z*,6*Z*,9*Z*)-[7,8-$^2H_2$]Trideca-3,6,9-trienoic Acid* ((8*S*)-**11**). A soln. of (8*S*)-**10** (0.32 g, 1.5 mmol) in dry THF (10 ml) is hydrogenated over *Lindlar*'s catalyst (100 mg, *Fluka*, Buchs, Switzerland) in the usual manner. When the uptake of H_2 ceases, the catalyst is filtered off, the solvent evaporated, and the crude acid purified by HPLC (*RP 18*, MeOH/H_2O 4:1): 0.29 g (90%). IR (film): 3600–3200*s* (br.), 3014*m*, 2964*s*, 2932*m*, 2875*m*, 2346*w*, 1711*s*, 1414*w*, 1263*m*, 1218*w*, 1162*m*, 1115*m*, 933*w*, 864*w*, 796*w*, 692*w*, 662*w*. ^{1}H-NMR ($CDCl_3/^2H_2O$, 400 MHz): 5.60–5.34 (*m*, 5 olef. H); 3.18 (*d*, 2 H–C(2)); 283 (*t*, 2 H–C(5)); 2.8 (br. *d*, 1 H–C(8)); 2.02 (*q*, 2 H–C(11)); 1.37 (*sext.*, 2 H–C(12)); 0.9 (*t*, 3 H–C(13)). MS (methyl ester; 70 eV): 193 (11, $M^{+} - OMe$), 177 (5), 175 (6), 165 (7), 163 (5), 151 (33), 150 (31), 137 (12), 135 (21), 123 (20), 121 (37), 111 (35), 107 (62), 97 (40), 95 (57), 82 (66), 81 (92),

80 (64), 69 (80), 68 (63), 59 (35), 55 (39), 41 (97), 39 (100). HR-MS (free acid): 210.1601 ($C_{13}H_{18}{}^2H_2O_2$, $M^{+\cdot}$, calc. 210.1588).

(8R,3Z,6Z,9Z)-[7,8-$^2H_2$]Trideca-3,6,9-trienoic Acid ((8*R*)-**11**). Prepared from (8*R*)-**10** (0.30 g, 1.44 mmol) as described for (8*S*)-**11**. Yield: 0.27 g (89%). Spectroscopic data: identical with those of (8*S*)-**11**. HR-MS (methyl ester): 224.1733 ($C_{14}H_{20}{}^2H_2O_2$, $M^{+\cdot}$, calc. 224.1745).

(5S,3Z,6Z)-[4,5-$^2H_2$]Deca-3,6-dien-1-ol ((5*S*)-**12**). At −78°, (2*S*)-**8** (0.56 g, 4.42 mmol) is added to a stirred soln. of {3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propylidene}triphenylphosphorane (prepared at 0° from the corresponding phosphonium bromide (3.4 g, 6.9 mmol) by addition of 1 equiv. of BuLi) in dry THF (100 ml). The soln. is allowed to come to r.t., and the product is isolated, deblocked, and purified as described for (8*S*)-**9**. Chromatography on silica gel furnished 0.45 g (61%) of (5*S*)-**12**. Colorless oil. IR (film): 3345*m* (br.), 3013*m*, 2962*s*, 2933*s*, 2874*s*, 2233*w*, 1648*w*, 1461*m*, 1377*w*, 1233*w*, 1111*w*, 1049*s*, 902*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 5.44–5.27 (*m*, 3 olef. H); 3.63 (*t*, 2 H–C(1)); 2.77 (br. *s*, 1 H–C(5)); 2.35 (*q*, 2 H–C(2)); 2.03 (*q*, 2 H–C(8)); 1.51 (br. *s*, OH); 1.39 (*sext.*, 2 H–C(9)); 0.89 (*t*, 3 H–C(10)). MS (70 eV): 156 (0.5, $M^{+\cdot}$), 138 (4), 123 (9), 109 (13), 95 (38), 81 (92), 80 (77), 69 (100), 68 (67), 56 (43), 55 (38), 41 (92), 39 (80).

(5R,3Z,6Z)-[4,5-$^2H_2$]Deca-3,6-dien-1-ol ((5*R*)-**12**). Prepared from (2*R*)-**8** (0.5 g, 43.9 mmol) as described for (5*S*)-**12**). Yield: 0.41 g (60%). Spectroscopic data: identical with those of (5*S*)-**12**.

(5S,3Z,6Z)-[4,5-$^2H_2$]Deca-3,6-dienoic Acid ((5*S*)-**13**). Alcohol (5*S*)-**12** (0.30 g, 1.92 mmol) is oxidized with Cr(VI) and purified as described for (8*S*)-**10**. Yield: 0.196 g (60%). IR (film): 3600–3200*m* (br.), 3015*m*, 2964*s*, 2936*s*, 2874*m*, 2236*w*, 1711*s*, 1457*w*, 1414*m*, 1377*w*, 1294*m*, 1217*m*, 1171*m*, 1111*w*, 932*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 5.56 (*t*, $J = 7.2$, 1 H–C(3)); 5.46–5.28 (*m*, 2 olef. H); 3.16 (*d*, 2 H–C(2)); 2.77 (br. *s*, 1 H–C(5)); 2.05 (*q*, 2 H–C(8)); 1.40 (*sext.*, 2 H–C(9)); 0.90 (*t*, 3 H–C(10)). MS (70 eV): 170 (4, $M^{+\cdot}$), 152 (8), 137 (5), 133 (5), 123 (8), 122 (8) 110 (19), 109 (21), 95 (28), 81 (96), 80 (73), 69 (81), 68 (62), 55 (41), 45 (79), 41 (100), 39 (89). HR-MS: 170.1263 ($C_{10}H_{14}{}^2H_2O_2$, $M^{+\cdot}$, calc. 170.1275).

(5R,3Z,6Z)-[4,5-$^2H_2$]Deca-3,6-dienoic Acid ((5*R*)-**13**). Prepared from (5*R*)-**12** (0.30 g, 1.92 mmol) as described for (5*S*)-**13**. Yield: 0.18 g (55%). Spectroscopic data: identical with those of (5*S*)-**13**.

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