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Enantiopure 2,9-Dideuterodecane – Preparation and Proof of Enantiopurity

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In memoriam Prof. Wittko Francke

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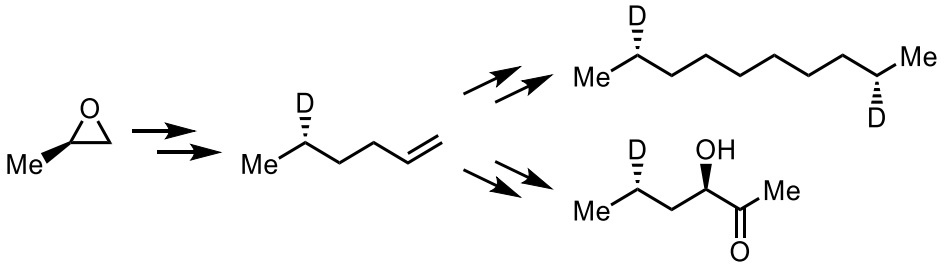
Abstract: (*R*,*R*)- and (*S*,*S*)-(2,9-$^{2}H_2$)-*n*-decane were prepared regio- and stereospecifically in 25-26% yield over five steps from commercially available enantiopure (*R*)- and (*S*)-propylene oxide, respectively. The synthetic procedure involved nucleophilic displacement of (*R*)- and (*S*)-4-toluenesulfonic acid 1-methyl-4-pentenyl ester with $LiAlD_4$ to furnish the respective (5-^{2}H)-1-hexenes. Subsequent olefin metathesis and reduction of the double bond furnished the title compounds. The optical purity of (*R*,*R*)- and (*S*,*S*)-(2,9-$^{2}H_2$)-*n*-decanes could not be determined by chromatography or polarimetry. Therefore, (*R*,*R*)- and (*R*,*S*)-(5-^{2}H)-3-hydroxy-2-hexanones were prepared from their respective hexenes by Wacker oxidation, followed by enantioselective α-hydroxylation. The enantiopurity could then be determined by NMR spectroscopy because the stereospecifically deuterated hydroxyketones showed separated signals for the subterminal carbon atom C-5 in the ^{13}C NMR spectrum.

Graphical Abstract: Optically active (*S*,*S*)-(2,9-$^{2}H_2$)-*n*-decane was prepared in five steps from (*R*)-propylene oxide. Its optical purity was determined at the stage of (*S*)-(5-$^{2}H_2$)-1-hexene, being an intermediate of the synthetic approach, by NMR spectroscopy after Wacker oxidation and enantioselective α-hydroxylation. (*R*,*R*)-(2,9-$^{2}H_2$)-*n*-decane was prepared analogously.

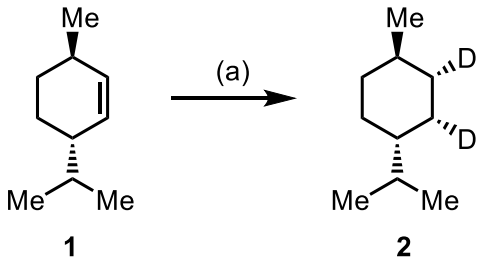


Keywords: Hydrocarbons, Deuteration, Biodegradation, Chirality

Introduction

With the discovery of deuterium in 1932[1] the question arose whether optically active compounds could be prepared whose activity is only based on the differences between deuterium and hydrogen.[2] Two types of compounds could meet this requirement: those that feature a hydrogen and a deuterium atom attached to the same carbon atom, or those in that the isotopically different substituents are not attached directly to a stereocenter.[2]

Several early attempts were made to prepare optically active compounds chiral solely by virtue of deuteration.[2] Notably, already in 1936 Clemo and McQuillen reported the resolution of racemic 1-phenyl-1-(phenyl-d_5)ethan-1-amine by multiple fractional crystallizations of the tartrate salt giving enantiomers with finite optical rotations.[3,4] Although this claim was meticulously questioned,[5] it cannot be dismissed that a skillful experimentalist could not achieve such a resolution. The first clear example of an optically active deuterium compound *per se* was reported in 1949 by Alexander and Pinkus, who reduced (+)-*trans*-2-menthene (Scheme 1, **1**) with D_2 in the presence of Raney nickel to yield the optically active (–)-2,3-dideutero-*trans*-menthane (Scheme 1, **2**).[6]



1 **2**

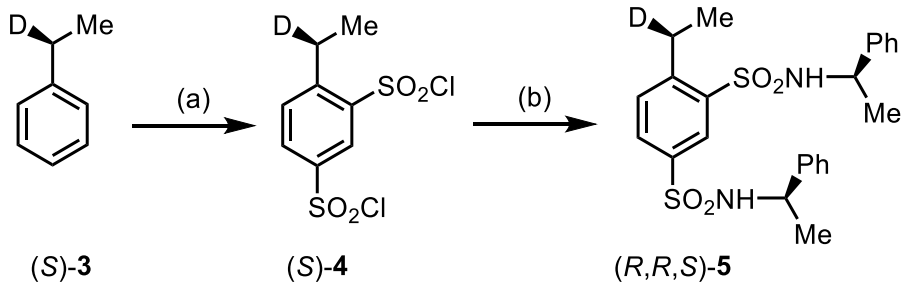
Scheme 1. Preparation of (–)-2,3-dideutero-*trans*-menthane (**2**) from (+)-*trans*-2-menthene (**1**) by Alexander and Pinkus.[6] Reagents: (a) D_2, Raney-Ni. The main diastereoisomer of the product is tentatively assigned according to Verbit.[2]

The first undisputed example of an optically active deuterium compound with only one stereocenter was reported by Eliel who prepared (*R*)-(1-^{2}H)ethylbenzene [(*R*)-**3**] by reduction of α-chloroethylbenzene with $LiAlD_4$.[7] Today, the descriptor optically active deuterium compound not only refers to deuterium compounds with measurable optical

activity, but also to deuterated compounds whose chirality exclusively depends on the differences between hydrogen and deuterium.[2]

Deuterium labeling has become one of the most important and powerful tools in the investigation of reaction mechanisms. As emphasized in several reviews, deuterium-labeled compounds are invaluable for the elucidation of enzymatic reaction mechanisms.[8–10] For mechanistic studies, the regio- and stereospecific incorporation of deuterium into an organic compound is often required. Measuring the optical rotation of deuterated optical isomers is challenging due to their often-low values, which may fall below the detection limit, and their associated large errors.

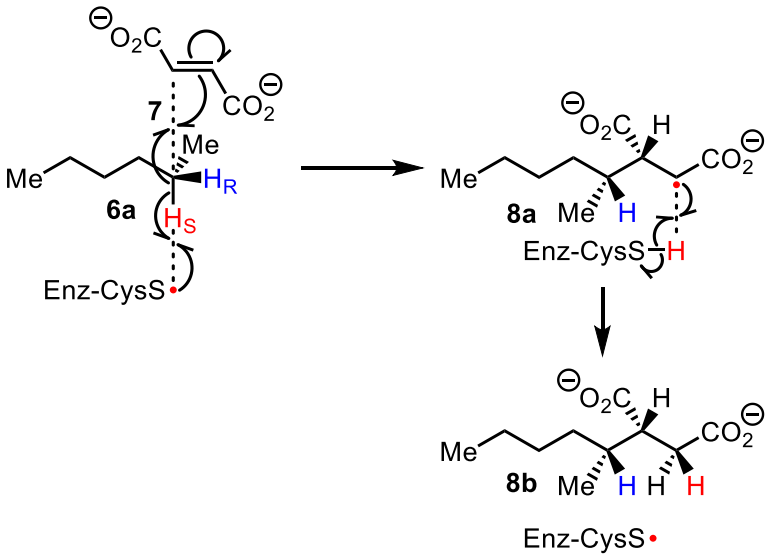
Therefore, other approaches for determining the enantiomeric excess with sufficient precision are required. One major strategy for the determination of the enantiomeric excess of optically active deuterated compounds is NMR spectroscopy. While some approaches make use of chiral shift reagents or chiral solvating agents, others pursue the strategy of chiral derivatization.[11,12] Recently, the enantiopurity of (*S*)-(1-^{2}H)ethylbenzene [(*S*)-**3**] was determined by NMR spectroscopy after chiral derivatization with (*R*)-α-phenethylamine (Scheme 2).[13]



Scheme 2. Synthesis of bis-sulfonamide **5** from (1-^{2}H)ethylbenzene (*S*)-**3**. Reagents: (a) $ClSO_3H$, (b) (*R*)-$PhCH(NH_2)Me$.[13]

As shown for the anaerobic degradation of *n*-hexane (**6a**) by the denitrifying betaproteobacterium *Aromatoleum aromaticum* HxN1, stereospecific deuterium-labeling can provide stereochemical information and profound mechanistic insights into enzyme mechanisms.[14] Activation of *n*-hexane (**6a**) occurs at the subterminal carbon atom (C-2) by the addition to fumarate (**7**) *via* a radical mechanism to furnish (1-methylpentyl)succinate (MPS, **8b**).[15] This reaction is catalyzed by the enzyme (1-methylpentyl)succinate synthase (Mas).[16] Stereospecifically labeled 2,5-dideuterated hexanes (*R*,*R*)- and (*S*,*S*)-**6b** (Figure 1) were used to demonstrate that the formation

of MPS (**8b**) proceeds with inversion at C-2 and that exclusively the pro-*S* hydrogen atom is abstracted from *n*-hexane (**6a**).[14] Based on these findings, a concerted reaction mechanism for the formation of MPS (**8b**) was proposed that would avoid the formation of a reactive 2-hexyl radical (Scheme 3). By combining incubation experiments with deuterium-labeled and non-labeled substrates with gas chromatographic, mass spectrometric and EPR analyses, the entire pathway of *n*-hexane (**6a**) degradation by strain HxN1 has been elucidated.[15,17,18]



Scheme 3: Proposed stereochemical course for the activation of *n*-hexane (**6a**) in strain HxN1 (modified from Jarling *et al*.).[14]

The mesophilic denitrifying betaproteobacterium strain OcN1 and the thermophilic sulfate-reducing deltaproteobacterium strain TD3 activate C_8-C_{12} and C_6-C_{16} alkanes, respectively, in an analogous manner to strain HxN1 by addition of C-2 of the alkane to fumarate yielding the corresponding alkylsuccinic acid derivatives.[19–22] To obtain mechanistic insights into the initial activation reactions of *n*-decane by strains OcN1 and TD3, stereospecifically 2,9-dideuterated *n*-decanes (*R*,*R*)- and (*S*,*S*)-**9a** are ideal model substrates. We speculate, based on evolutionary considerations, that addition of any *n*-alkane to fumarate by the (1-methylalkyl)succinate synthases in different anaerobic bacteria will show the same stereochemistry, although this still has to be proven.

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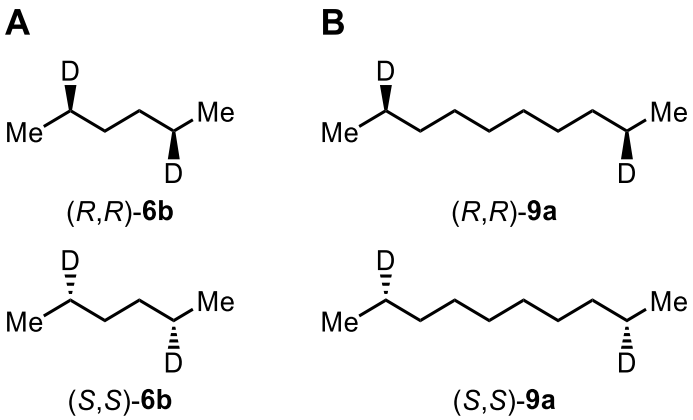

Figure 1. Model substrates for mechanistic investigations into the initial activation reaction in anaerobic degradation of *n*-alkanes: (A) **6** for *n*-hexane degradation by bacterial strain HxN1; (B) **9a** for *n*-decane degradation by bacterial strains OcN1 and TD3.

A literature survey yielded only examples of vicinal dideuterated *n*-decanes that were prepared by catalytic deuteration of an alkene precursor as shown, for example, by Morandi and Jensen.[23] However, to the best of our knowledge no access to the stereospecifically 2,9-dideuterated decanes (*R*,*R*)- and (*S*,*S*)-**9a** has been reported. As outlined above, the determination of the enantiomeric excess of deuterated optically active compounds is often difficult. Therefore, the objective of this study was the preparation of 2,9-dideuterated *n*-decanes (*R*,*R*)- and (*S*,*S*)-**9a**, as well as the development of a facile, reliable method for the determination of their enantiopurity.

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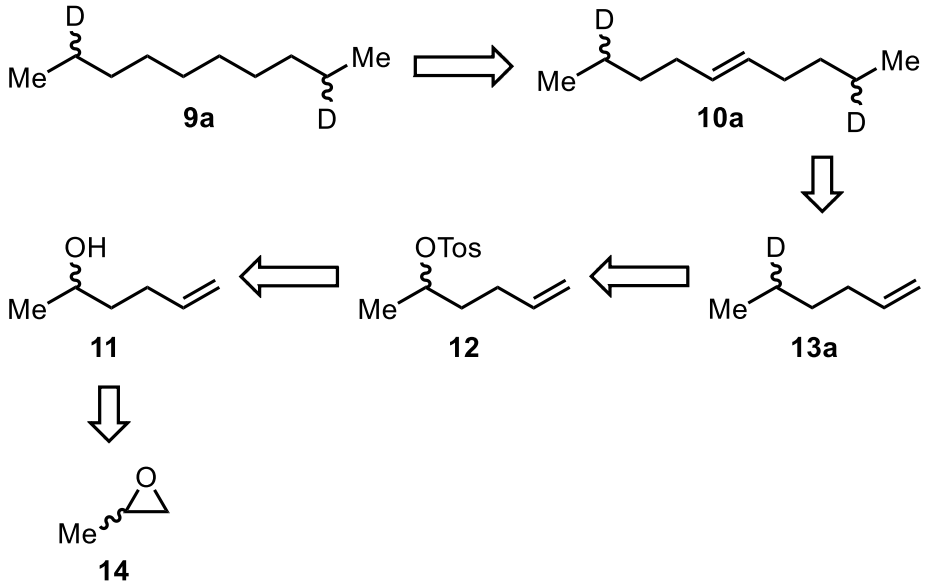
Results and Discussion

Our retrosynthetic analysis of racemic and enantiopure (2,9-$^{2}H_2$)-*n*-decanes, *rac*-, (*R*,*R*)- and (*S*,*S*)-**9a**, is based upon olefin metathesis of hexene **13a** and hydrogenation of the metathesis product **10a** (Scheme 4). The preparation of hexene **13a** may be realised by reduction of tosylate **12** with $LiAlD_4$, which is expected to proceed with inversion of the stereocenter at C-5.[14,24] The tosylate **12** can be prepared from the corresponding alcohol **11**. This, in turn, is easily obtained from commercially available racemic or enantiopure propylene oxides *rac*-, (*R*)- and (*S*)-**14**, by epoxide opening with an allylcuprate.

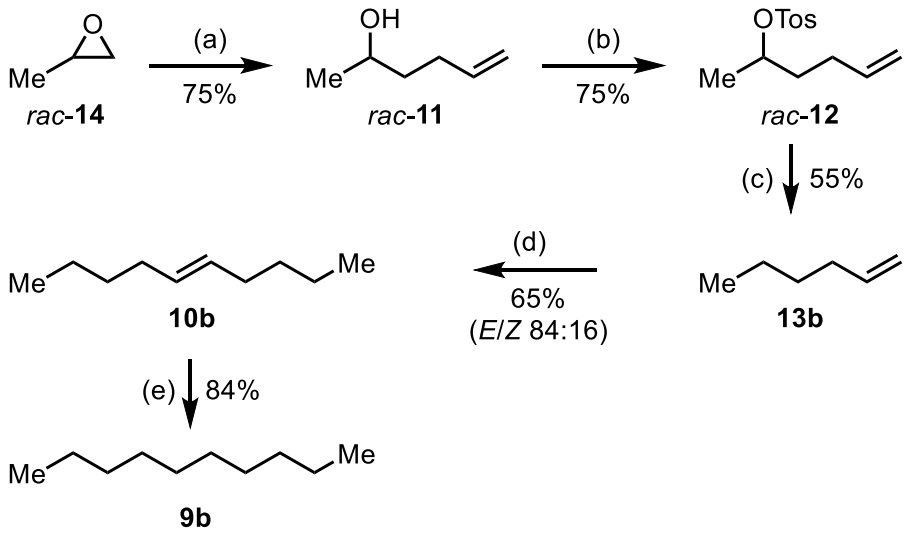


Scheme 4. Retrosynthetic analysis of (2,9-$^{2}H_2$)-*n*-decane (**9a**).

Since the stereocenter of deuterated hexene **13a** is not assumed to be affected by the metathesis or hydrogenation reactions, the enantiomeric excess of the final deuterated decane **9a** can be determined at the stage of this compound. We envisaged that Wacker oxidation of hexene **13a** to hexanone **16a** followed by enantioselective α-hydroxylation to hydroxyketone (*R*)-**17a** would lead to diastereotopic splitting of the protons at C-5. The enantiomeric excess could then be determined by integration of the ^{1}H or ^{2}H NMR signals. Prior to adopting this approach we synthesized (2,9-$^{2}H_2$)-*n*-decane **9a** by metathesis of the (*R*)- and (*S*)-enantiomers of the *O*-benzyl ether of compound **11**, followed by reduction to 2,9-dihydroxydecane, conversion to the di-tosylate and reduction with $LiAlD_4$ or $LiEt_3BD$ (see Scheme S1, Supplementary

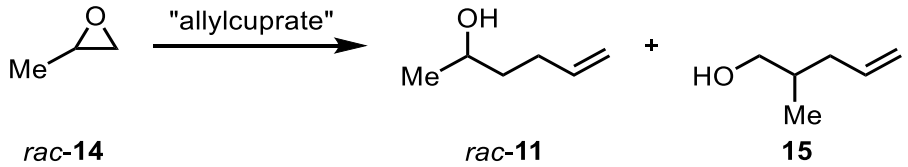
information). However, this method does not enable the optical purity of either enantiomer of (2,9-$^{2}H_2$)-*n*-decane **9a** to be established.

To test our strategy, the synthesis was initially carried out without the incorporation of deuterium using racemic propylene oxide (*rac*-**14**) as the starting material (Scheme 5).



Scheme 5. Synthesis of non-deuterated *n*-decane (**9b**). Reagents and conditions: (a) i: 1.4 equiv. C_3H_5MgBr, 1.4 equiv. CuCN, dry Et_2O, –78 °C, 17 h; ii: 0.2 equiv. TEMPO, 0.2 equiv. Bu_4NCl, 2.6 equiv. NCS, CH_2Cl_2/aq. $NaHCO_3$/aq. K_2CO_3, 23 °C, 1.5 h; (b) 3.5 equiv. TosCl, dry pyridine/dry CH_2Cl_2 1:1.3, 0 °C to 23 °C, 16 h; (c) 1.5 equiv. $LiAlH_4$, tetraglyme, 0 °C to 23 °C, 4 h; (d) 1 mol% Grubbs I catalyst, dry CH_2Cl_2, 23 °C, 68 h; (e) 0.1 equiv. 10 wt% Pd/C, H_2 (1 atm), *n*-pentane, 23 °C, 20 h.

The conversion of propylene oxide (*rac*-**14**) with diallylcuprate prepared from catalytic amounts of copper iodide and allylmagnesium bromide led to a mixture of the primary alcohol **15** and the secondary alcohol *rac*-**11** (Scheme 6).[25] After some experimentation, the use of stoichiometric amounts of copper cyanide was found to improve the yield of the secondary alcohol *rac*-**11** up to 95% (established by ^{1}H NMR). However, the primary alcohol **15** was still formed in 5% yield as the undesired by-product. Unfortunately, alcohols *rac*-**11** and **15** were not separable by column chromatography or distillation.



rac-**14** *rac*-**11** **15**

Scheme 6. Product mixture of secondary alcohol *rac*-**11** and primary alcohol **15**, from the ring-opening reaction of propylene oxide *rac*-**14** with an allylcuprate.

Therefore, the mixture of alcohols *rac*-**11** and **15** was submitted to selective TEMPO oxidation of the primary alcohol **15** to furnish 2-methyl-4-pentenal,[26] which was easily removed by column chromatography (Scheme 5, step a). The secondary alcohol *rac*-**11** was subsequently converted into its tosylate *rac*-**12**, using tosyl chloride (step b).[27] The tosylate *rac*-**12** in tetraglyme was reduced using $LiAlH_4$ to give 1-hexene (**13b**, step c), which was continuously distilled from the reaction flask by vacuum distillation. By attaching a cold trap (–196 °C) to the distillation apparatus, 1-hexene **13a** was isolated in 88–94% yield in later attempts. The olefin metathesis was performed using Grubbs I catalyst (step d) and decene **10b** was isolated by vacuum distillation using a cold trap (–196 °C).[28] Hydrogenation with Pd/C catalyst and 1 atm of hydrogen furnished the targeted *n*-decane (**9b**, step e).

The route developed for *n*-decane (**9b**) was modified for the synthesis of 2,9-dideuterated *n*-decane *rac*-**9a**. The tosylate *rac*-**12** was reduced with $LiAlD_4$ to give 2,9-dideuterated 5-decene *rac*-**10a** in 33% yield over four steps (Scheme 7, steps a–d). This type of reaction is known to proceed with inversion of configuration.[24] Decene **10a** was obtained as a mixture of (*E*)- and (*Z*)-isomers (*cf*. experimental section). However, the double bond geometry does neither influence the absolute configuration of the deuterated carbon atoms nor the enantiomeric excess of decane **9a**, because hydrogenation of (*E*)- and (*Z*)-**10a** yields the same product and the pre-existing stereocenters are not affected by this reaction. Note that while decene **10a** and decane **9a** exist as a mixture two diastereoisomers (*rac* and *meso, cf*. Scheme 7), they are denoted as *rac*-**10a** and *rac*-**9a**. The hydrogenation of decene *rac*-**10a** with a palladium on carbon catalyst was found to be more problematic than that of its unlabeled analogue **10b**, resulting in a mixture of products ranging from non-deuterated decanes to decanes with more than two deuterium atoms incorporated into the molecule.

This is best displayed by the distribution of the molecular ions in the electron impact mass spectrum (EIMS) of the decane product as shown in Figure 2. As hydrogenation reactions employing transition metal catalysts are known to be reversible,[29] the finding of a distributed deuterium incorporation could be explained by continuous hydrogenation and dehydrogenation reactions. Once hydrogenated, dehydrogenation followed by hydrogenation can occur at any position of the alkane, which may result in the formation of decanes with more than two deuterium atoms incorporated. In addition, random α,β-dideuterodecanes might occur along with the desired 2,9-dideuterodecane. In an attempt to reduce the randomization of deuterium in the final product, we initially investigated the effect of shortening the reaction time. However, mass spectrometry showed that after 1 h nearly the same deuterium pattern was obtained as after 20 h.

Due to the apparently microscopic reversibility of the system, we thought that catalytic hydrogenation reactions using transition metal catalysts would always lead to similar problems. Diimide reduction was found to be a suitable alternative for the reduction of dideuterated decene *rac*-**10a**.[30] The reaction conditions were optimized, generating the diimide by slow addition of acetic acid to a suspension of decene *rac*-**10a** and potassium azodicarboxylate in methanol over a period of 20 h (Scheme 7, steps e). The targeted dideuterated decane *rac*-**9a** could be obtained in 82% yield (27% overall yield over five steps). The reaction product *rac*-**9a** showed the well-defined expected isotopic pattern of the molecular ion in the EIMS (Figure 2, B).

The stereospecifically dideuterated decanes (*R*,*R*)- and (*S*,*S*)-**9a** were obtained analogously (*cf.* Scheme 7) starting with the commercially available enantiopure propylene oxides (*R*)- and (*S*)-**14**, respectively. The optical rotations of the stereospecifically deuterated hydrocarbons **9a**, **10a** and **13a** were found to be zero (c = 1 g L^{-1} in DCM) and could, therefore, not be used to determine their enantiopurity.

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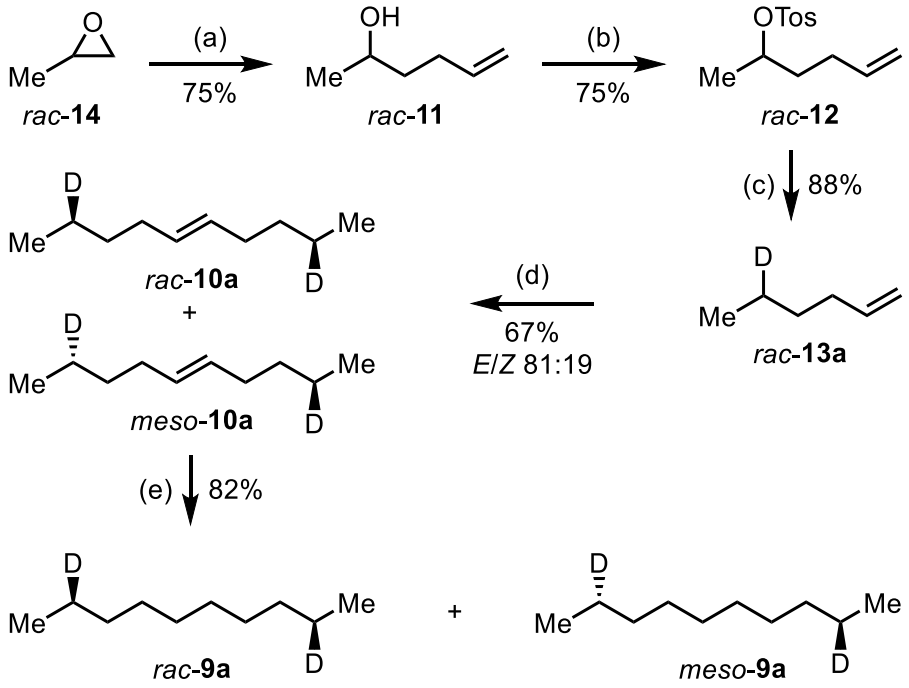

Scheme 7. Synthesis of dideuterated *n*-decane *rac*-**9a**. Reagents and conditions:(a) i: 1.4 equiv. C_3H_5MgBr, 1.4 equiv. CuCN, dry Et_2O, –78 °C, 17 h; ii: 0.2 equiv. TEMPO, 0.2 equiv. Bu_4NCl, 2.6 equiv. NCS, CH_2Cl_2/aq. $NaHCO_3$/aq. K_2CO_3. 23 °C, 1.5 h; (b) 3.5 equiv. TosCl, dry pyridine/dry CH_2Cl_2 1:1, 0 °C to 23 °C, 16 h; (c) 1.5 equiv. $LiAlD_4$, tetraglyme, 0 °C to 23 °C, 10 h; (d) 0.8 mol% Grubbs I catalyst, dry CH_2Cl_2, 23 °C, 48 h; (e) 14 equiv. potassium azodicarboxylate, 43 equiv. AcOH, MeOH, 23 °C, 20 h. Yields are given for the racemic decane *rac*-**9a**. For the yields of the (*R,R*)- and the (*S,S*)-series see experimental section.

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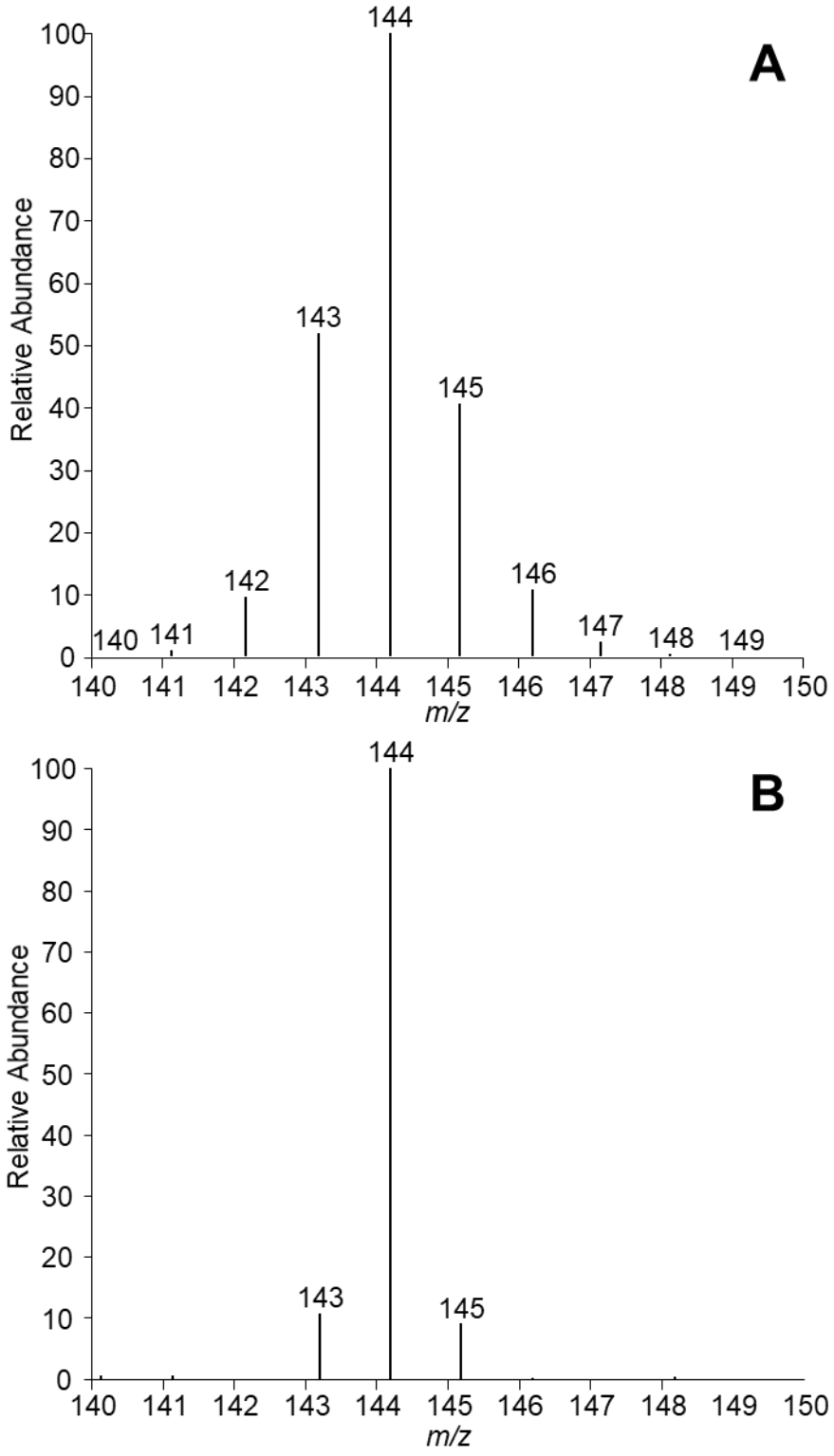
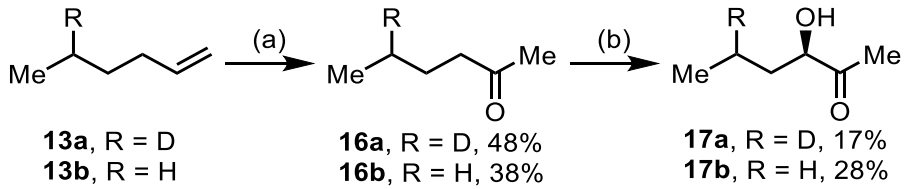


Figure 2. Distribution of the molecular ions of dideuterated decane **9a** (*m/z* 144) obtained by: (A) catalytic hydrogenation of (2,9-$^{2}H_2$)decene (*rac*-**10a**) after 20 h using palladium on carbon as the catalyst; (B) reduction with diimide.

As outlined above, determining the enantiopurity of deuterated 1-hexenes (*R*)- and (*S*)-**13a** would also establish that of the stereospecifically dideuterated decanes (*R*,*R*)- and (*S*,*S*)-**9a**. A literature survey revealed that the protons of the methylene group at C-5 of 3-hydroxy-2-hexanone (**17b**) show the desired diastereotopic splitting in the ^{1}H NMR spectrum.[31] Enantioselective hydroxylation of 2-hexanone (**16b**) can easily be achieved by α-aminoxylation with nitrosobenzene using L- or D-proline as the catalyst, followed by cleavage of the N–O-bond with copper sulfate.[31–33] The enantiopurity of stereospecifically deuterated hexenes (*R*)- and (*S*)-**13a** could therefore be determined based on ^{2}H NMR of their corresponding hydroxyketones (*R*,*R*)- and (3*R*,5*S*)-**17a**, synthesized *via* Wacker oxidation to hexanones (*R*)- and (*S*)-**16a** followed by enantioselective hydroxylation.

Following this concept, initially the hydroxylation reaction was optimized using commercially available non-deuterated 2-hexanone (**16b**). Dropwise addition of excess of nitrosobenzene (2 equiv.) over a period of 24 h, followed by treatment with catalytic amounts of copper sulfate and excess methanol furnished the 3-hydroxy-2-hexanone (**17b**) in 52% yield. The Wacker oxidation of 1-hexene (**13b**) occurred smoothly to give 2-hexanone (**16b**) in 81% yield (established by ^{1}H NMR) using standard conditions.[34] Hydroxylation of crude 2-hexanone (**16b**) obtained by Wacker oxidation of 1-hexene (**13b**) was found to be problematic. Therefore, 2-hexanone (**16b**) was submitted to column chromatography prior to α-hydroxylation using diethyl ether and pentane as the eluents. However, yields of 2-hexanone (**16b**) decreased due to this purification step, as 2-hexanone (**16b**) is relatively volatile (b.p. = 127°C, 1 atm).[35] Applying these optimized reaction conditions, hydroxyketone (*R*)-**17b** was obtained in 11% overall yield with 99% *ee* as established by GLC on a chiral phase (Scheme 8). Following this approach but using racemic deuterated 1-hexene (*rac*-**13a**), hydroxyketone (*R*)-**17a** was obtained, which showed unexpectedly but gratifyingly, two sets of signals for C-5 in the ^{13}C NMR (Figure 3, A). Therefore, the enantiopurity of deuterated hexenes (*R*)- and (*S*)-**13a** can easily and directly be determined by integration of the ^{13}C NMR signals. As expected, in case of deuterated hexene *rac*-**13a** no isomeric excess at the subterminal C-5 was observed (Figure 3, A). With these promising preliminary results, we turned to the preparation of both enantiomers of deuterated hexenes (*R*)- and (*S*)-**13a** starting with commercially available enantiopure propylene oxides (*R*)- and (*S*)-**14**, respectively.

Hexenes (*R*)- and (*S*)-**13a** were converted into hydroxyketones (*R*,*R*)- and (3*R*,5*S*)-**17a**, which displayed only one set of signals for C-5 in the ^{13}C NMR spectrum (Figure 4, B and C). Considering the accuracy of NMR spectroscopy, quantitative stereoselectivity is assumed for the reaction introducing the deuterium atom into the precursors of hydroxyketones (*R*,*R*)- and (3*R*,5*S*)-**17a** since the other diastereoisomer is not detectable. This finding actually establishes the enantiopurity of hexenes (*R*)- and (*S*)-**13a** and consequently also of the deuterated decanes (*R*,*R*)- and (*S*,*S*)-**9a**. Therefore, the nucleophilic displacement from tosylates (*S*)- and (*R*)-**12** to hexenes (*R*)- and (*S*)-**13a** proceeds with almost full inversion at C-5 following a S_N2 reaction mechanism. It follows that the alternative synthetic approach to the enantiomeric (2,9-$^2H_2$)-*n*-decanes **9a** (see Supplementary Information) also gave optically pure materials.



13a, R = D
13b, R = H

16a, R = D, 48%
16b, R = H, 38%

17a, R = D, 17%
17b, R = H, 28%

Scheme 8. Synthesis of (*R*)-3-hydroxy-2-hexanone [(*R*)-**17b**, R = H] and deuterated (3*R*,5*R**)-3-hydroxy-2-hexanone [(*R*)-**17a**, R = D]. Reagents and conditions: (a) 0.1 equiv. $Pd(OAc)_2$, 1.0 equiv. TFA, O_2 (1 atm), DMSO/H_2O 10:1, 70 °C, 7 h; (b) i: 2.0 equiv. C_6H_5NO, 0.2 equiv. L-proline, DMSO, 23 °C, 26 h; ii: 0.3 equiv. $CuSO_4$, MeOH, 23 °C, 7 h. For the yields of the (*R,R*)- and the (*R*,*S*)-series of compound **17a** see experimental section.

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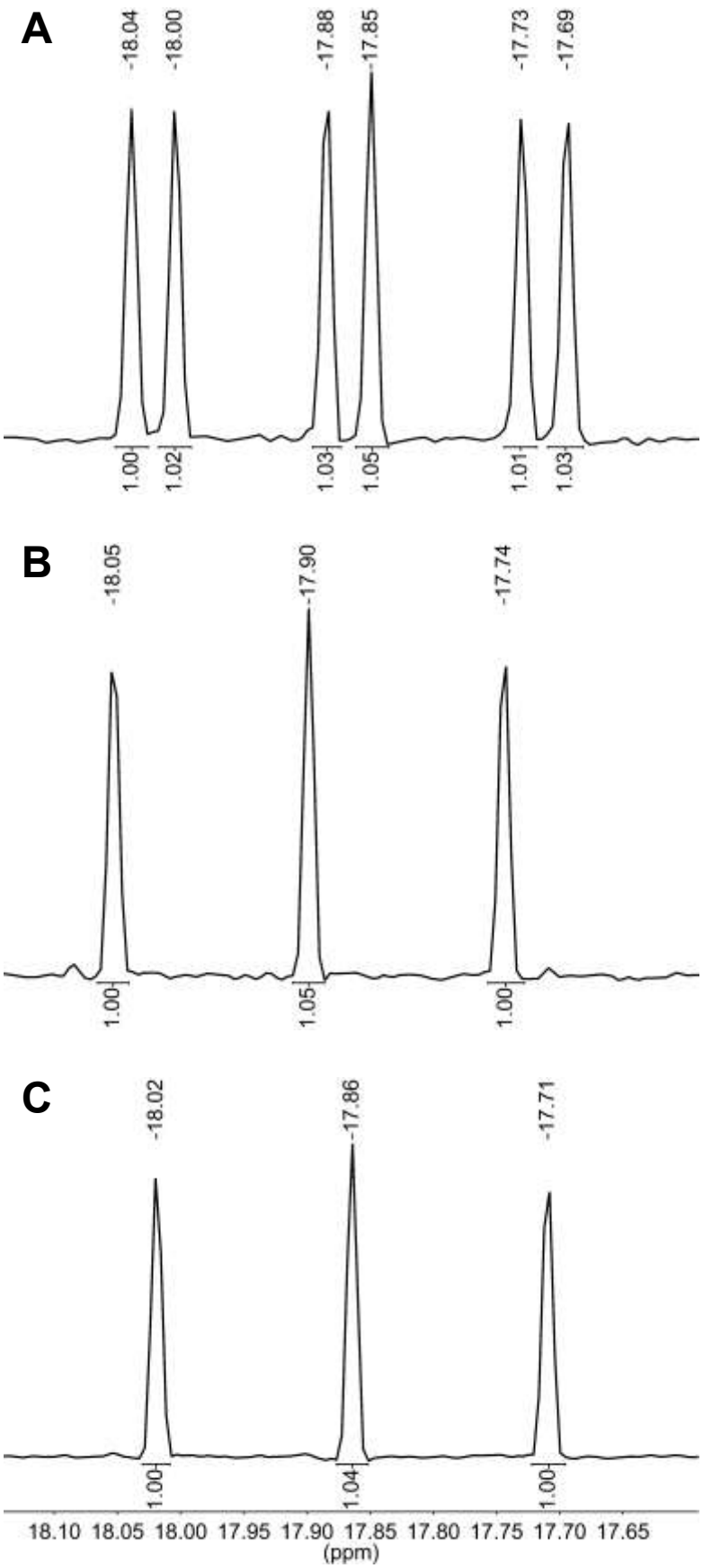

Figure 3. ^{13}C signals of C-5 of the hydroxyketones (A) (3*R*,5*R**)-**17a**, (B) (*R*,*R*)-**17a** and (C) (3*R*,5*S*)-**17a**.

Conclusion

Enantiopure (2,5-$^2H_2$)-*n*-hexane **6b** was reported to be an excellent model substrate for the mechanistic investigation of the activation reaction of *n*-hexane (**6a**) catalyzed by the (1-methylpentyl)succinate synthase of the bacterium *Aromatoleum aromaticum* strain HxN1.[14] The activation mechanisms of *n*-alkanes in the mesophilic denitrifying betaproteobacterium strain OcN1 and the thermophilic sulfate-reducing deltaproteobacterium strain TD3 are expected to occur in a similar manner. Therefore we envisioned stereospecifically 2,9-dideuterated decanes (*R*,*R*)- and (*S*,*S*)-**9a** to be ideal model substrates for investigating the activation mechanisms in the bacterial strains OcN1 and TD3. Starting from commercially available propylene oxide **14**, we developed a reliable synthetic approach to dideuterated decane *rac*-**9a** in 27% yield over five steps. The synthetic approach involved nucleophilic substitution of tosylate *rac*-**12** with $LiAlD_4$ in order to introduce the deuterium, followed by olefin metathesis and reduction of the double bond. Starting from enantiopure propylene oxide the stereospecifically dideuterated decanes (*R*,*R*)- and (*S*,*S*)-**9a** were obtained in a similar manner and in 25% and 26% overall yield, respectively. As compounds (*R*,*R*)- and (*S*,*S*)-**9a** should be prepared in optically pure form for mechanistic investigations an analytical tool was needed in order to prove their optical purity. Since the chromatographic separation of enantiomers of optically active deuterated compounds is quite challenging, and the optical rotation values of decanes (*R*,*R*)- and (*S*,*S*)-**9a** were determined to be zero (c = 1 g L^{-1} in DCM), an alternative approach was required for the determination of the optical purity. Therefore, we describe a method for the determination of enantiopurity by NMR spectroscopy after Wacker oxidation of hexenes (*R*)- and (*S*)-**13a** followed by enantioselective hydroxylation to furnish hydroxyketones (*R*,*R*)- and (3*R*,5*S*)-**17a** with 99% *ee*. These products showed a triplet for subterminal C-5 in the ^{13}C NMR spectrum with different chemical shifts. No residual signals arising from the other epimer were detected. Thus, the nucleophilic displacement from tosylates (*S*)- and (*R*)-**12** must have proceeded with, based on the detection limit of NMR spectroscopy, complete inversion of configuration at C-5.

Experimental Section

General: Unless otherwise noted, all synthetic transformations were performed under inert conditions (nitrogen atmosphere, exclusion of air and moisture). Preparative column chromatography was carried out using Merck SiO_2 (40–63 µm, type 60 A) with hexanes (mixture of isomers, bp. 64–71 °C), *n*-pentane, *tert*-butyl methyl ether (MTBE) and Et_2O as eluents. TLC was performed on aluminum plates coated with SiO_2 F_{254}. GLC analyses were performed on a Thermo Scientific Focus GC gas chromatograph equipped with a flame ionization detector using a CP-Sil 19 CB fused silica capillary column (30 m length, 0.25 mm internal diameter, 0.25 µm film thickness). GC-MS analyses were performed on a Shimadzu GCMS-QP2020 using a Macherey-Nagel OPTIMA 5 HT fused silica capillary column (30 m length, 0.25 mm internal diameter, 0.25 µm film thickness). Helium was used as carrier gas. Gas chromatographic separation of both enantiomers of 3-hydroxy-2-hexanone [(*R*)-**17b** and (*S*)-**17b**] was performed using a Shimadzu GC-2010 Plus gas chromatograph equipped with a flame ionization detector using a Hydrodex β-6TBDM column (25 m length, 0.25 mm internal diameter). Hydrogen was used as carrier gas. ^{1}H, ^{2}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 and 300 instruments. Multiplicities of carbon signals were determined with DEPT experiments. HRMS spectra of products were obtained with a Waters Q-TOF Premier (ESI) or Thermo Scientific DFS (EI) spectrometer. IR spectra were recorded on a Shimadzu IRSpirit spectrometer equipped with a diamond ATR unit. All starting materials were commercially available.

***rac*-5-Hexen-2-ol (*rac*-11).** According to a modified procedure reported previously in the literature,[25] allylmagnesium bromide (1.0 mol/L solution in Et_2O, 135 mL, 135 mmol, 1.4 equiv.) was added dropwise over a period of 50 min to a suspension of degassed CuCN (12.1 g, 135 mmol, 1.4 equiv.) in dry Et_2O (25 mL) at –78 °C. After stirring for 90 min at this temperature, *rac*-propylene oxide (*rac*-**14**, 5.54 g, 95.4 mmol) was added dropwise over a period of 25 min and stirring was continued for 17 h. The reaction mixture was warmed to ambient temperature, diluted with saturated, aqueous NH_4Cl solution (200 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with saturated, aqueous NaCl solution (2 x 200 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated to furnish a mixture (11.5 g) containing the title compound *rac*-**11** (9.07 g, 90.5 mmol, 95%, established by ^{1}H NMR) and the regioisomeric compound **15** (483 mg, 4.82 mmol, 5%, established by ^{1}H NMR) as a yellow liquid. Because product *rac*-**11** and the regioisomeric primary alcohol **15** were not separable by column chromatography or distillation, the mixture was submitted to a TEMPO oxidation as reported previously in the literature.[26] TEMPO (150 mg, 960 µmol, 0.2 equiv.), Bu_4NCl (267 mg, 961 µmol, 0.2 equiv.), CH_2Cl_2 (50 mL) and an aqueous buffer solution (50 mL, containing 2.10 g $NaHCO_3$ and 346 mg K_2CO_3) were added to the mixture of regioisomers containing the primary alcohol **15** (483 mg, 4.82 mmol). Subsequently, NCS (1.67 g, 12.5 mmol, 2.6 equiv.) was added and the reaction mixture was stirred for 90 min. The reaction mixture was diluted with H_2O (50 mL), the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with saturated, aqueous NaCl solution (1 x 200 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was submitted to column chromatography (SiO_2, pentane/Et_2O 3:2, R_f = 0.26) to furnish the title compound *rac*-**11** (7.12 g, 71.1 mmol, yield over two steps 75%, based on 82% purity established by ^{1}H NMR) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.2 Hz, 3H), 1.44–1.47 (m, 1H), 1.49–1.63 (m, 2H), 2.06–2.25 (m, 2H), 3.83 (sex, J = 6.2 Hz, 1H), 4.94–4.99 (m, 1H), 5.05 (dq, J = 17.2 Hz, J = 1.6 Hz, 1H), 5.84 (ddt, J = 16.9 Hz, J = 10.2 Hz, J = 6.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 23.41 (CH_3), 30.17 (CH_2), 38.28 (CH_2), 67.45 (CH), 114.64 (CH_2), 138.53 (CH) ppm. All spectroscopic data were in accordance with the literature.[36] $C_6H_{12}O$ (100.16).

(*R*)-5-Hexen-2-ol [(*R*)-11]. According to the procedure reported above for the racemic compound *rac*-**11** allymagnesium bromide (1.0 mol/L solution in Et_2O, 107 mL, 107 mmol, 1.4 equiv.), CuCN (9.60 g, 107 mmol, 1.4 equiv.) and (*R*)-propylene oxide [(*R*)-**14**, 4.37 g, 75.2 mmol] were converted in dry Et_2O (25 mL) to furnish a mixture containing primary alcohol **15** (449 mg, 4.48 mmol, 6% established by ^{1}H NMR) and secondary alcohol (*R*)-**11** (7.09 g, 70.8 mmol, 94%, established by ^{1}H NMR). The mixture was submitted to TEMPO oxidation as reported above using TEMPO (141 mg, 902 µmol, 0.2 equiv.), Bu_4NCl (250 mg, 900 µmol, 0.2 equiv.), CH_2Cl_2 (50 mL), aqueous buffer solution (50 mL, containing 2.10 g $NaHCO_3$ and 346 mg K_2CO_3) and NCS (1.56 g, 11.7 mmol, 2.6 equiv.) to furnish the title compound (*R*)-**11** (4.90 g, 48.9 mmol, 65%, based on 90% purity established by ^{1}H NMR) after column chromatography (SiO_2, pentane/Et_2O 3:2, R_f = 0.26) as a colorless liquid. The spectroscopic data are in accordance with the literature and with those of the racemic compound.[37] $[\alpha]_D^{20}$ = –20 (CH_2Cl_2, 1.0 g L^{-1}). Lit. $[\alpha]_D^{21.7}$ = –15.9 (Et_2O, 0.48 g L^{-1}).[38]

(*S*)-5-Hexen-2-ol [(*S*)-11]. According to the procedure reported above for the racemic compound *rac*-**11** allymagnesium bromide (1.0 mol/L solution in Et_2O, 107 mL, 107 mmol, 1.3 equiv.), CuCN (9.60 g, 107 mmol, 1.3 equiv.) and (*S*)-propylene oxide [(*S*)-**14**, 4.73 g, 81.4 mmol] were converted in dry Et_2O (25 mL) to furnish a mixture containing primary alcohol **15** (485 mg, 4.84 mmol, 6% established by ^{1}H NMR) and secondary alcohol (*S*)-**11** (7.67 g, 76.6 mmol, 94%, established by ^{1}H NMR). The mixture was submitted to TEMPO oxidation as reported above using TEMPO (151 mg, 966 µmol, 0.2 equiv.), Bu_4NCl (270 mg, 972 µmol, 0.2 equiv.), CH_2Cl_2 (50 mL), aqueous buffer solution (50 mL, containing 2.10 g $NaHCO_3$ and 346 mg K_2CO_3) and NCS (1.68 g, 12.6 mmol, 2.6 equiv.) to furnish the title compound (*S*)-**11** (5.51 g, 55.0 mmol, 68%, based on 82% purity established by ^{1}H NMR) after column chromatography (SiO_2, pentane/Et_2O 3:2, R_f = 0.26) as a colorless liquid. The spectroscopic data are in accordance with the literature and with those of the racemic compound.[39] $[\alpha]_D^{20}$ = +13 (CH_2Cl_2, 1.0 g L^{-1}). Lit. $[\alpha]_D^{24.2}$ = +17.3 (CH_2Cl_2, 2.9 g L^{-1}).[40]

4-Toluenesulfonic acid 1-methyl-4-pentenyl ester (*rac*-12). According to a slightly modified procedure reported previously in the literature,[27] TosCl (48.6 g, 255 mmol, 3.5 equiv.) was added in portions over a period of 30 min to a solution of alcohol *rac*-**11** (7.30 g, 72.9 mmol) in pyridine (50 mL) and dry CH_2Cl_2 (65 mL) at 0 °C. The mixture was warmed to ambient temperature and stirred for 16 h. The reaction mixture was diluted with saturated, aqueous NH_4Cl solution (150 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed with hydrochloric acid (1.0 mol/L, 200 mL), saturated, aqueous $NaHCO_3$ (200 mL) and saturated, aqueous NaCl (200 mL) solutions, dried over $MgSO_4$ and the solvent was evaporated. The crude product was submitted to column chromatography (SiO_2, hexanes/MTBE 2:3 R_f = 0.58) to furnish the title compound *rac*-**12** (14.0 g, 55.0 mmol, 75%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.3 Hz, 3H), 1.51–1.63 (m, 1H), 1.65–1.77 (m, 1H), 1.88–2.09 (m, 2H), 2.43 (s, 3H), 4.62 (sex, *J* = 6.3 Hz, 1H), 4.88–4.91 (m, 1H), 4.93–4.96 (m, 1H), 5.66 (ddt, *J* = 17.5 Hz, *J* = 9.8 Hz, *J* = 6.5 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 20.84 (CH_3), 21.70 (CH_3), 29.10 (CH_2), 35.71 (CH_2), 79.97 (CH), 115.42 (CH_2), 127.77 (2 x CH), 129.82 (2 x CH), 134.57 (CH), 137.11 (C), 144.57 (C) ppm. All spectroscopic data were in accordance with the literature.[27] $C_{13}H_{18}O_3S$ (254.35)

(*R*)-4-Toluenesulfonic acid 1-methyl-4-pentenyl ester [(*R*)-12]. According to the procedure reported above for the racemic compound *rac*-**12**, alcohol (*R*)-**11** (4.81 g, 48.0 mmol) and TosCl (32.0 g, 168 mmol, 3.5 equiv.) were converted in dry pyridine (50 mL) and dry CH_2Cl_2 (50 mL) to furnish the title compound (*R*)-**12** (10.4 g, 41.1 mmol, 86%) as a colorless oil. The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = –7 (CH_2Cl_2, 1.0 g L^{-1}).

(*S*)-4-Toluenesulfonic acid 1-methyl-4-pentenyl ester [(S)-12]. According to the procedure reported above for the racemic compound *rac*-**12**, alcohol (*S*)-**11** (5.52 g, 55.1 mmol) and TosCl (36.8 g, 193 mmol, 3.5 equiv.) were converted in dry pyridine (50 mL) and dry CH_2Cl_2 (50 mL) to furnish the title compound (*S*)-**12** (11.2 g, 44.0 mmol, 80%) as a colorless oil. The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = +7 (CH_2Cl_2, 1.0 g L^{-1}).

1-Hexene (13b). $LiAlH_4$ (300 mg, 7.91 mmol, 1.5 equiv.) was added to a solution of tosylate *rac*-**12** (1.34 g, 5.27 mmol) in tetraglyme (7 mL) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 4 h. The product was purified and isolated by vacuum distillation into a cold trap (–196 °C) to yield the title compound **13b** as a colorless liquid (244 mg, 2.90 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.2 Hz, 3H), 1.26–1.42 (m, 4H), 2.02–2.09 (m, 2H), 4.93 (ddt, J = 10.2 Hz, J = 2.2 Hz, J = 1.3 Hz, 1H), 5.00 (ddt, J = 17.1 Hz, J = 2.2 Hz, J = 1.6 Hz, 1H), 5.82 (ddt, J = 16.9 Hz, J = 10.2 Hz, J = 6.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 14.09 (CH_3), 22.34 (CH_2), 31.25 (CH_2), 33.65 (CH_2), 114.24 (CH_2), 139.37 (CH) ppm. All spectroscopic data were in accordance with the literature.[41] C_6H_{12} (84.16).

***rac*-(5-^{2}H)-1-Hexene (*rac*-13a).** According to the procedure reported above for the non-deuterated compound **13b**, $LiAlD_4$ (1.98 g, 47.2 mmol, 1.5 equiv.) and tosylate *rac*-**12** (8.00 g, 31.5 mmol) were converted in tetraglyme (38 mL). After warming the reaction mixture to room temperature, the product was continuously distilled into a cold trap (–196 °C) over a period of 10 h to furnish the title compound *rac*-**13a** as a colorless liquid (2.36 g, 27.7 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (dt, J = 7.2 Hz, J_{HD} = 1.1 Hz, 3H), 1.28–1.40 (m, 3H), 2.04–2.09 (m, 2H), 4.94 (ddt, J = 10.2 Hz, J = 2.2 Hz, J = 1.2 Hz, 1H), 5.01 (ddt, J = 17.1 Hz, J = 2.2 Hz, J = 1.6 Hz, 1H), 5.83 (ddt, J = 17.0 Hz, J = 10.2 Hz, J = 6.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 13.98 (CH_3), 21.95 (t, J = 19.2 Hz, CHD), 31.16 (CH_2), 33.64 (CH_2), 114.22 (CH_2), 139.37 (CH) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 1.29–1.40 (m, 1D) ppm. ^{1}H NMR data were in accordance with the literature.[42] HRMS (EI): calcd. 85.0996 (for $C_6H_{11}{}^2H^+$), found 85.1000 [M^+]. $C_6H_{11}{}^2H$ (85.17).

(*S*)-(5-^{2}H)-1-Hexene [(*S*)-13a]. According to the procedure reported above for the non-deuterated compound *rac*-**13a**, $LiAlD_4$ (2.56 g, 61.0 mmol, 1.5 equiv.) and tosylate (*R*)-**12** (10.3 g, 40.5 mmol) were converted in tetraglyme (50 mL) and continuously distilled over a period of 18 h to furnish the title compound (*S*)-**13a** as a colorless liquid (3.24 g, 38.0 mmol, 94%). The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = ±0 (CH_2Cl_2, 1.0 g L^{-1}).

(*R*)-(5-^{2}H)-1-Hexene [(*R*)-13a]. According to the procedure reported above for the non-deuterated compound *rac*-**13a**, $LiAlD_4$ (2.72 g, 64.8 mmol, 1.5 equiv.) and tosylate (*S*)-**12** (11.0 g, 43.2 mmol) were converted in tetraglyme (50 mL) and continuously distilled over a period of 14 h to furnish the title compound (*R*)-**13a** as a colorless liquid (3.36 g, 39.5 mmol, 91%). The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = ±0 (CH_2Cl_2, 1.08 g L^{-1}).

5-Decene (10b). Grubbs I catalyst (395 mg, 0.480 mmol, 1.0 mol%) was added to a degassed solution (one cycle of freeze, pump, thaw) of 1-hexene (**13b**, 4.00 g, 47.5 mmol) in dry CH_2Cl_2 (20 mL). The resulting suspension was degassed (one cycle of freeze, pump, thaw) and stirred for 64 h in the dark. The solvent was evaporated and the crude product was submitted to vacuum distillation into a cold trap (–196°C) to yield the title compound **10b** (2.17 g, 15.5 mmol, 65%, based on 96% purity established by ^{1}H NMR) as a colorless liquid. According to ^{13}C NMR the compound exists as a mixture of two diastereoisomers (*E*/*Z* = 84:16). ^{1}H NMR (300 MHz, $CDCl_3$), both diastereoisomers: δ = 0.84–0.93 (m, 12H), 1.23–1.40 (m, 16H), 1.92–2.06 (m, 8H), 5.33–5.36 (m, 2H), 5.37–5.45 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), (*E*)-isomer: δ = 14.13 (2 x CH_3), 22.36 (2 x CH_2), 32.00 (2 x CH_2), 32.45 (2 x CH_2), 130.46 (2 x CH) ppm; (*Z*)-isomer: δ = 14.16 (2 x CH_3), 22.51 (2 x CH_2), 27.06 (2 x CH_2), 32.13 (2 x CH_2), 130.00 (2 x CH) ppm. All spectroscopic data were in accordance with the literature.[41,43] $C_{10}H_{20}$ (140.27)

(2,9-$^2H_2$)-5-Decene (*rac*-10a). According to the procedure reported above for the non-deuterated compound **10b**, Grubbs I catalyst (92 mg, 0.11 mmol, 0.8 mol%) and 1-(5-^{2}H)-hexene (*rac*-**13a**, 1.20 g, 14.0 mmol) were converted in dry CH_2Cl_2 (10 mL) for 48 h to furnish the title compound *rac*-**10a** (671 mg, 4.72 mmol, 67%) as a colorless liquid. According to ^{13}C NMR the compound exists as a mixture of two diastereoisomers (*E*/*Z* = 81:19). ^{1}H NMR (300 MHz, $CDCl_3$), both diastereoisomers: δ = 0.84–0.94 (m, 12H), 1.22–1.36 (m, 12H), 1.92–2.06 (m, 8H), 5.32–5.36 (m, 2H), 5.37–5.45 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), (*E*)-isomer: δ = 14.01 (2 x CH_3), 21.97 (t, *J* = 19.2 Hz, 2 x CHD), 31.92 (2 x CH_2), 32.44 (2 x CH_2), 130.47 (2 x CH) ppm; (*Z*)-isomer: δ = 14.04 (2 x CH_3), 22.12 (t, *J* = 19.1 Hz, 2 x CHD), 27.05 (2 x CH_2), 32.05 (2 x CH_2), 130.00 (2 x CH) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 1.28–1.39 (m, 2D) ppm. IR (ATR): $\tilde{\nu}$ = 2957 (m), 2917 (s), 2873 (m), 2853 (m), 2152 (w), 1457 (m), 1439 (w), 1377 (w), 1140 (w),

966 (m), 890 (w), 691 (w), 661 (w) cm^{-1}. HRMS (EI): calcd. 142.1685 (for $C_{10}H_{18}{}^2H_2$), found 142.1684 [M^+]. $C_{10}H_{18}{}^2H_2$ (142.28).

(*S*,*S*)-(2,9-$^2H_2$)-5-Decene [(*S*,*S*)-10a]. According to the procedure reported for the non-deuterated compound **10b**, Grubbs I catalyst (164 mg, 0.20 mmol, 1.0 mol%) and (*S*)-(5-^{2}H)-1-hexene [(*S*)-**13a**, 1.70 g, 20.0 mmol] were converted in dry CH_2Cl_2 (10 mL) for 89 h to furnish the title compound (*S*,*S*)-**10a** (833 mg, 5.85 mmol, 59%, based on 83% purity established by ^{1}H NMR) as a colorless liquid. According to ^{13}C NMR the compound exists as a mixture of two diastereoisomers (*E*/*Z* = 81:19). The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = ±0 (CH_2Cl_2, 1.09 g L^{-1}).

(*R*,*R*)-(2,9-$^2H_2$)-5-Decene [(*R*,*R*)-10a]. According to the procedure reported for the non-deuterated compound **10b**, Grubbs I catalyst (239 mg, 0.29 mmol, 1.0 mol%) and (*R*)-(5-^{2}H)-1-hexene [(*R*)-**13a**, 2.44 g, 28.6 mmol] were converted in dry CH_2Cl_2 (10 mL) for 74 h to furnish the title compound (*R*,*R*)-**10a** (1.22 g, 8.57 mmol, 60%, based on 87% purity established by ^{1}H NMR) as a colorless liquid. According to ^{13}C NMR the compound exists as a mixture of two diastereoisomers (*E*/*Z* = 80:20). The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = ±0 (CH_2Cl_2, 1.01 g L^{-1}).

***n*-Decane (9b)**. **(a) Through catalytic hydrogenation of 5-decene (10b) using Pd/C.** 5-Decene (**10b**, 200 mg, 1.43 mmol) was added to a degassed (three cycles of freeze, pump, thaw) suspension of 10 wt% Pd/C (152 mg, 143 µmol) in *n*-pentane (10 mL). The resulting mixture was degassed again and stirred for 20 h at ambient temperature under an atmosphere of H_2 (balloon). Subsequently, the reaction mixture was filtered through a plug of SiO_2 (2 cm, rinsed with *n*-pentane) and the solvent was evaporated to yield the title compound **9b** (171 mg, 1.20 mmol, 84%, based on 92% purity established by ^{13}C NMR) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 6H), 1.18–1.36 (m, 16H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 14.29 (2 x CH_3), 22.86 (2 x CH_2), 29.53 (2 x CH_2), 29.83 (2 x CH_2), 32.09 (2 x CH_2) ppm. All spectroscopic data were in accordance with the literature.[44] $C_{10}H_{22}$ (142.29) **(b) Through diimide reduction of 5-decene (10b).** Dipotassium azodicarboxylate was freshly prepared according to a modified procedure reported previously in the literature:[30,45] Azodicarboxamide (2.32 g, 20.0 mmol) was added in ten portions over

a period of 1 h to a solution of KOH (8.00 g, 143 mmol, 7.1 equiv.) in H_2O (12 mL) at 0 °C. The resulting suspension was stirred for 1.5 h at 0 °C, filtered, washed with ice-cold MeOH and dried in high vacuum to furnish potassium azodicarboxylate (3.56 g, 18.3 mmol, 92%) as a yellow solid. A solution of AcOH (3.30 g, 54.9 mmol, 30 equiv.) in MeOH (9 mL) was added dropwise over a period of 12 h to a suspension of dipotassium azodicarboxylate (3.56 g, 18.3 mmol, 10 equiv.) and 5-decene (**10b**, 257 mg, 1.83 mmol) in MeOH (20 mL). Subsequently, stirring was continued for 6 h. The reaction mixture was diluted with aqueous H_2O_2 solution (20 mL 10 wt% and 10 mL 30 wt%) and extracted with cyclopentane (3 x 30 mL). The combined organic layers were washed with hydrochloric acid (1 mol/L, 90 mL), dried over $MgSO_4$ and evaporated to yield the title compound **9b** (225 mg, 1.58 mmol, 86%, based on 42% purity based on ^{1}H NMR) as a colorless liquid The spectroscopic data are in accordance with the literature and with those of the product of the catalytic hydrogenation.[44]

(2,9-$^2H_2$)-*n*-Decane (*rac*-9a). According to the procedure reported above for the non-deuterated compound **9b**, a solution of AcOH (8.00 mL, 8.40 g, 140 mmol, 43 equiv.) in MeOH (14 mL) was added dropwise over a period of 20 h to a suspension of (2,9-$^2H_2$)-5-decene (*rac*-**10a**, 469 mg, 3.25 mmol) and potassium azodicarboxylate (8.99 g, 46.3 mmol, 14 equiv.) in MeOH (65 mL) to furnish the title compound *rac*-**9a** (387 mg, 2.68 mmol, 82%, based on 63% purity established by ^{1}H NMR) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.91 (m, 6H), 1.19–1.34 (m, 14H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 14.17 (2 x CH_3), 22.46 (t, J = 19.1 Hz, 2 x CHD), 29.50 (2 x CH_2), 29.83 (2 x CH_2), 31.99 (2 x CH_2) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 1.25–1.39 (m, 2D) ppm. IR (ATR): $\tilde{\nu}$ = 2957 (m), 2920 (s), 2873 (w), 2853 (m), 2154 (w), 1644 (w), 1459 (w), 1400 (w), 1377 (w), 1273 (w), 1139 (w), 1073 (w), 967 (w), 891 (w), 724 (w), 661 (w) cm^{-1}. GC-MS (EI, 70 eV): *m*/*z* (%) 144 (6.5), 143 (0.74), 114 (6), 100 (10), 99 (7), 86 (36), 85 (15), 72 (45), 71 (34), 70 (11), 58 (100), 57 (95), 56 (30), 55 (16). HRMS (EI): calcd. 144.1842 (for $C_{10}H_{20}{}^2H_2$), found 144.1844 [M^+]. $C_{10}H_{20}{}^2H_2$ (144.30).

(*S*,*S*)-(2,9-$^2H_2$)-*n*-Decane [(*S*,*S*)-9a]. According to the procedure reported above for the non-deuterated compound **9b**, a solution of AcOH (6.60 mL, 6.93 g, 115 mmol, 48 equiv.) in MeOH (13 mL) was added dropwise over a period of 20 h to a suspension of (*S*,*S*)-(2,9-$^2H_2$)-decene [(*S*,*S*)-**10a**, 341 mg, 2.40 mmol] and potassium

azodicarboxylate (7.45 g, 38.4 mmol, 16 equiv.) in MeOH (60 mL) to furnish the title compound (*S*,*S*)-**9a** (296 mg, 2.05 mmol, 85%, based on 56% purity established by ^{1}H NMR) as a colorless liquid. The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = ±0 (CH_2Cl_2, 1.01 g L^{-1}).

(*R*,*R*)-(2,9-$^2H_2$)-*n*-Decane [(*R*,*R*)-9a]. According to the procedure reported above for the non-deuterated compound **9b**, a solution of AcOH (7.20 mL, 7.56 g, 126 mmol, 41 equiv.) in MeOH (13 mL) was added dropwise over a period of 20 h to a suspension of (*R*,*R*)-(2,9-$^2H_2$)-decene [(*R*,*R*)-**10a**, 437 mg, 3.07 mmol] and potassium azodicarboxylate (8.17 g, 42.1 mmol, 14 equiv.) in MeOH (60 mL) to furnish the title compound (*R*,*R*)-**9a** (376 mg, 2.61 mmol, 85%, based on 57% purity established by ^{1}H NMR) as a colorless liquid. The spectroscopic data are in accordance with those of the racemic compound. $[\alpha]_D^{20}$ = ±0 (CH_2Cl_2, 1.06 g L^{-1}).

2-Hexanone (16b). According to a procedure reported previously in the literature,[34] TFA (813 mg, 7.13 mmol, 1 equiv.) was added over a period of 3 min to a solution of 1-hexene (**13b**, 600 mg, 7.13 mmol) and $Pd(OAc)_2$ (159 mg, 708 µmol, 0.1 equiv.) in DMSO (14 mL) and H_2O (1.4 mL) under an atmosphere of O_2 (balloon). The mixture was warmed to 70 °C and stirred for 7 h. The reaction mixture was diluted with Et_2O (15 mL), filtered through a plug of SiO_2 (2 cm, rinsed with Et_2O), washed with H_2O (50 mL), aqueous, saturated NaCl (50 mL), dried over $MgSO_4$ and filtered. The crude product was submitted to column chromatography (SiO_2, pentane/Et_2O 9:1) to furnish the title compound **16b** (269 mg, 2.69 mmol, 38%, based on 26% purity established by ^{1}H NMR) as a slightly yellow liquid which was directly used in the next step without further purification or characterization. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.61 (m, 2H), 2.14 (s, 3H), 2.42 (t, *J* = 7.4 Hz, 2H) ppm; not all signals could be identified with certainty due to overlapping solvent signals. The ^{1}H NMR data were in accordance with the literature.[46] $C_6H_{12}O$ (100.16).

(*R*)-3-Hydroxy-2-hexanone [(*R*)-17b]. According to a modified procedure reported previously in the literature,[31-33] a solution of nitrosobenzene (576 mg, 5.38 mmol, 2 equiv.) in DMSO (6.5 mL) was added over a period of 24 h to a solution of 2-hexanone (**16b**, 269 mg, 2.69 mmol) and L-proline (62 mg, 0.54 mmol, 0.2 equiv.) in DMSO (3.4 mL) at ambient temperature. After stirring was continued for 2 h, anhydrous $CuSO_4$

(129 mg, 808 µmol, 0.3 equiv.) and MeOH (4.2 mL) were added and stirring was continued for further 7 h. The reaction mixture was diluted with aqueous, saturated NH_4Cl (30 mL) and the aqueous layer extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with aqueous, saturated NaCl (60 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude product was submitted to column chromatography (SiO_2, pentane/MTBE 2:1, R_f = 0.21) to furnish the title compound (*R*)-**17b** (88 mg, 0.76 mmol, 28%, based on 37% purity established by ^{1}H NMR, 99% *ee*) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3H), 1.31–1.44 (m, 1H), 1.45–1.60 (m, 2H), 1.74–1.86 (m, 1H), 2.20 (s, 3H), 3.45 (d, *J* = 4.6 Hz, 1H), 4.16–4.21 (m, 1H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 14.03 (CH_3), 18.25 (CH_2), 25.32 (CH_3), 35.77 (CH_2), 76.83 (CH), 210.16 (C) ppm. All spectroscopic data were in accordance with the literature.[47] $C_6H_{12}O_2$ (116.16).

(*S*)-3-Hydroxy-2-hexanone [(*S*)-17b]. According to the procedure reported above for the preparation of the non-deuterated compound (*R*)-**17b**, 2-hexanone (**16b**, 400 mg, 3.99 mmol), a solution of nitrosobenzene (428 mg, 4.00 mmol, 1 equiv.) in DMSO (4.8 mL), D-proline (92 mg, 0.80 mmol, 0.2 equiv.), anhydrous $CuSO_4$ (192 mg, 1.20 mmol, 0.3 equiv.) and MeOH (6 mL) were converted in DMSO (5 mL) to furnish the title compound (*S*)-**17b** (148 mg, 1.28 mmol, 32% based on 75% purity established by ^{1}H NMR, 99% *ee*) after column chromatography (SiO_2, pentane/MTBE 2:1, R_f = 0.22) as a yellow liquid. All spectroscopic data were in accordance with those of the (*R*)-enantiomer.

(5-^{2}H)-2-Hexanone (*rac*-16a). According to the procedure reported above for the non-deuterated compound **16b**, hexene *rac*-**13a** (821 mg, 9.64 mmol), $Pd(OAc)_2$ (319 mg, 1.42 mmol, 0.15 equiv.) and TFA (1.11 g, 9.74 mmol, 1.0 equiv.) were converted in DMSO (28 mL) and H_2O (2.8 mL) to furnish the title compound *rac*-**16a** (472 mg, 4.67 mmol, 48%, based on 37% purity established by ^{1}H NMR) after column chromatography (SiO_2, pentane/Et_2O 9:1) as a slightly yellow liquid which was directly used in the next step without further purification or characterization. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (dt, *J* = 7.3 Hz, J_{HD} = 1.0 Hz, 3H), 1.50–1.58 (m, 2H), 2.13 (s, 3H), 2.42 (t, *J* = 7.5 Hz, 2H) ppm; not all signals could be identified with certainty due to overlapping solvent signals. All spectroscopic data were in accordance with the literature.[48] $C_6H_{11}{}^2HO$ (101.17).

(3*R*)-(5-^{2}H)-3-Hydroxy-2-hexanone [(3*R*,5*R)-17a].** According to the procedure reported above for the preparation of the non-deuterated compound (*R*)-**17b**, hexanone *rac*-**16a** (472 mg, 4.67 mmol), a solution of nitrosobenzene (999 mg, 9.33 mmol, 2 equiv.) in DMSO (11 mL), L-proline (107 mg, 929 µmol, 0.2 equiv.), $CuSO_4$ (223 mg, 1.40 mmol, 0.3 equiv.) and MeOH (7.2 mL) were converted in DMSO (5.8 mL) to furnish the title compound (3*R*,5*R**)-**17a** (95 mg, 0.81 mmol, 17% based on 52% purity established by ^{1}H NMR, 99% *ee*) after column chromatography (SiO_2, pentane/MTBE 2:1, R_f = 0.22) as a yellow liquid. According to ^{13}C NMR, the compound exists as two epimers (*er* 1:1). ^{1}H NMR (500 MHz, $CDCl_3$), both epimers: δ = 0.95 (dt, J = 7.2 Hz, J_{HD} = 1.0 Hz, 2 x 3H), 1.34–1.42 (m, 1H), 1.43–1.55 (m, 3H), 1.77–1.82 (m, 2 x 1H), 2.19 (s, 2 x 3H), 3.42 (brs, 2 x 1H), 4.15–4.21 (m, 2 x 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), both epimers: δ = 13.82 (2 x CH_3), 17.85 (t, J = 19.5 Hz, CHD), 17.88 (t, J = 19.4 Hz, CHD), 25.21 (2 x CH_3), 35.66 (CH_2), 35.68 (CH_2), 76.80 (CH), 76.82 (CH), 210.12 (2 x C) ppm. ^{2}H NMR (77 MHz, $CDCl_3$), both epimers: δ = 1.30–1.42 (m, 1D), 1.42–1.53 (m, 1D) ppm. $[\alpha]_D^{20}$ = –133 (CH_2Cl_2, 1.09 g L^{-1}). IR (ATR): $\tilde{\nu}$ = 3466 (w), 2959 (w), 2932 (w), 2874 (w), 2166 (w), 1710 (s), 1457 (w), 1419 (w), 1397 (w), 1380 (w), 1357 (m), 1289 (w), 1249 (w), 1219 (w), 1187 (w), 1116 (m), 1083 (w), 1060 (w), 1016 (w), 999 (w), 966 (w), 756 (w), 696 (w), 670 (w), 624 (w), 599 (w), 546 (w), 509 (w) cm^{-1}. HRMS (ESI, pos. mode): calcd. 140.0792 (for $C_6H_{11}{}^2HNaO_2^+$), found 140.0791 [M$^+$]. $C_6H_{11}{}^2HO_2$ (117.17).

(*R*)-(5-^{2}H)-2-Hexanone [(*R*)-16a]. According to the procedure reported above for the non-deuterated compound **16b**, hexene (*R*)-**13a** (600 mg, 7.05 mmol), $Pd(OAc)_2$ (157 mg, 699 µmol, 0.1 equiv.) and TFA (804 mg, 7.05 mmol, 1.0 equiv.) were converted in DMSO (14 mL) and H_2O (1.4 mL) to furnish the title compound (*R*)-**16a** (318 mg, 3.14 mmol, 45%, based on 41% purity established by ^{1}H NMR) after column chromatography (SiO_2, pentane/Et_2O 9:1) as a slightly yellow liquid which was directly used in the next step without further characterization. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (dt, J = 7.4 Hz, J_{HD} = 1.0 Hz, 3H), 1.51–1.59 (m, 2H), 2.14 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H) ppm; not all signals could be identified with certainty due to overlapping solvent signals. The spectroscopic data were in accordance with those of the racemic compound.

(*R*,*R*)-(5-^{2}H)-3-Hydroxy-2-hexanone [(*R*,*R*)-17a]. According to the procedure reported above for the preparation of the non-deuterated compound (*R*)-**17b**, hexanone (*R*)-**16a** (318 mg, 3.14 mmol), a solution of nitrosobenzene (673 mg, 6.28 mmol, 2 equiv.) in DMSO (7.6 mL), L-proline (73 mg, 0.63 mmol, 0.2 equiv.), $CuSO_4$ (150 mg, 0.94 mmol, 0.3 equiv.) and MeOH (4.9 mL) were converted in DMSO (4 mL) to furnish the title compound (*R*,*R*)-**17a** (23 mg, 0.20 mmol, 6% based on 34% purity established by ^{1}H NMR, 99% *ee*) after column chromatography (SiO_2, pentane/MTBE 2:1, R_f = 0.22) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (dt, J = 7.2 Hz, J_{HD} = 1.0 Hz, 3H), 1.41–1.53 (m, 2H), 1.74–1.80 (m, 1H), 2.17 (s, 3H), 4.15 (dd, J = 7.5, 3.7 Hz, 1H) ppm; the signal of the hydroxy group could not be identified with certainty. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 13.84 (CH_3), 17.90 (t, J = 19.4 Hz, CHD), 25.22 (CH_3), 35.70 (CH_2), 76.83 (CH), 210.10 (C) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 1.31–1.46 (m, 1D) ppm. $[\alpha]_D^{20}$ = –67 ($CDCl_3$, 1.15 g L^{-1}). IR (ATR): $\tilde{\nu}$ = 3466 (w), 2959 (w), 2929 (w), 2874 (w), 2856 (w), 2162 (w), 1712 (s), 1642 (w), 1602 (w), 1499 (w), 1457 (w), 1443 (w), 1419 (w), 1399 (w), 1356 (w), 1314 (w), 1290 (w), 1249 (w), 1216 (w), 1189 (w), 1113 (m), 1083 (w), 1061 (w), 1016 (w), 966 (w), 869 (w), 796 (w), 754 (w), 694 (w), 670 (w), 624 (w), 544 (w), 509 (w) cm^{-1}.

(*S*)-(5-^{2}H)-2-Hexanone [(*S*)-16a]. According to the procedure reported above for the non-deuterated compound **16b**, hexene (*S*)-**13a** (600 mg, 7.04 mmol), $Pd(OAc)_2$ (157 mg, 699 µmol, 0.1 equiv.) and TFA (804 mg, 7.05 mmol, 1.0 equiv.) were converted in DMSO (14 mL) and H_2O (1.4 mL) to furnish the title compound (*S*)-**16a** (400 mg, 3.95 mmol, 56%, based on 46% purity established by ^{1}H NMR) after column chromatography (SiO_2, pentane/Et_2O 9:1) as a slightly yellow liquid which was directly used in the next step without further characterization. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (dt, J = 7.4 Hz, J_{HD} = 1.0 Hz, 3H), 1.53–1.58 (m, 2H), 2.13 (s, 3H), 2.42 (t, J = 7.5 Hz, 2H) ppm; not all signals could be identified with certainty due to overlapping solvent signals. The spectroscopic data were in accordance with those of the racemic compound.

(3*R*,5*S*)-(5-^{2}H)-3-Hydroxy-2-hexanone [(3*R*,5*S*)-17a]. According to the procedure reported above for the preparation of the non-deuterated compound (*R*)-**17b**, hexanone (*S*)-**16a** (400 mg, 3.95 mmol), a solution of nitrosobenzene (846 mg, 7.90 mmol, 2 equiv.) in DMSO (9.7 mL), L-proline (92 mg, 0.79 mmol, 0.2 equiv.), $CuSO_4$

(189 mg, 1.18 mmol, 0.3 equiv.) and MeOH (6.2 mL) were converted in DMSO (5 mL) to furnish the title compound (3*R*,5*S*)-**17a** (100 mg, 0.85 mmol, 22% based on 87% purity established by ^{1}H NMR, 99% *ee*) after column chromatography (SiO_2, pentane/MTBE 2:1, R_f = 0.22) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (dt, J = 7.4 Hz, J_{HD} = 0.9 Hz, 3H), 1.32–1.41 (m, 1H), 1.48–1.54 (m, 1H), 1.78 (ddd, J = 14.0, 10.4, 3.8 Hz, 1H), 2.18 (s, 3H), 3.43 (d, J = 4.3 Hz, 1H), 4.16 (dt, J = 7.2, 3.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 13.85 (CH_3), 17.86 (t, J = 19.5 Hz, CHD), 25.24 (CH_3), 35.68 (CH_2), 76.82 (CH), 210.10 (C) ppm. ^{2}H NMR (77 MHz, $CDCl_3$): δ = 1.42–1.54 (m, 1D) ppm. $[\alpha]_D^{20}$ = –108 (CH_2Cl_2, 1.06 g L^{-1}). IR (ATR): $\tilde{\nu}$ = 3467 (w), 2959 (w), 2933 (w), 2874 (w), 2162 (w), 1710 (s), 1457 (w), 1357 (m), 1289 (w), 1250 (w), 1222 (w), 1187 (w), 1117 (m), 1083 (w), 1059 (w), 1016 (w), 967 (w), 667 (w), 626 (w), 596 (w), 546 (w) cm^{-1}.

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Conflict of interest

The authors declare no conflict of interest.

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