Synthesis of Deuterium-Labeled Perfume Ingredients as Internal Standards for Their GC/MS Quantification

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The synthesis of various D-labeled perfume ingredients (orris-like, sandalwood-like, musky, and amber-like) is presented. These substances, possessing practically identical H_2O/solid and solid/gas partition coefficients as their unlabeled analogues, are used as internal standards for the validation of a new analytical GC/MS method for the determination of low residual concentrations in H_2O after biodegradability tests.

Introduction. – A recently introduced European legislation, REACH[1]) concerns the environmental impact of most of the chemical compounds produced or imported into the European Economic Community (EEC). It follows that the biodegradability (*i.e.*, the persistence of a particular sample in the environment) is a major concern, and poor results may jeopardize or restrict the use of this compound in the EEC.

The measurement of biodegradability involves the introduction of a known concentration of a compound into an aqueous medium seeded with micro-organisms harvested either from a domestic sewage treatment plant or collected in natural surface waters, and then to measure the evolution of this concentration dependent on time. This is extremely challenging for the analytical chemist, as many of the compounds under threat are sparingly soluble in water. In this context, *Chaintreau* and *Debonneville* at *Firmenich SA*, recently presented a new analytical GC/MS method [1a], based on internal cold-labeled standards, to measure the residual concentration of a sparingly H_2O-soluble perfume ingredient after biodegradation tests[2]). To validate this analytical method, the preparation of specifically labeled molecules was necessary. We present here the synthesis of a variety of labeled ingredients, both in terms of the olfactive family and the number of D-atoms incorporated [1b], constituted by the orris-like (D_5)- and (D_3)*Myrrhone*®, with additionally three examples in the sandalwood-like series ((D_3)*Dartanol*®, (D_3)*Polysantol*®, and (D_3)- and (D_4)*Firsantol*®), as well as two musk-like esters ((D_3)*Helvetolide*® and (D_3)- and (D_4)*Romandolide*®). In the case of an alternative analytical method, based on radioactivity measurements, using radio-labeled ingredients, we also prepared (5*Z*)-5-muscenone and muscone incorporating a

[1]) Directive (EC) No. 1907/2006 of December 18, 2006, of the European Parliament and of the Council concerning the Registration, Evaluation, Authorization, and Restriction of Chemicals.

[2]) Biodegradation tests performed on lipophilic substances possessing a $-\log(P) > 4.5$ are positive when the biodegradability exceeds 59% within a period of 10 d.

CD_3 substituent, thus providing a potential protocol for an authorized external laboratory, specialized in the synthesis of tritiated molecules. Finally, we discuss the preparation of (D_4)*Cetalox*® as an internal standard for ambergris-like odorants.

Results and Discussion. – This new analytical protocol, which consists in establishing a standard correlation between MS-fragment ratios and known concentrations of both the ingredient and its internal isotopic standard, involves several prerequisites. The chosen MS signal should be of sufficient intensity to optimize the method sensitivity, and should be characteristic of the compound (molecular ion or well-defined fragment ion, since signals below *m*/*z* *ca*. 55 are too common, and could originate from other components of the perfume mixture or impurities). For more accuracy, as well as dependability of the attribution, a second signal should also be available as control element. Since the sensitivity and linearity of the method (0.2 ppb to 100 ppm) is based on the accumulation of the ingredient by extraction from H_2O onto a solid phase, with ulterior thermal desorption in a GC/MS apparatus, both the ingredient and its internal standard should possess very similar H_2O/solid and solid/gas partition coefficients. This is possible with D-labeled molecules[3]), where there are at least three D-atoms to avoid superimposition with the minor naturally abundant isotope signals of the unlabeled ingredient. The signal thus appears in an empty space, in between two clusters of MS fragments. The labeled ingredient should not contain more than five to six D-atoms, so as to avoid different physical properties[4]) and superimposition of the MS signals with another, higher fragment cluster. Finally, from a purely economic point of view, it is better to introduce the D label during the later stages of a synthetic route.

For our first target (*Scheme 1*), direct aldol condensation of the known aldehyde **1** [2] with 3.0 mol-equiv. of (D_6)acetone (=(1,1,1,3,3,3-D_6)propan-2-one), in the presence of MeONa/MeOD afforded in 23% yield (D_5)*Myrrhone*® (**2a**)[5]) [2b][3][6]) (*Scheme 1*). Comparison of the mass spectra shows that the analytical measurement can be performed with the ion at *m*/*z* 116/111, while the control experiment is made with the molecular ion at *m*/*z* 213/208[7]) (the first cited *m*/*z* value always refers to the D-containing ion, and the value after the slash to the corresponding ion devoid of D-atom(s)). Nevertheless, this molecule possesses D-atoms in potentially exchangeable

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[3]) Theoretically, enantiomers could also be used, but this option would be limited to chiral and optically pure substrates. Furthermore, analysis of the optical purity is less sensitive than the herein described labeling method, and a straightforward synthesis of a pure enantiomer is not always available.

[4]) Such as, for example, the GC retention times or the partition coefficients. The solid PDMS foam used for H_2O-extraction/absorption/thermal-desorption is a polydimethylsiloxane of the general formula $Me_3SiO(Me_2SiO)_nSiMe_3$ ($n = 15$ to 1000). One advantage of this method is that a quantitative extraction of H_2O is not necessary, since only the ratio of the signals is important.

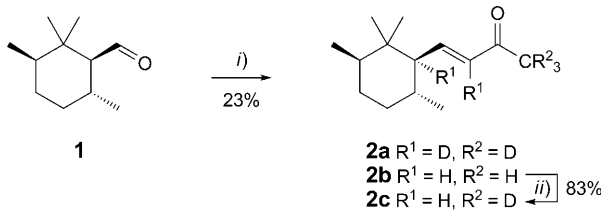
[5]) This compound possesses excellent and typical orris, violet, powdery, and myrrh olfactive properties.

[6]) The reference(s) correspond(s) to the unlabeled material.

[7]) Several other signals such as *m*/*z* 129/124, 170/165, 180/175, or 198/193 may also be used for confirmation.

positions, which, depending on the pH of the experiment, could eventually falsify the analysis[8]).

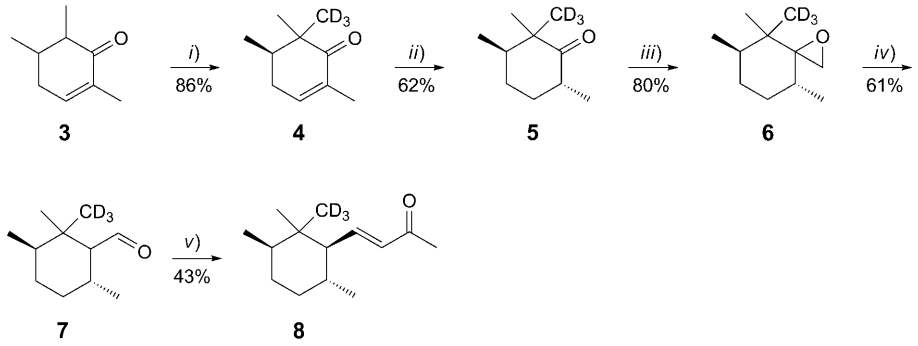
Scheme 1



i) Na, MeOD, (D_6)acetone. *ii*) MeOD, EtN^iPr_2, 20°.

For this reason, we prepared a D_3 analogue by alkylation of the commercially available enone **3** [4] (lithium diisopropylamide (LDA), THF, CD_3I, yield 86%), *i.e.*, 1:2 *cis*/*trans* mixture **4** [4d][5][6]) (*Scheme 2*). Hydrogenation under epimerizing conditions (H_2, Pd/C, NaOH, EtOH) afforded in 62% yield the saturated ketone **5** with the 3,6-dimethyl substituents in an equatorial orientation [6][6]). *Corey–Chaykovsky* oxiranylation (Me_2S, Me_2SO_4, DMSO, NaOH, yield 80%) allowed to cleanly isolate oxirane **6**[9]) [6a][6d][6]), which was isomerized (MgI_2, toluene, yield 61%) to the corresponding aldehyde **7**[10]). Final aldol condensation, in the presence of an excess of 6.0 mol-equiv. of acetone, afforded in 43% yield the all-equatorial (D_3)*Myrrhone*® (**8**) as an inseparable 1:2 *cis*/*trans* mixture at the quaternary center. The concentration measurement may be determined with the fragment at *m*/*z* 153/150, while the control experiment is performed with the molecular ion at *m*/*z* 211/208[11]).

Scheme 2



i) LDA, THF, CD_3I. *ii*) H_2, Pd/C, NaOH, EtOH. *iii*) Me_2S, Me_2SO_4, DMSO, NaOH. *iv*) Mg, I_2, toluene. *v*) Na, MeOH, acetone.

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[8]) Direct D exchange (D_2O, pyridine, 101°, yield 26%, or MeOD, EtN^iPr_2, 20°, yield 83% [1b]) with the unlabeled material **2b** [2b] afforded (D_3)*Myrrhone*® **2c** of the same olfactive properties. The main ion (*m*/*z* 114/111) as well as the $M^{+\bullet}$ signal (211/208) are suitable for measurement and confirmation, respectively.

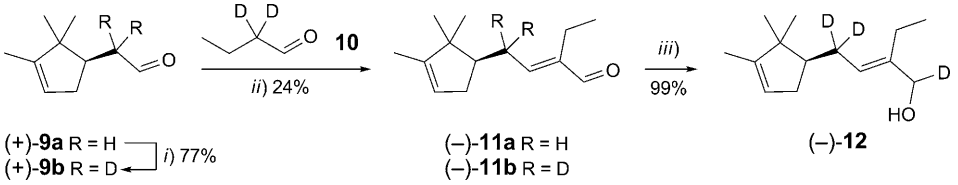
[9]) As a 2:1 mixture of (3*RS*,5*RS*,8*RS*)-**6**/(3*RS*,5*SR*,8*SR*)-**6**.

[10]) As a 1.2:1 mixture of (1*RS*,3*RS*,6*RS*)-**7**/(1*RS*,3*SR*,6*SR*)-**7**.

[11]) Further typical fragments are at *m*/*z* 178/175 and 196/193.

We chose *Dartanol*® as a first example of a sandalwood-like alcohol [7] (*Scheme 3*). The unreported α-dideuterated campholenal intermediate (+)-**9b** [7][6]), was obtained in 77% yield from (+)-**9a** by exchange with D_2O/pyridine [8]. Subsequent condensation (Na, D_2O, MeOD, yield 24%) with 2.0 mol-equiv. of the reported α-dideuterated butanal **10** [9], afforded enal (−)-**11b** [10][6]), which was finally reduced with $LiAlD_4$ to quantitatively afford (D_3)*Dartanol*® ((−)-**12**), suitable for MS measurements at *m*/*z* 196/193 and 211/208 ($M^{+\bullet}$)[12]). We also unsuccessfully attempted to prepare (−)-**11b** from (−)-**11a**, by direct exchange (D_2O, pyridine, 101°, <5% conversion after three weeks; MeOD, EtN^iPr_2, 20°, <5% conversion after one week).

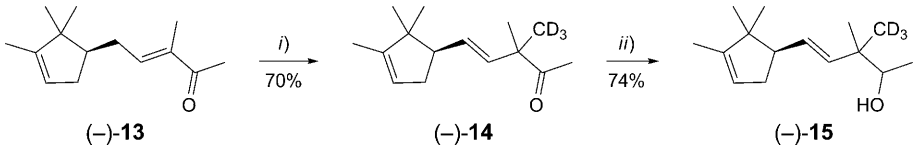
Scheme 3



i) D_2O, pyridine. *ii*) Na, D_2O, MeOD. *iii*) $LiAlD_4$, THF.

With respect to *Polysantol*® (*Scheme 4*), we opted for an alkylation of the known enone (−)-**13** [11] (^{t}BuOK, DMSO, CD_3I, yield 70%) to afford an inseparable *ca.* 1:1.1 diastereoisomer mixture of ketone (−)-**14** [11][12][6]), which was reduced with $LiAlH_4$ to the target molecule (−)-**15** in 74% yield [11][12][6]). The measurement was performed with the molecular ion at *m*/*z* 181/178, while the control experiment relied on the *m*/*z* 166/163 fragment[13]).

Scheme 4



i) ^{t}BuOK, DMSO, CD_3I. *ii*) $LiAlH_4$, Et_2O.

For the next sandalwood-like molecule (*Scheme 5*), we reduced the known aldehyde (−)-**16a** [11a] to the allylic deuterated alcohol (−)-**17a** with $LiAlD_4$ (91% isolated yield, [11a][13][6])). A subsequent *Claisen* reaction ($EtC(OEt)_3$, pivalic acid (=2,2-dimethylpropanoic acid), 140°) afforded the monodeuterated ester (−)-**18a**[14]) [11a][6]) in 72% yield, prior to final reduction ($LiAlD_4$, THF, yield 88%). The analysis

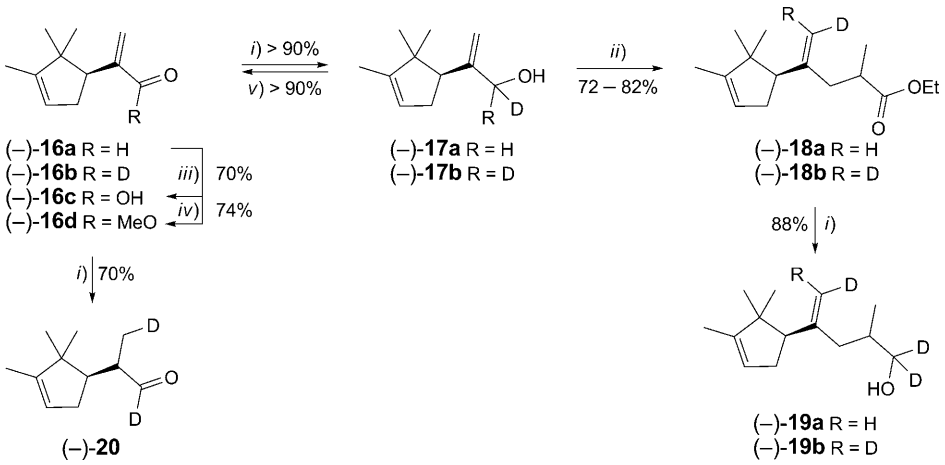
12) A further ion at *m*/*z* 164/161 may eventually be used.

13) Alternatively, the major signal is at *m*/*z* 72/69, while the minor signals at *m*/*z* 138/135 and 152/149 were discarded. Similarly, due to its fragmentation pattern, we also discarded the possibility of labeling position 1′ by a CD_3MgI *Grignard* reaction with the corresponding α-geminal dimethylated aldehyde or *via* D exchange of the intermediate unlabeled analogue of methyl ketone (−)-**14**.

14) As a 1:1.2 mixture with respect to the Me substituent and a 1:1 (*E*)/(*Z*) mixture with respect to the methylene group.

for (D_3)*Firsantol*® (−)-**19a**[13]) [11a][13][6]) may be effected with the main molecular-ion peak at *m*/*z* 211/208, while the control is performed with the *m*/*z* 196/193 signal[15]). Since we also wanted to have an example of a D_4 substrate, we also oxidized aldehyde (−)-**16a** with $AgNO_3$/NaOH to afford the unreported unsaturated acid (−)-**16c** in 70% yield. This was then esterified (MeOH, DCC, *N*,*N*-dimethylpyridin-4-amine (DMAP), yield 74%) to the corresponding methyl ester (−)-**16d**. Unfortunately, when reduced with 0.5 mol-equiv. of $LiAlD_4$, ester (−)-**16d** was prone to a more rapid 1,4-hydride addition, leading to the dideuterated aldehyde (−)-**20**[16])[17]) in 70% yield [11a][14][6]). This drawback was overcome by oxidizing the monodeuterated allyl alcohol (−)-**17a** (pyridinium chlorochromate (PCC), CH_2Cl_2, yield > 90%) to a *ca.* 45:55 mixture (−)-**16a**/(−)-**16b**. This mixture was then reduced ($LiAlD_4$, THF, yield > 90%) to a *ca.* 45:55 mixture of allyl alcohols (−)-**17a**/(−)-**17b**. This oxidation-reduction sequence was repeated four more times, thus ensuring a double D-incorporation superior to 97%. When alcohol (−)-**17b** was submitted to the *Claisen* reaction ($EtC(OEt)_3$, pivalic acid, 140°), the corresponding ester (−)-**18b** was isolated in 82% yield, while subsequent reduction with $LiAlD_4$ furnished the desired (D_4)*Firsantol*® (−)-**19b** in 88% yield. Here again, the main molecular-ion peak at *m*/*z* 212/208 served for the measurement, while the fragment at *m*/*z* 197/193 was used for confirmation[18]).

Scheme 5



i) $LiAlD_4$, THF. *ii*) $EtC(OEt)_3$, pivalic acid, 140°. *iii*) $AgNO_3$, NaOH. *iv*) MeOH, DCC, DMAP. *v*) PCC, CH_2Cl_2.

As examples of a musk-like perfume ingredient (*Scheme 6*), we esterified the known intermediate alcohols (+)-**21a** [15] and (+)-**21b** [16] with (D_3)propanoic acid in

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15) Although of lower intensity, the signal at *m*/*z* 178/175 may also be used.

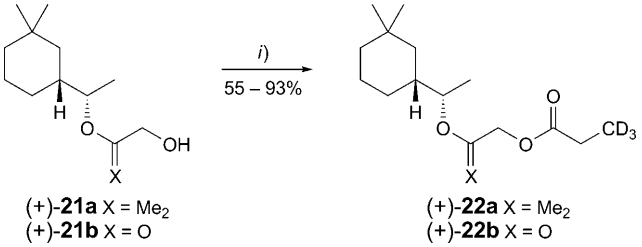
16) As a 1:1.1 mixture of diastereoisomers.

17) Reduction of acid (−)-**16c** (0.75 mol-equiv. of $LiAlD_4$, THF, yield 45%) afforded a 2:3 mixture (−)-**20**/(−)-**17b**.

18) The signal at *m*/*z* 179/175 was neglected because of its lower intensity.

the presence of DCC and DMAP in CH_2Cl_2 to afford directly (D_3)*Helvetolide*® ((+)-**22a**)[19]) [15a][17][6]) (yield 55%), as well as the (D_3)*Romandolide*® analogue (+)-**22b** [16][17][6]) (yield 93%), respectively. In the first case, measurement is made with the major peak at *m*/*z* 132/129, and confirmed with the *m*/*z* 60/57 fragment. Similarly, for the (D_3)*Romandolide*® analogue, analysis is performed with the *m*/*z* 118/115 fragment, but the test control also involves the *m*/*z* 60/57 fragment. To have an alternative solution, as well as a second D_4 example, we decided to introduce the labels in the non-ester part of the molecule.

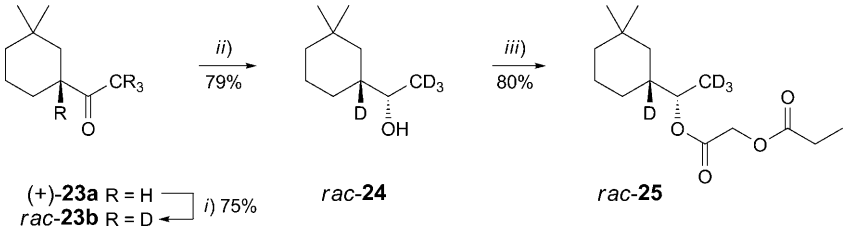
Scheme 6



i) DCC, DMAP, CH_2Cl_2, (D_3)propanoic acid.

Consequently, the known methyl ketone (+)-**23a** [18] (*Scheme 7*) was subjected to D-exchange (Na, D_2O, MeOD, yield 75%) to afford the racemic tetradeuterated ketone *rac*-**23b**. Further reduction (L-*Selectride*®, THF, −78°, yield 79%) furnished a 75:25 mixture of the desired diastereoisomers *rac*-**24**[20]) [16][18][6]), which were subsequently esterified according to the known procedure [16], thus affording *rac*-(D_4)*Romandolide*® *rac*-**25** in 58% yield[21]). In this case, the measurement and the control experiment can be effected with the *m*/*z* 127/123 and 142/138 fragments, respectively.

Scheme 7



i) Na, D_2O, MeOD. *ii*) *L-Selectride*, THF, −78°; then, H_2O_2, NaOH. *iii*) 2-Chloro-2-oxoethyl propanoate, pyridine, Et_2O.

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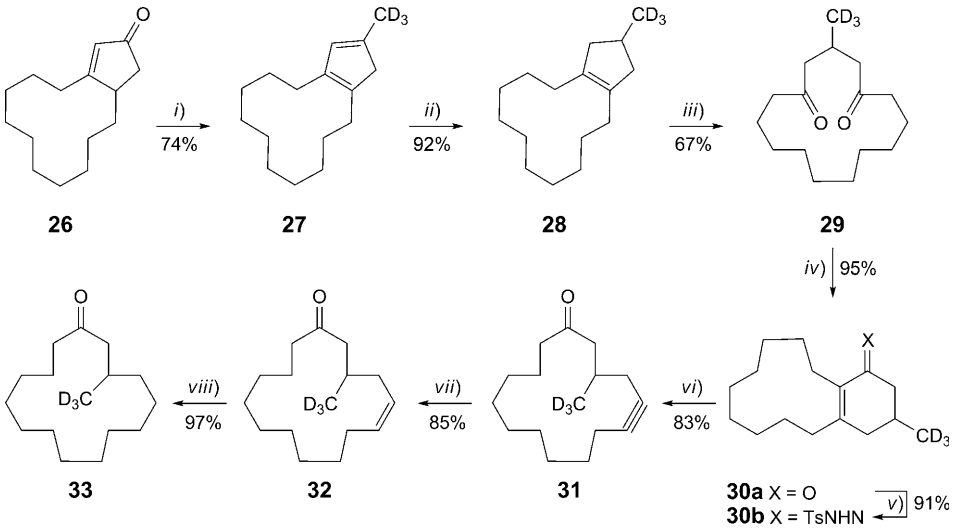
[19]) With excellent musky, fruity olfactive notes.

[20]) Under similar conditions, the diastereoselectivity was even worse with either (*R*)-*Alpine-Hydride*® (70:30), *LS-Selectride*® (60:40), or 9-borabicyclo[3.3.1]nonane (9-BBN; 55:45). Alternative $NaBH_4$/EtOH or $LiAlH_4/Et_2O$ conditions were practically unselective according to ^{1}H- and ^{13}C-NMR analyses, thus contrasting with the original report, based on GC and IR analyses [18]. The two diastereoisomers remained inseparable on modern 30 m long apolar GC capillary columns.

[21]) Since the internal standard is added after the biodegradation process, its optical purity does not influence the biodegradability.

As examples of macrocyclic musks (*Scheme 8*), we introduced, in 74% yield, the desired labels *via* a CD_3MgI *Grignard* addition to the known bicyclic enone **26** [19]. The transient tertiary allyl alcohol spontaneously dehydrated [20] to afford a complex mixture of at least four conjugated dienes, containing **27** [21][6]) as a major component. *In situ* isomerization of the mixture[22]) occurred under mono-hydrogenation conditions, in the presence of *Lindlar* catalyst (H_2, *Lindlar* cat., AcOEt, yield 91%) to selectively furnish the more stable tetrasubstituted bicyclic alkene **28** [21][22][6]). Subsequent ozonolysis (O_3, EtOH, $-78°$, then H_2, Pd/C, yield 67%) afforded muscodione **29**, a known intermediate for either (5*Z*)-5-muscenone or muscone synthesis [23][6]). Accordingly, intramolecular aldol condensation (KOH, EtOH, 78°, yield 95%) furnished the bicycloalkenone **30a**. The corresponding tosylhydrazone **30b** (H_2NNHTs, cat. AcOH, MeOH, 64°, yield 91%) was treated with AcO_2H to afford, after *Eschenmoser* fragmentation, the cyclopentadecynone **31** in 83% yield. *Lindlar* conditions and/or perhydrogenation (H_2, Pd/C, EtOH) allowed isolating either the desired (5*Z*)-5-(D_3)muscenone (**32**) or (D_3)muscone (**33**) in 85 and 95–97% yield, respectively. In the first case, both the ratio and the control experiment may be determined with the *m*/*z* 239/236 ($M^{+\bullet}$) and 196/193 ions, while the *m*/*z* 88/85 and 241/238 ($M^{+\bullet}$) signals may be used for **33**, respectively.

Scheme 8



i) CD_3MgI, Et_2O. *ii*) H_2, *Lindlar* cat., AcOEt. *iii*) O_3, EtOH, $-78°$; then, H_2, Pd/C. *iv*) KOH, EtOH, 78°. *v*) $TsNHNH_2$, cat. AcOH, MeOH, 64°. *vi*) AcO_2H, toluene, H_2O. *vii*) H_2, *Lindlar* cat., EtOH. *viii*) H_2, Pd/C, EtOH.

Finally, in the ambergris series, we treated the racemic lactone **34a** [24] with MeONa in refluxing MeOD and isolated the unreported dideuterated sclareolide **34b**

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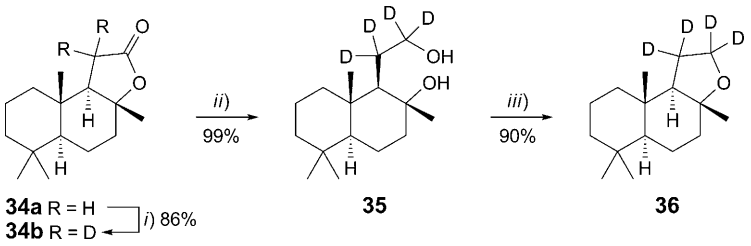
[22]) Alternatively, isomerization of the dienes may be quantitatively performed in the presence of the catalyst TsOH in cyclohexane, prior to mono-hydrogenation.

in 86% yield (*Scheme 9*). Further reduction ($LiAlD_4$, THF) afforded the tetradeuterated diol **35** [25][6]) in quantitative yield (*Scheme 9*). The synthesis of (D_4)*Cetalox*® (**36**)[23]) [25a][6]) was completed by cyclization under known conditions (TsCl, pyridine, 90%) [25a]. This compound gave the best results in terms of sensitivity and linearity of the analytical GC/MS method, by measuring the ratios for the *m*/*z* 225/221 signal, with confirmation by using the *m*/*z* 101/97 fragment[24]).

Scheme 9



i) Na, MeOD, 65°. *ii*) $LiAlD_4$, THF. *iii*) TsCl, pyridine.

Conclusion. – We have prepared 13 unreported analogues of perfume ingredients, labeled with three to five D-atoms, which served to validate a new analytical GC/MS protocol, based on internal deuterated standards, for the determination of low concentrations of lipophilic compounds in water [1]. The scope of this methodology may potentially be extended to the quantification of trace amounts of allergens[25]).

We are indebted to Dr. *Jean-Yves de Saint Laumer* for B3LYP/6-31G** calculations.

Experimental Part

General. See [27].

*(3*E*)-4-(2,2,3*c*,6*t*-Tetramethyl-1*r*-(1-*$^2H_1$*)cyclohexyl)(1,1,1,3-*$^2H_4$*)but-3-en-2-one* (**2a**). Metallic Na (0.5 g, 21.8 mmol) was added portionwise to MeOD (5 ml) under N_2. After complete dissolution, (D_6)acetone (2.88 g, 43.7 mmol) was added dropwise, followed after 15 min by aldehyde **1** (2.45 g, 14.5 mmol). The mixture was heated to reflux for 6 h, then poured onto ice, and extracted with Et_2O (3 × 15 ml). The org. phase was washed to neutrality with brine, dried (Na_2SO_4), and concentrated. Purification by CC (SiO_2, cyclohexane/AcOEt 95:5) afforded pure **2a** (23%). B.p. 120°/0.3 mbar. IR: 2962, 2916, 2870, 2252, 2114, 1686, 1662, 1614, 1454, 1390, 1374, 1367, 1287, 1263, 1225, 1201, 1176, 1039, 996, 920, 887, 715. ^{1}H-NMR: 0.74 (*d*, *J* = 7, 3 H); 0.76 (*s*, 3 H); 0.83 (*s*, 3 H); 0.85 (*d*, *J* = 7, 3 H); 0.96–1.05 (*m*, 1 H); 1.18–1.22 (*m*, 1 H); 1.29–1.35 (*m*, 1 H); 1.40–1.48 (*m*, 1 H); 1.5–1.6 (*m*, 1 H); 1.7–1.79 (*m*, 1 H); 6.62 (*s*, 1 H). ^{13}C-NMR: 198.4 (*s*); 150.2 (*d*); 41.8 (*d*); 36.7 (*s*); 35.3 (*t*); 31.3 (*d*); 30.6 (*t*); 27.9 (*q*); 21.7 (*q*); 16.2 (*q*); 14.4 (*q*). MS: 213 (20, $M^{+\cdot}$), 198 (12), 195 (13), 180 (10), 170 (18), 151 (40), 129 (32), 116 (100), 114 (69), 100 (40), 97 (37), 83 (60), 69 (24), 55 (32), 46 (55).

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[23]) Possesses a typical elegant and warm amber note.

[24]) This racemic internal standard may also be used for the quantification of (−)-*Ambrox*®.

[25]) Directive (EC) No. 15/2003 of February 27, 2003, of the European Parliament and of the Council concerning the compulsory quantification of 24 volatile allergens in cosmetic and detergent products [26].

*(3*E*)-4-(2,2,3*c*,6*t*-Tetramethyl-1*r*-cyclohexyl)(1,1,1-$^2H_3$)but-3-en-2-one* (**2c**). A soln. of *Myrrhone*® (**2b**; 1000 mg, 4.8 mmol) and EtN^iPr_2 (180 mg, 1.4 mmol) in MeOD (9.2 ml) was stirred for 72 h. D_2O (18.4 ml) was added, and the aq. phase was extracted with Et_2O (3 × 20 ml). The org. phase was dried (Na_2SO_4) and concentrated and the residue bulb-to-bulb distilled: pure **2b** (83%), >97% D-incorporation. IR: 2963, 2918, 2874, 2253, 1668, 1625, 1455, 1390, 1376, 1367, 1266, 1178, 1033, 990, 914, 819. ^{1}H-NMR: 0.74 (*d*, *J* = 6.2, 3 H); 0.76 (*s*, 3 H); 0.83 (*s*, 3 H); 0.85 (*d*, *J* = 6.2, 3 H); 0.96–1.05 (*m*, 2 H); 1.18–1.22 (*m*, 1 H); 1.29–1.35 (*m*, 1 H); 1.40–1.48 (*m*, 1 H); 1.5–1.6 (*m*, 1 H); 1.7–1.79 (*m*, 1 H); 6.02 (*d*, *J* = 15.8, 1 H); 6.60 (*dd*, *J* = 10.1, 16.1, 1 H). ^{13}C-NMR: 198.5 (*s*); 150.2 (*d*); 133.6 (*d*); 59.9 (*d*); 41.9 (*d*); 36.9 (*s*); 35.4 (*t*); 31.5 (*d*); 30.7 (*t*); 28.0 (*q*); 21.8 (*q*); 16.2 (*q*); 14.5 (*q*). MS: 211 (12, $M^{+\bullet}$), 168 (14), 150 (39), 137 (13), 127 (24), 123 (23), 114 (100), 112 (68), 109 (28), 107 (20), 98 (42), 95 (41), 81 (69), 69 (21), 67 (17), 55 (43), 46 (62), 41 (37).

6-[($^2H_3$*)Methyl]-2,5,6-trimethylcyclohex-2-en-1-one* (**4**). At −15° 1.6M BuLi in hexane (29.4 ml, 47 mmol) was added dropwise to a soln. of $^iPr_2NH$ (4.79 g, 47 mmol) in THF (40 ml). After 30 min, enone **3** was added, followed after 1.5 h by CD_3I (6.82 g, 47 mmol). After 15 min, the temp. was equilibrated to 20°, and after 24 h, the mixture was poured onto ice and extracted with Et_2O (3 × 40 ml). The org. phase was washed to neutrality with brine, dried (Na_2SO_4), and concentrated. Purification by bulb-to-bulb distillation afforded **4** (86%). B.p. 80°/0.85 mbar. IR: 2969, 2924, 2880, 2222, 2150, 2062, 1667, 1453, 1431, 1379, 1361, 1298, 1255, 1213, 1205, 1135, 1052, 1021, 964, 934, 918, 837. ^{1}H-NMR: 0.95 (*s*, 2 H); 0.97 (*d*, *J* = 7, 3 H); 1.14 (*s*, 1 H); 1.76 (*q*, *J* = 1, 3 H); 1.92–1.99 (*m*, 1 H); 2.04–2.12 (*m*, 1 H); 2.26–2.36 (*m*, 1 H); 6.59 (*m*, 1 H). ^{13}C-NMR: 205.2 (*s*); 142.4 (*d*); 133.5 (*s*); 44.9 (*s*); 38.6 (*d*); 31.7 (*t*); 22.5 (0.33 *q*); 18.2 (0.66 *q*); 16.5 (*q*); 15.6 (*q*). MS: 155 (20, $M^{+\bullet}$), 82 (100), 54 (12).

2-[($^2H_3$*)Methyl]-2,3,6-trimethylcyclohexanone* (**5**). A suspension of **4** (5.60 g, 36 mmol), NaOH (0.56 g, 14 mmol), and 5% Pd/C (0.56 g) in EtOH (50 ml) was hydrogenated (906 ml of H_2) in 90 min. The mixture was filtered over *Celite*® and rinsed with Et_2O, the filtrate dried (Na_2SO_4) and concentrated to afford, after bulb-to-bulb distillation, pure **5** (62%). B.p. 80°/3.01 mbar. IR: 2966, 2929, 2873, 2228, 2161, 2066, 1702, 1455, 1380, 1321, 1247, 1230, 1172, 1162, 1123, 1050, 1031, 1001, 984, 944, 924, 838. ^{1}H-NMR: 0.95 (*d*, *J* = 7, 3 H); 0.98 (*d*, *J* = 7, 3 H); 1.02 (*s*, 2 H); 1.05 (*s*, 1 H); 1.22–1.34 (*m*, 1 H); 1.55–1.70 (*m*, 3 H); 1.95–2.02 (*m*, 1 H); 2.60–2.70 (*m*, 1 H). ^{13}C-NMR: 217.5 (*s*); 48.5 (*s*); 43.1 (*d*); 40.0 (*d*); 35.2 (*t*); 30.2 (*t*); 22.5 (0.33 *q*); 19.0 (0.66 *q*); 15.7 (*q*); 15.1 (*q*). MS: 157 (45, $M^{+\bullet}$), 112 (12), 99 (100), 87 (33), 72 (52), 69 (23).

*(3*RS*,5*RS*,8*RS*)-4-[(*$^2H_3$*)Methyl]-4,5,8-trimethyl-1-oxaspiro[2.5]octane* (**6**). Me_2SO_4 (2.87 g, 23 mmol) was added dropwise to a soln. of Me_2S (1.53 g, 25 mmol) in DMSO (11 ml) under N_2 and efficient mechanical stirring. NaOH in small beads (1–2 mm d., 8.0 g, 200 mmol) was added, followed by **5** (3.30 g, 19 mmol). After 40 h at 20°, the mixture was extracted with Et_2O (3 × 30 ml), and the org. phase was washed to neutrality with H_2O, dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation afforded pure **6**[9]) (80%). B.p. 100°/3.2 mbar. IR: 3055, 3014, 2960, 2920, 2878, 2856, 2222, 2157, 2073, 1492, 1457, 1380, 1346, 1204, 1172, 1147, 1122, 1085, 1056, 1040, 1025, 995, 945, 924, 913, 894, 865, 848, 836, 817, 789, 770, 629. ^{1}H-NMR: major: 0.68 (*d*, *J* = 7, 3 H); 0.75 (*s*, 1 H); 0.83 (*d*, *J* = 7, 3 H); 0.93 (*s*, 2 H); 1.35–1.49 (*m*, 3 H); 1.50–1.60 (*m*, 2 H); 2.08–2.18 (*m*, 1 H); 2.61 (*d*, *J* = 4, 1 H); 2.70 (*d*, *J* = 4, 1 H); minor: 0.69 (*d*, *J* = 7, 3 H); 0.75 (*s*, 1 H); 0.85 (*d*, *J* = 7, 3 H); 0.95 (*s*, 2 H); 1.35–1.49 (*m*, 3 H); 1.50–1.60 (*m*, 2 H); 2.08–2.18 (*m*, 1 H); 2.59 (*d*, *J* = 4, 1 H); 2.71 (*d*, *J* = 4, 1 H). ^{13}C-NMR: major: 65.3 (*s*); 45.9 (*t*); 38.3 (*d*); 37.3 (*s*); 32.7 (*t*); 31.3 (*t*); 30.1 (*d*); 20.7 (0.33 *q*); 18.9 (0.66 *q*); 16.4 (*q*); 15.2 (*q*); minor: 65.9 (*s*); 45.3 (*t*); 41.9 (*d*); 37.7 (*s*); 34.2 (*t*); 31.3 (*d*); 30.8 (*t*); 22.2 (0.33 *q*); 16.8 (0.66 *q*); 15.9 (*q*); 15.1 (*q*). MS: major: 171 (19, $M^{+\bullet}$), 156 (75), 153 (48), 128 (40), 126 (100), 123 (32), 99 (50), 84 (51), 81 (33), 55 (25), 41 (28); minor: 171 (19, $M^{+\bullet}$), 156 (80), 153 (50), 128 (40), 126 (100), 123 (40), 114 (27), 99 (50), 95 (30), 84 (48), 81 (33), 55 (27), 41 (28).

2-[($^2H_3$*)Methyl]-2,3,6-trimethylcyclohexanecarbaldehyde* (**7**). I_2 (1.21 g, 4.8 mmol) was added portionwise to a suspension of Mg (0.11 g, 4.8 mmol) in THF (15 ml). After 30 min, toluene (15 ml) was added, and the THF was distilled off. When the distillation temp. reached 110°, **6** (2.47 g, 19 mmol) was added, and after 2 h, the cold mixture was extracted with H_2O/Et_2O. The org. phase was washed to neutrality with brine, dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation afforded pure **7**[10]) (61%). B.p. 100°/3.0 mbar. IR: 2957, 2919, 2874, 2715, 2217, 2067, 1717, 1458, 1383, 1194, 1171, 1147, 1054, 1017, 922, 894. ^{1}H-NMR: major: 0.87 (*d*, *J* = 7, 3 H); 0.88 (*d*, *J* = 7, 3 H); 0.89 (*s*, 2 H); 0.94 (*s*, 1 H); 1.0–

1.5 (*m*, 2 H); 1.55–1.67 (*m*, 2 H); 1.73–1.85 (*m*, 1 H); 1.90–2.05 (*m*, 2 H); 10.02 (*d*, *J* = 5, 1 H); minor: 0.81 (*d*, *J* = 7, 3 H); 0.84 (*d*, *J* = 7, 3 H); 0.90 (*s*, 2 H); 0.96 (*s*, 1 H); 1.0–1.5 (*m*, 2 H); 1.55–1.67 (*m*, 2 H); 1.73–1.85 (*m*, 1 H); 1.90–2.05 (*m*, 2 H); 9.68 (*d*, *J* = 5, 1 H). ^{13}C-NMR: major: 207.6 (*s*); 65.0 (*d*); 37.1 (*d*); 36.3 (*s*); 31.4 (*t*); 31.3 (*t*); 30.5 (*d*); 27.5 (0.33 *q*); 21.0 (0.66 *q*); 20.1 (*q*); 15.8 (*q*); minor: 208.1 (*s*); 67.4 (*d*); 41.7 (*d*); 36.7 (*s*); 34.7 (*t*); 31.2 (*t*); 28.1 (*d*); 27.7 (0.33 *q*); 20.7 (*q*); 15.1 (*q*); 14.0 (0.66 *q*). MS: major: 171 (30, $M^{+\bullet}$), 127 (44), 101 (64), 86 (100), 84 (97), 71 (61), 69 (39), 55 (48), 41 (34); minor: 171 (11, $M^{+\bullet}$), 127 (10), 101 (12), 88 (31), 86 (30), 84 (100), 71 (19), 55 (19), 41 (14).

*(3*E*)-4-[(1*RS*,3*RS*,6*RS*)-2-[(*$^2H_3$*)Methyl]-2,3,6-trimethylcyclohexyl]but-3-en-2-one* (**8**). Obtained in 43% yield as described for **2a**, with 6.0 mol-equiv. of acetone in MeOH. B.p. 140°/0.45 mbar. IR: 2956, 2917, 2871, 2855, 2216, 2066, 1697, 1673, 1621, 1456, 1380, 1358, 1260, 1249, 1227, 1181, 1167, 1157, 1061, 988. ^{1}H-NMR: 0.74 (*d*, *J* = 7, 3 H); 0.76 (*s*, 2 H); 0.83 (*s*, 1 H); 0.85 (*d*, *J* = 7, 3 H); 0.9–1.08 (*m*, 2 H); 1.15–1.33 (*m*, 2 H); 1.40–1.60 (*m*, 2 H); 1.70–1.76 (*m*, 1 H); 2.27 (*s*, 3 H); 6.03 (*d*, *J* = 15, 1 H); 6.62 (*dd*, *J* = 11, 15, 1 H). ^{13}C-NMR: 198.2 (*s*); 150.2 (*d*); 133.4 (*d*); 59.8 (*d*); 41.8 (*d*); 36.6 (*s*); 35.3 (*t*); 31.5 (*d*); 30.7 (*t*); 27.9 (0.33 *q*); 21.7 (*q*); 16.1 (*q*); 14.4 (0.66 *q*). MS: 211 (18, $M^{+\bullet}$), 196 (12), 193 (10), 165 (18), 153 (38), 124 (38), 111 (100), 109 (91), 95 (78), 81 (58), 55 (25), 43 (62).

*(+)-2-[(1*R*)-2,2,3-Trimethylcyclopent-3-en-1-yl](2,2-*$^2H_2$*)acetaldehyde* ((+)-**9b**). A mixture of aldehyde (+)-**9a** (15.2 g, 100 mmol), pyridine (0.79 g, 10 mmol), and D_2O (10 g, 500 mmol) was heated under reflux for one week. Then the aq. phase was extracted with Et_2O (2 × 10 ml) and the org. phase dried (Na_2SO_4) and concentrated; this operation was repeated twice. Bulb-to-bulb distillation afforded pure (+)-**9b** (77%). $\alpha_D^{20} = +7.6$ (neat, *l* = 1 dm). B.p. 60°/10 mbar. IR: 3038, 2956, 2931, 2868, 2836, 2713, 2125, 1722, 1461, 1444, 1385, 1361, 1271, 1202, 1114, 1012, 981, 947, 799. ^{1}H-NMR: 0.8 (*s*, 3 H); 1.01 (*s*, 3 H); 1.63 (*q*, *J* = 1, 3 H); 1.87–1.95 (*m*, 1 H); 2.28 (*t*, *J* = 7, 1 H); 2.38–2.42 (*m*, 1 H); 5.24 (*s*, 1 H); 9.8 (*s*, 1 H). ^{13}C-NMR: 203.1 (*d*); 148.0 (*s*); 121.6 (*d*); 47.0 (*s*); 44.2 (*d*); 35.5 (*t*); 25.7 (*q*); 20.1 (*q*); 12.6 (*q*). MS: 154 (2, $M^{+\bullet}$), 108 (100), 95 (23), 93 (60), 91 (10), 67 (8), 41 (8).

*(−)-(2*E*)-2-Ethyl-4-[(1*R*)-2,2,3-trimethylcyclopent-3-en-1-yl](4,4-*$^2H_2$*)but-2-enal* ((−)-**11b**). Metallic Na (80 mg, 3.5 mmol) was added to a mixture of MeOD (6 ml) and D_2O (200 mg, 10 mmol). This soln. was heated to reflux, and a mixture of aldehydes (+)-**9b** (4.39 g, 29 mmol) and **10** (4.21 g, 57 mmol) was added dropwise. After 1 h, the cold mixture was poured onto ice and extracted with Et_2O (3 × 20 ml). The org. phase was washed to neutrality with brine, dried (Na_2SO_4), and concentrated. Bulb-to bulb distillation afforded (−)-**11b** (24%). $[\alpha]_D^{20} = -8.0$ (*c* = 1.3, $CHCl_3$). B.p. 90°/0.25 mbar. IR: 2962, 2935, 2873, 2203, 2116, 1685, 1638, 1464, 1443, 1375, 1364, 1276, 1240, 1205, 1137, 1085, 1061, 1046, 1016, 970, 946, 920, 842, 800. ^{1}H-NMR: 0.87 (*s*, 3 H); 0.99 (*t*, *J* = 7, 3 H); 1.03 (*s*, 3 H); 1.63 (*s*, 3 H); 1.85–1.95 (*m*, 1 H); 1.95 (*t*, *J* = 7, 1 H); 2.29 (*q*, *J* = 7, 2 H); 2.3–2.35 (*m*, 1 H); 5.25 (br. *s*, 1 H); 6.48 (*s*, 1 H); 9.38 (*s*, 1 H). ^{13}C-NMR: 195.1 (*s*); 154.4 (*d*); 148.4 (*s*); 145.4 (*s*); 121.5 (*d*); 49.7 (*d*); 47.1 (*s*); 35.5 (*t*); 29.9 (*q*); 19.8 (*q*); 17.4 (*t*); 13.3 (*q*); 12.6 (*q*). MS: 208 (9, $M^{+\bullet}$), 193 (6), 175 (8), 165 (15), 138 (15), 123 (33), 109 (90), 108 (100), 93 (43), 79 (20), 67 (21), 55 (11), 41 (16).

*(−)-(2*E*)-2-Ethyl-4-[(1*R*)-2,2,3-trimethyl-3-cyclopenten-1-yl](1,4,4-*$^2H_3$*)but-2-en-1-ol* ((−)-**12**). A soln. of (−)-**11b** (250 mg, 1.2 mmol) in THF (3 ml) was added dropwise to a suspension of 1.0M $LiAlD_4$ in THF (1.2 ml, 1.2 mmol) under N_2. After 30 min, the reaction was quenched with H_2O (0.02 ml), 15% NaOH soln. (0.02 ml), and H_2O (0.06 ml). After filtration over *Celite®*, the dry soln. (Na_2SO_4) was concentrated. Bulb-to-bulb distillation afforded quantitatively (−)-**12**. $\alpha_D^{20} = -4.5$ (neat, *l* = 1 dm). B.p. 100°/0.3 mbar. IR: 3321, 3036, 2955, 2930, 2892, 2867, 2834, 2188, 2127, 1652, 1463, 1380, 1359, 1301, 1267, 1221, 1188, 1112, 1089, 1029, 973, 945, 917, 798, 695. ^{1}H-NMR: 0.8 (*s*, 3 H); 1.0 (*s*, 3 H); 1.02 (*t*, *J* = 7, 3 H); 1.35 (br. *s*, 1 OH); 1.60 (*q*, *J* = 1, 3 H); 1.78 (*t*, *J* = 7, 1 H); 1.8–1.98 (*m*, 1 H); 2.15 (*q*, *J* = 7, 2 H); 2.25–2.3 (*m*, 1 H); 4.04 (*s*, 1 H); 5.23 (*s*, 1 H); 5.4 (*s*, 1 H). ^{13}C-NMR: 148.6 (*s*); 140.7 (*s*); 126.0 (*d*); 121.7 (*d*); 66.9 (*d*); 50.4 (*d*); 46.8 (*s*); 35.6 (*t*); 25.9 (*q*); 21.1 (*t*); 19.8 (*q*); 13.2 (*q*); 12.6 (*q*). MS: 211 (13, $M^{+\bullet}$), 196 (16), 178 (28), 164 (15), 136 (19), 123 (62), 109 (100), 95 (42), 93 (50), 81 (20), 79 (22), 67 (30), 57 (30), 41 (18).

*(−)-(4*E*)-3-[(*$^2H_3$*)Methyl]-3-methyl-5-[(1*R*)-2,2,3-trimethylcyclopent-3-en-1-yl]pent-4-en-2-one* ((−)-**14**). Ketone (−)-**13** (15.0 g, 73 mmol) was added dropwise to a soln. of ^{t}BuOK (9.79 g, 87 mmol) in DMSO (60 ml). After 1 h, CD_3I (12.61 g, 87 mmol) was added dropwise at 5°. After 1 h at 20°, the mixture was quenched with H_2O (10 ml) and extracted with Et_2O (3 × 15 ml). The org. phase was washed to neutrality with H_2O, dried (Na_2SO_4), and concentrated and the residue bulb-to-bulb distilled: (−)-**14**

(70%). $[\alpha]_D^{20} = -26.4$ ($c = 2.8$, $CHCl_3$). B.p. 120°/0.17 mbar. IR: 3036, 2955, 2929, 2865, 2225, 2137, 2066, 1709, 1460, 1374, 1352, 1226, 1106, 1052, 1012, 979, 797. ^{1}H-NMR: 0.75 (*s*, 3 H); 0.95 (*s*, 3 H); 1.23 (*s*, 3 H); 1.61 (*s*, 3 H); 2.05–2.09 (*m*, 1 H); 2.12 (*s*, 3 H); 2.2–2.3 (*m*, 1 H); 2.38 (*q*, $J = 7$, 1 H); 5.23 (*s*, 1 H); 5.51 (*d*, $J = 16$, 1 H); 5.59 (*dd*, $J = 7, 16$, 1 H). ^{13}C-NMR: 211.7 (*s*); 148.0 (*s*); 135.0 (*d*); 131.5 (*d*); 121.4 (*d*); 54.1 (*d*); 50.1 (*s*); 48.4 (*s*); 35.3 (*t*); 25.5 (*q*); 25.4 (*q*); 24.2 (*q*); 20.5 (*q*); 12.7 (*q*). MS: 223 (2, $M^{+\bullet}$), 180 (32), 121 (12), 115 (14), 109 (27), 72 (100), 43 (28).

*(−)-(4*E*)-3-[(*$^2H_3$*)Methyl]-3-methyl-5-[(1*R*)-2,2,3-trimethylcyclopent-3-en-1-yl]pent-4-en-2-ol* ((−)-**15**). A soln. of (−)-**14** (200 mg, 0.90 mmol) in Et_2O (2 ml) was added dropwise to a suspension of $LiAlH_4$ (17 mg, 0.45 mmol) in Et_2O (3 ml). After 0.5 h, H_2O (0.02 ml), NaOH 15% (0.02 ml), and then H_2O (0.06 ml) were successively added. After 10 min, the mixture was filtered, the filtrate concentrated, and the residue bulb-to-bulb distilled: (−)-**15** (74%). $[\alpha]_D^{20} = -15.8$ ($c = 1.2$, $CHCl_3$). B.p. 120°/0.34 mbar. IR: 3413, 3036, 2954, 2928, 2864, 2214, 2062, 1652, 1460, 1374, 1358, 1272, 1222, 1148, 1127, 1075, 1046, 1012, 980, 946, 926, 882, 796, 723. ^{1}H-NMR: 0.75 (*s*, 3 H); 0.95 (*s*, 3 H); 1.00 (*s*, 3.3 H); 1.01 (*s*, 2.7 H); 1.11 (*d*, $J = 7$, 3 H); 1.55 (br. *s*, 1 OH); 1.61 (*s*, 3 H); 2.05–2.13 (*m*, 1 H); 2.22–2.28 (*m*, 1 H); 2.38 (*q*, $J = 7$, 1 H); 3.49 (*q*, $J = 7$, 1 H); 5.24 (*s*, 1 H); 5.42 (*dd*, $J = 7, 16$, 1 H); 5.51 (*ddd*, $J = 1, 7, 16$, 1 H). ^{13}C-NMR: 148.0 (*s*); 137.4 (*d*); 130.5 (*d*); 121.5 (*d*); 74.2 (*d*); 54.3 (*d*); 48.1 (*s*); 40.7 (*s*); 35.6 (*t*); 25.4 (*q*); 24.0 (0.9 *q*); 22.1 (1.1 *q*); 20.5 (*q*); 17.5 (*q*); 12.7 (*q*). MS: 225 (1, $M^{+\bullet}$), 181 (34), 166 (21), 138 (10), 121 (28), 109 (50), 107 (21), 93 (13), 72 (100), 43 (15).

*(−)-2-[(1*S*)-2,2,3-Trimethylcyclopent-3-en-1-yl](1-*$^2H_1$*)prop-2-enal* ((−)-**16b**). A soln. of alcohol (−)-**17a** (6.10 g, 37 mmol) in CH_2Cl_2 (15 ml) was added dropwise to a suspension of *Celite*® (17.95 g) and PCC (11.96 g, 56 mmol) in CH_2Cl_2 (30 ml) under N_2. After 1.5 h, the mixture was filtered through *Celite*® and the column was rinsed with Et_2O. The filtrate was dried (Na_2SO_4) and concentrated and the residue bulb-to-bulb distilled: (−)-**16a**/(−)-**16b** *ca.* 45:55 (91%). The reduction ($LiAlD_4$)/oxidation sequence was repeated three more times to afford pure (−)-**16b**. $\alpha_D^{20} = -103.6$ (neat, $l = 1$ dm). B.p. 90°/0.3 mbar. IR 3039, 2958, 2932, 2867, 2728, 2138, 2062, 1711, 1679, 1620, 1461, 1412, 1385, 1362, 1321, 1282, 1238, 1222, 1199, 1176, 1149, 1115, 1064, 1015, 976, 942, 873, 802, 631. ^{1}H-NMR: 0.68 (*s*, 3 H); 1.04 (*s*, 3 H); 1.61 (*s*, 3 H); 2.32–2.37 (*m*, 2 H); 3.21 (*t*, $J = 7$, 1 H); 5.3 (*s*, 1 H); 6.12 (*s*, 1 H); 6.35 (*s*, 1 H). ^{13}C-NMR: 151.3 (*s*); 147.3 (*s*); 135.5 (*t*); 121.4 (*d*); 48.2 (*s*); 46.4 (*d*); 34.7 (*t*); 26.5 (*q*); 21.7 (*q*); 12.8 (*q*). MS: 165 (41, $M^{+\bullet}$), 150 (100), 135 (26), 132 (38), 122 (62), 108 (90), 94 (50), 91 (45), 77 (40), 67 (20), 53 (22), 41 (33), 39 (30).

*(−)-2-[(1*S*)-2,2,3-Trimethylcyclopent-3-en-1-yl]prop-2-enoic Acid* ((−)-**16c**). A soln. of NaOH (2.75 g, 68.75 mmol) in H_2O (110 ml) was added dropwise to a soln. of aldehyde (−)-**16a** (2.30 g, 14 mmol) and $AgNO_3$ (2.75 g, 16.2 mmol) in H_2O/EtOH 1:1 (50 ml). After 24 h, the mixture was filtered through *Celite*® and the filtrate extracted with Et_2O (2 × 50 ml). The aq. phase was acidified with 15% HCl soln. and extracted with Et_2O (3 × 50 ml) and the extract dried (Na_2SO_4) and concentrated: pure (−)-**16c** (70%). $\alpha_D^{20} = -102.35$ (neat, $l = 1$ dm). B.p. 120°/0.3 mbar. IR: 3200, 3039, 2958, 2934, 2867, 1690, 1620, 1460, 1432, 1362, 1293, 1266, 1221, 1192, 1154, 1015, 945, 801, 689, 648. ^{1}H-NMR: 0.76 (*s*, 3 H); 1.08 (*s*, 3 H); 1.61 (*s*, 3 H); 2.32–2.37 (*m*, 2 H); 3.24 (*t*, $J = 7$, 1 H); 5.29 (*s*, 1 H); 5.75 (*s*, 1 H); 6.48 (*s*, 1 H); 11.1 (br. *s*, 1 OH). ^{13}C-NMR: 174.0 (*s*); 147.2 (*s*); 141.1 (*s*); 127.3 (*t*); 121.3 (*d*); 49.3 (*d*); 48.3 (*s*); 35.0 (*t*); 26.6 (*q*); 21.3 (*q*); 12.8 (*q*). MS: 180 (48, $M^{+\bullet}$), 165 (70), 147 (58), 137 (28), 124 (41), 119 (100), 105 (25), 93 (51), 91 (56), 79 (36), 77 (38), 67 (27), 41 (35).

*(−)-Methyl 2-[(1*S*)-2,2,3-Trimethylcyclopent-3-en-1-yl]prop-2-enoate* ((−)-**16d**). A soln. of acid (−)-**16c** (5.30 g, 29 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a soln. of DCC (6.57 g, 32 mmol), DMAP (53 mg, 0.43 mmol), and MeOH (1.41 g, 44 mmol) in CH_2Cl_2 (43 ml). After 24 h, Et_2O (50 ml) was added, the mixture filtered through *Celite*®, the filtrate dried (Na_2SO_4) and concentrated, and the residue purified by CC (SiO_2, cyclohexane/AcOEt 97:3): pure (−)-**16d** (74%). $\alpha_D^{20} = -100.62$ (neat, $l = 1$ dm). B.p. 80°/0.3 mbar. IR: 3039, 2954, 2934, 2854, 2120, 1721, 1623, 1435, 1405, 1384, 1374, 1361, 1288, 1274, 1257, 1191, 1137, 1061, 1045, 1014, 1001, 985, 969, 940, 891, 852, 816, 802, 727, 700, 654. ^{1}H-NMR: 0.72 (*s*, 3 H); 1.04 (*s*, 3 H); 1.60 (*s*, 3 H); 2.35 (*dt*, $J = 1, 7, 2$ H); 3.23 (*t*, $J = 7$, 1 H); 3.74 (*s*, 3 H); 5.29 (*s*, 1 H); 5.6 (*s*, 1 H); 6.26 (*s*, 1 H). ^{13}C-NMR: 168.9 (*s*); 147.2 (*s*); 141.6 (*s*); 124.6 (*t*); 121.3 (*d*); 51.8 (*q*); 50.0 (*d*); 48.1 (*s*); 34.7 (*t*); 26.5 (*q*); 21.2 (*q*); 12.8 (*q*). MS: 194 (31, $M^{+\bullet}$), 179 (35), 162 (15), 151 (18), 147 (50), 138 (27), 119 (100), 105 (20), 91 (32), 77 (18), 59 (9), 41 (12).

(−)-2-[(1S)-2,2,3-Trimethylcyclopent-3-en-1-yl](1-$^2H_1$)prop-2-en-1-ol ((−)-**17a**). A soln. of (−)-**16a** (5.00 g, 30 mmol) in THF (12 ml) was added dropwise to a suspension of 1.0M $LiAlD_4$ in THF (7.62 ml, 7.62 mmol). After 3 h, H_2O (0.32 ml), 15% NaOH soln. (0.32 ml), and H_2O (0.96 ml) were successively added. The mixture was filtered through *Celite*®, the filtrate dried (Na_2SO_4) and concentrated, and the residue bulb-to-bulb distilled: (−)-**17a** (91%). $\alpha_D^{20} = -66.74$ (neat, $l = 1$ dm). B.p. 100°/0.3 mbar. IR: 3318, 3089, 3038, 2956, 2928, 2866, 2149, 1643, 1445, 1383, 1360, 1305, 1221, 1173, 1147, 1115, 1072, 1034, 1014, 946, 892, 857, 801, 683. ^{1}H-NMR: 0.78 (*s*, 3 H); 1.08 (*s*, 3 H); 1.55 (*d*, *J* = 7, 1 OH); 1.6 (*s*, 3 H); 2.22–2.38 (*m*, 2 H); 2.6 (*t*, *J* = 7, 1 H); 4.12 (br. *d*, *J* = 7, 1 H); 5.0 (*s*, 1 H); 5.23 (*s*, 1 H); 5.28 (br. *s*, 1 H). ^{13}C-NMR: 149.5 (*s*); 147.4 (*s*); 121.6 (*d*); 110.7 (*t*); 65.9 (*d*); 53.8 (*d*); 47.7 (*s*); 33.8 (*t*); 26.8 (*q*); 21.0 (*q*); 12.8 (*q*). MS: 167 (29, $M^{+\bullet}$), 149 (18), 134 (100), 108 (31), 106 (56), 93 (50), 91 (35), 79 (28), 77 (25), 67 (18), 55 (17), 41 (26).

(−)-2-[(1S)-2,2,3-Trimethylcyclopent-3-en-1-yl](1,1-$^2H_2$)prop-2-en-1-ol ((−)-**17b**). Obtained in 91% yield from (−)-**16b**, as described for (−)-**17a**. $\alpha_D^{20} = -68.0$ (neat, $l = 1$ dm). B.p. 100°/0.3 mbar. IR: 3331, 3090, 3038, 2956, 2927, 2866, 2190, 2095, 1642, 1461, 1383, 1375, 1360, 1306, 1239, 1221, 1178, 1101, 1035, 1014, 967, 902, 864, 833, 800, 678. ^{1}H-NMR: 0.78 (*s*, 3 H); 1.08 (*s*, 3 H); 1.59 (br. *s*, 1 OH); 1.6 (*s*, 3 H); 2.22–2.38 (*m*, 2 H); 2.61 (*t*, *J* = 7, 1 H); 5.0 (*s*, 1 H); 5.23 (*s*, 1 H); 5.28 (br. *s*, 1 H). ^{13}C-NMR: 149.5 (*s*); 147.5 (*s*); 121.6 (*d*); 110.7 (*t*); 53.8 (*d*); 47.7 (*s*); 33.9 (*t*); 26.8 (*q*); 21.0 (*q*); 12.8 (*q*). MS: 168 (21, $M^{+\bullet}$), 150 (18), 135 (100), 120 (10), 107 (50), 93 (48), 91 (25), 79 (22), 77 (20), 57 (11), 41 (20).

(−)-Ethyl 2-Methyl-4-[(1R)-2,2,3-trimethylcyclopent-3-en-1-yl]pent-4-enoate ((−)-**18a**). A soln. of pivalic acid (0.24 g, 2.8 mmol) in triethyl orthopropanoate (1.67 g) was added dropwise at 90° to a soln. of (−)-**17a** (4.00 g, 24 mmol) in triethyl orthopropanoate (11.0 g, 72 mmol in total). After 1 h, EtOH was distilled off and the temp. gradually increased to 140° within 3 h. The cold mixture was diluted with Et_2O, the org. phase washed with H_2O, dried (Na_2SO_4), and concentrated, and the residue bulb-to-bulb distilled: (−)-**18a**[14]) (72%). $\alpha_D^{20} = -56.02$ (neat, $l = 1$ dm). B.p. 110°/0.3 mbar. IR: 3038, 2957, 2934, 2869, 2256, 2018, 1734, 1615, 1461, 1375, 1361, 1348, 1280, 1252, 1233, 1157, 1114, 1096, 1052, 1014, 927, 846, 801, 761. ^{1}H-NMR: major: 0.75 (*s*, 3 H); 1.09 (*s*, 3 H); 1.18 (*d*, *J* = 7, 3 H); 1.23 (*t*, *J* = 7, 3 H); 1.60 (*q*, *J* = 1, 3 H); 2.07–2.13 (*m*, 1 H); 2.15–2.23 (*m*, 1 H); 2.28–2.38 (*m*, 1 H); 2.46–2.55 (*m*, 2 H); 2.62–2.72 (*m*, 1 H); 4.12 (*q*, *J* = 7, 2 H); 4.86 (*s*, 1 H); 5.28 (*s*, 1 H); minor: 0.77 (*s*, 3 H); 1.09 (*s*, 3 H); 1.13 (*d*, *J* = 7, 3 H); 1.25 (*t*, *J* = 7, 3 H); 1.60 (*q*, *J* = 1, 3 H); 2.07–2.13 (*m*, 1 H); 2.15–2.23 (*m*, 1 H); 2.28–2.38 (*m*, 1 H); 2.46–2.55 (*m*, 2 H); 2.62–2.72 (*m*, 1 H); 4.10 (*q*, *J* = 7, 2 H); 4.89 (*s*, 1 H); 5.28 (*s*, 1 H). ^{13}C-NMR: major: 176.5 (*s*); 147.3 (*s*); 147.1 (*s*); 121.5 (*d*); 111.8 (*d*); 60.1 (*t*); 55.9 (*d*); 47.8 (*s*); 41.4 (*t*); 38.5 (*d*); 34.1 (*t*); 27.0 (*q*); 20.9 (*q*); 17.6 (*q*); 14.3 (*q*); 12.8 (*q*); minor: 176.7 (*s*); 147.5 (*s*); 146.9 (*s*); 121.6 (*d*); 111.8 (*d*); 60.2 (*t*); 55.5 (*d*); 47.8 (*s*); 40.8 (*t*); 38.1 (*d*); 34.1 (*t*); 26.9 (*q*); 20.9 (*q*); 16.9 (*q*); 14.2 (*q*); 12.8 (*q*). MS: major: 251 (58, $M^{+\bullet}$), 236 (30), 190 (20), 162 (59), 150 (51), 136 (100), 134 (60), 122 (28), 120 (27), 108 (46), 91 (22), 55 (13), 41 (18); minor: 251 (58, $M^{+\bullet}$), 236 (30), 190 (20), 162 (64), 150 (54), 136 (100), 134 (60), 122 (28), 120 (27), 108 (46), 91 (22), 55 (13), 41 (18).

(−)-Ethyl 2-Methyl-4-[(1R)-2,2,3-trimethylcyclopent-3-en-1-yl](5,5-$^2H_2$)pent-4-enoate ((−)-**18b**). Obtained in 82% from (−)-**17b**, as described for (−)-**18a**. $\alpha_D^{20} = -51.15$ (neat, $l = 1$ dm). B.p. 120°/0.31 mbar. IR: 3038, 2957, 2933, 2315, 2205, 1734, 1597, 1461, 1375, 1361, 1256, 1170, 1158, 1115, 1050, 1014, 926, 855, 800, 761, 736, 723, 694, 651. ^{1}H-NMR: major: 0.75 (*s*, 3 H); 1.09 (*s*, 3 H); 1.18 (*d*, *J* = 7, 3 H); 1.23 (*t*, *J* = 7, 3 H); 1.60 (*q*, *J* = 1, 3 H); 2.07–2.13 (*m*, 1 H); 2.15–2.23 (*m*, 1 H); 2.28–2.38 (*m*, 1 H); 2.46–2.55 (*m*, 2 H); 2.62–2.72 (*m*, 1 H); 4.12 (*q*, *J* = 7, 2 H); 5.28 (*s*, 1 H); minor: 0.77 (*s*, 3 H); 1.09 (*s*, 3 H); 1.13 (*d*, *J* = 7, 3 H); 1.25 (*t*, *J* = 7, 3 H); 1.60 (*q*, *J* = 1, 3 H); 2.07–2.13 (*m*, 1 H); 2.15–2.23 (*m*, 1 H); 2.28–2.38 (*m*, 1 H); 2.46–2.55 (*m*, 2 H); 2.62–2.72 (*m*, 1 H); 4.10 (*q*, *J* = 7, 2 H); 5.28 (*s*, 1 H). ^{13}C-NMR: major: 176.5 (*s*); 147.3 (*s*); 147.0 (*s*); 121.5 (*d*); 60.1 (*t*); 55.9 (*d*); 47.8 (*s*); 41.3 (*t*); 38.5 (*d*); 34.1 (*t*); 27.0 (*q*); 20.9 (*q*); 17.6 (*q*); 14.3 (*q*); 12.8 (*q*); minor: 176.7 (*s*); 147.5 (*s*); 146.8 (*s*); 121.6 (*d*); 60.2 (*t*); 55.5 (*d*); 47.8 (*s*); 40.8 (*t*); 38.1 (*d*); 34.1 (*t*); 26.9 (*q*); 20.9 (*q*); 16.9 (*q*); 14.2 (*q*); 12.8 (*q*). MS: major: 252 (70, $M^{+\bullet}$), 237 (35), 191 (21), 163 (60), 151 (51), 137 (100), 135 (56), 121 (30), 109 (49), 107 (47), 93 (30), 79 (20), 55 (17), 41 (21); minor: 252 (62, $M^{+\bullet}$), 237 (35), 191 (26), 163 (60), 151 (51), 137 (100), 135 (60), 121 (30), 109 (49), 107 (47), 93 (30), 79 (20), 55 (17), 41 (21).

(−)-2-Methyl-4-[(1R)-2,2,3-trimethylcyclopent-3-en-1-yl](1,1,5-$^2H_3$)pent-4-en-1-ol ((−)-**19a**). Obtained in 88% yield from (−)-**18a** and 0.5 mol-equiv. of $LiAlD_4$, as described for (−)-**17a**. $\alpha_D^{20} = -67.14$ (neat, $l = 1$ dm). B.p. 110°/0.3 mbar. IR: 3331, 3036, 2955, 2925, 2868, 2191, 2080, 1738, 1717, 1656, 1613,

1460, 1374, 1360, 1304, 1269, 1221, 1195, 1169, 1134, 1115, 1083, 1057, 1013, 970, 920, 840, 801, 698. ^{1}H-NMR: major: 0.77 (*s*, 3 H); 0.96 (*d*, *J* = 7, 3 H); 1.10 (*s*, 3 H); 1.52 (br. *s*, 1 OH); 1.59 (*s*, 3 H); 1.8–2.0 (*m*, 2 H); 2.12–2.22 (*m*, 2 H); 2.25–2.38 (*m*, 1 H); 2.51–2.6 (*m*, 1 H); 4.9 (*s*, 1 H); 5.27 (*s*, 1 H); minor: 0.77 (*s*, 3 H); 0.88 (*d*, *J* = 7, 3 H); 1.11 (*s*, 3 H); 1.47 (br. *s*, 1 OH); 1.59 (*s*, 3 H); 1.8–2.0 (*m*, 2 H); 2.12–2.22 (*m*, 2 H); 2.25–2.38 (*m*, 1 H); 2.51–2.6 (*m*, 1 H); 4.92 (*s*, 1 H); 5.27 (*s*, 1 H). ^{13}C-NMR: major: 148.6 (*s*); 147.4 (*s*); 121.6 (*d*); 111.7 (*d*); 55.4 (*d*); 47.8 (*s*); 41.8 (*t*); 34.1 (*t*); 34.0 (*d*); 27.0 (*q*); 21.0 (*q*); 17.3 (*q*); 12.8 (*q*); minor: 147.8 (*s*); 147.4 (*s*); 121.6 (*d*); 111.4 (*d*); 55.1 (*d*); 47.7 (*s*); 41.3 (*t*); 34.3 (*t*); 34.0 (*d*); 27.0 (*q*); 21.0 (*q*); 16.3 (*q*); 12.8 (*q*). MS: major: 211 (100, $M^{+\bullet}$), 196 (61), 178 (20), 150 (31), 136 (93), 120 (35), 108 (63), 93 (42), 79 (31), 67 (19), 55 (20), 41 (32); minor: 211 (100, $M^{+\bullet}$), 196 (62), 178 (18), 150 (28), 136 (88), 120 (35), 108 (60), 93 (38), 79 (30), 67 (16), 55 (20), 41 (30).

*(−)-2-Methyl-4-[(1*R*)-2,2,3-trimethylcyclopent-3-en-1-yl](1,1,4,4-$^2H_4$)pent-4-en-1-ol* ((−)-**19b**). Obtained in 88% yield from (−)-**18b** and 0.5 mol-equiv. of $LiAlD_4$, as described for (−)-**17a**. $\alpha_D^{20} = -60.7$ (neat, *l* = 1 dm). B.p. 130°/0.3 mbar. IR: 3340, 3037, 2955, 2925, 2868, 2313, 2189, 2081, 1656, 1595, 1459, 1374, 1360, 1331, 1306, 1274, 1221, 1134, 1116, 1085, 1056, 1012, 970, 919, 799, 758, 721, 693, 650, 609. ^{1}H-NMR: major: 0.77 (*s*, 3 H); 0.96 (*d*, *J* = 7, 3 H); 1.10 (*s*, 3 H); 1.45 (br. *s*, OH); 1.59 (*s*, 3 H); 1.8–2.0 (*m*, 2 H); 2.12–2.22 (*m*, 2 H); 2.25–2.38 (*m*, 1 H); 2.51–2.6 (*m*, 1 H); 5.27 (*s*, 1 H); minor: 0.77 (*s*, 3 H); 0.88 (*d*, *J* = 7, 3 H); 1.11 (*s*, 3 H); 1.39 (br. *s*, 1 OH); 1.59 (*s*, 3 H); 1.8–2.0 (*m*, 2 H); 2.12–2.22 (*m*, 2 H); 2.25–2.38 (*m*, 1 H); 2.51–2.6 (*m*, 1 H); 5.27 (*s*, 1 H). ^{13}C-NMR: major: 148.5 (*s*); 147.4 (*s*); 121.6 (*d*); 55.5 (*d*); 47.8 (*s*); 41.8 (*t*); 34.1 (*t*); 34.0 (*d*); 27.0 (*q*); 21.0 (*q*); 17.3 (*q*); 12.8 (*q*); minor: 147.8 (*s*); 147.4 (*s*); 121.6 (*d*); 55.1 (*d*); 47.7 (*s*); 41.2 (*t*); 34.2 (*t*); 34.0 (*d*); 27.0 (*q*); 21.0 (*q*); 16.3 (*q*); 12.8 (*q*). MS: major: 212 (100, $M^{+\bullet}$), 197 (59), 179 (17), 151 (28), 137 (99), 123 (31), 121 (39), 109 (52), 107 (58), 93 (50), 79 (30), 67 (20), 55 (20), 41 (28); minor: 212 (100, $M^{+\bullet}$), 197 (59), 179 (17), 151 (28), 137 (90), 123 (30), 121 (39), 109 (50), 107 (55), 95 (38), 93 (48), 79 (28), 67 (20), 55 (20), 41 (28).

*(−)-2-[(1*R*)-2,2,3-Trimethylcyclopent-3-en-1-yl](1,3-$^2H_2$)propanal* ((−)-**20**). Obtained in 70% yield[16]) from (−)-**16d** and 0.5 mol-equiv. of $LiAlD_4$, as described for (−)-**17a**. $\alpha_D^{20} = -8.03$ (neat, *l* = 1 dm). B.p. 100°/0.3 mbar. IR: 3038, 2957, 2933, 2869, 2183, 2047, 1715, 1647, 1560, 1463, 1436, 1385, 1375, 1362, 1299, 1214, 1177, 1118, 1016, 968, 903, 846, 799, 753. ^{1}H-NMR: major: 0.93 (*s*, 3 H); 1.11 (*s*, 3 H); 1.15 (*dt*, *J* = 1, 7, 2 H); 1.59 (*s*, 3 H); 1.92–2.0 (*m*, 1 H); 2.0–2.18 (*m*, 1 H); 2.24–2.36 (*m*, 1 H); 2.48–2.56 (*m*, 1 H); 5.22 (*s*, 1 H); minor: 0.86 (*s*, 3 H); 0.99 (*s*, 3 H); 1.07 (*dt*, *J* = 1, 7, 2 H); 1.59 (*s*, 3 H); 1.92–2.0 (*m*, 1 H); 2.0–2.18 (*m*, 1 H); 2.24–2.36 (*m*, 1 H); 2.48–2.56 (*m*, 1 H); 5.25 (*s*, 1 H). ^{13}C-NMR: major: 148.4 (*s*); 121.4 (*d*); 51.8 (*d*); 47.9 (*d*); 47.6 (*s*); 33.5 (*t*); 27.1 (*q*); 19.9 (*q*); 13.2 (*t*); 12.4 (*q*); minor: 148.6 (*s*); 121.1 (*d*); 50.8 (*d*); 47.9 (*d*); 46.9 (*s*); 33.4 (*t*); 26.4 (*q*); 20.3 (*q*); 13.1 (*t*); 12.5 (*q*). MS: major: 168 (1, $M^{+\bullet}$), 125 (16), 108 (100), 93 (40), 82 (11), 77 (8), 67 (6), 55 (5), 41 (8); minor: 168 (1, $M^{+\bullet}$), 125 (8), 108 (100), 93 (65), 82 (7), 77 (7), 67 (6), 55 (5), 41 (8).

*(+)-2-{(1*S*)-1-[(1*R*)-3,3-Dimethylcyclohexyl]ethoxy}-2-methylpropyl (3,3,3-$^2H_3$)Propanoate* ((+)-**22a**). (D_3)Propanoic acid (1.00 g, 13 mmol) was added to a soln. of alcohol (+)-**21a** (2.96 g, 13 mmol), DCC (2.68 g, 13 mmol), and DMAP (29.6 mg, 0.243 mmol) in CH_2Cl_2 (50 ml). After 24 h, Et_2O (50 ml) was added, and the mixture was filtered through *Celite*®, the filtrate dried (Na_2SO_4) and concentrated, and the residue bulb-to-bulb distilled: (+)-**22a** (55%). $\alpha_D^{20} = +7.3$ (neat, *l* = 1 dm). B.p. 90°/0.32 mbar. IR: 2972, 2924, 2863, 2232, 2128, 2085, 1740, 1462, 1425, 1385, 1365, 1343, 1268, 1160, 1118, 1042, 978, 952, 927, 902, 849, 820, 756, 694. ^{1}H-NMR: 0.8–0.9 (*m*, 2 H); 0.88 (*s*, 3 H); 0.90 (*s*, 3 H); 1.05–1.08 (*m*, 1 H); 1.07 (*d*, *J* = 7, 3 H); 1.19 (*s*, 6 H); 1.3–1.39 (*m*, 2 H); 1.4–1.48 (*m*, 2 H); 1.52–1.59 (*m*, 1 H); 1.63–1.7 (*m*, 1 H); 2.35 (*s*, 2 H); 3.35–3.38 (*m*, 1 H); 3.95 (*s*, 2 H). ^{13}C-NMR: 174.3 (*s*); 73.7 (*s*); 71.8 (*d*); 70.3 (*t*); 42.3 (*t*); 40.4 (*d*); 39.4 (*t*); 33.7 (*q*); 30.7 (*s*); 28.4 (*t*); 27.5 (*t*); 24.7 (*q*); 24.1 (*q*); 23.8 (*q*); 22.3 (*t*); 19.7 (*q*). MS: 287 (0, $M^{+\bullet}$), 212 (1), 197 (5), 139 (44), 132 (100), 123 (8), 97 (7), 83 (25), 69 (15), 60 (45), 55 (11).

*(+)-2-{(1*S*)-1-[(1*R*)-3,3-Dimethylcyclohexyl]ethoxy}-2-oxoethyl (3,3,3-$^2H_3$)Propanoate* ((+)-**22b**). Obtained in 93% yield as described for (+)-**22a**. $\alpha_D^{20} = +11.5$ (neat, *l* = 1 dm). B.p. 120°/0.32 mbar. IR: 2928, 2862, 2234, 2118, 1746, 1452, 1422, 1385, 1364, 1282, 1218, 1157, 1102, 1069, 1054, 1031, 1010, 971, 948, 891, 845, 790, 728, 695, 623. ^{1}H-NMR: 0.82–0.86 (*m*, 2 H); 0.88 (*s*, 3 H); 0.91 (*s*, 3 H); 1.0–1.1 (*m*, 1 H); 1.19 (*d*, *J* = 7, 3 H); 1.30–1.46 (*m*, 2 H); 1.55–1.70 (*m*, 2 H); 1.75–1.95 (*m*, 2 H); 2.45 (*s*, 2 H); 4.60 (*s*, 2 H); 4.78 (*quint.*, *J* = 7, 1 H). ^{13}C-NMR: 173.8 (*s*); 167.6 (*s*); 76.3 (*d*); 60.8 (*t*); 41.1 (*t*); 39.1 (*t*); 38.3 (*d*); 33.5 (*q*); 30.5 (*s*); 28.3 (*t*); 27.0 (*t*); 24.6 (*q*); 21.9 (*t*); 17.0 (*q*). MS: 273 (0, $M^{+\bullet}$), 258 (1), 138 (51), 123 (100), 118 (61), 109 (59), 95 (50), 90 (28), 83 (57), 81 (33), 69 (68), 60 (76), 55 (39), 41 (30).

1-(3,3-Dimethyl(1-$^2H_1$)cyclohexyl)(2,2,2-$^2H_3$)ethanone (*rac*-**23b**). Metallic Na (150 mg, 6.5 mmol) was added to MeOD (50 ml). After complete dissolution, D_2O (10 ml) was added, followed by ketone (+)-**23a** (10.0 g, 65 mmol). After 24 h at 95°, the cold soln. was poured onto ice and extracted with Et_2O (3 × 50 ml). The org. phase was washed to neutrality with brine, dried (Na_2SO_4), and concentrated and the residue bulb-to-bulb distilled: *rac*-**23b** (75%). B.p. 100°/1 mbar. IR: 2926, 2863, 2847, 2253, 2137, 1701, 1456, 1386, 1365, 1282, 1260, 1239, 1189, 1161, 1079, 1024, 981, 935, 869, 805, 723. ^{1}H-NMR: 0.88–0.99 (*m*, 1 H); 0.92 (*s*, 3 H); 0.95 (*s*, 3 H); 1.05–1.2 (*m*, 2 H); 1.33–1.47 (*m*, 2 H); 1.52 (*m*, 1 H); 1.6–1.68 (*m*, 1 H); 1.82–1.9 (*m*, 1 H). ^{13}C-NMR: 212.5 (*s*); 41.1 (*t*); 38.6 (*t*); 33.1 (*q*); 30.5 (*s*); 28.2 (*t*); 24.4 (*q*); 21.6 (*t*). MS: 158 (38, $M^{+\bullet}$), 143 (21), 140 (11), 112 (69), 96 (28), 84 (41), 75 (21), 70 (100), 56 (38), 46 (71), 41 (28).

*(1*RS*)-1-[(1*SR*)-3,3-Dimethyl(1-$^2H_1$)cyclohexyl](2,2,2-$^2H_3$)ethanol* (*rac*-**24**). At −78°, 1.0M *L-Selectride* in THF (55 ml, 55 mmol) was added dropwise to a soln. of *rac*-**23b** (7.5 g, 47 mmol) in THF (20 ml). After 2 h, the temp. was slowly equilibrated to 20°, and after 18 h, 30% NaOH soln. (40 ml) was added, followed by 30% H_2O_2 soln. (30 ml). The mixture was extracted with Et_2O (50 ml), the org. phase washed to neutrality with brine, dried (Na_2SO_4), and concentrated and the residue bulb-to-bulb distilled: *rac*-**24** (79%). B.p. 80°/0.3 mbar. IR: 3360, 2921, 2861, 2225, 2133, 1686, 1460, 1384, 1363, 1339, 1289, 1248, 1206, 1186, 1134, 1103, 1066, 1047, 1029, 979, 934, 864, 847, 772, 732. ^{1}H-NMR: 0.8–0.9 (*m*, 1 H); 0.88 (*s*, 3 H); 0.92 (*s*, 3 H); 1.02–1.18 (*m*, 2 H); 1.3–1.6 (*m*, 4 H); 1.65–1.72 (*m*, 1 H); 3.49 (*s*, 1 H). ^{13}C-NMR: 72.2 (*d*); 41.4 (*t*); 39.3 (*t*); 33.6 (*q*); 30.6 (*s*); 28.3 (*t*); 24.8 (*q*); 22.1 (*t*). MS: 160 (1, $M^{+\bullet}$), 142 (7), 127 (32), 113 (48), 98 (100), 96 (19), 82 (22), 70 (69), 56 (42), 48 (38), 41 (27).

*2-[(1*RS*)-1-[(1*SR*)-3,3-Dimethyl(1-$^2H_1$)cyclohexyl](2,2,2-$^2H_3$)ethoxy}-2-oxoethyl Propanoate* (*rac*-**25**). A soln. of 2-chloro-2-oxoethyl propanoate [28] (2.9 g, 19.0 mmol) in Et_2O (20 ml) was added in 10 min at 20° to a soln. of *rac*-**24** (3.0 g, 18.75 mmol) and pyridine (1.52 g, 19.2 mmol) in Et_2O (50 ml). After 30 min, a second portion of both pyridine and 2-chloro-2-oxoethyl propanoate were added. After 1 h, the reaction was quenched with 15% HCl soln. (10 ml) and extracted with Et_2O. The org. phase was washed to neutrality with brine, dried ($MgSO_4$), and concentrated. Purification by CC (SiO_2, cyclohexane/AcOEt 97:3 → 95:5) afforded *rac*-**25** in 80% yield. B.p. 150°/0.3 mbar. IR: 2945, 2926, 2864, 2846, 2234, 2131, 1746, 1715, 1463, 1422, 1386, 1364, 1286, 1225, 1162, 1093, 1055, 1025, 982, 946, 843, 808, 726. ^{1}H-NMR: 0.82–0.86 (*m*, 2 H); 0.88 (*s*, 3 H); 0.91 (*s*, 3 H); 1.0–1.1 (*m*, 1 H); 1.19 (*t*, *J* = 7, 3 H); 1.30–1.46 (*m*, 2 H); 1.55–1.70 (*m*, 1 H); 1.75–1.95 (*m*, 2 H); 2.45 (*q*, *J* = 7, 2 H); 4.60 (*s*, 2 H); 4.78 (*s*, 1 H). ^{13}C-NMR: 173.8 (*s*); 167.7 (*s*); 76.2 (*d*); 60.8 (*t*); 41.0 (*t*); 39.1 (*t*); 33.5 (*q*); 28.1 (*t*); 27.2 (*t*); 24.6 (*q*); 21.9 (*t*); 9.0 (*q*). MS: 274 (0, $M^{+\bullet}$), 214 (1), 142 (42), 127 (78), 115 (88), 109 (60), 98 (40), 96 (31), 87 (48), 84 (44), 82 (40), 69 (78), 57 (100), 55 (27), 41 (26).

*4,5,6,7,8,9,10,11,12,13-Decahydro-2-[($^2H_3$)methyl]-1*H*-cyclopenta[12]annulene* (=*4,5,6,7,8,9,10,11,12,13-Decahydro-2-[($^2H_3$)methyl]-1*H*-cyclopentacyclododecene*; **27**). A soln. of CD_3I (10.0 g, 68 mmol) in Et_2O (30 ml) was added to a suspension of Mg (1.64 g, 68 mmol) in Et_2O (30 ml). After complete disappearance of the Mg, a soln. of enone **26** (14.00 g, 63 mmol) in Et_2O (30 ml) was added. After 2 h, the mixture was poured onto sat. aq. NH_4Cl soln. at 0° and extracted with Et_2O (3 × 50 ml). The org. phase was washed to neutrality with brine, dried (Na_2SO_4), and concentrated and the residue purified by CC (SiO_2, cyclohexane/Et_2O 100:0 → 98:2, then EtOH): **27** (74%)[22]. B.p. 140°/0.1 mbar. IR: 3042, 2925, 2850, 2219, 2188, 2112, 1633, 1466, 1444, 1378, 1345, 1043, 876, 727, 699. ^{1}H-NMR: 1.17–1.25 (*m*, 6 H); 1.29–1.38 (*m*, 8 H); 1.5–1.58 (*m*, 4 H); 2.25 (*t*, *J* = 7, 2 H); 2.34 (*t*, *J* = 7, 2 H); 2.78 (*s*, 2 H); 5.95 (*s*, 1 H). ^{13}C-NMR: 141.4 (*s*); 139.7 (*s*); 138.3 (*s*); 129.5 (*d*); 46.2 (*t*); 28.0 (*t*); 27.0 (*t*); 26.9 (*t*); 26.5 (*t*); 24.7 (*t*); 24.6 (*t*); 24.5 (*t*); 23.7 (*t*); 22.4 (*t*); 22.3 (*t*). MS: 221 (62, $M^{+\bullet}$), 164 (11), 150 (22), 136 (19), 122 (48), 110 (50), 108 (48), 97 (100), 94 (28), 91 (28), 79 (19), 55 (11), 41 (20).

*2,3,4,5,6,7,8,9,10,11,12,13-Dodecahydro-2-[($^2H_3$)methyl]-1*H*-cyclopenta[12]annulene* (=*2,3,4,5,6,7,8,9,10,11,12,13-Dodecahydro-2-[($^2H_3$)methyl]-1*H*-cyclopentacyclododecene*; **28**). A suspension of **27** (110 mg, 0.505 mmol) and *Lindlar* catalyst (5.5 mg) in AcOEt (10 ml) was hydrogenated (11.3 ml of H_2) in 30 min. The mixture was filtered through *Celite*®, the filtrate dried (Na_2SO_4) and concentrated, and the residue bulb-to-bulb distilled: pure **28** (92%). B.p. 130°/0.1 mbar. IR: 2921, 2855, 2672, 2207, 2127, 2062, 1466, 1444, 1344, 1320, 1300, 1245, 1235, 1198, 1088, 1053, 1012, 980, 840, 820, 762, 728, 699. ^{1}H-NMR: 1.15–1.21 (*m*, 4 H); 1.3–1.37 (*m*, 8 H); 1.4–1.49 (*m*, 4 H); 1.83–1.88 (*m*, 2 H); 2.0–2.14 (*m*, 4 H); 2.15–2.24 (*m*, 1 H); 2.38–2.45 (*m*, 2 H). ^{13}C-NMR: 134.9 (2*s*); 43.7 (2*t*); 30.0 (*d*); 25.3 (2*t*); 25.0 (2*t*); 24.7 (2*t*);

24.5 (2*t*); 22.3 (2*t*). MS: 223 (80, $M^{+\cdot}$), 166 (8), 152 (18), 138 (22), 124 (21), 110 (62), 97 (100), 93 (40), 84 (44), 81 (50), 79 (48), 67 (36), 55 (35), 41 (58).

3-[(²H₃)Methyl]cyclopentadecane-1,5-dione (**29**). O_3 (0.43 g, 9 mmol) was passed through a soln. of **28** (2.0 g, 9 mmol) in EtOH (20 ml) at −78°. After 45 min, N_2 was passed through the soln., and the temp. was equilibrated to 20°. Then 10% Pd/C (100 mg) was added, and the mixture was hydrogenated (272 ml of H_2). The mixture was filtered through *Celite*®, and concentrated and the residue bulb-to-bulb distilled: **29** (67%)[26]). B.p. 120°/0.05 mbar. IR: 2925, 2854, 2211, 2126, 2067, 1705, 1458, 1440, 1403, 1367, 1292, 1270, 1208, 1149, 1118, 1104, 1053, 1008, 898, 858, 722, 631. ^{1}H-NMR: 1.15–1.20 (*m*, 4 H); 1.20–1.27 (*m*, 5 H); 1.28–1.31 (*m*, 4 H); 1.56–1.64 (*m*, 4 H); 2.34 (*t*, *J* = 7, 4 H); 2.38–2.43 (*m*, 4 H). ^{13}C-NMR: 211.1 (2*s*); 48.8 (2*t*); 41.7 (2*t*); 27.8 (2*t*); 26.9 (2*t*); 26.5 (2*t*); 25.6 (*d*); 22.7 (2*t*). MS: 255 (35, $M^{+\cdot}$), 237 (12), 255 (35), 219 (8), 212 (10), 198 (38), 158 (10), 145 (25), 129 (21), 114 (37), 100 (62), 88 (61), 72 (100), 55 (74), 41 (57).

14-[(²H₃)Methyl]bicyclo[9.4.0]pentadec-1(11)-en-12-one (=*2,3,4,5,6,7,8,9,10,11,12,13-Dodecahydro-3-[(²H₃)methyl]-1*H*-benzocycloundecen-1-one*; **30a**). A soln. of **29** (200 mg, 0.78 mmol) and KOH (42 mg, 0.745 mmol) in EtOH (5 ml) was heated under reflux for 4 h. The cold mixture was acidified with 10% HCl soln. and extracted with Et_2O (5 × 5 ml). The org. phase was washed with H_2O (2 × 5 ml) and brine (2 × 5 ml), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation afforded pure **30a** (95%). B.p. 140°/0.18 mbar. IR: 2925, 2860, 2212, 2122, 2064, 1663, 1610, 1467, 1446, 1372, 1345, 1313, 1264, 1213, 1188, 1149, 1134, 1052, 743, 711. ^{1}H-NMR: 1.19–1.25 (*m*, 2 H); 1.27–1.35 (*m*, 10 H); 1.38–1.46 (*m*, 2 H); 1.54–1.64 (*m*, 2 H); 1.66–1.74 (*m*, 1 H); 1.97–2.08 (*m*, 2 H); 2.31–2.39 (*m*, 2 H); 2.43–2.56 (*m*, 2 H). ^{13}C-NMR: 199.9 (*s*); 158.3 (*s*); 136.6 (*s*); 46.6 (*t*); 38.3 (*t*); 32.4 (*t*); 29.6 (*d*); 26.7 (*t*); 26.3 (*t*); 26.10 (*t*); 25.7 (*t*); 25.4 (*t*); 25.3 (*t*); 24.7 (*t*); 23.7 (*t*). MS: 237 (41, $M^{+\cdot}$), 222 (8), 194 (38), 180 (100), 166 (28), 107 (17), 96 (12), 91 (10), 79 (17), 67 (12), 55 (11), 41 (16).

14-[(²H₃)Methyl]bicyclo[9.4.0]pentadec-1(11)-en-12-one para-*Toluenesulfonylhydrazone* (=*2,3,4,5,6,7,8,9,10,11,12,13-Dodecahydro-3-[(²H₃)methyl]-1*H*-benzocycloundecen-1-one 2-(4-Methylphenyl)sulfonylhydrazone*; **30b**). A mixture of **30a** (100 mg, 0.422 mmol), *p*-tosylhydrazine (86.3 mg, 0.464 mmol), MeOH (3 ml), and AcOH (10 mg) was heated under reflux for 5 h, stored at 25° overnight, cooled to 0°, and filtered to afford pure **30b** (91%). IR: 3204, 2986, 2922, 2902, 2862, 2843, 2815, 2208, 2120, 2061, 1597, 1473, 1399, 1319, 1163, 1091, 1048, 1019, 931, 907, 814, 675. ^{1}H-NMR: 1.17–1.45 (*m*, 14 H); 1.53–1.58 (*m*, 1 H); 1.62–1.79 (*m*, 2 H); 2.17 (*d*, *J* = 10, 1 H); 2.42 (*s*, 3 H); 2.28–2.53 (*m*, 6 H); 7.29 (*d*, *J* = 8.2, 2 H); 7.86 (*d*, *J* = 8.2, 2 H). ^{13}C-NMR: 155.5 (br. *s*); 146.2 (br. *s*); 144.0 (*s*); 135.6 (*s*); 132.0 (*s*); 129.5 (2*d*); 128.6 (2*d*); 36.8 (*t*); 32.7 (*t*); 31.8 (*d*); 27.5 (*t*); 26.7 (*t*); 26.1 (*t*); 26.0 (*t*); 25.7 (*t*); 25.6 (*t*); 25.2 (*t*); 24.8 (*t*); 23.9 (*t*); 21.6 (*q*). LC/MS: 406.25982 ($[C_{23}D_3H_{31}N_2O_2S + H]^{+\cdot}$).

3-[(²H₃)Methyl]cyclopentadec-5-yn-1-one (**31**). AcO_2H (40%, 1.2 ml, 6.6 mmol) and H_2O (1.8 ml, 100 mmol) were added to a soln. of **30b** (880 mg, 2.2 mmol) in toluene (35 ml). The two-phase system was warmed at 30° and vigorously stirred for 4 h. After 18 h at 20°, the ice-cooled mixture was poured into aq. $NaHSO_3$ soln. and extracted with Et_2O (3 × 20ml). The org. phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated and the residue bulb-to-bulb distilled: pure **31** (83%). B.p. 90°/0.06 mbar. IR: 2928, 2857, 2212, 2125, 2069, 1711, 1459, 1438, 1461, 1371, 1346, 1299, 1205, 1135, 1110, 1083, 1056. ^{1}H-NMR: 1.2–1.6 (*m*, 12 H); 1.58–1.65 (*m*, 1 H); 1.77–1.85 (*m*, 1 H); 1.98 (*ddt*, *J* = 2.6, 8.5,

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[26]) Trace amounts (<1%) of the intermediate ozonide [23c][6]), possessing an identical MS fragmentation pattern as muscodione **29**, could also be isolated: ^{1}H-NMR: 1.20–1.25 (*m*, 2 H); 1.34–1.44 (*m*, 4 H); 1.45–1.55 (*m*, 13 H); 1.75–1.85 (*m*, 4 H); 1.95–2.03 (*m*, 2 H). ^{13}C-NMR: 110.0 (2*s*); 39.3 (2*t*); 32.5 (2*t*); 26.9 (2*t*); 25.7 (2*t*); 25.0 (2*t*); 23.2 (*d*); 21.7 (2*t*). A much higher content (<20%) was observed when 5.0 mol-equiv. of Me_2S were used at 20° as reducing agent, after ozonolysis in either CH_2Cl_2 or AcOEt at −78°. B3LYP/6-31G** Calculations show that all the most stable conformers possess a $-(CH_2)_{10}-$ moiety bisecting the O–C–O angles [29]. The most stable diastereoisomer has its CD_3 substituent in the equatorial position at a chair-like six-membered heterocycle. For comparison, both a boat-equatorial conformation (7.51 kcal/mol) and a chair-like conformation with an axial CD_3 (2.7 kcal/mol) are higher in energy. The global yield of the ozonolysis–hydrogenation–aldol reaction in EtOH was 64%. The next step may also be performed in the same solvent.

16.5, 1 H); 2.18–2.23 (*m*, 2 H); 2.26–2.31 (*m*, 1 H); 2.31–2.40 (*m*, 3 H), 2.46 (*ddd*, *J* = 3.8, 8.5, 15, 1 H); 2.93 (*dd*, *J* = 4.7, 17.9, 1 H). ^{13}C-NMR: 211.8 (*s*); 81.9 (*s*); 78.7 (*s*); 49.1 (*t*); 41.6 (*t*); 28.0 (*t*); 28.0 (*d*); 27.3 (*t*); 26.9 (*t*); 26.5 (*t*); 26.4 (*t*); 26.2 (*t*); 25.6 (*t*); 24.7 (*t*); 18.4 (*t*). MS: 237 (8, $M^{+\cdot}$), 219 (29), 180 (29), 152 (21), 140 (39), 138 (53), 124 (35), 121 (40), 110 (58), 107 (24), 96 (69), 93 (58), 91 (31), 84 (60), 81 (62), 79 (100), 77 (24), 72 (28), 69 (30), 67 (45), 55 (61), 43 (32), 41 (60).

(5Z)-3-[($^{2}H_{3}$)Methyl]cyclopentadec-5-en-1-one (**32**). A soln. of **31** (237 mg, 1 mmol) in EtOH (5 ml) was hydrogenated over *Lindlar* catalyst (24 mg) in the presence of one drop of isoquinoline. After 1 h, the mixture was filtered over *Celite*®, the filtrate concentrated, and the residue bulb-to-bulb distilled: pure **32** (85%). IR: 3008, 2925, 2856, 2211, 2124, 2068, 1708, 1459, 1442, 1407, 1366, 1272, 1200, 1147, 1107, 1054, 970, 780, 748, 710. ^{1}H-NMR: 1.25–1.34 (*m*, 10 H); 1.36–1.44 (*m*, 2 H); 1.62 (*t*, *J* = 6.6, 2 H); 1.89–1.95 (*m*, 1 H); 1.99–2.05 (*m*, 2 H); 2.08–2.15 (*m*, 2 H); 2.24 (*dd*, *J* = 5.6, 15.3, 1 H); 2.30–2.48 (*m*, 3 H); 5.41–5.43 (*m*, 2 H). ^{13}C-NMR: 211.9 (*s*); 131.9 (*d*); 127.2 (*d*); 49.4 (*t*); 42.4 (*t*); 33.4 (*t*); 29.5 (*d*); 28.0 (*t*); 27.0 (*t*); 26.9 (*t*); 26.5 (*t*); 26.4 (*t*); 26.2 (*t*); 26.1 (*t*); 22.8 (*t*). MS: 239 (58, $M^{+\cdot}$), 221 (8), 196 (7), 181 (18), 135 (17), 125 (22), 112 (34), 98 (57), 84 (90), 81 (64), 71 (100), 67 (74), 58 (32), 55 (87), 43 (46), 41 (83).

3-[($^{2}H_{3}$)Methyl]cyclopentadecanone (**33**). A soln. of **32** (250 mg, 1.11 mmol) in EtOH (3 ml) was hydrogenated over 5% Pd/C (24 mg). After 1 h, the mixture was filtered over *Celite*®, the filtrate concentrated, and the residue bulb-to-bulb distilled: pure **33** (97%). IR: 2924, 2855, 2208, 2119, 2067, 1709, 1458, 1407, 1365, 1271, 1128, 1072, 1052, 710. ^{1}H-NMR: 1.16–1.24 (*m*, 2 H); 1.25–1.4 (*m*, 18 H); 1.55–1.72 (*m*, 2 H); 2.0–2.1 (*m*, 1 H); 2.18 (*dd*, *J* = 5, 14.5, 1 H); 2.38–2.44 (*m*, 3 H). ^{13}C-NMR: 212.1 (*s*); 50.4 (*t*); 42.1 (*t*); 35.5 (*t*); 29.8 (*d*); 27.6 (*t*); 27.1 (*t*); 26.7 (*t*); 26.6 (2*t*); 26.5 (*t*); 26.3 (*t*); 26.2 (*t*); 25.0 (*t*); 23.0 (*t*). MS: 241 (37, $M^{+\cdot}$), 223 (19), 209 (22), 183 (13), 125 (33), 100 (33), 88 (100), 83 (31), 71 (70), 58 (58), 55 (89), 43 (42), 41 (70).

*(3a*RS*,5a*SR*,9a*SR*,9b*RS*)-(1,1-$^{2}H_{2}$)Decahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-2(1*H*)-one* (**34b**). Sclareolide (**34a**; 20 g, 80 mmol) was dissolved at 60° in MeOD (300 ml). Metallic Na (0.15 g, 6.5 mmol) was added under N_2. The mixture was heated at 60° for a total of 160 h. Two more portions of metallic Na (0.05 g, 2.2 mmol each) were added after 48 h and 120 h, resp. The mixture was quenched with CF_3COOD (10 ml). Evaporation of the solvent under *vacuum* followed by bulb-to-bulb distillation of the crude material afforded 18.3 g of 95% pure **34b** (86%). An anal. sample was prepared by crystallization from cold MeOD. IR: 2965, 2922, 2943, 2900, 2270, 1770, 1461, 1451, 1437, 1390, 1363, 1281, 1223, 1204, 1187, 1169, 1148, 1120, 1065, 1044, 1019, 938, 917, 870, 845, 708, 652. ^{1}H-NMR: 0.84 (*s*, 3 H); 0.89 (*s*, 3 H); 0.91 (*s*, 3 H); 1.05 (*d*, *J* = 3, 1 H); 1.08 (*d*, *J* = 3, 1 H); 1.20 (*dt*, *J* = 4.5, 13.7, 1 H); 1.33 (*s*, 3 H); 1.35–1.49 (*m*, 4 H); 1.65–1.72 (*m*, 2 H); 1.88 (*dq*, *J* = 3, 13.7, 1 H); 1.95 (*s*, 1 H); 2.07 (*dt*, *J* = 3, 11.5, 1 H). ^{13}C-NMR: 177.0 (*s*); 86.4 (*s*); 58.9 (*d*); 56.6 (*d*); 42.2 (*t*); 39.5 (*t*); 38.7 (*t*); 36.0 (*s*); 33.2 (*q*); 33.1 (*s*); 21.6 (*q*); 20.9 (*q*); 20.6 (*t*); 18.1 (*t*); 15.1 (*q*). MS: 252 (0, $M^{+\cdot}$), 237 (42), 209 (32), 193 (22), 152 (20), 137 (40), 125 (69), 123 (100), 109 (58), 95 (58), 82 (48), 69 (60), 55 (30), 43 (57).

rac-*(1α,2β,4aβ,8aα)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalene-1-(α,α,β,β-$^{2}H_{4}$)ethanol* (**35**). Obtained in quantitative yield as described for (−)-**17a**, with 0.5 mol-equiv. of $LiAlD_4$. IR: 3371, 3299, 2920, 2864, 2221, 2183, 2091, 1461, 1387, 1337, 1305, 1193, 1181, 1155, 1130, 1100, 1083, 1042, 1018, 970, 960, 935, 911, 843. ^{1}H-NMR: 0.79 (*s*, 6 H); 0.87 (*s*, 3 H); 0.92–0.96 (*m*, 2 H); 1.11–1.18 (*m*, 1 H); 1.19 (*s*, 3 H); 1.24–1.31 (*m*, 1 H); 1.26 (*s*, 1 H); 1.36–1.51 (*m*, 3 H); 1.55–1.70 (*m*, 3 H); 1.90 (*dt*, *J* = 4.5, 13, 1 H); 3.0 (*s*, 2 OH). ^{13}C-NMR: 73.1 (*s*); 58.9 (*d*); 56.0 (*d*); 44.3 (*t*); 41.9 (*t*); 39.4 (*t*); 39.0 (*s*); 33.4 (*d*); 33.3 (*s*); 24.6 (*q*); 21.5 (*q*); 20.5 (*t*); 18.4 (*t*); 15.3 (*q*). MS: 258 (0, $M^{+\cdot}$), 243 (9), 225 (92), 196 (26), 178 (33), 169 (18), 155 (49), 137 (43), 125 (27), 123 (29), 113 (28), 109 (54), 105 (29), 101 (27), 99 (33), 95 (53), 87 (28), 83 (48), 81 (49), 71 (70), 69 (96), 55 (58), 43 (100), 41 (78).

*(3a*RS*,5a*SR*,9a*SR*,9b*RS*)-(1,1,2,2-$^{2}H_{4}$)Decahydro-3a,6,6,9-tetramethylnaphtho[2,1-*b*]furan* (**36**). Obtained in 90% yield as described in [25a] for the unlabeled material. IR: 3000, 2970, 2938, 2838, 2225, 2206, 2120, 2095, 1456, 1438, 1405, 1380, 1362, 1241, 1229, 1196, 1162, 1124, 1090, 1060, 1018, 986, 919, 893, 814, 698, 668, 655. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.84 (*s*, 3 H); 0.88 (*s*, 3 H); 0.96 (*dd*, *J* = 3, 12, 1 H); 1.04 (*dt*, *J* = 3, 13, 1 H); 1.08 (*s*, 3 H); 1.18 (*dt*, *J* = 5, 13.7, 1 H); 1.30 (*dq*, *J* = 3, 13, 1 H); 1.38 (*s*, 1 H); 1.40–1.50 (*m*, 4 H); 1.67 (*tq*, *J* = 3, 14, 1 H); 1.73–1.78 (*m*, 1 H); 1.94 (*dt*, *J* = 4, 11.5, 1 H). ^{13}C-NMR: 79.9 (*s*); 60.0 (*d*); 57.3 (*d*); 42.5 (*t*); 40.0 (*t*); 39.8 (*t*); 36.2 (*s*); 33.6 (*q*); 33.1 (*s*); 21.2 (2 *q*); 20.7 (*t*); 18.4 (*t*); 15.1 (*q*). MS: 240 (4, $M^{+\cdot}$), 225 (100), 141 (7), 137 (18), 109 (5), 101 (20), 95 (9), 81 (9), 69 (9), 55 (6), 43 (10), 41 (7).

REFERENCES

[1] a) A. Chaintreau, C. Debonneville, *Anal. Chem.* **2009**, *81*, in press; b) A. F. Thomas, 'Deuterium Labeling in Organic Chemistry', Appleton-Century-Crofts, New York, 1971.

[2] a) L. Ruzicka, C. F. Seidel, W. Brugger, *Helv. Chim. Acta* **1947**, *30*, 2168; b) C. Chapuis, R. Brauchli, *Helv. Chim. Acta* **1993**, *76*, 2070; c) K.-H. Schulte-Elte, C. Margot, C. Chapuis, D. P. Simmons, D. Reichlin, to *Firmenich SA*, US1994-218543, 1994, March 28 (*Chem. Abstr.* **2000**, *132*, 313341).

[3] C. Fehr, I. Farris, to *Firmenich SA*, WO2007/10420A1, 2007, Jan. 25 (*Chem. Abstr.* **2007**, *146*, 184620).

[4] a) T. Ichikawa, H. Owatari, T. Kato, *Bull. Chem. Soc. Jpn*. **1968**, *41*, 1228; b) F. Demande, to *BASF*, FR2003508, 1969, Nov. 07 (*Chem. Abstr.* **1970**, *72*, 100274x); c) B. Maurer, A. Hauser, W. Thommen, K.-H. Schulte-Elte, G. Ohloff, *Helv. Chim. Acta* **1980**, *63*, 293; d) K.-H. Schulte-Elte, W. K. Giersch, B. Winter, H. Pamingle, G. Ohloff, *Helv. Chim. Acta* **1985**, *68*, 1961; e) R. Detlef, W. Burst, W. Kaiser, M. Stroezel, to *BASF*, US5994589A1, 1999, Nov. 30 (*Chem. Abstr.* **1999**, *131*, 201525).

[5] L. Ruzicka, *Helv. Chim. Acta* **1919**, *2*, 144; K.-H. Schulte-Elte, H. Pamingle, to *Firmenich SA*, US4626602A1, 1986, Dec. 02 (*Chem. Abstr.* **1985**, *102*, 166981); B. Maurer, A. Hauser, J.-C. Froidevaux, *Helv. Chim. Acta* **1989**, *72*, 1400; C. Chapuis, K.-H. Schulte-Elte, H. Pamingle, C. Margot, to *Firmenich SA*, US5118865A1, 1992, Jun. 02 (*Chem. Abstr.* **1992**, *116*, 235920).

[6] a) C. Chapuis, C. Margot, K.-H. Schulte-Elte, H. Pamingle, to *Firmenich SA*, US5017711A1, 1991, May 21 (*Chem. Abstr*. **1991**, *114*, 43240); b) C. Chapuis, B. Winter, K.-H. Schulte-Elte, *Tetrahedron Lett*. **1992**, *33*, 6135; c) C. Chapuis, R. Brauchli, W. Thommen, *Helv. Chim. Acta* **1993**, *76*, 535; d) C. Chapuis, R. Brauchli, *Helv. Chim. Acta* **1993**, *76*, 2070; e) C. Margot, D. P. Simmons, D. Reichlin, D. Skuy, *Helv. Chim. Acta* **2004**, *87*, 2662.

[7] K. Schulze, K. Wyssywa, H. Trauer, A. K. Habermann, *J. Prakt. Chem*. **1993**, *335*, 537; C. Chapuis, *Chem. Biodiversity* **2004**, *1*, 980.

[8] J. J. Gajewski, N. D. Conrad, *J. Am. Chem. Soc*. **1979**, *101*, 6693; F. D. Kopinke, G. Zimmermann, *J. Prakt. Chem*. **1981**, *323*, 992; L. Crombie, S. J. Holloway, *J. Chem. Soc., Perkin Trans. 1* **1985**, 2425.

[9] T. Pasto, *Org. Mass Spectrom*. **1975**, *10*, 222; F. D. Kopinke, G. Bach, B. Ondruschka, D. Renneke, G. Zimmermann, *J. Prakt. Chem*. **1983**, *325*, 375; P. Seguineau, J. Villieras, *Tetrahedron Lett.* **1988**, *29*, 477; R. D. Bowen, D. Richard, P. J. Derrick, *J. Chem. Soc., Perkin Trans. 2* **1992**, *7*, 1041; R. D. Bowen, P. J. Derrick, *Org. Mass Spectrom*. **1993**, *28*, 1197.

[10] E. J. Brunke, C. H. Kappey, to *Dragoco Co GmbH*, DE84-3441902, 1986, Jan. 30 (*Chem. Abstr.* **1987**, *106*, 50513x); A. Takashi, H. Makoto, I. Hisaho, A. Akira, Y. Tetsuro, to *Takasago Intl. Co*, US5994291A1, 1999, Nov. 30 (*Chem. Abstr.* **1998**, *128*, 244210); V. Rautenstrauch, R. Churlaud, R. H. Maurris, K. Abdur-Rashid, to *Firmenich SA*, US2003/415086A1, 2003, Apr. 25 (*Chem. Abstr.* **2002**, *136*, 403482).

[11] a) K.-H. Schulte-Elte, B. Müller, H. Pamingle, to *Firmenich SA*, US4610813A1, 1986, Sep. 09 (*Chem. Abstr.* **1986**, *105*, 191435); b) J. M. Castro, P. Linares-Palomino, S. Salido, J. Altarejos, M. Nogueras, A. Sanchez, *Tetrahedron Lett*. **2004**, *45*, 2619.

[12] C. Chapuis, A. Gautier, P.-A. Blanc, to *Firmenich SA*, US5512543A1, 1996, Apr. 30 (*Chem. Abstr.* **1995**, *123*, 17516).

[13] C. Chapuis, P.-A. Blanc, to *Firmenich SA*, US5696075A1, 1997, Dec. 09 (*Chem. Abstr.* **1996**, *124*, 261418).

[14] K. Schulze, A. K. Habermann, H. Uhlig, K. Wyssuwa, *J. Prakt. Chem*. **1993**, *335*, 687.

[15] a) W. K. Giersch, K.-H. Schulte-Elte, to *Firmenich SA*, US5166412, 1992, Nov. 24 (*Chem. Abstr.* **1992**, *117*, 7513); b) A. S. Williams, to *Firmenich SA*, EP1459735, 2004, Sept. 22 (*Chem. Abstr.* **2004**, *141*, 301056).

[16] A. S. Williams, to *Firmenich SA*, US6384269B1, 2002, May 07 (*Chem. Abstr.* **2000**, *132*, 194523).

[17] P. Kraft, W. Eichenberger, *Eur. J. Org. Chem*. **2004**, 354.

[18] H. R. Ansari, *Tetrahedron* **1973**, *29*, 1559.

[19] B. A. McAndrew, S. W. Russel, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1172; J. Tsuji, T. Yamada, I. Schimizu, *J. Org. Chem*. **1980**, *45*, 5209; A. Osomi, A. Shirahata, Y. Araki, H. Sakurai, *J. Org. Chem*. **1981**, *46*, 4631; V. Ognyanov, M. Hesse, *Helv. Chim. Acta* **1987**, *70*, 1393.

[20] A. G. Davies, E. Lusztyk, J. Lusztyk, *J. Chem. Soc., Perkin Trans. 2* **1982**, 729; M. A. Baig, D. V. Banthorpe, G. Carr, D. Whittaker, *J. Chem. Soc., Perkin Trans. 2* **1989**, 1981.
[21] V. Rautenstrauch, R. L. Snowden, S. M. Linder, *Helv. Chim. Acta* **1990**, *73*, 896.
[22] A. Eschenmoser, D. Felix, to *Firmenich SA*, US4328383A1, 1982, May 04 (*Chem. Abstr.* **1982**, *96*, 6267).
[23] a) G. Ohloff, J. Becker, K.-H. Schulte-Elte, *Helv. Chim. Acta* **1967**, *50*, 705; b) A. Eschenmoser, ZA6766415, 1968, Mar. 06 (*Chem. Abstr.* **1969**, *70*, 88108v); c) R. W. Gray, A. S. Dreiding, *Helv. Chim. Acta* **1977**, *60*, 1969; d) C. Fehr, J. Galindo, O. Etter, *Eur. J. Org. Chem*. **2004**, 1953; e) O. Knopf, to *Firmenich SA*, WO2005/77875A1, 2005, Aug. 25 (*Chem. Abstr.* **2005**, *143*, 248092); f) O. Knopf, J. Kuhne, C. Fehr, *Angew. Chem., Int. Ed*. **2007**, *46*, 1307.
[24] A. Saito, H. Matsushita, Y. Tsujino, H. Kaneko, *Chem. Lett*. **1981**, 757; A. Saito, H. Matsushita, H. Kaneko, *Chem. Lett*. **1983**, 729; A. Saito, H. Matsushita, H. Kaneko, *Chem. Lett*. **1984**, 591; T. Kawanobe, K. Kogami, M. Matsui, *Agric. Biol. Chem*. **1986**, *50*, 1475; T. Koga, Y. Aoki, T. Hirose, H. Nohira, *Tetrahedron: Asymmetry* **1998**, *9*, 3819.
[25] a) S. Escher, W. Giersch, Y. Niclass, G. Bernardinelli, G. Ohloff, *Helv. Chim. Acta* **1990**, *73*, 1935; b) H. Tanimoto, T. Oritani, *Tetrahedron: Asymmetry* **1996**, *7*, 1695; c) L. Saudan, P. Dupau, J.-J. Riedhauser, P. Wyss, to *Firmenich SA*, WO2006/106483, 2006, Oct. 12 (*Chem. Abstr*. **2006**, *145*, 388187).
[26] A. Chaintreau, D. Joulain, C. Marin, C.-O. Schmidt, M. Vey, *J. Agric. Food Chem*. **2003**, *51*, 6398; F. David, C. Devos, D. Joulain, A. Chaintreau, P. Sandra, *J. Sep. Sci.* **2006**, *29*, 1587; M. Bassereau, A. Chaintreau, S. Duperrex, D. Joulain, H. Leijs, G. Loesing, N. Owen, A. Sherlock, C. Schippa, P.-J. Thorel, M. Vey, *J. Agric. Food Chem*. **2007**, *55*, 25.
[27] C. Chapuis, R. Brauchli, *Helv. Chim. Acta* **1992**, *75*, 1527.
[28] A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, C. M. Suter, *J. Am. Chem. Soc.* **1949**, *71*, 3372.
[29] A. D. Becke, *Phys. Rev.* **1988**, *38*, 3098.

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