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# A Concise Synthesis of *rac*-Ambrox® *via* the $Pd^0$ Catalyzed Carboalkoxylation of an Allylic Ammonium Salt, as Compared to a Formaldehyde Hetero Diels-Alder Approach

**Christian Chapuis***, **David Skuy**, and **Claude-Alain Richard**

Dedicated to Dr. *V. Rautenstrauch* on the occasion of his 82th birthday

Acidic cyclisation of either the diethylallylamines **29b** or **30**, followed by a 1.5 mol-% Pd-catalyzed carbomethoxylation of quaternized **31b**, leads to the methyl ester **36a**. This latter could also be obtained in optically pure form by carbomethoxylation of the corresponding (+)-acetate. Final reduction-cyclisation may be conducted as earlier described, towards the desired odoriferous *rac*-Ambrox® **38a**, or its pure (-)-enantiomer. Generation of a π-allyl Pd complex from an allylic ammonium salt, followed by carboalkoxylation is novel. In only five chemical steps starting from farnesene **2**, the present work constitutes the most concise total synthesis of *rac*-Ambrox® **38a** to date.

**Keywords:** Palladium, carbomethoxylation, allylic, ammonium, Ambrox®

**Introduction:** -The simple conditions previously reported by *Margot* and *Schlosser* for the "formal" hetero *Diels-Alder* reaction between paraformaldehyde and myrcene **1** [1-4], encouraged us to extend this reaction to other dienes. In particular, to the now readily available farnesene **2** [5-8] (*Scheme* 1), δ-pyronene **3**[1]) [9-18] (*Scheme* 2), the known bicyclic diene **4**[2]) [22-32], and 2,3-dimethylidenenorbornane **5**[3]) [35-39]; as well as to the unreported diene **6** (*Scheme* 3). Our simple basic concept consisted of cleaving the resulting dihydropyran allylic C-O bond *via* a *Birch* reduction [3][40], followed by cyclization of the corresponding homoallylic alcohol under acidic conditions [41-45], in order to create new tetrahydrofuran derivatives, which might possess amber-like scents [46]. We also wanted to apply unreported carboalkoxylation conditions to achieve a short synthesis of *rac*-Ambrox®.

**Results and discussion.** – The known tetrahydropyran **7**[4]) [1-4] was obtained in 64% crude yield from **1** (paraformaldehyde, AcOH, 130°C). A simple distillation allowed the isolation of >96% pure material in 18% yield. Further catalytic cyclization (0.1 mol.-equiv. $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 20°C) afforded the bicyclic ether **8** in 47% yield. Then *Birch* cleavage under simple conditions (Li, $H_2NCH_2CH_2NH_2$, 20°C, 69% yield) furnished the primary homoallylic alcohol **9**, which was subsequently, quantitatively, cyclized to give a 87:13 mixture of tetrahydrofuran derivatives *trans*-/*cis*-**10** ($MeSO_3H$, $CH_2Cl_2$, 20°C).

HERE SCHEME 1

[1]) See the Supplementary Material for analytical data.

[2]) For the (+)-enantiomer, see [19-21].

[3]) This "formal" HDA-cycloaddition may also be seen either as a neutral *Prins*, or concerted ene-type reaction followed by acidic cyclisation, although this alternative stepwise mechanism is not applicable to dienes such as **5**. Alternatively, acidic protonation of formaldehyde reacting with the diene by forming a tertiary allylic cation could lead, after cyclization, towards the observed skeletons. For a diastereoselective example of such a "formal" HDA-reaction, see [33], for alternative catalytic conditions, see [34].

[4]) This compound exhibits a lemon, rosy, citronellol, geraniol and citral scent, as well as the following $^{13}$C-NMR analytical data: 135.6 (*s*); 131.7 (*s*); 124.0 (*d*); 119.6 (*d*); 65.6 (*t*); 64.4 (*t*); 37.1 (*t*); 28.6 (*t*); 25.9 (*t*); 25.7 (*q*); 17.7 (*q*). Bp: 94°C/0.7 mbar.

Similarly, the homologous farnesene **2** was subjected to the same sequence to afford the corresponding pure dihydropyran **11** in 15% isolated yield,[5]) while cyclization allowed us to isolate traces of isomerized α-**12**, as well as pure β-**12** (14% yield). When this latter was submitted to hydrogenation conditions (5% Pd/C, AcOEt, 88% yield), a 77:23 mixture of *trans/cis* stereoisomers **13** was obtained. This stereochemistry may eventually result from the faster hydrogenation of α-**12**, a less stable, but more accessible, trisubstituted double bond when compared to β-**12**, thus driving the equilibrium towards the double bond isomerization.[6]) *Birch* reduction of β-**12**, led to the homoallylic alcohol **14** (59% yield), which was finally cyclized to the Ambrox® constitutional isomers **15** ($MeSO_3H$, $CH_2Cl_2$, 51% yield, 55:45 mixture of stereoisomers). Neither derivatives **12**, **13** nor **15** exhibited a strong amber-like scent, although all of them were weakly olfactorily active, despite analytical evidence for the absence of regioisomers. Since the reversed regioselectivity would have been synthetically more interesting during the cycloaddition, we decided to invert the sequence by studying the hetero *Diels-Alder* reaction of the cyclic dienes. Thus, when δ-pyronene **3** was used, the [4+2] cycloaddition afforded a 9:1 mixture of regioisomers **8** and **16**[7]) in 66% crude yield. Regioisomer **8** could be isolated pure in 38% yield by CC/$SiO_2$, while *Birch* reduction of a 8:2 mixture of **8**/**16**[8]) gave the reported minor homo-allylic alcohol **18** [48-50], which was subsequently cyclized to afford the bicyclic ether **19** [51-52] in 69% yield as a 83:17 *trans/cis* mixture.[9])

HERE SCHEME 2

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[5]) When **2** was treated with paraformaldehyde and 0.05 mol-equiv. of $SnCl_4$ in $CH_2Cl_2$ at 20°C, we isolated the *Prins* by-product in 7% yield. For analytical data of (*E*)-5-methyl-9-methylene-2-(prop-1-en-2-yl)undeca-5,10-dien-1-ol, see the Supplementary Material.

[6]) Ground state energy (B3LYP-6-31G**): β-**12**: 0.00 kcal/mol; α-**12**: 1.29 kcal/mol; (6a*RS*,10a*RS*,10b*SR*)-7,7,10a-trimethyl-3,4,6,6a,7,8,9,10,10a,10b-decahydro-1H-benzo[h]isochromene: 1.90 kcal/mol; (6a*RS*,10a*RS*,10b*RS*)-7,7,10a-trimethyl-3,5,6,6a,7,8,9,10,10a,10b-decahydro-1H-benzo[h]isochromene: 1.79 kcal/mol [47].

[7]) *J. Coulomb* (*Firmenich SA*, unpublished results, 2010) obtained a 3:1 mixture of **8**/**16** in 39% yield by using 0.1 mol.-equiv. of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at 20°C for 4 h.

[8]) Under modified *Birch* conditions (Li, $MeNH_2$, THF, -78°C, [3]) the reduction of **8**/**16** additionally afforded traces of the side product **17**, isolated in 10% yield, as a result of a double bond isomerization.

[9]) *C. Fehr* (*Firmenich SA*, unpublished results, 2008) isolated **19** in 78% yield as a 88:12 *trans/cis* mixture by using 0.6 mol.-equiv of $FeCl_3$, 50 mg/mmol $SiO_2$ 60Å, in $CH_2Cl_2$/$ClCH_2CH_2Cl$, after 3.5 h at 20°C [53].

The analogous cycloaddition performed on diene **4** afforded again, essentially, the undesired regioisomer β-**12** in 25% isolated yield. We also applied these hetero *Diels-Alder* conditions to diene **5** (22% isolated yield), since the *Birch* reduction of dihydropyran **20** led to the homo-allylic alcohol **21** (Li, $H_2NCH_2CH_2NH_2$, 20°C, 41% yield),[10]) earlier used as optically active intermediate in a synthesis of (-)-(*Z*)-β-santalol [54]. Further direct intramolecular acidic cyclization gave the five-membered ring ether **22** in 48% yield, as a 79:21 *endo/exo* mixture. For the sake of completeness, we also wanted to perform this hetero cycloaddition on the unreported diene **6** (*Scheme* 3). We initially decided to synthetize it by applying the *Wittig* methodology described by *Vig et al.* [55-56]. Thus a haloform reaction on the commercially available dihydro-β-ionone **23a** afforded the reported acid **23b** [57-61], which was quantitatively transformed into the corresponding known acid chloride **23c** [9]. Alternatively, reduction of acid **23b** (*Scheme* 3) to the known primary alcohol **24a**[11]) [19][57][60], allowed us, after re-oxidation to the reported aldehyde **23d** [9][62] (PCC, $CH_2Cl_2$, 66% yield)[12]) to perform either a vinyl *Grignard* addition leading to the allylic alcohol **24b** (vinylMgBr, 0.2 mol.-equiv. $LaCl_3{\cdot}2LiCl$, THF, 0°C [63]), isolated in 42% yield besides **24a**, or a more efficient ethynyl *Grignard* addition towards the analogue **24c** (HCCMgBr, $Et_2O$, 94% yield). Treatment of this latter secondary propargylic alcohol **24c** with $LiAlH_4$ also generated **24b** in 49% yield.[13]) With two potential precursors in hand, we first treated the acid chloride **23c** in the presence of $Li_2MnCl_4$ with vinylMgBr (14% yield), and co-isolated in 6% yield the known by-product **25**, resulting from a concurrent intramolecular *Friedel-Craft* reaction [9].[14]) The desired intermediate enone **23e** was more

[10]) This alcohol, possessing paper, woody, straw, and sawdust organoleptic facets, exhibits the following complementary analytical data: IR: 3325, 2951, 2866, 1444, 1378, 1276, 1115, 1039, 1021, 986, 870. MS: 152 (20, $M^{+\cdot}$), 124 (29), 93 (100), 91 (32), 80 (26), 77 (20).

[11]) This alcohol exhibits the following complementary $^{13}$C-NMR analytical data: 136.9 (*s*); 127.1 (*s*); 63.6 (*t*); 39.9 (*t*); 35.0 (*s*); 33.6 (*t*); 32.8 (*t*); 28.6 (2*q*); 24.9 (*t*); 19.8 (*q*); 19.6 (*t*). Dusty, metallic, weak odor.

[12]) Incidentally, oxidation of aldehyde **23d** under *Jones* conditions afforded acid **23b** in 81% yield.

[13]) With 32% isolated yield ($CC/SiO_2$+1%/w $AgNO_3$), *Lindlar* hydrogenation of **24c** in cyclohexane was less efficient.

[14]) This compound with the following $^{13}$C-NMR analytical data: 222.6 (*s*); 156.1 (*s*); 114.7 (*d*); 51.3 (*s*); 41.1 (*t*); 40.6 (*t*); 34.9 (*s*); 33.2 (*t*); 29.8 (*q*); 26.8 (*q*); 23.2 (*q*); 18.5 (*t*), exhibits a beetroot, earthy, pine and incense scent. We also isolated (1*RS*,5*RS*)-6,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-2-one in 3% yield (see Supplementary Material). This compound, first delivered to our perfumers by *B. Winter* (*Firmenich*

cleanly obtained by oxidation ($MnO_2$, $CH_2Cl_2$, 34% yield) of the vinylic carbinol **24b**.[15]) The final *Wittig* reaction ($Ph_3PCH_3^+Br^-$, NaH, DMSO, THF) unfortunately afforded diene **6** in a poor 15% yield. Alternatively, treatment of farnesene **2** with commercially available DABSO[16]) in the presence of $BF_3{\cdot}OEt_2$ in MeCN at 50°C [66], afforded a 2:1 mixture of sulfolenes **26**/**27** in 36% crude yield (13 and 2% isolated yield, respectively). Cyclization of pure **26** with $BF_3{\cdot}OEt_2$ in MeCN at 0°C afforded, after 80% partial conversion, pure **27**. Under the same conditions, a crude 2:1 mixture of **26**/**27** also afforded in 66% yield a 2:1 mixture of **27**/**28**. Alternatively, cyclisation of pure **26** with $BF_3{\cdot}OEt_2$ and AcOH in $CH_2Cl_2$ at 30°C gave essentially **28** in 47% yield [67]. An alternative sequence was explored by treating the known vinyl carbinol **24d** [68-69] with DABSO in the presence of MsCl [66], but, as underlined in the original report, the use of a $DMAP{\cdot}SO_2$ complex should be more efficient to afford directly sulfolene **27**, since our conversion was very poor. The thermal treatment of **27** at 160°C in pyridine then afforded the desired diene **6** in 57% yield, while that of **28** afforded diene **4** in 68% yield [70].[17])

HERE SCHEME 3

Since this approach was not much more attractive than the *Wittig* methodology, we envisaged another strategy starting from the known precursors **29a**,**b** [72-78]. Thus, cyclisation of **29b** using an excess of $BF_3{\cdot}OEt_2$ and AcOH in $CH_2Cl_2$ at 30°C afforded quantitatively a 26:58:16 mixture of **30**/**31g**/**31a** from which pure **31g** was isolated in 33% yield after chromatography,[18])

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*SA*, unpublished results, 2006), exhibits the following olfactory properties: aromatic, beeswax, honey, camphoraceous, woody, Kephalis.

[15]) Similar oxidation of **24c** afforded **23f** in 41% yield.

[16]) 1,4-Diazabicyclo[2.2.2]octane *bis* (sulfur dioxide) adduct. The MS analyses of **26** and **27** are reminiscent to that of **2**, and **6**, due to the easy chelotropic elimination of $SO_2$, respectively [64-65]. This instability, with respect to the reaction temperature conditions, is in all cases detrimental to the isolated yields. Treatment of **5** with either DABSO, or *Riecke* Mg failed [64-65].

[17]) Alternative treatment of **27** with $NaHCO_3$ in EtOH at 120°C in analogy to [71] gave *ca*. only 30% conversion after 18h. Alternatively, treatment of **27** with AcOH and $(CH_2O)_n$ at 130°C failed to afford directly the desired heterocycloadduct. Under these conditions, myrcenol [55], with the following complementary $^{13}$C-NMR analytical data: 146.2 (*s*); 138.9 (*d*); 115.7 (*t*); 113.2 (*t*); 70.8 (*s*); 43.7 (*t*); 31.7 (*t*); 29.2 (2*q*); 22.9 (*t*), afforded the corresponding cycloadduct in 13% yield (see Supplementary Material).

[18]) The $^{13}$C-NMR analysis of the crude material showed no traces of the β-isomer **31b**.

while an excess of conc. $H_2SO_4$ in $CH_2Cl_2$ at 30°C furnished in quantitative yield a 74:26 mixture of **31b**/**31r**.[19]) Both rearranged and tetrasubstituted olefins, separable by chromatography, were isolated in 7% and 39% yield, respectively. The monocyclization could be selectively obtained by using $MeSO_3H$ in $CH_2Cl_2$ at 0°C, thus affording in 60% yield a 78:22 mixture of *E/Z*-**30** after distillation. The best *Brønsted* acid conditions were observed with an excess of $CF_3SO_3H$ in $MeNO_2$ at -20° to 0°C, affording in 81% yield either a 7:3 mixture of **31a**/**31g** when the reaction was immediately quenched at -20°C, or **31b**[20]) in 75% yield when the reaction was quenched at 0°C before the formation of **31r**. Pure homoallylic amine **31g** was treated with 60% aq. $H_2O_2$ in EtOH, to afford pure diene **4** in 58% yield after distillation.[21])

HERE SCHEME 4

The carbonylation of allylic amines in the presence of either a Pd-phosphine or a dicobalt octacarbonyl complex to afford β,γ-unsaturated amides has been reported [79-80][22]), and *Rautenstrauch et al.* earlier observed that quaternisation of the commercially available geranyldiethylamine **29a** with either $H^+$ or EtI in EtOH at 60°C [86-87], followed by *in situ*

[19]) Theoretical B3LYP-6-31G** calculations suggest the following ground state energies: (1*RS*,2*SR*,4a*RS*)-**31r** 0.00 kcal/mol; (1*RS*,2*RS*,4a*SR*)-**31r** 0.38 kcal/mol; (1*RS*,2*SR*,4a*SR*)-**31r** 0.93 kcal/mol; (1*RS*,2*RS*,4a*RS*)-**31r** 1.42 kcal/mol [47]. The isolated stereoisomer does not correspond to the thermodynamically more stable one. Its stereochemistry was confirmed by NOE evidences between the pseudo axial secondary Me and the axial Me of the *gem*-diMe moiety, as well as between the pseudo axial $CH_2$-N and the quaternary Me of the ring junction. Treatment of **30** with either 30% $H_2O_2$/EtOH, or MCPBA/$CH_2Cl_2$ failed to afford **6** after distillation. The *Wittig* preparations of **6** (*vide supra*) nevertheless allowed, for analytical purposes, to obtain both cycloadduct **32** (AcOH, $(CH_2O)_n$, 130°C, 57% yield), and its *Birch* reduced corresponding homoallylic alcohol **33** (35% yield, *Scheme* 4).

[20]) When **29f** was similarly cyclized with either $CF_3SO_3H$, or $H_2SO_4$ at 0° to 20°C, the pyrolidine derived analogue of **31b** was isolated in 46% yield (see Supplementary Material).

[21]) When a 55:45 mixture of **31g**/**31a** was treated with 60% aq. $H_2O_2$ in EtOH, both pure **4** and **31a** were isolated by CC/$SiO_2$ in 25% and 27% yield, respectively. The corresponding *N*-oxides could not be put in evidence.

[22]) For 2-((4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetamide, see [77]. For Ni-catalyzed carboxylation of benzylic ammonium derivatives using $CO_2$, see [81]. For a review on this subject, see [82]. For carbomethoxylation of benzylic amines using $Pd_2(dba)_3$, see [83-84]. For Ni-catalyzed C-P coupling of benzyl and allyl ammonium salts with $R_2P(O)H$ derivatives, see [85].

carboethoxylation (0.01 mol.-equiv. $Pd(PPh_3)_4$, CO, 60 bar, EtOH, 60°C, 72h) enable a clean one-C atom homologation to afford the known ethyl ester **34a** in 73% yield as a 85:15 *E/Z* mixture [88-90][23]). The EtOH may eventually be substituted by MeOH, since both the kinetic and conversion are increased in this later case. Quaternization may also be performed from the commercially available primary allylic amine **29c** with either three mol.-equiv. of MeI, or by simple protonation with one mol.-equiv. of 96% $H_2SO_4$ in MeOH/THF to afford in 24-25% yield **34c** as a 84:16 to 80:20 mixture of *E/Z* stereoisomers after 48h at 60°C under 60 bars of CO [91][24]). In our hands, farnesyldiethylamine **29b** likewise afforded the ethyl ester **34b** in 15% yield as a 76:24 *E/Z* mixture (EtI, EtOH, 60°C, 60 bar CO, 0.01 mol.-equiv. $Pd(PPh_3)_4$) [92]. The chemical yield increased to 32% when a 1:1 mixture of EtOH/THF was used.[25]) Similarly, the monocyclofarnesyldiethylamine **30** also furnished the known ethyl ester **35b** in 52% yield as a 65:35 *E/Z* mixture (EtI, 0.01 mol.-equiv. $Pd(PPh_3)_4$, CO, 60 bar, EtOH, 60°C, 87h) [98-99][26]). In order to avoid *E/Z*-mixtures, we applied these unreported conditions to **31b** (MeI, 0.015 mol.-equiv. $Pd(PPh_3)_4$, MeOH/THF 1:1, CO, 60 bar, 60°C, 144h, 45% conversion, 31% yield), so that the alkyl esters **36a**,**b** [92][104-108][27]) may further be reduced into ambrol **37** as described by

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[23]) *V. Rautenstrauch, J. Currie*, and *A. Charpilloz*, (*Firmenich SA*, unpublished results 1991-1992). This ethyl ester exhibits the following complementary MS analytical data: *E*-stereoisomer 210 (2, $M^{+\cdot}$), 167 (20), 122 (17), 109 (5), 107 (8), 96 (9), 93 (8), 81 (10), 69 (100), 41 (30). *Z*-stereoisomer 210 (3, $M^{+\cdot}$), 167 (14), 122 (23), 109 (13), 107 (16), 96 (9), 93 (7), 81 (12), 69 (100), 41 (33).

[24]) The Me ester **34c** exhibits a rosy-like scent. Supplementary $^{13}$C-NMR analytical data of the *Z*-stereoisomer: 173.0 (*s*); 139.3 (*s*); 132.0 (*s*); 123.9 (*d*); 116.4 (*d*); 51.7 (*q*); 33.6 (*t*); 32.2 (*t*); 26.3 (*t*); 25.7 (*q*); 23.4 (*q*); 17.6 (*q*).

[25]) When the reaction temperature is superior to 75°C, *Hofmann* elimination becomes a competing side reaction. The corresponding known Me esters **34d** [93-97], (80:20 3*E*/3*Z* mixture, were more efficiently obtained using 0.01 mol.-equiv of either $Pd(PPh_3)_4$, or $PdBr_2$/$(CH_2PoPy_2)_2$ (MeOH/THF, CO, 60 bar, 60°C, 22h, 52-55% yield, respectively, see Supplementary Material).

[26]) See the Supplementary Material for the corresponding known Me ester **35a** [100-103]. The *E*-stereoisomer possesses a bitter almond and tobacco-like scent in opposition to the weakly metallic character of the Z-counterpart. See also the Supplementary Material for complementary analytical data of the corresponding known acid **35c** [93-97][100-103].

[27]) The reaction in pure and less nucleophilic EtOH was much more sluggish due to the poor solubility of **31b**. For comparison, complementary analytical data of the reported Me-ester α-analogues [104-105] are available in the Supplementary Material. Alternatively, (+)-**36a** was also obtained in 15-20% yield from the reported corresponding (+)-((4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-

*Hagiwara et al.* [114-115][28]), prior to the final known cyclisation to *rac*-Ambrox® **38a** [44-45][53][77]. This regioselective carboalkoxylation methodology does not generate a supplementary stereogenic center, as a critical point for the stereochemistry of the final product. The known cyclization of *N*,*N*-diethyl geranylamine **29a** towards β-cyclogeranyldiethylamine **39** (40% aq. $H_2SO_4$, 120°C, 20h, 54%, [76]), followed by carbomethoxylation afforded the known methyl β-homocyclogeranate **40a** (MeI, 0.015 mol.-equiv. $Pd(PPh_3)_4$, MeOH, THF, CO, 60°C, 60 bar, 47% conversion, 25% yield) [117-118][29]). Finally, diene **5** was treated with $Et_2NH$ and *n*BuLi in THF to afford the unreported diethyl amine **41** in 52% yield. When submitted to carbomethoxylation conditions (MeI, 0.015 mol.-equiv. $Pd(PPh_3)_4$, MeOH, CO, 60 bars, 60°C,

yl)methyl acetate [109] ($[\alpha]_D^{20}$ = +117.8, c = 2.0, $CHCl_3$; 0.01 mol.-equiv. $Pd(PPh_3)_4$, MeOH/THF 1:1, CO 60 bar, 70°C, 168h), in analogy to achiral former examples [88-91]. For KBr as additive, see [110]. The essential side product was (-)-(4a*S*,8a*S*)-1,1,4a,6-tetramethyl-5-methylene-1,2,3,4,4a,5,8,8a-octahydronaphthalene (21% yield) [45]. *In situ* isomerization of the homoallylic unsaturation of either drimenylacetate [111-112], or **31a**,**g**, under modified reaction conditions is actually under study. In a comparative example, we also treated directly the (+)-bicyclofarnesol ($[\alpha]_D^{20}$ = +112.4, c = 2.2, $CHCl_3$, [30][45]) with 1.3 mol.-equiv. of KH complexed with 1.6 mol.-equiv. of 18-c-6-ether, and performed the carbonylation (CO, 60 bar, 60°C, toluene, 72h, 40% conversion) under the conditions reported by *Rautenstrauch*, [113] to afford the homologated acid (+)-**36c** in 2.8% yield after extractive hydrolysis [77].

[28]) For the hydrogenation of unsaturated esters into the corresponding unsaturated alcohols, see [116].

[29]) This material is characterized by a foul odor. For the ethyl ester **40b**, see [119]. Under protonating carboxylative conditions (96% $H_2SO_4$, THF, 0.01 mol.-equiv $Pd(PPh_3)_4$, 70% yield, *Rautenstrauch*, private communication), the reported odorless β-homocyclogeranic acid **40c** was isolated with the following complementary analytical data [119-121]: MS: 182 (22, $M^{+\cdot}$), 167 (70), 149 (8), 121 (22), 107 (100), 93 (13), 91 (15), 81 (11), 79 (13), 55 (9), 43 (10), 41 (15). When diethylgeranylamine **29a** was cyclized with $CF_3SO_3H$ in $MeNO_2$ at 0°C, pure α- and γ-diethylcyclogeranylamines were isolated in 30% and 13% yield, respectively. When δ-pyronene **3** was treated with lithium diethylamide, both **39** and its main regioisomer were obtained as a 1:4 mixture in poor yield (see Exp. Part). It is thus preferable to use either cyclogeranyl chloride, or β-cyclocitral as starting material for amination. In analogy to the work of *M. Beller et al.* [122], we also advantageously tested on **39** a commercially available ligand (0.01 mol.-equiv. $PdBr_2$, 0.02 mol.-equiv. P,P'-bis(di*t*Bu phosphine)-o-xylene, MeI, CO, 60 bar, 60°C, MeOH, 2h, 31% yield). For a recent and efficient generation of $Pd^0$, see [123]. For *in situ* generation of CO, see [124].

22% yield), we obtained the unreported methyl ester **42** as precursor of either **21**, or (*Z*)-β-santalol [54].[30])

**Conclusion.** – The paraformaldehyde hetero *Diels-Alder*-like methodology applied to both diene **2**, and **6**, afforded the unsuitable regioisomers **11**, and **32** for further transformations towards *rac*-Ambrox® **38a**, respectively. This regioselectivity could not be inverted by starting from the cyclic dienes **4**, as we also obtained the heterocyclic intermediate β-**12**. After several unsatisfactory alternative attempts, this obstacle was finally circumvented by using a more efficient and regioselective methodology consisting of acidic cyclisation of either the diethylallylamines **29b** or **30**, followed by a 1.5 mol-% Pd-catalyzed carbomethoxylation of quaternized **31b**, leading to the methyl ester **36a**. This latter could also be obtained in optically pure form by carbomethoxylation of the corresponding (+)-acetate. Final reduction-cyclisation may be conducted as earlier described, towards the desired odoriferous *rac*-Ambrox® **38a**, or its pure (-)-enantiomer. Generation of a π-allyl Pd complex from an allylic ammonium salt, followed by carboalkoxylation according to the "in house" procedure of *Rautenstrauch et al*., is novel[31]) [131]. With only five chemical steps from farnesene **2**, the present report constitutes the most concise total synthesis of *rac*-Ambrox® **38a**, to date. In this latter case, sclareolide **38b** may be obtained in 73% yield according to the established lactonization procedure [77][27])[32]). This methodology allows for both the separation and recuperation of either the desired ester, or the non-converted starting material and/or unreactive homoallylic isomers, by a simple acidic washing of the reaction mixture. In order to extend the scope of this carboalkoxylation using Pd(II) coordinated to amphotere diphosphines as $Pd^0$ precatalysts [122-123], we are now exploring either the possibilities to start from pure, or mixtures of the corresponding α-, or γ-

[30]) The corresponding acid and ethyl ester exhibit the following complementary analytical data: [54] MS: 166 (22, $M^{+\cdot}$), 138 (88), 93 (100), 91 (30), 79 (10), 77 (22); 194 (28, $M^{+\cdot}$), 166 (99), 121 (19), 93 (100), 92 (82), 91 (38), 79 (11), 77 (23), respectively. The latter exhibits a fruity, carob-bean, overripe fruit and estery scent.

[31]) For allylic ammoniums as precursors of putative π-allyl Pd complexes, see for example [125-127]. For sterically less demanding leaving groups, we also similarly prepared the known characterized precursor **29d** [128-130], as well as the unreported analogs **29e** and **29f**. The regioisomer (2*E*,5*E*)-2-ethylidene-*N*,*N*,6,10-tetramethylundeca-5,9-dien-1-amine as main side product of **29d** was also isolated for analytical purpose (see Supplementary Material).

[32]) For the quantitative $LiAlH_4$ reduction of acid **36c** to alcohol **37**, see also [77].

homoallylic amines/acetates, owing to the potential concomitant isomerization of the unsaturation in either the presence of a supplementary additive, or by replacing MeOH/EtOH by $H_3O^+$ in THF. Finally, we shall also study some examples of lactonization using bifunctional hydroxy allyl amines.

## Experimental Part

*General*, see [77]. The reactions with CO under pressure were performed by trained personnel, in a specific secured high pressure laboratory cabin, equipped with detectors.

*1,3,3-Trimethyl-2-(3-methylenepent-4-en-1-yl)cyclohex-1-ene* **6**. NaH (55% in min. oil, 137 mg, 3.13 mmol) was added to a soln. of $Ph_3PCH_3Br$ (1306 mg, 3.66 mmol) in DMSO (5 ml). After 0.5 h at 20°C, then 0.5 h at 50°C, the reaction mixture was cooled to 20°C and a soln. of **23e** (220 mg, 1.045 mmol) in THF (5 ml) was added. After 18h at 20°C, the reaction mixture was poured onto $H_2O$ and extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$ (2 x 10 ml), dried ($Na_2SO_4$) and concentrated in vacuo. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) afforded **6** in 15% yield. Alternatively, a soln. of **27** (12 mg, 0.045 mmol) in pyridine (3 ml was heated at 150°C for 5 h. The cold reaction mixture was poured onto $H_2O$, and extracted with $Et_2O$ (3 x 10 ml). The org phase was washed with $H_2O$ (2 x 5 ml), dried ($Na_2SO_4$), concentrated, then purified by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) to afford **6** in 57% yield. Rf = 0.92 (cyclohexane/AcOEt 95:5). IR: 2952, 2923, 2853, 1594, 1457, 1376, 1359, 989, 901, 890. $^1$H-NMR: 6.40 (*dd*, *J* = 11.6, 18.0, 1H); 5.29 (*d*, *J* = 17.4, 1H); 5.07 (*d*, *J* = 10.3, 1H); 5.03 (*d*, *J* = 8.4, 2H); 2.27-2.23 (*m*, 2H); 2.18-2.15 (*m*, 2H); 1.93 (*t*, *J* = 6.4, 2H); 1.63 (*s*, 3H); 1.61-1.57 (*m*, 2H); 1.45-1.43 (m, 2H); 1.02 (*s*, 6H). $^{13}$C-NMR: 147.4 (*s*); 139.2 (*d*); 137.1 (*s*); 127.4 (*s*); 115.1 (*t*); 113.1 (*t*); 39.9 (*t*); 35.0 (*s*); 32.8 (*t*); 31.7 (t); 28.6 (2*q*); 27.8 (t); 20.0 (*q*); 19.6 (*t*). MS: 204 (13, $M^{+\cdot}$), 189 (30), 175 (10), 161 (14), 148 (16), 137 (32), 133 (34), 123 (30), 121 (25), 119 (30), 111 (21), 109 (21), 107 (33), 105 (23), 95 (100), 93 (38), 91 (32), 81 (63), 79 (34), 77 (23), 69 (30), 67 (25), 65 (11), 55 (22), 53 (15), 41 (37).

*8,8-Dimethyl-3,4,5,6,7,8-hexahydro-1H-isochromene* **8**. $BF_3{\cdot}OEt_2$ (0.49 g, 0.44 ml, 3.38 mmol) was added dropwise to a soln. of **7** (5.62 g, 33.7 mmol) in $CH_2Cl_2$ (100 ml) at 20°C. After 96 h at 20°C the reaction mixture was poured onto sat. aq. $NaHCO_3$ (100 ml). The aq. phase was extracted with $Et_2O$ (3 x 50 ml), and the combined org. phase was washed with $H_2O$ (50 ml), brine (50 ml), then dried ($Na_2SO_4$) and concentrated in vacuo. The residual oil was purified by

CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 95:5) to afford pure **8** in 47% yield. Alternatively, a mixture of δ-pyronene **3** (30g, 220 mmol), paraformaldehyde (7.27g, 242 mmol) and AcOH (56.9g, 947 mmol) was heated at 130°C for 5 h. After 85% conversion the cold reaction mixture was poured onto $H_2O$/ice (100 ml), then extracted with $Et_2O$ (3 x 100 ml). The org. phase was carefully washed with sat. aq. $NaHCO_3$, then with $H_2O$, and brine to neutrality. The org. phase was dried ($Na_2SO_4$), and concentrated in vacuo. Purification of a 9:1 mixture of **8**/**16** by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 95:5) afforded **8** in 38% yield. IR: 2956, 2928, 2903, 2867, 2846, 2830, 1742, 1457, 1433, 1382, 1361, 1238, 1161, 1130, 1097, 1038, 1024, 988, 935, 890, 817, 696. $^1$H-NMR: 4.08 (*quint*, *J* = 2.4, 2H); 3.74 (*t*, *J* = 5.7, 2H); 1.98-1.95 (*m*, 2H); 1.89-1.86 (*m*, 2H); 1.66-1.62 (*m*, 2H); 1.46-1.44 (*m*, 2H); 0.99 (*s*, 6H). $^{13}$C-NMR: 134.1 (*s*); 125.1 (*s*); 64.9 (*t*); 64.8 (*t*); 39.6 (*t*); 32.3 (*s*); 30.5 (*t*); 29.9 (*t*); 27.5 (2*q*); 19.1 (*t*). MS: 166 (30, $M^{+\cdot}$), 151 (100), 123 (12), 121 (23), 109 (33), 96 (28), 93 (26), 91 (15), 81 (10), 79 (21), 77 (12), 67 (10), 41 (11). Woody, camphoraceous, terpenic, dusty.

*2-(2,3,3-Trimethylcyclohex-1-en-1-yl)ethan-1-ol* **9**. Li (15.1 mg, 2.18 mmol) was added portionwise to a soln. of **8** (330 mg, 1.98 mmol) in $H_2NCH_2CH_2NH_2$ (1.35 ml). Two supplementary portion of Li were added after 24 and 48h. After a total of 67h the reaction mixture was poured into satd. aq. $NH_4Cl$ (10 ml) and extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$, dried ($Na_2SO_4$), and concentrated in vacuo. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 8:2) afforded pure **9** in 69% yield. IR: 3323, 2955, 2926, 2907, 2865, 1456, 1384, 1373, 1359, 1204, 1084, 1039, 1023, 616. $^1$H-NMR: 3.63 (br*dt*, *J* = 4.0, 6.5, 2H); 2.28 (*t*, *J* = 6.5, 2H); 1.95 (*tq*, *J* = 1.5, 6.2, 2H); 1.63 (*t*, *J* = 1.5, 3H); 1.60-1.56 (*m*, 2H); 1.45-1.42 (*m*, 2H); 1.40 (br*t*, *J* = 4.0, 1OH); 1.00 (*s*, 6H). $^{13}$C-NMR: 136.9 (*s*); 125.6 (*s*); 61.0 (*t*); 39.5 (*t*); 37.2 (*t*); 34.7 (*s*); 30.7 (*t*); 28.2 (2*q*); 19.5 (*t*); 13.4 (*q*). MS: 168 (56, $M^{+\cdot}$), 153 (100), 135 (30), 123 (73), 109 (86), 107 (63), 105 (14), 95 (30), 93 (48), 91 (36), 81 (48), 79 (40), 77 (21), 69 (18), 67 (26), 55 (23), 43 (19), 41 (29). Woody, cedar, phenolic, pyrogenous.

*7,7,7a-Trimethyloctahydrobenzofuran* **10**. $MeSO_3H$ (151 mg, 1.57 mmol) was added dropwise to a soln. of **9** (220 mg, 1.307 mmol) in $CH_2Cl_2$ (15 ml) at 20°C. After 15 min. the reaction mixture was poured into sat. aq. $NaHCO_3$. After separation and extraction of the aq. phase with $Et_2O$ (3 x 10 ml), the org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), concentrated, to afford quantitatively a 87:13 *trans*-/*cis*-**10** mixture. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1)

afforded *trans*-**10** (64% yield), and *cis*-**10** (1.4% yield). *Trans*-stereoisomer Rf = 0.23 (99:1 cyclohexane/AcOEt). IR: 2952, 2926, 2872, 1477, 1459, 1451, 1438, 1386, 1363, 1171, 1148, 1126, 1096, 1072, 1035, 1016, 1004, 985, 942, 918, 888, 864, 735. $^{1}$H-NMR: 3.93 (*q*, *J* = 8.3, 1H); 3.87 (*dt*, *J* = 2.8, 9.2, 1H); 2.24-2.18 (*m*, 1H); 1.88 (*dt*, *J* = 6.1, 12.2, 1H); 1.59 (*dt*, *J* = 4.4, 12.2, 1H); 1.56-1.52 (*m*, 1H); 1.50-1.39 (*m*, 3H); 1.13-1.08 (*m*, 2H); 1.02 (*s*, 3H); 0.99 (*s*, 3H); 0.94 (*s*, 3H). $^{13}$C-NMR: 85.9 (*s*); 63.9 (*t*); 40.3 (*d*); 36.8 (*t*); 35.6 (*s*); 32.4 (*t*); 30.0 (*t*); 25.7 (2*q*); 20.6 (*t*); 19.3 (*q*). MS: 168 (12 $M^{+\cdot}$), 153 (10), 97 (100), 95 (20), 84 (10), 55 (9), 43 (22), 41 (11). *Cis*-stereoisomer Rf = 0.30 (99:1 cyclohexane/AcOEt).$^{1}$H-NMR: 3.82 (*dt*, *J* = 2.0, 9.1, 1H); 3.74 (*q*, *J* = 8.1, 1H); 1.94-1.88 (*m*, 1H); 1.86-1.81 (*m*, 1H); 1.76-1.66 (*m*, 2H); 1.59-1.53 (*m*, 1H); 1.51-1.42 (*m*, 1H); 1.39 (*dt*, *J* = 4.6, 13.7, 1H); 1.31-1.23 (*m*, 1H); 1.17-1.12 (*m*, 1H); 1.01 (*s*, 3H); 0.98 (*s*, 3H); 0.97 (*s*, 3H). $^{13}$C-NMR: 84.7 (*s*); 64.4 (*t*); 41.1 (*d*); 37.9 (*s*); 37.6 (*t*); 29.7 (*t*); 28.6 (*t*); 26.1 (*q*); 23.0 (*t*); 20.4 (*q*); 15.1 (*q*). MS: 168 (9, $M^{+\cdot}$), 153 (7), 97 (100), 95 (18), 84 (11), 55 (10), 43 (27) ; 41 (13), 28 (30). Camphoraceous, sulfury, blackcurrant.

*(*E*)-4-(4,8-Dimethylnona-3,7-dien-1-yl)-3,6-dihydro-2H-pyran* **11**. A mixture of **2** (40g, 196 mmol), paraformaldehyde (12.94 g, 430 mmol) and AcOH (50.5g, 842 mmol) was heated at 130°C for 52h. The cold reaction mixture was poured into $H_2O$/ice (200 ml) and extracted with $Et_2O$ (3 x 100 ml). The org. phase was carefully washed with sat. aq. $NaHCO_3$, and $H_2O$, and brine, then dried ($Na_2SO_4$), and concentrated in vacuo. Two successive purifications by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 95:5) afforded **11** in 15% yield.[33]) IR: 2964, 2919, 2850, 1742, 1673, 1646, 1594, 1448, 1382, 1376, 1233, 1128, 1034, 990, 971, 892, 849. $^{1}$H-NMR: 5.41-5.40 (*m*, 1H); 5.13-5.08 (*m*, 2H); 4.12-4.10 (*m*, 2H); 3.78 (*t*, *J* = 5.7, 2H); 2.12 (*q*, *J* = 7.1, 2H); 2.07-1.97 (*m*, 8H); 1.68 (*s*, 3H); 1.60 (*s*, 6H). $^{13}$C-NMR: 135.6 (*s*); 135.4 (*s*); 131.3 (*s*); 124.3 (*d*); 123.8 (*d*); 119.6 (*d*); 65.5 (*t*); 64.4 (*t*); 39.7 (*t*); 37.1 (*t*); 28.6 (*t*); 26.7 (*t*); 25.8 (*t*); 25.7 (*q*); 17.7 (*q*); 16.0 (*q*). MS: 234 (1, $M^{+\cdot}$), 136 (13), 121 (9), 109 (13), 96 (33), 93 (15), 83 (11), 81 (30), 79 (10), 69 (100), 67 (14), 55 (10), 53 (9), 41 (43). Metallic, very weak.

*(6a*RS*,10a*RS*)-7,7,10a-Trimethyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-1H-benzo[h]isochromene* β-**12**. $BF_3{\cdot}OEt_2$ (0.294 g, 2.03 mmol), was added dropwise to a soln. of **11** (4.75 g, 20.27 mmol)

[33]) An enriched intermediate fraction allowed, after preparative GC purification, to isolate a minor side product (6% of the crude reaction mixture) corresponding to the acetate of the *Prins* reaction (see the Supplementary Material for analytical data).

in $CH_2Cl_2$ (100 ml) at 20°C. After 72 h the reaction mixture was poured into sat. aq. $NaHCO_3$ (100 ml). After separation, the aq. phase was washed with $Et_2O$ (3 x 100 ml). The org. phase was washed with $H_2O$, brine, then dried ($Na_2SO_4$), and concentrated in vacuo. Two successive purifications by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) afforded β-**12** in 14% yield. Alternatively, a mixture of **4** (200 mg, 0.979 mmol), paraformaldehyde (32.3 mg, 1.077 mmol) and AcOH (588 mg, 9.79 mmol) was heated at 130°C for 24 h. The cold reaction mixture was poured into $H_2O$/ice and extracted with $Et_2O$ (3 x 10 ml). The org. phase was carefully washed with sat. aq. $NaHCO_3$, then washed with $H_2O$, and brine, dried ($Na_2SO_4$), and concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) afforded β-**12** in 27% yield. IR: 2923, 2865, 2845, 1742, 1458, 1386, 1375, 1364, 1236, 1161, 1134, 1120, 1093, 1070, 1027, 987, 961, 941, 914, 885, 854, 817, 689. $^1$H-NMR: 4.13-4.07 (*m*, 1H); 4.01 (*dquint*, *J* = 2.8, 15.7, 1H); 3.88 (*ddd*, *J* = 2.8, 6.1, 8.5, 1H); 3.53 (*ddd*, *J* = 4.0, 10.0, 10.8, 1H); 2.15-1.86 (*m*, 4H); 1.76-1.39 (*m*, 6H); 1.20 (*dd*, *J* = 2.1, 12.4, 1H); 1.13 (*ddd*, *J* = 4.0, 13.7, 18.2, 1H); 1.04 (*s*, 3H); 0.99 (*t*, *J* = 4.0, 1H); 0.89 (*s*, 3H); 0.85 (*s*, 3H). $^{13}$C-NMR: 137.2 (*s*); 123.9 (*s*); 64.6 (*t*); 64.3 (*t*); 51.5 (*d*); 41.7 (*t*); 36.6 (*s*); 35.8 (*t*); 33.2 (*q*); 33.1 (*s*); 31.7 (*t*); 29.6 (*t*); 21.6 (*q*); 19.7 (*q*); 18.7 (*t*); 18.6 (*t*). MS: 234 (24, $M^{+\cdot}$), 219 (33), 149 (10), 123 (10), 119 (10), 109 (22), 105 (10), 96 (100), 91 (14), 69 (11), 41 (10). Woody, amber-like, weak.

*(6a*RS,*10a*RS,*10b*RS*)-7,7,10a-Trimethyl-3,4,6,6a,7,8,9,10,10a,10b-decahydro-1H-benzo[h]isochromene* α-**12**. Isolated in analytical amounts during the purification of β-**12**. IR: 2922, 2894, 2865, 2844, 1742, 1459, 1441, 1387. 1375, 1364, 1237, 1160, 1134, 1119, 1105, 1093, 1070, 1027, 987, 961, 914, 884, 855, 828, 815, 688. $^1$H-NMR: 5.46 (*dd*, *J* = 2.1, 5.4, 1H); 3.91 (*dd*, *J* = 6.1, 10.9, 1H); 3.74 (*dd*, *J* = 1.3, 5.8, 1H); 3.23 (*ddd*, *J* = 2.7, 11.1, 13.3, 1H); 3.18 (*t*, *J* = 11.1, 1H); 2.37-2.29 (*m*, 1H); 2.16-2.10 (*m*, 2H); 2.08-1.96 (*m*, 2H); 1.89-1.40 (*m*, 3H); 1.22-1.10 (*m*, 4H); 0.91 (*s*, 3H); 0.88 (*s*, 3H); 0.83 (*s*, 3H). $^{13}$C-NMR: 133.3 (*s*); 121.1 (*d*); 68.5 (*t*); 68.4 (*t*); 51.5 (*d*); 49.7 (*d*); 42.1 (*t*); 39.8 (*t*); 34.5 (*s*); 34.1 (*t*); 33.6 (*q*); 32.8 (*s*); 23.2 (*t*); 22.3 (*q*); 18.6 (*t*); 15.2 (*q*). MS: 234 (33, $M^{+\cdot}$), 219 (22), 149 (9), 124 (42), 109 (100), 105 (15), 96 (14), 91 (17), 81 (12), 79 (10), 69 (10), 55 (9), 41 (12).

*(4a*RS,*6a*RS,*10a*RS,*10b*RS*)-7,7,10a-Trimethyldodecahydro-1H-benzo[h]isochromene* **13**. A suspension of β-**12** (47 mg, 0.201 mmol) and 10% Pd/C (21.34 mg, 0.02 mmol) in EtOH (15 ml)

was hydrogenated under 1 atm. of $H_2$ for 17 h at 20°C. The reaction mixture was filtered over Celite®, concentrated, and purified by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) to afford **13** in 88% yield as a 77:23 mixture of *trans/cis* stereoisomers. A single fraction reaching 90% purity for the major *trans*-diastereoisomer was used for analyses. IR: 2918, 2865, 2843, 1462, 1445, 1387, 1364, 1136, 1094, 999, 983, 954, 865, 657. $^1$H-NMR: 3.95 (*dd*, *J* = 4.2, 10.8, 1H); 3.88 (*dd*, *J* = 4.2, 10.8, 1H); 3.29 (*ddd*, *J* = 2.3, 11.1, 12.8, 1H); 3.12 (*t*, *J* = 11.1, 1H); 1.75 (*dq*, *J* = 3.0, 12.4, 1H); 1.61-1.57 (*m*, 2H); 1.55-1.48 (*m*, 2H); 1.43-1.37 (*m*, 2H); 1.34-1.23 (*m*, 2H); 1.17 (*dt*, *J* = 4.2, 13.4, 1H); 1.05-0.98 (*m*, 4H); 0.91 (*dd*, *J* = 2.3, 12.4, 1H); 0.86 (*s*, 3H); 0.85 (*s*, 3H); 0.82 (*s*, 3H). $^{13}$C-NMR: 68.2 (*t*); 68.1 (*t*); 55.2 (*d*); 54.4 (*d*); 42.0 (*t*); 38.8 (*t*); 35.9 (*s*); 34.8 (*t*); 34.5 (*d*); 34.5 (*t*); 33.5 (*q*); 33.2 (*s*); 21.9 (*q*); 21.4 (*t*); 18.7 (*t*); 15.0 (*q*). MS: 236 (96, $M^{+\cdot}$), 221 (100), 203 (11), 177 (18), 151 (41), 135 (16), 123 (85), 121 (17), 109 (45), 107 (22), 105 (11), 96 (46), 95 (36), 93 (25), 91 (17), 83 (40), 81 (31), 79 (23), 77 (10), 69 (27), 67 (26), 55 (28), 41 (29). The minor (4a*SR*,6a*RS*,10a*RS*,10b*RS*)-7,7,10a-trimethyldodecahydro-1H-benzo[h]isochromene *cis*-stereoisomer exhibits the following analytical data, deduced from the mixture. $^1$H-NMR: 4.16 (*d*, *J* = 12.0, 1H); 3.98 (*dd*, *J* = 4.9, 12.0, 1H); 3.36 (*ddd*, *J* = 3.2, 12.0, 15.2, 1H); 3.32 (*dd*, *J* = 4.2, 12.0, 1H); 2.06-2.04 (*m*, 1H); 1.98 (*dq*, *J* = 5.0, 13.0, 1H); 1.92-1.86 (*m*, 1H); 1.69-1.65 (*m*, 1H); 1.61-1.57 (*m*, 1H); 1.55-1.48 (*m*, 1H); 1.43-1.37 (*m*, 3H); 1.34-1.23 (*m*, 2H); 1.17 (*dt*, *J* = 4.2, 13.4, 1H); 1.05-0.98 (*m*, 4H); 0.91 (*dd*, *J* = 2.3, 12.4, 1H); 1.18 (*s*, 3H); 0.86 (*s*, 3H); 0.83 (*s*, 3H).. $^{13}$C-NMR: 68.3 (*t*); 68.2 (*t*); 55.7 (*d*); 49.3 (*d*); 42.2 (*t*); 40.3 (*t*); 38.0 (*s*); 34.1 (*d*); 33.7 (*t*); 33.7 (*q*); 33.2 (*s*); 29.8 (*t*); 21.7 (*q*); 19.0 (*q*); 18.4 (*t*); 18.3 (*t*). MS: 236 (62, $M^{+\cdot}$), 221 (37), 203 (17), 177 (17), 151 (12), 135 (14), 123 (100), 121 (24), 109 (37), 107 (19), 105 (100), 96 (25), 95 (35), 93 (21), 91 (14), 83 (53), 81 (31), 79 (20), 69 (23), 67 (21), 55 (25), 41 (23). Woody, amber-like, weak.

*2-((4a*RS*,8a*RS*)-1,5,5,8a-Tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)ethan-1-ol*

**14**. Li (23 mg, 3.35 mmol) was added to a soln. of β-**12** (392 mg, 1.676 mmol) in $MeNH_3$ (2M in THF, 8.38 ml, 16.76 mmol) at -78°C. After 18 h, solid $NH_4Cl$ (100 mg) was added to the blue reaction mixture, followed by $Et_2O$ (10 ml), and $H_2O$ (5 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), and concentrated in vacuo. Purification by CC/$SiO_2$ (99:1 to 8:2) afforded **14** in 59% yield. IR: 3323, 2924, 2865, 2850, 1457, 1449, 1379, 1373, 1366, 1083, 1040, 972, 862. $^1$H-NMR: 3.62 (*t*, *J* = 7.0, 2H); 2.30-2.20 (*m*, 2H); 2.06-2.03 (*m*, 2H); 1.80 (*dt*, *J* = 3.4, 12.5, 1H); 1.74-1.56 (*m*, 3H); 1.58 (*t*, *J* = 2.0, 3H); 1.50-1.38 (*m*, 3H); 1.14 (*dt*, *J* = 3.5,

13.2, 1H); 1.10 (*dd*, *J* = 2.0, 12.8, 1H); 1.06 (*dt*, *J* = 3.5, 13.2, 1H); 0.97 (*s*, 3H); 0.89 (*s*, 3H); 0.84 (*s*, 3H). $^{13}$C-NMR: 140.4 (*s*); 124.3 (*s*); 61.1 (*t*); 51.6 (*d*); 41.6 (*t*); 38.5 (*s*); 37.1 (*t*); 37.0 (*t*); 33.3 (*s*); 33.2 (*q*); 31.8 (*t*); 21.6 (*q*); 19.6 (*q*); 19.1 (*t*); 19.0 (*t*); 12.6 (*q*). MS: 236 (22, $M^{+\cdot}$), 221 (37), 203 (17), 191 (58), 177 (17), 175 (16), 151 (52), 149 (22), 147 (17), 139 (16), 135 (34), 133 (29), 125 (43), 123 (27), 121 (62), 119 (37), 117 (12), 109 (66), 107 (68), 105 (54), 97 (19), 95 (100), 93 (52), 91 (69), 83 (26), 81 (57), 79 (52), 77 (37), 69 (72), 67 (39), 65 (14), 55 (63), 53 (22), 43 (29), 41 (73), 39 (17), 28 (36).

*(5a*RS*,9a*RS*)-6,6,9a,9b-Tetramethyldodecahydronaphtho[1,2-b]furan* **15**. $MeSO_3H$ (44.6 mg, 0.465 mmol) was added dropwise to a soln. of **14** (91.5 mg, 0.387 mmol) in $CH_2Cl_2$ (10 ml) at 20°C. After 75 min. the reaction mixture was poured into sat. aq. $NaHCO_3$. After separation, the aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), then concentrated in vacuo. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 95:5) afforded **15** in 51% yield as a 55:45 mixture of stereoisomer. IR: 2933, 2869, 1459, 1381, 1371, 1257, 1241, 1144, 1107, 1086, 1010, 987, 920, 879, 801. $^1$H-NMR: 3.95 (*q*, *J* = 9.0, 1H); 3.87 (*ddd*, *J* = 2.5, 8.5, 10.2, 1H); 2.21-2.15 (*m*, 1H); 1.91 (*dt*, *J* = 6.9, 11.6, 1H); 1.70-1.65 (*m*, 1H); 1.62-1.57 (*m*, 1H); 1.52-1.50 (*m*, 1H); 1.49-1.41 (*m*, 2H); 1.36-1.32 (*m*, 1H); 1.29-1.19 (*m*, 2H); 1.15-1.08 (*m*, 2H); 1.04-0.92 (*m*, 2H); 0.99 (*s*, 3H); 0.98 (*s*, 3H); 0.88 (*s*, 3H); 0.86 (*s*, 3H). $^{13}$C-NMR: 88.0 (*s*); 64.1 (*t*); 45.4 (*d*); 41.5 (*t*); 39.9 (*s*); 39.9 (*d*); 33.9 (*q*); 33.5 (*t*); 33.1 (*s*); 32.3 (*t*); 30.8 (*t*); 22.5 (*q*); 21.1 (*t*); 18.7 (2*q*); 18.6 (*t*). MS: 236 (21, $M^{+\cdot}$), 97 (100), 84 (8), 43 (8), 41 (6). Animal, naphtaline, ambrinol, buttery, very weak.

*5,5-Dimethyl-3,4,5,6,7,8-Hexahydro-1H-isochromene* **16**. Obtained in analytical amount during the CC/$SiO_2$ purification of a 9:1 mixture of **8**/**16** (see above **8**). IR: 2956, 2928, 2902, 2866, 2846, 2830, 1741, 1458, 1432, 1382, 1360, 1333, 1295, 1267, 1239, 1222, 1161, 1119, 1097, 1023, 995, 988, 953, 935, 891, 864, 817, 695. $^1$H-NMR: 3.89 (brs, 2H); 3.77 (*t*, *J* = 5.7, 2H); 2.06-2.03 (*m*, 2H); 1.75-1.72 (*m*, 2H); 1.67-1.61 (*m*, 2H); 1.49-1.46 (*m*, 2H); 0.98 (*s*, 6H). $^{13}$C-NMR: 133.0 (*s*); 126.3 (*s*); 68.6 (*t*); 65.4 (*t*); 39.1 (*t*); 33.1 (*s*); 27.3 (2*q*); 26.0 (*t*); 23.8 (*t*); 18.8 (*t*). MS: 166 (91, $M^{+\cdot}$), 151 (99), 123 (23), 121 (14), 110 (46), 109 (38), 107 (18), 105 (15), 97 (100), 95 (20), 93 (28), 91 (26), 81 (29), 79 (32), 77 (21), 69 (18), 67 (20), 55 (17), 53 (11), 43 (18), 41 (23), 39 (14). Potato, cellar.

*(Z)-(6-ethylidene-2,2-Dimethylcyclohexyl)methanol* **17**. Li (0.183g, 26.3 mmol) was added portionwise to a soln. of **8** (2.19 g, 13.17 mmol) in $MeNH_2$ (2M in THF, 65.9 ml, 132 mmol) at -78°C. After 2h and persistent blue color, the $MeNH_2$ was allowed to evaporate and solid $NH_4Cl$ (3.0 g) was added. The reaction mixture was partitioned between $Et_2O$ (50 ml) and $H_2O$ (50 ml), and the org. phase was washed with $H_2O$ (50 ml), then brine (50 ml), dried ($Na_2SO_4$), and concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 8:2) afforded **9** in 10% yield, as well as **17** in 10% yield. IR: 3349, 2950, 2925, 2865, 1455, 1383, 1363, 1118, 1032, 973, 933, 907, 819, 624. $^1$H-NMR: 5.62 (*dq*, *J* = 1.5, 6.2, 1H); 3.71 (*dt*, *J* = 5.3, 9.7, 1H); 3.65 (br*t*, *J* = 10.3, 1H); 2.56 (*dd*, *J* = 5.6, 10.9, 1H); 2.38-2.25 (*m*, 1H); 2.12-2.06 (*m*, 1H); 2.03-1.99 (*m*, 1H); 1.70-1.56 (*m*, 1H); 1.62 (*dd*, *J* = 2.0, 6.8, 3H); 1.49 (*tt*, *J* = 3.5, 13.5, 2H); 1.35-1.20 (*m*, 1H); 0.93 (*s*, 3H); 0.90 (*s*, 3H). $^{13}$C-NMR: 137.4 (*s*); 123.0 (*d*); 60.4 (*t*); 48.7 (*d*); 35.2 (*t*); 33.7 (*s*); 31.7 (*t*); 28.8 (*q*); 27.7 (*q*); 23.5 (*t*); 12.8 (*q*). MS: 168 (8, $M^{+\cdot}$), 150 (22), 137 (78), 135 (28), 123 (55), 121 (23), 109 (50), 107 (62), 105 (12), 95 (86), 93 (43), 91 (37), 83 (17), 81 (100), 79 (63), 77 (31); 69 (73), 67 (51), 65 (13), 57 (12), 55 (43), 53 (23), 43 (23), 41 (57), 39 (26), 28 (38). Earthy, camphoraceous.

*4,4,7a-Trimethyloctahydrobenzofuran* **19**. $MeSO_3H$ (28.8 mg, 0.3 mmol) was added to a soln. of **18** (500 mg, 2.98 mmol) in $CH_2Cl_2$ (10 ml). After 4 h at 20°C the reaction mixture was poured into $H_2O$/ice (10 ml), and the aq. phase was extracted with $Et_2O$ (2 x 10 ml). The org. phase was washed with sat. aq $NaHCO_3$, $H_2O$, brine, dried ($Na_2SO_4$), and concentrated. Bulb-to-bulb distillation afforded **19** in 69% yield as a 83:17 *trans/cis* mixture. B.p.: 115°C/ 2 mbar. Further purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 95:5) afforded analytically pure material. *Trans*-stereoisomer IR: 2933, 2867, 1456, 1374, 1256, 1243, 1206, 1157, 1111, 1091, 1077, 1068, 1047, 1006, 956, 949, 937, 855. $^1$H-NMR: 3.88 (*dt*, *J* = 2.7, 8.6, 1H); 3.80 (*q*, *J* = 8.1, 1H); 1.89-1.80 (*m*, 2H); 1.78-1.64 (*m*, 2H); 1.52 (*tt*, *J* = 3.4, 13.4, 1H); 1.49-1.26 (*m*, 3H); 1.14 (*dt*, *J* = 4.5, 13.4, 1H); 1.07 (*s*, 3H); 0.96 (*s*, 3H); 0.85 (*s*, 3H). $^{13}$C-NMR: 79.9 (*s*), 64.0 (*t*); 56.4 (*d*); 41.1 (*t*); 38.7 (*t*); 33.1 (*s*); 32.8 (*q*); 23.6 (*t*); 21.2 (*t*); 20.0 (2*q*). MS: 168 (0, $M^{+\cdot}$), 153 (100), 125 (34), 198 (9), 97 (9), 95 (17), 85 (12), 69 (30), 55 (13), 43 (17), 41 (12). *cis*-Stereoisomer $^1$H-NMR: 3.83-3.79 (*m*, 1H); 3.76 (*dd*, *J* = 8.4, 16.9, 1H); 1.96-1.91 (*m*, 2H); 1.60 (*t*, *J* = 9.4, 1H); 1.56-1.33 (*m*, 5H); 1.32 (*s*, 3H); 1.17 br*dd*, *J* = 3.5, 11, 1H); 1.02 (*s*, 3H); 0.92 (*s*, 3H). $^{13}$C-NMR: 80.8 (*s*); 63.9 (*t*); 54.0 (*d*); 34.5 (*t*); 33.7 (*t*); 32.4 (*s*); 30.4 (*q*); 29.4 (*t*); 28.7 (*q*); 27.1 (*q*);

20.0 (*t*). MS: 168 (2, $M^{+\cdot}$), 153 (50), 125 (100), 95 (9), 84 (9), 69 (16), 55 (10), 43 (23), 41 (12). Chemical, solvent.

*3,4,5,6,7,8-Hexahydro-1H-5,8-methanoisochromene* **20**. A soln. of **5** (224 mg, 1.872 mmol), paraformaldehyde (62 mg, 2.06 mmol) and $SnCl_4$ (24 mg, 0.094 mmol) in $CH_2Cl_2$ (10 ml) was stirred for 72 h at 20°C. The reaction mixture was poured into $H_2O$/ice (5 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with sat. aq. $NaHCO_3$, $H_2O$, brine, dried ($Na_2SO_4$), then concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 95:5) afforded **20** in 22% yield. Rf = 0.44 (cyclohexane/AcOEt 95:5). IR: 2953, 2917, 2867, 2830, 1456, 1447, 1427, 1386, 1299, 1277, 1225, 1147, 1090, 1063, 962, 936, 884, 836, 678. $^1$H-NMR: 4.30 (*dt*, *J* = 2.5, 15.4, 1H); 4.02 (*dt*, *J* = 2.5, 15.4, 1H); 3.73 (*ddd*, *J* = 4.4, 6.6, 11.0, 1H); 3.62 (*dt*, *J* = 5.5, 11.0, 1H); 2.71 (br*s*, 1H); 2.69 (br*s*, 1H); 2.21-2.15 (*m*, 1H); 2.11-2.05 (*m*, 1H); 1.65 (*dd*, *J* = 2.0, 9.0, 2H); 1.35 (*dquint*, *J* = 2.0, 8.0, 1H); 1.09 (*dt*, *J* = 1.6, 8.0, 1H); 1.05 (*dt*, *J* = 2.2, 10.0, 2H). $^{13}$C-NMR: 138.2 (*s*); 137.1 (*s*); 64.6 (*t*); 64.5 (*t*); 46.4 (*t*); 44.9 (*d*); 42.5 (*d*); 26.2 (*t*); 26.0 (*t*); 24.4 (*t*). MS: 150 (40, $M^{+\cdot}$), 122 (48), 121 (31), 109 (21), 105 (18), 92 (68), 91 (100), 79 (27), 77 (25), 65 (15), 51 (10), 41 (9), 39 (16). Woody, dusty, cellar.

*7a-Methyloctahydro-4,7-methanobenzofuran* **22**. $MeSO_3H$ (174 mg, 1.811 mmol) was added to a soln. of **21** (230 mg, 1.509 mmol) in $CH_2Cl_2$ (15 ml) at 20°C. After 30 min. the reaction mixture was poured into sat. aq. $NaHCO_3$ (10 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), then concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) afforded **22** in 48% yield as a 79:21 *endo/exo* mixture. A second CC/$SiO_2$ afforded the pure *endo* stereoisomer in 18% yield. Rf = 0.15 (cyclohexane/AcOEt 99:1). IR: 2953, 2922, 2853, 1459, 1376, 1260, 1070, 886, 802, 722. $^1$H-NMR: 4.02 (*dt*, *J* = 5.0, 8.7, 1H); 3.95 (*q*, *J* = 7.7, 1H); 2.17 (br*t*, *J* = 4.5, 1H); 2.08-2.07 (*m*, 1H); 1.89-1.83 (*m*, 1H); 1.80-1.72 (*m*, 2H); 1.65 (*dquint*, *J* = 1.5, 10, 1H); 1.53-1.48 (*m*, 2H); 1.45 (br*t*, *J* = 1.5, 1H); 1.43 (br*t*, *J* = 1.5, 1H); 1.41-1.36 (*m*, 1H); 1.25 (*s*, 3H). $^{13}$C-NMR: 90.5 (*s*); 71.5 (*t*); 51.5 (*d*); 48.3 (*d*); 41.9 (*t*); 41.2 (*d*); 26.8 (*q*); 26.7 (*t*); 22.2 (*t*); 22.1 (*t*). MS: 152 (1, $M^{+\cdot}$), 137 (10), 123 (15), 97 (8), 84 (100), 79 (8), 67 (12), 43 (33). Odourless.

*5-(2,6,6-Trimethylcyclohex-1-en-1-yl)pent-1-en-3-one* **23e**. A suspension of **24b** (640 mg, 3.06 mmol) and $MnO_2$ (5310 mg, 61.1 mmol) in $CH_2Cl_2$ (30 ml) was stirred for 18h at 20°C. The reaction mixture was filtered over *Celite*®, and concentrated. Purification by CC/$SiO_2$

(cyclohexane/AcOEt 99:1) afforded **23e** in 34% yield. IR: 2927, 2907, 2865, 2829, 1700, 1681, 1616, 1472, 1457, 1399, 1360, 1261, 1203, 1184, 1093, 984, 958, 763. $^{1}$H-NMR: 6.36 (*dd*, *J* = 10.5, 17.6, 1H); 6.22 (*dd*, *J* = 1.4, 17.6, 1H); 5.82 (*dd*, *J* = 1.4, 10.5, 1H); 2.68-2.63 (*m*, 2H); 2.3 (*dd*, *J* = 8.2, 9.1, 2H); 1.91 (*t*, *J* = 5.9, 2H); 1.61-1.54 (*m*, 2H); 1.59 (*s*, 3H); 1.44-1.41 (*m*, 2H); 0.99 (*s*, 6H). $^{13}$C-NMR: 200.8 (*s*); 136.6 (*d*); 136.2 (*s*); 128.0 (*s*); 127.7 (*t*); 40.4 (*t*); 39.8 (*t*); 35.1 (*s*); 32.8 (*t*); 28.5 (2*q*); 22.5 (*t*); 19.8 (*q*); 19.5 (*t*). MS: 206 (2, $M^{+\cdot}$), 188 (18), 173 (20), 136 (27), 123 (27), 121 (100), 119 (22), 109 (10), 107 (23), 95 (28), 93 (65), 91 (24), 81 (29), 79 (32), 77 (19), 69 (12), 67 (14), 55 (60), 41 (25). Odourless.

*5-(2,6,6-Trimethylcyclohex-1-en-1-yl)pent-1-yn-3-one* **23f**. A suspension of **24c** (976 mg, 4.73 mmol) and $MnO_2$ (8230 mg, 95 mmol) in $CH_2Cl_2$ (50 ml) was stirred for 25h at 20°C. The reaction mixture was filtered over *Celite*®, and concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) afforded **23f** in 41% yield. IR: 2928, 2907, 2866, 2830, 2091, 1679, 1472, 1457, 1404, 1381, 1361, 1280, 1262, 1221, 1191, 1175, 1099, 1042, 1018, 998, 752, 688, 641. $^{1}$H-NMR: 3.24 (*s*, 1H); 2.68-2.65 (*m*, 2H); 2.37-2.34 (*m*, 2H); 1.91 (*t*, *J* = 6.5, 2H); 1.59 (*s*, 3H); 1.58-1.55 (*m*, 2H); 1.43-1.41 (*m*, 2H); 0.99 (*s*, 6H). $^{13}$C-NMR: 187.3 (*s*); 135.1 (*s*); 128.6 (*s*); 81.4 (*s*); 78.4 (*d*); 46.2 (*t*); 39.7 (*t*); 35.0 (*s*); 32.7 (*t*); 28.4 (2*q*); 22.3 (*t*); 19.7 (*q*); 19.4 (*t*). MS : 204 (7, $M^{+\cdot}$), 189 (26), 171 (42), 161 (17), 156 (12), 147 (23), 143 (14), 136 (27), 133 (21), 131 (11), 129 (10), 123 (40), 121 (100), 119 (42), 109 (11), 107 (26), 105 (40), 95 (20), 93 (51), 91 (45), 81 (30), 79 (38), 77 (26), 69 (11), 67 (16), 65 (10), 55 (22), 53 (37), 41 (26). Ionone-like, weak.

*5-(2,6,6-Trimethylcyclohex-1-en-1-yl)pent-1-en-3-ol* **24b**. Freshly prepared vinylMgBr (1M/THF, 2.78 ml, 2.78 mmol) was added dropwise at 0°C to a soln. of **23d** (478 mg, 2.65 mmol) and $LaCl_3{\cdot}2LiCl$ (0.6M/THF, 0.883 ml, 0.53 mmol) in THF (20 ml). After 0.5h, the reaction mixture was poured into sat. aq. $NH_4Cl$ (10 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with brine, dried ($Na_2SO_4$), then concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 9:1) afforded **24b** in 42% yield besides **24a**. Alternatively, a soln. of **24c** (1.3g, 6.3 mmol) in THF (30 ml) was added dropwise to a suspension of $LiAlH_4$ (0.239 g, 6.3 mmol) in THF (20 ml) at 0°C. After 8d at 20°C, 10% aq. NaOH (15 ml) was added. The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), then concentrated. Purification by CC/$SiO_2$+3%

$AgNO_3$ (cyclohexane/AcOEt 99:1) afforded **24b** in 49% yield. IR: 3311, 2926, 2865, 2829, 1472, 1457, 1431, 1381, 1360, 1277, 1203, 1169, 1116, 1051, 989, 919, 734, 647, 622. $^1$H-NMR: 5.90 (*ddd*, *J* = 5.3, 10.5, 17.5, 1H); 5.24 (*dt*, *J* = 1.2, 17.5, 1H); 5.13 (*dt*, *J* = 1.2, 10.5, 1H); 4.10 (br*q*, *J* = 5.3, 1H); 2.22-2.05 (*m*, 2H); 2.00-1.92 (*m*, 1H); 1.90 (*t*, *J* = 6.5, 2H); 1.63-1.54 (*m*, 3H); 1.59 (*s*, 3H); 1.43-1.40 (*m*, 2H); 1.01 (*d*, *J* = 5.3, 1OH); 0.99 (*s*, 3H); 0.98 (*s*, 3H). $^{13}$C-NMR: 141.1 (*d*); 136.7 (*s*); 127.2 (*s*); 114.7 (*t*); 73.9 (*d*); 39.8 (*t*); 37.5 (*t*); 35.0 (*s*); 32.7 (*t*); 28.6 (2*q*); 24.3 (*t*); 19.8 (*q*); 19.5 (*t*). MS: 208 ($M^{+\cdot}$), 175 (20), 136 (13), 133 (12), 125 (30), 123 (100), 121 (39), 119 (21), 109 (22), 107 (27), 105 (21), 97 (12), 95 (52), 93 (38), 91 (31), 81 (48), 79 (31), 77 (18), 69 (26), 67 (25), 57 (19), 55 (25), 53 (11), 41 (23). Woody, weak.

*5-(2,6,6-Trimethylcyclohex-1-en-1-yl)pent-1-yn-3-ol* **24c**. EthynylMgBr (0.5M/THF, 10.6 ml, 5.3 mmol) was added dropwise to a soln. of **23d** (956 mg, 5.3 mmol) in $Et_2O$ (20 ml) at 0°C. After 18h at 20°C, the reaction mixture was poured into sat. aq. $NH_4Cl$ (10 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), then concentrated in vacuo. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 9:1) afforded **24c** in 94% yield. IR: 3309, 2954, 2926, 2906, 2865, 2829, 1473, 1456, 1440, 1381, 1360, 1203, 1059, 1041, 1014, 997, 973, 937, 889, 652, 624. $^1$H-NMR: 4.37 (*dq*, *J* = 2.1, 6.5, 1H); 2.50 (*d*, *J* = 2.1, 1H); 2.21-2.11 (*m*, 2H); 2.00 (*d*, *J* = 5.3, 1H); 1.90 (*t*, *J* = 6.5, 2H); 1.81-1.77 (*m*, 2H); 1.61 (*s*, 3H); 1.59-1.55 (*m*, 2H); 1.43 (*s*, 1OH); 1.42-1.40 (*m*, 1H); 1.00 (*s*, 6H). $^{13}$C-NMR: 136.1 (*s*); 127.6 (*s*); 84.9 (*s*); 73.0 (*d*); 62.6 (*d*); 39.8 (*t*); 37.9 (*t*); 35.0 (*s*); 32.8 (*t*); 28.6 (2*q*); 23.9 (*t*); 19.8 (*q*); 19.5 (*t*). MS: 206 (1, $M^{+\cdot}$), 191 (7), 173 (11), 150 (13), 145 (13), 135 (17), 133 (10), 131 (13), 123 (100), 121 (23), 119 (14), 117 (13), 109 (17), 107 (22), 105 (20), 95 (35), 93 (28), 91 (31), 81 (40), 79 (27), 77 (18), 69 (16), 67 (18), 55 (26), 53 (11), 41 (22).

*(*E*)-3-(4,8-Dimethylnona-3,7-dien-1-yl)-2,5-dihydrothiophene 1,1-dioxide* **26**. Freshly distilled farnesene **2** (1.0 g, 4.84 mmol) was added to a soln. of DABSO (1.285 g, 5.09 mmol) in MeCN (6 ml) at 20°C. After 15 min., $BF_3{\cdot}OEt_2$ (2.105 g, 1.88 ml, 14.53 mmol) was added at 0°C. After 15 min. at 20°C and 19h at 50°C, the solvent was concentrated and the residue was purified by CC/$SiO_2$ (cyclohexane/AcOEt 9:1) to afford a 2:1 mixture of **26**/**27** in 36% yield. A second purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) afforded pure **26** in 13% yield, as well as pure **27** in 2% yield, besides a mixture of both in 13% yield. Rf = 0.28 (cyclohexane/AcOEt 85 :15). IR: 2964, 2921, 2854, 1667, 1646, 1444, 1403, 1376, 1309, 1232, 1140, 1119, 1026,

984, 908, 781, 706, 630, 608. $^{1}$H-NMR: 568 (brs, 1H); 5.08 (*t*, *J* = 6.3, 2H); 3.79 (brs, 2H); 3.68 (brs, 2H); 2.21 (*dt*, *J* = 6.3, 7.3, 2H); 2.18 (*quint*, *J* = 7.3, 2H); 2.06 (*quint*, *J* = 7.3, 2H); 1.99 (*t*, *J* = 7.3, 2H); 1.68 (*s*, 3H); 1.61 (*s*, 3H); 1.60 (*s*, 3H). $^{13}$C-NMR: 138.5 (*s*); 136.9 (*s*); 131.6 (*s*); 124.1 (*d*); 122.3 (*d*); 117.1 (*d*); 57.9 (*t*); 57.0 (*t*); 39.6 (*t*); 33.1 (*t*); 26.6 (*t*); 25.7 (*q*); 25.4 (*t*); 17.7 (*q*); 16.1 (*q*). MS: 268 (0, $M^{+\cdot}$), 204 (7), 161 (22), 133 (38), 120 (27), 107 (14), 105 (11), 93 (70), 91 (24), 81 (22), 79 (27), 77 (15), 69 (100), 67 (26), 55 (16), 53 (14), 41 (54).

*3-(2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethyl)-2,5-dihydrothiophene 1,1-dioxide* **27**. See above for analytically pure material. Alternatively, $BF_3{\cdot}OEt_2$ (181 mg, 0.162 ml, 1.252 mmol) was added dropwise to a soln. of a 2:1 mixture of **26**/**27** (168 mg, 0.626 mmol) in MeCN (6 ml) at 0°C. After 1.5 h at 0°C, the reaction mixture was poured into sat. aq. $NaHCO_3$ (15 ml) and extracted with $Et_2O$ (3 x 15 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), and concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) afforded a 2:1 mixture of **27**/**28** in 66% yield. Alternatively, $BF_3{\cdot}OEt_2$ (180 mg, 0.161 ml, 1.244 mmol) was added dropwise to a soln. of **26** (167 mg, 0.622 mmol) in MeCN (6 ml) at 0°C. After 1 h at 0°C, the reaction mixture was poured into sat. aq. $NaHCO_3$ (15 ml) and extracted with $Et_2O$ (3 x 15 ml). The org. phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), and concentrated. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) afforded a 4:1 mixture of **27**/**26** in 68% yield. Rf = 0.32 (cyclohexane/AcOEt 85 :15). IR: 2925, 2865, 1472, 1456, 1440, 1403, 1380, 1360, 1310, 1245, 1232, 1140, 1119, 908, 782, 707, 612. $^{1}$H-NMR: 5.71 (*s*, 1H); 3.81 (*s*, 2H); 3.72 (*s*, 2H); 2.33-2.18 (*m*, 2H); 2.16-2.12 (*m*, 2H); 1.91 (*t*, *J* = 6.9, 2H); 1.70-1.66 (*m*, 1H); 1.61-1.55 (*m*, 1H); 1.58 (*s*, 3H); 1.43-1.41 (*m*, 2H); 0.98 (*s*, 6H). $^{13}$C-NMR: 139.0 (*s*); 135.7 (*s*); 128.3 (*s*); 116.3 (*d*); 57.8 (*t*); 57.1 (*t*); 39.6 (*t*); 34.9 (*s*); 33.5 (*t*); 32.7 (*t*); 28.5 (2*q*); 25.9 (*t*); 19.8 (*q*); 19.4 (*t*). MS: 268 (0, $M^{+\cdot}$), 204 (12), 189 (28), 148 (12); 137 (28), 133 (33), 123 (28), 121 (21), 119 (27), 111 (19), 109 (19), 107 (31), 105 (21), 95 (100), 93 (40), 91 (36), 81 (56), 79 (36), 77 (21), 69 (28), 67 (23), 65 (11), 55 (21), 41 (34).

*(5aRS,9aRS)-6,6,9a-Trimethyl-1,3,4,5,5a,6,7,8,9,9a-decahydronaphtho[1,2-c]thiophene 2,2-dioxide* **28**. $BF_3{\cdot}OEt_2$ (107 mg, 0.095 ml, 0.738 mmol) was added dropwise to a soln. of **26** (66 mg, 0.246 mmol) and AcOH (29.5 mg, 0.492 mmol) in $CH_2Cl_2$ (10 ml) at 0°C. After 30 min. at 20°C and 9h at 30°C, the cold reaction mixture was poured onto sat. aq. $NaHCO_3$ (10 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with brine, dried

($Na_2SO_4$), and concentrated in vacuo. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) afforded **28** in 47% yield. Rf = 0.18 (cyclohexane/AcOEt 9:1). IR: 2923, 1866, 2847, 1457, 1442, 1388, 1366, 1304, 1248, 1235, 1217, 1142, 1108, 1020, 972, 894, 803, 784, 699, 633. $^1$H-NMR: 3.74-3.71 (*m*, 4H); 2.13-2.10 (*m*, 1H); 1.83-1.79 (*m*, 1H); 1.66-1.44 (*m*, 6H); 1.26-1.18 (*m*, 2H); 1.15 (*dd*, *J* = 3.8, 10.4, 1H); 1.05 (*s*, 3H); 0.92 (*s*, 3H); 0.87 (*s*, 3H). $^{13}$C-NMR: 138.8 (*s*); 126.2 (*s*); 60.0 (*t*); 56.5 (*t*); 51.1 (*d*); 41.4 (*t*); 37.1 (*t*); 36.7 (*s*); 33.2 (*s*); 33.0 (*q*); 27.9 (*t*); 21.4 (*q*); 19.3 (*q*); 18.5 (*t*); 18.1 (*t*). MS: 268 (3, $M^{+\cdot}$), 124 (77), 109 (100), 105 (12), 93 (10), 91 (18), 81 (10), 79 (12), 69 (10), 41 (11).

*(2*E*,6*E*)*-N-*ethyl*-N*,3,7,11-tetramethyldodeca-2,6,10-trien-1-amine* **29e**. (*E*)-β-Farnesene was treated with ethylmethylamine and *n*BuLi in THF according to the procedure described for **29b** in [77] to afford **29e** in 63% yield. IR: 2967, 2924, 2855, 2786, 1668, 1447, 1380, 1326, 1296, 1268, 1221, 1196, 1170, 1132, 1106, 1060, 1038, 981, 962, 939, 886, 830, 803. $^1$H-NMR: 5.27 (br*t*, *J* = 6.8, 1H); 5.13-5.08 (*m*, 2H); 2.96 (*d*, *J* = 6.05, 2H); 2.41 (*q*, *J* = 10.2, 2H); 2.20 (*s*, 3H); 2.13-2.10 (*m*, 2H); 2.08-2.02 (*m*, 4H); 1.98-1.95 (*m*, 2H); 1.68 (*s*, 3H); 1.64 (*s*, 3H); 1.60 (*s*, 6H); 1.08 (*t*, *J* = 7.0, 3H). $^{13}$C-NMR: 138.3 (*s*); 135.2 (*s*); 131.3 (*s*); 124.4 (*d*); 124.0 (*d*); 121.5 (*d*); 54.9 (*t*); 51.1 (*t*); 41.4 (*q*); 39.8 (*t*); 39.7 (*t*); 26.8 (*t*); 26.4 (*t*); 25.7 (*q*); 17.7 (*q*); 16.4 (*q*); 16.0 (*q*); 12.6 (*q*). MS: 263 (7, $M^{+\cdot}$), 194 (46), 126 (24), 112 (100), 81 (11), 72 (29), 69 (23), 58 (10), 44 (10), 41 (16). For the analytical data of a regioisomer side product, see the Supplementary Material.

*1-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)pyrrolidine* **29f**. (*E*)-β-Farnesene was treated with pyrrolidine and *n*BuLi in THF according to the procedure described for **29b** in [77] to afford **29f** in 62% yield. IR: 2964, 2924, 2874, 2855, 2777, 1669, 1444, 1376, 1347, 1312, 1291, 1264, 1232, 1202, 1138, 1108, 1032, 984, 962, 883, 834, 741. $^1$H-NMR: 5.33 (br*t*, *J* = 6.7, 1H); 5.13-5.08 (*m*, 2H); 3.09 (*d*, *J* = 7.0, 2H); 2.51 (br*t*, *J* = 5, 4H); 2.13-1.95 (*m*, 4H); 1.79-1.76 (*m*, 8H); 1.68 (*s*, 3H); 1.65 (*s*, 3H); 1.60 (*s*, 6H). $^{13}$C-NMR: 137.5 (*s*); 135.1 (*s*); 131.3 (*s*); 124.4 (*d*); 124.0 (*d*); 121.8 (*d*); 54.0 (2*t*); 53.4 (*t*); 39.7 (2*t*); 26.8 (*t*); 26.4 (*t*); 25.7 (*q*); 23.5 (2*t*); 17.7 (*q*); 16.4 (*q*); 16.0 (*q*). MS: 275 (7, $M^{+\cdot}$), 208 (11), 206 (47), 138 (18), 124 (100), 122 (10), 84 (50), 81 (11), 70 (25), 69 (20), 55 (10), 41 (18). For the analytical data of a regioisomer side product, see the Supplementary Material.

*(*E*)*-N,N-*Diethyl-3-methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-2-en-1-amine* **30**. $BF_3{\cdot}OEt_2$ (15.19 g, 13.56 ml, 105 mmol) was added dropwise to a soln. of **29b** (9.712 g, 35 mmol) and AcOH (4.20g, 69.9 mmol) in $CH_2Cl_2$ (100 ml) at 0°C. After 1 h at 0°C and 9 h at 30°C, the reaction mixture was poured into sat. aq. $NaHCO_3$ (200 ml). The basic aq. phase was extracted with $Et_2O$ (3 x 100 ml). The org. phase was washed with brine, dried ($Na_2SO_4$), and concentrated to afford quantitatively a 26:58:16 mixture of **30**/**31g**/**31a**. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 6:4 to 1:1) followed, for the combined non-polar fractions, by a second CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) afforded **30** in 17% yield, besides pure **31g** and a mixture of **31g**/**31a** (*vide infra*). Alternatively, $MeSO_3H$ (0.068 ml, 101 mg, 1.049 mmol) was added dropwise over 2h to a soln. of **29b** (145 mg, 0.524 mmol) in $CH_2Cl_2$ (10 ml) at 0°C. The reaction mixture was poured into sat. aq. $NaHCO_3$ (10 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was dried ($Na_2SO_4$), concentrated and bulb-to-bulb distilled to afford a 78:22 mixture of *E*-/*Z*-**30** in 60% yield. IR: 2965, 2928, 2868, 2828, 1666, 1454, 1381, 1360, 1288, 1202, 1166, 1117, 1057, 986, 803, 764, 615. $^1$H-NMR: 5.30 (*t*, *J* = 6.9, 1H); 3.06 (*d*, *J* = 6.9, 2H); 2.52 (*q*, *J* = 7.2, 4H); 2.10-2.03 (*m*, 4H); 1.90 (*t*, *J* = 6.4, 2H); 1.68 (*s*, 3H); 1.60 (*s*, 3H); 1.59-1.55 (*m*, 2H); 1.43-1.40 (*m*, 2H); 1.04 (*t*, *J* = 7.2, 6H); 0.99 (*s*, 6H). $^{13}$C-NMR: 138.7 (*s*); 137.0 (*s*); 127.0 (*s*); 121.2 (*d*); 50.6 (*t*); 46.7 (2*t*); 40.4 (*t*); 39.9 (*t*); 35.0 (*s*); 32.8 (*t*); 28.6 (2*q*); 27.5 (*t*); 19.8 (*q*); 19.6 (*t*), 16.4 (*q*); 11.8 (2*q*). MS: 277 (9, $M^{+\cdot}$), 262 (8), 204 (11), 189 (19), 140 (100), 137 (85), 126 (26), 124 (19), 121 (10), 111 (10), 95 (40), 93 (13), 91 (11), 86 (32), 81 (30), 79 (10), 74 (41), 69 (16), 67 (14), 58 (58), 55 (12), 41 (18).

N-*Ethyl*-N-*(((1*RS*,4a*RS*,8a*RS*)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)ethanamine* **31a**. A 60% aq. $H_2O_2$ soln. (2.039 g, 1.837 ml, 36.0 mmol) was added dropwise to a soln. of a 55:45 mixture of **31g**/**31a** (1.996 g, 7.19 mmol) in EtOH (10 ml) at 20°C. After 1 h at 20°C the EtOH was concentrated at 20°C and replaced by AcOEt (20 ml). 10% Pd/C (20 mg) was added and the suspension was stirred at 20°C for 4.5 h, until no more gas evolved. This suspension was filtered over *Celite*®. The org. phase was washed with brine ($Na_2SO_4$), concentrated and purified by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) to afford pure **31a** in 27% yield (60% yield based on pure **31a**), besides pure **4**.[34]) Alternatively, $CF_3SO_3H$ (0.62 ml, 1.05g, 7.0 mmol) was added dropwise to a soln. of **29b** (971 mg, 3.5 mmol) in $MeNO_2$ (10 ml) at

[34]) When pure **31g** was treated under the same conditions, pure **4** was isolated in 58% yield.

-20°C. After 2h at -20°C the reaction mixture was poured onto sat. aq. $NaHCO_3$ (10 ml). The aq phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$ (3 x 10 ml), dried ($Na_2SO_4$), then concentrated to afford after bulb-to-bulb distillation a 7:3 mixture of **31a**/**31g** in 81% yield. IR: 2963, 2922, 2865, 2846, 2796, 1455, 1442, 1380, 1365, 1343, 1304, 1267, 1212, 1197, 1162, 1133, 1121, 1074, 1056, 1007, 982, 962, 918, 845, 810, 775, 636. $^1$H-NMR: 5.39 (br*d*, *J* = 4.2, 1H); 2.61 (*ddt*, *J* = 7.2, 14.6, 20.2, 2H); 2.37 (*dq*, *J* = 7.0, 13.6, 4H); 2.23 (*dd*, *J* = 8.2, 12.7, 1H); 2.02 (*dq*, *J* = 3.0, 13.0, 1H); 1.99-1.94 (*m*, 1H); 1.87-1.84 (*m*, 1H); 1.77 (*s*, 3H); 1.53 (*dt*, *J* = 3.2, 13.3, 1H); 1.44 (*quint*, *J* = 3.5, 1H); 1.43-1.39 (*m*, 2H); 1.23-1.15 (*m*, 2H); 0.97 (*t*, *J* = 7.0, 6H); 0.88 (*s*, 3H); 0.86 (*s*, 3H); 0.75 (*s*, 3H). $^{13}$C-NMR: 136.3 (*s*); 121.9 (*d*); 52.8 (*t*); 51.6 (*d*); 50.3 (*d*); 46.0 (2*t*); 42.2 (*t*); 39.1 (*t*); 36.1 (*s*); 33.3 (*q*); 33.1 (*s*); 23.8 (*t*); 22.4 (*q*); 22.0 (*q*); 18.9 (*t*); 13.7 (*q*); 11.4 (2*q*). MS: 277 (0, $M^{+\cdot}$), 86 (100).

N-*Ethyl*-N-*(((4a*RS,*8a*RS*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)ethanamine* **31b**. $CF_3SO_3H$ (0.62 ml, 1.05g, 7.0 mmol) was added dropwise to a soln. of **29b** (971 mg, 3.5 mmol) in $MeNO_2$ (10 ml) at 0°C. After 7h at 0°C the reaction mixture was poured onto sat. aq. $NaHCO_3$ (10 ml). The aq. phase was extracted with $Et_2O$ (3 x 10 ml). The org. phase was washed with $H_2O$ (3 x 10 ml), dried ($Na_2SO_4$), then concentrated to afford after bulb-to-bulb distillation **31b** in 75% yield. IR: 2963, 2922, 2866, 2843, 2790, 1455, 1381, 1367, 1342, 1287, 1194, 1168, 1120, 1067, 1047, 1025, 978, 811, 798, 776. $^1$H-NMR: 3.06 (*d*, *J* = 13.0, 1H); 2.88 (*d*, *J* = 13.0, 1H); 2.55 (*dq*, *J* = 7.0, 12.8, 2H); 2.22 (*dq*, *J* = 7.0, 12.8, 2H); 2.07-2.02 (*m*, 2H); 1.66-1.50 (*m*, 2H); 1.61 (*s*, 3H); 1.47-1.37 (*m*, 3H); 1.17 (*ddd*, *J* = 4.0, 13.2, 26.0, 2H); 1.12-1.07 (*m*, 2H); 1.09 (*s*, 3H); 0.98 (*t*, *J* = 7.0, 6H); 0.87 (*s*, 3H); 0.85 (*s*, 3H). $^{13}$C-NMR: 138.0 (*s*); 129.8 (*s*); 51.4 (*d*); 51.4 (*t*); 45.9 (2*t*); 42.0 (*t*); 38.3 (*s*); 37.0 (*t*); 33.9 (*t*); 33.5 (*q*); 33.4 (*s*); 21.9 (*q*); 21.0 (*q*); 20.2 (*q*); 19.2 (*t*); 19.1 (*t*); 11.9 (2*q*). MS: 277 (45, $M^{+\cdot}$), 189 (5), 133 (8), 119 (10), 107 (10), 105 (13), 93 (11), 91 (13), 86 (61), 72 (88), 58 (100), 55 (11), 41 (12).

N-*Ethyl*-N-*(((1*RS,*4a*RS,*8a*RS*)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)ethanamine* **31g**. Isolated in 33% yield during the purification of a 26:58:16 mixture of **30**/**31g**/**31a** (*vide supra*). IR: 2964, 2930, 2867, 2843, 2795, 1643, 1459, 1442, 1382, 1366, 1201, 1167, 1120, 1056, 1056, 993, 977, 963, 883, 774, 668. $^1$H-NMR: 4.87 (br*q*, *J* = 1.5, 1H); 4.72 (br*q*, *J* = 1.5, 1H); 2.58 (*dd*, *J* = 7.0, 14.0, 20.0, 2H); 2.52-2.43 (*m*, 4H); 2.39 (*ddd*, *J* = 2.3, 4.2, 12.6, 2H); 2.03 (*dt*, *J* = 5.0, 12.8, 1H); 1.88-1.84 (*m*, 2H); 1.72 (*dquint*, *J* = 2.8, 13.0, 1H); 1.56

(*tq*, *J* = 3.5, 13.0, 1H); 1.48 (*dquint*, *J* = 3.3, 14.0, 1H); 1.41-1.37 (*m*, 1H); 1.31 (*dq*, *J* = 4.0, 12.8, 1H); 1.20 (*dt*, *J* = 4.0, 12.8, 1H); 1.15-1.10 (*m*, 1H); 0.99 (*t*, *J* = 7.0, 6H); 0.88 (*s*, 3H); 0.81 (*s*, 3H); 0.69 (*s*, 3H). $^{13}$C-NMR: 148.6 (*s*); 107.3 (*t*); 55.7 (*d*); 54.0 (*d*); 48.2 (*t*); 46.9 (2*t*); 42.1 (*t*); 39.5 (*s*); 38.9 (*t*); 38.4 (*t*); 33.7 (*q*); 33.6 (*s*); 24.3 (*t*); 21.8 (*q*); 19.4 (*t*); 14.8 (*q*); 10.9 (2*q*). MS: 277 (1, $M^{+\cdot}$), 86 (100).

N-*Ethyl*-N-*(((1*RS,*2*SR,*4a*SR*)-2,4a,5,5-tetramethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-yl)methyl)ethanamine* **31r**. Conc. $H_2SO_4$ (0.274 g, 0.149 ml, 2.80 mmol) was added dropwise to a soln. of **29b** (485 mg, 1.748 mmol) in $CH_2Cl_2$ (20 ml) at 0°C. After 18h at 20°C, the reaction mixture was poured into sat. aq. $NaHCO_3$ (20 ml). The aq. phase was extracted with $Et_2O$ (3 x 20 ml). The org. phase was washed with brine, dried ($Na_2SO_4$), and concentrated to afford quantitatively a 26:74 mixture of **31r**/**31b**. Purification by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 1:1) afforded pure **31r** in 8% yield, as well as pure **31b** in 32% yield. IR: 2963, 2923, 2869, 2838, 2797, 1456, 1376, 1350, 1291, 1201, 1176, 1067, 1028, 834, 803, 770, 663. $^1$H-NMR: 5.32 (*t*, *J* = 3.5, 1H); 2.78 (*dd*, *J* = 10.9, 12.6, 1H); 2.60 (*dq*, *J* = 6.0, 7.0, 2H); 2.41 (*dq*, *J* = 6.0, 7.0, 2H); 2.10 (*dd*, *J* = 2.8, 12.6, 1H); 2.08-1.98 (*m*, 3H); 1.91 (*dt*, *J* = 5.6, 18.2, 1H); 1.85 (*dt*, *J* = 4.0, 13.7, 1H); 1.76-1.69 (*m*, 2H); 1.28-1.24 (*m*, 1H); 1.21-1.08 (*m*, 2H); 1.00 (*t*, *J* = 7.0, 6H); 0.99 (*s*, 3H); 0.95 (*s*, 3H); 0.90 (*d*, *J* = 7.4, 3H); 0.83 (*s*, 3H). $^{13}$C-NMR: 142.1 (*s*); 123.7 (*d*); 61.0 (*t*); 49.4 (*d*); 47.7 (2*t*); 39.8 (*s*); 35.4 (*s*); 33.4 (*t*); 29.3 (*d*); 24.8 (*t*); 24.5 (*q*); 23.8 (*t*); 23.5 (*q*); 23.3 (*q*); 23.2 (*t*); 20.0 (*q*); 12.1 (2*q*). MS: 277 (0, $M^{+\cdot}$), 86 (100).

*4-(2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethyl)-3,6-dihydro-2H-pyran* **32**. Obtained in 57% yield according to the procedure used for **11**. IR: 2954, 2919, 2850, 1744, 1461, 1377, 1233, 1129, 1029, 971, 851, 720. $^1$H-NMR: 5.44 (br*s*, 1H); 4.13 (br*d*, *J* = 2.6, 2H); 3.80 (*t*, *J* = 5.5, 2H); 2.11-2.00 (*m*, 6H); 1.91 (*t*, *J* = 6.2, 2H); 1.60 (*s*, 3H); 1.58-1.55 (*m*, 2H); 1.43-1.40 (*m*, 2H); 0.99 (*s*, 6H). $^{13}$C-NMR: 136.9 (*s*); 136.5 (*s*); 127.3 (*s*); 118.9 (*d*); 65.6 (*t*); 64.5 (*t*); 39.8 (*t*); 35.0 (*s*); 32.8 (*t*); 32.0 (*t*); 29.4 (*t*); 28.6 (2*q*); 26.8 (*t*); 19.8 (*q*); 19.6 (*t*). MS: 234 (18, $M^{+\cdot}$), 137 (100), 123 (12), 121 (10), 95 (59), 93 (10), 91 (11), 81 (38), 79 (11), 69 (12), 67 (11), 55 (10), 41 (19).

*(Z)-3-(2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethyl)pent-3-en-1-ol* **33**. Obtained in 35% yield from **32** according to the procedure used for **9**. IR: 3322, 2925, 2865, 1455, 1375, 1360, 1204, 1041, 864, 826, 817, 625. $^1$H-NMR: 5.45 (*q*, *J* = 6.9, 1H); 3.67 (*dt*, *J* = 6.6, 11.3, 2H); 2.38 (*t*, *J* = 6.6, 2H); 2.08-2.01 (*m*, 4H); 1.90 (*t*, *J* = 6.3, 2H); 1.69-1.55 (*m*, 1H); 1.65 (*d*, *J* = 6.3, 3H); 1.60

(*s*, 3H); 1.44-1.40 (*m*, 4H); 0.99 (*s*, 6H). $^{13}$C-NMR: 136.9 (*s*); 136.8 (*s*); 127.2 (*s*); 121.5 (*d*); 61.0 (*t*); 39.8 (*t*); 37.4 (*t*); 35.0 (*s*); 33.2 (*t*); 32.8 (*t*); 28.6 (2*q*); 28.1 (*t*); 19.8 (*q*); 19.5 (*t*); 13.4 (*q*). MS: 236 (7, $M^{+\cdot}$), 192 (11), 137 (100), 121 (11), 95 (63), 93 (10), 81 (39), 79 (12), 69 (12), 67 (10), 55 (10), 41 (13).

*Ethyl (3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienoate* **34b**. A 100 ml *Keim* autoclave (stainless steel, with glass insert) was charged with EtOH/THF (1:1, 40 ml), amine **29b** (500 mg, 1.802 mmol), EtI (281 mg, 1.802 mmol) and $Pd(PPh_3)_4$ (31.2 mg, 0.027 mmol) before to be sealed. The reactor was purged with CO, and pressurized to 30 bar, then heated to 60°C. After 1 h, the pressure was adjusted to 60 bar and the reaction mixture was stirred for 96h. The cold reactor was purged with $N_2$, and the mixture was poured onto $H_2O$/$Et_2O$ 1:1, then acidified with 10% aq. HCl. The org phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), concentrated and purified by CC/$SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) to afford **34b** in 31-32% yield as a 76:24 *E/Z* mixture. IR: 2965, 2921, 2854, 1737, 1445, 1375, 1314, 1254, 1150, 1108, 1096, 1033, 984, 941, 836, 744, 694. $^1$H-NMR: (3*E*, 7*E*)-isomer 5.33 (*t*, *J* = 7.2, 1H); 5.13-5.06 (*m*, 2H); 4.13 (*q*, *J* = 7.2, 2H); 3.04 (*d*, *J* = 7.2, 2H); 2.11-1.95 (*m*, 8H); 1.68 (*s*, 3H); 1.60 (*s*, 9H); 1.26 (*t*, *J* = 7.2, 3H). (3*Z*, 7*E*)-isomer 5.33 (*t*, *J* = 7.2, 1H); 5.13-5.06 (*m*, 2H); 4.12 (*q*, *J* = 7.2, 2H); 3.04 (*d*, *J* = 7.2, 2H); 2.11-1.95 (*m*, 8H); 1.75 (*s*, 3H); 1.64 (*s*, 9H); 1.26 (*t*, *J* = 7.2, 3H). (3*E*, 7*E*)-isomer $^{13}$C-NMR: 172.5 (*s*); 139.0 (*s*); 135.2 (*s*); 131.3 (*s*); 124.4 (*d*); 123.9 (*d*); 115.8 (*d*); 60.5 (*t*); 39.7 (*t*); 39.6 (*t*); 26.7 (*t*); 26.4 (*t*); 25.7 (*q*); 17.7 (*q*); 16.4 (*q*); 16.0 (*q*); 14.2 (*q*). MS: 278 (3, $M^{+\cdot}$), 167 (5), 136 (25), 121 (45), 107 (9), 95 (11), 93 (19), 81 (38), 69 (100), 41 (30), 29 (11).

*Methyl 2-((4a*RS*,8a*RS*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate* **36a**. Similarly to **34b**, a mixture of **31b** (250 mg, 0.836 mmol), $Pd(PPh_3)_4$ (14.5 mg, 0.013 mmol) and MeI (237 mg, 1.672 mmol) in THF/MeOH (20 ml, 50:50) was heated at 60°C under 60 bar of CO for 144 h. The cold reaction mixture, containing 45% of a new product, was poured onto $H_2O$ (10 ml), then acidified at 0°C with 10% HCl. The org phase was separated, washed with $H_2O$. The aq. phase was extracted with $Et_2O$ (3 x 5 ml). The org. phase was dried ($Na_2SO_4$), and concentrated. The residual oil was purified by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) to afford **36a** in 31% yield. (38% yield of recuperated **31b**, the conversion was not better after 10-12 days). $R_f$ = 0.22 (99:1). IR: 2950, 2920, 1730, 860. $^1$H-NMR: 3.66 (*s*, 3H); 3.02 (*dd*, *J* = 17.0, 63.0, 2H); 2.50-1.05 (*m*, 11H); 1.56 (br*s*, 3H); 0.93 (*s*, 3H); 0.89 (*s*, 3H); 0.83 (*s*, 3H).

$^{13}$C-NMR: 173.4 (*s*); 133.8 (*s*); 130.2 (*s*); 51.6 (*q*) ; 51.4 (*d*); 41.5 (*t*); 38.5 (*s*); 36.2 (*t*); 33.6 (*t*); 33.3 (*s*); 33.2 (*q*); 32.9 (*t*); 21.6 (*q*); 20.0 (*q*); 19.7 (*q*); 18.9 (2*t*). MS: 264 (28, $M^{+\cdot}$), 249 (37), 217 (11), 205 (12), 190 (100), 179 (31), 175 (84), 167 (12), 163 (25), 153 (32), 141 (13), 135 (12), 133 (24), 121 (35), 119 (43), 109 (26), 107 (26), 105 (42), 95 (19), 93 (29), 91 (29), 81 (14), 79 (16), 77 (14), 55 (14), 41 (19). Camphoraceous and vaguely woody-like.

*Ethyl 2-((4a*RS*,8a*RS*)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate* **36b**. A mixture of **36c** (1.61g, 6.5 mmol) in EtOH (30 ml) and $H_2SO_4$ (96%, 0.2g) was heated at reflux for 18h. The cold reaction mixture was concentrated, then partitioned between $H_2O$ and AcOEt. The org phase was washed several times with $H_2O$, then satd aq. $NaHCO_3$. The org. phase was dried ($Na_2SO_4$, concentrated, then purified by CC/$SiO_2$, 99:1 to 97:3 cyclohexane/AcOEt) to afford a 14:24:62 mixture of β-:α-:γ-isomers. Pure **36b** was obtained by prep GC for analyses. IR: 2952, 2922, 2854, 1734, 1458, 1376, 1259, 1157, 1024, 885, 860, 800. $^1$H-NMR: 4.16-4.09 (*m*, 2H); 3.01 (*dd*, *J* = 16.9, 66.3, 2H); 2.50-1.05 (*m*, 11H); 1.56 (*s*, 3H); 1.23 (*t*, *J* = 7.0, 3H); 0.93 (*s*, 3H); 0.83 (*s*, 3H); 0.88 (*s*, 3H). $^{13}$C-NMR: 173.0 (*s*); 133.9 (*s*); 130.2 (*s*); 60.3 (*t*); 51.4 (*d*); 41.5 (*t*); 38.5 (*s*); 36.3 (*t*); 33.6 (*q*); 33.6 (*t*); 33.3 (*s*); 33.1 (*t*); 21.6 (*q*); 20.1 (*q*); 19.7 (*q*); 18.9 (2*t*); 14.4 (*q*). MS: 278 (18, $M^{+\cdot}$), 263 (23), 217 (10), 205 (14), 193 (19), 190 (100), 175 (84), 167 (22), 163 (29), 149 (10), 147 (14), 135 (10), 133 (20), 121 (29), 119 (35), 109 (23), 107 (24), 105 (37), 95 (16), 93 (26), 91 (24), 81 (13), 79 (16), 77 (11), 69 (18), 55 (15), 41 (18). For analytical data of the other isomers, see the Supplementary Material.

N-*Ethyl*-N-*((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)ethanamine* **39**. Obtained in 44% yield after treatment with 40% aq. $H_2SO_4$ at 120°C for 20h according to [76], followed by CC/$SiO_2$ (cyclohexane/AcOEt 9:1 to 8:2) purification of the resulting 60:25:15 mixture of β-/α-/γ-isomers. IR: 2953, 2923, 2853, 2791, 1458, 1379, 1288, 1268, 1197, 1176, 1165, 1119, 1067, 1050, 986, 800, 776, 721. $^1$H-NMR: 3.0 (*s*, 2H); 2.37 (*q*, *J* = 7.0, 4H); 1.96 (*t*, *J* = 6.5, 2H); 1.65 (*s*, 3H); 1.64-1.61 (*m*, 2H); 1.40-1.38 (*m*, 2H); 1.09 (*s*, 6H); 0.99 (*t*, *J* = 7.0, 6H). $^{13}$C-NMR: 134.7 (*s*); 130.7 (*s*); 51.9 (*t*); 46.0 (2*t*); 40.8 (*t*); 34.3 (*s*); 33.4 (*t*); 28.9 (2*q*); 20.5 (*q*); 19.3 (*t*); 12.1 (2*q*). MS: 209 (28, $M^{+\cdot}$), 95 (12), 93 (10), 86 (58), 81 (10), 73 (40), 72 (34), 58 (100), 41 (9). For analytical data of both *N*,*N*-Diethyl-α-cyclogeranylamine [13][76], and *N*,*N*-Diethyl-γ-cyclogeranylamine [13][76], see the Supplementary Material. Alternatively, obtained in 8% yield when **3** was treated with *n*BuLi/$HNEt_2$ according to the procedure used for **44**. The major

regioisomer of this latter reaction (80:20 mixture) was *N*-ethyl-*N*-((2,3,3-trimethylcyclohex-1-en-1-yl)methyl)ethanamine isolated in 17% yield after acidic extraction and CC/$SiO_2$ (cyclohexane/AcOEt 9:1 to 8:2, see the Supplementary Material).

*Methyl 2-(2,6,6-trimethylcyclohex-1-en-1-yl)acetate* **40a**. Similarly to **34b**, a mixture of **39** (100 mg, 0.478 mmol, 80:20 β/α), $Pd(PPh_3)_4$ (8.28 mg, 0.0072 mmol) and MeI (136 mg, 0.955 mmol) in THF/MeOH (20 ml, 50:50) was heated at 60°C under 60 bar of CO for 142 h. The cold reaction mixture, containing 47% of a new product plus **39** (26:14 mixture of β/α), was poured onto $H_2O$ (10 ml), then acidified at 0°C with 10% HCl. The org phase was separated, washed with $H_2O$. The aq. phase was extracted with $Et_2O$ (3 x 5 ml). The org. phase was dried ($Na_2SO_4$), and concentrated. The residual oil was purified by CC/$SiO_2$ (cyclohexane/AcOEt 99:1) to afford pure **40a** in 25% yield. IR: 2923, 2853, 1746, 1458, 1433, 1376, 1362, 1329, 1295, 1258, 1194, 1154, 1131, 1119, 1046, 1004, 932, 884, 749, 673. $^1$H-NMR: 3.66 (*s*, 3H); 3.06 (*s*, 2H); 1.99 (*t*, *J* = 6.5, 2H); 1.59 (brs, 3H); 1.61-1.58 (*m*, 2H); 1.48-1.41 (*m*, 2H); 0.96 (*s*, 6H). $^{13}$C-NMR: 173.4 (*s*); 131.4 (*s*); 130.4 (*s*); 51.6 (*q*); 39.3 (*t*); 34.7 (*s*); 33.6 (*t*); 32.7 (*t*); 27.9 (2*q*); 20.3 (*q*); 19.4 (*t*). MS: 196 (20, $M^{+\cdot}$), 181 (55), 149 (22), 137 (14), 121 (40), 107 (100), 93 (20), 91 (17), 81 (13), 79 (17), 77 (11), 75 (12), 55 (8), 41 (12).

N-*Ethyl*-N-*((3-methylbicyclo[2.2.1]hept-2-en-2-yl)methyl)ethanamine* **41**. *n*BuLi (1.6M/THF, 43.5 ml, 69.6 mmol) was added dropwise during 1h to a soln. of **5** (10.0g, 69.6 mmol) and $Et_2NH$ (9.58g, 131 mmol) in THF (100 ml) at 0°C. After 20 min at 20°C, the reaction mixture was heated at 50°C for 8h. The cold reaction mixture was poured into $H_2O$ (20 ml) at 0°C, then rendered acidic with 10% aq. HCl. The aq. phase was washed with $Et_2O$ (3x20 ml), then rendered basic by addition of 30% aq. NaOH. This aq. phase was extracted with $Et_2O$ (3 x 20 ml) and this org. phase was dried ($Na_2SO_4$), then concentrated *in vacuo* to afford pure **41** in 52% yield. Bp. 80°C/0.2 mbar. IR: 2954, 2868, 2792, 1469, 1445, 1380, 1369, 1329, 1287, 1275, 1199, 1177, 1116, 1067, 1051, 1036, 1021, 985, 870, 803, 776. $^1$H-NMR: 2.94 (*s*, 2H); 2.83 (brs, 1H); 2.58 (brs, 1H); 2.53 (*dq*, *J* = 7.0, 12.8, 2H); 2.40 (*dq*, *J* = 7.0, 12.5, 2H); 1.64 (*s*, 3H); 1.62-1.60 (*m*, 2H); 1.33 (*dquint*, *J* = 2.0, 7.8, 1H); 1.06-0.98 (*m*, 3H); 1.01 (*t*, *J* = 7.0, 3H). $^{13}$C-NMR: 139.8 (*s*); 137.8 (*s*); 49.0 (*t*); 47.9 (*d*); 47.7 (2*t*); 46.5 (*t*); 44.9 (*d*); 26.5 (*t*); 25.7 (*t*), 11.8 (*q*); 11.6 (2*q*). MS: 193 (34, $M^{+\cdot}$), 178 (25), 164 (38), 152 (13), 150 (12), 121 (86), 112 (18), 105 (13), 93 (100), 91 (50), 86 (22), 79 (52), 77 (36), 72 (56), 58 (83), 56 (12).

*Methyl 2-(3-methylbicyclo[2.2.1]hept-2-en-2-yl)acetate* **42**. A 100 ml *Keim* autoclave (stainless steel, with glass insert) was charged with MeOH/THF (1:1, 40 ml), amine **41** (500 mg, 2.59 mmol), MeI (734 mg, 5.17 mmol) and $Pd(PPh_3)_4$ (44.8 mg, 0.039 mmol) before to be sealed. The reactor was purged with CO, and pressurized to 30 bar, then heated to 60°C. After 1 h, the pressure was adjusted to 60 bar and the reaction mixture was stirred for 168 h. The cold reactor was purged with $N_2$, and the mixture was poured onto $H_2O/Et_2O$ 1:1, then acidified with 10% aq. HCl. The org phase was washed with $H_2O$, brine, dried ($Na_2SO_4$), concentrated and purified by $CC/SiO_2$ (cyclohexane/AcOEt 99:1 to 9:1) to afford **42** in 22% yield. IR: 2956, 2870, 1733, 1715, 1445, 1367, 1276, 1255, 1200, 1158, 1121, 1031, 932, 868, 669. $^1$H-NMR: 3.67 (*s*, 3H); 3.09 (*d*, *J* = 15.1, 1H); 2.97 (*d*, *J* = 15.1, 1H); 2.76 (brs, 1H); 2.61 (brs, 1H); 1.64 (*s*, 3H); 1.63-1.60 (*m*, 2H); 1.40-1.36 (*m*, 1H); 1.06-1.01 (*m*, 3H). $^{13}$C-NMR: 172.4 (*s*); 140.3 (*s*); 132.1 (*s*); 51.7 (*q*); 47.6 (*d*); 46.8 (*t*); 45.9 (*d*); 32.6 (*t*); 26.2 (*t*); 25.5 (*t*), 11.9 (*q*). MS: 180 (20, $M^{+\cdot}$), 152 (80), 121 (13), 105 (8), 93 (100), 92 (80), 91 (40), 79 (12), 77 (25).

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**Author Contribution Statement**

C. C. conceived and designed the experiments, analyzed the data, and wrote the manuscript. D. S. and C.-A. R. performed the synthetic work.

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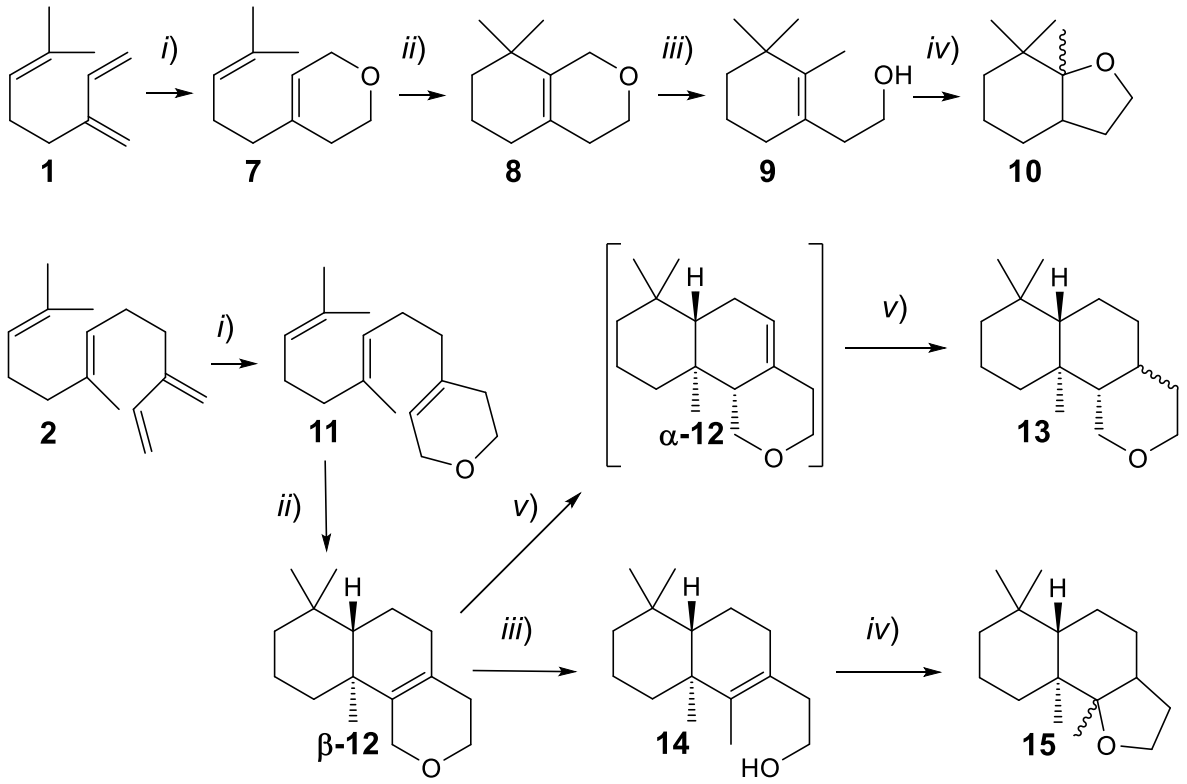
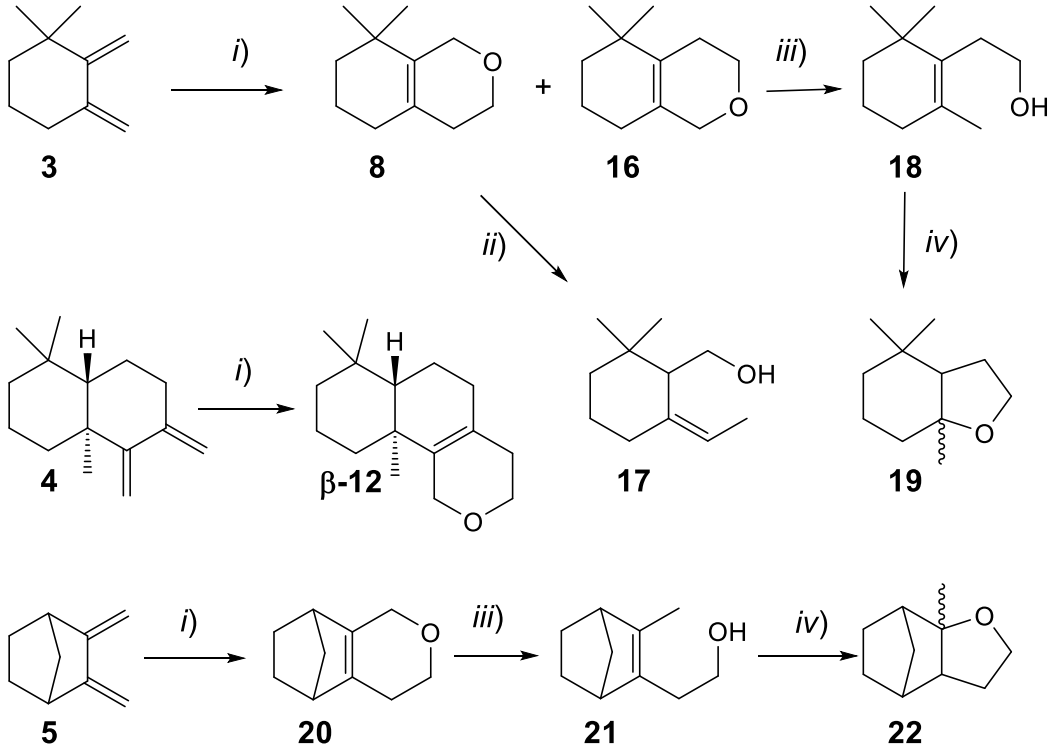
*Scheme* 1



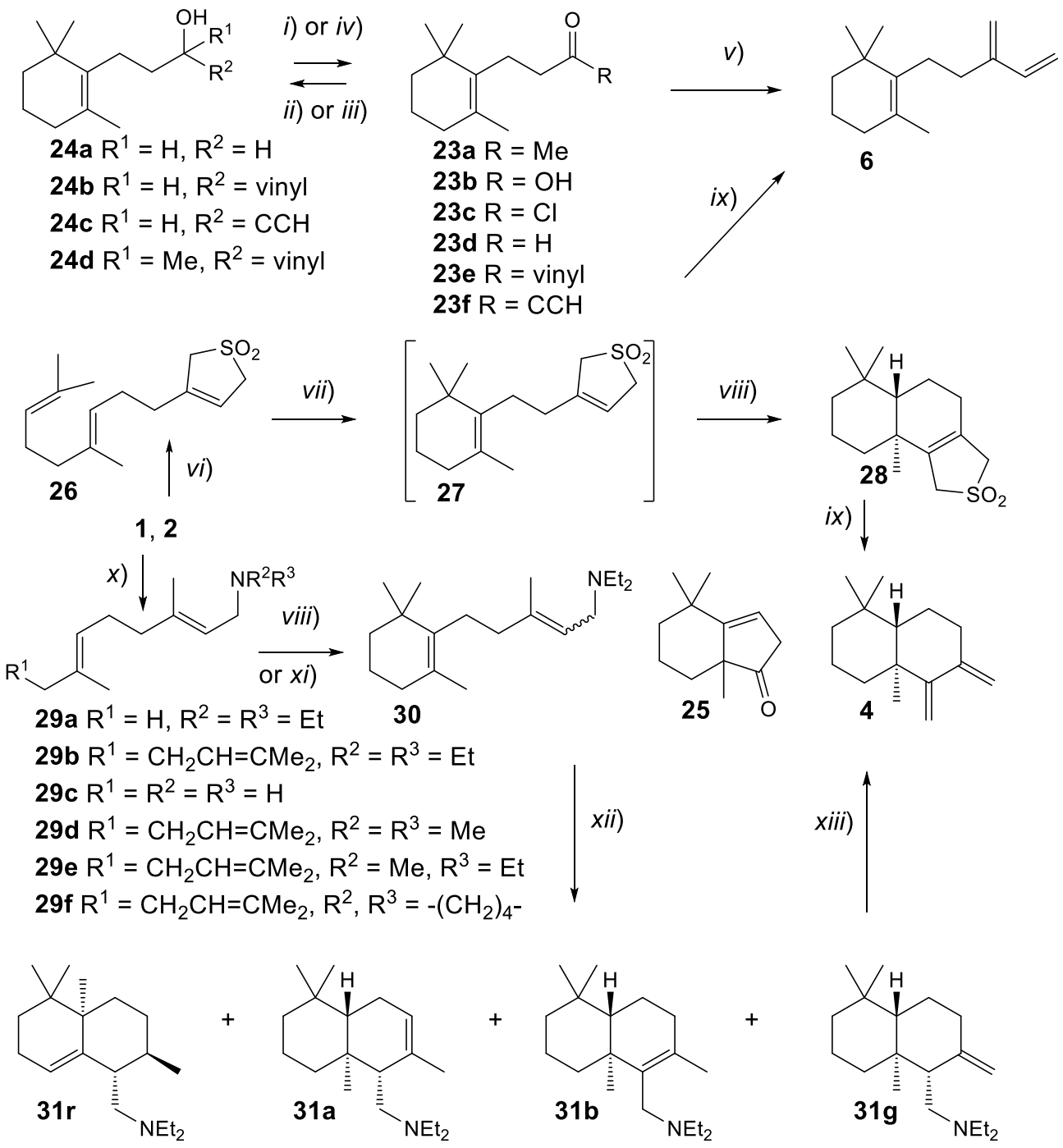

*i*) $(CH_2O)_n$, AcOH, 15-66%; *ii*) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 20°C, 14-47%; *iii*) Li, $H_2NCH_2CH_2NH_2$, 20°C, 59-69%; *iv*) $Me_3SO_3H$, $CH_2Cl_2$, 20°C, 51-98%; *v*) $H_2$, 5% Pd/C, AcOEt, 88%.

*Scheme* 2



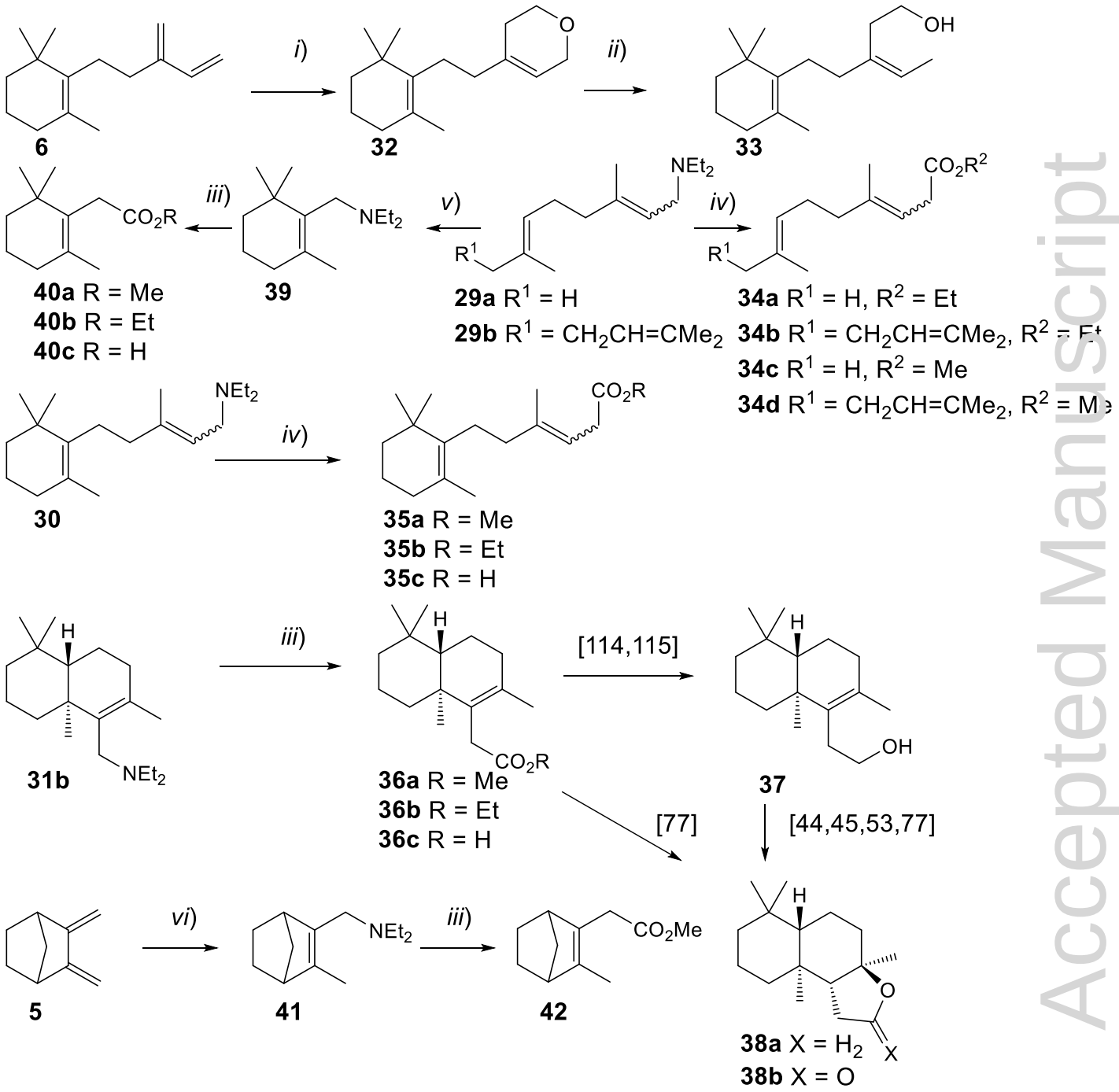

*i*) $(CH_2O)_n$, AcOH, 22-66%; *ii*) Li, $MeNH_2$, THF, -78°C, 10%; *iii*) Li, $H_2NCH_2CH_2NH_2$, 20°C, 41%; *iv*) $Me_3SO_3H$, $CH_2Cl_2$, 20°C, 48-69%.

*Scheme* 3




*i*) PCC, $CH_2Cl_2$, 66%; *ii*) vinylMgBr, $LaCl_3{\cdot}2LiCl$, THF, 0°C, 42%; *iii*) HCCMgBr, $Et_2O$, 94%; *iv*) MnO2, $CH_2Cl_2$, 34-41%; *v*) $Ph_3PCH_3{}^+Br^-$, NaH, DMSO, THF, 15%; *vi*) DABSO, $BF_3{\cdot}OEt_2$, MeCN, 50°C, 36%; *vii*) $BF_3{\cdot}OEt_2$, MeCN, 0°C, 66-80%; *viii*) $BF_3{\cdot}OEt_2$, AcOH, $CH_2Cl_2$, 30°C, 47-98%; *ix*) 160°C, py, 57-68%; *x*) $R^1R^2NH$, *n*BuLi, THF, 77-87%; *xi*) $MeSO_3H$, $CH_2Cl_2$, 0°C, 60%; *xii*) $CF_3SO_3H$, $MeNO_2$, 0°C, 75%; *xiii*) 60% $H_2O_2$, EtOH, 58%.

*Scheme* 4




*i*) $(CH_2O)_n$, AcOH, 57%; *ii*) Li, $H_2NCH_2CH_2NH_2$, 20°C, 35%; *iii*) MeI, MeOH, 0.015 mol.-equiv. $Pd(PPh_3)_4$, CO, 60 bar, 60°C, 22-31%; *iv*) EtI, EtOH, 0.01 mol.-equiv. $Pd(PPh_3)_4$, CO, 60 bar, 60°C, 52-73%; *v*) $H_2SO_4$, 120°C, 54%; *vi*) *n*BuLi, $HNEt_2$, THF, 20-50°C, 52%.

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