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Enantioselective synthesis of each stereoisomer of the pyranoid linalool oxides: the linalool route

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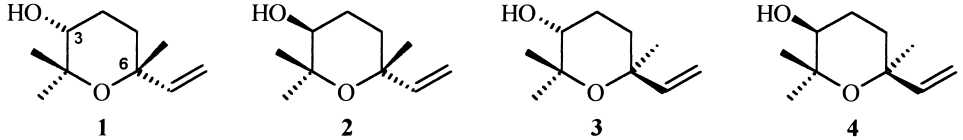
Abstract

Each of the four enantiomerically pure tetrahydropyran linalool oxides was prepared by separate enantioselective Sharpless dihydroxylation of (*R*)- or (*S*)-linalyl acetate with AD-mix-α or AD-mix-β, followed by a completely stereoselective *N*-phenylselenophthalimide cyclization of an intermediate allylic alcohol.

1. Introduction

A 2,2,6,6-tetrasubstituted pyran ring is an important structural fragment of many oxygenated natural products and constitutes the basic skeleton of the four pyranoid linalool oxides **1** (3*R*,6*R*), **2** (3*S*,6*R*), **3** (3*R*,6*S*) and **4** (3*S*,6*S*). The latter compounds, as different mixtures of stereoisomers, have been found as constituents of many tea, flower and fruit aromas, such as grapes and *Carica papaya* fruits.[1,2] Even though compounds **1**–**4** are usually minor constituents of these fragrances, they are considered to be important contributors to a particular 'note' or 'character' of the scent.[3] However, to our knowledge, nobody has yet described the distinctive odour of each stereoisomer. In addition, they seem to have a strong biological significance in certain pollination systems, acting as insect attractants.[3]



1 **2** **3** **4**

Recently, numerous syntheses of linalool oxides have been published, describing valuable selective methods of the construction of substituted pyran rings which were later employed in the synthesis

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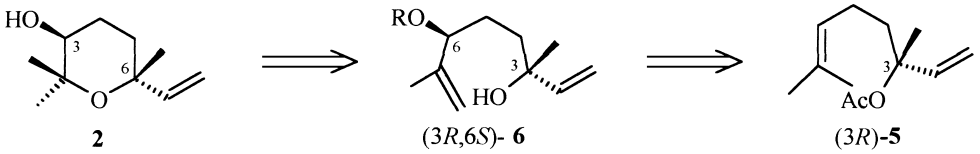
of more oxygenated natural products. Three general procedures[4,5] were elaborated for assembling linalool oxide-like tetrahydropyran structures: (i) by using a nucleophilic attack of a hydroxy group to a double bond activated by coordination with a bromo,[6,7] mercury[8] or selenium reagent;[9–13] (ii) by controlled cyclization of an epoxyalcohol in acidic medium;[10,14–16] and (iii) by an intramolecular displacement of an allylic *N*-phenylcarbamate or carbonate moiety in the presence of a Lewis acid[17] or a palladium catalyst,[18] respectively. Unfortunately, these cyclizations generally proceed with poor stereoselectivity, giving mixtures of *cis*- and *trans*-linalool oxides in almost equal amounts and often together with the corresponding isomeric tetrahydrofuran oxides. A few years ago, we described[16] a highly enantioselective synthesis of compound **4** starting from (*R*)-(−)-linalool; however, our approach suffered a serious drawback in terms of atom economy, since the vinyl group was first cleaved and then reinstalled after the crucial cyclization step. We describe here a different stereocontrolled strategy that allows the separate construction of each stereoisomeric linalool oxide, without sacrificing any carbon atoms of the starting linalool.

2. Results and discussion

In our synthetic approach we envisioned a Δ^5-alkenol derived from linalyl acetate as a key substrate for the tetrahydropyran cyclization, anticipating that the 6-*exo*-cyclization mode would be largely favoured over the 7-*endo* one. Scheme 1 shows the retrosynthesis for (3*S*,6*R*)-*trans*-linalool oxide **2** as a model compound. Thus, assuming that the absolute configuration of compound **6** is retained in the cyclization step, the starting enantiomer of linalyl acetate provides the C-6 stereocentre of the target compound while the C-3 stereochemistry has to be installed by an asymmetric reaction. On the basis of previous results on (*R*)-(−)-linalool, we expected the Sharpless asymmetric dihydroxylation (AD) of the distant double bond of linalyl acetate to be highly regio- and stereoselective, thus affording an immediate precursor of olefin **6** of high enantiomeric purity and with a predictable absolute configuration at the secondary carbinol stereocentre. In conclusion, all the four stereoisomers **1**–**4** should become easily accessible starting from (*R*)- or (*S*)-linalyl acetate and using either AD-mix-α or AD-mix-β to install the other stereocentre.

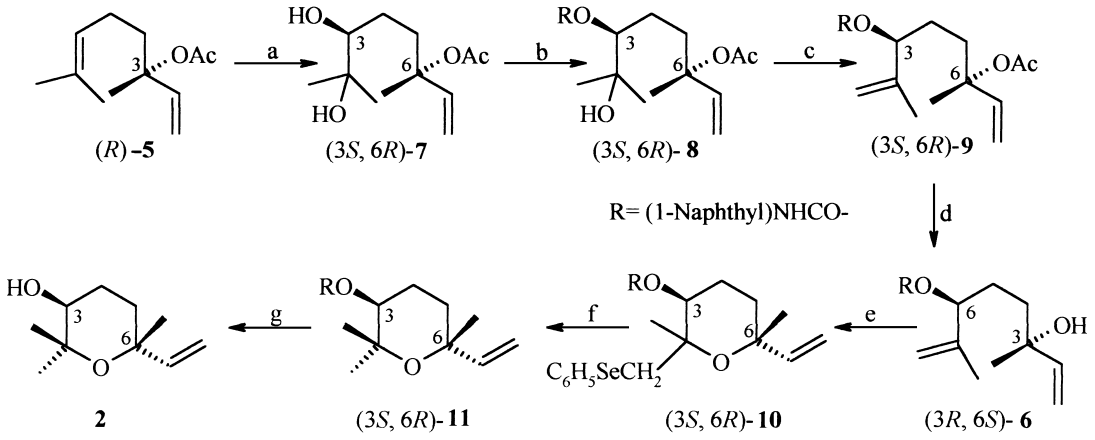


2 (3*R*,6*S*)- **6** (3*R*)-**5**

Scheme 1. Retrosynthetic analysis

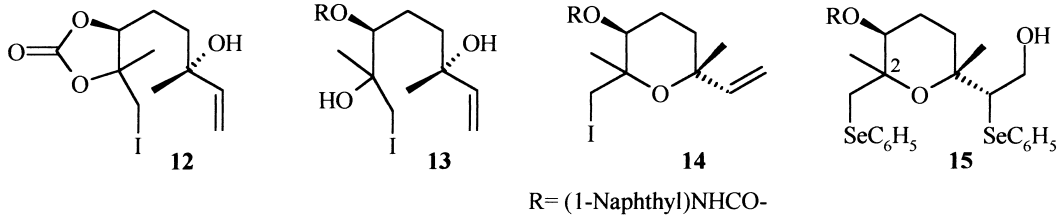
In the event, starting from (3*R*)-**5**, 98% ee, AD-mix-α gave the corresponding triol monoacetate, (3*S*,6*R*)-**7**, in 92% yield and 95% de (^{1}H NMR), while AD-mix-β afforded (3*R*,6*R*)-**7** in 83% yield and 97% de after flash column chromatography. In a similar fashion, (3*S*)-**5**, 96% ee,[19] provided the remaining two stereoisomers, (3*S*,6*S*)-**7** and (3*R*,6*S*)-**7**, 95 and 95% de, respectively. In these asymmetric reactions of **5**, dihydroxylation of the 1,2-double bond was negligible. The absolute configurations of the four products **7** were established via the Mosher's esters and confirmed by the stereochemistry of individual linalool oxide stereospecifically synthesized from each of them (vide infra). Compared with the AD of the parent free alcohol linalool, we noticed the dihydroxylations of acetates **5** was sluggish, requiring a higher osmium concentration (1 mol% OsO_4) and higher temperature (4°C) to go to completion. This was possibly due to the more pronounced steric and electron withdrawing effects of the acetoxy group; moreover, the free OH group of linalool may assist the hydroxylation of the double bond through precoordination with the osmium species. With all stereoisomers **8** in hand, we examined

different electrophilic species as effective promoters of the crucial cyclization step to pyran derivatives: for this (3*S*,6*R*)-**8**, used as a model compound, was first converted with standard reactions into the desired protected allylic diol (3*R*,6*S*)-**6** in satisfactory overall yield (Scheme 2).



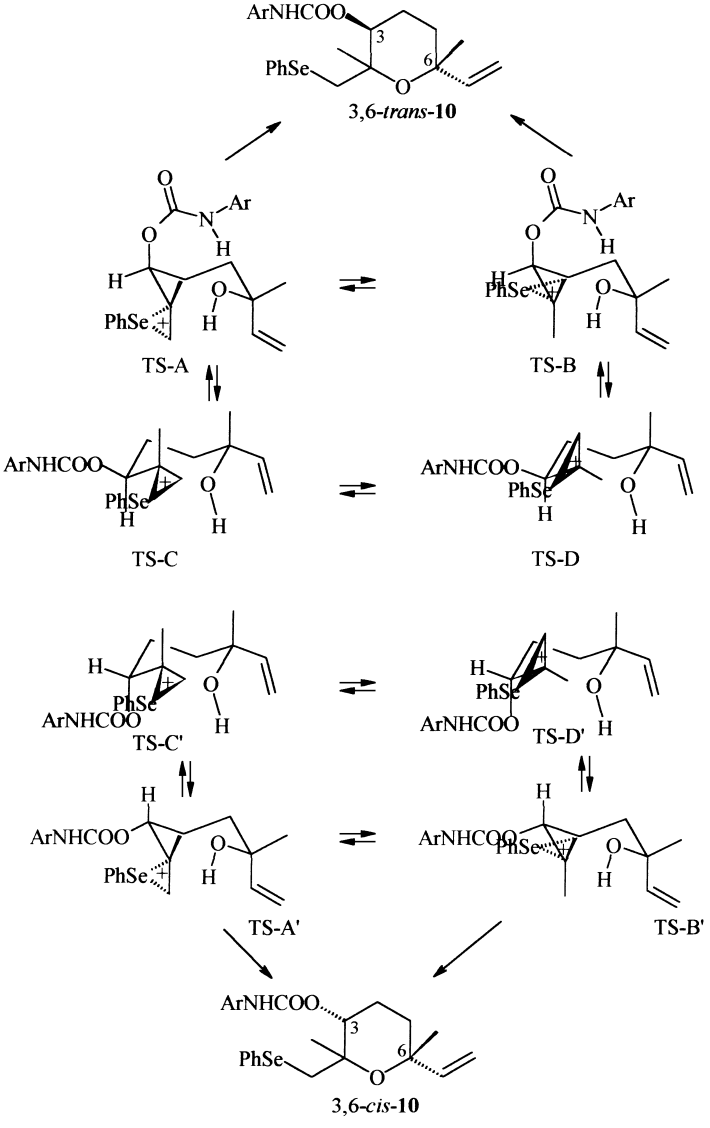
Scheme 2. (a) AD-mix-α; (b) (1-Naphthyl)NCO; (c) $POCl_3$; (d) MeONa, MeOH; (e) *N*-PSP, cat. pyridinium *p*-toluenesulphonate; (f) Ph_3SnH; (g) 10% MeONa, MeOH, reflux

Exposure of the latter compound to NBS in dry CH_2Cl_2 afforded, instead of the expected tetrahydropyran product, the carbonate **12**, arising from intramolecular cyclization of the carbamate group at C-6 onto the 7,8-double bond of **6**. Equally unsuccessful was the reaction of **6** with I_2 in wet Et_2O, while I_2 in MeCN returned unreacted starting material and 12% of a mixture of iodohydrin **13** and iodotetrahydropyran **14**.



Eventually, we resorted to electrophilic organoselenium reagents that are known to promote intramolecular cyclization of unsaturated alcohols to rings of different sizes. Indeed, formation of a tetrahydropyran ring by cyclization of a linalool derivative was achieved by Konstantinovic et al.;[9] later, however, Urones[10] cast serious doubts upon this claim. In the event, upon exposure to *N*-(phenylseleno)phthalimide (*N*-PSP)[13,20,21] and cat. *p*-TsOH in CH_2Cl_2, compound (3*R*,6*S*)-**6** smoothly afforded phenyl selenoethers (3*S*,6*R*)-**10** as an inseparable mixture of diastereoisomers at C-2. These compounds were accompanied by variable amounts of unreacted **6** and diselenides **15** (mixture of stereoisomers), depending on the number of equivalents of *N*-PSP employed, reaction temperature and extent of conversion of compound **6**. Interestingly, we noticed the selenoetherification across the 7,8-double bond of **6** was significantly slower than the 'PhSeOH' addition to the 1,2-olefin. Therefore, with respect to the original procedure of Williard,[13] in order to reduce the amount of the side product **15,** eventually we used only 1.2 equivalents of *N*-PSP, and the temperature of the reaction was kept below 5°C. Moreover, the reaction was stopped at ca. 60% conversion of **6**. Under these optimized conditions, tetrahydropyran **10** was produced in 45% yield based on recovered starting material. Other electrophilic Se reagents, such as PhSeCl or PhSeSePh–H_2O_2, proved inferior promoters of the cyclization of (3*R*,6*S*)-**6** to the corresponding pyran. Though the tetrahydropyranyl yield with *N*-PSP was modest, the regio- and

stereoselectivities were, however, excellent. Actually, no oxepane product arising from the alternative 7-*endo* type cyclization was observed, while the ee and de of target compound **2** were higher than 98% (GC analysis on a β-cyclodextrine capillary column). The latter, $[\alpha]_D^{20}$ +11.0 (CH_2Cl_2), was eventually obtained from **10** by C–Se bond cleavage with Ph_3SnH[22] followed by hydrolysis of the 1-naphthylcarbamate group in strong alkaline conditions. Compound **2** showed ^1H and ^{13}C NMR data identical with the literature.[14,17] Following an identical synthetic route, we converted each stereoisomeric diacyl triol **8** (see above) into the corresponding linalool oxide: thus, (3*R*,6*R*)-**8** gave pyran **1**, (3*R*,6*S*)-**8** afforded **3** and (3*S*,6*S*)-**8** led to **4**. Each compound showed NMR data identical with those reported in the literature,[14,17] and de and ee >96%. In the Experimental, for the sake of clarity, we report only one set of reactions carried out in the diastereomeric series started from (*R*)-**5**. Interestingly, we noticed the cyclizations of (3*R*,6*R*)- and (3*S*,6*S*)-**6** to be more sluggish than the corresponding (3*R*,6*S*)- and (3*S*,6*R*)-**6**, respectively; in addition, starting material (3*R*,6*R*)- or (3*S*,6*S*)-**6** rapidly degraded above 20%



Scheme 3.

conversion. The different reactivity of each diastereomer pair can be explained considering the chair-like transition states leading to the *cis*- and *trans*-tetrahydropyran derivatives **10**, respectively. The eight transition states for the pair (3*R*,6*R*)- and (3*S*,6*R*)-**6** are displayed in Scheme 3. The higher reactivity of the former compound may be due to a higher stability of TSA and TSB compared to the other transition states, owing to the smallest *gauche* and 1,3-diaxial interactions and the possible H-bond between the axial carbamate substituent and the OH group.

3. Conclusions

This paper describes the first diastereo- and enantioselectively controlled synthesis of each of the four stereoisomeric linalool oxides **1**–**4**. The four compounds were produced in high ee and de. These results illustrate the usefulness of the selenoetherification reaction of enantiomerically enriched Δ^5-alkenols for bridging two quaternary carbon atoms with an ether bond and pave the way for the preparation of a wide array of 2,2,6,6-tetrasubstituted pyran derivatives of high enantiomeric excess.

Interestingly, a perfume expert asked to distinguish the scent of the four stereoisomers **1**–**4** perceived no appreciable difference. Their odour was described as not intense, having a resin-like character with overtones of citrus fruits, of flowers and balsam.

4. Experimental

4.1. General

Melting points were determined on a Fisher–Johns hot plate and are uncorrected. IR data (film) were obtained on a Perkin–Elmer FT-IR Paragon 100 PC spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$ solution unless otherwise indicated, using a Bruker CXP 300 spectrometer. Chemical shifts are reported in δ units with Me_4Si as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad are used throughout. Coupling constants (*J*) are in hertz. The multiplicity (in parentheses) of each carbon atom was determined by DEPT experiments. Mass spectra (direct inlet system) were recorded at 70 eV (0.5 mA) with a Finnigan MAT 8222 instrument. All experiments were run in oven-dried glassware under an argon atmosphere. Analytical TLC was carried out on 0.25 mm glass-supported silica gel plates and visualization was effected with short-wavelength UV light (254 nm) or with 0.5% vanillin solution in H_2SO_4:EtOH (4:1) followed by heating. Flash column chromatography was accomplished with 230–400 mesh silica gel. De and ee were determined by GC using a Hewlett–Packard mod. 5890 instrument, equipped with an EASY DEX 6 β-CD capillary column (25 m×0.32 mm id and 0.25 μm film thickness) (column A) and a Carlo Erba mod. 4160 instrument, equipped with a 30% 2,3-diethyl-6-*t*-butyldimethylsilyi-β-CD on a PSO86 capillary column (25 m×0.25 mm id and 0.15 μm film thickness) (column B). Optical activity was measured with a Perkin–Elmer 241 polarimeter. All commercial reagent grade solvents were dried and degassed by standard techniques just before use. Yields are reported for chromatographically and spectroscopically pure isolated compounds. Actually, isolated yields of volatile compounds **1**–**4** were lowered by extensive losses occurring during evaporation of solutions containing them. (*R*)-(−)-Linalool was a generous gift from R.C. Treatt & Co. Ltd., while (*S*)-(+)-linalool was synthesized according to the literature.[19]

4.2. (−)-(R)-3-Acetoxy-3,7-dimethylocta-1,6-diene (3R)-5

Ac_2O (5.574 g, 54.6 mmol) and DMAP (146 mg, 1.2 mmol) were added to a solution of (−)-(*R*)-linalool (6.000 g, 0.0384 mol) in pyridine (3.700 g, 0.0468 mmol). The mixture was stirred at 90°C for 44 h, then quenched by adding MeOH and aqueous $NaHSO_4$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, and taken to dryness. Separation of the residue by column chromatography (gradient from hexane to 10% hexane:EtOAc) afforded (*R*)-linalyl acetate (3*R*)-**5** (7.489 g, 97% yield) as a colourless oil. $[\alpha]_D^{20}$ −3.0 (*c* 1.0, CH_2Cl_2); IR 3057, 2984, 2937, 2876, 1734, 1653, 1442, 1368, 1240, 1168, 1096, 1043, 939, 926, 737, 704, 608 cm^{-1}; ^1H NMR δ 1.55 (s, 3H), 1.6 and 1.7 (s and s, 2×3H), 2.0 (s, 3H), 5.0–5.3 (m, 3H), 6.0 (m, 1H); EIMS $C_{12}H_{20}O_2$ *m/z*: 136 (M−AcOH, 14), 121 (M−Me, 20), 107 (10), 93 (100), 80 (42), 71 (35), 69 (68), 55 (20), 43 (100), 41(58); CIMS (NH_3) $C_{12}H_{20}O_2$ *m/z*: 231 (M+NH_4+NH_3), 214 (M+NH_4), 154 (M−AcOH+NH_4). Anal. calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.35; H, 10.32.

4.3. (3S,6R)-6-Acetoxy-2,6-dimethyloct-7-en-2,3-diol (3S,6R)-7

AD-mix-α (12.00 g) was added to a stirred 1:1 mixture of *t*BuOH:H_2O (51 mL), and stirring was continued at room temperature (25°C) until two bright yellow phases were obtained. $MeSO_2NH_2$ (484 mg, 5.08 mmol) was added, followed by linanyl acetate (*R*)-**5** (1.000 g, 5.10 mmol) at 0°C. The heterogeneous mixture was stirred vigorously at 4°C for 20 h, then quenched with solid Na_2SO_3; stirring was continued for 30 min, until decoloration, allowing the mixture to warm to room temperature. CH_2Cl_2 was added and after separation of the layers the aqueous phase was further extracted with the same organic solvent. The combined organic layers were treated with aq. 2 M KOH, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 1:2) to afford (3*S*,6*R*)-**7** as a colourless oil (1.080 g, 92%, 95% de). $[\alpha]_D^{20}$ −19.3 (*c* 0.6, CH_2Cl_2); IR 3418, 2975, 1734, 1644, 1371, 1255, 1170, 1075, 1021, 911, 733 cm^{-1}; ^1H NMR of major stereoisomer: δ 1.15 (s, 3H), 1.20 (s, 3H), 1.55 (s, 3H), 1.20–1.61 (m, 2H), 1.7–1.9 (m, 1H), 2.01 (s, 3H), 2.10–2.22 (m, 1H), 3.30 (br d, *J*=10, 1H), 5.10–5.20 (2H, *AB*X), 5.93 (1H, AB*X*); ^{13}C NMR of major stereoisomer: δ 169.95 (s), 141.63 (d), 113.24 (t), 82.79 (s), 78.52 (d), 73.00 (s), 37.04 (t), 26.46 (q), 25.54 (t), 23.55 (q), 23.26 (q), 22.08 (q); CIMS (NH_3) $C_{12}H_{22}O_4$ *m/z*: 248 $(M+NH_4)^+$, 230 $(M)^+$, 188 (M−AcOH+NH_4^+). Anal. calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.48; H, 9.70.

4.4. (3R,6R)-6-Acetoxy-2,6-dimethyloct-7-en-2,3-diol (3R,6R)-7

(*R*)-Linalyl acetate (2.000 g, 10.2 mmol) was submitted to AD-mix β (24.00 g) in the same conditions as indicated in Section 4.3 to afford the diol (3*R*,6*R*)-**7** as a colourless oil (1.957 g, 83.3% yield, 97% de). $[\alpha]_D^{20}$ −2.9 (*c* 1.4, CH_2Cl_2); IR 3422, 2975, 1734, 1644, 1369, 1264, 1160, 1075, 1021, 911, 733 cm^{-1}; ^1H NMR of major stereoisomer: δ 1.18 (s, 3H), 1.22 (s, 3H), 1.25–1.55 (m, 2H), 1.58 (s, 3H), 1.88–2.10 (m, 2H), 2.02 (s, 3H), 2.35 (br s, 1H), 3.32 (br d, *J*=10, 1H), 5.11–5.20 (2H, *AB*X), 5.95 (1H, AB*X*); ^{13}C NMR of major stereoisomer: δ 169.87 (s), 141.24 (d), 113.23 (t), 82.85 (s), 78.37 (d), 72.87 (s), 36.90 (t), 26.32 (q), 25.45 (t), 23.63 (q), 23.12 (q), 21.98 (q); CIMS (NH_3) $C_{12}H_{22}O_4$ *m/z*: 248 $(M+NH_4)^+$, 230 $(M)^+$, 188 (M−AcOH+NH_4^+). Anal. calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.50; H, 9.68.

4.5. (3S,6R)-6-Acetoxy-3-(N-1-naphthyl)carbamoyloxy-2,6-dimethyloct-7-en-2-ol (3S,6R)-8

Dry pyridine (9.83 g, 124.3 mmol), followed by *N*-1-naphthylisocyanate (4.24 g, 25 mmol), was added to a solution of (3*S*,6*R*)-**7** (1.080 g, 4.69 mmol) in dry CH_2Cl_2 (30 mL) at 0°C under an argon atmosphere. The mixture was stirred for 2.5 h at the same temperature then quenched with water; vigorous stirring was continued for 30 min, to completely hydrolyse *N*-1-naphthylisocyanate in excess. The mixture was then filtered through a Celite pad. After separation of the layers the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were treated with a saturated solution of $NaHSO_4$, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:EtOAc, 3:2) to afford (3*S*,6*R*)-**8** (1.310 g, 70%). $[\alpha]_D^{20}$ −13.4 (*c* 2.8, CH_2Cl_2); IR 3340, 2978, 2937, 1734, 1713, 1538, 1371, 1237, 1177, 1073, 1005, 793, 772 cm^{-1}; ^1H NMR δ 1.22 (s, 3H), 1.27 (s, 3H), 1.55 (s, 3H), 1.60–1.90 (m, 4H), 2.01 (s, 3H), 2.10 (br s, 1H, OH), 4.76 (br d, *J*=10, 1H), 5.10–5.20 (2H, *AB*X), 5.91 (1H, AB*X*), 7.15 (br s, 1H, NH), 7.40–7.98 (m, 7H); EIMS $C_{23}H_{29}NO_5$ *m/z*: 399 (M^+, 25), 339 (M−AcOH, 5), 187 (70), 169 (100), 143 (70), 115 (20), 109 (20), 81 (30), 71 (25), 57 (18), 43 (45); HRMS *m/z*: 399.2051 (calcd for $C_{23}H_{29}NO_5$: 399.2046).

4.6. (3R,6R)-6-Acetoxy-3-(N-1-naphthyl)carbamoyloxy-2,6-dimethyloct-7-en-2-ol (3R,6R)-8

Compound (3*R*,6*R*)-**7** (1.687 g, 7.32 mmol) was submitted to the same conditions as indicated for (3*S*, 6*R*)-**7** in Section 4.5 to afford after purification (3*R*,6*R*)-**8** (2.107 g, 72% yield). $[\alpha]_D^{20}$ +12.6 (*c* 1.9, CH_2Cl_2); IR 3330, 3054, 2978, 2937, 1732, 1713, 1540, 1371, 1237, 1177, 1073, 1025, 1005, 793, 772 cm^{-1}; ^1H NMR δ 1.25 (s, 3H), 1.27 (s, 3H), 1.55 (s, 3H), 1.56–1.82 (m, 2H), 1.88–2.00 (m, 2H), 2.04 (s, 3H), 2.15 (br s, 1H), 4.76 (br d, *J*=10.5, 1H), 5.05–5.20 (2H, *AB*X), 5.93 (1H, AB*X*), 7.15 (br d, 1H, NH), 7.40–7.98 (m, 7H); EIMS $C_{23}H_{29}NO_5$ *m/z*: 399 (M^+, 10), 339 (M−AcOH, 3), 187 (52), 169 (100), 143 (62), 115 (20), 109 (18), 81 (38), 71 (28), 59 (23), 57 (18), 43 (70); HRMS *m/z*: 399.2049 (calcd for $C_{23}H_{29}NO_5$: 399.2046).

4.7. (3S,6R)-6-Acetoxy-3-(N-1-naphthyl)carbamoyloxy-2,6-dimethylocta-1,7-diene (3S,6R)-9

$POCl_3$ (4.384 g, 28.60 mmol) was slowly added via syringe to a stirred solution of (3*S*,6*R*)-**8** (1.145 g, 2.87 mmol) in dry pyridine (10 mL) at 0°C under an argon atmosphere. The mixture was stirred at room temperature for 1.5 h, then poured onto ice. After separation of two layers, the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were treated with aq. $NaHSO_4$, aq. 5% $NaHCO_3$ and brine, then dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel (hexane:AcOEt, 7:3 to 6:4) to afford pure (3*S*, 6*R*)-**9** (0.71 g, 65%). $[\alpha]_D^{20}$ +6.1 (*c* 1.23, CH_2Cl_2); IR 3322, 3052, 2928, 1732, 1651, 1538, 1499, 1370, 1255, 1103, 1003, 791, 771 cm^{-1}; ^1H NMR δ 1.55 (s, 3H), 1.60–1.95 (4H), 1.76 (s, 3H), 2.04 (s, 3H), 4.92–5.22 (m, 5H), 5.94 (m, 1H, AB*X*), 7.01 (br s, 1H, NH), 7.41–7.98 (m, 7H); EIMS $C_{23}H_{27}NO_4$ *m/z*: 381 (M^+, 17), 187 (42), 169 (37), 143 (98), 135 (27), 115 (22), 107 (44), 93 (72), 79 (25), 71 (33), 55 (54), 43 (100). Anal. calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.49; H, 7.21; N, 3.56.

4.8. (3R,6R)-6-Acetoxy-3-(N-1-naphthyl)carbamoyloxy-2,6-dimethylocta-1,7-diene (3R,6R)-9

Compound (3*R*,6*R*)-**8** (1.532 g, 3.83 mmol) was submitted to the same conditions as indicated for (3*S*, 6*R*)-**8** in Section 4.7 to afford after purification (3*R*,6*R*)-**9** (0.876 g, 60%). $[\alpha]_D^{20}$ −11.7 (*c* 3.60, CH_2Cl_2); IR 3322, 3054, 2976, 1733, 1653, 1539, 1499, 1370, 1255, 1221, 1103, 1023,1003, 792, 771 cm^{-1}; ^1H

NMR δ 1.55 (s, 3H), 1.60–1.95 (4H), 1.75 (s, 3H), 2.04 (s, 3H), 4.95 (br s, 1H), 5.05 (br s, 1H), 5.10–5.20 (m, 3H), 5.93 (1H, AB*X*), 7.00 (br s, 1H, NH), 7.41–7.98 (m, 7H); EIMS $C_{23}H_{27}NO_4$ *m/z*: 381 (M^+, 21), 187 (43), 169 (40), 143 (100), 135 (26), 115 (22), 107 (44), 93 (69), 79 (23), 71 (21), 55 (40), 43 (77). Anal. calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.51; H, 7.16; N, 3.59.

*4.9. (3*R,*6*S*)-6-(*N-*1-Naphthyl)carbamoyloxy-3,7-dimethylocta-1,7-dien-3-ol (3*R,*6*S*)-**6**

To a solution of (3*S*,6*R*)-**9** (485 mg, 1.27 mmol) in dry MeOH was added 10% MeONa in MeOH (341 mg, 6.31 mmol of MeONa). The mixture was stirred at room temperature for 1 h under an argon atmosphere. The reaction was quenched by adding water and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were treated with a saturated solution of NH_4Cl, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 7:3) to afford (3*R*,6*S*)-**6** (330 mg, 76.5%). $[\alpha]_D^{20}$ +0.26 (*c* 0.50, CH_2Cl_2); IR 3450–3300, 3080, 3050, 2966, 2924, 1702, 1534, 1497, 1220, 1103, 1071, 1001, 791, 770 cm^{-1}; ^1H NMR δ 1.30 (s, 3H), 1.45–1.80 (4H), 1.76 (br s, 3H), 4.94 (br s, 1H), 5.03 (br s 1H), 5.08–5.27 (m, 3H), 5.89 (1H, AB*X*), 6.95 (br s, 1H, NH), 7.40–7.90 (m, 7H); EIMS $C_{21}H_{25}NO_3$ *m/z*: 339 (M^+, 8), 187 (48), 169 (M^+−AcOH, 14), 143 (100), 115 (21), 107 (21), 93 (30), 81 (16), 71 (27), 67 (20), 55 (16), 43 (32). Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.20; H, 7.49; N, 4.10.

*4.10. (3*R,*6*R*)-6-(*N-*1-Naphthyl)carbamoyloxy-3,7-dimethylocta-1,7-dien-3-ol (3*R,*6*R*)-**6**

Compound (3*R*,6*R*)-**9** (497 mg, 1.30 mmol) was submitted to the same conditions as indicated for (3*S*,6*R*)-**9** to afford (3*R*,6*R*)-**6** (362 mg, 82%). $[\alpha]_D^{20}$ −19.6 (*c* 1.00, CH_2Cl_2); IR 3450–3300, 2970, 2930, 1710, 1650, 1534, 1500, 1255, 1220, 1103, 1071, 1001, 920, 791, 772 cm^{-1}; ^1H NMR δ 1.30 (s, 3H), 1.50–1.80 (m, 4H), 1.72 (br s, 3H), 4.93 (br s, 1H), 5.02 (br s, 1H), 5.05–5.27 (m, 3H), 5.88 (1H, AB*X*), 7.02 (br s, 1H, NH), 7.40–7.90 (m, 7H); EIMS $C_{21}H_{25}NO_3$ *m/z*: 339 (M^+, 7), 187 (46), 169 (M^+−AcOH, 13), 143 (100), 115 (20), 107 (23), 93 (32), 81 (18), 71 (30), 67 (21), 55 (32), 43 (49). Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.36; H, 7.38; N, 4.04.

*4.11. (2*RS,*3*S,*6*R*)-Tetrahydro-3-(*N-*1-naphthyl)carbamoyloxy-6-ethenyl-2-phenylselenylmethyl-2,6-dimethyl-2*H*-pyran (2*RS,*3*S,*6*R*)-**10**

A catalytic amount of PPTS and *N*-PSP (362 mg, 1.20 mmol) was added at −78°C to a stirred solution of (3*R*,6*S*)-**6** (340 mg, 1.0 mmol) in CH_2Cl_2 under an argon atmosphere. The mixture was stirred at −78°C for 2 h; then it was allowed to warm to 0°C and maintained at this temperature for 24 h. Stirring was then continued at 5°C for 5 h. The mixture was then filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane:AcOEt, 7:3) to afford (2*RS*,3*S*,6*R*)-**10** (165 mg, 42% yield on the recovered starting material) and unreacted (3*R*,6*S*)-**6** (70 mg). Compound (2 *RS*,3*S*,6*R*)-**10**: $[\alpha]_D^{20}$ +69.3 (*c* 0.2, CH_2Cl_2); IR 3422, 3053, 2983, 1730, 1532, 1495, 1209, 895, 704 cm^{-1}; ^1H NMR δ 1.20 (s, 3H), 1.40 (s, 3H), 1.70–2.10 (m, 4H), 3.00–3.30 (br m, 2H, C*H*$_2$SePh), 4.90 (br s, 1H), 4.95–5.10 (2H, *AB*X), 5.95 (1H, AB*X*), 6.95 (br s, 1H, NH), 7.01–7.98 (m, 7H); EIMS $C_{27}H_{29}NO_3Se$ *m/z*: 491–499 (cluster Se), 324 (30), 188 (13), 169 (34), 155 (43), 137 (100), 115 (12), 95 (24), 93 (27), 81 (31), 79 (15), 67 (11), 55 (21), 43 (90).

*4.12. (2*RS,*3*R,*6*R*)-Tetrahydro-3-(*N-*1-naphthyl)carbamoyloxy-6-ethenyl-2-phenylselenylmethyl-2,6-dimethyl-2*H-*pyran (2*RS,*3*R,*6*R*)-**10***

In the case of (3*R*,6*R*)-**6** (230 mg, 0.678 mmol), the mixture was stirred at −78°C for 2 h, at 0°C for 45 h, and at 5°C for 24 h. Chromatographic separation afforded (2*RS*,3*R*,6*R*)-**10** (30 mg, 40% yield on the recovered starting material) and unreacted (3*R*,6*R*)-**6** (187 mg). (2*RS*,3*R*,6*R*)-**10**, $[\alpha]_D^{20}$ +9.3 (*c* 0.2, CH_2Cl_2); IR 3428, 3054, 2983, 1712, 1533, 1495, 1209, 909, 704 cm^{-1}; ^1H NMR δ 1.26 and 1.42 (2 br s, 2x3H), 1.60–2.20 (m, 4H), 3.00–3.60 (m, 2H), 4.70–5.20 (m, 3H), 5.95 (1H, AB*X* of minor diastereisomer), 6.17 (1H, AB*X* of major diastereisomer), 6.90 (br s, 1H, NH), 7.10–7.98 (m, 7H); EIMS $C_{27}H_{29}NO_3Se$ *m/z*: 491–499 (M^+ cluster Se), 324 (66), 188 (30), 169 (60), 155 (67), 143 (30), 137 (91), 115 (21), 109 (17), 95 (42), 93 (47), 81 (58), 79 (21), 67 (20), 55 (39), 43 (100).

*4.13. (3*S,*6*R*)-Tetrahydro-3-(*N-*1-naphthyl)carbamoyloxy-6-ethenyl-2,2,6-trimethyl-2*H-*pyran (3*S,*6*R*)-**11***

Ph_3SnH (211 mg, 0.6 mmol) was added to a refluxing stirred solution of (2*RS*,3*S*,6*R*)-**10** (100 mg, 0.2 mmol) in dry toluene (2 mL) under an argon atmosphere. The mixture was refluxed and stirred for 24 h, then allowed to cool to room temperature. After evaporation of toluene, the residue was dissolved in MeCN. The solution was then filtered and extracted five times with hexane to remove tin compounds. MeCN was evaporated and the residue was purified by RP 18 column chromatography (from MeOH:H_2O, 7:3, to 100% MeOH) to afford (3*S*,6*R*)-**11** (42 mg, 61% yield). $[\alpha]_D^{20}$ +13.9 (*c* 0.9, CH_2Cl_2). IR 3315, 2966, 2929, 1706, 1534, 1497, 1345, 1216, 1084, 792, 770, 665 cm^{-1}; ^1H NMR δ 1.25 (br s, 6H), 1.30 (br s, 3H), 1.88 (m, 2H), 2.12 (m, 2H), 4.75 (br s, 1H), 4.95–5.11 (2H, *AB*X), 5.98 (1H, AB*X*), 7.05 (br s, 1H, NH), 7.45–7.95 (m, 7H); HRMS *m/z*: 339.1829 (calcd for $C_{21}H_{25}NO_3$: 339.1834).

*4.14. (3*R,*6*R*)-Tetrahydro-3-(*N-*1-naphthyl)carbamoyloxy-6-ethenyl-2,2,6-trimethyl-2*H-*pyran (3*R,*6*R*)-**11***

Compound (2*RS*,3*R*,6*R*)-**10** (30 mg, 0.06 mmol) was submitted to the same conditions as described for (2*RS*,3*S*,6*R*)-**10** to afford after purification (3*R*,6*R*)-**11** (15 mg, 73% yield). $[\alpha]_D^{20}$ −10.0 (*c* 0.50, CH_2Cl_2); IR 3300, 2977, 2949, 1705, 1538, 1499, 1367, 1346, 1216, 1072, 1035, 914, 835, 789, 770 cm^{-1}; ^1H NMR δ 1.18 (br s, 6H), 1.25 (br s, 3H), 1.60–2.20 (m, 4H), 4.70 (dd, *J*=10.5 and 3.5, 1H), 4.95–5.08 (m, 2H, *AB*X), 5.95 (1H, AB*X*), 6.90 (br s, 1H, NH), 7.45–7.95 (m, 7H); HRMS *m/z*: 339.1837 (calcd for $C_{21}H_{25}NO_3$: 339.1834).

*4.15. (3*S,*6*R*)-Tetrahydro-6-ethenyl-2,2,6-trimethyl-2*H-*pyran-3-ol **2***

To a solution of (3*S*,6*R*)-**11** (39 mg, 0.11 mmol) in dry MeOH was added 10% MeONa in MeOH (33 mg, 0.61 mmol of MeONa). The mixture was heated at reflux for 2–3 h under an argon atmosphere, then cooled to room temperature, diluted with water and extracted with Et_2O. The combined organic layers were treated with a saturated solution of NH_4Cl, brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:CH_2Cl_2:EtOAc, 60:30:10) to afford compound **2** (10.5 mg, 54%) as a semisolid oil. $[\alpha]_D^{20}$ +11.0 (*c* 0.5, CH_2Cl_2); IR 3434, 2975, 2938, 1640, 1462, 1402, 1366, 1229, 1190, 1140, 1114, 1075, 1018, 980, 958, 914, 830 cm^{-1}; ^1H NMR δ 1.23 (s, 2× 3H), 1.24 (s, 3H), 1.65–2.05 (m, 4H), 3.43 (m, 1H), 4.92–5.08 (2H, *AB*X), 5.95 (1H, AB*X*);

^{13}C NMR δ 146.8 (d), 110.5 (t), 75.2 (s), 73.6 (s), 71.2 (d), 30.9 (q), 27.5 (t), 27.1 (q), 26.4 (q), 24.2 (t); EIMS $C_{10}H_{18}O_2$ *m/z*: 155 ($M-Me^+$, 5), 137 (3), 112 (4), 94 (61), 79 (17), 68 (100), 59 (71), 43 (36); HRMS *m/z*: 170.1311 (calcd for $C_{10}H_{18}O_2$: 170.1307).

*4.16. (3*R*,6*R*)-Tetrahydro-6-ethenyl-2,2,6-trimethyl-2*H*-pyran-3-ol **1***

Compound (3*R*,6*R*)-**11** gave compound **1** according to the same procedure described in Section 4.15; yield 58%; mp 94–95°C; $[\alpha]_D^{20}$ +1.9 (*c* 0.5, CH_2Cl_2); IR 3426, 2975, 2945, 1634, 1450, 1407, 1362, 1229, 1185, 1153, 1114, 1085, 1001, 980, 909, 865, 830, 748 cm^{-1}; ^{1}H NMR δ 1.16 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 1.50–1.77 (m, 3H), 2.13 (m, 1H), 3.44 (m, 1H), 4.95–5.05 (2H, *AB*X), 5.97 (1H, AB*X*); ^{13}C NMR δ 146.2 (d), 110.6 (t), 75.8 (s), 74.8 (d), 73.4 (s), 32.4 (t), 31.5 (q), 29.4 (q), 25.6 (t), 20.7 (q); EIMS $C_{10}H_{18}O_2$ *m/z*: 155 ($M-Me^+$, 2), 137 (2), 102 (3), 97 (3), 94 (65), 79 (14), 68 (100), 59 (71), 43 (29); HRMS *m/z*: 170.1302 (calcd for $C_{10}H_{18}O_2$: 170.1307).

*4.17. (3*R*,6*S*)-Tetrahydro-6-ethenyl-2,2,6-trimethyl-2*H*-pyran-3-ol **3** and (3*S*,6*S*)-tetrahydro-6-ethenyl-2,2,6-trimethyl-2*H*-pyran-3-ol **4***

These compounds were synthesized from (*S*)-(+)-linalool[19] according to the same procedures from **5** through **11** described above for the corresponding enantiomers. Spectral and physical data, except the opposite signs of optical rotation, were identical to those of the corresponding enantiomers.

Column B (see above) was used for the separation of the four stereoisomers **1**–**4**. The temperature of the column was increased from 60 to 200°C with a gradient of 1°C min^{-1}. The detector (FID) was at 250°, the glass injector (split ratio 1:30) at 230° and the carrier gas was H_2, 1.5 cc min^{-1}. The elution order of the linalool oxides was found to be: 3*R*,6*S*-**3** (R_t=23.35 min), 3*S*,6*R*-**2** (R_t=24.63 min), 3*S*,6*S*-**4** (R_t=25.42 min) and 3*R*,6*R*-**1** (R_t=25.96 min).

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