Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 981–989

TETRAHEDRON: *ASYMMETRY*

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

Giovanni Vidari,* Anna Di Rosa, Francesca Castronovo and Giuseppe Zanoni

Dipartimento di Chimica Organica, Università di Pavia, Via Taramelli 10, 27100 Pavia, Italy

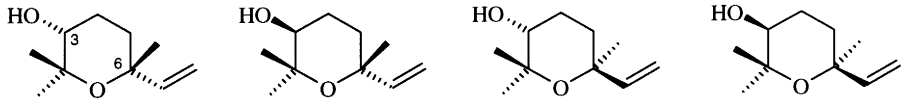
Received 10 December 1999; accepted 6 January 2000

Abstract

Each of the four enantiomerically pure tetrahydropyran linalool oxides was synthesized by an acid-catalyzed cyclization of an appropriate epoxy-alcohol obtained by consecutive Sharpless dihydroxylation (AD) and epoxidation (AE) reactions of geraniol derivatives. An interesting example of double asymmetric induction was observed during the AE of a bis(homoallylic) *N*-naphthylcarbamate.

1. Introduction

The four linalool oxides **1** (3*R*,6*R*), **2** (3*S*,6*R*), **3** (3*R*,6*S*), and **4** (3*S*,6*S*), as different mixtures of stereoisomers, have been found as constituents of many flower and fruit aromas, such as grapes and *Carica papaya* fruits.[1,2] Even as minor constituents of these fragrances, compounds **1**–**4** are considered to be important contributors to a particular 'note' or 'character' of the scent.[3]



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

In addition, they probably have a strong biological significance in certain pollination systems, acting as insect attractants.[3] Interestingly, the 2,2,6,6-tetrasubstituted pyran ring is also encountered in a few marine natural products[4–6] as well as in terrestrial fungal metabolites.[7] As a part of our ongoing project on the synthesis of these synthetically appealing natural products,[8] we became interested in the stereoselective synthesis of linalool oxides **1**–**4**, as model compounds for testing general approaches[9,10] to enantiomerically enriched substituted pyran ring derivatives. It must be stressed that most previous syntheses of linalool oxide-like pyran derivatives[11–24] were usually poorly stereoselective, giving mix-

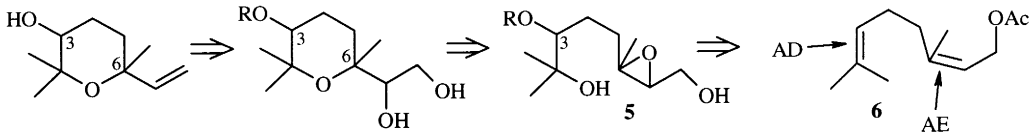
* Corresponding author. Tel: 0039 0382507322; fax: 0039 0382507323; e-mail: vidari@chifis.unipv.it

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00014-8

tures of *cis*- and *trans*-stereoisomers in almost equal amounts. In addition, the latter compounds were often accompanied by the corresponding isomeric tetrahydrofuran oxides. Recently, we described a highly enantioselective synthesis of each of the four pyrans **1**–**4** based on a stereospecific selenocyclization of the appropriate chiral Δ^5-alkenols derived from (*R*)-(−)- or (*S*)-(+)-linalool.[25] In this paper, we describe a different strategy centred on a stereospecific acid-catalyzed cyclization of a chiral epoxy-alcohol to afford the hydroxylated THP ring. Moreover, in contrast to the former chiron-like approach in which the C-3 stereogenic centre of the starting linalool was preserved through the synthetic pathway, eventually becoming the C-6 carbon of the final compound, in this variant both stereogenic carbons of the target compound are introduced into an achiral precursor by two consecutive asymmetric steps.

2. Results and discussion

Based on the general retrosynthetic analysis shown in Scheme 1, each stereoisomer of pyranoid linalool oxides **1**–**4** may become available via the stereospecific 6-*exo*-tet hydroxy epoxide opening of the corresponding intermediate **5**.

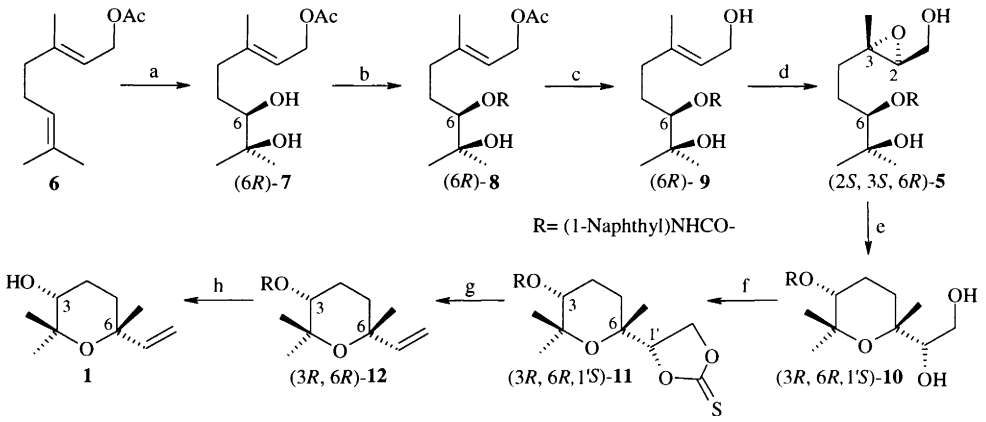


Scheme 1. Retrosynthetic analysis

For the sake of simplicity, our approach to compounds **5** was based on the so called 'naked' carbon skeleton strategy,[26] i.e., selective placement of stereochemically defined oxygen functions onto a naked unsaturated carbon skeleton. For this goal we planned to use the Sharpless catalytic asymmetric dihydroxylation (AD)[27] and asymmetric epoxidation (AE)[28] reactions, which allow the sterecontrolled functionalization of prostereogenic olefins in a highly predictable way, depending on the chiral ligand used. Thus, we envisioned the stereodivergent synthesis of each pyranoid linalool oxide in two major steps using the same starting compound, i.e., the 'naked' carbon skeleton of geranyl acetate **6** that already contains all the carbon atoms of the target products. First, the AD reaction was used to dihydroxylate the remote double bond of **6**, and then the AE reaction was used to epoxidize the allylic double bond.

In principle, the stereochemical issues associated with the synthesis of the four stereoisomers **5** was thus reduced to a correct combination of the asymmetric inductions of one of the two AD with one of the two AE reactions. In addition, previous studies[29] established that, in order to prevent the undesired formation of a five-membered THF ring via the highly preferred 5-*exo*-tet ring closure, construction of diol **5** required installation of the epoxy ring after the dihydroxylation step and protection of the secondary hydroxy group. A total of two AD reactions followed by four AE reactions was thus necessary to reduce our synthetic plan to practice. The synthesis of linalool oxide **1** (Scheme 2) simplifies our synthetic pathway while in the Experimental, for the sake of clarity, we report only one set of reactions carried out in the diastereomeric series starting from (6*R*)-**7**.

Dihydroxylation of compound **6** with AD-mix-α gave the corresponding triol monoacetate (6S)-**7**, 91% ee, in 84% yield, while AD-mix-β afforded (6*R*)-**7**, 94% ee, in 85% yield after flash chromatography. In both reactions, dihydroxylation of the 1,2-double bond of compound **6** was <5%, confirming our previous results.[30] Protection of the secondary OH group of stereoisomers **7** was troublesome. Eventually, it was protected as 1-naphthylcarbamate[29] which, compared with other more traditional protective groups, was smoothly introduced at the severely hindered neopentylic position and proved to be inert



Scheme 2. (a) AD-mix-β; (b) (1-naphthyl)NCO; (c) K_2CO_3, MeOH; (d) L-(+)-DET, Ti(O-*i*-Pr)$_4$, *t*-BuOOH; (e) cat. 10-camphorsulfonic acid; (f) 1,1′-thiocarbonyldiimidazole; (g) $P(OMe)_3$, reflux; (h) 10% MeONa, MeOH, reflux

in the following synthetic steps. Finally, selective hydrolysis of the allylic acetate group provided the key substrates (6*R*)- and (6*S*)-**9** which were submitted to the stereodivergent epoxidation steps. Overall yields of **9** from **7** were in the range of 75–83%. The catalytic variant of the Katsuki–Sharpless AE reaction[31] of (6*R*)-**9**, in the presence of L-(+)-diethyl tartrate, afforded (2*S*,3*S*,6*R*)-epoxide **5** as the major stereoisomer, whereas, in the presence of the D-(−) auxiliary, (2*R*,3*R*,6*R*)-**5** was the major one. As expected, starting from the (6*S*)-**9** enantiomer, L-(+)-diethyl tartrate gave (2*S*,3*S*,6*S*)-**5**, while D-(−)-tartrate provided the remaining (2*R*,3*R*,6*S*)-epoxide.

The absolute configuration of these four stereoisomers was proved by that of the final products **1**–**4**. Epoxides **5** were always accompanied by variable amounts of the corresponding pyran derivatives **10** resulting from an intramolecular etherification reaction which was probably catalyzed by Ti(IV) species.[32] Also, the chromatographic separation of compounds **5** on silica gel gave rise to significant quantities of cyclic products **10**. A sample of (2*S*,3*S*,6*R*)-**5**, 91% de, was, however, eventually produced and converted (Scheme 2) into (3*R*,6*R*,1′*S*)-**10**, 90% de, thus demonstrating that the conversion **5**→**10** occurred with complete stereospecificity. Therefore, we continued our synthesis using crude epoxides **5** which were separately converted into the corresponding pyran derivatives, and the diastereomeric excess of each starting epoxide was estimated to match that established for the corresponding compound **10**. In a series of experiments, overall yields of diastereomerically enriched compounds **10** from **9** were in the range of 26–58%; de of (3*R*,6*R*,1′*S*)- and (3*S*,6*S*,1′*R*)-**10** reached 90–92%, while that of (3*R*,6*S*,1′*R*)- and (3*S*,6*R*,1′*S*)-**10** was a surprising low 20–25%. These data clearly indicated that the overall diastereoselectivity observed in the Sharpless AE of allylic alcohols **9** was controlled not only by the known intrinsic enantiofacial selectivity of the chiral Ti(IV) reagents towards allylic alcohols,[28] but also by the stereodirecting effects of the bis(homoallylic) *N*-naphthylcarbamoyloxy and tris(homoallylic) hydroxy groups. Indeed, allylic and homoallylic carbamate groups have been employed to control peroxy acid epoxidation of olefins and a steering effect similar to that of the corresponding free hydroxy groups has been found.[33] Though we could not find other examples in the literature, we assume that carbamate groups can also control the stereochemistry of the titanium tartrate ester-catalyzed asymmetric epoxidation of distant double bonds in a manner similar to that observed for bis(homoallylic) and tris(homoallylic) alcohols.[34] In conclusion, in the epoxidation of olefins **9** we were faced with a relative new example of substrate–reagent double asymmetric induction in which the combinations (6*R*)-**9**+L-DET and (6*S*)-**9**+D-DET constituted the matched pair, while (6*R*)-**9**+D-DET and (6*S*)-**9**+L-DET formed

the mismatched pair;[35] in the latter reactions, asymmetric induction of the chiral reagent prevailed over that of the substrate.

Chromatographic separations afforded diastereomerically enriched pyrans **10** which were separately converted into the corresponding linalool oxides **1**–**4** by conventional reactions. The four compounds were eventually produced in high ee and de. In conclusion, the 'naked' carbon skeleton strategy[26] proved to be suitable for the divergent asymmetric synthesis of each linalool oxide stereoisomer from abundantly available achiral geraniol. In addition, though still preliminary, our results show that carbamates may be useful as neighbouring directing groups to control Sharpless asymmetric epoxidation of prochiral olefins.

3. Experimental

3.1. 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 br=broad are used throughout. Coupling constants (*J*) are reported 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. Diastereomeric excesses and enantiomeric excesses were determined by ^{1}H NMR in the presence of Eu(tfc)$_3$ and/or 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*-butyldimethylsilyl-β-CD on PSO86 capillary column (25 m×0.25 mm id and 0.15 μm film thicknerss) (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 solution containing them.

3.2. Acetic acid (R)-6,7-dihydroxy-3,7-dimethyl-oct-2-enyl ester (6R)-7

AD-mix-β (28.764 g) was added to a stirred 1:1 mixture of *t*-BuOH:H_2O (205 mL), and stirring was continued at room temperature (25°C) until two bright yellow phases were obtained. $MeSO_2NH_2$ (1.940 g, 20.4 mmol) was added, followed by geranyl acetate **6** (4.000 g, 20.4 mmol) at 0°C. The heterogeneous mixture was stirred vigorously at 0°C for 48 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 dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane:AcOEt 7:3) to afford (6*R*)-**7**, as a colourless oil (4.000 g, 85%, ee 94%). $[\alpha]_D^{20}$ +25.2 (*c* 0.95, $CHCl_3$); IR 3445, 2979, 1725, 1668, 1440, 1380, 1365, 1325, 1240,

1160, 1080, 1020, 960 cm^{-1}; ^1H NMR δ 1.20 (s, 3H), 1.24 (s, 3H), 1.40–1.70 (m, 2H), 1.72 (br s, 3H), 2.10 (s, 3H), 2.10–2.40 (m, 2H), 3.35 (br d, *J*=10, 1H), 4.65 (d, *J*=7, 2H), 5.42 (br t, *J*=7, 1H); ^{13}C NMR δ 171.1 (s), 141.9 (s), 118.4 (d), 77.1 (d), 72.9 (s), 61.2 (t), 36.4 (t), 29.3 (t), 26.2 (q), 22.9 (q), 20.8 (q), 16.2 (q). Anal. calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.47; H, 9.71.

*3.3. Acetic acid (*S*)-6,7-dihydroxy-3,7-dimethyl-oct-2-enyl ester (6*S*)-**7***

Under the same conditions as described for (6*R*)-**7**, geranyl acetate **6** (712 mg, 3.63 mmol) was dihydroxylated in the presence of AD-mix-α to afford (6*S*)-**7** (699 mg, 84%, ee 91%). $[\alpha]_D^{20}$ −24.2 (*c* 1.1, $CHCl_3$). The IR, ^1H NMR and ^{13}C NMR data were identical to those of the enantiomer (6*R*)-**7**.

*3.4. Acetic acid (*R*)-7-hydroxy-3,7-dimethyl-6-(naphthalen-1-ylcarbamoyloxy)-oct-2-enyl ester (6*R*)-**8***

Dry pyridine (12 mL, 0.148 mmol), followed by *N*-1-naphthylisocianate (3.526 g, 20.84 mmol), was added to a solution of (6*R*)-**7** (4.0 g, 17.36 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 complete hydrolysis of excess *N*-1-naphthylisocyanate. The mixture was then filtered through a pad of Celite. 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:AcOEt 3:2) to afford (6*R*)-**8** (6.3 g, 91%). $[\alpha]_D^{20}$ +9.8 (*c* 1.0, CH_2Cl_2); IR 3330–3420 (OH and NH), 2975, 2936, 1718, 1540, 1499, 1373, 1231, 1105, 1048, 1025, 792, 771, 665 cm^{-1}; ^1H NMR δ 1.26 (br s, 6H), 1.70 (s, 3H), 1.70–1.92 (m, 2H), 2.05 (s, 3H), 2.05–2.30 (m, 2H), 4.59 (d, *J*=7, 2H), 4.79 (dd, *J*=10 and 2, 1H), 5.38 (br t, *J*=7, 1H), 7.18 (br s, 1H, NH), 7.40–8.00 (7H, ArH); ^{13}C NMR δ 170.86 (s), 154.89 (s), 141.04 (s), 133.99 (s), 132.41 (s), 128.51 (d), 127.07 (s), 126.07 (d), 125.84 (d), 125.62 (d), 125.21 (d), 120.59 (d), 119.80 (d), 118.79 (d), 80.79 (d), 72.42 (s), 51.12 (t), 35.78 (t), 27.81 (t), 26.46 (q), 24.98 (q), 20.75 (q), 16.32 (q); EIMS $C_{23}H_{29}NO_5$ *m/z* 399 (M^+, 22), 187 (99), 170 (24), 169 (97), 152 (21), 143 (100), 115 (27), 109 (36), 94 (22), 81 (53), 71 (35), 69 (24), 59 (27), 57 (22), 55 (22), 43 (77), 41 (20).

*3.5. Naphthalen-1-yl-carbamic acid (*R*)-6-hydroxy-1-(1-hydroxy-1-methyl-ethyl)-4-methyl-hex-4-enyl ester (6*R*)-**9***

Powdered K_2CO_3 (2.074 g, 15 mmol), followed by H_2O (0.5 mL), was added to a solution of acetate (6*R*)-**8** (5.900g, 14.78 mmol) in MeOH (150 mL). The mixture was stirred at rt for 3 h and then quenched by addition of 5% HCl and extracted with AcOEt. The solvent was evaporated and the residue purified by column chromatography on silica gel (hexane:AcOEt 65:35 to 50:50) to afford (6*R*)-**9** (4.780 g, 91%). $[\alpha]_D^{20}$ +5.0 (*c* 2.3, CH_2Cl_2); IR 3330, 3053, 2976, 2933, 1704, 1540, 1501, 1379, 1258, 1228, 1105, 1004, 793, 771 cm^{-1}; ^1H NMR δ 1.20 (br s, 6H), 1.62 (s, 3H), 1.60–1.90 (m, 2H), 2.00–2.20 (m, 2H), 2.35 (br s, 1H, OH), 2.79 (br s, 1H, OH), 4.10 (m, 2H), 4.80 (dd, *J*=10 and 2, 1H), 5.43 (br t, *J*=7, 1H), 7.33–7.95 (8H, NH and ArH). EIMS $C_{21}H_{27}NO_4$ *m/z* 357 (M^+, 26), 188 (24), 187 (77), 170 (38), 169 (80), 152 (15), 143 (78), 127 (14), 115 (45), 109 (36), 94 (15), 81 (63), 71 (31), 69 (25), 59 (32), 55 (22), 43 (100), 41 (27). Anal. calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.65; H, 7.54; N, 3.88.

*3.6. Naphthalen-1-yl-carbamic acid (*R*)-2-hydroxy-1-[2-((2*S*,3*S*)-3-hydroxymethyl-2-methyl-oxiranyl)-ethyl]-2-methyl-propyl ester (2*S*,3*S*,6*R*)-**5**

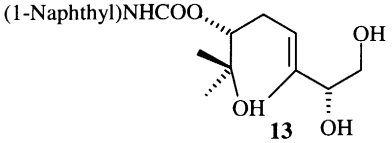
A mixture of powdered, commercially activated 4 Å molecular sieves (100 mg) and dry CH_2Cl_2 (3 mL) was cooled to 0°C. L-(+)-DET (14.1 mg, 68.38 mmol) and Ti(*O*-i-Pr)$_4$ (13.9 mg, 48.9 mmol) were added sequentially. After the mixture was cooled to −20°C, *t*-butyl hydroperoxide (0. 360 mL, 1.96 mmol, 5.5 M in nonane) was added and the resulting mixture was stirred for 20 min, whereupon (6*R*)-**9** (350 mg, 0.98 mmol, in 0.5 mL of dry CH_2Cl_2) was slowly added dropwise. Vigorous stirring was maintained at ca. −20°C for 20 h. After the reaction mixture was warmed to 0°C, H_2O was added (ca. 20 times the weight of Ti(*O*-i-Pr)$_4$ used in the reaction) and the mixture was stirred for 40 min, while allowing it to warm to room temperature. Hydrolysis of tartrates was then effected by adding 1 mL of a 30% aqueous solution of NaOH saturated with NaCl. After 15 min of vigorous stirring, a sudden phase separation occurred. The lower organic phase was removed and combined with two CH_2Cl_2 extracts of the aqueous phase. In some experiments where work-up was difficult, TBHP was reduced by using a solution of $FeSO_4 \cdot 7H_2O$. Drying over $MgSO_4$, followed by filtration through a pad of Celite and evaporation of volatiles, provided a white solid (340 mg, 93%) which was used in the following step. An analytical sample of (2*S*,3*S*,6*R*)-**5**, mp 156–157°C, $[\alpha]_D^{20}$ −5.0 (*c* 0.8, MeOH), was obtained by column chromatography on silica gel (from hexane:AcOEt 25:75 to 100% AcOEt). IR 3460, 2981, 1738, 1704, 1537, 1503, 1464, 1373, 1240, 1045, 848, 783 cm^{-1}; ^1H NMR (CD_3OD) δ 1.15–1.40 (3 br s, 9H), 1.55–1.95 (m, 4H), 2.96 (br t, 1H, AB*X*), 3.60 (dd, 1H, *A*BX), 3.75 (dd, 1H, A*B*X), 4.75 (br d, *J*=10, 1H), 7.38–8.05 (m, 7H, ArH); ^{13}C NMR (CD_3OD) δ 158.1 (s), 135.9 (s), 134.9 (s), 130.2 (s), 129.6 (d), 127.4 (d), 127.3 (d), 127.2 (d), 126.8 (d), 123.5 (d), 123.2 (d), 81.9 (d), 73.3 (s), 64.7 (d), 62.3 (s), 61.9 (t), 36.7 (t), 26.8 (q), 26.4 (t), 17.2 (2 q). EIMS $C_{21}H_{27}NO_5$ *m/z* 373 (M^+, 7), 312 (12), 187 (30), 169 (70), 143 (98), 125 (27), 116 (17), 115 (37), 109 (11), 97 (11), 81 (14), 71 (38), 69 (16), 59 (18), 57 (14), 55 (19), 43 (100), 41 (21). Diastereomeric excess was estimated to be ca. 91% by integration of the ^{13}C NMR signals of the corresponding diastereoisomers.

*3.7. Naphthalen-1-yl-carbamic acid (*R*)-2-hydroxy-1-[2-((2*R*,3*R*)-3-hydroxymethyl-2-methyl-oxiranyl)-ethyl]-2-methyl-propyl ester (2*R*,3*R*,6*R*)-**5**

(6*R*)-**9** (1.500 g, 4.201 mmol) was submitted to D-(−)-DET (78 mg, 0.38 mmol) and Ti(*O*-i-Pr)$_4$ (83.6 mg, 0.29 mmol) under the same conditions as indicated in Section 3.6 to afford crude (2*R*,3*R*,6*R*)-**5** (1.097 g, 70%) which was used immediately in the following step.

*3.8. Naphthalen-1-yl-carbamic acid (3*R*,6*R*)-6-[(*S*)-1,2-dihydroxy-ethyl]-2,2,6-trimethyl-tetrahydro-pyran-3-yl ester (3*R*,6*R*,1′*S*)-**10**

A solution of crude epoxide (2*S*,3*S*,6*R*)-**5** (180 mg, 0.48 mmol) in CH_2Cl_2 was cooled to 0°C. A catalytic amount of (1*S*)-10-camphorsulfonic acid was added and the reaction mixture was stirred at the same temperature for a period of 2 h. The solution was neutralized by adding 5% aq. $NaHCO_3$, dried over $MgSO_4$ and then evaporated. Separation by column chromatography on silica gel (CH_2Cl_2:AcOEt 1:1) afforded 126 mg of pyran derivatives **10** (71% yield) and 6 mg of rearranged product **13**.



13

Integration of the two signals at δ 4.65 (minor diastereomer) and 4.80 (major diastereomer) in the ^{1}H NMR spectrum of **10** showed a diastereomeric excess of 91%. Separation of the two diastereomeric products by flash column chromatography on silica gel (hexane:AcOEt 25:75) afforded 110 mg of the major diastereomer (3*R*,6*R*,1′*S*)-**10**. $[\alpha]_D^{20}$ −19.3 (*c* 1.5, CH_2Cl_2); IR 3408, 3053, 2978, 2934, 1702, 1542, 1500, 1382, 1235, 1217, 1107, 1068, 1018, 792, 771, 736, 701 cm^{-1}; ^{1}H NMR (at 50°C) δ 1.17 (s, 3H), 1.24 (s, 3H), 1.30 (s, 3H), 1.80–2.20 (m, 4H), 2.65 (br s, 1H, OH), 2.89 (br s, 1H, OH), 3.35 (br, 1 H), 3.62 (br, 2H), 4.80 (br s,1H), 7.15 (br s, 1H, NH), 7.38–7.97 (7H, ArH); ^{13}C NMR δ 154.1 (s), 134.1 (s), 132.3 (s), 128.6 (d), 126.3 (d), 126.0 (d), 125.6 (d), 125.4 (d), 120.7 (s), 78.0 (s), 76.2 (d), 74.0 (s), 72.5 (d), 62.4 (t), 27.4 (q), 27.3 (q), 23.3 (q), 23.2 (t), 20.6 (t); EIMS $C_{21}H_{27}NO_5$ *m/z* 373 (M^+, 14), 312 (59), 188 (17), 170 (18), 169 (69), 143 (59), 125 (66), 115 (16), 109 (16), 97 (17), 81 (18), 71 (40), 69 (21), 57 (23), 55 (22), 43 (100), 41 (20). Anal. calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.63; H, 7.38; N, 3.64.

*3.9. Naphthalen-1-yl-carbamic acid (3*R,*6*S*)-6-[(*R*)-1,2-dihydroxy-ethyl]-2,2,6-trimethyl-tetrahydro-pyran-3-yl ester (3*R,*6*S,*1′*R*)-**10***

Crude (2*R*,3*R*,6*R*)-**5** (1.057 g, 2.83 mmol) was submitted to the same conditions as indicated in Section 3.8 to afford pyran derivatives **10** (693 mg, 66% yield) as a mixture of diastereoisomers. Integration of the two signals at δ 4.60 (major diastereoisomer) and 4.77 (minor diastereoisomer) in the ^{1}H NMR spectrum showed a diastereomeric excess of 20%. Separation of this mixture by column chromatography on silica gel (hexane:AcOEt 25:75) afforded 388 mg of the major diastereoisomer and 257 mg of the minor one. (3*R*,6*S*,1′*R*)-**10**), white crystalline solid; mp 175–176°C; $[\alpha]_D^{20}$ −6.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 1.10–1.30 (br s, 9 H), 1.80–2.20 (m, 4 H), 2.66 (br s, 1H, OH), 2.89 (br s, 1H, OH), 3.40 (m, 1H), 3.58 (m, 2H), 4.65 (br s, 1H), 6.98 (br s, 1H, NH), 7.38–7.97 (7H, ArH); ^{13}C NMR δ 153.7 (s), 134.0 (s), 132.2 (s), 128.7 (d), 126.2 (d), 125.9 (d), 125.6 (d), 125.4 (d), 120.4 (s), 77.8 (d), 76.9 (d), 76.1 (s), 74.2 (s), 62.4 (t), 30.7 (q), 29.8 (q), 29.7 (t), 22.1 (q), 21.4 (t). Anal. calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.44; H, 7.36; N, 3.68.

*3.10. Naphthalen-1-yl-carbamic acid (3*R,*6*R*)-2,2,6-trimethyl-6-vinyl-tetrahydro-pyran-3-yl ester (3*R,*6*R*)-**12***

A mixture of the diol (3*R*,6*R*,1′*S*)-**10** (104 mg, 0.278 mmol) and *N*,*N*′-thiocarbonyldiimidazole (TCDI, 50 mg, 0.278 mmol) in dry toluene (4 mL) was heated at reflux for 1.5 h under an argon atmosphere. The solvent was then removed by evaporation (azeotrope with MeOH). Purification of the crude product by column chromatography on silica gel (hexane:AcOEt 1:1) gave thiocarbonate (3*R*,6*R*,1′*S*)-**11** (71 mg, 61%); IR 3300, 3050, 2981, 2948, 1714, 1598, 1537, 1498, 1384, 1293, 1214, 1177, 1104, 1071, 978, 793, 735 cm^{-1}. ^{1}H NMR δ 1.10–1.45 (3 br s, 9H), 1.70–2.15 (m, 4H), 4.58–4.78 (m, 4H), 6.90 (br s, 1H NH), 7.40–7.97 (7H). EIMS $C_{22}H_{25}NO_5S$ *m/z* 415 (M^+, 27), 187 (32), 169 (36), 143 (49), 125 (19), 115 (18), 109 (17), 81 (17), 71 (40), 69 (16), 57 (16), 55 (17), 43 (100), 41 (17). A solution of the thiocarbonate **11** (70 mg, 0.168 mmol) and freshly distilled $P(OMe)_3$ (2 mL) was heated at reflux for 24 h under an argon atmosphere.[36] Excess of $P(OMe)_3$ was removed by distillation under reduced pressure. Separation of the residue by column chromatography on silica gel (hexane:AcOEt 4:1) afforded 16 mg of unreacted thiocarbonate **11** and (3*R*,6*R*)-**12** (42.2 mg, 74% yield, 95% on the recovered starting material); $[\alpha]_D^{20}$ −10.5 (*c* 1.0, CH_2Cl_2) [lit.[25]] $[\alpha]_D^{20}$ −10.0 (*c* 0.5, CH_2Cl_2); IR and ^{1}H NMR spectra were identical with the literature.[25]

3.11. Naphthalen-1-yl-carbamic acid (3R,6S)-2,2,6-trimethyl-6-vinyl-tetrahydro-pyran-3-yl ester (3R, 6S)-**12**

Following the same procedure as described in Section 3.10, diol (3*R*,6*S*,1′*R*)-**10** (290 mg, 0.77 mmol) gave thiocarbonate (3*R*,6*S*,1′*R*)-**11** (203 mg, 63%) which was subsequently converted into (3*R*,6*S*)-**12** (114 mg, 69% yield). $[\alpha]_D^{20}$ −16.9 (*c* 1.3, CH_2Cl_2); IR and ^{1}H NMR spectra were identical with the corresponding spectra of the enantiomer (3*S*,6*R*)-**12** reported in the literature.[25]

3.12. (3R,6R)-2,2,6-Trimethyl-6-vinyl-tetrahydro-pyran-3-ol **1**

To a solution of (3*R*,6*R*)-**12** (40 mg, 0.12 mmol) in dry MeOH was added 10% MeONa in MeOH (33 mg, 0.61 mmol of MeONa). The mixture was heated at reflux for 3 h under an argon atmosphere, then cooled to room temperature, diluted with H_2O, 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:AcOEt 60:30:10) to afford compound **1** (19 mg, 93%); $[\alpha]_D^{20}$ +2.1 (*c* 1.0, CH_2Cl_2); IR 3426, 2975, 2945, 1634, 1450, 1407, 1362, 1229, 1185, 1153, 1114, 1085, 1001, 980, 909, 865, 830 748, 698 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 (m, 2H, *AB*X), 5.97 (1H, AB*X*). The data matched those reported in the literature.[19,22,25,37,38]

3.13. (3R,6S)-2,2,6-Trimethyl-6-vinyl-tetrahydro-pyran-3-ol **3**

Compound (3*R*,6*S*)-**12** (85 mg, 0.25 mmol) gave compound **3** (30 mg, 71%) according to the same procedure described in Section 3.12; $[\alpha]_D^{20}$ −11.5 (*c* 1.0, CH_2Cl_2); IR 3434, 2975, 2938, 1640, 1462, 1402, 1366, 1229, 1190, 1140, 1114, 1075, 1018, 980, 958, 914, 830 cm^{-1}. ^{1}H NMR δ 1.23 (s, 2×3H), 1.24 (s, 3H), 1.65–2.05 (m, 4 H), 3.43 (m, 1H), 4.92–5.08 (2H, *AB*X), 5.95 (1H, AB*X*). The data matched those reported in the literature.[19,22,25,37,38]

3.14. (3S,6R)-2,2,6-Trimethyl-6-vinyl-tetrahydro-pyran-3-ol **2** and (3S,6S)-2,2,6-Trimethyl-6-vinyl-tetrahydro-pyran-3-ol **4**. Diastereomeric and enantiomeric excesses

The title compounds were synthesized from geranyl acetate **6** according to the procedures from **6** through **12** described above for the corresponding enantiomers, and employing AD-mix-α and L-(+)-DET, and AD-mix-α and D-(−)-DET, respectively, in the two asymmetric steps. Spectral and physical data, except the opposite signs of optical rotation, were identical to those of the corresponding enantiomers reported in previous sections.

The four stereoisomers **1**–**4** could be separated on an enantioselective GC column (column B, see above) using the conditions indicated in a previous paper.[25] The enantiomeric excess of each stereoisomer was >98%, while the diastereomeric excesses were: **1**, 99%; **2**, 90%; **3**, 97%; **4**, 90%, respectively.

Acknowledgements

We thank Dr. Mariella Mella and Prof. Giorgio Mellerio for NMR and MS measurements, respectively. Prof. Carlo Bicchi of the University of Turin is acknowledged for enantioselective GC analysis. Financial

support for this work was provided by the Italian CNR and MURST (ex. 40%), and the EU Commission (Contract No. ERBFAIRCT961781).

References

1. Winterhalter, P.; Katzenberger D.; Schreier, P. *Phytochemistry* **1986**, *25*, 1347–1350.
2. Flath, R. A.; Forrey, R. R. *J. Agric. Food Chem*. **1977**, *25*, 103–109.
3. Borg-Karlson, A. K.; Unelius, C. R.; Valterova, I.; Nilsson, L. A. *Phytochemistry* **1996**, *41*, 1477–1483.
4. Urones, J. G.; Basabe, P.; Marcos, I. S.; Pineda, J.; Lithgow, A. M.; Moro, R. F.; Brito Palma, F. M. S.; Araujo, M. E. M. Gravalos, M. D. G. *Phytochemistry* **1992**, *31*, 179–182.
5. Urones, J. G.; Basabe, P.; Marcos, I. S.; Pineda, J.; Lithgow, A. M.; Moro, R. F.; Brito Palma, F. M. S.; Araujo, M. E. M.; Gravalos, M. D. G. *Phytochemistry* **1992**, *31*, 2105–2109.
6. Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287–4290.
7. De Bernardi, M.; Garlaschelli, L.; Toma, L.; Vidari, G.; Vita Finzi, P. *Tetrahedron* **1991**, *47*, 7109–7116.
8. Vidari, G.; Pazzi, N.; Lanfranchi, G.; Serra, S. *Tetrahedron Lett.* **1999**,*40*, 3067–3070.
9. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362.
10. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408.
11. Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem*. **1998**, *63*, 2982–2987.
12. Broka, C. A.; Lin, Y.-T. *J. Org. Chem*. **1988**, *53*, 5876–5885.
13. Matsuki, Y.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1979**, *42*, 4081–4084.
14. Konstantinovic, S.; Bugarcic, Z.; Milosavljevic, S.; Schroth, G.; Mihailovic, M. L. *Liebigs Ann. Chem*. **1992**, 261–268.
15. Urones, J. G.; Diez, D.; Marcos, I.. S.; Basabe, P.; Lithgow, A., M.; Moro, R. F.; Garrido, N., M. Escarcena, R. *Tetrahedron* **1995**, *51*, 3691–3704.
16. Urones, J. G.; Diez, D.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Escarcena, R.; Lithgow, A. M.; Dominguez, M. F.; Sanchez, J. M. *Synlett* **1995**, 855–856.
17. Scarborough, R. M.; Smith III, A. B.; Barnette, W. E.; Nicolaou, K. C. *J. Org. Chem*. **1979**, *44*, 1742–1744.
18. Wrensford, G.; Grab, L. A.; Salvino, J. M.; Williard, P. G. *Tetrahedron Lett.* **1990**, *31*, 4257–4260.
19. Felix, D.; Melera, A.; Seibl, J.; Kovats, E. *Helv. Chim. Acta* **1963**, *46*, 1513–1536.
20. Corma, A.; Iglesias, M.; Sanchez, F. *J. Chem. Soc., Chem. Commun.* **1995**, 1635–1636.
21. Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925–6928.
22. Méou, A.; Bouanah, N.; Archelas, A.; Zhang, X. M.; Guglielmetti, R.; Furstoss, R. *Synthesis* **1991**, 681–682.
23. Fournier-Nguerfack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353–4362.
24. Klein, E.; Farnow, H.; Rojahn, W. *Liebigs Ann*. **1964**, *675*, 73–82.
25. Vidari, G.; Di Rosa, A.; Zanoni, G.; Bicchi, C. *Tetrahedron: Asymmetry* **1999**, *10*, 3547–3557.
26. Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423–430.
27. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483–2547.
28. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p. 103.
29. Vidari, G.; Franzini, M.; Garlaschelli, L.; Maronati, A. *Tetrahedron Lett.* **1993**, *34*, 2685–2688.
30. Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488.
31. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
32. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560.
33. Kocovsky, P.; Story, I. *J. Org. Chem.* **1990**, *55*, 3236–3243.
34. Johnson, R. A.; Sharpless, K. B. In C*omprehensive Organic Synthesis*; Trost, B. M., Ed. Addition reactions with formation of carbon–oxygen bonds: (ii) Asymmetric methods of epoxidation; Pergamon Press: Oxford, 1991; Vol. 7, pp. 389–436.
35. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.
36. Bien, S.; Segal, J. *J. Org. Chem.* **1977**, *42*, 3983–3984.
37. Weinert, B.; Wust, M.; Mosandi, A.; Hanssum, H. *Phytochem. Anal.* **1998**, *9*, 10–13.
38. Miyazawa, M.; Yokote, K.; Kameoka, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1067–1068.