Synthesis of All Four Stereoisomers of Enantiomerically Pure *cis*- and *trans*-Linalyl Oxides

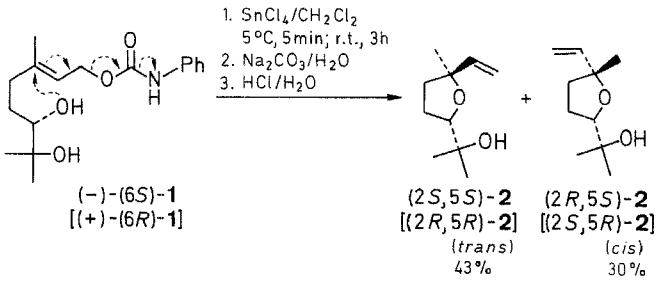
A. Méou, N. Bouanah, A. Archelas, X.M. Zhang, R. Guglielmetti, R. Furstoss*

Laboratoire de Chimie Organique et Bioorganique, URA CNRS n° 1320, Faculté des Sciences de Luminy, 70, route Léon Lachamp, case 901, F-13288 Marseille Cedex 9, France

The four enantiomerically pure *cis*- and *trans*-linalyl oxides can be prepared in one step and good yield from (6*S*)- or (6*R*)-6,7-dihydroxygeranyl phenylcarbamate.

The 2,2,5-trisubstituted tetrahydrofuran moiety is an attractive chiral building block since it is widely present in naturally occuring compounds. For instance, tetracyclic ethers such as thyrsiferol derivatives which exhibit remarkable bioactivity possess such an asymmetric subunit.[1] This is also the case for various polyether antibiotics whose total synthesis has attracted considerable attention in recent years and has been extensively reviewed.[2] The synthesis of these optically pure compounds depends primarily on the availability of appropriately substituted tetrahydrofuran chirons. The linalyl oxides seem to be promising chirons owing to their vinyl and hydroxy functionalities which can be further elaborated to yield more complex molecules. They have previously been prepared in optically active form (as a mixture of the *cis*/*trans* diastereoisomers, but accompanied by the *cis*- and *trans*-tetrahydropyran isomers) by peracid epoxidation of (−)-(*R*)-linalool[3] or (in poor yields) by a bioconversion performed with (−)-(*R*)- or (+)-(*S*)-linalool[4] (which are not easily commercially available). We describe here a short and efficient synthesis of the four enantiomerically pure stereoisomers of linalyl oxide starting from the chiral synthons (−)-(6*S*)-**1** and (+)-(6*R*)-**1** obtained by microbiological oxidation of geranyl phenylcarbamate.[5,6]

Treatment of (−)-(6*S*)-**1** with one equivalent of tin(IV) chloride in dry dichloromethane affords a mixture of two optically active diastereoisomeric products **2** in a ratio of 1:1 (as estimated by GC analysis) in 73% yield. There was no evidence of the formation of the tetrahydropyran isomers (easily distinguishable by GC and TLC) which could arise upon cyclization involving the tertiary hydroxy group. Replacement of $SnCl_4$ by $BF_3 \cdot OEt_2$ resulted in lower yield (60%).



The two isomeric products could be cleanly separated by flash chromatography and were identified as the tetrahydrofurans *trans*-**2** and *cis*-**2** by comparison of their ^{1}H-NMR spectra with those of the previously well characterized *trans* and *cis* isomers.[3] The enantiomeric purity of the isomers was examined by ^{1}H-NMR analysis using $Eu(tfc)_3$ as chiral shift reagent and was found to be ca. 100% in both cases.

The sign and magnitude of the optical rotations (measured in chloroform)[7] of the two isomers of **2** allow to identify the isomer which is eluted first in the chromatographic separation as (2*S*,5*S*)-**2** (*trans*)- and the other as (2*R*,5*S*)-**2** (*cis*). Similarly, the easy accessibility[6] of the diol (+)-(6*R*)-**1** makes possible the synthesis of the optically pure diastereoisomers (2*R*,5*R*)-**2** (*trans*) and (2*S*,5*R*)-**2** (*cis*), thus rendering all four stereoisomers of the linalyl oxides readily available in fair yields and high enantiomeric excess. These results can be rationalized by assuming that the configuration at C-6 is fully retained in the cyclization step.

To the best of our knowledge, this intramolecular Lewis acid induced S_N2' displacement of a phenylcarbamate leaving group has not yet been reported. This convenient cyclization procedure might also prove useful for the synthesis of other interesting functionalized chiral tetrahydrofuran and tetrahydropyran derivatives.

Anhydrous $SnCl_4$ was purchased from Aldrich Chemical Co. and was used without purification. Reagent-grade CH_2Cl_2 was distilled over NaH prior to use. GC analyses were performed on a 25-m capillary column (OV 1701). Separation and purification of the products were achieved by flash chromatography (silica gel 60 H, Merck). Optical rotations were measured on a Perkin-Elmer 241C polarimeter. IR spectra were obtained on a Perkin-Elmer 1310 Infrared spectrophotometer. ^{1}H-NMR spectra were recorded at 80 MHz on a Bruker AW80 spectrometer and ^{13}C-NMR spectra at 200 MHz on a Bruker AM200 spectrometer.

(2*S*,5*S*)- and (2*R*,5*S*)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-vinyltetrahydrofuran [(2*S*,5*S*)-2 and (2*R*,5*S*)-2, respectively]:
To a stirred ice-cooled (5°C) solution of (6*S*)-6,7-dihydroxygeranyl phenylcarbamate (−)-(6*S*)-**1** (307 mg, 1 mmol) in dry CH_2Cl_2 (30 mL) under N_2 is added $SnCl_4$ (0.12 mL, 1 mmol) via a syringe. After 5 min at 5°C, the cooling bath is removed and stirring is continued for 3 h at r.t. The mixture is then cooled to 10°C and Et_2O (30 mL) is added, followed by 1 M aq Na_2CO_3 (15 mL). The aqueous phase is extracted with Et_2O (15 mL). The combined organic fractions are washed with H_2O (15 mL), 1 M aq HCl (3 × 15 mL), and H_2O (2 × 15 mL), and dried ($MgSO_4$). The solvent is evaporated and the residue flash-chromatographed [eluent: hexane → hexane/Et_2O (3:2)] to give (2*S*,5*S*)-**2** as the first product and then (2*R*,5*S*)-**2**.

Product (2*S*,5*S*)-**2**: yield: 73 mg (43%); $[\alpha]_D^{25}$ +4.73° (*c* = 2.07, $CHCl_3$) [Lit.[4] $[\alpha]_D^{25}$ +7.3° (*c* = 0.047, $CHCl_3$)].

$C_{10}H_{18}O_2$	calc.	C 70.55	H 10.66	O 18.79
(170.3)	found	70.30	10.83	18.43

IR (neat): ν = 3450 (OH), 3080 (C=CH$_2$), 1630 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.10 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.50–1.80 (m, 4H), 3.77 (m, 1H), 4.90–5.30 (m, 2H), 5.70–6.10 (m, 1H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 24.4, 26.4, 27.0, 27.2, 37.6, 71.2, 83.1, 85.8, 111.3, 144.0.

Product (2*R*,5*S*)-**2**: yield: 53 mg (30%); $[\alpha]_D^{25}$ −2.94° (*c* = 2.14, $CHCl_3$) [Lit.[3] $[\alpha]_D^{20}$ +3.37° (neat); Lit.[4] $[\alpha]_D^{25}$ −4.1° (*c* = 0.053, $CHCl_3$)].[7]

$C_{10}H_{18}O_2$	calc.	C 70.55	H 10.66	O 18.79
(170.3)	found	70.33	10.73	18.67

IR (neat): ν = 3440 (OH), 3080 (C=CH_2), 1600 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.10 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.50–1.85 (m, 4H), 3.86 (m, 1H), 4.80–5.30 (m, 2H), 5.70–6.20 (m, 1H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 24.5, 26.1, 26.6, 27.4, 38.1, 71.3, 82.9, 85.7, 111.4, 144.6.

The enantiomeric excesses of (+)-(2*S*,5*S*)-**2** and (−)-(2*R*,5*S*)-**2** were determined by means of a chiral shift ^{1}H-NMR experiment [Eu(tfc)$_3$/(+)-(2*S*,5*S*)-**2** = 0.15; Eu(tfc)$_3$/(−)-(2*R*,5*S*)-**2** = 0.15]. They were shown to be greater than 99% in both cases.

Received: 24 January 1990; revised: 9 April 1990

(1) Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5665.
(2) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
(3) Felix, D.; Melera, A.; Seibl, J.; Kovàts, E. sz. *Helv. Chim. Acta* **1963**, *46*, 1513.
(4) David, L.; Veschambre, H. *Tetrahedron Lett.* **1984**, *25*, 543.
(5) Fourneron, J. D.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1989**, *54*, 4686.
(6) Depending on the experimental conditions, the corresponding diol (+)-(6*R*)-**1** can also be obtained from geranyl phenylcarbamate with an e.e. > 95%: Archelas, A.; Zhang, X. M., Furstoss, R., unpublished results.
(7) It has been shown that *cis*-linalyl oxide gives opposite signs for the specific rotation when measured neat or in solution; see Ref. 4.