Pergamon

Tetrahedron, Vol. 53, No. 2, pp. 673-680, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)00999-4

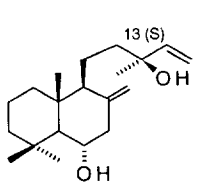
Chemistry of Larixol.II- Hemisynthesis of (-)-Borjatriol.

Denyse Herlem and Françoise Khuong-Huu*

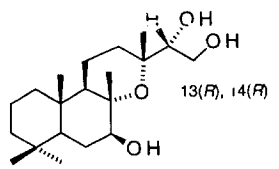
CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France.

Abstract: Starting from Larixol (**1**), the hemisynthesis of (-)-Borjatriol (**2**) has been realized. The key steps of this hemisynthesis were the introduction of hydroxyls at C(7), C(8), C(14) and C(15) starting from the mixture of epoxides **5** and **6**. Copyright © 1996 Elsevier Science Ltd

Larixol (**1**) is a diterpene in the labdane series which has been isolated, as 6-acetate, from the terebenthin of *Larix decidua , L. europea and L. sibirica.*[1] Its structure has been determined by Norin and al.[2] in 1965 and the absolute configuration of the side chain was defined as 13-(*S*).[3] Viewing its structure, larixol (**1**) looks to be an excellent candidate as an abundant, cheap and readily available starting material for the hemisynthesis of polyoxygenated diterpenes which often present interesting biological activities but the availability of which from natural sources is often very scarce. In a previous paper, we reported a degradative study of the side chain of larixol, to obtain chiral intermediates for the synthesis of various diterpenes, and the microbial hydroxylation of A ring leading to compounds potentially useful for the synthesis of forskolin type compounds.[4] Forskolin itself and other bioactive diterpenes possess 6β and 7β hydroxyls. In our efforts toward the synthesis of optically active polyhydroxylated diterpenes, we were interested by the introduction of 6β and 7β hydroxyls in the larixol skeleton using the methodology previously developed for the total synthesis of (dl)-crotomachlin.[5] Here, to illustrate the potentiality of our approach, we report a hemisynthesis of (-)-Borjatriol (**2**),[6] 8α,13(*R*)-oxylabdane-7β,14(*R*),15-triol, a diterpene which presents antiinflammatory properties.[7] A hemisynthesis of (-)-Borjatriol, from (+)-podocarp-8(14)-en-13-one, has been recently published.[8]



1



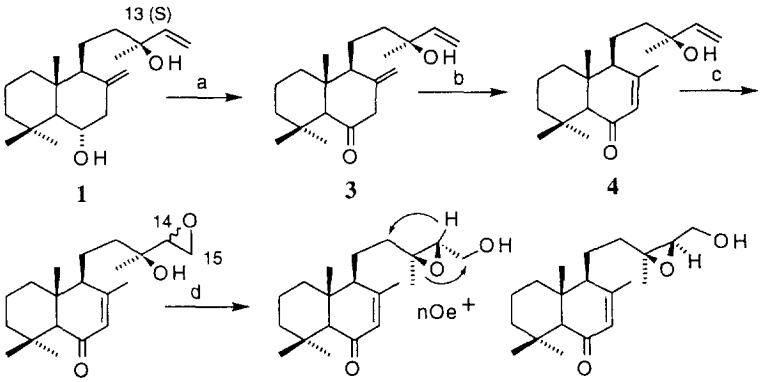
2

Larixol (**1**) was oxidised with Dess-Martin periodinane[9] to ketone **3**, which was in turn transformed to conjugated ketone **4** with methanolic sodium methoxide (93 % for two steps). Then, the 14-15 double bond was selectively epoxided with *t*-butyl hydroperoxide in the presence of $VO(acac)_2$ according to Sharpless'procedure.[10]

* fax (1) 69 07 72 47; e-mail Francoise.Khuong@icsn.cnrs-gif.fr

A mixture of diastereomeric epoxides **5** and **6** was obtained (93 %) in a 7/3 ratio. These epoxides could be separated by HPLC and the C(14)-configuration was determined after nOe experiments realized with Payne rearranged[11] isomers **7** and **8**. With the major isomer, nOe effects between C(16)-methyl group and C(15)-H_2 and between C(14)-H and C(12)-H_2, indicated a *cis* relationship between them. Consequently the absolute configuration at C(14) was 14(*S*), (**7**) (scheme 1). As we need a 14(*R*) configuration, an inversion of this center has to be effected.

Scheme 1



a) Dess-Martin periodinane, 1.2 eq, CH_2Cl_2, 1 h, rt, then ether, 2N aqueous NaOH, 1 h, 99 %; b) 1N methanolic NaOMe, 1 h, rt quantitative; c) t-BuOOH, 3 eq, cat. $VO(acac)_2$, lutidine, 1 eq, 40 °C, 5 h, 93 %; d) 0.5N aqueous NaOH, t-BuOH, H_2O, rt, 3 h, 95 %.

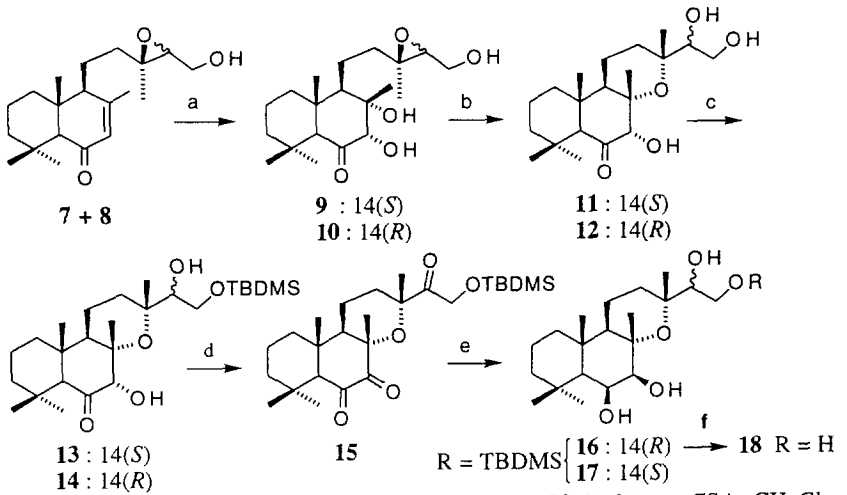
According to the strategy we chose to achieve our objective, we performed the next steps with the mixture of epoxides. When it was possible, after each reaction, the major compound was isolated for description. It could be noted that epoxidation with mCPBA furnished a 1/1 mixture of diastereomers and some epoxidation of the 7-8 double bond occurred.

The hydroxyls at C(7) and C(8) of B-ring of **7** and **8** have been introduced by catalytic OsO_4 in the presence of NMO[12] giving the 7α,8α,15-triols **9** and **10**. Acidic rearrangement, with catalytic CSA in CH_2Cl_2 led to the 13(*R*)-tetrahydropyran derivatives **11** and **12**.[13] After selective protection of the (C-15)-primary hydroxyl as *t*-butylsilyldimethyl ether, oxidation of **13** and **14** with Dess-Martin periodinane gave the triketone **15** which was in turn reduced with sodium borohydride. Two isomers 6β, 7β, 14(*R*) **16** and 6β, 7β, 14(*S*) **17** were obtained in a 7/1 ratio (scheme 2). The chemical shift of the C(14)-H in the ^{1}HNMR spectrum of the major compound **16** indicates that its configuration is 14-(*R*). Confirmation of this attribution was made by transformation of **16** to (-)-borjatriol **2**. Desilylation of **16** with tetrabutylammonium fluoride gave tetrol **18**.

During the oxidation of **13** and **14**, a secondary product was obtained to which the structure **19** was attributed, migration of the *t*-butyldimethylsilyl group occurring in the slighty acidic conditions of the reaction.

The reduction of this compound with $NaBH_4$ led to the tetrol **18**, after cleavage of the t-butyldimethylsilyl ether group with HF (scheme 3).

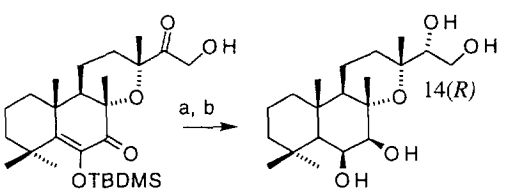
Scheme 2



7 + 8 **9** : 14(*S*) **10** : 14(*R*) **11** : 14(*S*) **12** : 14(*R*) **13** : 14(*S*) **14** : 14(*R*) **15**

a) NMO, 4 eq, cat. OsO_4, t-BuOH, acetone, H_2O, overnight, rt, 70 %; b) cat. CSA, CH_2Cl_2, rt, 30 min., quantitative; c) TBDMSCl, 1.7 eq, imidazole, 2.9 eq, THF, rt, overnight, 98 %; d) Dess-Martin periodinane, 2 eq, CH_2Cl_2, py, rt, 48 h, then aqueous $Na_2S_2O_7$, ether, 1 h; e) $NaBH_4$ 1 eq, EtOH, rt, overnight; f) nBu_4NF, THF, rt, 1 h, 84 %.

Scheme 3



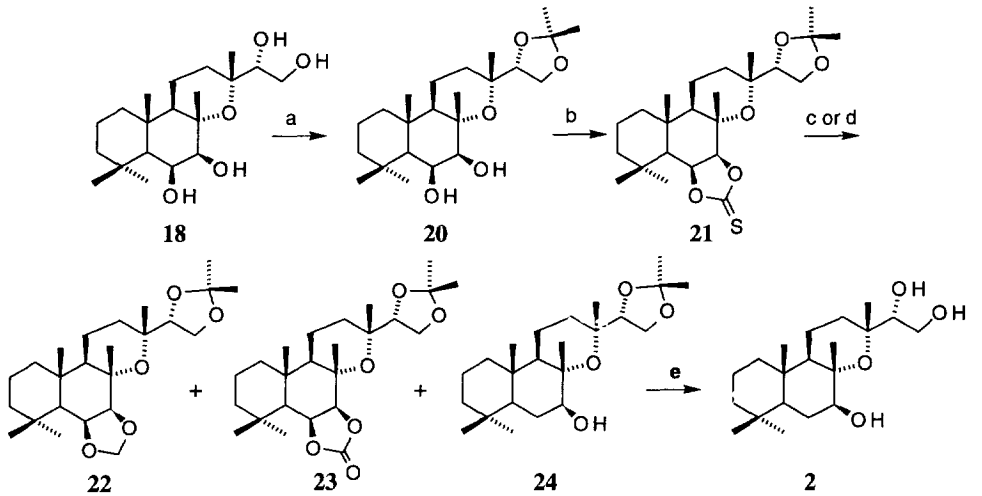
19 **18**

a) $NaBH_4$, excess, EtOH, rt, 1 h, 93 %; b) HF aqueous, 2 eq, THF, rt, 1 h, quantitative.

The vicinal 14,15-dihydroxyls of **18** were selectively protected as isopropylidene **20**. When reacted with thiocarbonyldiimidazole, the 6,7 diol was then transformed into the thiocarbonate **21**. Radical reduction of the thiocarbonyl group with *n*-tributyltin hydride[14] in dioxane gave a mixture of methylenedioxy **22**, carbonate **23** and deoxy-compound **24** in a 2.3/0.6/14 ratio.[15] When the reaction was performed in toluene these products were obtained in 1/1/2.6 ratio. Deprotection of **24** gave triol **2**.The spectroscopic data of **2** and **24** were identical to those of (-)-borjatriol **2** and of its isopropylidene derivative (scheme 4).[6]

In conclusion, in this paper, we described the introduction of oxygen functionalities at C(7), C(8), C(14) and C(15) in the larixol skeleton leading to the synthesis of (-)-borjatriol in efficient way providing an entry to the hemisynthesis of another polyhydroxylated diterpenes such as forskolin derivatives.

Scheme 4



a) excess dimethoxypropane, CH_2Cl_2, cat. CSA, rt, 15 min, 78 %; b) thiocarbonyldiimidazole, 1.2 eq, DBU, toluene, py, reflux, 4 h, 55 %; c) Bu_3SnH, 5.5 eq, dioxane, reflux; d) Bu_3SnH, 5.5 eq, toluene, reflux; e) CSA, MeOH, 79 %.

Acknowledgements : We thank Messrs. J. Bastide and D. Derory from the "Office National des Forêts, Service Départemental des Hautes-Alpes" to provide us a sample of larch terebenthin and Professor P. Potier for his encouragement.

Experimental

Melting points (mp) were determined in capillary tubes and are uncorrected. IR spectra were determined with a NICOLET FT-IR 205 spectrometer, UV spectra with a PERKIN-ELMER I ambda 205 spectrometer. ^1H NMR spectra were performed in $CDCl_3$, unless otherwise stated, chemical shifts δ were expressed in ppm, coupling constants in Hz. 2D COSY ^1H-^1H and ^1H-^{13}C experiments permitted the chemical shift assignments.They were recorded on BRUKER WP-200, BRUKER AC-250 or WP-300. ^{13}C NMR spectra were performed in $CDCl_3$ or CD_3OD, recorded on Bruker WP-200, Bruker AC-250 or WP-300. Mass spectra (MS) were run on AEI MS-50 or AEI MS-9 spectrometers. Usual work-up means that water was added to the reaction mixture which was then extracted three times with CH_2Cl_2; the combined organic layers were washed with brine, dried over Na_2SO_4 or $MgSO_4$ and evaporated.

8(17),14-labdadien-13(*S*)-ol-6-one (3).

Solid Dess-Martin periodinane (16.62 g, 39.2 mmol) was added portionwise to a solution of **1** (10 g, 32.6 mmol), in CH_2Cl_2 (250 mL). After completion of the reaction monitored by TLC, ether (200 mL) and aqueous 2N NaOH (200 mL) were added. The mixture was stirred for 1 h and then extracted three times with ether. The organic phases were washed with brine, dried on $MgSO_4$ and evaporated to give **3** (9.9 g, 99 %), as an oil, $C_{20}H_{32}O_2$, CIMS: MH^+ 305, peak at 287 ; ^1H NMR, 250 MHz, δ ppm: 0.70 (3H, s, CH_3), 1.0 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.33 (3H, s, CH_3), 2.17 (1H, s, C-5H), 3.03 (2H, m, C-7H_2),4.73 and 4.90 (2H, 2s, C-17H_2), 5.1 (1H, d, J=10, C-15H_{cis}), 5.23 (1H, d, J=16, C-15H_{trans}), 5.97 (1H, dd, J=10, J'=16, C-14H); ^{13}C NMR δ ppm: 15.7 (CH_3), 18.2 (CH_2), 21.6 (CH_3), 27.7 (CH_3), 32.5 (C-4), 32.7 (CH_3), 38.8 (CH_2), 41.1 (CH_2), 41.5 (C-10), 42.7 (CH_2), 55.7 (C-7), 57.3 (C-9), 66.3 (C-5), 73.2 (C-13), 110.0 (C-17), 111.7 (C-15), 143.4 (C-8), 145.1 (C-14), 207.6 (C=O).

7,14-labdadien-13(*S*)-ol-6-one (4).

Methanolic sodium methoxide (100 mL of 1 % solution) was added to a solution of **3** (9.9 g, 32.56 mmol) in MeOH (200 mL). After 1 h at room temperature, water was added and the solution was extracted three times with CH_2Cl_2. The organic phases were washed with brine, dried on $MgSO_4$ and evaporated to give **4** (9.9 g,

quantitative), $C_{20}H_{32}O_2$, Calc %: C 78.9, H 10.59, O 10.51 found: C 78.9 H 10.32, O 10.81; CIMS: MH^+ 305, peak at 287; IR cm^{-1}: 3400 (OH), 1669 ($\nu_{C=O}$), 1629 (C=C), 1164 (C-O); UV Λ_{max}, EtOH : 238.8 (ε 11789); ^1H NMR, 250 MHz, δ ppm: 0.8 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.30 (3H, s, (CH_3), 1.88 (3H, s, (C-17H_3), 2.02 (1H s, C-5H), 5.07 (1H, d, J=10, C-15H_{cis}), 5.2 (1H, d, J=16, C-15H_{trans}), 5,72 (1H, m, C-7H), 5.91 (1H, dd, J=10, J'=16, C-14H); ^{13}C NMR, δ ppm: 14.77 (CH_3), 18.2 (CH_2), 21.4 (CH_2), 21.5 (CH_3), 21.7 (CH_3), 27.8 (CH_3), 32.4 (C-4), 33.4 (CH_3), 38.7 (CH_2), 43.2 (CH_2), 43.5 (C-10), 44.7 (CH_2), 56.4 (C-9), 63.6 (C-5), 73.3 (C-13), 112.2 (C-15), 128.3 (C-7), 144.8 (C-14), 159.2 (C-8), 200.4 (C=O).

14,15-epoxy-7-labden-13(*S*)-ol-6-one (5) and (6).

t-BuOOH (486 mg, 5.4 mmol, 3 eq, 1.8 mL of a 3 M solution in i-octane) and $VO(acac)_2$ (14.3 mg, 0.054 mmol) and 2,6-lutidine (0.21 mL, 1.8 mmol) were added successively to a solution of **4** (548 mg, 1.8 mmol) in anhydrous toluene (5 mL). The mixture was stirred for 5 h at 40 °C under argon and then cooled at 0 °C by external ice-bath before addition of $P(OMe)_3$ (468 mg, 3.6 mmol, 2 eq). After dilution with H_2O and extraction with ether, evaporation of the organic phases gave an oil which was purified by flash chromatography. Elution with CH_2Cl_2/MeOH 99/1 and 98/2 gave a mixture of **5** and **6** (540 mg, 93 %) in a 7/3 ratio as determined by HPLC (CH_3CN/H_2O 35/65, silica gel C18, column 3.9x150 mm, 0.9 mL/min). Preparative HPLC afforded analytical samples of **5** and **6**.

-5,.amorphous, $[\alpha]_D$ +40 ($CHCl_3$, c = 2.2), $C_{20}H_{32}O_3$, Calc %: C 74.94, H 10.07 O 14.98; found: C 74.94, H 9.87, O 15.17 CIMS: MH^+ 321, peak at 303; IR ν cm^{-1}: 3400 (OH),1667 ($\nu_{C=O}$), 1623 (C=C), 1150 (C-O); UV Λ_{max}, EtOH : 239 (ε 10154); ^1H NMR, 250 MHz, δ ppm: 0.83 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.91 (3H, s, C-17H_3), 2.02 (1H s, C-5H), 2.79 (1H, dd, J=5, J'=4, C-15H_a), 2.84 (1H, dd, J=5, J'=3, C-15H_b), 2.92 (1H, dd, J=4, J'=3, C-14H), 5.73 (1H, s, C-7H); ^{13}C NMR, δ ppm: 14.46 (CH_3), 17.9 (CH_2), 20.4 (CH_2), 21.3 (CH_3), 21.8 (CH_3), 25.4 (CH_3), 32.0 (C-4), 33.2 (CH_3), 38.5 (CH_2), 41.1 (CH_2), 42.9 (CH_2), 43.1(C-10), 43.9.(C-15), 56.4 (C-9), 57.5 (C-14), 63.4 (C-5), 69.2 (C-13), 128.3 (C-7), 158.5 (C-8), 199.9 (C=O).

-6, amorphous, ^1H NMR, 250 MHz, δ ppm: 0.85 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.92 (3H, s, C-17H_3), 2.04 (1H s, C-5H), 2.76 (1H, dd, J=5, J'=4, C-15-H_a), 2.86 (1H, dd, J=5, J'=3, C-15-H_b), 2.93 (1H, dd, J=4, J'=3, C-14H), 5.75 (1H, s, C-7H).

13(*S*),14-epoxy-7-labden-15-ol-6-one (7) and (8).

A solution of the mixture of epoxides resulting from the precedent reaction (1.6 g, 5 mmol) in *t*-BuOH (25 mL) and 0.5 N aqueous NaOH (25 mL) was stirred for 3 h at rt. After addition of a saturated NH_4Cl solution (25 mL), t-BuOH was removed by distillation under reduced pressure. Standard work-up of the residue led to a mixture of **7** and **8** (1.52 g, 95 %) as an oil.

A similar reaction with pure **5** afforded **7** (14*S*), oil, $[\alpha]_D$+13 ($CHCl_3$, c = 1.1), $C_{20}H_{32}O_3$, CIMS: MH^+ 321, peak at 303; HRCIMS: MH^+ 321.2449 (calc. for $C_{20}H_{33}O_3$ 321.2429); IR cm^{-1}: 3400 (OH),1665 ($\nu_{C=O}$), 1630 (C=C), 1053 (C-O); UV Λ_{max}, EtOH : 238 (ε 10844); ^1H NMR, 250 MHz, δ ppm: 0.83 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.32 (3H, s, C-16H_3), 1.88 (3H, s, C-17H_3), 2.03 (1H s, C-5H), 2.03 (1H, m, C-9H), 2.97 (1H, dd, J=6, J'=5, C-14-H), 3.69 (1H, A of ABX, J=12, J'=6, C-15H_a), 3.82.(1H, B of ABX, J=12, J'=5, C-15H_b), 5.74 (1H, s, C-7H); ^{13}C NMR, δ ppm: 14.7 (CH_3), 16.8 (CH_3), 18.2 (CH_2), 21.6 (CH_3), 22.1 (CH_3), 22.3 (CH_2), 32.3 (C-4), 33.5 (CH_3), 38.8 (CH_2), 40.8 (CH_2), 43.2 (CH_2), 43.4 (C-10), 56.3.(C-9), 61.1 (C-13), 61.2 (C-15), 62.9 (C-14), 63.6 (C-5), 128.8 (C-7), 158.6 (C-8), 200.5 (C=O); nOe interactions: C-16H_3- C-15H_2, C-7H-C-17H_3, C-12H_2-C-14H.

13(S),14-epoxy-labdane-7α, 8α,15-triol-6-one (9) and (10).

NMO (858 mg, 7.3 mmol) in H_2O (3 mL) was added to a solution of **7** + **8** (580 mg, 1.8 mmol) in acetone (30 mL) and then OsO_4 (1.3 mL of a 0.065 M solution in t-BuOH, 21 mg, 0.08 eq). After 24 h at rt, standard work-up and flash chromatrography afforded triols **9** + **10** (450 mg, 70 %). Careful chromatographic separation (silica gel) led to pure **9** .

-9, (14*S*), oil, crystals, mp 107°C (ether), $[\alpha]_D$ +12 ($CHCl_3$, c = 1.3), $C_{20}H_{34}O_5$, CIMS: MH^+ 355, peaks at 337, 319; HRCIMS: MH^+ 355.2472 (calc. for $C_{20}H_{35}O_5$ 355.2484); IR cm^{-1}: 3400 (OH),1715 ($\nu_{C=O}$), 1075 and 1032 (C-O); ^1H NMR, 250 MHz, δ ppm: 0.74 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.19 (3H, s, (CH_3), 1.33 (3H, s, CH_3), 1.83 (1H, m, C-9H), 2.86 (1H s, C-5H), 3.08 (1H, t, J=5, C-14H), 3.52 (1H, s, C-7H), 3.74.(2H, d, J=5, C-15H_2); ^{13}C NMR, δ ppm: 15.67 (CH_3), 16.48 (CH_3), 18.04 (CH_2), 20.13 (CH_2), 21.03 (CH_3), 21.81 (CH_3), 31.69 (CH_3), 31.88 (C-4), 39.88 (CH_2), 40.17 (CH_2), 40.23 (C-10),

42.03 (CH_2), 53.55.(C-9), 58.84 (C-5), 60.90 (C-15), 61.80 (C-13), 62.79 (C-14), 76.93 (C-8), 83.04 (C-7), 212.02 (C=O) .

8α,13(R)-oxylabdane-7α,14,15-triol-6-one (11) and (12).

Catalytic CSA (40 mg, 6 mol%), was added to a solution of **9 +10** (1 g, 2.82 mmol) in anhydrous CH_2Cl_2 (30 mL). After 30 min at rt, neutralization with aqueous sodium $NaHCO_3$ followed by standard work-up led to **11** and **12** (1 g, quantitative). The same reaction with pure **9** led to **11** 14(*S*), mp 125 °C (ether) ; ^{1}H NMR, 250 MHz, δ ppm: 0.76 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.32 (3H, s, CH_3), 2.0 (1H, dd, J=10, J'=2, C-9H), 2.89 (1H s, C-5H), 3.33 (1H, t, J=4, C-14H), 3.59 (1H, s, C-7H), 3.71 (1H, A of ABX, J=12, J'=4, C-15H_a), 3.87 (1H, B of ABX, J=12, J'=4, C-15H_b); ^{13}C NMR, δ ppm: 14.3 (CH_2), 15.6 (CH_3), 17.6 (CH_2), 20.9 (CH_3), 22.1 (CH_3), 23.3 (CH_3), 31.2 (CH_3), 31.2 (C-4), 32.1 (CH_2), 38.7 (CH_2), 39.1 (C-10), 41.7 (CH_2), 50.0.(C-9), 59.1 (C-5), 61.5 (C-15), 77.4 (C-8 or C-13), 77.7 (C-8 or C-13), 78.1 (C-14), 82.2 (C-7), 211.1 (C=O).

8α,13(*R*)-oxylabdane-15-t-butyl-dimethyl-silyloxy-7α,14-diol-6-one (13) and (14).

Imidazole (325 mg, 4.7 mmol, 2.9 eq) and TBDMSCl (426 mg, 2.8 mmol, 1.7, eq) were added to a solution of **11** and **12** (770 mg, 1.6 mmol) in anhydrous THF (50 mL). The mixture was kept overnight at rt under argon and standard work-up led to **13+14** (1 g). Silica gel chromatography gave samples of each compound for description.

-13, (14*S*), amorphous, $C_{26}H_{48}O_5Si$, CIMS: MH^+ 469, peaks at 451, 433; HRCIMS: MH^+ 469.3337 (calc. for $C_{26}H_{49}O_5Si$ 469.3349); IR cm^{-1}: 3450 (OH),1712 ($\nu_{C=O}$), 1106 (C-O); ^{1}H NMR, 250 MHz, δ ppm: 0.09 (6H, s, $SiCH_3$), 0.75 (3H, s, CH_3), 0.90 (9H, s, t-Bu), 0.92 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.22 (3H, s, CH_3), 2.0 (1H, dd, J=10, J'=3, C-9H), 2.87 (1H s, C-5H), 3.45 (1H, dd, J=4, J'=8, C-14H), 3.56 (1H, s, C-7H), 3.56 (1H, A of ABX, J=12, J'=8, C-15H_a), 3.74 (1H, B of ABX, J=12, J'=4, C-15H_b); ^{13}C NMR, δ ppm: -5.4 ($SiCH_3$), 14.9 (CH_2), 16.3 (CH_3), 18.4 (CH_2), 21.7 (CH_3), 22.7 (CH_3), 22.9 (CH_3), 25.9 (t-Bu), 31.9 (CH_3), 31.9 (C-4), 33.7 (CH_2), 39.4 (CH_2), 39.9 (C-10), 42.4 (CH_2), 50.9.(C-9), 59.8 (C-5), 62.8 (C-15), 76.3 (C-8 or C-13), 78.2 (C-8 or C-13), 78.8 (C-14), 83.4 (C-7), 210.9 (C=O).)

-14, (14*R*), amorphous, ^{1}H NMR, 250 MHz, δ ppm: 0.088 (6H, s, $SiCH_3$), 0.75 (3H, s, CH_3), 0.90 (9H, s, t-Bu), 0.92 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.19 (6H, s, 2 CH_3), 2.0 (1H, dd, J=10, J'=3, C-9H), 2.89 (1H s, C-5H), 3.41 (1H, dd, J=4, J'=8, C-14H), 3.56 (1H, s, C-7H), 3.62 (1H, A of ABX, J=12, J'=8, C-15H_a), 3.73 (1H, B of ABX, J=12, J'=4, C-15H_b).

8α,13(*R*)-oxylabdane-15-t-butyldimethylsilyloxy-6,7,14-trione (15).

Solid Dess-Martin periodinane (10 g, 3 eq, 23.6 mmol) was added to a solution of **13 + 14** (3.715 g, 7.9 mol) in CH_2Cl_2 (500 mL) and pyridine (2 mL). The mixture was stirred for 48 h and then ether and aqueous $S_2O_7Na_2$ were added. The mixture was stirred for 1 h and extracted with ether. The organic phases washed with brine, dried over $MgSO_4$ and evaporated. Silica gel chromatography of the residue gave **15** (1.8 g, 49 %) and **19** (1.3 g, 35 %).

-15, amorphous, $C_{26}H_{44}O_5Si$, $[\alpha]_D$+9 ($CHCl_3$, c = 1.2), CIMS: MH^+ 465; HRCIMS: MH^+ 465.3043 (calc. for $C_{26}H_{45}O_5Si$ 469.3036); IR cm^{-1}: 3450 (OH),1728 ($\nu_{C=O}$), 1157 and 1071 (C-O); ^{1}H NMR, 250 MHz, δ ppm: 0.12 (6H, s, $SiCH_3$), 0.76 (3H, s, CH_3), 0.93 (9H, s, t-Bu), 0.94 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.98 (1H s, C-5H), 4.45 and 4.66 (2H, AB, J=16, C-15H_2).

-19, 8α,13(R)-oxylabd-5-ene-6-t-butyldimethylsilyloxy-15-ol,7,14-dione, amorphous, $[\alpha]_D$ -14 ($CHCl_3$, c = 1.1), CIMS: MH^+ 465; IR cm^{-1}: 1735, 1686 ($\nu_{C=O}$), 1623 (c=c), 1039 (C-O); ^{1}H NMR, 250 MHz, δ ppm: 0.05 (6H, s, $SiCH_3$), 0.89 (9H, s, t-Bu), 1.23 (3H, s, CH_3), 1.3 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.47 (3H, s, CH_3), 4.63 and 4.73 (2H, AB, J=20, C-15H_2); ^{13}C NMR, δ ppm: -5.2 ($SiCH_3$), 15.3 (CH_2), 15.8 (CH_2), 18.5 (C), 20.0 (CH_3), 24.4 (CH_3), 25.9 (t-Bu and CH_3), 26.8 (CH_3), 28.0 (CH_3), 31.4 (CH_2), 33.2 (CH_2), 35.5 (C), 35.9 (CH_2), 38.1 (C), 50.9.(C-9), 65.6 (C-15), 76.1 (C-8 or C-13), 80.6 (C-8 or C-13), 140.3 (C-5), 145.5 (C-6), 194.6 (C=O), 211.8 (C=O).

8α,13(*R*)-oxylabdane-15-t-butyldimethylsilyloxy-6β,7β,14(*R*)-triol (16).

Solid $NaBH_4$ (264 mg, 6.98 mmol) was added to a solution of **15** (810 mg, 1.7 mmol) in EtOH 95°C (50 mL). The mixture was stirred overnight at rt and standard work-up gave a mixture of **16** and **17**. Silica gel chromatography gave **16** (548 mg, 67 %) and **17** (78 mg, 9.5 %). **16**- amorphous, $[\alpha]_D$+6.8 ($CHCl_3$, c = 1.4), $C_{26}H_{50}O_5Si$, CIMS: MH^+ 471, peaks at 453, 435; HRCIMS: MH^+ 471.3490 (calc. for $C_{26}H_{51}O_5Si$ 471.3505); ^{1}H NMR, 250 MHz, δ ppm: 0.08 (6H, s, $SiCH_3$), 0.90 (9H, s, t-Bu), 0.98 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.33 (1H, dd, J=5, J'=9, C-14H), 3.36 (1H, d, J=5, C-7H), 3.54 (1H, A of ABX, J=13, J'=9, C-15H_a), 3.70 (1H, B of ABX, J=13, J'=5, C-15H_b), 4.39 (1H, dd, J=4, J'=2, C-6H); ^{13}C NMR, δ ppm: -4.6 ($SiCH_3$), 14.8 (CH_2), 17.7 (CH_3), 18.5 (C), 19.3 (CH_2),

21.0 (CH_3), 23.3 (CH_3), 24.2 (CH_3), 26.5 (t-Bu), 33.4 (CH_3), 34.6 (CH_2), 34.8 (C), 37.8 (C), 41.7 (CH_2), 44.6 (CH_2), 57.0 (CH), 57.3 (CH), 63.9 (C-15), 71.6 (C-6), 74.9 (C-O), 78.8 (C-O), 80.7 (C-14), 81.7 (C-7).

17-^{1}H NMR δ ppm: 0.07 (6H, s, $SiCH_3$), 0.89 (9H, s, t-Bu), 0.97 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.35 (1H, m, C-14H), 3.35 (1H, d, J=4, C-7H), 3.57 (1H, A of ABX, J=12, J'=8, C-15H_a), 3.73 (1H, B of ABX, J=12, J'=4, C-15H_b), 4.39 (1H, dd, J=4, J'=2, C-6H).

8α,13(*R*)-oxylabdane-6β,7β,14(*R*),15-tetrol (18).

n-Bu_4NF, $3H_2O$ (73 mg, 0.28 mmol) was added to a solution of **16** (91 mg, 0.2 mmol) in anhydrous THF (30 mL). After 1 h at rt, standard work-up led to **18** (58 mg, 84 %), crystals, mp 210 °C (MeOH), $[\alpha]_D$+13 (MeOH, c=0.8), $C_{20}H_{36}O_5$, CIMS: MH^+ 357, peaks at 339, 321, 303; HRCIMS: MH^+ 357.2645 (calc. for $C_{20}H_{37}O_5$ 357.2688); ^{1}H NMR, 250 MHz, δ ppm: 0.94 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.49 (3H, s, CH_3), 3.20 (1H, m, C-14H), 3.30 (1H, d, J=4, C-7H), 3.61 (2H, m, C-15H_2), 4.3 (1H, dd, J=4, J'=2, C-6H); ^{13}C NMR, δ ppm: 14.7 (CH_2), 17.6 (CH_3), 19.2 (CH_2), 20.6 (CH_3), 23.3 (CH_3), 24.1 (CH_3), 33.3 (CH_3), 34.7 (CH_2), 34.7 (C), 37.8 (C), 41.7 (CH_2), 44.6 (CH_2), 57.0.(CH), 57.5 (CH), 63.4 (C-15), 71.8 (C-6), 75.6 (C-O), 79.2 (C-O), 80.4 (C-14), 81.3 (C-7); ^{13}C NMR, (CD_3OD), δ ppm: 14.7 (CH_2), 17.6 (CH_3), 19.2 (CH_2), 20.6 (CH_3), 23.3 (CH_3), 24.1 (CH_3), 33.3 (CH_3), 34.7 (CH_2), 34.7 (C), 37.8 (C), 41.7 (CH_2), 44.6 (CH_2), 57.0 (CH), 57.5 (CH), 63.4 (C-15), 71.7 (C-6), 75.6 (C-O), 79.1 (C-O), 80.4 (C-14), 81.3 (C-7).

$NaBH_4$ reduction of 19.

$NaBH_4$ (461 mg,12 mmol) was added portionwise to a solution of **19** (982 mg, 2.16 mmol) in EtOH (30 mL). The mixture was stirred for 1 h at rt and then standard work-up led to a residue (919 mg) which was solved in THF (30 mL). The solution was cooled to 0 °C by external ice-bath and HF (0.1 ml of a 48 % aqueous solution) was added. The solution was warmed to rt and kept for 6 h. After neutralization with aqueous $NaHCO_3$, extraction with CH_2Cl_2 gave **18** (702 mg, 93 % for two steps).

8α,13(*R*)-oxylabdane-14,15-isopropylidene-6β,7β,14(*R*), 15-tetrol (20).

A suspension of **18** (210 mg, 0.58 mmol) in CH_2Cl_2 (20 mL) in the presence of dimethoxypropane (0.5 mL, 3.8 mmol) and catalytic CSA (10 mg) was stirred for 15 min at rt. Complete dissolution occurred and after completion of the reaction monitored by TLC, alcalinization by aqueous $NaHCO_3$ followed by standard work-up gave **20** (183 mg, 78 %) after purification by column chromatography, amorphous, $[\alpha]_D$+6 ($CHCl_3$, c = 1.8), $C_{23}H_{40}O_5$, CIMS: MH^+ 397, peaks at 339, 321, 303; HRCIMS: MH^+ 397.2970 (calc. for $C_{23}H_{41}O_5$ 377.2953); ^{1}H NMR, 250 MHz, δ ppm: 0.97 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.34 (1H, d, J=4, C-7H), 3.89 (3H, m, C-14H, C-15H_2), 4.39 (1H, dd, J=4, J'=2, C-6H); ^{13}C NMR, δ ppm: 13.6 (CH_2), 16.8 (CH_3), 18.3 (CH_2), 19.8 (CH_3), 23.2 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 25.9 (CH_3), 31.2 (CH_2), 32.5 (CH_3), 33.8 (C), 36.8 (C), 40.7 (CH_2), 43.6 (CH_2), 55.9.(CH), 55.4 (CH), 64.9 (C-15), 70.5 (C-6), 72.9 (C-O), 77.7 (C-O), 80.7 (C-14), 82.4 (C-7), 108 (C).

8α,13(*R*)-oxylabdane-6β,7β-thiocarbonyldioxy-14,15-isopropylidene-14(*R*), 15-diol (21).

A solution of **20** (72 mg, 0.18 mmol) in toluene (3 mL) and pyridine (0.5 mL) was warmed at 110 °C for 4 h, under argon, in the presence of 1,1'-thiocarbonyldiimidazole (40 mg, 0.22 mmol) and DBU (0.1 mL). After standard work-up, the brown residue which was obtained gave **21** (44 mg, 55 %), after column chromatography (eluent heptane/AcOEt 95:15), amorphous, $C_{24}H_{38}O_5S$; HRCIMS: MH^+ 439.2495 (calc. for $C_{24}H_{39}O_5$ 409.2518); ^{1}H NMR, 250 MHz, δ ppm: 1.02 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.92 (3H, m, C-14H, C-15H_2), 4.61 (1H, d, J=8, C-7H), 5.11 (1H, dd, J=8, J'=4, C-6H).

Bu_3SnH Reduction of 21, Compounds 22, 23 and 24.

a) A 25 mL round-bottomed flask equiped with a magnetic stirrer and a reflux condenser with a Claisen top fitted with a septum and dry argon inlet, was charged with a solution of **21** (177 mg, 0.4 mmol) in anhydrous dioxane (3mL). The mixture was flushed with argon and brought to reflux and stirred. A solution of Bu_3SnH (0.6 mL, 648 mg, 2.2 mmol) and AIBN (13 mg) in anhydrous dioxane (3 mL) was then added dropwise to the refluxing mixture, by a syringe, through a long needle which pierces the septum and ends at least 3 cm above the lower end of the cooling zone of the reflux condenser.[16] After complete addition, the solution was cooled to rt and poured on a silica gel column. Elution with heptane/AcOEt 9:1 and heptane/AcOEt 8:2 gave successively **22** (10 mg, 6 %), **23** (3mg, 1.7 %), and **24** (140 mg, 90 %).

b) **21** (59 mg, 0.13 mmol), Bu_3SnH (0.25 mL, 270 mg, 0.9 mmol) and AIBN (4 mg) were reacted in the same way using toluene (2 x 2 mL) as solvent. Silica gel chromatography gave **22** (10 mg, 18 %), **23** (10 mg, 18 %) and **24** (26 mg 52 %).

-22, (8α,13(R)-oxylabdane-14,15-isopropylidene-6β,7β-methylenedioxy-14(R),15-diol, oil, $C_{24}H_{40}O_5$, CIMS: MH^+ 409, peaks at 391, 379, 361, 343; HRCIMS: MH+ 409.2963 (calc. for $C_{24}H_{41}O_5$ 409.2953); ^1H NMR, 250 MHz, δ ppm: 0.99 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.4 (3H, s, CH_3), 3.78 (1H, d, J=6, C-7H), 3.95 (3H, m, C-14H, C-15H_2), 4.15 (1H, dd, J=6, J'=3, C-6H), 4.86 and 5.21 (2H, 2s, OCH_2O).

- 23, 8α,13(R)-oxylabdane-14,15-isopropylidene-6β,7β-dioxycarbonyl-14(R),15-diol, oil, IR ν cm^{-1}: 1778 ($\nu_{C=O}$), 1032 (C-O) ; δ ppm: 1.02 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.92 (3H, m, C-14H, C-15H_2), 4.36 (1H, d, J=8, C-7H), 4.99 (1H, dd, J=8, J'=4, C-6H).

-24,(8α,13(R)-oxylabdane-14,15-isopropylidene-7β, 14(R),15-triol, crystallized (pentane), mp 161-162° C $[\alpha]_D$+6.8 ($CHCl_3$, c = 0.7), $C_{23}H_{40}O_4$, CIMS: MH^+ 381, peaks at 363, 305; HRCIMS: MH^+ 381.3002 (calc. for $C_{23}H_{41}O_4$ 381.3004); ^1H NMR, 250 MHz, δ ppm: 0.78 (3H, s, CH_3), 0.81 (3H, s, CH_3), 0.87 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.83 (1H, ddd, J=13, J'=4, J''=2, C-6Hα), 3.49 (1H, dd, J=4, J'=10, C-7H), 3.97 (3H, m, C-14H, C-15H_2); ^{13}C NMR, δ ppm: 14.2 (CH_2), 15.9 (CH_3), 18.5 (CH_2), 19.5 (CH_3), 21,3 (CH_3), 24.9 (CH_3), 25.3 (CH_3), 26.3 (CH_3), 26.7 (CH_2), 31.4 (CH_2), 33.3 (C, CH_3), 37.1 (C), 38.9 (CH_2), 41.9 (CH_2), 54.2.(CH), 56.2 (CH), 65.3 (C-15), 73.5 (C-O) 78.6 (C-O), 80.9 (C-7), 82.7 (C-14), 109.3 (C); litt.ref : 14.18, 15.89, 18.49, 19.43, 21.29, 24,87, 25.18, 26.28, 26.74, 31.35, 33.22, 33.29, 37.05, 38.85, 41.92, 54.18, 56.17, 65.31, 73.48, 78.58, 80.84, 82.65, 109.27.

8α, 13(*R*)-oxylabdane-7β, 14(*R*), 15-triol, borjatriol (2)

A solution of **24** (79 mg,0.2 mmol) and CSA (13 mg) in MeOH (4 mL) was kept 5 h at rt. After alcalinization with aqueous $NaHCO_3$, standard work-up and silica gel chromatography gave starting material **24** (8 mg, 10 %) and **2** (55 mg, 79 %), amorphous, $[\alpha]_D$-2 ($CHCl_3$, c = 2) (litt.[6]. $[\alpha]_D$-2.3, litt.[8] $[\alpha]_D$-1.3), its triacetate, mp 121°C (ethanol-water), $[\alpha]_D$+48 ($CHCl_3$, c = 4.5), litt.[6] $[\alpha]_D$+50, litt.[8] $[\alpha]_D$+49 ; $C_{20}H_{36}O_4$, CIMS: MH^+ 341, m/z 323, 305, 287; HRCIMS: MH^+ 341.2679 (calc. for $C_{20}H_{37}O_4$ 341.2691) ; ^1H NMR, 250 MHz, δ ppm: 0.77 (3H, s, CH_3), 0.80 (3H, s, CH_3), 0.88 (3H, s, CH_3), 1.23 (3H, s, (CH_3), 1.29 (3H, s, CH_3), 1.83 (1H ddd, J=13, J'=5, J''=2, C-6Hα), 3.24 (1H, dd, J=6, J'=4, C-14H), 3.53 (1H, dd, J=10, J'=4, C-7H), 3.67 (2H, m, C-15H_2); ^{13}C NMR, δ ppm: 14.3 (CH_2), 15.9 (CH_3), 18.5 (CH_2), 19.5 (CH_3), 21,3 (CH_3), 23.0 (CH_3), 27.5 (CH_2),33.2 (C), 33.3 (CH_3), 34.0 (CH_2), 37.0 (C), 38.9 (CH_2), 42.0 (CH_2), 54.3.(CH), 56.2 (CH), 62.8 (C-15), 75.2 (C-O), 79.1 (C-O), 79.4 (C-7), 80.5(C-14); litt.ref : 14.2, 15.9, 18.5, 19.5, 21.3, 23.5, 27.5, 33.2, 33.3, 33.6, 37.0, 38.9, 42.0, 54.3, 56.2, 62.9, 75.5, 78.3, 79.2, 80.5.

References and Notes

1 Wienhaus, H. *Angew. Chem.* **1947**, *59*, 248; Wienhaus, H.; Pilz, W.; Seibt, H.; Dässler, H.G. *Chem. Ber.* **1960**, *93*, 2625-2627; Haueser,.J. *Bull. Soc. Chim. France* **1965**, 2645-2648; Shmidt, E.N.; Lisina, A.I.; Pentegova, V.A. *Izv. Sibi. Nauk Ser. Khim.* **1964**, *1*, 52 .

2 Norin, T.; Ohloff, G.; Willhalm, B. *Tetrahedron Letters* **1965**, 3523-3528.

3 Sandermann, W.; Bruns, K.*Chem. Ber.* **1966,** *99*, 2835-2841; Carman, R.M. *Tetrahedron Letters*, **1967**, 219-220 ; Bruns, K. *Tetrahedron Letters* **1970**, 3263-3264.

4 Herlem, D.; Ouazzani, J.; Khuong-Huu, F. *Tetrahedron Letters*, **1996**, *37*, 1241-1244.

5 Herlem, D.; Khuong-Huu, F.; Kende, A.S. *Tetrahedron*, **1994**, *50*, 2055-2070

6 Rodriguez, B.; Valverde, S. *Tetrahedron*, **1973**, *29*, 2837-2843; Valverde, S.; Rodriguez, B. *Phytochemistry*, **1977**, *16*, 1841.

7 Villar, A.; Salom, R.; Alcaraz, M.J. *Planta Medica*, **1984**, 90-92; Baeberan, F.A.T.; Mañez, S.; Villar, A. *J. Nat. Prod.* **1987**, *50*, 313-314.

8 Abad, A.; Agullò, C.; Arnò, M.; Cuñat, A.C.; Zaragozà, R.J. *J. Org. Chem.* **1992**, *57*, 50-54.

9 Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4157; Dess, D.B.; Martin, J.C.*J.Am. Chem. Soc.* **1991**, *113*, 7277-7287.

10 Sharpless, K.B.; Michaelson, R.C. *J. Amer. Chem. Soc.* **1973**, *95*, 6136-6137.

11 Payne, G.B. *J. Org. Chem.* **1962**, *27*, 3819-3822.

12 Van Rheenen, V.; Kelly, R.C.; Cha D.Y. *Tetrahedron Letters*, **1976**, 1973; for a review, Schröder, M. *Chem. Rev..***1980**, *80*, 187.

13 Moulines, J.; Lamidey, A.M.; Bats, J.P.; Morisson, V. *Synth. Comm.* **1993**, *23*, 2991-2998.

14 Barton, D.H.R.; McCombie, S.W. *J.C.S Perkin I.* **1975**, 1574-1585.

15 Tsuda, Y.; Kanemitsu, K.; Kakimoto, K.; Kikuchi, T. *Chem. Pharm. Bull.* **1987**, *35*, 2148-2150.

16 Giese, B.; Gröninger, K.S. *Org. Synth.* **1990**, *69*, 66-68.

(*Received in Belgium* 23 *July* 1996; *accepted* 25 *October* 1996)