Tetrahedron Letters,Vol.23,No.34,pp 3513-3516,1982 0040-4039/82/343513-04$03.00/0
Printed in Great Britain

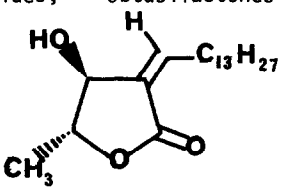
A SHORT STEREOSELECTIVE SYNTHESIS OF (±)-LITSENOLIDES C_1 AND C_2.

Pierre BARBIER and Claude BENEZRA*

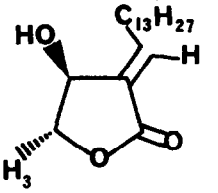
Laboratoire de Dermato-Chimie, Associé au CNRS (LA 31),
UNIVERSITE LOUIS PASTEUR, Clinique Dermatologique, CHU
de STRASBOURG, 67091 Strasbourg, FRANCE.

Abstract : A five-step synthesis of the above substances from ethyl phenylthioacetate and 1-bromotetradecane is described.

Litsenolides C_1 and C_2, α-alkylidene-β-hydroxy-γ-butyrolactones **1** and **2** are present in *Litsea japonica* (Thunb.) Juss[1], a Lauraceae plant. The synthesis of litsenolide C_1 **1** has been reported recently[2] ; it involved a seven-step sequence from α-bromo-γ-methyl-γ-butyrolactone. Litsenolide C_2 **2** (the E-isomer) was obtained as a side product. The syntheses of related mabubanolides, obtusilactones and epilitsenolides have also been described[3].



1



2

As a part of continuing efforts in the synthesis and study of the allergenic properties of α-methylene-γ-butyrolactones[4], we have described recently[5] a general method for the synthesis of β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones. Litsenolides C_1 and C_2, along with epilitsenolides C_1 and C_2 (*cis*-β-hydroxy-γ-methyl groups), were obtained as a mixture of their acetoxy derivatives[6]. We wish to report now a new approach toward the synthesis of litsenolide C_1 and the first preparation of litsenolide C_2 from easily accessible starting materials.

The synthesis (Scheme I) involved the preparation of a long chain phenylsulfide **3** from ethyl phenylthioacetate and 1-bromotetradecane in the presence of sodium hydride[7]. The resulting compound **3** (obtained in 53% yield) was then treated with LDA and 2-acetoxypropional dehyde **4** [5], giving sulfide **5** [8] (in 45% yield). Treatment of the latter by $Ba(OH)_2$ followed by acidification gave lactone **6** [9] (as a mixture of diastereomers, but with the γ-methyl- and the β-hydroxy-substituents in *trans* relationship). A 2 : 9 mixture of litsenolides C_1 and C_2 was finally obtained by oxidation of sulfide **6** into sulfoxide **7** [10](90% yield), followed by thermal elimination[11]. They could easily be separated by column chromatography on a silica gel column. Litsenolides C_1 and C_2 gave IR and NMR spectra identical to the described ones[1].

We have used the reaction of ethyl phenylthioacetate[12] and ethyl 2-phenylthiopropionate anions with α-acetoxy aldehydes for a new general synthesis of β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones[5b].

We thank the French C.N.R.S. for a fellowship (Bourse d'Ingénieur-Docteur) to PB (1977-1980).

REFERENCES AND NOTES.

1. K. Takeda, K. Sakurawi, H. Ishii, *Tetrahedron*, 28, 3757-3766 (1972)

2. R.H. Wollenberg, *Tetrahedron Letters*, 3139-3142 (1980)

3. A. Tanaka, K. Yamashita, *Chemistry Letters*, 319-322 (1981) ; S.W. Rollinson, R.A. Amos, J.A. Katzenellenbogen, *J. Amer. Chem. Soc.*, 103, 4114-4125 (1981)

4. G. Schlewer, J.L. Stampf, C. Benezra, *J. Med. Chem.*, 23, 1031-1038 (1980)
G. Dupuis, C. Benezra, G. Schlewer, J.L. Stampf, *Molecular Immunology*, 17, 1045-51 (1980)

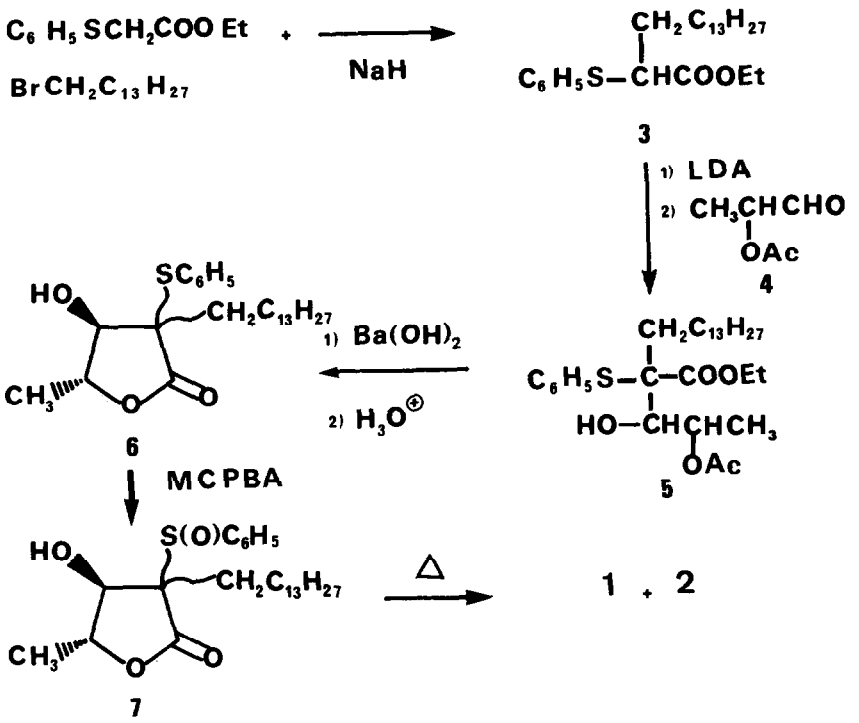
5. a) J.P. Corbet, C. Benezra, *J. Org. Chem.*, 46, 1141-1147 (1981) ; b) P. Barbier, C. Benezra, *J. Org. Chem.*, submitted.

6. J.P. Corbet, Thèse de Doctorat d'Etat, Université Louis Pasteur de Strasbourg, Mai 1980.
C. Benezra, Allergenic Natural and Synthetic α-Methylene-γ-Butyrolactones : Synthetic and biological activity aspects, *12th IUPAC International Symposium on the Chemistry of Natural Products*, September 21-27, 1980, Puerto de la Cruz, Tenerife, Spain.

7. Compound **3** (ethyl 2-phenylthiohexadecanoate) was prepared in the following way : in dimethoxyethane (DME, 10 mL) containing NaH (0.020 mol) at rt was added a solution of ethyl phenylthioacetate (04.0 g, 0.020 mol) in DME (6 mL) : after 1 h, a solution of 1-bromotetradecane (5.65g, 0.020 mol) in DME (6 mL) was added. After stirring for 1.5h at rt, refluxing 30 mn, distilled water was added. After workup with ether and chromatography on silica gel (250 g), hexane-ether 9:1 eluted sulfide **3** (4.20 g, 0.011 mol, 53% yield) : oil, ^{1}H NMR ($CDCl_3$) : 0.90 (br t, 3H), 1.17 (t, 3H, J = 7.0) 1.20-2.10 (m, 26H), 3.52(dd,1H,J=J'=7.2), 4.10 (q, 2H, J = 7.0), 7.10-7.60 (m, 5H) ; IR ($CDCl_3$) : 1730, 1580 cm^{-1}. Anal. Calcd for $C_{24}H_{40}O_2S$: C 73.46, H. 10.20 S 8.16 Fd C 74.06 H 10.29 S 7.90

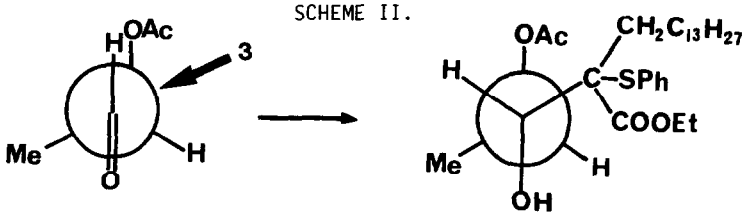
8. To a solution of LDA (prepared from 4.160 mmol of diisopropylamine and BuLi) in THF (50 mL) at -78°C was added a solution of sulfide **3** (1.630 g, 4.160 mmol) in THF (6 mL) and the mixture was stirred for 30 mn. A solution of α-acetoxypropionaldehyde **4**

SCHEME I.



The main interest of this synthetic scheme is the exclusive formation of isomers with a *trans* β-hydroxy-γ-methyl relationship. This stereoselectivity can be explained by Cram's rule (Scheme II) applied to the reaction of sulfide **3**. with aldehyde **4** . The predicted preferred direction of attack (from the small, H, substituent side) would lead to a compound with R,R (or S,S) configurations : only one couple of enantiomers is obtained.

SCHEME II.



from (2R)-2-Acetoxypropionaldehyde ⟶ (3R, 4R)-configuration.
from (2S)-2-Acetoxypropionaldehyde ⟶ (3S, 4S)-configuration.

There was no evidence for the formation of any compound with a *cis* β-acetoxy-γ-methyl relationship.

(0.433 g, 4.160 mmol) in THF (6 mL) was then added. After 1h at -78°C, hydrolysis with a saturated solution of NH_4Cl, usual workup and column chromatography on silica gel (100 g), hexane-ether 75:25 eluted compound **5** (0.960 g, 1.89 mmol, 45% yield) Oil, ^1H NMR ($CDCl_3$) : 0.80-1.0 (m, 6H), 1.0-1.90 (m, 26H), 1.95-2.03 (2s, 3H) 3.90-4.20 (m, 3H), 5.0-5.4 (m, 1H), 7.0-7.7 (m, 5H) ; IR ($CHCl_3$) : 3600, 3500, 1730 ; MS : 508 ($M^{+\cdot}$). Anal. Calcd for $C_{29}H_{48}O_5S$: C 68.50, H 9.45, S 6.29 Fd : C 68.71 H 9.58, S 6.51.

9. Sulfide **5** (0.900 g, 1.77 mmol) in a THF (20 mL) -$Ba(OH)_2$ saturated solution (60 mL) was stirred 4h at rt ; the pH was then adjusted to 4.0 with HCl 2N. Workup with ether gave crude compound **6** which was recrystallized in hexane (0.669 g, 1.59 mmol, 90% yield). Mp 84-85° ; ^1H NMR ($CDCl_3$) : 0.8-1.0 (m, 6H) 1.0-2.0 (m, 26H), 3.5-4.3 (m, 2H) 7.1-7.7 (m, 5H) ; IR ($CHCl_3$) : 3600, 3400, 1770 cm^{-1} ; MS : 420 ($M^{+\cdot}$). Anal. Calcd for $C_{25}H_{40}O_3S$: C 71.43, H. 9.52 , S 7.62. Fd : C 71.49, H 9.66, S 7.70.

10. Sulfoxide **7** was obtained from sulfide **6** by MCPBA oxidation in CH_2Cl_2. Sulfoxide **7** oil, Anal. Calcd for $C_{25}H_{40}O_4S$: C 68.81, H 9.17, S 7.34. Fd : C 68.63, H. 9.32, S 7.40.

11. Reflux of sulfoxides **7** (0.516 g, 1.18 mmol) in toluene (50 mL) ∿ for 30 mn, removal of the solvent and column chromatography on silica gel (40 g) ; hexane-ether 75:25 eluted successively litsenolides C_1 **1** (0.040 g, 0.13 mmol) and C_2 **2** (0.180 g, 0.580 mmol).

12. This substrate does not lead to β-acetoxy-α-methylene-γ-butyrolactones but instead to butenolides : P. Barbier and C. Benezra, *Tetrahedron Letters*, preceding Communication.

(Received in UK 22 June 1982)