Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Direct Access to a Potential LTB_4-Antagonist, SM-9064, via, Disilyl Derivatives

Vito Fiandanese [a] & Angela Punzi [a]
[a] Centro CNR di Studio sulle Metodologie Innovative di Sintesi Organiche, Dipartimento di Chimica, Università , via Amendola 173, 70126, Bari, Italy
Published online: 23 Sep 2006.

To cite this article: Vito Fiandanese & Angela Punzi (1993) A Direct Access to a Potential LTB_4-Antagonist, SM-9064, via, Disilyl Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:2, 173-182, DOI: 10.1080/00397919308009765

To link to this article: http://dx.doi.org/10.1080/00397919308009765

SYNTHETIC COMMUNICATIONS, 23(2), 173-182 (1993)

A DIRECT ACCESS TO A POTENTIAL LTB_4-ANTAGONIST, SM-9064, *via* DISILYL DERIVATIVES

Vito Fiandanese* and Angela Punzi

Centro CNR di Studio sulle Metodologie Innovative di Sintesi Organiche, Dipartimento di Chimica, Università, via Amendola 173, 70126 Bari, Italy

ABSTRACT: The synthesis of SM-9064, a potential LTB_4 antagonist, which is effective in some types of inflammation, has been easily achieved in a few steps by electrophilic substitution reactions between (1*E*,3*E*,5*E*)-1,6-bis(trimethylsilyl)-1,3,5-hexatriene and acyl chlorides in the presence of aluminum trichloride, followed by reduction reaction and formation of pyrrolidine derivative.

Leukotriene B_4, (5*S*,12*R*)-5,12-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid (LTB_4), a highly biologically active 5-lipoxygenase product of neutrophil arachidonate metabolism, is a significant mediator of a number of inflammatory diseases[1], e.g. gout, psoriasis, and ulcerative colitis. It promotes

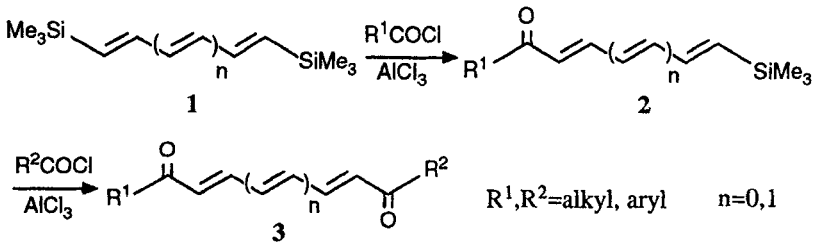
* To whom correspondence should be addressed

chemotaxis and chemokinesis of leukocytes and stimulates aggregation and degranulation of human neutrophils. Consequently, several works[2-8] were reported on the synthesis and the evaluation of the biological effect of receptor level antagonists of leukotriene B_4, which, therefore, might be therapeutically useful in the treatment of inflammatory diseases. Several compounds were synthesized such as leukotriene B_4 dimethylamide[2], some derivatives containing a 2,6-disubstituted pyridine ring in place of carbons 7-9 of the natural eicosanoid[3], phenylene, furyl and thienyl analogs of leukotriene B_4[4], or polyaromatic derivatives such as SC-41930[5]. Also a series of unsaturated fatty acid derivatives[6-8], with a conjugated triene moiety, was reported to possess an anti-leukotriene B_4 activity and, in particular, SM-9064[7,8], (5*E*,7*E*,9*E*)-*N*,*N*-tetramethylene-4,11-dihydroxy-13-(*p*-methoxyphenyl)-trideca-5,7,9-trienamide, synthesized in several steps by Wittig-type reactions, was evaluated in detail[8] and showed a selective inhibition of chemotaxis induced by LTB_4.

The highly interesting biological activity and the trienyl structure of this compound prompted us to devise a simple and direct synthetic route based upon our previously reported procedure[9]. Indeed, owing to our interest in the synthesis of stereodefined products[10,11], we have recently[9] described a new approach, based upon the chemoselective and sequential substitution of the trimethylsilyl groups of the conjugated 1,4-disilylated diene **1** (n=0) and 1,6-disilylated triene **1** (n=1) with acyl chlorides, leading to silylated ketones **2** and dicarbonyl compounds **3** with a conjugated (all *E*) diene or triene structure (Scheme 1).

We have successfully applied our methodology to the synthesis of a natural product, ostopanic acid[12], a plant cytotoxic acid, of both the (6*E*)-isomer and a structural analog of leukotriene B_3[12], and of the methyl ester of β-parinaric acid[13], an interesting fluorescent probe for biological membranes.

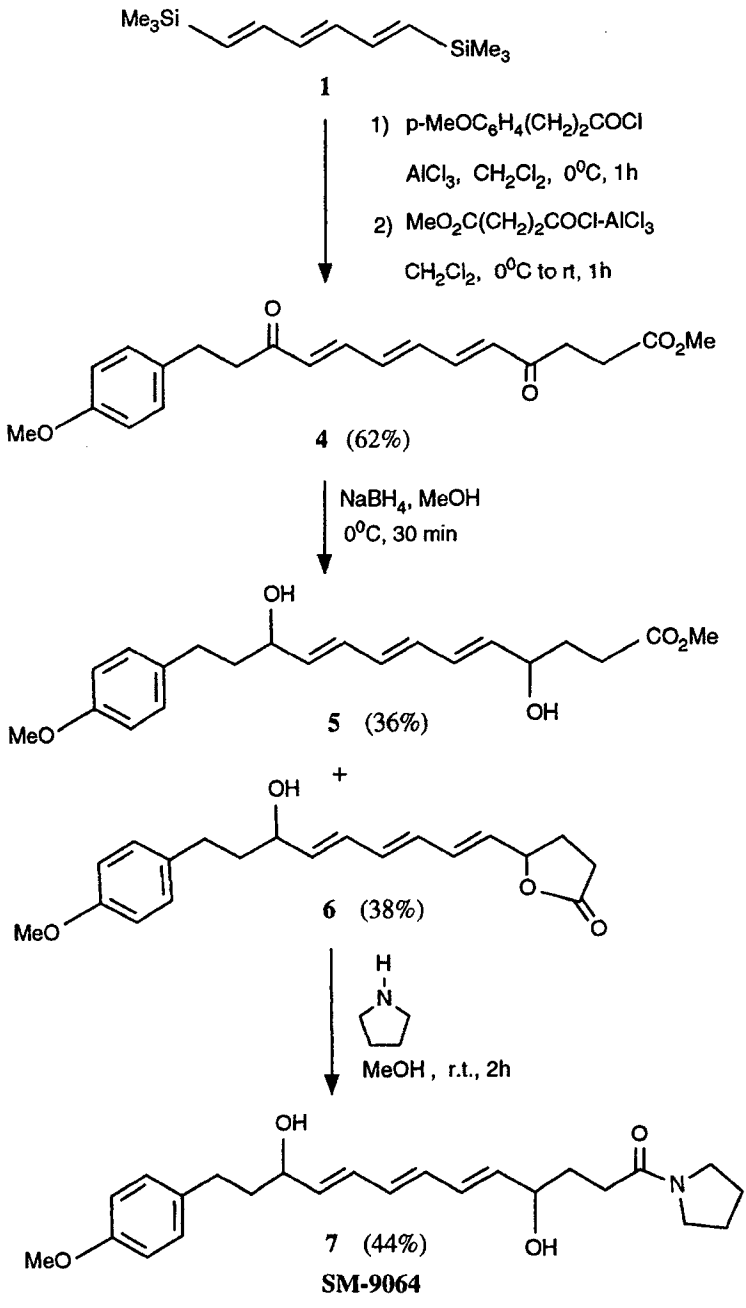
Scheme 1



Therefore, in view of the ease of preparation of 1,6-diacylhexatrienes, the synthetic route appeared to be suited ideally to the construction of the target molecule SM-9064 **7** (Scheme 2). The key step involves the one-pot double substitution of the trimethylsilyl groups of the triene **1** (n=1) with different acyl clorides to afford dione **4** in 62% yield. The reduction of diketo ester **4** is easily achieved with $NaBH_4$ in MeOH, leading to a mixture of the dihydroxy ester **5** and the γ-lactone **6**. These compounds are separately reacted with pyrrolidine in MeOH, affording the target molecule **7** in an overall 44% yield.

In conclusion, this further application of our procedure, providing an easy and direct access to a highly interesting leukotriene B_4 antagonist, confirms the versatility and the validity of the methodology.

Scheme 2



EXPERIMENTAL

Methyl succinyl chloride was commercially available (Aldrich), 3-(*p*-methoxyphenyl)-propanoyl chloride was prepared from the related commercially available acid (Aldrich). Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. GC analyses were performed with a SPB-1 (methylsilicone, 30 m x 0.25 mm id) capillary column. IR spectra were recorded on a Perkin Elmer 883 spectrometer. ^{1}H NMR data were measured at 200 MHz and ^{13}C data at 50.3 MHz on a Varian XL 200 spectrometer. Melting points are uncorrected and were determined with a Kofler apparatus. Purity of the compounds was verified by TLC (Merck plastic sheets with silica gel 60 F_{254}). All solvents were distilled prior to use.

Methyl (5*E*,7*E*,9*E*)-4,11-dioxo-13-(*p*-methoxyphenyl)-trideca-5,7,9-trienoate (4).

A CH_2Cl_2 solution (15 mL) of freshly distilled 3-(*p*-methoxyphenyl)-propanoyl cloride (1.46 g, 7.4 mmol) was added in the first step, under nitrogen, to a cold (0 °C) CH_2Cl_2 solution (30 mL) of compound **1** (1.50 g, 6.7 mmol) containing a suspension of anhydrous $AlCl_3$ (1.95 g, 14.8 mmol). (In this case we have adopted a variation of the procedure, due to the particular type of acyl chloride employed. Indeed, it is not possible to prepare previously the complex acyl chloride-$AlCl_3$, because of the possibility of an *intramolecular* cyclization of the 3-(*p*-methoxyphenyl)-propanoyl chloride *meta* to methoxy group, which should lead to 6-methoxy-1-indanone[14]). After complete addition at 0 °C, the mixture was stirred at the same temperature and the reaction was monitored by capillary

GC analysis. After reaction completion (1h), a solution (30 mL) of methyl succinyl chloride-$AlCl_3$ complex, previously prepared from 10 mmol (1.50 g) of succinyl chloride and 20 mmol (2.64 g) of $AlCl_3$, was dropped at 0 °C and the reaction mixture was slowly brought to room temperature and stirred for 1h, the time required for completion. Then the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated. The residue, purified by flash chromathography on silica gel (elution with 7:3 diethyl ether-petroleum ether), afforded 62% yield of **4**.

mp 123-124°C (*from* $CHCl_3$ / Et_2O). ^1H NMR ($CDCl_3$, 200 MHz) δ 2.64 (t, J = 6.6 Hz, 2H), 2.75-3.05 (m, 6H), 3.66 (s, 3H), 3.76 (s, 3H), 6.29 (dd, J = 15.4, 5.9 Hz, 2H), 6.50-6.69 (m, 2H), 6.71-6.92 (m, 2H), 7.00-7.35 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.79, 29.12, 35.42, 42.96, 51.87, 55.25, 113.88, 129.28, 131.77, 132.28, 132.98, 138.19, 138.50, 140.48, 140.77, 157.94, 173.24, 197.86, 199.35 ppm. IR ($CHCl_3$) ν 1735, 1685, 1665, 1605, 1010 cm^{-1}.

Methyl (5*E*,7*E*,9*E*)-4,11-dihydroxy-13-(*p*-methoxyphenyl)-trideca-5,7,9-trienoate (5) and γ-Lactone (6).

A mixture of **4** (0.66 g, 1.85 mmol) and $NaBH_4$ (0.14 g, 3.7 mmol) in 50 mL of MeOH was stirred at 0 °C. After reaction completion (0.5 h), the solvent was evaporated and dilute aqueous hydrochloric acid was added. Then the mixture was extracted with ethyl acetate, dried, and evaporated. Flash chromatography of the residue (elution with 8:2 CH_2Cl_2-ethyl acetate) yielded 0.23 g (38% yield) of γ-lactone **6** (R_f = 0.64) as a colorless oil.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65-2.15 (m, 4H), 2.30-2.80 (m, 5H), 3.77 (s, 3H), 4.17 (q. like, J = 6.4 Hz, 1H), 4.98 (q. like, J = 6.9 Hz, 1H), 5.60-5.88 (m, 2H), 6.05-6.50 (m, 4H), 6.82 (d, J = 8.6 Hz, $2H_{arom}$), 7.10 (d, J = 8.6 Hz, $2H_{arom}$) ppm. IR ($CHCl_3$) ν 3600, 3550-3300, 1770, 1610, 1515, 1000 cm^{-1}.

Further elution gave 0.24 g (36% yield) of the dihydroxy ester **5** (colorless oil) as a mixture of the two diastereoisomers (R_f = 0.28, 0.33).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50-2.15 (m, 6H), 2.43 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 3.66 (s, 3H), 3.78 (s, 3H), 4.07-4.33 (m, 2H), 5.60-5.84 (m, 2H), 6.14-6.36 (m, 4H), 6.82 (d, J = 8.6 Hz, $2H_{arom}$), 7.10 (d, J = 8.6 Hz, $2H_{arom}$) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 30.00, 30.73, 31.88, 38.92, 51.75, 55.23, 71.46, 71.52 (diastereomer), 71.80, 71.82 (diastereomer), 113.78, 129.31, 130.36, 130.41 (diastereomer), 130.57, 130.63 (diastereomer), 132.07, 132.47, 133.80, 135.66, 136.56, 157.71, 174.41 ppm. IR ($CHCl_3$) ν 3600, 3550-3300, 1735, 1610, 1515, 1000 cm^{-1}.

(5*E*,7*E*,9*E*)-*N*,*N*-tetramethylene-4,11-dihydroxy-13-(*p*-methoxyphenyl)-trideca-5,7,9-trienamide (7).

Compounds **5** and **6** were separately reacted with pyrrolidine in MeOH at room temperature as described below.

Pyrrolidine (0.47 g, 6.7 mmol) was added to a solution of the dihydroxy ester **5** (0.24 g, 0.67 mmol) in MeOH (20 mL) and the mixture was stirred at room temperature. After 2 h, the solvent was evaporated and H_20 was added. Then the mixture was extracted with ethyl acetate, dried, and evaporated. Flash

chromatography of the residue (elution with 9:1 ethyl acetate-MeOH) yielded 0.12 g of compound **7** as a colorless oil.

^{1}H NMR ($CDCl_3$ + D_2O, 200 MHz) δ 1.65-2.10 (m, 8H), 2.30-2.45 (m, 2H), 2.48-2.75 (m, 2H), 3.38 (t, J = 6.6 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 3.76 (s, 3H), 4.05-4.40 (m, 2H), 5.61-5.81 (m, 2H), 6.13-6.38 (m, 4H), 6.80 (d, J = 8.6 Hz, $2H_{arom}$), 7.09 (d, J = 8.6 Hz, $2H_{arom}$) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.37, 26.05, 30.75, 30.91, 31.47, 38.96, 45.94, 46.81, 55.24, 71.57, 71.82, 113.76, 129.32, 129.76, 130.59, 131.77, 132.53, 133.89, 136.11, 136.74, 157.71, 172.26 ppm. IR ($CHCl_3$) ν 3600, 3550-3200, 1615, 1515, 1000 cm^{-1}.

The reaction of compound **6** with pyrrolidine was performed in a similar manner, starting from a MeOH solution (10 mL) of **6** (0.12 g, 0.37 mmol) and 0.26 g (3.7 mmol) of pyrrolidine, leading to 0.065 g of **7**. Taking also into account the amount (0.12 g) of compound **7** deriving from the reaction of the dihydroxy ester **5**, the overall yield was 44%.

ACKNOWLEDGEMENTS

Work supported by National Research Council of Italy (C.N.R.), Progetto Finalizzato Chimica Fine II.

REFERENCES

1. Rokach, J. *Bioactive Molecules (Vol. II): Leukotrienes and Lipoxygenases;* Elsevier: New York, 1989.

2. Showell, H.J.; Otterness, I.G.; Marfat, A. and Corey, E.J. *Biochem. Biophys. Res. Commun.* **1982**, *106*, 741.

3. Morris, J. and Wishka, D.G. *Tetrahedron Lett.* **1988**, *29*, 143.

4. Djuric, S.W.; Haack, R.A. and Miyashiro, J.M. Eur. Patent 296,580 1988; *Chem. Abstr.* **1989**, *111*, 146810. Djuric, S.W.; Haack, R.A. and Yu, S.S. Eur. Patent 319,900, 1989; *Chem. Abstr.* **1990**, *112*, 76932.

5. Djuric, S.W.; Collins, P.W.; Jones, P.H.; Shone, R.L.; Tsai, B.S.; Fretland, D.J.; Butchko, G.M.; Villani-Price, D.; Keith, R.H.; Zemaitis, J.M.; Metcalf, L. and Bauer, R.F. *J. Med. Chem.* **1989**, *32*, 1145. Fretland, D.J.; Levin, S.; Tsai, B.S.; Djuric, S.W.; Widomski, D.L.; Zemaitis, J.M.; Shone, R.L. and Bauer, R.F. *Agents Actions*, **1989**, *27*, 395; *Chem. Abstr.* **1989**, *111*, 33445. Fretland, D.J.; Widomski, D.L.; Zemaitis, J.M.; Djuric, S.W. and Shone, R.L. *Inflammation (N.Y.)* **1989**, *13*, 601; *Chem. Abstr.* **1989**, *111*, 224967.

6. Nakamura, T.; Kawakami, H. and Ono, K. Eur. Patent 260,655, 1988; *Chem. Abstr.* **1988**, *109*, 109867.

7. Teniou, A. and Gree, R. *Bull. Soc. Chim. Belg.* **1991**, *100*, 411.

8. Namiki, M.; Igarashi, Y.; Sakamoto, K.; Nakamura, T. and Koga. Y. *Biochem. Biophys. Res. Commun.* **1986**, *138*, 540.

9. Babudri, F.; Fiandanese, V.; Marchese, G. and Naso, F. *J. Chem. Soc., Chem. Commun.* **1991**, 237.

10. For reviews see: Naso, F. *Pure Appl. Chem.* **1988**, *60*, 79. Fiandanese, V. *Pure Appl. Chem.* **1990**, *62*, 1987.

11. Fiandanese, V.; Marchese, G.; Naso, F. and Ronzini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 647. Fiandanese, V.; Marchese, G.; Naso, F. and Ronzini, L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1115. Fiandanese, V.; Miccoli, G.; Naso, F. and Ronzini, L. *J. Organomet. Chem.* **1986**, *312*, 343. Fiandanese, V.; Marchese, G.; Mascolo, G.; Naso, F. and Ronzini, L. *Tetrahedron. Lett.* **1988**, *29*, 3705. Fiandanese, V.; Marchese, G.; Naso, F.; Ronzini, L. and Rotunno, D. *Tetrahedron Lett.* **1989**, *30*, 243.

12. Babudri, F.; Fiandanese, V. and Naso, F. *J. Org. Chem.* **1991**, *56*, 6245.

13. Babudri, F.; Fiandanese, V.; Naso, F. and Punzi, A. *Synlett* **1992**, 221.

14. House, H.O. and Hudson, C.B. *J. Org. Chem.* **1970**, *35*, 647.

(Received in UK 27 July, 1992)