*Tetrahedron* Vol. 42, No. 3, pp. 917 to 922, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00


# A NOVEL, EFFICIENT SYNTHESIS OF (±)-ERYTHRO-SPHINGOSINE

Giuliana Cardillo,* Mario Orena, Sergio Sandri, Claudia Tomasini

Centro per lo Studio della Fisica delle Macromolecole
Istituto Chimico " G. Ciamician " - Via Selmi 2, 40126 Bologna,
Italy

(*Received in UK 6 November* 1985)

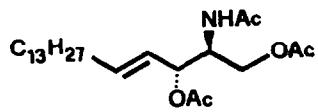
SUMMARY A stereoselective synthesis of (±)-erythro-sphingosine triacetate (1) is described. The key reaction that determines the right stereochemistry is the iodocyclization of 1-trichloroacetimido-(2E,4E)-octadecadiene (5). The 4,5-dihydro-1,3-oxazine (6) through cleavage with HCl and treatment with Amberlyst A 26 in the $AcO^-$ form, followed by full acetylation, affords (1) in good yield.

In the last years new reactions which allow vicinal functional groups to be introduced in a desired stereo- and regio-relationship were devised. Of particular interest are new strategies which proceed through an heterocyclic ring formation. The use of heterocyclic intermediates as precursors of functionalized units have found an increasing interest since the formation of a cycle enables to obtain a high control on the stereochemistry and the heterocyclic ring constitutes an easily removable protecting group. Thus allylic phosphates,[1] carbonates,[2] amides,[3] urethanes[4] and imidates[5] were cyclized to achieve 1,2- or 1,3-asymmetric induction. The iodocyclofunctionalization of allylic trichloroacetimidates is a versatile reaction that allows to introduce an aminodiol unit, frequently occurring in biologically interesting compounds. This reaction was indeed utilized in the functionalization of cyclic systems in the enantioselective synthesis of amino sugars.[6,7] Moreover a total diastereomeric induction, leading to pure erythro or threo isomer was recently achieved in acyclic compounds, starting from primary allylic trichloroacetimidates.[8] In fact the stereochemistry of the two centers newly introduced crucially depends upon the configuration of the double bond, arising from an anti attack to the intermediate iodonium cation.

Preliminary studies suggest that various factors can affect the regiochemistry of this reaction, which could proceed through a 5-exo or 6-endo mode.[9] When electronic factors play the dominant role, the attack is directed towards the more stabilized carbocation.

In this paper we would like to report an efficient, diastereoselective synthesis of

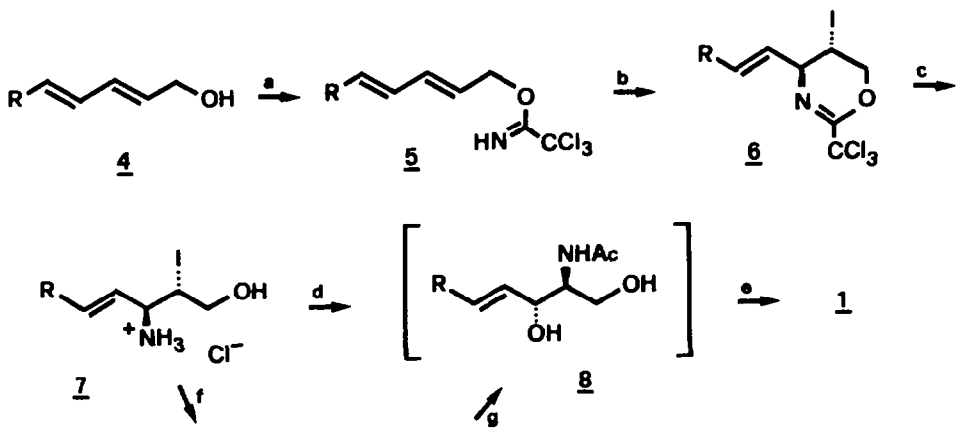
(±)-erythro-sphingosine triacetate 1 (erythro-2-acetamido-1,3-diacetoxyoctadec-(2E)-ene), the most widely occurring of the sphingolipid bases.[10]

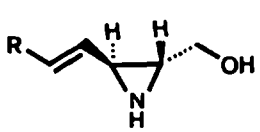



1

Since the aim here is to direct the cyclization in an endocyclic sense, we utilized as starting material (2E,4E)-octadecadien-1-ol 4, that ensured the stabilization of the intermediate allylic cation, leading to a 6-endo closure.


The dienol 4 was readily available through a Wittig-Horner reaction of methyl 4-dimethylphosphono-2-butenoate 2 and tetradecanal,[10g] followed by reduction of the ester 3 with LAH.




R = n-$C_{13}H_{27}$

9

a) NaH cat., THF, 0 °C, $CCl_3CN$ b) N-iodosuccinimide, $CHCl_3$, r.t. c) 2N HCl d) Amberlyst A 26 in the $AcO^-$ form, refluxing benzene e) $Ac_2O$/pyridine, r.t. f) Amberlyst A 26 in the $CO_3^{2-}$ form, MeOH g) HCl, then Amberlyst A 26 in the $AcO^-$ form, refluxing benzene

Although the Wittig-Horner reaction with stabilized anions is described to afford the diene exclusively in the (E,E)-configuration,[10g] we have observed in g.l.c. that a diastereomeric mixture (E,E):(E,Z) in a 70:30 ratio was obtained: an isomerization with a catalytic amount of iodine in benzene was therefore required.[11,12] The dienol 4 was

successively converted to the corresponding trichloroacetimidate 5 by treatment with a catalytic amount of NaH followed by addition of trichloroacetonitrile in THF at 0 °C.[13] The cyclization of 5, performed with N-iodosuccinimide in $CHCl_3$ at r.t. gave the corresponding 4,5-dihydro-1,3-oxazine 6 in 95% yield. The IR absorption at 1670 $cm^{-1}$, a diagnostic feature for a C=N stretching in 2-trichloromethyl-4,5-dihydro-1,3-oxazines,[5] confirmed the 6-endo closure. The acidic cleavage of 6 with 2N HCl in acetone afforded in 92% yield the corresponding salt 7 which was successively treated with Amberlyst A 26 in the $AcO^-$ form in refluxing benzene for 12 h.[14] After filtration of the resin and removal of the solvent, the corresponding amide[15] was isolated (IR 1660, 1510 $cm^{-1}$) and directly acetylated to give in good yield (±)-erythro-sphingosine triacetate 1, characterized on the basis of its m.p.[10b] and IR,[10a], $^1H$ NMR[10f], $^{13}C$ NMR[10d] spectra.

This reaction proceeds via the intermediate aziridine 9, that can be easily isolated under mild basic conditions by treating in methanol the salt 7 with Amberlyst A 26 in the $CO_3^{2-}$ form for 1 h at r.t. The aziridine was converted to the corresponding hydrochloride and regioselectively opened[16] with Amberlyst A 26 in the $AcO^-$ form in refluxing benzene, affording exclusively the erythro-amide 8 which was directly acetylated to give (+)-erythro-sphingosine triacetate 1.

## EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or sodium benzophenone immediately prior to use. All reactions involving organometallic reagents were carried out under an argon atmosphere. M.p. (Pyrex capillary) were determined on a Buchi 510 hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 682 spectrophotometer either on films or, for solids, on Nujol mulls. $^1H$ NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer with tetramethylsilane as internal reference. $^{13}C$ NMR spectra (20 MHz) were recorded using a Varian FT 80-A spectrometer. All chemical shifts were measured relative to tetramethylsilane $\delta_C = 0$. Mass spectra were obtained with a double-focusing Varian MAT 112 instrument at an ionizing voltage of 70 eV. Mass spectral data (MS) are tabulated as m/e values. Analytical g.l.c. was carried out on a Carlo Erba capillary gas cromatograph (Fractovap 4160) equipped with a SE-52 flexible glass capillary column (25 m x 0.3 mm i.d.; carrier gas He; $p_{He}$ 0.6 kg $cm^{-2}$). Chromatograms, peak areas, and retention times were obtained by using a Perkin-Elmer Sigma 10 data processor. T.l.c. and column chromatography were carried out on Kieselgel $GF_{254}$ (Merck). Solvent ratios are in volume before mixing. Solutions were dried over anhydrous magnesium sulphate.

Methyl 4-dimethylphosphono-2-butenoate (2). The title compound was prepared as reported in Ref. 17 in 75% yield; IR (neat) 1730 and 1655 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.80 (dd, 2H, J = 6 Hz, J = 24 Hz), 3.6 (s, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 6.0 ($\underline{A}BX_2P$, 1H, J = 7 Hz; J = 15 Hz), 6.8 ($A\underline{B}X_2P$, 1H, J = 6 Hz, J = 15 Hz).

Methyl (2E,4E)-octadecadienoate (3). A solution of 2 (7.7 g, 40 mmol) in dry THF (20 mL) was slowly added to a stirred, cooled (0 °C) solution of LDA prepared in dry THF (30 mL) from diisopropylamine (22 mL, 40 mmol) and n-butyllithium (22 mL, 40 mmol; 1.8 M in n-hexane) for 1 h at 0 °C. The red solution was allowed to reach -40 °C and tetradecanal (8.5 g, 40 mmol), dissolved in dry THF (20 mL) was dropped into the reaction mixture. After 2 h the reaction was quenched by addition of water and extracted with ether. Volatiles were evaporated under reduced pressure, the residue was dissolved in 1:1 benzene:ether (20 mL) and iodine (120 mg, 0.5 mmol) was added. The solution was allowed to stand 6 h at r.t., poured in ice-water and extracted twice with ether. The combined organic extracts were successively washed with a 10% $Na_2S_2O_3$ aqueous solution and brine, dried and concentrated in vacuo. After chromatography of the residue through silica gel (cyclohexane), the ester 3 (8.0 g, 68% yield) was obtained as a colorless oil; IR (neat) 1720, 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (t, 3H), 1.3 (m, 22H), 1.8 - 2.4 (m, 2H), 3.75 (s,

3H), 5.8 - 7.7 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 145.4, 144.9, 128.4, 118.8, 51.4, 33.0, 31.8, 29.2, 29.6, 29.5, 29.4, 29.2, 22.7, 14.1; MS, m/e, 294 ($M^+$)(28), 264(21), 195(100), 165(71).
Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.49; H, 11.64. Found: C, 77.4; H, 11.6.

(2E,4E)-Octadecadien-1-ol (4). A solution of 3 (7.35 g, 25 mmol) in dry ether (50 mL) was slowly added to a magnetically stirred suspension of LAH (0.58 g, 15 mmol) in dry ether, kept at -10 °C. After stirring for 0.5 h at -10 °C, the complex was decomposed by adding sat. aqueous $NH_4Cl$ and then extracted with ether. The organic layer, after washing with water, was dried and evaporated. The residue was purified by chromatography on silica gel (cyclohexane:AcOEt 9:1) to give 4 (5.3 g, 80% yield) as a white solid: m.p. 52 - 54 °C; IR(nujol) 3350 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.9 (t, 3H), 1.3 (m, 22H), 1.8 - 2.1 (m, 2H), 2.2 (bs, 1H, OH), 4.15 (d, 2H; J = 6 Hz), 5.3 - 6.4 (m, 2 H); $^{13}$C NMR ($CD_3COCD_3$) $\delta$ 134.5, 132.2, 130.9, 130.8, 62.9, 33.2, 32.6, 30.7, 30.4, 30.2, 28.9, 27.8, 23.3, 14.3; MS, m/e, 266 ($M^+$)(9), 248(4), 238(7), 223(7), 211(8), 140(14), 112(41), 85(100).
Anal. Calcd for $C_{18}H_{34}O$: C, 81.13; H, 12.86. Found: C, 81.2; H, 12.9.

1-Trichloroacetimido-(2E,4E)-octadecadiene (5). A solution of 4 (4.8 g, 18 mmol) in dry THF (30 mL) under argon was added to a stirred suspension of NaH (50% in mineral oil; 100 mg, 2 mmol; previously washed with dry pentane) in dry THF (20 mL) at 0 °C. After 1 h the resulting mixture was added dropwise to a solution of trichloroacetonitrile (2.9 g, 20 mmol) in dry THF (30 mL) with stirring at 0 °C. After 1.5 h at r.t. the volatiles were evaporated under reduced pressure and pentane (20 mL) containing methanol (2 mL) was added to the residue: successive filtration through Celite pad and removal of the solvent gave 5 in a quantitative yield as a yellow oil rather unstable at r.t.; IR (neat) 3350 and 1665 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.95 (t, 3H), 1.3 (m, 22H), 1.9 - 2.4 (m, 2H), 4.8 (d, 2H; J = 7 Hz), 5.5 - 6.8 (m, 4H), 8.3 (m, 1H, NH); $^{13}$C NMR ($CD_3COCD_3$) $\delta$ 135.6, 134.3, 128.7, 122.7, 68.4, 31.6, 30.9, 28.7, 28.4, 28.2, 21.6, 12.7.

trans-5-Iodo-4-tetradec-(1E)-en-1-yl-2-trichloromethyl-4,5-dihydro-1,3-oxazine (6). To a solution of 5 (6.1 g, 15 mmol) in $CHCl_3$ (150 mL), N-iodosuccinimide (3.6 g, 16 mmol) was added and the mixture was stirred for 12 h. Then a 10% $Na_2S_2O_3$ aqueous solution was added, the organic phase was separated and the volatiles were removed in vacuo. After chromatography on silica gel (cyclohexane) the oxazine 6 was recovered (7.6 g, 95% yield) as a white solid; m.p. 47 - 49 °C; IR (nujol) 1685 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (t, 3H), 1.25 (m, 22H), 1.9 - 2.3 (m, 2H), 3.9 - 4.2 (dt, 1H, CHI, J = 7.5 Hz), 4.3 - 4.8 (m, 3H), 5.5 - 5.9 (m, 2H); $^{13}$C NMR ($CD_3COCD_3$) $\delta$ 135.4, 128.7, 71.1, 62.5, 32.7, 32.4, 30.2, 30.0, 29.8, 29.6, 27.3, 23.1, 21.6, 14.3; MS, m/e, 535($M^+$)(1), 496(3), 407(5), 280(11), 263(6), 111(100).
Anal. Calcd for $C_{20}H_{33}NOCl_3I$: C, 36.20; H, 5.01; N, 2.11. Found: C, 36.1; H, 5.0; N, 2.2.

erythro-3-Amino-2-iodooctadec-(4E)-en-1-ol Hydrochloride (7). The 4,5-dihydro-1,3-oxazine 6 (6.4 g, 12 mmol) was dissolved in acetone (50 mL), 2N HCl (10 mL) was added and the resulting solution was stirred for 12 h at r.t. Volatiles were removed in vacuo and the residue was taken up in dry ether, to give after filtration the hydrochloride 7 (4.9 g, 92% yield) as a white solid; m.p. 132 - 134 °C (dec); IR (nujol) 3410 $cm^{-1}$; $^1$H NMR ($CD_3OD$) $\delta$ 0.9 (t, 3H), 1.3 (m, 22H), 1.9 - 2.3 (m, 2H), 3.0 - 3.9 (m, 4H), 4.85 (bs, 4H, OH, $NH_3^+$); $^{13}$C NMR ($CD_3OD$) $\delta$ 142.0, 124.5, 66.3, 55.7, 35.1, 33.4, 30.7, 29.7, 23.7, 14.4.

erythro-2-Acetamido-1,3-diacetoxyoctadec-(4E)-ene (+)-erythro sphingosine triacetate (1). To a solution of 7 (4.4 g, 10 mmol) in dry benzene (20 mL), Amberlyst A 26 in the $AcO^-$ form (Rohm and Haas, 10 g; $\sim$ 3.8 mequiv/g) was added and the suspension was refluxed for 12 h. After filtration of the resin and removal of the solvent under reduced pressure, the amide 8 (IR (neat) 1660 and 1510 $cm^{-1}$), was directly acetylated with acetic anhydride (2 mL) in pyridine (5 mL). After 18 h at r.t. the volatiles were stripped off in vacuo and the residue was chromatographed on silica gel (cyclohexane:AcOEt 8:2) to give 1 (2.9 g, 68% yield) was obtained as a white solid; m.p. 89 - 90 °C (Lit.[10b] 90 - 91 °C); IR (nujol) 3290, 1740, 1660, 1550 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.9 (t, 3H), 1.3 (m, 22H), 1.97 (s, 3H), 2.08 (s, 6H), 1.9 - 2.1 (m, 2H), 4.05 (m, 1H), 4.3 (m, 1H), 4.4 - 4.5 (m, 1H), 5.25 - 5.6 (m, 2H), 5.65 - 5.85 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.9, 170.0, 169.7, 137.4, 124.2, 73.9, 62.6, 50.7, 32.3, 31.9, 29.7, 29.5, 28.9, 23.3, 22.7, 21.1, 20.8, 14.1; MS, m/e, 425($M^+$)(2), 366(6), 305(2), 292(5), 264(6), 239(3), 187(5), 144(88), 102(55), 85(93), 84(100).
Anal. Calcd for $C_{24}H_{43}NO_5$: C, 67.73; H, 10.18; N, 3.29. Found: C, 67.9; H, 10.2; N, 3.3.

trans-2-Hydroxymethyl-3-pentadec-(1E)en-1-yl-aziridine (9). To a solution of 7 (2.2 g; 5

mmol) in methanol (10 mL), Amberlyst A 26 in the $CO_3^{2-}$ form (Rohm and Haas, 5 g; ~ 3.8 mequiv/g) was added and the suspension was stirred for 1 h at r.t. The resin was then filtered off and the solvent removed in vacuo, to give 9 as a colorless oil in a quantitative yield; IR (neat) 3350 $cm^{-1}$; $^1H$ NMR (dmso-$d_6$) δ 0.85 (t, 3H), 1.25 (m, 22H), 1.7 - 2.2 (m, 4H), 3.2 (bs, 2H, OH, NH), 3.85 (m, 2H), 5.2 - 5.8 (m, 2H); $^{13}C$ NMR (dmso-$d_6$) δ 136.5, 123,7, 55.7, 31.7, 31.2, 28.9, 22.0, 13.8
Anal. Calcd for $C_{18}H_{35}NO$: C, 76.81; H, 12.53; N, 4.98. Found: C, 76.7; H, 12.6; N, 5.0.

erythro-2-Acetamido-1,3-diacetoxyoctadec-(4E)-ene [(±)-erythro-sphingosine triacetate] (1).
To a solution of the aziridine 9 (1.1 g; 4 mmol) in methanol (5 mL), 2N HCl (1 mL) was added and the solvent was removed in vacuo. The residue was then dissolved in benzene (10 mL) and then Amberlyst A 26 in the $AcO^-$ form (Rhom and Haas, 4 g; ~ 3.8 mequiv/g) was added and the suspension was refluxed for 12 h. The resin was filtered off and the residue was treated with acetic anhydride (1 mL) in pyridine (3 mL) at r.t. for 18 h. After removal of the volatiles, the crude product was purified by silica gel chromatography (cyclohexane:AcOEt 8:2) to give 1 (1.1 g; 65% yield) as a white solid: m.p. 89 - 90 °C (Lit.[10b] 90 - 91 °C).

Aknowledgement: We thank M.P.I., Rome, for a grant.

## REFERENCES

1. Bartlett, P.A.; Jernstedt, K.K. J. Am. Chem. Soc., 99, 4829 (1977).

2. (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Soc., Chem. Commun., 465 (1981).
(b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Org. Chem., 47, 4626 (1982).
(c) Bartlett, P.A.; Meadows, J.D.; Brown, E.G.; Morimoto, A.; Jernstedt, K.K. J. Org. Chem., 47, 4013 (1982).

3. (a) Cardillo, G.; Orena, M.; Sandri, S. J. Chem. Soc., Chem. Commun., 1489 (1983).
(b) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. J. Am. Chem. Soc., 106, 1079 (1984).
(c) Knapp, S.; Rodriques, K.E.; Levorse, A.T.; Ornaf, R.M. Tetrahedron Lett., 1803 (1985).

4. (a) Georges, M.; MacKay, D.; Fraser-Reid, B. J. Am. Chem. Soc., 104, 1101 (1982).
(b) Bartlett, P.A.; Tanzella, D.; Barstow, J.F. Tetrahedron Lett., 619 (1982).
(c) Takano, S.; Hatakeyama, S. Heterocycles, 19, 1243 (1982).
(d) Hirama, M.; Uei, M. Tetrahedron Lett., 5307 (1982).
(e) Parker, K.A.; O'Fee, R. J. Am. Chem. Soc., 105, 654 (1983).
(f) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. Tetrahedron Lett., 4963 (1984).
(g) Harding, K.E.; Stephens, R.; Hollingsworth, D.R. Tetrahedron Lett., 4631 (1984).
(h) Kobayashi, S.; Isobe, T.; Ohno, M. Tetrahedron Lett., 5079 (1984).

5. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Soc. Chem. Commun., 1308 (1982).

6. (a) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. Tetrahedron, 39, 3801 (1983).
(b) Pauls, H.W.; Fraser-Reid, B. J. Org. Chem., 48, 1392 (1983).

7. Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. J. Org. Chem., 49, 3951 (1984).

8. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. J. Chem. Soc., Perkin I, 935 (1985).

9. Baldwin, J.E. J. Chem. Soc., Chem. Commun., 734 (1976).

10. (a) Grob, C.A.; Gadient F. Helv. Chim. Acta, 60, 1145 (1957).
(b) Shapiro, D.; Segal, H.; Flowers, H.M. J. Am. Chem. Soc., 80, 1194 (1958).
(c) Reist, E.J.; Christie, P.H. J. Org. Chem., 35, 4127 (1970).
(d) Stoffel, W.; Zierenberg, O.; Tunggal, B.D. Hoppe Seiler's Z. Physiol. Chem., 354, 1962 (1972).
(e) Newman, H. J. Am. Chem. Soc., 95, 4098 (1973).
(f) Tkakzuk, P.; Thornton, E.R. J. Org. Chem., 46, 4393 (1981).
(g) Garigipati, R.S., Weinreb, S.M. J. Am. Chem. Soc., 105, 4499 (1983).
(h) Bernet, B.; Vasella, A. Tetrahedron Lett., 5491 (1983).

11. Cainelli, G.; Cardillo, G.; Contento, M.; Grasselli, P.; Umani Ronchi A. Gazz. Chim. It., 103, 117 (1973).

12. In an attempt to synthesize 3 according ref. 10g from tetradecyltriphenylphosphonium salt and 4-tetrahydropyranyloxy-2-butyn-1-al, the Z-configuration of the double bond was exclusively observed [ $^1$H NMR ($CDCl_3$) $\delta$ 5.45 (d, 1H, $H_A$, J = 11 Hz), 5.65, 5.95 (dt, 1H, $H_B$, J = 11 Hz, J = 8 Hz) ]. This result was probably due to the different protecting group and to different work-up of the reaction.

13. Overman, L.E. J. Am. Chem. Soc., 98, 2901 (1976).

14. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Soc., Chem. Commun., 1309 (1982).

15. Winstein, S.; Boschan, R. J. Am. Chem. Soc., 72, 4669 (1950).

16. Berti, G.; Camici, G.; Macchia, B.; Macchia, F.; Monti, L. Tetrahedron Lett., 2591 (1972).

17. Werbel, L.M.; Headen, N.; Elslager, E.F. J. Med. Chem., 10, 366 (1967).