Tetrahedron Letters, Vol.31, No.35, pp 5077-5080, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

TOTAL SYNTHESIS OF TRIYNE CARBONATE L-660, 631 METHYLESTER FROM D-GLUCOSE

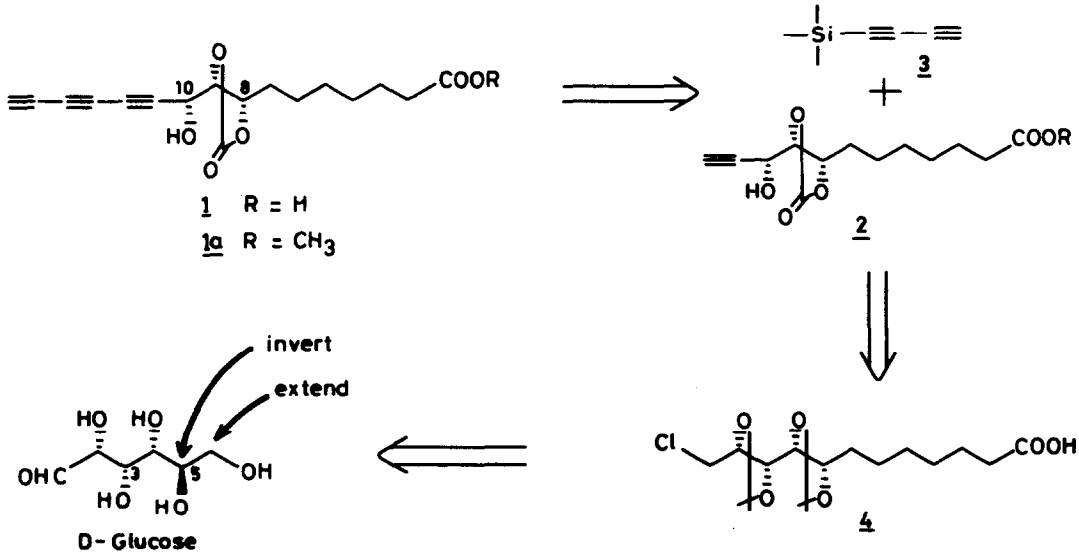
J S Yadav* and D Rajagopal
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract *A stereocontrolled synthesis of methylester of triyne carbonate L-660,631, a new anti-fungal agent, is described starting from D-glucose.*

Recently, two groups from Merck Sharp & Dohme and Schering-Plough Corporation independently reported[1,2] the isolation of a structurally unique molecule containing a novel triacetylenic dioxalone unit from the fermentation broths of actinomycetes and microbispora sp. respectively. The former group has established[1,3] its complete structure as **1** by degradation and synthesis and named it as L-660,631, while the latter group has described[2] only its gross structure and called it EV-22. **1** is a new broad spectrum anti-fungal agent active in vitro against pathogenic yeasts and filamentous fungi and is an extremely potent inhibitor of cytosolic β-ketothiolase, the initial enzyme of cholesterol biosynthesis, and may be useful in studying the mechanism of action of this important enzyme[4]. We describe herein the stereoselective synthesis of triyne carbonate L-660,631 methylester from D-glucose using our recently developed acetylenic technology[5].

Retrosynthetic analysis (Scheme 1) indicated that formation of **1a** could be visualised from

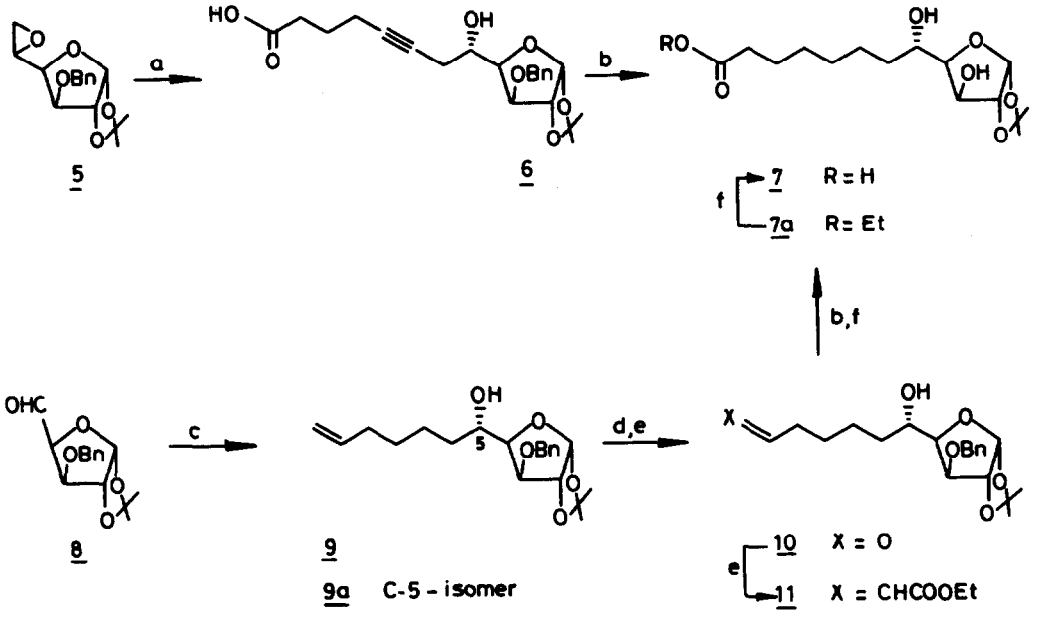
Scheme 1



2 by means of acetylene-acetylene coupling reaction with 3. 2 could be realized from 4 using base induced double elimination of β-alkoxychloride as a key reaction, recently described by us[5]. 4 is easily accessible from D-glucose involving one inversion at C-5.

As per our synthetic plan (Scheme 2), we carried out the extension of side chain at C-6

Scheme 2

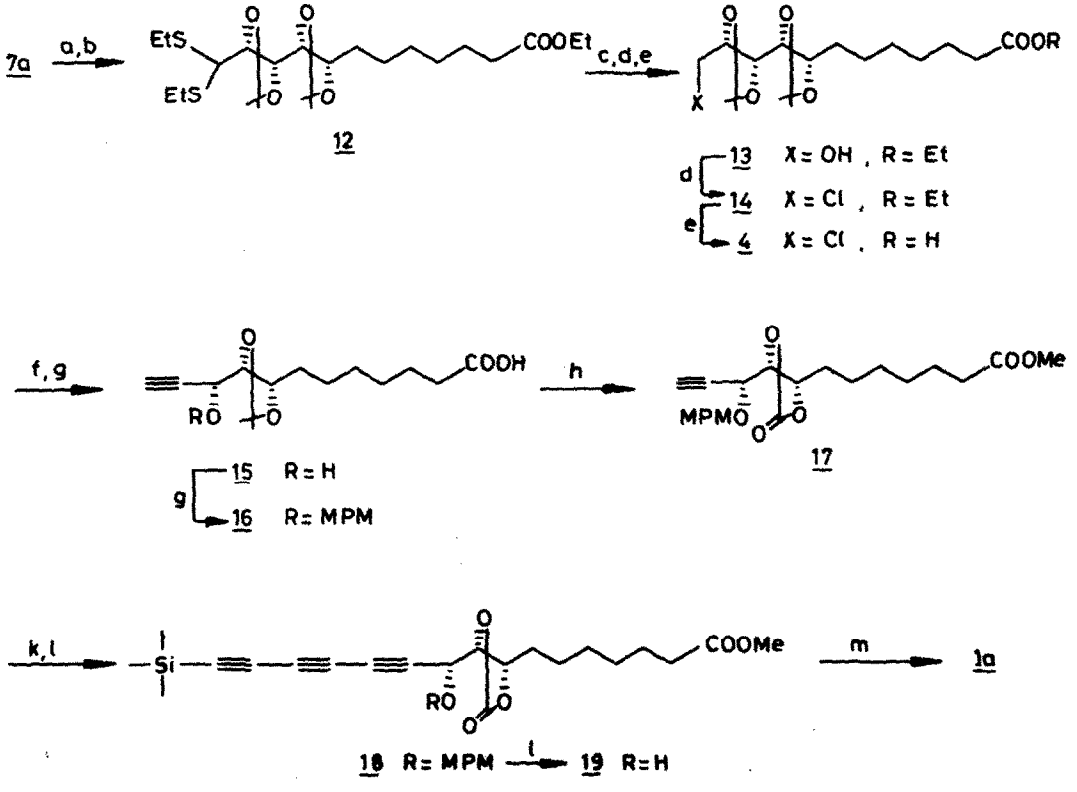


a) LiOOC $(CH_2)_3C \equiv CLi$, HMPA, rt b) H_2, Pd-C, EtOH, 30 psi, rt c) hex-5-enylmagnesium bromide, ether-THF, rt d) OsO_4-$NaIO_4$, rt e) $Ph_3P{=}CHCOOEt$, C_6H_6, rt f) LiOH, aq.DME

of D-glucose involving nucleophilic ring opening of the known[6] 5,6-epoxide (5, C-5 already inverted) with lithium dianion of 5-hexynoic acid to obtain 6 which on hydrogenation over Pd-C afforded acid (7) in overall 10-15% yield. Though this route is short and straight forward we encountered[7] difficulties in scale up beyond one mmol to obtain large amount of 7, required for the synthesis. As an alternative route, reaction of 8[8] with hexenylmagnesium bromide gave separable isomeric mixture[8] of 9 and 9a in the ratio of 8:2. Treatment of 9 with osmium tetroxide and sodium metaperiodate (THF:water) gave the aldehyde 10 which was subsequently converted first to 11, then by hydrogenation to 7a, in an overall yield of 49% from 8. Treatment of 7a (Scheme 3) with conc. HCl and ethanethiol gave the tetrol, which was protected as diisopropylidene derivative 12 in quantitative yield from 7a. Dethiokelatization of 12 followed by reduction gave 13. Reaction of 13 with triphenylphosphene-CCl_4 under reflux gave the chloro compound

14 which in turn was hydrolysed with LiOH to the acid 4. The key base induced double elimination of the β-alkoxy chloride 4 gave the acetylenic product 15. The hydroxyl group of 15 was protected as p-methoxyphenylmethyl ether 16. Treatment of 16 with 3NHCl/THF, followed by esterification with diazomethane afforded the ester diol, which on further reaction with carbonyl diimidazole

Scheme 3



a) EtSH, conc.HCl, 0° b) CH_3COCH_3, H_2SO_4, $CuSO_4$, rt c) i. $BF_3.Et_2O$, HgO (red), THF, rt ii. $NaBH_4$, EtOH, rt, 55% from 7a d) Ph_3P, CCl_4, reflux e) LiOH, aq.DME, rt f) LDA, THF, -25°, 51% from 13 g) NaH, MPM-Br, THF, rt h) i. 1.5N HCl in THF:H_2O (1:1), rt ii. CH_2N_2, ether iii. carbonyldiimidazole, C_6H_6, rt k) 3 (5 eq), CuCl-TMEDA, acetone, O_2, rt l) DDQ, 1:20 H_2O-CH_2Cl_2, rt, 42% from 15 m) n-Bu_4NF

gave the carbonate 17. The crucial acetylene-acetylene coupling[9] was effected by addition of 17 and monotrimethylsilylbutadiyne (3)[10] to a complex of CuCl-TMEDA in acetone while bubbling oxygen for 1 min. to obtain 18. Deprotection of MPM ether gave trimethylsilyl derivative 19 which is found to be stable at room temperature. Treatment of 19 with tetrbutylammonium fluoride in THF-acetic acid (6:1) gave the highly unstable triyne carbonate 1a $[\alpha]_D$ -48.5° (c 0.33, $CDCl_3$) lit.[3] $[\alpha]_D$ -41.2° (c 0.23, $CDCl_3$) whose ^1H NMR data was compared with the reported values of synthetic 1a[3,11,12].

In conclusion we have demonstrated here a highly stereocontrolled total synthesis of sensitive unstable fully conjugated triacetylenic carbonate by a simple and operationally feasible acetylenic technology developed by us which could be extended to the synthesis of similar natural acetylenic compounds.[13]

References and Notes

1. M.D. Lewis and R. Menes, Tetrahedron Letters, **28**, 5129 (1987).
2. J.J. Wright, M.S. Puar, B. Pramanik and A. Fishman, J C S Chem. Comm., **6**, 413 (1988).
3. M.D. Lewis, J.P. Duffy, J.V. Heck and R. Menes, Tetrahedron Letters, **29**, 2279 (1988).
4. (a) A.J. Kempf, O.D. Hensens, R.E. Schwartz, R.S. Sykes, C.F. Wichmann, K.E. Wilson, D.I. Zink and L. Zitno. Abstracts of the New York Academy of Science 1st International Conference on Drug Research in Immunologic and Infectious Diseases; Antifungal drugs; Synthesis, Preclinical and Clinical Evaluation, Garden City, Long Island, New York (1987). (b) J.C. Onishi, G.K. Aburzzo, R.A. Fromtling, G.M. Garsity, J.A. Milligan, B.A. Pelak and W. Rozdilsky, ibid (1987). (c) M. Patel, M. Conover, A. Horan, D. Loebenberg, J. Marquez, R. Mierzw, M.S. Paur and R. Yarborough, J. of Antibiotics, **41**, 794 (1988).
5. (a) J.S. Yadav, M.C. Chander and B.V. Joshi, Tetrahedron Letters, **29**, 2737 (1988). (b) J.S. Yadav, M.C. Chander and C.S. Rao, Tetrahedron Letters, **30**, 5455 (1989).
6. R.L. Whistler and W.C. Lake, Methods Carbohydr. Chem., **6**, 286 (1972).
7. Similar difficulty was also encountered by G. Just and C. Luthe, Can. J. Chem., **58**, 1799 (1980).
8. T.D. Inch, Carbohydr. Res., **5**, 45 (1967).
9. E. Jones, A. Kendrick and A.B. Holmes, Organic Synthesis, **65**, 52 (1987).
10. L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, p 118 (1988).
11. The free acid **1** could not be obtained because it rapidly polymerized. Eventhough its methyl ester **1a** was known for its unstability, it was handled in dilute solution with due care.
12. a) All new compounds gave expected spectral data and exact Mass (HRMS); b) $[\alpha]_D$ in $CHCl_3$ and 200 MHz ^1H NMR ($CDCl_3$) of some selected compounds; **1a:** δ 2.21 (s, 1H), 2.32 (t, 2H, J=7.4 Hz), 2.80 (bs, 1H, OH), 3.67 (s, 3H), 4.3 (t, 1H, J=4.6 Hz), 4.63 (t,q merged, 2H); **19** $[\alpha]_D$ -43.5° (c 0.8): δ 0.15 (s, 9H), 2.26 (t, 2H, J=7.5 Hz), 3.62 (s, 3H), 4.27 (t, 1H, J=5.1 Hz), 4.50-4.65 (t, q merged, 2H), **15** $[\alpha]_D$-24.8° (c 1.1): δ 2.32 (t, 2H, J=7.25 Hz), 2.52 (d, 1H, J=1.5 Hz), 3.77 (dd, 1H, $J_1=J_2=4.5$ Hz), 3.93 (m, 1H), 4.30 (dd, 1H, J=1.5 Hz, J=4.5 Hz); **7** $[\alpha]_D$ -17.2° (c 1.8): δ 1.38 (s, 3H), 1.54 (s, 3H), 2.35 (t, 2H, J=7.25 Hz), 4.03 (d,m, merged, 2H), 4.25 (d, 1H, J=1.5 Hz), 4.50 (d, 1H, J=4.3 Hz), 5.96 (d, 1H, J=4.25 Hz); **4** $[\alpha]_D$ -27.9° (c 1.0): δ 2.30 (t, 2H, J=7.25 Hz), 3.64 (d, 2H, J=6 Hz), 3.50-4.48 (m, 5H).
13. F. Bohlmann, T. Burchhardt and C. Zedro (ed), "Naturally Occurring Acetylenes", Academic, New York, 1973.
    IICT Communication No.2619.

(Received in UK 1 July 1990)