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SYNTHESIS OF A FUROFURANIC MODEL OF NATURAL ANTIFEEDING SUBSTANCES

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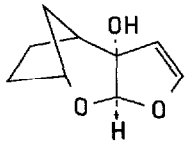
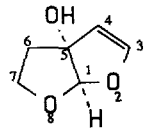
Summary : *A furofuranic model of azadirachtin is synthesized, using in the key step a single electron transfer cyclization .*

Research in pest control has recently focused on azadirachtin[1] . Recent studies have indicated that the pyranofuran subunit 1 of this molecule may be partially responsible for this activity[2] . To complete these studies we propose here a synthesis by a new method of another model (structure 2) also encountered in various natural products such as aflatoxin[3] .

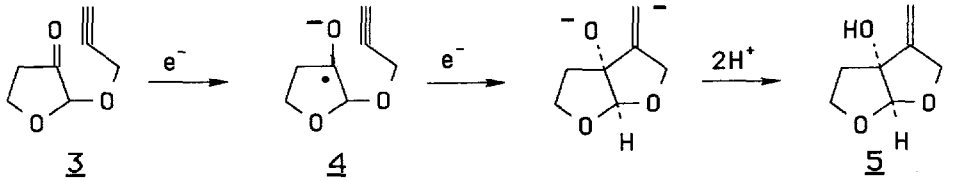


1



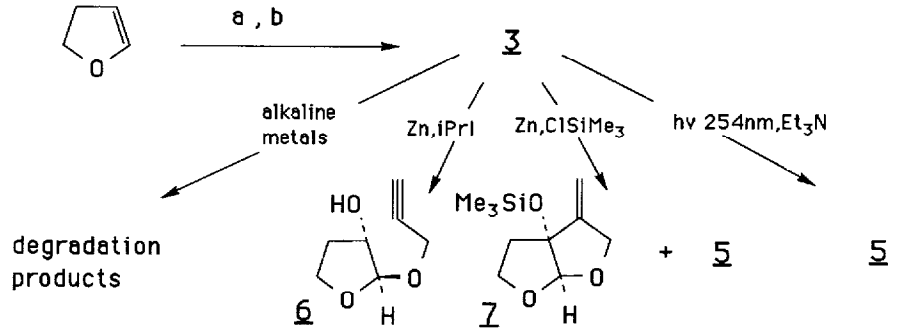
2

As radical cyclization proved to be an excellent approach towards the furofuran skeleton[4], we have investigated the possibility of starting with acetylenic ketone 3 which could lead through a single electron transfer cyclization to alcohol 5 .



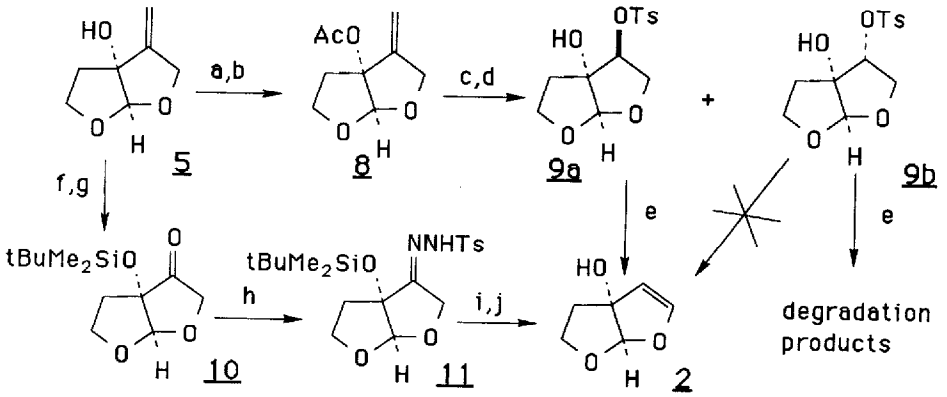
3 4 5

Ketone 3 was prepared according to our previously published procedures[5]. Various electron donnors were tried for generating the radical anion 4 . Alkaline metals such as sodium in liquid ammonia[6] or the naphtalene sodium radical anion[7] did not give any useful reaction whereas activated zinc and the isopropyl iodide[8] gave alcohol 6 . Activated zinc-trimethylsilyl chloride and 2,6-lutidine[9] on the other hand led to a mixture of cyclized compounds 5 and 7 (yields 5 : 12 %, 7 : 10 %) . The best method however turned out to be the photochemical activation in the presence of triethylamine[10] (as electron source). This procedure afforded alcohol 5 in an acceptable yield (57 %) . The structure of 5 was deduced on the basis of NRM data[11] .



a:i)mCPBA,CH_2CL_2,0°C;ii)$HOCH_2C{\equiv}CH$,TsOH cat.;b:DCC,DMSO,H_3PO_4 cat.,AcOEt or CrO_3,H_2SO_4,Acetone.

Two routes were next tried to convert compound 5 into 2 . The first was inspired from the methodology we have developed in earlier syntheses of similar compounds .



a: Ac_2O,DMAP,Et_3N,CH_2Cl_2(82%);b:O_3,-78°C,CH_2Cl_2;Me_2S,-78°C(100%);c:$LiAlH_4$,THF,0°C(82%);
d:TsCl,Pyridine(31%);e:DBU,Toluene,Reflux(48%);f:$tBuMe_2SiCl$,Imidazole,CH_2Cl_2(88%);g:O_3,-78°C,CH_2CL_2;
Me_2S,-78°C(100%);h:H_2NNHTs,MeOH,H_2O(72%);i:$HOCH_2CH_2OH$,Na,140°C,0,25h.(81%);j:nBu_4NF,THF(79%).

Alcohol 5 was protected as the acetate[12] and then ozonized . Reduction of 8 followed by treatment with tosyl chloride and pyridine, gave two isomeric tosylates 9a and 9b . However, only isomer 9a yielded the desired product 2 on heating with DBU in a moderate yield . A much superior approach based on the Bamford-Stevens reaction[13,14] was successfully developed. The structure of 2 was deduced from both ^{1}H and ^{13}C NMR spectroscopy[15] . This gave sufficient amounts of pure 2 for biological testing which is now underway .

REFERENCES and NOTES

1 . (a) For a recent report on the structure of azadirachtin and related compounds, see D.A.H. Taylor, Tetrahedron, (1987), 43, 2779 .
(b) For a review on the biological activity of azadirachtin, see : H. Rembold and E. de Souza Garcia, J. Insect. Physiol., (1984), 30, 939 .

2 . (a) S.V. Ley, D. Santafianos, W.M. Blaney and M.S.J. Simmonds, Tetrahedron Lett., (1987), 28, 221 .
(b) D. Pflieger, B. Münckenstrum, P.C. Robert, M.J. Simonis and J.S. Kienlen, Tetrahedron Lett., (1987), 28, 1519 .

3 . (a) For a report about aflatoxins, see : L.A. Goldblatt : "Aflatoxin", Academic Press, New York (1969) .
(b) G. Büchi, S. Weinred, J. Amer. Chem. Soc., (1971), 73, 746 .

4 . M. Pezechk, A. Brunetière and J.Y. Lallemand, Tetrahedron Lett., (1986), 27, 3715 and references cited therein .

5 . M. Jalali-Naini and J.Y. Lallemand, Tetrahedron Lett., (1986), 27, 497 .

6 . G. Stork, R.K. Boeckmann Jr., D.F. Taber, S. Still and J. Singer, J. Amer. Chem. Soc., (1979), 101, 7107 .

7 . S.K. Pradhan, T.V. Radhakrishnan and R. Subramanian, J. Org. Chem., (1976), 41, 1943 .

8 . T. Shono, H. Hamaguchi, J. Nishiguchi, M. Sasaki, T. Miyamoto, M. Miyamoto and S. Fujita, Chem. Lett., (1981), 1217 .

9 . E.J. Corey and S.G. Pyne, Tetrahedron Lett., (1983), 24, 2821 .

10 . D. Belotti, J. Cossy, J.P. Pete and C. Portella, Tetrahedron Lett., (1985) 26, 4591 .

11 . ^{1}H NMR (400 MHz, $CDCl_3$) ; δ (ppm) : 5.40 (s, H-1) ; 5.35 (t, H-9, J = 2 Hz) ; 5.15 (t, H-9, J = 2 Hz) ; 4.61 (t, H-3, J = 2 Hz) ; 4.12 (td, H-7, J = 4, 6, 6 Hz) ; 3.96 (td, H-7, J = 10, 10, 6 Hz) ; 2.28 (m, H-6) .

^{13}C NMR (50.3 MHz, $CDCl_3$) ; δ (ppm) : 151.6 (C-4) ; 112.6 (C-1) ; 107.1 (C-9) ; 86.5 (C-5) ; 71.6 (C-3) ; 68.4 (C-7) ; 40.0 (C-6) .

12 . Ozonization of 5 failed but was successful on 5 protected as acetate leading to ketone 8 .

13 . Dihydrofuranshave already been prepared using this method, M.A. Gianturco, D. Friedel and V. Flanagan, Tetrahedron Lett., (1965), 1847 .

14 . (a) W.R. Bamford and T.S. Stevens, J. Chem. Soc., (1952), 4735 .
(b) R.H. Shapiro, "Organic Reactions", (1976), 23, 405 .

15 . ^{1}H NMR (200 MHz, $CDCl_3$) ; δ (ppm) : 6.60 (d, H-3, J = 3 Hz) ; 5.64 (s, H-1) ; 5.06 (d, H-4, J = 3 Hz) ; 4.13 (ddd, H-7, J = 7.5, 1, 9 Hz) ; 3.85 (ddd, H-7, J = 12, 5.5, 9 Hz) ; 2.24 (td, H-6, J = 12, 7.5, 12 Hz) ; 2.20 (dd, H-6, J = 12, 5.5 Hz) .
^{13}C NMR (50 MHz, $CDCl_3$) ; δ (ppm) : 150.34 (C-3) ; 113.43 (C-1) ; 104.70 (C-4) ; 90.61 (C-5) ; 69.34 (C-7) ; 38.98 (C-6) .

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