Tetrahedron Letters,Vol.23,No.18,pp 1867-1870,1982 0040-4039/82/181867-04$03.00/0
Printed in Great Britain 

# SYNTHESIS OF THE RIGHT HAND FRAGMENT OF TYLONOLIDE

Linda D.-L. Lu
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Abstract: The synthesis of the lactonic thioester 6, corresponding to the C(1)-C(9) fragment of tylonolide hemiacetal, via the bicyclic ester 5 , is described.

Tylosin (1), isolated from fermentation broths of Streptomyces fradiae,[1] is a representative member of the well-known family of 16-membered polyoxomacrolide antibiotics.[2] Degradative studies on 1[3] and the efficient preparation of tylonolide hemiacetal (2), (the intact aglycone of 1),[4] as well as the recent crystallographic analysis of protylonolide[5] establish the structure and stereochemistry of 1 and 2 as shown below. A successful partial synthesis of 2 is also recorded: a seco-acid derivative (3) prepared from 2 undergoes ring closure to form a macrocyclic lactone which is converted to 2. Thus, the construction of this highly chiral seco-acid framework has emerged as a major problem in the total synthesis. One approach in solving this problem is the use of an available monosaccharide from the "chiral pool"[6] as has been demonstrated in the successful synthesis of 2.[7] We have adopted a different strategy. Taking advantage of the stereochemical similarity of 2 to methynolide (4), our synthetic scheme patterns after that of 4 and in fact begins with a key intermediate (5)[8] used earlier. This letter describes an efficient synthesis of the racemic C(1)-C(9) fragment (6) of 2.

Thus, treatment of lactonic ester 5 with 2 equiv $(CH_3)_3SiI$ for 1 1/4 h at 100° gives the crystalline acid 7, mp 162-162.5°, in 90% yield.[9,10] Homologation of 7 is accomplished via the photolysis of the corresponding diazoketone (9:1 THF:$H_2O$, 450W medium-pressure Hanovia lamp, Pyrex filter, 4 1/2 h) to yield crystalline 8, mp 148-149°, quantitatively; subsequent reduction via the mixed anhydride, using $NaBH_4$(1.1 equiv $NEt_3$, 1.1 equiv $ClCO_2Et$, THF, 0°, 30 min; 4 equiv $NaBH_4$, 0°, 1 h) gives rise to 9 (80%).

The primary hydroxyl group of 9 is silylated [1.4 equiv t-$C_4H_9(C_6H_5)_2SiCl$,[11] 2.8 equiv $C_3H_4N_2$, DMF, RT, 8 h] to give 10 (84%) which is reduced to the diol 11 (2 equiv $LiAlH_4$, $Et_2O$, -30°→-20°, 20 min) in 87% yield. The diol 11 is monotosylated (TsCl, pyridine, 3°, 24 h), and the resulting hydroxytosylate 12 is immediately silylated with excess $(CH_3)_3SiCl$ in pyridine to give 13 (80% from diol). Reductive removal of the tosyl group (2 equiv $LiAlH_4$, $Et_2O$, 10°, 12 h) provides 14 in 80% yield.[12]

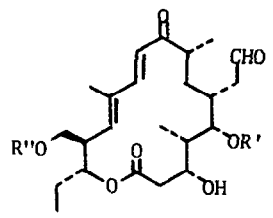
Under carefully controlled conditions (0.8 equiv $KMnO_4$, 30 equiv $NaIO_4$, 1 equiv $K_2CO_3$, 1:1 t-BuOH:$H_2O$, RT, 65 h),[13] 14 is transformed to the crystalline acid 15, mp 109.5-110°, in 75% yield.[14] The conversion of 15 into the corresponding labile aldehyde 16 is effected in 90% yield through Rosenmund reduction [5% Pd-$BaSO_4$, $(Me_2N)_2CS$ (0.05 mg/mmol), toluene, 70°, 1 h] of the acid chloride.

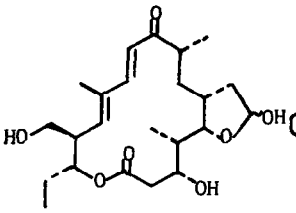
The final transformation of this sequence uses a boron-mediated aldol condensation:[15] reaction of aldehyde 16 with enolate 17 in ether provides a 2:1 mixture of 6 and its C(3)-epimer in a combined yield of 64%. The $^1$H NMR (250MHz) of 6 [7.65(m, 4H, Ar-TBDPSi), 7.43(m, 6H, Ar-TBDPSi), 4.25(dd, J=11.06, 1.5, H-5), 4.12(m, H-3), 3.78(dt, J=10.9, 5.2, H-6"a), 3.69(m, H-6"b), 3.12(d, J=3.0, OH), 2.74(d, J=6.2, H-2), 2.25(m, H-8), 1.50-2.10(m, H-4,6,7), 1.46(s, t-$C_4H_9$S), 1.11-1.28(m, H-6'), 1.20(d, J=7.0, H-8'), 1.06(s, t-$C_4H_9$Si), 0.96(d, J=7.7, H-4')] is very similar to that of the corresponding methyl ester (6a) [(270MHz) 7.70(m, 4H, Ar-TBDPSi), 7.44(m, 6H, Ar-TBDPSi), 4.31(dd, J=10.54, 1.50, H-5), 4.17(m, H-3), 3.84(dt, J=10.5, 5.1, H-6"a), 3.76(s, $CO_2CH_3$), 3.73(m, H-6"b), 3.24(d, J=2.8, OH), 2.64(d, J=6.4, H-2), 2.32(m, H-8); 1.67-2.15(m, H-4,6,7), 1.17-1.39(m, H-6'), 1.25(d, J=7.15, H-8'), 1.11(s, t-$C_4H_9$Si), 1.02(d, J=7.15, H-4')] derived from tylonolide (2) (see below) except for the signals due to the methoxyl and t-butylthio groups. The C(3)-epimer of 6 [(250MHz) 7.65(m,4H, Ar-TBDPSi), 7.43(m, 6H,Ar-TBDPSi), 4.56(dd, J=11.03, 1.01, H-5), 4.12(m, H-3), 3.78(dt, J=10.9, 5.2, H-6"a), 3.69(m, H-6"b), 3.19(d, J=4.6, OH), 2.83(dd, J=15.5, 3.0, H-2a), 2.53(dd, J=15.5, 9.0, H-2b), 2.25(m, H-8), 1.50-2.10(m, H-4,6,7), 1.48(s, t-$C_4H_9$S), 1.11-1.28(m, H-6'), 1.21(d, J=7.0, H-8'), 1.06(s, t-$C_4H_9$Si), 0.85(d, J=7.7, H-4')] and 6 are clearly discernible in the coupling pattern of their spectra. Since the stereochemistry at C(4), C(5), C(6), and C(8) of 6 is secured from the mode of its synthesis, we conclude that 6 should be formulated as shown.

Compound 6a has been prepared from the β-hydroxycarboxylic acid 18, a degradation product of tylonolide (2).[4] Thus, DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) oxidation of 18 (in t-$C_4H_9OH$, 30°, 3 h), and subsequent methyl ester formation ($CH_2N_2$, ether) followed by triethylsilyl protection of the diol-ester ($Et_3SiCl$, $C_3H_4N_2$, DMF, RT, 5 1/2 h) produces 19 (70% from 18). Lemieux-Rudloff oxidation of 19 ($KMnO_4$-$NaIO_4$, RT, 24 h) provides the half-acid ester 20 in 76% yield. A sequence of reactions, (1) esterification ($CH_2N_2$, ether), (2) acid hydrolysis (70% HOAc/$H_2O$, 80°, 20 min), (3) reduction ($NaBH_4$ in i-PrOH, RT, 1/2 h), and finally (4) silylation [1.1 equiv t-$C_4H_9(C_6H_5)_2SiCl$, 2.2 equiv $C_3H_4N_2$, DMF, RT, 2 h) furnishes the lactonic ester 6a in modest yields.

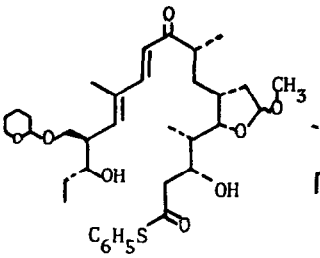
Significant $^1$H NMR Data of New Compounds:

7: (90MHz) 8.56(br., $CO_2H$), 5.82(m, H-1), 5.50(m, H-2), 4.80(d, J=2.93, H-4), 3.08(m, H-3, 5,7), 2.43(ddd, J=8.55, 3.42, 0.92, H-6), 1.12(d, J=7.33, H-9). 8: (90MHz) 2.59(s, H-10). 9: (90MHz) 3.70(t, J=6.15, H-11), 1.73(m, H-10). 10: (250MHz) 7.65,7.42(m, 4H; m, 6H, Ar-TBDPSi), 1.07(s, 9H, t-$C_4H_9$-Si). 11: (250MHz) 5.62(m, H-1,2), 3.81(m, H-11a), 3.71(m, H-11b), 3.54(d, J=6.3, H-8). 12: (90MHz) 7.71,7.37(m, 6H; m, 8H, Ar-Ts & Ar-TBDPSi), 3.87 (d, J=6.6, H-8), 2.43(s, Ts-$CH_3$). 13: (250MHz) 7.78(d, J=8.5, Ar-Ts), 7.66, 7.39(m, 4H; m, 6H, Ar-TBDPSi), 7.31(d, J=8.09, Ar-Ts), 3.82(d, J=7.0, H-8), 0.03(s, $(CH_3)_3$Si). 14: (250MHz) 7.68,7.40(m, 4H; m, 6H, Ar-TBDPSi), 3.71(m, H-4,11), 1.00,0.99(2 pr. d, J=7.0, 7.0, H-8,9). 15: (250MHz) 7.65,7.42(m, 4H; m, 6H, Ar-TBDPSi), 4.65(dd, J=10.67, 1.83, H-4), 3.76(m, H-11), 2.74(dq, J=6.99, 1.47, H-7), 2.30(m, H-3), 1.50-2.11(m, H-5,6), 1.26-1.41(m, H-10), 1.22(d, J=6.99, H-9), 1.17(d, J=6.99, H-8), 1.07(s, t-$C_4H_9$-Si). 16: (250MHz) 9.69 (s, CHO), 4.67(dd, J=11.03, 1.84, H-4), 2.49(dq, J=6.99, 1.84, H-7), 2.31(m, H-3), 1.22(d, J=6.99, H-8), 1.17(d, J=6.98, H-9). 19: (250MHz) 7.31(dd, J=15.8, 3.1, H-11), 6.20(d, J=15.8, H-10), 6.06,6.05(2d, 1H, J=9.5, 9.9, H-13), 4.93(m, H-6"), 4.55(m, CH-THP), 4.13(m, H-3,15), 3.84(m, H-5,14'), 3.69(s, $CO_2CH_3$), 3.34,3.32(2s, 3H, $OCH_3$), 3.50(m, THP-H), 2.85 (m, H-8), 2.54(d, J=6.6, H-2), 0.95(m, $(CH_3CH_2)_3$Si, H-4,15",THP-H), 0.60(m, $(CH_3CH_2)_3$Si), 1.15(d, J=6.7, H-8'). 20: (250MHz) 4.95(m, H-6"), 4.14(m, H-3,5), 3.67(s, $CO_2CH_3$), 3.33 (s, $OCH_3$), 2.53(m, H-2,8), 1.24(d, J=7.0, H-8'), 0.90(m, $(CH_3CH_2)_3$Si, H-4'), 0.55(m, $(CH_3CH_2)_3$Si).

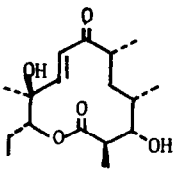




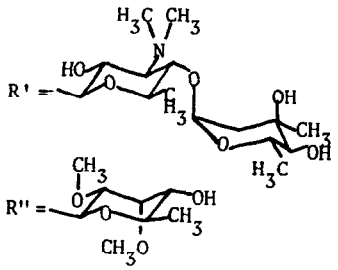
2



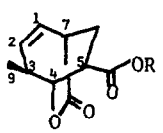
3



4

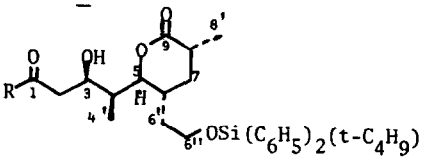


1



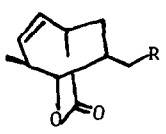
5: R = $CH_3$

7: R = H



6 : R = $S(t\text{-}C_4H_9)$

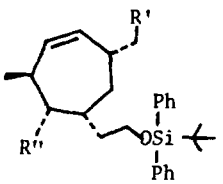
6a: R = $OCH_3$



8: R = $CO_2H$

9: R = $CH_2OH$

10: R = $CH_2OSi(C_6H_5)_2$-$(t\text{-}C_4H_9)$

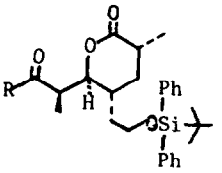


11: R' = R'' = OH

12: R' = OTs, R'' = OH

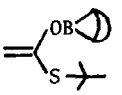
13: R' = OTs, R'' = $OSi(CH_3)_3$

14: R' = H, R'' = $OSi(CH_3)_3$

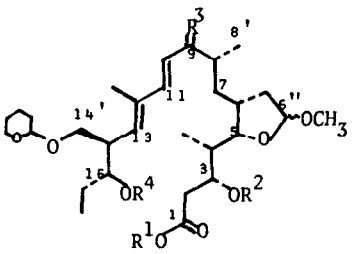


15: R = OH

16: R = H

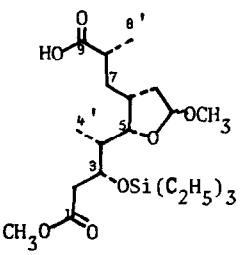


17

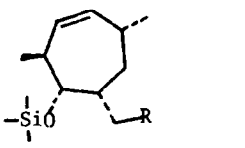


18: $R^1$ = $R^2$ = $R^4$ = H, $R^3$ = H, OH

19: $R^1$ = $CH_3$, $R^3$ = O, $R^2$ = $R^4$ = $Si(C_2H_5)_3$

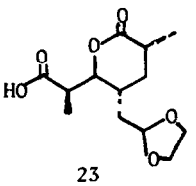


20



21: R = $CH_2OSi$

22: R = CH



23

## Acknowledgements

The author was a recipient of a Post-Graduate Scholarship from the Natural Sciences and Engineering Research Council Canada, May 1979-April 1981. Sincere gratitude is extended to Professor S. Masamune for helpful discussions and encouragement throughout the course of this work. Partial support from NIH (Grant No. AI 15403 awarded to S.M.) is gratefully acknowledged.

## References and Footnotes

1. (a) Hamill, R.L.; Haney, M.E. Jr.; Stamper, M.; Wiley, P.F. Antibio. Chemother., (Washington, D.C.), 11, 328 (1961). (b) McGuire, J.M.; Boniece, W.S.; Higgins, C.E.; Hoehn, M.M.; Stark, W.M.; Westhead, J.; Wolfe, R.N. ibid., 11, 320 (1961).
2. For a recent review on the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G.S.; Corcoran, J.W. Angew. Chem. Int. Ed. Engl., 16, 585 (1977).
3. (a) Morin, R.B.; Gorman, M. Tetrahedron Lett., 2339 (1964). (b) Morin, R.B.; Gorman, M.; Hamill, R.L.; Demarco, P.V. ibid., 4737 (1970).
4. Masamune, S.; Hayase, Y.; Chan, W.K.; Sobczak, R.L. J. Am. Chem. Soc., 98, 7874 (1976).
5. Ōmura, S.; Matsubara, H.; Nakagawa, A. J. Antibiot., 33, 915 (1980).
6. For reviews, see (a) Hanessian, S. Accounts Chem. Res., 12, 159 (1979). (b) Fraser-Reid, B. ibid., 8, 192 (1975). (c) Seebach, D.; Hungerbühler, E. "Modern Synthetic Methods 1980", Ed.: Scheffold, R.; Salle and Sauerländer-Verlag, Frankfurt and Aarau, 1980.
7. Tatsuta, K; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. Tetrahedron Lett., 3997 (1981).
8. (a) Masamune, S.; Kim, C.U.; Wilson, K.E.; Spessard, G.O.; Georghiou, P.E.; Bates, G.S. J. Am. Chem. Soc., 97, 3512 (1975). (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. ibid., 97, 3513 (1975).
9. (a) Ho, T.-L., Olah,G.A. Angew. Chem. Int. Ed. Engl., 15, 774 (1976). This is the procedure actually used, but see also (b) Jung, M.E.; Lyster, M.A. J. Am. Chem. Soc., 99, 968 (1977).
10. Satisfactory IR, $^1$H NMR, and mass spectral data have been obtained for all stable compounds reported. Melting points were not corrected. NMR spectra ($\delta$, ppm from TMS, J in Hz) were measured in $CDCl_3$ solution.
11. Hanessian, S.; Lavallee, P. Can. J. Chem., 53, 2975(1975).
12. Compound 21 (see structure) also has been synthesized from 5. However, the $(CH_3)_2Si(t\text{-}C_4H_9)$ group refuses to withstand the conditions of the subsequent oxidation.
13. Lemieux, R.U.; von Rudloff, E. Can. J. Chem., 33, 1701, 1710 (1955); von Rudloff, E. ibid., 34, 1413 (1956).
14. In a similar sequence of transformations, the acid-labile cycloheptene 22 (see structure) also has been prepared from 5 and was initially envisaged as the precursor to the right-hand side of 2. However, the Lemieux-Rudloff oxidation of 22 proved to be very capricious. Moreover, the resulting acid, 23, was unstable even when stored at low temperature in solution.
15. Hirama, M.; Garvey, D.S.; Lu, L.D.-L.; Masamune, S. Tetrahedron Lett., 3937 (1979).

(Received in USA 22 February 1982)