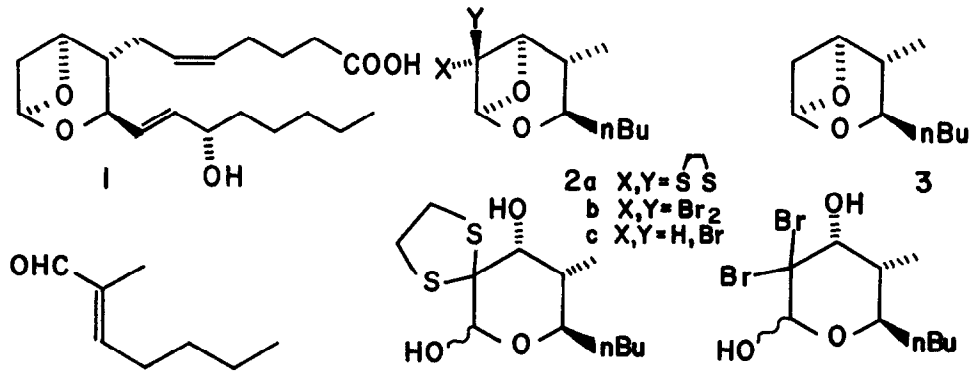
Tetrahedron Letters,Vol.26,No.16,pp 1955-1958,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

PREPARATION OF THE 2,6-DIOXA[3.1.1]BICYCLOHEPTANE NUCLEUS OF THROMBOXANE A_2

Shripad S. Bhagwat, Philip R. Hamann and W. Clark Still
Department of Chemistry, Columbia University, New York, NY 10027

SUMMARY: The putative TXA_2 nucleus has been synthesized by a Mitsunobu-type cyclization of a bromotetrahydropyran-1,3-diol followed by tin hydride reduction and its stability toward hydrolysis has been investigated.

In 1975, Hamberg, Svensson and Samuelsson proposed structure 1 for the elusive platelet-aggregating agent thromboxane A_2 (TXA_2).[1] Although 1 has yet to be isolated and physically characterized, synthesis has been used to provide analogs[2] in which ring oxygens are replaced by sulfur or carbon and derivatives[3] bearing heterosubstitution at C7 ([3.1.1]bicycloheptane numbering). To gain access to the previously unknown unsubstituted system, we have examined dioxabicycloheptanes having C7 substitution which facilitates cyclization and isolation but which can be removed to yield the desired 7-methylene parent system. In this letter we report preparation of the 7-methylene TXA_2 model 3 via the 7-bromo derivatives 2b and 2c.



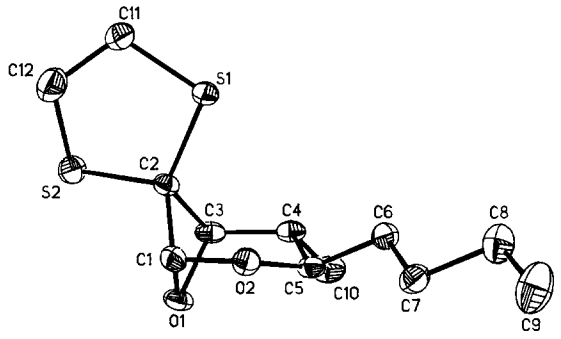
1 3 4 5 6

A TXA_2 model bearing methyl and butyl appendages in place of the alpha and beta prostanoic acid sidechains was prepared by addition of a magnesiomethyl dithioacetate[4] to unsaturated aldehyde 4 (83% yield). Hydroboration (a. $ThBH_2$, THF, 0° C, 48 hrs; b. Me_3NO, reflux, 2 hrs) gave a 1,3-diol stereoselectively[5] as a 2:1 mixture of lactone and hemiacetal (58% yield) which was reduced to 5 (DIBAL, CH_2Cl_2, -70° C; 87% yield). Cyclization to bicyclic oxetane 2a (mp (pentane) = 40-42° C; 32% yield (>90% at 40% conversion)) was effected with a modified Mitsunobu reaction[6] using $EtO_2CN{=}NCO_2Et$ and $(MeO)_3P$ (THF, 25° C, 2 hrs). Selected spectral data for the bicyclic oxetane is given below along with its x-ray crystal structure.

^1H ($CDCl_3$): 5.45 (d, 4.3 hz, H1), 4.46 (d, 4.3 hz, H3), 3.67 (m, H5), 2.23 (p, 7.1 hz, H4), 1.08 (d, 7.0 hz, H10).

^{13}C ($CDCl_3$): 111.41, 95.36, 76.86, 40.39, 39.28, 38.34, 33.84, 28.12, 22.69, 16.06, 13.97 (C2 not seen).

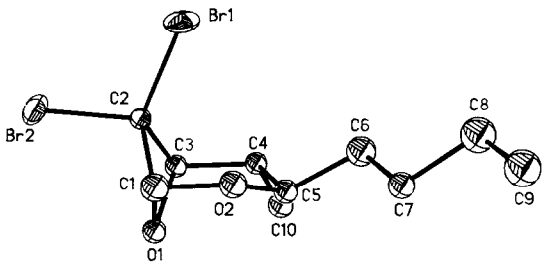
IR ($CDCl_3$): 2960, 2930, 2870, 1050.



While some form of reductive desulfurization could be envisaged to transform 2a into 3, no conditions could be found to bring about the conversion. Instead, elimination to enol ethers was found with reagents like Raney nickel and reductive removal of a single (equatorial) sulfur was observed with free radical reducing agents like Bu_3SnH.

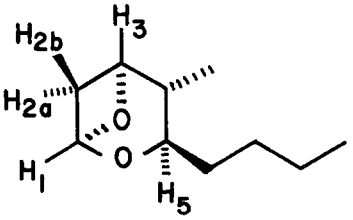
To facilitate reduction to 3, dibromide 2b was prepared from 4. In this case, the use of 3 equivalents of $ThBH_2$ (THF, 0° C, 36 hrs) on the Reformatsky[7] product of 4 and ethyl tribromoacetate followed by an alkaline peroxide workup yielded the desired hemiacetal 6 directly (58% yield). It was cyclized by analogy to the conversion of 5 -> 2a using $EtO_2CN{=}NCO_2Et/(MeO)_3P$[8] to 2b (29% yield; mp (pentane) = 15° C; spectral data and x-ray crystal structure below). We should add that the beta-monobromo compound 2c could also be cyclized but the unbrominated analog led to no detectable quantities of the corresponding parent oxetane 3 under our best cyclization conditions.

^{1}H (C_6D_6) 5.55 (d, 4.3 hz, H1), 4.27 (d, 4.3 hz, H3), 3.67 (ddd, 9.9, 7.2, 2.6 hz, H5), 0.67 (d, 6.9 hz, H10).
^{13}C (C_6D_6) 110.74, 96.72, 78.00, 61.65, 40.54, 34.14, 28.85, 23.27, 15.77, 14.61.
IR (neat) 2960, 2934, 2873, 1455, 1091, 1042, 789.
MS (CI, NH_3) 344, 346, 348 (m+NH_4)



When dibromide 2b was stirred at 22° C with 3 equiv Bu_3SnH in C_6D_6, the monobromo derivative 2c was smoothly formed (60-70% yield). Further reaction (cat. AIBN, sunlamp) cleanly produced the desired parent system 3 (80% yield by nmr) whose spectral properties are listed below. Alternatively 2b or 2c was reduced with a polymer-bound tin hydride[9] and the reagent filtered to yield tin-free solutions of 3.

^{1}H (C_6D_6) 5.67 (t, 4.0 hz, H1), 4.14 (ddd, 6.6, 4.0, 0.6 hz, H3), 4.04 (q, 6.2 hz, H5), 2.73 (ddd, 8.9, 6.6, 3.6 hz, H2a), 1.43 (dd, 8.9, 0.6, H2b).
^{13}C (C_6D_6) 105.8, 85.0, 78.6, 41.8, 41.2, 37.3, 28.6, 23.6, 14.9, 14.5.
IR (neat) 2959, 2930, 1461, 1141, 1112, 1020, 859.
MS (CI, NH_3) 188 (m+NH_4)



In contrast to the heterosubstituted precursors 2a-c which survive silica gel chromatography, the unsubstituted oxetane 3 could not be chromatographed without hydrolysis to the corresponding tetrahydropyrandiol. Oxetane 3 undergoes slow opening in neutral MeOH at 21° C (half-life ca. 30 min) to the corresponding methoxytetrahydropyran. In the calcium-free Krebs-Henseleit medium[10] used in the TXA_2 studies[1] (containing 20% THF and adjusted with CO_2 to a pH meter reading of 7.4), the half-life of 3 is 15-40 seconds at 20° C thus is comparable to that of natural TXA_2 (32 sec at 37° C) within experimental error.

Acknowledgement: We would like to thank Professor H.E. Ensley and Dr. C.H. Mitch for their contributions to the early phases of this work and the National Institutes of Health for support (HL25634).

1. M. Hamberg, J. Svensson and B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A., 72, 2994 (1975).

2. M.F. Ansell, M.P.L. Caton, M.N. Palfreyman and K.A. Stuttle, Tetrahedron Lett., 4497 (1979); K.C. Nicolaou, R.L. Magolda, J.B. Smith, K. Aharony, E.F. Smith and A.M. Lefer, Proc. Natl. Acad. Sci. U.S.A., 76, 2566 (1979); S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron Lett., 3661 (1979); E.J. Corey, J.W. Ponder and P. Ulrich, Tetrahedron Lett., 137 (1980); K.M. Maxey and G.L. Bundy, ibid., 445 (1980); K.C. Nicolaou, R.L. Magolda and D.A. Claremon, J. Am. Chem. Soc., 102, 1404 (1980); T.K. Schaff, D.L. Bussolotti, M.J. Parry and E.J. Corey, J. Am. Chem. Soc., 103, 6502 (1981); S. Ohuchida, N. Hamanaka, S. Hashimoto and M. Hayashi, Tetrahedron Lett., 2883 (1982); S. Ohuchida, N. Hamanaka and M. Hayashi, Tetrahedron, 39, 4257, 4263, 4269, 4273 (1983).

3. H. Ito, R. Eby, S. Kramer and C. Schuerch, Carbohydr. Res., 86, 193 (1980); A.J. Varma and C. Schuerch, J. Org. Chem., 46, 799 (1981); J. Fried, E.A. Hallinan and M.J. Szwedo, J. Am. Chem. Soc., 106, 3871 (1984).

4. M. Braun and M. Esdar, Chem. Ber., 114, 2924 (1981).

5. W.C. Still and J.C. Barrish, J. Am. Chem. Soc., 105, 2487 (1983).

6. Review: O. Mitsunobu, Synthesis, 1 (1981).

7. K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto and H. Nozaki, Bull. Chem. Soc. Japan, 53, 3301 (1980).

8. To 2.5 ml dry CH_2Cl_2 (0°) was added 0.18 ml each of $(MeO)_3P$ and DEAD. After stirring at 25° for 10 min, the solution was added at 0° to 346 mg (1.0 mmol) dibromodiol 6 in 15 ml dry CH_2Cl_2. The mixture was warmed to 25° and stirred for 3 hrs. Solvent removal and flash chromatography on silica gel gave 2b (100 mg, 29%, R_f (silica gel, 1% THF in pentane) = 0.29).

9. N.M. Weinshenker, G.A. Crosby and J.Y. Wong, J. Org. Chem., 40, 1966 (1975).

10. H.A. Krebs and K. Henseleit, Hoppe-Seyler's Z. Physiol. Chem., 210, 33 (1932). We would like to thank Dr. Bob Gorman of the Upjohn Company for the recipe.

(Received in USA 25 January 1985)