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A SIMPLE SYNTHESIS OF A STABLE THROMBOXANE A_2 ANALOGUE

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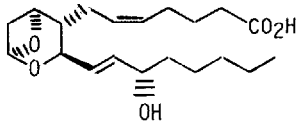
ABSTRACT - A simple synthetic route, which appears to have some general utility, has been used to obtain a Bicyclo[2.2.1]heptane analogue of Thromboxane A_2.

Thromboxane A_2 (TXA_2), an unstable metabolite of arachidonic acid in platelets, is believed to have structure 1.[1,2] It is a potent vasoconstrictor and inducer of platelet aggregation.[3,4] Analogues of TXA_2[5] that inhibit thromboxane synthetase or antagonise TXA_2 are of current interest in the treatment of shock[6] and, in combination with prostacyclin, of thrombocytopenic purpura.[7] Here, synthesis of the stable analogue (±)-2[8] is reported by a simple route chosen because of its applicability to other stable ring systems using resolvable[9] ketonic intermediates.



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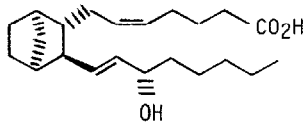

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Alkylation of (±)-norcamphor 3 by treatment with lithium diisopropylamide [1 eq.] in THF at -78° for 1 h, followed by allyl bromide [1.1 eq.], at -78° → 25°, gave *exo*-3-allylnorcamphor 4 (85%) as a colourless oil [b.p. 92°/10 mm., ν_{max} 1750 cm^{-1}, m/e 150 (M^+)]. Confirmation of the expected[10] exo-stereochemistry for 4 was provided by reduction of the ketone with sodium borohydride[11] to the *endo*-alcohol 5a which gave a CHOH signal at δ 3.70 (1H, t) with a coupling constant of 4Hz.[12] Reaction of ketone 4 with methoxymethylmagnesium bromide[13] (prepared from 2.2 eq. $MeOCH_2Br$ and 2.2 eq. Mg) gave the mixed epimeric alcohols 6 (75%) as a colourless oil [b.p. 104-6°/5 mm, m/e 196 (M^+), δ 3.37 (5H, s, CH_2OMe), epimer ratio (g.l.c.) 4:1]. Oxidative cleavage of alcohols 6 with osmium tetroxide-sodium periodate afforded aldehydes 7 (80%) as a pale yellow oil [ν_{max} 1725 cm^{-1}, δ 9.56 and 9.60 (1H, 2s, CHO)] and Wittig reaction

of 7 with $Ph_3P{=}CH(CH_2)_3CO_2Na$ in DMSO yielded crude acid 8a (*ca.* 60%). The latter, after esterification with diazomethane and purification by column chromatography, afforded esters 8b [ν_{max} 1740 cm^{-1}, m/e 296 (M^+), δ 5.36 (2H, m, olefinics), 3.62 (3H, s, CO_2Me), 3.38 (5H, s, CH_2OMe)]. Deprotection of the masked aldehyde moiety in esters 8b was accomplished with formic acid[14] (5 min reflux under N_2), the *endo*-aldehyde 9 (70%) being obtained as a pale yellow oil [ν_{max} 1725, 1740 cm^{-1}, δ 9.70 (1H, d, J 1.5Hz, CHO), 5.36 (2H, m, olefinics), 3.62 (3H, s, CO_2Me)]. The presence of an endo-formyl group in aldehyde 9 was inferred by ^1H n.m.r. comparisons[15] with the known *endo*- and *exo*-2-formylnorbornanes[16] and moreover, it was inert to base-catalysed epimerisation conditions, indicating that the more stable trans-isomer had been formed in the deprotection step. Aldehyde 9 underwent a Wittig-Horner reaction with the sodio derivative of diethyl 2-oxoheptylphosphonate and the resulting enone 10a [ν_{max} 1740, 1675, 1620 cm^{-1}, m/e 360 (M^+), δ 6.85 (1H, d x d, J7 and 15.5Hz, H-13), 6.03 (1H, d, J 15.5Hz, H-14), 5.32 (2H, m, H-5 and H-6), 3.65 (3H, s, CO_2Me)], on reduction with sodium borohydride afforded a mixture of epimeric alcohols 10b [m/e 362 (M^+), δ 5.87-4.95 (4H, m, olefinics), 4.05 (1H, m, CHOH), 3.63 (3H, s, CO_2Me)], distinguishable by t.l.c. (Rf 0.51 and 0.55 on silica in hexane-ether 2:1). Hydrolysis with dilute aqueous KOH in methanol gave 11, a mixture (Rf 0.36 and 0.42 on silica in CH_2Cl_2-MeOH, 19:1) of target acid 2 with its C-15 epimer [ν_{max} 3345, 1710 cm^{-1}, δ 6.25 br (2H, OH and CO_2H, exchangeable), 5.80-5.20 (4H, m, olefinics), 4.10 (1H, m, CHOH)]. Separation by preparative h.p.l.c. afforded the individual epimers. These had a pronounced hypotensive action in the anaesthetized rat test but, disappointingly, were only weak inhibitors of ADP-induced platelet aggregation and TXA_2 synthetase.

One limitation to the wider application of this simple route appeared to be the sensitivity to steric effects[14] of the Grignard additions with $MeOCH_2MgBr$. For example, *exo*-3-octenylnorcamphor 12, obtained by alkylation of the lithium enolate of norcamphor with (E)-1-bromo-oct-2-ene,[17] did not react with $MeOCH_2MgBr$. In this case, however, the ketone 12 could be homologated to the aldehyde 14b *via* the spiroepoxides 13. Thus, reaction of 12 with dimethylsulphoxonium methylide[18] gave the mixed epimers 13 which, on brief treatment with $BF_3.Et_2O$, afforded predominantly the *exo*-aldehyde 14a [δ 9.60 (1H, d, J 1.5Hz, CHO)]. Base-catalysed epimerisation in refluxing NaOMe-MeOH solution afforded the *endo*-aldehyde 14b [δ 9.72 (1H, d, J 1.5Hz, CHO)].

The methods described above have been applied successfully to the elaboration of other bicyclic ketones to give stable TXA_2 analogues.[19]

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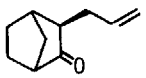

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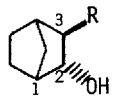
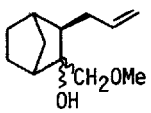


5; a, R = Allyl
b, R = H



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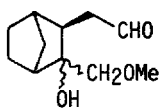

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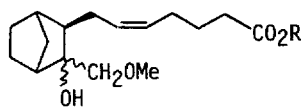
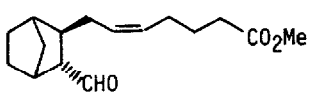


8; a, R = H
b, R = Me



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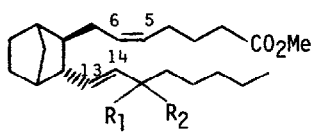
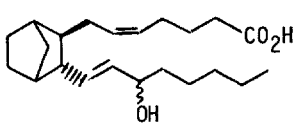


10; a, R_1 R_2 = O
b, R_1 R_2 H, OH



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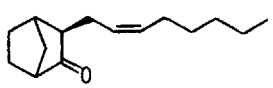

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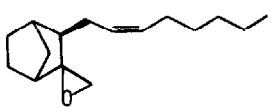

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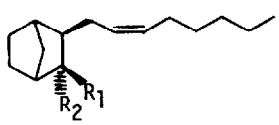

14; a, R_1 = CHO, R_2 = H
b, R_1 = H, R_2 = CHO

References and notes

1 B. Samuelsson, M. Goldyne, E. Granstrom, M. Hamberg and C. Malmsten, *Am. Rev. Biochem.*, 47, 997 (1978).

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

3 P. Needleman, S. Moncada, S. Bunting, J. R. Vane, M. Hamberg and B. Samuelsson, *Nature*, 261, 588 (1976)

4 P. Needleman, P. Kulkarni and A. Raz, *Science*, 195, 409 (1977).

5 Syntheses of three stable TXA_2 analogues have recently been reported: S. Ohuchida, N. Hamanaka and M. Hayashi, *Tetrahedron Lett.*, 3661 (1979); M. F. Ansell, M. P. L. Caton, M. N. Palfreyman and K. A. J. Stuttle, *Tetrahedron Lett.*, 4497 (1979); K. M. Maxey and G. L. Bundy, *Tetrahedron Lett.*, 445 (1980).

6 A. M. Lefer, H. Araki, J. B. Smith, K. C. Nicolaou and R. L. Magolda, *Prostaglandins and Medicine*, 3, 139 (1979).

7 C. N. Hensby, P. J. Lewis, P. Hilgard, G. J. Mufti, J. Hows and J. Webster, *The Lancet*, 748 (1979).

8 Formulae 2 to 14 depict relative, not absolute, stereochemistry.

9 A. J. Irwin and J. B. Jones, *J. Am. Chem. Soc.*, 98, 8476 (1976).

10 For precedent see E. J. Corey, R. Hartmann and P. A. Vatakencherry, *J. Am. Chem. Soc.*, 84, 2611 (1962) and U. S. Patent 3,662,008.

11 H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, 88, 2811 (1966).

12 The $J_{2exo,3exo}$ coupling of 9Hz observed for the CHOH signal of endo-norbornanol 5b was clearly absent. See also P. Barraclough and D. W. Young, *Tetrahedron Lett.*, 2293 (1970).

13 H. Normant and C. Crisan, *Bull. Soc. Chim. France*, 459 and 463 (1959).

14 M. de Botton and H. Normant, *Compt. Rend.*, 258, 6449 (1964).

15 R. R. Fraser, *Can. J. Chem.*, 40, 78 (1962).

16 P. K. Freeman and K. B. Desai, *J. Org. Chem.*, 36, 1554 (1971).

17 M. de Gaudemaris and P. Arnaud, *Bull. Soc. Chim. France*, 315 (1962).

18 R. S. Bly, C. M. DuBase, Jr., and G. B. Konizer, *J. Org. Chem.*, 33, 2188 (1968).

19 P. Barraclough, unpublished results.

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