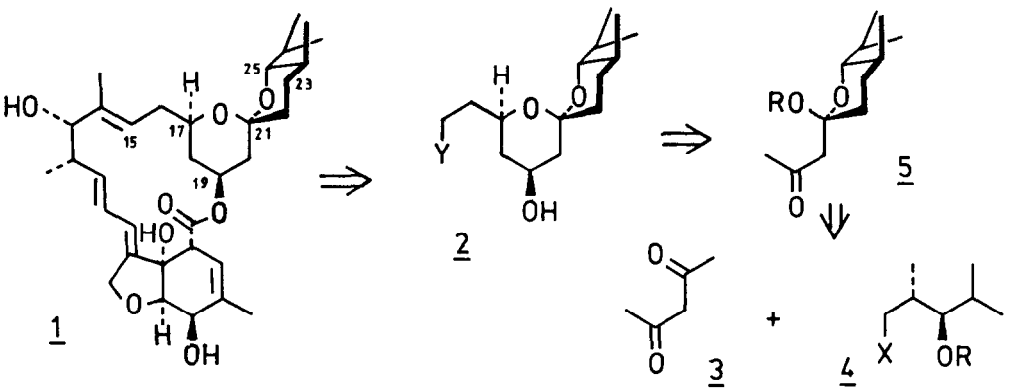
Tetrahedron Letters,Vol.28,No.18,pp 1997-2000,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STEREOCONTROLLED SYNTHESIS OF THE SPIROKETAL UNIT OF 22,23-DIHYDROAVERMECTIN B_{1b}.

J. Ardisson, J.P. Férézou, M. Julia *, L. Lenglet and A. Pancrazi.
Ecole Normale Supérieure, Laboratoire de Chimie,
24, rue Lhomond - 75231 PARIS CEDEX 05 - FRANCE -

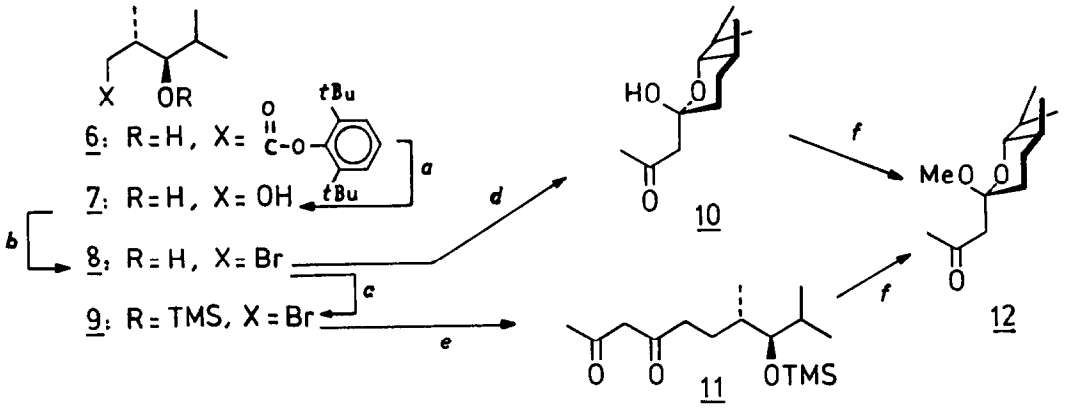
Summary : *A diastereocontrolled synthesis of the spiroketal sub-unit of 22,23-dihydroavermectin B_{1b} has been developed using a formal double condensation at both ends of pentane 2,4-dione 3 with intermediate formation of the ketal 5.*

Owing to their unique biological activities, the sixteen-membered lactones milbemycins [1] and avermectins [2] are currently focusing considerable synthetic efforts. Several total syntheses of milbemycin β_3 have been reported to date [3] whereas only one recent report appeared on the total synthesis of avermectin B_{1a}, one of the members of the more complex avermectin family [4]. As a first target in our program on the synthesis of avermectins we chose the aglycon of 22,23-dihydroavermectin B_{1b}, 1, one of the components of the commercial "Ivermectin" selected on the basis of its broad-spectrum antiparasitic properties [2c]. This report deals with the synthesis of the spiroketal sub-unit 2 corresponding to the C-15 to C-25 fragment of 1.



Our approach involved a stepwise condensation at both ends of pentanedione 3 followed by a simple acidic cyclisation. This route was already tested for the formation of model spiroketals of milbemycins with a subsequent original organoselenium-mediated cyclisation step [5]. Furthermore, having in mind that the spiroketal moiety of 1 exists in its more thermodynamically stable form due to both the anomeric effects and the equatorial orientation of all peripheral substituents, some control of the chirality at the C-17, C-19 and C-21 centres of 1 might be anticipated from the early introduction of asymmetry at the chiral carbons of the hydroxyhalide 4 corresponding to the C-23 to C-25 fragment. We envisioned that the ketal 5 would be a versatile intermediate for developing this strategy.

In order to test this approach the racemic anti-C_7 synthon 4 was prepared by the reaction of isobutyraldehyde with 2,6-di-ter-butylphenyl propanoate according to Heathcock [6] to give 6 which was reduced to the diol 7 [7] with $LiAlH_4$ (mp: 45-46°C, anti/syn : 99/1, 71% overall yield). Routine transformation of 7 afforded the bromoalcohol 8 (92%) which was converted into the trimethylsilylderivative 9 [8] in quantitative yield.



a) $LiAlH_4$, ether b) TsCl, pyridine, -35°C then LiBr acetone c) TMCS, HMDS, pyridine, pentane, 35°C d) LDA-HMPT, 5.5eq., THF, -78°C, 3, then 20°C e) LDA-HMPT, 4.5eq., THF, -78°C, 3, then 20°C f) citric acid, MeOH.

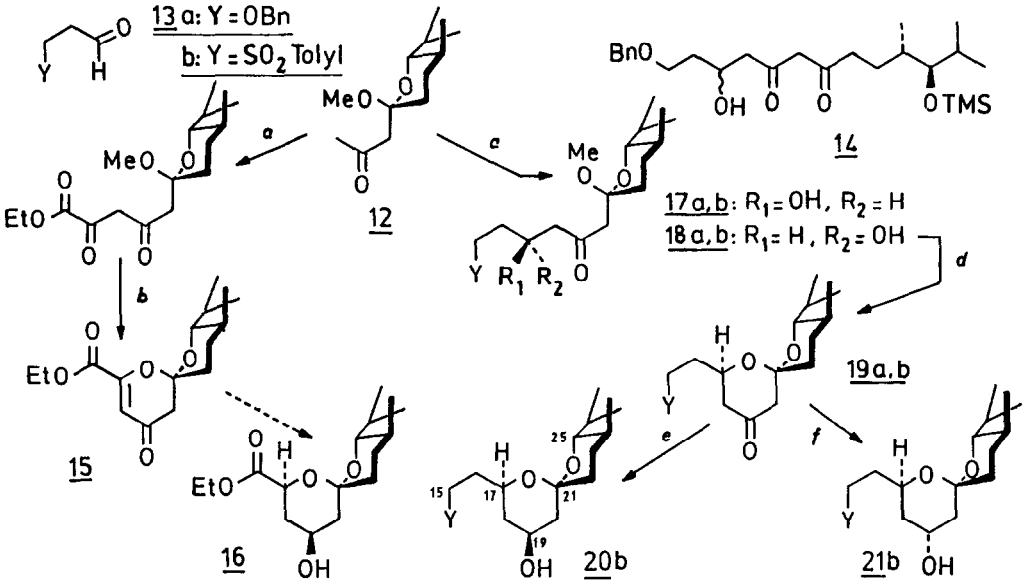
Direct alkylation of the dianion of pentane 2,4-dione 3 [9] with the bromo alcohol 8 using LDA-HMPT in THF provided the hemiketal 10 in 50% yield after acidic work up and chromatography. The efficiency of this step was improved when the dianion of 3 was treated with the trimethylsilyloxyhalide 9 to give the diketone 11 (enol/ketone : 75/25) in 90% yield. Further acidic treatment of both 10 or 11 yielded the methylketal 12 in over 90% yield [8]. As expected from anomeric control and conformational stability, a single isomer was detected and tentatively identified as bearing an axial methoxy group.

We next turned to the second condensation step at the other end of the pentanedione moiety. The dianion of 11 was allowed to react with the benzyloxyaldehyde 13a [10] to give a 1 : 1 mixture of the ketol epimers 14. (enol/ketone : 70/30) in 70% yield. However further exploitation of the reaction products was troublesome as separation of the diastereoisomers proved difficult either at this stage or after acidic cyclisation. The reaction of the kinetic enolate of the methylketal 12 with either esters (acylation approach) or aldehydes (aldol approach) was then examined.

Acylation of the enolate of 12 with diethyl oxalate followed by direct thermolysis of the crude reaction mixture at 250°C gave after distillation the spirodihydropyrone 15 as a single pure isomer in 54% yield [8]. This product is analogous to an intermediate in Barrett's milbemycin synthesis [3g,h,5g]. The route for converting 15 into the hydroxyspiroketal 16 has been thoroughly investigated by this author.

The alternative aldol approach was then developed. Preliminary results showed that reaction of the enolate of 12 with benzyloxypropanal 13a gave a mixture of the two diastereomeric alcohols 17a and 18a (55/45, 75%) which were easily separable by chromatography. HCl treatment of 18a yielded quantitatively the expected spirotetrahydropyrone 19a [8].

More interestingly from a synthetic point of view, the kinetic enolate of 12 was cleanly condensed at -78°C with the highly reactive p-toluenesulfonyl aldehyde 13b[11] to produce the sulfonyl alcohols 17b and 18b (55/45) in 80% yield. Flash chromatography followed by acidic cyclisation of the less polar 18b isomer led quantitatively to the crystalline ketosulfone 19b (diisopropylether-hexane ; mp: 101-103°C)[8].



a) LDA, THF, -78°C, diethyloxalate, then -15°C b) 250°C then distillation 0.1mmHg c) LDA, THF, -78°C then 13 a or b, 1h. d) HCL, $CHCl_3$ e) $LiAlH_4$, benzene, 20°C f) L-Selectride, THF, 0°C.

Subsequent reduction of the carbonyl group of 19b with $LiAlH_4$ in benzene provided the easily separable spiroketals 20b and 21b (80/20) in 98% yield. The observed selectivity is in agreement with already reported observations [3b,d,5b,h] and probably reflects a chelation control of the hydride with the axial anomeric oxygen.

Alternatively, the epimeric non-natural spiroketal 21b could be obtained by L-Selectride reduction (21b/20b : 95/5) in 88% yield. Both isomers easily crystallized from ether-hexane (mp: 118-120°C for 20b and 104-106°C for 21b) and their stereochemistry was deduced from 400MHz NMR measurements including proton homonuclear correlation (COSY) experiments. The chemical shifts and the J values observed for the three CHO-protons at the C-17, C-19 and C-25 centres are of diagnostic value for the stereochemistry assigment [8]. Particularly the C-17 proton in 21b is axial whereas the C-19 proton is equatorial with concomitant conservation of both axial anomeric effects.

Work is in progress to extend this simple route to the synthesis of optically active spiroketal 20 from the readily available (2S,3R)-diol 7 [7] as well as to improve the stereocontrol in the aldolisation step.

Financial help from the CNRS (U.A.1110) is gratefully acknowledged. We thank Dr Hervé du Penhoat, C. Dérouet and V. Michon for NMR spectra.

REFERENCES

1) H. Mishima, M. Kurabayashi, C. Tamura, S. Sato, H. Kuwano and A. Saito, Tetrahedron Lett., 711 (1975) ; Y. Takiguchi, H. Mishima, M. Okuda, M. Terao, A. Aoki and R. Fukuda, J. Antibiot. 33, 1120 (1980).

2) a) G. Albers-Schonberg, B.H. Arison, J.C. Chabala, A.W. Douglas, P. Eskala, M.H. Fisher, A. Lusi, H. Mrosik, J.L. Smith and R.H. Tolman, J. Am. Chem. Soc., 103, 4216 (1981). b) J.P. Springer, B.H. Arison, J.M. Hirshfield and K. Hoogsteen, ibid., 103, 4221 (1981). For reviews see also c) M.H. Fisher "The avermectins" in Recent Advances in the Chemistry of Insect Control ; N.F. Janes Ed.; The Royal Society of Chemistry Special Publication n°53, London, p53 (1985) and d) H.G. Davies and R.H. Green, Natural Products Reports, 3, 87 (1986).

3) a) A.B. Smith III, S.R. Show, J.D. Bloom, A.S. Thompson and K.N. Winzenberg, J. Am. Chem. Soc., 104, 4015 (1982) ; b) D.R. Williams, B.A. Barner, K. Nishitani and J.G. Phillips, ibid., 104, 4708 (1982) ; c) R. Baker, M.J. O'Mahony and C.J. Swain, J. Chem. Soc. Chem. Commun. 1326 (1985) ; d) S.D.A. Street, C. Yeates, P. Kocienski and S.F. Campbell, ibid., 1386 (1985) ; e) C. Yeates, S.D.A. Street, P. Kocienski et S.F. Campbell, ibid., 1388 (1985) ; f) S.R. Schow, J.D. Bloom, A.S. Thompson, K.N. Winzenberg and A.B. Smith III, J. Am. Chem. Soc., 108, 2662 (1986) ; g) S.V. Attwood, A.G.M. Barrett, R.A.E. Carr and G. Richardson, J. Chem. Soc. Chem. Commun., 479 (1986) ; h) A.G.M. Barrett, R.A. Carr, S.V. Attwood, G. Richardson and N.D.A. Walshe, J. Org. Chem., 51, 4840 (1986) ; i) R. Baker, M.J. O'Mahony and C.J. Swain, Tetrahedron Lett., 27, 3059 (1986).

4) S. Hanessian, A. Ugolini, D. Dubé, P.J. Hodges and C. André, J. Am. Chem. Soc., 108, 2776 (1986).

5) A.M. Doherty, S.V. Ley, B. Lygo and D.J. Williams, J. Chem. Soc., Perkin Trans 1, 1371 (1984) ; S.V. Ley, Chem. and Ind., 101 (1985). For other approaches of spiroketal syntheses see also : a) M.T. Crimmins and D.M. Bankaitis, Tetrahedron Lett., 24, 4551 (1983) ; b) D.R. Williams and B.A. Barner, ibid., 427 (1983) ; c) S.J. Danishefsky and W.H. Pearson, J. Org. Chem., 48, 3866 (1983) ; d) J. Godoy, S.V. Ley and B. Lygo, J. Chem. Soc., Chem. Commun., 1381 (1984) ; e) D. Culshaw, P. Grice, S.V. Ley and G.A. Strange, Tetrahedron Lett., 26, 5837 (1985) ; f) I.T. Kay and M.D. Turnbull "Synthetic approaches to the avermectin toxophore" p229 in ref. 2c) ; g) A.G.M. Barrett, R.A.E. Carr, M.A.W. Finch, J.C. Florent, G. Richardson and N.D.A. Walshe, J. Org. Chem., 51, 4254 (1986) ; h) M. Hirama, T. Nakamine and S. Itô, Tetrahedron Lett., 27, 5281 (1986).

6) C.H. Heathcock, M.C. Pirrung, S.H. Montgomery and J. Lampe, Tetrahedron 37, 4087 (1981).

7) R. Baker, C.J. Swain and J.C. Head, J. Chem. Soc. Chem. Commun., 309 (1985).

8) All new compounds gave satisfactory analytical and spectral data (microanalysis, ^{1}H and ^{13}C NMR, mass spectrometry and other physical methods). $^{1}HNMR(CDCl_3)$:

250MHz ; 12 : 0.79, 0.83 and 1.03(9H,3d,J=6.75Hz), 1.34-1.55(3H,m), 1.68(2H,m), 1.91(1H,dsept,J=7,2.25Hz), 2.24(3H,s), 2.44 and 2.94(2H,ABsyst.,J=12.5Hz), 3.12(1H,dd,J=9.5,2.5Hz) and 3.24(3H,s). 15 : 0.77, 0.78 and 0.84(9H,3d,J=6.75Hz), 1.35(3H,t,J=7Hz), 1.51-1.90(5H,m), 2.10(1H,m), 2.59 and 2.71(2H,ABsyst.,J=17Hz), 3.22(1H,dd,J=10,2Hz), 4.33(2H,m) and 6.24(1H,s).

400MHz ; 20 : 0.75, 0.77 and 0.88(9H,3d,J=7Hz), 1.04(1H,ddd,J=11.5,11.5,11.5Hz, H-18ax), 1.16(1H,dd,J=11.5,11.5Hz,H-20ax), 1.38-1.57(6H,m), 1.70-1.87(4H,m), 1.92(1H, ddd,J=11.5,4.5,1.5Hz,H-17eq), 2.06(1H,s,OH), 2.44(3H,s), 2.86(1H,br d,J=8Hz), 3.06(1H, ddd,J=14,11,4.75Hz), 3.34(1H,ddd,J=14,11,5Hz), 3.55(1H,dddd,J=11.5,8.5,3,2Hz,H-17ax), 4.04(1H,dddd,J=11.5,11.5,4.5,4.5Hz,H-19ax), 7.35 and 7.76(4H,2d,J=8.5Hz). 21 : 0.81, 0.83 and 0.98(9H,3d,J=7Hz), 1.34(1H,ddd,J=13.5,11.5,2.5Hz,H-18ax), 1.45-1.62(6H,m), 1.71 (1H,dddd,J=13.5,3,2.25,2Hz,H-18eq), 1.77-1.87(3H,m), 1.93(1H,dsept,J=7.2Hz), 2.45(3H,s), 3.06-3.15(2H,m), 3.40(1H,ddd,J=14,10.5,6Hz), 3.88(1H,dddd,J=12,7,6,2Hz,H-17ax), 4.02(1H, dddd,J=3,3,3,3Hz,H-19eq), 7.35 and 7.79(4H,2d,J=8.5Hz).

9) S.N. Huckin and L. Weiler, J. Am. Chem. Soc., 96, 1082 (1974).

10) J.P. Kutney, N. Abdurahman, C. Glestos, P. Le Quesne, E. Piers and I. Vlattas, J. Am. Chem. Soc., 92, 1727 (1970).

11) G.K. Cooper and L.J. Dolby, Tetrahedron Lett., 4675 (1976).

(Received in France 6 February 1987)