Tetrahedron Letters, Vol.31, No.21, pp 3043-3046, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF A FUNCTIONALISED BIS-SPIROACETAL

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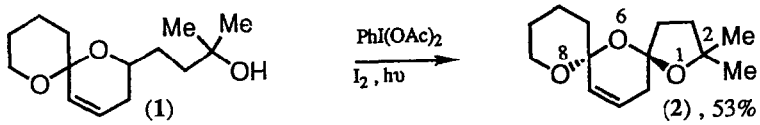
ABSTRACT: The synthesis of bis-spiroacetal (15) bearing an hydroxymethyl group at C-2 is described establishing a methodology for preparation of the polyether antibiotics salinomycin and narasin. Formation of an important iodohydrin intermediate has been accomplished by a highly efficient reaction of an epoxide with LiI catalysed by $BF_3.Et_2O$ in THF. Displacement of the resulting neopentyl iodide was achieved in high yield by reaction of the iodide with potassium superoxide in dimethylsulphoxide/tetrahydrofuran in the presence of 18-crown-6.

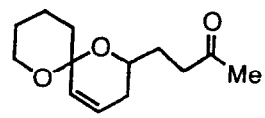
The 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system is a key structural feature of the polyether antibiotics salinomycin and narasin[1], and has therefore attracted the attention of synthetic chemists. Whilst Kishi *et al*[2] and Yonemitsu *et al*[3] have focused on the use of a thermodynamically controlled intramolecular ketalization to establish the tricyclic bis-spiroacetal ring system, Albizati and Perron[4] and Kocienski *et al*[5] have made elegant use of an oxidation-rearrangement of a 2-furyl ketone to construct the required bis-spiroacetal system.



(1) (2), 53%

Scheme 1

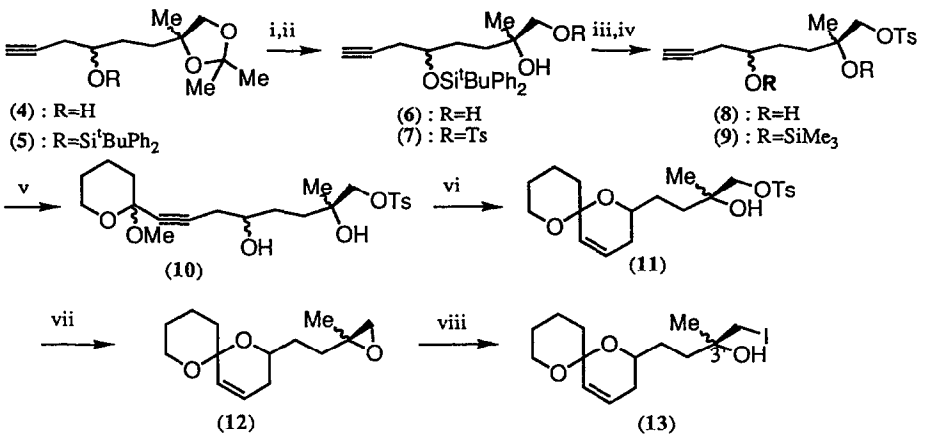
We have previously reported[6] the synthesis of the model bis-spiroacetal (2) containing this same ring system *via* an oxidative cyclisation of hydroxyspiroacetal (1) (Scheme 1) using iodobenzene diacetate and iodine under photolytic conditions. We now wish to report our methodology to introduce a suitable functional group, CH_2X, at C-2 which provides a handle for further elaboration of the right hand side of this molecule. The group X must be such that it does not stablize a free radical as this may result in C-C bond cleavage to generate the methyl ketone (3) rather than 1,5-hydrogen abstraction to generate the required ring system.



(3)

In addition, in order to be applicable to the synthesis of the naturally occurring antibiotics, the group CH_2X must be able to be introduced in optically active form and also have the potential for conversion to an oxygen functionality.

The group "X" which best fulfilled these criteria was found to be iodine. Our present work therefore focused on the spirocyclisation of the key iodohydrin (13) which was synthesized without control of stereochemistry at C-3′ (Scheme 2). The stereochemistry required at this position for the synthesis of salinomycin itself, however, could be easily introduced by incorporation of a resolution step into the synthesis of the previously reported[7] acetonide (4) from which it is derived.



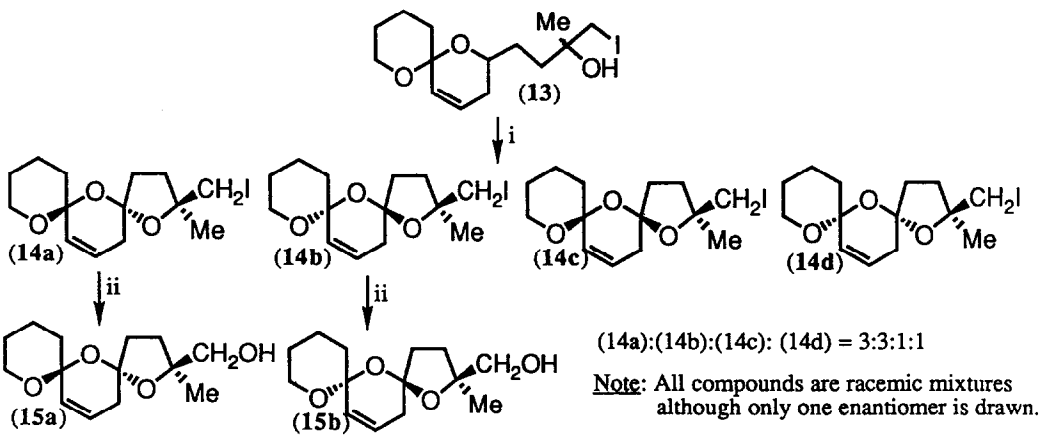
Reagents : (i) MeOH, Amberlite IR-118 resin, 2 days, 76%; (ii) TsCl, py, RT, 1 day, 84%; (iii) 5% HF in CH_3CN, 95% ; (iv) N-trimethylsilylimidazole (excess), CH_2Cl_2,16h., 95% ; (v) ^{n}BuLi, -78°C, 1h., then δ-valerolactone, -78°C to -50°C, 2h., then MeOH, Amberlite IR-118 resin, RT, 18h., 76% ; (vi) H_2, Lindlar, EtOAc, then H^+, CH_2Cl_2, RT, 1h., 91% ; (vii) NaH, THF, RT, 1h., 94% ; (viii) LiI, $BF_3.Et_2O$, THF, -50°C, 24h.,96%.

Scheme 2

The key step in the synthesis of the iodohydrin (13) involved the condensation of the highly functionalised acetylene (9) with δ-valerolactone. After protection of the secondary alcohol (4) as a *tert*-butyldiphenylsilyl ether (5) the acetonide was liberated under mild acidic conditions to give the diol (6) which then underwent selective tosylation on the primary alcohol to give the tosylate (7). The *tert*-butyldiphenylsilyl ether was then removed and the resultant diol (8) reprotected as the bis-trimethylsilyl ether (9). The interchange of silyl protecting groups at this stage avoided complications experienced when trying to remove the more robust *tert*-butyldiphenylsilyl group after the lithium acetylide addition had taken place. Treatment of the acetylene (9) with n-butyl-lithium at -78°C in tetrahydrofuan followed by the addition of δ-valerolactone gave the methoxyacetal (10) in 76% yield after treatment with acidic methanol. Hydrogenation of the acetylene to the *cis*-

alkene over Lindlar catalyst followed by acid catalysed cyclisation then gave the spiroacetal-tosylate (11). Displacement of the tosylate by iodide was effected indirectly *via* the epoxide (12) which formed upon the addition of sodium hydride in tetrahydrofuran. Finally, treatment of the epoxide (12) with lithium iodide and boron trifluoride ethereate in tetrahydrofuran at -50°C afforded the iodohydrin (13) as a mixture of diastereomers that were not separated. This is a new method for halohydrin formation, however halohydrins have been noted as by-products in Lewis acid catalysed cuprate reactions where a halide salt is present.[8]

With the iodohydrin (13) in hand, spirocyclisation to the desired iodo-bis-spiroacetal (14) (Scheme 3) was achieved using iodobenzene diacetate (2.7 equiv) and iodine (1.6 equiv) in cyclohexane upon irradiation with two 270 W tungsten filament lamps for 24h. After careful optimisation, ensuring the reaction mixture was kept cool continuously in a water bath with rigorous exclusion of oxygen, the bis-spiroacetal was obtained in 76% yield as a 3:3:1:1 mixture of isomers (14a): (14b): (14c): (14d). The two *trans*-bis-spiroacetals (14a,14b) were the favoured products of the reaction similar to our previous example[6] and were separated by flash chromatography from the two *cis*-bis-spiroacetals (14c,14d). Separation, however, of the individual *trans*-iodides [i.e. (14a) from (14b)] and the *cis*-iodides [i.e. (14c) from (14d)] was not possible.



Reagents : (i) $PhI(OAc)_2$ (3 equiv.) , I_2 , (2 equiv.), cyclohexane, hυ, 24h., 76%; (ii) KO_2 , 18-crown-6, DMSO/THF, RT, 81%.

Scheme 3

Conversion of the major *trans*-iodides (14a,14b) into the corresponding alcohols (15a,15b) by an SN2 displacement was a difficult process due to the steric hindrance of the neopentyl-like configuration. Successful displacement, however, was finally realised in 81% yield with an excess of potassium superoxide in dimethylsulphoxide/tetrahydrofuran for 2 days using 18-crown-6 to enhance to the nucleophilicity of the superoxide anion. In this case, separation of the two *trans* alcohols (15a,15b) was easily effected by flash chromatography due to their different

Rf values. This is a consequence of the ability of the hydroxyl group in the favoured conformation of isomer (15b) to participate in intramolecular hydrogen bonding to the oxygen atom of the neighbouring spiroacetal ring (Figure). Similar hydrogen bonding is not possible in the other isomer (15a).

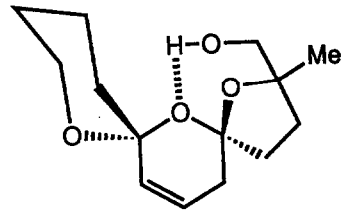


Figure.

References and Notes

1. D.E Cane, W.D Celmer and J.W Westley, *J.Am.Chem.Soc.*, 1983, **105**, 3594 and references cited therein.
2. Y. Kishi, S. Hatakeyama and M.D Lewis, "Frontiers of Chemistry", ed K.J Laidler, Pergamon, Oxford, 1982, p.287.
3. K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.* 1987, **28**, 3253.
4. F. Perron and K.F Albizati, *J.Org.Chem.* 1989, **54**, 2047.
5. P. Kocienski, Y. Fall and R. Whitby, *J.Chem.Soc. Perkin Trans. I*, 1989, 841.
6. (a) R. Baker and M.A Brimble, *J.Chem.Soc. Perkin Trans. I*, 1988, 125.
   (b) R. Baker, M.A Brimble and J.A Robinson, *Tetrahedron Lett.* 1985, **26**, 2115.
7. R. Baker and M.A Brimble, *Tetrahedron Lett.* 1986, **27**, 3311.
8. A. Alexakis, D. Jachiet and J.F Normant, *Tetrahedron*, 1986, **42**, 5607.
9. ^{1}H NMR data for (*15a*): δ_H (270MHz;$CDCl_3$): 1.47(s,3H,Me), 1.62-2.07 (m,7H, 3-H, 3'-H, 4'-H, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H), 2.16 (1H, ddd, $J_{15,15'}$17.2, $J_{15',14}$5.9, $J_{15',13}$1.1 Hz, 15'-H), 2.50(1H,ddd, $J_{15,15'}$17.2, $J_{15,14}$2.6, $J_{15,13}$2.6 Hz, 15-H), 2.72(1H,ddd, $J_{4,4'}$12.8, $J_{4,3'}$4.8 Hz, 4-H), 3.41 (1H,d,J 11.0 Hz, CH_AH_BOH), 3.49 (1H,d, J 11.0 Hz, CH_AH_BOH), 3.70 (1H,m, 9_{eq}-H), 4.03(1H,ddd,$J_{9ax,9eq}$ 11.0,$J_{9ax,10ax}$ 11.0, $J_{9ax,10eq}$ 3.7 Hz, 9ax-H), 5.61 (1H,ddd,$J_{13,14}$10.3, $J_{13,15}$ 2.6, $J_{13,15'}$ 1.1 Hz, 13-H), and 5.86 (1H,ddd, $J_{14,13}$10.3, $J_{14,15'}$5.9, $J_{14,15}$2.6 Hz, 14-H).

   ^{1}H NMR data for (*15b*): δ_H(270 MHz; $CDCl_3$): 1.20(s,3H,Me), 1.53-1.80 (m, 6H, 3'-H, 4'-H, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H), 2.15 (1H,ddd, $J_{15,15'}$17.2, $J_{15',14}$6.2, $J_{15',13}$1.1 Hz, 15'-H), 2.48-2.61 (2H, m, 3-H, 15-H), 2.81 (1H,m, 4-H), 3.41 (1H,dd,$J_{HA,HB}$10.6, $J_{HA,OH}$10.6 Hz, CH_AH_BOH), 3.56 (1H,d,$J_{HA,OH}$10.6 Hz,OH),3.64 (1H,d,$J_{HA,HB}$10.6 Hz, CH_AH_BOH), 3.66-3.70 (1H,m,9_{eq}-H), 4.03-4.12 (1H,m, 9_{ax}-H), 5.58 (1H,ddd,$J_{13,14}$10.3, $J_{13,15}$2.9, $J_{13,15'}$1.1 Hz, 13-H), and 5.87 (1H,ddd,$J_{14,13}$10.3, $J_{14,15'}$6.2, $J_{14,15}$2.2 Hz, 14-H).

(Received in UK 16 February 1990)