Pergamon

Tetrahedron Letters, Vol. 35, No. 29, pp. 5289-5292, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00983-X

Preparation of a Novel C-13 Thioacetal Derivative of Amphotericin B

Andrew W. Taylor* and David T. MacPherson

SmithKline Beecham Pharmaceuticals, Great Burgh,
Yew Tree Bottom Road, Epsom, Surrey, KT18 5XQ, U.K.

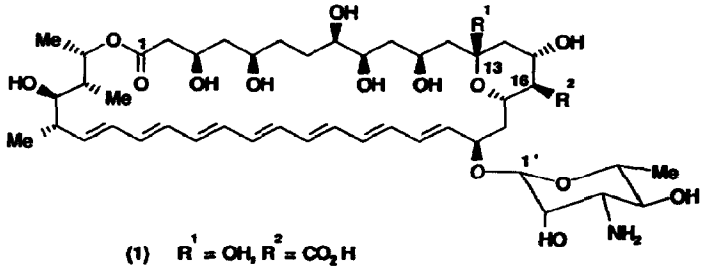
Abstract: **The transformation of amphotericin B (1) into a novel 13-thioacetal derivative (4) is described. A selective protecting group strategy involves the intermediacy of the nonasilyloxy derivative (10), facilitating modification of the remaining free hemiacetal hydroxyl at C-13.**

The polyene macrolide antibiotic amphotericin B[1] (1) remains the drug of choice for the treatment of many serious systemic fungal infections in man[2], particularly in immunocompromised patients. However, its therapeutic utility is impaired by a variety of severe side-effects, especially nephrotoxicity[3]. Many amphotericin derivatives have been prepared with the primary aim of reducing the toxicity of the parent antibiotic, with chemical modification[4] concentrated almost exclusively at the mycosamine amino group and at the C-16 (carboxylate) position. Work in this latter area in our laboratories[5] has culminated in the identification of the 16-hydroxymethyl amphotericin analogue[6] (2) as a potential potent new systemic antifungal agent[7] with nephrotoxicity much reduced compared to that of amphotericin B (1) itself.

Recently, we have also reported the synthesis of the first amphotericin B analogues exclusively modified at the C-13 (hemiacetal) position[8]. Biological evaluation of these compounds highlighted the 13-methoxy and 13-anhydro derivatives[9] (3),(6) as antifungal agents with potentially lower mammalian toxicity than amphotericin B, but interest in them was reduced when it was suspected that partial reversion of the analogues to amphotericin B was occurring *in vivo*, presumably by hydrolytic attack on the C-13 acetal of (3) and enol ether of (6), respectively. However, these leads were sufficiently encouraging for us to target new derivatives of amphotericin B containing more chemically stable C-13 functionalisation. This paper reports the preparation of the 13-thioacetal (4).

The free amino and carboxylic acid functions of amphotericin B had already been suitably protected as the N-fluorenylmethoxycarbonyl and allyl ester groups in (9)[8] for our earlier anomeric exchange reactions at C-13 . However, to further increase solubility in non-polar, aprotic organic solvents and to maximise the potential for thioacetalisation at C-13, it was desirable to selectively protect all secondary hydroxyl groups while retaining the hemiacetal free hydroxyl.

Although persilylation of (9) with 2,6-lutidine:trimethylsilyl trifluoromethanesulphonate had caused dehydration of the hemiacetal concomitant with trimethylsilylation of all other hydroxyl groups, affording enol ether (7)[8], persilylation of the same intermediate (9) with, sequentially, 2,6-lutidine (17 equiv.) and triethylsilyl trifluoromethanesulphonate (13 equiv.) in hexane (2h., room temperature) gave the required 13-hydroxy nonatriethylsilyl derivative (10) as the major isolated product[10] (45%) after chromatographic purification. Typically, less than 10% of the unwanted enol ether (8) was observed in the crude reaction product.



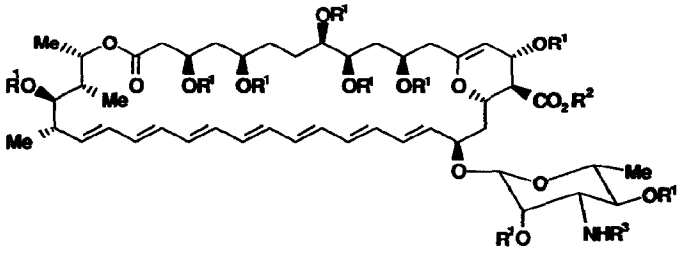
(1) $R^1 = OH, R^2 = CO_2H$

(2) $R^1 = OH, R^2 = CH_2OH$

(3) $R^1 = OMe, R^2 = CO_2H$

(4) $R^1 = SEt, R^2 = CO_2H$

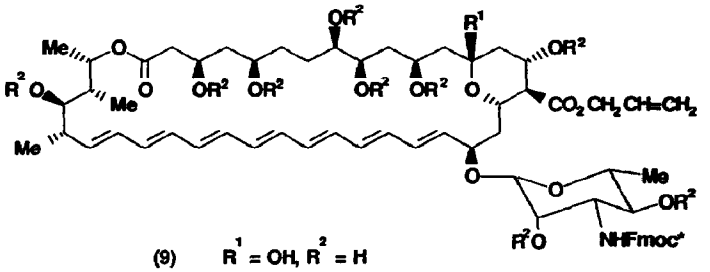
(5) $R^1 = SEt, R^2 = CO_2CH_2CH{=}CH_2$



(6) $R^1, R^2, R^3 = H$

(7) $R^1 = SiMe_3, R^2 = CH_2CH{=}CH_2, R^3 = Fmoc^*$

(8) $R^1 = SiEt_3, R^2 = CH_2CH{=}CH_2, R^3 = Fmoc^*$



(9) $R^1 = OH, R^2 = H$

(10) $R^1 = OH, R^2 = SiEt_3$

(11) $R^1 = SEt, R^2 = SiEt_3$

(12) $R^1 = SEt, R^2 = H$

* Fmoc = 9-fluorenylmethoxycarbonyl

The tendency of the rather hindered hemiacetal hydroxyl to dehydrate initially caused problems in attempts to convert the nonasilyloxy derivative (**10**) to thioacetal (**11**). Thus when (**10**) in diethyl ether was sequentially treated with ethanethiol (11 equiv.) and magnesium bromide[11] (5 equiv.) in ether, the unwanted enol ether (**8**) predominated in a mixture of reaction products. However, when (**10**) in ether was sequentially treated with solid magnesium bromide (5 equiv.) and excess ethanethiol (100 equiv.), (1h., room temperature), the desired thioacetal (**11**)[12] was optimally obtained in 74% yield.

After removal of the silyl groups from (**11**) (HF: pyridine complex in pyridine:tetrahydrofuran, 24h, room temperature, 74% yield),[13] the amino group of (**12**) was liberated with piperidine (2 equiv.) in dimethylsulphoxide:methanol (3:1) (2h., room temperature),[14] affording ester (**5**) in 73% yield. Finally, cleavage of this allyl ester with pyrrolidine (4 equiv.) and tetrakis (triphenylphosphine) palladium (0.1 equiv.) in tetrahydrofuran (N_2, 1h., room temperature) afforded the target polyene (**4**) as a precipitate. Further work-up gave the product[15] in analytical purity (42% yield).

On biological evaluation, the thioacetal (**4**) was found to have much lower antifungal activity than, for example, its methyl acetal analogue (**3**). However, the methodology described above should provide a base from which further modification at this biologically important C-13 position can be explored.

ACKNOWLEDGEMENTS

We would like to thank the following for their help and encouragement during the course of this work: Dr D.F. Corbett, Dr M.J. Driver and, for 2D-nmr assignments, Dr S. Connor.

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10. All new compounds were characterised by full spectral data, viz. 400 MHz ^{1}Hnmr, D.E.P.T.135 ^{13}Cnmr, uv, ir and FABms. Nmr assignments were underpinned by comparison with the assignments made for target compound (4) by 2D methods. Compound (10) was isolated by filtering off solids from the reaction mixture, washing the hexane solution with sodium bicarbonate solution and water, and drying and concentrating the solution to a low volume which was directly applied to a medium-pressure silica gel column.

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12. cf. ^{13}C D.E.P.T. 135 data for carbon no. 13 in the following compounds (δ ppm, d_6-acetone): (**10**), 98.49; (**8**), 154.51; (**11**), 89.26.

13. Hydrogen fluoride (80 equivalents, 2M in pyridine-tetrahydrofuran (2:3)) was added by plastic syringe to the substrate (**11**), 0.04M in tetrahydrofuran in a plastic bottle. Work-up was by precipitation into excess dry hexane:ether (1:1), washing with dry ether and medium pressure chromatography on silica gel (methylene chloride:methanol, 12:1).

14. Methodology as fully described for deprotection of other N-Fmoc amphotericin B analogues in reference 8.

15. The product (4) was reprecipitated from tetrahydrofuran:methanol-ether, and residual pyrrolidine removed by trituration with very dilute acetic acid (pH 3-4) and water washing (1ml per 100mg substrate). Nmr data for (4), with assignments confirmed by 2D methods, as follows: δ^{1}H (deuterio -MeOH: pyridine,1:1) 1.15 (3H,d,J 7.2 Hz,39-CH_3), 1.20 (3H,t,J 7.4 Hz,SEt-CH_3), 1.25 (3H,d,J 6.4 Hz,40-CH_3), 1.35 (3H,d,J 6.3 Hz,38-CH_3), 1.45 (3H,d,J 5.9 Hz,6'-CH_3), 1.5-1.8 (6H,complex,4,6-CH_2;1 of 7,10-CH_2), 1.9 2.1 (5H,complex,1 of 7,10,12 and 14-CH_2;36-CH), 2.2 (2H,complex,1 of 12,18-CH_2), 2.40 (1H,dd,J 16.8,3.3 Hz,1 of 2-CH_2), 2.4-2.6 (5H,complex,1 of 2.14 and 18-CH_2;16,34-CH), 2.60 (2H,q,J 7.5 Hz,S-CH_2), 3.44 (1H,m,35-CH), 3.51 (1H,br d,J 10 Hz,8-CH), 3.65 (1H,dd,J 10.1,2.8 Hz,3'-CH), 3.72 (1H,m,5'-CH), 3.85 (2H,complex,9,4'-CH), 3.98 (1H,m,5-CH), 4.47 (2H,complex,3,11-CH), 4.52 (1H,d,J 2.8 Hz,2'-CH), 4.73 (2H,m,15,17-CH), 4.93 (1H,m,19-CH), 5.04 (1H,s,1'-CH), 5.52 (1H,m,37-CH), 5.57 (1H,dd,J 14.1,9.8 Hz,33-CH), 6.08 (1H,dd,J 14.3,7.5 Hz,20-CH), 6.2-6.5 (complex,polyene-CH). δ^{13}C (deuterio -MeOH:pyridine,1:1) 12.5 (39), 14.9 (SEt-CH_3), 17.5 (38), 18.2 (6'), 19.1 (40), 22.2 (SEt-CH_2), 30.8 (7), 36.3 (6), 38.8 (18), 41.4 (10), 41.7 (36), 43.3 (2), 43.5 (34), 44.0 (14), 44.8 (4), 50.1 (12), 57.5 (3'), 59.8 (16), 68.2 (15 or 17), 68.5 (3), 68.7 (11), 69.3 (2'), 70.0 (17 or 15), 70.7 (4'), 70.8 (37), 72.1 (5), 74.4 (5'), 74.8 (9), 75.7 (8), 77.0 (19), 78.7 (35), 89.7 (13), 99.9 (1'), 131-135 (non-terminal polyene -CH=), 136.9 (20), 137.6 (33), 172.0 (1), 179.4 (carboxylate-C).

(*Received in UK 22 April 1994; accepted 20 May 1994*)