Pergamon

Tetrahedron Letters, Vol. 35, No. 41, pp. 7665-7668, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01600-3

A Convenient and Concise Synthesis of a Key Lactone Intermediate in Milbemycin Chemistry.

Nigel Hussain* and David O. Morgan.

SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent. TN11 9AN.

Roderick J. J. Dorgan and Graham S. Macaulay.

SmithKline Beecham Animal Health, Walton Oaks, Dorking Road, Tadworth, Surrey. KT20 7NT.

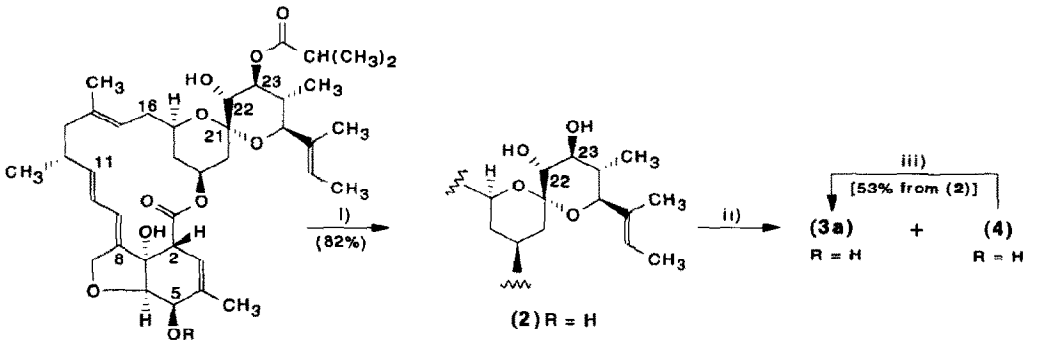
Abstract: A short, convenient and inexpensive synthesis of lactone (3) from milbemycin (1) is described. This lactone is a key intermediate in the synthesis of milbemycins.

In recent years there has been considerable interest shown in a certain class of 16-membered ring macrolides. The milbemycins and the closely related avermectins have been shown to possess excellent antiparasitic/insecticidal activity and have been the subject of intense total and partial syntheses.[1a,1b] In our laboratories we have isolated many milbemycins from *Streptomyces* sp. E225[2,3] and from one of these milbemycins have described the synthesis of the lactones of the type (3).[4] These lactones have proved to be very versatile intermediates for the preparation of semi-synthetic milbemycins.[5a,b]

We have actively been looking for alternative ways to make lactone (3).[6] We now wish to report a short and convenient synthesis of lactone (3a) from milbemycin (1) which employs cheap reagents and is easy to carry out (Scheme 1).

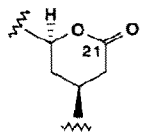
Removal of the C23-ester moiety in milbemycin (1) was carried out using sodium hydroxide (1.5 equivalents) in aqueous methanol at O°C. The product (2)[7] typically contains around 2-3% of C2-epimer (9). Purification by recrystallization from toluene results in pure diol (2). Control of temperature is important in order to limit the formation of (9), and conjugated by-product (10). The subsequent steps represent a two "pot" sequence to provide lactone (3a). First part of the sequence involves: cleavage of the C22/23-diol function in (2) to provide dialdehyde (5); *in situ* reduction of the two aldehyde groups in (5) followed by acidification to give a new C21/22-diol (6); and cleavage of the C21/22-diol function in (6) to provide a mixture of lactone (3a) and ester (4).[8] The second part of the sequence involves converting the ester (4) back to lactone (3a) in the above mixture.

Treatment of (2) with sodium periodate (2 equivalents) in aqueous ethanol[9] resulted in smooth conversion to the dialdehyde (5) which proved unstable upon attempted isolation. *In situ* reduction with sodium borohydride (3 equivalents) at O°C gave diol (7)[10] which upon acidification with dilute hydrochloric acid (*ca.* 15 equivalents) resulted in formation of hemiacetal (6).[10] Interestingly, no acetal (8) was observed. *In situ* cleavage of (6) with a second portion of sodium periodate (1 equivalent) resulted in smooth conversion to a mixture of desired lactone (3a) and its ethyl ester (4). This mixture was treated with *p*-toluenesulphonic acid (1 equivalent) in tetrahydrofuran which resulted in the conversion of (4) to (3a).[11] The lactone can be recrystallized from toluene. The overall yield of (3a) from (1) was 43.5%.



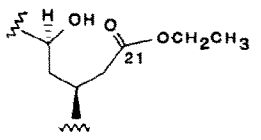
Scheme 1

i) NaOH / MeOHaq / 0°C, ii) a) $NaIO_4$ / EtOHaq / rt, b) $NaBH_4$ at 0°C then HClaq, c) $NaIO_4$, iii) H^+ / THF.

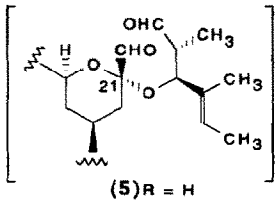


(3a) R = H
(3c) R = TES
(3b) R = TBDMS

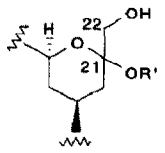
TES = $Si(CH_2CH_3)_3$
TBDMS = $Si(CH_3)_2{}^tBu$



(4) R = H



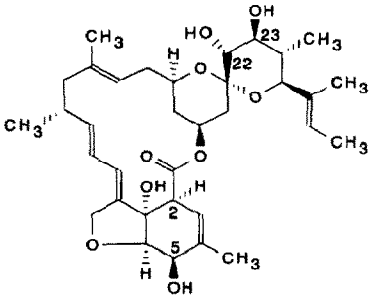
(5) R = H



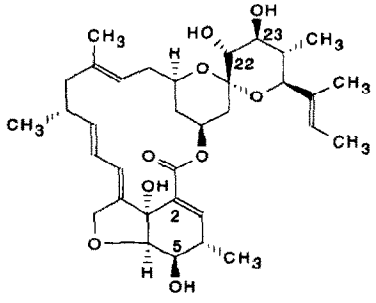
(6) R = R' = H

(7) R = H, R' =

(8) R = H, R' = CH_2CH_3



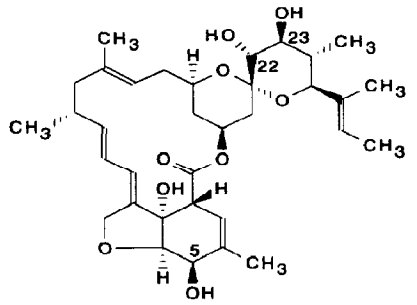
(9)



(10)

The C23-ester removal in milbemycin (**1**) was investigated further to eliminate the formation of impurities (**9**) and (**10**). Of the many methods tried, only three gave clean diol (**2**). These were diisobutylaluminium hydride, methylmagnesium iodide and an enzyme(porcine liver esterase - in the form of pig liver acetone powder). Diisobutylaluminium hydride (at -70°C) gave yields of 70% but complete reaction was never achieved (even with 8 equivalents of reagent). Likewise, methylmagnesium iodide (at O°C) gave similar results. However, the esterase [at pH7 (phosphate buffer) in ethyl acetate and at ambient temperature] gave excellent yields on a small scale but on scale up the yields were poor (30-40%) with no apparent impurities seen although complete reaction had occurred.[12]

The sequence from (**2**) to (**3a**) has been carried out by isolating the intermediate (**7**) (Scheme 2). The reduction step was quenched using acetic acid, since quenching with dilute hydrochloric acid resulted in formation of a mixture of (**6**) and (**7**). Conversion of alcohol (**7**) to the desired lactone (**3a**) [via a mixture of (**3a**) and (**4**)] proceeded in excellent yield. Hence, the steps where loss of yield occurs is the first cleavage/reduction. The diol (**6**) has also proved to be a versatile intermediate and has led to novel milbemycins being synthesized, these results will be reported in due course.



(**2**)

$NaIO_4$ / EtOHaq / rt
then $NaBH_4$ at 0°C
then AcOH
(66%)

(**7**)

i) $NaIO_4$ / EtOH / H_3O^+ / rt
ii) H^+ / THF
(86%)

(**3a**)

Scheme 2

Lactone (**3a**) was easily converted to its 5-TBDMS derivative (**3b**) [in 87% yield, using *tert*-butyldimethylsilyl chloride and imidazole in N,N-dimethylformamide] and its 5-TES derivative (**3c**) [in 76% yield, using triethylsilyl chloride and imidazole in tetrahydrofuran]. These lactones (**3b**) and (**3c**) have been used to synthesize a variety of semi-synthetic milbemycins.[5a,b]

In conclusion, we have demonstrated a cheap, and efficient synthesis of a key lactone intermediate (**3a**) from (**1**) involving a 3 "pot" sequence.

ACKNOWLEDGEMENTS:

We thank the Analytical Services Unit at Great Burgh for the spectral data. We also thank Dr. Norman J. Lewis and Dr. David C. Lathbury (SmithKline Beecham Pharmaceuticals, Tonbridge, Kent.) and Prof. Jim Thomas (Manchester University.) for helpful discussions.

REFERENCES AND NOTES:

1. For recent reviews of the area see a) Davies H. G. and Green R. H., *Chem. Soc. Rev.*, **1991**, *20*, 271-339. Also *Idem., Ibid.*, **1991**, *20*, 211-269. b) Albizati K. F. and Perron F., *Chem. Rev.*, **1989**, *89*, 1617.
2. Banks R. M., Brewer M. D., Fish J. P., Hood J. D., Manger B. R. and Poulton M. E., *J. Antibiotics*, **1989**, *42*, 1593.
3. Baker G. H., Dorgan R. J. J., Everett J. R., Hood J. D. and Poulton M. E., *J. Antibiotics*, **1990**, *43*, 1069.
4. Baker G. H., Dorgan R. J. J., Hussain N., Macaulay G. S. and Morgan D. O., *Tetrahedron Lett.*, **1994**, *35*, 2377.
5. a) Baker G. H., Dorgan R. J. J., Hussain N., Macaulay G. S. and Morgan D. O., *Tetrahedron Lett.*, **1994**, *35*, 2381. b) Baker G. H., Dorgan R. J. J., Hudner J.F., Hussain N. and Morgan D. O., *Tetrahedron Lett.*, **1994**, *35*, 2385.
6. Merck and Co. workers have carried out considerable chemistry in the avermectin series and have identified several synthetically useful intermediates. See Fisher M. H., Meinke P. T., Mrozik H. and O'Connor S. P., *Tetrahedron Lett.*, **1994**, *35*, 5343 and references therein.
7. All new compounds were characterized by Mass-spec., ^{1}H nmr and ^{13}C nmr.
8. The ratio of lactone (**3a**) / ester (**4**) is *ca.* 2:1 by tlc (silica gel, using 1:2 hexane / ethyl acetate).
9. The water is a necessity since without this the diol cleavage is very sluggish.
10. Compounds (**6**) and (**7**) are present as one isomer at C21 (of undetermined stereochemistry) by ^{1}H nmr (270 MHz) and ^{13}C nmr (67.8 MHz) carried out in $CDCl_3$.
11. For (**3a**) - Partial ^{1}H nmr (270MHz, $CDCl_3$): δ 5.78(2H, m), 5.47(1H, bs), 5.37(1H, m), 5.17(1H, m), 5.00(1H, m), 4.70(2H, m), 4.25(2H, m), 3.96(1H, d(J=6.3Hz)), 3.33(2H, m), 3.11(1H,m), 1.89(3H, s), 1.56(3H, s), and 1.02(3H, d(J=6.6Hz)). ^{13}C nmr (67.8MHz, $CDCl_3$): 172.71ppm, 168.52, 142.93, 139.55, 139.09, 138.25, 123.45, 120.22, 118.82, 117.64, 80.36, 79.32, 76.61, 68.24, 67.52, 66.04, 48.32, 45.55, 36.78, 35.89, 34.53, 34.04, 22.26, 19.89, and 15.65. MS (FAB, NOBA/Na): m/z 467(MNa^{+}).
12. Irreversible binding to the enzyme/proteins may have taken place.

(*Received in UK* 22 *July* 1994; *revised* 15 *August* 1994; *accepted* 19 *August* 1994)