Tetrahedron Letters No. 28, pp 2633 - 2636. 0040-4039/79/0708-2633$02.00/0


# SYNTHESIS OF THE MACROLIDE ANTIBIOTIC A26771B METHYL ESTER

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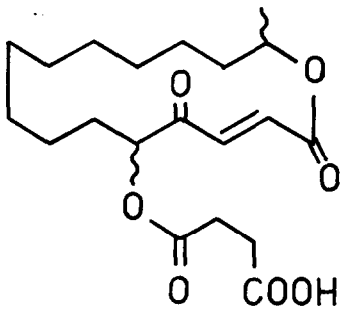
*Abstract.* The total synthesis of the title compound (1) is reported.

The isolation and structure elucidation of the 16-membered lactone antibiotic A26771B (1) from *Penicillium turbatum* (Westling) was recently reported[1]. The compound shows optical activity but its absolute (and relative) stereostructure is unknown at present. We report here the total synthesis of (±)-1 methyl ester and its diastereomer, based on the strategy of combining a saturated $C_{11}$ chain, functional at C-1 and C-10, with furfural and subsequent modification of the furan moiety[2].

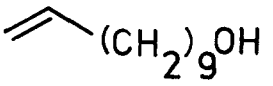
Thus, 10-undecen-1-ol was converted to the bromide (2) ($Ph_3P$, $Br_2$, DMF, 89%) and thence to the bromo alcohol (3), b.p. 138°/1 torr, *via* mercuration-reduction[3] (83 %). Following the protection of 3 to give 4 (77 %), the Grignard reagent was prepared using 1,2-dibromoethane activation[4] and reacted with furfural giving the 2-furylcarbinol (5)[5] (63 %), δ 1.10 (d, 3H, J = 6.0 Hz), 3.4-3.9 (m, 3H), 4.60 (t, 1H, J = 7.0 Hz), 4.70 (m, 1H), 6.25 (m, 2H), 7.30 (m, 1H). Introduction of the succinate group (1.5 eq's of succinic anhydride, pyridine, 48 h at 70°), and methylation ($CH_2N_2$ in $Et_2O$) without purification of the acid then gave the ester 6 (92 % overall from 5), δ 2.60 (br s, 4H), 3.70 (s, 3H), 5.85 (t, 1H, J= 7.0 Hz).

Since the second assymmetric sentre, introduced at this stage, is quite remote from the existing one, their relative configuration cannot be controlled. Therefore the synthesis will inevitably lead, in 1:1 ratio, to two diastereomers (each ±) of the penultimate intermediate, i.e., the pre-cyclisation hydroxyacid. However, the relative configuration of the natural lactone being unknown, obviously both diastereomers are required in view of completing the formal synthesis.

Elaboration of the furan moiety started with the oxidative addition of methanol[6] to 6 (1 eq of $Br_2$ and 2 eq's of $Na_2CO_3$ in MeOH, 2 h at -10°). Despite the presence of excess base the THP ether protection was partially hydrolyzed, and a



1



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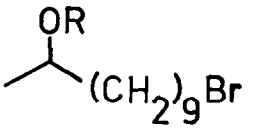
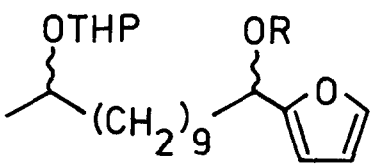


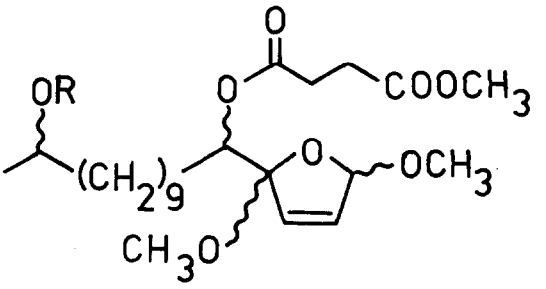
3 R = H

4 R = THP



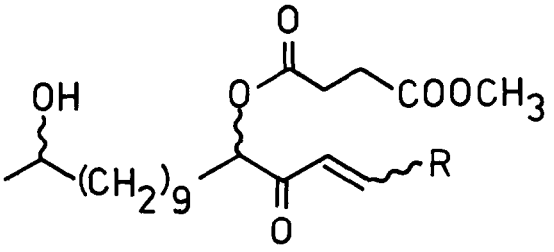
5 R = H

6 R = $COCH_2CH_2COOCH_3$



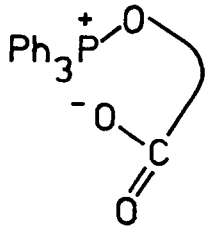
7 R = THP

8 R = H

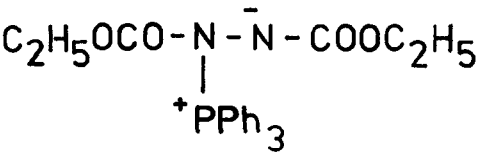


(E) & (Z) 9 R = CHO

(E) 10 R = COOH



11



12

1:2 mixture of 7 and 8 was obtained in 83 % combined yield. Insofar in the next step the protection would be hydrolysed at any rate, both products could be utilized. Preparative TLC (here and hereafter, silica gel, $CHCl_3$-EtOAc 10:1) furnished pure 7 [δ 3.08 and 3.18 (each s, together 3H), 3.37 and 3.49 (each s, together 3H), 5.00 and 5.15 (each t, together 1H), 5.48 (br s, 1H), 5.66-6.16 (m, 2H)] and 8 ($^1$H NMR as above except for the THP group).

The hydrolytic ring cleavage of the dihydrofurans 7 and 8 proved quite difficult to perform, optimal conditions involving a $H_2O$:AcOH:THF (1:2:2) mixture (10.5 h, 60°). Surprisingly, the required (E) ketoaldehyde (E-9) [δ 5.21 (t, 1H), 6.90, 7.20 and 9.85 (each 1H, ABX-system, $J_{AB}$ = 16.0 Hz, $J_{AX}$ = 6.5 Hz, $J_{BX}$ < 1Hz)] was obtained directly in 28 % yield after preparative TLC. A control experiment in the dark gave the (Z) ketoaldehyde (Z-9) [26 %, δ 6.20, 7.10 and 10.20 (each 1H, ABX-system, $J_{AB}$ = 12.0 Hz, $J_{AX}$ = 7.0 Hz, $J_{BX}$ < 1 Hz)] which was quantitatively isomerised on daylight lamp irradiation to (E)-9.

A highly selective reagent was then required for the oxidation of the α,β-unsaturated aldehyde in the presence of other sensitive functionality as in (E)-9. Of the various reagents tested (e.g., $MnO_2$ or AgO/NaCN[7]), sodium chlorite[8] proved far superior, furnishing the (E) ketoacid 10 in 69 % yield after prep. TLC [$\bar{\nu}_{max}$ 1680, 1710, 1730 $cm^{-1}$, δ 6.84 and 7.21 (each 1H, AB-q, J = 16.0 Hz)].

For the remaining lactonisation step, a number of published procedures were tested. The 2-pyridyl thiol ester methods, either thermal[9] or with silver ion[10], and the N-methylpyridinium-2-yl carboxylate method[11] failed to produce any lactones (by TLC evidence). To our knowledge, there exists in the literature only one instance where a γ-keto-α,β-enoic acid with a remote hydroxy group has been directly lactonised (actually dimerised). This operation was performed with $Ph_3P$-diethyl azodicarboxylate (DEAD)[13] in 15 % yield as the last step in a synthesis[12] of vermiculine; in all other reported syntheses of vermiculine and the related pyrenophorin, the keto carbonyl is protected. Obviously, in unprotected systems the enone functionality is very susceptible towards nucleosphiles.

A very low yield (ca. 1 %) of the required lactone in a highly complex mixture of other reaction products resulted from the treatment[13] of a mixture of 10 and $Ph_3P$ with DEAD. It is clear that in this procedure, 10 may also react directly with DEAD, thus preventing the formation of the required[13] (postulated) intermediate 11. Therefore, the betain 12[14] was preformed from $Ph_3P$ and DEAD, and then reacted with 10, giving an 8 % yield of lactonised product after prep. TLC.

In the lactonisation product, for the first time two diastereomers are discernible in $^1$H and $^{13}$C NMR, although the two compounds are not resolved by TLC. Slightly different values are observed for the olefinic AB quartet in $^1$H NMR and

for the olefinic carbon atoms in $^{13}C$ NMR, showing that the natural isomer and its diastereomer are present in ca. 3:2 ratio, presumably a result of unlike lactonisation rates of the diastereomeric hydroxyacids 10. In other portions of the NMR spectra, as well as in UV, IR and MS, the synthetic and natural materials are indistinguishable.

*Acknowledgement.* This work was supported by a grant from the Research Foundation of Orion Yhtymä.

## FOOTNOTES AND REFERENCES

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(Received in UK 5 April 1979)