Pergamon

Tetrahedron Letters, Vol. 35, No. 20, pp. 3345-3348, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0512-V

Titanium Mediation of Aldol Reactions in Fridamycin and Vineomycinone Syntheses

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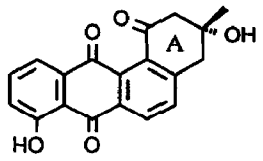
Abstract: Fridamycin E, derivatives of *ent*-fridamycin E and enantiopure intermediates for vineomycins have been synthesised using a titanium(IV)-mediated addition of (*l*)-menthyl acetate to acetonyl-substituted anthrarufin ethers.

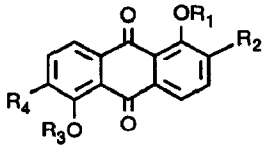
An important requirement in the synthesis of several classes of anthracycline antibiotics is the elaboration of a 3-hydroxy-isovaleryl moiety e.g. as the A-ring of angucyclines like rabelomycin **(1)**[1] or as the side chain in fridamycin E **(2)**[2] or the vineomycins. For this step in his synthesis of vineomycinone B_2 methyl ester **(3)** Danishefsky[3] added the magnesium enolate **(14)** to the acetonyl side chain of the diphenol **(4)**. He found it was necessary to have the free phenols because the reagent attacked the quinone carbonyls of the equivalent dimethyl ether **(5)**. We now report that the reagent derived from $ClTi(^iPrO)_3$ and **(15)**[4] reacts selectively with an acetonyl side chain on an anthrarufin ether providing asymmetric syntheses of fridamycin E and enantiopure intermediates for vineomycinones.

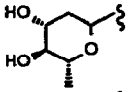
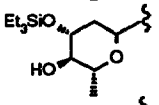
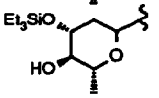
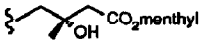
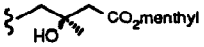
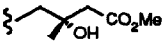
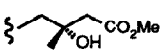
Having developed a very efficient synthesis of the furanoketone **(17)** (84% overall yield) from anthrarufin **(6)**[5] we felt that the elaboration of the acetonyl moiety into the hydroxy-isovalerate chain would provide very versatile enantiopure intermediate compounds. We also felt that the use of the titanium enolate **(16)** could be advantageous, both because its expected low basicity[6] would not result in generation of a ketone enolate, and because the β-chelating propensity of titanium (IV)[7] could result in protection of the quinone carbonyls. In the event treatment of the ketone **(17)** with 3 equivalents of the reagent prepared by adding $ClTi(O^iPr)_3$ to **(15)**[4,8] gave a 79% yield of a 1:1 mixture of the diastereomers **(18)** and **(19)** which were separated by h.p.l.c.

To enable us to use n.m.r. comparisons to establish the absolute configurations of **(18)** and **(19)** we carried out the analogous addition to the ketone **(7)**, separated the resultant mixture of **(8)** and **(9)** (1:1,83%) and established their configurations by converting **(8)** to fridamycin E **(2)**[9] by transesterification (K_2CO_3, MeOH), ether cleavage (BBr_3, CH_2Cl_2,-78°C) and ester hydrolysis (KOH, H_2O).[10] The ketone **(7)** was prepared from the mono-Claisen rearranged product **(10)**[5] in an overall yield



(1)



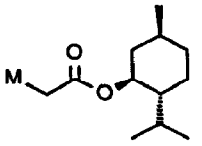
	R_1	R_2	R_3	R_4
(2)	H		H	H
(3)	H		H	
(4)	H		H	
(5)	Me		Me	
(6)	H	H	H	H
(7)	Me		Me	H
(8)	Me		Me	H
(9)	Me		Me	H
(10)	H	$CH_2C(Cl)=CH_2$	$CH_2C(Cl)=CH_2$	H
(11)	Me		Me	H
(12)	Me		Me	H
(13)	Me		Me	CHO

of 96% by ether cleavage (BBr_3, CH_2Cl_2, -78°C), methylation (Me_2SO_4, K_2CO_3, Me_2CO) and solvomercuration ($Hg(O_2CCF_3)_2$, CF_3CO_2H, HCO_2H).

The h.p.l.c. elution orders indicated that the pairs of compounds **(8)** and **(18)** and **(9)** and **(19)** had the same configurations at C3, which was confirmed by ^1H n.m.r. comparisons of the menthyl esters, and of the methyl esters derived from them by transesterifications. Thus for the menthyl esters comparison of spectra for a 2:1 mixture of **(18)** and **(19)** and a 2:1 mixture of **(8)** and **(9)**, obtained with the inclusion of 0.1 equivalents of $Eu(hfc)_3$, revealed that signals for the methylene groups of the side chain (H2, H4) and for the 7-OMe groups of **(8)** and **(18)** showed the same sense of non-equivalence, and that for **(9)** and **(19)** these signals also showed a similar sense of non-equivalence. Since the conversion to fridamycin E establishes that **(8)** has the C3(*R*)-configuration, those of **(9)** and **(19)** can be assigned as (*S*) and that of **(18)** as (*R*).

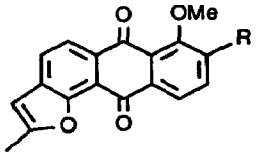
A similar comparison of the spectra of a 2:1 mixture of the methyl esters **(11)** and **(12)**, and a 2:1 mixture of **(20)** and **(21)** obtained in the presence of 6 equivalents of 2,2,2-trifluoro-1-(9-anthryl)ethanol revealed that the resonances for H2 and H4 of **(11)** and **(20)** showed the same sense of non-equivalence , and so did the appropriate signals of **(12)** and **(21)**, confirming that **(20)** has the 3(*R*)-configuration and **(12)** and **(21)** each have the 3(*S*)-configuration.

Finally ozonolysis of the furan ring of **(17)** unmasked the aldehyde giving **(13)** in 81% yield. Thus this enantiopure compound is available for building the carbon sugar of the vineomycins, or for syntheses of novel analogues.

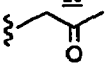


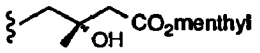
M

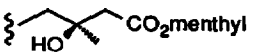
(14) MgBr
(15) Li
(16) $Ti(O^iPr)_3$

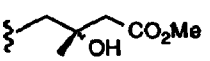


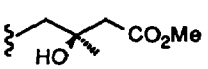
R

(17) 

(18) 

(19) 

(20) 

(21) 

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7. Keck, G.E., and Castellino, S., *J. Am. Chem. Soc.*, 1986, **108**, 3847.
8. Although we now know[4] that reaction via the enolate **(16)** cannot play a significant role in these reactions, it is clear the desired aldol-like additions are facilitated by the inclusion of $ClTi(O^iPr)_3$, since, not surprisingly, in its absence the lithium enolate **(15)** attacks the carbonyls of the quinones as well as the acetonyl side chains of **(7)** and**(17)**.[11]
9. $[\alpha]_D$ +12°; m.p. 163-164°C; correct i.r., ^1H and ^{13}C n.m.r. spectra: *c.f.* ref. 1 for *ent*-fridamycin E.
10. Attempted hydrolyses of the menthyl esters were unsuccessful.
11. Pausler M.G., Ph.D. Thesis, University of Auckland, 1992.

(*Received in UK* 7 *December* 1993; *accepted* 10 *March* 1994)