Regioselectivity of Selenoxide Elimination: Synthesis of the Cyclohexenediol Fragment of Non-aromatic β-Milbemycins

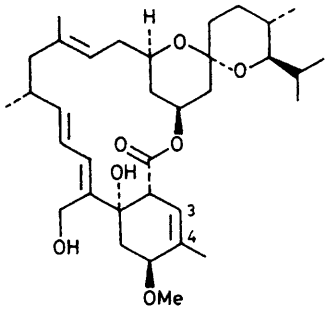
Simon V. Mortlock, Nicholas A. Stacey, and Eric J. Thomas*

The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, U.K.

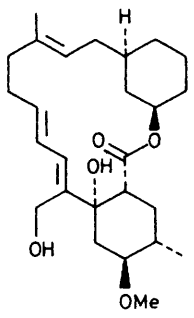
Whereas selenoxide elimination from the hydroxyselenide (**6**) gave predominantly exocyclic elimination, preferred endocyclic elimination was observed from the corresponding ketone (**5**), and was applied to a synthesis of the cyclohexenediol fragment of the non-aromatic β-milbemycins.

As discussed in the preceding communication, the total synthesis of milbemycins and avermectins is of considerable interest at present.[1] We were interested in developing a synthesis of the cyclohexenediol 'lower hemisphere' fragment of milbemycin E (**1**) based on the Robinson annelation–furan oxidation strategy used to prepare the milbemycin analogue (**2**).[2] To achieve this it was necessary to find conditions for the regioselective introduction of the C(3)—C(4) double bond. This in the α-milbemycin and avermectin series is complicated by isomerization to the more stable, conjugated C(2)–C(3) double-bond isomers, and attempts to deconjugate these would appear to give predominantly the wrong configuration at C(2).[3]

During the course of our work an unexpected[4] change in the regioselectivity of selenoxide elimination was observed. We now report this observation together with details of a synthesis of the (cyclohexenyl)hydroxybutenolide (**15**) which may be useful for non-aromatic β-milbemycin synthesis.



(1)

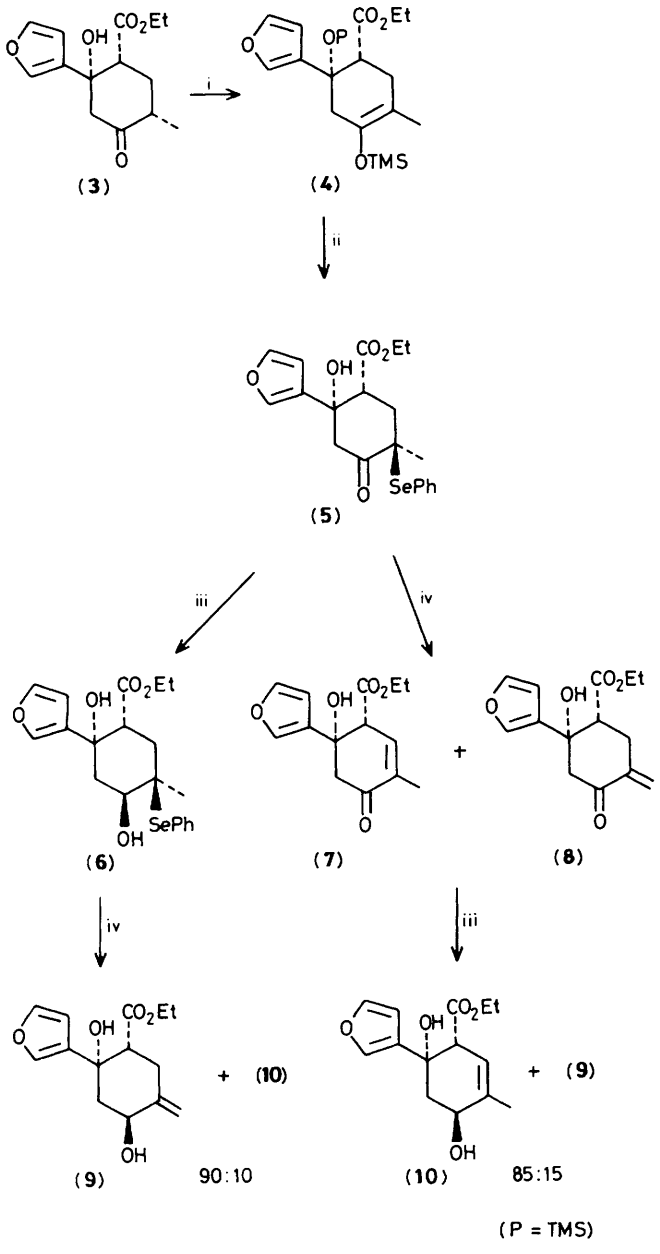


(2)

Regioselective phenylselenylation of hydroxy-ketone (**3**)[2] was achieved using trimethylsilyl trifluoromethanesulphonate (TMSOTf)–triethylamine to generate the enol ether (**4**) which was treated with PhSeCl and NBu^n_4F to provide the tertiary selenide (**5**) as a single diastereoisomer (Scheme 1). Reduction using sodium triacetoxyborohydride gave the 5β-alcohol (**6**) (milbemycin numbering[5]), but this on oxidative elimination did not give the desired cyclohexenol (**10**) efficiently; instead the product of exocyclic elimination, the methylenecyclohexanol (**9**), was the major product, (**9**) : (**10**) = 90 : 10. However, if the oxidative elimination was carried out on the phenylselenoketone (**5**), endocyclic elimination predominated to give more of the cyclohexenone (**7**); (**7**) : (**8**) = 85 : 15. This mixture of ketones was then reduced using sodium triacetoxyborohydride to provide, after chromatography, the desired cyclohexenol (**10**), 70% from (**5**).

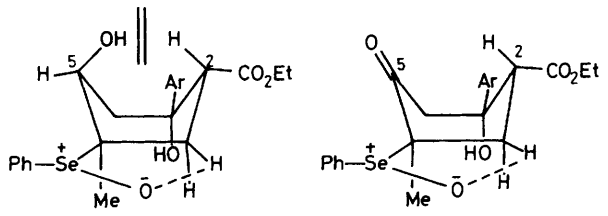
The origin of this change of selenoxide elimination regioselectivity was not investigated. Endocyclic elimination is usually observed for tertiary cyclohexyl selenides.[4] However, unfavourable interaction between the C(5) hydroxy group and H(2) in the boat conformation required for endocyclic elimination from alcohol (**6**) may allow exocyclic elimination to predominate in this case (see Figure 1). When C(5) is sp^2 hybridized, as for the ketone (**5**), this interaction is much reduced and the more usually observed *endo*-mode of elimination is preferred.

To prepare the (cyclohexenyl)hydroxybutenolide (**15**) required for milbemycin synthesis, the silylated furanyl keto-ester (**11**) was condensed with methyl isopropenyl ketone to provide the hydroxycyclohexanone (**12**) which was converted into the cyclohexenediol (**13**) as described above (Scheme 2). Selective monobenzoylation of the secondary C(5) hydroxy group then gave benzoate (**14**) which was oxidized using singlet oxygen to the hydroxybutenolide (**15**).[6]



Scheme 1. *Reagents:* i, TMSOTf, Et_3N (95%); ii, PhSeCl, NBu^n_4F (65%); iii, $NaBH(OAc)_3$ [75% of (**6**), 70% of (**10**) from (**5**)]; iv, H_2O_2, CH_2Cl_2, then for elimination from (**6**) add to CCl_4 heated under reflux (65%).

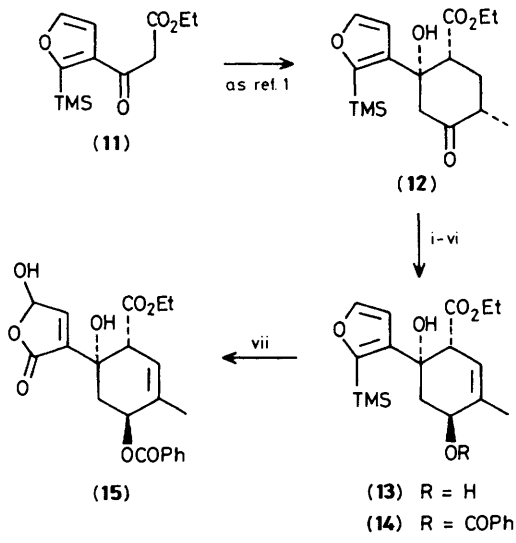
This work establishes a procedure for the introduction of the C(3)–C(4) double bond into milbemycin precursors. The hydroxybutenolide (**15**) may be incorporated into a milbemycin synthesis using the procedures developed for the synthesis of analogue (**2**);[2] alternatively the selenoxide procedure could be used to introduce the double bond at the end of the synthesis.



Boat conformation required for elimination from alcohol (6).

Boat conformation required for elimination from keton (5).

Figure 1.



Scheme 2. *Reagents:* i, TMSOTf, Et_3N (85%); ii, PhSeCl (50%); iii, NBu^n_4F (70%); iv, H_2O_2, CH_2Cl_2 (90%); v, $NaBH(OAc)_3$ (30—50%); vi, PhCOCl, Et_3N, 4-*N*,*N*-dimethylaminopyridine (DMAP) (60%); vii, O_2, *hv*, tetraphenylporphyrin (40% after column, 90% crude).

We thank the S.E.R.C. and I.C.I. Plant Protection Division for support under the CASE scheme (to N. A. S.). We also thank Dr. M. D. Turnbull (I.C.I. Plant Protection) and Dr. H. A. J. Carless (Birkbeck College, London) for helpful discussions, Dr. A. E. Derome and Mrs. E. McGuiness for n.m.r. spectra, and Dr. R. T. Aplin for mass spectra.

Received, 23rd February 1987; Com. 234

References

1 G. Khandekar, G. C. Robinson, N. A. Stacey, P. G. Steel, E. J. Thomas, and S. Vather, *J. Chem. Soc., Chem. Commun.*, 1987, preceding Communication.
2 M. J. Hughes, E. J. Thomas, M. D. Turnbull, R. H. Jones, and R. E. Warner, *J. Chem. Soc., Chem. Commun.*, 1985, 755.
3 B. Fraser-Reid, H. Wolleb, R. Faghih, and J. Barchi, *J. Am. Chem. Soc.*, 1987, **109**, 933.
4 C. Paulmier, 'Selenium Reagents and Intermediates in Organic Synthesis,' Pergamon, Oxford, 1986, p. 134.
5 H. G. Davies and R. H. Green, *Nat. Prod. Rep.*, 1986, **3**, 87.
6 S. Katsumura, K. Hori, S. Fugiwara, and S. Isoe, *Tetrahedron Lett.*, 1985, **26**, 4625.