Tetrahedron Letters, Vol.27, No.1, pp 105-108, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

SYNTHETIC STUDIES TOWARDS THE ACYLTETRONIC ACID IONOPHORE M 139603

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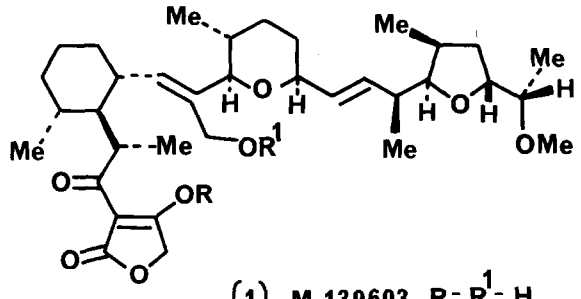
Summary: The synthesis of the optically pure tetrahydrofuran fragment of the acyltetronic acid ionophore M139603 from (S)-(+)-methyl-3- hydroxy-2-methylpropionate is described and its comparison made with authentic material derived from the natural product by degradation.

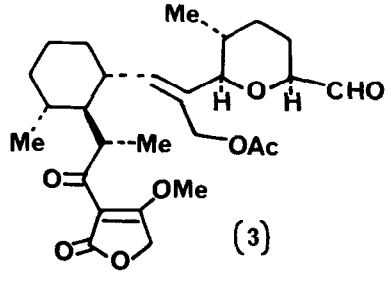
Since the discovery of the novel acyltetronic acid antibiotic M139603 (1) by the ICI group,[1] several papers have appeared describing its structural,[1,2] biosynthetic[3] and metal binding properties.[2,4] Here we report the first synthetic studies in this area.



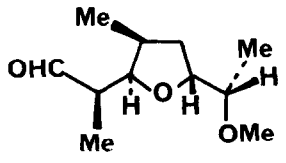
(1) M 139603 R= R^1= H

(2) R = Me R^1 = Ac

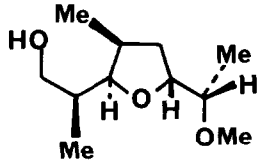
M139603 sodium salt (1) R=Na, R^1=H, was first converted to the substituted derivative † (2) R=Me, R^1 = Ac for degradation work. This was achieved in 80% overall yield by reaction with acetic anhydride in pyridine at room temperature followed by protonation with 20% aqueous phosphoric acid in ethanol/acetone (1:1) and treatment with ethereal diazomethane. Selective ozonolysis of (2) at -78° in CH_2Cl_2 and triphenylphosphine work-up gave the two aldehydes (3) and (4) in 91 and 98% yields respectively. Reduction of (4) with sodium borohydride in methanol at -20°C gave the tetrahydrofuran fragment (5) in 93% yield which is also the target molecule for total synthesis, vide infra.



(3)



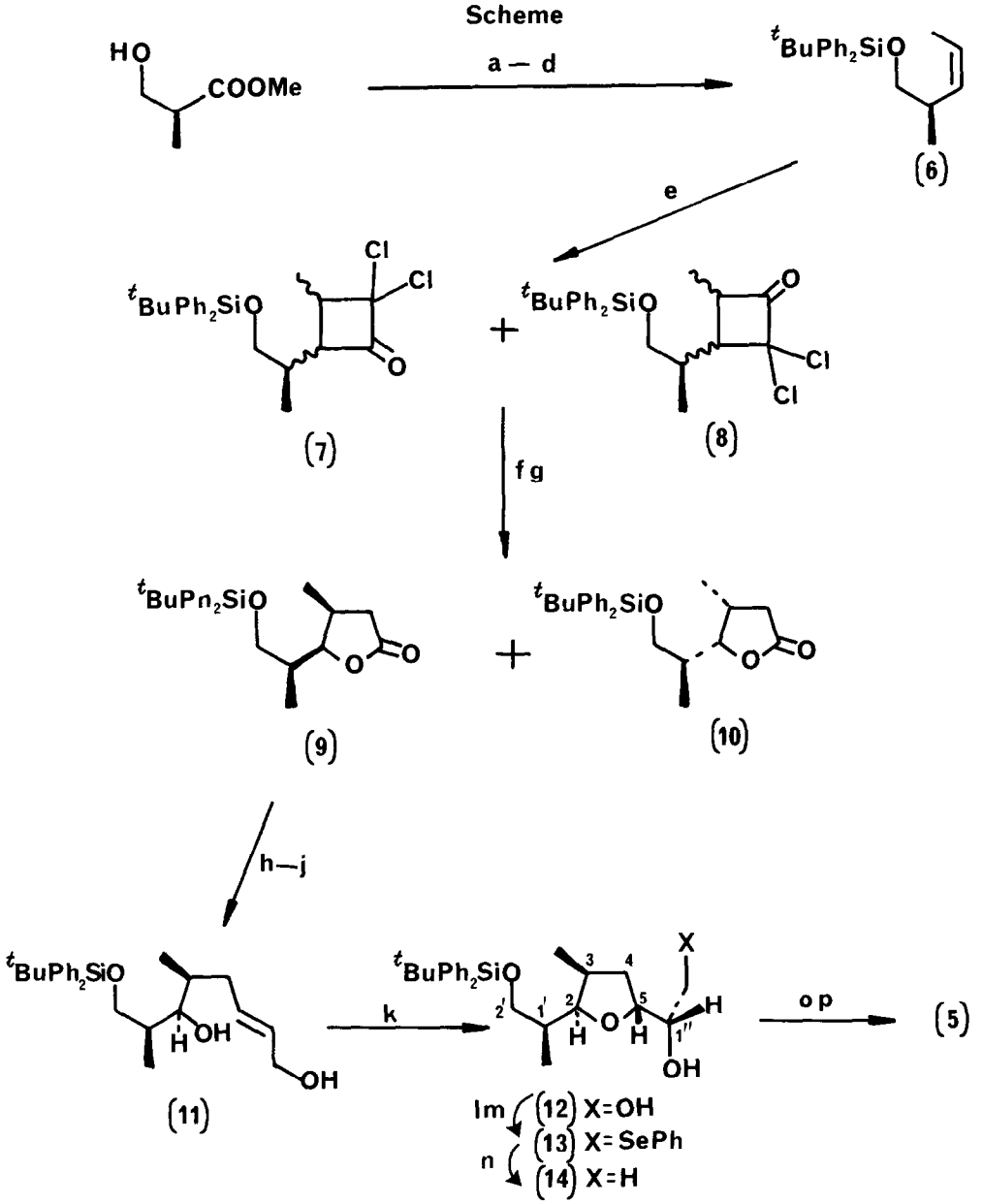
(4)



(5)

(S)-(+)-Methyl-3-hydroxy-2-methylpropionate was converted to the protected cis-alkene (6) in 44% overall yield following standard procedures. The high cis-selectivity in the Wittig reaction for the formation of (6) was obtained by allowing the cooled (-78°C) reaction mixture to warm rapidly to room temperature. The bulky ^{t}butyldiphenylsilyl protecting group in (6) was deliberately chosen to bias the regioselectivity in the next reaction in favour of the required dichloroketene adduct (7) as opposed to the regioisomer (8). Thus slow addition of trichloroacetyl chloride to a refluxing mixture of the cis-alkene (6) and freshly prepared zinc-copper couple in diethyl ether afforded a 75% yield of an unstable 6:1 mixture of adducts (7) and (8). The use of other less bulky substituents, such as thiophenyl, in place of the ^{t}butyldiphenylsilyloxy group in (6) gave poor regiochemical control, typically only a 2:1 ratio in favour of the required isomer. Since (7) and (8) were unstable no effort was made to separate these isomers. Instead they were dechlorinated using the zinc and solid NH_4Cl in THF/methanol method[5Δ] and the major cyclobutanone then oxidised under Baeyer-Villiger conditions to a 77% yield of a separable 1:1 mixture of diastereoisomeric lactones (9) and (10) (Scheme). The lactone (9) was further elaborated by reduction with Dibal in toluene, coupled with carboethoxymethylidenetriphenylphosphorane and reduced with Dibal in THF to the trans-allylic alcohol (11) in 66% overall yield. The use of THF in the last reaction was crucial since attempts to perform the Dibal reduction in toluene led to substantial quantities of cyclic material. In the next phase of the synthesis we planned that the allylic hydroxyl in (10) would permit use of the enantioselective Sharpless epoxidation[6] and that under the reaction conditions spontaneous tetrahydrofuran ring formation would occur.[7] Thus, when (11) was treated with titanium (IV) isopropoxide (2 eq), L-(+)-diethyltartrate (2.4 eq) and ^{t}butylhydroperoxide (5 eq)[††] at -20°C an excellent yield (75%) of the water soluble diol (12) was obtained after a sodium fluoride work-up.[8] Now that the hydroxyl group in (10) had served its purpose as a directing group for the epoxidation it could be removed by reduction to introduce the necessary terminal methyl substituent. This was achieved by conversion of (12) to the primary mesylate and hence to the selenide (13) by displacement with sodium phenylselenide (prepared under ultrasonic conditions)[Φ] in THF in 51% yield. Direct conversion of (12) to (13) using various methods was unsuccessful. Finally, (13) upon rapid treatment with Raney nickel in ether gave (14) (100%) which could be alkylated and deprotected with tetra-n-butylammonium fluoride to the target tetrahydrofuran (5) (72%) (Scheme), $[\alpha]_D^{25}$ + 38.8° (c 5.0, $CHCl_3$); ν_{max} (film) 3450; δ (250 MHz) 0.75 (3H, d, J 7 Hz, CH(Me)CH_2OH), 0.90 (3H, d, J 7 Hz, C-3 CH_3), 1.08 (3H, d, J 6.5 Hz, CH(Me)OMe), 1.63 (1H, dd, J 12.5 and 6.5 Hz, 4-H_α), 1.83 (1H, m, 1'-H), 1.95 (1H, ddd, J 12.5, 9.5, and 7 Hz, 4-H_β), 2.29 (1H, m, from decoupling, J 7, 6.5, and 4 Hz, 3-H), 3.33 (1H, m, 1"-H), 3.36 (3H, s, OMe), 3.50 - 3.67 (4H, m, 2'-H, OH and 2-H), and 3.98 (1H, ddd, J 9.5, 6.5, and 5 Hz, 5-H). This synthetic compound was identical in all respects to that derived earlier by degradation of the natural product.

Scheme



Reagents for Scheme

a) $^{t}BuPh_2SiCl/DMAP/Et_3N$, RT b) Dibal in toluene, -78°C c) $(COCl)_2$, DMSO, 2 eq, -60°C d) $CH_3CH=PPh_3$, -78°C, RT e) Cl_3CCOCl, Zn/Cu, Et_2O, reflux, 5h, f) Zn, NH_4Cl, THF/MeOH, RT, 24h g) H_2O_2 3 eq, HOAc (glacial), 5°C, 8h, h) Dibal in toluene, -78°C i) $Ph_3P=CHCO_2Et$, CH_2Cl_2, 24h j) Dibal in THF, -78°C k) $Ti(O^{i}Pr)_4$ 2 eq, L(+)DET 2.4 eq, $^{t}BuOOH$ 5 eq, -20°C, 6h, l) MsCl, Hünigs base, -30°C m) PhSeNa, THF n) Raney (Ni), ether, 10 min o) NaH, DMPU, MeI, 3h p) n-Bu_4NF, THF, RT.

Additionally this chemical synthesis of (5) unambiguously established the absolute configuration of the natural product about which there was some doubt.[9] Derivatisation of (5) and coupling studies with (3) and other novel aldehydes are presently under investigation.

Acknowledgements

We acknowledge support from the SERC and Pfizer Central Research Sandwich, UK and Coopers Animal Health Ltd. Berkhamsted, for generous supplies of M139603.

Footnotes

† All new compounds gave satisfactory spectral and microanalytical data.

Δ The commonly used Zn/HOAc method was much less successful in this example.

†† Attempted epoxidation of the allylic alcohol (10) under 'standard' Sharpless conditions[6] was unsuccessful.

ϕ S.V. Ley and I. O'Neil, unpublished observations.

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(Received in UK 24 October 1985)