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CHEMICAL TRANSFORMATIONS OF S541 FACTORS (A)-(D): PREPARATION AND REACTIONS OF THE 23-KETONES

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Summary:-

The stereoselectivities observed for the reactions of the ketones (5) and (7) with sodium borohydride, Grignard reagents and methoxylamine are described and X-ray data for the oxime (9) are presented.

The four major metabolites S541 Factors A-D [(1)-(4) respectively] have been isolated from the fermentation broth of *S. thermoarchaensis*.[1,2]

The crystalline 23-ketone (5) mp 213-215 °C was obtained (40-50% yield) by pyridinium dichromate or Swern[3] oxidation of (2). The same oxidation methods were also used to convert the 5-acetates of (1), (3) and (4)[1] into the corresponding 23-ketones [*e.g.* (6)] whereupon de-esterification furnished the required ketols [*e.g.* (7)].

Reduction of the ketone (5) with sodium borohydride (3 eq) in ethanol (r.t., 1h) provided a 2:1 mixture of the natural product (2) and its 23-epimer (11) which were readily separated by silica gel chromatography.[4] When the ketone (5) was treated with the same reducing agent (1.5 eq) in EtOH-Et_2O (1:4) for 24h at room temperature, the major isolated product (44%) was the crystalline Δ^2-derivative (15).[5]

Treatment of the 23-ketone (7) with methyl magnesium iodide (10 eq, Et_2O, r.t., 16h) gave a 19:1 mixture of the epimers (12), (75%) and (13).[4] Clearly the addition of the bulky Grignard reagent to the 23-ketone (7) is highly stereoselective. Reaction of the ketone (7) with trimethylsilylmethylmagnesium chloride was stereospecific furnishing the hydroxysilane (14) as the only reaction product (75% yield). The silane (14) was smoothly converted (70%) into the 23-methylene derivative (8) by heating with sulphuric acid in tetrahydrofuran (0.3% w/v acid, Δ, 6h). This two-step Peterson olefination sequence proved to be the method of choice for the preparation of (8); the alternative Wittig procedure on the ketone (7) afforded compound (8) in markedly inferior yield.

Treatment of the ketone (7) with methoxylamine hydrochloride (2 eq) and NaOAc (2 eq) in MeOH-H_2O (5:1) for *ca.* 1h at ambient temperature provided stereospecifically the crystalline 23(E)-methoxyimine (9) [*ca.* 80% yield, $[\alpha]_D^{22}$ + 132° (*c* 1.23, $CHCl_3$)].

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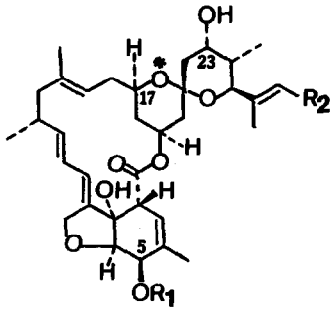
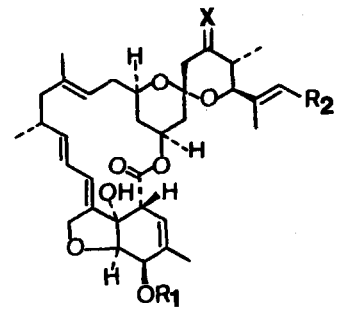
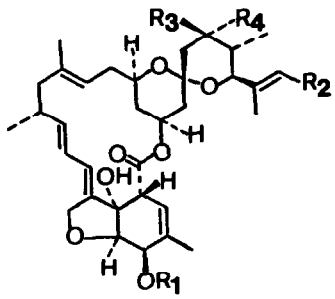


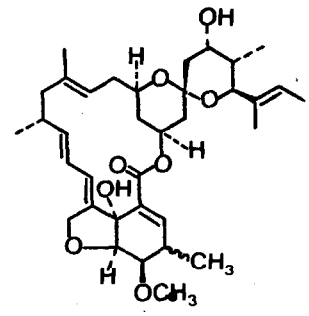
(1) R_1 = H, R_2 = Me
(2) R_1 = Me, R_2 = Me
(3) R_1 = H, R_2 = Et
(4) R_1 = H, R_2 = Pr^i



(5) R_1 = R_2 = Me, X = O
(6) R_1 = Ac, R_2 = Me, X = O
(7) R_1 = H, R_2 = Pr^i, X = O
(8) R_1 = H, R_2 = Pr^i, X = CH_2
(9) R_1 = H, R_2 = Pr^i, X = (E)NOMe
(10) R_1 = H, R_2 = Pr^i, X = (Z)NOMe



(11) R_1 = R_2 = Me, R_3 = OH, R_4 = H
(12) R_1 = H, R_2 = Pr^i, R_3 = Me, R_4 = OH
(13) R_1 = H, R_2 = Pr^i, R_3 = OH, R_4 = Me
(14) R_1 = H, R_2 = Pr^i, R_3 = CH_2SiMe_3, R_4 = OH



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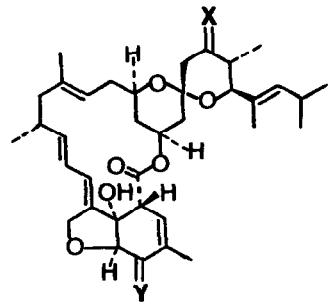

(16) X = Y = O
(17) X = O, Y = NOMe
(18) X = NOMe, Y = O
(19) X = H, α-OEt, Y = O
(20) X = H, α-OEt, Y = H, Me

The structure of (9) was confirmed by X-ray methods (Figure).[6] The (E)-oxime was partially isomerised by heating with 2-mercaptobenzthiazole in boiling toluene to give the 23(Z)-isomer (10). Oxidation of the ketol (7) with activated manganese dioxide (r.t., 3½h) afforded the crystalline 5,23-diketone (16) [mp 190 °C (dec.)]. Controlled oxidation of (4) provided the corresponding 5-keto derivative which was then transformed by oximation and pyridinium dichromate oxidation into the 23-keto-5-methoxyimine (17). When the diketone (16) was reacted with methoxylamine hydrochloride (1.06 eq) in MeOH under the usual conditions, the 23(E)-methoxyimine (18) was obtained in 54% yield; the isomeric compound (17) was formed in only trace amounts.

Manganese dioxide oxidation of 23-alkoxy derivatives of (4) afforded the corresponding 5-ketones. Exposure of the ketone (19) to MeMgI (1.01 eq, Et_2O, 0.5 °C) for 1h gave a 1:1 mixture of 5-methyl epimers (20). Such mild reaction conditions contrast sharply with those (*vide supra*) required for addition of MeMgI to the 23-keto group of (7), reflecting the greater accessibility of the α,β-unsaturated ketone to nucleophilic attack. The preferential functionalisation of the 23-ketone moiety of the diketone (16) with methoxylamine appears anomalous at first sight. However reaction of the ketone group with the amine should take place from the less hindered side to give initially, the hemiaminal (21) (SCHEME). Stabilization of this tetrahedral intermediate should be facilitated by the 17-oxygen atom (*) which can now form a hydrogen bond with the pendant hydroxyl group. Such bonding has been postulated in closely related compounds[1] and should stabilize the intermediate prior to dehydration. The stereochemistry adopted by the 23-oxime after the loss of a molecule of water from (21) is probably controlled by the adjacent equatorial methyl group at C-24.

All compounds described herein have been compared to Ivermectin for antiparasitic activity by the standard mouse/*N. dubius* model.[7] Preliminary results are encouraging and indicate that the 23-methylene derivative (8), the 23(E)-methoxyimine (9) and the 23-keto-5-methoxyimine (17) are as potent in this test as Ivermectin.

Acknowledgements

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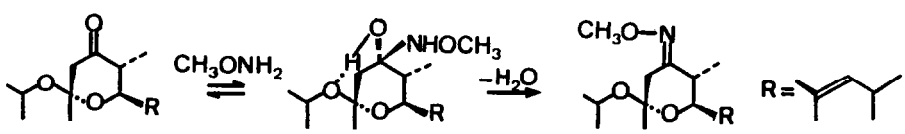

(21)

SCHEME

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1. M.V.J. Ramsay, S.M. Roberts, J.C. Russell, A.H. Shingler, A.M.Z. Slawin, D.R. Sutherland, E.P. Tiley and D.J. Williams, *Tetrahedron Lett.*, 1987, *28*, 5353.
2. G.T. Carter, J.A. Nietsche and D.B. Borders, *J. Chem. Soc., Chem. Commun.*, 1987, 402; the Cyanamid workers labelled compounds (1), (2) and (4) LL-F28249 β, γ and α respectively.
3. This reaction also provides small quantities (*ca.* 6%) of the 23-keto, 7-methylthiomethyl ether, presumably formed through capture of the $MeS{=}CH_2^+$ ion by the tertiary hydroxyl group at C-7.
4. As expected, compounds with an hydroxyl group at C-23 which are able to hydrogen-bond with the 17α-oxygen atom [*e.g.* (2) and (12)] are always less polar (higher Rf) than their corresponding 23-epimers [*i.e.* (11) and (13)]. The 23-OH groups of the natural products (1)-(4) give rise to a sharp singlet (δ *ca.* 3.8-3.6) in their p.m.r. spectra (250 Hz, $CDCl_3$). The compound (12) also shows such a signal at δ 4.04 whereas the corresponding resonance for (13) is at higher field. As expected, the methyl group at C-23 in compound (13), shielded by the directed lone pair of electrons of the 17α-oxygen atom, appears at a higher field (δ 1.29) than the corresponding methyl group (δ 1.58) of epimer (12). The 23-OH group of (14) is observed as a sharp singlet at δ 3.99.
5. B. Fraser-Reid, H. Wolleb, R. Fraghih and J. Barchi, Jr., *J. Am. Chem. Soc.*, 1987, *109*, 933; S. Hanessian, D. Dube and P.J. Hodges, *ibid*, 7063.
6. Crystal data for (9): $C_{37}H_{53}NO_8$, M = 639.8, orthorhombic, a = 9.598(3), b = 16.299(8), c = 24.201(8)Å, U = 3786Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.12g cm^{-3}, μ(Cu-K_α) = 6 cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically to give R = 0.110, R_ω = 0.120 for 1690 independent observed reflections [$|F_o| \geq 3\sigma(|F_o|)$, $\theta \leq 58^o$]. The crystals were of poor quality, and consequently the refinement was of limited accuracy. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1988.
7. N.S. Baker, *Proc. Book. Amer. Vet. Med. Assoc.*, 91st Annual Meeting, 1954, pp. 185-192.

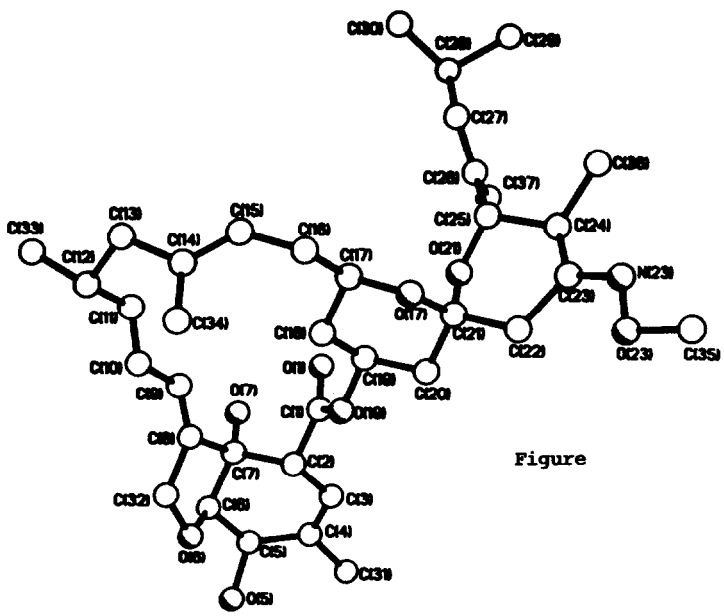

Figure The molecular structure of (9). Neither of the two hydroxy protons (those on O(5) and O(7) were located. There are two significant intramolecular distances: O(5)...O(6) 2.67, O(7)...O(1) 2.74Å.

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