Tetrahedron Letters,Vol.29,No.30,pp 3667-3670,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE SYNTHESIS OF THE SPIROKETAL UNIT OF MILBEMYCINS AND 22,23-DIHYDROAVERMECTINS

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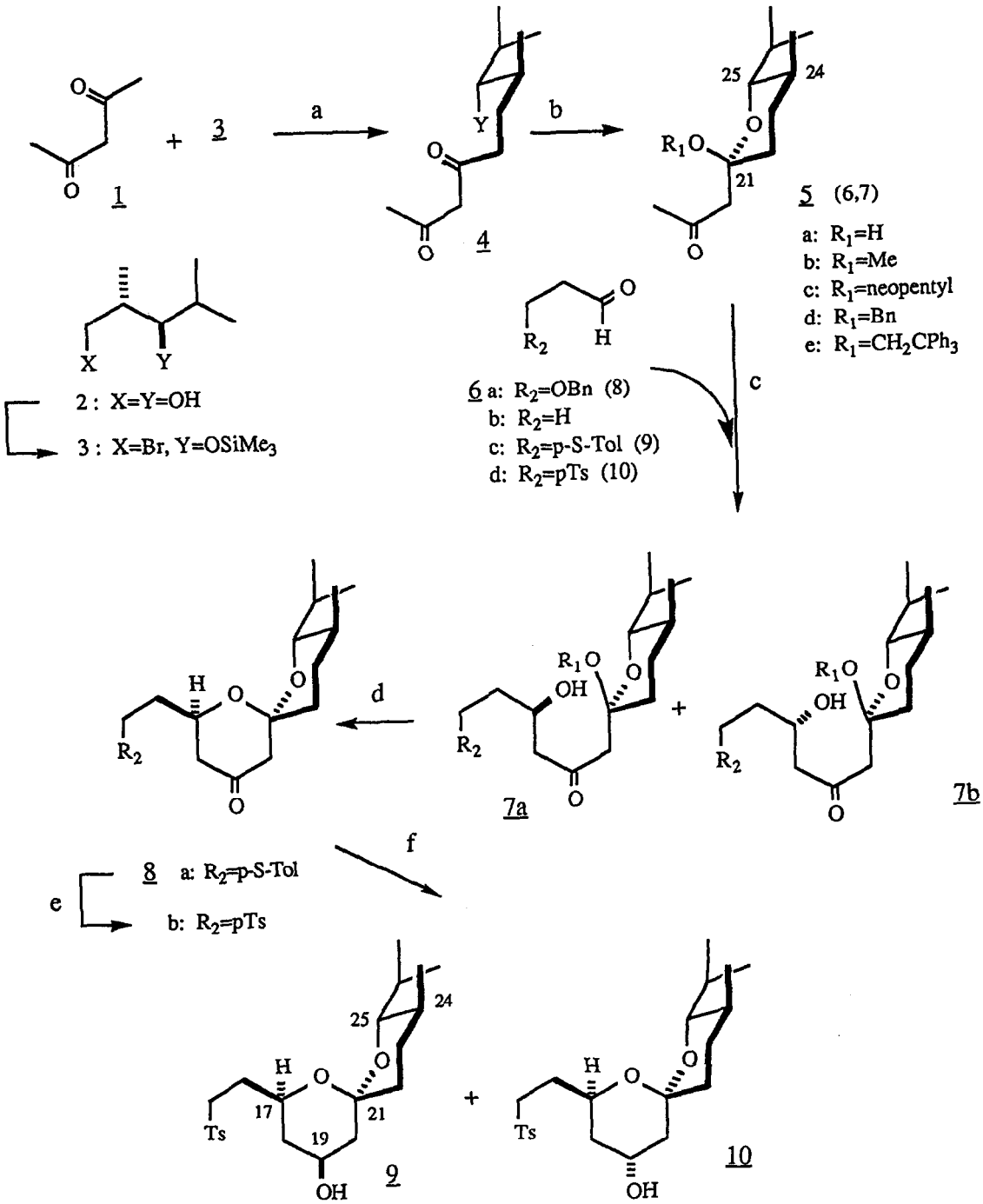
Summary : The crystalline spiroketal sub-unit 9 has been synthesized in ten steps from the 2S,3R-diol 2 using a remote partial stereocontrol for the aldolisation step.

The unique biological activity of milbemycins and avermectins as well as their challenging structural features (1) led us to develop a program towards their synthesis (2). Numerous routes to the spiroketal moiety of these molecules have been reported (3). Our approach of the spiroketal system of milbemycins and 22,23-dihydroavermectins (b series) involved a stepwise condensation at both ends of 2,4-pentanedione 1 as shown on the Scheme (2a). This letter presents an enantioselective synthesis of the subunit 9 using a remote stereocontrol for the crucial aldolisation reaction. Previous work had shown the possibility of controlling the chiral center at C-21 (4) by use of a suitable synthon affording the correct stereochemistry at C-24 and C-25. Control of the C-17 center of 9 was next investigated.

Considering that the lithium cation of the kinetic enolate of 5 is likely to be coordinated with both oxygen atoms of the ketal function, it can be reasonably expected that the diastereofacial approach on the enolate might depend on the relative bulk of the R^1O- group and tetrahydropyranyl unit (O-C21 (to) C25) of 5 (5). A series of racemic ketals 5b to 5e with R^1 groups of increasing bulkiness was therefore tested in the aldolisation reaction with aldehydes 6a to 6d (see Table). The yields were always good (75-90%). The triphenylethylether 5e led to an improved diastereoselectivity with aldehydes 6a, b and c (entries 4,6,9) but unfortunately not with 6d (entries 12 to 14). The lack of stereoselectivity in the latter case might involve the bulk or the coordinating power of the sulfonyl group of 6d. Moreover a rapid aldol equilibration seemed to take place with this very reactive aldehyde (entries 12,14).

The asymmetric synthesis of 9 was therefore carried out as shown on the scheme using the phenylthioaldehyde 6c as electrophile for the aldolisation reaction with the optically active triphenylethylketal 5e (entry 9).



Scheme a) LDA-HMPT, 4.5 eq, -78°C then 3, -78°C to 20°C b) THF/H_2O/acetic acid, 20°C c) 5b to 5c, see footnote table d) HCl, $CHCl_3$ e) m-CPBA, CH_2Cl_2, 0°C f) $LiAlH_4$, benzene, 70

The known (2S,3R)-diol 2 (11) was first converted into the trimethylsilyloxybromide 3, $[\alpha]_D^{20} = -39°$ (c 1.5, $CHCl_3$) in three steps according to reference (2a) : tosylation, bromination and silylation, in 85% overall yield. Alkylation of the dianion of 2,4-pentanedione 1 with 3 afforded the crude diketone 4 (Y = $OSiMe_3$, enol-ketone mixture) which was readily hydrolysed to give after chromatography the pure hemiketal 5a which crystalized on drying, m.p. = 52-54°C, $[\alpha]_D^{20} = +122°$ (c 2.0, $CHCl_3$), 75% yield. Protection of 5a with 2,2,2-triphenylethanol (12) gave the crystalline ketal 5e in 85% yield m.p. = 142-145°C, $[\alpha]_D^{20} = +122°$ (c 2.0, $CHCl_3$). Condensation of this ketal with the phenylthioaldehyde 6c gave a mixture of 7a and 7b (7a/7b = 72/28 from HPLC analysis of an aliquot, see table). Direct acidic work-up of the reaction mixture followed by oxidation of the thioether function of crude 8a (R^2 = p-S-Tol) and chromatography gave, after crystallization, the pure spirotetrahydropyrone 8b in 55% yield from 5e, m.p. = 134-136°C, $[\alpha]_D^{20} = +48°$ (c 2.2, $CHCl_3$). Final reduction of the C-19 carbonyl function of 8b with $LiAlH_4$ (2a) in benzene furnished, after chromatography, the expected spiroketal 9 in 68% yield, m.p. = 141-142°C, $[\alpha]_D^{20} = +47°$ (c 2.0, $CHCl_3$) together with 17% of the C-19 epimeric spiroketal 10, m.p. = 129-131°C, $[\alpha]_D^{20} = +45°$ (c 2.0, $CHCl_3$).

The optically active spiroketal 9 has been thus prepared from the readily available (2S,3R)-diol 2 in ten steps in a c.a. 20% overall yield.

Entry	Aldehyde	Ketal	Diastereoselectivity[b]	
			7a	7b
1	6a	5b	47	53
2	6a	5c	56	44
3	6a	5d	60	40
4	6a	5e	71	29
5	6b	5b	47	53
6	6b	5b	66	34
7	6c	5b	45	55
8	6c	5d	61	39
9	6c	5e	72	28
10	6c[c]	5e	64	36
11	6d	5b	43	57
12	6d	5e	44	56
13	6d[c]	5e	55	45
14	6d[d]	5e	53	47

Table Condensation of aldehydes 6 with enolates of 5 [a]

[a] Unless otherwise stated the aldehyde in THF at -78°C was added to the preformed lithium enolate of 5 (1.2 eq LDA, THF, -78°C, 30 min). After 1h at -78°C the reaction mixture was hydrolysed with saturated aqueous NH_4Cl and extracted with ether.
[b] Deduced from averaged HPLC peak area (silica-gel : isooctane/isopropylether and isooctane/ethyl acetate mixtures). Assignement of the configuration at C-17 was made after acidic cyclisation of 7, the natural isomer 7a giving one single product 8 whereas 7b gave at least two bicyclic products (13).
[c] The aldehyde was treated with one equivalent of $ZnCl_2$ before addition to lithium enolate.
[d] The reaction mixture was quenched after 30 seconds.

Financial help from the C.N.R.S. (U.A. 1110) is gratefully acknowledged. We thank Dr. Hervé du Penhoat, C. Derouet and V. Michon for N.M.R. spectra.

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(4) Except for the C_7 synthons 2 and 3 all carbon numbering refers to the avermectin system.

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(6) All new compounds exhibited ^1H NMR, IR, MS spectra and elemental analysis in full agreement with their proposed structure. See also ref. (2a).

(7) All ketals except 5b were prepared by reaction of hemiketal 5a with the corresponding alcohol in benzene/4Å molecular sieves/5% camphor sulfonic acid. The yields ranged from 70 to 85% after flash-chromatography using $NaHCO_3$ treated silica-gel. Ketal 5b was directly prepared in methanol/ 4 Å molecular sieves/camphor sulfonic acid.

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(Received in France 21 June 1988)