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Anti Aldol Reactions of α -Alkoxymethyl Ketones: Application to the Total Synthesis of (+)-Restricticin.

Ian Paterson* and Thorsten Nowak

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Abstract: The antifungal agent (+)-restricticin (1) was prepared in 12 steps from ketone (S)-8. The key steps are (i) the boron-mediated anti aldol reaction of (S)-8 with 9 to give 13 and (ii) the cyclisation reaction $4 \rightarrow 15$. Copyright © 1996 Elsevier Science Ltd

Restricticin (1) is a member of a novel class of potent antifungal natural products,^{1–3} independently isolated in three different laboratories. It acts by inhibiting the cytochrome P_{450} lanosterol C-14 demethylase in the steroid biosynthetic pathway.² This mode of action is shared with various clinical antifungal agents (*e.g.*, Fluconazole, Ketoconazole), resulting in considerable interest in restricticin and its analogues⁴ for the potential treatment of systemic fungal diseases.



Full structural characterisation of restricticin was first reported by groups at Merck¹ and Roche,² where the stereochemistry was assigned by NMR and circular dichroism studies. The structure is based on a highly substituted tetrahydropyran ring bearing four contiguous stereocentres with a glycine ester and conjugated (E,E,E)-triene sidechains. The closely related antifungal agent lanomycin (2), which has a shorter polyene sidechain, has also been isolated.³ The synthesis of restricticin⁵ and its biologically inactive precursor, restrictinol (3),^{5,6} starting from L-glucose and L-mannose have recently been described. We now report a conceptually different synthesis⁷ of (+)-restricticin, which exploits some asymmetric aldol chemistry developed in our laboratory.^{8,9} Our retrosynthetic analysis for restrictinol (Scheme 1) is based on formation of the tetrahydropyran ring from a stereochemically defined, open-chain precursor, as in 4, followed by Wittig-type introduction of the triene unit. We have already shown that the *E*-enol borinates 5 obtained from the chiral α -alkoxymethyl ketones 6 (P = Bn or Me) are effective reagents for *anti* aldol additions to aldehydes,^{8,9} leading to formation of the corresponding 1,2-*anti*-2,4-*anti* adducts 7 with high diastereoselectivity. This chemistry was previously employed in the stereocontrolled synthesis of a polyol segment of the immunosuppressant macrolide rapamycin.⁸ In the present case, the stereotetrad 4 should be easily accessible by using the *anti* aldol reaction of the related ketone (*S*)-8 with the enal 9, followed by a suitable reduction step. Activation of the primary hydroxyl in 4 to regioselective displacement by the allylic hydroxyl should then secure the ether linkage in 3. Our synthesis of the antifungal agent (+)-restricticin, which proceeded along these lines, is summarised in Scheme 2 and outlined below.¹⁰

The synthesis of the ketone 8, with benzyl and *para*-methoxybenzyl protected hydroxyl groups, started out from commercial (S) methyl 2-methyl-3-hydroxypropionate (10) by modification of the method employed in the enantiomeric series for formation of 6 (P = Bn).⁸ After Weinreb amide formation¹¹ and PMB protection to give 11, treatment with benzyloxymethyl lithium (formed from Sn \rightarrow Li exchange on BnOCH₂SnBu₃) provided 8, $[\alpha]_D^{20} + 17.2^\circ$ (c 0.97, CHCl₃), in 62% overall yield. Using our standard conditions,^{8,9a,b} a boron-mediated *anti* aldol reaction between 8 and (*E*)-2-methyl-3-benzyloxybutenal (9)¹² proceeded with high diastereoselectivity (\geq 98% ds). Thus ketone 8 was enolised by ^cHex₂BCl/Et₃N in Et₂O,¹³ to generate the *E*enol borinate 12, followed by addition of the aldehyde 9. This led to isolation of the pure *anti* aldol isomer 13, $[\alpha]_D^{20} - 5.0^\circ$ (c 0.76, CHCl₃), in 78% yield, where HPLC analysis of the crude aldol product indicated that less than 2% of other isomers was produced.

Hydroxyl-directed reduction¹⁴ of **12** using Me₄NBH(OAc)₃ gave the 1,3-*anti* diol **14** with 86% ds, which was followed by deprotection *via* the acetonide to give the triol **4** in 71% overall yield. The key cyclisation step, **4** \rightarrow **15**, was best performed by selective generation of the primary triflate **16** with Tf₂O in the presence of DBU (CH₂Cl₂, -78 °C) followed, in turn, by *in situ* ether formation. This gave the tetrahydropyran **15**,¹⁰ [α]_D²⁰ +42.8° (*c* 0.57, CHCl₃), in 71% yield,¹⁵ which was next converted into the corresponding methyl ether **17** in 2 steps (66%). Selective oxidation of the primary, allylic hydroxyl over the more hindered secondary hydroxyl in **17** to give **18** (88%) was smoothly achieved using the Dess-Martin periodinane.¹⁶ Introduction of the sensitive triene side-chain was now required. Wittig reaction between the ylide derived from the unsaturated phosphonium salt **19** and aldehyde **18** led to formation of a mixture of (*E*,*E*,*E*)-restrictionl (**3**) and its (*E*,*Z*,*E*)-isomer **20** in 90% yield, which were separated by HPLC. The final conversion of **3** into restricticin paralleled that previously reported.⁵ Restrictinol was first converted into its *N*-TEOC glycine ester by reaction with **21**, followed by TBAF deprotection. This gave (+)-restricticin, which had ¹H and ¹³C NMR data in full accord with that reported for the authentic compound.^{1,2a} The specific rotation recorded for **1**, $[\alpha]_D^{20}$ +91.6° (*c* 0.2, MeOH), was in reasonable agreement with that reported in the literature, $[\alpha]_D^{20}$ +100° (*c* 0.2, MeOH).^{2a}

In conclusion, the antifungal agent (+)-restricticin has been synthesised in 15 steps with 3.1% overall yield starting from the chiral ester (S)-10. The aldol reactions of the α -alkoxymethyl ketones 6 and 8 (together with variations on the hydroxyl protecting groups employed) should prove to be useful in the stereocontrolled synthesis of other highly oxygenated natural products of polyketide origin.⁸



Scheme 2: (a) MeONHMe.HCl, Me₃Al, CH₂Cl₂, 20 °C, 18 h; (b) PMBOC(CCl₃)=NH, TfOH (1 mol%), Et₂O, 0 \rightarrow 20 °C, 3.5 h; (c) BnOCH₂SnBu₃, ⁿBuLi, THF, -78 °C, 20 min; (d) ^cHex₂BCl, Et₃N, Et₂O, 0 °C, 2 h; 9, -78 \rightarrow -16 °C, 16 h; H₂O₂, MeOH, pH7 buffer; (e) Me₄NBH(OAc)₃, AcOH/MeCN (1:1), -16 °C, 48 h; (f) (MeO)₂CMe₂, PPTS, CH₂Cl₂, 20 °C, 18 h; (g) DDQ, CH₂Cl₂, pH7 buffer, 48 h; (h) HCl, MeOH, 20 °C, 18 h; (i) Tf₂O, DBU, CH₂Cl₂, -78 °C, 10 min; (j) NaH, MeI, DMF, 20 °C, 1.5 h; (k) 4,4'-di-*tert*-butylbiphenyl, Li, THF, -78 °C, 10 min; (l) Dess-Martin periodinane, CH₂Cl₂, 0 °C, 2 h; (m) 19, ⁿBuLi, THF, -78 \rightarrow 0 °C, 2 h; (n) 21, DCC, DMAP, CH₂Cl₂, 20 °C, 2 h; (o) TBAF, THF, 40 °C, 2 h.

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- All new compounds gave spectroscopic data in agreement with the assigned structures. 15 had ¹H NMR δ(500 MHz, CDCl₃)
 7.18-7.37 (10H, m), 5.87 (1H, t, J = 6.2 Hz), 4.53 and 4.51 (2H, ABq, J = 14.0 Hz), 4.46 and 4.44 (2H, ABq, J = 9.0 Hz),
 4.44 (2H, ABq, J = 9.0 Hz), 4.13 (2H, d, J = 6.2 Hz), 3.76 (1H, dd, J = 5.2, 8.6 Hz), 3.74 (1H, dd, J = 1.6, 11.6 Hz), 3.59 (1H, dd, J = 2.4, 11.6 Hz), 3.57 (1H, d, J = 9.3 Hz), 3.38 (1H, t, J = 9.3 Hz), 2.35 (1H, bs), 2.05-2.15 (1H, m), 1.77 (3H, s), 1.22 (3H, d, J = 7.1 Hz); ¹³C NMR δ(100.6 MHz, CDCl₃) 138.3, 138.0, 136.3, 128.6, 128.3, 128.0, 127.6, 127.5, 127.1, 85.7, 77.6, 74.4, 74.2, 72.3, 71.1, 66.4, 35.3, 12.5, 10.9; HRMS (CI, NH₃) [M + NH₄]⁺ found 400.2488, C₂₄H₃₄O₄N requires 400.2487.
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