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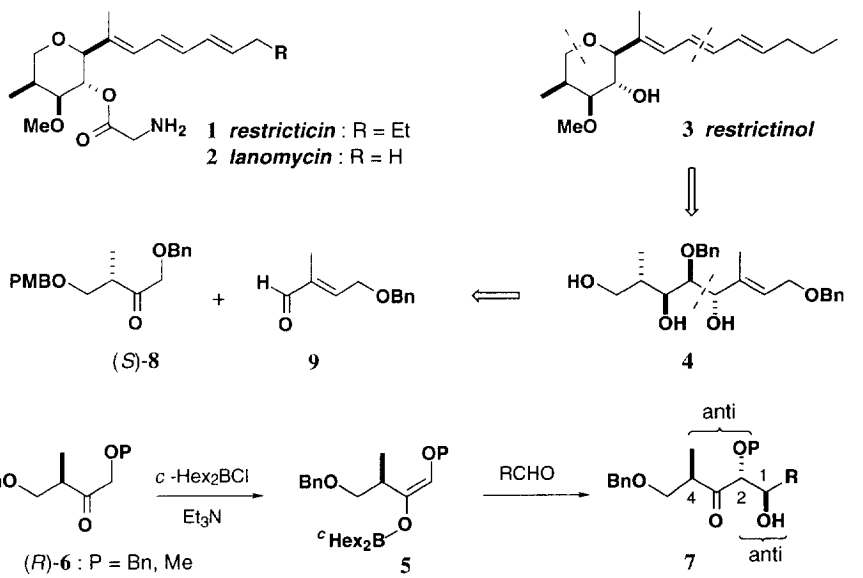
Anti Aldol Reactions of α-Alkoxymethyl Ketones: Application to the Total Synthesis of (+)-Restricticin.

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** → **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 analogues[4] for the potential treatment of systemic fungal diseases.



Scheme 1

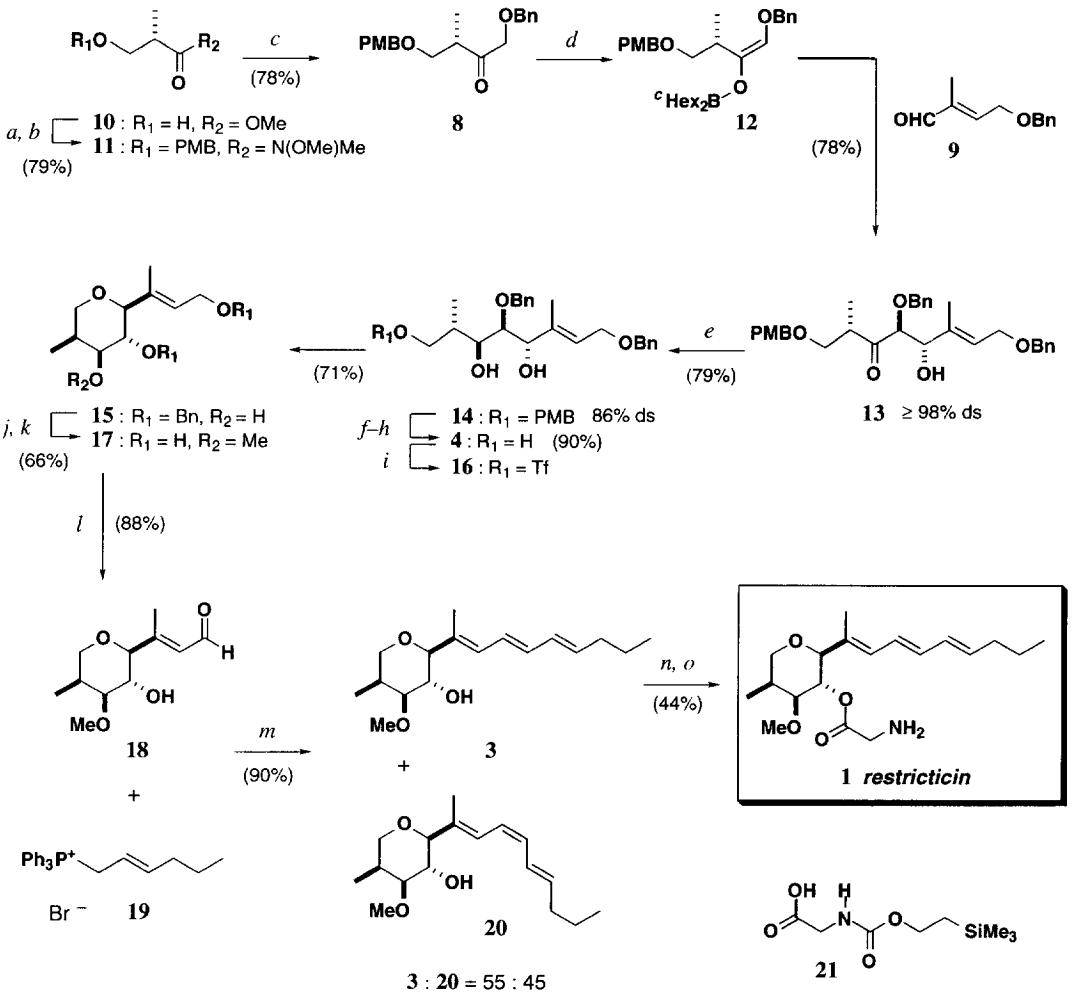
Full structural characterisation of restricticin was first reported by groups at Merck[1] and Roche,[2] where the stereochemistry was assigned by NMR and circular dichroism studies. The structure is based on a highly substituted tetrahydropyran ring bearing four contiguous stereocentres with a glycine 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 restricticin[5] 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 synthesis[7] 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 formation[11] and PMB protection to give **11**, treatment with benzyloxymethyl lithium (formed from Sn → Li exchange on $BnOCH_2SnBu_3$) provided **8**, $[\alpha]_D^{20}$ +17.2° (*c* 0.97, $CHCl_3$), 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 (≥98% ds). Thus ketone **8** was enolised by $^cHex_2BCl$ / Et_3N in Et_2O,[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° (*c* 0.76, $CHCl_3$), in 78% yield, where HPLC analysis of the crude aldol product indicated that less than 2% of other isomers was produced.

Hydroxyl-directed reduction[14] of **12** using $Me_4NBH(OAc)_3$ 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** → **15**, was best performed by selective generation of the primary triflate **16** with Tf_2O in the presence of DBU (CH_2Cl_2, –78 °C) followed, in turn, by *in situ* ether formation. This gave the tetrahydropyran **15**,[10] $[\alpha]_D^{20}$ +42.8° (*c* 0.57, $CHCl_3$), 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*)-restrictinol (**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 ^{13}C 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, Me_3Al, CH_2Cl_2, 20 °C, 18 h; (*b*) PMBOC(CCl_3)=NH, TfOH (1 mol%), Et_2O, 0 → 20 °C, 3.5 h; (*c*) $BnOCH_2SnBu_3$, ^nBuLi, THF, −78 °C, 20 min; (*d*) $^cHex_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; **9**, −78 → −16 °C, 16 h; H_2O_2, MeOH, pH7 buffer; (*e*) $Me_4NBH(OAc)_3$, AcOH/MeCN (1:1), −16 °C, 48 h; (*f*) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 20 °C, 18 h; (*g*) DDQ, CH_2Cl_2, pH7 buffer, 48 h; (*h*) HCl, MeOH, 20 °C, 18 h; (*i*) Tf_2O, DBU, CH_2Cl_2, −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, CH_2Cl_2, 0 °C, 2 h; (*m*) **19**, ^nBuLi, THF, −78 → 0 °C, 2 h; (*n*) **21**, DCC, DMAP, CH_2Cl_2, 20 °C, 2 h; (*o*) TBAF, THF, 40 °C, 2 h.

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10. All new compounds gave spectroscopic data in agreement with the assigned structures. **15** had ^{1}H NMR δ(500 MHz, $CDCl_3$) 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); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 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, NH_3) $[M + NH_4]^+$ found 400.2488, $C_{24}H_{34}O_4N$ requires 400.2487.

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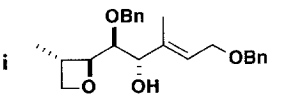
15. The oxetane **i** was obtained as a minor product (10-15%) in this cyclisation step.



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