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Synthetic studies on the phorboxazoles: a short synthesis of an *epi*-C23 tetrahydropyran core

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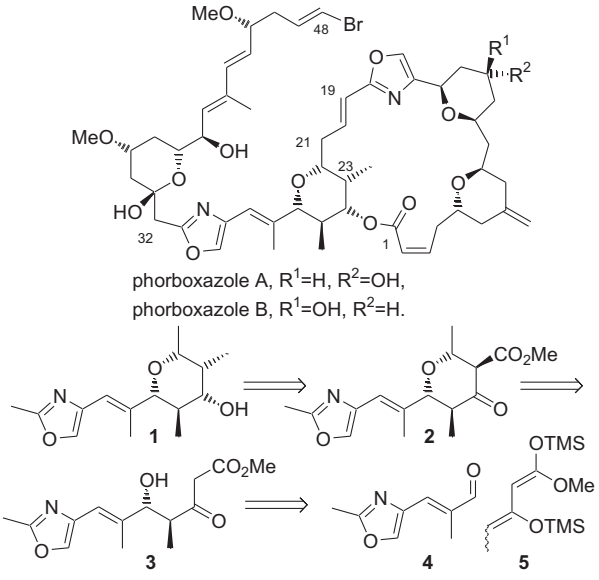
ABSTRACT

Studies on the synthesis of the anticancer natural products, the phorboxazoles, have led to the synthesis of the C21–C32 penta-substituted tetrahydropyran core which is epimeric to the natural product at C23. The synthesis was achieved in only seven linear steps. The key steps were the use of a Masamune–Abiko *anti*-aldol reaction, the formation of a dihydropyran precursor molecule by the use of a new 'Maitland–Japp-like' cyclisation, and a highly diastereoselective reductive alkylation of the dihydropyran double bond, to generate the corresponding tetrahydropyran ring in an excellent yield.

The phorboxazoles A and B (Scheme 1) are marine natural products which were isolated and characterized by Searle and Molinski in 1995,[1] and have been shown to exhibit potent anticancer activity;[1–3] since this initial report, the complex molecular architecture and potent anticancer activity of the phorboxazoles have made them attractive targets for synthesis by many groups. To date there have been six total syntheses of phorboxazole A[4] and three total syntheses of phorboxazole B.[5] In addition to these completed studies, groups have also targeted fragments of both of these molecules; particularly the C21–C32 penta-substituted tetrahydropyran core,[6] which is common to both. With our interest in the development of new methodologies for the synthesis of tetrahydropyran rings, we too were attracted to the synthesis of these natural products.

Our initial studies focused on the synthesis of the C21–C32 tetrahydropyran core applying the disconnections which we had used previously for the successful formation of tetrahydropyrans via the Maitland–Japp reaction[7] (Scheme 1). Realizing that **1** could arise from retrosynthetic precursor **2** by decarboxylation, axial alkylation of the kinetic enolate and reduction of the ketone confirmed **2** as our initial target. We envisaged that **2** could be formed from ester **3** by tandem Knoevenagel/Michael reaction, and that **3** would arise from an asymmetric aldol reaction of the *bis*-silylenol ether **5** on known aldehyde **4**.[8]

Our first route was concerned with the asymmetric aldol addition of **5** to known aldehyde **4**, by the application of the Soriente procedure.[9] However, it quickly became apparent that the extension of the Soriente methodology to the addition of **5** to aldehyde **4** (Scheme 2) was less than satisfactory. The primary cause for concern was the formation of the undesired *syn* diastereomer as the major product in a low yield, and in moderate enantiomeric excess only.



Scheme 1. Phorboxazoles A and B. Initial retrosynthetic strategy for the C21–C32 unit.

Given the failure of the Soriente protocol, which would have enabled us to investigate a one-pot catalytic asymmetric variation of our previously reported Maitland–Japp reaction, we were forced to examine the use of chiral auxiliaries for the installation of the desired *anti*-stereochemistry. To this end we turned our attention to the Masamune–Abiko auxiliary **6**, which has been used

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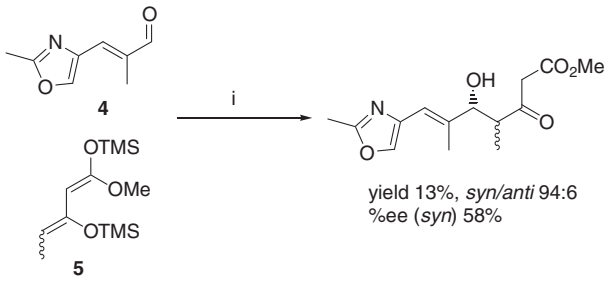
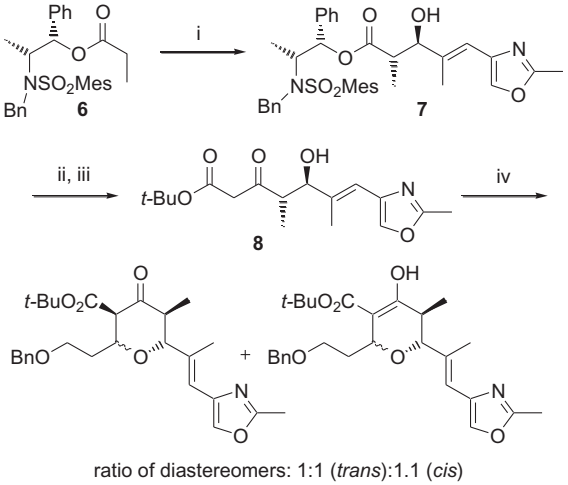


Scheme 2. Reagents and conditions: (i) Ti(O*i*-Pr)$_4$ (8 mol %), (*R*)-BINOL (8 mol %), 4 Å MS, THF, −78 °C to rt.

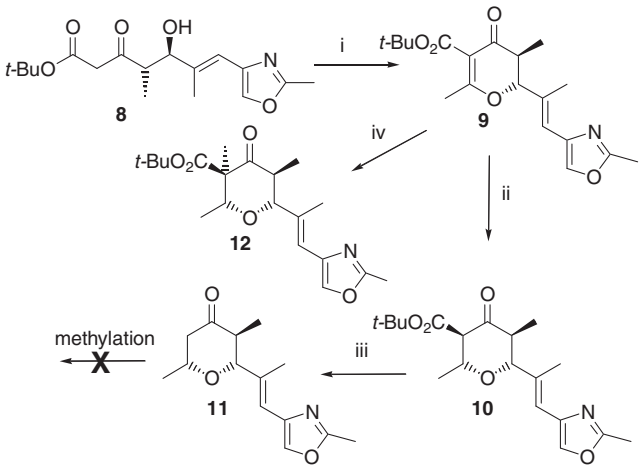
successfully in the asymmetric synthesis of *anti*-aldol products.[10] *Anti*-aldol reaction of the Masamune–Abiko auxiliary **6** with aldehyde **4**, promoted by (*c*-hex)$_2$BOTf and Et$_3$N, generated smoothly the aldol adduct **7** in a 91% yield, as a 14:1 mixture of diastereomers in which the desired *anti*-adduct predominated. The auxiliary, which was resistant to direct cleavage via Claisen condensation, was cleaved by the action of NaOMe to provide the methyl ester in 83% yield, which was in turn converted into β-ketoester **8** by a Claisen condensation with *t*-butyl acetate, which proceeded in 75% yield (Scheme 3).

With **8** in hand, we were now in a position to attempt the Lewis acid-catalyzed Maitland–Japp cyclisation with an aldehyde to form the penta-substituted tetrahydropyran ring. Frustratingly, no matter which conditions were used, the reaction returned a complex mixture of 2,6-*cis*/*trans* diastereomers, as well as interconverting keto/enol tautomers. In each case, the desired 2,6-*cis* diastereomer was the minor product in the mixture (~1:2 in the best set of conditions Scheme 3). Furthermore, a difficult separation of these diastereomers and tautomers furnished insufficient quantities of material to advance the synthesis,[11] so an alternative strategy was sought.

We decided to turn our attention to the dihydropyran-forming version of the Maitland–Japp reaction, which has recently been developed in our group[11] (Scheme 4). In our variation, β-ketoester **8** was treated with the dimethyl acetal of dimethyl acetamide, to yield dihydropyran **9** in 74% yield. Dihydropyran **9** was reduced with L-Selectride to tetrahydropyran **10** which was isolated as a single diastereomer in 71% yield. It was also found that an enolate which resulted from the reduction of **9** could be trapped with MeI



Scheme 3. Reagents and conditions: (i) Et$_3$N, (*c*-hex)$_2$BOTf, CH_2Cl_2, −78 °C, 3 h, then **4**, 91%; (ii) NaOMe, MeOH, 0 °C, 83%; (iii) LDA, *t*-BuOAc, THF, −30 °C, 75%; (iv) Sc(OTf)$_3$, BnO(CH$_2$)$_2$CHO, CH_2Cl_2, 68%.

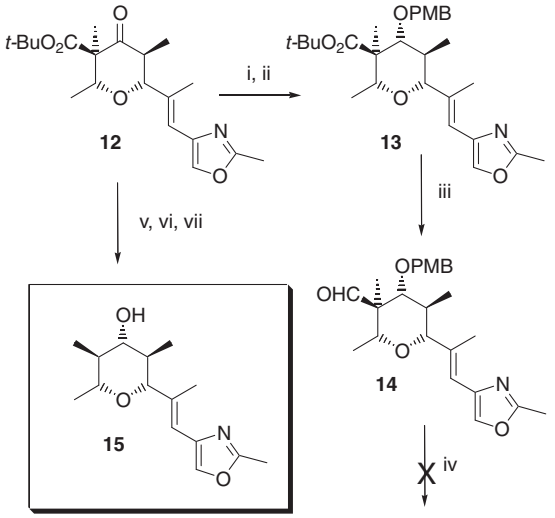


Scheme 4. Reagents and conditions: (i) MeC(OMe)$_2$NMe$_2$, PhMe, rt, 74%; (ii) L-Selectride, THF, −78 °C, 71%; (iii) microwave, DMF, H_2O, 93%; (iv) L-Selectride, THF, −78 °C, then MeI, rt, 75%.

to yield **12**, which has the desired axial methyl group present at the C23 position of the phorboxazoles. It is remarkable that only a single diastereomer was formed in this reaction. We attribute this selectivity to pseudo-axial attack of hydride on the double bond of **9** and then alkylation of the enolate from a pseudo-axial trajectory. The newly installed quaternary stereocentre prevents epimerisation at the 2-position as it blocks the retro-Michael reaction from occurring, which was responsible for the erosion of diastereoselectivity seen in our original Maitland–Japp reaction.[7c,d]

In order to continue with our synthesis as planned (Scheme 4), tetrahydropyran **10** was heated in a microwave oven[12] (160 °C, 10 min), which initiated the removal of the *t*-butyl ester and decarboxylation. We envisaged that kinetic deprotonation of **11** with LDA and a kinetic quench with MeI would furnish a ketone precursor to **1**. However, we found that despite investigating a range of deprotonation/methylation conditions we never observed any products resulting from alkylation. In all cases the starting material was returned unchanged.

These results led us to examine the use of **12** as a precursor to the synthesis of **1**. We rationalized that **12** had the desired



Scheme 5. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, −78 °C; (ii) KH, THF, PMBCl, 0 °C, 69% over two steps; (iii) DIBAL-H, PhMe, −78 °C, 72%; (iv) Wilkinson's catalyst, PhMe, reflux; (v) TFA, CH_2Cl_2; (vi) PhH, reflux, 93% over two steps; (vii) $NaBH_4$, MeOH, 0 °C, 60%.

axial methyl group at C23 in place, we should be able to effect the stereospecific removal of the ester functionality, via reduction to the aldehyde and Wilkinson's catalyst-mediated deformylation.[13] In order to examine this possibility the ketone carbonyl in **12** was reduced with DIBAL-H to generate the equatorial alcohol as the major product (4:1 ratio) which was protected as the PMB ether **13**. Compound **13** was then treated again with DIBAL-H to furnish the desired aldehyde **14** in 72% yield (Scheme 5). However, when **14** was treated with a stoichiometric amount of Wilkinson's catalyst in PhMe under reflux no reaction was observed. We assume that co-ordination of the catalyst to the nitrogen in the oxazole ring may be at the root of this lack of reactivity. Given our inability to remove the extra carbonyl function at C23 with retention of stereochemistry, it was decided to decarboxylate **12** in any case. Decarboxylation was achieved by treatment of ester **12** with TFA followed by heating under reflux in PhMe. It is worth noting that these conditions are somewhat more forcing than those which are usually required for the removal of a *t*-butyl ester and subsequent decarboxylation, and we believe that this is due to the presence of the C23 methyl group. The resulting ketone was reduced with $NaBH_4$ in MeOH to give a 2:3 ratio of alcohol **15** to the epimeric alcohol in a combined 60% yield. This final $NaBH_4$ reduction completes the synthesis of the C21–C32 tetrahydropyran core of the phorboxazoles, being epimeric at C23.

In conclusion we have synthesized in seven linear steps the C21–C32 core of the phorboxazoles being epimeric at C23. We have demonstrated the use of a new dihydropyran-forming version of the Maitland–Japp reaction and a stereoselective reductive methylation strategy for the construction of diastereomerically pure tetrahydropyrans containing quaternary stereocentres. Alternative investigations of a synthesis of the C21–C32 fragment of the phorboxazoles, with the correct stereochemistry at C23, are underway and will be reported in due course.

Acknowledgments

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