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The Asymmetric Maitland–Japp Reaction and Its Application to the Construction of the C1–C19 *Bis*-pyran Unit of Phorboxazole B

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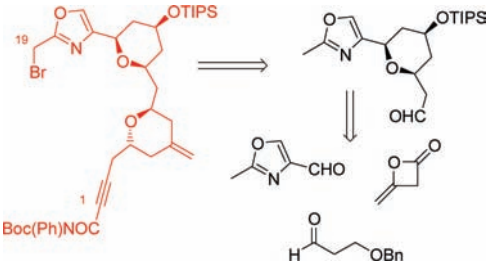
ABSTRACT



The synthesis of the C1–C19 *bis*-pyran unit of phorboxazole B has been achieved. The key pyran rings were constructed by means of an asymmetric Maitland–Japp reaction and a second Maitland–Japp resolution/cyclization reaction. The longest linear sequence was 14 steps, and the C1–C19 *bis*-pyran unit was formed in an impressive 10.4% yield.

The tetrahydropyran (THP) unit is present in a vast array of structurally complex and biologically active natural products. In recent years there has been renewed interest in developing new and more efficient routes to THPs in order to expedite the syntheses of these natural products.[1] Recent research in our group has focused on the development of a one-pot, multicomponent route to highly substituted THPs, and we recently achieved this *via* a THP-forming strategy based on the long-forgotten Maitland–Japp reaction.[2] However, in this earlier work, the goal of developing a general asymmetric Maitland–Japp reaction eluded us. More recent work on a version of the Maitland–Japp reaction which utilized diketene as a nucleophile (Scheme 1) provided us with the opportunity to rectify this deficiency. In the 'diketene Maitland–Japp' reaction the mono-γ-titanium enolate of a β-ketoester is formed by the nucleophilic ring-opening of diketene *via* ligand transfer from the activating Lewis acid. This 'nucleophile generated enolate' can then add to an aldehyde or imine to generate aldol[2e] or Mannich-like[3] products respectively. Initially either $TiCl_4$ or $Ti(iOPr)_4$ were used as a Lewis acid.

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(1) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–53.
(2) (a) Japp, F. R.; Maitland, W. *J. Chem. Soc.* **1904**, *85*, 1473–89. (b) Clarke, P. A.; Martin, W. H. C. *Org. Lett.* **2002**, *4*, 4527–9. (c) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2005**, 1061–3. (d) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Org. Biomol. Chem.* **2005**, *3*, 3551–63. (e) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438–40.
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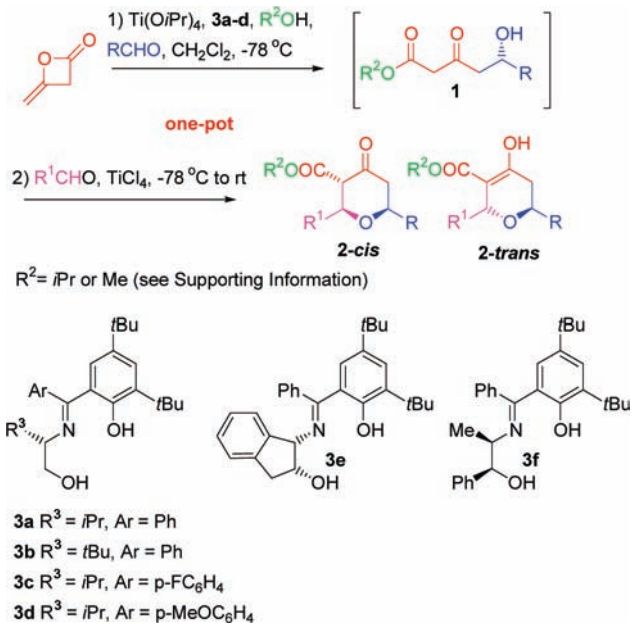
Scheme 1. Asymmetric Diketene Maitland−Japp Reaction



However, this generated carboxylic acids or isopropyl esters as products respectively, which we considered to be less useful for the synthesis of THPs. We noted, however, that the addition of an external alcohol nucleophile, such as methanol, to the enolate generating reaction enabled the formation of more synthetically useful methyl esters without detriment to the yield of the reaction. The use of Ti(*i*OPr)$_4$ as a Lewis acid also provided us with the opportunity to screen a number of chiral ligands and to monitor the effect these had on the enantioselectivity of the reaction. As we had previously shown that the enantiomeric integrity of the aldol product was not eroded by the Maitland−Japp cyclization conditions,[2d] we were hopeful that an asymmetric one-pot, multicomponent THP-forming reaction could be developed.

After a number of different ligand types failed we were pleased to find that the addition of a chiral Schiff's base ligand of type **3** to the initial enolate-forming/aldehyde addition reaction generated the desired δ-hydroxy-β-ketoester in an enantioenriched form (Scheme 1).[4] As can be seen from Table 1 a range of aromatic, aliphatic, branched aliphatic, and heteroatom-containing aldehydes could all be used in the reaction (entries a, d, e, and h respectivly). The enantioselectivities in general tended to be higher for aromatic aldehydes than aliphatic aldehydes (entries c and d). While the size of the substituent at the ligand's stereogenic center did not seem to have much effect on the enantioselectivity of the reaction (entries a and f), substitution on the ligand's nonphenolic aryl group did increase the enantioselectivity slightly (entries h, i, and j).

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Table 1. Asymmetric Addition of Diketene to Aldehydes

entry	ligand	RCHO	**1** yield (%)[a]	**1** % ee[b]
a	**3a**	Ph	44	82
b		*p*-MeOC$_6$H$_4$	35	64
c		*p*-NO$_2$C$_6$H$_4$	51	85
d		Pr	47	71
e		*i*Pr	47	59
f	**3b**	Ph	45	80
g		CH$_2$CH=CHMe	45	75
h		CH$_2$OBn	51	80
i	**3c**	CH$_2$OBn	47	87
j	**3d**	CH$_2$OBn	52	86
k	**3e**	CH$_2$OBn	47	71
l	**3f**	CH$_2$OBn	61	71[c]

[a] Isolated yield after 72 h. [b] Enantioselectivities were determined either by ^{1}H NMR shift reagent experiments with tris[3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato] europium(III) or by reduction to the *anti*-diol and chiral HPLC analysis. See Supporting Information for details. [c] ***ent*-1** was formed.

Inverting the sense of the stereocenters on the imine nitrogen resulted in the opposite enantiomer of the δ-hydroxy-β-ketoester being formed (entry l). In cases where the δ-hydroxy-β-ketoester was cyclized to a THP and the THP was crystalline, recrystallization increased the enantiopurity of the THP to >95% ee.[2d] Encouraged by the development of an asymmetric Maitland−Japp reaction and by the observation that the enantioselectivities of the resultant THPs could be enhanced by recrystallization, it was decided to attempt to apply this asymmetric Maitland−Japp reaction to the synthesis of the C1−C19 *bis*-pyran unit of the phorboxazoles.

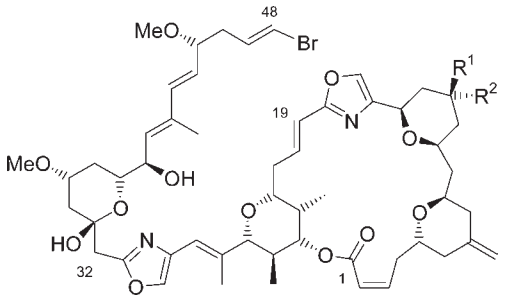

Figure 1. Phorboxazole A, **4**: R^1 = H, R^2 = OH; phorboxazole B, **5**: R^1 = OH, R^2 = H.

In 1995, Searle and Molinski reported the isolation of phorboxazoles A and B (Figure 1), C13 epimers, from the marine sponge *Phorbas* sp. endemic to the western coast of Australia.[5] These natural products have become a synthetic target with great interest due to their potent anticancer, antifungal,[5,6] and antibiotic[7] activity. In fact, these

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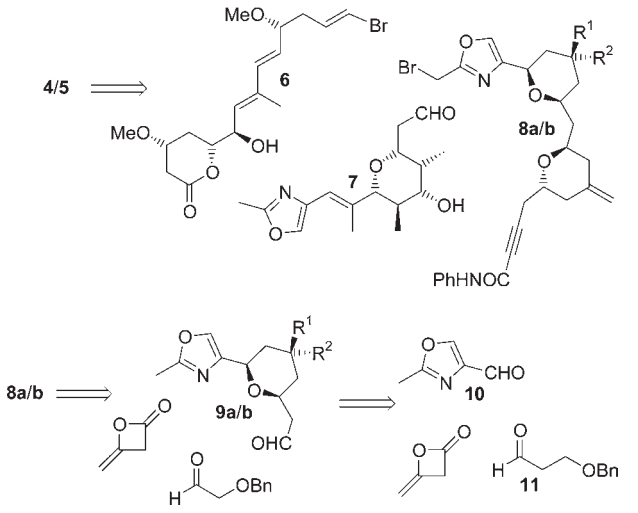
Scheme 2. Retrosynthetic Analysis of the *Bis*-pyran Units of the Phorboxazoles

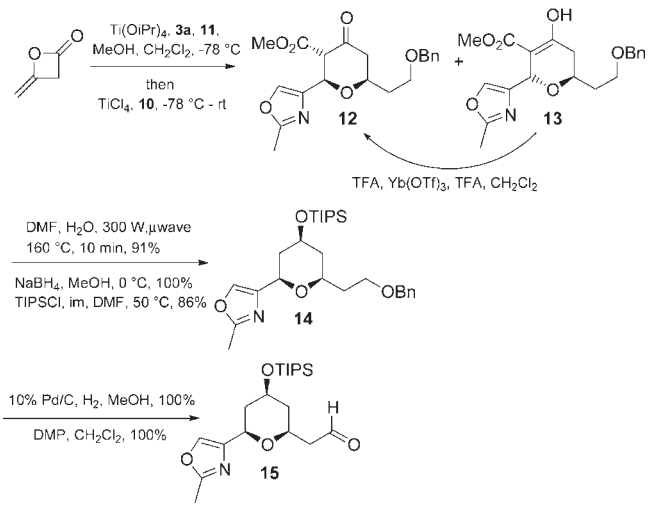


compounds exhibit extraordinary cytotoxic activity ($GI_{50} < 8 \times 10^{-10}$ M) against the entire panel of human tumor cell lines held at the National Cancer Institute. Together with spongistatins,[8] phorboxazoles are the most potent naturally occurring cytotoxic agents yet discovered. Furthermore, due to restricted access to the sponge, total synthesis is the solution to the phorboxazoles' limited availability problem.[9]

The phorboxazole skeleton consists of six rings including two 2,4-disubstituted oxazoles and four tetrahydropyran (THP) units, as well as 15 stereogenic centers organized into a macrolide lactone (C1−C26) and a side chain substructure (C27−C46). Not surprisingly, the novel architecture combined with the impressive bioactivity has attracted wide attention in the synthetic community.[7,9−12]

As such we were attracted to the possibility that our methodology could be used to construct the THP rings of the phorboxazoles in an expedient manner. To this end a retrosynthetic plan was developed for the synthesis of the C1−C19 *bis*-pyran fragment of phorboxazole B (Scheme 2).

Scheme 3. Synthesis of the First Tetrahydropyran **15**



Our synthesis of the C1−C19 fragment of the phorboxazoles began with an asymmetric Maitland−Japp reaction of diketene with aldehyde **11** as the first aldehyde and oxazole aldehyde **10** as the second aldehyde cyclization partner (Scheme 3). This generated a mixture of **12** and **13** in 52% and 27% yields respectively, with an enantiomeric excess of 73%. We have shown that the keto-*cis* and enol-*trans* forms of the THPs generated in the Maitland−Japp reaction are in equilibrium with each other under Lewis acidic conditions,[2c,d,13] and so we were able to separate **12** from **13** and re-equilibrate **13** to a 2:1 mixture of **12**:**13** by use of $Yb(OTf)_3$ in CH_2Cl_2. In this way the yield of **12** was increased to 70% after one re-equilibration with no loss of its enantiomeric integrity. Tetrahydropyran-4-one **12** was decarboxylated under microwave conditions, the ketone was reduced with $NaBH_4$ to afford the stereochemistry required for the synthesis of **5**, and the free hydroxyl group protected as a TIPS ether to yield **14**. The benzyl ether of **14** was removed with H_2 over 10% Pd/C and the primary alcohol oxidized with Dess−Martin periodinane to generate aldehyde **15**, which we hoped would be a suitable

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(12) For syntheses of the *bis*-pyran fragments which have not yet resulted in the report of a completed synthesis, see: (a) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905–14. (b) Greer, P. B.; Donaldson, W. A. *Tetrahedron* **2002**, *58*, 6009–18. (c) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749–54. (d) Yadav, J. S.; Rajaiah, G. *Synlett* **2004**, 1537–40. (e) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026–38. (f) Vitale, J. P.; Wolckenhauer, S. A.; Do, N. M.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 3255–58. (g) Yadav, J. S.; Prakash, S. J.; Gangadhar, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2722–28. (h) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 6874–77.

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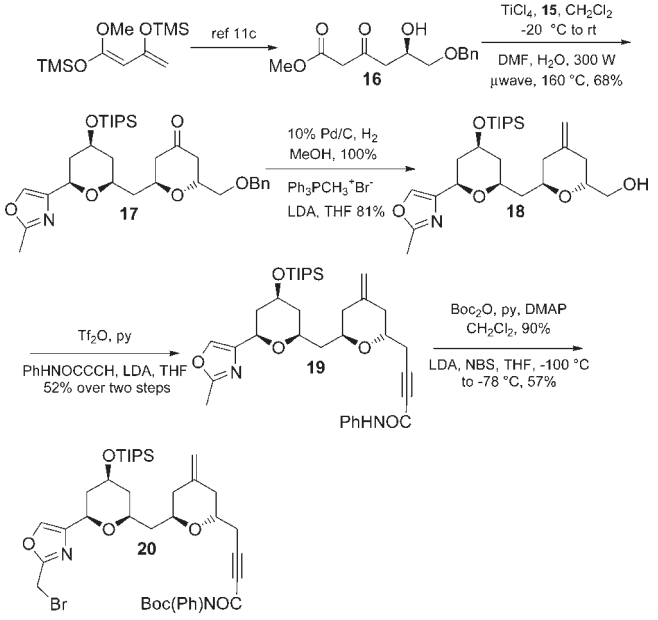
substrate for the formation of the second THP unit *via* the Maitland−Japp reaction.

Unfortunately, none of the THPs (**12** to **15**) were crystalline and so we were unable to use recrystallization to increase the enantiomeric excess of **15** before attempting the second Maitland−Japp reaction. Additionally, the best asymmetric Maitland−Japp reaction with benzyloxy acetaldehyde generated product in 87% ee which would mean that such a Maitland−Japp reaction would result in a complex mixture of multiple diastereomers in both enantiomeric series, requiring separation. As this was not an attractive proposition we decided to react **15** (73% ee) with a δ-hydroxy-β-ketoester **16** of enantiomeric purity and then to separate the two diastereomers which would be formed in about a 7.7:1 ratio. It was envisaged that this first example of a resolving Maitland−Japp reaction could be achieved by the use of Evans' Cu(pybox) catalyzed addition of Chan's diene to benzyloxy acetaldehyde.[11c] Pleasingly, this would also be in keeping with our earlier work on the Maitland−Japp reaction which utilized Chan's diene as a nucleophile instead of diketene.[2c,d,13]

Scheme 4. Synthesis of the C1−C19 *Bis*-pyran Unit **20**



Thus our synthesis of the C1−C19 fragment of **5** continued (Scheme 4) with the Evans Cu(*R*, *R*-pybox) catalyzed addition of Chan's diene to benzyloxy acetaldehyde, giving **16** in 90% yield and with a 99% ee. The δ-hydroxy-β-ketoester **16** was subjected to our tandem Maitland−Japp cyclization protocol using **15** (73% ee) as the aldehyde partner. The ^{1}H NMR of the crude reaction mixture was rather complex at this stage, so the mixture of diastereomers was subjected to microwave mediated decarboxylation. Pleasingly, however, flash column chromatographic purification resulted in the isolation of **17** in 68% yield, 99% ee (actually 84% yield based on the 73% ee of aldehyde **15**) and some of the diastereomer resulting from the minor enantiomer of **15** in 8% yield. This demonstrates that the Maitland−Japp reaction can be used not only to form stereochemically complex *bis*-THP units but also an efficient method for the constructive resolution of a starting aldehdye, efficiently generating the complex *bis*-THP unit as a single enantiomer and in excellent yield. Removal of the benzyl group of **17** and Wittig olefination generated alcohol **18**, which was converted to the triflate and displaced with the dianion of *N*-phenyl propynamide,[11c] to give **19**. The relatively acidic amide NH was protected with a Boc-group, and then the oxazole's methyl group was brominated by the formation of the anion with LDA at −78 °C and treatment with NBS. This yielded the C1−C19 *bis*-pyran fragment of phorboxazole B **20**, with functionality at either end to allow for coupling to the other fragments of the natural product.

In summary we have developed a one-pot, multicomponent asymmetric version of the Maitland−Japp reaction and applied it to the synthesis of the C1−C19 fragment **20** of phorboxazole B **5**. The longest linear sequence was 14 steps, and the overall yield was calculated to be 10.4% which compares favorably to the previously reported syntheses of this fragment.[10−12] The success of our strategy has spurred us on to attempt a total synthesis of phorboxazole B **5**, and this shall be reported in due course.

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Supporting Information Available. Full experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR of all new compounds is included. This material is available free of charge via the Internet at http://pubs.acs.org.