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Synthesis of the C20−C32 Tetrahydropyran Core of the Phorboxazoles and the C22 Epimer via a Stereodivergent Michael Reaction

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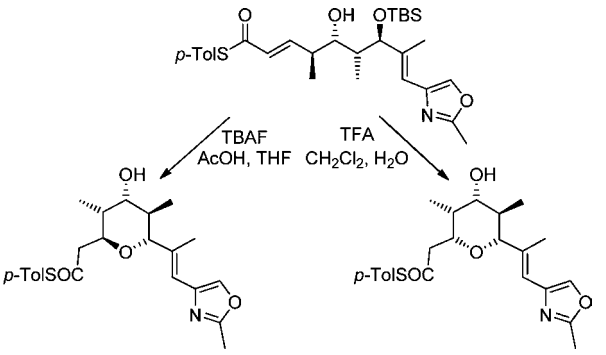
ABSTRACT



A stereoselective synthesis of the C20−C32 tetrahydropyran core of the phorboxazoles has been achieved in only seven steps and in a 31% overall yield. The C22 epimer was also synthesized. The key step was a silyl ether deprotection/oxy-Michael cyclization. When this step was conducted under Brønsted acid conditions, the C20−C32 core was formed with the desired 2,6-*cis*-stereochemistry. However, when the silyl ether deprotection/oxy-Michael cyclization was conducted under fluoride conditions buffered with acetic acid, the C22 epimer of the core was the sole product.

Since their isolation and characterization by Searle and Molinski in 1995, the phorboxazole natural products[1] (Scheme 1) have been the subject of intense synthetic study. This is in part due to their challenging molecular architecture which contains four differently substituted tetrahydropyran (THP) rings, two oxazole rings, seven alkene units, and 15 stereogenic centers. It is also due to their subnanomolar ($GI_{50} < 8 \times 10^{-10}$ M) activity against the entire range of human tumor cell lines held by the NIH. Due to the scarcity of these molecules from the natural source, the only way to realistically provide enough material for a full biological analysis is via an efficient total synthesis. To date, there have been seven successful total syntheses of phorboxazole A[2] and three of phorboxazole B.[3] In addition to these syntheses, several groups have targeted the C20−C32 penta-substituted THP core which is common to both structures.[4]

Over the past few years, we have spent some effort developing new and efficient routes, based on the Maitland−Japp reaction, for the synthesis of functionalized THP rings (Scheme 2).[5,6]

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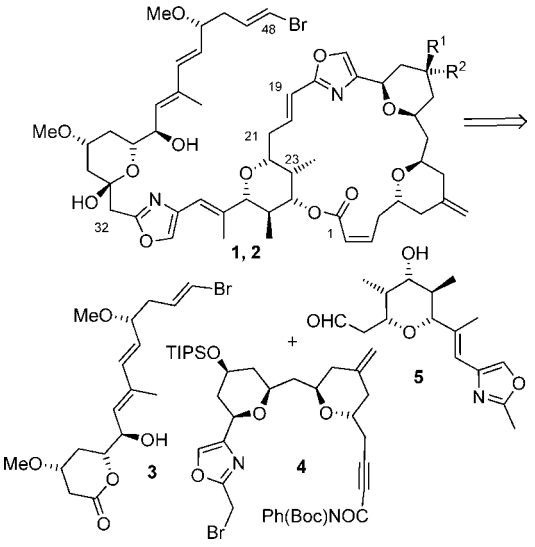
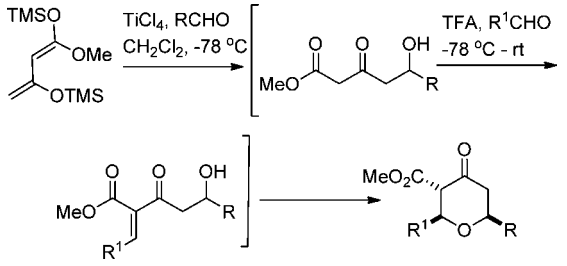
Scheme 1. Retrosynthetic Analysis of the Phorboxazoles: Phorboxazole A (**1**), R^1 = H, R^2 = OH; Phorboxazole B (**2**), R^1 = OH, R^2 = H



Scheme 2. Maitland–Japp Reaction



We considered phorboxazole a target which would provide a formidable test of our methodology. Our strategy was to break phorboxazole into three fragments **3**, **4**, and **5** of approximately equal complexity (Scheme 1). In the case of the C1–C19 2,6-*cis*- and 2,6-*trans*-bispyran fragment **4** of phorboxazole B, our asymmetric diketene Maitland–Japp reaction[5e] enabled us to complete an efficient synthesis.[7] This was later improved by our development of a highly asymmetric Chan's diene Maitland–Japp reaction.[5f] However, when we turned our attention to the synthesis of the C20–C32 core **5**, the Maitland–Japp chemistry was not able to provide access to diastereomerically pure THPs in sufficient quantities to continue the synthesis.[8] Therefore, an alternative strategy for the synthesis of this fragment was required.

The key ring-forming step in the Maitland–Japp reaction was a 6-*endo*-trig oxy-Michael reaction. We decided to investigate the use of the alternative 6-*exo*-trig reaction.[9] However, there are drawbacks with the use of 6-*exo*-trig reactions for the formation of *cis*-THP rings, in that many of these cyclizations produce the 2,6-*trans*-product under kinetic conditions. The 2,6-*cis*-product can be favored by operating under thermodynamic conditions, although oftentimes the 2,6-*cis*-selectivities of these reactions are low and the conditions forcing.[2j,10]

Recently, Fuwa speculated that the replacement of an α,β-unsaturated ester Michael acceptor with an α,β-unsaturated thioester Michael acceptor may lead to enhanced 2,6-*cis*-selectivity as it mimics the acyclic polyketide chain bound via a thioester linkage to the acyl carrier protein in the pyran synthase-mediated biosynthesis of THPs. Remarkably, he found that this change led to THP products being formed with excellent 2,6-*cis*-selectivities, although forcing conditions were still required (70 °C for 7.5 h).[11] We decided to study the 6-*exo*-trig oxy-Michael reaction of both an α,β-unsaturated ester Michael acceptor and an α,β-unsaturated thioester Michael acceptor to see if there was a significant difference in the diastereoselectivities.

Our synthesis commenced (Scheme 3) with an *anti*-aldol reaction using the Masamune–Abiko auxiliary **6** and aldehyde **7**,[12] promoted by $(cy\text{-}hex)_2BOTf$ and Et_3N. This produced the desired *anti*-aldol adduct **8** in 91% yield as a 14:1 mixture of diastereomers, which were separated by column chromatography. Protection of the allylic alcohol as a TBS-ether was achieved in 93% using TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 °C. Reductive removal of the

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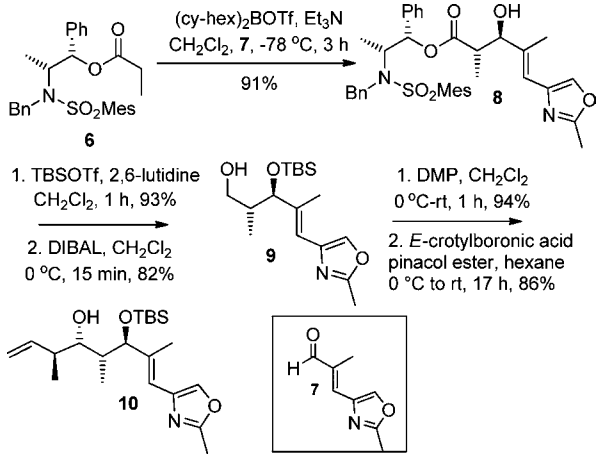
(12) (a) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750. (b) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215.

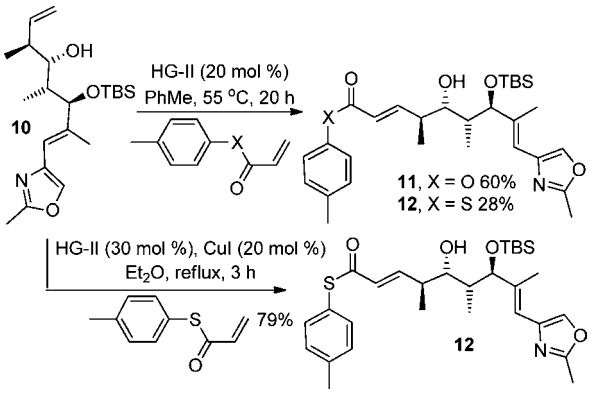
auxiliary with DIBAL-H in CH_2Cl_2 gave alcohol **9** in 82% yield. Oxidation with Dess–Martin periodinane gave the aldehyde in 94% yield. However, it was found that this aldehyde was unstable, and so it was immediately subjected to Felkin–Anh controlled addition of (*E*)-crotylboronic acid pinacol ester[13] to generate **10** as a single diastereomer in 86% yield, which contains the *anti*, *syn*-, *anti*-, stereochemical tetrad required for the synthesis of the C20–C32 core.

Scheme 3. Construction of the Stereochemical Tetrad



With **10** in hand, we could now consider converting it to both the oxoester **11** and the thioester **12**. It was decided to investigate the use of an olefin cross-metathesis reaction to achieve this transformation.[11] In the case of **11**, this would nessecitate the use of cresol acrylate[14] as a reagent, and in the case of the **12**, thiocresol acrylate[15] would be used. The Hoveyda–Grubbs II (HG-II) catalyst was used to promote these reactions (Scheme 4). The formation of ester **11** in 60% occurred without incident when **10** was heated at 55 °C in toluene with cresol acrylate and HG-II catalyst. However, the cross-metathesis reaction of **10** with thiocresol acrylate was not straightforward. Application of the same conditions provided **12** in only 28% yield. Increasing the temperature of the reaction resulted in a reduction in the yield of **12** to 20% at 70 °C and no product at 90 °C. Changing the solvent to CH_2Cl_2 and increasing the catalyst loading did lead to an increase in the yield of **12** to 50%. It is possible that thiocresol acrylate is particularly prone to self-dimerization under metathesis conditions, although we were never able to recover any of this dimer. It is also possible that the catalyst decomposed at elevated temperatures. However, application of conditions using a CuI additive, based on those recently reported by Lipshutz,[16] resulted in **12** being formed in an improved 79% yield.

Scheme 4. Synthesis of the Cyclization Precursors



With **11** and **12** in hand, we could now consider the cyclization step. Fuwa conducted his original cyclizations on the free alcohol using CSA in dichloroethane at 70 °C[11] but also reported conditions which delivered the cyclization in CH_2Cl_2 at rt.[11,17] As CSA has been used to remove TBS-ethers at rt, we attempted to remove the TBS-ether with CSA at rt and then, if required, raise the temperature to 70 °C to affect the cyclization.

Subjecting **11** to Fuwa's conditions at rt, and at elevated temperatures, resulted in decomposition with no identifiable products being returned (Table 1, entry a). When **12** was treated under these conditions, deprotection was seen to occur slowly at rt and more rapidly at higher temperatures. At higher temperatures (55 °C), some traces of a cyclized product **16** could be detected, but the major product was the deprotected ester **13** (Table 1, entries b and c). Extended reaction times led to additional products being formed, which seemed to derive from decomposition of the silyl ether **12**. As α,β-unsaturated thioesters are more enone-like than α,β-unsaturated oxoesters, it is perhaps not surprising that the Brønsted acid catalyzed Michael addition in **12** generated some cyclized product whereas **11** resulted in decomposition.

With this in mind, an alternative procedure to affect rapid silyl deprotection, before **11** or **12** could decompose, was needed. We therefore switched to TBAF buffered with AcOH. We anticipated that under these conditions fluoride-mediated deprotection would occur rapidly, and as α,β-unsaturated thioesters are more enone-like than α,β-unsaturated oxoesters, cyclization might occur to give the 2,6-*cis*-THP core. The phenomenon of enones undergoing Michael cyclization to give 2,6-*cis*-THPs, while α,β-unsaturated oxoesters cyclize to give 2,6-*trans*-THPs, was recently reported by Bates.[10a] When this was attempted using **11**, we found that in situ cyclization did follow deprotection to give the 2,6-*trans*-THP **14** as the sole product (Table 1, entry d). When these conditions were

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(14) Drewes, S. E.; Emslie, N. D.; Karodia, N. *Synth. Commun.* **1990**, *20*, 1915.
(15) Fuwa, H. Personal communication.
(16) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697.
(17) Fuwa, H.; Ichinokawa, N.; Noto, K.; Sasaki, M. *J. Org. Chem.* **2012**, *77*, 2588.

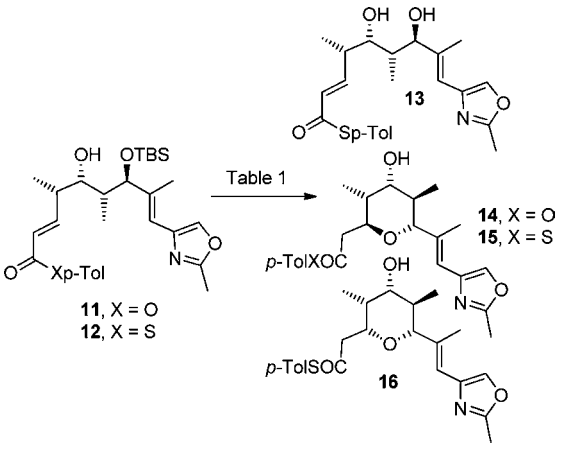
repeated with thioester **12**, deprotection and cyclization occurred rapidly to form 2,6-*trans*-THP **15** as the only product, contrary to our hypothesis (Table 1, entry e). While we were pleased that we had found conditions to effect deprotection and cyclization in the same pot, we were disappointed that the fluoride/Brønsted acid buffered conditions had led to the formation of the undesired 2,6-*trans*-THP **15**.[18]

We therefore returned to the use of a Brønsted acid catalyzed deprotection. We chose TFA as it is more acidic than CSA, and we hoped that it would promote faster deprotection of the silyl ether and catalyze the cyclization reaction. When thioester **12** was treated with TFA in CH_2Cl_2/H_2O, we were pleased to see cyclization occur and to isolate a 13:1 mixture of the desired 2,6-*cis*-THP **16** to undesired 2,6-*trans*-THP **15** (Table 1, entry f). Tetrahydropyrans **15** and **16** were generated cleanly as the only products and could be separated by SiO_2 flash column chromatography to provide **16** in a 71% yield.[18] When **11** was subjected to these conditions (Table 1, entry g), **13** was formed in 68% yield.

The successful formation of **16** constitutes a synthesis of the C20−C32 core of the phorboxazoles, which was achieved in only seven steps and a 31% overall yield. This compares favorably with previous syntheses of the fragment.[2−4] We were surprised to encounter a Michael cyclization reaction utilizing a thioester electrophile which could be made to generate either the 2,6-*cis*- or 2,6-*trans*-THP unit with excellent selectivity by initiating the cyclization with either TFA or TBAF buffered with AcOH, respectively. However, when an oxoester was used as a Michael acceptor, the AcOH buffered TBAF conditions generated the 2,6-*trans*-THP, while Brønsted acid mediated conditions led to silyl deprotection and decomposition. We are now seeking to examine this switch in the selectivity of the cyclization process more fully and to take the C20−C32 phorboxazole core **16** forward to complete a total synthesis of phorboxazole B.

(18) Stereochemistry of the THP rings was determined by ^{1}H NMR coupling constants and in the case of the 2,6-*cis*-THP by nOes between H2 and H6.

Table 1. Attempted Cyclization of **11** and **12**



entry	ester	conditions	yield %
a	**11**[a]	CSA, 10:1 DCE/MeOH, rt to 70 °C	[d]
b	**12**[a]	CSA, 3:1 DCE/MeOH, rt to 30 °C	**13** (56%),[e] **16** (trace)
c	**12**[b]	CSA, 3:1 DCE/MeOH, rt to 55 °C	**16** (20%)
d	**11**[c]	TBAF, AcOH, THF, rt	**14** (71%)
e	**12**[c]	TBAF, AcOH, THF, rt	**15** (35%)
f	**12**	TFA/CH_2Cl_2/H_2O, rt	**16**:**15** (71%), 13:1 ratio
g	**11**	TFA/CH_2Cl_2/H_2O, rt	**13** (68%)[e]

[a] CSA (0.2 equiv) used. [b] CSA (0.5 equiv) used. [c] TBAF (1.5 equiv), AcOH (0.2 equiv) used. [d] Decomposition of starting material occurred. [e] ^{1}H NMR yield.

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

The authors declare no competing financial interest.