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# Intramolecular Palladium(II)-Mediated Alkoxy Carbonylation as a Route to Functionalized Tetrahydropyrans. Synthesis of the C9–C32 Segment of Phorboxazole A

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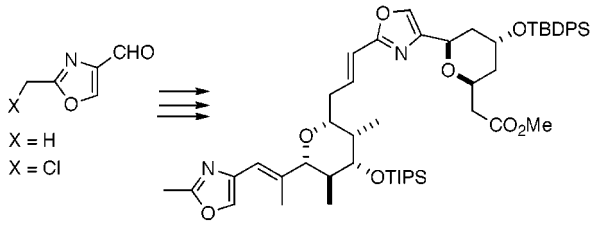
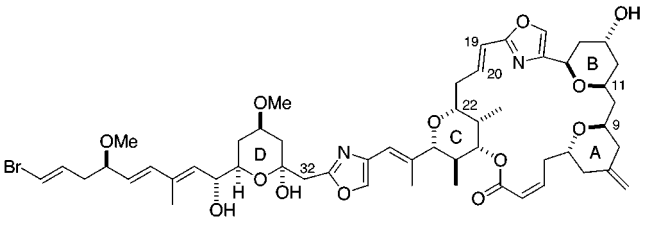
## ABSTRACT




**Hydroxy alkene 12, synthesized stereoselectively from 2-methyloxazole-4-carboxaldehyde, underwent intramolecular methoxy carbonylation in the presence of palladium(II) acetate to give 13 in which all five stereogenic centers around the tetrahydropyran correspond to those in ring C of phorboxazole A. Aldehyde 15, derived from 13, was linked to hydroxy alkene 23 via a Wittig coupling, and the composite 25 was subjected to a second palladium(II) acetate mediated methoxy carbonylation to yield 26, accompanied by acetoxy ester 27.**

The tetrahydropyran nucleus is a common structural motif among many classes of natural products, some of which exhibit striking biological properties. For example, phorboxazole A (**1**), a powerful cytotoxic agent isolated from *Phorbas* species of sponges, features three substituted tetrahydropyran units embedded within a 21-membered lactone ring.[1] We have previously reported that intramolecular palladium(II)-catalyzed alkoxy carbonylation of hydroxy alkenes affords a convenient entry to tetrahydropyrans.[2] It was further shown that 2,6-disubstituted tetrahydropyrans are generated exclusively with cis configuration in this process. Our observations followed upon earlier results of Semmelhack[3] and Liotta,[4] whose studies focused on the application of intramolecular alkoxy carbonylation to the synthesis of tetrahydrofurans. We have recently extended this methodology to the synthesis of tetrahydropyrans of greater stereochemical complexity, and we now wish to describe its application to the stereocontrolled assembly of a segment of phorboxazole A[5,6] that includes two of the four tetrahydropyrans, B and C, of this structure.

Synthesis of the C9−C32 portion of **1** commenced from methyl 2-methyl-4-oxazolecarboxylate (**2**),[8] which was reduced to aldehyde **3** and coupled in a Wittig reaction with




Phorboxazole A (**1**)

**Figure 1.**

(1) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126.
(2) White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1999**, *40*, 1463.
(3) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483.
(4) McCormick, M.; Monahan, R., III; Soria, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1989**, *54*, 4485.

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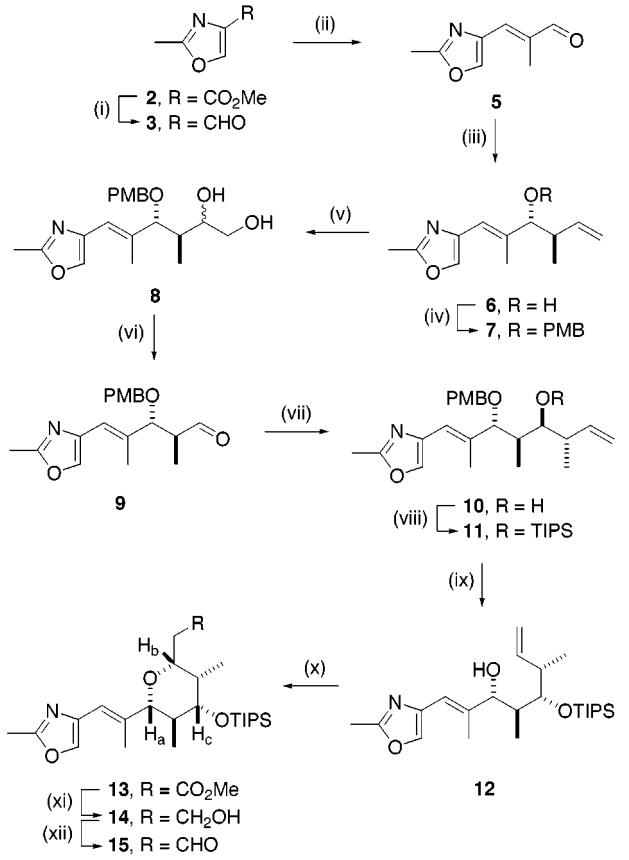
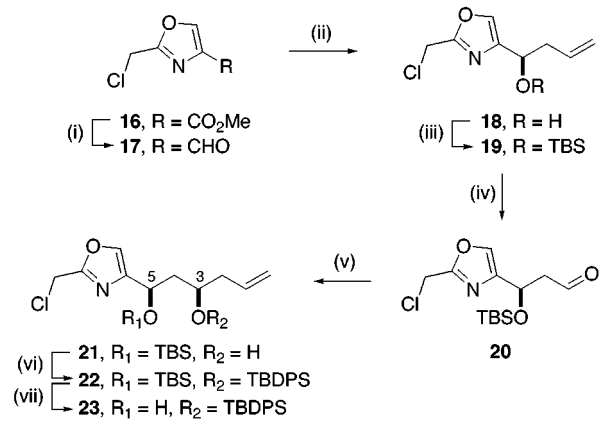
**Scheme 1**[a]




[a] Reagents and conditions: (i) DIBALH, −78 °C, 3 h, 69%; (ii) $Ph_3P{=}C(CH_3)CHO$ (**4**), $C_6H_6$, Δ, 20 h, 93%; (iii) *trans*-$CH_3CH{=}CHCH_3$, *t*-BuOK, *n*-BuLi, THF, then (+)-$(Ipc)_2BOMe$, THF, −70 °C, 6 h; $H_2O_2$, $NaHCO_3$, rt, 15 h, 67%, dr >96:4, er >96:4; (iv) NaH, THF, Δ, 40 min, then PMBCl, *n*-$Bu_4NI$, Δ, 6 h, 89%; (v) $OsO_4$ (cat.), NMO, THF−$H_2O$, rt, 10 h, 84%; (vi) $NaIO_4$, $H_2O$−THF, rt, 30 min, 98%; (vii) *trans*-$CH_3CH{=}CHCH_3$, *t*-BuOK, *n*-BuLi, THF, then (−)-$(Ipc)_2BOMe$; $HOCH_2CH_2NH_2$, MeOH, rt, 3 h, 53%, dr 6:1; (viii) TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, rt, 2 h, 99%; (ix) $AlCl_3$, EtSH, $CH_2Cl_2$, −20 → −4 °C, 3.5 h, 78%; (x) $Pd(OAc)_2$ (3 equiv), CO, MeOH−MeCN, 70 h, 86%; (xi) $LiAlH_4$, $Et_2O$, 0 °C, 3 h, 79%; (xii) Dess−Martin periodinane, $CH_2Cl_2$, rt, 3 h, 85%.

phosphorane **4**[9] to give (*E*) α,*β*-unsaturated aldehyde **5** (Scheme 1). Carefully optimized asymmetric crotyl addition to **5** under Brown's conditions[10] produced homoallylic alcohol **6** as a single anti diastereomer according to $^1H$ and $^{13}C$ NMR. The $^{19}F$ NMR spectrum of the Mosher ester of **6** indicated that the parent alcohol was obtained enantiomerically pure within the limits of the NMR measurement if the crotylation was carried out within a narrow temperature range around −70 °C. Etherification of **6** with *p*-methoxybenzyl (PMB) chloride in the presence of tetra-*n*-butylammonium iodide afforded **7**, which was selectively osmylated at the terminal alkene to yield **8**. Oxidative cleavage of this diol furnished **9**, and asymmetric crotylation of the resultant aldehyde with the reagent enantiomeric with that used on **5** produced a pair of diastereomeric alcohols in the ratio 6:1. These were separated chromatographically, and the major diastereomer **10** was converted to its triisopropylsilyl (TIPS) ether **11**. Conventional methods for cleaving the PMB ether from **11** were thwarted by side reactions; DDQ, for example, yielded the α,*β* unsaturated ketone resulting from oxidation of the allylic alcohol after PMB cleavage, whereas reductive methods invariably led to saturation of one or both double bonds. Fortunately, a method by Sauvé[11] employing a mild Lewis acid in the presence of ethanethiol proved highly effective for the selective unmasking of the PMB ether of **11**. This led to **12**, our precursor to the ring C tetrahydropyran moiety of **1**. Conditions for successful intramolecular alkoxy carbonylation of **11** required considerable experimentation. Only palladium(II) acetate was effective in mediating the reaction, and it was necessary to include either acetonitrile

**Scheme 2**[a]




[a] Reagents and conditions: (i) DIBALH, $CH_2Cl_2$, −78 °C, 98%; (ii) (+)-$(Ipc)_2BOMe$, $CH_2{=}CHCH_2MgBr$, $Et_2O$, −100 °C, 84%, er > 20:1; (iii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, rt, 99%; (iv) $OsO_4$ (cat.), $NaIO_4$, $H_2O$−THF, 70%; (v) (+)-$(Ipc)_2BOMe$, $CH_2{=}CHCH_2MgBr$, $Et_2O$, −100 °C, 66%, dr 12:1; (vi) TBDPSOTf, 2,6-lutidine, $CH_2Cl_2$, rt, 89%; (vii) HCl (3 N), THF−$H_2O$, 95%.

(5) For total syntheses of phorboxazole A, see: (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597. (b) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834.

(6) For the total synthesis of phorboxazole B, see: (a) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536. (b) Evans, D. A.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

(7) For other synthetic studies on phorboxazoles, see: (a) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319. (b) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099. (c) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (d) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905. (e) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315. (f) Williams, D. R.; Clark, M. P.; Berliner, M. A. *Tetrahedron Lett.* **1999**, *40*, 2287. (g) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291. (h) Wolbers, P.; Hoffman, H. M. R. *Synthsis* **1999**, *5*, 797. (i) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. (j) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527. (k) Wolbers, P.; Hoffmann, H. M. R.; Sassee, F. *Synlett* **1999**, *11*, 1808. (l) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469. (m) Pattenden, G.; Plowright, A. T. *Tetrahedron Lett.* **2000**, *41*, 983. (n) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (o) Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A. *Org. Lett.* **2000**, *2*, 3023. (p) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett.* **2000**, *41*, 3081.

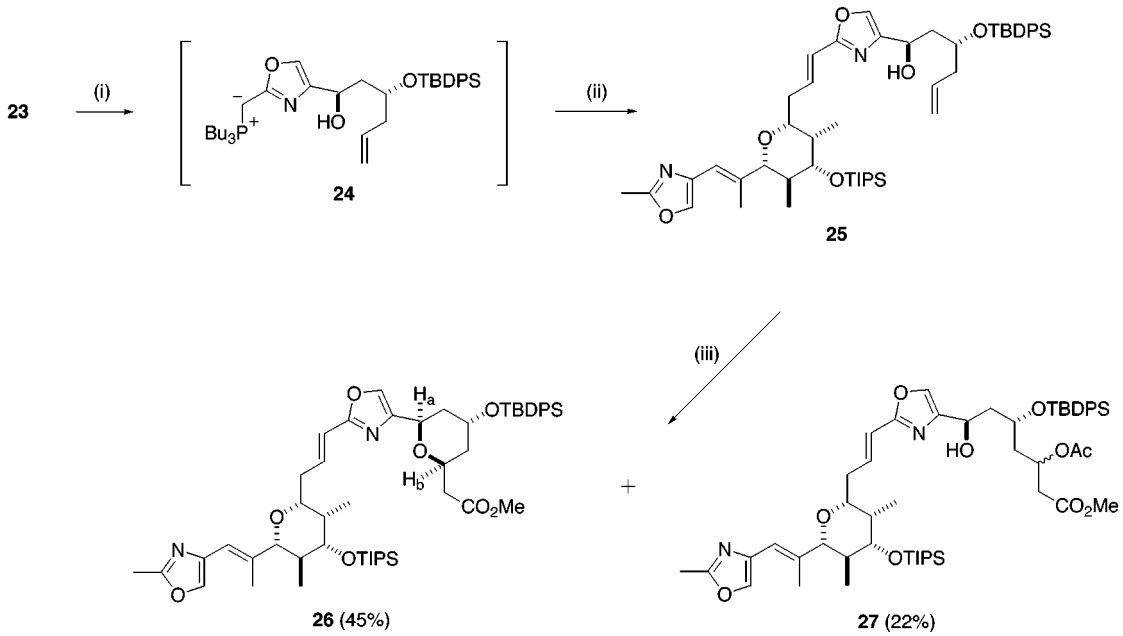
(8) (a) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96. (b) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Synth.*, in press.

(9) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235.

(10) Brown, H. C.; Bhat, K. S.; *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(11) Bouside, A.; Sauvé, G. *Synlett* **1997**, *9*, 1153.

**Scheme 3**[a]




[a] Reagents and conditions: (i) $Bu_3P$, DMF, rt, 3 h; (ii) **15**, DBU, 0 °C, 1 h, 96%; (iii) $Pd(OAc)_2$, CO, MeOH−MeCN (1:1), 120 h.

or benzonitrile as a cosolvent with methanol. Deactivation of the palladium species occurs during the reaction and is slowed by inclusion of a nitrile cosolvent, but successive quantities of $Pd(OAc)_2$ must be added to drive the reaction to completion. Under optimized conditions, a high yield of **13** was produced as a single stereoisomer. The configuration of the new stereocenter at C22 was established as (*R*) by NOE experiments, which showed signal enhancements due to $H_b$ (9.7%) and $H_c$ (6.2%) when $H_a$ was irradiated. The enhancements were even larger (20.6% and 9.0%, respectively) when the TIPS ether of **13** was replaced by a *tert*-butyldiphenylsilyl ether. In preparation for its coupling with the C9−C19 subunit of **1**, the ester group of **13** was reduced via alcohol **14** to aldehyde **15**.

Methyl 2-(chloromethyl)oxazole-4-carboxylate (**16**)[12] provided the starting point for the synthesis of the C9−C19 portion of **1**, and the ester function was reduced to aldehyde **17** in good yield with diisobutylaluminum hydride at low temperature (Scheme 2). Asymmetric allyl addition[13] to **17** gave (*R*) homoallylic alcohol **18** in high enantiomeric purity (er > 20:1) as determined by NMR measurement of its Mosher ester. After protection of **18** as its *tert*-butyldimethylsilyl ether **19**, the vinyl group was cleaved oxidatively to yield aldehyde **20**. A second asymmetric allyl addition to this aldehyde furnished syn product **21** accompanied by a small quantity of its anti diastereomer (syn:anti 12:1), which was removed chromatographically. Since the C3 alcohol would remain blocked while the C5 ether was unmasked, *tert*-butyldiphenylsilyl protection was chosen for the former, so that acidic hydrolysis of **22** gave exclusively alcohol **23**.

Coupling of **23** with **15** was accomplished by means of a Wittig reaction in which ylide **24**, prepared by displacement of chloride from **23** with tri-*n*-butylphosphine followed by deprotonation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), was condensed with aldehdye **15** (Scheme 3). In common with other routes to phorboxazoles[5,6] that have employed this strategy for assembling the C19−C20 double bond, **25** was obtained exclusively with (*E*) configuration at the new alkene linkage. Intramolecular alkoxy carbonylation of **25** again required successive addition of portions of $Pd(OAc)_2$, acetonitrile as a cosolvent with methanol, and an extended reaction time for completion of the process, but the reaction delivered **26** as a single stereoisomer. The configuration of the new stereocenter at C11 was established as (*S*) by a NOE experiment in which irradiation of $H_a$ produced a signal enhancement (9.9%) at $H_b$. A byproduct obtained from this reaction was acetate **27** (mixture of two diastereomers), which underwent elimination to an $\alpha,\beta$-unsaturated ester in the presence of DBU in toluene at reflux.

In summary, a convergent route to the C9−C32 portion of phorboxazole A (**1**) has been developed that assembles each of the tetrahydropyran moieties in this segment by palladium acetate mediated methoxy carbonylation of an acyclic hydroxy alkene precursor. Advantages of this methodology include a high degree of stereocontrol in constructing the 2,6-*cis* disubstituted tetrahydropyrans present in **1**, facile access to the alkenol precursors via asymmetric synthesis, and tolerance of functionality, which in this case includes alkene units elsewhere in the substrate.

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(12) Cardwell, K. S.; Hermitage, S. A.; Sjolin, A. *Tetrahedron Lett.* **2000**, *41*, 4239.
(13) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.

Thailand, for a scholarship. Financial support was provided by the NIH (GM50574).

**Supporting Information Available:** Experimental procedures and characterization data for **5**−**15** and **17**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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