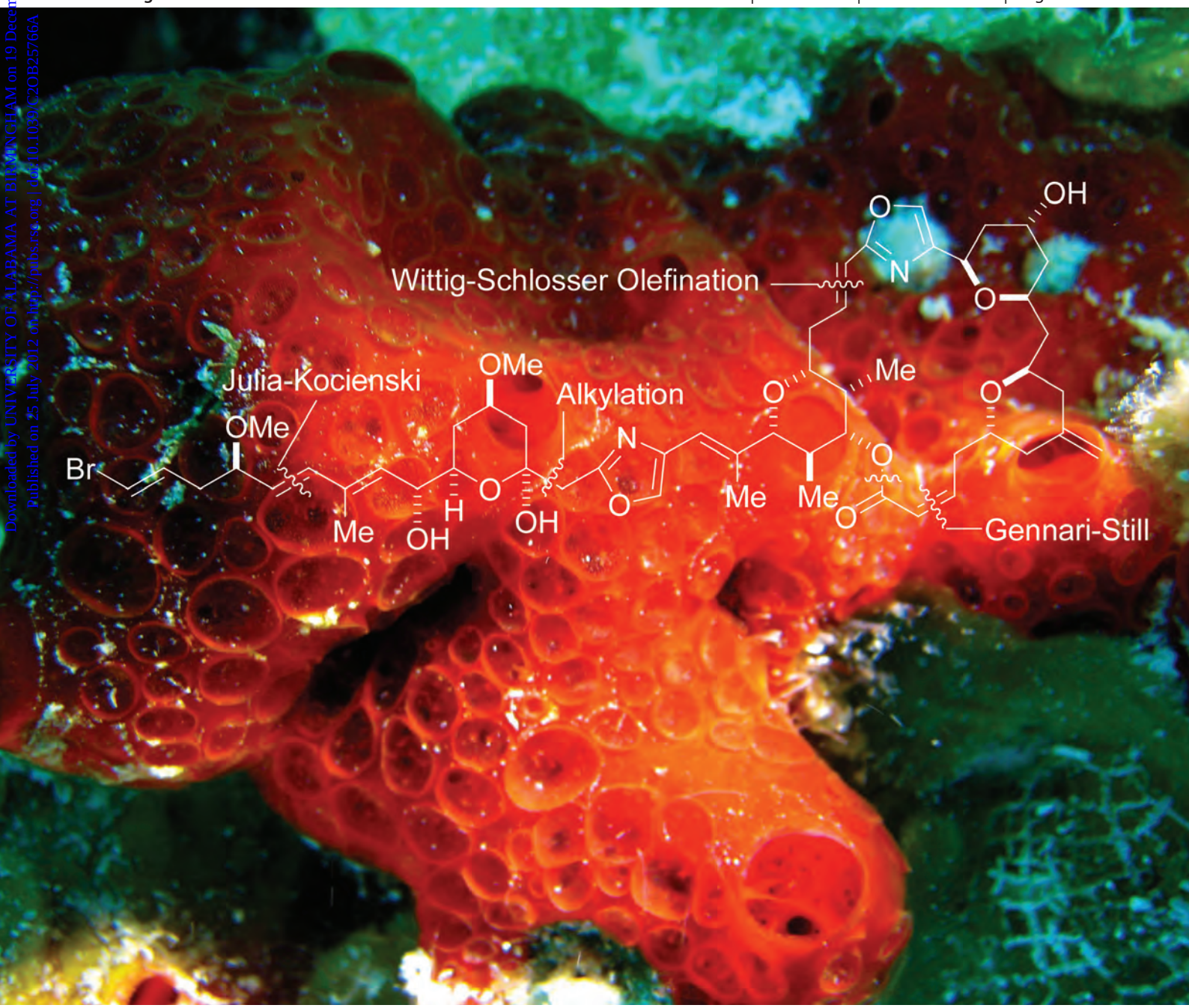
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 10 | Number 39 | 21 October 2012 | Pages 7849–8028



ISSN 1477-0520

RSC Publishing

PAPER

James D. White *et al.*

Total synthesis of the marine toxin phorboxazole A using palladium(II)-mediated intramolecular alkoxycarbonylation for tetrahydropyran synthesis

Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7884

www.rsc.org/obc

PAPER

Total synthesis of the marine toxin phorboxazole A using palladium(II)-mediated intramolecular alkoxycarbonylation for tetrahydropyran synthesis†

Punlop Kuntiyong, Tae Hee Lee, Christian L. Kranemann and James D. White*

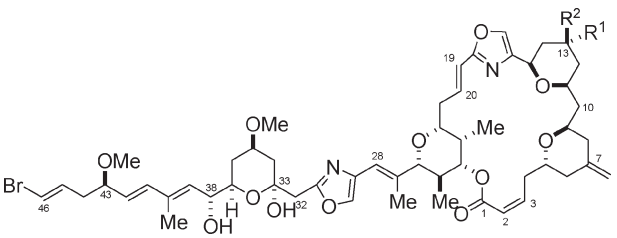
Received 20th April 2012, Accepted 24th July 2012
DOI: 10.1039/c2ob25766a

The potent antitumor agent phorboxazole A was synthesized from six subunits comprising C1–C2 (**115**), C3–C8 (**98**), C9–C19 (**74**), C20–C32 (**52**), C33–C41 (**84**) and C42–C46 (**85**). Tetrahydropyrans B and C containing *cis*-2,6-disubstitution were fabricated *via* palladium(II)-mediated intramolecular alkoxycarbonylation which, in the case of tetrahydropyran C, was carried out with catalytic palladium(II) and *p*-benzoquinone as the stoichiometric re-oxidant. Tetrahydropyran D was obtained by a stereoselective tin(IV)-catalyzed coupling of a C9 aldehyde with an allylsilane, and the C19–C20 connection was made using a completely stereoselective Wittig–Schlosser (*E*) olefination. Coupling of the oxazole C32 methyl substituent with the intact C33–C46 δ-lactone **3** was accompanied by elimination of the vinyl bromide to a terminal alkyne, but the C32–C33 linkage was implemented successfully with **83** and C33–C41 lactone **84**. The C42–C46 segment of the side chain was then appended *via* Julia–Kocienski olefination. The macrolide portion of phorboxazole A was completed by means of an Ando–Still–Gennari intramolecular (*Z*)-selective olefination at C2–C3 which required placement of a (dimethoxyphosphinyl)acetate moiety at C24. Final deprotection led to phorboxazole A *via* a route in which the longest linear sequence is 37 steps and the overall yield is 0.36%.

Introduction

Phorboxazole A (**1**) and its C-13 epimer phorboxazole B (**2**) were isolated in small quantity by Molinski and Searle from a species of marine sponge of the genus *Phorbas* sp. found in the Indian Ocean.[1] A combination of extensive NMR measurements, derivatization, and degradation studies established the structure and absolute configuration of phorboxazoles A and B which were found to possess an unprecedented carbon skeleton consisting of a highly oxygenated 21-membered macrolactone ring bearing a sixteen-carbon side chain.[2] Three tetrahydropyrans and an oxazole are embedded in the macrolactone portion while a second oxazole and a fourth tetrahydropyran in the form of a cyclic hemiacetal are present in the side chain.

Phorboxazole A, with tumor cell growth inhibition in the sub-nanomolar range, is among the most potent cytotoxic agents yet discovered. *In vitro* tests in the National Cancer Institute's panel of 60 human tumor cell lines showed that phorboxazole A inhibited the growth of colon tumor cells HCT-116 and HT29 at GI_{50} 4.36×10^{-10} and 3.31×10^{-10}, respectively. Cellular bioassays established that phorboxazole A arrests the cell cycle at the S phase and does not affect tubulin polymerization or interfere with the integrity of microtubules. The exact mechanism of action remains unknown but a structure-activity relationship study with phorboxazole A analogues indicated that both the macrolide portion and side chain are essential for activity, suggesting a bimodal interaction of the molecule with key cellular components.[3] The novel structure, potent activity and scarcity in nature of phorboxazoles A and B have combined to make their synthesis an inviting objective.[4–6] There has also been strong interest in the design and synthesis of biologically active phorboxazole A analogues.[7]



Phorboxazole A (**1**: R^1 = OH, R^2 = H)
Phorboxazole B (**2**: R^1 = H, R^2 = OH)

Department of Chemistry, Oregon State University, Corvallis, Oregon, USA. E-mail: james.white@oregonstate.edu

†Electronic supplementary information (ESI) available: Preparations and analytical details of synthetic compounds. See DOI: 10.1039/c2ob25766a

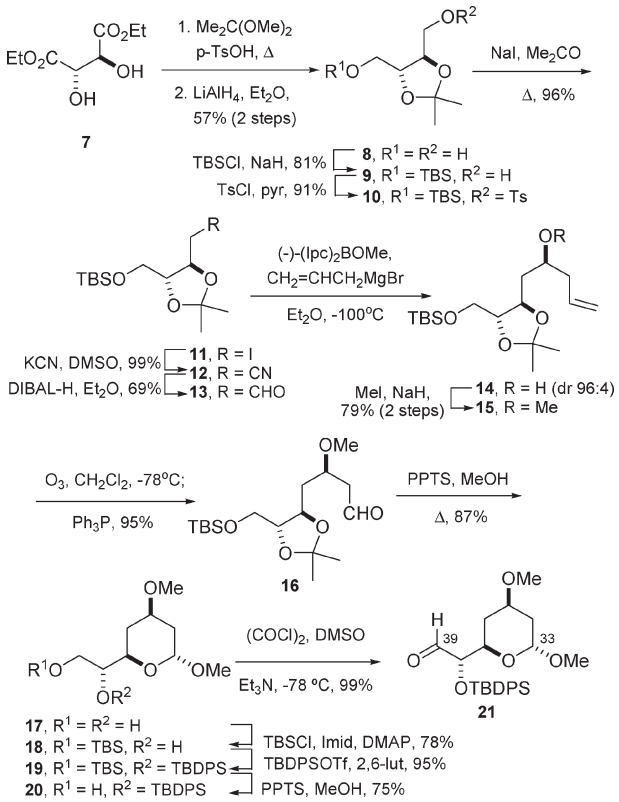
Results and discussion

Our approach to phorboxazole A was conceptualized from four subunits: (i) a C33–C46 side chain component **3**, (ii) a C20–C32 aldehyde **4** containing tetrahydropyran B and an oxazole, (iii) a C4–C19 portion **5** containing tetrahydropyrans C and D as well as a second oxazole, and (iv) a three-carbon unit such as **6** corresponding to C1–C3 (Scheme 1). Connection of side chain **3** with fragment **4** would be made *via* deprotonation at the C32 methyl group of **4** followed by addition of the resultant anion to the lactone carbonyl of **3**, a coupling tactic employed in Evans *et al.*' synthesis of phorboxazole B.[5a] A modified Wittig olefination was programmed for linkage of C19 with C20 as an (*E*) double bond. The script for the C1–C3 portion of **1** initially specified its introduction as the dianion of a propiolate, with semi-reduction of the alkyne and macrolactonization completing the synthesis. As events unfolded, this finale had to be abandoned and a different end game was devised.[8]

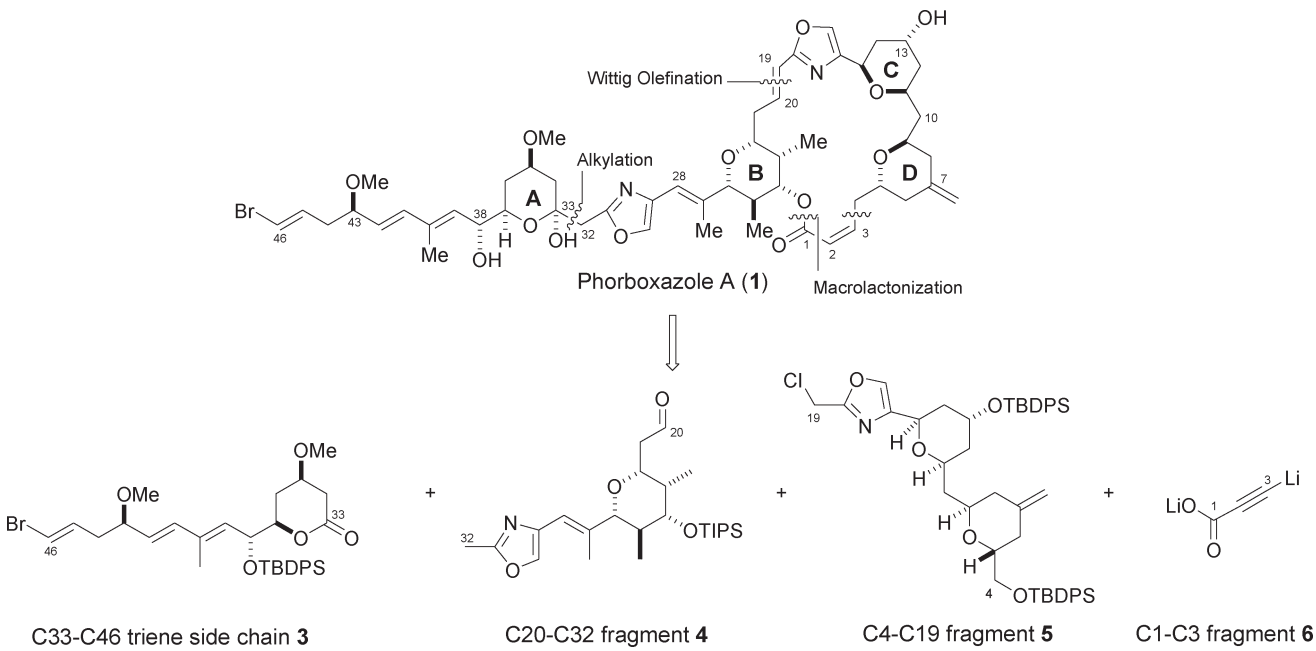
Synthesis of the C33–C46 side chain 3

Synthesis of **3** began from commercially available diethyl D-tartrate (**7**) as a C36–C39 platform from which chain extension could be deployed independently from each ester (Scheme 2). The vicinal diol of **7** was first converted to an acetonide and the pair of ethyl esters was reduced to diol **8**. Monosilylation of **8**[9] followed by tosylation of **9** gave **10**, and a Finkelstein reaction of the latter provided iodide **11**. Homologation of **11** with potassium cyanide afforded nitrile **12** which was reduced to aldehyde **13**.

Asymmetric allylation[10] of aldehyde **13** gave (*S*) homoallylic alcohol **14** in good yield and excellent diastereoselectivity (dr 96 : 4). After conversion of **14** to its methyl ether **15**, the terminal double bond was cleaved by ozonolysis to provide aldehyde **16**. Acid catalyzed methanolysis of the acetonide was followed by spontaneous cyclization to afford cyclic acetal **17**. In order to effect selective oxidation of diol **17**, the primary alcohol was protected with *tert*-butylchlorodimethylsilane and the secondary alcohol of **18** was masked as its *tert*-butyldiphenylsilyl ether **19**.



Scheme 2 Synthesis of C33–C39 subunit from diethyl tartrate.



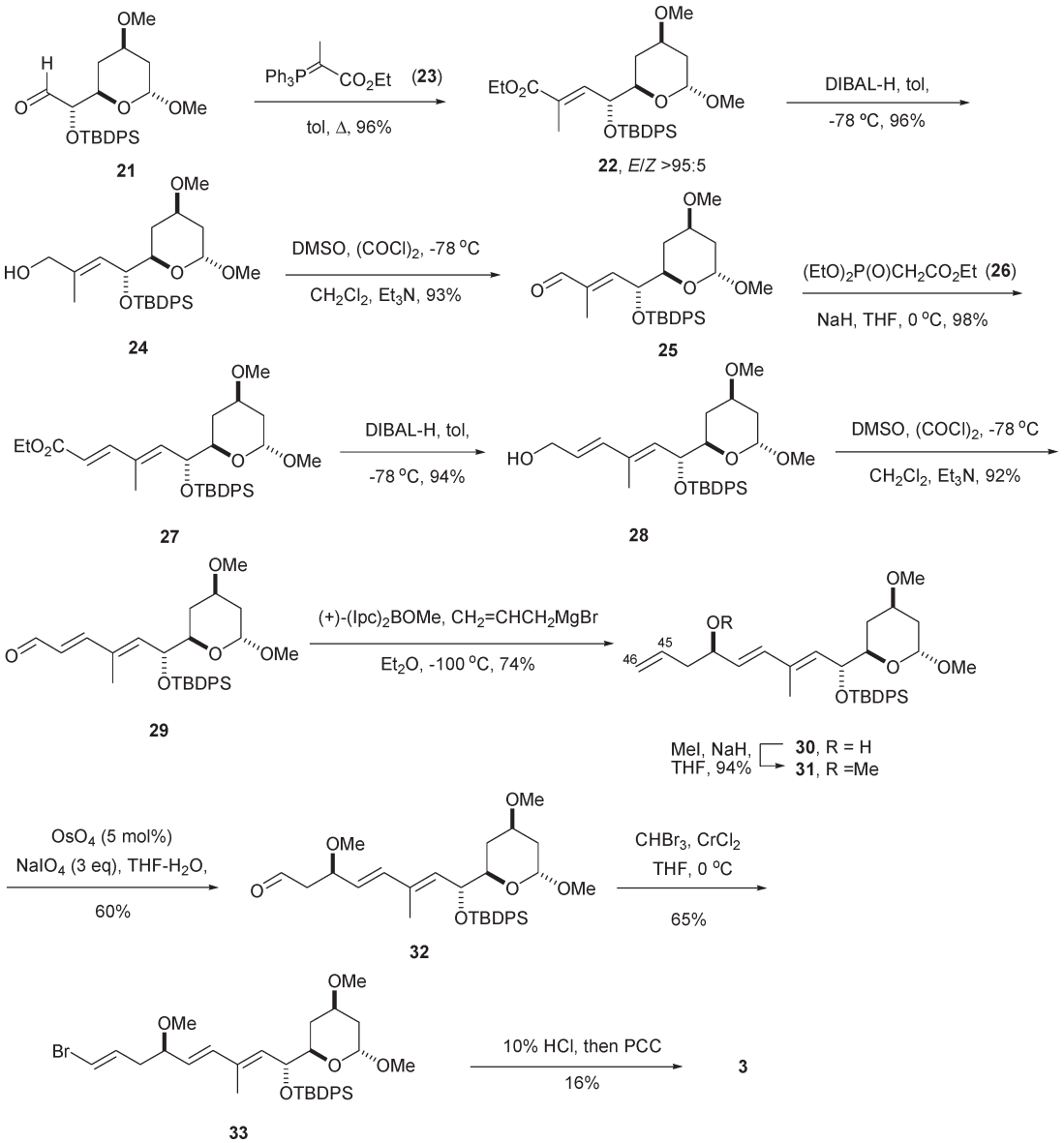
Scheme 1 Retrosynthetic analysis of phorboxazole A.

Selective deprotection of the primary alcohol and subsequent Swern oxidation of **20** then gave aldehyde **21**.

Several methods were explored with **21** for introducing the (*E*)-trisubstituted double bond at C39–C40. Triethyl 2-phosphonopropionate reacted with **21** to give an acceptable yield of α,β-unsaturated ester **22** but with an unfavourable (*E*/*Z*) ratio of 1 : 2. Fortunately, it was found that **21** reacted with ylide **23** to give a nearly quantitative yield of ester **22** with excellent stereoselectivity favouring the desired (*E*) isomer (Scheme 3).[11] The ester was reduced to primary alcohol **24** which was oxidized to aldehyde **25**, and Horner–Wadsworth–Emmons olefination of **25** with triethyl phosphonoacetate (**26**) cleanly provided (*E*,*E*)-dienoate **27**. The latter was converted *via* alcohol **28** to aldehyde **29** by a reduction-oxidation sequence analogous to that used with **22**. Asymmetric allylation[10] of **29** gave homoallylic alcohol **30** (dr > 20 : 1) in good yield, and the hydroxyl group was methylated to furnish triene ether **31**.

Oxidative cleavage of the terminal olefin of **31** was initially plagued by competing hydroxylation of the internal diene, but this could be avoided by using catalytic osmium tetraoxide and stoichiometric sodium periodate under carefully controlled conditions.[12] This protocol resulted in an acceptable yield of aldehyde **32**. The aldehyde was advanced to (*E*)-vinyl bromide **33** by a Takai reaction[13] with bromoform and chromous chloride, but halogen exchange during the reaction generated variable quantities of the (*E*)-chloroalkene from which separation of pure **33** was tedious. A solution to this problem was found in a subsequent Takai reaction that produced the (*E*)-bromoalkene exclusively (*vide infra*).

From **33**, there remained only the seemingly straightforward task of converting the methyl acetal to a δ-lactone in order to reach **3** (Scheme 3). However, attempted hydrolysis of acetal **33** under acidic conditions produced an intractable mixture that appeared to result from elimination of methanol from the side



Scheme 3 Synthesis of C33–C46 side chain **3** from aldehyde **21**.

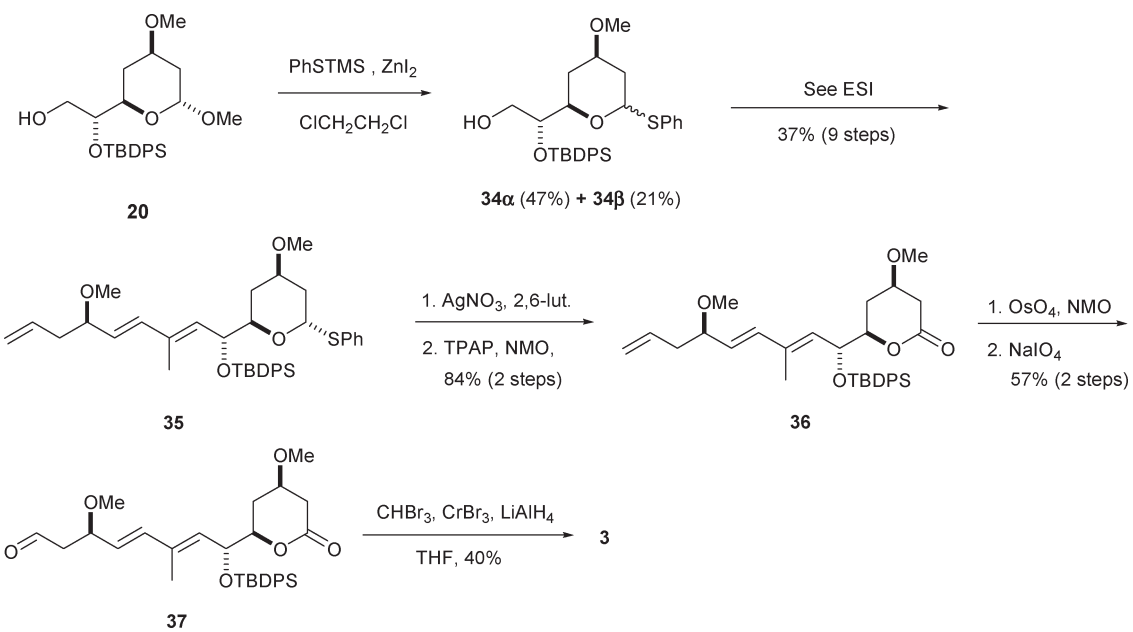
chain to give an unstable conjugated tetraene. This outcome indicated that a path to **3** would be needed that avoided acidic reagents for generating the lactone carbonyl from a precursor bearing the methoxy triene unit. In a previous study, we found that a thiophenyl acetal can serve as a convenient surrogate for a δ-lactone due to its facile hydrolytic cleavage in the presence of silver ion and *in situ* oxidation of the resultant hemiacetal.[14] We returned to **20** to exploit this tactic and found that treatment of this methyl acetal with trimethylsilylthiophenol and zinc iodide as described by Hanessian and Guindon[15] gave a 2 : 1 mixture of thioacetal anomers, **34α** and **34β**, in good yield (Scheme 4). The anomers were separated by chromatography, but in order to simplify spectral interpretation of subsequent intermediates only the major anomer **34α** was carried forward.

Thiophenyl acetal **34α** was advanced to triene **35** by a nine-step sequence analogous to that used to take **20** to **31** (Scheme 4). When **35** was exposed to silver nitrate-catalyzed hydrolysis, a mixture of anomeric hemiacetals was produced which yielded a single δ-lactone **36** upon oxidation with Ley's reagent.[16] Oxidative cleavage of the terminal olefin of **36** under conditions used with **31** gave aldehyde **37** but a conventional Takai reaction of **37** with chromous chloride and bromoform again produced the terminal (*E*)-chloroalkene as a troublesome by-product.[17] Modified conditions using chromous bromide, prepared by reduction of chromium(III) bromide with lithium aluminium hydride and used *in situ*,[13] solved this problem and led to the C33–C46 side chain of **1**, albeit in modest yield due to partial destruction of the lactone. A robust protecting group for the oxygen function at C38 of **3** was considered essential for subsequent coupling of this fragment with other phorboxazole subunits and the *tert*-butyldiphenylsilyl ether of **3** was left in place until a final stage of the synthesis for this purpose.

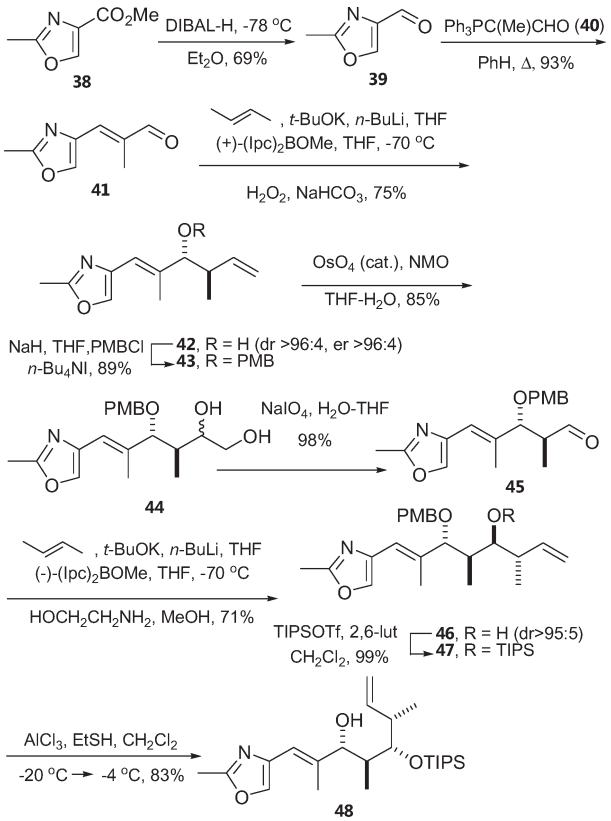
Synthesis of the C20–C32 subunit 4

Synthesis of this segment of the phorboxazole macrocycle presented an opportunity to explore a route to the embedded tetrahydropyran B *via* intramolecular palladium(II)-mediated alkoxycarbonylation that would expand the scope of the method and measure its stereoselectivity.[18] Although the method has been demonstrated in the context of tetrahydrofuran synthesis,[19] its application to the construction of tetrahydropyrans has received relatively little attention.[20] In the present case, the outcome leading from a hex-1-en-6-ol to the pentasubstituted tetrahydropyran of **4** was known[21] but many features of the reaction, including its mechanism, were obscure. Two observations were noted in a previous exercise that portended problems for the present study. First, it was seen that the palladium(II) species was reduced to inactive palladium(0), presumably by carbon monoxide, during the reaction so that many successive additions of the palladium salt were necessary to drive the reaction to completion. Second, intramolecular alkoxycarbonylation was critically dependent on the nature of the solvent, an alcohol alone being inadequate for success of the reaction. Later studies, particularly those directed toward tetrahydropyran C of **1**, clarified these issues (*vide infra*), but with acquisition of **4** as the immediate objective synthesis of its acyclic precursor became our next task.

Synthesis of **4** began from the known methyl 2-methyl-4-oxazolecarboxylate (**38**),[22] prepared by a modification of Cornforth's method.[23] Reduction of **38** to aldehyde **39** followed by Wittig olefination with 2-(triphenylphosphoranylidene)propionaldehyde (**40**) yielded unsaturated aldehyde **41** exclusively as the (*E*) isomer (Scheme 5). Asymmetric crotylation[24] of **41** with (−)-(*Z*)-crotyldiisopinylcampheylborane afforded homoallylic alcohol **42** with an *anti–syn* ratio of >96 : 4 according to ^{13}C NMR. The enantiomeric ratio of the major anti isomer was also >96 : 4, as measured by analysis of its Mosher ester using ^{19}F



Scheme 4 Completion of phorboxazole A side chain **3** from thioacetal **34α**.



Scheme 5 Synthesis of tetrahydropyran B precursor **48** from oxazole **38**.

NMR.[25] These data in combination with precedent established by Brown[24] allowed confident assignment of absolute configuration to **42** as (25*R*,26*R*). Etherification of **42** with *p*-methoxybenzyl chloride in the presence of tetra-*n*-butylammonium iodide afforded **43** which underwent oxidative cleavage of the terminal olefin *via* diol **44** to furnish aldehyde **45**. A second asymmetric crotylation, in this case with the (*Z*)-crotyldiisopinylcampheylborane enantiomeric with that used on aldehyde **41**, gave homoallylic alcohol **46** with a C23–C24 *anti–syn* ratio >95 : 5 and an enantiomeric ratio >96 : 4 by Mosher ester analysis. Alcohol **46** was protected as its triisopropylsilyl ether **47** without incident, but cleavage of the *p*-methoxybenzyl ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone unexpectedly led to an α,β-unsaturated ketone resulting from oxidation of the allylic alcohol after ether scission. The problem was solved by removing the *p*-methoxybenzyl group from **47** with ethanethiol and aluminium chloride[26] in a process that furnished alkoxycarbonylation substrate **48** in good yield.

Initial attempts to cyclize **48** in the presence of palladium(II) chloride and methanol under an atmosphere of carbon monoxide took several days and gave a disappointing yield of **49** but two observations resulted in a marked improvement in efficiency and rate. First, it was found that palladium(II) acetate was superior to other palladium salts in promoting the reaction; second, inclusion of acetonitrile as a co-solvent with methanol greatly retarded reduction of palladium(II) to palladium (0) (Scheme 6). Although alkoxycarbonylation of **48** still required addition of three equivalents of palladium(II) acetate, tetrahydropyran **49** was produced as the sole stereoisomer in high yield. The configuration of **49** was established by nuclear Overhauser experiments which proved that protons H_a, H_b, and H_c were axial and confirmed that all five stereocenters in this tetrahydropyran correspond in absolute configuration to C22–C26 of phorboxazole A. A mechanism involving a tightly complexed π-palladium(II) species configured as in **50** (Scheme 7) which collapses to tetrahydropyran **51** is believed to be responsible for the high level of stereoselectivity in the conversion of **48** to **49**. In preparation for coupling of **49** with a fragment representing C9–C19 of **1**, the ester was reduced and the resultant alcohol **52** was oxidized to aldehyde **4**.

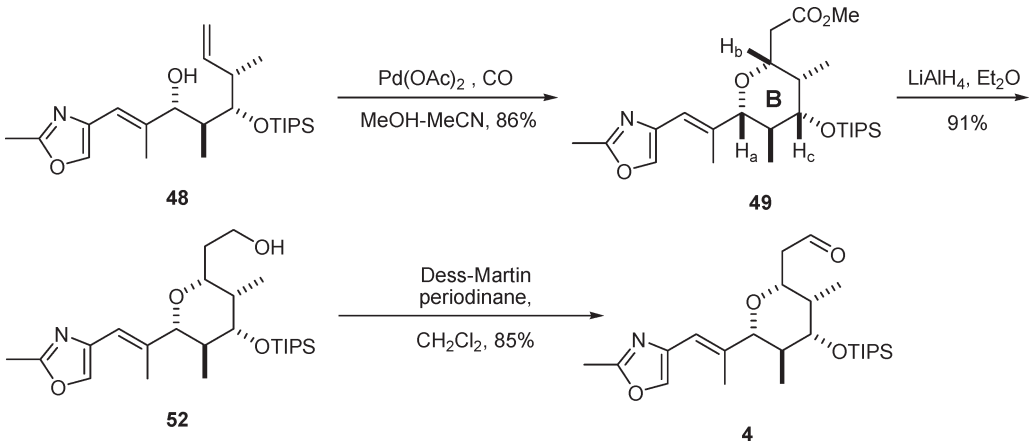
Synthesis of a C10–C19 subunit and its coupling to C20–C32

Connection of C19 to C20 was programmed *via* a modified Schlosser–Wittig (*E*)-olefination[27] along lines demonstrated for 2-halomethyloxazoles by Panek and Liu[28] and applied by Evans *et al.* in their synthesis of phorboxazole B (**2**).[5a] The partner needed for aldehyde **52** was therefore one bearing a phosphonium substituent at C19, and for this purpose chloromethyloxazole **53** was prepared by the method of Hermitage and co-workers[29] and was reduced to aldehyde **54** (Scheme 8). The aldehyde was reacted with (+)-allyldiisopinylcampheylborane[10] to give (*R*) homoallylic alcohol **55** in which the e.r. was >20 : 1 as measured from the ^{13}C NMR spectrum of its Mosher ester.[25] After protection of **55** as its *tert*-butyldimethylsilyl ether **56**, oxidative scission of the terminal alkene gave aldehyde **57**. The latter was subjected to a second asymmetric allylation with (+)-allyldiisopinylcampheylborane which produced *syn* alcohol **58** accompanied by *ca.* 8% of its anti isomer. Purified alcohol **58** was protected as its *tert*-butyldiphenylsilyl ether **59**, from which the *tert*-butyldimethylsilyl ether was cleaved selectively[30] to afford alkenol **60**.

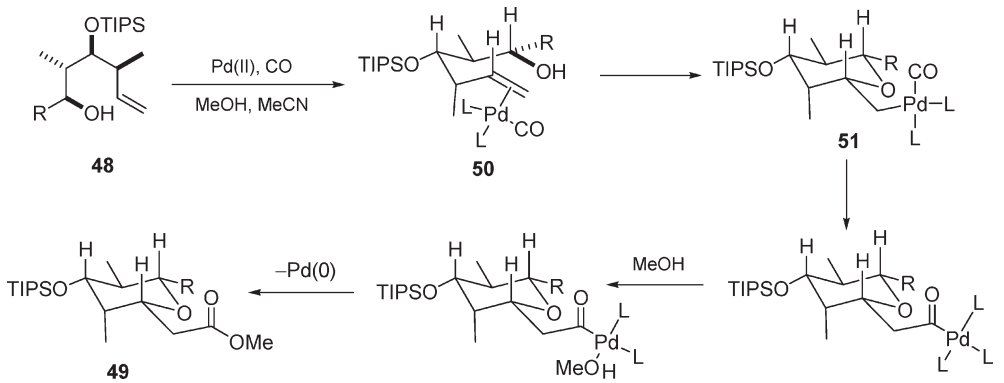
In the belief that the activated chlorine substituent of **60** was unlikely to survive exposure to palladium reagents, elaboration of tetrahydropyran C by alkoxycarbonylation of this substrate was deferred until after its coupling to **52**. Chloromethyloxazole **60** was therefore converted to phosphonium salt **61** with tri-*n*-butylphosphine, and the ylide prepared with 1,8-diazabicyclo-[5.4.0]undec-7-ene was reacted with aldehyde **52** in an olefination that provided alkene **62** in excellent yield and with exclusive (*E*) configuration of the C19–C20 double bond as determined by ^1H NMR (Scheme 9). Alkoxycarbonylation of **62** again required an excess of palladium(II) acetate and gave, in addition to the desired bistetrahydropyran **63**, ester **64** resulting from methoxycarbonylation of the terminal alkene without participation by the C15 hydroxy group (Scheme 10). This unsatisfactory result left us without a practical route to the C10–C19 portion of **1** and prompted a search for conditions that would afford a viable entry to this domain. For this exercise, we returned to alkenol **60**.

Alkoxycarbonylation studies and improved preparation of the C9–C19 fragment

A comprehensive study of the reaction of **60** with carbon monoxide and methanol in the presence of various palladium(II) salts revealed that the chlorine substituent could survive most



Scheme 6 Intramolecular alkoxycarbonylation of alkenol **48** to form tetrahydropyran B.



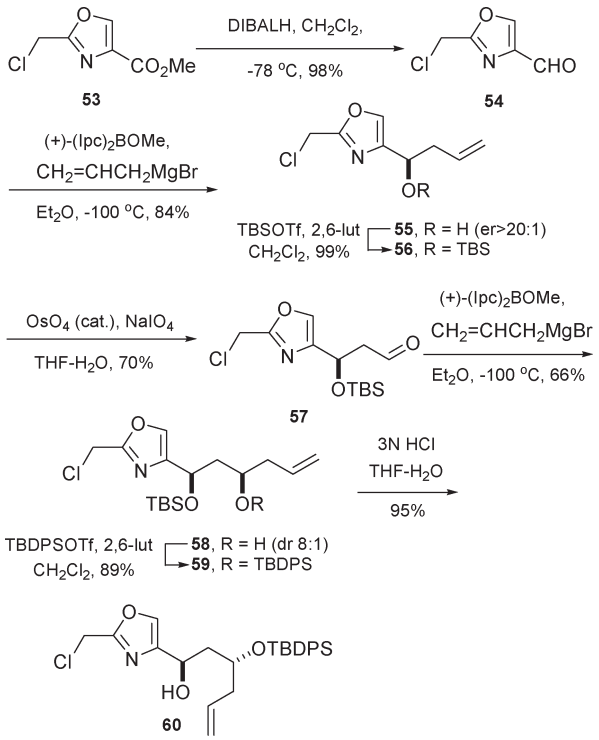
Scheme 7 Proposed mechanism of intramolecular palladium(II)-mediated alkoxycarbonylation of **48**.

alkoxycarbonylation conditions. However, the yield of **65** was generally low even with a large excess of the palladium(II) salt (Table 1, entry 1). When palladium(II) chloride was used in the reaction, a further complication arose in the form of γ-lactone **66** resulting from silyl ether cleavage followed by carbonylation and cyclization (Table 1, entries 2 and 3). We assumed that excess palladium(II) chloride was responsible for unmasking the silyl ether of **60**, and in order to suppress this aberrant process alkoxycarbonylation protocols that employed catalytic palladium(II) salts were investigated. It has been shown by Murahashi that tetrahydrofurans can be prepared by intramolecular alkoxylation of 4-pentenols using catalytic palladium(II) chloride with copper(II) chloride as the stoichiometric oxidant[31] and the process was extended to intramolecular alkoxycarbonylation by Semmelhack *et al.*,[19c] but those conditions with **60** again produced γ-lactone **66** as a major by-product (Table 1, entry 4). However, a report by Marshall that *p*-benzoquinone could serve as the stoichiometric oxidant for intramolecular alkoxycarbonylation of a 5-hexynol catalyzed by palladium(II) chloride[32] suggested that reexamination of **60** as a substrate with this precedent could be fruitful. In fact, exposure of **60** to 10 mol% of palladium(II) chloride–acetonitrile complex and 5.5 equivalents of *p*-benzoquinone in methanol–acetonitrile under a carbon monoxide atmosphere gave **65** in a reproducible yield of *ca* 60% (Table 1, entry 5) with stereoselectivity in favour of the (11*S*,15*R*) isomer >10 : 1. The *syn* relationship between protons at C11 and C15 was established by a nuclear Overhauser experiment. Formation of **66** was not observed under these conditions. This outcome permitted the preparation of **65** on a scale approximating 1 g and greatly facilitated our progress toward **1**.

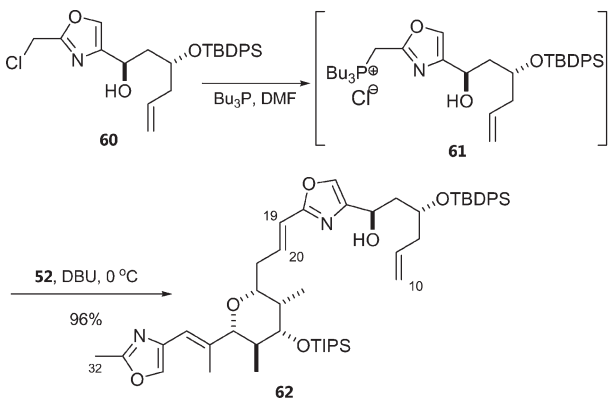
Synthesis of the C4–C8 fragment, its coupling with C9–C19 and assembly of a C4–C32 subunit

Synthesis of the phorboxazole moiety comprising C4–C8 is summarized in Scheme 11. (*S*)-(−)-Glycidol (**67**) was protected as its *tert*-butyldiphenylsilyl ether **68** which was reacted with lithium trimethylsilylacetylide to give alkynol **69**. The trimethylsilyl group was removed selectively from **69**, and the resultant alkyne **70** was treated with bromo-9-borabicyclo[3.3.1]nonane[33] to yield vinyl bromide **71**. The latter was converted to bis-silyl ether **72** and then cross-coupled[34] with trimethylsilylmethylmagnesium chloride in the presence of a catalytic quantity of 1,3-bis-(diphenylphosphino)propanenickel(II) chloride.[35] This sequence furnished allylsilane **73** in an overall yield of 69% for the six steps from **67**.

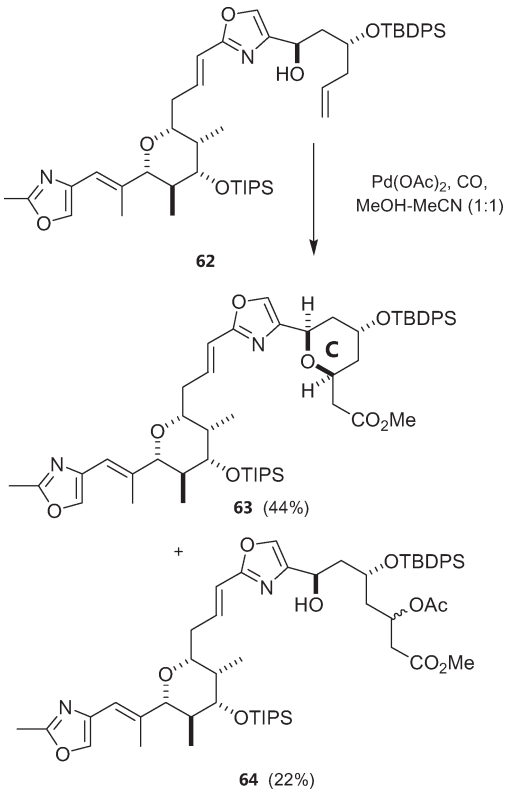
Aldehyde **74** required for reaction with **73** was obtained by reduction of ester **65** with diisobutylaluminium hydride, but when **73** and **74** were exposed to boron trifluoride etherate the desired homoallylic alcohol was obtained in less than 20% yield.



Scheme 8 Synthesis of tetrahydropyran C precursor **60** from oxazole **53**.



Scheme 9 Wittig coupling of **60** with **52** to yield C10–C32 subunit **62**.



Scheme 10 Intramolecular alkoxycarbonylation of C10–C32 to form tetrahydropyran C.

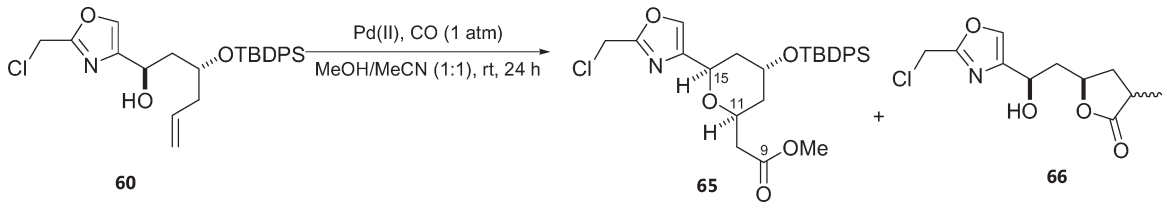
However, when stannic chloride was used as catalyst under Dias' conditions,[36] **75** was produced in good yield as a separable 2 : 1 mixture of C9 alcohols (Scheme 12). The configuration of these stereoisomeric alcohols was determined by preparing their (*R*) and (*S*) Mosher esters and using Kakisawa's model for assigning absolute configuration to the secondary esters.[37] This analysis established that the major, less polar isomer of **75** possessed (9*S*) configuration. In the hope that separation of C9 stereoisomers of **75** could be avoided, the mixture was oxidized to a ketone and the C5 silyl ether was cleaved in the expectation that reduction of the resultant cyclic hemiacetal would produce the required (9*R*) configuration of tetrahydropyran D. Although a cyclic hemiacetal (not depicted) was formed and was reduced to a tetrahydropyran with triethylsilane in the presence of a Lewis acid, the reduction was accompanied by saturation of the C7 *exo* methylene substituent.[38]

This result necessitated a change in our strategy for constructing tetrahydropyran D and led to a plan involving displacement of a leaving group at C9 of **75** by the C5 hydroxy substituent. It was recognized that this approach risked sacrificing the chlorine substituent in **75**, and to avoid this mishap the order of subunit assembly was reversed. Thus, instead of coupling C29–C46 with a C4–C19 segment, connection of **75** to C20–C46 would be completed first and tetrahydropyran D would be fabricated after this linkage was in place. The major (9*S*) stereoisomer of **75** was separated from the mixture and was reacted sequentially with tri-*n*-butylphosphine, 1,8-diazabicyclo[5.4.0]undecen-7-ene and aldehyde **52** to give olefin **76**. This alcohol was converted to its mesylate **77**, the C5 silyl ether was cleaved with acidic methanol, and alcohol **78** was treated with triethylamine to furnish **79** in 54% overall yield for the four steps from (9*S*)-**75**. With acquisition of the C4–C32 portion of phorboxazole A in the form of **79**, it appeared that advance towards the C4–C46 domain of **1** along lines drafted in Scheme 1 would be straightforward. However, this proved to be a false hope that required further revisions to the synthesis plan as described below.

Coupling of C20–C32 with C33–C46

As a prelude to assembling the complete C4–C46 segment of **1**, we first investigated the union of lactone **3** with a simpler partner

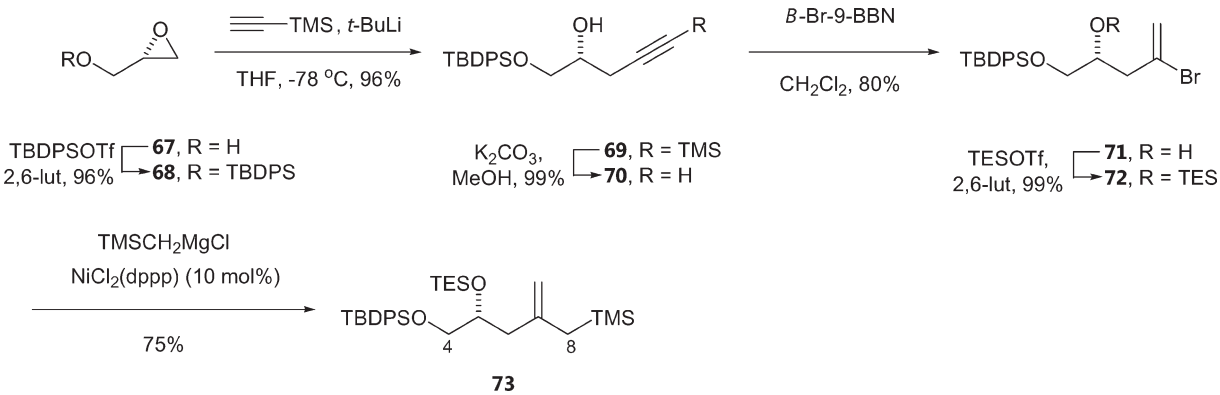
Table 1 Intramolecular alkoxycarbonylation of **60** using stoichiometric and catalytic palladium(II) salts



60 **65** **66**

Entry	Pd(II) salt	Equivs	Stoichiometric oxidant	Equivs oxidant	Yield (%) **65**	**66**
1	$Pd(OAc)_2$	3	None	—	41	0
2	$PdCl_2$	3	None	—	20	46
3	$PdCl_2(MeCN)_2$	3	None	—	23	51
4	$PdCl_2(MeCN)_2$	10 mol%	$CuCl_2$	4	21	33
5	$PdCl_2(MeCN)_2$	10 mol%	*p*-Benzoquinone	5.5	58[a]	0

[a] 17% of **60** was recovered.



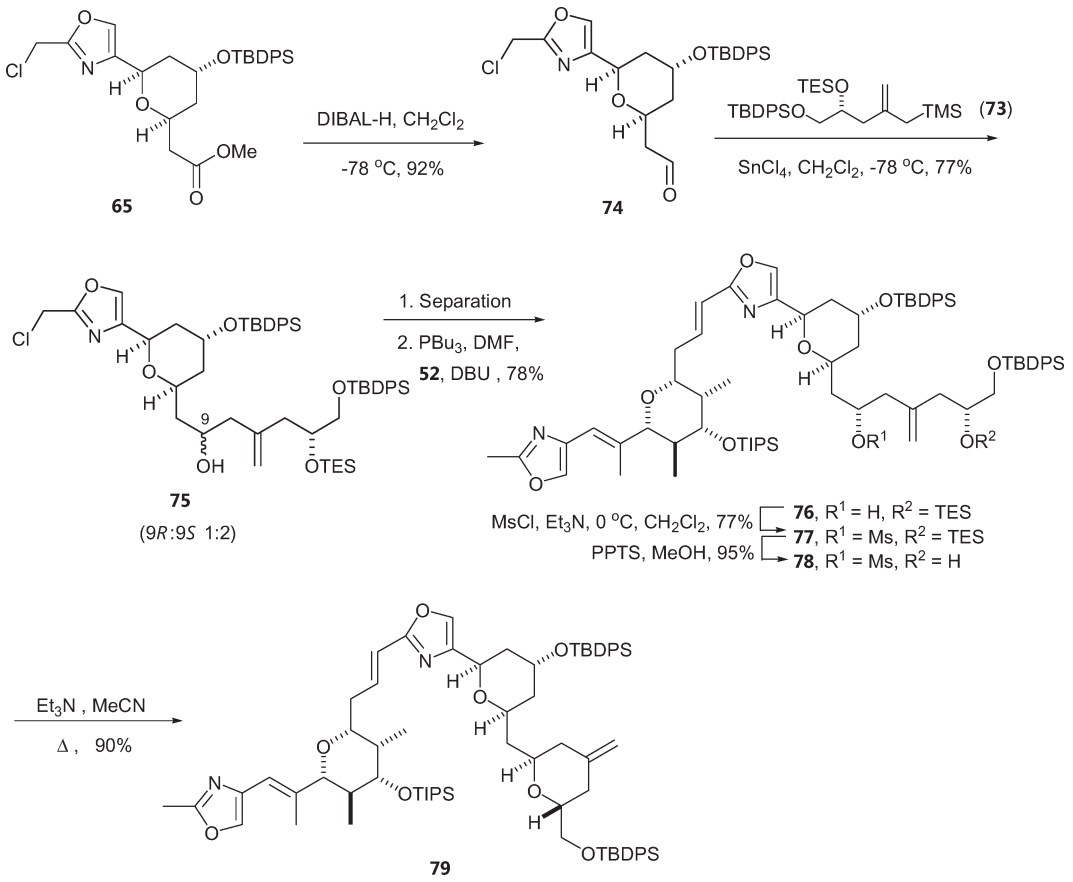
73

Scheme 11 Synthesis of C4–C8 subunit **73** from (*S*)-glycidol.

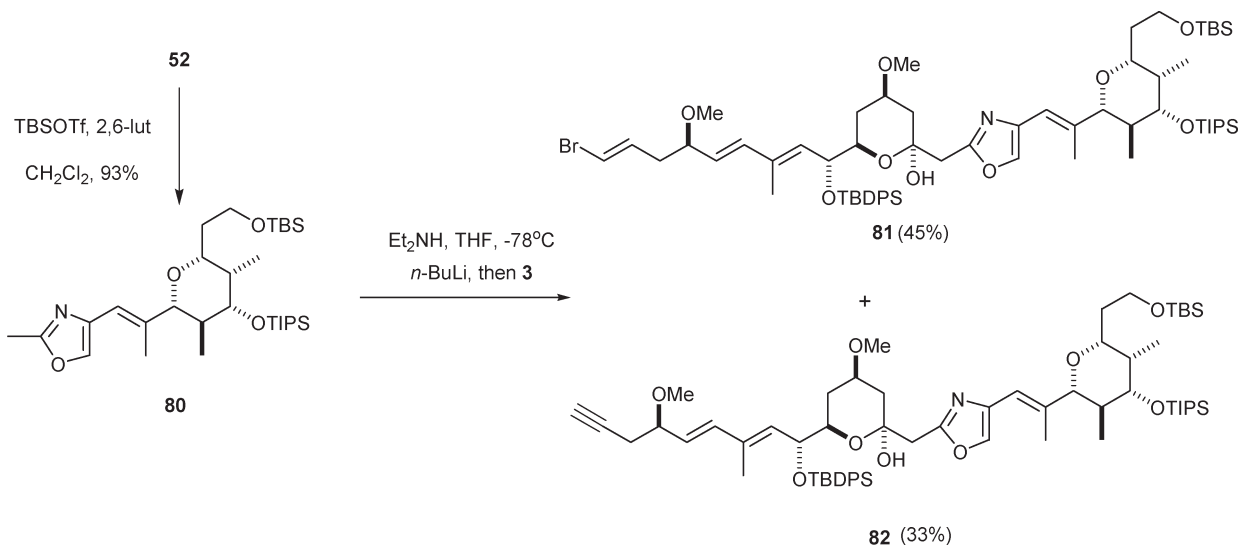
80 which was prepared by silylation of alcohol **52**. A similar coupling was carried out by Pattenden *et al.*[4e] and Evans *et al.*[5a] in their phorboxazole syntheses, but in our hands treatment of **80** with lithium diethylamide followed by **3** gave, in addition to the expected product **81**, the terminal alkyne **82** in nearly equal quantity (Scheme 13). Separation of the two products was accomplished by preparative thin-layer chromatography and an attempt was made to convert alkyne **82** to (*E*)-vinyl bromide **81** along lines used by Smith as the final step in his synthesis of **1**.[4b] Although reaction of **82** with silver nitrate and *N*-bromosuccinimide gave a bromoalkyne in good yield, subsequent palladium(II)-catalyzed stannylation failed to produce the desired (*E*)-vinylstannane. Our attempt to repair this deviant C32–C33 coupling was therefore abandoned.

Formation of terminal alkyne **82** along with **81** is due to difficulty in controlling the precise quantity of base needed to deprotonate **80** for linkage with **3**,[39] and in order to recast the C32–C33 union in a way that would avoid generating an alkyne an additional disconnection at C41–C42 was introduced into the synthesis plan. In this modification, a C42–C46 fragment would be installed after coupling C20–C32 unit **83** with lactone **84** and Julia–Kocienski olefination[40] with known sulfone **85**[4d] along lines employed by Williams *et al.*[4d,f] and Lin and co-workers[5b] would be used for the C41–C42 conjunction (Scheme 14). A further revision, made for reasons that became apparent later when a free alcohol in tetrahydropyran B was needed for macrocyclization, was replacement of the C24 triisopropylsilyl ether of **80** by a *p*-methoxybenzyl ether in **83**.

Oxazole **83** and lactone **84** were obtained from fragments synthesized previously en route to C20–C32 and C33–C46 subunits, respectively (Scheme 15). First, alcohol **86** was prepared from **34α** by oxidation to an aldehyde, Wittig olefination with ylide **23** and reduction of the resultant ester. After conversion of **86** to the primary *tert*-butyldimethylsilyl ether **87**, the phenylthio acetal was hydrolyzed and the resulting hemiacetal was oxidized to lactone **84**. In a parallel sequence, the triisopropylsilyl ether of **52** was cleaved to produce a diol in which the primary alcohol was selectively masked as the corresponding *tert*-butyldimethylsilyl ether. The latter was then reacted with *p*-methoxybenzyl chloride and tetra-*n*-butylammonium iodide to give **83**. In contrast to the coupling of **80** with **3**, condensation of the C32 anion of **83** with lactone **84** proceeded cleanly and in excellent yield to

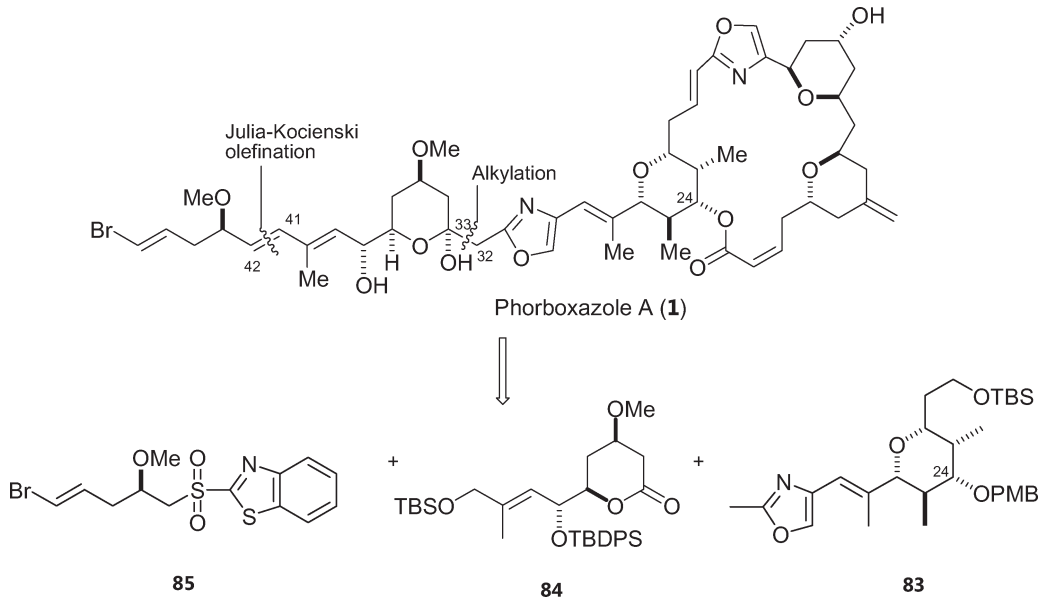


Scheme 12 Assembly of C4–C32 domain from **73**,**74** and **52**.

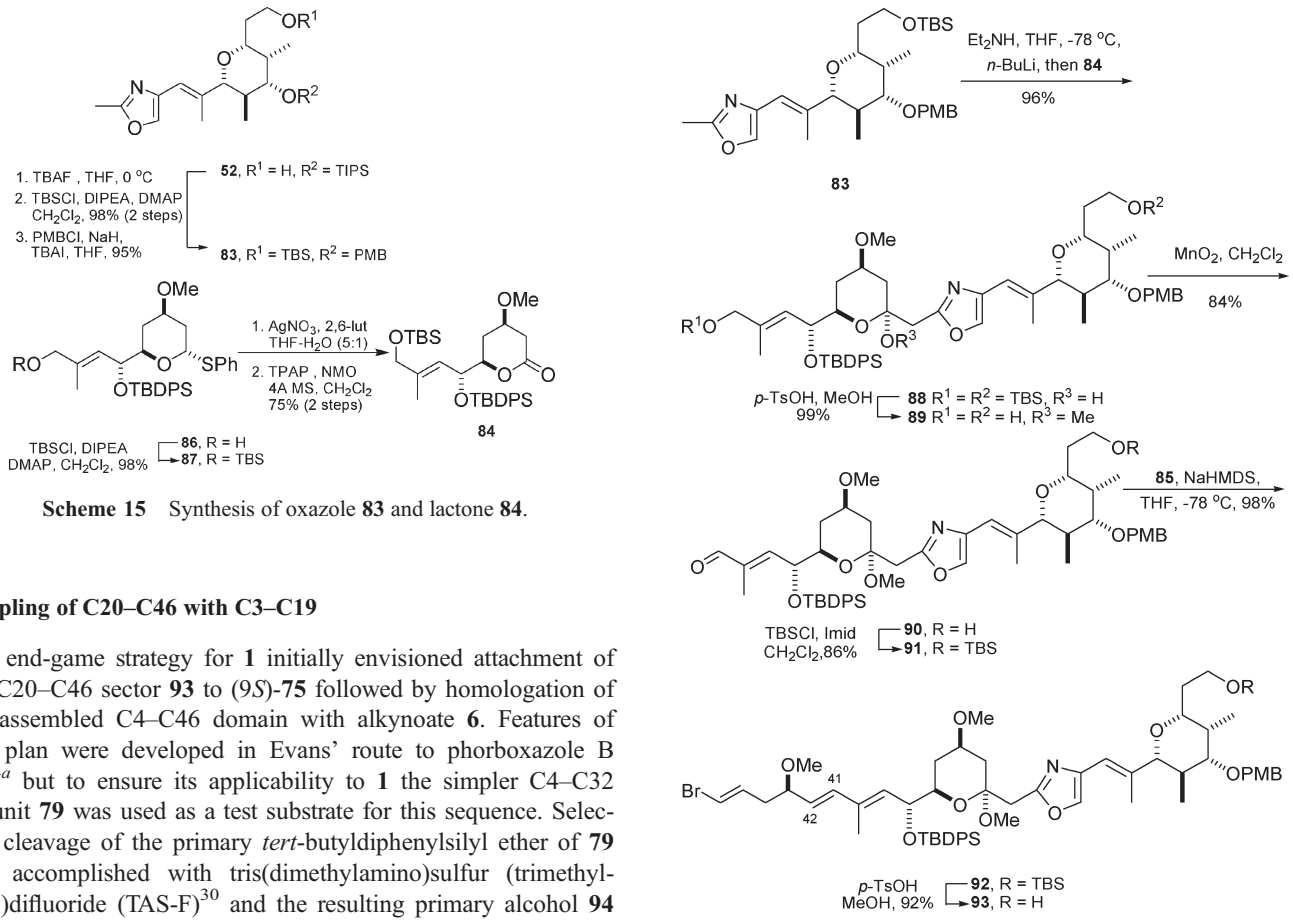


Scheme 13 Coupling of oxazole **80** with lactone **3**.

afford **88** as a single hemiacetal stereoisomer (Scheme 16). The two *tert*-butyldimethylsilyl ethers of **88** were cleaved and the allylic alcohol of diol **89** was selectively oxidized with manganese dioxide to afford α,β-unsaturated aldehyde **90**. After protection of **90** as silyl ether **91**, Julia–Kocienski olefination of this aldehyde with sulfone **85** furnished the fully funtionalized C20–C46 segment **92** of phorboxazole A containing the requisite C41–C42 (*E*) olefin. Unmasking the remaining *tert*-butyldimethylsilyl ether gave primary alcohol **93** and set the stage for coupling to the C3–C19 subunit.



Scheme 14 Revised route to phorboxazole A using C41–C42 olefination.

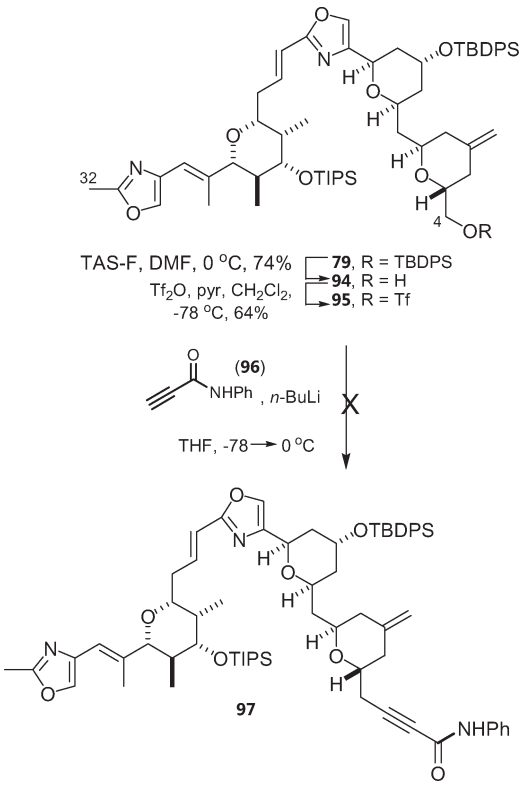


Scheme 15 Synthesis of oxazole **83** and lactone **84**.

Scheme 16 Synthesis of C20–C46 domain from oxazole **83**, lactone **84**, and sulfone **85**.

Coupling of C20–C46 with C3–C19

The end-game strategy for **1** initially envisioned attachment of the C20–C46 sector **93** to (9*S*)-**75** followed by homologation of the assembled C4–C46 domain with alkynoate **6**. Features of this plan were developed in Evans' route to phorboxazole B (**2**),[4a] but to ensure its applicability to **1** the simpler C4–C32 subunit **79** was used as a test substrate for this sequence. Selective cleavage of the primary *tert*-butyldiphenylsilyl ether of **79** was accomplished with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F)[30] and the resulting primary alcohol **94** was advanced to triflate **95** (Scheme 17). However, attempts to replicate the blueprint outlined in Scheme 1 by displacing the triflate from **95** with alkynoate nucleophiles, including the dianion of *N*-phenylpropiolamide (**96**), resulted in extensive decomposition with no evidence for the formation of **97**. This result caused us to reconsider our planned conclusion of the synthesis *via* macrolactonization and led to a final revision in which intramolecular olefination to form the C2–C3 (*Z*) double



Scheme 17 Attempted homologation of C4–C32 subunit with 96 *via* triflate 95.

bond would close the macrocycle. This realignment required two significant modifications to previously synthesized intermediates. First, an additional carbon representing C3 as an aldehyde had to be introduced into the precursor for **1**; second, a C1–C2 fragment that could initiate olefination would need to be positioned at the C24 hydroxy group. The first requirement was met by allylsilane **98**, a one-carbon homologue of **73**.

The route to **98** began with conversion of 1,3-propanediol to its mono-*tert*-butyldiphenylsilyl ether and oxidation to aldehyde **99** (Scheme 18). Asymmetric allylation[10] of **99** afforded (*R*) homoallylic alcohol **100** with e.r. > 96 : 4 as measured from the ^{19}F NMR spectrum of its Mosher ester.[25] After protection of this alcohol as its triethylsilyl ether **101**, ozonolytic cleavage of the vinyl group gave aldehyde **102** which was condensed with diazaphosphonate **103**[41] to give alkyne **104**. Exposure of this alkyne to *B*-bromo-9-borabicyclo[3.3.1]nonane[33] resulted in partial cleavage of the triethylsilyl ether, and in order to avoid handling a mixture the triethylsilyl ether of **104** was cleaved selectively with acidic methanol and the pure alkynol **105** was brominated to yield bromoalkene **106**. The latter was reprotected as **107** and was reacted with (trimethylsilylmethyl)magnesium chloride in the presence of Kumada *et al.*'s nickel(II) catalyst[35] to give **98** in an overall yield of 34% for the ten steps from 1,3-propanediol.

The condensation of aldehyde **74** with allylsilane **98** in the presence of stannic chloride gave the expected 2 : 1 mixture of C9 homoallylic alcohols in which the major component **108** was assigned (9*S*) configuration by NMR comparison with **75** of known configuration (Scheme 19). After separation from its minor (9*R*) diastereomer, **108** was coupled with aldehyde **109**, obtained by oxidation of **93**, using the olefination method previously employed with **75** (Scheme 20). The C9 alcohol of the resultant (*E*) alkene **110** was converted to mesylate **111**, the C5 triethylsilyl ether of **111** was cleaved, and the liberated alcohol **112** was treated with triethylamine in acetonitrile to deliver **113**. This sequence completed the four tetrahydropyran rings of phorboxazole A and produced a C3–C46 assemblage that housed all but two of the carbons needed for the final target.

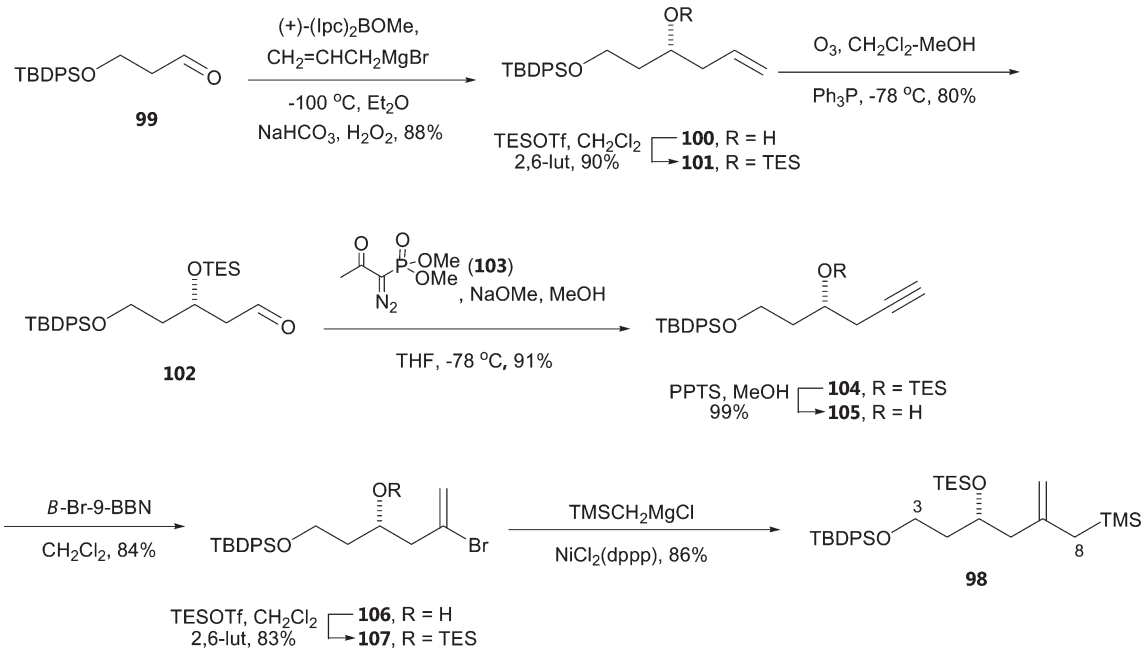
Macrocyclization and completion of the synthesis

Of the six completed syntheses of phorboxazoles,[4,5] all except that of Evans *et al.*[5a] employed intramolecular Gennari–Still olefination[42] to close the macrolactone. A modification of this approach that held appeal for us was the prospect of setting (*Z*) configuration at the C2–C3 alkene of **1** using an intramolecular variant of Ando's phosphonate methodology,[43] and this move became the pivotal gambit in our end-game strategy. First, the *p*-methoxybenzyl ether was cleaved with buffered 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Scheme 21) but the C24 hydroxy group of **114** proved to be too sterically hindered to react with (diphenoxyphosphinyl)acetic acid under Ando's conditions. Fortunately, esterification of **114** with (dimethoxyphosphinyl)acetic acid (**115**) in the presence of *N*,*N*-dicyclohexylcarbodiimide as described by Williams *et al.*[4d] afforded phosphonate **116** in high yield. In a previous study,[44] we had shown that a primary *tert*-butyldiphenylsilyl ether can be cleaved selectively with ammonium fluoride in methanol at 50 °C,[45] and application of this protocol to **116** led efficiently to alcohol **117**. Oxidation of **117** then furnished macrocyclization precursor **118**.

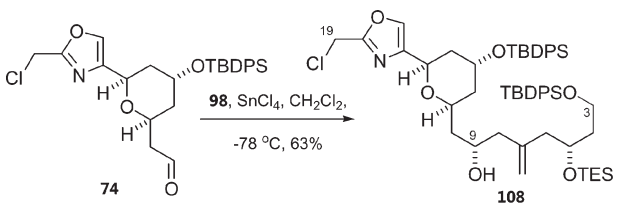
Intramolecular condensation of **118** under conditions described by Williams *et al.*[4d] produced the expected lactone **119** in high yield as an inseparable 3.5 : 1 mixture of C2–C3 olefin isomers in which the desired (*Z*) alkene predominated (Scheme 22). The mixture was reacted with tetra-*n*-butylammonium fluoride to cleave both silyl ethers, and diol **120** was obtained as the pure (2*Z*) olefin isomer after chromatography. Final acidic hydrolysis of the C33 methyl acetal then gave phorboxazole A (**1**). Although a sample of natural phorboxazole A was not available, the identity of our synthesized material was established by comparison of its ^{1}H NMR spectrum with that published for **1**[2a] and also by correspondence of its ^{13}C NMR spectrum with data recorded in the literature.[4d]

Conclusion

A synthesis of phorboxazole A was completed in which the longest linear sequence is 37 steps and the overall yield is 0.36%. Previous routes to **1** have overall yields that fall in the range 0.3%[4e] to 4.8%[4f] and are characterized by a longest linear sequence that is uniformly 30 to 38 steps A distinguishing feature of our route is application of intramolecular palladium(II)-mediated alkoxycarbonylation for fabrication of two of the four tetrahydropyrans of the molecule, along with the finding that this ring construction can be made catalytic in the metal. The scarcity of natural phorboxazole A, together with its extraordinary potency as an antitumor agent, puts a heavy premium on



Scheme 18 Synthesis of C3–C8 subunit **98** from propanal **99**.



Scheme 19 Assembly of C3–C19 domain from **74** from allylsilane **98**.

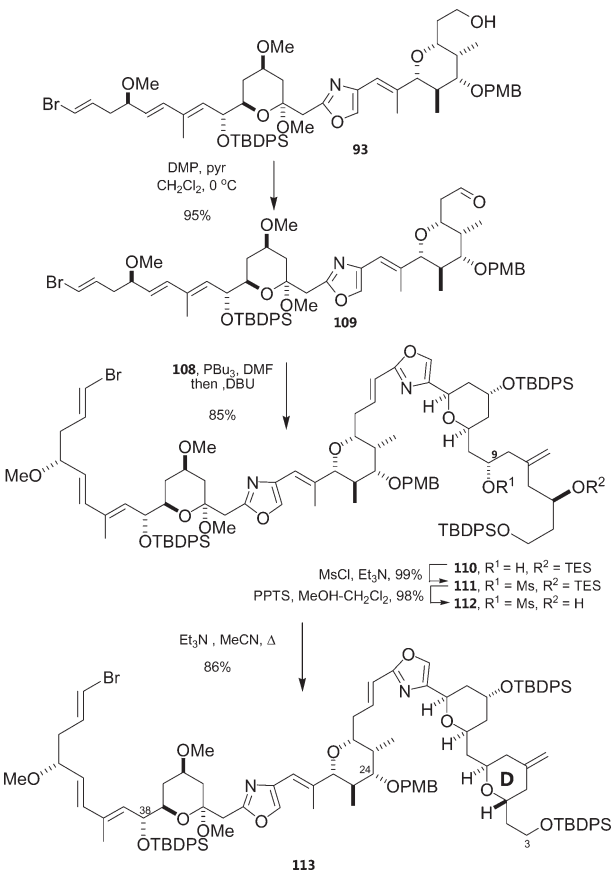
synthesis for studies of its biological properties and a modular route such as that described above is probably the most realistic means for acquiring phorboxazoles and their analogues in sufficient quantity for future research.

Experimental

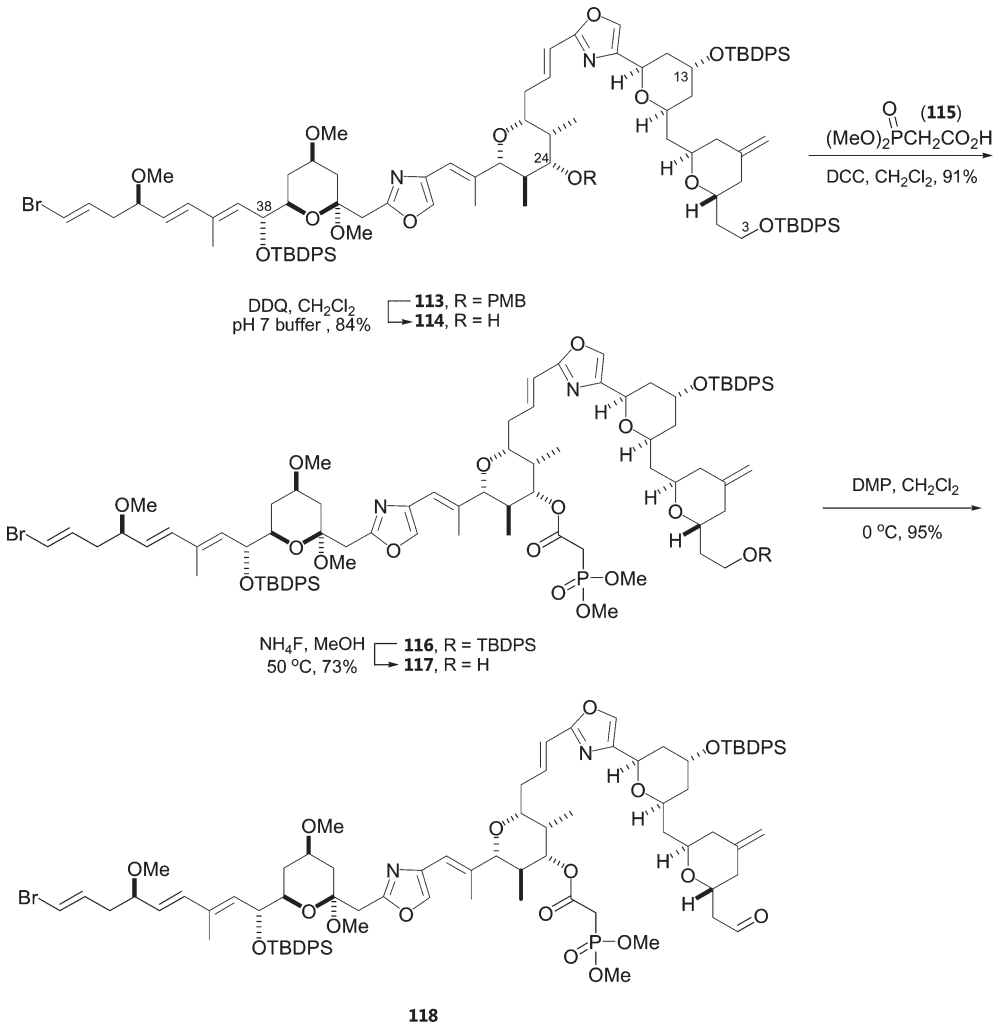
General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under an argon atmosphere. Toluene, diisopropylethylamine, triethylamine, pyridine and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under a stream of argon gas, and glass syringes were oven dried at 120 °C prior to use.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at a pressure less than 0.25 mm of mercury.



Scheme 20 Assembly of C3–C46 sector and tetrahydropyran D from aldehyde **109** and C3–C19 subunit **108**.

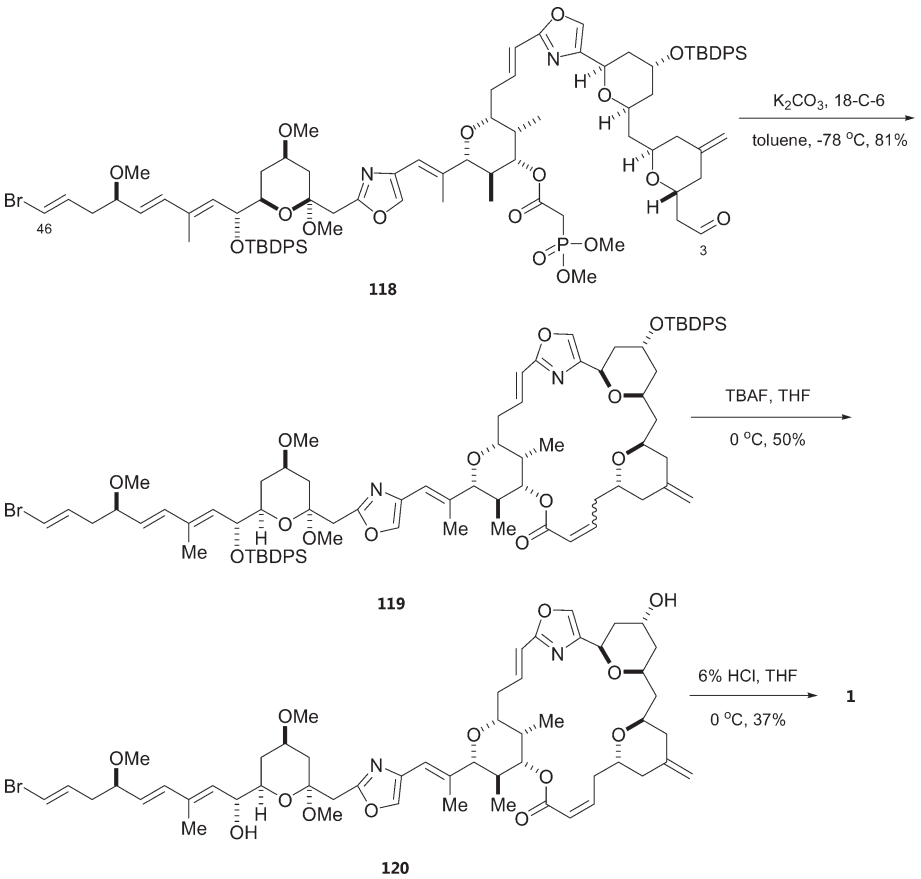


Scheme 21 Synthesis of macrolactonization precursor **118** from C3–C46 segment **113**.

Analytical thin-layer chromatography (TLC) was conducted using E. Merck precoated plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 3–5% solution of phosphomolybdic acid in ethanol, 10% ammonium molybdate in water, a 1% solution of vanillin in 0.1 M sulfuric acid in methanol or 2.5% *p*-anisaldehyde in 88% ethanol, 5% water, 3.5% concentrated sulfuric acid, and 1% acetic acid. Flash chromatography was carried out using silica gel (230–400 mesh ASTM or 40 μm particle size). Optical rotations were measured with a polarimeter at ambient temperature using a 0.9998 dm cell with 1 mL capacity. Infrared (IR) spectra were recorded on a FT-IR spectrometer. Proton nuclear magnetic resonance (NMR) spectra were measured at either 300 or 400 MHz and carbon-13 spectra were measured at 75 or 100 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad), coupling constant (*J*, in hertz) and number of protons. NMR analysis of (*R*) and (*S*) Mosher esters of alcohol mixtures from asymmetric reactions was carried out using ^{1}H, ^{13}C and ^{19}F signals, and absolute configurational assignments were made using Kakisawa's method[37] with these esters.

Chemical ionization (CI) high- and low-resolution mass spectra (HRMS and MS) were obtained using a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained at 70 eV. Fast atom bombardment (FAB) mass spectra were measured using a MS-50 spectrometer.

(2*R*,3*S*,4*R*,5*S*,6*R*)-3,5-Dimethyl-6-[(1*E*)-1-methyl-2-(2-methyloxazol-5-yl)vinyl]-4-triisopropylsilanyloxytetrahydropyran-2-yl}-acetic acid methyl ester (49). To a solution of **48** (973 mg, 2.3 mmol) in methanol (20 mL) under carbon monoxide at room temperature was added a solution of palladium(II) acetate (911 mg, 3.85 mmol) in acetonitrile (40 mL) and methanol (20 mL) and the mixture was stirred at room temperature for 20 h, at which time an additional quantity of palladium(II) acetate (427 mg, 1.8 mmol) was added. The black suspension was stirred for a further 24 h and was filtered through a short pad of silica. The filter pad was washed with a mixture of ether and ethanol (10 : 1) and the filtrate was concentrated under reduced



Scheme 22 Intramolecular olefination of C1–C46 sector **118** leading to phorboxazole A (**1**).

pressure to give crude **49** (1.29 g). Flash chromatography of this material on silica gel (toluene–methanol 20 : 1) gave pure **49** (947 mg, 86%) as a colourless oil: $[\alpha]_D^{23}$ +14.1 (*c* 1.19, $CHCl_3$); IR (neat) 3161, 2945, 2891, 2867, 1743, 1587, 1462, 1437, 1382, 1311, 1266, 1244, 1194, 1175, 1106, 1081, 1066, 1031, 998, 981, 883, 807, 677, 635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 1.09 (m, 21H), 1.71 (m, 1H), 1.91 (d, J = 1 Hz, 3H), 1.93 (m, 1H), 2.40 (dd, J = 6, 16 Hz, 1H), 2.45 (s, 3H), 2.63 (dd, J = 8, 16 Hz, 1H), 3.49 (d, J = 10 Hz, 1H), 3.67 (s, 3H), 3.68 (m, 1H), 3.94 (ddd, J = 2, 6, 8 Hz, 1H), 6.18 (s, 1H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.3, 13.0, 14.0, 14.1, 14.5, 18.4, 18.4, 35.1, 38.3, 39.2, 51.9, 74.8, 77.7, 89.0, 118.8, 135.8, 138.0, 138.1, 160.8, 172.0; MS (CI) *m*/*z* 479 (M^+), 448, 436, 404, 378, 355, 305, 285, 273, 243, 164, 131, 121; HRMS (CI) *m*/*z* 479.3072, calcd for $C_{26}H_{45}NO_5Si$ *m*/*z* 479.3067.

Methyl 2-((2*S*,4*R*,6*S*)-4-(*tert*-butyldiphenylsilanyloxy)-6-(2-((*E*)-3-((2*R*,3*S*,4*S*,5*S*, 6*R*)-3,5-dimethyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-*2H*-pyran-2-yl)acetate (63). To a solution of **62** (29 mg, 0.07 mmol) in anhydrous methanol (3 mL) under a carbon monoxide atmosphere was added a solution of palladium(II) acetate (15 mg, 0.14 mmol) in anhydrous acetonitrile (6 mL) and anhydrous methanol (3 mL). The initial orange colour of the solution turned black after 15 min at room temperature. Progress of the reaction was monitored by thin-layer chromatography and an additional quantity of palladium(II) acetate (15.1 mg, 0.14 mmol) in anhydrous acetonitrile (1.5 mL) and anhydrous methanol (1.5 mL) was added every 24 h during 6 d (total 90.6 mg, 0.84 mmol, 12 equiv of palladium(II) acetate). The mixture was concentrated under reduced pressure, the residue was taken up in ether (20 mL) and the suspension was filtered through a short column of silica, eluting with ether. The eluent was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (hexanes–ethyl acetate 3 : 1) to furnish **63** (14 mg, 44%) as a colourless oil: $[\alpha]_D^{23}$ +44.8 (*c* 1.10, $CHCl_3$); IR (film) 2930, 2865, 1740, 1462, 1427, 1110, 1084, 1066, 738, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 7 Hz, 3H), 0.95 (m, 33H), 1.80, (m, 6H), 1.88 (s, 3H), 2.15 (m, 1H), 2.40 (m, 2H), 2.50 (s, 3H), 2.54 (m, 1H), 2.67 (dd, J = 7, 15 Hz, 1H), 3.58 (M, 4H), 3.67 (s, 3H), 3.97 (m, 1H), 4.30 (s, 1H), 4.57 (ddq, J = 7, 10, 10 Hz, 1H), 5.06 (d, J = 10 Hz, 1H), 6.19 (s, 1H), 6.33 (d, J = 16 Hz, 1H), 6.64 (ddd, J = 7, 8, 16 Hz, 1H), 7.55 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.5, 14.2, 14.4, 14.7, 18.7, 19.7, 27.3, 27.4, 30.0, 35.6, 37.8, 38.4, 39.6, 41.0, 41.5, 52.0, 53.8, 66.0, 68.0, 69.6, 78.2, 89.3, 118.8, 119.0, 128.1, 130.2, 134.3, 134.7, 136.0, 136.1, 136.2, 138.2, 138.6, 142.9, 161.0, 161.4, 171.8; MS (FAB) *m*/*z* 925 (M^+), 867, 667, 625, 367, 327, 239, 197, 135, 87; HRMS (FAB) *m*/*z* 925.5219, calcd for $C_{53}H_{77}N_2O_8Si_2$ *m*/*z* 925.5219.

There was also obtained **64** (7 mg, 22%) as a mixture of two diastereomers: IR (film) 3385, 2945, 2865, 1739, 1457, 1436,

1110, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 7 Hz, 1H), 1.10 (m, 33H), 1.93 (s, 3H), 2.00 (m, 6H), 2.28 (m, 1H), 2.45 (s, 3H), 2.55 (ddd, J = 4, 7, 8 Hz, 1H), 2.80 (m, 2H), 3.55 (m, 10H), 4.00 (t, J = 6 Hz, 1H), 4.79 (m, 1H), 6.18 (s, 1H), 6.27 (dd, J = 4, 16 Hz, 1H), 6.65 (m, 1H), 7.19 (2s, 1H), 7.50 (s, 1H), 7.55 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.5, 13.3, 14.2, 14.4, 14.7, 18.6, 18.7, 19.7, 27.4, 35.6, 36.2, 36.8, 37.9, 39.3, 39.7, 52.1, 70.2, 78.2, 89.3, 118.4, 118.9, 128.1, 130.2, 133.9, 136.0, 136.3, 138.6, 161.0, 161.5, 172.2, 172.4, 175.4, 175.6; MS (FAB) 985 (M^+), 927, 849, 729, 427, 367, 327, 239, 199, 135, 87; HRMS (FAB) m/z 985.5422, calcd for $C_{55}H_{81}N_2O_{10}Si_2$ m/z 985.5430.

(2*S*,4*R*,6*R*)-2-((4-((*E*)-2-((2*R*,3*R*,4*S*,5*S*,6*R*)-6-(2-(*tert*-Butyldimethylsilanyloxy)ethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-6-((*R*,*E*)-2,2,7,10,10,11,11-heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodec-6-en-5-yl)-4-methoxytetrahydro-2*H*-pyran-2-ol (88). To a solution of **83** (20.1 mg, 38 μmol) and diethylamine (23 μL, 226 μmol) in tetrahydrofuran (350 μL) at −78 °C was added dropwise *n*-butyllithium (2.46 M solution in hexane, 20 μL, 49 μmol) during which the solution turned bright yellow. After 25 min, a solution of **84** (10.6 mg, 18.2 μmol) in tetrahydrofuran (175 μL) at −78 °C was added *via* syringe over 10 min (5 μL per 30 sec) during which the colour of the mixture faded to a light brownish-yellow. After 40 min, the reaction was quenched with water (1 mL) and the mixture was extracted with ether (10 mL × 3). The combined extract was washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane–ethyl acetate 9 : 1) to give **88** (19.4 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ +39.7 (*c* 0.86, $CHCl_3$); IR (neat) 3372, 2955, 2928, 2856, 1613, 1576, 1513, 1462, 1428, 1361, 1249, 1090, 1035, 836, 776, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.56 (m, 4H), 7.39 (s, 1H), 7.36–7.26 (m, 8H), 6.86 (d, J = 9 Hz, 2H), 6.11 (s, 1H), 5.28 (d, J = 8 Hz, 1H), 4.81 (s, 1H), 4.57 (d, J = 11 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 4.32–4.27 (m, 1H), 3.93–3.85 (m, 1H), 3.79 (s, 3H), 3.73–3.64 (m, 5H), 3.57–3.52 (m, 1H), 3.39 (d, J = 10 Hz, 1H) 3.32 (s, 3H), 3.18 (dd, J = 5, 10 Hz, 1H), 2.97 (d, J = 16 Hz, 1H), 2.91 (d, J = 16 Hz, 1H), 2.24–2.18 (m, 1H), 2.10–2.02 (m, 2H), 1.90–1.75 (m, 3H), 1.84 (s, 3H), 1.60–1.50 (m, 2H), 1.05–0.90 (m, 15H), 0.87 (s, 9H), 0.86 (s, 9H), 0.78 (d, J = 6 Hz, 3H), 0.01 (s, 6H), −0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.2, 138.6, 137.7, 136.0, 136.0, 135.5, 134.4, 134.3, 130.8, 129.4, 129.4, 129.3, 127.3, 127.2, 122.8, 118.1, 113.8, 96.5, 89.0, 83.5, 74.7, 73.5, 73.1, 71.9, 69.6, 67.6, 60.0, 55.6, 55.3, 40.6, 40.0, 36.2, 34.3, 33.3, 32.0, 30.3, 29.7, 26.9, 26.0, 25.9, 19.2, 18.4, 18.3, 14.2, 13.8, 13.6, 6.1, −5.2, −5.3; MS (ES) m/z (M^+ + H) 1112; HRMS (ES) m/z 1112.6499 (calcd for $C_{63}H_{98}NO_{10}Si_3$: 1112.6461, M^+ + H).

13,38-Bis(*O*-*tert*-butyldiphenylsilanyl)-33-(*O*-methyl)phorboxazole A (119). A suspension of potassium carbonate (11.7 mg, 0.085 mmol) and 18-crown-6 (104 mg, 0.393 mmol) in toluene (6 mL) was stirred at room temperature for 3 h, then was cooled to −78 °C and a solution of **118** (11.6 mg, 7.07 μmol) in toluene (3 mL) was added *via* syringe. The mixture was slowly warmed to room temperature and was stirred for 62 h. The mixture was washed with brine (5 mL × 2), the brine washes were extracted with ethyl acetate (2 mL × 3) and the combined extract was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane–ethyl acetate 3 : 1) to give **119** (8.7 mg, 81%) as a 3.5 : 1 (*Z* : *E*) mixture of C2 olefin isomers: ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.74–7.71 (m, 2H), 7.67–7.60 (m, 7H), 7.52 (s, 1H), 7.44–7.27 (m, 12H), 6.70 (ddd, J = 6, 8, 16 Hz, 1H), 6.28 (d, J = 16 Hz, 1H), 6.25 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.90 (bs, 1H), 5.34 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 5.01 (brs, 1H), 4.89 (d, J = 12 Hz, 1H), 4.82–4.75 (m, 1H), 4.63 (s, 1H), 4.53–4.48 (m, 2H), 4.31 (s, 1H), 4.21–4.07 (m, 3H), 4.00–3.95 (m, 1H), 3.60–3.52 (m, 5H), 3.28 (s, 3H), 3.26 (s, 3H), 3.21 (s, 3H), 2.95 (d, J = 15 Hz, 1H), 2.75 (d, J = 12 Hz, 1H), 2.58–2.49 (m, 1H), 2.48–1.04 (m, 20H), 1.93 (d, J = 1 Hz, 3H), 1.18 (d, J = 1 Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H), 0.96 (d, J = 7 Hz, 3H), 0.76 (d, J = 6 Hz, 3H); HRMS (MALDI) calcd for $C_{86}H_{109}N_2O_{13}Si_2{}^{79}BrNa$ (M + Na, $^{79}Br)^+$ 1535.6549, found 1535.6544.

Acknowledgements

We are grateful to the Ministry of Science and Technology of the Royal Thai Government for a predoctoral scholarship to P.K. and to the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship to C.L.K. Financial support was provided by the National Institute of General Medical Sciences (GM50574 and GM58889).

Notes and references

1 P. A. Searle and T. F. Molinski, *J. Am. Chem. Soc.*, 1995, **117**, 8126.
2 (*a*) P. A. Searle, T. F. Molinski, L. J. Brzezinski and J. W. Leahy, *J. Am. Chem. Soc.*, 1996, **118**, 9422; (*b*) T. F. Molinski, *Tetrahedron Lett.*, 1996, **37**, 7879; (*c*) T. F. Molinski, L. J. Brzezinski and J. W. Leahy, *Tetrahedron: Asymmetry*, 2002, **13**, 1013; (*d*) T. F. Molinski and J. Antonio, *J. Nat. Prod.*, 1993, **56**, 54.
3 F. M. Uckun and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1181.
4 Total syntheses of phorboxazole A: (*a*) C. J. Forsyth, F. Ahmed, R. D. Cink and C. S. Lee, *J. Am. Chem. Soc.*, 1998, **120**, 5597; (*b*) A. B. Smith III, P. R. Verhoest, K. P. Minbiole and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 4834; (*c*) M. A. Gonzalez and G. Pattenden, *Angew. Chem., Int. Ed.*, 2003, **42**, 1255; (*d*) D. R. Williams, A. A. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner and J. T. Reeves, *Angew. Chem., Int. Ed.*, 2003, **42**, 1258; (*e*) G. Pattenden, M. A. Gonzalez, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos and T. Ye, *Org. Biomol. Chem.*, 2003, **1**, 4173; (*f*) D. R. Williams, A. A. Kiryanov, U. Emde, M. P. Clark, M. A. Berliner and J. T. Reeves, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 12058; (*g*) A. B. Smith III, T. M. Razler, J. P. Ciavarri, T. Hirose, T. Ishikawa and R. M. Meis, *J. Org. Chem.*, 2008, **73**, 1192; (*h*) B. Wang, T. M. Hansen, L. Weyer, D. Wu, T. Wang, M. Christmann, Y. Lu, L. Ying, M. M. Engler, R. D. Cink, C. S. Lee, F. Ahmed and C. J. Forsyth, *J. Am. Chem. Soc.*, 2011, **133**, 1506.
5 Total syntheses of phorboxazole B: (*a*) D. A. Evans, D. M. Fitch, T. E. Smith and V. J. Cee, *J. Am. Chem. Soc.*, 2000, **122**, 10033; (*b*) D.-R. Li, D.-H. Zhang, C.-Y. Sun, J.-W. Zhang, L. Yang, J. Chen, B. Liu, C. Su, W.-S. Zhou and G.-Q. Lin, *Chem.–Eur. J.*, 2006, **12**, 1185.
6 Synthetic studies on phorboxazoles: (*a*) I. Paterson and E. A. Arnott, *Tetrahedron Lett.*, 1998, **39**, 7185; (*b*) P. Wolbers, A. M. Misske and H. M. R. Hoffmann, *Tetrahedron Lett.*, 1999, **40**, 4527; (*c*) P. Wolbers and H. M. R. Hoffmann, *Synlett*, 1999, 1808; (*d*) P. Wolbers and H. M. R. Hoffmann, *Synthesis*, 1999, 2291; (*e*) P. Wolbers and H. M. R. Hoffmann, *Tetrahedron*, 1999, **55**, 1905; (*f*) A. M. Misske and

H. M. R. Hoffmann, *Tetrahedron*, 1999, **55**, 4315; (*g*) S. Rychnovsky and C. R. Thomas, *Org. Lett.*, 2000, **2**, 1217; (*h*) J. V. Schaus and J. S. Panek, *Org. Lett.*, 2000, **2**, 469; (*i*) P. B. Greer and W. A. Donaldson, *Tetrahedron Lett.*, 2000, **41**, 3801; (*j*) H. Huang and J. S. Panek, *Org. Lett.*, 2001, **3**, 1693; (*k*) P. B. Greer and W. A. Donaldson, *Tetrahedron*, 2002, **58**, 6009; (*l*) I. Paterson and C. A. Luckhurst, *Tetrahedron Lett.*, 2003, **44**, 3749; (*m*) B. S. Lucas and S. D. Burke, *Org. Lett.*, 2003, **5**, 3915; (*n*) T. K. Chakraborty, V. R. Reddy and T. J. Reddy, *Tetrahedron*, 2003, **59**, 8613; (*o*) I. Paterson, A. Steven and C. A. Luckhurst, *Org. Biomol. Chem.*, 2004, **2**, 3026; (*p*) B. S. Lucas, L. M. Luther and S. D. Burke, *Org. Lett.*, 2004, **6**, 2965; (*q*) J. S. Yadav and G. Rajaiah, *Synlett*, 2004, 1537; (*r*) Y. Brinkmann, M. C. Carreno, A. Urbano, F. Colobert and G. Solladie, *Org. Lett.*, 2004, **6**, 4335; (*s*) J. P. Vitale, S. A. Wolckenhauer, N. M. Do and S. D. Rychnovsky, *Org. Lett.*, 2005, **7**, 3255; (*t*) J. S. Yadav, S. J. Prakash and Y. Gangadhar, *Tetrahedron: Asymmetry*, 2005, **16**, 2722; (*u*) B. S. Lucas, L. M. Luther and S. D. Burke, *J. Org. Chem.*, 2005, **70**, 3757; (*v*) B. Wang and C. J. Forsyth, *Org. Lett.*, 2006, **8**, 5223.

7 (*a*) A. B. Smith III, T. M. Razler, R. M. Meis and G. R. Pettit, *Org. Lett.*, 2006, **8**, 797; (*b*) J. Chen, L. Ying, T. M. Hansen, M. M. Engler, C. S. Lee, J. J. La Clair and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 901.

8 (*a*) J. D. White, P. Kuntiyong and T. H. Lee, *Org. Lett.*, 2006, **8**, 6039; (*b*) J. D. White, T. H. Lee and P. Kuntiyong, *Org. Lett.*, 2006, **8**, 6043.

9 M. Suzuki, M. Kambe, H. Tokuyama and T. Fukuyama, *J. Org. Chem.*, 2004, **69**, 2831.

10 U. S. Racherla and H. C. Brown, *J. Org. Chem.*, 1991, **56**, 401.

11 D. R. Williams, M. P. Clark, U. Emde and M. A. Berliner, *Org. Lett.*, 2000, **2**, 3023.

12 M. Schroeker, *Chem. Rev.*, 1980, **80**, 187.

13 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.

14 J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. Holoboski, L. E. Keown, C. S. Nylund Kolz and B. W. Phillips, *J. Org. Chem.*, 2002, **67**, 7750.

15 S. Hanessian and Y. Guindon, *Carbohydr. Res.*, 1980, **86**, C3.

16 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639.

17 B. M. Trost, J. Dumas and M. Villa, *J. Am. Chem. Soc.*, 1992, **114**, 9836.

18 J. D. White, J. Hong and L. A. Robarge, *Tetrahedron Lett.*, 1999, **40**, 1463.

19 (*a*) M. F. Semmelhack and N. Zhang, *J. Org. Chem.*, 1989, **54**, 4483; (*b*) M. McCormick, R. Monahan III, J. Soria, D. Goldsmith and D. Liotta, *J. Org. Chem.*, 1989, **54**, 4485; (*c*) M. F. Semmelhack, C. Kim, N. Zhang, C. Bodurow, M. Sanner, W. Dobler and M. Meier, *Pure Appl. Chem.*, 1990, **62**, 2035.

20 (*a*) M. F. Semmelhack and A. Zask, *J. Am. Chem. Soc.*, 1983, **105**, 2034; (*b*) K. R. Hornberger, C. L. Hamblett and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894. For application of intramolecular alkoxycarbonylation to a 7-hydroxyallene, see B. B. Snider and F. He, *Tetrahedron Lett.*, 1997, **31**, 5453.

21 J. D. White, C. L. Kranemann and P. Kuntiyong, *Org. Lett.*, 2001, **3**, 4003.

22 J. D. White, C. L. Kranemann and P. Kuntiyong, *Org. Synth.*, 2002, **79**, 244.

23 J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 1947, 96.

24 H. C. Brown, P. K. Jadhav and K. S. Bhat, *J. Am. Chem. Soc.*, 1988, **110**, 1535.

25 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.

26 A. Bouside and G. Sauve, *Synlett*, 1997, **9**, 1153.

27 M. Schlosser and B. Schaub, *J. Am. Chem. Soc.*, 1982, **104**, 5821.

28 P. Liu and J. S. Panek, *J. Am. Chem. Soc.*, 2000, **122**, 1235.

29 K. S. Cardwell, S. A. Hermitage and A. Sjolin, *Tetrahedron Lett.*, 2000, **41**, 4239.

30 (*a*) W. J. Middleton, *US Patent* 3,940,402, 1976; *Chem. Abstr.*, 1976, **85**, P6388j; (*b*) J. D. White and R. G. Carter, *Science of Synthesis*, ed. I. Fleming, Thieme, Stuttgart, Germany, 2002, vol. 4, pp. 371–412.

31 T. Hosokawa, M. Hirata and S.-I. Murahashi, *Tetrahedron Lett.*, 1976, 1821.

32 J. A. Marshall and M. M. Yanik, *Tetrahedron Lett.*, 2000, **41**, 4717.

33 H. C. Brown and S. U. Kulkarni, *J. Organomet. Chem.*, 1979, **168**, 281.

34 M. G. Organ and A. P. Murray, *J. Org. Chem.*, 1997, **62**, 1523.

35 T. Hayashi, T. Fujiwa, Y. Okamoto, Y. Katsuro and M. Kumada, *Synthesis*, 1981, 1001.

36 L. C. Dias, D. R. Santos and L. J. Steil, *Tetrahedron Lett.*, 2003, **44**, 6861.

37 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.

38 Evans' synthesis of phorboxazole B[5a] avoided this problem by masking the C7 *exo* methylene function as an alcohol.

39 A deuterium exchange experiment revealed that deprotonation can occur at the open C30 position of oxazole **80** under conditions that deprotonate C32.

40 P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett*, 1998, 26.

41 (*a*) S. Ohira, *Synth. Commun.*, 1989, **19**, 561; (*b*) S. Muller, B. Liepold, G. J. Roth and H. J. Bestmann, *Synlett*, 1996, 521.

42 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405.

43 K. Ando, *J. Org. Chem.*, 1999, **64**, 8406.

44 J. Hong and J. D. White, *Tetrahedron*, 2004, **60**, 5653.

45 W. Zhang and M. J. Robins, *Tetrahedron Lett.*, 1992, **33**, 1177.

46 E. A. Mash, K. A. Nelson, S. V. Deusen and S. B. Hemperly, *Org. Synth.*, 1990, **68**, 92.

47 P. N. Guivisdalsky and R. Bittman, *J. Org. Chem.*, 1989, **54**, 4637.