Total Synthesis of (+)-Calyculin A and (−)-Calyculin B: Cyanotetraene Construction, Asymmetric Synthesis of the C(26−37) Oxazole, Fragment Assembly, and Final Elaboration

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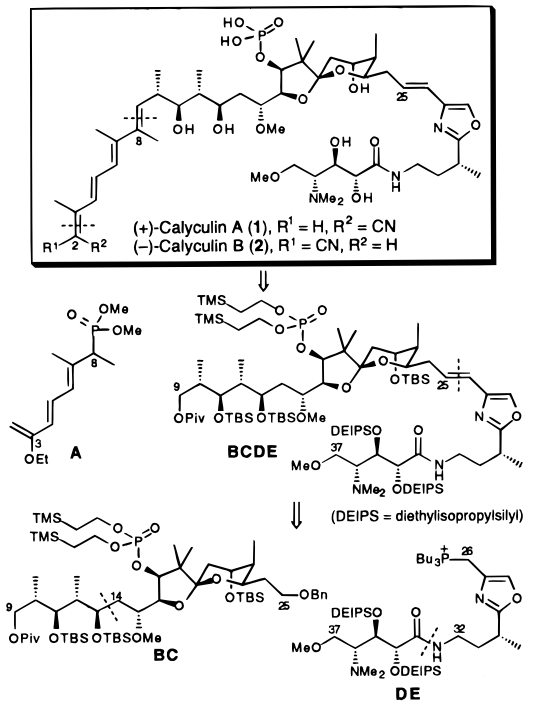
Received June 22, 1999

Abstract: A convergent total synthesis leading to (+)-calyculin A and (−)-calyculin B (**1** and **2**), antipodes of the potent, highly selective and remarkably cell-permeable phosphatase inhibitors calyculins A and B, has been achieved. In the preceding paper we outlined the asymmetric synthesis of the C(9−25) spiroketal dipropionate subunit (+)-**BC**; herein we describe construction of the C(1−8) cyanotetraene, an asymmetric synthesis of the C(26−37) oxazole, fragment assembly and final elaboration to (+)-**1** and (−)-**2**. Highlights of the synthesis include: application of a one-pot three-component Suzuki reaction for the construction of phosphonate **A**, a bifunctional triene precursor of the light sensitive C(1−8) cyanotetraene subunit, an asymmetric synthesis of the C(26−32) oxazole (−)-**D**, exploiting the Silks−Odom ^{77}Se NMR protocol to assess enantiomeric purity, construction of the C(33−37) subtarget (−)-**E** in a highly stereocontrolled fashion via an acyliminium ion, and a concise, highly efficient sequence for fragment assembly and elaboration to (+)-calyculin A and (−)-calyculin B. The synthesis of (−)-**2** also confirms the structure of calyculin B, previously based only on spectral comparison with calyculin A.

The calyculins comprise a family of potent, highly selective serine−threonine phosphatase inhibitors possessing a striking array of stereochemical and functional elements. In this, the second of a two-part full account,[1] we describe the completion of a highly convergent total synthesis of (+)-**1** and the first total synthesis of (−)-calyculin B (**2**).[2−4] From the outset, we envisioned an approach (Scheme 1) which would provide both **1** and **2** from a common advanced intermediate, avoid extensive manipulations of the light-sensitive[5] C(1−9) cyanotetraene, and permit flexibility in fragment coupling. Accordingly, disconnections at the C(2) and C(8) olefins led to phosphonate **A** (Scheme 1), possessing a latent C(3) carbonyl for penultimate Peterson olefination to access both **1** and **2**. Disconnection of **BCDE** at the C(25−26) olefin revealed subtargets **BC** and **DE**. Having described an efficient route to (+)-**BC** in the preceding paper, we detail here the synthesis and reactivity of phosphonate **A**, a concise, highly stereocontrolled route to (+)-**DE**, the union of subtargets **A**, (+)-**BC**, and (+)-**DE**, and completion of the total synthesis of (+)-calyculin A and (−)-calyculin B.

Scheme 1



(1) Part 1: Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, XXXX.

(2) At the start of our work, the absolute stereochemistry was unknown.

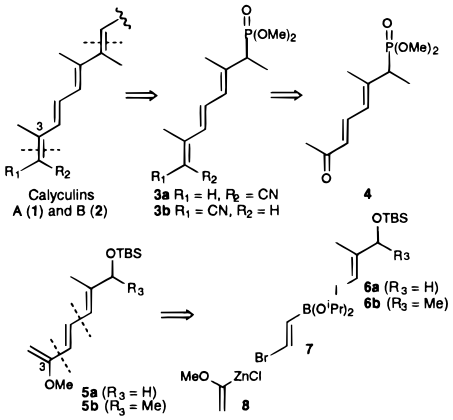
(3) Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1991**, *32*, 5605. (b) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 5983.

(4) Preliminary communications: (a) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596. (b) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765. (c) Iwashima, M.; Kinsho, T.; Smith, A. B., III. *Tetrahedron Lett.* **1995**, *36*, 2199. (d) Smith, A. B., III; Iwashima, M. *Tetrahedron Lett.* **1994**, *35*, 6051. (e) Salvatore, B. A.; Smith, A. B., III. *Tetrahedron Lett.* **1994**, *35*, 1329. (f) Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859. (g) Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855.

(5) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999.

10.1021/ja992135e CCC: $18.00
Published on Web 10/30/1999

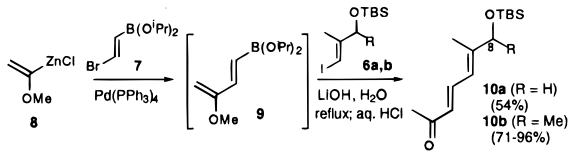
Scheme 2



Evolution of Phosphonate A. Initially we envisioned introduction of the C(1−9) cyanotetraene in one step employing Horner-Emmons reactions of unsaturated phosphonates **3a** and **3b** (Scheme 2) with a C(9) aldehyde derived from intermediate **BCDE**. Phosphonates **3a** and **3b** in turn would arise via Peterson olefination of ketophosphonate **4** with trimethylsilylacetonitrile. To fabricate **4** we planned to exploit a one-pot three-component Suzuki coupling[6] of *E*-bromovinyl boronate **7** with vinyl iodide **6a** or **6b** and organozinc **8**, followed by introduction of the phosphonate and mild acid hydrolysis of the intermediate enol ether. Importantly, the C(8) methyl could be present from the outset (i.e., **6b**), or introduced via α-methylation of the corresponding primary phosphonate.

We initiated the synthesis of **3a** and **3b** with known vinyl iodides **6a** and **6b**, available via Negishi carbometalation (Scheme 3).[7] Exposure of *E*-bromovinyl boronate **7** to vinyl

Scheme 3



zinc **8** in the presence of bis(triphenylphosphine)palladium(II) chloride (5 mol %) provided dienylboronate **9** (not isolated), which upon addition of a lithium hydroxide−methanol solution and vinyl iodide **6a** (or **6b**) established the C(3−8) carbon skeleton in the form of enol ethers **5a**,**b**; hydrolysis with dilute aqueous hydrochloric acid furnished ketones **10a** (or **10b**), albeit in variable but good yields.

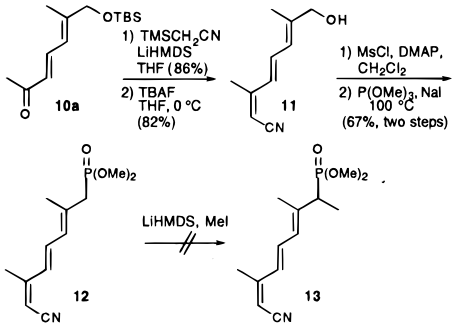
To test the viability of the Horner-Emmons tactic in the presence of the conjugated nitrile (i.e., after Peterson olefination), **10a** was treated with trimethylsilylacetonitrile and lithium bis(trimethylsilyl) amide; a mixture of *E*/*Z* olefins (∼2:1) resulted (Scheme 4), with the major isomer possessing the requisite C(2,3) *E* geometry as in calyculin B. Removal of the TBS group followed by conversion to the primary mesylate and Arbuzov reaction[8] with neat trimethyl phosphite and excess sodium iodide furnished phosphonate **12**; the overall yield for

(6) Ogima, M.; Hyuga, S.; Hara, S.; Suzuki, A. *Chem. Lett.* **1989**, 1959. (b) For a review on Suzuki coupling, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(7) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E.-I. *J. Org. Chem.* **1981**, *46*, 4093. Zirconium-catalyzed carboalumination, followed by quenching with iodine and protection of the allylic hydroxyl as the *t*-butyldimethylsilyl ether furnished **6a**,**b** from the corresponding propargylic alcohols.

(8) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

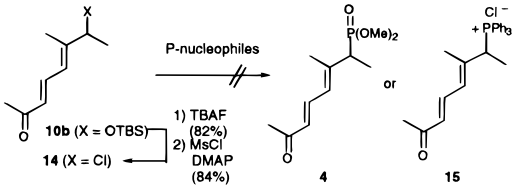
Scheme 4



the three steps was 55%. Unfortunately, α-methylation of **12** could not be achieved; treatment of **12** with a variety of bases led to severe olefin isomerization. This result did not build confidence in our ability to generate metalated phosphonate reagents in the presence of an unsaturated nitrile. We therefore decided to postpone Peterson olefination until after C(8−9) olefin construction.[9]

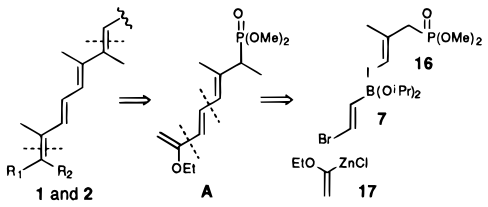
At this stage we also learned that introduction of the phosphonate group could not be readily achieved when C(8) was substituted with a methyl group (Scheme 5). For example,

Scheme 5



attempts to convert allylic chloride **14** to phosphonate **4** using the standard Arbuzov[8] or Becker[10] conditions proved unsuccessful. We therefore modified our approach to include the phosphonate prior to Suzuki coupling. In particular, we chose to employ a delicate balance of reactive functionality at the termini of the C(1−8) synthon (Scheme 6), which would require

Scheme 6

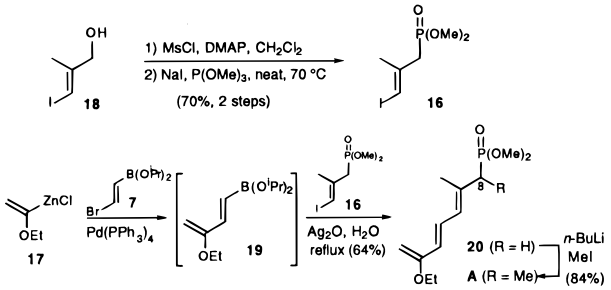


minimal manipulations after the Suzuki protocol. In the end, the successful strategy comprised direct use of the delicate enol ether derived from the Suzuki coupling (i.e., **A**), containing the phosphonate moiety for subsequent C(8) methylation and C(8−9) Horner-Emmons coupling. Peterson olefination would then be performed after generation of the C(8,9) olefin. Inclusion of the requisite phosphonate on the vinyl iodide (**16**) would also minimize the number of transformations performed on the sensitive trienol ether.

(9) The difficult methylation was consistent with reports by Evans et al. of the low reactivity of **13**, prepared by a different method, which did not undergo normal Horner-Emmons coupling, see: Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

(10) Engel, R. *Synthesis of Carbon-Phosphorous Bonds*; CRC Press: Boca Raton, FL, 1988; p 7.

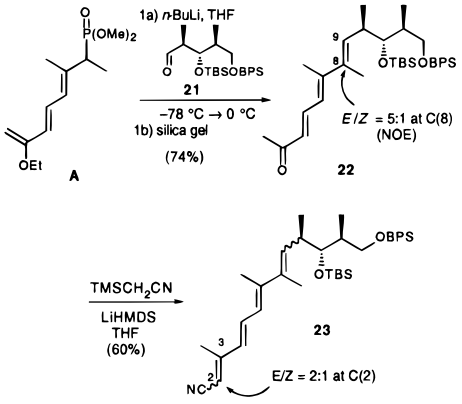
Scheme 7



Preparation of phosphonate **A** is illustrated in Scheme 7. Conversion of alcohol **18**[7] to the allylic chloride, followed by Arbuzov reaction with neat trimethyl phosphite and sodium iodide provided primary phosphonate **16** in 70% yield for two steps. This iodide proved quite unstable to the usual Suzuki coupling promoters (e.g., lithium methoxide and thallium hydroxide).[6b,11] However silver(I) oxide utilized by Kishi was found to be both mild and efficient in promoting the coupling of **16** with dienylboronate intermediate **19**.[11] In the event, treatment of vinyl iodide **16** at reflux with **19** (2 equiv, formed in situ) and Ag_2O (5−6 equiv) in aqueous THF provided **20** in approximately 60% yield. Although **20** could not be fully purified without significant decomposition, C(8) methylation (*n*-BuLi, MeI, −78 °C) occurred without complications, thereby completing assembly of phosphonate **A**.[12]

With phosphonate **A** in hand, we undertook a model study to explore both the Horner-Emmons coupling and Peterson olefination. Metalation of **A** (*n*-BuLi/THF), followed by introduction of model aldehyde **21**, provided a 5:1 (*E*/*Z*) mixture of C(8−9) olefins; hydrolysis of the enol ether (silica gel) gave ketone **22** in 74% yield. Peterson olefination then furnished cyanotetraene **23** as a 2:1 *E*/*Z* mixture (Scheme 8). These results

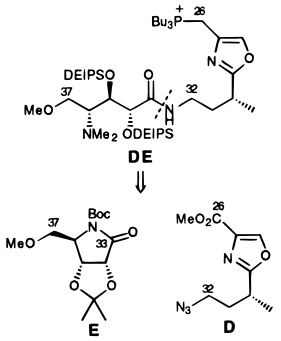
Scheme 8



suggested that phosphonate **A**, containing the sensitive bifunctional triene, would serve us well.

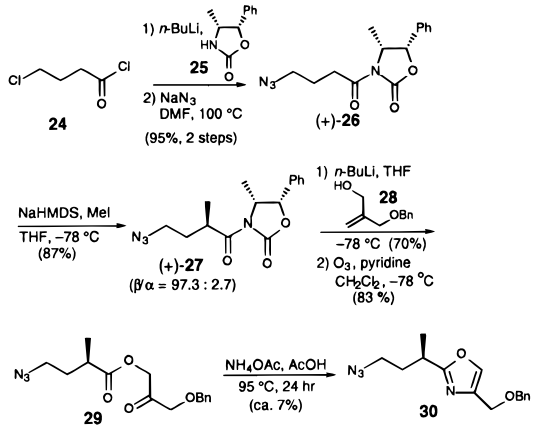
Evolution of the DE Subunit. Disconnection at the amide linkage of **DE** revealed two fragments, the C(26−32) oxazole **D** and lactam **E** (Scheme 9). Reduction of the azide in oxazole **D** followed by reaction with the acyl-activated lactam **E** would provide the **DE** subunit.

Scheme 9



Construction of the C(26−32) Oxazole via Davidson Cyclization. Reaction of commercially available 4-chlorobutyryl chloride (**24**, Scheme 10) with lithiated oxazolidinone **25**[13a]

Scheme 10



followed by displacement of the primary chloride with sodium azide furnished (+)-**26** in 95% yield for the two steps. Evans asymmetric methylation[13b] of the sodium enolate of (+)-**26** then led to (+)-**27** in high yield with excellent diastereoselectivity (94.6% de; HPLC). After separation by flash chromatography, displacement of the chiral auxiliary from (+)-**27** (β isomer) with the alkoxide derived from known allylic alcohol **28**[14] and subsequent ozonolysis of the exomethylene gave keto ester **29**. Unfortunately, all attempts at Davidson cyclization[15] resulted only in low yields (~7%)[16] of oxazole **30**.

Construction of the C(26−32) Oxazole via Oxazoline 31. This approach would entail removal of the chiral auxiliary from (+)-**27** (Scheme 11), coupling with a serine derivative, cyclodehydration, and then oxidation. Hydrolytic removal of the chiral auxiliary from (+)-**27** (β isomer), exploiting the Evans proto-

(11) Uenishi, J.-I.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

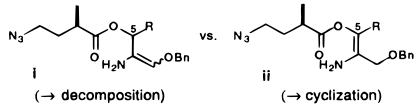
(12) Unstable phosphonate **A** was best stored in a frozen benzene solution, from which anhydrous **A** could be obtained upon concentration in vacuo (with azeotropic removal of adventitious moisture). Under these conditions, storage of **A** for up to one month had no detrimental effect on subsequent Horner-Emmons reactions.

(13) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(14) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5985. (b) Eliel, E. L.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.* **1962**, *84*, 2371.

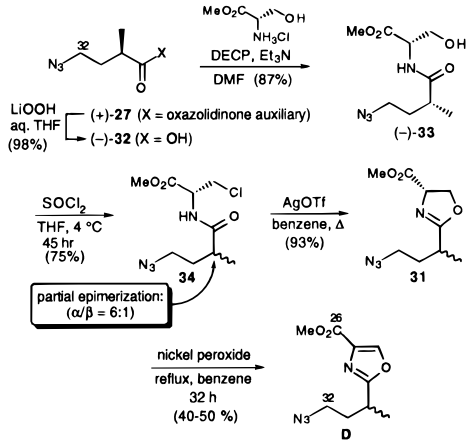
(15) Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* **1937**, *2*, 328.

(16) The Davidson oxazole cyclization has been employed successfully in a variety of cases in which the product oxazoles are 2,4,5-trisubstituted; low yields are typical for 2,4-disubstituted or monosubstituted oxazoles. This is likely due to reduced regiocontrol in enamine formation (i.e., **i** vs **ii**) during the cyclization; the reaction is more successful when the substituent at C(5) is aromatic. See Theilig, G. *Chem. Ber.* **1953**, *86*, 96.



col,[17] provided carboxylic acid (−)-**32**. Condensation with L-serine methyl ester was then attempted with dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP); amide (−)-**33** was produced in moderate yield (∼65%). Use of diethylcyanophosphonate[18] (DECP) as the coupling reagent proved preferable, furnishing (−)-**33** in 87% yield. Conversion of the latter to primary chloride **34** with $SOCl_2$ and treatment with silver triflate induced cyclization to afford oxazoline **31**.[19] Oxidation with nickel peroxide, following the precedent of Meyers et al.,[20] furnished **D** in 40−50% yield (Scheme 11).

Scheme 11



Unfortunately, the ^{13}C NMR spectrum of **31** revealed a 6:1 diastereomeric mixture. Subsequent HPLC analysis of alcohol (−)-**33** (>95%) and chloride **34** indicated that epimerization had occurred during chloride formation, not during amide coupling or cyclization. For example, cyclization of pure (−)-**34** under the above conditions led to a single oxazoline diastereomer. However, a report on the configurational instability of substituents α to the 2-position in oxazolines[21] suggested that additional epimerization might be occurring during oxazoline oxidation.

The Enantiomeric Purity of Oxazole D. To define the enantiomeric purity of oxazole **D**, we explored the attachment of a number of chiral auxiliaries to the C(26) carboxylic acid, to the corresponding C(26) alcohol, and to the C(32) amine. For example, reduction of (−)-**D** to the corresponding amine (H_2, Pd/C) and reaction with the Anderson−Shapiro chiral chlorodioxaphospholane[22] furnished phosphoramide **35**. Unfortunately, ^{31}P NMR analysis of an authentic diastereomeric mixture revealed only broad lines due to P−H(N) coupling; resolution of the NMR resonances was not feasible. Similarly, it was not possible to resolve the diastereomeric resonances of the Mosher esters derived from (−)-**D** (i.e., **36**) by ^1H and ^{19}F NMR (Figure 1). We therefore turned to the Silks−Odom selenium-77 NMR technique[23] which called for the preparation of **37** (Scheme 12).

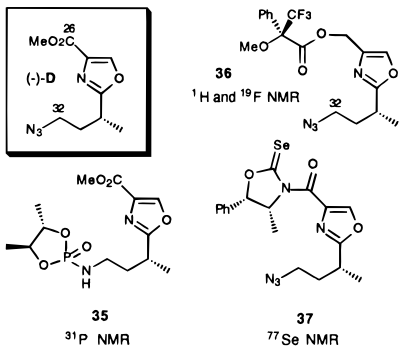
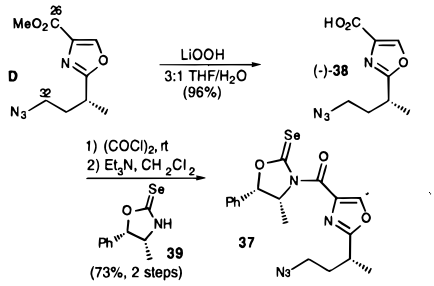


Figure 1.

To our delight, ^{77}Se NMR clearly resolved the diastereomeric resonances (Figure 2). Spectrum (a) depicts the ^{77}Se NMR of **37** derived from a known enantiomeric mixture (1.4:1) of oxazole **D**. Importantly, the resonances from the two diastereomers display baseline separation ($\Delta\delta$ > 2 ppm!). Parts b and

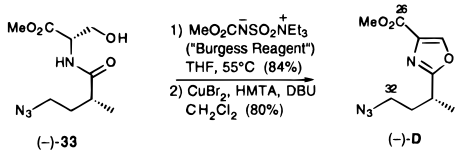
Scheme 12



c of Figure 2 depict the corresponding spectra of **37** derived from **D** prepared via the synthetic routes outlined in Schemes 10 and 11. The diastereomeric resonances in Figure 2b appear in the same ratio (∼6:1) as previously observed for chloride **34**. We therefore concluded that epimerization did not occur at the crucial C(30) stereogenic center during the Meyers nickel peroxide oxidation (Scheme 11).

Three subsequent observations led to the most efficient calyculin oxazole synthesis reported to date (Scheme 13). First,

Scheme 13



the degree of epimerization at C(30) in **34** could be reduced (∼< 5%) by employing the milder conditions of MsCl in pyridine. Second, cyclodehydration at 55 °C with the Burgess reagent,[24] as introduced by Wipf et al.,[25] proved superior to silver triflate and avoided the use of the intermediate chloride and the expensive silver triflate. Third, the Barrish−Singh $CuBr_2$ oxidation[26] proceeded in higher yield. Taken together these conditions afforded (−)-**D** in 67% yield (two steps), with little or no epimerization.[27]

(17) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(18) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, *14*, 1595.

(19) For example, see: (a) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 5155. (b) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 6501.

(20) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.

(21) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302.

(22) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304.

(23) Silks, L. A., III; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979. (b) Silks, L. A., III; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Org. Chem.* **1991**, *56*, 6733.

(24) Burgess E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Organic Syntheses;* Wiley & Sons: New York, 1988; Collect. Vol. VI, p 788. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(25) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907.

(26) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494.

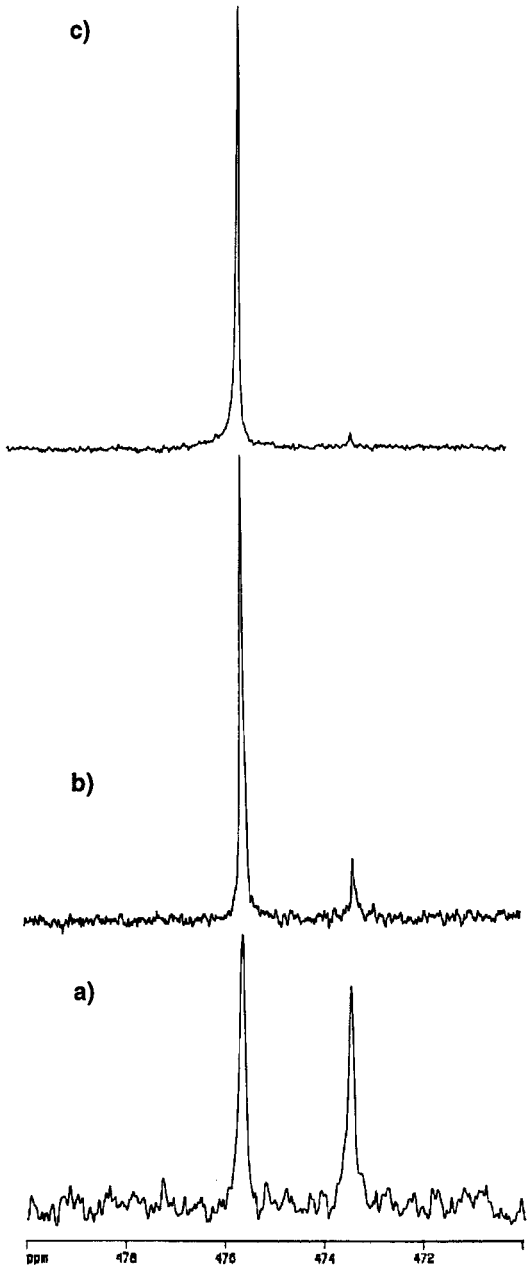
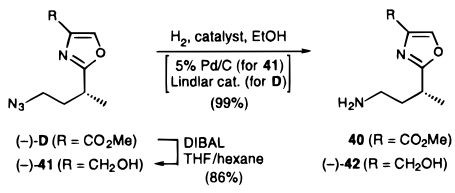


Figure 2.

To facilitate exploratory work, we prepared two additional oxazoles (Scheme 14). Reduction of the azide in (−)-**D** provided

Scheme 14

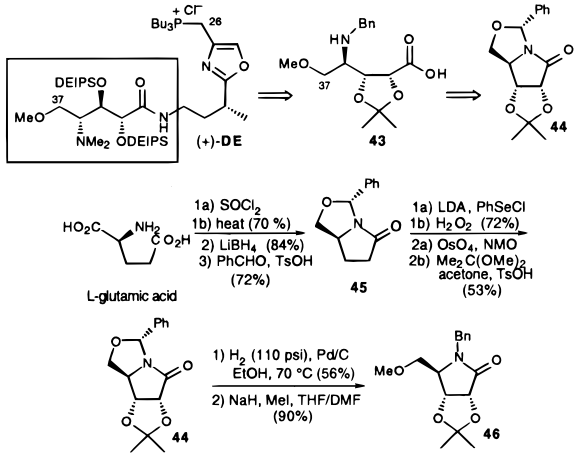


amine **40**, which proved to be unstable as the free base. Alternatively, ester reduction to alcohol (−)-**41**, followed by azide reduction furnished amine (−)-**42** which could be stored without event.

(27) Barrish−Singh oxidation did not compromise the integrity of the C(30) stereocenter, as judged by analysis of the optical rotation of (−)-**D** produced in this fashion.

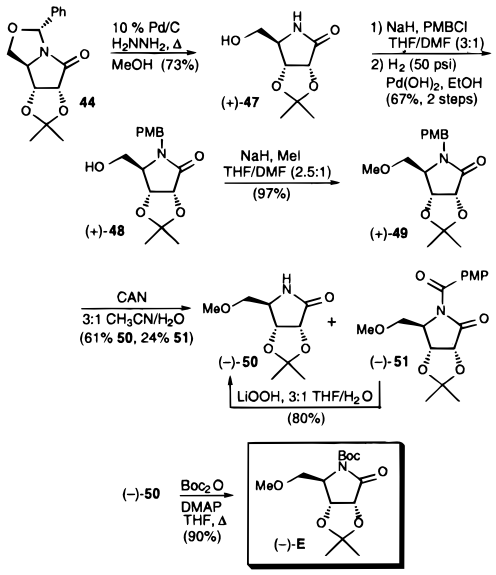
Construction of Lactam E. Initial efforts to prepare the C(33−37) acid (**43**) focused on a variation of the Hamada/Shioiri synthesis[28] of the γ-amino acid moiety found in the gastroprotective substance AI-77-B. Beginning with benzylidene aminal **44**,[28] a known compound available from L-glutamic acid (Scheme 15), selective hydrogenolysis[29] followed by methylation of the derived primary alcohol furnished (+)-**46** in 90% yield. However, neither hydrolytic opening of the lactam ring nor removal of the *N*-benzyl group proved viable (Scheme 15).

Scheme 15



Although the *N*-benzyl group could not be removed from lactam (+)-**46**, the benzylidene group in **44** was easily removed via transfer hydrogenation to provide (+)-**47** (Scheme 16).[28]

Scheme 16



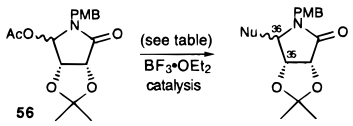
Installation of *p*-methoxybenzyl groups on both nitrogen and oxygen, followed by selective removal of the *O*-PMB group and *O*-methylation, furnished (+)-**49.**

Oxidative removal of the *N*-PMB group from (+)-**49** could then be achieved with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile[30] to furnish lactam (−)-**50** in 61% yield, accompanied by the over-oxidized imide (−)-**51** (24%). The

(28) Hamada, Y.; Kawai, A.; Kohno, Y.; Hara, O.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 1524. (b) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635.

(29) Sakura, N.; Ito, K.; Sekiya, M. *Chem. Pharm. Bull.* **1972**, *20*, 1156.

Table 1

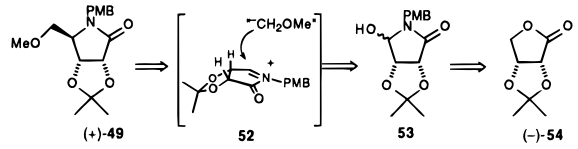


Entry	Nu	Conditions	Product	Yield	Ratio (β/α)
a		 , BF_3•OEt_2, CH_2Cl_2, 0 °C→rt	(+)-**57**	86%	only β
b	NC-	TMSCN, BF_3•OEt_2, toluene -20 °C→rt	**58**	70%	2.5:1
c	NC-	TMSCN, BF_3•OEt_2, CH_2Cl_2 0 °C→rt	**58**	85%	3.6:1
d	NC-	TMSCN, BF_3•OEt_2, THF 0 °C→rt	**58**	91%	5.9:1
e		 , BF_3•OEt_2, CH_2Cl_2 0 °C→rt	(+)-**59**	81%	only β
f		 , BF_3•OEt_2, CH_2Cl_2 0 °C→rt	**60** (and **53**)	46% (of **60**)	only β

latter could be readily redirected to the synthetic sequence by hydrolysis with LiOOH; a combined yield of 80% for lactam (−)-**50** was obtained. The *tert*-butyl carbamate derivative (−)-**E** was then generated from lactam (−)-**50** in 91% yield; the *t*-Boc moiety would serve to activate the lactam for ring opening.

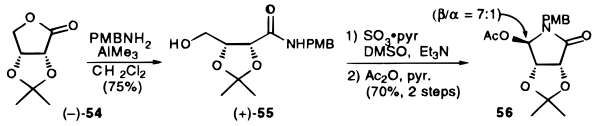
Although successful, the synthesis of lactam (+)-**49** (11 steps from L-glutamic acid, 8.6% overall yield) proved both lengthy and inefficient. We therefore explored an alternate route (Scheme 17), which was envisioned to take advantage of a stereocontrolled addition of an appropriate one-carbon nucleophile to the convex face of *N*-acyliminium ion **52** derived from hemiaminal **53**. The latter would be prepared from erythronolactone; the elegant indolizidine syntheses of Overman and Heitz[31] provided precedent for this tactic.

Scheme 17



Toward this end, treatment of commercially available isopropylidene-D-erythronolactone [(−)-**54**][32] (Scheme 18) with the

Scheme 18



aluminum amide[33] derived from *p*-methoxybenzylamine, followed by Parikh−Doering oxidation and acetylation led to **56** as a 7:1 anomeric mixture in 53% for the three steps.[34]

The reactivity of **56** was tested with *n*-butylcopper, vinyltrimethylsilane, and trimethylsilylacetylene;[35,36] no reaction occurred! Allyltrimethylsilane however reacted efficiently to furnish exclusively the *β*-allyl adduct (+)-**57** in 86% yield (Table 1; entry a). Encouraged by this success, we explored nucleophiles which could be more readily transformed to the required methoxymethyl moiety. Reaction of **56** with trimethylsilylcyanide promoted by boron trifluoride etherate in various solvents (entries b−d) led to **58** in good yield, but with only modest *β*-selectivities.[37]

We next explored enol ethers as the nucleophile. Shono and co-workers demonstrated that enol ethers add intermolecularly to *N*-acyliminium cations to furnish ketones after hydrolysis.[38] We reasoned that a ketone which could enolize only in one direction would serve as an effective hydroxymethyl synthon, assuming the sequence of addition, enolization, ozonolysis, and reduction. In the event, treatment of **56** with the trimethylsilyl (TMS) enol ether of pinacolone (**61**)[39] in the presence of BF_3•OEt_2 furnished ketone (+)-**59** as a single diastereomer in 81% yield (entry e). The analogous transformation with acetophenone was equally selective, but less efficient (entry f). Generation of the trimethylsilyl enol ether of **59** (Scheme 19) followed by ozonolysis with reductive workup ($NaBH_4$) led as expected to alcohol (+)-**48**, identical (^{1}H and ^{13}C NMR) to that prepared previously from L-glutamic acid. Importantly, this sequence proceeded in 54% overall yield for the 3 steps.

(30) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

(31) Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.

(32) Lactone (−)-**54** can be prepared from D-isoascorbic acid, see: Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1985**, *63*, 127.

(33) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.

(34) Single-crystal X-ray analysis of **56** (major anomer) identified it as the *β*-anomer as expected on steric grounds.

(35) Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand.* **1990**, *44*, 707. (b) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron Lett.* **1990**, *31*, 1775.

(36) Additions of Grignard species to sulfonylpyrrolidinones **i** prepared from **53** [MsCl, Et_3N; PhSH; monoperoxyphthalic acid magnesium salt hydrate (MMPP); 67% overall] were similarly unsuccessful.

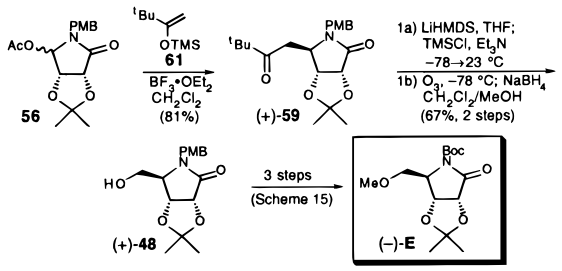
For related examples, see: Brown, D. S.; Hansson, T.; Ley, S. V. *Synlett* **1990**, 48. Brown, D. S.; Charreau, P.; Ley, S. V. *Synlett* **1990**, 749.

(37) The *β* orientation of nitrile **58** (major isomer) was assigned on the basis of ^{1}H NMR coupling constant analysis and confirmed by single-crystal X-ray analysis.

(38) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056.

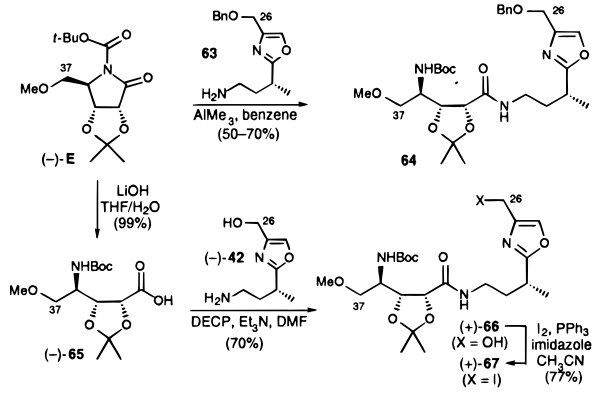
(39) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

Scheme 19



Union of Fragments C(26−32) and C(33−37). Two methods were investigated to couple the C(26−32) oxazole **30** with the C(33−37) lactam (−)-**E** (Scheme 20). Reaction of the

Scheme 20



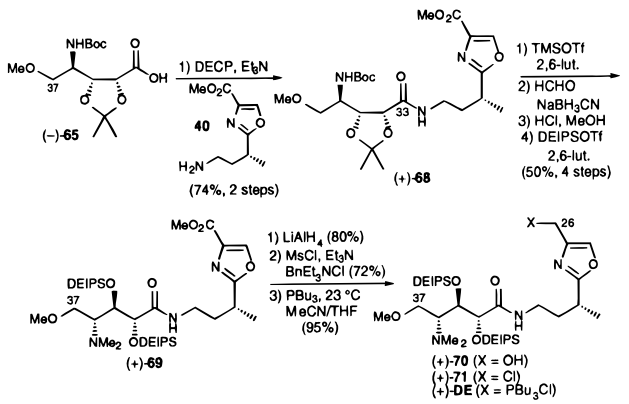
aluminum amide derived from amino oxazole **63** (prepared by Lindlar reduction[40] of azide **30**) with (−)-**E** was explored initially. This reaction proved extremely slow, furnishing consistent yields of **64** only when a large excess of the aluminum amide (>1.5 equiv) was employed. Better results were obtained by coupling γ-amino oxazole (−)-**42** with γ-amino acid (−)-**65**, available by lithium hydroxide hydrolysis of (−)-**E**;[41] diethylcyanophosphonate (DECP) proved to be the coupling agent of choice. With concentrations of (−)-**65** and (−)-**42** near 0.3−0.4 M, amide (+)-**66** was routinely obtained in ∼70% yield. With (+)-**66** in hand, formation of primary iodide (+)-**67**, progenitor of the phosphonium salt, was readily accomplished with triphenylphosphine, imidazole, and iodine.

A Second Generation C(26−37) Subtarget. In the end, we found that the acetonide at C(34,35) was not a viable protecting group due to its hydrolytic stability in the completely functionalized calyculin framework.[42] Although the related cyclopentylidene ketal could be more readily removed, eventual success was achieved with diethylisopropylsilyl (DEIPS) groups[43a] deployed at the C(34,35) diol. We also opted to transform the C(36) *N*-Boc moiety to the required *N*,*N*-dimethylamine prior to union with the C(9−25) spiroketal, based on preliminary experiments suggesting that 2-trimethylsilylethyl protection of the C(17) phosphate ester would not survive the Boc deprotection−reductive amination sequence.[43b]

Two additional considerations came to the fore. Interchange of the acetonide and DEIPS groups could not be effected with lactam (+)-**49** or (−)-**E**; this operation was therefore postponed until after establishing the amide linkage. Retaining the ester functionality at C(26) also appeared prudent until after the C(34,35) interchange.

Synthesis of the second generation C(26−37) subtarget (Scheme 21) began with the union of amino ester **40** with (−)-

Scheme 21



65 to furnish amide (+)-**68** in 75% yield. Removal of the *N*-Boc group with TMSOTf,[44] followed by reductive amination (HCHO, $NaBH_3CN$, aqueous HOAc, CH_3CN) introduced the two methyl groups at nitrogen with partial acetonide hydrolysis. Complete acetonide hydrolysis was readily achieved with HCl in anhydrous MeOH/ether. Silylation with diethylisopropylsilyl triflate (DEIPSOTf) in the presence of 2,6-lutidine then furnished (+)-**69** in 50% yield for the four steps, with only one chromatographic purification.

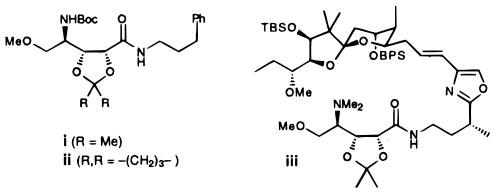
Reduction of the ester was next achieved with $LiAlH_4$ at −78 °C to afford alcohol (+)-**70** (Scheme 21); low-temperature workup with ethyl acetate was essential to prevent loss of one of the DEIPS groups. Turning next to ylide formation, use of both the C(26) iodide or bromide (e.g., I_2, PPh_3 or CBr_4, PPh_3) was feasible, albeit they proved unstable. On the other hand the chloride obtained by treatment of (+)-**70** with methanesulfonyl chloride in the presence of triethylamine and benzyltriethylammonium chloride was stable at 0 °C for weeks. Displacement with tri-*n*-butylphosphine in the mixed solvent system of CH_3CN/THF (2:1) led to clean conversion to phosphonium salt (+)-**DE** in 95% yield.

Wittig Coupling: A Model Study. Initially we explored the triphenyl- and tributylphosphonium salts **72a** and **72b**, generated in situ from iodide (+)-**67** (Scheme 22). Of particular concern was the *E*/*Z* coupling selectivity and the need for C(17) hydroxyl protection. Reaction with hydrocinnamaldehyde revealed a dramatic increase in the *E*/*Z* ratio with the tri-*n*-butylphospho-

(40) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.

(41) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

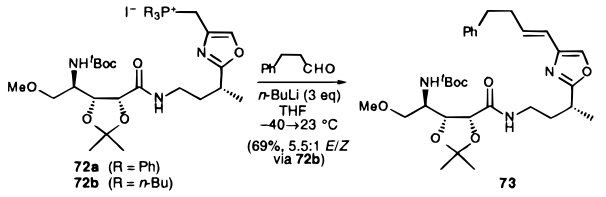
(42) The acetonide required strongly acidic conditions (CSA, MeOH, 45 °C, 24 h or 1.2 M aqueous HCl, THF, 50 °C, 12 h) to effect removal from model compound **i**, casting uncertainty upon its successful removal from fully protected calyculin. Indeed, although model compound **iii** could be deprotected, removal of the acetonide was unsuccessful with fully protected calyculin A. (b) Proton NMR comparison showed that cyclopentylidene hydrolysis from **ii** was 4.9 times faster than acetonide hydrolysis from **i**.



(43) (a) Toshima, K.; Mukaiyama, S.; Kinoshita, M.; Tatsuta, K. *Tetrahedron Lett.* **1989**, *30*, 6413. (b) Spoors, P. G.; Smith, A. B., III, unpublished results.

(44) Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223.

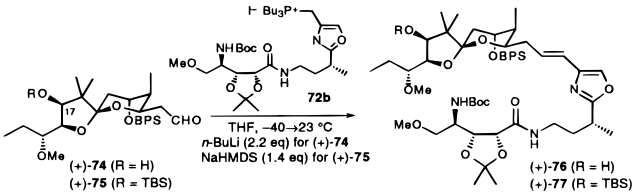
Scheme 22



nium salt, consistent with the observations subsequently reported by Armstrong and co-workers.[45,46] We also observed that the yield increased to 69% without significantly altering the *E*/*Z* selectivity when three equivalents of *n*-BuLi were employed.

With the more advanced model spiroketals (+)-**74** and (+)-**75**[47] (Scheme 23), moderate yields of the expected alkene

Scheme 23



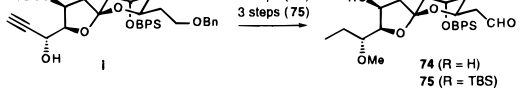
products (+)-**76** and (+)-**77** were obtained with similar *E* selectivities. Although the experiment with (+)-**74** established the compatibility of the Wittig coupling without protection at C(17),[48] better yields were obtained with protection.

Union of (+)-BC with (+)-DE. Aldehyde (+)-**78**, readily obtained in high yield from (+)-**BC**[1] by removal of the C(25) *O*-benzyl protecting group and Ley oxidation [catalytic perruthenate (TPAP), NMO],[49] was submitted to Wittig olefination (Scheme 24). As with the model studies, olefination with triphenylphosphonium salt **79**[50] (LiHMDS, THF) furnished (+)-**BCDE** with 2:1 *E*/*Z* selectivity, whereas the tri-*n*-butylphosphonium salt (+)-**DE** provided a 5:1 *E*/*Z* mixture. With *N*,*N*-dimethylformamide as solvent, the *E*/*Z* ratio improved further to 9:1, consistent with the results of Armstrong et al.[45] Evans and co-workers reported Wittig olefination with a related substrate (LDA, DMF, 0 °C) to be completely stereoselective. In our hands, their conditions afforded 10:1 *E*/*Z* selectivity, albeit the reaction was less efficient (∼32−69%). For material advancement we employed LiHMDS (1.5 eq) in DMF at 0 °C; isomer separation was achieved via radial chromatography.

(45) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609.

(46) The role of the phosphorous ligands on the stereoselectivity in Wittig reactions has been discussed in detail, see: Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948.

(47) Compounds **74** and **75** were prepared from **i**, the latter prepared during the synthesis of the C(9−25) fragment (+)-**BC** (see ref 1). *O*-Methylation, hydrogenation (Pearlman's catalyst) to saturate fully the alkyne, and removal of the C(25) *O*-benzyl afforded the C(25) primary alcohol. Ley oxidation (TPAP/NMO), with and without prior removal of the C(17) TBS group provided **74** and **75**, respectively.

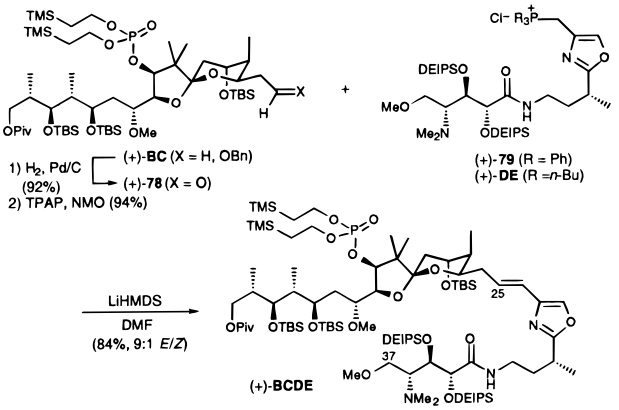


(48) Independently, Armstrong demonstrated similar transformations with the C(17) hydroxyl unprotected, see: Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153.

(49) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

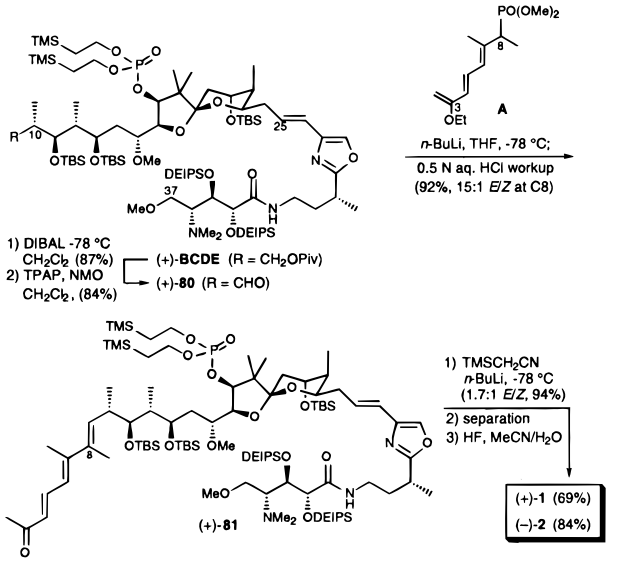
(50) Phosphonium salt **79** was prepared from the corresponding alkyl chloride (+)-**71** (PPh_3, MeCN/THF; 28% yield).

Scheme 24



Introduction of the C(1−8) Cyanotetraene. To attach the C(3−8) subunit, the pivaloate group was removed from the C(9) terminus of (+)-**BCDE** via reduction (DIBAL or $LiEt_3BH$) (Scheme 25). Initially this process proved capricious;[51] reliable

Scheme 25



results were eventually obtained by minimizing the amount of DIBAL followed by workup with sodium potassium tartrate. Ley oxidation[49] then afforded aldehyde (+)-**80** in high yield (84%). It should be emphasized that this oxidation proceeded in excellent yield despite the C(36) tertiary amine.[52]

Horner-Emmons coupling was then achieved via metalation of **A** with *n*-BuLi; a deep red-orange solution resulted. Addition of (+)-**80** led to olefination within 30 min, with high selectivity (>10:1).[53] With basic workup (aqueous $NaHCO_3$), the product containing the C(3) carbonyl function masked as an enol ether could be isolated (∼50−60%) and chromatographed. However, best results entailed direct conversion via acid treatment (0.5 N HCl) to ketone (+)-**81** (92% yield; *E*/*Z* = 15:1).

(51) This reductive deprotection initially provided variable yields and low mass balance. We speculate that chelation of the Lewis acidic boron and aluminum reagents by the C(36−37) permethylated 1,2-amino alcohol increased the product hydrophilicity and interfered with isolation; related C(9−25) substrates not possessing the 1,2-amino alcohol (i.e., before Wittig coupling) behaved normally.

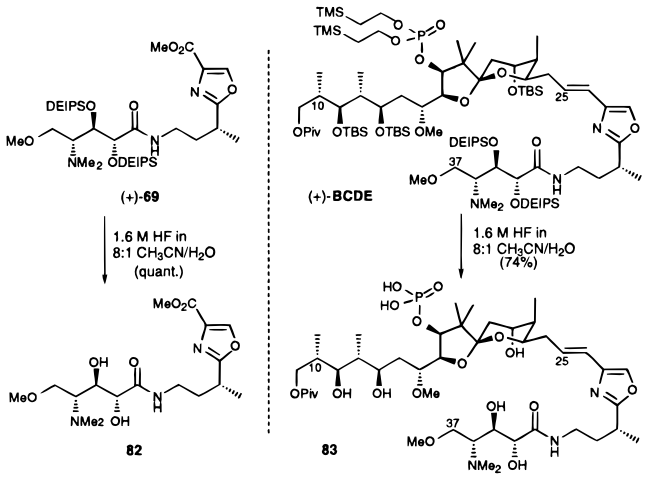
(52) If the C(36) tertiary amine is oxidized, the *N*-oxide product may be expected to be functionally similar to NMO. We did not detect the *N*-oxide.

(53) Determination of the *E*/*Z* selectivity by ^1H NMR spectroscopy was unreliable at this stage due to decomposition and the presence of interfering resonances.

Completion of the Calyculin Synthetic Venture. The stage was now set for Peterson olefination and global deprotection. In the event (Scheme 25), the desired cyanotetraene emerged in 94% yield as a 1.7:1 *E*/*Z* mixture. The *Z* and *E* isomers, corresponding to fully protected *ent*-calyculin A and *ent*-calyculin B respectively, were easily separable by careful radial chromatography.

All that remained was global deprotection. We recount here two important experiments which had earlier suggested the feasibility of this scenario. Oxazole (+)-**69**, when subjected to hydrolysis with HF (1.6 M in 8:1 CH_3CN/H_2O),[54] effectively afforded **82** (Scheme 26). In a similar fashion, treatment of (+)-

Scheme 26



BCDE with the same HF conditions led to **83** in 74% yield; prolonged exposure to HF was required to remove the remaining protecting group from the phosphate. The latter reaction established both the lability of the phosphate protection and the stability of the phosphate P−O(17) bond under the HF conditions.

Bolstered by these results, fully protected *ent*-calyculin A (Scheme 25) was exposed to HF (1.5 M in 10:1 CH_3CN/H_2O); after 2 d, the major component present contained only one trimethylsilylethyl-protecting group.[55] Prolonged exposure to HF (2 M in 8:1 CH_3CN/H_2O, 7 d) cleanly provided synthetic (+)-**1** in 69% yield. In a similar fashion, fully protected *ent*-calyculin B afforded synthetic (−)-calyculin B (**2**) (84% yield). Synthetic (+)-calyculin A and (−)-calyculin B were identical in all respects (^1H and ^{13}C NMR, IR, UV, HRMS, TLC, HPLC), except for chiroptic properties,[56] to natural (−)-**1** and (+)-**2**, respectively.[57]

Acknowledgment. Support was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-19033 and postdoctoral fellowships to G.K.F. and K.G.H. We also thank DuPont Pharmaceuticals, Inc. and Zeneca Pharmaceuticals, Inc. for support of this work. In addition, we thank Drs. George T. Furst and Patrick J. Carroll and Mr. John Dykins of the University of Pennsylvania Spectroscopic Service Center for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra, respectively.

Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures for all synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992135E

(54) We benefited significantly in this regard from the previous successes of Evans (see ref 9) and Masamune (see: Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673), each of whom demonstrated that calyculin A is stable to HF in aqueous acetonitrile.

(55) Interestingly, this monoprotected intermediate was more polar (TLC) than fully deprotected calyculin A. Together with precedent, this TLC behavior suggests that a fully deprotected phosphate is required for formation of a folded tertiary structure which exposes a less polar surface. Evans and coworkers observed that an intermediate with one *t*-butyldimethylsilyl group remaining coeluted with calyculin A on silica gel; it was proposed that this silyl group [tentatively assigned as C(11)−OTBS] was buried within a folded calyculin structure, minimizing the effect on the apparent overall polarity and accessibility to external reagents.[9] In our case, the phosphate group is last to be deprotected. Deprotection at C(11) appears normal; this implicates the free phosphate as critical for the folding process. Similar behavior was observed during deprotections of calyculins A and B.

(56) Synthetic (+)-calyculin A and (−)-calyculin B had optical rotations and CD spectra of equal magnitudes and opposite signs relative to the corresponding natural products.

(57) We thank Professors Nobuhiro Fusetani and Shigeki Matsunaga (University of Tokyo) for authentic samples of natural (−)-**1** and (+)-**2**, and for confirming that natural **2** has an [α] of +15° (*c* 0.07). Natural **2** was originally reported to have [α] −60° (*c* 0.05). We also thank Professor David Evans (Harvard University) for a sample of synthetic (+)-**1**.