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Asymmetric Synthesis of Calyculin A. 3. Assemblage of the Calyculin Skeleton and the Introduction of a New Phosphate Monoester Synthesis

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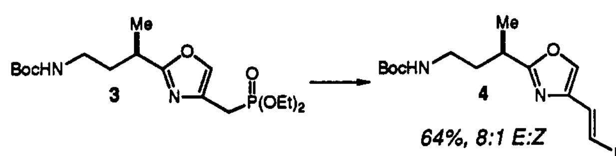
Summary: The synthesis of a fully protected analogue of calyculin A has been accomplished using a Wittig reaction to couple two fragments comprising the C_1–C_{25} and C_{26}–C_{37} portions of calyculin A. Associated model studies on the incorporation of the C_{17} phosphate monoester moiety are also described.

In the two preceding papers we described the synthesis of the two fragments comprising the fully elaborated C_1–C_{25} (1)[1a] and C_{26}–C_{37} (2)[1b] portions of calyculin A (Scheme I). We now disclose the successful union of these fragments and the synthesis of a fully protected version of calyculin A, as well as studies which address the incorporation of the C_{17} phosphate monoester.

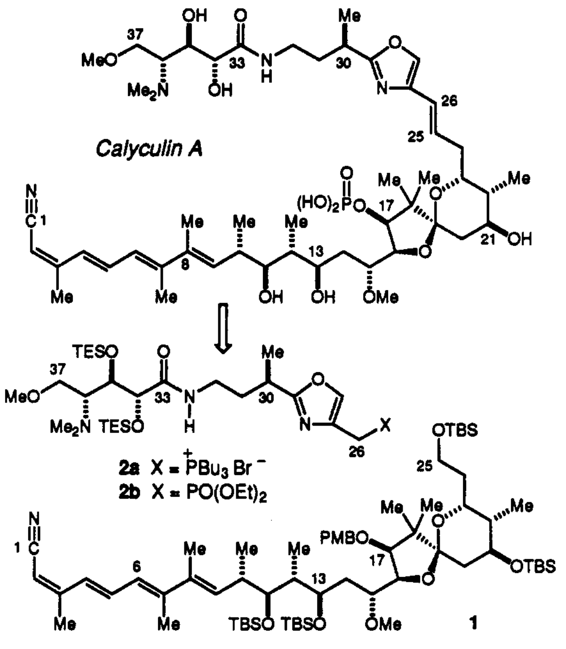
Assemblage of the Calyculin Skeleton. The C_{25}–C_{26} double bond in calyculin provides an obvious assemblage point in the design of a convergent synthesis of this structure, and such trans-selective olefinations are readily achieved with both stabilized phosphoranes and phosphonate-derived carbanions. In accord with the requirement for trans selectivity, the phosphorus activating group required for olefination is most logically associated with the C_{26}–C_{37} oxazole fragment. Our initial efforts focused on the use of the more conveniently handled neutral C_{26} phosphonate esters **2b** and truncated variants thereof. In preliminary model studies, the dianion derived from phosphonate **3**[1b] (2.2 equiv of NaHMDS, THF, 0 °C) reacted with propionaldehyde to give olefin **4**, as an 8:1 E/Z mixture in 64% yield (eq 1 (conditions: NaHMDS, THF, 0 °C; EtCHO, 25 °C)).



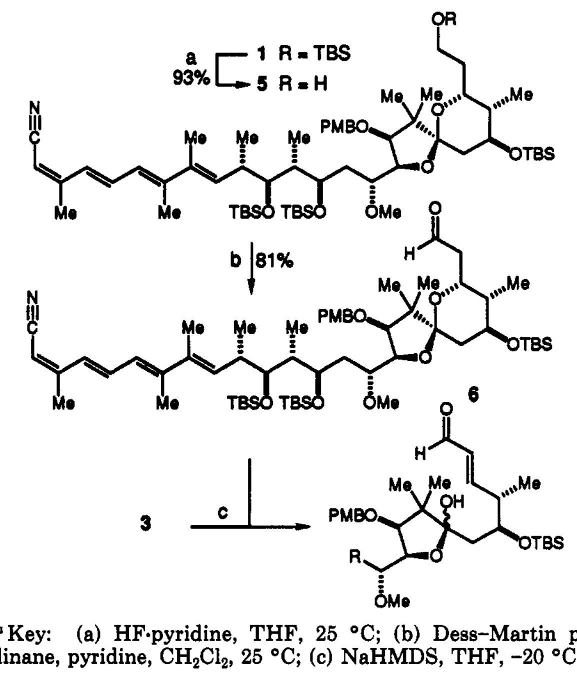
(1)

With this encouraging result in hand we turned our attention to the C_1–C_{25} aldehyde derived from **1**. Selective deprotection of the C_{25} *tert*-butyldimethylsilyl (TBS) ether in **1** was accomplished with pyridinium hydrofluoride in THF (12 h, 25 °C) to give alcohol **5** in 93% yield (Scheme II). It is noteworthy that intermediate **1** tolerates these reaction conditions. Oxidation using the Dess–Martin periodinane[2] provided aldehyde **6** in 81% yield, setting the stage for the phosphonate-based olefination. Unfortunately, addition of **6** to the sodium dianion derived from **3** at −20 °C led only to β-elimination of the labile spiroketal oxygen. Phosphonate **2b** was likewise found to be unsuitable for coupling to **6**. These results, which clearly highlight the base sensitivity of aldehyde **6**, necessitated the selection of less basic phosphorane reagents[3] for the reaction.

Scheme I



Scheme II[a]



[a] Key: (a) HF·pyridine, THF, 25 °C; (b) Dess–Martin periodinane, pyridine, CH_2Cl_2, 25 °C; (c) NaHMDS, THF, −20 °C; **6**.

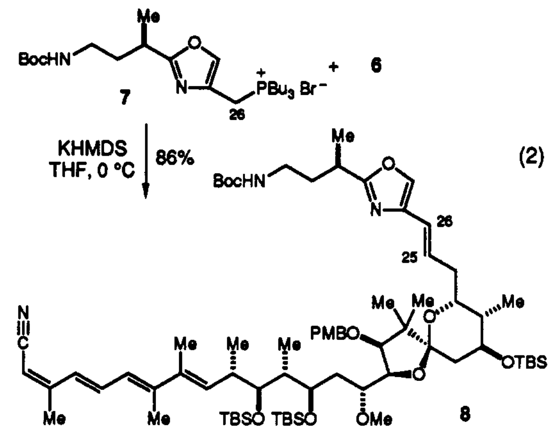
On the basis of the recently reported model studies of Armstrong and co-workers,[4] we turned to the 4-(oxazolylmethyl)tributylphosphonium salts. Not unexpectedly, the stabilized ylides derived from these salts were found to be highly E-selective in Wittig reactions with aldehydes. Employing a protocol similar to that described, we first investigated the reaction of tributylphosphonium salt **7**[1b]

(1) (a) Evans, D. A.; Gage, J. R. *J. Org. Chem.* First paper in this series. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* Preceding paper in this issue.
(2) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156–4158.
(3) Two relevant thermodynamic pK_a values in DMSO have been determined by Bordwell: $PhCH_2PO(OEt)_2$, 27.6; $PhCH_2PPh_3Cl$, 17.4. Bordwell, F. G., Northwestern University, personal communication. Also, see: Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *57*, 3513–3522.

(4) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609–1612.

0022-3263/92/1957-1964$03.00/0

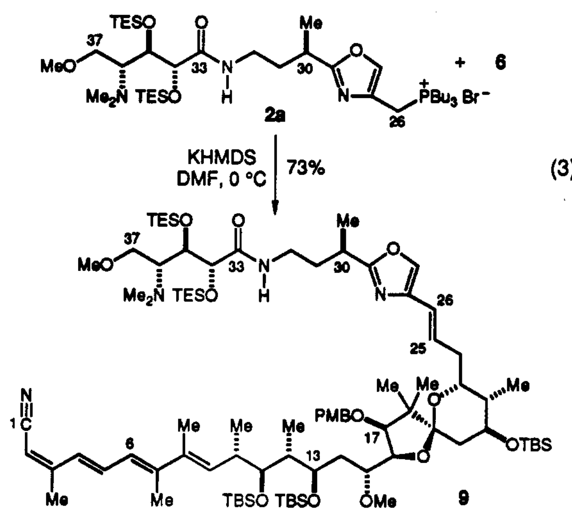
with **6**. Gratifyingly, addition of 1 equiv of KHMDS to a cooled (0 °C) solution of **7**[1b] and aldehyde **6** in THF afforded olefin **8** in 86% yield with >10:1 *E/Z* selectivity (eq 2). These Wittig-based fragment coupling conditions,



(2)

in which the amide base is added to a solution containing both the phosphonium salt and aldehyde constituents, were effectively employed by Kishi and co-workers in their synthesis of palytoxin.[5] The success of this protocol in these cases provides a dramatic demonstration of the higher apparent kinetic acidity of the stabilized phosphonium salts relative to the aldehyde, and, in our case, the carbamate proton. It is also significant that the C_1–C_9 cyanotetraene moiety, that structural component which contributes to the instability of the calyculins, survives these reaction conditions intact.

The above coupling procedure was then applied to the fully functionalized C_{26}–C_{37} phosphonium salt **2a**. Comixture of **2a** (1.5 equiv) with aldehyde **6** (1.0 equiv) in DMF followed by treatment with 1.5 equiv of KHMDS (0.94 M in THF, 0 °C, 20 min) using the protocol described above afforded the fully elaborated calyculin A structure **9** in 73% yield with >10:1 *E/Z* selectivity (eq 3). Although



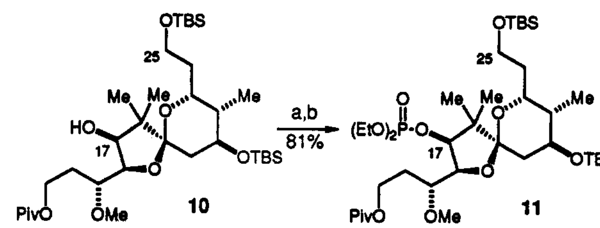
(3)

this reaction has not yet been fully optimized, preliminary results indicate that the in situ formation of phosphonium salt **2a** in DMF directly preceding the Wittig reaction affords equally good yields of coupling.

The preceding experiments fully substantiate the fact that a practical route to the calyculin A nucleus can be achieved by the methodology described in this and the preceding papers.[1]

In the completion of the calyculin A synthesis, there remains the task of removing the *p*-methoxybenzyl (PMB) ether, phosphorylating the C_{17} hydroxyl group, and removing the silicon-based protecting groups to reveal synthetic calyculin A. To date, we have found that deprotection (DDQ)[6] of the C_{17} PMB ether in compounds containing the cyanotetraene moiety are to be avoided. In addition to the desired ether cleavage, extensive degradation of such intermediates is to be expected.[7] In ongoing studies, our current plans involve the removal of this C_{17} protecting group prior to introduction of the cyanotetraene moiety into the spiroketal fragment.

Synthesis of Phosphate Monoesters. One of the remaining methodological challenges to be faced in the completion of the synthesis is the incorporation of the C_{17} phosphate monoester. To model the incorporation of this moiety into advanced intermediates, we chose spiroketal **10** as a representative substrate.[8] Treatment of **10** with dibenzyl chlorophosphate[9] in pyridine with added DMAP afforded, after 3 days, no reaction and partial loss of the primary TBS ether. The lithium alkoxide derived from **10** also failed to react with dibenzyl chlorophosphate. Finally, **10** proved to be similarly unreactive toward phosphorus oxychloride in pyridine. On the basis of the demonstrated low reactivity of the C_{17} alcohol moiety, the more electrophilic chlorophosphites were investigated. Treatment of alcohol **10** with diethyl chlorophosphite (3 equiv, pyridine, 12 h, 25 °C) followed by oxidation (30% H_2O_2) of the resultant phosphite triester gave the phosphotriester **11** in 81% overall yield (eq 4: (a) diethyl chlorophosphite, pyr., 25 °C; (b) 30% aqueous H_2O_2, CH_2Cl_2)).



(4)

With the success of the chlorophosphite ester phosphorylation procedure assured, suitably labile ester moieties were evaluated. The base-labile 2-cyanoethyl phosphate esters, a common protecting group in polynucleotide synthesis, attracted our attention.[10] Although this phosphorus ester protecting group has proven to be practical for the synthesis of *phosphodiesters*, the extension of this methodology to the synthesis of *phosphate monoesters* has not been demonstrated. Accordingly, these studies were initiated (Scheme III). As prepared,[11] the requisite bis(2-cyanoethyl) chlorophosphite is inevitably contaminated by some (~10%) of the corresponding dichlorophosphite. Since an excess of the chlorophosphite reagent was normally employed for functionalization of the C_{17} hydroxyl group, the more reactive dichlorophosphite

(5) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. J., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530.

(6) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.

(7) For example, 1 could be converted to its corresponding C_{17} alcohol in only 36% yield.

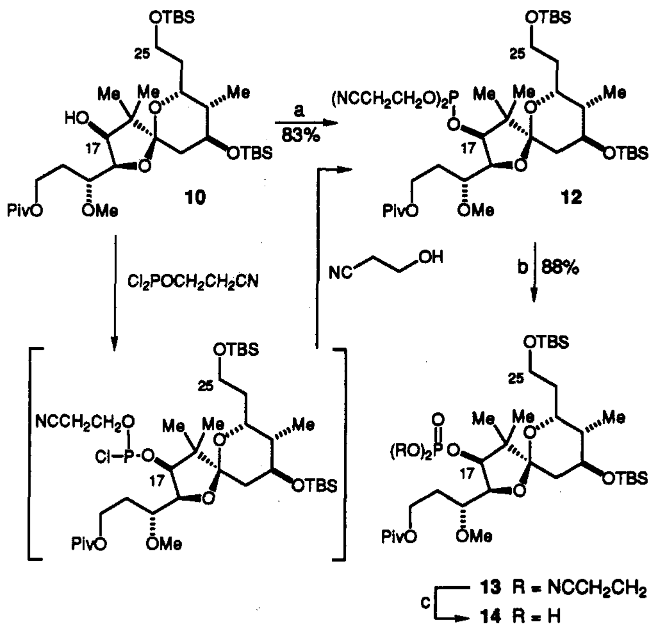
(8) This compound could be obtained from its corresponding PMB ether[1a] in 88% yield by reaction with DDQ.

(9) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Am. Chem. Soc.* **1945**, 382–385.

(10) For a review of phosphorous protection strategies for polynucleotide synthesis, see: Kössel, H.; Seliger, H. *Fortschr. Chem. Org. Naturstoffe* **1975**, *32*, 297–508.

(11) Westerduin, P.; Veeneman, G. H.; van Boom, J. H. *Rec. Trav. Chim. Pays-Bas* **1987**, *106*, 601–606.

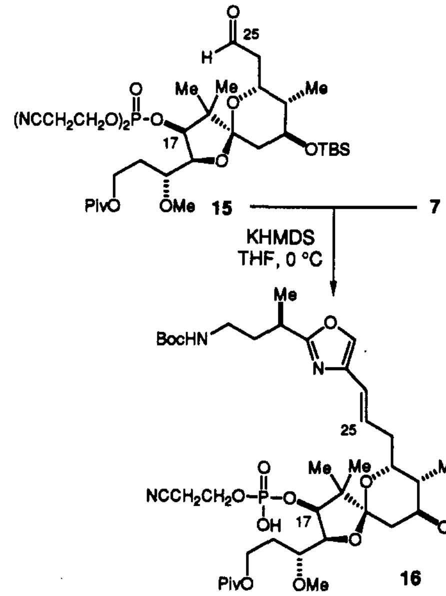
Scheme III[a]



[a] Key: (a) Bis(2-cyanoethyl) chlorophosphite, pyridine, 3-hydroxypropionitrile, 25 °C; (b) 30% aqueous H_2O_2, CH_2Cl_2, 25 °C; (c) DBU, TMSCl, CH_2Cl_2, 25 °C.

component consumed a disproportionate amount of alcohol **10**, forming a mixed chlorophosphite diester (Scheme III). Upon aqueous workup, this intermediate hydrolyzed and tautomerized to an unutilizable H-phosphonate byproduct. This problem was conveniently circumvented by the addition of 3-hydroxypropionitrile to intercept the mixed chlorophosphite diester prior to aqueous workup providing phosphite **12** in 83% yield. Oxidation of **12** with 30% H_2O_2 afforded phosphate triester **13** in 88% yield. *Upon treatment of **13** with DBU (CH_2Cl_2, 25 °C) only one of the cyanoethyl groups is removed*;[12] however, in the presence of chlorotrimethylsilane, complete deprotection is achieved under mild conditions to produce phosphate **14** in excellent yield as an insoluble white solid that could not be characterized by NMR spectroscopy. FABMS analysis of this compound displayed peaks at m/z 763 and 785, corresponding to M + Na and M − H + 2Na, respectively, for the desired phosphorus diacid.[13]

Finally, we have begun to address the possibility of carrying a mixed alkoxy bis(2-cyanoethyl) phosphate derivative through the Wittig reaction. Treatment of a cooled (0 °C) THF solution of phosphonium salt **7** and aldehyde **15**[14] with 2 equiv of KHMDS afforded olefin **16** in good yield with >10:1 E/Z selectivity (eq 5). The extra equivalent of base was intentionally used in this transformation to facilitate partial deprotection of the phosphate moiety.



(5)

The incidental loss of one of the 2-cyanoethyl protecting groups is not undesirable as deprotection of the phosphate would be the next step in our projected route to calyculin A. This route involves the synthesis of a modified version of **6** in which the protected phosphate has been installed prior to the key Wittig reaction. These efforts and the completion of the total synthesis of calyculin A are in progress and will be reported in due course.

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Supplementary Material Available: Full experimental details and analytical and spectral data for all compounds (except 14, 15, and 16) (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) Partial deprotection under these conditions was not unexpected. See ref. 11 and Tener, G. M. *J. Am. Chem. Soc.* **1961**, *83*, 159–168.

(13) Further confirmation of the identity of **14** was provided by its partial conversion to the corresponding dimethyl phosphate with diazomethane. Gage, J. R. Ph.D. Thesis, Harvard University, 1991.

(14) Obtained from **13** in 84% yield by deprotection with HF·pyridine followed by Dess–Martin periodinane oxidation.

A Novel and Practical Synthesis of the 6α-Hydroxymethyl Metabolite of Simvastatin

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Summary: The synthesis of the 6α-hydroxymethyl metabolite of simvastatin described here is predicted on the conversion of iodoepoxides **7** to the cyclic ether **8** via a novel radical catalytic cycle in which the rearrangement

