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 C1-C25 and C26-C37 portions of calyculin A. Associated model studies on the incorporation of the C17 phosphate monoester moiety are also described.

In the two preceding papers we described the synthesis of the two fragments comprising the fully elaborated C1-C25 (1) and C26-C37 (2) 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 C17 phosphate monoester.

**Assemblage of the Calyculin Skeleton.** The C26-C37 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 C26-C37 oxazole fragment. Our initial efforts focused on the use of the more conveniently handled neutral C26 phosphonate esters 2b and truncated variants thereof. In preliminary model studies, the dianion derived from phosphonate 3 (2.2 equiv of NaHMDS, THF, 0 °C) reacted with propionaldehyde to give olefin 4, as an 81% E/Z mixture in 64% yield (eq 1 (conditions: NaHMDS, THF, 0 °C; EtCHO, 25 °C)).

With this encouraging result in hand we turned our attention to the C1-C25 aldehyde derived from 1. Selective deprotection of the C25 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 provided aldehyde 6 in 81% yield, setting the stage for the phosphonate-based olefination. Unfortunately, addition of 6 to the sodium dianion derived from phosphonate 3 (2.2 equiv of NaHMDS, THF, 0 °C) led only to 8-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 phosphonate reagents for the reaction.

*Key: (a) HF-pyridine, THF, 25 °C; (b) Dess–Martin periodinane, pyridine, CH2Cl2, 25 °C; (c) NaHMDS, THF, −20 °C; 6.*

On the basis of the recently reported model studies of Armstrong and co-workers, 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 7b.
with 6. Gratifyingly, addition of 1 equiv of KHMDS to a cooled (0 °C) solution of 7b 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, 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 carboxylate proton. It is also significant that the C1-C9 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 C9-C17 phosphonium salt 2a. Coincident 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 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 C17 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 C17 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 C17 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 C17 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 chlorophosphate9 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 chlorophosphates. Finally, 10 proved to be similarly unreactive toward phosphorus oxychloride in pyridine. On the basis of the demonstrated low reactivity of the C17 alcohol moiety, the more electrophilic chlorophosphites were investigated. Treatment of alcohol 10 with diethyl chlorophosphate (3 equiv, pyridine, 12 h, 25 °C) followed by oxidation (30% H2O2) of the resultant phosphate triester gave the phosphotriester 11 in 81% overall yield (eq 4: (a) diethyl chlorophosphate, pyr., 25 °C; (b) 30% aqueous H2O2, CH2Cl2).

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 nucleotide synthesis, attracted our attention.10 Although this phosphorus ester protecting group has proven to be practical for the synthesis of phosphodiester, 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 di- and tri-chlorophosphite. Since an excess of the chlorophosphite reagent was normally employed for functionalization of the C17 hydroxyl group, the more reactive dichlorophosphate

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(7) For example, 1 could be converted to its corresponding C17 alcohol in only 36% yield.

(8) This compound could be obtained from its corresponding PMB ether4 in 88% yield by reaction with DDQ.


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 of 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% H2O2 afforded phosphate triester 13 in 88% yield.

Upon treatment of 13 with DBU (CH2Cl2, 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 13 with KHMDS (THF, 0 °C) and aldehyde 1514 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.

(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 HP-pyridine followed by Dess–Martin periodinane oxidation.

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