For the installation of the cyanotetraene portion, Horner-Emmons reaction of lithiated 17 with aldehyde 15 afforded, after aqueous workup, the moderately unstable stannytriene 18. Direct submission of this material to Stille coupling\(^{(24)}\) (MeCN\(_2\)PdCl\(_2\), DMF) with the known vinyl iodide 19\(^{25}\) gave 20 in 50% overall yield for the two steps. The stereoselectivity of this olefination is noteworthy. In related model studies with 17, 5:1 E/Z olefination selectivity was observed while in the actual system the selectivity was 7:1.

This synthesis of the C\(_1\)-C\(_{25}\) portion of the calyculin A nucleus has proven to be readily amenable to larger scale and has afforded multigram quantities of this fragment. In the following two papers, the synthesis of the other calyculin A subunits and their assemblage will be presented.

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### Supplementary Material Available: Full experimental details for all reactions, as well as analytical data for all intermediates (18 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.

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**Asymmetric Synthesis of Calyculin A. 2. The C\(_{26}\)-C\(_{37}\) \(\gamma\)-Amino Acid Fragments**

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**Summary:** New chiral imide enolate alklylation, aldol, and Michael addition bond constructions have been employed in the asymmetric synthesis of the C\(_{26}\)-C\(_{37}\) portion of calyculin A.

In the preceding paper, the synthesis of the C\(_1\)-C\(_{25}\) portion of calyculin A was described.\(^{(1)}\) We now report the synthesis of the C\(_{26}\)-C\(_{37}\) fragment containing the basic nitrogen constituents found in the natural product.

In conjunction with our plan for the union of these subunits during the construction of the C\(_{26}\)-C\(_{25}\) double bond, it was our intention to rely on a suitable phospholective dihydroxylation of an unsaturated pyroglutamic acid\(^{(3)}\) seemed attractive in that two of the three stereo

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\(^{(2)}\) For recent studies which have also addressed the synthesis of the C\(_1\)-C\(_{25}\) calyculin fragment, see: Smith, A. B., III; Salvatore, R. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* 1991, 32, 4859-4862.


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\(\text{Key: (a) aqueous NaOH, Br}_{2}OCICl, 0^\circ\text{C}; (b) Me}_{2}CCOCI, Et}_{N}, X, Li, -78 to -25^\circ\text{C}; (c) TiCl}_{4}, i-P\text{NET}_{3}, CH}_{2}Cl}_{2}, 0^\circ\text{C}; (d) LiBH}_{4}, MeOH, THF, 0^\circ\text{C}; (e) (COCl)$_2$ DMSO, i-P\text{NET}_{3}, -78 to -50^\circ\text{C}.\)
I) whose synthesis is described below.

N-Protection (Cbz) of sarcosine and subsequent N-acetylation of the (S)-phenylalanine-derived oxazolidone auxiliary (Xp) afforded the chiral glycolate derivative 2 in 80% overall yield (Scheme II). Formation of the titanium enolate6 of 2 (CH3Cl2, Et3N-N-i-Pr, 0 °C) followed by acid-catalyzed alkylation with dimethoxymethane (10 equiv) facilitated by BF4-OEt2 (10 equiv, 25 ºC, 2 h) provided 3 as an inseparable 98:2 mixture of diastereomers in 80% yield. Reductive removal of the chiral auxiliary7 to give 4 (93%), followed by Swern oxidation8 provided the racemization-prone aldehyde 5 which was employed without purification in subsequent aldol studies.

Although precedent for the desired anti glycolate aldol C6=C6 bond construction (Scheme I) was scarce, one recent report revealed that the addition of TMEDA to the Sn(II) enolate of a (bromoxy)acetate derivative resulted in a modest bias for the anti diastereomer in aldol reactions.9 We reasoned that this phenomenon might translate to chiral glycolic imides such as 6,10 where absolute stereochemical control might be obtained from the oxazolidone auxiliary. Accordingly, enolization of imide 6 with Sn(OTf)2 (1.5 equiv, Et3N, CH2Cl2, 45 min, -15 ºC) and addition of TMEDA (1.5 equiv, -78 ºC), followed by the addition of isobutyraldehyde (1.2 equiv, 2 h, -78 ºC), afforded the illustrated anti aldol adduct 7 in 63% isolated yield (eq 1). GLC analysis of the unpurified reaction mixture revealed a diastereomer ratio of 77:23 (7:2 other three diastereomeric aldol adducts).12 With these results in hand, we investigated the reaction of aldehyde 5 under similar conditions (eq 2). Addition of aldehyde 5 to 1.5 equiv of the Sn(II) enolate derived from imide 8, generated as with 6 above, in the presence of TMEDA, afforded the desired anti aldol adduct 10 in 60% yield14 (two steps from

\[ \text{Sn(OTf)2, Et3N, CH2Cl2, 45 min, -15 ºC} \]

(1)

63% isolated yield

\[ \text{TMEDA, i-PrCHO} \]

(2)

60% isolated yield from 4

4)

The synthesis of the \( \gamma \)-amino oxazole subunit bearing the C30 methyl-bearing stereocenter was initiated with the diastereoselective Michael reaction16 of the titanium enolate derived from N-propionyloxazolidinone 14 with tert-butyl acrylate which afforded the desired ester 11 in quantitative yield. The ensuing Curtius rearrangement16 of this substrate with dichlorophosphoryl azide (1.1 equiv, Et3N, tert-butyl alcohol, reflux, 15 h) then proceeded smoothly to afford 13 (71%), which, upon hydrolysis with basic hydrogen peroxide, gave the protected

\[ \text{*Key: (a) Ti(O-i-Pr)Cl3, i-Pr3NET, CH2Cl2, 0 ºC; tert-butyl acrylate; (b) 3:1 CH3Cl2:TFA, 25 ºC; (c) DPPA, Et3N, tert-butyl alcohol; (d) LiOH, 4:1 THF/H2O, 0 ºC; (e) i-BuOCOC1, NMM, THF, -25 ºC; l-serine Me ester-HCl, NMM, 25 ºC; (f) SOCl2, pyridine, 9:1 Et3O/THF, 0 ºC; (g) Nickel peroxide, CH2=CH2; (h) Boc2O, DMF, MeCN, 25 ºC; (i) KHMDS, THF, -78 ºC; PhSeCl; (j) 50% aqueous HCl, CH2Cl2, pyridine, 0 ºC.} \]

(14) A total of 24% of other diastereomers was also isolated from the reaction mixture.


in 91% yield, which was brominated to give 21 (85%).
Reaction of bromide 21 with tributylphosphine (1.1 equiv, 
DMF, 60 °C, 3 h) afforded phosphonium salt 22 in quanti-
tative yield; alternatively, the Michaelis–Becker reaction 20
provided phosphonate 23 in 95% yield. In model olefi-
nation studies, the conjugate bases of both 22 21 and 23
exhibited good trans selectivity with simple aldehydes.
Within the amino acid and oxazole fragments 9 and 19 in
hand, a practical coupling and protection sequence was
developed (Scheme V). Nitrogen deprotection (HCl, 
EtOAc) of oxazole 19 (1.25 equiv) afforded the derived
solid hydrochloride salt. To a suspension of this salt in 
CH2Cl2 was sequentially added Me3Al (2.50 equiv, 2.5 M 
in toluene) and imide 9 (1.0 equiv, 25 °C, 2 h) to give the
expected amide coupling product along with the analogous
product 24 having unexpectedly lost the PMB ether pro-
tecting group. Since this deprotection operation was de-
sired in subsequent steps, its in situ removal was promoted
by the introduction of an additional 3.75 equiv of Me3Al to
the reaction to provide diol 24 in 78% yield (Scheme V). 22
This transformation not only accomplished the
excision of the chiral auxiliary and formation of the desired
amide bond, but also the removal of the p-methoxybenzyl
ether protecting group in a single operation. Protection
of diol 24 as its bis(triethylsilyl)ether 23 to give 25 (91%),
was followed by reductive removal of the Cbz N-protecting
group and in situ reductive methylation to afford the
dimethylamine 26 in quantitative yield. Reduction of the
carbomethoxy group (74%) and bromination of the re-
sultant alcohol 27 gave 28 in 83% yield. Finally, treatment
of bromide 28 with tributylphosphine provided the tri-
butylphosphonium salt 1a, which was most conveniently
utilized without isolation. Following the same reaction
sequence, phosphonate 1b was also synthesized in 74% 
overall yield from intermediates 9 and 23.
With phosphorus reagents 1a, 1b, 22, and 23 in hand,
the coupling reactions with the C1–C2 portion of calyculin
A are described in the following paper. 24

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ties.

Supplementary Material Available: Full experimental
details for all reactions, analytical data for all intermediates, 
and details of the stereochemical assignments of 7 and 9 (10 pages).
This material is contained in many libraries on microfiche, im-
mediately 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.

(20) Michaelis, A.; Becker, T. Ber. 1897, 30, 1003–1009.
(21) Armstrong has also reported related model studies: Zhao, Z; 
(22) (a) Baasha, A.; Lipton, M.; Weinreb, S. M. Tetrahedron Lett. 1977, 
1988, 110, 2030—2036.
(23) The selection of tris(tributylsilyl) protecting groups for the 
C4 and C9 hydroxy functions was based on model studies which demonstrated that the 
C9 dimethylamino moiety strongly stabilizes these silyl ethers toward acidic cleavage.
tissue.