For the installation of the cyanotetraene portion, Horner–Emmons reaction of lithiated **17** with aldehyde **15** afforded, after aqueous workup, the moderately unstable stannyltriene **18**. Direct submission of this material to Stille coupling[24] ($(MeCN)_2PdCl_2$, 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.

Acknowledgment. Support has been provided by the National Science Foundation and the National Institutes of Health. An NSF predoctoral fellowship to J.R.G. (1986–1989) is gratefully acknowledged. We thank Dr. Andrew Tyler of the Harvard Mass Spectrometry Facility for providing mass spectra and acknowledge the NIH BRS Shared Instrumentation Grant Program 1 s10 RR01748-01A1 and NSF (CHE88-14019) for providing NMR facilities.

Supplementary Material Available: Full experimental details for all reactions, as well as analytical data for all intermediates (13 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.

(24) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.
(25) Chalchat, J.-C.; Thêron, F.; Vessière, R. *C. R. Acad. Sci. Paris Ser.* **1971**, *273*, 763–764.

Asymmetric Synthesis of Calyculin A. 2. The C_{26}–C_{37} γ-Amino Acid Fragments

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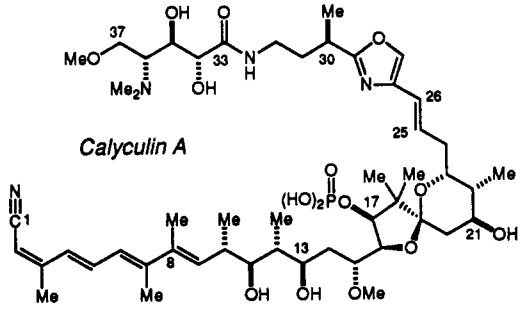
Received January 3, 1992

Summary: New chiral imide enolate alkylation, aldol, and Michael addition bond constructions have been employed in the asymmetric synthesis of the C_{26}–C_{37} portion of calyculin A.

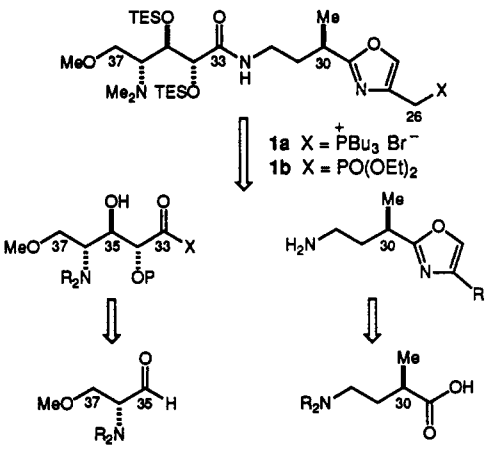
In the preceding paper, the synthesis of the C_1–C_{25} portion of calyculin A was described.[1] We now report the synthesis of the C_{26}–C_{37} fragment containing the basic nitrogen constituents found in the natural product.



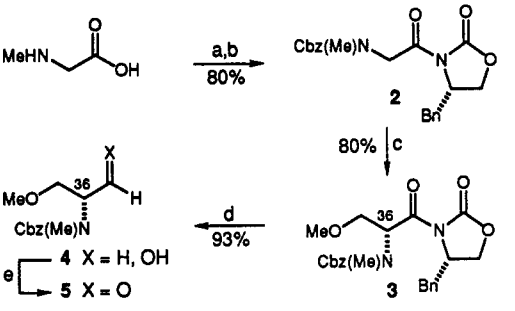
In conjunction with our plan for the union of these subunits during the construction of the C_{25}–C_{26} double bond, it was our intention to rely on a suitable phosphorus-based olefination procedure utilizing either phosphonium salts or the related phosphonate ester such as **1a** or **1b**. The abbreviated plan (Scheme I) for the assemblage of **1** involved disconnection at the amide linkage to reveal the illustrated γ-amino acid and γ-amino oxazole fragments whose syntheses are described below.[2]

Several routes were considered for the synthesis of the densely functionalized C_{33}–C_{37} γ-amino acid. Stereoselective dihydroxylation of an unsaturated pyroglutamic acid[3] seemed attractive in that two of the three stereocenters in the fragment could be established in one step. We were also attracted to the possibility of establishing both hydroxyl-bearing stereocenters in an anti-selective aldol reaction. The potential for convergency led us to investigate such a route despite the lack of precedent for transformations of this type. Disconnection of the C_{34}–C_{35} bond in this fashion reveals a D-serinal derivative (Scheme

Scheme I



Scheme II[a]



[a] Key: (a) aqueous NaOH, BnOCOCl, 0 °C; (b) Me_3CCOCl, Et_3N, X_pLi, −78 to 25 °C; (c) $TiCl_4$, *i*-PrNEt, CH_2Cl_2, 0 °C; $(MeO)_2CH_2$, $BF_3{\cdot}Et_2O$, 25 °C; (d) $LiBH_4$, MeOH, THF, 0 °C; (e) $(COCl)_2$, DMSO, *i*-Pr_2NEt, −78 to −50 °C.

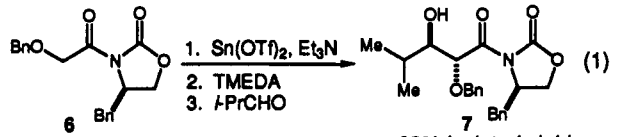
(1) Evans, D. A.; Gage J. R. *J. Org. Chem.* Preceding paper in this issue.
(2) For recent studies which have also addressed the synthesis of the C_{26}–C_{37} calyculin fragment, see: Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859–4862.
(3) A successful synthesis of the C_{33}–C_{37} fragment of calyculin A based on this strategy has recently appeared. See: Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 5983–5986.

0022-3263/92/1957-1961$03.00/0

I) whose synthesis is described below.

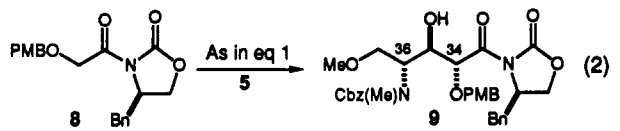
N-Protection (Cbz) of sarcosine and subsequent N-acylation of the (*S*)-phenylalanine-derived oxazolidone auxiliary (X_P)[4] afforded the chiral glycine derivative **2** in 80% overall yield (Scheme II). Formation of the titanium enolate[5] of **2** (CH_2Cl_2, Et_2N-*i*-Pr, 0 °C) followed by acid-catalyzed alkylation with dimethoxymethane (10 equiv) facilitated by $BF_3{\cdot}OEt_2$ (10 equiv, 25 °C, 2 h) provided **3**[6] as an inseparable 98:2 mixture of diastereomers in 80% yield. Reductive removal of the chiral auxiliary[7] to give **4** (93%), followed by Swern oxidation[8] provided the racemization-prone aldehyde **5** which was employed without purification in subsequent aldol studies.

Although precedent for the desired anti glycolate aldol C_{34}–C_{35} bond construction (Scheme I) was scarce, one recent report revealed that the addition of TMEDA to the Sn(II) enolate of a (benzyloxy)acetate derivative resulted in a modest bias for the anti diastereomer in aldol reactions.[9] We reasoned that this phenomenon might translate to chiral glycolate imides such as **6**,[10] where absolute stereochemical control might be obtained from the oxazolidinone auxiliary. Accordingly, enolization of imide **6** with $Sn(OTf)_2$ (1.5 equiv, Et_3N, CH_2Cl_2, 45 min, −15 °C) and addition of TMEDA (1.5 equiv, −78 °C), followed by the addition of isobutyraldehyde (1.2 equiv, 2 h, −78 °C), afforded the illustrated anti aldol adduct **7**[11] in 63% isolated yield (eq 1). GLC analysis of the unpurified reaction



(1)

63% isolated yield

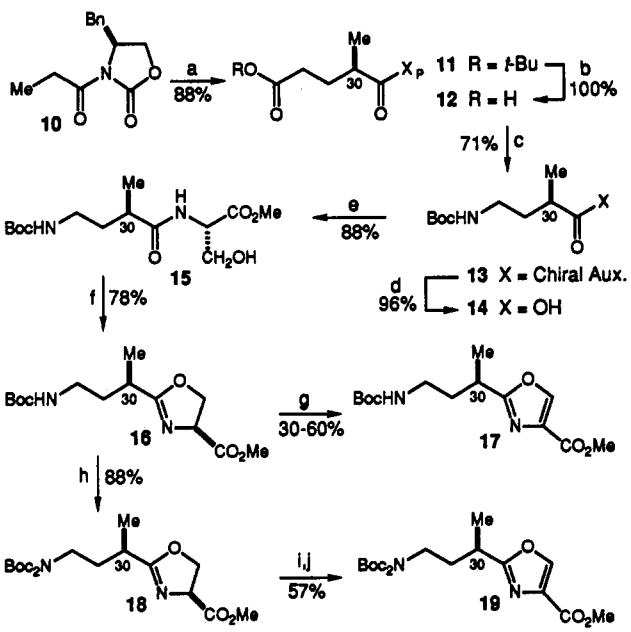


(2)

60% isolated yield from **4**

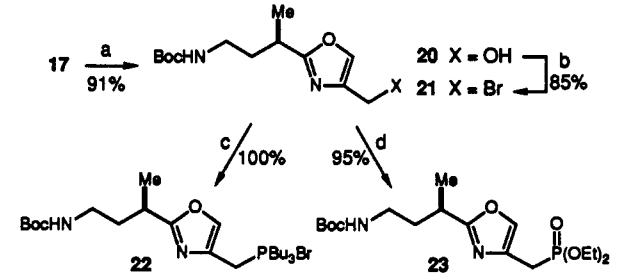
mixture revealed a diastereomer ratio of 77:23 (7:Σ other three diastereomeric aldol adducts).[12] With these results in hand, we investigated the reaction of aldehyde **5** under similar conditions (eq 2). Addition of aldehyde **5** to 1.5 equiv of the Sn(II) enolate derived from imide **8**, generated as with **6** above, in the presence of TMEDA, afforded the desired anti aldol adduct **9**[13] in 60% yield[14] (two steps from **4**).

Scheme III[a]



[a] Key: (a) $Ti(O\text{-}i\text{-}Pr)Cl_3$, $i\text{-}Pr_2NEt$, CH_2Cl_2, 0 °C; *tert*-butyl acrylate; (b) 3:1 CH_2Cl_2:TFA, 25 °C; (c) DPPA, Et_3N, *tert*-butyl alcohol; (d) LiOOH, 4:1 THF/H_2O, 0 °C; (e) *i*-BuOCOCl, NMM, THF, −25 °C; L-serine Me ester·HCl, NMM, 25 °C; (f) $SOCl_2$, pyridine, 9:1 Et_2O/THF, 0 °C; (g) Nickel peroxide, C_6H_6, reflux; (h) Boc_2O, DMAP, MeCN, 25 °C; (i) KHMDS, THF, −78 °C; PhSeCl; (j) 30% aqueous H_2O_2, CH_2Cl_2, pyridine, 0 °C.

Scheme IV[a]

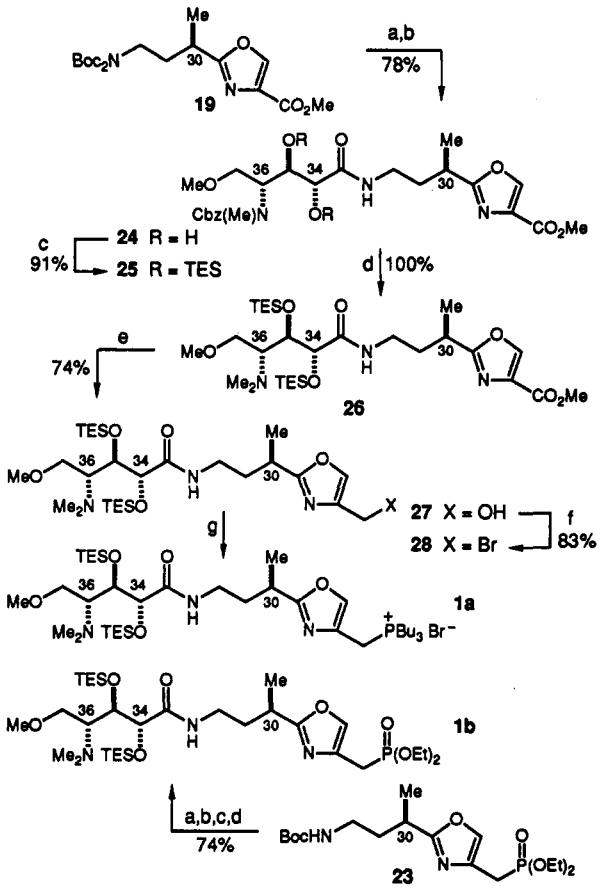


[a] Key: (a) DIBAL, THF, 0 °C; (b) CBr_4, Ph_3P, 2,6-lutidine, MeCN, 25 °C; (c) Bu_3P, DMF, 60 °C; (d) $(EtO)_2P(O)H$, NaH, 5:1 THF/DMF, 0 °C; **21**, THF, 25 °C.

The synthesis of the γ-amino oxazole subunit bearing the C_{30} methyl-bearing stereocenter was initiated with the diastereoselective Michael reaction[15] of the titanium enolate derived from *N*-propionyloxazolidinone **10**[4] with *tert*-butyl acrylate which afforded the desired ester **11** as a single diastereomer (>95:5 by ^1H NMR analysis) in 88% yield (Scheme III). In preparation for the introduction of the terminal amino substituent, acid-catalyzed removal of the *tert*-butyl ester moiety (TFA) then provided acid **12** in quantitative yield. The ensuing Curtius rearrangement[16] of this substrate with diphenylphosphoryl azide (1.1 equiv, Et_3N, *tert*-butyl alcohol, reflux, 15 h) then proceeded smoothly to afford **13** (71%), which, upon hydrolysis with basic hydrogen peroxide,[17] gave the protected

(4) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–91.
(5) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
(6) That the major product has the configuration shown was assigned by analogy to reactions of related titanium enolates. See ref 5.
(7) Penning, T. D.; Djuric', S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Syn. Commun.* **1990**, 307–312. We have found that the use of THF as solvent can dramatically improve this reaction in many cases.
(8) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185. The use of Hunig's base was critical in this oxidation to suppress racemization.
(9) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753–756.
(10) For a syn-selective, Sn(II)-mediated aldol reaction of a related system, see: Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.
(11) That **7** has the anti configuration was established by analysis of the vicinal coupling constant of the derived 1,3-diol acetonide (obtained after reductive removal of the auxilliary). The absolute configuration was determined by conversion **7** into D-α-hydroxyisovaleric acid. See the supplementary material for details.
(12) In the absence of TMEDA this reaction is completely stereorandom, producing all four diastereomers in nearly equal amounts.
(13) Proof of the all anti array of the three contiguous stereocenters was determined by conversion of **9** into an *N*-methylpyrrolidinone derivative and measurement of the relevant coupling constants and NOE's. See the supplementary material for details.
(14) A total of 24% of other diastereomers was also isolated from the reaction mixture.
(15) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750–5752.
(16) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
(17) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

Scheme V[a]



[a] Key: (a) HCl (g), EtOAc, 0 °C; (b) $AlMe_3$, CH_2Cl_2, 25 °C; **9**; $AlMe_3$; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) H_2 (1 atm), 10% Pd/C, aqueous formaldehyde, MeOH, AcOH; (e) DIBAL, THF, −25 °C; (f) CBr_4, Ph_3P, 2,6-lutidine, MeCN; (g) Bu_3P, DMF, 25 °C.

(*R*)-γ-amino acid **14** in 96% yield.[18] This acid was transformed into the desired oxazole by coupling (*i*-BuOCOCl, NMM) with L-serine methyl ester to give dipeptide **15** (88%), which was cyclized to oxazoline **16** ($SOCl_2$, pyr, 0 °C) in 78% yield. Nickel peroxide oxidation[19] of **16** to oxazole **17** proceeded in moderate and variable yields (30–60%), and due to the capricious nature of this transformation, an alternative oxazoline dehydrogenation procedure which proved to be much more reproducible was also developed. Thus, treatment of oxazoline **16** with Boc_2O (1.8 equiv, 0.07 equiv of DMAP, MeCN, 37 h) cleanly provided **18** in 88% yield. Enolization of **18** with KHMDS (1.1 equiv, −78 °C) followed by reaction with phenylselenenyl chloride and oxidative elimination of the resultant diastereomeric selenides afforded oxazole **19** in 57% overall yield. This latter procedure, although more involved, proved to be the method of choice for larger-scale reactions.

As models for phosphorus reagents **1a** and **1b**, the side chain of oxazole **17** was suitably modified (Scheme IV). Reduction of the carbomethoxy group provided alcohol **20** 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 quantitative yield; alternatively, the Michaelis–Becker reaction[20] provided phosphonate **23** in 95% yield. In model olefination studies, the conjugate bases of both **22**[21] and **23** exhibited good trans selectivity with simple aldehydes.

With 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 CH_2Cl_2 was sequentially added Me_3Al (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 protecting group. Since this deprotection operation was desired in subsequent steps, its in situ removal was promoted by the introduction of an additional 3.75 equiv of Me_3Al 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 resultant alcohol **27** gave **28** in 83% yield. Finally, treatment of bromide **28** with tributylphosphine provided the tributylphosphonium 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 C_1–C_{25} portion of calyculin A are described in the following paper.[24]

Acknowledgment. Support has been provided by the National Science Foundation and the National Institutes of Health. An NSF predoctoral fellowship to J.R.G. (1986–1989) is gratefully acknowledged. We thank Dr. Andrew Tyler of the Harvard Mass Spectrometry Facility for providing mass spectra and acknowledge the NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 and NSF (CHE88-14019) for providing NMR facilities.

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, 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.

(18) The absolute configuration of **14** was assigned by analogy; see ref 15.

(19) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497–501.

(20) Michaelis, A.; Becker, T. *Ber.* **1897**, *30*, 1003–1009.

(21) Armstrong has also reported related model studies: Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609–1612.

(22) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.

(23) The selection of triethylsilyl protecting groups for the C_{34} and C_{35} hydroxyl functions was based on model studies which demonstrated that the C_{36} dimethylamino moiety strongly stabilizes these silyl ethers toward acid cleavage.

(24) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* Following paper in this tissue.