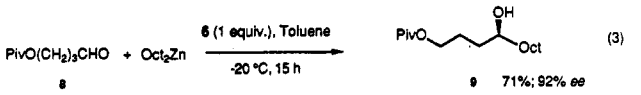
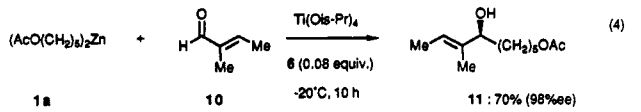
chain strongly influences the level of the stereoselectivity in these addition reactions. Thus, excellent enantioselectivites are observed if the acetoxy group is separated from the metal by four or five carbon atoms (92–93% ee, entries 1 and 7 of Table II). However, an erosion of the stereoselectivity is observed if only three carbons separate the metal from the acetoxy functionality (86% ee, entry 8). This lower enantioselectivity can be improved by replacing the acetoxy group by a pivaloyloxy group (92% ee, entry 9). The lowest selectivity has been observed with bis(3-carbethoxypropyl)zinc (**1j**) which adds to benzaldehyde affording ethyl 5-hydroxy-5-phenylpentanoate (**7j**) in only 60% ee (75% yield, entry 10).

Also, the enantioselective addition of Oct_2Zn to the 4-(pivaloyloxy)butyraldehyde **8**[18,19] is possible if stoichiometric amounts of **6** are used and allows the preparation of the monoprotected 1,4-diol **9** in 71% yield and 92% ee (eq 3).



This method can also be extended to the preparation of optically pure (98% ee) functionalized allylic alcohols.[10,8] Thus, the addition of **1a** (2 equiv) to (*E*)-2-methylbutenal (**10**) in the presence of a catalytic amount of **6** (0.08 equiv) and $Ti(OisPr)_4$ (ca. 2 equiv, −20 °C, 10 h) provides the allylic alcohol **11** in 70% yield (98% ee), eq 4.



In conclusion, we have reported a new iodine–zinc exchange reaction which allows the first preparation of functionalized dialkylzincs and their successful asymmetric addition to aldehydes in the presence of the chiral catalyst **6**. Extensions of this methodology are currently underway in our laboratories.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Michigan (office of the Vice President for Research) for support of this research. We also thank S. Chi for some preliminary experiments.

Supplementary Material Available: Spectral data of the compounds described in Tables I and II (9 pages). Ordering information is given on any current masthead page.

(16) **Typical Procedure. (a) Typical Procedure for the Reaction of the Copper Reagents FG-RCu(CN)Zn(FG-R) 4 with an Electrophile.** Preparation of 3-(3-cyanopropyl)cyclohexanone **5g**: A Schlenk tube equipped with a septum cap and an argon outlet was charged with 4-iodobutyronitrile (1.20 g, 6 mmol) and diethylzinc (3.0 mL, 30 mmol). The reaction mixture was warmed to 50–55 °C and was stirred for 12 h at this temperature. GLC analysis of a hydrolyzed reaction aliquot indicates the completion of the reaction. The ethyl iodide formed, and excess diethylzinc was removed in vacuum (50 °C, 2 h; ca. 0.1 mmHg). The resulting oil of bis(3-cyanopropyl)zinc **1d** was dissolved in dry THF (3 mL) and added to a THF solution (6 mL) of CuCN (270 mg, 3 mmol) and LiCl (255 mg, 6 mmol, dried 2 h at 150 °C under 0.1 mmHg) at −20 °C. The resulting light green solution was cooled to −78 °C, and Me_3SiCl (0.8 g, 7 mmol) and 2-cyclohexenone (0.335 g, 3.5 mmol) were added successively. The reaction mixture was slowly allowed to warm to −10 °C overnight and was worked up in the usual way to afford after purification by flash chromatography (30% AcOEt in hexane) the ketone **5g** (483 mg, 83% yield). **(b) Typical Procedure for the Catalytic Asymmetric Addition of Dialkylzinc (FG-R)$_2$Zn 1 to an Aldehyde.** Preparation of (*S*)-(−)-6-hydroxy-6-phenylhexyl acetate **7a**: A Schlenk tube equipped with a septum cap and an argon outlet was charged with 5-iodopentyl acetate (2.05 g, 8.0 mmol) and diethylzinc (4.0 mL, 40 mmol). The reaction mixture was warmed to 50 °C and was stirred for 4 h at this temperature. GLC analysis of a hydrolyzed reaction aliquot indicates the completion of the reaction. The ethyl iodide formed, and excess diethylzinc was removed in vacuum (50 °C, 2 h; ca. 0.1 mmHg). The resulting clear viscous oil of bis(5-acetoxypentyl)zinc was dissolved in toluene (4 mL) and was added at −60 °C to the titanium catalyst **6**, followed by benzaldehyde (210 mg, 2.0 mmol). The reaction mixture was warmed to −20 °C and was stirred for 2 h. After the usual workup (using 10% aqueous HCl/ether) and flash chromatography (10% EtOAc in hexane), the alcohol **7a** (370 mg, 79% yield, 93% enantiomeric excess) was obtained as a clear colorless oil. Its optical purity was determined by the ^{1}H NMR analysis of its derivative with (*S*)-(−)-*O*-acetylmandelic acid.[17] **Preparation of the Catalyst.** The catalyst **6** was prepared in the following way: a three-necked flask equipped with a septum, a thermometer, and an argon outlet was charged with *trans*-1(*R*),2(*R*)-bis(trifluorosulfinamido)cyclohexane (63 mg, 0.16 mmol, 8 mol %; ref 2a,b) and titanium tetraisopropoxide (1.2 mL, 4.0 mmol) in toluene (1 mL), and the solution was warmed to 40 °C for 0.5 h.

(17) Parker, D. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 83.

(18) 4-(Pivaloyloxy)butyraldehyde has been prepared from 1,4-butanediol in two reaction steps: (i) PivCl (0.4 equiv), DMAP cat., pyridine, CH_2Cl_2, 0–25 °C, 1 h; 50% yield; (ii) ClCOCOCl (1.1 equiv), DMSO (2.4 equiv), −60 °C, then Et_3N (excess), −60 to +10 °C, 95% yield.

(19) The presence of an oxygen substituent close to the carbonyl group or to the carbon–metal bond strongly changes the rate of the addition reaction. See also the excellent review article: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

(20) Most of the asymmetric additions have been performed on a scale using 2 mmol of aldehyde. The scale-up of the reaction (10 mmol of RCHO) is possible; comparable yields and the *same enantioselectivity* is observed. However, we noticed during the larger scale preparation of some dialkylzincs, such as **1j**, a rate decrease and a lower final conversion. This problem can be solved by the addition of a catalytic amount (0.3%) of CuI to the reaction mixture. The mechanism of the iodine–zinc exchange reaction is currently being investigated.

Asymmetric Synthesis of Calyculin A. 1. The C_1–C_{25} Spiroketal Fragment

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Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received January 3, 1992

Summary: An asymmetric synthesis of the C_1–C_{25} portion of calyculin A has been developed.

In 1986, Fusetani and co-workers reported the isolation of the unique marine natural product, calyculin A, from the sponge *Discodermia calyx*, along with its X-ray structure (relative configuration).[1] In subsequent papers, this group has reported the related structures, calyculins B–H, differing only in olefin geometry in the C_1–C_9 region

(1) (a) Structure: Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780–2781. (b) Activity: Ishihara, K.; Martin, B. L.; Brautigan, D. L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, H.; Uemura, K.; Hartshorne, K. *J. Biochem. Biophys. Res. Commun.* **1989**, *159*, 871–877.

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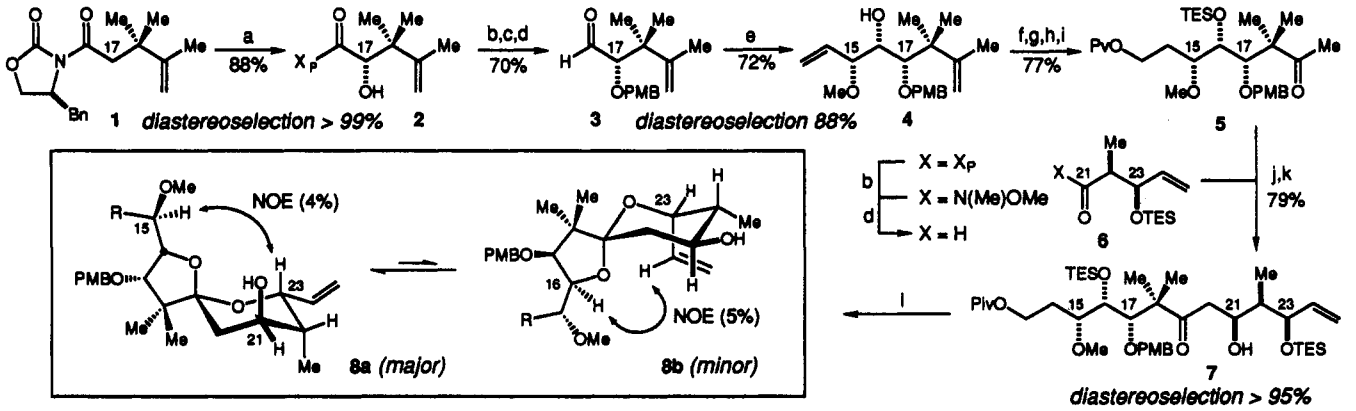
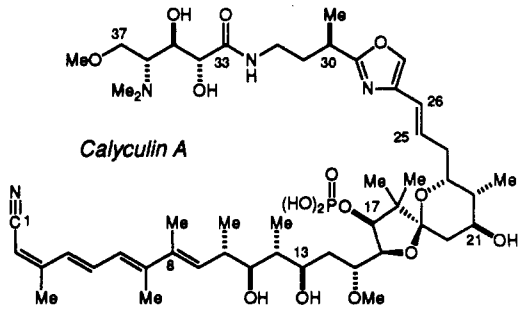
Scheme I[a]



[a] Key: (a) NaHMDS, 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −78 °C; (b) $AlMe_3$, MeNH(OMe)HCl, CH_2Cl_2, reflux; (c) NaH, PMBBr, THF/DMF, 0 °C; (d) DIBAL, toluene, −78 °C; (e) 1-methoxy-3-(tributylstannyl)propene, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −40 °C; (f) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (g) catecholborane, $(Ph_3P)_3RhCl$, THF; H_2O_2; (h) PvCl, CH_2Cl_2; (i) OsO_4, NMO, THF/*t*-BuOH/water; $NaIO_4$; (j) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (k) 6 (X = H), $BF_3{\cdot}OEt_2$, THF, −78 °C; (l) HF, acetonitrile, water.

and/or the presence of an additional methyl group at C_{32}.[2] Very recently, degradation and synthetic studies have led to an absolute configurational assignment for this family of natural products which is enantiomeric to the illustrated structure.[3]



Calyculin A is a tumor promoter and potent inhibitor of protein phosphatases 1 and 2A. This expressed biological activity and complex architecture of these natural products have made them attractive targets for stereoselective synthesis.[4] However, to date no completed synthesis of any of the calyculins has been reported. Herein we disclose an asymmetric synthesis of the C_1–C_{25} portion of calyculin A, and in the subsequent papers we describe the incorporation of this fragment into a fully protected version of the natural product.[5]

We sought to design a convergent route which would accommodate a good degree of flexibility with respect to the ordering of fragment coupling for the assemblage of the structural components of the molecule. Toward this end, disconnection of the C_{25}–C_{26} double bond affords two fragments of comparable complexity which served as our immediate synthetic targets. In the spiroketal fragment, we elected to introduce the C_{17} phosphate ester and the sensitive C_1–C_9 cyanotetraene moiety as late as possible in the synthesis plan to avoid the accompanying sensitivity which would be conferred upon the structure by these structural elements. Further retrosynthetic excision of the C_{10}–C_{13} anti dipropionate array left the construction of the spiroketal core of the molecule as our first objective.

The synthesis began with acylation of the (*S*)-phenylalanine-derived oxazolidinone[6] with 3,3,4-trimethylpent-4-enoic acid (Scheme I).[7] Asymmetric hydroxylation of 1 (NaHMDS, oxaziridine, THF, −78 °C) according to our established precedent[8] served to establish the C_{17} center with complete stereocontrol (88%). Subsequent transamination,[9] protection (PMB-Br, NaH), and reduction (DIBAL, toluene) produced aldehyde 3 (70% overall yield) which was subjected to chelate-controlled allylstannane addition ($MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −40 °C) to afford the differentiated triol 4 with moderate selectivity (7.5:1).[10] The minor diastereomeric contaminant in this reaction was readily separable by chromatography. After protection of the secondary alcohol, the two olefins were effectively differentiated by Rh(I)-catalyzed hydroboration (Rh-$(Ph_3P)_3Cl$, with catecholborane).[11] Protection of the primary alcohol and oxidation of the 1,1-disubstituted olefin to the corresponding methyl ketone then proceeded cleanly to provide methyl ketone 5 in a 77% overall yield from 4. The pivotal aldol reaction between the trimethylsilyl enol ether derived from 5 and aldehyde 6 (X = H) ($BF_3{\cdot}OEt_2$, THF, −78 °C, 8 h) to establish the C_{21} stereocenter was executed with complete Felkin–Anh stereocontrol[12] to provide aldol adduct 7 (80%) which was transformed (HF/MeCN/H_2O, 25 °C) to the readily se-

(2) (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930–3932. (b) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999–3006.

(3) (a) Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1991**, *32*, 5605–5606. (b) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 5983–5986.

(4) For preliminary efforts directed toward the synthesis of the calyculins see: (a) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357–7360. (b) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129–6132. (c) Hara, O.; Hamada, Y.; Shioiri, T. *Syn. Lett.* **1991**, 283–284, 285–286. (d) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609–1612. (e) Smith, A. B.; III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855–4858. (f) Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859–4862.

(5) See the following two papers in this issue.

(6) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–91.

(7) Andersen, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144–4151.

(8) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.

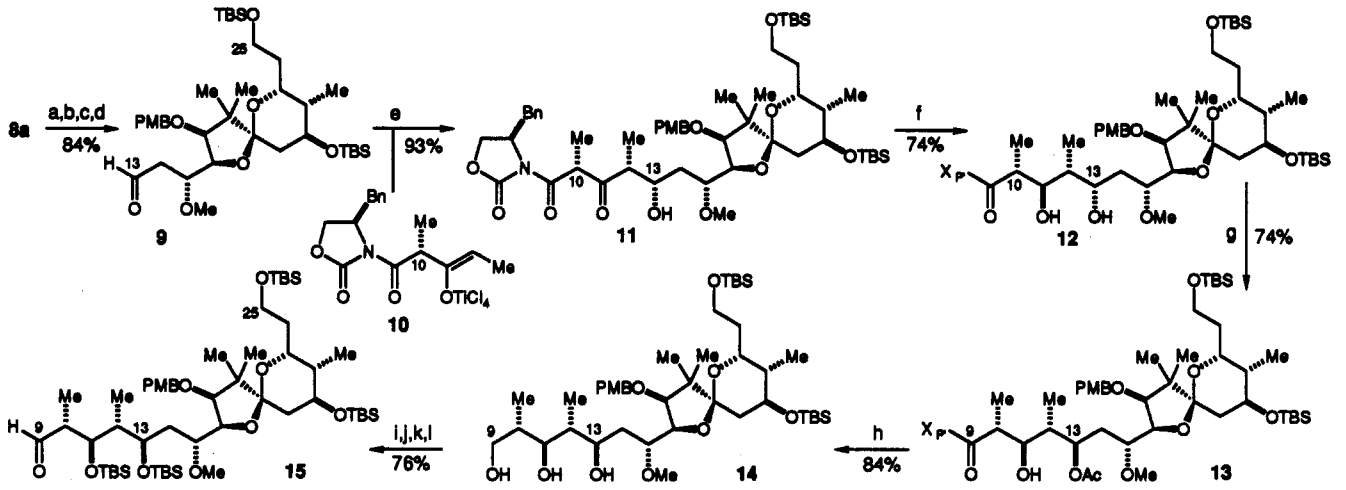
(9) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3816. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.

(10) (a) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139–142. (b) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143–146.

(11) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917–6918.

(12) In contrast, the lithium enolate derived from 5 afforded the opposite sense of asymmetric induction in the analogous aldol addition reaction (see ref 4b).

Scheme II[a]



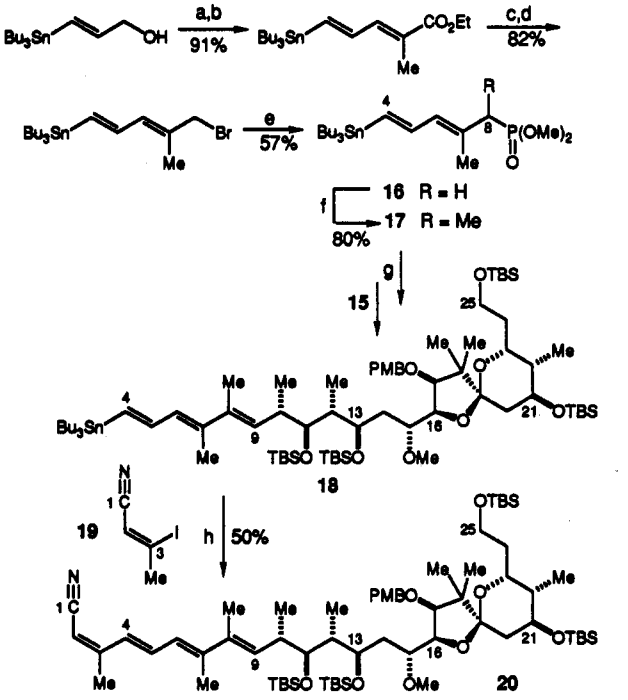
[a] Key: (a) 9-BBN, ultrasound, THF; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) DIBAL, CH_2Cl_2, −78 °C; (d) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60 °C; (e) CH_2Cl_2, −78 °C; (f) $Me_4NBH(OAc)_3$, MeCN/AcOH, −20 °C; (g) di-*tert*-butylazodicarboxylate, Ph_3P, AcOH, benzene; (h) $LiBH_4$, MeOH, THF, 0 °C; (i) PivCl, pyridine; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (k) DIBAL, CH_2Cl_2, −78 °C; (l) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60 °C.

parable spiroketals **8a** (71%) and **8b** (14%) as previously described.[4b] The observation that the minor (undesired) spiroketal diastereomer **8b** is formed first in this reaction sheds light on the sequence of events which is followed in the spiroketalization process.[13,14]

For the elaboration of the C_{10}–C_{13} region of the skeleton, we elected to take advantage of the convergent nature of the β-ketoimide-derived aldol chemistry recently developed in this laboratory (Scheme II).[15] Toward this end, sonication-induced hydroboration (9-BBN, THF) of the vinyl group in **8a**,[16] silylation, reductive removal of the pivaloyl ester, and Swern oxidation[17] afforded aldehyde **9**. Aldol addition of the titanium enolate **10** to aldehyde **9** afforded the adduct **11** (93%) as a single diastereomer with the "wrong" stereochemistry at C_{13}. After exploiting this center to direct the reduction of the C_{11} ketone ($Me_4NBH(OAc)_3$, MeCN/AcOH, −20 °C),[18] the C_{13} hydroxyl group was selectively inverted using a Mitsunobu reaction (di-*tert*-butylazodicarboxylate, Ph_3P, AcOH, benzene) to provide **13** in 74% yield along with 14% of recovered **12**.[19] It is noteworthy that the C_{11} alcohol was unaffected throughout this inversion procedure. Reductive removal of the chiral auxiliary[20] and acetate ester ($LiBH_4$, 0 °C) to give triol **14** (84%) followed by a short series of routine steps afforded an aldehyde **15** ready for appendage of the cyanotetraene moiety.

The phosphonate coupling partner needed for the cyanotetraene moiety was synthesized by the route outlined in Scheme III. The known 3-(tributylstannyl)-3-propen-1-ol[21] was oxidized and homologated via a Horner–Emmons reaction. Reduction to the allylic alcohol was followed by bromide formation (CBr_4, Ph_3P, MeCN) to provide an inseparable 6:1 (primary to secondary) mixture of allylic halides. This mixture was submitted to Michaelis–Becker conditions ($NaPO(OMe)_2$, DMF/THF)[22] to afford a 57% yield of the desired stannyl phosphonate **16**. The C_8 methyl group was conveniently incorporated by sequential lithiation (*n*-BuLi, THF, −78 °C)[23] and methylation with iodomethane to give **17** in good yield.

Scheme III[a]



[a] Key: (a) Swern Oxidation; (b) $(EtO)_2POCH(CH_3)CO_2Et$, *n*-BuLi, THF; (c) DIBAL, CH_2Cl_2, −60 °C; (d) CBr_4, Ph_3P, 2,6-lutidine, MeCN; (e) $NaPO(OMe)_2$, THF; (f) *n*-BuLi, MeI, THF, −78 to 0 °C; (g) *n*-BuLi, THF, −78 to 25 °C; (h) $(MeCN)_2PdCl_2$, DMF.

(13) At equilibrium, the ratio of **8a**:**8b** is 5.
(14) For recent studies which have also addressed the synthesis of the spiroketal moiety, see ref 4e.
(15) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868.
(16) Crimmins, M. T.; O'Mahony, R. *Tetrahedron Lett.* **1989**, *30*, 5993–5996.
(17) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
(18) Evans, D. A.; Chapman, K. T.; Carreira, E. M.; *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
(19) Mitsunobu, O. *Synthesis* **1981**, 1–28. Secondary alcohols branched on both sides generally do not undergo the Mitsunobu reaction. For a recent example, see: Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.
(20) Penning, T. D.; Djuric', S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307–312.
(21) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.
(22) Michaelis, A.; Becker, T. *Ber.* **1897**, *30*, 1003–1009.
(23) The fact that this reaction leads to proton abstraction rather than transmetalation is noteworthy.

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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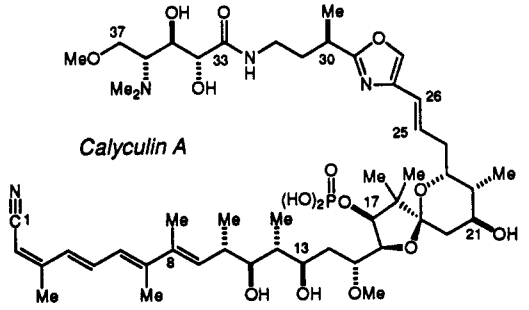
Received January 3, 1992

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.

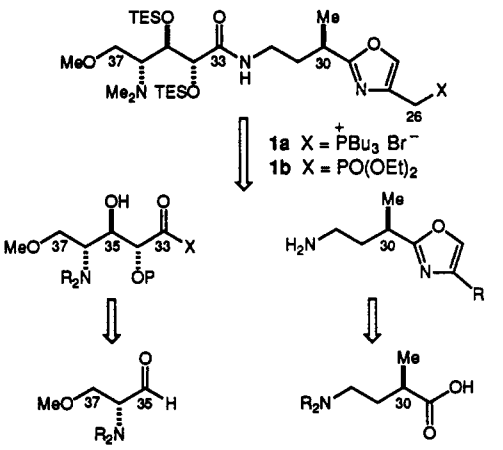
In the preceding paper, the synthesis of the C_1–C_{25} portion of calyculin A was described.[1] We now report the synthesis of the C_{26}–C_{37} fragment containing the basic nitrogen constituents found in the natural product.



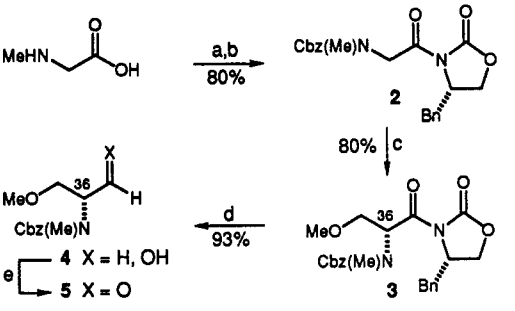
In conjunction with our plan for the union of these subunits during the construction of the C_{25}–C_{26} double bond, it was our intention to rely on a suitable phosphorus-based olefination procedure utilizing either phosphonium salts or the related phosphonate ester such as **1a** or **1b**. The abbreviated 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