

Stereocontrolled Synthesis of Calyculin A: Construction of the C(26)–C(37) Amide–Oxazole Unit

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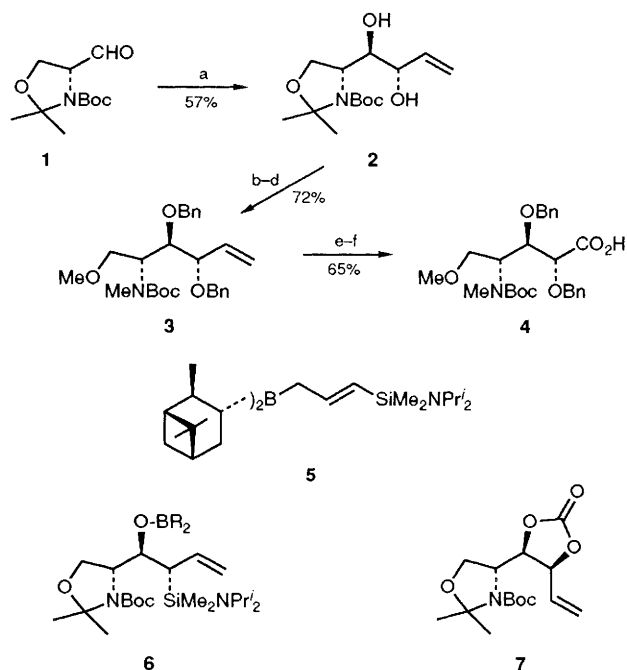
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(–)-*B*-[3-(Diisopropylaminodimethylsilyl)allyl]diisopinocampheylborane and Cornforth–Meyers chemistry, and Evans alkylation were employed to construct the C(26)–C(37) amide–oxazole unit of calyculin A.

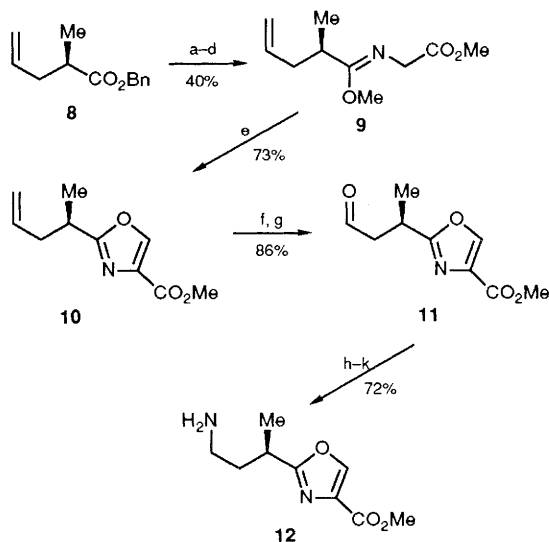
The calyculins are a group of potent yet selective phosphatase inhibitors elaborated by the sponge *Discodermia calyx*.¹ In the preceding communications,^{2,3} we outlined syntheses of the C(1)–C(5), the C(6)–C(14), and the C(15)–C(25) units. Additionally, we defined conditions for the generation of the tetraene nitrile unit using Stille chemistry. We now report a concise enantioselective method for the elaboration of the

remaining C(26)–C(37) amide oxazole unit **14**.[†] Initially, we sought to prepare amide **14** using D-ribonic acid γ -lactone as a precursor for the γ -amino acid unit. Although this radical

[†] The synthesis was started before the determination of the absolute stereochemistry of the calyculins. Arbitrarily, the synthesis was directed towards the antipode of the natural product.

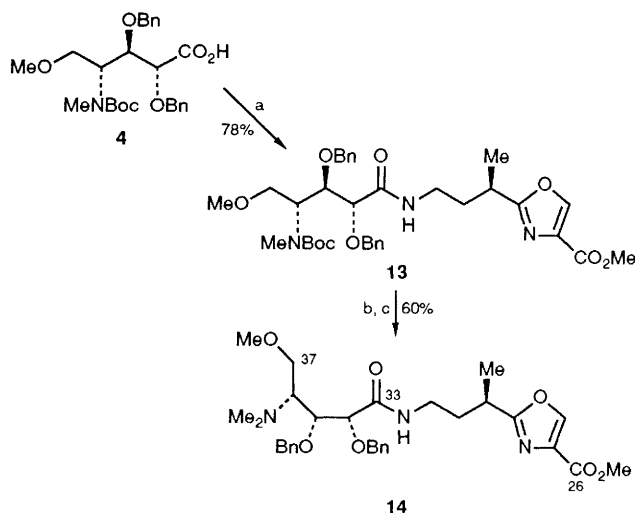


Scheme 1 Reagents and conditions: (a) **5**, THF, Et₂O, -78 °C; H₂O₂, KF, KHCO₃; (b) PhCH₂Br, NaH, DMF; (c) TsOH, MeOH; (d) MeI, NaH, DMF; (e) O₃, CH₂Cl₂, -78 °C; Me₂S; (f) NaClO₂, H₂O₂, NaH₂PO₄, H₂O, MeCN. THF = tetrahydrofuran; DMF = dimethylformamide; Ts = tosyl; Bn = PhCH₂.



Scheme 2 Reagents and conditions: (a) AlMe₃, NH₄Cl, CH₂Cl₂, 0 °C; (b) Cl₃CCOCl, Et₃N, CH₂Cl₂, 0 °C; (c) HCl, MeOH, 0 °C; (d) MeO₂CCH₂NH₃Cl, Et₃N, CH₂Cl₂; (e) Bu^tOK, HCO₂Me, Et₂O; AcOH; (f) OsO₄ (catalyst), *N*-methylmorpholine *N*-oxide, Me₂CO, H₂O; (g) NaIO₄, THF, H₂O; (h) NaBH₄, MeOH, 0 °C; (i) MeSO₂Cl, Et₃N, CH₂Cl₂; (j) NaN₃, DMF; (k) H₂, Pd/C, EtOH

based sequence⁴ gave derivatives of the C(33)–C(37) residue, the approach was too lengthy. Thus, the approach was switched to a serine based strategy⁵ using our recently published adaption⁶ of Brown allylborane chemistry⁷ (Scheme 1). The serine aldehyde **15** was smoothly homologated, without racemization, using reagent **5** to produce the diol **2**.^{6‡} We were pleased to discover that this reaction, which



Scheme 3 Reagents and conditions: (a) *N*-hydroxybenzotriazole, dicyclohexylcarbodiimide, DMF, 0–25 °C; **12**; (b) CF₃CO₂H, CH₂Cl₂ 25 °C; (c) MeI, Pr₂NEt, CH₂Cl₂

proceeds *via* **6** and oxidative cleavage of the C–Si bond with retention of stereochemistry, was highly stereocontrolled. The structure of **2** was confirmed by an X-ray crystallographic study of the derived carbonate **7**.⁶ Alkene **2** was converted into the corresponding protected γ -amino acid **4** *via* benzylation, cleavage of the isopropylidene group, *O,N*-dimethylation, ozonolysis and chlorite oxidation of the aldehyde intermediate. The use of benzyl protection⁸ considerably facilitated these transformations. It was decided to leave the Boc protecting group intact until after the calyculin amide bond formation since this greatly simplified the synthesis and prevented the unwanted formation of γ -lactams.

The synthesis of the oxazole residue is summarized in Scheme 2. Thus, the ester **8**, which was prepared by Evans alkylation,⁹ was converted *via* Weinreb amide formation,¹⁰ dehydration and imidation¹¹ into the glycine derivative **9**. Following the elegant methods described by Cornforth and Meyers,¹¹ **9** was smoothly C-formylated and cyclized to provide directly the corresponding oxazole ester **10**. All these transformations proceeded without any appreciable racemization. Subsequently, alkene **10** was smoothly converted into the corresponding amine **12** *via* catalytic osmylation–periodate cleavage,¹² reduction of the aldehyde **11**, methanesulfonylation, azide displacement and hydrogenation.¹³

Both the carboxylic acid **4** and the amine **12** were linked together to form the corresponding amide **13** using the methods in Scheme 3. After considerable experimentation, it was found that this amide coupling reaction was most efficiently carried out using dicyclohexylcarbodiimide and *N*-hydroxybenzotriazole.¹⁴ In addition, the use of benzyl protection for the diol and retention of the Boc group were crucial for success. The resultant amide **13** was converted into the requisite oxazole ester amide **14** *via* hydrolysis of the Boc group using trifluoroacetic acid^{5,8} and final *N*-methylation.

In conclusion, we have designed a concise method for the elaboration of the amide–oxazole unit of calyculin A. The silylborane reagent **5** and its antipode should find considerable general use for the synthesis of *anti*-vicinal diol arrays. These reactions further underscore the flexibility and power of

§ The enantiomeric purity of the alkene **10** was determined by preparing the (*R*)-Mosher ester from the primary alcohol derived from the aldehyde **11**. This single diastereoisomer was carefully compared with the mixture of diastereoisomers derived from the racemic modification of **11**. For the preparation of Mosher esters see J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

‡ All new compounds were fully characterized by spectral data and microanalyses or HRMS.

diisopinocampheylborane derivatives in asymmetric synthesis. Further progress in the calyculin area will be summarized in future communications.

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