Stereocontrolled Synthesis of Calyculin A: Construction of the C(15)–C(25) Spiroketal Unit

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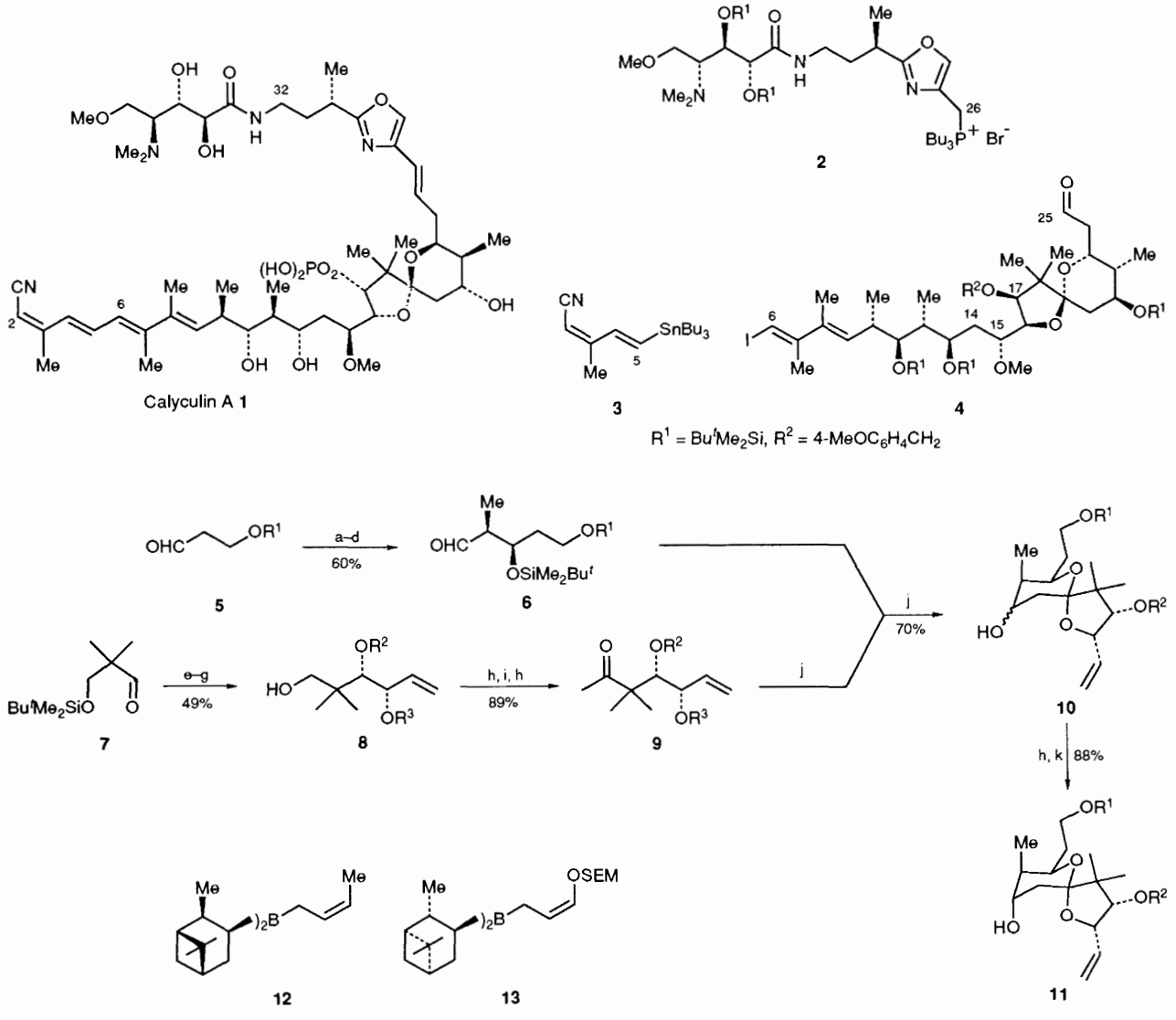
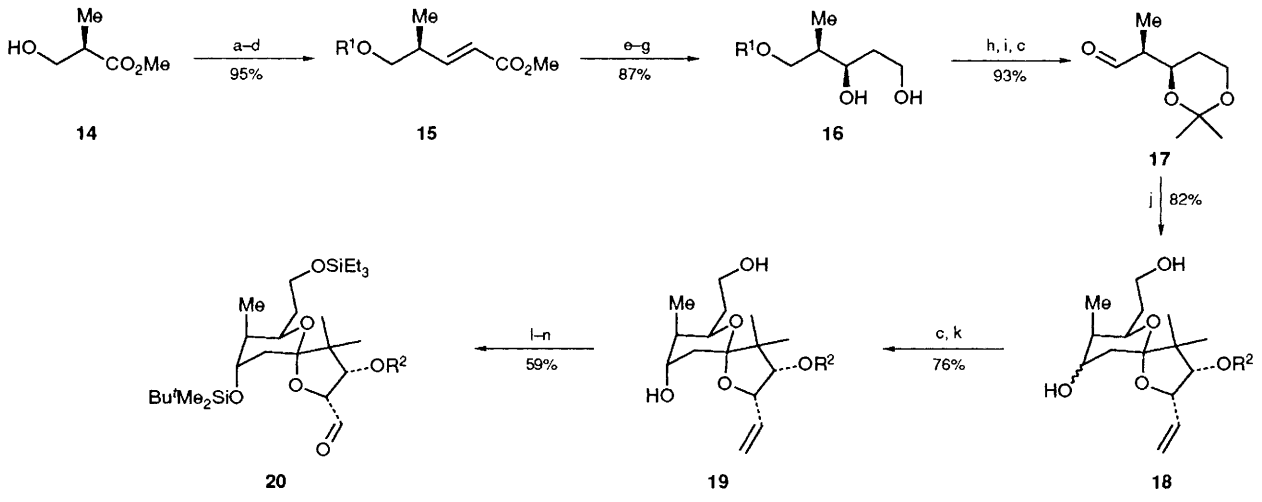
Two concise enantioselective syntheses of the C(15)–C(25) spiroketal unit of calyculin A, using derivatives of allyldiisopinocampheylborane efficiently to control 1,2- and 1,3-diol stereochemistries, are reported.

The calyculins are a group of marine natural products isolated from the sponge *Disocodermia calyx*.[1] Calyculin A **1** is a representative member of the series and the other calyculins differ from **1** by the presence of an additional methyl group at C-32 and/or by a change in the geometry of Δ^2 and/or Δ^6. These structurally unusual substances are all noted for their potent activity in the starfish egg assay. All are very powerful inhibitors of phosphatase enzymes and are particularly effective against PP-1 and PP-2A phosphatases. For example, calyculin A **1** is active against rabbit skeletal muscle type PP-2A phosphatases at 0.5–1.0 nmol dm^{-3} concentrations. Additionally, **1** is 20–300 times more active than okadaic acid against various PP-1 enzymes. In contrast, calyculin A **1** does not inhibit various acid, alkaline, and protein tyrosine phosphatases even at 1 μmol dm^{-3} concentration. Calyculin A **1** also shows other activities. It is equipotent with phorbol esters and teleocidins in inflammation and tumour promotion tests.

In common with many other marine and terrestrial natural



Scheme 1 *Reagents and conditions*: (a) **12**, THF, Et_2O, −78 °C; $NaBO_3 \cdot 4H_2O$, H_2O; (b) $Bu^tMe_2SiOSO_2CF_3$, THF, 2,6-lutidine; (c) OsO_4 (catalytic), *N*-methylmorpholine *N*-oxide, Me_2CO, H_2O; (d) $NaIO_4$, THF, H_2O; (e) **13**, THF, Et_2O, −78 °C; $HOCH_2CH_2NH_2$, NaH (catalytic); (f) $KN(SiMe_3)_2$, THF, DMF, *p*-$MeOC_6H_4CH_2Cl$; (g) Bu_4NF, THF; (h) Swern oxidation; (i) MeMgBr, THF; (j) LDA, THF, −78 °C, add **6**; TsOH, MeOH, 25 °C; (k) $KBHBu^s_3$, THF, −78 to −10 °C; NaOH, H_2O_2. THF = tetrahydrofuran; DMF = dimethylformamide; LDA = lithium diisopropylamide; Ts = *p*-tolylsulfonyl; SEM = (2-trimethylsilylethoxy)methyl.



Scheme 2 *Reagents and conditions*: (a) R^1Cl, Pr^i_2NEt, CH_2Cl_2; (b) $LiAlH_4$, Et_2O; (c) Swern oxidation; (d) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; (e) DIBAL-H, CH_2Cl_2; (f) Sharpless epoxidation; (g) Red-Al, THF; (h) PPTS, $Me_2C(OMe)_2$, PhH; (i) Na, NH_3, THF; (j) **9**, LDA, THF, −78 °C, add **17**; TsOH, MeOH, 25 °C (k) $KBHBu^s_3$, THF, −78 to −10 °C; NaOH, H_2O_2; (l) Et_3SiCl, Et_3N, imidazole, CH_2Cl_2, −40 to −20 °C; (m) Bu^tMe_2SiOTf, Pr^i_2NEt, CH_2Cl_2; (n) O_3, CH_2Cl_2, −78 °C; Me_2S. DIBAL-H = diisobutylaluminium hydride; PPTS = pyridinium toluene-*p*-sulfonate; Tf = trifluoromethylsulfonyl.

products, calyculin A **1** contains a spiroketal unit[2] and a 2,4-disubstituted oxazole residue.[3] Recent studies by both Fusetani and Shioiri have established the absolute stereochemistry of calyculin A as structure **1**.[4] In addition, several groups have reported synthetic studies on various fragments of calyculin, and Evans has completed the synthesis of the entire carbon skeleton of the natural product.[5] However, to date, no completed total syntheses have been reported. We now first report[6] our own approaches to these important natural products. Retrosynthetically, we considered that calyculin A **1** should be available from the oxazole amide **2**, the cyanostannane **3**, and the spiroketal diene **4**.† In turn, it should be possible to construct the spiroketal unit **4** using an aldol reaction to establish the C(14)–C(15) bond. Herein, we describe two concise enantioselective syntheses of the C(15)–C(25) calyculin spiroketal residues **11** and **20**.

Brown has introduced various allyl derivatives of diisopinocampheylborane as versatile reagents for the stereoselective construction of homoallylic alcohols.[7] This most elegant masked aldol chemistry forms the cornerstone of the asymmetric synthesis in Schemes 1 and 2. Thus, reaction of aldehyde **5** with (−)-(*Z*)-crotonyldiisopinocampheylborane **12**, the reagent derived from (+)-α-pinene,[7] gave the corresponding homoallylic alcohol and this was readily transformed[8,9] into the protected aldehyde **6**.‡ In this transformation, the *syn*-relative stereochemistry (>95%)§ and the enantiomeric purity of the product (>95%)¶ were both excellent.

The aldehyde **7** was smoothly converted into the protected *syn*-diol derivative **8** using, as a key step, addition of the (*Z*)-borane **13**. Again this process, which is a variation of Brown's methodology,[7,10] efficiently controlled both relative (>95%)§ and absolute (>95%)¶ stereochemistry. Reagent **13**, which is readily available from (3,5-dioxaoct-7-en-1-yl)trimethylsilane *via* lithiation (Bu^sLi, THF, −78 °C) and metathesis[7] with (+)-*B*-methoxydiisopinocampheylborane, should prove of general utility for the assembly of *syn*-1,2-diol arrays. The alcohol **8** was converted using three routine operations into the methyl ketone **9** (89%). Aldol coupling of ketone **9** and aldehyde **6** and acidification gave the spiroketal **10** as a mixture of stereoisomers. It is remarkable that these mild acidification reaction conditions resulted in cleavage of the usually robust[8] SEM protecting group, desilylation, and spirocyclization. Although the two epimers of **10** could be easily separated and authenticated, the mixture, on a larger scale, was oxidized and stereoselectively reduced using K-Selectride[11] to give only the required axial isomer **11**.

A second synthesis of the spiroketal unit of calyculin A was also undertaken. This provided additional material for the total synthesis and unequivocally established the structures in Scheme 1. Commercial methyl (*R*)-(+)-3-hydroxy-2-methylpropanoate **14** was converted into the aldehyde **17** *via* protection,[8] Swern oxidation,[12] and a Wittig homologation–Sharpless epoxidation sequence[13] as key processes. Aldol reaction of ketone **9** and aldehyde **17** gave, on acidification, the spiroketal **18**. Again, this substance was formed as a mixture of epimers. Swern oxidation gave the corresponding keto-aldehyde and this was smoothly reduced to provide the diol **19**. This substance was fully authenticated by an X-ray crystallographic study. ‖ Additionally, spiroketals **11** and **19** were correlated by deprotection. Finally, selective protection[8] of diol **19** and ozonolysis[14] gave the C(15)–C(25) spiroketal unit **20**.

In conclusion, we have designed two concise methods for the elaboration of the spiroketal unit of calyculin A **1**. These reactions underscore the flexibility and power of diisopinocampheylborane derivatives in asymmetric synthesis. Further progress in the area is summarized in the accompanying communications.

† 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.

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

§ In each case the diastereoselectivity was estimated from the ^1H NMR spectrum.

¶ In each case, enantiomeric purities were estimated *via* the preparation of the corresponding Mosher ester and ^1H NMR spectroscopy, see J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

‖ Details of the crystal structure of the diol **19** will be published elsewhere: M. A. Miller and O. P. Anderson, unpublished observations.

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