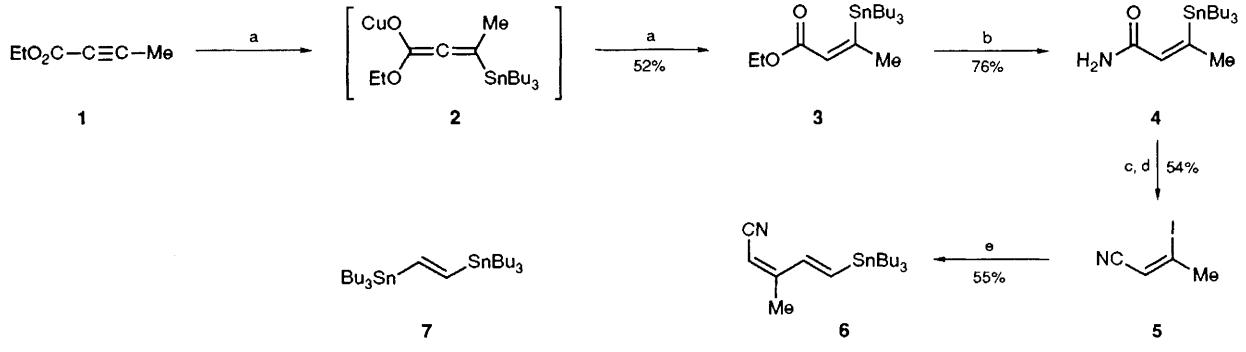
Stereocontrolled Synthesis of Calyculin A: Construction of the C(1)–C(14) Tetraene Nitrile Unit

Anthony G. M. Barrett,*[a] Jeremy J. Edmunds,[b] James A. Hendrix,[a] Kiyoshi Horita[a] and Christopher J. Parkinson[a]

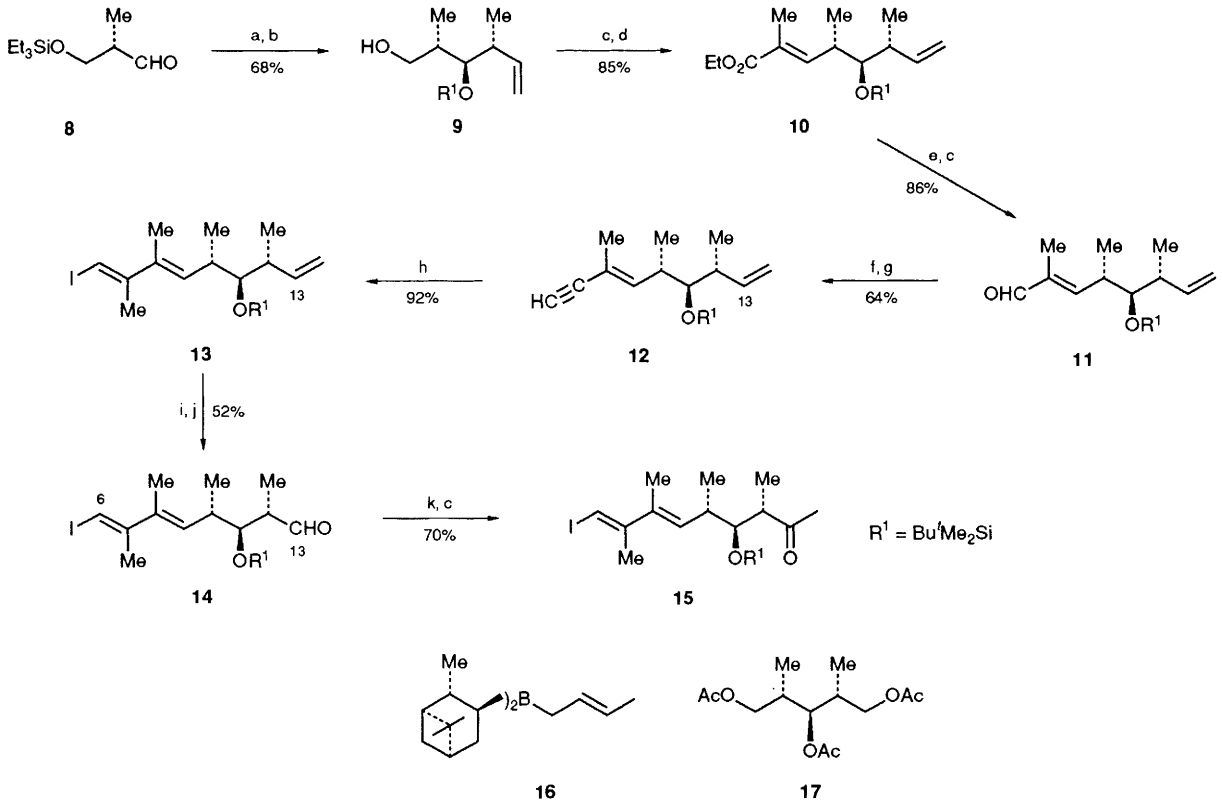
[a] *Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA*
[b] *Department of Chemistry, Northwestern University, Evanston, Illinois 60208, USA*

An enantioselective and geometrically selective synthesis of the C(1)–C(14) tetraene nitrile unit of calyculin A, using aldol chemistry with (+)-(*E*)-diisopinocampheylborane and Stille coupling, is described.

The calyculins are a group of potent yet selective phosphatase inhibitors elaborated by the sponge *Discodermia calyx*.[1] In the preceding communication, we outlined two syntheses of the C(15)–C(25) spiroketal residue of calyculin A.[2,3] We now report a concise, enantioselective method for the elaboration of the C(6)–C(14) ketone **15**, a geometrically selective method



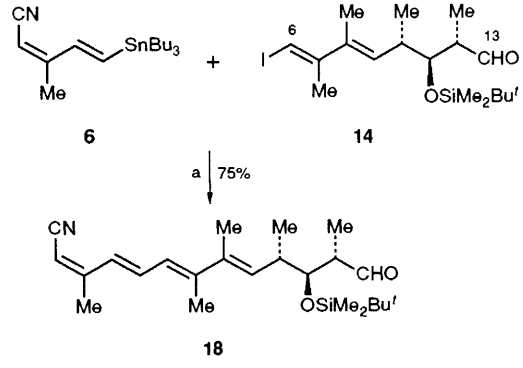
Scheme 1 *Reagents and conditions*: (a) $Bu_3SnSnBu_3$, BuLi, PhSCu, THF, −45 °C; MeOH, Et_2O; (b) $MeAl(Cl)NH_2$, PhH, 50 °C; (c) Cl_3CCOCl, Et_3N, CH_2Cl_2, 0 °C; (d) NIS, THF, Et_2O; (e) **7**, $PdCl_2(PPh_3)_2$, THF, 60 °C. THF = tetrahydrofuran; NIS = *N*-iodosuccinimide



Scheme 2 *Reagents and conditions*: (a) **16**, THF, −78 °C; $NaBO_3 \cdot 4H_2O$, H_2O; (b) THF, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, −78 °C; AcOH; (c) Swern oxidation; (d) $Ph_3P{=}C(Me)CO_2Et$, THF, 75 °C; (e) DIBAL-H, THF, 25 °C; (f) Ph_3P, CBr_4, CH_2Cl_2; (g) LDA, THF, −78 °C; (h) Me_3Al, Cp_2ZrCl_2, CH_2Cl_2; I_2, THF; (i) OsO_4 (catalyst), *N*-methylmorpholine *N*-oxide, Me_2CO, H_2O; (j) $NaIO_4$, THF, H_2O; (k) MeMgBr, THF, −78 °C. DIBAL-H = diisobutylaluminium iodide; LDA = lithium diisopropylamide; Cp = cyclopentadienyl.

for the construction of the diene **6**, and model studies on the formation of the tetraene nitrile unit.† We considered that the (*Z*,*E*)-cyanodiene **6** should be available using Stille chemistry[4] to construct the C-(3) to C-(4) bond. Such methodology should additionally be useful for the elaboration of the (*E*,*E*)-isomer of **6**, a building block appropriate for the elaboration of calyculins B, D, F and H. Conjugate addition of the cuprate[5] derived from tributylstannyllithium to ethyl but-2-ynoate **1** and quenching with methanol gave the (*Z*)-β-stannylcrotonate **3** (Scheme 1).‡§ The geometry of the product was unequivocally assigned as (*Z*) on account of the $^{117,119}Sn$-^1H *trans*-coupling constant in the ^1H NMR spectrum (*J* 97 Hz).[6] Presumably steric approach-controlled protonation of the copper allenoate **2**[7] resulted in the formation of the correct isomer. Ester **3** was smoothly transformed into the amide **4** using Weinreb methodology.[8] Destannylation was not a complication during this process on account of the Brønsted basicity yet Lewis acidity of the aluminium reagent. Dehydration and iododestannylation gave only the (*Z*)-iodide **5** and this was smoothly coupled with the distannane **7**[9] using Stille methodology.[4] Much to our delight this process proceeded with complete retention of geometry to provide the diene **6**.

The synthesis of the dienone **15** is summarized in Scheme 2. Brown homologation[10] of aldehyde **8**¶ using the reagent **16** derived from (−)-pinene gave the corresponding homoallylic alcohol and this was formed with excellent 2,3-*anti*- and 3,4-*anti*-stereocontrol (diastereoselectivity >96%). ‖ *tert*-Butyldimethylsilylation and selective de-triethylsilylation,[11] on work-up, gave the alcohol **9**. The high selectivity of the crotonylborane chemistry was verified by examination of both the ^1H and ^{13}C NMR spectra of **9**. Additionally, the triethylsilyl ether of **9** was converted into the triacetate **17** [(i) OsO_4, *N*-methylmorpholine *N*-oxide, Me_2CO, H_2O; (ii) $NaIO_4$, THF, H_2O;[12] (iii) $NaBH_4$, MeOH; (iv) *p*-$MeC_6H_4SO_3H$, MeOH; (v) Ac_2O, Et_3N, 4-*N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2; 36% overall from **8**]. Both the lack of optical rotation {$[\alpha]_D$ 0 ($CHCl_3$)} and the NMR spectra of this substance were in full agreement with the *meso*-stereochemistry **17**. Alcohol **9** was converted, *via* Swern oxidation[13] and Wittig homologation,[14] into the unsaturated ester **10**. No epimerization was observed in these transformations and **10**



Scheme 3 *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, THF, 60 °C

† 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.

§ The minor (*E*)-isomer (7%) was readily removed by chromatography on silica.

¶ Aldehyde **8** was readily available from commercial methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate [(i) Et_3SiCl, imidazole, DMF, DMAP (90%); (ii) DIBAL-H, hexanes, −70 °C (89%)].

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

was formed predominantly (>95%) as the required (*E*)-isomer. Ester **10** was converted, *via* aldehyde **11** and Corey homologation,[15] into the acetylene **12**. In this process lithium diisopropylamide was found to be superior to n-butyllithium in the elimination of the 1,1-dibromoalkene intermediate.

The second alkene unit, Δ^6, was introduced *via* a *syn*-methylzirconation strategy[16] and, in this reaction, only the required (*E*)-isomer was produced. It was found that this zirconation process depended strongly on the nature of the C-13 substituent. Whilst the conversion of dienyne **12** into triene **13** worked well, attempted methylzirconation of protected derivatives of the corresponding C-(13) primary alcohol, the C-(13), C-(14) diol and the C-(13) aldehyde were unsuccessful and gave intractable mixtures. Fortunately and remarkably, osmylation of triene **13** was selective for the isolated alkene (Δ^{13}). Subsequent periodate cleavage[12] gave the aldehyde **14** and this was readily transformed into the target calyculin A C(6)–C(14) methyl ketone **15**.

In our retrosynthetic analysis, we decided to delay construction of the C(5) to C(6) bond until late in the synthesis. However, in order to explore the methodology in a model study, we examined the coupling of stannane **6** and iodide **14**. Much to our delight, Stille coupling[4]** of **6** and **14** gave the tetraene nitrile **18** as a single geometric isomer.

In conclusion, we have designed a concise method for the elaboration of the tetraene nitrile unit of calyculin A. The strategy is flexible in that the timing of the elaboration of the C(5) to C(6) bond can readily be varied. These reactions further underscore the flexibility and power of diisopinocampheylborane derivatives in asymmetric synthesis. Further progress in the area is summarized in the accompanying communications.

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** Evans has also reported a palladium(0) method to elaborate the tetraene unit; ref. 2 in the preceding communication.

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