Total synthesis of calyculin A–Construction of the C(9)–C(37) fragment

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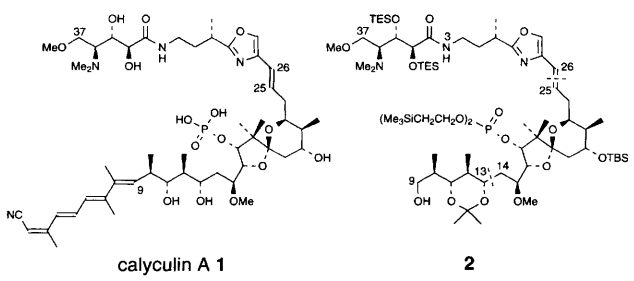
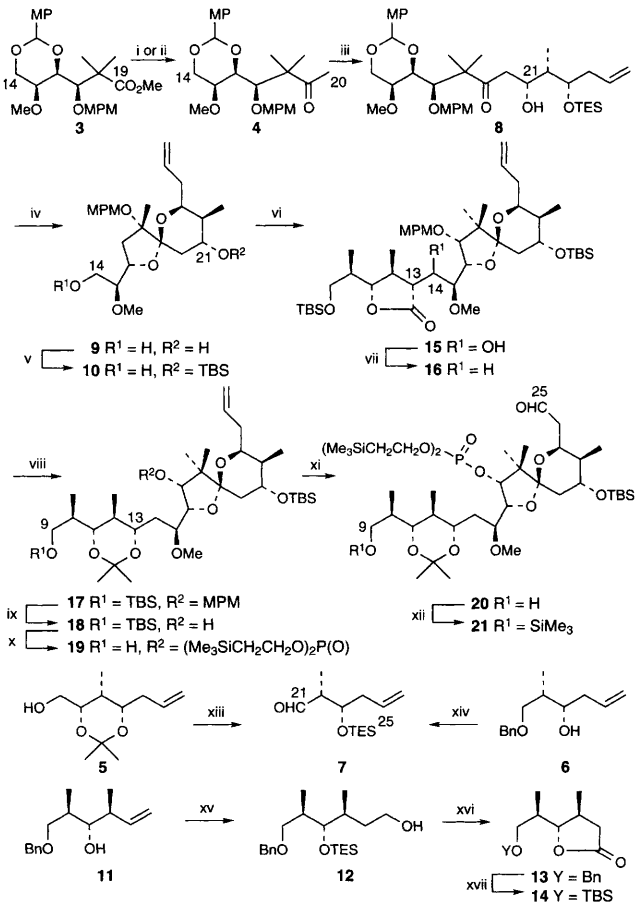
The potent protein phosphatase inhibitor calyculin A is formally synthesized *via* construction of the C(9)–C(37) fragment 2 by a Wittig reaction of the C(9)–C(25) spiroketal fragment with the C(26)–C(37) phosphonium salt.

Calyculin A **1** isolated from the marine sponge *Discodermia calyx*,[1] is an inhibitor of protein phosphatases 1 and 2A providing the opportunity to probe the cellular processes regulated by these enzymes.[2] The intriguing biological activity of calyculin A coupled with its structural curiosity has led several groups[3] including our own[4] to attempt the total synthesis of **1**. Two total syntheses have been recorded to date.[5] Here we describe an efficient synthesis of the C(9)–C(37) fragment **2** of calyculin A. The fragment **2** has already been transformed to calyculin A **1** by Masamune and coworkers.[5b] The key features of our synthetic strategy are the highly stereoselective aldol reaction for coupling the C(14)–C(20) methyl ketone **4** with the C(21)–C(25) aldehyde **7** and the construction of the C(12,13)-*anti* aldol by oxidative degradation of the γ-lactone moiety.

The previously prepared[4] methyl ester **3** was transformed into the C(14)–C(20) methyl ketone **4** {$[\alpha]_D^{23}$ + 4.25 (*c* 0.52, $CHCl_3$)} (Scheme 1). The C(21)–C(25) aldehyde **7** was easily prepared either from the primary alcohol **5**[6] or from the known[7] secondary alcohol **6**. With two requisite building blocks in hand, we investigated the aldol reaction between the C(14)–C(20) methyl ketone **4** and the C(21)–C(25) aldehyde **7**. Stereoselectivity was poor in the aldol reaction mediated with the lithium or sodium salt of **4**. Fortunately, the potassium enolate of **4**, prepared by treatment of **4** with KOBu^t in THF at −78 °C, underwent a highly diastereoselective reaction with **7**, providing a separable mixture of the desired (21*R*)-aldol **8** {$[\alpha]_D^{23}$ +22.7 (*c* 0.35, $CHCl_3$)} and its epimer in 55% yield (83% conversion) in a ratio of 18 : 1. The aldol adduct **8** was transformed to the spiroketal **9** {$[\alpha]_D^{23}$ −79.4 (*c* 0.38, $CHCl_3$)} in 63% yield by treatment with aqueous HF. The stereochemical assignment of the spiroketal **9** was unambiguously confirmed by a ^{1}H NOE experiment. Bis-silylation of the C(14) and C(21) hydroxy groups in **9** followed by selective removal of the C(14) *tert*-butyldimethylsilyl (TBS) group provided the primary alcohol **10** {$[\alpha]_D^{23}$ −104.6 (*c* 0.65, $CHCl_3$)} in 85% yield. For the elaboration of the C(9)–C(13) region of the skeleton, the lactone **14** was efficiently prepared from the secondary alcohol **11**.[7] Thus, silylation with triethylsilylchloride (TESCl) followed by hydroboration–oxidation afforded the alcohol **12**, which underwent successive oxidation and HF treatment to give the benzyl lactone **13**. The requisite C(9)–C(13) lactone **14** {$[\alpha]_D^{23}$ +19.8 (*c* 1, $CHCl_3$)} was obtained from **13** by replacement of the benzyl group with TBS.



calyculin A **1** **2**

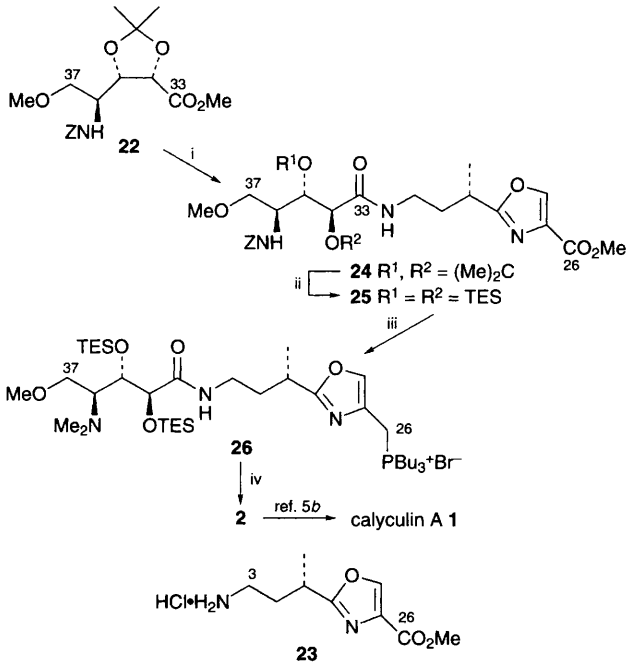


Scheme 1 *Reagents and conditions*: i, (*a*) DIBAL-H, CH_2Cl_2, −78 °C, 88%; (*b*) $PySO_3$, Et_3N, Me_2SO, CH_2Cl_2; (*c*) MeMgBr, THF (81% in two steps), (*d*) PDC, DMF, 94%; ii, Me_3SiCH_2Li, THF, then MeOH, 87%; iii, KOBu^t, THF, −78 °C, then **7** (55%, 83% conversion yield, 18 : 1); iv, 48% aq. HF–MeCN–CH_2Cl_2 (1 : 9 : 100), −10–0 °C, 2 h, 63%; v, (*a*) TBSOTf, Et_3N, CH_2Cl_2; (*b*) HF–py, py, THF (85% in two steps); vi, (*a*) TPAP, NMO, MS4A, CH_2Cl_2; (*b*) **14**, LDA, THF, −78 °C, (84% in two steps); vii (*a*) BuLi, PhOC(S)Cl, THF, 82%; (*b*) Bu_3SnH, AIBN, 100 °C (75%, **16**: **16**-C_{13}-epimer = 4 : 1); viii, (*a*) MeLi, THF, −78 °C; (*b*) 30% H_2O_2, AcOH, THF; (*c*) NsCl, Et_3N, THF; (*b*) DIBAL-H, CH_2Cl_2, −78 °C; (*e*) $Me_2C(OMe)_2$, pyridinium toluene-*p*-sulfonate CH_2Cl_2 (56% in five steps); ix, DDQ, CH_2Cl_2–H_2O (18 : 1), 94%; x, (*a*) PCl_3, py, $Me_3SiCH_2CH_2OH$ then 30% H_2O_2; (*b*) HF–py, py, THF (71% in two steps); xi, O_3, CH_2Cl_2, −78 °C, then Ph_3P (97%); xii, Me_3SiCl, Et_3N, CH_2Cl_2, 0 °C; xiii, (*a*) *p*-TsOH, MeOH, 60%; (*b*) $NaIO_4$, aq. THF; (*c*) TESCl, Et_3N, DMAP, CH_2Cl_2, 51%; xiv, (*a*) TESCl, Et_3N, DMAP, CH_2Cl_2, 71%; (*b*) Na, liq. NH_3, EtOH, 89%; (*c*) $Py{\cdot}SO_3$, Et_3N, Me_2SO, CH_2Cl_2, 78%; xv, (*a*) TESCl, Et_3N, DMAP, CH_2Cl_2; (*b*) 9-BBN, THF; (*c*) H_2O_2, aq. NaOH, 88%; xvi, (*a*) TPAP, NMO, MS 4 Å, CH_2Cl_2; (*b*) $NaClO_2$. NaH_2PO_4, 2-methylbut-2-ene, aq. Bu^{t}OH; (*c*) aq. HF, MeCN, 71%; xvii (*a*) HCO_2NH_4, 5% Pd–C, MeOH; (*b*) TBSCl, imidazole, DMF; 86%

The Pr_4NRuO_4 (TPAP) oxidation[8] of the alcohol **10** gave the aldehyde which was then coupled with the lithium enolate of the C(9)–C(13) lactone **14** to give a diastereoisomeric mixture of the coupled product **15** in 84% yield. Barton's deoxygenation[9] of the C(14) secondary hydroxy function of **15** furnished a readily separable mixture of the desired lactone **16** {$[\alpha]_D^{24}$ −83.6 (*c* 1, $CHCl_3$)} and its C(13)-epimer in 62% yield, ratio 4 : 1. The undesired C(13)-epimer was epimerized with MeLi in THF at −78 °C to give the desired lactone **16** in 63% yield.

We then applied the Ziegler–Brückner conditions[10] to the γ-lactone → 1,3-diol degradation to the lactone **16**. The acetonide **17** {$[\alpha]_D^{24}$ −89.9 (*c* 1, $CHCl_3$)} was obtained in 56% overall yield from **16** by five steps: (i) addition of MeLi; (ii) OH → OOH transformation with H_2O_2; (iii) sulfonylation with nosyl chloride (NsCl) followed by Criegee rearrangement; (iv) reductive cleavage of the acetate group and (v) protection of the diol. The relative stereochemistry of the C(11)–C(13) 1,3-diol moiety in the acetonide **17** was ascertained by analysis of its ^{13}C NMR spectrum (δ 19.4 and 30.3 corresponding to the acetonide methyl carbon).[11] After oxidative removal of the C(17) *p*-methoxybenzyl (MPM) group[12] from **17** in 94% yield, the liberated C(17) alcohol **18** was converted to its bis(2-trimethylsilylethyl)phosphate triester,[5a,b] followed by removal of the C(9) TBS group to give the alcohol **19** {$[\alpha]_D^{24}$ −77.8 (*c* 1.2, $CHCl_3$)} in 71% yield. Ozonolysis of the terminal alkene of **19** afforded the aldehyde **20** in 97% yield, whose C(9) hydroxy group was protected as the Me_3Si function to yield the C(9)–C(25) spiroketal fragment **21**, setting the stage for the Wittig-based C(25)–C(26) alkenation.

Construction of the C(26)–C(37) fragment **26** was initiated with the coupling of the previously prepared C(33)–C(37) γ-amino acid fragment **22**[13] with the C(26)–N(3) oxazole fragment **23**[14] by the diethyl phosphorocyanidate (DEPC) method,[15] giving the amide **24** {$[\alpha]_D^{24}$ −8.48 (*c* 1, $CHCl_3$)} in 90% yield, Scheme 2. After replacement of the acetonide group of **24** with Et_3Si (TES), transformation of this TES derivative **25** {$[\alpha]_D^{24}$ +5.74 (*c* 1, $CHCl_3$)} into the C(26)–C(37) tributylphosphonium salt **26** was accomplished by sequential reductive methylation, reduction with lithium aluminum hydride, bromination and phosphonium salt formation.[5a] Finally, addition of the aldehyde **21** to a cooled (0 °C) solution of the phosphonium salt **26** followed by the addition of LDA, and then deprotection of the C(9) Me_3Si group gave the C(9)–C(37) fragment **2** {$[\alpha]_D^{24}$ −46.1 (*c* 0.9, $CHCl_3$)},† which has already been converted to calyculin A **1** in 4 steps.[5b]



Scheme 2 *Reagents and conditions*: i, (*a*) aq. LiOH, THF, 0 °C; (*b*) **23**, DEPC, Et_3N, DMF (90% in two steps); ii, (*a*) camphorsulfonic acid, MeOH; (*b*) TESOTf, 2,6-latidine, CH_2Cl_2, 0 °C (83% in two steps); iii, (*a*) H_2, 5% Pd-C, aq. HCHO, AcOH, MeOH, 91%; (*b*) $LiAlH_4$, Et_2O, −78 °C, 67%; (*c*) CBr_4, Ph_3P, 2,6-lutidine, MeCN, 75%; (*d*) Bu_3P, DMF, room temp. 30 min; iv, (*a*) **21**, DMF, 0 °C, then LDA, THF, 0 °C; (*b*) K_2CO_3, MeOH, 0 °C (52% from **20**)

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Footnote

† Although direct comparison could not be made, spectroscopic data of C(9)–C(37) fragment **2** was in agreement with the reported data.[5b] High mass (FAB *m*-nitrobenzyl alcohol) calcd for $C_{70}H_{141}N_3O_{16}PSi_5$ (MH^+) 1450.8895, found 1450.8840.

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