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

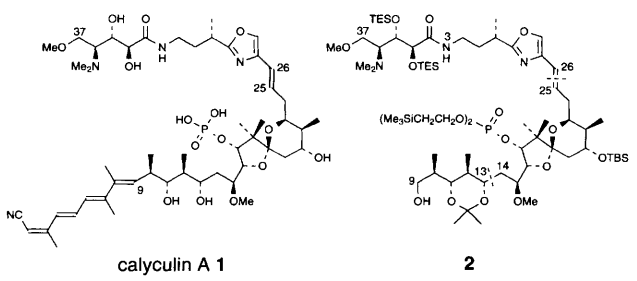
Fumiaki Yokokawa,[a] Yasumasa Hamada[b] and Takayuki Shioiri*[a]

[a] *Faculty of Pharmaceutical Sciences, Nagoya City University Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan*
[b] *Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba, 263, Japan*

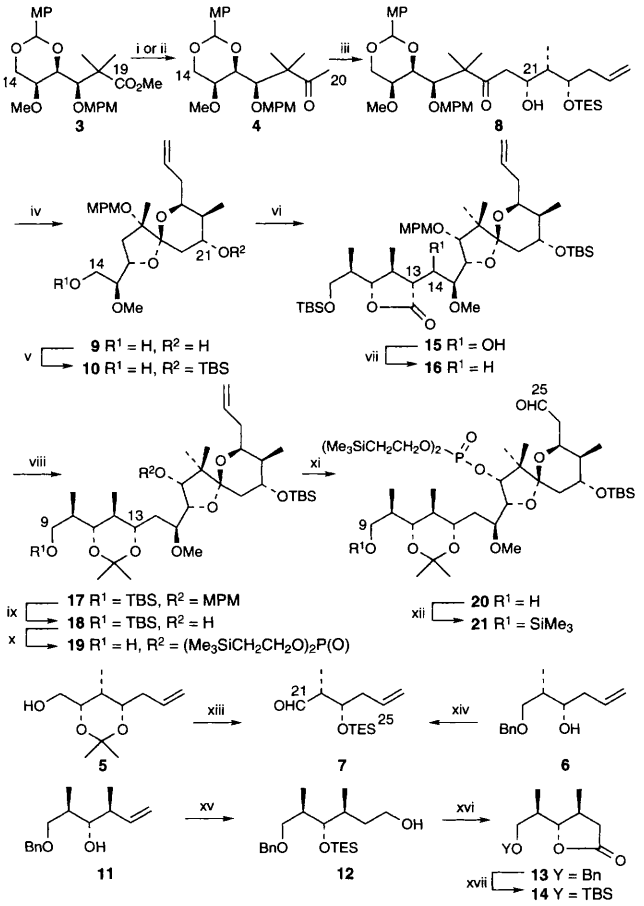
The potent protein phosphatase inhibitor calyculin A is formally synthesized *via* construction of the C(9)–C(37) fragment 2 by a Wittig reaction of the C(9)–C(25) spiroketal fragment with the C(26)–C(37) phosphonium salt.

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**

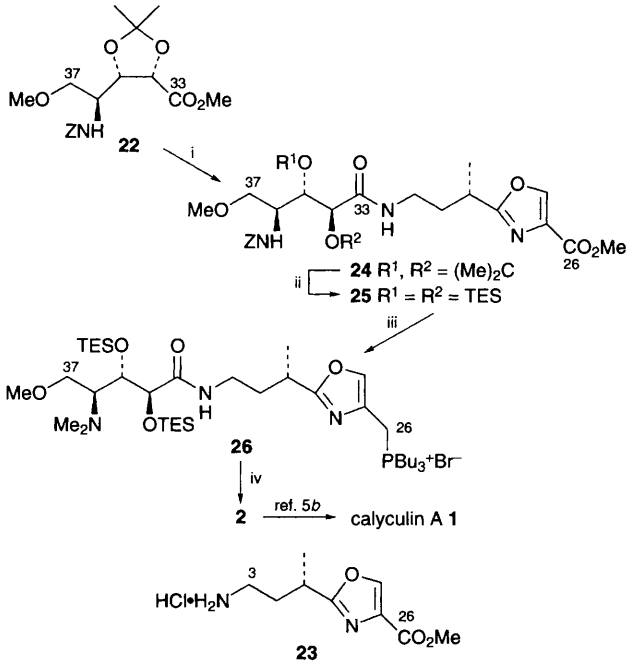


Scheme 1 *Reagents and conditions*: i, (*a*) DIBAL-H, CH_2Cl_2, −78 °C, 88%; (*b*) $PySO_3$, Et_3N, Me_2SO, CH_2Cl_2; (*c*) MeMgBr, THF (81% in two steps), (*d*) PDC, DMF, 94%; ii, Me_3SiCH_2Li, THF, then MeOH, 87%; iii, KOBu^t, THF, −78 °C, then **7** (55%, 83% conversion yield, 18 : 1); iv, 48% aq. 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·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**)

Partial support of this research by Grant-in-Aids from the Ministry of Education, Science, Sports and Culture, Japan is gratefully acknowledged. F. Y. gratefully acknowledges the postgraduate fellowship from the Japan Society for the Promotion of Science and the Sasakawa Scientific Research Grant from the Japan Science Society.

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.

References

1 Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto, S. Fujita and T. Furaya, *J. Am. Chem. Soc.*, 1986, **108**, 2780.

2 H. Ishihara, B. L. Martin, D. L. Brautigan, H. Karaki, H. Ozaki, Y. Kato, N. Fusetani, S. Watabe, K. Hashimoto, D. Uemura and D. J. Hartshorne, *Biochem. Biophys. Res. Commun.*, 1989, **159**, 871; M. Suganuma, H. Fujiki, H. Furuya-Suguri, S. Yoshizawa, S. Yasumoto, Y. Kato, N. Fusetani and T. Sugimura, *Cancer Res.*, 1990, **50**, 3521.

3 A. B. Smith III and M. Iwashima, *Tetrahedron Lett.*, 1994, **35**, 6051 and references cited therein.

4 K. Takebuchi, Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, 1994, **35**, 5239, and references cited therein.

5 (*a*) D. A. Evans, J. R. Gase and J. L. Leighton, *J. Am. Chem. Soc.*, 1992, **114**, 9434; (*b*) N. Tanimoto, S. W. Gerritz, A. Sawabe, T. Noda, S. A. Filla and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 673.

6 Y. Hamada, F. Yokokawa, M. Kabeya and T. Shioiri, *Tetrahedron*, submitted.

7 H. C. Brown, K. S. Bhat and R. S. Randad, *J. Org. Chem.*, 1989, **54**, 1570.

8 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639.

9 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans 1*, 1975, 1574; D. H. R. Barton and R. Subramanian, *J. Chem. Soc., Perkin Trans 1*, 1977, 1718; M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, 1981, **103**, 932.

10 F. E. Ziegler, A. Kneisley, J. K. Thottathil and R. T. Wester, *J. Am. Chem. Soc.*, 1988, **110**, 5434, and references cited therein; M. Menges and R. Bruckner, *Synlett*, 1993, 901.

11 S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945; D. A. Evans, D. L. Rieger and J. R. Gage, *Tetrahedron Lett.*, 1990, **31**, 7099; S. D. Rychnovsky, B. Rogers and G. Yang, *J. Org. Chem.*, 1993, **58**, 3511.

12 Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885.

13 F. Yokokawa, Y. Hamada and T. Shioiri, *Synlett*, 1992, 703.

14 F. Yokokawa, Y. Hamada and T. Shioiri, *Synlett*, 1992, 149.

15 S. Takuma, Y. Hamada and T. Shioiri, *Chem. Pharm. Bull*, 1982, **30**, 3147, and references cited therein.

Received, 11th December 1995; Com. 5/08060F