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CALYCULIN SYNTHETIC STUDIES. STEREOSELECTIVE CONSTRUCTION OF THE C(14)-C(25) SPIROKETAL SUBUNIT

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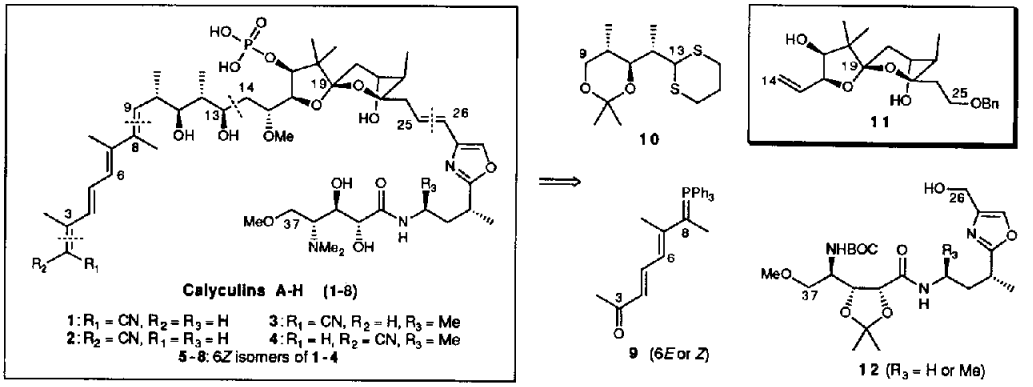
Summary: A convergent, stereocontrolled synthesis of the spiroketal fragment of calyculins A-H has been achieved. Key transformations include the novel iodine monobromide-induced iodocarbonate cyclization of (+)-**19**, efficient coupling of epoxide (+)-**14** with the sterically hindered dithiane **15**, and a multi-step, one-pot conversion of open-chain precursor (-)-**13** to spiroketal (+)-**11**.

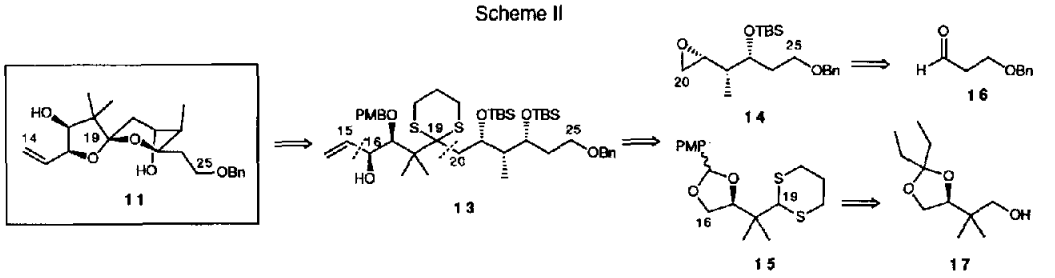
The calyculins (A-H, **1-8**), isolated from the Japanese sponge *Discodermia calyx*,[1] embody a striking array of stereochemical and functional elements. All eight congeners strongly inhibit protein phosphatases,[1c,2a] and **1** efficiently stimulates the contraction of smooth muscle fibers.[2b] The latter finding suggests that the calyculins may facilitate the investigation of cellular processes controlled by reversible phosphorylation of proteins.[2c] Calyculins A-D also display significant cytotoxicity against L1210 leukemia cells and suppress Ehrlich and P388 leukemia in mice.[1a,b] In addition, **1** acts as a potent tumor promoter in mouse-skin carcinogenesis.[2d] The structures of calyculins B-H were deduced by spectroscopic comparison with **1**, whose formulation was secured via single-crystal X-ray analysis;[1] the absolute configurations, however, remain unknown. Intrigued by their novel architecture and diverse biological activity, we recently initiated work directed toward the total synthesis of these unique marine metabolites. Retrosynthetic dissection of the calyculins generated four major building blocks: polyene ylide **9**, dithiane **10**, spiroketal **11**, and oxazole **12** (Scheme I). Herein we disclose an efficient construction of the central spiroketal subunit **11**.[3,4] Syntheses of fragments **10** and **12** are described in the accompanying letter.[5]

Scheme I



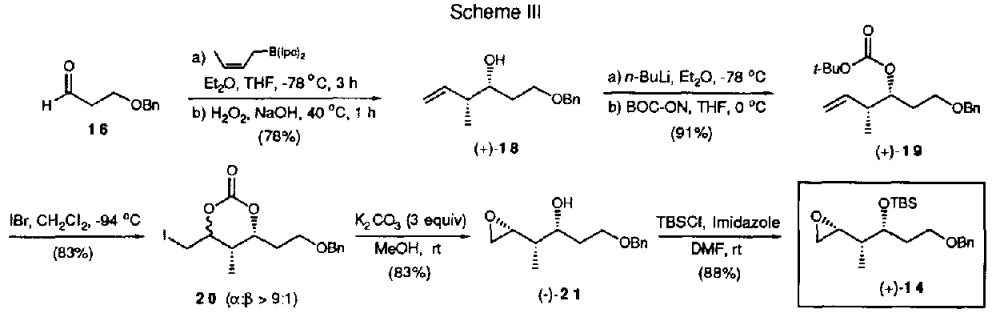
The highly functionalized spiroketal **11** incorporates six of the 15 stereocenters common to the calyculins. MM2 calculations revealed a substantial (6 kcal/mol) thermodynamic preference for the requisite C(19) configuration.[6] Further analysis of **11** led to the open-chain precursor **13** (Scheme II), which in turn was envisioned to arise via coupling of epoxide **14** with the sterically hindered dithiane **15**. The latter would derive from alcohol **17**, whereas epoxide **14** could be elaborated via Brown asymmetric addition of *(Z)*-crotyldiisopinocampheylborane[7] to aldehyde **16** followed by a Bartlett iodocarbonate cyclization.[8] Construction of the calyculins in homochiral form would establish the absolute stereochemistry of the natural products.

Scheme II



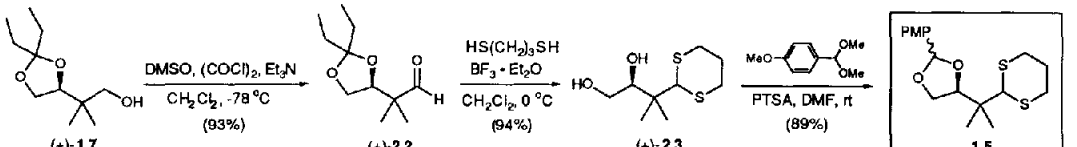
The synthesis of the calyculin spiroketal thus began with 3-benzyloxypropanal (**16**)[9] (Scheme III). Addition of *(Z)*-crotyldiisopinocampheylborane (generated *in situ* by successive treatment of *cis*-2-butene with *t*-BuOK, *n*-BuLi, (-)-*B*-methoxydiisopinocampheylborane, and BF_3•Et_2O)[7] and oxidation (H_2O_2, NaOH, 40 °C, 1 h) furnished alcohol **18** (90% ee),[10a,11] which in turn gave *tert*-butyl carbonate **19**[10] upon treatment with *n*-BuLi and BOC-ON [2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile].[8a] This maneuver set the stage for the requisite 1,3-asymmetric induction. Standard iodocarbonate cyclization of **19** (I_2, CH_3CN, -20 °C)[8] provided **20**[10a] in 79% yield, with modest stereoselectivity (α:β = 6:1). In an effort to improve the latter ratio we explored alternative sources of electrophilic iodine. To our delight, exposure of **19** to iodine monobromide (1.5 equiv) in CH_2Cl_2 at -94 °C for 15 min afforded iodocarbonate **20** in 83% yield with diastereoselectivity > 9:1 (α:β). A systematic investigation of this promising new cyclization protocol is now underway. Following separation of the epimers by flash chromatography, methanolysis of the predominate α diastereomer (K_2CO_3 in dry methanol)[8a] generated epoxy alcohol **21**.[10] Protection with TBSCl then furnished epoxide **14**.[10a]

Scheme III



As our point of departure for the preparation of dithiane **15** (Scheme IV), we selected alcohol (+)-**17**, readily available from *(S)*-dimethyl malate.[12] Following Swern oxidation of **17**, the resultant aldehyde **22**[10a] was treated with 1,3-propanedithiol and BF_3•Et_2O (2.5 equiv each) in methylene chloride at 0 °C for 30 min.[13] The latter tactic installed the dithiane moiety and also removed the pentylidene acetal, as desired. Diol **23**[10a] was then readily converted to *p*-methoxybenzylidene **15**[10] as a 3:2 mixture of epimers.

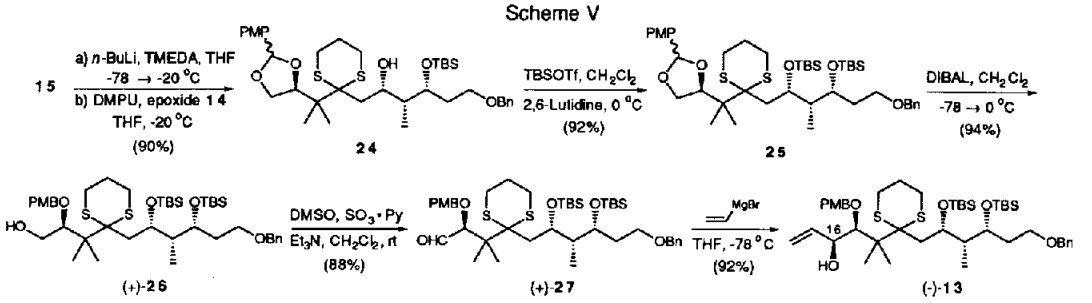
Scheme IV



Dithiane **15** (1.5 equiv) was successfully deprotonated with *n*-BuLi (1.5 equiv) and TMEDA (6 equiv) in THF

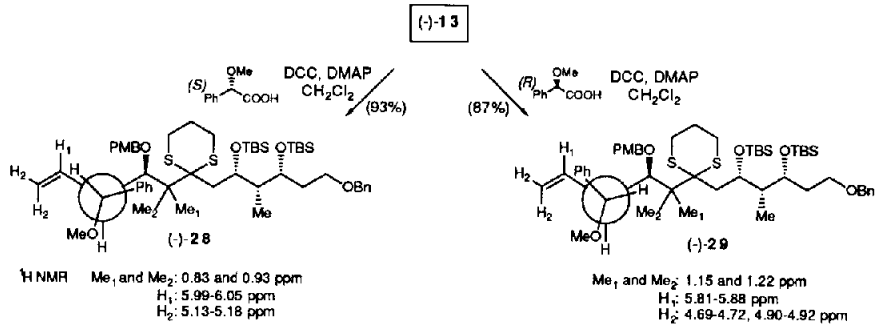
(Scheme V). Coupling with epoxide **14** (1 equiv) afforded hydroxy dithiane **24**[10] in good yield (ca. 75%); addition of DMPU (6 equiv) prior to the introduction of **14** further enhanced the efficiency of this process (90% yield).[14] Protection of **24** followed by hydride reduction (DIBAL-H, -78 °C)[15] of acetal **25**[10a] furnished primary alcohol **26**[10a] exclusively (NMR analysis). Oxidation (DMSO, SO_3•Py, Et_3N) provided aldehyde **27**,[10a] whereupon chelation-controlled addition of vinylmagnesium bromide in turn generated alcohol **13**[10a] (92%, >20:1 diastereoselectivity).[16] To facilitate characterization,

Scheme V



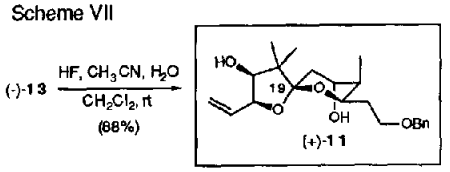
the major diastereomer was esterified with both *(R)* and *(S)*-*O*-methylmandelic acids (Scheme VI).[17] In the 500-MHz ^{1}H NMR spectra, Me_1 and Me_2 of ester **28**[10a] resonated further upfield than the corresponding methyls of **29**;[10a] in contrast, the vinylic protons H_1 and H_2 were shifted further upfield in **29** than in **28**. This analysis[17] confirmed the *S* configuration anticipated for the newly generated stereocenter at C(16).

Scheme VI

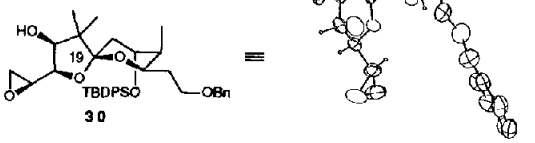


At this juncture, completion of the synthesis entailed deprotection and spirocyclization. We initially explored a three-step process, involving desilylation (TBAF), cyclization ($HgCl_2$), and removal of the *p*-methoxybenzyl ether. However, the overall yield for the first two steps proved to be only 49%; we thus sought to develop a more efficient protocol. Remarkably, exposure of dithiane **13** to a mixture of 48% aq HF, CH_3CN, and CH_2Cl_2 (1:9:50) effected all transformations in a single operation (Scheme VII): cleavage of the *p*-methoxybenzyl ether, removal of the silyl protecting groups, dithiane hydrolysis, and acid-catalyzed biscyclization led to spiroketal **11**[10a] in 88% yield as the only product. The *S* configuration of the C(19) spiroketal stereocenter, initially assigned via ^{1}H decoupling and ^{1}H NOE studies, was later confirmed by single-crystal X-ray analysis of the derived epoxide **30** (Scheme VIII). The exclusive formation of a single C(19) epimer has to date precluded the demonstration of kinetic or thermodynamic control in the spiroketalization reaction. Interestingly, Evans et al. obtained a 5:1 diastereomer mixture in the cyclization of a closely related substrate.[4b]

Scheme VII



Scheme VIII[18]



In summary, we have completed a convergent, stereoselective construction of the C(14)-C(25) subunit of the calyculins. Iodine monobromide was employed for the first time in a highly effective iodocarbonate cyclization. A systematic study of IBr-induced cyclizations will be reported in due course. Further progress toward the total synthesis of the calyculins is recorded in the accompanying letter.

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References

1. (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780. (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930. (c) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999.
2. (a) Ishihara, H.; Martin, B. L.; Brautigan, D. L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, K.; Uemura, D.; Hartshorne, D. J. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 871. (b) Hartshorne, D. J.; Ishihara, H.; Karaki, H.; Ozaki, H.; Sato, K.; Hori, M.; Watabe, S. *Adv. Prot. Phosphatases;* Merlevede, W.; Di Salvo, J., Eds.; Leuven University Press; Louvain, Belgium, 1989; Vol. 5, pp 219-231. (c) Cohen, P.; Holmes, C. F. B.; Tsukitani, Y. *Trends Biochem. Sci.* **1990**, *15*, 98. (d) Fujiki, H., Suganuma, M.; Yoshizawa, S.; Kanazawa, H.; Sugimura, T.; Manam, S.; Kahn, S. M.; Jiang, W.; Hoshina, S.; Weinstein, I. B. *Molecular Carcinogenesis* **1989**, *2*, 184.
3. For a review of the synthesis and chemistry of natural-product-derived spiroketals, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.
4. For other calyculin synthetic studies, see: (a) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357. (b) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129. (c) Scarlato, G. R.; Armstrong, R. W.; Zhao, Z.; Margolis, F. *Abstracts of papers*; 200th ACS National Meeting, Washington, D. C., 1990; ORGN 134. (d) Nakao, K.; Tanada, Y.; Nishio, A.; Matsubara, J.; Yokokawa, F.; Hamada, Y.; Shioiri, T. *Abstracts of papers*; 32nd Symposium on the Chemistry of Natural Products, Chiba, 1990; pp 617-623. (e) Hara, O.; Hamada, Y.; Shioiri, T. *Synlett* **1991**, 283, 285. (f) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609.
5. Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.*, accompanying Letter in this issue.
6. We also verified that the MM2 force field correctly evaluates the relative stabilities of known pairs of epimeric spiroketals. Full details will be provided in a subsequent report.
7. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
8. (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.
9. Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301.
10. (a) The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. (b) In addition, an analytical sample of this new compound gave satisfactory C and H combustion analysis.
11. The enantiomeric purity of alcohol **18** was determined by comparison of its optical rotation {$[\alpha]_D^{24}$ +12.1° (*c* 1.10, $CHCl_3$)} with a literature value for the (-)-antipode {$[\alpha]_D^{24}$ -13.2° (*c* 0.972, $CHCl_3$)} of known enantiomeric purity (98.5% ee). (a) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Kusakabe, M.; Sato, F. *Heterocycles* **1987**, *25*, 549. (b) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528.
12. (a) Lavallee, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679. (b) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth., Coll. Vol. VII*, **1990**,153.
13. Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998.
14. Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.
15. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.
16. For a comprehensive review of chelation-controlled addition to α-alkoxy aldehydes, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
17. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
18. The TBDPS group in the ORTEP was removed for clarity.

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