Tetrahedron Letters, Vol. 33, No. 15, pp. 1937-1940, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

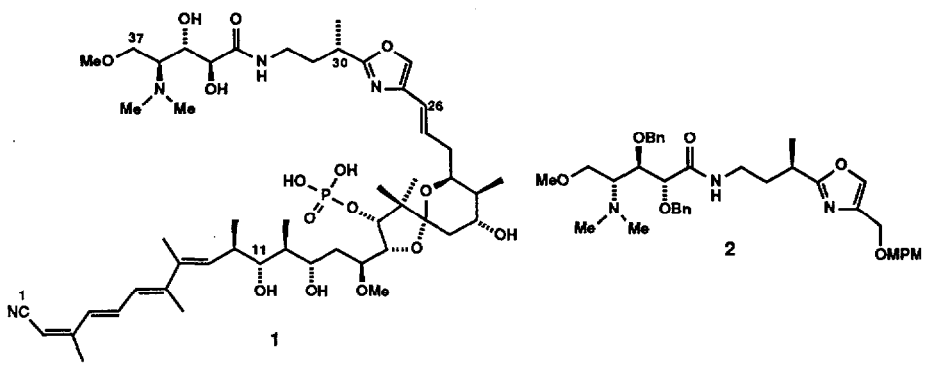
Towards the Synthesis of Calyculin: A Synthetic Intermediate Corresponding to the C(26)-C(37) Fragment

Henry A. Vaccaro, Daniel E. Levy, Akiyoshi Sawabe, Thomas Jaetsch, and Satoru Masamune*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139

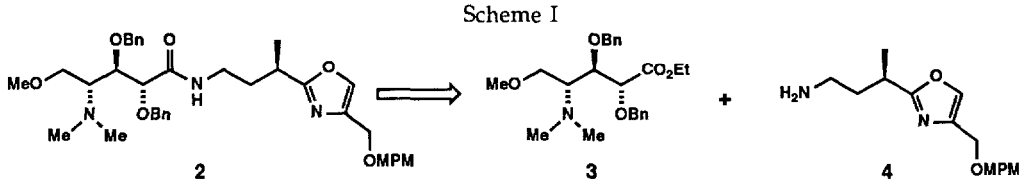
Abstract: The synthetic intermediate 2 corresponding to the C(26)-C(37) fragment of calyculin A (1) has been synthesized. Key transformations include the efficient one-pot construction of the oxazole system embedded in 1 without epimerization α [C(30)] to the ring, and the in situ formation of the dimethylamine by opening an N-methyllactam with Meerwein's reagent and trapping the resultant methylamine with formaldehyde.

The potent phosphatase inhibitor calyculin A (**1**), isolated from the marine sponge *Discodermia calyx*,[1] has aroused considerable synthetic interest[2] due mainly to its functionally and stereochemically unique structure as demonstrated by X-ray crystallography. Recent reports[3] concerning its absolute stereochemistry prompt us to disclose our synthesis of **2**, which corresponds to the C(26)-C(37) fragment of **1**. As is the case with other reported approaches[2] to this natural product, the stereochemistry of our target has been shown to be enantiomeric with that of **1**.



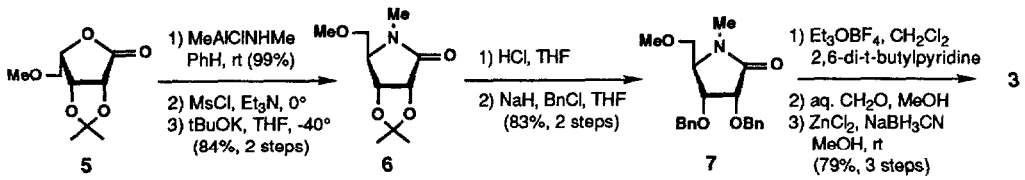
Straightforward retrosynthetic disconnection of **2** at the amide linkage leads to ester **3** and amino oxazole **4** as outlined in Scheme I.

Scheme I



As our starting material for the preparation of ester **3** (Scheme II), we selected lactone **5**, readily available from gulonolactone.[4] Addition of the Weinreb reagent[5] of methylamine to **5** and treatment of the mesylate derived from the crude hydroxyamide with potassium tert-butoxide provided lactam **6**,[6] with inversion of stereochemistry at the γ position. Cleavage of the acetonide and subsequent benzylation then provided lactam **7**. Since all attempts to couple analogues of **7** with an amine resulted in recovery of starting material, we prepared the imidate of lactam **7**[7] which on hydrolysis and capture of the free amine with aqueous formaldehyde furnished the corresponding imine. This imine was then reduced *in situ* to provide dimethylamino ester **3** in 79% yield.[8]

Scheme II

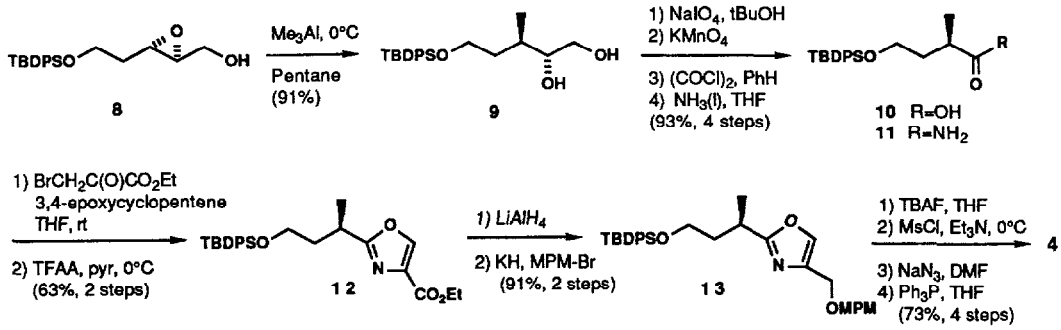


Having completed the synthesis of **3**, we turned our attention to the synthesis of the oxazole.[9] Classical methods for the synthesis of 2,4-disubstituted oxazoles from an amide and an α-haloketone[10] appeared to cause epimerization when applied to amides bearing an α-stereocenter[11] as in the present case. After extensive experimentation, we found that epimerization could be completely suppressed by conducting the reaction at room temperature, using a large excess of 3,4-epoxycyclopentene as an acid scavenger, as shown below.

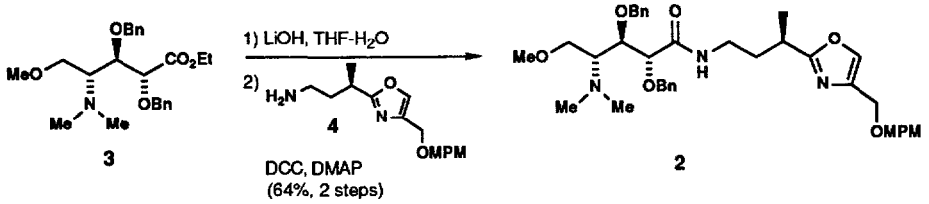
For preparation of amide **11**, we utilized epoxide **8**, readily obtained from Sharpless asymmetric epoxidation[12] of the corresponding allylic alcohol (Scheme III). Introduction of the methyl group by regioselective (>40:1) opening of **8** with trimethylaluminum[13] furnished 1,2-diol **9**. Treatment of **9** with sodium periodate and *in situ* oxidation of the resultant aldehyde with potassium permanganate[14] provided acid **10**, with an enantiomeric purity of 40:1.[15] Amide **11** was then prepared via the corresponding acid chloride.[16] Treatment of **11** with ethyl bromopyruvate and 3,4-epoxycyclopentene in THF furnished the corresponding 4-hydroxyoxazoline, which upon dehydration resulted in oxazole **12** (63% yield). The fact that no epimerization was caused during these processes was confirmed by the Mosher method after desilation of **12**. Reduction of the ester of **12** and protection of the resulting alcohol as its p-methoxybenzyl ether yielded **13**. Removal of the silyl ether, formation of the mesylate, displacement with sodium azide and subsequent reduction with triphenylphosphine provided amino-oxazole **4** in excellent overall yield.

With both **3** and **4** in hand, we turned to the last transformation, coupling of the fragments (Scheme IV). Hydrolysis of ester **3** with lithium hydroxide provided the corresponding acid, which was coupled with amine **4** using a standard procedure.[17,18]

Scheme III



Scheme IV



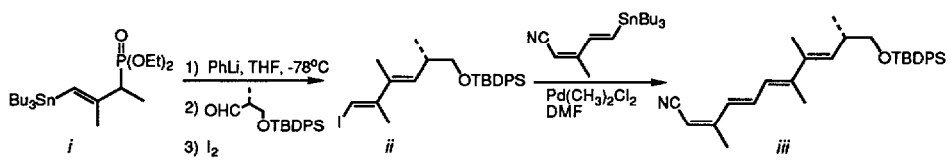
Acknowledgements. We thank Mr. Samuel Gerritz for stimulating discussions. Support for this work was provided by the National Institutes of Health, U.S.A. (CA48175-04) and Kao Corporation, Japan. H.A.V., D.E.L., and T.J. are holders of an American Cancer Society Postdoctoral Fellowship, an NCI T32-CA09112 Traineeship, and a Deutsche Forschungsgemeinschaft Postdoctoral Fellowship, respectively.

References

(1) Isolation: Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780.
Other calyculins: (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930. (b) Matsunga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999.
Biological activity: (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *Drugs Exptl. Clin. Res.* **1988**, *14*, 723. (b) Ishihara, H.; Ozaki, H.; Sato, K.; Hori, M.; Karaki, H.; Watabe, S.; Kato, Y.; Fusetani, N.; Hashimoto, K.; Uemura, D.; Hartshorne, D. J. *J. Pharmacol. Exp. Ther.* **1989**, *250*, 388. (c) 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. (d) Yabu, H.; Yoshino, M.; Usuki, T.; Someya, T.; Obara, K.; Ozaki, H.; Karaki, H. *Prog. Clin, Biol. Res.* (Frontiers in Smooth Muscle Research) **1990**, *327*, 623. (e) Suganuma, M.; Fujiki, H.; Furuya-Suguri, H.; Yoshizawa, S.; Yasumoto, S.; Kato, Y.; Fusetani, N.; Sugimura, T. *Cancer Res.* **1990**, *50*, 3521.

(2) (a) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609. (b) Evans, D. A.; Gage, J. R. *Ibid.* **1990**, *31*, 6129. (c) Hara, O.; Hamada, Y.; Shioiri, T. *Synlett.* **1991**, 283. Hara, O.; Hamada, Y.; Shioiri, T. *Ibid.* **1991**, 285. (d) Hara, O.; 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) Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855. Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Ibid.* **1991**, *32*, 4859. (f) Armstrong, R.W.; DeMattei, J.A. *Ibid.* **1991**, *32*, 5749.

(3) (a) Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1991**, *32*, 5605. (b) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shiori, T. *Ibid.* **1991**, *32*, 5983.
(4) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 1720. Hulyalkar, R. K.; Jones, J. K. N. *Ibid.* **1963**, *41*, 1898.
(5) Levin, J.I.; Turos, E.; Weinreb, S.M. *Synth. Commun.* **1982**, *12*, 989.
(6) Challis, B. C.; Challis, J. A. *The Chemistry of Amides*, Wiley: London, 1970; pp 731-754; and references cited therein.
(7) Meerwein, H. *Org. Synth. Coll. Vol. V*, 1080.
(8) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927.
(9) For an excellent review on the synthesis and reactions of oxazoles, see: (a) Turchi, I. J., Ed. *Oxazoles*, Wiley, New York, 1986. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (c) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99.
(10) Theilig, G. *Chem. Ber.* **1953**, *86*, 96. Kondrat'eva, G. Y.; Chzhi-Khén, K. *J. Gen. Chem. USSR* **1962**, *32*, 2315.
(11) For comparison, see: (a) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235. (b) Yonetani, K.; Hirotsu, Y.; Shiba, T. *J. Chem. Soc. Japan* **1975**, *48*, 3302.
(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(13) (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597. (b) Roush, W.R.; Adam, M.A.; Peseckis, S.M. *Ibid.* **1983**, *24*, 1377.
(14) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.
(15) We have observed that in the absence of pH 5 buffer, significant epimerization of the methyl center occurred.
(16) The enantiomeric purity of amide **11** was determined to be >20:1 by HPLC analysis (CHIRACEL OD column).
(17) It should be added that Sandra A. Filla and Emma R. Parmee of these laboratories have established a method for the synthesis of the C(1)-C(11) portion of calyculin A, as illustrated below.



(18) ^{1}H NMR of **2** (300 MHz, $CDCl_3$): δ 1.28 (d, *J*=7.0 Hz, 3H), 1.77 (m, 1H), 1.92 (m, 1H), 2.20 (s, 6H), 2.95 (m, 1H), 3.04 (m, 1H), 3.21 (m, 2H), 3.27 (s, 3H), 3.53 (dd, *J*=9.9, 2.5 Hz, 1H), 3.65 (dd, *J*=9.9, 7.5 Hz, 1H), 3.78 (s, 3H), 4.02 (m, 1H), 4.26 (d, *J*=1.5 Hz, 1H), 4.36 (d, *J*=0.9 Hz, 2H), 4.47 (d, *J*=11.5 Hz, 1H), 4.51 (s, 2H), 4.61 (d, *J*=11.9 Hz, 1H), 4.62 (d, *J*=11.5 Hz, 1H), 4.72 (d, *J*=11.9 Hz, 1H), 6.79 (br, 1H), 6.85 (d, *J*=8.8 Hz, 2H), 7.2-7.4 (m, 12H), 7.45 (s, 1H).

^{1}H NMR of *iii* (300 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.02 (d, buried, 3H), 1.79 (s, 3H), 1.95 (s, 3H), 2.05 (d, *J*=1.3 Hz, 3H), 2.76 (m, 1H), 3.51 (d, *J*=6.5 Hz, 2H), 5.05 (br, 1H), 5.58 (d, *J*=9.0 Hz, 1H), 6.32 (d, *J*=11.0 Hz, 1H), 6.81 (d, *J*=14.9 Hz, 1H), 6.97 (dd, *J*=14.9, 11.0 Hz, 1H), 7.37 (m, 6H), 7.63 (m, 4H).

(Received in USA 18 December 1991)