Total Synthesis of the Pseudopterane (±)-Kallolide B

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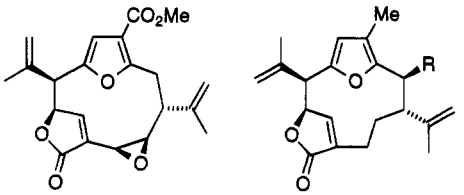
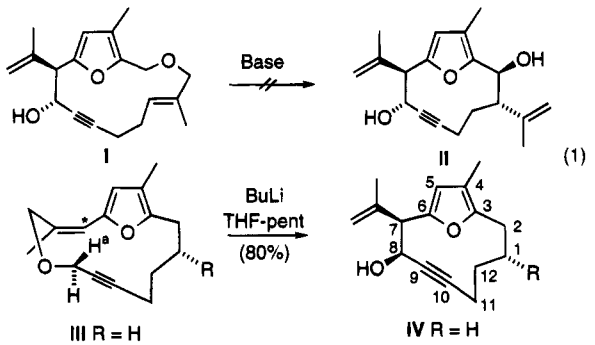
In 1982, Fenical and co-workers elaborated the structure of pseudopterolide, a novel furanocyclic diterpene obtained from the Caribbean gorgonian *Pseudopterogorgia*.[2] Subsequently, other members of this family were isolated and characterized, including kallolide A and B.[3]



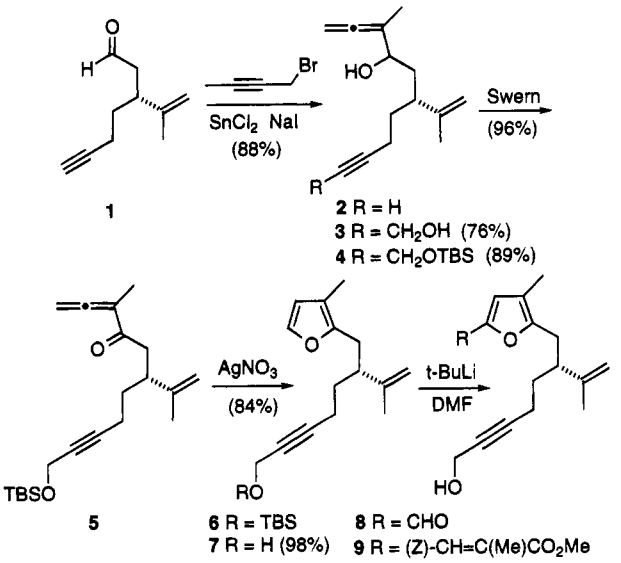
For several years, we have been interested in developing routes to these 12-carbon periphery furanocycles. An initial approach to a kallolide A precursor **II**, through [2,3] Wittig ring contraction of the 15-membered allylic ether **I**, was not successful (eq 1).[4] Exposure of furan **I**



to a variety of basic conditions led to small amounts of [1,2] rearrangement product and extensive decomposition. We subsequently found that the 15-membered allylic propargylic ether **III** smoothly rearranges to the *cis* propargylic alcohol **IV** upon treatment with BuLi in THF–pentane.[5]

A successful application of the foregoing approach to kallolide B would require that the new stereocenters at C–7 and C–8 in **IV** orient *anti* to an existing isopropenyl substituent at C-1. Such remote stereocontrol has previously been realized in our synthesis of the cembrane diol β-CBT.[6,7] In the case at hand, we carried out a Monte Carlo global minimization[8] of ether **III** (R = MeC=CH_2) which revealed that the propargylic H^a is almost exactly colinear with the π-system of the starred vinylic center. Hence, a concerted [2,3] Wittig rearrangement with a reactant-like transition state would be expected to lead to the *cis-anti* product **IV** (R = MeC=CH_2).[9] To test this prediction, we embarked upon a synthesis of ether **12** (**III**, R = MeC=CH_2).

Aldehyde **1**, available in five routine steps (72% yield) from 4-pentynol,[10] was converted to allenol **2** upon treatment with 1-bromo-2-butyne and $SnCl_2$/NaI.[11] Hydroxymethylation (BuLi, CH_2O) and TBS protection afforded the homologue **4**, which was oxidized to ketone **5**. Exposure to catalytic $AgNO_3$ led smoothly to the furan **6**.[12] Desilylation followed by formylation of the furan and subsequent Still-Horner-Emmons homologation yielded the (*Z*)-ester **9** (57%).[13]



Hydroxy ester **9** was converted to the chloride **10** (LiCl; MsCl; 2,6-lutidine) and reduced (DIBAH). The resulting chloro alcohol **11** cyclized in 83% yield upon exposure to NaH/18-C-6 in refluxing toluene. Treatment of ether **12** with BuLi in THF–pentane afforded the *cis,anti* alcohol **13** as the only detectable product in 86% yield. The

[†] Author to whom inquiries regarding the crystal structure of alcohol **13** should be addressed.

(1) NIH Postdoctoral Fellow 1993–1995.

(2) Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.

(3) (a) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741. (b) See also: Paquette, L. A. *Chemtracts-Org. Chem.* **1992**, *5*, 141 and references cited therein.

(4) Marshall, J. A.; Nelson, D. J. *Tetrahedron Lett.* **1988**, *29*, 741.

(5) Marshall, J. A.; Yu, B-c. *J. Org. Chem.* **1994**, *59*, 324.

(6) Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, *55*, 227.

(7) For an early example of this phenomenon, see: Still, W. C.; Mobilo, D. *J. Org. Chem.* **1983**, *48*, 4785; see also ref 3b.

(8) The program Macromodel V3.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multiple step interations (typically 1000) until the minimum energy conformer was found multiple times (10 or more). For a description of the program, see: (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(9) *Cf.* (a) Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421. (b) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375. (c) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795. (d) Hoffmann, R.; Bruckner, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 647.

(10) (1) Swern-Wittig condensation, see: Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198. (2) DIBAH reduction. (3) Orthoester Claisen rearrangement. (4) DIBAH reduction. (5) Swern oxidation. See the supplementary material for details.

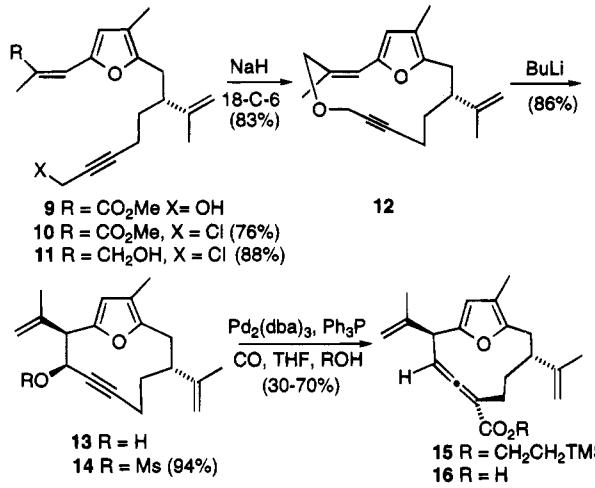
(11) A modification of the procedure of Mukaiyama was employed: Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621.

(12) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960. Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *54*, 7169.

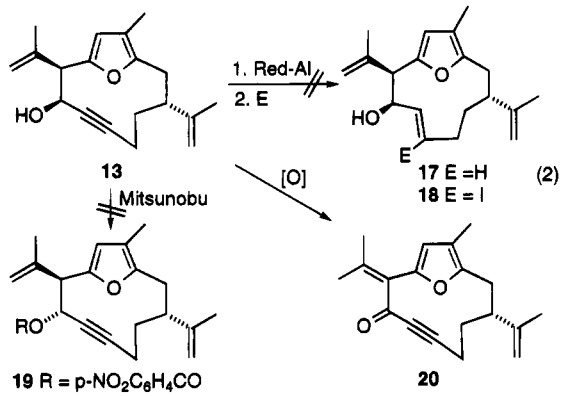
(13) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

0022-3263/95/1960-0796$09.00/0

stereochemistry of **13** was confirmed by single crystal X-ray structure analysis.[22]



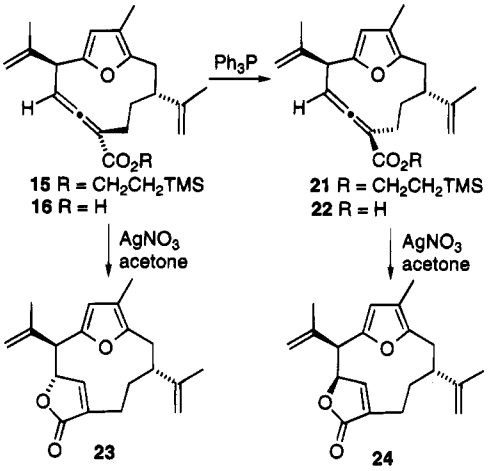
At this point, we planned to use a sequence for butenolide construction previously employed in our synthesis of aristolactone.[14] However, attempted hydroalanation of propargylic alcohol **13** with Red-Al followed by H_2O quench gave only recovered starting material. None of the olefin **17** was produced (eq 2). Accordingly,



we did not even attempt to prepare the required vinylic iodide **18** by this route. This unexpected turn of events required a significant change in strategy.

We eventually discovered that exposure of the propargylic mesylate **14** to $Pd(PPh_3)_4$, generated *in situ* from $Pd_2(dba)_3$, in the presence of CO and various alcohols or water afforded allenic esters such as **15** or the acid **16**.[15] Ester **15** was produced in *ca.* 70% yield. Although acid **16** was obtained from **14** in only 30% yield, no other byproduct could be detected.[16]

We suspected that the foregoing carbonylation sequence had proceeded with inversion of stereochemistry but we could not be certain.[15] Our suspicions were confirmed upon treatment of allenic acid **16** with catalytic $AgNO_3$, whereupon butenolide **23** was produced as the sole product.[17] The ^1H and ^{13}C NMR spectra of **23** were significantly different from those reported for kallolide B.[3]



We were now presented with the frustrating problem of inverting what we had originally perceived to be the desired stereochemistry at C-8 in alcohol **13**. Several attempts at Mitsunobu inversion to esters such as **19** were unsuccessful.[18] A possible two-step inversion through oxidation then reduction also was not feasible, as oxidation of alcohol **13** was accompanied by double bond migration affording the isopropylidene ketone **20**.[19] Having failed in these obvious solutions, we turned to an alternative possibility—inversion of the allenic ester.

Monte Carlo global minimization of allenic esters **15** (R = Me) and **21** (R = Me) revealed the latter to be the more stable by over 3 kcal/mol.[8] In fact, when ester **15** was heated in benzene with Ph_3P, a roughly 3:1 mixture favoring the diastereomer **21** was produced.[20] Cleavage of the TMS ethyl ester with TBAF enhanced this ratio to *ca.* 10:1. On treatment with catalytic $AgNO_3$ in acetone, this mixture afforded racemic kallolide B (**24**) and a small amount of the readily separable epimer **23**.[21] The reported ^1H and ^{13}C NMR spectra were in complete accord with the spectra of our synthetic material.[3]

Although linear in nature, the foregoing synthetic sequence is direct and efficient. The remarkably high remote diastereocontrol of the ring contraction leading to alcohol **13** is noteworthy, as is the efficient cyclization of allenic acids **16** and **22** to the strained butenolides **23** and **24**. Further applications of these constructs to furanocembranes and pseudopteranes are clearly possible.

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Supplementary Material Available: Experimental procedures and ^1H NMR spectra for all intermediates and ^{13}C NMR spectra for selected intermediates (45 pages).

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(14) Marshall, J. A.; Lebreton, J.; De Hoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883.

(15) *Cf.* Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731. Colas, Y.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 845. We have found that this methodology can be applied to nonracemic butenolides with excellent stereocontrol. Details will be published in due course.

(16) Allenic acid **16** was best used directly; attempted purification resulted in significant material loss.

(17) Although the yield (unoptimized) of this reaction was only 56%, no significant by products could be detected by TLC. Furthermore, the ^1H NMR spectrum of the crude product was comparable to that of the purified material.

(18) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(19) For a closely related example of such an oxidation without isomerization, see: Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.

(20) For the use of Ph_3P in isomerizations of acetylenic esters and ketones, see: (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659. (b) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.

(21) This is the second reported synthesis of a pseudopterane natural product; for the first, see ref 19.

(22) The author has deposited atomic coordinates for 13 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.