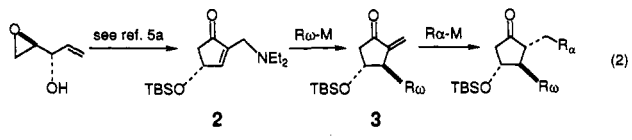
afford 3 in excellent yields, which in turn reacts with an α side chain as reported by Stork and his co-workers to afford PGs (eq 2).[5]

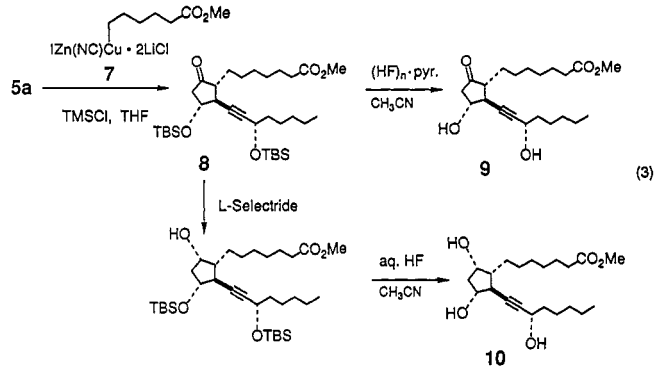


(2)

We expected that the amino group present in 2 would activate an alkynylaluminum compound by coordination, thus making it possible to introduce an alkynyl moiety into 2 at the opposite face of the C-11 hydroxyl group via a 1,4-addition pathway. Herein reported is the successful realization of this idea which undoubtedly simplifies the synthesis of 13-dehydro-PGs.[8]

When 2 was reacted with diethyl(3-(*tert*-butyldimethylsiloxy)-1-octynyl)aluminum (**4a**) in benzene at room temperature, 1,4-addition did occur to afford, after hydrolysis, a mixture of two diastereoisomers.[9,10] These were readily separated by column chromatography (SiO_2) to give **5a** having the desired 12β configuration and **6a** (12α isomer) in 82% and 14% yields, respectively. The assignment of the configuration of the two isomers follows from the ^1H NMR coupling constant between the two protons at C-11 and C-12 (PG numbering, J = 4.0 Hz for cis and J = 6.8 Hz for trans) and ^{13}C NMR chemical shifts of C-11 and C-12, since the resonances for these carbons in **6** (cis configuration) are always upfield of those in **5** (trans configuration).[11] Table I shows the yields, characteristic ^1H and ^{13}C NMR data, and $[\alpha]_D$ values of the products obtained by the reaction of 2 with various diethylalkynylaluminum compounds **4a-f**. As can be seen from the table, in every case, the 12β-isomer **5** was major; however, somewhat diminished diastereoselectivities were observed with the decrease of the steric bulk of alkynyl moiety.

With the compounnd **5a** in hand, we then carried out the synthesis of the methyl ester of 13-dehydro-PGE_1 and -PGF_1 by 1,4-addition of α side-chain unit onto it (eq 3).



(3)

Thus the reaction of **5a** with organocopper reagent **7**, prepared from the corresponding organozinc reagent and CuCN·2LiCl, in the presence of Me_3SiCl provided, after hydrolysis, disilyl ether of 13-dehydro-PGE_1 methyl ester (**8**) ($[\alpha]^{25}_D$ -47.3° (*c* 1.96, $CHCl_3$)) in 78% yield.[5c] Protodesilylation of 8 with $(HF)_n$-pyridine in acetonitrile afforded 13-dehydro-PGE_1 methyl ester (**9**) ($[\alpha]^{24}_D$ -43.8° (*c* 0.484, $CHCl_3$), mp 46.0-46.5 °C (lit.[12] mp 46 °C)) in 85% yield. While the reduction of 8 with L-Selectride (Aldrich) followed by protodesilylation (aqueous HF, CH_3CN) gave 13-dehydro-PGF_1 methyl ester (**10**) ($[\alpha]^{22}_D$ +21.7° (*c* 0.60, $CHCl_3$) in 58% overall yield from 8, mp 68.0-68.5 °C (lit.[12] mp 68 °C)). The spectroscopic data (^1H NMR, IR, and MS) of **9** and **10** are in good agreement with the literature.[12]

Since PG analogues having 17-methyl-15-hydroxy[13] and 15-dehydroxy-16-methyl-16-hydroxy[14] moiety as an ω side chain have been accepted as promising therapeutic agents, the synthesis of 13-dehydro version of these PGs using the enones **5c** and **5d** is in progress in our laboratory.

Supplementary Material Available: Experimental procedure for preparation of **5** and **6** and spectroscopic data (IR and ^1H and ^{13}C NMR) of **5a-f**, **6a-f**, **8-10**, and the disilyl ether of **10** (6 pages). Ordering information is given on any current masthead page.

(8) Previous synthesis of 13-dehydro-PGs: via epoxide ring opening by alkynyl anion; Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899. Fried, J.; Lin, C. H. *J. Med. Chem.* **1973**, *16*, 429. Fried, J.; Lee, M.-S.; Gaede, B.; Sih, J. C.; Yoshikawa, Y.; McCracken, J. A. *Adv. Prostaglandin Thromboxane Res.* **1976**, *1*, 183. Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489. See also ref 2g and 2j. Via dehydrohalogenation of 14-halo-PG intermediate; Smith, H. W.; Mich, K. U.S. Patent 4,029,681 (1977). Takahashi, A.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 1227. See also ref 2b and 21.

(9) The nucleophilic S_N2' addition of organometallic reagents to allylamine derivatives has been reported: Doomes, E.; Clarke, U.; Neitzel, J. J. *J. Org. Chem.* **1987**, *52*, 1540. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755.

(10) ^1H and ^{13}C NMR studies of the reaction mixture (before hydrolysis) demonstrated the formation of the aluminum enolate.

(11) For 2-alkynylcyclopent-3-en-1-ol: Briggs, A. J.; Walker, K. A. M. *J. Org. Chem.* **1990**, *55*, 2962. For 2-methylcyclopentanol: Christl, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463. For prostaglandins: Cooper, G. F.; Fried, J. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1579. Mizsak, S. A.; Slomp, G. *Prostaglandins* **1975**, *10*, 807. Arroniz, C. E.; Gallina, J.; Martinez, E.; Muchowski, J. M.; Velarde, E.; Rooks, W. H. *Ibid.* **1978**, *16*, 47.

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(14) Larsen, K. R.; Jensen, N. F.; Davis, E. K.; Jensen, J. C.; Moody, F. G. *Prostaglandins* **1981**, *21* (*Suppl*), 119. Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786. Kaymakcalan, H.; Wilson, D. E.; Khader, M.; Ramsamooj, E.; Adams, A. *Clin. Res.* **1981**, *29*, 758A. Wilson, D. E.; Levendglu, H.; Adams, A.; Ramsamooj, E. *Prostaglandins* **1984**, *28*, 5. Collins, P. W. *J. Med. Chem.* **1986**, *29*, 437. See also ref 13c.

(15) Ito, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1989**, *30*, 7083.

A Novel Method for the Synthesis of Spiroketal Systems. Synthesis of the Pheromones of the Common Wasp and the Olive Fruit Fly

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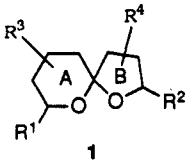
Received March 8, 1991

Summary: Total syntheses of the pheromones of the common wasp and the olive fruit fly were accomplished by a strategy in which the key transformation involved the cleavage of tetrahydrofuran with (*tert*-butyldimethylsilyl)manganese pentacarbonyl followed by sequential insertion of ethyl acrylate.

0022-3263/91/1956-3207$02.50/0

The [4.5]- and [5.5]spiroketal systems 1 and 2 are ubiquitous among polyacetate and polypropionate derived natural products.[1] Accordingly, numerous approaches to the stereoselective construction of these systems have been developed.[2] As an extension of the studies of alkyl-



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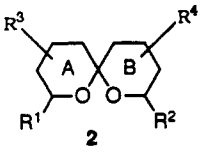


2

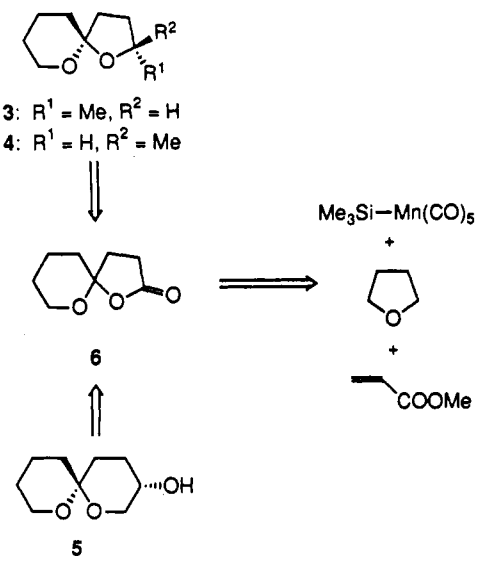
manganese pentacarbonyl methodology for organic synthesis,[3] we have investigated the general approach to spiroketal systems such as 1 and 2 illustrated in Scheme I. In this approach, spiroketal lactone 6 serves as the keystone for construction of both the [4.5] and [5.5] family of spiroketals. The viability of this strategy is demonstrated by synthesizing pheromones of the common wasp (3 and 4)[4] and the olive fruit fly (5), respectively, via the common intermediate spiro lactone 6 (Scheme I).[5]

Ring opening of tetrahydrofuran with TBDMS-Mn-$(CO)_5$[6] (generated in situ from the silyl triflate and sodium pentacarbonylmanganate(I) (7)[7]) afforded the unstable manganese complex 9 in excellent yield.[8,10] Complex 9 was characterized as its acyl derivative 10.[10] Sequential insertion[3] of manganese complex 9 and methyl acrylate at 7 kbar in ether gave manganacycle 11[10] regiospecifically in 71% overall yield from manganate anion 7 (Scheme II).[3] Photodemetalation of mangancycle 11 employing the standard protocols[3f] followed by exposure of the resulting ketone to camphorsulfonic acid (CSA) provided spiro lactone 6.

Attempts to homologate spiro lactone 6 to enol ether 12 using Tebbe and Tebbe-like reagents failed due to fragmentation of the spiroketal system.[11] On the other hand, treatment of lactone 6 with dimethyltitanocene according to the method of Petasis[12] afforded homologated enol ether 12 in excellent yield (Scheme III). Catalytic hydrogenation of 12 over $Pd/BaCO_3$ gave a 4:1 mixture of racemic pheromones 3 and 4. The natural pheromone mixture consists of diastereomeric spiroketals 3 and 4 in a 1:1 ratio.[4]

Oxidative rearrangement of enol ether 12 to [5.5]spiroketal-ketone 13 was most efficiently accomplished using dimethyldioxorane (which produced an extremely unstable epoxide) followed by brief treatment with camphorsulfonic acid. Reduction of ketone 13 according to the protocol of

Scheme I



6

5

Waltermire[13] produced a 13:1 mixture of pheromone 5 and its diastereomer 14.[14]

For the manganese-based strategy to be extended to the construction of more complicated spiroketal systems, it was crucial that substituents be incorporated in a regioselective fashion onto either of the spiroketal rings. In principle, introduction of substituents could be accomplished in two complimentary fashions: (1) Regioselective cleavage of substituted tetrahydrofuran derivatives by silylmanganese reagents would result in the introduction of substituents onto the A ring of the spiroketal systems. (2) Regioselective introduction of alkyl groups onto the B ring of the spiroketals would be accomplished by sequential insertion of α- or β-substituted acrylate ester derivatives. The viability of both strategies have been demonstrated in a preliminary series of transformations as outlined in Scheme IV.

Regioselective opening of 2-methyltetrahydrofuran with TBDMS-$Mn(CO)_5$ (in situ generation) followed by sequential insertion of phenylacetylene produced a 10:1 mixture of manganese complex 15 and 16. The excellent stereoselectivity observed in the cleavage of the tetrahydrofuran ring suggests that the first approach will be successful in placing substituents onto the A ring of the spiroketal systems 1 and 2 in more complex examples of this process.

(1) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
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(3) (a) DeShong, P.; Slough, G. A. *Organometallics* **1984**, *3*, 636. (b) DeShong, P.; Slough, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 7788. (c) DeShong, P.; Slough, G. A.; Rheingold, A. L. *Tetrahedron Lett.* **1987**, *28*, 2229. (d) DeShong, P.; Slough, G. A.; Sidler, D. R. *Tetrahedron Lett.* **1987**, *28*, 2233. (e) DeShong, P.; Slough, G. A.; Elango, V. *Carbohydr. Res.* **1987**, *171*, 342. (f) DeShong, P.; Sidler, D. R.; Rybczynski, P. J.; Slough, G. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 2575. (g) DeShong, P.; Sidler, D. R. *J. Org. Chem.* **1988**, *53*, 4892. (h) DeShong, P.; Slough, G. A.; Sidler, D. R.; Rybczynski, P. J.; Philipsborn, W. v.; Kunz, R.; Bursten, B. E.; Clayton, T. W., Jr. *Organometallics* **1989**, *8*, 1381. (i) DeShong, P.; Sidler, D. R.; Rybczynski, P. J.; Ogilvie, A. A.; Philipsborn, W. v. *J. Org. Chem.* **1989**, *54*, 5432.
(4) (a) Francke, W.; Hindorf, G.; Reith, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 862. (b) Mori, K.; Watanabe, H.; Yanagi, K.; Minobe, M. *Tetrahedron* **1985**, *41*, 3663. (c) Iwata, C.; Moritani, Y.; Sugiyama, K.; Fujita, M.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 2255.
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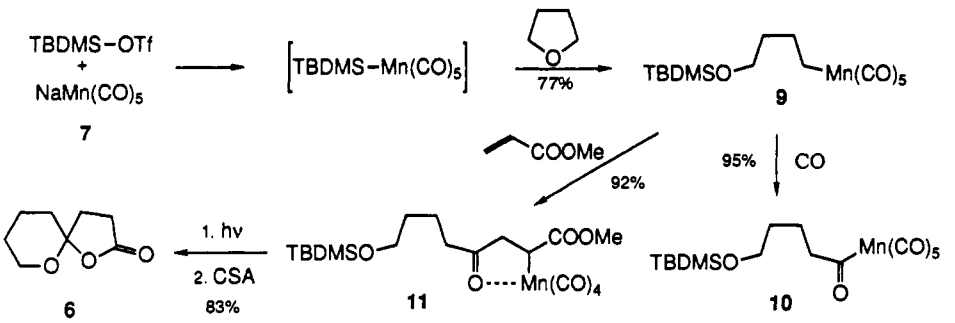
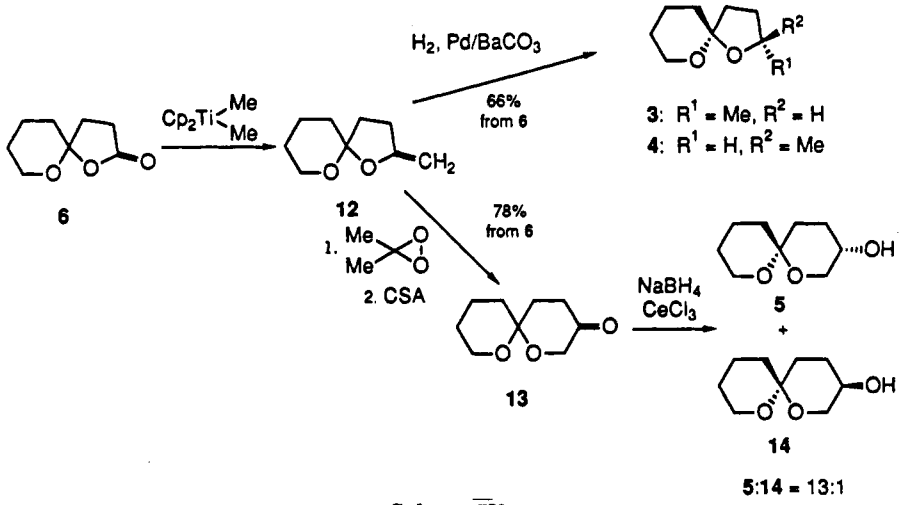
(7) Drew, D.; Darensbourg, M. Y.; Darensbourg, D. J. *J. Organomet. Chem.* **1975**, *85*, 73.
(8) This transformation could also be accomplished with the trimethylsilyl analogue of 7 according to the method of Gladysz.[9b] However, the TMS ether was hydrolytically unstable and could not be retained in subsequent transformations.
(9) (a) Berry, A. D.; MacDiarmid, A. G. *Inorg. Nucl. Chem. Lett.* **1969**, *5*, 601. (b) Brinkman, K. C.; Gladysz, J. A. *Organometallics* **1984**, *3*, 147.
(10) All compounds provided infrared, ^1H and ^{13}C NMR, and high-resolution mass spectral or C, H elemental analysis data consistent with the proposed structures.
(11) Professor Grubbs at Cal Tech has informed us that his laboratory has evidence implicating radical intermediates in the methylenation reaction with Tebbe's reagent. In our system, small quantities (<25%) of products which are consistent with radical fragmentation of the spiroketal ring system are produced.
(12) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(13) DeShong, P.; Waltermire, R. E., unpublished results. Waltermire, R. E. Ph.D. Dissertation, University of Maryland, 1989.
(14) The spectral data of the major diastereomer formed in the reduction was identical in all aspects with the data reported for pheromone 5.[5]

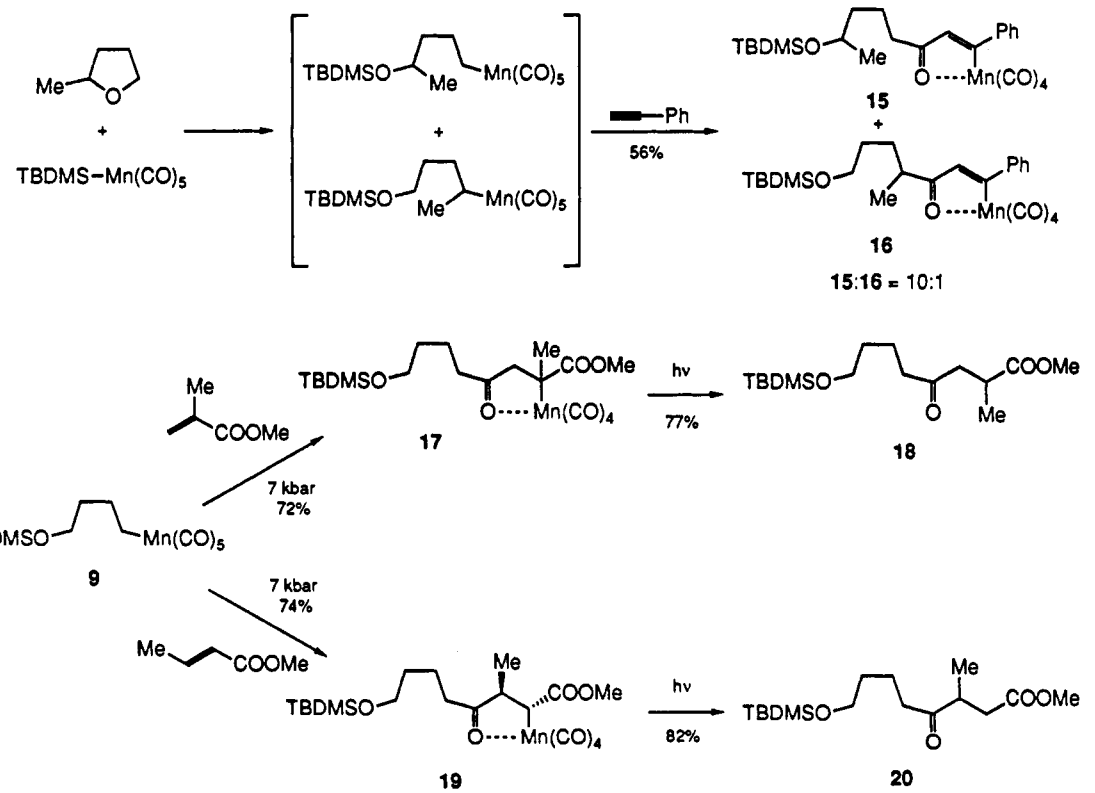
Scheme II



Scheme III



Scheme IV



Alternatively, regioselective sequential insertion of manganese complex **9** with either methyl methacrylate or methyl crotonate[10] afforded manganacycles **17** and **18**, respectively, in which an alkyl group had been attached with complete regioselectivity onto the portion of the acyclic precursor destined to become ring B of the spiroketal. In analogy with the simple system, photodemetalation of manganacycles **17** and **19** provided the anticipated ketones **18** and **20** in excellent yields. These encouraging results suggest that the sequential insertion methodology can be extended to the synthesis of substitutionally and stereochemically more complex spiroketal

systems. Application of this methodology to natural product synthesis are underway.

Acknowledgment. The generous financial support of the National Institutes of Health (GM 39815) and an unrestricted grant from Lederle Laboratories is acknowledged. We wish to thank Drs. Rick Sidler and Robert Waltermire for helpful discussions during the course of this investigation and Professors Kenji Mori (Tokyo University) and Chuzo Iwata (Osaka University) for providing spectral data of the pheromones.

Supplementary Material Available: Experimental procedures and spectral data for compounds 3-18 are provided (7 pages). Ordering information is given on any current masthead page.

Construction of the Tricyclic Core of the Marine Alkaloid Sarain A

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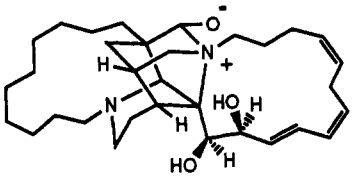
Received March 1, 1991

Summary: The alkaloidal nucleus of sarain A (1) has been synthesized by a short route involving a [3 + 2] azomethine ylide cycloaddition and an allylsilane/*N*-sulfonyliminium ion cyclization as key steps.

Sarain A (1) is a recently discovered polycyclic alkaloid produced by the marine sponge *Reniera sarai*.[1] The structure of sarain A was secured by X-ray crystallography on the diacetate derivative[1a] and by spectral studies on the alkaloid itself.[1b] The central alkaloidal nucleus of 1 possesses a unique structural array unprecedented in natural products. In this communication we describe the first synthetic approach to the tightly fused tricyclic core of sarain A.



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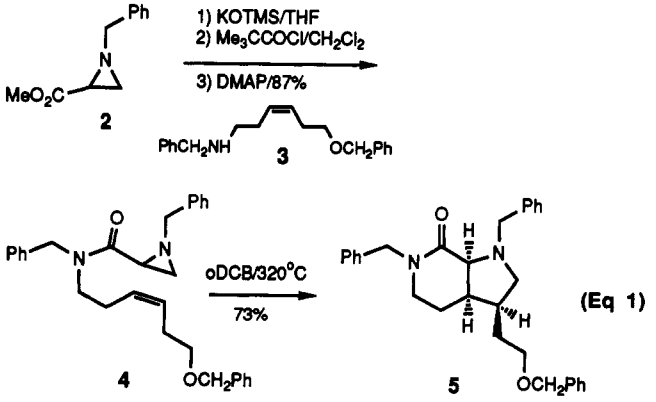
Our synthesis began with readily available aziridine ester 2[2] which was converted to the potassium carboxylate[3] and coupled via a mixed anhydride procedure[4] with amine 3[5] to afford amide 4 (eq 1). Thermolysis of 4 in *o*-dichlorobenzene at 320 °C in a degassed sealed tube gave bicyclic lactam 5 stereospecifically via an azomethine ylide/olefin [3 + 2] dipolar cycloaddition.[2,6,7] It should be noted that the nature of the protecting groups in precursor 4 proved critical to the cycloaddition. For example, protection of the side-chain oxygen as a TBS ether led to the corresponding cycloadduct in very low yield.[8] Similarly, if the amide nitrogen of 4 is unprotected[9] (i.e., NH) or is *N*-tosyl, yields of cycloadducts were again low.



(Eq 1)

Scheme I outlines the route used to process lactam 5 into a precursor for the remaining key cyclization. A notable step here involves coupling of the acetate 7 with a mixed silyl cuprate[10a] to produce the allylsilane 8 as a 1:1 mixture of *E*/*Z* isomers. Attempts to prepare silane 8 by the more standard Seyferth-Wittig[10b] procedure directly from aldehyde 6 afforded only complex mixtures. The mixture of allylsilanes was converted in two steps to *N*-tosyl lactam 9[11] which could be cleanly reduced to α-hydroxysulfonamide 10 using DIBALH.

(1) (a) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863. (b) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519.

(2) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309.

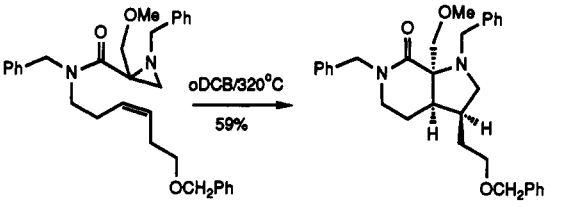
(3) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.

(4) Lambert, C.; Viehe, H. G. *Tetrahedron Lett.* **1985**, *26*, 4439.

(5) (a) Sisko, J., Ph.D. Thesis, The Pennsylvania State University, 1991. (b) Compound 3 was prepared via a straightforward route from methyl 6-[(2-tetrahydropyranyl)oxy]-(*Z*)-hex-3-enoate (Carvalho, J. F.; Prestwich, G. D. *J. Org. Chem.* **1984**, *49*, 1251). Details will be provided in a full paper.

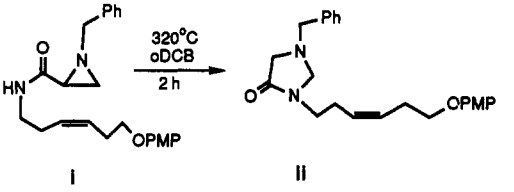
(6) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523. Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204. Takano, S.; Tomita, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1473.

(7) In order to introduce a functional handle for eventual construction of the triene diol macrocyclic ring of 1, we have successfully tested the following dipolar cycloaddition (J. R. Henry):



(8) We are grateful to Professor Kunio Ogasawara for informing us of similar unpublished observations on related cycloadditions.

(9) Thermolysis of amide i gave only a small amount of the desired cycloadduct and rearrangement product ii was the major product.[5a]



i ii

(10) (a) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805. (b) Seyferth, D.; Wursthorn, K. R.; Lim, T. F. O.; Sepelak, D. J. *J. Organomet. Chem.* **1979**, *181*, 293.

(11) Cf. Somfai, P.; He, H. M.; Tanner, D. *Tetrahedron Lett.* **1991**, *32*, 283.

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