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Studies toward the Synthesis of Spirolide C: Exploration into the Formation of the 23-Membered All-Carbon Macrocyclic Framework

Craig E. Stivala, Zhenhua Gu, Lindsay L. Smith, and Armen Zakarian*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

zakarian@chem.ucsb.edu

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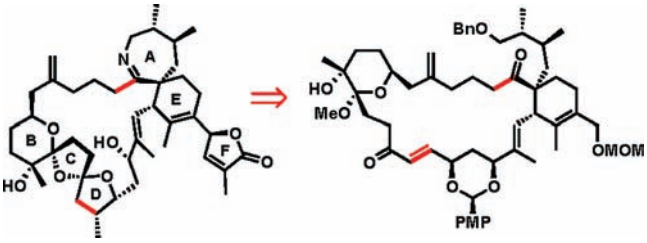
ABSTRACT



The synthesis of two complex subunits en route to spirolide C is described. A key alkyllithium addition to an aldehyde joins the fragments, which are advanced in order to investigate a ring-closing metathesis to form the 23-membered all-carbon macrocyclic framework.

The cyclic imine group of marine toxins is an emerging class of natural products with global distribution in marine environments.[1] After the discovery of the first member of this family in 1995, the group has grown to include more than 30 members with complex chemical structures, including pinnatoxins,[2] pteriatoxins,[3] spirolides,[4] gymnodimines,[5] and spiro-prorocentrimine.[6] Initially, the mode of action for spirolides, pinnatoxins, and gymnodimine was attributed to calcium-channel activation,[7] which has been subsequently revised to a potent and selective inhibition of nicotinic acetylcholine receptors (nAChRs), where the cyclic imines have been found to be among the most powerful nonpeptidic antagonists of nAChRs known to date.[8]

The structure of the spirolides combines the most challenging aspects within the cyclic imine group of toxins: the characteristic spiroimine subunit, the tetrasubstituted alkene

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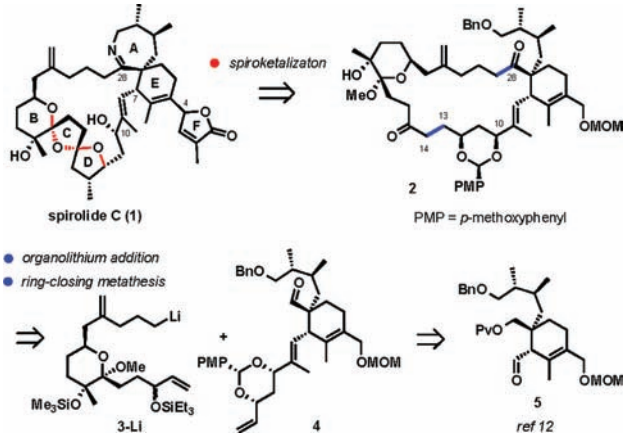
carrying a butenolide fragment, the 5,5,6-bispiroketal, and a highly functionalized 23-membered all-carbon macrocyclic framework.[9] Previously, the groups of Brimble[10] and Ishihara[11] described their approaches to solving selected problems posed by the complexity of spirolides, concentrating on the synthesis of the 5,5,6-spirobicyclic ring system and the construction of the spiroimine subunit. Herein, we disclose the progress of our own work,[12] with a focus on the formation of the 23-membered macrocyclic ring by ring-closing metathesis (RCM).

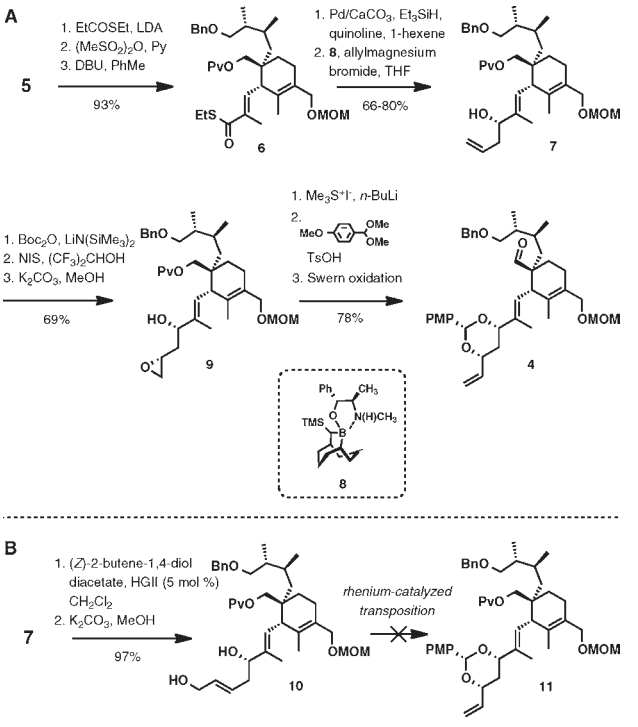
Scheme 1. Synthesis Plan for Spirolide C



An early strategic decision in our plan was to assemble the 5,5,6-bispiroketal *after* the construction of the macrocyclic framework to ensure the desired stereocontrol in the ketalization, which would be difficult to achieve in the acyclic system, in particular with regard to the formation of the 5,5-ketal, where no anomeric stabilization can be relied upon to control stereochemistry (Scheme 1).[10a,11] An example of the desired macrocyclic product is compound **2**, which could be accessed in a convergent manner from organolithium reagent **3** and aldehyde **4** followed by RCM (disconnections along the highlighted bonds at C13−C14 and C27−C28). Aldehyde **5**, previously prepared by a key diastereoselective Ireland−Claisen rearrangement, serves as a precursor to **4**.[13]

The synthesis of intermediate **4** began with a three-step preparation of thioester **6** from aldehyde **5** (Scheme 2A).

Scheme 2. Synthesis of Intermediate **4**



Aldol addition of *S*-ethyl thiopropionate followed by mesylation with methanesulfonic anhydride and elimination with DBU afforded **6** as a single stereoisomer in 93% overall yield. Thioester **6** was reduced to the corresponding α,β-unsaturated aldehyde under conditions reported by Fukuyama.[14] Soderquist asymmetric allylation was reproducible on varying scales and provided homoallylic alcohol **7** in 76% isolated yield with 5:1 diastereoselectivity.[15−17] Formation of the *tert*-butyl carbonate ($LiN(SiMe_3)_2$, Boc_2O) followed by iodolactonization (NIS, $(CF_3)_2CHOH$)[18] and treatment with methanolic potassium carbonate delivered epoxy alcohol **9** in 69% yield over the three steps. Treatment of epoxy alcohol **9** with the sulfur ylide generated from trimethylsulfonium iodide produced the requisite allylic diol[19] and was accompanied by the removal of the pivalate ester group. Protection of the 1,3-*syn*-diol as a *p*-methoxybenzylidene acetal

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(16) Brown asymmetric allylation generated homoallylic alcohol **7** in 91% yield as a 10:1 mixture of diastereomers; however, this result was irreproducible. Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.

(17) The separable minor diastereomer could be recycled through an oxidation−reduction sequence, providing an additional 7−10% yield of **7**.

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and oxidation of the primary hydroxy group under Swern conditions[20] completed the synthesis of intermediate **4**.

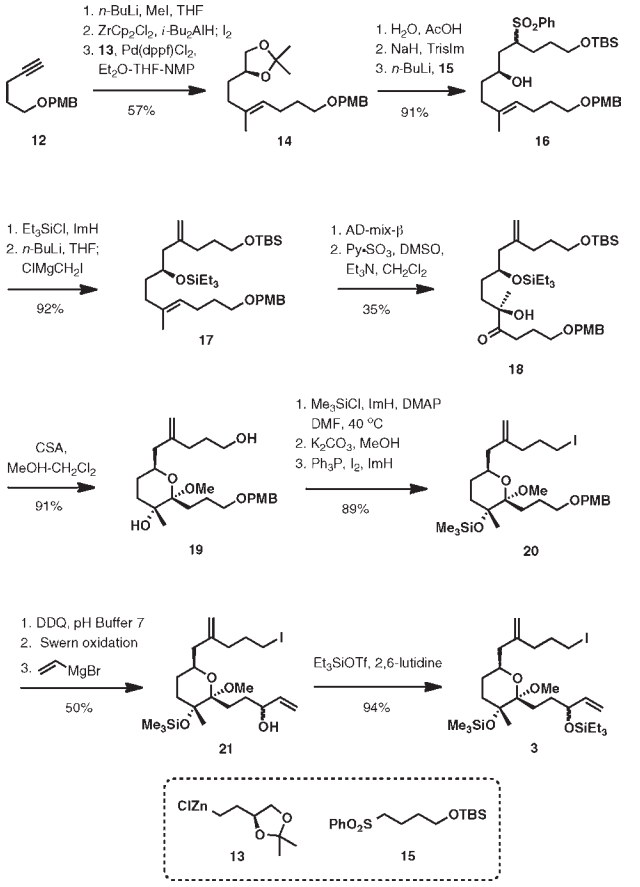
During the development of the synthetic route to **4** described above, we explored the synthesis of the desired 1,3-*syn*-diol acetal based on the recently developed Recat-alyzed transposition of allylic alcohols directed by hydroxy groups.[21] To this end, diol **10** was prepared from **7** by cross-metathesis with (*Z*)-2-butene-1,4-diol diacetate followed by methanolysis (97% over two steps, Scheme 2B).[22] However, only a small amount of **11** could be detected, and generally decomposition was observed under a variety of conditions.

The synthesis of the bispiroketal precursor fragment (**3**) was initiated by methylation of lithium acetylide generated from **12**[23] followed by hydrozirconation–iodination[24] to form the corresponding (*E*)-iodoalkene. Palladium-catalyzed cross-coupling of the iodide and the alkylzinc halide **13** afforded trisubstituted alkene **14** (57% over three steps).[25] Hydrolysis of the acetonide, epoxide formation,[26] and alkylation of lithiated sulfone **15** with the epoxide afforded **16** in excellent yield. Introduction of the exo-methylene group was accomplished by a Julia-type process after protection of the secondary hydroxyl group as a triethylsilyl ether.[27]

Sharpless asymmetric dihydroxylation[28] of diene **17** took place at the trisubstituted double bond, selectively affording the desired diol in 57% yield (85% based on re-covered **17**). Oxidation by the Parikh–Doering method[29] cleanly afforded hydroxy ketone **18**. Removal of the tri-ethylsilyl ether with concomitant ketalization afforded the sensitive methyl ketal **19** in 91% yield. Attempts to form the triethylsilyl ether at the tertiary hydroxy group ($TESOSO_2CF_3$, 2,6-lutidine; TESCl, ImH, DMF, 40 °C, 12 h) were thwarted by a facile elimination of the ketal methoxy group, affording the exocyclic vinyl ether. On the other hand, silylation of **19** with chlorotrimethylsilane in DMF at 40 °C efficiently delivered the desired monosily-lated product after treatment with potassium carbonate in methanol. Iododehydroxylation of the primary alcohol delivered **20** in 89% yield over three steps.

Careful oxidative removal of the *p*-methoxybenzyl ether with DDQ followed by a Swern oxidation of the resulting primary hydroxy group, addition of vinylmagnesium bro-mide generated an inconsequential ~1:1 mixture of dia-stereomers. Protection of the resulting secondary alcohol as its triethylsilyl ether completed the synthesis of the key intermediate **3** (Scheme 3).

Scheme 3. Synthesis of Intermediate **3**



The fragment coupling was accomplished as planned by a direct addition of the functionalized alkyllithium reagent **3-Li** generated by lithum-iodine exchange from iodide **3** with aldehyde **4** in 98% yield (Scheme 4).[30] Dess–Martin oxidation and desilylation delivered substrate **22** for key RCM studies.[31]

We carried out extensive studies on ring-closing metath-esis of tetraene **22**, the results of which are summarized in Table 1. In all cases, the HGII catalyst provided cleaner reactions than the GII catalyst. Although the formation of

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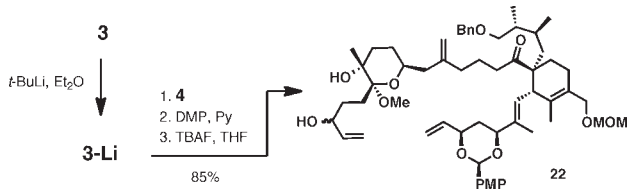
(32) See the Supporting Information for the structure of the ketone. (a) Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett.* **2001**, *42*, 3633–3636. (b) Renzulli, M. L.; Rocheblave, L.; Avramova, S. I.; Galletti, E.; Castagnolo, D.; Tafi, A.; Corelli, F.; Botta, M. *Tetrahedron* **2007**, *63*, 497–509. (c) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169–171.
(33) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

Scheme 4. Fragment Coupling



the 23-membered all-carbon macrocycle was found to be rather challenging, we succeeded in forming the desired product, albeit in low yield (entries 1−4). NMR studies have shown conclusively that the RCM process is initiated at the C14 terminal alkene selectively. The main byproduct was the C15 methyl ketone, presumably arising by fragmentation of the intermediate ruthenium carbene at C14.[32] Various attempts to minimize side reactions using additives such as 1,4-benzoquinone[33] or 2,6-lutidine[34] proved to be unproductive. To our delight, in no case was a RCM observed between the olefins at C13 or C14 and C24.[35]

Ring-closing metathesis with the C13 enone, prepared by oxidation of the C13 hydroxyl, was substantially cleaner, although slower (~5% conversion after 7 days), and prevented formation of C13 methyl ketone (entry 5). Increasing the reaction temperature from 40 to 85 °C resulted in complete decomposition (entry 6). Finally, fully silylated diol **22** was also more stable and resistant to the methyl ketone formation, but also exhibited low reactivity (entry 8).

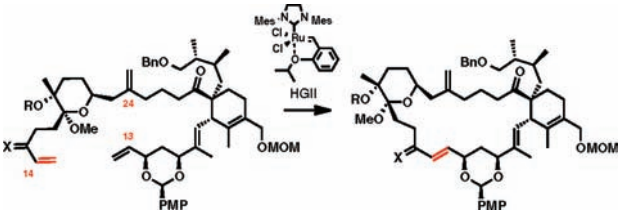
To conclude our study on the key formation of the 23-membered macrocyclic framework en route to the spirolides, we tested the hypothesis that a more compact substrate such as spiroketal **23** would be a superior substrate for RCM (Scheme 5). Intermediate **23** could be readily prepared from diol **22** in one step in a nearly quantitative yield. Indeed, when **23** was subjected to optimized conditions for RCM (GII 30 mol %, 1,2-dichloroethane, 60 °C, 24 h), a clean reaction ensued affording the anticipated macrocyclic product (25% isolated yield) and the recovered starting material (54% isolated yield).

In closing, we report the successful fragment coupling and extensive studies on RCM reactions of the 23-membered all-carbon macrocyclic ring system en route to the spirolides. While these studies revealed that the RCM is no doubt challenging, the powerful reaction was successful in forming the expected compounds and provided sufficient amounts of the macrocyclic products to enable key spiroketalization studies central to our approach in the synthesis of spirolides.

(34) 2,6-Lutidine was used to avoid possible fragmentation of the sensitive methyl ketal.

(35) For a similar problen in the synthesis of pinnatoxins, see: (a) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776. (b) Reference 8b.

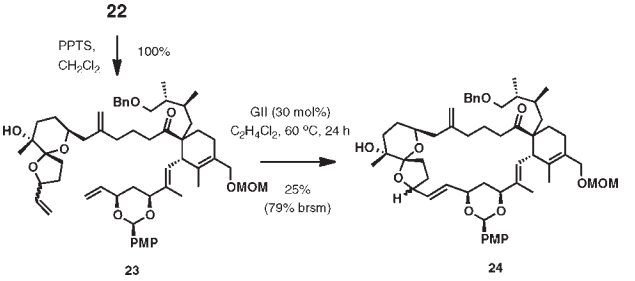
Table 1. RCM Studies of **22** and Its Derivatives[a]



entry	R; X	solvent	time (h), temp (°C)	conversion, %
1	H; H, OH	CH_2Cl_2	1, 40	10
2	H; H, OH	CH_2Cl_2	18, 40	10
3	H; H, OH	CH_2Cl_2	18, 20	20
4	H; H, OH	CH_2Cl_2	12, 40	17[b]
5	H; O	CH_2Cl_2	7 d, 40	5 (95 brsm)
6	H; O	$C_2H_4Cl_2$	24, 85	0
7	$SiMe_3$; H, $OSiEt_3$	CH_2Cl_2	24, 40	0
8	$SiMe_3$; H, $OSiEt_3$	PhMe	24, 90	10 (90 brsm)
9	$SiMe_3$; H, $OSiEt_3$	$C_2H_4Cl_2$	24, 90	0

[a] All reactions were carried out under an inert atmosphere of argon in degassed solvents. Reactions were performed on scales of 1−2 mg with a concentration of 0.005 M. Percent conversions were determined by NMR spectroscpy. [b] Isolated yield.

Scheme 5. RCM with Spiroketal **23**



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Supporting Information Available. Experimental procedures and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.