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An Unexpected Product Arising from Metal Alkylidene Mediated Ring-Closing Diene Metathesis

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Abstract: Ring-closing diene metathesis of siloxytriene **3** surprisingly afforded siloxytricycle **9** in which the newly formed ring is one carbon unit smaller than expected.
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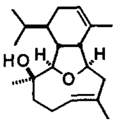
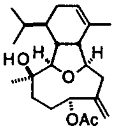
3-Deacetoxy-6-deacetylcalicophirin B (**1**) is the simplest member of the eunicellin (cladiellin) diterpenes, a group of approximately sixty marine natural products isolated from gorgonian and soft corals.[2] It is the major metabolite (0.6% dry weight) obtained from methanol extraction of an unknown soft coral collected at Majuro Atoll.[3] We recently reported that the hexahydroisobenzofuran moiety of eunicellin diterpenes can be assembled efficiently using a stereoselective Prins cyclization–pinacol rearrangement.[4] Employing this key transformation, the first total synthesis of a eunicellin diterpene, (–)-7-deacetoxyalcyonin acetate (**2**), was accomplished.[4] To generalize our synthetic entry to these marine metabolites, we turned our attention to **1**, a representative member of eunicellin metabolites that contain endocyclic unsaturation in the 9-membered oxacyclic ring. Since metal alkylidene mediated ring-closing diene metathesis[5] has been used to form medium sized rings in moderate to good yield,[6] this versatile reaction was investigated as a means of constructing the hexahydrooxonin ring of **1**. Herein, we report a surprising product arising from our attempts to prepare **1** by ring-closing metathesis.



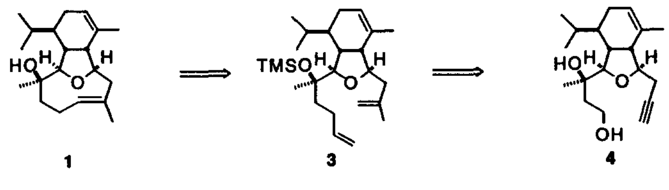
3-deacetoxy-6-deacetylcalicophirin B (**1**)



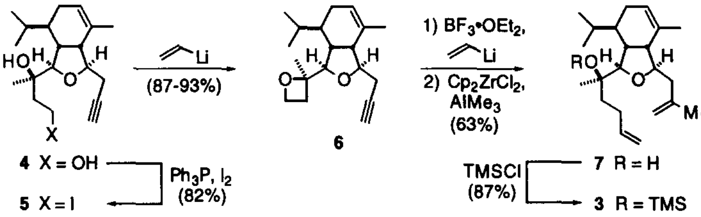
7-deacetoxyalcyonin acetate (**2**)

Ring-closing metathesis of siloxytriene **3** could lead to 3-deacetoxy-6-deacetylcalicophirin B (**1**), while the former triene should be available from diol **4**,[4] an intermediate in our earlier synthesis of **2** (Scheme 1). The initial objective, efficient conversion of **4** to **3**, was accomplished as shown in Scheme 2. Iodination of the primary hydroxyl group of diol **4** provided iodo alcohol **5**.[7] Deprotonation and subsequent cyclization gave oxetane **6**. Opening of the oxetane unit of **6** with vinyllithium in the presence of boron trifluoride etherate,[8] followed by carboalumination using trimethylaluminum[9] then afforded trienol **7**. Protection of the alcohol with chlorotrimethylsilane finally provided siloxytriene **3** in good overall yield.[10,11]

Scheme 1

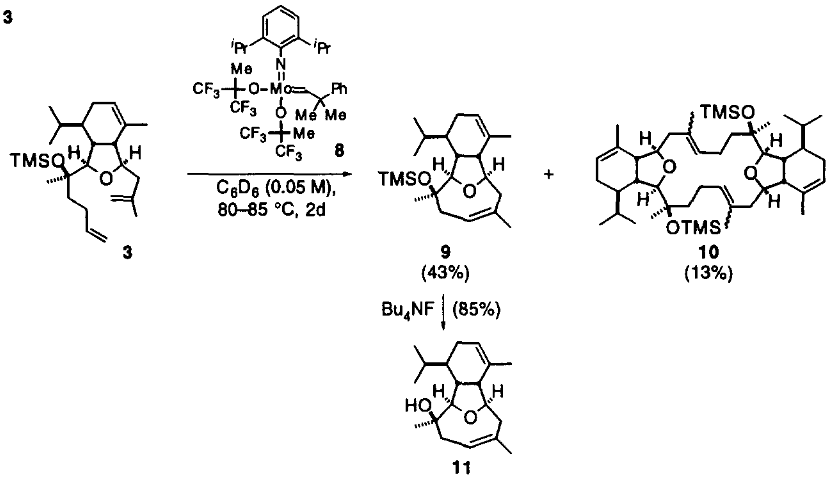


Scheme 2

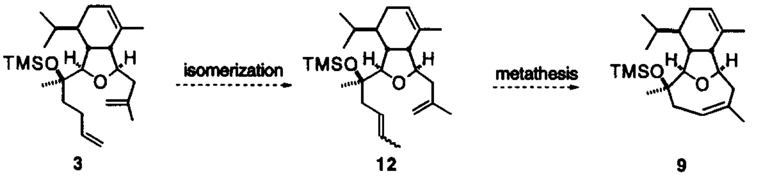


With a satisfactory route to **3** in hand, the key metal alkylidene mediated ring-closing diene metathesis was investigated. Attempted cyclization of **3** with bis(tricyclohexylphosphine)benzylidineruthenium dichloride[12] afforded a mixture of several compounds of undetermined structure. Reaction with 1 equiv of (2,6-diisopropylphenylimido)neophylidenemolybdenum bis(hexafluoro-*t*-butoxide) (**8**, 0.05 M)[13] in degassed benzene-d_6 did give two cyclized products (Scheme 3).[14,15] They were identified as siloxytricycle **9** (43%), containing an unexpected 8- and not the predicted 9-membered cyclic ether ring, and a single undetermined geometric isomer of symmetrical dimer **10** (13%). Deprotection of the former provided alcohol **11** whose ^{13}C NMR spectra did not match with that reported for 3-deacetoxy-6-deacetylcalicophirin B (**1**).[3] Careful analysis of **11**'s mass spectrum, IR spectrum, ^{1}H and ^{13}C NMR spectra, and NMR spectra obtained from distortionless enhancement by polarization transfer,[16] double-quantum-filtered correlated spectroscopy (DQF-COSY),[17] heteronuclear multiple-quantum coherence (HMQC),[18] and heteronuclear multiple-bond connectivity (HMBC)[18b,19] experiments confirmed its unexpected structure.[20]

Scheme 3



To our knowledge, formation of siloxytricycle **9** from treatment of siloxytriene **3** with molybdenum imido alkylidene complex **8** is the first example of the construction of a ring that is one carbon unit smaller than that anticipated from metal alkylidene mediated ring-closing diene metathesis. One possible explanation for this surprising result is that **3** isomerizes to siloxytrienes **12** prior to reaction with the metal alkylidene (eq 1).[21] When a solution of **3** in benzene-d_6 was maintained at 80 °C overnight, however, only starting material was returned. This result does not negate the possibility that the metal alkylidene (or an impurity) could induce isomerization; however, olefin isomerization with molybdenum catalysts has, to the best of our knowledge, no precedent.[22]



(eq 1)

In conclusion, during our efforts to install the hexahydrooxonin ring of 3-deacetoxy-6-deacetylcalicophirin B (**1**) using metal alkylidene mediated ring-closing diene metathesis, we isolated an unexpected product containing a tetrahydrooxacin ring. This result is the first example of ring-closing metathesis yielding a product that contains one less carbon unit than anticipated.

Acknowledgment. Support of this investigation by NIH Grant NS-12389 is gratefully acknowledged. NMR and mass spectra were determined at Irvine using instruments acquired with the assistance of the NSF and NIH shared instrumentation programs. We particularly thank Dr. D. W. C. MacMillan for providing diol **4**, Professors R. H. Grubbs, S. J. Miller and S. B. T. Nguyen for numerous discussions, and Professor D. J. Faulkner for providing copies of ^{1}H and ^{13}C NMR spectra of 3-deacetoxy-6-deacetylcalicophirin B.

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10. Trienol **7** and siloxytriene **3** were contaminated with approximately 10% of the disubstituted alkene regioisomers resulting from the carboalumination step.
11. Selected characterization data: **3**: a colorless oil; ^{1}H NMR (500 MHz, C_6D_6) δ 5.89 (ddt, *J* = 16.6, 10.3, 6.2 Hz, 1H), 5.43 (br s, 1H), 5.12 (d, *J* = 17.7 Hz, 1H) 4.91-5.00 (m, 2H), 4.91 (app s, 1H), 3.95 (td, *J* = 8.1, 3.5 Hz, 1H), 3.81 (d, *J* = 4.1 Hz, 1H), 2.43-2.53 (m, 3H), 2.26-2.31 (m, 2H), 2.10-2.13 (m, 2H), 1.52-1.97 (m, 4H), 1.85 (s, 3H), 1.67 (s, 3H), 1.17 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) 144.3, 139.5, 132.3, 122.4, 114.2, 112.2, 87.0, 82.5, 78.5, 49.3, 45.6, 41.4, 39.7, 39.3, 29.6, 28.0, 24.9, 23.7, 23.5, 23.1, 21.9, 17.7, 2.9; MS (EI) *m/z* 404.3110 (404.3110 calcd for $C_{25}H_{44}O_2Si$, M). **10**: a colorless solid, mp 166–170 °C; MS (FAB) *m/z* 775.5481 (775.5493 calcd for $C_{46}H_{80}NaO_4Si_2$, M+Na), 753, 751, 737, 663, 589. **11**: a colorless oil; MS (CI, isobutane) *m/z* 290.2237 (290.2246 calcd for $C_{19}H_{30}O_2$, M).
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14. Attempted metathesis reactions of trienol **7** with both the molybdenum and ruthenium alkylidene catalysts were unsuccessful, generating a mixture of several compounds of undetermined structure.
15. Extensive investigation of reaction conditions was precluded by the limited amounts of **3** that were available. Qualitatively similar results were seen in metathesis reactions of **3** employing 20 mol% of **8**.
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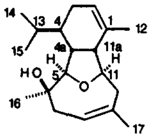
20. Key NMR data for **11** are summarized in Table 1.



11

Table 1. ^{1}H and ^{13}C NMR Data for Alcohol 11[a]

carbon	^{13}C (δ)	Multiplicity	^{1}H (δ), Multiplicity; *J* (Hz)	Connectivity[b]	
				Direct Carbon –Carbon	Long-Range Carbon–Hydrogen
1	133.5	0			3-II, 4a, 11, 12
2	122.3	1	5.40, d, 6.4	12,[d] 3-II	3-II, 4, 12
3	23.0	2	I: 2.22	3-II	2, 4a
			II: 1.89, dd, 17.7, 6.2	2, 3-I	
4	40.9	1	1.45,[c] m		
4a	40.7	1	3.13,t,7.4	5	
5	89.3	1	3.73, d, 7.2	4a	4a, 11, 16
6	77.0	0			4a, 16
7	38.3	2	I and II: 2.23		5, 8, 16
8	124.4	1	5.57, m	17[d]	10-II, 17
9	136.8	0			10-II, 11, 17
10	40.8	2	I: 2.25[c]	10-II	
			II: 1.98, dd, 13.9, 7.2	10-I, 11	
11	80.3	1	4.19, dd, 6.8, 4.4	10-II	5, 10-II
11a	48.4	1	2.25		2, 4, 4a, 10-II, 12
12	21.7	3	1.58, s	2[d]	
13	30.4	1	1.55, m	14, 15	3-II, 14, 15
14	21.9	3	0.89, d, 6.4	13	
15	21.4	3	1.01, d, 6.8	13	
16	31.3	3	1.32, s		
17	26.1	3	1.72, s	8[d]	8, 10-II

[a] Spectra were measured in C_6D_6 at 70 °C. [b] Only definite connectivities are reported; numbers refer to hydrogens. [c] Assignments for H-4 and H-10 may be interchanged. [d] The homonuclear correlation is due to allylic coupling.

21. The alkene region was very complex and would have precluded the detection of **12** in metathesis reactions that were followed by ^{1}H NMR. At short reaction times, the ratio of **9**:**10** was ~1:1.
22. (a) Double bond isomerization has been seen with Ru-based catalysts.[23] (b) Another potential explanation, which to our knowledge also lacks precedent, would involve β-hydride elimination of the molybdenum alkylidene derived from metathesis of the terminal vinyl group to generate a molybdenum hydride, which would form the analog of **3** having a propenyl, rather than a butenyl, side chain upon reductive elimination.[24]
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