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A synthesis of the bicyclo[3.3.0]octene core of geodin A

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Abstract—A synthesis of the bicyclo[3.3.0]octene core of the macrolactam tetramic acid geodin A is described. The key steps are a tandem metathesis and a Wharton rearrangement.

In 1999, Capon et al. described the structure of geodin A magnesium salt (Fig. 1), a tetramic acid-containing macrolactam isolated from a *Geodia* sp. sponge collected from the Great Australian Bight.[1]

Geodin A is the most recently isolated member of a growing class of tetramic acid-containing macrolactams including cylindramide A,[2] aburatubolactam A,[3] xanthobaccin A,[4] ikarugamycin,[5] discodermide,[6] and the alteramides.[7] These mixed polyketide-amino acid metabolites have been isolated from a number of sources including marine sponges, marine bacteria, and terrestrial bacteria,[8] and display a diverse range of biological activities including cytotoxicity, anti-microbial activity, and inhibition of superoxide generation. Intrigued by the questions relating to the biogenesis of compounds in this class, and motivated by their synthetically challenging structures and potent biological activity, we have initiated a program directed toward the synthesis of several of these compounds,[9] and in this letter we report a concise synthesis of the bicyclo[3.3.0]octadiene core of geodin A.

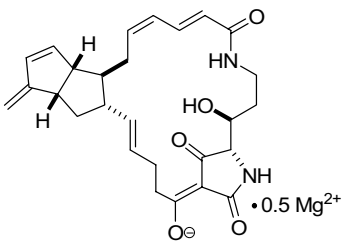

Figure 1. Geodin A.

Our strategy for the synthesis of geodin A is based on the coupling of two domains: a subunit containing the bicyclo[3.3.0]octene **1**, and a 3-hydroxyornithine-derived subunit (Fig. 2, **2**). The bicyclo[3.3.0]octene was envisioned to arise from **3**, which would ultimately arise from a tandem ring-opening–ring-closing–cross metathesis of functionalized bicyclo[2.2.1]heptene **4** with alkenyl ester **5**.[10]

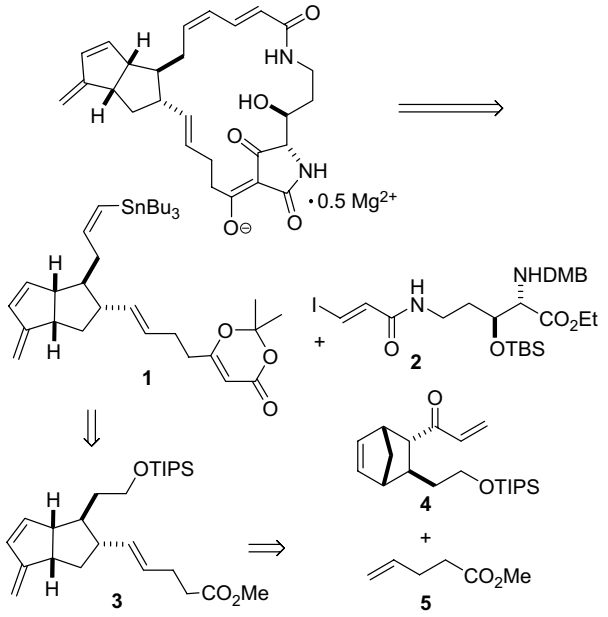

Figure 2. Abbreviated retrosynthesis of geodin A.

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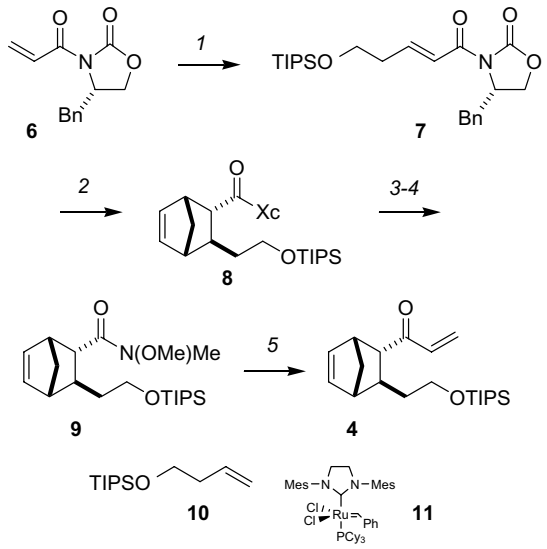
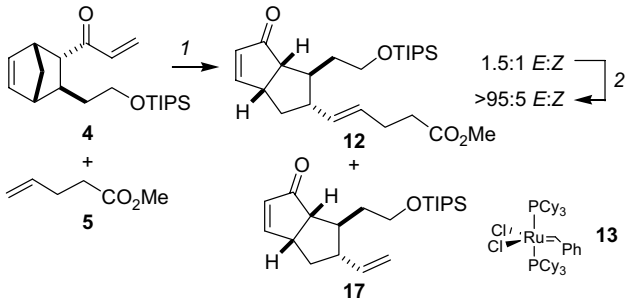


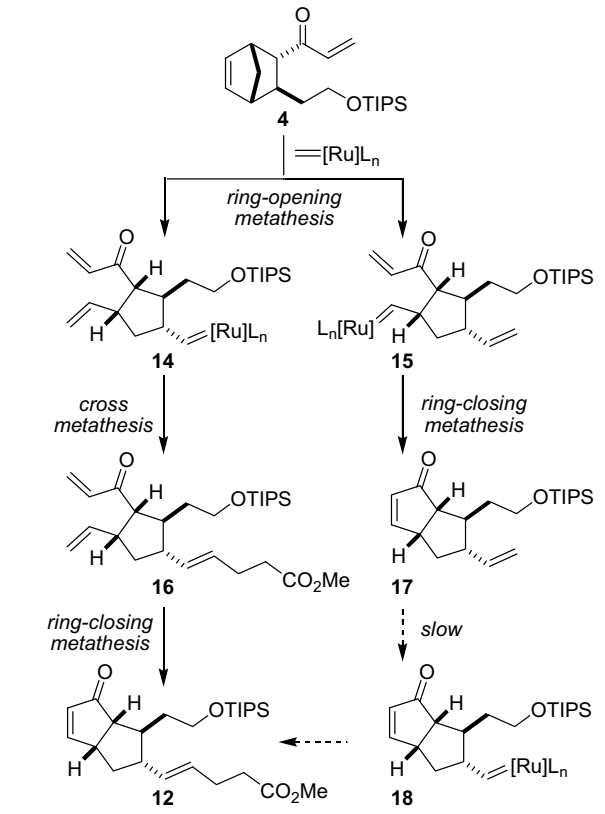
Scheme 1. Reagents and conditions: (1) 5 mol % **11**, 1.2 equiv **10**, CH_2Cl_2, 45 °C, 81%, >99:1 *E*:*Z*; (2) cyclopentadiene, Et_2AlCl, CH_2Cl_2, −78 °C, 96%, dr > 45:1; (3) LiOH, H_2O_2, THF–H_2O, −10 °C to 0 °C, 77%; (4) HN(OMe)Me. HCl, EDCI, CH_2Cl_2, 75%; (5) vinylmagnesium bromide, THF, reflux, 98%.

The synthesis of the metathesis precursor **4** is detailed in Scheme 1. Cross metathesis of *N*-acryloyl oxazolidinone **6** with triisopropylsilyl-protected butenol **10** in the presence of 5 mol % of **11** provided **7** in 81% yield and with >99:1 *E*:*Z* selectivity.[11] Diels–Alder reaction of **7** with cyclopentadiene in the presence of Et_2AlCl[12] proceeded to give **8** in excellent yield and diastereoselectivity (96%, >45:1). Norbornene **8** was converted to the corresponding Weinreb amide **9** by a two step sequence consisting of hydrolysis with LiOH–H_2O_2 (77% yield),[13] followed by EDCI-mediated coupling with *N*-methoxy-*N*-methylamine (75% yield). Subsequent reaction of amide **9** with excess vinylmagnesium bromide in THF at reflux provided the desired enone **4** in 98% yield, and set the stage for the key tandem ROM-RCM-CM sequence.

When a solution of enone **4** and 2.5 equiv of alkene **5**, in CH_2Cl_2 at reflux, was exposed to 4 mol % of catalyst **13**, tandem ring-opening–ring-closing–cross metathesis occurs to provide the bicyclo[3.3.0]octene **12** in 54% yield and with an *E*:*Z* ratio of 1.5:1, along with 30% of **17** (Scheme 2). The *E*:*Z* ratio for **12** could be improved to



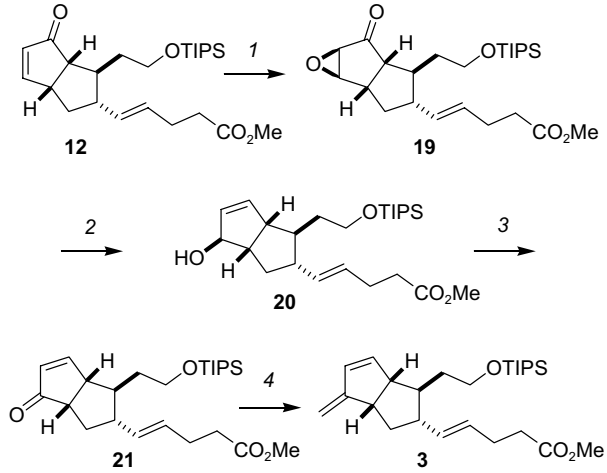
Scheme 2. Reagents and conditions: (1) 4 mol % **13**, 2.5 equiv of **5**, CH_2Cl_2, 45 °C, 54% of **12**, and 30% of **17**; (2) PhSH, AIBN, PhMe, 110 °C, 84%.



Scheme 3. Pathways for the tandem ring-opening–ring-closing–cross metathesis.

>95:5 *E*:*Z* by radical isomerization employing PhSH and AIBN in toluene.

Preliminary mechanistic studies suggest that the tandem ring-opening–ring-closing–cross metathesis occurs via the sequence shown in Scheme 3. Initial non-selective ring-opening metathesis of the norbornene leads to intermediates **14** and **15**. Compound **14** can undergo productive cross metathesis to yield **16**, which can be readily ring-closed to yield the desired product **12**. Inter-



Scheme 4. Reagents and conditions: (1) 30% H_2O_2, NaOH, MeOH–THF, −5 °C, 92% (dr > 95:5); (2) H_2NNH_2, AcOH, EtOH, rt; (3) Dess–Martin periodinane, CH_2Cl_2, rt, 80% (two steps); (4) Cp_2TiMe_2, PhMe, 58%.

mediate **15** can undergo ring-closing metathesis to yield **17**, which does not readily undergo cross metathesis.[14]

At this juncture transposition of enone was necessary, and we were attracted to the possibility of employing the Wharton fragmentation[15] of epoxy ketones to effect this transformation. To this end, epoxidation of enone **12** with hydrogen peroxide under basic conditions yielded α,β-epoxy ketone **19** in 92% yield and as a single diastereoisomer (Scheme 4). Despite limited precedent for the use of the Wharton fragmentation on complex substrates,[16] subjecting an ethanolic solution of **19** to hydrazine and catalytic acetic acid resulted in hydrazone formation and in situ Wharton fragmentation to give the desired allylic alcohol **20**. Subsequent Dess–Martin oxidation yielded enone **21** in 80% yield for the two steps. Olefination of compound **21** with the Petasis reagent[17] provided **3**[18] in 58% yield, and completed the synthesis of the carbocyclic core of geodin A.

In conclusion, we have described a concise 11-step synthesis of the bicyclo[3.3.0]octadiene core of geodin A. The synthesis features an efficient tandem ring-opening–ring-closing–cross metathesis reaction and the Wharton fragmentation of an α,β-epoxy ketone as the key steps. Further progress towards the total synthesis of geodin A will be reported in due course.

Acknowledgments

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14. Resubjecting **17** to the reaction conditions results in less than 10% conversion to the desired product and other metathesis catalysts were also ineffective for this cross metathesis.
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18. $[\alpha]_D$ +84.4 (*c* 0.05, $CHCl_3$); IR (thin film): 2919.59, 2862.51, 1749.49, 1455.95, 1097.17 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.06–6.08 (m, 1H), 5.96–5.97 (m, 1H), 5.39–5.44 (m, 1H), 5.24–5.28 (m, 1H), 4.79 (d, 2H, $J = 66.0$ Hz), 3.71–3.80 (m, 2H), 3.66 (s, 3H), 3.03–3.09 (m, 1H), 2.88–2.91 (m, 1H), 2.33–2.37 (m, 2H), 2.27–2.31 (m, 2H), 2.04–2.17 (m, 2H), 1.79–1.85 (m, 1H), 1.30–1.44 (m, 1H), 1.15–1.22 (m, 2H), 1.05–1.07 (m, 3H), 1.05 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.90, 142.38, 134.24, 131.60, 128.31, 103.08, 94.39, 90.03, 62.58, 57.62, 47.91, 45.64, 40.48, 37.05, 34.13, 29.69, 27.89, 18.04, 11.98; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{44}O_3SiNa$ (M^++Na) 455.2951, found 455.2943.