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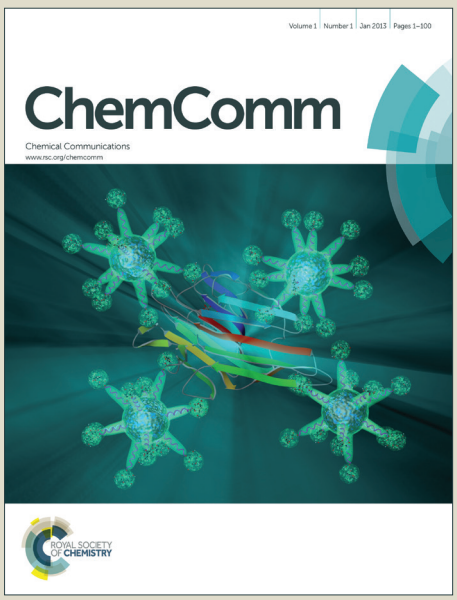

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Total Synthesis of (−)-Exiguolide via An Organosilane-Based Strategy†

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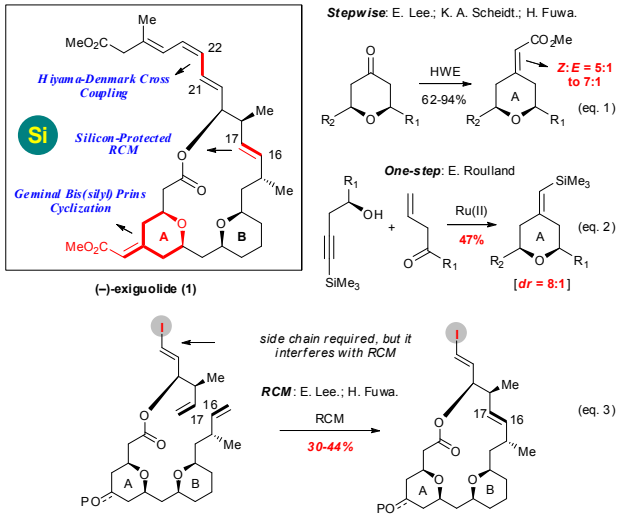
An organosilane-based strategy has been used to accomplish a convergent total synthesis of (-)-exiguolide. The key steps involve: 1) geminal bis(silyl) Prins cyclization to construct the A ring; 2) silicon-protected RCM reaction to construct the 20-membered macrocycle; and 3) Hiyama-Denmark cross-coupling of vinylsilane with vinyliodide to install the triene side chain.

(−)-Exiguolide (**1**) was isolated from the marine sponge *Geodia exigua* Thiele by Ohta and co-workers in 2006 (Scheme 1).[1] This unique, 20-membered macrolide inhibits fertilization of the gametes of sea urchin (*H. pulcherrimus*) but not embryogenesis of the fertilized egg, implying it may possess anticancer activity,[2] which was recently confirmed when **1** was found to inhibit proliferation of various cancer cell lines.[3] Cossy[4] proposed that **1** may even be a structurally simpler analogue of naturally occurring bryostatins,[5] which exhibit excellent activity against a wide range of cancers and other non-cancer diseases. Given that detailed investigations of **1** are hampered by its low natural abundance, the synthetic community has expended substantial effort to prepare the compound in the laboratory.[3, 6]

One of the most distinctive structural features of **1** is a methylene bis-*cis*-tetrahydropyran motif, in which the A ring contains an unusual exocyclic *Z*-methyl enoate.[7] Both Scheidt[3a] and Fuwa[3b-c] have shown that while the *Z*-isomer inhibits the growth of cancer cell lines, the *E*-isomer shows only minimal biological activity. Therefore efficient synthesis of **1** requires stereocontrolled assembly of the structurally unique A ring. In the previous total syntheses of **1**, three groups[3a, 6a-b] constructed the A ring using a stepwise strategy in which the *cis*-pyranone was generated first, followed by Fuji's asymmetric Horner–Wadsworth–Emmons reaction.[8] *Z*/*E* selectivity ranged from only 5:1 to 7:1 (Scheme 1, eq. 1). This moderate *Z*-selectivity probably reflects the fact that substitutions at C4 and C5 are methylene groups, which exert no steric or electronic bias to control enoate geometry. Roulland[6c-d] constructed the A ring in a single step via a ruthenium-catalyzed ene–yne cross-coupling/Michael addition process developed by Trost,[9] but the key step showed only moderate yield of 47% and a *cis*:*trans* ratio of 8:1 (Scheme 1, eq. 2). In addition, both Lee[6a] and Fuwa[3b] found that the C20-C21 vinyl iodide moiety, which is required to install the side chain, interfered severely with the RCM reaction to form the *E*-C16-C17 double bond. As a result, the macrocycle was constructed in only low to moderate yield with poor reproducibility (Scheme 1, eq. 3).

We envisioned solving all these synthetic challenges using an organosilane-based strategy involving the following steps (Scheme 1): (1) geminal bis(silyl) Prins cyclization[10] to construct the A ring and establish *cis*-*Z* stereochemistry in one step; (2) After Prins cyclization/bromination[11] to construct the B-ring, a silicon-protected RCM reaction[12] to give a 20-membered macrocycle via *E*-



Scheme 1 Organosilane-based strategy for the synthesis of (-)-exiguolide (upper left). Stepwise construction of the A ring (eq. 1). One-step construction of the A ring (eq. 2). Vinyliodide interferes with the RCM reaction that forms the macrocycle (eq. 3).

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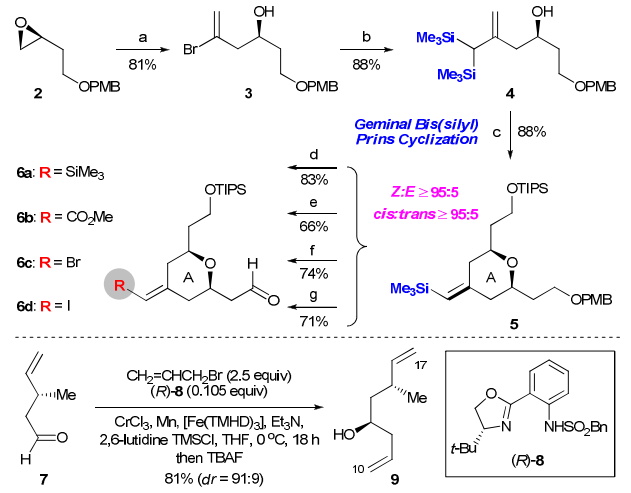
C16-C17 double bond formation; and (3) Hiyama-Denmark cross-coupling[13] of the silyl group (reacting as vinylsilane) and vinyliodide to install the triene side chain. Here we report detailed studies of this organosilane-based total synthesis of (−)-exiguolide (**1**).

We began our synthetic efforts from the known chiral epoxide **2**.[14] Epoxide ring opening by 1-trimethylsilylvinyl magnesium bromide and subsequent bromination gave vinyl bromide **3** in 81% yield.[15] Pd(0)-catalyzed Kumada coupling of **3** with bis(trimethylsilyl) magnesium chloride gave the key precursor **4** in 88% yield.[16] TMSOTf-promoted Prins cyclization of **4** with $TIPSOCH_2CH_2CHO$ constructed the A ring, generating the desired tetrahydropyran **5** in 88% yield with exclusive *cis*-*Z* selectivity.[10a] From **5**, four aldehydes containing different R groups were synthesized with retention of the *Z* configuration: **6a** (R = $SiMe_3$), **6b** (R = CO_2Me), **6c** (R = Br) and **6d** (R = I).[17] These aldehydes were used directly in Prins cyclization/bromination with homoallylic alcohol **9** to form the B ring. To prepare **9**, we subjected the known aldehyde **7**[18] to Kishi's Fe/Cr-mediated asymmetric allylation.[19] Sulfonamide (*R*)-**8** proved the most effective chiral ligand, giving **9** in 81% yield with 91:9 *dr*.

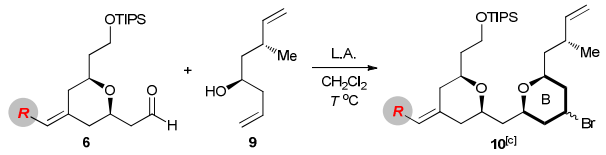
First, Prins cyclization/bromination to form the B ring was tested using **6a** at −78 °C with $Me_3SiBr/InBr_3$, which was developed by Loh[20] as the combined bromine source and Lewis acid to promote a non-racemic Prins cyclization.[21] Unfortunately, the cyclized product **11** was obtained in 44% yield rather than **10a**, with concurrent elimination of the silyl group (Table 1, entry 1). Replacing **6a** with the CO_2Me-substituted aldehyde **6b** gave the desired product **10b** as a 3:2 mixture of two bromo-isomers, but in a low yield of 30% (entry 2). No racemization was essentially observed, since the mixture of **10b** collapsed into a single product after bromide removal. Two major by-products were **12b** (28%) and **13** (23%). Promoting cyclization by Rychnovsky's protocol[22] using 2.2 equiv of $SnBr_4$ afforded a higher yield of 45% at temperatures from −78 to −20 °C with no loss of optical purity, but the reaction still generated substantial proportions of **12b** and **13** (entry 3). Similar results were observed in the reaction of Br-substituted aldehyde **6c**, although the yield of **10c** was higher at 59% (entry 4). To our delight, cyclization of I-substituted aldehyde **6d** with **9** proceeded smoothly to give **10d** in 86% yield with no detectable production of **12d** or **13** (entry 5).

The results in Table 1 indicate that the exocyclic R group on the A ring, although it lies far from the reactive site on the nascent B ring, nevertheless strongly influences the reaction course. We propose the following mechanism to rationalize this interesting effect (Scheme 3). Condensation of aldehyde **6** with **9** occurs first to generate the oxacarbenium **14**. Normally, the Prins



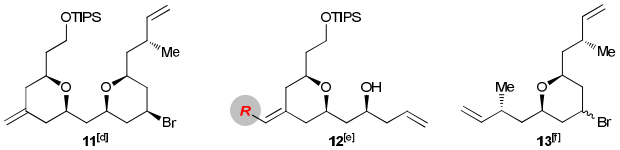
Scheme 2 Synthesis of the A ring. (a) (1) CH_2=CH($SiMe_3$)MgBr, CuCN, THF, -30 °C to rt, 1 h. (2) Br_2, MeONa/MeOH, CH_2Cl_2, -78 °C to rt, 2 h, 81%, 2 steps; (b) $(Me_3Si)_2CHMgCl$, MeMgCl, 5 mo% $Pd(PPh_3)_4$, THF, 40 °C, 10 h, 88%; (c) $TIPSOCH_2CH_2CHO$, TMSOTf, Et_2O, -78 °C, 15 min, 88%; (d) (1) DDQ, CH_2Cl_2/H_2O, 0 °C, 3 h. (2) IBX, THF/DMSO, rt, 30 min, 83%, 2 steps; (e) (1) NIS, CH_3CN/DMF, 0 °C, 1.5 h, 86%. (2) 15 mol% $PdCl_2(CH_3CN)_2$, dppf, CO, Et_3N, MeOH, DMF, 80 °C, 5 h, 93%. (3) DDQ, CH_2Cl_2/H_2O, 0 °C, 3 h. (4) IBX, THF/DMSO, rt, 30 min, 78%, 2 steps; (f) (1) NBS, DMF, 0 °C, 3 h, 91%. (2) DDQ, CH_2Cl_2/H_2O, 0 °C, 3 h. (3) IBX, THF/DMSO, rt, 30 min, 81%, 2 steps; (g) (1) NIS/ CH_3CN/DMF, 0 °C, 1.5 h, 86%. (2) DDQ, CH_2Cl_2/H_2O, 0 °C, 3 h. (3) IBX, THF/DMSO, rt, 30 min, 83%, 2 steps.

Table 1 Screening of Prins Cyclization/Bromination Conditions.[a]



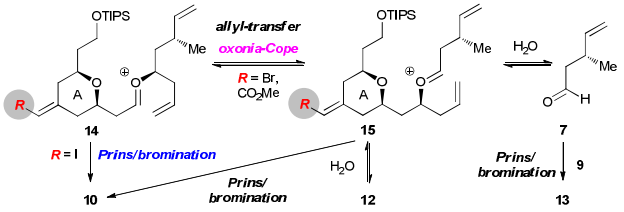
6 9 10[c]

Entry	6	Br source/L.A. (equiv)	*T* (°C)	Product (yield%[b])
1	**6a**	$TMSBr/InBr_3$ (1.2/0.2)	-78	**10a** (0); **11** (44)
2	**6b**	$TMSBr/InBr_3$ (1.2/0.2)	-78	**10b** (30); **12b** (28); **13** (23)
3	**6b**	$SnBr_4$ (2.2)	-78 to -20	**10b** (45); **12b** (22); **13** (55)
4	**6c**	$SnBr_4$ (2.2)	-78 to -20	**10c** (59); **12c** (14); **13** (9)
5	**6d**	$SnBr_4$ (2.2)	-78 to -20	**10d** (86); **12d** (0); **13** (0)



11[d] 12[e] 13[f]

[a] Reaction conditions: 0.15 mmol of **6**, 0.18 mmol of **9** in 2.0 mL of CH_2Cl_2. [b] Isolated yields after purification by silica gel column chromatography. [c] **10b**-**10d** were obtained as mixtures of two bromo-isomers in ratios ranging from 1:1 to 2:1; these mixtures collapsed into a single product after bromide removal. [d] The *cis*/*cis* stereochemistry on the B ring was assigned based on the results from ref. 20a. [e] The 1,3-*syn* stereochemistry was assigned based on the results from ref. 23. [f] **13** was obtained as a mixture of two bromo-isomers in ratios ranging from 6:4 to 7:3; the major isomer was characterized.



Scheme 3 Rationalization of the formation of **10**, **12** and **13** in the Prins cyclization/bromination reaction of **6b**-**6d** with **9**.

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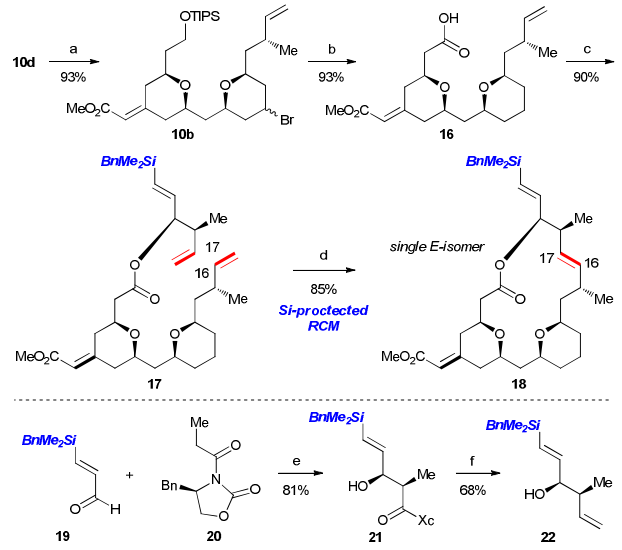
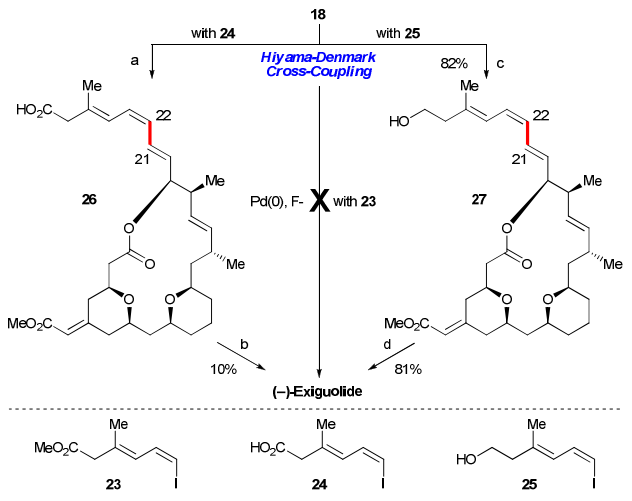
cyclization/bromination of **14** should form the B ring to give the desired cyclized product **10**. However, if the oxonia-Cope rearrangement of **14** is more favorable than Prins/bromination, then enantioselective allyl transfer[23] should occur, generating oxacarbenium **15**. While **15** can still undergo cyclization to give **10**, it can also undergo H_2O-promoted dissociation to generate by-product **12** and aldehyde **7**. Further Prins cyclization/bromination of **7** with **9** would afford another by-product **13**. We speculate that the electronic effect of the R group plays a key role in determining the actual reaction pathways. Because bromine is more electronegative than iodine, its stronger electron-withdrawing inductive effect should make the A ring more electron-deficient, driving oxonia-Cope rearrangement of **14** to generate the more stable oxacarbenium **15**. The ester group also destabilizes **14** but probably by an electron-withdrawing conjugation effect, which renders the corresponding A ring more electron-deficient.

Continuing the synthesis from **10d**, we subjected this compound to Pd(0)-catalyzed carbonylation[9] to deliver methyl enoate **10b** in 93% yield (Scheme 4). Then **10b** was converted to the acid **16** in 93% yield over the following four steps: reduction of the bromide on the B ring with $NaBH_4/InBr_3$,[24] removal of the silyl group to generate a primary alcohol, oxidation with Dess–Martin periodinane[25] to the aldehyde, and finally Pinnick oxidation.[26] The requisite vinylsilyl fragment **22** was prepared from aldehyde **19**[27] and chiral oxazolidinone **20**, which underwent Evans' asymmetric aldol[28] reaction to give **21** in 81% yield with ≥ 95:5 *dr*. This product was then subjected to Weinreb amide formation,[29] reduction to an aldehyde and Wittig olefination to generate **22** in 68% yield over three steps. Esterification of acid **16** with the **22** provided **17** in 90% yield. As expected, the bulky, inert silyl group at C21 effectively prevented the C20-C21 double bond from interfering with the RCM reaction in which the C16-C17 alkene formed. Macrocyclization catalyzed by 10 mol% Hoveyda-Grubbs second-generation catalyst[30] proceeded cleanly, affording macrocycle **18** in 85% yield as a single *E*-isomer.

Following the silicon-protected RCM reaction, the dimethylbenzyl silyl group[31] in **18** was ready (as vinylsilane) to undergo Hiyama-Denmark cross-coupling with vinyliodide **23**-**25**[32] to install the triene side chain (Scheme 5). Considerable attempts using various Pd(0) catalysts and fluorine sources failed to work for the ester-substituted vinyliodide **23**. This fragment was unstable in the presence of F^- and it decomposed quickly before any coupling could occur. Based on the hypothesis that **23** may be prone to double bond isomerization via F^--promoted enolization, we selected the acid-substituted **24** as an alternative coupling partner. The target compound was indeed obtained after methylation, but only in 10% yield because of the low coupling efficiency to form acid **26**. Successful coupling was finally achieved using primary hydroxyl-substituted vinyliodide **25**, which was assembled with **18** to give triene **27** in 82% yield. Although Pd(0) catalyst is generally effective enough to promote Hiyama-Denmark cross-coupling, we found Cu(I) to be essential for high reaction efficiency; no coupling occurred in the absence of 1.0 equiv of CuI.[33] Subsequent Dess-Martin oxidation of **27** to aldehyde, Pinnick oxidation to acid, and methylation with Me_3SiCHN_2 in MeOH/benzene produced (-)-exiguolide in 81% yield over three steps. Spectroscopic data for synthetic **1** were identical to those reported for the naturally occurring compound and for compound produced by other synthetic methods ($[\alpha]^D_{20}$ = – 84.6 [*c* 0.09 in $CHCl_3$], ref.[1] $[\alpha]^D_{20}$ = – 92.5 [*c* 0.069 in $CHCl_3$]).



Scheme 4 Synthesis of the macrocycle. (a) 15 mol% $PdCl_2(CH_3CN)_2$, dppf, CO, Et_3N, MeOH, DMF, 80 °C, 5 h, 93%; (b) (1) $NaBH_4$, $InBr_3$, THF, rt, 2 h. (2) HF•Pyridine, THF, rt, 1 h, 95%, 2 steps. (3) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt. (4) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, THF/*t*-BuOH/H_2O, rt, 1 h, 98%, 2 steps; (c) **22**, DIC, DMAP, CH_2Cl_2, rt, 4 h, 90%; (d) 10 mol% HG-II, benzene, reflux, 22 h, 85%; (e) Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C, 15 min, then **19**, -78 to -20 °C, 2 h, 81%, *dr* ≥ 95:5; (f) (1) NH(OMe)Me•HCl, $AlMe_3$, CH_2Cl_2, -15 to 0 °C, 1 h. (2) $LiAlH_4$, THF, 0 °C, 20 min. (3) Ph_3PCH_3I, *t*-BuOK, THF, 0 °C, 1 h, 68%, 3 steps.



Scheme 5 Hiyama-Denmark cross-coupling to install the triene side chain. (a) **24** (1.5 equiv), 10 mol% $[allylPdCl]_2$, 20 mol% Ruphos, TBAF, THF, rt to 50 °C, 3 h; (b) $TMSCHN_2$, MeOH/benzene, rt, 10 min, 10%, 2 steps; (c) **25** (1.5 equiv), 10 mol% $Pd(PPh_3)_4$, 100 mol% CuI, TBAF, Et_3N, THF, 30 °C, 3 h, 82%; (d) (1) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 1 h. (2) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, THF/*t*-BuOH/H_2O, rt, 1 h. (3) $TMSCHN_2$, MeOH/benzene, rt, 10 min, 81%, 3 steps.

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In summary, we have completed a convergent total synthesis of (-)-exiguolide from the known chiral epoxide **2** in 16.8% yield over 19 steps as the longest linear path. The synthesis relies on an organosilane-based strategy to overcome most synthetic challenges. Employing the geminal bis(silyl) Prins cyclization allowed one-step construction of the A ring with exclusive *cis-Z* stereochemical control. A silicon-protected RCM reaction substantially improved on the low efficiency of previous efforts to form the macrocycle. The silyl group persisted as vinylsilane, which underwent Hiyama-Denmark cross-coupling with vinyliodide to furnish the triene side chain. Further studies including synthesis and biological evaluations of (-)-exiguolide analogues are underway.

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