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Titanium(II)-mediated cyclization of (silyloxy)enynes: a synthesis of the C9–C19 subunit of dictyostatin-1

Gregory W. O'Neil and Andrew J. Phillips*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215, USA

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Abstract—Cyclization of (silyloxy)enynes with $ClTi(i\text{-}PrO)_3$ and *i*-PrMgCl gives cyclic siloxanes. This cyclization offers a new approach to mixed polyacetate-polypropionate polyketides, and has been applied to the synthesis of the C9–C19 subunit of dictyostatin-1.

Dictyostatin-1 (Fig. 1) is a marine-derived macrolide that was first isolated by Pettit et al. from a *Spongia* sp. marine sponge collected in the Republic of Maldives.[1] Dictyostatin-1 displays potent growth inhibition of the P388 murine leukemia cell line (ED_{50} 0.38 ng mL^{-1}), along with differential cytotoxicity in the NCI 60-cell line screen with sub-nanogram per milliliter ED_{50} values against other cancer cell lines such as NCI H460 non-small cell lung, KM 20L2 colon, SF-295 CNS, SK-MEL5 melanoma, OVCAR-3 ovarian, and A-498 renal.

Recent research at the Harbor Branch Oceanographic Institute described the isolation of dictyostatin-1 from a *Corallistidae* sp. lithistid sponge.[2] This material was used to assign the stereochemistry of dictyostatin-1[3] and also allowed further preliminary testing that illustrated two very important features of dictyostatin-1's biological profile: (i) it inhibits cell growth by the same mechanism of action as paclitaxel (tubulin polymerization), and (ii) it demonstrates potent activity against paclitaxel-resistant lines such as MCF-7/ADR and MES-SA/DX5.

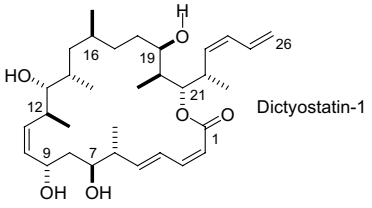
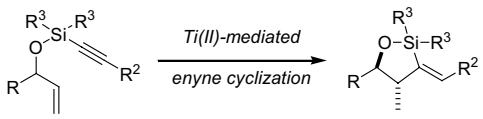


Figure 1. Dictyostatin-1.

Because of dictyostatin-1's potent biological activity, and limited supply from the natural source,[2] we have embarked on a total synthesis of dictyostatin-1. In considering a strategy for the synthesis of dictyostatin-1, we were attracted to the possibility of exploiting the cyclization of enynes by group 4 metals as a new approach to cyclic siloxanes (Scheme 1). We envisaged that cyclic siloxanes would provide versatile templates for the synthesis of the C1–C7, C9–C13, and C21–C26 regions of dictyostatin-1.

Five-membered cyclic siloxanes are traditionally synthesized[4] by intramolecular hydrosilylation of homopropargyl alkynols, radical additions to tethered alkynyl silanes, ring opening of alkylidenesiliranes, or silylformylation of alkynes, and have proven to be useful intermediates for the synthesis of a variety of polyketide functional group arrays.[5] In this Letter we describe our



Scheme 1. Synthesis of cyclic siloxanes by titanium(II)-mediated enyne cyclization.

Keywords: Total synthesis; Dictyostatin; Enyne cyclization.
* Corresponding author. Tel.: +1-303-735-2049; fax: +1-303-492-0439; e-mail: andrew.phillips@colorado.edu

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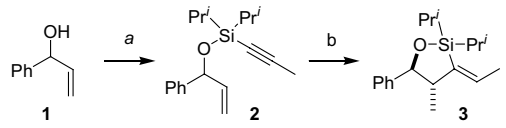


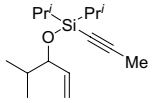
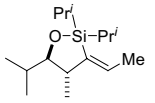
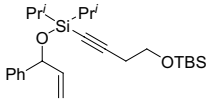
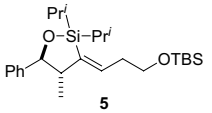
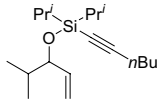
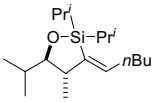
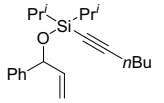
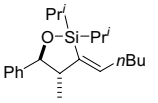
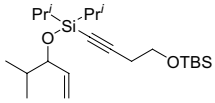
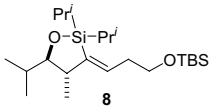
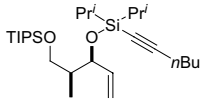
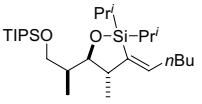
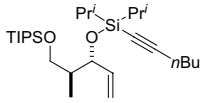
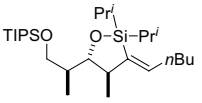
Scheme 2. Reagents and conditions: (a) bromodiisopropylpropynylsilane, DMAP, DMF, quantitative; (b) $ClTi(i\text{-}PrO)_3$, *i*-PrMgCl, Et_2O, −40 °C, 65%.

preliminary studies on a new synthesis of cyclic siloxanes based on a Ti(II)-mediated cyclization of (silyloxy)enynes, along with the successful application of this reaction to the synthesis of the C9–C19 subunit of dictyostatin-1.

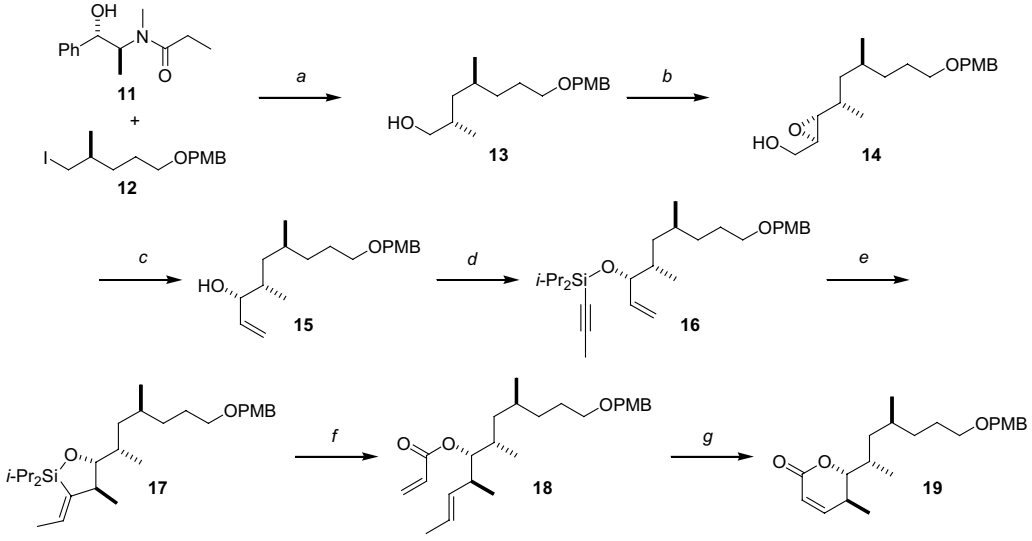
Our initial studies focused on readily accessible (silyloxy)enyne **2**, which was prepared by silylation of alcohol **1** with bromodiisopropylpropynylsilane (Scheme 2).[6] While a variety of reagents such as Pd(0), Zr(II), and other sources of Ti(II) were not suitable, we were pleased to discover that the desired cyclization could be effected with $(\eta^2\text{-propene})Ti(i\text{-}PrO)_2$ generated in situ from $ClTi(i\text{-}PrO)_3$ and *i*-PrMgCl at −40 °C.[7] Under these conditions **2** was cyclized to produce **3** as a single diastereoisomer in 65% yield.[8]

Further examples that illustrate the scope of this transformation are presented in Table 1.[9,10] As can be seen from the table a variety of systems are suitable as substrates, and the reaction produces exclusively the *anti* diastereoisomer.[11] It is noteworthy that the reaction can be applied to the synthesis of *syn*,*anti*- and *anti*,*anti*-stereotriads (entries 6 and 7 to produce compounds **9** and **10**, respectively).

Table 1. Reagents and conditions: $ClTi(i\text{-}PrO)_3$, *i*-PrMgCl, Et_2O, −40 °C

Entry	Substrate	Product	Yield (%)
1		 **4**	58
2		 **5**	57
3		 **6**	57
4		 **7**	58
5		 **8**	56
6		 **9**	53
7		 **10**	58

With conditions for the cyclization of (silyloxy)enynes established, we turned our attention to utilizing this transformation for the synthesis of the alkenyl substituted C9–C14 stereotriad of dictyostatin-1.[12] The synthesis began with the Myers alkylation[13] of pesudoephedrine derived amide **11** with iodide **12**, and subsequent reduction with lithium amidotrihydroborate



Scheme 3. Reagents and conditions: (a) (1) LDA, LiCl; (2) LiH_2NBH_3, 65% (two steps); (b) (1) Dess–Martin then Ph_3PCHCO_2Et; (2) DIBAL-H; (3) (−)-DIPT, $Ti(i\text{-}PrO)_4$, TBHP, 56% (three steps); (c) I_2, Ph_3P, imidazole then *t*-BuLi, 85%; (d) bromodiisopropylpropynylsilane, DMAP, DMF, 95%; (e) $ClTi(i\text{-}PrO)_3$, *i*-PrMgCl, 59%; (f) (1) TBAF, THF; (2) acryloyl chloride, Hünig's base, DMAP, 62% (two steps); (g) 5% $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$, PhH, 60 °C, 85%.

(LAB)[14] to give alcohol **13** in 65% yield over the two steps (Scheme 3). Alcohol **13** was advanced to epoxy alcohol **14** by a three-step sequence (56% overall yield) consisting of: (a) Dess–Martin oxidation–Wittig olefination; (b) DIBAL reduction, and (c) Sharpless asymmetric epoxidation. Installation of the allylic alcohol was achieved by conversion of this alcohol to the iodide, followed by immediate reaction with *tert*-BuLi[15] to provide allylic alcohol **15** in 85% yield. Subsequent silylation of alcohol **15** with bromo diisopropylpropynylsilane led to (silyloxy)enyne **16** in 95% yield. Treatment of a solution of **16** and $ClTi(i\text{-}PrO)_3$ with *i*-PrMgCl under conditions established in our preliminary studies produced cyclic siloxane **17** in 59% yield as a single diastereoisomer. Removal of the silicon (TBAF) and acylation with acryloyl chloride (65% over two steps, **17** → **18**), followed by ring-closing metathesis with Grubbs' $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ catalyst[16] provided lactone **19** in 85% yield, and completed the synthesis of the C9–C19 subunit of dictyostatin-1.

In summary, we have demonstrated that (silyloxy)enynes can be cyclized by in situ generated $(\eta^2\text{-propene})Ti(i\text{-}PrO)_2$. The reaction proceeds with excellent diastereoselectivity to provide cyclic siloxanes with an *anti* relationship between the oxygen and methyl bearing carbons. Mechanistic studies are ongoing, and further applications of this transformation to the synthesis of dictyostatin-1 will be reported in due course.

Acknowledgements

We thank the University of Colorado for support of this research.

References and notes

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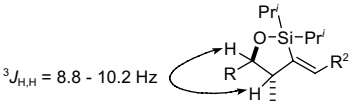
5. For examples of the use of cyclic siloxanes as synthetic intermediates see: (a) Marshall, J. A.; Ellis, K. C. *Org. Lett.* **2003**, *5*, 1729; (b) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373; (c) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835; (d) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153.
6. Synthesized from propynyllithium by silylation with chlorodiisopropylsilane and subsequent bromination with NBS (98% yield over two steps). The other bromo diisopropylalkynylsilanes were generated by the same approach. Silylation of the appropriate allylic alcohols with bromo diisopropylalkynylsilanes proceeds in >95% yields to provide the (siloxy)enynes for cyclization. Details will be reported in a full paper.
7. To the best of our knowledge the cyclization of (silyloxy)enynes by Ti(II) or Zr(II) reagents to produce cyclic siloxanes is not known. For recent reviews of the chemistry of these species see: (a) Sato, F.; Okamoto, S. *Adv. Synth. Cat.* **2001**, *343*, 759; (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; (c) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.
8. Analysis of ^1H NMR spectra of the crude reaction mixture showed only a single diastereoisomer. The stereochemistry is readily assigned by coupling constant analysis. $^3J_{H,H}$ values for cyclic siloxanes with an *anti* relationship between the oxygen and methyl bearing carbons are typically between 8.8–10.2 Hz, which is consistent with ϕ values of ~170°.



This was further confirmed by desilylation of **3** with TBAF to provide the known 1,2-*anti* 2-methyl-1-phenyl-pent-3-en-1-ol (Andersen, M.; Hildebrandt, B.; Koester, G.; Hoffmann, R. W. *Chem. Ber.* **1989**, *122*, 1777). The stereochemistry of all other products was assigned by similar approaches.
9. All new compounds were fully characterized by ^1H and ^{13}C NMR, HRMS, and IR.
10. *Representative experimental procedure*: *i*-PrMgCl (800 μL of a 1.6 M solution in Et_2O, 1.28 mmol) was added by syringe pump over a period of 2 h to a solution of silyloxyenyne **16** (98 mg, 0.21 mmol) and $ClTi(i\text{-}PrO)_3$ (167 mg, 0.64 mmol) in Et_2O (3 mL) at −40 °C. After addition of the *i*-PrMgCl was complete, the reaction was stirred at −40 °C for further 4 h before being quenched with *i*-PrOH. The reaction was diluted with Et_2O, washed with saturated aqueous NH_4Cl solution, filtered through Celite®, dried with $MgSO_4$, and evaporated to leave an oil that was chromatographed on SiO_2 gel with 10% Et_2O in hexanes to yield **17** (58 mg, 59%). ^1H NMR ($CDCl_3$, 500 MHz): ^1H NMR (500 MHz) δ 0.8–1.08 (m, 31H), 1.76 (dd, 3H, $J = 3.5$, 8.5 Hz), 2.25 (m 1H), 3.27 (dd, 1H, $J = 2.5$, 12 Hz), 3.43 (m, 2H), 3.80 (s, 3H), 4.43 (s, 2H), 6.08 (qd, 1H, $J = 3$, 8 Hz), 6.87 (d, 2H, $J = 11$ Hz) 7.26 (d, 2H, $J = 11$ Hz). ^{13}C NMR (400 MHz) δ 12.94, 13.43, 13.57, 15.12, 17.72, 17.77, 17.84, 18.33, 20.34, 20.79, 27.43, 29.98, 32.58, 33.58, 42.22, 42.47, 55.50, 70.86, 72.71, 85.62, 113.95, 129.45, 131.05, 131.69, 143.21, 159.28. HRMS (ESI): calcd. for $C_{28}H_{48}O_3Si$ ($M + H^+$) 461.3445, found 461.3448.
11. Further mechanistic studies will be required to establish the source of the observed diastereoselectivity.
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