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Sequencing of Three-Component Olefin Metatheses: Total Synthesis of Either (+)-Gigantecin or (+)-14-Deoxy-9-oxygigantecin

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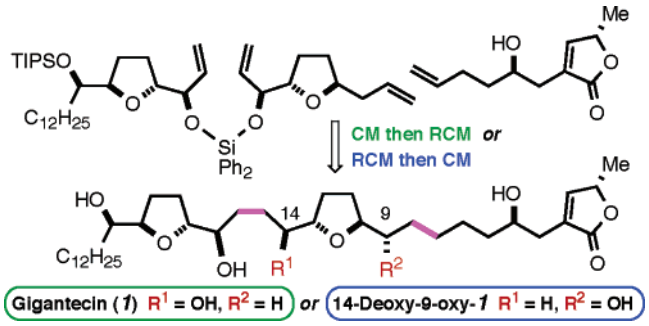
ABSTRACT



An efficient, flexible, and highly convergent strategy for accessing skipped bis-THF containing Annonaceous acetogenins is demonstrated by the synthesis of each of (+)-gigantecin (1) and its constitutional isomer (+)-14-deoxy-9-oxygigantecin (11). The skeleton of each compound is produced, at will, from the same precursors via a three-component ring-closing/cross-metathesis sequence that differs only in the ordering of the RCM vs CM events. Another notable aspect is the use of in situ epoxide-closing and -opening of iodohydrins with dimethylsulfonium methylide to provide inverted allylic alcohols.

Here we describe an efficient, highly convergent chemical synthesis of (+)-gigantecin (**1**)[1,2] utilizing a one-pot, three-component olefin metathesis coupling strategy. This potent cytotoxic antitumor agent, a rare *nonadjacent* bis-THF-containing acetogenin, was isolated both from the bark of *Goniothalamus giganteus* (Annonaceae) in Southeast Asia[1] and from the seeds of the Brazilian plant *Annona coriacea*.[2] A synthesis of (+)-gigantecin was achieved by Crimmins and She in 2004.[3]

Our retrosynthetic strategy (Scheme 1) relied upon two staged metathesis events—a bimolecular diene cross-metathesis[4,5] and a unimolecular, silicon-tethered ring-closing metathesis[6] to form the C7/C8 and C15/C16 bonds, respectively. Fragments **3**−**5**, all of similar structural complexity, were identified as the building blocks. We envisioined that the propinquity of the latter two would be enforced via the mixed silaketal **6**. Treatment with a ruthenium-based metathesis initiator in the presence of alkene **3** would then

(1) (a) Alkofahi, A.; Rupprecht, J. K.; Liu, Y. M.; Chang, C.-J.; Smith, D. L.; McLaughlin, J. L. *Experientia* **1990**, *46*, 539−541. (b) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237−278 (c) Gu, Z.-M.; Fang, X.-P.; Zeng, L.; Song, R.; Ng, J. H.; Wood, K. V.; Smith, D. L.; McLaughlin, J. L. *J. Org. Chem.* **1994**, *59*, 3472−3479.

(2) Yu, J.-G.; Hu, X. E.; Ho, D. K.; Bean, M. F.; Stephens, R. E.; Cassady, J. M. *J. Org. Chem.* **1994**, *59*, 1598−1599.

(3) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790−12791.

(4) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.

(5) For use of a related CM reaction in the synthesis of adjacent bis-THF acetogenins, see: Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396−10399.

(6) For application of a related RCM to the synthesis of the skipped THP/THF acetogenin, mucocin, see: Evans, P. A.; Cui. J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702−14703. For application to the skipped bis-THF, bullatanocin, see: Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154−3157.

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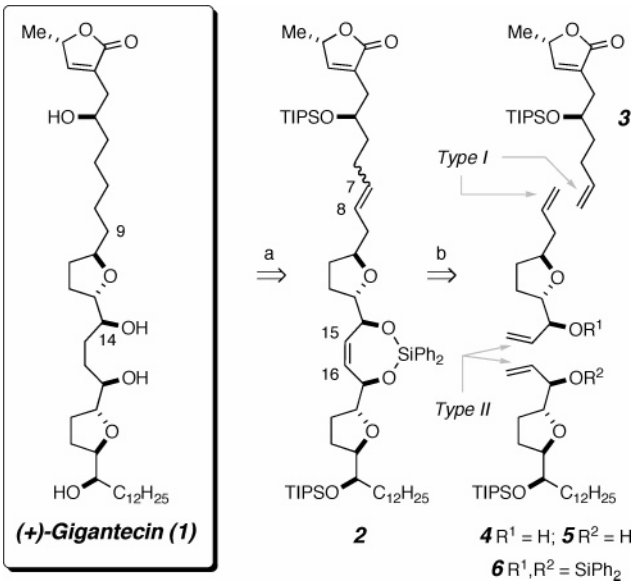
Scheme 1. Dual Metathetical Retrosynthetic Strategy[a]

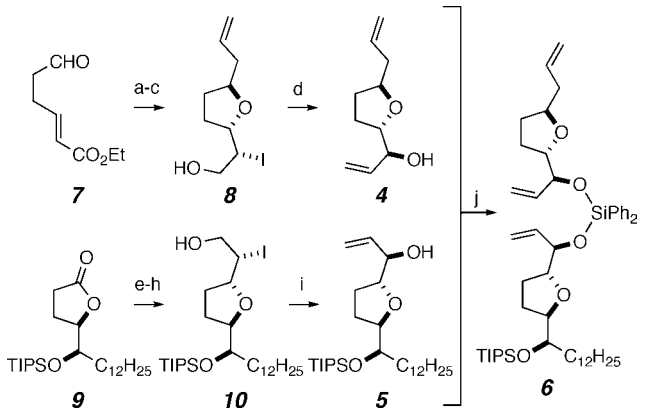


[a] Key: (a) hydrogenation; global desilylation; (b) three-component olefin metathesis coupling. For alkene reactivity "types", see ref 4.

produce triene **2**, which has the gigantecin (**1**) constitution. We presumed that chemoselective saturation of the disubstituted alkenes and global desilylation would be straightforward and provide **1**.

Butenolide fragment **3** was prepared[7] by a precedented sequence.[7c] Allylic alcohol **4** was synthesized (Scheme 2) by Leighton asymmetric allylation of aldehyde **7**,[8] ester reduction, and iodoetherification to give iodohydrin **8**. In situ

Scheme 2. Construction of the Silaketal Triene **10**[a]



[a] Reagents and conditions: (a) Leighton allylation,[8] CH_2Cl_2, −20 °C (87%); (b) DIBAL-H, PhMe, 0 °C to rt; (c) I_2, K_2CO_3, THF, −78 °C (33% yield from **7**); (d) $Me_3S^+I^-$, *n*-BuLi, THF, −45 °C to rt (71%); (e) DIBAL-H, hexanes, −78 °C; (f) $Ph_3PCHCO_2CH_2CH_3$, PhMe, 80 °C; (g) DIBAL-H, CH_2Cl_2, −78 °C to rt (87% yield from **9**); (h) I_2, K_2CO_3, THF, −78 °C (63%); (i) $Me_3S^+I^-$, *n*-BuLi, THF, −45 °C to rt (81%); (j) **5**, Ph_2SiCl_2, pyridine, PhMe, 0 °C to rt, then **4**, pyridine, PhMe, 0 °C to rt (52%).

epoxide formation upon treatment with dimethylsulfonium methylide ($Me_2S{=}CH_2$) followed by ring-opening provided the inverted allylic alcohol **4**.[9] The synthesis of **5** (Scheme 2) began with DIBAL-H reduction of **9**, the TIPS ether of a known lactone.[10] Wittig olefination of the lactol, reduction to the corresponding allylic alcohol, and another *trans*-selective iodoetherification provided **10**. This iodohydrin was also subjected to $Me_2S{=}CH_2$ to give the inverted allylic alcohol **5**. Finally, mixed silaketal **6** was prepared by sequential loading of **5** and then **4** onto Ph_2SiCl_2.[11]

We first explored the ring-closing metathesis (RCM) behavior of the mixed silaketal by itself. Namely, **6** (830 amu) was exposed to a metathesis initiator (the second-generation Hoveyda−Grubbs complex[12]) to induce unimolecular RCM. The resulting cyclic diene (830−28 amu) was immediately treated with **3** (4 equiv) and **G2** [Ru=CHPh-$(Cl)_2$ (PCy_3)(DHIMes)][13] to induce cross-olefin methathesis (CM), the successful outcome of which was evidenced by an (molecular) ion at 1126 amu (ESI MS). Diimide reduction (to 1130 amu)[14] and desilylation (HF, MeCN), followed by purification (SiO_2), provided a compound having the mass of gigantecin (**1**). However, critical inspection of its ^1H and ^{13}C NMR spectra revealed subtle but nonignorable differences—the product that had arisen from this "RCM then CM" sequence was *not* gigantecin. Moreover, the melting point (117−119 °C) of this isomer exceeded that of **1** (108−109 °C).

Recalling that analysis of electron impact mass spectral fragmentation patterns has played an important role in the assignment of connectivity and constitution of new members of the acetogenin family of natural products,[1b] we scrutinized this isomer of **1** in that way, thereby deducing it to be 14-deoxy-9-oxygigantecin (**11**). The diagnostic fragmentation patterns for **11** (and **1**)[1b] are summarized in Figure 1 (and further detailed in the Supporting Information).

How **11** had arisen from the sequential RCM of **10** and CM with **3** was revealed through analysis of the initial RCM product. Instead of providing the seven-membered cyclic silaketal, the RCM had yielded, instead, the 11-membered silaketal **12** (Scheme 3). In retrospect, this can easily be explained through preferential initiation of RCM at the least hindered, type I,[4] $\Delta^{8,8'}$-alkene in **10**. The resulting alkylidene

(7) (a) Opening of (*R*)-1,2-epoxyhex-5-ene[7b] with the TBS ether of (*S*)-1-lithiobut-1-yn-3-ol, TIPS protection, TBS removal, Red-Al reduction and iodination of the alkyne, and carbonylative lactonization[7c] gave **3**. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *20*, 6776−6777. (c) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801−1802.

(8) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946−948.

(9) (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449−5452. (b) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375−3378.

(10) Wang, Z.; Zhang, X.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407−6410.

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(12) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(13) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(14) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996−6000.

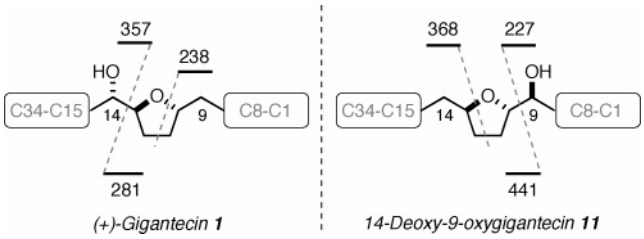
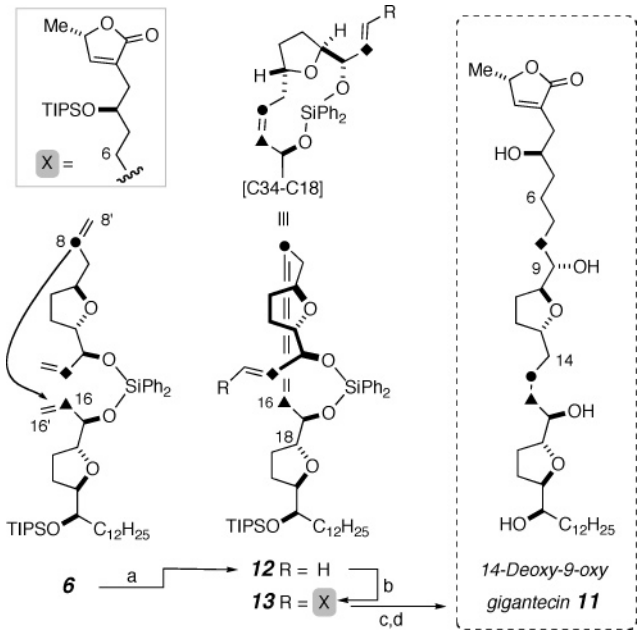


Figure 1. Comparative and diagnostic EI mass spectrometric fragmentation patterns for gigantecin (**1**)[2] vs 14-deoxy-9-oxygigantecin (**11**).

Scheme 3. "RCM then CM" Sequence (to **11**)[a]

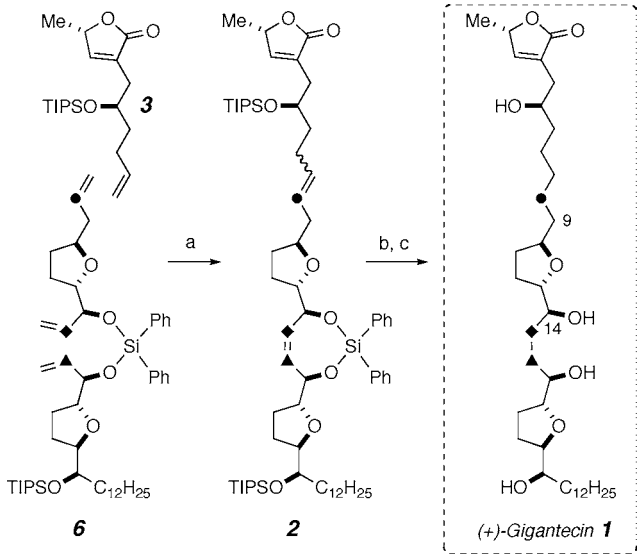


[a] Reagents and conditions: (a) second-generation Hoveyda–Grubbs initiator (15 mol %), PhMe, 80 °C (67%); (b) **G2** (20 mol %), **3**, CH_2Cl_2, 45 °C; (c) $TsNHNH_2$, NaOAc, H_2O, DME, Δ; (d) 5% HF/MeCN, CH_2Cl_2, rt (48% from **12**).

then closed onto the distal, $\Delta^{16,16'}$-alkene to produce the bicyclo[8.2.0] framework. This outcome is perhaps somewhat surprising given the 2,5-trans-substituted THF ring that is embedded within that new skeleton. The subsequent CM with **3** had given, rather than **2**, its constitutional isomer **13**. Following alkene reduction and desilylation, this turn of events expressed itself in the apparent relocation of the carbinol center from C14 to C9 (cf., **11** vs **1**).

To overcome this obstacle and to successfully construct (+)-gigantecin (**1**), we simply reversed the order of the two metathesis reactions (Scheme 4). Namely, we changed to the "CM then RCM" sequence. Triene **10** and alkene **3** (1:4 molar ratio), each of which contains a type I alkene, were

Scheme 4. "CM then RCM" Sequence (to **1**)[a]



[a] Reagents and conditions: (a) **G2** (20 mol %), CH_2Cl_2, 45 °C, syringe pump addition (9 h) (63%); (b) $TsNHNH_2$, NaOAc, H_2O, DME, Δ (79%); (c) 5% HF/MeCN, CH_2Cl_2, rt (87%).

combined and exposed to **G2**. The major products were **2** (63%, from CM of **3** with **10**) and the self-metathesis dimer of **3** (which could be recycled by metathesis cleavage in the presence of ethylene). A small amount of **13** (ca. 10%) was competitively produced. Diimide reduction and global deprotection gave **1** (69%, mp 108–109 °C[2]). It should be emphasized that **2** was produced, now in a one-pot operation, from precisely the same pair of precursors as was used to generate **13** via "RCM then CM."

A side comment about the ^1H NMR spectra of our samples of **1** vs **11** is in order. These are presented in Figure 2. Not surprisingly, they are quite similar. In fact, if we compare the data set for each of these isomers—at the level of a standard, tabulated listing of chemical shifts and discernible coupling constants—with the sets reported for natural gigantecin (**1**),[1c,2] we cannot conclude which is the better match.[15] However, *visual comparison* of the two vis-à-vis that of natural **1** (see Figure 2 as well as the Supporting Information for ref 2) clearly permits this distinction to be made. This underscores the value, for comparison purposes, of having access to "pictures" of authentic spectra whenever possible.

In summary (Scheme 5), we have shown that either gigantecin (**1**) or its constitutional isomer **11** can be assembled efficiently (13 or 14 linear steps, respectively) via a highly convergent, three-component metathetical coupling from the same precursors (i.e., **3** and **6**) simply by reversing the order of the two metathesis events. Specifically, RCM of **6** followed by CM with **3** gave **11**, whereas initial CM of

(15) For two other examples, see: (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841–843. (b) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36–37.

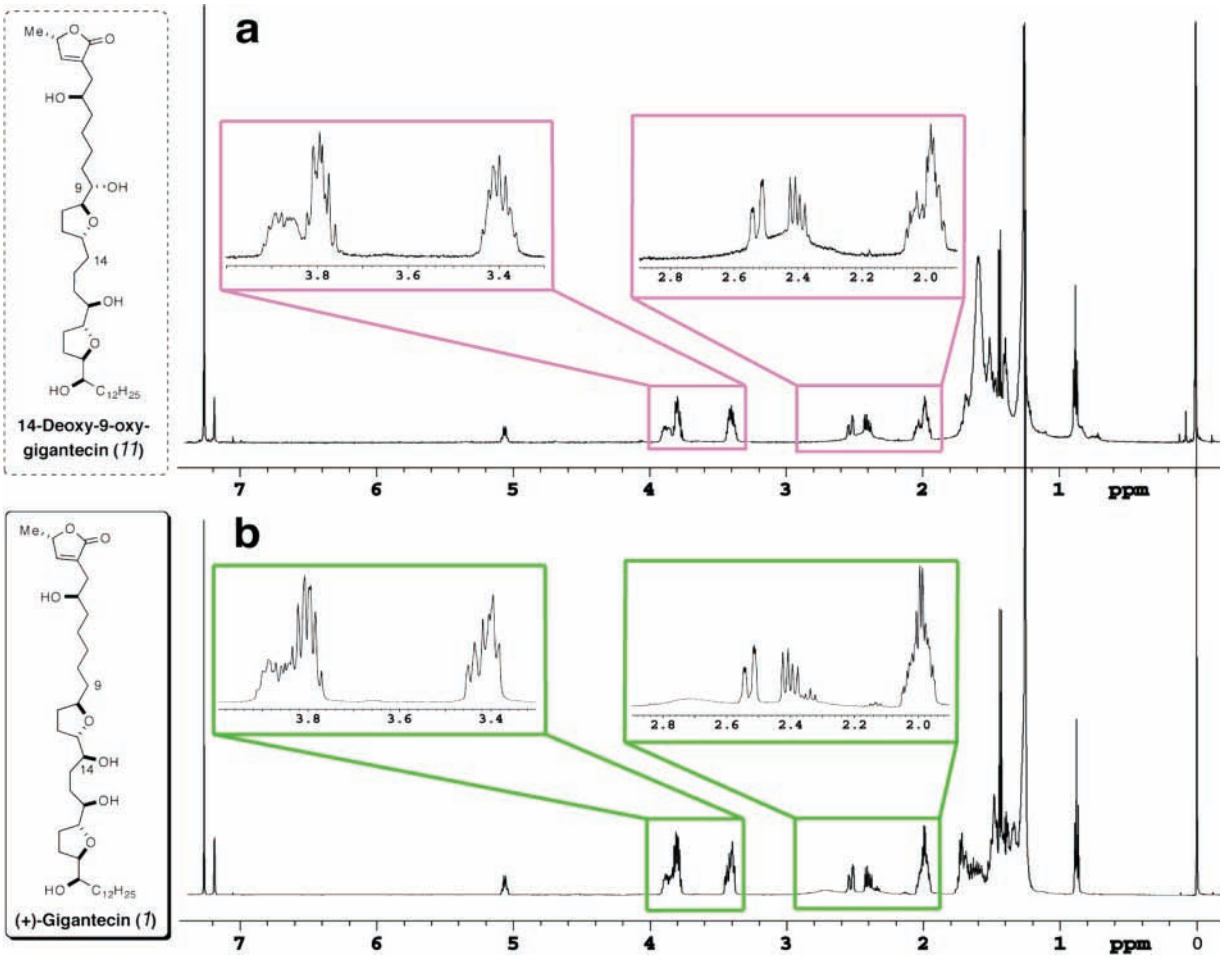
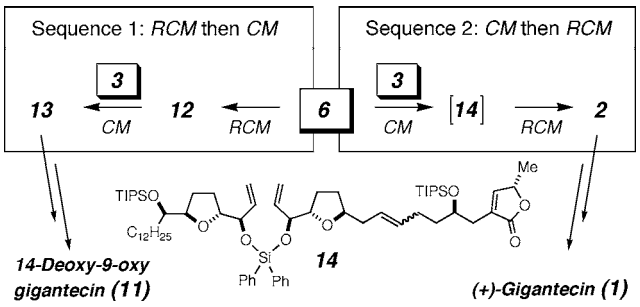


Figure 2. Proton NMR spectra (500 MHz, $CDCl_3$) for (a**)** 14-deoxy-9-oxygigantecin (**11**) and (b**)** (+)-gigantecin (**1**) samples prepared in the work described here.

Scheme 5. Summary of the Complementary Sequences



3 with **6** followed by RCM (of intermediate **14**) gave **1**. These results underscore the importance of properly sequencing multistage metathesis processes.

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Supporting Information Available: Spectroscopic characterization data and procedures for preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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