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Stereoselective Synthesis of the Rocaglamide Skeleton via a Silyl Vinylketene Formation/[4 + 1] Annulation Sequence

Matthew W. Giese[†] and William H. Moser*

Department of Chemistry and Chemical Biology, Indiana University−Purdue University, Indianapolis, Indiana 46202

wmoser@mmm.com

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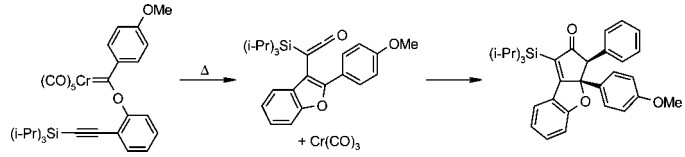
ABSTRACT



The tricyclic core of the cyclopentabenzofurans has been prepared in an efficient and stereoselective manner utilizing an intramolecular silyl vinylketene formation/[4 + 1] annulation sequence. This novel approach affords the ABC ring system where the adjacent phenyl and aryl substituents of the C ring have the required cis relationship.

The plant genus *Aglaia*, native to the tropical rain forests of Indonesia and Malaysia, has received significant attention in recent years as a source of densely functionalized natural products with interesting biological activities.[1] Noteworthy among these natural products are the rocaglamides, including the parent (**1**, Figure 1)[2] and the dioxanyloxy-modified derivative silvestrol (**2**),[3] which both comprise a cyclopenta[*b*]tetrahydrobenzofuran ring system. Rocaglamide, originally isolated from *Aglaia elliptifolia* in 1982,[2] was found to exhibit antileukemic activity in a murine in vivo model,[4] with subsequent members of this family demonstrating potent antileukemic and anticancer activity,[5] as well as NF-κB inhibitory activity at nanomolar concentrations in T-lymphocytes.[6] The rocaglate silvestrol **2** displays cytotoxic activity against human cancer cells comparable to the anticancer drug Taxol.[3]

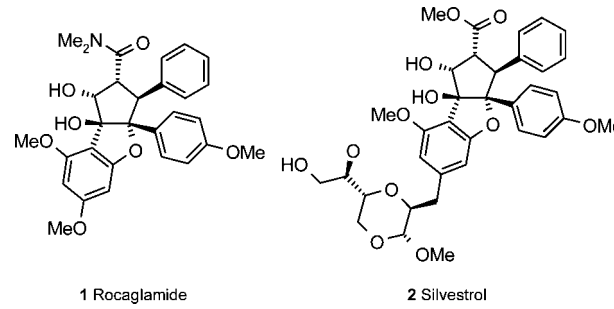


Figure 1. Representative rocaglamides.

* Corresponding author. Present address: 3M Corporate Research Materials Laboratory, 3M Center Bldg 201-04-N-01, St. Paul, MN 55144.

[†] Present address: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

(1) Proksch, P.; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B. W. *Curr. Org. Chem.* **2001**, *5*, 923.

(2) King, M. L.; Chiang, C. C.; Ling, H. C.; Fujita, E.; Ochiai, M.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1982**, 1150.

(3) Hwang, B. Y.; Su, B.-N.; Chai, H.; Mi, Q.; Kardono, L. B. S.; Afriastini, J. J.; Riswan, S.; Santarsiero, B. D.; Mesecar, A. D.; Wild, R.; Fairchild, C. R.; Vite, G. D.; Rose, W. C.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Swanson, S. M.; Kinghorn, A. D. *J. Org. Chem.* **2004**, *69*, 3350.

(4) Lee, S. K.; Cui, B.; Mehta, R. R.; Kinghorn, A. D.; Pezzuto, J. M. *Chem. Biol. Interact.* **1998**, *115*, 215.

(5) (a) Zhu, J. Y.; Lavrik, I. N.; Mahlknecht, U.; Giaisi, M.; Proksch, P.; Krammer, P. H.; Li-Weber, M. *Int. J. Cancer* **2007**, *121*, 1839. (b) Kim, S.; Salim, A. A.; Swanson, S. M.; Kinghorn, A. D. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 319.

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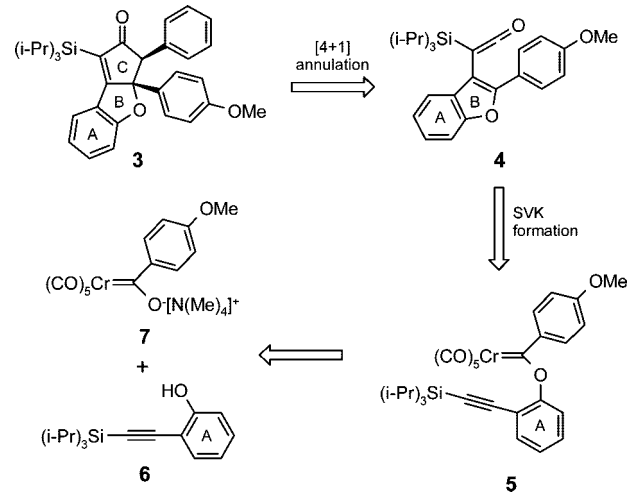
On the basis of their promising biological profiles and challenging architectural features, the rocaglamide family of compounds provides attractive targets for total synthesis.[7−10] A major obstacle that has plagued efforts toward total synthesis of rocaglamides or rocaglamide analogues, however, has been the stereocontrolled construction of the sterically congested cyclopentane ring. Specifically, difficulties encountered in the construction of the cyclopentane moiety bearing geminal aromatic rings in a *cis* disposition have either necessitated additional synthetic steps to epimerize stereogenic centers,[7d] required the separation of diastereomeric isomers,[7a−c,8,10b,d,j] or prevented completion of the final target altogether.[10j] These problems strongly motivate the development of more effective synthetic strategies.

Recently, we disclosed a novel route for the preparation of silyl vinylketenes bearing unique substitution patterns based on an arrested Dötz benzannulation reaction between Fischer alkoxy carbene complexes and trialkylsilyl-substituted alkynes.[11] Subsequently, we demonstrated that these silyl vinylketenes could function as four-carbon units in Danheiser's [4 + 1] annulation[13f] to yield densely functionalized cyclopentenones in an efficient and stereoselective manner.[12,13] As part of our continued efforts in this area, we now report an intramolecular silyl vinylketene formation/[4 + 1] annulation sequence that provides a rapid and stereocontrolled entry to the rocaglamide core.

Our retrosynthetic analysis, as depicted in Scheme 1, entailed formation of Fischer aryloxy carbene complex **5** via the combination of phenol **6** and tetramethylammonium acylate complex **7**. Thermally driven intramolecular alkyne insertion would form the B ring and yield silyl vinylketene

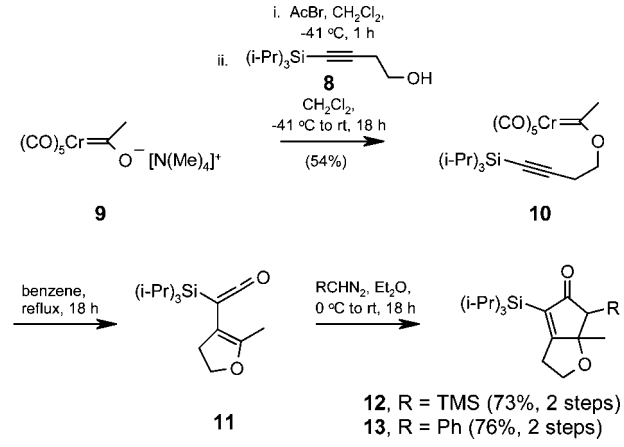
Scheme 1. Retrosynthetic Analysis



4, and subsequent [4 + 1] annulation with phenyldiazomethane would generate the C ring and complete the tricyclic rocaglamide skeleton **3**. Since we have observed that related [4 + 1] annulations proceed with complete cis diastereoselectivity between aryl substituents, we anticipated that this strategy would be ideally suited to the challenging construction of the congested rocaglamide core.

Due to difficulties associated with the preparation of Fischer aryloxy carbene complexes,[14] we decided to first test the viability of our approach by employing a simple aliphatic model system (Scheme 2). The desired triisopropylsilyl

Scheme 2. Model SVK Formation/[4 + 1] Sequence



(TIPS)-substituted alkyne **8**, which would serve as the aliphatic version of phenol **6**, was readily prepared in 76%

(6) Baumann, B.; Bohnenstengel, F.; Siegmund, D.; Wajant, H.; Weber, C.; Herr, I.; Debatin, K.-M.; Proksch, P.; Wirth, T. *J. Biol. Chem.* **2002**, *277*, 44791.

(7) Total syntheses of rocaglamide: (a) Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 7754. (b) Dobler, M. R.; Bruce, I.; Cederbaum, F.; Cooke, N. G.; Diorazio, L. J.; Hall, R. G.; Irving, E. *Tetrahedron Lett.* **2001**, *42*, 8281. (c) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657. (d) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 9022.

(8) Total synthesis of (−)-silvestrol: El Sous, M.; Khoo, M. L.; Holloway, G.; Owen, D.; Scammells, P. J.; Rizzacasa, M. A. *Angew. Chem., Int. Ed* **2007**, *46*, 7835.

(9) Total synthesis of aglaiastatin: Watanabe, T.; Kohzuma, S.; Takeuchi, T.; Otsuka, M.; Umezawa, K. *Chem. Commun.* **1998**, 1097.

(10) Synthetic methodology aimed at rocaglamides or analogues: (a) Magnus, P.; Stent, M. A. H. *Org. Lett.* **2005**, *7*, 3853. (b) Diedrichs, N.; Ragot, J. P.; Thede, K. *Eur. J. Org. Chem.* **2005**, 1731. (c) Sido, A. S. S.; Boulenger, L.; Désaubry, L. *Tetrahedron Lett.* **2005**, *46*, 8017. (d) Gerard, B.; Jones, G., II; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620. (e) Thede, K.; Diedrichs, N.; Ragot, J. P. *Org. Lett.* **2004**, *6*, 4595. (f) Schoop, A.; Greiving, H.; Göhrt, A. *Tetrahedron Lett.* **2000**, *41*, 1913. (g) Bruce, I.; Cooke, N. G.; Diorazio, L. J.; Hall, R. G.; Irving, E. *Tetrahedron Lett.* **1999**, *40*, 4279. (h) Hailes, H. C.; Raphael, R. A.; Staunton, J. *Tetrahedron Lett.* **1993**, *34*, 5313. (i) Feldman, K. S.; Burns, C. J. *J. Org. Chem.* **1991**, *56*, 4601. (j) Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77. (k) Davey, A. E.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 25.

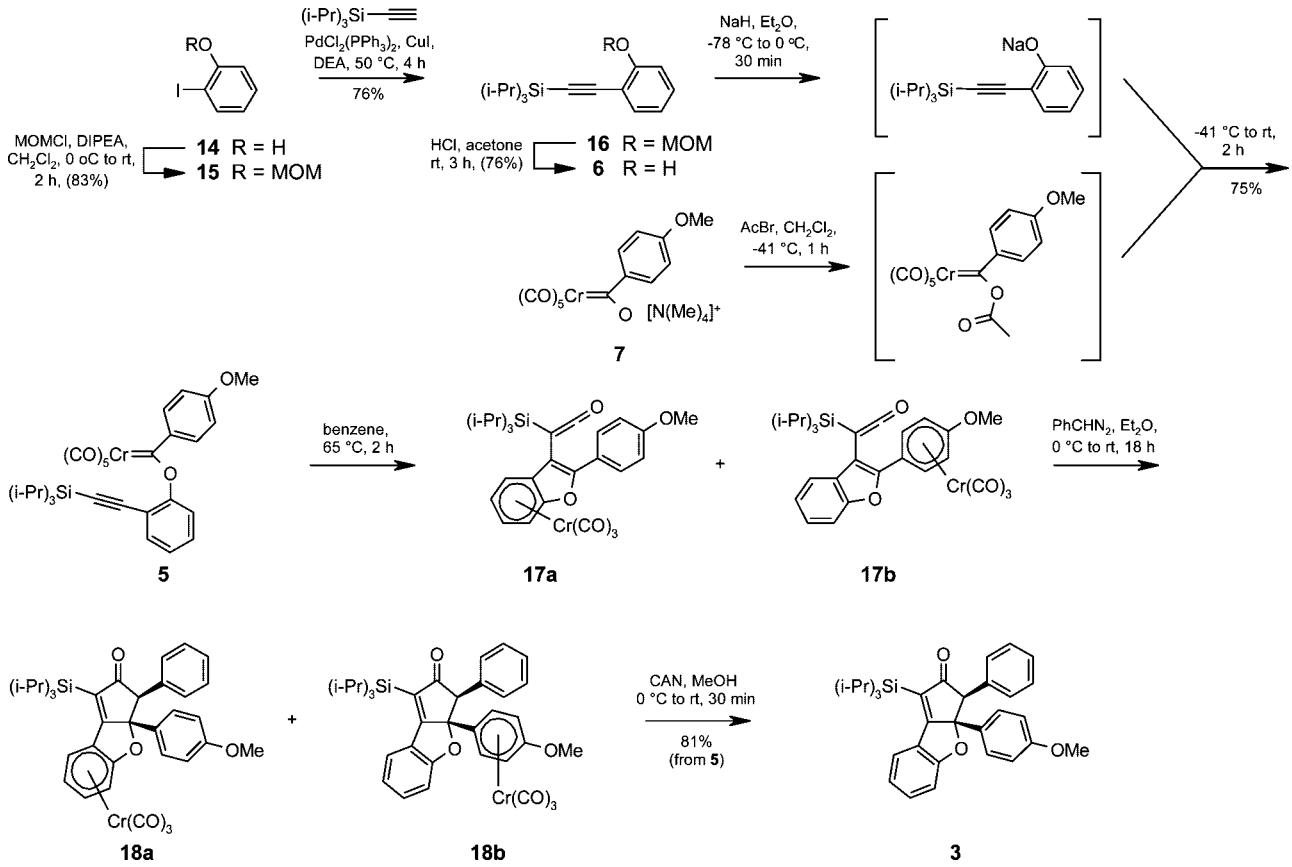
(11) Moser, W. H.; Sun, L.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389.

(12) Moser, W. H.; Feltes, L. A.; Sun, L.; Giese, M. W.; Farrell, R. W. *J. Org. Chem.* **2006**, *71*, 6542.

(13) (a) Li, Z.; Moser, W. H.; Deng, R.; Sun, L. *J. Org. Chem.* **2007**, *72*, 10254. (b) Davie, C. P.; Danheiser, R. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5867. (c) Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263. (d) Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465. (e) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690. (f) For a review of silylketene chemistry, see: George, D. M.; Danheiser, R. L. In *Science of Synthesis*; Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23, pp 53−99.

(14) (a) Pulley, S. R.; Sen, S.; Vorogushin, A.; Swanson, E. *Org. Lett.* **1999**, *1*, 1721. (b) Waters, M. L.; Brandvold, T. A.; Isaacs, L.; Wulff, W. D. *Organometallics* **1998**, *17*, 4298.

Scheme 3. Formation of the Tricyclic Rocaglamide Core via an Intramolecular SVK Formation/[4 + 1] Sequence



yield over three successive steps from commercially available 3-butyn-1-ol.[15]

Preparation of Fischer alkoxy carbene complex **10** (Scheme 2) began from tetramethylammonium acylate complex **9**,[16] which was converted to the corresponding acyloxy carbene complex by treatment with acetyl bromide at −41 °C for 1 h. Subsequent addition of a solution of **8** in CH_2Cl_2 via cannula and warming to room temperature overnight provided **10** as an orange oil. Although it was found to be somewhat unstable under atmospheric conditions, heating a degassed benzene solution of **10** at reflux for 18 h afforded a yellow oil without significant decomposition. Evidence for the desired intramolecular alkyne insertion to provide silyl vinylketene **11** was clearly provided by IR analysis, which showed the expected ketene stretch at 2082 cm^{-1}. The instability of **11** to silica gel precluded purification; however, NMR analysis indicated essentially pure product formation and the crude material was instead treated directly with either trimethylsilyldiazomethane or phenyldiazomethane.[17] In both cases, the [4 + 1] annulation reaction proceeded smoothly, providing the bicyclic cyclopentenones **12** and **13**, respectively. Importantly, both cyclopentenones were obtained as single diastereoisomers. Although no effort was made to determine which diastereoisomers had formed, a cis relationship between the methyl and carbenoid substituents was presumed in accord with our previous studies.[12]

With the viability of our intramolecular silyl vinylketene approach secured, we set out to prepare the Fischer aryloxy carbene complex required for an approach to the rocaglamide core (Scheme 3). Synthesis of phenol **6** commenced with commercially available 2-iodophenol **14**. Protection of **14** as the corresponding methoxymethyl (MOM) ether **15**,[18] followed by Sonogashira coupling to install the triisopropylsilyl alkyne, proceeded without incident. Subsequent removal of the MOM protecting group proved somewhat difficult, however, due to a facile cyclization process that is common to *o*-hydroxy acetylenic compounds.[19] Fortunately, experimentation with several cleavage conditions revealed that the MOM ether could readily be cleaved with 10% HCl in acetone to provide the requisite phenol **6** in good yield. Completion of aryloxy carbene complex **5** was then accomplished by combining the sodium phenolate of **6** with

(15) Details for the preparation of **8** can be found in the Supporting Information.

(16) (a) Fischer, E. O.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445. (b) Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660.

(17) Creary, X. In *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. VII, pp 438−443.

(18) Tsang, K. Y.; Brimble, M. A. *Tetrahedron* **2007**, *63*, 6015.

(19) (a) Fkyerat, A.; Dubin, G. M.; Tabacchi, R. *Helv. Chim. Acta* **1999**, *82*, 1418. (b) Lütjens, H.; Scammells, P. J. *Synlett* **1999**, 1079. (c) Defranq, E.; Zesiger, T.; Tabacchi, R. *Helv. Chim. Acta* **1993**, *76*, 425. (d) Pinault Frangin, M. Y.; Genet, J.-P.; Zamarlik, H. *Synthesis* **1990**, 935.

the acyloxy carbene complex derived from tetramethylammonium salt **7** according to the method described by Pulley.[14] The aryloxy carbene complex **5**, which was isolated in good yield as a dark red crystalline solid, displayed very good stability and could be stored at −20 °C for extended periods of time with no apparent decomposition.

At this juncture, we were pleased to find that aryloxy carbene complex **5** underwent a very clean intramolecular alkyne insertion to afford the desired silyl vinylketene. Specifically, treatment of a degassed solution of **5** in benzene for 2 h at 65 °C resulted in a near-quantitative conversion to a 2:1 isomeric mixture of **17a** and **17b**, which differed only in the position of the complexed $Cr(CO)_3$ fragment. Although it was possible to separate **17a** and **17b** via flash chromatography, we found it more convenient to directly carry the mixture forward.[20] Thus, crude reaction mixtures of **17a**/**17b** were dissolved in Et_2O/THF and added to an ethereal solution of phenyldiazomethane[17] at 0 °C, resulting in highly efficient [4 + 1] annulations to yield cyclopentenones **18a** and **18b**. Finally, oxidative removal of the $Cr(CO)_3$ fragment with ammonium cerium(IV) nitrate in methanol completed the synthesis of the desired tricyclic cyclopentenone **3** as a single diastereomer in 81% yield over the three steps from aryloxy carbene complex **5**. Importantly, isolation of **3** as a single diastereomer demonstrated that the [4 + 1] annulation had proceeded in a stereospecific fashion and verified that **17a/17b** and **18a/18b** mixtures differed only in the position of the complexed $Cr(CO)_3$ fragment. Moreover, X-ray analysis of **3** confirmed the anticipated cis disposition of the adjacent phenyl and aryl substituents on the newly generated cyclopentenone ring.[21]

(20) Experiments in our laboratory on the individual isomers **17a/17b** revealed that identical cyclopentenone **3** was obtained as a final product, regardless of which aryl ring was complexed to the chromium fragment.

(21) Details of the X-ray analysis are available in the Supporting Information.

It is noteworthy that the [4 + 1] annulations of both silyl vinylketenes **17a** and **17b** exclusively generate cyclopentenones bearing cis dispositions of the vicinal aryl substituents, particularly in light of the enhanced steric congestion present in the conversion of **17b** to **18b** due to the complexed $Cr(CO)_3$ fragment. Although the mechanism of the [4 + 1] annulation remains inconclusive, these results are consistent with a stereospecific 4π electrocyclic ring closure as suggested by us[12] and others.[13] In this instance, even the highly congested cis cyclopentenone **18b** would be the favored annulation product, as stereospecific conrotatory ring closure would proceed from a sterically favored 2-oxidopentadienyl cation intermediate.

In summary, an intramolecular silyl vinylketene formation/[4 + 1] annulation sequence is reported as a novel approach for the construction of the cyclopentabenzofuran core of the rocaglamide family of natural products. Importantly, the stereospecific nature of the [4 + 1] annulation offers an effective means of assembling the congested tricyclic carbon skeleton that has been problematic in some previous syntheses. The resultant tricyclic cyclopentenone from this approach appears to be well suited for further elaboration, and efforts are underway to utilize this methodology for the synthesis of rocaglamide and other rocaglate derivatives.

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Supporting Information Available: Full experimental procedures for all new compounds, copies of ^1H NMR and ^{13}C NMR, and X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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