Communications to the Editor

Sequential Intramolecular Cyclobutadiene Cycloaddition, Ring-Opening Metathesis, and Cope Rearrangement: Total Syntheses of (+)- and (−)-Asteriscanolide

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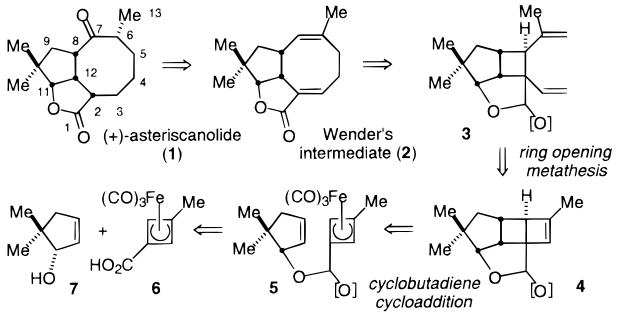
Received June 2, 2000

The value of new transformations can become apparent when brought to bear in complex molecule synthesis. To demonstrate the utility of intramolecular cyclobutadiene cycloadditions[1] and ring-opening metatheses,[2] we report herein the first application of these complementary transformations in the total syntheses of (+)- and (−)-asteriscanolide (**1**). The incorporation of these reactions into the synthesis of asteriscanolide provides a nine-step route (longest linear sequence) to the natural product. The key synthetic disconnections are illustrated in Scheme 1.

Since its discovery more than 15 years ago,[3] the novel sesquiterpene lactone ring system of **1** has drawn considerable attention from the synthetic community.[4] In particular, successful syntheses of asteriscanolide have been reported by the Krafft and Paquette laboratories.[5] Predating these more recent contributions, however, is the first and, to date, shortest synthesis of **1**, by Wender, Ihle, and Correia.[6] The Wender strategy centered on a Ni(0)-catalyzed intramolecular [4 + 4] cycloaddition of a highly functionalized bis-1,3-diene to provide the cyclooctadiene-containing intermediate **2**. This advanced cycloadduct was then converted to **1** in two steps. The intramolecular [4 + 4] cycloaddition-based approach provided an asymmetric synthesis of (+)-asteriscanolide in 13 steps from commercially available starting materials.

Scheme 1. Retrosynthetic Analysis of Asteriscanolide



As illustrated in Scheme 1, our strategy was to also prepare the natural product through the intermediacy of cyclooctadiene **2**; instead of using a [4 + 4] cycloaddition, however, we planned to generate **2** through a Cope rearrangement on the dialkenylcyclobutane **3**. Precursor **3**, in turn, would be prepared through a ring-opening metathesis of the highly functionalized cyclobutene **4** and ethylene. An intramolecular Diels−Alder reaction between cyclobutadiene (**6**) and dimethylcyclopentenol (**7**) would be employed to generate compound **4**.

Achieving the absolute stereochemistry of the natural product was dependent upon the stereochemical identity of allylic alcohol **7**. As illustrated in eq 1, compound **7** can be prepared in

nonracemic form from commercially available ketone **8**. A Pd-catalyzed Saegusa oxidation of the silyl enol ether derived from ketone **8** (60% yield),[7] followed by a (*S*)-B-Me-CBS-catalyzed enantioselective reduction[8] of the enone produces the (*S*)-dimethylcyclopentenol **7** in 94% ee[9] and 56% yield. While this configuration of **7** lead to the natural product, employing the (*R*)-CBS catalyst in the reduction delivered the antipode of **7**, which was used to prepare (−)-asteriscanolide.

Initial attempts to carry out the intramolecular Diels−Alder between the ester-linked cyclobutadiene and dimethylcyclopentenol (**5** → **4**) proved unsuccessful; the failure is presumably due to the unfavorable conformational constraints of the ester functionality. The cycloaddition became possible, however, if the two functional groups were connected instead through an ether linkage.

The successful route to **1** is summarized in Scheme 2. The iron-complexed cyclobutadiene portion (**10**) of the molecule can be prepared through the photolysis of the commercially available α-pyrone **9** in the presence of $Fe(CO)_5$ or by mild heating of the photolysis product with $Fe_2(CO)_9$.[10] Compound **11** was then

(1) (a) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196−9197. (b) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440−6441.

(2) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610−9611. (b) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478−1479. (c) Tallarico, J. A.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157−7158. (d) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *Tetrahedron* **1997**, *53*, 16511−16520. (e) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411−412. (f) Cuny, G. D.; Cao, J.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 5237−5240. (g) Cuny, G. D.; Hauske, J. R. *CHEMTECH* **1998**, *28*, 25−31. (h) Randall, M. L.; Snapper, M. L. *J. Mol. Catal.* **1998**, *133*, 29−40.

(3) San Feliciano, A.; Barrero, A. F.; Medarde, M.; Miguel del Corral, J. M.; Aramburu, A.; Perales, A.; Fayos, J. *Tetrahedron Lett.* **1985**, *26*, 2369−2372.

(4) (a) Sarkar, T. K.; Gangopadhyay, P.; Binay, K.; Nandy, S. K.; Fang, J.-M. Tetrahedron Lett. **1998**, *39*, 8365−8366. (b) Liu, S.; Crowe, W. E.; *ACS 216th National Meeting Abstracts*, American Chemical Society, Washington, DC, 1998; ORGN-235. (c) Booker-Milburn, K. I.; Cowell, J. K.; Harris, L. J. *Tetrahedron* **1997**, *53*, 12319−12338. (d) Lange, G. L.; Organ, M. G. *J. Org. Chem.* **1996**, *61*, 5358−5361. (e) Booker-Milburn, K. I.; Cowell, J. K. *Tetrahedron Lett.* **1996**, *37*, 2177−2180. (f) Juliano, C. A. Thesis Dissertation, Florida State University, 1994. (g) Booker-Milburn, K. I.; Cowell, J. K.; Harris, L. J. *Tetrahedron Lett.* **1994**, *35*, 3883−3886. (h) Meister, P. G. Thesis Dissertation, Ohio State University 1991. For recent reviews on the synthesis of cyclooctanoids, see: (i) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930. (j) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609.

(5) (a) Cheung, Y. Y.; Krafft, M. E.; Juliano-Capucao, C. A. *ACS 216th National Meeting Abstracts*, American Chemical Society, Washington, DC, 1998; ORGN-238. (b) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742-2748. (c) Krafft, M. E.; Juliano−Capucao, C. A. *Synthesis* **2000**, 0000.

(6) (a) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904−5906. (b) Ihle, N. C. Thesis Dissertation, Stanford University, 1989.

(7) (a) Yoshihiko, I.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013. (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zeng, D. *Tetrahedron Lett.* **1995**, *36*, 2423−2426.

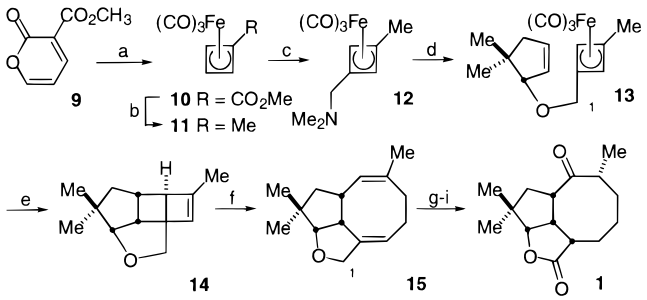
(8) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *37*, 1986−2012. (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763−784.

(9) Enantiomeric excess of **7** was determined by gas chromatography analysis on Supelco's Alpha Dex 120 fused silica capillary column.

(10) Agar, J.; Kaplan, F.; Roberts, B. W. *J. Org. Chem.* **1974**, *39*, 3451−3452.

10.1021/ja001946b CCC: $19.00
Published on Web 08/04/2000

Scheme 2. Total Synthesis of (+)-Asteriscanolide[a]



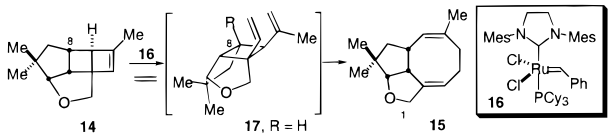
[a] Key: (a) hν, C_6H_6; $Fe_2(CO)_9$, 50 °C (64%), (b) LAH, $BF_3{\cdot}OEt_2$ (93%), (c) $Me_2NCH_2NMe_2$, H_3PO_4, CH_3CO_2H, 100 °C (67%); (d) MeI, THF; NaH, **7**, THF/DMF (50%), (e) Me_3NO, acetone, 56 °C (63%), (f) $H_2C{=}CH_2$, **16**, benzene, 50−80 °C (74%), (g) PCC, pyr, 4 Å MS, CH_2Cl_2 (79%), (h) Red-Al, CuBr; AcOH, THF (89%), (i) $BH_3{\cdot}OEt_2$, THF; PCC, 4 Å MS, CH_2Cl_2 (60%).

generated from **10** by exhaustive reduction of the ester functionality to a methyl group using LAH and $BF_3{\cdot}OEt_2$.[11] Further functionalization of the cyclobutadiene moiety was accomplished through an electrophilic aminomethylation[12] to provide the *p*-substituted cyclobutadiene complex **12** and the corresponding *o*-substituted product (67% yield, 3:1). After in situ methylation of cyclobutadiene **12**, etherification with the sodium salt of cyclopentenol **7** generated the cycloaddition precursor **13**.

The release of iron tricarbonyl from cyclobutadiene **13** under mild conditions (CAN, 23 °C, acetone) formed products resulting predominantly from intermolecular cycloadditions; however, increasing the reaction temperature and reducing the rate of the oxidation of the iron tricarbonyl group improved the efficiency of the intramolecular process. After optimization, the highly functionalized cycloadduct **14** could be obtained in 63% yield by heating compound **13** with trimethylamine *N*-oxide in acetone.

With the key cycloadduct **14** in hand, efforts turned toward generating the dialkenyl cyclobutane (i.e., **17**). Precedent for a selective ring-opening metathesis of a strained trisubstituted olefin, however, was lacking. Given that the metathesis partner was ethylene and the recent introduction of more reactive ruthenium alkylidenes (**16**),[13] there were grounds for optimism. Nonetheless, had the cross metathesis failed, recourse to a protocol involving oxidative cleavage of the trisubstituted olefin followed by bis-olefination of the bis-aldehyde was still available.

Gratifyingly, treatment of cyclobutene **14** with ruthenium benzylidene **16** (5 mol %, 50 °C, 10 h) in benzene under an ethylene atmosphere, followed by reflux (10 h) produced cyclooctadiene **15** in 74% yield. Evidently, the dialkenyl cyclobutane **17** formed initially in the ring-opening metathesis proceeds with the Cope rearrangement under the relatively mild reaction conditions. One reason we had not observed previously this facile rearrangement may be that, in contrast to our earlier examples,[2b] cyclobutane **17** lacks a β-alkyl substituent on C-8 (i.e., **17** R = H).



Completion of the formal synthesis of **1** was accomplished through allylic oxidation of compound **15**.[14] Treatment of **15** with PCC, 4 Å MS, and pyridine in CH_2Cl_2 provided a 79% yield of Wender's lactone **2**.[15] Further elaboration of intermediate **2** to the natural product followed the sequence described in the Wender synthesis: Selective 1,4-reduction of the unsaturated lactone was accomplished with Red-Al and CuBr.[16] To complete the synthesis, the C-7 ketone was then installed through a BH_3 reduction of the remaining olefin, followed by PCC oxidation of the resulting alkyl borane.[17]

This nine-step route to asteriscanolide serves, in part, to demonstrate the utility of several transformations that have not yet been tested in complex molecule synthesis. An intramolecular cyclobutadiene cycloaddition was employed to prepare a highly functionalized trisubstituted cyclobutene (**13** → **14**). This hindered cyclobutene was then subjected to a selective ring-opening metathesis with ethylene to generate directly the ring system of the natural product (**14** → [**17**] → **15**). The convergent nature of the synthesis (**7** + **12** → **13**), coupled with the effective preparation of the cyclooctadiene functionality using several new transformations allowed for a concise preparation of the natural product. Efforts to explore and expand further the utility of these transformations are underway.

Acknowledgment. We are grateful to the National Science Foundation and ACS PRF for generous support of this research. Discussions with John Tallarico and Suzanne Stokes are also appreciated. M.L.S. also acknowledges the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Glaxo-Wellcome, and DuPont for additional support.

Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001946B

(11) For an alternative preparation of complex **11**, see: Bunz, U. *Organometallics* **1993**, *12*, 3594−3597.

(12) For a similar reaction with ferrocene, see: Lednicer, D.; Hauser, C. R. *Organic Syntheses*; Wiley & Sons, New York, 1973; *Collect. Vol. 5*, pp 434−436.

(13) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753 and references therein. For references to related ruthenium catalysts, see: (c) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207 and references therein.

(14) (a) Bonadies, F.; Di Fabio, R. *J. Org. Chem.* **1984**, *49*, 1647−1649. (b) Bonadies, F.; Bonini, C. *Synth. Commun.* **1988**, *18*, 1573−1580.

(15) Spectrographic and physical properties of the compound generated were identical to previously reported data.

(16) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.

(17) (a) Rao, V. V. R.; Devaprabhakara, D.; Chandrasekaran, S. *J. Organomet. Chem.* **1978**, *162*, C9. (b) Lansbury, P. T.; Nickson, T. E. *Tetrahedron Lett.* **1982**, *23*, 2627. (c) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.