ORGANIC LETTERS

2001
Vol. 3, No. 22
3535−3538

One-Step Convergent Synthesis of the Steroid Ring System via the Coupling of γ,δ-Unsaturated Fischer Carbene Complexes with *o*-Ethynylbenzaldehyde

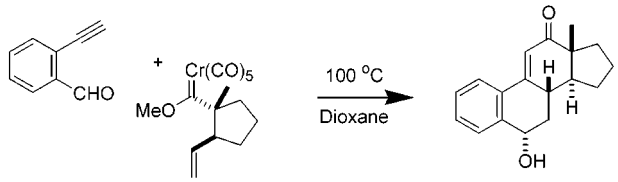
Binay K. Ghorai,[†] James W. Herndon,*[,†] and Yiu-Fai Lam[‡]

Department of Chemistry & Biochemistry, New Mexico State University, MSC 3C, Las Cruces, New Mexico 88003, and Department of Chemistry & Biochemistry, University of Maryland, College Park, Maryland, 20742-2021

jherndon@nmsu.edu

Received August 23, 2001

ABSTRACT



Simultaneous and stereoselective construction of the steroid B and C rings is observed in a tandem process involving the coupling of *o*-ethynylbenzaldehyde with 2-alkenylcyclopentylcarbene–chromium complexes.

Nearly one-third of all currently prescribed medications contain the steroid ring system.[1] Many medicinally important steroid derivatives do not occur in nature[2] and must be synthesized in the laboratory. In addition, recently discovered marine sterols of unusual structure have proven to be promising candidates for new pharmaceuticals.[3] Total synthesis of steroids[4] from simple components can potentially provide a more diverse array of steroidal therapeutic agents than simple derivatization of naturally occurring steroids. A variety of reaction processes exist for the construction of the steroid ring system; however, most of these processes involve multistep synthetic transformations. A few recent reports highlight the construction of the steroid ring system through tandem reaction processes.[5] Historically, some of the most notable demonstrations of this approach utilize intramolecular Diels−Alder reactions of *o*-quinonedimethanes[6] and occasionally isobenzofurans.[7] A disadvantage of this approach is that most of the carbons are already in place in the starting material and often necessitate a lengthy synthetic procedure, thus destroying the overall convergency and flexibility of the method. In a recent publication, we reported

[†] New Mexico State University.
[‡] University of Maryland.

(1) (a) Makin, H. L. J.; Trafford, D. J. H.; Nolan, J. *Mass Spectra and GC Data of Steroids*; Wiley-VCH: Weinheim, 1998. (b) Zeelen, F. J. *Medicinal Chemistry of Steroids*; Elsevier: Amsterdam, 1990.

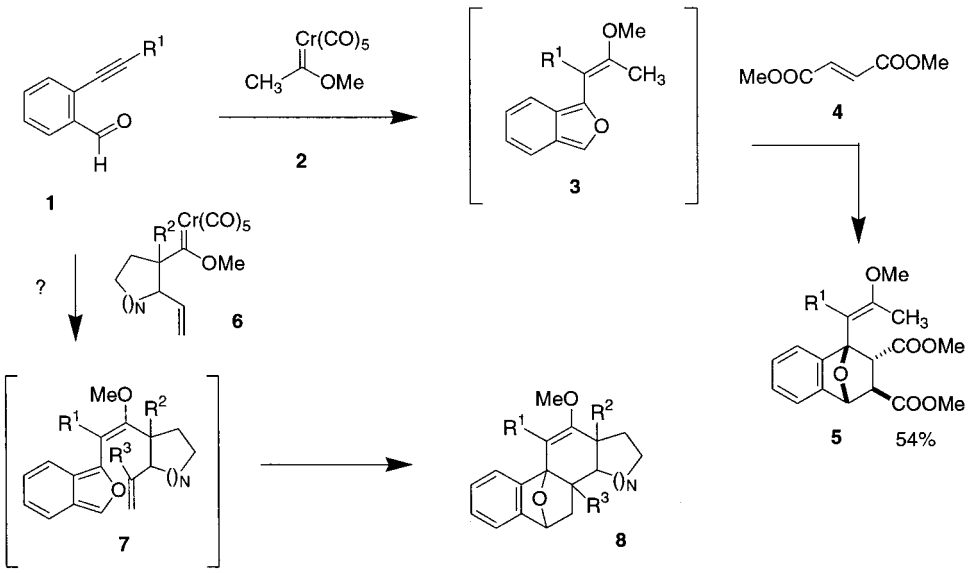
(2) Recent citations: (a) Cook, C. E.; Raje, P.; Lee, D. Y. W.; Kepler, J. A. *Org. Lett.* **2001**, *3*, 1013−1016. (b) Fortin, D.; Gaudette, F.; Marsault, E.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4167−4177. (c) Anderson, A.; Boyd, A. C.; Clark, J. K.; Fielding, L.; Gemmell, D. K.; Hamilton, N. M.; Maidment, M. S.; May, V.; McGuire, R.; McPhail, P.; Sansbury, F. H.; Sundaram, H.; Taylor, R. *J. Med. Chem.* **2000**, *43*, 4118−4125. (d) Cabeza, M.; Quiroz, A.; Heuze, I.; Bratoeff, E.; Herrera, H.; Ramirez, E.; Murillo, E. *Proc. West. Pharmacol. Soc.* **2000**, *43*, 31−32. (e) Sperry, T. S.; Thomas, P. *Biol. Reprod.* **1999**, *61*, 1152−1161. (f) Hastings, N. B.; Orchinik, M.; Aubourg, M. V.; McEwen, B. S. *Endocrinology* **1999**, *140*, 4459−4469. (g) Little, R. J.; Bodor, N.; Loftsson, T. *Pharm. Res.* **1999**, *16*, 961−967. (h) Park-Chung, M.; Malayev, A.; Purdy, R. H.; Gibbs, T. T.; Farb, D. H. *Brain Res.* **1999**, *830*, 72−87. (i) Nedvidkova, J.; Haluzik, M.; Pacak, K.; Schreiber, V.; Starka, L. *J. Steroid Biochem. Mol. Biol.* **1998**, *67*, 359−362. (j) Hult, M.; Jornvall, H.; Oppermann, U. C. T. *FEBS Lett.* **1998**, *441*, 25−28. (k) Gonzalez-Vidal, M. D.; Cervera-Gaviria, M.; Ruelas, R.; Escobar, A.; Morali, G.; Cervantes, M. *Arch. Med. Res.* **1998**, *29*, 117−124. (l) Lemus, A. E.; Jaimez, R.; Lemini, C.; Menjivar, M.; Silva, G.; Rubio-Poo, C.; Valenzuela, F.; Larrea, F. *Steroids* **1998**, *63*, 433−438. (m) Dijkema, R.; Schoonen, W. G. E. J.; Teuwen, R.; Van Der Struik, E.; De Ries, R. J. H.; Van Der Kar, B. A. T.; Olijve, W. J. *Steroid Biochem. Mol. Biol.* **1998**, *64*, 147−156. (n) Hoffmann, K.; Auer, T.; Stucker, M.; Hoffmann, A.; Altmeyer, P. *J. Eur. Acad. Dermatol. Venereol.* **1998**, *10*, 137−142.

(3) Lerch, M. L.; Faulkner, D. J. *Tetrahedron* **2001**, *57*, 4091−4094.

(4) (a) Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607−612. (b) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465−487.

10.1021/ol0166404 CCC: $20.00
Published on Web 10/04/2001

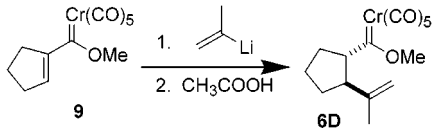
Scheme 1



that isobenzofurans (e.g., **3**, Scheme 1) can be generated from the couplings of Fischer carbene complexes (e.g., **2**) with *o*-alkynylbenzaldehyde derivatives (e.g., **1**)[8] and that these intermediates are captured moderately efficiently through intermolecular Diels−Alder reactions with electron deficient alkenes. In this Letter, the coupling of 2-ethynylbenzaldehyde with 2-alkenylcyclopentylcarbene complexes (**6**) will be discussed, which ultimately results in a compound containing the steroid ring system (**8**) in a single operation[9] from two components featuring only the steroid A and D rings intact. *The same reaction that joins the A and D rings also generates the reactive intermediates leading to the B and C rings.*

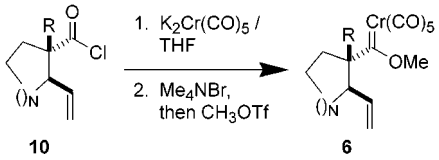
Requisite *trans* 2-alkenylcyclopentylcarbene complexes (**6**) were readily prepared using the series of reactions in Schemes 2 and 3. Michael addition of alkenyllithium reagents

Scheme 2



to cyclopentenylcarbene complex **9** offers the most straightforward route to the desired substrates (Scheme 2);[10] however, this reaction was only successful using 2-propenyllithium. Alternatively, the requisite carbene complexes could be prepared from the corresponding acid chlorides (**10**, Scheme 3) using pentacarbonylchromate dianions.[11] A

Scheme 3



general synthetic route to ester analogues of acid chloride **10** is depicted in Scheme 4. Michael addition of sulfoxide-stabilized carbanions (e.g., **16**) to ω-iodo-α,β-unsaturated ester derivatives (e.g., **15**),[12] followed by intramolecular S_N2

(5) (a) Michellys, P. Y.; Marin, P.; Toupet, L.; Pellissier, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 115−122. (b) Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971−8977.

(6) (a) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41−61. (b) For the most recent example, see: Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 843−845. (c) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3−16. (d) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463−1470. (e) Oppolzer, W.; Petrzilka, M.; Baettig, K. *Helv. Chim. Acta* **1977**, *60*, 2964−2967. (f) Quinkert, G.; Weber, W. D.; Schwartz, U.; Stark, H.; Baier, H. Duerner, G. *Liebigs Ann. Chem.* **1981**, 2335−2371.

(7) (a) Peters, O.; Debaerdemaeker, T.; Friedrichsen, W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 59−70. (b) Hildebrandt, K.; Friedrichsen, W. *Heterocycles* **1989**, *29*, 1243−1246.

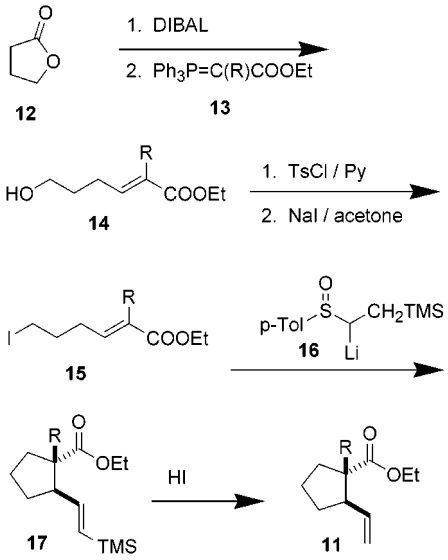
(8) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267−1269.

(9) Previous utilization of Fischer carbene complexes for steroid ring construction has been documented; however, they are unrelated to the reaction under discussion in this paper. (a) Bao, J.; Dragisch, V.; Winglowsky, S.; Wulff, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 9873−9875. (b) Aumann, R.; Meyer, A, G.; Frölich, R. *J. Am. Chem. Soc.* **1996**, *118*, 10853−10861. (c) Woodgate, P. D.; Sutherland, H. S.; Rickard, C. E. F. *J. Organomet. Chem.* **2001**, *627*, 206−220.

(10) For recent examples of successful Michael Additions using alkyllithiums and aryllithiums, see: (a) Barluenga, J.; Montserrat, J. M.; Florez, J.; Garcia-Granda, S.; Martin, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1392−1394. (b) Barluenga, J.; Bernad, P. L., Jr.; Concellon, J. M.; Pinera-Nicolas, A.; Garcia-Granda, S. *J. Org. Chem.* **1997**, *62*, 6870−6875. (c) Barluenga, J.; Bernad, P. L. Jr.; Concellon, J. M. *Tetrahedron Lett.* **1995**, *36*, 3937−3940.

(11) (a) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814−2819. (b) Semmelhack, M. F.; Lee, G. R. *Organometallics* **1987**, *6*, 1839−1844. (c) For specific use of this reaction for the synthesis of γ,δ-unsaturated carbene complexes, see: Moser, W. H. Hegedus, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 7873−7880.

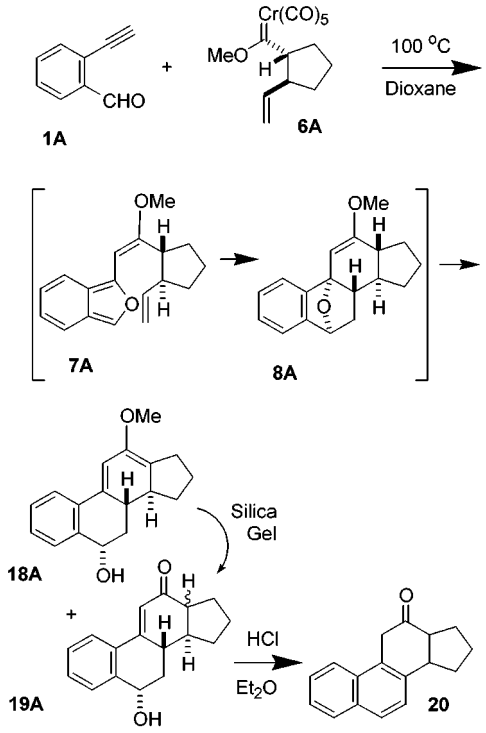
Scheme 4



reaction of the resulting enolate and spontaneous sulfoxide elimination (conversion of **15** to **17**), is the key step in this synthetic sequence. A carbene complex derivative featuring a six-membered ring has previously been reported.[11c]

Coupling of carbene complex **6A** (Scheme 5) with alkynyl aldehyde **1A** afforded tetracyclic compound **19A** as a mixture of two separable diastereomers in a combined yield of 66%. The crude reaction mixture also showed an impurity consistent with enol ether **18A**, which hydrolyzed to **19A** during

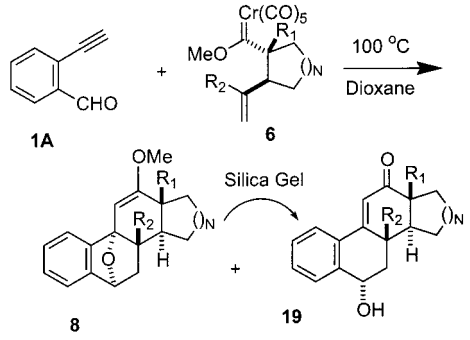
Scheme 5



chromatographic purification. The initial Diels−Alder product **8A** appears to be unstable with respect to ring opening processes.[13] The *cis* hydrindane was the major isomer (about 60:40); however, the isomer ratio was not consistent over several experiments. The isomers of **19A** differ at the position α to the ketone; **19A** *cis* and *trans* were interconverted by treatment with *p*-toluenesulfonic acid. Both products result from intramolecular *exo* selective Diels−Alder reaction[14] in isobenzofuran intermediate **7A**, which also proceeds with a very high degree of relative asymmetric induction relative to the allylic stereocenter in the starting carbene complex. Subsequent ring opening of the initial Diels−Alder product **8A** followed by proton transfer and hydrolysis affords the observed products, isomers of steroid derivative **19A**. As further verification of the steroid structure, treatment of **19A** with hydrochloric acid resulted in naphthalene derivative **20**.

This reaction process was tested for a variety of similar compounds (Scheme 6). Carbene complex **6B**, which features

Scheme 6



6, 8, 19
A R_1 = H, R_2 = H, N = 1
B R_1 = CH_3, R_2 = H, N = 1
C R_1 = H, R_2 = H, N = 2
D R_1 = H, R_2 = CH_3 , N = 1

an α methyl group, afforded tetracyclic compound **19B** as a single diastereomer in 49% yield. A trace amount of the oxanorbornene-intact compound **8B** could be observed in the crude reaction mixture. Carbene complex **6C**, which features a six-membered ring, also afforded the expected compound **19C** as a single diastereomer in 75% yield, assigned as the *trans* diastereomer. The stereochemical configuration at the carbon α to the ketone appears to be under thermodynamic control since compounds **19A** and **19C** are of the opposite

(12) Nakamura, S.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 1758−1766. We have noticed that sulfoxide elimination from the initial adduct of **15** and **16** is surprisingly rapid at room temperature; the literature suggests the use of fluoride ion for simultaneous silicon and sulfoxide elimination.

(13) The sensitivity of the initial isobenzofuran Diels−Alder adducts is well-noted. (a) Friedrichsen, W.; *Adv. Heterocycl. Chem.* **1999**, *73*, 1−96. (b) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093-2135.

(14) For discussions of endo−exo selectivity in intramolecular Diels−Alder reactions of isobenzofurans and related compounds, see: (a) Meegalla, S. K.; Rodrigo, R. *Synthesis* **1989**, 942−944. (b) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040−2046. (c) Tobia, D.; B. Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611−2615.

configuration at this carbon. The observed isomeric preferences parallel well-known trends in hydrindane[15] and decalin chemistry.[16] An additional example featuring a 1,1-disubstituted alkene (**6D**) also afforded the desired steroidal product (**19D**) in 60% yield. Formation of the *trans* hydrindane system might be due to an unfavorable 1,3-diaxial interaction between the methyl group and the five-membered ring in the *cis* isomer in this case.

In summary, a one-step synthesis of the steroid ring system from readily available components has been presented. Further examination of this reaction for biologically relevant steroids and application of the key reaction process for the synthesis of other pharmaceutically important compounds is currently under examination.

Acknowledgment. We thank the National Institutes of Health (S01-GM08136-26), the NSF, and the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. BKG is thankful to the Bengal Engineering College (Deemed University), Howrah, India for Sabbatical Leave.

Supporting Information Available: Experimental procedures, characterization data for carbene complexes and steroid derivatives, and discussion of stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0166404

(15) (a) Lo Cicero, B.; Weisbuch, F.; Dana, G.; *J. Org. Chem.* **1981**, *46*, 914−919. (b) Allinger, N. L.; Tribble, M. T. *Tetrahedron* **1972**, *28*, 1191−1202.

(16) Thompson, H. W.; Long, D. J. *J. Org. Chem.* **1988**, *53*, 4201−4209.