

# The Development of a Facile Tandem Wolff/Cope Rearrangement for the Synthesis of Fused Carbocyclic Skeletons

Richmond Sarpong, Julius T. Su, and Brian M. Stoltz\*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

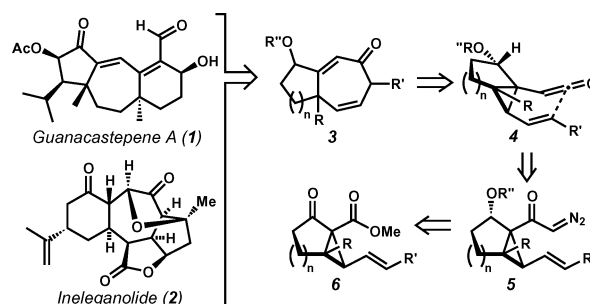
Received July 29, 2003; E-mail: stoltz@caltech.edu

The synthesis of medium-sized rings possessing functionality poised for further manipulation is a considerable challenge in synthetic chemistry.<sup>1</sup> In particular, seven-membered rings are increasingly common in many natural products of interest to the academic and pharmaceutical communities.<sup>2</sup> Our interest in the synthesis of fused  $[n - 7]$  bicyclic compounds ( $n = 5$  or  $6$ ) was piqued by the natural products guanacastepene (**1**)<sup>3</sup> and ineleganolide (**2**),<sup>4</sup> which have been identified as important synthetic targets due to their biological relevance and interesting structural architecture (Scheme 1). We envisioned either compound as arising from a core fused cycloheptadienone such as **3**, a motif not directly available using existing methodologies. Diene **3** was recognized to be the product of a ketene-Cope rearrangement with concomitant opening of a strained cyclopropane ring. In turn, ketene **4** could be produced by a Wolff rearrangement of diazo ketone **5**, readily available from known  $\beta$ -keto esters such as **6**.<sup>5</sup> Herein, we report the development of a new tandem Wolff/Cope rearrangement that allows mild, facile, and conceptually novel access to a range of  $[n - 7]$  bicycles.<sup>6</sup> We also describe the fortuitous observation that cycloheptadienones such as **3** can photolytically rearrange to the corresponding  $[n - 5]$  fused bicycles via a 1,3-acyl migration.

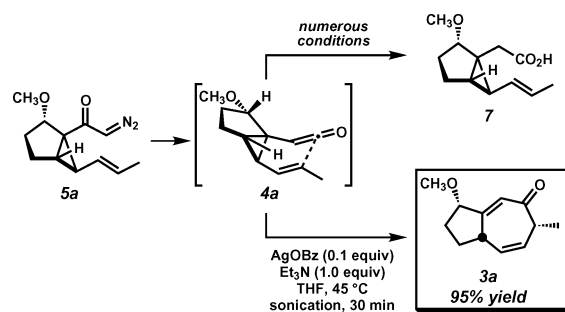
We initiated our efforts by preparing the parent fused  $[5 - 3]$  bicyclic diazo ketone **5a** and subjecting it to a battery of conditions known to promote Wolff rearrangements (Scheme 2). Since its discovery in 1902,<sup>7,8</sup> the Wolff rearrangement has been the subject of intense study, which has resulted in a variety of conditions known to promote the transformation.<sup>9</sup> Many of these standard protocols such as  $\text{Ag}_2\text{O}$ ,  $\text{AgOBz}$ ,  $\text{CuI}$ , and  $\text{Cu(0)}$  produced a complex mixture of products that included the homologated acid **7**.<sup>10</sup> Although production of **7** pointed toward the generation of the desired ketene intermediate (**4a**), it was clear that the strain release Cope rearrangement was not readily occurring. With this in mind, extensive literature searching and experimentation led to the use of modified sonochemical conditions, originally reported by Montero for simple Wolff rearrangements.<sup>11</sup> To our delight, treatment of diazo ketone **5a** under our modified Montero conditions employing  $\text{AgOBz}$  (0.1 equiv) and  $\text{Et}_3\text{N}$  (1.0 equiv) at  $45^\circ\text{C}$  in THF with sonication for 30 min led exclusively to the desired Wolff/Cope product (**3a**) in 95% isolated yield.

Using these optimized conditions, we investigated the substrate scope of this rearrangement for the synthesis of cycloheptadienones fused to five- or six-membered rings. As shown in Table 1, a variety of substitution on the diazo ketones is tolerated in the tandem rearrangement. The mild conditions support the rearrangement of substrates carrying a host of hydroxyl protection groups (entries 1–3) and even an enol ether (entry 4). Substitution on the olefin is also possible at both the terminal (entries 1–4 and 7) and internal positions (entry 5). Although olefin substitution is not a requirement for the tandem process, high yields of the cycloheptadienone products could be realized only under photolytic conditions in these cases (entries 6 and 8). Additionally, a bis-quaternary substituted

Scheme 1



Scheme 2



cyclopropane readily participates in the rearrangement and, in the case shown, produces a tricyclic dienone either under silver(I) or photochemical promotion (entry 7).<sup>12</sup> Finally, both  $[5 - 7]$  (entries 1–7) and  $[6 - 7]$  (entry 8) fused bicyclic dienones can be prepared by this methodology.

Although certain substrates produced high yields of the Wolff/Cope rearrangement products under both the sono- and photochemical conditions, others did not. For instance, while photolysis of **5a** did produce varying amounts of cycloheptadienone **3a**, prolonged exposure to light led to a new product, which was identified as the vinyl cyclopentenone **8a** (Scheme 3). This unexpected product likely arises by a Norrish Type I fragmentation followed by a recombination with the transient allyl radical, resulting in a net 1,3-acyl migration.<sup>13,14</sup> This mechanism and the intermediacy of **3a** were confirmed by independent photolysis of pure **3a**, which leads to the production of cyclopentenone **8a**. Of particular note is the complete diastereoselective nature of the rearrangement, which produces the fused bicyclo[3.3.0]octane (**8a**) as a single isomer. Interestingly, this cascade process constitutes a formal tandem Wolff/vinyl cyclopropane rearrangement.<sup>15</sup>

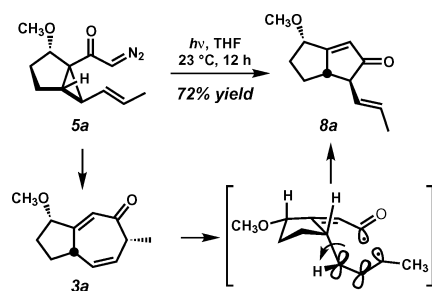
The application of this novel rearrangement trio (Wolff/Cope/1,3-acyl shift) to a variety of substrates is outlined in Table 2. Again, numerous protection groups as well as olefin substitution patterns are tolerated in the cascade. The diastereoselectivity of the process is maintained even for the production of an  $\alpha$ -quaternary substituted enone (entry 4). Furthermore, both  $[5 - 5]$  and  $[6 - 5]$  fused cyclopentenones are available in good yields. Finally, it is interesting

**Table 1.** Tandem Wolff/Cope Rearrangement

entry	substrate	product	conditions <sup>a</sup>	% yield
1.			R = CH <sub>3</sub> A	95
2.			R = MOM A	88
3.			R = PMB A	92
4.			A	98
5.			A	98
6.			B	80
7.			A B	76 94 <sup>b</sup>
8.			B	88

<sup>a</sup> Condition A: AgOBz (0.1 equiv), Et<sub>3</sub>N (1.0 equiv), THF, 45 °C, sonication for 30 min. Condition B: *hν* (310 nm), THF, 23 °C, 1 h.

<sup>b</sup> Experiment performed in PhH for 2 h.

**Scheme 3****Table 2.** Wolff/Cope/[1,3]-Acyl Shift Rearrangement

entry	substrate	product	conditions <sup>a</sup>	time	% yield
1.			R = CH <sub>3</sub> B	12 h	72
2.			R = MOM B	6 h	69
3.			R = PMB B	6 h	75
4.			B <sup>b</sup>	2 h	80
5.			A	0.5 h	57
6.			B <sup>c</sup> A	6 h 0.5 h	55 72

<sup>a</sup> Condition A: AgOBz (0.1 equiv), Et<sub>3</sub>N (1.0 equiv), THF, 45 °C, sonication. Condition B: *hν* (254 nm), THF, 23 °C. <sup>b</sup> Performed with a 450 W medium-pressure Hg lamp in THF at 40 °C. <sup>c</sup> *hν* (310 nm).

to note that in the cases of entries 5 and 6 (Table 2), better yields of the [6–5] fused bicycles were obtained using silver(I)/sonochemical activation than with photolytic initiation. Since we

have never observed the cycloheptadienone products from these substrates under nonphotolytic conditions (entries 5 and 6), we cannot exclude the possibility of a direct Wolff/vinyl cyclopropane rearrangement as a mechanism in these cases.

In summary, we have developed a set of mild processes for the conversion of vinyl cyclopropyl diazo ketones to highly functionalized cycloheptadienones (i.e., 5→3) and vinyl cyclopentenones (i.e., 5→8) by use of a target-inspired tandem Wolff/Cope rearrangement sequence. This facile methodology allows rapid access to a variety of structurally diverse, complex polycyclic enones. The utility of these new cascade sequences in complex synthetic problems is currently under investigation.

**Acknowledgment.** We are grateful to Research Corporation, Pfizer-UNCF (postdoctoral fellowship to R.S.), and the NSF (predoctoral fellowship to J.T.S.) for generous financial support. We also thank Neil K. Garg for assisting with advanced NMR experiments.

**Supporting Information Available:** Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603–609.
- (2) For reviews on seven-membered ring natural products, see: (a) Fraga, B. M. *Nat. Prod. Rep.* **1996**, *13*, 307–326. (b) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Greenwich, CT, 1999; Vol. 5, pp 1–45. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.
- (3) (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2117. (b) Recently, the total synthesis of guanacastepene was completed, see: Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. *J. Angew. Chem., Int. Ed.* **2002**, *41*, 2188–2191. (c) For a complete list of approaches to the guanacastepene core, see Supporting Information.
- (4) Duh, C.-Y.; Wang, S.-K.; Chia, M.-C.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033–6035.
- (5) For details, see Supporting Information.
- (6) A single example of a Wolff/Cope rearrangement has been reported, see: Freeman, P. K.; Kuper, D. G. *Chem. Ind. (London)* **1965**, 424–425.
- (7) Wolff, L. *Ann.* **1902**, 325, 129–195.
- (8) (a) For a review on the Wolff rearrangement, see: Doyle, M. P.; McKerver, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazocompounds*; Wiley: New York, 1998. (b) For a recent study of the Wolff rearrangement, see: Julian, R. R.; May, J. A.; Stoltz, B. M.; Beauchamp, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 4478–4486.
- (9) (a) Horner, L.; Spietschka, E. *Chem. Ber.* **1952**, *85*, 225–229. (b) Arndt, F.; Eistert, B. *Chem. Ber.* **1935**, *68*, 200–208. (c) Newman, M. S.; Beal, P. F. *J. Am. Chem. Soc.* **1950**, *72*, 5163–5165. (d) Yates, P.; Crawford, J. J. *J. Am. Chem. Soc.* **1966**, *88*, 1562–1563. (e) Yates, P.; Fugger, J. *Chem. Ind. (London)* **1957**, 1511–1511.
- (10) Analysis of the crude reaction mixtures suggested products resulting from reduction of the diazo group, C–H insertion, and cyclopropanation.
- (11) (a) Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* **1996**, *37*, 1781–1782. (b) Müller, A.; Vogt, C.; Sewald, N. *Synthesis* **1998**, 837–841.
- (12) The substrate in Table 1, entry 7 was designed using theoretical/computational insights. Su, J. T.; Sarpong, R.; Stoltz, B. M.; Goddard, W. A. California Institute of Technology, Pasadena, CA, 2003. Unpublished work.
- (13) For general reviews of Norrish Type I fragmentations, see: (a) Coyle, J. D.; Carless, H. A. *J. Chem. Soc. Rev.* **1972**, *1*, 465–480. (b) Chapman, O. L.; Weiss, D. S. *Org. Photochem.* **1973**, *3*, 197–277. (c) Horspool, W. M. *Photochemistry* **1994**, *25*, 67–100.
- (14) For a specific example which details a Norrish fragmentation with 1,3-acyl migration, see: Paquette, L. A.; Eizember, R. F. *J. Am. Chem. Soc.* **1967**, *89*, 6205–6208.
- (15) Recently, a dienyl Pauson–Khand reaction of enynes to access related vinyl cyclopentenones has been reported, see: Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1853–1857.

JA037587C