Pure Appl. Chem., Vol. 80, No. 5, pp. 1141–1148, 2008.
doi:10.1351/pac200880051141

Toward the total synthesis of ritterazine N*

Douglass F. Taber‡, Jean-Michel Joerger, and Karen V. Taluskie

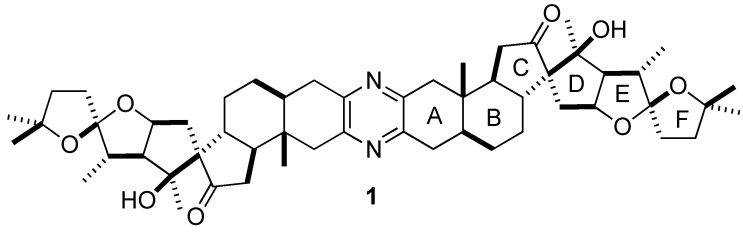
Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, USA

Abstract: Zr-mediated equilibrating cyclocarbonylation of a designed triene led with high diastereocontrol to the ABC 6-6-5 tricyclic core of ritterazine N. The 5-5 EF spiroketal side chain of ritterazine N was prepared by equilibrating cyclization of an acyclic keto diol. The two components were coupled, and the D ring was assembled by intramolecular aldol condensation.

Keywords: natural product synthesis; computational organometallic chemistry; spiroketal construction; ketone alkylation; chromatographic resolution.

INTRODUCTION

The ritterazines, represented by ritterazine N **1** (Fig. 1), found [1] in small quantities in the lipophilic extract of the tunicate *Ritterella tokioka*, induce apoptosis in apoptosis-resistant malignant cells. With the closely related cephalostatins, which show the same activity, they form a unique class of tris-decacyclic molecules featuring a pyrazine as the core ring, steroid-related structures, and spiroketal edge-rings (E and F). Partial syntheses from steroid precursors of several of the 6-6-6-5 cephalostatins and derivatives have been accomplished [2]. There has been no report of efforts other than our own [3] toward the 6-6-5-5 ritterazines.



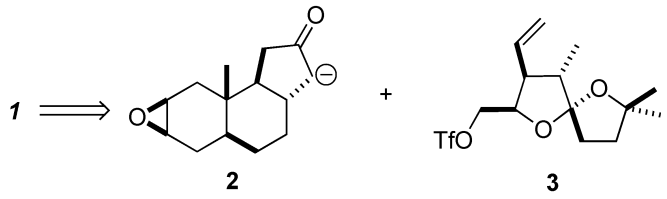
1

Fig. 1

To prepare ritterazine N **1**, we planned (Scheme 1) to alkylate the ketone **2** with the triflate **3**.

*Paper based on a presentation at the 14th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-14), 2–6 August 2007, Nara, Japan. Other presentations are published in this issue, pp. 807–1194.

‡Corresponding author: E-mail: taberdf@udel.edu

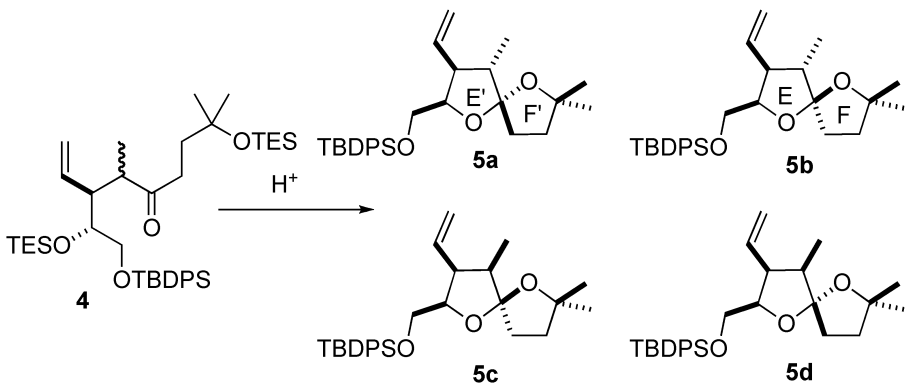


Scheme 1

RESULTS AND DISCUSSION

Synthetic approach to the spiroketal 3

We envisioned preparing **3** (Scheme 3) by the acid-catalyzed deprotection, cyclization, and equilibration of the ketone **4**, to give **5a**. Under acid-catalyzed conditions 6/5 and 6/6 spiroketals generally equilibrate toward a particular diastereoisomer due to anomeric or substituent stabilization in the six-membered rings, but 5/5-spiroketals typically equilibrate to nearly a 1:1 mixture of epimers. An advantage in the synthesis of **5a** is the presence of the methyl group adjacent to the spiro carbon, which we expected to exert significant stereocontrol. It was reasonable to expect that the methyl group on the E ring, which is cis to the vinyl group in **5c** and **5d**, would equilibrate to the trans form. MOPAC PM3 calculations [4] with model compounds further encouraged us to adopt this route to **5a** [3b].

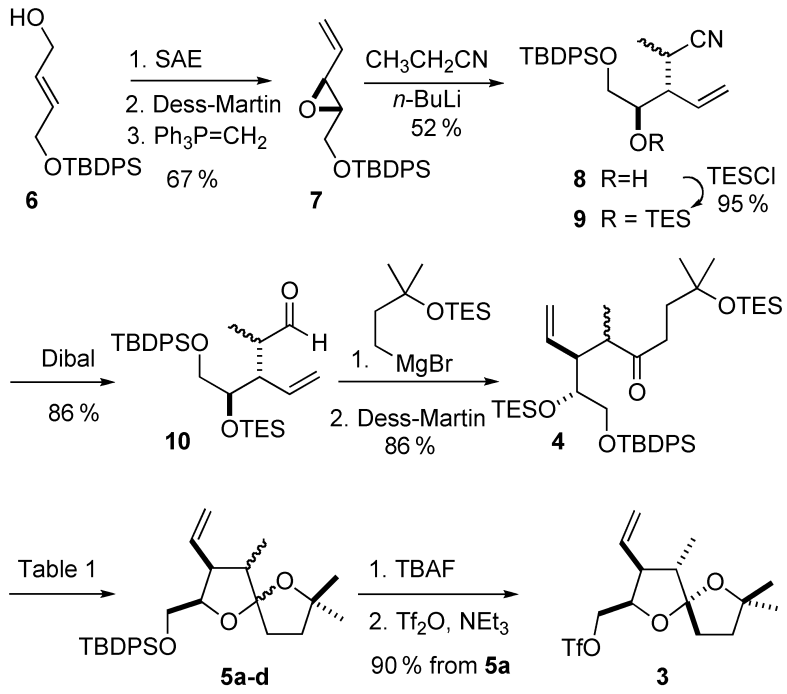


Scheme 2

Preparation of the spiroketal 3

The precursor **4** to the spiroketal **5** was prepared (Scheme 3) from the allylic alcohol **6** [5–8]. Sharpless epoxidation followed by oxidation to the aldehyde and methylenation gave the alkene **7**. Opening with the lithium salt of propionitrile provided **8** as the expected mixture of diastereomers. Attempted addition of nucleophiles converted **8** to the lactone, so the alcohol was protected as the TES ether before homologation to **4**.

The crucial deprotection/cyclization of **4** was carried out with aqueous HCl in THF (Table 1, entry 1). The four diastereomers **5a–5d** were separable by silica gel chromatography, and their structures could be assigned by NMR. The silyl ether **5a** was also converted to a crystalline derivative, and its structure was secured by X-ray analysis. Further equilibration of the mixture of **5a–5d** obtained in entry 1 was carried out with PPTS in CH_2Cl_2 (entry 2), which delivered **5a** in 74 % yield accompanied by 17 % of a mixture of the other three diastereomers. The recovered mixture of ketals **5b–5d** could be subjected again to equilibration. For example (entry 3), under PPTS-catalyzed conditions a mixture of **5c** and **5d** was converted to **5a** in 70 % yield, based on starting material not recovered [9].



Scheme 3

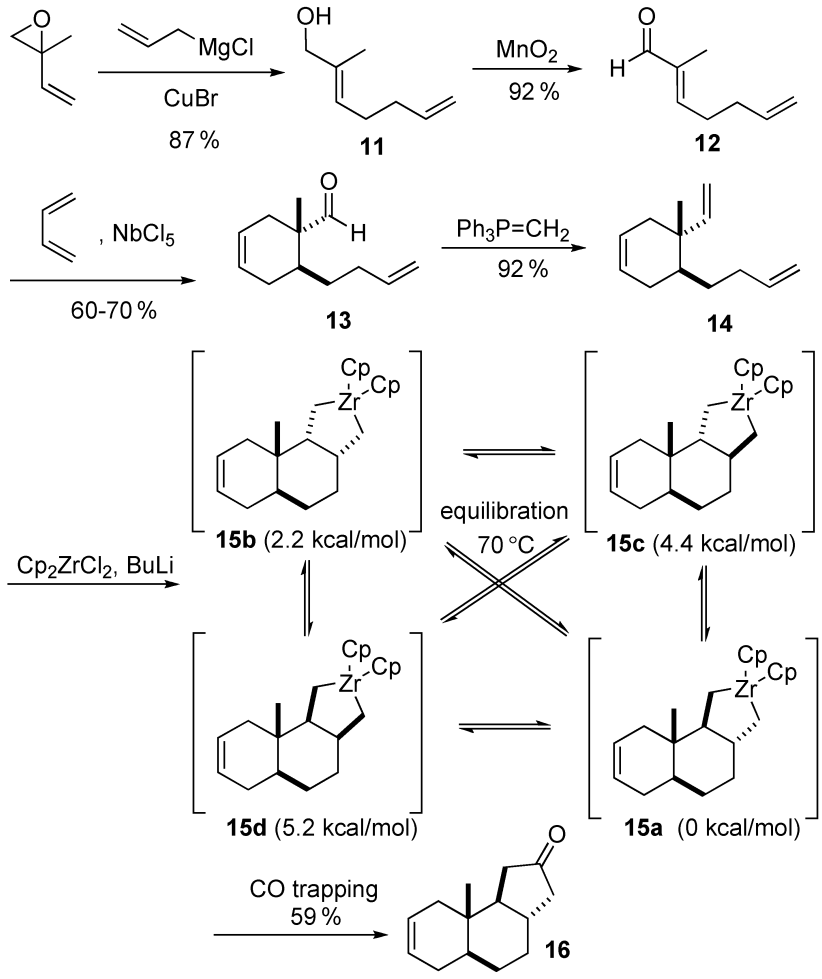
Table 1 Equilibration of diastereomers **5a–d**.

Entry	Starting material	Conditions	Yield			
			5a	**5b**	**5c**	**5d**
1	**4**	A[a]	37%[d]	3%[d]	33%[d]	15%[d]
2	Product mixture of entry 1	B[c]	74%[b]	17%[b] of a mixture of **5b-d**		
3	**5c** : **5d** = 71 : 29	B	62%[b]	3%[d]	8%[d]	3%[d]
4	**5a**	B	81%[b]	6%[b]	3%[b]	1%[b]
5	**5c**	C[e]	0[f]	0[f]	54%[f]	46%[f]
6	**5d**	C	0[f]	0[f]	40%[f]	60%[f]

[a]aq. 1 M HCl/THF (1:4), rt, 3 h.
[b]Isolated yield.
[c]PPTS (0.1 M), CH_2Cl_2, 80 °C (sealed flask), 5–7 h.
[d]Determined by NMR ratios from partially separated mixtures.
[e]In $CDCl_3$ for 4 weeks.
[f]NMR ratio.

Preparation of the steroid core

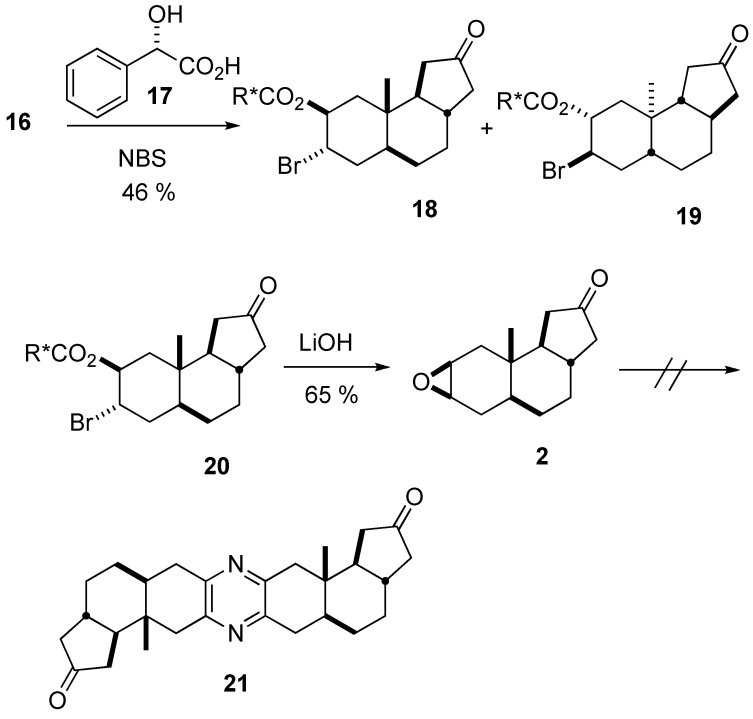
We have prepared **16** (Scheme 4) by cyclozirconation [10,11] of **14** followed by equilibration of the intermediate zirconacycles **15a–d** to the thermodynamically more stable **15a**, and trapping with carbon monoxide. The relative stability of the intermediate zirconacycles was predicted by ZINDO calculations [12].



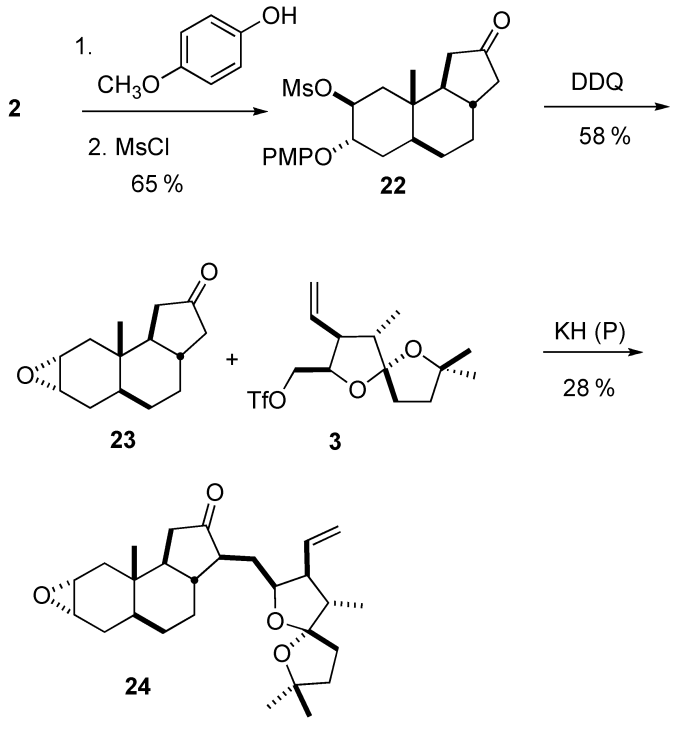
Scheme 4

Assembly of the building blocks and dimerization

The ketone **16** was racemic. To arrive at the enantiomerically pure epoxide **2**, we exposed (Scheme 5) racemic **16** to mandelic acid and *N*-bromosuccinimide in the presence of 2,6-lutidine [13]. As expected, just two diastereomeric bromomandelates were formed, the product of Br (+) complexation to the more accessible face of the alkene followed by diaxial opening with mandelate anion. The diastereomeric mandelates were separated by column chromatography. The structures were assigned by ^{1}H NMR analysis, following our earlier precedent [13]. This assignment was confirmed by X-ray analysis of the mesylate **22** (Scheme 6).



Scheme 5



Scheme 6

Saponification of the bromomandelate **20** led directly to the "up" epoxide **2**. We had previously shown that the analogous "down" epoxide, from direct epoxidation of **16**, could be dimerized to **21** by opening with azide, oxidation to the ketone, and reduction with Te/$NaBH_4$ [14,15]. To our surprise, only traces of **21** could be found when the same reductive protocol was applied to the azido ketone prepared from **2**. It was clear that we would need to convert the "up" epoxide to the "down" epoxide before proceeding with the synthesis.

Preparation and alkylation of the epoxy ketone

The epoxide of **2** was inverted (Scheme 6) by opening with 4-methoxy phenol, followed by mesylation, to give **22**. The mesylate **22** gave crystals that were suitable for X-ray analysis, confirming the previously assigned absolute configuration. Oxidative removal of the phenyl ether followed by cyclization then delivered the "down" epoxide **23**.

The alkylation of **23** was challenging. We anticipated that we could arrive at **24** by kinetic deprotonation of the more accessible methylene of **23**. In the event, the lithium enolate, prepared by exposing **23** to LDA, was not sufficiently reactive toward **3**, even at room temperature and above. We eventually found that exposure of **23** to KH, conveniently delivered as KH in paraffin [16], generated an enolate that reacted nearly quantitatively with the triflate **3**.

Successfully reacting **23** with **3** was not the end of the difficulties. The product was a mixture both of regioisomeric C-alkylation products, and also of enol ethers from O-alkylation. It was necessary to develop conditions for acidic hydrolysis of the O-alkylated byproducts without upsetting the acid-sensitive spiroketal. We found success by stirring the crude alkylated mixture with $CDCl_3$ (non-stabilized chloroform) containing a little bit of aqueous HCl. The regenerated **23** could then be separated from the alkylated product **24** and from the alkylated regioisomer by column chromatography.

The aldol condensation fails

We had originally envisoned (Fig. 2) that the diketone **25** could cyclize to the aldol product **1**. In the event, through a range of bases and solvents, we were not able to detect **1** in the crude reaction mix-

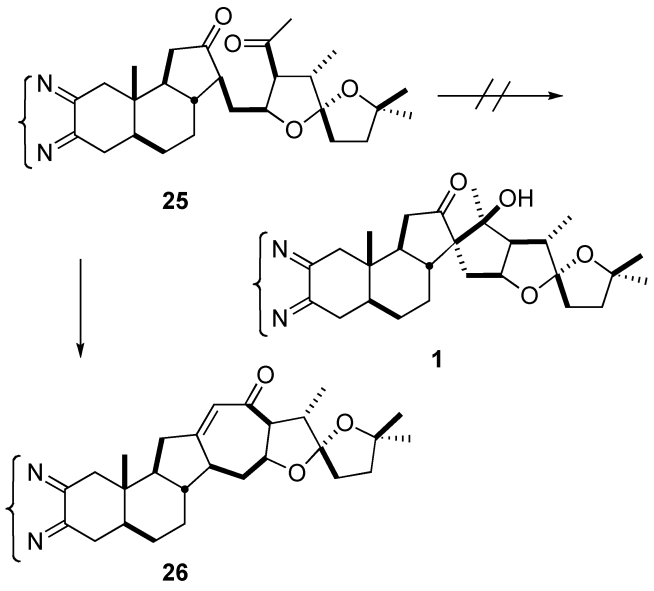
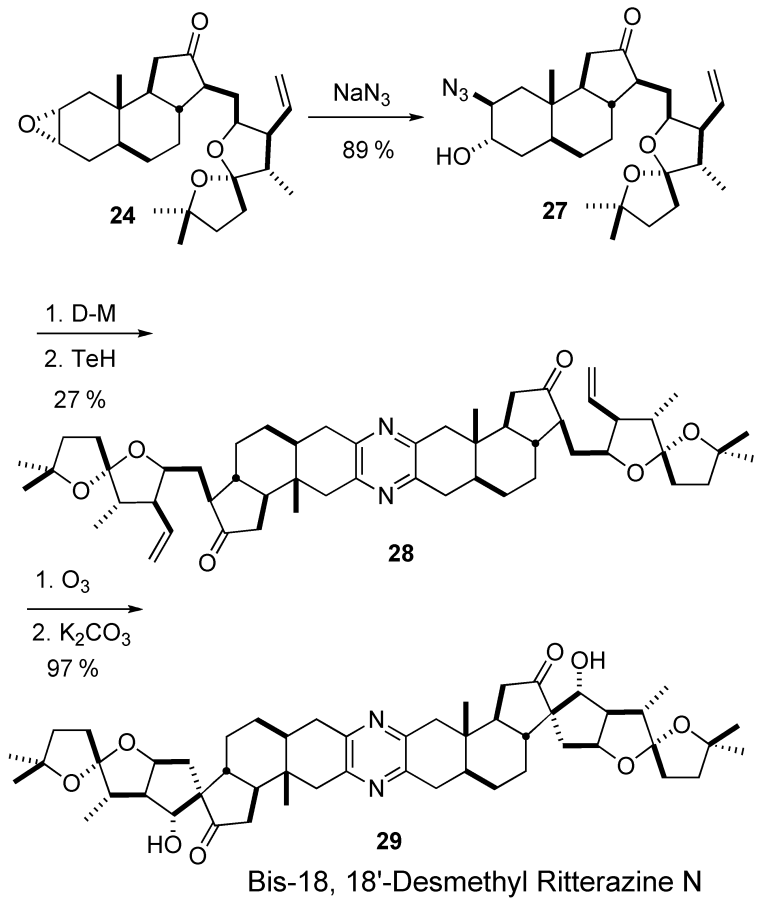


Fig. 2

tures. Rather, the product appeared to be the cycloheptenone **26**. We are investigating alternative strategies for the preparation of **1**.

Preparation of 18, 18'-desmethyl ritterazine N 29

In the course of our investigations, we prepared (Scheme 7) the dimerized pyrazine **28**. Diaxial opening of **24** with sodium azide delivered the alcohol **27**. The ketone from the oxidation of **27** was not stable, so we submitted it directly to dimerization condiions, to give **28**. We were pleased to observe that ozonolysis followed by brief exposure to base led to clean aldol condensation, to deliver 18, 18'-desmethyl ritterazine N **29** as a single diastereomer.



Scheme 7

CONCLUSION

We have prepared practical quantities of the enantiomerically pure ketones **2** and **23**, and of the triflate **3**, and we were able to alkylate the ketone **23** with the triflate **3**. The capability to dispense scrupulously dry KH in paraffin in micromole quantities [16] was critical for the success of this alkylation. For the first time, this makes derivatives such as **29**, having the full ring framework of the 6-6-5-5 ritterazines, available for further evaluation.

ACKNOWLEDGMENTS

We thank John Dykins for recording mass spectra, Steve Bai for NMR assistance, Glenn Yap for X-ray structures, and the NIH (GM 60287) for financial support of this work.

REFERENCES

1. S. Fukuzawa, S. Matsunaga, N. Fusetani. *J. Org. Chem.* **62**, 4484 (1997).
2. For leading references, see: (a) J. S. Lee, P. L. Fuchs *J. Am. Chem. Soc.* **127**, 13122 (2005); (b) M. Nawasreh, E. Winterfeldt. *Curr. Org. Chem.* **7**, 649 (2003).
3. For our published work toward the ritterazines, see: (a) D. F. Taber, K. V. Taluskie. *J. Org. Chem.* **71**, 2797 (2006); (b) D. F. Taber, J.-M. Joerger. *J. Org. Chem.* **72**, 3454 (2007).
4. For leading references to PM3, see: J. I. Seeman, J. B. Paine III, H. V. Secor, H. S. Im, E. R. Bernstein. *J. Am. Chem. Soc.* **114**, 5269 (1992).
5. M. G. Organ, J. T. Cooper, L. R. Rogers, F. Soleymanzadeh, T. Paul. *J. Org. Chem.* **65**, 7959 (2000).
6. Y. Mori, M. Asai, J.-i. Kawade, H. Furukawa. *Tetrahedron* **51**, 5315 (1995).
7. W. R. Roush, J. A. Straub, M. S. VanNieuwenhze. *J. Org. Chem.* **56**, 1638 (1991).
8. (a) M. Larchevêque, A. Debal. *Synth. Commun.* **10**, 49 (1980); (b) S. K. Taylor, D. DeYoung, L. J. Simons, J. R. Vyvyan, M. A. Wemple, N. K. Wood. *Synth. Commun.* **28**, 1691 (1998).
9. In parallel with our work, Shair reached the same conclusion about the relative configuration of the spiro center of the ritterazines: S. T. Phillips, M. D. Shair. *J. Am. Chem. Soc*. **129**, 6589 (2007).
10. For the development of intramolecular diene cyclozirconation, including computational analysis, see: (a) W. A Nugent, D. F Taber. *J. Am. Chem. Soc.* **111**, 6435 (1989); (b) D. F. Taber, J. P. Louey, Y. Wang, W. A. Nugent, D. A. Dixon, R. L. Harlow. *J. Am. Chem. Soc.* **116**, 9457 (1994).
11. For the development of Zr-based intramolecular diene cyclocarbonylation, see: (a) E. Negishi, S. R. Miller. *J. Org. Chem.* **54**, 6014 (1989); (b) D. F. Taber, Y. Wang. *J. Am. Chem. Soc.* **119**, 22 (1997); (c) D. F. Taber, W. Zhang, C. L. Campbell, A. R. Rheingold, C. D. Incarvito. *J. Am. Chem. Soc.* **122**, 4813 (2000).
12. For a leading reference to the use of ZINDO for transition-metal calculations, see: D. R. Kanis, M. A. Ratner, T. J. Marks, M. C. Zerner. *Chem. Mater.* **3**, 19 (1991). Both ZINDO and MOPAC were used as implemented on a Tektronix CAChe workstation.
13. D. F. Taber, J. Liang. *J. Org. Chem.* **72**, 4313 (2007).
14. (a) H. Suzuki, T. Kawaguchi, K. Takaoka. *Bull. Chem. Soc. Jap.* **59**, 665 (1986); (b) J. U. Jeong, S. C. Sutton, S. Kim, P. L. Fuchs. *J. Am. Chem. Soc.* **117**, 10157 (1995).
15. For an alternative route to pyrazines, see: D. F. Taber, P. W. DeMatteo, K. V. Taluskie. *J. Org. Chem*. **72**, 1492 (2007).
16. For the advantages of KH in paraffin, see: D. F. Taber, C. G. Nelson. *J. Org. Chem.* **71**, 8973 (2006).