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Intramolecular [1 + 4 + 1] Cycloaddition: Establishment of the Method

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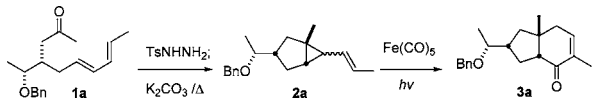
Abstract: Structurally complex and physiologically active natural products often include bicyclic and polycyclic ring systems having defined relative and absolute configuration. Approaches that allow the construction of more than one carbocyclic ring at a time have proven valuable, in particular those that allow at the same time the control of an array of new stereogenic centers. One of the most general and most widely used protocols has been the intramolecular Diels−Alder [4 + 2] cycloaddition, in which a single stereogenic center between the diene and the dienophile can control the relative and absolute configuration of the product. We report a two-step [1 + 4 + 1] procedure for bicyclic and polycyclic construction, based on the cyclization of an ω-dienyl ketone. This is complementary to, and will likely be as useful as, the intramolecular Diels−Alder cycloaddition.

Introduction

Carbocycles, as exemplified by calcitriol and taxol, can be potent drugs. Although computationally driven lead generation often suggests potential new drug candidates that are polycarbocyclic, such candidates are usually not pursued, because of the assumption that a carbocyclic drug would be impractical to manufacture.[1] We report a simple two-step route (eq 1) to the enantiomerically pure carbobicyclic scaffold **3a** from the acyclic ketone **1a** (eq 1).[2]



(1)

The construction of carbobicylic 5,6- or 6,6-systems is of great importance in the preparation of structurally complex and biologically intriguing natural products.[3] Among those ring forming strategies, intramolecular Diels−Alder (IDA) cycloaddition has received intensive attention for decades because condensation of the dienophile onto the diene directed by a single stereogenic center can generate simultaneously up to four new stereogenic centers in a highly steroselective and often predictable fashion.[4] Seeking a complementary protocol, we anticipated that cyclization of an acyclic diene ketone **1a** followed by Fe-mediated cyclocarbonylation of the resulting alkenyl cyclopropane **2a** could efficiently deliver the bicyclic enone **3a** with high diastereocontrol.

There were three concerns with this strategy. The first and most important question was whether we could develop a method for the cyclization of a dienyl ketone such as **1a** to the alkenyl cyclopropane **2a**. The second question was whether a substituent on the bridge between the ketone and the diene could direct the new stereogenic centers as they formed. The last question was whether Fe-mediated cyclocarbonylation would work with such congested alkenyl cyclopropanes.

Results and Discussion

Novel Metal-Free Synthesis of Bicyclic and Tricyclic Alkenyl Cyclopropanes. We had reported (Scheme 1) that heating the tosylhydrazone of an ω-alkenyl ketone **4** or aldehyde to reflux in toluene in the presence of K_2CO_3 delivered the bicyclic diazene **5** and that irradiation of the diazene converted it to the cyclopropane **6**.[5] In consideration of the high reaction temperature (130 °C), we envisioned that activation of the diazene **7** by an additional alkenyl substituent might enable spontaneous extrusion of N_2. The diradical intermediate **8** so generated could cyclize to the alkenyl cyclopropane **2b** or to the cyclopentene

(1) (a) For an overview of synthetic strategies for polycarbocyclic natural products, see. Taber, D. F.; Sheth, R. B.; Tian, W. *J. Org. Chem.* **2009**, *74*, 2433. For more recent examples, see. (b) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737. (c) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865. (d) Trost, B. M.; Ferreira, E. M.; Gutierrez, A. C. *J. Am. Chem. Soc.* **2008**, *130*, 16176. (e) Pardeshi, S. G.; Ward, D. E. *J. Org. Chem.* **2008**, *73*, 1071. (f) Li, L.; McDonald, R.; West, F. G. *Org. Lett.* **2008**, *10*, 3733. (g) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315. (h) Maity, P.; Lepore, S. D. *J. Am. Chem. Soc.* **2009**, *131*, 4196. (i) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556.

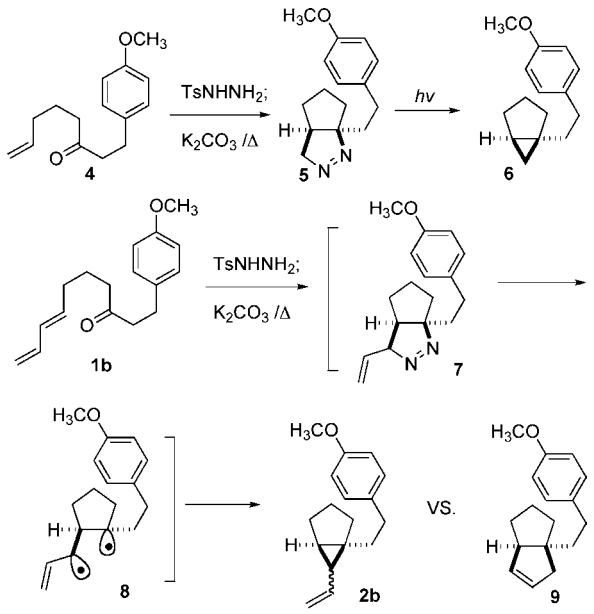
(2) For a previous example of intramolecular cyclopropanation followed by Fe-mediated cyclocarbonylation, see ref 1a.

(3) (a) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, 10264–10266. (b) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, 4552–4553. (c) Taber, D. F.; Nakajima, K.; Xu, M.; Rheingold, A. L. *J. Org. Chem.* **2002**, 4501–4504. (d) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, 4475–4479. (e) Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, 12169–12173. (f) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, 7411–7419.

(4) (a) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, 3992. (b) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, 5085. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, 4779–4807. (d) Craig, D. *Chem. Soc. Rev.* **1987**, 187–238.

(5) (a) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479. For earlier accounts of this sort of cyclization, see. (b) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756. (c) Brinker, U. H.; Schrievers, T.; Xu, L. *J. Am. Chem. Soc.* **1990**, *112*, 8609. (d) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424. (e) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659.

Scheme 1

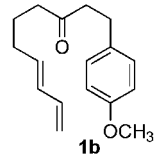
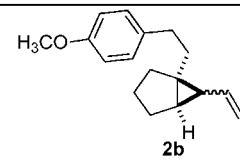
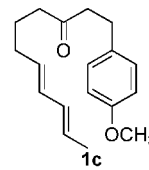
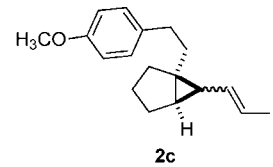
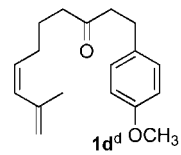
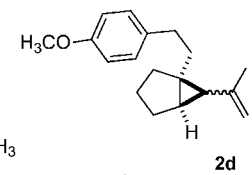
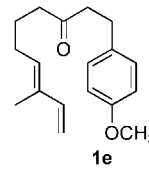
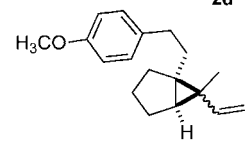
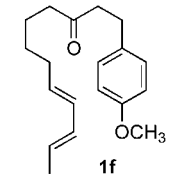
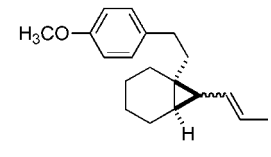
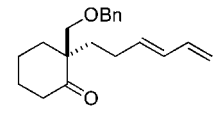
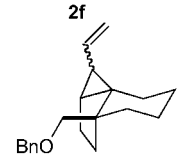


9. To explore this hypothesis, the diene ketone **1b** was exposed to our standard conditions. We were pleased to find that the reaction proceeded smoothly to provide the vinyl cyclopropane **2b** directly. Notably, neither the diazene intermediate **7** nor the cyclopentene **9** derived from rearrangement was observed.

We briefly examined the scope of this cyclization. Alkyl substituents at all positions of the diene were well tolerated. The formation of the fused 6,3-system was also successful (Table 1, Entry 5). Even the ketone **1g** cyclized smoothly to the strained tricyclic vinyl cyclopropane **2g** (Table 1, Entry 6). To our knowledge, this is the first direct protocol for the preparation of such alkenyl cyclopropanes.

Fe-Mediated Cyclocarbonylation. With the bicyclic alkenyl cyclopropanes readily available, we were prepared to explore the Fe-mediated cyclocarbonylation. Previous studies in our laboratory (Scheme 2) showed that the $Fe(CO)_5$-mediated cyclocarbonylation of alkenyl cyclopropanes was a general method for the construction of 5-alkyl cyclohexenones.[7] The organometallic cleavage of alkenyl cyclopropane **10** preferentially proceeded via the metallacycle **12**, leading to the cyclohexenone **14**. In consideration of the complexity of alkenyl cyclopropane **2c**, there are still two uncertainties for cyclocarbonylation. The first is whether this cyclocarbonylation would work with the much more sterically hindered substrate **2c**. The other factor to consider is whether the $Fe(CO)_5$-mediated carbonylation of bicyclic alkenyl cyclopropane **2c** could follow the same rule to give bicyclic cyclohexenone **3c** via metallacycle **16** with a more stable secondary carbon−metal bond or take a different route to deliver the bicyclic cyclohexenone **17** via a metallacycle **15** with the tertiary carbon−metal bond.

Table 1. Cyclization of ω-Dienyl Ketones

Entry	Substrate[a]	Product	Yield(%)[b,c]
1	 **1b**	 **2b**	78
2	 **1c**	 **2c**	83
3	 **1d**[d]	 **2d**	78
4	 **1e**	 **2e**	83
5	 **1f**	 **2f**	62
6	 **1g**	 **2g**	82

[a] The tosylhydrazone cyclizations were run at 130 °C, unless otherwise noted. For the preparation of the precursor diene iodides, see ref 4. [b] Yields are for pure chromatographed products. The cyclopropanes were ~1:1 mixtures of diastereomers. [c] Yields are based on the starting ketone. [d] Cyclization was run at 140 °C.

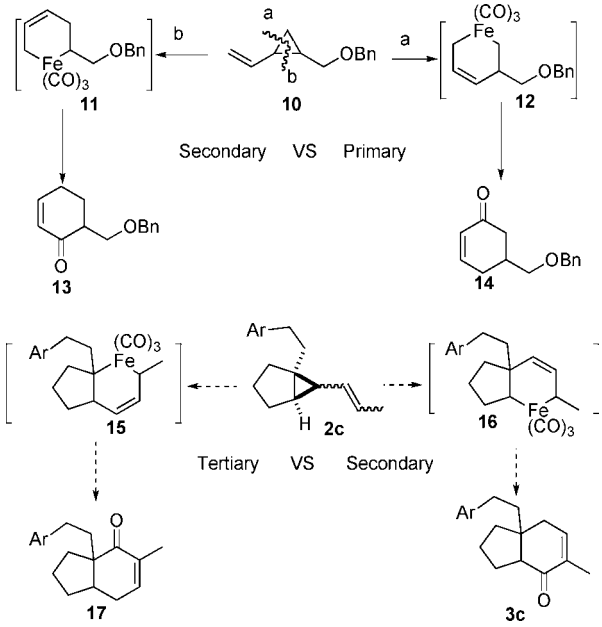
In practice we were pleased to observe that the Fe catalyzed reaction of **2c** proceeded smoothly to yield **3c** as the sole product. We have made a preliminary investigation (Table 2) of this reaction, which appears to be general. The reaction gave carbobicyclic 5,6-systems with good regiocontrol. Alkyl substituents at all positions of the alkenyl cyclopropane were again well tolerated. The formation of a 6,6-system was also successful (Entry 5). Cyclocarbonylation of **2g** even delivered the more complex tricyclic compound **3g** (Entry 6). Although in general the product cyclohexenones were conjugated, equilibration of **3e** delivered predominantly the nonconjugated enone, as illustrated. We note that $Fe(CO)_5$ is relatively innocuous (LD_{50} = 25 mg/kg) and certainly inexpensive (three cents/mmol).

Diastereocontrol in the Cycloaddition. We had earlier observed that the intramolecular dipolar cycloaddition to form the cyclic diazene could proceed with substantial diastereocontrol.

(6) For the preparation of the precursor diene iodides, see (a) Miller, C. A.; Batey, R. A. *Org. Lett.* **2004**, 699. (b) Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, 1022. (c) Wang, I.; Dobson, G. R.; Jones, P. R. *Organometallics* **1990**, *9*, 2510. (d) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085. (e) Elias, C. A.; Mihou, A. P. *Tetrahedron Lett.* **1999**, 4861.

(7) For the development of Fe-mediated cyclocarbonylation, see: (a) Victor, R.; Ben-Shoshan, R.; Sarel, S. *J. Org. Chem.* **1978**, *43*, 4971. (b) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807. (c) Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, *66*, 3423. (d) Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268. (e) Taber, D. F.; Sheth, R. B. *J. Org. Chem.* **2008**, *73*, 8030.

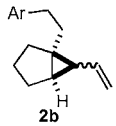
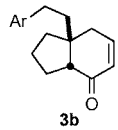
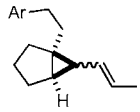
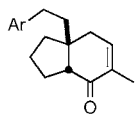
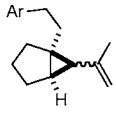
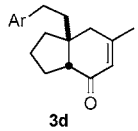
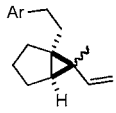
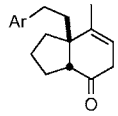
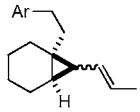
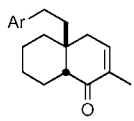
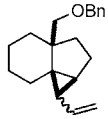
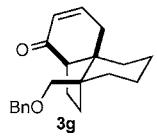
Scheme 2



To understand the diastereoselectivity of the intramolecular 1,3-dipolar cycloaddition of diazoalkanes, computational analysis of the possible transition states (TS) was performed to compare their relative stability (Figure 1). For the calculation, a simplified model structure **18** (Scheme 3) was used. There are four competing transion states (**TS-A-D**) which lead to four diazene diastereomers (**20-A-D**). To assess the relative energies of these transition states, we employed B3LYP density functional theory (DFT) calculations, using the 6-31+G(d,p) basis set as implemented in the Gaussian 03 program.[8] Computational results indicated that **TS-A** was more stable by 1.51 kcal/mol compared with its nearest competitor **TS-C**. Therefore **20-A** would be the kinetically favored product. We also observed that, for these two more stable TS, the C−C atom distance was about 2.25 Å and the C−N atom distance was about 2.3 Å. The diazo dipole was bent at 142°. These results are similar to those calculated for the intramolecular dipolar cycloaddition of a nitrile oxide.[9]

Encouraged by these calculations, we prepared the acyclic ketone **1a** from the commerical enantiomerically pure ester **21**.[10] Alkylation of **21** followed by protection of the alcohol provided

Table 2. Fe-Mediated Cyclocarbonylation

Entry	Vinylcyclopropane	Cyclohexenone	Yield(%)[a,b]
1	 **2b**	 **3b**	81
2	 **2c**	 **3c**	80
3	 **2d**	 **3d**	90
4	 **2e**	 **3e**	80
5	 **2f**	 **3f**	56
6	 **2g**	 **3g**	59

[a] Yields are for pure chromatographed material. [b] Reactions were run to 52−82% conversion. Yields are based on starting material not recovered.

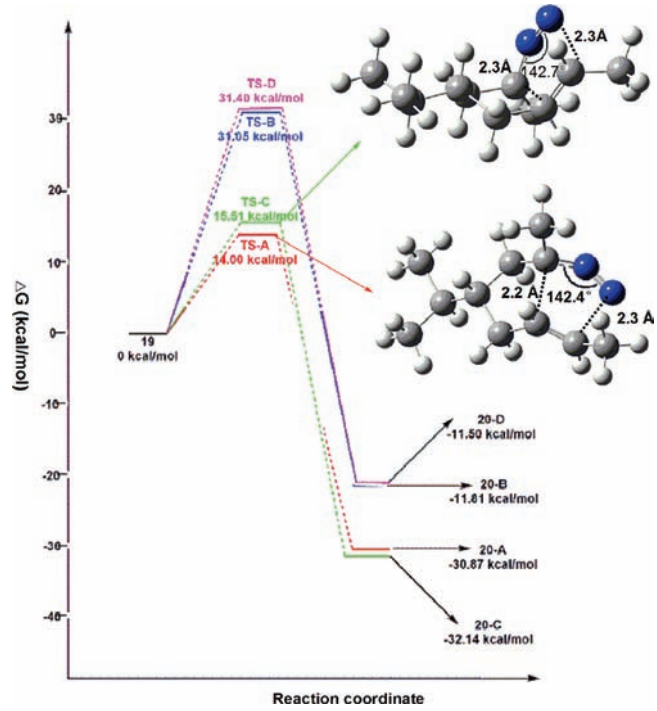
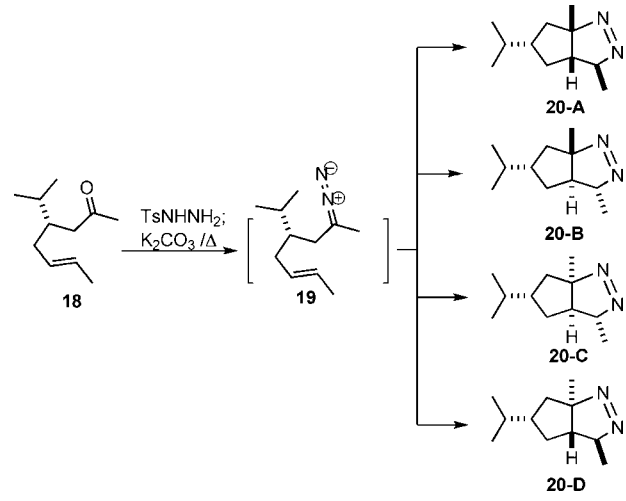
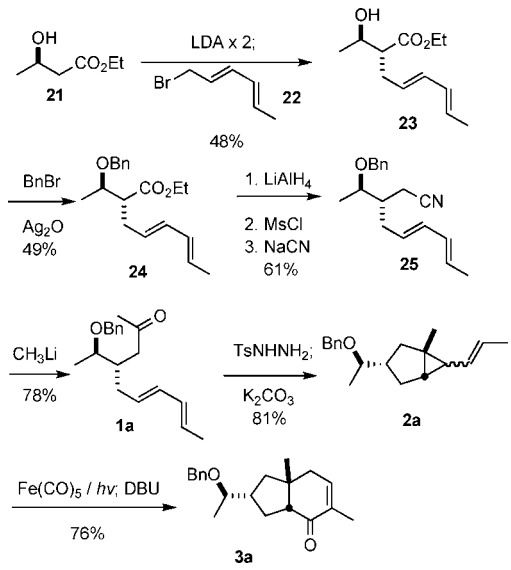


Figure 1. Calculation of the transition states.

Scheme 3



Scheme 4



the ester **24**. Reduction followed by mesylation and S_N2 substitution gave the nitrile **25**. Exposure of the nitrile to methyl lithium completed the assembly of the enantiomerically pure acyclic substrate **1a**. Application of the two-step [1 + 4 + 1] protocol delivered **3a** as a 6:1 mixture of diastereomers (Scheme 4). The structure of the major diastereomer, as illustrated, was confirmed by X-ray analysis. These results are consistent with the prediction based on the computationally based estimate of the differences in energy of the competing transition states for the intramolecular dipolar cycloaddition of **19**.

Conclusion

Alkenyl cyclopropanes are versatile building blocks for organic synthesis.[11] Their unique structural and electronic properties give rise to an array of interesting and characteristic transformations, which have been extensively developed by several research groups.[12] Direct construction of alkenyl cyclopropanes usually involves metal carbene chemistry.[13] Based on the intramolecular 1,3-dipolar cycloaddition of an in situ generated diazoalkane, we have uncovered an efficient metal-free synthesis of bicyclic alkenyl cyclopropanes that proceeds with substantial diastereocontrol. The diastereomer preferentially formed was consistent with our computational analysis of the competing transition states. We expect that the same computational approach will make it possible to design other dienyl ketones that will cyclize with high diastereocontrol.

The two-step [1 + 4 + 1] protocol for the rapid stereocontrolled assembly of carbobicyclic and carbotricyclic scaffolds outlined here should make such polycyclic intermediates readily available. We expect that this short and environmentally benign protocol will have many applications in target-directed synthesis.

Acknowledgment. We thank Dr. John Dykins for mass spectrometric measurements, supported by the NSF (0541775), Dr. Glenn Yap for the X-ray analysis, and the NIH (GM42056) for financial support. We also thank Professor Douglas J. Doren for helpful discussions.

Supporting Information Available: Experimental procedures, details of the X-ray analysis, and ^1H and ^{13}C NMR spectra for all new compounds, and a complete ref 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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