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Facile Construction of Novel Polycyclic Ring Systems Using a Metallocarbenoid-Induced Cyclization of Acetylenic Diazo Carbonyl Compounds

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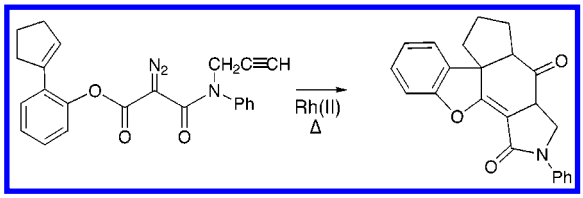
ABSTRACT

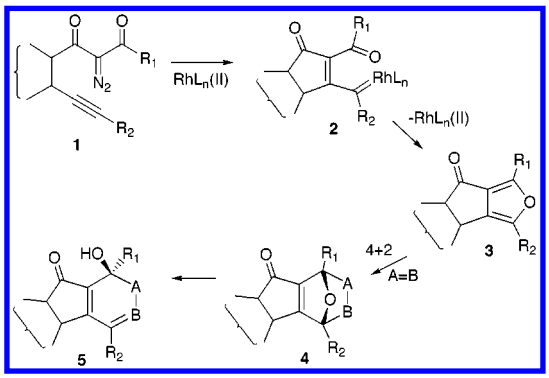


The Rh(II)-catalyzed reaction of diazo 2-propynyl maolonamic acid ester derivatives produce furo[3,4-*c*]furans in excellent yield. The methodology was applied to the synthesis of several polyheterocyclic systems by first generating a 2-alkoxy-substituted furan and then allowing it to undergo a subsequent intramolecular Diels–Alder cycloaddition. Ring opening of the resulting cycloadduct is followed by deprotonation to furnish a rearranged keto lactone.

Among the more recent catalytic strategies for the construction of common organic ring systems are the transition metal mediated carbocyclizations of substrates containing two or more elements of unsaturation.[1−6]

Another emerging area of synthesis involves the use of transition metal complexes derived from α-diazo carbonyl compounds to facilitate the fabrication of various polycyclic rings.[7−10] One of the approaches that we have found particularly effective in the design of new processes for ring assemblage is to employ diazoalkynyl-substituted carbonyl compounds.[11] The Rh(II)-catalyzed reaction of these systems has been used by our group for the synthesis of both carbocycles[12] and heterocycles.[13] In 1993 we reported on a novel construction of bicyclic furans by coupling a metal carbenoid cyclization onto a tethered alkyne with an electrocyclization reaction (Scheme 1).[13] The utility of this tandem cyclization approach to ring construction would be

Scheme 1



(1) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
(2) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1990; Vol. 5.
(3) Dötz, K. H. *Tetrahedron Symposia in Print*; Semmelhack, M. F., Ed.; Elsevier: New York, 1986; Vol. 42, p 5741.
(4) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271.
(5) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donavan, R. J. *Chem. Rev.* **1996**, *96*, 635.
(6) Mori, M.; Sakaibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.
(7) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley and Sons: New York, 1998.
(8) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091.
(9) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. IV, p 1046.
(10) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.

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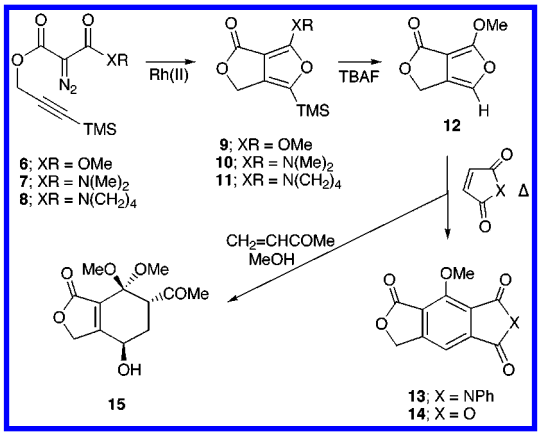
significantly expanded if the resulting furan was to undergo a subsequent [4 + 2]-cycloaddition, since a cyclohexane annulation would then result. The successful application of this ring annulation approach for heterocyclic synthesis is the subject of this communication.

Preparation of the propargyl diazo malonic ester system was straightforward and high yielding. Silyl propargyl alcohol was acylated with Meldrums acid and then allowed to react with DCC in the presence of an appropriately substituted alcohol to give the alkynyl ester derivative. Diazo transfer to the activated methylene position was readily accomplished using *p*-nitrobenzenesulfonyl azide and triethylamine.[14] 2-Diazo malonic acid methyl ester **6** was efficiently converted to furan **9** in high yield (95%) by treatment with a catalytic amount of rhodium acetate in benzene at 80 °C. The Rh(II)-catalyzed cyclization reaction was quite versatile with regard to the nature of the interacting carbonyl group. Thus, when the cyclization reaction was carried out with the closely related amides **7** and **8**, there was no notable difference in yield or reaction time required for cyclization to the amino-substituted furo[3,4-*c*]furans **10** and **11** (Scheme 2). Exposure of the methoxy silyl substituted

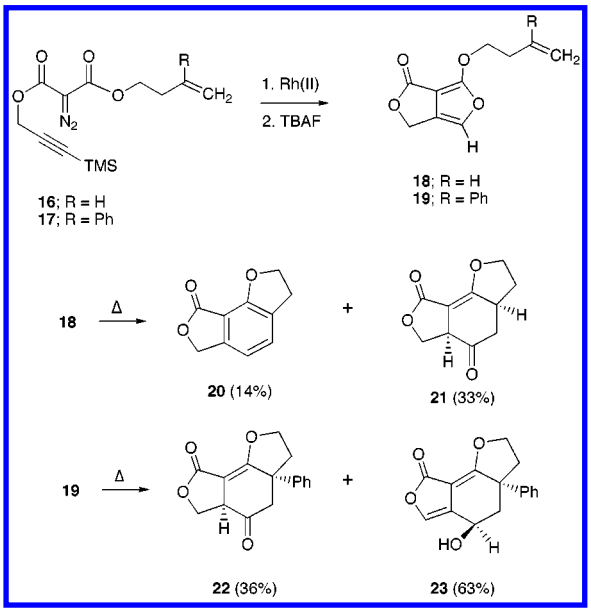
Scheme 2



furan **9** to TBAF in THF afforded the desilylated furan **12** which could be induced to undergo Diels−Alder cycloaddition at 145 °C with both *N*-phenylmaleimide and maleic anhydride to furnish the expected anisole derivatives **13** and **14** in 88% and 65% yield, respectively. Interestingly, the [4 + 2]-cycloaddition reaction of **12** with methyl vinyl ketone in nitromethane containing an 1 equiv of methanol occurred at room temperature and produced the ring-opened ketal **15** in quantitative yield.

To access synthetically more valuable targets, we focused our attention on an intramolecular variation of the *Rh(II)-catalyzed cyclization-Diels−Alder cycloaddition cascade*. In this regard, we first investigated the IMDAF (*intramolecular Diels−Alder of furans*) chemistry[15] of furan **18**, which was readily formed by the Rh(II)-catalyzed reaction of **16** followed by protodesilylation with TBAF (Scheme 3).

Scheme 3



Thermolysis of **18** afforded a 1:2-mixture of dihydrobenzofuran **20** and 1,7-dioxa-indacene dione **21** as the two major products.[16] In a similar manner, the related styryl-substituted furo[3,4-*c*]furan **19** was easily prepared by the Rh(II)-catalyzed reaction of diazo malonic ester **17**. Heating a sample of **19** afforded the related indacene dione **22**, but now as the minor component (36%) of the reaction mixture. The major product (63%) corresponded to the dienol-substituted lactam **23**.

A reasonable mechanism for the formation of the IMDAF products is outlined below. The initial step proceeds by the expected [4 + 2]-cycloaddition of the furan across the tethered π-bond to give cycloadduct **24**. Following opening of the oxybridge, proton loss is accompanied by dehydration to give dihydrobenzofuran **20**. When a phenyl group resides at the bridgehead carbon (i.e., **25b**), the deprotonation step is now required to occur from the alternate γ-positions,

(11) Padwa, A.; Krumpe, K. E.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 2623. Padwa, A.; Chiacchio, U.; Gareau, Y.; Kassir, J. M.; Krumpe, K. E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414. Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940.

(12) Padwa, A.; Straub, C. S. *Advances in Cycloaddition*; Harmata, M.; Ed.; JAI Press: Greenwich, CT, 1999; Vol. 6, p 55.

(13) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21.

(14) Regitz, M. *Chem. Ber.* **1966**, *99*, 3128. Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect Vol. V, pp 179−183. Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1985**, *50*, 425.

(15) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(16) All new compounds in this study were fully characterized (IR, NMR, elemental analysis, and/or HRMS). A combination of DQF-COSY, HMBC, and HMQC NMR experiments were used to assign the stereochemistry of the rearranged IMDAF products.

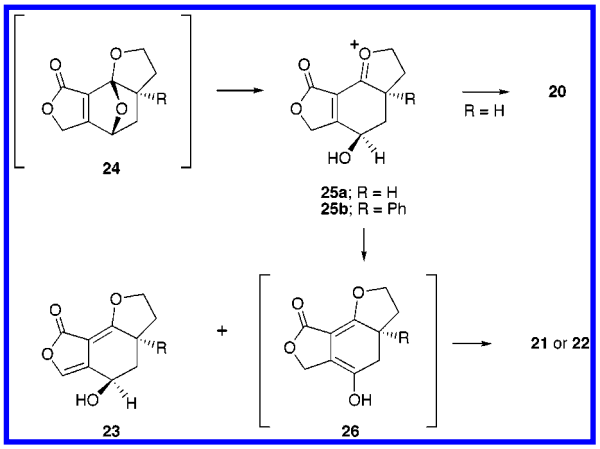
(17) An alternate possibility to rationalize the formation of **21** would involve proton loss from the α-position of **25a** followed by a rapid 1,5-sigmatropic hydrogen shift of the resulting cyclohexadienol to give enol **26a**.

(18) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schennker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

(19) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

thereby resulting in the formation of compounds **22** and **23** as shown in Scheme 4. A related pathway seemingly occurs

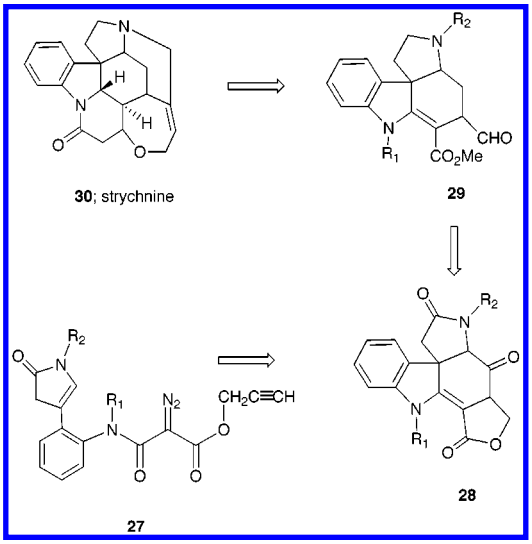
Scheme 4



with oxonium ion **25a** producing keto lactone **21** via enol **26a**.[17]

To further illustrate the viability of our cascade sequence as a practical strategy for the synthesis of complex heterocycles, we have explored the feasibility of this approach in the context of a total synthesis of strychnine (**30**).[18] The key step in our plan involves a sequential *cyclization-IMDAF cascade* of diazo amide **27** to furnish the rearranged

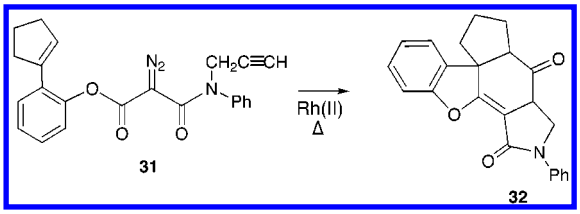
Scheme 5



cycloadduct **28** by a process similar to that outlined above. Lactone **28** will eventually be transformed into compound **29** which had previously been converted into strychnine by Kuehne and Feng.[19] Thus, the formation of **29** from diazo amide **27** would constitute a formal synthesis of this challenging alkaloid.

To evaluate this projected synthetic plan, model compound **31** (Scheme 6) was synthesized so as to probe the facility of

Scheme 6



both the ring cyclization and [4 + 2]-cycloaddition across the tethered five-ring π-bond. Easily prepared *N*-phenyl-*N*-prop-2-ynyl-malonamic acid methyl ester was hydrolyzed to the corresponding carboxylic acid which, in turn, was subjected to a DCC coupling with the known 2-cyclopentenylphenol.[20] Diazo transfer to the activated methylene group of the β-amido ester gave the α-diazo derivative **31**, possessing the necessary functionalities required for the planned cascade sequence.[21] Treatment of **31** with a catalytic quantity of rhodium(II) perfluorobutyrate followed by thermolysis at 145 °C afforded the novel pentacyclic product **32** as a single stereoisomer in 44% overall yield.[22] The structure and stereochemistry of **32** was confirmed by ^{1}H NMR and NOE experiments. Each of the bond-forming events is assumed to occur by a pathway similar to that outlined in Scheme 4.

In conclusion, the Rh(II)-catalyzed cyclization-IMDAF cascade of diazo malonate esters affords structurally elaborated polycyclic products with good to excellent efficiency. The structural features of the resultant products present numerous opportunities for post-cycloaddition manipulations that could be exploited to synthetic advantage. Further efforts to streamline this protocol and to utilize it to complete a formal total synthesis of strychnine is in progress and will be reported in due course.

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Supporting Information Available: Experiment procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Casiraghi, G.; Casnati, G.; Sartori, G.; Bolzoni, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2027.

(21) Diazo β-alkoxy esters such as **16** or **17** require the presence of a trimethylsilyl group on the alkyne carbon for efficient cyclization to occur. In contrast, diazo β-amido esters such as **31** undergo efficient reorganization to 2-amino substituted furans using simple terminal alkynes.

(22) By carrying out the thermolysis of **31** at 80 °C, it was possible to isolate the expected *o*-cyclopentenyl phenoxy substituted furan in 94% yield. Further heating of this furan at 145 °C afforded **32** in 45% isolated yield.