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A Formal [3 + 3] Cycloaddition Reaction. Improved Reactivity Using α,β-Unsaturated Iminium Salts and Evidence for Reversibility of 6π-Electron Electrocyclic Ring Closure of 1-Oxatrienes

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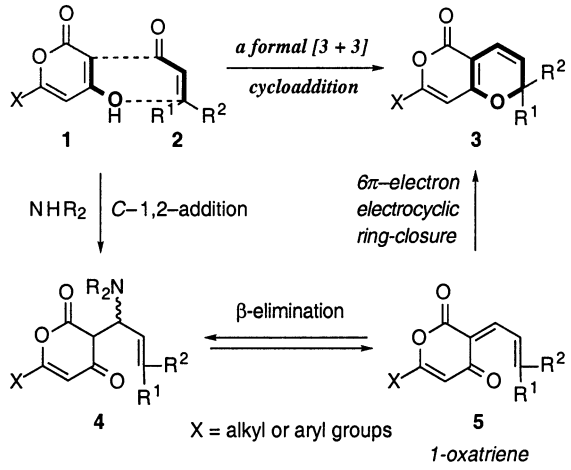
A detailed account regarding a formal [3 + 3] cycloaddition method using 4-hydroxy-2-pyrones and 1,3-diketones is described here. This formal cycloaddition reaction or annulation reaction is synthetically useful for constructing 2*H*-pyranyl heterocycles. The usage of α,β-unsaturated iminium salts is significant in controlling competing reaction pathways to give exclusively 2*H*-pyrans. Most significantly, experimental evidence is provided to support the mechanism of this reaction that involves a sequential Knoevenagel condensation and a reversible 6π-electron electrocyclic ring-closure of 1-oxatrienes.

Introduction

Cycloaddition and annulation reactions are among the most powerful methods in organic synthesis, owing to their ability to provide multiple bond formations with regio- and stereochemical control leading to polycyclic carbocycles and heterocycles through a concerted, stepwise, or sequential process.[1] We encountered an *annulation reaction* that was first cited by Link[2] in 1944 specifically involving 4-hydroxycoumarins and later was studied in detail by Moreno-Mañas.[3] This *annulation reaction* involves condensation of 6-methyl-4-hydroxy-2-pyrones **1** with α,β-unsaturated aldehydes **2** in the presence of a secondary amine leading to 2*H*-pyrans **3** (Scheme 1). Mechanistically, it has been proposed to involve a sequence that consists of a *C*-1,2-addition to an iminium salt generate in situ followed by β-elimination that gives an 1-oxatriene **5** (or Knoevenagel condensation) and a 6π-electron electrocyclic ring closure of **5**.[3−5]

SCHEME 1



This results in the formation of two σ-bonds and a new stereocenter adjacent to the oxygen atom, thereby constituting a sequential anionic-pericyclic process that is

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(1) For some reviews, see: (a) Trost, B. M.; Fleming, I. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford and New York, 1991; Vols. 4 and 5. (b) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford and New York, 1990. (c) Padwa, A.; Schoffstall, A.; Curran, D. P. In *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1990; pp 1−89.

(2) (a) Ikawa, M.; Stahmann, M. A.; Link, K. P. *J. Am. Chem. Soc.* **1944**, *66*, 902. (b) Seidman, M.; Robertson, D. N.; Link, K. P. *J. Am. Chem. Soc.* **1950**, *72*, 5193. (c) Seidman, M.; Link, K. P. *J. Am. Chem. Soc.* **1952**, *74*, 1885.

(3) (a) de March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. *J. Heterocycl. Chem.* **1984**, *21*, 1369. (b) de March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J. L. *J. Heterocycl. Chem.* **1984**, *21*, 85.

(4) For leading references on electrocyclic ring closures involving 1-oxatrienes, see: (a) Kametani, T.; Kajiwara, M.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1053. (b) Shishido, K.; Ito, M.; Shimada, S.-I.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943. (c) Shishido, K.; Shitara, E.; Fukumoto, K. *J. Am. Chem. Soc.* **1985**, *107*, 5810. (d) Shishido, K.; Hiroya, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1986**, *27*, 971.

(5) For leading references on electrocyclic ring-closures involving 1-azatrienes, see: (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763. (b) de Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 4501. (c) Okamura, W. H.; de Lera, A. R.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 4462. For an earlier account, see: (e) Oppolzer, V. W. *Angew. Chem.* **1972**, *22*, 1108. For a recent account similar to Okamura's elegant studies, see: (f) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099.

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formally the equivalent of a [3 + 3] cycloaddition,[6−8] a term described in Seebach's carboannulation of nitroalkenes with enamines.[9]

The significance of tandem strategies in natural product synthesis has been elegantly reviewed by Tietze.[10] This particular formal cycloaddition strategy should provide a unique approach to 1-oxadecalins and oxaspirocycles that are well represented in biologically relevant natural products such as arisugacins (**6**),[11] phomactin A (**7**),[12,13] penostatin A (**8**),[14] rhododarichrmoanic acid A (**9**),[15] pyripyropenes (**10**),[16] and orevactaene (**11**)[17] (Figure 1). We became interested in this reaction specifically because of arisugacin A (**6a**) that was isolated

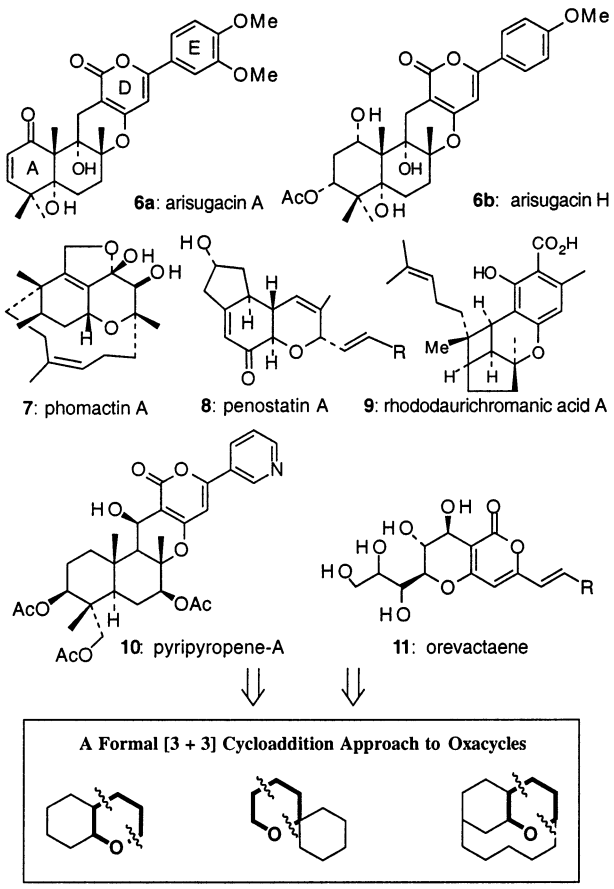


FIGURE 1.

from *Penicillium* sp. Fo-4259 by Õmura.[11] Arisugacin A (**6a**) is identified as the most potent and selective inhibitor known against acetylcholinesterase (AChE) with an IC_{50} value of 1 nM,[11] and thus, it possesses therapeutic significance in treatment of dementia diseases.[18]

Despite the obvious synthetic potential of this formal cycloaddition or annulation reaction, its application has remained little known because of the competing reaction pathways due to 1,2- versus 1,4-addition and the *C*-addition versus *O*-addition (Scheme 2). After Link's first report using 4-hydroxycoumarins and α,β-unsaturated ketones,[2] Moreno-Mañas reported a detailed study featuring reactions of 6-methyl-4-hydroxy-2-pyrone **12** and crotyl aldehyde.[3] A variety of products such as **13**−**17** were identified and isolated in various amounts, resulting from these competing reaction pathways. The synthetically most useful product **13** was found in very low yields.

These discouraging preliminary studies seriously hampered our efforts[19−21] to achieve a total synthesis of arisugacin A via this formal [3 + 3] cycloaddition strategy. Although Jonassohn[22] and Hua[23] reported the use of cyclic enals to improve the overall product distribution by suppressing the 1,4-addition pathway, a general solution remained elusive until we communicated

(6) Examples of [3 + 3] cycloaddition reactions in the truest sense are extremely scarce. There are limited examples of metal mediated [3 + 3] cycloaddition reactions. For recent reviews: a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(7) For a review, see: Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Shen, H. C.; McLaughlin, M. J.; Zehnder, L. R. In *Trends Heterocycl. Chem.* **2001**, *7*, 1−24.

(8) For recent reviews on stepwise [3 + 3] formal cycloadditions leading to bridged carbocycles, pyridines, or pyridones using enamines, enaminones, enol ethers, or β-ketoesters, see: (a) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27. (b) Rappoport, Z. The Chemistry of Enamines. In *The Chemistry of Functional Groups;* John Wiley and Sons: New York, 1994. (c) Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872 and refs 21−33 cited therein.

(9) (a) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. For related reactions, see: (b) Landesman, H. K.; Stork, G. *J. Am. Chem. Soc.* **1956**, *78*, 5129. (c) Hendrickson, J. B.; Boeckman, R. K. Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1307. (d) Alexakis, A.; Chapdelaine, M. J.; Posner, G. H. *Tetrahedron Lett.* **1978**, *19*, 4209.

(10) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. b) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47.

(11) (a) Õmura, S.; Kuno, F.; Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1995**, *48*, 745. For biological activities of arisugacin, see: (b) Kuno, F.; Otoguro, K.; Shiomi, K.; Iwai, Y.; Õmura, S. *J. Antibiot.* **1996**, *49*, 742. (c) Kuno, F.; Shiomi, K.; Otoguro, K.; Sunazuka, T.; Õmura, S. *J. Antibiot.* **1996**, *49*, 748. (d) Otoguro, K.; Kuno, F.; Õmura, S. *Pharmacol. Ther.* **1997**, *76*, 45. For C−H, see: (e) Otoguro, K.; Shiomi, K.; Yamaguchi, Y.; Arai, N.; Sunazuka, T.; Masuma, R.; Iwai, Y.; Õmura, S. *J. Antibiot.* **2000**, *53*, 50.

(12) For phomactin A, see: (a) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463. (b) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564. (c) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188.

(13) (a) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107. (b) Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275. (c) Foote, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, 365. (d) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687. (e) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507. (f) Mi, B.; Maleczka, R. E., Jr. *Org. Lett.* **2001**, *3*, 1491. (g) Chemler, S. R.; Iserloh, U.; Daneshefsky, S. J. *Org. Lett.* **2001**, *3*, 2949. (h) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615.

(14) For isolations of penostatins, see: (a) Takahashi, C.; Numata, A.; Yamada, T.; Minoura, K.; Enmoto, Konishi, K.; Nakai, M.; Matsuda, C.; Nomoto. K. *Tetrahedron Lett.* **1996**, *37*, 655. For synthesis, see: (b) Snider, B. B.; Liu, T. *J. Org. Chem.* **2000**, *65*, 8490.

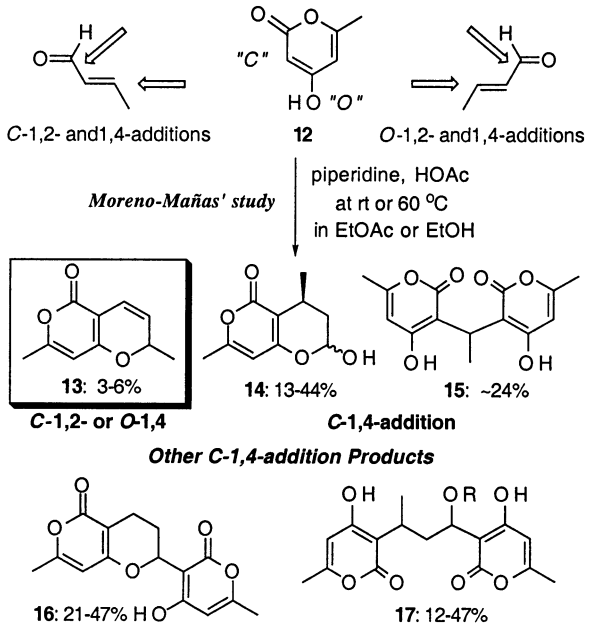
(15) For isolation of rhododaurichromanic acid: Kashiwada, Y.; Yamzaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioko, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

(16) (a) Tomoda, H.; Tabata, N.; Yang, D. J.; Namatame, I.; Tanaka, H.; Õmura, S.; Kaneko, T. *J. Antibiot.* **1996**, *49*, 292. (b) b) Obata, R.; Sunazuka, T.; Li, Z. R.; Tian, Z. M.; Harigava, Y.; Tabata, N.; Tomoda, H.; Õmur, S. *J. Antibiotics* **1996**, *49*, 1133. For total synthesis of pyripyropene A and E, see: (c) Smith, A. B., III; Kinsho, T.; Sunazuka, T.; Õmura, S. *Tetrahedron Lett.* **1996**, *37*, 6461. (d) Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Õmura, S.; Smith, A. B., III. *J. Org. Chem.* **1995**, *60*, 8126. For synthesis of a related natural product GERI-BP001, see: (d) Parker, K. A.; Resnick, L. *J. Org. Chem.* **1995**, *60*, 5726. For a biosynthesis of pyripyropene A, see: (e) Tomoda, H.; Tabata, N.; Nakata, Y.; Nishida, H.; Kaneko, T.; Obata, R.; Sunzazuka, T.; Õmura, S. *J. Org. Chem.* **1996**, *61*, 882. (f) Obata, R.; Sunazuka, T.; Tian, Z.; Tomoda, H.; Harigaya, Y.; Omura, S.; Smith, A. B., III. *Chem. Lett.* **1997**, 935.

(17) a) Shu, Y.-Z.; Ye, Q.; Li, H.; Kadow, K. F.; Hussain, R. A.; Huang, S.; Gustavson, D. R.; Lowe, S. E.; Chang, L. P..; Pirnik, D. M.; Kodukula, K. *Bioorg. Med. Chem. Lett.* **1997**, *17*, 22295. (b) Organ, M. G.; Bratovanov, S. *Tetrahedron Lett.* **2000**, *41*, 6945.

(18) John, V.; Lieberburg, I.; Thorsett, E. D. *Ann. Rep. Med. Chem.* **1993**, *28*, 197.

SCHEME 2



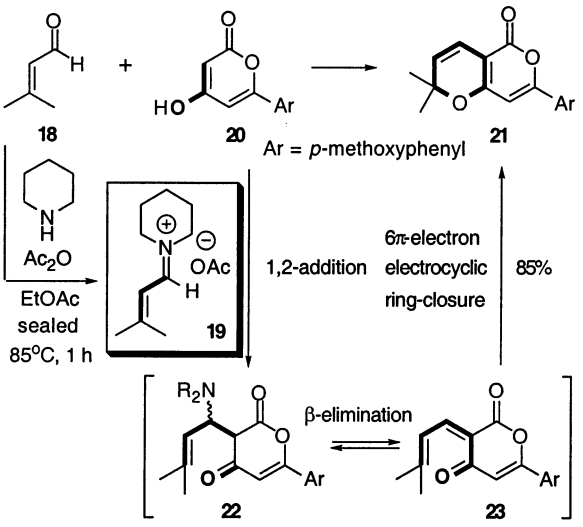
the use of α,β-unsaturated iminium salts.[24−26] We report here a detailed account of our study to particularly include various results on mechanistic support.

Results and Discussion

1. Synthetic Scope and Applications.

a. The Use of α,β-Unsaturated Iminium Salts. The challenge to solve the competing reaction pathway problem or to improve the pathway that would lead to the 2*H*-pyran **13** is an experimental one. Our solution eventually involved the utilization of α,β-unsaturated iminium salts because this reaction presumably involved generation of iminium salts in situ.

SCHEME 3



As shown in Scheme 3, 3-methyl-2-butenal (**18**) was incubated in the presence of 1.0 equiv of piperidine and 1.0 equiv of Ac_2O in EtOAc (added at −10 °C) at 85 °C in a sealed flask for 45 min to 1 h. The solution containing the iminium salt **19** was then transferred without cooling to a solution of pyrone **20**[27] in EtOAc. After the solution was stirred at 85 °C in a sealed flask for an additional 24−36 h, the 2*H*-pyran **21**[28] was obtained in 85% yield. Without pregenerating the iminium salt **19**, simply mixing 3-methyl-2-butenal (**18**) and pyrone **20** in the presence of L-proline[22] or a secondary amine led to 2*H*-pyran **21** in 47% as the best yield that was very difficult to reproduce.

It was quickly evident that the usage of α,β-unsaturated iminium salts is a general and efficient solution leading to 2*H*-pyranyl products exclusively via the *C*-1,2-addition pathway. This assertion was validated by a recent account reported by Cravotto.[26] In addition, reactions of the pyrone **24** with several acyclic α,β-unsaturated piperidine iminium salts **25**−**27** generated from the corresponding enals with only one β-substituent could be carried out to give pyranyl products **13** in much improved yield and the previously unknown **28**−**29** (Scheme 4). This further supports the significance of using α,β-unsaturated iminium salts.

This improved protocol has been applied to preparations of a series of bicyclic and tricyclic pyranyl heterocycles as shown in Schemes 5 and 6. These pyranyl heterocycles are currently being evaluated as potential structural analogues of arisugacin A (**6a**) especially with the compound **35** serving as the BCDE-ring analogue of **6a**.

An important experimental improvement since we first communicated this reaction[24] is that amine salts can be

(19) For our earlier efforts in total synthesis arisugacin A, see the following references. 4-Pyrone Diels−Alder route: (a) Hsung, R. P. *J. Org. Chem*. **1997**, *62*, 7904. (b) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, *39*, 9597. (c) Hsung, R. P. *Heterocycles* **1998**, *48*, 421. (d) Hsung R. P.; Zificsak, C. A.; Wei, L.-L.; Zehnder, L. R.; Park, F.; Kim, M.; Tran, T.-T. T. *J. Org. Chem*. **1999**, *64*, 8736. (e) Degen, S. J.; Mueller, K. L.; Shen, H. C.; Mulder, J. A.; Golding, G. M.; Wei, L.-L.; Zificsak, C. A.; Neeno-Eckwall, A.; Hsung, R. P. *Bioorg. Med. Chem. Lett.* **1999**, *973*, 3. For an acid condensation approach: (f) Zehnder, L. R.; Dahl, J. W.; Hsung, R. P. *Tetrahedron Lett*. **2000**, *41*, 1901.

(20) For our formal [3 + 3] cycloaddition approach, see: Zehnder, L. R.; Hsung, R. P.; Wang, J.-S.; Golding, G. M. *Angew. Chem., Int. Ed*. **2000**, *39*, 3876.

(21) For an identical route, see: Handa, M.; Sunazuka, T.; Nagai, K.; Kimura, R.; Shirahata, T.; Tian, Z. M.; Otoguro, K.; Harigaya, Y.; Ōmura, S. *J. Antibiot.* **2001**, *54*, 382.

(22) Jonassohn, M.; Sterner, O.; Anke, H. *Tetrahedron* **1996**, *52*, 1473.

(23) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem*. **1997**, *62*, 6888.

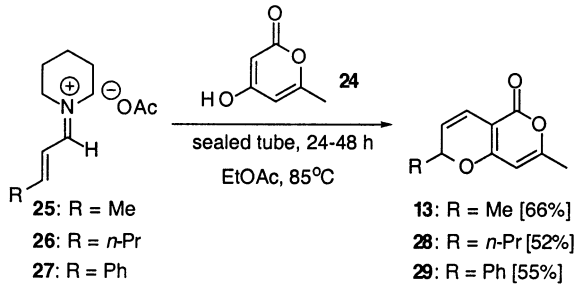
(24) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem*. **1999**, *64*, 690. For preliminary communications on the formal [3 + 3] cycloaddition approach, see: Shen, H. C.; Degen, S. J.; Mulder, J. A.; Hsung, R. P.; Douglas C. J.; Golding, G. M.; Johnson, E. W.; Mathias, D. S.; Morgan, C. D.; Mueller, K. L.; Shih, R. A. Abstract No. ORGN-664, 216th ACS National Meeting, Boston, MA, Fall 1998.

(25) For a recent citation in support the usage of α,β-unsaturated iminium salts, see: Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, 49.

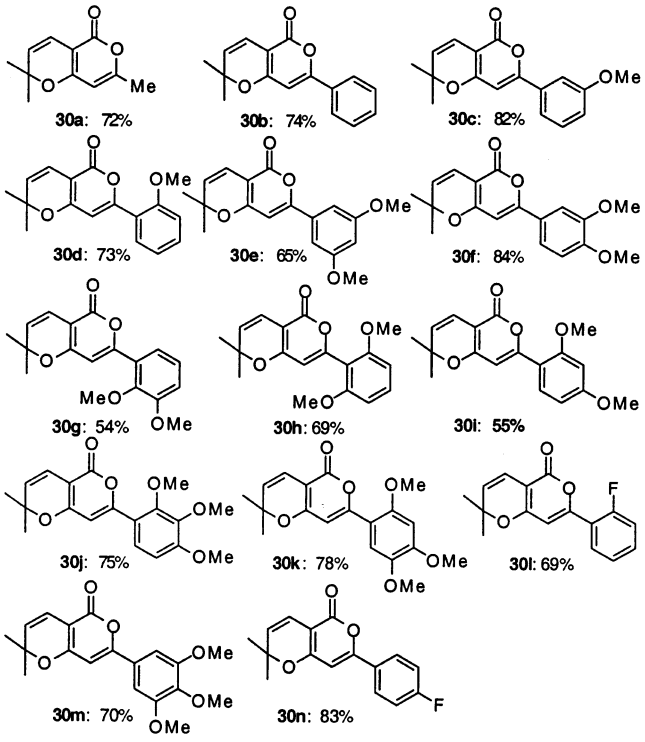
(26) For recent related studies in this area: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Robinson, P. D.; Meyers, C. Y.; Perchellet, E. M.; Perchellet, J.-P.; Chiang, P. K.; Biellmann, J.-P. *Acta Crystallogr.* **1999**, *C55*, 1698. (b) P. Benovsky, G. A. Stephenson, J. R. Stille, *J. Am. Chem. Soc.* **1998**, *120*, 2493. (c) Moorhoff, C. M. *Synthesis*, **1997**, 685. (d) Krasnaya, Z. A.; Bogdanov, V. S.; Burova, S. A.; Smirnova, Y. V. *Russ. Chem*. **1995**, *44*, 2118. (e) Heber, D.; Berghaus, Th. *J. Heterocycl. Chem*. **1994**, *31*, 1353. (f) Paulvannan,; K.; Stille, J. R. *Tetrahedron Lett*. **1993**, *34*. 6677. (g) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1990**, *73*, 1865.

(27) Douglas C. J.; Sklenicka, H. M.; Shen, H. C.; Golding, G. M.; Mathias, D. S.; Degen, S. J.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683.

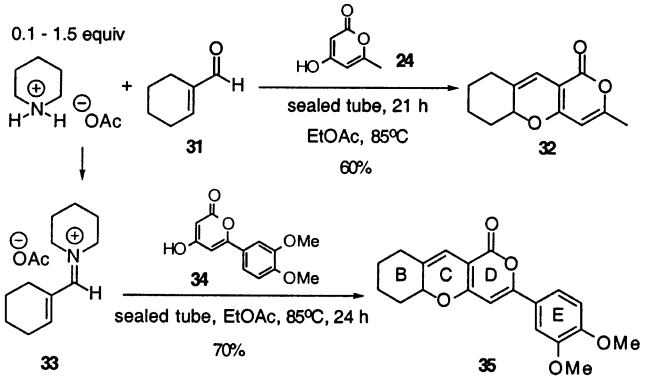
SCHEME 4



SCHEME 5

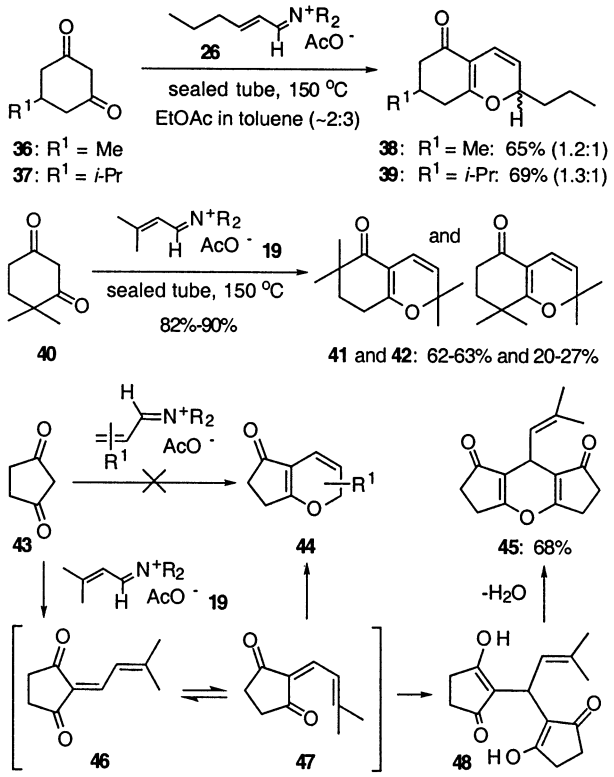


SCHEME 6



used to generate α,β-unsaturated iminium salts in a highly efficient manner. Specifically as shown in Scheme 6, utilization of 0.1−1.0 equiv piperidinium acetate salts not only could facilitate the reaction in the formation of α,β-unsaturated iminium salts, but more significantly, it renders the reaction to be carried out in one-pot. By mixing the pyrone **24** or **34** directly with α,β-unsaturated aldehyde **31** in the presence of piperidinium acetate, the desired formal cycloadducts **32** and **35** were isolated in

SCHEME 7



60% and 70% yields, respectively. This simplifies the formal [3 + 3] cycloaddition reaction experimentally, although most reactions can be carried out using either conditions.

b. Other β-Diketo Systems. This formal [3 + 3] cycloaddition reaction could be extended to include 1,3-diketones leading to a facile construction of 1-oxadecalins. In comparison with 4-hydroxy-2-pyrones, reactions of 1,3-diketones with α,β-unsaturated iminium salts appear to be slower.[29] Upon raising the temperature to 100−150 °C and using the solvent system consisting of a toluene/EtOAc mixture, the reaction of 1,3-cyclohexanedione proceeded in a synthetically useful manner.

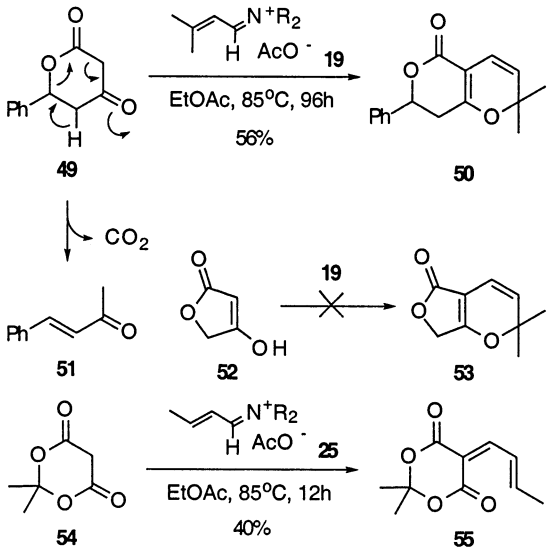
As shown in Scheme 7, 1,3-diketones **36** and **37** were reacted with the iminium salt **26** generated from 2-hexenal under the standard conditions to give the formal cycloadducts **38** and **39** in 65% and 69% yields, respectively. Attempts to generate any reasonable diastereoselectivity by desymmetrizing the symmetric diketones **36** and **37** were not successful. The reaction of diketone **40** with **19** did lead to the 2*H*-pyrans **41** and **42**[29c] in 82−90% overall yield with a ratio ranged from 4:1 to 7:3 in favor of **41**, thereby suggesting that the steric interaction of the two geminal dimethyl groups propelled the regioselectivity to favor **41**.

We also observed an intriguing contrast between 1,3-cyclopentanedione and 1,3-cyclohexandione. When 1,3-cyclopentanedione **43** was reacted with a variety of α,β-

(28) See the Supporting Information for preparations of all relevant new compounds and details of their full characterizations along with their ^{1}H NMR spectra.

(29) For earlier studies, see: a) Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972. (b) Tietze, L. F.; v. Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683. (c) de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, *16*, 3407. There were some disagreements in these citations regarding reaction yields and conditions.

SCHEME 8

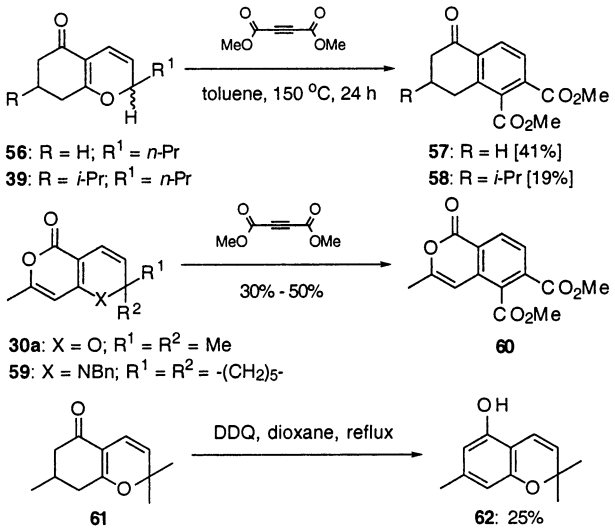


unsaturated iminium salts, no desired formal cycloadduct **44** (Scheme 7) was found. Instead, in one specific case, the diketone **45** was isolated (68% yield) and vigorously characterized using iminium salt **19**. Formation of **45** could be derived from dehydration of the intermediate **48**, which was the product of a second 1,4-addition of 1,3-cyclopentanedione to the intermediate **46** or **47**. This implies that for reactions of 1,3-cyclopentanedione, the electrocyclic ring-closure step is either very slow or is arrested and that a second 1,4-addition either occurred faster or is more favored.

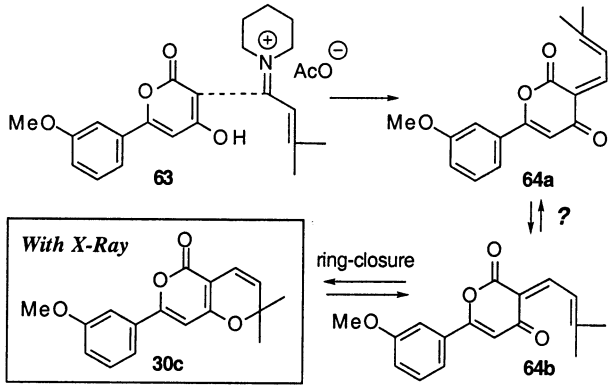
When the δ-lactone **49** was used as a β-diketo equivalent and condensed with **19**, the desired cycloadduct **50** was obtained in 56% yield (Scheme 8). However, at higher temperatures than 85 °C, decarboxylation of the starting δ-lactone **49** occurred to give **51** as the competing side product. Intriguingly, tetronic acid **52** did not yield any desired formal cycloadduct **53**, while Meldrum's acid **54** did condense with **25** to give the Knoevenagel condensation product **55**[30] with no additional 1,4-additions but also with the electrocyclic ring-closure step again arrested. Finally, acyclic β-diketo equivalents such as ethyl acetoacetate, dimethyl malonate, and 1,3-pentanediones were all unsuccessful in this reaction, limiting the scope of this reaction at this moment to the formation of fused bicyclic oxygen heterocycles.

c. Simple Applications. Since these formal cycloadducts represent unique cyclic dienes, we pursued their utility in Diels−Alder cycloaddition reactions, and dimethyl acetylenic dicarboxylate (DMAD) was found to be a suitable dienophile. Reactions of DMAD with 2*H*-pyrans (**30a**, **39**, and **56**) in toluene at 150 °C in a sealed tube led to aromatic compounds **57**,[31] **58**, and **60** in modest yields after thermal deformylation or decarbonylation of the initially bridged cycloadducts. Intriguingly as a comparison, the dihydropyridine **59**[32] also underwent

SCHEME 9



SCHEME 10



Diels−Alder cycloaddition with DMAD to give **60** in 50% yield after loss of *N*-benzyl cyclohexyl ketimine under the thermal conditions. It is noteworthy that this would represent an alternative route to synthesis of substituted tetralones.

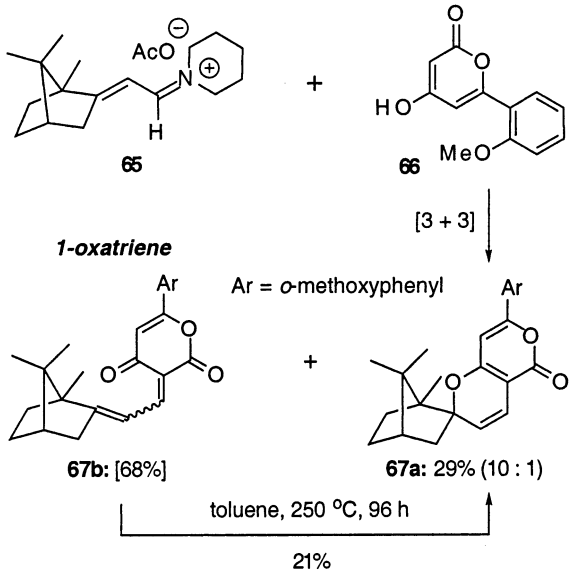
Moreover, DDQ oxidation of the 2*H*-pyrans such as **61** in dioxane led to the formation of chromene **62** in 25% yield (Scheme 9). Although this reaction is not particularly efficient, this oxidative aromatization could be readily achieved in a stepwise manner via α-selenization and oxidative elimination.[29a,b] This application showcases the potential of this formal [3 + 3] cycloaddition method in synthesis of substituted chromenes.

Mechanism

a. Regiochemical Assignment. The regiochemical issue of this formal [3 + 3] cycloaddition reaction was resolved unambiguously via an X-ray structural analysis of **30c** (Scheme 10). This regiochemical assignment is significant for endeavors in syntheses of the aforementioned natural products. Mechanistically, it supports again that the reaction could involve a *C*-1,2-addition to an iminium salt followed by β-elimination leading to an 1-oxatriene **64a** or **64b** (Knoevenagel condensation) and that the subsequent 6π-electron electrocyclic ring-closure of **64b** would lead the desired formal cycloadduct. The preference for **64b** to undergo ring closure is an interesting observation. Since both the Knoevenagel condensa-

(30) Stevenson, R.; Weber, J. V. *J. Nat. Prod.* **1988**, *51*, 1215.
(31) The compound **57** has been made before via a Diels−Alder reaction of DMAD with dioxolane of 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]-furans. See: (a) Tochtermann, W.; Heinke, T. *Tetrahedron Lett.* **1978**, *19*, 2145. (b) Tochtermann, W.; Heinke, K. *Chem Ber.* **1980**, *113*, 3249.
(32) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.

SCHEME 11



tion and electrocyclic ring-closure are reversible (see below), such a preference could simply be a reflection that stability of respective products is in favor of **30c**.

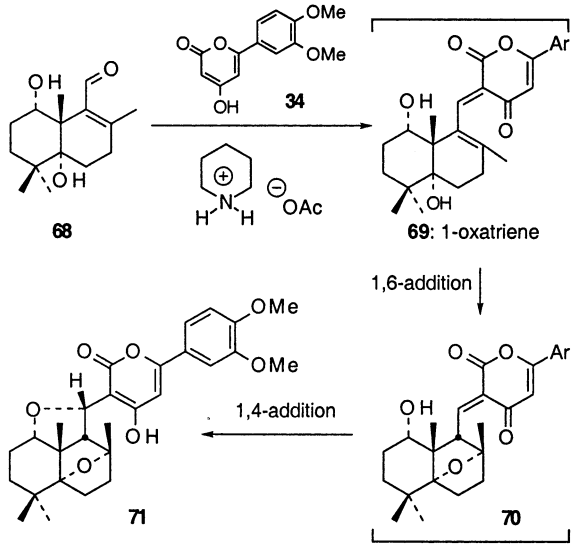
b. Evidence for a 1-Oxatriene Intermediate. While there are not definitive protocols to rule out other mechanistic pathways that could also logistically lead to the final outcome of this formal [3 + 3] cycloaddition reaction, we have experimental information to support the pathway involving the Knoevenagel condensation and electrocyclic ring-closure.

As shown in Scheme 11, reaction of the α,β-unsaturated iminium ion **65** derived from camphylidene acetaldehyde[33] with the pyrone **66** at 110 °C for 96 h led to the spirocycle **67a** in 29% yield with a diastereomeric ratio of 10:1 as assigned using NOE experiments. The major product isolated in 68% yield was spectroscopically assigned as the 1-oxatriene **67b**. Although only one isomer of **67b** was observed, stereochemistry of the olefin exocyclic to the pyrone moiety could not be easily distinguished.

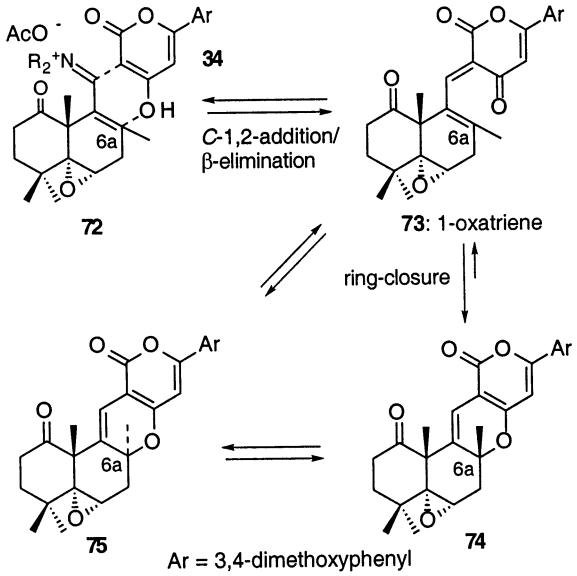
When **67b** was heated in toluene at 250 °C in a sealed tube for 96 h, the cyclized product **67a** was obtained in 21% yield with a ratio of 10:1 in favor of the same major isomer. Some decomposition of **67b** was also observed, but the two major compounds in the reaction mixture were unreacted **67b** and the cyclized product **67a**. While this result supports the structural assignment of **67b**, the high temperature and long reaction time also suggest that the ring-closure could be impeded with the steric encumbrance of the camphor group.

In addition, in our efforts in the total synthesis of arisugacin A [**6a**],[34] we isolated the hexacycle **71** from reaction of the enal **68** with the pyrone **34** using piperidinium acetate salt (Scheme 12). Although **71** was found

SCHEME 12



SCHEME 13



$\Delta E \geq -2.40$ kcal mol^{-1} in favor of **74**

6π-electron electrocyclic ring-closure

as a minor byproduct initially when the reaction was terminated in 2 h, the yield of **71** could be as high as 60−70% if the reaction time for **68** with **34** was extended to 18−24 h. The unambiguous assignment of **71** via X-ray structural analysis suggests the formation of the 1-oxatriene intermediate **69**. Two consecutive intramolecular trappings of **69** by two hydroxyl groups in 1,6- and 1,4-additions should lead to **71** through the initial intermediate **70**. Given that the hexacycle **71** was formed as a single diastereomer, it is also very reasonable to suggest that the stereochemical predisposition of two hydroxyl groups in **69** control the stereochemical outcome of the two conjugate additions.

c. Reversibility of 6π-Electron Electrocyclic Ring Closure. The best evidence for the reversibility of this ring closure is described in Scheme 13. In our efforts toward the total synthesis of arisugacin A (**6a**),[34] we were able to isolate both the desired major isomer **74** and the

(33) (a) Milas, N. A.; Priesing, C. P. *J. Am. Chem. Soc.* **1957**, *79*, 6298. (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (c) Keegan, G. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185. (d) Kagawa, M. *Chem. Pharm. Bull.* **1959**, *7*, 751.

(34) (a) Cole, K. P.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 8791. (b) Wang, J.; Cole, K. P.; Wei, L. L.; Zehnder, L. R.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 3337. (c) Cole, K. P.; Hsung, R. P.; Yang, X.-F. *Tetrahedron Lett.* **2002**, *43*, 3341.

minor isomer **75** from the formal cycloaddition reaction of the iminium salt **72**[34] with the pyrone **34**. With a pure minor isomer **75** in hand, it was possible to equilibrate **75** quantitatively to the desired major isomer **74**. This successful equilibration strongly suggests the reversibility of the ring-closure via the 1-oxatriene intermediate **73**, thereby leading to the final product **74** that is thermodynamically more stable than **75** by about 2.40 kcal mol^{-1} from PM3 calculations using Spartan Model.

The reversibility of this ring closure is also supported by another experiment. When the pure minor isomer **42** (Scheme 7) was heated at 150 °C for 26 h, the major isomer **41** was found in addition to some decomposition products without reaching the original ratio of 4:1 or 7:3.

Conclusion

We have described here a detailed account regarding a formal [3 + 3] cycloaddition strategy that is synthetically useful for constructing 2*H*-pyranyl heterocycles. We have shown that α,*β*-unsaturated iminium salts are useful in controlling competing reaction pathways to give exclusively 2*H*-pyrans and demonstrated that these reactions can be readily extended to 1,3-diketones. Most significantly, we have provided experimental evidence to support the mechanism of this reaction that involves a sequential Knoevenagel condensation and 6*π*-electorn electrocyclic ring-closure, and to support that the latter pericyclic ring closure is reversible for these 1-oxatrienes.

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Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectral and characterization data are given for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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