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SYNTHESIS OF BICYCLO[3.2.1]OCTANES BY A TANDEM DIELS-ALDER-CARBOCATION CYCLIZATION STRATEGY

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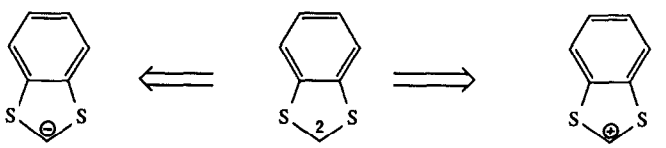
Summary: The bicyclo[3.2.1]octane ring system is assembled by a three-step process featuring a thermally induced [4+2] cycloaddition followed by a 1,3-benzodithiolium ion mediated cyclization onto an enol or silyl enol ether double bond.

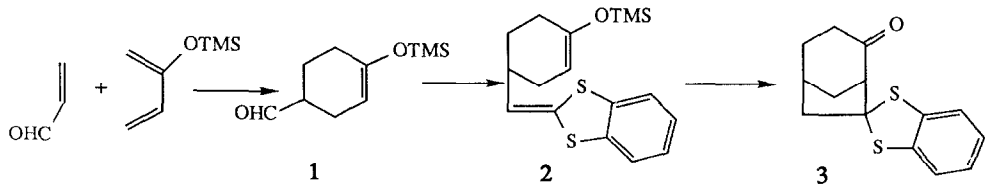
The bicyclo[3.2.1]octane carbon skeleton is a common structural subunit in a number of important natural products[1] and many methods have been developed to construct this ring system.[2] In connection with our studies



Scheme I

on the ambiphilic nature of derivatives of the 1,3-benzodithiole heterocyclic system, we wish to report a novel and effective method for assembling the bicyclo[3.2.1]octane carbon array bearing useful functionality which can be subsequently manipulated in a selective fashion. The utility of the 1,3-benzodithiole unit in this strategy is predicated on the ease with which this interesting heterocycle can be manipulated to accommodate either a carbanionic or a carbocationic center at C_2[3] (Scheme I). Our plan exploits what is in effect, a polarity reversal at the C_2 position in the heterocyclic nucleus in successive steps to introduce and cyclize the two-carbon bridge to form the requisite bicyclic array.

The general sequence for assembling the bicyclo[3.2.1]octane system is illustrated in equation 1. The six membered ring building block is initially prepared by a thermally induced [4+2] cycloaddition between readily available 2-trimethylsilyloxybutadiene[4] and an appropriate α,β-unsaturated carbonyl partner. Next, the free side chain carbonyl group is condensed with 2-lithio-2-diethoxyphosphinyl-1,3-benzodithiole[5], which we have found to

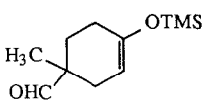
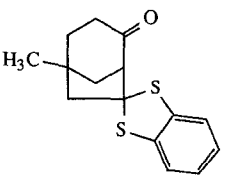
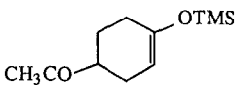
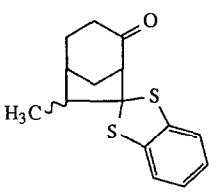
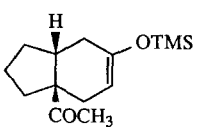
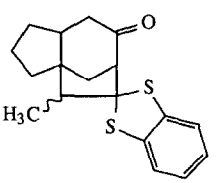
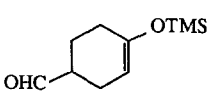
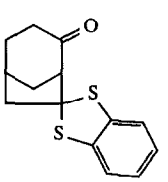


Eq. 1

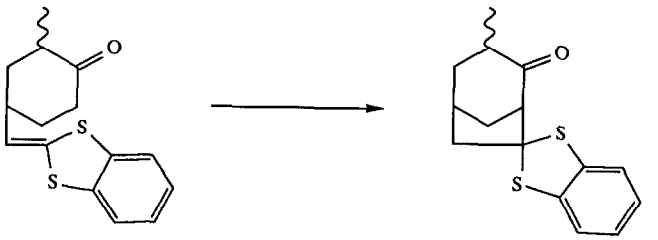
be a convenient source of the 1,3-benzodithiole carbanion,[3b] to provide the key ketene dithioacetal **2** in yields ranging from 79 to 91%. The silyl enol ether functions, at this stage, as a protecting group for the ketone in the six-membered ring thus preventing competitive reaction with the benzodithiole nucleophile. Exposure of the critical ketene dithioacetal to 1 eq of trifluoroacetic acid in acetonitrile at 0°C for 12-48 hr resulted in smooth cyclization *via* the electrophilic 1,3-benzodithiolium carbocation to provide the corresponding bicyclic product.

Table I presents several additional examples of bicyclo[3.2.1]octane species obtained using this protocol. Entry

Table I. Acid Catalyzed Cyclizations to the Bicyclo[3.2.1]octane System.

Entry	Cycloadduct	Product	Yield[a]
1			83%
2			77%[b]
3			35%[b]
4			71%

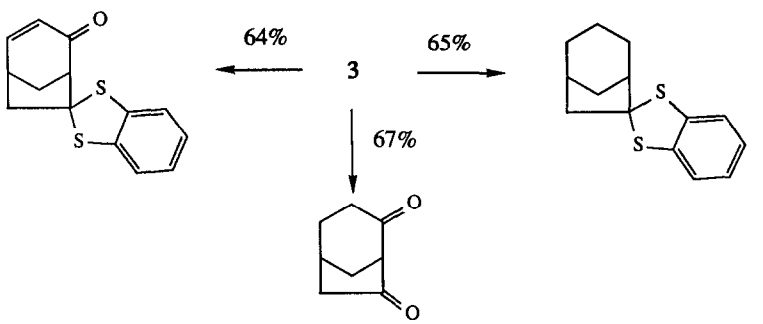
[a]Yield of purified, isolated product. [b]Stereochemistry of methyl substituent is undefined.



4 5

3 demonstrates that reasonably complex polycyclic systems can be fabricated by employing this sequence. However, the utility of this process can be limited in some instances by the reactivity of the dienophilic partner in the initial Diels-Alder step. Interestingly, the silyl enol ether functional group is apparently not a required participant in the cyclization step since cyclohexanone **4**, prepared by mild acid hydrolysis (5% aq TFA) of the silyl enol ether followed by methylation of the ketone enolate (LDA, -78°C), could also be cyclized under conditions identical to those described above to give compound **5** regioselectively. Bond formation in this case occurred exclusively at the less substituted α-carbonatom to yield ketone **5** as a mixture of epimers. Indeed, all entries in Table I could be prepared, incomparable yields, directly from the ketone employing similar conditions. It is quite possible that the reactive species in all of the cases examined to date is the enol tautomer of the ketone and not the silyl enol ether.

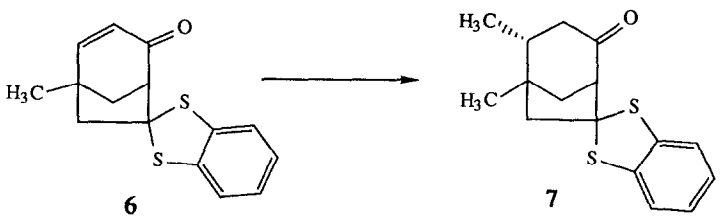
A critical feature of this strategy is that the resultant bicyclo[3.2.1]octane products are versatile synthetic intermediates which are amenable to further elaboration. For example, compound **3** can be easily hydrolyzed to the corresponding dione species with HgO, BF_3•Et_2O in aq THF.[6] Furthermore, the ketone can be selectively



removed by lithium aluminum hydride reduction to the alcohol and subsequent deoxygenation *via* the corresponding xanthate with Barton's Bu_3SnH procedure.[7]

Of particular significance is the ease with which the bicyclic compound **3** can be converted into the related α,β-unsaturated ketone without disturbing the benzodithiole moiety. This tranformation was effected by converting **3** into the silyl enol ether in conventional fashion, followed by selective oxidation with DDQ to the enone.[8] This conversion greatly enhances the potential for introducing additional substituents onto the basic ring system. We have shown that enone **6**, derived from the product of entry 1 (Table I), undergoes smooth conjugate addition with

lithium dimethyl cuprate to provide a single product in 95% yield.[9]



6 7

Clearly, the tandem Diels-Alder -1,3 benzodithiolium ion mediated cyclization protocol is a potentially useful addition to the existing collection of methods for assembling the bicyclo[3.2.1]octane ring system. Work is currently underway to utilize this methodology in several natural product syntheses.

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References

1 a) L. N. Mander *Acc. Chem. Res.*, **16**, 48 (1983).
b) M. Vandewalle; P. J. DeClercq *Tetrahedron*, **41**, 1767 (1985).
c) C. H. Heathcock; S. L. Graham, M. C. Pirrung; F. Plavac; C. T. White in "The Total Synthesis of Natural Products"; J.W. Apsimon, Ed.; Wiley:New York, 1982, vol. 5.

2. a) G. A. Kraus; Y.-S. Hon; J. Sy *J. Org. Chem.*, **51**, 2625 (1986).
b) S. D. Burke; M. S. Dike; J. O. Saunders; C. W. Murtiashaw; J. A. Oplinger *J. Am. Chem. Soc.*, **106**, 4558 (1984).
c) R. H. Schlessinger; J. L. Wood; A. J. Poss; R. A. Nugent; W. H. Parsons *J. Org. Chem.*, **48**, 1146 (1983).
d) H. M. R. Hoffman; R. Henning *Helv. Chim. Acta* , **66**, 828 (1983).
e) R. L. Funk; L. H. M. Horcher, J. U. Daggett; M. M. Hansen *J. Org. Chem.*, **48**, 2632 (1983).

3. a) N. Lozach; M. Stavaux Adv. *Heterocyclic Chem.* **27**, 151 (1980).
b) J. H. Rigby, A. Kotnis; J. Kramer *Tetrahedron Lett.*, **24**, 2939 (1983).

4. M. E. Jung; C. A. McCombs; Y. Takeda; Y. G. Pan; *J. Am. Chem. Soc.*, **103**, 6671 (1981)

5. K. Akiba; K. Ishikawa; N. Inamoto *Bull Chem. Soc. Jpn.*, **51**, 2674, (1978).

6. S. Ncube; A. Pelter; K. Smith; P. Blatcher; S. Warren *Tetrahedron Lett.*, 2345 (1978).

7. D. H. R. Barton; S. W. McCombie *J. Chem. Soc., Perkin Trans. I*, 1574 (1975).

8. I. Fleming; I. Patterson *Synthesis*, 736 (1979).

9. All compounds reported in this paper gave spectral (^{1}HNMR, ^{13}CNMR, IR, MS) and analytical data consistent with the assigned structures.

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