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DITHIOKETALS AS PRECURSORS FOR [2,3] SIGMATROPIC REARRANGEMENTS. SYNTHESIS OF BETWEENANENES WITH VINYLIC HETEROATOMS.

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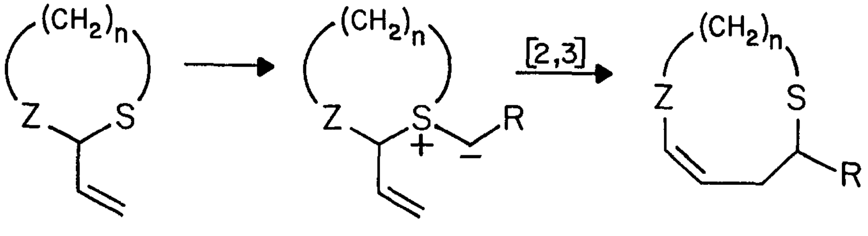
Abstract: Alkoxycarbonyl-stabilized ylides from *gem*-disulfides undergo [2,3]sigmatropic shifts and provided the first entry to betweenanenes with a heteroatom (sulfur) directly attached to the encapsulated olefinic carbon.

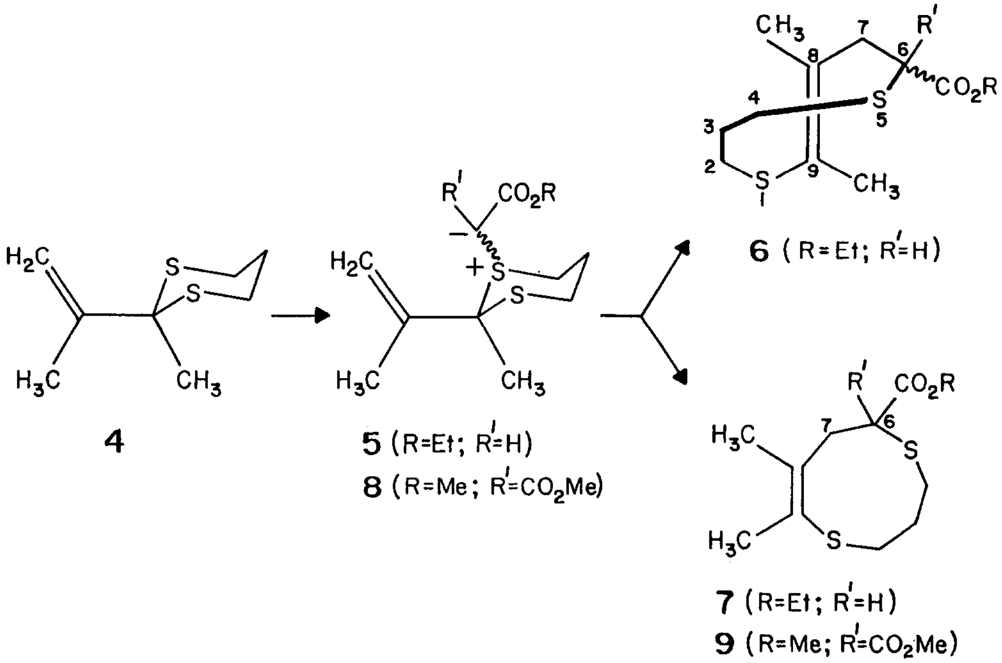
Ring growing methodology elegantly developed by Vedejs *et al.*[1] and extended by others[2] typically involves conversion of an α-vinyl cyclic sulfide (**1a**) to a transient sulfur ylide (**2a**), which isomerizes to an enlarged cycloalkene (**3a**). The scope and versatility of these rearrangement-expansions would be broadened if dithioketal (**1b**) could serve as ylide precursors. Such *gem*-dithiacompounds are accessible (e.g. from ketones) and could lead to macrocycles **3b** with one sulfur directly bonded to an alkene (i.e. a thio enol ether). The other sulfur becomes aliphatic, and this distinction might permit selective chemical manipulation later.[3] On the other hand, a *gem*-disulfide precursor also has the potential to divert the path from the desired **1b** → **2b** → **3b**. We now report a prototype study and a successful application of the scheme to the synthesis of the first betweenanene[4] having a heteroatom directly connected to the encapsulated olefinic unit.



1 2 3

a, Z = CH_2
b, Z = S

The known vinyl dithioketal 4[5] was combined with a carbenoid generated from Cu(II)-catalyzed decomposition of ethyl diazoacetate. The derived ylide 5 rearranged *in situ* and produced an E,Z mixture (56% yield) of the nine-membered thio enol sulfide; the ratio of E isomer (6) to Z isomer (7) was 4:1. By column chromatography we separated crystalline 7 from the E olefins 6, which were obtained as a mixture of epimers at C-6 (ratio major epimer: minor epimer was 3:1). These epimers exist because of the chiral plane at the alkene unit.[4] Analytical, spectral, and chemical properties of our products agreed with their assigned structures. For example, in the ^{1}H NMR spectrum of 6 (epimeric mixture) the C-6 hydrogen in *each* epimer appears as a doublet of doublets as a consequence of coupling to the adjacent diastereotopic methylene hydrogens. For the "major" E epimer, this pair of doublets centers at δ 3.5, whereas for the "minor" E epimer it falls at δ 3.3. In contrast, the methine H in the Z olefin 7 is a pseudo-triplet centered at δ 4.0. Evidently, in 7 the C-6 H experiences similar averaged coupling with each C-7 hydrogen as a result of conformational flexibility in the nine-membered ring.



4

5 (R=Et; R'=H)
8 (R=Me; R'=CO$_2$Me)

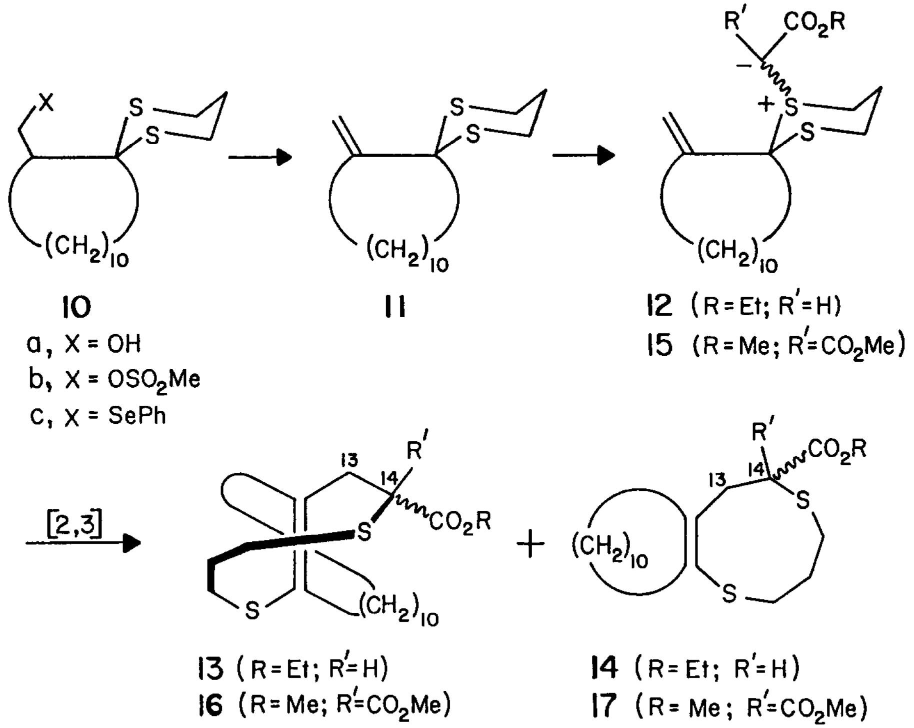
6 (R=Et; R'=H)

7 (R=Et; R'=H)
9 (R=Me; R'=CO$_2$Me)

We confirmed the E and Z assignments for 6 and 7, respectively, by enolization experiments. In EtOH/NaOEt, the "major" and "minor" epimers of 6 interconverted, and after 15 min at room temperature their relative proportion (via NMR) changed from an initial 3:1 to a final 1:3. In contrast, Z isomer 7 was stable to similar treatment as expected since diastereomerism is not possible.

When we conducted ring-expansion of 4 via ylide 8 (generated *in situ* from dimethyl diazomalonate), the product (36% yield, not optimized) consisted of a single isomer, the Z olefin 9. Its magnetically equivalent C-7 H's appeared as a singlet (δ 1.6), and its equivalent OCH_3 groups produced a sharp singlet at δ 3.8. Proton decoupled ^{13}C NMR confirmed the presence of only one type of carbonyl carbon (single peak δ 169.74). The chemical behavior of **9** agreed with its assigned Z configuration. Thus, treatment of **9** with NaOEt/EtOH effected transesterification and a retro-Claisen condensation to produce a single product identical in all respects to the Z olefin **7** obtained from our other route.[6]

With this methodology we succeeded in synthesizing the double-domed olefins (i.e. betweenanenes) **13** and **16** by the overall scheme shown.[7] Known 2-methoxycarbonyl cyclododecanone[8] was conventionally converted to **10a** with propane-1,3-dithiol followed by $LiAlH_4$ reduction. Alcohol **10a** was mesylated (91%) to **10b** and then transformed (81%) to the phenyl selenide **10c** with NaSePh.[9] Selective oxidative elimination of **10c** with $NaIO_4$ in dimethyl sulfoxide produced in 45-50% yield the olefinic dithioketal **11**, which was treated with ethyl diazoacetate as before. The transient ylide (**12**) rearranged <u>in situ</u> and gave (58% yield) a mixture of **13** and **14** in a 4:1 ratio. By column chromatography we separated crystalline Z isomer **14** from oily **13**, which itself consisted of two epimers at C-14 ("major" and "minor") in a 3:1 ratio. The physical and chemical properties of this epimeric mixture agreed with the bis-transoid olefinic geometry. For example, in the ^1H NMR of **13**, the C-14 methine H appears in <u>each</u> epimer as a doublet of doublets centered at δ 3.5 (major epimer) and at δ 3.3 (minor epimer). Molecular models indicate that rotation around the C13-C14 bond in **13** is restricted, and this situation would accentuate the diastereotopicity of the methylene hydrogens at C-



10
a, X = OH
b, X = OSO_2Me
c, X = SePh

11

12 (R = Et; R' = H)
15 (R = Me; R' = CO_2Me)

13 (R = Et; R' = H)
16 (R = Me; R' = CO_2Me)

14 (R = Et; R' = H)
17 (R = Me; R' = CO_2Me)

13. In contrast, the methine H in the corresponding Z isomer 14 showed up as a pseudo-triplet (δ 4.0) reminiscent of our earlier observations on olefin 7.

We confirmed that the major and minor isomers of 13 differ only in configuration at C-14 by interconverting them through enolization in EtOH/NaOEt. In less than one hour, their initial ratio (3:1, respectively) became a final ratio of 1:3, and no new isomers were produced. As expected, our Z olefin 14 remained homogeneous after the same alkaline treatment.

Similarly, when we used dimethyl diazomalonate as the carbenoid source for ylide formation, olefin 11 gave (via 15) the desired betweenanene 16 and its Z counterpart 17 in a 5:1 ratio (total yield 71%). After separation by column chromatography, each isomer was crystalline and was fully characterized.[7] In 16 the two CO_2Me groups are diastereomeric (because of the chiral plane at the olefinic unit)[4,10] and exhibited distinct, sharp OMe singlets (δ 3.81 and 3.79) in the ^{1}H NMR. In 17 the methoxycarbonyl groups are equivalent and, in agreement, this isomer showed only one OMe singlet (δ 3.78). Finally, we correlated 16 with our other betweenanene 13 by treating 16 with NaOEt/EtOH. We obtained in 62% yield a mixture of the same two epimers of 13 already in hand from our earlier route. Furthermore, the ratio of major:minor epimers was virtually the same (1:3) as that obtained by the enolization equilibration conducted earlier on 13.

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3. The same reasoning applied to monothioketals could lead to an enol ether functionality in the expanded sulfur ring.

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6. The configuration of the double bond in products 6, 7, and 9 is likely determined by stereochemistry of the intermediate ylides. See (a) Vedejs, E.; Arco, M. J.; Renga, J. M. Tetrahedron Lett. 1978, 523-526; (b) Cere, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. J. Org. Chem. 1981, 46, 486-490.

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