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# APPLICATION OF A THREE-CARBON RING EXPANSION PROCESS TO BRIDGED BICYCLIC SYSTEMS

Baoyu Mi and Robert E. Maleczka, Jr.*

*Department of Chemistry, Michigan State University , East Lansing, MI 48824, U.S.A.*

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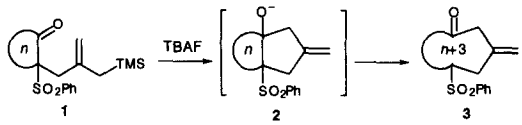
**Abstract:** Experimental data in combination with MMFF94 and AM1 calculations offer a model for predicting the viability of Trost's three-carbon ring expansion on bicyclic systems. 

*Keywords:* Bicyclic aliphatic compounds, Molecular modeling, Ring transformations.

Efficient construction of medium to macrocyclic compounds has long been a challenge for synthetic chemists. In 1980, Trost reported a silane mediated three-carbon condensative ring expansion approach leading to such systems (Scheme I).[1] In terms of bond-energy changes, Trost noted that the conversion of **2** to **3** is a neutral event,[2] therefore successful ring expansions of this type require a release of strain energy. In order to estimate this energy change, the strain energy of **2** was approximated as the sum of the strain energies of cyclopentane and an *n* membered cycloalkane, and then compared against the strain energy of the expanded product. This method of calculation proved useful in predicting the successful ring enlargements of 5, 8, and 12 membered rings, as well as the failure of 6 and 7 membered rings to expand.

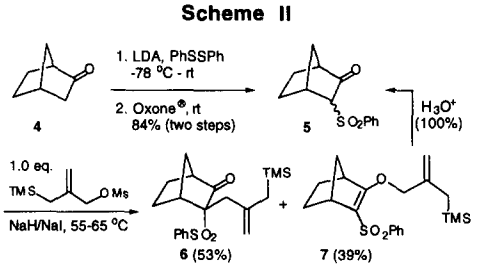
**Scheme I**




1 2 3

We were interested in applying this methodology to bicyclic molecules, and ultimately in natural product synthesis. However, we were soon to realize that estimating the strain release in bicyclic systems was difficult as not many strain energy data are available for the products. Furthermore approximating the strain energy of intermediate cyclopentyl species by adding the energies of the cyclopentane and the parent bicycle would afford equal numbers for [3.2.1] bicyclic molecules **18** and **23** (Scheme IV; *vida infra*), a conclusion we viewed with some skepticism. An alternative method might be to only consider the most strained ring component of the bicycle, but again we were unsure as to the accuracy of such an approach. Given this uncertainty in the theoretical treatment of these reactions, we decided to conduct an experimental investigation of the ring expansion on bridged multicyclic compounds.

**Scheme II**




Our study began with the purchase (**4** and bicyclo[3.2.1]octan-2-one) or preparation[3] of various [2.2.1], [3.2.1], [4.2.1], and [2.2.2] bicyclic ketones. Elaboration of these carbonyls into α,α-disubstituted ring expansion precursors **6**, **8**, **9**, and **10** followed the approach outlined in Scheme II.[4] Ketones such as norcamphor (**4**; Aldrich) were subjected to enolate formation and subsequent trapping with diphenyl disulfide. Oxone® oxidation of the α-phenylthio group furnished α-benzenesulfonyl bicyclic ketones in good to excellent yields.[5] Deprotonation of the β-ketosulfones with sodium hydride was followed by allylation with trimethylsilylallyl mesylate[6] in the presence of sodium iodide. In contrast to the highly selective installation of the α-trimethylsilylallyl side chain to monocyclic ketones,[1] it proved difficult to introduce this side chain at the α-carbon of the

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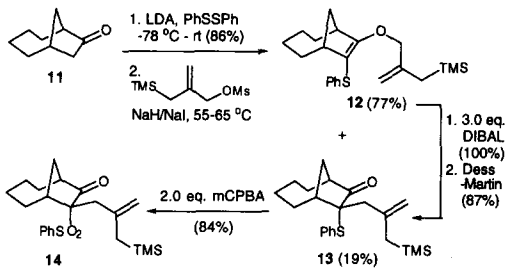
benzenesulfonyl bicyclic ketones without an intrusive amount of *O*-allylation. Furthermore, efforts to convert the *O*-allylated material into the *C*-allylated products via Claisen rearrangement failed, presumably due to the steric hindrance of the sulfone. However, the *O*-allylated byproducts could be quantitatively hydrolyzed back to the starting benzenesulfonyl bicyclic ketones. Though not ideal, this route provided us pure[4] **6**, **8**, **9**, and **10** with a level of through put necessary for our study.

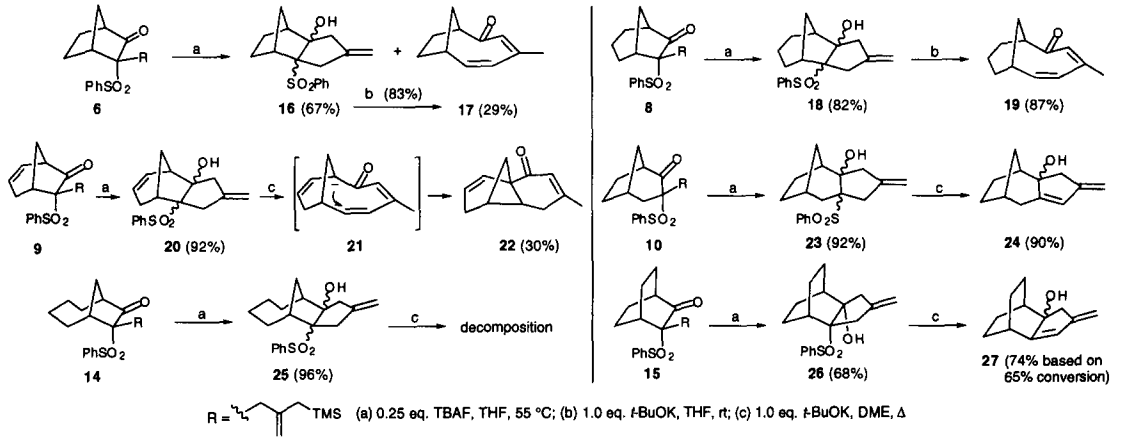
Attempts to synthesize the [2.2.2] and [4.2.1] ring expansion precursors via this approach failed in that their β-keto-sulfones afforded no significant amounts of *C*-allylated material. Fortunately, the *C*-allylated products could be accessed via a slightly modified route as depicted in Scheme III. While *O*-allylation of the sulfide derived from **11** again predominated, enol ether **12** could be rearranged via DIBAL mediated reductive [3,3]-sigmatropic shift[7] which when followed by a Dess-Martin oxidation[8] gave *C*-allylated **13** in high yield. Oxidation of sulfide **13** with *m*-CPBA, provided the desired product (**14**) in good yield.[4] Compound **15** was prepared in the same manner.[4]

**Scheme III**




With the desired [2.2.1] (**6**), [3.2.1] (**8**, **9**, and**10**), [4.2.1] (**14**), and [2.2.2] (**15**) molecules in place, we were now prepared to investigate their behavior under ring expanding conditions. As illustrated in Scheme IV, exposure of these compounds to TBAF successfully evoked the cyclization portion of the sequence (e.g. **15** → **26**) but for the most part, did not result in expansion. Only the bicyclo[2.2.1] ring system proceeded to give any ring expanded product (**17**), but even in this case the major product was the fused methylenecyclopentane (**16**).[4] Trost experienced a similar phenomena in the attempted ring expansion of cyclopentanone, where it was discovered that treatment of the intermediate alcohol with KH could effect the fragmentation and corresponding ring expansion along with elimination of the sulfone. We selected *t*-BuOK as the base rather than KH/18-Crown-6 to effect the ring expansion reaction of these cycloadducts so as to provide us the option of running the reaction under "protic" conditions and thereby compensate for the disfavored acid-base equilibrium between the alkoxide[9] and carbanion[10] expansion intermediates (Scheme V). In practice, treatment of alcohols **16** and **18** with *t*-BuOK led to ring expansion, movement of the olefin into conjugation with the ketone, and concurrent elimination of the benzenesulfonyl group to afford dienones **17** and **19** in high yield.[4] Interestingly exposure of **20** to the

**Scheme IV**

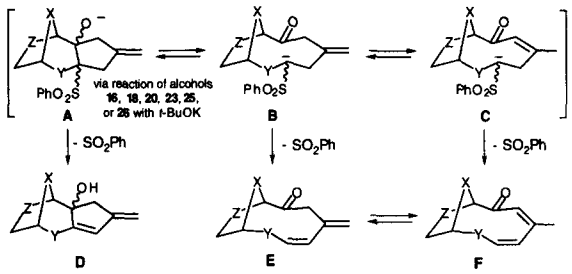


same conditions gave **22**,[4] presumably via the formation of fragmentation product **21** followed by transannular cyclization. In contrast, only simple elimination products **24** and **27** were observed[4] upon reacting alcohols **23** and **26** with *t*-BuOK, whereas no reaction was observed for **25**, except decomposition upon prolonged stirring with *t*-BuOK in refluxing DME.

The varied reactivities of **18** and **23**, both of which are [3.2.1] bicycles, validated our concern over approximating the strain energy of the intermediate cyclopentyl species by adding the energies of the cyclopentane and the parent bicycle. On the other hand, consideration of the most strained ring component of the [3.2.1] bicycle would appear to be predictive of these reactions as the expansion of **18** would involve going from a 5- to an 8- membered ring, the success of which was demonstrated by Trost, whereas **23** would involve a 6- to a 9- membered ring expansion, which Trost could not accomplish. However **25** also fails to expand, and this transformation is one of a 5- to 8- and an 8- to 11 expansion, both of which worked for the simple monocyclic systems. Clearly predicting the success of such ring expansions on bicyclic systems is not easily amenable to simple methods. Therefore we decided to attempt to establish a relatively straightforward method of calculation which would allow us to predict the course of these reactions.

We viewed molecular force field calculations[11] as a potentially useful tool for estimating the relative strain energies (SE) of multicyclic ring systems. Due to the poor parameterization of the benzenesulfonyl group in most molecular force field models, we decided to calculate strain energies of elimination products **D** and **E** (Scheme V). While not in equilibrium, the bond energy differences between the simple elimination product dienol **D** and ring expansion product dienone **E** are nearly identical to the small energy differences between **A** and **B**.[1,2] Therefore calculations on **D** and **E** were viewed as a reasonable means by which to predict the course of these strain energy dependent expansions.[12] As a check on the molecular force field studies, we also decided to conduct higher level semiempirical AM1 calculations which would provide heats of formations.

**Scheme V**




We started the computational study at the MMFF94 level,[11] examining the elimination products **D** and **E** which were derived from alcohols **16**, **18**, **20**, **23**, and **26** (Scheme V). Minimum energy conformers (within 3.0 kcal/mol of the global minimum) were located with the Osawa[13] searching method. A semiempirical AM1 level study was then performed on these MMFF94 derived conformers.[14] The calculated strain energy (SE) and heats of formation ($\Delta H_f$) values are listed in Table I. A satisfyingly consistent result was obtained from these theoretical calculations compared to the experimental results. There was excellent agreement between the trends determined by molecular mechanics strain energies and those by semi-empirical heats of formation. From the calculated SE and $\Delta H_f$ data (Table I), ring expansion product dienones from bicyclic ring systems **16**, **18**, and **20** are favored over the corresponding dienols. Experimentally, high yields of dienones **17** and **19** were obtained. The lower yield of **22** may be explained by the high absolute SE or $\Delta H_f$ of the unisolated intermediate trienone **21**. Finally, calculations on **17**, **19**, and **22** supported the observed movement of the exocyclic olefin into conjugation with the keto group.

**Table I**

| starting alcohol | SE (Kcal/mol) D | E | ΔSE | $\Delta H_f$ (Kcal/mol) D | E | $\Delta\Delta H_f$ |
|---|---|---|---|---|---|---|
| **16** | 57.62 | 41.93 | *-15.69* | 3.44 | -19.03 | *-22.47* |
| **18** | 47.30 | 43.17 | *-4.13* | -16.69 | -25.47 | *-8.78* |
| **20** | 68.52 | 62.75 | *-5.77* | 11.04 | 3.01 | *-8.03* |
| **23** | 38.45 | 48.74 | *10.29* | -22.73 | -22.94 | *-0.21* |
| **25** | 47.59 | 51.14 | *3.55* | -26.69 | -27.50 | *-0.81* |
| **26** | 45.96 | 53.23 | *7.27* | -22.63 | -20.47 | *2.16* |

These calculations can also serve to explain the failed ring expansions. For example, the expansion products from **23** and **25** are disfavored by MMFF 94 calculations while the AM1 results barely favor (by less than 1 Kcal/mol) expansion over the simple elimination product dienols. Experimentally exposure of **23** to *t*-BuOK gave elimination product **24**, whereas prolonged heating of **25** with *t*-BuOK gave no reaction other than decomposition. For ring system **26**, both the SE and $\Delta H_f$ values make the case against ring expansion, which would be consistent with the exclusive formation of dienol **27**. Based on these results, it would appear that the feasibility of performing these three carbon ring expansions on bicyclic molecules can accurately be predicted by comparing MMFF94 estimated strain energies of eliminated intermediates such as **E** and fused methylenecyclopentenes **D**.

In summary, we have studied the silane mediated three-carbon ring expansion process on several small to medium bridged bicyclic systems. Intermediate alcohols were isolated as the major products in all cases. Further treatment of the intermediate alcohols with *t*-BuOK afforded either ring expansion product dienones (**F**) or simple elimination product dienols (**D**). The theoretical study of this ring expansion process supported the assumption that it is a strain energy controlled process, which is successful when significant amount (at least 4 Kcal/mole) of strain energy is released. The combination of experimental and theoretical results have allowed us to develop an MMFF94 based method for predicting the feasibility of applying Trost's three-carbon condensative ring expansion to bicyclic systems.

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