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FUNCTIONALIZED CARBOCYCLIC RINGS VIA INTRAMOLECULAR DIELS-ALDER REACTIONS OF IN SITU-GENERATED, γ SUBSTITUTED, HETEROATOM-STABILIZED ALLYL CATIONS IN ACIDIC POLAR MEDIA

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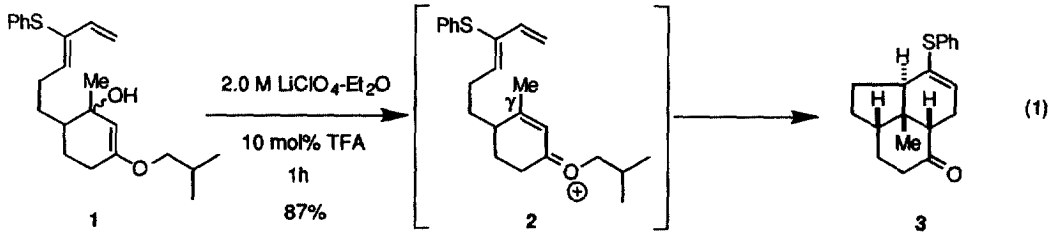
Abstract: The synthesis of highly structured carbocyclic ring systems possessing quaternary carbon atoms has been realized *via* intramolecular Diels-Alder reactions of *in situ*-generated, γ substituted, heteroatom-stabilized allyl cations in acidic polar media.

We have reported on a general strategy for the formation of carbocyclic ring systems which features intramolecular Diels-Alder reactions of *in situ*-generated heteroatom-stabilized allyl cations in acidic polar media.[2] In an effort to overcome some of the difficulties associated with this process and examine further the scope of this potentially useful cycloaddition protocol for the synthesis of carbocyclic ring systems, we have extended our studies to include cases wherein [1] a phenylthio group has been incorporated into the terminal diene unit and [2] substituents have been incorporated into the γ carbon of the heteroatom-stablized allyl cation so as to generate a quaternary carbon atom within the resulting carbocyclic array [cf. Equation 1]. We detail below the results of this investigation.



(1)

The impetus for investigating systems such as **1** stemmed, in part, from our inability to prepare in good yield tricyclic ketone **5** by exposure of **4** to acidic polar media. In our initial studies, substrate **4**, which was prepared from the corresponding vinylogous ester[2] by treatment with methyllithium in tetrahydrofuran-hexamethylphosphoramide (7.5:1) at -78 °C, was subjected to the standard conditions for cycloaddition. Slow addition [3h] of a 0.15 M solution of **4** in anhydrous diethyl ether to 5.0 M lithium perchlorate in diethyl ether containing 10 mol % of trifluoroacetic acid gave rise after a total of 8h to tricyclic ketone **5** in a disappointingly low yield of 20% accompanied by 40% of cyclohexenone **6**. The low yield associated with the formation of **5** led us to examine the effect of incorporating a heteroatom into the terminal diene so as to facilitate trapping of the incipient, heteroatom-stabilized allyl cation [cf. **2**]. Toward this end, we prepared substrate **1** from vinylogous ester **7**[3] employing the Pearson protocol[4] for elaboration of the 1-substituted-(*Z*)-2-thiophenyl-1,3-butadiene unit.

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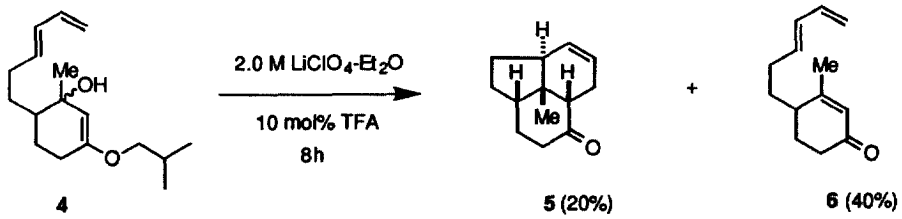
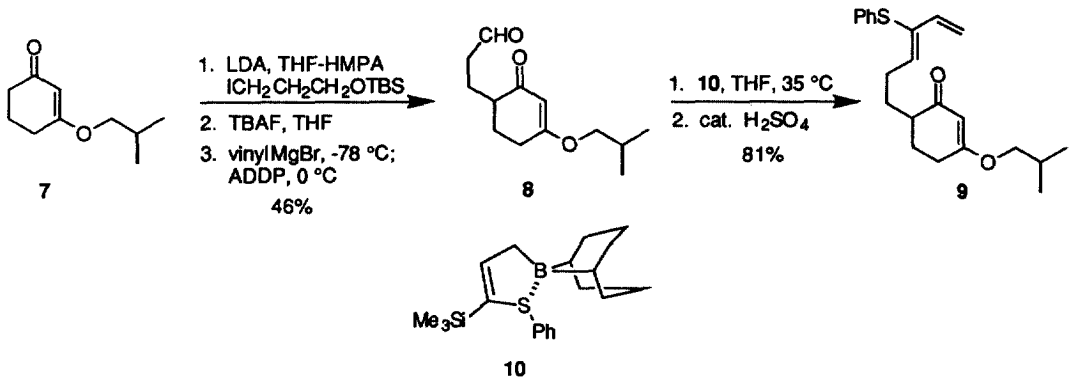


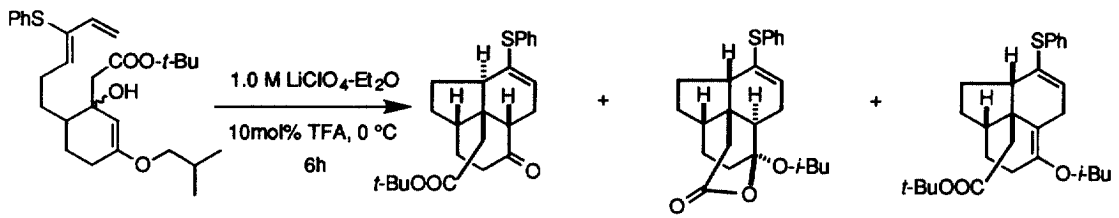
Alkylation [LDA, THF-HMPA, -78 °→0 °C] of vinylogous ester **7** with 3-iodo-*tert*-butyldimethylsilyloxy propane[5] followed by cleavage [TBAF, THF] of the silyl ether and subsequent oxidation of the resulting alcohol employing a modification of the procedure of Saigo and Mukaiyama[6] provided aldehyde **8** which was transformed into substrate **1** *via* a one-pot procedure using Pearson's chemistry. Condensation of **8** with allylborane **10** [generated *in situ* from 1-phenylthio-1-trimethylsilyl allene and 9-borabicyclo[3.3.1]nonane] gave rise to the corresponding β-boron oxysilane, which upon exposure to catalytic sulfuric acid afforded **9** in 81% yield.



Completion of the synthesis of **1** was accomplished by the addition of vinylogous ester **9** to a solution of methyl lithium [1.4 M in diethyl ether] in tetrahydrofuran-hexamethylphosphoramide (17:1) cooled to -78 °C. In the absence of hexamethylphosphoramide, **9** was recovered unchanged. Substrate **1** was obtained in near quantitative yield and was subjected directly to the cycloaddition protocol. Slow addition *via* syringe pump of a solution of **1** in diethyl ether to 2.0 M lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid afforded after 1h an 87% isolated yield of crystalline tricyclic ketone **3**, mp 58.5-59.5 °C, as the sole product. When 5.0 M lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid was utilized, the yield of **3** was reduced to 70%. The structural assignment for **3** follows from ^{1}H NMR data and extensive nOe measurements. The exclusive formation of cycloadduct **3** is consistent with previous observations and can be rationalized by [4 + 2] cycloaddition of a heteroatom-stabilized allyl cation *via* an exo transition state.

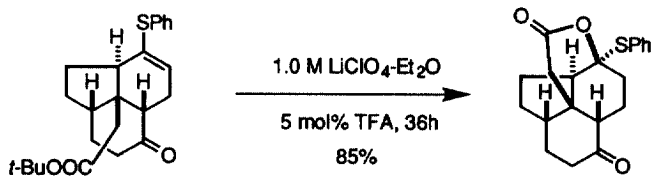
With the successful realization of **3** from **1**, attention was focussed on substrate **11**. The sensitive allylic alcohol **11** was prepared in 90% yield by addition of the lithium enolate of *tert*-butyl acetate to **9** in tetrahydrofuran-hexamethylphosphoramide. Unlike the cycloaddition of **1** which afforded exclusively **3**, the Diels-Alder reaction of **11** was highly dependent upon temperature and the concentration of lithium perchlorate in diethyl ether. Best results were obtained upon slow addition [2h] of a 0.3 M solution of **11** in diethyl ether to a solution of 1.0 M

lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid cooled to 0 °C. The reaction was quenched 6h after the addition was complete and provided three products **12-14** in 98% isolated yield. The identity of the major product **12** (71%) and the minor product **14** (17%) follow from their respective ^{1}H NMR spectra and nOe measurements. The formation of **13** (10%) suggests that it is derived from enol ether **14**, which presumably arises *via* a stepwise, endo-like transition state. In fact, exposure [8h, ambient temperature] of enol ether **14** to 10 mol % TFA in 1.0 M $LiClO_4$-Et_2O gave rise to an 85% isolated yield of **13**. The structure of **13** was unequivocally established by single-crystal X-ray analysis.[7]



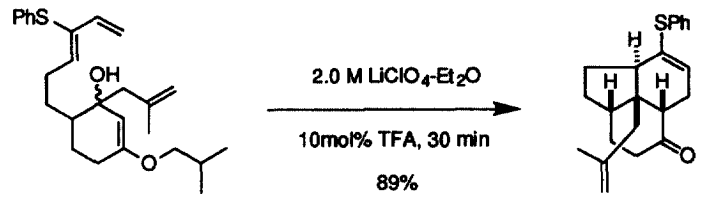
11 **12** (71%) **13** (10%) **14** (17%)

The cycloaddition of **11** and the subsequent cycloadducts are very sensitive to the temperature of the acidic polar medium. For example, when a 0.3 M solution of **11** in diethyl ether was slowly added [2h] to 2.0 M lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid at ambient temperature, the reaction was complete after 30 min and gave rise (95%) to three products **12** (42%), **13** (38%) and **15** (15%) with none of the enol ether **14** being detected. Tetracyclic lactone **15** arises from ester **12** *via* an acid-catalyzed lactonization initiated by protonation of the enol thioether during the course of the reaction. Even in the presence of 1.0 M $LiClO_4$-Et_2O containing 5 mol % TFA ester **12** is slowly transformed over 36h into tetracyclic lactone **15** in 95% yield (cf. **12**→**15**). The structure of **15** was unequivocally established by single-crystal X-ray analysis.[8]

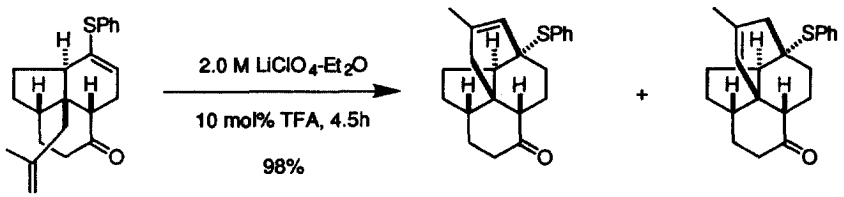


12 **15**

In contrast to the results obtained above with **11**, substrate **16**, possessing a methallyl group at the allylic carbon, underwent smooth intramolecular Diels-Alder reaction [2.0 M $LiClO_4$-Et_2O, 10 mol % TFA] within 30 min giving rise exclusively to tricyclic ketone **17**, mp 96.5-97.5 °C, in 89% isolated yield. As was the case with **11**, extended exposure [5h] of **16** to 2.0 M lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid led to the formation of the tetracyclic products **18** and **19** in >95% yield, with none of the anticipated product **17** being detected by either TLC or ^{1}H NMR. In a separate experiment, exposure [4.5h] of cycloadduct **17** to the reaction conditions [2.0 M $LiClO_4$-Et_2O, 10 mol % TFA] afforded, in 98% yield, **18** and **19** in a ratio of 1.5:1. The structure of **18** was unambiguously established by single-crystal X-ray analysis.[9]



16 17



17 18 19

In summary, the above described methodology provides an efficient, synthetically useful protocol for the elaboration of highly functionalized carbocyclic arrays in a one-pot procedure.

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References

1. Address correspondence to this author at Montana State University.
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7. Lactone **13**, mp 97-98 °C, crystallizes in space group $P2_1/a$ with cell dimensions at -165 °C of a = 15.072(7) Å, b = 13.624(7) Å, c = 21.707(11) Å, beta = 106.23(2) °, V = 4279.54 $Å^3$, D_C 1.237 g cm^{-3}, and Z = 8. All atoms were located and refined to final residuals of R(F) = 0.1019 and $R_W(F)$ = 0.0964.
8. Lactone **15**, mp 164.5-166.0 °C, crystallizes in space group $P2_1/c$ with cell dimensions at -165 °C of a = 8.214(2) Å, b = 12.720(3) Å, c = 15.972(3) Å, beta = 99.22(1) °, V = 1647.40 $Å^3$, D_C 1.381 g cm^{-3}, and Z = 4. All atoms were located and refined to final residuals of R(F) = 0.0409 and $R_W(F)$ = 0.0364.
9. Tetracyclic ketone **18**, mp 130-131 °C, crystallizes in space group P1bar with cell dimensions at -170 °C of a = 8.261(1) Å, b = 13.405(2) Å, c = 8.215(1) Å, alpha = 98.89(1) °, beta = 100.96(1) °, gamma = 94.66(1) °, V = 876.69 $Å^3$, D_C 1.282 g cm^{-3}, and Z = 2. All atoms were located and refined to final residuals of R(F) = 0.0297 and $R_W(F)$ = 0.0342.