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Annulations in Bridged Systems. An Approach to the Synthesis of Shikodonin

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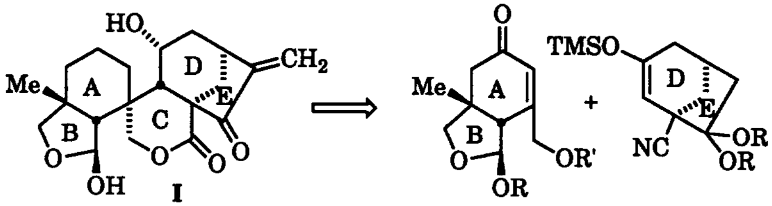
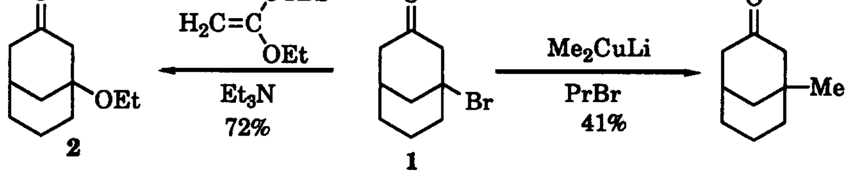
Abstract: *A broadly-useful strategy for the introduction of a bridgehead substituent and a substituent on an adjacent carbon is described. The addition of TMSX to a bridgehead enone generates an enol silyl ether regiospecifically. Reaction of the enol silyl ether with electrophiles results in a vicinal dialkylation.*

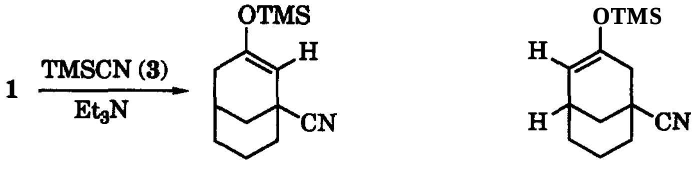
Adjacent stereogenic centers are often introduced by conjugate addition to an unsaturated ketone followed trapping the resulting enolate with an electrophile. This versatile strategy commonly employs a cuprate reagent as the nucleophile and a halide, epoxide or aldehyde as the electrophile.[1] A significant variant involves the use of an enol silyl ether as the nucleophile followed by silylation to form a new enol silyl ether. We have examined these protocols in the system shown below. Bicyclic compound **1** was chosen for a model study for our approach to the synthesis of shikodonin (I).2



Because of the instability of the bridgehead enone (in the absence of nucleophiles, it dimerizes at temperatures above -78 °C), the nucleophile needed to be present as the enone was formed.3 A number of unsuccessful attempts at conjugate addition/trapping with cuprates (conjugate addition but no alkylation) and with enol silyl ethers (ether 2 was formed) forced us to rethink the problem We decided to examine



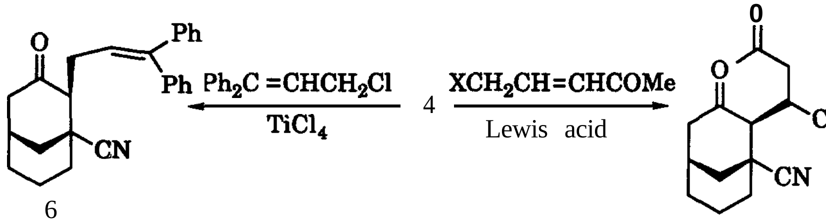
a two step approach using trimethylsilylcyanide (**3**)[4] as the nucleophilic reagent. Generation of the bridgehead enone by the reaction of triethylamine with bromoketone **1** in the presence of 3 cleanly afforded adduct 4 in 98% yield. Only a single isomer was formed. The proton NMR spectrum, wherein the vinyl proton of the enol silyl



4 5

ether was a singlet at δ 4.82, strongly supported the assigned structure. In analogy with other bridged systems, the vinyl proton of the enol silyl ether 5 would be split by the bridgehead proton into a doublet.

With enol silyl ether 4 in hand, the next task was to study electrophilic additions to 4. Of particular interest was whether the inductive effect of the nitrile would attenuate the reactivity of the enol silyl ether.

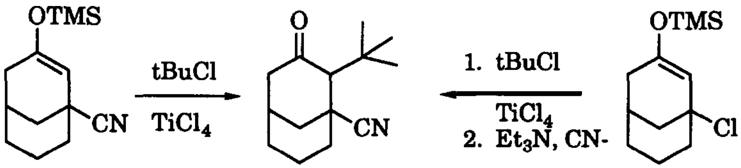


6

7: X=H
8: X=OEVE
9: X=OH

Alternatively, the Lewis acid catalyst required for complexation with our electrophile might simply remove the nitrile to generate an allylic carbocation.[5,6] To address these concerns, enol silyl ether 4 was reacted with 3,3-diphenyl-2-propenyl chloride and $TiCl_4$ to afford the alkylated keto nitrile 6 in 70% yield. Keto nitrile 6 was a single isomer, as evidenced by proton NMR and TLC. The exo stereochemistry was established by a NOE experiment. This reagent is known to react with enol silyl ethers that had been inductively deactivated.[7] Additionally, the reaction of 4 with enones afforded diketone 7 and 8 in 18% and 35% yields, respectively. These compounds appear to be single isomers by proton NMR and TLC. The exo stereochemistry is assigned in analogy with 6. Hydroxy nitrile 9 was not produced in this reaction.

The Michael acceptor which would be employed in the synthesis of shikodonin would be more hindered than our model system compounds. In order to determine whether sterically hindered electrophiles would react, enol silyl ether 4 was treated with tert-butyl chloride in the presence of titanium tetrachloride. The keto nitrile 10 was formed in 42% yield. In like manner, 10 could also be formed from chloride 11 (prepared from the reaction of 1 with TMSCl and triethylamine in 90% yield).



4 10 11

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