

NOVEL ANNULATION REACTIONS : THE DIRECT SYNTHESIS OF CYCLOPENTANES USING A
LEWIS ACID ACTIVATED BISFUNCTIONAL ANNULATING REAGENT

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Summary: In a novel one-pot reaction 3,3-Dimethoxy-1-trimethylstannylpropane (1) reacts in the presence of Lewis acids with O-silylated enolates in a [3+2] annulation to form fused cyclopentanes possessing a bridgehead hydroxy group.

A great amount of effort has been expended in devising new synthetic routes to cyclopentanoids¹ due to the widespread occurrence of five-membered rings in nature². Unfortunately many of these routes are multi-step procedures which are not readily applicable to the synthesis of the naturally occurring cyclopentanoids. A conceptually simple approach to five-membered rings is shown in FIG. I, for which the idealised

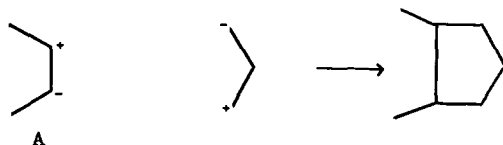
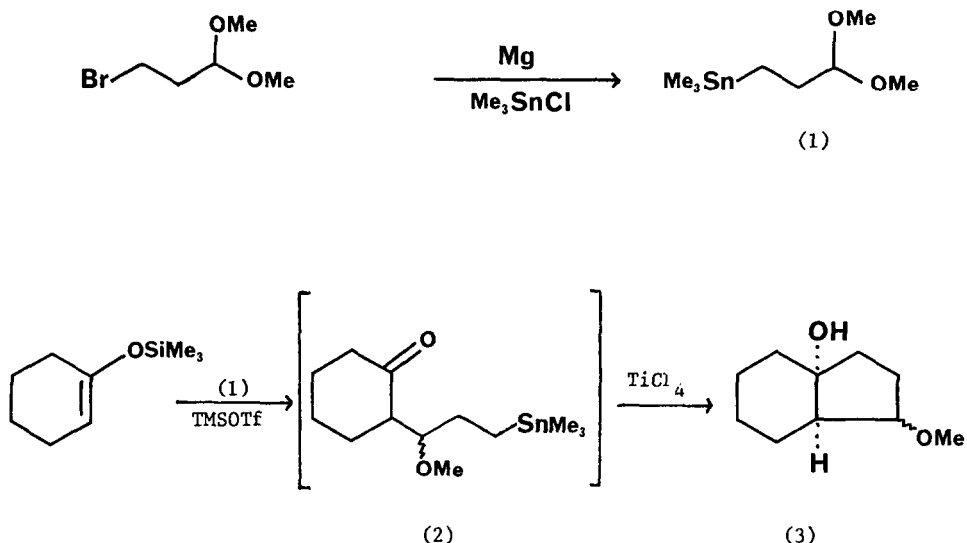


Fig. 1

fragments indicated have been realised in practice by, amongst others, the bifunctional conjunctive reagents developed by Knapp³, Trost⁴, and Danishefsky⁵ in their [3+2] annulation procedures, all of which utilise the natural polarity of an enone system for fragment A. However with the exception of Trost's trimethylenemethane palladium complexes⁶ it is inherent in all of the existing bifunctional conjunctive reagents that annulation occurs in two separate reactions. This arises since the electrophilic and nucleophilic centres so far employed require activation under two sets of different and incompatible conditions, so guaranteeing that they do not self destruct.

We now describe a new annulation procedure which utilises a bisfunctionalised conjunctive reagent in which one set of conditions (Lewis acids) activates both centres, but sequentially.

The trimethylstannyl acetal (1)⁷ is easily prepared in 61% yield by a Grignard reaction of 1-bromo-3,3-dimethoxypropane⁸. The reaction of (1) with an O-silylated enolate in the presence of trimethylsilyltrifluoromethanesulphonate (TMSOTf)⁹ gives the expected ketone (2) (which can be isolated if required). Further treatment of (2) with titanium tetrachloride



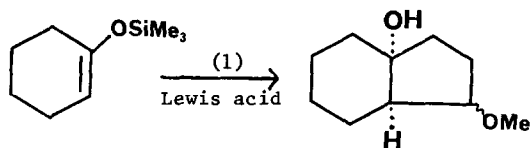
however activates the C-Sn bond to nucleophilic attack on the previously masked carbonyl group, as shown by Macdonald¹⁰, giving the cyclized alcohol (3) in 64% yield. As shown in TABLE I other Lewis acids can be used with the first entry giving the highest yields. Preliminary results indicate that there is some simple diastereoselectivity in the first bond forming reaction¹¹ and that as expected the second reaction results in formation of a *cis* fused product only¹², in yields which for a two-bond forming process are fairly good.

Other O-silylated enolates react as shown in the SCHEME so allowing the ready formation of the bicyclooctanol (4) and the perhydroazulene (5), each of which constitute the carbon skeleton of a large number of natural products.

Besides the obvious ease of building additional functionality into reagents such as (1) so as to facilitate natural product synthesis, this new strategy is notable since it can be readily extended to the synthesis of larger rings and to reactions with other enol derivatives such as O-silylated dienolates, all of which will be reported in the near future.

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TABLE I

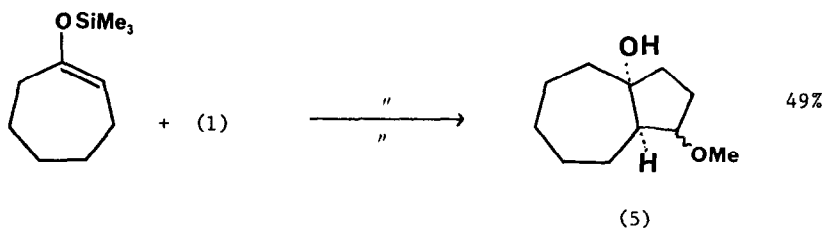
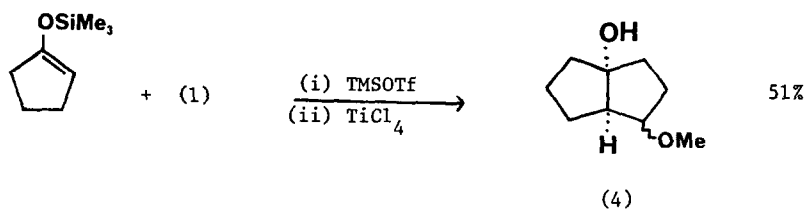


Entry	Lewis Acid [*]	Yield (%) [@]
1.	(i) TMSOTf (ii) TiCl ₄	64
2.	AlCl ₃	55
3.	(i) BF ₃ (ii) TiCl ₄	27
4.	TiCl ₄	50
5.	TiCl ₄ :Ti(OPr ⁱ) ₄ (3:1)	41

* SnCl₄ gave no products corresponding to (2) or (3).

@ Yields are for pure isolated material.

SCHEME



REFERENCES AND NOTES

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2. See, for example:- *Natural Products Chemistry*, Vol.I, K. Nakanishi et al. (Eds.) Academic Press (1974).
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4. B.M. Trost and D.M.T. Chan, *J.Amer.Chem.Soc.*, 1982, 104, 6879 and references therein.
5. S. Danishefsky and S.J. Etheredge, *J.Amer.Chem.Soc.*, 1982, 104, 4791.
6. B.M. Trost, *Chem. Soc. Reviews*, 1982, 141.
7. All new products gave satisfactory analytical and/or spectroscopic data.
8. A.R. Battersby, D.G. Buckley, J. Staunton and P.J. Williams, *J. Chem. Soc. Perkin Trans. I*, 1979, 2550.
9. S. Murata, M. Suzuki and R. Noyori, *J.Amer.Chem.Soc.*, 1980, 102, 3248.
10. T.L. Macdonald and S. Mahalingham, *J.Amer.Chem.Soc.*, 1980, 102, 2113.
11. This result is not unexpected, see for instance T. Mukaiyama and M. Hayashi, *Chem.Letters*, 1974, 15 and reference 9. Our preliminary results confirm that the degree of selectivity observed is dependent upon the Lewis acid employed.
12. The assignment of this stereochemistry arises from analogy to ref. 10 and from high field nmr analysis of the products including n.o.e. difference studies. These will be reported in a full account of this work.

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