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Regiocontrol in the Intramolecular Silyl Modified Sakurai (ISMS) Reaction. An Efficient Synthesis of a *Dacus oleae* Fruit Fly Pheromone.

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Abstract : *The ISMS reaction, which initially afforded a mixture of regioisomeric olefins, can now be controlled to produce only the exocyclic alkene. The ISMS methodology was used in a highly efficient synthesis of a Dacus oleae pheromone* **8**.

Tetrahydropyrans and spiroketals are key-subunits present in a variety of biologically active natural products such as the polyether antibiotics, the antiparasitic agents of the milbemycin and avermectin family and numerous pheromones.[1] Any synthetic approach towards these molecules requires the efficient preparation of tetrahydropyrans and spiroketals. In this letter, we report some of our results on the development of a new methodology : the **Intramolecular Silyl-Modified Sakurai** (ISMS) reaction, which allows the rapid and high yielding construction of these important-subunits. The power of the ISMS annelation is further demonstrated by the short and convergent synthesis of a *Dacus oleae* Fruit Fly pheromone 8.[2]

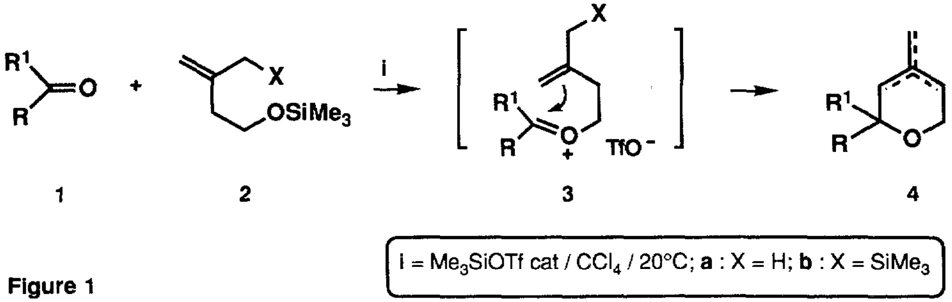
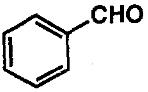
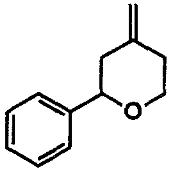
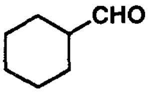
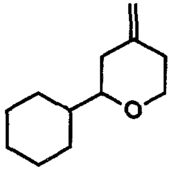
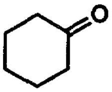
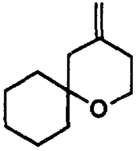
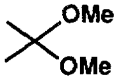
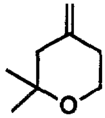
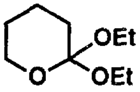
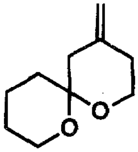


Figure 1

During some recent studies on neutral, radical-mediated oxidations,[3] we discovered that aldehydes and ketones could be converted into homoallylic ethers in a single step.[4] By using the annellating reagents **2a** and **2b**, tetrahydropyrans and spiroethers could also be prepared efficiently.[5] Unfortunately, in our original procedure, a mixture of regioisomeric alkenes **4** were formed with little control of the C-C double bond position. We reasoned that the formation of these isomers might be triggered by traces of triflic acid present in trimethylsilyl triflate or generated by its hydrolysis under the reaction conditions and investigated the effect of various basic additives. This study resulted in only marginal success.[6]

Table 1. Modified ISMS Annellations of Carbonyl Derivatives with **2b**

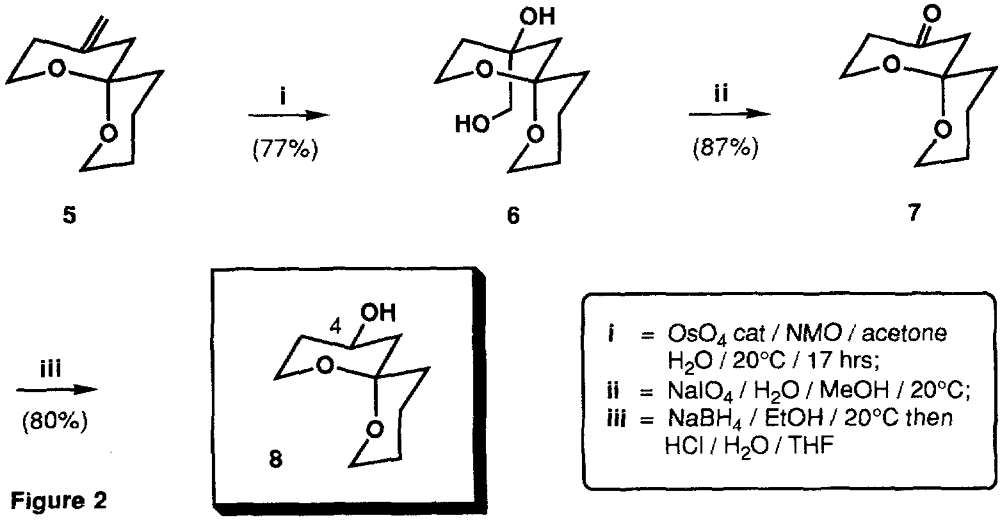
Entry	Substrate	Product	Yield[a]
1[b]			85%
2[b]			78%
3[c]			84%
4[d]			88%
5[d]			83%

(a) All yields refer to pure, chromatographically homogeneous, material; **(b)** EtOSiMe$_3$ (200 mol %) was added to the reaction mixture; **(c)** C_6H_{13}OTMS (10 ~ 15 mol %) was added to the reaction mixture; **(d)** No trimethylsilyl ether other than **2b** was added.

Remarkably, the addition of a simple trimethylsilyl ether, such as $C_6H_{13}OSiMe_3$ or $C_2H_5OSiMe_3$ to the reaction mixture - containing the carbonyl compound and the annellating reagent **2b** - dramatically modified the product ratio, leading to the almost exclusive formation of the *exo*cyclic isomer. Some example of this modified ISMS condensation are shown in Table 1.

As can be seen from Entries 1-3, both aldehydes and ketones afford smoothly the desired *exo*-methylene oxocene in high yield. The reaction conditions are substrate dependent. In the case of aldehydes (entries 1 and 2), 200 mol % of $C_2H_5OSiMe_3$ are required to stop the *exo-endo* isomerisation. However, with cyclohexanone (entry 3), only 10-15 mol % of $C_6H_{13}OSiMe_3$ is necessary.[7,8]

Interestingly, ketals [9] (entry 4) prove to be excellent substrates for the ISMS reaction. In these cases, no external trimethylsilyl ether is required. Furthermore, annellation of the ortholactone [10] derived from δ-valerolactone produces the important [5,5]-spiroketal system (Entry 5), the basic skeleton of numerous pheromones.[1] The efficient transformation of this *exo*methylene spiroketal subunit **5** into a *Dacus oleae* pheromone **8** is summarised in Figure 2.



i = OsO_4 cat / NMO / acetone H_2O / 20°C / 17 hrs;
ii = $NaIO_4$ / H_2O / MeOH / 20°C;
iii = $NaBH_4$ / EtOH / 20°C then HCl / H_2O / THF

Figure 2

Catalytic osmylation [11] proceeded, as expected, from the least hindered face of bicycle **5**, affording predominantly the isomer **6**. Cleavage of the vicinal diol **6** was accomplished quantitatively, using sodium periodate, and the resulting ketone **7** was reduced with sodium borohydride leading to a 1:1.2 mixture (at C_4) of the axial and equatorial alcohols **8**. Acid-catalysed equilibration finally produced the desired pheromone **8** (eq/axial ratio ~ 19:1) in 54% overall yield from **5**.

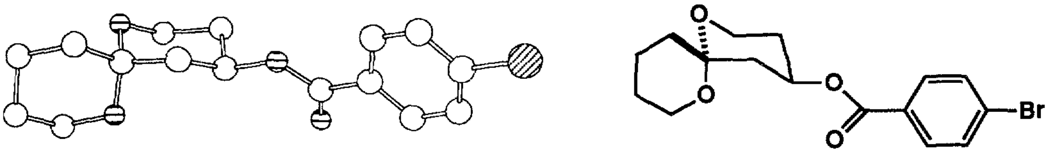


Figure 3

The structure of this pheromone was unambiguously established by X-ray crystallographic analysis of the derived *p*-bromobenzoate (Fig 3).[12,13] In conclusion, we have shown that the ISMS annellation is a powerful methodology for the preparation of tetrahydropyrans and spiroketals.[14] The synthetic utility of this condensation has been exemplified by the rapid and high-yielding synthesis of the Olive Fruit Fly pheromone **8**. Further work from this laboratory on synthetic applications of this novel methodology is currently underway and will be reported in due course.

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References and Notes

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6. Among other bases, pyridine, triethylamine and collidine were used, with the latter one showing the highest *exo-endo* ratio (8:1). However, these reactions are capricious. The purification of the final product is also far from trivial and proved to be deleterious for the *exo-endo* product ratio.
7. $EtOSiMe_3$ can also be used instead of $C_6H_{13}OSiMe_3$ with equally good results.
8. The role of the extra trimethylsilyl ether is not clearly understood at this early stage. However, it is tempting to speculate that the trimethylsilyl ether will react readily with any traces of triflic acid, generating the alcohol and the catalyst (TMSOTf). Furthermore, rapid and reversible formation of the corresponding acetal/ketal might also have a beneficial effect on the reaction rate and the *exo-endo* selectivity. This effect is further illustrated by the absence of *endo* isomer in the ISMS annellation of acetals, ketals and ortholactones.
9. Acetals are also excellent substrates for the ISMS reaction.
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12. We are grateful to Mr H. Adams for performing this X-ray analysis.
13. Prepared from **8** in 77% yield (pBrC$_6$H$_4$COBr/Et$_3$N/4-DMAP/CH$_2$Cl$_2$/20°C/17hrs).
14. For other approaches to tetrahydropyrans using allylsilanes, see: **a**. Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.*, **1988**, *53*, 911 **b**. Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.*, **1987**, *28*, 3441. **c**. Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.*, **1984**, *49*, 2808.

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