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Multicomponent cyclisations. Efficient methodologies for the preparation of complex natural products*

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* Dedicated to the vivid memory of J.-F. Cordier

Abstract. The Silyl-Modified Sakurai (SMS) reaction and its intramolecular variant, the ISMS cyclisation, are powerful methodologies that can provide easy access to a range of important subunits present in a variety of complex biologically active natural products.

Cascade and multicomponent condensation reactions are enjoying widespread success.[3] A few years ago, we reported an efficient preparation of homoallylic ethers from carbonyl compounds that we baptised the Silyl-Modified Sakurai (SMS) reaction.[4] This three component condensation involves the combination of a ketone or an aldehyde with a silyl ether and an allylsilane and is catalysed by trimethylsilyl triflate.

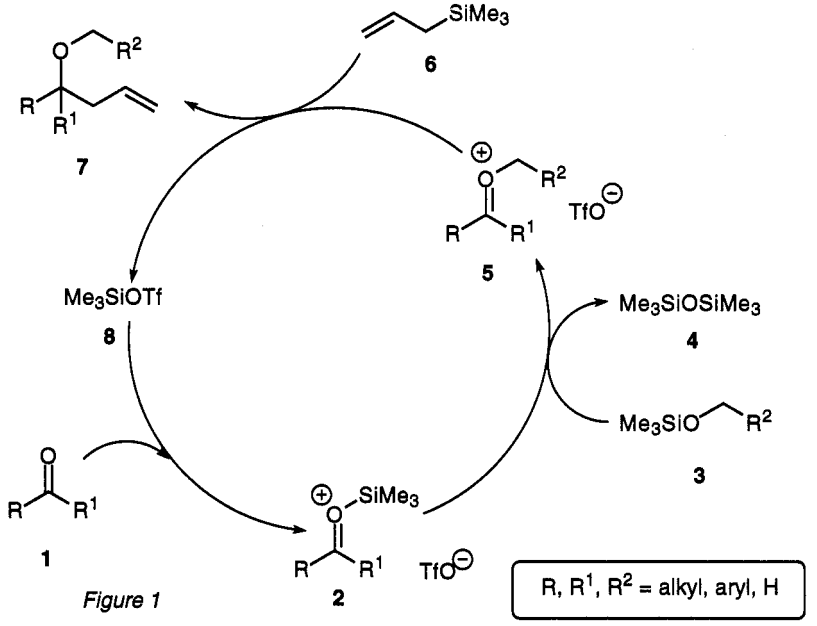


Figure 1

It is believed that this reaction proceeds by the initial addition of the silyl ether **3** to the activated carbonyl derivative **2** leading to the formation of oxonium ion **5** with concomitant loss of hexamethyldisiloxane **4**. Subsequent attack of the allylsilane **6** produces adducts **7** in excellent yield and regenerates the catalyst **8** (Figure 1).

The intramolecular version of the SMS reaction - the ISMS condensation - provides an easy entry into tetrahydropyran-type structures.[5] Thus addition of a catalytic amount of trimethylsilyl triflate to an equimolar amount of an aldehyde or a ketone **1** and annelating agent **10** - readily prepared in large scale by deprotonation and silylation of commercially available alcohol **9**[6] - smoothly affords *exo*-methylene tetrahydropyrans **12** via the intermediacy of oxonium cation **11** (Figure 2).

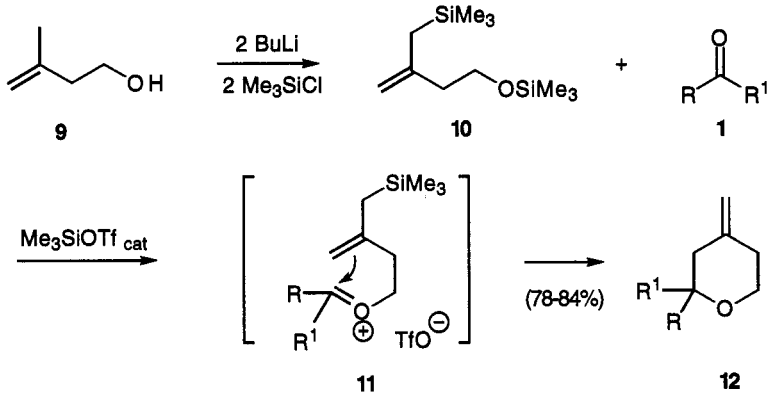


Figure 2

R, R^1 = alkyl, aryl, H

Acetals or ketals also undergo the ISMS condensation, generating adducts **12** in excellent yield.[7] More interestingly, orthoesters and ortholactones smoothly react with annelating agent **10** to produce cyclic acetals and spiroketals, two prolific subunits found in a range of natural products (Figure 3).[8,9]

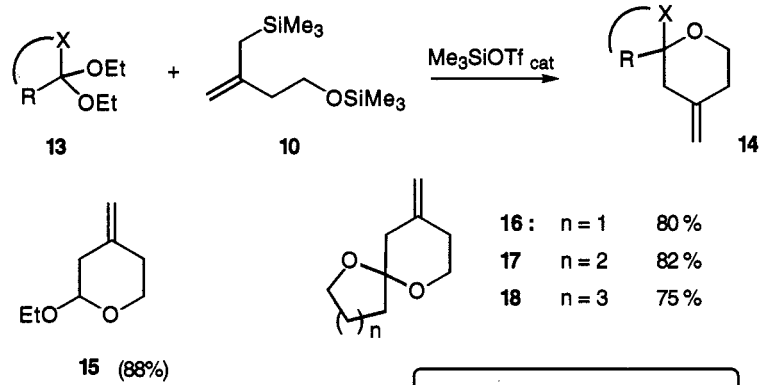


Figure 3

R = alkyl, H ; X = OEt, OR

The synthetic utility of the ISMS reaction is illustrated by the efficient (two-pot) preparation of spiroketal **20**, one of the major components of the *Dacus Oleae* sex pheromone mixture. Although several elegant synthesis of **20** have been reported earlier, the ISMS approach is by far the shortest and the most flexible (Figure 4).[10]

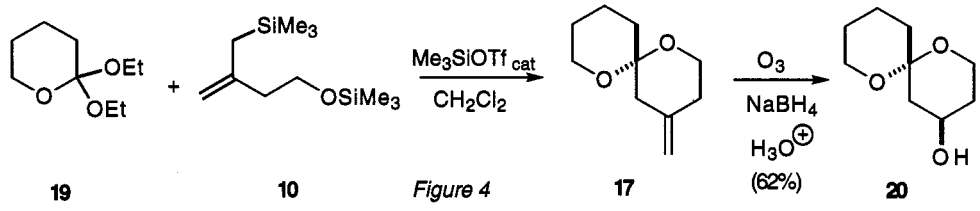


Figure 4

Condensation between ortholactone **19** and annelating agent **10**, catalysed by trimethylsilyl triflate, smoothly affords *exo*-methylene spiroketal **17** in up to 82% yield. Ozonolysis of the carbon-carbon double bond followed by $NaBH_4$ reduction of the ozonide and aqueous HCl work up gives the pheromone **20** as a 19:1 mixture of equatorial and axial epimers in 62% overall yield. Several other pheromones were also prepared by this simple approach.[8] It is interesting to note that the ISMS condensation of ortholactones provides a general and flexible route to spiroketals of varied sizes.

Having established an easy and efficient access to various spiroketal systems, and subsequently demonstrating the usefulness of the ISMS condensation by the concise synthesis of simple pheromones, we next turned our attention to a more challenging target *viz.* Milbemycin β3 (Mβ3) **21**.

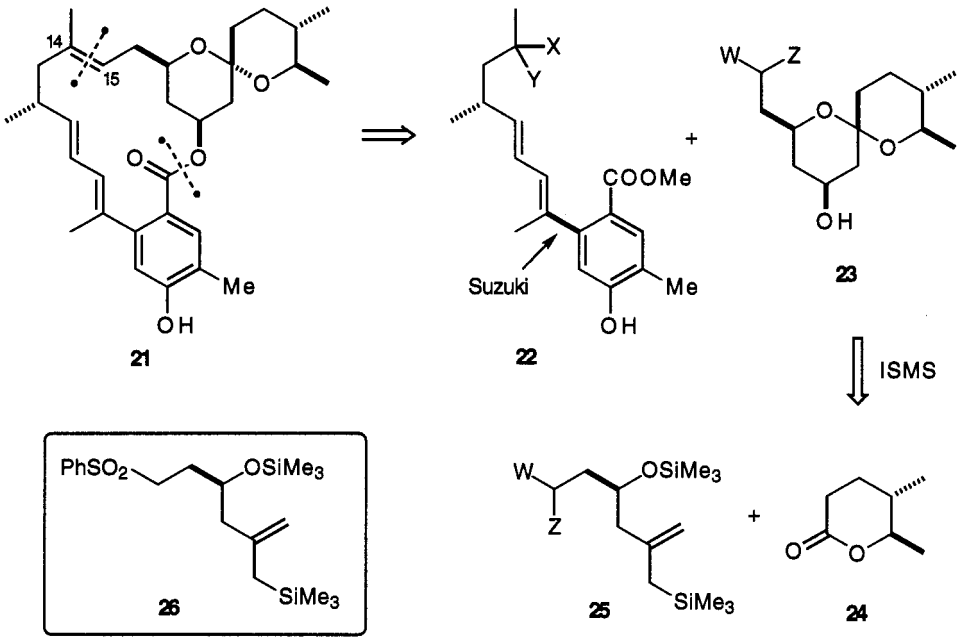


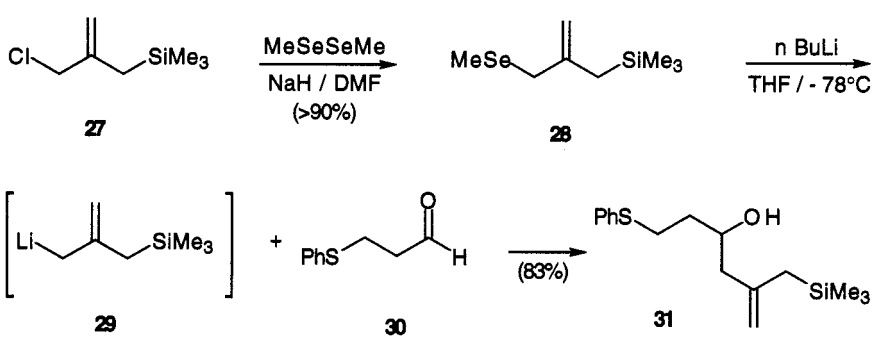
Figure 5

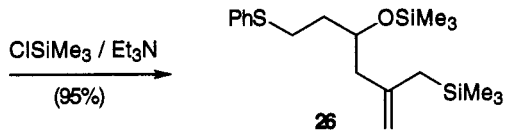
a: **X, Y** = O ;**W, Z** = H, SO_2Ph ; **b**: **X,Y** = H, SO_2Ph; **W, Z** = O.

Disconnection of the C_{14}-C_{15} double bond and cleavage of the lactone function of **21** generates two fragments: the aromatic substituted diene **22** and the spiroketal subunit **23** (Figure 5). At this stage, we envisioned that generation of the C_{14}-C_{15} double bond could result either from a Julia-Lythgoe coupling between substituted sulphone **22a** (X = H, Y = SO_2Ph) and aldehyde **23a** (Z = W = O) or via the complementary process that is the coupling between ketone **22b** (X = Y = O) and monosubstituted sulfone **23b** (Z = H, W = SO_2Ph).[11] Of these two possibilities, the latter seduced us most, especially as the spiroketal **23** could be constructed from the known lactone **24**[12] and the allylsilane **25.** The left-hand fragment **22** was to be obtained by a Suzuki coupling[13] between a vinylborane and a suitably functionalised aromatic portion.

Initial attempts at coupling commercially available chloride **27** with aldehyde **30**[14], using a variety of organometallic derivatives (Cr, Zn, Mg) failed. The beautiful method of Krief finally provided the solution.[15] Thus, transformation of chloride **27** into selenide **28** proceeded in essentially quantitative yields. Transmetallation from selenium to lithium, using *n*BuLi in THF at -78°C occurred instantaneously and produced the golden-orange allyllithium reagent **29** which was trapped with aldehyde **30**, affording in excellent overall yield the coupling product **31**. Silylation completed the synthesis of the required annelating agent **26**.[16]

Having obtained efficiently the desired allylsilane **26**, we turned our attention to the crucial ISMS cyclisation and decided initially to use the unsubstituted ortholactone **19** as a model for lactone **24**.

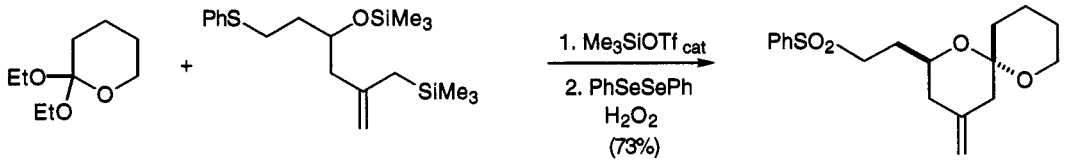




26

Figure 6

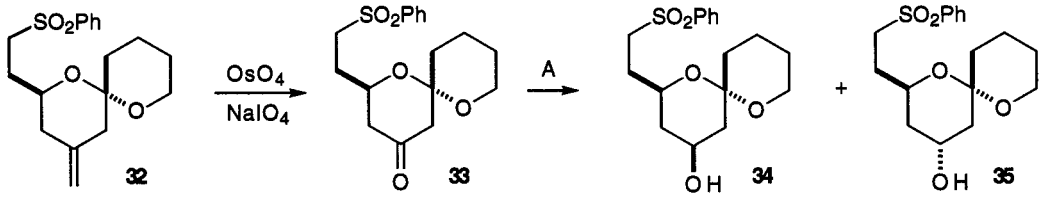
When stoichiometric amounts of ortholactone **19** and allylsilane **26** are treated with a catalytic amount of trimethylsilyl triflate, in CH_2Cl_2, smooth ISMS cyclisation ensues, providing the desired spiroketal **32** in essentially quantitative yield.[16] This adduct is then directly transformed into sulfone **32** using the Reich-Ley protocol, in 73% overall yield (Figure 7).[17]



19 26

Figure 7 32

The completion of the synthesis of the right-hand spiroketal subunit involves the oxidative cleavage of the *exo*-methylene double bond and the selective reduction of the ketone thus generated into the equatorial alcohol **34**. The formation of the ketone proceeded readily using Lemieux-Johnson-type conditions[18] (Figure 8).



32 33 34 35

Figure 8

A	34	35	Yield
L-Selec	< 5	>95	83%
SmI_2	75	25	89%
$SmIOBu^t$	90	10	85%

However, reduction using L-selectride® afforded almost exclusively the undesired α-epimer **35**, while SmI_2 in isopropanol, as reported by Evans,[19] provided only a modest 3:1 ratio of **34** and **35**. Fortunately, the excellent protocol of Kagan,[20] employing cat. $SmIOBu^t$ in the presence of isopropanol as the reducing agent, allowed us to obtain a much improved 9:1 ratio of the alcohols **34**:**35**. It is worth noting that the separation of **34** and **35** is trivial and the recycling of the axial alcohol into the desired equatorial isomer possible.

With large quantities of spiroketal **34** in hand, we then tackled the synthesis of fragment **22a** (X, Y = O).[21,22] Partial reduction of the lactone function of 4,6-dimethylvalerolactone **36** into the corresponding lactol followed by subsequent addition of 1-propynylmagnesium bromide afforded diol **37** in 85% overall yield. Selective protection of the propargylic alcohol function was achieved by reacting diol **37** with *t*-butyldiphenylsilyl chloride, in the presence of 4-DMAP (5 mol%). Further silylation of the secondary alcohol with TBSCl afforded the *bis*-silylated derivative **38** in 60% overall yield from lactone **36**. Hydroboration (catecholborane, neat, 70°C) resulted in essentially quantitative formation of the *E*-vinylborane **39**. However, the crucial Suzuki coupling employing classical conditions, which was next attempted, totally failed to afford the desired coupling product.

Whereas Kishi showed that resilient couplings of this type could be brought to fruition using TlOH,[21] Suzuki utilised the corresponding Tl_2CO_3 to promote some alkyl-aryl/alkyl-vinyl coupling reactions.[23] Since the presence of an ester function in the aromatic fragment **40** precluded the use of TlOH, we decided to initially study the effect of TlOEt. Disappointingly, mediocre yields of product **41** (12% yield) were obtained.

However, in the presence of Tl_2CO_3, a smooth reaction took place giving, after simple filtration of the insoluble greenish-yellow TlI, the desired styrene derivative in reproducible high yields. Jones oxidation in the presence of KF[24] chemoselectively produced the methyl ketone **41** in 70% overall yield from vinylborane **39** (Figure 9).

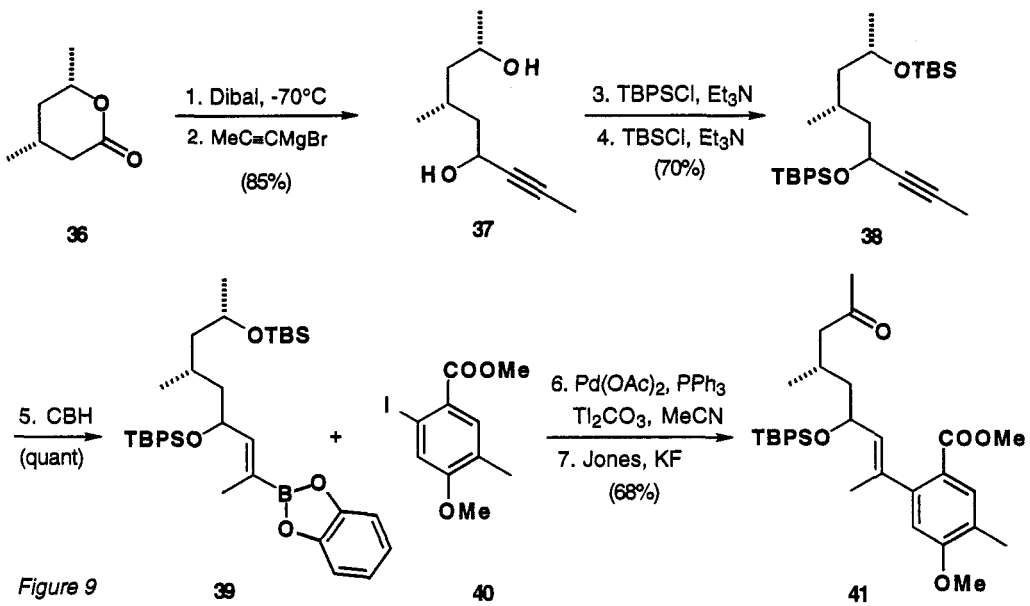


Figure 9

With both fragments **41** and **34** available, efforts are now focusing on their coupling and on the completion of the total synthesis.

In summary, we have demonstrated that the SMS and the ISMS condensations are powerful methodologies that can provide easy access to a range of important fragments present in a variety of biologically active natural products.

Acknowledgements

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References and notes

† Deceased on July 17th, 1996.
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