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.

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 96 - smoothly affords exo-methylene tetrahydropyrans 12 via the intermediacy of oxonium cation 11 (Figure 2).
Acetals or ketals also undergo the ISMS condensation, generating adducts 12 in excellent yield. More interestingly, orthoesters and ortholactones smoothly react with annelating agent 10 to produce cyclic acetal and spiroketals, two prolific subunits found in a range of natural products (Figure 3).8,9

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

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 NaBH4 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.

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Disconnection of the C14-C15 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 C14-C15 double bond could result either from a Julia-Lythgoe coupling between substituted sulphone 22a (X = H, Y = SO2Ph) 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 = SO2Ph). Of these two possibilities, the latter seduced us most, especially as the spiroketal 23 could be constructed from the known lactone 2412 and the allylsilane 25. The left-hand fragment 22 was to be obtained by a Suzuki coupling13 between a vinylborane and a suitably functionalised aromatic portion.

Initial attempts at coupling commercially available chloride 27 with aldehyde 3014, 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 nBuLi 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.

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When stoichiometric amounts of ortholactone 19 and allylsilane 26 are treated with a catalytic amount of trimethylsilyl triflate, in CH₂Cl₂, smooth ISMS cyclisation ensues, providing the desired spiroketal 32 in essentially quantitative yield. This adduct is then directly transformed into sulfone 32 using the Reich-Ley protocol, in 73% overall yield (Figure 7).

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 (Figure 8).

However, reduction using L-selectride® afforded almost exclusively the undesired α-epimer 35, while Sml₂ in isopropanol, as reported by Evans, provided only a modest 3:1 ratio of 34 and 35. Fortunately, the excellent protocol of Kagan, employing cat. SmlOBu² 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). 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 i-butylidiphenylsilyl 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.
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Whereas Kishi showed that resilient couplings of this type could be brought to fruition using TIOH, Suzuki utilised the corresponding Tl2CO3 to promote some alkyl-aryl/alkyl-vinyl coupling reactions. Since the presence of an ester function in the aromatic fragment precluded the use of TIOH, we decided to initially study the effect of TlOEt. Disappointingly, mediocre yields of product 41 (12% yield) were obtained.

However, in the presence of Tl2CO3, 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 chemoselectively produced the methyl ketone 41 in 70% overall yield from vinylborane 39 (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.

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References and notes

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