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New approaches toward the synthesis of (D-homo) steroid skeletons using Mukaiyama reactions

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Abstract—New, short, and flexible procedures have been developed for syntheses of steroid and D-homo steroid skeletons. A Mukaiyama reaction between the silyl enol ether of 6-methoxytetralone and 2-methyl-2-cyclopentenone or carvone, with transfer of the silyl group to the receiving enone, gave a second silyl enol ether. Addition of a carbocation, generated under Lewis acid conditions from 3-methoxy-2-butenol, 3-ethoxy-3-phenyl-2-propenol or 3-methoxy-2-propenol to this second silyl enol ether gave adducts, which could not be cyclized by aldol condensation to (D-homo) steroid skeletons. The Mukaiyama–Michael reaction of the silyl enol ether of 6-methoxy tetralone with 2-methyl-2-cylopentenone gave a second silyl enol ether, which reacted in high yield with a carbocation generated from 3-hydroxy-3-(4-methoxyphenyl)propene. Ozonolysis of the double bond in this adduct gave a tricarbonyl compound (Zieglers triketone), which has been used before in the synthesis of 9,11-dehydroestrone methyl ether. A second synthesis of C17 substituted CD-trans coupled (D-homo) steroid skeletons has been developed via addition of a carbocation, generated with $ZnBr_2$ from a Torgov reagent, to a silyl enol ether containing ring D precursor. The obtained seco steroids have been cyclized under formation of the 8–14 bond by treatment with acid. The double bonds in one of the cyclized products have been reduced to a C17-substituted all trans steroid skeleton.

1. Introduction

The application of sequential Michael additions or Mukaiyama reactions in domino reactions is well known.[1–14] In some Mukaiyama–Michael additions transfer of the silyl group from the starting silyl enol ether to the receiving enone is a convenient variant, because this newly formed silyl enol ether can undergo a second Mukaiyama–Michael addition, potentially with a different enone.[1–10] With methyl vinyl ketone (MVK) as the second enone an intermediate is obtained, which can undergo a ring closing 1,6-aldol cyclisation and in this way polycyclic compounds can be obtained in short one pot domino sequences.[1,15]

With a silyl enol ether derived from 6-methoxytetralone as the starting compound, high yielding additions to carvone and 2-methyl cyclopetenone have been achieved with transfer of the silyl group to new silyl enol ethers.[16] However, it appeared not to be possible to add methyl vinyl ketone via a Mukaiyama–Michael addition to these second silyl enol ethers.[15]

On the other hand alkylations of silyl enol ethers derived from 2-methyl-2-cyclopentanones with carbocation precursors are known in literature[17,18] and offer good prospect for steroid synthesis. Recently, we have published a short synthesis of (D-homo) steroid skeletons with cis fused CD ring systems using such an approach.[16] The key step in this synthesis is an intramolecular reaction of a carbocation precursor derived from a Torgov type reagent with a silyl enol ether in ring D, thus closing ring C by formation of the C12–C13 bond as the last step (see Scheme 1, **1**→**2**→**3**→**4**→**5**).

Short syntheses for trans CD fused (D-homo) steroids, also relying on the addition of easily generated carbocations to silyl enol ethers as key transformation, seemed feasible as well. Two such approaches, in which the sequence of bond formation in the nascent ring C has been varied, have been investigated. The first route should start again from adduct **3**, but now first the trans-fusion of the CD ring system should be secured via the introduction of an appropriately

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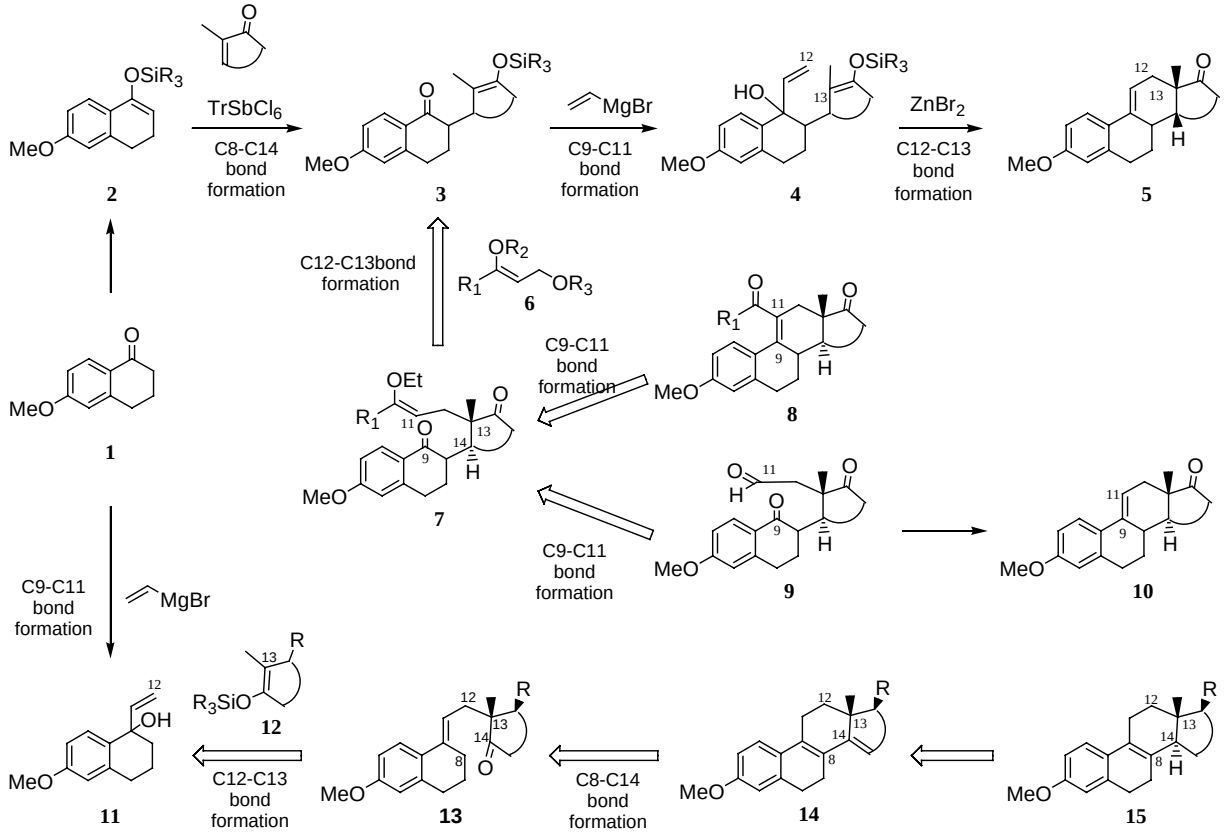

Scheme 1.

functionalised substituent at C13. For this purpose a congener of 3-methoxy-2-butenol[19–21] seemed most appropriate, as from this reagent a carbocation can be generated under mild Lewis acid conditions, compatible with the presence of a silyl enol ether in ring D. The enol ether in the introduced moiety in adduct **7** is located in the correct position for the closure of ring C by an aldol type cyclisation to steroid skeleton **8**, which should have a functional group at C11 as an additional advantage. Ozonolysis of the double bond in adduct **8** can be carried out as an alternative leading to Ziegler's triketone **9**, an intermediate, which has been cyclized before to steroid **10** using a McMurry reaction.[22–25] In these approaches the construction of the C9–C11 bond should be the last step in the closure of ring C (see Scheme 1, **1**→**2**→**3**→**7**→**8** or **1**→**2**→**3**→**7**→**9**→**10**).

A second approach to CD-trans-fused (D-homo) steroid skeletons might be possible in which the C12–C13 bond should be formed in the second step. An intermolecular Lewis acid catalysed reaction of the Torgov reagent **11** with a silyl enol ether containing ring D precursor **12** should lead to secosteroid **13** and an acid catalyzed cyclisation then should close ring C, now with formation of the C8–C14 bond as the last step. This method should give a quick access to a wide variety of C17-substituted steroid skeletons with a similar set of double bonds in the C and D rings as in the products from the normal Torgov reaction. Selective catalytic reduction then should yield the CD-trans-fused (D-homo) steroid skeletons (Scheme 1, **1**→**11**→**13**→**14**→**15**).[26]

2. Results and discussion

When silyl enol ether **16**, obtained from the reaction of the TMS ether of 6-methoxytetralone with 2-methyl -2-cyclopentenone as a 2:1 mixture of stereoisomers in 90% yield,[16] was brought in reaction with MVK, only desilylation of the starting material took place. However, it was found that the more reactive allylic alcohol **17**[27] did react with silyl enol ether **16** in a reasonable 52% yield, using 0.05–0.7 M concentrations of $LiClO_4$ in nitromethane[28–30,31] (Scheme 2). This result indicates that steric hindrance in the MVK addition with **16** is probably not the reason for the failure of this reaction, but that the lower reactivity of the carbonyl group in the tetralone part of the molecule for the aldol reaction fails to shift the equilibria toward cyclisation.[15] This was confirmed by the failure of other attempts to construct the C9–C11 bond via aldol type reactions (see Schemes 2 and 3).

Prolonged reaction times in a more concentrated $LiClO_4$ solution (4 M) did consume the addition product **18** but no cyclisation was observed and the isolated product was compound **19** in 28% yield, next to compound **20** in 33% yield; in the latter hydrolysis of the enol ether function has taken place. A selective reduction of the ring D carbonyl group of the main isomer of **18** led to one isomer of compound **21**, which was assumed to have the indicated structure. Application of mild Lewis acid cyclisation conditions rapidly led to acetal formation with the hydroxyl group of ring D, giving acetal **22** in 56% yield. Cyclisation of the main isomer of **18** under Lewis acid conditions did