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A new flexible synthesis of (D-homo) steroids

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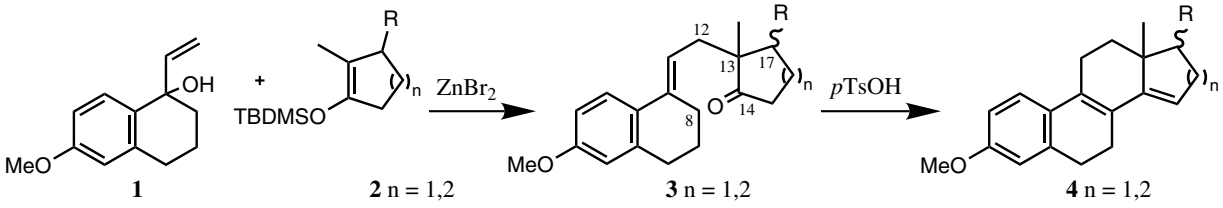
Abstract—A short, flexible and efficient procedure has been developed for the synthesis of C17 substituted steroid skeletons and D-homo steroid skeletons using a $ZnBr_2$ catalysed coupling of a silyl enol ether containing ring D precursor with a Torgov type reagent, followed by acid catalysed cyclisation of the adducts to (D-homo) steroid skeletons.

The construction of ring C as the final step in total syntheses of skeletons of steroids is well known because of the good results using the Torgov reaction.[1–12] Recently we published a short approach to the synthesis of (D-homo) steroids, where the closure of ring C relies on the construction of the C12–C13 bond via a Lewis acid catalysed *intramolecular* reaction of a Torgov type intermediate with a silyl enol ether in ring D.[13] Ring C closure in this way leads to a *cis* fused CD-ring system in the (D-homo) steroid.

It seemed feasible to develop a short synthesis for *trans* CD fused (D-homo) steroids using similar chemistry. An *intermolecular* Lewis acid catalysed reaction of a Torgov type reagent **1** with a silyl enol ether containing ring D precursor **2** should give quick access to C8–C14 seco steroid skeletons **3**.[14] Acid catalysed closure of ring C should lead to (D-homo) steroid skeletons **4** with a similar set of double bonds in the C and D rings as in the products from the normal Torgov reaction (Scheme 1). Selective (catalytic) reduction of the double bonds should then complete the synthesis of the *trans* CD fused (D-homo) steroids. Examples of the Lewis acid catalysed alkylations of silyl enol ethers with suitable carbocation precursors are known and showed good precedent for such an approach.[15–17]

The silyl enol ether containing ring D precursors **2** were obtained by conjugate addition followed by capture of the enolate with a silylating agent, via Mukaiyama Michael reactions on enones with transfer of the silyl group from the starting silyl enol ether to the enol of the adduct, or by direct silylation of ketones. Our experience with the synthesis of CD *cis* fused (D-homo) steroid skeletons had shown that *tert*-butyldimethylsilyl (TBDMS) enol ethers are often the best compromise between stability and reactivity in Lewis acid catalysed reactions, but sometimes the more reactive trimethylsilyl



1 **2** n = 1,2 **3** n = 1,2 **4** n = 1,2

Scheme 1.

Keywords: Torgov type reactions; Silyl enol ethers; Steroid synthesis.
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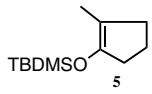
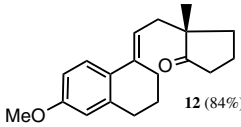
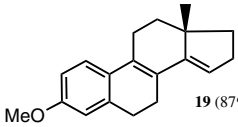
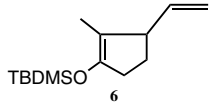
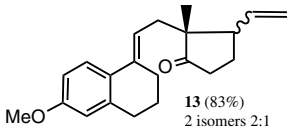
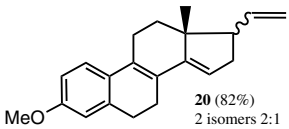
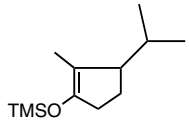
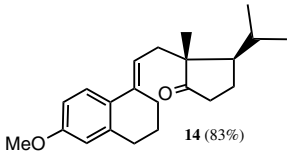
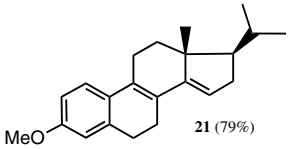
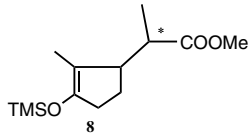
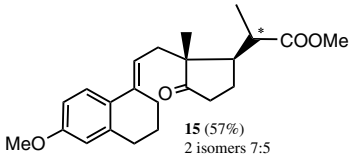
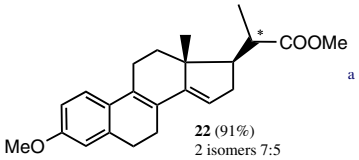
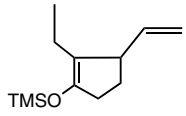
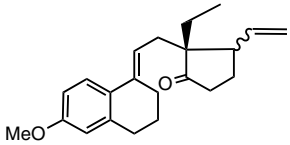
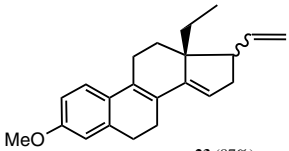
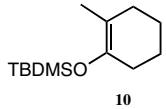
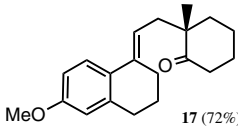
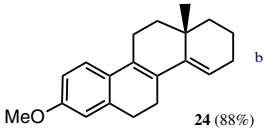
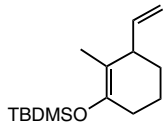
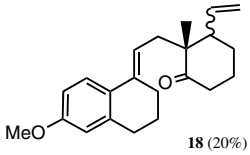
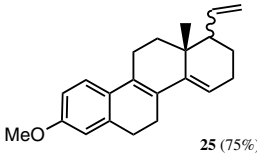
Table 1.

Silyl enol ethers	Coupling product (% yield)	Cyclisation product (% yield)
 **5**	 **12** (84%)	 **19** (87%)
 **6**	 **13** (83%) 2 isomers 2:1	 **20** (82%) 2 isomers 2:1
 **7**	 **14** (83%)	 **21** (79%)
 **8** 2 isomers 7:5	 **15** (57%) 2 isomers 7:5	 **22** (91%) 2 isomers 7:5 [a]
 **9**	 **16** (64%) 2 isomers 2:1	 **23** (87%) 2 isomers 2:1
 **10**	 **17** (72%)	 **24** (88%) [b]
 **11**	 **18** (20%) 2 isomers 2:1	 **25** (75%) 2 isomers 2:1

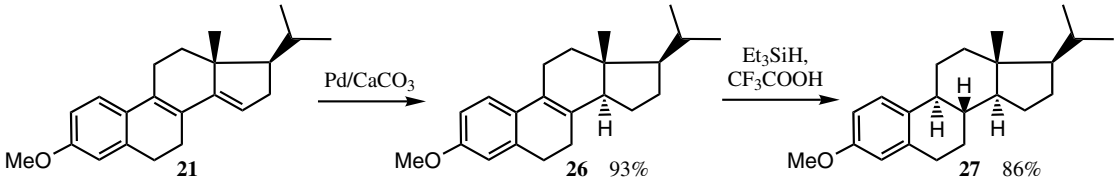
[a] For both isomers of **22** the depicted stereochemistry was confirmed using NOE experiments.
[b] Using P_2O_5 as a catalyst.

(TMS) enol ethers had to be used. $ZnBr_2$ was chosen as the Lewis acid catalyst[16] and all coupling reactions were performed at −10 °C, in CH_2Cl_2 as solvent.

Under these conditions reactions of the Torgov reagent **1** with silyl enol ethers of the substituted cyclopentanones **5**–**9** giving seco steroids **12**–**16** proceeded in good to excellent yields, as can be seen in Table 1. Steric hindrance did not hamper the yields and, indeed, improved the stereoselectivity from good to excellent as can be seen for compounds **13** and **14**. Even when the silyl enol ether had an ethyl group at C2, as in **9**, a good yield of its coupling product with the Torgov reagent could be achieved, leading to the seco steroid **16** with an angular ethyl group. 2-Ethyl substituted cyclopentanone derivatives often show lower reactivity than their 2-methyl congeners.[18]

The ring closure reactions of the seco steroids to the unsaturated steroids **19**–**23** all gave good results using mildly acidic conditions (catalytic *p*TsOH in benzene, 40 °C).[19]

Similar reactions with TBDMS enol ethers derived from cyclohexanones, ultimately leading to D-homo steroids, gave more diverse results. The reaction of the 2-methylcyclohexanone derivative **10** with the Torgov reagent proceeded in good yield, but the more substituted silyl enol ether **11** gave only moderate results. Apparently for the six-membered rings, steric hindrance influences the yield to a larger extent than in the corresponding five-membered rings. TMS enol ethers derived from cyclohexanones were also tried in this addition reaction but afforded similar results to the TBDMS derivatives.



Scheme 2.

In the D-homo series, the ring closure reactions also gave good results and the unsaturated D-homo steroids **24** and **25** could be isolated in good yields. However, in the case of compound **17** the cyclisation had to be carried out in the presence of P_2O_5 since with *p*TsOH the reaction yielded a low, 19% yield of compound **24** together with a 27% yield of the $\Delta_{9,11}$-14-hydroxycompound in which dehydration had not taken place after the cyclisation step. Similar problems with the cyclisation step have been reported previously for compounds with a carbonyl at C17a[2] although good cyclisations of these compounds have also been reported using *p*TsOH.[20]

The double bonds in the C and D rings in the steroid and D-homo steroid skeletons can be reduced catalytically to give C,D-*trans* fused steroids following literature procedures.[9,21–24] This reduction was tested on compound **21** using $Pd/CaCO_3$ as the catalyst and gave the 13,14-*trans*-reduced compound **26** in a 93% yield (Scheme 2). Further reduction to the all-*trans* ring system has been extensively reported in literature. Usually reduction in liquid ammonia is used for the *trans*-reduction of the $\Delta^{8,9}$ double bond. The Birch reduction can be applied when reduction of ring A to an enone is also desired. A large variation in yields is reported under these conditions[8,9,21–29] and an ionic reduction using triethylsilane and trifluoroacetic acid[21] was more effective and reliable in our hands.[30]

In conclusion, a short, flexible and efficient procedure has been developed for the synthesis of steroid and D-homo steroid skeletons. A variety of substituted silyl enol ether containing ring D precursors can be prepared and then used for the preparation of C17 substituted steroid skeletons by Lewis acid catalysed coupling with a Torgov type reagent, followed by acid-catalysed closure of ring C.

Acknowledgements

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