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A Biomimetic Approach to C-*nor*-D-*homo*-Steroids

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Abstract: A biomimetic three-step transformation of classical "6-6-6-5"-steroids into their C-*nor*-D-*homo*-counterparts gives an easy and fast access to this highly important substructure of natural products, as it is found in cyclopamine, and nakiterpiosin. A novel reagent combination allows for the rearrangement even of 17-keto steroids with high endoselectivity. In several examples the broadness of this strategy is outlined.

C-*nor*-D-*homo*-Steroids or [14(13→12)]-*abeo*-steroids constitute a class of natural products that possess a steroid skeleton with an unusual 6-6-5-6 ring pattern. Although they are a rather small subgroup compared to all known steroids, many biologically highly active members recruit themselves from this class. Among them are the structurally diverse *Veratrum* steroidal alkaloids[1] with cyclopamine as the most renowned one. Cyclopamine is a highly selective antagonist of transmembrane protein Smoothened and therefore has emerged as a novel and potent candidate for treatment of cancers dependent on hedgehog signaling.[2] Also nakiterpiosin, a C-*nor*-D-*homo*-steroid of marine origin, proved to be a potent antimitotic addressing the hedgehog pathway.[3]

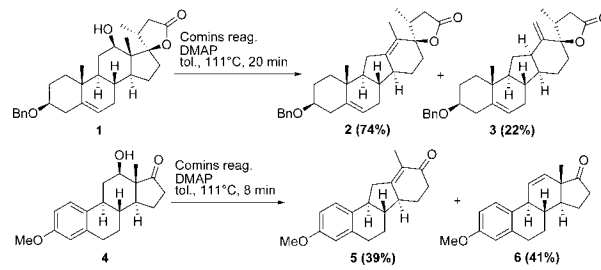
A general synthetic strategy for C-*nor*-D-*homo*-steroids is still elusive though several different strategies have been utilized including intramolecular Horner−Wadsworth−Emmons[4] and aldol condensations[5] using the (+)-Wieland−Miescher ketone as a starting material, the Nazarov cyclization,[3] and predominantly the degradation and rearrangement of abundantly available hecogenine.[6] Especially the last strategy attracted our attention since the same rationale that is also known from the biosynthesis[7] of these natural products is applied and therefore renders this approach biomimetic.

During our work on the synthesis of cyclopamine[8] we faced the problem of rearranging the 12β-hydroxy dehydroepiandrosterone derivative **1** to yield the desired C-*nor*-D-*homo*-system **2**. Although Hirschmann as early as 1952[6] and later Mitsuhashi[9] reported on similar rearrangements of hecogenine, the reaction conditions they applied were not successful in our case because transformation of the 12-hydroxy group into a mesylate and subsequent treatment with several bases at elevated temperature led to degradation and only traces of the desired product. Also the use of Bamford−Stevens conditions to the related 12-hydrazone derivative proved to be ineffective.

When we changed the leaving group for a triflate, the rearrangement occurred in one pot under rather mild conditions (triflic anhydride, pyridine, 50 °C) but to our dismay to yield the undesired isomer **3** with an exocyclic double bond as the main product and only small amounts of the desired endoisomer **2**.

We now examined other conditions to access predominantly the endocyclic product and report here an unprecedented procedure that involves treatment of 12-hydroxy steroids with the Comins reagent (*N*-(5-chloro-2-pyridyl) triflimide)[10] and DMAP in refluxing toluene. This method leads to a ratio of 7:2 of desired endocyclic double bond isomer **2** to byproduct **3** in almost quantitative yield and a reaction time of less than 30 min (Scheme 1).

Scheme 1



The Comins reagent has been used before only for the formation of vinyltriflates from enolizable ketones. The use of less reactive reagents for this rearrangement proved to be unsuccessful. McMurry's reagent (*N*-phenyl triflimide)[11] gave no reaction. Among several solvents screened for this procedure[12] toluene proved to be best suited; the amount of DMAP was also varied in a broad range showing that an excess was necessary.

With this powerful method in hand our attention was drawn to the class of 12-hydroxy-17-keto-steroids. These compounds have withstood all known procedures of rearrangement (Bamford−Stevens conditions as well as Wagner−Meerwein conditions using tosylates, mesylates, or phosphorus species[13] as a leaving group) since the ketone provides a strong deactivating influence on the *C*-14 migration terminus. Typically, these substrates give only elimination products like **6** or extensive degradation.[14] When we subjected hydroxy ketone **4** to our method we were pleased to isolate the desired C-*nor*-D-*homo*-steroid enone **5** together with elimination byproduct **6**.

Since the necessary starting materials have been shown to be easily accessible using Schönecker's C−H activation/hydroxylation sequence,[15] we started to acquire more examples of this type.

The 12β-hydroxy-dehydroepiandrosterone derivative **13** (see Table 1) gave a similar result as **4**, the corresponding *i*-steroid **14** (accessible in four steps from dehydroepiandrosterone) also provided the desired rearranged product. The combination of Schönecker's C−H activation/hydroxylation protocol and our reagent combination for rearrangement constitutes an efficient and biomimetic synthesis of the C-*nor*-D-*homo*-steroid skeleton—a building block for the synthesis of virtually any C-*nor*-D-*homo*-steroid that was only prepared in tedious sequences over several steps before.[16]

A byproduct that was isolated in small amounts in the rearrangement of **13** when using toluene but in higher yield when using xylenes under reflux conditions as a solvent was triflate **7**. On treatment of purified **7** in refluxing toluene with an excess of DMAP and Comins reagent, no rearrangement product **8** was obtained (Scheme 2). We therefore assume that **7** is not an intermediate in the formation of rearrangement products in this reaction. In another

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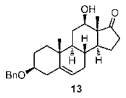
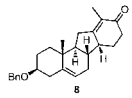
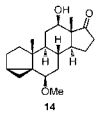
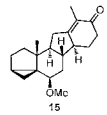
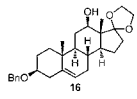
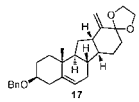
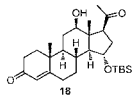
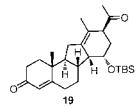
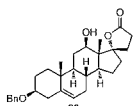
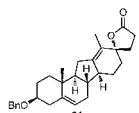
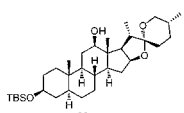
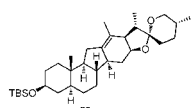
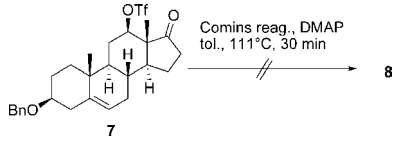
Table 1. Rearrangement of 12β-Hydroxy Steroids Using the Comins Reagent[a]

entry	substrate	t [min]	product[b]	yield [%][c]
1	 13	8	 8	32 (51)
2	 14	50	 15	33 (43)
3	 16	240	 17	43[d]
4	 18	20	 19	65:11[e]
5	 20	20	 21	47:40
6	 22	60	 23	63:32

[a] Reaction conditions: substrate (0.30 mmol), *N*-(5-chloro-2-pyridyl) triflimide (0.90 mmol), DMAP (1.80 mmol), toluene (10 mL), 111 °C. [b] Only the main isomer is shown. [c] The yields refer to isolated products in the order *endo*-product:*exo*-product. The values within parentheses are the yields of the elimination byproduct (Δ-11-12-steroids). [d] No *endo*-product was isolated. [e] Additionally, 9% of rearranged product with a Δ-13-17 double bond was isolated.

Scheme 2

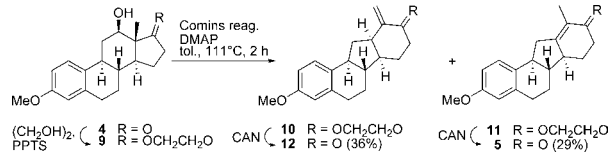


control experiment we subjected the substrates to the action of triflic acid in toluene under reflux conditions. In all cases but **4** and **13**, only excessive degradation was observed. **13** gave the elimination product **34** (see Supporting Information) while **4** remained unchanged. Thus, a mechanism based on acid induced cation formation does not seem to be responsible for the observed reaction outcome.

We also examined other substituents in position 17 and thereby explored the functional group tolerance of our method. Interestingly, by converting the 17-keto group into an acetal (like **9**) and treating these substrates under our conditions we could isolate both rearranged acetals **10** and **11** with a slight prevalence of the exocyclic double bond isomer **10**. On careful treatment with cerium ammonium nitrate in a pH 9 buffer solution,[17] we were able to isolate the corresponding enones **12** and **5**, respectively (Scheme 3).

Further examples included progesterone derivative **18**, DHEA-lactone **20** with inverted stereochemistry at *C*-17 with regard to lactone **1**, and hecogenine derivative **22** similar to the one used by

Scheme 3



Hirschmann in his initial studies.[6] These substrates proved to give the rearrangement in high yields and selectivity for the *endo*-products. All substrates shown in Table 1 could not be rearranged using the various conditions reported by Hirschmann[6] or Fu's PCl_5 system[13] with the exception of hecogenine derivative **22** which reacted readily under all conditions.

In conclusion, we developed a novel reagent combination for the rearrangement of 12β-hydroxy steroids. This method accesses otherwise difficult to obtain C-*nor*-D-*homo*-steroids and is characterized by giving predominantly the endocyclic double bond isomer and rendering for the first time available 17-keto steroids, a species completely unreactive to this type of rearrangement before. We therefore believe that the application of our method in total synthesis can both simplify and shorten routes to natural products bearing a C-*nor*-D-*homo*-steroid skeleton and help to enable convergent strategies. Future work will address mechanistic studies and biological testing of the obtained products.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Li, H.-J.; Jiang, Y.; Li, P. *Nat. Prod. Rep.* **2006**, *23*, 735–752.
(2) Heretsch, P.; Tzagkaroulaki, L.; Giannis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3418–3427, and citations therein.
(3) Gao, S.; Wang, Q.; Huang, L. J.-S.; Lum, L.; Chen, C. *J. Am. Chem. Soc.* **2010**, *132*, 371–383.
(4) Guile, S. D.; Saxton, J. E.; Thornton-Pett, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1763–1767.
(5) Brown, E.; Lebreton, J. *Tetrahedron* **1987**, *43*, 5827–5840.
(6) (a) Hirschmann, R.; Snoddy, C. S., Jr.; Wendler, N. L. *J. Am. Chem. Soc.* **1952**, *74*, 2693–2694. (b) Hiskey, C. F.; Hirschmann, R.; Wendler, N. L. *J. Am. Chem. Soc.* **1953**, *75*, 5135–5136. (c) Hirschmann, R.; Snoddy, C. S., Jr.; Hiskey, C. F.; Wendler, N. L. *J. Am. Chem. Soc.* **1954**, *76*, 4013–4025.
(7) Kaneko, K.; Mitsuhashi, H.; Hirayama, K.; Yoshida, N. *Phytochemistry* **1970**, *9*, 2489–2495.
(8) (a) Giannis, A.; Heretsch, P.; Sarli, V.; Stössel, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 7911–7914. (b) Heretsch, P.; Rabe, S.; Giannis, A. *Org. Lett.* **2009**, *11*, 5410–5412.
(9) (a) Mitsuhashi, H.; Shimizu, Y. *Tetrahedron* **1963**, *19*, 1027–1035. (b) Mitsuhashi, H.; Shibata, K.; Sato, T.; Shimizu, Y. *Chem. Pharm. Bull.* **1964**, *12*, 1–5.
(10) Comins, D. L.; Dheghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
(11) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.
(12) Solvents that gave no or a very slow reaction: benzene, dichloroethane, nitromethane, *n*-octane; solvents that gave similar or slightly lower yields: chlorobenzene, pyridine, xylenes.
(13) Fu, X.; Chan, T.-M.; Tann, C.-H.; Thiruvengadam, T. K. *Steroids* **2002**, *67*, 549–554.
(14) On treatment of **13** with PCl_5 in THF at−78 °C, no elimination occurred but 3-benzyl-12β-(4-chlorobutoxy)-dehydroepiandrosterone (**24**) was obtained in 50% yield, presumably by ring opening of a molecule of solvent facilitated by PCl_5. A similar observation using $SOCl_2$ at high temperatures has been reported: Ferrari, T.; Vogel, P. *Synlett* **1991**, 233–234.
(15) Schönecker, B.; Zheldakova, T.; Liu, Y.; Kötteritzsch, M.; Günther, W.; Görls, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3240–3244.
(16) (a) Johns, W. F.; Salamon, K. W. *J. Org. Chem.* **1979**, *44*, 958–961. (b) Green, M. J.; Abraham, N. A.; Fleischer, E. B.; Case, J.; Fried, J. *Chem. Commun.* **1970**, 234–235. (c) Johnson, W. S.; Cox, J. M.; Graham, D. W.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4524–4526.
(17) Marko, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207–3209.

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