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Grignard reagent induced tandem semipinacol rearrangement/ketone addition reaction of 20*S*-hydroxy-5α-pregnane-16(17)-epoxide

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ABSTRACT

A Grignard reagent induced tandem semipinacol rearrangement/chelation-controlled ketone addition process, which converts 20*S*-hydroxy-5α-pregnane-16(17)-epoxide into an unusual C20-substituted 17*S*-pregnane-3*S*,16*R*,20*S*-triol, is described.

By combining two or more distinct reactions into a single transformation, chemists can develop new synthetic approaches for the rapid construction of organic molecules with complex structures. The semipinacol rearrangement has been exploited in tandem processes in conjunction with various known reactions.[1] Particularly, the Lewis acid mediated semipinacol rearrangement of enantiopure α-hydroxyl epoxides has been studied extensively, and several tandem processes have been developed through the reactions of intermediate β-hydroxy ketone generated in situ.[2] For example, Jung described an elegant TBSOTf-promoted tandem non-aldol aldol/Mukaiyama aldol reaction of TBS-protected α-hydroxyl epoxides to give 1,5-diol stereoselectively.[3] Meanwhile, Tu and co-workers also reported examples of such semipinacol rearrangements in tandem with a Meerwein–Ponndorf–Verley reduction, SmI_2-catalyzed Tishchenko reaction or a boronic acid-mediated alkylation, respectively, to construct the chiral 1,3-diol units in high efficiency.[4] Despite the great advance of tandem semipinacol rearrangement of α-hydroxyl epoxides reported so far, reports on such tandem reactions initiated by a Grignard reagent or alkyl lithium were sparse. Herein, we report the serendipitous discovery of a Grignard reagent (or alkyl lithium) induced tandem semipinacol rearrangement/ketone addition reaction of 20*S*-hydroxy-5α-pregnane-16(17)-epoxide, which provides an efficient approach to the steroids with an unusual C17α side chain, a characteristic structural feature of several stemmosides (Fig. 1) that show interesting antiproliferative activity against Kaposi's sarcoma cell.[5]

During our synthetic study on betamethasome (Fig. 1), we envisioned that the required C16β-methyl group and C17α-hydroxyl group could be installed via the nucleophilic attack on the 16,17α-epoxide by a proper methylmetallic reagent. In order to investigate the feasibility of this key reaction, epoxide **3** was chosen as the substrate for model study, which can be easily prepared from (3*S*,16*S*,20*S*)-preganetriol (**1**) in three steps as shown in Scheme 1.

Since the trisubstituted 16,17α-epoxides are usually sterically hindered, a large excess of organometallic reagent, elevated temperature, and prolonged reaction time are needed to deliver the desired result.[6] In the event, treatment of **3** with 10 equiv methylcopper or lithium dimethyl cuprate in refluxing tetrahydrofuran (THF) only resulted in the cleavage of acetyls (Table 1, entry 1). Interestingly and quite unexpectedly, when **3** was exposed to

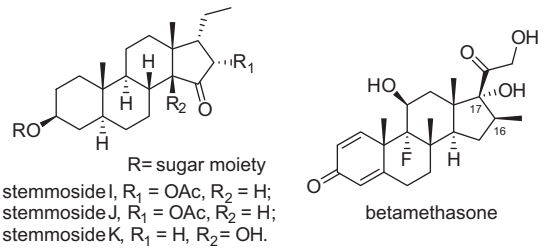

Figure 1. Structures of stemmoside I–K and betamethasone.

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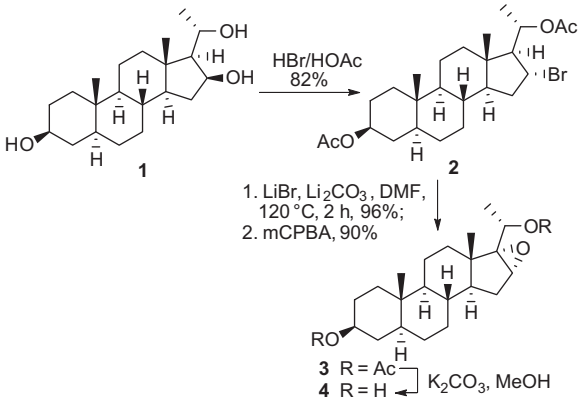
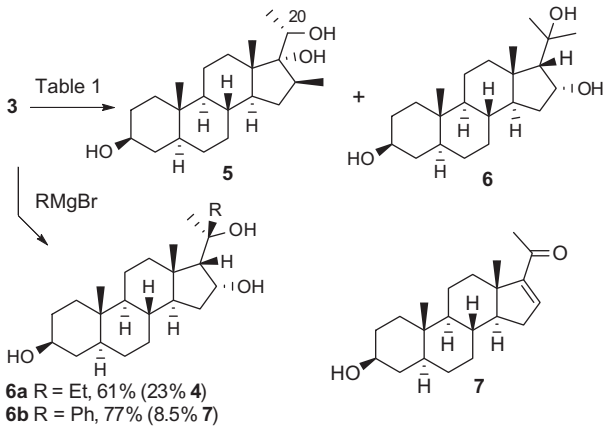


Scheme 1. Synthesis of epoxide **3**.

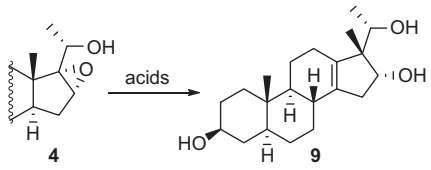


Scheme 2. Rearrangement of epoxide **3**.

Table 1
Conditions screened for epoxide opening.

Entry	Conditions[a]	Results
1	MeCu·LiI or Me_2CuLi, THF, reflux, 6 h	90% **4**
2	MeMgCl, CuI (1 equiv), THF, reflux, 3 h	60% **6**; 25% **5**
3	MeMgCl, CuI (1 equiv), DME, 80 °C, 3 h	61% **6**; 16% **5**
4	MeMgCl, CuI (1 equiv), DME, 100 °C, 3 h	87% **6**
5	MeMgCl, THF, reflux, 3 h	94% **6**
6	MeLi, THF, reflux, 3 h	85% **6**

[a] 10 equiv of methylmetallic reagents were used in all the reactions.



Scheme 3. Wagner–Meerwein rearrangement of epoxide **4**.

MeMgCl in the presence of CuI in THF or dimethoxyethane (DME) at 80 °C, triol **6** was isolated as major product along with the desired epoxide-opening product **5** in 16–25% yield (entries 2 and 3). Furthermore, conducting the reaction in boiling DME, or reacting with Grignard or methyllithium reagents afforded **6** as the only product in high yield (entries 4–6). These results suggested that the rearrangement of **3** is more rapid than the addition of organometallic reagent to the epoxide at high temperature.

The stereochemistry of triol **6** was identified by 2D NOESY analysis of its acetonide derivative **8** (Fig. 2). The crosspeaks from H_{18}–H_{17}–H_{16} interactions demonstrated that the configuration at C16 was not changed but C17-H was at β-position. The crosspeak between C20β-Me and C17-H indicated that the dioxane ring might adopt a boat conformation (in accordance with the molecular mechanics calculation result). With these stereochemical outcome confirmed, it was reasonable to propose that a stereospecific [1.2]-anti hydride shift has occurred in this semipinacol rearrangement, resulting in the inversion of pre-existing chiral center at C17.

To confirm the stereochemistry at C20 and expand this reaction, epoxide **3** was treated with ethyl and phenyl Gignard reagents in refluxing THF, respectively, which also provided the similar results,

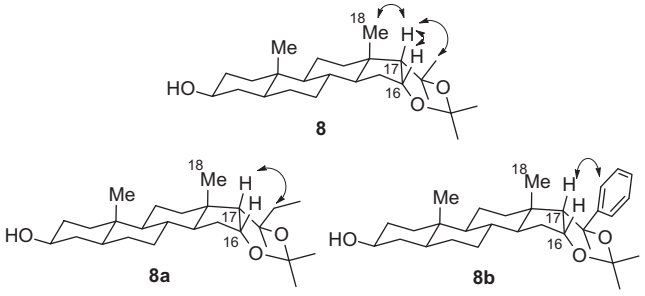


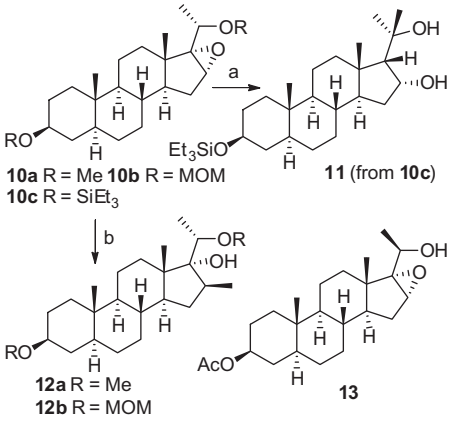
Figure 2. NOESY analysis of acetonides **8**, **8a**, and **8b**.

delivering the rearrangement products **6a**/**6b** in good yield (Scheme 2). The 2D NOESY analysis of their acetonide derivatives **8a**/**8b** demonstrated that both 20-R (ethyl and phenyl groups) and C17–H groups were on the same side of the dioxane ring (Fig. 2). This result demonstrated that the addition of Grignard reagents to the newly formed carbonyl group proceeded from β-face in a stereoselective manner, or precisely in a chelation-controlled manner. The stereochemistry of **6a** and **6b** at C20 is *R* and *S*, respectively.

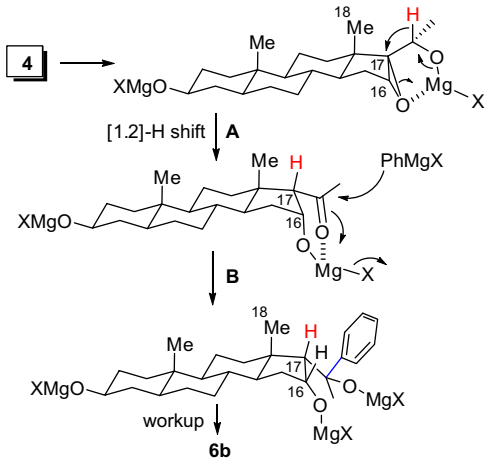
To gain insight into this novel transformation, **4** was treated with base (NaH or iPr_2NLi) and weak Lewis acid ($MgBr_2{\cdot}Et_2O$ or $ZnBr_2$) in reflux THF (CH_2Cl_2 or toluene) and no reaction was observed, indicating the effectiveness of Grignard reagents in our reaction system. In contrast, only Wagner–Meerwein rearrangement[7] product **9** was isolated under stronger acidic conditions ($Yb(OTf)_3$ in CH_2Cl_2,[8] TMSCl in MeOH, and iPr_2NEt/TMSOTf in CH_2Cl_2[9]) (Scheme 3), suggesting that the epoxide opening and the anti hydrogen shift were concerted and no classical carbocation was formed in the reaction.

To further elucidate the role of C20 magnesium alkoxide in the reaction, the C3 and C20 hydroxyls of **4** were protected as silyl ether or methyl/methoxymethyl (MOM) ethers to deliver **10a**–**c**. Treatment of epoxides **10a** and **10b** with Grignard reagent in the presence of Cu(I) salt gave the normal epoxide-opening product **12a** and **12b**, while **10c** still afforded tandem rearrangement-ketone adduct **11** in 60% yield possibly due to the facile cleavage of C20-silyl group in the reaction. The inability of C20–OH protected epoxides to undergo rearrangement indicated that a pushing effect of the magnesium oxide might exist to enhance the migratory aptitude of C20–H.

It was also noteworthy that when the C20*R*-isomer **13**[10] (Scheme 4) was used, treatment with MeMgCl with or without Cu(I) salt in refluxing DME gave only a very complex mixture and no comparable products was detected. The *S* stereochemistry of C20 was crucial for this process because the C20–H was on anti-periplanar position with epoxide, which was necessary for an efficient hydride shift.[11]



Scheme 4. Reagents and conditions: (a) MeLi/MeMgCl (1:1), DME, reflux, 3–5 h, 60%; (b) CuBr·Me_2S, MeMgCl, DME, 80 °C, 3 h, 91% for **12a**, 78% for **12b**.



Scheme 5. A plausible mechanism for the formation of **6b**. (A) Semipinacol rearrangement. (B) Chelation-controlled ketone addition.

On the basis of these experimental observations, a plausible pathway of this tandem process is proposed as shown in Scheme 5. First, the acetyls were cleaved by Grignard reagent, and the resulting α-hydroxy epoxide underwent a semipinacol rearrangement in the presence of Mg^{II} at elevated temperature. Due to the chelation effect between C20–OMg^{II} and epoxide, the C20–H and epoxide were placed on a privileged anti-periplanar conformation to promote the [1.2]-hydride shift. Then, a similar chelation between the newly formed C20-ketone and C16α-OMg^{II} altered the conformation of C20-ketone, and the resulting conformational immobility of transition state enabled the stereochemical control of ketone addition reaction, in which the C20-ketone was attacked by the organometallic reagent from the less hindered face to yield the corresponding product.

In conclusion, a tandem semipinacol rearrangement/ketone addition process has been discovered and investigated. This process offers unique opportunities to access steroids with an unusual C17α side chain which are not accessible by other synthetic methods. Efforts to expand the scope of this process and apply it in synthesis are in progress.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures and analytic data and copies of NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.122.

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