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Oxidative Fragmentation of Pregna-14,16-dien-20-ones to 14β-Hydroxyandrost-15-en-17-ones

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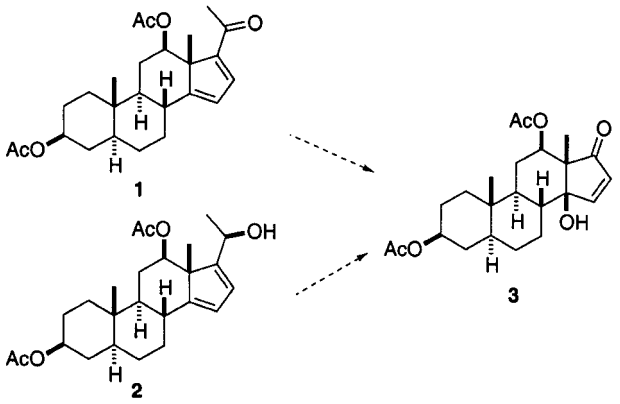
Two methods have been developed for efficient conversion of pregna-14,16-dien-20-ones into 14β-hydroxyandrost-15-en-17-ones. One procedure consists of treatment of the ring-D dienone successively with sodium borohydride and singlet oxygen. The reaction is illustrated by the conversion of pregna-14,16-dien-20-one **1** into 14β-hydroxyandrost-15-en-17-one **3**, via the corresponding allylic alcohol **2**. Although this two-step procedure is simple, it provides **3** in relatively low yield, accompanied by a smaller amount of the isomeric 14α-hydroxyandrost-15-en-17-one **6**. An alternative one-step conversion is achieved by treatment of dienone **1** with a peroxyacid in the presence of a strong protic acid. This process is illustrated by the two-step conversion of dienone **1** into hydroxy ketone **11** in 51% overall yield (Scheme 5) and by the analogous conversion of dienone **13** into hydroxy ketone **24** in 61% overall yield (Scheme 11).

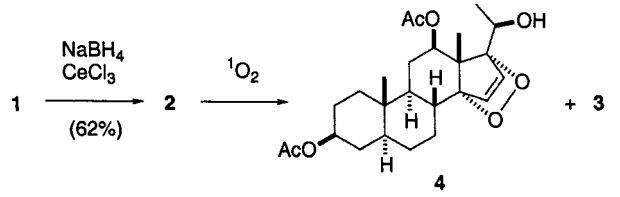
For several years, we have been investigating approaches to the synthesis of cephalostatins, a group of bis-steroidal pyrazines isolated from the marine tube worm *Cephalodiscus gilchristi*.[1] During the course of our investigations, we examined dienes **1** and **2** as possible precursors to hydroxy-enone **3** (Scheme 1). Although we initially thought the conversions would take several steps, we found that **3** could be generated from both dienes, in one-pot processes through unusual oxidation−fragmentation reactions. These results are described herein.

Keto diene **1** was synthesized from the steroid hecogenin in four steps following published procedures.[2] Reduction of **1** under Luche conditions[3] provided the C20 alcohol (**2**) (Scheme 2) as a single diastereomer[4] as determined by analysis of the *O*-methyl mandelate esters.[5] Synthesis of **3** would require the oxidative cleavage of the C17 side chain and the installation of the C14 hydroxy group. We envisioned achieving both transformations by the addition of singlet oxygen to the diene. The peroxide generated from the reaction could then be reduced and the resulting C17,C20 diol oxidized to the ketone.

SCHEME 1



SCHEME 2



In the event, treatment of **2** with singlet oxygen did provide an expected peroxide (**4**). However, the reaction also provided hydroxy enone **3**. When the cycloaddition reaction was performed on keto diene **1**, none of the desired peroxide was generated. The direct formation of hydroxy enone **3** was an unexpected but most fortuitous result. The singlet oxygen reaction produces two diastereomeric endoperoxides, the α isomer **4** and the β isomer

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(1) (a) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (b) Pettit, G. R.; Tan, R.; Xu, J.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 955.

(2) Micovic, I. V.; Ivanovic, M. D.; Piatak, D. M. *Synthesis* **1990**, 591.

(3) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(4) The modest yield of the reaction is due to the loss of material upon chromatography of the product. Typically the reaction proceeded well enough that no purification was necessary.

(5) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

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SCHEME 3

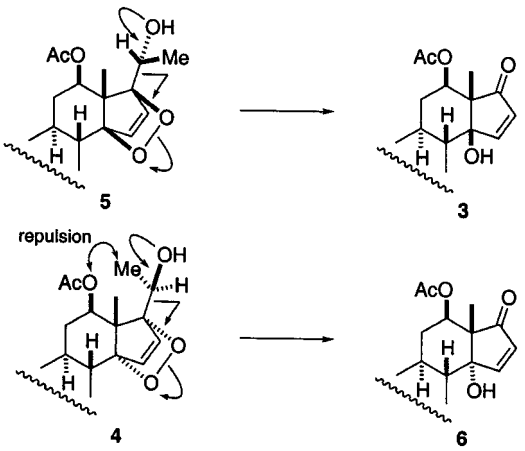


TABLE 1. Reaction of Dienone 2 with Singlet Oxygen

run	sensitizer	solvent	temp, °C	yield of **3**, %	yield of **4**, %
1	Rose Bengal	EtOH	23	23	13
2	TPP	EtOH	23	21	12
3	Rose Bengal	MeOH	0	54	30
4	TPP	CH_2Cl_2	0	16	39
5	Rose Bengal	CH_2Cl_2/MeOH	0	21	40
6	Rose Bengal, TEA salt	CH_2Cl_2	0	22	20

5. We believe that isomer **5** undergoes facile Grob fragmentation, as illustrated in Scheme 3, giving rise to hydroxy enone **3**. Diastereomer **4** is more stable because the necessary anti-periplanar conformation is disfavored by steric repulsion between the side-chain methyl group and the equatorial acetoxy group at C12 (see Scheme 3). However, fragmentation of **4** is induced by heating in methanol, giving the diastereomeric α-hydroxy enone **6**.

The singlet oxygen reaction was examined in more detail (Table 1). Factors such as sensitizer, solvent, and temperature were studied to determine their effect on product ratios and yield. Cooling the reaction to 0 °C (run 3) provided an increase in yield of both products, but upon lowering the temperature further, only starting material was recovered. A significant effect on the product ratio was observed when the solvent was changed from an alcohol (runs 1−3) to CH_2Cl_2 (runs 4−6). Since hydroxy groups can exert a directing effect on singlet oxygen addition reactions[6] and the use of a non-hydrogen bonding solvent such as CH_2Cl_2 should amplify this effect, these results indicate that the α peroxide **4** arises from the directed addition of the singlet oxygen to the more hindered a face of the diene by the C20 alcohol. In an alcoholic solvent, the C20 alcohol is hydrogen-bonded to the solvent molecules and is less likely to exert its directing influence on the singlet oxygen. Thus, more of the β peroxide is formed, which subsequently fragments to hydroxy-enone **3**.

While this singlet oxygen methodology can be used to generate hydroxy-enones **3** and **6**, the drawbacks, including irreproducible yields upon scale-up, difficulties in purification of the products, and generation of diastereomeric mixtures, led us to investigate other routes for synthesis of **3**. Since there is some precedent in the literature for performing a Baeyer−Villiger reaction in preference to epoxidation,[7,8] we envisioned a Baeyer−Villiger reaction on keto-diene **1** as a means of installing the C17 ketone via an enol acetate. This strategy also produced surprising results. Treatment of **1** with anhydrous *m*-CPBA and concentrated sulfuric acid in chloroform gave the desired hydroxy enone **3** in 30% yield, accompanied by 15% of the unexpected diketone **7**.

The formation of hydroxy enone **3** is dependent on both the use of anhydrous *m*-CPBA and the presence of a strong acid. Treatment of **1** with commercially available 75% *m*-CPBA and no added acid resulted in exclusive formation of the monoepoxide **8**. Moreover, treatment of **1** with 100% *m*-CPBA in the presence of H_2O also resulted solely in the formation of **8**. This result strongly indicates that the water present in commercial *m*-CPBA is responsible for the marked reactivity difference. The reason may be that, in the presence of water, the carbonyl group of the dienone is less likely to be protonated, thereby retarding the acid-catalyzed Baeyer−Villiger reaction, and epoxidation predominates. The fact that omission of the acid catalyst (and the use of anhydrous *m*-CPBA) also results exclusively in monoepoxide formation demonstrates that protonation of the carbonyl group is essential for the Baeyer−Villiger reaction to take place. Additionally, it was found that monoepoxide **8** does not convert to desired enone **3**, but rather reacts to produce the side-product diketone **7**. This transformation mostly likely takes place though a Baeyer−Villiger reaction to produce the enol acetate, which undergoes an acyl transfer reaction similar to a Fries rearrangement (Scheme 4) followed by the β elimination of the epoxide.

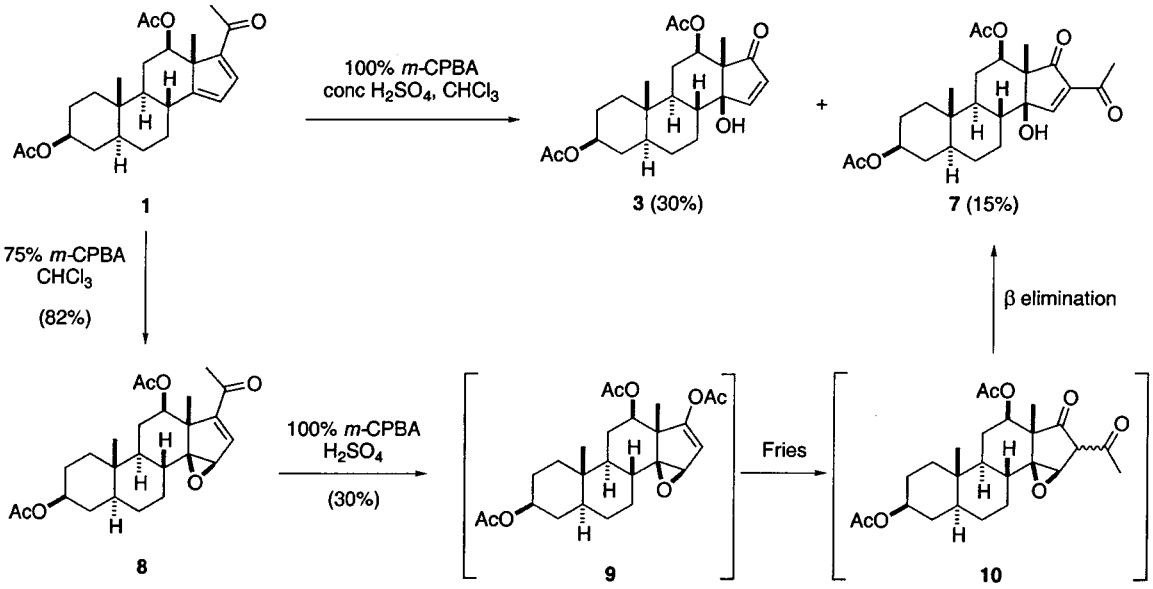
Though these experiments, it was made clear that to favor formation of **3**, the Baeyer−Villiger reaction must occur prior to epoxidation. Since the presence of H_2O promotes epoxidation, the use of anhydrous reaction conditions is essential. Therefore, in the optimized reaction conditions, H_2SO_4 was replaced with anhydrous $MeSO_3H$. Moreover, the use of excess *m*-CPBA increased the yield. This is largely a result of the fact that excess *m*-CPBA results in shorter reaction times and decreased exposure of the tertiary allyic alcohol present in the product to the very acidic reaction conditions. Also, the yield was improved when **3** was not isolated, but was hydrogenated prior to purification. These conditions (Scheme 5) provide the desired hydroxy-ketone (**11**) in a synthetically useful 51% yield.

While the singlet oxygen reaction is an interesting transformation from a mechanistic standpoint, the *m*-CPBA methodology proved to be the most synthetically useful route to hydroxy ketone **11** because it is easily scaleable and a single diastereomer of the product is obtained in acceptable yield. For these reasons, it appeared to be the method of choice if advanced intermediate **3** was to be used as part of our cephalostatin 1 project. However, since the methodology is well suited to preparing the C14 hydroxylated androstane steroid skeleton, it also has the potential to provide more immediate utility. 14-Hydroxy-androstane intermediates have been used extensively in the synthesis of cardiac glycosides,

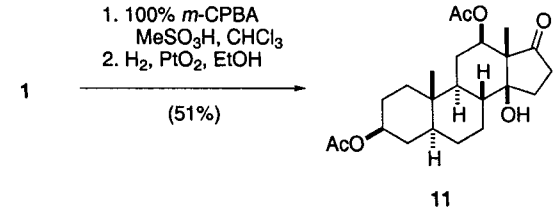
(6) Adam, W.; Peters, E. M.; Peters, K.; Prein, M.; von Schering, H. G. *J. Am. Chem. Soc.* **1995**, *117*, 6686.

(7) Montury, M.; Goré, J. *Tetrahedron* **1977**, *33*, 2819.
(8) Krow, G. R. *Org. React.* **1993**, *43*, 300.

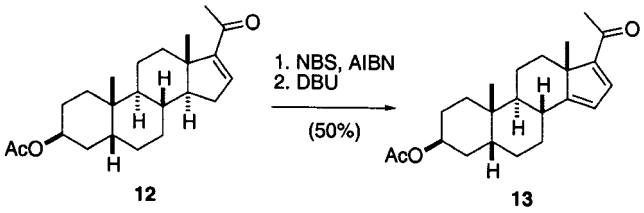
SCHEME 4



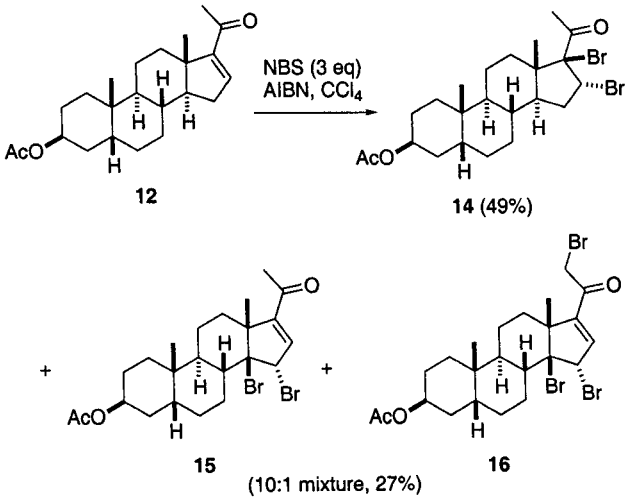
SCHEME 5



SCHEME 6



SCHEME 7



but their preparation is somewhat lengthy.[9,10] We therefore decided to explore the application of the *m*-CPBA oxidation−fragmentation route to the cardiac glycoside steroid skeleton. Our attention therefore turned to the synthesis of the requisite keto-diene **13** (Scheme 6).

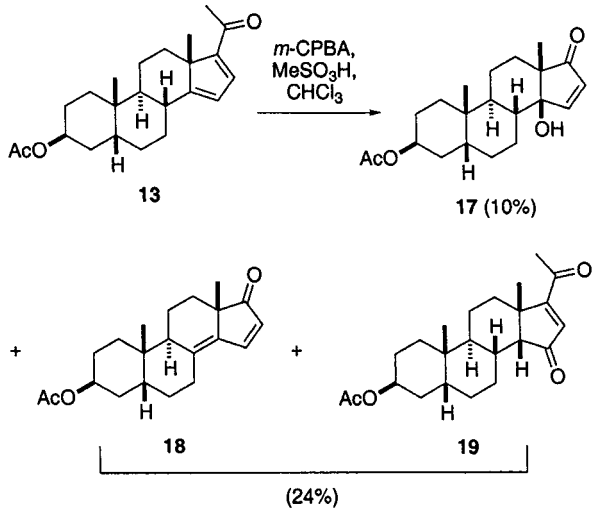
The preparation of dienone **13** by a route analogous to the preparation of dienone **1** has been reported several times in the literature and in each report significant amounts of enone **13** have been recovered after the bromination−elimination process.[11] To determine why this is the case, the reaction sequence was examined more closely. Examination of the bromination reaction in more detail showed that treatment of **12** with NBS under typical free radical conditions does not result in a simple allylic bromination reaction, but instead gives three products (Scheme 7). One of these, obtained as a crystalline solid, was found to be dibromide **14**, resulting from the *addition* of bromine to the double bond of enone **12**. The other two products were an inseparable mixture of dibromide **15** and tribromide **16**. Although products **15** and **16** cocrystallized, their structures were elucidated by single-crystal X-ray analysis of the crystalline mixture. In this structure determination, atom Br3, attached to C21, had a refined occupancy of 8%.

Dibromide **14** arises from addition of bromine to the enone olefin, while dibromide **15** and tribromide **16** are derived from addition of bromine to the desired diene **13**. The C21 bromine of **16** most likely comes from a bromination. When more equivalents of NBS are used in the reaction, more of **16** is obtained. When treated with base, **15** and **16** converted cleanly to the desired diene **13**, while **14** reverted back to the starting enone.

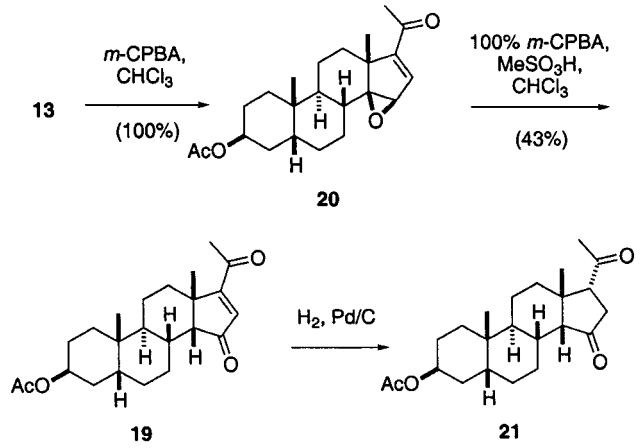
With dienone **13** in hand our attention turned once again to the oxidation−fragmentation reaction. Initial reactions proved to be problematic. When **13** was treated with purified *m*-CPBA and $MeSO_3H$, the conditions that were optimized for dienone **1**, three products were obtained (Scheme 8). The desired hydroxy enone **17** was

(9) Daniewski, A. R.; Kabat, M. M.; Masnyk, M.; Wicha, J.; Wojciechowska, W. *J. Org. Chem.* **1988**, *53*, 4855.
(10) Groszek, G.; Kabat, M. M.; Kurek, A.; Masnyk, M.; Wicha, J. *Bull. Pol. Acad. Sci., Chem.* **1986**, *34*, 313.
(11) (a) Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733. (b) Ferland, J. M.; Lefebvre, Y. *Can. J. Chem.* **1984**, *62*, 315. (c) Pettit, G. R.; Piatak, D. M. *Can. J. Chem.* **1966**, *44*, 844.

SCHEME 8



SCHEME 9

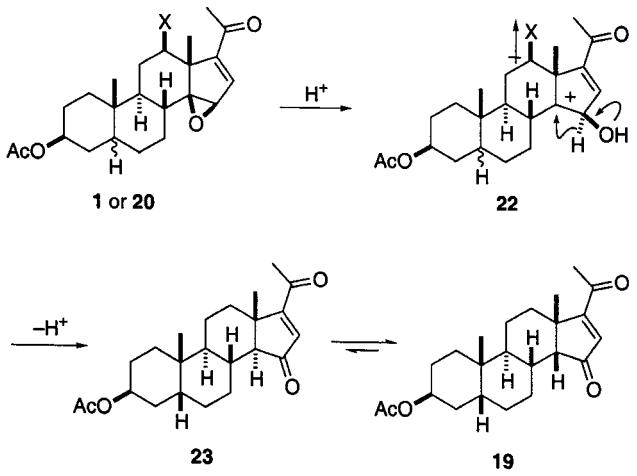


obtained in only 10% yield, along with an inseparable mixture of **18** and **19**.[12] Diene **18** arises by dehydration of the tertiary, allylic alcohol in **17**, and this transformation was confirmed by treatment of pure **17** with methanesulfonic acid in chloroform.

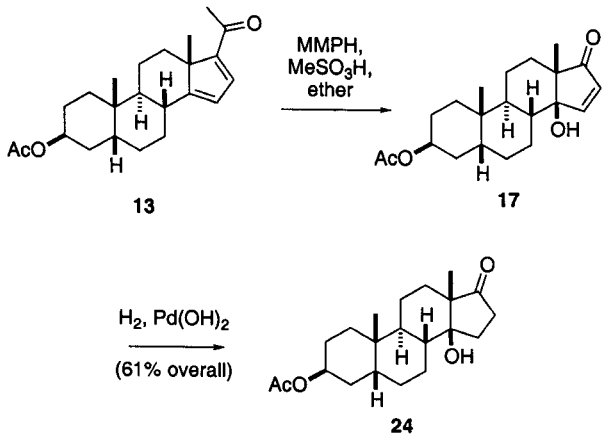
Diketone **19** appears to arise from monoepoxide **20**, as shown in Scheme 9. Treatment of dienone **13** with commercially available 75% *m*-CPBA in the presence of acid furnished epoxide **20** in quantitative yield. Subjection of **20** to the previous reaction conditions (anhydrous *m*-CPBA and methanesulfonic acid) gave enedione **19** in 43% yield. The structure of **19** was confirmed by conversion to the known diketone **21**.[13]

Interestingly, although monoepoxide **20** and monoepoxide **8** are similar in structure, they display very different reactivity. The reason for this discrepancy become apparent when one considers the likely mechanism of the formation of diketone **19** (Scheme 10). In the case of **20**, protonation of the epoxide leads to formation of tertiary cation **22** which undergoes a hydride shift to provide diketone **23**. Under the acidic conditions of the reaction, the trans ring fusion isomerizes to the more

SCHEME 10



SCHEME 11



stable cis configuration. In the case of monoepoxide **8** the C12 acetoxy group inductively disfavors formation of the tertiary carbocation **22** because of electrostatic interaction with the dipole of the C12 substituent. Therefore, this substrate instead undergoes Baeyer–Villiger reaction and subsequent Fries rearrangement as described previously.

Formation of the unwanted side-product **19** epoxide product was minimized by changing the reaction conditions from *m*-CPBA in $CHCl_3$ to magnesium monoperoxyphthalate (MMPP) in ether. Reduction of the initially formed hydroxy enone gave the saturated hydroxy ketone **24** in 61% overall yield (Scheme 11). Initially the perphthalic acid was generated by reaction of MMPP with methanesulfonic acid in ether and this solution was added to an ether solution of dienone **13**, as suggested by Böhme.[14] However, preparation of the oxidizing agent in this manner tended to be inconsistent, and better results were obtained when the perphthalic acid was generated in situ from magnesium monoperoxyphthalic acid (MMPP) and $MeSO_3H$.

By using the revised reaction conditions, the desired hydroxy ketone can be generated in good yield on this substrate, demonstrating that the oxidation–fragmenta-

(12) These two products did partially separate upon crystallization from ether.

(13) Ferland, J. M.; Lefebvre, Y. *Can. J. Chem.* **1984**, *62*, 315.

(14) Böhme, H. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 619.

tion reaction methodology is a useful means of generating important intermediates in the synthesis of cardiac glycosides.

In summary, two novel oxidatative fragmentation reactions have been discovered that provide a concise entry into the C14-hydroxylated androstane steroid skeleton. The Baeyer−Villiger peracid route is synthetically useful and has been demonstrated to work on dienes incorporating the steroid skeleton that is common to many of the cardiac glycosides.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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