

Studies Directed toward Asymmetric Synthesis of Cardioactive Steroids via Anionic Polycyclization

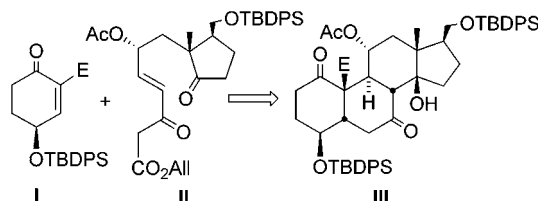
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ABSTRACT

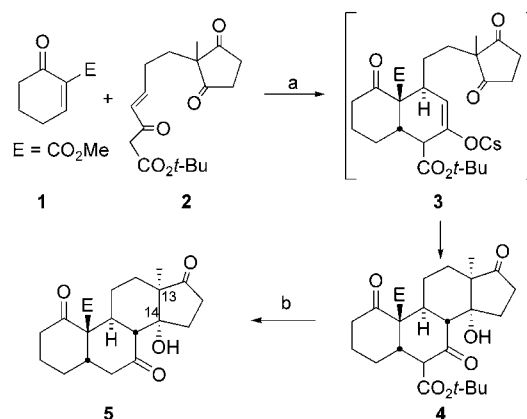


The use of anionic polycyclization (AP) in constructing the steroidal backbone of cardenolides was investigated. The reaction of 2-carbomethoxy-2-cyclohexenone **1** with the enolate of Nazarov reagent **2** gave, after decarboxylation and aldol condensation, steroid **5** with control of stereochemistry.

In 1988, our research group reported a new stereocontrolled synthesis of polycyclic compounds.¹ We have now found that the reaction between cyclohexenone **1** and the enolate of Nazarov reagent **2** affords, after selective decarboxylation, steroid **5** in good yield and with very good diastereoselectivity (Scheme 1). This tandem double Michael addition/aldol condensation, which we call the anionic polycyclization, is a very efficient method for the construction of polycyclic compounds stereoselectively.

Construction of steroid **5** was very encouraging; however, since most naturally occurring cardioactive steroids contain a β -hydroxyl at C-14, along with the *cis* A/B and C/D ring fusions,² it would be very interesting to pursue this stereochemistry. One such example is the natural product ouabain (**6a**, Figure 1), which is of particular interest because it has shown the potential for treating hypertension as well as congestive heart failure.³ This glycosidic steroid, extracted

Scheme 1^a



^a Reagents and conditions: (a) Cs₂CO₃, CHCl₃, rt; (b) pTSA, PhH, reflux, 47% (two steps).

from the leaves of *Digitalis*, has *cis* A/B and C/D ring fusions, a *trans* B/C juncture, and a butenolide at C-17. Ouabain was therefore seen as an ideal candidate for total synthesis.⁴

(1) Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, 29, 6033.
(2) Lociuio, S.; Tsai, T. Y. R.; Wiesner, K. *Tetrahedron* **1988**, 44, 35 and references therein.
(3) (a) Thomas, R.; Gray, P.; Andrew, J. *Adv. Drug Res.* **1990**, 19, 312.
(b) Scheiner-Bobis, G.; Schoner, W. *Nat. Med.* **2001**, 7, 1288. (c) Kawamura, A.; Abrell, L. M.; Maggiali, F.; Berova, N.; Nakanishi, K.; Labutti, J.; Magil, S.; Haupt, G. T., Jr.; Hamlyn, J. M. *Biochemistry* **2002**, 40, 5835.

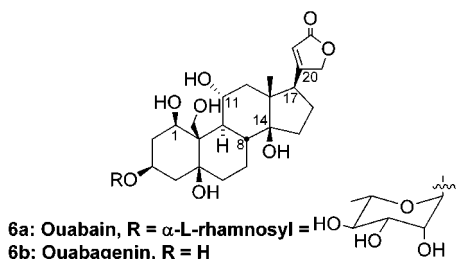


Figure 1. Target compounds ouabain and ouabagenin.

Early studies in our group⁵ directed toward anionic polycyclization using Nazarov reagents in which the C-17 carbonyl was protected against aldol condensation were not as successful as the studies using Nazarov reagent **2** (Scheme 1). The desired tetracyclic compound was not formed in one pot, but the reaction instead stopped after double Michael addition, yielding the tricycle. This was due to a lower reactivity in the intramolecular aldol condensation between C-8 and C-14, allowing enolization of the β -ketoester to impede the desired reaction pathway.⁶ Selective decarboxylation of the *tert*-butylester was therefore necessary before aldol condensation between C-8 and C-14 would occur. This variation furnished the desired tetracycle; however, the low yields were disappointing.

It was believed that poor regioselectivity in enol formation was affecting the yields for the intramolecular aldol condensation; thus the use of selective enolization by reduction of an α -bromoketone at C-8 should solve the problem.⁷ Upon treatment of tricycle **9** (Scheme 2) with SmI_2 at -20°C , tetracycle **10** (8 α -H) was obtained as the major product in a much improved yield of 63%. The desired isomer **11** (8 β -H) was formed with a very low yield of 7% but was obtained in 90% yield via acidic isomerization of **10**. The use of lower temperature for the reduction gave no aldol product, and temperatures higher than -20°C led to greater amounts of the retro-Michael product **12**.

The use of the α -bromoketone was a very effective solution to improve the yield for the aldol condensation; however, the need to isomerize **10** to **11** under acidic conditions was a point of concern since this may limit the range of functionalities available for the molecule. Also, the appearance of retro-Michael degradation using this reduction protocol was worrisome. With our sights set on the synthesis of (–)-ouabain it was felt that construction of a Nazarov reagent containing an acetate at C-11 in the α -orientation was in order.

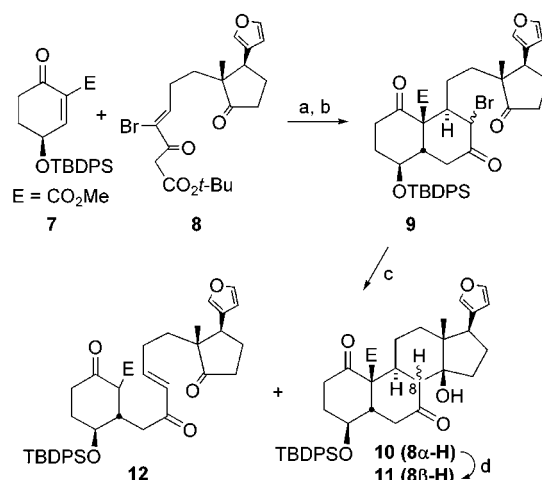
(4) One synthetic approach toward ouabagenin: Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, 39, 4643. Overman, L. E., Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, 39, 4647. Overman, L. E.; Rucker, P. V. *Heterocycles* **2000**, 52, 1297.

(5) (a) Ruel, R.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, 31, 3961. (b) Ruel, R.; D., P. *Can. J. Chem.* **1992**, 70, 1939.

(6) This can occur by protonation of the newly formed enolate (cf. **3**) followed by in situ protonation and deprotonation of the more acidic β -ketoester moiety.

(7) Chapdelaine, D.; Belzile, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, 67, 5669.

Scheme 2^a



^a Reagents and conditions: (a) Cs_2CO_3 , CH_2Cl_2 , rt; (b) pTSA, PhH, reflux, 56% (two steps); (c) SmI_2 , THF, -20°C , 63% (**10**), 7% (**11**), 25% (**12**); (d) anhydrous HCl, CH_2Cl_2 , 90%.

Another issue dealt with the choice of functionality at C-17 to allow for efficient access to the butenolide at a later point in the sequence. A report by Stork et al.⁸ demonstrated that the butenolide synthesis could be achieved via a nitrile. We therefore chose a CH_2OTBDPS group as a stable precursor to the nitrile at position 17. After verifying the overall strategy and getting a better idea of the synthetic steps necessary it may be deemed possible to go back and leave the nitrile unprotected throughout the route (or even to eventually use a β -furyl group). With these considerations in mind, compound **13** (Figure 2) became the targeted Nazarov reagent for exposure to the anionic polycyclization protocol.

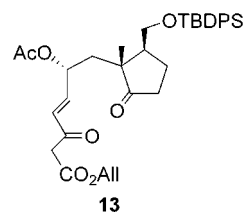


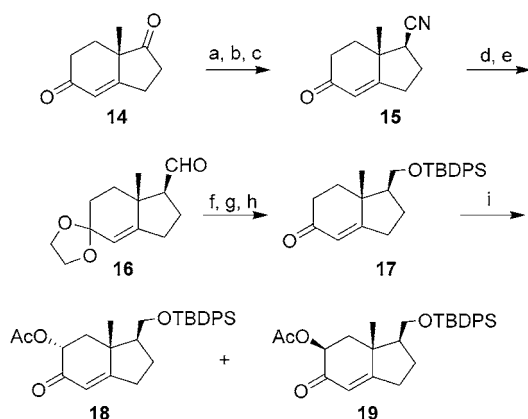
Figure 2. Targeted Nazarov reagent.

The synthesis began with selective reduction of the known Hajos–Parrish ketone⁹ (**14**, Scheme 3) using NaBH_4 . This was followed by tosylation and then cyanation as reported by Caine et al.^{10a} and Overman et al.^{10b} to give cyanoenone

(8) Stork, G.; West, F.; Lee, H.-Y.; Isaacs, R. C. A.; Manabe S. *J. Am. Chem. Soc.* **1996**, 118, 10660.

(9) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1985**, 63, 26

(10) (a) Caine, D.; Kotian, P. L. *J. Org. Chem.* **1992**, 57, 6587. (b) Deng, W.; Jensen, M. S.; Overman, L. E.; Rucker, P. V.; Vionnet, J.-P. *J. Org. Chem.* **1996**, 61, 6760.

Scheme 3^a

^a Reagents and conditions: (a) NaBH₄, EtOH, -15 °C, 94%; (b) TsCl, Pyr, 0 °C to rt, 93%; (c) NaCN, DMSO, rt, 85%; (d) (CH₂OH)₂, pTSA, PhH, reflux, 95%; (e) DIBAL-H, PhCH₃, 0 °C, 91%; (f) NaBH₄, EtOH, -20 °C, 96%; (g) 1 M HCl, acetone, rt, 95%; (h) TBDPSCl, imidazole, DMF, rt, 99%; (i) Pb(OAc)₄, PhCH₃, 138 °C, 88%, **18:19** = 8.3:1.

15 in 74% yield over three steps. Selective reduction of the nitrile using DIBAL-H to give the desired aldehyde was not successful in the presence of the ketone functionality. Reduction of the nitrile was therefore preceded by ketalization giving aldehyde **16** in 86% yield over two steps.

Reduction of the aldehyde, followed by hydrolysis of the ketal and then silylation of the alcohol afforded the desired protecting group at the pro-17 position in 90% yield over three steps. Acetoxylation using lead tetraacetate¹¹ at high temperature gave the thermodynamically favored equatorial product **18** in 78% yield. Lower temperatures and/or shorter reaction times decreased the isomeric ratio between **18** and **19** to as low as 1.4:1, respectively.

The enone of compound **18** was then oxidatively cleaved,¹² and the resulting carboxylic acid was converted to thioester¹³ **20** (Scheme 4) in 65% yield over two steps. Reduction to the aldehyde,¹⁴ followed by Wittig reaction¹⁵ and selective hydrolysis gave the targeted Nazarov reagent **13** in 71% yield over the last three steps.

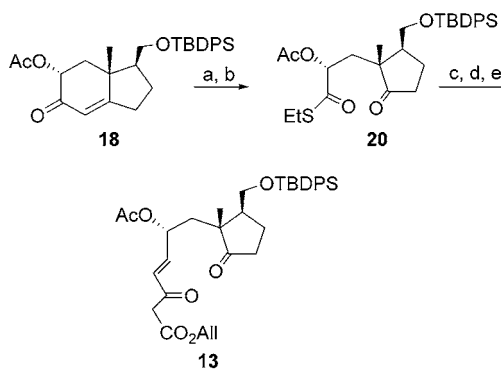
Although the earlier studies⁵ mentioned above showed that aldol condensation between C-8 and C-14 was low yielding, it was felt that this new Nazarov reagent possessing the α -acetate at C-11 could play a role in facilitating the desired aldol condensation. Also, even though cyclohexenone **7** (Scheme 5) would probably not be the final ring A precursor in the synthesis of ouabain, it was chosen for this initial trial since it was previously found to be a good substrate for double Michael addition (in terms of yield and facial selectivity).⁷

(11) Thompson, A.; Ourisson, G. *Tetrahedron* **1991**, *47*, 7045.
(12) Webster, F. X.; Enterrios, J. R.; Silverstein, R. M. *J. Org. Chem.* **1987**, *52*, 686.

(13) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709.

(14) Jutzi-Eme, A.-M.; Nuninger, F.; Eberle, M. K. *J. Org. Chem.* **1994**, *59*, 7249.

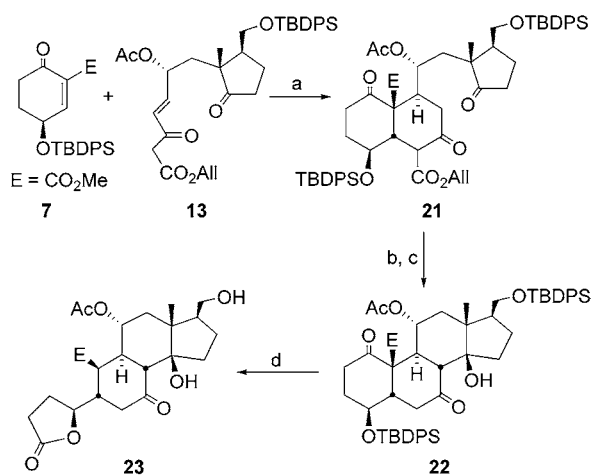
(15) Chapdelaine, D.; Dube, P.; Deslongchamps, P. *Synlett* **2000**, 1819.

Scheme 4^a

^a Reagents and conditions: (a) NaIO₄, RuCl₃, H₂O, CCl₄, CH₃CN, rt, 80%; (b) EtSH, DCC, DMAP, CH₂Cl₂, 0 °C to rt, 81%; (c) Et₃SiH, Pd(OAc)₂, acetone, sieves, rt; (d) Ph₃PCHC(OEt)CHCO₂-All, PhH, reflux, 85% (two steps); (e) 80% AcOH (aqueous), 80 °C, 84%.

With the stage set for anionic polycyclization, treatment of Nazarov reagent **13** with cyclohexenone **7**, under basic conditions, afforded tricycle **21** (Scheme 5) in 61% yield. Selective decarboxylation of the allyl ester in 71% yield, followed by exposure to base at elevated temperature, gave the desired tetracyclic aldol product, **22**, in a very satisfying yield of 71%. Very importantly, this showed that remote functionalities (i.e., the C-11 α -acetate) could be installed to promote efficient aldol condensation. Furthermore, the correct stereochemistry at C-8 was directly obtained, and no competition from the retro-Michael degradation was observed as was depicted in Scheme 2. The silyl groups were then removed via TBAF generating diol **23**, which was suitable for X-ray analysis.¹⁶

In regards to the stereochemical outcome of the aldol condensation, it could proceed via four stereoelectronically

Scheme 5^a

^a Reagents and conditions: (a) Cs₂CO₃, CH₂Cl₂, rt, 61%; (b) Pd(PPh₃)₄, morpholine, THF, rt, 71%; (c) KHMDS, THF, reflux, 71%; (d) TBAF, THF, rt, 85%.

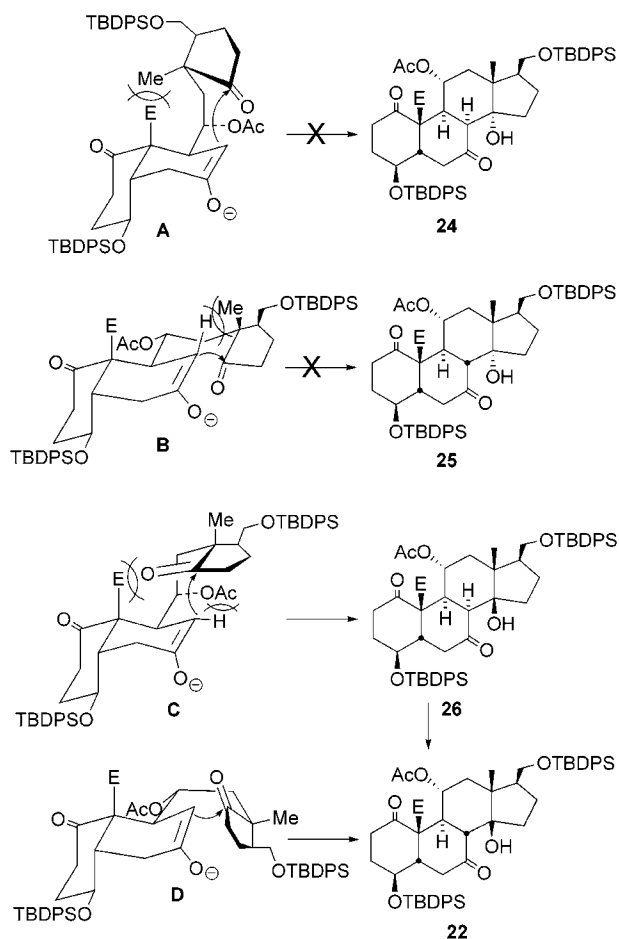


Figure 3. Comparison of the possible aldol pathways.

allowed transition states¹⁷ leading to four possible diastereomers (Figure 3). Taking into account the results described in Scheme 2, which shows that the kinetic product has an

8 α -H configuration as well as the rigorous basic conditions used in Scheme 5, it appears plausible that compound **22** was formed via pathway **C** to give first **26**, which was then isomerized in situ to the more stable isomer **22**. It is also possible that the pathway **D** produced directly the thermodynamic product **22** as it appears to occur with less steric hindrance according to molecular models.

With the synthesis of steroid **22** complete, and the stereoselective generation of five contiguous chiral centers from anionic polycyclization, the crucial groundwork has been established for the asymmetric total synthesis of ouabain. A literature procedure will be used for the butenolide synthesis at C-17, and other ring A cyclohexenones are currently under investigation to allow for easier access to ring A in the targeted natural product. Developments in these regards will be reported in due time. Although ouabain is the specific target in this line of research, other derivatives may show interesting biological activity.³ This will be assessed in the course of our efforts.

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Supporting Information Available: Experimental details and characterization data for all new compounds, as well as complete X-ray crystallographic data for compound **23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) The authors thank Dr. A. Decken for X-ray diffraction analysis (deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. CCDC no. 195519).

(17) For a general reference refer to: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, England, 1983; p 274.