

A Convergent Synthesis of the Cardenolide Skeleton: Intramolecular Aldol Condensation via Reduction of α -Bromoketones

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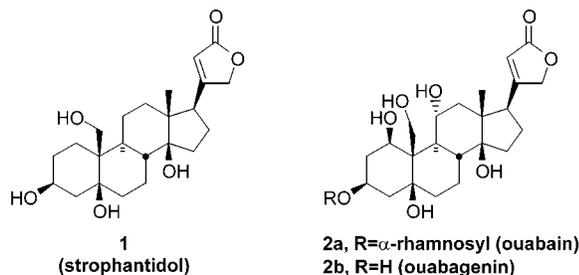
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Synthesis of the highly biologically valuable cardenolide backbone was achieved via anionic polycyclization. Bromoketone **18**, obtained from double-Michael cycloaddition between cyclohexenone **14** and γ,δ -unsaturated β -ketoester **16**, was efficiently aldolized under reductive conditions. The highly functionalized tetracyclic compound **52** is an important synthetic intermediate that is potentially amenable to natural cardenolide total synthesis.

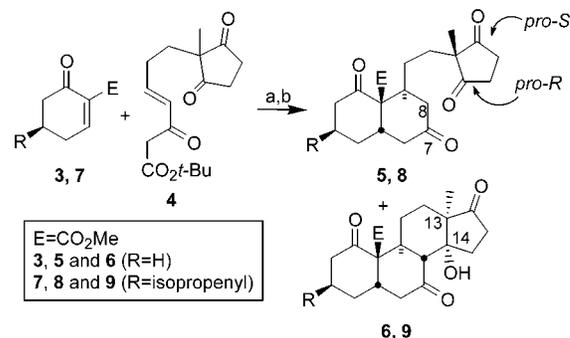
Introduction

Cardenolides constitute a special subset of the steroid natural products as their highly oxygenated structure (e.g., strophanthidol **1** and ouabain **2a**) possesses unusual cis A/B and C/D ring junctions. Moreover, it has been known for a long time that the digitalis extract, which contains a mixture of cardenolides, exhibits valuable clinical improvement for the treatment of certain cardiac diseases.¹ Surprisingly, relatively little work has been carried out on the total synthesis of cardenolides.²



We have previously reported on the reaction between cyclohexenones **3** and **7** (Scheme 1) with the symmetric Nazarov reagent **4** in order to access the tetracyclic products **6** and **9**.³ Under basic conditions, **6** was obtained as the sole product from cyclohexenone **3** via a cascade double-Michael–aldol condensation, so-called anionic polycyclization. Cyclohexenone **7** gave a 1:1 mixture of

SCHEME 1^a



^a Reagents and conditions: (a) Cs₂CO₃, CH₂Cl₂; (b) APTS, refluxing benzene, 47% (two steps) of **6** from **3**; 44% (two steps) of a 1:1 mixture of **8** and **9** from **7**.

the double-Michael adduct **8**, along with the tetracyclic compound **9**, in which the α configuration at C-13 and C-14 is precisely opposite to that found in the naturally occurring cardenolides.⁴

Subsequently, we decided to investigate the utility of Nazarov reagent **10** (Scheme 2), which can *only* lead to 13 β -methyl-14 β -hydroxysteroids.⁵ Thus, in the presence of cyclohexenone **7** and cesium carbonate, the double-Michael adduct **11** was isolated, along with a minor diastereomer⁶ in 85:15 ratio. Base-catalyzed aldolization of **11** at higher temperatures or the use of stronger bases furnished either **12** or **13** in low yields, along with the recovered starting material. We reasoned that the poor yields of tetracyclic products obtained are due to the following factors: (a) poor facial stereoselectivity in the

(1) Aronson, J. K. *An Account of the Foxglove and its Medical Uses, 1785–1985*; Oxford University Press: London, UK, 1985.

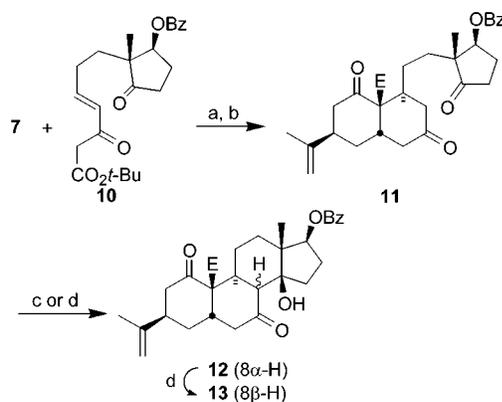
(2) Recent publications on this subject limited to the following: (a) The total synthesis of digitoxigenin: Stork, G.; West, F.; Lee, H. Y.; Isaac, R. C. A.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10 660. (b) One synthetic approach toward ouabagenin: Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4643 1998. Overman, L. E.; Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4647. Overman, L. E.; Rucker, P. V. *Heterocycles* **2000**, *52*, 1297.

(3) (a) Lavallée, J.-F.; Spino, C.; Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406. (b) Ruel, R.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1939.

(4) The aldol condensation is the result of a preferred attack of the double-Michael-issued enolate ion on the *pro-S* carbonyl of the cyclopentadione unit: Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6033.

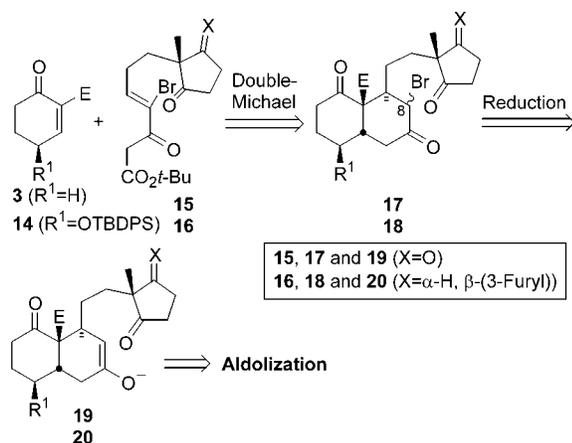
(5) Ruel, R.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3961.

(6) The side product (5 α ,9 β ,10 α -diastereomer of **11**) was the result of a cycloaddition syn to the isopropenyl group of **7**.

SCHEME 2^a

^a Reagents and conditions: (a) Cs₂CO₃, CH₂Cl₂; (b) APTS, refluxing benzene, 60%; (c) KHMDS, THF, 25% of **12**; (d) Cs₂CO₃, refluxing CH₃CN, 32% of **13** from either **11** or **12**.

SCHEME 3

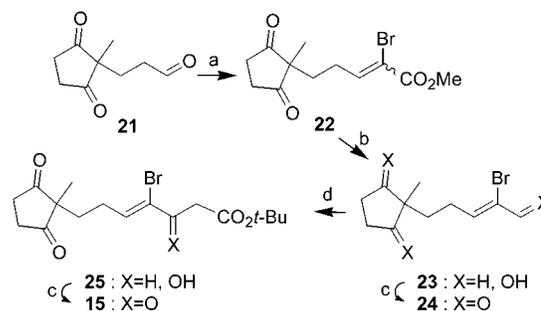


first coupling step (double-Michael cycloaddition), and (b) competitive retroaldol and degradation reactions during the second step (aldolization).

To circumvent the first of these two shortcomings, we developed the cyclohexenone **14** (Scheme 3), which is known to afford excellent levels of facial diastereocontrol in conjunction with various Nazarov reagents.⁷ An alternative strategy for the C ring formation was to synthesize precursors for regioselective enolization at the *pro*-8 position (steroid numbering) of the tricyclic double-Michael adduct. Interestingly, it was known that bromoacetates of ω -hydroxyaldehydes (and ketones) cleanly undergo intramolecular Reformatsky condensation using samarium(II) as the reducing agent to furnish β -hydroxy-lactones.⁸ This prompted us to initiate the synthesis of brominated Nazarov reagent **15**, as well as **16** (which contains a β -furyl substituent at the *pro*-17 position), to study their condensation with cyclohexenones **3** and **14**. The resulting tricyclic α -bromoketones **17** and **18** have been found to be excellent precursors of enolates **19** and **20** (via chemical reduction), both of which undergo intramolecular aldolization in high yields. We wish to report on the results of this latter approach herein.

(7) Belzile, J. M.Sc. Thesis, Université de Sherbrooke, 1999.

(8) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556. Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.

SCHEME 4^a

^a Reagents and conditions: (a) Ph₃P=C(Br)CO₂Me, refluxing benzene, 81% (*Z*:*E* = 4:1); (b) DIBAL-H, CH₂Cl₂, -78 to 0 °C, 74%; (c) Dess–Martin periodinane, CH₂Cl₂, 79% for **24** and 83% for **15**; (d) Zn, BrCH₂CO₂*t*-Bu, THF, 76%.

Results and Discussion

Synthesis of brominated Nazarov reagent **15** (Scheme 4) was initiated by olefination of the known aldehyde **21**⁴ with a stabilized phosphorane reagent⁹ to yield ester **22**¹⁰ as a separable (4:1) *Z*/*E* mixture. Following an overreduction–reoxidation sequence (via triol **23**) into aldehyde **24**, addition of the Reformatsky reagent derived from *tert*-butyl bromoacetate furnished alcohol **25**. Further oxidation with Dess–Martin periodinane¹¹ offered the γ,δ -unsaturated β -ketoester **15**.

Enantiopure Nazarov reagent **16** was prepared (Scheme 5) with the chiral borneol **27**.¹² Transesterification of commercial β -ketoester **26** followed by selective dehydrogenation via phenylselenide¹³ provided chiral enoate **29**. Highly diastereoselective addition of the higher order cuprate,¹⁴ derived from 3-bromofuran, yielded adduct **30**, from which **27** was recovered via methanolysis. Compound **31** was then methylated, followed by dealkoxy-carbonylation¹⁵ of β -ketoester **32** to yield methyl ketone **33**, which was subjected to a regioselective Michael addition¹⁶ with ethyl acrylate. As expected, the stereochemical outcome of the former three steps is well-controlled by 1,2-induction (from 7 to 10:1) provided by the furan group. Ketoester **34** was then reduced (a two-step sequence via diol **35**) into aldehyde **36**, from which **16** was elaborated via the same sequence used for **15**.

Cyclohexenone **14** was prepared by desymmetrization of the known 4-silanoxy-cyclohexanone **41** (Scheme 6).¹⁷ Following the addition of dimethyl carbonate to the racemic enolate of **41** (generated by sodium/potassium hydride),¹⁸ an equimolar mixture of enantiomeric β -ketoesters **42** and **43** (enol forms shown) was produced.¹⁹ Alternatively, enantioselective deprotonation could be

(9) Maerkl, G. *Chem. Ber.* **1961**, *94*, 2996.

(10) All new compounds in this publication were characterized by ¹H and ¹³C NMR, IR, and HRMS. [α]_D and mp were also recorded when pertinent. See Supporting Information.

(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(12) Urban, E.; Knühl, G.; Helmchen, G. *Tetrahedron* **1996**, *52*, 971.

(13) Liotta, D.; Bornum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S. *J. Org. Chem.* **1981**, *46*, 2920.

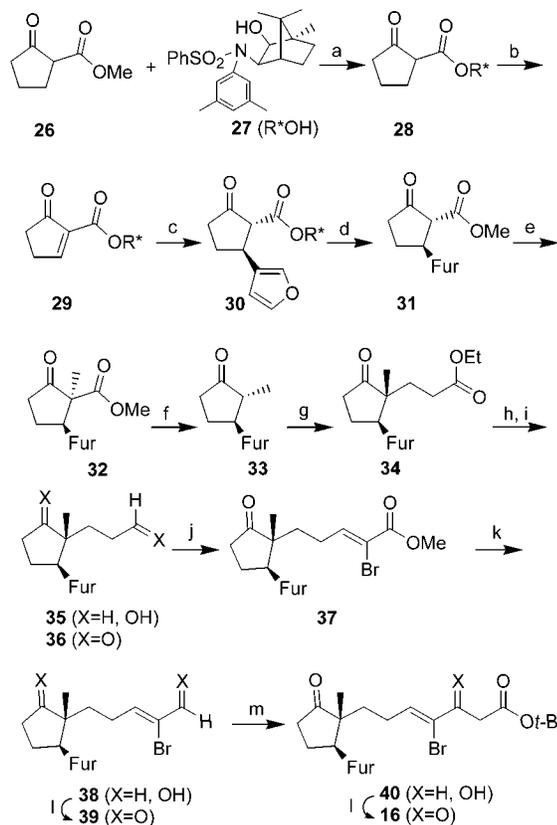
(14) Lipshultz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(15) Elsinger, F. *Org. Synth.* **1973**, *5*, 76.

(16) House, H. O.; Roelofs, W.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646.

(17) Nagao, Y.; Goto, M.; Ochiai, M. *Chem. Lett.* **1990**, *9*, 1507.

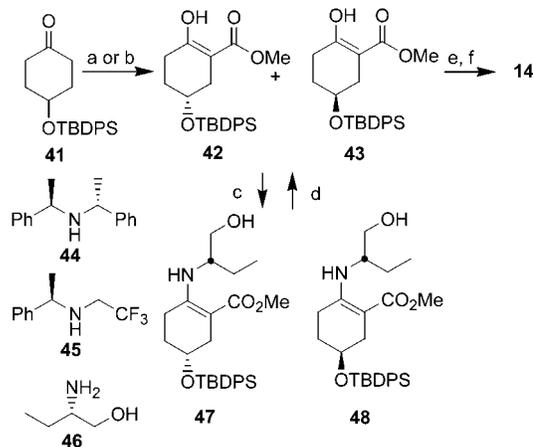
(18) Ruest, L.; Blouin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6* (3), 169.

SCHEME 5^a

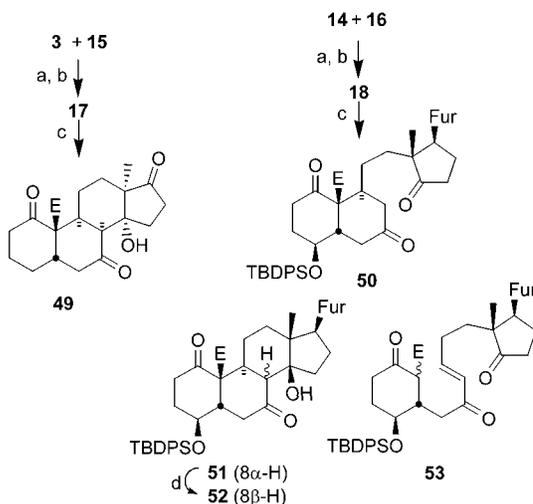
^a Reagents and conditions: (a) DMAP, refluxing toluene, 96%; (b) PhSeCl, pyridine, CH₂Cl₂ then H₂O₂, 98%; (c) i. 3-bromofuran, *n*-BuLi, THF, -78 °C. ii. 2-ThCuCNLi. iii. **29**, 70%; (d) MeOH, 150 °C, 93% for **31** and 100% for **27**; (e) KH, MeI, THF-DMF, 86%; (f) LiI~2H₂O, refluxing collidine, 89%; (g) *t*-BuOK, ethyl acrylate, *t*-BuOH, 65%; (h) DIBAL-H, THF; (i) Swern oxidation, 60% for 2 steps; (j) Ph₃P=C(Br)CO₂Me, refluxing benzene, 71% (*Z*:*E* = 4:1); (k) DIBAL-H, CH₂Cl₂, -78 to 0 °C, 80%; (l) Dess–Martin periodinane, CH₂Cl₂, 86% of **39** and 85% of **16**; (m) Zn, BrCH₂CO₂-*t*-Bu, THF, 99%.

effected with the chiral lithium amide derived from either amine **44** or **45**,²⁰ but the overall process involving carbomethoxylation with methyl cyanofornate²¹ yielded **43** as the major enantiomer in a rather poor 50% ee. Enantiomeric purity was increased to 80%, however, through condensation of the β-ketoesters mixture with (*S*)-2-aminobutanol **46**, followed by chromatographic separation of diastereomeric enamines **47** and **48** and further hydrolysis under acidic conditions. The usual sequential selenylation–oxidation finally led to chiral **14**.

The Nazarov reagent **15**, when reacted with cyclohexenone **3**, furnished tricyclic intermediate **17** (mixture of epimers at the *pro*-8 position) via double-Michael cycloaddition. Reduction with samarium(II) iodide²² gave the tetracyclic aldol product **49** (Scheme 7), for which the three-dimensional structure was ascertained by single-

SCHEME 6^a

^a Reagents and conditions: (a) NaH, KH (cat.), (MeO)₂CO, THF, 90% of **42** and **43** in 1:1 ratio; (b) **44** or **45**, *n*-BuLi, THF, -78 °C then CNCO₂Me, 79% of **42** and **43** in 1:4 ratio; (c) **46** neat, 55–60% of **47** and **48** in the same proportions as **42** and **43**, resolved by flash chromatography; (d) H₂SO₄(aq) 3 M, THF, 91%; (e) PhSeCl, pyridine, CH₂Cl₂; (f) H₂O₂(aq) 30%, CH₂Cl₂, 90% (2 steps).

SCHEME 7^a

^a Reagents and conditions: (a) Cs₂CO₃, CH₂Cl₂; (b) APTS, refluxing benzene, 65% of **17** for 2 steps and 56% of **18**; (c) SmI₂, THF, -78 °C, 84% of **49** from **17**; for reduction of **18**, see Table 1; (d) HCl anhyd., CH₂Cl₂, 90%.

crystal X-ray diffraction analysis.²³ It is noteworthy that the 13α-methyl, 14α-hydroxy configuration of **49** is the result of aldolization at the *pro*-*S* carbonyl of the cyclopentanedione unit of **17**, as observed previously.⁴ Tricyclic bromoketone **18** was obtained from the coupling between optically active cyclohexenone **14** and Nazarov reagent **16**. Upon reduction of the C–Br bond with samarium(II), the expected enolate **20** was produced nearly quantitatively, as only the reduced compound **50** was isolated after quenching at -78 °C (see Table 1). Warming up the reaction mixture allowed the aldolization to take place, and tetracyclic compounds **51** and **52** were obtained in varying ratios depending on the temperature and reaction time. At -20 °C, nearly only kinetic aldol product

(19) Compounds **42** and **43** have been found (¹H NMR analysis) to exist as a mixture of ketoesters and enol forms.

(20) (a) Majewski, M.; Lasny, R. *J. Org. Chem.* **1995**, *60*, 5825. (b) Bunn, B. J.; Cox, P. J.; Simpkins, N. *Tetrahedron* **1993**, *49*, 207.

(21) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(22) SmI₂ was freshly prepared following the known procedure: Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(23) We wish to thank M. Drouin (Université de Sherbrooke) for the crystallographic analysis.

TABLE 1. Reduction Products from Treatment of **18** with SmI_2

conditions (<i>T</i> , <i>t</i>)	isolated yield (%)			
	50	51	52	53
−78 °C, 0.5 h	78	0	0	0
−20 °C, 16 h	0	63	7	25
0 °C, 1.5 h	0	50	16	34
20 °C, 1 h	0	0	28	70

51 was obtained. In contrast, at room temperature, the more stable **52** was the only tetracyclic compound observed; however, it was accompanied by a larger amount of **53** resulting from a base-catalyzed fragmentation (retro-Michael) reaction from **50**–**52**.²⁴ Nevertheless, tetracyclic products were isolated in 70% (combined) yield by maintaining the reaction temperature between −20 and 0 °C. Moreover, substrate **52**, which has the correct stereochemistry for the synthesis of natural cardenolides, can be obtained by epimerization of **51** under acidic conditions in excellent yield.

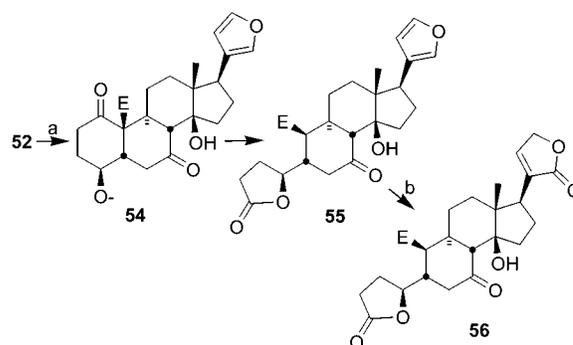
In an effort to ascertain the structure of **52** by X-ray crystallography, chemical derivatization was focused on the deprotection of the silyl ether functionality. Upon treatment of **52** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF, Scheme 8), the intermediate alkoxide **54** underwent a retro-Dieckmann rearrangement to yield γ -lactone **55**.²⁵ The furan unit was in turn oxidized, presumably by atmospheric oxygen during workup or storage, into butenolide **56**. Single-crystal X-ray diffraction analysis of **56** confirmed the absolute configuration of chiral centers at positions 4, 5, 8, 9, 13, 14, and 17 (Scheme 8).

Conclusion

Cardenolides are an important class of naturally occurring steroids, not only from the standpoint of their cardiotoxic activity but also because of the synthetic challenge they represent for the organic chemist. The double-Michael cycloaddition permitted rapid construc-

(24) The degradation cascade may be driven by efficient negative charge stabilization in the β -ketoester functionality of **53**, together with steric decompression of the tetracyclic (tricyclic) structures of **51** and **52** (**50**).

(25) This side reaction has already been observed in our laboratory with similar systems (Chapdelaine, D., Ph.D. Thesis, Université de Sherbrooke, 2001).

SCHEME 8^a

^a Reagents and conditions: (a) TASF, THF; (b) atmospheric oxygen, 70% for 2 steps.

tion of the AB fused ring unit. Completion of the anionic polycyclization triad via aldol condensation and ring C formation required selective enolization at the *pro*-8 position. α -Bromoketone as a regiospecific precursor of the $\Delta^{7,8}$ enolate fulfilled this latter requirement, and as such, highly valuable tetracyclic aldol products **51** and **52** were obtained with this strategy. Stereochemical control at C-8 was then achieved by thermodynamic epimerization.

The convergence of the overall process demonstrates the power of the anionic polycyclization strategy for the total synthesis of complex natural cardenolides. Applications of this attractive method for the total synthesis of this important subset of naturally occurring steroids are currently underway in our laboratory.

Acknowledgment. Financial support provided by BioChem Pharma Inc. (Basic Research Chair to P. Deslongchamps), Fonds FCAR, and NSERCC (for scholarships to D. Chapdelaine) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all new compounds; ¹H NMR spectra for all compounds, ¹³C NMR spectra for **47** and **48**, and ORTEP representations for **49** and **56**. This material is available free of charge via the Internet at <http://pubs.acs.org>. The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre: **49** (CCDC 179214) and **56** (CCDC 179215).

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