Natural Product Synthesis

DOI: 10.1002/anie.201302067

# A Convergent Total Synthesis of 19-Hydroxysarmentogenin**

*Ken Mukai, Daisuke Urabe, Satoshi Kasuya, Naoto Aoki, and Masayuki Inoue**

*Crossopetalum gaumeri* (Loes.), a medical plant among the Yucatec Mayan community, contains various highly cytotoxic natural products, including 19-hydroxysarmentogenin-3β-*O*-β-6-deoxyguloside (Figure 1).[1] This compound belongs to a family of cardenolides and bufadienolides, which are

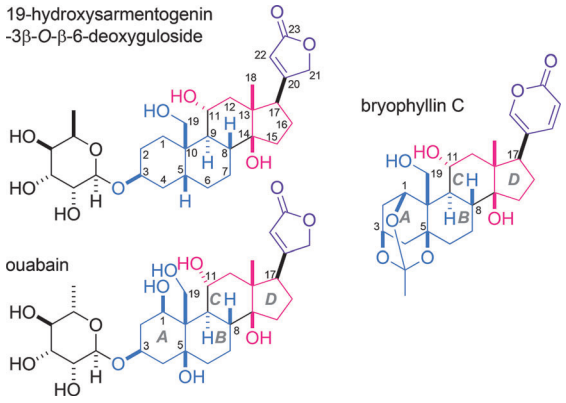
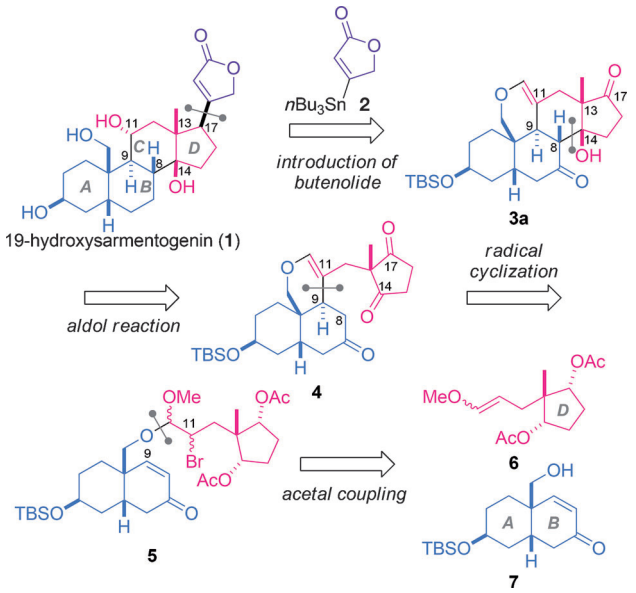



***Figure 1.*** Structures of cardenolides and bufadienolides.

typified by ouabain[2] and bryophilin C.[3,4] Cardenolides and bufadienolides have been used for hundreds of years in both Western and Eastern medicine, and share the capacity to slow the heart rate and to increase the force of contraction of heart muscle tissue.[5] The positive inotropic activity is attributed to a high affinity inhibitory interaction with the extracellular surface of the membrane-bound sodium pump ($Na^+/K^+$-ATPase) responsible for $Na^+/K^+$ exchange. In addition to their cardiac activity, these molecules exhibit strong cytotoxic activity against various cultured human cancer cells.[5] Accordingly, their potential use in oncology has been investigated. Furthermore, cardenolides and bufadienolides have been identified in mammalian tissues and plasma, and thus these compounds are also considered as endogenous factors to regulate physiological phenomena.[6]

Cardenolides and bufadienolides share a characteristic steroid-like framework that is distinct from conventional androstane/pregnane-type steroids in that they have *cis* A/B and C/D ring junctions, a tertiary 14β-hydroxyl group, and a 17β-unsaturated lactone. The unusual structural features render these natural products formidable targets for total synthesis. Numerous laboratories have reported synthetic studies on these natural products,[7,8] which has culminated in the successful total syntheses of ouabain by the Deslongchamps group and ouabagenin, its aglycon, by Baran.[9]

We became interested in devising a unified convergent strategy that would be applicable to the various biologically important cardenolide/bufadienolide structures alike. To establish such a strategy, we selected 19-hydroxysarmentogenin (**1**, Scheme 1), an aglycon of 19-hydroxysarmentogenin-3β-*O*-β-6-deoxyguloside, as the initial target. Herein, we report the total synthesis of **1** through the coupling of three readily available fragments.




***Scheme 1.*** Synthetic plan for 19-hydroxysarmentogenin (**1**).

The structural differences among the cardenolides and bufadienolides mainly arise from the substitutions at C1, C3, and C5 of the A ring, and the unsaturated lactone at C17, whereas the structures from C6 to C19 are conserved (Figure 1). Recognition of these varied and common motifs allowed us to retrosynthetically divide these molecules into two-variable (color-coded in cyan and purple) and one-consensus substructures (color-coded in pink). As shown in Scheme 1, the three simple fragments, chiral AB ring **7** (cyan), *meso*-D ring **6** (pink), and butenolide **2** (purple), were

[*] K. Mukai, Dr. D. Urabe, Dr. S. Kasuya, N. Aoki, Prof. Dr. M. Inoue
Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: inoue@mol.f.u-tokyo.ac.jp

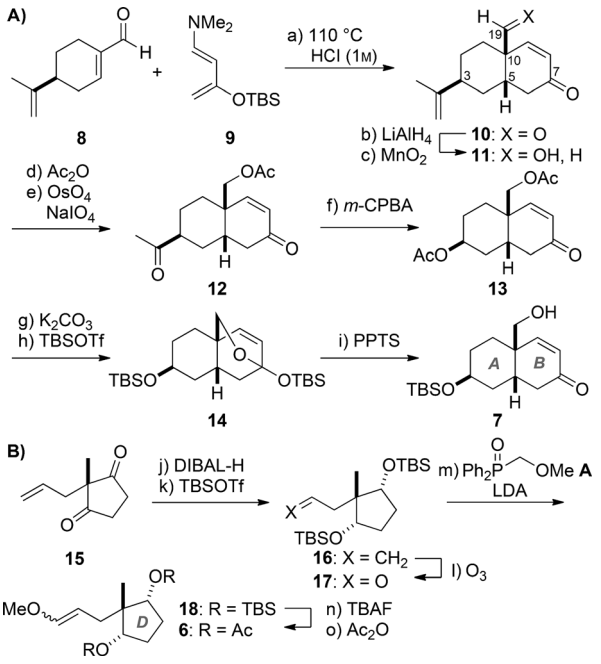
[**] This research was financially supported by the Funding Program for Next Generation World-Leading Researchers (JSPS) to M.I. and a Grant-in-Aid for Young Scientists (B) (JSPS) to D.U. A fellowship from JSPS to S.K. is gratefully acknowledged. We thank Dr. Kenji Yoza (Bruker AXS) for X-ray crystallographic analyses.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302067.

specifically designed for **1**, and were to be assembled into the entire structure in a convergent fashion. It was envisioned that other cardenolides and bufadienolides would be obtained by use of structural variants of **7** and **2** with the same **6**.

This convergent strategy required the correct introduction of six stereocenters (C8, 9, 11, 13, 14, 17) in the transformation from **7** into **1** (Scheme 1). Stereoselective construction of the C ring through formation of the two C–C bonds from chiral **7** and *meso*-**6** was especially challenging and was expected to require two key intramolecular reactions: 1) radical cyclization of bromide **5**, which was prepared by acetal tethering of **7** and **6**, would install the C9-stereocenter of **4**, and 2) the aldol reaction of **4** would simultaneously control the stereochemistry at C8, C13, and C14 of **3a**. Stereoselective attachment of butenolide **2** to **3a** would then lead to the target structure, **1**.

AB ring **7** was prepared in nine steps from (*S*)-perillaldehyde **8** (Scheme 2A). Diels–Alder reaction between **8**




***Scheme 2.*** Reagents and conditions: a) toluene, reflux; HCl (1 M), THF, RT, 78%; b) $LiAlH_4$, $Et_2O$, −78 °C to RT; c) $MnO_2$, $CH_2Cl_2$, RT, 66% (2 steps); d) $Ac_2O$, $Et_3N$, $CH_2Cl_2$, RT, 99%; e) $OsO_4$, $NaIO_4$, 2,6-lutidine, $H_2O$, dioxane, RT, 94%; f) *m*-CPBA, $CH_2Cl_2$, RT, 67%; g) $K_2CO_3$, MeOH, RT, 92%; h) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, RT; i) PPTS, $H_2O$, MeOH, 0 °C, 99% (2 steps); j) DIBAL-H, $CH_2Cl_2$, −78 °C, 63%; k) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, RT, 96%; l) $O_3$, $CH_2Cl_2$, −78 °C; $Ph_3P$, RT, 80%; m) **A**, LDA, THF, RT, 71% (*E*/*Z* = 1:1.2); n) TBAF, THF, 60 °C; o) $Ac_2O$, pyridine, DMAP, RT, 84% (2 steps). DIBAL-H = diisobutylaluminum hydride, DMAP = *N*,*N*-dimethyl-4-amino pyridine, LDA = lithium diisopropylamide, *m*-CPBA = *meta*-chloroperoxybenzoic acid, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

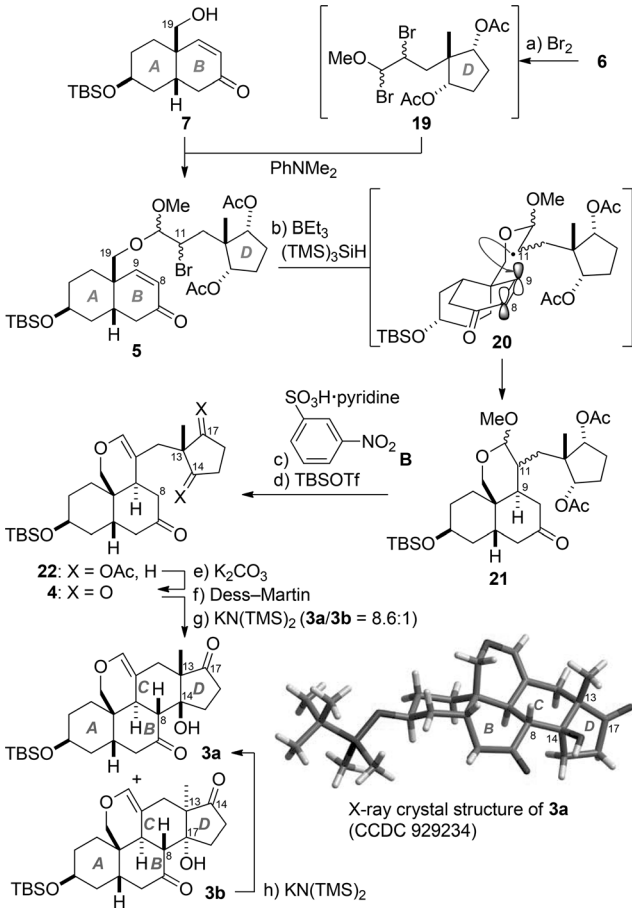
and the Rawal diene **9**,[10] followed by acidic treatment, resulted in stereoselective formation of *cis*-fused enone **10** with the requisite C5 and C10 stereocenters.[11] The two carbonyl groups of **10** were reduced with $LiAlH_4$ to give the corresponding hydroxy groups, and chemoselective oxidation of the C7 allylic alcohol afforded **11**. After acetylation of the primary alcohol of **11**, the C3 isopropenyl group was oxidatively converted into the methyl ketone of **12**. A Bayer–Villiger reaction of **12** using *meta*-chloroperoxybenzoic acid stereoselectively introduced the C3 acetoxy functional group. Next, the two acetyl groups of **13** were removed by methanolysis to provide the diol, the treatment of which with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine gave rise to bis(TBS) ether **14**. Finally, the internal acetal of **14** was transformed into the corresponding keto alcohol of the requisite fragment **7** by the action of pyridinium *para*-toluenesulfonate (PPTS) in methanol.

Because of its *meso* symmetry, D ring **19** was readily synthesized through six functional group manipulations from the known *meso* diketone **15**[12] (Scheme 2B). Stereoselective diisobutylaluminum hydride reduction of **15** and subsequent TBS protection of the resultant hydroxy groups afforded **16**. Ozonolysis of **16** produced aldehyde **17**, which was subjected to the Horner–Wittig reaction with **A** to provide enol ether **18**. A two-step manipulation of the protecting group converted TBS-protected **18** into acetyl-protected **6**.

Pentacycle **3a** was obtained from the prepared AB and D ring fragments **7** and **6** in only seven steps involving two cyclizations (Scheme 3). Before the first radical cyclization, the acetal tether of **5** was formed. Enol ether **6** was treated with bromine to give dibromide **19**. The bromine atom of **19** adjacent to the methoxy group was highly reactive towards nucleophiles, and thus was replaced in situ by the C19 oxygen of **7** in the presence of dimethyl aniline to furnish acetal **5**.[13] The remaining C11 bromine atom of **5** was then homolytically cleaved by treatment with $(TMS)_3SiH$ (TMS = trimethylsilyl) and $Et_3B$,[14] and the resultant C11 carbon radical **20** reacted with the C8=C9 bond from the top face of the molecule owing to the constraint of the acetal linkage. As a result, the C9–C11 bond was formed in the desired fashion, leading to the fused tricycle **21**.

Having successfully installed the C9 stereocenter, the substrate of the second cyclization was synthesized from **21**. The diastereomers **21** at the acetal and C11 positions were merged into the single isomer **22** by acid-induced vinyl ether formation,[15] thus generating **22** after reprotection of the partially desilylated C3 hydroxy group. Deacetylation of **22** and oxidation of the liberated hydroxy groups with Dess–Martin reagent[16] provided triketone **4**, the substrate for the crucial aldol reaction. Cyclization of the C ring required chemoselective C8 enolate formation and subsequent regio- and stereoselective attack on the C14 ketone in the presence of the C17 ketone for the correct installation of the C8, C13 and C14 stereocenters. To realize these selectivities, we screened the reagents and conditions, and found that a catalytic amount of $KN(TMS)_2$ (10 mol%) in refluxing THF induced C8–C14 bond formation to deliver the desired **3a** as the major product (**3a**/**3b** = 8.6:1) in a quantitative combined yield. Treatment of the isolated minor isomer **3b** with $KN(TMS)_2$ led to **3a**, thus indicating the thermodynamically controlled nature of the present aldol reaction. X-ray crystallographic analysis of **3a** established its characteristic three-dimensional structure. Interestingly, the B ring of **3a**




***Scheme 3.*** Reagents and conditions; a) **6** (2 equiv), $Br_2$, $CH_2Cl_2$, −78 °C; **7** (1 equiv), $PhNMe_2$, −78 °C to RT; b) $Et_3B$, $(TMS)_3SiH$, $O_2$, toluene, −65 °C; c) **B**, toluene, reflux; d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 65% (4 steps from **7**); e) $K_2CO_3$, MeOH, RT; f) Dess–Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, RT, 86% (2 steps); g) $KN(TMS)_2$ (10 mol%), THF, reflux, 100% (**3a**/**3b** = 8.6:1); h) $KN(TMS)_2$ (30 mol%), THF, reflux, 66% (**3a**/**3b** = 12:1). TMS = trimethylsilyl.

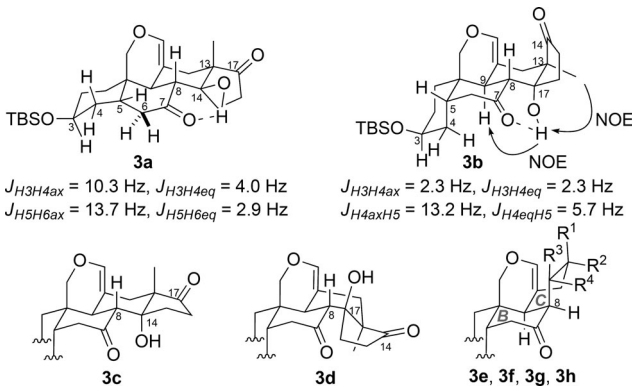



***Figure 2.*** Eight isomers potentially generated by the aldol reaction of **4**.

adopts the boat conformation in the X-ray and NMR structures, whereas the NMR data indicated the chair conformation of the B ring of **3b** (Figure 2).

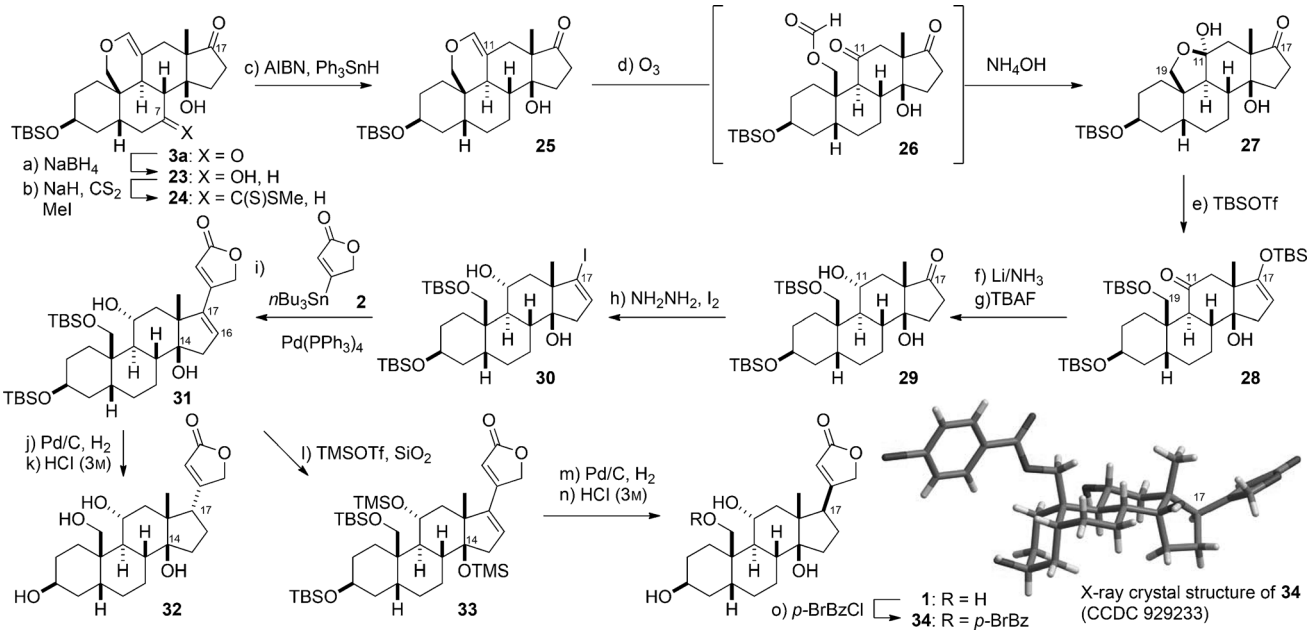
The aldol reaction generated only one major product, **3a**, out of the eight diastereomers (**3a**–**h**) possible under the thermodynamic conditions (Figure 2).[17] The *cis*-fused BC rings of diastereomers **3e**–**h** cause an unfavorable steric interaction between the C ring and the enol ether ring, and the *trans*-fused 6/5 ring system of **3c** or **3d** is more strained than its *cis* counterpart in **3a** or **3b**.[18] Thus, **3a** and **3b** are preferred over the other six diastereomers **3c**–**h**. Although compounds **3a** and **3b** would both be stabilized by hydrogen bonding, the lone pair of the C7 carbonyl group is more properly oriented toward the proton of the proximal hydroxy group in **3a** than in **3b**, and this factor is attributed to the selective formation of **3a** over **3b**.

Our total synthesis of **1** was completed from pentacycle **3a** through a 12-step sequence including attachment of the butenolide moiety (Scheme 4). The C7 ketone of **3a** was first chemoselectively reduced using $NaBH_4$ in the presence of the C17 ketone to produce **23**. Treatment of alcohol **23** with NaH, $CS_2$, and MeI led to the corresponding xanthate **24**, which underwent deoxygenation by the action of $Ph_3SnH$ and 2,2′-azobisisobutyronitrile to provide **25**.[19] Ozonolysis of the vinyl ether of **25** liberated the C11 oxygen functional group as the ketone, giving rise to **26**, which was deformylated with $NH_4OH$ to afford hemiacetal **27**. When **27** was subjected to the reagent mixture of TBSOTf, $Et_3N$, and $LiN(TMS)_2$,[20] the C19 primary alcohol and the C17 ketone were protected to give **28**. The remaining C11 ketone of **28** in turn underwent a stereoselective Birch reduction, and the TBS-enol ether was selectively desilylated with tetra-*n*-butylammonium fluoride in the presence of the other two TBS ethers to regenerate the C17 ketone of **29**. Ketone **29** was then transformed into vinyl iodide **30** using hydrazine and iodine.[21] Stille coupling[22] of iodide **30** and stannane **2**[23] using $Pd(PPh_3)_4$, LiCl, and CuCl[24] introduced the butenolide onto the steroid structure to furnish the adduct **31**.

The last requisite stereoselective transformation was hydrogenation of the C16=C17 bond to obtain the β-oriented butenolide. However, hydrogen in the presence of Pd/C added from the convex β-face of the *cis*-fused CD ring structure of **31**, resulting in the formation of 17-*epi*-19-hydroxysarmentogenin **32** after deprotection. Thus, to invert the face selectivity of the hydrogenation, the convex face of the CD ring was sterically shielded by the introduction of a bulky TMS group at the C14 tertiary alcohol to generate **33**. Hydrogenation of **33** under the same conditions indeed proceeded from the α face to give rise to the desired compound in high selectivity (d.r. = 6:1). Finally, the four silyl groups were removed under acidic conditions to deliver 19-hydroxysarmentogenin (**1**). The stereostructure of **1** was unambiguously confirmed by X-ray crystallographic analysis of the corresponding C19-*p*-bromobenzoate **34**.

In summary, the total synthesis of 19-hydroxysarmentogenin (**1**) was accomplished in a convergent fashion using three simple fragments: AB ring **7**, D ring **6**, and butenolide **2**. Salient methods employed in our successful synthesis include: 1) radical cyclization to install the C9 stereocenter of **21**, 2) intramolecular aldol reaction to form thermodynamically stable **3a** out of eight possible stereoisomers, and 3) stereoselective hydrogenation of **33** by controlling the steric bias of




***Scheme 4.*** Reagents and conditions: a) $NaBH_4$, THF, RT, (**23α/23β** = 2:1); b) NaH, THF; $CS_2$, MeI, −50 °C; c) AIBN, $Ph_3SnH$, benzene, reflux, 50% (3 steps); d) $O_3$, MeOH, −78 °C; $Me_2S$, RT; $NH_4OH$, 75%; e) TBSOTf, $Et_3N$, $CH_2Cl_2$, −60 °C; $LiN(TMS)_2$, RT, 83%; f) Li, $NH_3$, THF, −78 °C, 95%; g) TBAF, THF, −78 °C, 94%; h) $(H_2N)_2{\cdot}H_2O$, $Et_3N$, EtOH, 50 °C; $I_2$, $Et_3N$, THF, RT, 91%; i) **2**, $Pd(PPh_3)_4$ (20 mol%), LiCl, CuCl, DMSO, 60 °C, 89%; j) Pd/C, $H_2$, AcOEt, RT; k) HCl (3 M), MeOH, RT, 78% (2 steps); l) TMSOTf, 2,6-lutidine, $CH_2Cl_2$, RT; $SiO_2$, 81%; m) Pd/C, $H_2$, AcOEt, RT, 73%; n) HCl (3 M), MeOH, RT, 82%; o) *p*-BrBzCl, DMAP, $CH_2Cl_2$, RT, 65%. AIBN = 2,2′-azobisisobutyronitrile, Bz = benzoyl, DMSO = dimethylsulfoxide.

the substrate. Overall, the polycyclic architecture of **1** with nine stereocenters was efficiently constructed from (*S*)-perillaldehyde **8** with one chiral center in 28 steps. Application of this convergent strategy to other cardenolides and bufadienolides by changing the fragment structures is currently underway in our laboratory.

Received: March 12, 2013
Published online: April 15, 2013

**Keywords:** aldol reaction · convergent strategy · radical reactions · steroids · total synthesis

[1] a) B. Kopp, W. Kubelka, *Planta Med.* **1982**, *45*, 195; b) A. Ankli, J. Heilmann, M. Heinrich, O. Sticher, *Phytochemistry* **2000**, *54*, 531.

[2] L. F. Fieser, M. Fieser, *Steroids*, Reinhold, New York, **1959**, Chap. 20.

[3] U. Supratman, T. Fujita, K. Akiyama, H. Hayashi, *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1310.

[4] For reviews, see: a) P. S. Steyn, F. R. van Heerden, *Nat. Prod. Rep.* **1998**, *15*, 397; b) A. A. Agrawal, G. Petschenka, R. A. Bingham, M. G. Weber, S. Rasmann, *New Phytol.* **2012**, *194*, 28.

[5] a) I. Prassas, E. P. Diamandis, *Nat. Rev. Drug Discovery* **2008**, *7*, 926; b) H. Gao, R. Popescu, B. Kopp, Z. Wang, *Nat. Prod. Rep.* **2011**, *28*, 953.

[6] a) M. Nesher, U. Shpolansky, H. Rosen, D. Lichtstein, *Life Sci.* **2007**, *80*, 2093; b) A. Y. Bagrov, J. I. Shapiro, O. V. Fedorova, *Pharmacol. Rev.* **2009**, *61*, 9.

[7] For a recent review of synthetic studies on cardenolides and bufadienolides, see: B. Heasley, *Chem. Eur. J.* **2012**, *18*, 3092.

[8] For the total syntheses of digitoxigenin, see: a) G. Stork, F. West, H. Y. Lee, R. C. A. Isaacs, S. Manabe, *J. Am. Chem. Soc.* **1996**, *118*, 10660; b) M. Honma, M. Nakada, *Tetrahedron Lett.* **2007**, *48*, 1541; for the total synthesis of rhodexin A, see: c) M. E. Jung, D. Yoo, *Org. Lett.* **2011**, *13*, 2698; for the semi synthesis of digitoxin, see: d) K. Wiesner, T. Y. R. Tsai, *Pure Appl. Chem.* **1986**, *58*, 799; for the semi synthesis of strophanthidin, see: e) P. Kočvsky, I. Stieborová, *Tetrahedron Lett.* **1989**, *30*, 4295; for recent synthetic studies on cardenoloids, see: f) W. Deng, M. S. Jensen, L. E. Overman, P. V. Rucker, J. P. Vionnet, *J. Org. Chem.* **1996**, *61*, 6760; g) L. E. Overman, P. V. Rucker, *Tetrahedron Lett.* **1998**, *39*, 4643; h) Z. Yang, D. Shannon, V.-L. Truong, P. Deslongchamps, *Org. Lett.* **2002**, *4*, 4693; i) L. Chen, P. Delongchamps, *Can. J. Chem.* **2005**, *83*, 728; j) M. E. Jung, P. Davidov, *Angew. Chem.* **2002**, *114*, 4299; *Angew. Chem. Int. Ed.* **2002**, *41*, 4125; k) M. E. Jung, G. Piizzi, *J. Org. Chem.* **2003**, *68*, 2572.

[9] a) H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem.* **2008**, *120*, 1292; *Angew. Chem. Int. Ed.* **2008**, *47*, 1272; b) M. S. Reddy, H. Zhang, S. Phoenix, P. Deslongchamps, *Chem. Asian J.* **2009**, *4*, 725; c) H. Renata, Q. Zhou, P. S. Baran, *Science* **2013**, *339*, 59.

[10] S. A. Kozmin, J. M. Janey, V. H. Rawal, *J. Org. Chem.* **1999**, *64*, 3039.

[11] K. Tiefenbacher, J. Mulzer, *Angew. Chem.* **2008**, *120*, 6294; *Angew. Chem. Int. Ed.* **2008**, *47*, 6199.

[12] a) H. J. Bestmann, G. Schade, H. Lüike, T. Mönius, *Chem. Ber.* **1985**, *118*, 2640; b) T. Mandai, Y. Kaihara, J. Tsuji, *J. Org. Chem.* **1994**, *59*, 5847.

[13] a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya, M. Okawara, *J. Am. Chem. Soc.* **1982**, *104*, 5564; b) G. Stork, R. Mook, Jr., S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741; for a review, see: c) X. J. Salom-Roig, F. Denes, P. Renaud, *Synthesis* **2004**, 1903.

[14] a) K. Nozaki, K. Oshima, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547; for a review, see: b) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415.
[15] D. Nakagawa, M. Miyashita, K. Tanino, *Tetrahedron Lett.* **2010**, *51*, 2771.
[16] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
[17] Related intramolecular aldol reactions using the *pseudo-meso* D ring have been reported. However, one-step introduction of the correct C8, C13, and C14 stereochemistry of the cardenolides has not previously been achieved. The unique stereoselectivity and high yield of the present aldol reaction should be influenced by the presence of the additional enol ether ring in **4**; see: a) A. R. Daniewski, P. S. White, Z. Valenta, *Can. J. Chem.* **1979**, *57*, 1397; b) S. P. Douglas, J. F. Sawyer, P. Yates, *Tetrahedron Lett.* **1985**, *26*, 5955; c) J.-F. Lavallée, P. Delongchamps, *Tetrahedron Lett.* **1988**, *29*, 6033; d) R. Ruel, P. Deslongchamps, *Can. J. Chem.* **1990**, *68*, 1917; e) R. Ruel, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1939; f) D. Chapdelaine, J. Belzile, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5669.
[18] H. L. Gordon, S. Freeman, T. Hudlicky, *Synlett* **2005**, 2911.
[19] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.
[20] $LiN(TMS)_2$ was used to shift the equilibrium from the C11 acetal form to the corresponding keto form.
[21] D. H. R. Barton, R. E. O'Brien, S. Sternhell, *J. Chem. Soc.* **1962**, 470.
[22] a) Z. Liu, J. Meinwald, *J. Org. Chem.* **1996**, *61*, 6693; for a review on the Stille coupling, see: b) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1.
[23] G. J. Hollingworth, G. Perkins, J. B. Sweeney, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1913.
[24] X. Han, B. M. Stoltz, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 7600.