The Total Synthesis of a Natural Cardenolide: (+)-Digitoxigenin

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Received June 26, 1996

It has been said that the active components in the *Digitalis* extracts have been "the most ingested drugs in medicine".[1] These substances, usually called cardenolides, differ from ordinary steroids in three major respects: the C/D ring system is cis rather than trans fused, there is a tertiary hydroxyl at C-14, and the substituent at C-17 (a butenolide) is in the thermodynamically less stable β orientation.[2] As might be expected, many partial syntheses of cardenolides have been described starting with readily available steroids.[3,4]

We now report the total synthesis of natural (+)-digitoxigenin (**1**), the biologically active cardenolide which, as its trisaccharide derivative digitoxin, is one of the most frequently used of the active principles isolated from *Digitalis* species.

We divided the synthesis, which we carried out both to racemic and to natural (+)-digitoxigenin, in three parts: synthesis of the tricyclic enone **2**; elaboration of the fused 5-membered ring D to produce a tetracyclic system bearing both a 14-β-hydroxy substituent and a substituent at C-17 capable of further transformation; and, finally, elaboration of that substituent to the β-oriented butenolide system.

We chose to approach the construction of the tricyclic enone **2** via an intramolecular [4 + 2] cycloaddition, as schematized in Figure 1.

We initiated the synthesis from the monoketal (−)-**3**, prepared by applying to the readily available (*S*)-enantiomer of the Wieland Miescher ketone,[5] the sequence previously described[6] using its racemate. Ozonolysis of the trimethylsilyl enol ether of **3** gave, in a not unprecedented reaction,[7] a mixture of α-hydroxy ketones which was reduced ($NaBH_4$) to the corresponding glycols, followed by cleavage with periodate to the dialdehyde **4** (71% overall yield from **3**). The two aldehyde groups in **4** now had to be differentially elaborated.

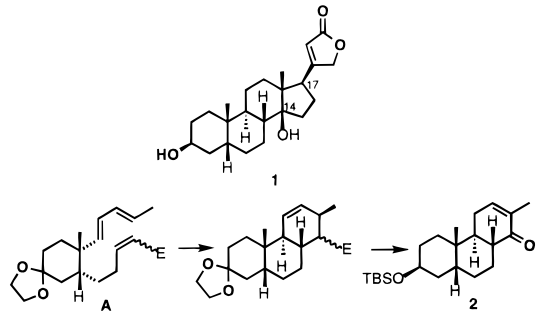
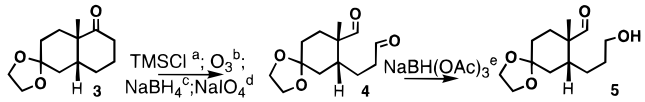


Figure 1.



Key: (a) NEt_3, DMF; 95%; (b) CH_2Cl_2/MeOH; DMS; 80% ketol; (c) MeOH, −20 °C to room temp.; (d) CH_2Cl_2/H_2O, 0 °C; 71% from **3**; (e) benzene; 67%.

We found the aldehyde alcohol **5**, which was formed (57%) by the selective reduction of **4** with sodium triacetoxyborohydride, to be useful for that purpose. Its condensation by the method of Yamamoto[8] with the lithio carbanion from (*E*)-2-butenyldiphenylphosphine oxide[9] cleanly led (77%) to the desired (*E*,*E*)-1,3- pentadienyl substituent,[10] which, after Swern oxidation, gave us the proper enantiomer **6** of the dienyl aldehyde that we had previously made by a different route in the *dl* series (vide supra). A variety of dienophiles could easily be made from the aldehyde function of **6**. However, even though some obvious candidates (cf., **A**, Figure 1, E = CN or NO_2) underwent ready intramolecular [4 + 2] cycloaddition, we were unable to transform these adducts into the required enone. Fortunately, the conjugated dithiane **7**, easily prepared by reaction of **6** with the appropriate dithiane phosphonate,[11] solved the problem, since it underwent the required cycloaddition (61%) at 180 °C.[12] Two new asymmetric centers are formed in the cycloaddition process, but the required orientation shown in **8** was anticipated from the endo transition state **8a** which we expected to be the lowest energy conformation. The high temperature required for the cycloaddition suggested that this expectation be viewed with some caution, but the stereochemistry shown in **8** was confirmed by X-ray analysis.[13] Conversion of the cyclic ketal at C-3 to a β-hydroxyl group was performed at this stage: acid hydrolysis to **9**, followed by

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(1) Inter alia: (a) Aronson, J. K. *An Account of the Foxglove and its Medicinal Uses 1785−1985*; Oxford University Press: London, 1985. (b) *Cardiac Glycosides*; Erdmann, E., Greff, K., Skou, J. C., Eds.; International Boehringer Mannheim Symposia; Springer Verlag: New York, 1986. (c) *Digitalis Glycosides*; Smith, Th., Ed.; Grime & Stratton, Inc.: Orlando, FL, 1986. (d) Gunthert, Th. W.; Linde, H. H. A. *Experientia* **1977**, *33*, 697.

(2) See: Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing Corp.: New York, 1959; Chapter 20.

(3) (a) Danieli, N.; Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc*. **1962**, *84*, 875. (b) For a review of early work, see: Sondheimer, F. *Chem. Br*. **1965**, *1*, 454. (c) Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733 and references therein. (d) Fritsch, W.; Haede, W.; Radscheit, K.; Stache, U.; Ruschig, H. *Liebigs Ann. Chem.* **1974**, 621. (e) Yoshii, E.; Koizumi, T.; Ikeshima, H.; Uzaki, K.; Hayashi, I. *Chem. Pharm. Bull*. **1975**, *23*, 2496. (f) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett*. **1979**, 3287. (g) Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem*. **1981**, *59*, 1403. (h) Kocovsky, P.; Cerny, V. *Coll. Czech. Commun.* **1981**, *46*, 446. (i) Welzel, P.; Stein, H.; Milkova, T. *Liebigs Ann. Chem.* **1982**, 2119. (j) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Chem. Commun*. **1983**, 985. (k) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, *50*, 1990. (l) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem*. **1986**, *58*, 799. (m) Kutney, J. P.; Piotrowska, K.; Somerville, J.; Huang, S. P.; Rettig, S. J. *Can. J. Chem*. **1989**, *67*, 580. (n) Groszek, G.; Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron* **1989**, *45*, 2223. (o) Kocovsky, P.; Stieborova, I. *Tetrahedron Lett.* **1989**, *30*, 4295.

(4) For some total synthesis contributions, see: (a) Stryker, J. M. *Diss. Abstr. Int. B* **1984**, *24*, 2432. (b) Daniewski, A. R.; Kabat, M. M.; Masnyk, M.; Wicha, J.; Wojciechowska, W. *J. Org. Chem*. **1988**, *53*, 4855 (for an interesting total synthesis of the 9,11-dehydro relative of a digitoxigenin derivative). (c) Ruel, R.; Deslongchamps, P. *Tetrahedron Lett*. **1990**, *31*, 3961 (d) Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347.

(5) Buchschacher, P.; Furst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, 368. Gutzwiller, J.; Buchschacher, P.; Furst, A. *Synthesis* **1977**, 167.

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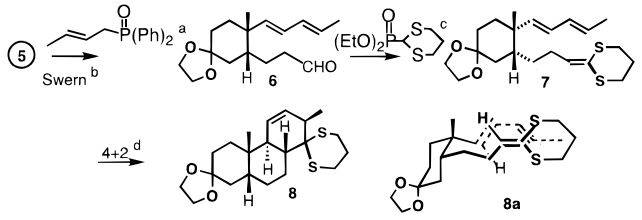
(9) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2386.

(10) In contrast, the use of the corresponding phosphonate gave a 4:1 *E*,*E* and *Z*,*E* mixture of dienes.

(11) Mlotkowska, B.; Gross, H.; Costisella, B.; Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A. *J. Prakt. Chem*. **1977**, *319*, 17.

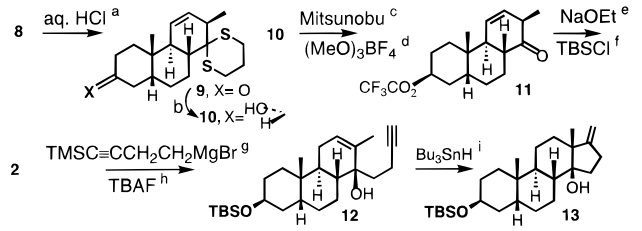
(12) Dr. J. Stelmach, in these laboratories, has recently found that a closely related intramolecular addition takes place in essentially quantitative yield at a sand bath temperature of ∼280 °C (internal temperature ∼200 °C).

S0002-7863(96)02163-4 CCC: $12.00



Key: (a) BuLi, THF/HMPA, 0 °C; room temp. 9 h; 77%; (b) 78%; (c) BuLi, THF, −78 to 0 °C; quantitative; (d) toluene, sealed tube, 200 °C, 36 h; 75%.

sodium borohydride reduction, gave the 3-α-hydroxy compound **10** which was then inverted to the 3-*β*-trifluoroacetate by a Mitsunobu reaction.[14] Cleavage of the dithiane by reaction with trimethyloxonium fluoborate[15] gave the *β*,*γ*-unsaturated ketone **11**, and the ring C double bond was now brought into conjugation by short treatment with sodium ethoxide, simultaneously releasing the required 3-*β* hydroxyl group. Protection of the latter as its *tert*-butyldimethylsilyl derivative finally gave the substance which had been the goal of the first phase of our digitoxigenin synthesis, the siloxyenone **2**.

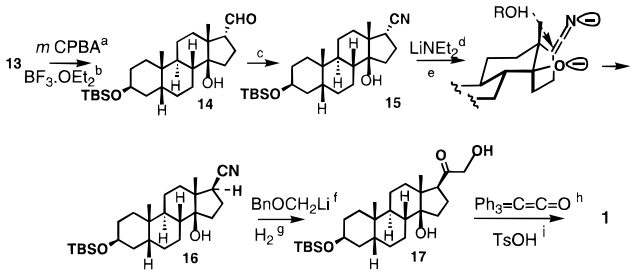


Key: (a) 1 N, THF, acetone; 80%; (b) $NaBH_4$, $CeCl_3$, EtOH; α-OH 72%; *β*-OH 6.5%; (c) DEAD, TFA, Ph_3P, BzONa, THF; 74%; (d) 81%; (e) EtOH; 79%; (f) imidazole, DMF; 99%; (g) THF, room temp. 75%; (h) Et_2O, room temp.; 89%; (i) AIBN, benzene, then SiO_2; 40%.

Elaboration of the C/D system began by addition of the Grignard reagent from the 1-trimethylsilyl derivative of 4-bromo-1-butyne. After selective desilylation (TBAF in ether), the butynylcyclohexenol **12** was obtained, stereospecifically, in 67% yield. This was the expected result because we had established earlier[16] that unhindered Grignard reagents undergo selective axial 1,2-addition to rigid cyclohexenone systems like **2**. The butyne side chain had been chosen because it appeared uniquely suitable for the application of the vinyl radical cyclization process.[17] In fact, reaction of **12** with tributylstannane, under radical conditions, led after destannylation with silica gel to the desired tetracyclic system **13**, mp 134−136 °C, in 40% yield.[18]

It remained only to transform the exocyclic methylene at C-17 into the required 17-*β*-butenolide to complete the synthesis.

A sequence involving oxidation of the methylene of **13** with perbenzoic acid, followed by BF_3-catalyzed rearrangement of the resulting epoxide to an aldehyde, led (66% overall yield) to a 17-aldehyde, but this proved, however, to be largely (9:1) *the unwanted, more stable,* α epimer **14**.[19] Transformation of that unwanted mixture into a 17-*β* substituent followed realization that increasing the effective size of the 14-*β* hydroxyl (pseudo-axial to ring D) should result in kinetic protonation from the α face, even though it is the concave face of the C/D system: Conversion of **14** to the corresponding α-nitrile **15** (93%), followed by formation of the dianion and protonation with 2,6-di-*tert*-butyl-4-methylphenol[21] gave the desired 17-*β*-cyano compound **16** as the major component of the recovered nitriles (90%; *β*/α > 4:1). The same result was obtained by performing the deprotonation−protonation sequence on the *trimethylsilyl ether* of the 14-hydroxyl (TMS triflate, 100%). In either case, the undesired isomer was easily separated and recycled.[21]



Key: (a) $NaHCO_3$; 90%; (b) −78 °C to room temp.; 70%; (c) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, then carbonyldiimidazole, CH_2Cl_2, room temp.; 95%; (d) 10 equiv, THF, 0 °C, 30 min; (e) BHT, THF, 30 min; 73%; (f) THF, −78 °C; 89%; (g) 10% Pd/C, EtOH; 96%; (h) NEt_3, benzene; 74%; (i) MeOH, room temp., 24 h; 97%.

Now that the C-17 stereochemistry problem had been solved, completion of the total synthesis required only three additional high-yield steps. Reaction of **16** with (benzyloxy)methyllithium,[22] followed by hydrogenolysis over Pd/C, gave (∼75%) the 21-hydroxy-20-ketone **17**, mp 169−171 °C, $[\alpha]^{24}_D$ + 38.5. Reaction of the latter with triphenylphosphoranylidene ketene[23] and liberation of the 3-hydroxyl group from its silyl ether, gave (+)-digitoxigenin (**1**), identical in all respects (^1H and ^{13}C NMR, high- and low-resolution mass spectrum, and rotation $[\alpha]^{23}_D$ + 18.0 (c = 0.87, MeOH); reported $[\alpha]^{17}_D$ + 19.0 (c = 1.36)[24]) with authentic material.

Acknowledgment. We thank the National Institutes of Health for the support of this work and for a postdoctoral Fellowship to F. West.

Supporting Information Available: Experimental details, mass, NMR spectra, etc., are given for the synthesis of all the intermediates to (+)-digitoxigenin (17 pages). See any curent masthead page for ordering and Internet access instructions.

JA962163M

(13) Performed on the 3-dioxolane, mp ≈ 125 °C, of the racemic substance. We thank Kirsten Folting of the Molecular Structure Center of the Chemistry Department of Indiana University for this determination.

(14) For example, see: Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem*. **1987**, *52*, 4235.

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(16) (a) Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887. (b) Trost, B. M.; Flores, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613.

(17) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. One important feature of vinyl radicals which is especially useful here is that they should be less sensitive to hindrance by the substrate than radicals derived from an sp^3 center.

(18) This was accompanied by ∼16% of the product of reduction without cyclization and ∼19% of the product from rearrangement of the intermediate cyclized homoallylic radical, for example, see: (a) Stork, G.; Mook, R., Jr. *Tetrahedron Lett*. **1986**, *27*, 4529. (b) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett*. **1986**, *27*, 4525. The vinyl radical cyclization step to **16** was improved (65%) when it was carried out via the 2-iodobutene derivable from **15**, but the overall yield was unaffected.

(19) *Concerted rearragement* of the epoxide should have led to the desirable *β* aldehyde, itself stable to the rearrangement conditions. Formation, however, of the α epimer implies that rearragement probably proceeds to the aldehyde enol in this case.

(20) This proton donor (BHT) was selected in the hope that the greater steric hindrance compared to donors such as water would result in greater selectivity. This appears to be true: protonation with water gave a 1:1 mixture of the C-17 epimers.

(21) Use of the trimethylsilyl ether of the 14-hydroxyl goup is desirable because separation of the 17 cyano epimers on silica is very easy.

(22) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

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(24) *Merck Index*, 11th ed.; Merck & Co: Rahway, NJ, 1989; p 3144.