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Enantioselective total synthesis of (+)-digitoxigenin

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Abstract—An enantioselective total synthesis of (+)-digitoxigenin is described. This total synthesis is accomplished in a convergent manner using two chiral fragments prepared via the catalytic asymmetric intramolecular cyclopropanation and baker's yeast mediated reduction developed by us, respectively. This convergent synthesis would be useful for preparing some new derivatives of digitoxigenin for SAR studies and could be applied for the total synthesis of other cardenolides left unprepared.

(+)-Digitoxigenin (Fig. 1), produced by *Digitalis purpurea* and *Digitalis lunata*, has clinically been used for the treatment of congestive heart failure.[1] Recently, it was reported that (+)-digitoxigenin and its glycosides strongly inhibited the proliferation of the HT-1080 cell line (IC_{50} values, 54–1600 nM)[2] and also exhibited strong cytotoxic activities against oral human epidermoid carcinoma (KB), human breast cancer cell (BC), and human small cell lung cancer (NCI-H187).[3] In addition, the congeners of (+)-digitoxigenin, toad poison bufadienolides and their derivatives, have been reported to show potent cytotoxicity toward primary liver carcinoma cells PLC/PRF/5, too.[4]

(+)-Digitoxigenin has a steroid-like framework; however, *cis* A/B and C/D ring junctions, a tertiary 14β-hydroxyl group, and a 17β-unsaturated lactone are characteristic structural features different from common steroids. Consequently, this unique structure as well as the potent bioactivities have drawn much attention from synthetic chemists, many synthetic studies have been

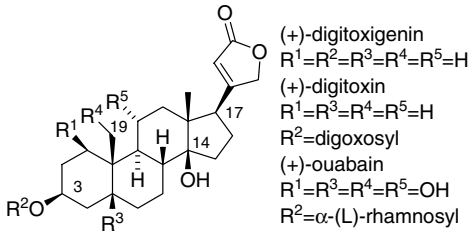

Figure 1.

reported;[5] however, most of them are partial syntheses and started from a commercially available steroid compound. Furthermore, an enantioselective total synthesis of cardenolides has been limited to the total synthesis of (+)-digitoxigenin reported by Stork's group.[6] For example, ouabain (Fig. 1),[7] which has also been used for the treatment of congestive heart failure[8] and possesses a highly oxygenated digitoxigenin skeleton, remains unsynthesized.[9]

Since modification of cardenolides has been concentrated on their sugar moiety,[10] we conceived of the convergent synthetic approach to (+)-digitoxigenin for SAR studies of the structurally divergent cardenolides and their derivatives that were inaccessible from natural products, and herein we report the enantioselective total synthesis of (+)-digitoxigenin in a convergent manner.

Our retrosynthetic analysis is outlined in Scheme 1. We expected that the advanced intermediate **1**, which incorporated a furan as a surrogate butenolide at the C17 position, would be prepared via a stereoselective intramolecular aldol reaction of **2** and subsequent deoxygenation. Diketone **2** was expected to be obtained via the coupling of enone **3** and bromide **4**.

Enone **3** was expected to be converted from tricyclo[4.4.0.$0^{5,7}$]decene derivative **5** because we have reported enantioselective preparation of **5** via the CuOTf-ligand **9** catalyzed asymmetric intramolecular cyclopropanation of **8** (Scheme 2).[11]

Bromide **4** was envisioned to be derived from alkene **6** via Suzuki–Miyaura coupling reaction and subsequent hydroxyl-directed stereoselective hydrogenation. Alkene

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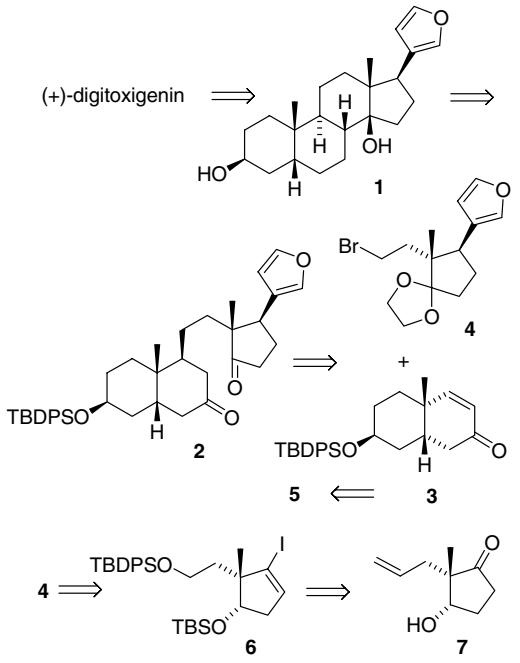
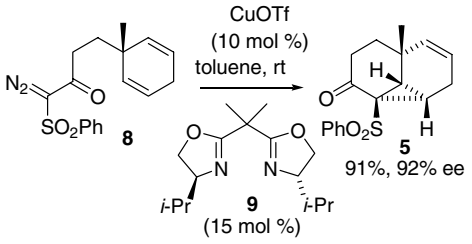


Scheme 1. Retrosynthetic analysis of (+)-digitoxigenin.

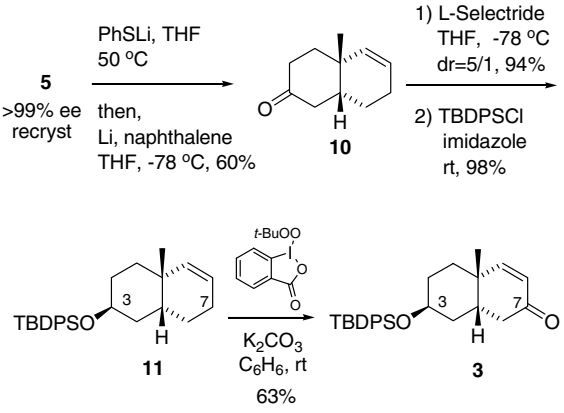


Scheme 2. Catalytic asymmetric intramolecular cyclopropanation of **8**.

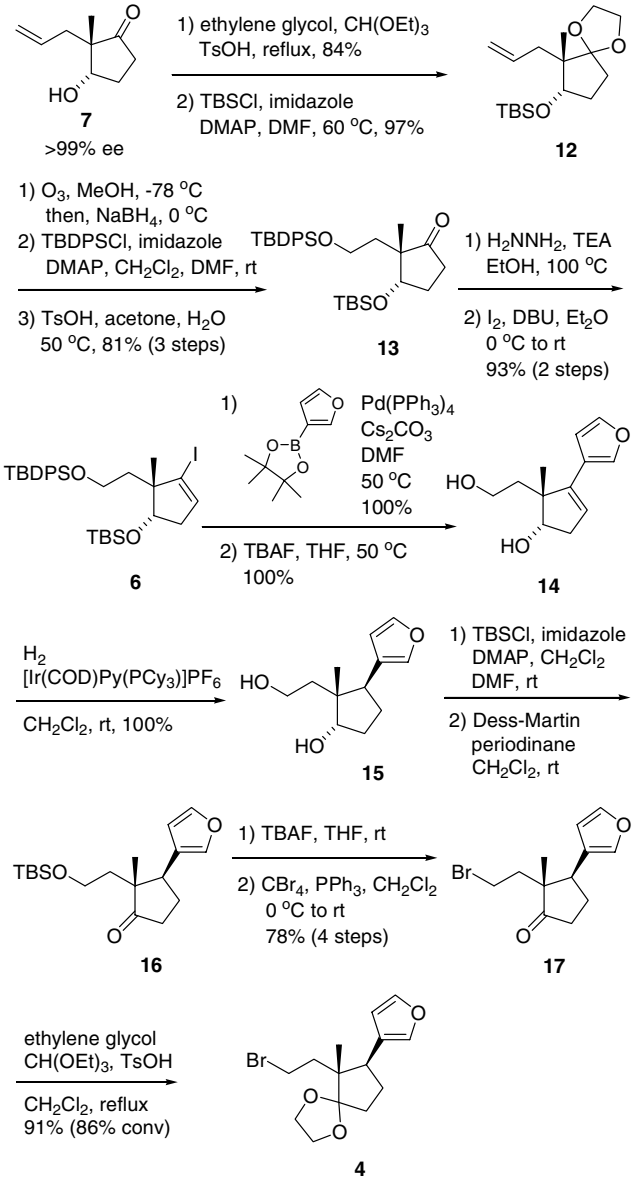
6 was anticipated to be obtained from previously prepared **7** by baker's yeast mediated reduction of the corresponding 1,3-cyclopentanedione derivative.[12]

As shown in Scheme 3, we commenced the synthesis of **3** starting with the conversion of **5** to the previously reported **10**[11a] by the improved one-pot procedure, which is a cyclopropane-ring opening reaction with lithium thiophenoxide, followed by the subsequent removal of the phenylthio group and the phenylsulfonyl group with lithium naphthalenide (60%).[13] Stereoselective reduction of **10** with the readily available reducing reagent[14] gave an undesired product; however, the reduction of **10** with L-Selectride provided the desired isomer stereoselectively (94%, dr = 5/1), which was protected as a TBDPS ether **11** (98%). Allylic oxidation at the C7 position of **11** was widely surveyed, and the reagent reported by Ochiai et al. successfully furnished the desired ketone **3** in a good yield (63%).[15]

Synthesis of another fragment **4** was started from **7** (Scheme 4).[12] Although **7** contained a small amount of the regioisomeric hydroxyl ketone which was derived from the baker's yeast reduction of the corresponding 1,3-dione, the ethylene ketal prepared from **7** was successfully separated by silica gel chromatography as a



Scheme 3. Synthesis of **3** from **5**.

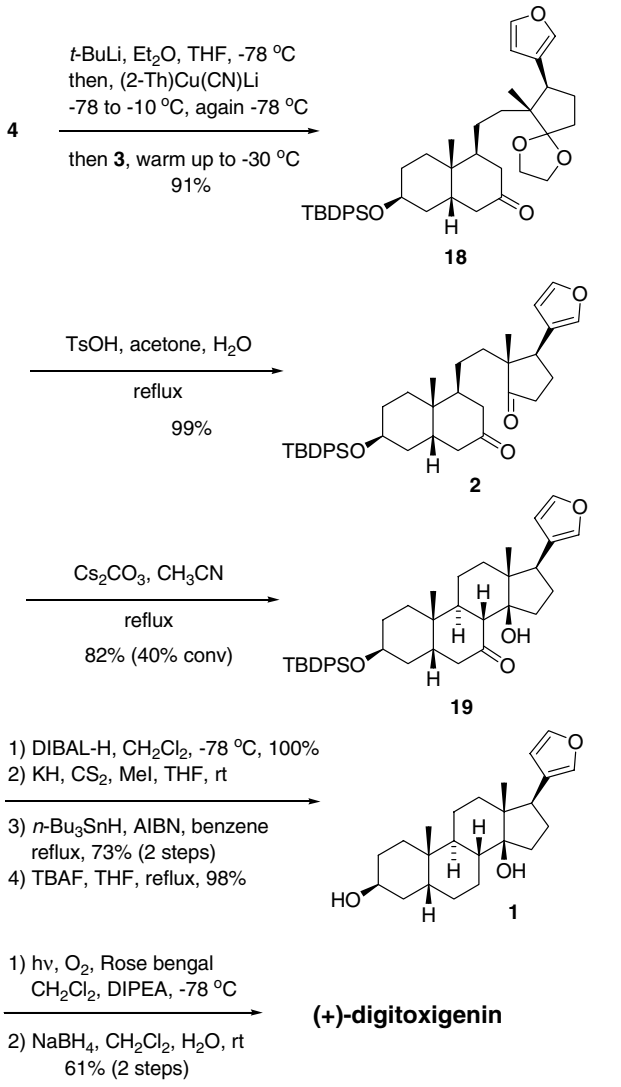


Scheme 4. Synthesis of **4** from **7**.

pure form (84%), which was converted to a TBS ether **12** (97%). Ozonolysis of the terminal alkene in **12** with a reductive workup using $NaBH_4$, followed by a TBDPS ether formation of the primary alcohol and selective deprotection of the ketone as an ethylene ketal under acidic conditions to afford **13** (81%, three steps). The reaction of **13** with hydrazine, and then with I_2 and DBU,[16] provided iodide **6** (93%, two steps). Suzuki–Miyaura coupling reaction of **6** with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan[17] successfully afforded the desired coupled product (100%), which was globally deprotected with TBAF to afford diol **14** (100%). The hydroxyl group-directed hydrogenation of **14** with Crabtree's catalyst[18] successfully provided **15** (100%). Selective conversion of the primary alcohol of **15** to the corresponding halide failed because the *cis* diol system of **15** was easily converted to a THF ring. Furthermore, selective oxidation of the secondary alcohol was fruitless. Consequently, the primary alcohol of **15** was protected as a TBS ether and the remaining secondary alcohol was oxidized by Dess–Martin oxidation to afford ketone **16**, followed by the deprotection of the TBS group with TBAF and subsequent reaction of the resulting alcohol with CBr_4 and PPh_3 to provide bromide **17** (78%, four steps). Finally, the ethylene ketal formation of bromide **17** under conventional conditions furnished **4** (91%, 86% conv).

With **3** and **4** in hand, we examined the coupling reaction of these fragments (Scheme 5) and found that the higher order cuprate derived from **4** by the use of *tert*-BuLi and lithium 2-thienylcyanocuprate[19] was effective for this 1,4-addition reaction, providing the desired product **18** as a single diastereomer (91%). The ethylene ketal in **18** was cleanly removed under the acidic conditions to afford the corresponding diketone **2** (99%), which was subjected to the intramolecular aldol reaction. Although most of the bases generated a mixture of **19** and its dehydrated product, the use of Cs_2CO_3 in CH_3CN[20] afforded the desired product **19** as a single product (82%, 40% conv). All attempts in the direct deoxygenation reaction of ketone **19** failed to afford the corresponding methylene compound; hence, this deoxygenation reaction was carried out via the conventional three steps; that is, DIBAL-H reduction (100%) of **19**, a methyl xantate formation, and tin-hydride reduction (73%, two steps). The TBDPS group in the product was removed by TBAF to provide **1** (98%), which was reacted with singlet oxygen in the presence of DIPEA under photo-irradiation conditions using Rose bengal as a sensitizer,[21] followed by the reduction of the resulting hemiacetal with $NaBH_4$ to furnish (+)-digitoxigenin (61%, two steps). Synthetic (+)-digitoxigenin proved to be identical in all respects to the natural product, indicating that we succeeded in the enantioselective total synthesis of (+)-digitoxigenin.

In summary, enantioselective total synthesis of (+)-digitoxigenin was achieved by effectively utilizing chiral building blocks prepared via the catalytic asymmetric intramolecular cyclopropanation developed by us. This convergent synthesis would be useful for preparing some new derivatives of digitoxigenin for SAR studies and could be applied for the total synthesis of other cardenolides left unprepared.



Scheme 5. Enantioselective total synthesis of (+)-digitoxigenin.

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References and notes

1. Hoffmann, B. F.; Bigger, J. T., Jr. In *The Pharmacological Basis of Therapeutics*; Goodman Gilman, A., Goodman, L. S., Rall, T. W., Murad, F., Eds.; MacMillan: New York, 1985; p 716.

2. Ueda, J.; Tezuka, Y.; Banskota, A. H.; Tran, Q. L.; Tran, Q. K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **2003**, *66*, 1427–1433.
3. Laphookhieo, S.; Cheenpracha, S.; Karalai, C.; Chantraprommma, S.; Rat-a-pa, Y.; Ponglimanont, C.; Chantraprommma, K. *Phytochemistry* **2004**, *65*, 507–510.
4. Kamano, Y.; Kotake, A.; Hashima, H.; Inoue, M.; Morita, H.; Takeya, K.; Itokawa, H.; Nandachi, N.; Segawa, T.; Yukita, A.; Saitou, K.; Katsuyama, M.; Pettit, G. R. *Bioorg. Med. Chem.* **1998**, *6*, 1103–1115.
5. (a) Danieli, N.; Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1962**, *84*, 875–876; (b) Sondheimer, F. *Chem. Br.* **1965**, *1*, 454–464; (c) Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1966**, *22*, 3189–3193; (d) Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733–749, and references cited therein; (e) Fritsch, W.; Haede, W.; Radscheit, K.; Ruschig, H. *Liebigs Ann. Chem.* **1969**, *721*, 168–185; (f) Pettit, G. R.; Houghton, L. E.; Knight, I. C.; Bruschweiler, F. *J. Org. Chem.* **1970**, *35*, 2895–2898; (g) Valcavi, U.; Innocenti, S. *El. Farmaco Ed. Sci.* **1974**, *29*, 194–203; (h) Fritsch, W.; Haede, W.; Radscheit, K.; Stache, U.; Ruschig, H. *Liebigs Ann. Chem.* **1974**, 621–629; (i) Yoshii, E.; Koizumi, T.; Ikeshima, H.; Uzaki, K.; Hayashi, I. *Chem. Pharm. Bull.* **1975**, *23*, 2496–2506; (j) Lenz, G. R.; Schulz, J. A. *J. Org. Chem.* **1978**, *43*, 2334–2339; (k) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, 3287–3290; (l) Kocovsky, P. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2998–3007; (m) Nickisch, K.; Kose, W.; Bohlmann, F. *Chem. Ber.* **1980**, *113*, 2038–2039; (n) Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem.* **1981**, *59*, 1403–1404; (o) Kocovsky, P.; Cerny, V. *Collect. Czech. Commun.* **1981**, *46*, 446–451; (p) Welzel, P.; Stein, H.; Milkova, T. *Liebigs Ann. Chem.* **1982**, 2119–2134; (q) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Chem. Commun.* **1983**, 985–987; (r) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1601–1605; (s) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem.* **1986**, *58*, 799–810; (t) Kutney, J. P.; Piotrowska, K.; Somerville, J.; Huang, S. P.; Rettig, S. J. *Can. J. Chem.* **1989**, *67*, 580–589; (u) Groszek, G.; Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron* **1989**, *45*, 2223–2226; (v) Kocovsky, P.; Stieborova, I. *Tetrahedron Lett.* **1989**, *30*, 4295–4298; For reviews of partial syntheses, see: (w) Hanson, J. R. *Nat. Prod. Rep.* **1993**, *10*, 313–325.
6. Stork, G.; West, F.; Lee, Y. H.; Isaacs, R. C.; Manabe, S. J. *Am. Chem. Soc.* **1996**, *118*, 10660–10661.
7. Arnaud, M. *C.R. Acad.* **1888**, *107*, 1011.
8. Bigelow, N. M.; Jacobs, W. A. *J. Biol. Chem.* **1932**, *96*, 647–658.
9. For synthetic studies on ouabain, see: (a) Hynes, J., Jr.; Overman, L. E.; Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4647–4650; (b) Larry, E.; Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4643–4646; (c) Overman, L. E.; Rucker, P. V. *Heterocycles* **2000**, *52*, 1297–1314; (d) Jung, M. E.; Davidov, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4125–4128; (e) Chapdelaine, D.; Belzile, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5669–5672; (f) Jung, M. E.; Piizzi, G. *Org. Lett.* **2003**, *5*, 137–140; (g) Jung, M. E.; Piizzi, G. *J. Org. Chem.* **2003**, *68*, 2572–2582; (h) Plano, M. F.; Labadie, G. R.; Sierra, M. G.; Cravero, R. M. *Tetrahedron Lett.* **2006**, *47*, 7447–7449.
10. (a) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300–314; (b) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem.* **1986**, *58*, 799–810; (c) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304–4309; (d) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653–3655; (e) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979–3981; (f) Langenhan, J. M.; Peters, N. R.; Guzei, I. A.; Hoffmann, F. M.; Thorson, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 12305–12310; (g) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339–4342.
11. Yield of **5** was improved to 91% from 78% (Ref. 11a). (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860–2861; (b) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007–9011.
12. Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223–3232.
13. Yield of **10** from **3** by the previous method using sodium amalgam[10a] was 45%.
14. For example, the reduction of **10** with $NaBH_4$ afforded the undesired isomer preferentially (86%, dr = 1/3).
15. Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716–7730.
16. Barton, D. H. R.; Bashiardes, G.; Fourrey, J. L. *Tetrahedron* **1988**, *44*, 147–162.
17. Commercially available.
18. Crabtree, R. H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *135*, 395–403.
19. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945–948.
20. Rue1, R.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3961–3964.
21. Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773–2776.