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A Stereoselective Synthesis of Digitoxin and Digitoxigen Mono- and Bisdigitoxoside from Digitoxigenin via a Palladium-Catalyzed Glycosylation

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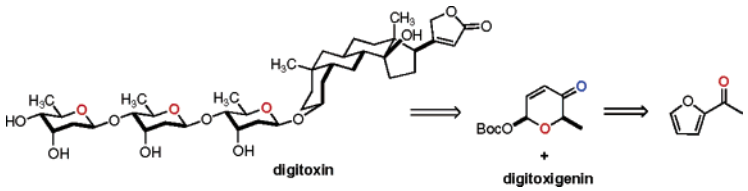
ABSTRACT



A convergent and stereocontrolled route to trisaccharide natural product digitoxin has been developed. The route is amenable to the preparation of both the digitoxigen mono- and bisdigitoxoside. This route featured the iterative application of the palladium-catalyzed glycosylation reaction, reductive 1,3-transposition, diastereoselective dihydroxylation, and regioselective protection. The natural product digitoxin was fashioned in 15 steps starting from digitoxigenin 2 and pyranone 8a or 18 steps from achiral acylfuran.

Oligosaccharides bearing deoxysugars have played a pivotal role in many pharmacologically important antibiotics, vaccines, and antitumor agents.[1] The cardiac glycoside digitoxin (**1**) (Figure 1), which possesses both potent cardiac[2] and anticancer activities,[3] is the combination of two natural products, the aglycon digitoxigenin (**2**)[4] and the trisaccharide digoxose (**3**).[5] Recently, Thorson has constructed a neoglycoside library of digitoxin analogues with improved anticancer activity yet lower cardiotoxicity.[6] To delineate the

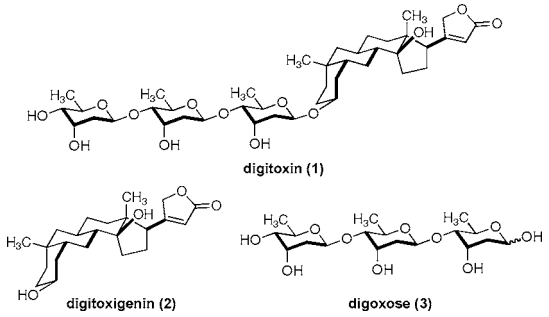


Figure 1. Digitoxin, digitoxigenin, and digoxose.

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(1) (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. (c) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1−84. (d) Marzabadi, C. H.; Frank, R. W. *Tetrahedron* **2000**, *56*, 8385−8417. (e) Kirschning, A.; Jesberger, M.; Schoning, K. U. *Synthesis* **2001**, 507−540. (f) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624. (g) He, X.; Liu, H.-W. *Annu. Rev. Biochem.* **2002**, *71*, 701−754.

(2) Digitoxin has been used to treat congestive heart failure and cardiac arrhythmia for over 200 years. However, extensive care must be taken when treated with digitoxin because the typical therapeutic dose (14−26 ng mL^{-1}) is dangerously close to the toxic dose (>35 ng mL^{-1}).

(3) Greeff, K. Cardiac Glycosides, Part 1: Experimental Pharmacology. In *Handbook of Experimental Pharmacology*; Springer-Verlag; Berlin; New York, 1981; Vol. 56.

(4) For the synthesis of digitoxigenin, see: (a) Danieli, N.; Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1962**, *84*, 875−876. (b) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, *35*, 3287−90. (c) Tsai, T. Y. R.; Minta, A.; Wiesner, K. *Heterocycles* **1979**, *12*, 1397−1402. (d) Marini-Bettolo, R.; Flecker, P.; Tsai, T. Y. R.; Wiesner, K. *Can. J. Chem.* **1981**, *59*, 1403−1410. (e) Kabat, M. M. *J. Org. Chem.* **1995**, *60*, 1823−1827. (f) Stork, G.; West, F.; Lee, H. Y.; Isaacs, R. C. A.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10660−10661. (g) Almirante, N.; Cerri, A. *J. Org. Chem.* **1997**, *62*, 3402−3404. (f) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421−5424.

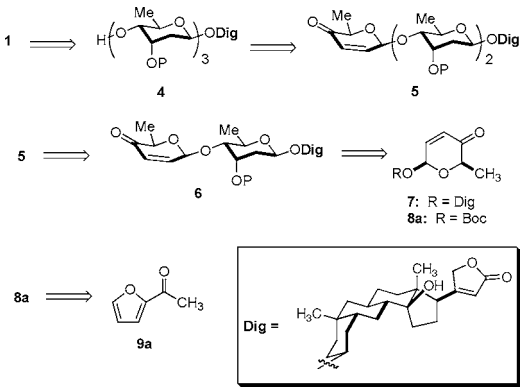
pharmalogical role the tris-2-deoxy sugar plays in the biological activity of digitoxin, synthetic access to digitoxin and its bis- and mono-saccharide analogues are desired.

There have been two syntheses of digitoxin (**1**), a carbohydrate approach by Wiesner (~20 steps from a protected 2-deoxy sugar) and a de novo approach by McDonald (20 steps from TMS-acetylene).[7] We planned to prepare digitoxin (**1**) via a de novo strategy, which could also be used to prepare various digitoxin analogues. Our goal was to design a more efficient route in terms of number of steps and stereocontrol than the previous approaches.[8]

The stereocontrolled synthesis of 2-deoxy sugars is not a problem readily solved by traditional carbohydrate methods.[9] The deoxymonosaccharides are not naturally abundant or readily available. They are usually prepared from common sugar in multiple steps. The control of anomeric stereochemistry in the installation of 2-deoxyglycosides is also challenging. Due to the missing control element at the 2-position, it is particularly difficult to synthesize β-2-deoxy-glycosides.[10] This problem was evident in the previous syntheses of digitoxin.[8,11] Herein we describe our successful de novo approach to address the 2-deoxy-β-glycosides using a diastereoselective palladium-catalyzed glycosylation reaction[12] and its application to syntheses of β-1,4-linked oligosaccharide natural product digitoxin (**1**). Our strategy (Scheme 1) features the iterative use of a β-selective palladium-catalyzed glycosylation reaction, followed by diastereoselective installation of the C-3/C-4 hydroxy groups and regioselective C-3 protection.

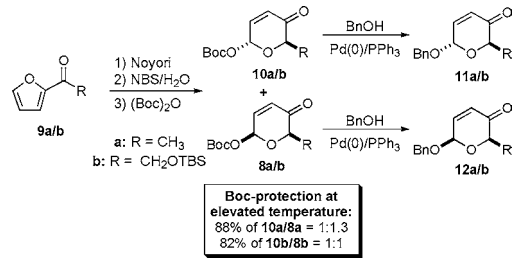
Previously, we have shown that acylfurans **9a**/**b** can be enantioselectively reduced (Noyori, >95% ee)[13] and diastereoselectively converted into the α-Boc-pyranones **10a**/**b**.[14] Alternatively, the β-pyranones **8a**/**b** can be isolated in a

Scheme 1. Digitoxin Retrosynthetic Analysis



~50% yields after chromatographic separation. If the Boc-protection is performed at elevated temperature ($(Boc)_2O$/NaOAc in benzene at 80 °C), the pyranones can be prepared as a diastereomeric mixture at the anomeric center (Scheme 2). The ratio of β-pyranones to α-pyranones at these higher

Scheme 2. Pyranone Synthesis



temperatures can be as high as 1.3:1. Fortunately, once the α-pyranones **10** and β-pyranones **8** have been separated they can be converted via palladium(0) catalysis into their corresponding mixed acetal pyranones with complete retention of stereochemistry (i.e., **10** to **11** and **8** to **12**). By means of a palladium-catalyzed glycosylation,[12a] the α-pyranones can be oligomerized and subsequently transformed into α-linked oligosaccharides.[12d] Encouraged by these results, we decided to investigate the use of the β-isomers **8a**/**b** for the synthesis of β-linked oligosaccharides (e.g., digitoxin **1**).

Our initial effort toward the preparation of 2-deoxysugars commenced with the synthesis of the 2-deoxy-L-allose. Thus, using only 5 mol % palladium, the β-pyranone ***ent*-8b**[14] was coupled with benzyl alcohol providing β-benzyloxy pyranone **13** in 84% yield (Scheme 3). A reduction of pyranone **13** under Luche conditions[15] gave a mixture allylic alcohols **14a**/**b** in 88% yield with the diastereomeric ratio of ca. 1.5:1. The diastereomeric ratio of alcohols could be improved

(5) The attempts at the selective hydrolysis of digitoxin (**1**) to form digoxose (**3**) have been futile; only the monosaccharide digitoxose was isolated. Surprisingly, **3** can be isolated from the dried twigs of *Orthenthera viminea*; see: Tiwari, K. N.; Khare, N. K.; Khare, A.; Khare, M. P. *Carbohydr. Res.* **1984**, *129*, 179−187.

(6) 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.

(7) (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.

(8) In both the Wiesner and McDonald syntheses of digitoxin at least one of the three glycosidic bonds was assembled with poor stereoselectivity; see ref 7.

(9) (a) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541−3542. (b) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510−4511.

(10) (a)Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (b) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236−2250.

(11) In contrast, McDonald is able to use his methodology to prepare an all-α-analogue of digitoxin with high stereocontrol; see: McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979−3981.

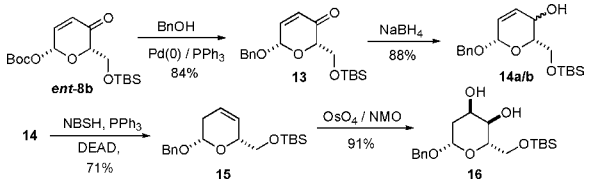
(12) (a)Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714−8715. (c) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337. For its application in the de novo synthesis of α-linked 1,4- and 1,6-oligosaccharides, see: (d) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429.

(13) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (b) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005−1009. (c) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407−6411.

(14) (a) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, *24*, 169−177. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921−3924.

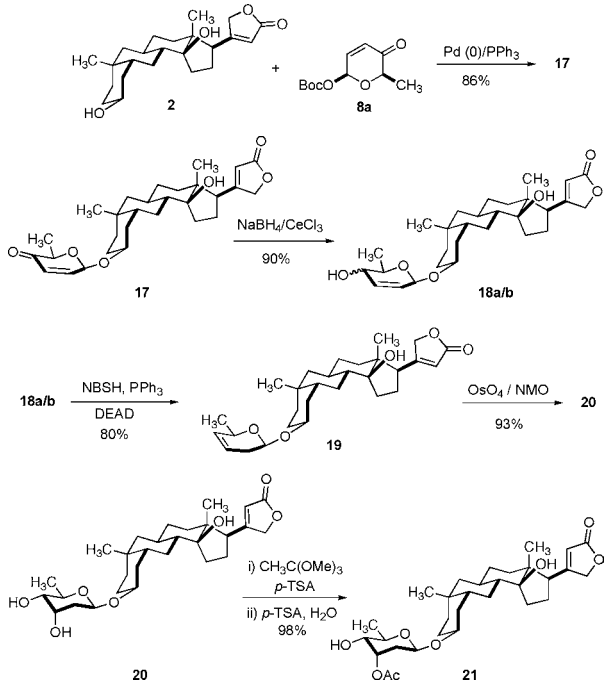
(15) For reduction of β-pyranones, the $CeCl_3$ is necessary to avoid 1,4-reduction products. For the Luche reduction, see: (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401−404.

Scheme 3. Synthesis of 2-Deoxy-L-allose



with the use of DibalH (dr = 6:1), albeit in slightly lower yields. Fortunately, we were able to use both diastereomers of **14a**/**b** in the subsequent reaction, which allowed us to use the operational simpler $NaBH_4$ procedure. Thus, exposing the mixture of allylic alcohols **14a**/**b** to the Myers' reductive rearrangement conditions[16] (NBSH, PPh_3/DEAD, NMM, −30 °C to rt) provided olefin **15** in 71% yield. Dihydroxylation of **15** using the Upjohn conditions[17] (OsO_4/NMO) gave exclusively the diol **16** in 91% yield. While this seven-step sequence to 2-deoxy-β-allose from acylfuran **9b** incorporates two nonselective steps, all of the post-glycosylation steps (**13** to **16**) lead to a single diastereomeric product.

Scheme 4. Synthesis of Digitoxigen Monodigitoxoside

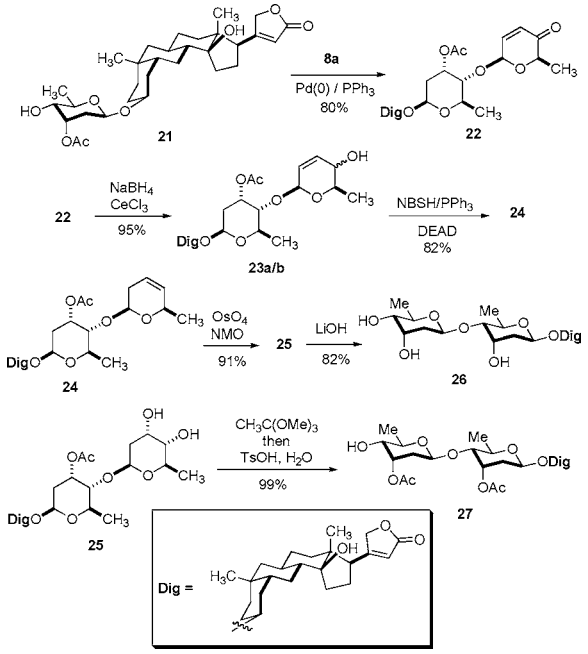


With the promising results of the synthesis of 2-deoxy-*allo*-sugar **16**, we next investigated the synthesis of digitoxin using the same strategy starting from the digitoxigenin and

(16) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841−4844. (c) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507. (d) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771−1774.

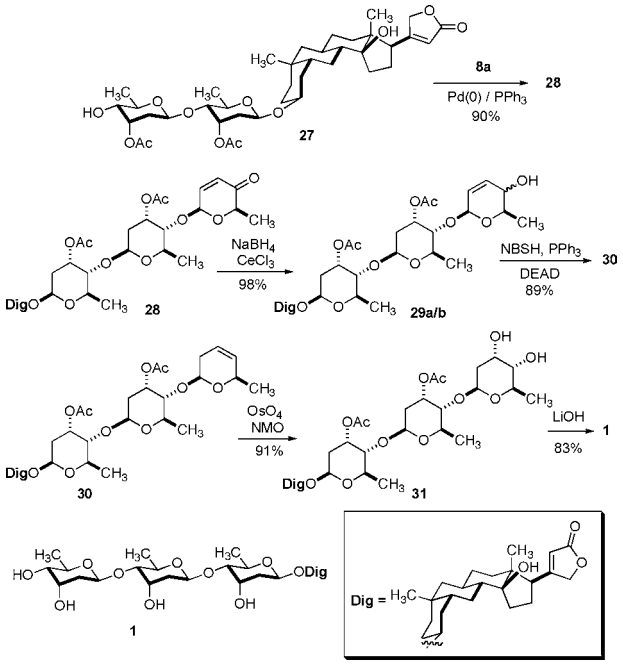
(17) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.

Scheme 5. Synthesis of Digitoxigen Bisdigitoxoside



β-pyranone **8a** (Schemes 4−6). Our initial concern about the compatibilities of the tertiary alcohol and furan formation of lactone in the aglycon proved to be superfluous. Thus, both the palladium catalyzed glycosylation and Luche reduction occurred with complete chemoselectivity (i.e. the tertiary alcohol and the butenolide ring of the aglycon were left untouched).

Scheme 6. Synthesis of Digitoxin (**1**)



In practice, palladium-catalyzed glycosylation of digitoxigenin **2** with the pyranone **8a** gave the β-glycoside **17** as a

single diastereomer and in good yield (86%). Luche reduction of **17** provided a mixture of allylic alcohols **18a/b** (90%), which were inseparable (Scheme 4). Reductive rearrangement of the diastereomeric mixture of allylic alcohols **18a**/**b** provided olefin **19** in 80% yield. Dihydroxylation of **19** using the Upjohn conditions (OsO_4/NMO) gave exclusively the digitoxigen monodigitoxoside **20** in 93% yield.[18,19]

As with all the other post-glycosylation transformation the regioselective acylation of diol **20** proved to be compatible with the aglycon functionality as well as the glycosidic bond. We found that simply applying an ortho ester formation/hydrolysis protocol to diol **20** provided the monoprotected sugar **21** (98% yield), which is ready for subsequent glycosylation (**21** to **22**, Scheme 5).[20]

We next explored the glycosylation of the *C*-4 secondary alcohol in **21** for the synthesis of disaccharide **26**. Thus, subjecting the alcohol **21** and pyranone **8a** to the typical palladium catalyzed glycosylation conditions afforded the *C*-4 glycosylated disaccharide **22** in 80% yield with complete stereocontrol at the anomeric center (Scheme 5). Similarly, Luche reduction of the keto-group in pyranone **22** provided a 1.6:1 mixture of allylic alcohols **23a**/**b**, which when exposed to the Myers' reductive 1,3-allylic transposition conditions provided olefin **24** in 82% yield. Once again, dihydroxylation of **24** gave exclusively the diol **25** in 91% yield. The digitoxigen bisdigitoxoside **26** was fashioned by deprotection of the acyl-protecting group in **25** (82% yield).

The installation of the final sugar occurred with the same efficiency and high degree of stereocontrol as seen in the conversion of aglycon **2** to monosaccharide **20** and monosaccharide **21** to disaccharide **26** (Schemes 4 and 5). Once again, this effort began with a regioselective protection of axial alcohol in diol **25**, which provided **27** in excellent yield (99%).

Subjecting the alcohol **27** and pyranone **8a** to our typical Pd(0)-catalyzed glycosylation stereoselectively installed the final pyran ring to fashion the 1,4-linked trisaccharides **28** in 90% yield (Scheme 6). A diastereomeric mixture of allylic alcohols **29a**/**b** was obtained in 98% yield when enone **28** underwent Luche reduction. Upon exposure to the Myers reductive rearrangement conditions, both allylic alcohols in **29a**/**b** reductively rearranged to corresponding olefin **30** in 89% yield. The digitoxose trisaccharide **31** was prepared with high yield and complete stereocontrol by dihydroxylation of olefin in **30**. Finally the natural product digitoxin (**1**) was prepared by deprotection of the two acetate-protecting groups in **31**, which gave synthetic material **1** (83%) with identical physical and spectral data to that of the commercially available natural product **1**[21] (^{1}H NMR, ^{13}C NMR, optical rotation, and melting point).

In conclusion, a straightforward and stereocontrolled 15-step route to digitoxin (**1**) from digitoxigenin (**2**) as well as corresponding mono- and disaccharides (**20** and **26**) has been developed. This new route featured the iterative use of the palladium catalyzed β-glycosylation reaction, Myers' reductive rearrangement, diastereoselective dihydroxylation and regioselective protection. This work not only shows the assembly of the nine stereocenters of the trisaccharide from an achiral starting material, it also demonstrates the functional group compatibility of this approach (e.g., the tertiary alcohol and both the double bond and carbonyl group of the butenolide). This unique application of our Pd-catalyzed glycosylation efficiently prepares a challenging and important 2-deoxy-β-glycoside target. This approach is mild and equally amenable to the preparation of various digitoxin analogues. The uses of this strategy for the synthesis of various analogues are ongoing.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Mono- and bis-digtoxosides has been prepared by gradual degradation of digitoxin, see: (a) Satoh, D., Aoyama, K. *Chem. Pharm. Bull.* **1970**, *18*, 94−98. (b) Templeton, F. J.; Setiloane, P.; Kumar, V. P. S.; Yan, Y.; Zeglam, H. T.; LaBella, F. S. *J. Med. Chem.* **1991**, *34*, 2778−2782. Our synthetic material **20** and **26** have identical physical and spectral data with degraded products in the terms of ^{1}H NMR, ^{13}C NMR, optical rotation, and melting point.

(19) The nomenclature of compounds **20** and **26** was used according to ref 18.

(20) Acetate protecting group was demonstrated to provide significant stabilization effect for the acid-sensitive glycosides. (a) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1697−1699. (b) Unverzagt, C.; Kunz, H. *Bioorg. Med. Chem.* **1994**, *2*, 1189−1201. (c) McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 7001−7002.

(21) Digitoxin purchased from Acros was used to do the comparison.