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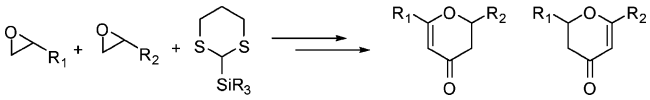
# A Versatile Strategy for the Synthesis of 2,6-Disubstituted Dihydropyranones

Hua Wang, Brian J. Shuhler, and Ming Xian*

*Department of Chemistry, Washington State University, Pullman, Washington 99164*

*mxian@wsu.edu*

*Received February 19, 2007*

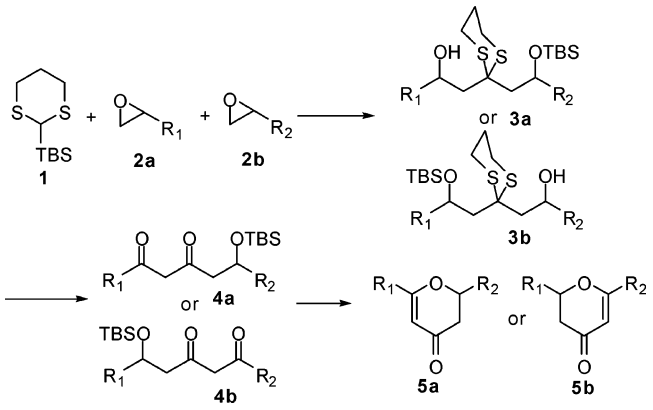


A concise synthesis of 2,6-disubstituted dihydropyranones was developed. This sequence is based on the Smith three-component dithiane linchpin coupling strategy. By simply switching the order of epoxide addition in the linchpin coupling step, two analogous dihydropyranones were prepared in good yield from the same starting materials. This sequence allows for considerable flexibility in the nature of $R_1$ and $R_2$ groups, which facilitates the preparation of a diverse array of 2,6-disubstituted dihydropyranones.

2,6-Disubstituted dihydropyranones have seemingly ubiquitous functionalities in many natural products. They are also important synthetic intermediates in the synthesis of biologically interesting molecules.[1] The syntheses of dihydropyranones have been well documented in literature. For example, hetero Diels−Alder reactions have been used to prepare this type of compounds in the last two decades.[2] New strategies that have been recently developed include the tandem aldol reaction/conjugate addition[3] and the oxidative cyclization of $\beta$-hydroxy-enones with palladium(II).[4] The addition of a variety of nucleophiles to unsaturated lactones that result from the reaction of Brassard's diene with aldehydes has also been employed to synthesize 2,6-disubstituted dihydropyranones.[5]

To synthesize diospongin B, a novel anti-osteoporotic agent,[6] as well as structurally modified analogues, we outline in this paper a versatile synthetic route to assemble 2,6-disubstituted dihydropyranones from readily available chiral epoxides. This route is based on the Smith protocol, that is, the three-component linchpin coupling of silyl dithiane (**1**) with two epoxides

**SCHEME 1**



(**2a** and **2b**, Scheme 1).[7] The location of the silyl protecting group on the coupling product can be simply orchestrated by the order of the epoxide additions. Therefore, two 1,5-diol derivatives (**3a** and **3b**) can be readily prepared from the same starting materials. Next, we expected the removal of the dithiane group and the oxidation of the unprotected hydroxyl to be achieved in a single step, or stepwise, to provide the diketones **4a** and **4b**. Finally, deprotection of the TBS ether and cyclization were expected to proceed in a single operation to furnish the structurally related dihydropyranones **5a** and **5b**.

To explore this sequence, we first examined the linchpin coupling reactions (Scheme 2). When the procedure developed by Tietze et al.[8] was employed for pseudo-symmetric compounds ($R_1 = R_2$, entries 1−3), only 70−80% yields of the products were formed, because of the incomplete silyl migration under such conditions. This problem was solved by the addition of 0.4 equiv of HMPA into the reaction mixture because polar solvents such as HMPA can significantly increase the rate of silyl migration.[7] In this manner, compounds **3a**−**c** were obtained in almost quantitative yields. When two different epoxides were involved in the linchpin coupling (entries 4−7), the procedure developed by Smith[7] was followed. Upon changing the order of epoxide addition, two pairs of 1,5-diol derivatives (**3d** and **3e**, **3f** and **3g**) were obtained in good yields.

With these 1,5-diol derivatives in hand, we then turned to investigate the stepwise preparation of diketones from these compounds (Scheme 3). Various dithiane group removal conditions were applied to compounds **3a**−**g**.[9] We were pleased to find that $HgCl_2/CaCO_3$ in $CH_3CN$/water was the most efficient method to remove dithiane groups on these substrates, which provided the desired product in excellent yield (see Supporting Information). The resulting $\beta$-hydroxyl ketones were then successfully converted to diketones upon treatment with Dess−Martin periodinane (DMP). This two-step sequence provided

(1) (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (b) Danishefsky, S. J.; Biolodeau, M. T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380.

(2) (a) Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. Jorgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093. (b) Evens, P. A.; Nelson, J. D. *J. Org. Chem.* **1996**, *61*, 7600.

(3) Gao, B.; Yu, Z. P.; Fu, Z. Y.; Feng, X. M. *Tetrahedron Lett.* **2006**, *47*, 1537.

(4) Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91.

(5) Winkler, J. D.; Oh, K. *Org. Lett.* **2005**, *7*, 2421.

(6) Yin, J.; Kouda, K.; Tezuka, Y.; Tran, Q.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, *70*, 54.

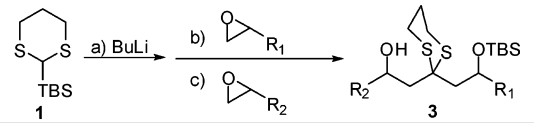
(7) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, M. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435.

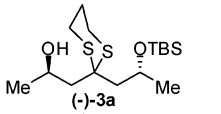
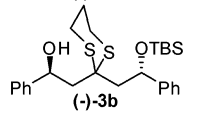
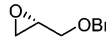
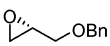
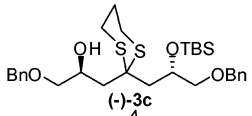
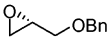
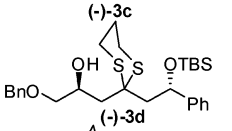
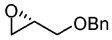
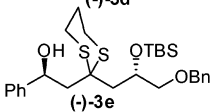
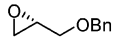
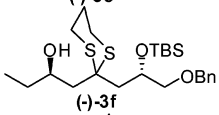
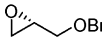
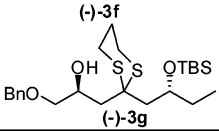
(8) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511.

(9) Burghardt, T. E. *J. Sulfur Chem.* **2005**, *26*, 411.

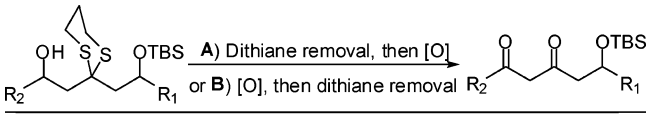
10.1021/jo070346t CCC: $37.00 
Published on Web 04/21/2007

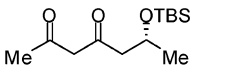
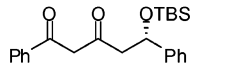
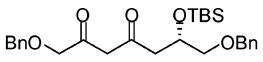
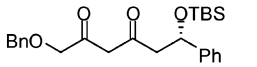
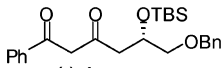
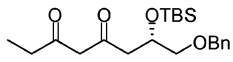
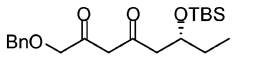
**SCHEME 2**




| entry | A | B | Prod. | Yield |
|---|---|---|---|---|
| 1 |  |  |  (-)-3a | 96% |
| 2 |  |  |  (-)-3b | 91% |
| 3 |  |  |  (-)-3c | 96% |
| 4 |  |  |  (-)-3d | 65% |
| 5 |  |  |  (-)-3e | 60% |
| 6 |  |  |  (-)-3f | 64% |
| 7 |  |  |  (-)-3g | 84% |

**SCHEME 3**




| entry | Sub. | Prod. | Yield |
|---|---|---|---|
| 1 | (-)-3a |  (-)-4a | **A** 72%<br>**B** 56% |
| 2 | (-)-3b |  (-)-4b | **A** 81%<br>**B** 68% |
| 3 | (-)-3c |  (-)-4c | **A** 87%<br>**B** 72% |
| 4 | (-)-3d |  (-)-4d | **A** 73%<br>**B** 58% |
| 5 | (-)-3e |  (-)-4e | **A** 79%<br>**B** 63% |
| 6 | (-)-3f |  (-)-4f | **A** 90%<br>**B** 58% |
| 7 | (-)-3g |  (-)-4g | **A** 79%<br>**B** 63% |

**A**: 1) $HgCl_2/CaCO_3$, reflux 2) DMP, r.t.
**B**: 1) DMP, r.t., 2) $HgCl_2/CaCO_3$, r.t.

the desired diketones **4a**−**g** in good yield (72−90%, Scheme 3, method A).

Alternatively, diketones could also be prepared from diol derivatives via a hydroxyl oxidation followed by removal of the dithiane group (Scheme 3, method B). It was previously suggested that DMP is not effective in the oxidation of hydroxyls on dithiane-containing substrates.[10] However, when our substrates (**3a**−**g**) were treated with a stoichiometric amount (1.0 equiv) of freshly prepared DMP for 15 min, the corresponding ketone products were obtained in good yield. If excess DMP (>2.0 equiv) was added or the reaction time was prolonged (>30 min), the yield dropped dramatically with the formation of a significant amount of unidentified byproducts. The ketone intermediates were then subjected to various conditions to remove the dithiane group. Again, $HgCl_2/CaCO_3$ turned out to be the best choice, albeit the yield was moderate (60−80%). In general, this two-step sequence provided diketone products in lower overall yield than the yield obtained from the dithiane group removal/oxidation sequence (method A).

Because DMP was reported to be an efficient reagent to remove the dithiane group[10] and has the ability to oxidize the hydroxyl groups in our substrates, we then sought conditions that would achieve diketone formation from 1,5-diol derivatives in one step using DMP. As shown in Scheme 4 (entry 1), after **3b** was completely converted to the ketone intermediate **5b** by treatment with DMP (1.0 equiv) in pure $CH_3CN$ (reaction monitored by TLC), $CH_2Cl_2/H_2O$ and more DMP were added to the reaction mixture to achieve the conditions reported by Panek et al.[10] However, the desired diketone **4b** was obtained only in very small amounts (10% yield) after 48 h. Most of the ketone intermediate **5b** (60%) was recovered from this reaction. 2-Iodoxybenzoic acid (IBX)[11] was also used in an attempt to achieve the one-step transformation. Again, only the ketone intermediate was obtained. We were unable to find suitable conditions for the removal of dithiane groups on these substrates using DMP or IBX. Surprisingly, when **3b** was treated with excess NBS, the desired diketone **4b** was obtained in 68% yield (Scheme 4, entry 2). Unfortunately, when this protocol was applied to other substrates, none of them gave the desired product.

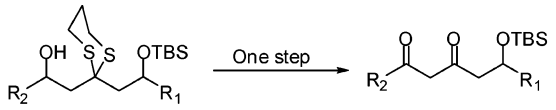
With the diketones **4a**−**g** in hand, we turned to the last step in the sequence. Treatment of the diketones with protic acids, either a stoichiometric amount of TFA or catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH), resulted in deprotection of the TBS ether, and ring cyclization took place smoothly in one step to furnish the dihydropyranones **6a**−**g** in outstanding yield (Scheme 5). In general, the reaction with TFA was completed within 2 h, while the reaction with *p*-TsOH required 2 or 3 days to complete, but the yields were similar.

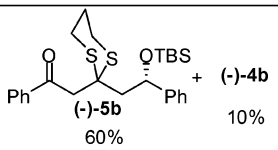
In summary, we have developed a concise synthetic sequence to form 2,6-disubstituted dihydropyranones. The Smith dithiane linchpin coupling strategy was utilized to construct 1,5-diol derivatives as key intermediates, which provide a flexible way

(10) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575.

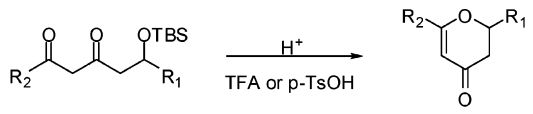
(11) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.

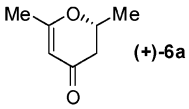
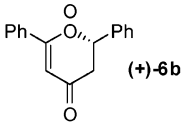
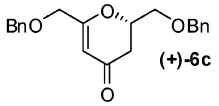
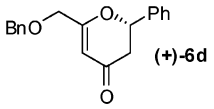
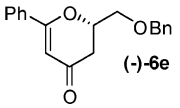
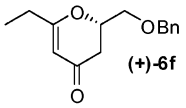
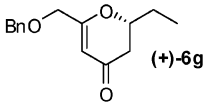
**SCHEME 4**




| Entry | Sub. | Reagent | Result |
|---|---|---|---|
| 1 | **(-)-3b** | DMP |  **(-)-5b** 60% + **(-)-4b** 10% |
| 2 | **(-)-3b** | NBS | **(-)-4b** 68% |

**SCHEME 5**




| Entry | Sub. | Prod. | Yield |
|---|---|---|---|
| 1 | **(-)-4a** |  **(+)-6a** | 95% |
| 2 | **(-)-4b** |  **(+)-6b** | 93% |
| 3 | **(-)-4c** |  **(+)-6c** | 95% |
| 4 | **(-)-4d** |  **(+)-6d** | 90% |
| 5 | **(-)-4e** |  **(-)-6e** | 95% |
| 6 | **(-)-4f** |  **(+)-6f** | 97% |
| 7 | **(-)-4g** |  **(+)-6g** | 89% |

to switch two groups on the C2 and the C6 positions. The transformation from 1,5-diol intermediates to dihydropyranones was studied in detail. This short sequence allows for considerable flexibility in the nature of the C2 and the C6 substitutents, which facilitates the preparation of a diverse array of 2,6-disubstituted dihydropyranones.

## Experimental Section

**Modified Procedure for the Coupling of TBS-Dithiane with an Excess of Epoxides.** To a well-stirred solution of TBS-dithiane **1** (120 mg, 0.51 mmol) in THF (1 mL), *n*-BuLi was added (1.6 M in hexane, 0.35 mL) via syringe at rt. The reaction mixture was stirred for 10 min. Then a solution of (*R*)-(+)-propylene oxide (120 mg, 0.51 mmol) in THF/HMPA (35.8 mg HMPA in 0.5 mL of THF) was added to the reaction mixture at −78 °C. The mixture was stirred and warmed to rt over 1.5 h, and the reaction was quenched with saturated aqueous $NH_4Cl$ (1 mL). After dilution of the mixture with $Et_2O$, the organic layer was separated. The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 30:1) provided (−)-**3a** (171.5 mg, 96%). $[\alpha]_D^{23} = -40.8$ (*c* 1.1, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.36−4.26 (m, 1H), 4.21−4.13 (m, 1H), 3.92 (d, $J$ = 3.6 Hz, 1H), 2.87−2.73 (m, 4H), 2.44−2.22 (m, 2H), 2.14−1.94 (m, 4H), 1.25 (d, $J$ = 6.0 Hz, 3H), 1.19 (d, $J$ = 6.6 Hz, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 66.9, 64.1, 51.4, 47.1, 46.9, 26.2, 25.7, 25.1, 24.7, 18.0, −3.6, −4.2; MS (ESI) *m*/*z* 389.5, $[M + K]^+$; HRMS ($ES^+$) *m*/*z* 373.1676 $[(M + Na)^+$; calcd for $C_{16}H_{34}O_2S_2SiNa$: 373.1667].

**General Procedure for the Conversion of Compounds 3a−g to Compounds 4a−g (Method A).** To a well-stirred solution of (−)-**3a** (31 mg, 0.09 mmol) in $CH_3CN/H_2O$ (4 mL/1 mL), $HgCl_2$/$CaCO_3$ (72 mg, 0.26 mmol; 36 mg, 0.35 mmol) was added in one portion. The reaction mixture was heated to 65 °C and was stirred for 2 h. After the starting material completely disappeared (monitored by TLC), the reaction mixture was cooled to rt. $Et_2O$ (20 mL) was then added to the mixture, and the mixture was filtered through celite. The filtrate was washed with water and brine and was dried over $Na_2SO_4$. The solution was then filtered and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 15:1) gave the corresponding ketone intermediate as a colorless oil (17.5 mg, 77%). $[\alpha]_D^{23} = -89.7$ (*c* 0.8, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.33−4.19 (m, 2H), 3.14 (d, $J$=3.0 Hz, 1H), 2.70−2.36 (m, 4H), 1.18 (s, 3H), 1.16 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 212.3, 66.7, 64.6, 53.8, 53.5, 26.7, 25.1, 23.1, 18.9, −3.5, −4.0; MS (ESI) *m*/*z* 283.5, $[M + Na]^+$.

The ketone intermediate (28 mg, 0.11mmol) was dissolved in $CH_2Cl_2$ (2 mL). To this solution, DMP (50 mg, 0.12 mmol) and $NaHCO_3$ (84 mg, 1mmol) were added at rt. The mixture was stirred for 15 min, and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The layers were separated. The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 50:1) gave (−)-**4a** as a colorless oil (26 mg, 94%). $[\alpha]_D^{23}$ −99.0 (*c* 0.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.53 (s, 1H), 4.27−4.21 (m, 1H), 2.43−2.24 (m, 2H), 2.07 (s, 3H), 1.20 (d, $J$ = 6.0 Hz, 3H), 0.87 (s, 10H), 0.06 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 192.6, 190.4, 101.6, 66.3, 48.3, 25.7, 25.3, 24.2, 18.0, −4.6, −5.1; MS (ESI) *m*/*z* 281.5, $[M + Na]^+$.

**General Procedure for the Conversion of Compounds 3a−g to Compounds 4a−g (Method B).** To a well-stirred solution of (−)-**3a** (30 mg, 0.09mmol) in $CH_2Cl_2$ (2 mL), DMP (40 mg, 0.09 mmol) and $NaHCO_3$ (84 mg, 1 mmol) were added at rt. The mixture was stirred for 10 min, and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The layers were separated. The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 93:7) gave the corresponding ketone intermediate as a colorless oil (28 mg, 93%). $[\alpha]_D^{23}$ −28.8 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.25 (m, 1H), 3.34 (d, $J$ = 15.6 Hz, 1H), 3.10 (d, $J$=15.6 Hz, 1H), 2.82−2.79 (m, 4H), 2.47 (dd, $J$ = 7.5, 15.0 Hz, 1H), 2.23 (s, 3H), 2.16 (dd, $J$ = 3.3, 15.0 Hz, 1H), 2.00−1.90 (m, 2H), 1.23 (d, $J$ = 6.3 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 204.6, 66.4, 51.2, 49.0, 47.1, 32.1, 26.5, 26.4, 26.0, 25.7, 24.8, 18.0, −3.9, −4.0; MS (ESI) *m*/*z* 371.5, $[M + Na]^+$.

The ketone intermediate (28 mg, 0.08 mmol) was dissolved in $CH_3CN/H_2O$ (6 mL/2 mL). To this solution, $HgCl_2$ (109 mg, 0.4 mmol) and $CaCO_3$ (80 mg, 0.8 mmol) were added. The mixture was then stirred at rt for 4 h. $Et_2O$ (20 mL) was then added to the mixture, and the mixture was filtered through celite. The aqueous

phase was extracted with $Et_2O$ (3 × 5 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 50:1) gave (−)-**4a** as a colorless oil (12.4 mg, 60%).

**One-Step Procedure for the Preparation of (−)-4b from (−)-3b.** To a well-stirred solution of NBS (310 mg, 1.74 mmol) in 10 mL of acetone/water (97/3), a solution of (−)-**3b** (47.2 mg, 0.1 mmol) in acetone (1 mL) was slowly added via syringe in 20 min at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction was then quenched with saturated aqueous $NaHSO_3$ (3 mL), and the layers were separated. The aqueous phase was extracted with $Et_2O$ (3 × 5 mL), and the organic layers were dried over $Na_2SO_4$, filtered, and concentrated. Flash chromatography provided (−)-**4b** as a colorless oil (26 mg, 68%). $[\alpha]_D^{23}$ −78.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.14 (m, 2H), 7.73−7.60 (m, 8H), 6.45 (s, 1H), 5.46 (dd, $J$ = 3.9, 9.0 Hz, 1H), 3.04 (dd, $J$ = 9.0, 13.5 Hz, 1H), 2.90 (dd, $J$ = 3.9, 13.5 Hz, 1H), 1.08 (s, 10H), 0.24 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 192.8, 184.1, 144.5, 135.0, 132.3, 128.6, 128.3, 127.0, 125.6, 98.2, 72.5, 50.8, 25.7, 18.1, −4.8, −5.3; MS (ESI) *m*/*z* 405.5, $[M + Na]^+$; HRMS ($ES^+$) *m*/*z* 405.1877 $[(M + Na)^+$; calcd for $C_{23}H_{30}O_3SiNa$: 405.1862].

**General Procedure for the Preparation of Dihydropyranones 6a−g from 4a−g.** To a well-stirred solution of (−)-**4b** (50 mg, 0.13 mmol) in $CH_2Cl_2$ (4 mL), 10 $\mu$L (14.8 mg, 0.13 mmol) of TFA was added. The mixture was stirred overnight, and the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL). The solution was diluted with $Et_2O$ (10 mL), and the layers were separated. The aqueous phase was extracted with $Et_2O$ (3 × 5 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) provided (+)-**6b** (31 mg, 93%) as a solid. mp. 90−91.5 °C; $[\alpha]_D^{23}$ +111.1 (*c* 1.0, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.62 (m, 2H), 7.30 (m, 8H), 5.95 (s, 1H), 5.42 (dd, $J$ = 3.3, 13.8 Hz, 1H), 2.79 (dd, $J$ = 14.1, 17.1 Hz, 1H), 2.58 (dd, $J$ = 3.6, 16.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 192.9, 170.2, 138.2, 132.5, 131.7, 128.8, 128.7, 128.6, 126.6, 102.2, 80.9, 42.9; MS (ESI) *m*/*z* 251.4, $[M + H]^+$, HRMS ($ES^+$) *m*/*z* 273.0899 $[(M + Na)^+$; calcd for $C_{17}H_{14}O_2Na$: 273.0891].

**Acknowledgment.** This work has been supported by the Washington State University.

**Supporting Information Available:** Synthetic procedures, characterization data of all new compounds, and $^1$H and $^{13}$C NMR spectra. This material is available free of charge on the Internet at http://pubs.acs.org.

JO070346T