Pergamon

Tetrahedron Letters 41 (2000) 183–187

TETRAHEDRON LETTERS

Enantioselective synthesis of 5-substituted α,β-unsaturated δ-lactones: application to the synthesis of styryllactones

Joel M. Harris and George A. O'Doherty *

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

Received 20 September 1999; accepted 22 October 1999

Abstract

A flexible enantioselective synthesis of highly functionalized 5-substituted α,β-unsaturated δ-lactones has been achieved by applying the Sharpless catalytic asymmetric dihydroxylation to vinylfuran as the key step. The resulting diols are produced in high enantio excess and can be stereoselectively transformed into differentially protected δ-lactones through a short reaction sequence.

Keywords: Sharpless dihydroxylation; asymmetric synthesis; lactones; carbohydrates.

Substituted α,β-unsaturated δ-lactones (e.g. styryllactones) are an important class of natural products with a wide range of biological activity.[1] Many natural products from various plants and fungi share the common 5-oxygenated-5,6-dihydro-2*H*-pyran-2-one structural motif, such as goniodiol, acetylphomalactone, and altholactone.[1d] These natural products have biological activity including antitumor and antifungal properties, as well as antibiotic potential. Due to the wide distribution of 5,6-dihydro-2*H*-pyran-2-ones in plants and fungi, many synthetic methodologies have been employed to synthesize this core structure.[1,2]

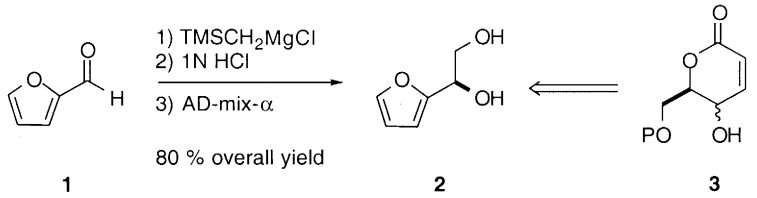
One of the most useful methodologies employed is the kinetic resolution of 2-furylcarbinols developed by Honda,[3] Sato,[4] and augmented by Zhou.[5] This strategy employs the kinetic resolution of racemic 2-furylcarbinols with the Sharpless epoxidation reaction conditions, to produce an optically active pyranone product resulting from the selective fast oxidation of only one enantiomer of the racemic 2-furylcarbinols. The optically pure pyranone or 2-furylcarbinol products of the kinetic resolution can both be used in the synthesis of natural products.

Recently, we developed an expeditious route to various D- or L-sugars from furan diols using Sharpless dihydroxylation to establish the absolute stereochemistry.[6] Continuing our investigations on the utility of this strategy, we turned our attention to the styryllactone class of natural products. For the synthesis of these natural products we envisioned δ-lactones **3** as excellent building blocks amenable for the synthesis of a variety of styryllactones (Scheme 1). We envisioned extending our earlier work to synthesize these

* Corresponding author.

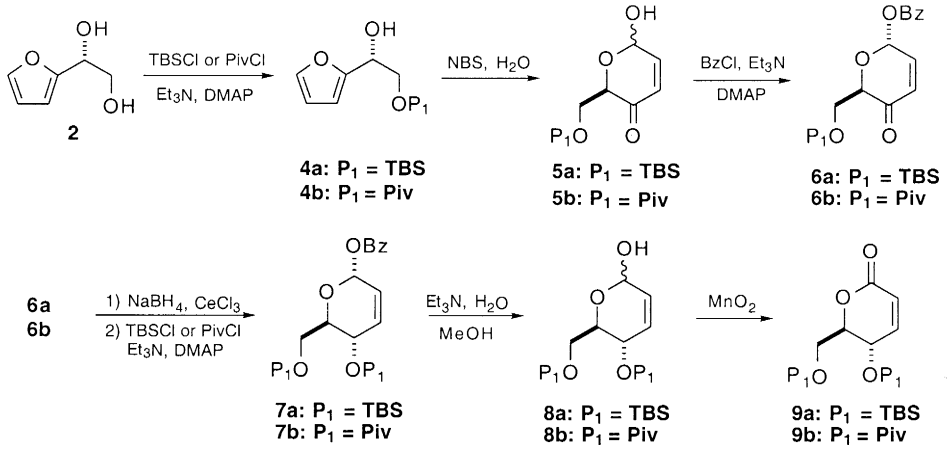
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02050-X

useful building blocks from pyranone **6** with differentiated oxygen functionality in a limited number of steps and avoiding kinetic resolution. Herein, we describe our approach to the synthesis of these key building blocks via an efficient enantioselective and diastereoselective oxidation and reduction sequence.



Scheme 1.

A key intermediate in our six-step enantioselective route to D- and L-hexoses from furfural was pyranone **6a** (Scheme 2). The asymmetry of **6a** was derived from diol **2**, which can be prepared on a one mole scale from a Sharpless dihydroxylation[7] of vinylfuran in 90–92% ee, and recrystallized to >97% ee[8] from the dibenzoate formed from diol **2**. Protection of diol **2** with either TBSCl or PivCl yields the mono-protected furans **4a** or **4b** in 90% and 70% yields, respectively. Using NBS[9] furans **4a** or **4b** can be oxidatively ring expanded to yield enones **5a** and **5b** in 95% yield. Protection of enone **5a** or **5b** with BzCl at −78°C yielded **6a** exclusively and **6b** in a 7:1 ratio with the axial benzoate predominating in 75% yield. With this expedient and enantioselective route to benzoate **6a** or **6b**, we initially investigated a synthesis of **3** from **6a** or **6b**.

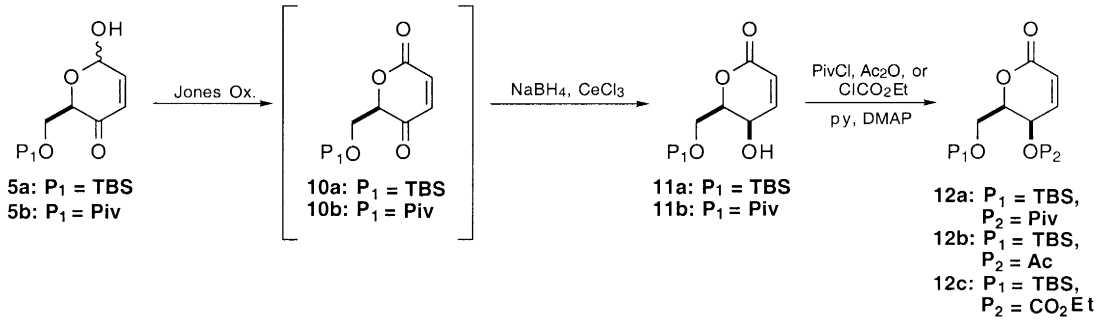


Scheme 2.

Luche reduction[10] of enone **6a** or **6b** provides **7** in >96% ee,[8] followed by protection provided allylic alcohol **7a** or **7b** as a single diastereomer in 75% yield over two steps. Deprotection of the anomeric benzoyl group proved troublesome, with the best results obtained using Et_3N, MeOH, H_2O in a 1:5:1 ratio, giving lactol **8a** or **8b** in 50–60% yield. Oxidation of **8a** or **8b** with MnO_2 provided the α,β-unsaturated δ-lactone **9a** or **9b** in 75–85% yield.[11]

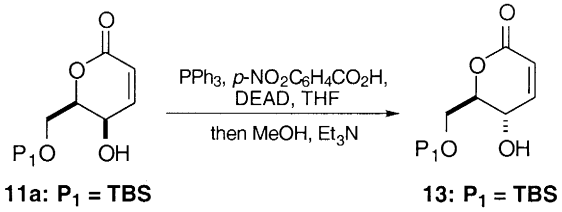
Having established the feasibility of preparing the α,β-unsaturated δ-lactone **9a** and **9b** with complete enantio- and diastereocontrol, we turned our attention to improving the efficiency of the route to **3**. The obvious disadvantage of the route in Scheme 2 is the requisite protection of the C-1 and C-4 hydroxyl groups. A significant reduction in steps could be achieved by oxidation of the lactol **5** to ketolactone **10** provided the carbonyl groups could be reductively differentiated (Scheme 3). Similar approaches have been used by other groups using CrO_3 and acetic acid.[12] A potential problem of this shorter

route is the possible racemization or β-elimination in the ketolactone. We envisioned using a reagent for fast oxidation of lactol **5** to ketolactone **10** that would be immediately compatible for exposure to Luche conditions.[13] This was most easily accomplished by Jones oxidation followed by Luche reduction (Scheme 3).



Scheme 3.

Treatment of an acetone solution of **5a** or **5b** with a slight excess of Jones reagent produced ketolactones **10a** or **10b** in ~20 min. Upon completion the reaction mixture was quenched with isopropyl alcohol, washed with a saturated $NaHCO_3$ solution, and extracted with ether. After solvent exchange (ether to MeOH), **10a**[14] and **10b** were treated with $NaBH_4$ to yield differentially protected δ-lactones **11a**[15] or **11b** in 60–70% yield over two-steps with no loss of enantiomeric excess.[8] The observed stereoselectivity of the reduction is explained by the apparent hydride attack on the less hindered face of the molecule.[16] Protection of the allylic alcohol using PivCl, Ac_2O, or $ClCO_2Et$ provided **12a**, **12b**, or **12c**[17] in 80%, 94%, and 90% yields, respectively. The diastereomeric lactone **13**[18] can be prepared from **11a** by a Mitsunobu reaction[19] followed by hydrolysis of the *p*-nitro-benzoyl group in 70% yield over two-steps (Scheme 4). This not only provides a shorter route to **11** and **13**, but also provides the δ-lactone in a higher overall yield (~45% to **11** and 32% to **13** from diol **2** as compared to ~20% to **9** from diol **2**).



Scheme 4.

In conclusion, this highly enantio- and diastereocontrolled route to the δ-lactones described illustrates the utility of the enantioselective dihydroxylation reaction of vinylfuran, eliminating the need for kinetic resolution of 2-furylcarbinols. The route provides rapid and enantioselective access to a densely functionalized molecule starting from a commercially available, inexpensive starting material. Further studies on the use of these chiral building blocks toward the synthesis of this class of natural products will be reported in due course.

Acknowledgements

We thank the University of Minnesota (grant in aid program), the American Cancer Society for an Institutional Research Grant (IRG-58-001-40-IRG-19) and the American Chemical Society — Petroleum Research Fund (ACS-PRF#33953-G1) for their generous support of our program.

References

1. (a) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem*. **1995**, *60*, 7567–7574 and references cited therein. (b) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; McLaughlin, J. L.; Fanwick, P. E. *J. Nat. Prod*. **1991**, *54*, 1034. (c) Argoudelis, A. D.; Zieserl, J. F. *Tetrahedron Lett*. **1966**, *18*, 1969. (d) For a review of 5,6-dihydro-2*H*-pyran-2-ones, see: Davies-Coleman, M. T.; Rivett, D. E. A. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, Ch., Eds.; Springer-Verlag: New York, 1989; Vol. 55, pp. 1–35.
2. (a) Schlessing, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1999**, *40*, 1257–1260. (b) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493–2514. (c) Chen, W.-P.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 103–105. (d) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3125–3126. (e) Yang, Z.-C.; Jiang, X.-B.; Wang, Z.-M; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 317–321. (f) Gomez, A. M.; Lopez de Uralde, B.; Valverde, S.; Lopez, J. C. *Chem. Commun*. **1997**, 1647. (g) Honda, T.; Sano, N.; Kanai, K. *Heterocycles* **1995**, *41*, 425–429. (h) Yang, Z.-C.; Zhou, W.-S. *Tetrahedron Lett*. **1995**, *36*, 5617–5618. (i) Masaki, Y.; Imaeda, T.; Oda, H.; Itoh, A.; Shiro, M. *Chem. Lett*. **1992**, 1209–1212. For a review, see: (j) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons: New York, 1993; pp. 3–131; 271–396.
3. (a) Kametani, T.; Tsubuki, M.; Tatsuzaki, Y.; Honda, T. *Heterocycles* **1988**, *27*, 2107–2110. (b) Kametani, T.; Tsubuki, M.; Tatsuzaki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 639–646. (c) Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1733–1737.
4. (a) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem*. **1988**, *53*, 1587–1590. (b) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem*. **1989**, *54*, 2085–2091.
5. (a) Yang, Z.-C.; Zhou, W.-S. *Tetrahedron Lett*. **1995**, *36*, 5617–5618. (b) Yang, Z.-C.; Jiang, X.-B.; Wang, Z.-M.; Zhou, W.-S. *J. Chem. Soc., Chem. Commun*. **1995**, 2389. (c) see Ref. 2e.
6. Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem*. **1999**, *64*, 2982–2983.
7. (a) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synlett* **1996**, 971. (b) Taniguchi, T.; Ohnishi, H.; Ogasawara, K. *Chem. Commun*. **1996**, 1477–1478. For a review, see: (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483–2547.
8. Enantiomeric excesses were determined by ^{1}H NMR and ^{19}F NMR of the Mosher ester derivative.
9. (a) Grapsas, I.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem*. **1990**, *64*, 823. (b) Georgiadis, M. P.; Couladoros, E. A. *J. Org. Chem*. **1986**, *51*, 2725–2727.
10. Luche, J.-L. *J. Am. Chem. Soc*. **1978**, *110*, 2226.
11. The absolute and relative stereochemistry of **9a** and **9b** were determined by correlation to our previous syntheses of a protected gulose and talose whose stereochemistry were determined by X-ray crystal analysis, see Ref. 6.
12. (a) Kuo, Y.-H.; Shih, K.-S. *Heterocycles* **1990**, *31*, 1941–1949. (b) Tsubuki, M.; Kanai, K.; Honda, T. *J. Chem. Soc., Chem. Commun*. **1992**, 1640–1641. (c) Zhou, W.-S.; Yang, Z.-C. *Tetrahedron Lett*. **1993**, *34*, 7075–7076. (d) see Refs. 2e, 2h.
13. Ketolactone **10** decomposed when attempting to purify by silica gel chromatography.
14. Preparation of compound **10a** was easily accomplished by dissolving **5a** in acetone, followed by dropwise addition of Jones reagent until the starting material was absent by TLC (~15–20 min) and the reaction was quenched with isopropyl alcohol, washed with sat. $NaHCO_3$, extracted with ether, and dried with $MgSO_4$. Data for compound **10a**: $[\alpha]_D^{21}$=+55.77 (c=3.71, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J*=10 Hz, 1H); 6.73 (d, *J*=10 Hz, 1H); 4.83 (dd, *J*=1.5, 2 Hz, 1H); 4.01 (dd, *J*=1.5, 12.5 Hz, 1H); 3.97 (dd, *J*=2, 12.5 Hz, 1H); 0.74 (s, 9H); −0.04 (s, 3H); −0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 192.3, 160.5, 138.8, 136.1, 84.3, 65.1, 25.4, 17.9, −5.9, −6.0; IR (thin film, cm^{-1}) 3949, 2928, 2892, 2856, 1719, 1697, 1461, 1360, 1306, 1261, 1128, 1083, 1023; HR CIMS calcd for $[(C_{12}H_{20}O_4Si)+H]^+$: 257.12091, Found: 257.1218. Anal. calcd for $C_{12}H_{20}O_4Si$: C, 56.23; H, 7.87. Found: C, 56.10; H, 7.68.
15. Data for compound **11a**: $[\alpha]_D^{21}$=−73.18 (c=0.9, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 6.25 (dd, *J*=6, 9.5 Hz, 1H); 5.73 (d, *J*=9.5 Hz, 1H); 3.96 (dd, *J*=7, 10 Hz, 1H); 3.87 (ddd, *J*=3, 5, 7 Hz, 1H); 3.79 (dd, *J*=5, 10 Hz, 1H); 3.76 (m, 1H); 3.00 (bs, 1H); 0.98 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, ppm) δ 163.1, 144.2, 122.7, 79.9, 61.7, 60.4, 26.0,

18.4, −5.3, −5.4; IR (thin film, cm^{-1}) 3424, 2954, 2930, 2885, 2857, 1714, 1472, 1257, 1137, 1098, 1059; HR CIMS calcd for $[(C_{12}H_{22}O_4Si)+H]^+$: 259.13656, Found: 259.1355. Anal. calcd for $C_{12}H_{22}O_4Si$: C, 55.79; H, 8.59. Found: C, 55.63; H, 8.45.

16. Various selectivities have been observed depending on the steric bulk of the substituent at C-5. (a) Honda, T.; Takada, H.; Miki, S.; Tsubuki, M. *Tetrahedron Lett.* **1993**, *34*, 8275–8278. (b) Tsubuki, M.; Takada, H.; Katoh, T.; Miki, S.; Honda, T. *Tetrahedron* **1996**, *52*, 14515–14532. (c) see Refs. 2e, 5a, 11a–c.
17. All new compounds were identified and characterized by ^1H NMR, ^{13}C NMR, FTIR, HRMS, and EA analysis.
18. Data for compound **13**: $[\alpha]_D^{21}=-20.45$ (c=1.11, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (dd, *J*=2.5, 10 Hz, 1H); 5.95 (dd, *J*=2, 10 Hz, 1H); 4.64 (ddd, *J*=2, 5.5, 9.5 Hz, 1H); 4.31 (ddd, *J*=4, 7, 9.5 Hz, 1H); 4.04 (dd, *J*=4, 10.5 Hz, 1H); 3.89 (dd, *J*=7, 10.5 Hz, 1H); 3.30 (bs, 1H); 0.90 (s, 9H); 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 162.4, 148.8, 119.6, 80.0, 65.5, 64.0, 25.7, 18.2, −5.56, −5.58; IR (thin film, cm^{-1}) 3432, 2954, 2929, 2857, 1712, 1472, 1256, 1138, 1101, 1055, 1025; HR CIMS calcd for $[(C_{12}H_{22}O_4Si)+H]^+$: 258.12874, Found: 259.1389. Anal. calcd for $C_{12}H_{22}O_4Si$: C, 55.79; H, 8.59. Found: C, 55.61; H, 8.59.
19. Mitsunobu, O. *Synthesis* **1981**, 1.