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New arene *cis*-dihydrodiol metabolites from β-bromostyrenes

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Abstract

Both (*E*)- and (*Z*)-β-bromostyrenes are substrates for toluene dioxygenase from *Escherichia coli* (JM109, pDTG601) and yield the corresponding diol metabolites in yields of 1 g/L, respectively.

The reports of new *cis*-diol metabolites[1] of aromatics continue to be published with increasing frequency as such compounds find an expanding utility in enantioselective synthesis.[2] Several years ago we published a report on the oxidation of *o*-, *m*-, and *p*-chlorostyrenes[3] by the recombinant organism designed and provided by David Gibson.[4] Several other bromoaromatics have also been found to be substrates for the enzyme[5] and some of these have been and are of interest as potential starting materials for the synthesis of morphine alkaloids.[6] Consequently, it is now possible to design a synthesis based on an *anticipated* rather than a *known* structure. In this manuscript we report the preparation and absolute stereochemistry of compounds **2a** and **2b**,[7] which were targeted as ideal synthons for intramolecular Diels–Alder cycloadditions.

The whole cell fermentation was carried out as previously reported.[8] Following isolation of the diols **2a** and **2b**, the absolute stereochemistry was determined as shown in Scheme 1. Diimide reduction (potassium azodicarboxylate (PAD), methanol and acetic acid, 50% yield) of the diols furnished diols **3a** and **3b**, the protection of which was followed by removal of the halogen via metal/halogen exchange (*t*-butyl lithium, 72%) to provide **4**. Further diimide reduction (PAD) of the vinyl group and deprotection afforded compound **5** (20%), which was shown to be identical (^{1}H NMR, melting point and $[\alpha]_D$)[9] to the material derived from styrene diol **6**[10] whose absolute configuration is known.[11] The two compounds are excellent intermediates for an approach to morphine[6] and progress in this area will be reported in due course.

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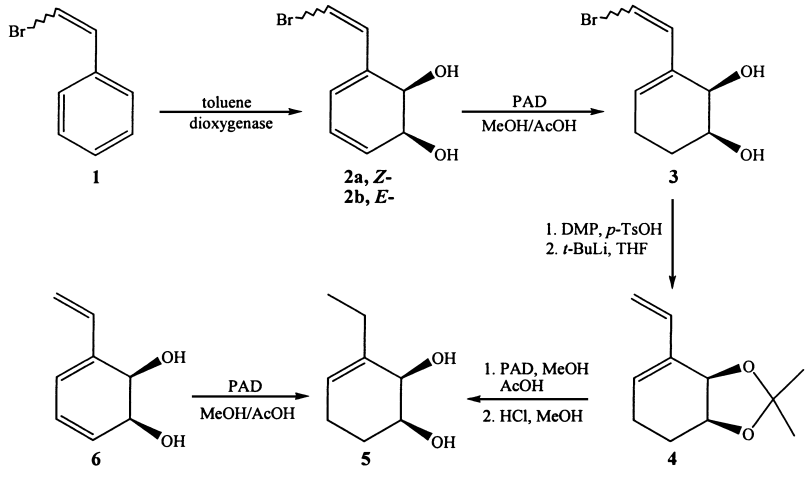

Scheme 1.

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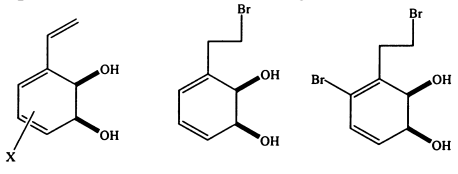
5. The following styrene-related metabolites have been identified: *o*-bromostyrene: Konigsberger, K.; Hudlicky, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2469; Ref. 3a,b; bromoethylbenzene: Stabile, M. R.; Hudlicky, T.; Meisels, M. L. *Tetrahedron: Asymmetry* **1995**, *6*, 537; *o*-bromo bromoethylbenzene: Stabile, M. R.; Hudlicky, T.; Meisels, M. L.; Butora, G.; Gum, A. G.; Fernley, S. P.; Thorpe, A. J.; Ellis, M. R. *Chirality* **1995**, *7*, 556.



6. (a) Hudlicky, T.; Boros, C. H.; Boros, E. E. *Synthesis* **1992**, 174; (b) Butora, G.; Hudlicky, T.; Fernley, S. P.; Stabile, M. R.; Gum, A. G.; Gonzalez, D. *Synthesis* **1998**, 665; (c) Hudlicky, T.; Butora, G.; Gum, A. G.; Abboud, K. A. *Synthesis* **1998**, 275.
7. Experimental data for the metabolites: **2a**: (*Z*)-β-bromostyrene diol was isolated as a brown oil; $[\alpha]_D^{25}$=40.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, *J*/Hz) δ 6.70 (d, *J*=8.3, 1H), 6.49 (d, *J*=5.6, 1H), 6.26 (d, *J*=8.3, 1H), 6.03 (ddd, *J*=9.6, 5.5, 2.0, 1H), 5.95 (dd, *J*=9.4, 2.8, 1H), 4.57 (d, *J*=6.1, 1H), 4.44–4.37 (m, 1H), 2.61 (br s, 1H), 2.31 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 134.3, 132.2, 130.7, 127.2, 124.0, 106.0, 69.3, 67.0. **2b**: (*E*)-β-bromostyrene diol was isolated as a white solid, mp=48–51°C; $[\alpha]_D^{23}$=83.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, *J*/Hz) δ 6.76 (d, *J*=14.0, 1H), 6.66 (d, *J*=14.2, 1H), 6.01–5.88 (m, 3H), 4.41 (td, *J*=5.9, 2.2, 1H), 4.25 (d, *J*=5.9, 1H), 2.29 (br s, 1H), 1.61 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 136.4, 135.8, 132.2, 124.8, 124.0, 108.1, 70.0, 66.6.
8. The fermentations were carried out as described previously (Refs. 3a, 6a) in a 12 L fermentor using IPTG as the inducer. Hudlicky, T.; Stabile, M. R.; Gibson, D. T.; Whited, G. M. *Org. Synth*. **1999**, *76*, 77.
9. Experimental data for **5** synthesized from β-bromostyrene diols **2a** and **2b**: mp=78–79°C; $[\alpha]_D^{25}$=−156.9 (*c* 1.0, $CHCl_3$).
10. Experimental data for **5** prepared from **6**: isolated as a white solid, mp=79–80°C; $[\alpha]_D^{27}$=−150.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, *J*/Hz) δ 5.54 (br s, 1H), 3.98 (d, *J*=3.8 Hz, 1H), 3.75–3.69 (m, 1H), 2.77 (br s, 2H), 2.21–2.05 (m, 4H), 1.73–1.65 (m, 2H), 1.03 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 139.1, 123.7, 69.8, 68.8, 27.1, 25.3, 24.0, 12.4; IR (KBr/cm^{-1}) ν 3275, 1459. HRMS (EI): calcd for $C_8H_{15}O_2$: *m/z* 143.1776; found: 143.1072. Anal. calcd for $C_8H_{14}O_2$+1/3H_2O: C, 65.10; H, 9.97; found: C, 65.21; H, 9.56.
11. Hudlicky, T.; Boros, C. H. *Tetrahedron Lett*. **1993**, *34*, 2557.