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ENANTIOSELECTIVE SYNTHESIS OF THE 6,8-DIOXABICYCLO-[3.2.1]OCTANE SKELETON BY ASYMMETRIC DIHYDROXYLATION

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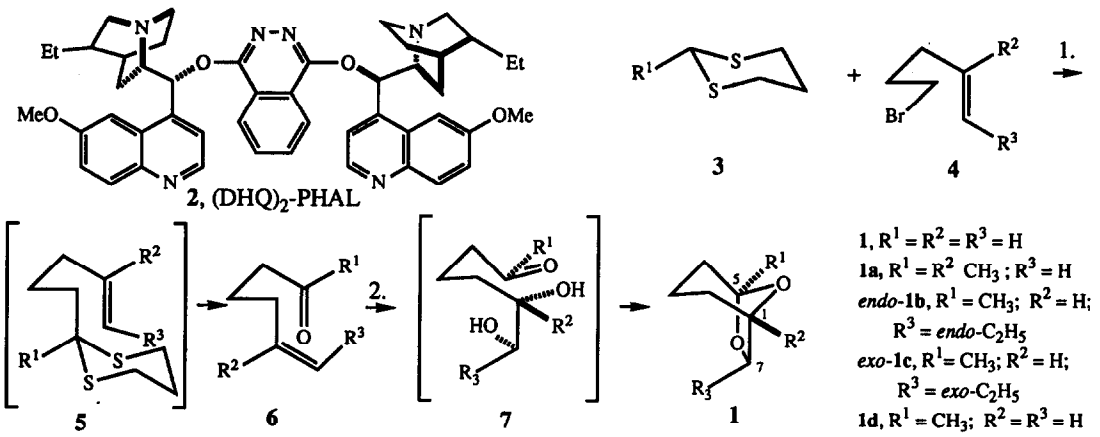
Summary (Keywords): Sharpless asymmetric dihydroxylation (AD) of 6-hepten-2-one with AD-mix-α® followed by acidification gives (1*S*,5*R*)-5-methyl-6,8-dioxabicyclo[3.2.1]octane in moderate ee. This methodology defines a two-pot enantioselective construction of the (-)-frontalin and brevicomin skeleton from the corresponding 2-alkyl-1,3-dithiane and 5-bromo-1-hexene derivatives.

The 6,8-dioxabicylo[3.2.1]octane ring system **1** ($R^1 = R^2 = R^3 = H$, see Scheme) defines the basic skeleton of the beetle aggregation pheromone (-)-frontalin (**1a**, $R^1 = R^2 = CH_3$; $R^3 = H$) and *endo*/*exo*-brevicomin (*endo*-**1b**, $R^1 = CH_3$, $R^2 = H$; R^3 = *endo*-C_2H_5; *exo*-**1c**, $R^1 = CH_3$, $R^2 = H$, R^3 = *exo*-C_2H_5).[1] Published enantioselective syntheses[2] of derivatives of **1** are lengthy or produce racemic derivatives.[3] Since the absolute stereochemistry of **1** can be set by a 1,2-diol, the adaptation of ligand accelerated catalytic (LAC) asymmetric dihydroxylation (AD)[4] appeared well-suited to the construction of this ring system. Recently, Sharpless disclosed improvements to the AD process[5] mediated by the 1,4-bis-dihydroquinine phthalazine ligand $(DHQ)_2$-PHAL (**2**). A premix of **2** with potassium ferricyanide, potassium carbonate and potassium osmate ("AD-mix-α"[6a,b]) makes the oxidation protocol exceptionally simple.

The monosubstituted olefin 6-hepten-2-one (**6**, $R^1 = CH_3$, $R^2 = R^3 = H$) was selected as an appropriate substrate for testing this LAC transformation into the (-)-frontalin framework. Thus, dithiane **3** ($R^1 = CH_3$) was converted into the 2-lithio-1,3-dithiane derivative **7** by reaction with *n*-BuLi in THF-hexane (0.5 M, -20 °C, 2 h) and alkylated with 5-bromo-1-hexene (-78 to -25 °C). Intermediate dithiane **5** ($R^1 = CH_3$, $R^2 = R^3 = H$) could be isolated and purified[8] (92%) but generally was reacted directly with 5 equiv of methyl iodide and 3 equiv of calcium carbonate in 10% aqueous acetonitrile (5 ml/g **5**, 25 °C, 96 h) affording 6-hepten-2-one (**6**, $R^1 = CH_3$, $R^2 = R^3 = H$; bp 40 °C at 10 torr) in 83% yield from **3**. Oxidation of **6** with AD-mix-α (1.4 g/mmol **6**)[5, 6a] in 1:1 *tert*-butyl alcohol-water (0.05 M, 0 °C, 18 h) provided the *S* diol **7** ($R^1 = CH_3$, $R^2 = R^3 = H$) in situ. Direct treatment of the reaction mixture with hydrochloric acid (pH = 2, 25 °C) gave (1*S*,5*R*)-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**1d**, $R^1 = CH_3$, $R^2 = R^3 = H$) in 84% yield admixed with approx 15-20 % of the corresponding (1*R*, 5*S*)[8] enantiomer (*ent*-**1d**).

Adaptation of the improved Sharpless LAC-AD methodology allows rapid and facile synthesis of the carbon-oxygen framework of (-)-frontalin and brevicomin in 60-70% ee. The modest ee might be due to the disruption

Scheme



(1). 1.05 equiv *n*-BuLi, **3** ($R^1 = CH_3$), -20 °C, 2 h; 1.15 equiv **4** (R^2 = H), -78 to -25 °C, 72 h; 5 equiv CH_3I, CH_3CN, 3 equiv $CaCO_3$, 25 °C, 94 h. (2). AD-mix-α, 1:1 *tert*-BuOH-H_2O, 0 °C, 18 h; HCl, 25 °C.

of the LAC process by the carbonyl of **6**. However, ee's in this range would prove useful in the synthesis of this class of pheromones since partially racemic mixtures remain biologically active in practical applications.[3,9]

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REFERENCES AND NOTES

1. Payne, T. L.; Andryszak, N. A.; Wieser, H.; Dixon, E. A.; Ibrahim, N.; Coers, J. *J. Chem. Ecol.* **1988**, *14*, 1217.
2. A recent account: Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron*, **1991**, *47*, 6967.
3. Yus, M.; Ramón, D. J. *J. Org. Chem.***1992**, *57*, 750.
4. Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
5. Sharpless, K. B. Presented at The Fifth Biennial Lilly Grantee Symposium, Indianapolis, Indiana, February 24-25, 1992; paper 6. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A., Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.: Wang, Z.: Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, *57*, 2768
6. (a) The AD-mixes are now commercially available from Aldrich Chemical Corporation. (b) AD-mix-α is a mixture of potassium ferricyanide (979.9 g), potassium carbonate (411.6 g), **2** (7.73 g) and potassium osmate (0.73 g). AD-mix-β is also available and is of a similar composition with the corresponding 1,4-bis-dihydroquinidine phthalazine analog of **2**. Oxidation of **6** with AD-mix-β gave *ent*-**1d** in approx 60 % ee.
7. Seebach, D; Corey, E. J. *J. Org. Chem.***1975**, *40*, 231.
8. All intermediates displayed expected ^1H NMR, ^{13}C NMR, IR, and mass spectral data. Purity was established by GC on 30 m x 0.25 mm x 0.25 μ DB-1 fused silica column at 50-220 °C and by TLC (silica gel with 4:1 hexane-ethyl acetate). Intermediates **6** and **1d** are volatile and yields are corrected for solvent content. Enantiomeric excesses were determined by HPLC of the purified primary mono-benzoate of **7** or *ent*-**7** (1 equiv of PhCOCl-pyridine with diol in CH_2Cl_2 and chromatography) on a Chiralcel® OD column with 200:10:1 hexane-isopropanol-diethylamine as eluent and by direct GC analysis on **1d** or *ent*-**1d** with a 50 m x 0.25 mm LIPODEX®-E at 50-220 °C with He carrier. See König, W. A.; Icheln, D.; Runge, T.; Pforr, I.; Krebs, A. *J. High Resolution Chromatography*. **1990**, *13*, 702.
9. Joshi, N. N.; Mamdapur, V. R.; Chadha, M. S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2963.

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