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Stereospecificity for the Zinc Borohydride Reduction of α-Aryloxy-β-Hydroxy Ketones

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ABSTRACT

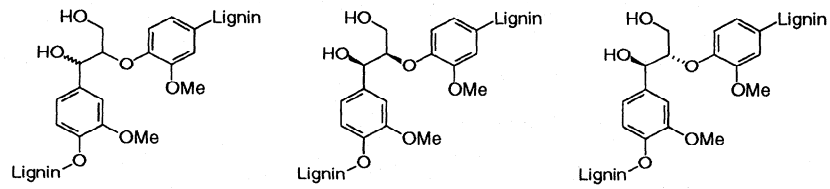
Several lignin model precursors have been submitted to zinc borohydride reductions and their resultant stereochemistries determined by NMR spectroscopy. Benzoyl carbonyls of α-aryloxy-β-hydroxy systems were reduced without significant stereoselectivity to produce both *threo* and *erythro* isomers. However, protection of the β-hydroxyl with either an acyl, alkyl, or silyl group and subsequent reduction gave *erythro*-specificities of up to 97%. A mechanism where competition for zinc cation complexation between the β-hydroxyl and the α-aryloxy substituent is invoked to explain the observed results. Protection of the β-hydroxyl prevents its complexation with the zinc cation; complexation occurs solely with the α-aryloxy substituent, affording the *erythro*-isomers.

INTRODUCTION

Recent investigations concerning the biochemistry of monolignol utilization in plants have suggested that lignification is much more complicated than a peroxidase-initiated random coupling of free radicals.[1,2] Numerous enzymes may be involved, and stereoselective coupling may be an important component of the lignification sequence. The complex structure of native lignin precludes accurate chemical assessment, and the lignin chemist has traditionally relied on the preparation and subsequent study of the chemical and biochemical fate of appropriate model

compounds. As chemical and biochemical investigations concerning lignification become more sophisticated, the need for facile routes to complex diastereomeric and enantiomeric lignin models will become imperative.

The most common interunit linkage in lignin is depicted as subunit **A**, which accounts for ca. 40-50% of all linkages in wood lignins.[3] A lignin dimer of this type exists as a pair of diastereomers, generally referred to as *threo* (**B**) and *erythro* (**C**). Although the *threo/erythro* terminology does not strictly apply here, it has been universally applied to these compounds by analogy with the related glycols. As two separate routes are currently required to prepare the *threo* and *erythro* model isomers of this interunit linkage,[4-7] it is of interest to identify a unified strategy for this important class of lignin diastereomers.



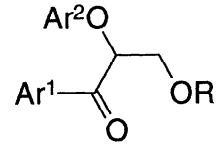
Of the two strategies, that originally outlined by Alder[5] is more flexible than the convergent synthesis of Nakatsubo[6,7] in that a wide variety of B-ring phenols can be added. Adler's method has since gone under several modifications (see for example ref. 4 and references cited therein). However, the key transformation for the generation of *threo* and *erythro* isomers is the selective reduction of the benzoyl carbonyl of α-aryloxy-β-hydroxy type systems (**i**).[4,5] Reduction affords the two diasteromers, and the ratio of each depends on the choice of solvent and reducing agent, as well as the β-substituents (OR^2 and R^3).[8-11] Generally, the reduction of α-aryloxy-β-hydroxy ketones with $NaBH_4$ in aqueous ethanol affords the *threo* isomer (70-90% *threo*),[10,11] and currently there is no particularly selective reduction to afford the *erythro*-isomers.[10] We have investigated the use of $Zn(BH_4)_2$ for the reduction of α-aryloxy-β-hydroxy ketones and have found that the β-hydroxyl group plays a crucial role in the stereochemical outcome. High *erythro* selectivity (up to 97%) can be obtained through the use of $Zn(BH_4)_2$ as long as the β-hydroxyl is protected. Therefore, reductions with sodium and zinc borohydrides allows one

precursor to be used for the diastereoselective generation of enriched *threo* or *erythro* isomers. The utility and mechanistic aspects of this reaction, with respect to lignin chemistry, are reported herein.

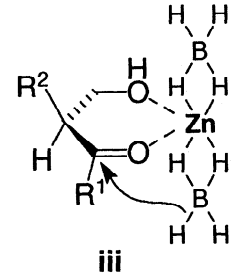
RESULTS AND DISCUSSION

The utility of zinc borohydride for the reduction of ketones resides in the ability of the zinc cation to complex with ester and hydroxyl functionalities α and β to the ketone to be reduced.[12-20] The reduction of structures of type **iii** and **iv** where R^2 = Me favors formation of *erythro* alcohols. Complexation of the zinc cation with the carbonyl and β-substituent on the face away from the α-substituent (R^2 = Me) and subsequent hydride attack produces the *erythro*-product. Extending this reduction pathway to lignin models of type **iii** (R^1 = aryl; R^2 = aryloxy), complexation/reduction on the face opposite the α-aryloxy group would afford, in lignin nomenclature, a *threo*-product.

The stereochemical outcome for the $Zn(BH_4)_2$ reduction of several lignin model



i R = H
ii R = acyl, alkyl, or silyl



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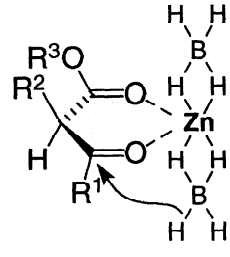

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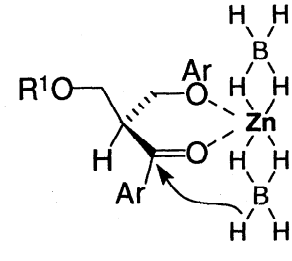

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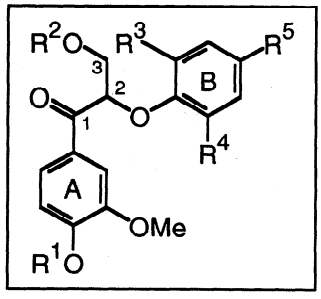
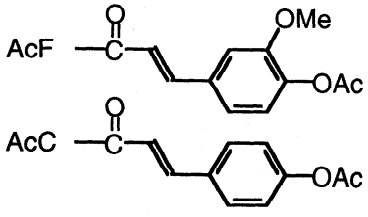
Table 1. Zinc Borohydride Reduction *threo/erythro* Product Ratios[a]

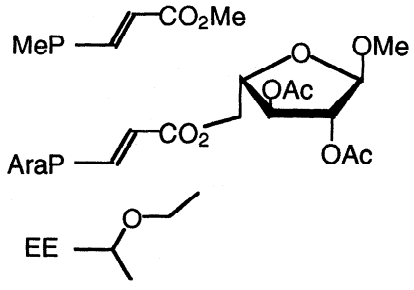
Compound	*threo:erythro*
1	55:45
2	52:48
3	70:30
4	60:40
5	64:36
6	5:95
7	5:95
8	5:95
9	14:86
10	3:97
11	4:96

[a]Determined by NMR spectroscopy via integration of the appropriate side-chain proton signals (±2%).



	R^1	R^2	R^3	R^4	R^5
1	Ac	H	H	H	MeP
2	Ac	H	H	OMe	MeP
3	Ac	H	OMe	OMe	MeP
4	Ac	H	H	OMe	AraP
5	Bn	H	H	OMe	H
6	Bn	Ac	H	OMe	H
7	Ac	AcC	H	OMe	H
8	Ac	AcF	H	OMe	H
9	Ac	Ac	OMe	OMe	MeP
10	Ac	TBDMS	H	OMe	H
11	Bn	EE	H	OMe	H





precursors is compiled in Table 1. It is readily apparent that the benzoyl carbonyls of α-aryloxy-β-hydroxy systems (**1-5**) did not undergo reduction with significant stereoselectivity. The *threo*-isomer was slightly favored in all cases with the α-(2,6-dimethoxyphenoxy) substituent (**3**) affording a 70% *threo*-product. However, acylation, alkylation, or silylation of the β-hydroxyl (**6-11**) and subsequent reduction typically gave the hydroxy compounds with high *erythro*-selectivity. The reduction of **9** (the acetylated derivative of **3**) provided an increased proportion of the *erythro*-product when compared to **3**, but was not as highly stereoselective.

For compounds of type **i**, competition between the α-aryloxy oxygen and the β-hydroxyl for complexation with the zinc cation would afford structures of type **iii** (R^1 = aryl, R^2 = aryloxy) and **v** (R^1 = H). Reduction of these complexes affords the intermediate *threo/erythro* reduction ratios observed for **1-5**.[9] That the *threo*-isomer predominated indicates that complexation with the β-hydroxyl (**iii**) was more influential than the α-aryloxy (**v**) substituent. Extending this rationale to compounds of type **ii**, protection of the β-hydroxyl group has allowed the α-aryloxy group to exert more of an influence over the course of the reduction, allowing a type **v** complex to be the predominant species. Hydride attack occurs on the face opposite that of the protected β-hydroxyl, affording the *erythro*-isomer. That the protective group on the β-hydroxyl is not complexing with the zinc cation is demonstrated by the reduction of **10** and **11**, where TBDMS and 1-ethoxyethyl groups were employed; high *erythro*-selectivity was observed in both cases.

There are several literature precedents concerning the reduction of lignin model compounds similar to type **i**. *Threo*-selectivity is generally observed with $NaBH_4$, and the ratio is very much dependent on the choice of solvent.[4,10,11] Simplified complexation mechanisms involving the β-hydroxyl and the sodium cation have been used to explain the results (type **iii**), although a complicated mechanism involving the lignin model, solvent and metal hydride is probably a closer approximation. The $NaBH_4$ reduction of **6** was found to give a predominantly *threo* product in methanol (70%)[11] and ethanol:H_2O (80%),[10] whereas the reduction of **5** under phase-transfer conditions (KBH_4/N-dodecyl-N-methylephedrium bromide in benzene/H_2O) gave a 1:3 *threo:erythro* mixture.[4] Clearly there are several driving forces involved in the reduction stereoselectivity, and no reductions have been reported for type **i** compounds with high (>90%)*threo* or *erythro* selectivity. In contast, high *erythro*-selectivity (>90%) has been invariably observed for borohydride reductions

when the β-hydroxylmethyl has been replaced by a methyl group.[8,9] This *erythro*-selectivity with a terminal methyl group has been observed with $NaBH_4$, lithium tri-*sec*-butyl borohydride, lithium aluminum hydride and $Zn(BH_4)_2$ reductants.[8,11] This suggests a general trend for this type of lignin model which may not involve complexation, but be solely a matter of sterics.

It should be mentioned that the reduction of the β-acetates **6** and **9** was accompanied by a slow 1,3-acetyl migration. This was observed in the ^{1}H-nmr spectra of the crude products, as the secondary acetate is typically a doublet with a chemical shift of ca. 6.1 ppm, whereas the unacetylated proton is a multiplet (due to coupling to the hydroxyl proton) and has a chemical shift in the vicinity of 4.9-5.0 ppm. Chemical shift changes of the same magnitude are also observed for the primary hydroxyl/acetate. No migrations were observed for the reduction products of the β-(4-acetoxycinnamates) **7** and **8**.[21] In order to eliminate this problem when determining the *threo:erythro* ratios (by NMR) for the reduction of **6** and **9**, the crude reduction products were acetylated prior to determination of the ratios.

The highly stereoselective reductions of hydroxyl-protected lignin ketone models obtained with $Zn(BH_4)_2$ allows for preparation of *erythro*-diastereomers of the guaiacylglycerol-β-guaiacyl ether lignin inter-unit substructure (subunit **A**), utilizing the strategy originally developed for the *threo*-diastereomers. The different stereoselectivities for $Zn(BH_4)_2$ and $NaBH_4$ (aq.-ethanolic) allows for the preparation of both *erythro* and *threo* diastereomers, respectively, utilizing the same ketone precursor. The reductant may also be quite useful for the stereoselective transformation of other α-aryloxy-β-hydroxy ketones of synthetic interest.

EXPERIMENTAL

The general chemical and spectroscopic techniques used throughout this study have been described.[2] All NMR experiments were performed with a 360 MHz instrument at 300 K with acetone-d_6 as the solvent and internal reference (central solvent peak, δ_H, 2.04 ppm; δ_C, 29.8 ppm). Acetylations were performed with acetic anhydride (Ac_2O) in methylene chloride (CH_2Cl_2) using 4-dimethylaminopyridine (DMAP) as catalyst.[2] The $Zn(BH_4)_2$ solution was prepared according to Gensler *et al.*[22] and stored in the refrigerator with a shelf-life on the order of 6 months. The settling of solids was observed over period of a few weeks; only the supernatant was used for the reductions.

Compounds **1-3**[23], **4**[2], **5**, **7** and **8**[21] and their reduction products were synthesized as described previously. $Zn(BH_4)_2$ reductions were typically performed with excess borohydride as follows. The carbonyl compound (100 mg) was dissolved in ethyl acetate (EtOAc, 3 mL) and cooled to 0 °C. An ethereal solution of $Zn(BH_4)_2$ (0.15 M, 3 mL) was added and the reaction was monitored by TLC. When complete disappearance of starting material was noted, the excess borohydride was quenched with water followed by acetic acid (alternatively, aq. NH_4Cl can be used). The solution was diluted with additional EtOAc, washed with aq. NH_4Cl (2x), and processed. Complete conversion was noted usually within 1-4 h and reduction yields were always greater than 90%.

Ketone **6**. 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanone[21] (100 mg, 0.24 mmol) was acetylated in CH_2Cl_2 (3 mL) with Ac_2O (0.05 mL) and DMAP (35 mg, 0.29 mmol) at room temperature. The reaction was complete in less than 15 min and subsequently diluted with CH_2Cl_2 and washed successively with cold 3% HCl and aq. NH_4Cl. Drying and processing gave **6** as a clear syrup (109 mg, 99%): δ_C 64.81 (C-3), 79.99 (C-2), 194.27 (C-1); δ_H 4.48 (1 H, dd, J = 6.8, 11.9 Hz, H-3a), 4.62 (1 H, dd, J = 3.9, 11.9 Hz, H-3b), 5.79 (1 H, dd, H-2). A standard $Zn(BH_4)_2$ reduction and subsequent acetylation (to account for the acetyl migration) gave the known[21] 1-(4-benzyloxy-3-methoxyphenyl)-1,3-diacetoxy-2-(2-methoxyphenoxy)propane as the *erythro* isomer (95% *erythro*, 86% yield from **6**).

Ketone **9**. *Preparation and Reduction.* Methyl 4-*O*-[1-(4-acetoxy-3-methoxybenzoyl)-2-hydroxyethyl]-*trans*-sinapate[23] was acetylated as described to afford **9** as a slightly amber syrup (95% yield): δ_C 64.60 (C-3), 81.83 (C-2), 194.96 (C-1); δ_H 4.51 (2 H, d, J = 5.4 Hz, H-3a,b), 5.64 (1 H, t, H-2). A standard $Zn(BH_4)_2$ reduction and subsequent acetylation gave the known[23] methyl 4-*O*-[2-acetoxy-2-(4-acetoxy-3-methoxyphenyl)-1-(acetoxymethyl)ethyl]-*trans*-sinapate as a *threo:erythro* mixture (14:86) in 93% yield from **9**.

Ketone **10**. 1-(4-acetoxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanone[23] (36.5 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (3 mL). Imidazole (10 mg, 0.15 mmol) and *t*-butyldimethylsilyl chloride (18 mg, 0.12 mmol) was added and the reaction was left for 48 h.[24] The mixture was diluted with CH_2Cl_2 and washed successively with cold aq. 3% HCl and aq. NH_4Cl, dried and processed. Purification by silica gel chromatography ($CHCl_3$ solvent) gave **10** as a clear syrup

(36.2 mg, 75%): δ_C 65.25 (C-3), 83.22 (C-2), 196.91 (C-1); δ_H 4.18 (1 H, dd, J = 4.8, 10.8 Hz, H-3a), 4.23 (1 H, dd, J = 5.3, 10.8 Hz, H-3b), 5.54 (1 H, t, J = 5.1 Hz, H-2). A standard $Zn(BH_4)_2$ reduction gave a 3:97 *threo:erythro* product in 96% yield: δ_C (*erythro*) 63.11 (C-3), 73.38 (C-1), 85.35 (C-2); δ_H (*erythro*) 3.85 (1 H, dd, J = 4.0, 11.1 Hz, H-3a), 3.94 (1 H, dd, J = 5.6, 11.1 Hz, H-3b), 4.45 (1 H, dt, J = 4.1, 5.4 Hz, H-2), 4.57 (0.75 H, d, J = 4.8 Hz, 1-OH), 4.97 (1 H, t, J = 4.9 Hz, H-1).

Ketone **11**. 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxy-phenoxy)propanone[21] (92 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. Ethyl vinyl ether (0.1 mL) and *p*-toluenesulfonic acid (ca. 1 mg) were added[25] and TLC (1:1, $CHCl_3$-EtOAc) indicated that complete conversion occurred in less than 10 min. The product was stabilized by the addition the Et_3N (0.05 mL) and the solution was diluted with CH_2Cl_2 and washed with aq. $NaHCO_3$, dried and processed to afford a diastereomeric mixture of **11** as an amber syrup (81 mg, 77%): δ_C 61.31 and 61.38 (C-3), 81.63 and 81.88 (C-2), 195.66 and 195.73 (C-1); δ_H (Isomer I) 4.00 (1 H, dd, J = 6.0, 10.8 Hz, H-3a), 4.06 (1 H, dd, J = 4.3, 10.8 Hz, H-3b), 5.85 (1 H, dd, J = 4.3, 6.0 Hz, H-2); (Isomer II) 4.01 (1 H, dd, J = 4.4, 10.7 Hz, H-3a), 4.08 (1 H, dd, J = 5.4, 10.7 Hz, H-3b), 5.59 (1 H, dd, J = 4.4, 5.4 Hz, H-2). The $Zn(BH_4)_2$ reduction product was treated in 95% EtOH (2 mL) with aq. 3% HCl (0.5 mL) for 1 h to effect cleavage of the 1-(ethoxy)ethyl protecting group. Subsequent workup gave the known[21] syrupy 1-(4-benzyloxy-3-methoxyphenyl)-1,3-dihydroxy-2-(2-methoxy-phenoxy)propane as a 4:96 *threo:erythro* mixture.

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