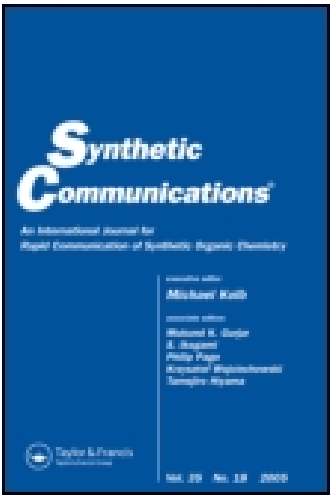

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile Method for the Preparation of Pure cis-2,4-Pentanediol

Lisa Bonner [a], Stewart Frescas [a] & David E. Nichols [a]
[a] Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Drive, West Lafayette, Indiana, 47907-2091, USA
Published online: 10 Jan 2011.

To cite this article: Lisa Bonner, Stewart Frescas & David E. Nichols (2004) A Facile Method for the Preparation of Pure cis-2,4-Pentanediol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:15, 2767-2771, DOI: 10.1081/SCC-200026213

To link to this article: http://dx.doi.org/10.1081/SCC-200026213

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 15, pp. 2767–2771, 2004

A Facile Method for the Preparation of Pure *cis*-2,4-Pentanediol

Lisa Bonner, Stewart Frescas, and David E. Nichols*

Department of Medicinal Chemistry and Molecular Pharmacology,
Purdue University, West Lafayette, Indiana, USA

ABSTRACT

The isolation of diastereomerically pure *cis*-2,4-pentanediol from a crude mixture of both *cis*- and *trans*-2,4-pentanediols is described through a short procedure involving thermodynamic acetal formation with acetophenone, followed by hydrogenolysis of the acetal protecting group.

Key Words: Acetophone acetal; *cis*-2,4-Pentanediol; Axial phenyl substitutent; Thermodynamic equilibrium.

INTRODUCTION

In conjunction with other studies in our laboratory,[1] we required gram quantities of diastereomerically pure *cis*-2,4-pentanediol. In addition to

*Correspondence: David E. Nichols, Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, USA; E-mail: drdave@pharmacy.purdue.edu.

DOI: 10.1081/SCC-200026213 0039-7911 (Print); 1532-2432 (Online)

our needs, this material is also important for a variety of other reasons, including the use of dihalide derivatives for stereochemical substitution[2] and organometallic chemistry studies.[3] Similar diastereomerically pure reagents are also very important as synthons for stereoselective synthesis. Although there are several previously published methods for the preparation of this compound,[4–6] none of them is either efficient or facile for obtaining diastereomerically pure *cis*-2,4-pentanediol. Of the many methods available for obtaining a mixture of *cis*- and *trans*-2,4-pentanediols, the most useful appears to be the reduction of commercially available 2,4-pentanedione with $NaBH_4$ in methanol, as described by Pritchard and Vollmer.[2] It is the further isolation of pure *cis*-diol from this mixture, which is the focus of this report.

Separation of the *cis*-isomer from the racemic *trans*-2,4-pentanediols has been accomplished in the past by preparation and separation of cyclic derivatives of the diols. For example, Pritchard and Vollmer[2] made cyclic sulfite esters from the diols, but fractional distillation to separate the diastereomers proved very difficult due to their similar boiling points. Gordillo and Hernandez[6] reported the use of cyclic phosphorochloridites to obtain diols with 98% diastereomeric purity, but only in unacceptable low yield (23%).

We reasoned that an asymmetric and sterically hindered carbonyl compound would selectively react with the *cis*-diol to form a six-membered cyclic acetal. The acetal should form preferentially from the *cis*-diol, leading to a product with the two terminal methyl groups situated in equatorial positions of a chair conformation, whereas in the *trans*-diols one of the methyl groups would be forced to reside in an axial orientation. Diaxial nonbonded interactions thus thermodynamically disfavor the formation of acetal from the *trans*-diol. Indeed, using hexane as a relatively low boiling solvent, we were delighted to discover that the acetal formed by allowing the diol mixture to react with a limiting amount of acetophenone yielded essentially a single product, determined to be the predicted result of selective acetal formation with the *cis*-diol. The acetals formed from the *trans*-diols would complicate the isolation procedure, but by limiting the amount of acetophenone used it is possible to form selectively the *cis*-acetal, leaving the *trans*-diols unreacted. The latter, which are more water soluble, are simply removed from the reaction mixture by washing with water. Therein lies the beauty of this method.

Conveniently, the *cis*-acetal is a solid at room temperature (m.p. 63.5–64°C[7]) that readily crystallizes. Surprisingly, this acetal exists predominantly as the conformer with the axial phenyl group, identified by Bailey et al.,[8] favored over the equatorial phenyl conformer by 2.55 kcal/mol (Fig. 1).

Because the desired thermodynamic product of this reaction is a solid and can be readily isolated and purified, the facility of this method becomes obvious. Acetal **1** was then simply cleaved by catalytic hydrogenation, which forms volatile ethylbenzene as a by-product, thus preventing equilibrium

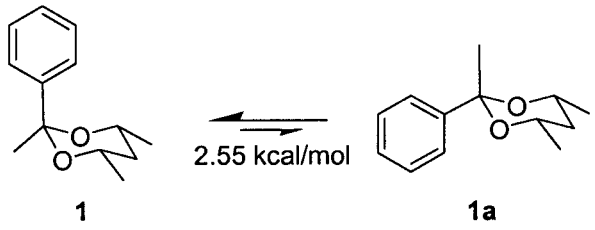

Figure 1. The equilibrium favors acetal conformation **1** with the axial phenyl substitute.

reaction between the desired diol product and acetophenone. Following hydrogenolysis of the crystalline acetal, pure *cis*-diol is produced in 100% diastereomeric purity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on an Advance DRX 500 MHz instrument and were run in $CDCl_3$. Values are reported in parts per million δ using the following abbreviations: s, singlet; d, doublet; m, multiplet. Reaction progress was monitored by thin-layer chromatography (TLC) with 9 : 1 chloroform : ethanol as the solvent and 10% phosphomolybdic acid in ethanol as the developer. The 2,4-pentanedione starting material was obtained from Aldrich (Milwaukee, WI).

cis- and *trans*-2,4-Pentanediol Mixture

The mixture of 2,4-pentanediols used as the starting material for this procedure was obtained by the reduction of 2,4-pentanedione with $NaBH_4$ in methanol as described by Pritchard and Vollmer.[2] The ratio of *cis*- : *trans*-diols was determined by ^{1}H NMR analysis to be 60 : 40.

(4*RS*,6*SR*)-2-Phenyl-2,4,6-trimethyl-1,3-dioxane (1)

To a 250-mL three-necked round bottom flask were added 7.0 g (0.0674 mol; 0.0404 mol *cis*-diol) of the mixed diol starting material, 5.0 g (0.0424 mol, 5% excess) of acetophenone, 0.1 g of TsOH as an acid catalyst, and 75 mL of hexane. The vessel was fitted with a Dean-Stark trap for azeotropic removal of water and the reaction was heated overnight on an oil bath at

80°C (reflux). The TLC of the cooled mixture in the morning indicated very little acetophenone and no *cis*-diol remaining, as well as showing compound **1** to be the major product. The reaction was neutralized with saturated sodium bicarbonate and washed vigorously four times with water to remove the unreacted *trans*-diols. The organic layer was dried over sodium sulfate, filtered, and the hexane was evaporated under reduced pressure. Upon cooling to room temperature, solid material began to crystallize and the product was stored in the freezer overnight. The semi-solid product was transferred to a Buchner funnel, sucked dry, and the colorless crystals were washed with isopropyl alcohol that had been previously chilled in a dry ice-acetone bath, to afford 5.07 g (61%) of fine, colorless needles. The filtrate from this first crop was concentrated, seeded and allowed to crystallize overnight in the freezer to afford a second crop of crystals (0.76 g; 70% total yield). The removal of acetophenone by careful vacuum distillation from the concentrated filtrate can allow for crystallization of a small additional amount of material if desired. ^{1}H NMR δ 1.31 (6H, d, $J = 6.0$ Hz), 1.39–1.49 (2H, m), 1.62 (3H, s), 3.80–3.91 (2H, m), 7.37–7.49 (5H, m).

(2*SR*,4*RS*)-Pentanediol (2)

To a 500 mL Parr pressure vessel were added 15.0 g (0.0728 mol) of compound **1**, 6.0 g of 5% Pd/C catalyst, 200 mL MeOH, and 5 drops of conc. H_2SO_4. The reaction was pressurized to 50 psi H_2 at 60°C and allowed to shake overnight. The next morning, concentrated ammonium hydroxide was added to neutralize the acid. The catalyst and ammonium sulfate salt were removed by filtration and washed with ethanol, taking care not to let the catalyst dry. The filtrate was evaporated under reduced pressure. The mass of the product was 7.344 g (97% yield), obtained as a viscous colorless oil, which by GC analysis was essentially a single peak.

ACKNOWLEDGMENT

This work was supported by grant DA02189 from NIDA.

REFERENCES

1. Nichols, D.E.; Frescas, S.; Marona-Lewicka, D.; Kurrasch-Orbaugh, D. Lysergamides of isomeric 2,4-dimethylazetidines map the binding orientation of the diethylamide moiety in the potent hallucinogenic agent *N,N*-diethyllysergamide (LSD). J. Med. Chem. **2002**, *45*, 4344.

2. Pritchard, J.G.; Vollmer, R.L. The *meso* and racemic forms of 2,4-pentanediol and certain of their derivatives. J. Org. Chem. **1963**, *28*, 1545.
3. Wu, J.; Ache, H.J. The effects of solvent–solute interactions on the stereochemical course of the high-energy chlorine-38 for chlorine substitution process in diastereomeric dichloroalkanes in the condensed phase. J. Am. Chem. Soc. **1977**, *99*, 6021.
4. Yang, G.K.; Bergman, R.G. Stereochemistry of metallacycle formation in the double alkylation of *bis*(triphenylphosphine)nitrogen(1+) *bis*(η^5-cyclopentadienyl)*bis*(μ-carbonyl)dicobaltate with α,γ-diiodoalkanes. J. Am.Chem. Soc. **1983**, *105*, 6045.
5. Bailey, W.F.; Eliel, E.L. Conformational analysis. XXIX. 2-Substituted and 2,2-disubstituted 1,3-dioxanes. The generalized and reverse anomeric effects. J. Am. Chem. Soc. **1974**, *96*, 1798.
6. Gordillo, B.; Hernandez, J. An alternative strategy for the purification of *meso*-2,4,pentanediol. Org. Prep. Proc. **1997**, *29*, 195.
7. Eliel, E.L.; Bailey, W.F.; Wiberg, K.B.; Connon, H.; Nader, F.W. Vorzugskonformation des phenylringes in 2-phenyl-1,3-dioxane. Justus Liebigs Ann. Chem. **1976**, *1976*, 2240.
8. Bailey, W.F.; Connon, H.; Eliel, E.L.; Wiberg, K.B. Calorimetric determination of the conformational enthalpy and entropy of 2-phenyl-1,3-dioxane. Effectively free rotation of an equatorial 2-phenyl group. Conformational equilibria in 2,2,-disubstituted 1,3-dioxanes. J. Am. Chem. Soc. **1978**, *100*, 2202.

Received in the USA May 5, 2004