Organic Process Research & Development

Article

pubs.acs.org/OPRD

Efficient Separation of Diastereomeric Mixtures of *syn*- and *anti*-2,4-Pentanediol

Heqi Pan, Siyu Tu, and Chunming Zhang*

Corporate R&D, The Dow Chemical Company, 1710 Building, Midland, Michigan 48674, United States

Andrew Young and Philip P. Fontaine

Performance Plastics R&D, The Dow Chemical Company, 2301 North Brazosport Boulevard, Freeport, Texas 77541, United States

Supporting Information

ABSTRACT: A simple and practical process was developed for the efficient separation of diastereomeric *syn*- and *anti*-2,4-pentanediol by selective acetalization of a diastereomeric mixture of the 2,4-pentanediols and selective hydrolysis of the corresponding acetals. The process relies upon the reaction rate differences of *syn*-2,4-pentanediol (*syn*-diol) and *anti* 2,4-pentanediol (*anti*-diol) in acetalization and of the corresponding acetals in hydrolysis: the *syn*-diol reacts faster to form a more stable acetal than the *anti*-diol, which in turn is more susceptible to hydrolysis by Brønsted acid. Acetalization of a 2,4-pentanediol diastereomeric mixture (*syn*/*anti* = 45:55) with acetophenone (0.95 equiv relative to *syn*-diol) leads to the formation of a *syn*-enriched acetal mixture with a *syn*/*anti* diastereomeric ratio ($dr_{s/a}$) of 6:1, leaving an *anti*-enriched diol mixture ($dr_{s/a}$ = 1:7). Subsequent kinetic resolution via selective hydrolysis of the minor *anti*-acetal with a catalytic amount of 1.0 N HCl at ambient temperature affords the pure *syn*-acetal ($dr_{s/a}$ > 99:1) in the organic phase and the *anti*-enriched 2,4-pentanediols ($dr_{s/a}$ = 1:6) in the aqueous phase, which are conveniently separated by a phase cut. Hydrolysis of the *syn*-acetal is facile in alcohol solvents at elevated temperatures (60−80 °C), yielding the pure *syn*-diol. A second acetalization of the *anti*-enriched 2,4-pentanediols leads to the pure *anti*-2,4-pentanediol. This separation gives the *syn*-diol in 75−79% yield with $dr_{s/a}$ > 99:1 and the *anti*-diol in 79−85% yield with $dr_{a/s}$ > 98:2. Additionally, the acetophenone used for the acetalization can be recovered in 88−92% yield, and therefore, the overall process is high-yielding, atom-economical, and potentially recyclable.

INTRODUCTION

1,3-diols are present, in either a *syn* or *anti* configuration, in a large variety of natural products and are valuable intermediates in the synthesis of drugs, natural products, and novel ligands for homogeneous catalysis.[1] These useful building blocks are often produced as mixtures of *syn* and *anti* diastereomers in varying ratios, and separation of the two isomers can be challenging. For example, separation of the *syn* and *anti* diastereomers of 2,4-pentanediol (**1**) has been a laborious and inefficient task.[2−5] Pritchard and Vollmer reported a separation of *syn*- and *anti*-2,4-pentanediol diastereomers by formation of the cyclic sulfite ester diastereomers followed by separation via fractional distillation (a difficult operation because of their similar boiling points) and then hydrolysis.[2] Diastereoselective formation of the *syn* cyclic sulfite ester could be effected in a *syn*/*anti* diastereomeric ratio ($dr_{s/a}$) of 96:4, but subsequent alkaline hydrolysis of the sulfite ester furnished *syn*-**1** with only moderate enrichment ($dr_{s/a}$ = 69:31).[3] Alternatively, Gordillo and Hernández obtained *syn*-**1** via conversion to a cyclic phosphorochloridite in low yield (23%), albeit with high selectivity ($dr_{s/a}$ = 99:1).[4] Recently, Nichols and co-workers prepared *syn*-**1** by selective formation of the *syn*-acetal (*syn*-**2**) with acetophenone and subsequent hydrogenolysis of the acetal protecting group.[5] None of the previously reported methods are adequate to obtain both *syn*-**1** and *anti*-**1** in high diastereomeric purity and high yield. Herein we report a simple and efficient separation of 2,4-pentanediol diastereomers that features a diastereoselective acetalization and a hydrolytic kinetic resolution of the corresponding acetals **2**, which leads to a high yield and high diastereomeric purity of both *syn*-**1** and *anti*-**1** (Scheme 1). Additionally, the acetophenone used for the acetalization can be recovered in high yield, resulting in an overall process that is atom-economical and potentially recyclable.

RESULTS AND DISCUSSION

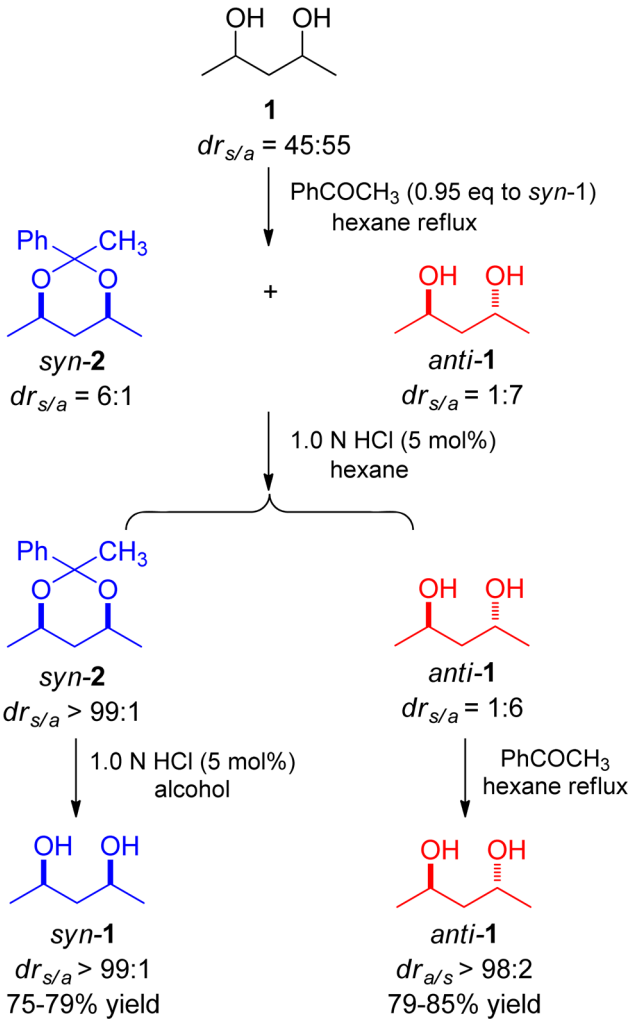
First-Generation Process for the Separation of *syn*- and *anti*-2,4-Pentanediol. Our research program required large quantities of diastereomerically pure *syn*-2,4-pentanediol (*syn*-**1**) and *anti*-2,4-pentanediol (*anti*-**1**). Commercially available 2,4-pentanediol is a mixture of the *syn* and *anti* diastereomers in a ratio of approximately 1:1. After reviewing potential synthetic routes, we chose to modify the cyclic acetal separation method originally developed by Nichols and co-workers for the preparation of the *syn*-**1** (Scheme 2). It featured a selective acetalization of *syn*-**1**, isolation of the resulting *syn*-acetal (*syn*-**2**) by recrystallization, and then hydrogenolysis of the acetal protecting group.[5]

In *syn*-**2**, the two methyl groups reside in equatorial positions in the preferred chair conformation. In contrast, in *anti*-**2** one of the methyl groups is forced into an axial position, where it

Received: February 10, 2015

DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Separation of *syn*- and *anti*-2,4-pentanediol



experiences unfavorable *syn*-pentane interactions with the acetal substituent (Scheme 3). These diaxial nonbonded interactions disfavor the formation of *anti*-**2**. Thus, the equilibrium position of an acetalization using a limiting amount of acetophenone to react with a mixture of *syn*-**1** and *anti*-**1** should favor the formation of *syn*-**2**. This selective acetalization was indeed observed and was utilized to obtain *syn*-**1**.[5] We envisioned that by adapting this reaction we could achieve our desired isolation of both 2,4-pentanediol diastereomers.

We first examined the impact of the acetophenone loading on the acetalization selectivity. The reaction of a mixture of 2,4-pentanediols (*syn*/*anti* = 45:55) with acetophenone was carried out in refluxing hexane in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA), and water generated in situ was azeotropically removed using a Dean–Stark trap with a condenser. The use of 1.3 equiv of acetophenone (relative to *syn*-**1**) yielded a mixture of *syn*- and *anti*-acetals **2** with $dr_{s/a}$ = 3:1.[6] The remaining unreacted diol **1** was highly enriched in the *anti* diastereomer *anti*-**1** ($dr_{s/a}$ = 6:94). Reducing the amount of acetophenone to 0.95 equiv improved the *syn* enrichment in the resulting acetal from $dr_{s/a}$ = 3:1 to 6:1, while the *anti* enrichment of the unreacted **1** was reduced to $dr_{s/a}$ = 11:89 (Table 1). Further reduction of the acetophenone loading to further enrich *syn*-**2** was not pursued, as it would lead to decreased *anti* enrichment in the unreacted **1**. Subjecting the recovered unreacted **1** to a second acetalization with 1.3–1.5 equiv of acetophenone (relative to the remaining *syn*-**1**) resulted in a high enrichment of *anti*-**1** ($dr_{s/a}$ < 2:98), which was isolated in 79–85% yield (based on *anti*-**1** in the starting diastereomeric mixture). This enabled us to obtain *anti*-**1** in high yield with high diastereomic purity.

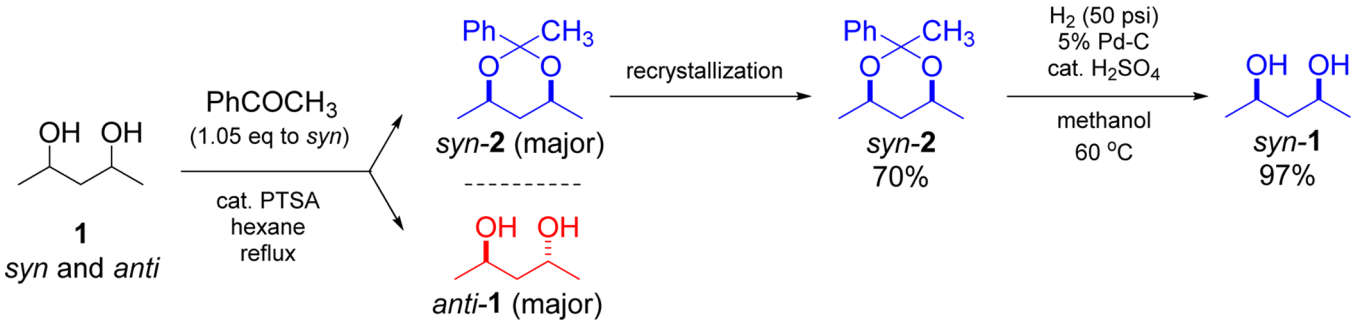
The pure *syn*-**2** was initially obtained by recrystallization of *syn*-enriched **2** ($dr_{s/a}$ = 6:1) from isopropanol.[5] This gave *syn*-**2** in 50–55% yield (based on *syn*-**1**) with $dr_{s/a}$ = 98:2. However, approximately 40% of the *syn*-**2** remained in the filtrate and was not recovered. The *syn*/*anti* ratio of **2** in the filtrate varied from 2:1 to 1:1 (Scheme 4).

The purified *syn*-**2** was then subjected to hydrogenolysis in the presence of 5% palladium on carbon (5% Pd/C) in methanol at a hydrogen pressure of 50–60 psi, which gave *syn*-**1** with $dr_{s/a}$ = 98:2 (Scheme 5). While we were able to obtain *syn*-**1** with high diastereomic purity by hydrogenolysis, we occasionally experienced incomplete reaction, likely as a result of catalyst deactivation. In such cases, it was necessary to resubject the materials to the hydrogenolysis conditions with new catalyst.

Study of Hydrolysis of the Acetals. Although we were able to obtain both *syn*-**1** and *anti*-**1** by minor modification of Nichols' method, this process suffered from a substantial loss of yield in the recrystallization of the *syn*-acetal and occasional incomplete hydrogenolysis in the cleavage of the acetal protecting group. Therefore, a more efficient and robust process for separation of *syn*- and *anti*-2,4-pentanediol was desired. Thus, we explored alternative methods for the purification of *syn*-**2** and the cleavage of the acetal protecting group.

It is well-known that hydrolysis of an acetal generally occurs under acidic conditions, and different hydrolysis reactivities for diastereomeric *syn*- and *anti*-acetals has been reported.[7−9] We

Scheme 2. Nichols' cyclic acetal route to *syn*-2,4-pentanediol



DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 3. Configurations of the *syn*- and *anti*-acetals

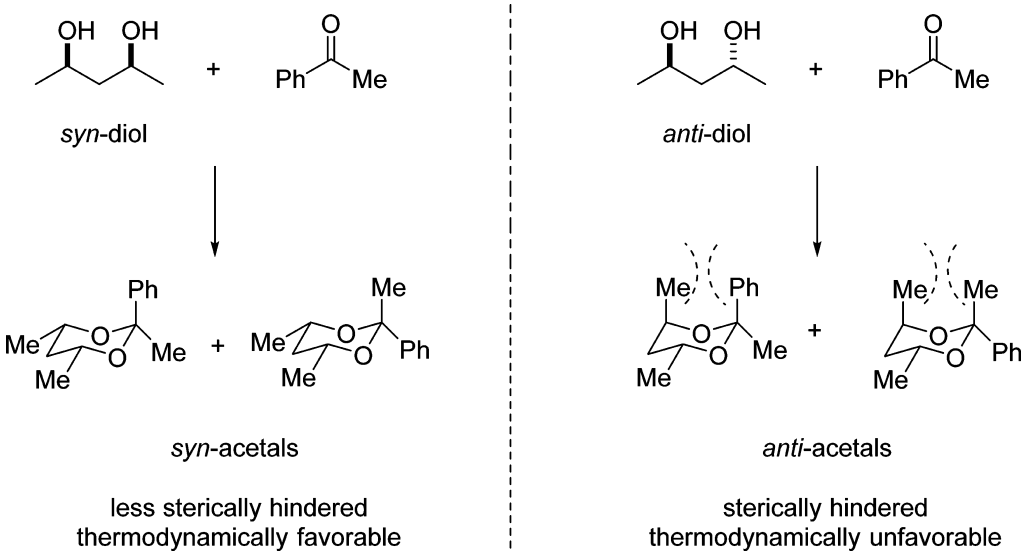
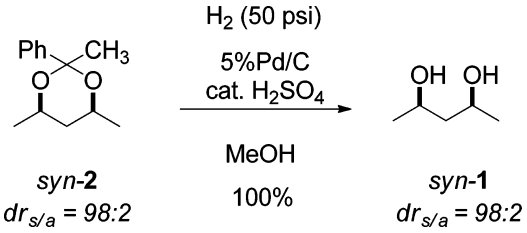


Table 1. Effects of the acetophenone loading on the acetalization selectivity

entry	starting diol *syn*/*anti*	equiv of acetophenone[a]	resulting acetal *syn*/*anti*[b]	recovered diol *syn*/*anti*[b]
1	45:55	1.3	3:1	6:94
2	45:55	0.95	6:1	11:89
3	11:89[c]	1.3	2:1	2:98

[a]Relative to *syn*-**1** in the starting diastereomeric mixture. [b]Estimated by ^{1}H NMR analysis. [c]Recovered from entry 2.

Scheme 5. Hydrogenolysis of *syn*-2 to *syn*-1

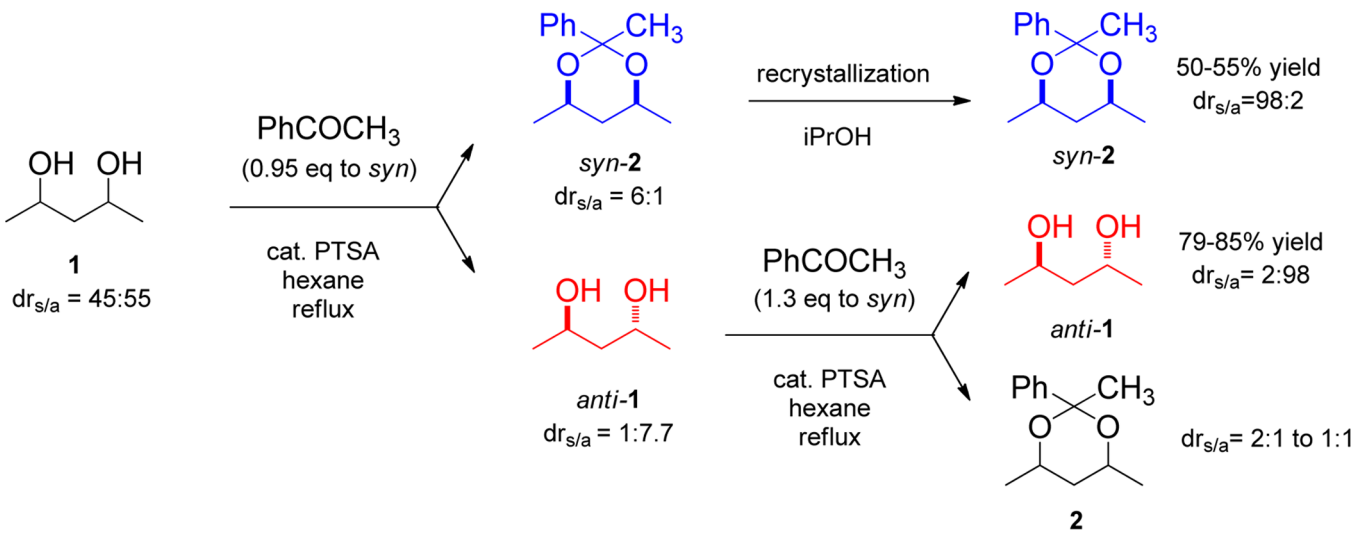


envisioned that the isomeric mixture of acetal **2** might be separable via a kinetic resolution. Specifically, selective hydrolysis of *anti*-**2** in a mixture of *syn*-**2** and *anti*-**2** could lead to pure *syn*-**2**.

We examined the hydrolysis of a mixture of *syn*-**2** and *anti*-**2** ($dr_{s/a}$ = 2:1, which was recovered from the supernatant of the *syn*-**2** recrystallization step) with 5 mol % 1.0 N hydrochloric acid solution in different solvents (Table 2). It was found that *anti*-**2** was selectively hydrolyzed and *syn*-**2** was left essentially untouched when the hydrolysis was conducted at room temperature in aprotic solvents such as tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), toluene, and hexane. In this manner, *syn*-**2** was obtained in 93−95% yield with excellent diastereomeric purity ($dr_{s/a}$ > 99:1), and *anti*-**1** was also isolated with high diastereomeric purity ($dr_{s/a}$ = 4−7:100). Conversely, in a protic solvent such as methanol (CH_3OH), the hydrolysis proceeded faster and with lower selectivity, leading to a lower yield of *syn*-**2** and a less *anti*-enriched diol **1** mixture.

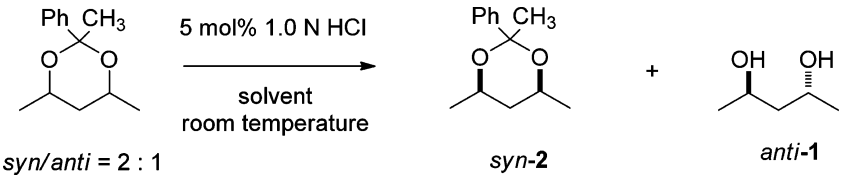
The hydrolysis of *syn*-**2** ($dr_{s/a}$ = 99:1) was then examined in methanol. It was found that the hydrolysis was slow at ambient

Scheme 4. Initial preparation of *syn*-2 and *anti*-1



DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

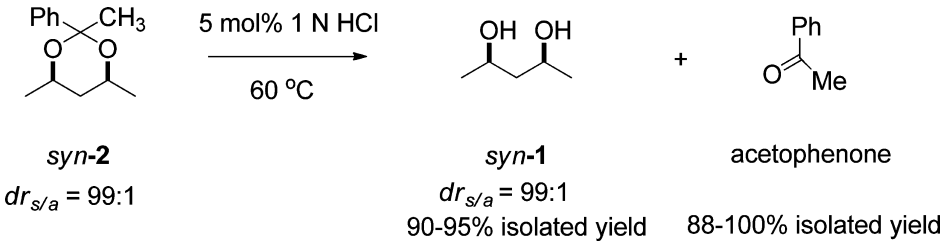
Table 2. Hydrolysis of a mixture of *syn*- and *anti*-2 in different solvents[a]



			syn-acetal		*anti*-diol	
entry	solvent	time (h)	*syn*/*anti*[b]	yield (%)[c]	*syn*/*anti*[b]	yield (%)[d]
1	hexane	63	99:1	95	5:100	85
2	toluene	60	99:1	95	7:100	84
3	CH_2Cl_2	48	99:1	95	4:100	87
4	THF	16	99:1	93	5:100	80
5	CH_3OH	16	99:1	74	50:100	110

[a]Hydrolysis was conducted with 20 mmol of acetal and 1 mmol of 1.0 N HCl in 30 mL of a solvent at ambient temperature. [b]Determined by ^{1}H NMR analysis. [c]Yields estimated by ^{1}H NMR analysis. [d]Isolated yields based on mass.

Scheme 6. Hydrolysis of *syn*-2



temperature (20−25 °C). Unreacted *syn*-**2** was still observed after 40 h. The reaction was accelerated at elevated temperature (60 °C) and was complete in 6−10 h. *syn*-**1** was isolated in 90−95% yield ($dr_{s/a}$ = 99:1), and the acetalizing reagent acetophenone was recovered in 88−100% yield (Scheme 6).

This study showed that selective hydrolysis of *anti*-**2** could happen in an aprotic solvent, while the hydrolysis of *syn*-2 was facile at elevated temperature in a polar protic solvent. This hydrolytic kinetic resolution strategy is a key element of the efficient separation of *syn*-**1** and *anti*-**1**.

Second-Generation Process for the Separation of *syn*- and *anti*-2,4-Pentanediol. Implementation of the selective hydrolysis strategy started with direct treatment of the acetalization reaction mixture with 5 mol % 1.0 N HCl at ambient temperature. *anti*-**2** was selectively hydrolyzed as desired, affording a mixture of *syn*-**2** ($dr_{s/a}$ = 100:1 to 100:0), acetophenone, and *anti*-enriched **1** ($dr_{s/a}$ = 1:6). This one-pot procedure accomplished the selective acetalization of *syn*-**1** and selective hydrolysis of *anti*-**2**, streamlining the separation and improving the recovery of both diastereomers. Phase separation of the reaction mixture gave an organic phase containing *syn*-**2** ($dr_{s/a}$ =100:1−0) along with acetophenone and an aqueous phase containing *anti*-enriched **1** ($dr_{s/a}$ = 1:6).

Next, hydrolysis of the *syn*-**2** with 5 mol % 1.0 N HCl in methanol[10] at 60 °C furnished the desired *syn*-**1** and acetophenone. These products were conveniently separated by organic/aqueous extraction. *syn*-**1** was obtained in 75−79% yield (based on *syn*-**1** in the starting diastereomic mixture of **1**) with high diastereomeric purity ($dr_{s/a}$ = 100:1 to 100:0). Meanwhile, the acetophenone was recovered in 92% yield.

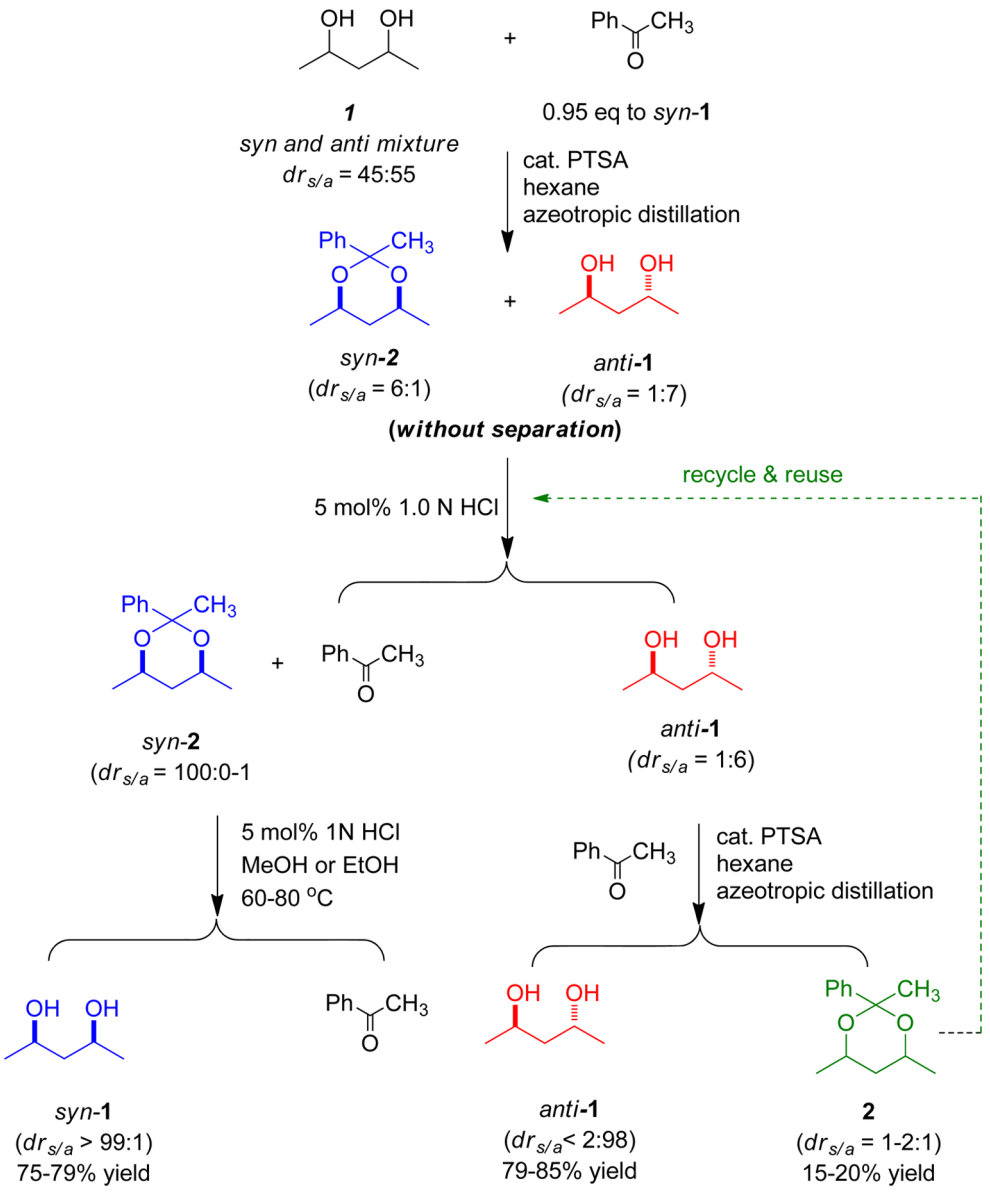
Finally, pure *anti*-**1** was obtained by a second selective acetalization of the *anti*-enriched **1** mixture. The aqueous phase from the previous acetalization containing the *anti*-enriched **1** ($dr_{s/a}$ = 1:6) was directly treated with acetophenone (1.3 equiv with respect to the minor component *syn*-**1**) in refluxing hexane and the water was azeotropically distilled out. This afforded pure *anti*-**1**, which was isolated in 79−85% yield (relative to *anti*-**1** in the starting diastereomic mixture of **1**) with $dr_{s/a}$ = 1:100 to 2:100. A crop of acetals **2** ($dr_{s/a}$ = 2:1 to 1:1) in yields of 15−20% (relative to the total starting **1**) was also isolated. This acetal mixture could be recycled into subsequent batches in the hydrolytic kinetic resolution step to obtain additional *syn*-**1** and *anti*-**1**. Theoretically, the yields of *syn*-**1** and *anti*-**1** both could be 100% via recycling and reusing the crop of acetal mixture from the second acetalization. The result is a simple and efficient process for separation and isolation of *syn*-**1** and *anti*-**1** (Scheme 7). This improved process was also applied to prepare other *syn*- and *anti*-1,3-diols.[11]

CONCLUSION

An efficient process for the separation and isolation of *syn*- and *anti*-2,4-pentanediol was developed, inspired by the Nichols cyclic acetal method. Selective acetalization of the *syn*-diol diastereomer from a mixture of *syn*- and *anti*-diols (*syn*/*anti* = 45:55) gave a mixture of *syn*-enriched acetals ($dr_{s/a}$ = 6:1) and *anti*-enriched diols ($dr_{s/a}$ ≈ 1:7). Without isolation, the resulting mixture was treated with 5 mol % 1.0 N HCl to afford pure *syn*-acetal (*syn*-**2**) and *anti*-enriched diol **1**. This facile one-pot synthesis of *syn*-**2** streamlined the experimental procedure and eliminated the recrystallization step, leading to improved yields of *syn*-**2**. Moreover, cleavage of the acetal protecting group of *syn*-**2** was accomplished by a convenient hydrolysis in methanol with 5 mol % 1.0 N HCl, which replaced the previous need for high-pressure hydrogenolysis. The hydrolysis method offered *syn*-**1** in both high overall yield (75−79%) and excellent diastereomeric purity ($dr_{s/a}$ = 100:0−1) and enabled recovery of the acetophenone (92%). *anti*-**1** was also readily obtained in 79−85% yield with high diastereomeric

DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 7. Second-generation process for the separation of *syn*- and *anti*-2,4-pentanediol



purity ($dr_{s/a}$ = 1−2:100). As the acetal mixture obtained from the second acetalization could be recycled to obtain additional *syn*-**1** and *anti*-**1**, theoretically *syn*- and *anti*-2,4-pentanediol could be quantitatively obtained. Compared with the previous process involving recrystallization and hydrogenolysis steps, this simplified process is more cost-effective, more robust for scale-up, and presents fewer safety concerns. Furthermore, this is the only method that affords both diastereomers of 2,4-pentanediol in high purity. Several hundred grams each of *syn*- and *anti*-2,4-pentanediol were conveniently prepared. Application of this facile method to the separation of other *syn*- and *anti*-1,3-diols is ongoing.[11]

EXPERIMENTAL SECTION

Solvents and common reagents were purchased from either Fisher or Sigma-Aldrich and were used as received. 2,4-Pentanediol was purchased from TCI America, Sigma-Aldrich, or Alfa Aesar, and its $dr_{s/a}$ was estimated by ^{1}H NMR analysis. Acetophenone was purchased from Alfa Aesar. PTSA and 5% Pd/C were purchased from Aldrich. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-400 (FT 400 MHz, ^{1}H; 101 MHz, ^{13}C) instrument in $CDCl_3$.

First-Generation Process. *Acetalization of 2,4-Pentanediol with Acetophenone.* 2,4-Pentanediol (115.77 g, a mixture of *syn* and *anti* diastereomers with $dr_{s/a}$ = 45:55 as determined by ^{1}H NMR analysis, of which 500 mmol was the *syn*-diol and 611 mmol was the *anti*-diol), PTSA (1.00 g, 5.2 mmol), acetophenone (57.07 g, 475 mmol, 0.95 equiv relative to the *syn*-**1**), and hexane (600 mL) were loaded into a 1 L three-neck round-bottom flask equipped with a Dean−Stark trap with a condenser (for azeotropic removal of water), a thermometer, a magnetic stirrer, and a nitrogen pad. The mixture was heated under reflux (reaction temperature 68−70 °C) under a nitrogen atmosphere for 40 h. Water generated from the reaction was azeotropically removed into the Dean−Stark trap (9.20 g of water was collected). The mixture was cooled to ambient temperature and allowed to settle for phase separation. The top hexane layer containing the acetal product **2** and the bottom oil layer containing the unreacted 2,4-pentanediols **1** were separated by phase cut. The ratio of *syn*-**2** and *anti*-**2** in the

DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

hexane layer was $dr_{s/a}$ = 6.0:1 as determined by ^{1}H NMR analysis, and the ratio of *syn*-**1** and *anti*-**1** in the oil layer was $dr_{s/a}$ = 1:7.7 as determined by ^{1}H NMR analysis.

The hexane layer was washed with (1) 2.0 N NaOH (10 mL) + water (250 mL) and (2) water (250 mL × 3), concentrated, and dried under reduced pressure to give crude *syn*-**2** as a semisolid (92.99 g, 90.1% yield, $dr_{s/a}$ = 6:1 as determined by ^{1}H NMR analysis).

Isolation of anti-2,4-Pentanediol. The above oil layer was subjected to acetalization again as described above with acetophenone (13.36 g, 111.2 mmol, 1.4 equiv relative to the *syn*-**1** in the oil) and PTSA (0.21 g, 1.1 mmol) in hexane (600 mL) at reflux in a 1 L three-neck round-bottom flask equipped with a Dean−Stark trap with a condenser for azeotropic removal of water, a thermometer, a nitrogen pad, and a magnetic stirrer for 16 h (1.90 g of water was collected in the Dean−Stark trap). The resulting mixture was allowed to settle and cooled to ambient temperature. The top hexane layer and the bottom oil layer were separated by phase cut. The oil phase was diluted with CH_2Cl_2 (100 mL). Solid sodium bicarbonate (2.40 g) was added in small portions with stirring. After 15 min of stirring, the solids were filtered off. The filtrate was concentrated and dried under reduced pressure to give *anti*-2,4-pentanediol (50.24 g, 78.94% yield, $dr_{s/a}$ = 2:100 as determined by ^{1}H NMR analysis). ^{1}H NMR (400 MHz/$CDCl_3$) δ 4.17 (m, 2H), 2.59 (br, 2H, O*H*), 1.61 (dd, J_1 = 6.4 Hz, J_2 = 1.2 Hz, 2H), 1.24 (d, J = 6.4 Hz, 6H). ^{13}C NMR (101 MHz/$CDCl_3$) δ 65.1 (s), 45.8 (s), 23.3 (s).

The hexane phase was concentrated to dryness using a rotary evaporator under reduced pressure to give a crop of mixed acetals (21.0 g, $dr_{s/a}$ = 1.3:1 as determined by ^{1}H NMR analysis).

Purification of the syn-Acetal by Recrystallization. Crude acetal *syn*-**2** (269.61 g, 1307 mmol, $dr_{s/a}$ = 6:1) and isopropanol (80 mL) were loaded into a 500 mL round-bottom flask equipped with a stirrer, a thermometer, a cold-water condenser, and a nitrogen pad. The mixture was heated under reflux with stirring until all of solids were dissolved and then was allowed to cool to ambient temperature overnight. The resulting precipitated solid was collected by filtration, rinsed with cold isopropanol (0−5 °C, 45−50 mL), suction-dried, and dried under vacuum (1−2 mmHg/ambient temperature) to afford pure *syn*-**2** (155.2 g, 752.4 mmol, $dr_{s/a}$ = 100:2 as determined by ^{1}H NMR analysis). ^{1}H NMR (400 MHz/$CDCl_3$) δ 7.39 (m, 4H), 7.29 (m, 1H), 3.79 (m, 2H), 1.53 (s, 3H), 1.28−1.37 (m, 2H), 1.22 (d, J = 6.4 Hz, 6H). ^{13}C NMR (101 MHz/$CDCl_3$) δ 142.4 (s), 128.6 (s), 127.4 (s), 126.6 (s), 101.1 (s), 66.5 (s), 40.0 (s), 33.1 (s), 21.8 (s).

The filtrate was concentrated to dryness under reduced pressure, giving a mixture of *syn*- and *anti*-acetals (114.4 g, $dr_{s/a}$ = 2:1).

Hydrogenolysis of syn-2. A 100 mL Parr reactor was charged with purified *syn*-**2** (30.03 g, 145.6 mmol), 5% Pd/C (3.00 g), methanol (30 mL), and one drop of concentrated H_2SO_4 (0.2−0.3 g). This mixture was subjected to hydrogenolysis at a hydrogen pressure of 50−80 psi at 60 °C, stirred at 300 rpm overnight, and cooled to ambient temperature. The hydrogen was released, and the reaction system was purged with nitrogen. The mixture was filtered through a bed of Celite (10 g), and the wet cake was washed with a small amount of methanol.[12] A sample of the filtrate was analyzed by ^{1}H NMR spectroscopy (in case the reaction was not complete, the filtrate was resubjected to hydrogenolysis with new palladium catalyst). The filtrate was concentrated under reduced pressure by rotary evaporation and further dried at 25 °C/1−2 mmHg to afford the desired *syn*-**1** (15.01 g, 100% yield, $dr_{s/a}$ = 100:2). ^{1}H NMR (400 MHz/$CDCl_3$) δ 4.07 (m, 2H), 2.89 (br, 2H), 1.55 (m, 2H), 1.22 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz/$CDCl_3$) δ 69.1 (s), 46.5 (s), 24.3 (s).

Selective Hydrolysis of the syn/anti-Acetal Mixture with 5 mol % HCl. A mixture of *syn*- and *anti*-**2** (4.12 g, 20 mmol, $dr_{s/a}$ = 2:1), a solvent (30 mL of CH_2Cl_2, THF, methanol, toluene, or hexane), and 1.0 N HCl (1.0 mL, 5 mol %) was stirred at ambient temperature until *anti*-**2** disappeared as monitored by ^{1}H NMR spectroscopy. Sodium bicarbonate powder (0.164 g, 2.0 mmol) was added, and the mixture was stirred for 30 min. The volatiles were removed under reduced pressure. The residual oil was partitioned in water (10 mL) and hexane (50 mL). *syn*-**2** in the hexane layer and diol **1** in the water layer were separated by phase cut. The hexane layer was concentrated to dryness and analyzed for *syn*-**2** by ^{1}H NMR spectroscopy. Diol **1** in the water phase was isolated according to the procedure for isolation of *anti*-**1**. The results are listed in Table 2.

Hydrolysis of syn-2 to syn-1. A mixture of *syn*-**2** (2.07 g, 10 mmol, $dr_{s/a}$ = 100:2), MeOH (15 mL), and 1.0 N HCl (0.5 mL, 5 mol %) was heated at 58−60 °C for 12 h and then cooled to ambient temperature. Sodium bicarbonate powder (0.30 g) was added in small portions with stirring. The resulting mixture was stirred for 30 min at ambient temperature. The solvent was evaporated under reduced pressure via rotary evaporation. The residue was taken up in hexane (100 mL) and water (20 mL). The resulting mixture was stirred for 30 min and then allowed to settle for phase separation. The hexane phase was washed with water (10 mL). The water layers were combined, washed with hexane (20 mL), and concentrated to dryness by azeotropic distillation with ethanol. The residue was triturated with CH_2Cl_2 (50 mL), and an insoluble solid was filtered off. The CH_2Cl_2 filtrate was concentrated to give *syn*-**1** (0.94 g, 90.3% yield, $dr_{s/a}$ = 100:2). The hexane layers were combined, washed with water (20 mL), and then concentrated to dryness, affording acetophenone (1.05 g, 88% yield).

Second-Generation Process. *One-Pot Process for Selective Acetalization and Selective Hydrolysis.* 2,4-Pentanediol (115.77 g, a mixture of *syn* and *anti* diastereomers with $dr_{s/a}$ = 45:55 as determined by ^{1}H NMR analysis, of which 500 mmol was *syn*-**1** and 611 mmol was *anti*-**1**), PTSA (0.38 g, 2.0 mmol), acetophenone (57.07 g, 475 mmol, 0.95 equiv relative to *syn*-**1**), and hexane (650 mL) were loaded into a 1 L three-neck round-bottom flask equipped with a Dean−Stark trap with a condenser for azeotropic removal of water, a thermometer, a magnetic stirrer, and a nitrogen pad. The mixture was heated under reflux (reaction temperature 68−70 °C) under a nitrogen atmosphere for 18 h. Water generated from the reaction was azeotropically removed into the Dean−Stark trap (9.56 g of water was collected). ^{1}H NMR analysis of the reaction mixture indicated that the ratio of *syn*-**2** and *anti*-**2** was $dr_{s/a}$ = 6.3:1 and the ratio of *syn*-**1** and *anti*-**1** was $dr_{s/a}$ = 1:7.0. The reaction mixture was cooled to ambient temperature (25 °C), and 1.0 N HCl (25 mL, 25 mmol, 5 mol % relative to *syn*-**1**) and the contents of the Dean−Stark trap (9.56 g of water generated from the condensation and a small amount of hexanes) were also added to the reaction mixture. The mixture was stirred at ambient temperature until all of the *anti*-**2** disappeared (17−20 h) as monitored by ^{1}H NMR spectroscopy (^{1}H NMR analysis of the resulting mixture showed a *syn*-**2**/

DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

acetophenone molar ratio of 6:1 and a *syn*-**1**/*anti*-**1** ratio of 1:6). The resulting mixture was allowed to settle for phase separation. The top hexane layer containing *syn*-**2** and acetophenone was kept in the reaction vessel (vessel A), and the bottom aqueous layer containing *anti*-enriched **1** was drained into a new vessel (vessel B). The hexane phase in vessel A was washed with water (25 mL × 3), and the water washings were added to vessel B.

Hydrolysis of syn-2 and Isolation of syn-1 and Acetophenone. The volatiles in vessel A were evaporated under reduced pressure to leave a residue of 92.36 g. Methanol (250 mL), water (10 mL), and 1.0 N HCl (25 mL) were added to the reaction vessel containing the residue. The mixture was heated at reflux for 4−8 h, resulting in deprotection of the acetal group. After the mixture was cooled to ambient temperature, sodium bicarbonate powder (2.5 g, 30 mmol) was added in portions, and the reaction mixture was stirred for 1 h and then concentrated under reduced pressure to remove the volatiles. The residue was taken up in water (50 mL) and hexane (300 mL), and the solution was stirred for 10−15 min and then allowed to settle for phase separation. The top hexane layer was extracted with water (50 mL × 2), and the washes were combined with the bottom aqueous layer. The hexane phase was concentrated under reduced pressure using a rotary evaporator to give acetophenone (50.57 g, 88.6% recovery). The combined water phases were evaporated and further azeotropically dried with 100 mL of toluene under reduced pressure using rotary evaporation. CH_2Cl_2 (100 mL) was added to triturate the residue. The insoluble salts were filtered off through a pad of Celite (5 g), rinsing with CH_2Cl_2 (50 mL). The filtrate liquid was concentrated to dryness under reduced pressure using rotary evaporation and further dried in a vacuum oven to give the desired *syn*-**1** (41.47 g, 78.9% yield, $dr_{s/a}$ = 100:0−1).

Purification and Isolation of anti-2,4-Pentanediol. To vessel B containing the aqueous phase were added hexane (650 mL) and acetophenone (17.0 g, 141 mmol, 1.4 equiv relative to *syn*-**1** as estimated by ^{1}H NMR analysis). The mixture was refluxed with a Dean−Stark trap with a condenser for azeotropic removal of water (36 h). The reaction mixture was cooled to ambient temperature and allowed to settle for phase separation. The bottom oil layer containing *anti*-**1** was drained into a separate vessel (vessel C), and the top hexane layer remained in vessel B.

Water (50 mL) was added to vessel B to wash the hexane phase. The water layer was added to vessel C. This process was repeated one more time.

Hexane (100 mL) was added to vessel C to wash the combined water phases. The hexane layer was combined with that in vessel B. The combined hexane solution was concentrated under reduced pressure to give a crop of mixed acetals (31.5 g, $dr_{s/a}$ = 1:0.84 based on ^{1}H NMR analysis).

The water phase in vessel C was neutralized by the addition of solid sodium bicarbonate in portions (approximately 3.0 g total was added). The water was evaporated under reduced pressure at 45 °C using rotary evaporation. The residue was dried azeotropically with toluene (100 mL) and then taken up in CH_2Cl_2 (100 mL). The insoluble salts were filtered off through a pad of Celite (5 g), rinsing with CH_2Cl_2 (50 mL). The filtrate was concentrated and dried in vacuum to give *anti*-**1** (52.42 g, 81.6% yield, $dr_{s/a}$ = 2:100).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral information for **1**, *syn*-**1**, *anti*-**1**, and *syn*-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: czhang@dow.com.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557−588. (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040. (c) Schneider, C. *Angew. Chem., Int. Ed.*. **1998**, *37*, 1375−1378.

(2) (a) Pritchard, J. G.; Vollmer, R. L. *J. Org. Chem.* **1963**, *28*, 1545−1549. (b) Eliel, E. L.; Hutchins, R. O. *J. Am. Chem. Soc.* **1969**, *91*, 2703−2715. (c) Bailey, W. F.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 1798−1806. (d) For an attempted but unsuccessful separation of *syn*- and *anti*-2,4-pentanediol by fractional distillation, see: Lim, D.; Kolinsky, M.; Votavova, E.; Ryska, M.; Lukas, J. *J. Polym. Sci., Part B: Polym. Lett.* **1966**, *4*, 573−576.

(3) Caron, G.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1994**, *5*, 657−664.

(4) Gordillo, B.; Hernández, J. *Org. Prep. Proced. Int.* **1997**, *29*, 195−199.

(5) Bonner, L.; Frescas, S.; Nichols, D. E. *Synth. Commun.* **2004**, *34*, 2767−2771.

(6) A single epimer was observed for the *syn*-acetal (*syn*-**2**), whereas a mixture of two epimers was observed for the *anti*-acetal (*anti*-**2**) in a ratio of approximately 1:1 as determined by ^{1}H NMR analysis.

(7) Fife, T. H.; Natarajan, R. *J. Am. Chem. Soc.* **1986**, *108*, 8050−8056.

(8) Bode, S. E.; Müller, M.; Wolberg, M. *Org. Lett.* **2002**, *4*, 619−621.

(9) Pihlaja, K. *Ann. Univers. Turkuensis, Ser. A1* **1967**, 144; *Chem. Abstr.* **1968**, *69*, 76439.

(10) The reaction proceeded equally well in ethanol and isopropanol.

(11) This method was also used to prepare *syn*-3,5-heptanediol and *anti*-3,5-heptanediol (The Dow Chemical Company, unpublished results).

(12) The filter cake must be kept wet to prevent it from catching fire. Thus, after filtration, a small amount of water was added to the wet cake.

DOI: 10.1021/acs.oprd.5b00043
Org. Process Res. Dev. XXXX, XXX, XXX−XXX