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Divergent Asymmetric Synthesis of 3,5-Disubstituted Piperidines

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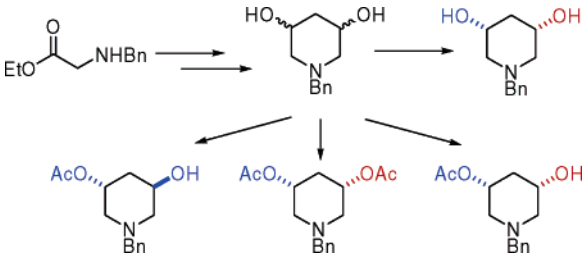

A divergent synthesis of various 3,5-dioxygenated piperidines with interesting pharmacological properties is described. A mixture of the achiral *cis*- and racemic *trans*-3,5-piperidine diol could be efficiently obtained from *N*-benzylglycinate in five steps by the use of chemoenzymatic methods. In the subsequent enzyme- and Ru-catalyzed reaction, the rac/meso diol mixture was efficiently transformed to the *cis*-(3*R*,5*S*)-diacetate with excellent diastereoselectivity and in high yield. Further transformations of the *cis*-diacetate selectively delivered the *cis*-piperidine diol and the *cis*-(3*R*,5*S*)-hydroxy acetate. Alternatively, the DYKAT could be stopped at the monoacetate stage to give the *trans*-(3*R*,5*R*)-hydroxy acetate.

Introduction

Substituted piperidines are common substructures in many natural products and pharmacologically active compounds, and novel methodologies for asymmetric synthesis of these targets are therefore of considerable interest.[1,2] Polyhydroxylated piperidines, also called iminosugars, have recently received much interest in the field of glycosidase inhibitors with applications in the treatment of cancer and AIDS.[3] More specifically, 3,5-piperidine diols, which are 3-deoxy derivatives of iminosugars, have been reported as substructures in compounds active in the treatment of Alzheimer's disease[4] and schizophrenia.[5,6] Furthermore, protected 3,5-dihydroxypiperidines have recently been employed as catalysts in asymmetric diethylzinc additions to aldehydes.[7]

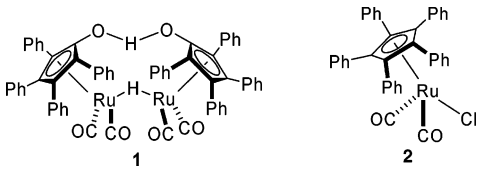

FIGURE 1. Ruthenium complexes used as epimerization catalysts.

In our recent dynamic kinetic asymmetric transformation (DYKAT) of 1,3-cyclohexanediol,[8] ruthenium catalysts **1**[9] and **2**[10] were employed to epimerize the hydroxyl groups of the diol in the presence of an enzyme that preferentially acetylated (*R*)-configured alcohols (Figure 1). The epimerization was found to be facile, whereas the monoacylation selectivity was poor, resulting in a mixture of (*R*)- and (*S*)-configured monoacetates. High selectivity was, however, obtained in the second acylation, giving the *cis*-diacetate in high yield. This compound could subsequently be enantioselectively transformed into the *cis*-monoacetate and the *trans*-diacetate.[8]

* To whom correspondence should be addressed. Phone: +46-(0)8-674 7178. Fax: +46-(0)8-154908.

(1) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.
(2) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633−640.
(3) Ouchi, H.; Mihara, Y.; Takahata, H. *J. Org. Chem.* **2005**, *70*, 5207−5214 and references therein.
(4) John, V.; Moon, J. B.; Pulley, S. R.; Rich, D. H.; Brown, D. L.; Jagodzinska, B.; Jacobs, J. S. WO Patent 2003043987, 2002-US37037, 2003.
(5) Hoffmann, T.; Koblet, A.; Peters, J.-U.; Schnider, P.; Sleight, A.; Stadler, H. U.S. Patent 2005/0090533, 2005.
(6) See also: Herbert, N. U.S. Patent 6828427 B1, 2004. Shepherd, R. G.; White, A. C. GB Patent 2060617 A, 1981.
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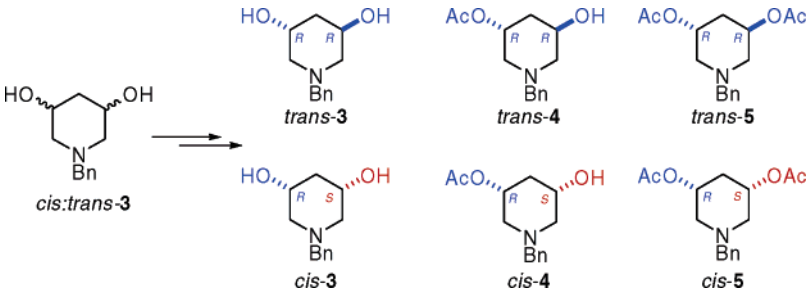
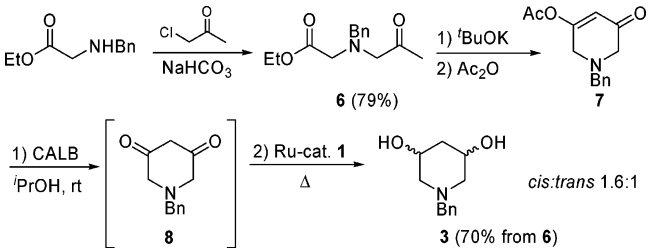


FIGURE 2. Target 3,5-oxygenated piperidines in the DYKAT of diol mixture 3.

SCHEME 1. Synthesis of Diol Mixture 3



We subsequently became interested in applying this chemistry to piperidine diols. Starting from a cis:trans mixture of 3,5-diol **3**, we envisioned an efficient, divergent synthesis of the oxygen-substituted piperidines **3**-**5**, several of which are novel compounds (Figure 2). Herein we describe the results obtained with this synthetic strategy.[11]

Results and Discussion

Our strategy toward the divergent synthesis of various 3,5-disubstituted piperidines relies on a straightforward synthesis of diol mixture **3**. Reported syntheses of *cis*-**3** derivatives are lengthy and involve either the chiral pool[12] or a chiral auxiliary,[13] despite the fact that *cis*-**3** is a meso compound. Also the synthesis of *trans*-**3** required the use of the chiral pool; a protected (*S*,*S*)-enantiomer was obtained in 14 steps,[14] whereas an efficient ring expansion of a hydroxyprolinol derivative gave the (*R*,*R*)-enantiomer.[15,16]

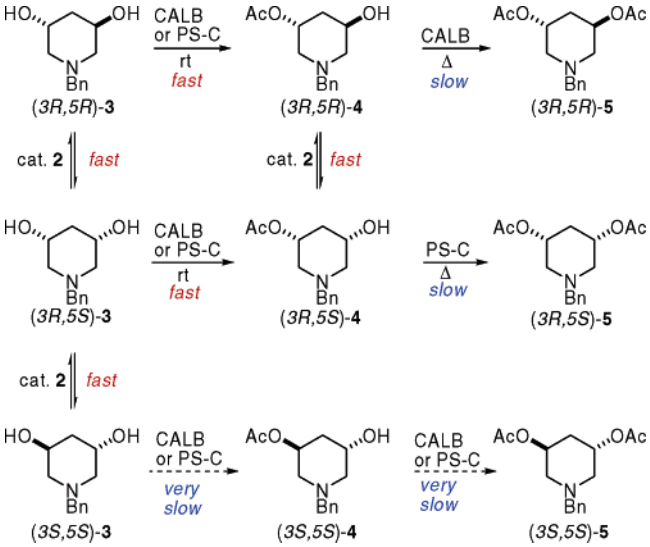
None of the reported syntheses of **3** met with our demands on efficiency and simplicity, as we sought a short route delivering both the *cis*- and *trans*-diols without tedious purification steps. The synthetic strategy depicted in Scheme 1 was thus designed to provide diols **3** as a cis:trans mixture by reduction of the corresponding diketone.

Commercially available *N*-benzylglycinate was reacted with chloroacetone to yield compound **6**.[17] An alternative pathway to **6**, avoiding chloroacetone, involved allylation of the *N*-benzylglycinate followed by Wacker oxidation but resulted in a lower overall yield. Claisen condensation of **6** and trapping of the enolate with acetic anhydride afforded *β*-acetoxyenone **7** in a clean reaction.[18,19] As compound **7** was found to be unstable on silica, the crude material was directly used in the following reaction.

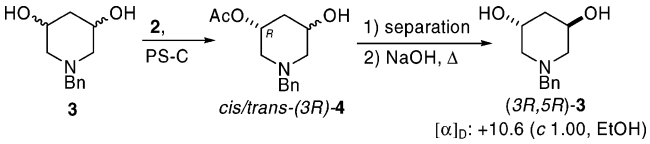
To avoid having to isolate diketone **8**, the best way to transform compound **7** into diols **3** was to employ a coupled deacetylation and reduction system in a sequential one-pot reaction. Thus, vinyl acetate **7** was treated with the commercially available enzyme *Candida antarctica* lipase B (CALB) in a mixture of 2-propanol and toluene in order to transfer the acetyl group from **7** to *i*-PrOH.

The deacetylation proceeded smoothly at room temperature, after which the enzyme was filtered off to give diketone **8** in a solution of toluene and *i*-PrOH. This mixture was directly

SCHEME 2. DYKAT of Diol Mixture 3



SCHEME 3. Determination of Absolute Configuration



(11) A similar approach using KR was recently published on 3,4-piperidine diols in moderate yields and selectivities, see: Solares, L. F.; Lavandera, I.; Gotor-Fernández, B., R.; Gotor, V. *Tetrahedron* **2006**, *62*, 3284−3291.

(12) Bentley, N.; Dowdeswell, C. S.; Singh, G. *Heterocycles* **1995**, *41*, 2499−2506.

(13) John, V.; Moon, J.; Pulley, S. R.; Rich, D. H.; Brown, D. L.; Jagodzinska, B. WO Patent 03/043987, 2003.

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(15) Cossy, J.; Dumas, C.; Michel, P.; Pardo, D. G. *Tetrahedron Lett.* **1995**, *36*, 549−552.

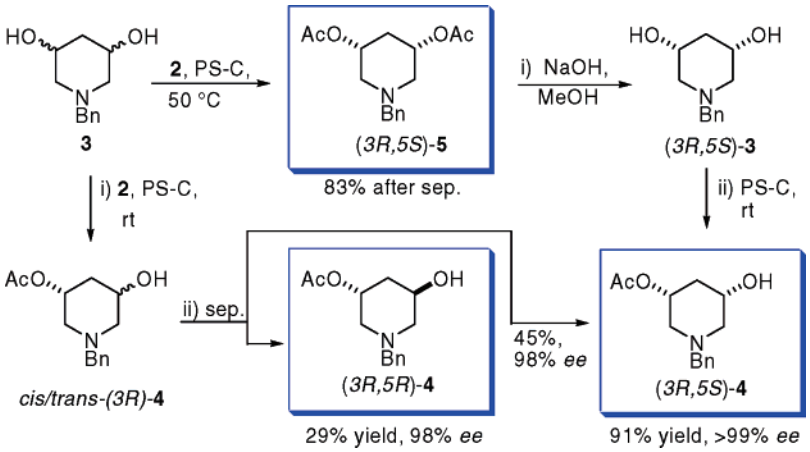
(16) Cossy, J.; Dumas, C.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1693−1699.

(17) Schmeck, C.; Mueller-Gliemann, M.; Schmidt, G.; Brandes, A.; Angerbauer, R.; Loegers, M.; Bremm, K.-D.; Bischoff, H.; Schmidt, D.; Schuhmacher, J. DE Patent 19627431, 96-19627431, 1998.

(18) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477−12487.

(19) The direct formation of diketone **8** from **7** by a Claisen condensation is reported but was judged too low-yielding and impractical due to workup and purification problems, see: Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458−7464.

SCHEME 4. Divergent Synthesis of Various 3,5-Disubstituted Piperidines



exposed to the transfer hydrogenation conditions we recently developed for cyclic 1,3-diketones.[20] Hence, Shvo catalyst **1** was added, and the reduction was smoothly accomplished at elevated temperature, delivering diols **3** in 70% isolated yield from glycinate **6**. Alternatively, β-acetoxyenone **7** could be transformed into diols **3** in one step with the Shvo catalyst and a catalytic amount of DMAP as deacetylation agent, although this procedure resulted in a lower yield of **3**.

Having succeeded in developing an efficient and high-yielding synthesis of diols **3** that required only two purification steps, we next looked into the transformation of diol mixture **3** into enantiomerically and diastereomerically pure 3,5-dioxygenated piperidines.

Investigation of DYKAT Conditions. The previously developed DYKAT system, which would be applied to diols **3**, consists of two parts working in tandem. The ruthenium catalyst (**1** or **2**) epimerizes the hydroxy groups and gives an equilibrium mixture of (*R*)- and (*S*)-configured alcohols. The enzyme preferentially catalyzes the acetylation of alcohols with (*R*)-configuration, thus shifting the equilibrium formed by the Ru catalyst upon consumption of the (*R*)-isomer and transforming all of the diol mixture into one single product.[8]

The possible products obtainable when this system is applied to diol mixture **3** are shown in Scheme 2. Initial studies of the epimerization of diols **3** with Ru catalysts **1** and **2** revealed that the Shvo catalyst **1** resulted in large amounts of diketone **8**,[21] whereas catalyst **2** gave a fast epimerization at room temperature and was thus employed in the remaining investigations.

The (CH_2NBn) moiety was expected to be the large group in the selectivity model described for lipases,[22] and the (*R*)-configured hydroxyl group was thus expected to be preferentially acetylated with CALB and *Pseudomonas cepacia* lipase (PS-C). Gratefully, monoacetylation of the diol mixture was highly enantioselective and the reaction was complete within 3 h at room temperature with both enzymes. As expected, the (*R*)-hydroxyl group was selectively acetylated,[23] resulting in a 3:2 mixture of (3*R*,5*S*)-**4** and (3*R*,5*R*)-**4**. Due to the presence of epimerization catalyst, this diastereomeric mixture was anticipated, and the ratio gives no information about the relative acylation rates of *trans*-(3*R*,5*R*)-**3** and *cis*-(3*R*,5*S*)-**3**. The absolute configuration was proven by separation of the *cis*- and *trans*-monoacetates **4** by column chromatography followed by basic hydrolysis of the *trans*-monoacetate (Scheme 3). Comparison of the optical rotation of *trans*-diol **3** with literature data confirmed the (3*R*,5*R*)-configuration.[15,16]

The second acylation step was much slower, but *cis*-diacetate (3*R*,5*S*)-**5** could be selectively obtained with PS-C at elevated temperature in 94% crude yield and 97% ds; the diastereomers could be separated to give pure *cis*-**5** in 83% yield. Since the different isomers of **4** are in fast equilibrium with one another (Scheme 2), the preferential formation of *cis*-diacetate (3*R*,5*S*)-**5** is consistent with a faster acylation of the *cis*-monoacetate compared to the *trans*-monoacetate. A similar selectivity was observed also in the previous investigation.[8] Having succeeded in selectively transforming diol mixture **3** into *cis*-diacetate **5**, we next looked into whether *trans*-diacetate (3*R*,5*R*)-**5** could be selectively formed under different reaction conditions.

Contrary to the 1,3-cyclohexanediol case, piperidine diol **3** was monoacetylated with high (*R*)-selectivity (vide supra). It was therefore considered likely that *trans*-diacetate (3*R*,5*R*)-**5** would be the major product in a DYKAT with CALB if only the reactivity problems could be addressed. Unfortunately, the acetylation selectivity dropped considerably upon increasing temperature, which proved necessary in order to obtain diacetylation, and *trans*-**5** could not be obtained in pure form.

Transformation of Diols 3 into Various Interesting 3,5-Disubstituted Piperidines. The highly selective synthesis of *cis*-diacetate (3*R*,5*S*)-**5** was subsequently exploited in order to efficiently transform the *cis:trans*-**3** mixture into pure *cis*-**3**, a compound previously reported only in lengthy syntheses.[12,13] *cis*-Diacetate **5** was thus hydrolyzed in excellent yield to *cis*-**3**, which subsequently was desymmetrized with high enantioselectivity using PS-C, thus delivering monoacetate (3*R*,5*S*)-**4** with >99% ee in 91% yield over two steps (Scheme 4). Alternatively, the highly enantioselective DYKAT of *cis:trans*-**3** could be stopped at the monoacetylation stage to obtain *trans*-monoacetate (3*R*,5*R*)-**4** with excellent enantiomeric excess by separation of the two monoacetate isomers.

Conclusions

Diols **3** could be efficiently synthesized as a cis:trans mixture in five steps from *N*-benzylglycinate. This mixture was selec-

(20) Leijondahl, K.; Fransson, A.-B. L.; Bäckvall, J.-E. *J. Org. Chem.*, in press.

(21) The ketone is formed in the epimerization cycle and cannot be rehydrogenated if hydrogen is lost from the catalyst, a feature previously reported with the Shvo catalyst.

(22) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656−2665.

(23) Calculated *E* values were >100 for both PS−C and CALB; PS−C was faster and thus employed in the remaining reactions.

tively transformed to *cis*-diacetate (3*R*,5*S*)-**5** in a dynamic process catalyzed by PS-C and ruthenium complex **2**. Further transformations of *cis*-diacetate **5** delivered *cis*-diol (3*R*,5*S*)-**3** and *cis*-monoacetate (3*R*,5*S*)-**4**, both of which are interesting subunits in pharmaceutical investigations. Finally, *trans*-monoacetate (3*R*,5*R*)-**4** could be obtained by stopping the DYKAT at the monoacetate stage. To summarize, an efficient, divergent synthesis of 3,5-oxygen-substituted piperidines has been developed, delivering products with high enantio- and diastereoselectivities. As several of these targets are novel, or only reported in multistep syntheses, this strategy should facilitate the synthesis of a range of 3,5-substituted piperidines that could be formed by further transformations of compounds **3**−**5**.

Experimental Section

1. Synthesis of 1-Benzylpiperidine-3,5-diol (*cis*:*trans*-3). a. Condensation of 6 to 5-Acetoxy-1-benzyl-3-oxo-1,2,6-tetrahydropyridine (7).[18] A solution of *t*-BuOK (2.68 g, 23.9 mmol) in anhydrous THF (60 mL) was cooled to 0 °C before addition of glycinate **6**[24] (5.68 g, 22.8 mmol) in THF (20 mL) via cannula over 15 min. The mixture turned red and was stirred at 0 °C for 2 h; this was then allowed to reach room temperature and stirred overnight (16 h). The reaction was then recooled to 0 °C, and distilled Ac_2O (2.26 mL, 23.9 mmol) was added. After stirring at 0 °C for 1 h EtOAc and H_2O were added and the mixture was extracted with EtOAc, washed twice with brine, dried (Na_2SO_4), and concentrated to give crude **7** (5.70 g) as an orange oil. Compound **7** slowly decomposed upon storage but was stable when frozen in benzene. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.27 (m, 5H), 6.10 (s, 1H), 3.71 (s, 2H), 3.39 (s, 2H), 3.24 (s, 2H), 2.20 (s, 3H).

b. Deacetylation to Give 1-Benzylpiperidine-3,5-dione (8). Crude **7** (5.70 g) was dissolved in anhydrous toluene (56 mL) and *i*-PrOH (36 mL, 20 equiv). Immobilized CALB (1.14 g) was added, and the mixture was stirred at room temperature overnight (16 h). The enzyme was filtered off and washed with toluene (5 mL), and the solution of **8** was immediately used in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.23 (m, 5H), 3.72 (s, 2H), 3.62 (br s, 1H), 3.27 (s, 4H), 2.36 (s, 1H).

c. Reduction of 8 to *cis*/*trans*-1-Benzylpiperidine-3,5-diols (3). To the solution of **8** was added Shvo catalyst **1**[9] (495 mg, 0.02 equiv, 0.45 mmol), and the solution was heated to 90 °C with a reflux condenser under Ar overnight (16 h). Alternatively, the reaction could be heated at 110 °C for 2 h in a sealed tube. The reaction mixture was then concentrated, and the residue was purified by column chromatography (EtOAc → EtOAc:MeOH 4:1 with 1% aq NH_4OH) to give **3** as a sticky brown oil (3.32 g, cis:trans 1.6:1, 70% yield from **6**). This material could be either used directly in the DYKAT reactions or treated with CH_2Cl_2 to crystallize out *cis*-**3**, leaving a 1:2 cis:trans mixture in the mother liquid. *cis*-(3*R*,5S)-**3**: white solid, mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 3.93 (m, 2H), 3.59 (s, 2H), 2.72 (dd, 2H, J = 11.4, 3.6 Hz), 2.62 (br s, 2H), 2.38 (dd, 2H, J = 11.4, 1.6 Hz), 1.88 (tt, 1H, J = 13.9, 4.4 Hz), 1.75 (tt, 1H, J = 13.9, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 129.0, 128.3, 127.2, 66.4, 62.5, 59.5, 37.6; IR (neat) 3426, 2939, 2817, 1370 cm^{-1}. For analysis data of *trans*-**3**, see refs 15 and 16.

2. Transformations of Diol Mixture 3. a. Transformation of Diols 3 to *cis*-(3*R*,5S)-1-Benzyl-3,5-diacetoxypiperidine (*cis*-5). A solution of ^{t}BuOK (0.5 M in THF, 60 μL, 0.03 mmol, 5 mol %) was added to Ru-cat. **2**[10] (19.2 mg, 0.03 mmol, 5 mol %), PS-C Amano II (60 mg), and Na_2CO_3 (63 mg, 0.6 mmol) in anhydrous toluene (1 mL). The resulting mixture was stirred for 6 min at room temperature under argon, followed by addition of *cis*:*trans*-**3** (124 mg, 0.6 mmol) dissolved in toluene (2 mL). The mixture was stirred for 4 min at room temperature, then isopropenyl acetate (180 mg, 1.8 mmol) was added, and the reaction mixture was stirred at 50 °C for 72 h. Then the reaction mixture was filtered through a silica gel plug with EtOAc to remove the enzyme, and the filtrate was concentrated to give a brown crude product, which was purified by column chromatography ($CHCl_3$:MeOH 10:1) to give the diacetates as a sticky light brown oil (164 mg, 94%, 97:3 cis:trans ratio). The diastereomers could be separated by careful column chromatography (pentane:EtOAc 20:1 → 3:1) to give *cis*-**5** (144 mg, 83%) as white needles: mp 81−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.22 (m, 5H), 4.88 (tt, 2H, J = 10.5, 4.4 Hz), 3.60 (s, 2H), 2.98 (dd, 2H, J = 10.1, 4.4 Hz), 2.35 (m, 1H), 2.05−1.97 (m, 2H), 2.00 (s, 6H), 1.40 (app. q, 1H, J = 11.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 137.2, 128.8, 128.2, 127.2, 67.5, 61.9, 55.8, 35.3, 21.0. IR (neat): 2955, 2809, 1744, 1233 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{22}NO_4$ (M + H): 292.1543. Found: 292.1532.

b. Transformation of *cis*-5 to (3*R*,5*S*)-1-Benzyl-3-acetoxy-5-hydroxypiperidine (*cis*-(3*R*,5*S*)-4) via Desymmetrization of *cis*-3. *cis*-Diacetate **5** (144 mg, 0.494 mmol) was refluxed in 5 M NaOH (1.5 mL) and MeOH (6 mL) for 1 h. The mixture was cooled and concentrated, dissolved in EtOAc and H_2O, extracted with 3 × EtOAc, dried (Na_2SO_4), and concentrated to yield crude *cis*-**3** (98 mg, 96%). For analysis data see above.

To the crude *cis*-**3** (98 mg, 0.473 mmol) in toluene (2.4 mL) was added isopropenyl acetate (142 mg, 1.42 mmol) and PS-C Amano II (47 mg). The mixture was stirred at room temperature for 4 h, then the reaction mixture was filtered through a silica gel plug with EtOAc, and the filtrate was concentrated to yield *cis*-(3*R*,5*S*)-**4** (112 mg, 91% over 2 steps) as a light yellow oil, which solidified in the freezer. The enantiomeric excess was analyzed by HPLC (ChiralCel OD-H ^{i}Hexane:^{i}PrOH 97:3, 0.5 mL/min, λ = 210.5 nm) to >99%: mp 92−93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 4.96 (app. quin, 1H, J = 4.6 Hz), 3.85 (app. quin, 1H, J = 4.6 Hz), 3.58 (AB-q, 2H, J = 13.3 Hz), 2.72 (br s, 1H), 2.53 (m, 4H), 2.06 (s, 3H), 1.93 (dt, 1H, J = 13.6, 3.9 Hz), 1.77 (dt, 1H, J = 13.6, 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 137.4, 128.7, 128.1, 127.0, 68.3, 65.2, 62.0, 59.3, 55.9, 36.6, 21.0. IR (neat): 3410, 2950, 2805, 1736, 1371, 1243, 1031 cm^{-1}. $[\alpha]_D$: +25.9 (*c* 1.35, CH_2Cl_2). HRMS (ESI) calcd for $C_{14}H_{20}NO_3$ (M + H): 250.1438. Found: 250.1426.

c. DYKAT Used in Monoacetylation to (3*R*,5R)-1-Benzyl-3-acetoxy-5-hydroxypiperidine (*trans*-(3*R*,5*R*)-4). A solution of ^{t}BuOK (0.5 M in THF, 40 μL, 0.02 mmol, 5 mol %) was added to Ru-cat. **2**[10] (12.8 mg, 0.02 mmol), PS-C Amano II (20 mg), and Na_2CO_3 (21 mg, 0.20 mmol) in anhydrous toluene (0.5 mL). The resulting mixture was stirred for 6 min at room temperature under argon, followed by addition of *cis*:*trans*-**3** (41 mg, 0.20 mmol) dissolved in toluene (0.5 mL). The mixture was stirred for 4 min at room temperature, then isopropenyl acetate (66 μL, 0.6 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h. Then the reaction mixture was filtered through a silica gel pad with EtOAc to remove the enzyme, and the filtrate was concentrated to give crude *cis*/*trans*-(3*R*)-**4** as a light yellow oil (49 mg, 99% yield, 1.6:1 cis:trans). The enantiomeric excess of the two diastereomers was determined to 98% ee by HPLC (ChiralCel OD-H, ^{i}Hexane:^{i}PrOH 97:3, 0.5 mL/min). The cis:trans mixture of **4** was separated by column chromatography (pentane:EtOAc 9:1 → 1:9) to give *trans*-(3*R*,5*R*)-**4** (14.1 mg, 29%) as a yellow oil and *cis*-(3*R*,5*S*)-**4** (22.5 mg, 45%). *cis*-**4** can, however, be obtained in higher yield via the diacetate route described above. Analysis data for *trans*-**4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.22 (m, 5H), 5.11 (tt, 1H, J = 8.6, 4.4 Hz), 3.99 (tt, 1H, J = 5.1, 3.1 Hz), 3.58 (AB-q, 2H, J = 13.2 Hz), 2.84 (dd, 1H, J = 10.8, 3.8 Hz), 2.58 (dd, 1H, J = 11.3, 4.7 Hz), 2.47 (br s, 1H), 2.40 (dd, 1H, J = 11.3, 1.7 Hz), 2.20 (dd, 1H, J = 11.5, 8.6 Hz), 2.02 (s, 3H), 1.98 (m, 1H), 1.60 (ddd, 1H, J = 13.1, 9.2, 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 137.2, 128.9, 128.3, 127.3, 67.5, 65.2, 62.2, 58.9, 56.4, 36.8, 21.1; IR (neat) 3411, 2950, 2805, 1734,

(24) The synthesis of **6** is described in the Supporting Information.

1372, 1244 cm^{-1}; $[\alpha]_D$ +28.9 (*c* 0.85, CH_2Cl_2). HRMS (ESI) calcd for $C_{14}H_{20}NO_3$ (M): 250.1438. Found: 250.1430.

3. Determination of Absolute Configuration. a. Hydrolysis of (3*R*,5*R*)-4 to (3*R*,5*R*)-1-Benzylpiperidine-3,5-diol (*trans*-(3*R*,5*R*)-3). *trans*-**4** (46 mg, 0.18 mmol) was refluxed in 5 M NaOH (0.5 mL) and MeOH (2 mL) for 1 h. The mixture was cooled to room temperature and concentrated; then water (1 mL) and CH_2Cl_2 (2 mL) were added followed by filtration through an Extrelut NT3 tube. The organic phase was eluted with CH_2Cl_2 (15 mL) and concentrated to yield crude *trans*-**3**. Purification through a silica plug (EtOAc → EtOAc:MeOH 4:1 with 1% aq. NH_4OH) delivered *trans*-(3*R*,5*R*)-**3** (36 mg, 96%) as a white solid, the NMR data of which were in agreement with the literature.[15,16] $[\alpha]_D$: +10.6 (*c* 1.00, EtOH). Literature values: $[\alpha]_D^{20}$ +15.2 (*c* 0.99, EtOH);[15] +151 (*c* 0.5, EtOH),[16] which confirm the (*R*,*R*) configuration.

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Supporting Information Available: General experimental conditions, synthesis of **6**, and NMR spectra of compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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