JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Stereoselective Synthesis of (*S*)-3-(Methylamino)-3-((*R*)-pyrrolidin-3-yl)propanenitrile

Manjinder S. Lall,*[,†] Garrett Hoge,[‡] Tuan P. Tran,[†] William Kissel,[§] Sean T. Murphy,[⊥] Clarke Taylor,[¶] Kim Hutchings,[#] Brian Samas,[†] Edmund L. Ellsworth,[∥] Timothy Curran,[▽] and H. D. Hollis Showalter[○]

[†]Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States

[‡]Dr. Reddy's, Cambridge, Cambridgeshire CB40PE, U.K.

[§]Ironwood Pharmaceuticals, Cambridge, Massachusetts 02142, United States

[⊥]Takeda California, San Diego, California 92121, United States

[¶]Lycera Corp., Ann Arbor, Michigan 48109, United States

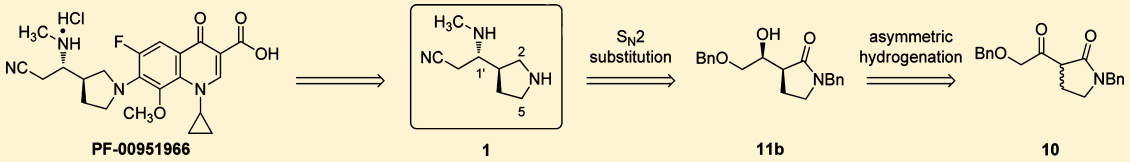
[#]AstraZeneca, Waltham, Massachusetts 02451, United States

[∥]Pfizer Worldwide Research and Development, Portage Street, Kalamazoo, Michigan 49007, United States

[▽]Vertex Pharmaceuticals, Cambridge, Massachusetts 02139, United States

[○]University of Michigan, Ann Arbor, Michigan 48109, United States

Supporting Information



ABSTRACT: (*S*)-3-(Methylamino)-3-((*R*)-pyrrolidin-3-yl)propanenitrile (**1**) is a key intermediate in the preparation of PF-00951966,[1] a fluoroquinolone antibiotic for use against key pathogens causing community-acquired respiratory tract infections including multidrug resistant (MDR) organisms. The current work describes the development of a highly efficient and stereoselective synthesis of **1** in 10 steps with an overall yield of 24% from readily available benzyloxyacetyl chloride. Two key transformations in the synthetic sequence involve (a) catalytic asymmetric hydrogenation with chiral DM-SEGPHOS-Ru(II) complex to afford *β*-hydroxy amide **11b** in good yield (73%) and high stereoselectivity (de 98%, ee >99%) after recrystallization and (b) S_N2 substitution reaction with methylamine to provide diamine **14** with inversion of configuration at the 1′-position in high yield (80%), after efficient purification using a simple acid/base extraction protocol.

INTRODUCTION

The discovery and development of new antibacterial agents has drawn considerable attention in recent years due to the alarming rise of resistant bacteria.[2] The relentless increase in antibiotic resistance to many now common-place bacterial pathogens such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant pneumococcus, and vancomycin-resistant *Enterococcus faecalis* (VRE) is proving difficult to treat effectively.[3] Perhaps more concerning is the emergence of multidrug resistant (MDR) bacteria.[4] Thus, there is an important need to introduce effective antibiotics to add to our current arsenal. Fluoroquinolone antibacterial agents have shown promise as an important class of therapeutically useful compounds.[2c] Most of the fluoroquinolone agents that show broad spectrum activity are substituted at the 7-position of the quinolone with cyclic aliphatic amines, especially diamine side chains.[5] Two diamines that have been particularly effective are *N*-methyl-*N*-{(1*S*)-1-[(3*R*)-pyrolidinon-3-yl]ethyl}amine[6a] and 3-aminopyrrolidine,[6b] both of which are attached to the fluoroquinolone core by way of their ring nitrogen to give highly active broad spectrum antibacterial agents.

In this article we disclose an efficient and stereoselective synthesis of diamine **1**, which is a key intermediate in the preparation of PF-00951966, a novel broad-spectrum fluoroquinolone antibiotic discovered at Pfizer (Figure 1).

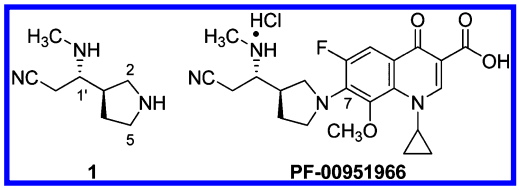


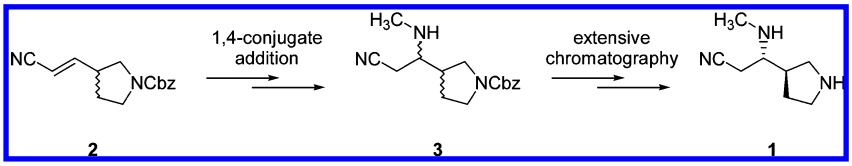
Figure 1. Structures of diamine **1** and fluoroquinolone PF-00951966.

PF-00951966 has a unique efficacy profile against pathogens causing community-acquired respiratory tract infections including

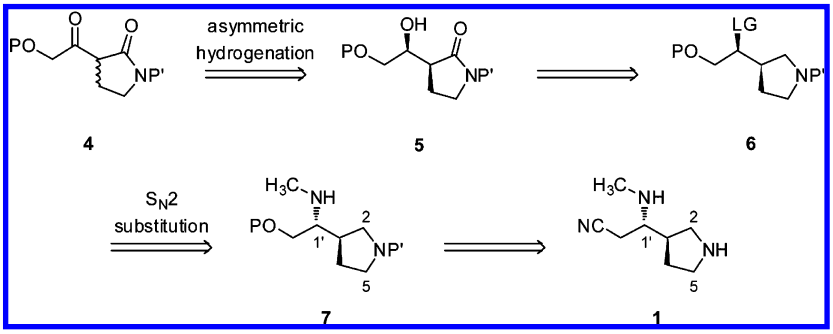
Received: March 13, 2012
Published: April 23, 2012

dx.doi.org/10.1021/jo3004716 | *J. Org. Chem.* 2012, 77, 4732–4739

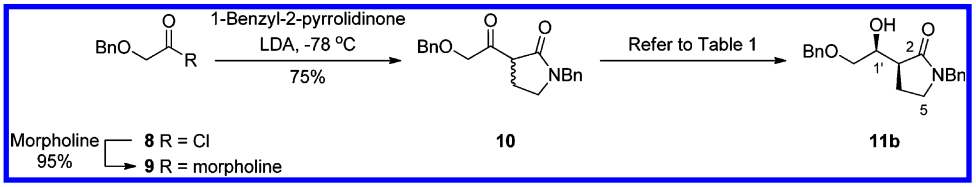
Scheme 1



Scheme 2



Scheme 3



multidrug resistant organisms. The original route to prepare **1** employed a nonstereoselective 1,4-conjugate addition to racemic α,β-unsaturated nitrile **2**, followed by extensive chromatographic purification to isolate the title compound (Scheme 1).[1]

Although this route facilitated SAR studies and led to rapid optimization of lead derivatives, it had several drawbacks for multigram-scale preparation of PF-00951966. Further, since the other three stereoisomers of PF-00951966 are much less active as antibacterial agents, the development of a stereoselective synthesis of intermediate diamine **1** was paramount.

RESULTS AND DISCUSSION

Our stereoselective route to prepare **1** is outlined in Scheme 2. We envisioned setting the absolute stereochemistry early on using a catalytic asymmetric hydrogenation approach from readily accessible β-keto amide **4**.

Ruthenium catalysts containing chiral phosphine ligands are uniquely capable of hydrogenating β-keto amides to give homochiral β-hydroxy amides, such as **5**, with extremely high enantioselectivity and efficiency.[7,8] After reduction of carboxamide **5** to the corresponding amine, the next key objective in the synthesis would involve activation of the hydroxyl group to form an appropriate leaving group followed by an S_N2 substitution reaction with methylamine to provide product **7** with inversion of configuration at the 1′-position. A variety of methods and examples are known for this type of displacement reaction.[9] Amine **7** should then readily convert to the desired diamine **1**, enlisting standard reagents and conditions. Interestingly, asymmetric hydrogenation of β-keto amides followed by reduction of the amide to the amine functionality is a practical route to prepare optically active 3-amino alcohols but has only been sparsely reported in the literature.[7] Furthermore, because most primary and secondary amides are solids, we were confident that **5** would be amenable to purification by crystallization.

The β-keto amide substrate **10** for the catalytic asymmetric hydrogenation reaction was prepared in good yield (75%) via a modified Claisen (amide) condensation, through reacting commercially available 1-benzyl-2-pyrrolidinone with freshly prepared lithium diisopropylamine in THF at −78 °C, followed by quenching with benzyloxyacetyl morpholine **9** (Scheme 3).

Initially we attempted to quench the lithiated 1-benzyl-2-pyrrolidinone anion with benzyloxyacetyl chloride **8**; however, this reaction gave **10** in low yield (45−55%) with numerous side-products[10] making purification difficult. With β-keto amide **10** in hand, the stage was set to investigate the asymmetric hydrogenation reaction. Dynamic kinetic resolution is an important consideration for the reduction of β-dicarbonyl compounds, such as **10**, with epimerizable substituents at the α-position.[11] Although the BINAP-Ru(II) system has been recognized as an efficient and general catalyst for the hydrogenation of β-keto substrates,[8c] we obtained low enantioselectivity in the hydrogenation of amide **10** as shown in Table 1 (entries 1−3). However, utilizing the comparatively more recent DM-SEGPHOS-Ru(II)[8a,d,e,12] catalyst to hydrogenate amide **10** resulted in improved enantioselectivity (Table 1, entry 4). Furthermore, the enantioselectivity was highly dependent on reaction temperature as well as pressure, and lowering these parameters greatly enhanced enantioselectivity (Table 1, entry 5). We also observed that good stereoselectivity was obtained in multiple solvents (Table 1, entries 5−7). As anticipated, the crude reaction mixture from the asymmetric hydrogenation could be recrystallized from acetone and H_2O (1:1) to afford β-hydroxy amide **11b** in good yield (73%) and enriched purity (de 98%, ee >99%) as white crystals.

dx.doi.org/10.1021/jo3004716 | J. Org. Chem. 2012, 77, 4732−4739

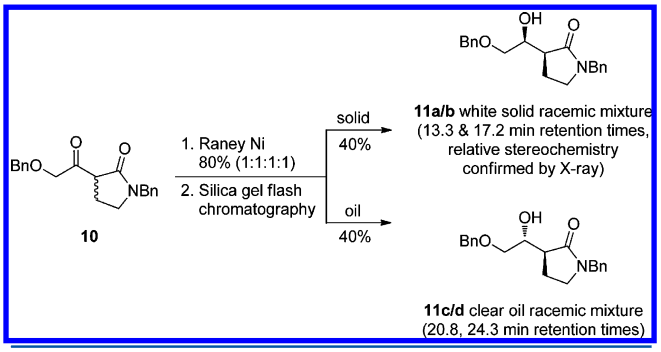
Table 1. Catalytic Asymmetric Hydrogenation of β-Keto Amide 10

entry	catalyst[a]	S/C[b]	solvent	H_2 (atm)	temp (°C)	time (h)	11 *de* (%)[c]	11 *ee* (%)[d]
1	$RuCl_2$[(*R*)-BINAP]	100	MeOH	24	80	15	67	50
2	[RuCl(cymene)((*R*)-BINAP)]Cl	100	MeOH	24	80	15	71	59
3	[RuCl(cymene)((*R*)-DM-BINAP)]Cl	100	MeOH	24	80	15	95	66
4	[RuCl(cymene)((*R*)-DM-SEGPHOS)]Cl	100	MeOH	24	80	15	92	79
5	[RuCl(cymene)((*R*)-DM-SEGPHOS)]Cl	100	MeOH	7	60	20	88	93
6	[RuCl(cymene)((*R*)-DM-SEGPHOS)]Cl	100	CH_2Cl_2	7	60	20	89	96
7	[RuCl(cymene)((*R*)-DM-SEGPHOS)]Cl	100	EtOAc	7	80	15	86	87

[a]BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DM-BINAP = 2,2′-bis(di-3,5-$(CH_3)_2C_6H_3$-phosphino)-1,1′-binaphthyl; DM-SEGPHOS = (4,4′-bi-1,3-benzodioxole)-5,5′-diyl-bis(di-3,5-$(CH_3)_2C_6H_3$-phosphine); cymene = 4-isopropyltoluene. [b]Substrate/catalyst mole ratio. [c]The diastereomeric excess was determined on a crude reaction aliquot by chiral HPLC[13] and ^{1}H NMR analysis; for details, see the Experimental Section. [d]The enantiomeric excess was determined on a crude reaction aliquot by chiral HPLC;[13] for details, see the Experimental Section.

The stereochemical purity of **11b** was assessed directly by chiral HPLC, using an analytical CHIRALCEL OJ-H column (0.46 × 25 cm, 15% isopropanol-hexane, 0.8 mL/min), in comparison with a sample mixture containing all four stereoisomers (**11a**/**b**/**c**/**d**). The stereoisomeric mixture (**11a**/**b**/**c**/**d**) was prepared by reduction of β-keto amide **10** in the presence of Raney Ni (methanol, 23 °C, 3.5 atm, 20 h, 80%), which gave a 1:1:1:1 mixture of stereoisomers (Scheme 4).[13]

Scheme 4



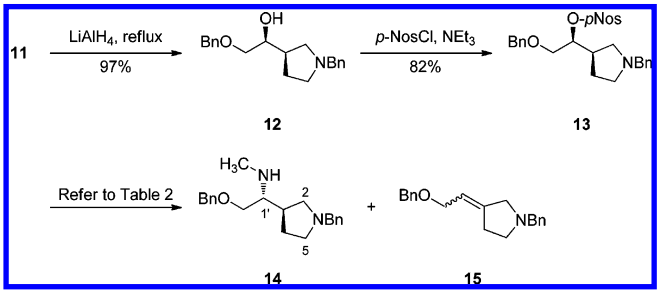
The diastereoisomers from the Raney Ni reduction could be separated by SiO_2 chromatography (dichloromethane–methanol 3%) to give diastereoisomer **11a**/**b** as a white solid racemic mixture and the other diastereoisomer **11c**/**d** as a clear oil racemic mixture. The single enantiomer **11b**, prepared from the asymmetric hydrogenation reaction, coeluted by chiral HPLC with one of the products (i.e., **11a**/**b** white solid racemic mixture) from the Raney Ni reduction having a retention time of 17.2 min. The other three stereoisomers eluted with retention times of 13.3, 20.8, and 24.3 min.[13] The relative stereochemistry of amide **11a**/**b** was confirmed by single-crystal X-ray analysis (Scheme 4).[14]

The remarkably high *syn*-diastereoselectivity observed with amide **11b** (prepared from the asymmetric hydrogenation reaction) has been previously rationalized with other similar amides in terms of a sterically constrained tricyclic transition state,[11d] where the chiral arrangement of the DM-SEGPHOS phenyl rings determines the absolute configuration of the new stereocenter.[15]

The carbonyl group of β-hydroxy amide **11b** is efficiently reduced with lithium aluminum hydride in refluxing THF, to provide optically active 3-amino alcohol **12** in excellent yield (97%) with sufficient purity for the subsequent step (Scheme 5).

The next key objective in the synthesis involved activation of the hydroxyl group in **12** with an appropriate leaving group

Scheme 5



followed by an S_N2 substitution reaction with methylamine, to furnish **14** with inversion of configuration at the 1′-position.[16] A suitable choice of reagents and conditions for nucleophilic substitution reactions demands careful consideration to the steric and electronic requirements of both the attacking nucleophile and the electrophile.[16] Consequently, the hydroxyl group of compound **12** was activated with a variety of sulfonate leaving groups (e.g., mesylate, nosylate, triflate)[17] and screened for successful displacement reaction with methylamine or a methylamine surrogate (i.e., Bn(Me)NH, MeO(Me)NH,[18a] $CF_3CONHMe$,[18b] NaN_3).[19] The amine displacement screen identified the *p*-nosylate group as a good leaving group because the reaction favored the desired amine product over a side-product, which was identified as olefin **15** resulting from elimination. In addition, the *p*-nosylate **13** intermediate was a solid and thought to be amenable to purification via recrystallization for future development. The initial displacement screen also identified methylamine as the amine of choice because the other amine surrogates offered no enhancement in desired product to olefin side-product ratio.[20] Moreover, methylamine is the preferred amine for synthetic convenience, which ultimately streamlines the synthesis by limiting additional synthetic steps.

With the choice of electrophile (**13**) and nucleophile (methylamine) secured, we focused our attention on optimizing the ratio of desired amine product (**14**) to olefin side-product (**15**). We observed that the **14**/**15** product distribution was critically dependent on solvent; Table 2 compiles the optimized results from the solvent screen. In general, polar solvents such as methanol and DMF gave amine **14** in disappointingly low ratio (Table 2, entries 1 and 2, respectively). Interestingly, the formation of desired amine **14** was better with the polar protic solvent methanol (Table 2, entry 1) than with DMF. This result may explain the superior selectivity observed with neat methylamine[21] (Table 2, entry 3). Despite the favorable ratio obtained in entry 3 (Table 2), a problem that was

dx.doi.org/10.1021/jo3004716 | J. Org. Chem. 2012, 77, 4732–4739

Table 2. *p*-Nosylate Displacement: Reaction of 13 with Methylamine[a]

entry	solvent	temp (°C)	time (h)	14/15[b]
1	MeOH	80	15	2/1
2	DMF	80	15	0.9/1
3[c,d]	neat	23	15	13/1
4	THF	80	15	2.2/1
5	MTBE	80	15	3.7/1
6	toluene	80	15	3.7/1
7	toluene/heptane (1:1)	80	15	4/1
8	toluene/heptane (1:1)	70	15	7/1
9	toluene/heptane (1:1)	60	15	8/1
10[e]	toluene/heptane (1:1)	40	15	3/1

[a]According to the procedure detailed in the Experimental Section, 1 equiv of **13** as a 0.1 M solution in solvent(s) at 0 °C was treated with 10% wt methylamine. [b]Ratio determined by ^{1}H NMR. [c]*p*-Nosylate **13** treated with 300 equiv of methylamine at 0 °C. [d]*N*-Methyl-*p*-nitrobenzenesulfonamide and alcohol **12** side products observed. [e]Reaction did not go to completion.

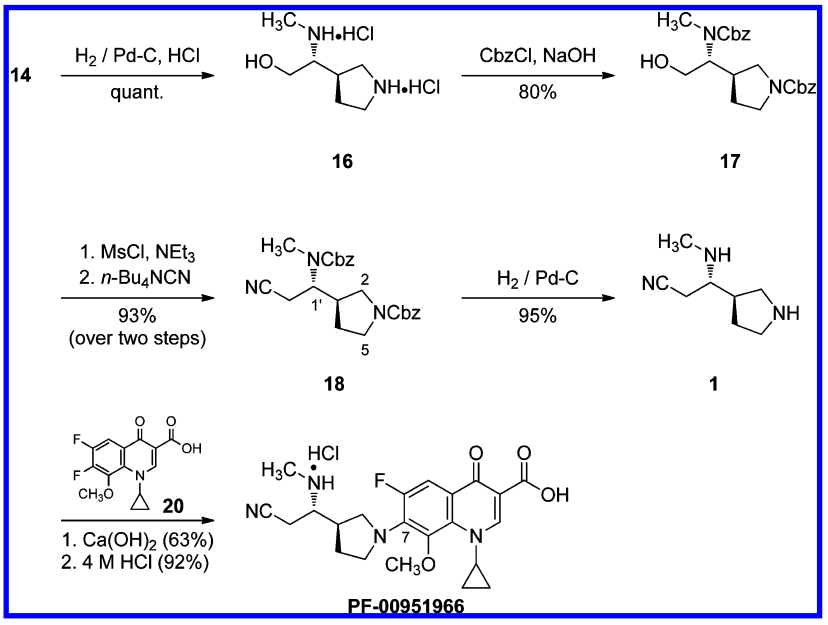
encountered with neat methylamine was the formation of unwanted additional side-products, such as *N*-methyl-*p*-nitrobenzenesulfonamide and alcohol **12** from sulfur−oxygen bond scission (the result of methylamine attack on the sulfur atom in **13**).[16] All attempts to minimize the side-products associated with running the reaction in neat methylamine (e.g., lowering reaction temperature, increasing reaction time) were unsuccessful. From entries 5 and 6 (Table 2), we found that running the reaction in nonpolar solvents favored the desired amine **14** over olefin **15**. Furthermore, introducing a nonpolar cosolvent such as heptane improved the ratio of desired amine to olefin (Table 2, entry 7). Under these nonpolar conditions, the ratio of **14**/**15** was highly dependent on reaction temperature, and lowering this parameter favored **14** (Table 2, entries 8, 9).

An attempt was made to execute the substitution reaction in the presence of Lewis acid additives (e.g., $BF_3{\cdot}OEt_2$, $InCl_3$, $MgCl_2$, $MgOTf_2$, $ZnCl_2$); however, no improvement in **14**/**15** ratio or yield was observed. The isolation of **14** was most conveniently accomplished by employing a standard acid (HCl)/base (NaOH) extraction protocol, using dichloromethane as extracting solvent. Presumably, the protonated amine **15** is reasonably soluble in dichloromethane, which is extracted into the organic solvent (DCM) with other organic impurities. Basification of the aqueous layer with 1 M NaOH liberates diamine **14**, which is extracted into dichloromethane and recovered with high purity and yield (80%) after solvent removal.

With diamine **14** in hand and a method developed for purification secured, our efforts focused on the remaining steps required to complete the synthesis of pyrrolidine **1** (Scheme 6).

Hydrogenolysis of the benzyl ether and benzyl amine protecting groups in **14** was accomplished under acidic (2 equiv HCl) conditions to give alcohol **16** as the bis-hydrochloride salt in good yield. Reduction in the absence of acid was problematic, leading to incomplete or slow debenzylation. Alcohol **16** was treated with benzyl chloroformate in the presence of NaOH to provide the bis-benzyl carbamate (Cbz) derivative **17**. The next transformation involved activating alcohol **17** with methanesulfonyl chloride to give the mesylate adduct, followed by displacement with a cyanide source. Our initial displacement conditions (0.07 M mesylate in acetonitrile, 2 equiv KCN, 70 °C, 90 min) gave mainly oxazolidinone **19**[22] side-product and nitrile **18** as the minor constituent. Enlisting the prescribed reaction conditions (0.2 M mesylate in MTBE, 2 equiv $(n\text{-Bu})_4NCN$, 50 °C, 3 h, 93% over two steps) gave smooth conversion to nitrile **18** with no detection of the oxazolidinone **19**[22] side-product by TLC or LCMS. The prepared nitrile **18** sample was identical in all respects in comparison to an authentic sample,[1,23] confirming that the desired stereoselectivity was attained in the asymmetric hydrogenation reaction and that the methylamine substitution reaction proceeded with inversion of configuration at the 1′-position in **14**.[24] The penultimate nitrile **18** underwent selective hydrogenolysis of the Cbz group utilizing isopropanol as solvent, with no detection of nitrile reduction, to provide diamine **1** as a clear oil. The overall yield of target diamine **1** from benzyloxyacetyl chloride was 24% over 10 steps. The final step involved coupling diamine **1** with difluoroquinolone **20** via an aromatic nucleophilic substitution

Scheme 6



dx.doi.org/10.1021/jo3004716 | J. Org. Chem. 2012, 77, 4732−4739

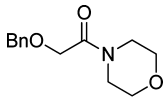
reaction, to afford the fluoroquinolone antibiotic PF-00951966 in 63% yield.

CONCLUSION

An efficient and stereoselective synthesis of diamine **1** was developed in 10 steps from benzyloxyacetyl chloride in 24% overall yield. The synthesis employs a catalytic asymmetric hydrogenation reaction using a chiral DM-SEGPHOS-Ru(II) complex to set the stereochemistry at the 3- and 1′-positions in *β*-hydroxy amide **11b** in good yield (73%) and high stereoselectivity (de 98%, ee >99%) after recrystallization. The stereochemistry at the 1′-position was then inverted utilizing a S_N2 substitution reaction with methylamine to provide diamine **14** in high yield (80%), after efficient purification using a simple acid/base extractive workup.

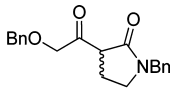
EXPERIMENTAL SECTION

All commercially available materials and solvents were used as received. Reaction temperatures were measured internally, unless indicated otherwise (rt = 20−23 °C).



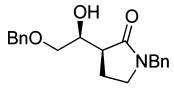
9

2-(Benzyloxy)-1-morpholinoethanone (9). A solution of morpholine (62 mL, 707 mmol) in toluene (300 mL) was treated with acid chloride **8** (52.2 g, 282 mmol) dissolved in toluene (100 mL) dropwise over 30 min. The temperature rose to 70 °C. The reaction was allowed to stir overnight. Water (100 mL) was added to the reaction, and the solids dissolved. The layers were separated, and the toluene layer was washed with water (100 mL), 1 N HCl (100 mL), aqueous K_2CO_3 (10 g in 100 mL), and water (100 mL). The organic layer was concentrated to give **9** (60 g, 95%) as a clear oil. The material was used in the next step without further purification: IR (ZnSe) 3020, 2950, 1650, 1490, 1260, 1120, 750, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21−7.28 (m, 5H), 4.52 (s, 2H), 4.09 (s, 2H), 3.51−3.57 (m, 6H), 3.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 137.0, 128.3, 127.9, 127.8, 73.0, 69.1, 45.4, 41.9; HRMS (ESI) Calcd for $C_{13}H_{17}NO_3Na$ $[M + Na]^+$ 258.1101, found 258.1097; HPLC %(AUC) = 95.23 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 7.1 min).



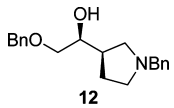
10

1-Benzyl-3-(2-(benzyloxy)acetyl)pyrrolidin-2-one (10). A solution of diisopropylamine (24 mL, 171 mmol) in THF (200 mL) was cooled to −10 °C and treated with *n*-BuLi (1.6 M in hexane, 98 mL, 157 mmol) dropwise over 15 min. The prepared solution was treated with 1-benzylpyrrolidin-2-one (25 g, 143 mL) to give a red solution. After 30 min of stirring, **9** (38.6 g, 164 mL) was added over 10 min while keeping the temperature below −5 °C. The reaction slowly lost the red color to become a pale yellow at completion. The reaction was allowed to warm to 10 °C and then quenched by the addition of aqueous $NaHCO_3$ (60 g, in 200 mL). The reaction was diluted with toluene (300 mL), and the aqueous phase separated. The aqueous phase was extracted with toluene (3 × 100 mL), and the combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 10−50%) to afford **10** (26 g, 75%) as a yellow oil: IR (ZnSe) 3030, 2940, 1720, 1670, 1480, 1270, 1110, 770, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.17 (m, 10H), 4.80 (dd, 1H, *J* = 18, 18 Hz), 4.62 (dd, 2H, *J* = 12, 21 Hz), 4.39 (dd, 2H, *J* = 15, 26 Hz), 4.30 (dd, 1H, *J* = 18, 18 Hz), 3.69 (dd, 1H, *J* = 6, 9 Hz), 3.31 (ddd, 1H, *J* = 5, 9, 14 Hz), 3.19 (ddd, 1H, *J* = 5, 9, 14 Hz), 2.48 (ddd, 1H, *J* = 5, 9, 13 Hz), 1.99 (ddd, 1H, *J* = 5, 9, 13 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 169.6, 137.4, 135.8, 128.8, 128.5, 128.1, 128.0, 127.9, 127.7, 74.9, 73.4, 51.8, 46.9, 45.2, 19.4; HRMS (ESI) Calcd for $C_{20}H_{22}NO_3$ $[M + H]^+$ 324.1594, found 324.1594; HPLC %(AUC) = 93.1 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 8.5 min). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.63; H, 6.70; N, 4.70.



11b

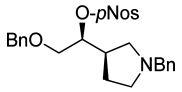
(*S*)-1-Benzyl-3-((*S*)-2-(benzyloxy)-1-hydroxyethyl)pyrrolidin-2-one (11b). A mixture of **10** (15 g, 46.4 mmol) and [RuCl-(cymene)((*R*)-DM-SEGPHOS)]Cl (0.48 g, 1 mol %, 0.48 mmol) in MeOH (150 mL) was loaded into an Endeavor autoclave. Hydrogen was introduced (100 psi), and the mixture was stirred at 60 °C for 20 h. After the hydrogen pressure was released, the solvent was removed to afford crude product. The material was purified by recrystallization from acetone−H_2O (1:1), to give **11b** (11.2 g, 73%, de 98%, ee >99%) as white needles. The enantiomeric and diastereomeric excess was assessed directly by chiral phase HPLC separation using an analytical CHIRALCEL OJ-H column (0.46 × 25 cm, 15% *i*-PrOH-hexane, 0.8 mL/min). The four stereoisomers eluted with retention times of 13.3, 17.2, 20.8, and 24.3 min; compound **11b** coeluted with a retention time of 17.2 min. Note: chiral phase HPLC conditions modified for developmental work to CHIRALCEL OJ-H column (0.46 × 25 cm, 20% *i*-PrOH-hexane, 1.0 mL/min), the desired stereoisomers **11b** eluted with a retention time of 14.6 min: $[\alpha]^{23}$ −12 (*c* 5.0, $CHCl_3$); IR (ZnSe) 3370, 3090, 2870, 1660, 1480, 1290, 1105, 750, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 10H), 4.56 (dd, 2H, *J* = 12, 15 Hz), 4.44 (dd, 2H, *J* = 14, 19 Hz), 4.37 (ddd, 1H, *J* = 4, 7, 8 Hz), 3.57 (dddd, 2H, *J* = 4, 10, 14, 23 Hz), 3.19 (m, 2H), 2.65 (ddd, 1H, *J* = 4, 9, 13 Hz), 2.50 (br s, 1H), 2.11 (m, 1H), 1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 138.2, 136.5, 128.9, 128.6, 128.2, 127.9, 127.8, 127.7, 73.5, 72.6, 69.2, 46.9, 45.4, 45.0, 18.9; HRMS (ESI) Calcd for $C_{20}H_{24}NO_3$ $[M + H]^+$ 326.1751, found 326.1750; HPLC %(AUC) = 98.8 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 5.6 min). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.62; H, 7.08; N, 4.16.



12

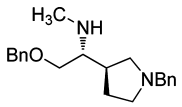
(*S*)-2-(Benzyloxy)-1-((*R*)-1-benzylpyrrolidin-3-yl)ethanol (12). A solution of **11b** (17.8 g, 54 mmol) dissolved in THF (34 mL) at 23 °C was treated dropwise with lithium aluminum (1 M in THF, 109 mL, 109 mmol). The mixture was refluxed under nitrogen for 2 h. The solution was cooled with an ice bath and quenched sequentially with H_2O (16 mL), 15% aqueous NaOH (16 mL), H_2O (16 mL); the mixture was stirred at 0 °C for 30 min and then treated with $MgSO_4$ (10 g). The suspension was filtered under vacuum and washed with THF (150 mL), and the filtrate was concentrated in vacuo to afford **12** (17.0 g, 97%) as a brown oil: $[\alpha]^{23}$ −4 (*c* 5.0, $CHCl_3$); IR (ZnSe) 3430, 3100, 2850, 1580, 1490, 1140, 780, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.19 (m, 10H), 4.50 (dd, 2H, *J* = 12, 17 Hz), 3.82 (ddd, 1H, *J* = 5, 7, 10 Hz), 3.76 (br s, 1H), 3.57 (s, 2H), 3.37 (dddd, 2H, *J* = 5, 10, 13, 15 Hz), 2.69 (ddd, 1H, *J* = 7, 9, 13 Hz), 2.52 (m, 2H), 2.34 (m, 2H), 1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.3, 128.8, 128.5, 128.4, 128.2, 127.8, 127.2, 73.8, 73.4, 72.8, 60.2, 58.3, 53.7, 39.4, 24.3; HRMS (ESI) Calcd for $C_{20}H_{26}NO_2$ $[M + H]^+$ 312.1958, found 312.1957. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.92; H, 8.26; N, 4.38.

dx.doi.org/10.1021/jo3004716 | J. Org. Chem. 2012, 77, 4732−4739



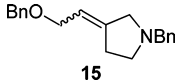
13

(*S*)-2-(Benzyloxy)-1-((*R*)-1-benzylpyrrolidin-3-yl)ethyl 4-Nitrobenzenesulfonate (13). A solution of **12** (9.21 g, 30 mmol) dissolved in DCM (45 mL) at 0 °C was treated with triethylamine (5 mL, 35 mmol) followed by 4-nitrobenzenesulfonyl chloride (7.9 g, 35 mmol). The mixture was stirred at 0 °C for 1 h and then warmed to room temperature, where stirring was continued for 15 h. The reaction was quenched with 5% aqueous $NaHCO_3$ (100 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic phases were washed with brine (100 mL) and dried over $MgSO_4$, and the solvent removed in vacuo. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 10−80%), to afford **13** (12 g, 82%) as a yellow solid: $[\alpha]^{23}$ 8 (*c* 5.0, $CHCl_3$); IR (ZnSe) 3120, 2870, 1520, 1390, 1180, 1090, 920, 880, 730, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 2H, *J* = 9 Hz), 7.98 (d, 2H, *J* = 9 Hz), 7.31−7.26 (m, 8H), 7.05 (m, 2H), 4.84 (ddd, 1H, *J* = 3, 7, 10 Hz), 4.30 (dd, 1H, *J* = 11 Hz), 4.17 (dd, 1H, *J* = 11 Hz), 3.65 (br s, 2H), 3.49 (m, 2H), 2.67 (m, 4H), 2.39 (m, 1H), 2.01 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 144.7, 139.1, 138.3, 129.2, 129.1, 128.6, 128.5, 128.3, 127.9, 127.1, 124.0, 73.5, 70.7, 60.7, 60.3, 56.4, 53.6, 39.8, 26.6; HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_6S$ $[M + H]^+$ 497.1741, found 497.1734; HPLC %(AUC) = 99.7 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 7.1 min).



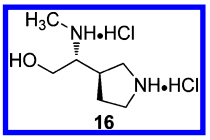
14

(*R*)-2-(Benzyloxy)-1-((*R*)-1-benzylpyrrolidin-3-yl)-*N*-methylethanamine (14). A 200 mL pressure vessel was charged with **13** (5 g, 10 mmol) and toluene/heptane 1:1 (100 mL) and treated with methylamine (10% wt, 10 g, 322 mmol). The mixture was heated at 60 °C for 15 h. The vessel was cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was taken up in DCM (100 mL) and H_2O (100 mL), and the aqueous layer was adjusted to pH 2 with 1 M HCl; the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 75 mL). The combined DCM layers were concentrated in vacuo to give **15** (see below). The aqueous layer was adjusted to pH 13 with 1 M NaOH and extracted with DCM (3 × 75 mL), and the combined organic extracts were concentrated in vacuo to afford **14** (2.5 g, 80%) as a brown oil: $[\alpha]^{23}$ 4 (*c* 5.0, $CHCl_3$); IR (ZnSe) 3210, 2830, 1540, 1170, 920, 720, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 10H), 4.51 (dd, 2H, *J* = 12, 14 Hz), 3.59 (dd, 2H, *J* = 13, 17 Hz), 3.55 (dd, 1H, *J* = 4, 10 Hz), 3.38 (dd, 1H, *J* = 4, 10 Hz), 2.73 (m, 1H), 2.57 (m, 1H), 2.49 (m, 2H), 2.42 (m, 2H), 2.38 (s, 3H), 2.08 (br s, 1H), 1.88 (m, 1H), 1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.5, 128.9, 128.5, 128.3, 127.7, 127.6, 126.9, 73.3, 69.7, 63.3, 60.7, 57.8, 54.1, 39.2, 34.3, 27.9; HRMS (ESI) Calcd for $C_{21}H_{29}N_2O$ $[M + H]^+$ 325.2274, found 325.2272; HPLC %(AUC) = 97.7 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 4.7 min).



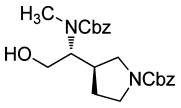
15

1-Benzyl-3-(2-(benzyloxy)ethylidene)pyrrolidine (15). A yellow oil: IR (ZnSe) 3180, 2850, 1510, 1120, 920, 740, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 10H), 5.51 (m, 1H), 4.49 (s, 2H), 4.00 (dd, 2H, *J* = 1, 7 Hz), 3.63 (s, 2H), 3.18 (dd, 2H, *J* = 2, 3 Hz), 2.68 (t, 2H, *J* = 7 Hz), 2.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.6, 138.5, 128.9, 128.4, 128.3, 127.8, 127.6, 127.2, 116.9, 72.1, 67.7, 60.6, 59.4, 54.1, 28.4; HRMS (ESI) Calcd for $C_{20}H_{23}NO$ $[M + H]^+$ 294.1852, found 294.1854; HPLC %(AUC) = 96.06 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 7.3 min).



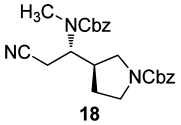
16

(*R*)-2-(Methylamino)-2-((*R*)-pyrrolidin-3-yl)ethanol Bishydrochloride (16). A solution of **14** (3.18 g, 9.8 mmol) in methanol (100 mL) and hydrochloric acid (12.4 M, 1.6 mL, 19.6 mmol) under argon was treated with 20% palladium on carbon (2 g) at 23 °C. The mixture was hydrogenated in a Parr shaker under 50 psi of hydrogen at 23 °C for 24 h. The solution was filtered through a pad of Celite (MeOH, 100 mL), the solvent was removed via rotary evaporation, and the product was dried under vacuum to afford **16** (2.3 g, quantitative) as a clear viscous oil: $[\alpha]^{23}$ 6 (*c* 5.0, H_2O); IR (ZnSe) 3380, 2950, 1630, 1590, 1470, 1210, 1040, 910 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.66 (br s, 1H), 9.15 (br s, 1H), 5.49 (s, 1H), 3.72 (m, 1H), 3.54 (m, 1H), 3.17 (m, 2H), 3.02 (m, 2H), 2.47 (m, 3H), 2.07 (m, 2H), 1.65 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 61.1, 57.04, 47.7, 45.3, 36.9, 30.4, 27.1; HRMS (ESI) Calcd for $C_7H_{16}N_2O$ $[M + H]^+$ 145.1335, found 145.1339. ELSD %(AUC) = 99.59 (Symmetry C-18, elution over 15 min, acetonitrile/ammonium acetate buffer, t_R = 1.5 min).



17

(*R*)-Benzyl 3-((*R*)-1-(((Benzyloxy)carbonyl)(methyl)amino)-2-hydroxyethyl)pyrrolidine-1-carboxylate (17). A solution of **16** (2.1 g, 9.8 mmol) in THF (50 mL) and NaOH (1 M, 44 mL, 44 mmol) at 0 °C was treated with benzyl chloroformate (2.8 mL, 19.6 mmol) dropwise over 10 min. The mixture was stirred at 0 °C for 3 h, diluted with EtOAc (50 mL), and washed sequentially with saturated $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 10−80%), to afford **17** (3.2 g, 80%) as a clear viscous oil: $[\alpha]^{23}$ 9.6 (*c* 5.0, $CHCl_3$); IR (ZnSe) 3430, 3250, 2920, 2870, 1690, 1670, 1440, 1130, 810, 720, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 10H), 5.13 (s, 4H), 3.91 (m, 1H), 3.79 (dd, 1H, *J* = 4, 12 Hz), 3.71−3.49 (m, 3H), 3.36 (ddd, 1H, *J* = 6, 10, 17 Hz), 3.11 (m, 1H), 2.89 (s, 3H), 2.55 (m, 2H), 1.97 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.9, 137.1, 136.6, 128.7, 128.6, 128.4, 128.2, 128.1, 127.9, 67.6, 66.9, 62.5, 50.9, 46.8, 38.2, 37.7, 29.8, 28.2; HRMS (ESI) Calcd for $C_{23}H_{28}N_2O_5$ $[M + H]^+$ 413.2071, found 413.2078; HPLC %(AUC) = 94.3 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 10.5 min).

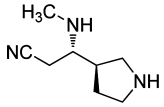


18

(*R*)-Benzyl 3-((*S*)-1-(((Benzyloxy)carbonyl)(methyl)amino)-2-cyanoethyl)pyrrolidine-1-carboxylate (18). A solution of **17** (2.1 g, 5.1 mmol) in dichloromethane (30 mL) at 0 °C was treated with triethylamine (0.9 mL, 6.7 mmol), followed by methanesulfonyl chloride (0.44 mL, 5.7 mmol) dropwise over 10 min. The mixture was stirred at 0 °C for 30 min and then quenched with saturated $NaHCO_3$ (20 mL). The organic layer was separated and washed with H_2O (20 mL) and then brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to afford the mesylate ester as a thick oil, which was used immediately in the next reaction: ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.36 (m, 10H), 5.08 (m, 4H), 4.39 (m 1H), 4.22 (dd, 2H), 3.62 (m, 2H), 3.37 (m, 1H), 3.09 (m, 1H), 2.83 (s, 3H), 2.82 (s, 3H), 2.57 (m, 1H), 2.00 (m, 1H), 1.62 (m, 1H); MS-APCI (*m*/*z*+) 491.1 (M + H).

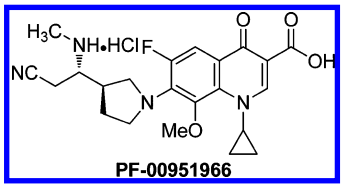
dx.doi.org/10.1021/jo3004716 | *J. Org. Chem.* 2012, 77, 4732−4739

The crude mesylate was dissolved in methyl *t*-butyl ether (25 mL) and treated with tetrabutylammonium cyanide (2.77 g, 10.3 mmol), and the mixture was stirred at 50 °C for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (30 mL). The organic layer was separated and washed with H_2O (30 mL) and then with brine (30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 10−80%), to afford **18** (2.03 g, 93%) as a clear viscous oil: $[\alpha]^{23}$ 30.4 (*c* 5.0, $CHCl_3$); IR (ZnSe) 3170, 2950, 2820, 2230, 1680, 1460, 1320, 1150, 790, 740, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 10H), 5.06 (s, 2H), 5.04 (s, 2H), 4.03 (br s, 1H), 3.57−3.42 (m, 2H), 3.31 (m, 1H), 3.03 (m, 1H), 2.88 (br s, 3H), 2.69−2.42 (m, 3H), 1.92 (m, 1H), 1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.6, 136.9, 136.3, 128.7, 128.6, 128.3, 128.1, 127.9, 127.8, 117.2, 68.1, 66.9, 49.7, 49.1, 45.9, 40.0, 29.8, 28.9, 20.4; HRMS (ESI) Calcd for $C_{24}H_{27}N_3O_4$ $[M + Na]^+$ 444.1894, found 444.1899; HPLC %(AUC) = 98.6 (Symmetry C-18, gradient elution over 15 min of acetonitrile and water, from 0 to 30%, t_R = 11.5 min). Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.05; H, 6.57; N, 9.99.



1

(*S*)-3-(Methylamino)-3-((*R*)-pyrrolidin-3-yl)propanenitrile (1). A solution of **18** (9.7 g, 23 mmol) in isopropanol (150 mL) under argon was treated with 10% palladium on carbon (2 g) at 23 °C. The mixture was hydrogenated in a Parr shaker under 50 psi of hydrogen at 23 °C for 4 h. The solution was filtered through a pad of Celite and rinsed with acetonitrile (100 mL), followed by methanol (100 mL). The solvent was removed via rotary evaporation, and the product was dried under vacuum to afford **1** (3.39 g, 95%) as a clear oil, which was used without further purification: $[\alpha]^{23}$ 2.4 (*c* 5.0, CH_3OH); IR (ZnSe) 3370, 2950, 2820, 2150, 1630, 1530, 1450, 1380, 1350 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.23 (m, 1H), 3.07 (m, 1H), 2.98 (m, 1H), 2.77 (m, 2H), 2.65 (m, 2H), 2.43 (m, 1H), 2.41 (s, 3H), 2.29 (m, 1H), 2.04 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 119.3, 60.7, 50.7, 47.2, 44.9, 33.7, 30.5, 21.2; HRMS (ESI) Calcd for $C_8H_{15}N_3$ $[M + H]^+$ 154.1339, found 154.1335.



PF-00951966

7-((*R*)-3-((*S*)-2-Cyano-1-(methylamino)ethyl)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Hydrochloride (PF-00951966). A solution of **1** (0.4 g, 2.6 mmol) in a mixture of isopropanol/methanol/acetonitrile (1:1:1, 15 mL) under nitrogen was treated with crushed molecular sieves (activated type 3A, 8−12 mesh, 0.4 g), followed by difluoroquinone **20** (0.85 g, 2.5 mmol) and $Ca(OH)_2$ (0.55 g, 7.5 mmol) at 23 °C. The mixture was heated to 30 °C for 6 h and then cooled to room temperature, where stirring was continued for an additional 22 h. The reaction mixture was treated with ethanol (5 mL) and heated to 80 °C for 5 h. The mixture was then treated with triethylamine (0.7 mL, 5 mmol) and heated at 80 °C for 7 h. The solution was filtered through a pad of Celite and rinsed with acetonitrile (25 mL), and the solvent was removed via rotary evaporation. The product was dried under vacuum to afford the free amine as a yellow solid (0.66 g, 63%). The yellow solid (0.46 g, 0.87 mmol) was suspended in dichloromethane (20 mL) and treated with 4 M HCl in dioxane (2.2 mL). The mixture was stirred at room temperature for 18 h, and then the solvent was removed in vacuo. The yellow solid was slurried in ethyl acetate and dichloromethane, collected by vacuum filtration, and rinsed with ethyl acetate. The bright yellow solid was dried under vacuum to give PF-00951966 (0.46 mg, 92%) as the hydrochloride salt: $[\alpha]^{23}$ −233.6 (*c* 5.0, H_2O); IR (ZnSe) 3450, 3170, 2940, 2210, 1650, 1430, 1380, 1120, 810, 710 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 8.50 (s, 1H), 6.41 (d, 1H, *J* = 13 Hz), 4.07 (m, 1H), 3.83−3.71 (m, 3H), 3.51 (m, 3H), 3.30 (m, 2H), 2.93 (s, 3H), 2.81 (m, 2H), 2.34 (m, 2H), 1.89 (m, 1H), 1.32 (m, 1H), 1.14 (m, 1H), 1.02 (m, 1H), 0.89 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 174.8, 168.9, 153.3 (d, J_{C-F} = 250 Hz), 150.0, 140.9, 137.2, 137.1, 134.3, 116.9, 116.2, 105.7, 104.8, 61.2, 57.0, 53.9, 41.4, 40.2, 30.9, 28.3, 18.1, 9.9, 8.3; HRMS (ESI) Calcd for $C_{22}H_{25}FN_4O_4$ $[M + H]^+$ 429.1933, found 429.1942; LCMS %(AUC) = 97.3 (Phenomenex Develosil Combi RP3 50 × 4.6 mm column, gradient elution over 4 min of acetonitrile and water, from 2 to 50%, t_R = 0.83 min). Anal. Calcd for $C_{22}H_{26}ClFN_4O_4$: C, 56.83; H, 5.64; N, 12.05. Found: C, 56.45; H, 5.78; N, 11.87.

■ ASSOCIATED CONTENT

Supporting Information

Copies of proton and carbon NMR spectra and single crystal X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: manjinder.lall@pfizer.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Dr. Mike Melnick and Susan Hagen for collaborative efforts and helpful discussions. For their technical expertise, we extend our gratitude to Norman Colbry, Mark Lovdahl, and Mark Marlatt. The staff in spectral and analytical services at Pfizer is recognized for their assistance in compound characterization. Finally, we thank Takasago Int. Corp. for kindly donating a sample of [RuCl(*p*-cymene)((*R*)-DM-SEGPHOS)]Cl.

■ REFERENCES

(1) (a) Ellsworth, E. L.; Taylor, C. B.; Murphy, S. T.; Rauckhorst, M. R.; Starr, J. T.; Hutchings, K. M.; Limberakis, C.; Hoyer, D. W. Preparation of quinolone antibacterial agents. WO 2005049602 A1, June 2, 2005. (b) Murphy, S. T.; Case, H. L.; Ellsworth, E.; Hagen, S.; Huband, M.; Joannides, T.; Limberakis, C.; Marotti, K. R.; Ottolini, A. M; Rauckhorst, M.; Starr, J.; Stier, M.; Taylor, C.; Zhu, T.; Blaser, A.; Denny, W. A.; Lu, G.-L.; Smaill, J. B.; Rivault, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2150−2155.

(2) (a) Theuretzbacher, U. *Curr. Opin. Pharmacol.* **2011**, *11*, 433−438. (b) Andersson, D. I.; Hughes, D. *Nat. Rev. Microbiol.* **2010**, *8*, 260−271. (c) Alekshun, M. N. *Expert Opin. Invest. Drugs* **2005**, *14*, 117−134. (d) Norrby, S. R.; Nord, C. E.; Finch, R. *Lancet Infect. Dis.* **2005**, *5*, 115−119. (e) *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews*; Infectious Diseases Society of America: Alexandria, VA, 2004. (f) Boggs, A. F. *Expert Opin. Ther. Pat.* **2003**, *13*, 1107−1112. (g) Walsh, C. In *Antibiotics: Actions, Origins, Resistance*; American Society for Microbiology (ASM) Press: Washington, D.C., 2003; pp 89−155. (h) Wright, G. D. *Chem. Biol.* **2000**, *7*, R127−R132.

(3) (a) O'Donnell, E. P.; Hurt, K. M.; Scheetz, M. H.; Postelnick, M. J.; Scarsi, K. K. *Drugs Today* **2009**, *45*, 379−393. (b) Zetola, N.; Francis, J. S.; Nuermberger, E. L.; Bishai, W. *Lancet Infect. Dis.* **2005**, *5*, 275−286. (c) Huang, V.; Zervos, M. J. *Infect. Dis. Clin. Pract.* **2005**, *13*, 93−95. (d) Kaplan, S. L. *Pediatr. Infect. Dis. J.* **2005**, *24*, 457−458. (e) Pfaller, M. A.; Jones, R. N.; Doem, G. V.; Kugler, K. *Antimicrob. Agents Chemother.* **1998**, *42*, 1762−1770.

(4) (a) Won, S. Y.; Munoz-Price, L. S.; Lolans, K.; Hota, B.; Weinstein, R. A.; Hayden, M. K. *Clin. Infect. Dis.* **2011**, *53*, 532−540. (b) Butler, M. S.; Cooper, M. A. *J. Antibiot.* **2011**, *64*, 413−425. (c) Dougherty, T. J.; Magee, T. V. *Exp. Opini. Ther. Pat.* **2005**, *15*, 1409−1421. (d) Levy, S. B.; Marshall, B. *Nat. Med.* **2004**, *10* (12,Suppl.), S122−S129. (e) Baquero, F. *J. Antimicrob. Chemother.* **1998**, *39*, 1−6. (f) Swartz, M. N. *Proc. Natl. Acad. Sci. U. S. A.* **1994**, *91*, 2420−2427.

(5) Domagala, J. M., Hagen, S. E. In *Quinolone Antimicrobial Agents*; Hooper, D. C., Rubinstein, E., Eds.; American Society for Microbiology (ASM) Press: Washington, D.C., 2003; pp 3−17.

(6) (a) Fleck, T. J.; McWhorter, W. W., Jr.; DeKam, R. N.; Pearlman, B. A. *J. Org. Chem.* **2003**, *68*, 9612−9617. (b) Cohen, M. A.; Huband, M. D.; Gage, J. W.; Yoder, S. L.; Roland, G. E.; Gracheck, S. J. *J. Antimicrob. Chemother.* **1997**, *40*, 205−211.

(7) For examples on catalytic asymmetric hydrogenation of β-keto amides and leading references, see: (a) Limanto, J.; Krska, S. W.; Dorner, B. T.; Vazquez, E.; Yoshikawa, N.; Tan, L. *Org. Lett.* **2010**, *12*, 512−515. (b) Touati, R.; Gmiza, T.; Jeulin, S.; Deport, C.; Ratovelomanana-Vidal, V.; Ben Hassine, B.; Genet, J.-P. *Synlett* **2005**, 2478−2482. (c) Yuwasa, Y.; Sotoguchi, T.; Seido, N. A Process for Producing Optically Active Derivatives. Eur. Pat. Appl. 855 390 B1, April 10, 2001. (d) Le Gendre, P.; Offenbecher, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron: Asymmetry* **1998**, *9*, 2279−2284. (e) Huang, H.-L.; Liu, L. T.; Chen, S.-F.; Ku, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1637−1640. (f) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350. (g) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−631.

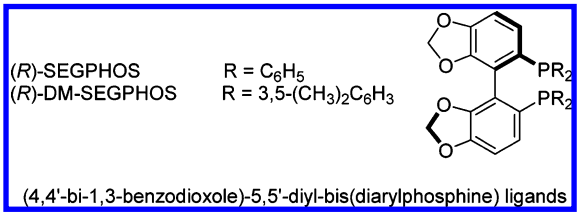
(8) For reviews on chiral ruthenium-phosphine complexes, see: (a) Kacer, P.; Kuzma, M.; Leitmannova, E.; Cerveny, L. *Organomet. Compd.* **2010**, 373−401. (b) Mezzetti, A. *Dalton Trans.* **2010**, *39*, 7851−7869. (c) Sumi, K.; Kumobayashi, H. *Topics Organomet. Chem.* **2004**, *6*, 63−95. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069. (e) Ager, D. J.; Lanemam, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355. (f) For a discussion on reactions and leading references, see: Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1070−1072. (g) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264−267.

(9) (a) Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227−1229. (b) Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781−6789. (c) Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633−13640. (d) Sato, T.; Otera, J. *Synlett* **1995**, 336−338. (e) Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K; Masterman, S.; Scott, A. D. *J. Chem. Soc.* **1937**, 1252−1271.

(10) On the basis of LCMS and ^{1}H NMR, side-products appear to be 1-benzyl-2-pyrrolidinone homocondensation products and γ-lactam ring-opened product.

(11) (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−55. (b) Akutagawa, S. *Appl. Catal., A* **1995**, *128*, 171−207. (c) Takaya, H.; Ohta, T.; Noyari, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers, Inc.: New York, 1993; pp 1−39. (d) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134−9135.

(12)



(13) Stereoisomer ratio (1:1:1:1) of sample **11a/b/c/d**, prepared from the Raney Ni reduction, was assessed directly by chiral HPLC separation using an analytical CHIRALCEL OJ-H column (0.46 × 25 cm, 15% isopropanol-hexane, 0.8 mL/min). The four stereoisomers eluted with retention times of 13.3, 17.2, 20.8, and 24.3 min.

(14) See the Supporting Information for details.

(15) The *syn* (**11a/b**) and *anti*-stereoisomer (**11c/d**) products are not interconvertible under the prescribed reactions conditions.

(16) Netscher, T.; Bohrer, P. *Molecules* **2002**, *7*, 601−617.

(17) Sulfonate esters were prepared in a similar manner as *p*-nosylate **13**; see the Experimental Section for details.

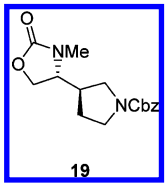
(18) (a) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016−6023. (b) Nordlander, J. E.; Catalane, D. B.; Eberlein, T. H.; Farkas, L. V.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. A. *Tetrahedron* **1978**, 4987−4990.

(19) The S_N2 substitution reactions were run in a similar manner as the conditions used to prepare diamine **14**; see the Experimental Section for details.

(20) The exception was NaN_3 (5 equiv of NaN_3, DMF, 0−23 °C, 15 h), which gave the desired azide substituted product with no detection of olefin by LCMS.

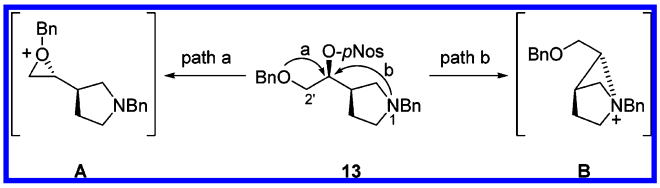
(21) Methylamine has a dielectric constant (ε) of 9.4 at 25 °C. Methanol has a dielectric constant (ε) of 32.63 at 25 °C. *CRC Handbook of Chemistry and Physics*, 63rd ed.; Weast, R. C., Astle, M. J, Eds.; CRC Press: Boca Raton, FL, 1982: pp E−51.

(22)



(23) Nitrile **18** and authentic sample[1] coeluted by chiral HPLC using an analytical CHIRALCEL OJ-H column (0.46 × 25 cm, 15% isopropanol-hexane, 0.8 mL/min) with a retention time of 37.4 min. ^{1}H NMR ($CDCl_3$, 400 MHz) of **18** and authentic sample[1] were in good agreement.

(24) Methylamine substitution with inversion of configuration is the desired and expected mode of nucleophilic attack; however, a number of alternative reaction pathways are feasible, which would lead to alternative products (i.e., anchimeric assistance from *O*-2′ or *N*-1 could give intermediates **A** or **B**, respectively, leading to **14** with retention of configuration at the 1′-position or structural isomer products of **14**.



dx.doi.org/10.1021/jo3004716 | *J. Org. Chem.* 2012, 77, 4732−4739