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Chiral Base-Catalyzed Enantioselective Synthesis of 4-Aryloxyazetidinones and 3,4-Benzo-5-oxacephams

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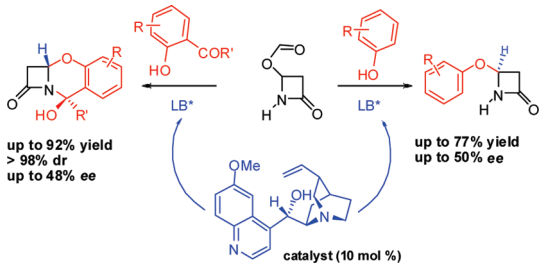

Readily available 4-formyloxyazetidinone was enantioselectively transformed into 3,4-benzo-2-hydroxy-5-oxacephams and 4-phenyloxyazetidinones upon treatment with 0.1 equiv of the cinchona alkaloid in toluene via intermolecular nucleophilic trapping of *N*-acyliminium intermediate by the hydroxyl moiety of phenols or *o*-hydroxybenzaldehydes. Additionally, the absolute configuration of title compounds was established by CD spectroscopy.

β-Lactam antibiotics represent the most powerful tool against bacterial infections.[1] Recently, β-lactams also have been observed to display interesting activity against nonbacterial diseases.[2] Owing to these attractive biological properties, the synthesis of mono- and polycyclic systems containing the β-lactam ring has been extensively investigated.[3] The main strategies of the synthesis of cephalosporin and penicillin congeners make use of 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporinic acid (7-ACA) as readily available chiral starting materials. Nevertheless, this biosynthetic approach is limited, and many novel β-lactam therapeutics are obtained via total synthesis.[4]

In 1974, Clauss, Grimm, and Prossel[5] reported that the 4-acetoxyazetidin-2-one undergoes a nucleophilic displacement of an acetoxy group with variety of nucleophiles. This observation prompted many laboratories to use racemic or chiral 4-acyloxyazetidinones as substrates for the synthesis of variety of β-lactam antibiotics.[6]

For several years, our laboratory has been interested in the synthesis of oxygen analogues of penicillin and cephalosporin. We have reported attractive diastereoselective approaches to clavams and oxacephams starting from the carbohydrate precursors.[7] The present paper describes for the first time an enantioselective approach to the construction of 3,4-benzo-2-hydroxy-5-oxacephams (**3**) and 4-phenoxyazetidinones (**5**). This new approach is based on the chiral Lewis base-promoted intermolecular nucleophilic substitution at C-4 of 4-formyloxyazetidinone (**1**) (Scheme 1).

Recently, the racemic 3,4-benzo-2-hydroxy-5-oxacephams (**3**) have been synthesized by the base-catalyzed (NaOH or EtONa/EtOH) condensation of a salicylaldehyde (**2a**) or *o*-hydroxyphenones (**2**) with the 4-acetoxyazetidinone.[8] It appears to be a stepwise process, which occurs via the nucleophilic substitution of acetoxy group followed by the addition of β-lactam NH group to the carbonyl group of the phenone (Scheme 2). In the case of salicylaldehyde (**2a**), despite two new stereogenic centers being formed (C-2 and C-6), the hydroxy group is always *syn* located to the bridgehead proton.[8]

Both acid- and base-catalyzed nucleophilic substitutions at C-4 of the azetidinone ring proceed via flat intermediates, an acyliminium cation in the case of the acid-catalyzed process, or a neutral 1,2-dehydro-azetidin-4-one (**6**) in the case of the base-catalyzed one, i.e. through the S_N1 or the

(1) (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; (b) *Frontiers of Antibiotics Research*; Umezwa, H., Eds.; Academic Press: Tokio, 1987; (c) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990. (d) Łysek, R.; Borsuk, K.; Furman, B.; Kałuża, Z.; Kazimierski, A.; Chmielewski, M. *Curr. Med. Chem.* **2004**, *11*, 1813.

(2) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. *Curr. Med. Chem.* **2003**, *10*, 1741.

(3) (a) *Comprehensive Heterocyclic Chemistry II*; Katrizky A. R., Rees C. W., Scriven E. F., Eds.; Pergamon: New York, 1996; Chapters 1.18−1.20; (b) Ojima, I.; Delaloge, F. *Chem. Rev. Soc.* **1997**, *26*, 377. (c) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383. (d) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377. (e) *Synthesis of β-Lactam Antibiotics, Chemistry, Biocatalysis and Process Integration*; Bruggink, A., Eds.; Kluwler: Dordrecht, The Netherlands, 2001.

(4) *The Organic Chemistry of β-Lactams*; Wild, H., Georg, G. I., Ed.; VCH Publishers: Weinheim, 1993; p 49.

(5) Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, 539.

(6) (a) Hungerbuhler, E.; Biollaz, M.; Ernest, I.; Kalvoda, J.; Lang, M.; Schneider, P.; Sedelmeier, G. In *New Aspects of Organic Chemistry I*; Yoshida, Z.; Shiba, T.; Ohshiro, Y., Eds.; VCH Publishers: Weinheim, 1989; p 419. (b) De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457. (c) Müller, J. C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *J. Antibiot.* **1983**, *36*, 217. (d) Hoppe, D.; Hilpert, T. *Tetrahedron* **1987**, *43*, 2467.

(7) (a) Kałuża, Z.; Furman, B.; Patel, M.; Chmielewski, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2719. (b) Kałuża, Z.; Furman, B.; Chmielewski, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1719. (c) Chmielewski, M.; Kałuża, Z.; Abramski, W.; Bełżecki, C.; Grodner, J.; Mostowicz, D.; Urbański, R. *Synlett* **1994**, 539. (d) Kałuża, Z.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **1997**, *62*, 3135. (e) Kałuża, Z.; Łysek, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2553. (f) Kałuża, Z. *Tetrahedron Lett.* **1998**, *39*, 8349. (g) Kałuża, Z. *Tetrahedron Lett.* **1999**, *40*, 1025. (h) Furman, B.; Thürmer, R.; Kałuża, Z.; Łysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem, Int. Ed.* **1999**, *38*, 1121.

(8) (a) Campbell, M. M.; Nelson, K. H.; Cameron, A. F. *J. Chem. Soc., Chem. Commun.* **1979**, 532. (b) Arnoldi, A.; Merlini, L.; Scaglioni, L. *J. Heterocycl. Chem.* **1987**, 75.

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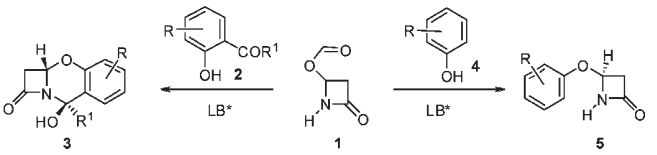
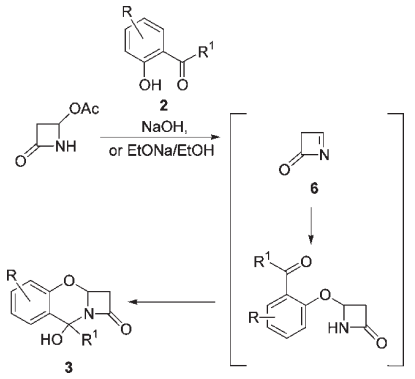
SCHEME 1. Synthetic Strategy



SCHEME 2. Base-Catalyzed Formation of Substituted 3,4-Benzo-2-hydroxy-5-oxacephams



elimination-addition mechanism, respectively.[9] The discrimination of the enantiotopic faces of the intermediate by a chiral nucleophile−catalyst complex should lead to the optically enriched product. This assumption prompted us to investigate the chiral Lewis acid catalyzed intramolecular formation of the 3,4-benzo-5-oxacepham.[10] The observed moderate yield which had not exceeded 50%, but a high asymmetric induction, suggested a kinetic resolution (asymmetric destruction) of the initially formed racemic oxacepham.[10]

Presently, we decided to investigate whether chiral Lewis bases could be used as catalysts in the asymmetric version of the same nucleophilic displacement reaction.[11] Among the well-known chiral Lewis bases the cinchonine alkaloids play a central role in the field of asymmetric catalysis.[12] The cinchonine alkaloid family consists of two pairs of diastereomers, often termed "pseudoenantiomeric" because the respective carbinolamine fragments have an enantiomeric relationship.

The 4-formyloxyazetidinone (**1**) undergoes condensation with the salicylaldehyde (**2a**) in the presence of catalytic amount of DBU and DABCO providing product ***rac*-3a** in 80% and 84% yield, respectively. This observation prompted us to check whether chiral amines could promote the same reaction in an enantioselective way. Our initial studies indicated that in the presence of (−)-sparteine, *N*-benzylprolinol, or nonracemic 2-dimethylamino-1,2-diphenylethanol the expected cepham (**3a**) is formed in a good yield but as a racemic mixture. However, when quinidine (**7**) was used, the condensation reaction went smoothly to give **3a** in 77% yield with 31% ee (Table 1, entry 1).

TABLE 1. Evaluation of Conditions for the Reaction of Azetidinone 1 with Salicylaldehyde (2a) in the Presence of Quinidine (7) as a Catalyst (All Reactions Were Carried out at Room Temperature)

entry	solvent	catalyst (equiv)	time[a] (h)	yield[b] (%)	ee[c] (%)
1	THF	1.0	48	77	31
2	THF[d]	1.0	96	70	33
3	CH_2Cl_2	1.0	24	83	24
4	Et_2O	1.0	24	65	6
5	**toluene**	**1.0**	**48**	**78**	**51**
6	DMF	1.0	48	40	0
7	DMF[e]	1.0	48	78	0
8	toluene	0.5	48	76	48
9	**toluene**	**0.1**	**48**	**77**	**49**
10	toluene[f]	0.1	12	65	49

[a]The reaction was carried out until disappearance of substrate **1** (TLC). [b]Isolated yield determined after flash chromatography on SiO_2. [c]The enantiomeric excess was determined by chiral HPLC. [d]At 0 °C. [e]In the presence of molecular sieves 4 Å. [f]5 equiv of $CaCO_3$ was added.

Note that when the reaction temperature was decreased to 0 °C, the same enantioselectivity was observed (entry 2). If dichloromethane or diethyl ether were used as solvents, the yield of reaction was unchanged but the enantioselectivity was reduced to 24% and 6%, respectively. The lack of enantioselectivity was noticed when DMF was used as a solvent. With toluene as solvent, the enantiomeric excess increased to 51% (entry 5). It is interesting that with 0.1 equiv of the quinidine (**7**) in toluene, the product was obtained with a similar yield and enantioselectivity (entry 9). As a general trend, it was found that the reaction rate increased upon the addition of $CaCO_3$ (5 equiv, entry 10). The enantiomeric excess was unchanged but the yield was reduced to 65%. A control experiment showed that $CaCO_3$ itself was not responsible for the activation of **1**, but it trapped formic acid liberated during substitution reaction.[13]

This initial positive result prompted us to further investigate the enantioselective condensation by varying cinchonine type chiral amines (Table 2). Due to the use of pseudoenantiomeric pairs of cinchonine alkaloids, the observed product enantiomeric excess is comparable but not the same. When $(DHQD)_2PHAL$ (**11**) was used, **ent-3a** was obtained in 52% yield with 46% ee (entry 5). Introduction of *N*-BOC-protected amine in the place of the hydroxy group diminished both chemical yield and the enantioselectivity (entry 6). No condensation occurred when catalyst contained an acyl- or silyl-protected hydroxy group or a free amino function in the place of the hydroxyl group (entries 7−10).

Subsequently, we analyzed the scope of this asymmetric reaction with various *o*-hydroxybenzaldehydes and ketones. As shown in Table 3, the enantiomeric excess as well as the product's yield depended on the nature of substituent in the phenol ring. In all cases only one diastereomer was formed in a good yield and with a moderate enantioselectivity.

The assignment of absolute configuration at the bridgehead carbon atom (C-6) was made by the electronic circular

(9) Nagaraja Rao, S.; More O'Ferral, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 2729.

(10) Kozioł, A.; Frelek, J.; Woźnica, M.; Furman, B.; Chmielewski, M. *Eur. J. Org. Chem.* **2009**, 338.

(11) (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965.

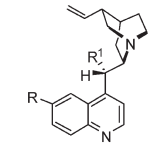
(12) (a) Pracejus, H. *Forschr. Chem. Forsch.* **1967**, *8*, 493. (b) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, *7*, 961. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc.Rev.* **2009**, *38*, 632.

(13) Combinations of a catalytic amount of quinidine **7** and different inorganic and organic bases (K_2CO_3, $NaHCO_3$, $MgCO_3$, Et_3N) were tested. In all cases, the expected 3,4-benzo-2-hydroxy-5-oxacepham **3a** was formed in good yield, but enantioselectivity was considerably reduced.

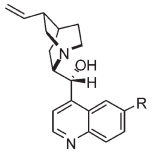
TABLE 2. Chiral Base Evaluation Studies for an Enantioselective Formation of 3a from 1 and 2a in the Presence of 0.1 Equiv of Chiral Lewis Base (7–16, Toluene, rt, 48 h)

entry	catalyst	yield[a] (%)	ee[b] (%)
1	**7**	77	49 (**3a**)
2[c]	**8**	46	14 (***ent*-3a**)
3[c]	**9**	69	14 (**3a**)
4[c]	**10**	63	6 (***ent*-3a**)
5	**11**	52	46 (***ent*-3a**)
6	**12**	36	16 (**3a**)
7	**13**	0	
8	**14**	0	
9	**15**	0	
10	**16**	0	

[a]Isolated yield determined after flash chromatography on silica gel. Reaction was carried out until disappearance of substrate **1** (TLC); [b]The enantiomeric excess was determined by chiral HPLC; [c]Reaction performed in THF.



7 R = OMe, R' = OH quinidine
9 R = H, R' = OH cinchonine
12 R = OMe, R' = NHBOC
13 R = OMe, R' = NH_2
14 R = OMe, R' = OAc
15 R = OMe, R' = OTBS
16 R = OH, R' = OH



8 R = OMe quinine
10 R = H cinchonidine

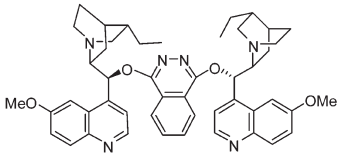


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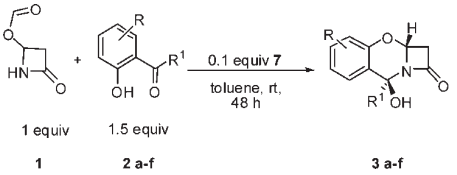
TABLE 3. Scope and Limitation of Reaction between 1 and Substituted *o*-Hydroxyphenones 2a–f in the Presence of 0.1 Equiv of Quinidine 7 (Toluene, rt, 48 h)



2a, 3a R = H, R^1 = H
2b, 3b R = 5-Br, R^1 = H
2c, 3c R = 4-OH, R^1 = H
2d, 3d R = H, R^1 = CH_3
2e, 3e R = H, R^1 = Ph
2f, 3f R = 5-F, R^1 = CH_3

entry	phenone	product	yield[a] (%)	ee[b] (%)
1	**2a**	**3a**	77	48
2	**2b**	**3b**	76	40
3	**2c**	**3c**	89	32
4	**2d**	**3d**	75	16
5	**2e**	**3e**	92	43
6	**2f**	**3f**	79	24

[a]Isolated yield determined after flash chromatography on SiO_2. Reaction was carried out until disappearance of substrate **1** (TLC). [b]The enantiomeric excess was determined by chiral HPLC.

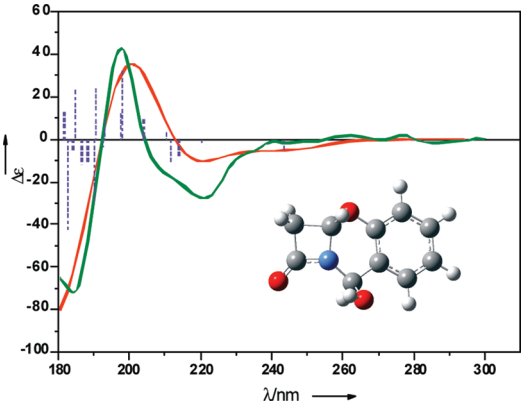


FIGURE 1. Experimental CD spectrum of **3a** (green line) and simulated CD spectrum of **3a** (red line). Molecular structure presents the lowest energy conformer of **3a** calculated at the B3LYP/6-31 G (d,p) level.

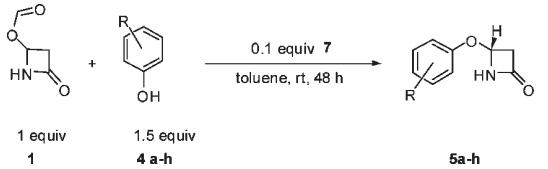
dichroism spectroscopy (CD) applying the helicity rule developed previously for oxacephams.[14] According to the rule, the positive sign of Cotton effect (CE) arising at around 220 nm corresponds to the (*R*) absolute configuration at the ring junction while it is negative for the (*S*) configuration at the same carbon atom. The positive sign of the CE at 221 nm obtained for compound **3a** and the negative one at 222 nm for ***ent*-3a** allowed us to establish the absolute configuration as (*R*) and (*S*), respectively. The very good agreement between the experimental and simulated CD spectrum obtained by the TDDFT quantum chemical calculations provided an additional corroboration of the configurational assignment (Figure 1). For compound **3d**, the configuration at the *N*,*O*-hemiacetal center (C-2) was established by the NOE experiments, which showed a spin–spin interaction between the hydroxy group proton and the bridgehead proton (H-6), whereas protons of CH_3 group did not show such interaction.

The scope of the base-catalyzed nucleophilic substitution at C-4 of **1** was further extended to the reaction leading to the 4-aryloxy compounds **5** (Table 4). Practically in all cases, under the same conditions a good chemical yield was found. Reaction of **1** with **4d** led probably to intramolecular *N*-acylation and formation of the unstable oxacepham-2-one, which underwent a rapid opening of the β-lactam ring and subsequently further decomposition.[15] The observed enantioselectivity (Table 4) was also similar to that found for the reactions with hydroxyphenones (Table 3). This result suggests that in the case of hydroxyphenones the first step of the reaction is not an acetal formation, but it involves a nucleophilic substitution via the elimination/addition mechanism, and consequently, the enantioselectivity is created by the intermolecular process. The second step leading to the ring closure is under the thermodynamic control and as such is

(14) (a) Łysek, R.; Borsuk, K.; Chmielewski, M.; Kałuża, Z.; Urbańczyk-Lipkowska, Z.; Klimek, A.; Frelek, J. *J. Org. Chem.* **2002**, *67*, 1472. (b) Frelek, J.; Kowalska, P.; Masnyk, M.; Kazimierski, A.; Korda, A.; Woźnica, M.; Chmielewski, M.; Furche, F. *Chemistry – Eur. J.* **2007**, *13*, 6732.

(15) (a) Chitwood, J. L.; Gott, P. G.; Martin, J. C. *J. Org. Chem.* **1971**, *36*, 2228. (b) Chmielewski, M.; Kałuża, Z.; Bełżecki, C.; Sałański, P.; Jurczak, J.; Adamowicz, H. *Tetrahedron* **1985**, *41*, 2441. (c) Mostowicz, D.; Bełżecki, C.; Chmielewski, M. *J. Carbohydr. Chem.* **1988**, *7*, 805. (d) Mostowicz, D.; Zegrocka, O.; Chmielewski, M. *Carbohydr. Res.* **1991**, *212*, 283. (e) Chmielewski, M.; Kałuża, Z.; Grodner, J.; Urbański, R. *ACS Symp. Ser.* Guiliano, R., Ed. 1992, *494*, 50. (f) Chmielewski, M.; Kałuża, Z.; Furman, B. *Chem. Commun.* **1996**, 2689.

TABLE 4. Scope and Limitation of Reaction between 1 and Substituted *o*-Hydroxyphenols 4a−i in the Presence of 0.1 Equiv of Quinidine 7 (Toluene, rt, 48 h)



entry	phenol	R	product	yield[a] (%)	ee[b] (%)
1	**4a**	2-Me	**5a**	77	48
2	**4b**	2-*t*-Bu	**5b**	54	46
3	**4c**	2-CH_2CO_2Me	**5c**	65	11
4	**4d**	2-CO_2Me	**5d**	0	
5	**4e**	3-NO_2	**5e**	82	43
6	**4f**	2-Me, 4-Ph	**5f**	77	50
7	**4g**	2-Me, 6-OMe	**5g**	69	46
8	**4h**	2-Me, 4-Br	**5h**	74	24

[a]Isolated yield determined after flash chromatography on SiO_2. Reaction was carried out until disappearance of substrate **1** (TLC). [b]The enantiomeric excess was determined by chiral HPLC.

preferentially leading to the *exo* location of the *N*,*O*-acetal hydroxy group.

To shed more light on the reaction mechanism, we performed experiments using 1 equiv of **1**, 1.5 equiv of **4a**, and 1.5 equiv of **4e**. As result, only compound **5e** was obtained in 82% yield and 43% ee. This may indicate that the phenolate anion, not the phenol itself, is an active reagent that approaches the neutral intermediate **6**. The more acidic *m*-nitrophenol wins the competition to form the phenolate anion. The enantioselectivity is probably induced by the counterion, the protonated chiral base, which accompanies the phenolate anion.

In conclusion, the enantioselective approach to the synthesis of 3,4-benzo-5-oxacephams and 4-aryloxyazetidinones is described. The key step of this method is based on the chiral Lewis base mediated, enantioselective intermolecular alkylation of the phenol hydroxy group which proceeds via the elimination/addition mechanism. It is important to note that the chiral Lewis base is used in catalytic amounts without affecting yield and enantioselectivity. It is in contrast with the previously described chiral Lewis acid mediated alkylation of the phenol hydroxy group by the *N*-acyliminium ion generated from the 4-formyloxyazetidinone (**1**). The latter reaction requires always an equimolar amount of promoter and proceeds in a low yield but with a high asymmetric induction as the intramolecular process or in a good yield but with a low asymmetric induction as the intermolecular process.[10]

Moreover, it should be noted that the present method can be applied to the synthesis of various phenoxy substituted azetidinones potentially having a biological activity.[16]

Experimental Section

Typical Procedure for Enantioselective Formation of 5a. To the solution of **1** (30 mg, 0.26 mmol, 1.0 equiv) and *o*-cresol (**4a**) (42 mg, 0.39 mmol, 1.5 equiv) in toluene (5 mL) at room temperature was added quinidine (**7**) (9 mg, 0.1 equiv) under argon atmosphere. The reaction mixture was stirred for 48 h until disappearance of starting material and diluted with water (5 mL). The aqueous phase was extracted with ether (3×10 mL). The organic extracts were combined and dried over Na_2SO_4. The solution was filtered and the filtrate evaporated. The crude product was purified by column chromatography (silica gel, 2:3 hexanes/diethyl ether) to yield 41 mg (0.23 mmol) of **5a** as yellow crystals: yield 77%, 48% ee; mp 99−100 °C; IR (film) 1786 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 3.13 (dt, J = 15.0, 1.3 Hz, 1H, CH_2), 3.35 (ddd, J = 15.0, 3.8, 2.4 Hz, 1H, CH_2), 5.65 (dd, J = 3.8, 1.3 Hz, 1H, CH−O), 6.58 (s, 1H, NH), 6.69 (d, J = 8.0 Hz, 1H, Ar), 7.96 (td, J = 7.5, 1.1 Hz, 1H, Ar), 7.15 (td, J = 8.0, 1.8 Hz, 1H, Ar), 7.19 (d, J = 7.5 Hz, 1H, Ar); ^{13}C NMR (125, $CDCl_3$) δ 16.2, 46.3, 76.3, 112.8, 122.4, 126.9, 127.9, 131.5, 154.1, 166.0; HR MS (ESI) calcd for $[M+Na]^+$ $C_{10}H_{11}NO_2Na$ 200.0682, found 200.0686; HPLC [OD-H, hexanes/IPA 8:2, 0.5 mL/min, $t_R[S]$ = 24.2 (minor), $t_R[R]$ = 32.0 (major)].

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Supporting Information Available: Experimental procedures and characterization data of compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org

(16) (a) Shah, S. K.; Dorn, C. P.; Finke, P. E.; Hale, J. J.; Halmann, W. K.; Krause, K. A.; Handler, G. O.; Kissinger, A. L.; Ashe, B. M.; Weston, H.; Knight, W. B.; Maycock, A. L.; Dellea, P. S.; Fletcher, D. S.; Hand, K. M.; Mumford, R. A.; Underwood, D. J.; Doherty, J. B. *J. Med. Chem.* **1992**, *35*, 3745. (b) Doherty, J. B.; Shah, S. K.; Finke, P. E.; Dorn, C. P.; Halmann, W. K.; Hale, J. J.; Kissinger, A. L.; Thompson, K. R.; Krause, K.; Handler, G. O.; Knight, W. B.; Maycock, A. L.; Ashe, B. M.; Gale, P.; Mumford, R. A.; Andersen, O. F.; Williams, H. R.; Nolan, T. E.; Frankenfield, D. L.; Underwood, D.; Vyas, K. P.; Kari, P. H.; Dahlgren, M. E.; Mao, J.; Fletcher, D. S.; Dellea, P. S.; Hand, K. M.; Osinga, D. G.; Petersom, L. B.; Williams, D. T.; Metzger, J. M.; Bonney, R. J.; Humes, J. L.; Pacholok, S. P.; Halon, W. A.; Opas, E.; Stolk, J.; Davies, P. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *93*, 8727. (c) Knight, W. B.; Greek, B. G.; Chabin, R. M.; Gale, P.; Maycock, A. L.; Weston, H.; Kuo, D. W.; Westler, W. M.; Dorn, C. P.; Finke, P. E.; Halmann, W. K.; Hale, J. J.; Liesch, J.; MacCoss, M.; Nadia, M. A.; Shah, S. K.; Underwood, D.; Doherty, J. B. *Biochemistry* **1992**, *31*, 8160. (d) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365.