Highly π-Facial Stereoselective Aldol Reaction of (*S*)-Proline-Derived Amide Enolate with Benzaldehydes

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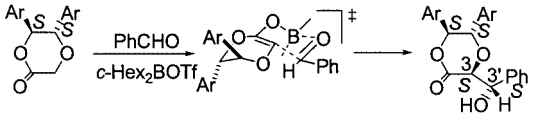
The asymmetric aldol reaction of the (*S*)-proline-derived bicyclic amide enolate **1** with benzaldehydes selectively affords the two diastereomeric aldol adducts (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a**, of four possible diastereomers, in good yield. The high control of π-facial stereoselectivity at the endocyclic C-3 stereocenter is due to perfect shielding by the pseudo-axial phenyl ring at the C-1 position.

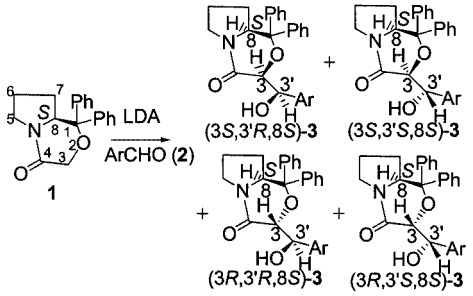
Introduction

The aldol reaction is an efficient method for the generation of two adjacent stereogenic centers in a single carbon−carbon bond-forming process.[1] In view of the value of stereoselective aldol reactions in organic synthesis, intensive efforts[2,3] have been expended to develop them. A persistent challenge has been to achieve asymmetric processes, for which chiral auxiliaries[4,5] as well as optically active Lewis acids[6] have been employed.

A relevant recent application of the chiral-auxiliary concept has been described by Andrus,[7−9] namely the asymmetric aldol reaction of benzaldehyde with the boron enolate of bis(4-methoxyphenyl)dioxanone (Scheme 1). The stereocontrol at the exocyclic stereogenic site (the C-3′ position in the aldol) is high, due to the chelating effect of the boron functionality, resulting in only one isomer being found. In contrast, the π-facial stereoselectivity at the endocyclic chirality center (the C-3 stereogenic center in the aldol) is only moderate [(3*S*)/(3*R*) = 86:14]. Evidently, for this aldol process, the two aryl groups are not sufficiently effective in preferentially shielding one face of the double bond in the boron enolate.[10,11] Presumably, the π-facial stereoselectivity of the aldol reaction with a cyclic enolate may be improved if the six-membered ring of the enolate is made conformationally more rigid and substituents with effective steric interactions are introduced. For this purpose we have chosen the bicyclic amide **1**, which is derived from (*S*)-proline and which, on deprotonation, would generate an (*E*)-configured cyclic enolate whose two π faces should be sterically differentiated in an electrophilic attack by benzaldehyde (Scheme 2).[12]



Scheme 1. Ar = 4-$MeOC_6H_4$-



Scheme 2

Inspection of molecular models reveals that the proline structural unit imparts greater conformational rigidity to the six-membered-ring enolate, while the two phenyl groups provide massive steric interactions with the attacking aldehyde. High π-facial stereoselectivity at the C-3 stereogenic center is thus anticipated. We report herein a highly π-facial stereoselective aldol reaction of the (*S*)-proline-derived amide enolate with benzaldehydes, in which the (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a** diastereomers are produced exclusively.

Results and Discussion

As shown in Scheme 3, (*S*)-α,α-diphenylprolinol was readily synthesized from commercially available (*S*)-proline

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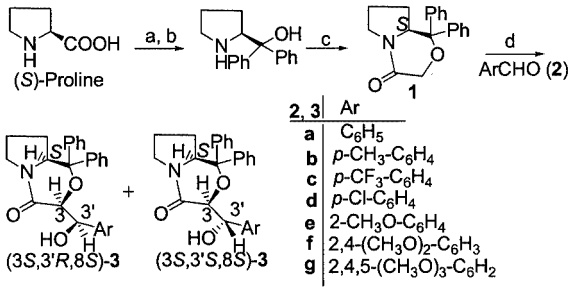
according to a literature procedure.[13] The total yield of (*S*)-α,α-diphenylprolinol over the two steps was 54%. *N*-Acylation of (*S*)-α,α-diphenylprolinol by treatment with bromoacetyl bromide, triethylamine and DMAP in THF at −78 °C, followed by cyclization with NaH/DMF, provided the cyclic amide **1** in 70% yield.[14] The structure of amide **1** was confirmed by HMQC and HMBC spectroscopy.

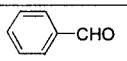
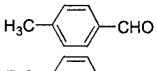
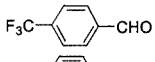
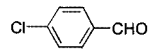
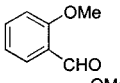
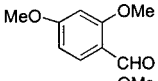
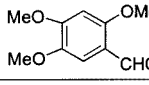


Scheme 3. a) C_2H_5COCl, K_2CO_3, CH_3OH, 0 °C, 93%; b) i. PhMgBr, THF; ii. KOH, methanol, reflux, 57%; c) i. $BrCOCH_2Br$, Et_3N, DMAP, THF; ii. NAH, DMF, 70%; d) LDA, THF, −78 °C, ArCHO (**2**)

The aldol reaction was first conducted with benzaldehyde (**2a**) by treatment of amide **1** with 1.1 equiv. of LDA (lithium diisopropylamide) in THF at −78 °C for 1 h. Of the four possible diastereomers, only the (3*S*,3′*R*,8*S*)-**3a** (50%) and (3*S*,3′*S*,8*S*)-**3a**[15] (40%) diastereomers were obtained (Scheme 3). The scope of the aldol reaction was assessed by employing several substituted benzaldehydes. The results are summarized in Table 1. As for the parent benzaldehyde (**2a**), the (3*S*,3′*R*,8*S*) and (3*S*,3′*S*,8*S*) diastereomers of the aldol **3** were obtained for all derivatives. The similar NMR spectroscopic data of these compounds confirmed that their configurations were the same. The yields range between 53 and 90% and the diastereoselectivity is moderate (*dr* up to 76:24). Both diastereomers could be readily obtained in pure form by silica-gel chromatography.

The structural assignment of the aldol adducts are exemplified for the (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a**. Their relative configurations were assessed from the ^1H and ^{13}C NMR spectra, together with 2D-NOE spectroscopy. In the NOE spectrum of adduct (3*S*,3′*R*,8*S*)-**3a**, the strong effect between the 8-H and 3-H protons shows clearly that these are on the same side and the configuration at the stereogenic center C-3 is therefore (*S*) (Figure 1). The same interaction is observed in the NOESY study of (3*S*,3′*S*,8*S*)-**3a**, which indicates that its C-3 chirality center also has the (*S*) configuration. Similar NOE effects are observed between the 3-H and 3′-H protons in both aldol adducts (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a**, which show that the environment of the 3′-H proton in the two diastereomers is similar. However, TLC and NMR spectra disclose that they are different aldol adducts. Examination of the molecular models of the adducts (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a** reveals that the carbon−carbon bond between the C-3 and C-3′ atoms in the two diastereomers may rotate without any hindrance. Thus, the similar NOE effects of (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a** show that the absolute configurations at the C-3 position in the two isomers are the same, while those at the C-3′ center are different. Indeed, an X-ray analysis of the aldol adduct (3*S*,3′*R*,8*S*)-**3e** confirmed this stereochemical assignment (Figure 1). Since the configuration in (*S*)-proline is known, the configurations of the other two stereocenters in the aldol adduct (3*S*,3′*R*,8*S*)-**3e** may be assigned as (3*S*) and (3′*R*), as shown in Figure 1. From the combined data of the X-ray structure for (3*S*,3′*R*,8*S*)-**3e** and the 2D-NOE effects of (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a**, the complete absolute configurations of the two diastereomers for all aldol adducts in Table 1 may be assigned as (3*S*,3′*R*,8*S*) and (3*S*,3′*S*,8*S*); the other two possible diastereomers (3*R*,3′*R*,8*S*) and (3*R*,3′*S*,8*S*) are not observed.

Table 1. π-Facial stereoselective aldol reaction of (*S*)-proline-derived bicyclic amide enolate **1** with benzaldehydes

Entry	ArCHO	Substrate	Yield (%)[a]	Aldol **3**[b] (3*S*,3′*R*)	(3*S*,3′*S*)
1		**2a**	90	55	45
2		**2b**	75	52	48
3		**2c**	59	69	31
4		**2d**	60	68	32
5		**2e**	66	74	26
6		**2f**	63	76	24
7		**2g**	53	64	36

[a] Yield of pure material isolated by chromatography. [b] Relative amounts were calculated from the isolated individual diastereomers, except for the last two Entries, which were determined by ^1H NMR spectroscopy (error ca. 5% of the stated values).

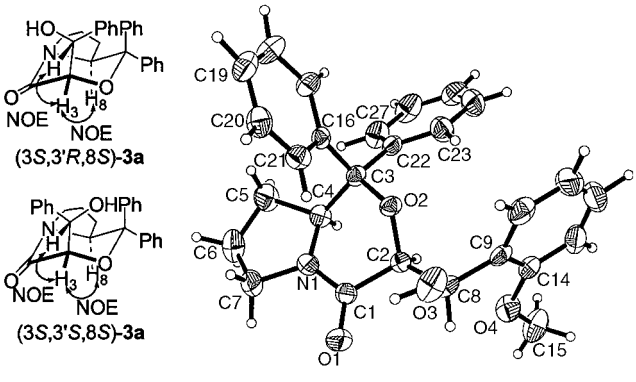
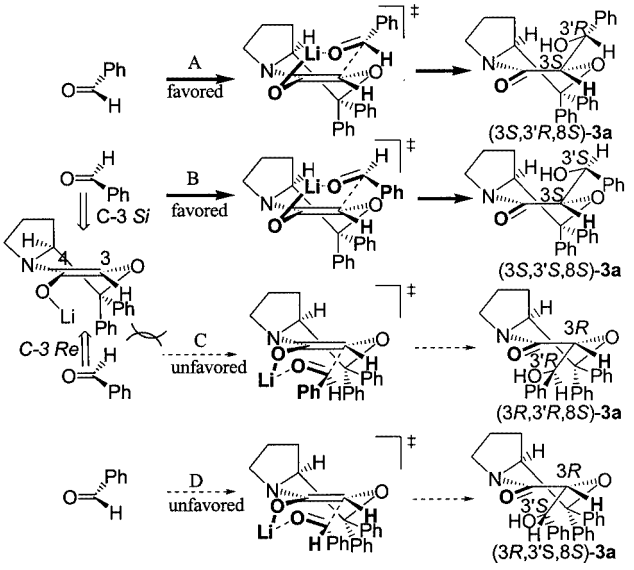


Figure 1. 2D-NOE spectroscopy of (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a** and the X-ray structure of (3*S*,3′*R*,8*S*)-**3e**

The formation of only the two diastereomeric adducts (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a**, which have the same (*S*) configuration at the new endocyclic C-3 stereogenic center of the enolate ring, shows a high π-facial stereoselectivity. Evidently, the attack of the benzaldehyde electrophile is ex-

clusively from above (C-3 *Si* face), as displayed in the mechanism of Scheme 4 for the asymmetric aldol reaction.[16,17] The reason for this becomes evident on inspection of molecular models of the enolate, which show that the (*S*)-configured proline ring lies nearly perpendicular to the enolate double bond. Steric effects thus oblige one of the phenyl groups at the C-1 position of the enolate to assume the pseudo-axial site (almost antiparallel to the proline five-membered ring), while the other phenyl group is situated pseudo-equatorially (essentially in-plane with the enolate double bond). That one of the two phenyl rings lies below the enolate double bond is confirmed by the NOE effects in both diastereomers (Figure 1), in which strong interactions occur between the 3-H and 8-H atoms and one of the hydrogen atoms in the benzene ring at the C-1 position. Consequently, the C-3 *Re* side of the enolate double bond is shielded by the pseudo-axial phenyl ring and the benzaldehyde attacks preferentially from the C-3 *Si* side (from above, pathways A and B). In both pathways A and B, the absolute configuration at the C-3 stereocenter should be (3*S*), as assigned by X-ray and NOESY analysis. The high degree of steric control is remarkable, as attack from the C-3 *Re* side (from below, pathways C and D) is not observed.



Scheme 4. Mechanism of the aldol reaction of (*S*)-proline-derived bicyclic amide enolate **1** with benzaldehyde

In contrast, the diastereoselectivity at the endocyclic C-3′ stereogenic center (the original carbonyl atom of the benzaldehyde electrophile) is low (52:48) to moderate (76:24), as shown for the various benzaldehyde derivatives in Table 1. The transition structures in Scheme 2 reveal that there are no severe steric interactions (with the pseudo-equatorial phenyl group, for example) in the two possible approaches of the benzaldehyde along the pathways A and B; thus, the two diastereomers (3*S*,3′*R*,8*S*)-**3a** and (3*S*,3′*S*,8*S*)-**3a** are formed in nearly equal amounts.

Conclusion

The aldol reaction of the amide enolate **1** with benzaldehydes proceeds with high π-facial control of stereoselectivity (C-3 *Si* attack) at the endocyclic C-3 stereocenter. This is because of perfect shielding by the pseudo-axial phenyl ring at the C-1 position. Evidently, the diastereoselectivity at the endocyclic C-3′ site is low because the steric interactions with the pseudo-equatorial phenyl ring at the C-1 position are ineffective.

Experimental Section

General Aspects: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker AC 200 (^{1}H: 200 MHz; ^{13}C: 50 MHz) or a Bruker Avance 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer with $CDCl_3$ as reference standard. The NMR shifts have been assigned according to the numbering of compound **1** in Scheme 2. For the IR spectra, a Perkin−Elmer 1420 ratio-recording infrared spectrophotometer was used. TLC analysis was conducted on precoated silica-gel foils 60 F_{254} (20 × 20 cm) from Merck (Darmstadt, Germany). The spots were visualised either by UV (254 nm) irradiation or by spraying with a 5% solution of polymolybdic acid in ethanol. Silica gel (32−62 mm) from Woelm (Erlangen, Germany) was used for column chromatography. The solvents were dried by standard methods and purified by distillation before use. Melting points (uncorrected) were determined with a Büchi B-545. Elemental analyses were carried out by the Microanalytical Division of the Institute of Inorganic Chemistry, University of Würzburg. All commercial reagents were used without further purification.

Pyrrolooxazinone 1: A mixture of (*S*)-α,α-diphenylprolinol[13] (253 mg, 1.0 mmol), triethylamine (0.14 mL, 2.0 mmol) and DMAP (30.0 mg) in dry THF (25 mL) was treated with bromoacetyl bromide (0.087 mL, 1.0 mmol) in THF (5 mL) over 5 min at room temperature (ca. 20 °C). The reaction mixture was stirred overnight, then the solvent was removed (40 °C, 20 Torr) in vacuo. The resulting oil was taken up in ethyl acetate (50 mL) and washed with 1 M NaOH. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated (40 °C, 20 Torr). The residue was dissolved in DMF (20 ml), then NaH (50 mg) was added. After stirring at room temperature for 24 h, water (5 mL) was added to the suspension and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated (40 °C, 20 Torr). The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 2:1) to afford **1** (206 mg, 70%) as colorless plates, m.p. 55−56 °C. $[\alpha]_D^{20}$ = 91.1 (*c* = 2.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3500, 1690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.7−1.9 (m, 2 H, 6-H, 7-H), 2.1 (m, 1 H, 6-H), 2.3 (m, 1 H, 7-H), 3.6 (d, *J* = 16.68 Hz, 1 H, 3-H), 3.7 (m, 1 H, 5-H), 3.8 (m, 1 H, 5-H), 4.05 (m, 1 H, 8-H), 4.21 (d, *J* = 16.56 Hz, 1 H, 3-H), 7.17−7.19 (m, 2 H), 7.26−7.29 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (t, C-6), 28.5 (t, C-7), 45.2 (t, C-5), 63.8 (t, C-2), 65.2 (d, C-8), 80.7 (s, C-1), 126.7, 127.5, 127.8, 127.9, 128.1, 128.9, 138.7, 143.6, 166.6 (s, C-4) ppm. HRMS (EI): calcd. for $C_{19}H_{19}NO_2$ [M^+] 293.1416; found 293.1411.

General Procedure for the Aldol Reaction of Amide 1 and Benzaldehyde: A well-stirred solution of amide **1** (211 mg, 0.72 mmol) in THF (5 mL) at −78 °C (dry ice/acetone) was treated dropwise with a solution of LDA (0.43 mL, 2 M in THF, 0.86 mmol) over 3 min. After stirring for 30 min at this temperature, benzaldehyde

(86.0 mg, 0.81 mmol) in THF (5 mL) was added over 5 min. The resulting mixture was stirred at −78 °C for 2 h, then warmed to room temperature. A saturated aqueous solution of NH_4Cl (5 ml) was added and the organic layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was evaporated (40 °C, 20 Torr) and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 2:1 as eluent) to provide the desired aldol adduct.

Pyrrolooxazinone 3a. Minor Isomer (3*S*,3′*S*,8*S*)-3a: Colorless needles, m.p. 176−178 °C. $[\alpha]_D^{20} = -345.9$ (c = 1.05, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3450, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25−1.33 (m, 2 H, 7-H, 6-H), 1.53 (m, 1 H, 6-H), 1.81 (m, 1 H, 7-H), 3.32 (m, 1 H, 5-H), 3.43 (m, 1 H, 5-H), 3.59 (d, J = 8.5 Hz, 1 H, 3-H), 3.98 (t, J = 7.08 Hz, 1 H, 8-H), 4.87 (d, J = 8.7 Hz, 1 H, 3′-H), 6.63−7.19 (m, 15 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (t, C-6), 30.8 (t, C-7), 44.8 (t, C-5), 62.9 (d, C-8), 74.2 (d, C-3′), 74.8 (d, C-3), 82.6 (s, C-1), 127.4, 127.6, 128, 128.3, 128.4, 128.6, 140.7, 142.6, 142.9, 172.5 (s, C-4) ppm. **Major Isomer (3*S*,3′*R*,8*S*)-3a:** Colorless plates, m.p. 165−166 °C. $[\alpha]_D^{20} = -276.7$ (c = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3495, 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (m, 2 H, 7-H, 6-H), 1.56 (m, 2 H, 7-H, 6-H), 3.25 (m, 1 H, 5-H), 3.60 (m, 1 H, 5-H), 3.97 (d, J = 3.54 Hz, 1 H, 3-H), 4.05 (t, J = 6.19 Hz, 1 H, 8-H), 4.18 (br., 1 H, OH), 5.21 (s, 1 H, 3′-H), 6.95−7.4 (m, 15 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5 (t, C-6), 29.5 (t, C-7), 44.6 (t, C-5), 62.2 (d, C-8), 73 (d, C-3′), 75.3 (d, C-3), 81.4 (s, C-1), 127.5, 127.8, 127.9, 128.5, 128.6, 129.1, 141.1, 143.1, 143.8, 171.2 (s, C-4) ppm. $C_{26}H_{25}NO_3$ (399.5): calcd. C 78.17, H 6.31, N 3.51; found C 77.81, H 6.64, N 3.45.

Pyrrolooxazinone 3b. Minor Isomer (3*S*,3′*S*,8*S*)-3b: Colorless needles, m.p. 179−180 °C. $[\alpha]_D^{20} = -243$ (c = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3450, 1675 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (m, 2 H, 7-H, 6-H), 1.66 (m, 1 H, 6-H), 1.92 (m, 1 H, 7-H), 2.29 (s, 3 H, CH_3), 3.43 (m, 1 H, 5-H), 3.58 (m, 1 H, 5-H), 3.72 (d, J = 8.7 Hz, 1 H, 3-H), 4.11 (t, J = 7.08 Hz, 1 H, 8-H), 4.97 (d, J = 8.72 Hz, 1 H, 3′-H), 6.78−7.28 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (q, CH_3), 23.4 (t, C-6), 30.8 (t, C-7), 44.8 (t, C-5), 63 (d, C-8), 74 (d, C-3′), 74.8 (d, C-3), 82.6 (s, C-1), 127.5, 127.6, 127.9, 128.2, 128.6, 129, 137.8, 142.7, 142.9, 172.6 (s, C-4) ppm. **Major Isomer (3*S*,3′*R*,8*S*)-3b:** Colorless powder, m.p. 162−163 °C. $[\alpha]_D^{20} = -112$ (c = 1.8, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3450, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (m, 2 H, 7-H, 6-H), 1.62 (m, 2 H, 7-H, 6-H), 2.28 (s, 3 H, -CH_3), 3.28 (m, 1 H, 5-H), 3.63 (m, 1 H, 5-H), 3.99 (d, J = 3.68 Hz, 1 H, 3-H), 4.09 (t, J = 6.2 Hz, 1 H, 8-H), 5.21 (d, J = 3.44 Hz, 1 H, 3′-H), 7.02−7.3 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (q, CH_3), 22.8 (t, C-6), 29.8 (t, C-7), 44.8 (t, C-5), 62.3 (d, C-8), 72.9 (d, C-3′), 75.4 (d, C-3), 81.4 (s, C-1), 127.2, 127.4, 127.7, 128.3, 128.7, 128.8, 137.2, 137.7, 142.7, 143.4, 170.7 (s, C-4) ppm. HRMS (CI): calcd. for $C_{27}H_{28}NO_3$ [M^+] 414.2069; found 414.2061.

Pyrrolooxazinone 3c. Minor Isomer (3*S*,3′*S*,8*S*)-3c: Colorless cubes, m.p. 172−173 °C. $[\alpha]_D^{20} = -191$ (c = 1.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (m, 2 H, 7-H, 6-H), 1.67 (m, 1 H, 6-H), 1.99 (m, 1 H, 7-H), 3.46 (m, 1 H, 5-H), 3.55 (m, 1 H, 5-H), 3.69 (d, J = 8.84 Hz, 1 H, 3-H), 4.13 (t, J = 7.2 Hz, 1 H, 8-H), 5.08 (d, J = 8.72 Hz, 1 H, 3′-H), 6.7−7.55 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (t, C-6), 30.9 (t, C-7), 44.8 (t, C-5), 62.9 (d, C-8), 73.6 (d, C-3′), 74.7 (d, C-3), 82.9 (s, C-1), 125.1, 125.2, 127.2, 127.6, 128.2, 128.4, 128.6, 142.5, 142.7, 144.7 (s, CF_3), 172.1 (s, C-4) ppm. **Major Isomer (3*S*,3′*R*,8*S*)-3c:** Colorless prisms, m.p. 136−137 °C. $[\alpha]_D^{20} = -130$ (c = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3495, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (m, 2 H, 7-H, 6-H), 1.60 (m, 1 H, 6-H), 1.74 (m, 1 H, 7-H), 3.31 (m, 1 H, 5-H), 3.56 (m, 1 H, 5-H), 4.01 (d, J = 3.4 Hz, 1 H, 3-H), 4.11 (t, J = 7.04 Hz, 1 H, 8-H), 5.31 (d, J = 3.28 Hz, 1 H, 3′-H), 6.95−7.5 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23 (t, C-6), 30.1 (t, C-7), 44.8 (t, C-5), 62.4 (d, C-8), 72.5 (d, C-3′), 75.2 (d, C-3), 81.9 (s, C-1), 125, 125.1, 127.3, 127.8, 128.0, 128.3, 128.5, 142.6, 143, 144.7 (s, CF_3), 170.4 (s, C-4) ppm. HRMS (CI): calcd. for $C_{27}H_{25}F_3NO_4$ [M^+] 468.1787; found 468.1783.

Pyrrolooxazinone 3d. Minor Isomer (3*S*,3′*S*,8*S*)-3d: Colorless powder, m.p. 158−159 °C. $[\alpha]_D^{20} = -219$ (c = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.5 (m, 2 H, 7-H, 6-H), 1.75 (m, 1 H, 6-H), 2.0 (m, 1 H, 7-H), 3.6 (m, 2 H, 5-H), 3.74 (d, J = 8.7 Hz, 1 H, 3-H), 4.20 (d, J = 7.2 Hz, 1 H, 8-H), 5.05 (d, J = 8.84 Hz, 1 H, 3′-H), 5.15 (br., 1 H, OH), 6.85−7.43 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (t, C-6), 30.8 (t, C-7), 44.8 (t, C-5), 62.9 (d, C-8), 73.5 (d, C-3′), 74.7 (d, C-3), 82.7 (s, C-1), 127.2, 127.3, 127.4, 127.6, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 128.9, 129, 129.4, 134, 139.3, 142.6, 142.8, 172.2 (s, C-4) ppm. **Major Isomer (3*S*,3′*R*,8*S*)-3d:** Colorless plates, m.p. 124−125 °C. $[\alpha]_D$ ^{20}= −267 (c = 0.55, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3450, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (m, 2 H, 7-H, 6-H), 1.70 (m, 2 H, 7-H, 6-H), 3.34 (m, 1 H, 5-H), 3.64 (m, 1 H, 5-H), 4.05 (d, J = 7.04 Hz, 1 H, 3-H), 4.17 (m, 1 H, 8-H), 4.35 (b, 1 H, OH), 5.28 (d, J = 6.4 Hz, 1 H, 3′-H), 7.07−7.48 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (t, C-6), 29.9 (t, C-7), 44.8 (t, C-5), 62.3 (d, C-8), 72.5 (d, C-3′), 74.5 (d, C-3), 81.6 (s, C-1), 126.8, 127.2, 127.6, 127.9, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129, 129.1, 129.7, 133.5, 139.3, 142.6, 143.2, 171.5 (s, C-3) ppm. HRMS (CI): calcd. for $C_{26}H_{25}ClNO_3$ [M^+] 434.1523; found 434.1520.

Pyrrolooxazinone 3e. Minor Isomer (3*S*,3′*S*,8*S*)-3e: Colorless needles, m.p. 148−149 °C. $[\alpha]_D^{20} = -290.3$ (c = 1.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3610, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.4−1.6 (m, 2 H, 7-H, 6-H), 1.7 (m, 1 H, 6-H), 1.98 (m, 1 H, 7-H), 3.4−3.72 (m, 2 H, 5-H), 3.66 (s, 3 H, OMe), 4.09 (d, J = 7.18 Hz, 1 H, 3-H), 4.23 (m, 1 H, 8-H), 5.58 (d, J = 7.94 Hz, 1 H, 3′-H), 6.7−7.4 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (q, -OMe), 23.3 (t, C-6), 44.7 (t, C-7), 55.4 (t, C-5), 63.1 (d, C-8), 67.3 (d, C-3′), 74.2 (d, C-3), 82.2 (s, C-1), 111, 120.9, 127.3, 127.4, 127.5, 127.8, 128, 128.1, 128.1, 128.2, 128.3, 128.5, 128.6, 128.8, 128.9, 129, 129.1, 143, 143.1, 143.3, 156, 157.9, 172.6 (s, C-4) ppm. $C_{27}H_{28}NO_4$ (430.2): calcd. C 75.50, H 6.34, N 3.26; found C 75.96, H 6.62, N 3.25. **Major Isomer (3*S*,3′*R*,8*S*)-3e:** Colorless cubes, m.p. 120−121 °C. $[\alpha]_D^{20} = -452.8$ (c = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3600, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35−1.6 (m, 2 H, 7-H, 6-H), 1.7 (m, 1 H, 6-H), 1.95 (m, 1 H, 7-H), 3.58 (m, 3 H, OCH_3), 3.7−3.4 (m, 2 H, 5-H), 4.14 (m, 1 H, 8-H), 4.22 (d, J = 2.29 Hz, 1 H, 3-H), 5.80 (d, J = 2.0 Hz, 1 H, 3′-H), 6.80−7.3 (m, 14 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (q, -OMe), 23.4 (t, C-6), 44.7 (t, C-7), 55.3 (t, C-5), 63.1 (d, C-8), 67.3 (d, C-3′), 74 (d, C-3), 82 (s, C-1), 110.2, 120.9, 127.3, 127.4, 127.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.1, 143.3, 143.4, 155.9, 171.3 (s, C-4) ppm. HRMS (CI): calcd. for $C_{27}H_{28}NO_4$ [M^+] 430.2018; found 430.2019.

Pyrrolooxazinone 3f. (3*S*,3′*R*,8*S*)-3f: Colorless plates, m.p. 129−130 °C. $[\alpha]_D^{20} = -286$ (c = 1.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3470, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (m, 2 H, 7-H, 6-H), 1.64 (m, 1 H, 6-H), 1.84 (m, 1 H, 7-H), 3.38 (m, 1 H, 5-H), 3.48 (s, 3 H, OCH_3), 3.60 (m, 1 H, 5-H), 3.70 (m, 1 H, 3-H), 3.73 (s, 3 H, OCH_3), 4.10 (m, 1 H, 8-H), 5.63 (d, J = 2.28 Hz, 1 H, 3′-H), 6.29−6.48 (m, 3 H, Ph-H), 6.9−7.5 (m, 10 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (t, C-6), 30.6 (t, C-7), 44.7 (t,

C-5), 55.4 (q, OMe), 55.8 (q, OMe), 62.9 (d, C-8), 67.1 (d, C-3′), 74.1 (d, C-3), 81.9 (s, C-6), 98.4, 104.4, 121.4, 127.5, 127.6, 127.7, 128, 128.1, 128.2, 128.5, 128.5, 128.6, 143.3, 143.5, 157, 160.4, 171.3 (s, C-4) ppm. $C_{28}H_{29}NO_5$ (459.5): calcd. C 73.18, H 6.38, N 3.05; found C 73.12, H 6.45, N 3.20.

Pyrrolooxazinone 3g. (3*S*,3′*R*,8*S*)-3g: Colorless needles, m.p. 229−230 °C. $[\alpha]_D^{20} = -300$ (c = 1.8, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3450, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (m, 2 H, 7-H, 6-H), 1.66 (m, 1 H, 6-H), 1.85 (m, 1 H, 7-H), 3.3−3.6 (m, 2 H, 5-H), 3.49 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.8 (m, 1 H, 3-H), 3.82 (s, 3 H, OCH_3), 4.10 (m, 1 H, 8-H), 5.66 (d, J = 2.28 Hz, 1 H, 3′-H), 6.36−6.44 (m, 2 H, Ph-H), 6.89−7.4 (m, 10 H, Ph-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (t, C-6), 30.7 (t, C-7), 44.8 (t, C-5), 56.3 (q, OMe), 56.6 (q, OMe), 57 (q, OMe), 62.9 (d, C-8), 67.0 (d, C-3′), 74.3 (d, C-3), 81.9 (s, C-1), 97.4, 112.7, 120.6, 127.4, 127.5, 127.6, 127.7, 127.8, 128, 128.1, 128.2, 128.4, 128.5, 128.6, 129.4, 143.2, 143.5, 150.3, 160.4, 171.1 (s, C-4) ppm. $C_{29}H_{31}NO_6$ (489.6): calcd. C 71.15, H 6.38, N 2.86; found C 70.72, H 6.43, N 2.77.

Crystallographic Data of Pyrrolooxazinone (3*S*,3′*R*,8*S*)-3e: $C_{27}H_{27}NO_4$ (429.5), colorless, triclinic; space group $P\bar{1}$: a = 953.01(10), b = 954.07(10), c = 1352.34(14) pm; α = 89.970(2), β = 103.718(2), γ = 111.876(2)°; V = 1.1032(2) nm^3, Z = 2; $D_{calcd.}$ = 1.293 g cm^{-3}. The data were collected from shock-cooled crystals with a Bruker SMART-APEX diffractometer with a D8 goniometer (graphite-monochromated Mo-K_α radiation, λ = 0.71073 Å), equipped with a low-temperature device in ω-scan mode at 193(2) K. A total of 15943 reflections were collected to a maximum 2θ of 56.38°, of which 5082 were unique [R(int) = 0.0224]. CCDC-194677 [(3*S*,3′*R*,8*S*)-**3e**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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