Stereoselective Reactions of *N*-(9-Phenylfluoren-9-yl)-4-oxoproline Enolates. An Expedient Route for the Preparation of Conformationally Restricted Amino Acid Analogues

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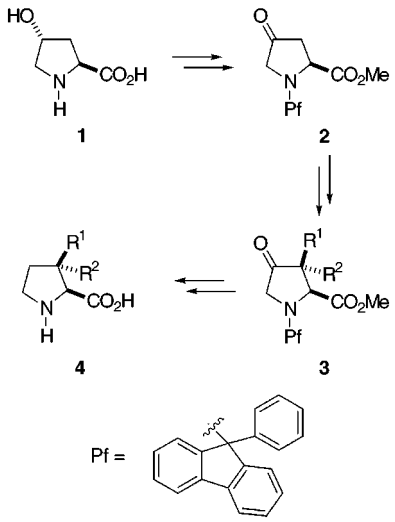
Methodology for the stereoselective preparation of 3-alkylprolines from *N*-(9-phenylfluoren-9-yl)-4-oxoproline is presented. The enolate of a *N*-(9-phenylfluoren-9-yl)-4-oxoproline ester was shown to give stereoselective aldol condensations with aromatic and aliphatic aldehydes. The enolate was preferentially approached by the electrophile through the Re face, and high threo selectivity was also observed and provided a route to trans 3-substituted prolines. The reactions are kinetically controlled except for the case of electron-rich or sterically hindered aromatic aldehydes. The ease of the equilibration between the *erythro*- and *threo*-aldolates is dictated by the electronic nature of the group at C-4 in substituted benzaldehydes, and the steric compression of the aldehyde group increases the rate of erythro/threo equilibration. Very high stereoselection was also observed in the reductions of the keto group in 3-substituted 4-oxoproline esters. Alkylation or Michael additions of the same enolate were poorly stereoselective, probably due to equilibration of the initially formed products. Kinetic protonation of enolates of 3-alkyl-4-oxoprolines proceeded with high diastereoselection to provide the corresponding *cis*-3-alkylprolines.

Introduction

Replacement of natural amino acids in peptides by proline analogues has been extensively used for the study of several fundamental biological processes.[1a−c] Chimeras possessing the combined characteristics of proline and another amino acid, in particular, have played a pivotal role in the establishment of the steric and conformational constraints for receptor affinity of amino acids and peptides.[1c] In this regard, proline analogues that bear side chains belonging to other amino acids at the 3-position of the pyrrolidine ring have been used as probes in the determination of the active conformations of biologically active peptides, such as cholecystokinin, angiotensin II, bradykinin, and the opioid peptides.[1c] The ability of 3-alkylprolines and related compounds to influence the cis−trans peptide bond isomerization in proteins, caused by the interaction of the C-3 substituent with the proline carboxyl group, has also attracted a good deal of attention. This conformational influence of 3-alkylprolines is being used to promote specific types of turns in peptides[2] and, in general, for the study of protein folding.[3] It must be pointed out, as well, that the introduction of cis- or trans 3-alkylprolines in peptides provoke different effects; thus, for instance, the cis epimer of 3-methylproline induces a greater proportion of the cis peptide bond conformation than the trans analogue, or than proline itself, in dipeptides, which results in a greater disturbance of the usual γ-turn conformation of this type of peptide.[2c,d] All these facts have contributed to make the synthesis of 3-alkylprolines a topic of current interest.

Scheme 1



Many synthetic methodologies have been developed for the synthesis of 3-substituted prolines,[1c,d] but efficient, versatile approaches that provide enantiomerically pure 3-alkylprolines in a stereoselective fashion are still lacking. A particularly attractive route, due to its efficiency and potential for stereocontrol, is depicted in Scheme 1.

The use of 4-hydroxyproline (**1**)[4] as starting material sets the correct configuration needed for the analogues

(1) (a) Marshall, G. R. In *Chemical Recognition in Biological Systems*; Creighton, A. M.; Turner, S., Eds.; Chemical Society: London, 1982; p 278. (b) Momany, F. A.; Chuman, H. *Methods Enzymol.* **1986**, *124*, 3. (c) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202, and references therein. (d) Sasaki, N. A.; Dockner, M.; Chiaroni, A.; Riche, C.; Potier, P. *J. Org. Chem.* **1997**, *62*, 765.

(2) (a) Baures, P. W.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L. *J. Pept. Res.* **1997**, *50*, 1. (b) Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M. *J. Med. Chem.* **1991**, *34*, 455. (c) Samanen, J.; Zuber, G.; Bean, J.; Eggleston, D.; Romoff, T.; Kopple, K.; Saunders: M.; Regoli, D. *Int. J. Pept. Protein Res.* **1990**, *35*, 501. (d) Delaney, N.; Madison, V. *J. Am. Chem. Soc.* **1982**, *104*, 6635.

(3) Beausoleil, E.; Sharma, R.; Michnick, S. W.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 6572.

(4) For a review on the use of 4-hydroxyproline in synthesis see: Remuzon, P. *Tetrahedron* **1996**, *52*, 13803.

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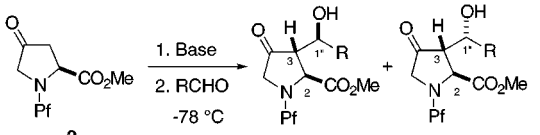
to show biological activity, while the alkylation of the 4-oxoproline **2** derived enolates should allow for the introduction of the desired substituents at C-3 in a manner that could be regio- and stereocontrolled by judicious choice of the reagents and reaction conditions. During our studies aimed at the synthesis of polyhydroxypyrrolidine glycosidase inhibitors, we developed a synthetic strategy that exploited the virtues of the aforementioned approach. We uncovered that the sense of the stereoinduction of the reaction of the enolates of prolinones **2** and **3** (R^1 = OMOM, R^2 = H) depended on the electrophile used: hydroxylation of **2** (LHMDS, MoOPH) proceeded almost completely through the Si face of the nucleophile, while protonation and methylation of the enolate of **3** proceeded almost exclusively through the Re face.[5,6] Lubell and co-workers have studied the monoalkylation of the enolates of the benzyl ester analogue of ketone **2**, and showed that these alkylations occurred with low stereoselectivity. This behavior starkly contrasted with the very high stereoselection observed by us in the reactions of the enolates of prolinones **2** and **3**, a discrepancy that could be explained if the initially formed monoalkylation products could undergo enolization and, then, reprotonation or further alkylation. If this were the case, the degree of stereoselection of the initial alkylation would be masked by the subsequent reprotonation step.[1c,3,7,8] To test this hypothesis, and with the aim of establishing an efficient, versatile route to 3-alkylated proline analogues, we decided to revisit the chemistry of the enolates of prolinone **2** and of related compounds in an attempt to develop conditions for their stereoselective functionalization at C-3.

Results and Discussion

Aldol Reactions. We decided first to study the aldol reactions of prolinone **2** with a series of aromatic and aliphatic aldehydes, with the expectation that the initially formed, negatively charged aldolate intermediate would hinder the further enolization of the products, and thus would preserve the degree of stereoselectivity of the initial electrophile approach. The results from this study are shown in Scheme 2.

Scheme 2



Entry	R	Time	Ratio 2/5/6	$J_{2,3}$ (Hz)	$J_{3,1''}$ (Hz)
1	Ph	15 min	-- / 10 / 1	**5a**: 5.0	**5a**: 7.9
		2 h	-- / 10 / 1	**6a**: 5.5	**6a**: 3.8
2	4-Cl-C_6H_4-	2h	-- / 18 / 1	**5b**: 5.4	**5b**: 7.8
				6b: 5.7	**6b**: 5.2
3	4-Br-C_6H_4-	2 h	-- / 10 / 1	**5c**: 5.3	**5c**: 7.6
				6c: 5.5	**6c**: 4.4
4	4-MeO-C_6H_4-	15 min	1.3/ 6.2 / 1	**5d**: 5.0	**5d**: 8.1
		2.5 h	0.7 / 3 / 1	**6d**: 4.8	**6d**: 4.1
		5 h	0.6 / 2.5 / 1		
5	2-Br-C_6H_4-	18 s	2.7 / 1.7 / 1	**5e**: 6.9	**5e**: 7.4
		5 min	-- / 1.3 / 1	**6e**: 6.4	**6e**: ----
		30 min	-- / 1.2 / 1		
6	3-MeO-C_6H_4-	15 min	2 / 10 / 1	**5f**: 4.7	**5f**: 7.9
		2.5 h	-- / 9 / 1	**6f**: 5.6	**6f**: 2.7
		5 h	-- / 3 / 1		
7	3,4-$(MeO)_2$-	15 min	15 / 13 / 1	**5g**: 5.3	**5g**: 7.9
	-C_6H_3-	2.5 h	13 / 12 / 1	**6g**: 5.4	**6g**: 3.7
		5 h	5 / 4 / 1		
8	3,4-(OCH_2O)-	15 min	6.6 / 9 / 1	**5h**: 4.7	**5h**: 8.0
	-C_6H_3-	2.5 h	2 / 4 / 1	**6h**: 5.0	**6h**: 3.8
		5 h	0.5 / 2.4 / 1		
9	3,4,5-$(MeO)_3$-	2.5 h	2 / 7 / 1	**5i**: 5.5	**5i**: 7.6
	-C_6H_2-	5 h	2 / 7 / 1	**6i**: 5.2	**6i**: 4.3
		6 h	2 / 7 / 1		
10	2,4,5-$(MeO)_3$-				
	-C_6H_2-	2 h	No reaction		
11	1-Naphthyl	15 min	6 / 8 / 1	**5j**: 5.8	**5j**: 7.8
		2.5 h	0.4 / 4 / 1	**6j**: 5.9	**6j**: 3.1
12	i-Pr-	2.5 h	-- / >20 / <1	**5k**: 4.4	**5k**: 6.5
13	i-Bu-	2.5 h	-- / >20 / <1	**5l**: 4.4	**5l**: ----
14	Cyclohexyl-	2.5 h	-- / >20 / <1	**5m**: 4.7	**5m**: 6.0

The enolate of **2** was generated with LHMDS or *n*-BuLi in THF at −78 or −55 °C and then treated with the appropriate aldehyde (neat or in THF solution, at −78 °C). The additions proceeded cleanly and usually in high yields with all the aldehydes tested, with the sole exception of the highly electron-rich and hindered 2,4,5-trimethoxybenzaldehyde (entry 10), which was unreactive toward the enolate of ketone **2** even at − 20 °C. Most of the reactions studied displayed a remarkable stereoselectivity since only two, in the worst cases, of the four possible diastereoisomeric aldol products could be detected in the crude reaction mixtures and, in most cases, one product was clearly predominant or exclusive.[9] A preliminary assignment of the erythro/threo configuration of the aldol products was based on the magnitude of $J_{3,1''}$, since it has been shown that the coupling constants in *erythro*-aldols (2−6 Hz) are smaller than in the threo isomers (7−10 Hz).[10] The major products from all the reactions showed $J_{3,1''}$ in the range of 6.5−8.1 Hz, while the minor products exhibited smaller $J_{3,1''}$ (2.7−5.2 Hz). These observations pointed to the *threo*-aldols as the predominant reaction products. The absolute configuration at C-3 could be tentatively established as trans (3*S*) by the fact that $J_{2,3}$ was in the range of 4.4−6.9 Hz for all the aldols prepared. It has been shown that in *N*-substituted 3-alkylproline esters the cis (3*R*) isomers showed larger (8−9 Hz) coupling constants than their trans (3*S*) counterparts (2−6 Hz).[11,1c]

Since the analysis of the ^{1}H NMR spectra of *β*-hydroxyketones **5** and **6** could not provide a definitive configurational assignment, the preparation of rigid derivatives of them, in which NOE studies could be safely carried out, was considered. Reduction of the major benzyl aldol **5a** provided exclusively one diol (**7a**),[12] which gave

(5) (a) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748. (b) Blanco, M.-J.; Sardina, F. J. *Tetrahedron Lett.* **1994**, *35*, 8493.

(6) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1998**, *63*, 3411.

(7) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658.

(8) A closely related approach has been used for the synthesis of kainic acid analogues: (a) Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1996**, *37*, 6923. (b) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Wood, M. E. *Tetrahedron Lett.* **1995**, *36*, 4869. (c) Baldwin, J. E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163. (d) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658.

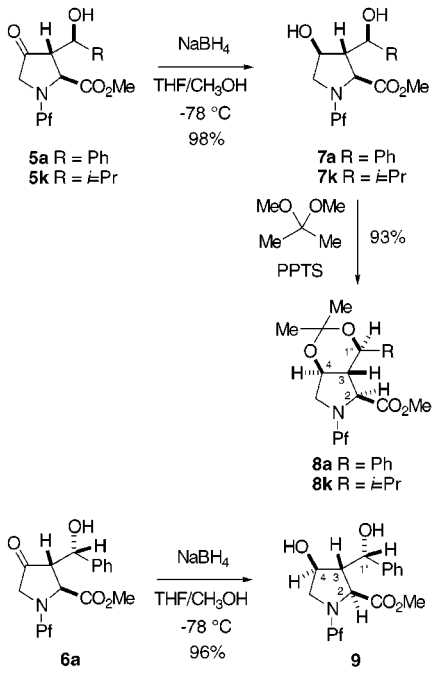
(9) Analyses were carried out by inspection of the CO_2Me singlets in the ^{1}H NMR spectra (500 MHz) of the crude reaction mixtures. Doping experiments using known amounts of various substituted proline methyl esters showed that the limit of detection was ≤2%.

(10) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol 3, pp 111−212.

(11) Mauger, A. B.; Irreverre, F.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 2019.

(12) For an explanation of the origin of the stereoselectivity in the reduction of the C-4 carbonyl group in 4-oxoprolines, see ref 6.

Scheme 3



acetonide **8a**, in excellent overall yield, when reacted with 2,2-dimethoxypropane. The coupling constants $J_{2,3}$ (10.7 Hz) and $J_{3,1''}$ (10.2 Hz) indicated a trans-diaxial disposition for H-3 and H-1″. NOE studies showed that when H-4 (δ 3.75 ppm) was irradiated strong enhancements were experienced by H-2 (δ 2.58 ppm) and H-1″ (δ 4.40 ppm); when H-1″ was irradiated enhancements were experienced by signals corresponding to H-4 and H-2; irradiation of H-2 led to enhacements of the signals originated by H-4 and H-1″. All these facts confirmed the stereochemical assignment of **8a** shown in Scheme 3, and thus led us to assign a (3*S*,4*S*,1″*R*) configuration to **5a**. The isopropyl aldol **5k** was submitted to the same protocol as **5a**, to yield acetonide **8k**, which was shown, by analysis of $J_{2,3}$ (10.7 Hz) and $J_{3,1''}$ (10.2 Hz) and of NOE enhancements, to have the same stereochemistry as **8a**.

The minor benzyl aldol **6a** was reduced with $NaBH_4$ to give diol **9** with very high stereoselectivity. Attempts to convert diol **9** into the corresponding cyclic acetonide (as for **5a**) or carbonate (by treatment with $COCl_2$, diphosgene or triphosgene, and a tertiary amine or NaH) met with failure, even under forcing conditions (complex mixtures were obtained). Nevertheless, NOE studies performed on diol **9** allowed us to assign the (3*S*,4*S*,1″*S*) configuration, since when H-4 (δ 3.61 ppm) was irradiated, H-2 (δ 3.29 ppm) and one of the hydrogens at C-5 (H-5b, δ 3.36 ppm) showed intensity enhancements; when H-1″ (δ 3.77 ppm) was irradiated a strong enhancement was experienced by H-2; finally, when H-5b was irradiated, enhancements were seen for the signals of H-4 (3.61 ppm), H-1″ and H-5a (3.17 ppm). These observations point to the fact that H-2, H-1″, and H-4 must be placed on the same face of the molecule and, thus, that **9** must be the epimer of **5a** at C-1″ and not at C-3. The failure of the formation of the acetonide or carbonate of **6a** could, then, be explained since the bulky Ph group of the side chain would have to occupy an axial position in the bicyclic product. The structures of the rest of the aromatic and aliphatic aldol products were assigned by comparison of their spectroscopic properties with those of **5a**,**k** and **6a**.

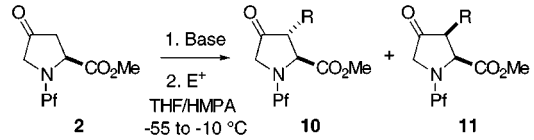
The analysis of the aldol reaction products showed that the condensation occurred with very high face selectivity with regard to the enolate component and with a preference for threo selectivity with respect to the overall addition,[13,14] but perusal of the data shown in Scheme 2 allowed us to extract some interesting additional conclusions. Aliphatic aldehydes gave highly stereoselective reactions (entries 12−14), most probably under kinetic control, but aromatic aldehydes showed a more puzzling behavior, since an interplay of stereoelectronic effects influenced both the reaction stereoselectivity and reversibility. Equilibration between *threo*- and *erythro*- aldols **5** and **6** was obviously taking place in some of the reactions studied, most notably in those in which the substituents on the aromatic ring of the electrophile were electron-donating or were placed ortho to the aldehyde group (entries 4−8 and 11), probably through the intervention of a retro-aldol reaction. Our data showed that the *rate* of equilibration was a complex function of the nature and the position of the aromatic ring substituents in the aldehyde. Interestingly, numerous studies on the influence of the structure, steric effects, and counterion of the *enolate* on the reversibility of the aldol condensation have been carried out, but to the best of our knowledge, none have addressed the influence of the structure of the aldehyde component on the rate of erythro/threo equilibration.[10,15] We observed that the 4-methoxy- (entry 4) and the 3,4-methylenedioxybenzyl aldols (entry 8) equilibrated significantly faster that their 3-methoxy (entry 6) and 3,4-dimethoxy (entry 7) counterparts. This order of reactivity argued against a simple explanation in which the electron-richness of the ring solely influenced the equilibration rate. The fact that the 3,4,5-trimethoxybenzyl aldols (entry 9) showed no signs of equilibration, even after 5 h at −78 °C, strongly suggested that the rate of equilibration is strongly influenced by the substituent at C-4: an electron-donating substituent increases the rate of equilibration of the *erythro*/*threo*-aldolates, but only if this substituent can become coplanar with the phenyl ring. If this coplanarity is prevented by steric factors, as in the 3,4-dimethoxy or the 3,4,5-trimethoxybenzyl aldols, the equilibration is retarded (entry 7) or even suppressed (entry 9). The destabilizing effect of direct electron donation by the substituent at C-4 on the newly formed negative charge of the aldolate might be the origin of the observed trend. Steric effects also play a role in the rate of equilibration, as can be deduced from entries 5 and 11. The aldol condensation with 2-bromobenzaldehyde proceeds very rapidly, but equilibration appears to take place with a high rate as well, giving a poorly stereoselective reaction. Equilibration between the 1-naphthyl

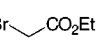
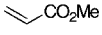
(13) These results are consistent with a chelated-chair transition state. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

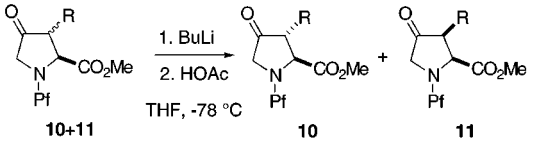
(14) Cyclopentanone enolates have been shown to give high threo selectivity in their reactions with aldehydes and ketones: (a) Fellman, P.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 1349. (b) Dubois, J. E.; Dubois, M. *J. Chem. Soc. Chem. Commun.* **1968**, 1567.

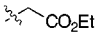
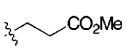
(15) (a) Braun, M. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1603−1607, and references therein. (b) Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681. (c) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598. (d) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

Scheme 4



Entry	E^+	Base (mol%)	Ratio 10/11	$J_{2,3}$ (Hz)
1		BuLi (105)	2 / 1	**10a**: 4.0 **11a**: 7.6
2		BuLi (105)	2 / 1	**10b**: 6.6 **11b**: 7.5
3		LHMDS (150)	2 / 1	**10c**: 4.5 **11c**: 8.1
4	CD_3OD[a]	BuLi (105)	>95 / <5	**10d**: 2.9



Entry	R	Initial ratio 10/11	Final ratio 10/11
5		2/1	<1 / >15
6		1/1	<1 / >20
7		1/1	<1 / >20

[a] Quench at -55 °C

aldols, in which the steric compression on the alkoxyde group is less than in the previous case, takes place with a reduced rate. These results suggest that increasing steric hindrance in the starting aldehyde (i.e. steric compression in the alkoxyde group of the aldolate), increases the rate of the retro-aldol reaction, which is causing the erythro/threo equilibration.[16]

In all cases the *threo*-aldol **5** was the kinetic product, and most reactions showed good-to-high stereoselectivity. Even in the cases where the aldol condensation appeared to be reversible, the 4-oxoproline enolate exclusively reacted through the Re face, thus opening a highly stereoselective route toward the trans 3-substituted prolines, since the 3-alkyl-4-oxoprolines can be converted into the corresponding 3-substituted prolines in two steps, without affecting the stereochemistry at C-3.[1c]

Alkylation and Protonation Reactions. With these results in hand we undertook the study of other C−C bond-forming reactions of the enolate of **2**, namely alkylation reactions and Michael additions, to check if they proceeded with the same degree of stereocontrol. Our findings are shown in Scheme 4 (entries 1−3).

The best reaction conditions usually involved the use of *n*-BuLi (105 mol %) as base, and THF/HMPA as solvent (reaction time 2 h). Under these conditions, all reactions proceeded to completion, but in stark contrast with the aldol condensations, they displayed low levels of stereoselection. The configuration at C-3 in each product **10** and **11** was established by the magnitude of the coupling constant $J_{2,3}$, following the precedent of Lubell et al. for the benzyl ester analogues of **10a**−**c** and **11a**−**c**.[1c] NOE experiments were carried out to assign the stereochemistry of deuterio ketone **10d**.[18]

An important fact that has to be taken into account when analyzing the stereochemical outcome of these reactions is that these alkylation or Michael reactions, unlike the aldol additions, did not take place at −78 °C. A higher temperature needed to be employed in the C−C bond forming step (up to −10 °C) due to the lower reactivity of the electrophiles used compared to the aldehydes utilized in the aldol condensations. The higher reaction temperature might be facilitating the deprotonation of the initially formed alkylation product, either by the excess base or by the unreacted starting enolate, a process that would lead to the erosion of the kinetic stereoselectivity of the alkylation.[17] When the reaction time was shortened (20 min) or the temperature lowered somewhat (temperature quench −20 °C), higher diastereomeric ratios (up to 4/1, but with conversions < 40%) were obtained, a fact that strengthens the deprotonation−reprotonation sequence as the cause for the low stereoselectivity of these reactions. When an electrophile that did react at −55 °C with the enolate of **2** was employed (CD_3OD, entry 4) a highly stereoselective reaction ensued, to give attack through the Re face of the enolate (85% deuterium incorporation).

In view of this highly stereoselective protonation we decided to study the protonation of the enolates prepared from mixtures of epimers of **10a**−**c** and **11a**−**c** (BuLi, THF, −78 °C) with acetic acid (Scheme 4, entries 5−7). Analysis of the ^{1}H NMR spectra of the crude protonation mixtures showed only the presence of the corresponding cis isomers **11a**−**c**, concurring with the results obtained in the deuteration of **2** (Scheme 4, entry 4). These results not only attested the high stereoselectivity of the enolate protonation process but, by inference, also lent support to the notion that the *initial* attack of electrophiles toward these 4-prolinone enolates proceeded with high stereoselectivity, and that the low level of stereoselection displayed by some of these processes is probably caused by the deprotonation of the initially formed adduct under the reaction conditions. A corollary of these studies is that reactions of *N*-Pf-4-prolinone (Pf = 9-phenylfluoren-9-yl) enolates with electrophiles can be expected to proceed stereoselectively if they can be carried out at low (−78 to −55 °C) temperature.

It is also interesting to note the great tendency of 4-oxoprolines toward enolization, since <2% of nucleophilic attack of BuLi on the carbonyl group at C-4 was detected in the crude reaction mixtures (limit of detection, ^{1}H NMR analysis).[6]

This alkylation−Michael addition-enolate reprotonation protocol opens a highly stereoselective route for the preparation of cis 3-alkylprolines, since the 3-alkyl-4-oxoprolines can be converted into the corresponding 3-substituted prolines in two steps.[1c]

Conclusion

We have developed a methodology for the preparation of either trans or cis 3-substituted prolines from 4-oxo-

(16) It is known that steric hindrance on the enolate favors the erythro/threo equilibration, probably due to the release of strain in the aldolate; see refs 10 and 15a.

(17) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

(18) Stereochemical assignment of **10d:** The diastereotopic hydrogens attached to C-3 in ketone **2** appeared at δ 2.28 (dd, J = 17.9, 3.1 Hz) and 2.45 ppm (dd, J = 17.9, 8.5 Hz). The signal at lower field was assigned to the pro-*S* H-3 since its irradiation caused enhancement of H-2 (δ 3.76 ppm) and the other H-3 signal, while irradiation of the signal at δ 2.28 ppm (pro-*R* H-3) caused enhancement of only the other H-3 proton, H-2 being unaffected. In the deuterated ketone **10d**, the signal at δ 2.45 ppm is not present and H-2 has a coupling constant of 2.9 Hz, typical of a trans arrangement, with the residual H-3 hydrogen (δ 2.20 ppm, bs).

prolines. The aldol and protonation reactions of enolates of *N*-Pf-4-oxoprolines were shown to proceed with high levels of stereoselection. The alkylation and Michael addition are less stereoselective, probably due to further deprotonation−reprotonation of the initially formed product. The aldol condensations of **2** with aromatic and aliphatic aldehydes provided trans 3-alkylprolines. The reactions of the enolate of **2** with alkyl halides or Michael acceptors proceeded with low stereoselectivity, but enolization−reprotonation of the initially obtained mixtures of epimers afforded the cis 3-substituted prolinones with very high stereocontrol.

Experimental Section

General Methods. For general methods, see ref 5a.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-Phenyl-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5a and 6a). Method A (Enolate generation at −78 °C). LHMDS (1.01 mL, 1.21 mmol, 260 mol %, 1.2 M in hexane) was added to a precooled (−78 °C) solution of **2** (179 mg, 0.467 mmol) in THF (1.2 mL). After 1 h of stirring at −78 °C, benzaldehyde (83 μL, 0.817 mmol, 175 mol %) was added to the reaction mixture. The resulting solution was stirred for 2.5 h at −78 °C and then it was quenched with H_3PO_4 (10%, 0.5 mL). The reaction mixture was partitioned between H_2O (45 mL) and ether (2 × 50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (EtOAc/hexanes 1/3) and gave 190 mg (85%) of **5a** and 32 mg (14%) of **6a** (ratio 6:1).

Method B (Enolate Generation at −55 °C). LHMDS (0.15 mL, 0.183 mmol, 140 mol %, 1.2 M in hexane) was added dropwise to a precooled (−58 °C) solution of **2** (50 mg, 0.130 mmol) in THF (0.5 mL). The resulting solution was allowed to stir at −56/−54 °C for 1 h. Then, the reaction mixture was cooled (−78 °C) and benzaldehyde (19 μL, 0.183 mmol, 140 mol %) was added. The resulting solution was stirred at −78 °C for 2 h. The procedure described in method A was followed for the workup. After purification, 58 mg (90%) of **5a** and 5 mg (8%) of **6a** were obtained (ratio 10:1).

Method C (Enolate Generation using *n*-BuLi as Base). *n*-BuLi (105 mol %, 2.25 M in hexanes) was added to a solution of **2** in THF at −55 °C. After stirring at −55 to −58 °C for 1 h, the enolate solution was cooled to −78 °C and treated with the corresponding aldehyde, and the resulting solution was stirred at −78 °C for the specified time. The procedure described in method A was followed for the workup. **5a:** $[\alpha]^{25}_D$ = −94.9° (*c* 1.25, $CHCl_3$); IR (NaCl) 3060, 1755, 1747, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (s, 3H), 2.92 (dd, *J* = 7.9 and 5.0 Hz, 1H), 3.33 (d, *J* = 18.0 Hz, 1H), 3.44 (d, *J* = 5.0 Hz, 1H), 3.79 (d, *J* = 18.0 Hz, 1H), 4.72 (d, *J* = 7.9 Hz, 1H), 7.18−7.70 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 51.2, 56.1, 58.8, 60.8, 73.4, 75.6, 120.0, 120.1, 125.8, 126.8, 126.9, 127.4, 127.5, 127.7, 127.9, 128.3, 128.4, 128.9, 129.0, 139.8, 140.1, 141.2, 141.3, 144.0, 146.3, 172.4, 213.8. Anal. Calcd for $C_{32}H_{27}NO_4$: C, 78.5; H, 5.6; N, 2.9. Found: C, 78.2; H, 5.6; N, 2.6. **6a:** $[\alpha]^{23}_D$ = −132.7° (*c* 1.03, $CHCl_3$); IR (NaCl) 3594, 1760, 1747, 1447 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (s, 3H), 2.95 (dd, *J* = 5.0 and 4.2 Hz, 1H), 3.26 (d, *J* = 17.5 Hz, 1H), 3.72 (d, *J* = 17.5 Hz, 1H), 3.84 (d, *J* = 5.5 Hz, 1H), 5.17 (d, *J* = 3.8 Hz, 1H), 7.19−7.72 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 51.1, 56.2, 59.4, 59.6, 71.9, 76.5, 120.0, 120.1, 125.5, 125.7, 125.9, 126.9, 127.0, 127.3, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 128.6, 128.9, 139.9, 140.9, 141.2, 141.6, 143.6, 146.4, 172.7, 211.8. Anal. Calcd for $C_{32}H_{27}NO_4$: C, 78.5; H, 5.6; N, 2.9. Found: C, 78.4; H, 5.6; N, 2.8.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(4-Chlorophenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5b and 6b). A mixture of compounds **5b** and **6b** was obtained from the reaction of the enolate **2** (prepared from 70 mg, 0.183 mmol) with 4-chlorobenzaldehyde (39 mg, 0.275 mmol, 150 mol %) by following method A described above. Purification by flash chromatography (EtOAc/hexanes 1/5) gave 74 mg (77%) of **5b** and 5 mg (5%) of **6b**. **5b:** $[\alpha]^{20}_D$ = −76.3° (*c* 1.0, $CHCl_3$); IR (NaCl) 3575, 1751, 1745, 1444 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (s, 3H), 2.88 (dd, *J* = 5.5 and 7.7 Hz, 1H), 3.33 (d, *J* = 18.2 Hz, 1H), 3.37 (d, *J* = 5.4 Hz, 1H), 3.79 (d, *J* = 18.2 Hz, 1H), 4.67 (d, *J* = 7.8 Hz, 1H), 7.09−7.70 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.4, 56.4, 58.8, 60.7, 72.7, 75.8, 120.1, 120.2, 122.3, 125.8, 126.9, 127.5, 127.8, 128.0, 128.5, 129.0, 129.1, 131.5, 138.9, 140.4, 141.1, 141.2, 144.2, 146.2, 172.6, 213.4. Anal. Calcd for $C_{32}H_{26}ClNO_4$: C, 73.3; H, 5.0; N, 2.7. Found: C, 73.2; H, 5.1; N, 2.6. **6b:** $[\alpha]^{22}_D$ = −126.5° (*c* 1.1, $CHCl_3$); IR (NaCl) 3570, 1750, 1745, 1444 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s, 3H), 2.90 (t, *J* = 5.0 Hz, 1H), 3.26 (d, *J* = 17.6 Hz, 1H), 3.73 (d, *J* = 17.4 Hz, 1H), 3.74 (d, *J* = 5.7 Hz, 1H), 5.11 (d, *J* = 5.2 Hz, 1H), 7.11−7.72 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.3, 56.3, 59.4, 71.4, 75.8, 77.2, 120.1, 120.2, 121.7, 125.8, 127.0, 127.4, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 128.9, 129.0, 131.5, 131.7, 140.0, 140.1, 141.1, 141.5, 143.7, 146.3, 172.6, 211.5. Anal. Calcd for $C_{32}H_{26}ClNO_4$: C, 73.3; H, 5.0; N, 2.7. Found: C, 73.1; H, 5.1; N, 2.6.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(4-Bromophenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5c and 6c). A mixture of compounds **5c** and **6c** was obtained from the reaction of the enolate of **2** (prepared from 77 mg, 0.20 mmol) with 4-bromobenzaldehyde (74 mg, 0.40 mmol, 200 mol %) by following method A described above. Purification by flash chromatography (EtOAc/hexanes 1/4) gave 98 mg (86%) of **5c** and 13 mg (11%) of **6c**. **5c:** $[\alpha]^{23}_D$ = −25.7° (*c* 0.46, $CHCl_3$); IR (NaCl) 2929, 1746, 1731, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 2.90 (t, *J* = 4.8 Hz, 1H), 3.06 (d, *J* = 5.8 Hz, 1H), 3.25 (d, *J* = 17.7 Hz, 1H), 3.73 (d, *J* = 17.6 Hz, 1H), 3.74 (d, *J* = 5.5 Hz, 1H), 5.10 (t, *J* = 4.4 Hz, 1H), 7.06−7.72 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.3, 56.3, 59.4, 71.4, 75.8, 77.2, 120.1, 120.2, 121.7, 125.8, 127.0, 127.4, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 128.9, 129.0, 131.5, 131.7, 140.0, 140.1, 141.1, 141.5, 143.7, 146.3, 172.6, 211.5. Anal. Calcd for $C_{32}H_{26}BrNO_4$: C, 67.6; H, 4.6; N, 2.5. Found: C, 67.8; H, 4.7; N, 2.5. **6c:** $[\alpha]^{23}_D$ = −61.4° (*c* 0.86, $CHCl_3$); IR (NaCl) 3100, 1757, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.84 (s, 3H), 2.86 (m, 1H), 3.30 (d, *J* = 18.1 Hz, 1H), 3.38 (d, *J* = 5.3 Hz, 1H), 3.55 (s, 1H), 3.78 (d, *J* = 18.2 Hz), 4.66 (d, *J* = 7.6 Hz, 1H), 7.01−7.70 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.4, 56.4, 58.8, 60.7, 72.7, 75.8, 120.1, 120.2, 122.3, 125.8, 126.9, 127.5, 127.8, 128.0, 128.5, 129.0, 129.1, 131.5, 138.9, 140.4, 141.1, 141.2, 144.2, 146.2, 172.6, 213.4. Anal. Calcd for $C_{32}H_{26}BrNO_4$: C, 67.6; H, 4.6; N, 2.5. Found: C, 67.8; H, 4.8; N, 2.6.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(4-Methoxyphenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5d and 6d). A mixture of compounds **5d** and **6d** was obtained from the reaction of the enolate of **2** (prepared from 78 mg, 0.20 mmol) with 4-methoxybenzaldehyde (49 μL, 0.41 mmol, 200 mol %) by following method A described above. Purification by flash chromatography (EtOAc/hexanes 1/4) gave 37 mg (35%) of **5d** and 21 mg (20%) of **6d**. **5d:** $[\alpha]^{19}_D$ = −93.4° (*c* 0.45, $CHCl_3$); IR (NaCl) 2928, 1755, 1746, 1514, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (s, 3H), 2.90 (t, *J* = 4.6 Hz, 1H), 3.72 (d, *J* = 17.4 Hz, 1H), 3.78 (s, 3H), 3.79 (d, *J* = 4.8 Hz, 1H), 5.06 (d, *J* = 4.1 Hz, 1H), 6.80−7.73 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.2, 55.2, 56.2, 59.6, 59.8, 72.0, 77.2, 113.9, 120.1, 120.2, 125.9, 127.0, 127.3, 127.7, 127.9, 128.4, 128.6, 128.9, 133.2, 140.0, 141.3, 141.6, 143.8, 146.5, 159.3, 172.7, 211.9. Anal. Calcd for $C_{33}H_{29}NO_5$: C, 76.3; H, 5.6; N, 2.7. Found: C, 76.5; H, 5.7; N, 2.7. **6d:** $[\alpha]^{24}_D$ = −71.9° (*c* 0.54, $CHCl_3$); IR (NaCl) 3664, 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.83 (s, 3H), 2.89 (dd, *J* = 5.4 and 7.9 Hz, 1H), 3.34 (d, *J* = 18.0 Hz, 1H), 3.41 (d, *J* = 5.0 Hz, 1H), 3.42 (br s, 1H), 3.78 (s, 3H), 3.79 (d, *J* = 16.2 Hz, 1H), 4.66 (d, *J* = 8.1 Hz, 1H), 6.80−7.71 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.3, 55.2, 56.2, 59.0, 61.0, 73.1, 75.6, 113.8, 120.0, 120.1, 125.8, 126.9, 127.3, 127.5, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.9, 129.0, 132.0, 140.1, 141.1, 141.2, 144.0, 146.3, 159.6, 172.4, 213.8.

Anal. Calcd for $C_{33}H_{29}NO_5$: C, 76.3; H, 5.6; N, 2.7. Found: C, 76.4; H, 5.7; N, 2.7.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)- 3-[1″-(2-Bromophenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5e and 6e). A mixture of compounds **5e** and **6e** was obtained from the reaction of the enolate of **2** (prepared from 60 mg, 0.157 mmol) with 2-bromobenzaldehyde (56 μL, 0.47 mmol, 300 mol %) by following method A described above. Purification by flash chromatography (EtOAc/hexanes 1/5) gave 35 mg (39%) of **5e** and 34 mg (39%) of **6e**. **5e:** $[\alpha]^{20}_D = -118.6°$ (*c* 1.1, $CHCl_3$); IR (NaCl) 3590, 1756, 1745, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H), 2.81 (d, J = 4.6 Hz, 1H), 3.16 (d, J = 17.4 Hz, 1H), 3.30 (m, 1H), 3.62 (d, J = 17.4 Hz, 1H), 3.93 (d, J = 6.4 Hz, 1H), 5.53 (br d, 1H), 7.07−7.74 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.2, 56.5, 57.1, 59.1, 70.2, 75.7, 120.0, 120.1, 121.4, 125.7, 127.0, 127.2, 127.3, 127.6, 127.8, 127.9, 128.0, 128.3, 128.8, 128.9, 129.1, 132.5, 139.5, 139.6, 141.0, 141.7, 143.0, 146.7, 172.0, 211.0. Anal. Calcd for $C_{32}H_{26}BrNO_4$: C, 67.6; H, 4.6; N, 2.4. Found: C, 67.4; H, 4.7; N, 2.4. **6e:** $[\alpha]^{26}_D = -85.4°$ (*c* 1.0, $CHCl_3$); IR (NaCl) 3580, 1755, 1742, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 3.05 (t, J = 7.3 Hz, 1H), 3.29 (d, J = 18.0 Hz, 1H), 3.69 (d, J = 17.2 Hz, 1H), 3.70 (d, J = 7.0 Hz, 1H), 3.97 (br s, 1H), 5.19 (d, J = 7.4 Hz, 1H), 7.08−7.73 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 51.5, 56.8, 57.9, 61.7, 71.9, 76.0, 120.1, 120.3, 122.6, 125.7, 127.1, 127.3, 127.6, 127.8, 128.1 (2C), 128.4, 128.9, 129.0, 129.1, 129.6, 132.4, 138.4, 140.0, 140.8, 141.4, 143.1, 146.3, 172.2, 213.2. Anal. Calcd for $C_{32}H_{26}BrNO_4$: C, 67.6; H, 4.6; N, 2.4. Found C, 67.3; H, 4.7; N, 2.4.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(3-Methoxyphenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5f and 6f). A mixture of compounds **5f** and **6f** was obtained from the reaction of the enolate of **2** (prepared from 50 mg, 0.13 mmol) with 3-methoxybenzaldehyde (24 μL, 0.20 mmol, 150 mol %) by following method C described above (reaction time, 2.5 h). Purification by flash chromatography (EtOAc/hexanes 1/3) gave 59 mg (87%) of **5f** and 7 mg (10%) of **6f**. **5f:** $[\alpha]^{20}_D = -148$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 2.86 (dd, J = 4.7, 7.9, 1H), 3.30 (d, J = 17.8, 1H), 3.43 (d, J = 4.7, 1H), 3.74 (s, 3H), 3.75 (d, J = 17.8, 1H), 4.69 (d, J = 7.9, 1H), 6.74 (m, 3H), 7.13−7.39 (m, 12H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.3, 55.2, 56.1, 58.9, 60.7, 73.3, 75.5, 111.9, 114.2, 119.1, 120.0, 125.9, 126.8, 127.3, 127.4, 127.7, 127.9, 128.4, 129.0, 129.4, 140.0, 141.2, 141.3, 141.4, 143.9, 146.2, 159.7, 172.5, 213.6. IR 1731, 1744 cm^{-1}. Anal. Calcd for $C_{33}H_{29}NO_5$: C, 76.3; H, 5.6; N, 2.7. Found: C, 76.2; H, 5.4; N, 2.7. **6f:** $[\alpha]^{20}_D = -172$ (*c* 1.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.67 (s, 3H), 2.83 (bt, J = 4.5, 1H), 2.97 (bs, 1H), 3.20 (d, J = 17.3, 1H), 3.65 (d, J = 17.3, 1H), 3.69 (s, 3H), 3.75 (d, J = 5.6, 1H), 5.05 (bd, J = 2.7, 1H), 6.71 (m, 3H), 7.10−7.45 (m, 12H), 7.59 (d, J = 7.4, 1H), 7.63 (d, J = 7.4, 1H); ^{13} C NMR ($CDCl_3$) δ 51.2, 55.2, 56.1, 59.4, 72.1, 75.5, 111.0, 113.4, 117.9, 120.0, 125.8, 126.7, 126.9, 127.3, 127.6, 127.8, 128.4, 128.8, 128.9, 129.4, 139.7, 141.0, 141.6, 142.5, 143.4, 146.3, 159.6, 172.5, 211.8. IR 1739, 1755 cm^{-1}. Anal. Calcd for $C_{33}H_{29}NO_5$: C, 76.3; H, 5.6; N, 2.7. Found: C, 76.5; H, 5.7; N, 2.5.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(3,4-Dimethoxyphenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5g and 6g). A mixture of compounds **5g** and **6g** was obtained from the reaction of the enolate of **2** (prepared from 77 mg, 0.20 mmol) with a solution of 3,4-dimethoxybenzaldehyde (50 mg, 0.30 mmol, 150 mol %) in THF (1 mL) by following method C described above (reaction time, 5 h). Purification by flash chromatography (EtOAc/hexanes 1/2) gave 44 mg (40%) of **5g** and 11 mg (10%) of **6g**; 38 mg of ketone **2** were recovered as well. **5g:** $[\alpha]^{20}_D = -119$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 2.87 (m, 1H), 3.26 (d, J = 18.2, 1H), 3.33 (d, J = 5.3, 1H), 3.40 (bs, 1H), 3.72 (d, J = 18.2, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.57 (d, J = 7.9, 1H), 6.63 (m, 3H), 7.09−7.37 (m, 11H), 7.60 (d, J = 7.8, 2H); ^{13}C NMR ($CDCl_3$) δ 51.4, 55.7, 55.8, 56.5, 59.0, 60.9, 73.2, 75.7, 109.4, 110.6, 119.3, 120.0, 120.1, 125.7, 126.8, 127.3, 127.4, 127.7, 127.9, 128.4, 128.9, 129.0, 132.3, 140.2, 141.0, 141.2, 144.0, 146.2, 148.9, 172.6, 213.9; IR (NaCl) 1735, 1751 cm^{-1}. Anal. Calcd for $C_{34}H_{31}NO_6$: C, 74.3; H, 5.7; N, 2.6. Found: C, 74.0; H, 5.6; N, 2.5. **6g:** $[\alpha]^{20}_D = -156$ (*c* 1.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3H), 2.82 (t, J = 4.2, 1H), 2.93 (bs, 1H), 3.24 (d, J = 17.6, 1H), 3.69 (d, J = 17.6, 1H), 3.74 (d, J = 5.4, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 5.00 (bt, J = 3.7, 1H), 6.68 (m, 3H), 7.10−7.35 (m, 10H), 7.42 (d, J = 7.5, 1H), 7.62 (t, J = 8.0, 2H); ^{13}C NMR ($CDCl_3$) δ 51.3, 55.8, 55.9, 56.1, 59.5, 59.6, 72.2, 75.6, 108.7, 110.8, 118.0, 120.0, 120.1, 125.7, 126.9, 127.3, 127.7, 127.8, 128.4, 128.8, 128.9, 133.5, 139.9, 141.0, 141.5, 143.6, 146.2, 148.5, 148.9, 172.6, 212.0; IR (NaCl) 1736, 1751 cm^{-1}. Anal. Calcd for $C_{34}H_{31}NO_6$: C, 74.3; H, 5.7; N, 2.6. Found: C, 74.1; H, 5.7; N, 2.3.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(1,3-Benzodioxol-5-yl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)-pyrrolidine-2-carboxylic Acid Methyl Ester (5h and 6h). A mixture of compounds **5h** and **6h** was obtained from the reaction of the enolate of **2** (prepared from 67 mg, 0.18 mmol) with a solution of 3,4-methylenedioxybenzaldehyde (40 mg, 0.26 mmol, 150 mol %) in THF (1 mL) by following method C described above (reaction time, 5 h). Purification by flash chromatography (EtOAc/hexanes 1/4) gave 57 mg (61%) of **5h** and 23 mg (25%) of **6h**. **5h:** $[\alpha]^{20}_D = -119$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.75 (dd, J = 4.7, 8.0, 1H), 2.81 (s, 3H), 3.29 (d, J = 17.9, 1H), 3.33 (d, J = 4.7, 1H), 3.74 (d, J = 17.9, 1H), 4.57 (d, J = 8.0, 1H), 5.85 (d, J = 1.4, 1H), 5.86 (d, J = 1.4, 1H), 6.55 (m, 3H), 7.13−7.36 (m, 11H), 7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.4, 56.1, 59.0, 60.8, 73.2, 75.6, 101.1, 107.1, 107.9, 120.1, 120.2, 120.5, 125.8, 126.8, 127.4, 1127.7, 127.9, 128.4, 128.9, 129.0, 133.8, 140.1, 141.1, 141.2, 144.0, 146.2, 147.8, 172.4, 213.7. IR 1740, 1751 cm^{-1}. Anal. Calcd for $C_{33}H_{27}NO_6$: C, 74.3; H, 5.1; N, 2.6. Found: C, 74.2; H, 4.9; N, 2.4. **6h:** $[\alpha]^{20}_D = -174$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 2.78 (m, 1H), 2.96 (bd, J = 4.7, 1H), 3.22 (d, J = 17.3, 1H), 3.75 (d, J = 17.3, 1H), 3.71 (d, J = 5.0, 1H), 4.95 (bt, J = 3.8, 1H), 5.85 (d, J = 1.6, 1H), 5.86 (d, J = 1.6, 1H), 6.62 (m, 3H), 7.12−7.45 (m, 11H), 7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.3, 56.0, 59.5, 59.6, 72.2, 75.5, 101.1, 106.4, 108.1, 119.1, 120.0, 120.1, 125.7, 126.9, 127.3, 127.7, 127.8, 127.9, 128.4, 128.9, 135.0, 139.8, 141.0, 141.5, 143.5, 146.3, 147.1, 147.7, 172.5, 211.7; IR 1734, 1752 cm^{-1}. Anal. Calcd for $C_{33}H_{27}NO_6$: C, 74.3; H, 5.1; N, 2.6. Found: C, 74.0; H, 5.0; N, 2.3.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1‴(3,4,5-Trimethoxyphenyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5i and 6i). A mixture of compounds **5i** and **6i** was obtained from the reaction of the enolate of **2** (prepared from 66 mg, 0.17 mmol) with a solution of 3,4,5-trimethoxybenzaldehyde (51 mg, 0.26 mmol, 150 mol %) in THF (1 mL) by following method C described above (reaction time, 5 h). Purification by flash chromatography (EtOAc/hexanes 1/2) gave 70 mg (70%) of **5i** and 10 mg (10%) of **6i**. **5i:** $[\alpha]^{20}_D = -122$ (*c* 1.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 2.87 (m, 1H), 3.25 (d, J = 18.7, 1H), 3.37 (d, J = 5.5, 1H), 3.43 (bs, 1H), 3.71 (m, 1H), 3.72 (s, 3H), 3.74 (s, 6H), 4.57 (d, J = 7.6, 1H), 6.30 (s, 2H), 7.10−7.35 (m, 11H), 7.59 (d, J = 7.7, 2H); ^{13}C NMR ($CDCl_3$) δ 51.4, 56.0, 56.5, 59.0, 60.5, 60.7, 73.3, 75.8, 119.9, 120.0, 125.7, 126.8, 127.3, 127.4, 127.7, 127.8, 128.4, 128.8, 128.9, 135.5, 137.6, 140.2, 140.9, 141.2, 144.1, 146.1, 153.1, 172.8, 213.6; IR (NaCl) 1736, 1751 cm^{-1}. Anal. Calcd for $C_{35}H_{33}NO_7$: C, 72.5; H, 5.7; N, 2.4. Found: C, 72.3; H, 5.7; N, 2.3. **6i:** $[\alpha]^{20}_D = -174$ (*c* 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.71 (s, 3H), 2.81 (m, 1H), 3.03 (t, J = 5.2, 1H), 3.26 (d, J = 17.5, 1H), 3.67 (m, 2H), 3.73 (s, 3H), 3.74 (s, 6H), 5.02 (t, J = 4.3, 1H), 6.35 (s, 2H), 7.13−7.46 (m, 11H), 7.62 (t, J = 8.0, 2H); ^{13}C NMR ($CDCl_3$) δ 51.3, 55.9, 56.0, 56.1, 59.2, 59.4, 60.7, 72.3, 75.6, 120.0, 125.7, 126.8, 127.3, 127.7, 127.8, 128.4, 128.9, 129.0, 136.7, 137.1, 139.9, 141.0, 141.5, 143.5, 146.2, 153.2, 172.6, 211.9; IR (NaCl) 1740, 1751 cm^{-1}. Anal. Calcd for $C_{35}H_{33}NO_7$: C, 72.5; H, 5.7; N, 2.4. Found: C, 72.2; H, 5.7; N, 2.3.

(2*S*,3*S*,1″*R*)- and (2*S*,3*S*,1″*S*)-3-[1″-(1-Naphthyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5j and 6j). A mixture of compounds **5j** and **6j** was obtained from the reaction of the enolate of **2** (prepared from 45 mg, 0.12 mmol) with a solution of 1-naphthaldehyde (24 μL, 0.18 mmol, 150 mol %) in THF

(1 mL) by following method C described above (reaction time, 2.5 h). Purification by flash chromatography (EtOAc/hexanes 1/4) gave 47 mg (75%) of **5j** and 11 mg (17%) of **6j**. **5j:** $[\alpha]^{20}_D = -139$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.20 (t, $J = 6.9$, 1H), 3.24 (d, $J = 17.9$, 1H), 3.36 (d, $J = 5.8$, 1H), 3.67 (d, $J = 17.9$, 1H), 3.75 (bs, 1H), 5.31 (d, $J = 7.8$, 1H), 7.06−7.44 (m, 15 H), 7.57−7.77 (m, 4H), 7.98 (m, 1H); ^{13} C NMR ($CDCl_3$) δ 51.0, 56.5, 58.1, 61.8, 71.6, 75.8, 120.0, 120.1, 123.3, 125.1, 125.6, 125.7, 125.8, 126.2, 126.8, 127.3, 127.6, 128.0, 128.3, 128.8, 128.9, 129.0, 130.6, 133.8, 134.8, 139.9, 141.0, 141.3, 143.5, 146.4, 171.9, 214.0; IR 1740, 1753 cm^{-1}. Anal. Calcd for $C_{36}H_{29}NO_4$: C, 80.1; H, 5.4; N, 2.6. Found: C, 79.9; H, 5.2; N, 2.3. **6j:** $[\alpha]^{20}_D = -198$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.93 (d, $J = 4.3$, 1H), 3.13 (dd, $J = 3.1$, 5.9, 1H), 3.19 (d, $J = 17.3$, 1H), 3.63 (d, $J = 17.3$, 1H), 3.89 (d, $J = 5.9$, 1H), 5.98 (bt, $J = 3.1$, 1H), 7.08−7.83 (m, 20H); ^{13} C NMR ($CDCl_3$) δ 51.0, 56.3, 58.3, 59.1, 68.3, 75.8, 120.0, 120.1, 121.9, 123.0, 125.1, 125.7, 126.6, 127.0, 127.3, 127.7, 127.9, 128.0, 128.3, 128.4, 128.8, 129.0, 129.3, 136.2, 139.7, 141.0, 141.8, 143.1, 146.6, 171.8, 211.7; IR 1740, 1753 cm^{-1}. Anal. Calcd for $C_{36}H_{29}NO_4$: C, 80.1; H, 5.4; N, 2.6. Found: C, 80.8; H, 5.2; N, 2.5.

(2*S*,3*S*,1″*R*)-3-[1″-(Isopropyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5k). Compound **5k** was obtained from the reaction of the enolate of **2** (prepared from 140 mg, 0.365 mmol) with isobutyraldehyde (54 μL, 0.602 mmol, 165 mol %, freshly distilled from CaH_2) by following method B described above. Purification by flash chromatography (EtOAc/hexanes 1/5) gave 120 mg (72%) of **5k:** $[\alpha]^{20}_D = -65°$ (*c* 1.72, $CHCl_3$); IR (NaCl) 2960, 1746, 1455, 745, 502 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.71 (d, $J = 6.5$ Hz, 3H), 0.80 (d, $J = 6.5$ Hz, 3H), 1.53−1.66 (m, 1H), 2.48 (dd, $J_{32} = 4.5$ Hz, $J_{31'} = 6.5$ Hz, 1H), 3.05 (s, 3H), 3.20 (dd, $J_{1'3} = 6.7$ Hz, $J_{1'2'} = 5.9$ Hz, 1H), 3.42 (d, $J = 4.4$ Hz, 1H), 3.45 (d, $J = 18.5$ Hz, 1H), 3.78 (d, $J = 17.6$ Hz, 1H), 7.16−7.67 (m, 13H), ^{13}C NMR ($CDCl_3$) δ 15.1, 18.6, 30.2, 50.7, 54.1, 55.1, 61.4, 74.8, 75.3, 119.4, 119.6, 124.3, 124.8, 125.7, 126.1, 126.7, 127.0, 127.3, 127.8, 128.2, 139.7, 140.3, 140.7, 143.8, 145.4, 171.8, 213.1. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 76.5; H, 6.4; N, 3.1. Found: C, 76.3; H, 6.4; N, 3.2.

(2*S*,3*S*,1″*R*)-3-[1″-(3-Methylbutyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5l). Compound **5l** was obtained from the reaction of the enolate of **2** (prepared from 43 mg, 0.11 mmol) with isovaleraldehyde (18 μL, 0.17 mmol, 150 mol %, freshly distilled from CaH_2) by following method C described above (reaction time, 5 h). Purification by flash chromatography (EtOAc/hexanes 1/4) gave 48 mg (91%) of **5l:** $[\alpha]^{20}_D = -132$ (*c* 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, $J = 6.6$, 3H), 0.86 (d, $J = 6.6$, 3H), 1.06 (m, 1H), 1.42 (m, 1H), 1.76 (m, 1H), 2.44 (t, $J = 5.3$, 1H), 2.89 (bs, 1H), 3.12 (s, 3H), 3.52 (d, $J = 17.7$, 1H), 3.53 (d, $J = 4.4$, 1H), 3.73 (m, 1H), 3.86 (d, $J = 17.7$, 1H), 7.23−7.32 (m, 5H), 7.40−7.48 (m, 6H), 7.73 (d, $J = 7.5$, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 23.5, 24.1, 43.8, 51.5, 56.0, 57.6, 61.9, 69.6, 75.6, 120.1, 120.3, 125.6, 126.8, 127.4, 127.5, 127.7, 128.1, 128.6, 129.0, 129.1, 140.3, 141.0, 141.2, 144.4, 145.9, 172.9, 213.1; IR (NaCl) 1740, 1751 cm^{-1}. Anal. Calcd for $C_{30}H_{31}NO_4$: C, 76.7; H, 6.7; N, 3.0. Found: C, 76.4; H, 6.4; N, 2.9.

(2*S*,3*S*,1″*R*)-3-[1″-(1-Cyclohexyl)-1″-hydroxymethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (5m). Compound **5m** was obtained from the reaction of the enolate of **2** (prepared from 70 mg, 0.18 mmol) with cyclohexanecarboxaldehyde (33 μL, 0.27 mmol, 150 mol %, freshly distilled from CaH_2) by following method C described above (reaction time, 6 h). Purification by flash chromatography (EtOAc/hexanes 1/4) gave 80 mg (88%) of **5m:** $[\alpha]^{20}_D = -73$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2-D_2O) δ 0.83−1.26 (m, 6H), 1.38−1.61 (m, 5H), 2.51 (dd, $J = 4.7$, 4.0, 1H), 2.99 (s, 3H), 3.25 (t, $J = 6.2$, 1H), 3.38 (d, $J = 17.6$, 1H), 3.40 (d, $J = 4.7$, 1H), 3.72 (d, $J = 17.6$, 1H), 7.16−7.40 (m, 11H), 7.66 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.2, 26.5, 26.6, 27.4, 30.1, 41.0, 52.0, 54.8, 56.7, 62.8, 76.3, 76.4, 120.5, 120.7, 126.1, 127.4, 127.8, 128.1, 128.2, 128.5, 129.0, 129.4, 129.5, 140.8, 141.5, 141.6, 144.8, 146.4, 173.3, 214.1; IR (NaCl) 1738, 1751 cm^{-1}. Anal. Calcd for $C_{32}H_{33}NO_4$: C, 77.6; H, 6.7; N, 2.8. Found: C, 77.4; H, 7.0; N, 2.8.

(2*S*,3*S*,4*S*,1″*R*)-3-[1″-Phenyl-1″-hydroxymethyl]-4-hydroxy-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (7a). $NaBH_4$ (27 mg, 0.679 mmol, 250 mol %) was added to a precooled (−78 °C) solution of **5a** (133 mg, 0.272 mmol) in MeOH/THF (1/1, 2.2 mL). The resulting suspension was stirred at −78 °C for 4 h and then H_3PO_4 (10%, 0.25 mL) was added. The reaction mixture was allowed to warm to room temperature. The resulting suspension was partitioned between H_2O (20 mL) and CH_2Cl_2 (25 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes 2/3) to give 131 mg (98%) of **7a** as a white foam. $[\alpha]^{28}_D = 172.5°$ (*c* 0.61, $CHCl_3$); IR (NaCl) 3585, 1729, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (d, $J = 2.9$ Hz, 1H), 2.26 (br d, $J = 9.9$ Hz, 1H), 2.43 (d, $J = 2.7$ Hz, 1H), 2.98 (s, 3H), 3.36 (dd, $J = 3.8$ and 10.0 Hz, 1H), 3.51 (d, $J = 10.1$ Hz, 1H), 3.79 (br d, $J = 9.9$ Hz, 1H), 4.23 (br d, $J = 10.8$ Hz, 1H), 4.40 (br d, $J = 8.5$ Hz, 1H), 6.61−7.81 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 51.5, 55.1, 59.2, 61.0, 73.0, 75.0, 75.4, 119.9, 120.3, 126.8, 127.0, 127.2, 127.4, 127.5, 127.8, 128.1, 128.3, 128.5, 128.9, 139.0, 141.3, 141.7, 142.4, 145.4, 147.9, 177.4. Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.2; H, 6.0; N, 2.9. Found: C, 78.4; H, 6.1; N, 2.9.

(2*S*,3*S*,4*S*,1″*R*)-3-[1″-Isopropyl-1″-hydroxymethyl]-4-hydroxy-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (7b). The same procedure as for **5k** was used; 75 mg of **5k** (0.165 mmol) afforded 73 mg (98%) of **7k** as a white foam. **7k:** $[\alpha]^{20}_D = +205°$ (*c* 1.25, $CHCl_3$); IR (NaCl) 3416, 1733, 1459, 749, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.55 (d, $J = 6.9$ Hz, 3H), 0.59 (d, $J = 6.9$ Hz, 3H), 1.18−1.31 (m, 1H), 1.32−1.60 (br d, 1H), 1.88 (d, $J = 8.5$ Hz), 2.52−2.56 (m, 2H), 3.12−3.15 (m, 1H), 3.17 (s, 3H), 3.37 (d, $J = 10.4$ Hz, 1H), 3.99 (br s, 1H), 4.23−4.24 (m, 1H), 7.1−7.8 (m, 13H), ^{13}C NMR ($CDCl_3$) δ 14.4, 20.0, 29.5, 50.9, 55.1, 55.6, 61.4, 72.9, 75.4, 76.0, 120.1, 120.2, 126.4, 127.2, 127.4, 127.5, 127.6, 128.2, 128.4, 128.8, 139.2, 141.4, 141.8, 143.8, 144.8, 147.8, 177.4. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 76.1; H, 6.8; N, 3.1. Found: C, 76.0; H, 6.9; N, 3.3.

(2*S*,3*S*,4*S*,1″*S*)-3-[1″-Phenyl-1″-hydroxymethyl]-4-hydroxy-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (9). By following the same procedure described above for **5a**, starting from **6a**, 65 mg (96%) of **9** was obtained as a white foam. $[\alpha]^{28}_D = 183.0°$ (*c* 0.46, $CHCl_3$); IR (NaCl) 3200, 1730, 1715, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (d, $J = 3.3$ Hz, 1H), 2.25 (d, $J = 9.2$ Hz, 1H), 3.17 (dd, $J = 3.9$ and 10.0 Hz, 1H), 3.29 (d, $J = 2.2$ Hz, 1H), 3.30 (s, 3H), 3.36 (d, $J = 10.2$ Hz, 1H), 3.61 (br d, $J = 10.3$ Hz, 1H), 3.77 (dd, $J = 3.1$ and 9.2 Hz, 1H), 4.08 (br d, $J = 11.8$ Hz, 1H), 7.09−7.81 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 52.0, 55.5, 59.4, 61.6, 72.8, 74.6, 75.6, 120.2, 120.4, 126.3, 126.5, 127.0, 127.2, 127.4, 127.5, 128.4, 128.5 (2C), 128.7; 128.9, 139.7, 141.6, 141.8, 145.6, 147.7, 177.9. Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.2; H, 6.0; N, 2.9. Found: C, 78.4; H, 6.1; N, 2.9.

(1*S*,4*S*,6*R*,9*S*)-8-Aza-9-carboxymethyl-4,4-dimethyl-2-phenyl-3,5-dioxa-*N*-(9′-phenylfluoren-9′-yl)bicyclo [3.4.0^{1,6}]-nonane (8a). A solution of **7a** (62 mg, 0.126 mmol) in DMF/acetone (3/1, 0.4 mL) and 2.2-dimethoxypropane (40 μL, 0.315 mmol, 250 mol %) was stirred with PPTS (2 mg, 0.001 mmol, 7 mol %) at room temperature for 36 h. The mixture was partitioned between H_2O (5 mL) and ether (2 × 8 mL). The combined organic layer was washed with brine, dried, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes 1/6) to afford 62 mg (93%) of **8a** as a white foam. $[\alpha]^{24}_D = 207.8°$ (*c* 0.54, $CHCl_3$); IR (NaCl) 2951, 1748 (CO), 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.44 (s, 3H), 2.31 (c, $J = 10.3$ Hz, 1H), 2.43 (s, 3H), 2.58 (d, $J = 10.7$ Hz, 1H), 3.47 (m, 2H), 3.75 (dd, $J = 10.2$ and 17.5 Hz, 1H), 4.40 (d, $J = 10.2$ Hz, 1H), 6.93−7.79 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 20.0, 29.8, 50.7, 51.8, 53.7, 60.2, 76.7, 77.6, 100.7, 119.8, 120.2, 125.5, 127.1, 127.2, 127.4, 127.5, 128.1, 128.3 (2C), 128.4, 129.0, 138.3, 139.0, 142.5, 143.7, 146.8, 147.5,

174.2. Anal. Calcd for $C_{35}H_{33}NO_4$: C, 79.1; H, 6.3; N, 2.6. Found: C, 79.4; H, 6.3; N, 2.7.

(1*S*,4*S*,6*R*,9*S*)-8-Aza-9-carboxymethyl-4,4-dimethyl-2-isopropyl-3,5-dioxa-*N*-(9′-phenylfluoren-9′-yl)bicyclo-[3.4.0^{1,6}]nonane (8k). The same procedure as for **7a** was used; 63 mg of **7k** (0.138 mmol) afforded 62 mg (93%) of **8k:** $[\alpha]^{21}_D = +215°$ (*c* 1.11, $CHCl_3$); IR (NaCl) 1756, 1737, 1602, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.55 (d, $J = 6.8$ Hz, 3H), 0.68 (d, $J = 6.6$ Hz, 3H), 1.07−1.38 (m, 1H), 1.17 (s, 3H), 1.26 (s, 3H), 1.91 (c, $J = 10$ Hz, 1H), 2.50 (d, $J = 10.7$ Hz, 1H), 3.19 (s, 3H), 3.21−3.28 (m, 2H), 3.37−3.40 (m, 1H), 3.43−4.47 (m, 1H), 7.01−7.73 (m, 13H). ^{1}H NMR (C_6D_6) δ 0.17−0.27 (m, 1H), 0.45 (d, $J = 6.9$ Hz), 0.59 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 3H), 1.16 (s, 3H), 2.09 (c, $J = 10.2$ Hz, 1H), 2.59 (d, $J = 10.7$ Hz, 1H), 2.79 (s, 3H), 2.98 (dd, $J = 2.2$ Hz, $J = 10.2$ Hz, 1H), 3.23−3.30 (m, 2H), 3.32−3.45 (m, 1H), 6.53−7.44 (m, 13H).^{13}C NMR ($CDCl_3$) δ 13.0, 18.4, 18.8, 28.7, 46.8, 50.4, 52.6, 59.3, 70.6, 76.5, 76.7, 98.6, 118.8, 119.1, 124.5, 126.0, 126.2, 126.3, 127.0, 127.4, 127.8, 138.1, 141.3, 142.6, 145.6, 146.7, 174.3. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 77.2; H, 7.0; N, 2.8. Found: C, 77.4; H, 6.8; N, 2.8.

(2*S*,3*R*)- and (2*S*,3*S*)-3-Allyl-4-oxo-*N*-(9′-phenylfluoren-9′-yl)-pyrrolidine-2-carboxylic Acid Methyl Ester (10a and 11a). *n*-BuLi (0.22 mL, 0.33 mmol, 105 mol %, 1.5 M in hexanes) was added to a cold (−55 °C) solution of **2** (120 mg, 0.31 mmol) in THF/HMPA (1.2 mL/0.12 mL). The resulting solution was stirred at −55 °C for 1 h, then allyl iodide (86 μL, 0.94 mmol, 300 mol %) was added. The reaction mixture was stirred while the temperature was allowed to reach −10 °C (2 h). H_3PO_4 (10%, 0.3 mL) was added and the reaction mixture was poured onto ether and washed with H_2O, aqueous saturated sodium thiosulfate, and brine. The organic layer was dried and concentrated to afford a residue that was purified by column chromatography (EtOAc/hexanes 1/8) to provide 81 mg of **10a** (61%) and 40 mg (30%) of **11a** as white foams. **10a:** $[\alpha]^{20}_D = 27.8°$ (*c* 0.85, $CHCl_3$); IR (NaCl) 2925, 1756, 1730, 1444 cm^{-1}; ^{1}H NMR (C_6D_6) δ 2.07 (m, 1H), 2.33 (m, 1H); 2.47 (m, 1H), 2.84 (s, 3H), 3.53 (d, $J = 17.2$ Hz, 1H), 3.60 (d, $J = 4.0$ Hz, 1H), 3.94 (d, $J = 17.3$ Hz, 1H), 4.86 (m, 2H), 5.49 (m, 1H), 6.96−7.57 (m, 13H); ^{13}C NMR (C_6D_6) δ 33.9, 50.8, 52.4, 55.4, 63.0, 75.9, 117.4, 120.1, 120.3, 126.1, 126.6, 127.0, 127.2, 128.8, 128.9, 134.8, 140.7, 141.5, 142.4, 145.4, 147.2, 172.9, 211.3. Anal. Calcd for $C_{28}H_{25}NO_3$: C, 79.4; H, 6.0; N, 3.3. Found: C, 79.1; H, 6.1; N, 3.3. **11a:** $[\alpha]^{19}_D = 86.1°$ (*c* 0.56, $CHCl_3$); IR (NaCl) 2925, 1755, 1725, 1444 cm^{-1}; ^{1}H NMR (C_6D_6) δ 2.33 (m, 3H, HC-3), 2.51 (m, 3H), 3.42 (d, $J = 17.0$ Hz, 1H), 3.72 (d, $J = 7.6$ Hz, 1H), 3.75 (d, $J = 16.9$ Hz, 1H), 4.56 (m, 2H), 5.33 (m, 1H), 6.73−7.52 (m, 13H); ^{13}C NMR (C_6D_6) δ 29.4, 50.3, 51.7, 54.0, 62.2, 75.3, 116.4, 120.0, 120.2, 120.3, 125.3, 125.6, 125.9, 126.7, 127.0, 128.9 (2C), 129.0, 129.5, 133.2, 134.8, 135.5, 140.1, 140.3, 141.6, 142.4, 145.9, 147.5, 151.6, 171.3, 211.1. Anal. Calcd for $C_{28}H_{25}NO_3$: C, 79.4; H, 5.6; N, 3.3. Found: C, 79.6; H, 6.0; N, 3.3.

(2*S*,3*R*)- and (2*S*,3*S*)-3-[1″-Carboxyethylmethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (10b and 11b). The same procedure as for **10a** and **11a** was used; 59 mg (0.15 mmol) of **2** gave 40 mg (55%) of **10b** and 22 mg (29%) of **11b** as white foams. **10b:** $[\alpha]^{20}_D = -37.8°$ (*c* 0.63, $CHCl_3$); IR (NaCl) 1759, 1735, 1739, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, $J = 7.2$ Hz, 3H), 2.46 (m, 2H), 2.90 (m, 1H), 3.12 (s, 3H), 3.43 (d, $J = 17.7$ Hz, 1H), 3.45 (d, $J = 6.6$ Hz, 1H), 3.78 (d, $J = 17.8$ Hz, 1H), 4.01 (c, $J = 7.2$ Hz, 2H), 7.25−7.73 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 13.9, 32.9, 49.0, 51.5, 55.9, 60.9, 63.8, 76.0, 120.0, 120.3, 126.1, 127.1, 127.3, 127.8, 127.9, 128.0, 128.5, 129.0, 140.6, 141.1, 141.6, 144.6, 146.1, 170.5, 172.9, 211.5. Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.2; H, 5.8; N, 3.0. Found: C, 74.4; H, 5.9; N, 3.1. **11b:** $[\alpha]^{21}_D = -142.6°$ (*c* 0.7, $CHCl_3$); IR (NaCl) 1760, 1735, 1740, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.17 (t, $J = 7.2$ Hz, 3H), 1.83 (dd, $J = 8.5$ y 17.6 Hz, 1H), 2.43 (m, 1H), 2.57 (dd, $J = 17.6$ y 5.2 Hz, 1H), 3.06 (s, 3H), 3.51 (d, $J = 17.6$ Hz, 1H), 3.69 (d, $J = 7.5$ Hz, 1H), 3.74 (d, $J = 17.6$ Hz, 1H), 4.09 (c, $J = 7.1$ Hz, 2H), 7.17−7.67 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 14.0, 32.7, 51.4, 53.2, 55.9, 60.6, 63.8, 74.6, 120.0, 120.3, 126.1, 127.1, 127.3, 127.8, 127.9, 128.0, 128.5, 129.0, 140.6, 141.1, 141.6, 144.6, 146.1, 170.5, 173.1, 211.8. Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.2; H, 5.8; N, 3.0. Found: C, 74.4; H, 5.9; N, 3.0.

(2*S*,3*R*)- and (2*S*,3*S*)-3-[2″-Carboxymethylethyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (10c and 11c). The same procedure as for **10a** and **11a** was used; 65 mg (0.17 mmol) of **2** gave 44 mg (55%) of **10c** and 21 mg (26%) of **11c** as white foams. **10c:** $[\alpha]^{19}_D = -42.6°$ (*c* 1.0, $CHCl_3$); IR (NaCl) 2930, 1750, 1740, 1738, 1444 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.36 (m, 2H), 1.59 (m, 1H), 1.96 (m, 1H), 2.45 (m, 1H), 2.85 (s, 3H), 3.29 (s, 3H), 3.48 (d, $J = 4.5$ Hz, 1H), 3.51 (d, $J = 18.0$ Hz, 1H), 3.87 (d, $J = 17.3$ Hz, 1H), 6.97−7.57 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 24.4, 31.1, 51.0, 51.4, 51.6, 55.2, 64.0, 75.2, 120.1, 120.3, 125.4, 125.7, 127.3, 127.6, 128.1, 128.9, 129.0, 140.4, 141.2, 141.5, 144.5, 146.3, 171.7, 173.0, 212.9. Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.2; H, 5.8; N, 3.0. Found: C, 73.9; H, 5.9; N, 2.9. **11c:** $[\alpha]^{20}_D = -134.3°$ (*c* 0.9, $CHCl_3$); IR (NaCl) 2932, 1752, 1740, 1735, 1444 cm^{-1}; ^{1}H NMR (C_6D_6) δ 2.09 (m, 4H), 2.60 (m, 1H), 2.78 (s, 3H), 3.25 (s, 3H), 3.65 (d, $J = 17.0$ Hz, 1H), 3.98 (d, $J = 16.0$ Hz, 1H), 4.00 (d, $J = 8.1$ Hz, 1H), 6.98−7.49 (m, 13H), ^{13}C NMR (C_6D_6) δ 20.6, 35.6, 50.5, 50.7, 50.9, 54.2, 62.6, 75.7, 120.2, 120.3, 125.7, 127.1, 128.8, 128.9, 142.3, 171.5, 175.8, 211.7. Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.2; H, 5.8; N, 3.0. Found: C, 73.9; H, 5.9; N, 3.0.

(2*S*,3*R*)-3-Deutero-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (10d). Method C was used for enolate generation. Quenching the reaction with CD_3OD (excess) at −55 °C afforded **10d** (83% yield, 85% D incorporation by ^{1}H NMR). **10d:** ^{1}H NMR ($CDCl_3$) δ 2.20 (bs, 1H), 3.20 (s, 3H), 3.48 (d, $J = 17.9$ Hz, 1H), 3.67 (d, $J = 2.9$, 1H), 3.77 (d, $J = 17.9$ Hz, 1H), 7.23−7.48 (m, 11H), 7.71 (m, 2H).

Deprotonation−Reprotonation of a Mixture of 10a/11a. Preparation of 11a. *n*-BuLi (58 μL, 0.1 mmol, 110 mol %, 1.8 M in hexanes) was added to a cold (−78 °C) solution of a 2/1 mixure of **10a** and **11a** (40 mg, 0.95 mmol) in THF (0.8 mL). The resulting solution was stirred at −78 °C for 90 min. Then HOAc (0.1 mL) was added. The reaction was poured onto ether and was washed with water. The organic layer was dried, filtered, and concentrated. The residue was purified by chromatography (EtOAc/hexanes 1/5), to afford pure **11a** (34 mg, 85%) as a white foam.

Deprotonation−Reprotonation of a Mixture of 10b/11b. Preparation of 11b. The same procedure as for **11a** was used; 40 mg (0.85 mmol) of a 1/1 mixture of **10b** and **11b** provided 34 mg (85%) of **11b** as a white foam.

Deprotonation−Reprotonation of a Mixture of 10c/11c. Preparation of 11c. The same procedure as for **11a** was used; 50 mg (0.106 mmol) of a 1/1 mixture of **10c** and **11c** provided 45 mg (90%) of **11b** as a white foam.

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