On the Stereoselectivity of the Reaction of *N*-(9-Phenylfluoren-9-yl)aspartate Enolates with Electrophiles. Synthesis of Enantiomerically Pure 3-Hydroxy-, 3-Amino-, and 3-Hydroxy-3-methylaspartates

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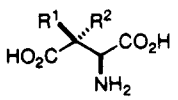
We have developed efficient and stereoselective preparations of enantiomerically pure (3*R*)- and (3*S*)-*N*-Pf-3-hydroxy- and *N*-Pf-3-aminoaspartates by reaction of *N*-Pf-aspartate enolates with electrophilic hydroxylating or aminating reagents. The stereoselectivity of the hydroxylation and amination reactions was shown to be dependent on the structure of the enolate (which is strongly affected by the presence of strong metal complexing agents) and whether the electrophile is able to complex the enolate counterion in the transition state of the reaction. We have also developed a regioselective preparation of enantiomerically pure *N*-Pf-3-hydroxy-3-methylaspartates, albeit with only modest stereoselectivity.

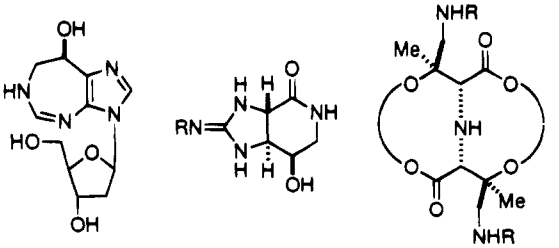
Introduction

2-Amino-3-hydroxy- and 2,3-diamino acids[1] have attracted a great deal of synthetic attention during the last decade.[2] This interest has stemmed from the biological roles played by these compounds[3] and from their dense functionalization, which makes them useful synthetic precursors for other biologically active molecules.[4] Particularly attractive members of this class of amino acids, and among the less synthetically accessible ones, are the aspartic acid derivatives **1**–**3**.



1a. R^1 = H, R^2 = OH
1b. R^1 = OH, R^2 = H
2a. R^1 = H, R^2 = NH_2
2b. R^1 = NH_2, R^2 = H
3a. R^1 = CH_3, R^2 = OH
3b. R^1 = OH, R^2 = CH_3

We became interested in compounds **1**–**3** not only because of the biological activities displayed by some of them,[5] but because of their interest as enantiomerically pure synthetic intermediates as well.[2a,6] We envisioned **1b** as an attractive intermediate for the synthesis of the antileukemic agent pentostatin (**4**),[7] **2b** as a suitable precursor for the streptothricin antibiotics (**5**),[8] and **3b** as a useful synthon for the core portion of the antitumor antibiotic carzinophilin A (**6**).[9]



4 **5** **6**

The general syntheses of 2-amino-3-hydroxy-[4] and 2,3-diamino acids[2b] are not directly applicable for the preparation of 3-substituted aspartic acid derivatives, such as **1**–**3**. In view of this fact, several specific, stereoselective approaches to the hydroxyaspartates **1a** and **1b** have been developed,[2a,10] but methods for the synthesis of the amines **2a,b** and the tertiary alcohols **3a,b** are lacking.

Rapoport and co-workers have pioneered the use of the 9-phenylfluoren-9-yl (Pf) group for protection of the amino group and of the stereogenic center in amino acid chemistry.[11,12] By extending their methodology for the chirospecific and regioselective alkylation of *N*-Pf-aspartates, we have recently developed a highly stereoselective, stereodivergent synthesis of enantiomerically pure de-

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(1) For the sake of clarity all compounds are numbered as derivatives of aspartic acid.

(2) (a) Palomo, C.; Cabré, F.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4819. (b) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017, and references therein. (c) Wagner, R.; Tilley, J. W. *J. Org. Chem.* **1990**, *55*, 6289. (d) Wagner, R.; Tilley, J. W.; Lovey, K. *Synthesis* **1990**, 785.

(3) (a) 3-Hydroxy-2-amino acids act as enzyme inhibitors: Walborski, H. M.; Baum, M.; Loncrini, D. F. *J. Am. Chem. Soc.* **1955**, *77*, 3637. (b) 2,3-Diamino acids are components of certain antibiotics or act as metal complexing agents.[2b]

(4) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553, and references therein.

(5) **1a** is present in several proteins involved in the blood clotting cascade: (a) Fernlund, P.; Stenflo, J. *J. Biol. Chem.* **1983**, *258*, 12509. **1a,b** and **2a,b** have been isolated from several microorganisms: (b) Hansson, T. G.; Kihlberg, J. O. *J. Org. Chem.* **1986**, *51*, 4490. (c) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barret, G. C., Ed.; Chapman and Hall: London, 1985; Chapter 4.

(6) Application of derivatives of **1a,b** in synthesis: (a) Mattingly, P. G.; Miller, M. J.; Cooper, R. D. G.; Daugherty, B. W. *J. Org. Chem.* **1983**, *48*, 3556. (b) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771.

(7) Truong, T. V.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 6090.

(8) (a) Kusumoto, S.; Imaoka, S.; Kambayashi, Y.; Shiba, T. *Tetrahedron Lett.* **1982**, *23*, 2961. (b) Borders, D. B.; Sax, K. J.; Lancaster, J. E.; Hausmann, W. K.; Mitscher, L. A.; Wetzel, E. R.; Patterson, E. L. *Tetrahedron* **1970**, *26*, 3123.

(9) Lwon, J. W.; Hanstock, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 3213.

(10) Sardina, F. J.; Paz, M. M.; Fernández-Megía, E.; de Boer, R. F.; Alvarez, M. P. *Tetrahedron Lett.* **1992**, *33*, 4637, and references therein.

(11) (a) Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159. (b) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068. (c) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164. (d) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239.

(12) (a) Lubell, W.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *54*, 3824. (b) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990.

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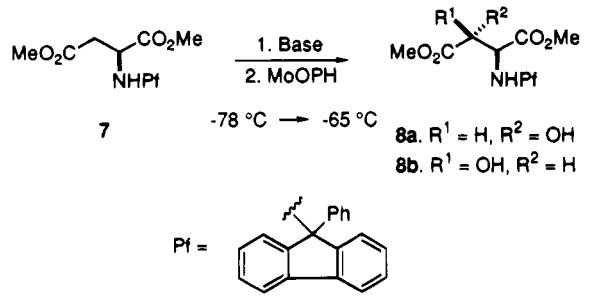
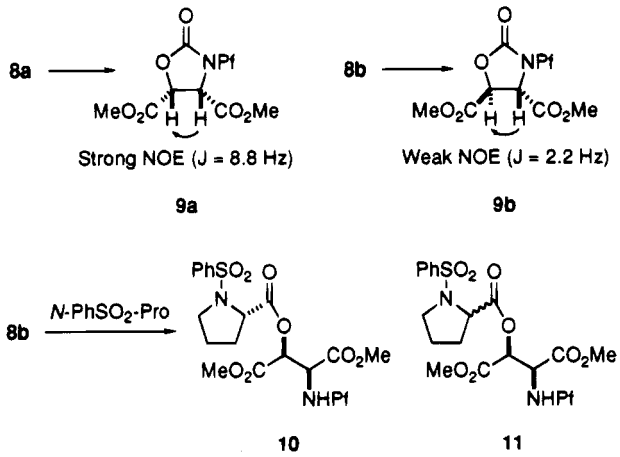
Scheme 1



Scheme 2



rivatives of **1a** and **1b**.[10] We now wish to present the application of this methodology for the preparation of derivatives of **1**–**3** along with some interesting results concerning the stereoselectivity of the reaction of *N*-Pf-aspartate enolates with different electrophiles.

Results and Discussion

Hydroxylation and Amination of *N*-Pf-aspartate Enolates. Synthetic Aspects. Our approach to the *N*-protected dimethyl esters of **1a,b** is shown in Scheme 1; it consists of the regioselective deprotonation of *N*-Pf-aspartate **7** at C-3, followed by the stereoselective hydroxylation of the resulting enolate with MoOPH.[10]

The stereochemistry of the resulting 3-hydroxyaspartates **8a,b** was assigned by analysis of the ^{1}H NMR spectra (NOE effects and coupling constants) of the cyclic carbamates **9a,b**. The enantiomeric purity of **8b** was determined by its derivatization with both L- and D,L-*N*-(phenylsulfonyl)proline, which gave the diastereomeric esters **10** and **11**.[10]

As can be seen from the results shown in Table 1, the configuration of the newly created asymmetric center was highly dependent on the reaction conditions: the nature of the base[13] and cosolvents used and the ionization state of the Pf-amino group (entries 12 and 13) all affected the stereochemical outcome of the reaction. Nevertheless, the hydroxylation reaction could be manipulated to very selectively afford either stereoisomer of **8**: **8a** could be obtained in 60% isolated yield (83% yield based on recovered starting material, entry 12), while **8b** was obtained in 74% yield (entry 6).

A completely different stereochemical outcome was obtained when an oxaziridine [*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, Davis' reagent][14] was substituted for MoOPH as the hydroxylating agent: under all the conditions tested (Li^+ or K^+ bases, with or without HMPA, DMPU or n-BuLi) a ≈1/1 ratio of **8a**/**8b** was obtained.

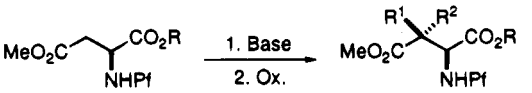
(13) BrMgHMDS did not lead to the formation of hydroxylated products.

Table 1

entry	base (mol %)	cosolvent	8b/8a	yield (%)
1	KHMDS (180)	none	3/1	90[a]
2	LHMDS (300)	none	1/8	65[a]
3	LDA (300)	none	2/1	45[a]
4	LTMP (180)	none	1/2	22[a]
5	LHMDS (300)	DMPU	8/1	92[a]
6	LHMDS (300)	HMPA	11/1	74[b]
7	LHMDS (300)	DME	1/2.5	70[a]
8	LHMDS (300)	TMEDA	1/8	80[a]
9	LHMDS (300)	PMDET[c]	1/5	75[a]
10	KHMDS (180)	18-crown-6	*d*	
11	LHMDS (300)	12-crown-4	*d*	
12	n-BuLi (100)/LHMDS (300)	none	1/20	60 (83)[b]
13	n-BuLi (100)/LHMDS (300)	HMPA	2/1	95[a]

[a] Yield of the mixture of epimers. [b] Yield of pure major epimer (yield based on recovered **7**). [c] *N,N,N′,N″,N″*-Pentamethyldiethylenetriamine. [d] No reaction.

Scheme 3



12a. R = *t*-Bu
12b. R = H

13. R = *t*-Bu
14. R = H
a. R^1 = H, R^2 = OH
b. R^1 = OH, R^2 = H

12a → 13

Base (cosolv.)	Oxidant	13b/13a	Yield[a]
KHMDS	MoOPH	7/1	95% (65%)[b]
LHMDS	MoOPH	-	-
LHMDS (HMPA)	MoOPH	4/1	70%
KHMDS	Davis' oxaz.	1/2	98%

12b → 14

Base (cosolv.)	Oxidant	14b/14a	Yield[a]
KHMDS	MoOPH	2/1	30%
LHMDS or LDA	MoOPH	-	-
LHMDS (HMPA)	MoOPH	-	-
KHMDS	Davis' oxaz.	7/1	86%
LHMDS	Davis' oxaz.	1/4	80%

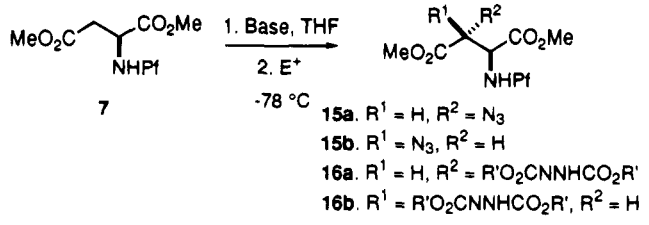
[a] Key: (a) yield of the mixture of epimers; (b) yield of pure **13b**.

In view of the number and complexity of the factors that affected the stereoselection in the reaction of the enolates of *N*-Pf-aspartate **7** with hydroxylating reagents, a study of the behavior of other differently substituted *N*-Pf-aspartates was undertaken. We chose the *t*-butyl ester **12a** and the acid **12b** due to their possible application for the preparation of 3-hydroxyaspartates adequately protected for peptide synthesis.[2c,d] The results of the hydroxylation of **12a,b** are shown in Scheme 3.

The *t*-butyl ester **12a** showed results analogous to those of the methyl ester **7**, with the exception that the enolate derived from **12a** and LHMDS (with or without n-BuLi) did not react with MoOPH (up to −20 °C). The assignment of the stereochemistry of **13a,b** was carried out by comparison of their coupling constants ($J_{2,3}$) with those shown by the dimethyl esters **8a,b** (molecular mechanics calculations show that the preferred conformations of **8a,b** are parallel to those of **13a,b**).

(14) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

Scheme 4



Base (cosolv.)	16a/16b (R' = *t*-Bu)	Yield	16a/16b (R' = Bn)	Yield
LHMDS	2.5/1	83% [a]	2/1	79% [a]
BuLi/LHMDS	2.3/1	85% [a]	1/1	85% [a]
KHMDS	2/1	82% [a]	1/1	80% [a]
LHMDS (HMPA)	30/1	80% (97%) [b]	18/1	75% (86%) [b]

E^+ = Trisyl azide or $R'O_2C\text{-}N{=}N\text{-}CO_2R'$

[a] Key: (a) yield of the mixture of epimers; (b) yield of pure **16a** (yield based on recovered **7**).

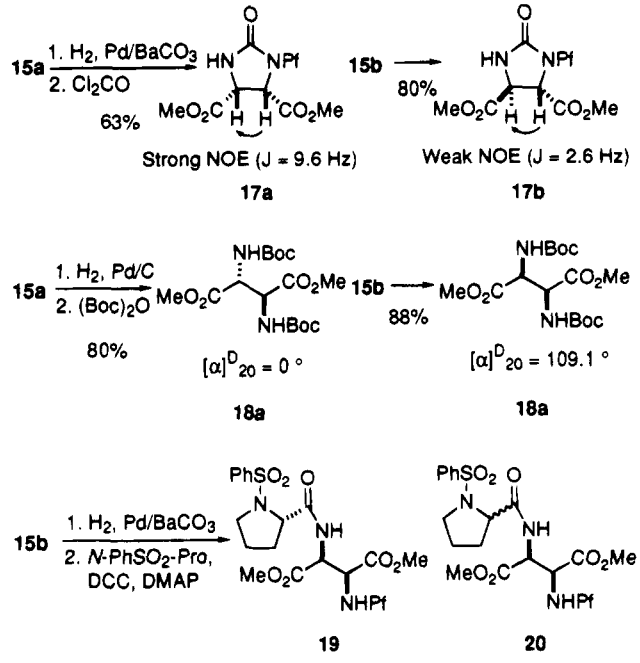
The behavior of the acid **12b** markedly differed from that of the diesters **7** and **12a**, as its Li^+ enolates were unreactive towards MoOPH, but, in any case, both the *t*-butyl ester **12a** and the acid **12b** could be stereodivergently hydroxylated, although with stereoselectivities lower than those obtained with the dimethyl ester **7**. The assignment of the stereochemistry of **14a,b** was carried out by chemical correlation (by methylation with CH_2N_2) with the dimethyl esters **8a,b**.

The desire to prepare the amino aspartates **2a,b** provided us with the opportunity to further study the control of the stereoselection in the reaction of the *N*-Pf-aspartate enolates with electrophiles. We chose 2,4,6-triisopropylbenzenesulfonyl (trisyl) azide and di-*t*-butyl- (DTBAD) and dibenzylazodicarboxylate (DBAD) as electrophilic aminating reagents, since their reactions with ester enolates are well documented.[15,16] The results of the amination reactions are shown in Scheme 4.

The formation of the azides **15a,b** displayed a very low level of stereoselection, since ≈1/1 mixtures of epimers were obtained under all the conditions tested (LHMDS with or without HMPA, LHMDS/BuLi or KHMDS). Despite this lack of selectivity, an efficient, selective preparation of (3*R*)- and (3*S*)-azidoaspartates was achieved due to the facts that **15a,b** are very easily separated (crystallization of a 1/1 mixture of **15a,b** gives pure **15b**) and that **15a** and **15b** can be epimerized (to give a ≈1/1 mixture) by treatment with Et_3N (DMSO, 60 °C), thus, a mixture of **15a,b** could be efficiently converted to either epimer by crystallisation followed by epimerization of the unwanted isomer. After three cycles of crystallization–epimerization **15b** could be obtained in 80% yield, while **15a** (approximately 92–95% pure) was obtained in 75% yield.

The stereochemistry of the 3-azidoaspartates **15a,b** was established by analysis of the ^1H NMR spectra (NOE effects and coupling constants) of the cyclic ureas **17a,b**,

Scheme 5



whose data were in agreement with those shown by the closely related carbamates **9a,b** (Scheme 5). The ureas **17a,b** were obtained by chemoselective hydrogenation of **15a,b** (H_2, $Pd/BaCO_3$), followed by treatment of the crude resulting amines with excess phosgene (**17a**, 60%; **17b**, 80%). Further stereochemical proof was obtained from the analysis of the optical rotations of the *meso*-diaminoaspartate **18a** ($[\alpha]_D = 0$) and chiral nonracemic diaminoaspartate **18b** ($[\alpha]_D = +109$), prepared as shown in Scheme 5. The enantiomeric purity of **15b** was determined by azide reduction (H_2, $Pd/BaCO_3$), followed by derivatization of the resulting primary amine with both L- and D,L-*N*-(phenylsulfonyl)proline (DCC, DMAP, 75% overall yield). ^1H NMR analysis of mixtures of the resulting diastereomeric amides, **19** and **20**, of known composition allowed us to determine that **15b** had an enantiomeric ratio (er) >99.5/0.5.

As can be seen from the results shown in Scheme 4, the use of DTBAD and DBAD allowed the preparation of the (3*S*)-aminoaspartate with high selectivity, but, surprisingly, the (3*R*) isomer could not be obtained as the major product of the reaction under any of the conditions tested. It is interesting that the enolate generated by treatment of **7** with 100 mol % of BuLi and 300 mol % of LHMDS gave opposite (and highly selective) stereochemical results when treated with MoOPH or with the dialkyl azodicarboxylates. It is important to note that very short reaction times had to be employed to avoid the epimerization of **16a** at C-3.

The stereochemistry of the 3-hydrazidoaspartates **16a,b** (R' = *t*-Bu) (which were separable by chromatography) was established by deprotection of the Pf group in both isomers, followed by *N*-reprotection with CbzCl (87%) (Scheme 6). The resulting tricarbamates were treated with TFA, to effect the hydrolysis of the Boc groups. The hydrazines thus formed were hydrogenolyzed (H_2, Raney Ni). Finally, protection of the resulting monoamines with CbzCl, gave mixtures of the dicarbamates **22a,b** and the cyclic ureas **23a,b**, depending on the reaction conditions. Analysis of the optical rotations shown by **22a,b** and **23a,b** allowed us to unequivocally assign the stereochemistry at C-3 in the hydrazides **16a,b**. The stereochem-

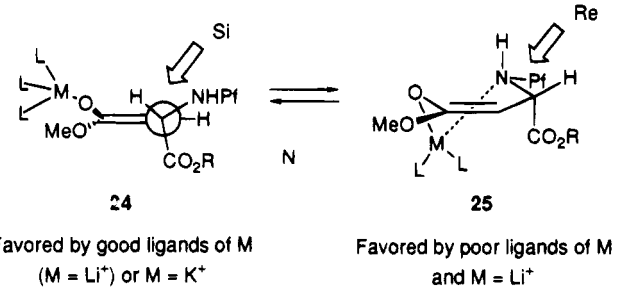
(15) Evans, D. A.; Evrard, D. A; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189, and references therein.

(16) (a) Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genêt, J. P. *Synlett* **1993**, 475. (b) Gmeiner, P.; Bollinger, B. *Liebigs Ann. Chem.* **1992**, 273. (c) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5511. (d) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5507. (e) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525. (f) Genet, J. P.; Juge, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765. (g) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824.

istry of the benzyl substituted hydrazides **16a,b** (R′ = Bn) was established by comparison of their spectroscopic data with those of their *t*-butyl substituted counterparts.

Reaction of *N*-Pf-aspartate Enolates with Electrophiles. Mechanistic Considerations. The results of the reactions of *N*-Pf aspartate enolates with electrophiles discussed above indicate that the degree of stereoselection and the stereochemistry of the newly introduced stereogenic center is the result of a very complex combination of factors: the structure of the enolate (geometry and counterion), the reaction conditions (use of complexing cosolvents) and the nature of the electrophile. We have rationalized the stereochemical results discussed above by considering which is the structure of the nucleophilic species present in the reaction, and the nature of its interaction with each electrophile. We believe that a clear distinction can be made between the electrophiles that do not form a complex with the nucleophile as a prerequisite for reaction (MoOPH) and those that do (Davis' oxaziridine, trisyl azide and the dialkyl azodicarboxylates).

With regard to the structure of the nucleophile, we propose that the reacting enolate is an equilibrium mixture of an open form (**24**) and a chelated form (**25**) (R = Me or *t*-Bu), both of which have the bulky N-Pf group in an equatorial position. The preferential ap-



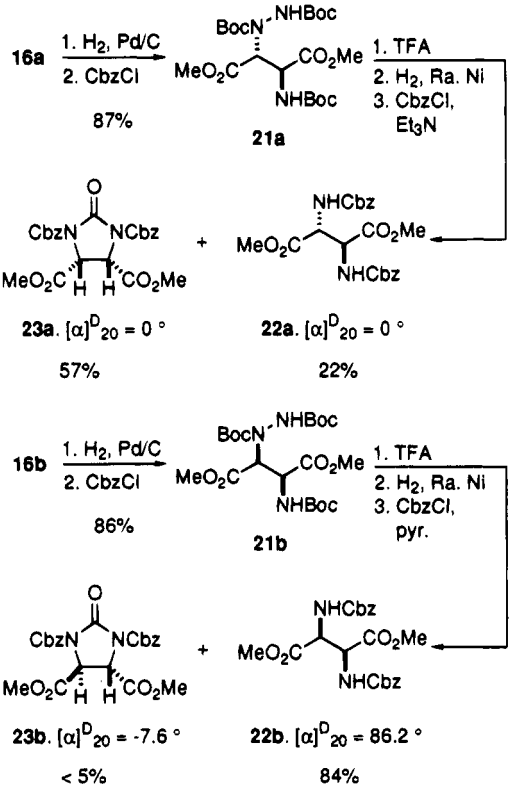
24 **25**

Favored by good ligands of M (M = Li^+) or M = K^+ — Favored by poor ligands of M and M = Li^+

proach of an electrophile which cannot complex to the metal cation (MoOPH) to the less hindered face of the predominant nucleophilic species in the reaction medium should yield the observed results (Table 1, Scheme 3). The K_{eq} of the aforementioned equilibrium should be strongly dependent on the nature of the enolate counterion (M) and its ligands (L): the open form **24** would be favored by strongly coordinating ligands (DMPU or HMPA, Table 1, entries 5 and 6), or by the use of K^+ as the enolate counterion. Poorly coordinating ligands (HMDS or THF) and/or deprotonation of the Pf-amino group (by addition of 100 mol % of n-BuLi, entry 12) would favor the chelated form **25**.

An interesting point to be made is that the degree of stereoselectivity observed seemed to be dependent on the Li^+ (a hard acid) coordinating power of the species present in the reaction medium: HMPA and DMPU (hard, neutral bases) are the best Li^+ complexing agents. LDA[17] is a better ligand than LTMP (negatively charged bases) and both are better ligands than DME (a borderline, neutral base), TMEDA or PMDET (softer neutral bases).[18] Another interesting aspect is that the complexation of the enolate counterion must not be pushed to far (to give a *naked* enolate, entries 10 and 11), since the resulting species are unreactive towards MoOPH.

Scheme 6



The difference in reactivity displayed by the *t*-butyl ester **12a**, and the diminished stereoselectivity displayed by its Li^+ enolate in the presence of HMPA can be attributed to the steric bulk of the CO_2-*t*-Bu, that cannot adopt a pseudoaxial position (as in **24** and **25**), thus reducing the difference in hindrance between the *Re* and *Si* faces in **24** and **25** (R = *t*-Bu). The corollary to these observations is that since MoOPH most probably does not form a complex with the metal cation then it should approach the nucleophile following the Bürgi–Dunitz trajectory,[19] which lies very close to the stereogenic center of the enolate, thus giving rise to a high degree of stereoselection.

With regard to the lack of selectivity observed for the hydroxylation of the enolates of **7** and **12a** with the Davis' reagent we believe that it can be explained by the proposed mechanism for the oxygen transfer from the oxaziridine to lithium enolates: it appears that in the transition state of the oxidation the metal cation is coordinated to both the enolate and the oxaziridine oxygen atoms.[20] In our particular case this would have two consequences: the oxaziridine would displace the Pf-amino group as the metal cation ligand (thus the enolate should acquire the open form **24**), and the electrophile should approach the enolate following a pathway far removed from the stereogenic center (the reaction becomes *quasi*-intramolecular); this should account for the observed loss of stereoselection.

The behavior of the acid **12b** markedly differs from that of the diesters **7** and **12a**, most probably due to the additional chelating group present in **12b** (the CO_2^- group), which complicates the mechanistic picture of this reaction.

(17) Treatment of **7** with LDA should give an enolate with the double bond stereochemistry opposite to that shown in **24** and **25**: Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

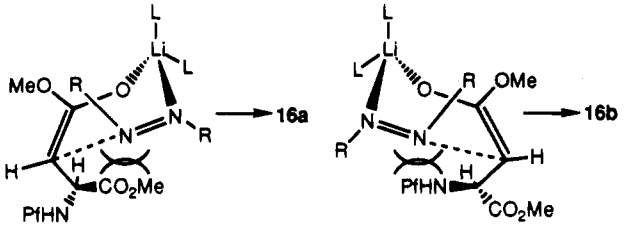
(18) Seebach, D. *Angew. Chem., Int. Ed. Eng.* **1988**, *27*, 1624.

(19) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

(20) Bach, R. D.; Andrés, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613, and references therein.

With regard to the results of the amination reactions, we believe that the lack of stereoselection displayed by the reactions of the enolate of **7** with trisyl azide can be attributed to an effect similar to that seen in the oxidation with Davis' oxaziridine: the SO_2 group should be a powerful ligand for the Li^+, giving rise to the complexation of the trisyl azide with the enolate which then should react in a *quasi*-intramolecular fashion, following a pathway far removed from the stereogenic center.

The stereoselectivity displayed by the reactions of the enolate of **7** with the dialkyl azodicarboxylates can be explained by considering the two diastereomeric transition states of the reaction, **26** and **27**.[16e,21] Based on steric



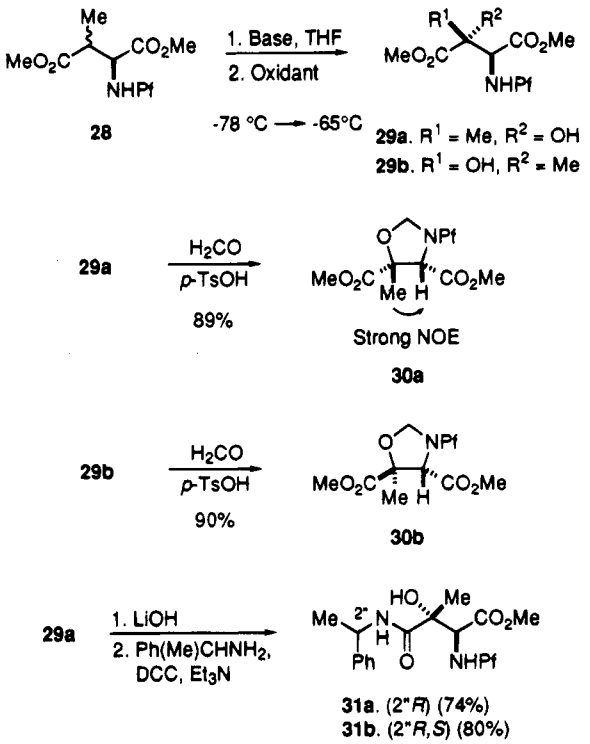
26 **27**

considerations, **26** should be favored over **27**, thus resulting in the preponderance of the (3*R*)-hydrazidoaspartate **16a** in the reaction mixture. These results are consistent with the literature precedents for reactions carried out in the absence of HMPA, both in the sense and the degree of the stereoinduction.[16a,c,d,f] The increase in selectivity observed when the amination reaction was performed in the presence of HMPA might be attributed to the fact that, in the transition states **26** and **27**, the $Li^+-OP(NMe_2)_3$ bond lengths (1.8–1.9 Å) should be shorter than those of the Li^+-OR_2 or the Li^+-NHR_2 complexes (2.1–2.2 Å),[22] this effect should lead to an elongation of the $Li^+-N{=}N$ bond in the HMPA complexes and, consequently, to an increase in the steric interaction of the electrophile with the substituents at C-2.[23]

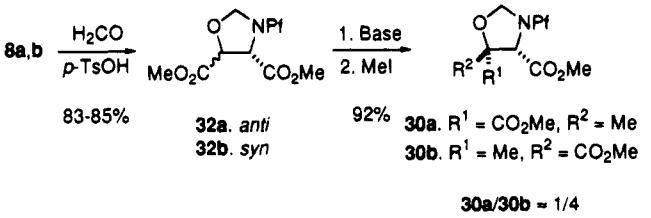
Synthesis of 3-Alkyl-3-hydroxyaspartates. Having established the methodology for the stereoselective monofunctionalization of C-3 in *N*-Pf aspartates we became interested in extending it to the preparation of 3,3-disubstituted aspartates, such as **3**. Two obvious approaches to achieve this goal were the hydroxylation of 3-alkyl-substituted aspartates, such as **28** (Scheme 7), and the alkylation of a suitably protected 3-hydroxyaspartate, such as **32** (Scheme 8). Besides the problem of controlling the stereochemistry of the newly created quaternary center, the question of the regiocontrol in the deprotonation of H-3 *vs* H-2 in **28** or **32** would be much more acute than in the case of the C-3 unsubstituted aspartates.

With regard to the regioselective enolization of 3-substituted *N*-Pf aspartates, we have recently proposed that the hindrance posed by the Pf group to the abstraction of the α-hydrogen in *N*-Pf amino acid esters is stereoelectronic in nature: the dihedral angle between the C-1 carboxyl group and H-2 is ≈0° or 180° in the most stable

Scheme 7



Scheme 8



conformer of the *N*-Pf amino esters.[12b] If this were true there would not be any problem in controlling the regioselectivity in the deprotonation of **28** or **32**, since H-3 would be much more acidic than H-2.

Treatment of the 3-methyl aspartate **28**[11c] with amide bases followed by the addition of a hydroxylating agent (MoOPH or Davis' oxaziridine) led exclusively to the 3-hydroxy-3-methyl aspartates **29a,b**. Despite the complete regioselectivity shown by the hydroxylation of **28**, the stereoselectivity of the reaction left much to be desired, since ≈1/1 to 1/2 mixtures of **29a** and **29b** were obtained under all the conditions tested. The stereochemical assignment of **29a,b** was performed by NOE analysis of the oxazolidines **30a,b**, prepared by treatment of **29a,b** with formaldehyde (90%). The enantiomeric purity of the tertiary alcohol **29a** was measured by regioselective hydrolysis of its ω-ester, followed by coupling of the resulting acid with (*R*) and (*R,S*) 1-methylbenzylamine. ^1H NMR analysis of mixtures of the resulting diastereomeric amides, **31a** and **31b**, of known composition allowed us to determine that **29a** had an enantiomeric ratio (er) >99.5/0.5.

Somewhat better results were obtained for the alkylation of the oxazolidine **32**, prepared from the hydroxyesters **8a,b** and formaldehyde in 83–85% yield. Treatment of **32** (as a mixture of epimers) with KHMDS, followed by reaction with MeI provided a 4/1 mixture of **30a** and **30b**. The major isomer, which has the correct relative stereochemistry for the preparation of carzino-

(21) The conclusions drawn do not change if the Li^+ of the enolate complexes the carbonyl oxygen of the azodicarboxylate to give a transition state with an eight-membered ring.

(22) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

(23) An analogous level of stereoselection was observed when DMPU was substituted for HMPA.

philin A (**6**), resulted from the approach of the electrophile *anti* to the bulky Pf group. No products arising from the alkylation at C-2 were detected in the crude reaction product.

Conclusion

We have developed efficient and stereoselective preparations of enantiomerically pure (3*R*) and (3*S*) *N*-Pf-3-hydroxy- and *N*-Pf-3-aminoaspartates by reaction of *N*-Pf-aspartate enolates with electrophilic hydroxylating or aminating reagents. The stereoselectivity of the hydroxylation and amination reactions was shown to be dependent on the structure of the enolate and wether the electrophile is able to complex the enolate counterion in the transition state of the reaction. We have also developed a regioselective preparation of enantiomerically pure *N*-Pf-3-hydroxy-3-methylaspartates, albeit with only modest stereoselectivity.

Experimental Section

General. All reactions were carried out under an atmosphere of dry Ar, unless otherwise noted. THF and Et_2O were distilled from Na/benzophenone; dioxane was distilled from Na; CH_2Cl_2, triethylamine and pyridine were distilled from CaH_2; MeOH was distilled from Mg. The solutions of KHMDS in THF were prepared as described by Brown.[24] Solutions of $COCl_2$ in toluene were obtained from FLUKA. W-2 Raney Ni was obtained from ALDRICH. Column chromatography was carried out using 230–400 mesh silica gel unless otherwise noted. NMR spectra were taken in $CDCl_3$ unless otherwise noted, and are referred to internal TMS (for $CDCl_3$ solutions) or the appropriate solvent signal (DMSO-d_6). NOE difference experiments were carried out on a Bruker WM-250 or a Bruker AMX-500 spectrometers. FAB-MS were carried out using 2,2'-dithioethanol as matrix unless otherwise noted.

(2*S*,3*R*)-Dimethyl *N*-(9'-Phenylfluoren-9'-yl)-3-hydroxyaspartate (8a). n-BuLi (0.095 mL, 0.19 mmol, 2 M in hexanes) was added dropwise to a stirred solution of **7** (72 mg, 0.18 mmol) in THF (1 mL) at −78 °C. After 15 min, LHMDS (0.530 mL, 0.54 mmol, 300 mol %, 1.02 M in THF−hexanes) was added and stirring was continued for 1.5 h at −78 °C. MoOPH (242 mg, 0.557 mmol, 310 mol %) was added and after 2 h at −78 to −65 °C the reaction was quenched with saturated Na_2SO_3 (2 mL). The resulting suspension was allowed to reach room temperature, H_2O was added (5 mL) and stirring was continued for 10 min. The suspension was partitioned between H_2O (5 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL) and the combined organic layers were washed with HCl (15 mL, 5%) and brine (15 mL), dried and concentrated to give a residue that was purified by column chromatography (hexanes/EtOAc, 3.5/1) to give 20 mg (28%) of **7** and 45 mg (60%) of **8a/8b** in a 20/1 ratio by ^1H NMR. Pure **8a** could be obtained after recrystallization from EtOAc/hexanes: mp 148 °C; $[\alpha]^{20}_D$ −311° (*c* 1.13, $CHCl_3$); IR (KBr) 3310, 2950, 1760, 1740 cm^{-1}; ^1H NMR δ 7.68–7.20 (m, 13H), 4.15–4.11 (m, 1H), 3.68 (s, 3H), 3.40 (s, 3H), 3.04 (d, J = 4.1 Hz, 1H); ^{13}C NMR δ 172.2, 172.1, 148.6, 147.9, 143.9, 141.2, 140.1, 128.8, 128.7, 128.5, 128.3, 127.7, 127.5, 126.2, 126.1, 125.4, 120.2, 120.0, 72.8, 72.7, 59.3, 52.2, 52.1. Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.9; H, 5.6; N, 3.4. Found: C, 72.1; H, 5.5; N, 3.3.

(2*S*,3*S*)-Dimethyl *N*-(9'-Phenylfluoren-9'-yl)-3-hydroxyaspartate (8b). A solution of **7** (1.027 g, 2.56 mmol) in THF (25 mL) was added dropwise to a stirred solution of LHMDS (7.25 mL, 7.68 mmol, 300 mol %, 1.06 M in THF−hexanes) in HMPA (3.2 mL) at −78 °C; the resulting solution was stirred for 65 min at −78 °C, then MoOPH (3.61 g, 8.32 mmol, 325 mol %) was added and the stirring was continued for 5 h 30 min from −78 to −62 °C. The reaction was quenched at −62 °C with saturated Na_2SO_3 (8 mL). The resulting suspension was allowed to reach room temperature. H_2O was added (20 mL) and stirring was continued for 10 min. The suspension was partitioned between H_2O (20 mL) and Et_2O (65 mL). The aqueous phase was extracted with Et_2O (2 × 65 mL) and the combined organic phase was washed with HCl (2 × 80 mL, 5%) and brine (80 mL), dried and concentrated to give a residue that was purified by column chromatography (hexanes/EtOAc, 3/1) to give 785 mg (74%) of **8a/8b**, in a 1/11 ratio by ^1H NMR. Pure **8b** could be obtained after two recrystallization from EtOAc/hexanes: mp 151 °C; $[\alpha]^{20}_D$ −311° (*c* 0.92, $CHCl_3$); IR (KBr) 3310, 2950, 1760, 1740 cm^{-1}; ^1H NMR δ 7.76–7.21 (m, 13H), 4.14 (d, J = 2.3 Hz, 1H), 3.55 (s, 3H), 3.40 (s, 3H), 3.04 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 173.1, 172.2, 148.5, 147.7, 144.1, 141.0, 140.0, 128.6, 128.5, 128.4, 127.8, 127.4, 127.3, 126.8, 126.0, 125.6, 120.0, 119.9, 72.4, 72.3, 57.7, 52.6, 52.0; EI-MS (*m/z*) 417 (M^+, 0.2), 328 (15), 241 (100), 239 (51). Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.9; H, 5.6; N, 3.4. Found: C, 72.1; H, 5.4; N, 3.3.

(4*R*,5*S*)-4,5-Bis(methoxycarbonyl)-1-(9'-phenylfluoren-9'-yl)oxazolidin-2-one (9a). Trichloromethyl chloroformate (0.130 mL, 1.079 mmol, 1000 mol %) was added dropwise to a stirred solution of **8a** (45 mg, 0.108 mmol) and DMAP (3 mg) in pyridine (1.8 mL) at 75 °C. After 25 min the reaction was allowed to reach room temperature and MeOH (3 mL) was added. The resulting solution was partitioned between CH_2Cl_2 (10 mL) and 1 M H_3PO_4 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (6 mL) and the combined organic phase was washed with brine (8 mL), dried and concentrated to give a solid that was purified by column chromatography (hexanes/EtOAc, 2/1) to give 40 mg (83%) of **9a**, as a white crystalline solid, and 7 mg (16%) of the correspondent symmetric carbonate. **9a**: mp >250 °C (CH_2Cl_2/hexanes); $[\alpha]^{20}_D$ −503° (*c* 0.145, $CHCl_3$); IR (KBr) 2950, 1770, 1740 cm^{-1}; ^1H NMR δ 7.81–7.20 (m, 13H), 5.07 (d, J = 8.9 Hz, 1H), 4.37 (d, J = 8.9 Hz, 1H), 3.68 (s, 3H), 3.11 (s, 3H); ^{13}C NMR δ 168.1, 166 5, 155.8, 145.7, 145.3, 140.4, 140.2, 129.7, 129.5, 128.6, 128.4, 127.7, 126.2, 125.3, 120.3, 119.8, 77.2, 72.9, 72.4, 60.5, 52.8, 52.2; EI-MS (*m/z*) 443 (M^+, 16), 366 (1), 322 (2), 254 (3), 242 (23), 241 (100). Anal. Calcd for $C_{26}H_{21}NO_6$: C, 70.4; H, 4.8; N, 3.2. Found: C, 70.8; H, 4.7; N, 3.2.

(4*S*,5*S*)-4,5-Bis(methoxycarbonyl)-1-(9'-phenylfluoren-9'-yl)oxazolidin-2-one (9b). Phosgene (3.73 mL, 7.19 mmol, 1000 mol %, 1.93 M in toluene) was added dropwise to a stirred solution of **8b** (300 mg, 0.719 mmol) and DMAP (9 mg, 0.074 mmol, 10 mol %) in pyridine (1.8 mL) at 75 °C. After 25 min, the reaction was allowed to reach room temperature and MeOH (3 mL) was added. The reaction mixture was partitioned between CH_2Cl_2 (100 mL) and 1 M H_3PO_4 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (60 mL) and the combined organic phase was washed with brine (80 mL), dried and concentrated to give a solid that was purified by a short chromatography (hexanes/EtOAc, 2.2/1) to give 319 mg (100%) of **9b** as a white crystalline solid. An analytical sample was obtained by recrystallization from CH_2Cl_2/hexanes: mp 216 °C; $[\alpha]^{20}_D$ −274° (*c* 0.2, $CHCl_3$); IR (KBr) 2950, 1770, 1740 cm^{-1}; ^1H NMR δ 7.73–7.26 (m, 13H), 4.65 (d, J = 2.2 Hz, 1H), 4.11 (d, J = 2.2 Hz, 1H), 3.72 (s, 3H), 3.29 (s, 3H); ^{13}C NMR δ 169.2, 168.1, 155.8, 145.9, 145.5, 140.0, 139.9, 129.6, 129.4, 128.5, 128.2, 127.7, 127.6, 126.3, 125.4, 120.1, 119.8, 72.8, 72.7, 60.6, 53.1, 52.5; EI-MS (*m/z*) 443 (M^+, 18), 366 (1), 322 (2), 254 (4), 242 (22), 241 (100). Anal. Calcd for $C_{26}H_{21}NO_6$: C, 70.4; H, 4.8; N, 3.2. Found: C, 70.7; H, 4.4; N, 3.0.

L-*N*-(Phenylsulfonyl)prolyl Ester 10. L-*N*-(Phenylsulfonyl)proline (122 mg, 0.48 mmol, 150 mol %), DCC (99 mg, 0.48 mmol, 150 mol %) and DMAP (4 mg, 0.03 mmol, 9 mol %) were added to a stirred solution of **8b** (133 mg, 0.319 mmol) in CH_2Cl_2 (4 mL). After 2.5 h the mixture was partitioned between Et_2O (40 mL) and HCl (20 mL, 5%). The organic phase was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried and concentrated to give a residue that was purified by column chromatography (hexanes/EtOAc, 2.5/1) to give 209 mg (100%) of **10** as a white foam: $[\alpha]^{20}_D$ −624° (*c* 0.125, $CHCl_3$); ^1H NMR δ 7.88 (dd, J = 1.5 Hz, J = 8.0 Hz, 2H), 7.68 (t, J = 7.1 Hz, 2H), 7.61–7.19 (m, 16H), 5.09 (d, J = 2.7 Hz, 1H), 4.43 (dd, J = 3.5 Hz, J = 8.3 Hz, 1H), 3.59 (s, 3H), 3.54–3.45 (m,

(24) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

1H), 3.38 (s, 3H), 3.35–3.23 (m, 2H), 2.32–1.63 (m, 4H); ^{13}C NMR δ 171.6, 171.0, 167.0, 148.4, 147.4, 144.2, 141.1, 139.9, 138.4, 132.7, 129.0, 128.6, 128.5, 128.4, 127.7, 127.5, 127.4, 127.2, 127.1, 126.1, 125.7, 120.0, 119.9, 74.1, 72.5, 59.9, 56.3, 52.4, 52.2, 48.3, 30.7, 24.4; EI-MS (*m/z*) 595 ([M − CO_2CH_3]$^+$, 1), 399 (1), 256 (3), 242 (22), 241 (100). Anal. Calcd for $C_{36}H_{34}N_2O_8S$: C, 66.0; H, 5.2; N, 4.3; S, 4.9. Found: C, 66.4; H, 5.1; N, 4.0; S, 4.9.

(2*S*,3*S*)-Methyl *tert*-Butyl *N*-(9′-Phenylfluoren-9′-yl)-3-hydroxyaspartate (13b). A solution of **12a** (90 mg, 0.203 mmol) in THF (0.65 mL) was added dropwise to a stirred solution of KHMDS (0.37 mL, 0.37 mmol, 180 mol %, 1 M in THF) at −78 °C. The resulting solution was stirred for 1 h at −78 °C; then MoOPH (199 mg, 0.46 mmol, 225 mol %) was added. The resulting suspension was stirred for 1 h at −78 °C and then quenched with saturated Na_2SO_3 (2 mL). The resulting suspension was allowed to reach room temperature. H_2O was added (5 mL) and stirring was continued for 10 min. The suspension was partitioned between H_2O (5 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic phase was washed with HCl (10 mL, 5%) and brine (10 mL), dried and concentrated to give a residue that was purified by column chromatography (hexanes/EtOAc, 3/1) to give 84 mg (90%) of a mixture of **13a** and **13b** in a 1/7 ratio by ^{1}H NMR. Pure **13b** could be obtained after recrystallization from CH_2Cl_2 /Et_2O (61 mg, 65%): mp 177–180 °C; [α]$^{20}_D$ −286° (*c* 0.77, $CHCl_3$); IR (KBr) 2980, 1750, 1730 cm^{-1}; ^{1}H NMR δ 7.69–7.18 (m, 13H), 4.11 (br s, 1H), 3.48 (s, 3H), 3.40 (br s, 2H), 2.91 (br s, 1H), 1.24 (s, 9H); ^{13}C NMR δ 172.4, 171.6, 148.9, 148.1, 144.5, 141.0, 140.1, 128.5, 128.4, 128.3, 127.8, 127.7, 127.3, 127.0, 126.1, 126.0, 119.9, 119.7, 81.9, 72.9, 72.6, 58.5, 52.4, 27.8; EI-MS (*m/z*) 460 (M$^+$, 0.1), 370 (21), 358 (5), 241 (100), 239 (57). Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.2; H, 6.4; N, 3.0. Found: C, 73.3; H, 6.7; N, 3.1.

(2*S*,3*R*)- and (2*S*,3*S*)-ω-Methyl *N*-(9′-Phenylfluoren-9′-yl)-3-hydroxyaspartate (14a,b). A solution of **12b** (80 mg, 0.207 mmol) in THF (2 mL) was added dropwise to a stirred solution of KHMDS (0.60 mL, 0.62 mmol, 300 mol %, 1.04 M in THF) at −78 °C. The enolate was allowed to form for 2 h at −50 °C, then the reaction mixture was cooled to −78 °C and Davis' oxaziridine (162 mg, 0.62 mmol, 300 mol %) was added. Stirring was continued for 2 h at −78 °C; then the reaction was quenched with Et_3N (0.2 mL) and saturated NH_4Cl (2 mL). The resulting suspension was allowed to reach room temperature, was poured into a mixture of saturated $NaHCO_3$ (5 mL) and CCl_4 (5 mL) and was filtrated through a pad of Celite. The organic phase was separated and the aqueous layer was washed with CCl_4 (5 mL). The aqueous phase was acidified to pH = 2 with 1 M H_3PO_4 and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layers were dried and concentrated to give 79 mg (95%) of a mixture of **14a** and **14b** in a 1/7 ratio by ^{1}H NMR. The use of LHMDS (400 mol %), with the same procedure as above, afforded a mixture of **14a** and **14b** in a 4/1 ratio. The products were unstable and were characterized as the dimethyl esters (**8a** and **8b**) after reaction with excess CH_2N_2 in ether.

(2*S*,3*R*)- and (2*S*,3*S*)-Dimethyl *N*-(9′-Phenylfluoren-9′-yl)-3-azidoaspartate (15a,b). A solution of **7** (1.41 g, 3.52 mmol) in THF (34 mL) was added dropwise to a stirred solution of KHMDS (3.69 mL, 4.57 mmol, 130 mol %, 1.24 M in THF) at −78 °C. The enolate was allowed to form for 1 h at −55 °C and then it was cooled to −78 °C. A precooled (−78 °C) solution of 2,4,6-triisopropylbenzenesulfonyl azide (Trisyl-N_3, 1.42 g, 4.58 mmol, 130 mol %) in THF (21 mL) was added via cannula to the above enolate solution and after an additional 6 min period the reaction was quenched with HOAc (0.97 mL, 16.9 mmol, 480 mol %). The resulting mixture was stirred at 25 °C for 90 min and was then partitioned between H_2O (350 mL) and CH_2Cl_2 (450 mL). The aqueous phase was washed with CH_2Cl_2 (200 mL) and the combined organic layers were washed with brine, dried and evaporated to afford a residue, which was purified by chromatography (hexanes/EtOAc, 6/1) to give a white solid (an ≈1/1 mixture of **15a** and **15b**). Recrystallization of the mixture from hexanes/EtOAc gave 475 mg (31%) of pure **15b** as white crystals. The mother liquor was concentrated and recrystallized twice from hexanes/Et_2O/EtOAc and hexanes/Et_2O to give a second and third crop (236 mg, 15%) of **15b**. The concentrated mother liquor, 700 mg (45%), afforded a pure **15a** as an oil.

15a: [α]$^{20}_D$ −221.4° (*c* 0.83, $CHCl_3$); IR (film) 2120, 1750 cm^{-1}; ^{1}H NMR δ 7.70 (t, *J* = 7.7 Hz, 2H), 7.40–7.20 (m, 11H), 3.81 (d, *J* = 5.8 Hz, 1H), 3.68 (s, 3H), 3.37 (s, 3H), 3.22 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR δ 172.0, 168.2, 148.1, 148.0, 144.0, 141.4, 140.0, 128.8, 128.7, 128.5, 128.1, 127.7, 127.5, 126.1, 126.0, 125.5, 120.2, 120.0, 72.9, 65.2, 58.1, 52.4, 52.2; FAB-MS (positive ion mode, *m/z*) 443 ([M + H]$^+$, 4), 417 (2), 317 (2), 289 (2), 273 (2), 257 (2), 242 (24), 241 (100).

15b: mp 152 °C; [α]$^{20}_D$ −325.2° (*c* 1.23, $CHCl_3$); IR (KBr) 2160, 2120, 1750 cm^{-1}; ^{1}H NMR δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.40–7.20 (m, 11H), 3.76 (d, *J* = 3.1 Hz, 1H), 3.51 (s, 3H), 3.40 (s, 3H), 3.38 (d, *J* = 10.0 Hz, 1H), 3.19 (dd, *J* = 3.1 Hz, *J* = 10.0 Hz, 1H); ^{13}C NMR δ 172.4, 168.1, 148.4, 147.5, 144.0, 141.2, 139.9, 128.6, 128.5, 128.4, 128.0, 127.4, 127.3, 126.7, 126.0, 125.7, 119.9 (2C), 72.8, 64.1, 58.2, 52.6, 52.2; FAB-MS (positive ion mode, *m/z*) 443 ([M + H]$^+$, 8), 289 (5), 242 (24), 241 (100). Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.9; H, 5.0; N, 12.7. Found: C, 67.6; H, 4.9; N, 12.5.

Di-*tert*-butyl Hydrazides 16a,b (R′ = t-Bu). A solution of **7** (290 mg, 0.723 mmol) in THF (5.4 mL) and HMPA (0.623 mL) were succesively added dropwise to a stirred solution of KHMDS (0.87 mL, 0.87 mmol, 120 mol %, 1 M in THF–hexanes) in THF (0.8 mL) at −78 °C. The enolate was allowed to form for 1 h at −55 °C and then the reaction mixture was cooled to −78 °C. A precooled (−78 °C) solution of di-*tert*-butyl azodicarboxylate (DTBAD, 216 mg, 0.94 mmol, 130 mol %) in CH_2Cl_2 (4 mL) was added *via* cannula to the above enolate solution and after an additional 4 min 30 s the reaction was quenched with HOAc (0.108 mL, 1.88 mmol, 260 mol %). The mixture was partitioned between Et_2O (100 mL) and phosphate buffer (pH 4.15) (80 mL). The organic layer was washed with H_2O (2 × 70 mL) and brine, dried and evaporated to give a residue [a 30/1 mixture of **16a** and **16b** (R′ = t-Bu)] which was purified by column chromatography (hexanes/EtOAc, 9/2) to give 365 mg (80%, 97% based on recovered **7**) of **16a** (R′ = t-Bu) as a white foam.

16a (R′ = t-Bu): R_f 0.36 (hexanes/EtOAc 3/1); [α]$^{20}_D$ −120.9° (*c* 1.77, $CHCl_3$); IR (film) 2920, 1730 cm^{-1}; ^{1}H NMR (45 °C) δ 7.68–7.65 (m, 2H), 7.45–7.15 (m, 11H), 6.20 (br s, 1H), 4.83 (br s, 1H), 3.56 (s, 3H), 3.42 (d, *J* = 6 Hz, 1H), 3.34 (s, 3H), 1.48–1.43 (m, 18H); ^{13}C NMR (52 °C) δ 172.6, 169.3, 155.1, 154.8, 149.1, 149.0, 144.9, 141.0, 140.2, 128.4, 128.3, 128.2, 128.0, 127.5, 127.1, 126.3, 126.2, 125.7, 119.9, 119.7, 82.1, 81.2, 81.0, 73.1, 55.9, 51.7, 51.6, 28.2 (3 × CH_3), 28.0 (3 × CH_3); FAB-MS (positive ion mode, *m/z*) 632 ([M + H]$^+$, 5), 392 (4), 317 (2), 280 (7), 254 (3), 242 (23), 241 (100). Anal. Calcd for $C_{35}H_{41}N_3O_8$: C, 66.5; H, 6.6; N, 6.7. Found: C, 66.8; H, 6.7; N, 7.0.

16b (R′ = t-Bu): R_f 0.28 (hexanes/EtOAc 3/1); [α]$^{20}_D$ −120.1° (*c* 1.2, $CHCl_3$); ^{1}H NMR (45 °C) δ 7.69 (dd, *J* = 0.9 Hz, *J* = 7.4, 2H), 7.37–7.16 (m, 11H), 6.09 (br s, 1H), 5.01 (br s, 1H), 3.57 (s, 3H), 3.22 (br s, 1H), 3.16 (s, 3H), [1.50 (s), 1.45 (s), 1.38 (s), 18H]; ^{13}C NMR (52 °C) δ 173.5, 168.9, 155.2, 154.8, 149.1, 148.8, 144.7, 141.2, 140.8, 128.7, 128.4, 128.3, 128.1, 127.6, 127.3, 126.3, 126.2, 125.3, 120.4, 120.0, 82.3, 80.8 (2C), 72.9, 56.2, 52.0, 51.6, 28.2 (3C), 28.1 (3C); FAB-MS (positive ion mode, *m/z*) 632 ([M + H]$^+$, 14), 392 (1), 280 (3), 273 (1), 267 (1), 254 (2), 242 (23), 241 (100). Anal. Calcd for $C_{35}H_{41}N_3O_8$: C, 66.5; H, 6.6; N, 6.7. Found: C, 66.6; H, 6.5; N, 6.5.

Dibenzyl Hydrazides 16 (R′ = Bn). As described above, by reaction of **7** (295 mg, 0.736 mmol) and dibenzyl azodicarboxylate (285 mg, 0.956 mmol, 130 mol %). The crude product was purified by column chromatography (gradient hexanes/EtOAc, 4/1 to 3/1) to give 384 mg (75%, 86% based on recovered **7**) of **16** (R′ = Bn) as a white foam [ratio of **16a** (R′ = Bn)/**16b**, 18/1]. **16a** (R′ = Bn) and **16b** could be separated in some extension by preparative TLC.

16a (R′ = Bn): R_f 0.39 (hexanes/EtOAc 2/1); [α]$^{20}_D$ −130.1° (*c* 0.95, $CHCl_3$); IR (KBr) 3320, 2960, 1740 cm^{-1}; ^{1}H NMR (55 °C) δ 7.64 (t, *J* = 7.1 Hz, 2H), 7.30–7.15 (m, 21H), 6.59 (br s, 1H), 5.17 (s, 2H,), 5.10 (s, 2H), 4.85 (br s, 1H), 3.52 (s, 3H),

3.39 (br s, 1H), 3.22 (s, 3H); ^{13}C NMR (DMSO-d_6, 90 °C) δ 171.2, 167.4, 155.9, 155.6, 148.1, 147.7, 144.5, 140.0, 139.3, 136.3, 135.8, 135.6, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 126.9, 126.8, 126.4, 125.2, 125.1, 124.9, 119.6, 119.4, 72.1, 67.2, 66.0, 65.5, 55.0, 51.1, 50.7; FAB-MS in 3-nitrobenzyl alcohol (positive ion mode, *m/z*) 700 ([M + H]$^+$, 5), 331 (2), 252 (2), 242 (23), 241 (100), 165 (3), 107 (2). Anal. Calcd for $C_{41}H_{37}N_3O_8$: C, 70.4; H, 5.3; N, 6.0. Found: C, 70.0; H, 5.2; N, 5.6.

16b (R′ = Bn): R_f 0.39 (hexanes/EtOAc 2/1); ^{1}H NMR (55 °C) δ 7.65 (dd, *J* = 3.1 Hz, *J* = 7.2 Hz, 2H), 7.32–7.14 (m, 21H), 6.47 (br s, 1H), 5.17 (s, 2H), 5.10–4.96 (m, 3H), 3.46 (s, 3H), 3.27 (br s, 1H), 3.16 (s, 3H).

(4*R*,5*S*)- and (4*S*,5*S*)-4,5-Bis(methoxycarbonyl)-1-(9′-phenylfluoren-9′-yl)imidazolidin-2-one (17a,b). A solution of **15a** or **15b** (100 mg, 0.226 mmol) and Pd/$BaCO_3$ (20 mg, 5%) in MeOH (3 mL) was purged with Ar and then stirred under 1 atm of H_2 for 1 h. The reaction mixture was filtered (Celite) and evaporated to give a residue. A stirred solution of the residue and DMAP (3 mg, 0.025 mmol) in pyridine (0.57 mL) was warmed at 70 °C under Ar; Cl_2CO (1.17 mL, 2.26 mmol, 1.93 M in toluene) was added. After 15 min, the brown mixture was cooled to 0 °C and H_2O was added until no CO_2 evolution was seen. The mixture was partitioned between CH_2Cl_2 (40 mL) and 1 M H_3PO_4 (35 mL). The water layer was washed with CH_2Cl_2 (30 mL); the combined organic layers were washed with H_2O (50 mL) and brine, dried and evaporated to give a residue which was purified by column chromatography (hexanes/EtOAc, 1/1.1) to give pure **17a** (63%) or **17b** (80%).

17a: $[\alpha]^{20}_D$ −180.1° (*c* 0.93, $CHCl_3$); ^{1}H NMR δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 6.9 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.39–7.33 (m, 4H), 7.29–7.17 (m, 5H), 5.42 (s, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.24 (d, *J* = 9.6 Hz, 1H), 3.61 (s, 3H), 3.08 (s, 3H); ^{13}C NMR δ 169.1 (2C), 160.5, 146.1, 145.6, 141.8, 140.2, 140.1, 129.2, 128.9, 128.6, 128.3, 128.1, 127.9, 127.0, 126.3, 125.1, 119.9, 119.5, 72.7, 60.3, 54.1, 52.6, 51.8; FAB-MS (positive ion mode, *m/z*) 443 ([M + H]$^+$, 8), 442 (3), 317 (1), 273 (1), 252 (2), 242 (23), 241 (100). Anal. Calcd for $C_{26}H_{22}N_2O_5 \cdot 0.5H_2O$: C, 69.2; H, 5.1; N, 6.2. Found: C, 69.5; H, 5.0; N, 5.9.

17b: mp 114–116 °C ($CHCl_3$/hexanes); $[\alpha]^{20}_D$ −20.2° (*c* 1.25, $CHCl_3$); IR (KBr) 3240, 1750, 1710 cm^{-1}; ^{1}H NMR δ 7.67–7.63 (m, 3H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.38–7.32 (m, 4H), 7.28–7.18 (m, 5H), 5.75 (s, 1H), 4 10 (d, *J* = 2.6 Hz, 1H), 3.94 (d, *J* = 2.6 Hz, 1H), 3.63 (s, 3H), 3.29 (s, 3H); ^{13}C NMR δ 170.5, 170.4, 160.7, 146.7, 146.2, 141.5, 140.1, 139.8, 129.1, 128.8, 128.3, 128.1, 127.9, 127.7, 127.0, 126.5, 125.3, 119.8, 119.6, 72.6, 60.4, 55.5, 52.9, 52.3; FAB-MS (positive ion mode, *m/z*) 443 ([M + H]$^+$, 7), 442 (2), 317 (2), 273 (2), 254 (3), 242 (23), 241 (100). Anal. Calcd for $C_{26}H_{22}N_2O_5 \cdot 0.75CHCl_3$: C, 60.4; H, 4.3; N, 5.3. Found: C, 60.3; H, 4.2; N, 5.3.

(2*S*,3*S*)- and *meso*-Dimethyl *N*,*N*′-Di-*tert*-butoxycarbonyl-3-aminoaspartate (18a,b). A solution of **15a** or **15b** (135 mg, 0.305 mmol) and Pd/C (34 mg, 10%) in MeOH (2.5 mL) was purged with Ar and then mechanically shaken under 52 psi of H_2 for 24 h. The resulting suspension was purged with Ar and $(Boc)_2O$ (200 mg, 0.916 mmol) was added. After stirring 5 h the mixture was filtered (Celite) and evaporated to give a residue which was purified by column chromatography (hexanes/EtOAc, 5/1) to give **18a** (80%) or **18b** (88%).

18a: mp 103–104 °C (hexanes); $[\alpha]^{20}_D$ +0.2° (*c* 2.09, $CHCl_3$); ^{1}H NMR δ 5.48 (br s, 2H), 4.86 (d, *J* = 6.6 Hz, 2H), 3.77 (s, 6H), 1.46 (s, 18H); ^{13}C NMR δ 169.7, 155.6, 80.5, 55.8, 52.8, 28.2 (3C); FAB-MS (positive ion mode, *m/z*) 377 ([M + H]$^+$, 8), 321 (11), 277 (11), 266 (6), 265 (63), 221 (100), 177 (19), 154 (23). Anal. Calcd for $C_{16}H_{28}N_2O_8$: C, 51.0; H, 7.5; N, 7.4. Found: C, 51.1; H, 7.5; N, 7.4.

18b: $[\alpha]^{20}_D$ +109.1° (*c* 1.04, $CHCl_3$); IR (film) 2940, 1740, 1730 cm^{-1}; ^{1}H NMR δ 5.39 (br d, *J* = 5.1 Hz, 2H), 4.77 (d, *J* = 8.2 Hz, 2H), 3.74 (s, 6H), 1.38 (s, 18H); ^{13}C NMR δ 170.0, 154.8, 80.4, 55.3, 53.0, 28.1 (3C); FAB-MS (positive ion mode, *m/z*) 377 ([M + H]$^+$, 16), 321 (18), 277 (11), 265 (88), 221 (100), 217 (23), 177 (26). Anal. Calcd for $C_{16}H_{28}N_2O_8$: C, 51.0; H, 7.5; N, 7.4. Found: C, 51.0; H, 7.5; N, 7.8.

L-*N*-(Phenylsulfonyl)prolylamide 19. A solution of **15b** (37 mg, 0.084 mmol) and Pd/$BaCO_3$ (12 mg, 5%) in MeOH (1 mL) was purged with Ar and then stirred under 1 atm of H_2 for 1 h 50 min. The reaction mixture was filtered (Celite) and evaporated to give a residue. A stirred solution of the residue, DMAP (1 mg, 0.008 mmol), DCC (26 mg, 0.13 mmol) and L-*N*-(phenylsulfonyl)proline (32 mg, 0.13 mmol) in CH_2Cl_2 (1.4 mL), was stirred under Ar for 1 h 45 min. HCl (2 mL, 5%) was added and the mixture was allowed to stir for 5 min and then it was partitioned between HCl (10 mL, 5%) and Et_2O (15 mL). The organic layer was washed with HCl (10 mL, 5%), saturated $NaHCO_3$ (2 × 10 mL) and brine, filtered (through a cotton plug), dried and evaporated to give a residue which was purified by column chromatography (hexanes/EtOAc, 1/1) to give 41 mg (75%) of **19** as a white solid. Recrystallization from EtOAc/hexanes afforded 27 mg as white needles: mp 179–180 °C; $[\alpha]^{20}_D$ −247.8° (*c* 1.11, $CHCl_3$); IR (KBr) 3400, 2960, 1760, 1740, 1690 cm^{-1}; ^{1}H NMR δ 7.99–7.95 (m, 2H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.71–7.55 (m, 5H), 7.44–7.15 (m, 10H), 4.68 (dd, *J* = 1.9 Hz, *J* = 9.0 Hz, 1H), 4.16 (dd, *J* = 2.5 Hz, *J* = 8.8 Hz, 1H), 3.68–3.61 (m, 1H), 3.46 (s, 3H), 3.39 (s, 3H), 3.32–3.22 (m, 2H), 3.12 (d, *J* = 7.7 Hz, 1H), 2.17–2.11 (m, 1H), 1.88–1.81 (m, 1H), 1.70–1.65 (m, 1H), 1.60–1.52 (m, 1H); ^{13}C NMR δ 173.1, 170.9, 168.8, 148.4, 147.3, 144.2, 141.3, 139.6, 136.2, 133.4, 129.4, 128.6, 128.5, 128.4, 128.0, 127.9, 127.4, 127.2, 126.6, 125.9, 125.7, 120.0, 119.9, 72.5, 62.3, 56.2, 54.7, 52.7, 52.5, 49.8, 30.0, 24.4; FAB-MS (positive ion mode, *m/z*) 654 ([M + H]$^+$, 7), 414 (4), 242 (22), 241 (100). Anal. Calcd for $C_{36}H_{35}N_3O_7S$: C, 66.1; H, 5.4; N, 6.4. Found: C, 65.7; H, 5.3; N, 6.4.

(2*S*,3*R*)- and (2*S*,3*S*)-Bis(*tert*-butoxycarbonyl) Hydrazides 21a,b. Pd/C (250 mg, 10%) was added to a solution of **16a** (997 mg, 1.58 mmol) in deoxygenated MeOH (15 mL). The flask was purged with argon and then evacuated (vacuum) and pressurized (H_2) three times. The reaction mixture was mechanically shaken under 52 psi of H_2 for 4 h 30 min. CH_2Cl_2 (15 mL) was added and the resulting mixture was filtered (Celite) and evaporated. To a stirred solution of the residue and DMAP (19 mg, 0.158 mmol) in CH_2Cl_2 (4.9 mL) under Ar was added pyridine (0.383 mL, 4.74 mmol). The reaction mixture was cooled to 0 °C and benzyl chloroformate (0.392 mL, 2.77 mmol) was added. After 30 min at room temperature the reaction mixture was partitioned between CH_2Cl_2 (300 mL) and saturated $NaHCO_3$ (250 mL). The aqueous layer was washed with CH_2Cl_2 (150 mL) and the combined organic phase was washed with 1 M H_3PO_4 (300 mL) and brine, dried and evaporated to give a residue which was purified by column chromatography (hexanes/EtOAc, 3/1) to give 724 mg (87%) of **21a** as a white foam: $[\alpha]^{20}_D$ −9.4° (*c* 1.37, $CHCl_3$); IR (film) 3320, 2980, 1730 cm^{-1}; ^{1}H NMR (3 rotamers in a 3.1/1.5/1 ratio) δ 7.41–7.28 (m, 5H), [6.89 (d, *J* = 10.0 Hz), 6.73 (d, *J* = 9.8 Hz), 5.99 (d, *J* = 9.4 Hz), 1H], [6.51 (s), 6.45 (s), 6.20 (s), 1H], 5.27–5.02 (m, 4H), [3.81 (s), 3.80 (s), 3.79 (s), 3H], [3.67 (s), 3.66 (s), 3.65 (s), 3 H], 1.48–1.41 (m, 18H); ^{13}C NMR (52 °C) δ 170.0, 169.1, 156.3, 155.7, 154.9, 154.7, 136.6, 128.3, 128.0, 127.8, 83.2, 83.0, 82.6, 82.1, 81.9, 77.2, 67.2, 66.8, 62.7, 60.8, 53.2, 52.9, 52.5, 52.4, 28.0 (3C), 27.8 (3C); FAB-MS (positive ion mode, *m/z*) 526 ([M + H]$^+$, 16), 470 (22), 415 (16), 414 (85), 392 (12), 371 (17), 370 (100), 326 (61). Anal. Calcd for $C_{24}H_{35}N_3O_{10}$: C, 54.8; H, 6.7; N, 8.0. Found: C, 54.6; H, 6.6; N, 8.0.

21b: Same procedure as **21a**. Hydrogenation of **16b** (327 mg, 0.518 mmol) in deoxygenated MeOH (5 mL) with Pd/C (82 mg, 10%) at 52 psi for 3 h 10 min followed by treatment of the dry residue with DMAP (6 mg, 0.05 mmol), pyridine (0.126 mL, 1.56 mmol) and benzyl chloroformate (0.13 mL, 0.91 mmol) in CH_2Cl_2 (1.5 mL) for 50 min gave a residue that was purified by column chromatography (hexanes/EtOAc, 3/1) to afford 233 mg (86%) of **21b** as a white foam: $[\alpha]^{20}_D$ −10.0° (*c* 1.14, $CHCl_3$); IR (KBr) 3340 (b), 2980, 1730 cm^{-1}; ^{1}H NMR δ 7.32–7.26 (m, 5H), 6.67 (br s, 1H), 6.21 (br s, 1H), 5.33 (br s, 1H), 5.09 (s, 2H), 4.99 (br s, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR δ 169.9, 168.9, 156.4, 155.4, 154.9, 136.4, 128.7, 128.4, 128.3, [83.8, 83.0 and 82.0, 2C], 67.3, 62.8, 60.8, 53.9, 53.1, 28.3 (3C), 28.2 (3C); FAB-MS (positive ion mode, *m/z*) 548 (6), 526 ([M + H]$^+$, 15), 470 (23), 415 (19),

414 (100), 392 (6), 371 (10), 370 (58). Anal. Calcd for $C_{24}H_{35}N_3O_{10}$: C, 54.8; H, 6.7; N, 8.0. Found: C, 54.5; H, 6.8; N, 7.8.

***meso*-Dimethyl *N,N'*-Bis(benzyloxycarbonyl)-3-aminoaspartate (22a).** Trifluoroacetic acid (2 mL) was added to a stirred solution of **21a** (70 mg, 0.133 mmol) in CH_2Cl_2 (2 mL). After 45 min W-2 Raney Ni was added and the resulting mixture was mechanically shaken under 52 psi of H_2 for 1 h. The mixture was purged with Ar, then filtered through a cotton plug, and evaporated to give a residue which was partitioned between CH_2Cl_2 (20 mL) and saturated K_2CO_3 (20 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried and evaporated to give a residue. Et_3N (0.138 mL, 0.997 mmol) was added to a stirred solution of the residue and DMAP (2 mg, 0.01 mmol) in CH_2Cl_2 (0.56 mL), under Ar. The reaction mixture was cooled to 0 °C and benzyl chloroformate (0.075 mL, 0.53 mmol) was then added. The resulting orange mixture was stirred for 5 days at room temperature and then was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL). The water layer was washed with CH_2Cl_2 (10 mL) and the combined organic phase was washed with 1 M H_3PO_4 (25 mL) and brine, dried and evaporated to give a residue which was purified by column chromatography (hexanes/EtOAc, 2/1) to give 13 mg (22%) of **22a** as an oil and 36 mg (57%) of ***meso*-1,3-bis(benzyloxycarbonyl)-4,5-bis(methoxycarbonyl)imidazolidin-2-one (23a)** as a white solid. Recrystallization of **22a** from EtOAc/hexanes afforded an analytical sample as white needles. Recrystallization of **23a** from CH_2Cl_2/hexanes afforded 29 mg as white needles.

22a: mp 83–84 °C; $[\alpha]^{20}_D$ +0.9° (*c* 1.35, $CHCl_3$); IR (film) 1730, 1720 cm^{-1}; ^1H NMR δ 7.35 (s, 10H), 5.84 (d, J = 6.2 Hz, 2H), 5.13 (s, 4H), 4.95 (d, J = 7.6 Hz, 2H), 3.75 (s, 6H); ^{13}C NMR δ 169.2, 156.4, 136.0, 128.6, 128.3, 128.2, 67.5, 56.4 52.9; FAB-MS (positive ion mode, *m/z*) 445 ([M + H]$^+$, 15), 401 (19), 311 (18), 309 (28), 263 (17), 231 (100), 139 (50), 93 (38). Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.4; H, 5.5; N, 6.3. Found: C, 59.2; H, 5.3; N, 6.3.

23a: mp 143–144 °C; $[\alpha]^{20}_D$ +0.4° (*c* 1.2, $CHCl_3$); IR (KBr) 1825, 1806, 1759, 1711 cm^{-1}; ^1H NMR δ 7.38–7.32 (m, 10H), 5.35, (d, J = 12.2 Hz, 2H), 5.23 (d, J = 12.2 Hz, 2H), 4.85 (s, 2H), 3.63 (s, 6H); ^{13}C NMR δ 166.8, 150.7, 146.5, 134.6, 128.6, 128.2, 69.1, 55.2, 53.1; FAB-MS (positive ion mode, *m/z*) 493 (21), 492 (100), 471 ([M + H]$^+$, 43), 359 (35), 181 (40). Anal. Calcd for $C_{23}H_{22}N_2O_9 \cdot 0.5CH_2Cl_2$: C, 55.0; H, 4.5; N, 5.5. Found: C, 55.0; H, 4.4; N, 5.3.

(2*S*,3*S*)-Dimethyl *N,N'*-Bis(benzyloxycarbonyl)-3-aminoaspartate (22b). The same procedure as with **22a** was used. The residue obtained from **21b** (84 mg, 0.160 mmol) after treatment with trifluoroacetic acid, hydrogenation at 52 psi and extraction with saturated K_2CO_3 was treated with DMAP (2 mg, 0.016 mmol), pyridine (0.039 mL, 0.48 mmol) and benzyl chloroformate (0.04 mL, 0.28 mmol) in CH_2Cl_2 (0.45 mL) for 1 h to give a residue that was purified by column chromatography (hexanes/EtOAc, 2.5/1) to afford 60 mg (84%) of **22b** as a white solid. Recrystallization from EtOAc/hexanes afforded an analytical sample as white crystals. The use of triethylamine instead of pyridine lead to the cyclic urea **23b** as the mayor product along with some **22b**. An analytical sample of **23b** could be obtained by recrystallization with EtOAc/hexanes.

22b: mp 118–119 °C; $[\alpha]^{20}_D$ +86.2° (*c* 1.29, $CHCl_3$); IR (KBr) 3400, 1750, 1745, 1720, 1520 cm^{-1}; ^1H NMR δ 7.34 (s, 10H), 5.67 (d, J = 7.1 Hz, 2H), 5.08 (s, 4H), 4.88 (d, J = 7.8 Hz, 2H), 3.78 (s, 6H); ^{13} C NMR δ 169.8, 155.7, 135.9, 128.5, 128.3, 128.1, 67.3, 55.7, 53.2; FAB-MS (positive ion mode, *m/z*) 446 (23), 445 ([M + H]$^+$, 100), 402 (19), 401 (93), 311 (26). Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.4; H, 5.5; N, 6.3. Found: C, 59.1; H, 5.3; N, 6.0.

23b: mp 95–98 °C; $[\alpha]^{20}_D$ −7.57° (*c* 1.11, $CHCl_3$); IR (KBr) 1810, 1740 cm^{-1}; ^1H NMR δ 7.41–7.31 (m, 10H), 5.35 (d, J = 12.3 Hz, 2H), 5.25 (d, J = 12.3 Hz, 2H), 4.68 (s, 2H), 3.76 (s, 6H); ^{13}C NMR δ 168.2, 150.9, 146.4, 134.8, 128.9, 128.4, 69.3, 55.6, 53.9; FAB-MS (positive ion mode, *m/z*) 494 (14), 493 (55), 471 ([M + H]$^+$, 100), 278 (12), 245 (11), 181 (44). Anal. Calcd for $C_{23}H_{22}N_2O_9$: C, 58.7; H, 4.7; N, 6.0. Found: C, 58.3; H, 4.5; N, 5.8.

(2*S*,3*R*)- and (2*S*,3*S*)-Dimethyl *N*-(9'-Phenylfluoren-9'-yl)-3-hydroxy-3-methylaspartate (29a,b). A (reaction with MoOPH): A solution of **28** (614 mg, 1.48 mmol) in THF (14 mL) was added dropwise to a stirred solution of KHMDS (2.15 mL, 2.66 mmol, 180 mol %, 1.24 M in THF) at −78 °C. The enolate was allowed to form for 1 h 50 min at −40 °C and then it was cooled to −78 °C. MoOPH (1.28 g, 2.96 mmol, 200 mol %) was added to the above enolate solution and stirring was continued for 3 h 15 min at −78 °C and then warmed slowly for 1 h 35 min to −65 °C. The reaction was quenched with saturated Na_2SO_3 (10 mL). H_2O (3 mL) was added and the reaction mixture was warmed to room temperature, stirred for 10 min and partitioned between Et_2O (150 mL) and H_2O (150 mL). The aqueous layer was extracted with Et_2O (2 × 80 mL) and the combined organic phase was washed with HCl (2 × 200 mL, 5%) and brine, dried and evaporated to give a residue that was carefully purified by column chromatography (hexanes/EtOAc, 4.5/1) to give 335 mg of **29a** as a white foam along with 176 mg of **29b** as a white crystalline solid, which was recrystallized from EtOAc/hexanes (80% combined yield).

B (reaction with Davis' oxaziridine). HMPA (0.180 mL) and a solution of **28** (49 mg, 0.118 mmol) in THF (1.5 mL) were succesively added dropwise to a stirred solution of LHMDS (0.345 mL, 0.354 mmol, 300 mol %, 1.03 M in THF–hexanes) at −78 °C. The enolate was allowed to form for 2 h at −40 °C and then cooled to −78 °C. Davis' oxaziridine (100 mg, 0.384 mmol, 325 mol %) was added to the above enolate solution and stirring was continued for 2 h 45 min at −78 °C. The reaction was quenched with Et_3N (0.1 mL) and saturated NH_4Cl (3 mL). The reaction mixture was partitioned between EtOAc (13 mL) and H_2O (7 mL). The aqueous layer was extracted with EtOAc (8 mL) and the combined organic phase was washed with H_2O (10 mL) and brine, dried and evaporated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) gave 47 mg (92%) of **29** as a mixture of diastereoisomers (1/1 by ^1H NMR).

29a: $[\alpha]^{20}_D$ −345° (*c* 1.4, $CHCl_3$); IR (film) 3500, 2960. 1740 cm^{-1}; ^1H NMR δ 7.69 (t, J = 7.7 Hz, 2H), 7.44–7.15 (m, 11H), 3.99 (s, 1H), 3.64 (s, 3H), 3.34 (d, J = 11.4 Hz, 1H), 3.23 (s, 3H), 2.66 (d, J = 11.4 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR δ 174.5, 173.0, 148.0, 147.9, 144.1, 141.3, 140.1, 128.7, 128.5, 128.4, 128.1, 127.4, 127.3, 126.6, 126.0, 125.7, 120.0, 119.9, 75.6, 72.5, 62.3, 52.4, 51.6, 21.7; FAB-MS in 3-nitrobenzyl alcohol (positive ion mode, *m/z*) 432 ([M + H]$^+$, 4), 257 (3), 242 (23), 241 (100). Anal. Calcd for $C_{26}H_{25}NO_5 \cdot 0.5H_2O$: C, 70.9; H, 6.0; N, 3.2. Found: C, 71.1; H, 5.6; N, 3.2.

29b: mp 138–144 °C; $[\alpha]^{20}_D$ −345.6° (*c* 0.75, $CHCl_3$); IR (KBr) 1740 cm^{-1}; ^1H NMR δ 7.68 (t, J = 7.7 Hz, 2H), 7.38–7.14 (m, 11H), 3.70 (s, 3H), 3.21 (s, 3H), 2.97 (s, 1H), 1.19 (s, 3H); ^{13}C NMR δ 175.3, 172.9, 148.3, 148.1, 144.5, 141.3, 140.1, 128.5, 128.4, 127.6, 127.4, 126.8, 126.0, 125.7, 120.0, 119.9, 76.3, 72.2, 61.1, 52.9, 51.3, 22.7; FAB-MS in 3-nitrobenzyl alcohol (positive ion mode, *m/z*) 432 ([M + H]$^+$, 6), 328 (2), 257 (5), 242 (36), 241 (100). Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.4; H, 5.9; N, 3.2. Found: C, 72.6; H, 5.9; N, 3.2.

(4*R*,5*S*)-4,5-Bis(methoxycarbonyl)-4-methyl-1-(9'-phenylfluoren-9'-yl)oxazolidine (30a). A solution of **29a** (99 mg, 0.23 mmol), *p*-TsOH (18 mg, 0.095 mmol) and H_2CO (689 mg, 6.89 mmol, 30% in H_2O) in THF (0.85 mL) was stirred for 11 days at room temperature, then the reaction mixture was partitioned between CH_2Cl_2 (25 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic phase was washed with saturated $NaHCO_3$ (25 mL) and brine, dried and evaporated. Purification of the residue by column chromatography (hexanes/EtOAc, 2.7/1) gave 91 mg (89%) of **30a** as a white crystalline solid that was recrystallized from Et_2O/hexanes: mp 161 °C; R_f 0.34 (hexanes/EtOAc 3/1); $[\alpha]^{20}_D$ +396.0° (*c* 0.62, $CHCl_3$); ^1H NMR δ 7.79–7.10 (m, 13H), 5.20 (d, J = 6.9 Hz, 1H), 5.13 (d, J = 6.9 Hz, 1H), 3.63 (s, 3H), 3.45 (s, 3H), 2.90 (s, 1H), 0.93 (s, 3H); ^{13}C NMR δ 172.5, 172.1, 148.6, 146.2, 143.9, 142.1, 138.8, 129.2, 128.6, 128.5, 128.0, 127.8, 127.6, 127.3, 127.1, 126.2, 119.9, 119.8, 85.6, 85.5, 77.3, 70.8, 52.2, 51.6, 23.4; FAB-MS

(positive ion mode, *m/z*) 444 ([M + H]$^+$, 6), 289 (2), 285 (2), 273 (2), 255 (2), 242 (23), 241(100). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.1; H, 5.7; N, 3.2. Found: C, 72.7; H, 5.6; N, 3.0.

(4*S*,5*S*)-4,5-Bis(methoxycarbonyl)-4-methyl-1-(9′-phenylfluoren-9′-yl)oxazolidine (30b). As described above, from **29b** (68 mg, 0.16 mmol), *p*-TsOH (12 mg, 0.063 mmol) and H_2CO (473 mg, 4.73 mmol, 30% in H_2O) in THF (0.5 mL) (4 days). Purification of the crude product by column chromatography (hexanes/EtOAc, 4.5/1) gave 63 mg (90%) of **30b** as a white foam that was recrystallized from Et_2O-hexanes: mp 173−174 °C; R_f 0.34 (hexanes/EtOAc 3/1); $[\alpha]^{20}_D$ +291.8° (*c* 0.68, $CHCl_3$); IR (KBr) 1750 cm^{-1}; ^{1}H NMR δ 7.73 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.54−7.41 (m, 4H), 7.35−7.12 (m, 7H), 5.08 (d, J = 4.2 Hz, 1H), 4.95 (d, J = 4.2 Hz, 1H), 3.59 (s, 1H), 3.49 (s, 3H), 3.37 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 172.6, 172.0, 148.1, 145.8, 142.4, 141.9, 139.0, 128.9, 128.6, 128.5, 127.8, 127.7, 127.3, 127.0, 126.0, 120.1, 120.0, 84.6, 83.0, 75.3, 65.9, 52.5, 51.5, 20.0; FAB-MS in 3-nitrobenzyl alcohol (positive ion mode, *m/z*) 444 ([M + H]$^+$, 3), 257 (3), 242 (24), 241 (100). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.1; H, 5.7; N, 3.2. Found: C, 72.8; H, 5.3; N, 3.1.

(2*S*,3*R*,1″*R*)- and (2*S*,3*R*,1″*RS*)-Methyl *N*-(9′-Phenylfluoren-9′-yl)-3-hydroxy-3-[*N*′-(1″-phenylethylcarbamoyl)-butanoate (31a, 31b). A solution of **29a** (100 mg, 0.232 mmol) and LiOH (136 mg, 3.25 mmol) in dioxane/H_2O (1/1, 6.5 mL) was stirred at 0 °C for 2 h 15 min. The pH of the reaction was adjusted to 2 with HCl (5%) and then the reaction mixture was allowed to warm to room temperature. The aqueous phase was washed with EtOAc (2 × 20 mL) and the combined organic phase was washed with brine, dried and evaporated to give 95 mg (98%) of **(2*S*,3*R*)-α-methyl *N*-(9′-phenylfluoren-9′-yl)-3-hydroxy-3-methylaspartate** as a foam: ^{1}H NMR δ 7.68 (t, J = 7.4 Hz, 2H), 7.39−7.13 (m, 11H), 6.21 (br s, 2H), 3.18 (s, 3H), 2.80 (s, 1H), 1.40 (s, 3H); ^{13}C NMR δ 177.0, 172.5, 146.5, 146.3, 142.9, 141.6, 140.5, 130.0, 129.5, 129.3, 129.0, 128.8, 128.1, 127.7, 127.2, 126.0, 120.5, 120.4, 74.2, 72.9, 60.4, 52.5, 22.4. **31a**: D-α-Methylbenzylamine (9 μL, 0.07 mmol, 105 mol %) was added to a stirred solution of the crude acid (28 mg, 0.067 mmol), DCC (21 mg, 0.1 mmol), HOBt (13 mg, 0.084 mmol) and Et_3N (0.014 mL, 0.1 mmol) in THF (0.8 mL) at 0 °C. The reaction mixture was stirred for 4 h at room temperature and for an additional 5 min after the addition of HCl (1 mL, 5%), then the resulting solution was partitioned between HCl (6 mL, 5%) and Et_2O (8 mL). The organic phase was washed with HCl (6 mL, 5%), saturated $NaHCO_3$ (2 × 6 mL) and brine, dried and evaporated. Purification of the residue by column chromatography (hexanes/EtOAc, 2.5/1) gave 26 mg (74%) of **31a** as a white foam: $[\alpha]^{20}_D$ −151.7° (*c* 0.9, $CHCl_3$); IR (film) 3400, 2980, 1740, 1660 cm^{-1}; ^{1}H NMR δ 7.69 (t, J = 7.2 Hz, 2H), 7.39−7.15 (m, 16H), 5.00 (quint, J = 7.4 Hz, 1H), 4.37 (s, 1H), 3.35 (br s, 1H), 3.25 (s, 3H), 2.81 (s, 1H), 1.47 (d, J = 6.9 Hz, 3H), 1.33 (s, 3H); ^{13}C NMR δ 174.5, 172.9, 147.7, 144.2, 143.1, 141.3, 140.4, 128.9, 128.8, 128.6, 128.5, 128.3, 127.5, 127.4, 127.3, 126.5, 126.2, 126.0, 125.5, 120.3, 120.1, 76.1, 72.7, 61.0, 51.9, 48.7, 23.9, 22.0; FAB-MS (positive ion mode, *m/z*) 521 ([M + H]$^+$, 5), 281 (2), 273 (1), 254 (2), 242 (23), 241 (100). Anal. Calcd for $C_{33}H_{32}N_2O_4 \cdot {}^1/_3H_2O$: C, 75.3; H, 6.3; N, 5.3. Found: C, 75.4; H, 6.1; N, 5.3.

(4*R*,5*S*)-4,5-Bis(methoxycarbonyl)-1-(9′-phenylfluoren-9′-yl)oxazolidine (32a). A solution of **8a** (118 mg, 0.283 mmol), *p*-TsOH (10 mg, 0.056 mmol) and H_2CO (283 mg, 2.83 mmol, 30% in H_2O) in THF (1 mL) was stirred for 4 days at room temperature; then the reaction mixture was partitioned between CH_2Cl_2 (30 mL) and H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (18 mL) and the combined organic phase was washed with saturated $NaHCO_3$ (30 mL) and brine, dried and evaporated. Purification of the residue by recrystallization from EtOAc/hexanes afforded 90 mg of **32a** as white crystals. Recrystallization of the concentrated mother liquors afforded an extra 11 mg (83% combined yield): mp 194−195 °C; R_f 0.34 (hexanes/EtOAc 3/1); $[\alpha]^{20}_D$ +328.0° (*c* 1.27, $CHCl_3$); IR (KBr) 1750, 1710 cm^{-1}; ^{1}H NMR δ 7.72 (d, J = 7.4 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.48−7.41 (m, 4H), 7.34−7.18 (m, 6H), 5.16 (d, J = 6.7 Hz, 1H), 5.11 (d, J = 6.7 Hz, 1H), 3.91 (d, J = 7.9 Hz, 1H), 3.65 (d, J = 8.0 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H); ^{13}C NMR δ 170.7, 170.6, 148.5, 146.0, 143.4, 141.7, 139.1, 129.3, 128.8, 128.6, 128.2, 128.1, 127.7, 127.0, 126.6, 125.6, 120.0, 119.9, 86.3, 77.2, 76.9, 64.2, 51.9 (2C); FAB-MS (positive ion mode, *m/z*) 430 ([M + H]$^+$, 7), 289 (11), 242 (22), 241 (100). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.7; H, 5.4; N, 3.3. Found: C, 72.5; H, 5.3; N, 3.2.

(4*RS*,5*S*)-4,5-Bis(methoxycarbonyl)-1-(9′-phenylfluoren-9′-yl)oxazolidine (32b). As described above, from **8b** (50 mg, 0.12 mmol) a mixture of **32a/32b** (1/2.1 according to ^{1}H NMR) was obtained after 20 h of stirring. Purification of the crude reaction product by column chromatography on silica gel (70−230 mesh, hexanes/EtOAc/Et_3N, 3/1/0.2) gave 44 mg (85%) of the above mixture as a white solid that was recrystallized from EtOAc/hexanes: R_f 0.34 (hexanes/EtOAc 3/1); ^{1}H NMR (mixture **32a/32b**, 1/2.1) δ 7.77−7.17 (m, 13H), 5.19−5.13 (m, 2H), 4.92 (d, J = 6.5 Hz, 1 *anti* H), 4.50 (d, J = 5.2 Hz, 1 *anti* H), 3.94 (d, J = 8.0 Hz, 1 *syn* H), 3.66 (d, J = 8.0 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 3.49 (d, J = 5.2 Hz, 1H), 3.42 (s, 3H); FAB-MS in 3-nitrobenzyl alcohol (positive ion mode, *m/z*) 430 ([M + H]$^+$, 4), 257 (3), 242 (23), 241 (100). Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.7; H, 5.4; N, 3.3. Found: C, 72.7; H, 5.0; N, 3.1.

(4*R*,5*S*)- and (4*S*,5*S*)-4,5-Bis(methoxycarbonyl)-4-methyl-1-(9′-phenylfluoren-9′-yl)oxazolidine (30a,b). A solution of **32** (42 mg, 0.098 mmol) in THF (1.2 mL) was added dropwise to a stirred solution of KHMDS (0.166 mL, 0.176 mmol, 180 mol %, 1.06 M in THF) at −78 °C. After stirring for 1.5h at −78 °C, MeI (0.03 mL, 0.49 mmol, 500 mol %) was added and stirring was continued for 2 h at −78 °C. The reaction was quenched with MeOH (1 mL) and partitioned between Et_2O (13 mL) and 1 M H_3PO_4 (8 mL). The aqueous layer was washed with Et_2O (2 × 8 mL) and the combined organic phase was washed with saturated $Na_2S_2O_3$ (20 mL) and brine, dried and evaporated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) gave 40 mg (92%) of a diastereomeric mixture of **30a** and **30b** in a 1/4 ratio.

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