Stereoselective Michael Addition of Glycine Anions to Chiral Fischer Alkenylcarbene Complexes. Asymmetric Synthesis of β-Substituted Glutamic Acids

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The reaction of lithium enolates of achiral *N*-protected glycine esters with chiral alkoxyalkenylcarbene complexes of chromium provided the corresponding Michael adducts with either high anti or syn selectivity depending on the nature of the nitrogen protecting group, and high diastereofacial selectivity when carbene complexes containing the (−)-8-phenylmenthyloxy group were employed. Subsequent oxidation of the metal−carbene moiety followed by deprotection of the amine group and hydrolysis of both carboxylic esters afforded enantiomerically enriched 3-substituted glutamic acids of natural as well as unnatural stereochemistry. Alternatively, when the deprotection step was performed previously to the oxidation, cyclic aminocarbene complexes were formed, which finally led to optically active 3-substituted pyroglutamic acids.

Introduction

The development of new stereoselective strategies for the synthesis of α-amino acids has evolved in a very active field in recent years.[1] Alkylation of glycine is one of the most useful preparative routes to construct higher α-amino acids. This requires the generation of the enolate, derived from the suitable protected glycine derivative, and its reaction with an electrophile to form a new carbon−carbon bond. The construction of an α-amino acid stereogenic center using this methodology has been solved by incorporating chiral nonracemic glycine synthons. Thus, the most classical ones include Schöllkopf bislactim ethers,[2] 5,6-disubstituted *N*-acyl oxazinones,[3] 2-(*tert*-butyl)-3-methyl-4-imidazolidinone,[4] or Oppolzer's camphor sultam.[5] An alternative asymmetric derivatization of glycine esters is the formation of Schiff's bases with chiral ketones such as camphor[6] or 2-hydroxypinan-3-one,[7] or the formation of a nickel(II) complex of a Schiff base of glycine derived from a chiral ketone like (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone.[8] In all these approaches the source of chirality, to generate the α-amino acid stereogenic center, is always present on the glycinate anion synthon. However, it is possible to get moderate to high enantioselectivity by alkylating diphenylmethyleneglycinate under phase-transfer catalysis (PTC) using chiral tetralkylammonium chlorides as catalysts.[9]

The use of aldimines and ketimines derived from glycine esters has become an easy way to prepare

† X-ray analyses.

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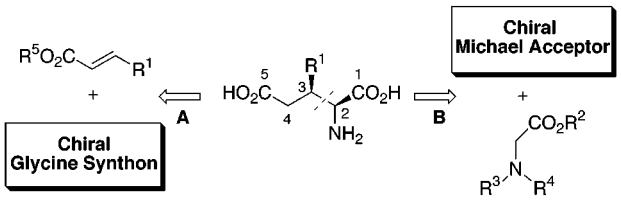
Scheme 1



α-amino acids following the initial work of Stork et al.[10] Since then, O'Donnell et al. have improved and developed the method to reach maturity.[11] Recently we have been interested in the synthesis of unnatural amino acids using the stable and commercially available ethyl *N*-(diphenylmethylene)glycinate.[12] The Michael addition reaction of anions derived from this synthon to different α,β-unsaturated esters showed a convenient means to prepare glutamic acid derivatives.[13] The preparation of enantiomerically pure glutamic acid derivatives, by a Michael addition reaction, can be achieved by two possible disconnection pathways of the C_2-C_3 bond as shown in Scheme 1. While pathway A has been widely explored using the chiral aforementioned glycine synthons,[2-8] disconnection pathway B, where the source of chirality resides on the Michael acceptor, has been much less investigated. To our knowledge only three isolated examples of synthetic approach B have been reported, in which ethyl (*E*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate,[14] (4*S*)-3-[(*E*)-4′-bromo-4,4′-difluoro-2′-butenoyl]-4-alkyl-2-oxazolidinone (alkyl = benzyl, isopropyl),[15] and (*R*)-4-methylene-2-phenyloxazolidin-5-one or the corresponding (*S*)-2-*tert*-butyl derivative[16] are employed as chiral Michael acceptors.[17]

It is well-recognized that Fischer alkenylcarbene complexes behave as reactive Michael acceptors. Since the pioneering work by Casey and co-workers on conjugate additions of phenyllithium, lithium diphenylcuprate,[18] and enolate anions,[19] some other carbon nucleophiles have been 1,4-added to heteroatom-stabilized group 6 vinylcarbene complexes.[20] More recent studies have demonstrated that Michael addition of metal enolates to alkoxy-[21] or nitrogen-stabilized (*O*-chelated imidazolidinone)[22] Fischer alkenylcarbene complexes occurs with syn diastereoselectivity irrespective of the enolate geometry or the nature of the counterion. Furthermore, we have described the first asymmetric Michael additions of alkyllithiums, β-oxygen-substituted organolithium compounds, and ketone or ester lithium enolates to enantiomerically pure (−)-8-phenylmenthyloxy alkenylcarbene complexes of chromium, which proceed with uniformly high levels of asymmetric induction and high syn diastereoselectivity when lithium enolates are involved.[23]

In this paper we report a novel approach for the stereoselective synthesis of racemic and chiral β-substituted glutamic acids through the sequential Michael addition of lithium enolates of achiral glycine esters to chiral alkoxyalkenylcarbene complexes of chromium, followed by oxidation of the metal−carbene moiety and basic hydrolysis of the resulting diester. The initial 1,4-addition takes place with either anti or syn selectivity depending on the substitution pattern of the *N*-protected glycine ester and occurs with high diastereofacial selectivity when the enantiomerically pure above-mentioned vinylcarbene complexes are used as Michael acceptors, allowing, therefore, the asymmetric preparation of glutamic acid derivatives of natural as well as unnatural stereochemistry.

Results and Discussion

Stereoselective Michael Additions of Glycine Anions to (±)-Menthyloxy and (−)-8-Phenylmenthyloxy Alkenylcarbene Complexes. Lithium enolates **2** and **3** were prepared by deprotonation of the corresponding *N*-protected glycine ester with LDA in THF at −78 °C. The results obtained in the reactions of

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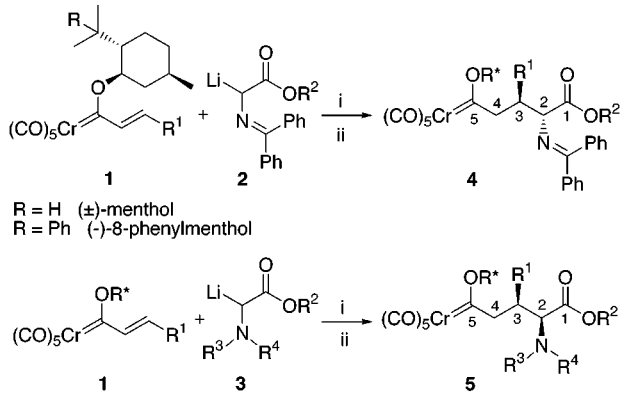
Table 1. Michael Additions of Lithium Glycine Enolates to (±)-Menthyl- and (−)-8-Phenylmenthyloxy Alkenylcarbene Complexes of Chromium

entry	carbene complex	R*	R^1	glycine anion	R^2	R^3	R^4	product[a]	yield (%)[b]	dr[c] anti:syn
1	**1a**	(±)-menthyl	Ph	**2a**	Et			**4a**	78	80:20[d,e]
2	**1a**	(±)-menthyl	Ph	**2b**	*t*-Bu			**4b**	79	82:18[d]
3	**1b**	(±)-menthyl	2-furyl	**2a**	Et			**4c**	80	75:25[d]
4	**1c**	(±)-menthyl	Bu	**2a**	Et			**4d**	62	50:50[f]
5	**1d**	(±)-menthyl	*t*-Bu	**2a**	Et			**4e**	30	50:50[f]
6	**1e**	(−)-8-Ph-menthyl	Ph	**2a**	Et			**4f**	65	96:4
7	**1e**	(−)-8-Ph-menthyl	Ph	**2b**	*t*-Bu			**4g**	87	80:20
8	**1f**	(−)-8-Ph-menthyl	2-furyl	**2a**	Et			**4h**	69	91:9[e]
9	**1g**	(−)-8-Ph-menthyl	3-furyl	**2a**	Et			**4i**	89	97:3
10	**1a**	(±)-menthyl	Ph	**3a**	Et	$PhCH_2$	$PhCH_2$	**5j**	86	10:90[d]
11	**1a**	(±)-menthyl	Ph	**3b**	*t*-Bu	$PhCH_2$	$PhCH_2$	**5k**	83	8:92[d]
12	**1a**	(±)-menthyl	Ph	**3c**	Et	$Me_2Si(CH_2)_2SiMe_2$		**5l**	14	0:100
13	**1e**	(−)-8-Ph-menthyl	Ph	**3a**	Et	$PhCH_2$	$PhCH_2$	**5m**	86	10:90
14	**1e**	(−)-8-Ph-menthyl	Ph	**3b**	*t*-Bu	$PhCH_2$	$PhCH_2$	**5n**	80	13:87

[a] Only the major diastereoisomer is shown. [b] Isolated yield based on the corresponding carbene complex **1**. [c] Diastereomeric ratio was determined by ^{1}H NMR at 300 or 200 MHz. [d] A mixture of two major and two minor isomers, each pair as a nearly equimolecular mixture. The ratio shown corresponds to the anti/syn diastereoselectivity. [e] Determined by ^{13}C NMR spectroscopy (inverse gated decoupling experiments using 1 mg of chromium acetylacetonate). [f] A roughly equimolecular mixture of four diastereoisomers was formed.

Scheme 2[a]



[a] Conditions: (i) THF, −78 °C; (ii) silica gel.

these glycine anions with racemic or enantiomerically pure vinylcarbene complexes **1** are summarized in Scheme 2 and Table 1. We observed that treatment of carbene complexes **1** with lithium enolates of benzophenone Schiff base derivatives of glycine alkyl esters **2** at −78 °C led to a rapid reaction (1−3 h) which afforded, after silica gel column chromatography, the corresponding and unexpected anti Michael adduct **4**. The anti/syn diastereoselectivity of this conjugate addition was good when 3-aryl-substituted carbene complexes **1a** (R^1 = Ph) and **1b** (R^1 = 2-furyl) were used as acceptors (Table 1, entries 1−3), while with aliphatic carbene complexes **1c** (R^1 = Bu) and **1d** (R^1 = *t*-Bu) the chemical yield was lower, no selectivity was observed, and a nearly equimolecular mixture of the four possible isomers was formed (Table 1, entries 4 and 5); in addition adducts **4d**,**e** were unstable and difficult to purify. These racemic complexes **1a**−**d** derived from (±)-menthol did not show any facial selectivity; in each case the major (anti) and the minor (syn) adducts were formed as a roughly 1:1 mixture of isomers. However, these conjugate addition reactions with chiral carbene complexes **1e**−**g** derived from (−)-8-phenylmenthol took place with high anti and facial selectivity, yielding as very major isomers adducts **4f**−**i**, each one observed by ^{1}H and ^{13}C NMR as almost a single diastereoisomer (Table 1, entries 6−9). On the other hand, the reactions of lithium enolates of *N*,*N*-dibenzylglycinates esters **3a**,**b** or *N*,*N*-disilylated glycine ester **3c** with the same Michael acceptors **1a**,**e** under identical experimental conditions led with high selectivity to the initially expected syn Michael adducts **5** (Table 1, entries 10−14). The highest selectivity was achieved with the enolate of the stabase[33] adduct of ethyl glycinate **3c**. This reaction provided a single diastereoisomer but unfortunately with a very low chemical yield to be synthetically useful (Table 1, entry 12). The assignment of either syn (Table 1, entries 6−9) or anti (Table 1, entries 13 and 14) stereochemistry to the minor diastereoisomers formed in the reactions with (−)-8-phenylmenthyloxy carbene complexes **1e**−**g** has not been confirmed, since these compounds were never isolated in pure form. The possibility that these minor products could be in each case the other diastereomeric anti or syn adduct cannot be ruled out.

The stereochemical assignment was made in the case of anti adducts **4** from a single-crystal X-ray structure determination carried out with enantiomerically pure compound **4h**.[24] This analysis unambiguously established the relative configuration as depicted in Scheme 2 and confirmed the drawn absolute configuration of the newly created stereogenic centers, which is in agreement with the sense of facial selectivity previously observed in other conjugate additions to (−)-8-phenylmenthyloxy alkenylcarbene complexes of chromium.[20f,23] The relative syn stereochemistry of adducts **5** was determined by the chemical transformation of carbene complex **5j** to tetrahydropyran **8** as shown in Scheme 3. This sequence involves initial oxidation of the chromium complex **5j** (used as a syn/anti, 90:10, mixture) to ester **6j** followed by procedures previously described for analogous structures.[25] Purification of the major diastereoisomer led to compound **8**. The coupling between the nonaromatic methine protons of this six-membered ring cyclic structure **8** ($J_{H3,H4}$ = 11.4 Hz) corresponds to a trans orientation of the phenyl and *N*,*N*-dibenzylamino groups. For

(24) Crystal data for **4h**: $C_{45}H_{45}CrNO_9$, red crystal, size 0.20 × 0.20 × 0.20 mm, M_r = 795.82, orthorhombic, space group $P2_12_12_1$, a = 14.164(3) Å, b = 14.981(6) Å, c = 19.904(7) Å, V = 4223(2) Å^3, Z = 4, D_x = 1.252 g/cm^3, μ = 3.26 cm^{-1}, F(000) = 1672, T = 293(2) K; final conventional R = 0.050 for 2642 "observed" reflections and $wR2$ = 0.161 (for all reflections) and 513 variables; GOF = 0.974; Flack's parameter χ = 0.05(4). Full details are available in the Supporting Information.

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Scheme 3

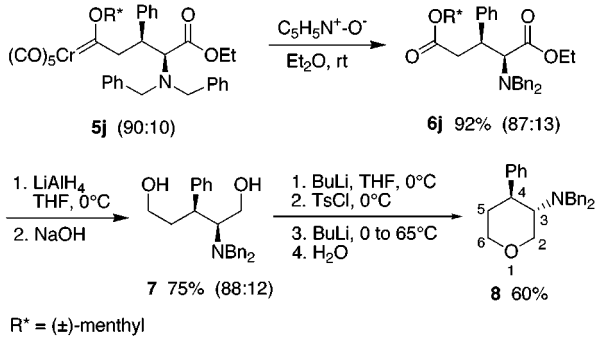
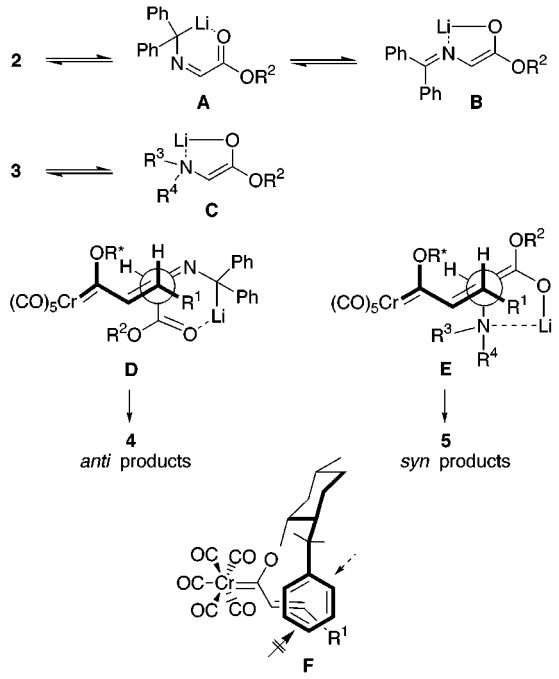


Chart 1



the remaining compounds **4** and **5**, the configurations have been assumed by analogy.

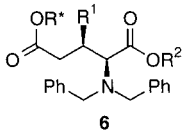
The syn/anti diastereoselectivity of these conjugate additions, which proved to be strongly dependent on the nature of the protective group on the glycine nitrogen atom, can be rationalized in terms of the model shown in Chart 1. This model was initially proposed by Nakamura et al.[21b] to explain the diastereoselective syn Michael addition of ketone and ester metal enolates to heteroatom-stabilized Fischer vinylcarbene complexes, which thus far seemed to be a general property.[22,23] This open chain model assumes an s-trans conformation for the vinylcarbene complex and that the Michael addition occurs with an anti relationship of the donor and acceptor π-systems, placing the bulkiest substituent of the enolate away from the $(CO)_5Cr{=}C(OR^*)$ grouping to avoid steric interactions. According to that, the formation of syn Michael adducts **5** can be explained by the sterically favorable approach **E** of anion **3** as a (*Z*)-enolate (1-oxaallylanion **C**) in which the R^3R^4N group is placed away from the metal−carbene moiety. The diastereoselective anti Michael additions observed with lithium enolates **2** could be explained likewise by this mechanistic model but assuming that this type of enolate interacts with the vinylcarbene complex as a 2-azaallylanion six-membered ring structure **A** instead of 1-oxaallylanion five-membered ring derivative **B**.[13a] Arrangement **A** could be favored by the stability provided by the two phenyl groups and the six-membered ring intramolecular coordination. Thus, approach topology **D** in which the CO_2R^2 group is placed away from the metal−carbene moiety explains the formation of anti Michael adducts **4**.[26] However, the possibility that these later reactions are under thermodynamic rather than kinetic control, and so proceed with syn selectivity followed by epimerization at C2, cannot be entirely eliminated. That epimerization would be a consequence of the greater acidity of the hydrogen bonded to C2 in compounds **4** compared to adducts **5**. Finally, the sense of chirality of the products derived from (−)-8-phenylmenthyloxy carbene complexes follows from the known model **F** of the most stable conformation of these complexes, which is favored by the alkene−arene π-stacking effect.[27] Nucleophile attack on these Michael acceptors occurs selectively from the opposite side of the phenyl group.[20f,23]

Oxidation of Michael Adducts 4 and 5. In the next step carbene complexes **4** and **5** were transformed to the corresponding carboxylic ester **6**, **9**, or **10** by oxidation of the metal−carbene functional group. The results are gathered in Table 2. Oxidative removal of the pentacarbonylchromium fragment was mainly effected with pyridine *N*-oxide using either THF or ether as solvent. This oxidation proved to be a slow reaction (reaction time between 2 and 5 days), probably because of steric inhibition imposed by the (±)-menthyl or (−)-8-phenylmenthyl group, and under these conditions partial decomposition of the starting carbene complex might become competitive, which could account for the commonly moderate chemical yields. Oxidation of racemic **4a**−**c** and chiral **4f**−**i** anti Michael adducts with pyridine *N*-oxide in THF (method A) or Et_2O (method C) led to the corresponding anti imino ester **9a**−**c**,**f**−**i**. In the case of the chiral compounds **9f**−**i** the reaction proceeded uniformly, maintaining the diastereomeric ratio of the corresponding starting material (Table 2, entries 6−10). On the other hand, in the oxidation reactions carried out with racemic products **4a**−**c**, the anti/syn diastereomeric ratio of imino esters **9a**−**c** seems to be dependent on the reaction conditions of time, temperature, and amount of oxidant (Table 2, entries 1 and 3−5). In both racemic and chiral sets of compounds, the reactions in ether, where pyridine *N*-oxide is less soluble, were slower than in THF, and in addition the anti/syn ratio of diastereoisomers when Et_2O is used as solvent can be significantly lower (Table 2, entries 1, 4, and 6 versus 3, 5, and 7, respectively). These lower selectivities could be explained as a result of partial epimerization at the amino acid (C2) center, which would be induced by the free pyridine generated in the reaction medium and favored at prolonged reaction times. Racemic **5j** and chiral **5m** syn Michael adducts were likewise oxidized with pyridine *N*-oxide in ether, affording the corresponding syn amino ester **6j**,**m** with high selectivity and in these cases high chemical yield as well (Table 2, entries 11 and 12). Ceric

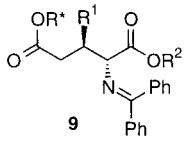
(26) Either anti (see refs 2a, 6c,d, 13e,f, and 15a) or syn (see refs 4c and 13a) selective Michael additions of glycine synthon anions to different α,β-unsaturated esters have been previously observed. As indicated in ref 13a these opposite results could be related with the structure of the glycine enolate reacting either as a 2-azaallylanion, which led to the anti adduct, or as an 1-oxaallylanion leading to the syn adduct when no possibility of formation of the 2-azaallylanion structure exists.

(27) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.

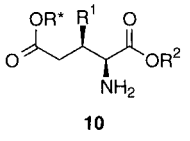
Table 2. Oxidation of Carbene Complexes 4 and 5. Obtention of Products 6, 9, and 10



6



9

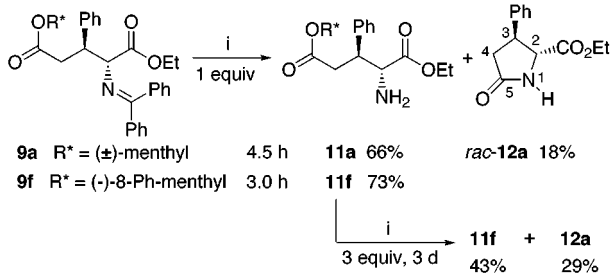


10

entry	starting complex	oxidation method[a]	R*	R^1	R^2	product[b]	yield(%)[c]	dr[d] anti:syn
1	**4a**	A	(±)-menthyl	Ph	Et	**9a**	76	62:38
2	**4a**	B	(±)-menthyl	Ph	Et	**10a**	50	14:86
3	**4b**	C	(±)-menthyl	Ph	*t*-Bu	**9b**[e]	70	47:53[f]
4	**4c**	A	(±)-menthyl	2-furyl	Et	**9c**	69	74:26
5	**4c**	C	(±)-menthyl	2-furyl	Et	**9c**	65	67:33
6	**4f**	A	(−)-8-Ph-menthyl	Ph	Et	**9f**	71	92:8
7	**4f**	C	(−)-8-Ph-menthyl	Ph	Et	**9f**	64	87:13
8	**4g**	A	(−)-8-Ph-menthyl	Ph	*t*-Bu	**9g**	60	80:20[g]
9	**4h**	A	(−)-8-Ph-menthyl	2-furyl	Et	**9h**	56	92:8[h]
10	**4i**	A	(−)-8-Ph-menthyl	3-furyl	Et	**9i**	52	100:0
11	**5j**	C	(±)-menthyl	Ph	Et	**6j**	92	13:87
12	**5m**	C	(−)-8-Ph-menthyl	Ph	Et	**6m**	59	5:95

[a] Method A: $C_5H_5N^+-O^-$, THF, rt. Method B: CAN, Me_2CO/H_2O, 0 °C to rt. Method C: $C_5H_5N^+-O^-$, Et_2O, rt. [b] Only the major diastereoisomer is shown. [c] Isolated yield based on the corresponding carbene complex **4** or **5**. [d] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [e] Almost a 1:1 mixture of **9b** and its corresponding syn diastereoisomer was formed in this case. [f] The reaction was refluxed for 6 h after 4 d at rt. [g] Determined by ^{13}C NMR spectroscopy. [h] In this case a 2:1 mixture of THF/Et_2O was used as solvent and the reaction was refluxed for 25 h.

Scheme 4[a]



[a] Reagents: (i) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, reflux.

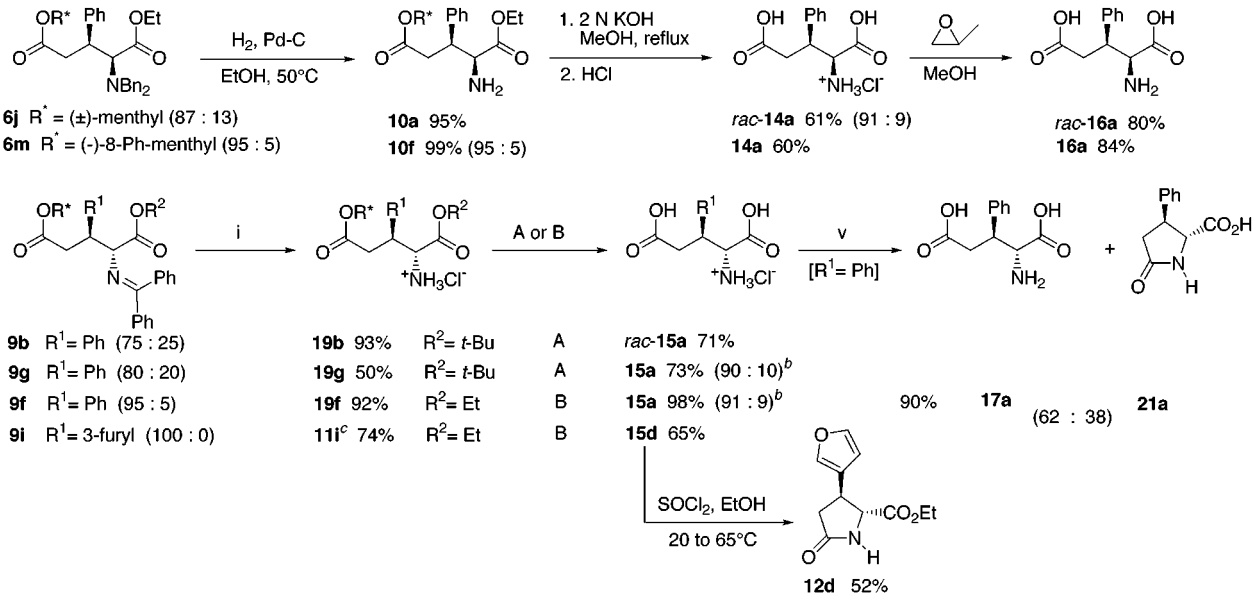
ammonium nitrate (CAN) can also be used as oxidizing agent, which removes the metal fragment at a higher reaction rate but provided the corresponding ester with lower chemical yield. Thus, the reaction of anti carbene complex **4a** with CAN was completed in 1 h, affording syn amino ester **10a** with 72% de (Table 2, entry 2). This result indicates that under these oxidation conditions epimerization at the α-amino acid center (C2 carbon) and hydrolysis of the benzophenone imine concurrently took place. Other oxidants, including DMSO tested with compound **4i**, oxone, or iodosobenzene both experimented with carbene complex **4h**, were unsuccessful, leading to even much lower chemical yields or mostly to an unidentified mixture of products.

The anti relative configuration assigned to oxidation products **9** was confirmed in two cases by conversion of imino esters **9a**,**f**, used as diastereomerically pure major (anti) isomers, to cyclic lactams *rac*-**12a** and **12a** as detailed in Scheme 4. Cleavage of the imine was performed with hydroxylamine hydrochloride and sodium acetate in ethanol at reflux.[6c] Under these conditions racemic compound **9a** led to a mixture of **11a** and its cyclized product *rac*-**12a** that were readily separated by column chromatography. Chiral derivative **9f**, bearing a bulkier chiral auxiliary, afforded after heating for 3 h amino diester **11f** as a single product; partial cyclization of **11f** to **12a** was observed at longer reaction time and with an excess of in situ generated hydroxylamine acetate. The coupling between the five-membered ring methine hydrogens ($J_{H2,H3}$ = 4.6 Hz) corresponds to a trans orientation[7a,28] of both hydrogen atoms in compounds **12a** and *rac*-**12a**. The stereochemistry of compound **10a** was established after transformation of this syn amino diester to the corresponding racemic α-amino acid *rac*-**16a** (*rac*-**14a**, 95%; *rac*-**16a**, 44%), and comparison of its NMR spectral data with those previously described for (2*S*,3*S*)-3-phenylglutamic acid.[8a] This transformation was effected following the procedure shown in the next section and Scheme 5 for this same product (**10a**) but generated in a different way.

Hydrolysis Reactions. Synthesis of 3-Substituted Glutamic Acids (Scheme 5). Finally, the syn amino and anti imino diesters **6** and **9**, respectively, were converted to the corresponding β-substituted glutamic acids by first removing the protective group on the nitrogen atom and then hydrolysis of the carboxylic esters. Thus, catalytic hydrogenation in the presence of palladium on carbon of *N*,*N*-dibenzyl derivatives **6j**,**m** furnished syn amino diesters **10a**,**f** respectively, which were further refluxed with 2 N KOH in methanol. After acidification with concentrated HCl the corresponding hydrochloride derivative of syn 3-phenylglutamic acid *rac*-**14a** or **14a** was isolated. Treatment of these derivatives with propylene oxide in methanol allowed the liberation of (2*S*,3*S*)-3-phenylglutamic acid as optically active **16a** or racemic *rac*-**16a** product, whose physical and spectral properties are in agreement with those previously reported.[8a] On the other hand, hydrolysis of the benzophenone imine group of compounds **9b**,**f**,**g**,**i** was effected with 5 N hydrochloric acid at room temperature. In this way, the corresponding anti amino diesters were isolated either directly as their hydrochloride derivatives in the case of **19b**,**f**,**g** or as the free amino diester **11i** by subsequent extraction of the reaction mixture under basic conditions. Hydrolysis of diesters **19b**,**f**,**g** and **11i** was carried out following two different reaction sequences depending on the nature of the R^2 group. The *tert*-butyl derivatives **19b**,**g** (R^2 = *t*-Bu) were first treated with

(28) (a) Mauger, A. B. *J. Org. Chem.* **1981**, *46*, 1032. (b) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352.

Scheme 5[a]

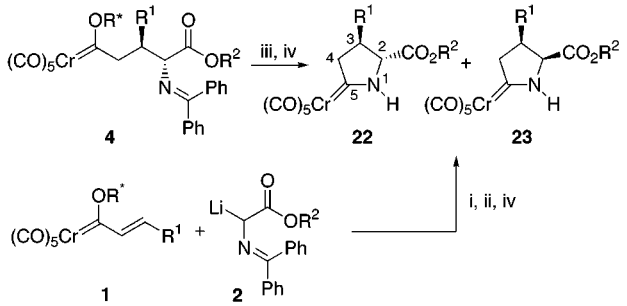


[a] Key: (i) 5 N HCl, THF, rt. Sequence A: (ii) CF_3CO_2H, CH_2Cl_2, rt; (iii) 2 N KOH, MeOH, reflux; (iv) HCl. Sequence B: (iii); (iv). (v) Propylene oxide, MeOH, rt or Dowex. [b] Anti/syn ratio. [c] Isolated as amino diester **11i** instead of its hydrochloride **19i** by extraction under basic conditions.

trifluoroacetic acid at room temperature and then with 2 N potassium hydroxide in methanol at reflux, whereas the ethyl derivatives **19f** and **11i** (R^2 = Et) were directly saponified (2 N KOH). Later acidic treatment (concentrated HCl) yielded the corresponding anti 3-arylglutamic acid hydrochlorides **15**. These anti open-chain amino acids were always isolated together with minor and variable amounts of the corresponding cyclic pyroglutamic acid derivative **21**. From these mixtures the corresponding pyroglutamic acid **21** can be ring opened by refluxing with 1 N HCl to give hydrochloride **15**. In the case of **15d** it was found that the minor cyclic product **21d** from a 60:40 mixture of **15d**/**21d** was completely converted into the major acyclic derivative **15d**, when a solution in MeOD (NMR sample) was allowed to stand at room temperature for 3 d. The anti relative configuration of hydrochloride **15d** was confirmed by cyclization of this amino acid to the corresponding ethyl pyroglutamate **12d** ($J_{H2,H3}$ = 5.7 Hz, which indicates a trans relationship between the substituents) with thionyl chloride in ethanol. The free amino acid can be isolated from the corresponding hydrochloride by reaction with propylene oxide or by cation-exchange chromatography (Dowex resin); in the case of **15a** a mixture of (2*R*,3*S*)-3-phenylglutamic acid (**17a**) and its cyclized product (2*R*,3*S*)-3-phenylpyroglutamic acid (**21a**) was obtained.

Cyclic Aminocarbene Complexes. Synthesis of 3-Substituted Pyroglutamic Acids. We found that deprotection of the benzophenone imine of anti Michael adducts **4** transformed these open-chain alkoxycarbene complexes to the corresponding cyclic aminocarbene derivatives **22** and **23** (Scheme 6). Consequently, successive treatment of **4** with 50% aqueous solution of HBF_4 and then with Et_3N led to an easily separable (silica gel column chromatography) mixture of diastereoisomeric aminocarbene complexes **22** ($J_{H2,H3}$ = 4−6 Hz) and **23** ($J_{H2,H3}$ = 6−10 Hz) in which the trans isomer **22** was always the major product (Table 3, entries 1−3). This procedure represents a milder and more direct way to remove the chiral auxiliary group. A 2 N solution of HCl

Scheme 6[a]



[a] Conditions: (i) THF, −78 °C; (ii) 50% HBF_4, THF, −78 to +20 °C; (iii) 50% HBF_4, THF, 0 to 20 °C; (iv) Et_3N, 0 to 20 °C.

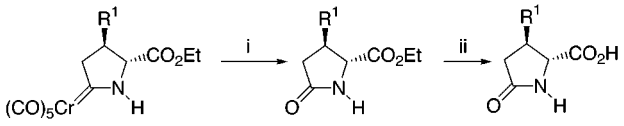
Table 3. Diastereoselective Synthesis of Cyclic Aminocarbene Complexes of Chromium 22

entry	starting complex	glycine anion	R^1	R^2	product[a]	yield (%)[b]	**22**:**23** ratio[c]
1	**4b**[d]		Ph	*t*-Bu	*rac*-**22b**	40[e]	68:32
2	**4c**[d]		2-furyl	Et	*rac*-**22c**	56	68:32
3	**4h**[d]		2-furyl	Et	**22c**	53	74:26
4	**1a**	**2a**	Ph	Et	*rac*-**22a**	56	80:20
5	**1b**	**2a**	2-furyl	Et	*rac*-**22c**	62	73:27
6	**1e**	**2a**	Ph	Et	**22a**[f]	95	94:6
7	**1f**	**2a**	2-furyl	Et	**22c**[g]	66	92:8

[a] Only the major diastereoisomer is shown. [b] Isolated yield based on the corresponding carbene complex **1** or **4**. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; integration of the CH−N signal. [d] Used as the mixture of anti/syn diastereoisomers shown in Table 1. [e] Using 2 N HCl instead of 50% HBF_4 aqueous solution, the reaction took a longer time (21 h vs 6 h) and a 78:22 mixture of *rac*-**22b**/*rac*-**23b** was formed in 43% yield. [f] 87% ee, determined by HPLC analysis on a chiral support. [g] 78% ee, determined by HPLC analysis on a chiral support.

can be alternatively used instead of 50% HBF_4 in H_2O, although in the former case the hydrolysis reaction was slower (Table 3, entry 1). Furthermore, these cyclic aminocarbene complexes can be directly and more efficiently synthesized from the reaction of alkenylcarbene complexes **1** with glycine anion **2** as shown in Scheme 6

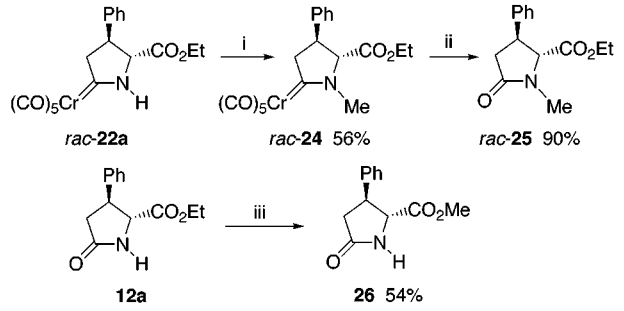
Scheme 7[a]



rac-**22a** R^1 = Ph	*rac*-**12a** 80%	*rac*-**21a** 70%
rac-**22c** R^1 = 2-furyl (75:25)	*rac*-**12c** 76% (70:30)	*rac*-**21c** 70%
22a R^1 = Ph	**12a** 53%	**21a** 79%
22c R^1 = 2-furyl	**12c** 33%[b]	**21c** 65%

[a] Key: (i) $C_5H_5N^+-O^-$, THF, rt; (ii) 2.5 N LiOH, THF, rt, then HCl. [b] Yield based on recovered starting carbene complex was 46%.

Scheme 8[a]



rac-**22a** *rac*-**24** 56% *rac*-**25** 90%

12a **26** 54%

[a] Reagents: (i) MeI, Cs_2CO_3, Me_2CO, H_2O, rt; (ii) $C_5H_5N^+-O^-$, THF, rt; (iii) CH_3COCl, MeOH, rt.

and Table 3, entries 4−7. This one-pot process afforded the trans isomer **22** with good diastereoselectivity, which was particularly high, and better than in the two-step reaction, when the chiral (−)-8-phenylmenthyloxy derivatives **1e**,**f** were employed (Table 3, entry 7 vs 3). Compounds **22a** and **22c** were also formed with high enantiomeric purity (87% and 78% ee, respectively; Table 3, entries 6 and 7), although this level of facial selectivity is somewhat lower that the previously observed in the Michael addition of ketone lithium enolates to chiral carbene complexes **1e**,**f**.[23b] Aminocarbene complexes **22** were transformed to the corresponding racemic or optically active lactams **12** by oxidative removal of the metal fragment with pyridine *N*-oxide (Scheme 7). This oxidation was also a very slow reaction, providing the ethyl pyroglutamate substrates **12** with moderate chemical yields. Experiments carried out using other solvents such as MeOH or ethyl acetate or other oxidants such as PhIO led to worse results. Basic hydrolysis of esters **12** with 2.5 N LiOH followed by acidic treatment yielded the enantiomerically enriched 3-arylpyroglutamic acids **21a**,**c**. The structure of these cyclic products was confirmed by conversion of two of them to known cyclic lactam derivatives as detailed in Scheme 8. Aminocarbene complex *rac*-**22a** was methylated on the nitrogen in the presence of Cs_2CO_3 as a base[29] to give complex *rac*-**24** which was subsequently transformed into *rac*-**25**[28b] by oxidation of the chromium−carbon double bond. Likewise, transesterification of **12a** furnished **26**.[2a]

In conclusion, our results demonstrate that the diastereoselective conjugate addition of achiral glycine synthons to chiral alkenylcarbene complexes represents a novel synthetic approach to racemic and optically enriched β-substituted glutamic or pyroglutamic acids, which are formed after sequential deprotection, oxidation, and hydrolysis of the initial 1,4-adducts. Cyclic aminocarbene complexes **22**, which in addition are stable compounds, may be envisaged as valuable intermediates for the asymmetric synthesis of more highly substituted glutamic acid derivatives.

Experimental Section

General Procedures. TLC was carried out on glass-backed silica gel plates coated with F_{254}; the chromatograms were visualized under ultraviolet light or by staining with Ce/Mo solution or with ninhydrin solution and subsequent heating. Flash column chromatography was performed on silica gel 60, 230−240 mesh. Ion-exchange chromatography was performed on Dowex 50wx8-100. Optical rotations were measured at room temperature, and concentration is reported in g/100 mL. Carbon multiplicities were assigned according to the outcome of DEPT experiments. Enantiomeric excess was determined by HPLC analysis (in comparison with the corresponding racemic mixtures) carried out on a Chiralcel OD-H chiral column with a UV/vis photodiode array detector and employing mixtures of hexane/*i*-PrOH of ratio 8:1 for **22a** and 75:1 for **22c** as eluants, flow rate 1.0 mL/min.

Et_2O and THF were freshly dried by distillation from sodium benzophenone under nitrogen. CH_2Cl_2 and MeOH were distilled from CaH_2 and stored over 4 Å molecular sieves. Hexane was distilled over P_2O_5. The following chemicals were prepared according to literature procedures: pentacarbonyl[1-[(1*R**,2*S**,5*R**)-menthyloxy]ethylidene]chromium,[30] pentacarbonyl[1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]ethylidene]chromium,[23b] pentacarbonyl[(*E*)-3-phenyl-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]-2-propenylidene]chromium (**1e**),[23b] pentacarbonyl[(*E*)-3-(2-furyl)-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]-2-propenylidene]chromium (**1f**),[23b] ethyl *N*-(diphenylmethylidene)glycinate,[31] *tert*-butyl *N*-(diphenylmethylidene)glycinate,[31] ethyl *N*,*N*-dibenzylglycinate,[32] *tert*-butyl *N*,*N*-dibenzylglycinate,[32] 1-(ethoxycarbonylmethyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilolidine,[33] and *trans*-1-iodo-1-hexene.[34] All the other chemicals were commercially available and were used as received. Carbene complexes **1a**, **1b**, **1e**, and **1f** were easily handled by storing them in THF solution at −20 °C under a nitrogen atmosphere.

Experimental procedures and spectral data for compounds not described here are presented in the Supporting Information.

General Procedure for the Synthesis of Carbene Complexes 4 and 5. All the operations were carried out under a nitrogen atmosphere. LDA (1.6 equiv) was prepared by adding BuLi (1.6 equiv) to a solution of *i*-Pr_2NH (1.6 equiv) in THF at −60 °C. After being stirred for 15 min at −60 °C, the LDA solution was cooled to −78 °C, and a solution of the appropriate protected glycine ester (1.6 equiv) was added via an addition funnel. The resulting yellow-orange solution of **2** or **3** was stirred for 30 min at −78 °C, and then, a THF solution of the corresponding alkenylcarbene complex **1** (1 equiv) was added dropwise from the addition funnel at −78 °C. Once the addition was concluded, the dark red starting carbene solution turned into a bright yellow one. After being stirred for 1−3 h at −78 °C, the reaction mixture was quenched with silica gel and allowed to quickly warm to room temperature by removing the cold bath. THF was removed under reduced pressure, and the silica-adsorbed product was placed on the top of a column and purified by flash chromatography. Elution with hexane/CH_2Cl_2, 9:1, removed some remaining starting carbene complex and no polar materials. Sequential elution with hexane/CH_2Cl_2, 4:1 and 1:1, gave pure carbene complexes **4** or **5** as one major diastereoisomer in the chiral examples (**4f**−**i**, **5m**,**n**)

(29) Sabaté, R.; Schick, U.; Moretó, J. M.; Ricart, S. *Organometallics* **1996**, *15*, 3611.

(30) Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364.

(31) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

(32) Banfi, L.; Cardani, S.; Potenza, D.; Scolastico, C. *Tetrahedron* **1987**, *43*, 2317.

(33) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.

(34) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138.

and as an aproximately 1:1 mixture of two major diastereoisomers in the racemic examples (**4a**−**e**, **5j**−**l**).

Pentacarbonyl[(3*S*,4*R*)-4-[*N*-(diphenylmethylidene)-amino]-4-ethoxycarbonyl-3-phenyl-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]butylidene]chromium (4f). Ethyl *N*-(diphenylmethylidene)glycinate (0.91 g, 3.4 mmol) in THF (15 mL) was treated with LDA prepared from *i*-Pr_2NH (0.45 mL, 3.4 mmol) and BuLi (2.5 M in hexane, 3.4 mmol) in THF (8 mL), according to the general procedure. After 30 min at −78 °C, a 0.425 M THF solution of carbene complex **1e** (5 mL, 2.125 mmol) was diluted in THF (20 mL) and added to the glycinate anionic solution of **2a** at −78 °C. The reaction mixture was stirred for 2 h at −78 °C and worked up as described above. Flash chromatography of the crude product afforded 1.10 g (1.3 mmol, 65% yield) of **4f** as a yellow foam in 96:4 ds: R_f = 0.45 (hexane/CH_2Cl_2, 1:1). Data on the 96:4 diastereomeric mixture: $[\alpha]_D$ = +82.2 (*c* 0.65, $CHCl_3$); IR (film) ν (cm^{-1}) 2063, 1950, 1741; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84−7.61 (4 H, m), 7.58−7.13 (14 H, m), 6.85 (2 H, m), 4.98 (1 H, td, *J* = 10.3, 3.9 Hz), 3.97 (5 H, m), 2.29 (1 H, t, *J* = 11.6 Hz), 2.09 (1 H, m), 1.63 (2 H, m), 1.35 (1 H, m), 1.27−1.03 (11 H, m + 2s + t, *J* = 7.3 Hz), 0.86 (1 H, m), 0.73−0.60 (4 H, m + d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 356.6 (C), 222.7 (C), 216.4 (C), 171.7 (C), 170.2 (C), 151.0 (C), 139.4 (C), 139.0 (C), 135.9 (C), 132.3 (CH), 130.5 (CH), 130.0 (CH), 129.5 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.8 (CH), 125.5 (CH), 125.3 (CH), 92.5 (CH), 71.2 (CH), 63.9 (CH_2), 60.8 (CH_2), 50.6 (CH), 47.1 (CH), 41.4 (CH_2), 39.4 (C), 33.8 (CH_2), 30.5 (CH), 27.7 (CH_3), 26.0 (CH_2), 24.5 (CH_3), 21.4 (CH_3), 13.8 (CH_3).

Pentacarbonyl[(3*R*,4*R*)-4-[*N*-(diphenylmethylidene)-amino]-4-ethoxycarbonyl-3-(2-furyl)-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]butylidene]chromium (4h). Ethyl *N*-(diphenylmethylidene)glycinate (0.43 g, 1.6 mmol) in THF (10 mL) was treated with LDA prepared from *i*-Pr_2NH (0.21 mL, 1.6 mmol) and BuLi (2.5 M in hexane, 1.6 mmol) in THF (5 mL), according to the general procedure. After 30 min at −78 °C, a 0.33 M THF solution of carbene complex **1f** (3 mL, 1 mmol) was diluted in THF (10 mL) and added to the glycinate anionic solution of **2a** at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and worked up as described above. Flash chromatography of the crude product afforded 0.55 g (0.69 mmol, 69% yield) of **4h** as a yellow solid in 91:9 ds: mp 103−104 °C; R_f = 0.31 (hexane/CH_2Cl_2, 1:1). Data taken from a pure sample of **4h**: $[\alpha]_D$ = +86.6 (*c* 0.5, $CHCl_3$); IR (film) ν (cm^{-1}) 2058, 1936, 1738, 1624; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.70 (2 H, d, *J* = 6.7 Hz), 7.45−7.12 (11 H, m), 7.14 (1 H, m), 6.94 (2 H, m), 6.23 (1 H, t, *J* = 1.9 Hz), 5.94 (1 H, d, *J* = 3.1 Hz), 5.22 (1 H, td, *J* = 10.6, 4.2 Hz), 4.13 (1 H, d, *J* = 5.8 Hz), 4.08−3.94 (4 H, m), 2.95 (1 H, dd, *J* = 14.3, 11.3 Hz), 2.20 (1 H, td, *J* = 12.5, 3.4 Hz), 1.83 (1 H, m), 1.53 (4 H, m), 1.28 (3 H, s), 1.23−1.13 (4 H, m + t, *J* = 7.3 Hz), 1.06 (3 H, s), 0.89−0.76 (4 H, m + d, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 354.7 (C), 223.5 (C), 216.3 (C), 171.7 (C), 170.2 (C), 153.5 (C), 150.5 (C), 140.9 (CH), 139.1 (C), 135.9 (C), 132.3 (CH), 130.5 (CH), 130.0 (CH), 128.9 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 125.4 (CH), 125.3 (CH), 110.2 (CH), 107.5 (CH), 93.0 (CH), 63.2 (CH_2), 60.9 (CH_2), 50.9 (CH), 42.4 (CH_2), 40.0 (CH), 39.9 (C), 33.9 (CH_2), 30.7 (CH), 27.1 (CH_3), 26.4 (CH_2), 25.1 (CH_3), 21.6 (CH_3), 13.9 (CH_3); MS *m*/*z* 711 (M^+ − 3CO, 0.1), 655 (M^+ − 5CO, 2.7), 337 (29), 123 (85), 119 (100). Anal. Calcd for $C_{45}H_{45}CrNO_9$: C, 67.91; H, 5.69; N, 1.75. Found: C, 68.08; H, 5.66; N, 1.79.

Pentacarbonyl[(3*S*,4*R*)-4-[*N*-(diphenylmethylidene)-amino]-4-ethoxycarbonyl-3-(3-furyl)-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]butylidene]chromium (4i). Ethyl *N*-(diphenylmethylidene)glycinate (0.43 g, 1.6 mmol) in THF (10 mL) was treated with LDA prepared from *i*-Pr_2NH (0.21 mL, 1.6 mmol) and BuLi (2.5 M in hexane, 1.6 mmol) in THF (5 mL), according to the general procedure. After 30 min at −78 °C, a 0.33 M THF solution of carbene complex **1g** (3 mL, 1 mmol) was diluted in THF (10 mL) and added to the glycinate anionic solution of **2a** at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and worked up as described above. Flash chromatography of the crude product afforded 0.70 g (0.89 mmol, 89% yield) of **4i** as a yellow solid in 97:3 ds: mp 128−129 °C; R_f = 0.31 (hexane/CH_2Cl_2, 1:1). Data taken from a pure sample of **4i**: $[\alpha]_D$ = +68.4 (*c* 0.5, $CHCl_3$); IR (film) ν (cm^{-1}) 2058, 1934, 1738, 1624; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2 H, d, *J* = 6.9 Hz), 7.50−7.15 (13 H, m), 6.93 (2 H, m), 5.99 (1 H, d, *J* = 1.5 Hz), 5.10 (1 H, td, *J* = 10.7, 4.1 Hz), 4.11−3.99 (2 H, m), 3.93 (1 H, d, *J* = 6.0 Hz), 3.92−3.84 (1 H, m), 3.78 (1 H, dd, *J* = 11.4, 3.1 Hz), 2.27 (1 H, m), 2.11 (1 H, t, *J* = 11.3 Hz), 1.82 (1 H, m), 1.52 (2 H, m), 1.50 (1 H, m), 1.25 (7 H, d + m, *J* = 1.2 Hz), 1.23−1.13 (4 H, t + m, *J* = 7.1 Hz), 0.87−0.78 (4 H, d + m, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 356.5 (C), 222.6 (C), 216.3 (C), 171.3 (C), 170.2 (C), 151.0 (C), 141.6 (CH), 140.1 (CH), 139.0 (C), 135.8 (C), 132.3 (CH), 130.5 (CH), 129.9 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 125.4 (CH), 125.3 (CH), 123.3 (C), 111.0 (CH), 92.7 (CH), 70.6 (CH), 63.8 (CH_2), 60.8 (CH_2), 50.9 (CH), 41.3 (CH_2), 39.5 (C), 37.8 (CH), 33.9 (CH_2), 30.6 (CH), 27.8 (CH), 26.1 (CH_2), 24.1 (CH_3), 21.5 (CH_3), 13.8 (CH_3); MS *m*/*z* 711 (M^+ − 3CO, 2.6), 655 (M^+ − 5CO, 67), 530 (32), 274 (63), 119 (100). Anal. Calcd for $C_{45}H_{45}CrNO_9$: C, 67.91; H, 5.69; N, 1.75. Found: C, 67.85; H, 5.63; N, 1.73.

Pentacarbonyl[(3*S*,4*S*)-4-(*N*,*N*-dibenzylamino)-4-ethoxycarbonyl-3-phenyl-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]-butylidene]chromium (5m). Ethyl *N*,*N*-dibenzylglycinate (0.68 g, 2.4 mmol) in THF (12 mL) was treated with LDA prepared from *i*-Pr_2NH (0.31 mL, 2.4 mmol) and BuLi (2.5 M in hexane, 2.4 mmol) in THF (7 mL), according to the general procedure. After 30 min at −78 °C, a 0.33 M THF solution of carbene complex **1e** (4.5 mL, 1.5 mmol) was diluted in THF (12 mL) and added to the glycinate anionic solution of **3a** at −78 °C. The reaction mixture was stirred for 3 h at −78 °C and worked up as described above. Flash chromatography of the crude product afforded 1.06 g (1.28 mmol, 86% yield) of **5m** as a yellow foam in 90:10 ds: R_f = 0.53 (hexane/CH_2Cl_2, 1:1). Data taken from the 90:10 diastereomeric mixture: $[\alpha]_D$ = +75.3 (*c* 1.21, $CHCl_3$); IR (film) ν (cm^{-1}) 2058, 1940, 1728, 1454; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.02 (15 H, m), 6.91−6.79 (4 H, m), 6.53 (1 H, d, *J* = 7.3 Hz), 4.76 (1 H, td, *J* = 10.8, 4.3 Hz), 4.46−4.31 (2 H, m), 3.75 (4 H, d + m, *J* = 14.1 Hz), 3.24 (3 H, m + d, *J* = 13.8 Hz), 3.03 (1 H, d, *J* = 11.2 Hz), 2.02 (1 H, td, *J* = 9.9, 3.0 Hz), 1.87 (1 H, d, *J* = 3.0 Hz), 1.59 (1 H, m), 1.49 (3 H, t, *J* = 7.3 Hz), 1.43−1.06 (8 H, m), 1.02 (1 H, m), 0.87 (1 H, t, *J* = 6.9 Hz), 0.68 (4 H, d + m, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 355.0 (C), 222.5 (C), 216.2 (C), 170.4 (C), 151.4 (C), 138.6 (C), 138.4 (C), 129.7 (CH), 129.2 (CH), 128.9 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.8 (CH), 126.5 (CH), 125.2 (CH), 91.5 (CH), 65.8 (CH_2), 65.4 (CH), 60.4 (CH_2), 54.1 (CH_2), 50.4 (CH), 43.4 (CH), 40.4 (CH_2), 39.0 (C), 34.0 (CH_2), 30.5 (CH), 29.8 (CH_3), 25.6 (CH_2), 22.1 (CH_3), 21.4 (CH_3), 14.7 (CH_3).

General Procedure for Oxidation of Carbene Complexes 4 and 5. Methods A and C. Carbene complexes **4** or **5** were placed in a round-bottom flask, flushed with N_2, and dissolved in THF (method A) or Et_2O (method C). Pyridine *N*-oxide (4−9 equiv) was added, and the reaction mixture was allowed to stir for 2−4 d. At this point, if some starting carbene complex still remained, as evidenced by TLC, the mixture was filtered through Celite and the resulting yellow solution was treated again with pyridine *N*-oxide until the oxidation was concluded. Then, the green reaction mixture was concentrated under reduced pressure, and the residue was taken up in EtOAc and filtered through Celite. The yellow filtrate was diluted 1:1 by volume with hexane, purged with air, and subjected to air oxidation under direct sunlight or bulblight. After 2−3 h the resulting brown suspension was filtered through Celite, and the filtrate was air oxidized again. These operations were successively repeated, if necessary, until a clear colorless solution was obtained (12−48 h). Solvent removal on a rotary evaporator gave the crude products which were purified by column chromatography. These compounds were obtained as one major diastereoisomer in the chiral examples (**9f**−**i**, **6m**) and as a roughly 1:1 mixture of two major diastereoisomers in the racemic examples (**9a**−**c**, **6j**).

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*S*,3*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylglutarate (6m). Method C. Car-

bene complex **5m** (1 g, 1.2 mmol) was dissolved in Et_2O (150 mL) and allowed to react with pyridine *N*-oxide (1 g, 10 mmol) for 4 d. Then, solvents were evaporated, and the residue was taken up in EtOAc (50 mL), treated as described above, and air oxidized for 2 d. Flash chromatography of the crude product (hexane/EtOAc, 9:1) yielded 0.46 g (0.71 mmol, 59% yield) of **6m** as an oil in 95:5 ds: R_f = 0.3 (hexane/EtOAc, 9:1). Data taken from the 95:5 mixture: $[\alpha]_D$ = +25.5 (*c* 1.78, $CHCl_3$); IR (film) ν (cm^{-1}) 1728; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.05 (14 H, m), 6.85 (6 H, m), 4.58 (1 H, td, *J* = 10.7, 4.4 Hz), 4.49−4.32 (2 H, m), 3.89 (2 H, d, *J* = 13.6 Hz), 3.66 (1 H, td, *J* = 11.1, 4.2 Hz), 3.45 (1 H, d, *J* = 11.6 Hz), 3.27 (2 H, d, *J* = 13.7 Hz), 2.00 (1 H, dd, *J* = 14.4, 4.1 Hz), 1.78 (2 H, dd + m, *J* = 14.4, 10.8 Hz), 1.53 (5 H, t + m, *J* = 7.0 Hz), 1.27 (7 H, 2s + m), 1.04 (3 H, m), 0.76 (4 H, d + m, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5 (C), 170.4 (C), 151.1 (C), 139.4 (C), 138.5 (C), 128.9 (CH), 128.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.6 (CH), 126.4 (CH), 125.1 (CH), 124.7 (CH), 73.6 (CH), 64.3 (CH), 60.0 (CH_2), 53.9 (CH_2), 49.8 (CH), 41.5 (CH), 40.7 (CH_2), 39.3 (C), 39.0 (CH_2), 34.1 (CH_2), 30.7 (CH), 27.2 (CH_3), 26.1 (CH_2), 24.9 (CH_3), 21.3 (CH_3), 14.6 (CH_3); MS *m*/*z* 572 ($M^+ - CO_2Et$, 2.7), 358 (3.3), 282 (100); HRMS calcd for $C_{43}H_{51}NO_4$ 645.3818, found 645.3812.

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*R*,3*S*)-2-[*N*-(diphenylmethylidene)amino]-3-phenylglutarate (9f). Method C. Carbene complex **4f** (1.40 g, 1.75 mmol) was dissolved in Et_2O (50 mL) and treated with pyridine *N*-oxide (1.48 g, 15.6 mmol) for 60 h. The suspension was filtered through Celite, more pyridine *N*-oxide (1.31 g, 13.84 mmol) was added, and the reaction was stirred at room temperature for 30 h. Then, solvents were evaporated, and the residue was taken up in EtOAc (50 mL), treated as described above, and air oxidized for 48 h. Flash chromatography of the crude product (hexane/EtOAc, 9:1) yielded 0.70 g (1.10 mmol, 64% yield) of **9f** as a white solid in 87:13 ds.

Method A. Carbene complex **4f** (1.57 g, 1.94 mmol) was dissolved in THF (70 mL) and allowed to react with pyridine *N*-oxide (1.61 g, 17 mmol) for 4 d. The suspension was filtered through Celite, more pyridine *N*-oxide (1.47 g, 15 mmol) was added, and the reaction was stirred at room temperature for 30 h. Then, solvents were evaporated, and the residue was taken up in EtOAc (50 mL), treated as described above, and air oxidized for 30 h. Flash chromatography of the crude product (hexane/EtOAc, 9:1) yielded 0.86 g (1.37 mmol, 71% yield) of **9f** as a white solid in 92:8 ds: mp 58−59 °C; R_f = 0.17 (hexane/EtOAc, 9:1). Data on the 92:8 mixture: $[\alpha]_D$ = +127.9 (*c* 0.68, $CHCl_3$); IR (film) ν (cm^{-1}) 1728, 1624; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2 H, d, *J* = 7.6 Hz), 7.50−7.34 (6 H, m), 7.30 (4 H, m), 7.22 (3 H, m), 7.08 (3 H, m), 6.78 (2 H, d, *J* = 7.6 Hz), 4.71 (1 H, td, *J* = 10.8, 4.3 Hz), 4.17 (1 H, d, *J* = 6.0 Hz), 4.11 (2 H, dq, *J* = 7.2, 2.3 Hz), 3.93 (1 H, m), 2.51 (2 H, dd, *J* = 15.4, 4.4 Hz), 2.43 (2 H, dd, *J* = 15.4, 11.4 Hz), 1.94 (1 H, td, *J* = 12.2, 3.2 Hz), 1.62 (2 H, m), 1.32 (5 H, m + s), 1.22 (3 H, s), 1.18 (3 H, t, *J* = 7.2 Hz), 1.05 (1 H, m), 0.94 (1 H, m), 0.82 (1 H, m), 0.76 (3 H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3 (C), 170.9 (C), 170.2 (C), 151.2 (C), 140.0 (C), 138.9 (C), 135.7 (C), 130.2 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 125.1 (CH), 124.7 (CH), 73.6 (CH), 69.9 (CH), 60.5 (CH_2), 50.0 (CH), 45.2 (CH), 40.9 (CH_2), 39.3 (C), 35.5 (CH_2), 34.1 (CH_2), 30.7 (CH), 27.5 (CH_3), 26.1 (CH_2), 24.5 (CH_3), 21.3 (CH_3), 13.7 (CH_3).

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*R*,3*R*)-2-[*N*-(diphenylmethylidene)amino]-3-(2-furyl)glutarate (9h). Method A. Carbene complex **4h** (0.44 g, 0.55 mmol) was dissolved in THF/Et_2O, 2:1 (30 mL), and treated with pyridine *N*-oxide (0.47 g, 4.97 mmol) for 60 h at reflux. The reaction was then allowed to cool to room temperature, solvents were evaporated, and the residue was taken up in EtOAc (50 mL), treated as described above, and air oxidized for 15 h. Flash chromatography of the crude product (hexane/EtOAc, 9:1) yielded 0.19 g (0.31 mmol, 56% yield) of **9h** as an oil in 92:8 ds: R_f = 0.30 (hexane/EtOAc/THF, 1:1:0.1). Data on the 92:8 diastereomeric mixture: $[\alpha]_D$ = +87.1 (*c* 1.0, $CHCl_3$); IR (film) ν (cm^{-1}) 1730; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2 H, d, *J* = 9.2 Hz), 7.46−7.33 (8 H, m), 7.31−7.18 (4 H, m), 7.09−7.04 (1 H, m), 6.88 (2 H, m), 6.18 (1 H, dd, *J* = 3.2, 1.8 Hz), 5.96 (1 H, d, *J* = 3.2 Hz), 4.80 (1 H, td, *J* = 10.7, 4.3 Hz), 4.29 (1 H, d, *J* = 5.3 Hz), 4.16 (2 H, m), 3.99 (1 H, m), 2.45 (2 H, d, *J* = 8.1 Hz), 2.0 (1 H, m), 1.65 (3 H, m), 1.40−1.25 (10 H, m + 2s + t, *J* = 6.9 Hz), 1.05 (1 H, m), 0.83 (5 H, m + d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4 (C), 171.3 (C), 170.3 (C), 153.9 (C), 151.3 (C), 141.0 (CH), 139.2 (C), 135.8 (C), 129.9 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 125.2 (CH), 124.9 (CH), 109.9 (CH), 106.5 (CH), 74.2 (CH), 67.6 (CH), 60.9 (CH_2), 50.2 (CH), 41.4 (CH_2), 39.5 (C), 38.9 (CH), 34.3 (CH_2), 34.0 (CH_2), 31.0 (CH), 27.1 (CH_3), 26.4 (CH_2), 25.3 (CH_3), 21.6 (CH_3), 14.0 (CH_3); MS *m*/*z* 619 (M^+, 4.5), 266 (100), 193 (35.7); HRMS calcd for $C_{40}H_{45}NO_5$ 619.3297, found 619.3288.

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*R*,3*S*)-2-[*N*-(diphenylmethylidene)amino]-3-(3-furyl)glutarate (9i). Method A. Carbene complex **4i** (1.12 g, 1.40 mmol) was dissolved in THF (40 mL) and treated with pyridine *N*-oxide (0.53 g, 5.63 mmol) for 3 d. Then, the reaction mixture was filtered through Celite and treated again with pyridine *N*-oxide (0.53 g, 5.63 mmol) for 4 d. Solvents were evaporated, and the residue was taken up in EtOAc (100 mL), treated as described above, and air oxidized for 24 h. Flash chromatography of the crude product (hexane/EtOAc, 9:1) yielded 0.44 g (0.70 mmol, 52% yield) of **9i** as a white foam in 100:0 ds: R_f = 0.48 (hexane/EtOAc, 9:1); $[\alpha]_D$ = +100.0 (*c* 2.6, $CHCl_3$); IR (film) ν 1728, 1626; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 (2 H, d, *J* = 7.9 Hz), 7.50−7.41 (6 H, m), 7.33−7.28 (5 H, m), 7.20 (1 H, s), 7.12 (1 H, m), 7.00 (1 H, m), 6.16 (1 H, m), 4.82 (1 H, td, *J* = 10.6, 4.0 Hz), 4.23−4.14 (3 H, m + d, *J* = 5.7 Hz), 3.88 (1 H, m), 2.43 (1 H, dd, *J* = 15.4, 4.0 Hz), 2.28 (1 H, dd, *J* = 15.4, 11.3 Hz), 2.02 (1 H, m), 1.76−1.59 (3 H, m), 1.44−1.32 (4 H, s + m), 1.27 (6 H, t + s, *J* = 7.4 Hz), 1.15 (1 H, m), 0.94−0.80 (5 H, m + d, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4 (C), 171.0 (C), 170.3 (C), 151.3 (C), 142.0 (CH), 139.6 (CH), 139.0 (C), 135.7 (C), 130.3 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 125.1 (CH), 124.8 (CH), 124.1 (C), 110.1 (CH), 73.9 (CH), 69.3 (CH), 60.6 (CH_2), 50.0 (CH), 41.1 (CH_2), 39.3 (C), 36.1 (CH), 35.8 (CH_2), 34.2 (CH_2), 30.9 (CH), 27.6 (CH_3), 26.2 (CH_2), 24.6 (CH_3), 21.5 (CH_3), 13.0 (CH_3); MS *m*/*z* 619 (M^+, 33), 546 ($M^+ - CO_2Et$, 2), 404 (12) 266 (100); HRMS calcd for $C_{40}H_{45}NO_5$ 619.3297, found 619.3286. Anal. Calcd for $C_{40}H_{45}NO_5$: C, 77.51; H, 7.31; N, 2.26. Found: C, 76.83; H, 7.45; N, 2.13.

General Procedure for Catalytic Hydrogenation of Compounds 6. A hydrogenation bottle was sealed with a rubber septum, evacuated, and filled with N_2. In the bottle were placed diester **6**, 5% Pd/C (40% weight), and EtOH. The bottle was set in the hydrogenator and charged with H_2 (three cycles to 40 psi). The reaction mixture was shaken at 50 °C for 15 h; H_2 was released, and the mixture was filtered through a bed of Celite. The filtrate was concentrated under reduced pressure to give the free amines. The crude products were quite clean and could be used in the next step without purification; however, for characterization purposes the compounds were chromatographied on silica.

Following this procedure hydrogenation of compound **6j** (0.40 g, 0.70 mmol) with 5% Pd/C (0.16 g) in EtOH (38 mL) gave 0.25 g (0.65 mmol, 95%) of the previously described primary amine **10a** as a white solid.

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*S*,3*S*)-2-amino-3-phenylglutarate (10f). Hydrogenation of compound **6m** (0.42 g, 0.65 mmol) with 5% Pd/C (0.18 g) in EtOH (38 mL) as described above gave 0.29 g (0.63 mmol, 99%) of **10f** as an oil in 95:5 ds. The product was characterized after flash chromatography (hexane/EtOAc, 1:1): R_f = 0.60 (hexane/EtOAc, 1:1). Data on the 95:5 mixture: $[\alpha]_D$ = +4.2 (*c* 0.71, $CHCl_3$); IR (film) ν (cm^{-1}) 3393, 3331, 1728; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.20 (8 H, m), 7.12−7.00 (2 H, m), 4.71 (1 H, td, *J* = 10.8, 4.3 Hz), 4.14 (2 H, q, *J* = 7.3 Hz), 3.59 (1 H, d, *J* = 4.7 Hz), 3.44 (1 H, m), 2.36 (1 H, dd, *J* = 15.5, 6.9 Hz), 2.24 (1 H, dd, *J* = 15.5, 8.2 Hz), 1.92 (1 H, m), 1.60 (1 H, m), 1.46−1.19 (14 H, m + 2s), 1.05 (1 H, m), 0.88−0.68 (5 H, m + d, *J* = 6.5 Hz);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2 (C), 171.3 (C), 151.4 (C), 138.3 (C), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 125.3 (CH), 124.9 (CH), 74.1 (CH), 60.8 (CH_2), 57.8 (CH), 50.1 (CH), 44.8 (CH), 41.2 (CH_2), 39.5 (C), 36.8 (CH_2), 34.3 (CH_2), 31.0 (CH), 27.6 (CH_3), 26.3 (CH_2), 24.9 (CH_3), 21.5 (CH_3), 14.1 (CH_3); MS *m*/*z* 465 (M^+, 2), 392 ($M^+ - CO_2Et$, 5), 251 (10), 160 (69), 119 (100); HRMS calcd for $C_{29}H_{39}NO_4$ 465.2879, found 465.2881.

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*R*,3*S*)-2-amino-3-phenylglutarate (11f).[6c,35] To a solution of hydroxylamine hydrochloride (27 mg, 0.38 mmol) in EtOH (15 mL) were added sodium acetate (31 mg, 0.38 mmol) and compound **9f** (0.24 g, 0.38 mmol). The mixture was refluxed for 3 h and then was poured into water. Extraction with CH_2Cl_2 (twice) and column chromatography of the concentrated extract on silica gel (hexane/EtOAc, 1:1) yielded 0.13 g (0.28 mmol, 73% yield) of **11f** as a white solid: mp 78−79 °C; R_f = 0.48 (hexane/EtOAc, 1:1); $[\alpha]_D$ = −14.0 (*c* 0.75, $CHCl_3$); IR (film) ν (cm^{-1}) 3389, 3323, 1728; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.18 (8 H, m), 7.11 (2 H, m), 4.68 (1 H, td, *J* = 10.8, 4.5 Hz), 3.97 (2 H, q, *J* = 7.3 Hz), 3.49 (1 H, d, *J* = 7.3 Hz), 3.25 (1 H, m), 2.42 (1 H, dd, *J*= 15.4, 5.6 Hz), 2.19 (1 H, dd, *J* = 15.5, 9.5 Hz), 1.91 (1 H, m), 1.58 (4 H, m), 1.39 (1 H, m), 1.30−1.23 (4 H, s + m), 1.18 (3 H, s), 1.05 (3 H, t, *J* = 7.3 Hz), 0.99−0.73 (4 H, d + m, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1 (C), 171.3 (C), 151.2 (C), 139.7 (C), 128.1 (CH), 127.9 (CH), 127.6 (CH), 126.8 (CH), 125.1 (CH), 124.8 (CH), 74.0 (CH), 60.4 (CH_2), 59.3 (CH), 50.0 (CH), 46.0 (CH), 40.9 (CH_2), 39.4 (C), 36.3 (CH_2), 34.1 (CH_2), 30.8 (CH), 27.3 (CH_3), 26.2 (CH_2), 24.9 (CH_3), 21.4 (CH_3), 13.7 (CH_3); MS *m*/*z* 465 (M^+, 2), 392 ($M^+ - CO_2Et$, 3), 234 (18), 199 (16), 160 (55), 119 (100); HRMS calcd for $C_{29}H_{39}NO_4$ 465.2879, found 465.2887. Anal. Calcd for $C_{29}H_{39}NO_4$: C, 74.80; H, 8.44; N, 3.00. Found: C, 73.97; H, 8.18; N, 3.08.

General Procedure for Hydrolysis of Compounds 10. Synthesis of Hydrochlorides 14. To a solution of amino diesters **10** in MeOH was added a solution of 2 N KOH (5 equiv). The reaction mixture was stirred at reflux for 3−4 h. Solvents were evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2. The aqueous residue was acidified with 2 N HCl at 0 °C until pH 1−2 and extracted again with CH_2Cl_2; the organic phases were combined, dried over Na_2SO_4, and concentrated on a rotary evaporator to give back the chiral auxiliary. The aqueous phase was evaporated under reduced pressure until dryness to give a white solid containing the crude product together with KCl. The solid was washed with MeOH (twice); the solution was separated with a pipet and concentrated in a rotary evaporator to afford a yellow solid. This operation was repeated again, and finally the crude hydrochloride was triturated with Et_2O several times and dried at 40 °C until a consistent solid was obtained.

(2*S*,3*S*)-3-Phenylglutamic Acid Hydrochloride (14a). Amino diester **10f** (0.26 g, 0.56 mmol) was treated with 2 N KOH (1.4 mL, 2.79 mmol) according to the general procedure. Workup of the reaction gave (−)-8-phenylmenthol (100 mg, 80% yield) and an aqueous residue which after purification afforded 88 mg (0.34 mmol, 60% yield) of **14a** as a yellow solid: $[\alpha]_D$ = +83.0 (*c* 0.47, 1 N HCl); IR (KBr) ν (cm^{-1}) 3385, 3285, 1728, 1658; ^{1}H NMR (MeOH-d_4, 300 MHz) δ 7.47 (5 H, m), 4.77 (1 H, d, *J* = 8.2 Hz), 4.25 (1 H, q, *J* = 8.3 Hz), 2.91 (2 H, d, *J* = 8.3 Hz); ^{13}C NMR (MeOH-d_4, 50 MHz) δ 180.8 (C), 173.9 (C), 139.7 (C), 129.6 (CH), 129.1 (CH), 128.7 (CH), 63.0 (CH), 45.2 (CH), 37.4 (CH_2); MS *m*/*z* 259 (M^+, 15), 244 (22), 224 ($M^+ - Cl$, 19), 206 ($M^+ - Cl - H_2O$, 57), 192 (21); HRMS calcd for $C_{11}H_{14}NO_4$ ($M^+ - Cl$) 224.0923, found 224.0931.

(2*S*,3*S*)-3-Phenylglutamic Acid (16a).[8a] Hydrochloride **14a** (22 mg, 0.085 mmol) was dissolved in the minimum amount of MeOH (1.5 mL); the same amount of propylene oxide was added, and the reaction mixture was stirred at room temperature for 30 min or until the product precipitated. Solvents were evaporated under reduced pressure to give a yellow solid. The operation was repeated. The resultant solid was dried, triturated with Et_2O several times, and dried again at 40 °C until a consistent solid was obtained. **16a** (16.0 mg, 0.075 mmol, 84% yield) was produced in this way: $[\alpha]_D$ = +180 (*c* 0.50, 6 N HCl);[36] ^{1}H NMR (D_2O, 400 MHz) δ 7.25 (5 H, m), 4.45 (1 H, d, *J* = 8.2 Hz), 3.88 (1 H, q, *J* = 7.7 Hz), 2.76 (1 H, dd, *J* = 17.1, 8.7 Hz), 2.54 (1 H, dd, *J* = 17.1, 6.3 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 181.5 (C), 177.1 (C) 140.2 (C), 129.0 (CH), 128.2 (CH), 127.9 (CH), 64.6 (CH), 43.0 (CH), 37.7 (CH_2).

General Procedure for Hydrolysis of Imines 9. Synthesis of Compounds 19 and 11i. To a solution of the corresponding imine **9** in THF was added 5 N HCl (7−10 equiv), and the reaction mixture was stirred at room temperature for 20−48 h. Solvents were evaporated under reduced pressure until dryness to give a white solid containing the crude product together with benzophenone. Purification of hydrochlorides **19** was carried out by washing the solid with hexane several times and drying it under vacuum. In the case of compound **9i** the corresponding hydrochloride turned out to be difficult to precipitate, and it was found more convenient to isolate the free amine **11i** after the reaction medium was basified.

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*R*,3*S*)-2-amino-3-phenylglutarate Hydrochloride (19f). Compound **9f** (0.45 g, 0.71 mmol) was allowed to react with 5 N HCl (1.4 mL, 7.0 mmol) in THF (12 mL) for 48 h. Workup of the reaction followed by purification as described above afforded 0.33 g (0.65 mmol, 92% yield) of compound **19f** as a white solid: mp 212−213 °C dec; $[\alpha]_D$ = − 4.6 (*c* 0.50, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.72 (3 H, br s), 7.32 (10 H, m), 4.57 (1 H, td, *J* = 10.7, 4.4 Hz), 4.31 (1 H, d, *J* = 6.8 Hz), 4.09 (2 H, dq, *J* = 7.3, 2.9 Hz), 3.69 (1 H, m), 2.75 (1 H, dd, *J* = 15.6, 4.5 Hz), 2.60 (1 H, dd, overlapped with DMSO signal), 1.91 (1 H, t, *J* = 9.7 Hz), 1.52 (2 H, br t), 1.10 (8 H, 2s + m), 1.04−0.92 (5 H, t + m, *J* = 7.3 Hz), 0.85−0.75 (4 H, d + m, *J* = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.8 (C). 167.9 (C), 150.4 (C), 136.2 (C), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 125.3 (CH), 125.1 (CH), 73.9 (CH), 61.5 (CH_2), 55.6 (CH), 49.5 (CH), 42.9 (CH), 40.5 (CH_2), 36.6 (CH_2), 33.7 (CH_2), 30.4 (CH), 26.7 (CH_3), 26.1 (CH_2), 25.8 (CH_3), 21.4 (CH_3), 13.6 (CH_3); MS *m*/*z* 466.5 (M^+ − HCl, 85), 252 (100), 119 (84), 105 (99). Anal. Calcd for $C_{29}H_{40}NO_4Cl$: C, 69.37; H, 8.03; N, 2.79. Found: C, 68.93; H, 7.84; N, 2.64.

1-Ethyl 5-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl](2*R*,3*S*)-2-amino-3-(3-furyl)glutarate (11i). Imino diester **9i** (0.57 g, 0.92 mmol) was treated with 5 N HCl (2 mL, 10 mmol) in THF (20 mL) for 36 h. Solvents were evaporated under reduced pressure, and the residue was diluted with water and basified at 0 °C with saturated aqueous $NaHCO_3$ solution until pH 8−9. The mixture was extracted with EtOAc, washed with water (twice) and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give the crude product. Purification by column chromatography (hexane/EtOAc, 2:1, 1:1) afforded 0.31 g (0.68 mmol, 74% yield) of compound **11i** as an oil and single diastereoisomer: R_f = 0.40 (hexane/EtOAc, 1:1); $[\alpha]_D$ = −12.5 (*c* 1.46, $CHCl_3$); IR (film) ν (cm^{-1}) 3391, 3323, 1726, 1601; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.05 (7 H, m), 6.18 (1 H, s), 4.72 (1 H, td, *J* = 10.8, 4.1 Hz), 4.07 (2 H, q, *J* = 7.0 Hz), 3.44 (1 H, d, *J* = 6.2 Hz), 3.19 (1 H, m), 2.24 (1 H, dd, *J* = 15.6, 5.6 Hz), 2.01 (1 H, dd, *J* = 15.6, 9.4 Hz), overlapped with 1.90 (1 H, m), 1.59 (4 H, m), 1.40−1.27 (4 H, m + s), 1.20−1.13 (6 H, s + t, *J* = 7.2 Hz), 1.03 (1 H, m), 0.86−0.68 (4 H, d + m, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.8 (C), 171.0 (C), 151.1 (C), 142.4 (CH), 139.4 (CH), 127.5 (CH), 125.0 (CH), 124.7 (CH), 123.4 (C), 109.5 (CH), 74.0 (CH), 60.4 (CH_2), 58.0 (CH), 49.9 (CH), 40.9 (CH_2), 39.2 (C), 36.6 (CH), 35.9 (CH_2), 34.1 (CH_2), 30.8 (CH), 27.4 (CH_3), 26.1 (CH_2), 24.6 (CH_3), 21.4 (CH_3), 13.7 (CH_3). Anal. Calcd for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.18; N, 3.07. Found: C, 70.71; H, 8.54; N, 2.94.

General Procedure for the Synthesis of Compounds 15. Method A. To a solution of the corresponding hydrochloride **19b**,**g** in CH_2Cl_2 was added trifluoroacetic acid, and the

(35) Compound **11f** was also obtained by two alternative methods: treatment of hydrochloride **19f** with Et_3N (2.5 equiv) in THF, 30 min, 25 °C, quantitative yield, and hydrogenation of compound **9f** (5% Pd/C, 30% weight) in EtOAc, 15 h, 25 °C, 65% yield.

(36) Lit.[8a] α (589 nm, 25 °C, *l* = 1 dm, *c* = 8.1 g dm^{-3} in 6 M HCl) = +11.1.

reaction mixture was stirred at room temperature for 3 h. Solvents were evaporated under reduced pressure until dryness, and the residue was diluted with MeOH. Workup was carried out following the same procedure described above for hydrolysis of compounds **10**.

Method B. The procedure used for hydrolysis of ethyl esters **19f** and **11i** was similar to that previously described for compounds **10**.

(2*R*, 3*S*)-3-Phenylglutamic Acid Hydrochloride (15a). Method A. Amino diester **19g** (54 mg, 0.10 mmol) was treated successively with trifluoroacetic acid (0.6 mL, 7 mmol) in CH_2Cl_2 (6 mL) and 2 N KOH (1.0 mL, 2.0 mmol) in MeOH (8 mL) according to the general procedure. Workup of the reaction gave (−)-8-phenylmenthol (21 mg, 88% yield) and an aqueous residue which after purification afforded 19 mg (0.07 mmol, 73% yield) of **15a** as a solid in 90:10 ds.

Method B. 19f (0.15 g, 0.29 mmol) was treated with 2 N KOH (0.75 mL, 1.45 mmol) in MeOH (8 mL) according to the general procedure. Workup of the reaction gave (−)-8-phenylmenthol (66 mg, 98% yield) and an aqueous residue which after purification afforded 75 mg (0.28 mmol, 98% yield) of **15a** as a solid in 91:9 ds. Data on the 91:9 mixture: $[\alpha]_D = -33.9$ (*c* 0.165, 6N HCl);[37] IR (KBr) ν (cm^{-1}) 3364, 1745, 1686; ^{1}H NMR (MeOH-d_4, 300 MHz) δ 7.35 (5 H, m), 4.27 (1 H, d, J = 4.8 Hz), 3.75 (1 H, m), 2.90 (1 H, dd, J = 17.1, 9.2 Hz), 2.47 (1 H, dd, J = 17.1, 5.7 Hz); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 179.8 (C), 173.8 (C), 143.7 (C), 130.2 (CH), 128.6 (CH), 128.0 (CH), 64.7 (CH), 45.5 (CH), 39.7 (CH_2); MS *m*/*z* 259 (M^+, 8), 241 ($M^+ - H_2O$, 9), 224 ($M^+ - Cl$, 29), 206 ($M^+ - Cl - H_2O$, 100), 185 (87).

Hydrochloride **15a** was converted into the free amino acid by ion-exchange chromatography on Dowex H^+ or by treatment with propylene oxide in MeOH as described above for compound **14a**. In the first case, the resin was acidified with 1 N HCl, charged into the column, and washed with 1 N HCl. Hydrochloride **15a** was dissolved in the minimun amount of MeOH and applied to the column. The resin was eluted with water until a neutral elution came out from the column and then with 2 N NH_4OH aqueous solution. The basic aliquots were combined and concentrated under reduced pressure to give a solid which was dried under vacuum, triturated with Et_2O, and dried again. ^{1}H NMR analysis of the solid show a nearly 1:1 mixture of glutamic **17a** and pyroglutamic **21a** acids (75% yield). When **15a** was treated with propylene oxide, a solid 62:38 mixture of **17a**/**21a** was obtained in 90% yield: ^{1}H NMR of this mixture (MeOH-d_4, 300 MHz) δ 7.28 (m, 10 H, **17a** + **21a**), 4.33 (d, 1 H, J = 6.4 Hz, **17a**), 4.02 (d, 1 H, J = 6.4 Hz, **21a**), 3.65 (m, 1 H, **17a**), 3.45 (m, 1 H, **21a**), 2.75 (dd, 1 H, **17a** overlapped with dd, 1 H, **21a**), 2.45 (dd, 1 H, **17a** overlapped with dd, 1 H, **21a**).

(2*R*,3*S*)-3-(3-Furyl)glutamic Acid Hydrochloride (15d). Method B. 11i (0.26 g, 0.57 mmol) was treated with 2 N KOH (1.5 mL, 2.85 mmol) in MeOH (10 mL) according to the general procedure. Workup of the reaction gave (−)-8-phenylmenthol (90 mg, 68% yield) and an aqueous residue which after purification afforded 92 mg (0.36 mmol, 65% yield) of **15d** as a white solid: mp 120−121 °C; $[\alpha]_D = +236.8$ (*c* 0.45, 1 N HCl); IR (KBr) ν (cm^{-1}) 3283, 1739, 1687, 1439; ^{1}H NMR (MeOH-d_4, 200 MHz) δ 7.50 (2 H, d, J = 1.2 Hz), 6.48 (1 H, t, J = 1.2 Hz), 4.23 (1 H, d, J = 5.4 Hz), 3.67 (1 H, m), 2.78 (1 H, dd, J = 16.8, 8.9 Hz), 2.41 (1 H, dd, J = 16.8, 6.4 Hz); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 179.7 (C), 173.7 (C), 145.4 (CH), 140.7 (CH), 127.5 (C), 110.2 (CH), 64.0 (CH), 38.5 (CH_2), 36.8 (CH).

Ethyl (2*R*,3*S*)-3-(3-Furyl)pyroglutamate (12d). A mixture of amino acid **15d** (66.5 mg, 0.26 mmol) and $SOCl_2$ (75 μL, 1 mmol) was stirred at room temperature for 40 min. Then absolute EtOH (3 mL) was added, and the mixture was allowed to react for 3 h at room temperature and then was refluxed for another 3 h. The resultant mixture was filtered, and the filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (hexane/EtOAc, 1:1, 1:2) afforded 30 mg (0.13 mmol, 52% yield) of pyroglutamate **12d** as an oil: R_f = 0.37 (hexane/EtOAc, 1:2); $[\alpha]_D = +80.5$ (*c* 0.58, $CHCl_3$); IR (film) ν (cm^{-1}) 1738, 1705; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (1 H, s), 7.42 (1 H, d, J = 1.0 Hz), 6.43 (1 H, d, J = 1.0 Hz), 4.30 (2 H, q, J = 7.0 Hz), 4.18 (1 H, d, J = 5.7 Hz), 3.72 (1 H, m), 2.83 (1 H, dd, J = 17.0, 9.2 Hz), 2.47 (1 H, dd, J = 17.0, 9.2 Hz), 1.33 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.5 (C), 170.9 (C), 143.7 (CH), 138.9 (CH), 119.9 (C), 108.9 (CH), 62.0 (CH), 61.8 (CH_2), 36.8 (CH_2), 34.0 (CH), 14.0 (CH_3).

General Procedure for the Preparation of Compounds 22 from Carbene Complexes 1. All the operations were carried out under a nitrogen atmosphere. LDA (1.6 equiv) was prepared by adding BuLi (1.6 equiv) to a solution of *i*-Pr_2NH (1.6 equiv) in THF at −60 °C. After being stirred for 15 min at −60 °C, the LDA solution was cooled to −78 °C, and a solution of the appropriate protected glycine ester (1.6 equiv) was added via addition funnel. The resulting yellow-orange solution was stirred for 30 min at −78 °C, and then, a THF solution of the corresponding alkenylcarbene complex **1** (1 equiv) was added dropwise from the addition funnel at −78 °C. After the addition was concluded, the dark red starting carbene solution turned into a bright yellow one. After the solution was stirred for 1−3 h at −78 °C, 50% HBF_4 aqueous solution (10 equiv) was added dropwise, the cold bath was removed, and the reaction mixture was stirred at room temperature until TLC evidenced no opened additon product (2 h). At that point, the reaction was cooled with an ice−saltwater bath, and 12 equiv of Et_3N was added via the addition funnel. After 20 min the solution was poured into a separatory funnel, EtOAc was added, and the organic phase was collected, dried (Na_2SO_4), filtered through Celite, and concentrated under reduced pressure to give a residue, whose ^{1}H NMR analysis provided the diastereoselectivity of the addition−cyclization reaction. Purification of the residue by flash chromatography led to isolation of pure cyclic carbene complexes **22**.

Pentacarbonyl[(3*R*,4*S*)-3-ethoxycarbonyl-4-phenyl-2-azacyclopentylidene]chromium (22a). Ethyl *N*-(diphenylmethylidene)glycinate (0.64 g, 2.4 mmol) in THF (15 mL) was treated at −78 °C with LDA prepared from *i*-Pr_2NH (0.31 mL, 2.4 mmol), BuLi (1.6 M in hexane, 2.4 mmol), and THF (5 mL). After 30 min, a 0.33 M THF solution of carbene complex **1e** (4.5 mL, 1.5 mmol) was diluted in THF (15 mL) and added to the glycinate anionic solution of **2a** at −78 °C. The reaction mixture was stirred for 3 h at low temperature, and then was successively treated with 50% HBF_4 (2.8 g, 16 mmol) and Et_3N (2.5 mL, 18 mmol) according to the general procedure. Workup of the reaction as described above gave a crude material containing carbene complex **22a** in 94:6 ds. Flash chromatography of the crude product (hexane/EtOAc, 6:1) afforded 0.58 g (1.4 mmol, 95% yield) of **22a** as a yellow solid: mp 117−118 °C; R_f = 0.31 (hexane/EtOAc, 6:1); $[\alpha]_D = +30.4$ (*c* 0.5, $CHCl_3$); IR (film) ν (cm^{-1}) 3289, 2054, 1923, 1728; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.11 (1 H, br s), 7.40−7.26 (3 H, m), 7.16 (2 H, d, J = 6.9 Hz), 4.64 (1 H, d, J = 5.6 Hz), 4.29 (2 H, m), 3.83 (1 H, dd, J = 18.9, 8.6 Hz), 3.64 (1 H, m), 3.45 (1 H, dd, J = 18.9, 5.6 Hz), 1.30 (1 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 279.7 (C), 222.4 (C), 217.2 (C), 168.8 (C), 140.7 (C), 129.1 (CH), 127.6 (CH), 126.6 (CH), 75.1 (CH), 62.5 (CH_2), 61.7 (CH_2), 45.4 (CH), 13.9 (CH_3); MS *m*/*z* 409 (M^+, 2.5), 408 ($M^+ - 1$, 8), 325 ($M^+ - 3CO$, 3.5), 297 ($M^+ - 4CO$, 3.5), 269 ($M^+ - 5CO$, 100), 215 (26); HRMS calcd for $C_{18}H_{15}CrNO_7$ 409.0253, found 409.0256. Anal. Calcd for $C_{18}H_{15}CrNO_7$: C, 52.80; H, 3.70; N, 3.42. Found: C, 52.35; H, 4.04; N, 3.37.

Pentacarbonyl[(3*R*,4*R*)-3-ethoxycarbonyl-4-(2-furyl)-2-azacyclopentylidene]chromium (22c). Ethyl *N*-(diphenylmethylidene)glycinate (1.71 g, 6.4 mmol) in THF (20 mL) was treated at −78 °C with LDA prepared from *i*-Pr_2NH (0.80 mL, 6.4 mmol), BuLi (1.6 M in hexane, 6.4 mmol), and THF (15 mL). After 30 min, a 0.33 M THF solution of carbene complex **1f** (12 mL, 4 mmol) was diluted in THF (20 mL) and added to the glycinate anionic solution of **2a** at −78 °C. The reaction mixture was stirred for 1 h at low temperature, and then was successively treated with 50% HBF_4 (7 g, 40 mmol)

(37) Lit.[8a] reports α for its enantiomer: α (589 nm, 25 °C, l = 1 dm, c = 8.67 g dm^{-3} in 6 M HCl) = +19.15.

and Et_3N (6.7 mL, 48 mmol) according to the general procedure. Workup of the reaction as described above gave a crude material containing carbene complex **22c** in 92:8 ds. Flash chromatography of the crude product (hexane/EtOAc, 9:1, 6:1) afforded 1.05 g (2.6 mmol, 66% yield) of **22c** as a yellow solid: mp 95−96 °C; R_f = 0.19 (hexane/EtOAc, 6:1); $[\alpha]_D$ = +18.2 (*c* 0.5, $CHCl_3$); IR (film) ν (cm^{-1}) 3383, 2058, 1930, 1730; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.08 (1 H, br s), 7.37 (1 H, d, *J* = 1.3 Hz), 6.33 (1 H, dd, *J* = 3.0, 1.7 Hz), 6.17 (1 H, d, *J* = 3.0 Hz), 4.74 (1 H, d, *J* = 6.1 Hz), 4.30 (2 H, m), 3.78−3.67 (2 H, m), 3.51 (1 H, dd, *J* = 22.0, 9.5 Hz), 1.33 (1 H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 279.1 (C), 222.5 (C), 217.2 (C), 168.4 (C), 152.0 (C), 142.3 (CH), 110.4 (CH), 106.6 (CH), 72.0 (CH), 62.6 (CH_2), 58.3 (CH_2), 38.9 (CH), 13.9 (CH_3); MS *m*/*z* 399 (M^+, 14), 343 ($M^+ - 1 - CO_2Et$, 6), 287 ($M^+ - 4CO$, 24), 259 ($M^+ - 5CO$, 100). Anal. Calcd for $C_{16}H_{13}CrNO_8$: C, 48.12; H, 3.28; N, 3.50. Found: C, 48.34; H, 3.57; N, 3.43.

General Procedure for Oxidation of Aminocarbene Complexes 22. Compounds **22** were oxidized following the same procedure (method A) described above for oxidation of compounds **4** and **5**; however, the greater stability of aminocarbene derivatives made necessary longer reaction times and/or more equivalents of pyridine *N*-oxide.

Ethyl (2*R*,3*S*)-3-Phenylpyroglutamate (12a). Carbene complex **22a** (0.16 g, 0.39 mmol) was oxidized with pyridine *N*-oxide (0.23 g, 2.4 mmol) in THF (40 mL) for 4 d according to the general procedure. Solvents were evaporated, and the residue was worked-up as described above. Flash chromatography of the crude product (hexane/EtOAc, 1:1, 1:2, EtOAc) afforded 48.6 mg (0.21 mmol, 53% yield) of **12a** as an oil: R_f = 0.27 (hexane/EtOAc, 1:1); $[\alpha]_D$ = −47.6 (*c* 0.55, $CHCl_3$); IR (film) ν (cm^{-1}) 3229, 1739, 1705; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.26 (5 H, m), 6.70 (1 H, br s), 4.31−4.11 (3 H, d + m, *J* = 4.6 Hz), 3.73 (1 H, m), 2.89 (1 H, dd, *J* = 17.4, 9.4 Hz), 2.55 (1 H, dd, *J* = 17.4, 7.1 Hz), 1.27 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.6 (C), 171.2 (C), 141.7 (C), 128.9 (CH), 127.4 (CH), 126.8 (CH), 62.8 (CH), 61.6 (CH_2), 43.8 (CH), 37.8 (CH_2), 14.0 (CH_3); MS *m*/*z* 233 (M^+, 24), 160 ($M^+ - CO_2Et$, 100), 117 (82), 104 (22); HRMS calcd for $C_{13}H_{15}NO_3$ 233.1051, found 233.1051.

Ethyl (2*R*,3*R*)-3-(2-Furyl)pyroglutamate (12c). Carbene complex **22c** (0.27 g, 0.67 mmol) was oxidized with pyridine *N*-oxide (0.57 g, 6.08 mmol) in THF (150 mL) for 5 d according to the general procedure. The reaction mixture was filtered through Celite and treated again with pyridine *N*-oxide (0.57 g, 6.08 mmol) for 3 d. Solvents were evaporated under reduced pressure, and the residue was worked-up as described above. Flash chromatography of the crude product (hexane/EtOAc, 1:1, EtOAc) afforded 50 mg (0.22 mmol, 33% yield) of **12c** as an oil: R_f = 0.16 (hexane/EtOAc, 1:1); $[\alpha]_D$ = −47.1 (*c* 0.92, $CHCl_3$); IR (film) ν (cm^{-1}) 3229, 1739, 1709; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36 (1 H, dd, *J* = 1.8, 0.9 Hz), 7.11 (1 H, br s), 6.31 (1 H, dd, *J* = 3.0, 1.8 Hz), 6.19 (1 H, d, *J* = 3.0 Hz), 4.32 (1 H, d, *J* = 5.5 Hz), 4.23 (2 H, dq), 3.80 (1 H, m), 2.77 (1 H, dd, *J* = 17.1, 8.8 Hz), 2.62 (1 H, dd, *J* = 17.1, 7.3 Hz), 1.27 (1 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.1 (C), 170.8 (C), 153.1 (C), 142.0 (CH), 110.2 (CH), 106.1 (CH), 61.7 (CH_2), 60.1 (CH), 37.3 (CH), 34.9 (CH_2), 13.9 (CH_3); MS *m*/*z* 223 (M^+, 46), 150 ($M^+ - CO_2Et$, 100), 94 ($M^+ - CO_2Et$ − furyl, 89); HRMS calcd for $C_{11}H_{13}NO_4$ 223.0844, found 223.0843.

General Procedure for Hydrolysis of Compounds 12. Synthesis of Pyroglutamic Acids 21. The corresponding ethyl pyroglutamate **12** was dissolved in THF, and 2.5 N LiOH aqueous solution (18 equiv) was added. The reaction mixture was stirred at room temperature for 8 h. After removal of the solvents in a rotary evaporator, the aqueous residue was acidified with 2 N HCl until pH 2−3 and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give a small amount of the title compound. Most of the product was obtained from the aqueous phase by evaporation of the solvent under reduced pressure and then flash chromatography purification (EtOAc/HCO_2H, 100:8) of the residue.

(2*R*,3*S*)-3-Phenylpyroglutamic Acid (21a). Compound **12a** (94 mg, 0.40 mmol) and 2.5 N LiOH (3 mL, 7.2 mmol) were stirred in THF (5 mL) for 8 h. The reaction mixture was worked-up according to the general procedure to give 15 mg of **21a** from the organic phase and 50 mg of **21a** after purification of the aqueous phase (0.31 mmol, 79%): white solid; $[\alpha]_D$ = −12.5 (*c* 0.40, MeOH); IR (KBr) ν (cm^{-1}) 3350, 1670, 1635; ^1H NMR (MeOH-d_4, 200 MHz) δ 7.5 (5H, m), 4.40 (1 H, d, *J* = 4.5 Hz), 3.84 (1 H, m), 3.04 (1 H, dd, *J* = 17.1, 9.9 Hz), 2.60 (1 H, dd, *J* = 17.1, 5.7 Hz); ^{13}C NMR (MeOH-d_4, 50 MHz) δ 180.2 (C), 179.3 (C), 145.4 (C), 130.0 (CH), 129.6 (CH), 128.1 (CH), 67.7 (CH), 46.4 (CH), 39.8 (CH_2); MS *m*/*z* 205 (M^+, 24), 160 ($M^+ - CO_2H$, 100), 117 (68); HRMS calcd for $C_{11}H_{11}NO_3$ 205.0739, found 205.0740.

(2*R*,3*R*)-3-(2-Furyl)pyroglutamic Acid (21c). Compound **12c** (99 mg, 0.44 mmol) and 2.5 N LiOH (3.2 mL, 7.9 mmol) were stirred in THF (4 mL) for 8 h. The reaction mixture was worked-up according to the general procedure to give after purification of the aqueous phase 55 mg (0.28 mmol, 65%) of **21c** as a white solid: mp 85−86 °C; R_f = 0.65 (EtOAc/HCO_2H, 10:1); $[\alpha]_D$ = −61.3 (*c* 0.31, MeOH); IR (KBr) ν (cm^{-1}) 3396, 1670, 1628; ^1H NMR (DMSO-d_6, 200 MHz) δ 8.26 (1 H, s), 7.72 (1 H, d, *J* = 1.0 Hz), 6.51 (1 H, dd, *J* = 3.3, 1.6 Hz), 6.43 (1 H, d, *J* = 3.3 Hz), 4.20 (1 H, d, *J* = 4.0 Hz), 3.81 (1 H, m), 2.73 (1 H, dd, *J* = 16.7, 9.2 Hz), 2.43 (1 H, dd, *J* = 16.7, 5.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 175.3 (C), 173.1 (C), 154.6 (C), 142.4 (CH), 110.5 (CH), 105.8 (CH), 59.8 (CH), 37.0 (CH), 34.7 (CH_2); MS *m*/*z* 195 (M^+, 23), 149 ($M^+ - 1 - CO_2H$, 2), 94 (100); HRMS calcd for $C_9H_9NO_4$ 195.0531, found 195.0534.

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Supporting Information Available: Experimental procedures and analytical and spectral data for compounds **1a**−**d**,**g**, **4a**−**e**,**g**, **5j**−**l**,**n**, **6j**, **7**, **8**, **9a**−**c**,**g**, *syn*-**9a**, **10a**, **11a**, *rac*-**12a**,**c**, *rac*-**14a**, *rac*-**15a**, **19b**,**g**, *rac*-**21a**,**c**, *rac*-**22a**−**c**, *rac*-**24**, *rac*-**25**, and **26** and crystallographic experimental section, table of X-ray crystal data, final fractional coordinates, anisotropic thermal parameters, bond lengths and angles, and a crystallographic plot for **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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