Stereoselective Formal [3 + 2] Cycloaddition of *N*-Alkylidene Glycine Ester Anions to Chiral Fischer Alkenylcarbene Complexes. Asymmetric Synthesis of 3,4,5-Trisubstituted Prolines

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The reaction between *N*-alkylidene glycine ester enolates, generated from glycine esters aldimines with LDA in THF at low temperature, and chiral alkoxyalkenylcarbene complexes of chromium provided directly 2,4,5-trisubstituted-3-pyrrolidinylcarbene complexes with total *exo* selectivity and very high *syn* and facial diastereoselectivity when carbene complexes bearing the (−)-8-phenylmenthyloxy group were employed. Oxidation of the metal carbene moiety followed by basic hydrolysis of the esters afforded enantiomerically highly enriched *syn*,*exo*-3,4,5-trisubstituted prolines, whereas acidic hydrolysis of the same functional groups proceeded with epimerization at the α-amino acid center leading to *anti*,*exo*-3,4,5-trisubstituted prolines of very high enantiomeric purity as well.

Introduction

[3 + 2] Cycloaddition reactions between 1,3-dipoles and alkenes is the most efficient method to obtain five-membered heterocyclic rings.[1] The possibility of controlling the stereochemical outcome of this reaction has converted it into a very powerful tool in synthetic chemistry.[2] The dipolar cycloaddition of azomethine ylides derived from α-amino esters to substituted alkenes furnishes proline derivatives, usually in a regio- and stereocontrolled fashion.[2,3] *N*-Metalated azomethine ylides are commonly generated from the corresponding amino ester by treatment with a base (Et_3N or DBU) in the presence of either a lithium or a silver salt. The groups of Kanemasa[4] and Grigg[5] have published extensive work in this field.

Padwa et al.[6] were the first who employed a chiral azomethine ylide to obtain optically active pyrrolidines. Since then, other chiral cyclic and acyclic azomethine ylides have been developed to achieve asymmetric control in the reaction.[2,5c,7] Another strategy to obtain optically active cycloadducts is the use of a chiral dipolarophile.[2,5c,8] α,*β*-Unsaturated ketones, esters, and amides bearing a chiral auxiliary bonded to the *β*-position[8c,d,h,k] or in the amino[8g] or alkoxy groups[8b,e,j] of the α,*β*-unsaturated carbonyl system have been used for this purpose. In this context, Grigg et al. have used chiral menthyl acrylates in the reaction with azomethine ylides derived from amino esters to obtain enantiomerically enriched proline esters with high diastereoselectivity.[5c,8b,j,k] Also, asymmetric induction in the cycloaddition of azomethine ylides derived from α-amino esters with α,*β*-unsaturated esters can be achieved in the presence of a chiral catalyst.[2,5c,9].

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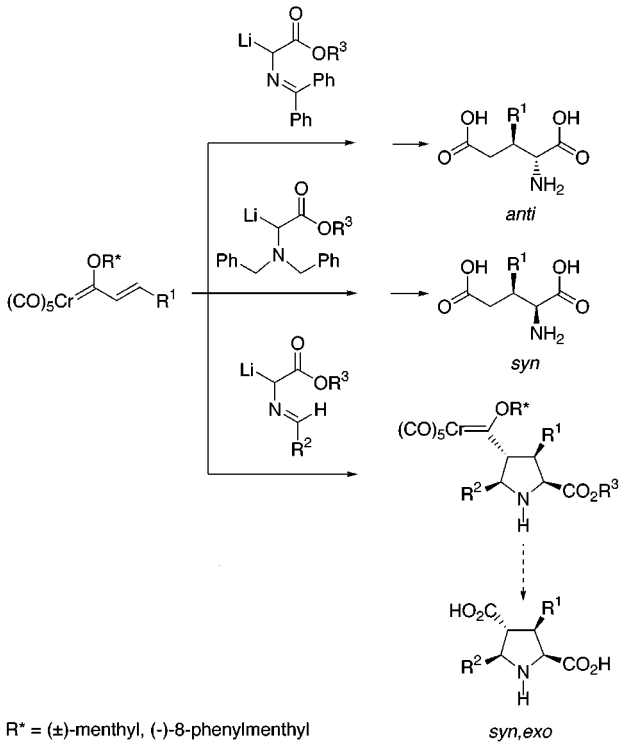
The asymmetric synthesis of chiral nonracemic prolines[10] is currently attracting much attention due to the interest to study conformational constraints into peptides that influence their biological properties.[11,12] In addition, the synthesis of proline derivatives that selectively incorporate the side chain functionality of other amino acids (chimeras),[10h,k,13] furnishing unique structural characteristics to the original amino acid or to the peptide, allows the analysis of their biological activity.[11,12,13a] In this context, the kainoid amino acid family[14] deserves special mention as a group of nonproteinogenic pyrrolidine dicarboxylic acids that exhibit potent neuroexcitatory activity. This property is attributed to their action as conformationally restricted analogues of the neurotransmitter glutamic acid.

Research in our group has been centered on the synthesis of optically active compounds utilizing Fischer alkenylcarbene complexes bearing (−)-8-phenylmenthol as chiral auxiliary. We have demonstrated that these compounds are excellent Michael acceptors when reacted with alkyllithiums and lithium enolates, and that they exhibited very high or total facial diastereoselectivity due to the phenyl group hindrance of the chiral auxiliary on the carbon−carbon double bond of the carbene complex.[15] The Michael addition of chloro- or iodomethyllithium to these chiral α,β-unsaturated carbene complexes, which is followed by a ring closure to give cyclopropylcarbene complexes with very high ee,[15c] can be considered as a nucleophilic addition/ring closure (NARC)[16] sequence for the construction of [2 + 1] cycloadducts. Also, we have shown their ability to act as dipolarophiles in [3 + 2] cycloaddition reactions with diazomethane derivatives and nitrilimines. Δ^2-Pyrazolines were obtained from these reactions in enantiomerically pure form.[17] On the other hand, we have recently reported the stereoselective Michael addition of lithium enolates of *N*-(diphenylmethylidene)glycinate esters to chiral Fischer alkenylcarbene complexes.[18] The Michael adducts were obtained with high *anti* selectivity and high diastereofacial selectivity. After oxidation of the metal carbene moiety and hydrolysis of the resulting esters, enantiomerically enriched 3-substituted glutamic acids of unnatural stereochemistry were obtained (Scheme 1). By contrast, the same reaction with lithium enolates of *N*,*N*-dibenzylglycinate esters, selectively furnished the corresponding *syn* Michael adducts, which finally led to the synthesis of natural enantiomerically enriched 3-substituted glutamic acids (Scheme 1).

Scheme 1



In the course of our investigations, we observed that when the glycine ester was successively protected as an aldimine, deprotonated, and added to a Fischer (±)-menthol-derived alkenylcarbene complex, the expected open chain Michael adduct was not detected at all, and instead a 2,4,5-trisubstituted-3-pyrrolidinylcarbene complex was isolated as the only product in good yield and

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Table 1. [3 + 2] Cycloadducts 3 of Lithium Glycine Enolates 2 and (±)-Menthyl- and (−)-8-Phenylmenthyloxy Alkenylcarbene Complexes of Chromium 1 and Their Oxidation Products 4.

entry	carbene complex	R*	R^1	glycine anion	R^2	3[a]	yield (%)[b]	dr[c]	4[a]	oxidation method[d]	yield (%)[e]	dr[c]
1	**1a**	(±)-menthyl	Ph	**2a**	*t*-Bu	**3a**	89	90:10[f]	**4a**	A	75	88:6:6[f,g]
2	**1a**	(±)-menthyl	Ph	**2b**	Ph	**3b**	86	85:15[f]	**4b**	A[h]	73	82:18[f]
3	**1b**	(±)-menthyl	2-furyl	**2b**	Ph	**3c**	87	≥99:1[f]	**4c**	A	83	92:8[f,i]
4	**1c**	(−)-8-Ph-menthyl	Ph	**2a**	*t*-Bu	**3d**	78	≥99:1	**4d**	B	62	85:11:4[g]
5	**1c**	(−)-8-Ph-menthyl	Ph	**2b**	Ph	**3e**	75	96:4	**4e**	B[j]	53	89:11[k]
6	**1d**	(−)-8-Ph-menthyl	2-furyl	**2b**	Ph	**3f**	99	≥99:1	**4f**	A[l]	65	92:8

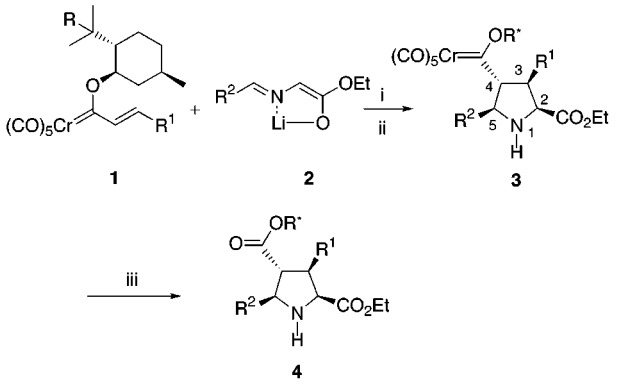
[a] Only the major diastereoisomer is shown. [b]Isolated yield based on starting carbene complex **1**. [c]Diastereomeric ratio was determined by ^{1}H NMR at 300 or 200 MHz. Ratio shown corresponds to the *syn* (*cis* relative configuration at C2,C3): *anti* (*trans* relative configuration at C2,C3) proportion. [d]Method A: $C_5H_5N^+-O^-$, Et_2O, rt. Method B: CAN, Me_2CO/H_2O, 0 °C to room temperature. [e]Isolated yield based on starting carbene complex **3**. [f]A mixture of two major and two minor isomers, each pair as a nearly equimolecular mixture. [g]In this oxidation reactions a small amount of a third diastereoisomer appeared. [h]Oxidation through method B afforded **4b** in 46% yield with several minor isomers. [i]Determined by ^{13}C NMR spectroscopy (inverse gated decoupling experiment using 1 mg of chromium acetylacetonate). [j]Oxidation through method A gave **4e** in 50% yield and 88:12 dr. [k]Determined by ^{1}H NMR at 400 MHz in C_6D_6. [l]Oxidation through method B gave **4f** in 21% yield and 95:5 dr.

selectivity (Scheme 1). It seemed that the enolate behaved this time as a formal azomethine ylide dipole and the carbene complex acted as a formal dipolarophile, giving rise to the corresponding [3 + 2] cycloadduct. We envisioned this result as a way to prepare conformationally restricted β,γ-disubstituted glutamic acids in an enantioselective fashion if chiral nonracemic alkenylcarbene complexes derived from (−)-8-phenylmenthol were employed. We wish to describe here the results obtained in the reaction of aldimine protected glycine ester enolates with chiral chromium alkenylcarbene complexes, as well as the manipulation of the reaction products in order to obtain enantiomerically enriched proline-glutamic acid chimeras.

Results and Discussion

Diastereoselective Formal [3 + 2] Cycloadditions of Aldimine Glycine Ester Enolates to Chiral Chromium Alkenylcarbene Complexes and Oxidation Reactions. Ethyl glycinate was treated with benzaldehyde or pivalaldehyde to give the corresponding aldimines, which were deprotonated with LDA in THF at −60 °C to give lithium enolates **2**. When a THF solution of racemic or enantiomerically pure alkenylcarbene complex **1** was added dropwise to **2** at −78 °C an instant reaction occurred that afforded *syn*,*exo* 3-pyrrolidinylcarbene complexes **3** after silica gel column chromatography (Scheme 2, Table 1). These [3 + 2] cycloadducts **3** were isolated in good yields, with total regioselectivity and very high stereoselectivity (*syn* refers to the relative configuration at C2,C3,[18] and *exo* denotes the relative stereochemistry at C4,C5[19]). The observed stereoselectivity is very high, considering that four stereocenters are created simultaneously and that diastereofacial selectivity of the chiral alkene can double the stereoisomers. In fact, racemic carbene complexes **1a**,**b** derived from (±)-menthol did not show any facial diastereoselectivity and in each case, the major and the minor cycloadducts **3a**−**c** consisted of roughly a 1:1 mixture of diastereoisomers (entries 1, 2, 3). However, the reactions with chiral carbene complexes **1c**,**d** derived from (−)-8-phenylmenthol took place with very high facial diastereoselectivity yielding in two cases **3d**,**f** only one diastereoisomer (entries 4, 6) and almost a single diastereoisomer in the other case **3e** (entry 5) as observed by ^{1}H and ^{13}C NMR spectroscopy. Compounds **3** were obtained exclusively as *exo*-cycloadducts. The minor isomer detected in some reactions (entries 1, 2, 5) corresponds to the epimeric isomer at the C2 carbon. Consequently, dr in Table 1 refers to the *syn* (*cis* relative configuration at C2,C3): *anti* (*trans* relative configuration at C2,C3) ratio.[18] In this sense, 2-furylvinyl carbene complexes **1b**,**d** showed better *syn*:*anti* selectivity in the reaction than 2-phenylvinyl carbene complexes **1a**,**c** (compare entries 3, 6 versus entries 2 and 5 respectively).

Scheme 2[a]



[a] Conditions: (i) THF, −78 °C; (ii) silica gel; (iii) method A: $C_5H_5N^+-O^-$, Et_2O. Method B: CAN, Me_2CO, H_2O.

The elimination of the metal fragment from cycloadducts **3** was effected through oxidation of these carbene complexes to obtain the corresponding racemic **4a**−**c** and enantiomerically enriched **4d**−**f** diesters. Oxidation with pyridine *N*-oxide (method A) was carried out at room temperature in ether as solvent. The reaction was slow, mainly with carbene complexes derived from (−)-8-phenylmenthol (entries 5, 6). In these long reaction times (up to 7 days) partial decomposition of the carbene complex may be competitive, which would account for the commonly moderate chemical yields. The lower steric demand of the menthol group compared to the (−)-8-phenylmenthol group could be responsible for shorter reaction times (2−3 days) with the racemic menthyl derived carbene complexes and therefore better chemical yields (entries 1, 2, 3). In addition, in both racemic and

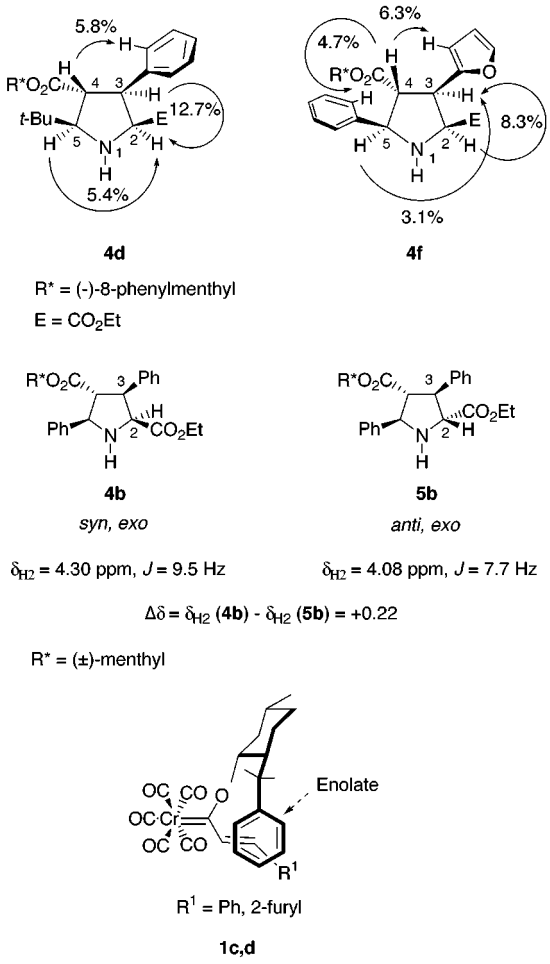
(19) In the [3 + 2] cycloaddition between *N*-metalated azomethine ylides and electron-deficient alkenes the *exo*,*endo* nomenclature has been employed to denote respectively a *trans* and *cis* relationship between the electron-withdrawing group at C4 coming from the alkene and the substituent at the C5 position coming from the azomethine ylide. See: Ayerbe, M.; Arrieta, A.; Cossío, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795.

chiral series of compounds, the ratio of diastereoisomers in the starting carbene complex was not maintained after the oxidation step. Indeed, a small loss in diastereoselectivity was observed. This effect had been previously noted in the oxidation of the Michael adducts obtained upon addition of *N*-diphenylmethylidene glycine esters enolates to Fischer alkenylcarbene complexes[18] and had been attributed to partial epimerization of the labile α-amino acid C2 carbon due to the free pyridine generated in the reaction medium and favored by long reaction times. Other oxidants (DMSO, iodosobenzene) proved to be unsuccessful. Only oxidation with ceric ammonium nitrate (CAN, method B) was an alternative oxidation method. The reactions were faster (3−12 h) but did not significantly improve the previous results. Thus, in the reaction of carbene complex **3b** with CAN, a major oxidation product within several minor diastereoisomeric products were obtained; the major compound **4b** was isolated in 46% yield. Oxidation of carbene complex **3d** with CAN proceeded in good yield (62%), but the major oxidation product was produced together with two minor diastereoisomers (entry 4). This oxidation procedure proved to be incompatible with the presence of a furyl group on the starting carbene complex, since oxidation of carbene complex **3f** with CAN yielded only 21% of product **4f**, while oxidation of the same compound with pyridine *N*-oxide increased the yield to 65% (entry 6). To improve the results on the oxidation step, protection of the amino group on carbene complexes **3** was accomplished. Thus, an *N*-acetyl pyrrolidinylcarbene complex was prepared in 49% yield by quenching the reaction between carbene complex **1a** and enolate **2b** with a small excess of acetyl chloride. However, oxidation of this *N*-protected carbene complex with pyridine *N*-oxide in ether afforded the corresponding diester in similar moderate 57% yield and with 81% de.

Structural elucidation of compounds **3** and **4** was based on ^{1}H and ^{13}C NMR analysis of the reaction products. The relative stereochemistry of the major diastereomeric pyrrolidine derivative **3**, **4** was determined as depicted in Scheme 2 through analysis of NOE experiments on the oxidation products **4d**,**f**. Irradiation of H4 on **4d** produced 5.8% NOE on the ortho protons of the phenyl group at C3 establishing a *trans* relationship between the substituents at C3 and C4. Irradiation on H3 produced 12.7% NOE on H2, while irradation of H5 produced 5.4% NOE on H2, which confirmed the *cis* relationship of substituents at C2, C3, and C5 (Chart 1). Further NOE experiments on proline ester **4f** obtained from enolate **2b** led to similar results, determining the *cis* relationship of the substituents at C2, C3, and C5 and a *trans* disposition of the (−)-8-phenylmenthol-derived ester with respect to the other three substituents (see most significative NOE enhancements in Chart 1). Relative configuration of carbene complexes **3** and proline esters **4a**−**c**,**e** was assigned by analogy.

On the other hand, oxidation of a sample of carbene complex **3b**, consisting as a 1:1 mixture of diastereoisomers, allowed separation and characterization of both the major *syn*,*exo*-**4b** and the minor *anti*,*exo*-**5b** isomers. Analysis of the ^{1}H NMR spectra of both compounds reveals that the most significant difference is found in the chemical shift and coupling constant of the H2 doublet signal (Chart 1). Applying to these compounds the Δδ empirical rule proposed for determining relative stereochemistry of stereoisomeric mixtures of kainoid

Chart 1

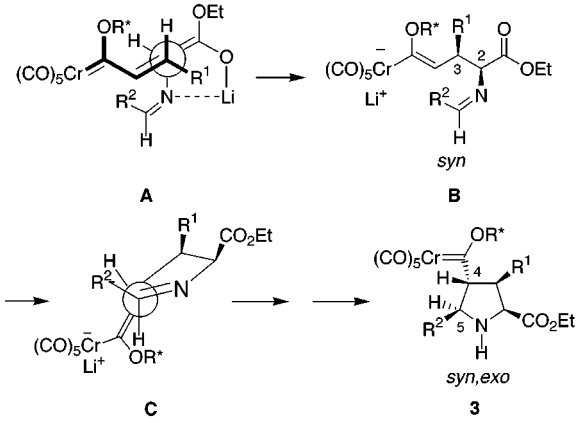


synthetic analogues,[20] led us to ascertain the relative configuration of **5b** as the C2 epimer of **4b**, since $\Delta\delta = \delta_{H2}\,(\text{cis}_{H2,H3}) - \delta_{H2}\,(\text{trans}_{H2,H3}) > 0$ (Chart 1).

The absolute stereochemistry of cycloadducts **3d**−**f** and **4d**−**f** was proposed to be (2*S*,3*S*,4*R*,5*R*) for 3-phenyl-substituted pyrrolidines **3d**,**e** and **4d**,**e** and (2*S*,3*R*,4*R*,5*R*) for 3-(2-furyl)-substituted proline derivatives **3f** and **4f** (according to numbering in Scheme 2). This assignment was based on the previous results obtained when the reaction was carried out under the same conditions but using a ketimine-protected glycine ester enolate.[18] Addition of the lithium enolate of ethyl *N*-(diphenylmethylidene)glycinate to chiral alkenylcarbene complex **1d** afforded a Michael adduct, whose X-ray structure analysis showed the *R* configuration for the carbon bearing the 2-furyl group. The same sense of asymmetric induction had been previously observed upon addition of different types of nucleophiles to chiral carbene complexes **1c**,**d**,[15] as well as in the [3 + 2] cycloaddition of the same chiral carbene complexes with 1,3-dipoles.[17] This facial selectivity can be interpreted by assuming that in the most stable conformation of **1c**,**d**, the phenyl group on the chiral auxiliary shields the double bond

(20) Although proline esters **4** and **5** do not belong to the kainoid family, as glutamate subunit containing derivatives, they can be considered esterified kainoid analogues. The Δδ rule is applicable for kainoid synthetic analogues and establishes that, when a pair of C2 epimers are available and their ^{1}H NMR spectra are recorded in D_2O at the same or nearly equal pD, the H2 chemical shift of the H2,H3-*trans* isomer appears at higher fields than that of the corresponding H2, H3-*cis* isomer, irrespective of the C4 substituent. See ref 14d.

Chart 2

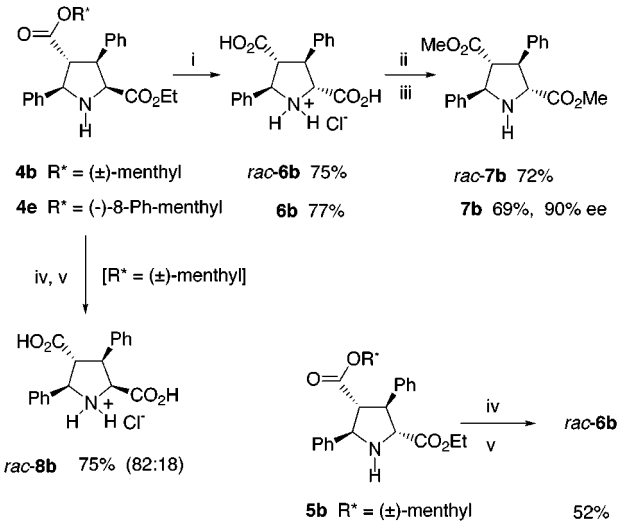


(*Re,Re*)-face of the alkene by π,π-orbital overlapping,[21] inducing nucleophilic attack selectively from the back (*Si,Si*)-face (Chart 1).

Mechanistic Proposal. The obtention of cycloadducts **3** can be rationalized through a stepwise mechanism: first addition of enolate **2** to the α,*β*-unsaturated carbene complex **1** to give the corresponding *syn* Michael adduct, followed by a 5-*endo-trig* ring closure in a NARC sequence. According to our previous results,[18] the *syn* diastereoselectivity observed in the first Michael addition step can be explained in terms of the model **A** shown in Chart 2. This 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 bulky substituent of the enolate away from the $(CO)_5Cr{=}C(OR^*)$ group. In contrast to the ketimine glycine ester enolate, the aldimine glycine ester enolates react as a five-membered ring 1-oxaallyl anion[18] furnishing *syn* anionic intermediate **B**, which in this case undergoes subsequent ring closure presumably favored by the higher reactivity and lower steric demand of the aldimine carbon in relation to the analogous ketimine center.[22] Intramolecular imine addition of the carbene complex enolate type anion to give the five-membered ring would occur through approach topology **C** in which H as the smallest substituent on the imine is placed in a *syn* disposition with the bulky metal fragment to avoid steric interactions. This arrangement would finally afford cycloadducts **3** with the observed *syn,exo* stereochemistry. Although the intramolecular imine addition step would be a disfavored 5-*endo-trig* ring closure,[23] there are several literature precedents for this type of cyclization.[24] Even in the related reaction of α,*β*-unsaturated esters and azomethine ylides, a 5-*endo-trig* closure is proposed to occur after an initial Michael nucleophilic addition in order to explain the final products.[5b]

From a formal point of view reaction products **3** might be considered as the result of a [3 + 2] cycloaddition between the enolate **2** acting as an azomethine ylide

Scheme 3[a]



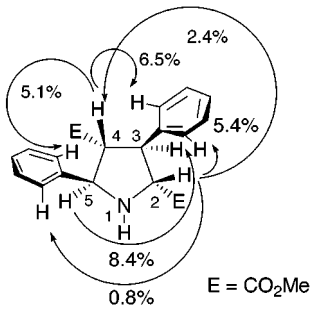
[a] Conditions: (i) CF_3CO_2H, 12 N HCl, 150 °C; (ii) Me_3SiCl, MeOH, rt; (iii) Et_3N, THF, rt; (iv) 2 N KOH, MeOH, 70 °C, (v) HCl.

dipole and the α,*β*-unsaturated carbene complex **1** acting as a dipolarophile. However, an alternative [3 + 2] concerted mechanism would be improbable, since alkenylcarbene complexes **1** are highly π-deficient systems and are most likely to behave as Michael acceptors rather than dipolarophiles.[19,25]

Hydrolysis Reactions. In the next step, pyrrolidine-2,4-dicarboxylates **4**, each as a pure diastereoisomer,[26] were subjected to hydrolysis to remove the chiral auxiliary. Basic hydrolysis of **4b** with 2 N KOH in refluxing MeOH for 3 h occurred with concomitant partial epimerization of the labile α-amino acid (C2) carbon resulting in an 82:18 mixture of pyrrolidine-2,4-dicarboxylic acid hydrochloride *rac*-**8b** and its 2-epimer *rac*-**6b**, respectively (Scheme 3). When an acidic hydrolysis was undertaken (TFA, 6 N HCl, 100 °C, 48 h), ^{1}H NMR of the crude hydrolysis product showed diacid *rac*-**8b**, but only in 29% yield, with the balance being the corresponding carboxylic acid containing unchanged the menthyl ester group. More forcing conditions (TFA, 12 N HCl, 150 °C in a sealed tube for 36 h) allowed complete hydrolysis but producing total epimerization at the C2 center. Only one product, diacid *rac*-**6b** was isolated in 75% yield, whose ^{1}H NMR revealed a *trans* relationship between the protons at C2 and C3. Confirmation of this structure was carried out by subjecting a pure sample of the minor *anti,exo* pyrrolidine **5b** diastereoisomer to basic hydrolysis. In this experiment, the same (identical NMR data) pyrrolidine-2,4-dicarboxylic acid *rac*-**6b** was isolated in 52% yield (Scheme 3).

The (−)-8-phenylmenthol derived ester **4e** proved to be more resistant to basic hydrolysis than the racemic diester **4b**. Treatment of pyrrolidine **4e** with 3 N KOH in MeOH under reflux for 16 h hydrolyzed both (−)-8-phenylmenthyl and ethyl esters, but led to partial epimerization of the labile C2 center. ^{1}H NMR of the

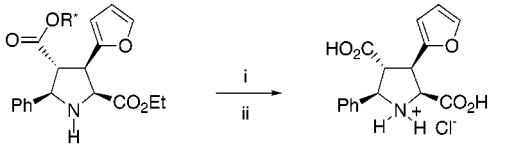
(21) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.
(22) For a related precedent, see: Tatsukawa, A.; Dan, M.; Ohbatake, M.; Kawatake, K.; Fukata, T.; Wada, E.; Kanemasa, S.; Kakei, S. *J. Org. Chem.* **1993**, *58*, 4221.
(23) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L. I.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
(24) (a) Cookson, R. C.; Smith, S. A. *J. Chem. Soc., Chem. Commun.* **1979**, 145. (b) Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* **1979**, *101*, 492. (c) Gregory, B.; Bullock, E.; Chen, T.-S. *J. Chem. Soc., Chem. Commun.* **1979**, 1070.
(25) For a stepwise mechanism supported by theoretical studies, see: Tatsukwa, A.; Kawakate, K.; Kanemasa, S.; Rudzinski, J. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2525.
(26) Racemic derivatives are indeed an 1:1 mixture of diastereoisomers due to the menthyl group, but both diastereoisomers have pyrrolidine rings with the same relative configuration.



7b

Figure 1.

Scheme 4[a]



4c R* = (±)-menthyl
4f R* = (-)-8-Ph-menthyl

rac-**8c** 43%
8c 37%, 96% ee

[a] Conditions: (i) LiOH, dioxane, H_2O, 100 °C; (ii) HCl.

crude reaction product revealed a 1:1 mixture of hydrolysis product **8b** and its 2-epimer diacid **6b** in 62% yield. Acidic hydrolysis of pyrrolidine **4e** (TFA, 12 N HCl, 150 °C, 36 h) took place with total epimerization of the C2 center and proline hydrochloride **6b** was isolated in 77% yield (Scheme 3). Both racemic and chiral dicarboxylic acids *rac*-**6b** and **6b** were esterified to afford the corresponding dimethyl diesters *rac*-**7b** and **7b**. HPLC analysis on a chiral support showed 90% ee for chiral proline ester **7b**. An NOE experiment on dimethyl diester **7b** showed the lack of the strong NOE between H2 and H3 existing in the *cis* proline esters **4d** and **4f**, as well as a 2.4% NOE between H2 and H4 and a 8.4% NOE between H5 and H3. Irradiation on H2 also produced a 5.4% NOE on the ortho protons of the phenyl group at C3 and 0.8% NOE on the ortho protons of the phenyl group at C5, in agreement with the proposed stereochemistry (Figure 1). This acidic hydrolysis establishes a protocol for the obtention of 4-carboxy-3,5-diphenylproline hydrochloride **6b** with unnatural stereochemistry at the amino acid center from pyrrolidine **4e**.

On the other hand, treatment of 3-(2-furyl)-substituted pyrrolidines **4c** and **4f** with LiOH in a 3:1 mixture of dioxane/H_2O at 100 °C for 6 and 16 h, respectively, showed to be smooth enough to hydrolyze both (±)-menthyl and (−)-8-phenylmenthyl esters, while maintaining the configuration at the C2 carbon (Scheme 4). 4-Carboxy-3-(2-furyl)-5-phenylproline hydrochlorides *rac*-**8c** and **8c** with natural stereochemistry at the amino acid center were obtained in 43% and 37% yield, respectively.[27] Chiral electrophoresis analysis of these compounds revealed that **8c** was obtained with 96% ee. When the hydrolysis reaction of **4c** was carried out employing THF instead of dioxane, the sterically hindered menthyl ester did not react and only the ethyl ester was hydrolyzed.

(27) When these basic conditions were used to hydrolize pyrrolidine **4b** partial epimerization of the C2 center was observed.

Conclusions

In summary, it has been demonstrated that chiral nonracemic Fischer alkenylcarbene complexes bearing (−)-8-phenylmenthol as chiral auxiliary undergo formal [3 + 2] cycloaddition reactions with aldimine-protected glycine ester enolates in a very high regio-, stereo-, and enantioselective manner giving *syn*,*exo*-cycloadducts. This methodology complements the related reaction between chiral α,β-unsaturated esters[5c,8b,c,d,e,h,j] or amides[8g] and *N*-metalated azomethine ylides, in which *anti*,*endo*-cycloadducts are generally favored.[28] The tetrasubstituted pyrrolidine cycloadducts can be converted by successive oxidation and hydrolysis, and depending on the hydrolysis conditions, into 4-carboxy trisubstituted prolines with either natural or unnatural configuration at the amino acid center. These systems can be considered as constrained analogues of β,γ-disubstituted glutamic acids and could have potential application for understanding the structures and properties of glutamate receptors.

Experimental Section[29]

General Procedure for the Synthesis of 3-Pyrrolidinyl Carbene Complexes 3. All the operations were carried out under a nitrogen atmosphere. LDA (1.6 equiv) was prepared by adding *n*-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, this LDA solution was cooled to −78 °C, and a solution of the corrresponding ethyl *N*-alkylidene glycinate (1.6 equiv) was added via an addition funnel. The resulting yellow-orange solution was stirred for 30 min at −78 °C, and then a THF solution of the corresponding α,β-unsaturated carbene complex **1** (1 equiv) was added dropwise from the addition funnel at −78 °C. By the end of the addition step, the dark red starting carbene complex solution had turned into a bright yellow one, which was stirred for 1 h at −78 °C and then quenched with silica gel at −78 °C for the adducts derived from phenylalkenyl carbene complexes **1a**,**c**, or with a saturated NH_4Cl aqueous solution and silica gel at −78 °C for the adducts derived from furylalkenyl carbene complexes **1b**,**d**, and allowed to quickly rise to room temperature. THF was evaporated under reduced pressure, and the silica-adsorbed product was placed on top of a column and purified by flash chromatography. Elution with hexane/CH_2Cl_2, 9:1 removed some starting carbene complex left and no polar materials. Sequential elution with hexane/CH_2Cl_2, 4:1, 1:1 and hexane/CH_2Cl_2/EtOAc, 1:1:0.1 gave the pure carbene complexes **3** as one major diastereoisomer in the chiral examples **3d**−**f** and as a mixture of two major diastereoisomers in the racemic examples **3a**−**c** due to the stereocenters of racemic menthol.

Pentacarbonyl[1-[(2*R*,3*R*,4*S*,5*S*)-2-*tert*-butyl-5-ethoxycarbonyl-4-phenyl-3-pyrrolidinyl]-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]methylidene]chromium (3d). Ethyl *N*-(2,2-dimethylpropylidene)glycinate (0.55 g, 3.2 mmol) in THF (8 mL) was treated with LDA prepared from *i*-Pr_2NH (0.42 mL, 3.2 mmol) and *n*-BuLi (1.6 mL, 3.2 mmol) in THF (8 mL), according to the general procedure. After 30 min at −78 °C, a 0.33 M THF solution of carbene complex **1c** (6 mL, 2 mmol) was diluted in THF (12 mL) and added to the glycinate solution of **2a** at −78 °C. The reaction mixture was stirred at − 78 °C for 1 h and worked up as described above. Flash chromatography of the crude product afforded 1.12 g (1.57 mmol, 78% yield) of compound **3d** as a yellow orangish solid in ≥99:1 dr: mp 122−123 °C; R_f = 0.55 (hexane/CH_2Cl_2 / EtOAc, 45:45:10); $[\alpha]_D$ = +80.29 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ

(28) For a few examples in which *exo* cycloadducts are obtained by reaction of azomethine ylides and chiral acrylates, see ref 8a,f,i.

(29) General methods and preparation of carbene complexes **1** have been recently published. See ref 18. Experimental procedures and spectral data for compounds not described here are presented in the Supporting Information.

7.40−7.25 (10 H, m), 5.74 (1 H, dt, J = 10.4, 4.3 Hz), 4.83 (1 H, dd, J = 8.2, 4.7 Hz), 4.03 (1 H, dd, J = 8.2, 9.5 Hz), 3.71−3.54 (2 H, m), 3.46 (2 H, m), 2.48 (1 H, dt, J = 12.7, 3.6 Hz), 2.38 (1 H, t, J = 9.9 Hz, NH), 2.17 (1 H, bd, J = 10.9 Hz), 1.70−1.52 (7 H, m + d, J = 4.2 Hz), 1.52−1.15 (3 H, m), 1.15−1.00 (10 H, m + s), 0.93−0.83 (4 H, m + d, J = 6.4 Hz), 0.78 (3 H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 360.8 (C), 222.1 (C), 215.8 (C), 170.0 (C), 149.5 (C), 140.9 (C), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 125.8 (CH), 125.5 (CH), 94.8 (CH), 82.8 (CH), 72.7 (CH), 65.8 (CH), 60.3 (CH_2), 52.5 (CH), 51.3 (CH), 44.3 (CH_2), 40.8 (C), 33.7 (CH_2), 33.3 (C), 32.1 (CH), 31.1 (CH_3), 27.6 ((CH_3)$_3$), 27.5 (CH_2), 21.9 (CH_3), 21.6 (CH_3), 13.5 (CH_3); IR (film) ν (cm^{-1}) 3329, 2058, 1940, 1741. MS (EI) m/z 569 (M^+ − 5CO, 1.7), 476 (4), 269 (15), 119 (100). Anal. Calcd for $C_{39}H_{47}CrNO_8$ (709.79): C, 66.00; H, 6.67; N, 1.97. Found: C, 66.15; H, 6.73; N, 2.00.

Pentacarbonyl[1-[(2*R*,3*R*,4*S*,5*S*)-5-ethoxycarbonyl-2,4-diphenyl-3-pyrrolidinyl]-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]methylidene]chromium (3e). Ethyl *N*-(phenylmethylidene)glycinate (0.61 g, 3.2 mmol) in THF (8 mL) was treated with LDA prepared from *i*-Pr_2NH (0.42 mL, 3.2 mmol) and *n*-BuLi (1.3 mL, 3.2 mmol) in THF (10 mL), according to the general procedure. After 30 min at −78 °C, a 0.33 M THF solution of carbene complex **1c** (6 mL, 2 mmol) was diluted in THF (12 mL) and added to the glycinate solution of **2b** at −78 °C. The reaction mixture was stirred at − 78 °C for 1 h and worked up as described above. Flash chromatography of the crude product afforded 1.09 g (1.49 mmol, 75% yield) of compound **3e** as a yellow oil, in 96:4 dr: $[\alpha]_D$ = +51.8 (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (2 H, d, J = 7.1 Hz), 7.42−7.23 (13 H, m), 5.68 (1 H, dt J = 10.4, 4.5 Hz), 5.30 (1 H, t, J = 8.6 Hz), 4.29 (1 H, d, J = 8.9 Hz), 4.20 (1 H, d, J = 9.0 Hz), 3.88 (1 H, t, J = 8.6 Hz), 3.76 (1 H, dd, J = 10.7, 7.1 Hz), 3.62 (1 H, dd, J = 10.7, 7.1 Hz), 2.59 (2 H, bm + dt, J = 12.3, 3.5 Hz), 2.01 (1 H, d, J = 12.4 Hz), 1.61 (2 H, m), 1.48−1.34 (7 H, m + s), 1.25 (2 H, m), 0.94 (3 H, d, J = 6.1 Hz), 0.88−0.74 (4 H, m + t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 364.3 (C), 222.7 (C), 215.0 (C), 171.4 (C), 149.7 (C), 139.4 (C), 128.8 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 125.8 (CH), 125.4 (CH), 125.1 (CH), 93.9 (CH), 87.5 (CH), 69.3 (CH), 66.1 (CH), 60.6 (CH_2), 52.9 (CH), 51.1 (CH), 45.0 (CH_2), 40.8 (C), 33.8 (CH_2), 32.3 (CH), 31.1 (CH_3), 27.2 (CH_2), 22.5 (CH_3), 21.5 (CH_3), 13.3 (CH_3); IR (film) ν (cm^{-1}) 3337, 2060, 1936, 1736; MS (EI) m/z 589 (M^+ − 5CO, 0.25), 131 (29), 119 (100), 91 (87). HRMS calcd for M^+ − 5CO, $C_{36}H_{43}CrNO_3$ 589.2648, found 589.2637. Anal. Calcd for $C_{41}H_{43}CrNO_8$ (729.78): C, 67.48; H, 5.93; N, 1.92. Found: C, 65.77; H, 5.98; N, 1.92.

Pentacarbonyl[1-[(2*R*,3*R*,4*R*,5*S*)-5-ethoxycarbonyl-4-(2-furyl)-2-phenyl-3-pyrrolidinyl]-1-[(1*R*,2*S*,5*R*)-8-phenylmenthyloxy]methylidene]chromium (3f). Ethyl *N*-(phenylmethylidene)glycinate (0.61 g, 3.2 mmol) in THF (10 mL) was treated with LDA prepared from *i*-Pr_2NH (0.42 mL, 3.2 mmol) and *n*-BuLi (1.3 mL, 3.2 mmol) in THF (10 mL), according to the general procedure. After 30 min at −78 °C, a 0.33 M THF solution of carbene complex **1d** (6 mL, 2 mmol) was diluted in THF (12 mL) and added to the glycinate solution of **2b** at −78 °C. The reaction mixture was stirred for 2 h and worked up as described above. Flash chromatography of the crude product afforded 1.42 g (1.97 mmol, 99% yield) of compound **3e** in ≥99:1 dr as a yellow oil which solidified after cooling: mp 90−91 °C; R_f = 0.52 (hexane/CH_2Cl_2 / EtOAc, 45:45:10); $[\alpha]_D$ = +37.3 (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.26 (11 H, m), 6.28 (1 H, d, J = 3.3 Hz), 6.13 (1 H, d, J = 3.3 Hz), 5.64 (1 H, td, J = 10.6, 4.7 Hz), 5.35 (1 H, t, J = 8.8 Hz), 4.16−4.04 (3 H, m), 3.83 (2 H, q, J = 7.4 Hz), 2.80 (1 H, bs), 2.60 (1 H, m), 1.97 (1 H, bd, J = 10.7 Hz), 1.60 (2 H, m), 1.58−1.20 (9 H, m), 1.10 (3 H, t, J = 7.3 Hz), 1.10−0.80 (4 H, m + d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 363.4 (C), 222.9 (C), 214.8 (C), 171.1 (C), 151.4 (C), 149.7 (C), 141.9 (CH), 139.1 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 125.8 (CH), 125.3 (CH), 110.2 (CH), 108.0 (CH), 93.7 (CH), 84.7 (CH), 69.6 (CH), 65.0 (CH), 61.1 (CH_2), 50.9 (CH), 47.1 (CH), 45.0 (CH_2), 40.6 (C), 33.8 (CH_2), 30.9 (CH), 27.0 (CH_2), 23.3 (CH_3), 21.5 (CH_3), 14.0 (CH_3), 13.6 (CH_3); IR (film) ν (cm^{-1}) 3340, 2060 1950, 1738. MS (EI) m/z 579 (M^+- 5CO, 4), 328 (77), 191 (54), 119 (100), 105 (89). HRMS calcd for M^+-5CO, $C_{34}H_{41}CrNO_4$ 579.2441, found 579.2441. Anal. Calcd for $C_{39}H_{41}CrNO_9$ (719.75): C, 65.08; H, 5.74; N, 1.94. Found: C, 64.97; H, 5.98; N, 1.94.

General Procedure for Oxidation of Carbene Complexes 3. Method A. An Et_2O solution of carbene complex **3** was treated with pyridine *N*-oxide (9−10 equiv) and stirred for 48−72 h. 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 disappearance of the carbene complex. 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 bulb light. 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 **4d**−**f** and as a roughly 1:1 mixture of two major diastereoisomers in the racemic examples **4a**−**c**.

Method B. Ceric ammonium nitrate (CAN, 4−5 equiv) was dissolved in the minimun amount of water, and this solution was added dropwise into an acetone solution of carbene complex **3** via an addition funnel at −5−0 °C. Then, the cold bath was removed, and the reaction was stirred for 3−24 h until starting carbene complex disappeared as evidenced by TLC. Solvents were evaporated, some water was added, and the mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give the crude product, which was purified by column chromatography.

2-Ethyl 4-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl] (2*S*,3*S*,4*R*,5*R*)-5-*tert*-Butyl-3-phenylpyrrolidine-2,4-dicarboxylate (4d). Method B. A solution of carbene complex **3d** (0.53 g, 0.75 mmol) in acetone (20 mL) was treated with CAN (2.05 g, 3.75 mmol) for 24 h according to the general procedure. Workup of the reaction mixture as described above gave a crude product which was purified by column chromatography (hexane/EtOAc, 4:1) to give 0.25 g (0.46 mmol, 62%) of **4d** in 85:11:4 dr. Further chromatographic purification allowed the isolation of pure major diastereoisomer as a colorless oil: R_f = 0.31 (hexane/EtOAc, 4:1); $[\alpha]_D$ = +83.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.01 (10 H, m), 4.65 (1 H, dt, J = 10.3, 3.9 Hz), 4.05 (1 H, d, J = 8.6 Hz), 3.77−3.58 (2 H, m), 3.45 (1 H, t, J = 8.6 Hz), 3.35 (1 H, d, J = 9.4 Hz), 2.44 (1 H, dd, J = 9.2, 8.0 Hz), 2.22 (1 H, bs), 1.98−1.82 (2 H, m), 1.50 (2 H, m), 1.26 (4 H, s + m), 1.14 (4 H, s + m), 1.01 (10 H, m + s), 0.90−0.78 (4 H, m + d, J = 6.4 Hz), 0.75 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.4 (C), 171.8 (C), 151.0 (C), 139.9 (C), 128.1 (CH), 127.9 (CH), 127.7 (CH), 126.7 (CH), 125.0 (CH), 124.9 (CH), 75.6 (CH), 69.1 (CH), 64.5 (CH), 60.3 (CH_2), 54.3 (CH), 52.1 (CH), 49.4 (CH), 40.8 (CH_2), 39.5 (C), 34.3 (CH_2), 33.0 (C), 31.0 (CH), 26.8 ((CH_3)$_3$), 26.6 (CH_2), 26.5 (CH_3), 26.4 (CH_3), 21.6 (CH_3), 13.4 (CH_3); IR (film) ν (cm^{-1}) 3342, 1724. MS (EI) m/z 533 (M^+, 1.8), 531 (7), 476 (M^+-*t*-Bu, 88), 262 (66), 119 (74). HRMS calcd for $C_{34}H_{47}NO_4$ 533.3505, found 533.3471.

2-Ethyl 4-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl] (2*S*,3*S*,4*R*,5*R*)-3,5-Diphenylpyrrolidine-2,4-dicarboxylate (4e). Method B. A solution of carbene complex **3e** (0.95 g, 1.30 mmol) in acetone (40 mL) was treated with CAN (3.85 g, 7.02 mmol) for 3 h according to the general procedure. Workup of the reaction mixture as described above gave a crude product which was purified by column chromatography (hexane/EtOAc, 4:1, 2:1, 1:1) to give 0.38 g (0.63 mmol, 53%) of **4e** in 89:11 dr. Further chromatographic purification allowed the isolation of pure major diastereoisomer as a colorless oil: R_f = 0.34 (hexane/EtOAc, 4:1); $[\alpha]_D$ = +41.4 (*c* 0.49, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.63 (2 H, d, J = 6.9 Hz), 7.51−6.91 (13 H, m), 4.60 (1 H, dt, J = 9.9, 3.4 Hz) overlapped with 4.58 (1 H,

d, J = 9.9 Hz,), 4.22 (1 H, d, J = 9.5 Hz), 3.86−3.70 (2 H, m + dd, J = 10.3, 7.3 Hz), 3.64 (1 H, dd, J = 10.3, 7.3 Hz), 2.93 (1 H, t, J = 10.3 Hz), 2.68 (1 H, bs), 1.70 (1 H, m), 1.59−1.25 (3 H, m), 1.02−0.86 (5 H, m + s), 0.85 (3 H, s), 0.85−0.6 (8 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9 (C), 172.1 (C), 150.8 (C), 140.6 (C), 137.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 127.1 (CH), 125.6 (CH), 125.2 (CH), 124.9 (CH), 75.3 (CH), 65.4 (CH), 64.9 (CH), 60.6 (CH_2), 57.3 (CH), 54.2 (CH), 50.0 (CH), 41.1 (CH_2), 39.4 (C), 34.3 (CH_2), 31.0 (CH), 26.6 (CH_2), 26.5 (CH_3), 25.6 (CH_3), 21.5 (CH_3), 13.4 (CH_3); IR (film) ν (cm^{-1}) 1722, 1454. MS (EI) m/z 553 (M^+, 10.7), 338 (100), 266 (17), 220 (17). HRMS calcd for $C_{36}H_{43}NO_4$ 553.3192, found 553.3182. Anal. Calcd for $C_{36}H_{43}NO_4$ (553.74): C, 78.08; H, 7.81; N, 2.52. Found: C, 77.27; H, 8.14; N, 2.61.

2-Ethyl 4-[(1*R*,2*S*,5*R*)-8-Phenylmenthyl] (2*S*,3*R*,4*R*,5*R*)-3-(2-Furyl)-5-phenylpyrrolidine-2,4-dicarboxylate (4f). Method A. Carbene complex **3f** (1.13 g, 1.57 mmol) and pyridine *N*-oxide (0.96 g, 10.1 mmol) were allowed to react in Et_2O (70 mL) for 3 days. The suspension was filtered through Celite, some more pyridine *N*-oxide (0.47 g, 5 mmol) was added, and the reaction mixture was stirred at room temperature for 4 days. Then solvents were evaporated, and the residue was air oxidized as described above. Flash chromatography of the crude product (hexane/EtOAc, 4:1) afforded 0.40 g (1.0 mmol, 65% yield) of compound **4f** as a colorless oil in 92:8 dr. Further chromatographic purification allowed the isolation of pure major diastereoisomer: R_f = 0.34 (hexane/EtOAc, 4:1); $[\alpha]_D$ = +40.6 (c 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (2 H, d, J = 7.3 Hz), 7.39−7.03 (9 H, m), 6.28 (1 H, dd, J = 3.0, 1.9 Hz), 6.09 (1 H, d, J = 3.2 Hz), 4.65 (1 H, dt, J = 10.6, 4.2 Hz), 4.47 (1 H, d, J = 9.9 Hz), 4.18 (1 H, d, J = 9.0 Hz), 4.03−3.85 (3 H, m), 3.03 (1 H, t, J = 10.2 Hz), 2.65 (1 H, bs), 1.74 (2 H, m), 1.46 (1 H, m), 1.36−1.16 (2 H, m), 1.06 (3 H, t, J = 7.1 Hz), 0.98 (3H, s), 0.84 (4 H, m + s), 0.77 (5 H, m + d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9 (C), 171.0 (C), 150.3 (C), 149.9 (C), 141.1 (CH), 139.2 (C), 127.9 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 126.5 (CH), 124.6 (CH), 124.2 (CH), 109.3 (CH), 106.7 (CH), 74.9 (CH), 65.3 (CH), 62.9 (CH), 60.4 (CH_2), 55.5 (CH), 49.3 (CH), 47.2 (CH), 40.5 (CH_2), 38.9 (C), 33.5 (CH_2), 30.3 (CH), 26.7 (CH_3), 26.1 (CH_2), 24.1 (CH_3), 20.8 (CH_3), 13.0 (CH_3); IR (film) ν (cm^{-1}) 3367, 1724. MS (EI) m/z 543 (M^+, 5), 476 (M^+ − Fu, 57), 328 (77), 119 (100). HRMS calcd for $C_{34}H_{41}NO_5$ 543.2984, found 543.2979.

(2*R*,3*S*,4*R*,5*R*)-3,5-Diphenylpyrrolidine-2,4-dicarboxylic Acid Hydrochloride (6b). A solution of diester **4e** (0.29 g, 0.52 mmol) in trifluoroacetic acid (0.5 mL) and 12 N HCl (4 mL) was heated at 150 °C in a pressure tube for 4 d. The solution was cooled to room temperature, trifluoroacetic acid was evaporated, and the mixture extracted with dichloromethane. The aqueous layer was evaporated to give the title compound as a white solid (0.14 g, 0.40 mmol, 77%): mp 195−196 °C; $[\alpha]_D$ = −21.06 (c 0.6, EtOH); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.90−7.45 (14 H, m), 4.91 (1 H, d, J = 10.5 Hz), 4.74 (1 H, d, J = 9.3 Hz), 3.90 (1 H, apparent t, J = 11.1, 10.9 Hz), 3.68 (1 H, apparent t, J = 11.3, 10.5 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 171.2 (C), 169.4 (C), 137.3 (C), 132.1 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 65.6 (CH), 63.2 (CH), 57.3 (CH), 52.1 (CH). MS (FAB) m/z 312 (M^+ − Cl, 3), 311 (M^+ - HCl, 10), 266 (M^+-HCl − CO_2H, 71), 220 (37), 163 (100). HRMS calcd for $C_{18}H_{17}NO_4$ (M^+ − HCl) 311.1157, found 311.1162.

Diethyl (2*R*,3*S*,4*R*,5*R*)-3,5-Diphenylpyrrolidine-2,4-dicarboxylate (7b).[30] A solution of compound **6b** (100 mg, 0.28 mmol) in MeOH (5 mL) was treated with Me_3SiCl (0.18 mL, 1.43 mmol) at room temperature under a nitrogen atmosphere for 36 h. Solvents were evaporated under reduced pressure, and THF (3 mL) was added to the residue followed by Et_3N (0.12 mL, 0.87 mmol). A solid appeared into the solution, and the reaction mixture was stirred for 90 min. The solid was filtered, and the filtrate was concentrated under reduced pressure. Flash chromatography of the residue afforded 67 mg (0.19 mmol, 69%) of the title compound as a colorless oil: $[\alpha]_D$ = −9.81 (c 0.53, $CHCl_3$); R_f = 0.31 (hexane/EtOAc, 3:1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38 (2 H, m), 7.30−7.16 (8 H, m), 4.56 (1 H, d, J = 9.5 Hz), 4.02 (1 H, d, J = 6.4 Hz), 3.75 (1 H, dd, J = 9.5, 6.7 Hz), 3.66 (3 H, s), 3.44 (3 H, s), 3.00 (1 H, t, J = 9.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.6 (C), 172.7 (C), 141.1 (C), 128.6 (CH), 128.3 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 126.6 (CH), 66.4 (CH), 65.9 (CH), 61.4 (CH), 53.4 (CH), 52.2 (CH_3), 51.8 (CH_3); IR (film) ν (cm^{-1}) 3340, 1736. MS (EI) m/z 339 (M^+,12), 308 (9), 280 (M^+ − CO_2CH_3, 100), 220 (50), 177 (26). HRMS calcd for $C_{20}H_{21}NO_4$ 339.1470, found 339.1468. Anal. Calcd for $C_{20}H_{21}NO_4$ (339.39): C, 70.78; H, 6.23; N, 4.12. Found: C, 70.20; H, 6.35; N, 4.04.

(2*S*,3*R*,4*R*,5*R*)-3-(2-Furyl)-5-phenylpyrrolidine-2,4-dicarboxylic Acid Hydrochloride (8c). To a solution of diester **4f** (0.35 g, 0.64 mmol), in 24 mL of dioxane−water (3:1) was added lithium hydroxide (0.11 g, 1.76 mmol), and the mixture was refluxed for 16 h. The solvent was evaporated, and the aqueous layer was extracted with EtOAc and then it was acidified with 6 N HCl and cooled in an ice water bath. A white solid (50 mg, 0.14 mmol) precipitated which was filtered and dried under reduced pressure and characterized as the title compound. Evaporation of the solvent afforded 30 mg (0.09 mmol) of the same product as a white solid (combined yield 37%). Data (including ee) were taken on the precipitated compound: mp 272−273 °C; $[\alpha]_D$ = + 51.3 (c 0.11, H_2O with a drop of TFA); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.65 (3 H, m), 7.46 (3 H, m), 6.46 (1 H, m), 6.33 (1 H, m), 4.47 (1 H, d, J = 9.9 Hz), 4.22 (1 H, d, J = 8.8 Hz), 4.10 (1 H, t, J = 8.9 Hz), 3.27 (1 H, t, J = 9.8 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 173.2 (C), 172.6 (C), 151.7 (CH), 142.3 (C), 140.5 (C), 128.4 (CH), 127.8 (CH), 127.3 (CH), 110.4 (CH), 107.0 (CH), 65.4 (CH), 62.8 (CH), 55.6 (CH), 46.0 (CH). MS (FAB) m/z 302 (M^+ − Cl, 2), 301 (M^+ − HCl, 8), 256 (M^+ − HCl − CO_2H, 19.5), 163 (97), 117 (100). HRMS calcd for $C_{16}H_{15}NO_5$ (M^+ − HCl) 301.0950, found 301.0957.

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Supporting Information Available: Experimental procedures and analytical and spectral data for ethyl *N*-(2,2-dimethylpropylidene)glycinate, ethyl *N*-(phenylmethylidene)-glycinate, compounds **3a**−**c**, **4a**−**c**, **5b**, and *rac*-**8b**, and chart with observed NOEs for compounds *rac*-**7b** and **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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