(600 μL, 3.0 mmol, 3.0 equiv) in THF (12 mL) was added sodium bis(trimethylsilyl)amide (1.5 mL, 3 equiv, 1.0 M in methylene chloride) dropwise via syringe at −78 °C. After 10 min, 3-chloro-1-iodopropane (322 μL, 3.0 mmol, 3.0 equiv) was added. After an additional 2 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and separated by column chromatography on silica gel (eluted with hexane–CH_2Cl_2–EtOAc, 5:4:1) to afford 240 mg (51.6%) of the 3′-chloride as a white solid. This material was used directly for the Finkelstein reaction without further purification: ^{1}H NMR (270 MHz, $CDCl_3$ vs TMS) δ 2.00–2.40 (4 H, m), 3.60 (2 H, t, J = 6.8 Hz), 4.85–5.30 (3 H, m), 5.98 (1 H, d, J = 2.8 Hz), 6.55 (1 H, d, J = 3.1 Hz), 6.95 (2 H, s), 7.00–7.40 (13 H, m).

The 3′-chloride (330 mg, 0.71 mmol, 1.0 equiv) and NaI (1.06 g, 7.1 mmol, 10 equiv) in acetone (15 mL) were stirred overnight at reflux temperature. After the solvent was evaporated, the resulting residue was dissolved in ethyl acetate (50 mL), washed with brine, and dried over Na_2SO_4. The residue was purified by column chromatography on silica gel (eluted with hexane–CH_2Cl_2–EtOAc, 5:4:1) to yield 350 mg (89%) of **18b** as a white solid: ^{1}H NMR (200 MHz, DMSO-d_6 vs TMS) δ 1.90 (2 H, m), 2.23 (2 H, m), 3.30 (2 H, t, J = 7.3 Hz), 4.85–5.35 (3 H, m), 6.27 (1 H, d, J = 3.0 Hz), 6.52 (2 H, s), 6.70 (1 H, d, J = 3.3 Hz), 7.00–7.45 (13 H, m); IR (NaCl, CH_2Cl_2) 1754, 1704, 1245, 1207, 699 cm^{-1}; mp 167–169 °C (recryst hexane–EtOAc, 5:1); $[\alpha]^{25}_D$ = =26.4 (c 0.5, CH_2Cl_2). The antipode (**18a**) was similarly obtained from **5a** in 45% yield (two steps); mp 168–71 °C (recryst hexane/EtOAc, 5:1); $[\alpha]^{25}_D$ = +25.6° (c 0.5, CH_2Cl_2).

Represenative Enolate Alkylation of 5 To Produce 11/16. To a stirred solution of **5a** (146 mg, 0.38 mmol, 1.5 equiv) in HMPA/THF (7 mL, 1:6) was added sodium bis(trimethylsilyl)amide (375 μL, 1.5 equiv, 1.0 M in CH_2Cl_2) dropwise via syringe at −78 °C. After 10 min a solution of **18a** (140 mg, 0.25 mmol, 1.0 equiv) was added. After an additional 2 h, the reaction mixture was allowed to warm to room temperature, quenched by phosphate buffer solution (pH of 7), extracted with methylene chloride, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and recrystallized in ethyl acetate to afford 62 mg (20%) of **11aa** as a white solid. This material was identical to that obtained above from the reduction of **10aa**.

Note Added in Proof. A recent paper describing the synthesis of differentially protected *meso*-2,6-diaminopimelic acid has appeared: Jurgens, A. R. *Tetrahedron Lett.* **1992**, *33*, 4727.

Acknowledgment. We are indebted to the National Science Foundation (CHE 8717017), the National Institutes of Health (GM 40988), and Hoffman-La Roche, Inc., for providing financial support.

Supplementary Material Available: Detailed procedure and spectral data for the Mosher amides **19**, **20**, and **21** (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric [1,3]-Dipolar Cycloaddition Reactions: Synthesis of Highly Substituted Proline Derivatives

Robert M. Williams,* Weixu Zhai, David J. Aldous, and Suzanne C. Aldous

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received June 23, 1992

The asymmetric [1,3]-dipolar cycloaddition reactions of azomethine ylides derived from (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one with various aldehydes and dimethyl maleate is described. The reactions prove to be highly endo-selective, installing three contiguous stereogenic centers in the newly formed five-membered ring with essentially complete stereochemical control. In the case of aldehydes higher than formaldehyde, a fourth stereogenic center is created; in most cases, poor stereoselectivity is observed at this center; the diastereomers formed in these cases can be separated by chromatography and separately converted into the amino acids. The bicyclic dipolar adducts can be cleaved with either catalytic hydrogenolysis or hydrolytic ring opening, esterification, and lead tetraacetate removal of the chiral auxiliary.

The [1,3]-dipolar cycloaddition reaction of azomethine ylides has become a powerful method for constructing pyrrolidine ring systems.[1] A large array of important natural alkaloids possess highly substituted pyrrolidine ring systems. Several natural products have been synthesized by utilization of the [1,3]-dipolar ring-forming reaction as a key step.[2] Recent attention in this area has focused on devising methods to directly provide optically active [1,3]-dipolar cycloaddition products from azo-

Table I. Dipolar Adducts 4

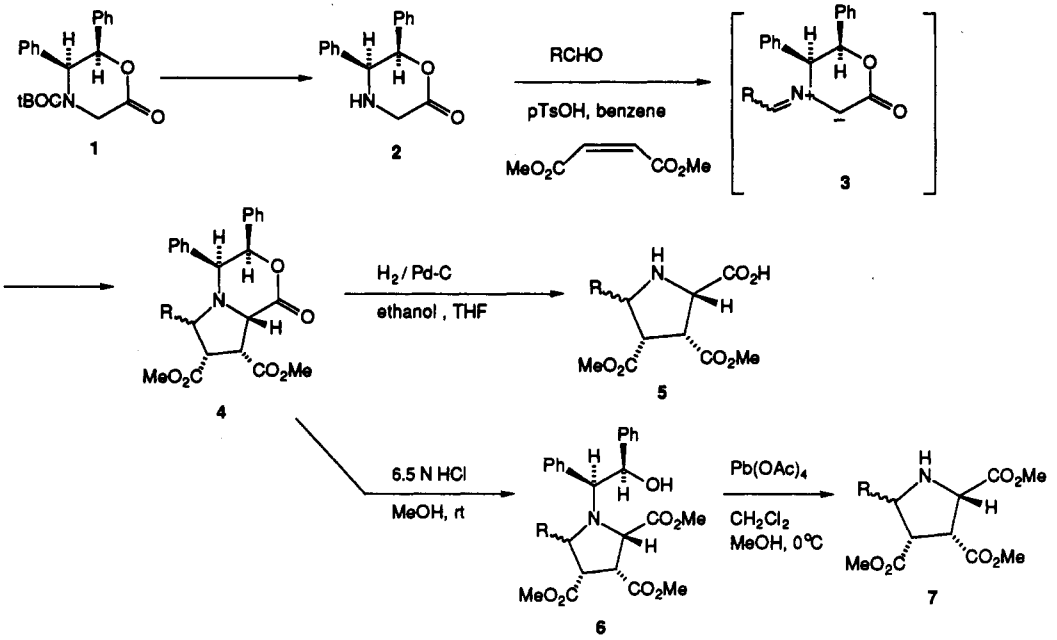
entry	aldehyde (R)	yield (% 4)	diastereomer ratio
1	formaldehyde	71 **4a**	
2	propionaldehyde	32 **4b**	1.33:1
3	isobutyraldehyde	52 **4c**	1:0
4	benzaldehyde	70 **4d**	1.7:1
5	*p*-anisaldehyde	71 **4e**	1:1
6	*p*-nitrobenzaldehyde	71 **4f**	1:1
7	2-furaldehyde	61 **4g**	1:1

(1) (a) For a review, see: Lown, W. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1. See also: (b) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451. (c) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (d) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1876. (e) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993. (f) Joucla, M.; Mortier, J. *Tetrahedron Lett.* **1987**, *28*, 2973. (g) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 3238. (h) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1988**, *53*, 3808. (i) Imai, N.; Nemoto, M.; Terao, Y.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1986**, *34*, 1078. (j) Imai, N.; Terao, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 2085. (k) Grigg, R.; Kemp, J.; Warnock, W. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2275. (l) Martin, S. F.; Cheavens, T. H. *Tetrahedron Lett.* **1989**, *30*, 7017. (m) Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 4727. (n) Burns, B.; Coates, B.; Neeson, S.; Stevenson, P. J. *Tetrahedron Lett.* **1990**, *31*, 4351. (o) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Chem. Lett.* **1986**, 973. (p) Joucla, M.; Mortier, J.; Hamelin, J. *Tetrahedron Lett.* **1985**, *26*, 277. (q) Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramanan, M. K.; Wong, G. S. K. *Chem. Ber.* **1986**, *119*, 813. (r) Husinec, S.; Savic, V.; Porter, A. E. A. *Tetrahedron Lett.* **1988**, *29*, 6649. (s) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 47. (t) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384.

(2) For examples, see: (a) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537. (b) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979. (c) Wang, C.-L. J. Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett.* **1984**, *25*, 4613. (d) Confalone, P. N.; Earl, R. A. *Tetrahedron Lett.* **1986**, *27*, 2695. (e) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1992**, *114*, 2767 and earlier references cited therein. (f) Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, Vol. 1, pp 323–358.

0022-3263/92/1957-6527$03.00/0 © 1992 American Chemical Society

Scheme I

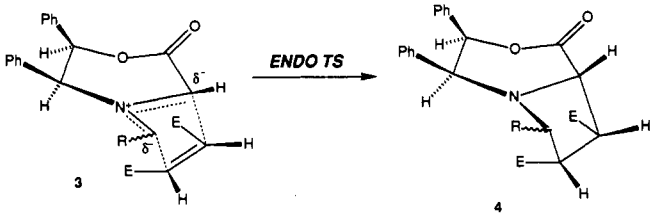


methine ylides.[3,4] Two general approaches have emerged: (1) utilization of a chiral, nonracemic dipolarophile[3] and (2) utilization of a chiral, nonracemic dipole.[4] Of these, the latter approach has been investigated much less frequently. In the course of developing general approaches to the synthesis of optically active α-amino acids,[5] we have examined the generation and [1,3]-dipolar cycloaddition reactions of azomethine ylides derived from 5,6-diphenylmorpholin-2-one.[6]

The starting material for this investigation is the 5,6-diphenylmorpholin-2-one (**2**) which is conveniently prepared from the commercially available[7] corresponding t-BOC derivative **1** by treatment with TFA.[8] The crude amino lactone **2** is subsequently treated with an aldehyde or ketone and a dipolarophile, such as dimethyl maleate in the presence of *p*-toluenesulfonic acid in warm benzene. Under these conditions, Schiff base formation and ylide generation (**3**) occur; subsequent [1,3]-dipolar addition of the dipolarophile provides the bicyclic adducts **4**. The specific examples studied with yields and diastereomer ratios are presented in Table I.

The formaldehyde system could be performed in two different ways. In the first system we examined, the lactone **2** was alkylated with chloromethyl methyl ether in benzene in the presence of triethylamine. The methoxymethylated substrate was used directly without further purification for the subsequent ylide generation/cycloaddition. Treatment of the crude methoxymethyl derivative with *p*-toluenesulfonic acid in hot benzene in the presence of dimethyl maleate generated ylide **3** (R = H) which suffered [1,3]-dipolar cycloaddition to yield adduct **4a** (R = H) in 70–73% yield. Due to the toxicity hazards of handling chloromethyl methyl ether, an alternative protocol involving paraformaldehyde was investigated. Treatment of **2** with paraformaldehyde in benzene containing dimethyl maleate and *p*-toluenesulfonic acid at room temperature for 70 h produced a single product, identical to that obtained from the *N*-methoxymethyl derivative (Scheme I). Although the yield in the latter case was not as high as the former, we prefer to recommend the paraformaldehyde protocol for safety reasons.

In the cases of higher aliphatic and aromatic aldehydes, the one-pot procedure of admixing lactone **2** with dimethyl maleate, the aldehyde, and *p*-toluenesulfonic acid in benzene at reflux temperature was utilized. In all cases, the endo selectivity of dipolar cycloaddition was excellent. In two cases (**4a** and **4d**), we have secured single-crystal X-ray structural analyses (see the supplementary material) that clearly demonstrate that the approach of the dipolarophile occurs from the less hindered face of the lactone resulting in reaction via an endo transition state.



The stereoselectivity realized at the C-7 position was generally poor with one notable exception. Isobutyr-

(3) (a) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (b) Barr, D. A.; Dorrity, M. J.; Grigg, R.; Malone, J. F. *Tetrahedron Lett.* **1990**, *31*, 6569. (c) Coulter, T.; Grigg, R.; Malone, J. F.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417. (d) Kanemasa, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 3633. (e) Wee, A. G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1363.

(4) (a) Rouden, J.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5133. (b) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron Asymm.* **1991**, *2*, 169. (c) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron Asymm.* **1991**, *2*, 997.

(5) Williams, R. M. In *Synthesis of Optically α-Amino Acids*; Pergamon Press: Oxford, 1989.

(6) A preliminary description of this work appears in Chapter 1 of ref 5.

(7) Both enantiomers of the t-BOC protected lactones **1** are commercially available from Aldrich: **1a** (2*R*,3*S*)-(−)-*tert*-butyl 6-oxo-2,3-diphenyl-4-morpholinecarboxylate (cat. no. 33-184-8); **1b** (2*S*,3*R*)-(+)-*tert*-butyl 6-oxo-2,3-diphenyl-4-morpholinecarboxylate (cat. no. 33-181-3).

(8) Trimethylsilyl iodide in chloroform or methylene chloride works equally effectively for this application.

(9) The numbering of the bicyclic adducts is based on a 1-aza-4-oxabicyclo[4.3.0]nonane ring system:

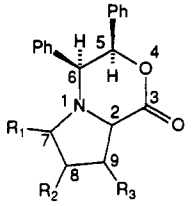


Table II. Conversion of Dipolar Cycloadducts 4 into Pyrrolidines 5 and 7

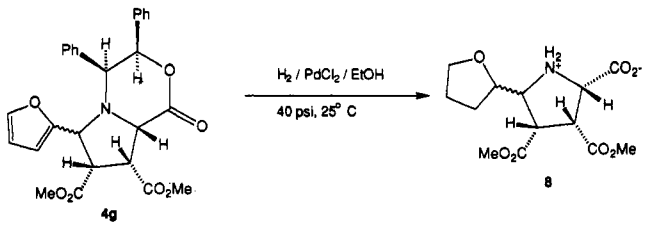
entry	substrate	method	yield (% 5)	yield (% 7)	% ee
1	**4a**	H_2/Pd–C	98		>99
2	**4b**	H_2/Pd–C	93		>99
3	**4c**	H_2/Pd–C	99		>99
4	**4d**	(1) 6.5 N HCl/MeOH (2) $Pb(OAc)_4$		57	>99
5	**4e**	(1) 6.5 N HCl/MeOH (2) $Pb(OAc)_4$		66	>99
6	**4f**	(1) 6.5 N HCl/MeOH (2) $Pb(OAc)_4$		56	>99
7	**4g**	H_2/Pd–C	99 (8)		>99

aldehyde furnished a single diastereomer (Table I, entry 3, **4c**) that was shown to have the all-syn relative stereochemistry by ^{1}H NMR nuclear Overhauser enhancement (NOE) studies. In all other cases, the relative stereochemistry of the five-membered ring was ascertained by ^{1}H NMR NOE studies. The relatively poor selectivity at the C-7 position presumably reflects the *E*:*Z* ratio of the incipient ylides (**3**) formed during Schiff base and ylide formation.

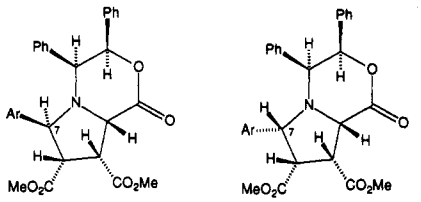
Conversion of the bicyclic adducts 4 into the corresponding pyrrolidinecarboxylic acids can be accomplished in two ways. For the simple aliphatic substrates **4a–c**, catalytic hydrogenation on a palladium catalyst proceeded in high yields to furnish the corresponding amino acids **5a–c** (Table II). The protocol is simple and follows directly from that previously reported from these laboratories.[10] For the aromatic aldehyde adducts **4d–f**, it was found that the catalytic hydrogenation procedure failed, presumably due to the lability of the additional benzylic C–N bond present in these systems. After considerable experimentation, we found a stepwise protocol for oxidatively removing the chiral auxiliary.[11] Initially, we attempted to effect hydrolytic ring opening with base; this procedure has been found to work well with cyclopropyl and α,α-disubstituted lactones derived from **1**. However, in the present case, extensive epimerization of stereogenic centers accompanied attempted saponification. Opening of the lactones **4d–f** with methanolic 6.5 N HCl at room temperature furnished the hydroxy methyl esters **6d–f** (Scheme I) in satisfactory yields. Treatment of these substances with lead tetraacetate in methylene chloride and methanol at 0 °C furnished the corresponding methyl esters **7d–f** in reasonably good overall yields. The furyl substrate **4g** proved to be a particularly troublesome compound to convert into an amino acid. The catalytic hydrogenation procedure worked well but also saturated the furan ring producing a tetrahydrofuran substituent of undetermined relative stereochemistry (Scheme II).

Subjecting **4f** to the stepwise oxidative protocol also produced an amino acid, but one in which the furan ring has suffered oxidative cleavage to a substituent of undetermined structure. We also observed an interesting difference in the ease of cleavage with respect to the relative stereochemistry at C-7. Isomers with the all-syn relative

Scheme II



stereochemistry were readily ring opened to the corresponding hydroxy methyl esters **6**; subsequent oxidative cleavage proceeded cleanly in each case. The corresponding C-7-anti isomers, on the other hand, gave products that displayed complicated ^{1}H NMR spectra that, upon methanolic HCl treatment, produced low yields of the desired amino esters **7**. In addition, the amino esters so obtained exhibited evidence for epimerization at the amino acid α-stereogenic center. No explanation for this behavior can be offered at the present time and is being further studied.



In summary, the asymmetric [1,3]-dipolar cycloaddition reactions of azomethine ylides derived from chiral, nonracemic glycinates provides access to a variety of highly substituted pyrrolidines. Studies aimed at controlling the stereochemistry of ylide formation and incorporation of substituents at the α-position as well as efforts to examine other symmetrical and unsymmetrical dipolarophiles are under study in these laboratories and will be reported on in due course.

Experimental Section

Determination of Optical Purity, General Procedure. The amino acids (5–10 mg) were converted into the corresponding Mosher amides as follows: The amino acids (**5**, 1.0 equiv) in dry THF were treated with propylene oxide (4.0 equiv) and (*R*)-(–)-methoxytrifluorophenylacetyl chloride (1.0 equiv). The resulting solution was heated to reflux temperature for 20 min. The resulting reaction mixtures were cooled, concentrated, and dried in vacuo. The crude Mosher amides were analyzed by ^{1}H and ^{19}F NMR spectroscopy and compared to spectra of authentic diastereomeric mixture of Mosher amides prepared by the same protocol from the corresponding racemic Mosher acid chloride.

(5*R*,6*S*)-2,3,5,6-Tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (2). To a solution of **1** (2.56 g, 10.12 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) was added trifluoroacetic acid (11.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The solvent and trifluoroacetic acid were evaporated under reduced pressure leaving an oily residue that was redissolved in CH_2Cl_2 (70 mL). To this solution was added Et_3N (3.15 mL), and the mixture was allowed to stand for 20 min at room temperature. The solvent was evaporated under reduced pressure leaving an oily residue that was redissolved in EtOAc (25 mL), washed with water (2 × 10 mL), dried over anhydrous Na_2SO_4, and evaporated to yield a white solid which was recrystallized from EtOAc/hexanes (mp 144–144.5 °C) leaving 1.78 g (97.3%) of pure **2**. ^{1}H NMR (300 MHz, $CDCl_3$): δ TMS 2.0 (1 H, br s), 4.03 (1 H, $^1/_2$ AB q, J = 18.3 Hz), 4.12 (1 H, $^1/_2$ AB q, J = 18.3 Hz), 4.63 (1 H, d, J = 3.8 Hz), 5.68 (1 H, d, J = 3.8 Hz), 6.81 (2 H, dd, J = 1.7, 6.9 Hz), 6.92 (2 H, dd, J = 1.7, 7.5 Hz), 7.13–7.26 (6 H, m). IR (NaCl, $CHCl_3$): 3322, 3033, 1737, 1604, 1547, 1496, 1455, 1378, 1342, 1209, 1065, 1036, 765 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 75.97; H, 6.01; N, 5.55.

(10) (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (c) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11.

(11) For related oxidative cleavage protocols for similar amino alcohol substrates, see: (a) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2253. (b) Inaba, T.; Fujita, M.; Ogura, K. Annual Meeting of the Chemical Society of Japan, April 1991, Abstract 1D202. (c) Weinges, K.; Brune, G.; Droste, H. *Liebigs Ann. Chem.* **1980**, 212. (d) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H.; Nixdorf, M.; Irngartinger, H. *Liebigs Ann. Chem.* **1985**, 566. (e) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.

(2S,5R,6S,8R,9R)-5,6-Diphenyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one (4a). Method A. To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (2) (208 mg, 0.822 mmol, 1.0 equiv) in dry benzene (50 mL) were added chloromethyl methyl ether (79.4 mg, 0.986 mmol, 1.2 equiv) and Et_3N (99.7 mg, 0.986 mmol, 1.2 equiv). The resulting mixture was allowed to stir at room temperature for 4 h, and then *p*-toluenesulfonic acid (156 mg, 0.822 mmol, 1.0 equiv) and dimethyl maleate (473 mg, 3.3 mmol, 4.0 equiv) were added. The reaction mixture was stirred for 3 d, evaporated, and separated on PTLC (silica gel, eluted with 3/1 hexane and EtOAc) to afford a white solid, which was recrystallized from EtOAc and hexane to produce 238 mg (70.8%) of **4a** as colorless needles. ^1H NMR (270 MHz, $CDCl_3$): δ TMS 2.95–3.10 (1 H, m), 3.21–3.45 (2 H, m), 3.66 (3 H, s), 3.75 (3 H, s), 3.78–3.85 (1 H, m), 4.58 (1 H, d J = 6.1 Hz), 4.80 (1 H, $^1/_2$ AB q, J = 3.9 Hz), 5.58 (1 H, $^1/_2$ AB q, J = 3.9 Hz), 7.07–7.26 (m, 10 H). IR (NaCl, $CHCl_3$): 2940, 2840, 2240, 1735, 1490, 1450, 1432, 1380, 1200, 1160, 1130, 1040, 900, 710 cm^{-1}. MS: *m/z* (relative intensity) 409 (M^+, 100), 363 (7.7), 348 (3.5). MP: 184.5–185 °C (recryst, EtOAc/hexane). $[\alpha]^{25}_D$ = +33.3° (*c* 0.18, CH_2Cl_2). Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.46; H, 5.67; N, 3.42. Found: C, 67.25; H, 5.64; N, 3.40.

Caution! Chloromethyl methyl ether is a highly toxic substance and cancer suspect agent. Extreme care should be taken in handling this reagent in a well-ventilated fume hood with protective gloves and eye protection.

Method B. To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (2) (266 mg, 1.05 mmol, 1.0 equiv) in dry benzene (50 mL) was added paraformaldehyde (725 mg, 24.18 mmol, 23.0 equiv), *p*-toluenesulfonic acid (60 mg, 0.315 mmol, 0.3 equiv), and dimethyl maleate (453.6 mg, 3.15 mmol, 3.0 equiv). The resulting mixture was allowed to stir at room temperature for 70 h. The mixture was then filtered, evaporated, and separated on PTLC (silica gel, eluted with 3/1 hexane/EtOAc) to afford a white solid, which was recrystallized from EtOAc and hexane yielding 165 mg of **4a** compound as white crystals (39%).

(2S,5R,6S,8R,9R)-5,6-Diphenyl-7(R)-ethyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7R)-4b] and (2S,5R,6S,8R,9R)-5,6-Diphenyl-7(S)-ethyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7S)-4b]. To a solution of **2** (258 mg, 1.02 mmol, 1.0 equiv) in dry benzene (35 mL) was added propionaldehyde (82.8 mg, 1.43 mmol, 1.43 equiv), *p*-toluenesulfonic acid (77.5 mg, 0.41 mmol, 0.4 equiv), anhydrous Na_2SO_4 (289.7 mg, 2.04 mmol, 2.0 equiv), and dimethyl maleate (440.6 mg, 3.06 mmol, 3.0 equiv). The resulting mixture was stirred at room temperature for 4 d, filtered, and evaporated, and the residue was separated on PTLC (silica gel, eluted with 3/1 hexane/EtOAc), affording two diastereomers: (7S)-**4b**, 60 mg, and (7R)-**4b**, 82 mg; combined yield 32%.

(7S)-4b. ^1H NMR (300 MHz, $CDCl_3$): δ TMS 0.85 (t, 3 H, J = 7.5 Hz), 1.72–2.23 (m, 2 H), 3.33–3.36 (m, 2 H), 3.61–3.66 (m, 1 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 3.73 (d, 1 H, J = 11.2 Hz), 4.67 (d, 1 H, J = 3.7 Hz), 6.34 (d, 1 H, J = 3.6 Hz), 7.07–7.42 (m, 10 H). IR (NaCl, $CHCl_3$): 2960, 1738, 1500, 1496, 1452, 1432, 1329, 1248, 1137, 1046, 696 cm^{-1}. MS (CI, NH_3): *m/z* 437 (M^+, 100). Mp: 194–195 °C (recryst EtOAc/hexanes) $[\alpha]^{25}_D$ = +58.2° (*c* 0.61, CH_2Cl_2). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 67.98; H, 6.44; N, 3.17.

(7R)-4b. ^1H NMR (300 MHz, $CDCl_3$): δ TMS 0.85 (t, 3 H, J = 7.6 Hz), 1.36–1.71 (m, 2 H), 3.12 (dd, 1 H, J = 8.1, 9.5 Hz), 3.78 (s, 6 H), 3.84 (m, 1 H), 3.95 (t, 1 H, J = 7.6 Hz), 4.41 (d, 1 H, J = 3.4 Hz), 4.76 (d, 1 H, J = 7.3 Hz), 6.03 (d, 1 H, J = 3.4 Hz), 7.32–6.93 (m, 10 H). IR (NaCl, $CHCl_3$): 2953, 1737, 1515, 1498, 1448, 1431, 1348, 1203, 1026, 698 cm^{-1}. MS (CI, NH_3): *m/z* 437 (M^+, 100). $[\alpha]^{25}_D$ = +24.8° (*c* 2.22, CH_2Cl_2). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.28; H, 6.36; N, 3.23. NOE data: irradiation of H_2 enhanced H_8 10.5%; irradiation of H_8 enhanced H7 10% and H_5 11.6%.

(2S,5R,6S,8R,9R)-5,6-Diphenyl-7(R)-isopropyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one (4c). To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (2) (312 mg 1.233 mmol, 1.0 equiv) in dry benzene (35 mL) was added isobutyraldehyde (124.5 mg, 1.726 mmol, 1.4 equiv), *p*-toluenesulfonic acid (93.7 mg, 0.493 mmol, 0.4 equiv), and dimethyl maleate (532.7 mg, 3.699 mmol, 3.0 equiv). The resulting mixture was heated at reflux for 48 h, cooled to room temperature, evaporated, and separated on PTLC (silica gel, eluted with 3/1 hexane/EtOAc) yielding **4c** as a white solid, which was recrystallized from EtOAc and hexane, 290.5 mg (52%). Mp: 167–168.5 °C; ^1H NMR (300 MHz, $CDCl_3$): δ TMS 0.84 (d, 3 H, J = 14.0 Hz), 0.89 (d, 3 H, J = 14.2 Hz), 1.84 (m, 1 H), 3.15 (t, 1 H, J = 8.2 Hz), 3.68–3.70 (m, 7 H), 3.85 (dd, 1 H, J = 4.8 Hz, 12.9 Hz), 4.45 (d, 1 H, J = 3.5 Hz), 4.62 (d, 1 H, J = 7.4 Hz), 6.06 (d, 1 H, J = 3.5 Hz), 6.92 (d, 2 H, J = 8.3 Hz), 7.30–7.05 (m, 8 H). IR (NaCl, neat): 2954, 1740, 1497, 1453, 1436, 1378, 1346, 1206, 1058, 699 cm^{-1}. $[\alpha]^{25}_D$ = +43.6° (*c* 0.14, CH_2Cl_2). Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.15; H, 6.48; N, 3.10. Found: C, 68.95; H, 6.43; N, 3.00. NOE data: irradiation of H_2 enhanced H_7 14.9%.

(2S,5R,6S,8R,9R)-5,6,7-Triphenyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7S)-4d and (7R)-4d]. To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (2) (92 mg, 0.36 mmol, 1.0 equiv) in dry benzene (70 mL) was added benzaldehyde (46 mg, 0.43 mmol, 1.2 equiv), *p*-toluenesulfonic acid (21 mg, 0.11 mol, 0.3 equiv), and dimethyl maleate (200 mg, 1.4 mmol, 3.9 equiv). The resulting mixture was heated to reflux for 24 h, cooled to room temperature, and evaporated, and the residue was separated by flash column chromatography (silica gel, eluted with 10% EtOAc in CH_2Cl_2) yielding two products, 78 mg (44%) of (7S)-**4d** and 45 mg (26%) of (7R)-**4d**.

(7S)-4d. ^1H NMR (300 MHz, $CDCl_3$): δ TMS 3.35 (dd, 1 H, J = 7.8, 10.4 Hz), 3.62 (s, 3 H), 3.82 (s, 3 H), 4.0 (t, H, J = 7.7 Hz), 4.20 (s, 1 H), 4.85 (d, 1 H, J = 10.4 Hz), 4.86 (d, 1 H, J = 7.4 Hz), 6.25 (s, 1 H), 6.75 (d, 2 H, J = 7.3 Hz), 7.35–6.90 (m, 13 H). MS (CI, NH_3): *m/z* 484 (M^+ – 1, 100). IR (NaCl, $CHCl_3$): 3030, 2950, 2240, 1735, 1600, 1495, 1450, 1435, 1380, 1350, 1200, 1170, 1050, 1020 cm^{-1}. $[\alpha]^{25}_D$ = +86.1° (*c* 0.33, CH_2Cl_2). Mp: 198–199 °C (recryst EtOAc/hexanes). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.93; H, 6.22; N, 3.20. Found: C, 68.28; H, 6.36; N. 3.23.

(7R)-4d. ^1H NMR (300 MHz, $CDCl_3$): δ TMS 2.99 (s, 3 H), 3.44 (d, 1 H, J = 5.6 Hz), 3.52–3.63 (m, 2 H), 3.72 (d, 1 H, J = 9.6 Hz), 3.75 (s, 3 H), 4.35 (d, 1 H, J = 3.8 Hz), 6.38 (d, 1 H, J = 3.7 Hz), 6.90 (dd, 2 H, J = 3.5, 5.56 Hz), 7.10–7.45 (m, 13 H). IR (NaCl, neat): 3062, 3030, 2950, 1746, 1604, 1496, 1455, 1435, 1383, 1306, 1270, 1206, 1142, 1099, 1061, 1031 cm^{-1}. MS (CI, NH_3): *m/z* 437 (M^+, 100). $[\alpha]^{25}_D$ = +165.2° (*c* 0.9, CH_2Cl_2). Mp: 228.5–29 °C (recryst EtOAc/hexanes). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 67.93; H, 6.44; N, 3.17.

(2S,5R,6S,8R,9R)-5,6-Diphenyl-7(R)-(p-methoxyphenyl)-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7R)-4e] and (2S,5R,6S,8R,9R)-5,6-Diphenyl-7-(S)-(p-methoxyphenyl)-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7S)-4e]. To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (2) (314 mg, 1.24 mmol, 1.0 equiv) in dry benzene (35 mL) was added *p*-anisaldehyde (236 mg, 1.74 mmol, 1.4 equiv), *p*-toluenesulfonic acid (94 mg, 0.50 mmol, 0.4 equiv), and dimethyl maleate (625 mg, 4.34 mmol, 3.5 equiv). The resulting mixture was heated to reflux for 48 h, cooled to room temperature, and evaporated to leave an oil, which was taken up in a small amount of CH_2Cl_2 and separated on PTLC (silica gel, eluted with 3/1 hexane/EtOAc) to afford 486 mg of a white solid. ^1H NMR indicated that the solid was a mixture of two diastereomers, which were further separated on PTLC (silica gel, eluted with 10/1 CH_2Cl_2/EtOAc), yielding 232 mg of (7S)-**4e** and 221 mg of (7R)-**4e**. Combined yield 71%.

7S Isomer 4e. ^1H NMR (300 MHz, $CDCl_3$): δ TMS 3.06 (s, 3 H), 3.40 (dd, 1 H, J = 5.4, 6.8 Hz), 3.44 (d, 1 H, J = 9.6 Hz), 3.55 (dd, 1 H, J = 5.5, 9.5 Hz), 3.63 (d, 1 H, J = 9.6 Hz), 3.72 (s, 3 H), 3.88 (s, 3 H), 4.34 (d, 1 H, J = 3.7 Hz), 6.38 (d, 1 H, J = 3.7 Hz), 6.90 (m, 2 H), 6.93 ($^1/_2$ AB q, 2 H, J = 8.2 Hz), 7.06–7.21 (m, 8 H), 7.26 ($^1/_2$ AB q, 2 H, J = 8.1 Hz). IR (NaCl, neat): 2980, 1737, 1611, 1512, 1438, 1247, 1208, 1031, 699 cm^{-1}. Mp: 214–214.5 °C. $[\alpha]^{25}_D$ = +227.2° (*c* 0.25, CH_2Cl_2). Anal. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.66; N, 2.71. Found: C, 69.75; H, 5.86; N, 2.73.

7R Isomer 4e. ^1H NMR (300 MHz, $CDCl_3$): δ TMS 3.24 (dd, 1 H, J = 7.8, 10.3 Hz), 3.65 (s, 3 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.99 (t, 1 H, J = 7.6 Hz), 4.20 (s, 1 H), 4.82 (s, 1 H), 4.85 (s, 1 H), 6.24 (s, 1 H), 6.75–7.28 (m, 14 H). Mp: 167–168 °C (recryst. EtOAc/hexanes). $[\alpha]^{25}_D$ = +97.6° (*c* 0.17, CH_2Cl_2). Anal. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.66; N, 2.71. Found: C, 69.51; H, 6.09; N, 2.62. NOE data: irradiation of H_2 enhanced H_7 and H_8 18.3%.

(2S,5R,6S,8R,9R)-5,6-Diphenyl-7(R)-(p-nitrophenyl)-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7R)-4f] and (2S,5R,6S,8R,9R)-5,6-Diphenyl-7(S)-(p-nitrophenyl)-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]-nonan-3-one [(7S)-4f]. To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-3-one (2) (272 mg, 1.07 mmol, 1.0 equiv) in dry benzene (40 mL) was added p-nitrobenzaldehyde (227 mg, 1.5 mmol, 1.4 equiv), p-toluenesulfonic acid (81.7 mg, 0.43 mmol, 0.4 equiv), and dimethyl maleate (619.2 mg, 4.3 mmol, 4.0 equiv). The resulting mixture was heated at reflux for 48 h, cooled to room temperature, evaporated, and separated by PTLC chromatography (silica gel, eluted with 3/1 hexane/EtOAc), yielding 209 mg of (7S)-4f and 187 mg of (7R)-4f. Combined yield 71%.

7S Isomer 4f. ^{1}H NMR (300 MHz, $CDCl_3$): δ TMS 3.26 (dd, 1 H, J = 7.5, 9.1 Hz), 3.62 (s, 3 H), 3.78 (s, 3 H), 4.16 (dd, 1 H, J = 7.1, 9.1 Hz), 4.37 (s, 1 H), 4.83 (d, 1 H, J = 10.5 Hz), 5.0 (d, 1 H, J = 6.9 Hz), 6.03 (s, 1 H), 6.63 (d, 2 H, J = 7.3 Hz), 6.92 (t, 2 H, J = 7.5 Hz), 7.03–7.08 (m, 3 H), 7.21–7.28 (m, 3 H), 7.34 (d, 2 H, J = 8.7 Hz), 8.0 (d, 2 H, J = 8.8 Hz). MS (CI, NH_3): m/z = 530 (M^+, 60), 500 (100). IR (NaCl, neat): 2952, 1739, 1520, 1437, 1348, 1212, 849, 698 cm^{-1}. Mp: 154–155 °C (recryst EtOAc/hexanes). $[\alpha]^{25}_D$ = +107.6° (c 0.29, CH_2Cl_2). Anal. Calcd for $C_{29}H_{26}N_2O_8$: C, 65.65; H, 4.94; N, 5.28. Found: C, 65.32; H, 5.22; N, 5.18.

7R Isomer 4f. ^{1}H NMR (300 MHz, $CDCl_3$): δ TMS 3.09 (s, 3 H), 3.55–3.64 (m, 3 H), 3.76 (s, 3 H), 3.86 (d, 1 H, J = 9.3 Hz), 4.24 (d, 1 H, J = 3.8 Hz), 6.37 (d, 1 H, J = 3.8 Hz), 6.85–6.92 (m, 2 H), 7.12–7.26 (m, 10 H), 8.31 (d, 2 H, J = 9.0 Hz). IR (NaCl, neat): 2970, 1738, 1630, 1526, 1428, 1351, 1226, 1108, 1076, 960, 856, 695 cm^{-1}. Mp: 170–170.5 °C (recryst EtOAc/hexanes). $[\alpha]^{25}_D$ = +173.5° (c 0.16, CH_2Cl_2). NOE data: irradiation of H_7 enhanced H_2, H_8, and H_9 22.9%.

(2S,5R,6S,8R,9R)-5,6-Diphenyl-7(R)-2′-furyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7R)-4g] and (2S,5R,6S,8R,9R)-5,6-Diphenyl-7(S)-2′-furyl-8,9-dicarbomethoxy-1-aza-4-oxabicyclo[4.3.0]nonan-3-one [(7S)-4g]. To a solution of (5R,6S)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-3-one (2) (376 mg, 1.487 mmol, 1.0 equiv) in dry benzene (35 ml) was added furaldehyde (200 mg, 2.081 mmol, 1.4 equiv), p-toluenesulfonic acid (113 mg, 0.595 mmol, 0.4 equiv), and dimethyl maleate (749.5 mg, 5.205 mmol, 3.5 equiv). The resulting mixture was heated at reflux for 24 h, cooled to room temperature, and evaporated, and the residue was separated by flash column chromatography (silica gel, eluted with 3/1 hexane/EtOAc), yielding 193.9 mg of (7S)-4g and 236.9 mg of (7R)-4g. Combined yield 61%.

(7S)-4g. ^{1}H NMR (300 MHz, $CDCl_3$): δ TMS 3.62 (m, 4 H), 3.75 (m, 4 H), 3.99 (t, 1 H, J = 7.4 Hz), 4.52 (d, 1 H, J = 3.3 Hz), 4.79 (d, 1 H, J = 9.2 Hz), 4.81 (d, 1 H, J = 10.1 Hz), 5.98 (dd, 2 H, J = 3.4 Hz J = 10.4 Hz), 6.13 (d, 1 H, J = 1.8 Hz), 6.78–7.30 (m, 10 H). IR (NaCl, neat): 2949, 1740, 1738, 1640, 1500, 1455, 1430, 1205, 1026, 731, 693 cm^{-1}. Mass spectrum (CI, NH_3): m/z (relative intensity) 475 (M^+, 100). $[\alpha]^{25}_D$ = +98.8° (c 1.41, CH_2Cl_2). Mp: 183–185 °C (recryst EtOAc/hexanes).

(7R)-4g. ^{1}H NMR (270 MHz, $CDCl_3$): δ TMS 3.34 (s, 3 H), 3.40 (m, 1 H), 3.51 (d, 1 H, J = 9.4 Hz), 3.62 (dd, 1 H, J = 5.6, 9.5 Hz), 3.78 (s, 3 H), 3.90 (d, 1 H, J = 9.5 Hz), 4.51 (d, 1 H, J = 3.8 Hz), 6.37 (d, 1 H, J = 3.7 Hz), 6.50 (dd, 1 H, J = 1.8 Hz, J = 3.2 Hz), 6.58 (d, 1 H, J = 3.1 Hz), 6.94–7.50 (m, 11 H). Mass spectrum (CI, NH_3): m/z (relative intensity) 475 (M^+, 100). IR (NaCl, neat): 2960, 1738, 1626, 1516, 1429, 1418, 1226, 1018, 965, 743, 686 cm^{-1}. $[\alpha]^{25}_D$ = +209.2° (c 0.38, CH_2Cl_2). Mp: 245 °C (recryst EtOAc/hexanes). Anal. Calcd for $C_{27}H_{25}NO_7$: C, 68.20; H, 5.29; N, 2.94. Found: C, 68.04; H, 5.09; N, 2.96. NOE data: irradiation of H_7 enhanced H_2, H_8, and H_9 22.1%; irradiation of H_6 enhanced H_5 and furan ring protons 61%.

(2S,3R,4R)-2-Carboxy-3,4-dicarbomethoxypyrrolidine (5a). To a stirred solution of 4a (130 mg, 0.32 mmol, 1.0 equiv) in 6 mL of EtOH and 2 mL of THF was added $PdCl_2$ (28 mg, 0.16 mmol, 0.5 equiv). The resulting mixture was hydrogenated at 60 psi at room temperature for 48 h, purged with nitrogen gas, filtered through Celite, and evaporated to dryness. The residue was then taken up in water (5 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The aqueous layer was evaporated leaving a white solid (83.2 mg, 98%). The crystal was dissolved in a minimum amount of water and filtered through a C-18 cartridge (Seppak, wet first with acetonitrile and then with water) and concentrated to afford pure crystal of 5a. ^{1}H NMR (300 MHz, D_2O): δ HOD 3.52 (s, 3 H), 3.56 (s, 3 H), 3.57–3.82 (m, 4 H), 4.46 (d, 1 H, J = 7.1 Hz). IR (NaCl, Nujol): 3361, 2905, 2729, 2356, 1732, 1738, 1302, 1220, 1168, 1080, 966 cm^{-1}. Mp: 176–179 °C. $[\alpha]^{25}_D$ = +50° (c 0.15 MeOH).

(2S,3R,4R,5S)-2-Carboxy-3,4-dicarbomethoxy-5-ethylpyrrolidine (5b). To a solution of (7S)-4b (70 mg, 0.16 mmol, 1.0 equiv) in 5 mL of ethanol and 2 mL of THF was added $PdCl_2$ (15 mg, 0.085 mmol, 0.53 equiv). The resulting mixture was hydrogenated at 60 psi of H_2 at room temperature for 48 h, purged with N_2, filtered through Celite to remove the catalyst, and evaporated in vacuo to leave white solid. The solid was washed with hexane, triturated with Et_2O, CH_2Cl_2, and THF, and evaporated to afford a white solid, which was dissolved in the minimum amount of water, filtered through a C-18 cartridge (Millipore C-18 Seppak, wet first with MeCN and then H_2O), and concentrated in vacuo to yield pure desired compound as a white powder, 44 mg (93%). ^{1}H NMR (270 MHz, D_2O): δ HOD 0.93 (t, 3 H, J = 7.4 Hz), 1.63–1.76 (m, 2 H), 3.51–3.61 (m, 1 H), 3.65 (s, 3 H), 3.68 (s, 3 H), 3.74 (dd, 1 H, J = 7.3, 9.2 Hz), 3.82 (dd, 1 H, J = 7.4 Hz, J = 10.0 Hz), 4.40 (d, 1 H, J = 10.0 Hz). IR (NaCl, neat): 3367, 3194, 2921, 2855, 1745, 1725, 1458, 1371, 1300, 1207, 1169, 717 cm^{-1}. Mp: 207–2.09.5°. $[\alpha]^{25}_D$ = 51.8° (c 0.085, H_2O).

(2S,3R,4R,5S)-2-Carboxy-3,4-dicarbomethoxy-5-isopropylpyrrolidine (5c). To a solution of (7S)-4c (180 mg, 0.399 mmol, 1.0 equiv) in 14 mL of ethanol and 4 mL of THF was added $PdCl_2$ (37 mg, 0.209 mmol, 0.52 equiv). The resulting mixture was hydrogenated at 60 psi of H_2 at room temperature for 48 h, purged with N_2, filtered through Celite to remove the catalyst, and evaporated in vacuo to leave white solid, which was washed with hexane and Et_2O and triturated with Et_2O, yielding white crystal. The crystal was dissolved in a minimum amount of water, filtered through a C_{18} cartridge (Millipore C-18 Seppak), and evaporated to afford 122.5 mg of a white solid (99%). ^{1}H NMR (300 MHz, D_2O): δ 0.71 (d, 3 H, J = 6.8 Hz), 0.85 (d, 3 H, J = 6.7 Hz), 1.88 (m, 1 H), 3.39 (m, 1 H), 3.48 (s, 3 H), 3.57 (s, 3 H, J = 6.8 Hz), 3.75 (dd, 1 H, J = 6.5, 6.8 Hz), 3.84 (dd, 1 H, J = 10.5 Hz, J = 9.3 Hz), 4.39 (d, 1 H, J = 6.2 Hz). IR (NaCl, neat): 3386, 2931, 1737, 1728, 1642, 1576, 1242, 1103, 1048, 820, 736 cm^{-1}. Mp: 180.5–184 °C. $[\alpha]^{25}_D$ = +36.7 (c 0.37, MeOH). Anal. Calcd for $C_{12}H_{20}NClO_6$: C, 48.58; H, 6.28; N, 4.36. Found: C, 48.08; H, 6.67; N, 4.04.

(2S,3R,4R,5R)-2-Carboxy-3,4-dicarbomethoxy-5-phenylpyrrolidine (5d). To (7R)-4d (50 mg, 0.103 mmol, 1.0 equiv) was added 6 N HCl/MeOH (5 mL). The resulting mixture was stirred at room temperature for 5 h and evaporated. The residue was taken up in EtOAc (5 mL) and H_2O (3 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic layer was dried and evaporated, leaving an oily solid which was dissolved in 5 mL of CH_2Cl_2 and 3 mL of MeOH. To the resulting solution was added $Pb(OAc)_4$ (50.3 mg, 0.113 mmol, 1.1 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, and 10 drops of 10% HCl was added. The mixture was stirred at room temperature for 1 h and then evaporated. The residue was taken up in EtOAc (5 mL) and H_2O (3 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic layer was dried, evaporated, and separated on PTLC (silica gel, eluted with 3/1 hexanes/EtOAc) to afford 19 mg of the desired compound as white solid: mp 98–99 °C (recrystallized from EtOAc/hexanes). $[\alpha]^{25}_D$ +18.2° (c 0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ TMS 3.23 (s, 3 H), 3.57 (dd, 1 H, J = 6.9, 7.4 Hz), 3.69 (s, 3 H), 3.72 (dd, 1 H, J = 6.5 Hz, J = 9.6 Hz), 3.81 (s, 3 H), 4.16 (d, 1 H, J = 8.2 Hz), 4.48 (d, 1 H, J = 5.8 Hz), 7.27–7.33 (m, 5 H). IR (NaCl, neat): 2953, 2360, 2342, 1758, 1731, 1438, 1264, 912, 733, 668 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.79; H, 5.96; N, 4.36. Found: C, 58.67; H, 6.15; N, 4.19.

(2S,3R,4R,5R)-2-Carboxy-3,4-dicarbomethoxy-5-(p-methoxyphenyl)pyrrolidine (5e). To (7R)-4e (100 mg, 0.194 mmol, 1.0 equiv) was added 6.5 N HCl/MeOH (10 mL). The resulting mixture was stirred at room temperature for 1 h and then evaporated. The residue was taken up in EtOAc (5 mL) and H_2O (3 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (6 mL × 3). The combined organic layer was dried

over anhydrous Na_2SO_4 and evaporated to leave white solid. The solid was dissolved in CH_2Cl_2 (8 mL) and MeOH (4 mL), and then Pb $(OAc)_4$ (95 mg, 0.213 mmol, 1.1 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, and 10 drops of 10% HCl was added. The mixture was stirred at room temperature for 1 h and then evaporated. The residue was taken up in EtOAc (10 mL) and H_2O (2 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic layer was dried and evaporated, leaving white solid, which was separated on PTLC (silica gel, eluted with 18/1 CH_2Cl_2/EtOAc) to afford 18 mg of the desired compound as white solid (66.1%), recrystallized from EtOAc/hexanes, mp 105–108 °C, $[\alpha]^{25}_D$ +71.4° (c 2.25, CH_2Cl_2). ^1H NMR (300 MHz, CDCl): δ TMS 3.26 (s, 3 H), 3.58 (t, 1 H, J = 7.4 Hz), 3.70 (s overlapping with t, 4 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 4.13 (d, 1 H, J = 8.8 Hz), 4.42 (d, 1 H, J = 7.0 Hz), 6.86 (d, 2 H, J = 8.8 Hz), 7.25 (d, 2 H, J = 8.7 Hz). IR (NaCl, neat): 2952, 1746, 1714, 1616, 1518, 1436, 1385, 1344, 1310, 1256, 1200, 1109, 1056, 1030, 951, 935, 835 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.10; H, 6.05; N, 3.99. Found: C, 58.04; H, 6.19; N, 3.95.

(2*S*,3*R*,4*R*,5*R*)-2-Carboxy-3,4-dicarbomethoxy-5-(*p*-nitrophenyl)pyrrolidine (5f). To (7*R*)-**4f** (68 mg, 0.128 mmol, 1.0 equiv) was added 6 mL of 6 N HCl/MeOH. The resulting mixture was allowed to stir at room temperature for 7 h and then evaporated. The residue was taken up in EtOAc (7 mL) and H_2O (6 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated to afford an oily solid. The solid was dissolved in 4 mL of CH_2Cl_2 and 2 mL of MeOH. To the resulting solution was added Pb$(OAc)_4$ (63 mg, 0.141 mmol, 1.1 equiv) at 0 °C, and then the mixture was allowed to stir at 0 °C for 10 min. To the reaction mixture was added 10 drops of 10% aqueous HCl, and the resulting mixture was stirred at rt for 1 h and then evaporated. The residue was taken up in EtOAc (5 mL) and H_2O (4 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, evaporated and separated on PTLC (silica gel, eluted with 2/1 hexanes/EtOAc) to yield 26 mg of white solid (56%), which was recrystallized from EtOAc/hexanes. Mp: 197.5–198 °C. $[\alpha]^{25}_D$ = +138.5° (c 0.13, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ TMS 3.28 (s, 3 H), 3.67 (t, 1 H, J = 7.0 Hz), 3.70 (s, 3 H), 3.77 (t, 1 H, J = 8.4 Hz), 3.81 (s, 3 H), 4.20 (d, 1 H, J = 8.8 Hz), 4.58 (d, 1 H, J = 6.8 Hz), 7.58 (d, 2 H, J = 8.6 Hz), 8.21 (d, 2 H, J = 8.8 Hz). IR (NaCl, neat) 2960, 1746, 1710, 1558, 1540, 1515, 1436, 1350, 1309, 1266, 1178, 1115, 1058, 954, 934, 861, 773 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_8$: C, 52.44; H, 4.96; N, 7.65. Found: C, 52.22; H, 5.13; N, 7.65.

(2*S*,3*R*,4*R*,5*R*)-2-Carboxy-3,4-dicarbomethoxy-5-(tetrahydrofuranyl)pyrrolidine (8). To a solution of (7*R*)-**4g** (90 mg, 0.189 mmol, 1.0 equiv) in 11 mL of ethanol and 2 mL of THF was added $PdCl_2$ (17 mg, 0.0959 mmol, 0.51 equiv). The resulting mixture was hydrogenated at 60 psi of H_2 at room temperature for 72 h, purged with N_2, filtered through Celite, and evaporated to leave an oil. The oil was washed with hexanes and Et_2O and triturated with Et_2O to yield a white solid, 62.9 mg (99%). The solid was purified by dissolving in water, and filtering through a C_{18} cartridge (Millipore, Seppak), and then evaporated in vacuo to give a white powder. Mp: 191–193.5 °C. $[\alpha]^{25}_D$ +32° (c 0.15, CH_3OH). ^1H NMR (270 MHz, D_2O): δ HOD 1.84–2.05 (m, 4 H), 3.62 (s, 3 H), 3.65 (m, 4 H), 3.76–3.86 (m, 2 H), 4.17–4.30 (m, 2 H), 4.43 (d, 1 H, J = 6.4 Hz), 4.48 (d, 1 H, J = 6.4 Hz). IR (NaCl, neat): 3300, 2948, 2468, 1738, 1729, 1605, 1271, 970 cm^{-1}.

Acknowledgment. We are indepted to the National Science Foundation (CHE 8717017), the National Institutes of Health (GM 40988), Symphony Pharmaceutical Co., Merck, Sharp & Dohme Research Laboratories, and Hoffman-La Roche, Inc., for providing financial support.

Supplementary Material Available: Atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, hydrogen coordinates, thermal parameters, and ORTEP stereostructures for **4a** and **4d** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Diastereoselective Alkylation of (3*S*)- and (3*R*)-3-Methylpiperazine-2,5-dione Derivatives. A Convenient Approach to Both (*S*)- and (*R*)-Alanine

Mario Orena,[†] Gianni Porzi,[‡] and Sergio Sandri*[,‡]

Dipartimento di Scienze dei Materiali e della Terra, Università di Ancona, Via Brecce Bianche, 60131 Ancona, Italy, and Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

Received January 23, 1992 (Revised Manuscript Received June 8, 1992)

Treatment of (3*S*)-3-methylpiperazine-2,5-dione **6a** with LHDMS followed by alkylation of the corresponding enolate with methyl iodide affords (3*S*,6*S*)-3,6-dimethyl derivative **7** in 98% de. The same reaction sequence carried out on (3*R*)-derivative **6b** leads to a 93:7 diastereomeric mixture of (3*R*,6*R*)-**8a** and (3*R*,6*S*)-**8b**. Cleavage of the heterocyclic ring of **7** and **8a** with 57% HI leads to (*S*)- and (*R*)-alanine, respectively. The configuration at C-3 (of **6a** and **6b**) and at C-6 (of **7** and **8a**) can be assigned on the basis of ^1H NMR spectroscopy and conformational analysis performed by MMPMI.

Recently, enantiomerically pure α-amino acids, both proteinogenic and nonproteinogenic, have been the target of a number of synthetic methods. A versatile and useful approach consists of the metalation and subsequent alkylation of bis-lactim ethers to afford, after hydrolysis, amino esters in high ee.[1] An interesting asymmetric synthesis of α-amino acids has also been carried out by means of the highly diastereoselective bromination of a chiral 1,4-oxazin-2-one followed by alkylation with retention of configuration. Subsequent hydrolytic cleavage leads to amino acids in high ee.[2]

As part of a program aimed at the use of piperazine-2,5-diones (containing a chiral group bonded to each of the N-atoms) in asymmetric synthesis, we have devised a new approach to the synthesis of α-amino acids in high optical purity by the alkylation of a chiral enolate anion. Similar

[†] Università di Ancona.
[‡] Università di Bologna.

(1) (a) Schollkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (b) Schollkopf, U. *Topics Curr. Chem.* **1983**, *109*, 65.
(2) Williams, R. M. *Synthesis of Optically Active Aminoacids*; Pergamon Press: London, 1989.

0022-3263/92/1957-6532$03.00/0 © 1992 American Chemical Society