(99.5%), hydrogen chloride (99.0%), and hydrogen bromide (99.8%) were purchased from Matheson. Bromine (99%) was obtained from the Dow Chemical Co.

Catalysts. Ferric oxychloride, FeO_xCl_y (10%), on alumina catalyst was prepared by impregnating Al_2O_3 (~200 m^2/g) with an aqueous solution of ferric chloride. After evaporation of water, the catalyst was dried in air at 105–115 °C and calcined at 350–450 °C for 5 h. Ferric oxybromide, FeO_xBr_y (10%), on alumina and gallium oxychloride GaO_xCl_y, on alumina (20%) were prepared similarly.

Tantalum oxyfluoride (20%) on alumina was prepared by slowly dissolving tantalum pentafluoride into cold methyl alcohol (−78 to −10 °C) with evolution of some hydrogen fluoride. The support was then treated with the solution as before and heated to 250–300 °C to obtain 20% tantalum oxyfluoride deposited on the alumina. Niobium oxyfluoride on alumina was prepared similarly.

Zirconium oxyfluoride (10%) on alumina was prepared as above by treating alumina with zirconium tetrafluoride dissolved in methyl alcohol.

SbF_5/Graphite (20%) (Alfa Inorganics) was used as obtained and Nafion-H was prepared from Du Pont Nafion-501 resin as previously reported and Nafion-H/TaF_5 by complexing Nafion-H with TaF_5.

Platinum (0.5%) on alumina was obtained from Air Products Co. with a surface area of ~100 m^2/g and 0.5% palladium on barium sulfate obtained from Strem Chemicals with a surface area specified only as "high".

Supported metal oxide catalysts were generally prepared as described previously for WO_3 on Al_2O_3.[4b] ZnO on alumina catalyst was prepared by using an aqueous slurry of ZnO (20 g in 100 mL of water); 80 g of alumina was then stirred into it with continuous stirring for 24 h. Water was thereafter removed in vacuum; the catalyst was dried at 150 °C and calcinated at ~450 °C for 4 h.

γ-Alumina supported metal oxide/hydroxide catalysts were prepared by placing γ-alumina (20 g), metal oxide (2.5 g), and metal hydroxide (2.5 g) in a 1-L round-bottom flask. Five hundred milliliters of water was added and the mixture stirred for 2 h. The water is then removed under reduced pressure and the resulting catalyst dried in a vacuum oven at 110 °C. Prior to use, the catalyst is loaded into a glass reactor tube with glass wool packed on both ends and calcined at 400 °C overnight in a Lindberg SB heavy duty tube furnace under nitrogen flow.

Regeneration of Deactivated Catalysts. Pt/Al_2O_3 and $Pd/BuSO_4$ catalysts are regenerated by heating at 380 °C overnight under a flow of N_2.

γ-Alumina-based hydrolysis catalysts are reactivated by steam treatment and subsequent calcination at ~450 °C.

General Procedure for the Catalytic Halogenation of Methane over Supported Acid or Platinum Metal Catalysts. All reactions were carried out at atmospheric pressure in a fixed-bed, continuous-flow, electrically heated (with a Lindberg furnace) 550 × 10 mm Pyrex glass tube reactor, similar to that described in our previous work.[4b,53] Generally 10 g of supported catalyst, previously calcinated, was placed in a stream of dry nitrogen into the reactor, and mixtures of methane and chloride or bromine (the latter introduced via a metered pump) in the ratios stated were passed through with a gaseous space velocity (volume of gas passed over volume of catalyst per hour) of between 50 and 1500 under conditions shown in the tables. Samples were taken at the outlet of the reactor and analyzed by GC and GC/MS. Hydrogen halides were determined by titration.

General Procedure for the Gas-Phase Heterogeneous Hydrolysis of Methyl Halide with Steam over Supported γ-Alumina-Based Catalysts. The Lindberg oven is set to the desired reaction temperature, and 10 g of precalcinated catalyst is placed into the reactor tube supported between glass wool plunges. Gaseous methyl chloride (bromide) is passed into the reaction chamber simultaneously with water, being introduced in ratios indicated into the heated chamber via a metered Sage Model 355 syringe pump. The eluent reaction mixture is monitored by analyzing both gaseous products and products collected in cold traps by GC and GC–MS.

Analyses. GC analyses of the reaction mixtures were conducted on the following instruments: (a) Hewlett-Packard 5130 A with a Poropak Q column (12 ft, $^1/_8$ in.); (b) Varian 3700 with an OV 101 glass capillary column (50 m). All percentage numbers are corrected for FID response factors and are given in mole percent.

MS analyses were carried out on a Hewlett-Packard 5985 A GC/MS spectrograph equipped with a Poropak column.

Acknowledgment. Our work was supported by the Loker Hydrocarbon Research Institute of the University of Southern California. Some aspects of the mechanistic studies were supported by the National Science Foundation.

Registry No. Methane, 74-82-8; CH_3Cl, 74-87-3; CH_2Cl_2, 75-09-2; CH_3Br, 74-83-9; FeOCl, 13870-10-5; $TaOF_3$, 20263-47-2; $NbOF_3$, 15195-33-2; $ZrOF_2$, 14984-80-6; GaOCl, 15588-51-9; TaF_5, 7783-71-3; SbF_5, 7783-70-2; $SbOF_3$, 15195-35-4; Pt, 7440-06-4; Pd, 7440-05-3; alumina, 1344-28-1; CH_3OH, 67-56-1; CH_3OCH_3, 115-10-6; V, 7440-62-2; Mn, 7439-96-5; Cr, 7440-47-3; Mg, 7439-95-4; Zr, 7440-67-7; Ba, 7440-39-3; Ti, 7440-32-6; Zn, 7440-66-6; Fe, 7439-89-6; Ni, 7440-02-0; Bi, 7440-69-9; Al, 7429-90-5.

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Conversion of Serine to Stereochemically Pure β-Substituted α-Amino Acids via β-Lactones

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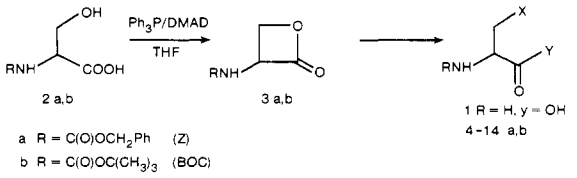
Abstract: Pure enantiomers of *N*-(benzyloxycarbonyl)serine (**2a**) or *N*-(*tert*-butoxycarbonyl)serine (**2b**) are cyclized without racemization to N-protected α-amino β-lactones **3a** and **3b** in 60–72% yield by using modified Mitsunobu conditions (Ph_3P, dimethyl azodicarboxylate). Treatment of the β-lactones with a variety of halogen, oxygen, sulfur, or nitrogen nucleophiles gives pure enantiomers of N-protected β-substituted alanines **4–14a** and **4b** in high yield. Only hard nucleophiles (e.g., methoxide) attack these lactones at the carbonyl.

A variety of β-substituted alanines **1** having a 2*S* configuration occur in higher plants,[1] whereas the 2*R* isomers are frequently constituents of microbial peptides with antibiotic or antitumor activity.[1,2] The ability of some of these compounds to act as enzyme inactivators[3] or as potential intermediates[4] in enantioselective synthesis of other amino acids[5] makes an efficient route

Scheme I



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to them desirable. We now report that either N-protected β-substituted D- or L-alanines **4–14** are easily obtained in stereochemically pure form by Mitsunobu-type cyclization[6] of readily available D- or L-serine derivatives **2** followed by nucleophilic opening of the resulting β-lactones **3** (Scheme I.) Since derivatives of α-amino β-propiolactone are usually difficult to prepare, the present approach should be useful in synthesis of β-lactone antibiotics recently isolated from bacterial cultures.[7] In addition, the products **4–14** can be easily deprotected to the parent amino acids **1** or incorporated directly into peptides.

Previous syntheses of N-protected α-amino β-lactones which employ carboxyl activation[7b,8,9] (e.g., carbodiimide reagents) typically give yields ranging from 26% (*N*-trityl)[8a] to 1% or less (*N*-acyl).[7b,8a,9] Alternative methods involving generation of a leaving group at the β position[7b,10] also proceed in low yield with the exception of Hofmann rearrangement and subsequent diazotization of (benzenesulfonyl)asparagines, which affords α-(benzenesulfonamido) β-lactones in up to 45% overall yields.[10] However, this method appears to be restricted to use of benzenesulfonyl protecting groups. We find that addition of optically pure *N*-benzyloxycarbonyl- (*Z*-) (**2a**)[11] or *N*-*tert*-butoxycarbonyl-(BOC-)substituted serines (**2b**) to the preformed adduct[6] of triphenylphosphine and dimethyl azodicarboxylate (DMAD)[12] at −78 °C gives β-lactones **3a** and **3b**, respectively, without racemization in isolated yields of 60–72%. Use of DMAD facilitates chromatographic isolation of the β-lactone while low temperatures suppress formation of alkene side products common with this type of reaction.[6] Preformation of the *N*-phosphonium Ph_3P–DMAD adduct allows generation of the β-lactone in the absence of free nucleophilic triphenylphosphine. An earlier attempt by other workers to cyclize *N*-(phenylacetyl)-L-serine to the corresponding β-lactone by using conventional Mitsunobu conditions proceeded in 1.4% yield.[7b]

General methods for synthesis of β-substituted alanines,[13–15] such as nucleophilic displacements on β-haloalanines, aminoacrylates, and aziridines, sometimes prove difficult because of lack of stereochemical control, poor yields, or numerous steps. In contrast, facile nucleophilic attack on β-lactones **3a** and **3b** results in ring opening with alkyl–oxygen cleavage to directly generate optically pure N-protected β-substituted alanines **4–14** in high yield (Table I). Only relatively "hard" nucleophiles like ammonia and methoxide attack the carbonyl to give acyl–oxygen cleavage (e.g., **4a** and **10a**). In earlier reports serine β-lactones were used mainly for synthesis of seryl peptides by attack of amines at the carbonyl.[8,10] However, with ammonia as the nucleophile, simply altering the solvent (e.g., **4a**, **5a**,**b**) inverts the 3:1 amide/amine ratio. In many cases the position of attack can be predicted from analogous reactions of β-propiolactone.[16,17]

In summary, lactones **3a** and **3b** are convenient precursors[18] for preparation of N-protected non-protein amino acids (e.g., **5a**,**b**[19], **8a**[13,20]), constituents of antibiotic and antitumor peptides (e.g., **5a**,**b**[21]), suicide substrates of bacterial enzymes (e.g., **9a**, **13a**),[3,22] and new analogues of known amino acids (e.g., **6a**, **7a**, **12a**,[23] **14a**). They also provide a route for conversion of inexpensive D-serine into rarer D-amino acids (e.g., **11a**)[24] in high yield and

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(17) Reaction of mercaptoethylamine (MEA) with **3a** in 50% aqueous MeCN or THF results primarily in attack by nitrogen rather than sulfur, in contrast to reactions of MEA with β-propiolactone in H_2O (Davis, R. E.; Suba, L.; Klimshin, P.; Carter, J. *J. Am. Chem. Soc.* **1969**, *91*, 104–107). This may be due to suppression of ionization of MEA by the presence of organic solvent.

(18) Crystalline Z- and BOC-serine β-lactones (**3a**) and (**3b**) are easily handled in air at room temperature and can be stored dry at −20 °C at least several months without decomposition. Solutions in pure organic solvents or aqueous solvents (pH 2–5) are stable for several days.

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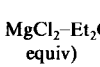
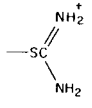
Table I. Products of Nucleophilic Attack on Z- and BOC-serine β-Lactones **3a** and **3b**

product	nucleophilic reagent	conditions	product structure[a] R	X	Y	% yield[b]	enantiomer[c]	mp, °C (lit.)	$[\alpha]^{22}_D$, deg (lit.)	ref
4a	NH_3(g) (excess)	CH_3CN, 0 °C, 20 min	Z	-OH	NH_2	77	L	131–2 (132)	+14.8 (*c* 1.0, EtOH) (+14.4, 14.9)	25
5a		THF, 0 °C, 3 h	Z	$-NH_3^+$	O^-	75	D	226–8 dec (228–30)[d]	+7.9 (*c* 0.4, N NaOH) (−7.8)[d]	26
5b		THF, 0 °C, 3 h	BOC	$-NH_3^+$	O^-	79	L	197–99 dec (198–200)	−2.7 (*c* 1, HOAc) (−2.7)	26
6a	$N(CH_3)_3$	THF, 0 °C, 2 h	Z	$-N(CH_3)_3^+$	O^-	100 (91)	L	100–100.5	−7.9 (*c* 1, MeOH)	
7a	$HSCH_2CH_2NH_3^+Cl^-$ (2 equiv)	50% aq CH_3CN, pH 5.5, 20 min	Z	$-^+NH_2CH_2CH_2SH$	O^-	(76)	D	127.5–128.5	+13.9 (*c* 1, MeOH)	
8a	(1.05 equiv)	CH_3CN, 50 °C, 12 h	Z		OH	(71)	D	168.5–169.5 (170–1)[d]	+53.1 (*c* 1, DMF) (−53.6)[d]	27
9a	NaOAc (13 equiv)	HOAc, 45 °C, 7 h	Z	-OAc	OH	97	L	88–89 (87.5–88.5)	−18.5 (*c* 2, DMF) (−18.6)	28
10a	NaOMe (1 equiv)	MeOH/THF, 22 °C, 25 min	Z	-OH	OMe	88	DL[e]	oil	0	
11a	$PhCH_2S^-Na^+$	DMF, 22 °C, 30 min	Z	$-SCH_2Ph$	-OH	78 (65)	D	95–97 (99)[d]	+45.0 (*c* 2, acetone) (+45.1)	24
12a	 (1.5 equiv)	75% aq THF, 22 °C, 75 min	Z		$-O^-$	(56)	DL	173–5		
						(79)	D	156–8 dec	+24.6 (*c* 1, N HCl)	
13a	$MgCl_2$–Et_2O (5 equiv)	Et_2O, 22 °C, 6.5 h	Z	-Cl	-OH	94 (69)	D	82–84 (88–89)[d]	−14.3 (*c* 1, MeOH) (+14.25)[d]	13a
14a	$MgBr_2$–Et_2O[f] (7 equiv)	Et_2O, 22 °C, 5 min	Z	-Br	-OH	99 (67)	L	70–71	+14.2 (*c* 1, MeOH)	
						99	D	68–69.5	−14.2 (*c* 1, MeOH)	

[a] See Scheme I. [b] Isolated chromatographically pure, recrystallized yields in parentheses. [c] Corresponds to starting material unless noted. [d] Literature value for L-enantiomer. [e] Racemized. [f] See ref 30.

optical purity. The scope and mechanism of this lactonization reaction with other protecting groups and threonine derivatives are currently under investigation, as are reactions of these β-lactones with organometallics, enolates, and ambident nucleophiles.

Experimental Section

All reactions were done under positive pressure of dry Ar; those requiring nonaqueous conditions were performed with oven-dried glassware which was cooled under Ar. All solvents were distilled before use. After extractions, all organic layers were dried over anhydrous Na_2SO_4. The term "in vacuo" refers to removal of solvent on a rotary evaporator followed by evacuation (<0.05 torr) to constant sample weight. Reactions involving generation/consumption of serine β-lactones were conveniently followed to completion by quantitatively monitoring the carbonyl IR absorption of the β-lactone in solution at 1847 cm^{-1}, or by TLC using bromocresol green spray (0.04% in EtOH, made blue by NaOH) followed by heating of the plate to detect the β-lactone as a yellow spot on a blue background. All literature compounds had ^1H NMR, IR, MS, and elemental analyses consistent with assigned structures. Melting points were obtained on a Thomas Hoover apparatus with open capillary tubes and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 or Bruker WP-80, WH-200, or WH-400 instrument. Infrared spectra (IR) were determined with a Nicolet 7199 FT-IR spectrometer. Mass spectra were obtained at an ionizing voltage of 70 eV on AEI instruments: MS-50 (EI), MS-12 (CI), MS-9 (POS-FAB). Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a microcell (100 mm, 0.9 mL).

***N*-(Benzyloxycarbonyl)serine β-Lactones (3a).** To a stirred solution of dried (in vacuo 72 h over P_2O_2) Ph_3P (6.43 g, 24.5 mmol) in 100 mL of anhydrous THF at −78 °C was added distilled dimethyl azodicarboxylate[12] (2.70 mL, 3.58 g, 24.5 mmol) dropwise over 10 min. After 10 min, a solution of dried Z-serine[11] (**2a**) (5.84 g, 24.4 mmol) in THF (100 mL) was added dropwise over 15 min to the stirred white slurry at −78 °C. The mixture was stirred 20 min at −78 °C and then 2.5 h at 20 °C. Solvent was removed in vacuo at 35 °C, and the residue was flash chromatographed on silica gel[31] (45% EtOAc/55% hexane) to afford 3.24 g of **3a** (60% yield) as a white crystalline solid which could be recrystallized from EtOAc/hexane (20 °C → −20 °C). The chirality of resultant β-lactone (**3a**) was identical with that of Z-serine (**2a**) starting material: mp 114–6 °C (DL), 133–4 °C (L), 133–4 °C (D); $[\alpha]^{22}_D$ −26.6° (L), +26.5° (D), (*c* 1, CH_3CN); IR (CH_2Cl_2 cast) 3350 (m), 1845 (s, sh), 1830 (s), 1685 (vs), 1530 (vs), 1270 (s) cm^{-1}; $\epsilon^{1847cm^{-1}}$ (0.1 mm KBr, THF) 0.25 mL mg^{-1} mm^{-1}, 57 M^{-1} mm^{-1}; ^1H NMR (100 MHz, CD_2Cl_2) δ 7.34 (s, 5 H), 5.84–5.50 (br s, 1 H), 5.14 (s, 2 H), 5.02 (dd, 1 H, 8, 6 Hz), 4.43 (d, 2 H, 6 Hz); ^{13}C NMR (50.32 MHz, CD_2Cl_2) δ 169.2, 155.8, 136.4, 129.0, 128.9, 128.7, 68.1, 66.6, 60.3. Anal. ($C_{11}H_{11}NO_4$) C, H, N. EI-MS: M^+ 221.0691 (221.0688 calcd).

***N*-(*tert*-Butoxycarbonyl)-L-serine β-Lactone (3b).** This material was prepared according to the procedure described for **3a** using BOC-L-serine (5.00 g, 24.4 mmol) and was isolated by flash chromatography on silica[31] using 35% EtOAc/65% hexane to yield 3.29 g (72%) of **3b**: mp 119.5–120.5 °C dec; $[\alpha]^{22}_D$ −26.7° (*c* 1, CH_3CN); IR (CH_2Cl_2 cast) 3358 (s), 1836 (s), 1678 (vs), 1532 (s), 1291 (m), 1104 (s) cm^{-1}; $\epsilon_{1847cm^{-1}}$ (0.1 mm KBr, THF or CH_3CN) 0.34 mL mg^{-1} mm^{-1}, 64 M^{-1} mm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 5.53 (br s, 1 H), 5.05 (dd, 1 H, 8, 6 Hz), 4.47 (d, 2 H, 6 Hz), 1.47 (s, 9 H); ^{13}C NMR (50.32 MHz, CD_2Cl_2) δ 170.0 (s), 155.1 (s), 81.5 (s), 66.6 (t), 59.9 (d), 28.2 (q). Anal. ($C_8H_{13}NO_4$) C, H, N. MS: EI MH^+ 188.0929 (188.0923 calcd); CI (NH_3) 205 (100%, M + NH_4^+), 392 (9%, 2M + NH_4^+).

Reactions of β-Lactones with Ammonia. Dry NH_3(g) was bubbled (~100 mL/min) through a solution of the β-lactone (**3a** or **3b**) (1 mmol) in 10–15 mL of anhydrous solvent at 0 °C for either 15 min (CH_3CN solvent) or 1 h (THF), and the mixture was allowed to react until all β-lactone was consumed. Solvent was removed in vacuo at 35 °C, and the residue was stirred with H_2O (25 mL) and extracted with $CHCl_3$ or Et_2O (4 × 30 mL). Evaporation of the aqueous phase provided amine products (e.g., **5a,b**),[26] while amides (e.g., **4a**)[25] were obtained from the organic layers; these compounds could be recrystallized from MeOH/Et_2O or MeOH/H_2O, respectively. All reactions with ammonia were quantitative with the balance of product being amine or amide.

***N*$^\alpha$-(Benzyloxycarbonyl)-β-(trimethylammonio)-L-alanine, Inner Salt (6a).** To a solution of Z-L-serine β-lactone (**3a**) (200 mg, 0.90 mmol) in THF (5 mL) at 0 °C was added liquid Me_3N (0.50 mL, 5.65 mmol). After 2 h the solvent was removed in vacuo at 35 °C to provide a quantitative yield of **6a** as a white powder which could be recrystallized from MeOH/Et_2O (recrystallized yield 91%): mp 100–100.5 °C; $[\alpha]^{22}_D$ −7.9° (*c* 1, MeOH); IR (MeOH cast) 3240 (w, br), 1710 (vs), 1625 (s), 1530 (m), 1490 (m), 1257 (m), 1058 (m) cm^{-1}; ^1H NMR (400 MHz, Me_2SO-d_6) δ 7.38 (s, 5 H), 7.11 (br d, 1 H, 4 Hz), 5.07 (s, 1 H), 4.04 (m, 1 H), 3.86 (dd, 1 H, 13.7, 3.1 Hz), 3.40 (dd, 1 H, 13.7, 8.4 Hz), 3.10 (s, 9 H). Anal. ($C_{14}H_{20}N_2O_4$) C, H, N. POSFAB-MS (glycerol): MH^+ 281 (100%), M_2H^+ 561 (2.8%).

***N*$^\alpha$-(Benzyloxycarbonyl)-β-(mercaptoethylamino)-D-alanine (7a).** To Z-D-serine β-lactone (**3a**) (100 mg, 0.45 mmol) in CH_3CN (5 mL) was added a solution of mercaptoethylamine hydrochloride (102 mg, 0.90 mmol) in degassed H_2O (5 mL). The pH of the mixture was raised to and maintained at pH 5.5 (±0.5) by the dropwise addition of 0.1 N NaOH with rapid stirring. After 20 min no further addition of NaOH was required, the volume was reduced to one-half in vacuo at 35 °C, the pH was adjusted to 6.8 with NH_4OH, and the mixture was extracted with CH_2Cl_2 (3 × 70 mL). The white solid obtained on drying and evaporation of CH_2Cl_2 was recrystallized from CH_2Cl_2/hexane to yield 102 mg (76%) of **7a**: mp 127.5–128.5 °C; $[\alpha]^{22}_D$ +13.9° (*c* 1, MeOH); IR (KBr disk) 3360 (br s), 3293 (s), 2560 (w), 1689 (vs), 1647 (vs), 1565 (m), 1544 (m), 1245 (m), 1020 (m) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.28 (s, 5 H), 6.85 (br s, 2 H), 5.86 (br d, 1 H, 8 Hz), 5.10 (s, 2 H), ~4.20 (m, 1 H), 4.08 (dd, 1 H, 12, 3 Hz), 3.64 (dd, 1 H, 12, 5.4 Hz), 3.39 (t, 2 H, 6 Hz), 2.80–2.37 (m, 2 H), 1.38 (t, 1 H, 8.4 Hz). Anal. ($C_{13}H_{18}N_2O_4S$) C, H, N, S. EI-MS: M^+ 298.0992 (298.0987 calcd).

***N*$^\alpha$-(Benzyloxycarbonyl)-β-(pyrazol-1-yl)-D-alanine (8a).** Pyrazole (81 mg, 1.2 mmol) in CH_3CN (4 mL) was added to a solution of Z-D-serine β-lactone (**3a**) (250 mg, 1.13 mmol) in CH_3CN (6 mL), and the mixture was heated to 50 °C for 12 h. Solvent was removed in vacuo and the residue dissolved in hot MeOH and filtered. Recrystallization of **8a** was achieved by addition of H_2O and cooling (yield 71%).[27]

***N*-(Benzyloxycarbonyl)-*O*-acetyl-L-serine (9a).** To 1.0 g of anhydrous NaOAc (dried 12 h at 120 °C; 12 mmol) dissolved in glacial acetic acid (15 mL) was added Z-L-serine β-lactone (**3a**) (0.90 mmol), and the stirred mixture was heated to 45 °C for 7 h. Solvent was removed in vacuo at 35 °C, and the residue was acidified to pH 2 by solution in 1 N HCl (~10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Organic phases were dried and evaporated in vacuo to afford a clear colorless syrup which solidified after successive trituration with, and evaporation of, toluene and ether to yield **9a** (97%). Recrystallization could be effected from $CHCl_3$/Et_2O.

***N*-(Benzyloxycarbonyl)-DL-serine Methyl Ester (10a).** To a solution of NaOMe (0.68 mmol) in MeOH (5 mL) was added a solution of Z-D-serine β-lactone (**3a**) (150 mg, 0.68 mmol) in THF (10 mL) dropwise with stirring over 5 min. After 25 min, HOAc (0.1 mL) was added and the volume was reduced to 2 mL in vacuo. The products, racemic **10a** (88% yield) and Z-dehydroalanine methyl ester[29] (12% yield), were separated by flash chromatography[31] using 55% EtOAc/45% hexane.

***N*-(Benzyloxycarbonyl)-*S*-benzyl-D-cysteine (11a).** To 227 mg of NaH (9.45 mmol) suspended in DMF (10 mL) was added dropwise benzylmercaptan (1.20 mL 9.95 mmol). After 1 h an aliquot of the resulting solution (1.15 mL) was added to Z-D-serine β-lactone (200 mg, 0.90 mmol) in DMF (7 mL). After 30 min, 0.05 N H_3PO_4 (20 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The EtOAc phases were dried and evaporated, and the residue chromatographed on silica to provide **11a** (78% yield).[24]

***N*$^\alpha$-(Benzyloxycarbonyl)-β-isothiureido-D-alanine (12a).** To thiourea (52 mg, 0.68 mmol) in 50% aqueous THF (5 mL) was added Z-D-serine β-lactone (**3a**) (100 mg, 0.45 mmol) in THF (5 mL). After 75 min at 22 °C the solvent was removed in vacuo and the residue recrystallized from MeOH to provide the D-antipode of **12a** (79% yield). Racemic **12a** was prepared analogously from Z-DL-serine β-lactone (**3a**): mp 173–5 °C (DL), 156–8 °C dec (D); $[\alpha]^{22}_D$ +24.6° (*c* 1, N HCl, D-isomer); IR (KBr disk) 3600–2700 (mult, br, s), 1715 (vs), 1690 (vs), 1597 (s), 1582 (vs), 1528 (m), 1485 (s), 1462 (m), 1450 (m), 1430 (m), 1400 (m), 1200 (m), 1046 (m), 733 (m), 695 (s) cm^{-1}; ^1H NMR (80 MHz, D_2O/DCl) δ 7.37 (s, 5 H), 5.10 (s, 2 H), 4.60 (m, 1 H), 3.68 (m, 2 H). Anal. ($C_{12}H_{15}N_3O_4S$) C, H, N. POSFAB-MS (glycerol): MH^+ 298 (100%), M_2H^+ 595 (1.5%).

***N*$^\alpha$-(Benzyloxycarbonyl)-β-chloro-D-alanine (13a).** Into a stirred flask containing Mg filings (5 g, 206 mmol) suspended in Et_2O (50 mL) and equipped with an acetone/CO_2(s) condensor was condensed Cl_2(l) (4.0 mL, 88 mmol) at −78 °C in the dark. The mixture was allowed to react 2 h, and 1 mL of the resulting suspension (~1.76 mmol of $MgCl_2$) was added dropwise with stirring to Z-D-serine β-lactone (**3a**) (150 mg, 0.68

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(29) IR and ^1H NMR data identical to literature (Wolfe, S.; Bowers, R. J.; Hasan S. K.; Kazmaier, P. M. *Can. J. Chem.* **1981**, *59*, 406–421) and also EI-MS provided (M^+) 235.0853 (4.0%, 235.0845 calcd). A similar dehydration has been observed in methoxide opening of β-propiolactone (see ref 16d).

(30) The reaction with magnesium bromide etherate is in direct contrast to reports that β-lactones incapable of ring expansion normally decarboxylate under these conditions. (Mulzer, J.; Brüntrup, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 793–794.)

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mmol) in Et_2O (30 mL)–THF (2 mL). After 6.5 h at 22 °C the suspension was cooled to 5 °C and 1 N H_3PO_4 (20 mL) was added carefully. The Et_2O phase was separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). After drying, solvent was removed in vacuo to obtain **13a** (94% yield),[13a] which could be recrystallized from EtOAc/hexane to yield a fluffy white solid (69%).

N^{α}-(Benzyloxycarbonyl)-β-bromo-L-alanine (14a). Magnesium bromide etherate was prepared by dropwise addition of distilled (over P_2O_5) Br_2(l) (1.0 mL, 19 mmol) to a suspension of excess Mg filings (1.0 g, 41 mmol) in Et_2O (20 mL) at 0 °C in a flask equipped with an acetone/CO_2(s) condensor. Following the disappearance of Br_2, dry benzene (5 mL) was added, and an aliquot (2 mL, 1.6 mmol $MgBr_2$) of this solution was added to Z-L-serine β-lactone (**3a**) (100 mg, 0.45 mmol) in Et_2O (20 mL)–THF (2 mL). After 5 min, the L-isomer of **14a** was isolated as outlined for **13a** (yield 99%, 67% recrystallized from CH_2Cl_2/hexane).[30] The D-antipode was obtained from Z-D-serine β-lactone (**3a**): mp 70–71 °C (L), 68–69.5 °C (D); $[\alpha]^{22}_D$ +14.2° (L), −14.2° (*D*), (c 1, MeOH); IR (KBr disk) 3390 (s), 1730 (vs), 1648 (s), 1525 (s), 1433 (m), 1290 (m), 1180 (m), 1072 (m), 992 (m), 756 (m), 698 (m) cm^{-1}; ^1H NMR (80 MHz, CD_2Cl_2) δ 8.63 (br s, 1 H), 7.38 (s, 5 H), 5.75 (br s, 1 H), 5.15 (s, 2 H), 4.87 (m, 1 H), 3.83 (m, 2 H). Anal. ($C_{11}H_{12}BrNO_4$) C, H, N, Br. POSFAB-MS (glycerol): MH^+ 302 (17%), $(M+2)H^+$ 304 (17%).

Acknowledgment. We are grateful to the National Institutes of Health (GM 29826), the Natural Sciences and Engineering Research Council of Canada, and the Alberta Heritage Foundation for Medical Research for financial support.

Registry No. DL-**2a**, 2768-56-1; L-**2a**, 1145-80-8; D-**2a**, 6081-61-4; L-**2b**, 3262-72-4; DL-**3a**, 98672-78-7; L-**3a**, 26054-60-4; D-**3a**, 98632-91-8; L-**3b**, 98541-64-1; L-**4a**, 70897-15-3; D-**5a**, 62234-37-1; L-**5b**, 76387-70-7; L-**6a**, 98541-65-2; D-**7a**, 98541-66-3; D-**8a**, 98632-92-9; L-**9a**, 19645-29-5; DL-**10a**, 14464-15-4; D-**11a**, 22911-80-4; D-**12a**, 98541-67-4; DL-**12a**, 98541-68-5; D-**13a**, 73491-16-4; L-**14a**, 98541-69-6; D-**14a**, 98541-70-9; Me_3N, 75-50-3; $HSCH_2CH_2NH_2{\cdot}HCl$, 156-57-0; NaOAc, 127-09-3; NaOMe, 121-41-4; $PhCH_2SH$, 100-53-8; pyrazole, 288-13-1; thiourea, 62-56-6; (*Z*)-dehydroalanine methyl ester, 21149-17-7.

Role of Agostic Interaction in β-Elimination of Pd and Ni Complexes. An ab Initio MO Study

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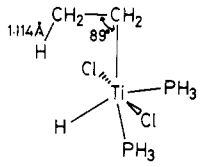
Abstract: We optimized the geometries of $Pd(C_2H_5)(H)(PH_3)$ (**1**), $Pd(H)_2(C_2H_4)(PH_3)$ (**2**), and the transition state between them and calculated the barriers for β-elimination and its reverse, insertion reaction. **1** has a distorted ethyl group, which is a sign of agostic interaction, a direct CH···M interaction. The low-energy barrier for **1** → **2** β-elimination is located in the direction of a direct extension of agostic interaction. Similar calculations for $Pd(CH_2CHF_2)(H)(PH_3)$ (**3**) and $Ni(C_2H_5)(H)(PH_3)$ (**4**), their transition states, and β-elimination products show that **3** and **4** have much weaker agostic interaction and higher barriers. Factors determining the differences among these systems in the structure and barrier height have been discussed in detail. Though it may not be easy to detect experimentally, the present study strongly suggests that in unstable reactive intermediates an agostic interaction may be taking place more commonly than has been suspected and that it is responsible to facile β-elimination.

Intramolecular interaction between a rather inert CH bond and the central metal in transition-metal complexes, called an agostic interaction, has attracted much attention lately, since the interaction is considered to be important in such reactions as α-elimination, β-elimination, orthometalation, and related reactions.[2] The interaction has been observed by the determination of crystal structures by X-ray and neutron diffraction methods. Complexes in which the central transition metal interacts with a CH bond exhibit characteristic structural features: the CH···M distance is shorter than the sum of van der Waals radii and the interacting CH bond distance is longer than the normal CH bond. NMR and IR spectra have also indicated the existence of such an interaction in some complexes. The driving force for the interaction has been considered to be the inclination to satisfy the 18-electron rule, since all the cases involve electron-deficient metals.

Recently, we have reported the first theoretical evidence for CH···M interaction found in ab initio molecular orbital calculations.[3] Our theoretical studies on $Ti(C_2H_5)(Cl)_2(H)(PH_3)_2$ (**5**) have reproduced essential structural features which have been experimentally observed in $Ti(C_2H_5)(Cl)_3$(dmpe) (dmpe = (dimethylphosphino)ethane) by X-ray structural analysis.[4a] The complex **5** has been calculated to have the Ti–C–C angle of 89°,



5

much smaller than the tetrahedral angle, and a CH^{β} bond distance of 1.114 Å, 0.03 Å longer than the normal CH bond. The optimized structure of $Ti(CH_3)(Cl)_3(PH_3)_2$ (**6**) also indicates the existence of agostic interaction between the methyl α-hydrogen and the metal. The recent neutron diffraction study gives the Ti–C–H angle of 94°, much closer to our theoretically predicted value of 100° than the earlier X-ray result of 69°.[4b,c,5] These

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