AIBN-Initiated Reactions of Bromotrichloromethane. Reaction mixtures were prepared as above using a pair of substituted toluenes or a pair of unsubstituted alkylbenzenes, an internal standard, and bromotrichloromethane. To this, 10–15% azobisisobutyronitrile was added. The sealed ampoules were wrapped in foil and submerged in the oil bath. Reaction times ranged from 48 to 336 h.

Photointiated Reactions of *N*-Bromosuccinimide (NBS). Reaction mixtures contained a pair of toluenes, NBS, an internal standard, and carbon tetrachloride in a ratio of 1:1:0.75:10. The ampoules were sealed and irratiated as above for 3 h.

Analysis. All analyses were carried out using a Varian 3400 gas chromatograph equipped with a flame ionization detector and an autosampler. The capillary columns used were DBWax, DB-5, and DB-225 to insure maximum separation.

Acknowledgment. One of us (K.W.K.) wishes to thank the administrators of the N. L. Tartar Fellowship for providing financial support. We are indebted to Dr. P. K. Freeman for the use of the capillary gas chromatograph.

An Enantioselective Synthesis of D-(−)- and L-(+)-2-Amino-3-phosphonopropanoic Acid

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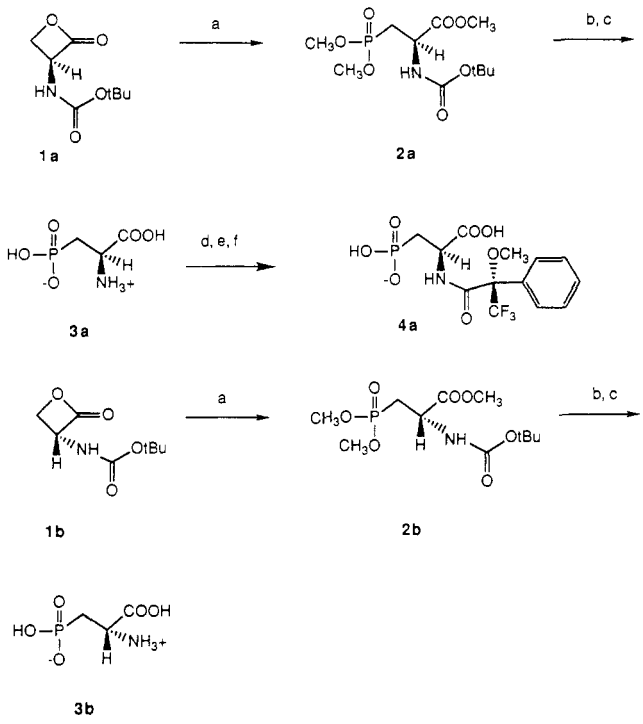
As a result of the observation that 2-amino-3-phosphonopropanoic acid (AP-3) is a selective, potent modulator of the quisqualic acid/phosphoinositide coupled metabotropic excitatory amino acid receptor subtype,[1,2] it became desirable to obtain the individual enantiomers of AP-3 for pharmacological evaluation. A previous report by Villanueva et al.[3] described the preparation of (*S*)-AP-3 from an optically active amino nitrile prepared by reaction of (diethylphosphono)acetaldehyde with hydrogen cyanide and (*S*)-(−)-α-methylbenzylamine. Acid hydrolysis, enrichment of the diastereomers by fractional recrystallization, and debenzylation led to the isolation of (*S*)-AP-3 in 86% enantiomeric excess.

Our desire to prepare the enantiomers of AP-3 in a more efficient, enantioselective fashion lead us to explore the feasibility of addition of triethyl phosphite to (*S*)-*N*-(*tert*-butoxycarbonyl)-3-amino-2-oxetanone (**1a**)[4] (Scheme I). Vederas and co-workers have reported on the addition of a number of nucleophiles to various derivatives of enantiomerically pure 3-amino-2-oxetanones to give products of corresponding stereochemical purity.[4,5] In fact, upon engaging in this chemistry, we became aware that they had conducted a preliminary investigation into the addition of trimethyl phosphite to *N*-BOC-3-amino-2-oxetanone (**1a**) and were able to suggest appropriate experimental conditions.[6] We found that the nucleophilic addition of trimethyl phosphite to **1a** gave (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate (**2a**) in excellent yields. Similarly, the addition of trimethyl phosphite to **1b** afforded the *R* isomer **2b**.

Scheme I[a]



[a] (a) $(CH_3O)_3P$, 70 °C, 42 h; (b) 6 N HCl, reflux; (c) propylene oxide, EtOH, 50 °C; (d) BSTFA; (e) (*R*)-(+)-MTPA-Cl; (f) H_2O.

The enantiomeric purity of **2a** and **2b** was confirmed by ^1H NMR studies with a chiral shift reagent. Addition of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TAE) to a 1:1 mixture of **2a** and **2b** in $CDCl_3$ affected the separation of the C-3 methylene protons at ~2.25 ppm as well as the diastereotopic methoxy signals of the dimethyl phosphonate moiety at ~3.6 ppm. Each methoxy signal appears as a doublet due to ^1H–^{31}P coupling but provided the best handle for determination of enantiomeric purity (supplementary material). The absence of observable antipode in the ^1H NMR spectrum of **2a** or **2b** containing TAE made it possible to establish the enantiomeric purity of **2a** and **2b** as greater than 97%. Additionally, optical rotations of **2a** and **2b** were approximately equal and opposite.

Exhaustive acid hydrolysis of the (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)-propanoate (**2a**) followed by treatment with propylene oxide afforded (*S*)-2-amino-3-phosphonopropanoic acid (**3a**) as its zwitterion. The *R* isomer was prepared in an analogous fashion. The optical rotation value of $[\alpha]^{24}_{365}$ = +61.7° (*c* = 2, 1 N NaOH) for the *S* isomer **3a** compared favorably with that reported by Villanueva[3] ($[\alpha]^{25}_{365}$ = +56° (*c* = 2, 1 N NaOH)) for a (*S*)-AP-3 sample of 86% enantiomeric excess. Inexplicably, the optical rotation of **3a** observed at 589 nm ($[\alpha]^{24}_{D}$ = +13.8°) was not in accordance with that reported by Villanueva ($[\alpha]^{25}_{D}$ = +44°).

Our desire to further quantitate the stereochemical purity of **3a** led us to first attempt the reconversion of **3a** to **2a**. Unfortunately, the clean reconversion of **3a** to **2a** by *N*-*tert*-butoxycarbonylation with BOC-ON and esterification with diazomethane proved difficult, so alternative methods of determining the stereochemical purity of **3a** were explored. Racemic AP-3 (**3c**) was prepared by modification of the method of Soroka and Mastalerz[7] as

(1) Schoepp, D. D.; Johnson, B. G. *J. Neurochem.* **1989**, *53*, 273.
(2) For a recent review of the quisqualic acid/phosphoinositide metabotropic receptor, see: Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. *Ann. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365.
(3) Villanueva, J. M.; Collignon, N.; Guy, A.; Savignac, P. *Tetrahedron* **1983**, *39*, 1299.
(4) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.
(5) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237.
(6) Vederas, J. C., personal communication.
(7) Soroka, M.; Mastalerz, P. *Rocz. Chem.* **1976**, *50*, 661.

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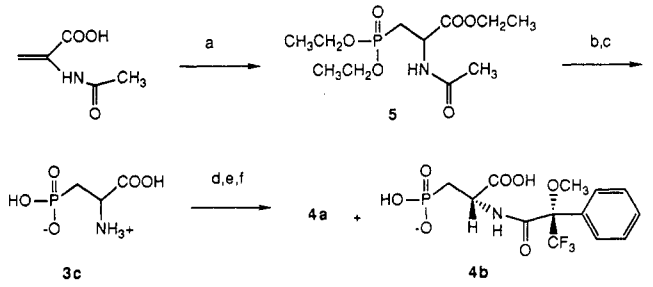
Scheme II[a]



[a] (a) $(EtO)_3P$, 120 °C; (b) 6 N HCl, reflux; (c) propylene oxide, EtOH, 50 °C; (d) BSTFA; (e) (*R*)-(+)-MTPA-Cl; (f) H_2O.

shown in Scheme II. Attempts to directly prepare the diastereomeric amides, **4a** and **4b**, by N-acylation of **3c** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride[8] (MTPA-Cl) using Schotten–Baumann conditions gave poor results. Subsequently, we found that a mixture of **4a** and **4b** could be conveniently prepared from **3c** by silylating with bis(trimethylsilyl)trifluoroacetamide[9] in CH_2Cl_2 followed by treatment with (*R*)-(+)-MTPA-Cl prepared as described by Mosher.[8] Silyl groups were removed by addition of H_2O, and the diastereomeric nature of the resultant α-methoxy-α-(trifluoromethyl)phenylacetamide was readily observable in the ^1H NMR spectrum, which is provided as supplementary material. The methoxy signals of the two diastereomers resonating at 3.43 and 3.47 ppm were clearly resolved in CD_3OD, and were identified as the best indicator of purity. Similar derivitization of (*S*)-AP-3 (**3a**) gave **4a** which was shown by ^1H NMR spectroscopy to contain less than 3% contamination of the **4b** based upon peak heights of the methoxy signals.

In summary, this report describes a facile enantioselective synthesis of D- and L-AP-3, as well as a convenient procedure for the preparation of chiral amide derivatives used in the determination of stereochemical purity of polyacidic amino acids. This technique afforded the convenience of a one-pot derivitization of amino acids possessing more than one acidic functionality in which it is not necessary to first esterify the acidic moieties. The pharmacological evaluation of **3a** and **3b** will be reported elsewhere.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. All ^1H and ^{13}C NMR spectra were obtained on either a GE QE-300, a Bruker WM 270, or a Bruker AM 500 spectrometer. ^1H NMR chemical shifts are reported in ppm (δ) downfield from tetramethylsilane or external DSS, while ^{13}C NMR chemical shifts are reported in ppm (δ) using tetramethylsilane or 1,4-dioxane-d_8 as the reference. Coupling constants (*J*) reported for ^{13}C NMR spectra refer to ^{13}C–^{31}P couplings. Optical rotations were measured at 23–25 °C on a Perkin-Elmer 241 polarimeter at wavelengths of 365 and 589 nm. Field desorption mass spectra were recorded on a Varian-MAT 731 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 with fluorescent indicator, and flash chromatography was carried out on EM Science silica gel 60 (0.040–0.063 mm). The term in vacuo refers to house vacuum system (5–20 mmHg).

(*S*)-Methyl *N*-(*tert*-Butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate (2a). Trimethyl phosphite (13.0 mL, 110 mmol) and (*S*)-*N*-(*tert*-butoxycarbonyl)-3-amino-2-oxetanone[4] (**1a**) (2.00 g, 10.7 mmol) were combined and heated at 70 °C in an oil bath under N_2 for 42 h. Upon cooling, the mixture was concentrated in vacuo, and further under high vacuum at room temperature to give 3.52 g of a thick oil. The residue was purified by flash chromatography (5% *i*-PrOH/$CHCl_3$) to give 2.73 g of **2a** as a clear oil (82%): $[\alpha]_D$ = +10.7° (*c* = 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 2.40 (dd, 2 H), 3.75–3.80 (9 H), 4.57 (m, 1 H), 5.73 (br d, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.05 (d, CH_2, *J* = 149 Hz), 28.19 (s, *t*-Bu *Me*), 48.98 (d, CH, *J* = 5.55 Hz), 52.44 (d, POMe, *J* = 6.47 Hz), 52.53 (d, POMe, *J* = 5.55 Hz), 52.53 (s, CO_2Me), 80.09 (s, *t*-Bu C), 155.1 (s, $NHCO_2$), 171.3 (d, CO_2, *J* = 9.25 Hz); FDMS *m/e* 312 (M + 1). Anal. Calcd for $C_{11}H_{22}NO_7P$: C, 42.45; H, 7.12; N, 4.50. Found: C, 42.23; H, 6.91; N, 4.46. Compound **2b** was prepared similarly from **1b**: $[\alpha]_D$ = −9.93° (*c* = 2.2, $CHCl_3$); the ^1H NMR spectrum was identical with that of **2a** except the NH proton was shifted, presumedly due to concentration effects. Anal. Calcd for $C_{11}H_{22}NO_7P$: C, 42.45; H, 7.12; N, 4.50. Found: C, 42.56; H, 7.06; N, 4.61.

(*S*)-2-Amino-3-phosphonopropanoic Acid (3a, L-AP-3). Compound **2a** (2.00 g, 6.43 mmol) was heated at reflux in 6 N HCl (30 mL) under N_2 for 22 h. Upon cooling, the mixture was concentrated in vacuo, diluted with absolute EtOH (40 mL), and treated with propylene oxide (6 mL). The resulting suspension was heated at 50 °C for 2 h before being concentrated in vacuo to give a white solid. Recrystallization was accomplished from 50% EtOH/H_2O to afford 0.344 g of white crystals (32%): mp 224–226 °C dec; $[\alpha]^{24}_{365}$ = +61.7°, $[\alpha]^{24}_{589}$ = +13.8° (*c* = 2, 1 N NaOH); $[\alpha]^{24}_{589}$ = +8.33° (*c* = 2, H_2O); ^1H NMR (D_2O) δ 2.14 (m, 1 H), 2.38 (m, 1 H), 4.20 (m, 1 H); ^{13}C NMR (D_2O) δ 28.78 (d, CH_2, *J* = 131 Hz), 50.35 (d, CH, *J* = 4.62 Hz), 172.5 (d, CO_2, *J* = 12.9 Hz); FDMS *m/e* 170 (M + 1). Anal. Calcd for $C_3H_8NO_5P$: C, 21.31; H, 4.77; N, 8.28. Found: C, 21.23; H, 4.88; N, 8.27. The D isomer **3b** was prepared analogously from **2b** to afford white crystals: mp 224–227 °C dec; $[\alpha]^{24}_{365}$ = −60.0°, $[\alpha]^{24}_{589}$ = −13.4° (*c* = 2, 1 N NaOH); $[\alpha]^{24}_{589}$ = −8.06° (*c* = 2, H_2O); the ^1H NMR spectrum was identical with that of **3a**. Anal. Calcd for $C_3H_8NO_5P$: C, 21.31; H, 4.77; N, 8.28. Found: C, 21.21; H, 4.86; N, 8.32.

DL-2-Amino-3-phosphonopropanoic Acid (3c). Racemic AP-3 (**3c**) was obtained by heating **5** (9.62 g, 32.6 mmol) at reflux in 6 N HCl for 24 h. The reaction was worked up as described for **3a** to give 5.33 g of a white powder (97%). Recrystallization from 50% EtOH/H_2O afforded white crystals: mp 221–223 °C dec (lit.[7] mp 228–232 °C dec); the ^1H NMR spectrum was consistent with that of **3a**.

(2*R*)-*N*-(2-Phosphono-1(*S*)-carboxyethyl)-2-methoxy-2-(trifluoromethyl)phenylacetamide (4a). To a suspension of **3a** (100 mg, 0.59 mmol) in 3 mL of CH_2Cl_2 was added bis(trimethylsilyl)trifluoroacetamide (BSTFA) (0.8 mL, 3.0 mmol). The suspension was stirred at 23 °C under N_2 for 17 h. Additional BSTFA was added as needed until the mixture was essentially homogeneous. Undistilled (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[8] (MTPA-Cl) (170 mg, 0.67 mmol) was added, and the mixture was stirred for 40 h. TLC (EtOAc–CH_3CN–HOAc–H_2O, 21:7:7:9; ninhydrin charred) did not show the presence of unreacted AP-3. Water (3 mL) was added, and the mixture was stirred for 30 min to hydrolyze the silyl protecting groups. The CH_2Cl_2 layer was discarded, and the aqueous portion washed with Et_2O/CH_2Cl_2 (2:1). Concentration of the aqueous portion gave a white foam which without further purification was analyzed for diastereomeric purity by ^1H NMR spectroscopy: ^1H NMR (CD_3OD) δ 2.33 (dd, 2 H), 3.43 (s, 3 H), 4.72 (dt, 1 H), 7.37–7.60 (m, 5 H). Less than 3% contamination of the *R,R* diastereomer (**4b**) was observed based upon peak heights of the methoxy signals. The mixture of **4a** and **4b** was prepared in an analogous fashion from **3c** and (*R*)-(+)-MPTA-Cl.

DL-Ethyl *N*-Acetyl-2-amino-3-(diethylphosphono)-propanoate (5). Compound **5** was obtained from the addition of triethyl phosphite to 2-acetamidoacrylic acid as described by Soroka and Mastalerz[7] except that it was isolated as a clear oil by flash chromatography over silica eluted with 5% *i*-PrOH/$CHCl_3$: ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 1.32 (t, 3 H), 1.33 (t, 3 H), 2.05 (s, 3 H), 2.36 (m, 2 H), 4.09 (m, 4 H), 4.21 (m, 2 H), 4.80 (m, 1 H), 6.86 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.97 (s, $CO_2CH_2CH_3$), 16.20–16.31 (2 d, overlapping, $POCH_2CH_3$), 22.93 (s, NHCO*Me*), 27.26 (d, PCH_2, *J* = 142 Hz), 47.72 (d, CH, *J* = 6.79 Hz), 61.68 (s, CO_2CH_2), 61.68–62.04 (2 d, overlapping, $POCH_2$), 169.9 (s, NHCO), 170.5 (d, CO_2, *J* = 8.30 Hz); FDMS *m/e* 296 (M + 1). Anal. Calcd for $C_{11}H_{22}NO_6P$: C, 44.75; H, 7.51;

(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(9) Fisher, J. W., personal communication.

N, 4.74. Found: C, 44.58; H, 7.55; N, 4.73.

Acknowledgment. We gratefully acknowledge helpful discussions with J. C. Vederas, P. L. Ornstein, J. W. Fisher, D. A. Evans, and D. D. Schoepp. We are also indebted to T. K. Elzey for assistance of with the ^{13}C NMR experiments and the physical chemistry department for providing analytical and spectral data.

Supplementary Material Available: The portion of the ^1H NMR spectra of **2a** and **2b** treated with (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TAE) used to establish enantiomeric purity, and the ^1H NMR spectra of the methoxy region of **4a** as compared to a diastereomeric mixture of **4a** and **4b** (2 pages). Ordering information is given on any current masthead page.

Diazotative Deaminosilylation of β-Amino Silanes

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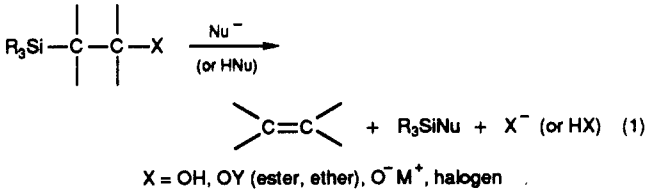
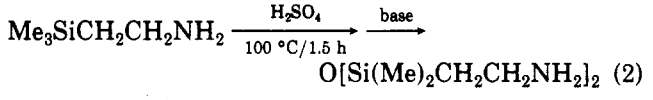
Introduction

The utilization of β-functional organosilanes as precursors to alkenes via elimination under thermolytic, acidic, or basic conditions is a useful synthetic technique.[1] Although a variety of functionalities have commonly been employed for this purpose (eq 1), the use of amino groups



(1)

is rare. Indeed, early work along these lines was discouraging, as Sommer and co-workers found that, in total contrast to the behavior of (β-hydroxyethyl)silanes, heating (β-aminoethyl)trimethylsilane with concentrated sulfuric acid caused silicon–methyl cleavage instead of β-elimination (eq 2).[2] We are aware of no other report concerning



(2)

the attempted elimination of a primary β-amino silane, although several authors have detailed the successful elimination of β-silyl quaternary,[3,4] and secondary[3] amines and of tertiary amine oxides.[4] The current approach to deaminosilylation of primary amines was predicated on the expectation that diazotization would produce a diazonium ion[5] which would suffer elimination directly or via a β-silyl carbocation[6] (Scheme I). Of the many methods available for diazotization,[7] the one initially reported by Friedman[8] employing isoamyl nitrite (iAmONO) was used, as this seemed to offer the best prospects for convenience, completeness of reaction, and maximization of the alkene/substitution-product ratio. Although this approach has proven successful, the outcome is not without complications when viewed as a synthetic method, and these results are detailed herein.

Scheme I

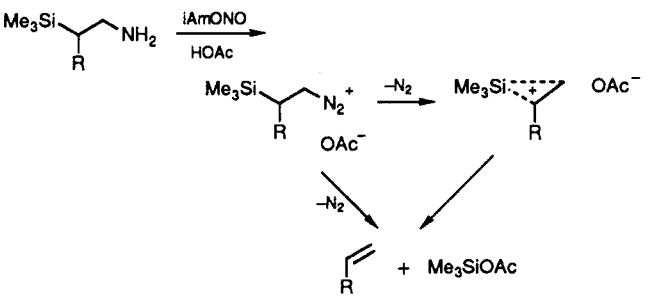
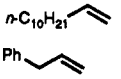
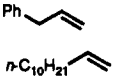
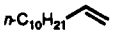
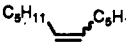
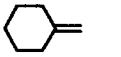


Table I. Deaminosilylation of β-Amino Silanes[a]

silane	product	% yield[b]
2		62[c]
5		68
6		52[c]
9		50
12		26

[a] In glacial HOAc with iAmONO (70 °C) followed by $BF_3{\cdot}Et_2O$; see Experimental Section for details. [b] VPC yields except where noted. [c] Isolated yield. [d] Stereochemistry undetermined.

Preparation of Materials

Scheme II outlines the preparation of the β-amino silanes and reference compounds employed in this work. Few entries to the primary β-amino silane moiety are extant,[9] and we purposefully explored a diversity of approaches to this sytem in order to expand the available synthetic methodology. Yields of all products were sufficient to our needs, and optimization of conditions was thus not generally carried out. Two aspects of these syntheses are worthy of note: (a) the preparation of **3**, the parent member of its class ((β-nitroalkyl)silanes) and (b) stereospecific (presumably anti) addition of iodine isocyanate to alkenylsilane **7** with regiochemistry opposite that expected for all-carbon analogues.[10] This would here lead to only the *S,S/R,R* enantiomeric pair of adducts, a prediction consistent with the ^1H NMR homogeneity of the product obtained. It is of interest to note that the silylated dodecanamines employed in this study are not extracted into 3 N hydrochloric acid from the usual organic

(1) Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1981.
(2) Sommer, L. H.; Marans, N. S.; Goldberg, G. M.; Rockett, J.; Pioch, R. P. *J. Am. Chem. Soc.* **1951**, *73*, 882.
(3) Nametkin, N. S.; Perchenko, N.; Grushevenko, I. A.; Kamneva, G. L.; Derenkovskaya, T. I.; Kuzovkina, M. E. *Izv. Akad. Nauk SSSR* **1973**, 865.
(4) Bac, N. V.; Langlois, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7666.
(5) Review: Patai, S., Ed. *The Chemistry of Diazonium and Diazo Groups*; Wiley: New York, 1978.
(6) The heightened stability of β-silyl carbocations is well documented. See ref 1.
(7) See: Baumgarten, R. J.; Curtis, V. A. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Chapter 22.
(8) (a) Bayless, J. H.; Mendicino, F. D.; Friedman, L. *J. Am. Chem. Soc.* **1965**, *87*, 5790. (b) Friedman, L.; Bayless, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 1790.
(9) For some other approaches, see: (a) Sommer, L. H.; Rockett, J. *J. Am. Chem. Soc.* **1951**, *73*, 5130. (b) Limburg, W. W.; Post, H. W. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 430. (c) Duboudin, F.; LaPorte, O. *J. Organomet. Chem.* **1979**, *174*, C18.
(10) Hassner, A.; Lorber, M. E.; Heathcock, C. *J. Org. Chem.* **1967**, *32*, 540. Our results confirm identical regiochemistry postulated for the addition of INCO to $Et_3SiCH{=}CH_2$ by Vakhrushov, L. P.; Filipov, E. F.; Chernov, N. F.; Ageev, V. P. *J. Gen. Chem. USSR* **1975**, *45*, 1878. Parallel stereo- and regiochemistry is exhibited by the addition of INCS to alkenylsilanes: Thomas, E. J.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1979**, 212.

0022-3263/90/1955-4474$02.50/0