not only in olefin homologation and hydrogenolysis but also in alkane hydrogenolysis and isomerization and in the Fischer-Tropsch synthesis.

Experimental Section

1. Materials. 1-Pentene, 2-pentene, 3-methyl-1-butene, 2-methyl-2-butene, and 2-methyl-1-butene (Fluka) were used as received.

1-Pentene-*1-*^{13}C was obtained by a methylene exchange of 1-pentene with ^{13}C-labeled ethylene (ca. 2/1 ratio) on a $SnMe_4$-treated MoO_3/TiO_2 catalyst at room temperature;[41] 48% ^{13}C-labeled and 52% unlabeled 1-pentene were produced in the reaction. The mixture was purified by column separation and vacuum evaporation to remove water. Hydrogen was purified by passage through a Pd thimble at 400 °C.

2. Catalysts. For the experiments in a flow system the Ru/SiO_2 catalyst was prepared by adsorbing $Ru_3(CO)_{12}$ (Johnson Matthey) from a hexane solution onto silica (Aerosil 200 Degussa) that had been pretreated at 500 °C under 10^{-4} Torr for 16 h. The cluster was then decomposed overnight under flowing H_2 at 300 °C. The final metal content was 1.0%, and the average particle size determined by electron microscopy was ca. 15 Å..

For the labeling experiments the Ru/SiO_2 catalyst was prepared by reducing $RuCl_3$ supported on SiO_2 (Merck, Kieselgel 60) with 200 Torr H_2 at 400 °C for 2 h in a closed circulation system with a glass loop maintained at -196 °C; the final metal content was 2.8 atom %.

3. Catalytic Reactions. Flow System. The reactor was a dynamic microreactor working at atmospheric pressure. The reagents were a mixture of pentene/H_2/argon. Pentene was introduced in a saturator, the temperature of which was stabilized at 0 °C, and the flow rate of the olefin was regulated by the flow of argon. Typically, the flow rates of argon and hydrogen were such that the final reaction mixture corresponded to pentene/H_2 = 1/1 (molar ratio).

The experiments were carried out according to the following procedure: the catalyst Ru/SiO_2 (ca. 200 mg) introduced in the reactor was heated at the reaction temperature under a flow of pure hydrogen; then the mixture pentene/H_2/argon was allowed to flow over the catalyst ($10^3 \times h^{-1} < GSV < 10^4 \times h^{-1}$) for 10 mn before the products of the reaction were analyzed by gas-phase chromatography.

Separation and analysis of the products were carried out with a fid gas-phase chromatograph Intersmat IGC 120 FB. Hydrocarbons from C_1 to C_4 were separated by employing a $^1/_8$ in. × 6 m squalane (7%)/alumina column. Hydrocarbons from C_5 to C_7 were separated employing a set of two columns including a $^1/_8$ in. × 4.5 m SE 30/Chromosorb column and a $^1/_8$ in. × 2 m DC 550/Chromosorb column.

Labeling Experiments. The reaction was carried out by introducing 1-pentene (48% ^{13}C; 40 Torr) in the presence of H_2 (4 Torr) on the Ru/SiO_2 (20 mg) at 110 °C in a closed glass circulation system with a volume of 260 mL, equipped with greaseless stop valves to prevent absorption of reactant and product gases.

The product distribution in the 1-pentene reaction was determined by means of an on-line gas chromatograph with fid detector (Shimadzu GC 4), fitted with a 13-m stainless steel column (3 mm i.d.) packed with Sebaconitrile 25% on Uniport C. The distribution of ^{13}C in each product was analyzed by mass spectrometry (Hitachi RMU-6) with low-ionization voltage (10-12 V) to prevent fragmentation. Products of 1-pentene homologation were concentrated in a sampling loop and separated by means of a column, then each product was trapped by a gas-collecting equipment.

Acknowledgment. E.R. thanks the foundation Gran Mariscal de Ayacucho (Venezuela) for financial support.

(33) Garin, F.; Maire, G.; Gault, F. G. *Nouv. J. Chim.* **1981**, *5*, 563-573.
(34) Yamaguchi, T.; Nakamura, S.; Tanabe, K. *J. Chem. Soc., Chem. Commun.* **1982**, 621-622.
(35) Strehlow, R. A.; Douglas, E. C. *J. Chem. Soc., Chem. Commun.* **1983**, 259-260.
(36) Kyba, E. P.; Chiou, H. S.; Cornell, M. E. *J. Chem. Soc., Chem. Commun.* **1983**, 1220-1222.
(37) Löffer, I. D.; Maier, W. F.; Andrade, J. G.; Thies, I.; von Raguë-Schleyer, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1177-1179.
(38) Jacobson, D. B.; Freiser, B. S. *Organometallics* **1984**, *3*, 513-519. Jacobson, D. B.; Freiser, B. S. *J. Am. Chem. Soc.* **1985**, *107*, 4373-4378.
(39) Huang, K. W.; Ekerdt, J. G. *J. Catal.* **1985**, *92*, 232-239.
(40) Morris, S. R.; Moyes, R. B.; Wells, P. B.; Whyman, R. *J. Catal.* **1985**, *96*, 23-31.
(41) Tanaka, K.; Tanaka, K. I. *J. Chem. Soc., Chem. Commun.* **1984**, *748*-749.

Asymmetric Synthesis with Chiral β-Lactams. α-Substituted Aromatic α-Amino Acids and Their Derivatives through Highly Stereoselective Alkylations

Iwao Ojima,* Hauh-Jyun C. Chen, and Kazuaki Nakahashi[1]

Contribution from the Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794. *Received April 1, 1987. Revised Manuscript Received August 24, 1987*

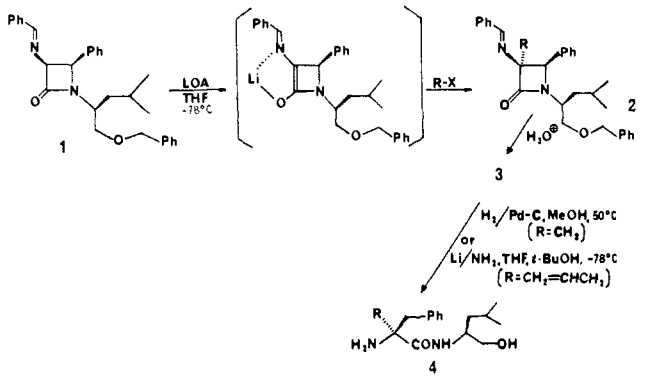
Abstract: A novel route to optically pure α-alkylated aromatic α-amino acids and their dipeptide derivatives was developed through the asymmetric alkylation at the C-3 position of a chiral β-lactam **1** followed by the reductive cleavage of the alkylated β-lactams **2**. The stereochemical course of the reaction is effectively controlled by the chiral center at the C-4 position of the β-lactam. This novel asymmetric alkylation was successfully applied for the synthesis of (*S*)-α-methyl-DOPA via a chiral β-lactam **4**, which was synthesized by the asymmetric [2 + 2] cycloaddition of a chiral ketene to an imine.

Recently the significance of nonproteinogenic amino acids has been recognized in connection with the design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymic reaction mechanisms.[2-6] Among those nonproteinogenic amino acids, α-substituted α-amino acids provide a challenging synthetic problem for chemists, since the α-substituted α-amino acids have chiral quaternary carbons, and thus, conventional enzymic optical resolution technology cannot be applied effectively; viz., no racemization can take place at the chiral α-carbons, and thus, D-isomers cannot be recycled to the optical resolution process. Therefore, the asymmetric synthesis of optically

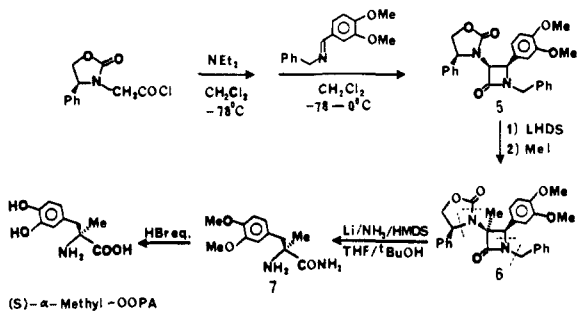
(1) Research Fellow, on leave from Fuji Chemical Industries, Ltd., 530 Chokeiji, Takaoka, Toyama, Japan, 1984-1986.
(2) E.g.: (a) Saari, W. S.; Halczenko, W.; Cochran, D. W.; Dobrinska, M. R.; Vincek, W. C.; Titus, D. G.; Gaul, S. L.; Sweet, C. S. *J. Med. Chem.* **1984**, *27*, 713-717. (b) Saari, W. S.; Freedman, M. B.; Hartman, R. D.; King, S. W.; Raab, A. W.; Randall, W. C.; Engelhardt, E. L.; Hirschmann, R.; Rosegay, A.; Ludden, C. T.; Scriabine, A. *Ibid.* **1978**, *21*, 746-753.
(3) (a) Hartwig, W.; Schöllkopf, U. *Liebigs. Ann. Chem.* **1982**, 1952-1970. (b) Groth, U.; Chiang, Y.-C.; Schöllkopf, U. *Ibid.* **1982**, 1756-1757. (c) Groth, U.; Schöllkopf, U.; Chiang, Y.-C. *Synthesis* **1982**, 864-866. (d) Groth, U.; Schöllkopf, U. *Ibid.* **1983**, 37-38.
(4) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390-5398 and references cited therein.
(5) Karady, S.; Amato, J. S.; Weistock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337.
(6) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.

0002-7863/88/1510-0278$01.50/0

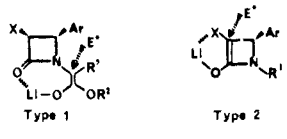
Scheme I



Scheme II



pure α-substituted α-amino acids is the method of choice. Schöllkopf et al.[3] have been developing a general method based on bis(lactim), and Seebach et al.[4] reported a method based on chiral proline derivatives using "self-reproduction of chirality". Karaday[5] and Williams[6] developed effective methods based on oxazolidinone and δ-azalactone respectively. We have been working on this important problem through extremely stereoselective alkylations of chiral β-lactams followed by the reductive cleavage of the alkylated β-lactams.[7] We have investigated two types of asymmetric alkylation, the alkylation of a side-chain carbon bonding to the β-lactam nitrogen (type 1) and the alkylation of the C-3 carbon of a β-lactam (type 2), and communicated excellent results for the type 1 alkylation.[8] We describe here preliminary results on the extremely stereoselective type 2 alkylation.



In the type 2 alkylation, an electrophile is expected to attack the C-3 from the opposite side of the bulky 4-aryl group of the β-lactam enolate to avoid steric conflict. If the reaction proceeds as designed, we should be able to create chiral quaternary carbons at the C-3 position of the β-lactams in a highly predictable manner, which is very beneficial for the synthesis of a series of new α-substituted α-amino acids and their derivatives.

The β-lactam enolate of 3-benzylideneamino β-lactam **1**[7f] was generated by adding lithium hexamethyldisilazide (LHDS, 1.2–1.4 equiv) in THF at −78 °C with stirring. After the mixture was stirred for another 30 min, allyl bromide (3 equiv) was added at the same temperature. Then, the reaction mixture was allowed to warm gradually to room temperature overnight and quenched with 1 N HCl. The usual workup gave 3-allyl-3-benzylideneamino β-lactam **2a** in 95% yield.[9] 3-Methyl-3-benzylideneamino β-lactam **2b** was also obtained in 94% yield by using methyl iodide. The HPLC analysis showed that the type 2 alkylations proceeded with extremely high stereoselectivities (>99.5% de) in both cases (Scheme I). The difference NOE experiments clearly showed the cis arrangement of the C-3 allyl and C-4 hydrogen.[9] Thus, it is proved that the electrophile did attack from the opposite side of the C-4 phenyl group as originally designed.

The reductive cleavage of a β-lactam **3**, which was obtained by deprotection of the 3-benzylideneamino group of **2**, through hydrogenolysis over 10% Pd–C (for **2b**, R = Me) or the Birch reduction ($Li/NH_3/THF/t$-BuOH) (for **2a**, R = allyl) gave the corresponding homochiral dipeptide **4**, bearing an α-alkylated α-amino acid residue at the N terminus, in high yield (**4a**, 90%; **4b**, 88%) (Scheme I).

Next, we applied the type 2 alkylation to the asymmetric synthesis of (*S*)-α-methyl-DOPA, which is an effective antihypertensive drug, as an example of the applicability of this method (Scheme II).

First, chiral β-lactam **5** (>99.5% de) was synthesized through the asymmetric [2 + 2] cycloaddition of a chiral ketene generated in situ from (*S*)-(4-phenyloxazolidinyl)acetyl chloride and triethylamine[10] to (3,4-dimethoxybenzylidene)benzylamine. Second, to the β-lactam **5** in THF was added LHDS (1.3 equiv) in THF at −78 °C, and the mixture was stirred for 1 h to generate the type 2 chiral β-lactam enolate. Methyl iodide (3 equiv) was then added to the enolate, and the mixture was stirred overnight at −78 °C with a gradual increase to room temperature. The usual workup and recrystallization from hexane/AcOEt (1:1) gave (3*S*)-3-methyl-3-oxazolidinyl β-lactam **6** (>99.5% de)[11] in 95% yield. The 3-methyl β-lactam **6** thus obtained was submitted to the Birch reduction with modified Evans–Sjogren conditions[10] (see the Experimental Section) to give (*S*)-*O*,*O*-dimethyl-α-methyl-DOPA amide (**7**) in 90% yield, which is a direct precursor of (*S*)-α-methyl-DOPA.[12]

Consequently, it is demonstrated that the type 2 asymmetric alkylation of chiral β-lactams provides a unique and effective route to a variety of α-substituted aromatic α-amino acids and their derivatives that have chiral quaternary centers.

Experimental Section

Asymmetric Alkylation of 3-Benzylideneamino β-lactam 1. Typically, to the solution of 3-benzylideneamino β-lactam **1** (1.29 mmol)[7f] in THF (20 mL) was added lithium hexamethyldisilazide (LHDS, 1.81 mmol) in THF (10 mL) at −78 °C with stirring. After the mixture was stirred for another 30 min, allyl bromide (3.88 mmol) was added at the same temperature. Then, the reaction mixture was allowed to warm gradually

(7) For a review of the Pd-catalyzed hydrogenolysis of 4-aryl-β-lactams and its application to peptide synthesis, i.e., the "β-Lactam Synthon Method", see: (a) Ojima, I. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symposium Series 185; American Chemical Society: Washington, DC, 1982; pp 109–138. For the application of this method to the syntheses of enkephalin analogues, labeled peptides, and other oligopeptides, see for example: (b) Yamashita, M.; Abe, R.; Hatanaka, N.; Ojima, I. In *Peptide Chemistry 1982*; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, Japan, 1983; pp 85–90. (c) Hatanaka, N.; Abe, R.; Ojima, I. *Chem. Lett.* **1982**, 445–448. (d) Ojima, I.; Shimizu, N. *J. Am. Chem. Soc.* **1986**, *108*, 3100–3102. (e) Ojima, I.; Chen, H.-J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 625–626. (f) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798–1805.

(8) (a) Ojima, I.; Qiu, X.; Nakahashi, K.; Shimizu, N. *Abstracts of Papers*, 191st National Meeting of the American Chemical Society, New York, NY; American Chemical Society, Washington, DC, April 13–18, 1986, ORGN 209. (b) Ojima, I.; Shimizu, N.; Qiu, X.; Chen, H.-J. C.; Nakahashi, K. *Bull. Soc. Chim. Fr.* **1987**, 649–658. (c) Ojima, I.; Qiu, X. *J. Am. Chem. Soc.* **1987**, *109*, 6537–6538.

(9) The NOE experiment by irradiating the C-4 proton exhibited an 11% increase in integration of the allylic methylene protons as well as the vinyl methine proton, which indicates the cis arrangement between the C-3 allyl group and C-4 proton.

(10) For the generation of (4-phenyloxazolidinyl)ketene from chiral (4-phenyloxazolidinyl)acetyl chloride, see: Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783–3786.

(11) The stereochemistry of the C-3 carbon was unambiguously assigned to be cis on the basis of the 2D difference NOE experiment, which showed NOE only between the C-3 methyl and C-4 hydrogen and no appreciable NOE between the C-3 methyl and ortho hydrogens of the C-4 3,4-dimethoxyphenyl group. The results clearly indicate the cis arrangement of the C-3 methyl and C-4 hydrogen. The NOESY spectrum of **6** is available in the supplementary material.

(12) For the hydrolysis of *O*,*O*-dimethyl-α-methyl-DOPA derivatives to (*S*)-α-methyl-DOPA, see: (a) Weinges, K.; Graab, G.; Nagel, D.; Stemmle, B. *Chem. Ber.* **1971**, *104*, 3594–3606. (b) Terashima, S.; Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* **1965**, 1399–1407.

to room temperature overnight and quenched with 1 N HCl (1.0 mL). The HPLC analysis (hexane/AcOEt = 4) of the reaction mixture showed the disappearance of **1**. The reaction mixture was concentrated, adjusted to pH 10, and extracted with methylene dichloride. The extract was washed with brine, dried over anhydrous sodium sulfate, solvent evaporated in vacuo to give (3*S*,4*R*)-1-[(*S*)-1-(benzyloxy)-4-methylpent-2-yl]-3-(benzylideneamino)-3-allyl-4-phenylazetidin-2-one (**2a**) in 95% yield.

In a similar manner, (3*S*,4*R*)-1-[(*S*)-1-(benzyloxy)-4-methylpent-2-yl]-3-(benzylideneamino)-3-methyl-4-phenylazetidin-2-one (**2b**) was obtained in 94% yield.

The HPLC analyses were carried out to determine the optical purities of **2a** and **2b** using hexane/AcOEt (4/1) as eluant, which indicated the optical purities being >99.5% for both compounds.

2a: colorless oil; $[\alpha]^{20}_D$ +26.8° (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (d, *J* = 6.4 Hz, 3 H), 0.93 (d, *J* = 6.4 Hz, 3 H), 1.41 (m, 1 H), 1.60–1.82 (m, 2 H), 2.69 (dd, *J* = 7.5, 14.1 Hz, 1 H), 2.78 (dd, *J* = 6.8, 14.1 Hz, 1 H), 3.26 (dd, *J* = 4.6, 9.5 Hz, 1 H), 3.43 (dd, *J* = 7.9, 9.5 Hz, 1 H), 3.79 (m, 1 H), 4.35 (s, 2 H), 4.87 (s, 1 H), 5.10–5.21 (m, 2 H), 5.95 (m, 1 H), 6.90–7.60 (m, 15 H), 8.69 (s, 1 H); IR (neat) 1740 ($\nu_{C=O}$), 1635 ($\nu_{C=C}$), 995, 915 ($\delta_{CH=CH_2}$) cm^{-1}. For microanalyses to elucidate the structure, see **3a**.

2b: colorless oil; $[\alpha]^{20}_D$ −5.56° (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (d, *J* = 6.2 Hz, 3 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 1.37–1.47 (m, 1 H), 1.67 (s, 3 H), 1.60–1.80 (m, 2 H), 3.25 (dd, *J* = 9.5, 4.7 Hz, 1 H), 3.43 (dd, *J* = 9.4, 8.0 Hz, 1 H), 3.83 (m, 1 H), 4.33 (s, 2 H), 4.72 (s, 1 H), 7.17–7.50 (m, 15 H), 8.70 (s, 1 H); IR (neat) 1740 ($\nu_{C=O}$), 1635 ($\nu_{C=N}$) cm^{-1}. For microanalyses to elucidate the structure, see **3b**.

(3*S*,4*R*)-1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-3-amino-3-allyl-4-phenylazetidin-2-one (3a) and (3*S*,4*R*)-1-[(*S*)-1-(Benzyloxy)-4-methylpent-2-yl]-3-amino-3-methyl-4-phenylazetidin-2-one (3b). To a solution of **2a** (589 mg, 1.23 mmol) in methanol (30 mL) was added 6 N HCl (1.5 mL) at room temperature, and the mixture was stirred for 3 h. Then methanol was removed, and the residual solution was adjusted to pH 10 and extracted with chloroform (30 mL). The chloroform extract was washed with brine and dried over anhydrous sodium sulfate, and the solvent was evaporated to give **3a** (472 mg, 98% yield). In a similar manner, **3b** was obtained in 98% yield.

3a: colorless oil; [a]$^{20}_D$ −4.94° (*c* 4.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.3 Hz, 3 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 1.29 (br s, 2 H), 1.46–1.80 (m, 3 H), 2.57 (m, 2 H), 3.33 (dd, *J* = 9.6, 4.1 Hz, 1 H), 3.48 (dd, *J* = 9.5, 7.8 Hz, 1 H), 3.78 (m, 1 H), 4.35 (s, 2 H), 4.68 (s, 1 H), 5.19 (m, 2 H), 5.90 (m, 1 H), 7.2–7.5 (m, 10 H); IR (neat) 3340, 3309 (ν_{NH}), 1740 ($\nu_{C=O}$), 1638 ($\nu_{C=C}$), 995, 915 ($\delta_{CH=CH_2}$) cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14. Found: C, 76.25; H, 8.11, N, 7.08.

3b: colorless oil; $[\alpha]^{20}_D$ −4.46 (*c* 3.8, $CHCl_3$); ^{1}NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.4 Hz, 3 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 1.3–1.7 (m, 5 H), 1.51 (s, 1 H), 3.31 (dd, *J* = 9.4, 4.4 Hz, 1 H), 3.45 (dd, *J* = 9.6, 7.7 Hz, 1 H), 3.83 (m, 1 H), 4.34 (s, 2 H), 4.56 (s, 1 H), 7.2–7.5 (m, 10 H); IR (neat) 3380, 3310 (ν_{NH}), 1740 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.65. Found: C, 75.46; H, 8.15; N, 7.55.

L-α-Allylphenylalanyl-L-leucinol (4a). To a reaction vessel containing Li (14.6 mg, 2.1 mmol) and THF (15 mL) was added condensed ammonia (10 mL) at −83 °C, which was controlled by a cryostated immersion cooler. A solution of **3a** (137 mg, 0.35 mmol) in THF (10 mL) and *tert*-butyl alcohol (1.0 mL) was added to this dissolving metal solution, and the mixture was stirred at −83 °C for 2 min. The reaction was quenched with solid ammonium chloride (200 mg) at the same temperature. After ammonia and solvents were removed in vacuo, the reaction mixture was acidified with 2 N hydrochloric acid (1.5 mL) and washed with chloroform (30 mL). Then, the reaction mixture was adjusted to pH 10 with sodium hydroxide (solid), and the mixture was extracted with chloroform (30 mL × 3). The chloroform extract was dried over anhydrous sodium sulfate, and the solvent was evaporated to give **4a** (95.9 mg, 90% yield) as a colorless oil.

4a: $[\alpha]^{20}_D$ −3.95° (*c* 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (d, *J* = 6.2 Hz, 3 H), 0.81 (d, *J* = 6.2 Hz, 3 H), 1.18–1.37 (m, 3 H), 1.60 (br s, 3 H) 2.17 (dd, *J* 13.5, 8.3 Hz, 1 H), 2.58 (d, *J* = 13.3 Hz, 1 H), 2.80 (dd, *J* = 13.5, 6.7 Hz, 1 H), 3.40 (d, *J* = 13.3 Hz, 1 H), 3.44 (dd, *J* = 11.0, 6.6 Hz, 1 H), 3.58 (dd, *J* = 11.0, 3.5 Hz, 1 H), 3.85 (m, 1 H), 5.13 (m, 2 H), 5.79 (m, 1 H), 7.15–7.32 (m, 5 H), 7.48 (d, *J* = 7.4 Hz, 1 H); IR (neat) 3600–3100 (ν_{OH}, ν_{NH}), 1710s, 1640 ($\nu_{C=O}$, $\nu_{C=C}$), 1510 (δ_{NH}), 960, 915 ($\delta_{CH=CH_2}$) cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.01; H 9.27; N, 9.20. Found: C, 70.84; H 9.06; N, 9.08.

L-α-Methylphenylalanyl-L-leucinol (4b). To a reaction vessel containing 10% Pd-C (574 mg), which was connected to a standard hydrogenation apparatus, was added a solution of **3b** (180 mg, 0.49 mmol) in methanol (15 mL) under hydrogen atmosphere (1 atm), and the mixture was stirred at 50 °C for 5.5 h. The TLC analysis of the reaction mixture showed the disappearance of **3b**. Then, the reaction mixture was filtered through a glass filter padded with a small amount of Celite, and the filtrate was evacuated to dryness to give **4b** (120 mg, 88%) as a colorless oil.

4b: $[\alpha]^{20}_d$ −5.91° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.83 (d, *J* = 6.3 Hz, 3 H) 0.84 (d, *J* = 6.3 Hz, 3 H), 1.26 (m, 2 H), 1.36 (m, 1 H), 1.30 (br s, 3 H), 1.40 (s, 3 H), 2.57 (d, = 13.3 Hz, 1 H), 3.41 (d, *J* = 13.3 Hz, 1 H), 3.48 (dd, *J* = 11.0, 6.4 Hz, 1 H), 3.61 (dd, *J* = 11.0, 3.6 Hz, 1 H), 3.87 (m, 1 H), 7.1–7.4 (m, 5 H), 7.52 (d, *J* = 7.3 Hz, 1 H); IR (neat) 3600–3120 (ν_{OH}, ν_{NH}), 1720 s, 1645 ($\nu_{C=O}$), 1515 (δ_{NH}) cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.42, N, 10.07. Found: C, 69.13; H, 9.46; N, 9.90.

(3*S*,4*R*)-1-Benzyl-3-[2-oxo-4(*S*)-phenyloxazolidinyl]-4-(3,4-dimethoxyphenyl)azetidin-2-one (5). To a solution of (4*S*)-(4-phenyloxazolidinyl)acetic acid (1.73 g, 7.83 mmol) in toluene (40 mL) were added oxalyl chloride (3.41 mL, 39.2 mmol) and two drops of dimethylformamide at room temperature with stirring, and the mixture was heated at 60 °C for 5 h. Removal of the solvents and excess oxalyl chloride under vacuum gave the corresponding acid chloride quantitatively. The acid chloride thus obtained was dissolved in methylene chloride (50 mL), and the solution was cooled to −78 °C. Triethylamine (2.0 mL, 14.1 mmol) was added to the acid chloride solution, and the mixture was stirred at −78 °C for 30 min. Then, a solution of (3,4-dimethoxybenzylidene)benzylamine (2.30 g, 9.0 mmol) in methylene chloride (20 mL) was added to the mixture at −78 °C with stirring. The reaction mixture was allowed to stir overnight with a gradual increase of temperature to room temperature. The reaction was quenched with water (10 mL) followed by the addition of citric acid (3.8 g), and the reaction mixture was stirred for 1.5 h to decompose the excess Schiff base. The methylene chloride layer was separated, washed with water, washed with brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The crude product thus obtained was purified on a silica gel column (eluant: $CHCl_3$/AcOEt = 3) to give **5** (3.23 g, 90%) as a colorless solid (>99.5% de by HPLC; hexane/AcOEt = 1): mp 159–160 °C; $[\alpha]^{20}_D$ +74.7° (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3 H), 3.92 (s, 3 H), 4.04 (d, *J* = 14.8 Hz 1 H), 4.20 (m, 3 H), 4.39 (d, *J* = 4.75 Hz, 1 H), 4.47 (d, *J* = 4.75 Hz, 1 H), 4.80 (d, *J* = 14.8 Hz, 1 H), 6.7–7.4 (m, 13 H); IR (KBr disk) 1765, 1738 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.72; H, 5.72; N, 6.11. Found: C, 70.94; H, 5.72; N, 6.10.

(3*S*,4*R*)-1-Benzyl-3-methyl-3-[2-oxo-(4*S*)-phenyloxazolidinyl]-4-(3,4-dimethoxyphenyl)azetidin-2-one (6). LHDS (2.90 mmol) in THF (15 mL) was added to the β-lactam **5** (2.23 mmol) in THF (35 mL) at −78 °C, and the mixture was stirred for 1 h. Methyl iodide (6.69 mmol) was then added to the enolate at the same temperature, and the mixture was stirred overnight: The reaction system was allowed to warm gradually to room temperature. The reaction was quenched with 10% ammonium chloride, and the reaction mixture was acidified to pH 7 with 1 N HCl. THF was removed, and the resultant mixture was extracted with methylene dichloride. After the usual workup and recrystallization from hexane/AcOEt (1:1), (3*S*)-3-methyl-3-oxazolidinyl β-lactam **6**[11] was obtained in 95% yield (>99.5% de by HPLC; hexane/AcOEt = 1) as a colorless solid: mp 185–186 °C, $[\alpha]^{20}_D$ +52.1° (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 3.70 (m, 3 H), 3.82 (s, 3 H), 3.91 (s, 3 H), 3.98 (d, *J* = 14.8 Hz, 1 H), 4.25 (s, 1 H), 4.80 (d, *J* = 14.8 Hz), 6.6–7.4 (m, 13 H); IR (KBr disk) 1765, 1740 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.97; N, 5.93. Found: C, 70.97; H, 6.02; N, 5.90.

(*S*)-2-Amino-3-(3,4-dimethoxyphenyl)-2-methylpropionamide (7). In a typical run, ammonia was condensed (30 mL) in a reaction flask containing a solution of **6** (0.50 mmol) in THF (40 mL), *tert*-butyl alcohol (4 mL), and lithium (5.0 mmol) at −78 °C with stirring for 8 min. Then, HMDS (10 mmol) was added and the reaction mixture was stirred for another 5 min. Solid ammonium chloride (600 mg) was added to the reaction mixture for quenching. The usual workup gave the corresponding deprotected azetidin-2-one, which was used in the next step without purification. To the solution of the deprotected azetidin-2-one (0.47 mmol) in THF (35 mL) was added LHDS (0.62 mmol) in THF (5 mL) and subsequently chlorotrimethylsilane (TMS-Cl, 2.5 mmol). The reaction mixture was stirred at 0 °C for 20 min and cooled to −78 °C, and then more lithium (2 mmol) was added to it. The reaction was quenched with solid ammonium chloride (600 mg). After the usual workup, **7** was obtained as a colorless oil: 96% yield; $[\alpha]^{20}_D$ −3.78 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 2.47 (br s, 2 H), 2.54 (d, *J* = 13.4 Hz, 1 H), 3.37 (d, *J* = 13.4 Hz, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 5.89 (br s, 1 H), 6.70–6.95 (m, 3 H), 7.34 (br s, 1 H); IR (KBr) 3600–3100 (ν_{OH}, ν_{NH}), 1650 ($\nu_{C=O}$), 1510 (δ_{NH}) cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.42; H, 7.54; N, 11.63.

Note Added in Proof. The Birch reduction of the 1-methyl derivative of **6** was found to proceed smoothly without adding TMS-Cl or HMDS to give the corresponding *N*-methyl derivative of **7** in excellent yield.

Acknowledgment. This research was supported by grants from the Center for Biotechnology, SUNY at Stony Brook, which is sponsored by the New York State Science and Technology Foundation, and from National Institutes of Health (NIGMS). Generous support from Ajinomoto Co., Inc., is also gratefully acknowledged.

Supplementary Material Available: General methods, sources of materials, and the NOESY spectrum of **6** (2 pages). Ordering information is given on any current masthead page.

Absolute Rate Constants for Some Intermolecular and Intramolecular Reactions of α-, β-, and γ-Silicon-Substituted Radicals[1]

James W. Wilt,[2a] J. Lusztyk,[3] Mehoob Peeran,[2b] and K. U. Ingold*[3]

Contribution from the Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60025, and the Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6. *Received August 25, 1986. Revised Manuscript Received July 24, 1987*

Abstract: Rate constants for hydrogen atom abstraction from *n*-Bu_3GeH (k^{GeH}) by $Me_3SiCH_2^\bullet$ (**1**$^\bullet$), $Me_3SiCH_2CH_2^\bullet$ (**2**$^\bullet$), and $Me_3SiCH_2CH_2CH_2^\bullet$ (**3**$^\bullet$) and from *n*-Bu_3SnH (k^{SnH}) by **1**$^\bullet$ and **3**$^\bullet$ have been determined at ambient temperatures. The order of decreasing radical reactivity is **1**$^\bullet$ > *n*-alkyl > **3**$^\bullet$ > **2**$^\bullet$. However, for bromine abstraction from the parent bromides by *n*-$Bu_3Sn^\bullet$ and *n*-$Bu_3Ge^\bullet$, the order of decreasing reactivity is **1**-Br > **2**-Br > **3**-Br ~ *n*-alkyl bromide. The Arrhenius equations for reaction of **1**$^\bullet$ and **3**$^\bullet$ with *n*-Bu_3SnH were also determined: $\log (k^{SnH}(\mathbf{1}^\bullet)/(M^{-1}\ s^{-1})) = (10.2 \pm 0.5) - (3.90 \pm 0.62)/\theta$ and $\log (k^{SnH}(\mathbf{3}^\bullet)/(M^{-1}\ s^{-1})) = (8.4 \pm 0.7) - (2.81 \pm 0.95)/\theta$, where $\theta = 2.3RT$ kcal/mol. These kinetic data are discussed in relation to previously measured[8] rate constant ratios, k_c^{5+6}/k^{SnH} and k_{exo}^5/k_{endo}^6, where k_c^{5+6} corresponds to the cyclization of α-, β-, and γ-dimethylsilyl-substituted 5-hexenyl radicals to form 5-membered (k_{exo}^5) and 6-membered (k_{endo}^6) silacycloalkylmethyl radicals.

The growing popularity of free-radical cyclization for the construction of ring systems can be partly attributed to their predictability. That is, provided the cyclization is under kinetic control the size of the ring that will be formed predominantly can be forecast by the Baldwin–Beckwith rules.[4] Few exceptions to these rules are known and even fewer have received detailed study.

The best known illustration of the Baldwin–Beckwith rules is provided by the contrathermodynamic 5-exo cyclization of the 5-hexenyl radical to cyclopentylmethyl rather than the thermodynamically preferred, 6-endo cyclization to the cyclohexyl radical[7] (k_{exo}^5/k_{endo}^6 = 72 at 25 °C).[8] There are innumerable variants of this reaction[7] with k_{exo}^5/k_{endo}^6 values that are generally at least as great as for 5-hexenyl and in which the new 5-membered ring contains substituents (including a second, fixed ring) or in which the ring contains heteroatoms from the first row of the periodic table (i.e., O and N). By and large, exceptions to the Baldwin–Beckwith rules arise when an atom from the second row is incorporated into the new ring.[8-11] For example, one of us has reported[8] that the replacement of a CH_2 group at the 2 (α), 3 (β), or 4 (γ) position of 5-hexenyl by an $SiMe_2$ group gave quite unexpected results, both in terms of exo/endo product ratios[10] and in terms of the *apparent* rates of cyclization of these three radicals. The standard experimental approach was followed in which an acyclic parent halide was reacted with *n*-Bu_3SnH under radical-chain conditions. Cyclization of the acyclic radical (rate constant, $k_c^{5+6} = k_{exo}^5 + k_{endo}^6$) competes with hydrogen atom abstraction from the tin hydride (rate constant k^{SnH}); see Scheme I for the competitive reactions of the α-dimethylsilyl-substituted radical. The results obtained[8] with the three $SiMe_2$-substituted radicals and with two all-carbon analogues are summarized in Table I. For the latter, values of k^{SnH} are known[12,13] and hence k_{exo}^5 and k_{endo}^6 can be calculated. However, values of k^{SnH} for the silicon-containing radicals are not known and therefore it was uncertain as to whether the different behavior of these radicals, relative to the behavior of the all-carbon radicals, was due to differences in their rates of attack on *n*-Bu_3SnH. In the present paper, we have resolved this uncertainty by determining values of k^{SnH} for **1**$^\bullet$, **2**$^\bullet$, and **3**$^\bullet$, which are appropriate analogues for the α-, β-, γ-dimethylsilyl-substituted 5-hexenyl radicals.

$Me_3SiCH_2^\bullet$ **1**$^\bullet$ $\quad$ $Me_3SiCH_2CH_2^\bullet$ **2**$^\bullet$ $\quad$ $Me_3SiCH_2CH_2CH_2^\bullet$ **3**$^\bullet$

(1) Issued as NRCC No. 28370.
(2) Loyola. (a) Died: May 13, 1987. To whom this paper is dedicated. (b) Present address: Department of Chemistry, St. Joseph's College, Bangalore-560001, India.
(3) NRCC.
(4) First advanced by Beckwith[5] and later supported by Baldwin.[6]
(5) Struble, D. L.; Beckwith, A. L. J.; Gream, G. E. *Tetrahedron Lett.* **1968**, 3701-3704. Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, *25*, 1081-1105.
(6) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.
(7) For reviews, see: (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4. (b) Surzur, J. M. *React. Intermed. (Plenum)* **1981**, *2*, 121-295. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3071-3100.
(8) Wilt, J. W. *Tetrahedron* **1985**, *41*, 3979-4000.
(9) (a) Chatgilialoglu, C.; Woynar, H.; Ingold, K. U.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1983**, 555-561. (b) Barton, T. J.; Revis, A. *J. Am. Chem. Soc.* **1984**, *106*, 3802-3805.
(10) Systems containing the $C{=}CCH_2OSiMe_2CH_2^\bullet$ moiety also undergo preferential 6-endo cyclization. See, e.g.: Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298-2300. Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098-8100.
(11) Bastien, G.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1979**, 601-605. Bastien, G.; Crozet, M. P.; Flesia, E.; Surzur, J. M. *Ibid.* **1979**, 606-613.
(12) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739-7742.
(13) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594-4596.

0002-7863/88/1510-0281$01.50/0