Synthesis of Compounds Containing Two Adjacent ^{13}C Labels by Photolytic Reactions of Chromium Carbene Complexes

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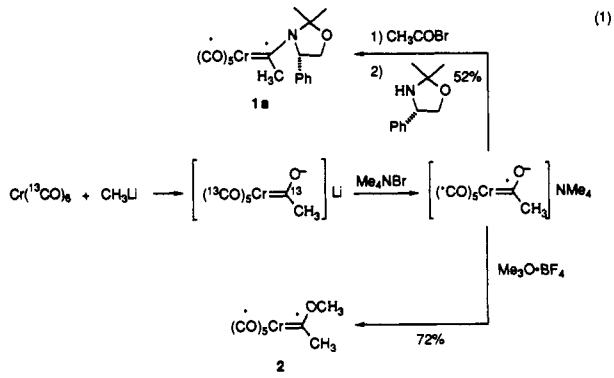
Abstract: Photolysis of ^{13}C-enriched chromium carbene complexes with a variety of substrates produced products having two adjacent positions enriched with ^{13}C. In this way 1,2-bis-^{13}C-enriched amino acid esters, a dipeptide, a cyclobutenone, a β-lactam, and a dioxocyclam were synthesized.

Introduction

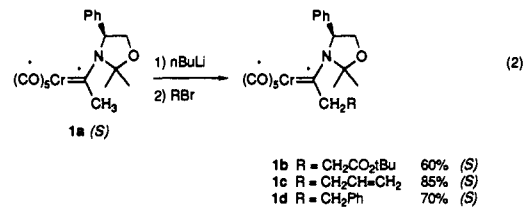
Following the discovery in these laboratories[1] that photolysis (visible light, Pyrex vessels) of heteroatom-stabilized "Fischer" type chromium carbene complexes[2] produced species having the reactivity of modified α-heteroatom ketenes, this chemistry was used to synthesize a wide range of compounds, including β-lactams,[3] cyclobutanones,[4] α-amino acid esters,[5] dipeptides,[6] captodative allenes,[7] and dioxocyclams[8] (14-membered tetraazamacrocycles). Since the carbene complexes used were readily synthesized from chromium hexacarbonyl (eq 1)[9] and since ^{13}C-enriched chromium hexacarbonyl is readily available,[10] this photochemical process offered the possibility of introducing two adjacent ^{13}C-enriched positions into all of the above compounds, a task not easily accomplished by conventional synthetic techniques. ^{13}C-labeled compounds are useful for mechanistic, spectroscopic, structural, conformational, and metabolic studies, and a general synthetic approach would be valuable. The development of such an approach is reported here.



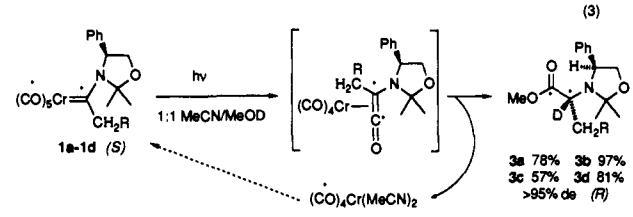
Results and Discussion

^{13}C-enriched chromium hexacarbonyl was prepared by the tributylphosphine oxide-catalyzed exchange of ^{13}CO with $(H_3N)_3Cr(CO)_3$ in hexane solvent.[10] By this procedure, a 65% yield of >75% ^{13}C-enriched material was obtained. By reusing the same hexane solvent for subsequent runs, yields of up to 85% were obtained. The two carbene complexes studied were prepared by the Fischer procedure[9] and by the acylation/exchange procedure,[5] respectively (eq 1). As expected, the yields of these complexes were comparable to those obtained with unenriched chromium hexacarbonyl.

^{13}C-enriched amino acids are extensively used as biochemical and biophysical probes,[11] and 1,2-$^{13}C_2$-enriched amino acids are used to provide conformational information in peptides in the solid state.[12] Carbene complex **1a** underwent facile α-deprotonation/alkylation to produce homologated carbene complexes **1b–d** (eq 2).[5] Photolysis of these complexes in 1:1 MeOD-



(H)/MeCN produced 1,2-$^{13}C_2$ 2D(H)-protected α-amino acid esters **3a–d** in good yield with ≥95% de (eq 3). (The Cr-$(^{13}CO)_4(MeCN)_2$ byproduct was easily recovered in 70–90% yield and was quantitatively reconverted to $Cr(^{13}CO)_6$, maximizing the efficient utilization of the ^{13}CO.) To provide a baseline for the ^{13}C NMR spectra of these isotopically labeled amino acids, complex **1a** was photolyzed in protiomethanol to produce protio **3a**. As expected, the ^{13}C-enriched positions in the ^{13}C NMR spectrum appeared as intense doublets at δ 174.4 and 53.0, J = 62.0 Hz. In the center of each of these doublets was a singlet from the ^{12}C–^{13}C isotopomer from incomplete labeling of the compound. The α-methyl signal was split into a doublet of doublets (J = 17.4, 19.4 Hz) by the two adjacent enriched carbons.



The ^{13}C NMR spectrum of 2-deuterio **3a** was unexpectedly complex, with the δ ~53.0 signal for the α-carbon appearing as a complex 12-line multiplet. Deuterium decoupling[13] simplified

(1) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.
(2) Seyferth, D., Ed. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1983.
(3) Hegedus, L. S.; Imwinkelreid, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.
(4) (a) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (b) Soderberg, B. C.; Hegedus, L. S.; Sierra, M. *J. Am. Chem. Soc.* **1990**, *112*, 4364.
(5) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelreid, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.
(6) Miller, J. R.; Pulley, S. R.; Hegedus, L. S.; DeLombaert, S. *J. Am. Chem. Soc.* **1992**, *114*, 5602.
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(10) Darensbourg, D. J.; Darensbourg, M. Y.; Walker, N. *Inorg. Chem.* **1981**, *20*, 1918.
(11) London, R. E. NMR of ^{13}C Enriched Amino Acids and Peptides. In *NMR Spectroscopy: New Methods and Applications*; Levy, G. C., Ed.; ACS Symposium Series 191; American Chemical Society: Washington, DC, 1982; pp 119–155.
(12) Separovic, F.; Smith, R.; Yannoni, C. S.; Cornell, B. A. *J. Am. Chem. Soc.* **1990**, *112*, 8324 and references therein.

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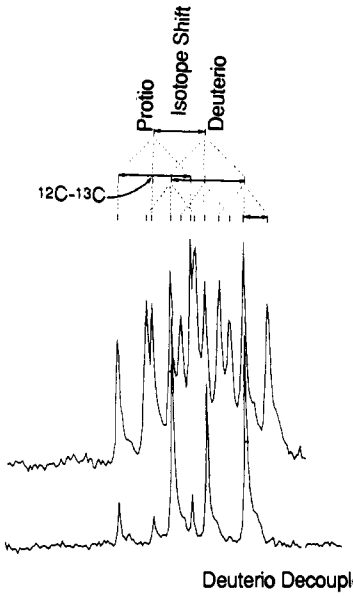
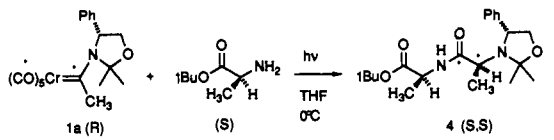


Figure 1.

the pattern into the expected doublet, J = 62.0 Hz, shifted upfield by 48.6 Hz due to the deuterium isotope effect, flanking the singlet due to the ^{12}C–^{13}C isotopomer.[14] In addition, the spectrum revealed small amounts of the α-protio derivative, not detectable in the ^1H NMR spectrum,[15] as a doublet flanking a singlet at δ 53.0. Splitting of each line of the *major* signal into a triplet, J = 20.0 Hz, by deuterium accounts for the observed 12 lines (Figure 1). The α-carbons of **3b–d** gave identical patterns in the ^{13}C NMR spectrum.

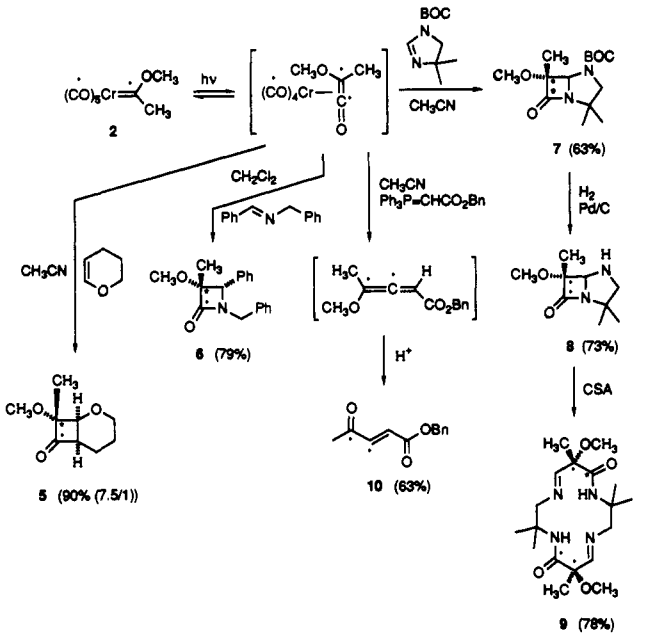
Using previously developed procedures[5,16] compound **3a** was converted to (*R*)-[1,2-$^{13}C_2$,2-^{2}H]alanine in 72% yield with an ee of 95% as determined by ^{19}F NMR spectroscopy on the Mosher's amide. This process should provide a general way to synthesize multiply labeled natural and unnatural amino acids, since the absolute configuration of the amino acid is determined by that of the chiral auxiliary in the chromium carbene complex (*R* → *S*; *S* → *R*). This methodology should be equally useful for the introduction of ^{14}C and ^3H into amino acids.

A major impetus for the synthesis of labeled amino acids is for their ultimate incorporation into peptides. Chromium carbene-based methodology is also applicable to this problem.[6] Photolysis of *R* carbene complex **1a** with the *tert*-butyl ester of (*S*)-alanine gave the labeled dipeptide **4** in 70% yield as a 94:6 ratio of diastereoisomers (eq 4). In this case, THF was the solvent required to obtain acceptable asymmetric induction, and acetonitrile seriously decreased the stereoselectivity of the peptide coupling process. However, addition of acetonitrile *after* the reaction was complete permitted recovery of the $(^{13}CO)_4Cr$ fragment (as $(^{13}CO)_4Cr(MeCN)_2$ as before) in reasonable yield. Studies designed to permit the introduction of multiply labeled amino acid fragments into Merrifield resin-supported polypeptides are in progress.



(4)

Scheme I



A number of other classes of multiply labeled organic compounds are also readily available by the photochemical reaction of chromium alkoxycarbene complex **2** with organic substrates (Scheme I). Thus, cyclobutanones,[4] β-lactams,[5,17] azapenams and dioxocyclams,[8] and β-keto enoates[6] were formed from the appropriate substrates in good yield, indicating the generality of the process. While of less intrinsic interest than multiply labeled amino acids and peptides, the ready availability of compounds such as these should be of general use for metabolic, structural, and mechanistic studies, as well as for the systematic study of the response of ^{13}C NMR spectroscopic features to structural changes.

Experimental Section

Materials. The following compounds were prepared according to literature procedures: $Cr(^{13}CO)_6$,[10] **1a–d**,[5] and **2**.[9]

General Procedure for the Synthesis of Amino Esters 3a–d. The chiral carbene complexes **1a–d** were dissolved in a mixture of 1:1 MeOD/MeCN in a large Pyrex test tube capped with a rubber septum. Ar was bubbled through the solution for 5 min to deaerate the solution. Photolysis (450-W Conrad-Hanovia 7825 medium-pressure mercury lamp) at 0 °C for 24 h gave a yellow solution which was air oxidized to remove the chromium residues or chromatographed on silica gel, eluting with CH_2Cl_2/hexane (1:1) to recover $Cr(^{13}CO)_4(MeCN)_2$ followed by EtOAc to obtain the labeled α-amino ester.

3a. From *S* carbene **1a** (110 mg, 0.27 mmol) in 20 mL of MeOD/MeCN (1:1) were obtained 65 mg (95%) of $Cr(^{13}CO)_4(NCMe)_2$ and 57 mg (78%) of the *R,S* amino ester **3a**: ^1H NMR (300 MHz)[18] δ 1.27 (m, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 3.45 (d, 3 H, J_{CH} = 3.5 Hz, OCH_3), 3.67 (dd, 1 H, J = 8.0, 7.0 Hz, OCH_2), 4.18 (dd, 1 H, J = 8.0, 7.0 Hz, OCH_2), 4.44 (td, 1 H, J = 7.0 Hz, J_{CH} = 2.4 Hz, NCHPh), 7.20–7.39 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 15.0 (dd, J_{CC} = 19.0, 17.0 Hz, CH_3), 23.1 (CH_3), 28.7 (CH_3), 51.4 (OCH_3), 52.7[18] (dt, J_{CC} = 62.0 Hz, J_{CD} = 20.0 Hz, $NCDCH_3$), 61.8 (OCH_2), 72.2 (NCHPh), 97.0 (NCO), 127.4, 127.6, 128.2, 142.0 (Ph), 174.4 (d, J_{CC} = 62.0 Hz, CO); IR (film) ν 1693 (C=O) cm^{-1} (61% ^{13}C incorporation); mass spectrum (CI) M + 1 267.

Photolysis in MeOH/MeCN gave the protio isotopomer: ^1H NMR (300 MHz) δ 1.21 (m, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 3.38 (d, 3 H, J_{CH} = 3.6 Hz, OCH_3), 3.50 (dm, 1 H, J_{CH} = 132.7 Hz, *CH), 3.60 (t, 1 H, J = 7.7 Hz, OCH_2), 4.11 (t, 1 H, J = 7.7 Hz, OCH_2), 4.38 (td, 1 H, J = 7.7 Hz, J_{CH} = 2.1 Hz, NCHPh), 7.27–7.32 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 15.2 (dd, J_{CC} = 19.4, 17.4 Hz, CH_3), 23.1 (CH_3), 28.7 (CH_3), 51.4 (OCH_3), 53.0 (d, J_{CC} = 62.0 Hz, $NCDCH_3$), 61.8 (OCH_2), 72.2 (NCHPh), 95.9 (NCO), 127.4, 127.6,

(13) We thank Dr. Bruce Hawkins for carrying out this decoupling experiment.

(14) Kalmowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley and Sons, Ltd.: London, 1988; p 168.

(15) This H–^{13}C carbon signal is intensified because of nuclear Overhauser enhancement in the intensity of ^{13}C resonances with *proton* decoupling (ref 14, p 626), while the intensity of the ^2H–^{13}C carbon signal is decreased by the quadrupolar deuterium (ref 14, p 633).

(16) Hegedus, L. S.; Lastra, E.; Narukawa, Y.; Snustad, D. *J. Am. Chem. Soc.* **1992**, *114*, 2991.

(17) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680.

(18) Only the peaks for the ^{13}C–^{13}C isotopomer are reported, although those for the other isotopomers are present as well. See the text for a discussion.

128.2, 130.9, 141.4 (Ph), 174.4 (d, J_{CC} = 62.0 Hz, CO).

3b. From *S* carbene **1b** (50 mg, 0.09 mmol) was obtained 34 mg of (*S*,*R*)-**3b** (97% yield): ^1H NMR (300 MHz) δ 1.36 (s, 3 H, CH_3), 1.39 (s, 9 H, $(CH_3)_3C$), 1.52 (s, 3 H, CH_3), 1.87 (m, 1 H, CH_2CO_2tBu), 2.16 (m, 3 H, $CH_2CH_2CO_2tBu$), 3.46 (d, 3 H, J_{CH} = 3.7 Hz, OCH_3), 3.69 (dd, 1 H, J = 8.1, 7.1 Hz, OCH_2), 4.19 (dd, 1 H, J = 8.1, 7.1 Hz, OCH_2), 4.52 (td, 1 H, J = 7.1 Hz, J_{CH} = 1.9 Hz, NCHPh), 7.20–7.37 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 23.2 (CH_3), 24.6 (dd, J_{CC} = 20.0, 18.0 Hz, CH_2*C), 28.1 ($(CH_3)_3C$), 28.9 (CH_3), 32.5 (CH_2), 51.4 (OCH_3), 56.6 (dt, J_{CC} = 60.5, J_{CD} = 20.3 Hz, *$CDCH_2$), 62.2 (OCH_2), 72.0 (NCHPh), 80.4 ($C(CH_3)_3$), 96.0 (NCO), 127.5, 127.6, 128.3, 142.0 (Ph), 169.6 (s, CO), 173.2 (d, J_{CC} = 60.5 Hz, CO); IR (film) ν 1728 (CO), 1693 (^{13}CO) cm^{-1}; mass spectrum (EI) M^+ 380, $M^+ - CH_3$ 365, $M^+ - *CO_2CH_3$ 320.

3c. From *S* carbene **1c** (50 mg, 0.11 mmol) was obtained 20 mg of product (*S*,*R*)-**3c** (57% yield): ^1H NMR (300 MHz) δ 1.20 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.52 (m, 1 H, CH_2), 1.90 (m, 3 H, CH_2CH_2), 3.38 (d, 3 H, J_{CH} = 3.7 Hz, OCH_3), 3.61 (dd, 1 H, J = 8.0, 7.8 Hz, OCH_2), 4.11 (dd, 1 H, J = 8.0, 7.8 Hz, OCH_2), 4.42 (td, 1 H, J = 8.0 Hz, J_{CH} = 1.9 Hz, NCHPh), 4.87 (m, 2 H, CH_2=CH), 5.62 (m, 1 H, CH=CH_2), 7.14–7.30 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 23.1 (CH_2), 28.7 (dd, J_{CC} = 18.0, 17.6 Hz, *$CDCH_2$), 28.9 (CH_3), 30.9 (CH_3), 51.3 (OCH_3), 57.0 (dt, J_{CC} = 60.5 Hz, J_{CD} = 20.0 Hz, *CCD), 62.2 (OCH_2), 72.0 (NCHPh), 95.9 (NCO), 115.3 (CH=CH_2), 127.4, 127.6, 128.2 (Ph), 137.5 (CH=CH_2), 141.7 (Ph), 173.4 (d, J_{CC} = 60.5 Hz, CO); IR (film) ν 1694 (C=O) cm^{-1} (70% ^{13}C incorporation); mass spectrum (CI) $M^+ + 1$ 307, (EI) $M^+ - CH_3$ 291, $M^+ - *CO_2CH_3$ 246.

3d. From *S* carbene **1d** (50 mg, 0.1 mmol) was obtained 30 mg of (*S*,*R*)-**3d** (82% yield): ^1H NMR (300 MHz) δ 1.23 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.85 (m, 1 H, CH_2), 2.29 (m, 1 H, CH_2), 2.52 (m, 2 H, CH_2), 3.46 (d, 3 H, J_{CH} = 3.8 Hz, OCH_3), 3.68 (dd, 1 H, J = 8.2, 7.0 Hz, OCH_2), 4.16 (dd, 1 H, J = 8.2, 7.0 Hz, OCH_2), 4.46 (td, 1 H, J = 7.0 Hz, J_{CH} = 2.1 Hz, NCHPh), 7.07–7.35 (m, 10 H, Ph); ^{13}C NMR (75 MHz) 23.0 (CH_3), 28.9 (CH_3), 31.2 (dd, J_{CC} = 19.5, 17.7 Hz, *$CDCH_2$), 33.1 (CH_2), 51.3 (OCH_3), 56.9 (dt, J_{CC} = 60.7 Hz, J_{CD} = 20.2 Hz, *CD), 62.1 (OCH_2), 72.0 (NCHPh), 95.9 (NCO), 126.0, 127.4, 127.6, 128.3, 128.4, 141.6 (Ph), 173.4 (d, J_{CC} = 60.7 Hz, CO); IR (film) ν 1693 (C=O) cm^{-1} (62% ^{13}C incorporation); mass spectrum (EI) M^+ 356, $M^+ - CH_3$ 341, $M^+ - *CO_2CH_3$ 296.

Synthesis of the Unlabeled Deuterated Amino Esters 3a–d. In order to compare the data obtained with the labeled compounds, the unlabeled materials were synthesized by the same method. ^{12}C protio isotopomers for **3a,b,d** have been previously described.[5]

^{12}C Protio 3c: ^1H NMR (300 MHz) δ 1.26 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.57 (m, 1 H, CH_2), 1.92 (m, 3 H, CH_2), 3.29 (t, 1 H, J = 3.0 Hz, CCH), 3.40 (s, 3 H, OCH_3), 3.62 (dd, 1 H, J = 7.9, 7.1 Hz, OCH_2), 4.11 (dd, 1 H, J = 7.9, 7.1 Hz, OCH_2), 4.49 (t, 1 H, J = 7.1 Hz, NCHPh), 4.94 (m, 2 H, CH_2=CH), 5.70 (m, 1 H, CH=CH_2), 7.23–7.36 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 23.1 (CH_2CH_2), 28.6 (CH_3), 28.9 (CH_3), 30.9 (CH_2CHCH_2), 51.3 (OCH_3), 57.3 ($COCHCH_2$), 62.2 (OCH_2), 72.0 (NCHPh), 95.9 (NCO), 115.3 (CH=CH_2), 127.4, 127.5, 128.2, 128.7 (Ph), 137.5 (CH=CH_2), 141.6 (Ph), 173.5 (CO); IR (film) ν 1737 (C=O) cm^{-1}. ^{12}C deuterio: All of the signals are the same except ^{13}C NMR 54.6 (t, J_{CD} = 26.0 Hz, CD). Anal. Calcd for $C_{18}H_{24}DNO_3$: C, 71.03; H, 8.60; N, 4.60. Found: C, 72.04; H, 8.31; N, 4.91.

3a, ^{12}C,D: ^1H NMR (300 MHz) δ 1.10 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 3.38 (s, 3 H, OCH_3), 3.59 (dd, 1 H, J = 7.8, 7.2 Hz, OCH_2), 4.10 (dd, 1 H, J = 7.8, 7.2 Hz, OCH_2), 4.37 (t, 1 H, J = 7.2 Hz, NCHPh), 7.15–7.31 (s, 5 H, Ph); ^{13}C NMR (75 MHz) 15.0 (CH_3), 23.1 (CH_3), 28.8 (CH_3), 51.4 (OCH_3), 52.6 (t, J_{CD} = 20.6 Hz, CD), 61.7 (OCH_2), 72.2 (NCHPh), 95.9 (NCO), 126.0, 126.6, 127.5, 128.3, 141.4 (Ph), 174.4 (CO); IR (film) ν 1726 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{20}DNO_3$: C, 68.17; H, 5.30; N, 7.63. Found: C, 68.32; H, 5.24; N, 7.51.

3b, ^{12}C,D: ^1H NMR (300 MHz) δ 1.36 (s, 3 H, CH_3), 1.40 (s, 9 H, $C(CH_3)_3$), 1.52 (s, 3 H, CH_3), 1.88 (m, 1 H, CH_2CO_2tBu), 2.17 (m, 3 H, $CH_2CH_2CO_2tBu$), 3.46 (s, 3 H, OCH_3), 3.69 (dd, 1 H, J = 8.1, 7.1 Hz, OCH_2), 4.18 (dd, 1 H, J = 8.1, 7.1 Hz, OCH_2), 4.51 (t, 1 H, J = 7.1 Hz, NCHPh), 7.26–7.34 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 23.1 (CH_3), 24.5 (s, CH_2), 28.0 ($C(CH_3)_3$), 28.9 (CH_3), 31.5 (CH_2), 51.3 (CH_3O), 56.8 (m, CD), 65.8 (OCH_2), 72.0 (NCHPh), 80.4 ($C(CH_3)_3$), 95.8 (NCO), 127.5, 127.6, 128.3, 141.1 (Ph), 172.2 (CO), 173.2 (CO); IR (film) ν 1732, 1656 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{30}DNO_5$: C, 66.65; H, 8.52; N, 3.70. Found: C, 66.77; H, 8.31; N, 3.58.

3d, ^{12}C,D: ^1H NMR (300 MHz) δ 1.23 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.86 (m, 1 H, CH_2), 2.29 (m, 1 H, CH_2), 2.51 (m, 2 H, CH_2), 3.46 (s, 3 H, OCH_3), 3.70 (dd, 1 H, J = 8.1, 7.0 Hz, OCH_2), 4.16 (dd, 1 H, J = 8.1, 7.0 Hz, OCH_2), 4.48 (t, 1 H, J = 7.0 Hz, NCHPh), 7.07–7.37 (m, 10 H, Ph); ^{13}C NMR (75 MHz) 28.8 (CH_3), 29.6 (CH_3), 31.2 (CH_2CH_2Ph), 33.0 (CH_2Ph), 51.3 (CH_3O), 56.9 (t, J_{CD} = 21.0 Hz, CD), 62.0 (CH_2O), 72.0 (NCHPh), 95.9 ($C(CH_3)_2$), 126.0, 127.4, 127.6, 127.7, 128.2, 128.4, 128.9, 141.2, 141.5 (Ph), 173.3 (CO); IR (film) ν 1736 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{26}DNO_3$: C, 74.55; H, 7.96; N, 3.95. Found: C, 74.55; H, 7.77; N, 3.95.

Deprotection of (*R*)-Alanine. The labeled, protected (*R*)-alanine methyl ester **3a** (57 mg, 0.21 mmol) was dissolved in 10 mL of 0.2 N HCl in MeOH and stirred for 30 min. The solvent was removed to obtain the open-chain amino alcohol, which was dissolved in 10 mL of MeOH and 5 mL of H_2O. Sodium formate (68 mg, 1.00 mmol) and 25 mg of 10% Pd/C was added. The mixture was heated at reflux for 4 h, after which time 20 mg more catalyst was added and the mixture was refluxed overnight. After cooling, the solution was filtered to remove catalyst, the solvents were removed, and the residue was dissolved in 0.1 N HCl and washed with CH_2Cl_2. Concentration of the aqueous phase under vacuum gave a white solid. Ion exchange chromatography with Dowex 50W-X8 (H^+ form) gave 15 mg (72% yield) of the pure alanine: ^1H NMR (300 MHz, D_2O) δ 1.60 ppm; ^{13}C NMR (75 MHz, D_2O) 20.0 (dd, J_{CC} = 18.3, 16.0 Hz), 53.9 (dt, J_{CC} = 53.6, J_{CD} = 23.7 Hz, *CD), 180.0 (d, J_{CC} = 53.6 Hz, CO).

This solid was dissolved in 3 mL of THF, 60 μL of propylene oxide, and 33 μL of Mosher's acid chloride and was stirred for 30 min at room temperature and 4 h at 50 °C. The solution was filtered and the solvents were removed under vacuum. Analysis by ^{19}F NMR showed 95% de.

Synthesis of the Precursor of the Matched Peptide Ala-Ala 4. The ^{13}C-labeled *R* chiral carbene **1a** (108 mg, 0.27 mmol) and (*S*)-alanine tBu ester (obtained from the HCl salt (50 mg, 0.27 mmol) by stirring for 2 h with NEt_3 (77 μL, 0.55 mmol)) were dissolved in 30 mL of THF, deoxygenated over 5 min, and then photolyzed in a sealed tube for 24 h. Acetonitrile (10 mL) was added and the mixture was stirred for 10 min, converting the $Cr(^{13}CO)_4(THF)_2$ into the more stable $Cr(^{13}CO)_4(MeCN)_2$. The solvents were removed and the products were separated by column chromatography on silica gel. The first fraction, obtained with CH_2Cl_2/hexane (1:1), gave 26 mg of pure $Cr(^{13}CO)_4(MeCN)_2$ (40% recovery). Elution with EtOAc gave a solution that was oxidized for 30 min to remove chromium residues and filtered. Removal of the solvent under vacuum gave 72 mg (70%) of a pale yellow oil, with 88% de. **4**: ^1H NMR (300 MHz) δ 0.76 (d, 3 H, J = 7 Hz, CH_3CH), 1.25 (s, 3 H, CH_3), 1.36 (m, 3 H, CH_3*CH), 1.39 (s, 9 H, $C(CH_3)_3$), 1.45 (s, 3 H, CH_3), 3.34 (dm, 1 H, J_{CH} = 131.8 Hz, *CH), 3.85 (m, 1 H, OCH_2), 4.07 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 4.23 (m, 2 H, OCH_2, NCHPh), 7.19–7.35 (m, 5 H, Ph), 7.54 (d, 1 H, J = 6.6 Hz, NH); ^{13}C NMR (75 MHz) 14.2 (dd, J_{CC} = 19, 17.8 Hz), 17.9, 21.0, 27.7 (CH_3), 27.9 ($(CH_3)_3C$), 48.2 ($C(CH_3)H$), 54.9 (d, J_{CC} = 54.3 Hz, *CCH_3), 60.0 (OCH_2), 72.4 (NCHPh), 81.5 ($C(CH_3)_3$), 97.1 (NCO), 127.5, 128.0, 128.8, 142.8 (Ph), 168.5 (NHCO), 173.1 (d, J_{CC} = 54.3 Hz, *CO); IR (film) ν 1723 (C=O), 1629 (*C=O) cm^{-1} (70% ^{13}C incorporation); mass spectrum (CI) M + 1 379.

General Procedure for the Synthesis of Cyclobutanones, β-Lactams, Keto Esters, and Azapenams. The labeled carbene complex **2** was placed in a dry Pyrex tube and dissolved in MeCN. The solution was flushed with argon, and the substrate was added. The reaction solution was irradiated overnight. The solvent was removed under vacuum (rotary evaporation), and the residue was taken up in a mixture of ether/hexane (1:1) and air oxidized in a light box equipped with six 20-W Vitalite fluorescent lamps until most of the chromium residue had turned brown and precipitated. This suspension was filtered to remove all of the chromium residues, and a clear solution was obtained. Removal of the solvents gave oils that were purified by chromatography on silica.

Synthesis of 8-Methoxy-8-methyl-2-oxabicyclo[4.2.0]octan-7-one 5. From 52 mg of carbene **2** (0.2 mmol) and 0.1 mL of dihydro-2*H*-pyran (1.1 mmol) was obtained 32 mg (90% yield) of a colorless oil. The ^1H NMR spectrum showed an isomer ratio 7.5:1: ^1H NMR (300 MHz) δ 1.22 (dd, 3 H, J_{CH} = 7.5, 2.5 Hz, CH_3), 1.36–1.59 (m, 3 H, CH_2), 2.03 (m, 1 H, CHCO), 3.22 (m, 1 H, CH_2), 3.25 (d, 3 H, J_{CH} = 4 Hz, OCH_3), 3.58 (m, 1 H, CH_2O), 3.75 (m, 1 H, CH_2O), 3.99 (apparent quartet of doublets, 1 H, J_{CH} = 5.5, 1 Hz, $CHC(OCH_3)$; ^{13}C NMR (75 MHz) 9.3 (d, J_{CC} = 40.7 Hz, CH_3), 18.4 (CH_2CH_2O), 22.0 (CH_2CH), 53.3 (CH_3O), 55.2 (dd, J_{CC} = 30.5, 8.5 Hz, CHCO), 64.8 (CH_2O), 70.8 (dd, J_{CC} = 40.2, 7.3 Hz, CHCO), 96.9 (d, J_{CC} = 34.5 Hz, $C(OCH_3)CH_3$), 208.2 (d, J_{CC} = 34.5 Hz, C=O); mass spectrum (EI) M^+ 123.

Synthesis of 1-Benzyl-3-methyl-3-methoxy-4-phenyl-β-azetidinone 6. From 51 mg of carbene **2** (0.2 mmol) and 49 mg of PhCH=NCH_2Ph (0.25 mmol) after photolysis in CH_2Cl_2 was obtained 45 mg (79.5%) of the labeled β-lactam: ^1H NMR (300 MHz) δ 1.46 (dd, 3 H, J_{CH} = 7.2, 2.5 Hz, CH_3), 2.98 (d, 3 H, J_{CH} = 4.3 Hz, OCH_3), 3.73 (dd, 1 H, J = 14.7 Hz, J_{CH} = 2.2 Hz, NCH_2Ph), 4.12 (m, 1 H, NCH_2Ph), 4.81 (dd, 1 H, J = 14.7 Hz, J_{CH} = 3.7 Hz, CHPh), 7.03–7.31 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 17.3 (d, J_{CC} = 39.8 Hz, CH_3), 43.8 (d, J_{CC} = 5.3 Hz, OCH_3), 52.9 (CH_2Ph), 67.4 (d, J_{CC} = 33.7 Hz, CHPh), 89.0 (d, J_{CC} =

47.6 Hz, C(OCH_3)CH_3), 127.7, 128.0, 128.2, 128.4, 128.5, 128.7 (Ph), 169.2 (d, J_{CC} = 47.6 Hz, CO); IR (film) ν 1710 (C=O) cm^{-1} (62% ^{13}C incorporation); mass spectrum (EI) M^+ 283. Anal. Calcd for the unlabeled material $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.60; H, 6.70; N, 4.94.

Synthesis of (5*R,6*R*)-4-(Benzyloxycarbonyl)-6-methoxy-2,2,6-trimethyl-1,4-diaza[6,7-$^{13}C_2$]bicyclo[3.2.0]heptan-7-one (7).** The carbene complex **2** (117 mg, 0.46 mmol) was allowed to react with 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline (106 mg, 0.46 mmol) according to the general procedure. After the photolysis the residue was chromatographed (EtOAc/hexane, 1:1), obtaining first a fraction of $Cr(^{13}CO)_4(MeCN)_2$ (43%) followed by 96 mg (66%) of the desired material as a mixture of two rotamers in ratio a/b 1.6:1: ^1H NMR (300 MHz) δ 1.17 (s, 3 H, CH_3), 1.18(a)/1.28(b) (s, br, 3 H, CH_3), 1.60 (s, 3 H, OCH_3), 3.12 (d, 1 H, J_{CH} = 10.4 Hz, CH_2), 3.34(a) (d, 3 H, J_{CH} = 4.1 Hz, OCH_3), 3.47(b) (d, 3 H, J_{CH} = 3.5 Hz, OCH_3), 3.73(b) (d, 1 H, J = 10.5 Hz, CH_2), 3.76(a) (d, 1 H, J = 10.4 Hz, CH_2), 5.07–5.21 (m, 3 H, CH_2Ph, CH), 7.30–7.35 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 13.7(a) (d, J_{CC} = 40.3 Hz, CH_3), 13.5(b) (d, J_{CC} = 42.6 Hz, CH_3), 21.9 (CH_3), 25.9 (CH_3), 53.5 (OCH_3), 60.4 (CH_2), 60.7(a) (CH), 61.1(b) (CH), 67.6 (CH_2Ph), 73.9(a) (d, J_{CC} = 37.4 Hz, CH), 74.3 (d, J_{CC} = 53.5 Hz, CH), 90.6 (d, J_{CC} = 45.9 Hz, *CCH_3), 127.9, 128.1, 128.4, 128.6 (Ph), 135.7(a) (Ph), 135.9(b) (Ph), 153.3(a), 153.8(b) (CO carbamate), 173.4(a) (d, J_{CC} = 45.9 Hz, CO lactam), 173.8(b) (d, J_{CC} = 45.9 Hz, CO lactam); IR (film) ν 1771, 1708 (CO) cm^{-1}.

Synthesis of (5*S,6*R**)-6-Methoxy-2,2,6-trimethyl-1,4-diazabicyclo[3.2.0]heptan-7-one 8.** Azapenam **7** was dissolved in methanol, and a few drops of triethylamine were added. Hydrogenation over palladium on carbon (5%) at 45 psi of H_2 for 10 min, filtration through Celite, and evaporation of the solvent gave the product (41 mg, 73%): ^1H NMR (300 MHz) δ 1.08 (s, CH_3), 1.27 (dd, J_{CH} = 7.4, 2.5 Hz, *CCH_3), 1.54 (s, CH_3), 2.28 (s, br, 1 H, NH), 2.60 (d, 1 H, J = 11.2 Hz, CH_2N), 3.04 (d, 1 H, J = 11.2 Hz, CH_2N), 3.43 (d, 3 H, J_{CH} = 4.4 Hz, OCH_3), 4.71 (d, 1 H, J_{CH} = 5.0 Hz, CH); ^{13}C NMR (75 MHz) δ 14.5 (d, J_{CC} = 41.0 Hz, *(CCH_3), 21.7 (CH_3), 24.9 (CH_3), 53.5 (OCH_3), 60.9 (CH_2), 62.0 (CH_2), 77.0 (CH), 90.0 (d, J_{CC} = 43.8 Hz, *CCH_3), 175.6 (d, J_{CC} = 43.8 Hz, CO); IR (film) ν 3352 (NH), 1702 (C=O) cm^{-1} (80% ^{13}C incorporation).

Synthesis of (6*R,13*S**)-3,3,6,10,10,13-Hexamethyl-6,13-dimethoxy-1,4,8,11-tetraazacyclotetradeca-7(*E*),14(*E*)-diene-5,12-dione 9.** The azapenam **8** and 25 mg of racemic camphorsulfonic acid in CH_2Cl_2 were stirred for 30 min at 80 °C and for 2 h at room temperature. The solution was washed with aqueous 5% $NaHCO_3$ and dried over $MgSO_4$, and the solvent was evaporated to give 40 mg (78%) of a single diastereoisomer as two conformers in solution a/b 1:1. Recrystallization from CH_2Cl_2/hexane gave a single rotamer (18 mg, 45%): ^1H NMR (300 MHz) δ 1.36 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.44 (s, br, 3 H, CH_3), 3.24 (d, 3 H, J_{CH} = 4.0 Hz, OCH_3), 3.42 (d, 1 H, J = 11.6 Hz, CH_2N), 3.97 (d, 1 H, J = 11.6 Hz, CH_2N), 7.08 (s, br, 1 H, CONH), 7.53 (d, 1 H, J_{CH} = 11.0 Hz, HCN); ^{13}C NMR (75 MHz) (enriched carbons only) 81.7 (d, J_{CC} = 51.3 Hz, *CCH_3), 169.2 (d, J_{CC} = 51.3 Hz, CO); IR (KBr) ν 1676 (C=O), 1629 (CN) cm^{-1}; mass spectrum (EI) M^+ 372. Other rotamer: ^1H NMR (300 MHz) δ 1.33 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.44 (s, br, 3 H, CH_3), 3.29 (d, 4 H, J_{CH} = 4.1 Hz, OCH_3 and CH_2N), 3.96 (d, 1 H, J = 12.0 Hz, CH_2N), 7.44 (s, br, 1 H, CONH), 7.52 (d, 1 H, J_{CH} = 11.0 Hz, HCN); ^{13}C NMR (75 MHz) 81.2 (d, J_{CC} = 52.0 Hz), 169.6 (d, J_{CC} = 52.0 Hz).

Synthesis of Benzyl 4-Oxo-2-pentenoate (10). The crude product from 64 mg (0.25 mmol) of the carbene **2** and Ph_3P=$CHCO_2Bn$ (0.113 g, 0.275 mmol) in MeCN was dissolved in 10 mL of ether and 10 mL of 5% aqueous HCl solution and stirred for 5 h. The layers were separated, and the aqueous portion was washed with diethyl ether. The combined ether layers were washed with saturated NaCl and dried over $MgSO_4$. Filtration and evaporation of the solvent gave 32 mg of a yellow oil (63% yield). This was a mixture of isomers (most cis) by ^1H NMR. Preparative layer chromatography with EtOAc/hexane (1:2) allowed the separation of both isomers. The cis keto ester was stable enough to run an ^1H NMR spectrum and a short ^{13}C NMR spectrum, but when the solution in $CDCl_3$ of this compound was left for 1 h, it isomerized to the trans isomer. Cis keto ester: ^1H NMR (300 MHz) δ 2.25 (d, 3 H, J_{CH} = 6.2 Hz, CH_3), 5.12 (s, 2 H, CH_2), 5.97 (dd, 1 H, J_{CH} = J = 12.0 Hz, CHC*H*), 6.41 (ddd, 1 H, J_{CH} = 159.4 Hz, J = 12.0 Hz, J_{CH} = 1.8 Hz, CHC=O), 7.19–7.29 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 142.2 (d, J_{CC} = 49.7 Hz, *C=C), 201.6 (d, J_{CC} = 49.7 Hz, *CO). Trans keto ester: ^1H NMR (300 MHz) δ 2.28 (d, 3 H, J_{CH} = 6.0 Hz, CH_3), 5.18 (s, 2 H, CH_2), 6.64 (dd, 1 H, J = 16.3 Hz, J_{CH} = 6.0 Hz, C*H*=CH), 6.85 (ddd, 1 H, J_{CH} = 80.6 Hz, J = 16.3 Hz, J_{CH} = 3.0 Hz, C*H*CO), 7.19–7.29 (m, 5 H, Ph); ^{13}C NMR (75 MHz) 29.7 (CH_3), 67.2 (OCH_2), 128.4, 128.7, 129.6, 130.6 (Ph, C=), 140.3 (d, J_{CC} = 51.0 Hz, C=C), 164.0 (m, CO), 197.5 (d, J_{CC} = 51.0 Hz, CO); IR (film) ν 1725, 1639; mass spectrum (EI) M^+ 130.

Synthesis of $Cr(^{13}CO)_6$ from Recovered $Cr(^{13}CO)_4(MeCN)_2$. The chromium acetonitrile complex (0.221 g, 0.84 mmol) was dissolved in 25 mL of hexane in a 100-mL flask, frozen at −146 °C, degassed, and brought to 1 atm with ^{13}CO. The flask was sealed and heated at 70 °C overnight. Filtration, followed by removal of the solvent under vacuum (rotary evaporation) in an ice bath, yields 0.160 g (80% yield) of $Cr(^{13}CO)_6$. The level of ^{13}C incorporation in this material rose to 79% from 72% in the starting material, from the mass spectrum.

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