The solution was stirred at 0–5 °C for 4 h and then at room temperature overnight. The insoluble impurities were removed by filtration. The filtrate was evaporated to dryness and the residue was recrystallized from ether–hexane to give 8.7 g of the epoxide **3** (94%): mp 147–148 °C; IR (Nujol) 1725 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.67 (d, 1 H, J = 5.0 Hz, CH_2), 2.97 (d, 1 H, J = 5.0 Hz, CH_2), 3.76 (t, 1 H, J = 9.2 Hz, C-5-H), 3.83 (d, 1 H, J = 9.5 Hz, C-3-H), 3.92 (t, 1 H, J = 9.4 Hz, C-4-H), 4.01 (t, 1 H, J = 9.5 Hz, C-6-H), and 5.47 (d, 1 H, J = 10.2 Hz, C-1-H); mass spectrum, m/e 656 (M^+), 565 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{42}H_{40}O_7$: C, 76.81; H, 6.14. Found: C, 76.57; H, 6.06.

DL-2-*C*-(Acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylmyoinositol (4). The method of Posternak[17] was used for preparation of **4**. In a mixture of 3.2 mL of glacial acetic acid and 0.6 g of anhydrous sodium acetate was refluxed 400 mg of **3** (0.61 mmol) for 10 min and the mixture was cooled to room temperature. After treatment with cold water, the solid product was collected and recrystallized from absolute ethanol to give 400 mg of **4** (90%): mp 177–179 °C; IR (Nujol) 3540, 1745, 1730 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3 H, CH_3), 2.46 (s, 1 H, OH), 3.70 (d, 1 H, J = 9.2 Hz, C-3-H), 3.71 (t, 1 H, J = 9.4 Hz, C-5-H), 3.86 and 4.02 (AB q, 2 H, J = 11.0 Hz, CH_2O), 4.04 (t, 1 H, J = 10.0 Hz, C-4-H), 4.12 (t, 1 H, J = 10.0 Hz, C-6-H), 5.42 (d, 1 H, J = 9.8 Hz, C-1-H); mass spectrum, m/e 716 (M^+), 625 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.72; H, 6.19. Found: C, 73.86; H, 6.27.

DL-2-*C*-(Acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylscylloinositol (5) from *DAST* and 4. To a solution of 0.2 mL of diethylaminosulfur trifluoride[1] (ca. 1.2 mmol) in 5 mL of methylene chloride at 0–5 °C under nitrogen was added a solution of 190 mg of **4** (0.27 mmol) in 5 mL of methylene chloride. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was purified via preparative TLC using 2000-μm silica gel plates developed twice with 20% acetone in hexanes. Rearrangement product **5** (95 mg) was obtained in 50% yield. An analytical sample was recrystallized from EtOH–hexane (1:4): mp 113–115 °C; IR (Nujol) 3480, 1740, 1725 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 3 H, CH_3), 3.08 (s, 1 H, OH), 3.70 (d, 1 H, J = 9.3 Hz, C-3-H), 3.75 (t, 1 H, J = 9.0 Hz, C-5-H), 3.81 (t, 1 H, J = 9.0 Hz, C-4-H), 3.90 (t, 1 H, J = 9.0 Hz, C-6-H), 4.37 and 4.55 (AB q, 2 H, J = 11.7 Hz, CH_2O), 5.40 (d, 1 H, J = 10.0 Hz, C-1-H); mass spectrum, m/e 716 (M^+), 625 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.72; H, 6.19. Found: C, 73.64; H, 6.21.

DL-1-*O*-Benzoyl-2-methylene-2-deoxy-3,4,5,6-tetra-*O*-benzylmyoinosose-2 (6). To a mixture[11] of 0.42 g of sodium acetate and 1.26 g of sodium iodide in 3.3 mL of 90% aqueous acetic acid at 0–5 °C was added 1.2 g of zinc dust with stirring followed by dropwise addition of a solution of 1.0 g of **3** (1.52 mmol) in 8.0 mL of tetrahydrofuran and 2.0 mL of acetic acid. The mixture was stirred vigorously for 1 h and filtered at low temperature. The solid residue was washed thoroughly with tetrahydrofuran. The combined filtrate and THF washing solution were concentrated in vacuo and the residue was purified via preparative TLC using 2000-μm silica gel plates developed with 25% ethyl acetate in hexanes. The purified product was further recrystallized from methanol–chloroform to yield 720 mg of **6** (74%): mp 141–143 °C; IR (Nujol) 1720 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.52 (t, 1 H, J = 9.4 Hz, C-5-H), 3.65 (t, 1 H, J = 9.0 Hz, C-4-H), 3.76 (t, 1 H, J = 9.0 Hz, C-6-H), 4.07 (d, 1 H, J = 9.4 Hz, C-3-H), 5.19 (d, 1 H, J = 1 Hz, CH_2=), 5.39 (d, 1 H, J = 1 Hz, CH_2=), 5.59 (d, 1 H, J = 9.6 Hz, C-1-H); mass spectrum, m/e 640 (M^+), 549 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{42}H_{40}O_6$: C, 78.72; H, 6.29. Found: C, 78.51; H, 6.26.

DL-1-*O*-Benzoyl-2-*C*-(hydroxymethyl)-3,4,5,6-tetra-*O*-benzylscylloinositol (7). To a stirred solution of 64 mg of **6** (0.1 mmol) in 3.0 mL of pyridine was added a solution of 240 mg of osmium tetroxide (0.95 mmol) in 6.0 mL of ether. After 2 h the reaction mixture was treated with 3 g of sodium bisulfite in 15 mL of water and 5 mL of pyridine. The resulting mixture was allowed to stand at room temperature overnight. The crude product was extracted with methylene chloride and purified via preparative TLC using a 1500-μm silica gel plate developed with 30% ethyl acetate in hexanes. The purified product was further recrystallized from aqueous ethanol–hexane to give 41 mg of **7** (75%): mp 135–136 °C; IR (Nujol) 3550, 3470, 1700 cm^{-1}; NMR (300 MHz, C_6D_6) δ 2.53 (dd, 1 H, J = 9.3, 4 Hz, primary OH), 3.36 (s, 1 H, tertiary OH), 3.56 (t, 1 H, J = 9.3 Hz, C-5-H), 3.57 (d, 1 H, J = 9.6 Hz, C-3-H), 3.76 (t, 1 H, J = 9.2 Hz, C-4-H), 3.80 (t, 1 H, J = 10.2 Hz, C-6-H), 3.90 and 3.98 (AB q, 1 H, J = 11.8 Hz, CH_2–O), 3.91 and 4.01 (AB q, 1 H, J = 11.2 Hz, CH_2–O), 5.79 (d, 1 H, J = 10.0 Hz, C-1-H); NMR (300 MHz, $CDCl_3$) δ 3.93 (t, 1 H, J = 11.0 Hz, C-6-H), 4.04 (dd, 1 H, J = 12.0, 2 Hz C-3-H), 5.49 (d, 1 H, J = 10.2 Hz, C-1-H) (the rest of the ring protons appeared at 3.60–3.80 ppm and were unassigned); mass spectrum, m/e 674 (M^+), 583 ($M^+ - CH_2Ph$). Anal. Calcd for $C_{42}H_{42}O_8 \cdot {}^1/_3H_2O$: C, 74.09; H, 6.32. Found: C, 74.03, H, 6.18.

DL-2-*C*-(Acetoxymethyl)-1-*O*-benzoyl-3,4,5,6-tetra-*O*-benzylscylloinositol (5) from Monoacetylation of 7. To a solution of 35 mg of **7** (0.05 mmol) in 0.5 mL of pyridine at 0–5 °C was added 0.1 mL of acetic anhydride. The mixture was stirred at room temperature for 3 h and then treated with water (0.1 mL). After removal of volatile solvents in high vacuum, the residue was recrystallized from ethanol–hexane to give 25 mg of **5** (60%): mp 113–115 °C; NMR and mass spectra were identical with those of the rearrangement product **5** (see above). Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.72; H, 6.19. Found: C, 73.44; H, 6.19.

DL-1-*O*-Benzoyl-2-*C*-(hydroxymethyl)-3,4,5,6-tetra-*O*-benzylmyoinositol (8). To a solution of 1.2 g of **3** (1.83 mmol) in 45 mL of dioxane was added dropwise 1.5 mL of 1 N H_2SO_4. The resulting solution was heated at 100 °C for 3.5 h, cooled to room temperature, and poured into 40 mL of cold 5% sodium bicarbonate solution. After removal of dioxane in vacuo, the aqueous mixture was extracted with chloroform (2 × 50 mL). The organic layer was washed with water and brine and dried (Na_2SO_4). Removal of solvent gave the crude product which was recrystallized consecutively from ethanol, ethanol–hexanes, and ether–hexane to give 0.78 g of pure **8** (63%): mp 152.5–153.5 °C; IR (Nujol) 3560, 3540, 1703 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.27 (d, 1 H, J = 1 Hz, C-2-OH), 3.13 (dd, 1 H, J = 10.2, 5.0 Hz, CH_2–O), 3.28 (dd, 1 H, J = 11.6, 5.0 Hz, CH_2–O), 3.54 (dd, 1 H, J = 11.5, 10.2 Hz, primary OH), 3.65 (t, 1 H, J = 9.6 Hz, C-5-H), 3.88 (d, 1 H, J = 9.5 Hz, C-3-H), 4.01 (t, 1 H, J = 9.8 Hz, C-4-H), 4.22 (t, 1 H, J = 9.8 Hz, C-6-H), 5.23 (d, 1 H, J = 10.0 Hz, C-1-H). Anal. Calcd for $C_{42}H_{42}O_8$: C, 74.76; H, 6.28. Found: C, 74.99; H, 6.23.

Epoxidation of 6 with *m*-Chloroperbenzoic Acid. To a refluxing solution of 40 mg of **6** (0.06 mmol) in 1.0 mL of chloroform was added 12.0 mg of *m*-chloroperbenzoic acid (large excess) in portions until the epoxidation was complete. The mixture was poured into excess cold sodium bicarbonate solution. Extraction of the aqueous mixture with chloroform gave the crude product which was purified via preparative TLC to give 41 mg of pure epoxide (98%). The physical data were identical with those of **3**.

Acknowledgment. We thank Dr. T. Y. Shen and Dr. B. H. Arison for helpful discussions and Messrs. J. L. Smith, J. P. Gilbert, and H. Flynn for their technical assistance.

(17) T. Posternak, *Helv. Chim. Acta*, **27**, 457 (1944).

An Example of an *N*-Acetyl Group More Labile to Methanolic Hydrogen Chloride than an Analogous *N*-*tert*-Butoxycarbonyl Group. β-Acetyl- and β-[[(Alkoxycarbonyl)amino]oxy]-α-*N*-acetyl-D-alanine Butylamides

John Charles Howard

Department of Cell and Molecular Biology, Medical College of Georgia, Augusta, Georgia 30912

Received July 21, 1980

During a recent study of the acylation of bovine serum albumin (BSA) with diacetylcycloserine (D-2-acetyl-4-acetamido-3-isoxazolidone, **1**) it was found that the ε-amino groups of lysine were not only acylated via ring opening

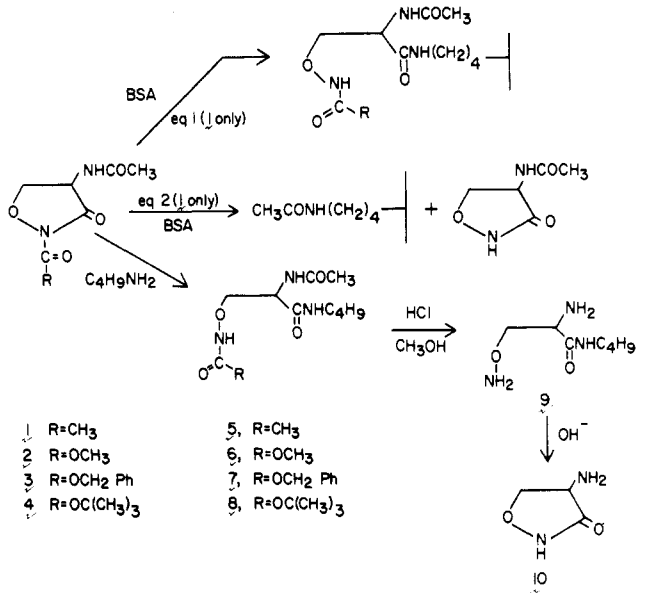
0022-3263/81/1946-1720$01.25/0

Table I. Yields and Physical Data

compd	% yield	mp, °C (cryst solv)	$[\alpha]^{25}_D$, deg (c, DMF)	formula[a]
2	61	131-132 ($CHCl_3$)	+52 (10)	$C_7H_{10}N_2O_5$
3	28	107-108 (EtOH)	+37 (10)	$C_{13}H_{19}N_2O_5$
4	34	85-86 (EtOAc)	+48 (10)	$C_{10}H_{16}N_2O_5 \cdot 0.25H_2O$[b]
6	93	128-129 (EtOAc)	+27 (3)	$C_{11}H_{21}N_3O_5$
7	97	143-144 (H_2O)	+20 (10)	$C_{17}H_{25}N_3O_5$
8	92	124-125 (EtOAc/ether)	+18 (7)	$C_{14}H_{27}N_3O_5$

[a] Satisfactory analytical data (±0.4%) for C, H, and N were reported for all compounds listed in the table. [b] Calcd for $C_{10}H_{16}N_2O_5 \cdot 0.25H_2O$: C, 48.29; H, 6.69; N, 11.18. Found: C, 48.28; H, 6.74; N, 11.26. This result is the average of single analyses for eight different samples. The SD for C was 0.26, for N, 0.10. Calcd for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60; N, 11.47.

Scheme I



of 1 to form diacetyl β-(aminooxy)alanyl amides (Scheme I, eq 1) but also were simply acetylated (eq 2).[1] This result was a disappointment because a sensitive method had been developed for the analysis of diacetyl β-(aminooxy)alanyl residues and it was hoped that the reaction would proceed entirely by the ring opening route, as had been indicated by the reaction of 1 with hydroxide ion and butylamine.[2] In an attempt to achieve this specificity consideration was given to the synthesis of compounds similar to 1 but which would have the ring acetyl group replaced by a function more likely to promote ring opening in reactions with amine groups. Replacement with an alkoxycarbonyl group was an obvious choice, suggested by the use of carbonic esters in the mixed anhydride method of peptide synthesis.[3] 2-(Methoxycarbonyl)- (2), 2-[(benzyloxy)carbonyl]- (3), and 2-(*tert*-butoxycarbonyl)-4-acetamido-3-isoxazolidones (4) were prepared from the corresponding alkoxycarbonyl chlorides and transformed by reaction with butylamine to the corresponding α-*N*-acetyl-β-[[(alkoxycarbonyl)amino]oxy]-D-alanyl butylamines 6, 7, and 8 (Scheme I and Table I), which were used as models for lysine residues acylated with the diacyl-β-(aminooxy)-D-alanyl group. These compounds were then subjected to the analytical method mentioned above, which had been developed by using diacetyl-β-(aminooxy)-D-alanine butylamide (5), the product of 1 and butylamine.[1,2] In this method the acetyl groups were first removed by 3% HCl in methanol at 65 °C for 10 min. The resulting β-(aminooxy)-D-alanine butylamide[4] (9) was then cyclized to cycloserine (10) which was measured colorimetrically (Scheme I). Conversions of (5) to cycloserine were consistently carried out with average overall yields of 46.6% and a standard deviation (SD) of 0.7%. Unexpectedly, both 6 and 7 gave no detectable cycloserine under these methanolysis conditions, indicating that the methoxycarbonyl and (benzyloxy)carbonyl groups were not being removed. Maximum cycloserine yields of 20–25% for both compounds were obtained after 3–4 h at 60–65 °C in 3–6% methanolic HCl by varying the methanolysis conditions. Under the original conditions the *tert*-butoxycarbonyl derivative (8) was converted to cycloserine in 29–31% yield. Consistent yields of 45.5% (SD 0.7%) were obtained by reducing the concentration of HCl to 0.16% and increasing the reaction time to 3 h at 61 °C. Since this result was almost identical with the value obtained with 5 under the original conditions four methanolyses of 5 were carried out under conditions optimal for 8. The average yield of cycloserine was 53% (SD 0.9%), clearly demonstrating that the acetyl group was removed more efficiently than the *tert*-butoxycarbonyl function.[5] The methanolysis rates for 5 and 8 were also compared. The results (Table II) showed that in 30 min twice as much 5 as 8 had undergone methanolysis.

Table II. Influence of Reaction Time on the Conversion of α-*N*-Acetyl-β-acetyl- and α-*N*-Acetyl-β-[[(*tert*-butoxycarbonyl)amino]oxy]-D-alanine Butylamides (5 and 8) by 0.16% HCl in Methanol to β-(Aminooxy)-D-alanine Butylamide (9) as Measured by the Conversion of 9 to Cycloserine (10)

compd[a]	time, min	% yield
5	30	41
5	60	50
5	120	52
5	180	53
8	30	18
8	60	38
8	120	45
8	180	47

[a] 1.85 μmol of 5 and 1.91 μmol of 8 were used.

When the methoxycarbonyl (6) and (benzyloxy)carbonyl (7) derivatives were subjected to methanolysis and subsequent ring closure under conditions optimal for 8, cycloserine yields of only 2% were obtained.

(1) Howard, J. C. *Int. J. Peptide Protein Res.* **1977**, *9*, 75.
(2) Howard, J. C.; McPherson, J. C., Jr.; Chuang, A. H. L. *J. Med. Chem.* **1974**, *17*, 236.
(3) Bodansky, M.; Klausner, Y. S.; Ondetti, M. A. "Peptide Synthesis", 2nd ed.; Wiley-Interscience: New York, 1976; pp 92–93.
(4) This compound is a viscous liquid which was characterized (ref 1) as an oxalate which contained 2.5 mol of oxalic acid and 1 mol of H_2O. We have since further characterized 9 by reconverting it to 5 in 71% yield by treatment with acetic anhydride in CH_3OH.
(5) It should be noted that the results of all methanolysis experiments are given in terms of the cycloserine (10) measured in the analytical method. Since it is known that the conversion of 9 to 10 proceeds in approximately 63% yield,[1] the optimum yields of 9 in the methanolysis reactions alone can be calculated to be 84% from 5 and 72% from 8.

These results are interesting because thay show that the acetyl group linked to the β-aminooxy residue of **5** is somewhat more easily removed by methanolysis than the *tert*-butoxycarbonyl of **8**, and much more easily removed than the methoxycarbonyl and (benzyloxy)carbonyl groups of **6** and **7**. This is at first surprising in that the *tert*-butoxycarbonyl group and to a lesser extent the (benzyloxy)carbonyl function are useful protective groups *because* of their acid lability.[6] It may be, however, that the rate of cleavage of an *N*-alkoxycarbonyl group is more dependent than an *N*-acetyl moiety on the basicity of the nitrogen to which it is linked. If this is true one would expect a more sluggish acid-catalyzed cleavage of the *N*-alkoxycarbonyl from the weakly basic hydroxylamine nitrogen than (for example) from the more basic α-amino nitrogen of an amino acid.[7] Some support for this explanation was obtained by the finding that **8** was not cleaved by trifluoroacetic acid (TFA) under conditions normally used for removal of the *N*-*tert*-butoxycarbonyl group.[8]

The removal of both acetyl groups from **5** under relatively mild conditions suggests that in circumstances where the esterification conditions characteristic of methanolic HCl are not objectionable, the acetyl group, one of the first protective groups,[9] may still be used to advantage.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 137-B spectrophotometer and visible spectra on a Cary 14 instrument. Melting points were observed in a calibrated Mel-Temp apparatus. Specific rotations were measured with a Rudolph Model 80 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Methyl and benzyl chloroformates and potassium *tert*-butoxide were purchased from Aldrich Chemical Co. and methyl chloroformate was distilled before use. Tetrahydrofuran (THF) was either distilled from $LiAlH_4$ or was Aldrich Gold Label grade. Dimethylformamide (DMF) was dried over CaO, distilled in vacuo, and stored over 4-Å molecular sieves. D-Cycloserine was purchased from Sigma and butane and phosgene from Matheson. Other chemicals were reagent grade and used without further purification unless specifically noted.

***tert*-Butoxycarbonyl Chloride.** The following rather detailed description of this useful compound is essentially the method of Carpino and co-workers[10] which is based on the original method of Choppin and Rogers.[11] **It is essential that all operations be carried out in a good hood.** A three-necked flask fitted with an efficient stirrer, low-temperature thermometer, and Drierite (anhydrous calcium sulfate) tube was placed in a dry ice–acetone bath and to it were added approximately 35 mL (0.51 mol) of liquid phosgene (previously collected in a cold-finger condenser and stored overnight in a Dewar flask of dry ice in the hood) and 150 mL of *n*-butane (also previously collected and stored overnight at −25 °C). To the rapidly stirred solution at −70 to −75 °C was added, in increments over 2 h, 33.0 g (0.29 mol) of potassium *tert*-butoxide via Gooch tubing attached to an Erlenmeyer flask. The mixture was stirred for an additional 2 h at −70 to −75 °C and then was filtered through a 350-mL medium-porosity fritted-glass funnel which contained a 0.5-in. layer of diatomaceous earth which had been dried at 100 °C. During the filtration and subsequent washing the contents of the funnel were protected from moisture by a 1-hole, size 15 rubber stopper equipped with a Drierite tube. The filter flask was chilled in a dry ice–acetone bath. The precipitated KCl was washed with liquid *n*-butane and the filtrate and washings were evaporated in an ice–salt bath to about 50 mL in a rotary evaporator. Evaporation was stopped when the pressure (water pump) dropped to about 60 mm. The residue was transferred to a 50-mL flask equipped with a side-arm ebullator and 14/35 joint (Ace Glass, Inc., 9478-92) and distilled in vacuo through a "trap to trap" apparatus (Ace, 7794), equipped with a receiver (Ace, 9477-703) and trap, both surrounded by dry ice–acetone baths. The distillation flask was placed initially in an ice bath, and distillation was started with water-pump vacuum to remove any residual phosgene. The ice bath was then removed and the distillation was continued with the vacuum pump (0.5 mm). The distillate weighed 24 g (61%); IR (CS_2) 1750 cm^{-1} (CO). The product showed no evidence of decomposition after 2 months storage at −25 °C.

α-*N*-Acetyl-D-cycloserine. To 10.2 g (0.100 mol) of D-cycloserine suspended with stirring in 500 mL of methanol was dropwise added in 10 min 10.1 mL (0.106 mol) of acetic anhydride. Stirring was continued for 2 h after addition; a cloudy solution resulted. This was filtered, the filtrate was evaporated in vacuo, and the residue was recrystallized from 165 mL of ethanol to yield 9–10 g (63–69%) of colorless crystals: mp 178–180 °C (lit.[12] mp 175–177 °C); IR (mull) 1700, 1620 cm^{-1} (CO).

2-(Alkoxycarbonyl)-4-acetamido-3-isoxazolidones (2–4). The procedure described below for the *tert*-butoxycarbonyl derivative (**4**) is typical of the general method. To a three-necked flask equipped with stirrer, thermometer, and Drierite tube were added 400 mL of dry THF and 28 mL (0.20 mol) of triethylamine (TEA). To this was slowly added 16.3 g (0.113 mol) of α-*N*-acetyl-D-cycloserine and the suspension cooled to −4 °C. The flask was then fitted with an ice-cooled addition funnel containing a cold solution of 24 g (0.18 mol) of *tert*-butoxycarbonyl chloride in 100 mL of CH_2Cl_2. This was dropwise added to the flask at −3 to −5 °C over 1.5 h; stirring at 0 to −3 °C was continued for an additional 1.5 h. The contents were then filtered to remove the HCl salt of TEA and the filtrate was evaporated in vacuo in a warm-water bath. The viscous liquid residue was dissolved in CH_2Cl_2, washed with 0.6 M $NaHCO_3$ and then H_2O, and finally dried ($MgSO_4$). Evaporation of the solvent in vacuo left 28 g of pale golden viscous liquid which, after storage for several days at 25 °C, slowly crystallized when stirred with 25 mL of EtOAc. Repeated crystallizations from EtOAc gave 9.4 g (34%) of colorless crystals: mp 85–86 °C; IR (mull) 3500 (H_2O), 1770, 1730, 1670 cm^{-1} (CO). This compound is unusual in that it crystallizes with about 0.25 mol of H_2O. This was established by repeated elemental analyses, loss of weight on heating, and formation (by heating at 78 °C) of a glass which had lost the crystalline compound's water of crystallization peak at 3500 cm^{-1}. Dissolving this glass in 95% EtOH which was then completely evaporated resulted in recovery of the original hydrate as identified by infrared spectrum and melting point.

α-*N*-Acetyl-β-[[(alkoxycarbonyl)amino]oxy]-D-alanine Butylamides (6–8). These were prepared by the addition of excess butylamine in THF or ether to a suspension of **2**, **3**, or **4** in the same solvent. Some product precipitated during the reaction, and the remainder was recovered by evaporation in vacuo followed by crystallization from an appropriate solvent (Table I).

Methanolysis of α-*N*-Acetyl-β-[[(*tert*-butoxycarbonyl)amino]oxy]alanine Butylamide (8). The following method gave optimum yields with both **5** and **8**. In the yield vs. reaction time experiment samples were removed and evaporated at the designated times (Table II). To each of seven centrifuge tubes (Kontes K-288250) was added 0.100 mL of methanol which contained 1.78 μmol of **8**. To this solution was added 0.50 mL of 0.19% HCl in methanol (prepared by the addition of 0.15 mL of acetyl chloride to 40 mL of methanol). The tubes were stoppered, secured with rubber bands, and placed in a water bath at 61 °C for 180 min. The methanol and HCl were then removed by evaporation in a nitrogen stream at 61 °C and 0.50 mL of 4 N NaOH was added to each tube. The tubes were stoppered and returned to the water bath (65 °C) for 30 min with frequent tipping to wet the sides of the tubes. They were then cooled and 3.4 mL of 3 M acetic

(6) Reference 3, pp 22, 25–31.
(7) The p*K*'s of the amino groups of alanine and *O*-methylhydroxylamine are 9.97 and 4.60, respectively (Albert, A.; Serjeant, E. P. "Ionization Constants of Acids and Bases"; John Wiley and Sons: New York, 1962; p 148, 153).
(8) Krundieck, C. L.; Baugh, C. M. *Biochemistry* **1969**, *8*, 1568.
(9) Bergmann, M.; Koster, H.; Witte, C. *Justus Liebigs Ann. Chem.* **1926**, *449*, 277.
(10) Carpino, L. A.; Parameswaran, K. N.; Kirkley, R. K.; Spiewak, J. W.; Schmitz, E. *J. Org. Chem.* **1970**, *35*, 3291.
(11) Choppin, A. R.; Rogers, J. W. *J. Am. Chem. Soc.* **1948**, *70*, 2967.
(12) Kuehl, F. A. U.S. Patent 2 845 432, 1958; *Chem. Abstr.* **1958**, *52*, 20198*d*.

acid was added, followed by 1.00 mL of "color reagent" prepared immediately before use by mixing equal volumes of 4% sodium nitroprusside and 4 N NaOH. The tubes were shaken and stored for 25 min, and the absorbance was measured at 625 nm. The reference cell contained a solution prepared from 0.50 mL of 4 N NaOH, 3.4 mL of 3 M acetic, and 1.00 mL of color reagent. Absorbance readings were converted to micromoles of cycloserine by use of a standard curve.[1] The average yield of two separate experiments (14 tubes) was 45.5% (SD 0.70). That the product of the ring-closure reaction was cycloserine and not α-*N*-acetycycloserine (which also gives the same color reaction) was established by TLC on unactivated silica gel sheets (Eastman), using propanol/H_2O (5:1, v/v) as solvent. Compounds were visualized as blue spots by spraying with a solution of 14 mL of 3 M acetic acid and 2 mL of 4 N NaOH to which was added directly before spraying a solution of 2 mL of 4 N NaOH and 4 mL of 4% sodium nitroprusside, mixed immediately before use.

Attempted Cleavage of 8 with TFA. To each of six centrifuge tubes was added 100 μL of a methanol solution containing 606 μg (1.91 μmol) of **8**. The solvent was evaporated and 0.20 mL of a 25% (v/v) solution of freshly distilled TFA in CH_2Cl_2 was added to each tube. The tubes were stored at room temperature and at successive 30-min intervals the contents of a tube was evaporated by a stream of nitrogen. When this process had been completed the contents of the tubes were analyzed by the NaOH–sodium nitroprusside method described above. No color was obtained. TLC analysis of the reaction products after treatment with TFA showed no differences from **8**.

Registry No. **1**, 51541-28-7; **2**, 75975-46-1; **3**, 75975-47-2; **4**, 75975-48-3; **5**, 51541-31-2; **6**, 75975-49-4; **7**, 75975-50-7; **8**, 75975-51-8; **9**, 62214-22-6; **10**, 68-41-7; *tert*-butoxycarbonyl chloride, 24608-52-4; D-cycloserine, 51541-30-1; butylamine, 109-73-9.

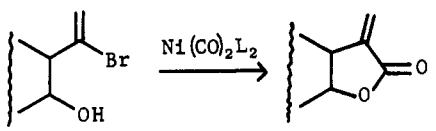
Intramolecular Carbonylation of Vinyl Halides To Form Methylene Lactones

M. F. Semmelhack*[1] and Steven J. Brickner

Baker Laboratory, Cornell University, Ithaca, New York 14853

Received June 23, 1980

Sesquiterpene α-methylene lactones continue to serve as stimuli for testing of new strategies for organic synthesis.[2] We have been interested in construction of the α-methylene lactone functionality by use of selective transition-metal-mediated methods.[3,4] For application in a specific synthesis project, we have developed an intramolecular carbonylation procedure (e.g., eq 1) which is



(1)

general and efficient.[5] This process is a variation of the base-promoted carboxylation of vinyl and aryl halides using nickel carbonyl which was discovered by Corey and Hegedus.[6-8] Here we report the formation of five- and six-membered lactones with a convenient nickel reagent and preliminary applications in a two-step cyclization–carbonylation procedure.

A test case is 2-bromo-5-hydroxy-1-pentene (**1**). In direct analogy with the alkoxide-promoted reaction,[6] we first used sodium hydride or *n*-butyllithium to generate the alkoxide. Then, reaction with nickel carbonyl proceeded slowly in tetrahydrofuran, giving carbonylation products **7** (see Chart I) in 20–50% yield after 0.5–1.0 h at 60 °C. Isomerization of the double bond to an endocyclic position was significant using sodium hydride (Table I, entry 1).[9] In

Table I. Carbonylation/Lactonization of 1–6

entry	substr	conditions[a]	product (yield, %)
1	1	$Ni(CO)_4$, NaH, 48 °C, 12 h	7 (25)[b,g]
2	1	$Ni(CO)_4$, BuLi, 59 °C, 1 h	7 (50)
3	1	$Ni(CO)_2L_2$[c], BuLi, 51 °C, 24 h	7 (42)
4	1	$Ni(CO)_4$, reflux, 1.1 h	7 (48), 9 (36)[h]
5	1	$Ni(CO)_4$, 55 °C, 112 h	7 (97),[d] 9 (3)
6	1	$Ni(CO)_2L_2$, 52 °C, 3 h	7 (64), 9 (7)
7	1	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 2 min	7 (64), 9 (0)
8	2	$Ni(CO)_4$, reflux, 1 h	8 (54),[i] 10 (28)[h]
9	2	$Ni(CO)_2L_2$, reflux, 1 h	8 (52), 10 (17)
10	2	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 5 min	8 (55)
11	3	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 1 min	11 (76)[j]
12	4	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 1 min	12 (76–80)[j]
13	4	$Ni(CO)_4$, Et_3N,[e] benzene, 50 °C, 2 h	12 (95)
14	5	$Ni(CO)_4$, Et_3N,[e] benzene, 50 °C, 2 h	13 (96)[f]
15	5	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 2 min	13 (56)
16	6	$Ni(CO)_2L_2$, Et_3N,[e] reflux, 2 min	14 (51)

[a] The solvent is THF unless otherwise noted. $Ni(CO)_4$ is used in 6-fold molar excess, and $Ni(CO)_2L_2$ is used in 1.1- to 2-fold molar excess. [b] The product consists of the *exo*-methylene product **7** and the corresponding endocyclic isomer in a ratio of 2:5. [c] L symbolizes triphenylphosphine. [d] Conversion was 57%. [e] Two molar equivalents with respect to vinyl bromide. [f] Conversion was 90%. [g] A. D. Harmon and C. R. Hutchinson, *J. Org. Chem.*, **40**, 3474 (1975). [h] J. Falbe, N. Hupper, and F. Korte, *Chem. Ber.*, **97**, 863 (1964). [i] C. R. Hutchinson, *J. Org. Chem.*, **39**, 1845 (1974). [j] J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).

(1) Fellow of the John Guggenheim Foundation, 1978–1979. Address correspondence to this author at the Frick Chemistry Laboratory, Princeton University, Princeton, NJ 08540.

(2) For recent examples and leading references, see: (a) F. Kido, K. Tsutsumi, A. Maruta, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **101**, 6420 (1979); (b) R. H. Schlessinger and coworkers, *ibid.*, **101**, 7626, 7627 (1979).

(3) M. F. Semmelhack and E. S. C. Wu, *J. Am. Chem. Soc.*, **98**, 3384 (1976).

(4) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and K. Hirotsu, *J. Am. Chem. Soc.*, **100**, 5565 (1978).

(5) A portion of this work was presented at the 178th National Meeting of the American Chemical Society, Washington, DC; Abstract ORGN 98.

(6) E. J. Corey and L. Hegedus, *J. Am. Chem. Soc.*, **91**, 1233 (1969).

(7) An efficient palladium-promoted carbonylation procedure which effects conversions parallel with that represented in eq 1 has been discovered by Norton, Shenton, and Schwartz [*Tetrahedron Lett.*, 52 (1975)] and developed by Norton and co-workers: T. F. Murray and J. R. Norton, *J. Am. Chem. Soc.*, **101**, 4107 (1979).

(8) (a) Closely related results were reported after this work was largely complete: I. Matsuda, *Chem. Lett.*, 773 (1978). (b) An equivalent transformation has been carried out on hydroxyvinyl bromides related to **3** and **4** in methyl alcohol, producing the corresponding hydroxy esters which were induced to lactonize: R. K. Boeckman and M. Ramaiah, *J. Org. Chem.*, **42**, 1583 (1977).

(9) The yields quoted are of material purified by short-path distillation or sublimation. The difference between the yield of a component in the crude product mixture and of isolated product is often significant for these easily polymerized compounds.

0022-3263/81/1946-1723$01.25/0