An Approach to the Synthesis of Neplanocin A

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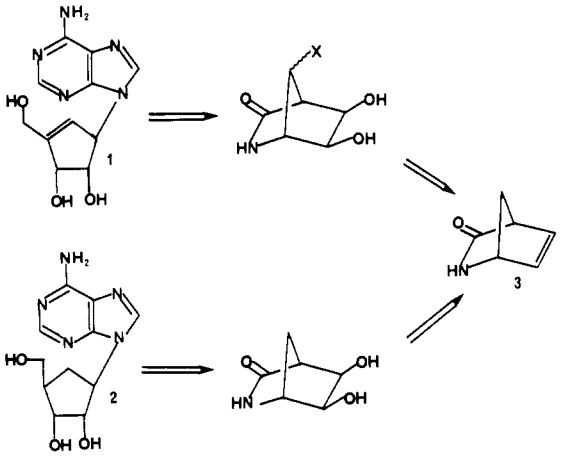
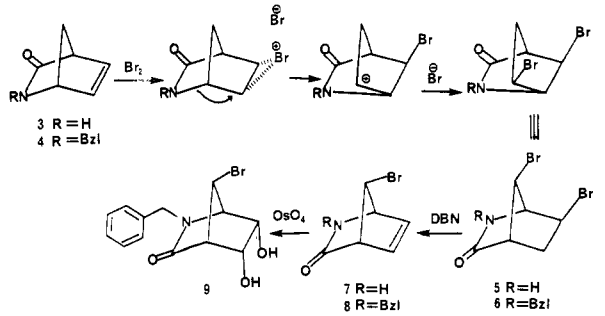
Neplanocin A (**1**), an unsaturated carbocyclic analogue of adenosine with potent antitumor activity in mice and low toxicity, was isolated from *Ampullariella regularis*.[1] The saturated analogue aristeromycin (**2**) which was first synthesized[2a] and then isolated[3] also has potent biological activity. Aristeromycin (**2**) has been synthesized efficiently from **3**[2b,c] which is readily available from the cycloadduct of cyclopentadiene and tosyl cyanide.[2b,c,4] We chose to develop an approach to **1** modeled after the conversion of **3** to **2** with an oxidation step inserted early in the sequence to provide the desired double bond of **1**. Since this work was initiated, three syntheses of neplanocin A have been reported.[5]



Treatment of **3** with bromine in CH_2Cl_2 gave **5** in 75% yield. Nitrogen participation in the rearrangement is well precedented in similar systems.[6] All attempts to convert **5** to **7** were unsuccessful. For increased solubility and prevention of participation of the amide anion, lactam **3** was benzylated with KOH and benzyl bromide in Me_2SO and gave **4** in 71% yield. Bromination of **4** as above gave **6** in quantitative yield. In contrast to **5**, **6** underwent facile dehydrobromination at 120 °C in DBN to give **8** in 70% yield.

Hydroxylation of **3** with osmium tetroxide or potassium permanganante in the aristeromycin syntheses leads selectively to the exo diol.[2b,c] Exo hydroxylation of **8** was expected to be more problematical since the bromine restricts access to the exo face. However, the benzyl group may restrict access to the endo face and epoxidation of 7-*syn*-bromonorbornene gives a 1:1.8 mixture of exo and endo epoxides.[7] Hydroxylation of **8** with catalytic OsO_4



and *N*-methylmorpholine *N*-oxide[8] gave a 62% yield of a single diol. The 500-MHz NMR spectrum indicated that the protons α to the hydroxyl groups absorb as a broad AB quartet (J = 6 Hz, $\nu = \delta$ 4.82, $\Delta\nu$ = 0.04 ppm). The absence of large couplings between H_1 and H_6 and H_4 and H_5 suggested that the diol was exo since Anet has shown that the coupling constants $J_{3,4}$ are 0 and 4.4 Hz in *exo,exo*- and *endo,endo*-1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-diol, respectively.[9,2c] This evidence was hardly convincing.

The structure of the diol **9** was therefore established by X-ray crystallography. The molecular structure is shown in Figure 1, from which it is apparent that the stereochemistry of the hydroxyl groups is endo. *syn*-7-Bromonorbornene which gives a mixture of epoxides is not a good model for **8**. Apparently, the planar amide is much less effective at blocking the endo face of the double bond than the CH_2CH_2 bridge in norbornene.

The crystal structure consists of isolated molecules interconnected by C=O···H—O hydrogen bonds as well as disordered $CDCl_3$ solvate molecules. The atomic coordinates, bond lengths and angles, and torsion angles are given in the supplementary material section. A comparison of this structure with those of four similar bicyclic lactams containing a 6-exo-OR substituent studied by Ammon et al.[10] reveals no unusual bond lengths or angles. Torsion angles are similar to those reported for the exo-substituted bicyclic lactams described in ref 10. Owing to the cis arrangement of the hydroxyl groups there is a twist of −3.93° about the C_5–C_6 bond. The C_7–C_1–N and C_7–C_4–C_3 angles are approximately 2° smaller than those in ref 10. The values for the title compound are 97.4 (9)° and 97.2 (9)°, while the averages for the four compounds in ref 10 are 99.95° and 101.55°. This decrease may be due to nonbonded contacts between the three oxygen atoms or to differences in packing.

Diol **9** is useless for the synthesis of neplanocin A. Attempted hydroxylation of **8** from the most hindered face by the Woodward–Prevost reaction was unsuccessful. The procedure of Corey and Das[11] could not be explored since the bromohydrin could not be prepared cleanly. Inversion of the stereochemistry at C_7 would lead to a substrate which would undergo exo hydroxylation with OsO_4. Unfortunately **8** did not react with phenyl selenide or other reactive nucleophiles. These results suggest that this approach will not be useful for the synthesis of neplanocin A. The double bond of **8** is not very reactive because of the three electron-withdrawing substituents, and the bromide of **8** exhibits the typical unreactivity of 7-*syn*-bromobicyclo[2.2.1]heptenes. We have, however, devel-

(1) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashe, M.; Ohani, M. *J. Antibiot.* **1981**, *34*, 359.
(2) (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885; 1969, *91*, 3075. (b) Cermak, R. C.; Vince, R. *Tetrahedron Lett.* **1981**, *22*, 2331 and references cited therein. (c) Kam, B. L.; Oppenheimer, N. J. *J. Org. Chem.* **1981**, *46*, 3268 and references cited therein.
(3) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255.
(4) (a) Jagt, J. C.; Van Leusen, A. M. *J. Org. Chem.* **1974**, *39*, 564. (b) Daluge, S.; Vince, R. *J. Org. Chem.* **1978**, *43*, 2311.
(5) (a) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049. (b) Lim, M.-I.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 5559. (c) Jung, M.; Offenbacher, G.; Retey, J. *Helv. Chim. Acta* **1983**, *66*, 1915.
(6) Raasch, M. S. *J. Org. Chem.* **1975**, *40*, 161.
(7) Davis, D. D.; Surmartis, A. J.; Robertson, G. L. *J. Organomet. Chem.* **1972**, *46*, C9.
(8) Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(9) Anet, F. A. L. *Can. J. Chem.* **1961**, *39*, 789.
(10) Ammon, H. L.; Mazzocchi, P. H.; Liu, L.; Colicelli, E. C.; Doherty, R.; Stewart, J. *Acta Crystallogr., Sect. B* **1982**, *B38*, 540.
(11) Corey, E. J.; Das, J. *Tetrahedron Lett.* **1982**, *23*, 4217.

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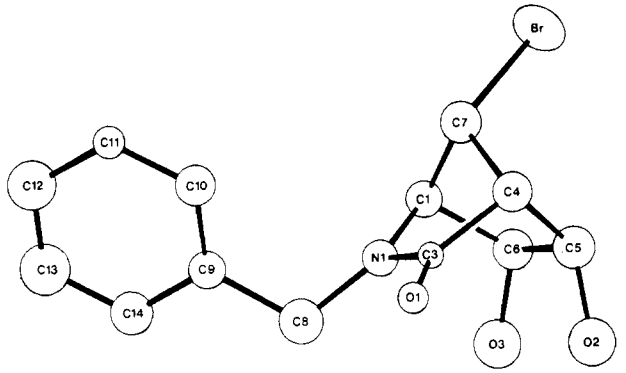

Figure 1. Perspective view of the molecule **9a** showing the atom numbering scheme. Atoms are represented as 50% thermal ellipsoids. The H atoms are omitted for clarity.

oped an efficient approach to 7-substituted-2-azabicyclo-[2.2.1]hept-5-en-3-ones which should be of general utility.

Experimental Section

2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one (4). To a suspension of finely ground KOH (1.21 g, 18.36 mmol) in Me_2SO (6 mL) was added a solution of lactam **3**[2b,c,4] (0.498 g, 4.57 mmol) in Me_2SO (3 mL). The solution was stirred briefly, benzyl bromide (1.57 g, 9.17 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 5 h under N_2. The mixture was then diluted with $CHCl_3$ (25 mL) and quenched with saturated aqueous NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (5 × 20 mL). The combined organic layers were extracted with H_2O (5 × 20 mL), dried ($MgSO_4$), and evaporated to produce 1.722 g of crude **4**. Chromatography on silica gel (60:40 hexane–EtOAc) gave 0.645 g (71%) of **4** with spectral data corresponding very closely to those reported.[12]

6,7-Dibromo-2-azabicyclo[2.2.1]heptan-3-one (5). To a solution of **3** (0.361 g, 3.31 mmol) in CH_2Cl_2 (4 mL) was added dropwise 0.530 g (3.31 mmol) of bromine in CH_2Cl_2 (2 mL). Initially, the bromine was taken up rapidly and a solid was deposited in the reaction flask. As the addition proceeded, however, the bromine persisted for increasingly longer periods. After completing the addition, the mixture was stirred at room temperature for 23 h and then filtered. The solid was washed with CH_2Cl_2 and dried to produce 0.666 g (75%) of **5** which was used in subsequent reactions without further purification. An analytical sample was obtained by recrystallization from $CHCl_3$: mp >250 °C; NMR (Me_2SO-d_6) δ 2.44 (m, 2), 2.78 (m, 1), 4.10 (m, 2), 4.56 (m, 1), 8.46 (m, 1); IR (KBr) 3195, 1704, 1267 cm^{-1}. Anal. Calcd for $C_6H_7Br_2NO$: C, 26.80; H, 2.62; Br, 59.42; N, 5.21. Found: C, 26.65; H, 2.65; Br, 59.67; N, 5.10.

2-Benzyl-6,7-dibromo-2-azabicyclo[2.2.1]heptan-3-one (6). Bromine (0.519 g, 3.24 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise to a solution of **4** (0.645 g, 3.24 mmol) in CH_2Cl_2 (8.0 mL). Initially, decolorization occurred rapidly, but as the addition proceeded the bromine persisted for longer periods. The reaction was stirred at room temperature for 23 h and evaporated to produce 1.164 g (100%) of **6** which was used in subsequent reactions without further purification: mp 119.5–123 °C; NMR ($CDCl_3$) δ 2.60 (m, 2), 2.97 (m, 1), 3.72–3.98 (m, 2), 4.04 (d, 1, J = 15 Hz), 4.26 (m, 1), 4.70 (d, 1, J = 15 Hz), 7.31 (m, 5); IR (KBr) 3030, 1712, 1496, 756, 706 cm^{-1}.

An analytical sample was prepared by recrystallization from hexane–EtOAc: mp 128.5–130 °C. Anal. Calcd for $C_{13}H_{13}Br_2NO$: C, 43.49; H, 3.65; N, 3.90; Br, 44.51. Found: C, 43.44; H, 3.74; N, 3.79; Br, 44.44.

2-Benzyl-7-bromo-2-azabicyclo[2.2.1]hept-5-en-3-one (8). A stirred solution of **6** (1.228 g, 2.86 mmol) in DBN (1.243 g, 10.01 mmol) was heated to 120 °C for 3.5 h under N_2. The mixture was cooled and diluted with CH_2Cl_2 (25 mL), washed with 5% HCl (2 × 15 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated to produce 0.643 g (81%) of crude **8**. Chromatography on silica gel (85:15 hexane–EtOAc) gave 0.553 g (70%) of **8**: mp 80–81.5 °C; NMR ($CDCl_3$) δ 3.61 (m, 1), 4.10 (m, 1), 4.16 (d, 1, J = 15 Hz), 4.42 (d, 1, J = 15 Hz), 4.65 (m, 1), 6.47 (apparent t, 2, J = 2 Hz), 7.08–7.44 (m, 5); IR (KBr) 3095–3020, 1701, 1657, 1409, 1252, 770, 695, 667 cm^{-1}. Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04; Br, 28.73. Found: C, 56.28; H, 4.50; N, 4.86; Br, 28.89.

2-Benzyl-7-*anti*-bromo-*endo*,*endo*-5,6-dihydroxy-2-azabicyclo[2.2.1]heptan-3-one (9). With use of the procedure of VanRheenen et al.,[8] a suspension of **8** (0.121 g, 0.435 mmol) in H_2O (2.5 mL) and acetone (1.0 mL) was treated with *N*-methylmorpholine *N*-oxide (0.114 g, 0.744 mmol). Addition of OsO_4 (5.5 mg, 0.022 mmol) resulted in an immediate deposition of a brown solid. The mixture was stirred at room temperature for 30 h and then quenched with a slurry of $Na_2S_2O_4$ (0.1 g) and Florisil (1.2 g) in H_2O (8 mL). The mixture was filtered. The filtrate was made acidic with 1 N H_2SO_4 and then saturated with NaCl and extracted with $CHCl_3$ (4 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to produce 0.084 g (62%) of **9** as a white solid which was recrystallized from $CDCl_3$: mp 147–148.5 °C; NMR ($CDCl_3$) δ 3.27 (m, 1), 3.80 (m, 1), 4.03 (m, 1), 4.08 (d, 1, J = 15 Hz), 4.83 (AB q, $\Delta\nu$ = 0.04 ppm, 2, J = 6 Hz), 5.16 (d, 1, J = 15 Hz), 7.33 (s, 5); IR (KBr) 3378 (br), 3040, 1705, 1615, 1507, 1256, 1123, 781, 710 cm^{-1}.

X-ray Crystal Structure Determination. Crystals of **9** were grown from $CDCl_3$. The crystal was coated with oil as a preventive measure (crystals turned opaque with time). Preliminary oscillation photos of the crystal chosen for study indicated that it was of good quality; the crystal was transferred to a Supper 455 goniometer and optically centered on a Syntex $P2_1$ diffractometer.

Table I. Data for the X-ray Diffraction Study of $C_{13}H_{14}BrNO_3 \cdot 0.5CDCl_3$

(A) Crystal Data[a]			
crystal system	monoclinic	V	2964.1 Å^3
space group	$C2/c[C_{2h}^6$ no. 15]	Z	8
a	23.851 (7) Å	formula wt.	372.4
b	6.288 (2) Å	ρ_{calcd}	1.67 g/cm^3
c	24.942 (7) Å	ρ_{obsd}[b]	1.65 g/cm^3
β	127.59 (3)°	μ(Mo Kᾱ)	32.1 cm^{-1}

(B) Measurement of Intensity Data	
radiation	Mo Kᾱ, graphite monochromator
reflections measured	$\pm h,k,l$ (to 2θ = 42°)
scan type, speed	θ–2θ, 2.93–5.33°/min
scan range	symmetrical, $[1.6 + \Delta(\alpha_2-\alpha_1)]$°
background measurement	one-fourth of scan time at each of the scan limits
no. of reflections measured	1479 total, 940 in unique set
standard reflections	020, 004, 400, period 60, showed a decrease of 3.8% (400) to 5.5% (020)
absorption correction	empirical, transmission factors 0.89–1.00
statistical information[c]	R_s = 0.042, R_{sv} = 0.016
(C) Solution and Refinement[d]	
solution	Patterson map and difference Fourier
refinement	full matrix least squares with anisotropic temperature factors for Br and Cl atoms; isotropic temperature factors for O, N, C; fixed H atoms; R = 0.054, R_w = 0.061; SDU = 1.144
final difference map	largest peaks: 0.65 e/Å^3 near O(2), 0.52 e/Å^3 near O(3), 0.46 e/Å^3 near O(3), 0.41 e/Å^3 near O(7) all other peaks random and ≲0.38 e/Å^3

[a] Cell constant determination: 12 pairs of $\pm(hkl)$ and refined 2θ, ω and χ values in the range 20° < $|2\theta|$ < 22°. [b] Measured by neutral bouyancy in CCl_4–CH_3I. [c] $R_s = \sum\sigma(|F_o|)/\sum|F_o|$. [d] $R = \sum||F_o| - |F_c||\sum|F_o|$. $R_w = [\sum\omega[|F_o| - |F_c|]^2/\sum\omega|F_o|^2]^{1/2}$. SDU = $[\sum\omega[|F_o| - |F_c|]^2/(m-n)]^{1/2}$ where m (906) is the number of observations and n (96) is the number of parameters.

(12) Mazzocchi, P. H.; Ammon, H. L.; Liu, L.; Colicelli, E.; Ravi, P.; Burrows, E. *J. Org. Chem.* **1981**, *46*, 4530.

Operations were performed as described previously.[13] The analytical scattering factors of Cromer and Waber were used;[14a] real and imaginary components of anomalous scattering for the Br and Cl atoms were included in the calculations.[14b] The hydroxyl hydrogen atoms can not be successfully refined. All other hydrogen atoms were put in calculated positions, (r_{C-H} = 0.95 Å). Details of the structure analysis and solution, in outline form, are presented in Table I.

Acknowledgment. We are grateful to the National Institutes of Health for financial support.

Registry No. 1, 72877-50-0; 3, 49805-30-3; 4, 78805-80-8; 5, 95936-41-7; 6, 95936-42-8; 8, 95936-43-9; 9, 95936-44-0; benzyl bromide, 100-39-0.

Supplementary Material Available: Tables of (i) atomic coordinates, (ii) bond lengths and angles, (iii) anisotropic thermal parameters for Br and Cl atoms and isotropic thermal parameters for O, N, and C atoms, (iv) hydrogen atom positions, and (v) torsion angles (5 pages). Ordering information is given on any current masthead page. Observed and calculated structure factors are available from the authors.

(13) Foxman, B. M. *Inorg. Chem.* **1978**, *17*, 1932. Foxman, B. M.; Mazurek, H. *Ibid.* **1979**, *18*, 113.
(14) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. IV: (a) pp 99–101, (b) pp 148–150.

Preparation of α-Oxo Amidines by the Direct Nucleophilic Acylation of Carbodiimides

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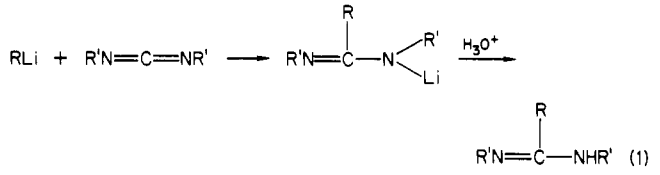
Results and Discussion

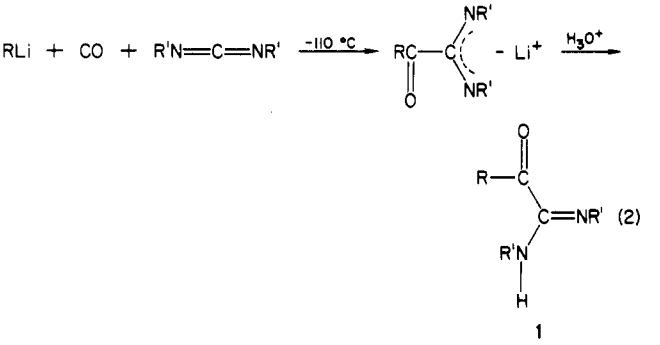
As J. Pornet and L. Miginiac have shown,[1] the alkylation and arylation of carbodiimides can be effected with Grignard and organolithium reagents to give amidines, often in good yield (eq 1). During the course of our studies



(1)

of direct nucleophilic acylation of organic electrophiles with in situ generated acyllithium reagents,[2] we have studied the nucleophilic acylation of various heterocumulenes: carbon disulfide and carbonyl sulfide,[3] isocyanates, and isothiocyanates.[4] In view of the known reactivity of carbodiimides toward organometallic reagents,[1] it was of interest to see if they would react with acyllithium reagents as well. The expected products α-oxo amidines, R'C(O)C(NR)NHR, could be of potential interest to the synthetic organic chemist.

We have found that carbodiimides may be acylated by our procedure. In such reactions a 4:4:1 tetrahydrofuran/diethyl ether/pentane solvent system containing the carbodiimide is cooled to −110 °C under a nitrogen atmosphere. This solution is then saturated with carbon monoxide (at atmospheric pressure), and, while the CO stream is continued, the alkyllithium reagent solution (*t*- or *sec*-C_4H_9Li) is added very slowly at a constant rate. Under these conditions, the alkyllithium reacts with CO, not with the carbodiimide. The acyllithium reagent which is formed adds to a C=N bond of the carbodiimide. After hydrolysis with saturated aqueous ammonium chloride, the respective α-oxo amidine is produced in good yield (eq 2).



(2)

1

These products are not very stable thermally. Satisfactory elemental analyses (±0.4%, C, H, N) could be obtained only with difficulty. When they are desired as intermediates in a synthesis, they should be used soon after they have been prepared. Their infrared spectra are characterized by bands at 1697–1700 ($\nu_{C=O}$) and 1635–1640 cm^{-1} ($\nu_{C=N}$). Their ^1H NMR spectra were consistent with the structures given.

Table I presents results obtained when *tert*- and *sec*-butyllithium were the organolithium reagents used. In contrast to these quite satisfactory results, such reactions were not successful with *n*-butyllithium. This reagent, we know, serves well in the nucleophilic acylation of other organic electrophiles,[2] hence it does react with CO under the reaction conditions used. However, the *n*-$C_4H_9C(O)Li$ reagent apparently reacts with dialkyl carbodiimides only very slowly at −110 °C, if at all, and in these reactions the carbodiimide was recovered in high yield. No major alternate product was formed aside from the hydrolysis product of the formal acyllithium dimer, *n*-$C_4H_9C(O)CH(OH)C_4H_9$-*n*. The lack of reaction was confirmed in an experiment in which the organic electrophile to which the *n*-C_4H_9Li/CO reagent was added was a 1:1 mixture of di-*n*-propylcarbodiimide and methyl isobutyrate. The only product formed (60% yield) was the α-diketone derived from nucleophilic acylation of the ester.

Direct nucleophilic acylations, using the Me_3CLi/CO and MeEtCHLi/CO in situ systems, of di-*tert*-butylcarbodiimide was unsuccessful and with diisopropylcarbodiimide only very low (<10%) product yields were obtained under our reaction conditions. Presumably adverse steric factors are operative when bulky groups are present both in the organolithium reagent and the carbodiimide.

Experimental Section

General Comments. The carbodiimides were purchased or were prepared from the corresponding thioureas by the method of Schmidt et al.[5] The organolithium reagents were purchased from ALFA-Thiokol/Ventron. The solvents were rigorously dried by using standard procedures.

IR spectra were recorded by using a Perkin-Elmer 1430 infrared spectrophotometer and NMR spectra with a JEOL FX-90X 90-MHz instrument.

Reactions of *sec*-C_4H_9Li/CO and *t*-C_4H_9Li/CO with Dialkylcarbodiimides. The reaction of the *sec*-BuLi/CO reagent

(1) Pornet, J.; Miginiac, L. *Bull. Soc. Chim. Fr.* **1974**, 994.
(2) For a review of our early results see: Seyferth, D.; Weinstein, R. M.; Wang, W.-L.; Hui, R. C.; Archer, C. M. *Isr. J. Chem.* **1984**, *24*, 167.
(3) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 2623.
(4) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 5251.
(5) Schmidt, E.; Hitzler, F.; Lahde, E. *Ber. Deutsch. Chem. Ges.* **1938**, *71*, 1933.

0022-3263/85/1950-1985$01.50/0