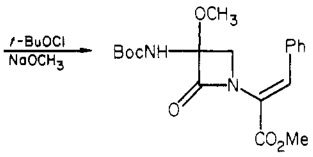
Most naturally occurring monobactams are characterized by the cephamycin-type chain. Adaptation of methods[17] developed for the preparation of cephamycin has led to a procedure for converting **11** to racemic **17** in high yield. The reagents used are *tert*-butyl hypochlorite and sodium methoxide.

11



17

In summary, chiral synthesis of 2-azetidinones[18] variously substituted at C-3 can be achieved in good yield by starting with easily available L-serinylphenylserine. These compounds can be converted readily to N-unsubstituted β-lactams; upon sulfonation of the β-lactam nitrogen,[19] these compounds can become members of the monobactam family with the correct absolute configuration (3*S*) for antibacterial activity.

Experimental details and the applications of this synthetic method to the preparation of various types of β-lactams will be described in a future publication.

Acknowledgment. We are grateful to Provost R. Cotellessa for his interest in this work and to the Stevens Institute of Technology for the support of this research. We thank Dr. Om Prakash for chemical-ionization mass spectra.

Registry No. 1 (R = $PhCH_2$), 85097-39-8; 2 (R = $PhCH_2$), 85097-40-1; 3, 85097-41-2; 4, 85097-42-3; 11, 85097-43-4; 12, 85097-44-5; 13, 80582-10-1; 15, 67509-41-5; 17, 85097-45-6.

Supplementary Material Available: Physical properties, spectral data, and analyses for compounds **3**, **4**, **8**, **11**, **13**, **15**, **17** (2 pages). Ordering information is given on any current masthead page.

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(16) Cleavage of the urethane protective group of **15** with formic acid followed by acylation with *tert*-butoxycarbonyl-D-alanine under the influence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole led to a Boc compound, mp 125–126 °C.[1] Removal of the N-protective group from this intermediate and reaction with *tert*-butoxycarbonyl-D-glutamic acid benzyl ester, dicyclohexylcarbodiimide, and 1-hydroxybenzotriazole produced **19**, mp 160.5–161 °C.

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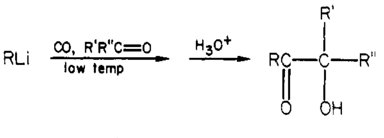
High-Yield Acyl Anion Trapping Reactions: Syntheses of α-Hydroxy Ketones and 1,2-Diketones

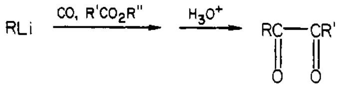
Summary: The in situ generation of $n\text{-}C_4H_9C(O)Li$ by the reaction of $n\text{-}C_4H_9Li$ with CO at −110 °C in the presence of ketones gives good (50–90%) yields of α-hydroxy ketones. When the $n\text{-}C_4H_9C(O)Li$ reaction is carried out in the presence of esters, good (65–80%) yields of α-diketones are obtained, thus demonstrating that RC(O)Li can be reagents of practical utility. Similar reactions were observed with $sec\text{-}C_4H_9Li$ and $tert\text{-}C_4H_9Li$.

Sir: Much effort has been expended on the development of reagents and procedures for nucleophilic acylation. In the absence of a *stable* alkali metal or magnesium acyl reagent, which would provide an acyl anion *directly* on reaction with a suitable electrophile, numerous acyl anion synthons have been developed.[2] Attempts to adapt the reaction of organolithium reagents with carbon monoxide, which gives an acyl- or aroyllithium as the initial product,[3,4] have met with only limited success. The synthesis of dialkyl and diaryl ketones by the introduction of CO into an ethereal RLi[5] or R_2CuLi[6] solution at low temperature and the preparation of diarylalkylcarbinols by the atmospheric-pressure carbonylation of solutions of aryllithium reagents at −78 °C in THF in the presence of bromoalkanes[7] represent useful preparative applications.

In experiments designed to extend the synthetic applicability of the RLi + CO reaction, we examined the possibility of preparing acyltrimethylsilanes, $RC(O)SiMe_3$, by the slow, controlled addition of the alkyllithium solution to a solution of Me_3SiCl that was being kept saturated at −110 °C with gaseous carbon monoxide. As reported,[8] such syntheses were successful, and in the case of primary alkyllithiums, they provided acyltrimethylsilanes in good yield. The success of this procedure was due to a combination of favorable relative rates under these reaction conditions: first, the RLi + CO reaction was faster than the alkylation of Me_3SiCl by RLi; second, the reaction of the RC(O)Li thus formed with Me_3SiCl was faster than any other irreversible reaction (such as dimerization[3,4]) that RC(O)Li might undergo. This $RC(O)SiMe_3$ synthesis represents a rather narrow and limited application of the RLi + CO reaction, but our success encouraged us to seek more generally useful organic applications, i.e., applications in which the "acyl anion synthon" alternative has been used in the belief that the unstable RC(O)Li species cannot be usefully applied. We report here the successful nucleophilic acylation of two classes of organic compounds: ketones, which react to give, after hydrolysis, α-hydroxy ketones (eq 1), and esters, which react to give 1,2-diketones (eq 2). Our results are summarized in Table I.



$$RLi \xrightarrow[\text{low temp}]{CO,\ R'R''C{=}O} \xrightarrow{H_3O^+} RC(=O)\text{—}C(R')(OH)\text{—}R'' \qquad (1)$$



$$RLi \xrightarrow{CO,\ R'CO_2R''} \xrightarrow{H_3O^+} RC(=O)\text{—}C(=O)R' \qquad (2)$$

The experimental procedure that was used in these reactions is very similar to that used in our acylsilane synthesis.[8] In one experiment, a 500-mL Morton (creased) three-necked flask was equipped with an overhead mechanical stirrer, a Claisen adapter fitted with a gas outlet

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(1) (a) Rhône-Poulenc Co. Graduate Research Fellow. (b) Visiting Scientist; on leave from the Chenguang Chemical Industry Research Institute, Sichuan Province, PRC.

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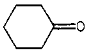
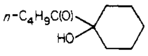
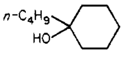
Table I. Nucleophilic Acylation of Ketones and Esters with the n-C_4H_9Li + CO Derived n-$C_4H_9C(O)Li$ Reagent[a]

reactant	products (% yield)
1. Ketones	
$CH_3C(O)C_2H_5$	n-$C_4H_9C(O)C(OH)(CH_3)(C_2H_5)$ (71) + n-$C_4H_9C(OH)(CH_3)(C_2H_5)$ (13)
$CH_3C(O)CH(CH_3)_2$	n-$C_4H_9C(O)C(OH)(CH_3)(CH(CH_3)_2)$ (92) + n-$C_4H_9C(OH)(CH_3)(CH(CH_3)_2)$ (5)
$CH_3C(O)C(CH_3)_3$	n-$C_4H_9C(O)C(OH)(CH_3)(C(CH_3)_3)$ (90) + n-$C_4H_9C(OH)(CH_3)(C(CH_3)_3)$ (2)
$(C_2H_5)_2CO$	n-$C_4H_9C(O)C(OH)(C_2H_5)_2$ (67) + n-$C_4H_9C(OH)(C_2H_5)_2$ (4)
$C_6H_5C(O)CH_3$[b]	n-$C_4H_9C(O)C(OSi(CH_3)_3)(CH_3)(C_6H_5)$ (43)[c] + $(CH_3)_3SiO(C_6H_5)C{=}CH_2$ (50)
	 (54) +  (31)
2. Esters	
$CH_3CO_2CH_3$	n-$C_4H_9C(O)C(O)CH_3$ (71)
$C_2H_5CO_2CH_3$	n-$C_4H_9C(O)C(O)C_2H_5$ (67)
n-$C_3H_7CO_2CH_3$	n-$C_4H_9C(O)C(O)C_3H_7$-n (66)
$(CH_3)_3CCO_2CH_3$	n-$C_4H_9C(O)C(O)C(CH_3)_3$ (80)
n-$C_5H_{11}CO_2C_2H_5$	n-$C_4H_9C(O)C(O)C_5H_{11}$-n (79)
$C_6H_5CO_2CH_3$	n-$C_4H_9C(O)C(O)C_6H_5$ (68)
$CH_3C(O)CO_2CH_3$	n-$C_4H_9C(OH)(CH_3)CO_2CH_3$ (65)

[a] All reactions were carried out as described in the text by using a ketone (or ester)/n-BuLi ratio of ~2. Yields are based on n-butyllithium. [b] Reaction mixture quenched with Me_3SiCl in order to determine amount of enolization. [c] In another experiment (hydrolytic workup) the yield was 90% *based on unrecovered* $C_6H_5C(O)CH_3$.

tube, and a low-temperature thermometer and in the third neck, a rubber septum that held a coarse-fritted gas dispersion tube (for the introduction of CO) and a syringe needle. The latter was connected via polyethylene tubing to an Orion Research, Inc., Model 341A syringe pump. The reaction flask was charged with 133 mL each of dry THF and diethyl ether, 33 mL of dry pentane, and 18 mmol of 3-pentanone. This mixture was cooled to −110 °C[9] with the aid of a liquid nitrogen filled Dewar flask. After the cooling had been initiated, the introduction of a slow stream of carbon monoxide was started. Carbon monoxide was bubbled into the solution for 30 min, and then n-butyllithium [4.0 mL of a 2.2 M solution in hexane (8.8 mmol)] was added at a rate of 0.24 mL/min by means of the syringe pump while the CO stream was continued. The temperature was maintained at −110 ± 5 °C during the course of the addition, and after the addition had been completed, the reaction mixture was stirred under CO for another 2 h at −110 °C. The reaction mixture then was allowed to warm to room temperature over the course of 1 h, with the introduction of CO being continued. After 1 h at room temperature, the mixture was hydrolyzed with 75 mL of saturated aqueous NH_4Cl. After phase separation and extraction of the aqueous phase with pentane, the combined organic layers were concentrated at reduced pressure and trap-to-trap distilled (45 °C at 0.01 mmHg) into a liquid nitrogen cooled receiver. Analysis of the distillate by GLC (15% SE-30 on Chromosorb P, 130–150 °C at 5°/min) showed the presence of two products that were collected and identified: (1) $(C_2H_5)_2(n\text{-}C_4H_9)COH$, 4% yield, and (2) 3-hydroxy-3-ethyl-4-octanone, n-$C_4H_9C(O)C(OH)$ $(C_2H_5)_2$, 67% yield.

It is clear from the results in Table I that under these conditions the addition of n-butyllithium to the C═O bond of ketones is more or less competitive with n-butyllithium addition to carbon monoxide but that the latter process is favored. Thus, when n-butyllithium is used, α-hydroxy ketone yields in excess of 50% may be obtained. The case of acetophenone is indicative of another potential problem: more readily enolizable ketones divert the nucleophile (n-C_4H_9Li or n-$C_4H_9C(O)Li$) from α-hydroxy ketone formation via a proton-abstraction reaction, and lower product yields result. When this side reaction does not intrude, this is a useful α-hydroxy ketone synthesis.[10]

The results obtained with the only aldehyde examined thus far, $(CH_3)_3CCHO$, suggest that the direct nucleophilic acylation procedure as described will not find general, practical application to aldehydes. In this reaction, n-C_4H_9Li addition to the aldehyde C═O bond was more rapid than the formation of n-$C_4H_9C(O)Li$: the yields of n-$C_4H_9CH(OH)C(CH_3)_3$ and n-$C_4H_9C(O)CH(OH)C(CH_3)_3$ were 50% and 17%, respectively. Most other aldehydic C═O bonds can be expected to be more reactive than that of pivaldehyde, thus giving even more unfavorable relative rates.

In contrast, as Table I shows, the acylation of esters by in situ generated n-$C_4H_9C(O)Li$ occurs very cleanly and in good yield. The n-C_4H_9Li + CO reaction must be considerably faster than that of n-butyllithium with most esters, and the n-$C_4H_9C(O)Li$/ester reaction must be more rapid than other potential side reactions of n-$C_4H_9C(O)Li$. Thus this reaction joins the available methods[10,11] as a new and useful procedure for the preparation of symmetrical and unsymmetrical 1,2-diketones. All the 1,2-diketones listed in Table I were isolated by GLC as yellow liquids and were fully characterized by C/H analysis and IR and ^1H NMR spectroscopy.

While our initial experiments were carried out with n-butyllithium, more recent studies showed that secondary and tertiary alkyllithiums may be used as well. Thus the *sec*-butyllithium/CO/$Me_3CC(O)Me$ reaction at −110 °C gave $MeEtCHC(O)C(OH)(CH_3)CMe_3$ in 55% yield, while a similar reaction using Me_3CCO_2Me as the electrophile gave $MeEtCHC(O)C(O)CMe_3$ in 66% yield. A reaction of the t-BuLi/CO reagent with methyl benzoate resulted in two products, $PhC(O)C(O)CMe_3$ (53%) and $PhC(O)CMe_3$ (27%), while this reagent converted $Me_3CC(O)Me$ to $Me_3CC(O)C(OH)(Me)CMe_3$ in 69% yield.

We have thus shown that nucleophilic acylation, when carried out by the in situ RLi + CO procedure, can, con-

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(9) Temperatures were measured on a pentane thermometer with only the bulb immersed in the solution. However, this thermometer is of the total immersion type and it read −70 °C (bulb immersed) vs. −78 °C (total immersion) in a dry ice/acetone bath. Thus the temperatures reported are probably 8–10 °C high for the low-temperature reactions.

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(11) "Methodicum Chimicum"; Korte, F., Ed.; Georg Thieme: Stuttgart, 1975; Vol. 5, C-O Verbindungen, pp 486–491. See also: Girard, P.; Couffignal, R.; Kagan, H. B. *Tetrahedron Lett.* **1981**, *22*, 3959.

trary to previous thinking, be used with good advantage in organic synthesis. It is obvious that in order to fully define the utility of the in situ generated RC(O)Li reagents, much more work is required. Chlorosilanes, ketones, aldehydes, and esters are by no means the only types of electrophiles that merit investigation, and broadly based studies are underway to include the many other classes of electrophiles whose nucleophilic acylation would be of synthetic interest. Most of our work in the nucleophilic acylation of chlorosilanes, ketones, aldehydes, and esters has been carried out by using alkyllithium reagents. To be studied yet are the other major types of organolithiums that are known: aryllithiums, vinyllithiums, allyllithiums, alkynyllithiums, and functionally substituted organolithium reagents of diverse kinds. These problems also are receiving our attention.

Note added in proof: Recent results of R. C. Hui in our laboratories have demonstrated that a 1:1 RLi-to-electrophile stoichiometry also is satisfactory. For example, in a *t*-BuLi/Co reaction with 2-methylcyclohexanone, the yield of acyllithium- to alkyllithium-derived products increases from 66% vs. 26% to 92% vs. 8% on going from a 1:2 to a 1:1 ratio of RLi to the ketone. If this is a general trend, it should readily extend the application of the methodology described here.

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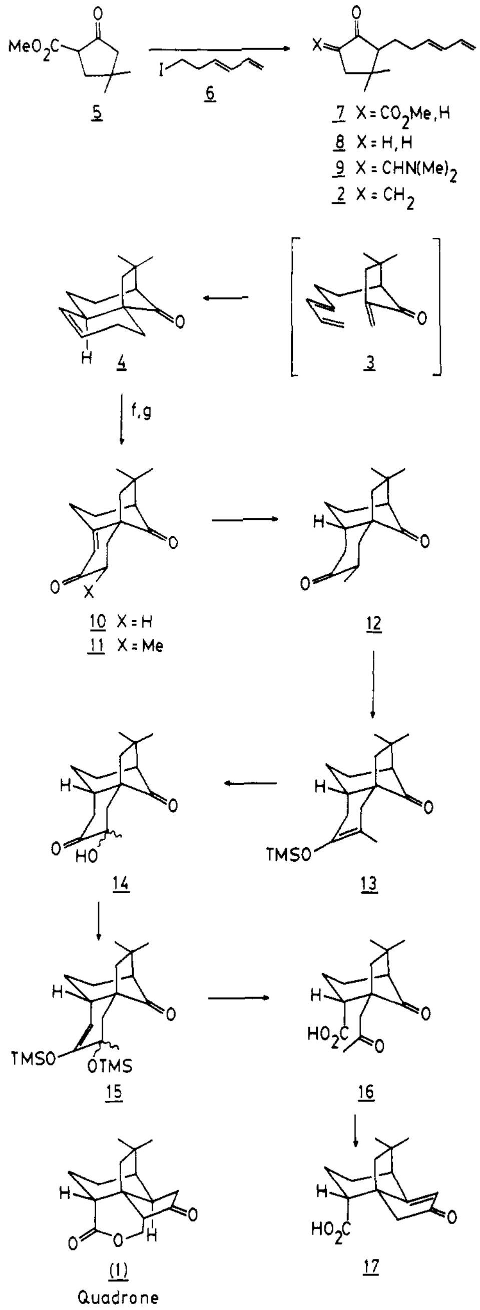
An Intramolecular Diels–Alder Route to Racemic Quadrone

Summary: A total synthesis of the sesquiterpene quadrone (1) that employs an intramolecular Diels–Alder reaction as the key strategic feature is described.

Sir: The cytotoxic properties and unusual tetracyclic structure of the sesquiterpene quadrone 1[1] have elicited considerable synthetic activity, which has resulted in the development of a number of elegant strategies leading to total syntheses of this natural product.[2] While considering possible routes to quadrone, we were struck with its structural similarity to the kaurane and quassin families of diterpenes[3] and thus attempted to develop a construction of 1 which contained elements that might be applied to the assemblage of these substances.



With respect to quadrone itself, we elected to examine the intramolecular Diels–Alder behavior of the α-methylene cyclopentanone system 2 in the hope of generating a tricyclic system potentially convertible into 1. The sole literature precedence available at the time we commenced this work suggested that 2 would prefer to undergo cycloaddition via the exo transition state 3, thus forming the tricycic substance 4, which possesses trans geometry about the decalin portion of this system.[4] Molecular models of 2 also predicted this result and further indicated that no significant influence on the cycloaddition reaction would be exerted by the *gem*-dimethyl residue present on the cyclopentanone ring of 2. The alternative endo transition state for reaction of 2 could be ruled out since this geometry requires the developing cyclohexanone ring system to adopt a boat conformation, thereby creating serious non-

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