# Tandem Anionic Cyclization Approach to Polycarbocyclic Products

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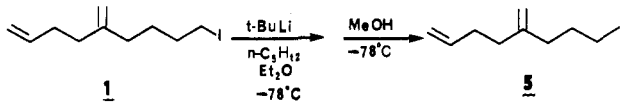
Recently we[2] and others[3] have reported that the relatively facile cyclization of an olefinic alkyllithium[4] may be used to advantage for the preparation of a variety of cyclic systems. Herein we report the extension of this approach to the construction of multicyclic systems by sequential, anion-initiated polyolefinic cyclization. While both cationic[5] and radical-initiated[6] polyolefinic cyclizations have been used to advantage for the construction of rather complex polycyclic systems, tandem (or higher order) anion-initiated cyclizations are unprecedented. As demonstrated by the model studies described below, tandem anionic cyclization of a diolefinic alkyllithium is a remarkably efficient process that proceeds in high yield and results in the formation of two new C-C bonds to give products bearing an easily functionalized $CH_2Li$ moiety.

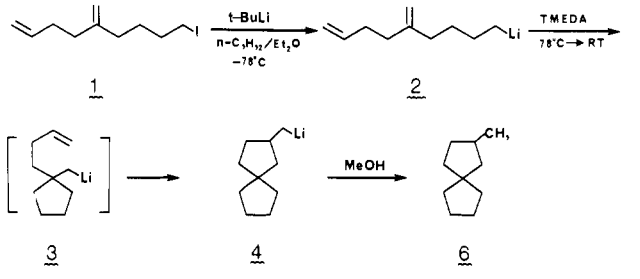
Treatment of a 0.1 M solution of iodide **1**[7,8] in *n*-pentane-diethyl ether (3:2 by vol) at -78 °C with 2.1 equiv of *t*-BuLi serves to cleanly generate the corresponding diolefinic alkyllithium (**2**) as demonstrated by the fact that methanol quench of such a reaction mixture at -78 °C affords diene **5** in virtually quantitative yield.




**1** **5**

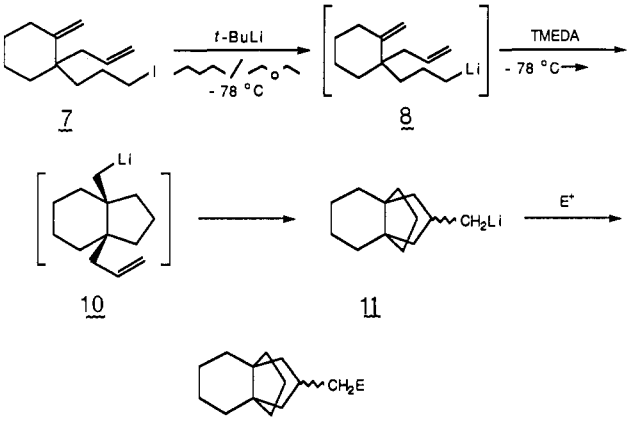
Tandem cyclization of **2** was effected as illustrated in Scheme I[9] (**2** → **3** → **4**) by addition of 2.1 equiv of dry, deoxygenated *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to the -78 °C solution of **2** in $n$-$C_5H_{12}$-$Et_2O$ followed by removal of the cooling bath. Upon reaching ca. +20 °C, the reaction mixture was allowed to sit at ambient temperature for 1 h. Quench of the product mixture with deoxygenated methanol gave 2-methylspiro[4.4]-nonane (**6**) in 84% isolated yield (Scheme I). The balance of the product was the uncyclized diene **5**; there was no evidence of product resulting from protonation of monocyclic organolithium **3**. Thus, tandem anionic cyclization of 5-hexen-1-yllithium units is indeed more rapid than reactions that consume the anion such as proton abstraction and oxidation by adventitious oxygen. The fact that the spirocyclic organolithium **4** is most likely largely protonated upon standing for 1 h at room temperature in the presence of TMEDA (see below) is of no consequence in the present instance since the hydrocarbon is the desired product. Relatively rapid proton abstraction from solvent is, however, a potentially serious problem[10] if one wishes to trap the product organolithium with an electrophile. In an effort to determine if functionalized polycyclics could be prepared in synthetically useful yield by addition of electrophiles to the organolithium resulting from tandem cyclization, we investigated tandem anionic cyclization as a route to substituted [4.3.3]propellanes.

**Scheme I**



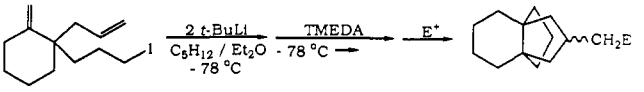

**1** **2** **3** **4** **6**

**Scheme II**




**7** **8** **10** **11**

**Table I.** Tandem Anionic Cyclization Route to Functionalized [4.3.3]Propellanes[a]




**7**

| entry | $E^+$ | E | isolated yield, % |
|---|---|---|---|
| 1 | $CH_3OH$ | H | 81 |
| 2 | $CH_3OD$ | D | 75 |
| 3 | $CO_2$ | $CO_2H$ | 60 |
| 4 | PhCHO | CH(OH)Ph | 80 |
| 5 | $(CH_3)_2C{=}O$ | $C(CH_3)_2OH$ | 80 |
| 6 | $CH_2{=}CHCH_2Br$ | $CH_2CH{=}CH_2$ | 82 |
| 7 | $(CH_3)_3Si{-}Cl$ | $Si(CH_3)_3$ | 73 |

[a] TMEDA (2.0-2.2 equiv) was added at -78 °C to a solution of **8**, generated by lithium-iodine exchange between **7** and *t*-BuLi, the mixture was stirred for 5 min at -78 °C and then allowed to warm to +12 °C over a 17-min period before addition of an excess of the electrophile. Product was isolated and purified by flash chromatography or bulb-to-bulb distillation.

Low-temperature lithium-halogen interchange[8] serves to generate diolefinic alkyllithium **8** in essentially quantitative yield. Indeed, methanol quench of the reaction mixture at -78 °C gives diene **9** in 89% isolated yield.

Preparative scale tandem cyclizations (**8** → **10** → **11**; Scheme II) were conducted as follows: 2 equiv of anhydrous, deoxygenated

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(2) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442.

(3) See, for example: (a) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. (b) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381, and references therein. (c) Koppang, M. D.; Ross, G. A.; Woolsey, N. F.; Bartak, D. E. *J. Am. Chem. Soc.* **1986**, *108*, 1441. (d) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1337.

(4) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999.

(5) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.

(6) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943 and references therein.

(7) Satisfactory C and H analyses and/or exact mass spectroscopic molecular weights have been determined for all new compounds and their IR, $^1H$ NMR, and $^{13}C$ NMR spectra are in accord with the assigned structures.

(8) Because of the dramatic halogen effect on the mechanism of the lithium-halogen exchange, the iodide rather than the corresponding bromide should be used in the interchange reaction (Bailey, W. F.; Patricia, J. J.; Nurmi, T. T. *Tetrahedron Lett.* **1986**, *27*, 1865). For a recent review of the literature dealing with the mechanism of the lithium-halogen exchange, see: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.

(9) For the sake of pictoral clarity, organolithiums are represented as monomers in the schemes.

(10) Alkyllithiums react at an appreciable rate at elevated temperatures with both ethereal solvents (Coates, G. E.; Green, M. L. H.; Wade, K. In *Organometallic Compounds*, 3rd ed.; Methuen: London, Vol. 1, p 9ff) and TMEDA (Kohler, F. H.; Hertkorn, N.; Blumel, J. *Chem. Ber.* **1987**, *120*, 2081).

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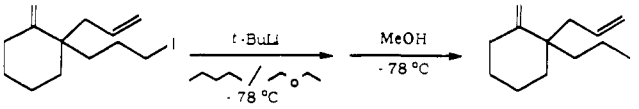


7 9

TMEDA was added to a −78 °C solution of **8** in $n$-$C_5H_{12}$-$Et_2O$, the cooling bath was removed, and the reaction mixture was allowed to warm for 17 min (to ca. +12 °C) before the addition of an excess of electrophile (Table I). As demonstrated by the results summarized in Table I, the product organolithium (**11**, Scheme II) can be trapped with any of a variety of electrophiles to give high (60–80%) isolated yields of functionalized product.[11] It is to be noted that the only other material detected in greater than trace amount from these tandem cyclization reactions was 10–15% of the easily removed *unfunctionalized* parent diene **9**. The presence of diene in the product mixture was not unexpected since, as noted elsewhere,[2] the formation of hydrocarbon formally derived from reduction of the halide is a general occurrence in lithium–halogen exchange reactions involving $t$-BuLi.

The results presented above demonstrate the potential of anion-initiated tandem cyclization as a route to functionalized polycarbocyclic products. Three features of the methodology are worthy of note: (1) The generation of the initial C–Li bond is easily and cleanly accomplished by low-temperature lithium–iodine interchange. (2) Tandem 5-exo-trig cyclization of a diolefinic alkyllithium in the presence of TMEDA is more rapid than competing reactions that consume the anion. (3) The tandem cyclization product is easily functionalized by reaction with any of a variety of electrophiles. We are in the process of extending this approach to the construction of more stereochemically complex systems through higher order sequential (tandem, triplet, etc.) cyclization of suitably constituted substrates.

**Acknowledgment.** We are grateful to the Humphrey Chemical Company of North Haven, CT for generous unrestricted support of our research.

(11) Tandem cyclization of **8**, followed by addition of an electrophile, afforded mixtures of the exo and endo isomers of 8-$CH_2E$ derivatives of [4.3.3]propellane (Table I) which, in our hands, could not be separated chromatographically.

## A Novel, Functional Variant of Cytochrome *c*: Replacement of the Histidine Ligand with Arginine via Site-Directed Mutagenesis

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An u derlying tenet of bioinorganic chemistry is the simple notion tnat a metalloprotein is a large coordination complex in which the protein plays the role of a chelating ligand. Thus, it has been possible to mimic the coordination chemistry of metal ions in proteins with low-molecular-weight synthetic analogues.[2] As an alternate strategy to probing metalloprotein structure and function by studying synthetic models, techniques of genetic manipulation may be useful for preparing mutant proteins that differ from the natural system in the ligation of the metal ions. At least three applications of ligand mutagenesis can be envisaged: (1) to generate coordination environments that have no naturally occurring analogues; (2) to define ranges for a protein's natural function (e.g., redox potential for an electron transport protein); and (3) to change the protein's natural function. One example of this last application has been reported recently for cytochrome $b_5$ in which the normal electron-transfer function has been replaced by peroxidase activity.[3] In this paper we report our preliminary work on yeast cytochrome *c* that illustrates the other two applications.

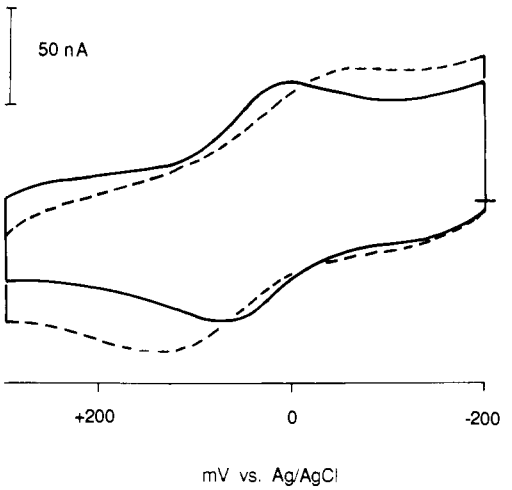


**Figure 1.** Cyclic voltammetry at a tin-doped indium oxide electrode of wild-type iso-2-cytochrome *c* (—) and C2-18R (– – –). Scan rate = 2 mV/s; protein concentration = $10^{-5}$ M in 0.8 M NaCl, 0.1 M phosphate buffer, pH 7.8. The potential of the Ag/AgCl reference electrode is +0.23 V vs NHE. The working electrode (0.3 $cm^2$) pretreatment and horizontal mounting (for slow scan rates) were done as described in ref 22.

Site-directed mutagenesis was carried out on the yeast iso-2-cytochrome $c$[4] gene (CYC7-H2)[5] at the position corresponding to histidine-18 (vertebrate numbering system).[6] Different plasmids, each containing a separate mutation of CYC7-H2, were used to transform a yeast strain lacking cytochrome $c$,[12] and the

(1) Fellow of the Alfred P. Sloan Foundation, 1985–1987.
(2) Holm, R. H.; Ibers, J. A. *Science (Washington, D.C.)* **1980**, *209*, 223–230.
(3) Sligar, S. G.; Egeberg, K. D.; Sage, J. T.; Morikis, D.; Champion, P. M. *J. Am. Chem. Soc.* **1987**, *109*, 7896–7897.
(4) There are two forms of cytochrome *c* in *Saccharomyces cerevisciae* termed iso-1 and iso-2. The less abundant (5% of the total cytochrome *c*) is the iso-2 protein: Sherman, R.; Stewart, J. W.; Helms, C.; Downie, T. A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 1437–1441.
(5) CYC7 is the structural gene that encodes iso-2-cytochrome *c*.[4] The CYC7-H2 gene is a mutation in which a Tyl element has been inserted 5′ to the iso-2-cytochrome *c* coding region of CYC7. The Tyl insertion causes a 20-fold increase in CYC7 expression in a and $\alpha$ haploid cell types of *S. cerevisiae*: Errede, B.; Cardillo, T. S.; Sherman, F.; Dubois, E.; Deschamps, J. Wiame, J.-M. *Cell* **1980**, *22*, 427–436.
(6) Methodologies for mutagenesis at the His-18 codon are described in ref 7, and other materials and methods are given in ref 8. The wild-type gene CYC7-H2 was cloned into pUC118.[9] The 25-mer synthetic oligonucleotide used for mutagenesis contained a mixed population of all four nucleotides at the three positions corresponding to the histidine-18 codon. The oligonucleotide was mixed with uridine-incorporated template in a 2:1 molar ratio, heated to 65 °C, and allowed to cool slowly to room temperature. The mixture was treated with T4 DNA polymerase and T4 DNA ligase and incubated at 37 °C for 1 h. The resultant mixture was transformed in *E. coli* JM109 cells[10] and plated for single colonies which were selected for their resistance to ampicillin. Single strand template DNA prepared[9] from each colony was sequenced by the dideoxy method.[11] After identification of mutants, plasmid DNA was prepared, and the plasmids were used to transform yeast strain E924-4D.[12]
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(8) Sherman, F.; Fink, G. R.; Hicks, J. B. *Methods in Yeast Genetics: A Laboratory Manual*; Cold Spring Harbor Laboratory: Cold Spring Harbor, NY, 1983.
(9) Vieira, J.; Messing, J. In *Methods in Enzymology*; Wu, R., Grossman, L., Eds., Academic Press: New York, (1987; Vol. 153, pp 3–11.
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