IR [(neat) 1720 cm^{-1}], NMR [($CDCl_3$) δ 2.35 (t, 4 H, J = 7.5 Hz)], and MS [m/z 156 (M+)] are in accord with literature values reported for **5**.[12] GC analysis of the crude reaction mixture revealed the presence of ca. 10% of the di-*n*-butylcarbinol (158 °C, column 1): IR (neat) 3500 cm^{-1}; MS, m/z 196 (M - H_2O), 157 ($M - C_4H_9$, base peak), 143 (M - C_5H_{11}).

Quenching Experiment for the Reaction of Acid 1a with Methyllithium. A solution of 0.200 g (1.4 mmol) of **1a** in 20 mL of dry THF was cooled to 0 °C (ice bath) and was treated, with stirring, with 9.0 mmol of methyllithium. With the addition complete (<1 min), the mixture was then stirred at 0 °C for an additional 3 h. At this point, 10 mL of the reaction mixture was removed by syringe and added dropwise to a vigorously stirred solution of 30 mL of saturated aqueous ammonium chloride. Extraction of the resulting mixture with 3 × 20 mL of diethyl ether, drying of the combined ethereal layers, filtration, and solvent removal gave a clear oil that was used for GC analysis (160 °C, column 1). It was determined in this manner that the ratio of ketone **2a** to carbinol **3a** was 63:37. The remainder of the reaction mixture was treated with 2.0 mL (16.0 mmol) of Me_3SiCl by rapid addition. After the solution had been allowed to warm to room temperature (5 min), 10 mL of saturated aqueous ammonium chloride was added in one portion. Workup as described above followed by GC analysis of the crude product (160 °C, column 1) showed a **2a** to **3a** ratio of 91:9. The physical properties of **2a** have been described above. Diol **3a**, obtained by flash chromatography (EtOAC) had the following properties: IR (neat) 3520 cm^{-1}; NMR (CCl_4) δ 0.73-.098 (br d, 3 H), 1.12 (s, 6 H), 0.9-1.8 (m, 7 H), 3.08 (br s, 2 H), 3.50-3.75 (t, 2 H, J = 6 Hz); MS, m/z 160 (M^+, <1), 159 (M - H), 145 (M - CH_3), 142 (M - H_2O), 59 (M - $C_6H_{13}O$, base peak). The NMR values cited are in agreement with the partial data given in the literature for 3,6-dimethyl-1,6-heptanediol (**3a**).[13]

Acknowledgment. We acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

Registry No. **1a**, 56493-06-2; **1b**, 85097-35-4; **1c**, 99-96-7; **1d**, 99-06-9; **1e**, 111-14-8; **1f**, 98-89-5; **1g**, 65-85-0; **1h**, 100-09-4; **1i**, 142-62-1; **2a**, 34221-73-3; **2b**, 85097-36-5; **2c**, 99-93-4; **2d**, 121-71-1; **2e**, 111-13-7; **2f**, 823-76-7; **2g**, 98-86-2; **2h**, 100-06-1; **5**, 820-29-1; MeLi, 917-54-4; Me_3SiCl, 75-77-4; *n*-butyllithium, 109-72-8.

(12) Detty, M. R.; Seidler, M. D. *J. Org. Chem.* **1981**, *46*, 1283.

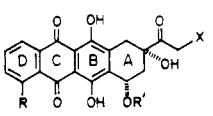
(13) Jakovac, I. J.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165.

Communications

Synthesis of (±)-4-Demethoxydaunomycinone†

Summary: Methods for the preparation of (±)-4-demethoxydaunomycinone from anthraquinone and naphthalene derivatives are described. The difference in the behavior of 1,3-butadienes substituted at the 2-position with 1,3-dithiane and 1,3-dithiolane groupings in the Diels–Alder reaction is discussed.

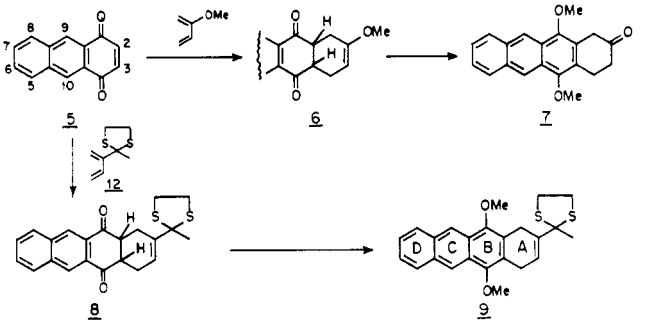
Sir: During the past decade, the anthracycline antibiotics such as daunomycin (**1**) and adriamycin (**2**) have emerged



1: R = OMe, X = H, R' = Daunosaminyl
2: R = OMe, X = OH, R' = Daunosaminyl
3: R = X = H, R' = Daunosaminyl
4: R = R' = X = H

as the most effective drugs available for the treatment of a broad spectrum of human cancers.[1] Recently it has been shown that 4-demethoxydaunomycin (**3**), a synthetic analogue of **1**, exhibits even greater activity than **1** and is also effective for oral therapy.[2] This has stimulated development of newer methods for the synthesis of 4-demethoxydaunomycinone (**4**),[3] the aglycone of **3**. We report the synthesis of **4** starting from easily available organic intermediates.

Our first attempt was to look into the feasibility of utilizing quinizarine (1,4-dihydroxyanthraquinone) and building the A ring of the anthracyclinone moiety by the Diels–Alder reaction. Many have investigated this approach by first converting quinizarine to quinizarine quinone, which served as the dienophile, but the main limitation was that most of the dienes add preferentially to the "internal" double bond.[4] Although several methods to resolve this difficulty have been devised, including the preparation of a few dienes with substituents that are likely to promote the addition at the "terminal" double bond,[5] the most attractive one is to make use of 1,4-anthraquinone (**5**) in the Diels–Alder (DA) reaction by which any diene can be added to build the tetracyclic system. Further, it



is easy to oxidize the 9,10-positions of the anthracene system to the corresponding anthraquinone derivative. Accordingly, we have shown that DA reaction between **5** (prepared from quinizarine by $NaBH_4$ reduction in AcOH[6]) and 2-methoxy-1,3-butadiene (benzene, 90 °C, 24 h) gave the adduct **6** (96%, mp 192–93 °C), which was converted to the tetracyclic ketone **7** (Me_2SO_4, K_2CO_3, acetone, reflux followed by acid workup) in 95% yield (mp 142–43 °C).[7]

(1) F. Arcamone, "Doxorubicin-Anticancer Antibiotics", Medicinal Chemistry (Monographs), Academic Press, New York, 1980, Vol. 17.
(2) S. Neidle, *Nature (London)* **268**, 195 (1977).
(3) (a) A. V. Rama Rao, V. H. Deshpande, and N. Laxma Reddy, *Tetrahedron Lett.*, **21**, 2661 (1980). (b) T. R. Kelly, J. Vaya, and L. Ananthasubramanian, *J. Am. Chem. Soc.*, **102**, 5983 (1980), and references cited therein.
(4) T. R. Kelly, *Annu. Rep. Med. Chem.*, **14**, 288 (1979).
(5) M. Chandler and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1007 (1980), and references cited therein.
(6) A. N. Grinev, I. S. Protopov and A. Cherkasova, *J. Org. Chem. USSR (Engl. Transl.)*, **8**, 220 (1972).
(7) G. Venkatswamy, Ph.D. Thesis, University of Poona, 1979. After completing this work, we noticed that a similar approach was used by Gupta et al. (D. N. Gupta, P. Hodge, and N. Khan *J. Chem. Soc., Perkin Trans. 1*, 689 (1981)) for the synthesis of anthracycline analogues.

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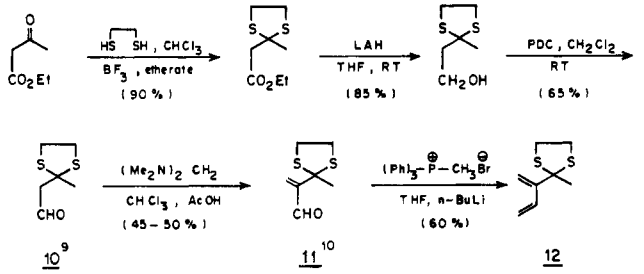
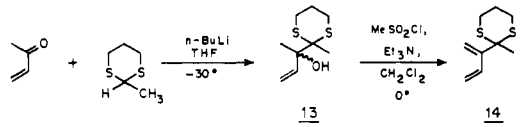
Scheme I



Scheme II



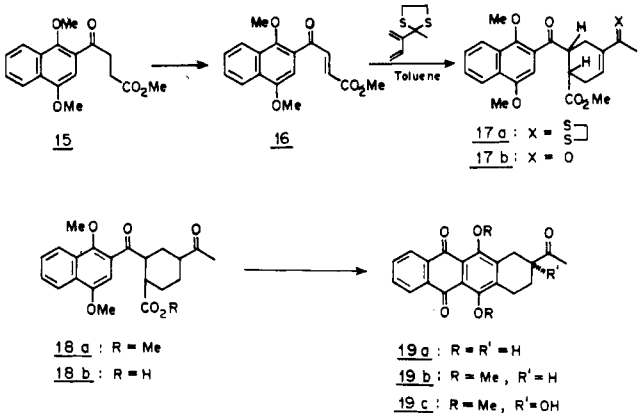
The side-chain elaboration on the ketone of **7** by a two-carbon homologation either by reacting with 2-lithio-2-methyl-1,3-dithiane[8] or with ethynylmagnesium bromide met with failure, probably due to base-catalyzed enolization of the starting ketone **7**.

Our next attempt was to prepare a suitably protected (as ketal or thioketal) 2-acetyl-1,3-butadiene, which on DA reaction with **5** was expected to give the desired product **8**. The diene **12** was made by starting from ethyl acetoacetate as shown in Scheme I.

DA reaction between **5** and **12** (toluene, reflux, 40 h) resulted in the formation of **8** (80% yield), which was converted to **9** (Me_2SO_4, K_2CO_3, reflux, acetone) in 90% yield (mp 185 °C). However, all our attempts at dethioketalization (HgO, $HgCl_2$, aqueous CH_3CN or NCS, $AgNO_3$, aqueous CH_3CN) resulted in the aromatization of the A ring.

While the preparation of the diene **12** is straightforward and can be carried out by starting from readily available intermediates, it has a few drawbacks. Its synthesis involves several steps, and the overall yield is not satisfactory for it to be considered an efficient synthesis. We have therefore considered an alternative route (Scheme II) for obtaining a 2-acetyl-1,3-butadiene in which the ketone group is protected by thioketalization with 1,3-propanedithiol. Addition of methyl vinyl ketone to 2-lithio-2-methyl-1,3-dithiane in THF at −30 °C and usual workup gave the alcohol **13**, which was dehydrated ($MeSO_2Cl$, Et_3N, 0 °C) to give the diene **14** (65% overall yield). The DA reaction between **5** and **14** however did not proceed even in refluxing toluene, and the quinone **5** was recovered. Our attempts to add the diene **14** even with reactive dienophiles such as 1,4-benzoquinone and 1,4-naphoquinone did not proceed. Although the difference in the substituents at the 2-position of the dienes **12** and **14** seems to be insignificant (the former having a dithiolane while the latter has dithiane group), their marked difference in the DA reaction with **5** is not clearly understood.

The observation that the A ring of **9** is prone to easy aromatization during deketalization can be attributed to the extended conjugation of the tetracyclic system. This unexpected trouble can be avoided if the A ring is built first on a dienophile such as **16** and bridged ultimately to form the B ring of the anthracyclinone moiety.[11] Compound **16** has been made by bromination of methyl 3-(1,4-dimethoxy-2-naphthoyl)propionate (**15**)[12] (Br_2, CCl_4, room temperature, 4 h) followed by dehydrobromination (Et_3N, CCl_4, room temperature) (mp 83–84 °C 95% yield). DA reaction between **16** and **12** (toluene, reflux, N_2, 60 h) resulted in the formation of **17a** (silica gel, acetone–petroleum ether mixture) in 70% yield.[13] Dethioketalization



of **17a** (*N*-chlorosuccinimide, $AgNO_3$, aqueous CH_3CN, 0.5 h) gave **17b** (65%), which was subjected to hydrogenation (Pd/C 10%, EtOH, 20 psi, 2 h) to yield **18a**. Alkaline hydrolysis of **18a** (2 N NaOH, MeOH, 60 °C, 12 h) and ring closure of the resultant acid (**18b**) with concentrated H_2SO_4 (20-fold excess, room temperature, 12 h) gave 4-demethoxy-7,9-dideoxydaunomycinone (**19a**) in 71% yield (mp 186–87 °C (lit.[14] mp 180–82 °C). Methylation of **19a** (Me_2SO_4, K_2CO_3, acetone) gave **19b** (mp 145–46 °C (lit.[15] 145–47 °C), which was converted to **19c** (according to the method adopted by Sih et al.[14] for daunomycinone synthesis) in 55% overall yield (mp 184–86 °C, identical with the product prepared earlier by us[3a]). As the conversion of **19c** to 4-demethoxydaunomycinone (**4**) has already been described,[16] we consider that our new synthesis of **19c** in effect constitutes a total synthesis of **4**.[17,18]

Registry No. (±)-**4**, 58924-49-5; **5**, 635-12-1; **6**, 85293-65-8; **7**, 85293-66-9; **8**, 85293-69-2; **9**, 85293-70-5; **10**, 65726-46-7; **11**, 85293-67-0; **12**, 85293-68-1; **13**, 61769-87-7; **14**, 85293-71-6; **15**, 85293-73-8; **16**, 85293-72-7; **17a**, 85293-74-9; **17b**, 85293-75-0; **18a**, 85293-76-1; **18b**, 85293-77-2; (±)-**19a**, 67122-26-3; (±)-**19b**, 84498-97-5; (±)-**19c**, 33628-86-3; $(Me_2N)_2CH_2$, 51-80-9; [PMe(Ph)$_3$]Br, 1779-49-3; 2-methoxy-1,3-butadiene, 3588-30-5; ethyl acetoacetate, 141-97-9; ethyl acetoacetate ethylene thioketal, 66278-17-9; 4-hydroxy-2-butanone ethylene thioketal, 27130-39-8; methyl vinyl ketone, 78-94-4; 2-lithio-2-methyl-1,3-dithiane, 27969-97-7.

(8) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).
(9) A similar approach was used earlier (T. Oishi, M. Nagai, and Y. Ban, *Tetrahedron Lett.*, 191 (1968)) for the preparation of 3-ketobutanol ethylene ketal.
(10) Conversion of **10** to **11** was carried out by a slight modification using AcOH instead of Ac_2O according to the method of Taylor and Shino (E. C. Tayler and Y. Shino, *J. Org. Chem.*, **33**, 1719 (1968)).
(11) J. S. Yadav, P. Corey, C. T. Hsu, K. Perlman, and C. J. Sih, *Tetrahedron Lett.*, **22**, 811 (1981). E. Vedejs and B. Nadar, *J. Org. Chem.*, **47**, 3193 (1982).
(12) **15** was prepared from 1,4-dimethoxynaphthalene by Friedel–Crafts reaction with 3-carbomethoxypropionyl chloride ($AlCl_3$, EDC, room temperature) in 85% yield. A different approach for the synthesis of **16** has been reported by Bridson et al. (J. N. Bridson, S. M. Bennett, and G. Butler, *J. Chem. Soc., Chem. Commun.*, 413 (1980)).
(13) The Diels–Alder adduct resulted in a mixture of two expected isomers in 2:1 ratio. No attempt was made to separate these isomers as the final product, **19a**, will result exclusively from both the isomers.
(14) F. Suzuki, S. Trenbeath, R. D. Gleim, and C. J. Sih, *J. Org. Chem.*, **43**, 4159 (1978).
(15) F. A. J. Kerdesky and M. P. Cava, *J. Am. Chem. Soc.*, **100**, 3635 (1978).
(16) F. Arcamone, L. Bernardi, B. Patellia, P. Giardino, A. DiMareo, A. M. Casazza, C. Soranzo, and G. Pratesi, *Experientia*, **34**, 1255 (1978).
(17) All compounds gave satisfactory combustion and spectroscopic data consistent with assigned structures.
(18) This work was assisted financially by a grant from Science and Technology Cell, Education and Youth Services Department, Maharashtra Government.

Supplementary Material Available: Experimental details for the compounds in this paper (10 pages). Ordering information is given on any current masthead page.

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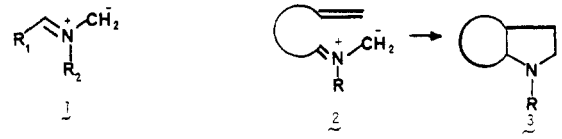
Received November 17, 1982

An Expedient Synthetic Approach to the Physostigmine Alkaloids via Intramolecular Formamidine Ylide Cycloadditions

Summary: New approaches for the direct generation of several highly reactive imidate methylides are described that rely upon acyl fluoride mediated desilylation. The utility of this methodology has been demonstrated in a stereospecific synthesis of *dl*-eserethole (**4**), which embodies the first example of an intramolecular dipolar addition of a formamidine ylide to an *unactivated* olefin as a central feature.

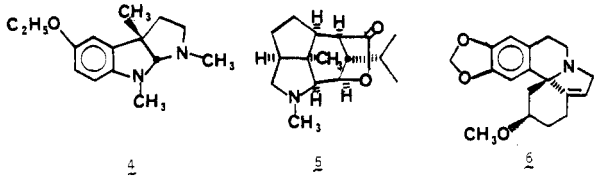
Sir: The prominent role that 1,3-dipolar cycloaddition reactions play in the elaboration of a variety of heterocycles has become increasingly apparent in recent years. The vast majority of studies bearing relevance to natural product synthesis have hinged upon the utilization of "classical" dipoles (as exemplified by nitrones, azomethine imines, and nitrile oxides).

Accounts concerned with the generation and subsequent 1,3-dipolar addition reactions of nonstabilized azomethine ylides (e.g., **1**) have, by comparison, remained relatively



R_1 = alkyl, RS-, R_2N-

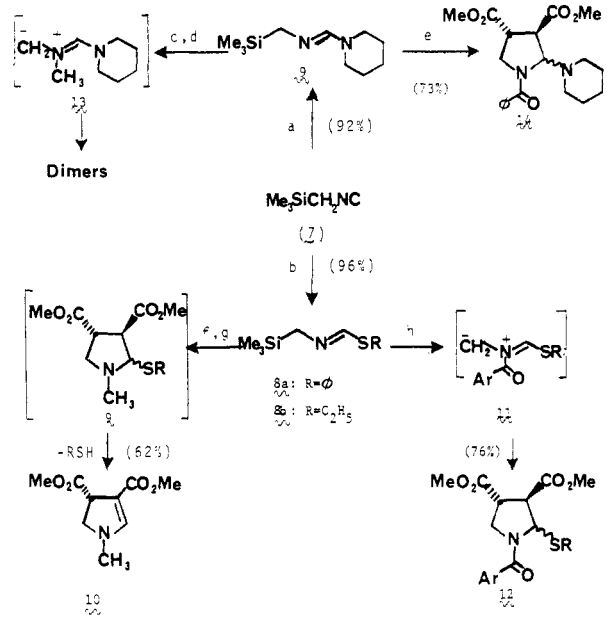
R_2 = alkyl



few in number.[1,2] In principle, the use of these species in intramolecular cyclization reactions (e.g., **2** → **3**) should facilitate efficient synthetic approaches to numerous naturally occurring alkaloids. Several representative examples include eserethole (**4**), dendrobine (**5**), and erythramine (**6**), in addition to alkaloids belonging to the dendrobatid and amarylidaceae groups.

The purpose of this communication is to report our observations on the utility and limitations exhibited by formamidine methylides, e.g., **1** (R_1 = R_2N), and thioformimidate methylides, e.g., **1** (R_1 = RS), as synthetic intermediates. In addition, we describe the first example of an *intramolecular* dipolar addition of a nonstabilized azomethine ylide to an appropriately situated olefin. Moreover, in contrast to their intermolecular counterparts, we have found that these cyclizations proceed efficiently with *unactivated* olefins.

Reports from several laboratories have disclosed the ability of organic isonitriles to enter into a diverse array of synthetic transformations. Of these, we have found the copper-mediated insertion reactions of protic nucleophiles[3] with **7** to be the most useful.[4] Treatment of isonitrile[5] **7**



(a) $C_5H_{10}NH$, CuCl. (b) RSH, $Cu(acac)_2$. (c) CH_3I. (d) CsF. (e) PhCO-F, $MeO_2CCH{:}CHCO_2Me$. (f) CH_3I. (g) CsF, $MeO_2CCH{:}CHCO_2Me$. (h) p-O_2N-C_6H_4COF, $MeO_2CCH{:}CHCO_2Me$, CH_3CN.

with thiophenol (1 equiv, 50 °C, 3 h) in the presence of a catalytic amount of $Cu(acac)_2$ furnished the anticipated thioformimidate **8a** in 96% yield. Similarily, exposure of **7** to piperidine (2 equiv, 110 °C, 2 h) and a catalytic quantity of Cu_2Cl_2 afforded the formamidine **9** (92%). In contrast to these observations, the reaction of **7** with a variety of alcohols under similar reaction conditions invariably resulted in desilylation of the isonitrile.

The conversion of thioformimidates such as **8** to the corresponding dipolar methylides is experimentally straightforward as illustrated by the following examples. Alkylation of **8a** with iodomethane (1 equiv) in CH_3CN at 25 °C (16 h) followed by the addition of dimethyl fumarate (1 equiv) and CsF (2.5 equiv) afforded the pyrroline **10** in 62% yield.[6] Alternatively, exposure of **8b** in CH_3CN to

(1) For an interesting recent example of pertinence to this communication, see: Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980** *102*, 7993 and references therein.

(2) Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167.

(3) Saegusa, T.; Kobayashi, S.; Hirota, K.; Okamura, Y.; Iro, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1638.

(4) An additional mode of isonitrile functionalization that imparts enhanced flexibility to the methodology described in this communication involves the alkylation of the lithio derivative corresponding to **7**. Schollkopf, U.; Jentch, R.; Madawinta, K.; Harms, R. *Justus Liebigs Ann. Chem.* **1976**, 2105.

(5) Smith, R.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.*, in press.

0022-3263/83/1948-1554$01.50/0