with both diol epoxide-1 enantiomers, in which cis attack on the epoxide predominates. The influence of absolute configuration on selectivity for cis vs. trans addition of deoxyribonucleotide residues in DNA to the benzo[c]phenanthrene diol epoxide enantiomers must reflect differences in interactions of these chiral diol epoxides with the asymmetric DNA molecule. Details of these interactions are presumably significant in bringing about the observed differences among the tumorigenic[7] as well as mutagenic[29] responses elicited by the enantiomeric diol epoxides.

(29) Wood, A. W.; Chang, R. L.; Levin, W.; Thakker, D. R.; Yagi, H.; Sayer, J. M.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1984**, *44*, 2320-2324.

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Supplementary Material Available: Listing of the ^{1}H NMR chemical shifts for the sugar hydrogens of the acetylated deoxyribonucleoside adducts, as well as CD spectra of the adducts derived from (+)-benzo[c]phenanthrene-(4*S*,3*R*)-diol (2*S*,1*R*)-epoxide-1 and (-)-benzo[c]phenanthrene-(4*R*,3*S*)-diol (2*S*,1*R*)-epoxide-2 (2 pages). Ordering information is given on any current masthead page.

Communications to the Editor

Nucleophilic Additions to Thionolactones. New Synthetic Technology for the Construction of Medium- and Large-Ring Ethers

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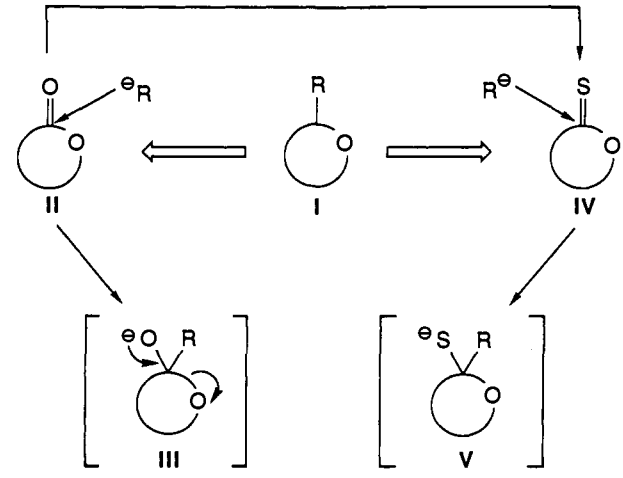
Medium- and large-ring molecular frameworks are abundant in nature[1] and are increasingly becoming targets for total synthesis. While a plethora of methods are now available for the synthesis of medium lactones and macrolactones, technology for the construction of the corresponding cyclic ethers is still emerging.[2] In this paper we report a new method for the construction of medium and large cyclic ethers from the readily available lactones[3] via the corresponding thionolactones.[4]

Scheme I outlines the general concepts that led to the development of the present technology. In view of their ready availability, lactones II were considered as excellent potential precursors to their ether counterparts I. Unfortunately, nucleophilic additions to medium and large macrolactones generally result in rupture of the ring, due to the high reactivity of the tetrahedral intermediates III obtained from the initial addition. On the other hand, nucleophilic addition to thionolactones IV (available from the corresponding lactones)[4] was expected[5,6] to lead to a more stable, and yet more nucleophilic, tetrahedral intermediate V due to the

Scheme I



unique properties of the thiolate anion. Facile alkylation of V followed by further elaboration of the resulting mixed thioketals was then expected to furnish the requisite cyclic ethers I with varying substitution. These expectations were fully realized resulting in a practical, flexible, and wide-scope method for the generation of medium and large cyclic ethers as the following results illustrate.

Thionocaprolactone[7] reacted smoothly with a variety of organometallic reagents, including methyllithium, allyllithium, and 2-furyllithium in THF at -78 °C, producing, after quenching with MeI, the corresponding addition products in good to excellent yields according to eq. 1 (Table I, entries 1-4). Furthermore, the methylthio group was easily and efficiently removed from these adducts by reduction with tin hydride reagents (e.g., Ph_3SnH, n-Bu_3SnH) as indicated in Table I.

To explore the generality and scope of this method in terms of ring size and substitution, a series of thionolactones were prepared[7] and subjected to the described sequence (organometallic addition-MeI trapping and Ph_3SnH-AIBN reduction) leading to a series of substituted oxocyclic systems in good to excellent yields. Table I includes some of these results illustrating the potential of the present technology in the construction of medium

(1) For some excellent recent reviews on such compounds from marine origins, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251, 551; **1986**, *3*, 1.

(2) For some recent examples see: (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. (c) Overman, L. E.; Blumenkoph, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. (d) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (e) Kocienski, P. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2093. (f) Schreiber, S.; Kelly, S. E. *Tetrahedron Lett.* **1984**, *25*, 1757. (g) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, *22*, 2601.

(3) For reviews on methods of constructing medium lactones and macrolactones, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew Chem. Int. Ed. Engl.* **1977**, *16*, 585. Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(4) For reviews on the synthesis of thionolactones, see: (a) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. (b) Jones, B. A.; Bradshaw, J. S. *Chem. Rev.* **1984**, *84*, 17.

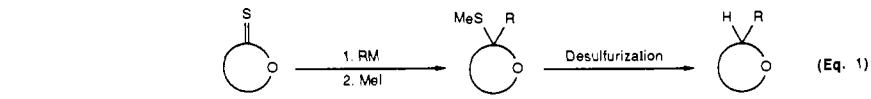
(5) For addition of organolithium reagents to thionoesters, see: Narasimhau, L.; Sanitra, R.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1978**, 719.

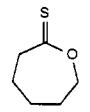
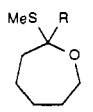
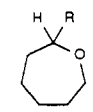
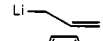
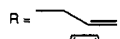
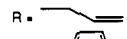
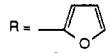
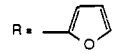
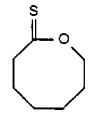
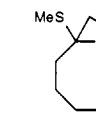
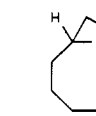
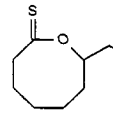
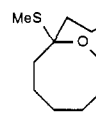
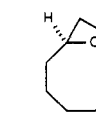
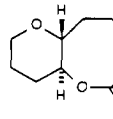
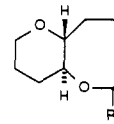
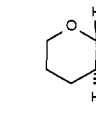
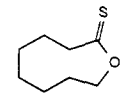
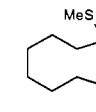
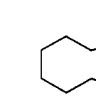
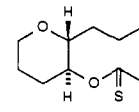
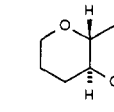
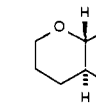
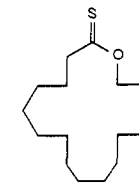
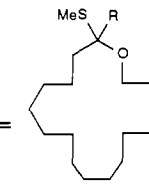
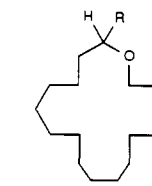
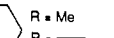
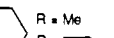
(6) In line with these properties is our recent successful bridging of macrodithionolactones to bicyclic systems.[2a]

(7) Thionocaprolactone (**1**) was prepared from caprolactone and Lawesson's reagent in 80% yield. The other thionolactones reported in this work were obtained similarly and in the following yields. Table I (entry, yield): 5, 40%; 6, 32%; 7, 56%; 9, 62%; 10, 80%; 11, 78%; Scheme II, compound **1**, 80%; Scheme III, compound **6**: 72%. The lactones were obtained from the corresponding hydroxy acids by lactonization: Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. Further details will be given in a forthcoming full account of this work.

0002-7863/87/1509-2504$01.50/0

Table I. Synthesis of Cyclic Ethers by Nucleophilic Addition to Thionolactones



Entry	Thionolactone[a]	Nucleophile[b]	Addition Product	Yield (%)	Reduction Product[c]	Yield (%)
1		MeLi	 R = Me	83	 R = Me	85
2			R = 	86	R = 	85
3			R = 	92	R = 	90
4[d]		$LiSn^nBu_3$	R = Sn^nBu_3	79	—	—
5		^{n}BuLi		96		84
6		^{n}BuLi		56		85
7		MeLi	 R = Me	83		90
8		$LiEt_3BH$	R = H	74	(via sulfone and $AlMe_3$)[2b]	82
9		Li		94		88
10		MeLi		96	 (4:1 ratio)	84
11		MeLi	 R = Me	78	 R = Me	90
12		Li	R = 	81	R = 	85

[a] See ref 7. [b] Additions were carried out with 1.1–2.5 equiv of nucleophile in THF at −78 °C followed by quenching with excess MeI (−78 → 25 °C); see experimental procedure, ref 12. [c] Reductions were carried out with 2.1–2.5 equiv of Ph_3SnH–catalytic AIBN in toluene at 110 °C. [d] Lithiation of this stannane (*n*-BuLi, −78 °C) followed by addition of electrophiles (e.g., PhCHO, allyl bromide) resulted in the formation of the corresponding adducts, thus widening the scope of these operations.

(seven-, eight-, and nine-membered) and large (17-membered) ring ethers. Furthermore, high diastereocontrol, when applicable, is observed in these reactions. Thus, in entries 6–8 and 10 a single addition product (unassigned stereochemistry) was obtained. Reduction of these products also proceeded with high stereocontrol (entries 6 and 7, indicated product exclusively; entry 10, 4:1 ratio, with indicated structure the major product). The cis structures of the final products were based on NOE studies (5–10% enhancements) involving the protons adjacent to oxygen. It is of interest to note that the alternative reduction sequence presented in entry 8 (Table I) involving a sulfone intermediate and $AlMe_3$[2b] led to the same diastereoisomer as in entry 7.

The convenient and clean generation of free radical species[8] from the mixed methyl thioketal intermediates prepared in these studies prompted us to explore the construction of complex polycyclic systems by involving unsaturated sites in chain reactions. Scheme II presents such a sequence leading efficiently and stereospecifically to tricyclic systems **4** (20%) and **5** (65%) from the nine-membered thionolactone **1**, via methylthio ether **2** and transient free radical species **3**[9].

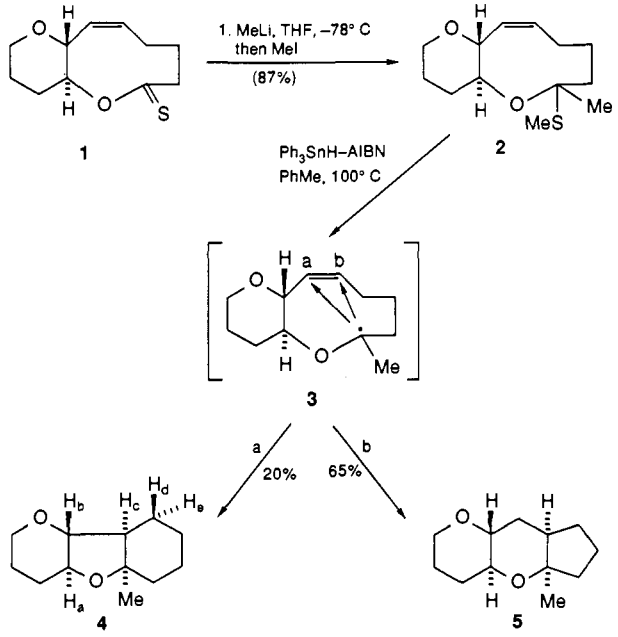
Finally, an application of the described technology in total synthesis is included. Scheme III outlines a short and efficient

(8) For a recent monograph on this subject see: Giese, B. *Radicals in* Organic *Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: 1986.

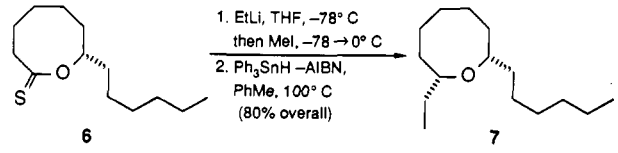
(9) The indicated stereochemistry of the newly formed ring junctures in **4** and **5** is tentatively assigned on the basis of mechanistic considerations, molecular modeling, and ^{1}H NMR data (500 MHz, $CDCl_3$). Thus the following coupling constants (J) were observed for compound **4**: $J_{a,b}$ = 8.5 (trans relationship), $J_{b,c}$ = 11.0, $J_{c,d}$ = 2.1 and $J_{c,e}$ = 5.5 Hz. These values were in close agreement with calculated coupling constants (MODEL, $J_{a,b}$ = 9.5, $J_{b,c}$ = 10.4, $J_{c,d}$ = 1.6, and $J_{c,e}$ = 5.5 Hz) for this structure. The calculated J values for the other three possible diastereoisomers were significantly different from the observed values. Structure **5** was favored by analogy. We thank Dr. N. A. Petasis for the calculations and Professor W. C. Still for his computer programs MODEL and MACROMODEL.

(10) The cis stereochemistry of compound **7** was assigned on the bais of a 5.1% NOE between the two C*H*–O protons (500 MHz, $CDCl_3$). The spectra (^{1}H and ^{13}C NMR and IR) were identical with those provided by Professor A. Fukazawa (Hokkaido, Japan) and Dr. A. B. Holmes (Cambridge, UK).

Scheme II



Scheme III



total synthesis of (±)-lauthisan (**7**),[11] the skeleton of the marine natural product laurencin, from the readily available thionolactone **6**.

The described chemistry opens new routes to mono- and polycyclic ether systems of medium and large sizes from thionolactones. Furthermore, the produced mixed methyl thioketals serve as excellent precursors for free radical generation and, thus, may be found useful in the construction of a variety of complex polycyclic systems via intra- and/or intermolecular trappings. The potential of the present technology in the total synthesis of novel and complex natural products is obvious and is currently under exploration in these laboratories.[12,13]

Acknowledgment. We express our many thanks to Mr. John Dykins of this Department for his mass spectroscopic assistance and useful comments. We are also grateful to Professor A. Fukuzawa, Hokkaido University, Japan, and Dr. A. B. Holmes, Cambridge University, UK, for providing us with copies of the NMR, IR, and mass spectra of naturally derived lauthisan. This work was financially supported by the National Institutes of Health, Merck Sharp and Dohme, Hoffmann-La Roche, and Smith Kline and French.

(11) For the naming of this skeleton, see: Blunt, J. M.; Lake, R. J.; Munro, M. H. G.; Yorke, S. C. *Aust. J. Chem.* **1981**, *34*, 2393. For preparation from laurencin, see: Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081. For a recent total synthesis, see ref 2d.

(12) **Representative Experimental Procedure** (Table I, entry 1). To a stirred solution of caprothionolactone (130 mg, 1.0 mmol) in anhydrous THF (3.0 mL) at −78 °C was added under argon MeLi (0.78 mL of 1.4 M solution in ether, 1.1 mmol). The reaction mixture was stirred at −78 °C for 5 min (TLC monitoring) before quenching with MeI (0.19 mL, 3.0 mmol). The reaction mixture was then allowed to reach ambient temperature with stirring (ca. 1 h). Dilution with ether (50 mL) followed by washing with water (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (silica, 10% ether in petroleum ether) gave the corresponding addition product (R = Me, Table I, entry 1, 132 mg, 83% yield).

(13) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogenous materials.

Bell-Shaped Temperature Dependence in Quenching of Excited $Ru(bpy)_3^{2+}$ by Organic Acceptor

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Electron transfer quenching reactions of excited tris(2,2'-bipyridine)ruthenium(II), $*Ru(bpy)_3^{2+}$, have received special attention as tests of Marcus theory[1] as well as in their application to redox photosensitization.[2] Nevertheless, the mechanism of oxidative quenching of $*Ru(bpy)_3^{2+}$ in acetonitrile, exhibiting negative temperature dependence in endoergic and moderately exoergic regions,[3] is not explicitly understood. We now report the origin of the negative temperature dependence and the reaction mechanism of oxidative quenching of $*Ru(bpy)_3^{2+}$.

The quenching rate constant (k_q) at a given temperature was obtained by conventional Stern–Volmer plots based on both the emission intensity and the lifetime of $*Ru(bpy)_3^{2+}$. The effect of diffusion on the observed quenching rate constant was corrected.[4] Typical temperature-dependent data for k_q in acetonitrile are shown in Figure 1. The activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of quenching were calculated by the Eyring equation,

$$\ln (k_q/T) = \ln (\langle \varkappa \rangle k_B K_{12}/h) - \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R \quad (1)$$

where K_{12} is the formation constant of an encounter complex.[5] The electronic transmission coefficient $\langle \varkappa \rangle$, was assumed to be unity throughout the work. The results are summarized in Table I. The findings are as follows: (a) $\Delta H^{\ddagger}$ is always positive when $\Delta G_{23} < -2$ kcal/mol[6] (Figure 1a, quencher (Q) = 1,4-naphthoquinone). (b) The Eyring plot is "bell shaped" (Figure 1b) when $-2 < \Delta G_{23} < 0$ kcal/mol (Q = duroquinone or *p*-nitrobenzaldehyde). (c) When $\Delta G_{23} > 0$ kcal/mol (Figure 1c, Q = methyl *m*-nitrobenzoate), the temperature dependence of k_q is negative (apparent $\Delta H^{\ddagger} < 0$) in the temperature range examined (−35 to 60 °C). The most striking feature is the finding of a bell-shaped Eyring plot (Figure 1b). This behavior is not due to temperature-dependent solvent viscosity.[4] Furthermore, the temperature

(1) (a) Newton, M. D.; Sutin, N. *Annu. Rev. Phys. Chem.* **1984**, *35*, 437. (b) Sutin, N. *Prog. Inorg. Chem.* **1983**, *30*, 441. (c) Kavarnos, G. J.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401.

(2) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, 46.

(3) (a) Kitamura, N.; Okano, S.; Tazuke, S. *Chem. Phys. Lett.* **1982**, *90*, 13. (b) Tazuke, S.; Kitamura, N. *Pure Appl. Chem.* **1984**, *56*, 1269. (c) Tazuke, S.; Kitamura, N.; Kawanishi, Y. *J. Photochem.* **1985**, *29*, 123.

(4) Observed bimolecular quenching rate constant (k_q^{obsd}) was corrected by the equation

$$1/k_q = 1/k_q^{obsd} - 1/k_{12}$$

where k_{12} is the diffusion rate constant in acetonitrile at a given temperature calculated by the Smoluchowski–Stokes–Einstein equation (Smoluchowski, M. *Z. Phys. Chem.* **1917**, *92*, 129):

$$k_{12} = 2RT/3000\ \eta(2 + r_A/r_B + r_B/r_A)$$

r_A and r_B are radii of $*Ru(bpy)_3^{2+}$ (7.1 Å) and a quencher (3.8 Å), respectively. Solvent viscosity (η) at each temperature was taken from: Janz, G. Z.; Tomkins, R. P.; *Nonaqueous Electrolyte Handbook*; Academic: New York, 1972.

(5) All the quenchers used in this study are neutral molecules, so the K_{12} is given by the following Fuoss equation:

$$K_{12} = 4\pi N r^3/3000,$$

where $r = r_A + r_B$.

(6) ΔG_{23} was calculated by

$$\Delta G_{23} = E_{1/2}(Ru^{3+/2+}) - E_{1/2}(A^{0/-}) - E_{0-0} + w_p$$

where $E_{1/2}(Ru^{3+/2+})$ and $E_{1/2}(A^{0/-})$ are the oxidation and reduction potentials of $*Ru(bpy)_3^{2+}$ and an acceptor, respectively (see Table I). E_{0-0} is the excitation energy of $Ru(bpy)_3^{2+}$, 2.08 eV. w_p is the electrostatic work necessary to separate two product ions to an infinite distance.[1b]

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