reaction systems with an optimal internal surface area and integrated redox-active dyes.

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Supplementary Material Available: Tables of bond lengths, valence angles, and atomic parameters for **3**, experimental details for the syntheses of **1–4**, and ^{1}H NMR spectra of **1–3** (11 pages); listing of observed and calculated structure factors for **3** (19 pages). Ordering information is given on any current masthead page.

Stereospecific Method to *E* and *Z* Terminal Fluoro Olefins and Its Application to the Synthesis of 2′-Deoxy-2′-fluoromethylene Nucleosides as Potential Inhibitors of Ribonucleoside Diphosphate Reductase

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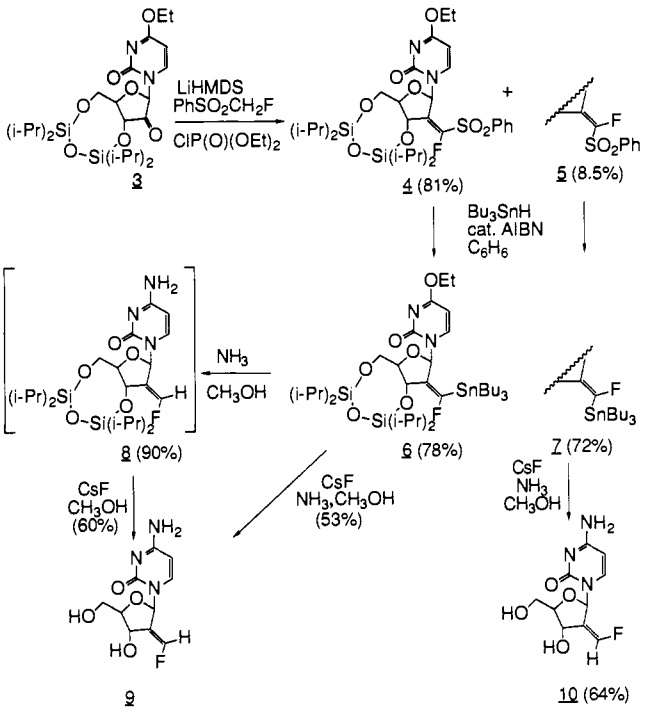
The terminal fluoro olefin group is a useful functionality in the design of mechanism-based enzyme inhibitors.[1] Because the potency of these inhibitors often depends on the geometry of the olefin, there is considerable interest in developing stereospecific methods for fluoro olefins. Most methods reported thus far[1a,2a-e] yield mixtures of *E* and *Z* isomers, which are often difficult to separate. The only general stereospecific synthesis[2f] relies on acetylenes as starting materials and provides the terminal fluoro olefins contaminated with 5–15% nonfluorinated olefins.

We report a stereospecific method to *E* and *Z* terminal fluoro olefins from (fluorovinyl)stannanes **1** and **2**,[3] which are readily accessible from ketones. The utility of this method is demonstrated with the synthesis of (*E*)- and (*Z*)-2′-deoxy-2′-(fluoromethylene)cytidine, **9** and **10**, respectively (Scheme I). The fluoro olefins **9** and **10** were designed as bioprecursors of mechanism-based inhibitors of ribonucleoside diphosphate reductase (RDR) (EC 1.17.4.1). It was envisioned that **9** and **10** would be transformed by the action of kinases to the corresponding diphosphate derivatives,[4] which could be substrates of RDR, and inactivate the enzyme via a fluoroallyl radical. This enzyme contains an essential tyrosyl radical and catalyzes the rate-determining step in the de novo synthesis of deoxyribonucleic acid (DNA).[5]

Scheme I



Using the Horner–Wittig reaction,[2a] 2′-ketonucleoside **3**[6] was converted to a mixture of readily separable fluorovinyl sulfones **4** and **5**.[7] Our lack of success in reducing the fluorovinyl sulfones to the fluoro olefin with amalgamated aluminum[2a,8] led to the discovery of a new and stereospecific method to fluoro olefins.

Fluorovinyl sulfones **4** and **5** were transformed to (fluorovinyl)stannanes **6** and **7** with 2 equiv of tributyltin hydride.[9] Analysis of the crude reaction mixtures by ^{19}F NMR showed the absence of **7** in **6** and vice versa. Watanabe and co-workers[10] proposed an electron-transfer mechanism for the conversion of vinyl sulfones to mixtures of (*E*)- and (*Z*)-vinylstannanes. On the basis of our observations that fluorovinyl sulfones obtained from ketones are transformed to (fluorovinyl)stannanes with retention of configuration,[9] a radical addition–elimination mechanism is proposed. To our knowledge, this is the first report of a stereospecific radical reaction of this kind involving tributyltin hydride.[11,12]

† Organic Chemistry.
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∥ Tumor Biology.

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(7) All new compounds gave spectral data consistent with their assigned structure and satisfactory HRMS or elemental analysis.

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(9) For monosubstituted fluorovinyl sulfones obtained from aldehydes, mixtures of [(*E*)- and -(*Z*)-fluorovinyl]stannanes were obtained. These results will be reported in due course.

(10) Watanabe, Y.; Ueno, Y.; Araki, T.; Endo, T.; Okawara, M. *Tetrahedron Lett.* **1986**, *27*, 215–218.

(11) For a leading reference on radical reactions with tributyltin hydride, see: Neumann, W. P. *Synthesis* **1987**, 665–683.

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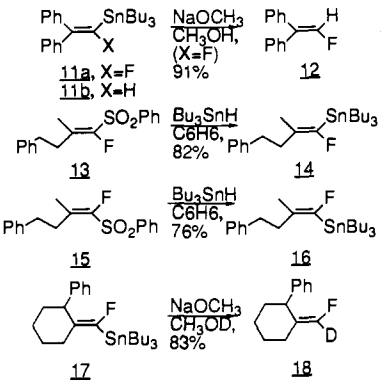
(*E*)-2'-Deoxy-2'-(fluoromethylene)cytidine (**9**) was obtained directly from **6** ($CsF/NH_3/CH_3OH$). ^1H and ^{19}F NMR analysis of crude **9** indicated the presence of only the *E* fluoro olefin. Alternatively, **6** was treated with methanolic ammonia to provide **8**,[13] which upon treatment with CsF yielded **9**. (*Z*)-2'-Deoxy-2'-(fluoromethylene)cytidine (**10**) was obtained from **7** by the "one-pot" procedure, i.e., $CsF/NH_3/CH_3OH$. The optimum conditions for the stereospecific destannylation reaction depend upon the functionalities present in the molecule. In most cases, refluxing methanolic sodium methoxide is the method of choice over methanolic ammonia or CsF in refluxing methanol.[14] The tributylstannyl group was not removed from nonfluorinated vinylstannane obtained from benzophenone (i.e., **11b**) under conditions (refluxing MeOH/NaOMe, 16 h) where the fluorinated vinylstannane (**11a**) provided 1,1-diphenyl-2-fluoroethylene (**12**)[8] in 91% yield.



Retention of configuration for the homolytic cleavage of a vinyl phenylsulfonyl group with concomitant replacement by tributyltin is also illustrated with the conversion of the less constrained acyclic (*E*)- and (*Z*)-fluorovinyl sulfones **13** and **15** to (*E*)- and (*Z*)-(fluorovinyl)stannanes **14** and **16**, with greater than 97% retention of configuration.[15] (Fluorovinyl)stannanes provide a convenient entry to deuterated fluoro olefins of defined stereochemistry. Thus, treatment of **17**, obtained exclusively from the corresponding fluorovinyl sulfone,[15] with sodium methoxide in refluxing CH_3OD gave the deuterio olefin **18**.

Compound **9**, administered to L1210 leukemia bearing mice (1 mg/kg, ip) inhibited RDR activity in tumor cells by 80% within 1 h and by 97% within 3 h.[16] Fluoro olefin **9** is a potent cytotoxic agent (IC_{50} = 58 nM), whereas the geometric isomer **10** is substantially less active (IC_{50} = 3870 nM).[16] The difference in activity between **9** and **10** is indicative of the importance of the geometry of the fluoro olefin for biological activity.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **4-18**, the corresponding adenosine and uridine analogues of **9** and **10**, and the fluoro olefins obtained from **14** and **16** and experimental procedures for biochemical results (22 pages). Ordering information is given on any current masthead page.

(12) For a leading reference on the chemistry of vinyl sulfones, see: Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951-6984.

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(14) Harpp, D. N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737-7745.

(15) Olefin geometries were based on $^{19}F-^{13}C$ and $Sn-^{13}C$ coupling constants. This will be discussed in more detail in a full paper. The olefin geometry for **9**, **10**, nondeuterated **18**, and the fluoro olefins formed from **14** and **16** were also confirmed by NOE experiments. The structure of the precursor fluorovinyl sulfone to **17** and for **9** were confirmed by X-ray crystallography: Dr. John C. Huffman, Indiana University.

(16) RDR activity was determined by the method of Engstrom et al.: Engstrom, Y.; Eriksson, S.; Thelander, L.; Akerman, M. *Biochemistry* **1979**, *18*, 2941-2948. An IC_{50} for growth inhibition was determined after a 72-h treatment. Further details are given in the supplementary material.

Intramolecular Dynamics in the Mixed Valence Cluster $(CH_3C_5H_4)_4Ru_4S_4^{2+}$: Observation of Mobile Metal-Metal Bonds

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We wish to describe experiments which probe the movement of metal-metal bonds within a metal cluster.[1] Previous work on the intramolecular dynamics of metal-metal bonds has focused on structural changes coupled to ligand rearrangements.[2] The dynamic NMR properties of $W_4(O^iPr)_{12}$ implicate single bond-double bond isomerization about its metallacyclobutadiene core.[3] The present study focuses on the intramolecular bond-no bond dynamics, uncomplicated by changes in ancillary ligation.

The compound $(MeCp)_4Ru_4S_4$ (**1**, MeCp = η^5-$CH_3C_5H_4$) features a distorted tetrahedral Ru_4 core stabilized by a pair of Ru-Ru bonds (2.768 (3) and 2.766 (3) Å) and four triply bridging sulfido ligands.[4] Cyclic voltammetry of a CH_2Cl_2 solution of **1** shows two one-electron oxidations at the relatively mild potentials of -62 and -183 mV (vs Ag/AgCl).[4] Previous work has shown that closely spaced pairs of redox steps in metal clusters can be indicative of localized bond breaking/making.[5] To investigate this point, a salt of the doubly oxidized cubane $[1]^{2+}$ was prepared by the addition of 2 equiv of TCNQ (tetracyanoquinodimethane) to a CH_2Cl_2 solution of **1**.[6] This afforded a purple microcrystalline precipitate of $[(MeCp)_4Ru_4S_4](TCNQ)_2 \cdot CH_2Cl_2$.[7] A coulometry experiment at 0.0 V (vs Ag/AgCl) confirmed that this salt contains the doubly oxidized cluster.

The structure of $[(MeCp)_4Ru_4S_4](TCNQ)_2$ was determined by single-crystal X-ray diffraction.[8] In the lattice the cluster dication is well isolated from the $(TCNQ)_2^{2-}$ anion, whose structure is unexceptional.[9] The structure of $[1]^{2+}$ differs from **1** by the addition of a Ru-Ru bond which gives rise to a chiral

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(7) IR (KBr, cm^{-1}) 2180 (s, ν_{CN}). Anal. Calcd for $C_{48}H_{36}N_8Ru_4S_4 \cdot CH_2Cl_2$: C, 43.80; H, 2.83; N, 8.34; S, 9.53. Found: C, 44.07; H, 2.71; N, 8.53; S, 9.25.

(8) X-ray crystallography of $C_{48}H_{36}N_8Ru_4S_4 \cdot CH_3CN$: dark red, opaque crystal: 0.14 × 0.32 × 0.64 mm, triclinic, *P*1 (C_i^1, no. 2); a = 10.401 (2) Å, b = 24.166 (6) Å, c = 9.914 (2) Å, α = 100.74 (2)°, β = 100.25 (2)°, γ = 93.19 (2)°, V = 2399 (2) Å^3, Z = 2, ρ_{calcd} = 1.797 g/cm^3. Diffraction data: mounted in Paratone-N oil (Exxon) at -75 °C, Enraf-Nonius CAD4 automated κ-axis diffractometer, Mo radiation ($\lambda(K\alpha)$ = 0.71073 Å), graphite monochromator, $2\theta < 46°$ ($\pm h \pm k - l$), 7242 intensities, 6661 unique (R_i = 0.027), 5966 observed ($I > 2.58\sigma(I)$); corrected for anomalous dispersion, absorption, Lorentz, and polarization effects. Solution: direct methods (SHELX-86); Ru and S positions were deduced from an E map; remaining non-hydrogen atoms located by difference Fourier synthesis; hydrogen atoms were included in "idealized" positions. Refinement: full-matrix least squares (SHELX-76), 364 variables against 5966 data converged with R = 0.034 and R_w = 0.049.

(9) Structural studies on other salts of $(TCNQ)_2^{2-}$ have shown that the C-N distances and (methano) carbon-(ring) carbon distances are like those reported for $[Nb_3(\mu\text{-}Cl)_6(C_6Me_6)_3]^{2+}(TCNQ)_2^{2-}$ (Goldberg, S. Z.; Spivack, B.; Stanley, G.; Eisenberg, R.; Braitsch, D. M.; Miller, J.; Abkowitz, M. *J. Am. Chem. Soc.* **1977**, *99*, 110) and $((Me_5C_5)_2Fe^+)_2(TCNQ)_2^{2-}$ (Candela, G. A.; Swartzendruber, L. J.; Miller, J. S.; Rice, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 2756).

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