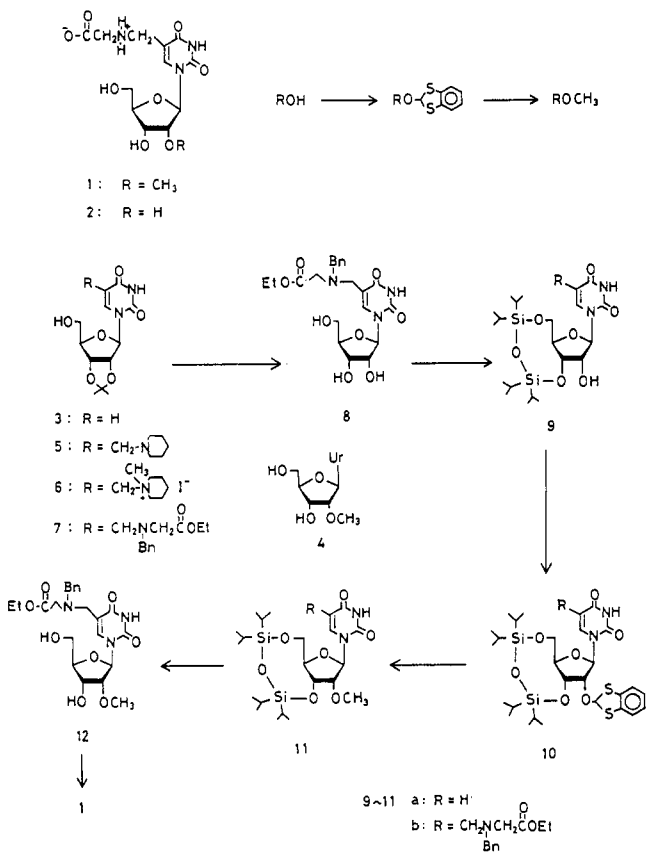
Scheme I



O-(dibutylstannylene)uridine with methyl iodide gave a 55:45 mixture of the 2′- and 3′-methylated species. Tin(II) chloride catalyzed methylation of uridine by use of diazomethane resulted in a mixture of 2′- and 3′-O-methyl isomers which were isolated in 58% and 28% yields, respectively, by tedious chromatographic separation.[13c] Methylation of 5′-O-trityluridine with diazomethane afforded a better selectivity but still required careful sepration from the 3′-isomer and acidic treatment for removal of the trityl group.[13d] Recently, we[13e] and Chattopadhyaya[13f] reported the 2′-O-methylation of N^3-protected 2′,3′-(tetraisopropyldisiloxane-1,3-diyl)uridine derivatives with MeI/Ag_2O. Although these procedures accomplish the regioselective 2′-O-methylation, they require protection of the imido group of the uracil moiety and ultimately could not be applied to **8** because of the simultaneous methylation on the tertiary amine residue. These problems led us to study an alternative methylation procedure for **8**. Finally, we found a new method for the 2′-O-methylation as shown in the Scheme I.

The present method involves a two-step reaction. First, the alcoholic function is protected with the 1,3-benzodithiol-2-yl (BDT) group as previously reported by us.[14] The protected species is then treated with Raney Ni (W-2) in refluxing ethanol. For example, treatment of 2′-*O*-(1,3-benzodithiol-2-yl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (**10a**)[15] with Raney Ni in ethanol under reflux for 1.5 h gave the 2′-*O*-methyluridine derivative (**11a**) in 58% yield, which was converted to **4a** in 78% yield by treatment with KF–Et_4NBr/CH_3CH–H_2O. Application of this procedure to the synthesis of **1** was performed as follows: The reaction of **8** with Markiewicz reagent[16] gave a 3′,5′-cyclic silyl ether derivative (**9b**) in 93% yield. Compound **9b** was treated with Nakayama reagent (1,3-benzodithiolium tetrafluoroborate)[17] in the presence of pyridine in methylene chloride at room temperature for 2.5 h gave the 3′-protected product (**10b**) in 70% yield. The Raney Ni reduction of the 2′-O-BDT ortho ester gave the 2′-O-methyl derivative (**11b**) in 51% yield. Desilylation of **11b** afforded **4b** in 88% yield. The catalytic hydrogenation of **4b** on Pd/C gave **12** in 33% yield. Finally, the hydrolysis of **12** by dilute NaOH followed by neutralization and then paper chromatography on Whatman 3MM using *i*-PrOH–concentrated NH_3–H_2O (7:1:2, v/v/v) gave **1** in 42% yield. The product **1** was identified with the authentic material from $tRNA^{Leu}$ by comparison with the 400-MHz NMR spectrum.

Registry No. **1**, 110419-13-1; **3**, 362-43-6; **4**, 2140-76-3; **4b**, 110419-11-9; **5**, 110419-05-1; **6**, 110419-06-2; **7**, 110419-07-3; **8**, 110419-08-4; **9b**, 110419-09-5; **10b**, 110433-14-2; **11b**, 110419-10-8; **12**, 110419-12-0; Bn-Gly-OEt, 6436-90-4; 1,3-benzodithiolium tetrafluoroborate, 57842-27-0.

Supplementary Material Available: Full NMR spectral data for new compounds **1** and **7**–**12** (2 pages). Ordering information is given on any current masthead page.

(13) (a) Furukawa, Y.; Kobayashi, K.; Kanai, Y.; Honjo, M. *Chem. Pharm. Bull.* **1965**, *13*, 1273. (b) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24. (c) Robins, M. J.; Naik, S. R.; Lee, A. S. K. *Ibid.* **1974**, *39*, 1891. (d) Heikkila, J.; Bjorkman, S.; Oberg, B.; Chattopadhyaya, J. *Acta Chim. Scand., Ser. B* **1982**, *B36*, 715. (e) Kamimura, T.; Masegi, T.; Hata, T. *Chem. Lett.* **1982**, 965. (f) Welch, C. J.; Chattopadhyaya, J. B. *Acta Chim. Scand., Ser. B* **1983**, *B37*, 147. (g) For a comprehensive review, see: Ueda, T. *Synthesis and Reaction of Pyrimidine Nucleosides*; Plenum Press, London, in press.

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(16) Markiewicz, W. T. *J. Chem. Res., Synop.* **1979**, 24. Markiewicz, W. T. *J. Chem. Res., Miniprint* **1979**, 0178.

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(18) The University of Tokyo.

Mitsuo Sekine,* Lilia S. Peshakova, Tsujiaki Hata* Shigeyuki Yokoyama,[18] Tatsuo Miyazawa[18]

Department of Life Chemistry
Tokyo Institute of Technology
Nagatsuta, Midoriku
Yokohama 227, Japan, and
Department of Biophysics and Biochemistry
Faculty of Science
The University of Tokyo
Hongo, Bunkyo-ku
Tokyo 113, Japan

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The First Versatile and Practical Building Blocks Equivalent to the Synthon of Monofluoromethylene Dicarbanion

Summary: New monofluorinated synthons have been prepared. The use of α-fluoro-α-nitro carboxylic esters as versatile building blocks was demonstrated by their conversion to various monofluorinated compounds via fluoromethyl anion and fluoromethylene dianion equivalents.

Sir: Fluorine-containing organic compounds have recently received increasing interest from both a new material[1] and a biological activity[2] viewpoint. However, the methods for

(1) Banks, R. E. *Preparation, Properties, and Industrial Applications of Organofluorine Compounds*; Ellis Horwood Ltd.: Chichester, 1982.

(2) (a) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha Ltd.: Tokyo, 1982. (b) Filler, R. *Biochemistry Involving Carbon–Fluorine Bonds*; American Chemical Society: Washington, DC, 1976.

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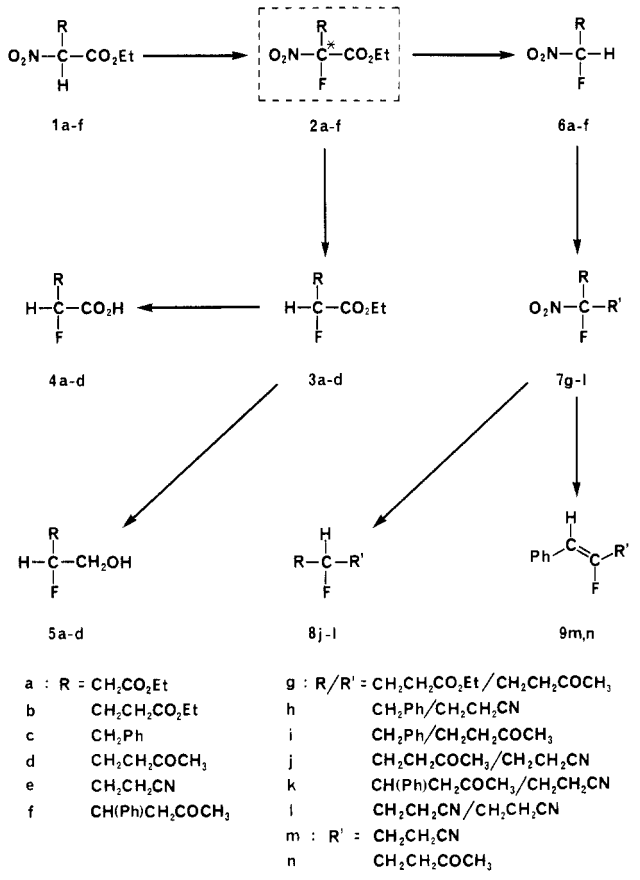
Scheme I



the introduction of a single fluorine atom into organic molecules are severely limited.[3] We thought that a useful technique for preparing monofluoro aliphatic molecules through some variant of active methylene condensations[4] would be of general synthetic interest. We have succeeded in developing general synthetic pathways to a wide variety of deliberately designed monofluoro compounds by the use of α-fluoro-α-nitro carboxylic ester building blocks.[5] Either or both carbanion-stabilizing groups allow further alkylations at the fluorine-containing chiral carbon, and either or both are easily removed or transformed without defluorination.[9] Our approach has the advantages of (1) readily available starting materials, (2) a simple, yet high-yield fluorination at an early stage, (3) a wide versatility capable of successive introduction of suitable alkyl groups at a later stage in a particular synthetic scheme, and (4) multiple functionalities which may be further transformed.

α-Nitro carboxylic esters **1a–f**, which were easily obtained by alkylation[10] (RX/NaOEt for **1a–c** or Michael addition in the presence of KF for **1d–f**) of commercially available nitroacetates, were fluorinated by our method. Thus, **1a–f** were converted to the corresponding potassium salts by addition of 2 equiv of spray-dried KF.[11] These salts were selectively fluorinated with freshly generated perchloryl fluoride[12] (THF, 22 °C/1 h) to give the trifunctional carbon compounds **2a–f** in quantitative yields.[13] The usefulness of **2a–f** as building blocks was demonstrated by converting them into the various monofluorinated compounds shown in Scheme I.

Removal of the nitro groups of **2a–d**, the presence of which is necessary for successful fluorination, was accomplished with n-Bu_3SnH[14] (AIBN/PhH, reflux/2 h, 54–88%) producing the α-fluoro carboxylic esters **3a–d**. Alkaline hydrolysis (aqueous NaOH/EtOH, 20 °C/3 h, 84–96%) of **3a–d** afforded the α-fluoro carboxylic acids **4a–d**. Reduction of **3a–d** was performed with $LiAlH_4$ (Et_2O, −50–20 °C/1 h, 72–96%) to give the β-fluoroalkanols **5a–d**.[15] Although the possibility of defluorination was anticipated under these reaction conditions, the monofluorinated derivatives **3–5** were obtained from **2** without difficulty.

We next studied the removal of the ester groups of **2**. In contrast to the successful conversion of **2d–f** into **6d–f** (81–95%), alkaline hydrolysis and decarboxylation of **2a–c** produced the fluoronitroalkanes **6a–c** only in poor yields, accompanied by unidentified byproducts associated with the multifunctional carbon structure.[7] The dealkoxycarbonylation of **2a–c**, however, was easily performed with 1 mol equiv of $NaBH_4$ (EtOH, −20 °C/2 h, 70–88%) to give **6a–c**. Successive alkylation of **6b–f** was achieved with reactions similar to the alkylation of nitroacetates[10] to give the dialkylated derivatives **7g–l** in 43–82% yields. Denitration of **7j–l** was accomplished with n-Bu_3SnH (PhH, reflux/2 h, 52–96%) to afford the fluoroalkanes **8j–l**,[16] which possess a fluorine atom at a position of the alkyl chains dependent on the choice of the two alkyl groups, R and R'. Dehydronitration of **7h,i** with MeSNa[17] (DMF, 0 °C/5 min, 53–70%) produced the Z-fluoro olefins **9m,n** in a regio- and diastereoselective manner,[18] as shown in Scheme I. We have thus developed synthons for $RCH(F)^-$ and $^-CH(F)^-$.

The resolution of the chiral building blocks **2c,d** was achieved either by repeated transesterification[19] or by the

(3) Conventional monofluorination procedures are applicable to limited structures and usually require special equipment, reagents, and drastic conditions and, therefore, generally result in lower selectivities when compared to other halogenations.

(4) Although an α-fluoro carbanion is much less stable than the α-fluorocarbocation, direct electrophilic introductions of functionalized substituents onto a fluorine-bearing chiral carbon atom is far easier than nucleophilic introductions from a synthetic standpoint. Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973; pp 64–96.

(5) Several convenient reagents have been developed[6] for the preparation of perfluorinated compounds. However, there have appeared no reports so far on monofluoro building blocks with wide synthetic usefulness, probably because of the instability of C–F bond adjacent to other functional groups[7] as well as the lack of practical methods for fluorination of such multifunctional carbon compounds.[8]

(6) Knunyants, I. L.; Yakobson, G. G. *Syntheses of Fluoroorganic Compounds*; Springer-Verlag Ltd.: Berlin, 1985; and references therein.

(7) Takeuchi, Y.; Asahina, M.; Hori, K.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1*, in press.

(8) Takeuchi, Y.; Asahina, M.; Murayama, A.; Hori, K.; Koizumi, T. *J. Org. Chem.* **1986**, *51*, 955–956.

(9) Also phosphoryl and sulfonyl groups and nitro and sulfonyl groups make capable combinations for this purpose. Studies with these groups are currently under way.

(10) Shipchandler, M. T. *Synthesis* **1979**, 666–686 and references therein.

(11) Ishikawa, N.; Kitazume, T.; Yamazaki, T.; Mochida, Y.; Tatsuno, T. *Chem. Lett.* **1981**, 761–764.

(12) Ordinary glassware can be used for this simple and safe procedure. Wehrenalp, G. B. *J. Inorg. Nucl. Chem.* **1956**, *2*, 266.

(13) As an alternative route, fluorination of nitroacetates followed by alkylation afforded **2a–f**, although the overall yields (ca. 40%) were unsatisfactory.

(14) (a) Tanner, D. D.; Blackburn, E. V.; Diaz, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 1557–1559. (b) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, 1705–1708. (c) Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692–3698.

(15) In the case of **3a,b** the ester groups of the side chain (R) were reduced to alcohols.

(16) In the case of **7l** the corresponding defluorinated product (ca. 25%) accompanied the main product.

(17) (a) Kornblum, N.; Carlson, S. C.; Smith, R. G. *J. Am. Chem. Soc.* **1971**, *101*, 647–657. (b) Kornblum, N.; Widmer, J.; Carlson, S. C. *Ibid.* **1979**, *101*, 658–664.

(18) The olefinic protons appear at δ 5.66 (J_{HF} = 38 Hz) for **9m** and δ 5.52 (J_{HF} = 39 Hz) for **9n**, respectively.

(19) (+)-**2c**, $[\alpha]^{26}_D$ + 65.6° (*c* 2.09, $CHCl_3$); (−)-**2c**, $[\alpha]^{26}_D$ −64.6° (*c* 2.41, $CHCl_3$). Takeuchi, Y.; Asahina, M.; Nagata, K.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1*, in press.

use of chiralcel OB.[20] These are the first reported optically active building blocks having fluorine and other labile groups directly attached to the chiral center.

Since the compounds **3–9** still possess a functionality to be used for further elaboration, including C–C bond formation, and are readily prepared from **1**,[22] these sequences have the potential of being versatile starting points for the construction of many monofluorinated compounds. Studies for application of the methodology are in progress.

Supplementary Material Available: Experimental details and spectral data for new compounds (11 pages). Ordering information is given on any current masthead page.

(20) Racemic **2d** was resolved on a Chiralcel OB column[21] by eluting with hexane/*i*-PrOH (9/1) to afford (+)-**2d**, $[\alpha]^{26}_D$ +42.2° (*c* 1.88, $CHCl_3$), and (−)-**2d**, $[\alpha]^{26}_D$ −42.8° (*c* 0.46 in $CHCl_3$), in 75% yields.

(21) (a) Shibata, T.; Okamoto, I.; Ishii, K. *J. Liq. Chromatogr.* **1986**, *9*, 313. (b) Ichida, A.; Shibata, T.; Okamoto, I.; Yuki, Y.; Namikoshi, H.; Toga, Y. *Chromatographia* **1984**, *19*, 280.

(22) The analytical and spectral data (including ^{19}F NMR) for all new compounds were in accord with the structures proposed.

Yoshio Takeuchi,* Kazuhiro Nagata, Toru Koizumi

Faculty of Pharmaceutical Sciences
Toyama Medical & Pharmaceutical University
Sugitani 2630, Toyama 930-01, Japan

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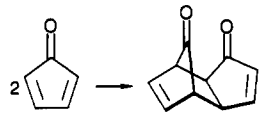
Decreased and Increased Solution Electron Affinities via the Replacement of a Single ^{12}C with ^{13}C

Summary: The reduction of a mixture of fluorenone and fluorenone with carbonyl-^{13}C with a very molar deficient quantity of sodium metal in HMPA leads to the formation of both anion radicals; ESR and ^{13}C NMR data show that the anion radical of the heavy isotopic isomer is present in a higher concentration than that of the light isotopic isomer. Similar experiments with benzophenone yield contrasting results.

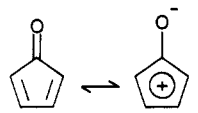
Sir: A ^{12}C–^{13}C isotope effect of unprecedented magnitude has been observed, which should lead to an enrichment procedure that is orders of magnitude more efficient than any used today.[1]

In a manner that is reminiscent of the situation with cyclobutadiene, neutral cyclopentadienone is very unstable toward dimerization[2] (reaction 1). This high reactivity



(1)

of cyclopentadienone may be seen as a reflection of the antiaromaticity contributed by the polarized structure, structure II in reaction 2, involving the cyclopentadienium



(2)

I II

(1) (a) Most of the world's ^{13}C is now produced by the cryogenic distillation of CO. The separation factor at the operating temperature is 1.008.[1b] (b) Lockhart, I. M. In *Isotopes: Essential Chemistry & Applications*; Elvidge, J. A., Jones, J. R., Eds.; The Chemical Society: London, 1979.

(2) Garbisch, E. W.; Sprecher, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6785.

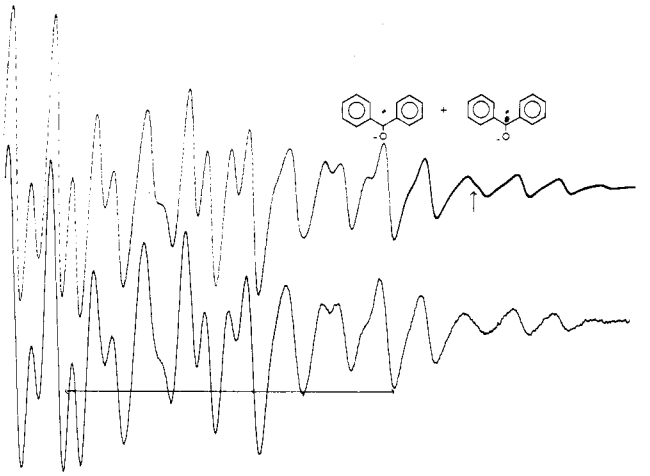


Figure 1. (Bottom) The first 22 lines of the ESR spectrum of a sample containing 0.089 M BZO + 0.10 M BZO-^{13}C reduced with a very small amount of sodium metal in HMPA. (Top) A computer simulation. This best simulation was obtained using a ratio of [BZO-$^{13}C^{\bullet-}$]/[BZO$^{\bullet-}$] = 0.65. The coupling constants used in the simulation are 3.49 (2 H), 2.40 (4 H), and 0.74 G (4 H). A 6.36-G (the arrow is 6.36 G long) splitting for the ^{13}C was added to the simulation of the spectrum for BZO-$^{13}C^{\bullet-}$. These parameters correspond to an equilibrium constant of 0.58. The vertical arrow indicates the first line in the BZO$^{\bullet-}$ spectrum. Continued reduction of this mixture results in dramatic increases in the relative intensity of the ESR signal for BZO-$^{13}C^{\bullet-}$. When the reduction of this same solution was continued until the number of moles of sodium was equal to that of the benzophenones, the best computer simulation was obtained by using a ratio of [BZO-$^{13}C^{\bullet-}$]/[BZO$^{\bullet-}$] = 1.1.

cation.[3] The addition of an extra electron results in some divergence from the 4n π character of the five-member ring system in cyclopentadienone, and the corresponding anion radical endures long enough for ESR observation at room temperature.[4] Very recent theoretical work on benzophenone[5] as well as the Raman and IR studies carried out upon the anion radicals and neutral molecules of tetracyanoethylene[6] and benzene[7] shows that the effect of an added electron is best characterized as resulting in a weakening of multiple bonds and a strengthening of single bonds coupled with a net reduction in bond order. Thus, the addition of an extra electron to a fully conjugated ketone to yield the ketyl should result in a general bond lengthening. From this it is predicted that the zero-point energy (ZPE) effects[8] would result in benzophenone (BZO) having a higher electron affinity than benzophenone substituted at the carbonyl position with a ^{13}C (BZO-^{13}C). On the other hand, a general bond order increase is to be expected when an electron is added to a substituted cyclopentadienone such as fluorenone (FLU = dibenzocyclopentadienone) for the reasons mentioned above.

A simple competition between BZO and BZO-^{13}C for an added electron can be staged by reducing a carefully prepared mixture of BZO and BZO-^{13}C with a very deficient amount of sodium metal. When this reaction is carried out in hexamethylphosphoramide (HMPA) the solvated ketyls are free of ion association,[9] and the equi-

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(4) Russell, G. A.; Takano, T.; Kosugi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 1491.

(5) Chipman, D. M.; Prebenda, M. F. *J. Phys. Chem.* **1986**, *90*, 5557.

(6) (a) Katkale, M. S.; Devlin, J. P. *J. Phys. Chem.* **1979**, *83*, 1636. (b) Khatkale, M. S.; Devlin, J. P. *J. Chem. Phys.* **1979**, *60*, 1851.

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