with 3:1 hexane–ether afforded 15.2 mg (57%) of vinyloxirane IVc: IR (film) ν 2968, 2922, 2854, 1453, 1383, 1300, 1071, 765, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aryl H), 5.82 (dt, 1 H, J = 5.6, 15.8 Hz, vinyl H), 5.64 (d, 1 H, J = 15.8 Hz, vinyl H), 4.61 (s, 2 H, SCH_2O), 4.59, 4.48 (AB q, 2 H, J = 11.9 Hz, benzyl H), 4.05 (d, 2 H, J = 5.5 Hz, C=CHCH_2), 3.58, 3.51 (AB of ABX, J_{AB} = 11.1 Hz, J_{AX} = 5.0 Hz, J_{BX} = 5.8 Hz, CH_2OBn), 3.15 (X of ABX, 1 H, J_{AX} = 5.0 Hz, J_{BX} = 5.7 Hz, CH_2CH), 2.13 (s, 3 H, SCH_3), 1.43 (s, 3 H, epoxy CH_3); $[\alpha]^{23}_D$ +11.2° (c 1.52, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.28; H, 7.53. Found: C, 65.22; H, 7.38.

(*E*)-(2*R*,5*S*)-6-(Benzyloxy)-2,4-dimethyl-5-hydroxy-1-[(methylthio)methoxy]-3-hexene (30c). The lower order cyanocuprate, prepared as described from 8.7 mg (0.097 mmol) of copper cyanide[14] and 0.07 mL (0.097 mmol) of 1.4 M methyllithium in diethyl ether, was added to 5.7 mg (0.020 mmol) of vinyloxirane Ic, affording 5.1 mg (85%) of allylic alcohol **30c**: IR (film) ν 3448, 2958, 2921, 2861, 1496, 1454, 1302, 11163, 1073, 9056, 735, 698, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aryl H), 5.33 (d, 1 H, J = 9.2 Hz, vinyl H), 4.59 (s, 2 H, SCH_2O), 4.55 (s, 2 H, benzyl H), 4.21 (d, 1 H, J = 5.4 Hz, carbinyl H), 3.6–3.2 (m, 4 H, $BnOCH_2$ and $MTMOCH_2$), 2.69 (m, 1 H, CHCH$_3$), 2.42 (bs, 1 H, OH), 2.10 (s, 3 H, SCH_3), 1.63 (s, 3 H, vinyl CH_3), 0.97 (d, 3 H, J = 6.7 Hz, CHCH_3); $[\alpha]^{24}_D$ −24° (c 0.80, $CHCl_3$); HRMS Calcd for $C_{17}H_{26}O_3SNH_4$ (M + NH_4) 328.1946, found m/e 328.1957.

(*E*)-(2*S*,5*S*)-6-(Benzyloxy)-2,4-dimethyl-5-hydroxy-1-[(methylthio)methoxy]-3-hexene (31c). The lower order cyanocuprate prepared as described from 23.1 mg (0.258 mmol) of copper cyanide,[14] and 0.19 mL (0.258 mmol) of 1.4 M methyllithium in diethyl ether was added to 15.2 mg (0.052 mmol) of vinyloxirane IVc, affording 11.6 mg (73%) of allylic alcohol **31c**: IR (film) ν 3454, 2921, 1454, 1071, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aryl H), 5.33 (d, 1 H, J = 9.2 Hz, vinyl H), 4.58 (s, 2 H, SCH_2O), 4.55 (s, 2 H, benzyl H), 4.21 (X of ABX, 1 H, J_{AX} = 3.0 Hz, J_{BX} = 8.5 Hz, carbinyl H), 3.51, 3.39 (AB of ABX, J_{AB} = 9.5 Hz, J_{AX} = 3.2 Hz, J_{BX} = 8.6 Hz, CH_2OBn), 3.35, 3.30 (AB of ABX, J_{AB} = 8.0 Hz, J_{AX} = 5.5 Hz, J_{BX} = 6.9 Hz, CH_2OMTM), 2.69 (m, 1 H, CHCH$_3$), 2.47 (bs, 1 H, OH), 2.09 (s, 3 H, SCH_3), 1.63 (s, 3 H, vinyl CH_3), 0.97 (d, 3 H, J = 6.7 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 134.2, 130.0, 128.5 (2 C), 127.8, 127.7 (2 C), 75.4, 75.2, 73.6, 73.3, 72.8, 32.4, 17.6, 13.8, 12.8; $[\alpha]^{24}_D$ +15.4° (c 1.87, $CHCl_3$); HRMS calcd for $C_{17}H_{26}O_3SNH_4$ (M + NH_4) 328.1946, found m/e 328.1939.

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Supplementary Material Available: ^{1}H NMR spectra for **5a,c, 6a–c, 7, 12, 20a–c, 30c, 31c** and Chem 3D structures for the six lowest energy conformers of **8c, 9c, 13c,** and **14c** as calculated by MacroModel V3.0 (28 pages). Ordering information is given on any current masthead page.

Notes

Regio- and Stereoselective Iodofluorination of Alkenes with Bis(pyridine)iodonium(I) Tetrafluoroborate

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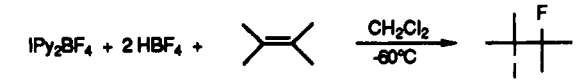
Selectively fluorinated compounds are a subject of current interest.[1] A classical preparation is the addition of fluoride to alkanes[2] and, in this way, mixed halogens have been challenging species. Iodine monofluoride[3] is particularly attractive, although it must be synthesized in situ. To do that, different combinations of reagents have been proposed.[4]

Scheme I



Recently, we have reported[5] that when cyclohexene was treated with bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) in the presence of tetrafluoroboric acid at −30 °C, in methylene dichloride, *trans*-1-fluoro-2-iodocyclo-

(1) (a) Patrick, T. B. *J. Chem. Educ.* **1979**, *56*, 228. (b) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha and Elsevier Biomedical Press: Amsterdam, 1982. (c) Smart, B. E. In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: Weinheim, 1986; Vol. 3, Chapter 4, pp 141–191. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (e) Dugad, L. B.; Gerig, T. *Biochemistry* **1988**, *27*, 4310.

(2) (a) Gerstenberger, M. R. C.; Haas, A. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 647. (b) Haas, A.; Lieb, M. *Chimia* **1985**, *39*, 134.

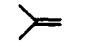
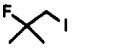
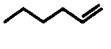
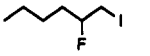
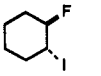
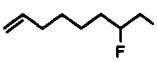
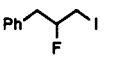
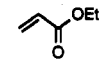
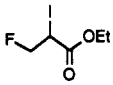
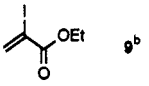
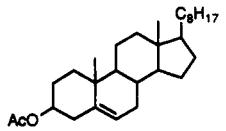
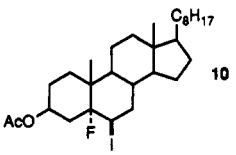
(3) Iodine monofluoride has been described in a very few publications. No reports of the reactivity of isolated IF toward organic compounds have been published. It is known the tendency of this compound to disproportionate giving rise to hypervalent iodine species (IF_3 and IF_5). See, for instance: Schmeisser, M.; Sartori, P.; Naumann, D. *Chem. Ber.* **1979**, *103*, 880. Pyridine complexes of IF can be isolated: Schmidt, H.; Meinert, H. *Angew. Chem.* **1959**, *71*, 126.

(4) For instance, from the elements (F_2 + I_2): (a) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342. (b) Purrington, S.; Kagan, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997. From metal fluorides and iodine: (c) Schmidt, H; Meinert, H. *Angew. Chem.* **1960**, *72*, 493. (d) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; Interscience: New York, 1975; Vol. 5, p 351. (e) Owen, G. R.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 3010. From *N*-iodoamides and a source of fluoride: (f) Bowers, A.; Cuéllar Ibáñez, L.; Denot, E.; Beccerra, R. *J. Am. Chem. Soc.* **1960**, *82*, 4001. (g) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872. (h) Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* **1987**, 562. Hypervalent iodine compounds: (i) Zupan, M.; Pollak, A. *J. Org. Chem.* **1976**, *41*, 2179. (j) Hauptschein, M.; Braid, M. *J. Am. Chem. Soc.* **1961**, *83*, 2383.

(5) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319.

0022-3263/91/1956-2234$02.50/0

Table I. Vicinal Fluoroiodo Compounds

entry	alkene	product	yield,[a] %
1		 1	69
2		 2	78
3		 3	89
4		 4	82
5		 5	78
6		 6	91
7		 7	84
8		 8	57
		 9[b]	3
9		 10	58

[a] Yield of isolated products, relative to starting IPy_2BF_4. Satisfactory microanalyses obtained in all the new compounds: C, ±0.41; H, ±0.24. [b] Detected in the crude of 8 by GC–mass spectrometry.

hexane was obtained in a 67% yield, with the tetrafluoroborate counteranion acting as a source of fluoride.[6]

In this paper, the generality and optimal conditions for the reaction of iodofluorination of alkenes using IPy_2BF_4 are reported.

Results and Discussion

The general reaction is outlined in Scheme I. In a typical experiment, bis(pyridine)iodonium(I) tetrafluoroborate is dissolved in anhydrous methylene dichloride under an inert atmosphere. The resulting solution, cooled to −60 °C, is treated with tetrafluoroboric acid (2 equiv of 54% ethereal solution), and after 10 min of stirring at that temperature a shot of the olefin (1 equiv) is added. Further stirring at −60 °C, followed by pouring the reaction mixture in aqueous sodium hydrogen carbonate, affords vicinal fluoroiodo derivatives in good yield (Table I). No other products are detected by either GC–MS or ^1H NMR analysis of the residue after evaporation of solvents.

An analysis of the data depicted in Table I shows that the reaction takes place regio- and stereoselectively. In this sense, entries 1, 2, and 6 clearly illustrate a regioselective addition across the double bond, yielding exclusively one isomer whose structure is that predicted by Markovnikov's rule for an addition of electrophilic iodine. Also, in good agreement with these observations is the stereochemistry found when cyclic alkenes are used as starting

Scheme II

$$IPy_2BF_4 + 2\,HBF_4 \underset{-78°C}{\overset{CH_2Cl_2}{\rightleftharpoons}} 2\,PyHBF_4\downarrow + IBF_4$$

materials, entries 3, 4, and 9 in Table I. Only one stereoisomer is formed in each case, corresponding to an anti addition, giving rise to the preparation of trans-substituted vicinal fluoroiodo compounds. Selective monofunctionalization of nonconjugated dienes can be achieved (see entries 4 and 5). In connection with this, and also relative to entry 6, an alternative type of process should be expected, namely an intramolecular ring closure induced by electrophilic iodine species.[7] Nevertheless, vicinal fluoroiodo derivatives are the only products obtained in each case (entries 4, 5, and 6). Thus, the length of the tether seems to be a limiting factor to determine the nature of the products, of the reaction of IPy_2BF_4 with polyunsaturated compounds. Entries 6 and 7 prove that when the alkene starting material has an attached phenyl group, aromatic electrophilic substitution does not compete at any significant rate with the functionalization of the olefin. Acrylates could be also iodofluorinated in this way, although the reaction requires a slightly modified experimental procedure. Carbon–carbon double bonds of steroidal systems also can be readily functionalized by the use of this combination of reagents. Monosubstituted and vicinal disubstituted alkenes give higher yields (78–91%, entries 2, 3, 4, 5, and 6, Table I) than 1,1-di- and trisubstituted ones (entries 1 and 9).

The products were characterized by standard spectroscopic techniques (^1H and ^{13}C NMR, MS), and by comparison with literature references.[4a,g] All new compounds gave satisfactory elemental analysis. In order to unequivocally assign the structure of the only isomer obtained in each case, ^{13}C NMR has been particularly useful. The trans relationship between iodine and fluorine, in cyclic systems, is based on the ^1H NMR. In order to do that, ^1H–^1H and ^1H–^{19}F are helpful tools.[8]

The reaction is quite general, irrespective of the structure of the starting alkene. Nevertheless, in the case of acrylates, it requires a modified experimental approach. Using our standard conditions, the yield is lower than 10% for compound 8. It did not improve significantly by the addition of an external source of fluoride ion, as for instance tetrabutylammonium fluoride. The best yield for the preparation of compound 8 was achieved when the iodinating reagent was the light orange solution, resulting from the removal by filtration, of pyridinium tetrafluoroborate from the mixture of IPy_2BF_4–HBF_4 in methylene dichloride (under argon atmosphere, at −78 °C). In keeping with the equilibrium depicted in Scheme II, there is an increase in the concentration of reactive iodinating species in solution after filtration. As a result, the system is reactive enough to add both fluorine and iodine to the acrylate. A small quantity (<5%) of ethyl 2-iodoacrylate 9 was always detected in the reaction crude by GC–MS (entry 8, Table I).

The new type of solution is much less stable in comparison with the same combination prior to filtration. Extensive decomposition takes place at low temperature in less than 1 h, while no appreciable change in its properties is shown by the reagent without separation of $PyHBF_4$.

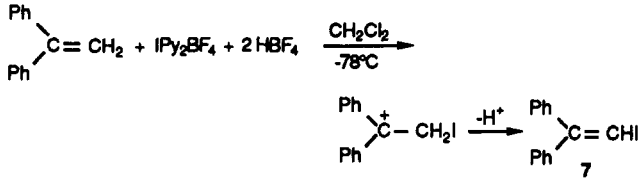
In general, with the above mentioned exception, these reactions are very clean and fast at −60 °C. However, by

(6) The equilibrium between BF_4^- and $BF_3 + F^-$ has been long ago postulated; see: Sharp, D. W. A. In *Advances Fluorine Chemistry*; Butterworths Scientific Publ.: London, 1960; Vol. 1, p 68. Examples of tetrafluoroboric acid and their salts as nucleophilic F/transfer in ref 2a, p 655.

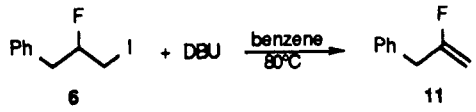
(7) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1546.

(8) Hall, L. D.; Jones, D. L. *Can. J. Chem.* **1973**, *51*, 2914.

Scheme III



Scheme IV



simply cooling the solutions down to −80 °C or at lower temperatures, the process could be slowed down. No significant iodofluorinatioin was observed when cyclohexene was allowed to react with IPy_2BF_4–HBF_4, at −85 °C in CH_2Cl_2 for 30 min. Subsequent addition of dry methanol afforded the corresponding 1-iodo-2-methoxycyclohexane.[9]

The features of this process are compatible with an ionic mechanism, involving an initial electrophilic attack of iodine to the alkene to produce a cyclic three members iodonium ion.[10] Subsequent ring opening by nucleophilic attack of fluoride ion (from BF_4^-),[6] gives the final product with remarkable regio- and stereoselectivity. When the substituents attached to the carbon–carbon double bond are able to strongly stabilize a positive charge, the nature of the products of the reaction change, and iodofunctionalized olefins are obtained (see entry 7, Table I; compound **7** was identical with the product of the reaction of addition of IPy_2BF_4 and benzene to phenylacetylene[11]). In this case, a feasible explanation invokes an open structure for the intermediate ion, being a carbocation rather than a bridged iodonium ion, followed by β-elimination of a proton (Scheme III).

An interesting application of the iodofluorinated compounds is their conversion to fluoro-substituted alkenes. Vicinal fluoroiodo compounds can be dehydroiodinated in the presence of bases. Thus, for instance, treatment of **6** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at reflux gave 2-fluoro-3-phenyl-1-propene (**11**), in a 60% yield (Scheme IV). The overall process (Table I, entry 6, and Scheme IV) is of significance from a synthetic point of view, and it means the regioselective conversion of a 1-alkene to a 2-fluoro-1-alkene, without contamination by any other isomeric olefin.

In short, this paper describes a new methodology to selectively attach iodine and/or fluorine to an alkene, broadening the scope of synthetic applications of IPy_2BF_4. Experimental conditions are mild; all the reagents are readily accessible, enhancing the convenience of the process, specially at the laboratory scale.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a Varian FT-80A or a Bruker AC-300 spectrometer with $CDCl_3$ as the solvent and are reported in ppm from TMS. Mass spectra were obtained at 70 eV on an HP 5987 A apparatus equipped with an HP 5880 gas chromatography using a capillary column. GC analyses for chemical purity were performed on a Varian Vista 6000 instrument through an OV-101 column. Elemental analyses were carried out on a Perkin-Elmer 240 elemental analyzer. Melting points were measured on a Buchi-Tottoli apparatus and are uncorrected. Bis(pyridine)iodonium(I) tetrafluoroborate was prepared by a previously reported procedure.[12] Alkenes were distilled prior to use, and CH_2Cl_2 was dried over P_2O_5 and distilled under nitrogen.

General Procedure To Prepare Vicinal Fluoroiodo Compounds. To a solution of IPy_2BF_4 (2 mmol, 0.74 g) in dried CH_2Cl_2 (15 mL) cooled at −60 °C under nitrogen was added HBF_4 (4 mmol, 0.6 mL of ethereal 54% solution). After the mixture was stirred for 5 min, the starting olefin (2 mmol) was added, and the resultant mixture was stirred for 30 min at −60 °C. The resulting solution was poured into a 5% aqueous solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (25 mL). The organic layer was successively washed with the following aqueous solutions, 0.1 N HCl acid (10 mL), 5% $NaHCO_3$ (15 mL), 0.1 N $Na_2S_2O_3$ (15 mL), and water (15 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. Compounds were purified by column chromatography over silica gel using hexane/ether, 95/5, as eluent and by crystallization. Physical properties and spectra data are recorded below.

2-Fluoro-1-iodo-2-methylpropane (1): unstable oil, spectral data matched those reported in the literature.[13]

2-Fluoro-1-iodohexane (2) and *trans*-1-Fluoro-2-iodocyclohexane (3): oils, with the same physical and spectral properties as reported in the literature.[4g]

***trans*-4-Fluoro-5-iodo-1-cyclohexene (4)**: oil; ^1H NMR δ 6.0–5.4 (CH=CH, 2 H, m), 5.0 (CHF, 1 H, dm, J_{HF} = 46 Hz), 4.5 (CHI, 1 H, m), 3.4–2.5 (CH_2CH_2, 4 H, m); ^{13}C NMR δ 126.1 (CH=), 124.2 (CH=, d, $^3J_{CF}$ = 5.2 Hz), 91.4 (CHF, d, J_{CF} = 178.7 Hz), 35.0 (CH_2CH_2CHF, d, $^3J_{CF}$ = 3.5 Hz), 31.6 (CH_2CHF, d, $^2J_{CF}$ = 22.3 Hz), 26.2 (CHI, d, $^2J_{CF}$ = 22.5 Hz); MS *m/e* 226 (M^+), 127 (I^+), 99 [$(M - I)^+$], 79 [$(M - IFH)^+$]. Anal. Calcd for C_6H_8FI: C, 31.88; H, 3.57. Found: C, 32.39; H, 3.40.

7-Fluoro-8-iodo-1-octene (5): oil; ^1H NMR δ 6.6–6.5 (CH=, 1 H, m), 5.2–4.7 (CH_2=, 2 H, m), 4.55 (CHF, 1 H, dm, J_{HF} = 47.3 Hz), 3.4 (CH_2I, 2 H, dd, J_{HF} = 18.9 Hz, J_{HH} = 6.5 Hz), 2.3–1.3 [$(CH_2)_4$, 8 H, m]; ^{13}C NMR δ 141.4 (CH=), 117.4 (CH_2=), 94.1 (CHF, d, J_{CF} = 179.2 Hz), 36.2 (CH_2CHF, d, $^2J_{CF}$ = 17.2 Hz), 34.6 (CH_2), 32.1 (CH_2), 25.6 (CH_2CH_2CHF, d, $^3J_{CF}$ = 3.8 Hz), 8.3 (CH_2I, d, $^2J_{CF}$ = 17.9 Hz); MS *m/e* 256 (M^+), 129 [$(M - I)^+$]. Anal. Calcd for $C_8H_{14}FI$: C, 37.53; H, 5.51. Found: C, 37.67; H, 5.27.

2-Fluoro-1-iodo-3-phenylpropane (6): oil; ^1H NMR δ 7.2 (Ar, 5 H, br s), 4.6 (CHF, 1 H, dm, J_{HF} = 47.3 Hz), 4.3 (CH_2I, 2 H, dd, J_{HF} = 15 Hz, J_{HH} = 6 Hz), 3.9 (CH_2Ph, 2 H, dd, J_{HF} = 15 Hz, J_{HH} = 6 Hz); ^{13}C NMR δ 137.4 (ipso-Ar, d, $^3J_{CF}$ = 3.1 Hz), 131.0 (Ar), 130.2 (Ar), 128.6 (Ar), 93.7 (CHF, d, J_{CF}, d, J_{CF} = 178.5 Hz), 42.3 (CH_2Ph, d, $^2J_{CF}$ = 21.2 Hz), 8.0 (CH_2I, d, $^2J_{CF}$ = 23.9 Hz); MS *m/e* 264 (M^+), 173 [$(C_2H_3FI)^+$], 153 [$(C_2H_2I)^+$], 127 (I^+), 91 [$(C_7H_7)^+$]. Anal. Calcd for $C_9H_{10}FI$: C, 40.93; H, 3.82. Found: C, 41.22; H, 3.73.

2-Iodo-1,1-diphenylethene (7): mp 39–40 °C (from methanol) (lit[14] mp 40–41 °C); ^1H NMR δ 7.3–7.1 (Ar, 10 H, m), 4.7 (CHI, 1 H, s); ^{13}C NMR δ 153.2 (Ph_2C=), 142.5 (ipso-Ar), 141.8 (ipso-Ar), 130.2 (Ar), 129.2 (Ar), 128.8 (Ar), 128.3 (Ar), 80.8 (=CHI); MS *m/e* 306 (M^+), 179 [$(M - I)^+$], 178 [$(M - HI)^+$], 102 [$(Ph_2C_2H)^+$].

Ethyl 3-Fluoro-2-iodopropanoate (8). A solution of IPy_2BF_4 (2 mmol, 0.74 g) in anhydrous CH_2Cl_2 (25 mL) cooled at −78 °C was treated with HBF_4 (4 mmol, 0.6 mL of ethereal 54% solution). The precipitated $PyHBF_4$ was filtered off under Ar and at −78 °C. Distilled ethyl acrylate (2 mmol, 0.2 g) was added to the resulting orange solution, and the mixture was stirred 20 min at this temperature. The mixture was poured into a 5% aqueous solution of $NaHCO_3$ (25 mL) and then worked up as described above. The resulting oil (0.35 g) containing **8** and ethyl 2-iodoacrylate **9** (ca. 3%, detected by GC–mass spectrometry) was

(9) Selected spectroscopic data, recorded in $DCCl_3$ solution on a Brucker AC-300 spectrometer. ^1H NMR: δ ppm 4.35 (dd, *J* = 10.6, 8.6, 4.2 Hz, 1 H), 3.55 (ddd, *J* = 12.5, 8.6, 3.8 Hz, 1 H), 3.7 (s, 3 H). ^{13}C NMR: δ (ppm) 85.1, 58.6, 39.0, 37.4, 31.8 (C–I), 28.7, 25.2.

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chromatographed, yielding 0.30 g of **8** (57%), although attempts to obtain a sample of analytical purity failed because of decomposition: ^{1}H NMR δ 5.0–4.3 (CH_2F, CHI, 3 H, m), 4.2 (OCH_2, 2 H, q, J_{HH} = 6 Hz), 1.3 (CH_3, 3 H, t, J_{HH} = 6 Hz); ^{13}C NMR δ 170.4 (C=O, d, $^3J_{CF}$ = 3.5 Hz), 84.9 (CH_2F, d, J_{CF} = 177.1 Hz), 63.8 (OCH_2), 17.6 (CHI, d, $^2J_{CF}$ = 22.8 Hz), 15.5 (CH_3); MS *m/e* 246 (M^+), 226 [$(M - HF)^+$], 201 [$(M - EtO)^+$], 173 [$(M - CO_2Et)^+$], 154 [$(C_2H_3I)^+$], 119 [$(M - I)^+$], 91 [$(C_3H_4FO_2)^+$].

5α-Fluoro-6β-iodocholesteryl Acetate (10). **10** was prepared in a similar way as the above compounds, using a solution of cholesteryl acetate in anhydrous CH_2Cl_2 (15 mL) as starting olefin. **10** was crystallized from the crude of the reaction using ethyl alcohol (mp 131–133 °C, lit.[4a] mp 132 °C), giving 58% of pure **10** with the same spectral data as reported in the literature.[4a]

Reaction of 6 with DBU. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.9 mL, 6 mmol) was added to a solution of 2-fluoro-1-iodo-3-phenylpropane (**6**) (0.79 g, 3 mmol) in benzene (10 mL). After reflux for 5 h, the mixture was quenched with water (20 mL) and extracted with benzene (2 × 10 mL), and the organic layer was washed with water (10 mL) and then dried over Na_2SO_4. Benzene was distilled through a fractionating column, and crude fluoroalkene **11** was purified by distillation at reduced pressure, 62–65 °C (20 mm): ^{1}H NMR δ 4.65 (=CH_2, H cis to F, 1 H, dd, J_{HF} = 15 Hz, J_{HH} = 3 Hz), 4.3 (=CH_2, H trans to F, 1 H, dd, J_{HF} = 50 Hz, J_{HH} = 3 Hz), 3.55 ($PhCH_2$, 2 H, d, J_{HF} = 16.3 Hz); ^{13}C NMR δ 165.8 (=CF, d, J_{CF} = 256.7 Hz), 135.9 (ipso-Ar, d, $^3J_{CF}$ = 5 Hz), 128.8 (Ar), 128.4 (Ar), 126.8 (Ar), 91.1 (=CH_2, d, $^2J_{CF}$ = 19.6 Hz), 38.3 ($PhCH_2$, d, $^2J_{CF}$ = 28.7 Hz); MS *m/e* 136 (M^+), 135 [$(M - H)^+$], 133 [$(M - H_3)^+$], 115 [$(M - H_2F)^+$], 91 [$(C_7H_7)^+$]. Anal. Calcd for C_9H_9F: C, 79.39; H, 6.66. Found: C, 79.62; H, 6.47.

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Registry No. **1**, 19869-79-5; **2**, 1786-51-2; **3**, 6906-08-7; **4**, 6906-08-7; **5**, 132047-45-1; **6**, 129976-36-9; **7**, 19997-66-1; **8**, 132047-46-2; **9**, 132047-47-3; **10**, 2560-88-5; **11**, 66622-72-8; $(H_3C)_2C{=}CH_2$, 115-11-7; $H(CH_2)_4CH{=}CH_2$, 592-41-6; $H_2C{=}CH(CH_2)_4CH{=}CH_2$, 3710-30-3; $PhCH_2CH{=}CH_2$, 300-57-2; $(Ph)_2C{=}CH_2$, 530-48-3; $H_2C{=}CHCO_2Et$, 140-88-5; IPy_2BF_4, 15656-28-7; HBF_4, 16872-11-0; 1-cyclohexene, 110-83-8; 1,4-cyclohexadiene, 628-41-1; cholesteryl acetate, 604-35-3.

Enzymatic Approach to the Synthesis of the Pyrrolo[1,4]benzodiazepine Antibiotics[1]

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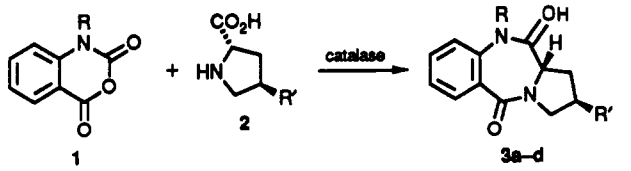
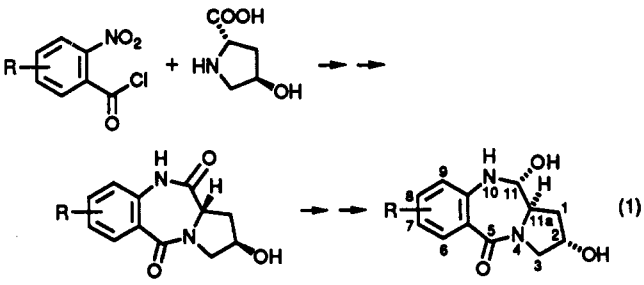
The pyrrolo[1,4]benzodiazepine (PBD) family of antitumor antibiotics[2] such as anthramycin, sibiromycin, tomaymycin, neothramycins A and B, prothacarcin, and chicamycins A and B are produced by various actinomycetes. These biosynthetically derived compounds are well known for inhibiting DNA replication on account of DNA–antibiotic adduct[3] through their C-11 carbinolamine functionality.

Leimgruber et al.[4] were the first to demonstrate the synthesis of anthramycin. This classical approach developed to the synthesis of PBD skeleton has proven sound enough that most of the syntheses devised for this antibiotic are based on it. Therefore, the dilactam obtained by the reaction of the pyrrolo ring with an aromatic electrophile[5] can be subsequently transformed to the carbinolamine or its equivalent imine in few steps (eq 1) by the combination of some methodologies.[6]

Scheme I[a]



[a] R = H, CH_3; R′ = H, OH.



(1)

We have been interested in the structural modifications for the synthetic analogues of PBD antibiotics[7] and also for the exploration of enzymes as biocatalysts[8] in organic synthesis. In this connection, enzymatic routes to the pyrrolo[1,4]benzodiazepine ring system are reported herein that utilize catalase-mediated condensation and liver microsomes mediated reductive cyclization. Furthermore, stereoselective reduction of pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-triones by bakers' yeast has been investigated.

Results and Discussion

Catalase-Mediated Condensations. The condensation of isatoic anhydride with proline is a well-established method for the preparation of aromatic ring unsubstituted PBD heterocyclic systems. This reaction is usually performed[7a] in solvents like DMSO/DMF at high temperatures (115–150 °C).

In an attempt to carry out this type of condensation under mild conditions many enzymatic methods were explored, as this can be of interest in the handling of sensitive groupings as well as their stereochemistry in the proline

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