The First Enantiocontrolled Synthesis of *E,E* Conjugated Dienes with a Fluorine Atom in the Allylic Position

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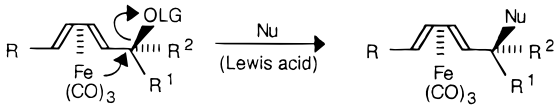
The organic chemistry of fluorine and fluorine-containing molecules has become a rapidly developing field of research.[1] Fundamental studies dealing with the influence of fluorine on structure and reactivity of organic molecules have proved to be very interesting. However, the major reason for this rapid expansion lies in the modification of biological activity induced by substitution of a hydrogen or a hydroxy group by fluorine (*fluorobioorganic chemistry*).[2] Thus, the stereo- and enantiocontrolled synthesis of fluoroorganic compounds has become a particularly important field of research. Many approaches have been studied, and new efficient reagents allowing either electrophilic or nucleophilic fluorination have been described.[1,3] However, it is important to point out that very few examples of chiral, nonracemic, molecules with a fluorine atom in the allylic position have been described until now.[4] Furthermore, to the best of our knowledge, there have been no reports of efficient methods for the synthesis of such fluoro derivatives. Among the fluorinating agents (diethylamino)sulfur trifluoride (DAST) is one of the most efficient for the transformation of a C−OH bond into a C−F bond[5] but, in the case of allylic alcohols, the reaction is usually neither regioselective[6] (allylic transposition occurring) nor stereoselective.[7] Important exceptions have been reported in the vitamin D area[8] and in sugar chemistry[9]

Scheme 1



OLG : leaving group

for instance, where anchimeric assistance produced an overall retention of configuration. These observations led us to consider the possible use of transition metal complex chemistry in this fluorination method. In this context, the organoiron complexes[10] appeared particularly attractive for two major reasons. Firstly, as a powerful temporary protective group for a diene unit, the $Fe(CO)_3$ group was expected to exclude any allylic transposition and secondly this group, like other transition metal complexes, is known not only to assist the nucleofuge departure[11] but also to induce stereoselectivity during the capture of the nucleophile especially if the *in situ* method is used (Scheme 1).[12]

We herein demonstrate the usefulness of this new approach and describe the first examples of enantiocontrolled synthesis of functionalized dienes with a fluorine, on a secondary or a tertiary allylic carbon atom. The alcohols **1a** and **3a** were chosen as models since they are readily prepared even in optically pure form.[13] The reaction of the Ψ-exo derivative **1a** with DAST gave fluoride **2a** in good yield with complete diastereoselectivity (NMR control).[14] This reaction occurs with overall retention of configuration, as unambiguously established by X-ray crystallographic analysis of **2a** (Figure 1).[15] Under the same conditions the Ψ-endo isomer **3a** reacted with DAST to give a 96:4 ratio[14] of **4a** and **2a**; the fluorine derivative **4a** was easily isolated in diastereomerically pure form by flash chromatography (SiO_2) (Scheme 2).

The decomplexation of **2a** or **4a**, using Me_3NO, gave the corresponding chiral dienes (+)-**5** and (−)-**5**. The optical purity of these derivatives (ee ≥ 90%) was established by ^1H and ^{19}F high field NMR using $Eu(hfc)_3$ as the chiral shift reagent. The organometallic complex

(1) German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*; Springer Verlag: Berlin, 1989. Knunyants, I. L.; Yakobson, G. G. *Syntheses of Fluoroorganic Compounds*; Springer Verlag: Berlin, 1987.

(2) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982. Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Biorganic Chemistry*; Wiley Interscience: New York, 1991. Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991. Abeles, R. H.; Alston, T. A. *J. Biol. Chem.* **1990**, *265*, 16705.

(3) See, for instance: Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111. Bravo, P.; Resnati, G. *Tetrahedron Asymmetry* **1990**, *1*, 661. Hewitt, C. D., Silvester, M. J. *Aldrichim. Acta* **1988**, *21*, 3.

(4) For a recent example, see: Piva, O. *Synlett* **1994**, 729.

(5) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. Hudlicky, M. *Org. React. New York* **1988**, *35*, 513.

(6) Middleton, W. J. US Patent 3914265, 1975. Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511.

(7) Bezuglov, V. V.; Bergelson, L. D. *Bioorg. Khim.* **1979**, *5*, 1531 (Engl. transl. 1137).

(8) Paaren, H. E.; Fivizzani, M. A.; Schnoes, H. K.; Deluca, H. F. *Arch. Biochem. Biophys.* **1981**, *209*, 579.

(9) Canfarini, F.; Giolitti, A.; Guidi, A.; Pasqui, F.; Pestellini, V.; Arcamone, F. *Tetrahedron Lett.* **1993**, *34*, 4697. Jeong, L. S.; Nicklaus, M. C.; George, C.; Marquez, V. E. *Tetrahedron Lett.* **1994**, *35*, 7569.

(10) Franck-Neumann, M. *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Eds.; Springer-Verlag: Berlin, 1987; p 247. Pearson, A. J. *Acc. Chem. Res.* **1980**, *13*, 463. Pearson, A. J. *Trans. Met. Chem.* **1981**, *6*, 67. Pearson, A. J. *Pure Appl. Chem.* **1983**, *55*, 1767. Gree, R. *Synthesis* **1989**, 341. Knölker, H. J. *Synlett* **1992**, 371. Gree, R.; Lellouche, J. P. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1995; Vol. 4, p 129.

(11) Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3065.

(12) Uemura, M.; Minami, T.; Yamashita, Y.; Hiyoshi, K.; Hayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 641. For recent examples, see: Donaldson, W. A.; Bell, P. T.; Jin, M.-J. *J. Org. Chem.* **1992**, *441*, 449. Donaldson, W. A.; Jin, M.-J. *Bull. Soc. Chim. Belg.* **1993**, *102*, 297. Donaldson, W. A.; Jin M.-J.; Bell, P. T. *Organometallics* **1993**, *12*, 1174. Donaldson, W. A.; Jin, M.-J. *Tetrahedron* **1993**, *49*, 8787. Donaldson W. A.; Shang, L. *Tetrahedron Lett.* **1995**, *36*, 1575. Hessler, E.; Schmalz, H. G.; Dürner, G. *Tetrahedron Lett.* **1994**, *35*, 4547. Roush, W. R.; Wada, C. K. *Tetrahedron Lett.* **1994**, *35*, 7347. Quirosa-Guillou, C.; Lellouche, J. P. *J. Org. Chem.* **1994**, *59*, 4693. Gree, D.; Gree R.; Lowinger, T. B.; Martelli, J.; Negri, J. T.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8841. Hachem, A.; Toupet, L.; Gree, R. *Tetrahedron Lett.* **1995**, *36*, 1849. Gree, D. M.; Martelli, J. T.; Gree, R. L.; Toupet, L. J. *J. Org. Chem.* **1995**, *60*, 2316.

(13) Gree, R.; Laabassi, M.; Mosset, P.; Carrie, R. *Tetrahedron Lett.* **1984**, *25*, 3693.

(14) In each case, the diastereoselectivity of the fluorination reaction was established by high field (Bruker ARX 400) NMR analysis (^1H, ^{13}C and ^{19}F) of the crude reaction mixtures.

(15) The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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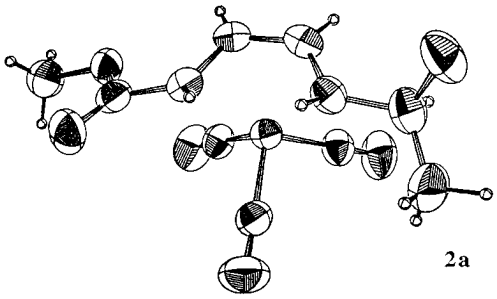
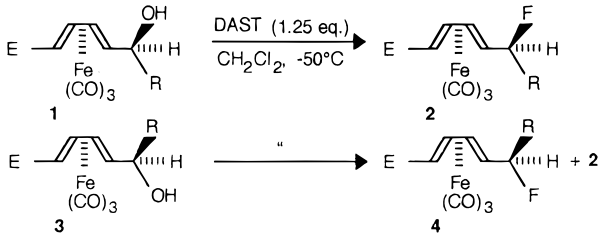


Figure 1.

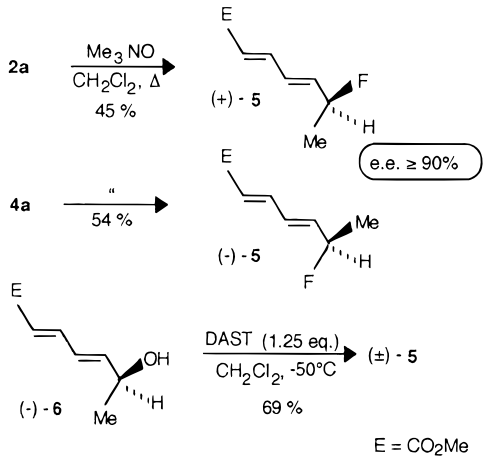
Scheme 2



E = -CO_2Me

a: R = Me; **2a** (86%); **4a** (86%); b: R = -CH_2-C≡CH; **2b** (79%); **4b** (55%); c: R = -CH_2-CH=CH_2; **2c** (76%); **4c** (55%)

Scheme 3



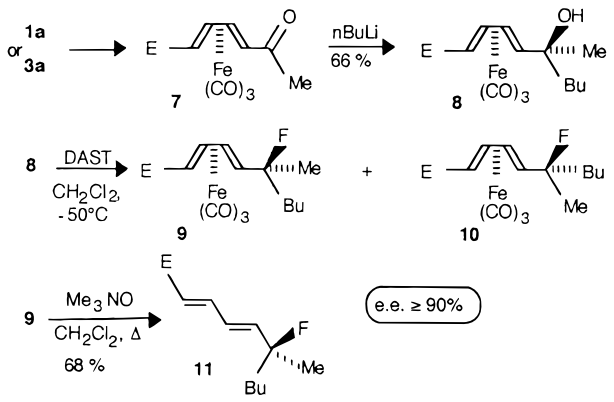
E = CO_2Me

must play a key role in this stereoselectivity since under the same conditions, the optically pure dienol (−)-**6**[13] also gave the fluoride **5** *but with complete racemization* (Scheme 3).

Preliminary results[16] indicate that this methodology can be extended to more functionalized derivatives. Both the propargylic **1b** and the allylic system **1c** reacted with DAST to give, with complete stereocontrol, the corresponding fluorides **2b** and **2c**. For the Ψ-endo isomers **3b** and **3c**, the size of the R group appears to be important since the ratios of retention versus inversion drop to 75:25 for **3b** and 65:35 for **3c**.

Versatile methods for the synthesis of tertiary alkylfluorides have yet to be developed,[17] especially for the preparation of optically active compounds. Our preliminary results indicate that this new methodology can be extended to the challenging problem of *allylic* tertiary

Scheme 4



fluorides. The optically pure methyl ketone **7**, easily obtained by oxidation of **1a** or **3a**,[18] reacted with *n*-butyllithium to give stereoselectively tertiary alcohol **8**. Reaction of **8** with DAST produced a 80:20 mixture (NMR control)[14] of **9** and **10**. Complex **9** was easily separated by crystallization (55% yield) and its stereochemistry (overall retention) attributed by analogy with preceeding results. Decomplexation of **9** gave the desired tertiary fluoride **11**, whose optical purity (ee ≥ 90%) was again established by ^{1}H and ^{19}F NMR in the presence of Eu(hfc)$_3$ (Scheme 4).

Additional studies will be necessary in order to fully understand the mechanism of these reactions and their stereoselectivities. However, it is important to point out that reaction of the corresponding, *isolated*, cation (obtained from **1a** as the BF_4 salt)[19] with nBu_4NF gave only a very complex mixture which does not contain the fluorides **2** or **4**. This could be correlated with results obtained in the case of cyclohexadienyl cations complexed to $Fe(CO)_3$, where the intermediate adducts are labile and decompose *in situ*.[20]

In conclusion, this new approach to fluorine allylic compounds is a further confirmation of the potentialities for organoiron complexes in synthesis. The methodology described herein should allow the stereo- and enantiocontrolled synthesis of fluoro analogs of polyunsaturated natural products, such as leukotrienes as well as provide the opportunity of studying the influence of the allylic C−F bond on the diastereoselectivity of reactions on vicinal double bonds. Furthermore, our preliminary results indicate that this metallo-assistance strategy could be extended to other organometallic complexes and allow stereocontrolled synthesis of fluorides in benzylic positions (*via* chromium derivatives) or in propargylic positions (*via* cobalt complexes), for instance. Such studies are under active investigation in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all compounds (10 pages).

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(16) These reactions have been studied starting with type **b** and **c** complexes in racemic form, and thus, these results correspond to diastereoselectivities.

(17) Takeuchi, Y.; Kanada, A.; Kawahara, S.; Koizumi, T. *J. Org. Chem.* **1993**, *58*, 3483. Abouabdellah, A.; Welch, J. T. *Tetrahedron Asymmetry* **1994**, *5*, 1005. Ihara, M.; Kawabuchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron Asymmetry* **1994**, *5*, 1041.

(18) Djedaini, F.; Gree, D.; Martelli, J.; Gree, R.; Leroy, L.; Bolard, J.; Toupet, L. *Tetrahedron Lett.* **1989**, *30*, 3781.

(19) Gree, R.; Laabassi, M.; Mosset, P.; Carrié, R. *Tetrahedron Lett.* **1985**, *26*, 2317.

(20) Powell, J.; Horvath, M. J. *Organometallics* **1993**, *12*, 4073.