Tetrahedron Letters,Vol.29,No.37,pp 4727-4730,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ABSOLUTE CONFIGURATION DETERMINATION OF SOME OPTICALLY ACTIVE MULTIFUNCTIONAL CARBON COMPOUNDS

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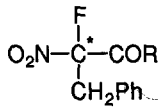
Abstract: The absolute configuration of novel chiral molecules, optically active multifunctional carbon compounds, has been determined for the first time by X-ray analysis after successful conversion into crystalline derivatives.

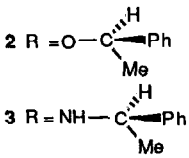
We have recently reported the synthesis[1] and resolution[2,3] of multifunctional carbon compounds, novel carbon molecules with three or four different labile groups directly attached to a central carbon atom.[4] This new class of chiral compounds, especially in their optically active forms of known absolute configurations, is of special significance in organic synthesis, in the mechanistic study of reactions, and further, in chiroptical investigations. However, the determination of the absolute configuration of these compounds which have such unexpectedly low polarity[3] has been very difficult because of the paucity of reactions to be applied for derivatization.[5] We thought that X-ray analysis would be the most reliable method since both stereochemical correlations and polarimetric means such as CD were, for the time being, not applicable for our purpose. This paper contains the first description of the successful conversion of such reactive polyfunctionalized compounds into crystalline derivatives and their consequent absolute configuration determination through X-ray analysis.

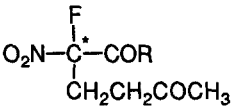
Attempted conversion of the trifunctional esters (**1**) and (**4**) into the corresponding acids, amides, or even alcohols was effectively impossible because of the tendency of the nitroacetate structure to undergo ready decarboxylation[6] and because of the concomitant side reactions due to the presence of various functionalities. However, N-monoalkylated amide derivatives were found to be rather stable. Thus, the more polar phenethyl ester diastereomer (**2a**),[7] obtained by treatment of (±)-(**1**) with R(+)-α-phenethyl alcohol/$Ti(OPr^i)_4$ followed by diastereomeric separation[2], was treated with R(+)-α-phenethylamine under mild conditions to afford the crystalline amide (**3a**).[8] Since the enantiomer (-)-(**1**) had been obtained from (**2a**),[2] the absolute configuration of (-)-(**1**) could be established through that of the amide (**3a**).

On the other hand, diastereomeric separation of the isomers derivatized by the reaction of (±)-(**4**) with R(+)-α-phenethyl alcohol was unsuccessful. Attempts to transform the keto group also failed since the compound (**4**) was sensitive to hydrazines, hydroxylamine, and other reagents. Therefore, (±)-(**4**) was converted into the diastereomeric R(+)-α-phenethyl amides and the two isomers, (**5a**) and (**5b**), were separated.[9] Since the less polar isomer (**5b**) was

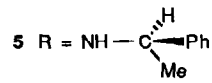


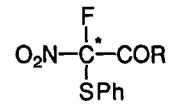
1 R = OEt



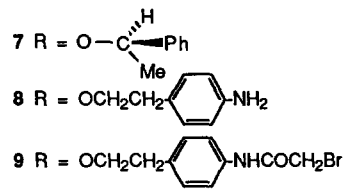


4 R = OEt





6 R = OEt

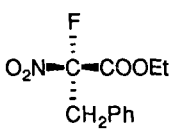


obtained by reaction of (+)-(**4**)[10] with R(+)-α-phenethylamine, the absolute configuration of (-)-(**4**) was now determined through X-ray analysis of the crystalline, more polar isomer (**5a**).

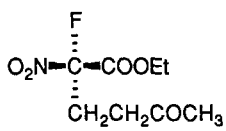
In contrast to the behaviour of (**1**) and (**4**), the tetrafunctional carbon compound (**6**) was extremely difficult to derivatize because of the presence of an additional heteroatom-containing group (SPh) on the chiral center. Reaction of (**6**) with various aliphatic and aromatic amines, hydroxylamine, and hydrazines easily produced the deethoxycarbonylated products.[5] After various attempts at derivatization, we have finally found a route for conversion of the very sensitive compound (**6**) into a crystalline derivative. Thus, the more polar phenethyl ester diastereomer (**7a**), obtained by transesterification of (±)-(**6**) with R(+)-α-phenethyl alcohol followed by diastereomeric separation,[2] was again treated with 4-aminophenethyl alcohol in the presence of $Ti(OPr^i)_4$ to afford another ester (**8a**).[11] The aniline derivative (**8a**) was bromoacetylated,[12] under fairly mild conditions, to produce the crystalline product (**9a**).[13] Having the stereochemistry of (-)-(**6**) correlated to that of (**7a**),[2] the absolute configuration of (-)-(**6**) was thus established through that of (**9a**).

The absolute structure for compounds (**3a**), (**5a**), and (**9a**) is shown in **Figures 1-3** from the results of X-ray crystallographic analyses (Structure Determination; Direct Method, Refinement; Block Diagonal-Matrix Least Squares Method, Final R Value; 0.054, 0.061, and 0.051 for (**3a**), (**5a**), and (**9a**), respectively).[14] Both of the bond angle and the bond length around the unusual chiral center must be a matter of big concern of structural chemists. Although some deviations from values for the normal tetrahedral structure can be observed,[15] it will require some time before the influence of various kinds of heteroatoms on the spacial disposition around sp^3 carbon atom has been completely clarified.

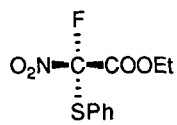
The optically active ethyl fluoronitroacetates, (+)-(**1**), (+)-(**4**), and (+)-(**6**), can now be



S(+)-**1**



S(+)-**4**



R(+)-**6**

Figure 1. Structure of Compound (**3a**).

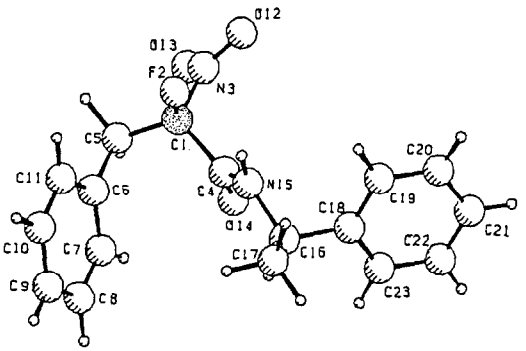


Figure 2. Structure of Compound (**5a**).

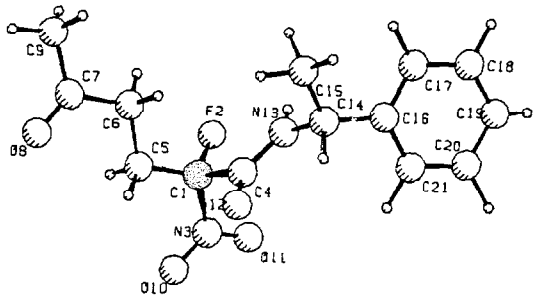
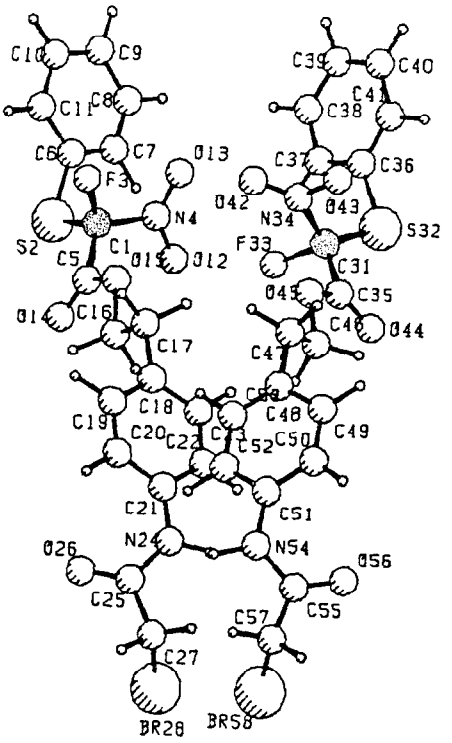


Figure 3. Structure of Compound (**9a**).



depicted as shown. It is of special interest that the absolute stereochemistries of these chiral α-fluoro-α-nitroacetates happen to be in accord with the signs of their optical rotations. The optically active multifunctional carbon compounds provide the suitable models for theoretical chiroptical investigations through the relationships between polarimetric behavior and the kinds of functional groups attached to the chiral center. α-Fluoro-α-nitroacetates are converted, by substitution at the chiral center via radical,[1,10] electrophilic,[10] and also nucleophilic[5] reactions into various monofluoro derivatives. The results obtained here are also applicable to mechanistic investigations and to the field of synthetic fluorine chemistry generally, which has not been much exploited to date in spite of recent increasing interest.[16]

References and Notes

1) Y. Takeuchi, M. Asahina, A. Murayama, K. Hori, and T. Koizumi, J. Org. Chem., 1986, **51**, 955.

2) Y. Takeuchi, M. Asahina, K. Nagata, and T. Koizumi, J. Chem. Soc., Perkin Trans 1, 1987, 2203.

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4) H. Hirschmann and K.R. Hanson, Top. Stereochem., 1983, **14**, 183.

5) Y. Takeuchi, M. Asahina, K. Hori, and T. Koizumi, J. Chem. Soc., Perkin Trans 1, 1988,

1149.

6) M.T. Shipchandler, Synthesis, 1979, 666 and references cited therein.

7) Of the two phenethyl ester (or phenethylamide) diastereomers, the more polar and the less polar isomers were designated by the symbols **a** and **b**, respectively. Therefore, an enantiomer derived from the **a** diastereomer was also represented by the symbol **a**.

8) The compound (**3a**) was obtained as colorless needles in 23 % yield after repeated crystallization from Pr^i_2O/CCl_4=4/1; m.p. 129.0-129.5 °C; IR(KBr) $\nu_{max.}$ cm^{-1} 3000(NH), 1680 (CONH), and 1568(NO_2); 270 MHz ^{1}H NMR($CDCl_3$, TMS) δ 1.29(3H, d, J=7.0 Hz, Me), 3.64(1H, dd, J_{Ha-F}=20.4, J_{Ha-Hb}=14.6 Hz, CHaHb-Ph), 3.96(1H, dd, J_{Hb-F}=29.6, J_{Hb-Ha}=14.6 Hz, CHaHb-Ph), 5.02(1H, q, J=7.0 Hz, CH), 6.36(1H, br s, NH), 7.26(5H, m, CH_2-Ph), and 7.35(5H, m, CH-Ph); 254 MHz ^{19}F NMR($CDCl_3$, $CFCl_3$) δ -133.1(dd, J_{F-Ha}=20.4, J_{F-Hb}=29.6 Hz); m/z 317(M^+ + 1), 301(M^+ - Me), and 301(M^+ - NO_2).

9) Reaction of (±)-(**4**) with sodium phenethylamide, prepared from R(+)-α-phenethylamine and 1 equiv of NaH in THF, at room temperature for 24h produced the diasteromeric mixture (**5a** and **5b**) and the more polar isomer was isolated by preparative TLC(hexane/Et_2O) to afford (**5a**) as colorless needles in 14 % yield after repeated crystallization from CCl_4/hexane/AcOEt=20/10/1; m.p. 81.5-82.0 °C; IR(KBr) $\nu_{max.}$ cm^{-1} 3360(NH), 1715(COMe), 1685 (CONH), and 1570(NO_2); 270 MHz ^{1}H NMR($CDCl_3$, TMS) δ 1.54(3H, d, J=7.1 Hz, CH-Me), 2.13(3H, s, COMe), 2.25-2.85(4H, m, CH_2CH_2), 5.09(1H, q, J=7.1 Hz, CH), 6.71(1H, br s, NH), and 7.35(5H, m, Ph); 254 MHz ^{19}F NMR($CDCl_3$, $CFCl_3$) δ -133.0(t, J_{F-H}=21.4 Hz); m/z 281(M^+ - Me) and 250(M^+ - NO_2).

10) Y. Takeuchi, K. Nagata, and T. Koizumi, J. Org. Chem., 1987, **52**, 5061.

11) A solution of (**7a**) and 4-aminophenethyl alcohol in THF was heated at reflux for 2h in the presence of $Ti(OPr^i)_4$ to give (**8a**) as a yellow oil in 76 % yield; IR(neat) $\nu_{max.}$ cm^{-1} 3400(NH), 1760(COO), and 1580(NO_2); 60 MHz ^{1}H NMR($CDCl_3$, TMS) δ 2.55(2H, br s, NH_2), 2.87(2H, t, J=7 Hz, $ArCH_2$), 4.42(2H, t, J=7.0 Hz, OCH_2), 6.55 and 6.98(4H, ABq, J=9.0 Hz, para-substituted Ar), and 7.38(5H, m, Ph); m/z 350(M^+).

12) V.M. Nikodem, S. Cheng, and J.E. Rall, Proc. Natl. Acad. Sci., 1980, **77**, 7064.

13) A solution of (**8a**) and N-hydroxysuccinimidyl bromoacetate in THF was heated at reflux for 1.5h to afford the amide (**9a**) in 95 % yield. Recrystallization from toluene/hexane/Et_2O=6/2/1 gave an analytical sample as colorless needles; m.p. 142°C; IR(KBr) $\nu_{max.}$ cm^{-1} 2950(NH), 1760(COO), 1658(CONH), and 1570(NO_2); 270 MHz ^{1}H NMR($CDCl_3$, TMS) δ 2.99(2H, t, J=6.8 Hz, $ArCH_2$), 4.01(2H, s, CH_2Br), 4.50(2H, t, J=6.8 Hz, OCH_2), 7.30(4H, m, Ar), 7.50(5H, m, Ph), and 8.16(1H, s, NH); 254 MHz ^{19}F NMR($CDCl_3$, $CFCl_3$) δ -100.7(s); m/z 470,472(M^+), 424,426(M^+ - NO_2), and 240,242($BrCH_2CONH$-Ar-$CH_2CH_2^+$).

14) Details for the X-ray crystallographic data can be obtained on request from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

15) Bond lengths(Å) and angles(°) around the chiral center (C1) for the three compounds are as follows. Bond Length for (**3a**): 1.379(C1-F2), 1.540(C1-N3), 1.547(C1-C4), 1.511(C1-C5). Bond Angle for(**3a**): 104.5(F2-C1-N3), 110.1(F2-C1-C4), 111.1(F2-C1-C5), 106.4(N3-C1-C4), 110.9(N3-C1-C5), 113.4(C4-C1-C5). Bond Length for (**5a**): 1.383(C1-F2), 1.548(C1-N3), 1.540 (C1-C4), 1.504(C1-C5). Bond Angle for (**5a**): 102.7(F2-C1-N3), 110.3(F2-C1-C4), 111.3(F2-C1-C5), 106.5(N3-C1-C4), 112.4(N3-C1-C5), 113.1(C4-C1-C5). Bond Length for (**9a**): 1.857(C1-S2), 1.332(C1-F3), 1.504(C1-N4), 1.499(C1-C5). Bond Angle for (**9a**): 110.2(S2-C1-F3), 107.5(S2-C1-N4), 107.5(S2-C1-C5), 104.1(F3-C1-N4), 115.8(F3-C1-C5), 111.5(N4-C1-C5).

16) a) R.E. Banks, "Preparation, Properties, and Industrial Applications of Organofluorine Compounds," Ellis Horwood Ltd., Chichester, 1982; b) R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Kodansha Ltd., Tokyo, 1982; c) R. Filler, "Biochemistry Involving Carbon-Fluorine Bonds," American Chemical Society, Washington DC, 1976.

(Received in Japan 13 April 1988; accepted 20 June 1988)