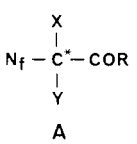
Communications

The First Synthesis and Resolution of Some Chiral Carbon Compounds Having Four Different Labile Ligands†

Summary: The first synthesis and resolution of compounds possessing four different labile ligands, including carbonyl, halogen, nitrogen-containing, and sulfur- or oxygen-containing functionalities, has been achieved.

Sir: The chemistry of compounds containing a carbon atom bearing more than three different labile functional groups (structure A) has received little attention. These



A

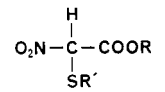
X = F, Br
Y = OR′, SR′, SOR′
N_f = NR'_2, NO_2, N_3
R = R″, OR″, NR''_2

compounds should have considerable significance in theoretical and synthetic organic chemistry. The reactivity of one functional group will be altered by the presence of the other functional groups and the multifunctionality would provide great versatility in synthesis by proper manipulation of the different labile groups. Among the compounds with multifunctional structures, those having both carbonyl and halogen groups in addition to other heteroatom groups seem especially valuable from a synthetic viewpoint. Their potential as probes in pure and applied synthetic chemistry has not been exploited, because of likely structural instability and the paucity of synthetic approaches. We report the first synthesis and structural determination of such a new class of compounds (A), in which ester carbonyl, halogen, nitrogen, and other non-carbon functional groups are directly attached to the central carbon. Fluorine was chosen as the halogen because of the enhanced stability of the C–F bond and because of the inherent biological interest in fluorine-containing compounds.[1]

A potentially promising approach to these structures involved the use of α-fluoro enolates or enol silyl ether intermediates.[2] Although carbon electrophiles (RCOR′, RX) react with these enolates or enol ethers to give fluoro derivatives,[3] nitrogen (NO_2, NH_2) or sulfur (SR) electrophiles[4,5] failed to produce any tri- or tetrafunctional compounds, perhaps because of instability of the products or poor reactivity of the α-fluoro enolate toward the heteroatom electrophiles.[6]

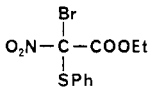
After extensive investigation of starting substrates and of the sequence of introduction of labile functionalities, we succeeded in finding several routes to A. Reaction of the potassium salts[7] of ethyl and benzyl nitroacetates with arenesulfenyl chlorides (THF, 20 °C/2 h, 84–95%) gave α-nitro-α-(arylthio)acetates **1a–c**. The acetate **1a** was easily brominated (NBS/CCl_4, AIBN/reflux/20 h, 78%) to yield the first tetrafunctional carbon compound **2**. Although **2** is reactive, efforts to convert it to the corresponding fluoro derivative **3a** with metal fluorides[8] were unsuccessful. The introduction of fluorine was accomplished by treatment of the potassium salts of **1a–c** with perchloryl fluoride (THF, 0 °C/3 h, 51–76%), to provide the novel fluorinated compounds **3a–c**. An alternate route to **3a–c** was achieved by converting α-fluoro-α-nitroacetates[7] into their potassium salts followed by treatment with arenesulfenyl chlorides (THF, 20 °C/2 h, 79–85%).

Since the fluorination method was found to be applicable only to those compounds having a nitro group as the nitrogen functionality, we examined the use of available fluorine-containing compounds as starting materials. Treatment of ethyl bromofluoroacetate with several heteroatom nucleophiles, e.g., PhSH (NEt_3/THF, reflux/1 h,

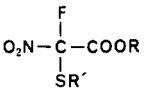


1

a: R = Et, R′ = Ph
b: R = CH_2Ph, R′ = Ph
c: R = Et, R′ = Ph(p-Cl)

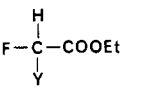


2



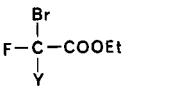
3

a: R = Et, R′ = Ph
b: R = CH_2Ph, R′ = Ph
c: R = Et, R′ = Ph(p-Cl)



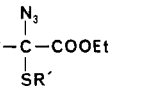
4

a: Y = SPh
b: Y = SEt
c: Y = OPh
d: Y = OCOPh



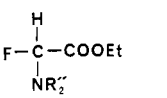
5

a: Y = SPh
b: Y = SEt
c: Y = OPh



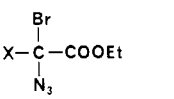
6

a: R′ = Ph
b: R′ = Et



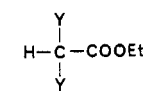
7

a: R″–R″ = phthalyl
b: R″ = R″ = $COOBu^t$
c: R″–R″ = N_2



8

a: X = F
b: X = NO_2

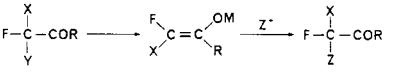


9

a: Y = SEt
b: Y = OCH_2Ph

(1) (a) Filler, R., Ed. "Biochemistry Involving Carbon–Fluorine Bonds"; American Chemical Society: Washington DC; 1976. (b) Schlosser, M. *Tetrahedron* **1978**, *34*, 3. (c) Bey, P.; Gerhart, F.; Van Dorsselaer, V.; Danzin, C. *J. Med. Chem.* **1983**, *26*, 1551. (d) Silverman, R. B.; Abeles, R. H. *Biochemistry* **1977**, *16*, 5515. (e) Jordan, A. *S. Afr. J. Sci.* **1977**, *73*, 201.

(2) Several types of α-fluoro enol derivatives were prepared[3] for electrophilic functionalization, as shown by the scheme below.



X = F, Br
Y = H, F
R = Ph, CH_2Ph, OEt
M = Li, Na, TMS
Z = SPh, SEt, NO_2, NH_2

(3) (a) Elkik, E.; Imbeaux-Oudotte, M. *Tetrahedron Lett.* **1978**, 3793. (b) Yamana, M.; Ishihara, T.; Ando, T. *Ibid.* **1983**, *24*, 507. (c) Buchanan, R. L.; Dean, F. H.; Pattison, F. *Can. J. Chem.* **1962**, *40*, 1571. (d) Molines, H.; Massoudi, M. H.; Cantacuzene, D.; Wakselman, C. *Synthesis* **1983**, 322. (e) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186. (f) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720.

(4) (a) Feuer, H.; Panda, C. S.; Hou, L.; Bevinakatti, H. S. *Synthesis* **1983**, 187. (b) Dampwan, P.; Zajac, W. *Ibid.* **1983**, 545 and references cited therein. (c) Olah, G. A. *Aldrichimica Acta* **1979**, *12*, 43.

(5) (a) Sheradsky, T.; Nir, Z. *Tetrahedron Lett.* **1969**, 77. (b) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Ibid.* **1982**, *23*, 3835. (c) Bernheim, M.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1010.

(6) Brownbridge, P. *Synthesis* **1983**, 1 and references cited therein.

(7) (a) Ostaszyński, A.; Wielgat, J.; Urbański, T. *Tetrahedron* **1969**, *25*, 1929. (b) Fokin, A. V.; Galakhov, V. S.; Radchenko, V. P. *Zh. Obsh. Khim.* **1969**, *39*, 1345.

† This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

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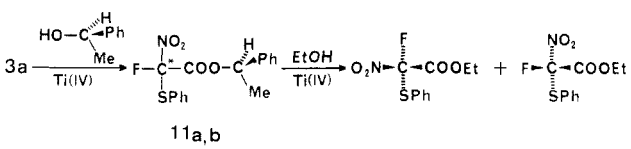
Scheme I



11a,b

96%), EtSH (NaOEt/THF, 0 °C/1 h, 93%), PhOH (NaH/THF, 20 °C/0.5 h, 98%), KOCOPh (DMF, 20 °C/3 h, 86%), potassium phthalimide (DMF, 100 °C/5 h, 89%), di-*tert*-butyl iminodicarboxylate potassium salt (DMF, 120 °C/1 h, 66%), and NaN_3 ($Et_2O/EtOH/H_2O$, 20 °C/10 h, 67%), produced the geminally functionalized fluoroacetates, **4a–d** and **7a–c**, respectively. Although **4d** and **7a–c** could not be brominated, **4a–c** produced rather unstable bromides **5a,b** (NBS/BPO/CCl_4, reflux/1.5–10 h, 43–60%) and **5c** (Br_2/CCl_4, reflux/4 h, 21%). The sulfur functionalized bromides **5a,b** were immediately treated with NaN_3 (AcOEt/EtOH/H_2O, 20 °C/16–28 h, 32–40%) to afford the tetrafunctional carbon compounds **6a,b**.

We also examined possible synthesis of the title compounds starting with ethyl dibromofluoro- and dibromonitroacetates **10a,b**. When **10a,b** were treated carefully with 1 equiv of NaN_3 under the conditions mentioned above, the azido derivatives **8a,b** were obtained in 47% and 15% yields, respectively. An attempt to introduce the amino group by treating **10a,b** with $HNEt_2$ yielded only $Et_2NCOCOOEt$, probably formed by hydrolysis during workup. Attempts to introduce the S or O functionality into **10a** by treatment with NaSPh, NaSEt, or $NaOCH_2Ph$ gave mainly the unexpected reduced products **4a**, **9a**, and **9b**, respectively. The tetrafunctional compounds described here[9] have not been reported previously, despite their structural simplicity.[10,11]

We have also succeeded in resolving this unique structure (Scheme I). The ester **3a** was transesterified ((+)-α-phenethyl alcohol/$Ti(OPr^i)_4$, 110 °C/2 h, 85%)[12] to give a mixture of diastereomeric phenethyl esters (in a ratio of 1:1) and two isomers were separated: **11a** (less polar isomer), $[\alpha]_D$ +136.3°;[13] **11b** (more polar one), $[\alpha]_D$ −93.4°. Each isomer was successfully transformed (EtOH/$Ti(OEt)_4$, 90 °C/2.5 h, 83%)[12] into the optically active ethyl ester: (+)-**3a**, $[\alpha]_D$ +134.2°; (−)-**3a**, $[\alpha]_D$ −132.6°.[14] The racemic α-fluoroglycine derivative **7a** could be also resolved in the same manner: (+)-**7a**, $[\alpha]_D$ +12.7°; (−)-**7a**, $[\alpha]_D$ −13.1°. To our knowledge, this work describes the first synthesis of optically active compounds having four distinctly different labile functional groups.[15] Studies on the broad usefulness of optically active multifunctional carbon compounds are now in progress.[16]

(8) (a) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647. (b) Hudlicky, M. "Organic Fluorine Chemistry"; Plenum Press: New York, London, 1971. (c) Chambers, R. D. "Fluorine in Organic Chemistry"; John Wiley: New York, 1973.

(9) Yields are not optimized. The spectral and analytical data for all new compounds were in accord with the structures proposed.

(10) Even the trifunctionalized carbon structures **1a–c** and **7a–c** are not known. As for the ester of α-fluoro alcohol **4d**, see: Ortiz de Montellano, P. R.; Vinson, W. A. *J. Am. Chem. Soc.* **1979**, *101*, 2222.

(11) Spectral analyses of these unusual structures should also be noted. In their ^{13}C NMR spectra, the central carbon shift positions of **3a–c** (δ 119.0–119.6) are unexpectedly low, probably the lowest of the reported data for ethyl acetate derivatives. The most interesting data must be those of ^{19}F NMR and mass spectra for the compounds bearing four labile groups on a carbon atom. All of these data will be reported elswhere.

(12) (a) Schnurrenberger, P.; Züger, M. F.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1197. (b) Seebach, D.; Hungerbühler, E.; Naef, R. *Synthesis* **1982**, 138. (c) Rehwinkel, H.; Steglich, W. *Ibid.* **1982**, 826.

(13) All optical rotations were measured in chloroform at 24–25 °C (*c* 0.9–4.0).

(14) Absolute configuration of the enantiomers has not yet been determined. No racemization[12] at the tetrafunctionalized asymmetric center was observed as checked by Chiralcel OB chromatography.

(15) Hirschmann, H.; Hanson, K. R. *Top. Stereochem.* **1983**, *14*, 183.

(16) Considering that the conventional direct fluorination methods often lack selectivity, the fluorinated compounds obtained here can be useful synthon molecules bearing both fluorine and an asymmetric carbon atom. These compounds are excellent precursors of α-fluoro-α-amino acid derivatives and, further, candidates for models to study steric aspects of reaction mechanisms.

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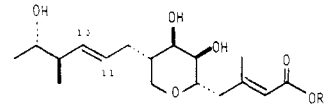
An Enantiospecific Synthesis of Monic Acid C

Summary: Monic acid C (**2**) has been prepared in optically pure form from dihydropyran, thus affording a route to the naturally occurring pseudomonic acids A and C.

Sir: The pseudomonic acids are naturally occurring pyrans from *Pseudomonas fluorescens* that have been found to possess significant antibacterial and antimycoplasmal activity.[1] Upon saponification, pseudomonic acid C (**1**) gives monic acid C (**2**),[2] from which both **1** and its more abundant congener pseudomonic acid A (**3**) have been reconstituted. Several pathways to these materials in racemic



1, R = $(CH_2)_8CO_2H$
2, R = H
3, R = $(CH_2)_8CO_2H$, 10,11-epoxide

form have been published[3] and three enantioselective syntheses, all from carbohydrate precursors, have been described.[4] We now report a synthesis of **2** from dihydropyran in which the incorporation of absolute stereochemistry as well as deployment of the cis-oriented side chains is effected by conceptually novel methods.

The reaction of dihydropyran with bromine and (−)-borneol in the presence of *N*,*N*-dimethylaniline (CH_2Cl_2, −78 °C) gave the bromo acetal **4** together with its diastereoisomer (1:1) in 84% yield.[5] Without separation, this mixture was treated with 1,8-diazabicyclo[5.4.0]undec-7-

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(2) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2827.

(3) (a) Jackson, R. F. W.; Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2159. (b) Snider, B. B.; Phillips, G. B.; Cordova, R. *J. Org. Chem.* **1983**, *48*, 3003. (c) Schönenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333. (d) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. (e) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett.* **1981**, *22*, 2059.

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(5) Sweet, F; Brown, R. K. *Can. J. Chem.* **1968**, *46*, 707.

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