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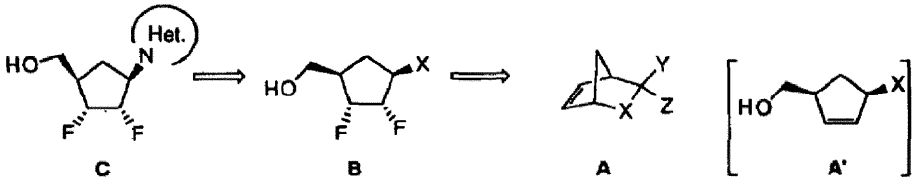
ADDITION OF MOLECULAR FLUORINE TO BICYCLO[2.2.1]HEPT-2-ENE DERIVATIVES AND CONVERSION TO FLUORINE-CONTAINING CARBOCYCLIC NUCLEOSIDES[1]

Akemi Toyota,* Chie Habutani, Nobuya Katagiri and Chikara Kaneko

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

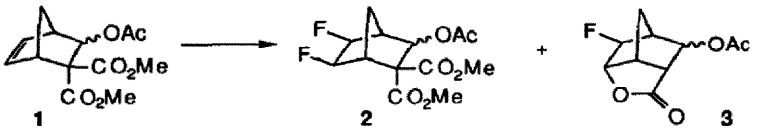
Abstract: Addition of molecular fluorine to bicyclo[2.2.1]hept-2-ene derivatives has been found to give *exo,exo*-difluoro adducts in fair yields. The difluoro adduct (13c) was converted to the fluorine containing carbocyclic adenosine and guanosine analogs.

Two major types of organic reactions using molecular fluorine as the fluorinating reagent are the substitution of C-H's[2] and the addition to C=C bonds.[3] Electrophilic nature of both reactions has been deduced from accumulated experimental results[4] and verified by *ab initio* MO calculation using intrinsic reaction coordinate method.[5, 6] Our attempts to perform direct fluorination of 3-(hydroxymethyl)cyclopentenes (**A'**) have been found to give a complex mixture, due to many functionalities (e.g. allylic, tertiary hydrogens, a double bond, and a hydroxyl group). Therefore, in order to obtain the fluorine-containing carbocyclic sugar units (**B**), we chose bicyclo[2.2.1]hept-2-ene derivatives (**A**) as the fluorinating substrates which have tertiary hydrogens with somewhat lower *p*-character[4] than sp^3 and a more activated double bond than that of **A'**.[7] We describe here successful addition of fluorine to bicyclo[2.2.1]hept-2-ene derivatives (**A**) and their conversion to fluorine-containing carbocyclic nucleosides (**C**).

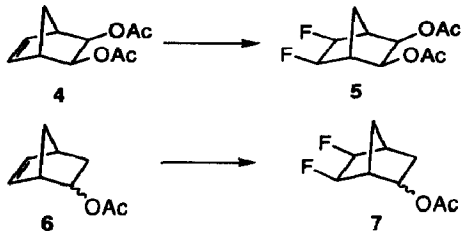


C **B** **A** **A'**

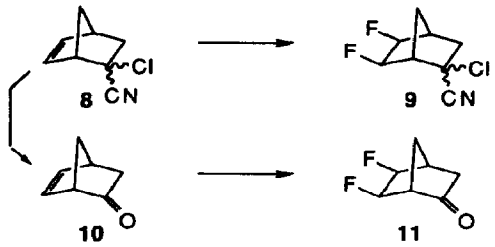
In a typical experiment, stream of 5% fluorine in nitrogen was passed through a solution of the bicyclic heptene (**1**)[8] (*endo/exo* = *ca.* 1) in $CFCl_3$-$CHCl_3$-EtOH (5:4:1)[3] at -78 °C to give the corresponding *cis* adduct (**2**)[9](52%) together with the lactone (**3**) (20%). Fluorination of **4**[10] under the similar reaction conditions gave the *exo* adduct (**5**)[11] in 40% yield. Fluorination of the monoacetate (**6**)[12] (*endo/exo* = *ca.* 4) gave the adduct (**7**) in a lower yield (23%).



1 **2** **3**

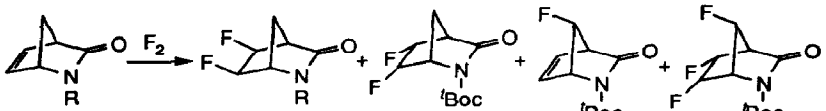


Treatment of the adduct (**8**) (*endo*/*exo* = *ca.* 6)[13] derived from cyclopentadiene and chloroacrylonitrile with F_2 gave **9** in 52% yield. The same reaction if applied to the ketone (**10**) obtained from **8** provided **11**[14] in 30% yield.



Addition of fluorine to 2-azabicyclo[2.2.1]hept-5-en-3-one (**12a**)[15] and its acetate (**12b**)[16] afforded the corresponding adducts (**13a** and **13b**) in 35% and 40% yields, respectively. We reported previously that **12a** was easily converted to *cis*-4-(hydroxymethyl)cyclopent-2-enylamine by introduction of an electron-withdrawing group at the nitrogen atom followed by reductive amido bond cleavage reaction ($NaBH_4$, MeOH, ambient temp.).[16] While conversion of **12a** to **12b** proceeded only in 17% yield, *tert*-butoxycarbonyl group was found to be introduced quantitativly by using di-*tert*-butyl dicarbonate [17] to give **12c**.[18] The fluorination reaction of **12c** was studied in detail. Besides the *exo* difluoro adduct (**13c**)[19] (43%), the *endo* isomer (**14**)[20] (5%), monofluoro product (**15**)[21] (2%) and trifluoro product (**16**)[22] (4%) were isolated. The *exo* configulation of F_2 in **13c** was evident from the larger coupling (J = 7 Hz) of C_4-H (3.17 ppm) with C_5-F compared to the absence of the corresponding coupling in **14** and lowfield shift of C_{7anti}-H (2.34 ppm) compared to the corresponding proton (1.44 ppm) of **14** due to deshielding effect of the fluorine groups. Long range couplings (J = 9 Hz) of C_{7syn}-H (2.13 ppm) with C_5-F and C_6-F in **14** also supported its *endo* structure. The similar long-range couplings (J = 8 Hz) of C_{7syn}-H (5.07 ppm) were observed in **16**

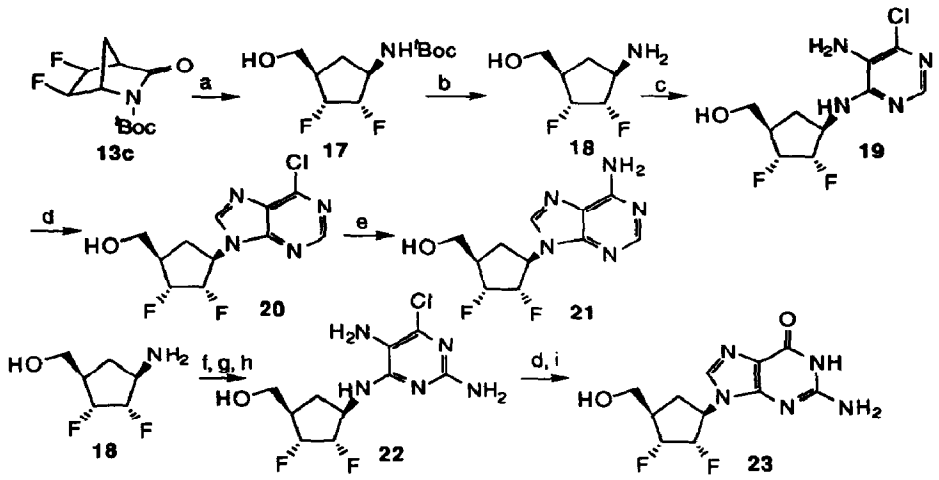
The monofluorination product (**15**) was considered to be formed *via* addition-rearrangement with nitrogen participation which was well precedented in the bromination of similar system.[23] In accordance with the above conclusion, the fluorination of **15** afforded **16** as the major product. It is obvious that the fluorine at 7-position has restricted access to the *exo* face of **15**.[24]



12a: R = H
12b: R = Ac
12c: R = ^{t}Boc

13a: R = H
13b: R = Ac
13c: R = ^{t}Boc

14 **15** **16**



Scheme 1. a, $NaBH_4$, MeOH, -20 °C; b, TFA, r.t.; c, 5-amino-4,6-dichloropyrimidine, Pr^i_2NEt, BuOH, reflux; d, $(EtO)_3CH$, HCl; e, NH_3, MeOH, 80 °C; f, 2-amino-4,6-dichloropyrimidine; g, $4\text{-}ClC_6H_4N_2^+Cl^-$, HOAc, NaOAc, H_2O; h, Zn, HOAc, EtOH, H_2O; i, 10% *aq.* HCl, reflux

Reductive amido bond cleavage of **13c** by using sodium borohydride at -20 °C gave **17** in 84% yield. Usual construction of purine rings[25] from **18** then afforded desired carbocyclic fluorinated nucleosides (**21** and **23**). Thus, treatment of **17** with TFA and coupling of the resulted amino alcohol (**18**) with 5-amino-4,6-dichloropyrimidine furnished the diamine (**19**) in 40% yield. Treatment of **19** with triethyl orthoformate under acidic conditions followed by amination led to the adenosine derivative (**21**) in 49% yield. Coupling of **18** with 2-amino-4,6-dichloropyrimidine followed by diazotization using 4-chlorophenyldiazonium chloride and reduction of the diazo compound with zinc-acetic acid afforded the aromatic amine (**22**) in 32% overall yield. The ring closure of **22** as in the case of **19** followed by acidic hydrolysis afforded the guanosine analog (**23**) in 53% yield.

In conclusion, we have found that fluorination of bicyclo[2.2.1]hept-2-ene derivatives by diluted fluorine affords selectively the *exo* adducts. This reaction could be used for the synthesis of not only fluorinated carbocyclic nucleoside analogs but also other fluorine compounds.

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19. **13c**: mp 133-136 °C (hexane), ^{1}H-NMR ($CDCl_3$) δ: 1.53 (9H, s, CO_2t-Bu), 2.21 (1H, dm, J = 11 Hz, C_{7s}-H), 2.34 (1H, dm, J = 11 Hz, C_{7a}-H), 3.10 (1H, dm, J = 7 Hz, C_4-H), 4.62 (1H, m., C_1-H), 4.88 (1H, dm, J = 47 Hz, C_6-H), 5.04 (1H, dm, J = 48 Hz, C_5-H).
20. **14**: mp 138-141 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.53 (9H, s, CO_2t-Bu), 1.44 (1H, dm, J = 12 Hz, C_{7a}-H), 2.13 (1H, ddddd, J = 12, 9, 9, 2, and 2 Hz, C_{7s}-H), 3.25 (1H, m, C_4-H), 4.80 (1H, m, C_1-H), 5.05 (1H, dddd, J = 50, 7, 3, and 3 Hz, C_6-H), 5.13 (1H, dddd, J = 47, 8, 4, and 3 Hz, C_5-H).
21. **15**: oil, ^{1}H-NMR ($CDCl_3$) δ: 1.51 (9H, s, CO_2t-Bu), 3.51 (1H, d, J = 2 Hz, C_4-H), 5.02 (1H, br s, C_1-H), 5.18 (1H, d, J = 60 Hz, C_7-H), 6.57 (1H, dm, J = 5.5 Hz, C_5-H), 6.78 (1H, dd, J = 5.5 and 2 Hz, C_6-H).
22. **16**: oil, ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s, CO_2t-Bu), 3.56 (1H, br s, C_4-H), 4.88 (1H, br s, C_1-H), 5.07 (1H, ddddd, J = 53, 7.7, 7.7, 2.6, and 2.6 Hz, C_7-H), 5.34 (1H, dddd, J = 50, 10, 4, and 3.3 Hz, C_6-H), 5.41 (1H, dddd, J = 51, 7.3, 4, and 3.3 Hz, C_5-H).
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