Pergamon

Tetrahedron Letters 39 (1998) 4687–4690

TETRAHEDRON LETTERS

α-FLUORINATION OF 6-PHENYLSULFINYL-2-AZABICYCLO[2.2.1]HEPTAN-3-ONE AND SYNTHESIS OF 2'-FLUORO SUBSTITUTED CARBOVIR

Akemi Toyota,* Akiko Nishimura and Chikara Kaneko

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Received 16 March 1998; accepted 24 April 1998

Abstract: Fluorination of phenylsulfinyl bicycloamide using molecular fluorine proceeded preferentially with inversion of the carbon atom having the sulfinyl group to afford α-fluorinated sulfonyl bicycloamide in fair yield. The fluorinated sulfonyl bicycloamide was converted to 2'-fluoro substituted carbovir *via* reductive desulfonylchlorination. © 1998 Elsevier Science Ltd.

Although carbovir has attracted much attention due to its activity against HIV comparable to that of AZT,[1] there is no investigation concerning the synthesis of 2'- or 3'- halogeno substituted analogs except 3'-chloro substituted carbovir which was synthesized by our laboratory.[2] Since none of the fluoro substituted carbovirs were reported to date, we have been interested in their synthesis. After all attempts to obtain the desired fluorocyclopentenylamines (e.g. **D**) by dehydroiodination of the iodofluoro adducts (**A**, **B** and **C**) obtained in our previous works[3] proved fruitless, we planned to synthesize the fluoro substituted carbovir by using α-fluorination reaction of sulfoxide with molecular fluorine recently developed in our laboratory.[4, 5] As shown in Scheme 2, our route starts from the bicycloamide (**E**) and ends up with the 2'-cyclopentenylamine (**H**), the versatile precursor of 2'-fluorocarbocyclic nucleosides (**E** → **F** → **G** → **H**). We describe here the

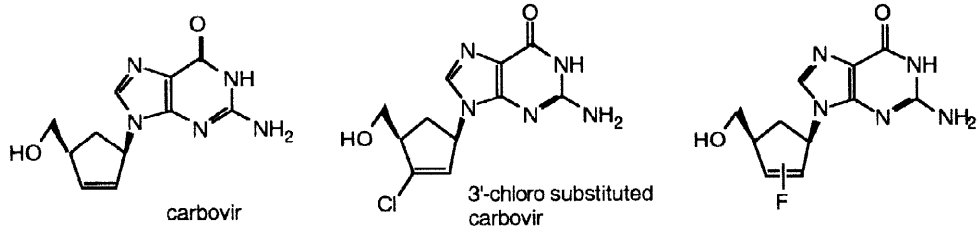
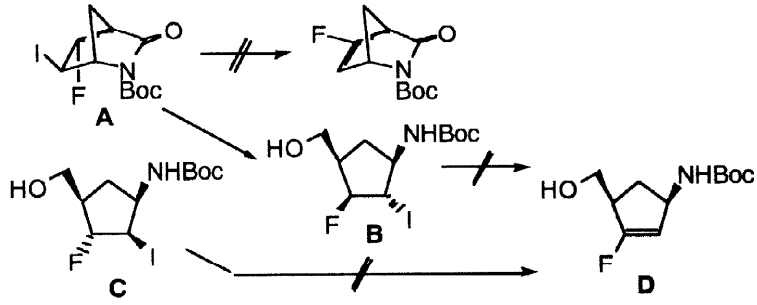
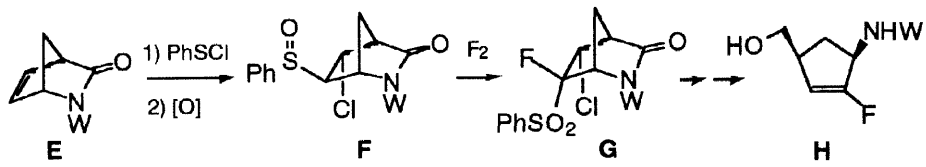


Figure 1



Scheme 1

0040-4039/98/$19.00
PII: S0040-4039(98)00878-8



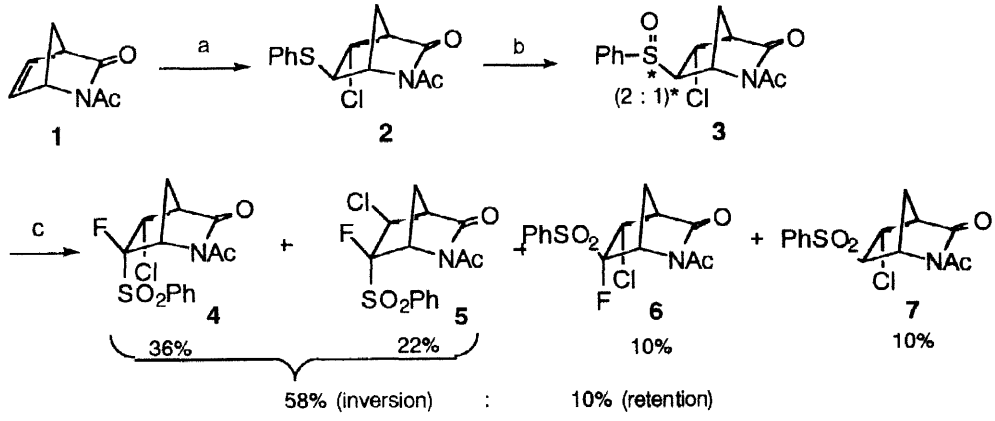
Scheme 2

first synthesis of 2'-fluoro substituted carbovir according to this route (Scheme 2).

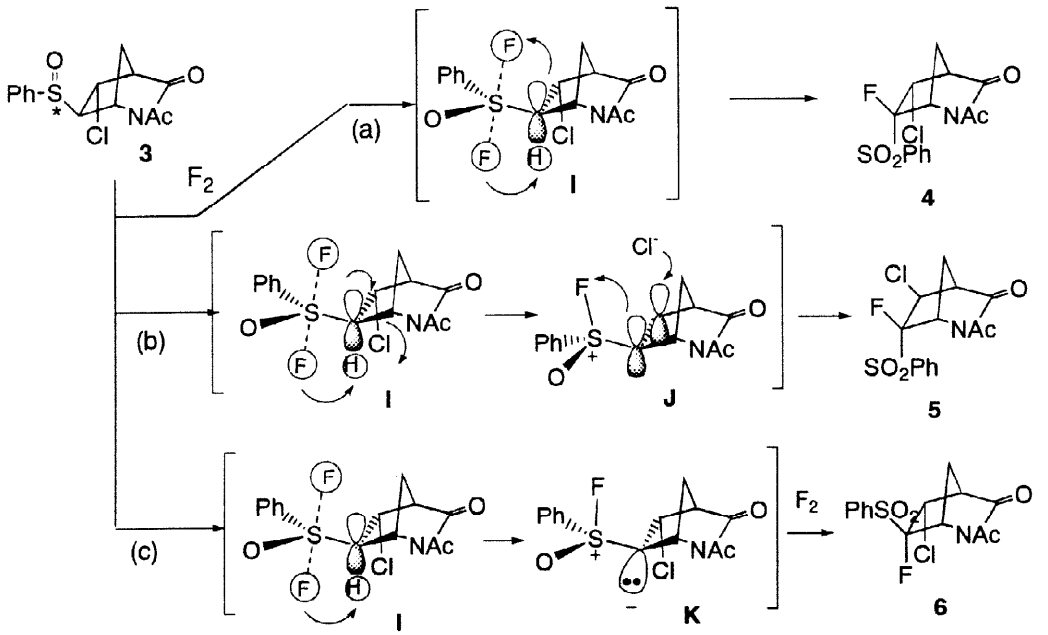
Addition of phenylsulfenyl chloride to the *N*-acetyl bicycloamide (**1**) gave *exo* 6-phenylsulfenyl adduct (**2**) (87%) as the sole product. Though the same regioselectivity has previously been observed in the addition reactions of phenylselenenyl chloride to various bicycloamides,[2, 6] the stereoselectivity is not the same. Thus, while the addition of phenylselenenyl chloride gave both the *endo* and *exo* phenylseleno adducts, the present reaction led to no formation of the *endo* phenylsulfenyl product. The lack of the *endo* product in the present reaction is best explained by a much smaller amplitude of the empty *d*-orbital of the sulfur atom than that of the selenium atom.[7]

Oxidation of the sulfide with *m*CPBA gave the sulfoxide (**3**) as a diastereomeric mixture (2 : 1) quantitatively. Fluorinaiton of **3** by 5% F_2 /N_2 was carried out as reported in our previous work.[4] As expected, the fluorinated products (**4**,[8] **5**,[9] and **6**[10]) were obtained in good total yield. The *endo* configuration of the chlorine atom in **4** and **6** was evident from the larger coupling constants (J = 4 Hz) of C_4-H with C_5-H compared to the smaller corresponding coupling constant (J = 2.5 Hz) in **5**. Based on the determination of the configuration of C_5-H in **4** ~ **6**, the *exo* configuration of the fluorine atom in **4** was deduced unequivocally from the larger coupling constant (J = 27.5 Hz) of C_5-H with C_6-F compared to the corresponding coupling (J = 7.5 Hz) in **6**.[3, 11] The *exo* configuration of the fluorine atom in **5** was determined by the vicinal coupling constant (J = 7.5 Hz) of C_5-H with C_6-F.

The result shows that fluorination of **3** proceeded preferentially with inversion of configuration of C_6 (path a) just as that of cyclopropyl phenyl sulfoxide.[5] The fluorinated product (**4**) is considered to be formed *via* intramolecular dehydrofluorinaion and stereoselective fluorine migration from the sulfurane-like intermediate (**I**).[5] Dechlorination of **I** and attack of the chloride anion from the *exo* face to **J** before the fluorine migration (path b) would afford another fluorine inversion product (**5**). The product (**6**) would be formed *via*



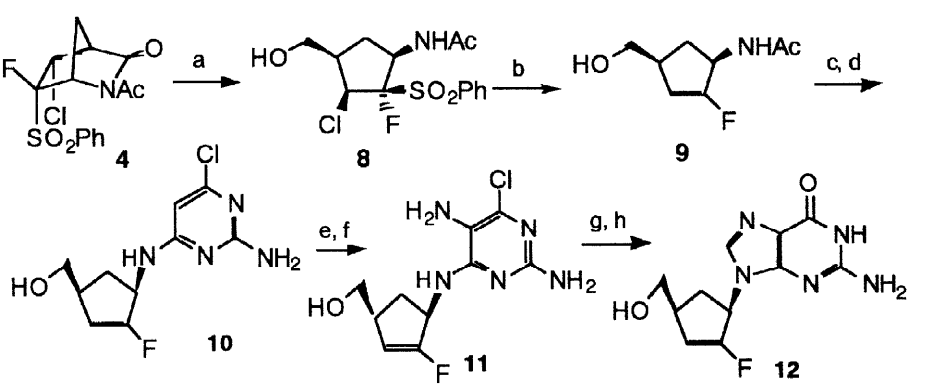
Scheme 3. a, PhSCl, NEt_3 (0.1 eq.), MeCN, -20 °C → r.t; b, *m*CPBA, CH_2Cl_2, -40 °C → 20°C; c, 5% F_2/N_2, MeCN, -20 °C.



Scheme 4

fluorine addition of the ylide species (**K**) formed by the dehydrofluorination of **I** (path c).

Reductive amide bond cleavage[11] of **4** using sodium borohydride gave **8** in 59% yield. Treatment of **8** with Mg in ethanol in the presence of a catalytic amount of $HgCl_2$[12] gave the fluoroalkene (**9**) in 65% yield. Similarly, **5** and **6** were converted to **9** in 47% and 44% yields, respectively. Usual construction of the purine ring[13] from **8** afforded the desired carbocyclic nucleoside (**12**). Thus, treatment of **9** with 10% aq. HCl followed by coupling with 2-amino-4,6-dichloropyrimidine furnished the diamine (**10**) in 43% yield. Diazotization of **10** using 4-chlorophenyldiazonium chloride followed by reduction with zinc-acetic acid afforded the triamine (**11**) in 40% yield. The ring closure of **11** with triethyl orthoformate under acidic conditions followed by alkaline hydrolysis gave the 2'-fluoro substituted carbovir (**12**)[14] in 68% yield.



Scheme 5. a, $NaBH_4$, MeOH, -25 °C → r t ; b, Mg, cat. $HgCl_2$, EtOH-THF (4 : 1); c, 10% aq. HCl, reflux; d, 2-amino-4,6-dichloropyrimidine, *i*-Pr_2NEt, *n*-BuOH, reflux; e, 4-$ClC_6H_4N_2^+Cl^-$, HOAc, NaOAc, H_2O; f, Zn, HOAc, EtOH, H_2O; g, $(EtO)_3CH$, HCl; h, 1% aq. NaOH, *t*-BuOH, reflux.

In summary, we have found that α-fluorination of 6-phenylsulfinyl-2-azabicyclo[2.2.1]hept-2-ene (**1**) using molecular fluorine affords fluorinated products (**4**, **5**, and **6**) in good yields. The adducts (**4**, **5**, and **6**) were converted to 2'-fluoro substituted carbovir (**12**).

Acknowledgment. This work is supported in part by a Grant-in-Aid from the Tokyo Biochemical Research Foundation to A. T.

REFERENCES AND NOTES

1. Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912.; Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17; Martinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963-7966.
2. Toyota, A.; Nishimura, A.; Kaneko, C. *Heterocycles* **1997**, *45*, 2105-2108.
3. Toyota, A.; Ono, Y.; Kaneko, C. *Tetrahedron Lett.* **1995**, *36*, 6123-6126.
4. Toyota, A.; Ono, Y.; Chiba, J; Sugihara T.; Kaneko, C. *Chem. Pharm. Bull.* **1996**, *44*, 703-708.
5. Toyota, A.; Ono, Y.; Kaneko, C.; Hayakawa, I. *Tetrahedron Lett.* **1996**, *37*, 8507-8510.
6. Palmer, C. F.; Parry, K. P.; Roberts S. M.; Sik, V. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1021-1028.
7. We considered that the formation of *endo* phenylselenenyl products was due to the interaction of the empty *d*-orbital of the Se atom with the HOMO derived by through-space interaction between the two unsaturated functions (C=C and NR-C=O).[2] Since the *d*-orbital of S atom has much smaller amplitude than that of the Se atom, the corresponding interaction (leading to the *endo* product) would not be expected in the present reaction.
8. **4**: ^{1}H-NMR ($CDCl_3$) δ: 2.16 (1H, m, C_{7s}-H), 2.26 (1H, m, C_{7a}-H), 2.61 (3H, s, Ac), 3.34 (1H, dd, J = 4 and 2 Hz, C_4-H), 4.64 (1H, dd, J = 27.5 and 4 Hz, C_5-H), 5.01 (1H, m, C_1-H), 7.68 (3H, m, Ph-H x 3), 8.09 (2H, m, Ph-H x 2).
9. **5**: ^{1}H-NMR ($CDCl_3$) δ: 2.25 (1H, d, J = 12 Hz, C_{7s}-H), 2.40 (1H, d, J = 12 Hz, C_{7a}-H), 2.53 (3H, s, Ac), 3.17 (1H, d, J = 2.5 Hz, C_4-H), 4.82 (1H, dd, J = 7.5 and 2.5 Hz, C_5-H), 5.24 (1H, m, C_1-H), 7.70 (3H, m, Ph-H x 3), 7.99 (2H, m, Ph-H x 2).
10. **6**: ^{1}H-NMR ($CDCl_3$) δ: 2.28 (1H, m, C_{7s}-H), 2.57 (1H, m, C_{7a}-H), 2.42 (3H, s, Ac), 3.26 (1H, m, C_4-H), 4.97 (1H, dd, J = 7.5 and 4 Hz, C_5-H), 5.25 (1H, m, C_1-H), 7.69 (3H, m, Ph-H x 3), 7.96 (2H, m, Ph-H x 2).
11. Toyota, A.; Habutani, C.; Katagiri, N.; Kaneko, C. *Tetrahedron Lett.* **1994**, *35*, 5665-5668.
12. Lee, G. H.; Choi E. B.; Lee, E.; Pak, C. S. *Tetrahedron Lett.* **1993**, *34*, 4541-4542.
13. Evans, C. T.; Roberts, S. M.; Shoberu, K. A.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 589-592.
14. **12**: ^{1}H-NMR ($CDCl_3$-CD_3OD = 1:1) δ: 1.81 (1H, dt, J = 13 and 5 Hz, $C_{5'}$-Hα), 2.73 (1H, dt, J = 13 and 9 Hz, $C_{5'}$-Hβ), 2.84 (1H, m, $C_{4'}$-H), 3.49 (1H, dd, J = 10.5 and 5 Hz, CHH'O), 3.58 (1H, dd, J = 10.5 and 5 Hz, CHH'O), 5.24 (1H, br, NH_2), 5.40 (1H, m, $C_{1'}$-H), 5.42 (1H, t, J = 2 Hz, $C_{3'}$-H), 7.69 (1H, s, C_8-H).