

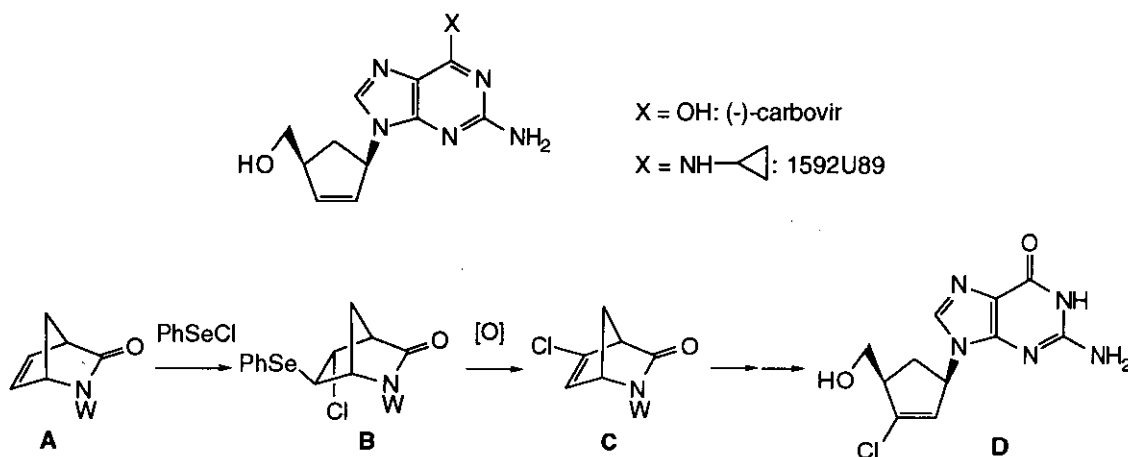
# STERESELECTIVITY IN ADDITION OF PHENYLSELENYL CHLORIDE TO BICYCLO[2.2.1]HEPT-2-ENE DERIVATIVES AND SYNTHESIS OF 3'-CHLORO SUBSTITUTED CARBOVIR

Akemi Toyota,\* Akiko Nishimura, and Chikara Kaneko

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

**Abstract**-Addition of phenylselenenyl chloride to bicyclo[2.2.1]hept-2-enes was examined and the stereoselectivities have been clarified. The adducts derived from 2-azabicyclo[2.2.1]hept-5-en-3-ones having an electron-withdrawing group at 2-position were converted to 3'-chloro substituted carbovir.

There is current interest in the possible use of the carbovir derivative, (-)-1592U89 succinate as an oral chemotherapeutic agent for the treatment of AIDS infections.<sup>1</sup> Although (-)-carbovir has activity against HIV comparable to that of AZT, there is no investigation concerning with 2'- or 3'- halogeno substituted analogs. For the synthesis of 2'- or 3'-halogeno 2',3'-unsaturated carbocyclic nucleoside precursor, we have studied addition of phenylselenenyl chloride to bicyclo[2.2.1]hept-2-enes and found that *endo* selectivity of phenylselenenylation increases as electron density on the ring nitrogen atom increases. This paper contains the result of the phenylselenenylation, a rationale for the observed stereoselectivity and the the first synthesis of 3'-chloro substituted carbovir (**D**) from the adduct (**B**).



Scheme 1

Addition of phenylselenenyl halides to the *N*-substituted (**1a**, **1b**) and non-substituted lactams (**1d**)

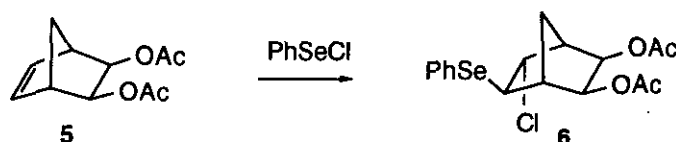
gave *exo* 6-phenylseleno (**2a**, **2b** or **2d**), *endo* 6-phenylseleno (**3a**, **3b** or **3d**) and *endo* 5-phenylseleno products (**4a** or **4b**), respectively. Palmer *et al.* reported that the addition of PhSeBr to the *N*-tosyllactam (**1c**) and *N*-benzylactam (**1e**) provided *endo* 6-phenylseleno products preferentially.<sup>2</sup> As shown in Table 1, the high regioselectivity (**2** + **3** vs **4**) was observed in all cases. The regioselectivity could be explained in terms of homoallylic participation,<sup>3</sup> i. e., the hyperconjugative interaction of the  $\pi$ -orbital of carbonyl with *p*-orbital of the C(5) carbonium ion. Similar mechanism was proposed to account for the regioselectivity of bicyclo[2.2.1]hept-5-en-3-ones.<sup>4</sup> Concerning with the stereoselectivity observed in these reactions, *exo* selectivity of phenylseleno group was found to decrease with the order of *N*-substituents, Ac > *tert*-Boc > TolSO<sub>2</sub> > H > PhCH<sub>2</sub>.

Table 1. Addition of phenylselenenyl halide to 2-azabicyclo[2.2.1]hept-5-en-3-ones.

| entry | Substrate                           | X  | Product, Isolated Yield, % <sup>a</sup> |      |     |
|-------|-------------------------------------|----|-----------------------------------------|------|-----|
| 1     | <b>1a</b> (R = Ac)                  | Cl | 74                                      | 7    | 7   |
| 2     | <b>1a</b> (R = Ac)                  | Br | 92                                      | 5    | 3   |
| 3     | <b>1b</b> (R = Boc)                 | Cl | 56                                      | 30   | 4   |
| 4     | <b>1c</b> (R = SO <sub>2</sub> Tol) | Br | (31)                                    | (43) | (0) |
| 5     | <b>1d</b> (R = H)                   | Cl | 16                                      | 71   | 0   |
| 6     | <b>1e</b> (R = PhCH <sub>2</sub> )  | Br | (0)                                     | (55) | (0) |

<sup>a</sup> The numbers in parentheses are the reported data in ref. 2.

Similar phenylselenenylation of norbornene derivative (**5**) was found to give the *exo* phenylseleno product (**6**) as the sole product.



Scheme 2

Garratt and Kabo reported that the addition of PhSeCl to norbornene also gave *exo* phenylseleno product but similar reaction of norbornadiene afforded *endo*-seleno compound preferentially.<sup>5</sup> Palmer *et al.* have explained that the preferential *endo* attack of phenylseleno group to norbornadiene and the unsaturated lactams (**1c** and **1e**) is due to the relative ease of access of nucleophile to C-5 (*exo* vs *endo* approach).<sup>2</sup> But this explanation cannot explain the difference of the stereoselectivity found in the addition reactions of phenylselenenyl halide to norbornadiene and norbornene, or **1a** and **1e**. We considered that the *endo* selectivity of norbornadiene is due to the favorable interaction of empty *d*-orbital of Se atom with the

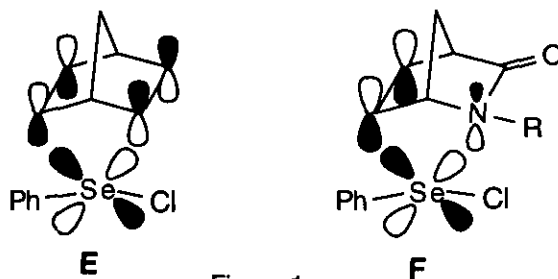
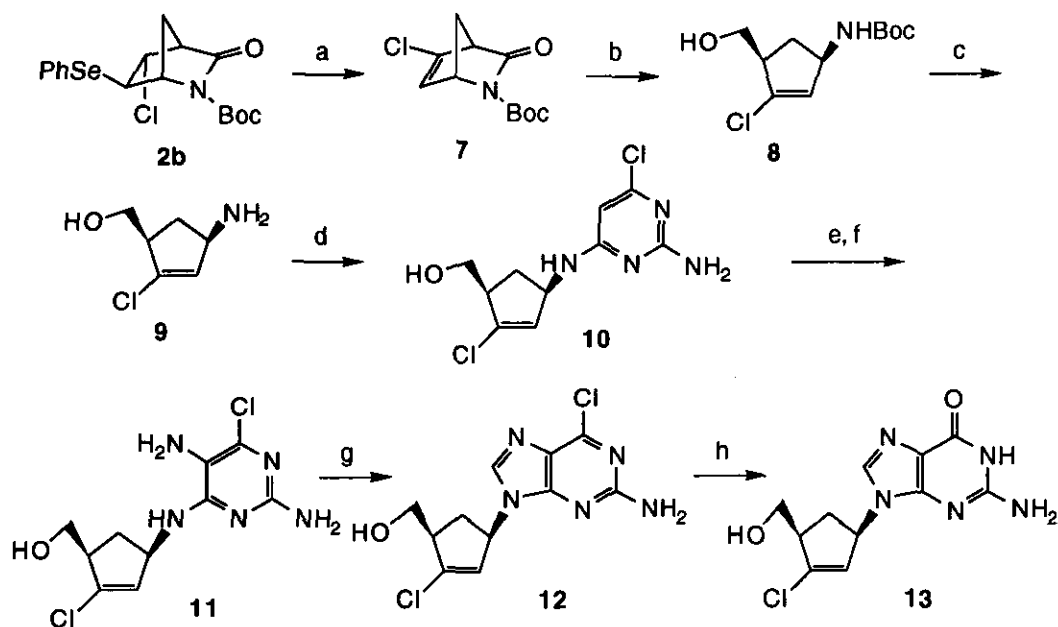


Figure 1

HOMO (**E**) derived by through-space interaction between the two unsaturated functions.<sup>6</sup> In unsaturated lactams (**1**), this interaction is only possible for **1d** and **1e**, because HOMO energy level of  $N=C$  (having sufficient double bond character) in the amide functions in them is comparable with that of ethylene ( $C=C$ ); hence, similar interaction (**F**) is possible. When the nitrogen in **1** is substituted with an electron withdrawing group, the corresponding energy level becomes much lower and hence, the through-space interaction vanished due to large energy gap. Actually, *endo* preference is not observed in **1a-1c** (cf. Table 1).

Treatment of **2b** with excess  $H_2O_2$  (30% aqueous solution) gave only decomposed products. When the oxidative elimination of phenylseleno group was carried out using 1 equivalent of  $H_2O_2$  in the presence of 1 equivalent of  $NaHCO_3$ , chloroalkene (**7**) was obtained in 67% yield. Alternatively, **2b** was oxidized with



Scheme 3. a, *m*CPBA,  $NaHCO_3$  (2 eq.),  $CH_2Cl_2$ ,  $-78^\circ C$ ; ii,  $NEt_3$  (1.2 eq.); b,  $NaBH_4$ , MeOH,  $-35^\circ C \rightarrow r t$ ; c, TFA,  $r t$ ; d, 2-amino-4,6-dichloropyrimidine,  $Pr'_2NEt$ ,  $^tBuOH$ , 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,  $^tBuOH$ , reflux.

*m*CPBA at -78 °C followed by treatment of NEt<sub>3</sub> to give **7** in 77% yield. Similar reaction of **3b** gave the same compound (**7**) in 92% yield. Reductive amide bond cleavage<sup>7</sup> of **7** by using sodium borohydride at -35 °C → room temperature gave **8** in 98% yield. Usual construction of purine ring<sup>8</sup> from **8** then afforded the desired carbocyclic nucleoside (**13**). Thus, treatment of **8** with TFA and coupling of the resultant amino alcohol (**9**) with 2-amino-4,6-dichloropyrimidine furnished the diamine (**10**) in 76% yield. Diazotization of **10** using 4-chlorophenyldiazonium chloride followed by reduction with zinc-acetic acid afforded the triamine (**11**) in 61% yield. The ring closure of **11** with triethyl orthoformate under acidic conditions followed by alkaline hydrolysis gave the 3'-chloro substituted carbovir (**13**) in 53% yield. In conclusion, we have clarified the stereoselectivities of phenylselenylation of bicyclo[2.2.1]hept-2-enes. The adduct (**2b**) from 2-azabicyclo[2.2.1]hept-2-ene (**1b**) was converted to 3'-chloro substituted carbovir.

## ACKNOWLEDGMENT

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## REFERENCES AND NOTES

1. D. W. Kimberlin, D. M. Coen, K. K. Biron, J. I. Cohen, R. A. Lamb, M. McKinlay, E. A. Emimi, and R. J. Whitley, *Antiviral Res.*, **1995**, *26*, 369.
2. C. F. Palmer, K. P. Parry, S. M. Roberts, and V. Sik, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1021.
3. Review of homoallylic participation: T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, p. 288, Harper & Row, Pub., N. Y., 1976.
4. P.-A. Carrupt and P. Vogel, *Tetrahedron Lett.*, **1984**, *25*, 2879.
5. D. G. Garratt and A. Kabo, *Can. J. Chem.*, **1980**, *58*, 1030.
6. Given a pair of occupied orbitals which exists in a molecule in a small distance (two ethylenes in norbornadiene), a direct through-space interaction between them (a pair of degenerated  $\pi$ -HOMOs) leads to two energy levels in the usual in-phase and out-of-phase combinations. As a result, the out-of-phase combination is higher in energy than in-phase one and hence, becomes the actual HOMO (cf. **E**). Thus, from two ethylene HOMOs in norbornadiene which without interaction are in the same energy level, the one depicted in **E** becomes the true HOMO. Since the energy level of HOMO of  $>\text{N}=\text{C}<$  of  $-\text{N}-\text{C}(\text{O})-$  has double bond character with lower energy level, the true HOMO of **1d** is the HOMO of ethylene  $\pi$ -MO ( $\text{C}_5=\text{C}_6$ ) mixed with  $>\text{N}=\text{C}<$  in out-of phase overlap as shown in **F**. In **1a** and **1b**, the energy levels of the HOMO of  $>\text{N}=\text{C}<$  are much lower, the corresponding interaction is not significant; hence, no *endo*-preference is observed.
7. A. Toyota, C. Habutani, N. Katagiri, and C. Kaneko, *Tetrahedron Lett.*, **1994**, *35*, 5665.
8. C. T. Evans, S. M. Roberts, K. A. Shoberu, and A. G. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 589.

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