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

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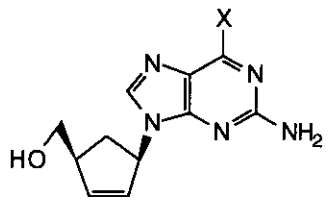
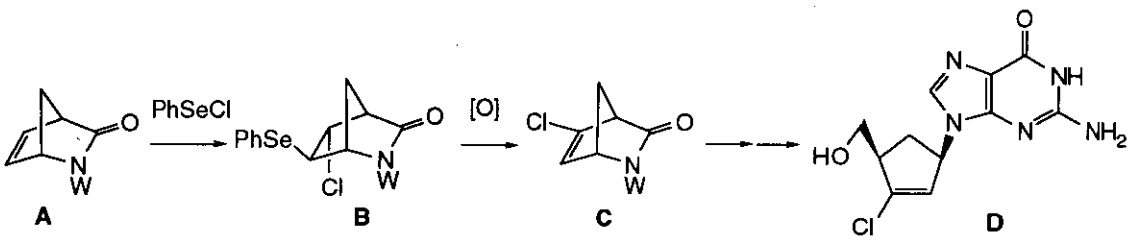
Abstract-Addition of phenylselenyl chloride to bicyclo[2.2.1]hept-2-enes was examined and the stereoselectivities have been clarified. The adducts derived from 2-azabicyclo[2.2.1]hept-5-en-3-ones having an electron-withdrawing group at 2-position were converted to 3'-chloro substituted carbovir.

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.[1] 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 phenylselenyl chloride to bicyclo[2.2.1]hept-2-enes and found that *endo* selectivity of phenylselenylation increases as electron density on the ring nitrogen atom increases. This paper contains the result of the phenylselenylation, a rationale for the observed stereoselectivitiy and the the first synthesis of 3'-chloro substituted carbovir (**D**) from the adduct (**B**).



X = OH: (-)-carbovir

X = NH—◁: 1592U89

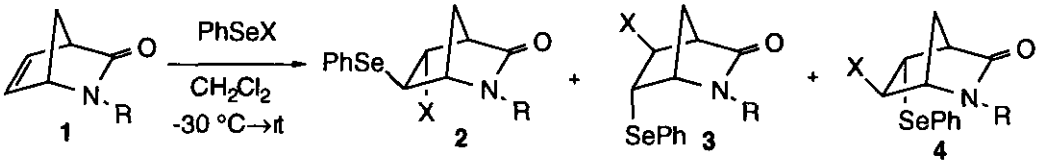


Scheme 1

Addition of phenylselenyl 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*-benzyllactam (**1e**) provided *endo* 6-phenylseleno products preferentially.[2] 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,[3] i. e., the hyperconjugative interaction of the π-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.[4] 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 > $TolSO_2$ > H > $PhCH_2$.

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

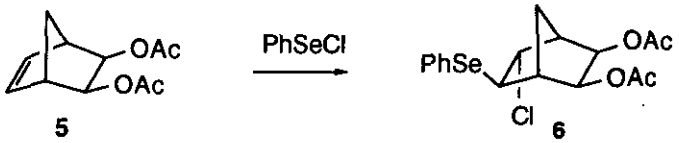


1 **2** **3** **4**

entry	Substrate	X	Product, Isolated Yield, %[a]		
1	**1a** (R = Ac)	Cl	74	7	7
2	**1a** (R = Ac)	Br	92	5	3
3	**1b** (R = Boc)	Cl	56	30	4
4	**1c** (R = SO_2Tol)	Br	(31)	(43)	(0)
5	**1d** (R = H)	Cl	16	71	0
6	**1e** (R = $PhCH_2$)	Br	(0)	(55)	(0)

a The numbers in parentheses are the reported data in ref. 2.

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



5 **6**

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.[5] 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).[2] But this explanation cannot explain the difference of the stereoselectivity found in the addition reactions of phenylselenyl 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

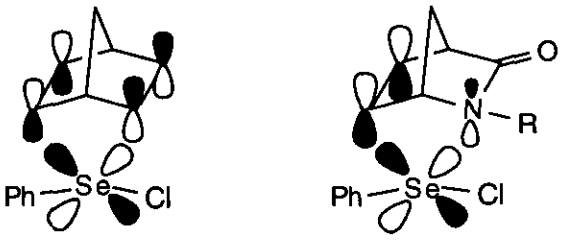
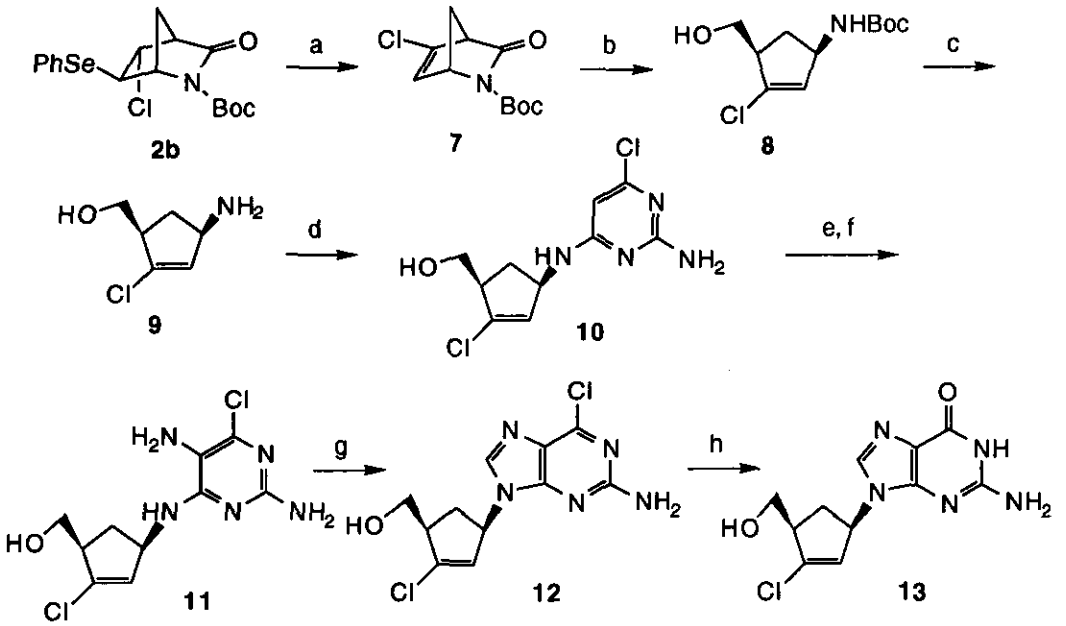


Figure 1

HOMO (**E**) derived by through-space interaction between the two unsaturated functions.[6] 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, i, *m*CPBA, $NaHCO_3$ (2 eq.), CH_2Cl_2, -78°C, ii, NEt_3 (1.2 eq.); b, $NaBH_4$, MeOH, -35 °C → r t; c, TFA, r t; d, 2-amino-4,6-dichloropyrimidine, Pr^i_2NEt, ^nBuOH, 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_3 to give **7** in 77% yield. Similar reaction of **3b** gave the same compound (**7**) in 92% yield. Reductive amide bond cleavage[7] of **7** by using sodium borohydride at -35 °C → room temperature gave **8** in 98% yield. Usual construction of purine ring[8] 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

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

REFERENCES AND NOTES

1. D. W. Kimberlin, D. M. Coen, K. K. Biron, J. I. Cohen, R. A. Lamb, M. McKinlay, E. A. Emini, 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 homoalloylic 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 π-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 >N⋯C< of -N-C(O)- has double bond character with lower energy level, the true HOMO of **1d** is the HOMO of ethylene π-MO ($C_5=C_6$) mixed with >N⋯C< in out-of phase overlap as shown in **F**. In **1a** and **1b**, the energy levels of the HOMO of >N⋯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.

Received, 1st August, 1997