A New Route to N^1-Substituted Uracil Derivatives Using Hypervalent Iodine

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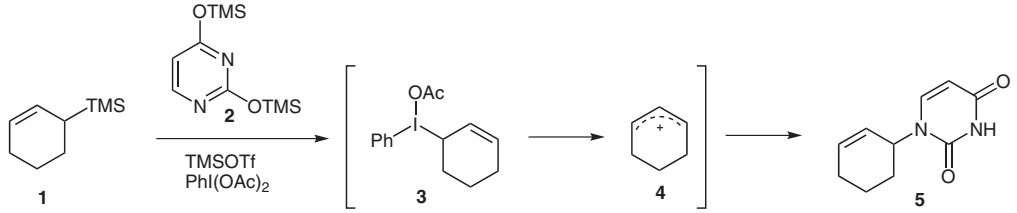
Abstract: In continuation of our previous study, oxidative coupling reactions of uracil with allylsilane or enol ethers were examined using diacetoxyiodobenzene. The reaction of persilylated uracil with 3,4-dihydro-2*H*-pyran in the presence of TMSOTf and $PhI(OAc)_2$ resulted in the formation of a dihydropyranyluracil derivative, although the yield was low. In an extension of the oxidative coupling reaction, a novel glycosylation reaction using glycal derivatives as substrates was also developed. The treatment of persilylated uracil and 3,4-dihydro-2*H*-pyran with $(PhSe)_2$ and $PhI(OAc)_2$ in the presence of a catalytic amount of TMSOTf gave a 2,3-*anti*-derivative of 1-(3-phenylselanyltetrahydropyran-2-yl)uracil stereoselectively and in good yield.

Key words: hypervalent iodine, nucleoside, oxidative coupling, glycosylation, glycal

Nucleoside derivatives are widely used clinically as drugs and as biological tools. There is no doubt about the importance of developing new nucleoside derivatives, since they promise to contribute to the progress of medical treatment and biological chemistry. The three general methods for the synthesis of nucleoside derivatives include: 1) synthesis starting from a natural nucleoside,[1] 2) construction of a nucleobase moiety on an appropriate sugar portion after manipulation,[2] and 3) glycosylation of a base with an appropriately modified sugar.[3] Although the transformation of naturally occurring nucleosides is a straightforward method for preparing new derivatives, it is obvious that limitations to obtaining new compounds with structural diversity exist. In contrast, the third method, which involves a glycosylation reaction, has an advantage in that various nucleoside derivatives containing different base moieties can be synthesized from a common sugar-intermediate in a minimum number of steps. In the past, we synthesized a wide variety of nucleoside derivatives by developing novel glycosylation reactions.[4–6] An example of this is the use of a Pummerer-type thioglycosylation reaction for the synthesis of 4′-thionucleosides.[4] This reaction involves two steps: 1) oxidation of a sulfide to the corresponding sulfoxide and 2) a trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed coupling reaction of the sulfoxide with persilylated nucleobases. Recently, the concept of the thioglycosylation reaction coupled with oxidation was applied to the synthesis of carbocyclic nucleosides.[6] As a result, we successfully developed a hypervalent iodine-catalyzed reaction for condensing a base and a pseudosugar by which a basic carbocyclic nucleoside skeleton was constructed.[6] The reaction, as with the Pummerer-type thioglycosylation, involves 2 steps:[6] 1) the generation of the carbocation **4** by the oxidative reaction of an allylsilane **1** with diacetoxyiodobenzene [$PhI(OAc)_2$] and TMSOTf, and 2) the subsequent addition of bis(trimethylsilyl)uracil (**2**) as shown in Scheme 1.

In this report, some preliminary applications of the oxidative coupling reaction to allylsilane or enol ether using a TMSOTf/$PhI(OAc)_2$ system are described. In addition, the results triggered the development of a novel glycosylation reaction using oxidative conditions. The synthesis of a 2′-phenylselenonucleoside from a glycal derivative using the TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ system is also reported.

Initially, the reaction of allyltrimethylsilane (**6**) and bis(trimethylsilyl)uracil (**2**) was examined using the conditions reported in a previous report.[6] Although the conditions for the reaction of allyltrimethylsilane (**6**) were modified slightly, 1-allyluracil (**10a**) was obtained in 69% yield from **6** on treatment with 1 equivalent of $PhI(OAc)_2$, TMSOTf, and **2** in dichloromethane (Table 1, entry 1). The same principles were applied to the reaction of benzyltrimethylsilane (**7**), but no trace of the desired **10b** was



Scheme 1 Our previous study

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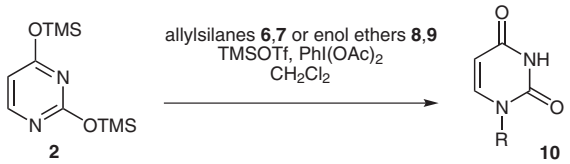
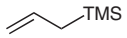
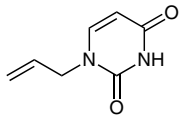
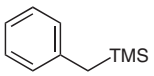
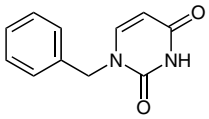
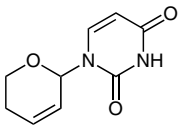
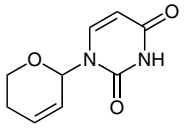
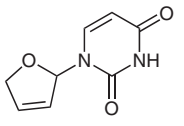
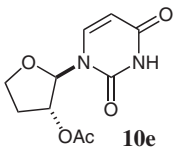
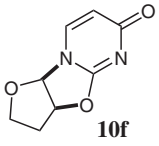
detected (entry 2). The reason is not clear at this time. One plausible explanation is that the electrophilic substitution of the phenyl ring might preferentially occur under the conditions used. The reaction of 3,4-dihydro-2*H*-pyran (**8**) was examined next. As in the case mentioned above, the reaction conditions for preparing **10c** from **8** needed to be optimized. After several attempts, it was found that a dihydropyranyluracil derivative **10c** was produced in 31% yield when **8** was treated with $PhI(OAc)_2$ (1.5 equiv), TMSOTf (0.4 equiv), and **2** (2.0 equiv) at –40 °C to room temperature (entry 3). It was found that 0.2 equivalent of $Cu(OTf)_2$, instead of TMSOTf, also catalyzed the reaction.[7] However, when **8** was reacted with **2** under the above conditions in the presence of $Cu(OTf)_2$ at room temperature, **10c** was formed in 24% yield (entry 4). Although other metal triflates, for example, $Sc(OTf)_3$ and $Y(OTf)_3$, were found to catalyze the reaction, the yields were lower than that obtained using $Cu(OTf)_2$ (data not shown). The oxidative coupling reaction was also applied to 2,3-dihydrofuran (**9**). In contrast to the results for **8**, the reaction gave an inseparable mixture of dihydrofuryl derivatives **10d** and **10e**[8] in 5.5% yield along with O-cyclo derivative **10f** in 8.9% yield (entry 5).

Even though, except for **10a**, none of the yields shown in Table 1 were completely satisfactory, it is important to note that the oxidative coupling reaction proceeded with enol ethers and gave a nitrogen-substituted product. A proposed mechanism for the oxidative coupling reaction is shown in Scheme 2.[9] When the dihydropyran **8** or **9** re-

Table 1 Summary of the Oxidative Coupling of Bis(TMS)uracil **2** with Allylsilanes and Enol Ethers



Entry	Compound	Product	Yield (%)
1	 **6**	 **10a**	69
2	 **7**	 **10b**	ND[a]
3	 **8**	 **10c**	31[b]
4	 **8**	 **10c**	24[c]
5	 **9**	 **10d**  **10e**  **10f**	5.5 (**10d**/**10e** = 3:1), 8.9 (**10f**)[d,e]

[a] Not detected.

[b] Method A: $PhI(OAc)_2$ (1.5 equiv), TMSOTf (0.4 equiv), and **2** (2.0 equiv) at –40 °C to r.t.

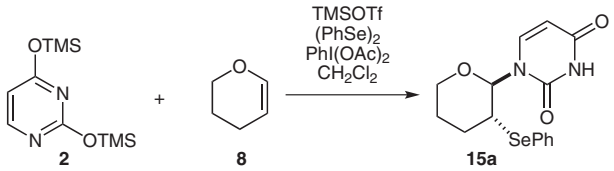
[c] Method B: $PhI(OAc)_2$ (1.5 equiv), $Cu(OTf)_2$ (0.2 equiv), and **2** (2.0 equiv) at r.t.

[d] Method C: $PhI(OAc)_2$ (1.5 equiv), TMSOTf (0.4 equiv), and **2** (2.0 equiv) at 0 °C to r.t.

[e] The ratio was determined based on ^1H NMR spectroscopy.

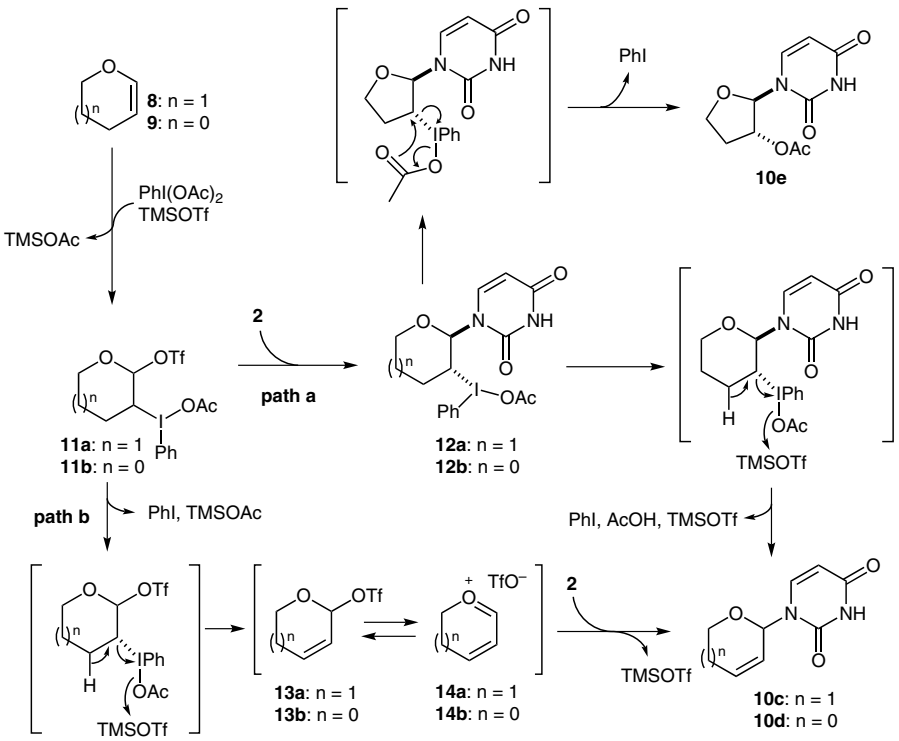
acts with $PhI(OAc)_2$ in the presence of TMSOTf, an acetoxyiodobenzene derivative **11a**,**b** is initially produced. Two pathways shown in Scheme 2 are possible for the conversion of **11a**,**b** into the N^1-substituted uracils **10c** and **10d**: the nucleophilic attack of bis(TMS)uracil **2** occurs prior to the elimination (path a) or an allylic carbocation **14a**,**b** generated from **11a**,**b** reacts with **2** (path b). Since the formation of **10e** and **10f** from dihydrofuran **9** was observed, the preferred pathway for the oxidative coupling reaction appears to involve path a, rather than path b (Scheme 2). In the case of the reaction with **8**, the elimination would generally proceed with **10c** being formed via **12a** as depicted in Scheme 2. In the case of **9**, however, a similar 2-iodophenyl intermediate **12b** preferentially gives rise to the 2,2′-O-cyclo derivative **10f**. The reason why the reaction of **9** prefers the intramolecular nucleophilic attack to the elimination is not clear at this time. The conformational flexibility of the tetrahydrofuran ring in the reaction of **9** might make the formation of five-membered ring system easy. The above mechanism explains why the reaction gave only poor yields: it is likely that the formation of an allyl cation like **14a**,**b**, through path b, may compete and this would result in the formation of dihydropyrans and furans.

To improve the yields in the oxidative coupling reaction, the use of a co-catalyst was examined. Very recently, Singh and Wirth reported on a new selenium-catalyzed cyclization of γ,δ-unsaturated carboxylic acids to 3,6-dihydro-2*H*-pyran-2-ones using hypervalent iodine as an oxidant in the presence of catalytic amounts of diphenyl diselenide [$(PhSe)_2$].[10] Given the proposed reaction mechanism, we hypothesized that the instability of the intermediate **11a**,**b** (or competing path b) might be a factor in the low yield of the oxidative coupling reaction and that this could be avoided if $(PhSe)_2$ was used as a co-catalyst. When **2** and **8** were treated with $PhI(OAc)_2$ and $(PhSe)_2$ in the presence of catalytic amounts of TMSOTf, the *trans*-isomer of 1-(3-phenylselanyltetrahydropyran-2-yl)uracil (**15a**) was selectively produced, as shown in Scheme 3.[11] The result differed from the one expected and was deemed to be important, since this reaction has the potential for use in producing 2′-deoxynucleosides as well as dideoxydidehydronucleosides such as **10c** and **10d**, which constitute an important class of antiviral agents[12] (Scheme 3).



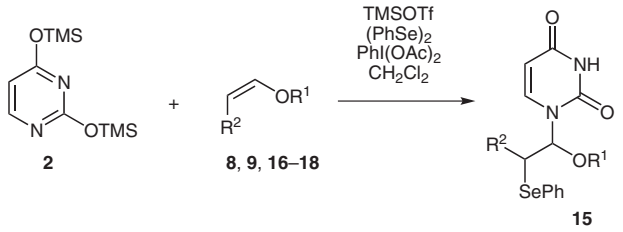
Scheme 3 Synthesis of 1-(3-phenylselanyltetrahydropyran-2-yl)uracil (**15a**)

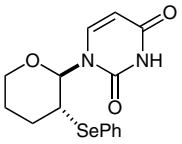
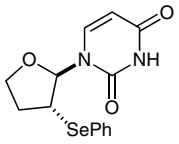
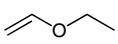
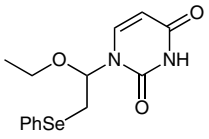
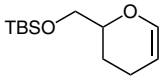
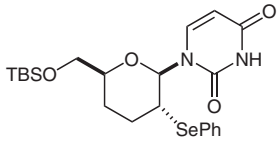
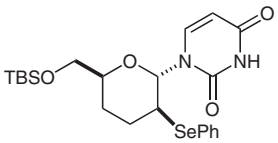
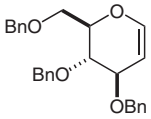
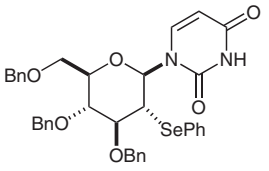
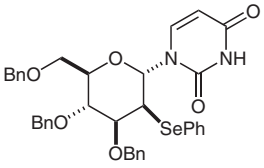
The oxidative coupling of **2** with enol ethers and glycals using the TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ system was examined and the results are summarized in Table 2. As described above, the reaction with **8** gave **15a** stereoselectively and in 73% yield (Table 2, entry 1). Similarly, reaction with **9** furnished 1-(3-phenylselanyltetrahydrofuran-2-yl)uracil (**15b**) in 31% yield (entry 2). In



Scheme 2 A proposed reaction mechanism for the oxidative coupling of 3,4-dihydro-2*H*-pyran (**8**) and dihydrofuran **9** with TMSOTf/$PhI(OAc)_2$

Table 2 Summary of the Oxidative Coupling Reaction of Bis(TMS)uracil **2** with Enol Ethers Using TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ System



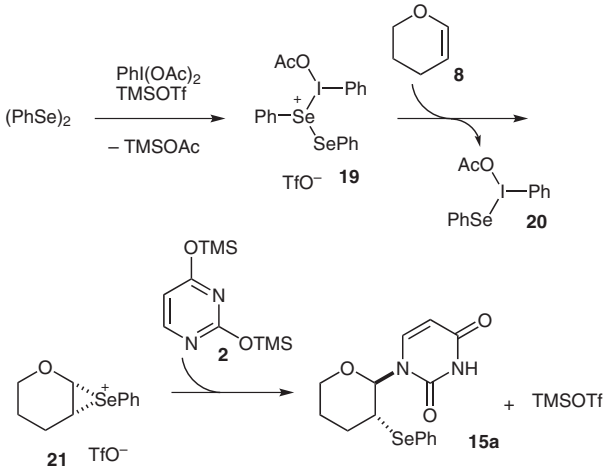
Entry	Compound	Product	Yield (%)
1	 **8**	 **15a**	73[a]
2	 **9**	 **15b**	31[a]
3	 **16**	 **15c**	69[b]
4	 **17**	 +  **15d** **15e**	80[c] (**15d**/**15e** = 2:1[d])
5	 **18**	 +  **15f** **15g**	64[c] (**15f**/**15g** = 1:1[d])

[a] Performed at r.t.
[b] Performed at –5 °C.
[c] Performed at –20 °C.
[d] The ratio was determined based on ^{1}H NMR spectroscopy.

both cases, the reaction selectively produced the *trans*-isomer and the best results were obtained when the reaction was conducted at room temperature. In contrast, the reaction with the ethyl vinyl ether (**16**) at room temperature gave 1-(1-ethoxy-2-phenylselanylethyl)uracil (**15c**) in low yield (data not shown). The reaction of **2** with **16** at –5 °C, on the other hand, afforded **15c** in 69% yield (entry 3). In all of the above cases, 1 equivalent of $PhI(OAc)_2$ and $(PhSe)_2$ in the presence of 0.1 equivalent of TMSOTf were employed. When the same reactions were performed with 0.5 equivalent of $(PhSe)_2$, the isolated yields of the products were decreased (data not shown). As an extension, the oxidative coupling of the glycal derivatives **17**[13] and **18**, which can be considered to constitute a new gly-

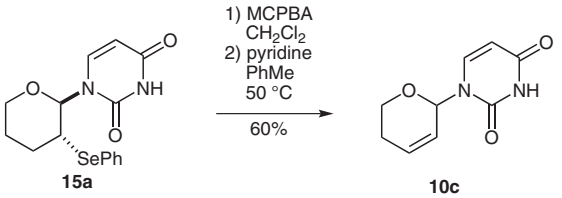
cosylation reaction applicable to the synthesis of 2′-deoxy- and 2′,3′-dideoxydidehydronucleosides, were tried. The reaction of **17** gave **15d** and **15e** in 80% yield with the predominant formation of β-nucleoside **15d** (entry 4).[14] On the other hand, the oxidative glycosylation reaction of D-glucal **18** gave a mixture of **15f** and **15g** in 64% yield and lacked stereoselectivity (entry 5).

A proposed reaction mechanism for the oxidative coupling under TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ system is shown in Scheme 4. Diphenyl diselenide is oxidized to a phenylselenium derivative **19** by the action of TMSOTf and $PhI(OAc)_2$. The phenylselenium derivative **19** then reacts with an enol ether, for example, dihydropyran **8**, to form an episelenium ion **21**. Nucleophilic attack of **2** to **21** results in the formation of **15a** along with the regeneration of TMSOTf that can be used in the next cycle of the reaction. During the course of the oxidative coupling, a hypervalent iodine derivative **20**, formed along with **19**, might have the ability to convert **8** into **21**. However, at least 1 equivalent of diphenyl diselenide was required to achieve the yields described above. The results suggest that **20** could not act as an electrophilic selenium reagent in this reaction.



Scheme 4 Proposed reaction mechanism for the oxidative coupling for the TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ system

Until now, we have not succeeded in the direct formation of dihydropyranyluracil derivatives, for example, **10c** as originally planned. One of the reasons for this is the instability of the dihydropyranyluracil under the acidic conditions of the reactions. Even in the case of the *syn*-elimination of selenoxide derivatives of nucleosides, the addition of a base is frequently required.[15] Indeed, the conversion of **15a** into **10c** was achieved using the two-step synthesis shown in Scheme 5 and pyridine was needed as an additive. We attempted to add triethylamine in the conditions in entry 1 of Table 2. However, this resulted in the suppression of the reaction with decreased yields (data not shown).



Scheme 5 Synthesis of **10c**

In conclusion, in continuation of our previous study, the development of a novel oxidative coupling reaction of persilylated uracil with allylsilanes and enol ethers to produce a dihydropyranyluracil derivative in the presence of TMSOTf and $PhI(OAc)_2$ is presented. As an extension of the oxidative coupling reaction, a novel glycosylation reaction starting from glycal derivatives by using a TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ system was also developed. The latter promises to serve as a new route to the synthesis of 2′-deoxynucleosides and dideoxydidehydronucleosides, which are medicinally and biologically important class of compounds.

Melting points are uncorrected. NMR spectra were recorded at 400 MHz (^{1}H), 100 MHz (^{13}C) using $CDCl_3$ as a solvent. As an internal standard, TMS was used for $CDCl_3$. Mass spectra were recorded using EI and CI ionization modes. Isobutane was used as the reagent gas in CI mass spectra. Silica gel used for chromatography was from Fuji Silysia PSQ 100B. When the reagents sensitive to moisture were used, the reaction was performed under argon atmosphere.

***N*^{1}-Allyluracil (10a)**

To a solution of bis(trimethylsilyl)uracil (**2**; 138 μL, 0.53 mmol), $PhI(OAc)_2$ (171 mg, 0.53 mmol), and allyltrimethylsilane (84 μL, 0.53 mmol) in CH_2Cl_2 (3 mL) was added TMSOTf (96 μL, 0.53 mmol) at 0 °C. The mixture was stirred at r.t. for 1 h. To the mixture were added excess of solid $NaHCO_3$ (ca. 1 g) and sat. aq $NaHCO_3$ (0.5 mL). The mixture was diluted with CH_2Cl_2 (30 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (50–100% EtOAc in hexane) to give **10a** (55.6 mg, 69%); white crystals; mp 100–101 °C.

IR (KBr): 921, 1201, 1466, 1688, 2927 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (td, *J* = 1.9, 3.6 Hz, 2 H), 5.28 (d, *J* = 16.9 Hz, 1 H), 5.33 (d, *J* = 10.1 Hz, 1 H), 5.73 (dd, *J* = 1.9, 8.2 Hz, 1 H), 5.93–5.83 (m, 1 H), 7.15 (d, *J* = 8.2 Hz, 1 H), 8.69 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.0, 102.5, 119.5, 131.4, 143.7, 150.8, 163.7.

EI-MS: *m*/*z* = 152 [M$^+$].

HRMS (EI): *m*/*z* calcd for $C_7H_8N_2O_2$: 152.0586 [M$^+$]; found: 152.0580.

***N*^{1}-(5,6-Dihydro-2*H*-pyran-2-yl)uracil (10c)**

Method A (Table 1, entry 3): To a solution of bis(trimethylsilyl)uracil (**2**; 256 μL, 1.0 mmol), $PhI(OAc)_2$ (241 mg, 0.75 mmol), and 3,4-dihydro-2*H*-pyran (**8**; 45.6 μL, 0.50 mmol) in CH_2Cl_2 (5 mL) was added TMSOTf (36.3 μL, 0.20 mmol) at –40 °C. After allowing to reach r.t. in 2 h, the mixture was stirred at r.t. overnight. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure, and the residue was puri-

fied by silica gel column chromatography (75–100% EtOAc in hexane) to give **10c** (30.2 mg, 31%).

Method B (Table 1, entry 4): To a solution of bis(trimethylsilyl)uracil (**2**; 256 μL, 1.0 mmol), $PhI(OAc)_2$ (241 mg, 0.75 mmol) and 3,4-dihydro-2*H*-pyran (**8**; 45.6 μL, 0.50 mmol) in CH_2Cl_2 (3 mL) was added TMSOTf (36.3 μL, 0.20 mmol) at 0 °C. After stirring at r.t. for 2 h, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (75–100% EtOAc in hexane) to give **10c** (25.3 mg, 24%); white crystals; mp 113–115 °C.

IR (KBr): 820, 1243, 1385, 1676, 3019 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.01–2.34 (m, 2 H), 3.86–3.96 (m, 2 H), 5.64 (d, *J* = 10.6 Hz, 1 H), 5.72 (d, *J* = 8.2 Hz, 1 H), 6.36–6.40 (m, 2 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 9.00 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 61.7, 77.6, 102.1, 123.7, 133.1, 140.9, 150.7, 163.1.

EI-MS: *m*/*z* = 194 [M^+].

HRMS (EI): *m*/*z* calcd for $C_9H_{10}N_2O_3$: 194.0691 [M^+]; found: 194.0695.

1-(2,3-Dihydrofuran-5-yl)uracil (10d)

Method C (Table 1, entry 5): To a solution of bis(trimethylsilyl)uracil (**2**; 256 μL, 1.0 mmol), $PhI(OAc)_2$ (241 mg, 0.75 mmol), and dihydrofuran **9** (37.8 μL, 0.50 mmol) in CH_2Cl_2 (5 mL) was added TMSOTf (36.3 μL, 0.20 mmol) at 0 °C. After allowing to reach r.t., the mixture was stirred at r.t. for 4 h. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (50 → 75 → 100% EtOAc in hexane) to give a mixture of **10d** and **10e** (5 mg, **10d**/**10e** = 3:1, 5.5%) as less polar products and **10f** (8 mg, 8.9%) as a more polar product.

10d and 10e

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 0.75 H), 2.14–2.17 (m, 0.25 H), 2.26–2.36 (m, 0.25 H), 4.15 (td, *J* = 6.7, 9.2 Hz, 0.25 H), 4.34 (td, *J* = 3.5, 8.7 Hz, 0.25 H), 4.71–4.76 (m, 0.75 H), 4.81–4.87 (m, 0.75 H), 5.37 (dt, *J* = 1.9, 4.4 Hz, 0.25 H), 5.71–5.74 (m, 1.25 H), 5.83–5.85 (m, 0.75 H), 6.44–6.46 (m, 0.75 H), 7.00–7.02 (m, 0.75 H), 7.08 (d, *J* = 8.2 Hz, 0.75 H), 7.23 (d, *J* = 8.2 Hz, 0.25 H), 8.67 (br s, 0.25 H), 8.73 (br s, 0.25 H).

EI-MS: *m*/*z* = 180 [M^+] (**10d**).

CI-MS: *m*/*z* = 241 [M^+ + 1] (**10e**).

10f

White crystals; mp 248–250 °C (sublimed).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.17–2.24 (m, 1 H), 2.48 (d, *J* = 4.6, 14.3 Hz, 1 H), 4.23–4.30 (m, 2 H), 5.41 (t, *J* = 5.3 Hz, 1 H), 6.12 (d, *J* = 7.2 Hz, 1 H), 6.50 (d, *J* = 5.3 Hz, 1 H), 7.71 (d, *J* = 7.2 Hz, 1 H).

EI-MS: *m*/*z* = 180 [M^+].

HRMS (EI): *m*/*z* calcd for $C_8H_8N_2O_3$: 180.0535 [M^+]; found: 180.0536.

Oxidative Coupling Reaction of Bis(TMS)uracil (2) with Enol Ethers Using TMSOTf/$PhI(OAc)_2$/$(PhSe)_2$ System; General Procedure

To a solution of bis(trimethylsilyl)uracil (**2**; 138 μL, 0.53 mmol), $PhI(OAc)_2$ (171 mg, 0.53 mmol), $PhSe)_2$ (165 mg, 0.53 mmol), and enol ether (0.53 mmol) in CH_2Cl_2 (3 mL) was added TMSOTf (9.6 μL, 0.053 mmol) at the temperature shown in Table 2. After stirring at the same temperature for 1 h, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (Table 2).

***N*^{1}-[*trans*-3-(Phenylselanyl)tetrahydro-2*H*-pyran-2-yl]uracil (15a)**

By the general procedure described above, compound **15a** (128.6 mg, 73%) was obtained from 3,4-dihydro-2*H*-pyran (**8**; 45.6 μL, 0.50 mmol) after purification by silica gel column chromatography (33 → 50 → 75% EtOAc in hexane); white foam.

IR (KBr): 744, 1066, 1257, 1688, 3056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.81–1.67 (m, 3 H), 2.44 (d, *J* = 13.0 Hz, 1 H), 3.23 (dt, *J* = 3.9, 10.6 Hz, 1 H), 3.64 (t, *J* = 12.1 Hz, 1 H), 4.08 (d, *J* = 13.0 Hz, 1 H), 5.36 (dd, *J* = 1.9, 8.2 Hz, 1 H), 5.69 (d, *J* = 10.1 Hz, 1 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 7.34–7.22 (m, 3 H), 7.53 (d, *J* = 6.8 Hz, 2 H), 8.14 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9, 30.8, 43.6, 68.6, 85.6, 102.4, 126.8, 128.6, 129.3, 135.8, 139.2, 150.3, 162.7.

EI-MS: *m*/*z* = 352 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_2O_3Se$: 352.0326 [M^+]; found: 352.0320.

***N*^{1}-[*trans*-3-(Phenylselanyl)tetrahydrofuran-2-yl]uracil (15b)**

By the general procedure described above, compound **15b** (52 mg, 31%) was obtained from dihydrofuran **9** (37.8 μL, 0.53 mmol) after purification by silica gel column chromatography (33 → 50 → 75% EtOAc in hexane); white foam.

IR (KBr): 744, 1066, 1257, 1688, 3056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.10–2.17 (m, 1 H), 2.36–2.43 (m, 1 H), 3.81–3.87 (m, 1 H), 4.12 (q, *J* = 7.8 Hz, 1 H), 4.20–4.25 (m, 1 H), 5.62 (d, *J* = 8.3 Hz, 1 H), 5.93 (d, *J* = 3.9 Hz, 1 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 7.28–7.34 (m, 3 H), 7.64 (d, *J* = 4.2 Hz, 2 H), 8.09 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 43.5, 69.0, 92.9, 102.1, 126.8, 126.6, 129.3, 135.6, 139.6, 150.0, 163.2.

EI-MS: *m*/*z* = 338 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}N_2O_3Se$: 338.0170 [M^+]; found: 338.0160.

***N*^{1}-[1-Ethoxy-2-(phenylselanyl)ethyl]uracil (15c)**

By the general procedure described above, compound **15c** (125 mg, 69%) was obtained from ethyl vinyl ether (**16**; 138 μL, 0.53 mmol) after purification by silica gel column chromatography (9% EtOAc in CH_2Cl_2); whitish brown solid; mp 99.0–101.0 °C.

IR (KBr): 762, 1332, 1626, 1701, 3057 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3 H), 3.17 (dd, *J* = 5.7, 12.9 Hz, 1 H), 3.27 (dd, *J* = 5.7, 12.9 Hz, 1 H), 3.56 (q, *J* = 7.2 Hz, 2 H), 5.67 (dd, *J* = 1.5, 7.8 Hz, 1 H), 5.88 (t, *J* = 5.7 Hz, 1 H), 7.25–7.27 (m, 3 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.51–7.53 (m, 2 H), 9.07 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 31.7, 53.4, 65.4, 84.6, 102.5, 127.5, 129.2, 133.1, 138.6, 150.8, 163.3.

EI-MS: *m*/*z* = 340 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}N_2O_3Se$: 340.0329 [M^+]; found: 340.0321.

1-[(2*R,3*R**,6*S**)-6-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-(phenylselanyl)tetrahydro-2*H*-pyran-2-yl]uracil (15d) and 1-[(2*S**,3*S**,6*S**)-6-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-(phenylselanyl)tetrahydro-2*H*-pyran-2-yl]uracil (15e)**

By the general procedure described above, compounds **15d** (135 mg, 51%) and **15e** (75 mg, 29%) were obtained from **17**[13] (121 mg,

0.53 mmol) after purification by silica gel column chromatography (33% EtOAc in hexane).

15d
White crystals; mp 174.0–176.0 °C.

IR (KBr): 689, 776, 1386, 1667, 1703, 2953 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.89 (s, 9 H), 1.46–1.55 (m, 1 H), 1.72–1.80 (m, 2 H), 2.42–2.45 (m, 1 H), 3.16 (s, 1 H), 3.55 (dd, *J* = 1.9, 10.2 Hz, 1 H), 3.61–3.69 (m, 2 H), 5.40 (dd, *J* = 1.9, 8.2 Hz, 1 H), 5.82 (d, *J* = 10.2 Hz, 1 H), 7.00 (d, *J* = 8.2 Hz, 1 H), 7.22–7.30 (m, 3 H), 7.54–7.55 (m, 2 H), 9.16 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3, 18.2, 25.7, 28.7, 30.2, 43.5, 65.4, 78.8, 85.2, 102.2, 126.7, 128.5, 129.3, 135.8, 139.2, 150.3, 162.8.

EI-MS: *m*/*z* = 496 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{22}H_{32}N_2O_4SeSi$: 496.1308 [M^+]; found: 496.1295.

15e
White crystals; mp 165.0–167.0 °C.

IR (KBr): 649, 775, 1387, 1666, 1705, 2952 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.82 (s, 9 H), 1.80–1.97 (m, 3 H), 2.16–2.21 (m, 1 H), 3.14–3.21 (m, 1 H), 3.71 (dd, *J* = 5.3, 10.5 Hz, 1 H), 3.79 (dd, *J* = 6.7, 10.5 Hz, 1 H), 3.98 (s, 1 H), 5.32 (dd, *J* = 1.9, 8.2 Hz, 1 H), 6.02 (d, *J* = 10.5 Hz, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 7.14–7.23 (m, 3 H), 7.46–7.47 (m, 2 H), 8.52 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5, 18.1, 25.8, 26.1, 26.5, 43.6, 62.7, 74.9, 81.5, 102.1, 126.9, 128.5, 129.3, 135.6, 139.2, 150.0, 162.6.

EI-MS: *m*/*z* = 496 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{22}H_{32}N_2O_4SeSi$: 496.1308 [M^+]; found: 496.1299.

N^1-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-*O*-phenylselanyl-β-D-*gluco*-pyranosyl)uracil (15f) and N^1-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-*O*-phenylselanyl-α-D-*gluco*-pyranosyl)uracil (15g)
By the general procedure described above, compounds **15f**,**g** (231 mg, 64%) were obtained as an inseparable mixture from tri-*O*-benzyl-D-glucal (**18**; 220 mg, 0.53 mmol) after purification by silica gel column chromatography (33% EtOAc in hexane).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.30 (t, *J* = 10.1 Hz, 0.5 H), 3.60–3.88 (m, 4.5 H), 4.24 (s, 0.5 H), 4.39 (t, *J* = 6.8 Hz, 0.5 H), 4.42–4.55 (m, 3.5 H), 4.60–4.64 (m, 1 H), 4.86 (d, *J* = 10.6 Hz, 0.5 H), 4.91 (d, *J* = 10.1 Hz, 0.5 H), 4.99 (d, *J* = 10.1 Hz, 0.5 H), 5.13 (dd, *J* = 2.2, 8.0 Hz, 0.5 H), 5.33 (dd, *J* = 1.9, 7.8 Hz, 0.5 H), 5.91 (d, *J* = 10.6 Hz, 0.5 H), 6.29 (d, *J* = 10.6 Hz, 0.5 H), 6.83–6.88 (m, 1 H), 7.16–7.53 (m, 20 H), 8.61 (br s, 0.5 H), 9.01 (br s, 0.5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.6, 51.4, 67.4, 68.2, 71.1, 71.7, 73.0, 73.3, 73.4, 75.1, 76.1, 76.2, 77.4, 78.7, 79.0, 82.5, 101.8, 102.5, 127.6, 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.6, 129.3, 129.4, 134.6, 135.1, 136.6, 137.4, 137.7, 137.7, 137.8, 137.8, 139.5, 150.1, 150.2, 162.6, 162.7.

EI-MS: *m*/*z* = 684 [M^+].

HRMS (EI): *m*/*z* calcd for $C_{37}H_{36}N_2O_6Se$: 684.1739 [M^+]; found: 684.1752.

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References

(1) Recent reports: (a) Fan, X.; Wang, Y.; Qu, Y.; Xu, H.; He, Y.; Zhang, X.; Wang, J. *J. Org. Chem.* **2011**, *76*, 982. (b) Peacock, H.; Maydanovych, O.; Beal, P. A. *Org. Lett.* **2010**, *12*, 1044. (c) Plant, A.; Thompson, P.; William, D. M. *J. Org. Chem.* **2009**, *74*, 4870. (d) Smith, D. B.; Kalayanov, G.; Sund, C.; Winqvist, A.; Pinho, P.; Maltseva, T.; Morisson, V.; Leveque, V.; Rajyaguru, S.; Le, Pogam. S.; Najera, I.; Benkestock, K.; Zhou, X.-X.; Maag, H.; Cammack, N.; Martin, J. A.; Swallow, S.; Johansson, N. J.; Klumpp, K.; Smith, M. *J. Med. Chem.* **2009**, *52*, 219. (e) Spitale, R. C.; Heller, M. G.; Pelly, A. J.; Wedekind, J. E. *J. Org. Chem.* **2007**, *72*, 8551.

(2) Recent reports: (a) Dalençon, S.; Youcef, R. A.; Pipelier, M.; Maisonneuve, V.; Dubreuil, D.; Huet, F.; Legoupy, S. *J. Org. Chem.* **2011**, *76*, 8059. (b) Saneyoshi, H.; Deschamps, J. R.; Marquez, V. E. *J. Org. Chem.* **2010**, *75*, 7659. (c) Jiang, M. X.-W.; Jin, B.; Gage, J. L.; Priour, A.; Savela, G.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 4164.

(3) Recent reports: (a) Huang, Q.; Herdewijin, P. *J. Org. Chem.* **2011**, *76*, 3742. (b) Reddy, P. G.; Chun, B.-W.; Zhang, H.-R.; Rachakonda, S.; Ross, B. S.; Sofia, M. J. *J. Org. Chem.* **2011**, *76*, 3782. (c) Seth, P. P.; Vasquez, G.; Allerson, C. A.; Berdeja, A.; Gaus, H.; Kinberger, G. A.; Prakash, T. P.; Migawa, M. T.; Bhat, B.; Swayze, E. E. *J. Org. Chem.* **2010**, *75*, 1569. (d) Prévost, M.; St-Jean, O.; Guindon, Y. *J. Am. Chem. Soc.* **2010**, *132*, 12433. (e) Stauffer, C. S.; Datta, A. *J. Org. Chem.* **2008**, *73*, 4166. (f) Sabatino, D.; Damha, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8259. (g) Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, *71*, 2352. (h) Neogi, A.; Majhi, T. P.; Mukhopadhyay, R.; Chattopadyay, P. *J. Org. Chem.* **2006**, *71*, 3291. (i) Gagneron, J.; Gosselin, G.; Mathé, C. *J. Org. Chem.* **2005**, *70*, 6891.

(4) (a) Yoshimura, Y.; Yamazaki, Y.; Saito, Y.; Natori, Y.; Imamichi, T.; Takahata, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3313. (b) Yoshimura, Y.; Yamazaki, Y.; Saito, Y.; Takahata, H. *Tetrahedron* **2009**, *65*, 9091. (c) Yoshimura, Y.; Yamazaki, Y.; Kawahata, M.; Yamaguchi, K.; Takahata, H. *Tetrahedron Lett.* **2007**, *48*, 4519. (d) Yoshimura, Y.; Kuze, T.; Ueno, M.; Komiya, F.; Haraguchi, K.; Tanaka, H.; Kano, F.; Yamada, K.; Asami, K.; Kaneko, N.; Takahata, H. *Tetrahedron Lett.* **2006**, *47*, 591. (e) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140. (f) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822.

(5) (a) Yoshimura, Y.; Asami, K.; Imamichi, T.; Kuroda, T.; Shiraki, K.; Tanaka, H.; Takahata, H. *J. Org. Chem.* **2010**, *75*, 4161. (b) Yoshimura, Y.; Asami, K.; Matsui, H.; Tanaka, H.; Takahata, H. *Org. Lett.* **2006**, *8*, 6015.

(6) Yoshimura, Y.; Ohta, M.; Imahori, T.; Imamichi, T.; Takahata, H. *Org. Lett.* **2008**, *10*, 3449.

(7) During the course of our investigation, the intramolecular oxidative C–N bond forming reaction using $Cu(OTf)_2$ and $PhI(OAc)_2$ has been reported: Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996.

(8) The H-H COSY spectrum of **10d** and **10e** showed that there is no cross peak corresponding to the correlation between H1′ and H2′ of **10e**. This revealed that a dihedral angle of H1′-C1′-C2′-H2′ should be around 90°. From this result, **10e** was determined to be a 1′,2′-*trans*-isomer.

(9) The C2-acylglycosylation of glycals with $PhI(OCOR)_2$ in the presence of $Et_2O{\cdot}BF_3$ was reported to proceed via a C2-phenyliodonium (I^{III}) intermediate: Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939.

(10) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504.
(11) In contrast, the reaction of glycal derivatives with $(PhSe)_2$, $PhI(OAc)_2$, and NaN_3 gave 2-azido-1-phenylseleno-glycoside selectively: (a) Litjens, R. E. J. N.; den Heeten, R.; Timmer, M. S. M.; Overkleeft, H. S.; van der Marel, G. A. *Chem.–Eur. J.* **2005**, *11*, 1010. (b) Jiaang, W.-T.; Chang, M.-Y.; Tseng, P.-H.; Chen, S.-T. *Tetrahedron Lett.* **2000**, *41*, 3127. (c) Santoyo-Gonzalez, F.; Calvo-Flores, F. G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Robles-Díaz, R. *J. Org. Chem.* **1993**, *58*, 6122.
(12) For example, see: (a) De Clercq, E. *Biochem. Pharmacol.* **2011**, *82*, 99. (b) Esté, J. A.; Cihlar, T. *Antiviral Res.* **2010**, *85*, 25. (c) Meadows, D. C.; Gervey-Hague, J. *ChemMedChem* **2006**, *1*, 16. (d) Imamichi, T. *Curr. Pharm. Design* **2004**, *10*, 4039.
(13) Imanieh, H.; Quayle, P.; Voaden, M.; Conway, J. *Tetrahedron Lett.* **1992**, *33*, 543.
(14) The stereochemistries of **15d**,**e** were determined by NOE experiments: **15d** showed a NOE (3.1%) between H-6 of the uracil ring and one of the methylene protons on the siloxymethyl group on C6 of tetrahydropyran. On the other hand, in the case of **15e**, NOEs (9.9% and 2.3%) were found between the H-2 of tetrahydropyran (anomeric proton) and the methylene protons of the siloxymethyl group. The stereochemistries of **15f**,**g** were estimated by comparison with the ^{1}H NMR spectra of **15d**,**e**.
(15) (a) Díaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501. (b) Wilson, L.; Lotta, D. *Tetrahedron Lett.* **1990**, *31*, 1815.

