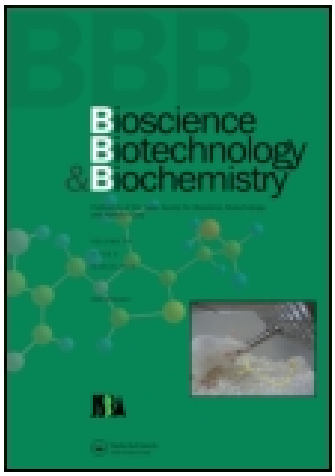

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A New Nucleophilic Ring Opening of an Activated Cyclopropane and a Formal Synthesis of (±)-Carbovir

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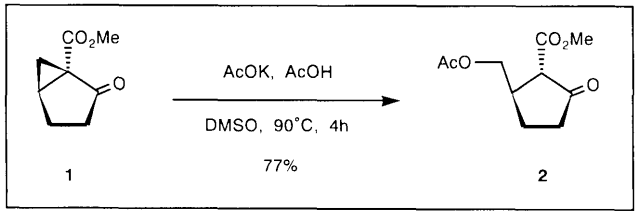
The reaction of bicyclo[3.1.0]hexane 1, possessing a doubly activated cyclopropane ring, with acetic acid and potassium acetate in DMSO proceeded smoothly to give the adduct 2 in good yield. A formal total synthesis of the potent anti-HIV agent (±)-carbovir (9) was done by converting 2 into a known precursor 8 in 8 steps *via* allyl alcohol 7 including the regioselective introduction of a double bond (4 to 5) and attachment of the nucleobase using the Mitsunobu reaction (7 to 8).

Recently carbocyclic nucleosides have attracted much attention as anti-HIV,[1] anti-cancer,[2] and purinergic agents,[3] and as components of antisence oligonucleotides.[4] A large number of synthetic approaches to carbocyclic nucleosides, especially to suitably functionalized carbocyclic moieties, have appeared.[5] Many of these compounds commonly have a hydroxy methyl group at position 4 of the carbocyclic ring system and the unit is essential to show various biological activities. Therefore, it is important to introduce this unit efficiently into the cyclopentane ring for the synthesis of this type of molecules. Cyclopropanation-nucleophilic ring opening[6] would be one solution for this issue. In this paper, we wish to describe a novel opening reaction of doubly activated cyclopropane for introducing the hydroxy methyl group into the cyclopentane ring and its application for the synthesis of the potent anti-HIV agent carbovir (**9**).[7]

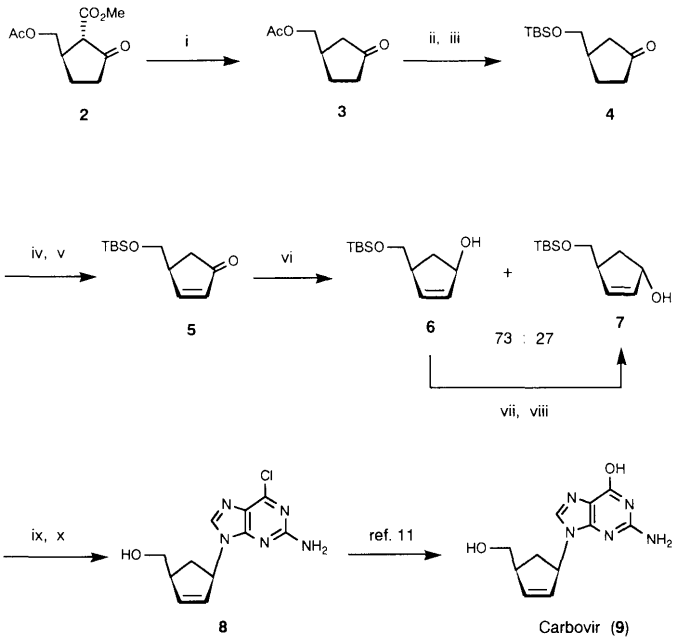
At first we investigated homoconjugate addition of nucleophiles to activated cyclopropane **1**[8] (Scheme 1). After several attempts, we found that the treatment of **1** with potassium acetate and acetic acid in dimethylsulfoxide at 90°C, the conditions usually used for epoxide opening,[9] gave adduct **2** in 77% yield.

We next synthesized carbovir precursor **8** from **2** (Scheme 2). Thus, demethoxycarbonylation of **2** using sodium chloride in wet dimethylsulfoxide at 160°C gave acetate **3** in 95% yield. The acetate **3** was converted into silyl ether **4** in 87% yield by treatment with potassium carbonate followed by *t*-butylchlorodimethylsilane and imidazole. The next stage was the regioselective introduction of a double bond into the cyclopentane ring. Phenylselenylation of ketone **4** using lithium diisopropylamide and phenylselenyl chloride at −78°C proceeded regioselectively to yield the 2-phenylselenoketone exclusively. Then the selenide underwent oxidative elimination using sodium periodate to yield enone **5** in 15% yield from **4**. Reduction of **5** with sodium borohydride in the presence of cerium chloride[10] gave the diastereomeric mixture of allyl alcohols **6** and **7** in the ratio of 73:27 in 97% yield. The minor component **7** is the known key intermediate for carbovir.[11] The diastereomer **6** could be easily converted into **7** by a Mitsunobu reaction[12] followed by hydrolysis of the ester.

The ^{1}H-NMR spectra of **6** and **7** were coincident with those provided by Dr. Asami, and it meant a formal total synthesis of (±)-carbovir was completed. Additionally, according to Asami's protocol,[11] *trans*-allyl alcohol **7** was converted into the (±)-carbovir precursor **8**[13] by attachment of



Scheme 1.



Scheme 2. Reagents and conditions: i, NaCl, H_2O, DMSO, 160°C, 3 h, 95%; ii, K_2CO_3, MeOH, t_R, 30 min; iii, TBSCl, imidazole, DMF, t_R, 5 h, 87% (2 steps); iv, LDA,PhSeCl, HMPA, THF, −78°C, 45 min; v, $NaIO_4$, MeOH, THF, H_2O, t_R, 3 h, 15% (2 steps); vi, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, t_R, 10 min, 78%; vii, $PhCO_2H$, DEAD, Ph_3P, THF, t_R, 15 h, 62%; viii, K_2CO_3, MeOH, t_R, 15 h, 97%; ix, 2-amino-6-chloropurine, DEAD, $(n\text{-Bu})_3P$, dioxane, t_R, 1 h; x, TBAF, THF, t_R, 1 h, 24% (2 steps).

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2-amino-6-chloropurine using the Mitsunobu reaction[14] followed by desilylation.

In conclusion, a new synthetic route to carbocyclic nucleosides is demonstrated by use of a cyclopropanation-homoconjugate addition process, in particular using the newly discovered homoconjugate addition of acetic acid to a doubly activated cyclopropane. An advantage of this method is that compound **2** with three contiguous functional groups can be obtained readily, so various carbocyclic nucleoside derivatives could be prepared from **2**. Because the enantiomer of **1** has also been prepared using optical resolution[15] and asymmetric synthesis,[16] chiral carbovir could be synthesized by this process.

Experimental

Melting points (mp) are uncorrected. Infrared (IR) spectra were measured with a Perkin Elmer FT-IR 1760X spectrometer. NMR spectra were obtained with a JEOL JNM-GX 270 NMR spectrometer, using tetramethylsilane as an internal standard, and mass spectra were taken by a JEOL JMS-AX 500 mass spectrometer.

(2S,3R*)-2-Methoxycarbonyl-3-acetoxymethylcyclopentanone* (**2**). A mixture of **1** (10 g, 64.9 mmol), potassium acetate (32.5 g, 0.33 mol), and acetic acid (23 g, 0.38 mol) in dry DMSO (200 ml) was heated at 90°C for 4 h. After cooling, the reaction mixture was diluted with ether, and the organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography on silica gel (eluting with hexane–EtOAc = 1 : 1) afforded **2** (10.7 g, 77%) as an oil. IR ν_{max} cm^{-1}: 1038, 1238, 1373, 1439, 1732, 2955; ^{1}H-NMR δ ($CDCl_3$): 1.59–1.83 (1H, m), 2.08 (3H, s), 2.17–2.57 (3H, m), 2.90–3.06 (1H, m), 3.08 (1H, d, J = 11.0 Hz), 3.77 (3H, s), 4.11 (1H, dd, J = 6.4, 11.3 Hz), 4.25 (1H, dd, J = 5.0, 11.3 Hz); ^{13}C-NMR δ ($CDCl_3$): 20.8, 23.5, 37.5, 39.6, 52.5, 58.3, 65.6, 168.9, 170.6, 210.1; MS *m/z* (%): 214 (M^+, 8), 183 (7), 172 (34), 154 (88), 141 (60), 122 (49), 109 (90), 99 (100), 85 (41), 67 (29), 59 (41), 55 (72); HR-MS: Found, *m/z* 214.0839 (M^+); Calcd. for $C_{10}H_{14}O_5$, 214.0841.

(±)-3-Acetoxymethylcyclopentanone (**3**). The mixture of keto ester **2** (5.0 g, 23.4 mmol), NaCl (1.5 g, 26.0 mmol), and water (1.3 g) in DMSO (22 ml) was heated at 160°C for 3 h. After cooling, it was poured into water and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluting with hexane–EtOAc = 3 : 1) to give **3** (3.5 g, 95%) as an oil. IR ν_{max} cm^{-1}: 2958, 1741, 1370, 1240, 1161, 1075, 1038; ^{1}H-NMR δ ($CDDl_3$): 1.64–1.81 (1H, m), 1.94–2.69 (6H, m), 2.07 (3H, m), 4.08 (1H, dd, J = 5.9, 11.0 Hz), 4.15 (1H, dd, J = 6.1, 11.0 Hz); ^{13}C-NMR δ ($CDCl_3$): 20.6, 25.8, 35.7, 37.6, 41.5, 66.8, 170.8, 217.8; MS *m/z* (%): 156 (M^+, 14), 139 (4), 128 (3), 114 (29), 96 (91), 85 (100), 68 (37), 55 (41); HR-MS: Found, *m/z* 156.0781 (M^+); Calcd. for $C_8H_{12}O_3$, 156.0786; semicarbazone mp 165–166°C. *Anal.* Found: C, 54.50; H, 9.37; N, 14.64%. Calcd. for $C_9H_{15}N_3O_3$; C, 54.69; H, 9.54; N, 14.72%.

(±)-3-(t-Butyldimethylsilyloxy)methylcyclopentanone (**4**). To a solution of acetate **3** (2.3 g, 14.7 mmol) in MeOH (23 ml) was added K_2CO_3 (4.1 g, 29.5 mmol), and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ether and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude keto alcohol, which was used without purification in the next step.

This keto alcohol was dissolved in DMF (7.5 ml) and treated with TBDMSCl (2.7 g, 17.6 mmol) and imidazole (3.6 g, 52.8 mmol) for 5 h at room temperature. The reaction mixture was diluted with ether, and successively washed with sat. $NaHCO_3$ aq., water, and brine. The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluting with hexane–EtOAc = 10 : 1) to give silyl ether **4** (2.9 g, 87% from **3**) as an oil. IR ν_{max} cm^{-1}: 2955, 2930, 2858, 1746, 1256, 1105, 839, 777; ^{1}H-NMR δ ($CDCl_3$): 0.00 (6H, s), 0.84 (9H, s), 1.65–1.80 (1H, m), 1.95–2.41 (6H, m), 3.58 (1H, br. s), 3.60 (1H, br. s); MS *m/z* (%): 171 ($(M-t\text{-Bu})^+$, 18), 115 (60), 97 (48), 83 (88), 75 (40), 68 (30), 55 (100); HR-MS: Found, *m/z* 228.1573 (M^+); Calcd. for $C_{12}H_{24}O_2Si$, 228.1546; semicarbazone mp 190–191°C. *Anal.* Found: C, 50.42; H, 7.02; N, 19.62%. Calcd. for $C_{13}H_{27}N_3O_2Si$; C, 50.69; H, 7.09; N, 19.71%.

(±)-4-(t-Butyldimethylsilyloxy)methyl-2-cyclopentenone (**5**). To a solution of diisopropylamine (1.6 ml, 10.6 mmol) in THF (110 ml) at −78°C was added a solution of 15% *n*-BuLi in hexane (6.0 ml, 10.6 mmol) and HMPA (1.2 ml). The reaction mixture was stirred at −78°C for 20 min, and then ketone **4** (2.2 g, 9.6 mmol) in THF (2 ml) was introduced. The reaction was stirred at −78°C for 45 min and PhSeCl (2.0 g, 11.0 mmol) was added. Stirring was continued for 1 h, before the mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude α-phenylseleno ketone, which was used directly in the next reaction.

To a solution of selenide in MeOH (24 ml) and THF (8 ml) was added water (3.2 ml). The resulting suspension was cooled to 10°C, and $NaIO_4$ (6.2 g, 28.8 mmol) was added. The mixture was stirred at room temperature for 3 h, and then poured into ether and sat. $NaHCO_3$ aq. The organic layer was washed with water and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a crude product, which was purified by chromatography on silica gel (eluting with hexane–EtOAc = 10 : 1) to yield enone **5** (0.32 g, 15%) as an oil and recovered ketone **4** (1.51 g, 76%). IR ν_{max} cm^{-1}: 2955, 2930, 2858, 1718, 1472, 1256, 1095, 839, 778; ^{1}H-NMR δ ($CDCl_3$): 0.00 (6H, s), 0.83 (9H, s), 2.07 (1H, dd, J = 2.3, 18.8 Hz), 2.40 (1H, dd, J = 6.6, 18.8 Hz), 3.03–3.15 (1H, m), 3.56 (1H, dd, J = 6.7, 9.8 Hz), 3.69 (1H, dd, J = 5.5, 9.8 Hz), 6.17 (1H, dd, J = 2.0, 5.5 Hz), 7.63 (1H, dd, J = 2.4, 5.5 Hz); ^{13}C-NMR δ ($CDCl_3$): −5.5, 25.7, 37.5, 44.2, 64.8, 134.9, 166.0, 209.7; MS *m/z* (%): 169 ($(M-t\text{-Bu})^+$, 100), 139 (32), 127 (4), 111 (14), 103 (7), 95 (12), 89 (27), 82 (21), 73 (54), 67 (11), 59 (22), 53 (27); HR-MS: Found, *m/z* 226.1387 (M^+); Calcd. for $C_{12}H_{22}O_2Si$, 226.1389.

(1R,4S*)-4-(t-Butyldimethylsilyloxy)methyl-2-cyclopentenol* (**6**) *and (1S*,4S*)-4-(t-Butyldimethylsilyoxy)methyl-2-cyclopentenol* (**7**). To a solution of enone **5** (0.24 g, 1.06 mmol) in EtOH (5 ml) was added $CeCl_3 \cdot 7H_2O$ (0.59 g, 1.58 mmol). The mixture was stirred for 5 min at room temperature, and then $NaBH_4$ (60 mg, 1.58 mmol) was added. After stirring for 10 min, the reaction was quenched by the addition of water. The mixture was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. Filtration and concentration *in vacuo* provided a crude residue, which was purified by chromatography on silica gel (eluting with hexane–EtOAc = 5 : 1) to give desired *anti*-alcohol **7** (more polar, 65 mg, 26%) and undesired *syn*-alcohol **6** (less polar, 0.17 g, 71%) as an oil. **7**: IR ν_{max} cm^{-1}: 3338, 3059, 2930, 1625, 1472, 1385, 1361, 1256, 1187, 1104, 940, 838, 776, 666; ^{1}H-NMR δ ($CDCl_3$): 0.03 (6H, s), 0.88 (9H, s), 1.66 (1H, br. s), 1.79 (1H, ddd, J = 3.4, 11.9, 14.0 Hz), 1.93 (1H, ddd, J = 4.7, 7.0, 14.0 Hz), 2.98–3.12 (1H, m), 3.44 (1H, dd, J = 6.9, 9.8 Hz), 3.53 (1H, dd, J = 6.1, 9.8 Hz), 4.83–4.92 (1H, m), 5.87 (1H, dt, J = 5.6, 2.1 Hz), 5.96 (1H, ddd, J = 0.9, 2.1, 5.6 Hz); ^{13}C-NMR δ ($CDCl_3$): −5.4, 18.3, 25.7, 37.0, 47.4, 66.7, 134.2, 137.2; MS *m/z* (%): 171 ($(M-t\text{-Bu})^+$, 68), 155 (21), 139 (4), 125 (5), 111 (5), 105 (17), 95 (44), 89 (60), 75 (100), 67 (10), 59 (23); HR-MS: Found, *m/z* 228.1548 (M^+); Calcd. for $C_{12}H_{24}O_2Si$, 228.1546. **6**: IR ν_{max} cm^{-1}: 3382, 2956, 2858, 1472, 1388, 1362, 1257, 1086, 1042, 1008, 837, 777; ^{1}H-NMR δ ($CDCl_3$): 0.06 (6H, s), 0.89 (9H, s), 1.54 (1H, br. d, J = 14.0), 2.28 (1H, ddd, J = 7.0, 8.5, 14.0 Hz), 2.69–2.83 (1H, m), 3.57–3.67 (2H, m), 4.52–4.63 (1H, m), 5.75 (1H, dd, J = 2.4, 5.5 Hz), 5.96 (1H, dt, J = 2.1, 5.5 Hz); ^{13}C-NMR δ ($CDCl_3$): −5.5, 26.0, 37.0, 46.3, 64.4, 75.5, 134.9, 135.2.

Conversion of syn-alcohol **6** *into anti-alcohol* **7**. To a solution of *syn*-alcohol **6** (0.17 g, 0.75 mmol) and Ph_3P (0.39 g, 1.5 mmol) in dry THF (3.5 ml) were successively added benzoic acid (0.18 g, 1.5 mmol) and DEAD (0.26 g, 1.5 mmol) at room temperature. After 15 h, the solvent was evaporated, and the residue was purified by chromatography on silica gel (eluting with hexane) to give benzoate (0.16 g, 62%) as an oil.

To a solution of benzoate in MeOH (2 ml) was added K_2CO_3 (0.21 g, 1.5 mmol), and the resulting mixture was stirred at room temperature. After 15 h, the mixture was diluted with ether and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography on silica gel (eluting with hexane–EtOAc = 5 : 1) gave *anti*-alcohol **7** (84 mg, 79%).

(1R,4S*)-2-Amino-6-chloro-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-purine* (**8**). Tri-*n*-butylphosphine (53 mg, 0.26 mmol) was added at room temperature to a stirred mixture of 2-amino-6-chloropurine (23 mg, 0.13 mmol), **7** (30 mg, 0.13 mmol) and DEAD (46 mg, 0.26 mmol) in dioxane (1 ml). The mixture was stirred at room tempeature for 1 h, then

the solvent was removed *in vacuo*. The residue was used without purification in the next reaction.

To a solution of the above residue in THF (1 ml) at room temperature was added *n*-Bu_4NF (0.13 ml of a 1 M solution in THF, 0.13 mmol), and the resulting solution was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (eluting with MeOH–$CHCl_3$ = 20 : 1) to give **8** (9 mg, 24%). ^{1}H-NMR δ ($CDCl_3$): 1.71 (1H, br. s), 2.02 (1H, dt, J = 5.5, 14.4 Hz), 2.82 (1H, dt, J = 9.5, 14.4 Hz), 3.07–3.18 (1H, m), 3.76 (1H, dd, J = 3.7, 10.7 Hz), 3.88 (1H, dd, J = 3.7, 10.7 Hz), 5.14 (2H, br. s), 5.50–5.56 (1H, m), 5.81 (1H, dt, J = 2.1, 5.5 Hz), 6.17 (1H, dt, J = 2.1, 5.5 Hz), 7.89 (1H, s); ^{13}C-NMR δ ($CDCl_3$): 32.8, 47.6, 61.1, 64.9, 125.9, 129.8, 138.8, 141.8, 151.5, 152.9, 158.4.

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