added one part (0.15 ml) of sodium methoxide solution, prepared from sodium metal (230 mg) and absolute methanol (10 ml) at 0°, and the resulting mixture was stirred at room temperature for 40 hr. Evaporation of the solvent at room temperature under the reduced pressure gave a syrup, which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated to give the acetal (**17**) (16 mg, 96.5%) as a brownish syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1375 (NO_2). NMR ($CDCl_3$) δ: 7.15 (1H, s, ArH), 5.65 (1H, s, C<u>H</u>$(OCH_3)_2$), 5.35 (1H, distorted q, 1-H), 4.15 (2H, distorted q, 3-H_2), 3.86 (3H, s, $ArOCH_3$), 3.42 and 3.20 (each 3H, s, $2\times OCH_3$), 3.2—2.5 (2H, m, 2-H_2), 2.42 (3H, s, $ArCH_3$). MS *m/e*: 288 (M^+ −OMe−OH).

2,3-Dihydro-1-hydroxy-7-methoxy-6-methyl-8-nitro-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (18)——To a suspension of the aldehyde (**2**) (1.1 g) in methanol (20 ml) was added dropwise 10% methanolic KOH solution (2.2 ml) and stirred for 30 min at room temperature. Then, the solvent was concentrated and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent gave pale brownish needles, which were recrystallised from methanol to give the aldehyde (**18**) as colourless needles (904 mg, 94%), mp 188.5—186.5°. *Anal.* Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.88; H, 4.80; N, 9.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (C=O), 1520 and 1355 (NO_2). NMR ($CDCl_3$) δ: 9.74 (1H, s, C<u>H</u>O), 7.26 (1H, s, 5-H), 5.52 (1H, t, $J=7.0$ Hz, 1-H), 4.74 (1H, s, O<u>H</u>, D_2O exchangeable), 4.5—4.1 (2H, m, 3-H_2), 3.87 (3H, s, OCH_3), 3.4—2.5 (2H, m, 2-H_2), 2.42 (3H, s, $ArCH_3$).

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Studies on the Syntheses of Heterocyclic Compounds. DCCLV.[1] Iminoketene Cycloaddition. (4).[2] Alternative Syntheses of 5,6,7,8-Tetrahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline and Rutecarpine

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Treatment of the sulfinamide anhydride (**2**), prepared from anthranilic acid (**1**), with 3,4-dihydro-6,7-dimethoxyisocarbostyril (**9**) gave 5,6,7,8-tetrahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (**10**), which was also obtained by heating isatoic anhydride (**3**) with **9**. Similarly, rutecarpine (**6**) was synthesised by the reactions of 1,2,3,4-tetrahydro-1-keto-β-carboline (**13**) with the sulfinamide anhydride (**2**) or isatoic anhydride (**3**). Heating 3,4-dihydro-β-carboline (**5**) with **3** also afforded rutecarpine (**6**). Furthermore the phosphates (**8a**) and (**12**) were isolated on treatment of the urethanes (**7a**) and (**11**) with phosphoryl chloride.

Keywords——5,6,7,8-tetrahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazolone; rutecarpine; iminoketene cycloaddition; sulfinamide anhydride; isatoic anhydride

We have recently reported total syntheses of rutecarpine, evodiamine and other quinazolinone alkaloids by a cycloaddition reaction of the iminoketene (**4**), generated *in situ* from anthranilic acid or N-methylanthranilic acid with thionyl chloride *via* sulfinamide anhydrides

1) Part DCCLIV: T. Kametani, Y. Kigawa, K. Takahashi, H. Nemoto, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 1918 (1978).
2) Part 3: T. Kametani, C.V. Loc, T. Higa, M. Ihara, and K. Fukumoto, *J. C. S. Perkin I*, **1977**, 2347.
3) Location: *Aobayama, Sendai 980, Japan.*

to imines[4,5] and amides.[2,6] On the other hand, isatoic anhydride (3) had been shown to be a useful compound for the synthesis of the quinazolinone derivatives.[7] The same iminoketene intermediate was postulated in both reactions, although a higher temperature in the reaction of 3 was required to form the reactive species.[7] Since we have compared the reactions of the sulfinamide anhydride (2) and isatoic anhydride (3) with several lactams and imines, we here wish to report the results as well as interesting findings.

In previous work,[5] we had accomplished a total synthesis of rutecarpine (6) upon treatment of the sulfinamide anhydride (2) with 3,4-dihydro-β-carboline (5) at room temperature in 80% yield. However, the reaction of 3,4-dihydro-β-carboline (5) with isatoic anhydride (3) at 190—200° for 2 hr gave rutecarpine (6) in a poor yield. This fact would indicate that isatoic anhydride (3) is not a proper precursor for the condensation with the unstable imine such as 5. Therefore, the reactions of sulfinamide anhydride with isocarbostyril (9) and 1-keto-β-carboline (13) which would be expected to be more stable toward heating, were examined.

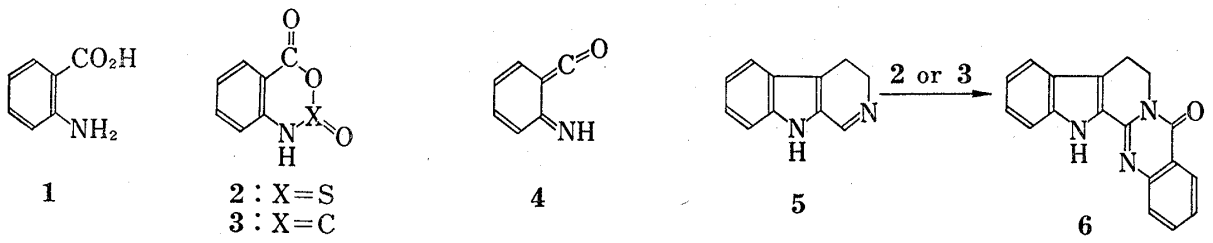

Chart 1

In order to obtain the isocarbostyril (9), the urethane (7) was heated for 3 hr with phosphoryl chloride in acetonitrile, but only a compound which was positive in Beilstein test and in qualitative analysis for phosphorus by ammonium molybdate was formed in 85% yield. The structure of this product was assigned the phosphate (8a) by infrared (IR) [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=N)], nuclear magnetic resonance (NMR) [($CDCl_3$) δ: 1.35 (3H, t, J=7 Hz, CH_3), 2.75—3.10 (2H, m, $ArCH_2$), 4.28 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$)] and high-resolution mass spectra. The direct formation of the desired isocarbostyril (9) from ethyl carbamate (7a) was not detected by thin-layer chromatography. The phosphate (8a) was converted to the lactam (9) by treatment with boron trifluoride etherate in dry benzene under reflux for 2 hr, followed by hydrolysis with aqueous 10% sodium hydroxide solution for 3 hr.[8]

On the other hand, the methyl carbamate (7b) gave the lactam (9) by the same reaction condition as the case of the ethyl carbamate (7a) but the corresponding phosphate (8b) was too labile for isolation. Isolation of the phosphate intermediate during Bischler-Napieralski type reaction had not previously been reported. It seems thus to be very interesting that the phosphate (8a) was obtained as a rather stable form from ethyl carbamate (7a).

In a similar manner, the phosphate (12) was obtained, by treatment of the urethane (11) with phosphoryl chloride in acetonitrile under reflux for 5 hr, as colorless crystals, mp 103—104° (dec.), the structure of which was also determined by its IR [$\nu_{max}^{CHCl_3}$ cm^{-1} 1735 (C=N)], NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, CH_3), 3.00—3.35 (2H, m, $-C\underline{H}_2CH_2N{=}C-$), 3.78—4.22 (2H, m, $-CH_2C\underline{H}_2N{=}C-$), 4.28 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$)] and high-resolution mass spectra.

4) T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, *Heterocycles*, **4**, 23 (1976).
5) T. Kametani, T. Higa, C.V. Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Am. Chem. Soc.*, **98**, 6186 (1976).
6) T. Kametani, C.V. Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 1487 (1976); *idem*, *J. Am. Chem. Soc.*, **99**, 2306 (1977).
7) *a*) E. Späth and N. Platzer, *Ber.*, **68**, 2225 (1935); *b*) W. Steiger, T. Kappe, and E. Ziegler, *Monatsh. Chem.*, **100**, 146 (1969); V.P. Arya, K.G. Dave, V.G. Khadse, and S.J. Shenoy, *Indian J. Chem.*, **14B**, 879 (1976).
8) Y. Tsuda, K. Isobe, J. Toda, and J. Taga, *Heterocycles*, **5**, 157 (1976).

However, the phosphate (**12**) was not converted to the lactam (**13**)[9] under the same conditions as above.

The sulfinamide anhydride (**2**), prepared from anthranilic acid (**1**) with thionyl chloride in boiling benzene, was treated with 3,4-dihydro-6,7-dimethoxyisocarbostyril (**9**) in dry benzene at room temperature overnight to afford the 5,6,7,8-tetrahydro-8-oxoisoquinolo[1,2-*b*]quinazoline (**10**) in 57% yield. The same compound (**10**) was synthesized from isatoic anhydride (**3**) in 70% yield, namely on fusing **9** with isatoic anhydride (**4**) at 190—200° for 2 hr.

On the other hand, treatment of the sulfinamide anhydride (**2**) with 1,2,3,4-tetrahydro-1-keto-*β*-carboline (**13**)[9] under the same conditions as above afforded rutecarpine (**6**) in 19.7% yield, whose IR and NMR spectra were superimposable upon those of the authentic sample[5]

Furthermore, rutecarpine (**6**) was prepared by the reaction of isatoic anhydride (**3**) with **13** on heating at 190—200° for 2 hr in 42.3% yield.

These results indicate that isatoic anhydride (**3**) reacts with amides and imines, which are stable toward heating, to form the condensed product in higher yield than the sulfinamide anhydride (**2**), but it seems to be interesting that the formation of **6** and **10** by our sulfinamide anhydride method was recognized even at room temperature.

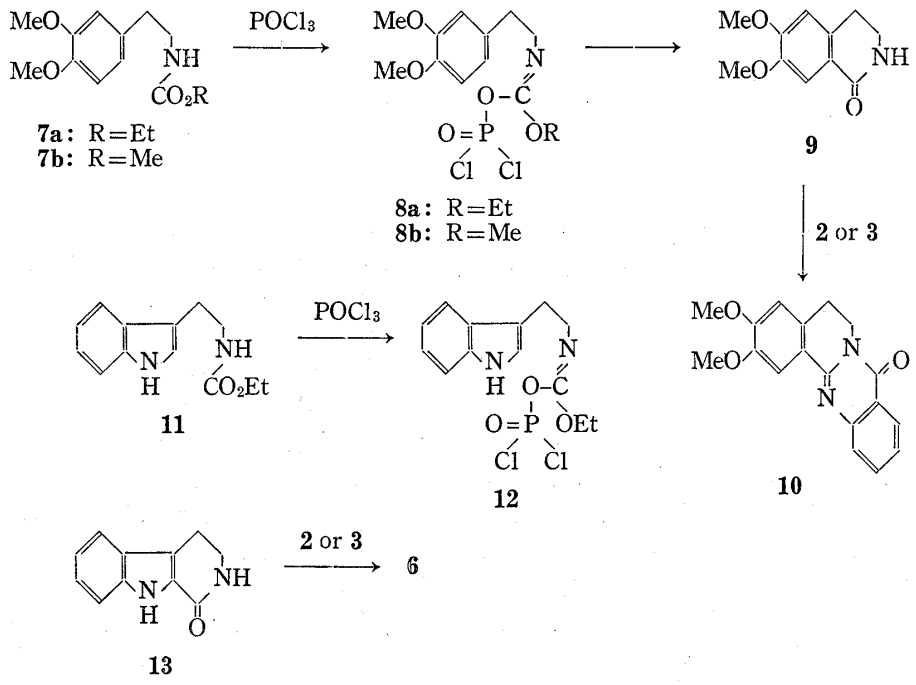

Chart 2

Experimental[10]

Reaction of the Urethane (7a) with Phosphoryl Chloride in Acetonitrile——To a solution of **7a** (1.4 g) in acetonitrile (40 ml) was added phosphoryl chloride (5.0 g) and the mixture was refluxed for 3 hr. After evaporation of the solvent and the excess reagent, the residue was partitioned between a saturated aqueous sodium hydrogen carbonate solution and chloroform. The chloroform layer was separated, washed with water, dried over Na_2SO_4 and evaporated to give a yellowish residue, which was subjected to chromatography

9) R.A. Abramovitch and D. Shapiro, *J. Chem. Soc.*, **1956**, 4589.

10) All melting points were measured with a Yanagimoto micro melting point apparatus (MP–S2) and are uncorrected. IR spectra were taken with a Hitachi 215 grating spectrophotometer, NMR spectra with a JNM–PMX-60 (60 MHz) instrument (for solution in deuteriochloroform with tetramethylsilane as internal standard). MS spectra were measured with Hitachi RMU-7 and JEOL JMX–D100 mass spectrometers.

11) J.J. Dobbie and A. Lauder, *J. Chem. Soc.*, **75**, 673 (1899).

on silica gel. Elution with benzene afforded the phosphate (**8a**) (1.73 g, 85%) as a colorless oil. Calcd. for $C_{13}H_{18}Cl_2NO_5P$ (M^+; *m/e*): 369.0302 and 371.0270. Found: 369.0301 and 371.0281. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=N). NMR ($CDCl_3$) δ: 1.35 (3H, t, $J=7$ Hz, CH_3), 2.75—3.10 (2H, m, $ArC\underline{H}_2$), 3.83 (6H, s, $2\times OCH_3$), 4.28 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.72 (3H, broad s, $3\times$ArH), MS *m/e*: 373, 371, 369 (M^+).

3,4-Dihydro-6,7-dimethoxyisocarbostyril (9)——(a) To a solution of the phosphate (**8a**) (1.35 g) in dry benzene (50 ml) was added boron trifluoride etherate (1.1 g) and the mixture was refluxed for 2 hr. Evaporation of the excess reagent and the solvent afforded a brown oil, to which was added aqueous 10% sodium hydroxide solution (50 ml) and the resulting mixture was refluxed for 3 hr. The oily product was extracted with chloroform and the extract was washed with water, dried over Na_2SO_4 and evaporated to give a yellow oil, which was subjected to chromatography on silica gel. Elution with benzene–methanol (99: 1 v/v) afforded the isocarbostyril (**9**) (110 mg, 14.6%) as colorless prisms, mp 173.5—174.5° (lit.,[11] mp 175°), after recrystallization from benzene. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1660 (C=O). NMR ($CDCl_3$) δ: 2.77—3.10 (2H, m, $ArC\underline{H}_2CH_2$), 3.42—3.73 (2H, m, $ArCH_2C\underline{H}_2$), 3.90 (6H, s, $2\times OCH_3$), 6.57 (1H, broad s, NH), 6.65 (1H, s, 5-H), 7.53 (1H, s, 8-H).

(b) To a solution of **7b** (500 mg) in acetonitrile (50 ml) was added phosphoryl chloride (3.0 g) and the resulting mixture was refluxed for 3 hr. After evaporation of the excess reagent and the solvent, the residue was partitioned between a saturated aqueous sodium hydrogen carbonate solution and chloroform. The chloroform layer was washed with water, dried over Na_2SO_4 and evaporated to give a yellowish residue, which was subjected to chromatography on silica gel. Elution with benzene–methanol (99: 1 v/v), followed by recrystallization from benzene, afforded the isocarbostyril (**9**) (164 mg, 37.9%) as colorless prisms, mp 173.5—174.5° (lit.,[11] mp 175°), IR and NMR spectra of which were identical with those of the above compound prepared by the method (a).

Reaction of the Urethane (11) with Phosphoryl Chloride in Acetonitrile——To a solution of **11** (1.2 g) in acetonitrile (50 ml) was added phosphoryl chloride (5.5 g) and the mixture was refluxed for 5 hr. After evaporation of the solvent and the excess reagent, the residue was partitioned between a saturated aqueous sodium hydrogen carbonate solution and chloroform. The chloroform layer was separated, washed with water, dried over Na_2SO_4 and evaporated to give a brown residue, which was subjected to chromatography on silica gel. Elution with benzene afforded the phosphate (**12**) (151 mg, 7.7%) as colorless needles, mp 103—104° (dec.) (from chloroform–*n*-hexane). Calcd. for $C_{13}H_{15}Cl_2N_2O_3P$ (M^+; *m/e*): 348.0214 and 350.0181. Found: 348.0206 and 350.0175. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=N), NMR ($CDCl_3$) δ: 1.28 (3H, t, $J=7$ Hz, CH_3), 3.00—3.35 (2H, m, $-C\underline{H}_2CH_2N{=}C-$), 3.78—4.22 (2H, m, $-CH_2C\underline{H}_2N{=}C-$), 4.28 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.93—7.78 (5H, m, $4\times$ArH and 2-H), 8.16 (1H, broad s, NH); MS *m/e*: 352, 350, 348 (M^+). *Anal.* Calcd. for $C_{13}H_{15}Cl_2N_2O_3P$: C, 44.72; H, 4.33; N, 8.02. Found: C, 44.96; H, 4.16; N, 8.04.

5,6,7,8-Tetrahydro-2,3-dimethoxy-8-oxoisoquinolo[1,2-*b*]quinazoline (10)——(a) A mixture of anthranilic acid (**1**) (137 mg) and thionyl chloride (3 g) in dry benzene (20 ml) was refluxed for 2 hr under a current of nitrogen. The solvent and the excess reagent were then evaporated under reduced pressure at 25—30° to leave a pale yellow syrup, to which was added a solution of 3,4-dihydro-6,7-dimethoxyisocarbostyril (**9**) (207 mg) in dry benzene (30 ml) in one portion at room temperature. The mixture was allowed to stand overnight at room temperature to give a white solid. After evaporation of the solvent from the mixture, the residue was extracted with chloroform. The extract was washed successively with aqueous 10% sodium hydroxide solution and water, dried over Na_2SO_4 and evaporated. The residue was recrystallized from chloroform–ether to give the quinazoline (**10**) (163 mg, 57%) as colorless needles, mp 247—248° (lit.,[5] mp 249—250°), IR and NMR spectra of which were identical with those of the authentic sample.[5]

(b) A mixture of isatoic anhydride (**3**) (200 mg) and 3,4-dihydro-6,7-dimethoxyisocarbostyril (**9**) (200 mg) was heated at 190—200° for 2 hr and the product was then extracted with chloroform. The extract was washed successively with aqueous 10% sodium hydroxide solution and water, dried over Na_2SO_4 and evaporated. The residue was recrystallized from chloroform–ether to give the quinazoline (**10**) (193 mg, 70%) as colorless needles, mp 247—248° (lit.,[5] mp 249—250°), after recrystallization from chloroform–ether, IR and NMR spectra of which were superimposable on those of the above compound.

Rutecarpine (6)——(a) A mixture of isatoic anhydride (85 mg) and 3,4-dihydro-β-carboline (**5**) (85 mg) was heated at 190—200° for 2 hr and then extracted with chloroform. The extract was washed successively with aqueous 10% sodium hydroxide solution and water, dried over Na_2SO_4 and evaporated to afford a brown residue, which was subjected to chromatography on silica gel. Elution with benzene gave a solid, recrystallization of which from ethyl acetate gave rutecarpine (**6**) (25 mg; 17.5%) as colorless needles, mp 256—257° (lit.,[5] mp 258°), IR and NMR spectra of which were identical with those of authentic compound.[5]

(b) To the sulfinamide anhydride (**2**), prepared from anthranilic acid (**1**) (250 mg) by the same method as above, was added a solution of 1,2,3,4-tetrahydro-1-keto-β-carboline (**13**)[9] (280 mg) in dry benzene (20 mg) and dry dioxane (30 ml) in one portion at room temperature. The mixture was set aside overnight at room temperature. After evaporation of the solvent, the residue was extracted with chloroform. The extract was washed successively with aqueous 10% sodium hydroxide solution and water, dried over Na_2SO_4 and evaporated to give a yellow solid, which was subjected to chromatography on silica gel. Elution with benzene afforded rutecarpine (**6**) (85 mg, 19.7%) as colorless needles, mp 256—257° (lit.,[5] mp 258°), IR and NMR spectra of which were identical with those of the sample prepared by the method (a).

(c) A mixture of isatoic anhydride (3) (295 mg) and 1,2,3,4-tetrahydro-1-keto-β-carboline (13)[9] (280 mg) was heated at 190—200° for 2 hr and extracted with chloroform. The extract was washed successively with aqueous 10% sodium hydroxide solution and water, dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ethyl acetate afforded rutecarpine (6) (183 mg, 42.3%) as colorless needles, mp 256—257° (lit.,[5] mp 258°), IR and NMR spectra of which were superimposable on those of the above sample prepared by the method (a).

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Studies on Catalytic Hydrogenation of the Exocyclic Double Bond in Reducing Disaccharides

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Effects of solvents and catalysts in catalytic hydrogenation of the exocyclic double bond in disaccharide-5-ene heptaacetates, synthesized from maltose, lactose, and cellobiose, were investigated. A stereospecific hydrogenation proceeded in such a way that the corresponding 6-deoxy-L-ido isomer was predominant over the 6-deoxy-D-gluco isomer.

Preparations of 6-deoxy-maltose, 6-deoxy-α-cellobiose, 4-O-α-D-glucopyranosyl-6-deoxy-L-idopyranose, and 4-O-β-D-glucopyranosyl-6-deoxy-L-idopyranose were also described.

Keywords——catalytic hydrogenation; maltose-5-ene heptaacetate; lactose-5-ene heptaacetate; cellobiose-5-ene heptaacetate; 6-deoxy-maltose; 6-deoxy-α-cellobiose; disaccharides having 6-deoxy-L-idopyranose

We reported previously[2] that the exocyclic double bond in lactose-5-ene heptaacetate (8) was reduced as formation of the 6-deoxy-L-ido isomer (11) was predominant over the 6-deoxy-D-gluco isomer (5). Khan and Jenner[3] showed subsequently that catalytic hydrogenation of sucrose-5-ene heptaacetate gave the L-ido and the D-gluco isomers in the yields of 45 and 10%, respectively. Except for the two papers, no paper has been reported on catalytic hydrogenation of the exocyclic double bond in disaccharides. Therefore, to clarify the mode of hydrogenation in disaccharide-5-ene heptaacetate, we reduced this compound under different conditions. In this paper, we report the results in full detail.

Authentic heptaacetyl-6-deoxy-β-maltose (4)[4] or -lactose (5)[2] was synthesized from the corresponding 6-deoxy-6-iodo compound (1 or 2), respectively. Heptaacetyl-6-deoxy-β-cellobiose (6) was prepared from heptaacetyl-6-deoxy-6-iodo-β-cellobiose (3).[5] Disaccharide-5-ene heptaacetate (7, 8, or 9) was synthesized by stirring 1, 2, or 3 in dry pyridine with dry silver fluoride, respectively. In the preparation of 8,[2] silver fluoride was added in twice and time of stirring was reduced to almost 1/3, which improved the yield.

1) Location: *Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan.*
2) T. Chiba, M. Haga, and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **22**, 398 (1974).
3) R. Khan and M.R. Jenner, *Carbohyd. Res.*, **48**, 306 (1976).
4) M. Mori, M. Haga, and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **22**, 1331 (1974).
5) S. Tejima and Y. Okamori, *Chem. Pharm. Bull.* (Tokyo), **20**, 2036 (1972).