Chem. Pharm. Bull. 41(2) 282—286 (1993) Vol. 41, No. 2

Chemoenzymatic Carbon–Carbon Bond Formation Leading to Non-carbohydrate Derivative. Stereoselective Synthesis of Pentamycin C-11—C-16 Fragment

Masayuki SHIMAGAKI,* Hiroaki MUNESHIMA, Masahide KUBOTA, and Takeshi OISHI*,[1)]

The Institute of Physical and Chemical Research (RIKEN), 2-1, Hirosawa, Wako-shi, Saitama 351-01, Japan.

Received July 14, 1992

Chemoenzymatic formation of 8 from an aldehyde 5 and dihydroxyacetone phosphate 6 was achieved by the use of fructose 1,6-diphosphate aldolase as a catalyst. Transformation of 8 to 20, corresponding to pentamycin C-11—C-16 fragment, was accomplished *via* 18a and 18b by chemical processes.

Keywords aldolase; pentamycin; asymmetric aldol condensation; 7-*O*-benzyl-6-deoxy-D-xyloheptulose; α-hydroxyaldehyde; dihydroxyacetone phosphate

Up to now an enzyme, fructose 1,6-diphosphate (FDP) aldolase has been applied to syntheses of carbohydrates and carbohydrate-like compounds.[2)] Recently, the synthesis of exo-brevicomin, a non-carbohydrate, has been reported by the use of this enzyme.[3)] We describe here a stereoselective carbon–carbon bond formation reaction leading to a non-carbohydrate derivative corresponding to pentamycin C-11—C-16 fragment A by using this aldolase.

We have already reported the stereochemistry of pentamycin, a polyene macrolide antibiotic, as shown in **1**.[4)] The configurations at the C-15 and C-14 positions of **1** are expected to be the same as those of the C-3 and C-4 positions of an aldol **7**, respectively, when they are constructed from an aldehyde **5** and dihydroxyacetone phosphate (DHAP) **6**, catalyzed by FDP aldolase.

Initially, we synthesized the optically active α-hydroxy aldehyde derivative **5**. According to the literature,[5)] D-glucose was converted to a vinyl derivative **2**, which was treated with borane methylsulfide complex (BMS) to give a primary alcohol **3**. Benzylation (benzyl trichloroacetimidate-trifluoromethanesulfonic acid (TfOH)[6)]) of **3** and hydrolysis of the protecting groups (20% NaOH–EtOH and aqueous AcOH) gave a benzyloxy triol **4**. The triol **4** was treated with $NaIO_4$ in ether–H_2O or AcOEt–H_2O in expectation of cleaving the 1,2- and 2,3-bonds, but the desired product was obtained only in low yield. However, when the reaction medium was changed to CH_2Cl_2–H_2O and the pH was adjusted to 2.5, 3,4-benzyloxy-(2*R*)-formyloxybutanal (**5**) was obtained in 89% yield (crude). It is interesting to note that **5** was found to be stable even at pH 1—3, although usual formyl esters are stable only at pH 4—8.5. As **5** decomposed upon silica gel treatment, giving the hydroxy aldehyde, **5** was subjected to subsequent reactions without further purification.

Next, we intended to construct the aldol **7** from the optically active **5** and DHAP **6** by the use of FDP aldolase. The aldol **7** was easily detected by UV on TLC and could be separated by preparative TLC (pTLC) (silica gel), since **7** contains a benzyl group in the molecule. The aldehyde **5** and DHAP **6**, derived from FDP, by the use of FDP aldolase and triose phosphate isomerase (TPI) were incubated in FDP aldolase solution at pH 6.8—7.2 at ambient temperature and the mixture was gently stirred for 24 h under argon.[7,8)] The pH of the resultant reaction mixture was adjusted to 4.5 and the mixture was treated with acid phosphatase at 37 °C for 14 h. The products were neutralized and separated by pTLC (silica gel) with AcOEt–MeOH (7 : 1) as an eluent to give a mixture of 7-*O*-benzyl-6-deoxy-D-xyloheptulose (**8**) (3.7 : 1) in 42% yield, presumably *via* **7**. It was not clear at this

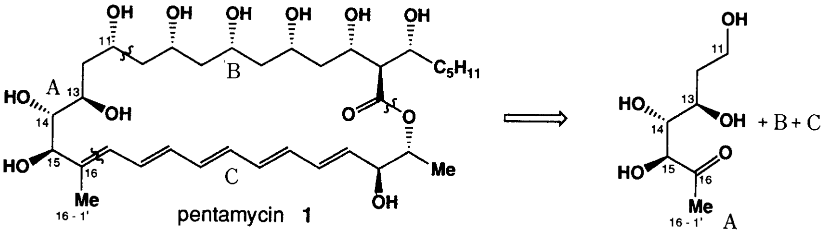


Chart 1

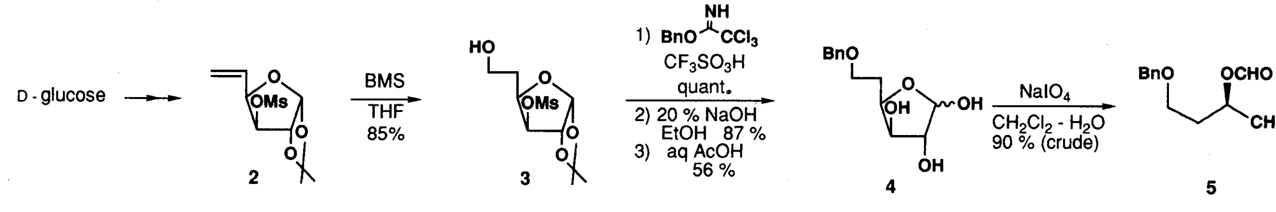


Chart 2

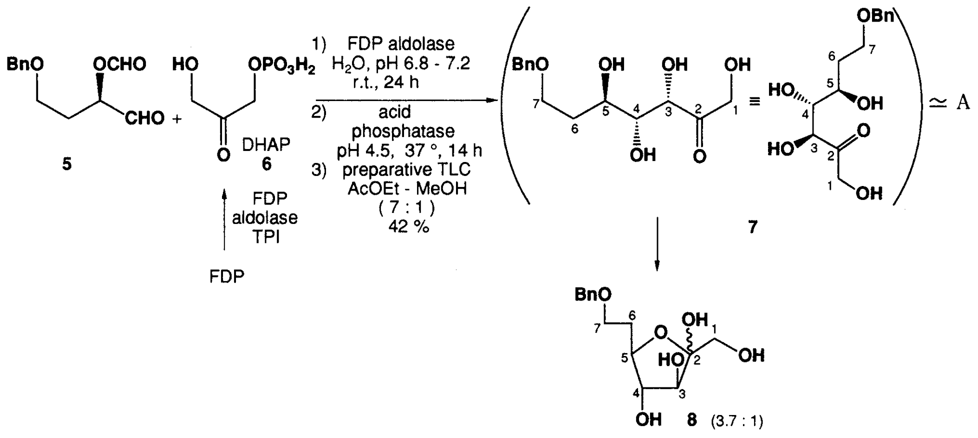
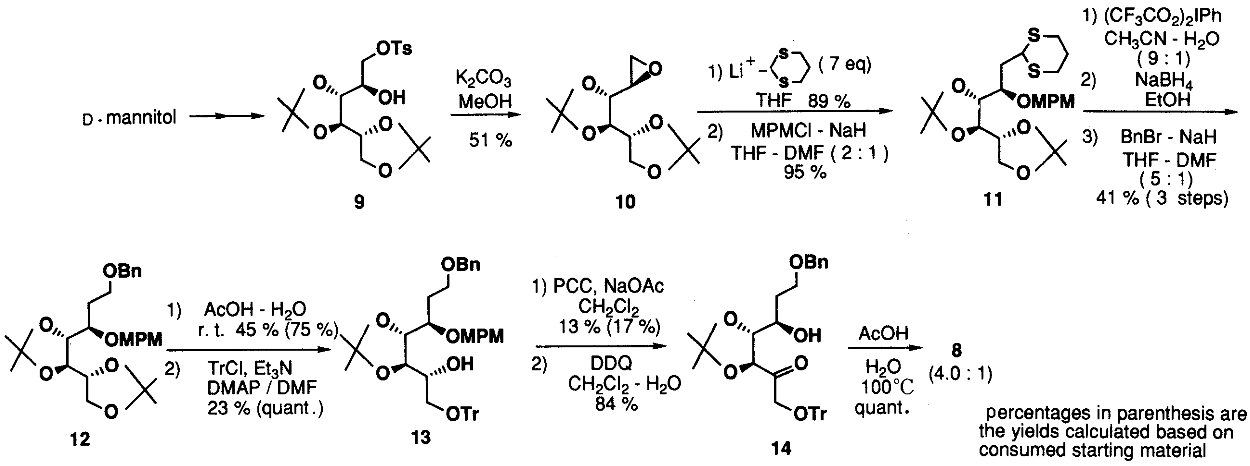


Chart 3



percentages in parenthesis are the yields calculated based on consumed starting material

Chart 4

stage whether they were isomers at the C-5 position or at the anomeric position of **8**.[7]

Thus, we synthesized optically active authentic **8**, starting from D-mannitol, by chemical transformation. According to the literature,[9] D-mannitol was transformed to a diisopropylidene tosylate **9**. The tosyl alcohol **9** was treated with methanolic K_2CO_3 to give an (5*R*)-epoxide **10**. Epoxide opening of **10** with an excess of dithiane anion, followed by protection with the 4-methoxyphenylmethyl (MPM) group gave an elongated MPM-dithioacetal **11**. The dithioacetal **11** was deprotected with bistrifluoroacetoxy iodobenzene,[10] reduced with $NaBH_4$ and then benzylated with benzyl bromide (BnBr)–NaH to give **12**. The diacetonide **12** was treated with aqueous AcOH at ambient temperature and treated with trityl chloride (TrCl)–Et_3N to give **13**. Pyridinium chlorochromate (PCC) oxidation of **13**, followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) treatment gave **14**. The acetonide **14** was then deblocked with aqueous AcOH at 100 °C to give a mixture of **8** (4.0 : 1). The 400 MHz NMR spectrum of an anomeric mixture of the synthetic **8** was found to be identical with that of the hemiacetal synthesized enzymatically, which proved that **8** was a mixture at the anomeric position and not at the C-5 position.

Then, we examined removal of the hydroxyl group at the C-1 position of **8** to produce the pentamycin C-11—C-16 fragment. As an attempt at direct removal of the primary hydroxyl group of **8** failed, the anomeric hydroxyl group was initially protected. Methylation of **8** in MeOH with *p*-toluenesulfonic acid (*p*-TsOH) gave **15a** in 41% yield and **15b** in 38% yield. They were tried to react with *p*-toluenesulfonyl chloride (TsCl)–pyridine, 1,1′-thiocarbonyldiimidazole or methyl imidazoyldithiocarbonate, but no reaction occurred. However, both **15a** and **15b** were successfully converted to mono-methyl xanthates **16a** and **16b** in 58% and 70% yields, respectively, by successive treatment with NaH, CS_2 and MeI, together with a mixture of di-xanthates **17a** and **17b**. The di-xanthates **17a** and **17b** were easily re-converted to **15a** and **15b**, respectively, by K_2CO_3–MeOH treatment. The xanthates **16a** and **16b** were reduced with *n*-Bu_3SnH in the presence of azobisisobutyronitrile (AIBN) in refluxing toluene to give the 1-methyl derivatives **18a** and **18b** in 83% and 89% yields, respectively.

Finally, we examined the conversion of the cyclic acetals **18a** and **18b** to a linear compound. Many attempts at direct conversion of the masked carbonyl group to the thioacetal group of **18a** and **18b** failed. Thus, a trans-acetalization was examined after protection of all of the hydroxyl groups. The diol **18b** could be transformed to an expected tri-methyl ether **19b** with Ag_2O–MeI at 0 °C-ambient temperature in 73% yield, but the results were not reproducible. We changed the base from Ag_2O to NaH and the reaction was performed at 0 °C-ambient tem-

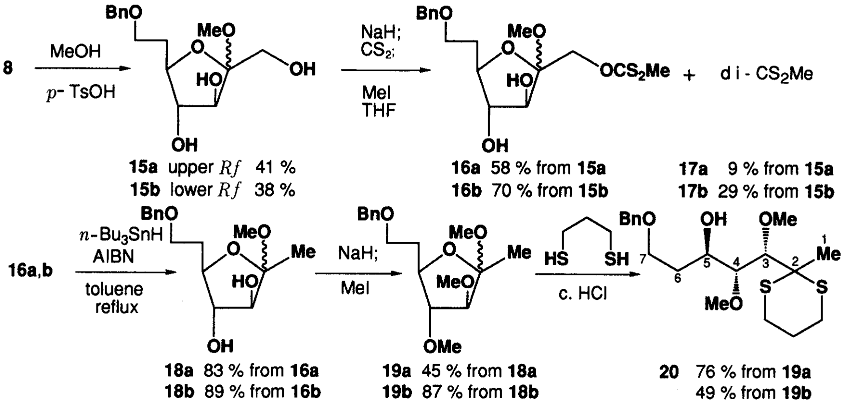


Chart 5

perature, but no desired product was obtained. However, when the reaction was performed at −40 °C—0 °C, **19a** and **19b** were obtained in 45% and 87% yields from **18a** and **18b**, respectively. Ketonic reagents (hydrazine, hydroxylamine or Wittig reagent) did not react with these tri-methoxy compounds **19a** and **19b**. Treatment of **19a** and **19b** with 1,3-propanedithiol in the presence of a small amount of concentrated HCl at 0 °C-ambient temperature gave no thioacetal. However, when the reaction temperature was lowered to −35 °C-ambient, the same linear compound **20** was obtained from **19a** and **19b** in 76% and 49% yields, respectively, as a sole product. Thus, the chemoenzymatic synthesis of **20**, corresponding to the C-11—C-16 part A of pentamycin was achieved with high stereoselectivity *via* a relatively short pathway.

Experimental

NMR spectra were measured on a JEOL FX-60, EX-270, GX-400 or GX-500 instrument in $CDCl_3$ and chemical shifts are given by δ values. High-resolution MS (Hi-MS) and MS were taken with a Hitachi M-80 or M-80A spectrometer, respectively.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-D-glucofuranose (3) BMS (2.40 ml, 24.0 mmol) was added slowly to 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-D-glucofuranosene-5 (**2**)$^{5)}$ (5.39 g, 20.4 mmol) in tetrahydrofuran (THF) (50 ml) with stirring under ice cooling. The mixture was stirred at ice temperature for 10 min and at room temperature for 2 h. The resultant mixture was cooled with ice and after addition of 15% NaOH solution (33 ml) and 30% H_2O_2 solution (33 ml), the mixture was stirred at ice temperature for 10 min and at room temperature overnight. The reaction mixture was extracted with AcOEt, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) as an eluent to give **3** (3.00 g, 10.6 mmol, 52%). NMR (60 MHz) δ: 1.32, 1.51 (3H × 2, each s, CMe × 2), 1.95 (2H, dd, J=5.0, 6.1 Hz, 5-CH_2), 3.12 (3H, s, SO_2Me), 3.74, 3.92 (2H, ABq, J=5.4 Hz, 6-CH_2), 4.45 (1H, dt, J=2.8, 6.6 Hz, 4-CH), 4.78 (1H, d, J=3.7 Hz, 2-CH), 4.98 (1H, d, J=2.8 Hz, 3-CH), 5.93 (1H, d, J=3.7 Hz, 1-CH). MS m/z: 283 (M+1).

6-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-D-glucofuranose Benzyltrichloroacetimidate (1.189 ml, 6.40 mmol) and CF_3SO_3H (0.07 ml) was added to a solution of **3** (1.504 g, 5.33 mmol) in ether (12 ml). The mixture was stirred under ice cooling for 5 min and at room temperature for 17 h, then poured onto saturated $NaHCO_3$ solution and diluted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (3 : 1) as an eluent to give a benzyloxy derivative (1.975 g, 5.31 mmol, quant.). NMR (60 MHz) δ: 1.32, 1.52 (3H × 2, each s, CMe × 2), 1.98 (2H, dt, J=6.4, 6.4 Hz, 5-CH_2), 2.96 (3H, s, SO_2Me), 3.62 (1H, t, J=5.9 Hz, 6-CH_2), 4.51 (2H, s, CH_2Ph), 4.68—4.95 (2H, m, 2,4-CH), 4.91 (1H, d, J=2.8 Hz, 3-CH), 5.92 (1H, d, J=3.8 Hz, 1-CH), 7.32 (5H, s, C_6H_5). MS m/z: 373 (M+1), 372 (M).

6-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-D-glucofuranose A solution of the benzyloxy derivative (577 mg, 1.55 mmol) and 10% NaOH (4.3 ml) in EtOH (9 ml) was heated at 100 °C for 10 h. The reaction mixture was diluted with AcOEt and the aqueous layer was removed. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) as an eluent to give a hydroxy derivative (325 mg, 1.15 mmol, 74%). NMR (60 MHz) δ: 1.31, 1.49 (3H × 2, each s, CMe × 2), 2.05—2.09 (2H, m, 5-CH_2), 3.12 (1H, d, J=2.9 Hz, OH), 3.50—3.71 (2H, m, 6-CH_2), 4.06—4.18 (2H, m, 3,4-CH), 4.52 (2H, s, CH_2Ph), 4.55 (1H, d, J=3.7 Hz, 2-CH), 5.89 (1H, d, J=3.7 Hz, 1-CH), 7.32 (5H, s, C_6H_5). MS m/z: 295 (M+1).

6-*O*-Benzyl-5-deoxy-D-glucofuranose (4) A solution of the hydroxy derivative (2.42 g, 8.66 mmol) in AcOH (48 ml) and water (16 ml) was heated at 100 °C for 6 h. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 8 to 1 : 5) as an eluent to give **4** (1.22 g, 4.81 mmol, 56%). NMR (500 MHz, D_2O) δ: 1.76—1.97 (2H × 2, each m, 5-CH_2 × 2), 3.61—3.68 (1H × 2, each m, 3-CH × 2), 3.98 (1H, dd, J=1.8, 4.3 Hz, 2-CH), 4.00 (1H, m, 2-CH), 4.03, 4.07 (1H × 2, each m, 4-CH × 2), 4.20—4.24, 4.26—4.29 (2H × 2, each m, 6-CH_2 × 2), 4.526, 4.530 (2H × 2, each s, CH_2Ph × 2), 5.09 (1H, s, 1-CH), 5.36 (1H, d, J=4.3 Hz, 1-CH), 7.39 (5H × 2, each s, C_6H_5 × 2). MS m/z: 255 (M+1), 237 (M−H_2O+1), 219 (M−2H_2O+1).

4-Benzyloxy-(2*R*)-formyloxybutanal (5) A solution of **4** (301 mg, 1.18 mmol) in CH_2Cl_2 (27 ml) was added dropwise to a solution of $NaIO_4$ (557 mg, 2.60 ml) in water (9 ml) over 5 min at room temperature. The mixture was further stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent gave crude **5** (233 mg), which was used without purification. When the crude **5** was chromatographed on silica gel, deformylation took place giving the hydroxyaldehyde. NMR (60 MHz) δ: 1.90—2.40 (2H, m, 3-CH_2), 3.44—3.76 (2H, m, 4-CH_2), 4.50 (2H, s, CH_2Ph), 5.00—5.60 (1H, m, 2-CH), 7.31 (5H, s, C_6H_5), 8.06 (1H, s, OCHO), 9.68 (1H, br s, CHO).

7-*O*-Benzyl-6-deoxy-D-xyloheptulose (8)$^{7)}$ The pH of the solution of **5** (45.2 mg, 0.203 mmol) and FDP (3Na, 5H_2O) (41.3 mg, 0.0818 mmol) in H_2O (0.6 ml) was adjusted to 7.2 with 10% NaOH solution. The mixture was gently stirred at room temperature under argon for 24 h, after the addition of a small amount of triose phosphate isomerase and FDP aldolase (type IV: from rabbit muscle, Sigma Chemical Company; 0.048 ml, 27.8 units) (the pH was shifted to 6.8 at the end of the reaction). The pH of the mixture was re-adjusted to 4.5 and the mixture was incubated at 37 °C for 14 h with acid phosphatase (type I: from wheat germ, Sigma Chemical Company; 5 mg, 2.6 units). EtOH was added and the pH of the mixture was adjusted again to 7.0, then the mixture was filtered by suction. After removal of the solvent, the residue was developed on pTLC (silica gel) with AcOEt–MeOH (7 : 1) to give **8** (19.5 mg, 0.0687 mmol, 42%). NMR (400 MHz, D_2O) major : minor = 4.0 : 1. Major isomer δ: 1.81—2.15 (2H, m, 6-CH_2), 3.433, 3.487 (2H, ABq, J=12.0 Hz, 1-CH_2), 3.60—3.70 (1H, m, 7-CH), 3.737 (1H, dt, J=4.6, 7.8 Hz, 5-CH), 3.946 (1H, dd, J=7.8, 8.2 Hz, 4-CH), 3.991 (1H, d, J=8.2 Hz, 3-CH), 4.510 (2H, s, CH_2Ph), 7.370 (5H, s, C_6H_5). Minor isomer δ: 1.81—2.15 (2H, m, 6-CH_2), 3.517, 3.560 (2H, ABq, J=12.0 Hz, 1-CH_2), 3.60—3.70 (2H, m, 5,7-CH), 3.785 (1H, dd, J=5.8, 7.2 Hz, 4-CH), 3.993 (1H, d, J=5.8 Hz, 3-CH), 4.510 (2H, s, CH_2Ph), 7.370 (5H, s, C_6H_5). Hi-MS m/z: (a mixture of major and minor products) Calcd for $C_{14}H_{18}O_5$ (M−18) 266.1154. Found: 266.1142.

1,(2*R*):(3*R*,4*R*)-Diisopropylidenedioxy-(5*R*),6-epoxyheptane (10) K_2CO_3 was added to a solution of 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-D-mannitol (**9**)[9] (4.07 g, 9.78 mmol) in MeOH (45 ml) with stirring under ice cooling. The mixture was stirred at room temperature for 7 h. The reaction mixture was diluted with AcOEt, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (5 : 1 and 2 : 1) to give **10** (1.21 g, 4.96 mmol, 51%). NMR (60 MHz) δ: 1.34 (3H, s, CMe), 1.39 (3H × 3, each s, CMe × 3), 2.80 (2H, d, J = 3.6 Hz, 6-CH_2), 3.19 (1H, dt, J = 3.6, 3.6 Hz, 5-CH), 3.6—4.3 (4H, m, 1,2,3,4-CH). MS m/z: 229 (M − O + 1).

1,(2*R*):(3*R*,4*R*)-Diisopropylidenedioxy-(5*R*)-hydroxy-7,7-propylenedithioheptane BuLi (1.67 M, 19.6 ml, 32.7 mmol) was added to a solution of 1,3-dithiane (3.45 g, 28.7 mmol) in THF (30 ml) at −32 °C. The temperature of the mixture was gradually raised to 0 °C. The mixture was cooled again to −70 °C and the mixture of **10** (1.00 g, 4.09 mmol) in THF (10.0 ml) was added to it and stirred for 19 h at room temperature. The reaction mixture was diluted with AcOEt, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) to give a dithioacetal (1.34 g, 3.68 mmol, 90%). NMR (500 MHz) δ: 1.356, 1.362, 1.370, 1.452 (3H × 4, each s, CMe × 4), 1.88—1.94 (2H, m, 6-CH_2), 2.10—2.22 (1H, m, $SCH_2\underline{C}H_2CH_2S$), 2.83—2.96 (5H, m, SCHS, SCH_2 × 2), 3.39 (1H, br s, OH), 3.72—3.76 (3H, m, one of 1-CH_2), 3.976 (1H, dd, J = 5.8, 8.9 Hz, 3-CH), 4.053 (1H, ddt, J = 2.4, 6.1, 6.1 Hz, 5-CH), 4.195 (1H, dd, J = 6.1, 8.9 Hz, 4-CH), 4.356 (1H, dd, J = 4.3, 10.4 Hz, one of 1-CH_2). MS m/z: 364 (M).

1,(2*R*):(3*R*,4*R*)-Diisopropylidenedioxy-(5*R*)-methoxyphenylmethoxy-7,7-propylenedithioheptane (11) NaH (60%, 0.312 g, 7.80 mmol) was washed twice with dry *n*-pentane and suspended in dimethylformamide (DMF) (4 ml). A solution of the dithioacetal (0.948 g, 2.60 mmol) in THF (6 ml) was added dropwise to the suspension at −70 °C. The temperature was gradually raised to room temperature. The mixture was cooled again to −70 °C and MPMCl (1.06 ml, 7.80 mmol) was added with stirring. The temperature was gradually raised to room temperature and stirring was continued for 12 h. MeOH (1 ml) was added dropwise to the reaction mixture under ice cooling and the mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with AcOEt and the organic layer was filtered by suction through Celite. The filtrate was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (7 : 1 and 5 : 1) as an eluent to give **11** (1.20 g, 2.48 mmol, 95%).

1,(2*R*):(3*R*,4*R*)-Diisopropylidenedioxy-6-formyl-(5*R*)-methoxyphenylmethoxyheptane $(CF_3COO)_2IPh$[10] (134 mg, 0.310 mmol) was added to **11** (100 mg, 0.207 mmol) in MeCN (0.45 ml) and water (0.05 ml) under ice cooling. The mixture was stirred at room temperature for 22 min. The reaction mixture was diluted with AcOEt and poured onto saturated $NaHCO_3$ solution. The organic layer was separated and washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent gave the crude aldehyde (82 mg).

1,(2*R*):(3*R*,4*R*)-Diisopropylidenedioxy-7-hydroxy-(5*R*)-methoxyphenylmethoxyheptane $NaBH_4$ (30.0 mg) was added to a solution of the aldehyde (82 mg, 0.207 mmol) in EtOH (2.0 ml) under ice cooling. The mixture was stirred at room temperature for 4.5 h. The reaction mixture was diluted with AcOEt, washed with brine and dried over Na_2SO_4. Removal of the solvent gave a crude alcohol (74.0 mg).

7-Benzyloxy-1,(2*R*):(3*R*,4*R*)-diisopropylidenedioxy-(5*R*)-methoxyphenylmethoxyheptane (12) NaH (60%, 107 mg, 2.62 mmol) was washed twice with dry *n*-pentane and suspended in DMF (16 ml). A solution of the alcohol (345 mg, 0.872 mmol) in THF (5.5 ml) was added dropwise to the suspension under ice cooling. The mixture was stirred for 10 min, then BnBr (0.208 ml, 1.74 mmol) was added portionwise and the whole was stirred at room temperature for 24.5 h. MeOH (3.5 ml) was added portionwise to the reaction mixture under ice cooling and the mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with AcOEt, washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (7 : 1) as an eluent to give **12** (226 mg, 0.465 mmol, 41%). NMR (500 MHz) δ: 1.330, 1.353, 1.353, 1.379 (3H × 4, each s, CMe × 4), 1.85—1.91 (2H, m, 6-CH_2), 3.5—4.2 (cluster of signals, 1,1,2,3,4,5,7,7-CH), 3.748 (3H, s, PhOMe), 4.490 (2H, s, CH_2Ph), 4.587 (1H, d, J = 11.9 Hz, one of CH_2PhOMe), 4.768 (1H, d, J = 11.6 Hz, one of CH_2PhOMe), 6.763 (2H, d, J = 8.7 Hz, CH = C(OMe)CH), 7.113 (2H, d, J = 8.7 Hz, CH = C(Ar)CH), 7.30 (5H, s, C_6H_5). MS m/z: 486 (M), 363 (M − MPM).

7-Benzyloxy-1,(2*R*)-dihydroxy-(3*R*,4*R*)-isopropylidenedioxy-(5*R*)-methoxyphenylmethoxyheptane A solution of **12** (97.2 mg, 0.200 mmol) in AcOH (1 ml) and water (0.5 ml) was stirred at room temperature for 33 h. After removal of the solvent, the residue was developed on pTLC (silica gel) with *n*-hexane–AcOEt (1 : 2) to give a diol (40.9 mg, 0.0908 mmol, 45%) (75% calculated based on consumed **12**) and the recovered **12** (38.0 mg, 0.0782 mmol). MS m/z: 447 (M + 1).

7-Benzyloxy-(2*R*)-hydroxy-(3*R*,4*R*)-isopropylidenedioxy-(5*R*)-methoxyphenylmethoxy-1-triphenylmethyloxyheptane (13) A solution of the diol (13.9 mg, 0.0312 mmol) in DMF (0.2 ml) was added TrCl (10.4 mg, 0.0373 mmol) and Et_3N (8.70 μl, 0.0624 mmol) under ice cooling. The mixture was stirred under ice cooling for 1 h and then at room temperature for 22 h. The reaction mixture was diluted with AcOEt, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with *n*-hexane–AcOEt (1 : 1) to give **13** (5.0 mg, 0.00727 mmol, 23%) (quantitative, calculated based on consumed diol) and the recovered diol (10.7 mg, 0.0240 mmol). **13**: NMR (500 MHz) δ: 1.254, 1.317 (3H × 2, each s, CMe × 2), 1.92—1.97 (2H, m, 6-CH_2), 2.94 (1H, br s, OH), 3.229 (1H, dd, J = 6.7, 9.8 Hz), 3.360 (1H, dd, J = 3.1, 9.8 Hz), 3.573 (2H, ddt, J = 5.5, 7.3, 11.9 Hz, 7-CH_2), 3.691 (1H, dt, J = 4.7, 6.7 Hz), 3.752 (3H, s, OMe), 3.841 (1H, dd, J = 7.3, 7.3 Hz), 4.083 (1H, dd, J = 5.7, 6.7 Hz), 4.435, 4.450 (2H, each s, CH_2Ph), 4.465 (1H, d, J = 11.3 Hz, one of $C\underline{H}_2PhOMe$), 4.529 (1H, d, J = 11.3 Hz, one of $C\underline{H}_2PhOMe$), 6.779 (2H, d, J = 8.5 Hz, $C\underline{H}$ = C(OMe)$C\underline{H}$), 7.189 (2H, d, J = 8.5 Hz, $C\underline{H}$ = C(Ar)$C\underline{H}$), 7.21—7.45 (20H, m, C_6H_5, Tr). MS m/z: 429 (M − TrO), 258 (Tr − 1).

7-*O*-Benzyl-6-deoxy-3,4-*O*-isopropylidene-5-*O*-methoxyphenylmethyl-1-*O*-triphenylmethyl-D-xyloheptulose NaOAc (1.70 mg, 0.0207 mmol) and PCC (44.5 mg, 0.206 mmol) were added to a solution of **13** (47.3 mg, 0.0688 mmol) in CH_2Cl_2 (1 ml) under ice cooling. The mixture was stirred at room temperature for 43.5 h. The reaction mixture was diluted with AcOEt, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with *n*-hexane–AcOEt (1 : 1 × 2) to give a ketone (6.2 mg, 0.00904 mmol, 13%) (18% calculated based on consumed **13**) and the recovered **13** (13.1 mg, 0.0144 mmol). The ketone: IR 1730 cm^{-1}. MS m/z: 561 (M − H_2O − 1).

7-*O*-Benzyl-6-deoxy-3,4-*O*-isopropylidene-1-*O*-triphenylmethyl-D-xyloheptulose (14) DDQ (3.10 mg, 0.0137 mmol) was added to a solution of the ketone (6.2 mg, 0.00904 mmol) in CH_2Cl_2 (0.5 ml) and water (0.025 ml) under ice cooling. The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with AcOEt, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with *n*-hexane–AcOEt (2 : 1) to give **14** (4.3 mg, 0.00760 mmol, 84%). NMR (500 MHz) δ: 1.139, 1.364 (3H × 2, each s, CMe × 2), 1.64—1.73, 1.83—1.91 (2H, m, 6-CH_2), 3.62—3.68, 3.71—3.77 (2H, m, 7-CH), 3.89—3.91 (1H, m, 5-CH), 4.007 (1H, dd, J = 6.6, 6.6 Hz, 4-CH), 4.17, 4.21 (2H, ABq, J = 14.0 Hz, 1-CH_2), 4.328 (1H, d, J = 6.6 Hz, 3-CH), 4.510 (2H, s, CH_2Ph), 7.20—7.50 (20H, m, C_6H_5, Tr).

7-*O*-Benzyl-6-deoxy-D-xyloheptulose (8) A solution of **14** (1.7 mg, 0.0030 mmol) in AcOH (0.6 ml) and water (0.2 ml) was heated at 100 °C for 2 h. After removal of the solvent, the residue was developed on pTLC (silica gel) with AcOEt–MeOH (7 : 1) to give **8** (0.9 mg, 0.0031 mmol, quant.). The NMR spectrum (400 MHz, D_2O major : minor = 3.7 : 1) was the same as that of the product derived from the enzymatic reaction, except for difference in the intensity of signals. Hi-MS m/z: Calcd for $C_{14}H_{18}O_5$ (M − 18) 266.1154. Found: 266.1217.

7-*O*-Benzyl-6-deoxy-2-*O*-methyl-D-xyloheptulose (15a and 15b) A solution of **8** (25.9 mg, 0.0912 mmol) in MeOH (2.5 ml) was stirred at room temperature for 15 h with a small amount of TsOH. The mixture was washed with 10% Na_2CO_3 solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with AcOEt–MeOH (7 : 1) to give **15a** (11.0 mg, 0.0369 mmol, 41%) and **15b** (10.3 mg, 0.0345 mmol, 38%). **15a**: $[\alpha]_D^{26.5}$ +59.7° (c = 1.19, $CHCl_3$). NMR (270 MHz) δ: 1.987 (2H, dt, J = 5.3, 6.3 Hz, 6-CH_2), 3.290 (3H, s, OMe), 3.58—3.87 (5H, m, 1,1,4,7,7-CH), 3.719 (1H, dt, J = 5.0, 8.2 Hz, 5-CH), 4.145 (1H, d, J = 4.3 Hz, 3-CH), 4.518, 4.528, (2H, ABq, J = 11.5 Hz, CH_2Ph), 7.33 (5H, m, C_6H_5). Hi-MS m/z: Calcd for $C_{14}H_{19}O_5$ (M − OMe) 267.1232. Found: 267.1236. **15b**: $[\alpha]_D^{26.5}$ −25.7° (c = 1.07, $CHCl_3$). NMR (270 MHz) δ: 1.92—2.02 (2H, m, 6-CH_2), 3.300 (3H, s, OMe), 3.60—3.70 (4H, m, 1,1,7,7-CH), 3.837 (1H, dt, J = 6.6, 6.9 Hz, 5-CH), 3.959 (1H, dd, J = 6.9, 7.6 Hz, 4-CH), 4.148 (1H, d, J = 7.6 Hz, 3-CH), 4.517 (2H, s, CH_2Ph), 7.33 (5H, s, C_6H_5). Hi-MS m/z: Calcd for $C_{15}H_{22}O_6$ (M) 298.1414. Found: 298.1362; Calcd for

$C_{14}H_{19}O_5$ (M−OMe) 267.1232. Found: 267.1231.

7-*O*-Benzyl-6-deoxy-2-*O*-methyl-1-*O*-(methylthio)thiocarbonyl-D-xyloheptulose (16a) A solution of **15a** (32.2 mg, 0.108 mmol) in THF (2 ml) was added to a suspension of NaH (60%, 3.5 mg, 0.0864 mmol) in THF (0.5 ml) under ice cooling. The ice bath was removed after 3 min and the mixture was stirred at room temperature for 10 min. After cooling with ice, CS_2 (6.5 μl, 0.108 mmol) was added. The ice bath was removed after 3 min and the mixture was stirred at room temperature for 10 min. After further cooling of the mixture with ice, MeI (10.2 μl, 0.162 mmol) was added. The ice bath was removed after 3 min and the mixture was stirred at room temperature for 30 min. Brine was added to stop the reaction and the mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with AcOEt–MeOH (9 : 1) to give **16a** (24.3 mg, 0.0626 mmol, 58%) and a mixture of di-xanthates (4.7 mg, 0.0098 mmol, 9%). **16a**: NMR (500 MHz, D_2O treatment) δ: 1.97—2.12 (2H, m, 6-CH_2), 2.588 (3H, s, SMe), 3.325 (3H, s, OMe), 3.56—4.12 (5H, m, 3,4,5,7,7-CH), 4.509, 4.553 (2H, ABq, J=11.9 Hz, CH_2Ph), 4.833, 4.857 (2H, each s, 1-CH_2), 7.27 (5H, s, C_6H_5). MS m/z: 388 (M), 387 (M−1), 355 (M−MeOH−1).

7-*O*-Benzyl-6-deoxy-2-*O*-methyl-1-*O*-(methylthio)thiocarbonyl-D-xyloheptulose (16b) The isomeric methyl ether **15b** (24.3 mg, 0.0815 mmol) was treated in the same manner as described above to give **16b** (22.1 mg, 0.0570 mmol, 70%) and a mixture of di-xanthates (11.4 mg, 0.0238 mmol, 29%). **16b**: NMR (500 MHz, D_2O treatment) δ: 1.96—2.03 (2H, m, 6-CH_2), 2.571 (3H, s, SMe), 3.359 (3H, s, OMe), 3.56—4.08 (5H, m, 3,4,5,7,7-CH), 4.516, 4.545 (2H, ABq, J=11.4 Hz, CH_2Ph), 4.673, 4.677 (2H, each s, 1-CH_2), 7.32 (5H, s, C_6H_5). MS m/z: 388 (M), 356 (M−MeO−1).

7-*O*-Benzyl-1,6-dideoxy-2-*O*-methyl-D-xyloheptulose (18a) A solution of **16a** (13.2 mg, 0.0340 mmol) in toluene (1.5 ml) was heated at 140 °C for 12 h with n-Bu_3SnH (45.8 μl, 0.170 mmol) in the presence of a small amount of AIBN. After removal of the solvent, the residue was developed on pTLC (silica gel) with AcOEt–MeOH (9 : 1) to give **18a** (8.0 mg, 0.0284 mmol, 83%) and **15a** (2.6 mg, 0.0087 mmol). **18a**: NMR (400 MHz) δ: 1.394 (3H, s, 1-Me), 1.98—2.04 (2H, m, 6-CH_2), 3.278 (3H, s, OMe), 3.60—3.80 (5H, m, 3,4,5,7,7-CH), 4.544, 4.507 (2H, ABq, J=11.7 Hz, CH_2Ph), 7.33 (5H, s, C_6H_5). Hi-MS m/z: Calcd for $C_{14}H_{19}O_4$ (M−OMe) 251.1281. Found: 251.1204. MS m/z: 282 (M), 281 (M−1), 251 (M−OMe), 250 (M−OMe−1).

7-*O*-Benzyl-1,6-dideoxy-2-*O*-methyl-D-xyloheptulose (18b) The isomeric xanthate **16b** (11.0 mg, 0.0284 mmol) was treated in the same manner as described above to give **18b** (7.3 mg, 0.0253 mmol, 89%) and **15b** (0.8 mg, 0.0028 mmol). **18b**: NMR (400 MHz) δ: 1.403 (3H, s, 1-Me), 1.88—2.00 (2H, m, 6-CH_2), 3.267 (3H, s, OMe), 3.58—3.80 (5H, m, 3,4,5,7,7-CH), 4.504, 4.532 (2H, ABq, J=11.9 Hz, CH_2Ph), 7.32 (5H, s, C_6H_5). Hi-MS m/z: Calcd for $C_{14}H_{19}O_4$ (M−OMe) 251.1281. Found: 251.1286. MS m/z: 282 (M), 281 (M−1), 280, 279, 251 (M−OMe), 250 (M−OMe−1).

7-*O*-Benzyl-1,6-dideoxy-2,3,4-*O*-trimethyl-D-xyloheptulose (19a) from 18a A solution of **18a** (3.4 mg, 0.0121 mmol) in THF (0.35 ml) was added to NaH (60%, 1.9 mg, 0.0484 mmol) at −40 °C. MeI (4.5 μl, 0.0726 mmol) was added with stirring. The reaction temperature was gradually raised to 0 °C. Brine was added to stop the reaction and the mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with n-hexane–AcOEt (2 : 1) to give **19a** (1.7 mg, 0.00549 mmol, 45%). NMR (500 MHz) δ: 1.355 (3H, s, Me), 1.90—2.05 (2H, m, 6-CH_2), 3.227, 3.403, 3.417 (3H × 3, each s, OMe × 3), 3.388 (1H, dd, J=2.8, 6.4 Hz, 4-CH), 3.506 (1H, d, J=2.8 Hz, 3-CH), 3.605 (2H, m, 7-CH_2), 3.858 (1H, m, 5-CH), 4.498, 4.530 (2H, ABq, J=12.1 Hz, CH_2Ph), 7.35 (5H, m, C_6H_5). Hi-MS m/z: Calcd for $C_{16}H_{23}O_4$ (M−OMe) 279.1594. Found: 279.1564. MS m/z: 279 (M−OMe).

7-*O*-Benzyl-1,6-dideoxy-2,3,4-*O*-trimethyl-D-xyloheptulose (19b) from 18b The isomeric methyl derivative **18b** (4.8 mg, 0.0170 mmol) was treated in the same manner as described above to give **19b** (4.6 mg, 0.0148 mmol, 87%). NMR (500 MHz) δ: 1.446 (3H, s, Me), 1.93—1.98 (2H, m, 6-CH_2), 3.256, 3.283, 3.305 (3H × 3, each s, OMe × 3), 3.551 (1H, d, J=7.0 Hz, 3-CH), 3.616 (1H, m, one of 7-CH_2), 3.794 (1H, dd, J=5.5, 7.0 Hz, 4-CH), 3.954 (1H, dt, J=5.5, 8.5 Hz, 5-CH), 4.219 (1H, m, one of 7-CH_2), 4.506, 4.542 (2H, ABq, J=6.0 Hz, CH_2Ph), 7.32 (5H, m, C_6H_5). MS m/z: 310 (M), 309 (M−1), 295, 256.

7-Benzyloxy-3,4-dimethoxy-5-hydroxy-2,2-propylenedithioheptane (20) from 19a A solution of **19a** (1.7 mg, 0.00548 mmol) in CH_2Cl_2 (0.35 ml) was cooled to −35 °C and stirred with ethanedithiol (12 μl) until the reaction temperature reached to room temperature in the presence of a small amount of concentrated HCl. The mixture was washed with 10% Na_2CO_3 solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was developed on pTLC (silica gel) with n-hexane–AcOEt (3 : 2) to give **20** (1.6 mg, 0.00415 mmol, 76%). $[\alpha]_D^{24}$ +134° (c=0.04, $CHCl_3$). NMR (500 MHz, D_2O treatment) δ: 1.605 (3H, s, 1-Me), 1.85—1.95 (2H, m, $SCH_2C\underline{H}_2CH_2S$), 1.95—2.10 (2H, m, 6-$CH_2$), 2.55—2.63, 2.69—2.73 (2H × 2, each m, one of SCH_2 × 2), 3.393 (1H, dd, J=3.5, 7.7 Hz, 4-CH_2), 3.421, 3.428 (3H × 2, each s, OMe × 2), 3.500 (1H, d, J=3.5 Hz, 3-CH), 3.55—3.63 (2H, m, 7-CH_2), 4.021 (1H, ddd, J=7.7, 7.7, 7.7 Hz, 5-CH), 4.508 (2H, s, CH_2Ph), 7.34 (5H, m, C_6H_5). Hi-MS m/z: Calcd for $C_{19}H_{30}O_4S_2$ (M) 386.1583. Found: 386.1564.

7-Benzyloxy-3,4-dimethoxy-5-hydroxy-2,2-propylenedithioheptane (20) from 19b The isomeric tri-methyl ether **19b** (3.3 mg, 0.0106 mmol) was treated in the same manner as described above to give **20** (2.0 mg, 0.00518 mmol, 49%). The NMR spectrum (500 MHz, D_2O treatment) was identical with that of the product derived from **19a**. $[\alpha]_D^{25}$ +136° (c=0.05, $CHCl_3$). Hi-MS m/z: Calcd for $C_{19}H_{30}O_4S_2$ (M) 386.1583. Found: 386.1605.

Acknowledgement This study was supported by Special Coordination Funds of the Science and Technology Agency of the Japanese Government. We are indebted to Drs. T. Nakata, K. Horikoshi and T. Akiba of this Institute for their kind suggestions. We also thank Dr. K. Nozaki of Taiho Pharmaceutical Co., Ltd. for giving us his kind information about FDP aldolase.

References and Notes

1) Present address: *Meiji College of Pharmacy, 1-35-23, Nozawa, Setagaya, Tokyo 154, Japan.*
2) Review: E. J. Toone, E. S. Simon, M. D. Bednarski, and G. M. Whitesides, *Tetrahedron*, **45**, 5365 (1989).
3) M. Schultz, H. Waldmann, W. Vogt, and H. Kunz, *Tetrahedron Lett.*, **31**, 867 (1990).
4) T. Nakata, N. Hata, T. Suenaga, and T. Oishi, Abstracts of Papers, 30th Symposium on the Chemistry of Natural Products, Fukuoka, Oct. 1988, p. 540.
5) J. K. N. Jones and J. L. Thompson, *Can. J. Chem.*, **35**, 955 (1957); W. P. Shyluk, J. Honeyman, and T. E. Timell, *ibid.*, **33**, 1202 (1955).
6) T. Iversen and D. R. Bandle, *J. Chem. Soc., Chem. Commun.*, **1981**, 1240; H.-P. Wessel, T. Iversen, and D. R. Bandle, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.
7) J. R. Durrwachter, H. M. Sweers, K. Nozaki, and C. Wong, *Tetrahedron Lett.*, **27**, 1261 (1986).
8) M. D. Bednarsky, E. S. Simon, N. Bischofberger, W. Fessner, M. Kim, W. Lees, T. Saito, H. Waldmann, and G. M. Whitesides, *J. Am. Chem. Soc.*, **111**, 627 (1989); C. H. Osten, A. J. Sinskey, C. F. Barbas, III, R. L. Pederson, Y. Wang, and C. Wong, *ibid.*, **111**, 3924 (1989); A. Straub, F. Effenberger, and P. Fischer, *J. Org. Chem.*, **55**, 3926 (1990).
9) L. F. Wiggins, *J. Chem. Soc.*, **1946**, 13; T. D. Inch, R. V. Ley, and P. Rich, *J. Chem. Soc.*, (*C*), **1968**, 1683; T. D. Inch and G. J. Lewis, *Carbohydr. Res.*, **16**, 455 (1971).
10) G. Stork and K. Zhao, *Tetrahedron Lett.*, **30**, 287 (1989).