A Convenient Synthesis of 6-Hydroxy-7,9-bis(*p*-methoxybenzyl)-5-methylene-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione

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The title compound, the key intermediate for a total synthesis of bicyclomycin, was synthesized from *N,N'*-diacetyl anhydroglycine through twelve steps. The three-carbon branch for the construction of the bicyclic skeleton was introduced to the 2,5-piperazinedione ring as an alkylidene substituent, and then the olefinic function was converted into a diol function. The formation of bicyclic ring was achieved by treatment with *N*-bromosuccinimide followed by the intramoleculer substitution of the primary hydroxyl group in the side chain, and finally the secondary hydroxyl group was converted to the methylene function by an improved Peterson reaction.

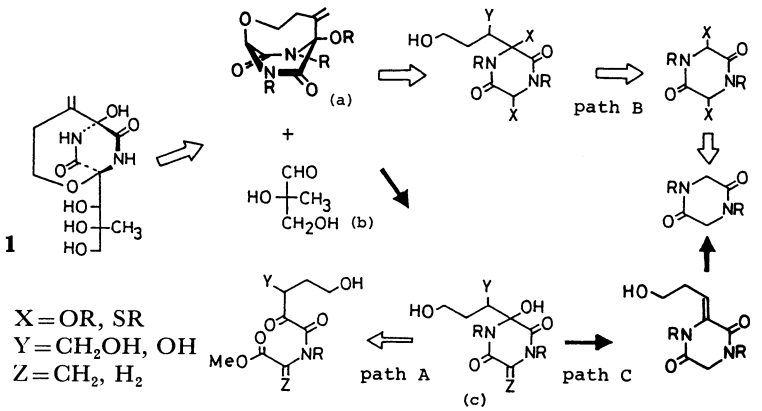
Bicyclomycin (**1**) produced by *Streptomyces sapporonensis*[1] and *S. Aizunensis*[2] from leucine and isoleucine[3] is a member of the large class of naturally occurring 2,5-piperazinediones (PDO) with an unusual structure.[4] Several synthetic efforts have been made for **1**, and both racemic[5] and optically active **1**[6,7] were recently synthesized.

Two strategies have been selected for synthesis of **1**, that is, the introduction of a carbon chain, which is necessary for the bicyclic bridge, before (path A)[8] or after formation of PDO ring (paths B and C). However, no report which reached the final goal through path A has appeared because the reaction steps are rather complicated. In the path B,[9] the substituent X for activation of C-3 and C-6 was used for both the introduction of methylene-branched four-carbon unit and cyclization into the bicyclic key intermediate (a), and it was converted into **1** by the aldol condensation with methyl-branched four-carbon unit (b).[5,6] In our previous communication,[10] the olefinic function of an alkylidene-PDO was oxidized stereoselectively to a diol function (c: Y=OH, Z=H_2), then cyclized by the treatment with *N*-bromosuccinimide (NBS), and finally the secondary hydroxyl group was converted into the methylene group to yield the title compound. This paper describes detailed data of the communication.

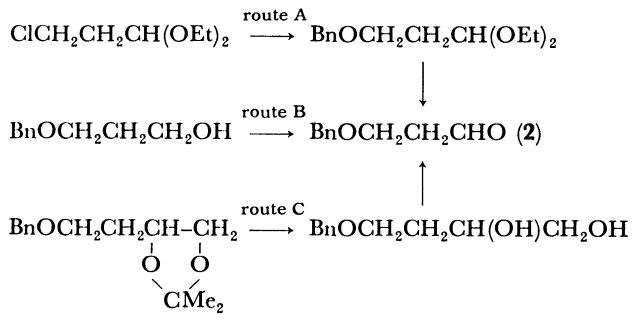
Results and Discussion

First of all, three different synthetic routes of 3-benzyloxypropanal (**2**) which is the three-carbon unit for the construction of bicyclic ring were examined. In the first route, the reaction of benzyl alcohol with 3 equivalents of 3-chloro-1,1-diethoxypropane[11] gave 3-benzyloxy-1,1-diethoxypropane in 71% yield, acidic hydrolysis of which gave **2** in 97% yield (route A). In the second one, oxidation of 3-benzyloxy-1-propanol[12] with chromium trioxide and pyridine gave **2** in 72% yield (route B). In the last one, partial hydrolysis of 4-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol[13] and oxidation of the product with lead tetraacetate gave **2** in 90% overall yield (route C). This route was the most convenient for large scale preparation of **2**.

Then, condensation of *N,N'*-diacetylanhydroglycine with **2** in *N,N*-dimethylformamide (DMF) in the presence of equimolar potassium *t*-butoxide[14] gave only one isomer of 1-acetyl-3-(3-benzyloxypropylidene)-PDO (**3**) in 82% yield, whose configuration was deduced to be *Z* from the fact that its *N*-acetylation with acetic anhydride did not proceed.[15] Oxidation with lead tetraacetate[16] and *m*-chloroperbenzoic acid[8d] which were successful in the case of 3-benzylidene-1,4-dialkyl-PDO and 3-alkylidene-1,4-dialkyl-PDO could



Scheme 1. Retro-synthesis of bicyclomycin



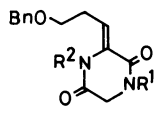
Scheme 2. Syntheses of 3-benzyloxypropanal (**2**)

not be applied to **3**, probably due to the electron-withdrawing effect of *N*-acetyl group. Reaction of **3** with osmium tetraoxide and sodium chlorate[17a] gave the corresponding diol (**6**) in 58% yield, but, the use of *N*-methylmorpholine-*N*-oxide[17b] or hydrogen peroxide[17c] as the cooxidant gave poor results. An osmium oxidation of 3-(3-benzyloxypropylidene)-1,4-bis(*p*-methoxybenzyl)-PDO (**5**) which was prepared from **3** *via* *N*-deacetylated product (**4**) in 72% overall yield, gave **7** in 46% yield, in which a partial oxidative *N*-de(*p*-methoxybenzyl)ation was deduced by the formation of *p*-anisaldehyde.

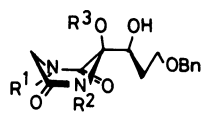
Isopropylidenation of the diol function in **6** with 2-methoxypropene–pyridinium *p*-toluenesulfonate in acetone gave the desired product (**9a**) and its 3-epimer (**9b**) in 95 and 2% yield, respectively. In this reaction, the suspended **6** dissolved by addition of a small amount of acetone within 5 min and then **9a** deposited from the reaction mixture. In a similar way, **7** was converted into the *O*-isopropylidene derivative (**12**) in 94% yield. However, the isopropylidenation of **6** with 2,2-dimethoxypropane–*p*-toluenesulfonic acid gave a 1:2 mixture of **9a** and partial *O*-methylation product (**8**) in 94% yield. The formation of **8** indicates the acid-catalyzed substitution of the tertiary hydroxyl group of **6** with methanol liberated by acetal exchange. On the other hand, the reaction of **6** with acetone-anhydrous copper(II) sulfate and acetone–acid (*p*-toluenesulfonic acid or sulfuric acid) gave negative and complex results, respectively.

On the other hand, mono(*p*-methoxybenzyl)ation of deacetylated derivative (**10**), which was obtained quantitatively by treatment of **9a** with hydrazine, with equimolar sodium hydride and *p*-methoxybenzyl bromide gave **11** in 87% yield. A further *p*-methoxybenzylation of **11** gave **12** in 76% yield, together with a enol ether (**18**: 11%). When *p*-methoxybenzyl chloride instead of the bromide is used, a 1:1 mixture of **12** and **18** was formed. The yield of one step synthesis of **12** from **10** was 62%. Hydrogenolysis of **9a** in methanol in the presence of palladium–carbon gave the *O*-debenzylated product (**13**) in 75% yield. This conversion could be also achieved by treatment of **9a** with equimolar NBS to afford **13** and *O*-benzoylated by-product (**14**) in 92 and 6% yields, respectively. A similar reduction of **11** or **18** and **12** gave the same **15** and **16** in quantitative yields, respectively. Compound **16** was also obtained from **15** by successive *p*-methoxybenzylation (**17**) and hydrogenolysis.

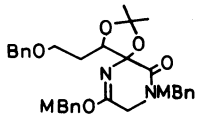
Cyclization of **16** in chloroform with 1.1 equimolar NBS[8b] and excess barium carbonate at room temperature for 4 d gave the corresponding bicyclic derivative (**19**) in 86% yield. The use of 2 equimolar NBS gave **19** in only 11% yield, due to the oxidation of *p*-methoxybenzyl groups. The same reaction without barium carbonate for 24 h gave **19**, the corresponding spiro cyclic compound (**21**), starting material (**16**) in 12, 63, and 7% yields, respectively. However, a similar reaction of **15** for 24 h in the presence of barium carbonate gave the corresponding bicyclic (**20**), spiro (**22**), and recovered **16** in 30, 16, and 42% yields, respectively. The structures of spiro derivatives, **21** and **22**, were proved by conversion into acetates, **23a**,



3: R^1=Ac, R^2=H
4: R^1=R^2=H
5: R^1=R^2=MBn



6: R^1=Ac, R^2=R^3=H
7: R^1=R^2=MBn, R^3=H
8: R^1=Ac, R^2=H, R^3=Me



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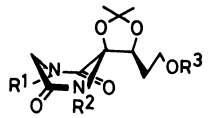
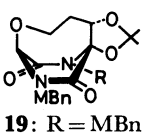
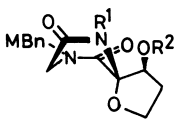


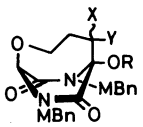
9a: R^1=Ac, R^2=H, R^3=Bn
9b: 3-epimer of **9a**
10: R^1=R^2=H, R^3=Bn
11: R^1=MBn, R^2=H, R^3=Bn
12: R^1=R^2=MBn, R^3=Bn
13: R^1=Ac, R^2=R^3=H
14: R^1=Ac, R^2=H, R^3=Bz
15: R^1=MBn, R^2=R^3=H
16: R^1=R^2=MBn, R^3=H
17: R^1=R^2=R^3=MBn



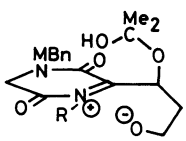
19: R=MBn
20: R=H



21: R^1=MBn, R^2=H
22: R^1=R^2=H
23a: R^1=MBn, R^2=Ac
23b: 5-epimer of **23a**
24: R^1=H, R^2=Ac



29: R=X=H, Y=OH
30: R=H, X, Y=O
31: R=H, X=OH, Y=CH_2TMS
32: R=H, X, Y=CH_2
33: R=TBS, X, Y=CH_2



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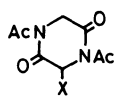
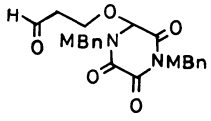


26: X=Br
27: X=OAc
28: X=SAc



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23b, and **24**, respectively. Compounds **23a** and **23b** were an epimeric pair of spiro configuration. The formation of spiro derivatives accompanied with *O*-deisopropylidenation may be the acid-assisted formation of iminium (**25**) or imino intermediate. An attempted similar reaction of **13** did not proceed and the starting material was recovered, probably due to electron-withdrawing effect of *N*-acetyl group. Considering that the reaction of *N,N'*-diacetylanhydroglycine with equimolar NBS and successive treatment of the unstable monobromo derivative (**26**) with sodium acetate or potassium thioacetate gave the corresponding 2-substituted PDO (**27** and **28**) in 71 and 68% yields, respectively, the difference in the reactivity between **13** and *N,N'*-diacetylanhydroglycine may be attributed to the absence and presence of a resonance system in the PDO-ring.

Then, the treatment of **19** with a 1:1 mixture of 2 M (M=mol dm^{-3}) hydrochloric acid and tetrahydrofuran (THF) at 40 °C for 24 h gave the corresponding *O*-deisopropylidenated product (**29**) in 83% yield. The reaction with 70% acetic acid at an elevated temperature or with trifluoroacetic acid at room temperature gave a complex result. The selective oxidation of the secondary hydroxyl group of **29** with dimethyl sulfoxide-oxalyl dichloride[18] gave the desired 5-oxo compound (**30**) in 91% yield, while oxidation with pyridinium chlorochromate gave an undesired ring-cleavaged compound **34** in 61% yield. Direct conversion of carbonyl function of **30** into methylene group with the Witting reagent $Ph_3P{=}CH_2$, methylenedimagnesium dibromide,[19] and Tabbe reagent $Cp_2TiCH_2AlClMe_2$[20] could not be performed. Therefore, an improved Peterson reaction as stepwise conversion was used for this purpose. Addition of trimethylsilylmethylmagnesium chloride to **30** gave the addition product (**31**) in 52% yield, as a 4:1 mixture of diastereomers. However, the next elimination reaction did not proceed under the usual conditions,[21] and barely the treatment with 0.08 M sulfuric acid in THF at room temperature for 3 d gave the methylene derivative (**32**) in 48% yield. Because an activation method by introduction of *O*-sulfonyl or halogen function[21] can not be used in this case, the elimination was accomplished by treatment of 5,6-ditrifluoroacetate of **31** with tetrabutylammonium fluoride followed by removal of the remaining trifluoroacetyl group at *O*-6 to give **32** in 81% yield. Treatment of **32** with *t*-butyldimethylsilyl triflate[22] gave the corresponding 6-*O*-protected derivative (**33**) in 80% yield.

^{1}H NMR data of 6-substituted PDO, spiro cyclic and bicyclic derivatives, and ^{13}C NMR data of 6-substituted PDO are summarized in Tables 1—4, respectively.

Among *O*-isopropylidene derivatives (Table 1), the chemical shift of H-1' protons of **9a** is lower than that of **9b** by 0.78 ppm. This phenomenon indicates that the carbonyl group in PDO ring and H-1' of **9a** are in *cis*-relation in regard with the isopropylidene ring. It is interesting that the difference in the chemical shift of two methyl protons of isopropylidene group in 4-(*p*-methoxybenzyl)-PDO (**12**, **16**, and **17**) is commonly 0.22 ppm, whereas those in others are within 0.07 ppm. These facts support that the mono(*p*-methoxybenzyl)-ation of **10** occurred selectively at the farer nitrogen from oxolane-ring to give 1-substituted product (**11**). The lower chemical shift of methylene protons of *O*-(*p*-methoxybenzyl) group and singlet signal of methyl protons of isopropylidene group in **18** prove the enol ether structure. Some of above-mentioned observations are also supported from ^{13}C NMR data (Table 4). In a comparison of ^{13}C NMR chemical shifts for **9a** and **9b** the larger differences were observed for C-1' and acetyl carbon. The lower field shift of C-3 and C-1' in 4-substituted derivatives (**12** and **16**) may be due to the anisotropic effect of the 4-(*p*-methoxybenzyl) group. In the case of **18**, the enolated carbonyl carbon shifted markedly to the upper field, whereas C-6 resonates in slightly higher field.

Spiro cyclic (Table 2) and bicyclic derivatives (Table 3) can be easily distinguished from the appearance of an AB-quartet of H-8a and H-8b and of a singlet of H-1, respectively, and the large coupling of the former is characteristic to H-6 of original PDO-ring. The absence and the presence of isopropylidene protons also support their structures. Moreover, it is characteristic that one of methylene protons at C-3 of the bicyclic derivatives resonated at extraordinary higher field than the other proton at C-3 as well as the corresponding methylene protons of spiro cyclic derivatives, which indicates the diamagnetic anisotropy in the perpendicular direction of the PDO-ring.

In the cases of **23a** and **23b**, a larger difference was observed in the chemical shift of H-4 protons, indicating that H-4 and carbonyl group in PDO-ring of **23a** are in *cis*-relation in regard with the five-membered ring. The configuration of **24** is probably similar to that of **23a**. The presence of sp^2 C-5 carbon in **30** and **33** in clearly shown by ^{13}C NMR (see Experimental).

Experimental

General. Melting points were determined with a Mel-Temp apparatus or with a Yanagimoto micro melting-point apparatus, and were not corrected. IR spectra (cm^{-1}) were recorded with a Hitachi EPI-G2 grating spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JMN PS-100 and a JEOL FX-90Q spectrometers, respectively, in $CDCl_3$ with tetramethylsilane as the internal standard, unless otherwise noted. Column chromatography was performed on Wakogel C-200 or C-300.

Preparation of 3-Benzyloxypropanal (2). a) A mixture of 3-chloro-1,1-diethoxypropane (257 g, 1.54 mol), benzyl alcohol (55.5 g, 0.513 mol), sodium hydroxide (103 g, 2.57 mol), and tetrabutylammonium hydrogensulfate (17.4 g, 0.051 mol) in saturated sodium chloride (410 cm^3) was vigorously stirred at 60 °C for 12 h and then at 100 °C for 48 h, poured into ice-water, and extracted with benzene. The usual processing of

Table 1. ^{1}H NMR data of 6-substituted 2,5-piperazinedione derivatives

Compound	H-6a ($J_{6a,6b}$)	H-6b	H-1′ ($J_{1',2'}$)	H-2′	H-3′ ($J_{2',3'}$)	CMe_2	Others
3	—4.36s—		6.32t (8.0)	2.6—2.3m	3.59t (5.2)	—	9.30bs(NH), 7.23s(Ph), 4.52s(CH_2 in Bn), 2.59s(Ac)
5	—3.82s—		6.29t (7.5)	2.51dt	3.54t (7.0)	—	7.28s(Ph), 7.18d, 6.90d, 6.98d and 6.71d(8H, J=8.0 Hz, 2×MBn), 4.86s, 4.51s and 4.46s(3×CH_2 in Bn and MBn), 3.72s and 3.71s (2×OMe)
6	4.50d (17.8)	4.22d	4.4—4.1m	2.0—1.5m	3.66t (5.0)	—	7.70bs(NH), 7.36s(Ph), 4.77bs and 2.55bs(2×OH), 4.49s(CH_2 in Bn), 2.54s(Ac)
7	4.21d (17.5)	3.64d	4.44t (7.5)	2.2—1.5m	3.9—3.5m	—	7.28s(Ph), 7.32d, 7.09d and 6.74d(8H, J=8.5 Hz, 2×MBn), 5.04bs and 1.96bs(2×OH), 4.75d, 4.31d and 4.4—3.5m(J=14.0 Hz, 2×CH_2 in MBn), 4.46s (CH_2 in Bn), 3.73s(6H, 2×OMe)
8	—4.38s—		4.17dd (8.0,4.0)	2.1—1.7m	3.9—3.4m	—	7.31s(Ph), 7.14s(NH), 4.51s(CH_2 in Bn), 3.37s (OMe), 2.62s(Ac), 2.21bs(OH)
9a	4.46d (18.0)	4.04d	5.00t (6.4)	2.2—1.9m	3.8—3.5m	1.49s 1.44s	7.40s(NH), 7.29s(Ph), 4.51d and 4.37d(J=12.0 Hz, CH_2 in Bn) 2.48s(Ac)
9b	4.36d (18.5)	4.06d	4.22 (6.0)	2.4—2.1m	3.8—3.4m	1.50s	7.82s(NH), 7.26s(Ph), 4.43s(CH_2 in Bn), 2.49s(Ac)
10[a]	3.94d (18.0)	3.54d	4.88 (6.5)	2.1—1.8m	3.7—3.5m	1.49s 1.47s	7.40s(Ph), 7.40bs and 6.44bs(2×NH), 4.46s(CH_2 in Bn)
11	3.92d (18.0)	3.62d	5.04t (6.4)	1.96ddt	3.62dd (2.4,6.4)	1.42s	7.80s(NH), 7.41s(Ph), 7.16d and 6.89d(4H, J=8.0 Hz, MBn) 4.47s(CH_2 in Bn), 4.65d and 4.10d(J=14.4 Hz, CH_2 in MBn)
12	—3.83s—		4.80t (6.6)	1.82dt	3.62t (6.0)	1.75s 1.53s	7.40s(Ph), 7.29d, 6.85d, 7.21d and 6.85d(8H, J=8.5 Hz, 2×MBn), 4.88d, 4.46d, 4.56d and 4.42d(J= 15.6 and 14.0 Hz, 2×CH_2 in MBn), 4.46s(CH_2 in Bn), 3.78s(2×OMe).
13	4.74d (18.8)	4.10d	5.01t (7.2)	2.2—1.9m	3.9—3.7m	1.54s 1.48s	7.68bs(NH), 2.28bs(OH), 2.62s(Ac)
14	4.69d (18.0)	4.04d	5.05t (7.0)	2.3—2.0m	4.28t (6.0)	1.49s 1.42s	8.05—7.8m(2H, Bz), 7.6—7.0m(4H, NH and Bz), 2.46s(Ac)
15	3.97d (18.0)	3.80d	5.01t (6.8)	2.1—1.7m	3.73t (6.0)	1.46s	8.07s(NH), 7.10d and 6.84d(4H, J=8.0 Hz, MBn), 4.56d and 4.52d (J=14.0 Hz, CH_2 in MBn), 3.79s (OMe), 2.88bs(OH)
16	—3.86s—		4.74t (5.6)	2.2—1.6m	3.9—3.6m	1.73s 1.52s	7.26d, 6.82d, 7.18d and 6.77d(8H, J=8.0 Hz, 2×MBn), 4.87d, 4.42d, 4.74d and 4.37d(J=14.5 and 14.5 Hz, 2×CH_2 in MBn) 3.78s and 3.75s(2×OMe), 2.25bs(OH)
17	—3.82s—		4.72t (7.0)	1.9—1.6m	3.54t (6.0)	1.73s 1.51s	7.26d, 6.86d, 7.20d, 6.78d, 7.12d and 6.78d(12H, J=8.5 Hz, 3×MBn), 4.82d, 4.40d, 4.52d and 4.31d(J =14.5 and 14.0 Hz, 2×CH_2 in NMBn), 4.36s(CH_2 in OMBn), 3.75s(9H, 3×OMe)
18[b]	3.86d (18.4)	3.56d	4.90t (6.5)	2.0—1.6m	3.57dd (6.2,2.5)	1.57s	7.37s(Ph), 7.36d, 6.94d, 7.20d and 6.88d(8H, J=8.5 Hz, 2×MBn), 5.16s(CH_2 in OMBn), 4.44s (CH_2 in Bn), 4.68d and 4.24d(J=13.8 Hz, CH_2 in NMBn), 3.83s and 3.80s(2×OMe)

a) Measured in DMSO-d_6. b) The same numbering of carbon skeleton as those of PDO derivative is used.

Table 2. ^{1}H NMR data of spiro cyclic derivatives

Compound	H-8a ($J_{A,B}$)	H-8b	H-4 ($J_{3a,4}$)	H-3a	H-3b ($J_{3b,4}$)	H-2 ($J_{3a,3b}$)	Others
23a	3.92d (18.0)	3.69d	5.50dd (7.0)	2.60m (6.0)	2.20m (12.0)	4.6—4.2m	7.34d, 6.85d, 7.20d, and 6.81d(8H, J=8.5 Hz, 2×MBn), 4.79d, 4.09d, 4.61d and 4.49d(J=14.0 and 14.5 Hz, 2×CH_2 in MBn), 3.77s and 3.72s (2×OMe), 2.08s(Ac)
23b	3.98d (18.5)	3.76d	5.05t (7.5)	2.5—2.2dt		4.6—4.2m	2.27d, 6.85d, 7.22d, and 6.82d(8H, J=8.0 Hz, 2×MBn), 4.95d, 4.13d, 4.63d and 4.41d(J= 14.5 Hz, 2×CH_2 in MBn), 3.82s (2×OMe), 1.79s (Ac)
24	3.98d (18.0)	3.77d	5.72dd (7.0)	3.0—2.5m (4.2)	2.3—1.9m	4.2—3.8m	7.23d and 6.91d(4H, J=8.0 Hz, MBn), 6.9bs (NH), 4.59d and 4.56d(J=14.0 Hz, CH_2 in MBn), 3.81s(OMe), 2.11s(Ac)

TABLE 3. ^{1}H NMR DATA OF BICYCLIC DERIVATIVES

Compound	H-1	H-5 ($J_{5,4a}$)	H-4a,b ($J_{5,4b}$)	H-3a ($J_{3a,4}$)	H-3b ($J_{3a,3b}$) ($J_{3b,4}$)	Others
19	5.19s	4.18dd (10.8)	2.4—1.6m (3.8)	4.02ddd (1.4,8.0)	3.31ddd (13.5) (9.0,1.4)	7.25d, 6.82d, 7.25d and 6.80d(8H, J=8.0 Hz, 2×MBn), 4.93d, 4.30d 4.84d and 4.30d(J=14.0 Hz, 2×CH_2 in MBn), 3.79s and 3.76s (2×OMe), 1.72s and 1.66s(2×CMe)
20	5.09s	4.13dd (10.4)	2.4—1.8m (5.0)	3.98ddd (2.0,6.0)	3.31ddd (14.0) (9.0,1.8)	7.26d and 6.82d(4H, J=8.4 Hz, MBn), 6.9bs(NH), 4.87d and 4.18d(J=14.2 Hz, CH_2 in MBn), 3.80s (OMe), 1.56s (2×CMe)
29	5.20s	4.1—3.6m	2.4—1.5m	4.1—3.6m	3.21dd (13.8) (9.6)	7.26d, 6.78d, 7.26d and 6.74d(8H, J=8.0 Hz, 2×MBn), 5.19bs(OH) 4.90d, 4.51d, 4.82d and 4.30d(J=14.0 Hz, 2×CH_2 in MBn), 3.80s and 3.78s(2×OMe)
30	5.40s	—	2.3—2.1m	3.9—3.6m	3.19ddd (13.5) (7.0,4.0)	7.26d, 6.79d, 7.17d and 6.70d (8H, J=8.0 Hz 2×MBn), 5.34bs(OH) 5.04d, 4.36d, 4.90d and 4.19d(J=13.6 and 14.2 Hz, 2×CH_2 in MBn) 3.82s and 3.77s(2×OMe)
32	5.24s	—	2.3—2.1m	3.9—3.7m	3.4—3.1m	7.36d, 6.84d, 7.28s and 6.76d(8H, J=8.0 Hz, 2×MBn), 5.59s and 5.08s(olefinic), 5.00bs(OH), 4.90d, 4.20d, 4.61d and 4.43d(J=14.0 and 14.5 Hz, 2×CH_2 in MBn), 3.81s and 3.78s(2×OMe)
33	5.15s	—	2.4—1.6m	3.8—3.5m	3.4—3.2m	7.26d, 6.73d, 7.22d and 6.84d(8H, J=8.5 Hz, 2×MBn), 5.55s and 5.03s(olefinic), 5.15d, 3.97d, 4.77 and 4.61d (J=14.0 Hz, 2×CH_2 in MBn), 3.81s and 3.77s(2×OMe), 0.92s, 0.42s and 0.15s(TBS)

TABLE 4. ^{13}C NMR DATA OF 6-SUBSTITUTED 2,5-PIPERAZINEDIONE DERIVATIVES

Compound	C-6	C-3	C-3′	C-2′	C-1′	C-2 and 5	Others
9a[a]	46.3t	88.7s	72.6t	28.5t	78.7d	165.4s, 167.1s	172.0s and 28.5q(Ac), 139.0s, 129.0d, 128.0d and 127.9d(aromatic), 110.8s, 27.5q and 26.0q(Ip), 67.3t(OCH_2)
9b[a]	46.3t	89.5s	72.9t	29.4t	80.8d	166.1s, 166.5s	172.2s, 26.9q(Ac), 138.9s, 129.0d and 128.3d (aromatic), 111.0s and 27.4q(Ip) 67.3t (OCH_2)
11	48.6t	87.2s	72.8t	28.8t	78.9d	162.2s, 167.1s	159.4s, 138.1s, 129.8d, 128.4d, 127.4d, 126.9s and 114.2d(aromatic), 110.3s, 27.9q and 25.2q(Ip), 66.8t(OCH_2), 55.2q(OMe) 49.2t (NCH_2)
12	47.0t	93.2s	73.1t	29.8t	82.5d	163.3s, 164.5s	159.4s, 158.4s, 137.9s, 129.8d, 129.1s, 128.7d, 128.4d, 127.7d, 127.6d, 126.7s, 114.3d and 113.5d(aromatic), 111.9s, 26.1q and 25.1q(Ip) 66.9t(OCH_2), 55.1q(2×OMe) 49.4t and 48.5t (2×NCH_2)
16	47.0t	93.2s	59.6t	31.6t	83.0d	163.4s, 164.5s	159.4s, 158.3s, 129.8d, 129.0s, 128.6d, 126.6s, 114.2d and 113.4d(aromatic), 112.0s, 26.0q and 25.1q(Ip), 55.1q and 55.0q(2×OMe) 49.5t, 48.5t(2×NCH_2)
18[c]	45.5t	89.5s	73.0t	29.3t	80.7d	164.8s, 159.2s[b]	159.7s[b], 159.5s[b], 138.5s, 130.2d, 129.9d, 128.4d, 128.3s, 127.6d, 127.4s, 114.3d and 114.0d(aromatic), 110.5s, 28.5q and 26.1q(Ip), 67.7t(2×OCH_2) 55.3q (2×OMe), 49.2t(NCH_2)

a) Measured in DMSO-d_6. b) The Assignment may be exchanged. c) The same numbering of carbon skeleton as those of PDO derivative is used.

the extract gave a crude oil which was purified by distillation to give colorless oily 3-benzyloxy-1,1-diethoxypropane (86.2 g, 71%). Bp 118—120 °C/11 Torr[†]; ^{1}H NMR: δ=7.72 (s, 5H, Ph), 4.69 (t, 1H, $J_{1,2}$=6.0 Hz, H-1), 4.49 (s, 2H, CH_2Ph), 3.85—3.3 (m, 6H, H-3 and 2×OCH_2 in Et) 1.93 (dt, 2H, $J_{2,3}$=6.0 Hz, H-2), 1.19 (t, 6H, J=7.5 Hz, 2× Me in Et). A solution of the above oil (30.0 g, 126 mmol) in acetone (60 cm^3) and 1 M hydrochloric acid (60 cm^3) was stirred at room temperature for 3 h, evaporated to a half volume, and extracted with chloroform. The usual processing of the extract and distillation of the product gave **2** (20.0 g, 97%). Bp 71—74 °C/1.3 Torr, IR: 1720 (C=O), ^{1}H NMR: δ=9.72 (t, 1H, $J_{1,2}$=2.0 Hz, H-1), 7.32 (s, 5H, Ph), 4.52 (s, 2H, CH_2Ph), 3.78 (t, 2H, $J_{2,3}$=6.0 Hz, H-3), 2.56 (dt, 2H, H-2).

Found: C, 73.09; H, 7.20%. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.34%.

b) A mixed solution of chromium trioxide (55.0 g, 550 mmol) and pyridine (90 cm^3) in dry dichloromethane (1.1 dm^3) was vigorously stirred at room temperature for 30 min, 3-benzyloxy-1-butanol (15.2 g, 92.0 mmol) was added dropwise to it, then stirred for 2 h, and filtered. After the usual

[†] 1 Torr≈133.322 Pa.

work-up, the rough product was passed through a short silica-gel column, and purified by distillation to give **2** (10.9 g, 72%).

c) A mixed solution of 4-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol (112 g, 0.474 mol) in dioxane (400 cm^3) and 1 M hydrochloric acid (400 cm^3) was kept at room temperature for 12 h, poured into ice-water, and then extracted with dichloromethane. The usual processing of the extract gave a crude syrupy 4-benzyloxy-1,2-butanediol. ^1H NMR: δ=7.33 (s, 5H, Ph), 4.52 (s, 2H, CH_2Ph), 4.2—3.4 (m, 5H, H-1, 2, and 4), 3.2 and 2.6 (each bs, 2H, 2×OH), 1.9—1.6 (m, 2 H, H-3). To a solution of the above syrup in benzene (900 cm^3) was added lead tetraacetate (280 g, 0.576 mol) with stirring, the mixture was kept for 12 h at room temperature, and then filtered. The filtrate was poured into water and extracted with ethyl acetate. The usual processing of the extract and distillation of the oily product gave colorless **2** (69.8 g, 90%).

1-Acetyl-3-(3-benzyloxypropylidene)-2,5-piperazinedione (3). To a solution of 1,4-diacetyl-PDO (20.0 g, 101 mmol) and **2** (21.5 g, 131 mmol) in *N,N*-dimethylformamide (DMF, 80 cm^3) was added dropwise a solution of potassium *t*-butoxide (11.8 g, 106 mmol) in *t*-butyl alcohol (212 cm^3) at 0 °C with stirring, and the mixture was kept at 0 °C for 2 h and at room temperature for 12 h, neutralized with acetic acid and poured into ice-water. The crystals formed were filtered and recrystallized from ethanol–ether to give **3** (25.0 g, 82%) as prisms. Mp 119 °C; IR: 3180 (NH), 1715 (Ac), 1680 (amide), 1640 (C=C).

Found: C, 63.85; H, 5.83; N, 9.27%. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27%.

*3-(3-Benzyloxypropylidene)-1,4-bis-(*p*-methoxybenzyl)-2,5-piperazinedione (5).* To a solution of **3** (5.0 g, 16.6 mmol) in DMF (20 cm^3) was added 70% hydrazine hydrate (2.37 g, 33.2 mmol) at 0 °C, and the mixture was kept at 0 °C for 3 h, poured into ice-water. The *N*-deacetylated product (**4**) deposited (4.32 g) was filtered and dried. To a suspension of sodium hydride in DMF was added dropwise a solution of **4** in DMF (50 cm^3) at 0 °C with stirring, and after 2 h, *p*-methoxybenzyl bromide (7.67 g, 38.2 mmol) was further added dropwise. The reaction mixture was stirred for 2 h at 0 °C and for 12 h at room temperature, neutralized with acetic acid, poured into ice-water, and then extracted with ethyl acetate. The usual work-up of the extract gave a crude syrup, which was purifield on a silica-gel column (hexane–ethyl acetate 7:3) to give colorless syrupy **5** (5.97 g, 72%).

Found: C, 71.72; H, 6.58; N, 5.52%. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60%.

Oxidation of 3 and 5 with Osmium Tetraoxide. To a solution of **3** (7.40 g, 24.5 mmol) in dioxane (120 cm^3) was added a solution of sodium chlorate (10.4 g, 98.0 mmol) in water (30 cm^3) and osmium tetraoxide (62 mg, 0.24 mmol) with stirring. After 3 days at room temperature, the reaction mixture was evaporated to a half volume, poured into water, and then extracted with chloroform. The usual work-up of the extract gave a crude syrup, which was crystallized from ethyl acetate–ether to give 1-acetyl-3-(3-benzyloxy-1-hydroxypropyl)-3-hydroxy-PDO (**6**) as colorless prisms. Purification of the residue obtained from the filtrate on a silica-gel column (dichloromethane–acetone 4:1) gave the second crops of **6** as a monohydrate. Total yield of **6** was 5.04 g (58%). Mp 92 °C, IR: 3250 (OH, NH), 1735 (Ac), 1710, and 1680 (amide).

Found: C, 54.10; H, 6.41; N, 7.75%. Calcd for $C_{16}H_{20}N_2O_6 \cdot H_2O$: C, 54.23; H, 6.26; N, 7.91%.

A similar oxidation of **5** (380 mg, 0.759 mmol) gave a crude syrup, which was crystallized from acetone–ether to give 3-(3-benzyloxy-1-hydroxypropyl)-3-hydroxy-1,4-bis(*p*-methoxybenzyl)-PDO (**7**) as colorless prisms in 46% (187 mg) yield. Mp 140—141 °C; IR: 3450 (OH), 1665 (amide).

Found: C, 66.92; H, 6.48; N, 5.27%. Calcd for $C_{30}H_{34}N_2O_7$: C, 67.40; H, 6.41, N, 5.24%.

Isopropylidenation of 6 and 7. Method A: To a suspension of dried **6** (3.90 g, 11.6 mmol) in acetone (16 cm^3) was added 2-methoxypropene (9.6 cm^3) and catalytic amount of pyridinium *p*-toluenesulfonate with stirring. Compound **6** once dissolved within 5 min and new precipitate deposited after 15 min. After keeping the mixture for 24 h at room temperature, the precipitate was filtered and recrystallized from chloroform–ether to give 1-acetyl-3-(3-benzyloxy-1-hydroxy propyl)-3-hydroxy-3,1′-*O*-isopropylidene-PDO (**9a**) as colorless prisms. The residue from the filtrate was purified on a silica-gel column (chloroform–acetone 9:1) to give **9a** and its 3-epimer (**9b**).

9a: yield, 4.15 g (95%). Mp 151 °C, IR: 3200 (NH), 1730sh (Ac), 1710, and 1685 (amide).

9b: yield, 92 mg (2.1%), mp 138—140 °C (prisms from chloroform–ether).

Found for **9a**: C, 60.52; H, 6.42; N, 7.23%, and for **9b**: C, 60.73; H, 6.51; N, 7.30%. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.62; H, 6.43; N, 7.44%.

Method B: To a solution of **6** (500 mg, 1.45 mmol) in acetone (20 cm^3) was added 2,2-dimethoxypropane (1 cm^3) and catalytic amount of *p*-toluenesulfonic acid with stirring at room temperature. After 12 h, the reaction mixture was neutralized with pyridine, and evaporated. The residue was separated on a silice-gel column (chloroform–acetone 9:1) to give **9a** (169 mg, 31%) and syrupy 1-acetyl-3-(3-benzyloxy-1-hydroxypropyl)-3-methoxy-PDO (**8**: 343 mg, 63%).

Found: C, 58.06; H, 6.21; N, 7.89%. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.33; N, 8.00%.

A similar treatment of **7** (3.90 g, 7.30 mmol) by the method A, and purification of the product on a silica-gel column (hexane–ethyl acetate 4:1) gave 3-(3-benzyloxy-1-hydroxypropyl)-3-hydroxy-3,1′-*O*-isopropyridene-1,4-bis(*p*-methoxybenzyl)-PDO (**12**: 3.92 g, 94%). Mp 131 °C (prisms from ether–hexane).

Found: C, 68.68; H, 6.69; N, 4.84%. Calcd for $C_{33}H_{38}N_2O_7$: C, 68.97; H, 6.67; N, 4.88%.

3-(3-Benzyloxy-1-hydroxypropyl)-3-hydroxy-3,1′-O-isopropylidene-2,5-piperazinedione (10). A solution of **9a** (530 mg, 1.41 mmol) in DMF (5 cm^3) and 70% hydrazine (0.20 cm^3) was stirred at 0 °C for 3 h, and poured into ice-water. The precipitate deposited was filtered and recrystallized from methanol–ether to give **10** (470 mg, 99%) as colorless needles of mp 164 °C.

Found: C, 60.86; H, 6.54; N, 8.25%. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38%.

p-*Methoxybenzylation of 10, 11, and 15.* The reaction procedure is exemplified by the preparation of 3-(3-benzyloxy-1-hydroxypropyl)-3-hydroxy-3,1′-*O*-isopropylidene-1-(*p*-methoxybenzyl)-PDO (**11**). To a suspension of 50% sodium hydride (316 mg, 6.58 mmol) in DMF (50 cm^3) was added dropwise a solution of **10** (2.0 g, 5.98 mmol) in DMF (20 cm^3) at 0 °C with stirring. After keeping the conditions for 1 h, *p*-methoxybenzyl bromide (1.44 g, 7.16 mmol) was further added. The mixture was stirred at 0 °C for 2 h and then

at room temperature for 12 h, neutralized with acetic acid, poured into ice-water, and extracted with ethyl acetate. The usual work-up of the extract gave crude crystals, which were recrystallized from ethanol–ether to give **11** as colorless prisms. The residue from the filtrate was separated on a silica-gel column (hexane–ethyl acetate 7:3) to give **11** and **12** (242 mg, 7.0%). **11**: yield, 2.35 g (87%). Mp 131 °C, IR: 3190 (NH), 1690 (amide).

Found: C, 65.98; H, 6.75; N, 5.88%. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; H, 6.16%.

A repeating similar reaction of **11** (410 mg, 0.903 mmol), and separation of products on a silica-gel column (hexane–ethyl acetate 4:1) gave **12** (392 mg, 76%) and 3-(3-benzyloxy-1-hydroxypropyl)-3-hydroxy-3,1′-*O*-isopropylidene-1-(*p*-methoxybenzyl)-5-(*p*-methoxybenzyloxy)-3,6-dihydro-2(1*H*)-pyrazinone (**18**: 58 mg, 11%) as a colorless syrup.

Found: C, 68.81; H, 6.84; N, 4.73%. Calcd for $C_{33}H_{38}N_2O_7$: C, 68.97; H, 6.67; N, 4.88%.

One-step reaction of **10** (2.0 g, 5.98 mmol) with 2 equimolar sodium hydride and *p*-methoxybenzyl bromide gave **12** (2.13 g, 62%) and **18** (441 mg, 13%). A similar reaction of **15** (623 mg, 1.71 mmol) with 2 equimolar reagents gave syrupy 3-hydroxy-3-[1-hydroxypropyl-3-(*p*-methoxybenzyloxy)]-3,1′-*O*-isopropylidene-1,4-bis(*p*-methoxybenzyl)-PDO (**17**) in 57% (568 mg) yield.

Found: C, 67.42; H, 6.64; N, 4.47%. Calcd for $C_{34}H_{40}N_2O_8$: C, 67.53; H, 6.67; N, 4.63%.

Hydrogenolysis of O-*Benzyl Group of* ***9a, 11, and 12.*** The reaction procedure is exemplified by the preparation of 3-(1,3-dihydroxypropyl)-3-hydroxy-3,1′-*O*-isopropylidene-1,4-bis(*p*-methoxybenzyl)-PDO (**16**). A solution of **12** (74 m, 0.13 mmol) in ethanol (50 cm^3) was catalytically hydrogenated with 10% palladium–carbon (30 mg) at room temperature for 24 h. The usual processing of the reaction mixture gave **16** (62 mg, 98%) which was crystallized from ether–hexane. Mp 159 °C (prisms), IR: 3500 (OH), 1670 (amide).

Found: C, 64.21; H, 6.61; N, 5.70%. Calcd for $C_{26}H_{32}N_2O_7$: C, 64.45; H, 6.61; N, 5.78%.

A similar hydrogenolysis of **11** (1.16 g, 2.56 mmol) gave 3-(1,3-dihydroxypropyl)-3-hydroxy-3,1,-*O*-isopropylidene-1-(*p*-methoxybenzyl)-PDO (**15**) in quantitative (930 mg) yield. Mp 180 °C (prisms from ethanol–ether), IR: 3450 (OH), 3220 (NH), 1680 (amide).

Found: C, 59.48; H, 6.48; N, 7.53%. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69%.

Compounds **15** and **16** were also obtained from **18** (83 mg, 0.144 mmol) and **17** (96 mg, 0.165 mmol) in 92% (48 mg) and 99% (79 mg) yields, respectively. 1-Acetyl-3-(1,3-dihydroxypropyl)-3-hydroxy-3,1′-*O*-isopropylidene-PDO (**13**) was obtained from **9a** (0.500 g, 1.33 mmol) in 75% (286 mg) yield. Mp 194—195 °C (prisms from ethanol–ether).

Found: C, 50.21; H, 6.29; N, 9.65%. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79%.

Oxidative Removal of O-*Benzyl Group of* ***9a*** *with* N-*Bromosuccinimide.* A mixed suspension of **9a** (100 mg, 0.266 mmol) in chloroform (40 cm^3), trilead(II) dicarbonate dihydroxide (1 g) and NBS (57 mg, 0.32 mmol) was vigorously stirred at room temperature for 24 h, and then filtered. The filtrate was treated by usual procedure and the products were separated on a silica-gel column (benzene–ethyl acetate 5:2) to give **13** (66 mg, 92%) and 1-acetyl-3-(3-benzoyloxyl-1-hydroxypropyl)-3-hydroxy-3,1′-*O*-isopropylidene-PDO (**14**: 6 mg, 6%) as a colorless hard syrup.

Found: C, 58.33; H, 5.71; N, 7.08%. Calcd for $C_{19}H_{22}N_2O_7$: C, 58.45; H, 5.68; N, 7.18%.

Cyclization of ***15*** *and* ***16*** *with* N-*Bromosuccinimide.* The reaction procedure is exemplified by the preparation of 5,6-dihydroxy-5,6-*O*-isopropylidene-7,9-bis(*p*-methoxybenzyl)-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione (**19**). A suspension of **16** (97 mg, 0.20 mmol), barium carbonate (1.0 g) and powdered 4 A molecular sieves (1 g) in dry chloroform (10 cm^3) was vigorously stirred at room temperature for 12 h, NBS (39.2 mg, 0.22 mmol) was added to it, and the resulting mixture was further stirred for 72 h, then filtered. The filtrate was poured into saturated sodium hydrogencarbonate and extracted with chloroform. The usual work-up of the extract gave a crude syrup, which was purified on a silica-gel column (hexane–ethyl acetate 7:3) to give **19** (83 mg, 86%). Mp 130 °C (prisms from ether–hexane); IR: 1705, 1685 (amide). ^{13}C NMR: δ=166.6s and 164.5s (C-8,10), 159.3s, 158.4s, 130.0d, 129.0d, 128.8d, 126.8s, 114.0d, and 113.4d (aromatic), 113.0s, 25.4q and 24.2q (Ip), 91.5s (C-6), 86.6d and 82.3d (C-1,5), 60.8t (C-3), 54.9q (2×OMe), 48.0t and 45.9t (2×NCH_2), 28.2t (C-4).

Found: C, 64.38; H, 6.28; N, 5.76%. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.71; H, 6.27; N, 5.81%.

A similar cyclization of **16** (97 mg, 0.20 mmol) in chloroform (10 cm^3) without barium carbonate and molecular sieves at room temperature for 24 h gave **19** (12 mg, 12%) and 4-hydroxy-6,9-bis(*p*-methoxybenzyl)-1-oxa-6,9-diazaspiro[4.5]-decane-7,10-dione (**21**: 54 mg, 63%). The usual acetylation of **21** in pyridine with acetic anhydride, and purification of the product on a silica-gel column (hexane–ethyl acetate 2:3) gave the 4-acetate (**23a**: 46 mg, 41%, mp 171 °C, prisms from ethanol–ether) and it's 5-epimer (**23b**, 48 mg, 44%) as colorless syrup.

^{13}C NMR for **23a**: δ=170.0s and 20.2q (Ac), 166.2s and 163.9s (C-7, 10), 159.2s, 158.5s, 129.7s, 126.6s, 129.5d, 114.1d, and 113.3d (aromatic), 93.2s (C-5), 77.7d (C-4), 67.1t (C-2), 55.0q (2×OMe), 48.8t and 48.7t (NCH_2×2), 46.8t (C-8), 31.1t (C-3), and for **23b**: δ=169.5s, and 20.3q (Ac), 164.1s (C-7, 10), 159.5s, 158.5s, 129.7s, 129.5s, 126.6s, 114.1d, and 113.3d (aromatic), 93.3s (C-5), 78.3d (C-4), 68.6t (C-2), 55.2q, 55.1q (2×OMe), 49.1t (2×NCH_2), 44.5t (C-8), 29.6t (C-3).

Found for **23a**: C, 63.93; H, 6.10; N, 5.85%, and for **23b**: C, 64.13; H, 6.16; N, 5.73%. Calcd for $C_{25}H_{28}N_2O_7$: C, 64.09; H, 6.02; N, 5.98%.

A similar cyclization of **15** (182 mg, 0.499 mmol) in chloroform (10 cm^3) without molecular sieves at room temperature gave 5,6-dihydroxy-5,6-*O*-isopropylidene-9-(*p*-methoxybenzyl)-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione (**20**: 54 mg, 30%) and 4-hydroxy-9-(*p*-methoxybenzyl)-1-oxa-6,9-diazasprio[4.5]decane-7,10-dione (**22**: 24 mg, 16%). **20**: mp 181—182 °C (prisms from chloroform–ether), IR: 3200 (NH), 1695 (amide).

Found; C, 59.23; H, 6.04; N, 7.73%. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73%.

The usual acetylation of **22** (30 mg, 0.098 mmol) in pyridine with acetic anhydride, and purification of the product on a preparative TLC (hexane–acetone 1:1) gave 4-acetoxy-9-(*p*-methoxybenzyl)-1-oxa-6,9-diazaspiro[4,5]decane-7,10-dione (**24**: 14 mg, 41%). Mp 148 °C (prisms from ethanol–ether), IR: 3220 (NH), 1735 (Ac), 1690, and 1670 (amide).

Found: C, 58.46; H, 5.72; N, 7.85%. Calcd for $C_{17}H_{20}N_2O_6$:

C, 58.61; H, 5.79; N, 8.04%.

3-Acetoxy- (**27**) *and 3-Acetylthio-1,4-diacetyl-2,5-piperazinediones* (**28**). A solution of NBS (94 mg, 0.53 mmol) and *N,N'*-diacetylanhydroglycine (100 mg, 0.51 mmol) in chloroform (10 cm^3) was stirred at room temperature for 12 h, poured into saturated sodium hydrogencarbonate, and extracted with chloroform. The usual processing of the extract gave crude syrupy monobromo derivative (**26**). IR: 1730 (Ac), 1720, and 1710 (amide); ^1H NMR: δ=6.85 (s, 1H, H-3), 5.22 and 4.27 (ABq, 2H, J=17.5 Hz, H-6), 2.62 (s, 6H, Ac×2). When this reaction was performed in the presence of potassium acetate (742 mg, 7.6 mmol), 3-acetoxy derivative (**27**) was obtained as a colorless hard syrup after purification on a silica-gel column with benzene–ethyl acetate (7:3). Yield, 91 mg (71%), IR: 1740 and 1730 (Ac), 1710 and 1700 (amide). ^1H NMR: δ=7.22 (s, 1H, H-3), 5.10 and 4.25 (ABq, 2H, J=18.0 Hz, H-6), 2.59 (s, 6H, 2×NAc), 2.13 (s, 3H, OAc).

Found: C, 46.80; H, 4.82; N, 10.99%. Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93%.

The reaction in the presence of potassium thioacetate instead of potassium acetate as above, and the product was purified on a silica-gel column (benzene–ethyl acetate 7:3) to give **28** as a colorless hard syrup in 68% yield. IR: 1740 and 1720 (Ac), 1710 and 1700 (amide); ^1H NMR: δ=6.60 (s, 1H, H-3), 5.13 and 4.26 (ABq, 2 H, J=18.0 Hz, H-6), 2.61 (s, 6H, 2× NAc), 2.45 (s, 3H, SAc).

Found: C, 44.23; H, 4.41; N, 10.24%. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.44; N, 10.29%.

*5,6-Dihydroxy-7,9-bis(*p*-methoxybenzyl)-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione* (**29**). A solution of **19** (51.0 mg, 0.106 mmol) and 2 M hydrochloric acid (2 cm^3) in tetrahydrofuran (THF, 5 cm^3) was heated at 50 °C, for 24 h, poured into saturated sodium hydrogencarbonate, and extracted with dichloromethane. The usual processing of the extract gave a crude syrup, which was purified on a flash column (hexane–ethyl acetate 3:2) to give **29** (40.5 mg, 83%) as a colorless syrup. Mp 154—155 °C (prisms from ethanol–ether), IR: 3450(OH), 1675 (amide), ^{13}C NMR (DMSO): δ= 169.9s and 163.9s, (C-8,10), 159.7s, 158.6s, 131.6s, 130.8d, 129.3d, 128.6s, 114.8d, and 114.1d, (aromatic), 86.9s (C-6), 83.1d (C-1), 78.3d (C-5), 60.1t (C-3), 55.9q (2×OMe), 47.9t and 46.9t (2×NCH_2), 30.5t (C-4).

Found: C, 59.98; H, 5.71; N, 5.85%. Calcd for $C_{23}H_{26}N_2O_7 \cdot H_2O$: C, 59.99; H; 6.13; N, 6.08%.

*6-Hydroxy-7,9-bis(*p*-methoxybenzyl)-2-oxa-7,9-diazabicyclo[4.2.2]decane-5,8,10-trione* (**30**). A solution of oxalyl dichloride (0.115 cm^3, 1.35 mmol) in dichloromethane (5 cm^3) and dimethyl sulfoxide (DMSO, 0.5 cm^3) in dichloromethane (2 cm^3) were mixed with vigorous stirring at −78 °C for 5 min, then a solution of dried **29** (270 mg, 0.611 mmol) in DMSO (2.5 cm^3) and dichloromethane (2 cm^3) was added dropwise to the mixture. The reaction mixture was stirred for 20 min at −78 °C, then a solution of triethylamine (0.511 cm^3, 3.66 mmol) in dichloromethane (1 cm^3) was further added to it, and stirred for 5 min. The temperature being raised to 0 °C, the reaction mixture was poured into saturated ammonium chloride, and extracted with dichloromethane. The usual processing of the extract gave a crude syrup, which was purified on a flash column (hexane–ethyl acetate 4:1) to give **30** (246 mg, 91%) as crystals. Mp 138 °C (prisms from ether–hexane), IR: 3360 (OH), 1730 (C=O), 1680 (amide), ^{13}C NMR: δ=202.6s (C-5), 164.2s and 161.7s, (C-8,10), 159.7s, 159.5s, 131.7d, 130.4d, 126.1s, 125.8s, 114.3d, and 113.8d (aromatic), 86.4s (C-6), 83.0d (C-1), 57.9t (C-3), 55.2q and 55.1q (2×OMe), 48.5t and 43.8t (2×NCH_2), 40.3t (C-4).

Found: C, 53.09; H, 5.54; N, 6.17%. Calcd for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36%.

*6-(2-Formylethoxy)-1,4-bis(*p*-methoxybenzyl)-2,3,5-piperazinetrione* (**34**). To a solution of **29** (12.0 mg, 0.027 mmol) in dichloromethane (1 cm^3) was added sodium acetate (4.8 mg, 0.059 mmol) and pyridinium chlorochromate (11.6 mg, 0.054 mmol) with vigorous stirring at room temperature. After stirring for 24 h, the mixture was poured into water, and extracted with dichloromethane. The usual processing of the extract gave a crude product, which was purified on preparative TLC (ether) to give **34** (7.2 mg, 61%) as a colorless syrup. ^1H NMR: δ=9.59 (t, 1H, $J_{3',4'}$=1.5 Hz, CHO), 7.29, 6.84, 7.24, and 6.78 (each d, 8H, J=8.5 Hz, MBn×2), 5.17 and 4.17 (ABq, 2H, J=13.5 Hz, CH_2 in MBn), 4.89 (s, 2H, CH_2 in MBn), 4.85 (s, 1H, H-6), 3.9—3.7 (m, 2H, H-2'), 3.81 and 3.88 (each s, 6H, 2×OMe), 2.63 (dt, 2H, $J_{2',3'}$=6.0 Hz, H-3').

Found: C, 62.93; H, 5.52; N, 6.20%. Calcd for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36%.

*6-Hydroxy-7,9-bis(*p*-methoxybenzyl)-5-methylene-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione* (**32**). To a mixture of magnesium (49.7 mg, 2.05 mmol) and trimethylsilylmethyl chloride (418 mg, 1.05 mmol) in dry ether (10 cm^3) was added catalytic amount of iodine with vigorous stirring at 40 °C. After the stirring was continued for 30 min, the mixture was diluted with dry ether (120 cm^3), cooled to −30 °C, and a solution of **29** (300 mg, 0.682 mmol) in THF (10 cm^3) was further added dropwise to it. The reaction mixture was stirred at −30 °C for 4 h, poured into saturated ammonium chloride, and extracted with chloroform. The usual processing of the extract gave a crude syrup, which was purified on a flash column (hexane–ethyl acetate 7:3) to give colorless syrupy 5,6-dihydroxy-7,9-bis(*p*-methoxybenzyl)-5-trimethylsilylmethyl-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione (**31**: 192 mg, 52%) as a mixture of 5-epimers. To a solution of **31** (192 mg, 0.354 mmol) in dichloromethane (6 cm^3) was added 4-dimethylaminopyridine (864 mg, 7.08 mmol) and trifluoroacetic anhydride (743 mg, 3.54 mmol) with vigorous stirring at room temperature. After stirring was continued for 1 h, a solution of tetrabutylammonium chloride (1.48 g, 5.32 mg) in acetonitrile (30 cm^3) and potassium fluoride (616 mg, 10.6 mmol) was further added, and the mixture was heated at 40 °C for 12 h, then *O*-detrifluoroacetylated by addition of methanol (5 cm^3), poured into saturated ammonium chloride, and extracted with chloroform. The usual processing of the extract gave a crude syrup, which was purified on a flash column (hexane–ethyl acetate 4:1) to give colorless syrupy **32** (125 mg, 81%).

Found: C, 65.82; H, 6.11; N, 6.28%. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39%.

Another method for the elimination reaction was accomplished as follows: a solution of **31** (14.0 mg, 0.0267 mmol) in 0.08 M sulfuric acid in THF (0.5 cm^3) was permitted to stand for 12 h at room temperature, poured into saturated sodium hydrogencarbonate, and extracted with chloroform. The usual processing of the extract gave a crude syrup, which was purified on a flash column (hexane–ethyl acetate 7:3) to give **32** (5.6 mg, 48%).

*6-(t-Butyldimethylsilyloxy)-1,9-bis(*p*-methoxybenzyl)-5-methylene-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione* (**33**).
To a solution of **32** (10.0 mg, 0.0228 mmol) in dichloromethane (1 cm^3) was added 2,6-lutidine (12.2 mg, 0.114 mmol)

and 0.1 M *t*-butyldimethylsilyl triflate (0.342 cm^3, 0.0342 mmol) solution in dichloromethane with vigorous stirring at room temperature. The mixture was stirred for 12 h, poured into saturated ammonium chloride, and extracted with ethyl acetate. The extract was washed successively with 0.1 M hydrochloric acid, saturated sodium hydrogencarbonate, and saturated sodium chloride, dried over anhydrous magnesium sulfate, and then evaporated. The residue was purified on a flash column (hexane–ethyl acetate 4:1) to give **33** (10.1 mg, 80.2%) as a colorless hard syrup. ^{13}C NMR: δ=167.7s and 163.4s (C-8,10), 159.4s, 158.9s, 130.7d, 130.3d, 128.0s, 126.7s, 114.4d, and 113.3d, (aromatic), 148.6s and 118.0t (olefinic), 87.9s (C-6), 81.5d (C-1), 63.8t (C-3), 55.3q and 55.2q (2×OMe), 47.2t and 44.0t (NCH_2×2), 35.7t (C-4).

Found: C, 65.41; H, 7.28; N, 5.03%. Calcd for $C_{30}H_{40}N_2O_6Si$: C, 65.20; H, 7.30; N, 5.07%.

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