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Synthetic Studies on 8-Deoxyserratinine Type Alkaloids. Selective Cyclization of the 1,2-Cyclohexanediacetaldehyde Derivative by Intramolecular Aldol Condensation

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In connection with the synthesis of 8-deoxyserratinine type alkaloids, the regioselective cyclization reaction of the 1,2-cyclohexanediacetaldehyde derivative (**6**) by intramolecular aldol condensation was investigated. The acetal (**5**) was stereoselectively prepared by two routes using the Diels–Alder reaction. The first route involved the Diels–Alder reaction of the dienophile (**12**), obtained from **8** *via* **9**, **10** and **11**, with butadiene in the presence of 0.5 eq. $AlCl_3$ and acetalization of the adduct (**13**) to give **5** in 8% yield from 8. The second route involved conversion of the adduct (**15**), obtained by the Diels–Alder reaction of **8** with butadiene in the presence of 0.5 eq. $BF_3 \cdot Et_2O$, into **5** [22% yield based on the consumed dienophile (**8**)] *via* **16** and **17**. The dialdehyde (**6**) was obtained from the *cis*-decalone derivative (**5**) *via* **18**. Cyclization of **6** using excess morpholine-camphoric acid in dry Et_2O–HMPA and subsequent treatment with $(EtO)_2POCH_2CN$ gave **21**, which was suitable for our purpose, and **22** in a 25: 1 ratio.

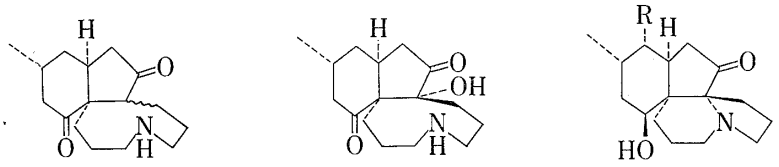
Keywords——Lycopodium alkaloids; Diels–Alder reaction; stereoselective cycloaddition; dialkyl *cis*-decalone derivative; regioselective intramolecular aldol condensation; 1,2-cyclohexanediacetaldehyde derivative

Among Lycopodium alkaloids, fawcettimine (**1**)[2] and alopecuridine(**2**),[3] which possess a nitrogen-containing nine-membered ring, and 8-deoxyserratinine (**3**)[4] belong to the serratinine group alkaloids, which have unusual skeletal structures. Based on a biogenetic hypothesis, fawcettimine (**1**) was suggested to be the precursor of serratinine group alkaloids.[2] Although chemical correlation of serratinine (**4**) with fawcettimine (**1**) and 8-deoxyserratinine (**3**) was achieved,[5] the total synthesis of these alkaloids has not yet been accomplished. In a preliminary communication,[6] we have already reported the stereoselective total synthesis of fawcettimine (**1**) and 8-deoxyserratinine (**3**). We report here details of the stereoselective synthesis of the key intermediate (**5**), which bears three chiral centers as a common stereostructural feature of 8-deoxyserratinine type alkaloids, and the regioselective intramolecular aldol cyclization reactions of the dialdehyde (**6**).

Stereoselective Synthesis of Compound (5)

The stereoselective synthesis of compound (**7**), possessing a suitable stereostructure for the present synthesis has already been reported.[7] This compound, however, turned out to be inappropriate for further synthesis because acetalization of this compound with ethylene glycol-*p*-toluenesulfonic acid gave a complex mixture owing to hydrolysis of the acetoxy group. Reduction of the carbonyl group of (**7**) with various reducing reagents gave an epimeric mix-

1) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
2) Y. Inubushi, H. Ishii, T. Harayama, R.H. Burnell, W.A. Ayer, and B. Altenkirk, *Tetrahedron Lett.*, **1967**, 1069.
3) W.A. Ayer, B. Altenkirk, and Y. Fukazawa, *Tetrahedron*, **30**, 4213 (1974).
4) Y. Inubushi, H. Ishii, B. Yasui, T. Harayama, M. Hosokawa, R. Nishino, and Y. Nakahara, *Yakugaku Zasshi*, **87**, 1394 (1967).
5) H. Ishii, B. Yasui, R. Nishino, T. Harayama, and Y. Inubushi, *Chem. Pharm. Bull.*, **18**, 1880 (1970).
6) T. Harayama, M. Takatani, and Y. Inubushi, *Tetrahedron Lett.*, **1979**, 4307.



1 2 3 : R=H 4 : R=OH

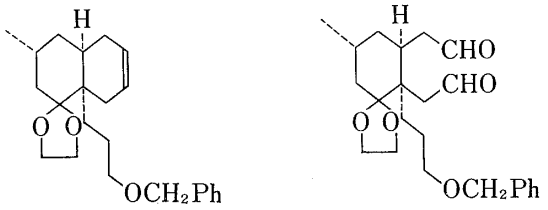


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Chart 1

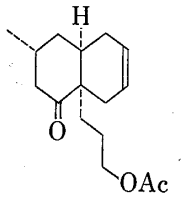
ture. Thus, synthesis of compound (**13**), having a benzyl ether function as a protective group for the hydroxyl function, was attempted.

The alcohol (**9**)[7] obtained from the α,β-unsaturated ketone (**8**)[7] in three steps was benzylated with NaH-benzyl chloride to give the benzyl ether (**10**) in 83% yield. Removal of the pyranyl group of (**10**) with 4% hydrochloric acid in tetrahydrofuran (THF) gave the alcohol (**11**) in 87% yield and this was oxidized with Jones' reagent to furnish the dienophile (**12**) in 60% yield.

We have reported that the addition of butadiene in the Diels-Alder reaction of 2,5-dialkylcyclohex-2-en-1-ones with butadiene in the presence of aluminum chloride takes place stereoselectively from the side opposite to the 5-alkyl group.[8,9] By taking advantage of this type of Diels–Alder reaction, compound (**13**) was synthesized from the dienophile (**12**) and butadiene as follows. The Diels–Alder reaction of the dienophile (**12**) with butadiene was carried out in the presence of 0.5 eq. $AlCl_3$ in CH_2Cl_2 at room temperature for 5 days to provide the adduct (**13**) in 27% yield. The infrared (IR) spectrum of **13** showed a band due to a six-membered ketone at 1700 cm^{-1} and the nuclear magnetic resonance (NMR) spectrum revealed signals attributable to olefinic protons at δ 5.59 (2H, br. s.). The stereochemistry of **13** was confirmed by conversion of **13** to the stereochemically established keto-acetate (**14**)[7] through reduction of a double bond and hydrogenolysis of a benzyl ether group by catalytic reduction and subsequent acetylation. Acetalization of **13** occurred efficiently only under strictly controlled reaction conditions. Thus, treatment of **13** with a large amount of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in a relatively large quantity of benzene gave the acetal (**5**) in 72% yield. The acetal (**5**) showed no carbonyl absorption band in the IR spectrum and signals due to the methylene protons of the acetal group appeared at δ 3.88 (4H, s) in its NMR spectrum. The eight-step sequence of reactions mentioned above was unsatisfactory due to both the number of reaction steps and the low overall yield (8% from **8** to **5**).

7) T. Harayama, M. Takatani, and Y. Inubushi, *Chem. Pharm. Bull.*, **27**, 726 (1979).
8) T. Harayama, H. Cho, and Y. Inubushi, *Chem. Pharm. Bull.*, **25**, 2273 (1977).
9) T. Harayama, H. Cho, and Y. Inubushi, *Chem. Pharm. Bull.*, **26**, 1201 (1978).

Thus, an alternative synthetic route to the compound (**5**) was elaborated. The Diels–Alder reaction of the dienophile (**8**) with butadiene was carried out in the presence of various kinds of Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$, and $BF_3 \cdot Et_2O$); $BF_3 \cdot Et_2O$ was found to be most efficient, yielding the adduct (**15**) in 29% yield (53% yield based on the consumed dienophile). The IR spectrum of **15** showed the carbonyl band at 1700 cm^{-1} and the NMR spectrum exhibited signals due to olefinic protons at δ 4.83—6.02 (5H, m). The stereostructure of **15** was determined by conversion of **15** to the acetal (**5**). In contrast with **13**, acetalization of **15** with ethylene glycol and *p*-toluenesulfonic acid preceeded smoothyly to give the acetal (**16**). Hydroboration of **16** with disiamylborane, followed by oxidation with H_2O_2–aq. NaOH afforded the alcohol (**17**) from **15** in 51% yield. The alcohol (**17**) showed signals due to two olefinic protons at δ 5.56 (2H, m) in its NMR spectrum, indicating that disiamylborane reacted selectively with a double bond in the side chain. Benzylation of **17** with NaH–*n*–$Bu_4N^+I^-$-benzyl bromide provided the acetal in 83% yield. In the latter route, the acetal (**5**) was obtained in 12% overall yield from **8** (22% yield based on the consumed dienophile (**8**)) in 4 steps, and separation of the adduct (**15**) from the dienophile (**8**) in the reaction products was readily performed by fractional distillation. Thus, the latter route was superior to the former.



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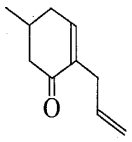

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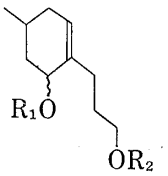
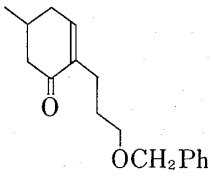


9 : R_1=THP, R_2=H
10 : R_1=THP, R_2=CH_2Ph
11 : R_1=H , R_2=CH_2Ph



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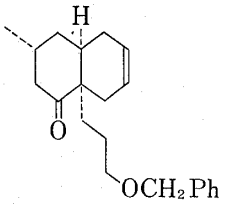

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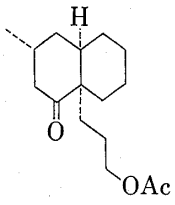

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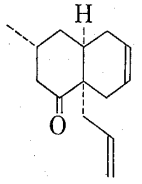

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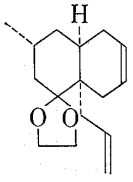

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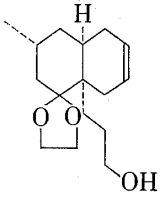

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Chart 2

Regioselective Intramolecular Aldol Cyclization of the Dialdehyde (6)

Osmylation of compound (**5**) with OsO_4-N-methylmorpholine-N-Oxide[10] provided the diol (**18**) in 92% yield. This was subsequently treated with $HIO_4 \cdot 2H_2O$ to give the dialdehyde (**6**) quantitatively. It was anticipated that intramolecular aldol cyclization of the dialdehyde (**6**) would occur in two ways (routes a and b) to furnish two kinds of aldehydes, *i.e.* compounds (**19**) and (**20**). For the present synthesis, it was necessary to find suitable reaction conditions to give compound (**19**) selectively (see Chart 3).

We first tried to apply Woodward's method[11] (Method A in Table I), which was used for the formation of the D ring in steroid synthesis, to the cyclization of the dialdehyde (**6**). Thus, a mixture of the dialdehyde and a catalytic amount of piperidine acetate in benzene was heated at 60° for 3 hr under a nitrogen atmosphere. Conventional work-up gave a mixture of (**19**) and (**20**). Since these compounds seemed to be unstable to separation procedures, the mixture was treated immediately with $(EtO)_2POCH_2CN$ by Wadsworth–Emmons' method and the reaction products were separated by chromatography to give the nitriles (**21**) and (**22**) in a 1:22 ratio in 50% total yield. Examination of the NMR spectrum showed compound (**21**) to be a mixture of E- and Z-isomers due to a double bond in the side chain in a 3:7 ratio. [E-isomer: δ 5.71 (0.3H, d, J=17 Hz), δ 7.05 (0.3H, d, J=17 Hz); Z-isomer: δ 5.11 (0.7H, d, J=12 Hz), δ 6.66 (0.7H, d, J=12 Hz)]. The structure assignment of compounds

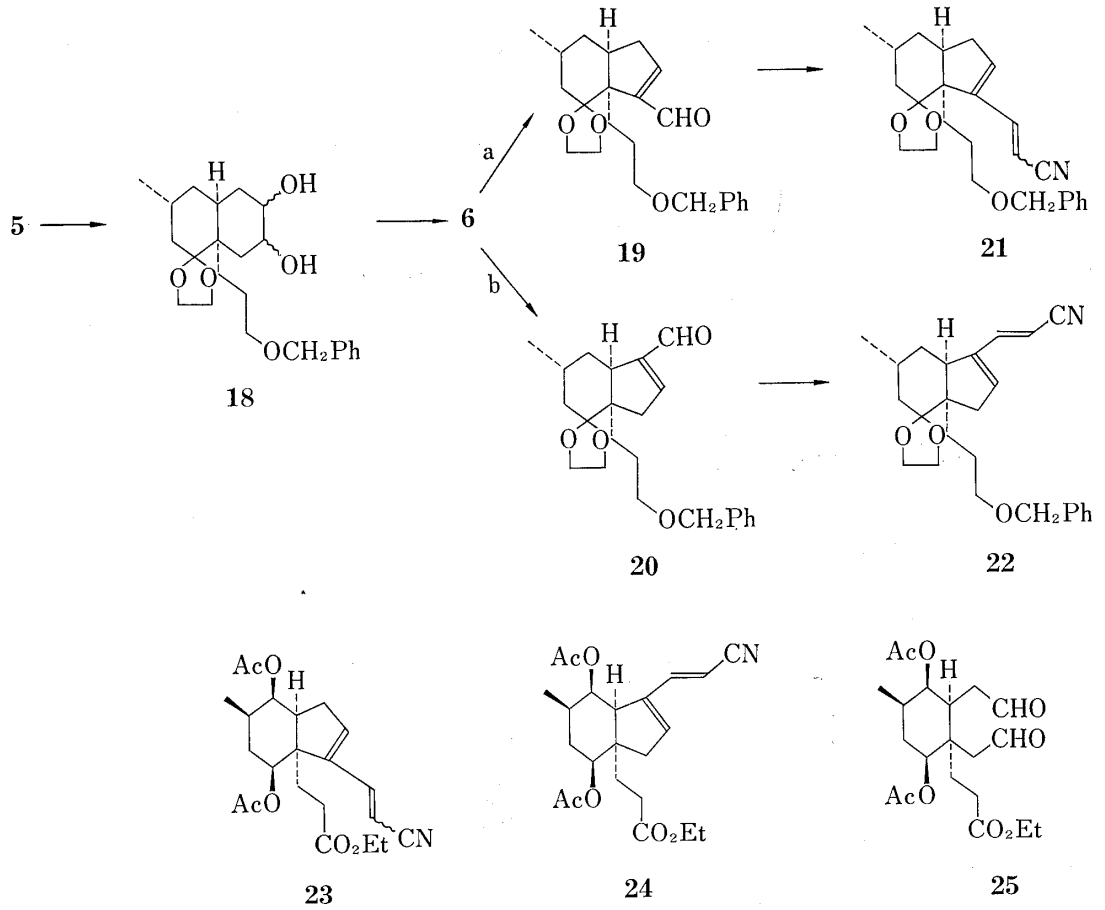


Chart 3

10) V. VanRheenen, R.C. Kelly, and D.Y. Cha, *Tetrahedron Lett.*, **1976**, 1973.
11) R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W.M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

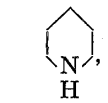
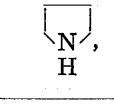
(**21**) and (**22**) depended mainly on the signal patterns of the allylic methylene protons in the NMR spectrum compared with those of compounds (**23**)[12] and (**24**),[12] the structures of which are established. In view of this results, cyclization using these reaction conditions was abandoned.

Corey's method[13] employing 0.2 eq. of $(PhCH_2)_2NH_2^+ \cdot CF_3COO^-$, which was used for the synthesis of gibberellic acid (Method B), was applied to the dialdehyde (**6**) to furnish compound (**21**) and (**22**) in a 1:19 ratio. This method, therefore, was also unsuitable for the present synthesis. The regioselective formation of compound (**22**) by Methods A and B can be rationalized by assuming that nucleophilic attack of the enamine function, generated from the less hindered aldehyde group and the amine, on the other aldehyde group took place to give (**20**).

Next, we adopted Method C, which was successfully applied to the dialdehyde (**25**)[14] in the synthesis of serratinine.[12] Thus, the dialdehyde (**6**) was treated with excess pyrrolidine acetate in absolute methanol at 0° for 20 hr under an argon atmosphere and the reaction products (without separation) were treated with Wadsworth-Emmons' reagent to give a mixture of (**21**) and (**22**) in a 1:1 ratio (see Table I). This method, therefore, was also unsuitable for the present case.

Since the desired regioselectivity could not be attained, we decided to examine the effects of solvents and reagents used in the reactions on the regioselectivity. The solvent effects were examined using the dialdehyde (**6**) and excess pyrrolidine–AcOH in various kinds of solvents. As shown in Table II, nonpolar aprotic solvents seemed to be preferable to protic solvents,

Table I. The Resulfts of Intramolecular Aldol Condensation of **6**

Method	Solvent	Reagent	Conditions	Ratio of **21**/**22**	Total yield (%)
A	Dry C_6H_6	 , AcOH[a]	60°, 3 hr	1/22	50
B	Dry C_6H_6	$(PhCH_2)_2NH_2^+ \cdot CF_3CO_2^-$ [b]	60°, 3.5 hr	1/19	77
C	Abs. MeOH	 , AcOH[c]	0°, 20 hr	1/1	18

a) Catalytic amounts.
b) 0.2 eq.
c) 5.8 eq. of pyrrolidine, 6.8 eq. of acetic acid.

Table II. Solvent Effects on the Intramolecular Aldol Condensation of **6** with Excess Pyrrolidine Acetate

Method	Solvent	Ratio of **21**/**22**	Total yield (%)
D	Abs. MeOH–HMPA[a]	8.5/1	8
E	DMF	3/4	5
F	Abs. $(CH_3)_2CHOH$	1/1.6	30
G	Dry THF	2.3/1	29
H	Dry THF–HMPA[a]	3.3/1	21
I	Dry Et_2O	2.4/1	31
J	Dry Et_2O–HMPA[a]	3/1	33

a) 1.5 eq. of HMPA.

12) T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.*, **23**, 1511 (1975).
13) E.J. Corey, R.L. Danheiser, S. Chandrasekaran, P. Siret, G.E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978).
14) T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.*, **21**, 1061 (1973).

and the addition of hexamethylphosphoramide (HMPA) resulted in a marked increase in the proportion of compound (**21**) in the reaction products. This effect of HMPA may be attributable to stabilization of the iminium cation intermediate as described later in connection with the reaction mechanism.

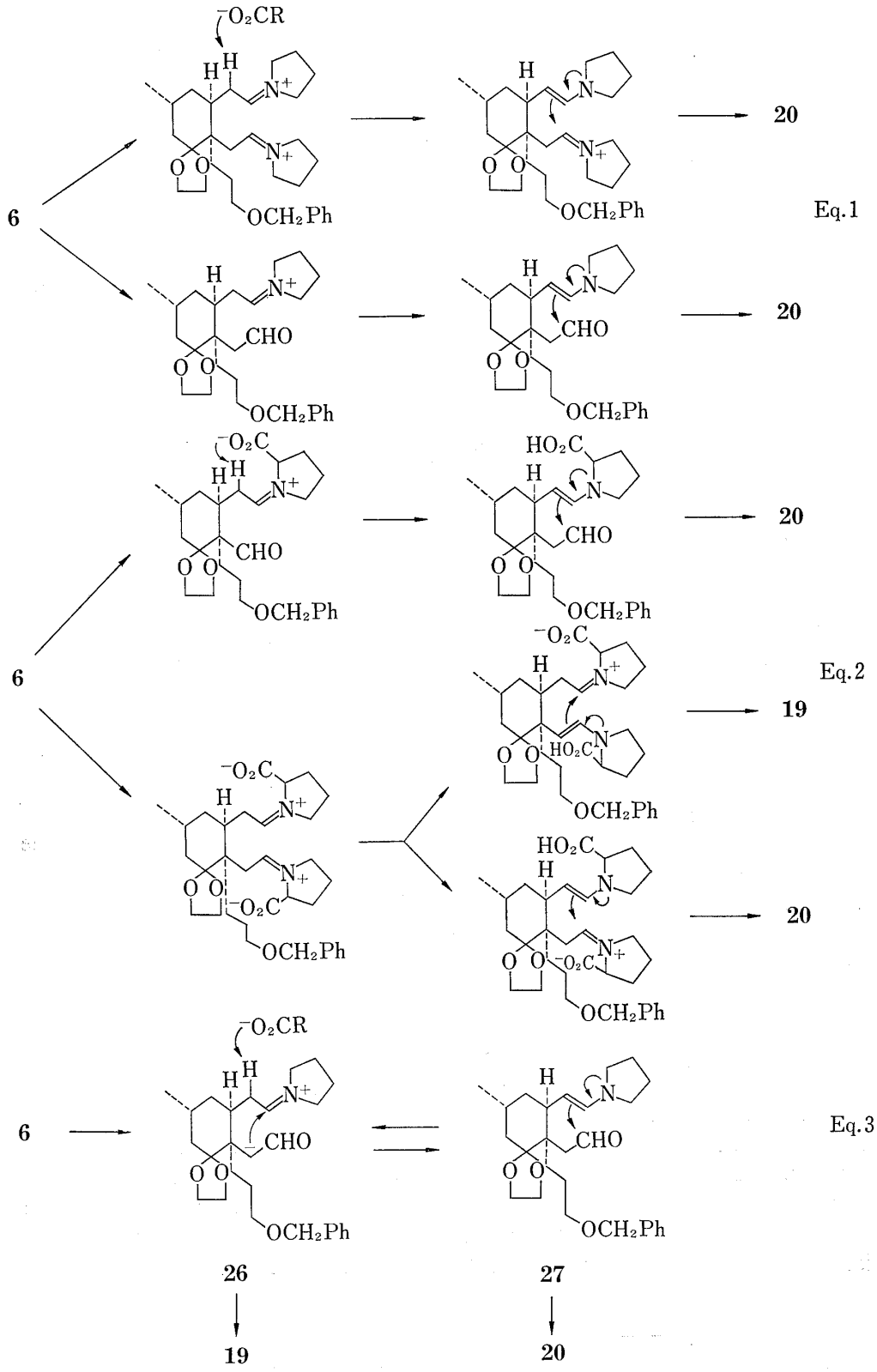


Chart 4

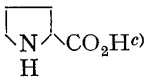
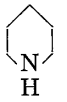
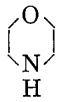
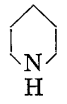
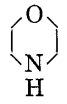
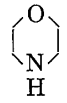
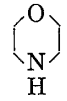
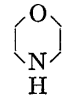
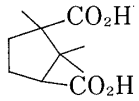
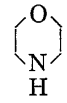
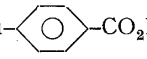
At this stage of examination of the reaction conditions, we tried to take into account the mechanism of formation of compound (**20**). As excess amine is used in Method C, it is possible that two reaction intermediates may be initially formed, *i.e.* the diiminium species and the monoiminium species formed by the interaction of pyrrolidine with the less hindered aldehyde function, as shown by equation 1 in Chart 4. The former is convertible into the enamine-iminium species from which compound (**20**) is formed. The later is also convertible to the enamine species from which compound (**20**) is formed. In order to determine the actual route, *i.e.* the route *via* the diiminium intermediate or the route *via* the monoiminium intermediate, the following experiment was attempted. The dialdehyde (**6**) was treated with an excess of *l*-proline in Et_2O–HMPA containing a small quantity of absolute ethanol (required for dissolving *l*-proline[15]) at room temperature for 20 hr under an argon atmosphere (Method K) and the reaction products (without separation) were treated with Wadsworth–Emmons' reagent to give a mixture of (**21**) and (**22**) in a 1: 30 ratio. In the iminium salt generated from *l*-proline and the aldehyde group of compound (**6**), the carboxylate anion of *l*-proline as the counter anion to the iminium cation is located in a position where the counter anion and the methylene group adjacent to the iminium function are accessible to each other. Consequently, deprotonation of the methylene protons concerned by counter anion capture may occur readily to convert the iminium species to the enamine species. This situation is common to both the diiminium intermediate and the monoiminium intermediate. Thus, it is reasonable to assume that the monoiminium intermediate will give compound (**20**) selectively *via* the enamine intermediate, while the diiminium intermediate will give a mixture of (**19**) and (**20**). The high regioselectivity observed in the reaction by Method K suggests that the cyclization reaction proceeds *via* the monoiminium intermediate.

From the viewpoint of this monoiminium mechanism, the large difference in regioselectivity between Methods K and L is explicable as followed. In Method L, the monoiminium species (**26**) was first formed from the less hindered aldehyde group of the dialdehyde (**6**) and pyrrolidine. The equilibrium position of the iminium (**26**) and the enamine (**27**) is shifted to the iminium side compared with that in the case of Method K because the acetate anion in Method L is distant from the methylene group concerned, in contrast with the carboxylate anion of *l*-proline in Method K. If we make the simplifying assumption that there is no marked difference in the reaction rate between two reactions, *i.e.* the conversion of the iminium compound (**26**) to (**19**) and that of the enamine (**27**) to compound (**20**), the proportion of (**19**) derived from the iminium species in Method L will be larger than in the case of Method K (see equation 3 in Chart 4).

Based on this consideration of the reaction mechanism, it was presumed that if the monoiminium intermediate is selectively formed and maintained as such in the reaction mixture, the desired compound (**19**) would be obtained selectively by nucleophilic attack of the carbanion arising from the other aldehyde function on the iminium function. Thus, we planned the use of a less reactive amine which would react selectively with the less hindered aldehyde group of the dialdehyde (**6**), and a bulky acid which would inhibit the transformation of the iminium function into enamine by preventing the attack of the counter anion on methylene protons adjacent to the iminium function of **26**. The intramolecular aldol condensation of the dialdehyde (**6**) was carried out using various kinds of amines and acids in dry Et_2O–HMPA as shown in Table III. The proportion of compound (**21**) increased in the order pyrrolidine, piperidine, and morpholine in regard to amines, and acetic acid, isovaleric acid, camphoric acid, and caprylic acid in regard to acids. Consequently, Method T was selected as the most suitable for obtaining the desired compound (**21**) in view of the yield and easiness of the work-up process. Thus, the dialdehyde (**6**) was treated with excess morpholine-camphoric acid in

15) The change of regioselectivity caused by addition of a small quantity of absolute ethanol to the Et_2O–HMPA solvent system was examined in Method T (*vide post*) and no effect was found.

TABLE III. The Results of Intramolecular Aldol Condensation of **6** with Various Kinds of Amine and Acid in Dry Et_2O–HMPA at 0° for 20 hr

Method	Reagent		Ratio of **21/22**	Total yield (%)
	Amine[a]	Acid[b]		
K		 [c]	1/30	24
L (= J)		AcOH	3/1	33
M		AcOH	5/1	22
N		AcOH	13/1	21
O		$(CH_3)_2CHCH_2CO_2H$	3/1	28
P		$(CH_3)_2CHCH_2CO_2H$	7/1	37
Q		$(CH_3)_2CHCH_2CO_2H$	16/1	38
R		$CH_3(CH_2)_6CO_2H$	50/1	39
S		*p*-TsOH	21/1	17
T			25/1	40
U		*t*-Bu- 	6.5/1	34

a) 5.8 eq.
b) 6.8 eq.
c) 6.8 eq. of *l*-proline in dry Et_2O–HMPA containing a small quantity of abs. EtOH at room temperature for 20 hr

dry Et_2O–HMPA at 0° for 20 hr under an argon atmosphere and the reaction products (without separation) were treated with Wadsworth–Emmons' reagent to give a mixture of compounds (**21**) and (**22**) in a 25 : 1 ratio in 40% total yield.

Experimental

All NMR spectra were taken on a Varian A-60 spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard, and IR spectra were recorded on a Shimadzu IR 400 spectrometer in $CHCl_3$. Low-resolution mass spectra were taken with a Hitachi RMU-6C spectrometer with a heated direct inlet system. Column chromatography was performed on silica gel [Merck Kieselgel 60, 70—230 mesh (A), Mallinckrodt silicic acid, 100 mesh (B) or basic alumina (Aluminium Oxyd. G. Brockmann, Activity II-III) (C)].

The Pyranyl Ether-Benzyl Ether (10)——A solution of 30.2 g (0.119 mol) of the alcohol (**9**) in 100 ml of dry benzene was treated with 10.2 g (0.213 mol) of 50% NaH containing mineral oil at 0° under stirring. The mixture was refluxed for 2 hr, then 33.0 g (0.261 mol) of benzyl chloride was added and reflux was continued for a further 4 hr. After cooling, the reaction mixture was carefully poured into cold water to decompose excess NaH and was extracted with ether. The extract was washed with water, dried over $MgSO_4$ and concentrated. The residue in *n*-hexane was chromatographed on silica gel (A) and elution with $CHCl_3$ gave 33.9 g (83%) of the pyranyl ether–benzyl ether (**10**), bp 150°/0.08 mmHg. IR cm^{-1}: ν_{C-C} 1495, ν_{C-O-C} 1007—1135, δ_{CH} 700. NMR δ: 0.95 (3H, m, >CH–C<u>H</u>$_3$), 3.47 and 3.49 (total 2H, t, J=6.5 Hz, –C<u>H</u>$_2$–OBzl), 4.50 (2H, s, –C<u>H</u>$_2$–Ph), 4.75 (1H, m, –C<u>H</u><O–O–), 5.51 (1H, m, olefinic proton), 7.31 (5H, s, aromatic protons). MS *m/e*: 344 (M^+). *Anal.* Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.49; H, 9.41.

The Alcohol (11)——HCl (4% solution, 42 ml) was added to a solution of 26.5 g (0.077 mol) of compound (**10**) in 300 ml of freshly distilled THF. The mixture was stirred for 22 hr at room temperature and concentrated under reduced pressure. The concentrated solution was diluted with water and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated. The residue in *n*-hexane was chromatographed on silica gel (A) and elution with $CHCl_3$ provided 17.4 g (87%) of the alcohol (**11**), bp 148—149°/0.13 mmHg. IR cm^{-1}: ν_{OH} 3600, 3425. NMR δ: 0.95 (3H, d, J=5 Hz, >CH–C<u>H</u>$_3$), 1.96 (1H, br. s, O<u>H</u>), 3.48 (2H, t, J=6.5 Hz, –C<u>H</u>$_2$–OBzl), 4.00—4.40 (1H, m, >C<u>H</u>–OH), 4.50 (2H, s, –C<u>H</u>$_2$–Ph), 5.45 (1H, m, olefinic proton), 7.32 (5H, s, aromatic protons). *Anal.* Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.13; H, 9.50.

The Dienophile (12)——A solution of 27.5 g (0.106 mol) of the alcohol (**11**) in 100 ml of acetone was treated dropwise with 33.3 ml (0.09 mol) of Jones' reagent at 0° under stirring. The mixture was stirred at room temperature for 10 min. Excess reagent was decomposed with methanol and the mixture was diluted with water then extracted with ether. The extract was washed with water, dried over $MgSO_4$ and concentrated. Distillation of the residue gave 16.3 g (60%) of the dienophile (**12**), bp 174.5—175.5°/0.9 mmHg. IR cm^{-1}: $\nu_{C=O}$ 1669. NMR δ: 1.02 (3H, m, >CH–C<u>H</u>$_3$), 3.46 (2H, t, J=6.5 Hz, –C<u>H</u>$_2$–OBzl), 4.48 (2H, s, –C<u>H</u>$_2$–Ph), 6.67 (1H, m, olefinic proton), 7.32 (5H, s, aromatic protons). MS *m/e*: 258 (M^+). *Anal.* Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.03; H, 8.87.

The Adduct (13)——To a solution of 4.19 g (16.2 mmol) of the dienophile (**12**) in 15 ml of dry CH_2Cl_2 were added 1.09 g (8.1 mmol) of $AlCl_3$ powder and 2.63 g (48.7 mmol) of butadiene at −30°. The mixture was allowed to stand at room temperature in a sealed tube for 5 days. The reaction mixture was diluted with water and extracted with ether. The extract was dried over $MgSO_4$ and evaporated down to leave the residue. The residue in *n*-hexane was chromatographed on silica gel (B), and elution with CH_2Cl_2 gave 1.39 g (27%) of the adduct (**13**), bp 180°/0.08 mmHg. IR cm^{-1}: $\nu_{C=O}$ 1700. NMR δ: 1.00 (3H, m, >CH–C<u>H</u>$_3$), 3.44 (2H, t, J=6.4 Hz, –C<u>H</u>$_2$–OBzl), 4.47 (2H, s, –C<u>H</u>$_2$–Ph), 5.59 (2H, br. s, olefinic protons), 7.12—7.47 (5H, m, aromatic protons). MS *m/e*: 312 (M^+). *Anal.* Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.88; H, 9.06.

Conversion of (13) to the Keto-Acetate (14)——A mixture of a solution of 156 mg (0.5 mmol) of the adduct (**13**) in 25 ml of 99% EtOH and 100 mg of 10% Pd–C was stirred under a hydrogen atmosphere at room temperature. When the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was evaporated down to leave the residue. A solution of the residue in 5 ml of pyridine was treated with 169 mg (1.66 mmol) of Ac_2O under ice-cooling. The mixture was allowed to stand at room temperature for 7 hr and then evaporated to dryness under reduced pressure. The residue was made acidic with 5% HCl solution and extracted with ether. The extract was successively washed with water and 2% $NaHCO_3$ solution, then dried over $MgSO_4$ and concentrated. The residue in $CHCl_3$ was chromatographed on silica gel (A) and elution with the same solvent gave 67 mg (50%) of the keto-acetate (**14**), which was identical with an authentic sample.

The Acetal (5)——To a solution of 19.25 g (61.7 mmol) of the adduct (**13**) in 2 l of dry benzene were added 153 g (2.47 mol) of ethylene glycol and 4 g (21.0 mmol) of *p*-toluenesulfonic acid. The mixture was refluxed for 39 hr, while water was removed in a Dean–Stark apparatus. After cooling, the mixture was washed with 5% $NaHCO_3$ solution and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated to leave the residue. The residue in *n*-hexane was chromatographed on basic alumina (C) and the column was eluted with 15% ether in *n*-hexane. The earlier eluate gave 15.72 g (72%) of the acetal (**5**), bp 190°/0.08 mmHg. IR cm^{-1}: ν_{C-C} 1495, ν_{C-O-C} 1030—1180, δ_{C-H} 700. NMR δ: 0.97 (3H, d, J=6.5 Hz, >CH–C<u>H</u>$_3$), 3.45 (2H, m, –C<u>H</u>$_2$–OBzl), 3.88 (4H, s, –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 4.49 (2H, s, –O–C<u>H</u>$_2$–Ph), 5.61 (1H, m, olefinic proton), 7.32 (5H, s, aromatic protons). MS: *m/e* 356 (M^+). Further elution of the column with the same solvent afforded 0.94 g of the starting material (**13**).

The Adduct (15)——To a solution of 5 g (33.3 mmol) of the α,β-unsaturated ketone (**8**) in 20 ml of dry CH_2Cl_2 were added 2.36 g (16.6 mmol) of $BF_3 \cdot Et_2O$ and 5.40 g (99.9 mmol) of butadiene at −30°. The mixture was allowed to stand at room temperature in a sealed tube for 10 days. The reaction mixture was diluted with 5% $NaHCO_3$ solution and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and concentrated to leave the residue. Distillation of the residue gave 2.27 g of the starting material (**8**), bp 56—60°/2 mmHg, as a first fraction and 1.97 g [29% (53% based on the consumed starting

material)] of the adduct (**15**), bp 92°/2 mmHg, as a second fraction. IR cm^{-1}: $\nu_{C=O}$ 1700, $\nu_{C=C}$ 1644, δ_{C-H} 992, 922. NMR δ: 1.02 (3H, d, J=6.5 Hz, >CH–C$\underline{H}_3$), 4.83—6.02 (5H, m, olefinic protons). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.31; H, 10.16.

The Acetal (16)——A mixture of a solution of 1.016 g (4.98 mmol) of the adduct (**15**) in 80 ml of dry benzene with 1.876 g (30.26 mmol) of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 4 hr, while water was removed in a Dean–Stark apparatus. After cooling, the reaction mixture was made basic with 5% $NaHCO_3$ solution and extracted with ether. The extract was dried over $MgSO_4$ and concentrated to leave the residue. The residue in *n*-hexane was chromatographed on basic alumina (C) and elution with the same solvent gave 0.969 g (79%) of the acetal (**16**), bp 96—97°/0.1 mmHg. IR cm^{-1}: $\nu_{C=C}$ 1640, ν_{C-O-C} 1037—1177, δ_{C-H} 997, 920. NMR δ: 1.00 (3H, d, J=6.5 Hz, >CH–C$\underline{H}_3$), 3.92 (4H, s, –OC$\underline{H}_2$C$\underline{H}_2$O–), 4.78—5.22 (2H, m, olefinic protons), 5.63 (2H, m, olefinic protons), 5.77—6.29 (1H, m, olefinic proton). *Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.55; H, 9.50.

The Alcohol (17)——A solution of disiamylborane prepared from 13.8 ml (9.66 mmol) of 0.7 M BH_3–THF solution and 1.69 g (24.12 mmol) of 2-methyl-2-butene in 10 ml of freshly distilled THF was mixed with a solution of 0.904 g (3.65 mmol) of the acetal (**16**) in 5 ml of anhyd. THF. The whole was stirred at 0° for 2 hr. Excess reagent was then destroyed by addition of water, and 1.6 ml of 3 N NaOH solution was added. Next, 1.6 ml of 30% H_2O_2 was added dropwise at a rate such that the temperature did not exceed 10°. The mixture was diluted with 5% sodium thiosulfate solution and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and concentrated to leave the residue. The residue in *n*-hexane was chromatographed on basic alumina (C) and elution with 50% $CHCl_3$ in *n*-hexane provided 624 mg (64%) of the alcohol (**17**), bp 149°/0.14 mmHg. IR cm^{-1}: ν_{OH} 3600, 3440. NMR δ: 1.12 (3H, d, J=6.5 Hz, >CH–C$\underline{H}_3$), 2.30 (1H, br.s, O$\underline{H}$), 3.73 (4H, s, –OC$\underline{H}_2$C$\underline{H}_2$O–), 5.56 (2H, m, olefinic protons). *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.27; H, 10.08.

The Acetal (5) from the Adduct (15)——A solution of 73 mg (0.274 mmol) of the alcohol (**17**) in 4 ml of freshly distilled THF was treaed with 27.5 mg (0.573 mmol) of NaH containing 50% mineral oil, a catalytic amount of *n*-$Bu_4N^+I^-$ and 1 ml of HMPA at 0°. The mixture was stirred for 30 min under an argon atmosphere at room temperature, then a solution of 94 mg (0.549 mmol) of benzyl bromide in 1 ml of anhyd. THF was added and stirring was continued for a further 24 hr. Excess NaH was decomposed by the addition of water and the mixture was extracted with ether. The extract was washed with water, dried over $MgSO_4$ and concentrated to leave the residue. The residue in *n*-hexane was chromatographed on basic alumina (C), and elution with 10% CH_2Cl_2 in *n*-hexane afforded 81 mg (83%) of the acetal (**5**), which was identical with an authentic sample.

The Diol (18)——A solution of 16.18 g (45.4 mmol) of the acetal (**5**) in 22.5 ml of acetone was added to a mixture of 6.33 g (59.2 mmol) of N-methylmorpholine-N-oxide, 57 ml of distilled water and 0.24 g (0.94 mmol) of OsO_4 in 9.5 ml of *tert*-BuOH at 0° under stirring. The mixture was stirred for 22 hr under an argon atmosphere at room temperature in the dark. A solution of 11 g of $NaHSO_3$ in water was added with stirring. After 10 min, 35 g of magnesium silicate was added to the mixture and vigorous stirring was continued for a further 10 min. The precipitates were filtered off and the filtrate was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated to leave the residue. The residue in CH_2Cl_2 was chromatographed on basic alumina (C) and elution with 3% MeOH in CH_2Cl_2 afforded 16.27 g (92%) of the diol (**18**) as an oil. IR cm^{-1}: ν_{OH} 3550, 3425. NMR δ: 0.88 (3H, d, J=6 Hz, >CH–C$\underline{H}_3$), 2.58 (2H, br. s, OH), 3.44 (2H, m, –C$\underline{H}_2$–OBzl), 3.88 (4H, s, –OC$\underline{H}_2$C$\underline{H}_2$O–), 3.99 (2H, m, –OC$\underline{H}$–C$\underline{H}$O–), 4.50 (2H, s, –OC$\underline{H}_2$–Ph), 7.32 (5H, s, aromatic protons). MS *m/e*: 390 (M^+).

The Dialdehyde (6)——A solution of 4.14 g (10.62 mmol) of the diol (**18**) in 100 ml of freshly distilled THF was treated with 2.98 g (13.07 mmol) of periodic acid at 0° under stirring. The mixture was stirred at room temperature for 45 min, diluted with water and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and concentrated to give quantitatively 4.11 g of the dialdehyde (**6**). IR cm^{-1}: ν_{C-H} 2830, 2730, $\nu_{C=O}$ 1712.

Intramolecular Aldol Condensation of the Dialdehyde (6)——1) Method (A): One drop each of piperidine and AcOHwas added to a solution of 226 mg (0.582 mmol) of the dialdehyde (**6**) in 10 ml of dry benzene. The mixture was heated at 60° for 3 hr under a nitrogen atmosphere. After cooling, the reaction mixture was diluted with water and extracted with ether. The extract was dried over $MgSO_4$ and concentrated to afford a mixture of the α,β-unsaturated aldehydes (**19**) and (**20**). Diethylcyanomethyl phosphonate (184 mg, 1.52 mmol) was added dropwise to a suspension of 95 mg (1.98 mmol) of NaH containing 50% mineral oil in 10 ml of dry benzene at 0°. The mixture was stirred at room temperature under an argon atmosphere for 1 hr. A solution of the mixture of **19** and **20** described above in 2 ml of dry benzene was added to the reaction mixture and stirring was continued for a further 1 hr. Excess NaH was decomposed with MeOH and the mixture was diluted with water then extracted with ether. The extract was dried over $MgSO_4$ and concentrated to leave the residue. The residue was chromatographed on basic alumina (C) and the column was eluted with 20% ether in *n*-hexane. The earlier eluate gave 5 mg (2% from **6**) of the conjugated nitrile (**21**) as an oil. IR cm^{-1}: $\nu_{C\equiv N}$ 2220, $\nu_{C=C}$ 1610, 1585. NMR δ: 0.92 (3H, t, J=6 Hz, >CH–C$\underline{H}_3$), 3.45 (2H, t, J=6 Hz, –C$\underline{H}_2$–OBzl), 3.50—3.93 (4H, m, –OC$\underline{H}_2$C$\underline{H}_2$O–), 4.49 (2H, s, O–C$\underline{H}_2$Ph), 5.11 (0.7H, d, J=12 Hz, olefinic proton), 5.71 (0.3H, d, J=17 Hz, olefinic proton), 6.37 (0.3H, m, olefinic proton), 6.66

(0.7H, d, $J=12$ Hz, olefinic proton), 7.02 (0.7H, m, olefinic proton), 7.05 (0.3H, d, $J=17$ Hz, olefinic proton), 7.31 (5H, s, aromatic protons). MS *m/e*: 393 (M^+). Further elution of the column with the same solvent afforded 110 mg (48% from **6**) of the conjugated nitrile (**22**) as an oil. IR cm^{-1}: $\nu_{C\equiv N}$ 2220, $\nu_{C=C}$ 1622, 1590. NMR δ: 0.88 (3H, m, >CH–C$\underline{H}_3$), 3.40 (2H, t, $J=6$ Hz, –C$\underline{H}_2$–OBzl), 3.65—4.00 (4H, m, –OC$\underline{H}_2$C$\underline{H}_2$O–), 4.47 (2H, s, –O–C$\underline{H}_2$Ph), 5.18 (1H, d, $J=17$ Hz, olefinic proton), 6.07 (1H, m, olefinic proton), 7.02 (1H, d, $J=17$ Hz, olefinic proton), 7.31 (5H, s, aromatic protons). MS *m/e*: 393 (M^+).

2) Method (B): A solution of 129 mg (0.333 mmol) of the dialdehyde (**6**) in 10 ml of dry benzene was treated with 21 mg (0.066 mmol) of dibenzylammonium trifluoroacetate. The mixture was heated for 3.5 hr at 50° under a nitrogen atmosphere. The usual work-up gave a mixture of **19** and **20**. The mixture was treated with Wadsworth–Emmons' reagent, prepared from 48 mg (0.999 mmol) of 50% NaH and 101 mg (0.835 mmol) of diethylcyanomethyl phosphonate in 7 ml of dry benzene, to give 5 mg (4% from **6**) of **21** and 95 mg (73% from **6**) of **22**.

3) Method (K): To a solution of 129 mg (0.333 mmol) of the dialdehyde (**6**) in 7 ml of dry ether were added 261 mg (2.267 mmol) of *l*-proline, 89 mg (0.500 mmol) of HMPA and 3.5 ml of abs. EtOH. The mixture was stirred at room temperature under an argon atmosphere for 20 hr. The reaction mixture was diluted with water and extracted with ether. The extract was dried over $MgSO_4$ and concentrated to give a mixture of **19** and **20**. The mixture was treated with Wadsworth–Emmons' reagent prepared from 48 mg (0.999 mmol) of 50% NaH and 101 mg (0.835 mmol) of diethylcyanomethyl phosphonate in 7 ml of dry benzene, to afford 1 mg (1% from **6**) of **21** and 30 mg (23% from **6**) of **22**.

4) General Procedure for Intramolecular Aldol Condensation of **6** using Excess Amine and Acid: To a solution of the dialdehyde (**6**) in dry ether were added 5.8 eq. of the amine, 6.8 eq. of the acid and 1.5 eq. of HMPA at 0° under vigorous stirring. The mixture was stirred at 0° under an argon atmosphere for 20 hr, then the reaction mixture was diluted with water and extracted with ether. The extract was washed with a large amount of water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was treated with 2.5 eq. of Wadsworth-Emmons' reagent prepared from 50% NaH and diethylcyanomethyl phosphonate in dry benzene. Separation of the crude products by column chromatography on basic alumina (C) gave **21** and **22**.