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Regioselective Intramolecular Aldol Condensation by Using Excess Morpholine-Camphoric Acid

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Regioselective intramolecular aldol condensations of type I dialdehydes were explored under various reaction conditions, including those of the Woodward and the Corey methods. The results obtained by the use of excess morpholine–camphoric acid are given in Table I in comparison with those obtained by the previous methods. The structure assignments of products by nuclear magnetic resonance analysis are also described.

Keywords——dialkyl *cis*-decalone derivatives; 1,2-cyclohexadiacetaldehyde derivative; NMR analysis; regioselective intramolecular aldol condensation; excess morpholine-camphoric acid

Intramolecular aldol condensation of dialdehyde derivatives is one of the most important methods for the construction of the carbocyclic skeleton of many classes of natural products.[1–4] This type of reaction, however, generally proceeds in two ways to furnish two kinds of α,β-unsaturated aldehydes in a certain ratio, for example, type IA and type IB aldehydes when applied to an unsymmetrical 1,2-cyclohexanediacetaldehyde such as I. Therefore, much attention has been devoted to regioseletivity in reactions of this type.[1–5]

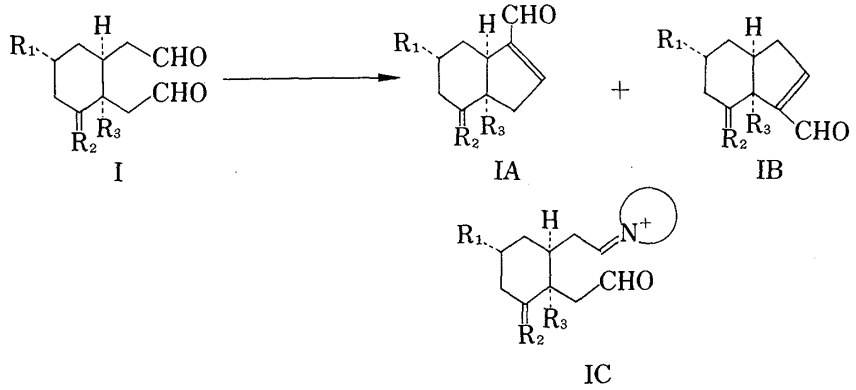


Chart 1

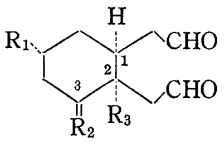
In connection with the synthesis of 8-deoxyserratinine type alkaloids, we have already reported that the excess morpholine–camporic acid method gives regioselectively the type IB compound, probably *via* a monoimmonium intermediate IC in the intramolecular aldol condensation of the type I compound.[6] On the other hand, the previous methods, the Woodward[1] and the Corey[7] methods, provided regioselectively the type IA compound. In order to examine the generality of the present method, aldol condensation reactions of II,[6] III, IV, V, VI, VII,[8] and VIII[2] were carried out under four different reaction conditions (*vide infra*). We report here details of the results obtained by these methods and the structure assignments of products by nuclear magnetic resonance (NMR) analysis.

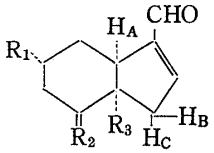
Synthesis of Dialdehydes

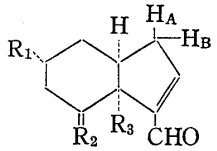
The known diadehydes (II,[6] VII,[8] and VIII)[2] were prepared by the reported methods, and the new dialdehydes (III, IV, V, and VI) were synthesized as follows.

Dialdehyde (III)

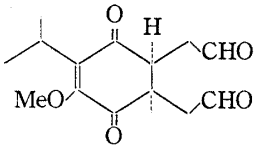
Acetylation of the alcohol (IX)[6] afforded the acetate (X) in 96% yield. It was dihydroxylated by the VanRheenen method[9] to give the major diol (XIa) and the minor diol (XIb) in 77% and 4% yields, respectively. The diols (XI) were oxidized with periodic acid to give the dialdehyde (III) quantitatively.



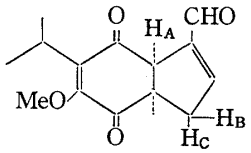




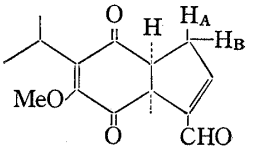
II : $R_1=CH_3$, $R_2=-O(CH_2)_2O-$, $R_3=-(CH_2)_3OCH_2C_6H_5$ — IIA — IIB
III : $R_1=CH_3$, $R_2=-O(CH_2)_2O-$, $R_3=-(CH_2)_3OAc$ — IIIA — IIIB
IV : $R_1=R_3=CH_3$, $R_2=-O(CH_2)_2O-$ — IVA — IVB
V : $R_1=$iso-Pr, $R_2=-O(CH_2)_2O-$, $R_3=CH_3$ — VA — VB
VI : $R_1=R_3=CH_3$, $R_2=O$ — VIA — VIB
VII : $R_1=$iso-Pr, $R_2=O$, $R_3=CH_3$ — VIIA — VIIB



VIII

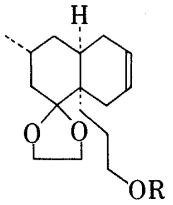


VIIIA

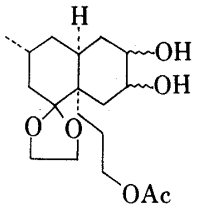


VIIIB

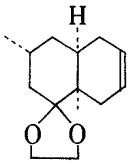
Chart 2



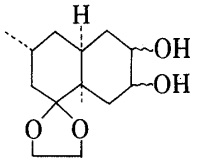
IX : R=H
X : R=Ac



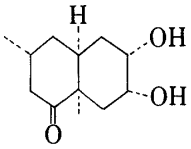
XIa : *α-cis* glycol
XIb : *β-cis* glycol



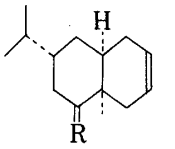
XII



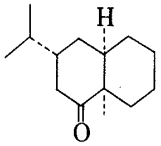
XIIIa : *α-cis* glycol
XIIIb : *β-cis* glycol



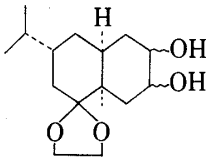
XIV



XV : R=O
XVII : R=



XVI



XVIIIa : *α-cis* glycol
XVIIIb : *β-cis* glycol

Chart 3

Dialdehydes (IV) and (VI)

Dihydroxylation of the acetal (XII)[10] by the VanRheenen method[9] provided the major diol (XIIIa) and the minor diol (XIIIb) in 78% and 5% yields, respectively. Deacetalization of the diol (XIIIa) with HCl afforded the diol–ketone (XIV) in 92% yield. Treatment of the diols (XIII) and the diol–ketone (XIV) with periodic acid gave quantitatively the aldehydes (IV) and (VI), respectively.

Dialdehyde (V)

The unsettled configuration of an isopropyl group in XV, reported by Kaneko *et al.*,[8] was determined as follows. Thus, the Diels–Alder adduct (XV) was hydrogenated over platinum oxide to give the ketone (XVI), which was found to be identical with a sample of the stereochemically established ketone (XVI)[10] by comparison of the infrared (IR) and the NMR spectra. Dihydroxylation of the acetal (XVII) derived from XV gave the major diol (XVIIIa) and the minor diol (XVIIIb) in 60% and 7% yields, respectively. Oxidation of the diols (XVIII) with periodic acid gave the aldehyde (V) quantitatively.

Results of Aldol Condensations

All dialdehydes (without purification) were subjected to intramolecular aldol condensation by four different methods; Method A (the Woodward method),[1] with a catalytic amount of piperidine acetate in C_6H_6 at 60° for 3—4 hr; Method B (the Corey method),[7] with 0.2 eq of dibenzylammonium trifluoroacetate in C_6H_6 at 50° for 3—4 hr; Method C, with 5.8 eq of morpholine and 6.8 eq of camphoric acid in dry Et_2O–HMPA (1.5 eq) at 0° for 1—2 days; Method D, with a small amount of ethanol added to the Method C solvent system in order to prepare a homogeneous solution. Isolation of the aldol products was performed by preparative thin-layer chromatography (TLC).

Table I. The Ratio of Type A/Type B Products and Total Yield of the Intramolecular Aldol Condensations

	Method A		Method B		Method C		Method D	
II	19/1	62%	21/1	80%	1/25	54%	1/25	50%
III	4.1/1	68%	19.8/1	78%	1/26	58%	1/13	43%
IV[a]	1.8/1	53%	5.2/1	89%	1/44	38%	1/27	47%
V	1.7/1	29%	7/1	43%	1/10	16%	1/26	53%
VI	3.8/1	67%	2/1	78%	3.3/1	18%	4/1	38%
VII	10.3/1	62%	1.9/1	73%	1.3/1	16%	1.5/1	51%
VIII	1/1	18%	2.5/1	37%	1.7/1	16%	1/1	22%[b]

a) Aldol reaction of IV with 0.2 eq of L-proline methyl ester and trifluoroacetic acid in benzene at 60° gave IVA and IVB in 4.9/1 ratio and 92% total yield. Reaction with 5.8 eq of L-proline methyl ester and 6.8 eq of camphoric acid in dry Et_2O–HMPA–EtOH at 0° afforded IVA and IVB in 1/2.9 ratio and 61% total yield.
b) The yield upon column chromatographic separation on Florisil was 53%, with the same product ratio.

The structure assignments of products mainly depended on the signal patterns of the allylic methylene protons in their NMR spectra. Thus, three allylic proton signals (H_A, H_B, and H_C) of the type A product appeared as a splitting pattern (see Table II) and allylic proton signals (H_A and H_B) of the type B product appeared virtually as a broad singlet (see Table III). In the case of acetals such as IVA, IVB, *etc.*, the signals of acetal methylene protons appeared as a broad singlet in the type A product and as a multiplet in the type B product, and could also be used to distinguish between the type A product and the type B product. The validity of these NMR spectroscopic structure assignments was supported ultimately by transformation of the acetal (IIIB) and the ketone (VIIIB) into natural alkaloids of established structures, 8-deoxyserratinine[4] and dendrobine,[2] respectively.

The aldol condensation of VII by the Woodward method was carried out by Kaneko

Table II. NMR Data for Type A Products (60 MHz, δ value)

Product	CHO	CH=C–CHO	Acetal protons	H_A	H_B	H_C	*tert*-CH_3	*sec*-CH_3
IIA[a]	9.74(s)	6.78(m)	3.93(br. s)	3.00(m)	2.80(ddd) J=20, 2, 2 Hz	2.25(dd) J=20, 2 Hz	—	0.89(br. d) J=4 Hz
IIA[a]	9.67(s)	6.75(m)	3.93(br. s)	3.00(m)	2.83(ddd) J=20, 2, 2 Hz	2.22(dd) J=20, 2 Hz	—	0.93(br. d) J=4 Hz
IVA	9.70(s)	6.78(m)	3.93(br. s)	2.85(m)	2.81(ddd) J=18, 2, 2 Hz	2.17(dd) J=18, 2 Hz	1.10(s)	0.90(br. d) J=4 Hz
VA	9.67(s)	6.75(m)	3.92(br. s)	2.93(m)	2.82(ddd) J=19, 2, 2 Hz	2.14(dd) J=19, 2 Hz	1.07(s)	0.82(d) J=5 Hz
VIA	9.67(s)	6.85(m)	—	3.10(m)	3.22(ddd) J=20, 2, 2 Hz	2.20(ddd) J=20, 2, 2 Hz	1.26(s)	1.00(d) J=5 Hz
VIIA	9.70(s)	6.86(m)	—	3.13(m)	3.22(ddd) J=20, 2, 2 Hz	2.22(ddd) J=20, 2, 2 Hz	1.26(s)	0.90(d) J=5 Hz
VIIIA[a]	9.75(s)	6.88(m)	—	3.79(m)	3.13(ddd) J=19, 2, 2 Hz	2.53(ddd) J=19, 2, 2 Hz	1.40(s)	1.17(d) J=6 Hz

For signals of the compounds marked
a) which are not given in this table, see the corresponding compound in "Experimental."

Table III. NMR Data for Type B Products (60 MHz, δ value)

Product	CHO	CH=C–CHO	Acetal protons	H_A and H_B	*tert*-CH_3	*sec*-CH_3
IIB[a]	9.72(s)	7.05(m)	3.66—3.96(m)	2.45(br. s)	—	0.92(d, J=6 Hz)
IIIB[a]	9.67(s)	7.03(m)	3.60—4.15(m)	2.43(br. s)	—	0.92(d, J=6 Hz)
IVB	9.67(s)	7.00(m)	3.50—3.95(m)	2.35(br. s)	1.43(s)	0.92(d, J=6 Hz)
VB	9.67(s)	7.00(m)	3.67—4.00(m)	2.37(br. s)	1.42(s)	0.88(d, J=6 Hz)
VIB	9.72(s)	6.89(m)	—	2.27 and/or 2.53(br. s)	1.47(s)	1.02(d, J=6 Hz)
VIIB	9.72(s)	6.88(m)	—	2.25 and/or 2.50(br. s)	1.45(s)	0.90(d, J=6 Hz)
VIIIB[a]	9.70(s)	6.93(m)	—	3.02(br. s)	1.46(s)	1.13(d, J=6 Hz)

For signals of the compounds marked
a) which are not given in this table, see the corresponding compound in "Experimental."

et al., and they reported that the structure of the only well-defined product was represented by the formula (VIIB), while the other could not be isolated in a pure form.[8] We reexamined this reaction and obtained the major and the minor products in a 10.3: 1 ratio. Judging from the NMR analysis mentioned above, we concluded that the structure of the major product is reasonably represented by the formula (VIIA) rather than the reported formula (VIIB).

The results obtained by the present methods (Methods C and D) are shown in Table I compared with those obtained by the previous methods (Methods A and B). As can be seen from Table I, the use of morpholine–camphoric acid gave preferentially the type B products, in contrast to the previous methods (see runs II—V in Table I). Although the regioselectivity is affected by the structure of the starting material, for example, by conversion of the C_3 acetal group of compound (IV) to the C_3 carbonyl group of compound (VI) (see runs VI—VIII in Table I), the present method should have considerable utility because its regioselectivity is opposite to that observed in the previous methods.

Experimental

Melting points were measured on a microscopic hot stage (Yanagimoto melting points apparatus) and are uncorrected. All NMR spectra were taken on a Varian A-60 spectrometer or a JNM-PMX 60 NMR 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 JEOL JMS-01SG-2 spectrometer. Column chromatography was performed on basic alumina (Aluminium Oxyd. G. Brockmann, Activity II—III) and preparative TLC on silica gel (Merck Kieselgel 60, PF_{254}).

The Acetate (X)——Ac_2O (437 mg, 4.3 mmol) was added to a solution of 518 mg (1.9 mmol) of the alcohol (IX) in 15 ml of pyridine, and the mixture was allowed to stand at room temperature for 36 hr. The reaction mixture was concentrated to leave the residue. The residue was diluted with $CHCl_3$ and the whole was washed with 5% HCl and 2% $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated down to leave the residue. The residue in *n*-hexane was chromatographed on basic alumina, and elution with 50% ether in *n*-hexane gave 573 mg (96%) of the acetate (X). IR cm^{-1}: $\nu_{C=O}$ 1725, ν_{C-O} 1260—1210. NMR δ: 0.99 (3H, d, $J=7$ Hz, >CH–C$\underline{H}_3$), 2.03 (3H, s, OCOC$\underline{H}_3$), 3.82—4.11 (6H, m, –O–C$\underline{H}_2$–C$\underline{H}_2$–O– and –C$\underline{H}_2$–OAc), 5.60 (2H, m, olefinic protons). MS *m/e*: 308 (M^+).

The Diols (XIa) and (XIb)——A solution of 564 mg (1.92 mmol) of the acetate (X) in 10 ml of acetone was added to a mixture of 267 mg (2.50 mmol) of N-methylmorpholine-N-oxide, 15 ml of distilled water and 5.9 mg (0.02 mmol) of OsO_4 in 3 ml of *tert*-BuOH under stirring. The mixture was stirred for 16 hr under an argon atmosphere at room temperature in the dark. A solution of 3.1 g of $NaHSO_3$ in water was added with stirring. After 10 min, 3.8 g of magnesium silicate was added to the mixture and vigorous stirring was continued for a further 30 min. The precipitate was 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, and elution with 1% MeOH in CH_2Cl_2 gave 25 mg (4%) of the diol (XIb). IR cm^{-1}: ν_{O-H} 3500, 3350, $\nu_{C=O}$ 1725. NMR δ: 0.92 (3H, d, $J=6$ Hz, >CH–C$\underline{H}_3$), 2.03 (3H, s, OCOC$\underline{H}_3$), 3.30—4.15 (4H, m, 2×>C$\underline{H}$–OH, and –C$\underline{H}_2$OAc), 4.00 (4H, m, –OC$\underline{H}_2$–C$\underline{H}_2$–O–). MS *m/e*: 328 (M^+). Elution with 3% MeOH in CH_2Cl_2 afforded 487 mg (77%) of the diol (XIa). IR cm^{-1}: ν_{O-H} 3550, 3400, $\nu_{C=O}$ 1725. NMR δ: 0.88 (3H, d, $J=6$ Hz, >CH–C$\underline{H}_3$), 2.02 (3H, s, –OCOC$\underline{H}_3$), 3.88 (4H, s, –O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 3.80—4.25 (4H, m, 2×>C$\underline{H}$–OH and –C$\underline{H}_2$–OAc). MS *m/e*: 328 (M^+).

The Diols (XIIIa) and (XIIIb)——A solution of 5.79 g (26.1 mmol) of the acetal (XII) in 18 ml of acetone was added to a mixture of 3.63 g (33.9 mmol) of N-methylmorpholine-N-oxide, 30 ml of distilled water and 0.13 g (0.5 mmol) of OsO_4 in 6 ml of *tert*-BuOH at 0° under stirring. The mixture was stirred for 21 hr under an argon atmosphere at room temperature in the dark. A solution of 9.39 g of $NaHSO_3$ in water was added with stirring. After 5 min, 30.6 g of magnesium silicate was added to the mixture and vigorous stirring was continued for a further 15 min. The precipitate was 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 50% *n*-hexane in $CHCl_3$ was chromatographed on basic alumina, and elution with $CHCl_3$ afforded a solid mass. Recrystallization from ether–*n*-hexane gave 0.34 g (5%) of the diol (XIIIb) as colorless plates, mp 119—120°. IR cm^{-1}: ν_{O-H} 3510, 3350. NMR δ: 0.90 (3H, d, $J=6$ Hz, >CH–C$\underline{H}_3$), 1.13 (3H, s, >C–C$\underline{H}_3$), 3.30—4.30 (6H, m, 2×>C$\underline{H}$–OH and –O–C$\underline{H}_2$–C$\underline{H}_2$–O–). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.45; H, 9.64. Further elution with the same solvent provided a solid mass. Recrystallization from ether–*n*-hexane gave 5.20 g (78%) of the diol (XIIIa) as colorless prisms, mp 113—115°. IR cm^{-1}: ν_{O-H} 3560, 3450. NMR δ: 0.88 (3H, d, $J=6$ Hz, >CH–C$\underline{H}_3$), 1.00 (3H, s, >C–C$\underline{H}_3$), 3.93 (4H, s, –O–C$\underline{H}_2$–C$\underline{H}_2$–O), 4.03 (2H, m, 2×>C$\underline{H}$–OH). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.74; H, 9.68.

The Keto-diol (XIV)——A solution of 1.5 g (5.86 mmol) of the diol (XIIIa) in freshly distilled tetrahydrofuran was treated with 8 ml of 5% HCl solution. The mixture was stirred for 2 days 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 water, dried over K_2CO_3, and concentrated to leave the residue. The residue was recrystallized from ether to give 1.14 g (92%) of (XIV) as colorless plates, mp 122.5—123°. IR cm^{-1}: ν_{O-H} 3400, $\nu_{C=O}$ 1695. NMR δ: 1.04 (3H, br. s, >CH–C$\underline{H}_3$), 1.24 (3H, s, >C–C$\underline{H}_3$), 3.54—4.08 (2H, m, 2×>C$\underline{H}$–OH). *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.94; H, 9.70.

The Ketone (XVI)——A solution of 95 mg (0.46 mmol) of the adduct (XV) in 7 ml of EtOH was mixed with 50 mg of 10% Pd-C catalyst and the mixture was stirred under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated. The residue in *n*-hexane was chromatographed on basic alumina, and elution with the same solvent afforded 67 mg (70%) of the ketone (XVI). The IR and NMR spectral data and the retention time on gas-liquid chromatography (GLC) were identical with those of an authentic sample.

The Acetal (XVII)——A solution of 4.53 g (22 mmol) of the adduct (XV) in 300 ml of dry benzene was added to a mixture of 6.27 g (101.1 mmol) of ethylene glycol and 400 mg of *p*-toluenesulfonic acid. The mixture was refluxed for 6 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. Distillation of the residue gave 4.65 g (85%) of XVII, bp 108—111°/0.8 mmHg. IR cm^{-1}: $\nu_{C=C}$ 1655; ν_{C-O} 1200—1050. NMR δ: 0.89 (6H, d, $J=6$ Hz, $\underline{CH}_3$>$\underline{CH}_3$>CH–), 1.00 (3H, s, >C–C$\underline{H}_3$), 3.73 (4H, s, –O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 5.60 (2H, m, olefinic protons). *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.61; H, 10.30.

The Diols (XVIIIa) and (XVIIIb)——A solution of 600 mg (2.4 mmol) of the acetal (XVII) in 9 ml of acetone was added to a mixture of 334 mg (3.12 mmol) of N-methylmorpholine-N-oxide, 23 ml of distilled

water and 7.4 mg (0.03 mmol) of OsO_4 in 3.6 ml of *tert*-BuOH at room temperature under stirring. The mixture was stirred for 20 hr under an argon atmosphere in the dark. A solution of 1.1 g of $NaHSO_3$ in water was added to the mixture under vigorous stirring. After the mixture had been stirred for a further 10 min, the precipitate was 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 50% *n*-hexane in $CHCl_3$ was chromatographed on basic alumina, and elution with $CHCl_3$ afforded 48 mg (8%) of XVIIIb. IR cm^{-1}: ν_{O-H} 3560, 3350. NMR δ: 0.91 (6H, d, J=6 Hz, $\underline{CH}(CH_3)_2$), 1.17 (3H, s, $>C-C\underline{H}_3$), 3.20—4.40 (6H, m, $2\times>C\underline{H}-OH$ and $-O-C\underline{H}_2-C\underline{H}_2-O-$). MS *m/e*: 284 ($M^+$). Elution with 3% MeOH–$CHCl_3$ gave 483 mg (70%) of (XVIIIa). IR cm^{-1}: ν_{O-H} 3550, 3390. NMR δ: 0.92 (6H, d, J=5.0 Hz, $CH_3>C\underline{H}-$), 1.15 (3H, s, $>C-C\underline{H}_3$), 3.97 (4H, s, $-O-C\underline{H}_2-C\underline{H}_2-O-$), 3.86—4.21 (2H, m, $2\times>C\underline{H}-OH$). MS *m/e*: 284 ($M^+$).

The Dialdehydes (III), (IV), (V), and (VI)——A solution of the diol (XI) in freshly distilled tetrahydrofuran (THF) was treated with 1.23 eq of HIO_4 at 0° under stirring. The mixture was stirred at room temperature for 1—1.5 hr, then the reaction mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and concentrated to give the aldehyde (III) quantitatively. The same treatments of the diols (XIII, XIV, and XVIII) gave the aldehydes (IV, VI, and V), respectively.

General Procedure for Intramolecular Aldol Condensation of the Dialdehyde——1) Method A (The Woodward Method): A catalytic amount of piperidine acetate was added to a solution of the dialdehyde in dry benzene. The mixture was heated at 60° for 3—4 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 leave a mixture of the α,β-unsaturated aldehydes. The mixture was separated by preparative TLC on silica gel.

2) Method B (the Corey Method): A solution of the dialdehyde in dry benzene was treated with 0.2 eq of dibenzylamine trifluoroacetate. The mixture was heated at 50° for 3—4 hr under a nitrogen atmosphere. The usual work-up gave a mixture of the α,β-unsaturated aldehydes. The mixture was separated by preparative TLC on silica gel.

3) Method C: A solution of the dialdehyde in dry ether was added to a mixture of 5.8 eq of morpholine, 6.8 eq of camphoric acid and 1.5 eq of HMPA at 0° under vigorous stirring. The mixture was stirred at 0° under an argon atmosphere for 1—2 days, 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 to leave a mixture of α,β-unsaturated aldehydes. The mixture was separated by preparative TLC on silica gel.

4) Method D: A solution of the dialdehyde in dry ether was treated with 5.8 eq of morpholine, 6.8 eq of camphoric acid, 1.5 eq of HMPA and a small amount of abs. EtOH. The mixture was vigorously stirred at 0° under an argon atmosphere for 1—2 days. The usual work-up gave a mixture of α,β-unsaturated aldehydes. The mixture was separated by preparative TLC on silica gel.

α,β-Unsaturated Aldehyde (IIA): Oil. IR cm^{-1}: $\nu_{C=O}$ 1668, $\nu_{C=C}$ 1623, 1610. NMR δ: 3.42 (2H, t, J=5 Hz, $-C\underline{H}_2-O-$), 4.48 (2H, s, $-O-C\underline{H}_2-C_6H_5$), 7.33 (5H, s, aromatic protons). MS *m/e*: 370 (M^+).

α,β-Unsaturated Aldehyde (IIB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1675, $\nu_{C=C}$ 1590. NMR δ: 3.45 (2H, m, $-C\underline{H}_2-O$), 4.49 (2H, s, $-O-C\underline{H}_2-C_6H_5$), 7.33 (5H, s, aromatic protons). MS *m/e*: 370 (M^+).

α,β-Unsaturated Aldehyde (IIIA): Colorless needles, mp 105—106° (recrystallization from ether–*n*-hexane). IR cm^{-1}: $\nu_{C=O}$ 1730, 1675, $\nu_{C=C}$ 1625, 1610. NMR δ: 2.02 (3H, s, $-OCOC\underline{H}_3$), 4.00 (2H, m, $-C\underline{H}_2-$OAc). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.23; H, 8.15.

α,β-Unsaturated Aldehyde (IIIB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1720, 1670, $\nu_{C=C}$ 1590. NMR δ: 2.02 (3H, s, $-OCOC\underline{H}_3$), 4.00 (2H, m, $-C\underline{H}_2-$OAc). MS *m/e*: 322 (M^+).

α,β-Unsaturated Aldehyde (IVA): Oil. IR cm^{-1}: $\nu_{C=O}$ 1675, $\nu_{C=C}$ 1623, 1608. MS *m/e*: 236 (M^+).

α,β-Unsaturated Aldehyde (IVB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1680, $\nu_{C=C}$ 1593. MS *m/e*: 236 (M^+).

α,β-Unsaturated Aldehyde (VA): Oil. IR cm^{-1}: $\nu_{C=O}$ 1670, $\nu_{C=C}$ 1617, 1603. MS *m/e*: 264 (M^+).

α,β-Unsaturated Aldehyde (VB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1680, $\nu_{C=C}$ 1588. MS *m/e*: 264 (M^+).

α,β-Unsaturated Aldehyde (VIA): Oil. IR cm^{-1}: $\nu_{C=O}$ 1700, 1680, $\nu_{C=C}$ 1615, 1605. MS *m/e*: 192 (M^+).

α,β-Unsaturated Aldehyde (VIB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1703, 1680, $\nu_{C=C}$ 1610. MS *m/e*: 192 (M^+).

α,β-Unsaturated Aldehyde (VIIA): Oil. IR cm^{-1}: $\nu_{C=O}$ 1695, 1680, $\nu_{C=C}$ 1615, 1605. MS *m/e*: 220 (M^+).

α,β-Unsaturated Aldehyde (VIIB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1705, 1683, $\nu_{C=C}$ 1613. MS *m/e*: 220 (M^+).

α,β-Unsaturated Aldehyde (VIIIA): Oil. IR cm^{-1}: $\nu_{C=O}$ 1685, $\nu_{C=C}$ 1592. NMR δ: 3.20 (1H, q, J=6 Hz, $-C\underline{H}(CH_3)_2$), 3.88 (3H, s, $-OC\underline{H}_3$). MS *m/e*: 262 (M^+).

α,β-Unsaturated Aldehyde (VIIIB): Oil. IR cm^{-1}: $\nu_{C=O}$ 1700, 1680, 1655, $\nu_{C=C}$ 1610, 1590. NMR δ: 3.20 (1H, q, J=6 Hz, $-C\underline{H}(CH_3)_2$), 3.90 (3H, s, $-OC\underline{H}_3$). MS *m/e*: 262 (M^+).

Aldol Reaction of IV with a Catalytic Amount of L-Proline Methyl Ester and Trifluoroacetic Acid—— A solution of 84 mg (0.3 mmol) of IV in 10 ml of dry benene was added to a mixture of a catalytic amount of L-proline methyl ester and trifluoroacetic acid. The mixture was heated at 60° for 4 hr under a nitrogen atmosphere. The usual work-up gave a mixture of IVA and IVB. The mixture was separated by pre-

parative TLC on silica gel to give 54 mg (76%) of IVA and 11 mg (16%) of IVB.

Aldol Reaction of (IV) with Excess L-Proline Methyl Ester and Camphoric Acid——A solution of 84 mg (0.3 mmol) of IV in 10 ml of dry ether was added to a mixture of 225 mg (1.75 mmol) of L-proline methyl ester, 204 mg (1.02 mmol) of camphoric acid, 81 mg (0.45 mmol) of HMPA and 5 ml of abs. EtOH. The mixture was vigorously stirred at 0° for 24 hr under an argon atmosphere. The reaction mixture was diluted with water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated to leave a mixture of IVA and IVB. The mixture was separated by preparative TLC on silica gel to afford 11 mg (16%) of IVA and 32 mg (45%) of IVB.

References and Notes

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