

Synthesis of 1,3-Dioxin-4-ones and Their Use in Synthesis.¹⁾ XVIII. Synthesis of Azetidin-2-ones from 1,3-Dioxin-4-ones via 3-Hydroxycarboxamides

Jun-ichi SAKAKI,* Satoshi KOBAYASHI, Masayuki SATO, and Chikara KANEKO*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan. Received May 10, 1989

A general method for the synthesis of azetidin-2-ones from 1,3-dioxin-4-ones is described. The method consists of 1) the formation of β -ketocarboxamides, 2) their reduction to 3-hydroxycarboxamides, 3) mesylation, and 4) base-mediated cyclization of 3-mesyloxycarboxamides to the final azetidinones. Stereochemical demand in the cyclization step has been clarified by using 5,6-tri- and -tetramethylene derivatives of 2,2-dimethyl-1,3-dioxin-4-one. Microbiological reduction of the acetoacetamides by baker's yeast gave (*S*)-3-hydroxybutanamides of $\geq 98\%$ optical purity, whose cyclization afforded (*R*)-4-methylazetidin-2-ones.

Keywords β -lactam; azetidin-2-one; 1,3-dioxin-4-one; β -ketocarboxamide; 3-hydroxycarboxamide; asymmetric reduction; baker's yeast; (*S*)-3-hydroxybutanamide; (*R*)-4-methylazetidin-2-one

Previous papers in this series have described the preparation of β -ketocarboxamide derivatives by heating of 2,2-dimethyl-1,3-dioxin-4-ones having a variety of alkyl groups at the 5- and/or 6-positions in an appropriate solvent containing amines.^{2,3)} Furthermore, recent work in our laboratories has not only disclosed a facile synthetic method for 5,6-unsubstituted dioxinones⁴⁾ (e.g. A: $R^1, R^2 = H$), but also provided regioselective methods for the introduction of a variety of substituents into the 5- and/or 6-positions of these dioxinones.^{5,6)} Though previous methods for the synthesis of β -ketocarboxamides (B) have not been proved to be consistently practicable,⁷⁾ it is evident that a variety of α -substituted β -ketocarboxamides can now be prepared from the corresponding dioxinones by the above route. Since 3-hydroxycarboxamides (C) can readily be obtained from them by appropriate reduction, it seems worth while examining the cyclization of these hydroxyamides to azetidin-2-ones (E) and to clarify the stereochemical demand in the entire reaction sequence (A $\rightarrow$ B $\rightarrow$ C $\rightarrow$ D $\rightarrow$ E).

In this paper, we report 1) synthesis of 3-hydroxycarboxamides (C) by the reduction with sodium borohydride of β -ketocarboxamides (B), which are readily obtainable from the dioxinones (A), and cyclization of suitably functionalized amides (D) derived from C to the corresponding β -lactams (E) via manipulation of the 3-hydroxyl group to a suitable leaving group (L) followed by ring closure under appropriate

basic conditions, 2) clarification of the stereochemical aspects of the entire process using the 5,6-polymethylene derivatives of the dioxinones, and 3) an extension of this method to the enantioselective synthesis of azetidin-2-ones by the use of baker's yeast in the reduction step (B $\rightarrow$ C).

Fundamental Experiments Using 2,2,6-Trimethyl-1,3-dioxin-4-one as the Model Starting Material for the Synthesis of 4-Methylazetidin-2-ones Using 2,2,6-trimethyl-1,3-dioxin-4-one (**1**) as the starting material, its conversion to 4-methylazetidin-2-ones (**5**) was examined. Thus, **1** and four amines (aniline, its *p*-methoxy derivative, benzylamine, and *O*-benzylhydroxylamine) were refluxed in xylene to give the corresponding β -ketocarboxamides (**2a–d**), all in satisfactory yields.⁸⁾ Reduction of the ketoamides (**2**) with sodium borohydride in methanol then gave the alcohols (**3a–d**). Treatment of **3** with mesyl chloride in pyridine gave the corresponding mesylates (**4a–d**). Both the reduction and mesylation reactions proceeded smoothly without formation of any by-product and hence the overall yields of **4** from **2** should be almost quantitative, though actual isolation yields of **3** in the reduction step were in the range of 76% to 85%.⁹⁾

Finally, the mesylates (**4**) were treated with sodium hydride¹⁰⁾ (an equimolar amount to **4**) in a mixture of dichloromethane and *N,N*-dimethylformamide (DMF) (4:1) at room temperature to give the β -lactams (**5**). Though **4c** gave

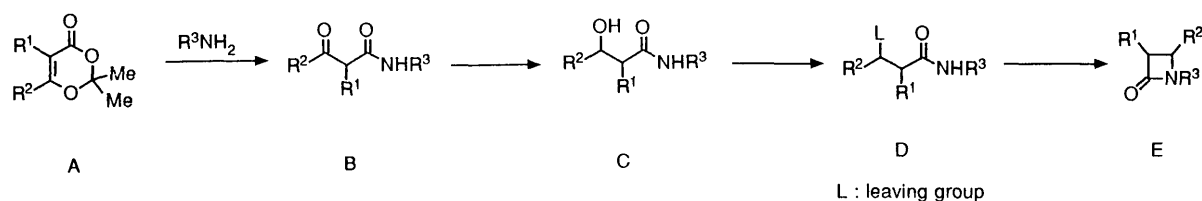


Chart 1

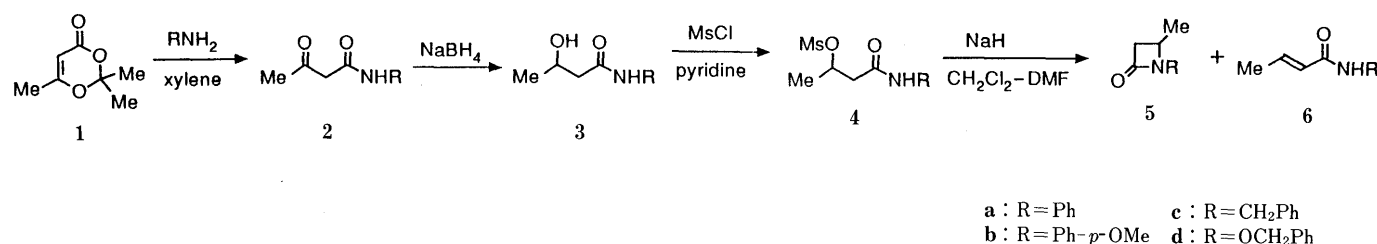


Chart 2

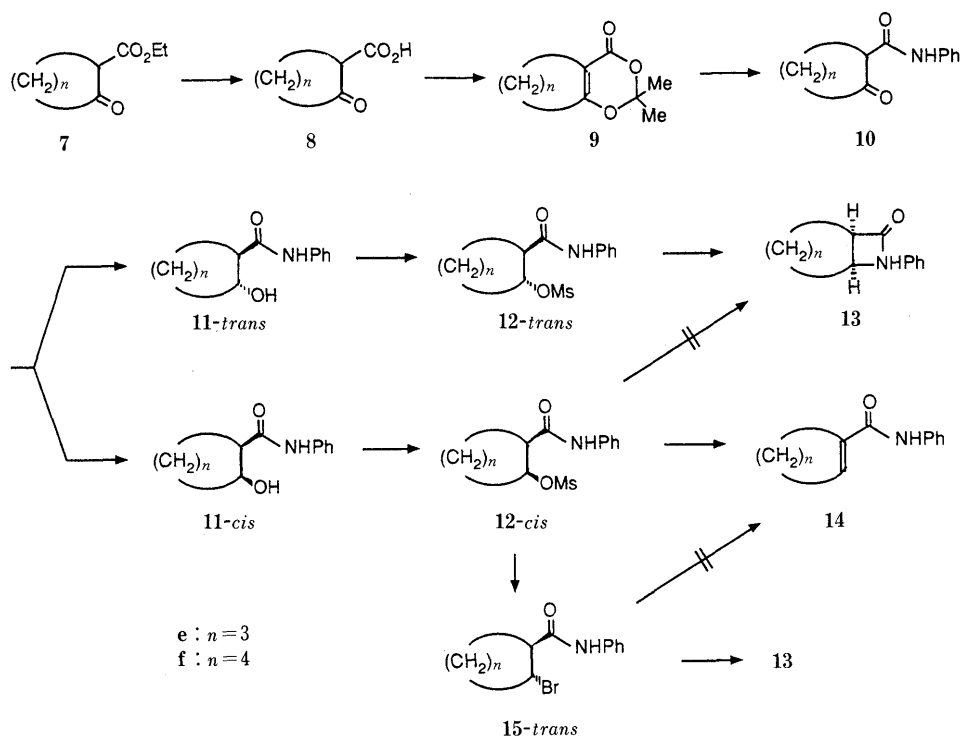


Chart 3

the enamide (**6c**) as the major product, the cyclization of **4a,b,d** afforded the β -lactams (**5a,b,d**) in high yields together with very small amounts of the enamides (**6a,b,d**). The yields of **6a,b,d** did not exceed 5%, though they increased somewhat if higher concentration of **4** was used in the cyclization reaction. It should be noted that the use of DMF as the solvent is essential for the cyclization, because none of the β -lactam was obtained if the reaction was carried out in dichloromethane alone.

Stereochemical Aspects of the Cyclization Step Using 5,6-Tri- and -Tetramethylene-1,3-dioxin-4-ones as the Starting Materials In order to clarify the stereochemical aspects of β -lactam formation from the dioxinones, we then applied our method to the dioxinones (**9e** and **9f**) having a three- or four-methylene bridge between the 5- and 6-positions. This was done because the use of **9** not only shows clearly what stereochemical demand exists in the reduction step from the β -ketoamides to the 3-hydroxyamides (**10**→**11**) but also reveals how the ease of β -lactam formation depends upon the relative configuration (*cis* and *trans* relationship) between the amide and mesyloxy groups of the mesyloxyamides (**12**).

Though the 5,6-tetramethylene derivative (**9f**) of 2,2-dimethyl-1,3-dioxin-4-one was prepared previously in our laboratories from 2-oxocyclohexanecarboxylic acid (**8f**),²⁾ the corresponding trimethylene derivative (**9e**) has only been synthesized by other methods. Thus, Jäger¹¹⁾ synthesized **9e** by reacting adipoyl chloride and acetone in the presence of triethylamine, while Stetter and Kiehs¹²⁾ obtained several derivatives of **9e** by heating of 2-diazodihydroresorcinol in the presence of appropriate carbonyl compounds.

We at first synthesized **9e** according to our general procedure.¹³⁾ Thus, 2-oxocyclopentanecarboxylic acid (**8e**) obtained readily by hydrolysis of the corresponding ester (**7e**) was treated with acetone and acetic anhydride in the pres-

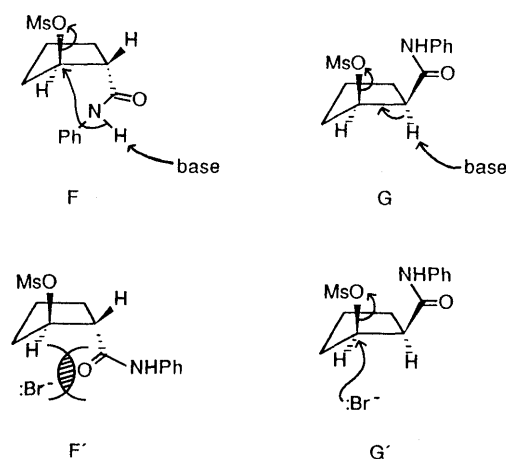


Fig. 1. Transition States for the Reaction of **12e-trans** and **12e-cis** with NaH or NaBr

ence of a small amount of sulfuric acid at 0 °C to give **9e**.¹⁴⁾ Heating of **9e** with aniline afforded the anilide (**10e**). Reduction of **10e** with sodium borohydride then afforded a mixture of the alcohols (**11e-trans** and **11e-cis**).¹⁵⁾ Though the two isomers were not separable at this stage, they could be separated readily after their conversion to the mesylates (**12e**). Thus, the mesylates, when subjected to silica gel column chromatography, afforded the less polar and the more polar isomers in 67 and 30% yields, respectively. As described below, the former was determined as **12e-trans** and the latter as **12e-cis**. When **12e-trans** was subjected to the afore-mentioned cyclization (NaH, CH₂Cl₂-DMF), the β -lactam (**13e**) was obtained in an almost quantitative yield. In contrast, **12e-cis** afforded under the same condition the enamide (**14e**) as the sole product and no **13e** was detected in the reaction mixture.

Assuming that small carbocycles can not accommodate a four-membered ring fused *trans*, we can explain the above results reasonably as follows. Thus, the reaction of **12e-trans** with base may proceed *via* transition state F in which the attack of the base (NaH) on the amide group is concerted with the approach of the nitrogen atom to the rearside of the carbon-oxygen bond, which ultimately yields the *cis*- β -lactam (**13e**). Alternatively, in transition state G, the electron pair derived from the hydrogen atom attached to the carbon atom having the amide group accomplished the concerted elimination of the mesyloxy group to give the enamide (**14e**).¹⁶⁾

The mesylate (**12e-cis**) can also be transformed to **13e** by an indirect route. Thus, treatment of **12e-cis** with sodium bromide in dimethyl formamide (85 °C, 2 h) afforded the bromide (**15e-trans**), together with the simple elimination product (**14e**). The bromide (**15e-trans**), when subjected to the same cyclization reaction (NaH, CH₂Cl₂-DMF), afforded the β -lactam. Complete inversion at the reacting center in the step from **12e-cis** to **15e-trans** is explained by assuming that the reaction has proceeded through an ordinary S_N2 mechanism (*cf.* G'). When **12e-trans** was subjected to the same bromination reaction under the same conditions (NaBr/DMF, 85 °C, 2 h), the starting material was recovered quantitatively. This fact implies that neither the expected S_N2 reaction giving the *cis* isomer of **15f** nor the concerted E2 reaction giving **14f** proceeds under these conditions. The former process is prohibited by steric hindrance (*cf.* F') and the latter by inaccessibility of the *trans* periplanar conformation necessary to the concerted elimination of methanesulfonic acid.

The same sequence of reactions and the same stereo-

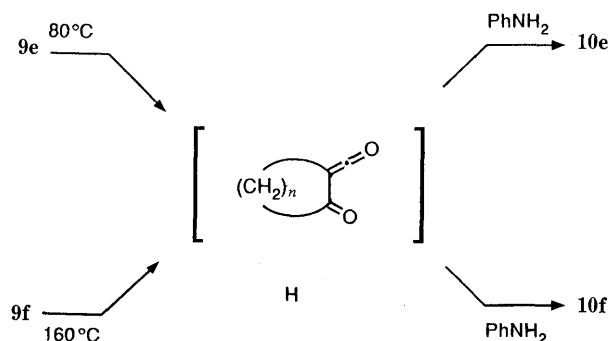


Chart 4

chemical demands were also observed in the conversion of the 5,6-tetramethylene derivative (**9f**) giving either the β -lactam (**13f**) or the enamide (**14f**).

With two 5,6-polymethylene derivatives of the dioxinone (**9e** and **9f**) in our hands, we became interested in examining how the ease of thermal electrocyclic ring-opening reaction of these dioxinones to the corresponding acylketenes¹⁷⁾ is affected by the length of the methylene chain. As already noted, ease of the thermal ring-opening reaction depends strongly upon the pattern of alkyl substitution of the dioxinones.¹³⁾ Thus, for example, thermal ring-opening reaction of 5,6-unsubstituted 2,2-dimethyl-1,3-dioxin-4-one to formylketene occurs at 80 °C (reflux in benzene) and that of the 5- or 6- monoalkyl derivatives at 120 °C (reflux in toluene), and the ring opening reactions of 5,6-dialkylated derivatives to acylketenes require 160 °C (reflux in mesitylene). It was found that while thermal ring-opening reaction of the tetramethylene derivative (**9f**) occurred only in refluxing mesitylene and hence showed the same reactivity as that of an ordinary 5,6-dialkylated dioxinone, the trimethylene derivative (**9e**) was extremely labile to heat and ring-opened to the corresponding ketene (H: *n*=3) even on heating in benzene. These results show that fusion of a five-membered ring to the 5,6-positions of the dioxinone ring accelerates the ring opening reaction, probably due to the strain involved in a five-membered ring.

Finally, the conversion of the acetoacetanilide (**17a**) obtained from the 5,6-dimethyl dioxinone²⁾ (**16**) to the 3,4-dimethylazetidin-2-one was examined. The reduction followed by mesylation afforded the mesylate (**19a**) as a mixture of two isomers. Though two alcohols could not be separated, the corresponding mesylates could be separated by silica gel column chromatography into the less and more polar ones in *ca.* 1 : 1.6 ratio. The base-mediated cyclization of **19a** as a mixture afforded the corresponding β -lactams (**20a**), quantitatively. Two isomers could be separated readily by silica gel column chromatography to give the less polar and the more polar lactams in *ca.* 1.6 : 1 ratio. It was verified further that the base-mediated cyclization of each mesylate (**19a-syn** or *-anti*) either to the *trans* or *cis*-lactam (**20a-trans** or *-cis*) proceeded in almost quantitative yield with complete stereoselection.

The stereochemistry of each lactam (**20a-trans** or *-cis*) was determined by proton nuclear magnetic resonance (¹H-NMR) spectroscopy from the coupling constants between C₃-H and C₄-H (*J*_{3,4}=5.8 Hz for *cis*- and *J*_{3,4}=2.0 Hz for

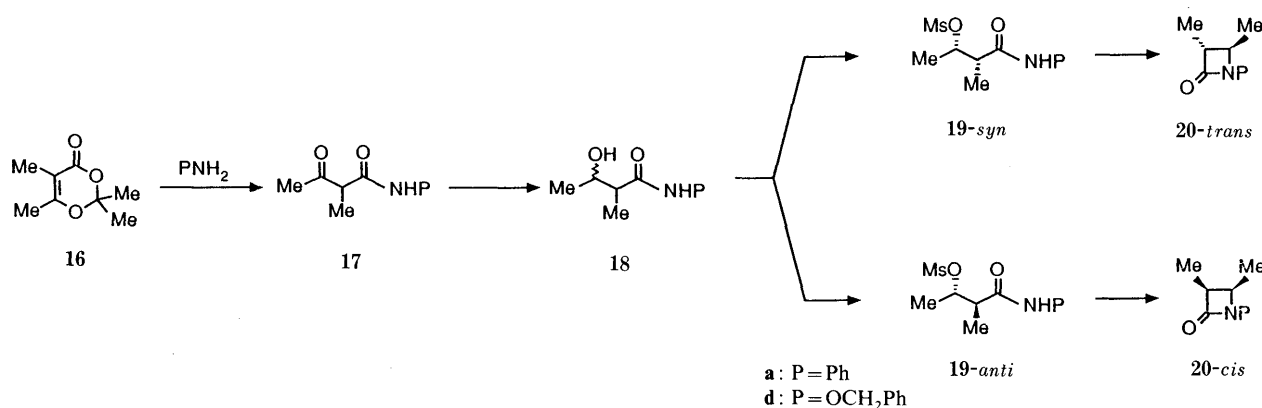


Chart 5

trans-isomers). Since the cyclization had occurred by complete inversion at the reacting center (C_3) (*vide supra*), the less polar mesylate was determined to be the *anti*-isomer (**19a-anti**) and the more polar one, the *syn*-isomer (**19a-syn**).¹⁸⁾

A similar reaction sequence also proceeded if we used the corresponding hydroxylamine derivative (**17d**) as the starting material instead of the anilide (**17a**). The final β -lactams (**20d-cis** and *-trans*) obtained in this case would readily afford the 1-unsubstituted azetidinones (**20**, $P = H$) either by the well known two-step procedure¹⁹⁾ (removal of the benzyl group by catalytic hydrogenation followed by reduction of the hydroxylamine with titanium trichloride) or by direct deblocking of the 1-alkoxyl group using sodium in ammonia.²⁰⁾

Enantioselective Synthesis of 4-Substituted Azetidin-2-ones It has become clear from the afore-mentioned study that the synthesis of β -lactams from 1,3-dioxin-4-ones *via* the β -hydroxycarboxamides is very useful and has wide applicability. In this connection, we next examined the enantioselective synthesis of β -lactams by using the chiral hydroxybutanamides as the key intermediates. It is well known that baker's yeast displays a remarkable enantioselectivity when used in the reduction of β -ketoesters.²¹⁾

Accordingly, the corresponding carboxamides were subjected to this reduction in order to see whether this microbiological reduction is still applicable to this class of compounds and, furthermore, what kind of substituents are necessary at the nitrogen atom in them.

Three acetoacetamides (**2a-c**), when incubated with fermenting baker's yeast for a few days at 32 °C, were converted to the corresponding (*S*)-3-hydroxybutanamides [(*S*)-**3a-c**] in satisfactory isolated yields, though the attempted reduction of **2d** had ended in complete recovery of the starting material.

For the determination of the absolute structure and the optical purity of each product, the racemic amides (**3a-c**) were converted into the corresponding (+)-MTPA esters (**21a-c** and **22a-c**) by treatment with (+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid [(+)-MTPA].²²⁾

In the 500 MHz 1H -NMR spectrum of each mixture of the (+)-MTPA esters, two distinctly separated doublets due to two types of secondary methyl groups were observed, as shown in Table I.

According to Mosher *et al.*,²²⁾ the (+)-MTPA esters (**21** and **22**) of (*S*)- and (*R*)-**3** would take the conformations (I) for **21** and J for **22** shown in Fig. 2. Obviously, in the diastereomer (**22**) the methyl group is juxtaposed with the α -phenyl group (*cf.* J), while in the other diastereomer (**21**) it is the CH_2CONHR group that is juxtaposed with the phenyl group (*cf.* I). Hence, the diastereomer (**22** as conformer J) will have the resonance for the methyl group up-field (more shielded) from that for the methyl group in **21** (as conformer I). Thus, the NMR data shown in Table I indicate that **21** having the lower set of doublets should be the (3*S*)-isomer and **22** having the upper set of doublets should be the (3*R*)-isomer.

Then, the optical purity of the microbiological reduction products of the acetoacetamides (**2a-c**) was evaluated on the basis of the intensity of the secondary methyl signals of their (+)-MTPA esters in the 500 MHz spectra. All of the esters were found to be almost optically pure (more than

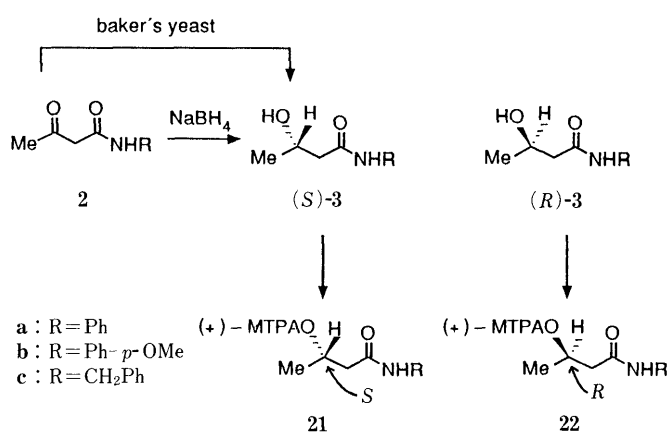
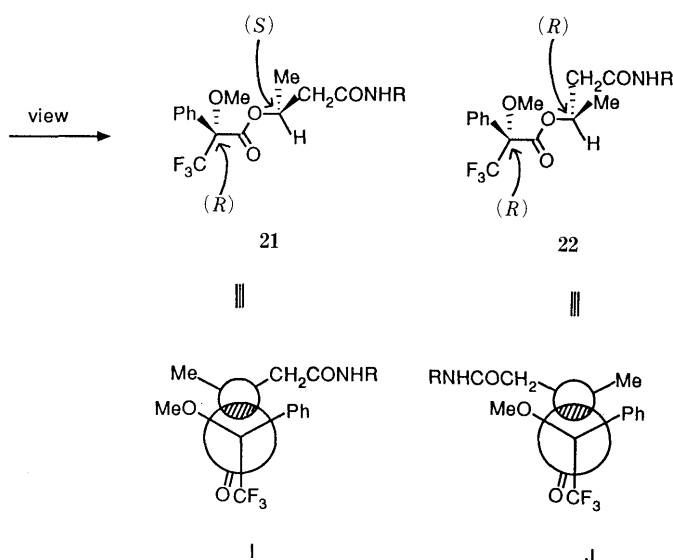


Chart 6

TABLE I. Chemical Shifts of the Secondary Methyl Signals of **21a-c** and **22a-c**

R	21 [(3 <i>S</i>)-isomer]	22 [(3 <i>R</i>)-isomer]
Ph	1.49	1.42
Ph- <i>p</i> -OMe	1.49	1.42
CH ₂ Ph	1.40	1.32

Fig. 2. Configurational Correlation Model for (+)-MTPA Derivatives (**21** and **22**) of (*S*)- and (*R*)-**3**

98% ee), since only the lower set of doublets was observed in each spectrum. According to Mosher's configurational correlation method²²⁾ all of the 3-hydroxycarboxamides obtained by the microbiological reduction were assigned as the (*S*)-enantiomers. In accordance with this assignment, all of these chiral alcohols showed positive specific rotations.

Unequivocal determination of the (3*S*)-structures of these alcohols was made as follows. Thus, reaction of commercial (*S*)-sodium 3-hydroxybutyrate (**23**, optical purity *ca.* 80%) with benzyl bromide afforded the (*S*)-benzylester (**24**), whose *tert*-butyldimethylsilylether (**25**) was then converted to (*S*)-**3a** *via* three steps (catalytic hydrogenation, anilide formation, and deprotection of the

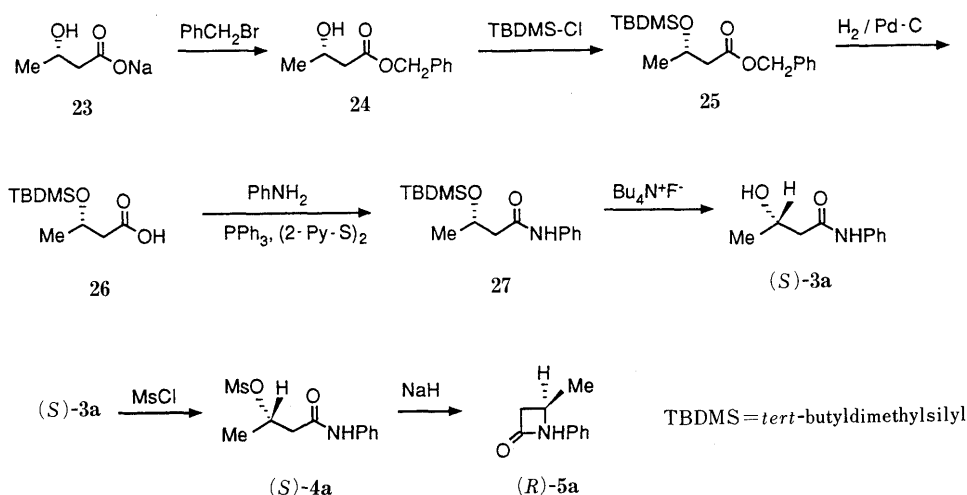


Chart 7

TABLE II. β -Ketobutanamides (**2a–d**)^{a)}

Compd.	R	Yield (%)	mp (°C) (lit. mp)	Recrystal. solvent ^{b)}	Elemental analysis (%)			Spectral data
					Calcd (Found)			
					C	H	N	
2a	Ph	67	80 (85) ²⁶⁾	A				
2b	Ph- <i>p</i> -OMe	73	117	B	63.74 (63.70)	6.33 6.40	6.76 6.82)	IR (CHCl ₃): 3350, 1715, 1680 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 2.32 (3H, s, Me), 3.54 (2H, s, CH ₂), 3.80 (3H, s, OMe), 6.87 (2H, d, <i>J</i> =9.0 Hz, Ar-H), 7.45 (2H, d, <i>J</i> =9.0 Hz, Ar-H), 8.33—9.30 (1H, br, NH)
2c	CH ₂ Ph	79	101—102	B	69.08 (69.03)	6.86 6.75	7.33 7.55)	IR (CHCl ₃): 3360, 1715, 1670 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 2.27 (3H, s, Me), 3.45 (2H, s, CH ₂), 4.51 (2H, d, <i>J</i> =5.2 Hz, CH ₂ Ph), 6.87—7.57 (1H, br, NH), 7.30 (5H, s, Ph)
2d	OCH ₂ Ph	60	62 (77—79) ²⁷⁾	C				

a) In all cases, xylene was used as a solvent, and the reaction temperature was kept at 140°C. b) A, hexane–ether; B, hexane–AcOEt; C, ether.

silyl group). The sign of the specific rotation of the product derived from **23** was the same as that of the above-mentioned microbiological reduction product of acetoacetanilide (**2a**).

Thus, it has now become evident that, like acetoacetic esters,²³⁾ the corresponding amides (**2a–c**) can be reduced to the (*S*)-derivatives [(*S*)-**3a–c**] in high chemical yield with almost 100% ee. Since the conversion of (*S*)-**3a** to (*R*)-**5a** via the mesylate [(*S*)-**4a**] proceeded with both in high chemical yield and complete stereoselection, enantiomeric synthesis of (*R*)-4-methylazetidin-2-one [(*R*)-**5a**] has now been accomplished.²⁴⁾

We plan to apply this microbiological reduction to higher β -ketocarboxamides²¹⁾ or α -substituted acetoacetamides²⁵⁾ in order to extend our approach (the dioxinones $\rightarrow$ β -ketoamides $\rightarrow$ 3-hydroxyamides $\rightarrow$ azetidin-2-ones) to the synthesis of a variety of chiral lactams.

Experimental

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. Optical rotations were measured with a JASCO DIP-340 digital polarimeter. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer and ¹H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI or JEOL JNM-GX 500 spectrometer with tetramethylsilane (TMS) as an internal standard, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublets of doublets; br, broad. Low- and high-resolution mass spectra (MS) were obtained on JEOL JMS-01SG-2 and JEOL JMS-DX-303 spectrometers, respectively. Wakogel (C-

TABLE III. β -Ketoamides (**10** and **17**)

Compd.	Yield (%)	mp (°C) (lit. mp)	Recrystal. solvent ^{a)}	Reaction solvent ^{b)} (Reaction temp.) (°C)
10e	51	101 (100–101) ¹¹⁾	A	A (80)
10f	62	106–107 (106–108) ²⁸⁾	A	A (160)
17a	76	132–134 (135–139) ²⁹⁾	B	B (140)
17d^{c)}	50	70–71	C	B (140)

a) A, hexane–AcOEt; B, hexane–ether; C, ether. b) A, mesitylene; B, xylene. c) Anal. Calcd for C₁₂H₁₅NO₃: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.17; H, 7.05; N, 6.46. IR (CHCl₃): 3425, 1720 (sh), 1690 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.36 (3H, d, *J*=7.0 Hz, Me), 2.18 (3H, s, COMe), 3.03–3.60 (1H, m, CH), 4.89 (2H, s, CH₂Ph), 7.38 (5H, s, Ph), 8.33–8.93 (1H, br, NH).

200) and Merck Kiesel-gel 60 F254 were employed for silica gel column and preparative thin layer chromatography (TLC), respectively. The ratios of solvent mixtures for chromatography are shown as volume/volume.

Preparation of 2,2-Dimethyl-1,3-dioxin-4-one Derivatives a) Preparation of 1,3-Dioxin-4-ones (**1**, **9f**, and **16**): These dioxinones were prepared according to our reported procedure.²⁾

b) Preparation of 2,2-Dimethyl-5,6-trimethylene-1,3-dioxin-4-one (**9e**): Employing the reported procedure,²⁾ ethyl 2-oxocyclopentanecarboxylate was hydrolyzed to give the carboxylic acid (**8e**). Concentrated sulfuric acid (0.62 g, 6.2 mmol) was added dropwise to a mixture of **8e** (3.97 g, 31 mmol), acetone (3.6 g, 62 mmol), and acetic anhydride (6.32 g, 62 mmol)

TABLE IV. β -Hydroxyamides (3, 11, and 18)

Compd.	Yield (%)	mp (°C) (lit. mp)	Recrystal. solvent ^{a)}	Elemental analysis (%)			Spectral data
				Calcd (Found)			
				C	H	N	
3a	84	106 (109) ²⁶⁾	A				
3b	85	129—130 (135) ³⁰⁾	B				
3c	84	65—66	A	68.35 (68.15)	7.83 7.75	7.25 7.42)	IR (CHCl ₃): 3460, 3275, 1670 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.23 (3H, d, <i>J</i> =6.0 Hz, Me), 1.99—2.47 (3H, m, CH ₂ , OH), 3.97—4.43 (1H, m, CH), 4.47 (2H, d, <i>J</i> =5.2 Hz, CH ₂ Ph), 5.77—6.26 (1H, br, NH), 7.27 (5H, s, Ph)
3d	76	85—86	C	63.13 (63.14)	7.23 7.23	6.70 6.60)	IR (CHCl ₃): 3440, 1680 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.17 (3H, d, <i>J</i> =6.4 Hz, Me), 2.02—2.47 (2H, m, CH ₂), 3.11—3.44 (1H, br, OH), 3.82—4.50 (1H, m, CH), 4.83 (2H, s, CH ₂ Ph), 7.31 (5H, s, Ph), 8.33—8.87 (1H, br, NH)
11e	96	130—133	B	70.21 (69.93)	7.37 7.28	6.83 6.61)	IR (CHCl ₃): 3450, 3350, 1670 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.40—2.38 (6H, m, (CH ₂) ₃), 2.41—2.95 (1H, m, CHCO), 3.32 (1H, br s, OH), 4.20—4.56 (1H, m, CHOH), 6.82—7.71 (5H, m, Ph), 9.00—9.38 (1H, br, NH)
11f	74	143—148	B	71.19 (71.26)	7.82 8.06	6.39 6.41)	IR (CHCl ₃): 3450, 3350, 1675 cm ⁻¹ . ¹ H-NMR (CD ₃ OD) δ: 0.56—2.73 (9H, m, (CH ₂) ₄ , CHCO), 3.56—4.39 (1H, m, CHOH), 6.98—7.81 (5H, m, Ph), 9.23—9.89 (1H, br, NH)
18a	81	122—125	D	68.35 (68.40)	7.83 7.81	7.25 7.34)	IR (CHCl ₃): 3450, 3325, 1670 cm ⁻¹ . ¹ H-NMR (CD ₃ OD) δ: 1.17 (1/2.6 × 3H, d, <i>J</i> =7.1 Hz, Me), 1.21 (1.6/2.6 × 3H, d, <i>J</i> =5.4 Hz, Me), 1.23 (1/2.6 × 3H, d, <i>J</i> =6.4 Hz, Me), 1.25 (1.6/2.6 × 3H, d, <i>J</i> =6.8 Hz, Me), 2.17—2.79 (1H, m, CHCO), 3.54—4.18 (1H, m, CHOH), 6.61—7.59 (6H, m, Ph, NH)
18d	81	Oil		High-resolution MS <i>m/z</i> C ₁₂ H ₁₇ NO ₃ 223.1207 (223.1157)			IR (CHCl ₃): 3425, 3350, 1680 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.14 (1.1/2.1 × 3H, d, <i>J</i> =7.1 Hz, Me), 1.15 (1.0/2.1 × 3H, d, <i>J</i> =5.4 Hz, Me), 1.17 (1.1/2.1 × 3H, d, <i>J</i> =7.1 Hz, Me), 1.21 (1.0/2.1 × 3H, d, <i>J</i> =5.7 Hz, Me), 1.96—2.53 (2H, m, CHCO, OH), 3.46—4.11 (1H, m, CHO), 4.84 (2H, s, CH ₂ Ph), 7.18—7.71 (1H, br, NH), 7.32 (5H, s, Ph)

a) A, hexane-ether; B, hexane-AcOEt; C, ether; D, AcOEt.

with stirring below 5 °C. The mixture was stirred under ice-cooling for 3 h, during which time crystalline **8e** dissolved. After being kept in a refrigerator (*ca.* 0 °C) for 12 h, the mixture was poured into 10% sodium carbonate solution (75 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min, and separated crystals were collected by suction, washed with water, dried, and recrystallized from pentane-ether to give **9e** (2.61 g, 50%) as colorless needles, mp 37—38 °C (lit.¹⁰⁾ mp 38 °C).

General Procedure for the Synthesis of β -Ketoamides (2a—c, 10, and 17a) A solution of equimolar amounts (5 mmol each) of a 2,2-dimethyl-1,3-dioxin-4-one derivative and an amine (aniline, *p*-anisidine, or benzylamine) in an appropriate solvent (10 ml) was heated for 1.5 h at the indicated temperature. After evaporation of the solvent *in vacuo*, the residue was recrystallized from an appropriate solvent.

***N*-Benzyloxy-3-oxobutanamide Derivatives (2d and 17d)** A solution of equimolar amounts (20 mmol each) of **1** (or **16**) and *O*-benzylhydroxylamine in 100 ml of xylene was added dropwise to boiling xylene (200 ml) over 15 min, during which time about 100 ml of the solvent was distilled off through a condenser. Heating was continued for an additional 45 min to distill another 200 ml of the solvent. The residue was recrystallized from an appropriate solvent.

General Procedure for the Synthesis of β -Hydroxyamides (3, 11, and 18) A solution of β -ketoamide (5 mmol) in methanol (15 ml) was treated with NaBH₄ (5 mmol) in small portions under ice-cooling. After stirring for 30 min at room temperature, methanol was removed under reduced pressure and the residue was neutralized by adding 10% HCl. The organic layer extracted with ethyl acetate was dried over anhydrous MgSO₄ and evaporated *in vacuo*. The residue thus obtained was recrystallized from an appropriate solvent.

General Procedure for the Synthesis of β -Mesyloxyamides (4, 12, and 19) Mesyl chloride (12 mmol) was added in small portions to a cold solution (0 °C) of β -hydroxyamide (10 mmol) in pyridine (10 ml). After additional stirring for 3 h at room temperature, pyridine was removed *in vacuo*. The residue was diluted with water and extracted with CH₂Cl₂. The organic layer was dried over anhydrous MgSO₄ and evaporated *in vacuo*. In the case of **4**, the residue was recrystallized from an appropriate solvent. In the case of **12** or **19**, the residue obtained was separated by silica gel column chromatography [**12**, hexane-AcOEt (7:1); **19**, hexane-AcOEt (5:1)] into the diastereoisomers, each of which was recrystallized from an

appropriate solvent.

General Procedure for the Synthesis of β -Lactams (5, 13, and 20) and Enamides (14) A solution of the mesylate or bromide (1 mmol) in 10 ml of DMF-CH₂Cl₂ (1:4) was added over 3 h to a stirred mixture of 60% mineral oil dispersion of NaH (1 mmol), 2 ml of DMF, and 8 ml of CH₂Cl₂ at room temperature. After additional stirring for 1 h, CH₂Cl₂ was removed under reduced pressure. The resulting mixture was diluted with water and extracted with ether. The organic phase was dried over anhydrous MgSO₄ and evaporated *in vacuo*. While the enamides derived from the *cis*-isomers could be purified simply by recrystallization from hexane-ether, the β -lactams derived from the *trans*-isomers were purified by silica gel column chromatography [hexane-AcOEt (5:1)].

Bromination of Cyclic *cis*-Mesylate (12-*cis*) A suspension of equimolar amounts (0.5 mmol each) of **12-*cis*** and NaBr in DMF (3 ml) was heated for 2 h at 85 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over anhydrous MgSO₄. After evaporation of the solvent *in vacuo*, the residue was purified by silica gel column chromatography [hexane-AcOEt (7:1)] and then recrystallized from hexane-ether.

General Procedure of Asymmetric Reduction of β -Ketoamides by Baker's Yeast A mixture of baker's yeast (Oriental Yeast Co., 30 g), sucrose (10 g), and water (30 ml) was shaken for 30 min at 32 °C. The β -ketoamide **2** (1 g) was added to this suspension, and shaking was continued for a few days at the same temperature. Water was removed from this reaction mixture under reduced pressure, and the residue was extracted with CH₂Cl₂ several times. After the combined CH₂Cl₂ solution was dried over anhydrous MgSO₄ and evaporated *in vacuo*, the residue was purified by silica gel column chromatography [hexane-AcOEt (5:1)] and the product was finally recrystallized from the solvent used in the corresponding racemic series.

(+)-MTPA Esterification of β -Hydroxyamides (Chiral or Racemic 3) 1,3-Dicyclohexylcarbodiimide (DCC, 93 mg, 0.45 mmol) was added to a solution of (+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid [(+)-MTPA, 105 mg, 0.45 mmol] in CH₂Cl₂ (5 ml) with stirring under ice-cooling. After stirring of the mixture for 30 min, β -hydroxyamide (0.3 mmol) and 4-dimethylaminopyridine (3.7 mg, 0.03 mmol) were added to the solution and the whole was stirred for 30 min at the same temperature, and then for 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel

TABLE V. β -Mesyloxyamides (**4**, **12**, and **19**)

Compd.	Yield (%)	mp (°C)	Recrystal. solvent ^{a)}	Elemental analysis (%)				Spectral data
				Calcd (Found)				
				C	H	N	S	
4a	83	119—120	A	51.35 (51.26)	5.88 5.90	5.44 5.29	12.46 12.51	IR (CHCl ₃): 3450, 1690 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.48 (3H, d, <i>J</i> = 6.6 Hz, Me), 2.70 (2H, d, <i>J</i> = 6.0 Hz, CH ₂), 3.02 (3H, s, SO ₂ Me), 5.18 (1H, tq, <i>J</i> = 6.6, 6.0 Hz, CH), 6.97—7.67 (6H, m, Ar-H, NH)
4b	86	88—89	A	50.16 (49.99)	5.96 6.07	4.88 4.93	11.14 11.19	IR (CHCl ₃): 3450, 1685 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.47 (3H, d, <i>J</i> = 6.0 Hz, Me), 2.47—2.87 (2H, m, CH ₂), 2.97 (3H, s, SO ₂ Me), 4.75 (3H, s, OMe), 4.87—5.53 (1H, m, CH), 6.78 (2H, d, <i>J</i> = 9.4 Hz, Ar-H), 7.37 (2H, d, <i>J</i> = 9.4 Hz, Ar-H), 8.08 (1H, br s, NH)
4c	78	109—110	B	53.12 (52.86)	6.32 6.49	5.17 5.25	11.79 11.92	IR (CHCl ₃): 3460, 1680 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.48 (3H, d, <i>J</i> = 6.0 Hz, Me), 2.56 (2H, d, <i>J</i> = 6.2 Hz, CH ₂), 2.87 (3H, s, SO ₂ Me), 4.41 (2H, d, <i>J</i> = 5.2 Hz, CH ₂ Ph), 5.17 (1H, tq, <i>J</i> = 6.2, 6.0 Hz, CH), 6.04—6.60 (1H, br, NH), 7.15 (5H, s, Ph)
4d	96	71	C	50.16 (49.90)	5.97 5.86	4.88 4.87	11.14 11.19	IR (CHCl ₃): 3420, 1695 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.47 (3H, d, <i>J</i> = 6.1 Hz, Me), 2.17—2.68 (2H, m, CH ₂), 2.97 (3H, s, SO ₂ Me), 4.84—5.38 (1H, m, CH), 4.86 (2H, s, CH ₂ Ph), 7.36 (5H, s, Ph), 8.75—9.05 (1H, br, NH)
12e-<i>trans</i>^{b)}	67	102—103	A	55.11 (54.93)	6.05 6.04	4.95 4.78	11.29 11.31	IR (CHCl ₃): 3450, 1685 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.54—2.40 (6H, m, (CH ₂) ₃), 2.76—3.14 (1H, m, CHCO), 3.03 (3H, s, SO ₂ Me), 5.10—5.47 (1H, m, CHO), 6.99—7.69 (5H, m, Ph), 7.70—8.11 (1H, br, NH)
12e-<i>cis</i>^{b)}	30	134	A	(55.12)	6.15	5.25	11.23	IR (CHCl ₃): 3450, 1690 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.48—2.47 (6H, m, (CH ₂) ₃), 2.84—3.28 (1H, m, CHCO), 2.86 (3H, s, SO ₂ Me), 5.18—5.47 (1H, m, CHO), 6.91—7.86 (5H, m, Ph), 7.89—8.15 (1H, br, NH)
12f-<i>trans</i>^{b)}	48	154—155	A	56.55 (56.59)	6.45 6.73	4.71 4.62	10.76 10.69	IR (CHCl ₃): 3450, 1685 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 0.81—2.78 (9H, m, (CH ₂) ₄ , CHCO), 2.93 (3H, s, SO ₂ Me), 4.54—5.20 (1H, m, CHO), 6.92—7.81 (6H, m, Ph, NH)
12f-<i>cis</i>^{b)}	41	134—135	A	(56.28)	6.34	4.74	10.73	IR (CHCl ₃): 3460, 1680 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 0.58—2.96 (9H, m, (CH ₂) ₄ , CHCO), 2.95 (3H, s, SO ₂ Me), 5.00—5.38 (1H, m, CHO), 6.87—8.12 (6H, m, Ph, NH)
19a-<i>anti</i>^{c)}	35	98—99	D	53.12 (53.01)	6.32 6.29	5.17 5.16	11.79 11.81	IR (CHCl ₃): 3450, 1690 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.26 (3H, d, <i>J</i> = 6.4 Hz, MeCHCO), 1.51 (3H, d, <i>J</i> = 6.2 Hz, MeCHO), 2.63 (1H, dq, <i>J</i> = 9.2, 6.4 Hz, CHCO), 2.92 (3H, s, SO ₂ Me), 4.93 (1H, dq, <i>J</i> = 9.2, 6.2 Hz, CHO), 7.03—7.75 (6H, m, Ph, NH)
19a-<i>syn</i>^{c)}	56	104—105	D	(53.36)	6.58	5.15	11.85	IR (CHCl ₃): 3450, 1690 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.30 (3H, d, <i>J</i> = 6.8 Hz, MeCHCO), 1.47 (3H, d, <i>J</i> = 6.4 Hz, MeCHO), 2.85 (1H, dq, <i>J</i> = 6.8, 5.4 Hz, CHCO), 3.04 (3H, s, SO ₂ Me), 5.01 (1H, dq, <i>J</i> = 6.4, 5.4 Hz, CHO), 7.04—7.71 (5H, m, Ph), 7.77—8.21 (1H, br, NH)
19d-<i>anti</i>^{c)}	43	117	D	51.81 (51.60)	6.36 6.22	4.65 4.70	10.62 10.71	IR (CHCl ₃): 3425, 1695 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.13 (3H, d, <i>J</i> = 7.0 Hz, MeCHCO), 1.48 (3H, d, <i>J</i> = 6.1 Hz, MeCHO), 2.10—2.53 (1H, m, CHCO), 2.94 (3H, s, SO ₂ Me), 4.54—5.09 (1H, m, CHO), 4.88 (2H, s, CH ₂ Ph), 7.35 (5H, s, Ph), 8.12—8.60 (1H, br, NH)
19d-<i>syn</i>^{c)}	48	98	D	(51.76)	6.27	4.73	10.76	IR (CHCl ₃): 3425, 1695 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.17 (3H, d, <i>J</i> = 7.0 Hz, MeCHCO), 1.37 (3H, d, <i>J</i> = 6.2 Hz, MeCHO), 2.18—2.81 (1H, m, CHCO), 2.95 (3H, s, SO ₂ Me), 4.63—5.11 (1H, m, CHO), 4.93 (2H, s, CH ₂ Ph), 7.34 (5H, s, Ph), 8.85—9.29 (1H, br, NH)

a) A, hexane-AcOEt; B, hexane-CH₂Cl₂; C, ether; D, hexane-ether. b) The *trans* isomers are less polar than the corresponding *cis* isomers on silica gel chromatography. c) The *anti* isomers are less polar than the corresponding *syn* isomers on silica gel chromatography.

column chromatography [hexane-AcOEt (5:1)] to give the (+)-MTPA ester. **21a** and **22a**: Yield 78%. ¹H-NMR (CDCl₃) δ : 1.42 (3/2H, d, J = 6.0 Hz, 3*R*-Me), 1.49 (3/2H, d, J = 6.0 Hz, 3*S*-Me), 2.60–2.73 (2H, m, CH₂), 3.52 (3/2H, s, 3*R*-OMe), 3.53 (3/2H, s, 3*S*-OMe), 5.58–5.70 (1H, m, CH), 7.02–7.68 (11H, m, aromatic protons, NH). **21b** and **22b**: Yield 68%. ¹H-NMR (CDCl₃) δ : 1.42 (3/2H, d, J = 6.0 Hz, 3*R*-Me), 1.49 (3/2H, d, J = 6.0 Hz, 3*S*-Me), 2.58–2.70 (2H, m, CH₂), 3.44 (3/2H, s, 3*R*-OMe), 3.57 (3/2H, s, 3*S*-OMe), 3.80 (3H, s, *p*-OMe), 5.59–5.68 (1H, m, CH), 6.79–7.58 (10H, m, aromatic protons, NH). **21c** and **22c**: Yield 42%. ¹H-NMR (CDCl₃) δ : 1.32 (3/2H, d, J = 6.0 Hz, 3*R*-Me), 1.40 (3/2H, d, J = 6.0 Hz, 3*S*-Me), 2.38–2.56 (2H, m, CH₂), 3.42 (3/2H, s, 3*R*-OMe), 3.49 (3/2H, s, 3*S*-OMe), 4.12–4.42 (2H, m, CH₂Ph), 5.53–5.61 (1H, m, CH), 7.16–7.59 (11H, m, aromatic protons, NH).

Benzyl (S)-3-Hydroxybutanoate (24) Benzyl bromide (2.05 g, 12 mmol) was added to a solution of (S)-(+)-sodium 3-hydroxybutyrate (optical purity *ca.* 80%) **23** (1.26 g, 10 mmol) in dry DMF (10 ml) under ice-cooling. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over anhydrous MgSO₄ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography [hexane-AcOEt (5:1)] to give **24** (1.34 g, 69%) as a colorless oil. $[\alpha]_D^{25} + 26.4^\circ$ (c = 2.17, CHCl₃).

High-resolution MS m/z Calcd for C₁₁H₁₄O₃ (M⁺): 194.0942. Found: 194.0937. IR (CHCl₃): 3600, 1725 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.23 (3H, d, J = 6.0 Hz, Me), 2.51 (2H, d, J = 6.2 Hz, CH₂CO), 3.13 (1H, br s, OH), 4.25 (1H, tq, J = 6.2, 6.0 Hz, CHOH), 5.19 (2H, s, CH₂Ph), 7.41 (5H, s, Ph).

Benzyl (S)-3-tert-Butyldimethylsilyloxybutanoate (25) *tert*-Butyldimethylchlorosilane (0.111 g, 0.74 mmol) and imidazole (44 mg, 0.732 mmol) were added successively to a cold solution (0°C) of **24** (94.8 mg, 0.49 mmol) in dry DMF (2 ml), and the whole was stirred for 1 h under ice-cooling. The reaction mixture was diluted with water and extracted with ether. The organic phase was dried over anhydrous MgSO₄. The residue obtained after evaporation of the solvent *in vacuo* was purified by silica gel column chromatography [hexane-AcOEt (20:1)] to give **25** (0.11 g, 73%) as a colorless oil. $[\alpha]_D^{27} + 14.8^\circ$ (c = 1.70, CHCl₃). High-resolution MS m/z Calcd for C₁₇H₂₈O₃Si (M⁺): 308.1806. Found: 308.1772. IR (CHCl₃): 1735 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.03 (6H, s, SiMe₂), 0.84 (9H, s, *tert*-Bu), 1.17 (3H, d, J = 5.9 Hz, Me), 2.35–2.59 (2H, m, CH₂CO), 3.95–4.55 (1H, m, CH), 5.07 (2H, s, CH₂Ph), 7.30 (5H, s, Ph).

(S)-3-tert-Butyldimethylsilyloxybutanoic Acid (26) Compound **25** (91.1 mg, 0.296 mmol) was hydrogenated over 10% Pd-C (50 mg) in absolute methanol (4 ml) at room temperature under atmospheric pressure

TABLE VI. Azetidin-2-ones (**5**, **13**, and **20**)

Compd.	Yield (%)	High-resolution MS <i>m/z</i> Calcd (Found)	Spectral data
5a ²⁶⁾	99		
5b ^{a)}	98		IR (CHCl ₃): 1740 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.47 (3H, d, <i>J</i> = 5.8 Hz, Me), 2.59 (1H, dd, <i>J</i> = 14.6, 2.8 Hz, C ₃ -H), 3.20 (1H, dd, <i>J</i> = 14.6, 5.4 Hz, C ₃ -H), 3.76 (3H, s, OMe), 4.09 (1H, ddq, <i>J</i> = 5.8, 5.4, 2.8 Hz, C ₄ -H), 6.83 (2H, d, <i>J</i> = 9.2 Hz, Ar-H), 7.29 (2H, d, <i>J</i> = 9.2 Hz, Ar-H)
5c ^{31, b)}	41		
5d	93	C ₁₁ H ₁₃ NO ₂ 191.0946 (191.0959)	IR (CHCl ₃): 1765 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.18 (3H, d, <i>J</i> = 6.0 Hz, Me), 2.21 (1H, dd, <i>J</i> = 13.2, 2.4 Hz, C ₃ -H), 2.81 (1H, dd, <i>J</i> = 13.2, 5.0 Hz, C ₃ -H), 3.63 (1H, ddq, <i>J</i> = 6.0, 5.0, 2.4 Hz, C ₄ -H), 4.95 (2H, s, CH ₂ Ph), 7.39 (5H, s, Ph)
13e	93 (from 12e-trans)	C ₁₂ H ₁₃ NO 187.0996 (187.1026)	IR (CHCl ₃): 1735 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.40—2.23 (6H, m, (CH ₂) ₃), 3.61 (1H, dd, <i>J</i> = 8.2, 3.9 Hz, CHCO), 4.44 (1H, dd, <i>J</i> = 3.9, 3.8 Hz, CHN), 7.05—7.50 (5H, m, Ph)
13f	97 (from 12f-trans)	C ₁₃ H ₁₅ NO 201.1153 (201.1152)	IR (CHCl ₃): 1740 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.33—2.15 (8H, m, (CH ₂) ₄), 3.38 (1H, ddd, <i>J</i> = 6.8, 5.7, 3.9 Hz, CHCO), 4.25 (1H, ddd, <i>J</i> = 5.7, 4.3, 4.2 Hz, CHN), 7.05—7.47 (5H, m, Ph)
20a-cis	93 (from 19a-anti)	C ₁₁ H ₁₃ NO 175.0996 (175.1003)	IR (CHCl ₃): 1740 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.26 (3H, d, <i>J</i> = 7.8 Hz, C ₃ -Me), 1.39 (3H, d, <i>J</i> = 6.2 Hz, C ₄ -Me), 3.40 (1H, dq, <i>J</i> = 7.8, 5.8 Hz, C ₃ -H), 4.24 (1H, dq, <i>J</i> = 6.2, 5.8 Hz, C ₄ -H), 6.78—7.64 (5H, m, Ph)
20a-trans	97 (from 19a-syn)	C ₁₁ H ₁₃ NO 175.0996 (175.1001)	IR (CHCl ₃): 1740 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.32 (3H, d, <i>J</i> = 7.8 Hz, C ₃ -Me), 1.47 (3H, d, <i>J</i> = 6.2 Hz, C ₄ -Me), 2.84 (1H, dq, <i>J</i> = 7.8, 2.0 Hz, C ₃ -H), 3.73 (1H, dq, <i>J</i> = 6.2, 2.0 Hz, C ₄ -H), 6.87—7.52 (5H, m, Ph)
20d-cis	94 (from 19d-anti)	C ₁₂ H ₁₅ NO ₂ 205.1102 (205.1094)	IR (CHCl ₃): 1760 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 0.98 (3H, d, <i>J</i> = 6.0 Hz, C ₄ -Me), 1.04 (3H, d, <i>J</i> = 7.8 Hz, C ₃ -H), 2.86 (1H, dq, <i>J</i> = 7.8, 5.8 Hz, C ₃ -H), 4.64 (1H, dq, <i>J</i> = 6.0, 5.8 Hz, C ₄ -H), 4.87 (2H, s, CH ₂ Ph), 7.31 (5H, s, Ph)
20d-trans	97 (from 19d-syn)	C ₁₂ H ₁₅ NO ₂ 205.1102 (205.1108)	IR (CHCl ₃): 1760 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.17 (3H, d, <i>J</i> = 6.2 Hz, C ₄ -Me), 1.19 (3H, d, <i>J</i> = 7.4 Hz, C ₃ -Me), 2.43 (1H, dq, <i>J</i> = 7.4, 2.0 Hz, C ₃ -H), 3.20 (1H, dq, <i>J</i> = 6.2, 2.0 Hz, C ₄ -H), 4.94 (2H, s, CH ₂ Ph), 7.37 (5H, s, Ph)

a) Melting point 92—93 °C. Anal. Calcd for C₁₁H₁₃NO₂: C, 69.08; H, 6.86; N, 7.33. Found: C, 68.94; H, 7.11; N, 7.18. b) In this case only, the enamide (**6c**) was obtained concomitantly (yield 51%), but was not separable by silica gel column chromatography.

TABLE VII. Enamides (**14**) and Bromides (**15**)

Compd.	Yield (%)	mp (°C)	High-resolution MS <i>m/z</i> Calcd (Found)	Spectral data
14e	89	123—124	C ₁₂ H ₁₃ NO 187.0996 (187.1000)	IR (CHCl ₃): 3450, 1670, 1600 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.34—3.06 (6H, m, (CH ₂) ₃), 6.50—6.75 (1H, m, C=CH), 6.91—7.73 (6H, m, Ph, NH)
14f	90	112	C ₁₃ H ₁₅ NO 201.1153 (201.1159)	IR (CHCl ₃): 3450, 1675, 1605 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.34—2.60 (8H, m, (CH ₂) ₄), 6.57—6.87 (1H, m, C=CH), 6.87—7.84 (6H, m, Ph, NH)
15e	58	126	C ₁₂ H ₁₄ BrNO 267.0259 (267.0252)	IR (CHCl ₃): 3450, 1690 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.47—2.63 (6H, m, (CH ₂) ₃), 2.82—3.30 (1H, m, CHCO), 4.25—4.72 (1H, m, CHBr), 6.87—8.14 (6H, m, Ph, NH)
15f	21	175	C ₁₃ H ₁₆ BrNO 281.0415 (281.0390)	IR (CHCl ₃): 3450, 1680 cm ⁻¹ . ¹ H-NMR (CDCl ₃) δ: 1.11—2.87 (9H, m, (CH ₂) ₄ , CHCO), 4.16—4.93 (1H, m, CHBr), 7.06—7.71 (6H, m, Ph, NH)

TABLE VIII. (*S*)-3-Hydroxybutanamides [(*S*)-**3**]

	(<i>S</i>)- 3a	(<i>S</i>)- 3b	(<i>S</i>)- 3c
Yield (%)	51 (73) ^{a)}	49 (76) ^{a)}	64
mp (°C)	105 ^{b)}	102	81
[α] _D	+26.3 ^{c b)}	+34.2°	+33.9°
	(<i>c</i> = 1.50, Me ₂ CO)	(<i>c</i> = 2.07, CHCl ₃)	(<i>c</i> = 1.27, CHCl ₃)

a) Yields based on the consumed starting material. b) Lit.³²⁾ mp 105 °C, [α]_D²⁰ +24.0° (*c* = 1.50, Me₂CO).

for 1 h. After filtration to remove the catalyst, the filtrate was concentrated and purified by silica gel column chromatography [hexane–AcOEt (5:1)] to give **26** (41.1 mg, 64%) as a colorless oil. [α]_D²⁶ +14.3° (*c* = 1.83, CHCl₃). High-resolution MS *m/z* Calcd for C₁₀H₂₃O₃Si (M⁺ + 1): 219.1415. Found: 219.1421. IR (CHCl₃): 3050, 1715 cm⁻¹. ¹H-NMR (CDCl₃) δ:

0.04 (6H, s, SiMe₂), 0.86 (9H, s, *tert*-Bu), 1.24 (3H, d, *J* = 6.0 Hz, Me), 2.45 (2H, d, *J* = 5.9 Hz, CH₂CO), 4.27 (1H, tq, *J* = 6.0, 5.9 Hz, CH), 10.82 (1H, brs, CO₂H).

(*S*)-3-*tert*-Butyldimethylsilyloxybutananilide (**27**) Triphenylphosphine (787 mg, 3 mmol) and 2,2'-dipyridyl disulfide (661 mg, 3 mmol) were added to a solution of **26** (436 mg, 2 mmol) in acetonitrile (20 ml), and the solution was stirred for 10 min at room temperature. To this solution, an acetonitrile solution (5 ml) of aniline (186 mg, 2 mmol) was added, and the whole was stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography [hexane–AcOEt (10:1)]. Recrystallization of the product thus obtained from hexane–ether afforded **27** (433 mg, 74%) as colorless needles. mp 99—100 °C. [α]_D²⁷ –15.9° (*c* = 2.04, CHCl₃). High-resolution MS *m/z* Calcd for C₁₆H₂₇NO₂Si (M⁺): 293.1810. Found: 293.1796. IR (CHCl₃): 3450, 1680 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.05 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.90 (9H, s, *tert*-Bu), 1.22 (3H, d, *J* = 6.2 Hz, Me), 2.10—2.73 (2H, m, CH₂), 3.96—4.49 (1H, m, CH), 6.78—7.59 (5H, m, Ph), 8.03—8.58 (1H, br, NH).

(S)-3-Hydroxybutananilide [(S)-3a] Under ice-cooling, $[\text{CH}_3(\text{CH}_2)_3]_4\text{NF}$ [1.0 M solution in tetrahydrofuran (THF)] (0.2 ml) was added to a solution of **27** (51.3 mg, 0.18 mmol) in THF (1 ml) and the mixture was stirred for 30 min under ice-cooling, and for a further 30 min at room temperature. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with AcOEt. The organic layer was dried over anhydrous MgSO_4 and evaporated *in vacuo*. The residue, after being purified by silica gel chromatography [hexane–AcOEt (3:1)], was recrystallized from hexane–AcOEt to give (S)-**3a** (29.6 mg, 92%) as colorless needles. mp 105 °C. $[\alpha]_{\text{D}}^{23} +20.5^\circ$ ($c=0.91$, Me_2CO).

(S)-3-Mesyloxybutananilide [(S)-4a] Following the general procedure for synthesis of β -mesyloxyamides, the title compound was synthesized from (S)-**3a**. Yield 73%. $[\alpha]_{\text{D}}^{26} +33.4^\circ$ ($c=2.46$, CHCl_3).

(R)-4-Methyl-N-phenylazetidin-2-one [(R)-5a] Following the general procedure for synthesis of β -lactams, (R)-**5a** was obtained from (S)-**4a**. Yield 96%. $[\alpha]_{\text{D}}^{25} -117.5^\circ$ ($c=1.34$, CHCl_3). High-resolution MS m/z Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}$ (M^+): 161.0840. Found: 161.0843.

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References and Notes

- Part XVII: M. Sato, K. Takayama, and C. Kaneko, *Chem. Pharm. Bull.*, **37**, 2615 (1989).
- M. Sato, H. Ogasawara, and T. Kato, *Chem. Pharm. Bull.*, **31**, 1896 (1983); M. Sato, H. Ogasawara, S. Komatsu, and T. Kato, *ibid.*, **32**, 3848 (1984).
- Synthesis of some acetoacetamides by heating of 2,2,6-trimethyl-1,3-dioxin-4-one in the presence of amines was reported originally by M. F. Carroll and A. R. Bader, *J. Am. Chem. Soc.*, **75**, 5400 (1953).
- M. Sato, K. Sekiguchi, H. Ogasawara, and C. Kaneko, *Synthesis*, **1985**, 224. See also, M. Sato, H. Ogasawara, K. Sekiguchi, and C. Kaneko, *Heterocycles*, **22**, 2563 (1984).
- M. Sato, N. Yoneda, and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 4577 (1986).
- M. Sato, N. Katagiri, K. Takayama, M. Hirose, and C. Kaneko, *Chem. Pharm. Bull.*, **37**, 665 (1989).
- a) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948); b) C. R. Hauser and C. J. Eby, *J. Am. Chem. Soc.*, **79**, 725 (1957); c) G. Shaw and G. Sugowdz, *J. Chem. Soc.*, **1954**, 665; d) H. Kano and Y. Makisumi, *Yakugaku Zasshi*, **76**, 1311 (1956); e) J. S. Hubbard and T. M. Harris, *Tetrahedron Lett.*, **1978**, 4601; f) Y. Akasaki, M. Fukuyama, and M. Hatano, Japan Kokai 77106816 (1977) [*Chem. Abstr.*, **88**, 74396x (1978)].
- The amides (**2a**, **2c**, and **2d**) were prepared according to the procedure previously developed in our laboratories. See reference 2.
- Low isolation yields (based on **2**) of **4** probably reflect high solubility of **3** in water.
- H. H. Wasserman, D. J. Hlasta, A. W. Tremper, and J. S. Wu, *Tetrahedron Lett.*, **1979**, 549.
- G. Jäger, *Chem. Ber.*, **105**, 137 (1972).
- H. Stetter and K. Kiehs, *Chem. Ber.*, **98**, 2099 (1965).
- For reviews of the synthesis as well as reactions of 1,3-dioxin-4-ones, see: a) M. Sato, *Yakugaku Zasshi*, **108**, 805 (1988); b) M. Sato, *Yuki Gosei Kagaku Kyokai Shi*, **46**, 596 (1988).
- Quite recently, Henegar and Winkler synthesized **9e** by reacting the anisyl ketoester with acetone in trifluoroacetic acid containing either acetic or trifluoroacetic anhydride. K. E. Henegar and J. D. Winkler, *Tetrahedron Lett.*, **28**, 1051 (1987).
- Though the ratio of the isomers could be determined from the 500 MHz ^1H -NMR spectrum of the mixture, the separation failed due to their almost identical chromatographic behavior on either column or plate.
- The same explanation has previously been proposed for the base-catalyzed reaction of 2-aminocyclooctylsulfate. Though the *trans*-isomer cyclized to 9-azabicyclo[6.1.0]nonane, the *cis*-isomer afforded only cyclooctanone. D. V. Kashelkar and P. E. Fanta, *J. Am. Chem. Soc.*, **82**, 4927 (1960).
- M. Sato, H. Ogasawara, K. Takayama, and C. Kaneko, *Heterocycles*, **26**, 2611 (1987) and references cited therein.
- For definitions of *syn*- and *anti*-isomers, see: S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980).
- P. G. Mattingly and M. J. Miller, *J. Org. Chem.*, **45**, 410 (1980); M. A. Krook and M. J. Miller, *ibid.*, **50**, 1126 (1985).
- In this deblocking, the alkoxyl group in N-OR need not necessarily be a benzyloxy group. D. M. Floyd, A. W. Fritz, J. Pluscec, E. R. Weaver, and C. M. Cimarusti, *J. Org. Chem.*, **47**, 5160 (1982).
- The review for the reduction of β -ketoesters and related compounds by baker's yeast, see: C. J. Sih and C.-S. Chen, *Angew. Chem. Int. Ed. Engl.*, **23**, 570 (1984).
- J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973). See also, J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
- The yeast reduction of ethyl acetoacetate was reported to give ethyl (S)-3-hydroxybutanoate in a very high optical yield: K. Mori, *Tetrahedron*, **37**, 1341 (1981); A. I. Meyers and R. A. Amos, *J. Am. Chem. Soc.*, **102**, 870 (1980).
- It should be noted that an attempted synthesis of (S)-**5a** from the mesylate [(S)-**4a**] via the 3-bromide has failed, due to racemization at the 3-position during the bromination step. This fact indicates that the complete inversion at the bromination step (**12-cis** to **13** in Chart 3) is realized only in the cyclic series.
- The microbiological reduction of ethyl 2-methyl-3-oxobutyrate by baker's yeast has been reported. a) G. Fráter, *Helv. Chim. Acta*, **62**, 2825 (1979); b) R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt, and G. Snatzke, *Chem. Ber.*, **114**, 2786 (1981); c) H. Akita, A. Furuichi, H. Koshiji, K. Horikoshi, and T. Oishi, *Chem. Pharm. Bull.*, **31**, 4376 (1983).
- A. K. Bose, M. S. Manhas, D. P. Sahu, and V. R. Hegde, *Can. J. Chem.*, **62**, 2498 (1984).
- T. Kato, N. Katagiri, and N. Minami, *Chem. Pharm. Bull.*, **20**, 1368 (1972).
- S. Hünig, K. Hübner, and E. Benzing, *Chem. Ber.*, **95**, 926 (1962).
- K. F. Hebenbrock, *Justus Liebigs Ann. Chem.*, **1978**, 320.
- E. Kawashima, T. Takada, K. Tabei, and T. Kato, *J. Heterocycl. Chem.*, **22**, 1409 (1985).
- S. Kim, P. H. Lee, and T. A. Lee, *Synth. Commun.*, **18**, 247 (1988).
- B. S. Deol, D. D. Ridley, and G. W. Simpson, *Aust. J. Chem.*, **29**, 2459 (1976).