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An Asymmetry Induced Azepine-Ring Formation through the Ene Reactions at the Periphery of Heterocyclic Systems

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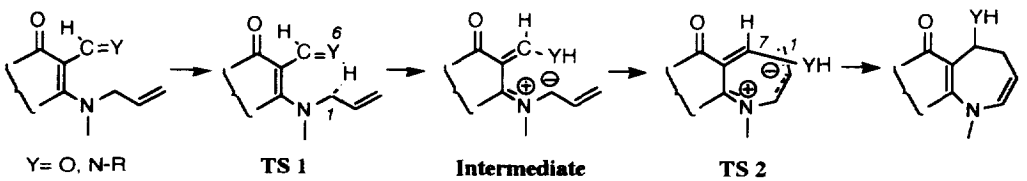
Abstract: The azepine-ring formation through the ene reactions proceeds in a concerted manner although the PM3 molecular orbital calculations of the model reactions suggests that the azepine-ring formation is constituted of two consecutive orbital-allowed reactions. Both imine and carbonyl ene reactions using the aldehydes bearing a chiral center at the alkenylamino moiety have performed a self-immolating chirality transfer to the azepine ring.

Introduction

In the two preceding papers,[1,2] we reported that the stereoselective azepine-ring formation through the thermal imine and carbonyl ene reactions at the periphery of pyridine and pyrido[1,2-*a*]pyrimidine systems. The investigation on their mechanism based on the PM3 molecular orbital calculations revealed that the azepine-ring formation was constituted of two consecutive orbital-allowed reactions;[2,3] the [1,6] sigmatropic shift (**TS 1**) of the allylic hydrogen yielding a conjugated azomethine ylide (**Intermediate**) and its [1,7] electrocyclic ring-closure (**TS 2**) (Scheme 1). The TS 1 corresponds to the transition state of the antarafacial hydrogen shift and the "Intermediate" does to the minimum in the potential energy surface close to the TS 1 as depicted previously.[2] The elaborated structure analysis by PM3 method of some intermediates between TS 1 and TS 2 revealed that they were responsible to the conformational changes of the alkenyl moiety; the alkenyl moiety was situated at an outer-side in the TS 1 moved to inside in the "Intermediate". It was suggested that the azepine-ring formation showed a concerted nature as a whole because the energy gap between the TS 1 and "Intermediate" was very small (less than 3 kcal mol^{-1}). It should be emphasized that the helical structure of the conjugated azomethine ylide intermediates resulted from the antarafacial hydrogen shift seemed to be kept in the course of the reaction coordinate from TS 1 to TS 2.[4] This means that the azepine-ring formation is expected to proceed in a highly stereoselective manner. In order to obtain better understandings on the reaction mechanism of the azepine-ring formation, we examined the ene reaction of aldehydes bearing a chiral center at the alkenylamino moiety.

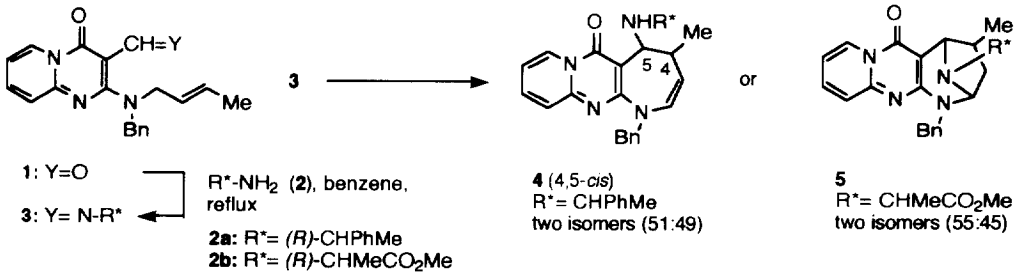
Scheme 1.



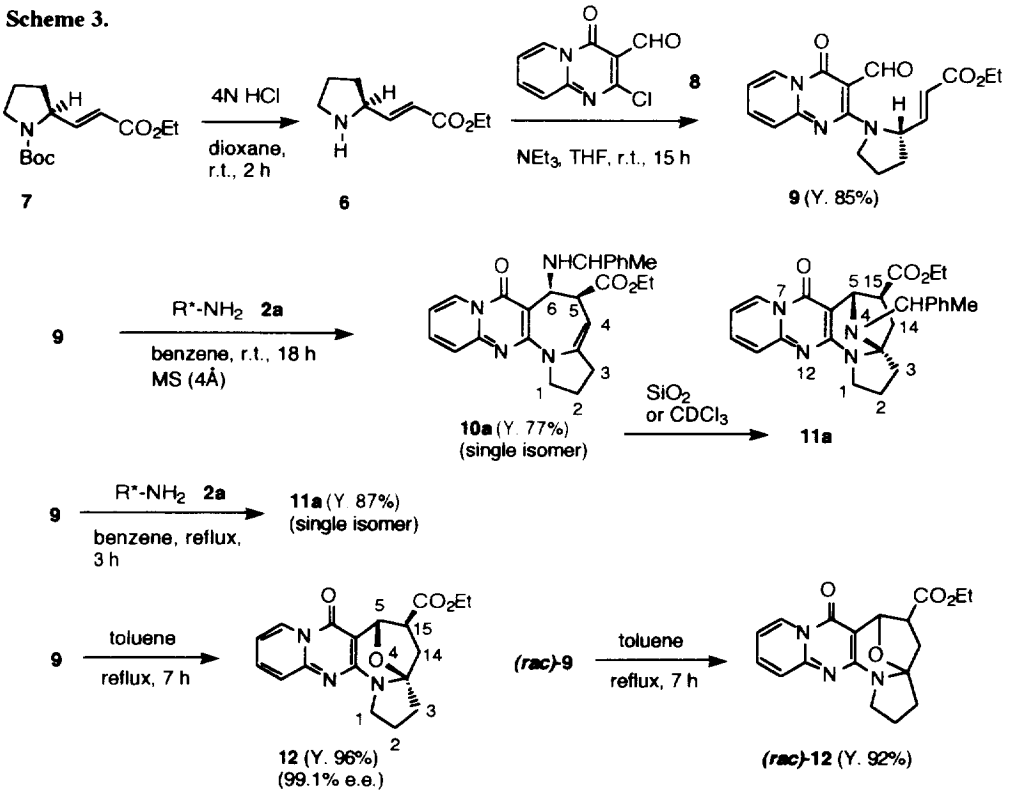
Results and Discussion

At first, the thermal reaction of imines **3**, obtained from aldehyde **1** and chiral primary amines **2a,b** *in situ*, was examined; in both cases mixtures of two diastereomers **4** and **5** were obtained (Scheme 2). The chiral centers situated at the outer-side of the helix did not provide any sufficient stereo-controls of the diastereomers.

Scheme 2.



Scheme 3.

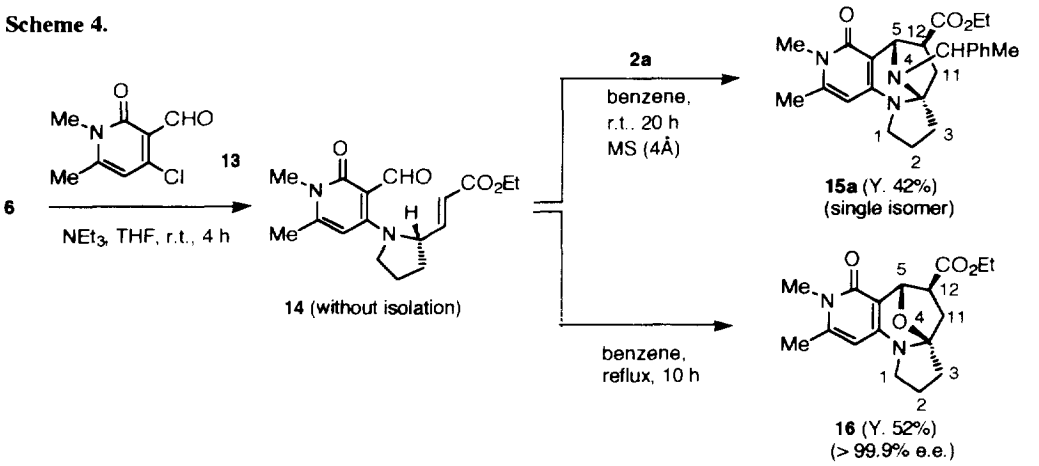


A chiral alkenyl amine **6** was prepared *in situ* by deprotection of *N*-Boc pyrrolidine **7** derived from L-proline according to the literatures.[5] The reaction of amine **6** and 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine 3-carboxaldehyde (**8**)[6] gave the expected chiral aldehyde **9**. The reaction of aldehyde **9** with D-1-phenylethylamine (**2a**) in benzene in the presence of molecular sieves (4Å) at room temperature gave azepine **10a** in 77% yield as a single isomer. Azepine **10a** was sensitive to acidic conditions such as silica gel

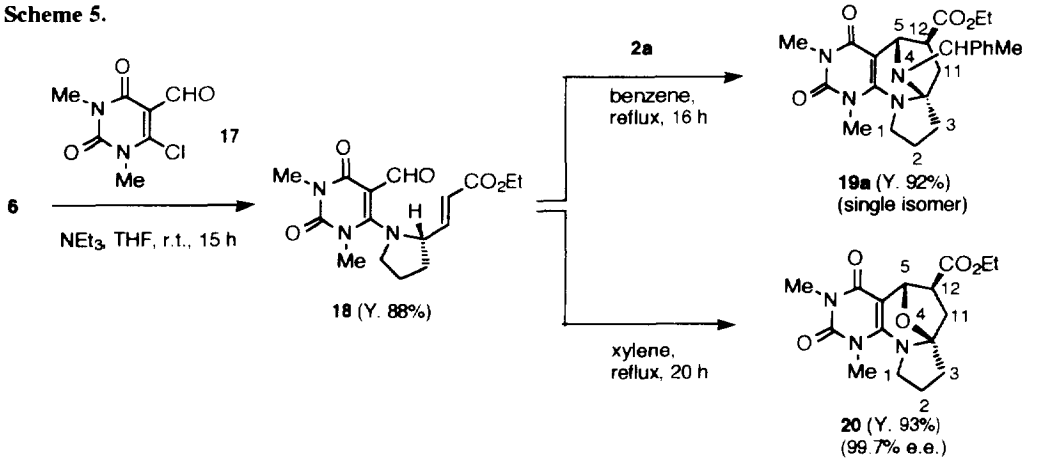
chromatography or the solution of deuteriochloroform affording bridged compound **11a**. Product **11a** was also obtained in the reaction of aldehyde **9** and amine **2a** in refluxing benzene (Scheme 3). This suggested that the chirality in the corresponding imine of aldehyde **9** transferred efficiently to the resulting azepine-ring. This prompted us to examine the carbonyl ene reaction of aldehyde **9**. Heating **9** in refluxing toluene and usual work-up gave [1,3]oxazine **12** in 96% yield as a single isomer. An intrinsic stereoselective nature of the carbonyl ene reaction was confirmed by the comparison with the thermal reaction of racemic aldehyde ***(rac)*-9**; the enantioselectivity of the reaction of **9** was deduced to be perfect (99.0% e.e. by a chiral HPLC method, see Experimental Section).

Similarly, two other aldehydes were prepared and examined the imine and carbonyl ene reactions. Chiral alkenyl amine **6** was allowed to react with 4-chloro-1,6-dimethyl-2-oxo-1,2-dihydropyridine 3-carboxaldehyde (**13**)[7] giving the desired chiral aldehyde **14**. Aldehyde **14**, however, was not so stable and decomposed during isolation procedures. The reaction of aldehyde **14**, without isolation, with amine **2a** in benzene at room temperature gave pyrimidine **15a** in a low yield. Also, thermal reaction of aldehyde **14** in refluxing xylene afforded oxazine **16** in a moderate yield. The ^{1}H NMR spectra and/or HPLC analysis of these products showed that **15a** was a single isomer (d.e.; more than 99%) and that **16** was also enantiomerically pure (Scheme 4). This means that both ene reactions proceed with an induction of the chirality of the aldehyde **14**.

Scheme 4.



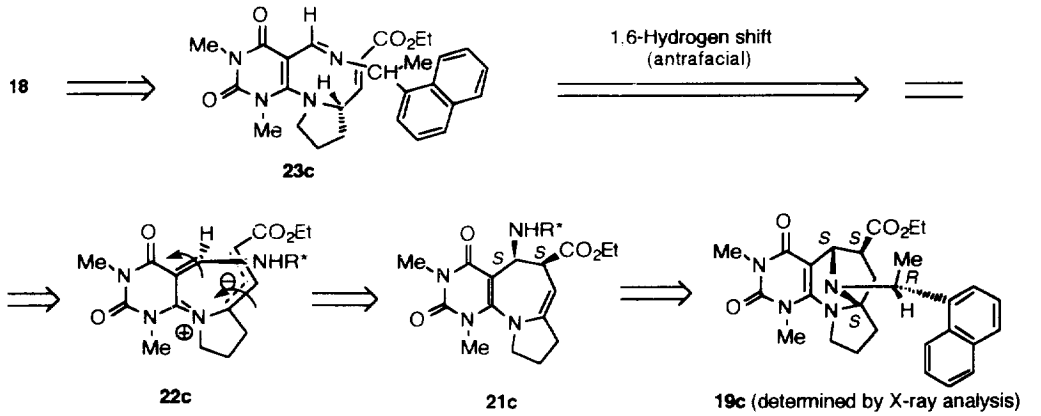
Scheme 5.



On the other hand, when chiral aldehyde **18**, obtained from chiral amine **6** and 6-chloro-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine 5-carboxaldehyde (**17**),[8] was allowed to react with amine **2a** in refluxing benzene; pyrimidine **19a** was formed in 92% yield also as a single isomer. The carbonyl ene reaction of **18** was carried out in refluxing xylene to give an enantiomerically pure (more than 99.7% e.e.) oxazine **20** (Scheme 5).

In order to elucidate the reaction mechanism, we attempted to determine the structure of pyrimidine **19**. The structure of pyrimidine **19c**, derived from the reaction of **18** with D-1-(1-naphthyl)ethylamine (**2c**), was unambiguously confirmed by X-ray single-crystal structure analysis (Fig. 1).[9] As a consequence, the stereochemistry of azepine **21c**, the precursor of **19c**, was deduced to be (5*S*, 6*S*) based on the *R* absolute stereochemistry derived from the 1-(1-naphthyl)ethylamino portion. The structure of the azomethine ylide intermediate **22c** was formed by the conrotatory ring-opening of the azepine **21c**. The intermediate **22c** was formed *via* an antarafacial [1,6] hydrogen shift of chiral imine **23c** and the transition state of the hydrogen shift was stereogenetic in the course of the azepine-ring formation (Scheme 6).

Scheme 6.



In these three papers, we have described the synthetic utility and mechanistic novelty of the imine and carbonyl ene reactions at the periphery of heterocyclic systems. Further investigations on the reaction mechanism and scope of these ene reactions are in progress in our laboratory.

Experimental Section

General Methods. Descriptions of usual instruments, general procedures, chromatographic procedures, and preparation of aldehyde **1** have been reported previously.[1] UV Spectra were obtained with a HITACHI 220 spectrophotometer and specific rotations were recorded on a HORIBA SEPA-200 polarimeter.

Preparation of Chiral Aldehydes 9 and 18. Typical Procedure: A solution of (2'*S*,3*E*)-ethyl 4-[1-(*t*-butoxycarbonyl)pyrrolidin-2-yl]but-3-enoate[5] (**7**; 0.269 g, 1.0 mmol) in 3.9 N hydrochloric acid-dioxane (1.5 ml) was stirred at room temperature for 2 h. To the mixture THF (5 ml) was added and the resulting mixture was cooled in ice bath. A THF solution (10 ml) of triethylamine (1.20 ml; 8.6 mmol) and then 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine 3-carboxaldehyde (**8**)[6] was added to the mixture and the reaction mixture was stirred for 4 h. The mixture was dried over anhydrous magnesium sulfate. The magnesium sulfate and triethylamine hydrochloride was removed by filtration and the filtrate was evaporated to dryness at room

temperature. The residue was subjected to a column chromatography on silica gel to give chiral aldehyde **9** (0.299 g, 85%) with hexane/ethyl acetate= 3:2. Similarly, racemic aldehydes ***(rac)*-9** and ***(rac)*-14** were obtained from DL-proline.

2-{*(S)*-2-[2-*(E)*-(Ethoxycarbonyl)vinyl]pyrrolidin-1-yl}-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine 3-carboxaldehyde (**9**): pale yellow oil; IR (NaCl) cm^{-1} 1710, 1680, 1640 (CO); ^1H NMR ($CDCl_3$) δ= 1.26 (3 H, t, *J*= 6.9 Hz, OCH_2CH_3), 1.80-2.34 (4 H, ov, $-CH_2CH_2-$), 3.24, 3.97 (each 1 H, br, m, $>NCH_2-$), 4.16 (2 H, q, *J*= 6.9 Hz, OCH_2CH_3), 5.24 (1 H, br m, >CHCH=CH-), 5.91 (1 H, d, *J*= 15.5 Hz, >CHCH=CH-), 6.86-6.91 (2 H, ov, >CHCH=CH- and 7-H), 7.20 (1 H, d, $J_{8\text{-}9}$= 8.9 Hz, 9-H), 7.65 (1 H, dd, $J_{7\text{-}8}$= 6.6, $J_{8\text{-}9}$= 8.9 Hz, 8-H), 8.82 (1 H, d, $J_{6\text{-}7}$= 6.9 Hz, 6-H), 10.26 (1 H, s, CHO). Anal. Found: C, 63.02; H, 5.82; N, 12.40%. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31%.

6-{*(S)*-2-[2-*(E)*-(Ethoxycarbonyl)vinyl]pyrrolidin-1-yl}-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine 5-carboxaldehyde (**18**): colorless oil; IR (NaCl) cm^{-1} 1715, 1650 (CO); ^1H NMR ($CDCl_3$) δ= 1.27 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 1.80-2.50 (4 H, ov, $-CH_2CH_2-$), 3.18, 3.73 (each 1 H, each m, $>NCH_2-$), 3.35, 3.43 (each 3 H, each s, 1- and 3-Me), 4.15 (2 H, q, *J*= 7.3 Hz, OCH_2CH_3), 4.74 (1 H, br m, >CHCH=CH-), 5.73 (1 H, dd, *J*= 15.5 Hz, *J*= 1.0 Hz, >CHCH=CH-), 6.53 (1 H, dd, *J*= 15.5 Hz, *J*= 8.3 Hz, >CHCH=CH-), 9.95 (1 H, s, CHO). Anal. Found: C, 57.02; H, 6.50; N, 12.70%. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53%.

Thermal Reaction of Aldehyde 1 with Chiral Amines 2. Typical Procedure: A solution of aldehyde **1** (0.10 g, 0.30 mmol) and amine **2a** (0.05 ml, 0.39 mmol) in dry toluene (5 ml) was heated under reflux for 7 h and evaporated to dryness. The residue was subjected to column chromatography on silica gel to give a inseparable mixture (51: 49) of azepines **4a** and **5a** with hexane/ethyl acetate= 3:1.

(4*S*,5*S*) and (4*R*,5*R*)-1-Benzyl-5-[*(R)*-1-phenylethylamino]-4-methyl-6-oxo-1,4,5,6-tetrahydropyrido-[1',2':1,2]pyrimido[4,5-*b*]azepine (**4**) were obtained in 91% yield as an inseparable mixture of two diastereomers: pale yellow oil; IR (NaCl) cm^{-1} 3330 (NH), 1655 (CO); ^1H NMR ($CDCl_3$) major diastereomer **4-1**: δ= 1.32 (3 H, d, *J*= 6.6 Hz, 4-Me), 1.34 (3 H, d, *J*= 6.3 Hz, CHPh*Me*), 1.65 (1 H, br, 5-NH), 2.75 (1 H, m, 4-H), 3.70 (1 H, q, *J*= 6.3 Hz, *CH*PhMe), 4.54 (1 H, dd, $J_{2\text{-}3}$= 10.2, $J_{3\text{-}4}$= 2.3 Hz, 3-H), 4.87 (1 H, br s, 5-H), 4.96, 5.22 (each 1 H, each d, J_{gem}= 15.2 Hz, CH_2Ph), 5.90 (1 H, dd, $J_{2\text{-}3}$= 10.2, $J_{2\text{-}4}$= 3.0 Hz, 2-H), 6.81-7.56 (13 H, ov, Ph and 9-, 10-, and 11-H), 8.76 (1 H, d, $J_{8\text{-}9}$= 6.6 Hz, 8-H); minor diastereomer **4-2**: δ= 1.10-1.12 (6 H, ov, CHPh*Me* and 4-Me), 1.65 (1 H, br, 5-NH), 2.64 (1 H, m, 4-H), 3.63 (1 H, q, *J*= 6.6 Hz, *CH*PhMe), 4.47 (1 H, br s, 5-H), 4.57 (1 H, br d, $J_{2\text{-}3}$= 9.6 Hz, 3-H), 4.96, 5.58 (each 1 H, each d, J_{gem}= 15.2 Hz, CH_2Ph), 6.01 (1 H, br d, $J_{2\text{-}3}$= 9.6 Hz, 2-H), 6.81-7.56 (13 H, ov, Ph and 9-, 10-, and 11-H), 8.86 (1H, d, $J_{8\text{-}9}$= 6.6 Hz, 8-H); ^{13}C NMR ($CDCl_3$) of **4-1** and **4-2**: δ= 20.5, 20.7 (4-Me), 23.9, 25.2 (CHPh*Me*), 37.5 (4-C), 53.9, 55.0 (5-C), 55.5 (CH_2Ph), 55.4, 56.3 (*C*HPhMe), 104.5, 104.7 (5a-C), 112.7, 112.9 (3-C), 113.0 (9-C), 124.7, 124.8 (11-C), 125.8, 126.5 (5-Ph-*p*), 126.1, 127.2 (5-Ph-*o*), 127.0, 127.2 (1-Ph-*p*), 127.5 (ov, 1-Ph-*o*), 127.6, 127.7 (8-C), 127.6, 127.9 (5-Ph-*m*), 128.1, 128.3 (2-C), 128.4, 128.5 (1-Ph-*m*), 134.9, 135.2 (10-C), 139.0, 139.1 (1-Ph-*i*), 146.3, 147.3 (5-Ph-*i*), 147.5, 147.6 (11a-C), 156.6, 156.8 (12a-C), 158.1 (ov, 6-C); mass *m/z* 436 (M^+). Anal. Found: C, 76.85; H, 6.54; N, 12.50%. Calcd for $C_{28}H_{28}N_4O$: C, 77.03; H, 6.47; N, 12.84%.

A similar reaction of aldehyde **1** and amine **2b** gave also diastereomeric azepines **5-1** and **5-2**, which were separated each other by column chromatography with hexane/ethyl acetate= 3:1. However, the structural determination of these diastereomers could not be attained.

1-Benzyl-3-[*(S)*-1-(methoxycarbonyl)ethyl]-13-methyl-1,2,3,4-tetrahydro-2,4-ethanopyrido[1',2':1,2]-pyrimido[4,5-*d*]pyrimidin-5(5*H*)-one (**5-1**): Yield 41%; yellow prisms from hexane-benzene; mp 153-155 °C; IR (KBr) cm^{-1} 1730, 1665 (CO); ^1H NMR ($CDCl_3$) δ= 1.19 (3 H, d, *J*= 6.6 Hz, 13-Me), 1.31 (3 H, d, *J*= 6.9 Hz, CH*Me*CO_2Me), 1.70 (1 H, ddd, $J_{2\text{-}12}$= 5.0, $J_{12\text{-}13}$= 4.0, J_{gem}= 12.9 Hz, 12-H*exo*), 2.22 (1 H, dd, $J_{12\text{-}13}$= 8.9, J_{gem}= 12.9 Hz, 12-H*endo*), 2.36 (1 H, m, 13-H), 3.08 (1 H, q, *J*= 6.9 Hz, C*H*MeCO$_2$Me), 3.42 (3 H, s, OMe), 4.20 (1 H, s, 4-H), 4.42, 5.07 (each 1 H, each d, J_{gem}= 14.9 Hz, CH_2Ph), 4.58 (1 H, d, $J_{2\text{-}12}$= 5.0 Hz, 2-H), 6.88 (1 H, ddd, $J_{7\text{-}8}$= 7.3, $J_{8\text{-}9}$= 6.6, $J_{8\text{-}10}$= 1.3 Hz, 8-H), 7.23-7.35 (6 H, ov, Ph and 10-H), 7.56 (1 H, ddd, $J_{7\text{-}9}$= 1.7, $J_{8\text{-}9}$= 6.6, $J_{9\text{-}10}$= 8.9 Hz, 9-H), 8.91 (1 H, dd, $J_{7\text{-}8}$= 7.3, $J_{7\text{-}9}$= 1.7 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 17.7 (CH*Me*CO_2Me), 22.4 (13-Me), 41.5 (13-C), 43.8 (12-C), 48.5 (*C*H_2Ph), 51.6 (OMe), 53.3 (*C*HMeCO$_2$Me), 59.5 (4-C), 74.4 (2-C), 91.6 (4a-C), 112.4 (8-C), 124.3 (10-C), 127.3 (Ph-*p*), 127.8 (7-C), 128.5 (Ph-*o*), 128.5 (Ph-*m*), 135.7 (9-C), 138.3 (Ph-*i*), 150.1 (10a-C), 154.8 (11a-C), 155.5 (5-C), 174.0 (CO_2). Anal. Found: C, 68.96; H, 6.25; N, 13.31%. Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39%.

1-Benzyl-3-[*(S)*-1-(methoxycarbonyl)ethyl]-13-methyl-1,2,3,4-tetrahydro-2,4-ethanopyrido[1',2':1,2]-pyrimido[4,5-*d*]pyrimidin-5(5*H*)-one (**5-2**): Yield 34%; colorless prisms from hexane; mp 134-135 °C; IR (KBr) cm^{-1} 1740, 1665 (CO); ^1H NMR ($CDCl_3$) δ= 0.91 (3 H, d, *J*= 6.6 Hz, CH*Me*CO_2Me), 1.18 (3 H, d, *J*= 6.6 Hz, 13-Me), 1.67 (1 H, ddd, $J_{2\text{-}12}$= 5.3, $J_{12\text{-}13}$= 3.6, J_{gem}= 12.9 Hz, 12-H*exo*), 2.21 (1 H, dd, $J_{12\text{-}13}$= 8.9, J_{gem}= 12.9 Hz, 12-H*endo*), 2.39 (1 H, m, 13-H), 3.17 (1 H, q, *J*= 6.9 Hz, C*H*MeCO$_2$Me), 3.68 (3 H, s, OMe), 4.03 (1 H, s, 4-H), 4.39-4.47 (2 H, ov, C*H*HPh and 2-H), 5.12 (1 H, d, J_{gem}= 14.8 Hz, CH*H*Ph), 6.88 (1 H, ddd, $J_{7\text{-}8}$= 6.9, $J_{8\text{-}9}$= 6.6, $J_{8\text{-}10}$= 1.3 Hz, 8-H), 7.25-7.40 (6 H, ov, Ph and 10-H), 7.56 (1 H, ddd, $J_{7\text{-}9}$= 1.7, $J_{8\text{-}9}$= 6.6, $J_{9\text{-}10}$= 8.6 Hz, 9-H), 8.89 (1 H, dd, $J_{7\text{-}8}$= 6.9, $J_{7\text{-}9}$= 1.7 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 16.6 (CH*Me*CO_2Me), 22.1 (13-Me), 42.3 (13-C), 43.4 (12-C), 48.1 (*C*H_2Ph), 52.0 (OMe), 54.1 (*C*HMeCO$_2$Me), 61.6 (4-C), 72.3 (2-C), 92.2 (4a-C), 112.3 (8-C), 124.1 (10-C), 127.6 (Ph-*p*), 127.8 (7-C), 128.5 (Ph-*o*), 128.6 (Ph-*m*), 135.6 (9-C), 138.5 (Ph-*i*), 150.0 (10a-C), 154.9 (11a-C), 155.3 (5-C), 174.1 (CO_2). Anal. Found: C, 68.89; H, 6.24; N, 13.34%. Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39%.

Imine and Carbonyl Ene Reaction Using Chiral Aldehydes 9, 14, and 18. Typical Procedure: A dry toluene solution (5 ml) of aldehyde **9** (0.182 g, 0.53 mmol) and amine **2a** (0.08 ml, 0.62 mmol) in the presence of molecular sieves (4Å) was stirred at room temperature for 18 h and evaporated to dryness. Azepine **10a** (0.183 g, 77%) was obtained by partial crystallization with hexane-benzene. Compound **10a** was liable and converted easily to bridged compound **11a** under acidic conditions. A solution of aldehyde **9** (0.105 g, 0.31 mmol) in dry toluene (5 ml) was deoxygenated by passing through dry nitrogen for 0.5 h and heated under reflux for 7 h. The toluene was evaporated and the residue was subjected to column chromatography on silica gel to afford [1,3]oxazine **12** (0.100 g, 94%) with hexane/ethyl acetate= 2:5.

(5*S*,6*S*)-5-Ethoxycarbonyl-6-[*(R)*-1-phenylethylamino]-2,3,5,6-tetrahydropyrrolo[1,2-*g*]pyrido-[1',2':1,2]pyrimido[4,5-*b*]azepin-7(1*H*,7*H*)-one (**10a**); colorless prisms from hexane-benzene; mp 141-143 °C; IR (KBr) cm^{-1} 3300 (NH), 1720, 1650 (CO); ^1H NMR ($CDCl_3$) δ= 1.28 (3 H, d, *J*= 6.6 Hz, NHCHPh*Me*), 1.36 (3 H, t, *J*= 7.3 Hz, OCH$_2$C*H*$_3$), 1.79-1.97 (3 H, ov, 2-H and 6-NH), 2.68- 2.79 (2 H, ov, 3-H), 3.38 (1 H, dd, $J_{4\text{-}5}$= 2.6, $J_{5\text{-}6}$= 2.6 Hz, 5-H), 3.68 (1 H, q, *J*= 6.6 Hz, NHC*H*PhMe), 3.85, 4.11 (each 1 H, each m, 1-H), 4.21, 4.36 (each 1 H, each dq, *J*= 7.3, J_{gem}= 10.6 Hz, OC*H*$_2$CH$_3$), 5.19 (1 H, d, $J_{4\text{-}5}$= 2.6 Hz, 4-H), 5.66 (1 H, d, $J_{5\text{-}6}$= 2.6 Hz, 6-H), 6.80-6.98 (6 H, ov, Ph and 10-H), 7.18 (1 H, d, $J_{11\text{-}12}$= 8.9 Hz, 12-H), 7.53 (1 H, dd, $J_{10\text{-}11}$= 6.6, $J_{11\text{-}12}$= 8.9 Hz, 11-H), 8.81 (1 H, d, $J_{9\text{-}10}$= 6.9 Hz, 9-H); ^{13}C NMR ($CDCl_3$) δ= 14.4 (OCH$_2$*C*H$_3$), 22.1 (2-C), 24.2 (NHCHPh*Me*), 35.0 (3-C), 47.3 (5-C), 52.7 (6-C), 52.9 (1-C), 56.2 (NH*C*HPhMe), 60.8 (O*C*H$_2$CH$_3$), 95.1 (4-C), 101.3 (6a-C), 113.0 (10-C), 124.7 (12-C), 125.5 (Ph-*o*), 125.7 (Ph-*p*), 127.5 (Ph-*m*), 127.7 (9-C), 135.2 (11-C), 138.3 (3a-C), 147.4 (Ph-*i*), 147.9 (13a-C), 155.4 (12a-C),

157.9 (7-C), 173.0 (CO_2). Anal. Found: C, 70.52; H, 6.36; N, 12.52%. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.61%

(3a*S*,5*S*,15*S*)-15-Ethoxycarbonyl-4-[(*R*)-1-phenylethyl]-1,2,3,3a,4,5-hexahydro-3a,5-ethanopyrrolo-[*b*]pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidin-6(6*H*)-one (**11a**): colorless needles from hexane-benzene; mp 123-125 °C; IR (KBr) cm^{-1} 1725, 1665 (CO); ^1H NMR ($CDCl_3$) δ= 1.27 (3 H, d, *J*= 6.6 Hz, CHPh*Me*), 1.37 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 1.49-1.79 (4 H, ov, 2- and 3-H), 2.44-2.57 (2 H, ov, 14-H), 3.03 (1 H, dd, $J_{14\text{-}15}$= 5.3, $J_{14\text{-}15}$= 8.3 Hz, 15-H), 3.46 (1 H, q, *J*= 6.6 Hz, C*H*PhMe), 3.59, 3.73 (each 1 H, each m, 1-H), 4.25, 4.36 (each 1 H, each dq, *J*= 7.3, J_{gem}= 10.9 Hz, OCH_2CH_3), 5.23 (1 H, s, 5-H), 6.90 (1 H, ddd, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 6.6, $J_{9\text{-}11}$= 1.3 Hz, 9-H), 7.15-7.38 (6 H, ov, Ph and 11-H), 7.59 (1 H, ddd, $J_{8\text{-}10}$= 1.7, $J_{9\text{-}10}$= 6.6, $J_{10\text{-}11}$= 8.9 Hz, 10-H), 8.97 (1 H, dd, $J_{8\text{-}9}$= 6.9, $J_{8\text{-}10}$= 1.7 Hz, 8-H); ^{13}C NMR ($CDCl_3$) δ= 14.4 (OCH_2CH_3), 22.9 (2-C), 25.1 (CHPh*Me*), 32.5 (3-C), 45.4 (1- and 14-C), 49.3 (15-C), 54.0 (*C*HPhMe), 58.7 (5-C), 61.0 (OCH_2CH_3), 85.1 (3a-C), 90.2 (5a-C), 112.4 (9-C), 123.9 (11-C), 126.4 (Ph-*o*), 126.5 (Ph-*p*), 128.1 (8-C), 128.4 (Ph-*m*), 136.1 (10-C), 148.6 (Ph-*i*), 151.2 (11a-C), 154.1 (12a-C), 155.2 (6-C), 173.8 (CO_2). Anal. Found: C, 70.09; H, 6.49; N, 12.53%. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.61%.

(3a*R*,5*S*,15*S*)-15-Ethoxycarbonyl-1,2,3,3a-tetrahydro-3a,5-ethanopyrrolo[4,5*b*]pyrido[1',2':1,2]-pyrimido[4,5-*d*][1,3]oxazin-6(5*H*,6*H*)-one (**12**): colorless needles from hexane-benzene; mp 160 °C; $[\alpha]_D^{25}$ +97.48° [*c*= 1.075 (g dl^{-1}), $CHCl_3$]; UV(EtOH) λ_{max} nm (log ε): 266.8 (4.98); IR (KBr) cm^{-1} 1730, 1680 (CO); ^1H NMR ($CDCl_3$) δ= 1.33 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 1.97-2.17 (2 H, ov, 2-H), 2.28-2.49 (2 H, ov, 3-H), 2.50- 2.60 (2 H, ov, 14-H), 3.34 (1 H, dd, $J_{14\text{-}15}$= 5.6, $J_{14\text{-}15}$= 7.6 Hz, 15-H), 3.65-3.84 (2 H, ov, 1-H), 4.24 (2 H, q, *J*= 7.3 Hz, OCH_2CH_3), 5.81 (1 H, s, 5-H), 6.93 (1 H, ddd, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 6.6, $J_{9\text{-}11}$= 1.3 Hz, 9-H), 7.34 (1 H, ddd, $J_{8\text{-}11}$= 1.0, $J_{9\text{-}11}$= 1.3, $J_{10\text{-}11}$= 8.9 Hz, 11-H), 7.60 (1 H, ddd, $J_{8\text{-}10}$= 1.7, $J_{9\text{-}10}$= 6.6, $J_{10\text{-}11}$= 8.9 Hz, 10-H), 8.94 (1 H, ddd, $J_{8\text{-}9}$= 6.9, $J_{8\text{-}10}$= 1.7, $J_{8\text{-}11}$= 1.0 Hz, 8-H); ^{13}C NMR ($CDCl_3$) δ= 15.5 (OCH_2CH_3), 24.5 (2-C), 36.0 (3-C), 43.8 (14-C), 48.1 (1-C), 54.7 (15-C), 62.6 (OCH_2CH_3), 78.3 (5-C), 95.3 (5a-C), 100.5 (3a-C), 114.2 (9-C), 125.5 (11-C), 129.1 (8-C), 137.5 (10-C), 152.5 (11a-C), 154.8 (12a-C), 156.5 (6-C), 173.9 (CO_2). Anal. Found: C, 63.27; H, 5.62; N, 12.29%. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31%.

The imine and carbonyl ene reactions using aldehyde **14** were performed without isolation of the aldehyde.

(3a*S*,5*S*,12*S*)-12-Ethoxycarbonyl-7,8-dimethyl-4-[(*R*)-1-phenylethyl]-1,2,3,3a,4,5-hexahydro-3a,5-ethanopyrrolo[2,1-*b*]pyrido[4,5-*d*]pyrimidin-6(7*H*)-one (**15a**): Yield 42%; colorless needles from hexane-benzene; mp 160-161 °C; IR (KBr) cm^{-1} 1725, 1635 (CO); ^1H NMR ($CDCl_3$) δ= 1.23 (3 H, d, *J*= 6.6 Hz, CHPh*Me*), 1.34 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 1.42-1.78 (4 H, ov, 2- and 3-H), 2.31 (3 H, s, 8-Me), 2.37 (1 H, dd, $J_{11\text{-}12}$= 9.6, J_{gem}= 13.2 Hz, 11-H*endo*), 2.49 (1 H, dd, $J_{11\text{-}12}$= 9.6, J_{gem}= 13.2 Hz, 11-H*exo*), 2.97 (1 H, dd, $J_{11\text{-}12}$= 3.6, $J_{11\text{-}12}$= 9.6 Hz, 12-H), 3.19, 3.43 (each 1 H, each m, 1-H), 3.31 (1 H, q, *J*= 6.6 Hz, C*H*PhMe), 3.48 (3 H, s, 7-Me), 4.20, 4.35 (each 1 H, each dq, *J*= 7.3, J_{gem}= 10.6 Hz, OCH_2CH_3), 5.07 (1 H, s, 5-H), 5.55 (1 H, s, 9-H), 7.13-7.37 (5 H, ov, Ph); ^{13}C NMR ($CDCl_3$) δ= 14.4 (OCH_2CH_3); 21.4 (8-Me), 23.0 (2-C), 25.2 (CHPh*Me*), 30.2 (7-Me), 32.2 (3-C), 45.2 (11-C), 46.0 (1-C), 49.7 (12-C), 54.1 (*C*HPhMe), 59.0 (5-C), 60.7 (OCH_2CH_3), 84.5 (3a-C), 95.0 (9-C), 98.5 (5a-C), 126.3(Ph-*p*), 126.4 (Ph-*o*), 128.3 (Ph-*m*), 145.3 (Ph-*i*), 148.0, 149.1 (8- and 9a-C), 160.8 (6-C), 174.2 (CO_2). Anal. Found: C, 71.23; H, 7.41; N, 9.97%. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97%.

(3a*R*,5*S*,12*S*)-12-Ethoxycarbonyl-7,8-dimethyl-1,2,3,3a,4,5-hexahydro-3a,5-ethanopyrrolo[5,1-*b*]-pyrido[4,5-*d*][1,3]oxazin-6(5*H*,7*H*)-one (**16**): Yield 52 %; colorless oil; $[\alpha]_D^{25}$ +182.52° [*c*= 0.984 (g dl^{-1})

$CHCl_3$]; UV(EtOH) λ_{max} nm (log ε) 233.2 (4.62); IR (NaCl) cm^{-1} 1725, 1640 (CO); ^1H NMR ($CDCl_3$) δ= 1.31 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 1.90-2.15 (2 H, ov, 2-H), 2.23-2.41 (3 H, ov, 3-H and 11-H*endo*), 2.29 (3 H, s, 8-Me), 2.52 (1 H, dd, $J_{11\text{-}12}$= 3.3, J_{gem}= 13.2 Hz, 11-H*exo*), 3.25- 3.33 (2 H, ov, 1- and 12-H), 3.45 (3 H, s, 7-Me), 3.53 (1 H, m, 1-H), 4.20 (2 H, q, *J*= 7.3 Hz, OCH_2CH_3), 5.57 (1 H, s, 9-H), 5.61 (1 H, s, 5-H); ^{13}C NMR ($CDCl_3$) δ= 14.3 (OCH_2CH_3), 21.3 (8-Me), 23.5 (2-C), 30.1 (7-Me), 34.6 (3-C), 41.9 (11-C), 48.1 (1-C), 54.0 (12-C), 61.1 (OCH_2CH_3), 77.4 (5-C), 97.2 (9-C), 98.8 (3a-C), 104.1 (5a-C), 145.8, 148.2 (8-C, 9a-C), 160.1 (6-C), 173.0 (CO_2). Anal. Found: C, 64.12; H, 7.12; N, 8.50%. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80%.

(3a*S*,5*S*,12*S*)-12-Ethoxycarbonyl-7,9-dimethyl-4-[(*R*)-1-phenylethyl]-1,2,3,3a,4,5-hexahydro-3a,5-ethanopyrrolo[*b*]pyrimido[4,5-*d*]pyrimidine-6,8(7*H*,9*H*)-dione (**19a**): Yield: 92%; colorless prisms from hexane-benzene; sublimated at *ca.* 210 °C and decomposed at 269-271 °C; IR (KBr) cm^{-1} 1720, 1685, 1625 (CO); ^1H NMR ($CDCl_3$) δ= 1.22 (3 H, d, *J*= 6.6 Hz, CHPh*Me*), 1.34 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 1.62-1.89 (4 H, ov, 2- and 3-H), 2.32 (1 H, dd, $J_{11\text{-}12}$= 9.2, J_{gem}= 13.9 Hz, 11-H*endo*), 2.74 (1 H, dd, $J_{11\text{-}12}$= 3.0, J_{gem}= 13.9 Hz, 11-H*exo*), 2.94 (1 H, dd, $J_{11\text{-}12}$= 3.0, $J_{11\text{-}12}$= 9.2 Hz, 12-H), 3.35, 3.45 (each 3 H, each s, 7- and 9-Me), 3.35-3.54 (2 H, ov, C*H*PhMe and 1-H), 3.75 (1 H, m, 1-H), 4.20, 4.35 (each 1 H, each dq, *J*= 7.3, J_{gem}= 10.6 Hz, OCH_2CH_3), 4.98 (1 H, s, 5-H), 7.17-7.39 (5 H, ov, Ph); ^{13}C NMR ($CDCl_3$) δ= 14.4 (OCH_2CH_3), 23.4 (2-C), 25.5 (CHPh*Me*), 27.7 (9-Me), 31.8 (3-C), 35.4 (7-Me), 43.6 (11-C), 49.6 (12-C), 52.1 (1-C), 54.4 (*C*HPhMe), 58.4 (5-C), 60.9 (OCH_2CH_3), 87.7, 87.7 (3a- and 5a-C), 126.4 (Ph-*o*), 126.7 (Ph-*p*), 128.2 (Ph-*m*), 147.8 (Ph-*i*), 151.8, 153.0 (8- and 9a-C), 160.4 (6-C), 173.6 (CO_2). Anal. Found: C, 65.82; H, 6.97; N, 12.76%. Calcd for $C_{24}H_{30}N_4O_4$: C, 65.73; H, 6.90; N, 12.78%.

(3a*R*,5*S*,12*S*)-12-Ethoxycarbonyl-7,9-dimethyl-1,2,3,3a-tetrahydro-3a,5-ethanopyrrolo[4,5-*b*]pyrimido-[4,5-*d*][1,3]oxazine-6,8(5*H*,7*H*,9*H*)-dione (**20**): Yield 93%; colorless needles from hexane-benzene; mp 144-145 °C; $[\alpha]_D^{25}$ =180.53 ° [*c*= 1.017 (g dl^{-1}), $CHCl_3$]; UV (EtOH) λmax nm (log ε) 282.6 (4.19); IR (KBr) cm^{-1} 1720, 1680, 1630 (CO); ^1H NMR ($CDCl_3$) δ= 1.30 (3 H, t, *J*= 7.3 Hz, OCH_2CH_3), 2.00-2.31 (3 H, ov, 2- and 3-H and 11-H*endo*), 2.67 (1 H, dd, $J_{11\text{-}12}$= 2.0, J_{gem}= 13.9 Hz, 11-H*exo*), 3.16-3.25 (2 H, ov, 1- and 12-H), 3.33, 3.34 (each 3 H, each s, 7- and 9-Me), 3.64 (1 H, m, 1-H), 4.20 (2 H, q, *J*= 7.3 Hz, OCH_2CH_3), 5.45 (1 H, s, 5-H); ^{13}C NMR ($CDCl_3$) δ= 14.1 (OCH_2CH_3), 23.7 (2-C), 27.6 (9-Me), 33.1 (7-Me), 34.6 (3-C), 52.8 (1-C), 53.7 (12-C), 61.2 (OCH_2CH_3), 75.1 (5-C), 95.0 (5a-C), 101.2 (3a-C), 151.8, 152.3 (8- and 9a-C), 160.1 (6-C), 172.2 (CO_2). Anal. Found: C, 57.28; H, 6.30; N, 12.56%. Calcd for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53%.

The reaction of aldehyde **18** with *(R)*-(+)-1-(1-naphthyl)ethylamine (**2c**) in refluxing benzene for 12 h gave oxazine **19c** in 84% yield.

(3a*S*,5*S*,12*S*)-12-Ethoxycarbonyl-7,9-dimethyl-4-[(*R*)-1-(1-naphthyl)ethyl]-1,2,3,3a,4,5-hexahydro-3a,5-ethanopyrrolo[*b*]pyrimido[4,5-*d*]pyrimidine-6,8(5*H*,7*H*,9*H*)-dione (**19c**): colorless prisms from ethyl acetate; mp 254-255 °C; IR (KBr) cm^{-1} 1720, 1680, 1620 (CO); ^1H NMR ($CDCl_3$) δ= 1.34-1.49 (8 H, ov, OCH_2CH_3 and CHAr*Me* and 3-H), 1.74 (2 H, m, 2-H), 2.35 (1 H, dd, $J_{11\text{-}12}$= 9.2, J_{gem}= 13.9 Hz, 11-H*endo*), 2.81 (1 H, dd, $J_{11\text{-}12}$= 2.6, J_{gem}= 13.9 Hz, 11-H*exo*), 3.01 (1 H, dd, $J_{11\text{-}12}$= 2.6, $J_{11\text{-}12}$= 9.2 Hz, 12-H), 3.39, 3.47 (each 3 H, each s, 7- and 9-Me), 3.41-3.50 (2 H, ov, 1-H), 3.71 (1 H, q, *J*= 8.9 Hz, C*H*ArMe), 4.24, 4.38 (each 1 H, each m, OCH_2CH_3), 5.09 (1 H, s, 5-H), 7.42-7.99 (7 H, ov, Ar); ^{13}C NMR ($CDCl_3$) δ= 14.4 (OCH_2CH_3), 23.1 (2-C), 23.6 (CHAr*Me*), 27.8 (9-Me), 32.6 (3-C), 35.4 (7-Me), 43.3 (11-C), 49.6, 49.9 (1- and 12-C), 52.2 (4-C), 58.7 (5-C), 61.0 (OCH_2CH_3), 87.8, 87.9 (3a- and 5a-C), 121.7, 124.7, 125.2, 125.7, 126.1, 127.2, 129.3, 130.1, 133.8, 142.6 (naphthyl-C), 151.9, 153.2 (8- and 9a-C), 160.6 (6-C), 173.6 (CO_2). Anal. Found: C, 66.70; H, 6.78; N, 11.38%. Calcd for $C_{28}H_{32}N_4O_4$: C, 68.83; H, 6.60; N, 11.47%.

Single-crystal X-Ray Structure Determination of Oxazine 19c. For X-ray diffraction study, single crystals (prisms) of oxazine **19c** were recrystallized from propan-2-ol. A crystal of approximate dimensions 0.200 x 0.280 x 0.680 mm was used for data collection. Measurements were made on a Rigaku AFC5S diffractometer by employing graphite-monochromated Mo-K_α radiation.

The unit-cell dimension was obtained by least-squares analysis of 10 reflections within the range of $9.2° < 2\theta < 11.4°$. The crystal data are shown as follows: crystal system: orthorhombic; space group: $p2_12_12_1$(#19); cell constants: *a*: 8.55 (3)Å, *b*: 37.00 (2)Å, *c*: 8.04 (1)Å, V: 2542 (10)Å^3; Z value: 4; Dc: 1.278 g cm^{-3}. The ω-2θ scan technique to a maximum 2θ-value of 54.9° was used. Scans of $(1.22 + 0.30 \tan\theta)°$ were made at a speed of 32.0° min^{-1} (in omega). A total of 2711 observed reflections was collected and all calculations were performed using TEXAN[10] program. The structure was solved by direct methods (MITHRIL)[11] and refined by least-squares to *R* 0.066. ORTEP[12] drawing of **19c** is shown in Fig. 1.[9]

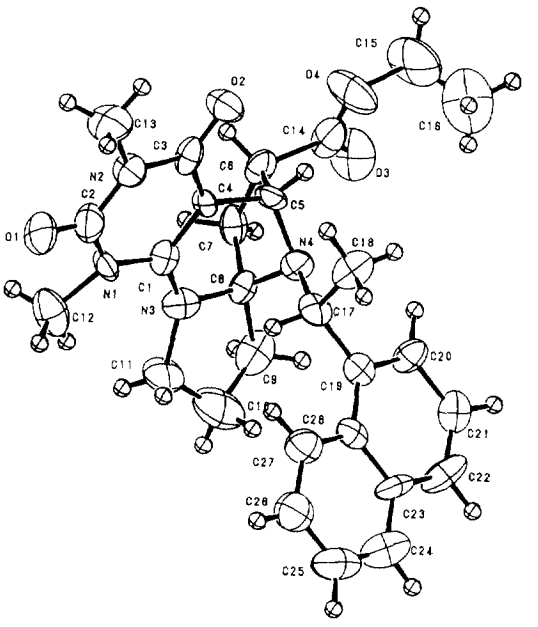


Fig. 1. ORTEP drawing of oxazine **19c** with crystallographic numbering scheme.

Measurement of Enantioselectivity of [1,3]Oxazines 12, 16, and 20. General Procedures: HPLC measurements were performed with a TOSOH HPLC-8010 (CCPP-D pump, UV-8010 UV detector, and CO-8010 column oven) and a DICEL CHIRALCEL OJ (id 4.6 mm x 250 mm) column; pressure: 16.0 kgf cm^{-2}; flow rate: 0.5 ml min^{-1}; temperature: 35 °C. Crude oxazine **12**, **16**, and **20** and the corresponding racemic oxazine ***(rac)*-12**, ***(rac)*-16**, and ***(rac)*-20** were used without recrystallization. For oxazine ***(rac)*-12**, two peaks (retention time: 43.5 and 53.1 min) were observed with hexane/propan-2-ol= 19:1 as an elution. The enantiomer excess (e.e.) of oxazine **12** was determined by the area of the two peaks [retention time: 42.3 min (99.43) and 67.8 min (0.43)]. Similarly, oxazine ***(rac)*-16** gave two peaks (retention time: 45.8 and 64.7 min) with hexane/propan-2-ol= 6:1 and ***(rac)*-20** did also (retention time: 42.8 and 90.8 min) with hexane/propan-2-ol= 9:1, respectively. In a similar manner the enantiomer excess of oxazine **16** and **20** was determined; for **16** [retention time; 42.3 min (95.85) and 67.8 min (0.05)] and for **20** [retention time: 42.8 min (94.09) and 94.4 min (0.16)].

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