H_2S, 7783-06-4; ClC(O)SCl, 2757-23-5; MeOC(O)N(Me)Ph, 28685-60-1; PhN(Me)C(O)SEt, 40088-76-4; $MeOCCl_2SSSCCl_2OEt$, 88766-60-3; MeOC(O)SSC(O)Cl, 87462-93-9; MeOC(O)SSSC(O)Cl, 88766-61-4; disulfane, 13465-07-1; *N*-methylbenzamine, 100-61-8.

Supplementary Material Available: Tabulations of all UV, mass spectral, chromatographic, and analytical data, together with the complete data that is summarized in Table IV (6 pages). Ordering information is given on any current masthead page.

Probes for Narcotic Receptor Mediated Phenomena. 4.[1] Synthesis of (±)-2,3,4,5,6,6a-Hexahydro-3-methyl-8-hydroxy-1*H*-4,11b-methanobenzofuro-[3,2-*d*]azocine, an Oxide-Bridged 5-(*m*-Hydroxyphenyl)morphan†

Terrence R. Burke, Jr., Arthur E. Jacobson, and Kenner C. Rice*

Section on Medicinal Chemistry, Laboratory of Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

J. V. Silverton

Laboratory of Chemistry, National Heart and Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

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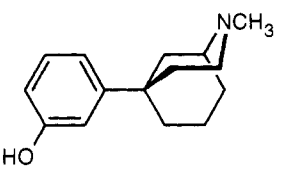
The synthesis of racemic 2,3,4,5,6,6a-hexahydro-3-methyl-3-hydroxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine (**2**) is described. The route utilized a key photochemical conversion of the aryloxy enone **7** to the hexahydrodibenzofuran **8**, which established the relative stereochemistry of the oxide and methano bridges of **2**. A 1,4-Michael-type addition of nitrogen to the β-carbon of the α,β-unsaturated compound **12** established the fourth and final ring. The title compound **2** represents an oxide-bridged derivative of the potent 5-(*m*-hydroxyphenyl)morphan class of opioid analgesics. Unlike the 5-(*m*-hydroxyphenyl)morphans, which have a freely rotating phenyl group, **2** has the phenyl ring conformationally restricted at an angle of 86° relative to atoms 1, 2, 4, and 12 of the piperidine ring as determined by X-ray analysis. The lack of in vivo agonist or antagonist activity of **2** in contrast to the parent 5-(*m*-hydroxyphenyl)morphan **1** suggests that the phenyl ring torsion angle is unsuitable for binding to the opioid receptor system.

Opioid receptors are stereospecific, saturable, high-affinity binding sites in the mammalian central nervous system (CNS) that mediate the analgesic effects of morphine and its surrogates and probably also control certain aspects of the perception of pain, pleasure, and mood by interaction with opiate-like peptides (endorphins) produced in the CNS. In the first two reports of our study of the structure and function of these receptors,[2] we described the preparation of site-directed alkylating agents specific for individual subpopulations of opioid receptors and identification of a M_r 58000 subunit of the opioid δ-receptor. We have also begun examining the topographical features of the opioid receptor system through a structure–activity study based upon the 5-phenylmorphan class of opioid analgesics.[1]

Since the discovery of the 5-phenylmorphans by May in 1954,[3] certain of these compounds have been found to have morphine-like activity and potential therapeutic value. We have undertaken a synthetic study of the 2-methyl-5-(*m*-hydroxyphenyl)morphan nucleus to differentiate aspects of its structure that are important for its observed biological activity. Since the phenylmorphan ring system itself is rigid, we are examining the role of the phenyl ring torsion angle with respect to the fixed piperidine ring as it relates to biological activity and opioid receptor binding. The importance of the phenyl ring torsion angle has previously been cited as one factor effecting the enantiomeric difference in potency between prodine isomers.[4,5]

In our approach toward an unambiguous definition of the phenyl torsion angles for a homologous series of 2-methyl-5-(*m*-hydroxyphenyl)morphans, we have adapted the use of an oxide bridge to covalently link the 2-position of the phenyl ring with atoms 1, 12, or 6a of the morphan moiety in **2**. The arrangement of these sites about the



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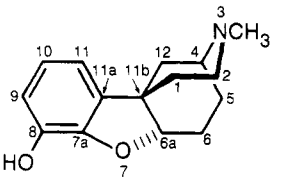

2

phenyl–morphan bond and the possibility of α,β isomers at each position results in six possible rotational isomers, with the phenyl ring of each isomer being rotated approximately 60° from that of the previous isomer (Figure 1).

The first isomer chosen for synthesis, **2**, has an oxide bridge distantly comparable to that of morphine, and in fact, the *O*-methyl ether of the 11-methyl analogue has previously been obtained by degradation of naturally occurring thebaine.[6] Examination of models indicated that

† Dedicated to Dr. Ulrich Weiss on the occasion of his 75th birthday.

(1) For the previous paper in this series, see: Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. In "Problems of Drug Dependence 1983"; Harris, L. S., Ed.; NIDA Research Monograph: Washington, DC, in press.

(2) (a) Klee, W. A.; Simonds, W. F.; Sweat, F. W.; Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C. *FEBS Lett.* **1982**, *150*, 125 (paper 1 in this series) (b) Rice, K. C.; Jacobson, A. E.; Burke, T. R., Jr.; Bajwa, B. S.; Streaty, R. A.; Klee, W. A. *Science (Washington, D.C.)* **1983**, *220*, 314 (paper 2 in this series).

(3) May, E. L.; Murphy, J. G. *J. Org. Chem.* **1954**, *19*, 618.

(4) Larson, D. L.; Portoghese, P. S. *J. Med. Chem.* **1973**, *16*, 195.

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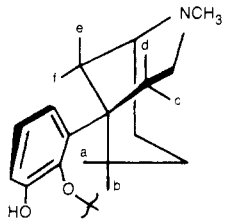


Figure 1. View of 5-(*m*-hydroxyphenyl)morphan ring system showing six possible sites of oxide bridge attachment, a–f.

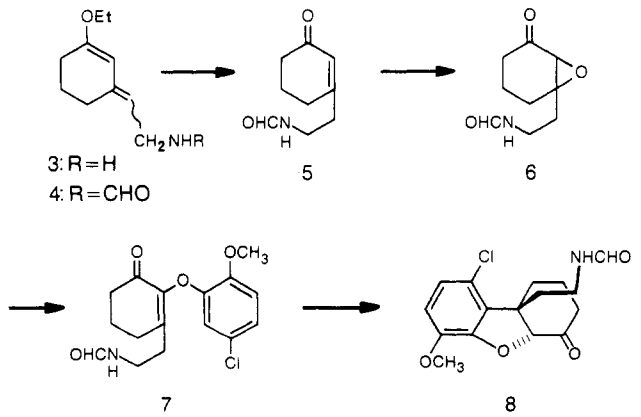
the plane of the phenyl ring for **2** should be held at an angle of approximately 90° with respect to a plane through atoms 1, 2, 4, and 12 of the piperidine ring. In this report, we describe synthesis of the novel **2**, which represents the first entry into the 4,11b-methanobenzofuro[3,2-*d*]azocine ring system by total synthesis.

Synthetic Strategy

A promising approach for construction of the tetracyclic methanobenzofuro[3,2-*d*]azocine skeleton of **2** utilized as an advanced intermediate the cis-fused tricyclic hexahydrodibenzofuran **8**, which we expected would be available by using the recently developed heteroatom-directed photoarylation protocol introduced by Schultz and his co-workers.[7,8] Since the required stereochemical relationship of the oxide bridge and the ultimate methano bridge of **2** would be established during the photochemical conversion of **7** to **8**, we viewed the latter as a highly desirable, initial synthetic objective. We anticipated that conversion of **8** to the corresponding α,β-unsaturated ketone, followed by Michael-type addition of the nitrogen atom, would then afford the completed tetracyclic ring system of **2** (as in **14**). Final adjustment of the oxidation state followed by *O*-demethylation of **19** was then expected to provide **2**.

Synthesis

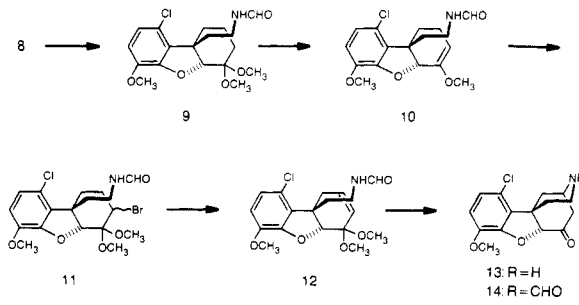
The precursor **7** of photocyclization product **8** was obtained in four steps from 1-ethoxy-3-(2-aminoethylidene)-1-cyclohexene (**3**)[9,10] by using a route parallel to that of Schultz.[10] Free amine **3** was first formylated



with ethyl formate to give crystalline **4**. Treatment of enol ether **4** with dilute HCl hydrolyzed the ether linkage and isomerized the double bond, yielding the more stable enone **5**. Epoxidation of **5** in aqueous MeOH with basic hydrogen peroxide afforded epoxide **6** as a yellow oil in 83% overall yield from **3**.

Formation of an aryloxy enone suitable for photocyclization next required opening epoxide **6** with an appropriately chosen phenol. The phenol chosen, 5-chloroguaicol, contained the necessary latent oxygen functionality needed for the phenolic function of **2** in addition to an electron-withdrawing (and necessarily for us reductively removable) substituent that Schultz had previously shown was necessary in such cases to avoid side-product formation during the photocyclization.[7,8] The required 5-chloroguaicol was obtained in 50% overall yield from commercially available 5-chlorosalicylaldehyde by methylation with methyl iodide–K_2CO_3 in acetone followed by alkaline hydrolysis of the formate ester resulting from Baeyer–Villiger oxidation of the aldehyde function with *m*-chloroperoxybenzoic acid. Opening epoxide **6** with the potassium salt of 5-chloroguaicol afforded a substantial amount of byproducts as expected[8-10] but gave crystalline **7** in 35% yield following chromatography. Photocyclization of **7** (Pyrex-filtered irradiation of a 0.02 M solution in degassed 1:1 benzene:MeOH) proceeded stereospecifically to give the expected cis-fused product **8** in 62% yield.

Having established three of the desired four rings, completion of the fundamental skeleton of **2** could be achieved by formation of the 3,4 carbon–nitrogen bond in **2**. Our primary strategy for this transformation involved conversion of **8** to the corresponding α,β-unsaturated ketone, which we anticipated would undergo ring closure via a facile 1,4-Michael-type addition of the nitrogen atom. The introduction of the double bond was effected by the four-step sequence of Weller and Rapoport,[11] which had proven highly effective for conversion of dihydrocodeinone to codeinone. Ketalization of **8** using trimethylorthoformate gave dimethyl ketal **9**, which underwent elimi-



nation of MeOH to enol ether **10** upon azeotropic distillation with *p*-toluenesulfonic acid in ethanol-free $CHCl_3$. Addition of methyl hypobromite yielded an epimeric mixture of bromo dimethyl ketals **11**, which underwent HBr elimination when refluxed with potassium *tert*-butoxide in THF to give unsaturated ketal **12** in 45% yield from **8**.

Ketal **12** was heated in wet methanolic HCl to hydrolyze the ketal and formyl functions, thereby allowing nucleophilic ring closure by nitrogen to form *N*-nortetracyclic **13**. We viewed **13** as a potentially valuable intermediate since, in addition to methyl, other N substituents could readily by introduced that might afford derivatives with altered pharmacological profiles as in the morphinan series. Unfortunately **13** proved to be moderately unstable, probably because of retro-Michael reaction followed by condensation of the amino and keto functions. Since this instability

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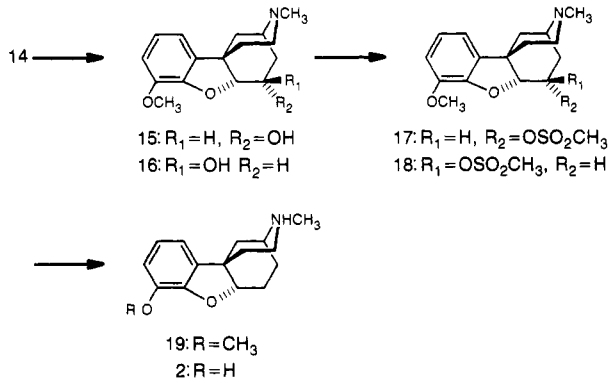
(9) Yee, Y. K. "Total Synthesis of Lycoramine and Studies Related to the Synthesis of Eudesmane and Elemane Sesquiterpenes". Ph.D. Dissertation, Rensselaer Polytechnic Institute, 1978, p 145.
(10) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065.
(11) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171.

made purification and subsequent use in the synthetic scheme difficult, the ring closure was reexamined and the reaction time for hydrolysis of ketal **12** was reduced from 2 h to 30 min. With a shorter reaction time, the *N*-formyl intermediate **14** was isolated as a stable crystalline solid in 53% yield. NMR of this compound revealed the presence of two rotamers (~2:3) as in the case of other polycyclic *N*-formyl derivatives.[12]

With the tetracyclic ring system of **14** completed, all that remained for synthesis of **2** were functional group transformations of which the most difficult was removal of the 6-keto group. Reduction of **14** with $LiAlH_4$ afforded a



mixture of partially dechlorinated epimeric alcohols that was hydrogenated over 10% Pd/C to complete the dechlorination and provided an 86% yield of an epimeric mixture of alcohols **15** and **16** present in an approximate four to one ratio. The oxide bridge H_{6a} protons appeared at about δ 4.4. As in the case of the H_5 proton in the 4,5-epoxymorphinans, these low-field absorptions of H_{6a} are attributed to the deshielding effect of the aromatic ring.[11,13] For the major isomer, $J_{6a-6} = 0$ Hz while for the minor isomer $J_{6a-6} = 9$ Hz.

The epimeric mixture of **15** and **16** was treated with methanesulfonyl chloride in CH_2Cl_2/NEt_3 to give the corresponding methanesulfonate esters **17** and **18** as a foam in 66% yield. When the mixture of **17** and **18** was reduced with either $LiAlH_4$ or potassium tri-*sec*-butylborohydride, a mixture resulted containing substantial amounts of **15** and **16**, resulting from hydride attack at sulfur, rather than carbon. When $LiEt_3BH$ was used, the attack at sulfur was reduced relative to the desired hydride displacement at C-6 and pure **19** was obtained in 36% yield following chromatography. The synthesis was completed by BBr_3-mediated O-demethylation[14] of **19** to yield **2** as a crystalline solid.

Conclusion

The bond lengths and crystal conformation of **2** are given in Figure 2.[15] The crystal structure confirms the structure of the anticipated product. The torsion angle between least-squares planes through atoms 1, 2, 4, and 12 of the piperidine ring of **2** and the six atoms comprising the phenyl ring was calculated as 86° on the basis of X-ray data. The lack of antinociceptive activity (sc, mice) in both the hot-plate assay[16] and tail flick assay[17] and antagonist activity in tail flick antagonism vs. morphine[18] may indicate that **2** does not bind to opioid receptors. Its binding affinity to opioid receptor subpopulations is being investigated and will be reported elsewhere. Since the parent compound **1**, having a freely rotating phenyl group, is a potent narcotic agonist, it may be argued that the lack of activity of **2** is due to a phenyl ring torsion angle that is incompatible with binding to the receptor. Presently, work is in progress to prepare the other five rotational isomers in this series. Should any of them prove to bind to opioid receptors, valuable information will be gained regarding the receptor requirements for equatorial phenyl ring orientation.

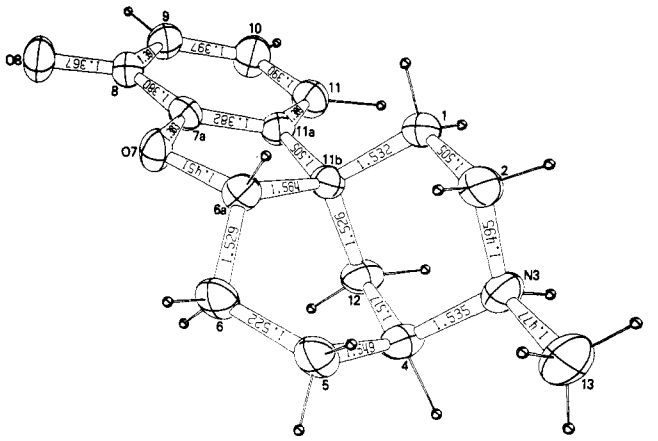


Figure 2. ORTEP[15] drawing of (±)-**2** showing crystal conformation and bond lengths.

Experimental Section

Melting points were determined on a Fischer-Johns apparatus and are corrected. NMR spectra were recorded on a Varian 220-MHz spectrometer with $(CH_3)_4Si$ as the internal reference. IR spectra were recorded on a Beckman IR 4230 spectrometer. Electron-ionization mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Chemical-ionization mass spectra were obtained with a Finnigan 1015D spectrometer with a Model 6000 data collection system and exact-mass spectra were obtained on a V. G. Micromass 7070F spectrometer. Thin-layer chromatography (TLC) plates for analytical (250 μm) and preparative (1000 μm) TLC were purchased from Analtech, Inc., Newark, DE. TLC system A refers to 9:1:0.1 $CHCl_3$:MeOH:concentrated aqueous NH_3. Column chromatography was performed by using 230–400-mesh EM silica gel. Both mass spectra and elemental analyses were obtained from the Section on Analytical Services and Instrumentation, NIADDK.

1-Ethoxy-3-[2-(*N*-formamido)ethylidene]cyclohexene (4). Addition of **3**[9,10] (177.0 g, 1.05 mol) to ethyl formate (500 mL, dried over K_2CO_3, then distilled from P_2O_5) gave a turbid solution, which was converted to a homogeneous solution by the addition of absolute EtOH (50 mL). The solution was kept at 20 °C for 20 h during which time it turned a light yellow color. Evaporation of the solvents under reduced pressure left a yellow oil, which was dissolved in isopropyl alcohol (100 mL) and then diluted with Et_2O (600 mL), followed by ligroin (600 mL). Crystallization occurred rapidly, soon forming a solid mass of needlelike crystals. After 20 min ligroin (400 mL) was added and the mixture was filtered. The filter cake washed with hexane (3 × 50 mL) and dried under vacuum to give **4** (188.0 g, 92%) as white needles. A sample was recrystallized for analysis: mp 69–73 °C; NMR ($CDCl_3$) δ 1.25–1.33 (m, 3 H, CH_3), 1.68–1.75 (m, 2 H), 2.12–2.29 (m, 4 H), 3.65–3.79 (m, 2 H), 3.86 (t, 2 H, J = 7 Hz), 4.95 (t, 0.4 H, J = 7 Hz), 4.84 (t, 0.6 H, J = 7 Hz), 5.10 (s, 0.6 H), 5.35 (s, 0.4 H), 4.45 (br s, 1 H, NH) 7.95 (s, 1 H, CHO); IR (KBr) 3293, 2978, 2935, 2868, 1648, 1530, 1379 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.67; H, 9.02; N, 6.93.

(12) Buchs, P.; Rice, K. C.; Brossi, A. *J. Org. Chem.* **1982**, *47*, 4134.
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3-[2-(*N*-Formamido)ethyl]-2-cyclohexen-1-one (5). A solution of enol ether **4** (54.4 g, 0.28 mol) in THF (200 mL) was stirred with H_2O (30 mL) containing 2 drops of 37% HCl. After 1 h saturated aqueous $NaHCO_3$ (2 mL) was added along with NaCl (10 g) and H_2O (30 mL). The mixture was extracted with EtOAc (4 × 100 mL), dried ($MgSO_4$), and evaporated, yielding **5** (44.5 g, 95%) as a yellow oil: NMR ($CDCl_3$) δ 2.02–1.93 (m, 2 H), 2.29 (t, 4 H, J = 6 Hz) 2.41 (t, 2 H, J = 7 Hz), 3.48–3.32 (m, 2 H), 5.70 (s, 1 H), 6.52 (br s, 1 H, NH), 7.93 (s, 1 H, CHO); IR (neat) 3300, 3059, 2950, 2750, 1660, 1525, 1385 cm^{-1}; exact mass calcd for $C_9H_{13}NO_2$ m/e 167.0946, found 167.0939.

(±)-3-[2-(*N*-Formamido)ethyl]-2-cyclohexen-1-one Oxide [(±)-6]. A solution of **5** (43.4 g 0.26 mmol) in MeOH (200 mL) was stirred at 20 °C with 30% H_2O_2 (80 mL). Aliquots of concentrated aqueous NaOH were added periodically to maintain pH 9–10, and the reaction was terminated after 3 h. The excess H_2O_2 was destroyed by cooling the mixture in ice–H_2O and adding 5% Pd/C (500 mg) under an atmosphere of argon. The resulting suspension was stirred at 20 °C for 1 h and then filtered through Celite. Evaporation of solvent gave an oil, which was partitioned between saturated aqueous NaCl (20 mL) and EtOAc (2 × 200 mL). The combined organic extract was washed with brine (20 mL), dried ($MgSO_4$), and evaporated to afford (±)-**6** (40.4 g, 93%) as a yellow oil: NMR ($CDCl_3$) δ 1.73–1.57 (m, 1 H), 2.12–1.80 (m, 6 H), 2.43 (dt, 1 H, J = 15, 4 Hz), 3.05 (s, 1 H), 3.36 (dd, 2 H, J = 12, 6 Hz), 6.45 (br, 1 H, NH), 7.91 (s, 1 H, CHO); IR (neat) 3310, 3060, 2955, 2892, 1713, 1667, 1525, 1388 cm^{-1}; exact mass calcd for $C_9H_{13}NO_3$ m/e 183.0895, found 183.0894.

2-Methoxy-5-chlorophenol (5-Chloroguaicol). A solution of 2-methoxy-5-chlorobenzaldehyde[19] (199.0 g, 1.12 mol) was stirred on ice while 85% *m*-chloroperoxybenzoic acid (249.0 g, 1.23 mol, 1.1 equiv) was added. The reaction was allowed to gradually come to 20 °C and stirred overnight. The mixture was filtered to remove a thick white solid and then evaporated to a golden oil, which was dissolved in MeOH (200 mL) and stirred with a solution of 20% aqueous NaOH (500 mL) to give a black solution. After 10 min, the reaction was acidified by addition of 37% HCl (200 mL) and extracted with CH_2Cl_2 (2 × 500 mL). The CH_2Cl_2 was washed with aqueous $NaHCO_3$ (2 × 180 mL), dried ($MgSO_4$), and evaporated, yielding a brown oil. Distillation yielded 2-methoxy-5-chlorophenol (126.0 g, 71%) as a light yellow oil, which crystallized; bp 80–84 °C (0.1 mm, bath 117–122 °C); mp 34–35 °C (previously reported as an oil, lit.[20] bp 225–230 °C); NMR ($CDCl_3$) δ 3.60 (s, 3 H), 5.82 (br, 1 H), 6.51 (d, 1 H, J = 8 Hz), 6.59 (dd, 1 H, J = 2, 8 Hz), 6.71 (dd, 1 H, J = 2 Hz); IR ($CHCl_3$) 3445, 2948, 2908, 2850, 1599, 1489, 1464, 1442, 1333 cm^{-1}.

2-(2-Methoxy-5-chlorophenoxy)-3-[2-(*N*-formamido)ethyl]-2-cyclohexen-1-one (7). A solution of 2-methoxy-5-chlorophenol (32.8 g, 218 mmol) in dry THF (250 mL), with KH (35% in oil, 4.9 mL) and 18-crown-6 (11.5 g, 43.6 mmol) was stirred and refluxed. A solution of epoxide (±)-**6** (40.0 g, 218 mmol) in dry THF (250 mL) was added during 1 h, after which the mixture was refluxed overnight. Evaporation of solvent left a residue, which was dissolved in CH_2Cl_2 (400 mL) and washed with 1 N NaOH (3 × 500 mL) and brine (500 mL), dried ($MgSO_4$), and evaporated to a golden syrup. The syrup was flash chromatographed over a 9 × 15 cm silica gel column using a progressive solvent combination of CH_2Cl_2 (500 mL), 1% MeOH in CH_2Cl_2 (4 L), and then 2% MeOH in CH_2Cl_2 (3.5 L). Crystallization of the resulting syrup from MeOH:Et_2O gave **7** (24.4 g, 35%) as white crystals: mp 101–102 °C; CIMS (NH_3), m/e 324 (M + 1); NMR ($CDCl_3$) δ 2.03 (d, 2 H, J = 6 Hz), 3.55–2.39 (m, 6 H), 3.41 (dd, 2 H, J = 6, 12 Hz), 3.75 (s, 3 H) 5.93 (br, 1 H, NH) 6.35 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H J = 8 Hz), 6.73 (dd, 1 H, J = 2, 8 Hz), 7.89 (s, 1 H, CHO); IR ($CHCl_3$) 3438, 3380, 2939, 2864, 2839, 1682, 1589, 1492 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}ClNO_4$: C, 59.36; H, 5.60; N, 4.33. Found: C, 59.33; H, 5.56; N, 4.18.

(±)-4-Oxo-6-methoxy-9-chloro-9bβ-[2-(*N*-formamido)ethyl]-1,2,3,4,4aβ,9b-hexahydrodibenzofuran [(±)-8]. A solution of **7** (5.0 g, 15.5 mmol) in 1:1 benzene:MeOH (750 mL) was stirred and purged with argon. After 10-min, irradiation was initiated with a Pyrex-filtered mercury vapor Hanovia lamp and continued for 6 h. The solvent was evaporated to yield a foam, which was dissolved in MeOH (2 mL). White crystals rapidly formed, and after slow addition of Et_2O (75 mL), 4.0 g of white crystalline solid was obtained. Recrystallization from Et_2O:MeOH gave pure (±)-**8** (3.1 g, 62%): mp 139–140 °C; CIMS (NH_3) m/e 341 (M + NH_4); NMR ($CDCl_3$) δ 2.61–1.61 (m, 8 H), 3.30–2.98 (m, 2 H), 3.77 (s, 3 H), 4.61 (s, 1 H), 5.84 (br s, 1 H), 6.57 (d, 1 H, J = 8 Hz), 6.66 (d, 1 H, J = 8 Hz), 7.89 (s, 1 H); IR (KBr) 2940, 2872, 1730, 1680, 1589, 1529, 1489 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}ClNO_4$: C, 59.36; H, 5.60; N, 4.33. Found: C, 59.29; H, 5.62; N, 4.30.

(±)-4,4,6-Trimethoxy-9-chloro-9bβ-[2-(*N*-formamido)ethyl]-1,2,3,4,4aβ,9b-hexahydrodibenzofuran [(±)-9]. A solution of (±)-**8** (16.8 g, 52.0 mmol) prepared by gentle warming in MeOH (150 mL) was cooled to 20 °C and treated with trimethylorthoformate (35 mL) and H_2SO_4 (250 μL). The mixture was kept overnight, diluted with saturated aqueous $NaHCO_3$ (300 mL), extracted (3 × 200 mL of $CHCl_3$), dried ($MgSO_4$), and evaporated, yielding a white solid. The material was dissolved in a small volume of CH_2Cl_2, applied to a silica gel column, and eluted with EtOAc to yield (±)-**9** (14.8 g, 77%) as a crystalline, white solid: mp 157–159 °C; CIMS (NH_3) m/e 387 (M + NH_4); NMR ($CDCl_3$) δ 2.60–1.16 (m, 8 H), 3.60–3.00 (m, 2 H), 3.24 (s, 3 H), 3.37 (s, 3 H), 3.83 (s, 3 H), 4.46 (d, 1 H, J = 2 Hz), 5.68 (br, 1 H), 6.62 (d, 1 H, J = 8 Hz), 6.73 (d, 1 H, J = 8 Hz), 8.05 (s, 1 H); IR (KBr) 2945, 2872, 2839, 1686, 1586, 1510, 1488, 1430, 1387 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}ClNO_5$: C, 58.46; H, 6.54; N, 3.79. Found: C, 58.60; H, 6.39; N, 3.67.

(±)-4,6-Dimethoxy-9-chloro-9bβ-[2-(*N*-formamido)ethyl]-1,2,4aβ,9b-tetrahydrodibenzofuran [(±)-10]. A mixture of *p*-TsOH·H_2O (240 mg) and ethanol-free $CHCl_3$ (500 mL) was heated to solution (30 min) and concentrated to $^1/_2$ volume by distillation at atmospheric pressure. A solution of (±)-**9** (11.4 g, 30.9 mmol) in dry, ethanol-free $CHCl_3$ (250 mL) was added and distillation was continued (oil bath 110 °C) until approximately 400 mL of distillate was collected during 30 min. The mixture was cooled to 20 °C and gased with NH_3 for 5 min, and the volume was adjusted to 200 mL with $CHCl_3$. The solution was washed (1 × 50 mL, 2% NH_4OH), dried ($MgSO_4$), and evaporated to yield a yellow oil. Trituration with ether at −70 °C gave white crystalline (±)-**10** (8.3 g). The filtrate yielded an additional 800 mg of product, giving a total of 9.1 g (87%) of (±)-**10**: mp 122–124 °C; NMR δ 2.23–1.68 (m, 6 H), 3.34–2.95 (m, 2 H), 3.45 (s, 3 H), 3.70 (s, 3 H), 4.68 (s, 1 H), 4.80 (t, 1 H, J = 3 Hz), 5.93 (br, 1 H), 6.50 (d, 1 H, J = 9 Hz), 6.58 (d, 1 H, J = 9 Hz), 7.85 (s, 1 H); IR (KBr) 3320, 3000, 2845, 1662, 1580, 1482 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}ClNO_4$: C, 60.45; H, 5.97; N, 4.15. Found: C, 60.53; H, 6.13; N, 4.12.

(±)-3-Bromo-4,4,6-trimethoxy-9-chloro-9bβ-[2-(*N*-formamido)ethyl]-1,2,3,4,4a,9b-hexahydrodibenzofuran [(±)-11]. A suspension of (±)-**10** (9.1 g, 27.0 mmol) in MeOH (100 mL) was warmed gently until all solid had dissolved and then cooled to −70 °C. A solution of *N*-bromoacetamide (3.73 g, 27.0 mmol) in MeOH (20 mL) was cooled to −70 °C and then added to the solution of **10**. The reaction mixture was allowed to come to 20 °C gradually. After 1 h the mixture was diluted with $CHCl_3$ (300 mL) and washed (200 mL of $NaHCO_3$). The aqueous layer was extracted with $CHCl_3$ (150 mL), which was combined with the original $CHCl_3$ extract. The solution was washed (2 × 200 mL of $NaHCO_3$), dried ($MgSO_4$), and evaporated to a foam. The foam was triturated with Et_2O (60 mL), yielding a white crystalline solid. Crystallization was completed by diluting with ligroin (50 mL) and cooling to −70 °C to yield (±)-**11** (10.6 g, 87%) as white crystals: mp 118.5–119.5 °C; NMR ($CDCl_3$) δ 2.50–1.73 (m, 6 H), 3.16–2.95 (m, 2 H), 3.21 (s, 1.2 H), 3.35 (s, 1.8 H), 3.39 (s, 1.2 H), 3.50 (s, 1.8 H), 3.75 (s, 3 H), 4.16–4.06 (m, 0.6 H), 4.33–4.25 (m, 0.4 H), 4.22–4.17 (m, 0.4 H), 4.53 (s, 0.6 H), 5.51 (br, 1 H), 6.68–6.48 (m, 2 H), 7.91–7.85 (m, 1 H); IR (film) 3290, 2945, 2865, 2840, 1662, 1583, 1525, 1484 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}BrClNO_5$: C, 48.18; H, 5.17; N, 3.12. Found: C, 48.57; H, 4.72; N, 3.03.

(±)-4,4,6-Trimethoxy-9-chloro-9bβ-[2-(*N*-formamido)ethyl]-1,4,4aβ,9b-tetrahydrodibenzofuran [(±)-12]. A solution

(19) Prepared by methylation of 2-hydroxy-5-chlorobenzaldehyde with CH_3I/K_2CO_3 in refluxing acetone, mp 78.5–79.5 °C (lit. mp 79–81 °C: Pfleger, R.; Waldmann, K. *Chem. Ber.* **1957**, *90*, 2395).

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of (±)-11 (12.3 g, 27.5 mmol) in dry THF (200 mL) was heated to reflux and stirred for 12 h with potassium *tert*-butoxide (6.15 g, 54.9 mmol). The resulting suspension of KBr was evaporated to a foam and partitioned between H_2O (100 mL) and CH_2Cl_2 (2 × 100 mL). The combined organic phase was washed with brine (100 mL), dried ($MgSO_4$), and evaporated to a foam. Trituration with Et_2O gave (±)-12 (7.8 g, 77%) as off-white crystals: mp 188–190 °C; EIMS, *m/e* 367 (M^+); NMR ($CDCl_3$) δ 2.16–1.85 (m, 2 H), 2.45–2.25 (m, 1 H), 3.00–2.73 (m, 2 H), 3.09 (s, 3 H), 3.55–3.25 (m, 1 H), 3.39 (s, 3 H), 3.69 (s, 3 H), 4.83 (s, 1 H), 5.68–5.32 (m, 2 H), 5.89–5.76 (m, 1 H), 6.45 (d, 1 H, *J* = 8 Hz), 6.55 (d, 1 H, *J* = 8 Hz), 7.87 (s, 1 H). IR (KBr) 3050, 2945, 2838, 1694, 1587, 1489 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}ClNO_5$: C, 58.78; H, 6.03; N, 3.82. Found: C, 58.57; H, 5.84; N, 3.95.

(±)-2,3,4,5,6,6a-Hexahydro-3-formyl-8-methoxy-11-chloro-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocin-6-one [(±)-14]. Compound **12** (2.60 g, 7.10 mmol) was dissolved in MeOH (40 mL) with warming, cooled to 20 °C, then combined with H_2O (8.0 mL) containing 37% HCl (50 μL), lowered immediately into an oil bath at 115 °C, and stirred. After 5 min a suspension of white crystals began developing. The reaction mixture was removed after 30 min, cooled, filtered, and washed with Et_2O to yield (±)-14 (1.20 g, 53%) as white crystals: mp 224–230 °C; NMR (Me_2SO-d_6) δ 3.18–1.52 (m, 8 H), 3.64–3.45 (m, 1 H), 3.77 (s, 3 H), 5.30 (s, 1 H), 6.84 (d, 1 H, *J* = 8 Hz), 6.93 (d, 1 H, *J* = 8 Hz), 8.04 (s, 0.4 H), 8.09 (s, 0.6 H); IR (KBr) 3060, 2905, 2875, 2845, 1729, 1659, 1589, 1490, 1443, 1434 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; N, 4.53. Found: C, 59.81; H, 5.00; N, 4.29.

(±)-2,3,4,5,6,6a-Hexahydro-3-methyl-6-hydroxy-8-methoxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine [(±)-15 and 16]. To a suspension of (±)-14 (2.90 g, 9.0 mmol) in dry refluxing THF (750 mL) was added $LiAlH_4$ (1.72 g, 45.2 mmol). The resulting clear homogenous solution was stirred at reflux for 1.5 h and then cooled in ice and treated with saturated aqueous Na_2SO_4 (4 mL). The mixture was filtered, and the filter cake washed well with THF (200 mL). Evaporation of the combined THF gave a foam, which was dissolved in MeOH (100 mL) containing AcOH (15 mL), H_2O (50 mL), and $NaOAc{\cdot}3H_2O$ (2.2 g) and hydrogenated at 45 psig H_2 over 10% Pd/C (500 mg). After 10 h the mixture was filtered, evaporated to a volume of 3 mL, mixed with 1 N NaOH (50 mL), extracted with CH_2Cl_2 (2 × 100 mL), washed with 1 N NaOH (1 × 50 mL) and then brine (100 mL), dried (Na_2SO_4), and evaporated to yield a foam, which solidified (2.13 g, 86%). TLC (System A) showed two epimeric alcohols, with the major isomer (R_f 0.51) and the minor isomer (R_f 0.45) present in an approximate 4:1 ratio. A chromatographically pure sample of the faster moving alcohol was obtained by preparative TLC in the same system and crystallized as the HCl salt from Et_2O–MeOH: mp 288 °C dec; EIMS, *m/e* 275 (M^+); NMR (free base, $CDCl_3$) δ 2.75–1.45 (m, 9 H), 2.30 (s, 3 H), 3.27–3.16 (m, 1 H), 3.89 (s, 3 H), 4.45 (s, 2 H), 7.00–6.68 (m, 3 H); IR (KBr) 3384, 3012–2838, 2614–2511, 1619, 1589, 1489, 1462 cm^{-1}. The major alcohol showed H_{6a} at δ 4.45, J_{6a-6} = 0 Hz. The minor alcohol showed H_{6a} at δ 4.39, J_{6a-6} = 9 Hz.

Anal. Calcd for $C_{16}H_{21}NO_3{\cdot}HCl{\cdot}^1/_2CH_3OH$: C, 60.45; H, 7.38; N, 4.27. Found: C, 60.56; H, 7.19; N, 4.30.

(±)-2,3,4,5,6,6a-Hexahydro-3-methyl-6-[(methylsulfonyl)oxy]-8-methoxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocines [(±)-17 and 18]. The mixture of epimeric alcohols (±)-15 and 16 (2.1 g, 7.6 mmol) was dissolved in $CHCl_3$ (10 mL) containing Et_3N (4 mL). The solution was cooled in ice–H_2O while CH_3SO_2Cl (1.74 g, 15.3 mmol) was added and then kept at 20 °C for 2 h after which additional CH_3SO_2Cl (870 mg, 7.6 mmol) was added. After an additional 30 min the mixture was diluted (100 mL of CH_2Cl_2) and washed (100 mL $NaHCO_3$), and the sodium bicarbonate was back-extracted with CH_2Cl_2 (100 mL). The combined organic was dried (Na_2SO_4), and evaporated to yield a light brown foam (2.60 g). Purification by silica gel flash chromatography (3.5 × 15 cm, 100 mL of 1% MeOH in CH_2Cl_2; 600 mL of 3% MeOH in CH_2Cl_2) gave 1.78 g (66%) of a foam, which showed spots for the two epimers in TLC System A. The minor isomer had R_f 0.44 and the major isomer had R_f 0.37: EIMS, *m/e* 353 (M^+); NMR ($CDCl_3$) δ 2.41–2.00 (m, 8 H), 2.27 (s, 3 H), 2.80–2.61 (m, 1 H), 3.05 (s, 2 H), 3.36–3.16 (m, 2 H), 3.23 (s, 0.9 H), 3.84 (s, 3 H), 4.57–4.48 (m, 1 H), 5.36–5.27 (m, 1 H), 6.91–6.61 (m, 3 H); IR ($CHCl_3$) 2939, 2840, 2798, 1623, 1594, 1490, 1458, 1352, 1168, 908 cm^{-1}.

(±)-2,3,4,5,6,6a-Hexahydro-3-methyl-8-methoxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine [(±)-19]. A stirred solution of (±)-17 and 18 (1.56 g, 4.4 mmol) in THF (20 mL) at 20 °C was treated with 75 mL of 1.0 M $LiEt_3BH$ in THF and then refluxed for 2 h. The reaction was cooled and excess hydride cautiously destroyed with H_2O. The mixture was then acidified to pH 6 (Hydrion paper) with 37% HCl and concentrated to 10 mL. (**CAUTION**: spontaneous ignition of vapors occurred during evaporation under reduced pressure.) The syrup was partitioned between H_2O (50 mL) and $CHCl_3$ (3 × 100 mL). The $CHCl_3$ was washed with brine (2 × 100 mL), dried (Na_2SO_4), filtered through Celite and evaporated, yielding a white foam (1.26 g). Flash chromatography (3.5 × 14 cm, 600 mL of 3% MeOH in CH_2Cl_2; 200 mL of 4% MeOH in CH_2Cl_2) gave (±)-19 (409 mg, 36%). A sample was dissolved in acetone, mixed with 1.2 equiv of oxalic acid–$2H_2O$ and evaporated to dryness. Crystallization from isopropyl alcohol gave the oxalate salt: mp 188–190 °C; EIMS, *m/e* 259 (M^+); NMR ($CDCl_3$) (free base) δ 2.74–1.61 (m, 10 H), 2.34 (s, 3 H), 3.23–3.11 (m, 1 H), 3.89 (s, 3 H), 4.57 (t, 1 H, *J* = 7 Hz), 6.89–6.70 (m, 3 H); IR ($CHCl_3$) 2940, 2805, 1623, 1594, 1490, 1458, 1280 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_2{\cdot}^1/_2C_2H_2O_4{\cdot}H_2O$: C, 65.16; H, 7.40; N, 4.47. Found: C, 65.22; H, 7.31; N, 3.96; exact mass calcd for $C_{16}H_{21}NO_2$ *m/e* 259.1572. Found: 259.1577.

(±)-2,3,4,5,6,6a-Hexahydro-3-methyl-8-hydroxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine [(±)-2]. A solution of (±)-19 (100 mg, 0.39 mmol) in $CHCl_3$ (2 mL) was stirred at 20 °C while a solution of BBr_3 (386 mg, 1.54 mmol) in $CHCl_3$ (1 mL) was slowly added. A white semisolid formed during addition of the BBr_3, which crystallized upon stirring with a glass rod. An additional 96 mg (0.39 mmol) of BBr_3 was added after 5 min. After an additional 10 min, 3.5 N NH_4OH (10 mL) was added, and the phases were mixed well. The organic phase was separated and combined with $CHCl_3$ extracts of the residual NH_4OH (2 × 1 mL) and then washed with $NaHCO_3$ (1 × 5 mL). Evaporation of solvent gave a light brown, highly crystalline solid (99 mg). Trituration with Et_2O:MeOH gave (±)-2 (91 mg, 100%) as white crystals: mp 295–299 °C; CIMS (NH_3), *m/e* 246 (M + H); NMR ($CDCl_3$, Me_2SO-d_6) δ 2.57–1.54 (m, 10 H), 2.48 (s, 3 H), 2.95–2.82 (m, 1 H), 4.61–4.48 (m, 1 H), 6.68–6.48 (m, 3 H); IR (KBr): 3429, 3225, 2945, 1630, 1595, 1470 cm^{-1}. A sample was converted to the HCl salt and crystallized from isopropyl alcohol–Et_2O to yield white crystals, mp 300–306 °C dec.

Anal. Calcd for $C_{15}H_{20}NO_2Cl{\cdot}^1/_2H_2O$: C, 61.96; H, 7.28; N, 4.82. Found: C, 61.74; H, 7.28; N, 4.81.

Crystallographic data for (±)-2 ($C_{15}H_{19}NO_2{\cdot}HCl$): M_r 281.78; space group $P2_1/c$; radiation Cu Kα (graphite monochromator); wavelength 1.5418 Å; cell dimensions *a* = 11.880 (2) Å, *b* = 10.674 (3) Å, *c* = 11.537 (2) Å, β = 110.05 (2)°, *V* = 1374.3 Å^3, D_x = 1.362 g/mL, *Z* = 4; sin θ/λ(max) = 0.6231 Å^{-1}, 2792 reflections ($1049 < \sigma(I)$); function minimized $\sum w\Delta^2$; *R* 0.075.

The phase problem was solved by the use of the programs of MULTAN78.[21] The model was refined by using the programs of XRAY72,[22] and all hydrogen atoms were visible in a difference map. The final *R* factor, using anisotropic thermal parameters, $\exp(-2\pi^2(\sum_i\sum_j U_{ij}a_i^*a_{jj}^*h_ih_j))$, for the heavier atoms and isotropic parameters for the H atoms, was 7.6%. The atomic parameters for the heavier atoms and the bond angles are included in the supplementary material. The observed and calculated structure factors and full refinement parameters were submitted to the referees and may be obtained from J.V.S.

Acknowledgment. We thank Mr. Noel Whittaker for chemical-ionization and high-resolution mass spectra, Mr. William Landis for electron-ionization mass spectra, and Mrs. Paula Parisius and Alice Wong for combustion

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analyses. Helpful discussions with Dr. A. G. Schultz are gratefully acknowledged.

Registry No. (±)-**2**, 88304-40-9; (±)-**2**·HCl, 88335-59-5; **3**, 64982-52-1; **4**, 88304-27-2; **5**, 88304-28-3; (±)-**6**, 88304-29-4; **7**, 88304-30-7; (±)-**8**, 88304-31-8; (±)-**9**, 88304-32-9; (±)-**10**, 88304-33-0; (±)-**11** (isomer 1), 88304-34-1; (±)-**11** (isomer 2), 88304-41-0; (±)-**12**, 88304-35-2; (±)-**14**, 88304-36-3; (±)-**15**, 88304-37-4; (±)-**16**, 88335-56-2; (±)-**17**, 88304-38-5; (±)-**18**, 88335-58-4; (±)-**19**, 88304-39-6; (±)-**19**·$^1/_2C_2H_2O_4$, 88335-84-6; 2-methoxy-5-chlorobenzaldehyde, 7035-09-8; 2-methoxy-5-chlorophenol, 3743-23-5; 2,3,4,5,6,6a-hexahydro-3-methyl-6-hydroxy-8-methoxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine hydrochloride, 88335-57-3.

Supplementary Material Available: Tables of atomic parameters for the heavier atoms and bond angles (3 pages). Ordering information is given on any current masthead page.

Electroorganic Chemistry. 82. β-Amino Acid Esters from α-Methoxycarbamates and Ketene Silyl Acetals; Cyclization to β-Lactams

Tatsuya Shono,* Kenji Tsubata, and Nobuyuki Okinaga

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

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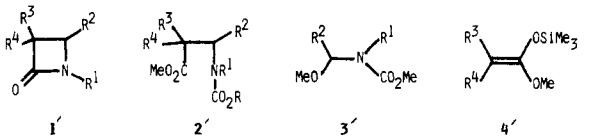
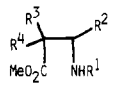
A new synthetic method of β-lactams 1′ is described. The key intermediates, *N*-carbomethoxy-β-amino acid esters 2′, were synthesized by the reaction of α-methoxylated carbamates 3′ with ketene methyl trimethylsilyl acetals 4′ catalyzed by titanium tetrachloride in 66–93% yields. 2′ were deprotected to 5′ by 25% HBr in HOAc (R = Me) or hydrogenolysis (R = CH_2Ph) in 42–78% yields. 1′ were prepared by treating 5′ with Grignard reagents (PhMgBr or EtMgBr) in 38–95% yields.

β-Lactams are some of the most important antibiotics, as exemplified by penicillins and cephalosporins, and hence preparation of new compounds containing a β-lactam moiety has always attracted much attention. We report herein a new synthetic method of β-lactams[1] utilizing the reaction of α-methoxylated carbamates[2] with ketene methyl trimethylsilyl acetals[3] as the key reaction.



1′ 2′ 3′ 4′



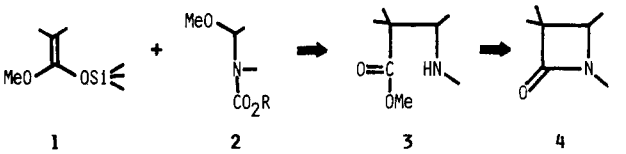
5′

R^1 = H, Me, iso-Bu. R^2 = H, Me, iso-Pr.

R^1-R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$. R^3,R^4 = Me,Me; H,Ph; H,Et; H,n-C_6H_{13}. R = Me, CH_2Ph.

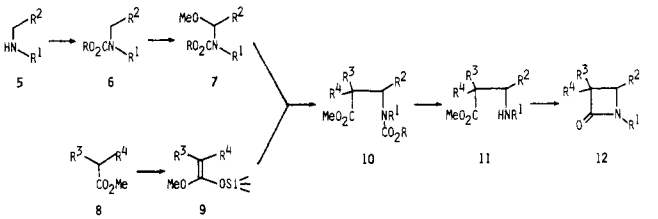
As shown in Scheme I, the cyclization step comprises the formation of a nitrogen–carbon bond between amino and methoxycarbonyl groups in β-amino acid esters **3** synthesized from **1** and **2**. Since **1** and **2** are prepared from esters and amines respectively, the 2-azetidinone skeleton **4** is constructed by a formal [2 + 2] addition of an ester and an amine. The overall procedure is shown in Scheme II, which suggests that a variety of substituents R^1–R^4 can be introduced to β-lactams **12** through the proper choice of the starting materials (**5** and **8**).

Scheme I



1 2 3 4

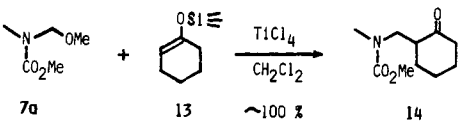
Scheme II



5 6 7 8 9 10 11 12

Results and Discussion

Reaction of α-Methoxylated Carbamates 7 with Ketene Methyl Trimethylsilyl Acetals 9. As we have already reported, α-methoxylated carbamates (**7**) react with various nucleophiles under acidic conditions.[4] For example, the reaction of **7a** with silyl enol ether **13** afforded *N*-(carbomethoxyamino)methylated cyclohexanone **14** (eq 1).[4a] In order to prepare β-alanine derivatives **10**, the



7a 13 ~100 % 14 (1)

reaction of **7** with ketene methyl trimethylsilyl acetals **9** was investigated. The reaction of **7a** with **9a** gave **10a** in satisfactory yield under similar reaction conditions to those

(1) Interesting methods recently developed, for example: (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

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