(5 mL) was added dropwise to a cold (−28 °C) solution of **1a** (250 mg, 2 mmol) and tetramethylethylene (109 mg, 1.3 mmol) in dichloromethane (10 mL). After the addition was complete, the reaction mixture was stirred for 1 h at −28 °C and for 2 h at room temperature. The mixture was cooled to −50 °C and filtered to remove the precipitated salt (85%). The filtrate was extracted with 10% aqueous potassium hydroxide (3 × 15 mL) and then with 2 N HCl (2 × 15 mL). The organic layer was dried ($MgSO_4$) and evaporated. Kugelrohr distillation separated benzyl alcohol and *O*-benzylbenzaldoxime from a third component. The unknown compound was isolated by preparative TLC (silica gel/chloroform) and purified by preparative VPC (OV-101). The clear oil was identified as 3-[(*O*-benzylhydroxyl)amino]-2,3-dimethyl-1-butene, **9**: NMR δ 1.26 (s, 6 H, $(CH_3)_2$), 1.85 (broadened s, 3 H, allylic CH_3), 4.76 (s, 2 H, benzylic CH_2), 4.94 (m, 1 H, vinyl H), 4.99 (m, 1 H, vinyl H), 7.40 (s, 5 H, C_6H_5); IR (neat) 3080, 3060, 3020, 2870, 1640, 1490, 1450, 1170, 1060 cm^{-1}; MS, *m/e* 205 (parent), 190 (P − 15), 123, 105, 77. In a repeat experiment, mesitylene was added to the crude product mixture. NMR analysis showed **9** to be present in a yield of 8.5%. The low yield discouraged further investigation of **9**.

Acknowledgment. This project was supported in part by the National Science Foundation (Grants CHE-8304000 and CHE-8709853) whom we would like to thank.

Registry No. **1a**, 622-33-3; **1b**, 4665-68-3; **1c**, 4759-21-1; **1d**, 37477-16-0; **1e**, 1782-38-3; **2**, 35673-10-0; **4**, 116006-92-9; **5**, 100-51-6; **6**, 17146-21-3; **12**, 65311-52-6; **13**, 30542-59-7; $C_5H_{11}CH_2OH$, 111-27-3; *t*-BuOH, 75-65-0; $C_6H_5CH(OH)C_6H_5$, 91-01-0; $C_6H_5CH_2OCH_2C_6H_5$, 574-42-5; *O*-(*n*-hexyl)hexaldoxime, 116006-90-7; cyclohexanol, 108-93-0; *O*-cyclohexylcyclohexanone, 116006-91-8; oxime benzophenone, 119-61-9; tetramethylethylene, 563-79-1; 3-[(*O*-benzylhydroxy)amino]-2,3-dimethyl-1-butene, 116006-93-0.

Synthesis of 1-*O*-Methyl-β,D-ezoaminuroic Acid†

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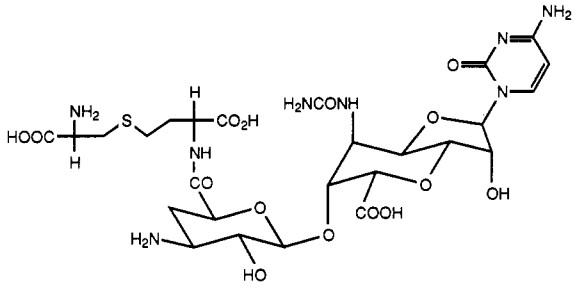
The synthesis of the title compound from the Diels–Alder adduct of diethyl ketomalonate and 1,3-butadiene (nine steps, 13% overall yield) is described. The key step is a transannular "bromolactamization" reaction, which sets up the stereocontrolled functionalization of the pyran ring. The use of resolved *p*-methoxyphenethylamine as the source of the amino group allows the synthesis of both the D (natural) and L (unnatural) series amino sugars.

Ezomycin A_1 (**1**) is an antifungal antibiotic isolated by Takaoka, Sakata, and co-workers from a *Streptomyces*[1] and shown by Sakata to possess the structure shown below: an amino sugar (ezoaminuroic acid, **2**) linking an octosyl nucleoside and a pseudodipeptide (cystathionine).[2] Several groups have studied approaches to the synthesis of the octose,[3–6] and Suami recently completed the synthesis of the octose nucleoside portion in protected form.[6c] An early synthesis of a derivative (**24**) of **2** from 1,6-anhydro-β,D-glucopyranose, reported by Ogawa,[7] required 12 steps and proceeded in about 2% overall yield.



1, ezomycin A_1

We undertook the synthesis of ezoaminuroic acid to showcase the "iodolactamization" procedure we have developed over the last few years.[8–10] As the accompanying retrosynthetic analysis of **2** illustrates, the logical precursor, lactam **3**, should be makable by a transannular cyclization of unsaturated amide **5**, followed by several functional group modifications. We describe in this article not only the successful synthesis that indeed gives the methyl glycoside of **2** according to the prescribed path but also the difficulties with the "iodolactamization" procedure and with lactam nitrogen protection that we were forced to circumvent in order to arrive at the target amino sugar.

Results and Discussion

Halolactamization Studies. The carboxamide **10**, which contains all the pyranose carbons and the functional groups appropriate for cyclization studies, was prepared with good efficiency on a multigram scale as shown below. Diels–Alder reaction of diethyl ketomalonate (**6**) with excess 1,3-butadiene in a sealed tube afforded the diester **8**,[11] which was hydrolyzed and decarboxylated to give the dihydropyrancarboxylic acid **9**. Conversion of **9** to its acid

† This paper is dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

(1) (a) Takaoka, K.; Kuwayama, T.; Aoki, A. Japanese Patent 615332, 1971. (b) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1973**, *37*, 697.

(2) Sakata, K.; Sakurai, A.; Tamura, S. *Tetrahedron Lett.* **1974**, 4327. For comprehensive referencing to the ezomycin structure determination work, see ref 6c.

(3) Anzai, K.; Saita, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 169.

(4) (a) Hanessian, S.; Liak, T. J.; Dixit, D. M. *Carbohydr. Res.* **1981**, *88*, C14. (b) Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129.

(5) (a) Kim, K. S.; Szarek, W. A. *Can. J. Chem.* **1981**, *59*, 878. (b) Kim, K. S.; Szarek, W. A. *Carbohydr. Res.* **1982**, *100*, 169.

(6) (a) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T.; Ishii, T.; Ohba, S.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1753. (b) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T. *Ibid.* **1986**, *59*, 3523. (c) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T. *Ibid.* **1987**, *60*, 1057.

(7) Ogawa, T.; Akatsu, M.; Matsui, M. *Carbohydr. Res.* **1975**, *44*, C22.

(8) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803.

(9) Knapp, S.; Levorse, A. T. *Tetrahedron Lett.* **1987**, *28*, 3213.

(10) Knapp, S.; Levorse, A. T. *J. Org. Chem.*, in press.

(11) Bonjouklian, R.; Ruden, R. A. *J. Org. Chem.* **1977**, *42*, 4095.

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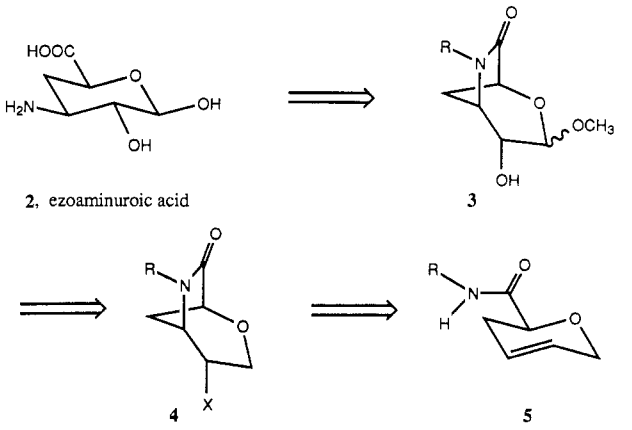
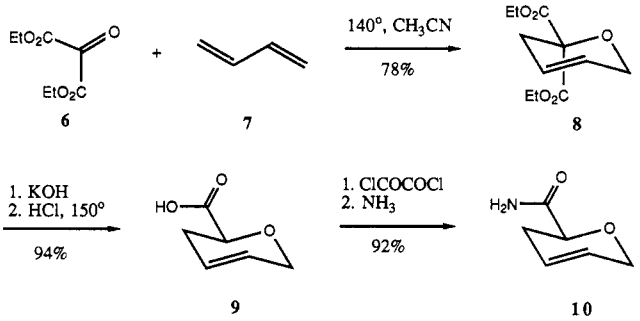
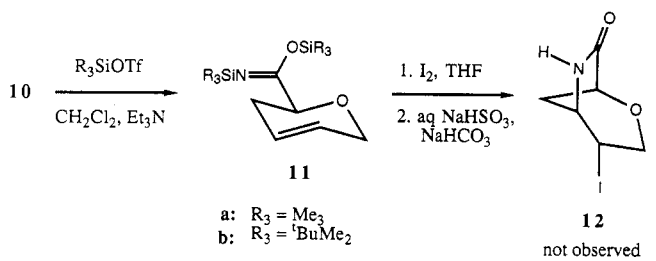


chloride followed by treatment with liquid ammonia at low temperature gave **10**,[12] isolable in pure form by crystallization from diisopropyl ether. Our intention was to apply the "iodolactamization" technique, which had already been demonstrated successfully for a variety of other unsaturated amides,[8,10] to this transannular case.

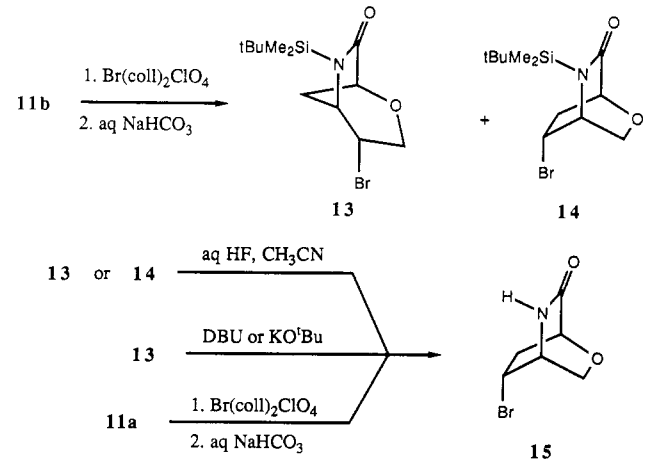


Conversion of **10** to its *N,O*-bis(trimethylsilyl) derivative **11a** with trimethylsilyl trifluoromethane sulfonate proceeded without apparent complication, but attempted cyclization of **11a** using the usual conditions (iodine in THF) simply returned the starting amide **10** after bisulfite quenching. That the problem arose after the silylation step was suggested by the failure to isolate the *lactone* (O-cyclized) product, which normally results if the carbonyl group remains unsilylated.[8] Carboxamide **10** was converted to the *N,O*-bis(*tert*-butyldimethylsilyl) derivative **11b** in the hope that iodocyclization followed by quench would give the *N-tert*-butyldimethylsilyl iodo lactam,[8] which might be more easily isolated than **12**. This attempt, however, also returned no cyclized product. Whether the desired iodo lactam had not formed at all or had formed but not survived the workup and chromatographic conditions was not revealed by these experiments. Conceivably the ring strain inherent in the bicyclo[3.2.1] system slows or reverses this cyclization. We had reported the failure of a related reaction requiring a geometry nearly identical with this one in our studies of carbonimidothioate cyclizations.[13] It was clear in any case that modifications to what had been a trustworthy procedure were necessary.

The cyclization of **11b** was next attempted by using as the electrophile bromonium bis(collidine)perchlorate.[14] Not only is this a more reactive electrophile than iodine, but the *bromo* lactam that results should also have greater stability than **12**. Treatment of **11b** with bromonium bis(collidine)perchlorate at −78 °C, followed by warming



to room temperature and bicarbonate quenching, gave in good yield two *N*-silyl bromo lactams, **13** and **14**, in a ratio of about 2:1, respectively, after column chromatography. The bicyclo[3.2.1] lactam **13** shows a carbonyl absorption frequency at 1705 cm^{-1}, whereas the [2.2.2] product **14**, which is less strained, shows the corresponding absorption at 1690 cm^{-1}. Conducting the cyclization at higher temperatures resulted in the formation of more **14** relative to **13**, suggesting that the [3.2.1] lactam will be favored under only the mildest conditions and that a pathway interconverting the two must be avoided, lest the desired product "ring expand" to the more stable [2.2.2] ring system. In confirmation, removal of the *tert*-butyldimethylsilyl group of either **13** or **14** with aqueous hydrogen fluoride gave the same product, the rearranged [2.2.2] bromo lactam **15**. Attempted dehydrobromination of **13**, which had been the next step projected for preparation of **3**, also produced **15**, rather than an alkene. Finally, the bromocyclization reaction of **11a** led after quenching and chromatography to a single lactam product, **15**, in 83% yield.



Cyclization with an *N*-Alkyl Substituent. The ease with which **13** had lost the *N*-silyl group and rearranged under both basic and acidic conditions meant that a more resistant group was needed.[15] An alkyl or aryl protecting group was a possibility, although we had not previously attempted the iodocyclization of such an N-substituted amide. Using an alkylamine as the source of nitrogen has the advantage that if it can be incorporated as an optically pure enantiomer, subsequent intermediates are pairs of diasteriomers, and thus separable into D and L series amino sugars. We therefore prepared the amides **16a–d** from **9** and (*S*)- and (*R*)-*p*-methoxyphenethylamine, which can be

(12) Mochalin, V. B.; Kornilov, A. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1974**, *44*, 2288.
(13) Knapp, S.; Patel, D. V. *J. Am. Chem. Soc.* **1983**, *105*, 6985.
(14) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190.

(15) Early survey of methods for protecting amide nitrogen: McOmie, J. F. W. *Protective Groups in Organic Chemistry*; Plenum: New York, 1973; p 405. Some recent examples of lactam N-protection: (TBDMS) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (Benzyloxy) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557. (*p*-Methoxyphenyl) Corley, E. G.; Karady, S.; Abramson, N. L.; Ellison, D.; Weinstock, L. M. *Tetrahedron Lett.* **1988**, *29*, 1497. (2,4-Dimethoxybenzyl) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698. (STr) Burnett, D. A.; Hart, D. J.; Liu, J. *J. Org. Chem.* **1986**, *51*, 1930. See also ref 20 and 21.

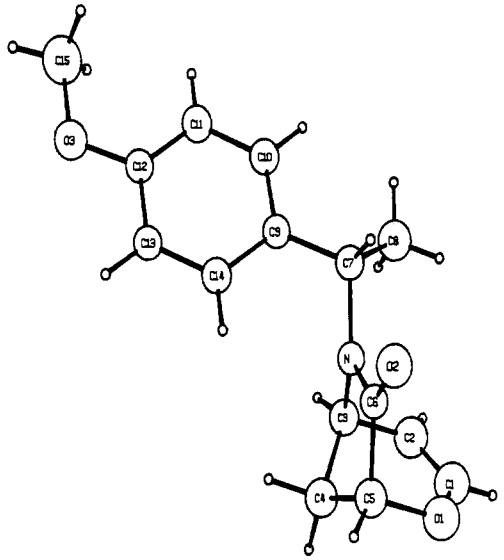
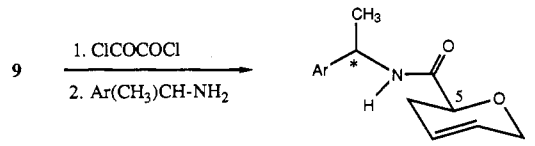


Figure 1. ORTEP representation of **18d**.

made from *p*-methoxyacetophenone[16] and resolved according to published procedures.[16,17] Both pairs of diasteriomers were taken through the next few steps, but for reasons explained below, only the *N*-(*R*)-*p*-methoxyphenethylamides **16a** and **16b** made their way through the entire synthesis.

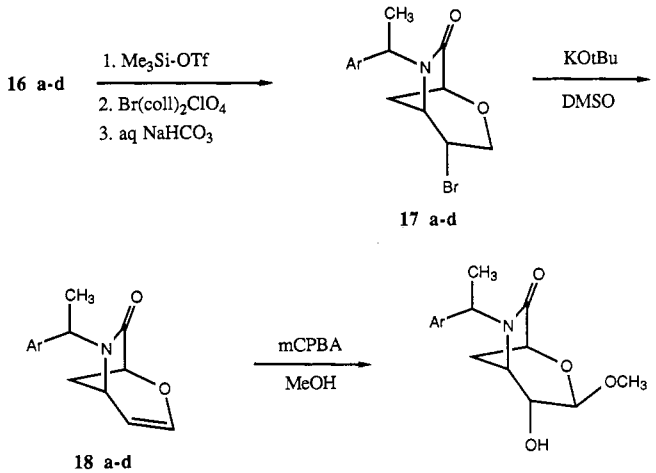


16

a,b: R/D,L; Ar = p-methoxyphenyl
c,d: S/D,L; Ar = p-methoxyphenyl

The amides **16a–d** were subjected to the bromocyclization sequence involving the use of trimethylsilyl trifluoromethanesulfonate as the silylating agent, and bromonium bis(collidine)perchlorate as the electrophile. Remarkably, the desired [3.2.1] lactams **17a–d** were the only cyclization products isolated in both cases, and the isolated yields exceeded 75%. Neither the [2.2.2] lactams nor the lactones were formed in detectable quantities, and most of the remaining mass balance consisted of recovered starting amides. Silylation had therefore taken place on oxygen, the N-substituent had not interfered with the ability of the carboxamide group to achieve the necessary pseudoaxial conformation, and rearrangement or reversion of the products was not a problem. The bromo lactams were not separable at this stage by column chromatography.

Treatment of **17a/b** and **17c/d** with potassium *tert*-butoxide in dimethyl sulfoxide solution at room temperature promoted efficient dehydrobromination to the glycals **18a/b** and **18c/d**, whose structures were apparent from their IR and NMR spectra, and these pairs of glycals were now easily separated. Oxidation of any, and eventually all, of the glycals with *m*-chloroperoxybenzoic acid (mCPBA) in methanol solution gave a single hydroxy lactam **19** in each case. NMR analysis did not permit the assignment of stereochemistry, although we were to learn later that the products are in fact the β-anomers. Frequently this reaction leads to a mixture of both anomers following isomerization of the initial product of "trans-diaxial" addition under the acidic reaction conditions.[18] Attack of the oxidation reagent was expected, however, to occur from the less hindered α face of the bridged pyranose, setting the proper stereochemistry at C(2).[19] Completion of the synthesis seemed to require only removal of the N-substituent and hydrolysis of the lactam.[20]



diasteriomers separated, X-ray structure of **18 d**

The higher R_f isomer in the (*S*)-*p*-methoxyphenethyl series, **18d**, crystallized in suitable form for X-ray crystallographic analysis, and the structure and absolute configuration of **18d** were thereby conveniently determined. The ORTEP representation of **18d** is shown in Figure 1. Because the N-substituent is known to have the *S* configuration, **18d** must belong to the L series (carbohydrate nomenclature). Therefore **18c** (the lower R_f isomer) and **18a**, which has higher R_f than **18b**, belong to the natural D series, and thus are suitable precursors to **2**. The atoms that form the bicyclo[3.2.1] ring system of **18d** lie in two planes: the three atom bridge, O(1), C(1), and C(2), along with the bridge-head carbons C(3) and C(5), constitute one plane (planar to within ±0.01 Å), and N(1), C(6), and C(4) define the other. The two planes make a dihedral angle of 90.5 (2)°. The π bond at C(1)–C(2) appears more exposed on the α face, the same side as C(4), in accord with the reaction of **18d** with mCPBA to give **19d**.

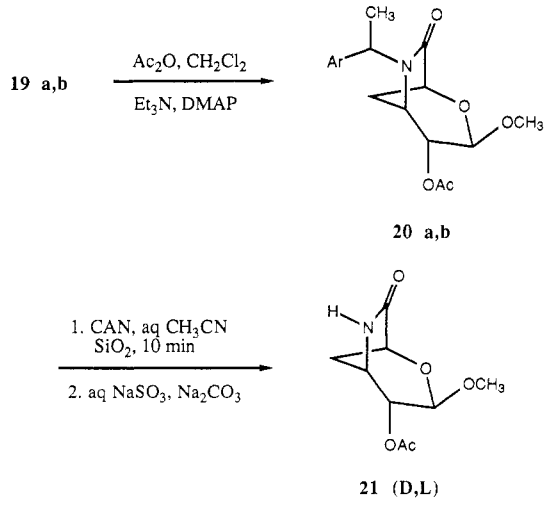
Since the glycal **18a** was now known to have the D configuration and since it was easier to purify by chromatography than its diasteriomer **18c**, the synthesis proceeded with the former. The hydroxy lactam **19a** derived from **18a** was subjected to CAN in aqueous acetonitrile following conditions that had been successful for similar deprotection of amide nitrogen.[22a,b,23,25] Although *p*-

(16) Guthrie, R. D.; Hedrick, J. L. *J. Am. Chem. Soc.* **1973**, *95*, 2971.
(17) (a) Bernhard, H. O.; Kompis, I.; Johne, S.; Groger, D.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 1266. (b) Newman, P. *Amines and Related Compounds*; Optical Resolution Information Center: Riverdale, NY, 1977, Vol. 1, p 143.
(18) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571.
(19) (a) Knapp, S.; Lal, G. S.; Sahai, D. *J. Org. Chem.* **1986**, *51*, 380. (b) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.
(20) An earlier route used (*R*)-(phenethyl) as the N-substituent. This route was abandoned when we were unable to remove the phenethyl group using sodium or lithium in liquid ammonia,[21] hydrogenolysis,[22] or CAN.[23] Lactam hydrolysis[24] prior to phenethyl removal was also unsuccessful.
(21) (a) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523. (b) Evans, D. A.; Sjogren, E. B. *Ibid.* **1985**, *26*, 3787.
(22) (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3253. (b) Williams R. M.; Armstrong, R. W.; Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733. (c) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; Wiley: New York, 1978; p 116.

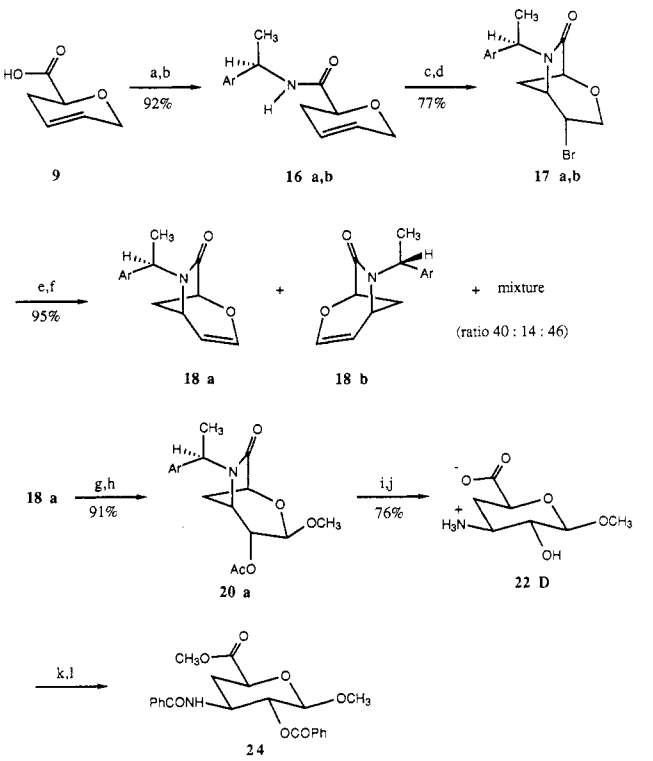
methoxyacetophenone was formed, indicating that oxidation of **19a** had occurred, no lactam could be isolated. NMR analysis of the crude product indicated that the anomeric methoxy group had not survived the reaction conditions. Treatment of **19a** with 2,3-dichloro-5,6-dicyanobenzoquinone or NBS similarly gave *p*-methoxyacetophenone, but no lactam. Evidently reaction was occurring at more than one site in the molecule.

Operating under the hypothesis that attaching an electron-withdrawing group at C(2) would reduce the tendency of C(1) to undergo oxidation, we prepared the acetate derivative **20a** from **19a** and studied its reaction with CAN under the conventional conditions. After only 3 min at room temperature, CAN liberated the *p*-methoxyphenethyl group from **20a** as *p*-methoxyacetophenone, and we observed for the first time the desired deprotected lactam, **21**(D). Yields of **21**(D) varied, but were generally about 20%. Control experiments established that **21**(D) was stable to CAN in aqueous acetonitrile (the initial conditions) but was slowly destroyed by treatment with cerium(III) chloride under the same conditions, suggesting that cerium(III) in the CAN reaction was the problematic agent. Some improvement in the yield was realized by quickly chromatographing the crude reaction mixture as soon as TLC analysis indicated that starting material had mostly disappeared, which may have had the effect of removing the cerium(III) salts so that further damage to product did not occur. A better solution based on this experiment soon presented itself, however.

We found that running the CAN reaction *in the presence of an equal weight of silica gel* moderated the rate of oxidation somewhat and greatly diminished the damage caused by the cerium(III) salts, making it possible for the first time to run the reaction of **20a** to completion. Presumably the silica is acting as a Lewis base toward cerium(III). Furthermore, quenching the reaction with aqueous sodium carbonate and sulfite reduced and precipitated[26] any cerium salts that remained in solution, which facilitated the isolation of **21**(D). By use of these improved reaction conditions, the deprotection of **20a** could be carried out reproducibly in yields of 75–79%.



Scheme I. Synthesis of 1-*O*-Methyl-β,D-ezoaminuroic Acid[a]

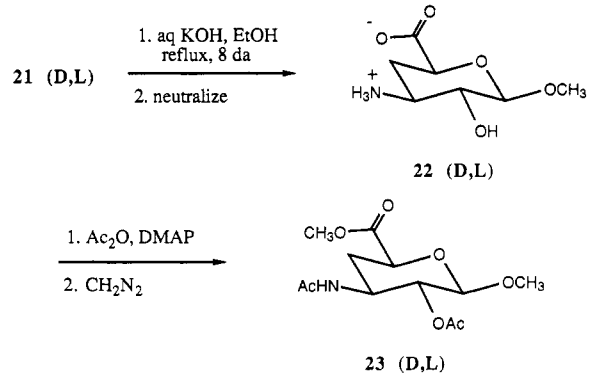


[a] Reagents: (a) ClCOCOCl, toluene; (b) (*R*)-(+)-(*p*-MeOPh)CH(CH$_3$)NH$_2$, Et$_3$N, toluene; (c) Me$_3$Si–OTf, Et$_3$N, pentane; (d) Br(coll)$_2$ClO$_4$, CH$_2$Cl$_2$, −78 to −25 °C, aqueous Na$_2$CO$_3$; (e) KO^{t}Bu, DMSO; (f) separate diasteriomers by column chromatography; (g) mCPBA, MeOH; (h) Ac$_2$O, Et$_3$N, DMAP; (i) CAN, SiO$_2$, aqueous CH$_3$CN, 10 min, aqueous Na$_2$SO$_3$, Na$_2$CO$_3$; (j) KOH, EtOH, reflux, 8 days, HCl; (k) Ac$_2$O, DMAP; (l) CH$_2$N$_2$, Et$_2$O, MeOH.

Completion of the Synthesis. The synthesis of the title compound **22**(D) was completed by hydrolyzing the lactam with potassium hydroxide, followed by neutralization of the amino carboxylate to the zwitterion. The structure of **22**(D) follows from its decoupled 400-MHz ^{1}H NMR spectrum, obtained in deuterium oxide solution without removal of the potassium chloride that remained from the neutralization. In particular, the coupling between protons at C(1) and C(2) (about 8 Hz) indicates that **22**(D) is the β anomer, so that the methoxy stereochemistry could now be assigned with certainty for the compounds that preceded **22**(D). Further characterization of the amino sugar was obtained by conversion of **22**(D) to its *N*,*O*-diacetyl methyl ester **23**(D), which shows [α] −23.3° and correct elemental analysis, as well as NMR and IR spectra consistent with the assigned structure. The same synthesis was then repeated in the L series, beginning with the pure lower R_f diasteriomer **18b** and giving finally a small quantity of **23**(L), [α] +17.7°.[27]

The entire synthesis of **22**(D) from **9** is displayed in its final form in Scheme I, with yields shown for each step. The zwitterion **22**(D) was converted to an additional derivative, the *N*,*O*-dibenzoyl methyl ester **24**, which had also been prepared during the structure determination work[28] and subsequently synthesized from glucose.[7] The melting point, optical rotation, and ^{1}H NMR spectrum of **24** are in agreement with the literature values. To summarize, we have demonstrated the application of the "halo-

(23) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.
(24) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
(25) Zibuck, R.; Liverton, N. J.; Smith, A. B. III *J. Am. Chem. Soc.* **1986**, *108*, 2451.
(26) (a) Trombe, F.; Blaise, M.; Caro, P. *C. R. Seances Acad. Sci., Ser. C* **1966**, *263*, 521. (b) Moeller, T. In *Comprehensive Inorganic Chemistry*: Bailar, J. C., Emeleus, H. J., Nyholm, R., Trotman-Dickenson, A. F., Eds.; Pergamon: Elmsford, NY, 1973; Vol. 4, p 82.
(27) The lower rotation of **23**(L) compared with **23**(D) is probably due to the small quantity and somewhat lower purity of the sample, rather than the presence of its enantiomer.
(28) Sakata, K.; Sakurai, A.; Tamura, S. *Tetrahedron Lett.* **1974**, 1533.



lactamization" procedure, in modified form, to the synthesis of 1-O-methyl-β,D-ezoaminuroic acid, **22**(D), wherein the overall efficiency compares very favorably with the more traditional approach[7] and reaffirms some of the advantages of carbohydrate total synthesis from noncarbohydrate starting materials.

Experimental Section

Apparatus and Reagents. Melting points of samples sealed in evacuated capillary tubes were determined on an Electrothermal apparatus and are uncorrected. Optical rotations [α] were taken with a Perkin-Elmer 141 polarimeter at 23 °C, sodium D line, with a 1-dm or 0.1-dm cell. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 710 spectrophotometer, and Fourier transform (FT-IR) spectra on a Mattson Cygnus 100 spectrophotometer (absorption maxima are reported in cm^{-1}). Proton nuclear magnetic resonance (NMR) spectra were obtained from deuteriochloroform solutions, unless otherwise specified, with a Varian Associates T-60, XL-400, or VXR-200 spectrometer. Carbon-13 NMR spectra were obtained on the latter instrument at 50 MHz. Chemical shifts are reported in parts per million with the residual chloroform signal (7.24 ppm) as internal standard, and coupling constants (*J*) are reported in hertz. Chemical ionization mass spectra (CI-MS) were obtained on a VG Analytical Model 7070EQ spectrometer with isobutane as the carrier gas. Elemental analysis was performed by Robertson Laboratory, Madison, NJ.

Precoated silica gel plates (E. Merck Si250F, 5715-7) were used for analytical thin-layer chromatography (TLC). Machery Nagel silica gel 60 (230–400 mesh) was employed for column chromatography. Acetonitrile, pentane, toluene, triethylamine, and dichloromethane were distilled from calcium hydride. Dimethyl sulfoxide was distilled from dimsyl sodium. Bulk grade ether and petroleum ether were distilled prior to use. Other solvents and reagents were obtained commercially and used as received. Organic solutions were dried over anhydrous sodium sulfate. All reactions were run under an argon atmosphere.

Diethyl 3,6-Dihydro-2*H*-pyran-2,2-dicarboxylate (8).[11] A stainless steel Hoke cylinder was charged with 10 g (57.5 mmol) of diethyl ketomalonate, one crystal of 2,6-di-*tert*-butyl-4-methylphenol, excess 1,3-butadiene (about 20 mL), and 100 mL of acetonitrile. The cylinder was sealed and heated at 140 °C for 24 h. The resulting mixture was concentrated to half the original volume, and 50 mL of 95% ethanol was added to precipitate polymeric materials, which were removed by filtration through Celite. The filtrate was concentrated to an oil, and the product was distilled at 100 °C (0.8 mm) to give 10.2 g of a colorless oil (78% yield); NMR (200 MHz) δ 5.85 (d, 1 H, *J* = 6.7), 5.73 (d, 1 H, *J* = 6.5), 4.29 (s, 2 H), 4.16 (q, 4 H, *J* = 7), 2.59 (s, 2 H), 1.18 (t, 6 H, *J* = 7.3); IR (film) 2970, 2950, 2900, 1740, 1630, 1475, 1455, 1400, 1380, 1240, 1140, 1100, 1020, 800, 780, 720 cm^{-1}.

3,6-Dihydro-2*H*-pyran-2-carboxylic Acid (9). A solution of diester 8 (10.2 g, 44.7 mmol) in 100 mL of 4:1 ethanol/water was treated with 50 mL of 2 N aqueous potassium hydroxide and stirred for 48 h at 23 °C. The reaction mixture was concentrated to half the original volume, acidified to pH 3 with 5 N aqueous hydrochloric acid, and extracted with five 40-mL portions of ethyl acetate. The combined organic extracts were dried and concentrated, leaving the diacid as a golden oil (7.63 g, 99% crude yield): NMR (200 MHz) δ 10.50–10.60 (br s, 2 H), 5.80 (d, 1 H, *J* = 10), 5.68 (d, 1 H, *J* = 10.2), 4.39 (s, 2 H), 2.69 (s, 2 H); IR (film) 3500, 2980, 2930, 2850, 1730, 1645, 1425, 1270, 1195, 1120, 1100, 1040, 975, 880, 830, 740, 710.

The diacid (5.0 g, 28.7 mmol) was heated at 150 °C in a Kugelruhrofen apparatus for 1 h. The product **9** distilled at 100 °C (10 mm) as a colorless oil (3.42 g, 95% yield): NMR (200 MHz) δ 10.11–10.20 (br s, 1 H), 5.80 (d, 1 H, *J* = 8.7), 5.72 (d, 1 H, *J* = 9), 4.19–4.42 (m, 3 H), 2.37–2.39 (br s, 2 H); IR (film) 3450, 3040, 2940, 2900, 2850, 2600, 1745, 1655, 1440, 1390, 1370, 1340, 1320, 1295, 1230, 1185, 1100, 1035, 980, 955, 930, 880, 795, 750, 660 cm^{-1}.

***N*-[(*R*)-1-(*p*-Methoxyphenyl)ethyl]-2,5-dihydro-6*H*-pyran-6-carboxamide (16a).** Oxalyl chloride (1.93 mL) was added to a stirred solution of 2.35 g (18.4 mmol) of **9** in 2 mL of toluene. After the evolution of gas was no longer apparent (about 30 min), the reaction mixture was concentrated to half the original volume and added dropwise to a stirred solution of 3.0 g (19.9 mmol) of (*R*)-(+)-1-(*p*-methoxyphenyl)ethylamine[16,17] and 3.0 g (30.0 mmol) of triethylamine in 10 mL of toluene at 23 °C. The reaction mixture was concentrated to a residue and partitioned between 10% aqueous sodium hydroxide and 50 mL of dichloromethane. The aqueous phase was washed with three additional 10-mL portions of dichloromethane. The combined organic extracts were dried and concentrated, and the residue was crystallized from isopropyl ether to afford **16a** (4.40 g, 92%) as a mixture of diasteriomers: mp 101–102 °C; CI-MS 262 (M + 1); NMR (400 MHz) δ 7.23–7.30 (m, 2 H), 6.85–6.90 (m, 2 H), 6.80–6.82 (br s, 1 H), 5.13 (app quin, 1 H, *J* = 7.3), 4.90 (td, 1 H, *J* = 11, 3.6), 4.26 (d, 2 H, *J* = 2.5), 3.81 (s, 3 H), 2.50 (app t, 1 H, *J* = 14), 2.16–2.28 (m, 1 H), 1.51 (app dd, 3 H, *J* = 13.2, 6.6); IR (film) 3300, 2960, 2930, 2840, 1650, 1620, 1585, 1510, 1445, 1375, 1310, 1290, 1250, 1180, 1090, 1035, 835, 750 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.28; N, 5.36. Found: C, 68.82; H, 7.12; N, 5.15.

3,6-Dihydro-2*H*-pyran-2-carboxamide (10).[12] Carboxylic acid **9** (1.0 g, 11.72 mmol) was converted to its acid chloride as described for **16a**. The resulting toluene solution was added slowly to a stirred solution of liquid ammonia and 1 mL of toluene at −78 °C and allowed to warm to 23 °C over 1 h. The reaction mixture was concentrated to a residue and partitioned between 10% aqueous sodium hydroxide and dichloromethane. The aqueous phase was washed with three additional 10-mL portions of dichloromethane. The combine organic extracts were dried and concentrated, and the crude product was crystallized from isopropyl ether to afford 890 mg (90% yield) of **10**: mp 110–111 °C (lit.[12] mp 111–112 °C). NMR (400 MHz) δ 6.52–6.63 (br s, 1 H), 5.87–5.91 (m, 1 H), 5.75 (d, 1 H, *J* = 10), 5.30–5.41 (br s, 1 H), 4.29 (s, 2 H), 4.05 (dd, 1 H, *J* = 10.8, 3.8), 2.48 (d, 1 H, *J* = 17.7), 2.77 (ddt, 1 H, *J* = 17.2, 10.6, 2.2); IR (film) 3280, 3190, 2950, 2860, 1660, 1460, 1380, 1370, 1335, 1250, 1190, 1100, 1075, 1035, 980, 950, 920, 870, 820, 780, 720, 650 cm^{-1}.

4-*exo*-Bromo-6-[(*R*)-1-(*p*-methoxyphenyl)ethyl]-6-aza-2-oxabicyclo[3.2.1]octan-7-one (17a). A suspension of 1.0 g (3.83 mmol) of amide **16a** in a mixture of 640 μL (4.59 mmol) of triethylamine, 930 μL of trimethylsilyl trifluoromethanesulfonate, and 5 mL of pentane was stirred for 1 h, during which time the solid dissolved. The pentane supernatant was transferred by cannula under argon to another reaction flask, and the oily residue was washed with an additional 2 mL of pentane. The combined pentane solution was concentrated in the second flask under reduced pressure by using an aspirator pump equipped with a calcium sulfate drying tube. The resulting residue was dissolved in 1 mL of dichloromethane and cooled to −78 °C. A solution of 2.42 g (5.75 mmol) of bromonium bis(collidine)perchlorate[18] in 2 mL of dichloromethane was added in one portion, and the reaction mixture was stirred at −78 °C for 5 min and then warmed to room temperature over a 15-min period. The reaction was quenched with 1 mL of saturated aqueous sodium carbonate, and the organic phase was washed with 10% aqueous sulfuric acid and brine, dried, concentrated, and chromatographed with 1:1 toluene/ethyl acetate as the eluant. Bromo lactam **17a** was obtained as a mixture of diasteriomers (1.0 g, 77%). A sample crystallized from ether/hexane had mp 94–95 °C: NMR (400 MHz) δ 7.38 (d, 2 H, *J* = 8.4), 7.23 (d, 2 H, *J* = 8.3), 6.90 (d, 4 H, *J* = 8.5), 5.57 (q, 1 H, *J* = 6.3), 5.45 (q, 1 H, *J* = 7.5), 4.43 (dd, 1 H, *J* = 14, 3.7), 4.23 (dd, 1 H, *J* = 15, 4.1), 4.15 (d, 1 H, *J* =

20), 4.03 (dd, 1 H, J = 13.8, 3.8), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.76–3.80 (m, 2 H), 3.68–3.69 (br s, 1 H), 3.00–3.02 (m, 1 H), 2.80 (d, 1 H, J = 12.4), 2.75 (d, 1 H, J = 11.2), 1.85–1.89 (m, 1 H), 1.67–1.73 (m, 1 H), 1.64 (d, 3 H, J = 7.3), 1.55 (d, 3 H, J = 7.5); IR (film) 2960, 2930, 2840, 1700, 1670, 1580, 1520, 1450, 1400, 1375, 1300, 1245, 1200, 1175, 1150, 1075, 1060, 1040, 1020, 970, 900, 860, 830, 810, 770 cm^{-1}.

***N*-*tert*-Butyldimethylsilyl Bromo Lactams 13 and 14.** Carboxamide **10** (89 mg, 0.699 mmol) was converted to its *N*,*O*-bis(*tert*-butyldimethylsilyl) derivative **11b** as described for **17a**, except that *tert*-butyldimethylsilyl trifluoromethanesulfonate was used as the silylating agent. Bromocyclization as described for **17a** produced a crude product, which was chromatographed with 1:2 ether/petroleum ether as the eluant to give 0.123 g (55%) of the bicyclo[3.2.1] product **13** and 0.058 g (26%) of the bicyclo[2.2.2] product **14**, both as oils (R_f's 0.91 and 0.77, respectively, with ether as eluant): IR (**13**, film) 2940, 2900, 2850, 1705, 1470, 1440, 1390, 1380, 1355, 1300, 1275, 1260, 1235, 1100, 1095, 1080, 1060, 1020, 955, 865, 840, 810, 790, 780, 735, 705 cm^{-1}; IR (**14**, film) 2925, 2860, 2840, 1690, 1460, 1440, 1410, 1380, 1360, 1305, 1295, 1280, 1260, 1235, 1205, 1175, 1160, 1085, 1100, 1020, 950, 860, 840, 805, 780, 765, 730 cm^{-1}.

8-Bromo-5-aza-2-oxabicyclo[2.2.2]octan-6-one (15). By the procedure described for **17a**, 50 mg (0.394 mmol) of carboxamide **10** was bromocyclized and chromatographed to give 67 mg (83%) of **15** as a low-melting solid, pure by TLC (R_f 0.40, ether). CI-MS 206 (M + 1); IR (film) 1705 cm^{-1}. The product was conveniently characterized as its *N*-acetate derivative (prepared with acetic anhydride in pyridine), mp 90–92 °C: NMR (60 MHz) δ 5.1–5.4 (m, 1 H), 3.8–4.6 (m, 4 H), 2.56 (s, 3 H), 2.05–2.30 (m, 2 H); IR (KBr) 3040, 2970, 2900, 2860, 2830, 1748, 1690, 1462, 1376, 1350, 1298, 1278, 1248, 1226, 1101, 1064, 1028, 1005, 985, 953, 937, 860, 829, 780, 740 cm^{-1}; CI-MS 248 (M + 1). Removal of the *N*-silyl group of either **13** or **14** with hydrogen fluoride in aqueous acetonitrile[29] also produced **15** as the only lactam product.

6-[(*R*)-1-(*p*-Methoxyphenyl)ethyl]-6-aza-2-oxabicyclo-[3.2.1]oct-3-en-7-one (18a). A solution of 1.0 g (2.95 mmol) of bromo lactam **17a** in 2 mL of dimethyl sulfoxide was treated with 396 mg (3.54 mmol) of solid potassium *tert*-butoxide in one portion, then stirred for 12 h at 23 °C. The reaction mixture was partitioned between 10 mL of brine and 10 mL of dichloromethane, and the aqueous layer was vigorously extracted with five additional 10-mL portions of dichloromethane. The combined organic extracts were dried and concentrated, affording 0.726 g (95%) of the product as an equal mixture of two diasteriomers.

The diasteriomers were separated by chromatography with 1:1 ether/petroleum ether as the eluant, resulting in 290 mg of pure high R_f isomer (**18a**), 100 mg of pure low R_f isomer (**18b**), and the remainder as a mixture of the two. NMR analysis at 400 MHz confirmed that neither pure sample contained more than 2% of its diasteriomer. The high R_f isomer, crystallized from ether/petroleum ether, had mp 114–115 °C: NMR (**18a**, 400 MHz) δ 7.27 (d, 2 H, J = 8.6), 6.94 (d, 2 H, J = 8.5), 5.93 (d, 1 H, J = 5.4), 5.32 (q, 1 H, J = 7), 4.95 (d, 1 H, J = 5), 4.45 (app t, 1 H, J = 5.6), 3.81 (s, 3 H), 3.64 (app t, 1 H, J = 5.4), 2.12 (m, 1 H), 1.61 (m, 1 H), 1.41 (d, 3 H, J = 7.2); IR (film) 3070, 3010, 2970, 2850, 1700, 1635, 1590, 1520, 1455, 1430, 1260, 1230, 1200, 1075, 1060, 1015, 955, 930, 850, 790, 775, 740, 690 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.50; H, 6.56; N, 5.41. Found: C, 69.51; H, 6.80; N, 5.24.

The low R_f isomer (**18b**), crystallized from ether/petroleum ether, had mp 46–47 °C: NMR (**18b**, 400 MHz) δ 7.21 (d, 2 H, J = 8.7), 6.88 (d, 2 H, J = 8.5), 6.27 (d, 1 H, J = 5.4), 5.35 (q, 1 H, J = 6.4), 5.28 (app t, 1 H, J = 7), 4.67 (s, 1 H), 3.82 (s, 3 H), 3.47–3.49 (m, 1 H), 2.05–2.09 (m, 1 H), 1.71–1.77 (m, 1 H), 1.63 (d, 3 H, J = 7); IR (film) 3070, 3010, 2970, 2850, 1700, 1635, 1590, 1513, 1400, 1250, 1220, 1180, 1170, 1065, 1030, 840, 800, 785 cm^{-1}.

Crystal Structure Determination. Details of the crystal structure determination of **18d** are given in Table I. A clear, colorless prism, obtained by slow diffusion of hexane into a dichloromethane solution of **18d**, was mounted inside a sealed capillary. The Enraf–Nonius structure determination package was used for data collection, data processing, and structure solution. Intensity data were collected with use of Mo Kα radiation and corrected for Lorentz, polarization, and absorption (empirical) effects.

Table I. Crystal and Refinement Data for 18d

formula	$C_{15}H_{17}NO_3$
fw	259.31
a, Å	5.749 (2)
b, Å	8.756 (1)
c, Å	13.203 (2)
β, deg	94.87 (2)
V, Å^3	662.2 (5)
space group	$P2_1$
Z	2
no. ref used to detn cell constants	25 ($11.42 < 2\theta < 15.93°$)
d_{calcd}, g/cm^3	1.300
radiation used	graph. mono. Mo Kα (0.71073 Å)
linear abs coeff, cm^{-1}	0.85
crystal dimensions, mm	0.03 × 0.21 × 0.45
rel trans factor range	0.91 < I < 1.00
diffractometer	Enraf–Nonius CAD-4
data collection method	θ–2θ
2θ range, deg	$4 < 2\theta < 46$
temp, K	300 (1)
scan range, deg	0.8 + 0.30 tan θ
weighting scheme[a]	$w = 4(F_o)^2/[\sigma(F_o)^2]^2$
no. of std reflcns	3
% variation in std intens	±0.5
no. unique data collected	995
no. data used in refinement	814 ($F_o^2 > \sigma(F_o^2)$)
data:parameter ratio	4.8
final GOF	1.36
final R_F, R_{wF}	0.049, 0.046
systematic absences observed	$0k0$, $k = 2n + 1$
data collected	$h,k,\pm l$
final largest shift/esd	0.03
highest peak in final diff map, e/Å^3	0.17

[a] $[\sigma(F_o)^2]^2 = [S^2(C + R^2B) + (pF_o^2)^2]/(Lp)^2$, where S is the scan rate, C is the integrated peak count, R is the ratio of scan to background counting time, B is the total background count, and p is a factor used to downweight intense reflections. For this structure, p = 0.04.

The structure was solved by direct methods by using the program MULTAN 82[30] and refined by full-matrix least-squares techniques. H atoms were either located on a difference Fourier map or placed at calculated positions by assuming ideal bond geometry with the C–H distance equal to 0.95 Å. Before the final refinement cycles, H atom temperature factors were set according to $B_H = 1.3\ B_N$, where N is the equivalent isotropic temperature factor of the atom bonded to H. H atom parameters were not refined. With all non-H atoms anisotropic (172 parameters), the refinement converged with R_{wF} = 0.046 and R_F = 0.049. A view of the molecule, showing the atom numbering scheme, is given in Figure 1.

4-*exo*-Hydroxy-3-*endo*-methoxy-6-[(*R*)-1-(*p*-methoxyphenyl)ethyl]-6-aza-2-oxabicyclo[3.2.1]octan-7-one (19a). A solution of 500 mg (1.93 mmol) of the high R_f vinyl ether **18a** and 497 mg (2.89 mmol) of mCPBA in 2 mL of methanol was stirred at 23 °C for 12 h. The reaction mixture was concentrated to a residue and partitioned between 3 mL of saturated aqueous carbonate and 5 mL of dichloromethane. The aqueous phase was washed with two additional 5-mL portions of dichloromethane. The combined organic extracts were dried, concentrated, and chromatographed with ether/petroleum ether as the eluant, affording 545 mg (92%) of **19a**. A sample crystallized from ether sublimed at 86 °C in the evacuated (1 mm) capillary: NMR (400 MHz) δ 7.31 (d, 2 H, J = 8.1), 6.85 (d, 2 H, J = 6.9), 5.16 (q, 1 H, J = 6.8), 4.49 (s, 1 H), 4.04 (s, 1 H), 3.80 (s, 3 H), 3.64 (s, 1

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H), 3.32 (s, 3 H), 2.99 (d, 1 H, J = 3.6), 2.42 (d, 1 H, J = 11.7), 1.78–1.87 (m, 1 H), 1.53 (d, 3 H, J = 6.8); IR (film) 3400, 2970, 2940, 1705, 1615, 1580, 1515, 1440, 1415, 1375, 1305, 1260, 1240, 1180, 1120, 1060, 1035, 985, 920, 885, 820, 785, 765, 730 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.29; H, 6.68; N, 4.20.

4-*exo*-Acetoxy-3-*endo*-methoxy-6-[(*R*)-1-(*p*-methoxyphenyl)ethyl]-6-aza-2-oxabicyclo[3.2.1]octan-7-one (20a). A solution of 200 mg (0.65 mmol) of alcohol **19a**, 136 μL (0.975 mmol) of triethylamine, 92 μL (0.975 mmol) of acetic anhydride and one crystal of 4-(*N*,*N*-dimethylamino)pyridine in 2 mL of dichloromethane was stirred at 23 °C for 3 h. The reaction mixture was concentrated and chromatographed with 1:2 ether/petroleum ether as the eluant. Acetate **20a** (229 mg, 99%) was obtained as a solid. A sample crystallized from ether/hexane had mp 118–119 °C: NMR (400 MHz) δ 7.33 (d, 2 H, J = 8.5), 6.87 (d, 2 H, J = 8.6), 5.13 (q, 1 H, J = 6.9), 4.49 (s, 1 H), 4.05 (d, 1 H, J = 3), 3.79–3.84 (br s, 4 H), 3.03 (s, 3 H), 2.30 (d, 1 H, J = 12), 2.00 (s, 3 H), 1.76–1.86 (m, 1 H), 1.56 (d, 3 H, J = 7); IR (film) 2970, 2940, 2840, 1740, 1705, 1615, 1585, 1440, 1415, 1375, 1300, 1260, 1240, 1180, 1120, 1060, 1035, 980, 920, 885, 820, 790, 765 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.89; H, 6.59; H, 4.01. Found: C, 61.28; H, 6.56; N, 3.60.

4-*exo*-Acetoxy-3-*endo*-methoxy-6-aza-2-oxabicyclo-[3.2.1]octan-7-one [21(D)]. A suspension of 100 mg (0.287 mmol) of acetate **20a**, 472 mg (0.861 mmol) of CAN, 472 mg of silica gel, and 1 mL of a 3:1 mixture of acetonitrile/water was stirred for 10 min at 23 °C and then quenched with 1 mL of saturated aqueous sodium sulfite and 1 mL of saturated aqueous sodium carbonate. The liquid was decanted from the insoluble cerium carbonate salts, and the aqueous phase washed with three 5-mL portions of dichloromethane. The combined organic extracts were dried, concentrated, and chromatographed with ether as the eluant to afford 47 mg (76%) of **21(D)** as a white solid. A sample crystallized from ether/hexane had mp 132–133 °C: CI-MS 216 (M + 1); [α] −113.3° (*c* 1.0, methanol); NMR (200 MHz) δ 5.95–6.00 (br s, 1 H), 4.82 (d, 1 H, J = 3.5), 4.66 (s, 1 H), 3.95 (d, 1 H, J = 6.9), 3.86 (app t, 1 H, J = 5.3), 3.36 (s, 3 H), 2.40 (d, 1 H, J = 12), 2.11 (s, 3 H), 1.97–2.05 (m, 1 H); IR (film) 3300, 2950, 2900, 2840, 1725, 1700, 1460, 1440, 1370, 1300, 1235, 1120, 1095, 1060, 1025, 970, 920, 870, 815 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.05; N, 6.51. Found: C, 50.24; H, 6.07; N, 6.38.

1-*O*-Methyl-β,D-ezoaminuroic Acid [22(D)]. A solution of 100 mg (0.465 mmol) of **21(D)** and 78 mg (1.39 mmol) of potassium hydroxide in 5 mL of 95% ethanol was heated at reflux for 8 days. NMR analysis of the crude reaction mixture at this point showed only the presence of the desired amino carboxylate salt: NMR (crude hydrolyzed product, 200 MHz, D_2O) δ 4.08 (d, 1 H, J = 7.6, H-1), 3.80 (d, 1 H, J = 12, H-5), 3.31 (s, 3 H, OCH_3), 2.84 (app t, 1 H, J = 8.8, H-2), 2.69 (app td, 1 H, J = 10, 3, H-3), 1.97 (dd, 1 H, J = 12.6, 2.1, H-4_{eq}), 1.20 (app q, 1 H, J = 12.3, H-4_{ax}). The reaction mixture was neutralized with 278 μL of 5 N hydrochloric acid and concentrated to a residue consisting of the product as its zwitterion and potassium chloride: NMR (crude neutralized product, 400 MHz, D_2O) δ 4.35 (d, 1 H, J = 7.6, H-1), 4.25 (dd, 1 H, J = 11.8, 2, H-5), 3.47 (s, 3 H, OCH_3), 3.41 (app td, 1 H, J = 11.2, 4.7, H-3), 3.32 (app t, 1 H, J = 7.5, H-2), 2.37 (ddd, 1 H, J = 12.9, 4.0, 2.0, H-4_{eq}), 1.72 (app q, 1 H, J = 12.6, H-4_{ax}).

2,3-*O*,*N*-Diacetyl-1-*O*-methyl-β,D-ezoaminuroic Acid Methyl Ester [23(D)]. A suspension of 40 mg of the crude amino acid **22(D)** in a solution of 40 mg of 4-(*N*,*N*-dimethylamino)-pyridine in 1 mL of acetic anhydride was stirred for 24 h. The excess acetic anhydride was removed under vacuum, and the residue was dissolved in 1 mL of 3:1 ether/methanol and treated with excess diazomethane. The residual reagent was quenched with acetic acid, and the mixture was concentrated and chromatographed with ethyl acetate as eluant to give 20 mg of the ezoaminuroic acid derivative **23(D)**. A sample crystallized from ethyl acetate/hexane had mp 156–157 °C: [α] −23.3° (*c* 1.16, $CHCl_3$); NMR (400 MHz) δ 5.87 (d, 1 H, J = 7.3, N-H), 4.62 (dd, 1 H, J = 9.4, 7, H-2), 4.40 (d, 1 H, J = 7.7, H-1), 4.09 (app dd, 2 H, J = 11.6, 2.1, H-3 and H-5), 3.75 (s, 3 H, CO_2CH_3), 3.51 (s, 3 H, OCH_3), 2.46 (ddd, 1 H, J = 13.4, 4.8, 2.5, H-4_{eq}), 2.07 (s, 3 H, $OCOCH_3$), 1.91 (s, 3 H, $NHCOCH_3$), 1.63 (app q, 1 H, J = 11.8, H-4_{ax}); FT-IR (KBr) 3277, 2960, 2922, 2238, 1745, 1665, 1560, 1452, 1400, 1387, 1287, 1250, 1236, 1172, 1131, 1109, 1087, 1061, 896 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.83; H, 6.57; N, 4.83. Found: C, 49.67; H, 6.55; N, 5.00.

The same procedure applied to the L series amino acid **22(L)** gave 5 mg of 2,3-*O*,*N*-diacetyl-1-*O*-methyl-β,L-ezoaminuroic acid methyl ester [**23(L)**]: mp 153–154 °C; [α] +17.7° (*c* 0.62, $CHCl_3$).[27]

2,3-*O*,*N*-Dibenzoyl-1-*O*-methyl-β,D-ezoaminuroic Acid Methyl Ester (24). Approximately 30 mg of the crude amino acid **22(D)** was converted to its methyl ester hydrochloride by treatment with thionyl chloride in methanol.[31] The crude ester was benzoylated directly with benzoyl chloride and 4-(*N*,*N*-dimethylamino)pyridine in dichloromethane solution, and the dibenzoate was isolated by chromatography followed by crystallization: yield 5 mg; mp 236–236.5 °C (lit.[28] mp 237.5–238 °C, lit.[7] mp 241–242 °C); [α] +55.2° (*c* 0.62, methanol) [lit.[28] [α] +58° (*c* 0.75, methanol), lit.[7] [α] +60.7° (*c* 0.44, methanol)]; NMR (400 MHz) δ 8.02 (d, 2 H, J = 7.6), 7.64 (d, 2 H, J = 7.4), 7.55 (app t, 1 H, J = 7.5), 7.38–7.49 (m, 5 H), 6.88 (d, 1 H, J = 7.2), 5.05 (dd, 1 H, J = 10.3), 4.70 (d, 1 H, J = 7.3), 4.45 (m, 1 H), 4.43 (dd, 1 H, J = 11, 2.3), 3.79 (s, 3 H), 3.60 (s, 3 H), 2.78 (ddd, 1 H, J = 15.8, 4.3, 2.6), 1.85 (app q, 1 H, J = 11.2); FT-IR (film) 3266, 3083, 3000, 2958, 2922, 2845, 1746, 1727, 1641, 1603, 1555, 1450, 1436, 1395, 1378, 1348, 1320, 1308, 1269, 1254, 1225, 1170, 1159, 1117, 1101, 1067, 1032, 1022, 983, 956, 708, 698, 685 cm^{-1}.

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Supplementary Material Available: Listings of final atomic coordinates, anisotropic thermal parameters, bond distances, bond angles, and observed and calculated structure factors for **18d** have been deposited at the Cambridge Crystallographic Data Center.

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