Cycloadditions in Syntheses. Part 27.[1] *rel*-(1*R*,4*R*,5*S*)-5-Hydroxy-2-azabicyclo[2.2.0]hexan-3-one and its Derivatives: Synthesis and Transformation to Azetidin-2-ones[2]

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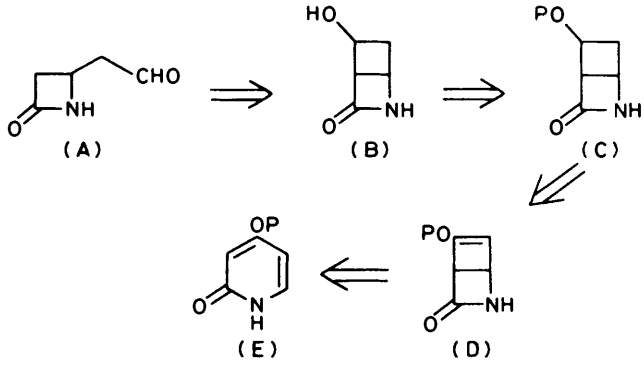
The title compound, a synthetic equivalent of 4-(2-oxoethyl)azetidin-2-one, has been synthesized as a stable crystalline compound from the 2-pyridone having an appropriately protected 4-hydroxy group *via* photopyridine formation, catalytic hydrogenation, and deblocking of the protecting group. Successful conversion of the title compound and its derivatives into azetidin-2-ones having a terminally oxygenated ethyl side chain at the 4-position is also described.

The recent discovery of thienamycin and related antibiotics has stimulated enormous interest in the area of carbapenem synthesis.[3] Previously, we have reported that 2-pyridones having an oxygen functional group at the 4-position afford, upon photolysis (≥ 300 nm) in a transparent solvent (*e.g.* acetonitrile, ether, *etc.*), the corresponding 2-azabicyclo-[2.2.0]hex-5-en-3-ones (so-called photopyridones).[4] Since 2-pyridones † having an alkoxy or acetoxy group at the 4-position do not dimerize under ordinary irradiation conditions, these photopyridones are obtained in high yields, even in multi-gram scale experiments. Utilizing these photopyridones, we have now accomplished a general and efficient synthetic method of *rel*-(1*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.0]-hexan-3-one (**4a**) and its derivatives, all of them being stable compounds. Furthermore, successful conversion of these compounds into azetidin-2-ones having a terminally oxygenated ethyl side-chain at the 4-position has demonstrated that they are equivalents of 4-(2-oxoethyl)azetidin-2-one ‡ and its substituted derivatives. Though the latter compounds are considered as versatile synthetic intermediates for carbapenem nuclei,[5] they have to be used immediately they are formed owing to their extreme instability.

Our plan for the present study is illustrated by the retro-synthesis shown in Scheme 1. Thus, 4-(2-oxoethyl)azetidin-2-one (A) could be formed readily by retro-aldol-type C–C bond cleavage of 5-hydroxy-2-azabicyclo[2.2.0]hexan-3-one (B). In turn, the latter compound (B) may be obtained from a 4-oxygenated 2-pyridone having an appropriately protected oxygen function at the 4-position, (E), *via* the corresponding photopyridone (D) by catalytic hydrogenation [formation of (C)] followed by deblocking of the protecting group.

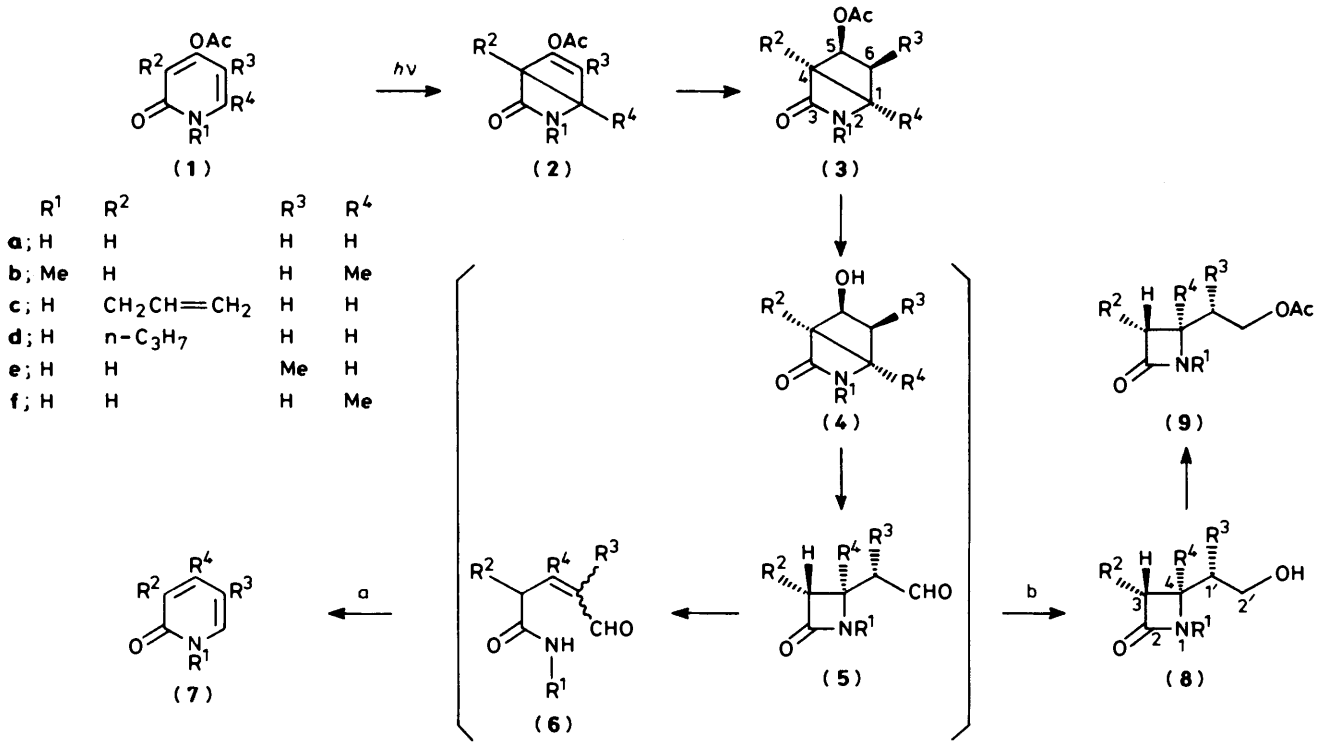
In order to realize our plan, we chose initially 4-acetoxy-2-pyridones (**1a**—**f**) as the starting materials. Irradiation (≥ 300 nm) of compounds (**1a**—**f**) in acetonitrile or other transparent solvents then afforded the photopyridones (**2a**—**f**), all in high yield. Catalytic hydrogenation of these photopyridones afforded the expected dihydro derivatives (**3a**,**b**,**d**—**f**). This step proceeded stereospecifically and, in each case, afforded a single stereoisomer in nearly quantitative yield. The *endo*-configuration of the 5-acetoxy group in each product (**3**) was deduced from n.m.r. spectroscopy. For example, the coupling constant between the protons 4-H and 5-H of (**3a**) is 8.0 Hz, indicating a *cis*-relationship. As expected, hydrogenation should occur from the less hindered side of the molecules (**2a**—**f**). An attempted hydrolysis of the dihydro derivative (**3b**) under basic conditions (1% K_2CO_3–methanol; room temperature) did not give the corresponding hydroxy derivative (**4b**) but instead gave 1,4-dimethyl-2-pyridone (**7b**)[6] in 64% yield as the sole product. The formation of compound (**7b**) is best explained by assuming the intermediacy of 4-formylmethyl-1,4-dimethylazetidin-2-one (**5b**) formed by retro-aldol-type ring opening of the simple hydrolysis product (**4b**). Retro-Michael reaction (cleavage of the N–C-4 bond) of (**5b**), initiated by abstraction of a proton in the active methylene function, would give compound (**6b**), which would then cyclize to the final product (**7b**). In order to obtain the azetidinone derivative from bicycle (**3b**), the formyl function in compound (**5b**) should be reduced before the above N–C-4 bond cleavage occurs. In accord with this expectation, treatment of compound (**3b**) with 1% K_2CO_3 in methanol in the presence of an excess of sodium borohydride followed by acetylation (Ac_2O–pyridine) afforded 4-(2-acetoxyethyl)-1,4-dimethylazetidin-2-one (**9b**) in 95% yield. The same three-step procedure has also been applied to the synthesis of 4-(2-acetoxyethyl)azetidin-2-one (**9a**), which again proceeded in high overall yield.



Scheme 1. P is a protecting group

† Throughout this and the following paper, 2-pyridone means pyridin-2(1*H*)-one.

‡ The most general method of synthesis of 4-(2-oxoethyl)azetidin-2-one is the oxidation of 4-(2-hydroxyethyl)azetidin-2-one: see ref. 5.



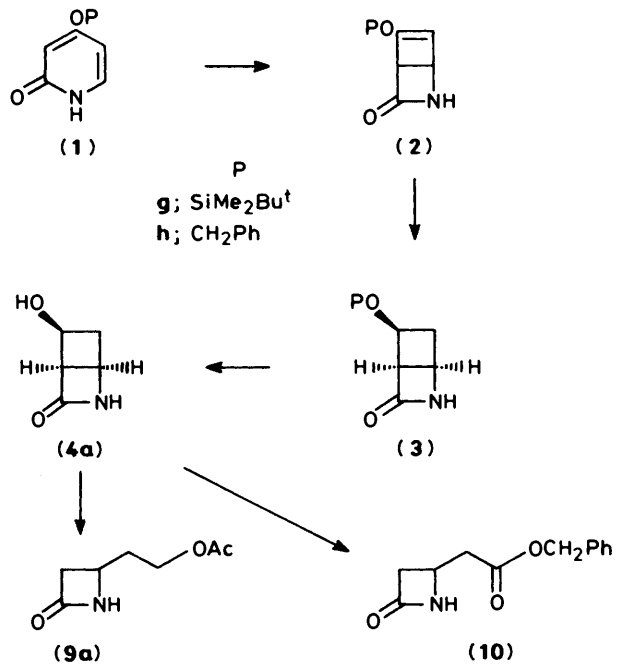
Scheme 2. a, 1% K_2CO_3–MeOH. b, 1% K_2CO_3–$NaBH_4$–MeOH

Added to high overall yield and easy handling, this three-step synthetic method for azetidinone derivatives has wide applicability for a variety of substituted derivatives of 4-(2-hydroxyethyl)azetidin-2-one (**8a**). Namely, if a C-3-, C-5-, or C-6-substituted derivative of 4-acetoxy-2-pyridone were to be used as the starting material, 4-(2-hydroxyethyl)azetidin-2-ones (**8**) having either a C-3, C-1′, or C-4 substituent should be obtained. All of these expectations were realized as described in the Experimental section. Two characteristic features in the above method seem to deserve comment. First, from 4-acetoxy-3-allyl-2-pyridone (**1c**), only *trans*-4-(2-acetoxyethyl)-3-propylazetidin-2-one (**9d**) was formed. Since retro-aldol reaction of (**4d**) should initially afford the azetidinone enolate of aldehyde (**5d**), a thermodynamically more stable *trans*-configuration between 3-H and 4-H is reasonable for (**9d**). The small coupling constant (2.5 Hz) between these two protons in the ^1H n.m.r. spectrum of (**9d**) supports this view. Secondly, *rel*-(4*S*)-4-[(1*S*)-2-acetoxy-1-methylethyl]azetidin-2-one (**9e**)* was obtained as the sole product from 4-acetoxy-5-methyl-2-pyridone (**1e**). Consideration of the proposed mechanism (Scheme 2) as well as selective formation of compound (**9e**) clearly indicates that the configuration at the 1′-position in (**9e**) is the same as that in the starting material (**4e**).

Thus, our initial plan was realized in that the photopyridones (**2a**—**f**) were good precursors for the azetidinones (**8**) and (**9**). However, actual isolation of compound (**4a**) or its derivatives was not accomplished. Obviously, though these compounds (**4**) were surely involved in the above transformation, ready retro-aldol ring opening of compounds (**4**) to (**5**) under basic conditions had prevented the isolation of the bicycles (**4**). Accordingly, we then tried hydrolysis of the acetate (**3a**) [the dihydro derivative of the photopyridone (**2a**) obtained from 4-acetoxy-2-pyridone (**1a**)] under acidic conditions. After several attempts had ended in failure,† we chose the dimethyl-t-butylsilyl group for the protection of the 4-hydroxy group of the starting 2-pyridone, because its removal at the final stage would be expected to occur under mildly acidic conditions. Thus, a solution of 4-hydroxy-2-pyridone in *NN*-dimethylformamide (DMF) was treated with dimethyl-t-butylsilyl chloride (TBDSC) in the presence of triethylamine to give 4-(dimethyl-t-butylsiloxy)-2-pyridone (**1g**). The u.v. spectrum of this compound in ether showed its absorption maximum at 295 nm, indicating a 2-pyridone structure. Irradiation of pyridone (**1g**) in ether at ≥ 300 nm gave the photopyridone (**2g**) as the sole product in 57% overall yield. Hydrogenation of the olefinic bond in (**2g**) by means of palladium–charcoal in methanol gave the dihydro derivative (**3g**). The *endo*-configuration of the siloxy group was evident from its n.m.r. spectrum ($J_{4,5}$ 8.0 Hz). As expected, removal of the dimethyl-t-butylsilyl group of compound (**3g**) was successfully carried out at room temperature with toluene-*p*-sulphonic acid (PTSA) monohydrate in aqueous tetrahydrofuran (THF) to give *rel*-(1*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.0]hexan-3-one (**4a**) in 80% yield as a crystalline compound. The i.r. spectrum of (**4a**) showed the hydroxy and β-lactam carbonyl groups at 3 500 and 1 740 cm^{-1}, respectively. Furthermore, its structure was confirmed rigorously by its n.m.r. spectrum (see Experimental section). The product (**4a**) is stable at room temperature either in its crystalline state or in a protic solvent, even in one containing hydrochloric acid.

* 1-β-Methylcarbapenem has aroused much interest recently. For its synthesis, however, (4*S*)-4-[(1*R*)-2-acetoxy-1-methylethyl]azetidin-2-one [an isomer of (**9e**)] should be the necessary starting material: see D. H. Shim, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, 1984, **21**, 29.

† Though compound (**3a**) was stable in conc. HCl–MeOH at room temperature, the same hydrolysis at an elevated temperature resulted in the decomposition of the acetate (**3a**) and none of the β-lactam was obtained.



Scheme 3.

The stability of compound (**4a**) under acidic conditions prompted us to investigate a simpler synthesis of this bicycle from 4-benzyloxy-2-pyridone (**1h**). Thus, catalytic hydrogenation of the photopyridone (**2h**) prepared from (**1h**) gave the azabicyclohexane (**3h**) in almost quantitative yield. Although debenzylation of compound (**3h**) did not occur by catalytic hydrogenation under neutral conditions even at high pressure, hydrogenolysis of the bicycle (**3h**) over palladium–charcoal in methanol containing 0.3% (v/v) conc. HCl under atmospheric pressure gave the desired product (**4a**) in nearly quantitative yield.

Thus, we now have accomplished the synthesis of compound (**4a**) in three steps from pyridone (**1h**) in very high overall yield. This method is especially useful, because 4-benzyloxy-2-pyridone (**1h**) can be prepared readily, like other 4-alkoxy-2-pyridones, from pyridine 1-oxide *via* nitration, nitro-group replacement with a benzyloxy group by nucleophilic substitution, followed by 2-pyridone formation by acetic anhydride.[7] Furthermore, as we expected, compound (**4a**) is a chemical equivalent of 4-(2-oxoethyl)azetidin-2-one (**5a**) as demonstrated in the following two experiments. Thus, treatment of bicycle (**4a**) with sodium borohydride in methanol containing aqueous potassium carbonate followed by acetylation afforded 4-(2-acetoxyethyl)azetidin-2-one (**9a**) in almost quantitative yield. As another example, compound (**4a**) was treated with potassium permanganate in the presence of potassium carbonate in water. The expected carboxylic acid was then benzylated by the addition of benzyl bromide to the reaction mixture to give 4-(benzyloxycarbonylmethyl) azetidin-2-one (**10**) in 66% yield. The fact that both of these reactions occur readily at room temperature indicates clearly that retro-aldol-type ring opening of bicycle (**4a**) to the azetidinone (**5a**) is a straightforward process even in a weakly basic medium.

In conclusion, we have achieved the synthesis of *rel*-(1*R*,4*R*,5*S*)-5-hydroxy-2-azabicyclo[2.2.0]hexan-3-one (**4a**) from readily available a 4-oxygenated 2-pyridone *via* photopyridone formation, reduction, and subsequent deblocking, and demonstrated its equivalence to 4-(2-oxoethyl)azetidin-2-one (**5a**), which though used as an important key intermediate for carbapenem synthesis is a very unstable compound. Since compound (**4a**) can be synthesized on a multigram scale and is a stable crystalline compound, we believe that this bicycle as well as its derivatives will become more versatile intermediates for the synthesis of carbapenem nuclei than is aldehyde (**5a**) at present. As shown in Scheme 2, possible introduction of a substituent at a desired position in the azetidinone (**5a**) sheds further light on the wide applicability of the present method.

Experimental

M.p.s were determined on a Yanaco micromelting point apparatus (MP-S2), and are uncorrected. I.r. spectra were recorded on a JASCO A-102 spectrophotometer. ^{1}H N.m.r. spectra were recorded using tetramethylsilane as internal standard on JEOL JNM PMX-60 and FX-100 spectrometers at 60 MHz and 100 MHz, respectively. Mass spectra were recorded on a Hitachi model M-52, and high-resolution mass spectra on a JEOL JMS-01SG-2 system. U.v. spectra were recorded on a Hitachi 320 spectrophotometer. The irradiation source used for photoreactions was a high-pressure mercury lamp (Ushio 450 W, Pyrex filter) or Rayonet photochemical reactor lamps (Cat. No. RPR-3000 A). Wakogel (C-200) was employed for silica gel column chromatography. Merck Kieselgel 60F 254 was employed for t.l.c.

5-*Acetoxy*-2-*azabicyclo*[2.2.0]*hex*-5-*en*-3-*one* (**2a**).—A solution of 4-acetoxy-2-pyridone[8] (**1a**) (158 mg, 1.03 mmol) in a mixture of acetonitrile (37.5 ml) and ether (132.5 ml) under argon was irradiated by high-pressure mercury lamp (Ushio 450 W, Pyrex filter) for 1 h. The solvent was evaporated off under reduced pressure to give the *product* (**2a**) (148 mg, 93%) as prisms (from dichloromethane–ether), m.p. 103—105 °C (Found: M^+, 153.0423. $C_7H_7NO_3$ requires M, 153.0424); $\nu_{max.}$(KBr) 3 235, 1 772, 1 735, 1 603, 1 208, and 1 205 cm^{-1}; δ_H($CDCl_3$) 2.15 (3 H, s, Ac), 4.31 (2 H, br s, 1- and 4-H), 5.69 (1 H, s, 6-H), and 6.47 (1 H, br s, NH).

5-*Acetoxy*-1,2-*dimethyl*-2-*azabicyclo*[2.2.0]*hex*-5-*en*-3-*one* (**2b**).—A solution of 4-acetoxy-1,6-dimethyl-2-pyridone[8] (**1b**) (314 mg, 1.7 mmol) in ether (340 ml) was irradiated under argon by a high-pressure mercury lamp (Ushio 450 W, Pyrex filter) for 15 h. The solvent was evaporated off under reduced pressure, and the residue was subjected to silica gel column chromatography (15 g). Elution with dichloromethane–methanol (100:1) gave a crystalline substance, which was recrystallized from hexane–ether to give the *product* (**2b**) (256 mg, 82%) as prisms, m.p. 66—67 °C (Found: M^+, 181.0730. $C_9H_{11}NO_3$ requires M, 181.0737); $\nu_{max.}$(KBr) 1 772, 1 738, and 1 600 cm^{-1}; δ_H($CDCl_3$) 1.60 (3 H, s, 1-Me), 2.13 (3 H, s, Ac), 2.70 (3 H, s, 2-Me), 4.00 (1 H, br s, 4-H), and 5.74 (1 H, d, J 1.0 Hz, 6-H).

5-*Acetoxy*-4-*allyl*-2-*azabicyclo*[2.2.0]*hex*-5-*en*-3-*one* (**2c**).—A solution of 4-acetoxy-3-allyl-2-pyridone (**1c**) (200 mg, 1.04 mmol) in a mixture of acetonitrile (37.5 ml) and ether (132.5 ml) was irradiated under argon by high-pressure mercury lamp (Ushio 450 W, Pyrex filter) for 1.5 h. The solvent was evaporated off under reduced pressure to give the *product* (**2c**) (178 mg, 88%) as prisms (from ether), m.p. 93—94 °C (Found: M^+, 193.0734. $C_{10}H_{11}NO_3$ requires M, 193.0737); $\nu_{max.}$(KBr) 3 230, 1 763, 1 710, and 1 603 cm^{-1}; δ_H($CDCl_3$) 2.15 (3 H, s, Ac), 2.62 (2 H, d, J 6.3 Hz, CH_2C=), 4.12 (1 H, s, 1-H), 4.9—5.3 (2 H, m, C=CH_2), 5.72 (1 H, s, 6-H), 5.79 (1 H, ddt, J 16.8, 9.2, and 6.3 Hz, CH=C), and 6.28 (1 H, br s, NH).

5-*Acetoxy*-6-*methyl*-2-*azabicyclo*[2.2.0]*hex*-5-*en*-3-*one* (**2e**).—A solution of 4-acetoxy-5-methyl-2-pyridone (**1d**) (115 mg, 0.69 mmol) in a mixture of acetonitrile (37.5 ml) and ether

(132.5 ml) was irradiated under argon by a high-pressure mercury lamp (Ushio 450 W, Pyrex filter) for 3 h. The solvent was evaporated off under reduced pressure, and the residue (116 mg) was subjected to silica gel (10 g) column chromatography. Elution with dichloromethane–methanol (30:1) gave a yellow oil, which was purified by preparative t.l.c. with hexane–ether (10:1) as developing solvent to give the product (**2e**) (70 mg, 61%) as prisms (from hexane–ether), m.p. 91—92 °C (Found: M^+, 167.0561. $C_8H_9NO_3$ requires M, 167.0581); $\nu_{max.}$(KBr) 3 160, 1762, 1 728, and 1 615 cm^{-1}; δ_H($CDCl_3$) 1.73 (3 H, d, J 1.7 Hz, 6-Me), 2.15 (3 H, s, Ac), 4.10 (1 H, d, J 2.5 Hz, 4-H), 4.38 (1 H, m, 1-H), and 6.40 (1 H, br s, NH).

5-*Acetoxy*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3a**).—A mixture of compound (**2a**) (305 mg, 2 mmol) and 10% Pd–C (48 mg) in methanol (18 ml) was shaken in hydrogen under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give a solid (286 mg), which was subjected to silica gel (5 g) column chromatography. Elution with dichloromethane–methanol (50:1) gave the *product* (**3a**) (275 mg, 89%) as prisms (from hexane–ether), m.p. 62—63 °C (Found: C, 54.3; H, 5.85; N, 8.95. $C_7H_9NO_3$ requires C, 54.2; H, 5.85; N, 9.05%); $\nu_{max.}$(KBr) 3 410, 1 732, and 1 720 cm^{-1}; δ_H($CDCl_3$) 2.03 (3 H, s, Ac), 2.16 (1 H, ddd, J 4.8, 1.0, and 13.5 Hz, 6-H_{endo}), 2.79 (1 H, ddd, J 8.8, 4.5, and 13.5 Hz, 6-H_{exo}), 3.78 (1 H, ddd, J 2.5, 4.5, and 1.0 Hz, 1-H), 4.01 (1 H, dt, J 7.5 and 2.5 Hz, 4-H), 5.13 (1 H, ddd, J 7.5, 8.8, and 4.8 Hz, 5-H), and 6.81 (1 H, br s, NH).

5-*Acetoxy*-1,2-*dimethyl*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3b**).—A mixture of compound (**2b**) (177 mg, 0.98 mmol) and 10% Pd–C (28 mg) in methanol (10.5 ml) was shaken in hydrogen under atmospheric pressure for 1 h. The solvent was evaporated off under reduced pressure, and the residue (156 mg, 87%) was recrystallized from hexane–ether to give the *product* (**3b**) as prisms, m.p. 70.5—71.5 °C (Found: C, 58.85; H, 7.3; N, 7.4. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.15; N, 7.65%); $\nu_{max.}$(KBr) 1 735 and 1 237 cm^{-1}; δ_H($CDCl_3$) 1.47 (3 H, s, 1-Me), 2.00 (3 H, s, Ac), 2.10 (1 H, dd, J 5.2 and 13.5 Hz, 6-H_{endo}), 2.43 (1 H, dd, J 8.0 and 13.5 Hz, 6-H_{exo}), 2.73 (3 H, s, 2-Me), 3.68 (1 H, d, J 8.0 Hz, 4-H), and 5.15 (1 H, td, J 8.0 and 5.2 Hz, 5-H).

5-*Acetoxy*-4-*propyl*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3d**).—A mixture of compound (**2c**) (135 mg, 1.04 mmol) and 10% Pd–C (22 mg) in methanol (8 ml) was shaken in hydrogen under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give a solid, which was subjected to silica gel (4 g) column chromatography. Elution with dichloromethane–methanol (50:1) gave the *product* (**3d**) (121 mg, 88%) as an oil (Found: M^+, 197.1044. $C_{10}H_{15}NO_3$ requires M, 197.1050); $\nu_{max.}$($CHCl_3$) 3 390 and 1 752 cm^{-1}; δ_H($CDCl_3$) *inter alia* 2.02 (1 H, ddd, J 14.5, 4.0, and 1.0 Hz, 6-H_{endo}), 2.03 (3 H, s, Ac), 2.70 (1 H, br d, J 4.2 Hz, 1-H), 4.95 (1 H, dd, J 8.5 and 4.0 Hz, 5-H), and 6.82 (1 H, br s, NH).

5-*Acetoxy*-6-*methyl*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3e**).—By the same procedure as described above for the synthesis of compound (**3a**), the 2-azabicyclo[2.2.0]hexan-3-one (**3e**) was obtained in quantitative yield from compound (**2e**) as prisms (from dichloromethane–ether), m.p. 121—122 °C (Found: C, 56.7; H, 6.6; N, 8.15. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.55; N, 8.3%); $\nu_{max.}$(KBr) 3 190, 1 750sh, and 1 737 cm^{-1}; δ_H($CDCl_3$) 1.07 (3 H, d, J 7.0 Hz, 6-Me), 2.65—3.15 (1 H, m, 6-H), 3.82 (1 H, ddd, J 4.7, 2.7, and 1.5 Hz, 1-H), 3.93 (1 H, dt, J 8.8 and 2.7 Hz, 4-H), 5.22 (1 H, ddd, J 8.8, 7.5, and 1.5 Hz, 5-H), and 6.50 (1 H, br s, NH).

5-*Acetoxy*-1-*methyl*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3f**).—A mixture of compound (**2f**)[4] (78 mg, 0.47 mmol) and 10% Pd–C (10 mg) in methanol (4 ml) was shaken in hydrogen under atomspheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the product (**3f**) (76 mg, 96%) as prisms (from dichloromethane–ether), m.p. 106—107 °C (Found: C, 56.7; H, 6.6; N, 8.15. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.55; N, 8.3%); $\nu_{max.}$(KBr) 3 210, 1 738, 1 713, and 1 380 cm^{-1}; δ_H($CDCl_3$) 1.45 (3 H, s, 1-Me), 2.03 (3 H, s, Ac), 2.25 (1 H, dd, J 13.7 and 5 Hz, 6-H), 2.63 (1 H, dd, J 13.7 and 8.5 Hz, 6-H), 3.70 (1 H, dd, J 7.7 and 2.5 Hz, 4-H), 5.13 (1 H, ddd, J 7.7, 8.5, and 5.0 Hz, 5-H), and 6.45 (1 H, br s, NH).

4-(2-*Acetoxyethyl*)*azetidin*-2-*one* (**9a**).—Sodium borohydride (70 mg, 1.85 mmol) and potassium carbonate (50 mg, 0.36 mmol) were added to a stirred, ice-cooled solution of compound (**3a**) (29 mg, 0.19 mmol) in methanol (5 ml). The mixture was stirred at room temperature for 1 h. Acetone (0.5 ml) was added to the reaction mixture, and the resulting mixture was neutralized with acetic acid–methanol (1:10), and concentrated under reduced pressure to give a residue, to which pyridine (1 ml) and acetic anhydride (2 ml) were added. The mixture was stirred at room temperature for 46 h, and concentrated under reduced pressure to give an oily residue, to which water was added. The mixture was extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the product (**9a**) (22 mg, 75%) as needles (from ether), m.p. 44—47 °C (lit.,[9] 44—47 °C); $\nu_{max.}$($CHCl_3$) 3 420, 1 760, and 1 740 cm^{-1}.

4-(2-*Acetoxyethyl*)-1,4-*dimethylazetidin*-2-*one* (**9b**).—Sodium borohydride (103 mg, 2.7 mmol) and potassium carbonate (70 mg, 0.5 mmol) were added to a stirred, ice-cooled solution of compound (**3b**) (50 mg, 0.27 mmol) in methanol (7 ml). The mixture was stirred at room temperature for 1 h, and acetone (0.5 ml) was added to the reaction mixture. The resulting mixture was neutralized with acetic acid–methanol (1:10), and concentrated under reduced pressure to give a residue, to which acetic anhydride (2 ml) and pyridine (1 ml) were added. The mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure to give a residue, to which water and dichloromethane were added. The dichloromethane layer was washed with water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the *product* (**9b**) (48 mg, 95%) as an oil (Found: M^+, 185.1049. $C_9H_{15}NO_3$ requires M, 185.1050); $\nu_{max.}$(neat) 1 753sh, 1 735, 1 383, and 1 235 cm^{-1}; δ_H($CDCl_3$) 1.37 (3 H, s, 4-Me), 1.96 (2 H, t, J 6.5 Hz, 4-CH_2CH_2O), 2.00 (3 H, s, Ac), 2.60 (1 H, d, J 14.5 Hz, 3-H_a), 2.68 (3 H, s, 1-Me), 2.90 (1 H, d, J 14.5 Hz, 3-H_b), and 4.09 (2 H, t, J 6.5 Hz, 4-CH_2CH_2O).

4-(2-*Acetoxyethyl*)-3-*propylazetidin*-2-*one* (**9d**).—By the same procedure as described for the synthesis of compound (**9a**), the azetidin-2-one (**9d**) was obtained as an oil in quantitative yield from compound (**3d**); $\nu_{max.}$($CHCl_3$) 3 410, 1 755sh, and 1 737 cm^{-1}; δ_H($CDCl_3$) *inter alia* 2.07 (3 H, s, Ac), 2.7—2.95 (1 H, m, 3-H), 3.38 (1 H, ddd, J 2.5, 6.0, and 6.8 Hz, 4-H), and 6.41 (1 H, br s, NH).

4-(2-*Acetoxy*-1-*methylethyl*)*azetidin*-2-*one* (**9e**).—By the same procedure as described above for the synthesis of compound (**9a**), the *azetidin*-2-*one* (**9e**) was obtained as prisms (from ether) in quantitative yield from compound (**3e**), m.p. 68—70 °C (Found: C, 56.0; H, 7.65; N, 8.1. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.65; N, 8.2%); $\nu_{max.}$(KBr) 3 280, 1 738, and 1 727 cm^{-1}; δ_H($CDCl_3$) 0.95 (3 H, d, J 6.7 Hz, CH*Me*), 1.6—2.15 (1 H, m, C*H*Me), 2.03 (3 H, s, Ac), 2.60 (1 H, ddd, J 14.5, 2.8, and 1.2 Hz, 3-H), 3.05 (1 H, ddd, J 14.5, 5.0, and 2.5 Hz, 3-H), 3.40 (1 H, ddd, J 8.5, 5.0, and 2.8 Hz, 4-H), 3.83 (1 H, dd, J 10.8 and 5.7 Hz,

CHHO), 4.20 (1 H, dd, *J* 10.8 and 4.8 Hz, CHHO), and 6.28 (1 H, br s, NH).

4-(2-*Acetoxyethyl*)-4-*methylazetidin*-2-*one* (**9f**).—By the same procedure as described above for the synthesis of compound (**9a**), the *azetidin*-2-*one* (**9f**) was obtained as prisms (from ether) in 84% yield from compound (**3f**), m.p. 75 °C (Found: C, 55.95; H, 7.4; N, 8.15. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.65; N, 8.2%); $\nu_{max.}$(KBr) 3 220, 1 760, 1 745, and 1 723 cm^{-1}; $\delta_H(CDCl_3)$ 1.45 (3 H, s, 4-Me), 2.00 (2 H, t, *J* 6.3 Hz, 4-CH_2), 2.03 (3 H, s, Ac), 2.60 (1 H, dd, *J* 14.5 and 1.5 Hz, 3-H), 2.90 (1 H, dd, *J* 14.5 and 1.5 Hz, 3-H), 4.17 (2 H, t, *J* 6.3 Hz, CH_2O), and 6.32 (1 H, br s, NH).

4-(*Dimethyl-t-butylsiloxy*)-2-*pyridone* (**1g**).—A mixture of 4-hydroxy-2-pyridone (0.56 g, 5 mmol), TBDSC (0.75 g, 5 mmol), and triethylamine (0.61 g, 6 mmol) in anhydrous DMF (8 ml) was shaken at room temperature for 16 h. The reaction mixture was poured into ice–water, and the mixture was extracted with ether. The extract was dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crystalline residue was purified by recrystallization from anhydrous hexane to give the product (**1g**)* needles (1.0 g, 88%), m.p. 114 °C (softened at 105 °C); $\nu_{max.}(CHCl_3)$ 1 640 cm^{-1}; $\lambda_{max.}(Et_2O)$ 295 nm; $\delta_H(CDCl_3)$ 0.26 (6 H, s, $SiMe_2$), 0.96 (9 H, s, SiBu^t), 5.8—5.9 (2 H, m, 3- and 5-H), and 7.22 (1 H, d, *J* 6 Hz, 6-H).

5-(*Dimethyl-t-butylsiloxy*)-2-*azabicyclo*[2.2.0]*hex*-5-*en*-3-*one* (**2g**).—An ethereal solution (300 ml) of the pyridone (**1g**), prepared by the reaction of 4-hydroxy-2-pyridone (0.56 g, 5 mmol) with TBDSC (0.75 g, 5 mmol) in the presence of triethylamine (0.61 g, 6 mmol) in anhydrous DMF (8 ml), was irradiated by Rayonet photochemical reactor lamps (Cat. No. RPR-3000 Å) for 8 h. The solvent was evaporated off under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–ethyl acetate (3:1) gave the *product* (**2g**) (0.65 g, 57%)† as needles (from hexane), m.p. 65 °C (Found: C, 58.4; H, 8.2; N, 6.2. $C_{11}H_{19}NO_2Si$ requires C, 58.6; H, 8.5; N, 6.2%); $\nu_{max.}(CHCl_3)$ 3 425, 1 750, 1 625, and 1 615 cm^{-1}; $\delta_H(CDCl_3)$ 0.22 (6 H, s, $SiMe_2$), 0.93 (9 H, s, SiBu^t), 4.20 (2 H, br s, 1- and 4-H), 5.08 (1 H, br s, 6-H), and 6.15 (1 H, br s, NH).

5-(*Dimethyl-t-butylsiloxy*)-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3g**).—A mixture of compound (**2g**) (0.3 g, 1.3 mmol) and 10% Pd–C (40 mg) in methanol (10 ml) was shaken in hydrogen under atmospheric pressure until the absorption of hydrogen ceased. The catalyst was filtered off, and the filtrate was condensed under reduced pressure. The crystalline residue was purified by recrystallization from hexane to give the *product* (**3g**) (2.28 g, 92%) as leaves, m.p. 75 °C (Found: C, 57.65; H, 8.9; N, 5.9. $C_{11}H_{21}NO_2Si$ requires C, 58.1; H, 9.3; N, 6.15%); $\nu_{max.}(CHCl_3)$ 3 400 and 1 750 cm^{-1}; $\delta_H(CDCl_3)$ 0.08 (3 H, s, SiMe), 0.10 (3 H, s, SiMe), 0.88 (9 H, s, SiBu^t), 2.01 (1 H, dd, *J* 14 and 4 Hz, 6-H_{endo}), 2.64 (1 H, ddd, *J* 14, 8, and 4 Hz, 6-H_{exo}), 3.58—3.75 (1 H, m, 1-H), 3.88 (1 H, ddd, *J* 8, 2.5 and 2.5 Hz, 4-H: the signal becomes a dd with *J* 8 and 2.5 Hz on addition of D_2O), 4.55 (1 H, td, *J* 8 and 4 Hz, 5-H), and 6.38 (1 H, br s, NH).

5-*Benzyloxy*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**3h**).—A mixture of compound (**2h**)[4] (201 mg, 1 mmol) and 10% Pd–C (50 mg) in methanol (30 ml) was shaken in hydrogen under atmospheric pressure until the absorption of hydrogen ceased. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The crystalline residue was purified by recrystallization from hexane–acetone to give the *product* (**3h**) (137 mg, 67%) as needles, m.p. 105—107 °C (Found: C, 71.0; H, 6.7; N, 6.7. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); $\nu_{max.}(CHCl_3)$ 3 400 and 1 755 cm^{-1}; $\delta_H(CDCl_3)$ 2.06 (1 H, dd, *J* 14 and 4.5 Hz, 6-H_{endo}), 2.52 (1 H, ddd, *J* 14, 8.5 and 4 Hz, 6-H_{exo}), 3.72 (1 H, m, 1-H), 3.99 (1 H, dd, *J* 7 and 2 Hz, 4-H), 4.30 (1 H, m, 5-H), 4.34 (1 H, d, *J* 12 Hz, CHHPh), 4.70 (1 H, d, *J* 12 Hz, CHHPh), 6.40 (1 H, br s, NH), and 7.24—7.40 (5 H, m, Ph).

rel-(1R,4R,5S)-5-*Hydroxy*-2-*azabicyclo*[2.2.0]*hexan*-3-*one* (**4a**).—(i) A mixture of compound (**3g**) (100 mg, 0.44 mmol) and PTSA monohydrate (30 mg) in THF–water (5:1) (6 ml) was kept at room temperature for 12 h. Ethyl acetate (30 ml) and pyridine (15 mg) were added successively to the reaction mixture. The resulting mixture was dried over anhydrous sodium sulphate, and condensed under reduced pressure. The crystalline residue was purified by recrystallization from acetone to give the *product* (**4a**) (40 mg, 80%) as plates, m.p. 116—120 °C (Found: C, 52.95; H, 6.25; N, 12.15. $C_5H_7NO_2$ requires C, 53.1; H, 6.25; N, 12.4%); $\nu_{max.}$(KBr) 3 200 and 1 715 cm^{-1}; $\delta_H(CD_3OD)$ 1.94 (1 H, dd, *J* 14 and 5 Hz, 6-H_{endo}), 2.68 (1 H, ddd, *J* 14, 9, and 5 Hz, 6-H_{exo}), 3.64—3.78 (1 H, m, 1-H), 3.82 (1 H, dd, *J* 9 and 3 Hz, 4-H), and 4.56 (1 H, td, *J* 9 and 5 Hz, 5-H).

(ii) A mixture of compound (**3h**) (304 mg, 1.5 mmol) and 10% Pd–C (60 mg) in methanol (9 ml) containing 0.3% conc. hydrochloric acid (v/v) was shaken in hydrogen under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The crystalline residue was purified by recrystallization from acetone to give the product (**4a**) (137 mg, 81%).

Synthesis of 4-(2-*Acetoxyethyl*)*azetidin*-2-*one* (**9a**) *from Compound* (**4a**).—Sodium borohydride (102 mg, 2.7 mmol) and potassium carbonate (40 mg, 0.29 mmol) were added to a stirred, ice-cooled solution of compound (**4a**) (30 mg, 0.27 mmol) in methanol (4 ml). The mixture was stirred at room temperature for 3 h, and neutralized with acetic acid–methanol (1:10). The solvent was evaporated off under reduced pressure to give a residue, to which pyridine (1 ml) and acetic anhydride (2 ml) were added. The mixture was shaken at room temperature for 18 h. The mixture was concentrated under reduced pressure to give a residue, to which water and chloroform were added. The chloroform layer was washed with water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The resulting residue (40 mg) was subjected to column chromatography. Elution with hexane–ethyl acetate (1:2) gave the product (**9a**) (30 mg, 71%) as needles (from hexane), m.p. 44—47 °C; $\nu_{max.}(CHCl_3)$ 1 755 and 1 735 cm^{-1}. The spectral data were identical in every respect with those of an authentic sample prepared from compound (**3a**).

4-(*Benzyloxycarbonylmethyl*)*azetidin*-2-*one* [*Benzyl* (4-*Oxoazetidin*-2-*yl*)*acetate*] (**10**).—Compound (**4a**) (15 mg, 0.135 mmol) was added to a stirred, ice-cooled solution of potassium carbonate (20 mg, 0.145 mmol) and potassium permanganate (26 mg, 0.165 mmol) in water (2 ml). The mixture was stirred and ice-cooled for 2 h. Ethanol (0.1 ml) was then added to the reaction mixture, and the resulting mixture was stirred at room temperature for 30 min. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (1 ml), and benzyl bromide (51 mg, 0.3 mmol) was added to the solution. The mixture was stirred at room temperature for 4 h. The solvent was evaporated off under reduced pressure to give a residue, to which dichloromethane was added. The precipitate was filtered off, and the filtrate was

* Owing to its relative instability, satisfactory microanalytical data were not obtained for compound (**1g**) and the ethereal extract of this compound from the reaction mixture was immediately used for the photolysis.

† The yield corresponds to the overall yield from 4-hydroxy-2-pyridone.

concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (1:1) gave the product (**10**) (19.5 mg, 66%) as leaves (from hexane–dichloromethane), m.p. 95—96 °C (lit.,[10] 93—94 °C).

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References

1 Part 26, T. Naito, Y. Makita, S. Yazaki, and C. Kaneko, *Chem. Pharm. Bull.*, 1986, **34**, 1505.
2 Preliminary communications, C. Kaneko, T. Naito, and A. Saito, *Tetrahedron Lett.*, 1984, **25**, 1591; N. Katagiri, M. Sato, T. Naito, M. Muto, T. Sakamoto, S. Saikawa, and C. Kaneko, *ibid.*, p. 5665.
3 K. Hirai, *J. Synth. Org. Chem. Jpn.*, 1980, **38**, 97; 'Chemistry and Biology of β-Lactam Antibiotics,' eds. R. B. Morin and M. Gorman, Academic Press, New York, 1982, vol 2; M. Shibuya, *J. Synth. Org. Chem. Jpn.*, 1983, **41**, 62; R. Labita and C. Morin, *J. Antibiot.*, 1984, **37**, 1103; W. Durckheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180.
4 C. Kaneko, K. Shiba, H. Fujii, and Y. Momose, *J. Chem. Soc., Chem. Commun.*, 1980, 1177; H, Fujii, K. Shiba, and C. Kaneko, *ibid.*, p. 537.
5 S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1135; R. W. Ratcliffe, T. N. Salzman, and B. G. Christensen, *Tetrahedron Lett.*, 1980, **21**, 31; S. Takano, C. Kasahara, and K. Ogasawara, *Chem. Lett.*, 1982, 631; L. D. Cama, K. J. Wildonger, R. Guthikonda, R. W. Ratcliffe, and B. G. Christensen, *Tetrahedron*, 1983, **39**, 2531; D. H. Shih, J. A. Fayter, and B. G. Christensen, *Tetrahedron Lett.*, 1984, **25**, 1684.
6 R. Adams and A. W. Schrecker, *J. Chem. Soc.*, 1948, 1186.
7 T. Sugasawa, K. Sakakura, and T. Toyoda, *Chem. Pharm. Bull.*, 1974, **22**, 763; K. Takeda and K. Igarashi, *Shionogi Kenkyusho Nempo*, 1951, **1**, 1.
8 C. Wang, *J. Heterocycl. Chem.*, 1970, **7**, 389.
9 F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1130.
10 J. H. Bateson, A. J. G. Baxter, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3242.

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