Preparation of optically active photopyridone by lipase-catalysed asymmetric resolution[1]

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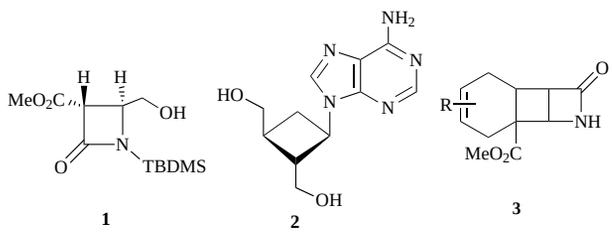
Optically active photopyridones possessing synthetic versatility are obtained conveniently by lipase-catalysed enantioselective acylation or hydrolysis of racemic photopyridones, and the absolute configurations are determined by chemical correlation, X-ray crystallographic and CD spectral analyses.

Introduction

Racemic photoisomers, 3-oxo-2-azabicyclo[2.2.0]hex-5-enes, of 2(1*H*)-pyridones containing β-lactam and cyclobutene moieties have great potential as synthetic intermediates. Photopyridines would be synthons of carbapenems **1**,[2] carbocyclic oxetanocin **2**,[3] which has a similar activity as AZT (zidovudine) against human immunodeficiency virus (HIV), and also of polycyclic ring systems contained a fused β-lactam, **3**.[4] Despite the many

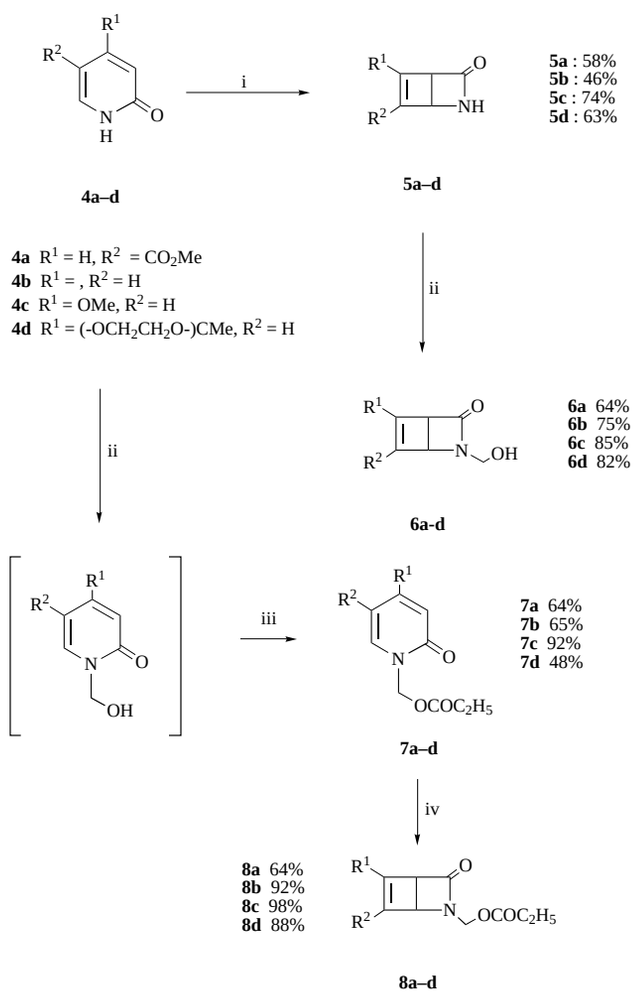


1 **2** **3**

synthetic studies of racemic photopyridones,[5] little attention has been focussed on those of optically active photopyridones.[6] Lipase enzymes have been used for syntheses of optically active organic compounds: the enzymic reaction requires no coenzymes, and lipases are commercially available. Most substrates of the lipase-catalysed asymmetric resolution have been compounds in which stereogenic carbon atoms were adjacent to the reaction site.[7] In this paper, we report the lipase-catalysed enantioselective acylation or hydrolysis of synthetic versatile racemic photopyridones **6a–d** and **8a–d**, in which chiral centres are remote from the reactive site. The *N*-hydroxymethyl group of the chiral photopyridones (−)-**6a–d** obtained is easily removed under the basic conditions used.[7] Moreover, the chiral photopyridone (−)-**6a** obtained is potentially a valuable synthetic intermediate; since it contains an electrophile group it may act as a dienophile leading to richly functionalized, polycyclic ring systems with a fused β-lactam ring.[4] The optically active tetracyclic compound is expected to possess interesting chemical properties and pharmacological activity. The absolute configurations of the optically active photopyridones obtained were determined by chemical correlation, X-ray crystallographic analysis using the anomalous dispersion effect of oxygen atoms or a bromine atom, and/or CD spectral analysis. Although CD spectral analysis has been a useful method for determination of the absolute configuration in optically active compounds, its application for optically active photopyridones has not yet been reported.

Results and discussion

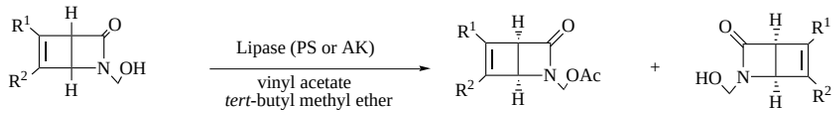
We selected eight kinds of racemic photopyridones, **6a** or **8a** (act as a dienophile), **6b** or **8b** (simple photopyridone), **6c** or **8c** (synthetic intermediate of carbapenem antibiotics), and **6d** or **8d** (synthetic intermediate of carbocylic oxetanocin analogue) as substrates for lipase-catalysed resolution. Preparations of the substrates, the racemic *N*-(hydroxymethyl)photopyridones **6a–d** or the racemic *N*-(propionyloxymethyl)photopyridones **8a–d**, for lipase-catalysed acylation or hydrolysis are described in Scheme 1. The racemic *N*-(hydroxymethyl)photopyridones



Scheme 1 *Reagents and conditions*: i, *hv*, benzene or MeCN, 24 h; ii, $HCHO_{aq.}$, K_2CO_3 (cat.), sonication; iii, $(EtCO)_2O$, pyridine, room temp., 24 h; iv, *hv*, benzene, 24 h

6a–d[7d,e] were obtained from treatment of the racemates **5a–d**, derived from the photoisomerization of the pyridones **4a–d**, with paraformaldehyde under sonication in good yields. The racemic *N*-(propionyloxymethyl)photopyridones **8a–d** were

Table 1 Enzyme-catalysed enantioselective acylation of compounds (±)-**6a–d**

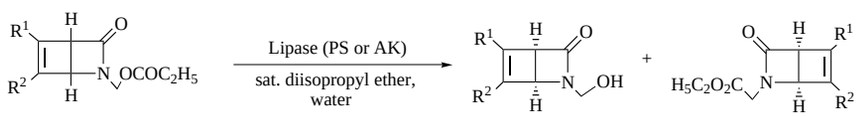


(±)-**6a–d** (–)-**9a–d** (+)-**6a–d**

Substrate	R^1	R^2	Lipase	Time (*t*/h)	Temp. (*T*/°C)	Chemical yield (%)	Product (−)-**9a–d** $[\alpha]_D$	(CHCl$_3$)	E.e. (%)[a]	Recovery of compound (+)-**6a–d** Chemical yield (%)	E.e (%)
						(−)-**9a**					
6a	H	CO_2Me	PS	4	20	8	−342	(*c* 1.32)		70	10
			AK	2	20	10	−325	(*c* 0.10)		68	12
						(−)-**9b**					
6b	H	H	PS	4	20	14	−94	(*c* 1.50)	97	56	18
			AK	2	20	26	−95	(*c* 3.82)	98	67	31
						(−)-**9c**					
6c	OMe	H	PS	0.5	20	12	−36	(*c* 0.81)	90	81	9
			AK	0.5	20	10	−41	(*c* 1.55)	93	86	11
						(−)-**9d**					
6d	$\overline{OCH_2CH_2OCMe}$	H	PS	1	20	14	−35	(*c* 0.58)	91	79	17
			AK	1	20	3	−33	(*c* 0.06)	81	93	3

[a] Optical yields were determined by HPLC analysis (Chiralpak AS, EtOH or Pr^{i}OH–hexane).

Table 2 Enzyme-catalysed enantioselective hydrolysis of compounds (±)-**8a–d**



(±)-**8a–d** (–)-**6a–d** (+)-**8a–d**

Substrate	R^1	R^2	Lipase	Time (*t*/h)	Temp. (*T*/°C)	Chemical yield (%)	Product (−)-**6a–d** $[\alpha]_D$	(CHCl$_3$)	E.e. (%)[a]	Recovery of compound (+)-**8a–d** Chemical yield (%)	E.e. (%)
						(−)-**6a**					
8a	H	CO_2Me	PS	4	20	23	−450	(*c* 1.59)	96	72	33
			AK	8	25	21	−465	(*c* 1.21)	>98	72	44
						(−)-**6b**					
8b	H	H	PS	2	28	34	−240	(*c* 1.49)	>98	57	51
			AK	2	20	25	−275	(*c* 1.83)	>98	73	34
						(−)-**6c**					
8c	OMe	H	PS	2	20	28	−134	(*c* 2.44)	95	65	49
			AK	2	20	27	−135	(*c* 1.44)	97	67	40
						(−)-**6d**					
8d	$\overline{OCH_2CH_2OCMe}$	H	PS	4	20	12	−68	(*c* 1.81)	92	72	18
			AK	16	25	28	−70	(*c* 1.59)	92	61	52

[a] Optical yields were determined by HPLC analysis (Chiralpak AS, EtOH or Pr^{i}OH–hexane).

synthesized by photoisomerization of the 1-propionyloxymethyl-2(1*H*)-pyridones **7a–d** also in good yields. The pyridones **7a–d** were obtained by *N*-hydroxymethylation and subsequent *O*-propionylation of the pyridones **4a–d**. The structures of the pyridones **4d**, **7a–d** and the racemic photopyridones **5a–d**, **6a–d**, **8a–d** were characterized by IR, ^{1}H NMR spectroscopy, mass and high-resolution mass spectrometry (HRMS).

First, we examined the transesterification of the racemic photopyridones **6a–d** by the two lipases [PS (*pseudomonas cepacia*) and AK (*pseudomonas fluorescens*)] in *tert*-butyl methyl ether using vinyl acetate as an acyl donor, to obtain the chiral acetates (−)-**9a–d**. The lipases, PS and AK, can assume a variety of conformations in solution to accommodate a wide variety of substrates. The enantiomeric excess (e.e.) of the chiral acetates (−)-**9a–d** and the recovered chiral alcohols (+)-**6a–d**, which were isolated from the mixture by silica gel column chromatography, was determined by HPLC on a chiral phase. The results are summarized in Table 1. Lipase PS catalysed the transesterification of the hydroxy group on substrates (±)-**6b–d** rapidly with a high degree of enantioselectivity (90–97% e.e.) in spite of the relatively long distance between the reaction site and the asymmetric centre. Although lipase AK catalysed the same reaction of substrates (±)-**6b,c** with a high enantioselectivity similar to that for lipase PS, compound (±)-**6d** showed a moderate enantioselectivity with lipase AK. In the acylation, a satisfactory result in terms of the chemical yield was not obtained. In addition, the recovered alcohols (+)-**6b–d** were obtained in only low optical yields (3–31% e.e.). The e.e. of product (−)-**9a** or (+)-**6a** was not confirmed by HPLC analysis on several chiral phases.

Next, we examined the resolution of the racemic esters **8a–d** under hydrolytic conditions using diisopropyl ether saturated with water in the presence of two lipases, PS and AK. The e.e. of the chiral alcohols (−)-**6a–d** obtained and the recovered chiral esters (+)-**8a–d** (18–52% e.e.) was determined by HPLC

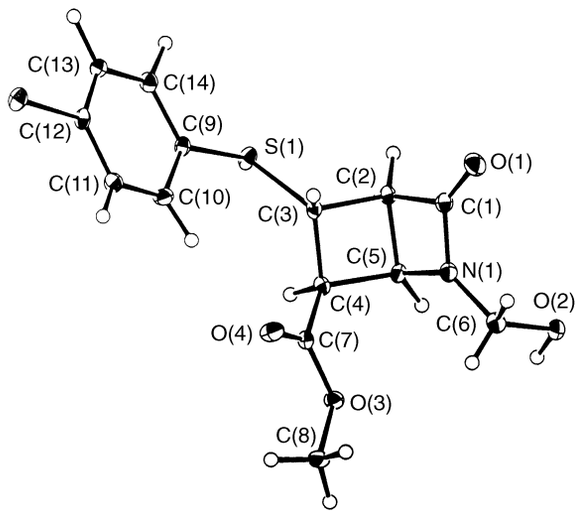


Fig. 1 ORTEP drawing of compound (−)-**11**: thermal ellipsoids are scaled to include 30% probability

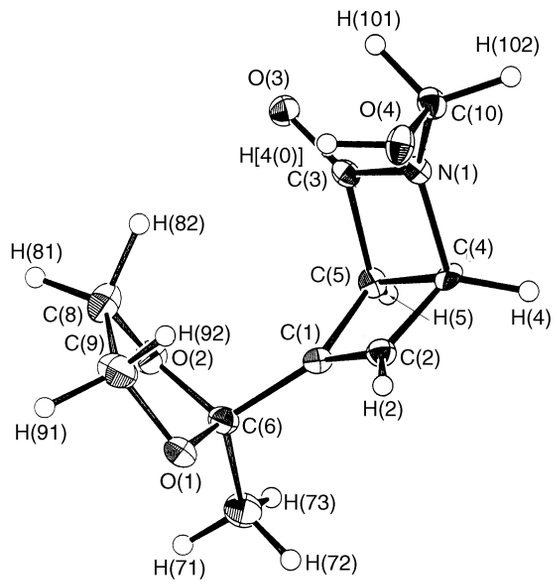
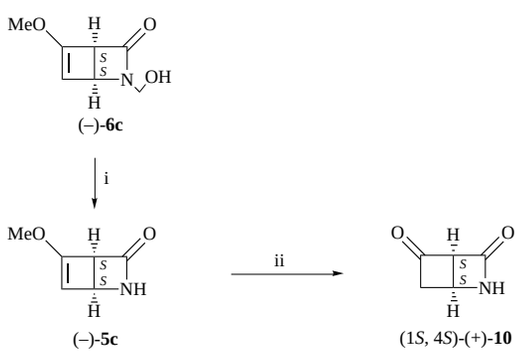


Fig. 2 ORTEP drawing of compound (−)-**6d**: thermal ellipsoids are scaled to include 30% probability

on a chiral phase in a similar manner to that for the above transesterification. The results are summarized in Table 2. Both lipases, PS and AK, catalysed the hydrolysis of the propionyloxy group on esters (±)-**8a–d** rapidly with a high degree of enantioselectivity (92–98% e.e.) and moderate chemical yields; catalysis of substrate (±)-**8b** gave the best results [(−)-**6b**, > 98% e.e.]. From the above results for the lipase-catalysed resolution of photopyridones using lipase PS or AK, it was concluded that the lipase-catalysed hydrolysis was operative, rather than lipase-catalysed acylation.

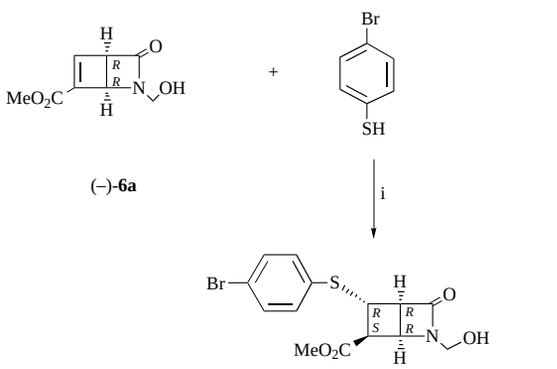
The absolute configurations of the chiral photopyridones were determined by chemical correlation, X-ray crystallographic analyses, and CD spectral measurements. The CD spectra of optically active photopyridones have not yet been reported. The absolute stereochemistry of (1*S*,4*S*)-(−)-**6c** was confirmed by conversion into a synthetic intermediate of chiral carbapenem antibiotics, as shown in Scheme 2. The chiral



Scheme 2 *Reagents and conditions*: i, 28% NH_3, MeOH (20%); ii, $(CO_2H)_2{\cdot}2H_2O$, silica gel, CH_2Cl_2 (60%)

N-unsubstituted photopyridone (−)-**5c** {$[\alpha]_D$ −308 (*c* 0.8, $CHCl_3$)}† obtained by dehydroxymethylation of compound (−)-**6c** was treated with oxalic acid and silica gel to give the chiral carbapenem antibiotics intermediate (1*S*,4*S*)-(+)-**10**[6a] {$[\alpha]_D$ +325 (*c* 0.10, $CHCl_3$); lit.,[6a] $[\alpha]_D$ +338 (*c* 1.05, $CHCl_3$)}. The absolute configuration of the chiral photopyridone (−)-**6a** was determined to be 1*R*,4*R* from that of the chiral Michael adduct (1*R*,4*R*,5*R*,6*S*)-(−)-**11** as shown in Fig. 1, which was determined by employing the large X-ray anomalous dispersive effects of Br and S atoms (Fig. 1). The chiral photopyridone (−)-**6a** appeared to be a strong Michael acceptor in Michael reactions. A Michael reaction of ene (−)-**6a** with 4-bromo(thiophenol) was carried out under basic reaction conditions (Et_3N, dichloro-

† $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.



Scheme 3 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, room temp.

methane, room temp., 12 h) and the chiral Michael adduct (−)-**11** destined for X-ray crystallographic analysis was obtained stereoselectively in good yield (80%) (Scheme 3). For an X-ray absolute determination of compound (−)-**6d**, introduction of any heavy atom was unsuccessful. Therefore, a direct determination using the anomalous dispersive effect of oxygen atoms was attempted by careful data collection and re-measurements of Bijveot pairs at low temperature (170 K). As a result, the absolute stereochemistry of compound (−)-**6d** was determined unambiguously to be 1*S*,4*R* as shown in Fig. 2. The molecule (−)-**6d** was a strained skeleton with non-standard bond lengths. For example, the central C(4)–C(5) bond (1.619 Å) and the double bond C(1)=C(2) (1.373 Å) are considerably lengthened, and the lengths of other bonds are also longer than those of the normal bonds. The dihedral angle between two *cis*-fused four-membered rings is 114.0°.

The CD spectral analysis of UV-active compounds is considered a reliable method for the determination of absolute configuration. The CD spectra of (−)-**6a,c,d** showed similarly strong negative Cotton effects at 247.0, 217.0 and 224.5 nm, respectively (Fig. 3). The absolute configuration of (1*S*,4*R*)-(−)-**6b** was determined by comparing a negative Cotton effect at 228.5 nm with that of (−)-**6a,c,d** (Fig. 3). Therefore, the absolute configurations of the chiral *N*-(acetoxymethyl)-photopyridones (−)-**9a–d** were determined to be (1*R*,4*R*), (1*S*,4*R*), (1*S*,4*S*) and (1*S*,4*R*), respectively.

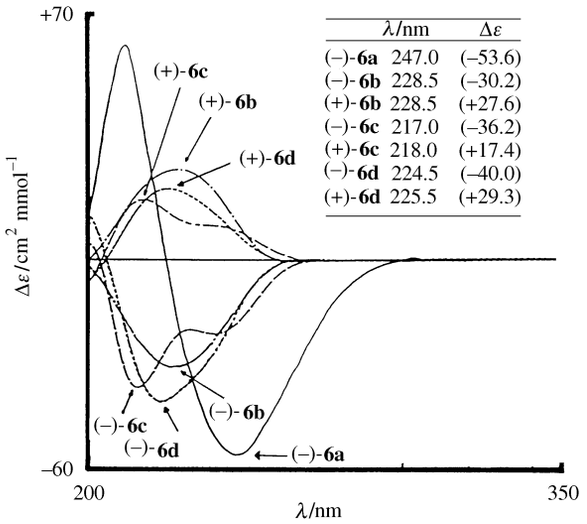
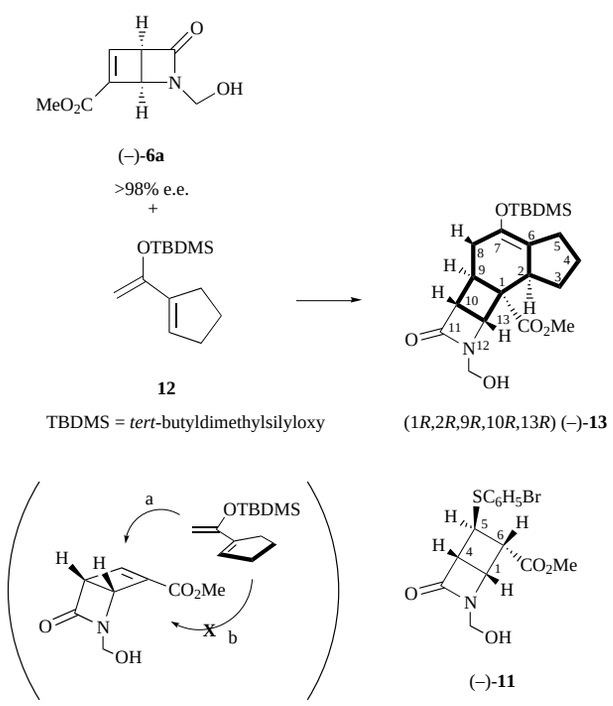


Fig. 3 CD spectra of compound (−)-**6a–d** and (+)-**6b–d**

Next, we investigated Diels–Alder cyclization of the chiral photopyridone (−)-**6a** with a diene since Diels–Alder adducts thus obtained could have a skeleton of the protoilludane type, such as is found in formannosin or illudol ring systems.[8] Furthermore, the β-lactam ring in the adduct may also be cleaved easily. A mixture of photopyridone (−)-**6a** and the diene **12**[9] in toluene was heated at 45 °C, and a new type of tetracyclic compound, methyl (−)-*cis*-*transoid*-*cis*-7-(*tert*-butyldimethylsilyloxy)-12-hydroxymethyl-11-oxo-12-azatetracyclo[7.4.0.0^{2,6}.0^{10,13}] tridec-6-ene-1-carboxylate (−)-**13**, with a fused β-lactam ring system, was regio- and stereo-selectively obtained in 20% yield (Scheme 4). It was suggested that the product (−)-**13** was



Scheme 4 *Reagents and conditions*: i, toluene 45 °C, 36 h (20% yield)

the 1:1 cycloadduct of substrates (−)-**6a** and **12** from the mass spectrum and that the IR spectrum showed the corresponding lactam and ester carbonyl absorptions. Although the ^{1}H NMR spectrum provided the chemical shift, multiplicity, and integration for the assigned structure, the indication of the relative stereochemistry could not be gained from the data. Considering that the chiral adduct (−)-**13** was stereoselectively obtained, the *cis-anti* stereochemistry [C(1)–C(9) positions] of compound (−)-**13** was deduced from the basis of steric factors; the diene **12** attacked from the less hindered side of substrate (−)-**6a** (upper side a). Furthermore, the *cis-transoid* stereochemistry was confirmed by the observation of ^{1}H NMR data. Namely, the coupling constants between H(1) and H(6) having a *cis* configuration and between H(4) and H(5) having a *trans* configuration were observed as 6.9 and 3.3. Hz, respectively, in compound (−)-**11** whose structure was determined by X-ray analysis. In compound (−)-**13**, the coupling constant between H(9) and H(10) was observed as 2.9 Hz, almost identical to *trans* isomers' value (3.3 Hz) for compound (−)-**11**. In addition, an NOE enhancement was observed between H(10) and Hβ(8e) while no NOE enhancement was produced between H(9) and H(13) in (−)-**13**. From these results, the *cis-transoid* stereochemistry of compound (−)–**13** was determined. Furthermore, the *cis* stereochemistry [C(1)–CO_2Me–H(2) position] was also confirmed by the observation of NOE enhancement between H(2) and H(9), and the absence of any NOE between H(2) and H(13).

We explored a simple preparation of optically active photopyridones by lipase-catalysed asymmetric resolution and determination of their absolute configuration using CD spectral analysis, which was the first example of an application of this technique relating to optically active photopyridones. The methods reported here should be applicable to the preparation of optically active photopyridones.

Experimental

Mps were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a Perkin-Elmer 1725X spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-PMX 60, a JEOL JNM-EX 270 (^{1}H NMR 270 MHz, ^{13}C NMR 67.8 MHz) and JNM-GSX400 spectrometers with $SiMe_4$ as an internal standard. The coupling patterns are indicated as follows: singlet = s, doublet = d, triplet = t, multiplet = m and broad = br. *J* Values are given in Hz. MS were taken on a Hitachi RMG-6MG and a JEOL-JNM-DX 303 spectrometer. Optical rotations were measured with a JASCO-DIP-360 digital polarimeter. CD were measured with a JASCO J-720 spectrophotometer. The e.e. values of the *N*-hydroxymethyl and *N*-acetoxymethyl bicyclic lactams were determined by HPLC analysis using chiralpak AS.

Synthesis of photopyridones (±)-5a–d

A solution of pyridones **4a,c,d** (4 mmol) in benzene (1000 cm^3) or **4b** (4 mmol) in MeCN (1000 cm^3) under nitrogen was irradiated for 24 h respectively. The solvent was removed, and the residue was chromatographed on silica gel (Et_2O) to afford the corresponding photopyridones (±)-**5a–d**.

Methyl 3-oxo-2-azabicyclo[2.2.0]hex-5-ene-6-carboxylate 5a.[1] Yield 290 mg (58%), prisms (from Et_2O), mp 85–86 °C (lit.,[1] 83–84 °C).

3-Oxo-2-azabicyclo[2.2.0]hex-5-ene 5b.[5d] Yield 230 mg (46%), prisms (from Et_2O), mp 64–65 °C (lit.,[5d] 65.5–66.5 °C).

5-Methoxy-3-oxo-2-azabicyclo[2.2.0]hex-5-ene 5c.[5b] Yield 370 mg (74%), prisms (from Et_2O), mp 89–90 °C (lit.,[5b] 94–95 °C).

5-[1,1-(Ethylenedioxy)ethyl]-3-oxo-2-azabicyclo[2.2.0]hex-5-ene 5d. Yield 315 mg (63%), prisms (from Et_2O), mp 48–50 °C; HRMS *m/z*: Found: M$^+$, 181.0695. $C_9H_{11}NO_3$ requires M, 181.0739; ν_{max}(film)/cm^{-1} 1746 (NC=O); δ_H($CDCl_3$) 1.55 (3 H, s, CH_3), 3.98–4.02 (4 H, m, CH_2CH_2), 4.18 (1 H, dd, $J_{1,4}$ 2.2, $J_{4,6}$ 1.1, 4-H), 4.31 (1 H, d, $J_{1,4}$ 2.2, 1-H), 6.02 (1 H, br s, NH) and 6.39 (1 H, d, $J_{4,6}$ 1.1, 6-H); δ_C($CDCl_3$) 23.2 (CH_3), 46.3 (C-1), 58.2 (C-4), 64.9 and 65.3 (CH_2CH_2), 104.9 (CCH_3), 134.5 (C-6), 154.3 (C-5) and 171.3 (C=O).

Synthesis of *N*-hydroxymethyl-3-oxo-2-azabicyclo[2.2.1]hex-5-enes (±)-6a–d

A mixture of lactam (±)-**5a–d** (10 mmol), paraformaldehyde (1 g) and potassium carbonate (0.2 g, 1.5 mmol) in water (20 cm^3) was reacted under sonication for 6 h at room temperature. Extraction with $CHCl_3$, drying ($MgSO_4$), and removal of the solvent *in vacuo* provided the crude *N*-hydroxymethyl analogue, which was purified by silica gel TLC (Et_2O) to give (±)-**6a–d**.

Methyl 2-hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene-6-carboxylate 6a. Yield 228 mg (64%), prisms (from Et_2O); mp 73–74 °C; HRMS *m/z*: Found: M^+, 183.0500. $C_8H_9NO_4$ requires M, 183.0532; ν_{max}(film)/cm^{-1} 1752 (NC=O) and 1724 (C=O); δ_H($CDCl_3$) 3.81 (3 H, s, CH_3), 4.22 (1 H, dd, $J_{1,4}$ 2.2, $J_{4,5}$ 1.1, 4-H), 4.61 (1 H, dd, $J_{1,5}$ 2.5, $J_{1,4}$ 2.2, 1-H), 4.62 (1 H, d, *J* 11.3, CH_2), 4.87 (1 H, d, *J* 11.3, CH_2) and 7.10 (1 H, dd, $J_{1,5}$ 2.5, $J_{4,5}$ 1.1, 5-H); δ_C($CDCl_3$) 52.3 (CH_3), 52.6 (C-1), 55.5 (C-4), 66.5 (CH_2), 144.1 (C-6), 145.2 (C-5), 163.1 and 166.9 (C=O).

2-Hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene 6b. Yield 296 mg (75%), an oil; HRMS *m/z*: Found: M^+, 125.0528. $C_6H_7NO_2$ requires M, 125.0477; ν_{max}(film)/cm^{-1} 1731 (NC=O); δ_H($CDCl_3$) 4.19 (1 H, br s, 4-H), 4.45 (1 H, t, $J_{1,4} = J_{1,5} = 2.3$, 1-H), 4.54 (1 H, d, *J* 11.2, CH_2), 4.81 (1 H, d, *J* 11.2, CH_2), 6.52 (1 H, t, $J_{1,5} = J_{5,6} = 2.3$, 5-H) and 6.67 (1 H, dd, $J_{5,6}$ 2.3, $J_{1,6}$ 1.3, 6-H); δ_C($CDCl_3$) 53.7 (C-1), 58.0 (C-4), 66.4 (CH_2), 138.3 (C-5), 142.5 (C-6) and 170.6 (C=O).

2-Hydroxymethyl-5-methoxy-3-oxo-2-azabicyclo[2.2.0]hex-5-ene 6c. Yield 315 mg (85%), prisms (from Et_2O); mp 70–72 °C; HRMS *m/z*: Found: M^+, 155.0548. $C_7H_9NO_3$ requires M, 155.0582; *m/z* 155 (M^+); ν_{max}(film)/cm^{-1} 1729 (NC=O); δ_H($CDCl_3$) 3.67 (3 H, s, CH_3), 4.24 (1 H, br s, 4-H), 4.28 (1 H, br s, 1-H), 4.50–4.64 (2 H, m, CH_2) and 5.18 (1 H, br s, 6-H); δ_C($CDCl_3$) 46.0 (C-1), 56.9 (CH_3), 59.1 (C-4), 66.6 (CH_2), 101.5 (C-6), 158.5 (C-5) and 169.3 (C=O).

5-[1,1-(Ethylenedioxy)ethyl]-2-hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene 6d. Yield 287 mg (82%), prisms (from Et_2O); mp 72–73 °C; HRMS *m/z*: Found: M^+, 211.0852. $C_{10}H_{13}NO_4$ requires M, 211.0845; *m/z* 211 (M^+); ν_{max}(film)/cm^{-1} 1743 (NC=O); δ_H($CDCl_3$) 1.53 (3 H, s, CH_3), 4.00 (4 H, s, CH_2CH_2), 4.20 (1 H, dd, $J_{1,4}$ 2.2, $J_{4,6}$ 1.2, 4-H), 4.32 (1 H, d, $J_{1,4}$ 2.2, 1-H), 4.57 (1 H, d, *J* 11.4, NCH_2), 4.81 (1 H, d, *J* 11.4, NCH_2) and 6.50 (1 H, d, $J_{4,6}$ 1.2, 6-H); δ_C($CDCl_3$) 23.0 (CH_3), 49.2 (C-1), 56.8 (C-4), 65.0 and 65.4 (CH_2CH_2), 66.5 (NCH_2), 104.8 (CCH_3), 134.4 (C-6), 152.2 (C-5) and 169.6 (C=O).

Synthesis of *N*-propionyloxymethyl-2(1*H*)-pyridones (±)-7a–d

A mixture of a pyridone (±)-**4a–d** (24 mmol), paraformaldehyde (3.0 g) and potassium carbonate (1.5 g, 0.01 mol) in water (30 cm^3) was treated under sonication for 3 h at room temperature. After filtration of the reaction mixture, the aqueous layer was extracted with $CHCl_3$ (3 × 20 cm^3). The combined organic layer was concentrated to give the crude product, which was used for the next step. Ethanol (40 cm^3) and propionic anhydride (36 mmol) were added to the crude product and the mixture was stirred at room temperature before being concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2. The solution was washed successively with saturated aq. $NaHCO_3$, aq. HCl (2.7 mol dm^{-3}), and saturated aq. NaCl. The organic layer was dried over $MgSO_4$ and was then concentrated *in vacuo*. The crude product was chromatographed on a silica gel column eluted with diethyl ether to give title products **7a–d.**

Methyl 6-oxo-1-propionyloxymethyl-1,6-dihydropyridine-3-carboxylate 7a. Yield 3.7 g (64%), prisms (from Et_2O); mp 62–63 °C; HRMS *m/z*: Found: M^+, 239.0810. $C_{11}H_{13}NO_5$ requires M, 239.0794; ν_{max}(film)/cm^{-1} 1748 (C=O), 1723 (C=O) and 1678 (NC=O); δ_H($CDCl_3$) 1.14 (3 H, t, *J* 7, CH_2CH_3), 2.42 (2 H, q, *J* 7, CH_2CH_3), 3.87 (3 H, s, CO_2CH_3), 5.89 (2 H, s, NCH_2), 6.54 (1 H, d, $J_{3,4}$ 10, 3-H), 7.84 (1 H, dd, $J_{3,4}$ 10, $J_{4,6}$ 2, 4-H) and 8.37 (1 H, d, $J_{4,6}$ 2, 6-H).

1-Propionyloxymethyl-2(1*H*)-pyridone 7b. Yield 3.7 g (65%), oil; HRMS *m/z*: Found: M^+, 181.0713. $C_9H_{11}NO_3$ requires M, 181.0739; ν_{max}(film)/cm^{-1} 1747 (C=O) and 1672 (NC=O); δ_H($CDCl_3$) 1.13 (3 H, t, *J* 8, CH_3), 2.40 (2 H, q, *J* 8, CH_2CH_3), 5.93 (2 H, s, NCH_2), 6.20 (1 H, t, $J_{4,5} = J_{5,6} = 7$, 5-H), 6.60 (1 H, d, $J_{3,4}$ 7, 3-H), 7.39 (1 H, t, $J_{3,4} = J_{4,5} = 7$, 4-H) and 7.60 (1 H, dd, $J_{5,6}$ 7, $J_{4,6}$ 2, 6-H).

4-Methoxy-1-propionyloxymethyl-2(1*H*)-pyridone 7c. Yield 4.7 g (92%), prisms (from Et_2O); mp 38–40 °C; HRMS *m/z*: Found: M^+, 211.0838. $C_{10}H_{13}NO_4$ requires M, 211.0845; ν_{max}(film)/cm^{-1} 1743 (C=O) and 1665 (NC=O); δ_H($CDCl_3$) 1.13 (3 H, t, *J* 3.5, CH_2CH_3), 2.40 (2 H, q, *J* 3.5, CH_2CH_3), 3.80 (3 H, s, OCH_3), 5.76–6.10 (4 H, m, 3- and 5-H, NCH_2) and 7.33–7.56 (1 H, m, 6-H).

4-[1,1-(Ethylenedioxy)ethyl]-1-propionyloxymethyl-2(1*H*)-pyridone 7d. Yield 2.1 g (48%), prisms (from Et_2O); mp 83–85 °C; HRMS *m/z*: Found: M^+, 267.1096. $C_{13}H_{17}NO_5$ requires M, 267.1107; ν_{max}(film)/cm^{-1} 1746 (C=O) and 1672 (NC=O); δ_H($CDCl_3$) 1.13 (3 H, t, *J* 8, CH_2CH_3), 1.57 (3 H, s, CH_3), 2.40 (2 H, q, *J* 8, CH_2CH_3), 3.70–4.13 (4 H, m, CH_2CH_2), 5.86 (2 H, s, NCH_2), 6.23 (1 H, dd, $J_{5,6}$ 8, $J_{3,5}$ 2, 5-H), 6.68 (1 H, d, $J_{3,5}$ 2, 3-H) and 7.46 (1 H, d, $J_{5,6}$ 8, 6-H).

Synthesis of *N*-(propionyloxy)photopyridones (±)-8a–d

A solution of pyridones **7a–d** (4 mmol) in benzene (1000 cm^3) under nitrogen was irradiated for 24 h. The solvent was removed, and the residue was chromatographed on silica gel [diethyl ether–hexane (1:1)] to afford the corresponding photopyridones **8a–d**.

Methyl 3-oxo-2-propionyloxymethyl-2-azabicyclo[2.2.0]hex-5-ene-6-carboxylate 8a. Yield 640 mg (64%), oil; HRMS *m/z*: Found: M^+, 239.0794. $C_{11}H_{13}NO_5$ requires M, 239.0811; ν_{max}(film)/cm^{-1} 1772 (NC=O) and 1729 (C=O); δ_H($CDCl_3$) 1.13 (3 H, t, *J* 7.6, CH_2CH_3), 2.30 (2 H, q, *J* 7.6, CH_2CH_3), 3.80 (3 H, s, CO_2CH_3), 4.22 (1 H, dd, $J_{4,5}$ 1.1, $J_{1,4}$ 2.2, 4-H), 4.72 (1 H, dd, $J_{1,5}$ 2.5, $J_{1,4}$ 2.2, 1-H), 5.13 (1 H, d, *J* 11.0, NCH_2), 5.30 (1 H, d, *J* 11.0, NCH_2) and 7.14 (1 H, dd, $J_{1,5}$ 2.5, $J_{4,5}$ 1.1, 5-H); δ_C($CDCl_3$) 8.7 (CH_2CH_3), 27.3 (CH_2CH_3), 51.9 (CO_2CH_3), 53.9 (C-1), 55.5 (C-4), 66.0 (NCH_2), 144.2 (C-6), 146.0 (C-5), 161.5, 167.4 and 173.6 (C=O).

3-Oxo-2-propionyloxymethyl-2-azabicyclo[2.2.0]hex-5-ene 8b. Yield 920 mg (92%), oil; HRMS *m/z*: Found: M^+, 181.0659. $C_9H_{11}NO_3$ requires M, 181.0738; ν_{max}(film)/cm^{-1} 1757 (NC=O) and 1747 (C=O); δ_H($CDCl_3$) 1.15 (3 H, t, *J* 7.5, CH_2CH_3), 2.36 (2 H, q, *J* 7.5, CH_2CH_3), 4.19 (1 H, br s, 4-H), 4.48 (1 H, t, $J_{1,4} = J_{1,5} = 2.6$, 1-H), 5.14 (2 H, s, NCH_2) and 6.50–6.55 (2 H, m, CH=CH); δ_C($CDCl_3$) 8.9 (CH_3), 27.3 (CH_2), 55.2 (C-1), 58.5 (C-4), 65.7 (NCH_2), 139.3 (C-5), 141.9 (C-6), 170.0 and 174.6 (C=O).

5-Methoxy-3-oxo-2-propionyloxymethyl-2-azabicyclo[2.2.0]-hex-5-ene 8c. Yield 980 mg (98%), yellow oil; HRMS *m/z*: Found: M^+, 211.0827. $C_{10}H_{13}NO_4$ requires M, 211.0844; ν_{max}(film)/cm^{-1} 1762 (NC=O) and 1742 (C=O); δ_H($CDCl_3$) 1.15 (3 H, t, *J* 7.5, CH_2CH_3), 2.36 (2 H, q, *J* 7.5, CH_2CH_3), 3.66 (3 H, s, OCH_3), 4.25 (1 H, br s, 4-H), 4.30 (1 H, br s, 1-H), 5.06 (1 H, d, *J* 11.2, NCH_2), 5.07 (1 H, br s, 6-H) and 5.16 (1 H, d, *J* 11.2, NCH_2); δ_C($CDCl_3$) 8.9 (CH_3), 27.3 (CH_2), 47.7 (C-1), 56.9 (OCH_3), 59.7 (C-4), 66.0 (NCH_2), 101.0 (C-6), 158.9 (C-5), 168.8 and 174.6 (C=O).

5-[1,1-(Ethylenedioxy)ethyl]-3-oxo-2-propionyloxymethyl-2-azabicyclo[2.2.0]hex-5-ene 8d. Yield 880 mg (88%), oil; HRMS *m/z*: Found: M^+, 267.1114. $C_{13}H_{17}NO_5$ requires M, 267.1109; ν_{max}(film)/cm^{-1} 1762 (NC=O) and 1746 (C=O); δ_H($CDCl_3$) 1.15 (3 H, t, *J* 7.5, CH_2CH_3), 1.52 (3 H, s, CH_3), 2.35 (2 H, q, *J* 7.5, CH_2CH_3), 3.92–4.03 (4 H, m, CH_2CH_2), 4.18 (1 H, br s, 4-H), 4.36 (1 H, d, $J_{1,4}$ 2.3, 1-H), 5.10 (1 H, d, *J* 11.2, NCH_2), 5.16 (1 H, d, *J* 11.2, NCH_2) and 6.36 (1 H, d, $J_{4,6}$ 1.0, 6-H); δ_C($CDCl_3$) 8.9 (CH_2CH_3), 23.1 (CCH_3), 27.3 (CH_2CH_3), 50.7 (C-1), 57.2 (C-4), 64.9 and 65.3 (CH_2CH_2), 65.8 (NCH_2), 104.8 (CCH_3), 133.9 (C-6), 153.1 (C-5), 169.4 and 174.5 (C=O).

General procedure for lipase-catalysed transesterification of *N*-hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-enes (±)-6a–d

A mixture of substrate (±)-**6a–d** (2.4 mmol), lipase (PS or AK) (0.3 g) and vinyl acetate (7.2 mmol) in *tert*-butyl methyl ether (100 cm^3) was stirred at room temperature. The lipase was removed by filtration and was washed with diethyl ether. The combined organic layer was concentrated, and the residue was chromatographed on a silica gel column eluted with diethyl ether to give the corresponding *N*-acetoxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-**9a–d** and *N*-hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (+)-**6a–d**. Enantiomeric excesses of products (−)-**9a–d** or (+)-**6a–d** were determined by HPLC analysis using a chiral column [Chiralpak AS, EtOH or Pr^iOH–hexane]. The reaction times, enantiomeric excesses, and chemical yields are listed in Table 1. The spectral data of the products (−)-**9a–d** or (+)-**6a–d** were identical with those of the corresponding racemic compounds (±)-**9a–d** or (±)-**6a–d**, respectively.

(1*R*,4*R*)-(−)-Methyl 2-acetoxymethyl-3-oxo-2-azabicyclo-[2.2.0]hex-5-ene-6-carboxylate (−)-9a. Oil; HRMS *m/z*: Found: M^+, 225.0652. $C_{10}H_{11}NO_5$ requires M, 225.0657; ν_{max}(film)/cm^{-1} 1769 (NC=O), 1747 (C=O) and 1727 (C=O); $\delta_H(CDCl_3)$ 2.03 (3 H, s, Ac), 3.80 (3 H, s, CO_2CH_3), 4.22 (1 H, br s, 4-H), 4.71 (1 H, t, $J_{1,4} = J_{1,5} = 2.3$, 1-H), 5.14 (1 H, d, *J* 11.2, CH_2), 5.28 (1 H, d, *J* 11.2, CH_2) and 7.14 (1 H, d, $J_{1,5}$ 2.3, 4-H); $\delta_C(CDCl_3)$ 20.7 ($OCOCH_3$), 51.9 (CO_2CH_3), 53.8 (C-1), 55.5 (C-4), 66.0 (CH_2), 144.2 (C-6), 146.0 (C-5), 161.5, 167.4 and 171.2 (C=O).

(1*S*,4*R*)-(−)-2-Acetoxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-9b. Oil; HRMS *m/z*: Found: M^+, 167.0635. $C_8H_9NO_3$ requires M, 167.0582; ν_{max}(film)/cm^{-1} 1746 (C=O); $\delta_H(CDCl_3)$ 2.08 (3 H, s, Ac), 4.19 (1 H, br s, 4-H), 4.49 (1 H, t, $J_{1,4} = J_{1,5} = 2.3$, 1-H), 5.11 (1 H, d, *J* 11.5, CH_2), 5.15 (1 H, d, *J* 11.5, CH_2) and 6.52–6.56 (2 H, m, 5- and 6-H); $\delta_C(CDCl_3)$ 20.7 (CH_3), 55.2 (C-1), 58.5 (C-4), 65.8 (CH_2), 139.3 (C-5), 141.9 (C-6), 170.0 and 171.1 (C=O); HPLC, flow rate 1.0 cm^3 min^{-1}; hexane–ethanol 90:10; Chiralpak AS; t_R (min) 18 (+)-**9b**, 26 (−)-**9b**.

(1*S*,4*S*)-(−)-2-Acetoxymethyl-5-methoxy-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-9c. Oil; HRMS *m/z*: Found: M^+, 197.0717. $C_9H_{11}NO_4$ requires M, 197.0688; ν_{max}(film)/cm^{-1} 1762 (NC=O) and 1746 (C=O); $\delta_H(CDCl_3)$ 2.08 (3 H, s, Ac), 3.66 (3 H, s, OCH_3), 4.25 (1 H, br s, 4-H), 4.30 (1 H, br s, 1-H) and 5.03–5.16 (3 H, m, 6-H, CH_2); $\delta_C(CDCl_3)$ 20.7 (CH_3), 47.7 (C-1), 56.9 (CH_3O), 59.7 (C-4), 66.1 (CH_2), 100.9 (C-6), 158.9 (C-5), 168.8 and 171.1 (C=O). HPLC, flow rate 0.5 cm^3 min^{-1}; hexane–ethanol 90:10; Chiralpak AS; t_R (min) 42 (+)-**9c**, 48 (−)-**9c**.

(1*S*,4*R*)-(−)-Acetoxymethyl-5-[1,1-(ethylenedioxy)ethyl]-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-9d. Yellow oil; HRMS *m/z*: Found: M^+, 253.0946. $C_{12}H_{15}NO_5$ requires M, 253.0950; ν_{max}(film)/cm^{-1} 1758 (NC=O) and 1746 (C=O); $\delta_H(CDCl_3)$ 1.52 (3 H, s, CCH_3), 2.08 (3 H, s, Ac), 3.93–4.03 (4 H, m, CH_2CH_2), 4.18 (1 H, br s, 4-H), 4.36 (1 H, d, $J_{1,4}$ 2.3, 1-H), 5.09 (1 H, d, *J* 11.2, CH_2), 5.14 (1 H, d, *J* 11.2, CH_2) and 6.38 (1 H, d, $J_{1,6}$ 1.3, 6-H); $\delta_C(CDCl_3)$ 20.7 (CH_3), 23.1 (CCH_3), 50.7 (C-1), 57.2 (C-4), 64.9 and 65.3 (CH_2CH_2), 65.8 (NCH_2), 104.8 (CCH_3), 133.8 (C-6), 153.1 (C-5), 169.3 and 171.1 (C=O). HPLC, flow rate 1.0 cm^3 min^{-1}; hexane–ethanol 90:10; Chiralpak AS; t_R (min) 35 (+)-**9d**, 44 (−)-**9d**.

General procedure for lipase-catalysed hydrolysis of *N*-propionyloxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-enes (±)-8a–d

A mixture of an ester (±)-**8a–d** (1.9 mmol) and lipase (PS or AK) (0.3 g) in diisopropyl ether saturated with water (100 cm^3) was stirred at room temperature. The lipase was removed by filtration. The filtrate was concentrated, and the residue was chromatographed on a silica gel column eluted with diethyl ether to give the corresponding *N*-hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-**6a–d** and *N*-propionyloxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (+)-**8a–d**. Enantiomeric excesses of products (+)-**8a–d** or (−)-**6a–d** were determined by HPLC analysis using a chiral column (Chiralpak AS, EtOH or Pr^iOH–hexane). The reaction times, enantiomeric excesses and chemical yields are listed in Table 2. The spectral data of the products (−)-**6a–d** or (+)-**8a–d** were identical with those of the corresponding racemic compounds (±)-**6a–d** or (±)-**8a–d**, respectively.

(1*R*,4*R*)-(−)-Methyl 2-hydroxymethyl-3-oxo-2-azabicyclo-[2.2.0]hex-5-ene-6-carboxylate (−)-6a. Prisms (from Et_2O); mp 72–73 °C; HPLC flow rate 0.5 cm^3 min^{-1}; hexane–ethanol 80:20; Chiralpak AS; t_R (min) 24 (+)-**6a**, 31 (−)-**6a**.

(1*S*,4*R*)-(−)-2-Hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-6b. Oil; HPLC flow rate 0.5 cm^3 min^{-1}; hexane–ethanol 95:5; Chiralpak AS; t_R (min) 45 (−)-**6b**, 51 (+)-**6b**.

(1*S*,4*S*)-(−)-2-Hydroxymethyl-5-methoxy-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-6c. Prisms (from Et_2O); mp 68–70 °C; HPLC flow rate 0.5 cm^3 min^{-1}; hexane–ethanol 85:15; Chiralpak AS; t_R (min) 20 (−)-**6c**, 22 (+)-**6c**.

(1*S*,4*R*)-(−)-5-[1,1-(Ethylenedioxy)ethyl]-2-hydroxymethyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-6d. Prisms (from Et_2O); mp 72–73 °C; HPLC flow rate 0.5 cm^3 min^{-1}; hexane–isopropyl alcohol 90:10; Chiralpak AS; t_R (min) 35 (+)-**6d**, 40 (−)-**6d**.

Michael reaction of photopyridine (−)-6a with 4-bromo(thiophenol)

A mixture of compound (−)-**6a** (100% e.e., 20 mg, 0.11 mmol), 4-bromo(thiophenol) (20 mg, 0.11 mmol) and Et_3N (11 mg, 0.11 mmol) in CH_2Cl_2 (10 cm^3) was stirred for 12 h at room temperature. The solvent was removed and the residue was chromatographed on a silica gel column to give (1R,4R,6S)-(−)-*methyl* 5-(4-*bromophenylthio*)-2-*hydroxymethyl*-3-*oxo*-2-*azabicyclo*[2.2.0]*hexane*-6-*carboxylate* (−)-**11** (33 mg, 80%), prisms (from $CHCl_3$–hexane); mp 137–139 °C; ν_{max}(KBr)/cm^{-1} 1745 and 1727; $[a]_D$ −57 (*c* 0.3, $CHCl_3$); $\delta_H(CDCl_3)$ 2.87 (1 H, br s, OH), 3.40 (1 H, dd, *J* 5.8, *J* 6.9, 6-H), 3.55 (1 H, dd, *J* 2.9, *J* 3.3, 4-H), 3.73 (3 H, s, CO_2CH_3), 4.29 (1 H, dd, *J* 2.9, *J* 6.9, 1-H), 4.42 (1 H, dd, *J* 3.3, *J* 5.8, 5-H), 4.66 (1 H, dd, *J* 8.0, *J* 11.7, CH_2OH), 4.77 (1 H, dd, *J* 8.0, *J* 11.7, CH_2OH), 7.19 (2 H, dd, *J* 1.8, *J* 6.6, 4-BrC_6H_4) and 7.46 (2 H, dd, *J* 1.8, *J* 6.6, 4-BrC_6H_4); $\delta_C(CDCl_3)$ 41.3 (C-1), 49.4 (C-6), 51.0 (C-5), 52.6 (CH_3), 55.7 (C-4), 65.8 (CH_2), 121.2, 131.0, 132.5 and 133.0 (4-BrC_6H_4), 166.0 and 171.0 (C=O) (Found: C, 45.16; H, 3.79; N, 3.44. $C_{14}H_{14}BrNO_4S$ requires C, 45.17; H, 3.79; N, 3.76%); *m/z*: 372 (M^+).

(1*S*,4*S*)-(−)-5-Methoxy-3-oxo-2-azabicyclo[2.2.0]hex-5-ene (−)-5c

A solution of substrate (−)-**6c** (100% e.e., 0.6 g, 4.80 mmol) and aq. NH_3 (16.4 mol dm^{-3}; 0.6 cm^3) in MeOH (6 cm^3) was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was purified by silica gel TLC (Et_2O) to give title compound (−)-**5c**. The spectral data of the product was identical with those of racemate (±)-**5c**: 97 mg (20%), 100% e.e. [the e.e. was determined by HPLC analysis using a chiral column (Chiralpak AS, EtOH–hexane)], mp 92–93 °C; $[a]_D$ −308 (*c* 0.8, $CHCl_3$).

(1*S*,4*S*)-(+)-3,5-Dioxo-2-azabicyclo[2.2.0]hexane (+)-10

To a suspension of oxalic acid dihydrate (30 mg, 0.2 mmol), water (0.2 cm^3), and silica gel (2 g) was added a solution of compound (−)-**5c** (100% e.e., 0.2 g, 1.6 mmol) in CH_2Cl_2 (3 cm^3) and the mixture was stirred at room temperature for 2 h. Silica gel was removed by filtration. The filtrate was concentrated and the residue was recrystallized from CH_2Cl_2–diethyl ether to afford title dione (+)-**10**. The spectral data of the product were identical with those of (+)-**10**: yield 106 mg (60%); mp 92–94 °C; $[a]_D$ +325 (*c* 1.2, $CHCl_3$) {lit.,[6a] 94–96 °C, $[a]_D$ +338.5 (*c* 1.05, $CHCl_3$)}.

(1*R*,2*R*,9*R*,10*R*,13*R*)-(−)-*cis*-*transoid*-*cis*-Methyl 7-*tert*-butyldimethylsilyloxy-12-hydroxymethyl-11-oxo-12-azatetracyclo-[7.4.0.0^{2,6}.0^{10,13}]tridec-6-ene-1-carboxylate (−)-13

A solution of compound (−)-**6a** (100% e.e, 60 mg, 0.3 mmol) and diene **12** (0.27 cm^3, 2.1 mmol) in toluene (10 cm^3) was stirred for 24 h at 45 °C under N_2. The reaction mixture was concentrated to dryness *in vacuo*. The residue was subsequently purified by silica gel column chromatography with diethyl ether as eluent to afford the *adduct* (−)-**13** (81 mg, 20%), $[\alpha]_D$ −20 (*c* 0.7, $CHCl_3$); prisms (from CH_2Cl_2–Et_2O); mp 142–144 °C; HRMS *m/z*: Found: M^+, 407.2174. $C_{21}H_{33}NO_5Si$ requires M, 407.2128; ν_{max}(film)/cm^{-1} 1762 (NC=O); δ_H($CDCl_3$) 0.12 (6 H, d, *J* 1.6, $Si(CH_3)_2C(CH_3)_3$], 0.93 (9 H, s, $Si(CH_3)_2C(CH_3)_3$], 1.54–1.92 (4 H, m, CH_2CH_2), 2.08 (1 H, dd, *J* 12.8, $J_{8,9}$ 2.6, 8-H), 2.22–2.39 (2 H, m, CH_2), 2.41–2.56 (1 H, m, 8-H), 2.59–2.65 (1 H, m, 2-H), 2.94 (1 H, dd, $J_{10,13}$ 3.6, $J_{9,10}$ 2.9, 10-H), 3.25–3.29 (1 H, m, 9-H), 3.71 (3 H, s, CO_2CH_3), 3.87 (1 H, d, $J_{10,13}$ 3.6, 13-H), 4.68 (1 H, d, *J* 11.2, NCH_2) and 4.79 (1 H, d, *J* 11.2, NCH_2); δ_C($CDCl_3$) 3.7 [$Si(CH_3)_2C(CH_3)_3$], 25.6 [$Si(CH_3)_2C(CH_3)_3$], 26.0, 27.8 and 28.2 ($CH_2CH_2CH_2$), 33.7 (C-8), 40.0 (C-9), 44.0 (C-2), 50.6 (C-10), 52.1 (CO_2Me), 52.4 (C-13), 56.1 (C-1), 65.9 (NCH_2), 117.9 (C-6), 141.1 (C-7), 169.2 and 175.9 (C=O).

X-Ray structure determinations

Absolute structure determination of compound (−)-6d. $C_{10}H_{13}NO_4$, *M* = 211.22. Orthorhombic, *a* = 7.687(1), *b* = 19.010(3), *c* = 7.365(1) Å, *V* = 1048.2(2) Å^3 (cell constants were determined by least-squares refinement on diffractometer angles, 56 < 2θ < 67° for 25 automatically centred reflections, λ = 1.541 78 Å). Space group $P2_12_12_1$ (No. 19), *Z* = 4, D_x = 1.10 g cm^{-3}, μ(Cu-Kα) = 5.0 cm^{-1}. Prisms, crystal size = 0.20 × 0.20 × 0.25 mm, Rigaku AFC5R diffractometer (45 kV, 200 mA), temperature 170 K, graphite-monochromated Cu-Kα radiation, 2θ–ω scan mode, scan width = 1.0 + 0.35 tan θ, 2θ scan speed = 6° min^{-1}, a Friedel pair of [$F_o(h,k,l)$ and $F_o(-h,-k,-l)$] measured alternately, 2039 reflections within 5 < 2θ < 128° measured. Direct methods were applied for the location of all non-hydrogen atoms. Full-matrix least-squares refinement was employed with anisotropic thermal parameters. All hydrogen atoms were found in the difference Fourier syntheses and were refined isotropically. 1786 [$I_o > 2\sigma(I_o)$] Reflections were used in the refinement of 188 parameters. The weighting scheme $\omega = 4F_o^2/\sigma^2(F_o^2)$ with $\sigma(F_o)$ calculated from counting statistics. Finally, anomalous dispersion effects were introduced and then converged to give the final *R*-value of 0.0584 (R_w = 0.0697) and for its enantiomer an *R*-value of 0.0589 (R_w = 0.0705). For the correct absolute structure, final refinement gave goodness-of-fit = 1.37, the maximam shift/error = 0.0423 and the $\Delta\rho_{max}$ = 0.20 and $\Delta\rho_{min}$ = −0.21 e Å^{-3}. The difference *R* ratio for the two enantiomers was 1.008 and 1.011 for *R*- and R_w-values. Hamilton's *R*-factor ratio is rarely beyond *R* (1, 1506, 0.005) = 1.002 for 99.5% probability level.[10] To obtain the most reliability, careful re-measurements were examined for the more sensitive Bijvoet pairs. A total of 60 reflections with $I_o > 10\sigma(I_o)$ and with larger $\Delta F_c/[F_c(H) + F_c(-H)]$ were selected and all of their eight Bijvoet pairs were re-measured at slow scan speed (2° min^{-1}) with five repeats. In the order of large $\Delta F_c/[F_c(H) + F_c(-H)]$-values, the first 20 reflections all gave the correct sign relationships of nonequality between the F_o- and F_c-values for the average of four pairs. The following 30, 40, 50 and 60 reflections gave consistency of signs for numbers of 28, 34, 39 and 42 reflections, respectively. These results indicate that the determination of absolute configuration is correct, and is in agreement with results from CD spectral analyses.

Absolute structure determination of compound (−)-11. $C_{14}H_{14}BrNO_4S$, *M* = 372.23. Monoclinic, *a* = 6.063(4), *b* = 7.342(4), *c* = 16.497(6) Å, β = 93.47(3)°, *V* = 733.0(14) Å^3 (determined by least-squares refinement on diffractometer angles, for 25 automatically centred reflections, 30 < 2θ < 42°, λ = 0.710 69 Å). Space group $P2_1$ (No. 4), *Z* = 2, D_x = 1.69 g cm^{-3}, μ(Mo-Kα) = 29.25 cm^{-1}. Plates, crystal size = 0.15 × 0.30 × 0.40 mm, Rigaku AFC5R diffractometer (45 kV, 200 mA), *T* = 150 K, graphite-monochromated Mo-Kα radiation, 2θ–ω scan mode, scan width = (1.1 + 0.35 tan θ), 2θ scan speed = 6° min^{-1}. 2097 Reflections [only $F_o(h,k,l)$] were measured in the range of 3° < 2θ < 58°. Absorption correction was employed using the ψ-scan method (max., min. transmission factors = 1.0, 0.819). Direct methods were applied for the location of the Br atom, and the successive Fourier syntheses for the unique location of non-hydrogen atoms. Full-matrix least-squares refinement was employed with anisotropic thermal parameters for non-hydrogen atoms. All hydrogen atoms were found in the difference Fourier syntheses and were included without refinement. A total of 1837 [$I_o > 3\sigma(I_o)$] reflections were used in the refinement of 193 parameters. The weighting scheme $w = 4F_o^2/\sigma^2(F_o^2)$ with $\sigma(F_o)$ calculated from counting statistics. Finally, anomalous dispersion effects were introduced and refinement converged to give the final *R*-value of 0.036 (R_w = 0.041) and for its enantiomer an *R*-value of 0.047 (R_w = 0.054). For the correct absolute structure, final refinement gave goodness-of-fit = 1.76, the maximum shift/error = 0.08, and the $\Delta\rho_{max}$ = 0.32 and $\Delta\rho_{min}$ = −0.29 e Å^{-3}. The difference *R* ratio for two enantiomers (1.305 and 1.317 for *R*- and R_w-values) is significantly beyond the 99.5% confidence level. To enlarge the determination, we carried out a similar re-measurement in the case of compound (−)-**6d**. The 30 most sensitive Bijvoet pairs all gave consistency in their sign relationships. All computation programs and sources of scattering factor data are given in ref. 11. Full details of crystal data, fractional atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).‡

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‡ See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/100.

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