Tandem Beckmann and Huisgen–White rearrangement as an alternative to the Baeyer–Villiger oxidation of the bicyclo[3.3.1]nonane system: first asymmetric synthesis of (−)-dihydropalustramic acid.[1] X-Ray molecular structure of 2β-ethyl-9-phenylsulfonyl-9-azabicyclo[3.3.1]nonan-3-one

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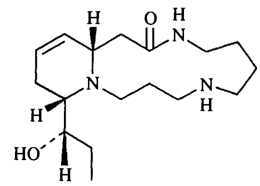
The transformation of the 'fork head ketone' 3b into the corresponding bicyclic lactone 13 *via* the Beckmann followed by the Huisgen–White rearrangement is described. Application of the method to a homochiral 2-ethyl-substituted bicyclic ketone (+)-3dα gave efficiently (−)-dihydropalustramic acid (−)-2a, a degradation product from the alkaloid palustrine 1, in good optical yield.

Introduction

The horsetail alkaloid palustrine 1[2] is a toxic principle of *Equisetum palustre* L., which is a harmful plant in moist meadows in Europe. It affects domestic animals, especially cows, causing loss of appetite, decreased weight, and decreased milk secretion.[3] (−)-Dihydropalustramic acid (−)-**2a** obtained from degradation of compound **1** is a key product in the structure elucidation of compound **1**,[4] and is also claimed to be a key intermediate in the synthesis of (−)-dihydropalustrine. Owing to the characteristic stereochemistry of the side chain (*threo-cis*) on the piperidine ring in compounds **1** or **2a**, several approaches have been reported.[5] Among them, we have been concerned with a design involving stereoselective cleavage of a nitrogen-bridged bicyclic system, 9-azabicyclo[3.3.1]nonan-3-one **3**. The versatility of compounds **3** and related systems for the synthesis of various bioactive natural products, such as indolizidine 223AB **4**,[6] monomorine I **5**[7] and (*cis*-6-methyltetrahydropyran-2-yl)acetic acid **6**,[8] has already been demonstrated.

Previous attempts to cleave the piperidone ring in sulfonamide **3c** *via* the Baeyer–Villiger oxidation were unsuccessful: the system displayed anomalous inactivity against the oxidation because of the back-side steric hindrance of the C^7-*endo* hydrogen which interfered with formation of the tetrahedral intermediate **7** in the considerably rigid molecule.[9]

On the other hand, Huisgen and White have reported the conversion of amides **8** into esters **9** by thermolysis of the corresponding *N*-nitroso intermediates **10**.[10] In this paper, we have examined, as an alternative to Baeyer–Villiger oxidation, the Huisgen–White rearrangement of a bicyclic lactam, benzyl 4-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate **11** which was derived readily by the Beckmann rearrangement of a ketoxime, benzyl 3-hydroxyimino-9-azabicyclo[3.3.1]nonane-9-carboxylate **12**, and we found the sequence to lead to the desired lactone, benzyl 4-oxo-3-oxa-10-azabicyclo-[4.3.1]decane-10-carboxylate **13**, in good yield (Scheme 1). Application of the sequence to a homochiral 2-ethyl derivative, (+)-benzyl 2-ethyl-3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (+)-**3d**, enabled us to complete the first asymmetric synthesis of compound (−)-**2a** in good optical yield.



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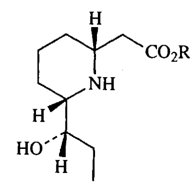
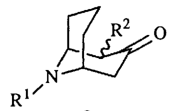


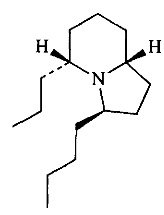
2

a R = H
b R = Me



3

a $R^1 = CO_2Me$, $R^2 = H$
b R^1 = Cbz, $R^2 = H$
c $R^1 = SO_2Ph$, $R^2 = H$
d R^1 = Cbz, R^2 = Et



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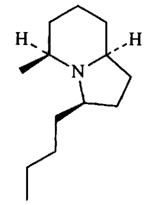

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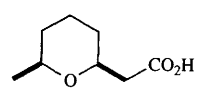

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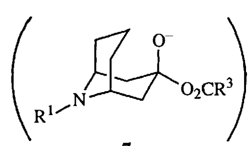
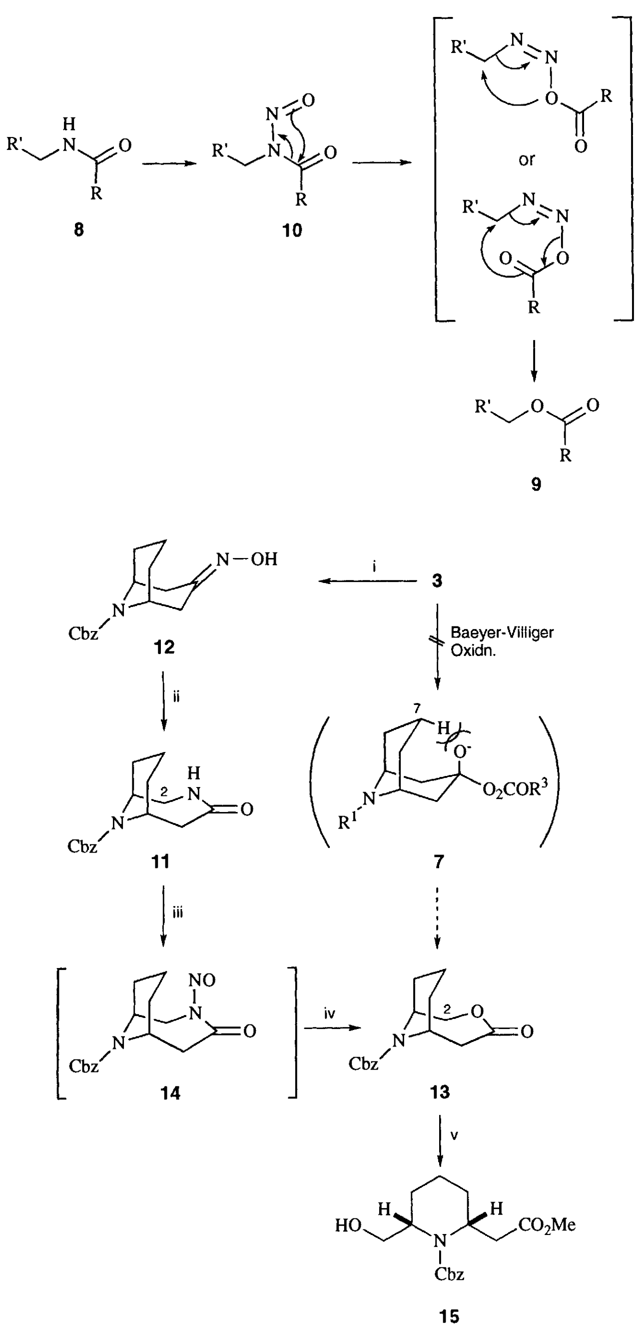


7

Cbz = CO_2CH_2Ph



Scheme 1 *Reagents and conditions:* i, $NH_2OH{\cdot}HCl$, AcONa; ii, TsCl, K_2CO_3; iii, N_2O_4; iv, reflux; v, MeOH, H^+

Results and discussion

Tandem Beckmann and Huisgen–White rearrangement of benzyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate 3b

Ketone **3b** was converted into bicyclic lactam **11** by treatment of oxime **12** with toluene-*p*-sulfonyl chloride in 92% overall yield from ketone **3**. Reaction of lactam **11** with nitrogen peroxide (dinitrogen tetraoxide), freshly prepared from lead nitrate and oxygen, gave a labile *N*-nitroso derivative, benzyl 3-nitroso-4-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate **14**, quantitatively. Thermolysis of compound **14** at 80 °C in the presence of potassium carbonate gave the desired rearrangement product **13** in 85% yield.

The IR spectrum of lactone **13** showed an absorption at 1735 cm^{-1} due to the ester carbonyl; and downfield shifts of signals due to C-2 protons which appeared at δ_H 3.21–3.51 in the ^1H NMR spectrum of lactam **11** were seen at δ_H 4.30–4.46 upon the aforementioned conversion, supporting the formation of the desired lactone **13**.

Methanolysis of lactone **13** in the presence of toluene-*p*-sulfonic acid (PTSA) afforded an α,α'-*cis*-substituted piperidine derivative, methyl [(2*R**)-*cis*-1-benzyloxycarbonyl-6-(hydroxymethyl)piperidin-2-yl]acetate **15**, in 85% yield, the spectral properties of which showed satisfactory correlation with those of a methyl carbamate analogue of compound **15**, which has previously been synthesized *via* the alternative route.[11]

As compound **15** was obtained effectively, the sequence was applied to an α-ethyl derivative (±)-**3d**, which led to a simple stereoselective synthesis of (±)-dihydropalustramic acid (±)-**2a**. In this paper, we present an asymmetric synthesis of compound (−)-**2a**, which was accomplished by application of the sequence to a homochiral reactant (+)-**3d**.

Synthesis of (+)-benzyl 2-ethyl-3-oxo-9-azabicyclo[3.3.1]-nonane-9-carboxylate (+)-3d

Koga and co-workers[12] have developed an efficient method for the enantioselective deprotonation of cyclic ketones by employing a chiral lithium amide **16**, and application of the method, by us,[11] to the bicyclo[3.3.1]nonane system **3a** leading to the corresponding chiral silyl enol ether, (−)-methyl 3-trimethylsiloxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate (−)-**17a**, in 93% enantiomeric excess (ee) has been described. As the initial trial for the asymmetric synthesis of the homochiral reactant (+)-**3d**, alkylation to the silyl enol ether, (−)-benzyl 3-trimethylsiloxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate (−)-**17b**, was attempted.

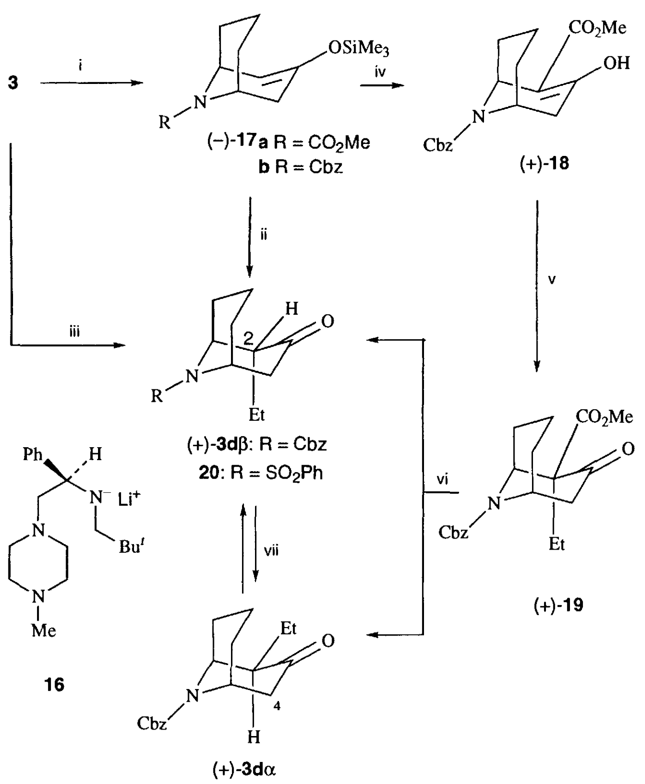
Thus, compound (−)-**17b**, derived from ketone **3b** according to Koga's protocol in 94% ee and in 96% chemical yield (cy), was treated with ethyl iodide in the presence of methyllithium to give the desired 2β-ethyl product (+)-**3dβ**, but in a low ee of ~10%. A chiral enolate itself, derived from chiral amide **16** and ketone **3d**, was also treated with ethyl iodide to give compound (+)-**3dβ**, but the ee was as low as ~6%. It was speculated that the low ee on ethylation in spite of employing the highly enantiomerically pure silyl enol ether (−)-**17b** should be ascribed to the relatively high reaction temperature (~room temp.), which would cause the loss of enantioselectivity.

Thus, compound (+)-**3d** was synthesized *via* (+)-9-benzyl 2-methyl 3-hydroxy-9-azabicyclo[3.3.1]non-2-ene-2,9-dicarboxylate (+)-**18**, which was obtained enantioselectively by the treatment of silyl enol ether (−)-**17b** with methyllithium followed by Claisen condensation of the resulting enolate with methyl cyanoformate[13] at −60 °C. The preferable enol form of product (+)-**18** was evidenced by the ^{13}C NMR spectrum, which displayed two kinds of sp^2-carbon signals at δ_C 170.6 and 99.3† attributable to a tetrasubstituted olefin, and no signal due to the ketonic carbonyl carbon. The ^1H NMR spectrum also showed a signal due to its enolic proton at δ_H 12.11.

Alkylation of compound (+)-**18** with ethyl iodide gave (+)-9-benzyl 2-methyl 2β-ethyl-3-oxo-9-azabicyclo[3.3.1]nonane-2α,9-dicarboxylate (+)-**19** as the sole product in 91% yield. The ^1H NMR spectrum displayed a triplet at δ_H 0.75 due to the methyl group of the introduced ethyl moiety, and eighteen signals in the ^{13}C NMR spectrum, including three carbonyl carbon signals at δ_C 154.6, 170.1 and 203.9, were consistent with the structure.

The ketonic cleavage of compound (+)-**19** by the action of 3% aq. potassium hydroxide in aq. dimethyl sulfoxide (DMSO) afforded two isomeric 2-ethyl ketones (+)-**3dα** and (+)-**3dβ** in the ratio 4:5 (Scheme 2). These two stereoisomers were readily separated by silica gel column chromatography, and the ready interconversion between these two under the reaction conditions was confirmed by subjecting each isomer (+)-**3dα**

† Peaks were split into two owing to restricted rotation about the C–N bond of the urethane moiety at the bridged position[14] (see Experimental section).



Scheme 2 *Reagents and conditions:* i, Me_3SiCl, chiral amide **16**, HMPA, −100 °C; ii, MeLi, HMPA, EtI, −60 °C to room temp.; iii, chiral amide **16**, HMPA, −100 °C; then EtI, −50 °C to room temp.; iv, MeLi, $NCCO_2Me$, HMPA, −60 °C; v, EtI, NaH, THF, MeOH; vi, KOH, DMSO, water, 120 °C; vii, KOH, EtOH

and (+)-**3dβ** independently to the alkaline conditions, which afforded the equilibrium mixture with the relative ratio 4:5. The optical purity of compounds (+)-**3dα** and (+)-**3dβ** was determined to be 94% on the basis of HPLC measurements.

Compound (+)-**3dα** displayed an IR absorption at 1705 cm^{-1} due to the ketonic carbonyl, and a peak due to the molecular ion at *m/z* 301 (11%) in the mass spectrum. In the ^1H NMR spectrum, signals due to the equatorial proton resonated at δ_H 2.34 as a doublet, and the axial one at δ_H 2.64 as a doublet of doublets. A doublet of triplets at δ_H 2.31 corresponded to the axial proton at C-2.

The β-ethyl isomer (+)-**3dβ** showed similar features in its IR (C=O at 1705 cm^{-1}) and mass [*m/z* 301 (12%)] spectra. Its ^1H NMR spectral properties were also similar to those of its counterpart (+)-**3dα**, except for the signal due to the equatorial proton at C-2, which appeared as a triplet at δ_H 2.19. Although this information was consistent with 2-ethyl ketone **3dα** and **3dβ**, it was difficult to discriminate unambiguously between these two stereoisomers on the basis of the spectroscopic properties. Therefore, final structural confirmation was established by the X-ray crystallographic analysis of the corresponding benzenesulfonamide **20**‡ (Fig. 1).

Tandem Beckmann and Huisgen–White rearrangement of (+)-benzyl 2-ethyl-3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (+)-3dα and (+)-3dβ

2-Ethyl ketones (+)-**3dα** and (+)-**3dβ**, thus obtained, were converted into their respective oxime in the usual manner. Compound (+)-**3dα** yielded exclusively the corresponding *E*-oxime (*E*)-(+)-**21α** in 91% yield, while its β-isomer (+)-**3dβ** afforded a small amount of *Z*-isomer (*Z*)-(+)-**21β** as a by-product, which was eliminated readily by column chromatography.

‡ Racemic 2β-ethyl ketone (±)-**3dβ** was used for the preparation of benzenesulfonamide **20**.

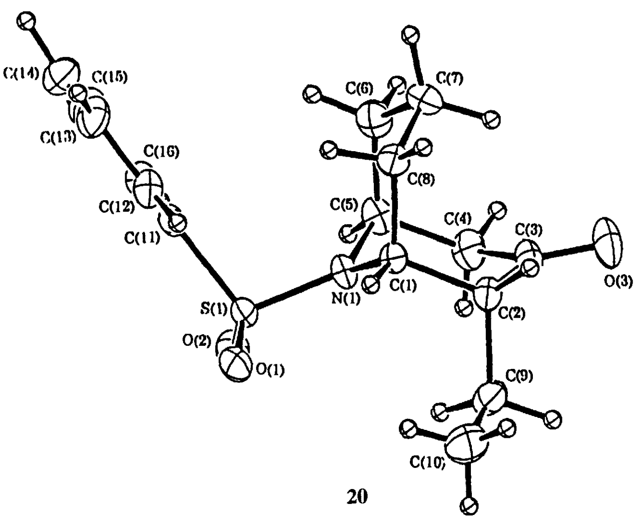


Fig. 1 ORTEP drawing of compound **20** with crystallographic numbering scheme

The Beckmann rearrangement of both *E*-oxime (*E*)-(+)-**21α** and (*E*)-(+)-**21β** *via* the tosyl ester gave the corresponding bicyclic lactam, benzyl 2α- and 2β-ethyl-4-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate (−)-**22α** and (−)-**22β**, in 92% and 91% yield, respectively. The mass spectra of both lactams (−)-**22α** and (−)-**22β** showed their molecular ion peaks at *m/z* 316, and their IR and ^1H NMR spectra gave satisfactory data.

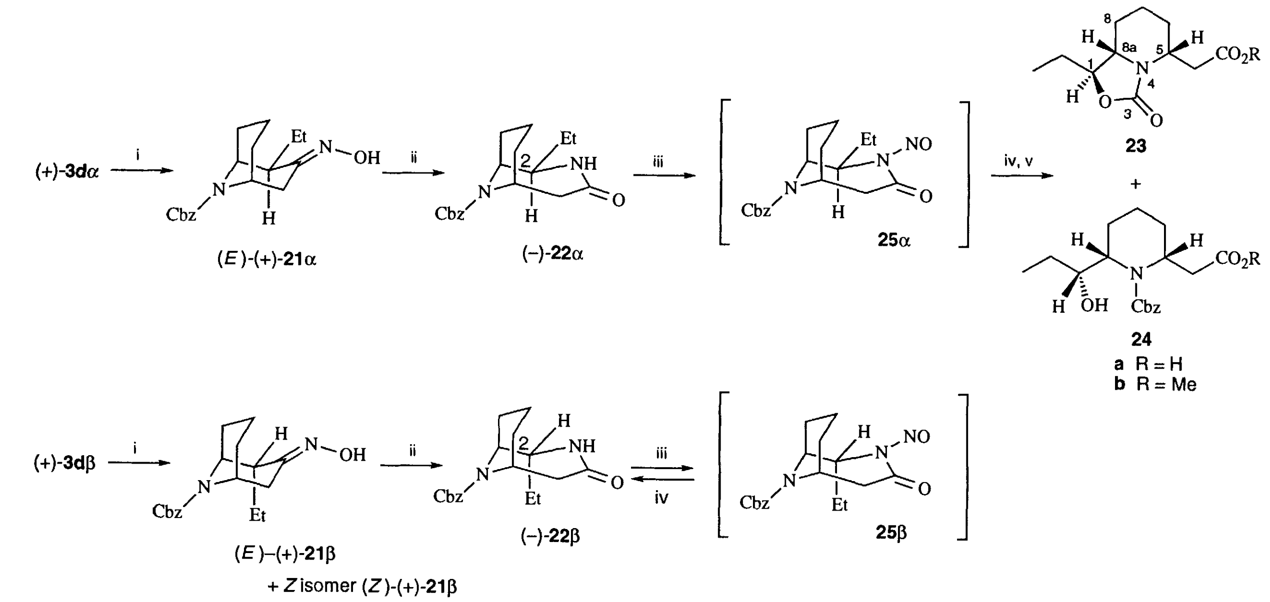
Treatment of 2α-ethyl lactam (−)-**22α** with nitrogen peroxide followed by evaporation of the mixture at 80 °C afforded a mixture of two acetic acid derivatives, {[1*S*-(1α,5β,8aα)]-1-ethyl-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetic acid **23a** and *erythro-cis*-1-(benzyloxycarbonyl)dihydropalustramic acid **24a** as a yellow oil, which was subjected to Fischer's esterification to give corresponding esters, methyl {[1*S*-(1α,5β,8aα)]-(+)-1-ethyl-3-oxohexahydro-3*H*-oxazolo-[3,4-*a*]pyridin-5-yl}acetate (+)-**23b** and methyl (2*R*)-*erythro-cis*-1-(benzyloxycarbonyl)dihydropalustramate (+)-**24b**, in 44 and 13% yield, respectively, from lactam (−)-**22α** (Scheme 3).

On the other hand, attempted thermal rearrangement of the *N*-nitroso derivative of β-isomer **25β** at 80 °C did not proceed to any detectable extent, and denitrosation occurred to give lactam (+)-**22β**, quantitatively. The rearrangements of both *N*-nitroso derivatives **25α** and **25β** in the presence of potassium carbonate, according to the protocol by Huisgen and White, gave complex mixtures.

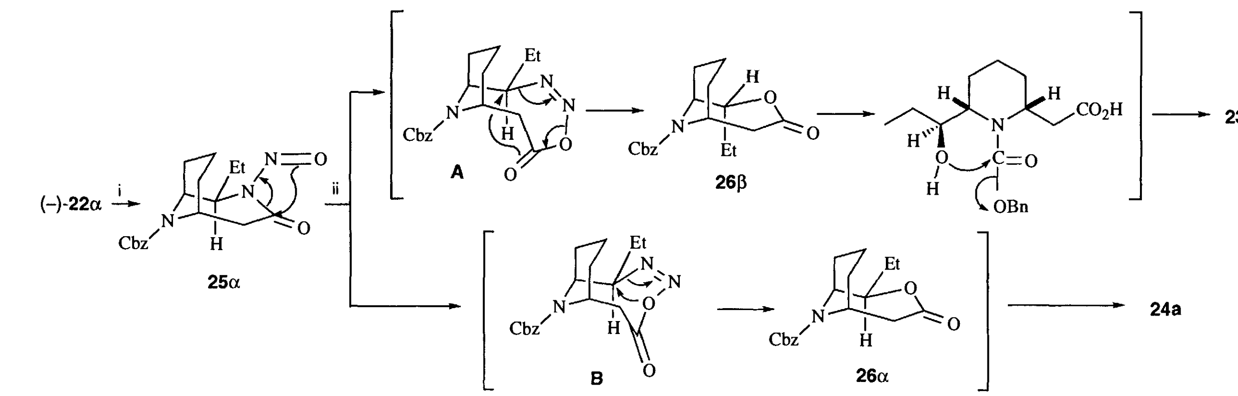
The mass spectrum of compound (+)-**23b** showed its molecular ion peak at *m/z* 241, supporting the debenzyloxylated structure. Its ^1H NMR spectrum displayed signals due to three kinds of methine protons on two fused rings at δ_H 3.90, 3.59 and 3.21, and no signal due to any aromatic protons was observed. Two singlets at δ_C 156.2 and 171.9 in the ^{13}C NMR spectrum corresponded to the oxazolidinone and the ester carbonyl, respectively. In the IR spectrum an absorption appeared at 1740 cm^{-1} corresponding to both the oxazolidinone and the ester carbonyl, and no absorption due to the urethane moiety was observed.

On the other hand, the mass spectrum of compound (+)-**24b** showed its molecular ion peak at *m/z* 349, and its ^1H NMR spectrum displayed a double triplet at δ_H 4.60 due to the secondary alcohol proton on the side chain. The IR spectrum showed two carbonyl bands at 1699 and 1735 cm^{-1}, due to the urethane and ester moiety, respectively.

The formation of oxazolidinone **23a** was ascribed to the easy ring opening of lactone **26β** followed by an intramolecular ester-exchange of the hydroxy group with the benzyloxycarbonyl as



Scheme 3 *Reagents and conditions:* i, $NH_2OH{\cdot}HCl$, AcONa, ii, TsCl, K_2CO_3; iii, N_2O_4; iv, reflux; v, MeOH, H^+



Scheme 4 *Reagents and conditions:* i, N_2O_4; ii, reflux

shown in Scheme 4. Inversion of the stereochemistry at C-2 would result from the intramolecular S_N2-type reaction, where the carbonyl oxygen attacked from the back-side of the N=N group as a leaving moiety through the intermediate **A**, while compound **24a** would be produced *via* the S_Ni process through the intermediate **B** and lactone **26α**.§

Hydrolysis of oxazolidinone ester (+)-**23b** with 47% hydrobromic acid followed by the re-esterification of the crude product furnished methyl (2*R*)-(−)-*threo-cis*-dihydropalustramate (−)-**2b** in 58% yield from compound (+)-**23b**. The optical purity of compound (−)-**2b** was determined to be >95% by comparison of the specific rotation with that reported.[4b]

In conclusion, we have shown that the tandem Beckmann and Huisgen–White rearrangements are an effective alternative to the Baeyer–Villiger oxidation of the bicyclo[3.3.1]nonanone system, and by employing homochiral 2-ethyl bicyclic ketone (+)-**3dα** as a reactant we could have achieved a first asymmetric synthesis of (−)-dihydropalustramic acid (−)-**2a**. We recently described the cleavage of the piperidone ring in this system *via* ozonolysis[7,11] or Norrish type-I reaction.[6] The present approach is another entry into the α-cleavage of the 'fork head ketone' into the α,α′-*cis*-bifunctionalized piperidine system. Furthermore, attempts to convert the bicyclic system **3** into other bioactive alkaloids are now in progress.

§ The rearrangement has been reported to proceed *via* dual modes (ref. 15).

Experimental

Mps (Yanagimoto MP-3S micromelting point apparatus) and bps are uncorrected. Optical rotations were determined with a JASCO DIP-370 digital polarimeter, and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured on a Shimadzu IR-435 grating infrared spectrophotometer. NMR spectra were recorded on either a JEOL JNM-GSX 270 (270 MHz ^1H, 67.5 MHz ^{13}C) or a JEOL JNM-GSX 500 (500 MHz ^1H, 125 MHz ^{13}C) spectrometer at ambient temperature. Chemical shifts and coupling constants (J) are given in δ values (ppm) and in hertz (Hz), respectively. All the NMR spectra were taken for $CDCl_3$ solutions with tetramethylsilane as internal standard. NMR signals for bicyclic benzyl carbamates, especially those due to protons and carbons at α- and β-positions to the nitrogen, were split into two peaks owing to the rotatory hindrance of the urethane moiety at the bridged position.[14] Low-resolution and high-resolution mass spectra (electron impact) were recorded on either a Shimadzu QP 1000EX spectrometer or a JEOL JMS-HX 100 spectrometer. Column chromatography was effected over Merck Kieselgel 60 (230–400 mesh) with a pump (FMI model RP). All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

Benzyl 3-hydroxyimino-9-azabicyclo[3.3.1]nonane-9-carboxylate 12

A mixture of benzyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate **3b**[1,6] (3.0 g, 11.0 mmol), hydroxylamine hydrochloride

(918 mg, 13.2 mmol), sodium acetate (1.08 g, 13.2 mmol), ethanol (10 cm^3) and water (5 cm^3) was heated under reflux for 1.5 h. After being cooled, the reaction mixture was poured into brine, and extracted with chloroform. The extract was washed with brine, and evaporated to give a solid (3.24 g) which, on recrystallization from benzene–hexane, gave *title oxime* **12** (3.07 g, 97%) as prisms, mp 103.5–104.5 °C (Found: M^+, 288.1469. $C_{16}H_{20}N_2O_3$ requires M, 288.1474); $\nu_{max}(CHCl_3)/cm^{-1}$ 3570, 3300 and 1685; δ_H 1.51 (1 H, br d, *J* 13.5), 1.62–1.94 (5 H, m), 2.17/2.25 (1 H, each dd, *J* 16.0 and 7.0), 2.40/2.42 (1 H, each d, *J* 15.5), 2.54/2.61 (1 H, each dd, *J* 15.5 and 6.0), 3.20/3.22 (1 H, each d, *J* 16.0), 4.54 (1 H, br s), 4.61 (1 H, br s), 5.17 (2 H, s), 7.29–7.39 (5 H, m) and 8.39/8.54 (1 H, each br s, exchangeable with D_2O); δ_C 16.7 (t), 28.3/28.6 (t), 29.9/30.2 (t), 30.8/31.2 (t), 35.0/35.5 (t), 46.1/46.6 (d), 47.0/47.4 (d), 67.2 (t), 127.8 (d), 128.0 (d), 128.5 (d), 136.7 (s), 154.4 (s) and 157.9/158.0 (s); *m/z* 288 (M^+, 0.8%) and 91 (100).

Benzyl 4-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate 11
A mixture of oxime **12** (3.0 g, 10.4 mmol), toluene-*p*-sulfonyl chloride (3.0 g, 15.7 mmol), potassium carbonate (3.6 g, 26.1 mmol), 1,2-dimethoxyethane (DME, 15 cm^3) and water (13 cm^3) was heated at 80 °C for 3 h, and the mixture was concentrated to half volume at reduced pressure. The residue was extracted with chloroform, and the extract was washed with brine, and evaporated to give a solid (3.1 g) which, on recrystallization from benzene, gave *title lactam* **11** (2.85 g, 95%) as needles, mp 141–142 °C (Found: M^+, 288.1464. $C_{16}H_{20}N_2O_3$ requires M, 288.1474); $\nu_{max}(CHCl_3)/cm^{-1}$ 3405, 1680 and 1665; δ_H 1.53–1.61 (1 H, m), 1.67–1.90 (4 H, m), 2.05–2.19 (1 H, m), 2.59–2.76 (2 H, m), 3.21–3.33 (1 H, m), 3.44–3.51 (1 H, m), 4.42/4.53 (1 H, each m), 4.57/4.62 (1 H, each m), 5.10–5.20 (2 H, m), 6.23/6.36 (1 H, each br s, exchangeable with D_2O) and 7.23–7.40 (5 H, m); δ_C 15.2/15.8 (t), 25.9/26.1 (t), 27.2/27.6 (t), 41.0/41.7 (t), 44.2/44.5 (d), 45.9/47.0 (t), 46.9/47.7 (d), 67.4/67.5 (t), 127.86 (d), 127.93 (d), 128.06 (d), 128.12 (d), 128.50 (d), 128.53 (d), 136.45/136.51 (s), 154.9/155.3 (s) and 175.7/176.5 (s); *m/z* 288 (M^+, 6%), 153 (15), 124 (57) and 91 (100).

Benzyl 4-oxo-3-oxa-10-azabicyclo[4.3.1]decane-10-carboxylate 13
A solution of nitrogen peroxide[16] in DME (2 cm^3) was added dropwise to a mixture of lactam **11** (340 mg, 1.18 mmol), sodium acetate (484 mg, 5.90 mmol) and DME (5 cm^3) at 0 °C, and the resulting mixture was stirred at that temperature for 15 min. The reaction mixture was diluted with diethyl ether, and washed with ice-cooled aq. sodium hydrogen carbonate. Removal of the solvent at reduced pressure left crude nitroso lactam **14** (375 mg) as a pale yellow oil, which was used in the next step without purification.

To a solution of the oil (375 mg) in 1,4-dioxane (15 cm^3) was added potassium carbonate (195 mg, 1.41 mol), and the mixture was heated at 80 °C for 2 h. The reaction mixture was filtered, and the filtrate was concentrated to give a pale brown oil (308 mg) which, on column chromatography ($CHCl_3$), gave *title lactone* **13** (290 mg, 85%) as prisms, mp 62.5–63 °C (from hexane–diethyl ether) (Found: M^+, 289.1341. $C_{16}H_{19}NO_4$ requires M, 289.1315); $\nu_{max}(CHCl_3)/cm^{-1}$ 1735 and 1691; δ_H 1.58–1.66 (1 H, m), 1.76–1.92 (4 H, m), 1.96–2.09 (1 H, m), 2.77–2.88 (2 H, m), 4.30–4.46 (2 H, m), 4.51/4.62 (1 H, each br s), 4.57/4.66 (1 H, each br m), 5.16 (2 H, s) and 7.31–7.40 (5 H, m); δ_C 15.85/15.90 (t), 24.8/25.2 (t), 26.5/26.9 (t), 40.6/40.8 (t), 44.6/45.1 (d), 48.2/48.8 (d), 67.6 (t), 72.7 (t), 128.0 (d), 128.3 (d), 128.6 (d), 136.2 (s), 154.4/154.5 (s) and 173.9/174.1 (s); *m/z* 289 (M^+, 0.6%), 172 (12), 154 (14), 124 (27) and 91 (100).

Methyl [(2*R)-*cis*-1-benzyloxycarbonyl-6-(hydroxymethyl)-piperidin-2-yl]acetate 15**
A mixture of lactone **13** (141 mg, 0.49 mmol), PTSA (15 mg, 0.087 mmol) and methanol (5 cm^3) was stirred at room temperature for 2 h. The reaction mixture was poured into aq. sodium hydrogen carbonate (5 cm^3), and extracted with chloroform. The extract was washed with brine, and evaporated to give the piperidineacetate **15** (133 mg, 85%) as an oil. Upon distillation at reduced pressure, compound **15** readily decomposed into methyl {(5α,8aβ)-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetate.

Piperidineacetate **15**: oil, bp 166–168 °C/0.008 mmHg (decomp.) (Found: M^+, 321.1606. $C_{17}H_{23}NO_5$ requires M, 321.1577); $\nu_{max}(CHCl_3)/cm^{-1}$ 3446, 1734 and 1676; δ_H 1.48–1.78 (6 H, m), 2.50 (1 H, dd, *J* 13.5 and 7.0), 2.62 (1 H, dd, *J* 13.5 and 8.0), 3.08 (1 H, br s, exchangeable with D_2O), 3.58 (3 H, s), 3.62 (1 H, m), 3.73 (1 H, m), 4.44 (1 H, m), 4.75 (1 H, m), 5.12 (1 H, d, *J* 12.5), 5.16 (1 H, d, *J* 12.5) and 7.26–7.40 (5 H, m); δ_C 14.7 (t), 24.8 (t), 28.6 (t), 39.4 (t), 47.5 (d), 51.88 (q), 51.94 (d), 64.5 (t), 67.4 (t), 127.7 (d), 127.9 (d), 128.4 (d), 136.6 (s), 156.8 (s) and 172.6 (s); *m/z* 321 (M^+, 0.3%), 290 (44), 246 (89), 172 (15) and 91 (100).

Oxazolopyridineacetate: oil (Found: M^+, 213.1012. $C_{10}H_{15}NO_4$ requires M, 213.1001); $\nu_{max}(CHCl_3)/cm^{-1}$ 1743; δ_H 1.36 (1 H, qd, *J* 13.0 and 3.5), 1.38 (1 H, qd, *J* 13.0 and 3.5), 1.53 (1 H, qt, *J* 13.0 and 3.5), 1.72 (1 H, dm, *J* 13.0), 1.82 (1 H, dm, *J* 13.0), 1.94 (1 H, dtt, *J* 13.0, 3.5 and 3.5), 2.58 (1 H, dd, *J* 17.0 and 6.0), 3.49 (1 H, dd, *J* 17.0 and 7.0), 3.60–3.68 (2 H, m), 3.70 (3 H, s), 3.82 (1 H, dd, *J* 8.5 and 7.0) and 4.35 (1 H, dd, *J* 8.5 and 8.5); δ_C 23.3 (t), 29.8 (t), 31.5 (t), 36.9 (t), 51.7 (q), 52.4 (d), 57.0 (d), 67.4 (t), 156.6 (s) and 171.9 (s); *m/z* 213 (M^+, 4%), 182 (17), 153 (100) and 140 (57).

(−)-Benzyl 3-trimethylsiloxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate (−)-17b
According to the method reported,[12] a solution of chiral amide **16** was prepared from the corresponding (−)-chiral amine (10.5 g, 36.3 mmol), a 1.6 mol dm^{-3} solution of butyllithium in hexane (23 cm^3, 36.8 mmol) and tetrahydrofuran (THF) (100 cm^3). To the solution at −100 °C was added hexamethylphosphoric triamide (HMPA, 7 cm^3, 40.3 mmol), and the mixture was at once allowed to warm to room temperature, and was then re-cooled to −100 °C. After addition of trimethylsilyl chloride (7.0 cm^3, 55.2 mmol), a solution of ketone **3b** (5.0 g, 18.3 mmol) in THF (50 cm^3) was added slowly to the mixture, and the resulting mixture was stirred for 10 min. To the mixture was added aq. sodium hydrogen carbonate (200 cm^3), and the mixture was allowed to warm to room temperature, and extracted with diethyl ether. The extract was evaporated to give an oil (21.6 g) which, on column chromatography (hexane–acetone, 15:1), gave *title siloxy ether* (−)-**17b** (6.07 g, 96%) as an oil, bp 154–156 °C/0.008 mmHg (Found: M^+, 345.1782. $C_{19}H_{27}NO_3Si$ requires M, 345.1760); $[\alpha]_D^{26}$ −19.0 (*c* 0.95, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1687; δ_H 0.20 (9 H, s), 1.38–1.96 (7 H, m), 2.51/2.59 (1 H, each dd, *J* 17.5 and 7.5), 4.48/4.55 (1 H, each br t-like), 4.70/4.76 (1 H, each br s), 4.81/4.85 (1 H, each d, *J* 5.5), 5.10–5.20 (2 H, m) and 7.28–7.40 (5 H, m); δ_C 0.2 (q), 15.8 (t), 28.7/29.1 (t), 31.7/32.1 (t), 34.2/34.6 (t), 46.0/46.4 (d), 47.0/47.4 (d), 66.78/66.81 (t), 104.2/104.5 (d), 127.6 (d), 127.7 (d), 127.81 (d), 127.84 (d), 128.4 (d), 137.1 (s), 151.0/151.6 (s) and 154.17/154.22 (s); *m/z* 345 (M^+, 1%), 302 (37), 258 (100), 91 (82) and 73 (75).

Attempted enantioselective alkylation of ketone 3b
Method A. Under argon, a 1.06 mol dm^{-3} solution of methyllithium in diethyl ether (3.9 cm^3, 4.13 mmol) was added dropwise to a solution of siloxy ether (−)-**17b** (570 mg, 1.65 mmol) in DME (5 cm^3) at −60 °C. After addition of HMPA (0.63 cm^3, 3.63 mmol) followed by stirring of the mixture at that temperature for 15 min, ethyl iodide (0.64 cm^3, 8.00 mmol) was added, and the mixture was allowed to warm gradually to room temperature, and the mixture was stirred for 12 h before being

poured into brine (20 cm^3), and extracted with diethyl ether. The extract was washed with brine, and evaporated to give a pale yellow oil (730 mg) which, on column chromatography (hexane–diethyl ether, 5:1), gave (+)-*benzyl* 2β-*ethyl*-3-*oxo*-9-*azabicyclo*[3.3.1]*nonane*-9-*carboxylate* (+)-**3dβ** (124 mg, 25%) as an oil, bp 130–131 °C/0.008 mmHg (Found: M^+, 301.1701. $C_{18}H_{23}NO_3$ requires M, 301.1678); $[\alpha]_D^{14}$ +4.8 (*c* 1.93, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1705 and 1687; δ_H 0.86/0.96 (3 H, each t, *J* 7.5), 1.41–1.86 (8 H, m), 2.15/2.23 (1 H, each t, *J* 7.5), 2.24/2.27 (1 H, each d, *J* 16.0), 2.68/2.72 (1 H, each dd, *J* 16.0 and 7.0), 4.50/4.61 (1 H, each br d-like), 4.72/4.80 (1 H, each br t-like), 5.11–5.24 (2 H, m) and 7.30–7.40 (5 H, m); δ_C 11.8/11.9 (q), 16.4 (t), 25.2/25.4 (t), 30.2/30.3 (t), 30.6 (t), 42.8/42.9 (t), 48.0/48.4 (d), 51.5/51.7 (q), 56.9/57.1 (d), 67.30/67.34 (t), 127.8 (d), 128.0 (d), 128.07 (d), 128.11 (d), 128.3 (d), 128.5 (d), 136.4/136.6 (s), 154.7 (s) and 212.3 (s); *m*/*z* 301 (M^+, 12%), 172 (23), 166 (43) and 91 (100).

The ee of 2β-ethyl ketone (+)-**3dβ** was determined to be ~10% on the basis of HPLC measurement using a chiral column AS (Daicel Chemical Industries Co., Ltd.) with a mixture of hexane, ethanol and propan-2-ol (10:1:1) as eluent.

Method B. To a solution of chiral lithium amide **16**, prepared from the corresponding (−)-chiral amine (1.0 g, 3.46 mmol), a 1.6 mol dm^{-3} solution of butyllithium in hexane (2.3 cm^3, 3.68 mmol), HMPA (0.7 cm^3, 4.03 mmol) and THF (10 cm^3), were added successively a solution of compound **3b** (500 mg, 1.83 mmol) in THF (5 cm^3) and ethyl iodide (0.7 cm^3 8.75 mmol) at −100 °C, and the resulting mixture was stirred at − 50 °C for 3 h. As the substrate **3b** was not consumed to any extent, the mixture was allowed to warm gradually to room temperature, and was stirred for 12 h before being poured into aq. sodium hydrogen carbonate (20 cm^3), and extracted with diethyl ether. The extract was washed successively with 10% hydrochloric acid and brine, and evaporated to give a pale yellow oil (860 mg) which, on column chromatography (hexane–diethyl ether, 5:1), gave 2β-ethyl ketone (+)-**3dβ** (341 mg, 62%) as an oil, $[\alpha]_D^{14}$ +2.7 (*c* 1.93, $CHCl_3$).

Spectral properties of the product were in accord with those of the specimen obtained by method **A**, and the ee of the 2β-ethyl ketone (+)-**3dβ** was determined to be ~6% in the same manner as described above.

(+)-9-Benzyl 2-methyl 3-hydroxy-9-azabicyclo[3.3.1]non-2-ene-(+)-2,9-dicarboxylate (+)-18

Following method A described above, a solution of siloxy ether (−)-**17b** (5.7 g, 16.5 mmol) in DME (30 cm^3) was treated with methyllithium (41 cm^3, 43.5 mmol; as a 1.06 mol dm^{-3} solution in diethyl ether). After addition of HMPA (6.3 cm^3, 36.3 mmol) followed by stirring of the mixture at −60 °C for 10 min, methyl cyanoformate (5.0 cm^3, 50 mmol) was added dropwise to the mixture, and the resulting mixture was stirred for 30 min. The reaction mixture was poured into brine (150 cm^3), acidified with 10% hydrochloric acid, and extracted with diethyl ether. The extract was washed with brine, and evaporated to give a pale yellow oil (11.8 g) which, on distillation at reduced pressure, gave *title compound* (+)-**18** (4.2 g, 77%) as an oil, bp 162–163 °C/0.006 mmHg (Found: C, 65.0; H, 6.3; N, 4.25. $C_{18}H_{21}NO_5$ requires C, 65.24; H, 6.39; N, 4.23%); $[\alpha]_D^{20}$ +5.2 (*c* 0.90, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1689, 1658 and 1624; δ_H 1.50–1.84 (6 H, m), 2.13/2.15 (1 H, each d, *J* 19.0), 2.75/2.83 (1 H, each dd, *J* 19.0 and 8.0), 3.77 (3 H, s), 4.53–4.67 (1 H, m), 5.07–5.19 (3 H, m), 7.30–7.40 (5 H, m) and 12.11 (1 H, s, exchangeable with D_2O); δ_C 15.4 (t), 28.4/28.8 (t), 31.2/31.6 (t), 32.9/33.2 (t), 45.3/45.5 (d), 45.8/46.0 (d), 51.5 (q), 67.0/67.2 (t), 99.1/99.5 (s), 127.6 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.4 (d), 128.5 (d), 136.7/136.9 (s), 154.1/154.2 (s), 170.5/170.6 (s) and 172.2/173.0 (s); *m*/*z* 273 (4%), 138 (17) and 91 (100).

(+)-9-Benzyl 2-methyl 2β-ethyl-3-oxo-9-azabicyclo[3.3.1]-nonane-2α,9-dicarboxylate (+)-19

A solution of compound (+)-**18** (3.13 g, 9.45 mmol) in THF (20 cm^3) was added dropwise to a suspension of sodium hydride (60% dispersion in liquid paraffin; 545 mg, 13.6 mmol; washed twice with benzene) in THF (10 cm^3) at 0 °C. To the resulting solution were added successively ethyl iodide (3.6 cm^3, 45.0 mmol) and absolute methanol (5 cm^3). After being heated under reflux for 6 h, the mixture was poured into brine (50 cm^3), and extracted with chloroform. The extract was washed with brine, and evaporated to give an orange oil (3.7 g) which, on column chromatography (hexane–acetone, 10:1), gave *title compound* (+)-**19** (3.1 g, 91%) as an oil, bp 178–180 °C/0.01 mmHg (Found: M^+, 359.1735. $C_{20}H_{25}NO_5$ requires M, 359.1733); $[\alpha]_D^{20}$ +94.4 (*c* 0.74, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1743, 1720 and 1689; δ_H 0.72/0.78 (3 H, each t, *J* 7.0), 1.55–1.86 (7 H, m), 2.14/2.27 (1 H, each dq, *J* 13.5 and 7.0), 2.31/2.34 (1 H, each d, *J* 12.0), 2.70/2.74 (1 H, each dd, *J* 12.0 and 7.0), 3.75/3.77 (3 H, each s), 4.52/4.65 (1 H, each br s), 4.72/4.80 (1 H, each br s), 5.15/5.17 (1 H, each d, *J* 12.0), 5.21/5.23 (1 H, each d, *J* 12.0) and 7.30–7.40 (5 H, m); δ_C 8.8/8.9 (q), 16.4 (t), 28.3/28.5 (t), 28.6/28.7 (t), 30.3/30.7 (t), 42.5/42.6 (t), 47.8/48.3 (d), 52.06/52.12 (q), 55.4/55.9 (d), 64.1/64.3 (s), 67.6 (t), 127.9 (d), 128.1 (d), 128.3 (d), 128.6 (d), 136.3/136.4 (s), 154.5/154.6 (s), 169.9/170.2 (s) and 203.9 (s); *m*/*z* 359 (M^+, 4%), 300 (21), 224 (78), 172 (42) and 91 (100).

Ketonic cleavage of compound (+)-19

A mixture of compound (+)-**19** (3.0 g, 8.4 mmol), potassium hydroxide (935 mg, 16.7 mmol), DMSO (16 cm^3) and water (7 cm^3) was heated at 120 °C for 6 h. The reaction mixture was poured into brine (30 cm^3), and extracted with benzene. The extract was washed with brine, and evaporated to give a pale yellow oil (2.6 g) which, on column chromatography (hexane–diethyl ether 5:1), gave (+)-*benzyl* 2α-*ethyl*-3-*oxo*-9-*azabicyclo*[3.3.1]*nonane*-9-*carboxylate* (+)-**3dα** (930 mg, 37%) and its stereoisomer (+)-**3dβ** (1.18 g, 47%).

2α-*Ethyl ketone* (+)-**3dα**: oil, bp 128–129 °C/0.008 mmHg (Found: M^+, 301.1649. $C_{18}H_{23}NO_3$ requires M, 301.1678); $[\alpha]_D^{26}$ +16.9 (*c* 1.01, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1705 and 1689; δ_H 0.94/0.98 (3 H, each t, *J* 7.0), 1.10–1.26 (1 H, m), 1.37 (1 H, qt, *J* 14.5 and 4.5), 1.48–1.85 (5 H, m), 2.01 (1 H, m), 2.26/2.36 (1 H, each dt, *J* 7.0 and 7.0), 2.33/2.35 (1 H, each d, *J* 15.5), 2.60/2.67 (1 H, each dd, *J* 15.5 and 7.0), 4.60/4.68 (1 H, each br t-like), 4.72/4.78 (1 H, each br t-like), 5.17–5.24 (2 H, m) and 7.30–7.40 (5 H, m); δ_C 11.6 (q), 16.1 (t), 19.0/19.1 (t), 24.8/25.1 (t), 30.1/30.5 (t), 45.3/45.6 (t), 48.6/49.0 (d), 51.1/51.4 (d), 53.9/54.3 (d), 67.2/67.3 (t), 127.7 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.5 (d), 136.57/136.62 (s), 154.3 (s) and 210.5/210.6 (s); *m*/*z* 301 (M^+, 11%), 172 (27), 166 (45) and 91 (100).

2β-Ethyl ketone (+)-**3dβ**: oil, $[\alpha]_D^{26}$ +62.7 (*c* 1.01, $CHCl_3$). Spectral properties of 2β-ethyl ketone (+)-**3dβ** were in accord with those of the specimen obtained by direct alkylation of ketone **3b** (see above). The ee of 2β-ethyl ketone (+)-**3dβ** was determined to be 94% by HPLC measurement.

Epimerization of compounds 3dα and 3dβ

Epimerization of compounds **3dα** and **3dβ** was carried out by using racemic species which were prepared according to the method described.[1]

A mixture of 2α-ethyl ketone **3dα** (113 mg, 0.38 mmol), potassium hydroxide (11.8 mg, 0.21 mmol), DME (4 cm^3) and water (2 cm^3) was stirred at room temperature for 12 h. The mixture was poured into brine (15 cm^3), and extracted with diethyl ether. The extract was washed with brine and evaporated to give a 4:5 mixture of 2-ethyl ketone **3dα** and **3dβ** (110 mg, 97%) as an oil. The relative ratio of compounds **3dα** and **3dβ** was determined on the basis of the ^1H NMR spectrum of the crude mixture.

A similar product ratio was obtained upon treatment of 2β-ethyl ketone **3dβ** (117 mg, 0.39 mmol) under the same conditions.

(+)-Benzyl 2-ethyl-3-hydroxyimino-9-azabicyclo[3.3.1]nonane-9-carboxylate (+)-21α and (+)-21β

A mixture of compound (+)-**3dα** (500 mg, 1.66 mol), anhydrous sodium acetate (164 mg, 2.0 mmol), hydroxylamine hydrochloride (139 mg, 2.0 mmol), ethanol (5 cm^3) and water (2 cm^3) was heated under reflux for 4 h. Work-up in a manner similar to that used for the preparation of oxime **12** gave a pale yellow oil (512 mg) which on distillation at reduced pressure gave (E)-(+)-*benzyl 2α-ethyl-3-hydroxyimino-9-azabicyclo*[3.3.1]*nonane-9-carboxylate* (*E*)-(+)-**21α** (478 mg, 91%) as an oil, bp 163–165/0.01 mmHg (Found: M^+, 316.1772. $C_{18}H_{24}N_2O_3$ requires M, 316.1787); $[\alpha]_D^{20}$ +35.2 (*c* 0.77, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3569, 3307 and 1685; δ_H 0.96/1.01 (3 H, each t, *J* 7.5), 1.27–1.40 (1 H, m), 1.40–1.50 (1 H, m), 1.55–1.84 (5 H, m), 1.92–2.03 (1 H, m), 2.10/2.16 (1 H, each dd, *J* 15.5 and 6.5), 2.37/2.45 (1 H, each dt, *J* 7.5 and 4.5), 3.27/3.28 (1 H, each d, *J* 15.5), 4.43/4.50 (1 H, each br t-like), 4.54/4.60 (1 H, each br s), 5.14–5.23 (2 H, m), 7.30–7.40 (5 H, m) and 7.40–9.00 (1 H, br, exchangeable with D_2O); δ_C 11.3 (q), 16.6 (t), 20.0/20.1 (t), 24.2/24.5 (t), 28.2/28.6 (t), 30.7/31.0 (t), 45.4/46.0 (d), 46.8/47.2 (d), 49.6/50.0 (d), 67.0/67.1 (t), 127.5 (d), 127.7 (d), 127.88 (d), 127.94 (d), 128.1 (d), 128.4 (d), 136.6/136.7 (s), 154.2/154.3 (s) and 160.1 (s); *m*/*z* 316 (M^+, 7%), 299 (26), 172 (17), 165 (14) and 91 (100).

In a similar manner, 2β-ethyl ketone (+)-**3dβ** (1.2 g, 3.98 mmol) afforded (E)-2β-*ethyl oxime* (*E*)-(+)-**21β** (1.02 g, 81%) and its *isomer* (*Z*)-(+)-**21β** (151 mg, 12%).

(E)-2β-*Oxime* (*E*)-(+)-**21β**: needles, mp 122–123 °C (from EtOH) (Found: M^+, 316.1759); $[\alpha]_D^{20}$ +66.7 (*c* 0.81, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3569, 3330 and 1684; δ_H 0.84/0.92 (3 H, each t, *J* 7.0), 1.36–2.00 (8 H, m), 2.16–2.31 (2 H, m), 3.13/3.15 (1 H, each d, *J* 16.0), 4.37/4.47 (1 H, each br d, *J* 4.5), 4.52/4.59 (1 H, each br t-like), 5.09–5.22 (2 H, m), 7.29–7.40 (5 H, m) and 7.56 (1 H, br s, exchangeable with D_2O); δ_C 11.6/11.7 (q), 16.6 (t), 25.7/25.9 (t), 26.0/26.1 (t), 29.8/30.2 (t), 30.8/31.2 (t), 46.2/46.7 (d), 46.95/47.04 (d), 50.9/51.2 (d), 67.0/67.1 (t), 127.6 (d), 127.8 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.4 (d), 136.5/136.7 (s), 154.7/154.8 (s) and 160.2/160.3 (s); *m*/*z* 316 (M^+, 15%), 299 (49), 172 (26), 165 (24) and 91 (100).

(Z)-2β-*Oxime* (*Z*)-(+)-**21β**: oil, bp 163–164 °C/0.008 mmHg (Found: M^+, 316.1767); $[\alpha]_D^{20}$ +61.8 (*c* 1.03, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3570, 3300 and 1685; δ_H 0.89/0.98 (3 H, each t, *J* 7.5), 1.36–2.00 (8 H, m), 2.27/2.29 (1 H, each d, *J* 15.0), 2.62/2.65 (1 H, each dd, *J* 15.0 and 6.0), 3.16/3.24 (1 H, each t, *J* 7.5), 4.32/4.42 (1 H, each br d, *J* 4.0), 4.53/4.61 (1 H, each br t-like), 5.09–5.22 (2 H, m), 7.30–7.38 (5 H, m) and 7.65 (1 H, br s, exchangeable with D_2O); δ_C 11.8/11.9 (q), 16.8 (t), 24.1/24.2 (t), 29.9/30.2 (t), 30.6/31.0 (t), 33.1/33.4 (t), 40.2/40.3 (d), 47.1/47.7 (d), 49.8/50.1 (d), 67.1/67.2 (t), 127.7 (d), 127.96 (d), 127.99 (d), 128.0 (d), 128.46 (d), 128.49 (d), 136.7/136.8 (s), 154.8 (s) and 161.4 (s); *m*/*z* 316 (M^+, 3%), 299 (7), 172 (8), 165 (6) and 91 (100).

Beckmann rearrangement of oximes (*E*)-(+)-21α and (*E*)-(+)-21β

A mixture of oxime (*E*)-(+)-**21α** (415 mg, 1.31 mmol), toluene-*p*-sulfonyl chloride (380 mg, 2.0 mmol), potassium carbonate (456 mg, 3.3 mmol), DME (5 cm^3) and water (2 cm^3) was heated at 80 °C for 6 h. Work-up in a manner similar to that used for the preparation of lactam **11** gave a pale yellow oil (445 mg) which, on column chromatography (benzene–acetone, 5:1), gave (−)-*benzyl 2α-ethyl-4-oxo-3,10-diazabicyclo*[4.3.1]*decane-10-carboxylate* (−)-**22α** (383 mg, 92%) as an oil, bp 179–180 °C/0.01 mmHg (Found: M^+, 316.1757); $[\alpha]_D^{19}$ −4.8 (*c* 1.17, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3397, 1690 and 1666; δ_H 0.93/1.05 (3 H, each t, *J* 7.5), 1.46–1.94 (7 H, m), 2.01–2.14 (1 H, m), 2.50–2.58 (1 H, m), 2.78/2.84 (1 H, each dd, *J* 15.0 and 3.0), 3.48/3.56 (1 H, each br m), 4.21/4.32 (1 H, each d, *J* 6.8), 4.48/4.54 (1 H, each br m), 5.10–5.25 (2 H, m), 5.58 (1 H, br s, exchangeable with D_2O) and 7.31–7.40 (5 H, m); δ_C 10.8/10.9 (q), 16.5 (t), 21.8/21.9 (t), 26.2/26.4 (t), 27.1/27.3 (t), 43.3/43.8 (t), 44.5/44.9 (d), 50.6/50.7 (d), 59.8/60.4 (d), 67.28/67.32 (t), 127.8 (d), 127.9 (d), 128.1 (d), 128.4 (d), 128.5 (d), 136.4 (s), 154.6/154.7 (s) and 176.3/176.6 (s); *m*/*z* 316 (M^+, 20%), 181 (14), 124 (77) and 91 (100).

In a similar manner, (*E*)-2β-ethyl oxime (*E*)-(+)-**21β** (950 mg, 3.00 mmol) afforded (−)-2β-*ethyl lactam* (−)-**22β** (865 mg, 91%) as prisms, mp 173–174 °C (from benzene) (Found: M^+, 316.1767); $[\alpha]_D^{20}$ −20.4 (*c* 1.04, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3395, 1686 and 1665; δ_H 0.92/1.03 (3 H, each t, *J* 7.5), 1.46–1.84 (7 H, m), 1.96–2.08 (1 H, m), 2.46/2.55 (1 H, each dd, *J* 14.0 and 8.0), 2.72/2.77 (1 H, each dd, *J* 14.0 and 8.0), 3.26/3.35 (1 H, each br m), 4.09/4.19 (1 H, each br t-like), 4.69/4.77 (1 H, each br m), 5.04–5.21 (2 H, m), 5.27/5.31 (1 H, each br s, exchangeable with D_2O) and 7.26–7.38 (5 H, m); δ_C 10.8/11.0 (q), 14.0/14.3 (t), 25.6/26.1 (t), 26.3/26.5 (t), 27.7/28.0 (t), 37.7/38.4 (t), 43.5/43.9 (d), 51.7/52.2 (d), 56.1/56.3 (d), 67.3/67.4 (t), 127.77 (d), 127.81 (d), 128.0 (d), 128.3 (d), 128.4 (d), 136.4/136.5 (s), 155.6/155.9 (s) and 173.3/173.8 (s); *m*/*z* 316 (M^+, 26%), 181 (15), 124 (85) and 91 (100).

Huisgen–White rearrangement of lactams (−)-22α and (−)-22β

A saturated solution of nitrogen peroxide in DME (2 cm^3) was added dropwise to a stirred suspension of lactam (−)-**22α** (530 mg, 1.68 mmol), sodium acetate (700 mg, 8.5 mmol) and DME (7 cm^3) at 0 °C. After being stirred for 15 min, the mixture was filtered, and the residue was washed with DME. The combined filtrate and washings were evaporated at 80 °C to give a ~3.4:1 mixture of {(1α,5β,8aα)-1-ethyl-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetic acid **23a** and (2*R*)-*erythro-cis*-1-(benzyloxycarbonyl)dihydropalustramic acid **24a** (660 mg) as a yellow oil, which was used in the next step without purification.

A mixture of the oil (660 mg), methanol (5 cm^3) and 3 drops of conc. sulfuric acid was heated under reflux for 3 h, and the reaction mixture was poured into aq. potassium carbonate (1.5 g in 30 cm^3), and extracted with diethyl ether. The extract was washed with brine, and evaporated to give a yellow oil (490 mg) which, on column chromatography (benzene–acetone, 50:1), gave methyl {[1*S*-(1α,5β,8aα)]-(+)-1-ethyl-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetate (+)-**23b** (178 mg, 44%) and *methyl* (2R)-(+)-erythro-cis-N-(*benzyloxycarbonyl*)*dihydropalustramate* (+)-**24b** (76 mg, 13%).

Oxazolidinone ester (+)-**23b**: oil, bp 121–122 °C/0.01 mmHg (lit.,[5f] oil) (Found: M^+, 241.1292. $C_{12}H_{19}NO_4$ requires M, 241.1314); $[\alpha]_D^{18}$ +5.3 (*c* 0.78, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740, δ_H 1.00 (3 H, t, *J* 7.5), 1.27–1.39 (2 H, m), 1.49 (1 H, qt, *J* 13.0 and 3.5), 1.62–1.73 (3 H, m), 1.81 (1 H, dm, *J* 13.0), 1.91 (1 H, dtt, *J* 13.0, 3.5 and 3.5), 2.53 (1 H, dd, *J* 16.7 and 6.0), 3.21 (1 H, ddd, *J* 11.0, 7.3 and 3.5), 3.50 (1 H, dd, *J* 16.7 and 7.5),¶ 3.59 (1 H, dddd, *J* 11.0, 7.5, 6.0 and 2.8), 3.70 (3 H, s) and 3.90 (1 H, dt, *J* 7.3 and 5.5); δ_C 9.2 (q), 23.2 (t), 26.6 (t), 29.9 (t), 31.7 (t), 37.0 (t), 51.6 (q), 52.2 (d), 61.8 (d), 80.9 (d), 156.2 (s) and 171.9 (s); *m*/*z* 241 (M^+, 35%), 210 (36), 197 (38), 181 (100), 168 (39), 154 (47), 124 (61), 96 (43) and 82 (77).

The methyl erythro-cis-*palustramate* (+)-**24b**: oil, bp 130–132 °C/0.01 mmHg (Found: M^+, 349.1861. $C_{19}H_{27}NO_5$ requires M, 349.1889); $[\alpha]_D^{18}$ +13.3 (*c* 0.80, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3320, 1735 and 1699; δ_H 0.92 (3 H, t, *J* 7.5), 1.08 (1 H, qd, *J* 13.0 and 3.7), 1.15 (1 H, qd, *J* 13.0 and 3.7), 1.35 (1 H, qt, *J* 13.0 and 3.7), 1.56–1.74 (4 H, m), 1.81 (1 H, dm, *J*

¶ Synthesis of the racemic oxazolidinone ester (±)-**23b** has been reported, but a signal corresponding to the marked proton is lacking (ref. 5*f*).

13.0), 1.85 (1 H, br, exchangeable with D_2O), 2.35 (1 H, dd, *J* 16.0 and 7.5), 2.39 (1 H, dd, *J*, 16.0 and 5.5), 2.78 (1 H, ddd, *J* 11.0, 5.0 and 2.5), 2.93 (1 H, dddd, *J* 14.0, 7.5, 5.5 and 2.5), 3.66 (3 H, s), 4.60 (1 H, dt, *J* 8.0 and 5.0), 5.17 (2 H, s) and 7.30–7.42 (5 H, m); δ_C 9.7 (q), 22.9 (t), 24.1 (t), 27.1 (t), 32.1 (t), 41.2 (t), 51.5 (q), 53.4 (d), 58.8 (d), 69.4 (t), 82.8 (d), 128.1 (d), 128.4 (d), 128.5 (d), 135.4 (s), 155.2 (s) and 172.7 (s); *m/z* 350 (M + 1, 0.8%), 349 (M^+, 0.1%), 182 (22), 156 (100), 124 (69) and 91 (64).

Lactam (−)-**22β** (150 mg, 0.47 mmol) was treated with nitrogen peroxide in a manner similar to that used for the rearrangement of lactam (−)-**22α**. Work-up resulted in the complete recovery of the starting material (−)-**22β**.

Methyl (−)-*threo-cis*-dihydropalustramate (−)-2b

A mixture of oxazolidinone ester (+)-**23b** (200 mg, 0.83 mmol), DME (1 cm^3), water (1 cm^3), and 47% hydrobromic acid (2 cm^3) was heated under reflux for 2 days. More 47% HBr (2 cm^3) was added, and reflux was continued for an additional 3 days . Removal of the solvent at reduced pressure left a pale yellow oil (132 mg), which was used in the next step without purification.

A mixture of the oil (132 mg), methanol (5 cm^3) and 3 drops of conc. sulfuric acid was heated at 50 °C for 4 h. Work-up in a usual manner gave a pale yellow oil (83 mg) which, on column chromatography ($CHCl_3$–EtOH, 50:1), gave title compound (−)-**2b** (104 mg, 58%) as an oil, bp 43–44 °C/0.006 mmHg (lit.,[4b] 60–65 °C/0.0001 mmHg); $[\alpha]_D^{16}$ −22.1 (*c* 0.80, MeOH) (lit.,[4b] −23). The spectral properties of compound (−)-**2b** were in accord with those reported.[4c]

X-Ray crystallography

Preparation of 2β-ethyl-9-phenylsulfonyl-9-azabicyclo-[3.3.1]nonan-3-one 20. Benzenesulfonamide **20** as a sample for X-ray crystallographic analysis was obtained by employing a racemic reactant **3dβ** as follows.

A suspension of 5% palladium on carbon (250 mg) in ethanol (10 cm^3) was pre-equilibrated with hydrogen. To the suspension was added a solution of compound **3dβ** (500 mg, 1.66 mmol) in ethanol (15 cm^3), and the mixture was hydrogenated at room temperature until the uptake of hydrogen ceased. The catalyst was filtered off, and the filtrate was evaporated to give an oil (255 mg), which was used in the next step without purification.

A mixture of the oil (255 mg), triethylamine (563 mm^3, 8.3 mmol), benzenesulfonyl chloride (256 mm^3, 1.8 mmol) and methylene dichloride (5 cm^3) was stirred at 0 °C for 12 h. After dilution of the mixture with methylene dichloride (20 cm^3), the resulting mixture was washed successively with 10% hydrochloric acid, aq. sodium hydrogen carbonate and brine, and evaporated to give a pale yellow solid (533 mg) which, on recrystallization from acetone–hexane, gave *title compound* **20** (398 mg, 78%) as plates, mp 122.5–123.5 °C (Found: M^+, 307.1246. $C_{16}H_{21}NO_3S$ requires M, 307.1243); $\nu_{max}(CHCl_3)/cm^{-1}$ 1702, 1351 and 1163; δ_H 0.93 (3 H, t, *J* 6.0), 1.45–1.74 (8 H, m), 2.16 (1 H, t, *J* 6.5), 2.26 (1 H, d, *J* 14.0), 2.80 (1 H, dd, *J* 14.0 and 6.0), 4.31 (1 H, br d-like), 4.45 (1 H, br d-like), 7.50–7.61 (3 H, m) and 7.88–7.92 (2 H, m); δ_C 11.7 (q), 16.0 (t), 25.3 (t), 29.0 (t), 29.4 (t), 43.8 (t), 50.2 (d), 53.3 (d), 57.2 (d), 126.9 (d), 129.2 (d), 132.6 (d), 141.4 (s) and 211.4 (s); *m/z* 307 (M^+, 1%), 222 (100), 166 (31), 141 (20) and 77 (38).

Crystal data for benzenesulfonamide 20. $C_{16}H_{21}NO_3S$, M = 307.41, orthorhombic, $a = 7.931(2)$, $b = 16.913(2)$, $c = 11.388(2)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$, $V = 1537.6(8)$ $Å^3$ (by least-squares refinement on diffractometer angle for 25 automatically centred reflections, $\lambda = 1.541\ 78$ Å), space group $Pna2_1$, $Z = 8$, μ(Cu-Kα) = 19.19 cm^{-1}, $F(000) = 656$, $D_c = 1.336$ g cm^{-3}, crystal dimensions: 0.50 × 0.55 × 0.50 mm.

Data collection and processing. ω–2θ Mode with θ scan width = 1.63 + 0.30 tan θ, ω-scan speed of 32.0 min^{-1}; 1341 Reflections ($77.54 \leqslant 2\theta \leqslant 79.76°$) were collected on a Rigaku AFC5R diffractometer with graphite-monochromated Cu-Kα radiation, and 1156 reflections with $I > 3\sigma(I)$ were used in the structure determination. No decay correction was applied.

Structure analysis and refinement. The structure was solved by direct methods (MITHRIL).[17] Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. All computations for the structure determination were carried out on a VAX station 3200 using the crystallographic program package TEXSAN.[18] Final refinements converged to R (R_w) = 0.041 (0.053). An ORTEP drawing of compound **20** is shown in Fig. 1. Tables of atomic coordinates, bond lengths and angles, and thermal parameters been deposited at the Cambridge Crystallographic Data Centre (CCDC).[‖]

‖ For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/4.

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