Tandem Beckmann and Huisgen–White rearrangement of the 9-azabicyclo[3.3.1]nonan-3-one system. Part 2.[1] The second mode of the rearrangement leading to 6-(prop-1-enyl)piperidin-2-ylacetic acid, a versatile intermediate for the syntheses of piperidine alkaloids (+)-pinidine and (+)-monomorine I

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The second mode of the Huisgen–White rearrangement of the bicyclic lactam, (−)-2-ethyl-4-oxo-3,10-diazabicyclo[4.3.1]decane (−)-13, leading to *cis*-[6-(prop-1-enyl)piperidin-2-yl]acetic acid (−)-9a under alkaline conditions is described. A reasonable reaction mechanism accounting for the preferable formation of the (*E*)-propenyl isomer (*E*)-9a is presented. Conversions of the olefinic acid 9a into two piperidine alkaloids (+)-pinidine (+)-10 and (−)-dihydropinidine (−)-21, and (−)-*cis*-2-formyl-6-methylpiperidine (−)-22, a key synthetic intermediate for an ants' trail pheromone (+)-monomorine I (+)-11, are also described.

Introduction

As part of the continuing interest in the application of the Baeyer–Villiger reaction to the stereo- and regio-specific synthesis of specifically substituted molecules, there has been much study of its mechanism, especially in respect of its migratory aptitude as well as its scope and limitations.[2] In the course of our exploratory study on the applicability of bicyclo[3.*n*.1]-alkan-3-one as a synthon to natural product synthesis, we earlier examined the Baeyer–Villiger reaction of 9-azabicyclo[3.3.1]nonan-3-one **1** (X = CH_2, NCO_2R, NSO_2Ph), where as a result of anomalous lack of reactivity no rearrangement product **2** was formed. This lack of activity towards oxidation was ascribed to the back-side steric hindrance of the 7-*endo* hydrogen which interfered with formation of the tetrahedral intermediate **3** in the markedly rigid molecule.[3] As an alternative to such an oxidation, we exposed the corresponding oxime **4** to a tandem Beckmann and Huisgen–White rearrangement, thereby inducing the rearrangement and obtaining the desired lactone **2** in moderate yield *via* the lactam **5**. Application of the sequence to a homochiral bicyclic reactant, (+)-benzyl 2α-ethyl-3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (+)-**6α**, enabled us to complete the first asymmetric synthesis of (−)-dihydropalustramic acid (−)-**7**, a degradation product of *Equisetum* spermidine alkaloid palustrine **8**.[1] In this paper, we report further examination of the reaction under different conditions, where a further mode of rearrangement leading to the olefinic acids, [(2*R*)-(*E*)- and (2*R*)-(*Z*)-*cis*-1-benzyloxycarbonyl-6-(prop-1-enyl)piperidin-2-yl]acetic acid (*E*)- and (*Z*)-**9a**, have been detected. Transformation of the acids (*E*)- and (*Z*)-**9a** into two piperidine alkaloids, (+)-pinidine **10**[4] and (+)-monomorine I (+)-**11**,[5] has been demonstrated.

Results and discussion

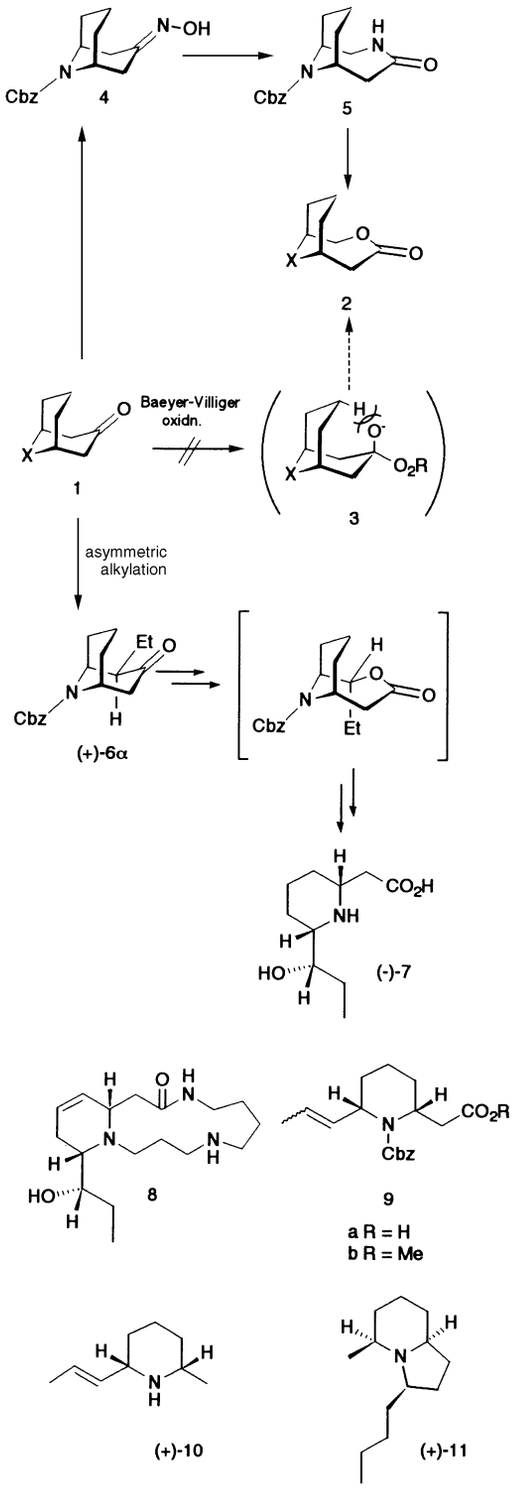
Tandem Beckmann and Huisgen–White rearrangement of (+)-benzyl 2-ethyl-3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (+)-6 under alkaline conditions

According to the method described in the preceding paper,[1] chiral reactants (+)-**6α** and (+)-**6β** with ~94% optical purity were prepared from compound **1** (X = NCbz) by employing enantioselective deprotonation as the key reaction. Since it was difficult to identify these two isomers, (+)-**6α** and (+)-**6β** from their spectroscopic properties, structural discrimination was established on the basis of a single-crystal X-ray analysis of the benzenesulfonamide of the β-isomer, 2-ethyl-9-phenylsulfonyl-9-azabicyclo[3.3.1]nonan-3-one (±)-**12β**, which was proved, in the preceding paper, to be in the twin chair conformation.[1] The crystal structure of the α-isomer (±)-**12α** has been examined in the present study, and found also to be in the twisted twin chair conformation (Fig. 1). Complete assignments of their ^1H and ^{13}C NMR signals have also been made in the present work by the use of two-dimensional NMR studies (Table 1).

It is noteworthy that in the ^{13}C NMR spectrum of the α-isomer (±)-**12α** considerable upfield shifts were observed for the signals due to C-8 and CH_2CH_3, which appeared at δ_C 24.9 and 19.0, respectively, owing to the γ-gauche effect. This observation is consistent with the crystal structure obtained by the X-ray analysis where as a result of the piperidone ring being slightly bent outside these two moieties are forced to face each other more closely. Remarkable NOE enhancement observed between the 8-*endo* proton and CH_2CH_3 also support their relative stereochemistry.

It is also interesting to note that, despite the 1,3-dipolar repulsion between the ethyl substituent and the axial hydrogen at C-4, which might cause the ring inversion of the piperidone ring into the boat, compound (±)-**12β** is still in the twin chair conformation of the two possible conformations, *i.e.* twin chair and chair-boat as shown in Scheme 2. In the β-isomer (±)-**12β**, the upfield shift of the signal arising from C-4 is small, and appeared at δ_C 43.8: ~2 ppm higher than one of the corresponding carbons (δ_C 45.7) of the α-isomer (±)-**12α**. This implies that the deformation of the piperidone ring in the β-isomer (±)-**12β** helps to reduce the 1,3-dipolar interaction between the ethyl and the 4-axial hydrogen, which is understandable from the side view of the molecule as shown in Fig. 2.

Both isomers (+)-**6α** and (+)-**6β** were converted into the corresponding bicyclic lactams, (−)-benzyl 2α- and 2β-ethyl-4-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate (−)-**13α** and (−)-**13β**, by Beckmann rearrangement of the corresponding oximes, (+)-benzyl 2α- and 2β-ethyl-3-hydroxyimino-9-



Scheme 1

azabicyclo[3.3.1]nonane-9-carboxylate (+)-**14α** and (+)-**14β**, respectively.[1]

Treatment of the β-isomer (−)-**13β** with nitrogen peroxide followed by thermolysis resulted in denitrosation to afford quantitatively the parent lactam (−)-**13β**, although similar treatment of the α-isomer (−)-**13α** had afforded the corresponding rearrangement product, {[1*S*-(1α,5β,8aα)]-1-ethyl-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetic acid *threo*-**15a**, as the main product.[1] On the other hand, nitrosation followed by alkaline degradation of the resulting *N*-nitroso compound **16β** gave, as the main product, a mixture of the olefinic acids (*E*)- and (*Z*)-**9a** accompanied by a small amount of (2*R*)-*erythro*-*cis*-1-(benzyloxycarbonyl)dihydropalustramic acid

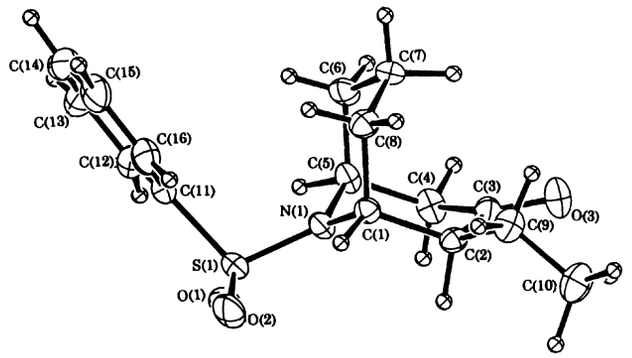
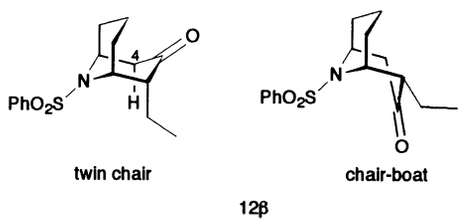


Fig. 1 ORTEP drawing of compound **12α** with crystallographic numbering scheme



12β

Scheme 2

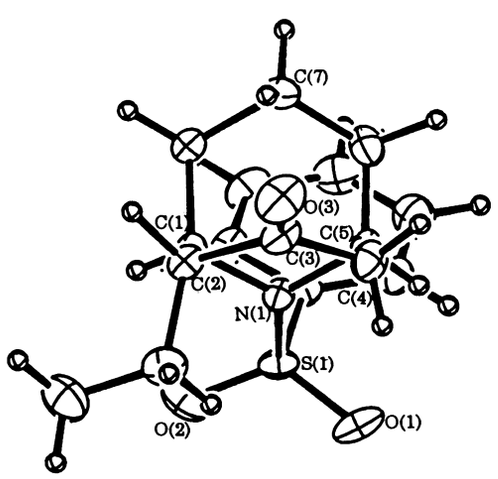


Fig. 2 ORTEP drawing of compound **12β** with crystallographic numbering scheme

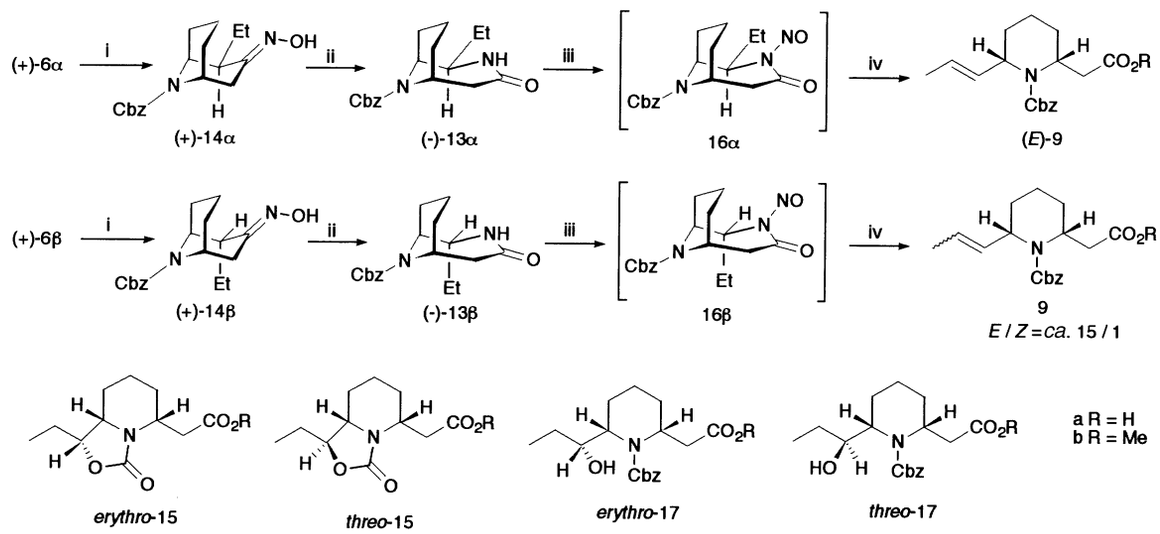
erythro-**17a** as a yellow oil. This was subjected to Fischer's esterification to give the corresponding esters, methyl [(2*R*)-(*E*)- and (2*R*)-(*Z*)-*cis*-1-benzyloxycarbonyl-6-(prop-1-enyl)piperidin-2-yl]acetate (*E*)- and (*Z*)-**9b** and methyl (2*R*)-(+)-*erythro*-*cis*-1-(benzyloxycarbonyl)dihydropalustramate (+)-*erythro*-**17b**,[1] in 54 and 3% yield, respectively from the lactam (−)-**13β**. Compounds (*E*)- and (*Z*)-**9b** were barely separable and the relative product ratio was determined to be *ca*. 15:1 on the basis of an ^{1}H NMR analysis of the mixture. Formation of a trace amount of methyl (2*R*)-*threo*-*cis*-1-(benzyloxycarbonyl)dihydropalustramate *threo*-**17b** has been detected by GC–MS analysis.

When 2α-nitroso lactam **16α** was treated with aq. sodium hydroxide, (*E*)-olefinic acid (*E*)-**9a** was also produced, but in a lower yield (~28%). It is interesting to note that no detectable amount of (*Z*)-olefinic acid (*Z*)-**9a** was formed from the α-isomer **16α**. Formation of oxazolidinones *threo*- and *erythro*-**15a** and dihydropalustramic acids *erythro*- and *threo*-**17a** were also detected. These acids were purified after derivatisation into the corresponding methyl esters (*E*)-(−)-**9b**, methyl {[1*S*-(1α,5β,8aα)]- and [1*R*-(1α,5α,8aβ)]-1-ethyl-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetate *threo*-[1] and *erythro*-**15b**

Table 1 ^{1}H and ^{13}C NMR data for benzenesulfonamides **12α** and **12β**

	12α		**12β**	
Position	δ_H [a]	δ_C [b]	δ_H [a]	δ_C [b]
1	4.42 (br m)	52.9 (d)	4.31 (br d-like)	53.3 (d)
2	2.38 (br dt, 7.0, 7.0)	54.4 (d)	2.16 (br t, 7.0)	57.2 (d)
3		209.7 (s)		211.4 (s)
4*endo*	2.33 (dd, 15.5, 1.0)	45.7 (t)	2.26 (dt, 14.0, 1.0)	43.8 (t)
exo	2.72 (dd, 15.5, 7.0)		2.80 (dd, 14.0, 7.0)	
5	4.50 (br m)	50.5 (d)	4.45 (br d-like)	50.2 (d)
6*endo*	1.60 (dm, 14.5)	30.2 (t)	*	29.0 (t)
exo	1.70 (tt, 14.5, 5.0)		*	
7*endo*	1.33 (qd, 14.5, 5.0)	15.9 (t)	*	16.0
exo	1.48 (dm, 14.5)		*	
8*endo*	1.72 (dm, 14.5)	24.9 (t)	*	29.4 (t)
exo	1.52 (tt, 14.5, 5.0)		*	
CH_3CH_2	1.14 (dqint, 15.0, 7.0)		1.60 (dqint, 15.0, 7.0)	25.3 (t)
	1.99 (dqint, 15.0, 7.0)	19.0 (t)	1.69 (dqint, 15.0, 7.0)	
CH_3CH_2	0.95 (t, 7.0)	11.6 (q)	0.93 (t, 7.0)	11.7 (q)
arom.	7.50–7.62 (3 H, m)	126.8 (d)	7.50–7.61 (3 H, m)	126.9 (d)
	7.87–7.93 (2 H, m)	129.3 (d)	7.88–7.92 (2 H, m)	129.2 (d)
		132.7 (d)		132.6 (d)
		141.1 (s)		141.4 (s)

[a] Recorded in $CDCl_3$ with chemical shifts relative to $\delta_H(Me_4Si)$ 0 at 500 MHz. [b] Recorded in $CDCl_3$ with chemical shifts relative to $\delta_C(CDCl_3)$ 77.00 at 125 MHz. * 1.45–1.70 (6 H, m, 6-, 7- and 8-H).



Scheme 3 *Reagents and conditions:* i, $NH_2OH{\cdot}HCl$, AcONa; ii, TsCl, K_2CO_3; iii, N_2O_4; iv, 5% aq. NaOH

(15%), and methyl *erythro*- and *threo-cis*-dihydropalustramate *erythro*- and *threo*-**17b** [1] (6%).

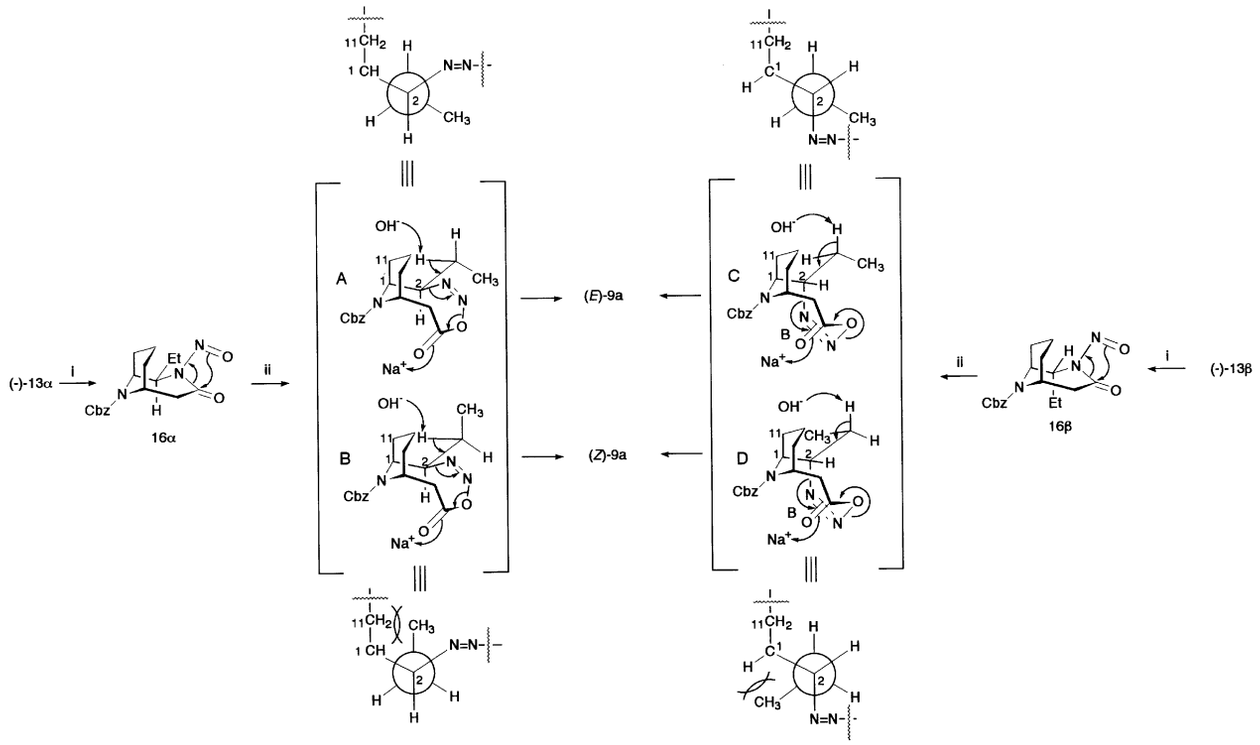
The IR spectrum of the olefinic ester (−)-**9b** showed absorption for the ester and urethane moieties at 1731 and 1687 cm^{-1}, respectively. A large coupling constant ($J_{trans;}$ 16.0 Hz) for the main olefinic signals appeared at δ_H 5.51 and 5.57 in the ^{1}H NMR spectrum confirming the *E*-configuration of the main product. In the ^{13}C NMR spectrum, two olefinic methyl signals corresponding to the *E*- and *Z*-configurations have been observed at δ_C 17.9 and 12.9, respectively.

Reaction mechanisms

It is suggested that in polar solvents formation of olefinic acids results from the β-elimination caused by attack of the solvent on the β-hydrogen rather than *via* the intramolecular pathway.[6] Thus, the formation of the olefinic acids **9a** would result from attack of a hydroxide anion on one of the methylene protons *anti* to the C^2–N bond. From the α-isomer **16α**, no (*Z*)-olefinic acid (*Z*)-**9a** has been produced. Speculation as to the stereochemistry of the intermediates in determining the regiochemical outcome of the β-elimination leading exclusively to the (*E*)-isomer (*E*)-**9a** is illustrated in Scheme 4, where Newman projections of each intermediate **A**, **B**, **C**, **D** through C^2–C_2H_5 bond are presented above or under the corresponding intermediate.

In order to avoid steric hindrance between C-11 and the methyl group, the CH_3–CH_2 bond in the ethyl moiety is likely to be orientated *anti* to the C^1–C^2 bond in the bicyclic system. Consequently, from the α-isomer **16α** elimination *via* the intermediate **A** is preferred, giving (*E*)-olefinic acid (*E*)-**9a** exclusively. Predominant formation of the (*E*)-isomer (*E*)-**9a** from the β-isomer **16β** is attributable to the preferred formation of the intermediate **C** rather than the intermediate **D**. The decreased selectivity for the (*E*)-olefin (*E*)-**9a** observed in the case of the β-isomer **16β** in comparison with the α-counterpart **16α** is reasonable because the steric hindrance around CH_3 in the intermediate **D** is not as much as that in the intermediate **B**.

Mechanisms for the formation of the oxazolidinones **15** *via* the corresponding lactones had been discussed in the preceding paper,[1] and their structures including the relative stereochemistry of the functionalities were determined by comparison of their spectroscopic properties with those of authentic specimens.



Scheme 4 *Reagents and conditions:* i, N_2O_4; ii, 5% aq. NaOH

Transformation of the olefinic esters (−)-9b into (+)-pinidine (+)-10 and (+)-monomorine I (+)-11

The methyl acetate function of compound (−)-**9b** was converted into the methyl group in the following manner. Attempted selective transformation[7] of compound (−)-**9b** into an aldehyde, (−)-benzyl (2*R*)-*cis*-2-(2-oxoethyl)-6-(propen-1-yl)piperidine-1-carboxylate (−)-**18**, using diisobutylaluminium hydride (DIBAL-H) was unsuccessful, and resulted in formation of a mixture of compound (−)-**18** and an alcohol, (−)-benzyl (2*R*)-*cis*-2-(2-hydroxyethyl)-6-(prop-1-enyl)piperidine-1-carboxylate (−)-**19**, even under careful treatment at lower temperature. Thus, the aldehyde (−)-**18** was prepared in two steps *via* DIBAL-H reduction followed by the Swern oxidation of the resulting alcohol (−)-**19** in 93% yield from compound (−)-**9b**. The ^{1}H NMR spectrum of the aldehyde (−)-**18** showed a triplet at δ_H 9.68 characteristic of the aldehyde proton. Compound (−)-**18** was then treated with tris(triphenylphosphine)-rhodium(I) chloride (Wilkinson complex) to give the desired decarbonylated product, (−)-benzyl (2*S*)-*cis*-2-methyl-6-(prop-1-enyl)piperidine-1-carboxylate (−)-**20**, in 94% yield, the ^{1}H NMR spectrum of which showed a doublet at δ_H 1.18 due to the newly formed methyl moiety. The relative product ratio between the (*E*)- and (*Z*)-isomers (*E*)- and (*Z*)-**20** was kept unchanged until this stage, when the 15:1 mixture of compounds (*E*)- and (*Z*)-**9b** was employed as the starting material. Treatment of the mixture (*E*)- and (*Z*)-**20** by boron tribromide caused deprotection and isomerization simultaneously, affording exclusively the desired (*E*)-olefin (+)-**10** in 86% yield, which is an enantiomer of pinidine, a major alkaloid of *Pinus* sp.[4a–c] When hydrogenated in the presence of 5% palladium-on-carbon, compound (−)-**20** afforded (−)-dihydropinidine (−)-**21**,[4a,b,f,8] a minor component isolated in 1993 from the Mexican Bean Beetle, *Ephilachna varivestis*.[8a]

On the other hand, Takahata and co-workers[5m] reported an asymmetric synthesis of (+)-monomorine I (+)-**11**, a trail pheromone of Falaoh's ants in Egypt, *Monomorium pharaonis*,[5a,b] *via* an aldehyde, (−)-benzyl (2*S*)-*cis*-2-formyl-6-methylpiperidine-1-carboxylate (−)-**22**. Thus, ozonolysis of olefin (−)-**20** was carried out to give compound (−)-**22** in 67% yield. The spectral properties were in accord with those of the authentic sample prepared *via* the alternative route.[5m]

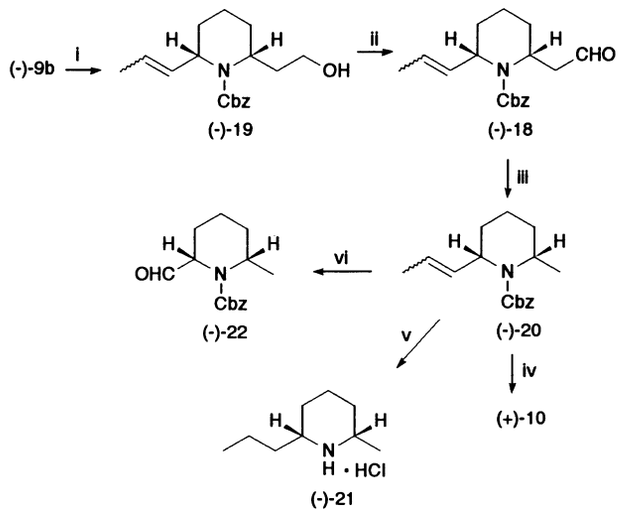
Consequently, by utilizing the dual mode of the Huisgen–White rearrangement, syntheses and/or formal synthesis of three more piperidine alkaloids (+)-pinidine (+)-**10**, (−)-dihydropinidine (−)-**21** and (+)-monomorine I (+)-**11** in addition to dihydropalustramic acid (−)-**7**, have been established starting from the 9-azabicyclo[3.3.1]nonane system **6** as the common starting material. Further investigations to convert the bicyclic system **1** into other bioactive naturally occurring compounds are now in progress.

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 ^{1}H, 67.5 MHz ^{13}C) or a JEOL JNM-GSX 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer. Chemical shifts and coupling constants (J) are given in δ values (ppm) and in Hz, respectively. All the NMR spectra were taken for $CDCl_3$ solutions with tetramethylsilane as internal standard. Low-resolution and high-resolution mass spectra (electron impact) were recorded on either a Shimadzu QP 1000EX 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.

Huisgen–White rearrangement of the lactams (−)-13α and (−)-13β

A saturated solution of nitrogen peroxide in DME (5 cm^3) was added dropwise to a stirred suspension of (−)-benzyl 2α-ethyl-4-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate (−)-**13α**[1] (300 mg, 0.95 mmol), sodium acetate (300 mg, 3.65 mmol) and DME (10 cm^3) at 0 °C. After being stirred for 15 min, the mix-



Scheme 5 *Reagents and conditions:* i, DIBAL-H; ii, $(COCl)_2$, DMSO, −55 °C; iii, $(Ph_3P)_3RhCl$, $CH_3(CH_2)_2CN$, 145 °C; iv, BBr_3, −10 °C; v, H_2, 5% Pd–C; vi, O_3, PPh_3, −55 °C

ture was added dropwise to well-stirred 5% aq. sodium hydroxide (300 cm^3) at −10 °C, and stirring was continued at that temperature until evolution of nitrogen ceased. The reaction mixture was acidified with 10% hydrochloric acid, and extracted with diethyl ether. The extract was washed with brine, and evaporated to give a pale yellow oil (298 mg), which was used in the next step without purification.

The Fisher's esterification of the oil (298 mg) with methanol (10 cm^3) gave a pale yellow oil (303 mg) which, on column chromatography (hexane–acetone, 20:1), gave (−)-*methyl* [(2R)-(E)-cis-1-*benzyloxycarbonyl*-6-(*prop*-1-*enyl*)*piperidin*-2-*yl*]*acetate* (*E*)-(−)-**9b** (88 mg, 28%), a 2:1 mixture of methyl {[1*S*-(1α,5β,8aα)]- and [1*R*-(1α,5α,8aβ)]-1-ethyl-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl}acetate *threo*- and *erythro*- **15b** (34 mg, 15%), and (+)-methyl (2*R*)-*erythro*-*cis*-1-(benzyloxycarbonyl)dihydropalustramate (+)-*erythro*-**17b** (20 mg, 6%). Formation of a trace amount of methyl (2*R*)-*threo*-*cis*-1-(benzyloxycarbonyl)dihydropalustramate *threo*-**17b** was detected by GC–MS analysis. The spectral properties of the oxazolidinone esters *erythro*- and *threo*-**15b** and methyl dihydropalustramate (+)-*erythro*-**17b** were in accord with those reported.[1,9]

Methyl (2R)-(E)-cis-*piperidin*-2-*ylacetate* (*E*)-(−)-**9b**: oil, bp 141–143 °C/0.01 mmHg (Found: C, 69.1; H, 7.8%; M^+, 331.1808. $C_{19}H_{25}NO_4$ requires C, 68.86; H, 7.60%; *M*, 331.1784); $[\alpha]_D^{16}$ −54.6 (*c* 1.10, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1731 and 1687; δ_H 1.46–1.84 (9 H, m, 3-, 4-, 5-H and CH=CHCH_3), 2.56 (1 H, dd, *J* 15.0 and 5.0, C*H*HCO_2CH_3), 2.64 (1 H, dd, *J* 15.0 and 9.5, CH*H*CO_2CH_3), 3.63 (3 H, s, CO_2CH_3), 4.69–4.75 (1 H, m, 2-H), 4.78 (1 H, br s, 6-H), 5.13 (1 H, d, *J* 13.0, OC*H*HPh), 5.17 (1 H, d, *J* 13.0, OCH*H*Ph), 5.51 (1 H, ddq, *J* 16.0, 5.0 and 1.0, C*H*=CHCH_3), 5.57 (1 H, dqd, *J* 16.0, 6.0 and 1.0, CH=C*H*CH_3) and 7.26–7.39 (5 H, m, arom.); δ_C 14.3 (t), 17.9 (q), 27.9 (t), 28.2 (t), 38.7 (t), 47.7 (d), 51.1 (d), 51.6 (q), 67.1 (t), 126.6 (d), 127.7 (d), 127.8 (d), 128.4 (d), 131.7 (d), 136.9 (s), 155.6 (s) and 171.8 (s); *m*/*z* 331 (M^+, 0.8%), 258 (10), 240 (7), 214 (16), 196 (48) and 91 (100).

Methyl (2R)-threo-cis-*dihydropalustramate* *threo*-**17b** (Found: M^+, 349.1861. $C_{19}H_{27}NO_5$ requires *M*, 349.1889); *m*/*z* 350 (M + 1, 0.8%), 349 (M^+, 0.1%), 182 (22), 156 (100), 124 (69) and 91 (64).

Treatment of (−)-benzyl 2β-ethyl-3-oxo-9-azabicyclo[3.3.1]-nonane-9-carboxylate (−)-**13β**[1] (300 mg, 0.95 mmol) with nitrogen peroxide followed by work-up according to the method described above afforded a 15:1 mixture of methyl (2*R*)-(*E*)-*cis*- and (2*R*)-(*Z*)-*cis*-piperidineacetate (*E*)- and (*Z*)-**9b** (169 mg, 54%) and (+)-methyl (2*R*)-*erythro*-*cis*-dihydropalustramate (−)-*erythro*-**17b** (10 mg, 3%). Formation of a trace amount of methyl (2*R*)-*threo*-*cis*-dihydropalustramate *threo*-**17b** was detected by GC–MS analysis.

A 15:1 mixture of methyl (2*R*)-(*E*)-*cis*- and (2*R*)-(*Z*)-*cis*-piperidineacetate (*E*)- and (*Z*)-**9b**: oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 1731 and 1687; δ_H 1.46–1.84 (9 H, m, 3-, 4-, 5-H and CH=CHCH_3), 2.56 (0.94 H, dd, *J* 15.0 and 4.5, C*H*HCO_2CH_3), 2.60 (0.06 H, m, C*H*HCO_2CH_3), 2.64 (0.94 H, dd, *J* 15.0 and 10.0, CH*H*CO_2CH_3), 2.70 (0.06 H, dd, *J* 15.0 and 10.0, CH*H*-CO_2CH_3), 3.63 (2.82 H, s, CO_2CH_3), 3.64 (0.18 H, s, CO_2CH_3), 4.69–4.75 (1 H, m, 2-H), 4.78 (0.94 H, br t-like, 6-H), 5.08 (0.06 H, br m, 6-H), 5.13 (1 H, d, *J* 13.0, OC*H*HPh), 5.17 (1 H, d, *J* 13.0, OCH*H*Ph), 5.48–5.62 (2 H, m, CH=CH) and 7.26–7.39 (5 H, m, arom.); δ_C[(*E*)-isomer/(*Z*)-isomer] 14.3/14.4 (t), 17.9/12.9 (q), 27.9/27.8 (t), 28.2/30.1 (t), 38.7/39.1 (t), 47.7/47.4 (d), 51.1/47.6 (d), 51.5/51.6 (q), 67.06/67.12 (t), 126.6/126.2 (d), 127.72/127.77 (d), 127.8/127.9 (d), 128.40/128.37 (d), 131.7/130.6 (d), 136.9/136.8 (s), 155.6/155.5 (s) and 171.83/171.75 (s).

(−)-Benzyl (2*R*)-*cis*-(2-hydroxyethyl)-6-(prop-1-enyl)piperidine-1-carboxylate (−)-19

A 1.5 mol dm^{-3} solution of diisobutylaluminium hydride in toluene (DIBAL-H; 2.9 cm^3, 4.35 mmol) was added dropwise to a solution of methyl piperidineacetate (−)-**9b** (633 mg, 1.91 mmol) in toluene (10 cm^3) at −10 °C, and the mixture was stirred at that temperature for 1 h. The reaction was quenched by addition of 5% hydrochloric acid, and the resulting mixture was extracted with diethyl ether. The extract was washed with brine, and evaporated to give a yellow oil (570 mg) which, on distillation at reduced pressure, gave *title compound* (−)-**19** (562 mg, 97%) as an oil, bp 119–120 °C/0.008 mmHg (Found: M^+, 303.1811. $C_{18}H_{25}NO_3$ requires *M*, 303.1835); $[\alpha]_D^{15}$ − 27.8 (*c* 0.44, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 and 1658; δ_H 1.46–1.80 (10 H, m, 3-, 4-, 5-H, CH=CHCH_3 and C*H*HCH_2OH), 1.87 (0.94 H, ddt, *J* 14.0, 11.0 and 3.5, CH*H*CH_2OH), 1.91 (0.06 H, ddt, *J* 14.0, 11.0 and 3.5, CH*H*CH_2OH), 3.20 (1 H, br s, CHH-CH_2O*H*), 3.40–3.48 (1 H, m, C*H*HOH), 3.52–3.60 (1 H, m, CH*H*OH), 4.41–4.50 (1 H, m, 2-H), 4.79 (0.94 H, m, 6-H), 5.08–5.16 (0.06 H, br m, 6-H), 5.11 (0.94 H, d, *J* 12.5, OC*H*HPh), 5.13 (0.06 H, d, *J* 12.5, OC*H*HPh), 5.16 (0.06 H, d, *J* 12.5, OCH*H*Ph), 5.21 (0.94 H, d, *J* 12.5, OCH*H*Ph), 5.40–5.60 (2 H, m, for *E*-**19**, 5.50, ddq, *J* 16.0, 5.0 and 1.0, C*H*=CHCH_3 and 5.56, dqd, *J* 16.0, 6.0 and 1.0, CH=C*H*CH_3) and 7.27–7.38 (5 H, m, arom.); δ_C[(*E*)-isomer/(*Z*)-isomer] 14.7/14.8 (t), 17.5/12.7 (q), 28.7/29.2 (t), 29.3/30.3 (t), 37.3/37.8 (t), 47.2/47.3 (d), 51.4/47.4 (d), 59.0/59.1 (t), 67.4/67.5 (t), 126.8/127.7 (d), 127.89/127.97 (d), 127.94/128.01 (d), 128.38/128.35 (d), 131.7/130.60 (d), 136.7/136.6 (s) and 156.8/156.7 (s); *m*/*z* 303 (M^+, 2%), 212 (49), 168 (15) and 91 (100).

(−)-Benzyl (2*R*)-*cis*-2-(2-oxoethyl)-6-(prop-1-enyl)piperidine-1-carboxylate (−)-18

Under argon, a mixture of dimethyl sulfoxide (525 mm^3, 7.4 mmol) and dichloromethane (7 cm^3) was added dropwise to a stirred solution of oxalyl chloride (315 mm^3, 3.7 mmol) in dichloromethane (7 cm^3) at −55 °C, and the mixture was stirred at that temperature for 5 min. To the mixture was added a solution of compound (−)-**19** (560 mg, 1.85 mmol) in dichloromethane (10 cm^3), and the resulting mixture was stirred at −55 °C for 20 min. After addition of a solution of triethylamine (2.7 cm^3, 18.5 mmol) in dichloromethane (7 cm^3) followed by stirring of the mixture at −55 °C for 1 h, the mixture was poured into water (15 cm^3), and extracted with diethyl ether. The extract was washed successively with 10% hydrochloric acid, aq. sodium hydrogen carbonate and brine, and evaporated to give a yellow oil (548 mg) which, on distillation at reduced pressure, gave *title aldehyde* (−)-**18** (534 mg, 96%) as an oil, bp 160–161 °C/0.008 mmHg (Found: C, 71.6; H, 7.5%; M^+, 301.1706. $C_{18}H_{23}NO_3$ requires C, 71.73; H, 7.69%; *M*, 301.1678); $[\alpha]_D^{16}$ −61.8 (*c* 0.41, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$

1721 and 1679; δ_H 1.46–1.86 (9 H, m, 3-, 4-, 5-H and CH=CHCH_3), 2.59 (0.94 H, ddd, *J* 16.0, 8.5 and 2.0, C*H*H-CHO), 2.64 (0.06 H, ddd, *J* 16.0, 8.5 and 2.0, C*H*HCHO), 2.71 (0.94 H, ddd, *J* 16.0, 6.0 and 2.0, CH*H*CHO), 2.75 (0.06 H, ddd, *J* 16.0, 6.0 and 2.0, CH*H*CHO), 4.79 (0.94 H, br t-like, 6-H), 4.82–4.90 (1 H, m, 2-H), 5.08–5.12 (0.06 H, br m, 6-H), 5.12 (1 H, d, *J* 12.5, OC*H*HPh), 5.16 (1 H, d, *J* 12.5, OCH*H*Ph), 5.48–5.62 (2 H, m, for *E*-**18**, 5.51, ddq, *J* 16.0, 5.0 and 1.0, C*H*=CHCH$_3$ and 5.56, dqd, *J* 16.0, 6.0 and 1.0, CH=C*H*CH$_3$), 7.26–7.36 (5 H, m) and 9.68 (1 H, t, *J* 2.0, CHO); δ_C[(*E*)-isomer/(*Z*)-isomer] 14.3/14.5 (t), 17.6/12.9 (q), 28.2/28.5 (t), 28.6/29.9 (t), 45.74/45.69 (d), 48.6/48.9 (t), 51.1/47.4 (d), 67.16/67.24 (t), 126.8/126.4 (d), 127.8/127.65 (d), 127.9/127.69 (d), 128.33/128.26 (d), 131.8/130.6 (d), 136.72/136.67 (s), 155.6/155.5 (s) and 200.3/200.2 (d); *m*/*z* 301 (M^+, 2%), 214 (10), 166 (19) and 91 (100).

(−)-Benzyl (2*S*)-*cis*-2-methyl-6-(prop-1-enyl)piperidine-1-carboxylate (−)-20

Under argon, a mixture of aldehyde (−)-**18** (520 mg, 1.73 mmol), tris(triphenylphosphine)rhodium(I) chloride (1.76 g, 1.90 mmol) and valeronitrile (20 cm^3) was heated at 140 °C for 30 min. The resulting precipitates were filtered off, and washed with diethyl ether. The filtrate and the washings were combined, and evaporated to give a pale yellow residue (923 mg), which was triturated with hot hexane. Evaporation of the solvent left a pale yellow oil (503 mg) which, on column chromatography (hexane–ethyl acetate, 100:1), gave *title compound* (−)-**20** (445 mg, 94%) as an oil, bp 94–96 °C/0.007 mmHg (Found: C, 74.8; H, 8.6%; M^+, 273.1750. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48%; *M*, 273.1729); $[\alpha]_D^{16}$ −21.0 (*c* 0.19, $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 1676; δ_H 1.18 (2.82 H, d, *J* 7.0, 2-CH_3), 1.25 (0.18 H, d, *J* 7.0, 2-CH_3), 1.42–1.82 (9 H, m, 3-, 4-, 5-H and CH=CHCH_3), 4.37–4.46 (1 H, m, 2-H), 4.71–4.75 (0.94 H, br m, 6-H), 5.02–5.08 (0.06 H, m, 6-H), 5.13 (1 H, d, *J* 12.5, OC*H*HPh), 5.16 (1 H, d, *J* 12.5, OCH*H*Ph), 5.46 (0.06 H, dqd, *J* 10.0, 7.0 and 1.0, CH=C*H*CH$_3$), 5.50–5.61 (1.88 H, m, CH=CH), 5.71 (0.06 H, ddq, *J* 10.0, 9.0 and 1.0, C*H*=CHCH$_3$) and 7.27–7.40 (5 H, m, arom.); δ_C[(*E*)-isomer/(*Z*)-isomer] 14.3/14.5 (t), 17.8/12.7 (q), 20.5/20.9 (q), 28.8/30.0 (t), 30.2/30.4 (t), 46.4/46.3 (d), 51.4/47.6 (d), 66.77/66.84 (t), 125.9/125.2 (d), 127.7 (d), 127.8 (d), 128.4 (d), 132.5/131.7 (d), 137.2/137.1 (s) and 155.8/155.7 (s); *m*/*z* 273 (M^+, 3%), 214 (23), 182 (100), 138 (26) and 91 (98).

(+)-Pinidine (+)-10

Under argon, a mixture of compound (−)-**20** (115 mg, 0.42 mmol), boron tribromide (117 cm^3, 1.23 mmol) and dichloromethane (7 cm^3) was stirred at −10 °C for 3 h. The reaction mixture was then treated with 10% aq. sodium hydroxide (6 cm^3), and extracted with dichloromethane. The extract was acidified with a saturated solution of hydrogen chloride in methanol (2 cm^3), and evaporated to dryness. The resulting solid (76 mg) was recrystallized from a mixture of ethanol and diethyl ether to give a hydrochloride of the title compound (+)-**10**·HCl (64 mg, 86%), mp 244–245 °C (lit.,[4d] 243–244 °C); $[\alpha]_D^{24}$ +10.6 (*c* 0.55, EtOH) [lit.,[4d] +10.2 (*c* 6.0, EtOH)]. The hydrochloride (+)-**10**·HCl (62 mg, 0.35 mmol) was treated with aq. ammonia (1 cm^3) to afford (+)-pinidine (+)-**10** quantitatively as an oil, bp 172–174 °C/760 mmHg [for (−)-**10**; lit.,[4a] bp 176–177 °C/751 mmHg]; $[\alpha]_D^{24}$ +10.3 (*c* 0.50, EtOH) [lit.,[4a] −10.5 (*c* 1.88, EtOH)]. The spectral properties of compounds (+)-**10**·HCl[4g] and (+)-**10**[4g] were in accord with those reported.

Dihydropinidine hydrochloride (−)-21·HCl

A suspension of 5% palladium-on-carbon (10 mg) in methanol (2 cm^3) was pre-equilibrated with hydrogen. To the suspension was added a solution of compound (−)-**20** (40 mg, 0.146 mmol) in methanol (3 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 acidified with a saturated solution of hydrogen chloride in methanol (2 cm^3), and then evaporated to dryness. The resulting solid (26 mg) was recrystallized from a mixture of ethanol and ethyl acetate to give dihydropinidine hydrochloride (−)-**21**·HCl (20 mg, 79%) as needles, mp 245–247 °C (lit.,[8f] 245–246.2 °C); $[\alpha]_D^{14}$ −12.6 (*c* 0.28, EtOH) [lit.,[4b] +12.7 (*c* 1.07, EtOH), lit.,[8e] −12.85 (*c* 1.09, EtOH), lit.,[8f] − 11.6 (*c* 3.0, EtOH)]. The spectral properties of compound (−)-**21**·HCl were in accord with those reported.[8f]

(−)-Benzyl (2*S*)-*cis*-2-formyl-6-methylpiperidine-1-carboxylate (−)-22

Ozone was bubbled through a solution of compound (−)-**20** (50 mg, 0.18 mmol) in dichloromethane (5 cm^3) at −60 °C until the blue colour of the reaction mixture persisted. Nitrogen was passed through the mixture at −60 °C until the blue colour was discharged. Then a solution of triphenylphosphine (62.4 mg, 1.3 mmol) in dichloromethane (2 cm^3) was added, and the resulting mixture was allowed to warm to room temperature. It was then evaporated to give a yellow oil (113 mg) which, on column chromatography (hexane), gave title compound (−)-**22** (32 mg, 67%). The ^{1}H NMR spectrum of compound (−)-**22** was in accord with one of the authentic sample synthesized by Takahata.

Compound **22**: oil, bp 81–83 °C/0.008 mmHg (Found: M^+, 261.1395. $C_{15}H_{19}NO_3$ requires *M*, 261.1365); $[\alpha]_D^{16}$ −107.9 (*c* 0.81, $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 1731 and 1687; δ_H 1.10 (3 H, d, *J* 6.5, CH_3), 1.36–1.70 (5 H, m, 3-, 4_{ax}- and 5-H), 2.34 (1 H, br d, *J* 13.5, 4_{eq}-H), 4.45–4.53 (1 H, m, 2-H), 4.66 (1 H, br s, 6-H), 5.18 (1 H, d, *J* 12.0, OC*H*HPh), 5.20 (1 H, d, *J* 12.0, OCH*H*Ph) 7.30–7.40 (5 H, m, arom.) and 9.62 (1 H, d, *J* 1.0, CHO); δ_C 15.1 (t), 18.9 (q), 22.6 (t), 29.5 (t), 46.7 (d), 59.4 (d), 67.5 (t), 127.9 (d), 128.1 (d), 128.5 (d), 136.4 (s), 155.8 (s) and 202.2 (d); *m*/*z* 261 (M^+, 0.3%), 260 (0.4), 232 (70), 188 (67) and 91 (100).

X-Ray crystallography

Preparation of 2α-ethyl-9-phenylsulfonyl-9-azabicyclo[3.3.1]-nonan-3-one (±)-12α. The benzenesulfonamide (±)-**12α** as a sample for X-ray chromatographic analysis was prepared by employing a racemic reactant (±)-**6α** 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 (±)-**6α** (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 (258 mg), which was used in the next step without purification.

A mixture of the oil (258 mg), triethylamine (563 mm^3, 4.0 mmol), benzenesulfonyl chloride (256 mm^3, 2.0 mmol) and dichloromethane (5 cm^3) was stirred at 0 °C for 12 h. After dilution of the mixture with dichloromethane (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 (563 mg) which, on recrystallization from acetone–hexane, gave *title compound* (±)-**12α** (438 mg, 86%) as plates, mp 118.5–119.5 °C (Found: C, 62.6; H, 6.9%; M^+, 307.1261. $C_{16}H_{21}NO_3S$ requires C, 62.51; H, 6.89%; *M*, 307.1243); $\nu_{max}(CHCl_3)$/cm^{-1} 1707, 1356 and 1163; *m*/*z* 307 (M^+, 1%), 222 (100), 166 (28), 141 (18) and 77 (35). ^{1}H and ^{13}C NMR data for compound (±)-**12α** are listed in Table 1.

Crystal data for benzenesulfonamide (±)-12α. $C_{16}H_{21}NO_3S$, M = 307.41, orthorhombic, *a* = 15.818(4), *b* = 15.822(3), *c* = 12.141(3) Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$, *V* = 3039(2) Å^3 (by least-squares refinement on diffractometer angle for 25 automatically centred reflections, $\lambda = 0.710\ 69$ Å), space group *Pbca*, *Z* = 8, μ(Mo-Kα) = 2.12 cm^{-1}, *F*(000) = 1312, D_c = 1.344 g cm^{-3}, crystal dimensions: 0.10 × 0.10 × 0.05 mm.

Data collection and processing. ω–2θ mode with θ scan

width = 1.42 + 0.30 tan θ, ω scan speed of 8.0 min^{-1}; 1341 reflections ($20.01 \leq 2\theta \leq 33.02°$) were collected on a Rigaku AFC5R diffractometer with graphite-monochromated Mo-Kα radiation and 1491 reflections with $I > 3\sigma(I)$ were used in the structure determination. No decay corrections was applied.

Structure analysis and refinement. The structure was solved by direct methods (MITHRIL).[10] 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.[11] Final refinements converged to $R(R_w) = 0.047$ (0.052). An ORTEP drawing of compound **12α** is shown in Fig. 1. Tables of atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).‡

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‡ For details of the deposition scheme, 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 207/66.

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