Chiral Synthesis of the Key Intermediate for 1β-Methylcarbapenem Antibiotics Starting from (−)-Carvone

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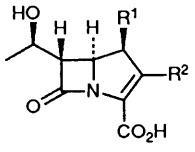
A stereoselective synthesis of the key intermediate for the preparation of 1β-methylcarbapenem antibiotics was achieved by using a cyclopentanone derivative, easily derived from (−)-carvone, as a starting material.

Recently, considerable effort[1] has been devoted towards the synthesis of the 1β-methylcarbapenem antibiotic **1**,[2] because of its broad-spectrum and potent antibacterial activity in addition to its remarkable chemical stability to renal dehydropeptidase I.



1 R^1 = Me, R^2 = $SCH_2C(NH)NH_2$
2 R^1 = H, R^2 = $SCH_2CH_2NH_2$

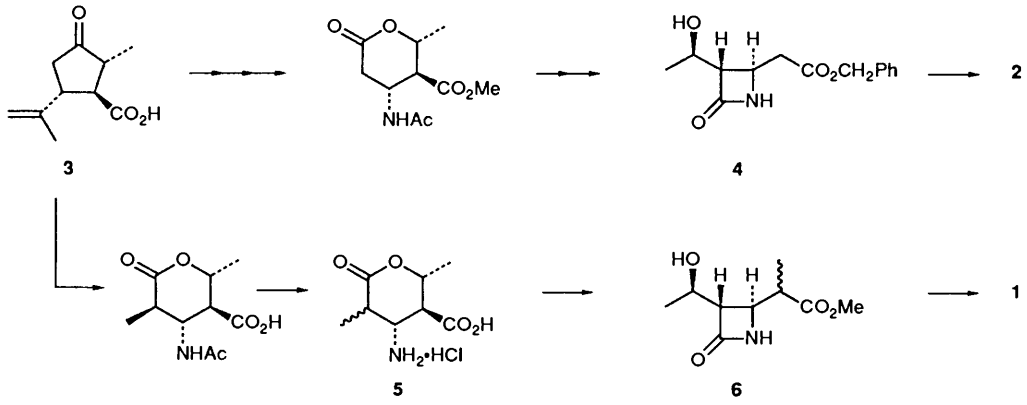
We have already developed[3] a stereoselective synthesis of the key intermediate **4** for thienamycin **2**, *via* Melillo's lactone,[4] employing the chiral cyclopentanone **3**, easily derived from (−)-carvone, as the starting material. By using essentially the same strategy,[3–6] the synthesis of the key intermediate **6** for 1β-methylcarbapenem was also achieved[7] as shown in Scheme 1, which involved the conversion of the isopropenyl group into an amine function and the Baeyer–Villiger oxidation of a cyclopentanone into a δ-lactone, as key steps; however, epimerisation of the methyl group at the 3-position of the lactone **5** was observed during the deprotection of the acetyl group on the amine function in this synthesis.

In this paper we report a stereoselective synthesis of compound **6**, starting from the chiral cyclopentanone **3**, where the carboxy group was converted into an amino group and regioselective 1,5-bond cleavage of the cyclopentanone was involved in the construction of the 1β-methyl function stereoselectively without epimerisation.

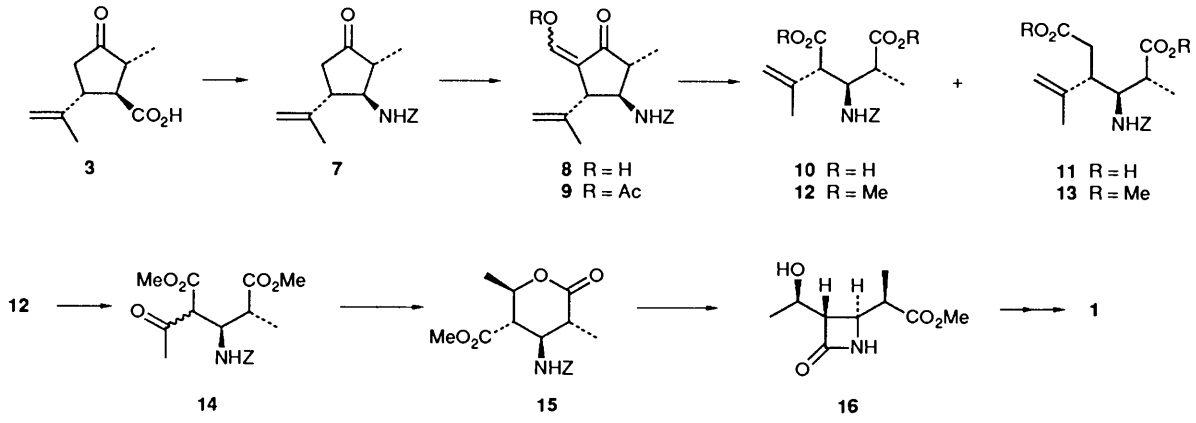
Results and Discussion

Thus, treatment of the keto acid **3** with diphenylphosphoryl azide[8] in benzene in the presence of triethylamine, followed by the addition of benzyl alcohol to the mixture, afforded the amino derivative **7**, stereoselectively, in 71% yield. Condensation of compound **7** with ethyl formate in the presence of sodium methoxide in diethyl ether gave the hydroxymethylene derivative **8** as a single stereoisomer, which was then acetylated by treatment with acetic anhydride to provide the acetoxymethylene compound **9**, again as a single stereoisomer, although the stereochemistry of the enol ester function could not be determined at this stage, in 90% yield from substrate **7**. Oxidation of the cyclopentanone **9** with 35% hydrogen peroxide brought about bond cleavage to give the diacids **10** and **11** which, without isolation, were subjected to esterification with methyl iodide and potassium carbonate to afford the diesters **12** and **13** in 41 and 21% yield, respectively. Ozonolysis of the major compound **12**, followed by reductive work-up with triphenylphosphine, afforded the ketone **14** in 71% yield. Although reduction of the ketone **14** with various kinds of reducing agents was attempted, the expected stereoselectivity could not be obtained; however, reduction with triethylsilane in trifluoroacetic acid (TFA)[6] furnished the desired δ-lactone **15** stereoselectively, whose spectroscopic data, including the specific optical rotation, were identical with those reported.[9] Since the δ-lactone **15** has already been transformed into the azetidinone **16**,[9] the key intermediate for our target carbapenem **1**, this synthesis constitutes its stereoselective synthesis (Scheme 2).

We next attempted to develop an alternative route to compound **16** as follows. Ketalisation of the acid **3** with ethylene glycol in the presence of toluene-*p*-sulphonic acid (PTSA) in benzene gave the acid **17**, which without purification was



Scheme 1



Scheme 2 Z = CO_2CH_2Ph

treated with diphenylphosphoryl azide, followed by heating with benzyl alcohol to provide the carbamate **18** in 59% yield from the acid **17**. Conversion of the isopropenyl group into an acetyl group was carried out by treatment of compound **18** with osmium tetraoxide and sodium periodate in *tert*-butyl alcohol to give the ketone **19** in 99% yield. Sodium borohydride reduction then afforded a mixture of the diastereoisomers of the hydroxy compound in the ratio ~1:1; however, stereoselective reduction could be achieved on exposure of ketone **19** to lithium tri-*sec*-butylborohydride (L-Selectride) in tetrahydrofuran (THF) to furnish the alcohol **20**. Although the stereochemistry of the hydroxy group in compound **20** could not be determined at this stage, this alcohol was subjected to further conversion into a δ-lactone. After deprotection of the ketal group of compound **20** by acid treatment, the resulting alcohol **21** was protected as the silyl ether **22** in the usual manner. Regioselective bond cleavage of compound **22** was accomplished as before by adoption of the same strategy as used for the preparation of diacid **10** from ketone **7**, *i.e. via* compounds **23** and **24** to give the diacids **25** and **26**, which on treatment with benzyl bromide and potassium carbonate in dimethyl sulphoxide (DMSO) provided the diesters **27** and **28** which, without separation, was used in the next reaction. Deprotection of the silyl group of the mixture of diesters **27** and **28** with boron trifluoride–diethyl ether in methylene dichloride took place to yield the δ-lactone **29** in 20% yield from the cyclopentanone **22**. The stereochemistry of this lactone was determined from its NMR spectrum which exhibited a signal for 3-H at δ 2.84, *J* 6.7 and 9.8 Hz, and one for 4-H at δ 4.21, *J* 6.7, 9.2 and 9.8 Hz, supporting its relative stereostructure as that shown. This stereochemical assignment was unambiguously confirmed by the conversion of lactone **29** into the β-lactam **31** as follows. Deprotection of the benzyloxycarbonyl group of compound **29** by catalytic hydrogenation over palladium–carbon, followed by treatment of the resulting amine with 10% hydrochloric acid, gave the hydrochloride **30** which, on exposure to methanol, followed by recyclisation of the resulting methyl ester with dicyclohexylcarbodiimide (DCC), afforded the β-lactam **31** and the lactone **32** in 75 and 23% yield, respectively. The NMR spectrum of compound **31** clearly indicated that this lactam had the *cis*-configuration between the 3- and 4-position, hence the stereochemistry of the hydroxy group of compound **20** was determined to have the *S*-configuration. In order to synthesize the desired β-lactam **16**, this *cis*-compound **31** was oxidised with pyridinium chlorochromate (PCC) to give the *trans*-β-lactam **33** with epimerisation at the 3-position, which on reduction with sodium borohydride gave the desired β-lactam **16** together with its diastereoisomer **34** as an inseparable mixture. Potassium tri-*sec*-butylborohydride (K-Selectride) was a superior reducing agent to sodium borohydride in terms of stereoselectivity and the conversion yield. Separation of the mixture was achieved by its conversion into the *p*-nitrobenzyloxycarbonyl derivatives **35** and **36**. Deprotection of *R*-compound **35** by catalytic hydrogenation over palladium–carbon furnished the β-lactam **16**, which was identical with the authentic sample derived from compound **15**. The pure epimer **34** was also obtained from *S*-ester **36** by catalytic reduction (Scheme 3).

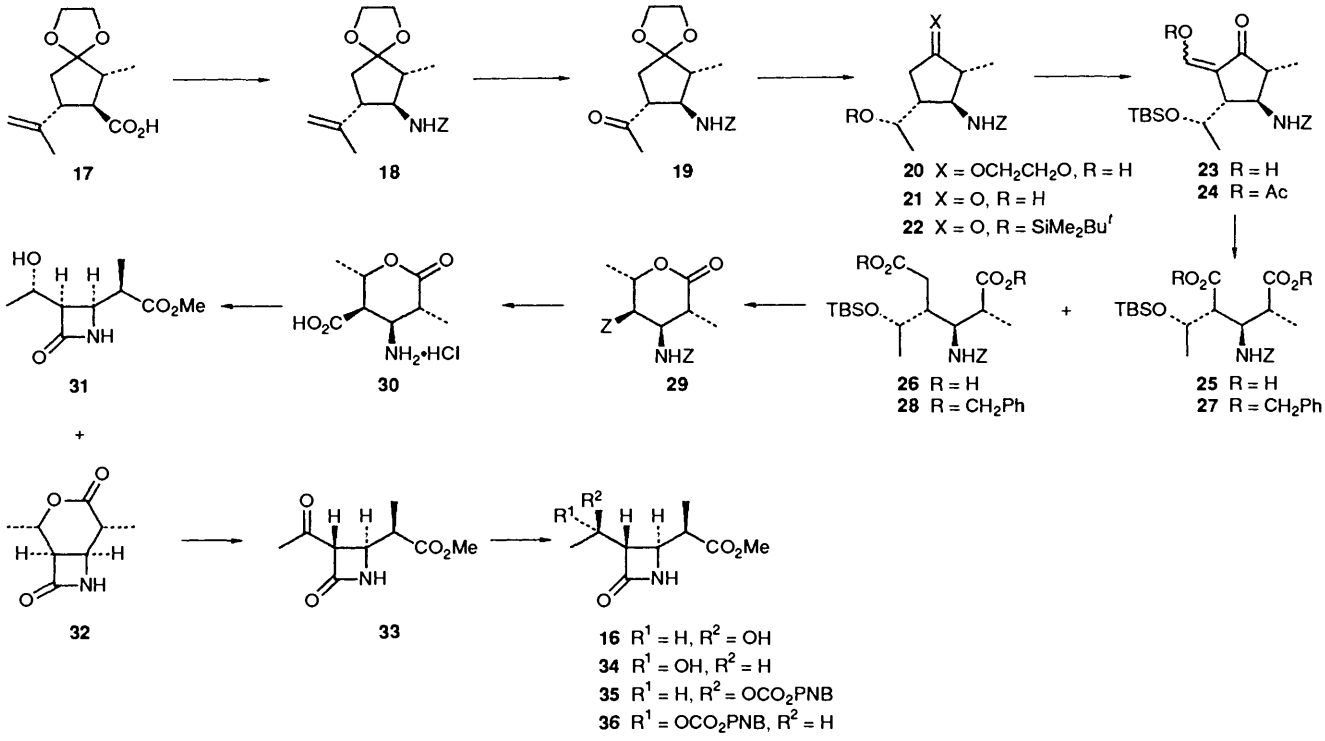
Hence, we have demonstrated alternative synthetic routes to the key intermediate for the preparation of 1β-methylcarbapenems starting from a chiral cyclopentanone easily derived from (−)-carvone, and this strategy should be widely applicable to the synthesis of other types of carbapenem antibiotics in optically active form.

Experimental

General Methods.—M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemial shifts are reported from internal Me_4Si. *J*-Values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer.

(2R,3S,4S)-3-*Benzyloxycarbonylamino*-4-*isopropenyl*-2-*methylcyclopentanone* **7**.—To a stirred solution of (1*S*,2*R*,5*R*)-5-isopropenyl-2-methyl-3-oxocyclopentanecarboxylic acid **3** (1.82 g, 10 mmol) in benzene (100 cm^3) were added triethylamine (1.52 g, 15 mmol) and diphenylphosphoryl azide (3.03 g, 12 mmol), and the mixture was stirred for 3 h at room temperature. After addition of benzyl alcohol (1.3 g, 12 mmol), the reaction mixture was refluxed for 1 h. The benzene solution was washed successively with aq. $NaHCO_3$, aq. $KHSO_4$ and brine, and was then dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (6:1) gave the *cyclopentanone* **7** (2.06 g, 71%) as needles, m.p. 92–94 °C (from benzene–cyclohexane) (Found: C, 71.0; H, 7.45; N, 4.8. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.37; N, 4.87%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1730, 1705 and 1640; δ 1.13 (3 H, d, *J* 7, Me), 1.70 (3 H, s, Me), 2.13–2.24 (2 H, m, 4- and 5-H), 2.49–2.68 (2 H, m, 2- and 5-H), 3.77–3.85 (1 H, m, 3-H), 4.88 (3 H, s, C=CH_2 and NH), 5.10 (2 H, s, CH_2Ph) and 7.34 (5 H, s, ArH); *m/z* 287 (M^+) (Found: M^+, 287.1527. $C_{17}H_{21}NO_3$ requires M, 287.1521).

(2R,3S,4R)-3-*Benzyloxycarbonylamino*-5-*hydroxymethylene*-4-*isopropenyl*-2-*methylcyclopentanone* **8**.—To a stirred solution of compound **7** (1.44 g, 5 mmol) and ethyl formate (6 cm^3) in Et_2O (100 cm^3) at 0 °C was added 28% NaOMe–MeOH (1.93 g,



Scheme 3 TBS = $SiMe_2Bu^t$, PNB = $CH_2C_6H_4NO_2$-*p*

10 mmol) and the mixture was stirred for 3 h at room temperature. After addition of AcOH (1 cm^3), the reaction mixture was washed with brine, dried over $MgSO_4$, and evaporated to give *compound* **8** (1.55 g, 98%) as a yellowish oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 3350, 1700 and 1665; δ 1.20 (3 H, d, *J* 6, Me), 1.67 (3 H, s, Me), 2.20–2.67 (1 H, m, 2-H), 3.20 (1 H, d, *J* 10, 4-H), 3.75 (1 H, m, 3-H), 4.88 (2 H, s, C=CH_2), 5.03 (2 H, s, CH_2Ph), 5.26 (1 H, d, *J* 9.1, NH), 6.87 (1 H, d, *J* 2, C*H*OH), 7.30 (5 H, s, ArH) and 10.79 (1 H, br s, OH); *m/z* 315 (M^+) (Found: M^+, 315.1476. $C_{18}H_{21}NO_4$ requires M, 315.1471), which was used in the next reaction without further purification.

(3R,4S,5R)-2-*Acetoxymethylene*-4-*benzyloxycarbonylamino*-3-*isopropenyl*-5-*methylcyclopentanone* **9**.—A mixture of compound **8** (1.26 g, 4 mmol) and Ac_2O (4 cm^3) was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was purified by short-column chromatography to afford *compound* **9** (1.3 g, 92%) as a mixture of geometric isomers (Found: C, 67.3; H, 6.55; N, 3.9%; M^+, 357.1564. $C_{20}H_{23}NO_5$ requires C, 67.21; H, 6.49; N, 3.92%; M, 357.1574); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300, 1760, 1700 and 1635; δ 1.20 (3 H, d, *J* 6, Me), 1.67 (3 H, s, Me), 2.17 (3 H, s, Ac), 2.31 (1 H, m, 2-H), 3.33 (1 H, d, *J* 7.9, 4-H), 3.75 (1 H, m, 3-H), 4.92 (2 H, s, C=CH_2), 5.08 (2 H, s, CH_2Ph), 5.54 (1 H, d, *J* 9, NH), 7.30 (5 H, s, ArH) and 8.15 (1 H, d, *J* 3, C*H*OAc).

Dimethyl (2S,3R,4R)-3-*Benzyloxycarbonylamino*-2-*isopropenyl*-4-*methylpentanedioate* **12** *and Dimethyl* (2R,3S,4S)-3-*Benzyloxycarbonylamino*-4-*isopropenyl*-2-*methylhexanedioate* **13**.—To a stirred emulsion of the acetate **9** (462 mg, 1.29 mmol) and 35% H_2O_2 (6 cm^3) in methanol (2 cm^3) was added K_2CO_3 (1 g). Immediately, an exothermic reaction occurred, then saturated aq. Na_2SO_3 was added to the mixture. After 5 min, a large amount of methanol was added and the mixture was filtered to remove insoluble materials. The filtrate was concentrated to give a residue, which was acidified with conc. HCl, and then extracted with chloroform–methanol (10:1). The organic layer was dried over Na_2SO_4 and evaporated to give a mixture of the diacids **10** and **11**, which were dissolved in DMSO (2.5 cm^3). To this solution were added K_2CO_3 (380 mg) and methyl iodide (0.17 cm^3), and the resulting mixture was stirred for 1 h at room temperature and then diluted with ethyl acetate (100 cm^3). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (6:1) gave the *pentanedioate* **12** (140 mg, 41%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 1720 and 1650; δ 1.10 (3 H, d, *J* 6.7, Me), 1.74 (3 H, s, Me), 2.74 (1 H, dq, *J* 3.7 and 6.7, 4-H), 3.28 (1 H, d, *J* 9.8, 2-H), 3.65 (3 H, s, CO_2Me), 3.69 (3 H, s, CO_2Me), 4.69 (1 H, ddd, *J* 3.7, 10.4 and 9.8, 3-H), 4.80 (1 H, br d, *J* 10.4, NH), 4.93 and 4.95 (each 1 H, each s, C=CH_2), 5.05 (2 H, s, CH_2Ph) and 7.29–7.32 (5 H, m, ArH); *m/z* 363 (M^+) (Found: M^+, 363.1682. $C_{19}H_{25}NO_6$ requires *M*, 363.1682). Further elution with the same solvent gave the diester **13** (103 mg, 21%) as an oil, δ 1.15 (3 H, d, *J* 6.7, Me), 1.73 (3 H, s, Me), 2.50 (2 H, d, *J* 7.9, 5-H_2), 2.56 (1 H, dq, *J* 6.7 and 6.7, 2-H), 2.76 (1 H, dt, *J* 6.7 and 7.9, 4-H), 3.63 (3 H, s, CO_2Me), 3.67 (3 H, s, CO_2Me), 4.14 (1 H, m, 3-H), 4.76–4.89 (3 H, m, NH and C=CH_2), 5.04 and 5.30 (each 1 H, each d, *J* 12.2, CH_2Ph) and 7.32 (5 H, s, ArH).

Dimethyl (2R/S,3R,4R)-2-*Acetyl*-3-*benzyloxycarbonylamino*-4-*methylpentanedioate* **14**.—A stream of ozone was bubbled through a solution of diester **12** (1.31 g, 3.6 mmol) in ethyl acetate (20 cm^3) at −78 °C until a persistent blue colour was observed. The reaction mixture was flushed with argon and treated with triphenylphosphine (1.89 g, 7.2 mmol) at the same temperature. The resulting mixture was allowed to warm to room temperature during 3 h. After evaporation of the solvent, the residue was chromatographed on silica gel with hexane–ethyl acetate (3:1) to give the *title compound* **14** (0.93 g, 71%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1700; δ 1.20 and 1.23 (total 3 H, each d, *J* 6.7 and 7.3, Me), 2.23 and 2.28 (total 3 H, each s, Ac), 2.63–2.77 (total 1 H, m, 4-H), 3.64, 3.66, 3.69 and 3.71 (total 6 H, each s, 2 × CO_2Me), 3.79 and 3.83 (total 1 H, each d, *J* 3.1 and 4.3, COCHCO), 4.51 and 4.61 (total 1 H, each ddd, *J* 4.3, 9.2, 11.0 and 3.1, 10.4, 10.4, 3-H), 5.01–5.14 (2 H, m, CH_2Ph), 5.93 and 5.99 (total 1 H, br d, *J* 11.0 and 10.4, NH) and 7.32 (5 H,

s, ArH); *m/z* 365 (M^+) (Found: M^+, 365.1474. $C_{18}H_{23}NO_7$ requires *M*, 365.1474).

(3R,4R,5S,6R)-4-*Benzyloxycarbonylamino*-3,4,5,6-*tetrahydro*-5-*methoxycarbonyl*-3,6-*dimethyl*-2H-*pyran*-2-*one** **15**.—To a stirred solution of diester **14** (498 mg, 1.37 mmol) in TFA (2 cm^3) was added Et_3SiH (1 cm^3) dropwise and the mixture was stirred for 2 days at ambient temperature. After addition of methanol (3 cm^3) the mixture was stirred for 30 min, and neutralised with saturated aq. $NaHCO_3$. The aq. layer was extracted with CH_2Cl_2 and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (5:3) to give compound **15** as needles (182 mg, 40%), whose spectroscopic data, including its specific optical rotation, were identical with those reported.[9]

(2R,3S,4S)-3-*Benzyloxycarbonylamino*-4-*isopropenyl*-2-*methylcyclopentanone Ethylene Ketal* **18**.—A solution of compound **3** (41 g, 0.2 mol) and ethylene glycol (22 cm^3, 0.4 mol) in benzene in the presence of a catalytic amount of PTSA was refluxed for 4 h. After addition of an appropriate amount of $CaCl_2$, the reaction mixture was filtered. To the filtrate were added triethylamine (42 cm^3, 0.3 mol) and diphenylphosphoryl azide (47 cm^3, 0.2 mol) and the resulting mixture was stirred for 2 h at room temperature. Benzyl alcohol (207 cm^3, 2 mol) was added to the mixture, which was refluxed for 1 h. The mixture was washed successively with aq. Na_2CO_3 and brine, and was then dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with cyclohexane–ethyl acetate (1:1) to give the *ketal* **18** (39 g, 59%) as needles, m.p. 119 °C (from benzene–cyclohexane) (Found: C, 67.1; H, 7.55; N, 4.15. $C_{19}H_{25}NO_4 \cdot 0.5H_2O$ requires C, 67.04; H, 7.70; N, 4.12%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400, 1710br and 1505; δ 1.03 (3 H, d, *J* 7, Me), 1.73 (3 H, s, Me), 1.76–1.88 (2 H, m, 2- and 5-H), 2.01 (1 H, dd, *J* 9 and 14, 5-H), 2.38 (1 H, distorted q, *J* 9, 4-H), 3.70 (1 H, m, 3-H), 3.81–3.97 (4 H, m, OCH_2CH_2O), 4.61 (1 H, d, *J* 9, NH), 4.76 and 4.79 (each 1 H, each s, $C{=}CH_2$), 5.08 (2 H, s, CH_2Ph) and 7.33 (5 H, s, ArH); *m/z* 331 (M^+) (Found: M^+, 331.1775. $C_{19}H_{25}NO_4$ requires M, 331.1782).

(2R,3R,4R)-4-*Acetyl*-3-*benzyloxycarbonylamino*-2-*methylcyclopentanone Ethylene Ketal* **19**.—To a stirred solution of compound **18** (2.0 g, 6 mmol) in *t*-butyl alcohol (10 cm^3) were added aq. 0.5 mol dm^{-3} $NaIO_4$ (44 cm^3, 22 mmol) and 0.4 mol dm^{-3} OsO_4 in THF (0.3 cm^3, 0.12 mmol) and the mixture was stirred for 6 h before being extracted with ethyl acetate, and the extract was washed successively with aq. $Na_2S_2O_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent gave the *ketal* **19** (1.97 g, 99%) as needles, m.p. 127 °C (from benzene–cyclohexane) (Found: C, 64.7; H, 7.0; N, 4.1%; M^+, 333.1576. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.20%; M, 333.1576); $\nu_{max}(CHCl_3)$/cm^{-1} 3400, 1700br and 1450; δ 0.97 (3 H, d, *J* 6.7, Me), 1.96–2.18 (3 H, m, 2- and 5-H_2), 2.23 (3 H, s, MeCO), 2.87 (1 H, ddd, *J* 7.9, 7.9 and 9.2, 4-H), 3.55–3.97 (5 H, m, OCH_2CH_2O and 3-H), 5.09 (2 H, s, CH_2Ph), 5.14 (1 H, br s, NH) and 7.31 (5 H, s, ArH).

(2R,3S,4R)-3-*Benzyloxycarbonylamino*-4-[(S)-1-*hydroxyethyl*]-2-*methylcyclopentanone* **21**.—To a stirred solution of the ketone **19** (12 g, 36 mmol) in dry THF (480 cm^3) at −78 °C was slowly added 1.0 mol dm^{-3} L-Selectride in THF (72 cm^3, 72 mmol) under argon. After the mixture had been stirred for 20 min, 10% NaOH (43 cm^3, 108 mmol) and 30% H_2O_2 (12.3 cm^3, 108 mmol) were added and the resulting mixture was warmed to 0 °C. After evaporation of the solvent, the residual aq. layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give the ketal **20**, which was dissolved in acetone (200 cm^3) containing 70% $HClO_4$ (1 cm^3) and water (10 cm^3). After the mixture had been stirred at ambient temperature for 3 h, a large excess of $NaHCO_3$ and Na_2SO_4 was added, and the suspension was stirred for 1 h. The suspension was filtered and the filtrate was evaporated to give a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (1:1) to afford the *cyclopentanone* **21** (8.51 g, 81%) as leaflets, m.p. 128 °C (from benzene–cyclohexane) (Found: C, 65.85; H, 7.35; N, 4.75%; M^+, 291.1470. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.27; N, 4.81%; M, 291.1470); $\nu_{max}(CHCl_3)$/cm^{-1} 3400br, 1700br and 1500br; δ 1.14 (3 H, d, *J* 6.8, Me), 1.20 (3 H, d, *J* 6.4, Me), 1.96–2.17 (3 H, m, 2-, 4- and 5-H), 2.52 (1 H, dd, *J* 6.4 and 16.9, 5-H), 3.02 (1 H, br s, OH), 3.72 (1 H, ddd, *J* 9.3, 8.1 and 11.0, 3-H), 3.84 (1 H, dq, *J* 4.2 and 6.4, C*H*OH), 5.03 (1 H, br d, *J* 8.1, NH), 5.13 (2 H, s, CH_2Ph) and 7.35 (5 H, s, ArH).

(2R,3S,4R)-3-*Benzyloxycarbonylamino*-4-[(S)-1-(t-*butyldimethylsiloxy*)*ethyl*]-2-*methylcyclopentanone* **22**.—To a solution of hydroxy ketone **21** (3.3 g, 11.3 mmol) in dimethylformamide (DMF) (30 cm^3) were added imidazole (1.7 g, 25 mmol) and *t*-butyldimethylsilyl chloride (3.4 g, 22.6 mmol) and the mixture was stirred for 12 h at room temperature. Ice–water was poured into the reaction mixture and the aq. layer was extracted with diethyl ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (6:1) to give the siloxy ketone **22** (4.59 g, 100%) as an oil, $\nu_{max}(CHCl_3)$/cm^{-1} 3300br, 1705br and 1520br; δ 0.02 (3 H, s, SiMe), 0.05 (3 H, s, SiMe), 0.86 (9 H, s, Bu^t), 1.16 (3 H, d, *J* 6.1, Me), 1.17 (3 H, d, *J* 6.1, Me), 2.12 (1 H, dd, *J* 10.4 and 17.7, 5-H), 2.00–2.40 (2 H, m, 2- and 4-H), 2.50 (1 H, dd, *J* 7.9 and 17.7, 5-H), 3.71 (1 H, ddd, *J* 6.1, 8.1 and 9.8, 3-H), 3.98 (1 H, dq, *J* 4.3 and 6.1, SiOCH), 4.87 (1 H, br d, *J* 8.1, NH), 5.12 (2 H, s, CH_2Ph) and 7.31–7.65 (5 H, m, ArH); *m/z* 390 ($M^+ - 15$) [Found: ($M^+ - CH_3$), 390.2095. $C_{21}H_{32}NO_4Si$ requires *m/z*, 390.2100].

(2R,3S,4R)-3-*Benzyloxycarbonylamino*-4-[(S)-1-(t-*butyldimethylsiloxy*)*ethyl*]-5-*hydroxymethylene*-2-*methylcyclopentanone* **23**.—To a stirred mixture of compound **22** (1.16 g, 2.86 mmol), methyl formate (3.44 g, 57.2 mmol), and diethyl ether (50 cm^3) at 0 °C was slowly added 28% NaOMe–MeOH (5.5 cm^3, 28.6 mmol) under argon. After the mixture had been stirred for 30 min, acetic acid (1.9 g, 31.46 mmol) was slowly added and the mixture was diluted with ethyl acetate (200 cm^3). The organic layer was washed with water, dried over Na_2SO_4 and evaporated to give the crude product **23** as an oil, δ 0.12 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.91 (9 H, s, Bu^t), 1.14 (3 H, d, *J* 6.1, Me), 1.17 (3 H, d, *J* 6.7, Me), 2.16 (1 H, dq, *J* 11.0 and 6.7, 2-H), 2.88 (1 H, ddd, *J* 2.5, 3.1 and 9.8, 4-H), 3.46 (1 H, ddd, *J* 9.8, 10.4 and 11.0, 3-H), 4.34 (1 H, dq, *J* 3.1 and 6.1, SiOCH), 5.06–5.20 (3 H, m, NH and CH_2Ph), 7.35 (5 H, s, ArH), 7.59 (1 H, dd, *J* 2.5 and 14.0, C=CH) and 10.33 (1 H, d, *J* 14.0, OH); $[\alpha]_D$ −44.13° (*c* 7.91, $CHCl_3$), which was used without further purification in the next step.

(3R,4S,5R)-2-*Acetoxymethylene*-4-*benzyloxycarbonylamino*-3-[(S)-1-(t-*butyldimethylsiloxy*)*ethyl*]-5-*methylcyclopentanone* **24**.—A solution of compound **23** in acetic anhydride (3 cm^3) was stirred for 2 h at room temperature and was then evaporated under reduced pressure to give a residue, which was dissolved in ethyl acetate (200 cm^3). The organic layer was washed with

* Methyl 4-benzyloxycarbonylamino-3,4,5,6-tetrahydro-2,5-dimethyl-6-oxo-2*H*-pyran-3-carboxylate.

saturated aq. $NaHCO_3$, dried, and evaporated to give the crude product **24** as an oil, δ −0.12 (3 H, s, SiMe), −0.01 (3 H, s, SiMe), 0.79 (9 H, s, Bu^t), 1.07–1.26 (6 H, m, 2 × Me), 2.22 (3 H, s, Ac), 2.39 (1 H, dq, *J* 7.3 and 6.7, 5-H), 2.94 (1 H, m, 3-H), 4.10 (1 H, ddd, *J* 7.3, 7.3 and 7.4, 4-H), 4.44 (1 H, dq, *J* 2.4 and 6.1, SiOCH), 5.10–5.23 (3 H, m, C*H*$_2$Ph and NH), 7.33 (5 H, s, ArH) and 8.12 (1 H, d, *J* 1.8, C=CH), which was used without further purification in the next step.

Dibenzyl (2R,3R,4R)-3-*Benzyloxycarbonylamino*-2-[(S)-1-(t-*butyldimethylsiloxy*)*ethyl*]-4-*methylpentanedioate* **27** *and Dibenzyl* (2R,3S,4R)-3-*Benzyloxycarbonylamino*-4-[(S)-1-(t-*butyldimethylsiloxy*)*ethyl*]-2-*methylhexanedioate* **28**.—To a stirred emulsion of compound **24** obtained above and 35% H_2O_2 (18 cm^3) in methanol (5 cm^3) was added K_2CO_3 (1 g). After termination of the exothermic reaction, saturated aq. $Na_2S_2O_3$ was added to the reaction mixture. After the mixture had been stirred for 5 min, methanol (50 cm^3) was added to the mixture and the resulting solid was removed by filtration. The filtrate was evaporated to give a residual aq. layer, which was acidified to pH 3 with conc. HCl by monitoring with a pH test paper, and the mixture was extracted with chloroform–methanol (10:1). The organic layer was dried over Na_2SO_4 and evaporated to give a mixture of the acids **25** and **26**.

To a solution of diacids **25** and **26** obtained above in DMSO (5 cm^3) were added K_2CO_3 (1 g) and benzyl bromide (1 g), and the mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with ethyl acetate (200 cm^3) and the organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a mixture of diesters **27** and **28** (740 mg) as an oil. The following spectroscopic data were obtained by careful separation by column chromatography on silica gel with ethyl acetate–hexane (1:10). For *compound* **27**: $\nu_{max}(CHCl_3)$/cm^{-1} 3450 and 1740; δ 0.02 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.84 (9 H, s, Bu^t), 1.11 (3 H, d, *J* 7.3, Me), 1.23 (3 H, d, *J* 6.7, Me), 2.73–2.84 (2 H, m, 2- and 4-H), 4.23 (1 H, dq, *J* 5.5 and 6.7, SiOCH), 4.58 (1 H, ddd, *J* 5.5, 7.8 and 10.4, 3-H), 4.98–5.13 (7 H, m, 3 × C*H*$_2$Ph and NH) and 7.27–7.34 (15 H, m, ArH); *m/z* 633 (M^+) (Found: M^+, 633.3119. $C_{36}H_{47}NO_7Si$ requires M. 633.3120); $[\alpha]_D$ −9.69° (*c* 5.99, $CHCl_3$).

For compound **28**: δ 0.01 (3 H, s, SiMe), 0.02 (3 H, s, SiMe), 0.85 (9 H, s, Bu^t), 1.13 (3 H, d, *J* 7.3, Me), 1.15 (3 H, d, *J* 6.1, Me), 2.26–2.35 (2 H, m, 4- and 5-H), 2.63 (1 H, dd, *J* 9.8 and 8.6, 5-H), 2.83 (1 H, dq, *J* 6.7 and 7.3, 2-H), 3.98 (1 H, dq, *J* 3.1 and 6.1, SiOCH), 4.13 (1 H, ddd, *J* 6.7, 8.6 and 9.8, 3-H), 5.03–5.15 (6 H, m, 3 × C*H*$_2$Ph), 5.37 (1 H, d, *J* 9.8, NH) and 7.32–7.34 (15 H, m, ArH).

(3R,4R,5R,6S)-5-*Benzyloxycarbonyl*-4-*benzyloxycarbonylamino*-3,4,5,6-*tetrahydro*-3,6-*dimethyl*-2H-*pyran*-2-*one** **29**.—To a stirred solution of the above mixture of diesters **27** and **28** in $CHCl_3$ (7 cm^3) was slowly added BF_3•OEt_2 (0.5 g). After the mixture had been stirred for 3 h, saturated aq. $NaHCO_3$ was added to the reaction mixture, which was stirred for 5 min. The aq. layer was extracted with ethyl acetate and the organic layer was dried over Na_2SO_4 and evaporated to give a residue, which was purified by column chromatography on silica gel with ethyl acetate–hexane (1:3) to give the *pyran* **29** (236 mg, 20% from **22**) as an oil, $\nu_{max}(CHCl_3)$/cm^{-1} 3450 and 1730; δ 1.32 (3 H, d, *J* 6.7, Me), 1.43 (3 H, d, *J* 6.7, Me), 2.84 (1 H, dq, *J* 9.8 and 6.7, 3-H), 3.03 (1 H, dd, *J* 6.1 and 6.7, 5-H), 4.21 (1 H, ddd, *J* 6.7, 9.2 and 9.8, 4-H), 4.83 (1 H, dq, *J* 6.1 and 6.7, 6-H), 5.04–5.17 (4 H, m, 2 × C*H*$_2$Ph), 5.16 (1 H, d, *J* 9.2, NH) and 7.28–7.39 (10 H, m, ArH); *m/z* 411 (M^+) (Found: 411.1680. $C_{23}H_{25}NO_6$ requires M, 411.1680); $[\alpha]_D$ +21.83° (*c* 1.61, $CHCl_3$).

* Benzyl 4-benzyloxycarbonylamino-3,4,5,6-tetrahydro-2,5-dimethyl-6-oxo-2*H*-pyran-3-carboxylate

(2S,3R,4R,5R)-4-*Amino*-3,4,5,6-*tetrahydro*-2,5-*dimethyl*-6-*oxo*-2H-*pyran*-3-*carboxylic Acid Hydrochloride* **30**.—A suspension of diester **29** (950 mg, 2.31 mmol) and 10% Pd–C (100 mg) in methanol (2 cm^3) was stirred for 12 h under hydrogen. After the addition of 10% HCl (1.26 cm^3, 3.47 mmol), the suspension was filtered to remove insoluble materials and the filtrate was concentrated to leave a residue, which was dried for 1 h under reduced pressure (1 mmHg) and used without purification in the next step.

Methyl (2R)-2-{(2S,3R)-3-[(1S)-1-*Hydroxyethyl*]-4-*oxoazetidin*-2-*yl*}*propanoate* **31** *and the Lactone* **32**.—A solution of lactone acid **30** in methanol (20 cm^3) was stirred for 36 h at room temperature under argon. After addition of propylene oxide, the mixture was refluxed for 10 min and cooled to room temperature. DCC (524 mg) was added to the solution and the resulting mixture was stirred for 4 h at 50 °C. Removal of the solvent gave a residue, which was extracted with ethyl acetate. The extract was filtered through a Celite pad, and the filtrate was evaporated to give a residue, which was purified by chromatography on silica gel with hexane–ethyl acetate (1:3) to give ester **31** (349 mg, 75% from **29**) as an oil, ν_{max}-$(CHCl_3)$/cm^{-1} 3420, 1760 and 1740; δ 1.28 (3 H, d, *J* 7.3, Me), 1.40 (3 H, d, *J* 6.7, Me), 2.25 (1 H, br s, OH), 2.82 (1 H, dq, *J* 10.4 and 6.7, 2-H), 3.27 (1 H, ddd, *J* 2.4, 4.9 and 7.3, COCH), 3.70 (3 H, s, OMe), 4.02 (1 H, dd, *J* 4.9 and 10.4, NCH), 4.13 (1 H, m, OCH) and 6.25 (1 H, br s, NH); $[\alpha]_D$ −31.48° (*c* 0.23, $CHCl_3$). Further elution with the same solvent gave lactone **32** (90 mg, 23%) as an oil, $\nu_{max}(CHCl_3)$/cm^{-1} 3420, 1770 and 1750; δ 1.35 (3 H, d, *J* 6.7, Me), 1.56 (3 H, d, *J* 6.1, Me), 2.73 (1 H, dq, *J* 8.5 and 6.7, C*H*Me), 3.35 (1 H, ddd, *J* 3.1, 6.1 and 11.0, COCH), 3.60 (1 H, dd, *J* 6.1 and 8.5, NCH), 4.70 (1 H, dq, *J* 11.0 and 6.1, OCH) and 6.38 (1 H, br s, NH).

Methyl (2R)-2-[(2S,3S)-3-*Acetyl*-4-*oxoazetidin*-2-*yl*]*propanoate* **33**.—A mixture of compound **31** (31.7 mg, 0.16 mmol), sodium acetate (4 mg, 0.05 mmol), PCC (68 mg, 0.32 mmol), Celite (100 mg) and dry methylene dichloride (1 cm^3) was stirred for 4 h at room temperature under argon and then subjected directly to column chromatography on silica gel with hexane–ethyl acetate (1:1) to give compound **33** (14.7 mg, 47%) as an oil, $\nu_{max}(CHCl_3)$/cm^{-1} 3400, 1780 and 1730; δ 1.24 (3 H, d, *J* 7.3, Me), 2.33 (3 H, s, Ac), 2.75 (1 H, dq, *J* 6.7 and 7.3, 2-H), 3.70 (3 H, s, OMe), 4.13 (1 H, d, *J* 2.4, COCHCO), 4.21 (1 H, dd, *J* 2.4 and 6.7, NCH) and 6.10 (1 H, br s, NH).

Methyl (2R)-2-{(2S,3S)-3-[(R/S)-1-*Hydroxyethyl*]-4-*oxoazetidin*-2-*yl*}*propanoate* **16** *and* **34**.—*Method A*. To a solution of compound **33** (15.7 mg, 0.08 mmol) in methanol (1 cm^3) was added $NaBH_4$ (5 mg, 0.13 mmol) and the mixture was stirred for 1 h at room temperature. After treatment with saturated aq. NH_4Cl, the mixture was extracted with ethyl acetate. The extract was dried over Na_2SO_4 and evaporated to give a residue, which was purified by chromatography on silica gel with ethyl acetate to give the alcohols **16** and **34** (5 mg, 32%), in the ratio 2:3, as an inseparable diastereoisomeric mixture.

Method B. To a solution of compound **33** (12.7 mg, 0.06 mmol) in dry diethyl ether (1 cm^3) at −40 °C was added 1.0 mol dm^{-3} K-Selectride in THF (64 mm^3, 0.06 mmol) during 20 min under argon. After the mixture had been stirred for 30 min, acetic acid (15 mm^3, 0.25 mmol) was added and the mixture was warmed to 0 °C, diluted with ethyl acetate (5 cm^3), and filtered to remove insoluble material. The filtrate was evaporated to give a residue, which was purified by chromatography on silica gel with ethyl acetate to give a mixture of the alcohols **16** and **34** (5 mg, 39%), in the ratio 3:2.

Methyl (2R)-2-{(2S,3S)-3-[(R/S)-1-(4-*Nitrobenzyloxycarbonyloxy*)*ethyl*]-4-*oxoazetidin*-2-*yl*}*propanoate* **35** *and* **36**.—A mixture of compounds **16** and **34** (18 mg, 0.09 mmol), *p*-(dimethylamino)pyridine (22 mg, 0.20 mmol), 4-nitrobenzyl chloroformate (40 mg, 0.18 mmol) and methylene dichloride (1 cm^3) was stirred for 1 h at room temperature under argon. After dilution with ethyl acetate (30 cm^3), the organic layer was washed successively with 0.25 mol dm^{-3} HCl and water, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by chromatography on silica gel with diethyl ether–hexane (5:1) to afford compounds **35** (6.5 mg, 19%) and **36** (12.1 mg, 36%) as oils. For compound **35**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 1770 and 1740; δ 1.23 (3 H, d, *J* 6.7, Me), 1.43 (3 H, d, *J* 6.1, Me), 2.67 (1 H, dq, *J* 6.7 and 7.3, 2-H), 3.21 (1 H, dd, *J* 7.9 and 2.4, COCH), 3.69 (3 H, s, OMe), 3.81 (1 H, dd, *J* 7.3 and 2.4, NCH), 5.13 (1 H, dq, *J* 7.9 and 6.1, OCH), 5.25 (2 H, s, CH_2Ph), 5.98 (1 H, br s, NH), 7.56 (2 H, d, *J* 9.2, ArH) and 8.24 (2 H, d, *J* 9.2, ArH). For compound **36**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 1770 and 1730; δ 1.24 (3 H, d, *J* 7.3, Me), 1.47 (3 H, d, *J* 6.7, Me), 2.67 (1 H, dq, *J* 6.7 and 7.3, 2-H), 3.26 (1 H, dq, *J* 2.4 and 4.3, COCH), 3.68 (1 H, dd, *J* 2.4 and 7.3, NCH), 3.71 (3 H, s, OMe), 5.13 (1 H, dq, *J* 4.3 and 6.7, OCH), 5.26 (2 H, s, CH_2Ph), 5.98 (1 H, br s, NH), 7.56 (2 H, d, *J* 9.2, ArH) and 8.24 (2 H, d, *J* 9.2, ArH).

Methyl (2R)-2-{(2S,3S)-3-[(R)-1-*Hydroxyethyl*]-4-*oxoazetidin*-2-*yl*}*propanoate* **16**.—A mixture of compound **35** (6.5 mg, 0.02 mmol), 10% Pd–C (2 mg), and ethyl acetate (1 cm^3) was stirred for 6 h under hydrogen. After filtration, the filtrate was concentrated to leave a residue, which was purified by chromatography on silica gel with ethyl acetate to give compound **16** (3.4 mg, 100%), whose spectral data were identical with those reported.[9]

Methyl (2R)-2-{(2S,3S)-3-[(S)-1-*Hydroxyethyl*]-4-*oxoazetidin*-2-*yl*}*propanoate* **34**.—A mixture of compound **36** (12.1 mg, 0.03 mmol), 10% Pd–C (4 mg), and ethyl acetate (2 cm^3) was stirred for 1 h under hydrogen and then treated as described for the preparation of compound **16**, to give compound **34** (6.4 mg, 100%) as a powder, $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1760 and 1730; δ 1.26 (3 H, d, *J* 6.7, Me), 1.33 (3 H, d, *J* 6.1, Me), 2.32 (1 H, br s, OH), 2.68 (1 H, dq, *J* 7.3 and 6.7, 2-H), 3.06 (1 H, dd, *J* 2.4 and 5.5, COCH), 3.71 (1 H, dd, *J* 7.3 and 6.7, 2-H), 3.06 (1 H, dd, *J* 2.4 and 5.5, COCH), 3.71 (1 H, dd, *J* 7.3 and 2.4, NCH), 3.72 (3 H, s, OMe), 4.12 (1 H, dq, *J* 5.5 and 6.1, OCH) and 5.99 (1 H, br s, NH).

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References

1 Y. Ito and S. Terashima, *Yuki Gosei Kagaku Kyokaishi*, 1989, **47**, 606 and references cited therein (*Chem. Abstr.*, 1990, **112**, 55296n).
2 D. H. Shih, F. Baker, L. Cama and B. G. Christensen, *Heterocycles*, 1984, **21**, 29.
3 T. Kametani, T. Honda, H. Ishizone, K. Kanada, K. Naito and Y. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1989, 646.
4 G. Melillo, I. Shinkai, T. Liu, K. Ryan and M. Sletzinger, *Tetrahedron Lett.*, 1980, **21**, 2783.
5 R. Bayles, A. P. Flynn, R. H. B. Galt, S. Kirby and R. W. Turner, *Tetrahedron Lett.*, 1988, **29**, 6341.
6 R. Bayles, A. P. Flynn, R. H. B. Galt, S. Kirby and R. W. Turner, *Tetrahedron Lett.*, 1988, **29**, 6345 and references cited therein.
7 T. Honda, H. Ishizone, K. Naito and Y. Suzuki, *Heterocycles*, 1990, **31**, 1225.
8 T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
9 M. Hatanaka, *Tetrahedron Lett.*, 1987, **28**, 83.

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