An Asymmetric Synthesis of Synthetic Intermediates to Thienamycin and Epithienamycins A and B

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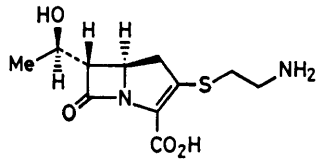
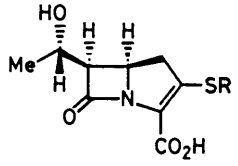
An asymmetric synthesis for the synthetic intermediates to carbapenem antibiotics was examined *via* isoxazoline derivatives prepared by 1,3-dipolar cycloaddition between the nitrile oxide and menthyl crotonate. The (4S)-*trans*-azetidinone (14) having the antipodal configuration of thienamycin was synthesised in 16—20% e.e., while 85.3% e.e. of the (4R)-*cis*-azetidinone, possessing the same absolute configuration of epithienamycins A and B, was obtained by the same reaction procedure. The c.d. assignment of 3,4-dialkylated β-lactams is also described.

We have recently reported a facile synthesis, *via* isoxazoline derivatives prepared by 1,3-dipolar cycloaddition,[1-3] of (±)-thienamycin (1) [4-7] and (±)-epithienamycins A(2) and B(3),[8,9] which possess potent and broad spectral antibacterial and β-lactamase-inhibiting activities. In continuation of this study, we have investigated an asymmetric synthesis of the β-lactam intermediates *via* optically active isoxazoline derivatives. Here we report both our results and the c.d. spectra of 3,4-dialkylated azetidinones.



(1)



(2) R = CH_2CH_2NHAc

(3) R = $CH{=}CHNHAc$

SCHEME 1

The asymmetric synthesis, *via* isoxazolines, of the thienamycin and epithienamycins A and B required optically active β-lactams (14) and (15): two possible routes were envisaged for their preparation. The first was an enantioselective synthesis of isoxazoline derivatives using chiral dipolarophiles and the second a specific conversion of diastereoisomeric isoxazolines into the chiral β-lactams. In order to examine the first possibility, the nitrile oxide (5), generated *in situ* from 3-nitropropanal dimethylacetal (4) [10] in the presence of phenyl isocyanate and triethylamine,[11] was allowed to react with (−)-menthyl crotonate. After reaction for 6 days at 4 °C in benzene, followed by purification using silica-gel column chromatography, three products were obtained in 40.3, 7.3, and 24.8% yields, respectively. The main and fastest moving product was the desired *trans*-substituted isoxazoline (7), which showed a characteristic 4-H signal at 3.73 p.p.m. (d, *J* 7.6 Hz). The structure of the second and minor product was assigned to the corresponding *cis*-isomer (8) based on the 4-H signal at 4.07 p.p.m. (d, *J* 10.4 Hz). The third product was the *trans*-substituted regioisomer (9) the n.m.r. spectrum of which showed the hydrogen, geminally substituted with the ester group, at 4.50 p.p.m. (d, *J* 6.8 Hz).

The *trans*-isoxazoline (7), $[\alpha]_D^{20}$ −58.9° (methanol), was shown to be homogeneous by silica-gel column and thin-layer chromatography using a variety of solvent systems. The ratio of the two epimers was not estimated by n.m.r. spectroscopy since no well-resolved signal based on diastereoisomeric properties was observed either in the 200 MHz proton or the 100 MHz carbon-13 n.m.r. spectra run in deuteriochloroform.

An epimeric mixture of the *trans*-isomer (7) was converted into the enantiomeric mixtures of the *trans*-azetidinone (14), $[\alpha]_D^{20}$ −2.5° (methanol); c.d. $[\theta]_{214}^{20}$ $+2.357 \times 10^3$ (methanol) in 26.9% overall yield and the *cis*-isomer (15), $[\alpha]_D^{20}$ +42.6° (methanol); c.d. $[\theta]_{213}^{20}$ -1.237×10^4 (methanol) in 13% yield by our previously reported method; [12] namely (i) catalytic hydrogenation of the compounds with Adams catalyst, (ii) silylation of the resulting amino-esters (10) and (11), (iii) cyclisation of the products with ethylmagnesium bromide, and (iv) deprotection of the *O*-silyl group. The i.r., n.m.r. and mass spectra of the two products were identical with those of the authentic racemates (14) and (15) which had been already transformed into (±)-thienamycin (1) [1,2] and (±)-epithienamycins A(2) and B(3),[3] respectively. The absolute configuration and the optical purity of the above products were determined by their conversion into diastereoisomeric esters according to Mosher's n.m.r. configuration–correlation method.[13]

Reaction of the above *trans*-azetidinone (14) with (*S*)-(+)-*O*-methylmandelyl chloride in the presence of 4-dimethylaminopyridine gave the diastereoisomeric esters (18). The signals due to methyls of the hydroxyethyl groups resonated at 1.27 and 1.41 p.p.m. in the ratio of 2 : 3 (d, *J* 6.4 Hz) and the 3-H signals were observed at 2.95 and 2.79 p.p.m. in the ratio of 2 : 3 (dd, *J* 8.6 and 2.3, and *J* 9.3 and 2.3 Hz, respectively). Mosher's model predicts that the signal due to the methyl group of the (1'S)-(*S*)-isomer (18) would appear at lower field than that of the (1'*R*)-(*S*)-isomer, while the 3-H of (18) would resonate at a higher field than that of the isomer. Thus, the above observation indicated that the product contained a *ca.* 20% enantiomeric excess (e.e.) of the (1'*S*)-isomer (14). Furthermore the n.m.r. spectrum of the diastereoisomeric mixture of esters (16), which was prepared by the reaction with (*S*)-(−)-α-trifluoromethyl-α-methoxyphenylacetyl chloride, showed signals due to the methyl groups at 1.42 and 1.52 p.p.m.

in the ratio of 29 : 21 (d, J 6.4 Hz); this result also suggested the presence of a *ca.* 16% e.e. of the (1′*S*)-isomer.

The above *cis*-azetidinone (15) was converted into a diastereoisomeric mixture of the (—)-α- trifluoromethyl-α-methoxyphenylacetates (17), the n.m.r. spectrum of which exhibited methyl group signals at 1.48 and 1.57 p.p.m. in the ratio of 12.6 : 1; this indicated a *ca.* 85.3% e.e. of the (1′*S*)-isomer. Some distinguishable chemical shifts for the above (*S*)-*O*-methylmandelyl esters and (*S*)-α-trifluoromethyl-α-methoxyphenylacetates are shown in the Table. It was found that whilst the above *trans*-azetidinone (14) has a 16—20% e.e. of the (1′*S*)-(3*R*)(4*S*)-isomer, which would be convertible into the antipode of the natural thienamycin, the *cis*-one (15) has a 85.3% e.e. of the (1′*S*)(3*R*)(4*R*)-configuration, which is the same as that of the natural epithienamycins A and B. Such a large difference of the optical purity in two azetidinones suggests that the second possibility, which had already been mentioned at the beginning, would operate during the formation of the β-lactams. Thus, the racemate of the isoxazoline derivative was transformed into the β-lactams *via* the menthyl ester as follows.

TABLE

N.m.r. chemical shifts for (*S*)-α-trifluoromethyl-α-methoxyphenylacetates and (*S*)-*O*-methylmandelyl esters of the *trans*- and *cis*-azetidinones. Carbon marked * is *S*.

			R = CO(MeO)C*CF_3Ph				R = CO(MeO)C*HPh			
1′	3	4	1′-Me	3-H	(*Me*O)CCF_3	C*H*(OMe)$_2$	1′-Me	3-H	C*H*(OMe)$_2$	(OMe)C*H*Ph
S	*R*	*S*	1.42	3.02		4.38	1.41	2.79	4.17	4.73
R	*S*	*R*	1.52	2.95		4.29	1.27	2.95	4.36	4.76
S	*R*	*R*	1.48		3.50	4.37				
R	*S*	*S*	1.57		3.55	4.26				

The racemic isoxazoline carboxylic acid (20) [1] was esterified with (—)-menthol in the presence of dicyclohexylcarbodi-imide and 4-dimethylaminopyridine.[14] The resulting menthyl ester (7), which must be a 1 : 1 mixture of two diastereoisomers, was subjected to the same reaction sequence leading to two β-lactams. The *trans*-β-lactam, obtained in 29.8% overall yield, showed a negative c.d. maximum, $[\theta]_{212}^{20}$ -1.000×10^3 (methanol), indicating an 8.4% e.e. of the (1′*R*)(3*S*)(4*R*)-isomer [enantiomer of (14)]—calculated on the basis of the previous c.d. maximum of a 16—20% e.e. of (14). The n.m.r. spectra of the (*S*)-α-trifluoromethyl-α-methoxyphenylacetates also suggested a *ca.* 7.7% e.e. of the (1′*R*)(3*S*)(4*R*)-isomer. Furthermore, a negative c.d. maximum, $[\theta]_{212}^{20}$ -8.099×10^3 (methanol), of the *cis*-β-lactam, obtained in 11.1% overall yield suggested the presence of a 55.9% e.e. of the (1′*S*)(3*R*)(4*R*)-isomer (15).

It was thus shown that the (4*R*)-enantiomers of *trans*-and *cis*-β-lactams were formed more selectively from the diastereoisomeric menthyl esters, the cyclisation of the protected amino-esters with Grignard reagent causing the selectivity. For *cis*-β-lactam formation, a more specific cyclisation was observed as a result of the production of the more hindered β-lactam. The reverse effect descreased the optical purity of the *trans*-β-lactam (14) starting from menthyl crotonate. On the other hand the e.e. of the *cis*-isomer (15) was increased by the cyclisation step. From a consideration of the above results, it was estimated that in the inseparable diastereomeric mixture formed by the above 1,3-dipolar cycloaddition the (5*S*)-isoxazoline (7) was present in more than 65% excess. Since the *p*-nitrobenzyloxycarbonyl-protected compound (19) derived from a 16—20% e.e. of the *trans*-(4*S*)-azetidinone (14) showed a positive Cotton effect $[\theta]_{213}^{25}$ $+2.891 \times 10^3$ (methanol), the positive Cotton effect around 212—214 nm could be attributed to the *S*-configuration at the C-4 position. The c.d. curves of the *trans*-(4*S*)-azetidinones (14) and (19) and *cis*-(4*R*)-azetidinone (15) calculated as 100% e.e. are shown in the Figure. The c.d. spectrum of (5*S*)-1-carbapenam (21) exhibited a negative Cotton effect at 231 nm [15] and this observation was consistent with the prediction based on a semi-empirical Extended Hückel and CNDO wave function calculation.[16] It is noteworthy that monocyclic β-lactams alkylated at C-4 have a reverse Cotton effect in contrast with the 1-carbapenam.

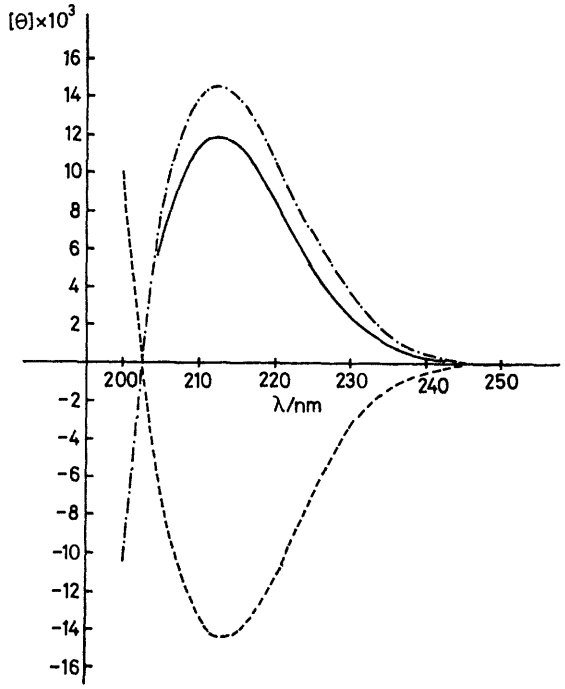
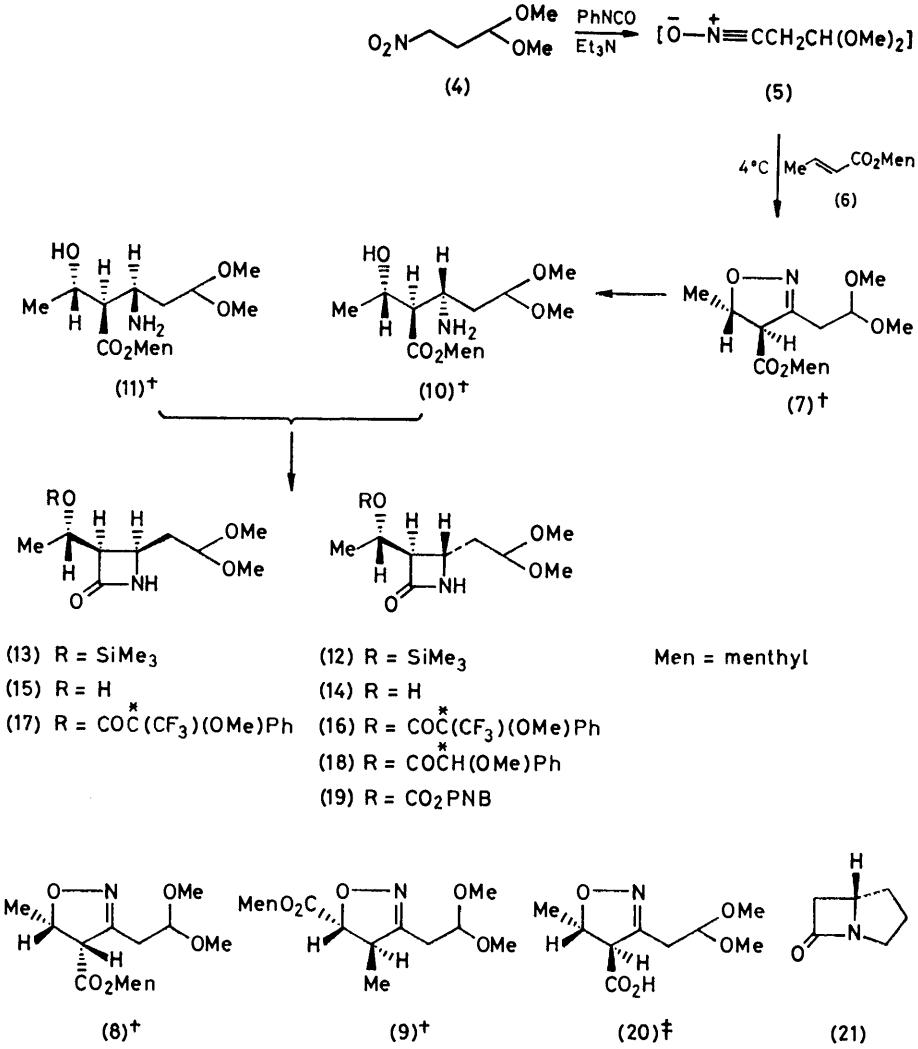


FIGURE The c.d. curves of 3(*R*)-[1′(*S*)-hydroxyethyl]-4(*S*)-(2,2-dimethoxyethyl)azetidin-2-one (14) (——), 3(*R*)-[1′(*S*)-hydroxyethyl]-4(*R*)-(2,2-dimethoxyethyl)azetidin-2-one (15) (- - - -) and 4(*S*)-(2,2-dimethoxyethyl)-3(*R*)-[1′(*S*)-*p*-nitrobenzyloxyethyl]azetidin-2-one (19) (— · — · —), which were calculated as being in 100% e.e.



(13) R = $SiMe_3$
(15) R = H
(17) R = $COC^{*}(CF_3)(OMe)Ph$

(12) R = $SiMe_3$
(14) R = H
(16) R = $COC^{*}(CF_3)(OMe)Ph$
(18) R = $COCH^{*}(OMe)Ph$
(19) R = CO_2PNB

Men = menthyl

(8)† (9)† (20)‡ (21)

* Carbon marked * is *S*. † One of diastereoisomers is described as a representative. ‡ Racemate.

SCHEME 2

EXPERIMENTAL

All optical rotations were measured with a JASCO DIP-4 instrument, c.d. spectra with a JASCO J-400X spectrophotometer, i.r. spectra with a Hitachi 260-10 spectrophotometer. N.m.r. spectra were obtained with JEOL-PMX-60, JEOL-PS-100 and Varian XL-200 spectrometers. Ordiary mass spectra were measured with a Hitachi M-52G while accurate mass spectra were taken with a JEOL-JMS-01SG-2 spectrometer. All products described in Experimental section were homogeneous on t.l.c. and h.p.l.c.

1,3-*Dipolar Cycloaddition between* (−)-*Menthyl Crotonate* (6) *and* 2,2-*Dimethoxyethylnitrile Oxide* (5).—A mixture of 3-nitropropanal dimethylacetal (4) [10] (2.92 g, 19.6 mmol), (−)-menthyl crotonate (6) [17] (4.00 g, 17.9 mmol), phenyl isocyanate (4.67 g, 39.2 mmol) and several drops of triethylamine in dry benzene (60 ml) was stirred at 4 °C for 6 days under argon. After filtration of the reaction mixture, the filtrate was washed with brine, dried (Na_2SO_4), and evaporated. The residue was subjected to silica-gel chromatography using n-hexane–ether (9 : 1) as eluant. From the first fraction, *trans*-4-menthyloxycarbonyl-3-(2,2-dimethoxyethyl)-5-methylisoxazolines (7) (2.56 g, 40.3%) were obtained as a pale yellowish syrup, $[\alpha]_D^{20}$ −58.9° (*c* 0.76, methanol) (Found: M^+ 355.238 7. $C_{19}H_{33}NO_5$ requires M^+ 355.235 9), $\nu_{max.}$ ($CHCl_3$) 1 722 cm^{-1} (C = O); δ($CDCl_3$) 0.76 (3 H, d, *J* 7.2 Hz, Me), 0.91 (6 H, d, *J* 7.6 Hz, 2 × Me), 1.39 (3 H, d, *J* 6.3 Hz, 5-Me), 2.71 [1 H, dd, *J* 14.2 and 5.7 Hz, $CH_2CH(OMe)_2$], 2.90 [1 H, dd, *J* 14.2 and 5.7 Hz, $CH_2CH(OMe)_2$], 3.34 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.73 (1 H, d, *J* 7.6 Hz, 4-H), and 4.60—4.96 [3 H, m, CO_2CH, 5-H, $CH(OMe)_2$].

The second fraction afforded *cis*-4-menthyloxycarbonyl-3-(2,2-dimethoxyethyl)-5-methylisoxazolines (8) (0.46 g, 7.3%) as a yellowish syrup, $[\alpha]_D^{20}$ −63.4° (*c* 0.70, methanol) (Found: M^+ 355.238 9. $C_{19}H_{33}NO_5$ requires M^+ 355.235 9), $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O); δ($CDCl_3$) 0.77 (3 H, d, *J* 7.0 Hz, Me), 0.90 (6 H, d, *J* 7.0 Hz, 2 × Me), 1.32 (3 H, d, *J* 6.2 Hz, 5-Me), 2.58 [1H, dd, *J* 14.5 and 5.0 Hz, $CH_2CH(OMe)_2$], 2.91 [1 H, dd, *J* 14.5 and 5.0 Hz, $CH_2CH(OMe)_2$], 3.33 (6 H, s, 2 × OMe), 4.07 (1 H, d, *J* 10.4 Hz, 4-H), 4.38—5.10 [3 H, m, 5-H, CO_2CH, $CH(OMe)_2$].

The third fraction gave *trans*-5-menthyloxycarbonyl-3-(2,2-dimethoxyethyl)-4-methylisoxazolines (9) (1.57 g, 24.8%) as a yellowish syrup, $[\alpha]_D^{20}$ −74.6° (*c* 0.78, methanol) (Found: M^+ 355.232 9. $C_{19}H_{33}NO_5$ requires M^+ 355.235 9),

$\nu_{max.}$ ($CHCl_3$) 1 723 cm^{-1} (C=O); δ($CDCl_3$) 0.73 (3 H, d, *J* 7.0 Hz, Me), 0.91 (6 H, d, *J* 7.0 Hz, 2 × Me), 1.30 (3 H, d, *J* 7.2 Hz, 4-Me), 2.47 [1 H, dd, *J* 1.45 and 5.4 Hz, $CH_2CH(OMe)_2$], 2.82 [1 H, dd, *J* 14.5 and 5.4 Hz, $CH_2CH(OMe)_2$], 3.37 (6 H, s, 2 × OMe), 4.50 (1 H, d, *J* 6.8 Hz, 5-H), 4.58 [1 H, t, *J* 5.5 Hz, $CH(OMe)_2$], and 4.40—5.05 (1 H, m, CO_2CH).

(−)-trans-4-*Menthyloxycarbonyl*-3-(2,2-*dimethoxyethyl*)-5-*methylisoxazolines* (7) *from the Isoxazolinecarboxylic Acid* (20).—To a stirred solution of the racemic isoxazoline (20) [1] (2.0 g, 9.3 mmol), (−)-menthol (1.45 g, 9.3 mmol), and dimethylaminopyridine (0.20 g, 1.6 mmol) in methylene chloride (40 ml), was added a solution of dicyclohexylcarbodi-imide (2.06 g, 10 mmol) at 0 °C under argon. The resulting mixture was then stirred for 30 min at 0 °C and for 3 h at room temperature. After filtration followed by evaporation of the filtrate, the residue was dissolved in benzene. The extract was washed with saturated aqueous potassium hydrogensulphate, and water, dried (Na_2SO_4), and evaporated. The residue was subjected to silica-gel chromatography. Elution with n-hexane–ether (9 : 1) afforded the isoxazolines (7) (1.90 g, 57.8%) as a syrup, $[\alpha]_D^{20}$ −47.5° (*c* 1.6, methanol). This compound was identical (i.r. and n.m.r. spectra and t.l.c.) with the authentic sample, obtained by the above 1,3-dipolar cycloaddition.

Menthyl 3-*Amino*-5-*hydroxy*-1,1-*dimethoxyhexane*-4-*carboxylates* (10) and (11).—A mixture of the above isoxazolines (7) (1.74 g, 4.9 mmol), prepared by 1,3-dipolar cycloaddition using menthyl crotonate, and platinum oxide (200 mg), which had been activated beforehand with hydrogen, in acetic acid (50 ml), were shaken at room temperature under hydrogen (6.5 atm) for 3 days. After filtration and washing with acetic acid, evaporation of the combined filtrates gave a pale yellowish syrup, which was dissolved in chloroform. The chloroform solution was washed with 10% aqueous ammonia and brine, dried (Na_2SO_4), and evaporated to afford the amino-esters (10) and (11) (1.75 g, 99.5%) as a pale yellowish syrup, $[\alpha]_D^{20}$ −41.36 (*c* 1.28, methanol) (Found: M^+ 359.265 6. $C_{19}H_{37}NO_5$ requires M^+ 359.267 1), $\nu_{max.}$ ($CHCl_3$) 1 715 cm^{-1} (C=O); δ($CDCl_3$): 0.67—1.00 (9 H, m, 3 × Me), 1.10—1.30 (3 H, m, Me), 3.13 (2 H, s, NH_2), and 3.33 (6 H, s, 2 × OMe).

trans- *and* cis-3-(1-*Hydroxyethyl*)-4-(2,2-*dimethoxyethyl*)-*azetidin*-2-*ones* (14) *and* (15).—(A) To a solution of the above amino-esters (10) and (11) (1.090 g, 3.0 mmol) and triethylamine (0.920 g, 9.1 mmol) in dry benzene (20 ml), was slowly added a solution of trimethylchlorosilane (0.824 g, 7.6 mmol) in dry benzene (8 ml) under nitrogen and with ice cooling; the mixture was stirred for 8 h at room temperature. After filtration, the filtrate was evaporated to give a syrup, which was dissolved in dry tetrahydrofuran. To the above solution, 3M-ethylmagnesium bromide in ether (3.0 ml) was slowly added under argon and with ice cooling; the resulting mixture was then stirred for 48 h at room temperature. The excess of reagent was decomposed with water (0.2 ml) with ice cooling, and the mixture was stirred for 30 min at room temperature. After addition of methylene chloride (40 ml), the mixture was well stirred and filtered. The filtrate was evaporated to give a residue, which was subjected to short-column chromatography on silica gel. Elution with benzene–acetone (4 : 1) gave the *O*-trimethylsilylazetidinones (12) and (13) (0.426 g, 51%) as a yellowish oil. A mixture of the above azetidinones (12) and (13) (0.426 g, 1.5 mmol), ammonium chloride (0.167 g, 3.1 mmol), water (20 ml), and ether (5 ml) was stirred for 20 h at room temperature. The aqueous layer was evaporated to give a residue, which was extracted with methylene chloride. After evaporation of the solvent, the resulting syrup was subjected to silica-gel column chromatography. Evaporation of the benzene–acetone (17 : 3) eluate afforded the *cis*-azetidinone (15) (0.080 g, 13.0%) as a syrup, $[\alpha]_D^{20}$ +42.6° (*c* 0.46, methanol), $[\theta]_{213}^{20}$ −1.237 × 10^4 (*c* 4.93 × 10^{-3}, methanol), whose i.r. and n.m.r. spectra and t.l.c. behaviours were identical with those of the racemate.[3]

Evaporation of the benzene–acetone (3 : 1) eluate gave the *trans*-azetidinone (14) (0.166 g, 26.9%) as a syrup, $[\alpha]_D^{20}$ −2.5° (*c* 0.40, methanol) $[\theta]_{214}^{20}$ +2.357 × 10^3 (*c* 1.23 × 10^{-2}, methanol), which was identical (i.r. and n.m.r. spectra) with the racemate.[1]

(B) The isoxazoline (7) (188 mg), prepared from the racemic acid (20), was transformed into the *trans*-azetidinone (14) (32 mg, 29.8%), $[\theta]_{212}^{20}$ −1.000 × 10^3 (*c* 1.26 × 10^{-2}, methanol), and the *cis*-azetidinone (15) (12 mg, 11.1%) $[\theta]_{213}^{20}$ −8.099 × 10^3 (*c* 1.21 × 10^{-2}, methanol) according to the same reaction sequence as described above.

trans-4-(2,2-*Dimethoxyethyl*)-3-[(S)-α-*methoxy*-α-*trifluoromethylphenylacetyloxyethyl*]*azetidin*-2-*one* (16).—To a stirred solution of the above azetidinone (14) (10 mg, 0.049 mmol) prepared by method (A) and 4-dimethylaminopyridine (7 mg, 0.057 mmol) in dry methylene chloride (5 ml) was added a solution of (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [13] (14 mg, 0.056 mmol) in dry methylene chloride (1 ml) at 0 °C under argon. The resulting mixture was stirred for 1 h at room temperature. After filtration followed by evaporation of the filtrate, the residue was dissolved in methylene chloride–benzene (1 : 3). The extract was washed with saturated aqueous potassium hydrogensulphate and water, and then dried (Na_2SO_4) and evaporated. The residue was subjected to silica-gel chromatography. Elution with benzene–acetone (19 : 1) afforded the azetidinone (16) (20 mg, 96.9%) as a yellowish syrup (Found: M^+ 419.156 4. $C_{19}H_{24}F_3NO_6$ requires M^+ 419.155 6), $\nu_{max.}$ ($CHCl_3$) 3 410 cm^{-1} (NH) and 1 760 cm^{-1} (C=O); δ($CDCl_3$) 1.42 (1.74 H, d, *J* 6.4 Hz, 1′-Me) and 1.52 (1.26 H, d, *J* 6.4 Hz, 1′-Me).

cis-4-(2,2-*Dimethoxyethyl*)-3-[(*S*)-α-*methoxy*-α-*trifluoromethylphenylacetyloxyethyl*]*azetidin*-2-*one* (17).—To a stirred solution of the azetidinone (15) (27 mg, 0.13 mmol) prepared by method (A) and 4-dimethylaminopyridine (24.3 mg, 0.20 mmol) in dry methylene chloride (5 ml), was added a solution of (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [13] (43.1 mg, 0.17 mmol) in dry methylene chloride (1 ml) at 0 °C under argon. The resulting mixture was stirred for 1 h at room temperature. The same work-up described as above afforded the azetidinone (17) (55 mg, 98.7%) as a pale yellowish syrup (Found: M^+ 419.153 6. $C_{19}H_{24}F_3NO_6$ requires M^+ 419.155 6), $\nu_{max.}$ ($CHCl_3$) 3 410 (NH) and 1 758 cm^{-1} (C=O); δ($CDCl_3$) 1.48 (2.78 H, d, *J* 6.3 Hz, 1′-Me), 1.57 (0.22 H, d, *J* 6.3 Hz, 1′-Me) 3.50 (2.78 H, d, *J* 1 Hz, OMe), 3.55 (0.22 H, d, *J* 1.4 Hz, OMe), 4.26 [0.074 H, t, *J* 4.3 Hz, $CH(OMe)_2$], and 4.37 [0.926 H, t, *J* 4.3 Hz, $CH(OMe)_2$].

trans-4-(2,2-*Dimethoxyethyl*)-3-[(S)-α-*methoxyphenylacetyloxyethyl*]*azetidin*-2-*one* (18).—To a stirred solution of the azetidinone (14) (17 mg, 0.084 mmol) prepared by method (A) and 4-dimethylaminopyridine (40 mg, 0.33 mmol) in dry methylene chloride (5 ml), was added a solution of (*S*)-*O*-methylmandelyl chloride [13] (46.5 mg, 0.25 mmol) in dry methylene chloride (1 ml) at 0 °C under argon, and the mixture was then stirred for 1 h at room temperature. The

same work-up described as above afforded the azetidinone (18) (9 mg, 31%) as a pale yellowish syrup (Found: M^+ 351.169 4. $C_{18}H_{25}NO_6$ requires M^+ 351.168 2), $\nu_{max.}$ 3 415 (NH) and 1 760 cm^{-1} (C=O); $\delta(CDCl_3)$ 1.27 (1.2 H, d, J 6.4 Hz, 1′ – Me), 1.41 (1.8 H, d, J 6.4 Hz, 1′ – Me), 2.79 (0.6 H, dd, J 9.3 and 2.3 Hz, 3-H), 2.95 (0.4 H, dd, J 8.6 and 2.3 Hz, 3-H), 4.17 [0.6 H, dd, J 6.9 and 4.1 Hz C*H*$(OMe)_2$], 4.36 [0.4 H, dd, J 5.5 and 5.3 Hz, C*H*$(OMe)_2$], 4.73 [0.6 H, s, CO(OMe)C*H*Ph], 4.76 (0.4 H, s, CO(OMe)C*H*Ph), 5.94 (0.6 H, s, NH), and 6.07 (0.4 H, s, NH).

trans-4-(2,2-*Dimethoxyethyl*)-3-[1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]*azetidin*-2-*one* (19).—To a solution of the azetidinone (14) (35 mg, 0.172 mmol), prepared by method (A) and 4-dimethylaminopyridine (63 mg, 0.517 mmol) in dry methylene chloride (5 ml), was added a solution of *p*-nitrobenzyl chloroformate (74 mg, 0.345 mmol) in dry methylene chloride (3 ml) at −5 °C with stirring. The mixture was stirred for 1 h at −5 to *ca.* 0 °C under argon. After filtration, followed by evaporation of the filtrate, the residue was extracted with methylene chloride. The extract was washed with saturated aqueous potassium hydrogensulphate and water and then dried (Na_2SO_4), and evaporated. The residue was subjected to silica-gel chromatography. Elution with benzene–acetone (17 : 3) afforded the azetidinone (19) (29 mg, 44%) as a pale yellowish syrup $[\alpha]_D^{20}$ −2.63° (*c* 0.5, methanol), $[\theta]_{213}^{20}$ 2.892 × 10^3 (*c* 3.199 × 10^{-4}, methanol), which was identical (i.r. and n.m.r. spectra and t.l.c.) with the authentic racemate.[1]

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