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QUINOLIZIDINES—V[1]

A NOVEL SYNTHETIC ROUTE TO IPECAC ALKALOIDS THROUGH CHEMICAL INCORPORATION OF ETHYL CINCHOLOIPONATE DERIVED FROM THE CINCHONA ALKALOID CINCHONINE

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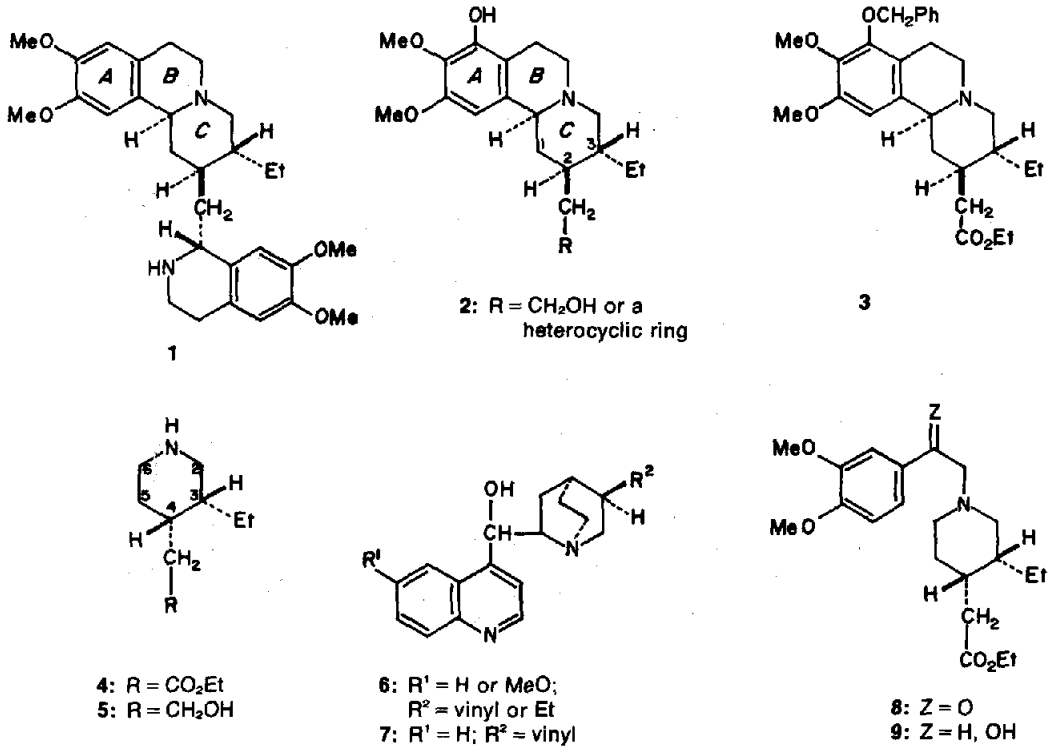
Abstract—A new synthetic route to (−)-emetine (**1**) and related Ipecac alkaloids has been exploited in terms of the synthesis of the tricyclic ester (−)-**30** from ethyl cincholoiponate [(+)-**4**], a degradation product of the *Cinchona* alkaloid cinchonine (**7**). The steps involved are those in the sequence (+)-**4**→(+)-**8**→**9**→**10**→(−)-**12**→(−)-**13**→(+)-**21**→(+)-**22**→**28**→**29**→(−)-**30**. In the $Hg(OAc)_2$–EDTA oxidation of the amino alcohol **9** to the 6-piperidone **10**, the *cis*- and the *trans*-2-piperidone isomers **11** were the minor products. The successful conversion of the *cis*-lactam acid (−)-**13** into the *trans*-lactam acid (+)-**21** was effected on the basis of the fact that (±)-**13** and (±)-**21** are convertible to each other through *cis-trans* equilibration (**13**:**21** = 33:67) at 180° in 75 min. When this isomerisation step was skipped in the above reaction sequence, the 2,3-*cis*-tricycle (+)-**33**, synthetic precursor for chiral 2,3-*cis*-emetines, was obtained.

The Indian medicinal plant *Alangium lamarckii* Thw. (family *Alangiaceae*) is a rich source of fused quinolizidine alkaloids structurally related to the Ipecac alkaloids, e.g. emetine (**1**).[2] The isolation of new, highly ring-A-oxygenated benzo[*a*]quinolizidine alkaloids (type **2**) such as ankorine, alangicine, and alangimarckine from this plant[2] offered us opportunities to elucidate their structures and stereochemistry by means of synthesis.[1,3–8] In our recent chiral syntheses of these novel alkaloids,[4,6,8] the tricyclic ester (−)-**3** was a common key intermediate and we synthesised it from cincholoipon ethyl ester [(+)-**4**],[9] a degradation product of the major *Cinchona* alkaloids (**6**),[10] by the newly invented "cincholoipon-incorporating method". The method consisted of four main operations: (i) introduction of an appropriate phenethyl skeleton into (+)-**4** at N-1; (ii) construction of the lactam CO function at C-6; (iii) epimerisation at C-4 to form the 3,4-*trans* configuration which must correspond to the relative and absolute configuration of **2** at the 3- and the 2-positions; (iv) ring closure to complete the benzoquinolizidine part. Since one of the purposes of the above syntheses was to determine the absolute configuration of the new alkaloids, conservation, alteration, and occurrence of the asymmetric centers in the reactions should have proceeded smoothly as designed throughout the synthetic schemes adopted.[4,6,8] This led us to check the stereochemical outcome and synthetic generality by a parallel synthesis of (−)-emetine (**1**), a structurally analogous alkaloid of established stereochemistry. A number of the results described here have been reported in a preliminary form.[11]

Prior to examining the generation of the lactam CO function at C-6 of (+)-**4** [operation (ii)], we tried to extend the scope of the mercuric acetate–(ethylenedinitrilo)tetraacetic acid (EDTA) oxidation,[12] utilised by Möhrle[13] for conversion of cyclic amines into lactams, to include 1-(3,4-dimethoxyphenyl) - 2 - (3-substituted piperidino)ethanols that could serve as appropriate precursors of 3- or 1-substituted 9,10-dimethoxybenzo[*a*]quinolizidines. Previous reports[14] from our laboratory described the results of such oxidation studies with particular emphasis on the effect of various 3-substituents upon regioselectivity in the formation of the lactam CO function. On the basis of these model experiments, operations (i) and (ii) for the synthesis of (−)-emetine (**1**) were realised in the following way.

Treatment of (+)-**4**, prepared from commercially available cinchonine (**7**) in 50% overall yield according to the classical degradation procedure,[9a,15] with 3,4-dimethoxyphenacyl bromide[16] and K_2CO_3 in benzene afforded the amino ketone (+)-**8** in 89% yield. Reduction of (+)-**8** to a diastereoisomeric mixture of the amino alcohol **9** was effected in 90% yield with $NaBH_4$ in EtOH at 0–5°. Upon oxidation with $Hg(OAc)_2$–EDTA in boiling 1% AcOH aq, the mixture **9** gave an oily substance, from which the 6-piperidone **10** (41% yield) and an oil (35% yield) presumed to be a mixture of the *cis*- and the *trans*-2-piperidones **11** were isolated by chromatographic separation. The crude mixture of the isomeric piperidones **10** and **11** was hydrogenolysed, without prior chromatographic separation, with hydrogen activated on Pd-C catalyst in EtOH in the presence of a little 70% $HClO_4$ aq, producing the 6-piperidone (−)-**12** (44% yield from **9**), the 2-piperidone (−)-**14** (4% yield), and the *trans*-2-piperidone (+)-**16** (30% yield). The structure of (−)-**12** was confirmed by its akaline hydrolysis leading to the lactam acid (−)-**13** (96% yield), which was identical, on spectral comparison, with authentic (±)-**13**.[17] The LAH reduction of (−)-**14** in boiling ether furnished the *cis*-amino alcohol (+)-**15**,[18] identical with a sample prepared by the condensation of (+)-**5**[19] with 3,4-dimethoxyphenethyl bromide. On the other hand, a similar reduction of (+)-**16** gave the *trans*-amino alcohol (−)-**18** and its 3,4-*trans* structure was established by spectral identification with (±)-**18**[18] synthesised from (±)-**19** through (±)-**20**.[19] The 6-piperidone structure of



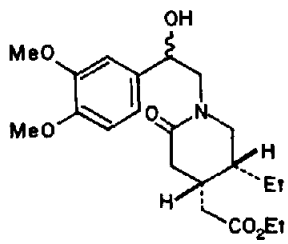
Scheme 1.

10 was confirmed by its conversion into (−)-**12** on catalytic hydrogenolysis. On a similar hydrogenolysis, the minor product **11** from the $Hg(OAc)_2$–EDTA oxidation of **9** provided a mixture of the *cis*-2-piperidone (−)-**14** and the *trans*-2-piperidone (+)-**16**. The occurrence of the *trans* isomer (+)-**16** is probably due to epimerisation of (−)-**14** at C-3 during the oxidation and/or work-up, and this was supported by a separate experiment, in which (−)-**14** was converted into (+)-**16** through (+)-**17** when treated successively with 2 N NaOH aq–EtOH and ethanolic HCl. Interestingly, the observed ratio of the 6- to the 2-oxidation [**10**:**11** = 54:46 or **12**:(**14** + **16**) = 56:44] in the $Hg(OAc)_2$–EDTA oxidation of **9** described above compares with that[14b] determined with simpler 3-alkylpiperidine derivatives.

Now that the *cis*-lactam acid (−)-**13** was successfully synthesised, the third main operation in the synthetic plan suggested its realisation in the form of isomerisation of (−)-**13** to the *trans*-lactam acid **21**. The key to this isomerisation would be given by the latent molecular symmetry of the 2-oxo-4-piperidineacetic acid system with respect to the exocyclic and the endocyclic CO functions. Our previous model experiments[19] have already shown that an isomeric pair of (±)-**23** and (±)-**25** or of (±)-**24** and (±)-**26** are convertible to each other through *cis-trans* equilibration (**23**:**25** = 33:67 or **24**:**26** = 33:67) under acid hydrolytic conditions or, more efficiently, on thermal treatment (e.g. at 180° without solvent). In the present study, we first followed the progress of isomerisation at 180° of the racemic *cis*-lactam acid (±)-**13**[17,20] to the *trans*-acid (±)-**21**,[21,22] instead of that of (−)-**13** to (+)-**21**, by determining the isomer ratio in the mixture according to the previously reported[19] ^{13}C NMR spectroscopic method. A rapid decrease of the amount of (±)-**13** was observed along with the occurrence and a rapid increase of (±)-**21** at earlier stages of the reaction, attaining to equilibrium in 75 min. The equilibration was also conducted in the reverse direction to yield the same mixture (**13**:**21** = 33:67) starting with (±)-**21**. It is assumed that the equilibrium is attained by a mechanism of intramolecular participation of the exocyclic carboxyl group, as discussed previously,[19] whereby the side chain at C-4 exchanges places with the endocyclic C-4–C-3–C-2 chain. Interestingly, a higher substituent at the N-1-position tends to cause the rate of isomerisation to slow down.[19]

On the basis of the above equilibration study, the chiral *cis*-lactam acid (−)-**13** was heated at 180° without any solvent for 80 min to give an equilibrated mixture (**13**:**21** = 33:67), from which the *trans*-lactam acid (+)-**21**, identical in spectral comparison with authentic (±)-**21**,[22] was isolated by recrystallisation. The yield of (+)-**21** was raised to 83% when the *cis*-lactam acid recovered from the mixture was repeatedly subjected to the same reaction. Esterification of (+)-**21** with ethanolic HCl was then effected at 25° for 24 hr to afford the lactam ester (+)-**22** in 92% yield. In principle, the mechanistic similarity between the acidic hydrolysis and the acid-catalysed alcoholysis of the lactam CO–N bond could not exclude the possibility that *trans* → *cis* isomerisation of (+)-**21** or (+)-**22** might occur under such Fischer–Speier esterification conditions. However, our previous work[23] has already revealed that *trans* → *cis* or *cis* → *trans* isomerisation of the model compounds (±)-**23**, (±)-**25**, (±)-**24**, and (±)-**26** does not occur at all under these particular conditions adopted for (+)-**21**. On reduction with LAH, the lactam ester (+)-**22** furnished the amino alcohol (+)-**27**, the enantiomer of (−)-**18**, in 96% yield.

Having solved the problems in operations (i), (ii), and



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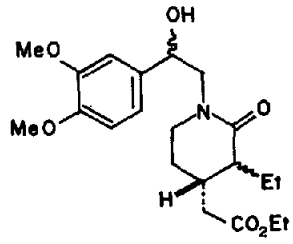

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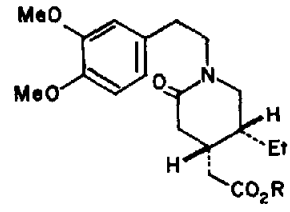
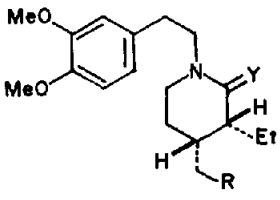
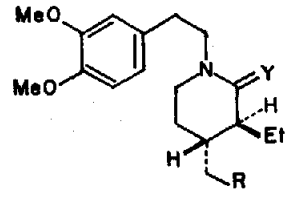


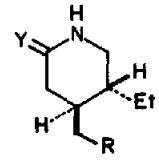
12: R = Et
13: R = H



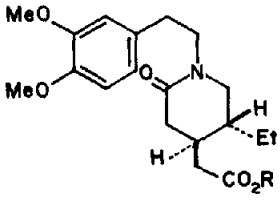
14: R = CO_2Et; Y = O
15: R = CH_2OH; Y = H_2



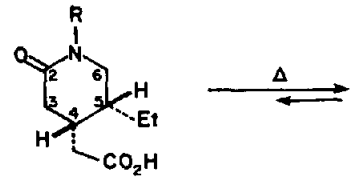
16: R = CO_2Et; Y = O
17: R = CO_2H; Y = O
18: R = CH_2OH; Y = H_2



19: R = CO_2Et; Y = O
20: R = CH_2OH; Y = H_2

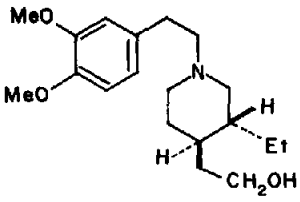


21: R = H
22: R = Et



23: R = H
24: R = $PhCH_2$

25: R = H
26: R = $PhCH_2$



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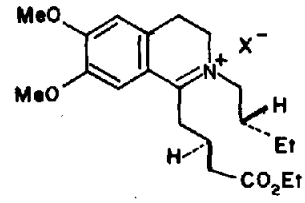
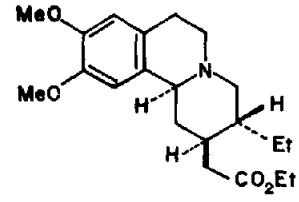


28: X = I
29: X = ClO_4



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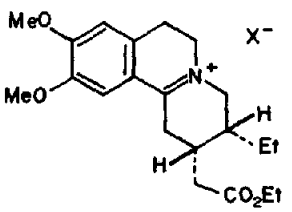
Scheme 2.

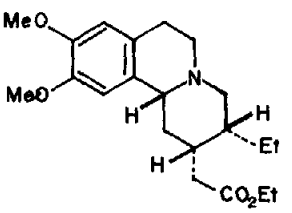
(iii), we next focused our attention on operation (iv) that is to complete the benzoquinolizidine part. The following transformations were patterned after those employed for the racemic series.[20–22] Thus, the lactam ester (+)-**22** was cyclised with $POCl_3$ to give the immonium iodide **28** in 95% yield. Conversion of the iodide salt into the perchlorate **29** (88% yield) and subsequent catalytic hydrogenation (Pt/H_2, EtOH, 18°) produced **30**·$HClO_4$, from which the desired tricyclic base (−)-**30** was obtained in 98% yield (from **29**). The physical properties of this sample of (−)-**30**, in good agreement with those reported,[24] and spectral comparison with authentic (±)-**30**[22] unequivocally established its structure.

An alternative method for operation (iii) was to isomerise (−)-**13** to (+)-**21** under acid hydrolytic conditions on the analogy of *cis-trans* isomerisation of the model compounds (±)-**23**, (±)-**25**, (±)-**24**, and (±)-**26** in boiling conc HCl aq or 6 N HCl,[19] although it seemed less efficient than the thermal method described above. When (−)-**13** was treated with boiling 10% HCl aq for 20 hr, a mixture of (+)-**21** and (−)-**13** was obtained. The mixture was successively subjected to esterification, Bischler–Napieralski cyclisation, and catalytic hydrogenation as described above for the conversion of (+)-**21** into (−)-**30**, providing (−)-**30** [28% yield from (−)-**13**] together with its 2,3-*cis*-isomer (+)-**33** (16% yield). This *cis isomer* [(+)-**33**] was more efficiently synthesised from (−)-**12** by cyclisation with $POCl_3$ to the iodide **31** (93% yield) followed by catalytic hydrogenation (92% yield, Pt/H_2, 80% EtOH aq, 1 atm, 20°, 45 min) of the corresponding perchlorate **32**. The structure of (+)-**33** was confirmed by the conformity of its IR ($CHCl_3$) and NMR ($CDCl_3$) spectra with those of authentic (±)-**33**.[17]

Since the 2,3-*trans*-tricycle (−)-**30** has been shown to



31: X = I
32: X = ClO$_4$



33

Scheme 3.

lead to O-methylpsychotrine,[24] emetine (1),[24b] psychotrine,[25] protoemetine,[26] and tubulosine alkaloids,[27] the above preparation of (−)-**30** formally concluded syntheses of these alkaloids. The 2,3-*cis*-tricycle (+)-**33** should give the four possible chiral 2,3-*cis*-emetines by following the same synthetic route as reported for the racemic series.[20a,28] Indeed, the results described above have only added one more example to almost a score of successful achievements[2,22,29] in the synthesis of emetine (**1**), but they have exemplified the correctness of the stereochemical outcome of the synthetic operations utilised in our recent chiral syntheses[4,6,8] of the *A. lamarckii* alkaloids (type **2**). It is hoped that such a "cincholoipon-incorporating method" could serve as a vehicle for general syntheses of structurally parallel alkaloids whereby the later reaction steps can take full advantage of high stereoselectivity due to the C-3 and C-4 chirality of cincholoipon ethyl ester [(+)-**4**] and of the practical convenience of making the optical resolution of products unnecessary.

EXPERIMENTAL

General

All m.ps are corrected. Unless otherwise stated, the organic solns obtained after extraction were dried over Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were determined with a Hitachi 323 UV spectrophotometer, a JASCO IRA-2 IR spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-PS-100 NMR spectrometer at 23° using Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-SL polarimeter.

(3R,4S)-(+)-1-(3,4-*Dimethoxyphenacyl*)-3-*ethyl*-4-*piperidineacetic acid ethyl ester* [(+)-**8**]

To a stirred mixture of ethyl cincholoiponate [(+)-**4**][9] (9.57 g, 48 mmol), anhyd K_2CO_3 (6.64 g, 48 mmol), and dry benzene (100 ml) was added a soln of 3,4-dimethoxyphenacyl bromide[16] (12.43 g, 48 mmol) in dry benzene (60 ml), and the resulting mixture was heated under reflux with stirring for 4 hr. After cooling, the mixture was stirred with H_2O (40 ml) and the benzene layer, after separated from the aqueous layer, was extracted with 10% HCl aq. The acid soln was washed with benzene, made basic with anhyd K_2CO_3, and extracted with AcOEt. The AcOEt extracts were washed with 10% Na_2CO_3 aq, dried over K_2CO_3, and evaporated *in vacuo* to leave an orange red oil (16.67 g). The oil was purified by column chromatography [Al_2O_3 (330 g), AcOEt—hexane (1:2, v/v)] to give (+)-**8** (16.13 g, 89%) as a faintly orange oil, $[\alpha]_D^{24}$ +2.3° (*c* 2.50, EtOH); MS *m/e*: 377 (M^+); IR (film): 1728 (ester C=O), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 7 Hz, CCH_2CH_3), 1.24 (3H, t, J = 7 Hz, OCH_2CH_3), 3.72 (2H, s, NCH_2COAr), 3.94 and 3.97 (3H each, s, two OMe's), 4.14 (2H, q, J = 7 Hz, OCH_2CH_3), 6.90 (1H, d, J = 8.5 Hz, 5'-H), 7.62 (1H, d, J = 2 Hz, 2'-H), 7.74 (1H, d-d, J = 8.5 and 2 Hz, 6'-H).

The starting ester (+)-**4** was prepared from commercially available cinchonine (**7**) in 50% overall yield according to the literature procedure[9a,15] and characterised as described previously.[19]

(3R,4S)-1-[2-(3,4-*Dimethoxyphenyl*)-2-*hydroxyethyl*]-3-*ethyl*-4-*piperidineacetic acid ethyl ester* (**9**)

A soln of (+)-**8** (13.8 g, 36.6 mmol) in EtOH (240 ml) was stirred under ice-cooling, and $NaBH_4$ (690 mg, 18.2 mmol) was added portionwise. After stirring was continued at 0–5° for 4 hr, acetone (2 ml) was added and the mixture was concentrated *in vacuo*. To the residue was added H_2O (60 ml) and the aqueous mixture was extracted with AcOEt. The AcOEt extracts were washed with 10% Na_2CO_3 aq, dried (K_2CO_3), and evaporated to give **9** (12.5 g, 90%) as a pale yellow oil, $[\alpha]_D^{24}$ −1.2° (*c* 1.00, EtOH); MS *m/e*: 379 (M^+); IR (film): 3440 (br, OH), 1730 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ: 0.94 (3H, unresolved t, diastereoisomeric CCH_2CH_3, s), 1.27 (3H, t, J = 7 Hz, OCH_2CH_3), 3.64 (1H, br, OH), 3.85 and 3.89 (3H each, s, two OMe's), 4.13 (2H, q, J = 7 Hz, OCH_2CH_3), 4.56–4.76 [1H, m, $CH(OH)Ar$], 6.85–7.00 (3H, m, Ar-H's). Although the oil (**9**) showed a single spot on tlc analysis, it was presumed to be a mixture of the two possible diastereoisomers due to the difference in configuration at the benzylic position. The crude oil was used directly in the next oxidation step without further purification.

The hydrogencarbonate salt of **9**

When the crude oil (**9**) was exposed to air, it gradually became red and viscous. Trituration of the resulting thick oil with ether produced minute crystals, m.p. 128–129°. Recrystallisation of the solid from AcOEt gave an analytical sample of **9**·H_2CO_3, but of unknown diastereoisomeric purity, as minute colorless needles, m.p. 129–130° (Found: C, 60.06; H, 8.20; N, 3.24. $C_{21}H_{33}NO_5 \cdot H_2CO_3$ requires: C, 59.84; H, 7.99; N, 3.17%); $[\alpha]_D^{30}$ −22.1° (*c* 0.75, EtOH).

The $Hg(OAc)_2$*—EDTA oxidation of the amino alcohol* **9**

To a soln of **9** (15.2 g, 40 mmol) in 1% AcOH aq (300 ml) were added (ethylenedinitrilo)tetraacetic acid disodium salt dihydrate (37.2 g, 100 mmol) and $Hg(OAc)_2$ (31.9 g), 100 mmol). The mixture was stirred and heated under gentle reflux for 1.5 hr, depositing metallic Hg and a brownish oil. After cooling, the mixture was extracted with $CHCl_3$, and the $CHCl_3$ extracts were washed successively with 10% HCl aq, H_2O, 5% NaOH aq, and H_2O, dried, and evaporated to leave a reddish brown oil (17.8 g). The residue was dissolved in a little $CHCl_3$ and the soln was passed through a column packed with Al_2O_3 (120 g). The column was eluted with $CHCl_3$ (500 ml) and the eluate was evaporated *in vacuo* to give a slightly brown oil (16.1 g), shown to be impure by four spots on tlc analysis (Al_2O_3, AcOEt). For the hydrolysis of substances presumed[14a] to be the acetates of **10** and **11**, the total amount of the oil was dissolved in EtOH (160 ml) containing anhyd K_2CO_3 (13.8 g, 100 mmol). After having been stirred at room temp for 5 hr, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue wad dissolved in $CHCl_3$ and the soln was washed successively with 5% NaOH aq and H_2O, dried, and concentrated to leave a mixture of **10** and **11** as a slightly brown oil (13.6 g, 86%), which was chromatographed on Al_2O_3. Earlier fractions eluted with AcOEt gave the 2-piperidone **11** (35% yield) and later fractions eluted with AcOEt–EtOH (9:1, v/v) afforded the 6-piperidone **10** (41% yield). The two lactam

alcohols, each of which was presumed to be a mixture of the two possible diastereoisomeric alcohols, were characterised as follows.

(4S,5R) - 1 - [2 - (3,4 - *Dimethoxyphenyl*) - 2 - *hydroxyethyl*] - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid ethyl ester* (**10**)

Obtained as a colorless oil, $[\alpha]_D^{20} - 23.0°$ (*c* 2.00, EtOH); IR ($CHCl_3$): 3340 (OH), 1728 (ester C=O), 1621 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 6.5 Hz, CCH_2CH_3), 1.27 (3H, t, J = 7 Hz, OCH_2CH_3), 3.84 and 3.86 (3H each, s, two OMe's), 4.12 (2H, q, J = 7 Hz, OCH_2CH_3), 4.60–5.05 (1H, br, OH), 4.85–5.05 [1H, m, CH(OH)Ar], 6.80–7.00 (3H, m, Ar-H's).

A mixture (**11**) *of* (3R,4S) - *and* (3S,4S) - 1 - [2 - (3,4 - *dimethoxyphenyl*) - 2 - *hydroxyethyl*] - 3 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid ethyl esters*

Isolated as a colorless oil, $[\alpha]_D^{20} + 14.9°$ (*c* 2.00, EtOH); IR ($CHCl_3$): 3330 (OH), 1728 (ester C=O), 1612 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.80–1.12 (3H, m, isomeric CCH_2CH_3's), 1.27 (3H, t, J = 7 Hz, OCH_2CH_3), 3.85 and 3.88 (3H each, s, two OMe's), 4.13 (2H, q, J = 7 Hz, OCH_2CH_3), 4.87–5.05 [1H, m, CH(OH)Ar], 6.75–7.00 (3H, m, Ar-H's). On catalytic hydrogenolysis as described below, this oil produced a mixture of (−)-**14** and (+)-**16** in 94% yield. The mixture was separated into its component parts by column chromatography [silica gel, ether–EtOH (97:3, v/v)].

Hydrogenolysis of the lactam alcohols **10** *and* **11**

The oily mixture (3.62 g, 9.2 mmol) of **10** and **11**, obtained by the above $Hg(OAc)_2$—EDTA oxidation of **9**, was dissolved in EtOH (60 ml) containing 70% $HClO_4$ aq (0.92 ml), and the soln was hydrogenated over 10% Pd-C (2.0 g) at 4 atm and room temp for 20 hr. The catalyst was removed by filtration and washed with a little EtOH. The filtrate and washings were combined and evaporated *in vacuo* to leave a syrup. The residue was partitioned by extraction with a mixture of $CHCl_3$ (60 ml) and H_2O (30 ml). The $CHCl_3$ extracts were washed successively with 10% Na_2CO_3 aq and H_2O, dried, and concentrated to afford a mixture of (−)-**12**, (−)-**14**, and (+)-**16** as a pale yellow oil (3.43 g, 99%). Purification of the oil by column chromatography [Al_2O_3 (275 g), AcOEt—hexane (1:1, v/v), AcOEt] furnished the 6-piperidone (−)-**12** (1.75 g, 44% yield from **9**) from later fractions as well as a mixture (1.51 g) of the 2-piperidones (−)-**14** and (+)-**16** from earlier fractions. The mixture of (−)-**14** and (+)-**16** was further separated into its component parts on a 250-g silica gel column using ether–EtOH (97:3, v/v) as eluent. The amounts of (−)-**14** (*Rf* 0.56) and (+)-**16** (*Rf* 0.41) isolated were 156 mg (4% yield from **9**) and 1.195 g (30% yield). The three piperidones were characterised as follows.

(4S,5R) - (−) - 1 - (3,4 - *Dimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid ethyl ester* [(−) - **12**]

A colorless oil, $[\alpha]_D^{18} - 8.4°$ (*c* 1.00, EtOH); MS *m/e*: 377 (M^+). The IR (film or $CHCl_3$) and NMR ($CDCl_3$) spectra of this sample were superimposable on those of authentic (±)-**12**.[17] When the catalytic hydrogenolysis of the lactam alcohol **10** was effected as described above for that of a mixture of **10** and **11**, (−)-**12** was obtained in 94% yield.

(3R,4S) - (−) - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid ethyl ester* [(−) - **14**]

A colorless oil, $[\alpha]_D^{25} - 3.5°$ (*c* 1.00, EtOH); MS *m/e*: 377 (M^+); IR ($CHCl_3$): 1727 (ester C=O), 1622 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.99 (3H, t, J = 7 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.85 and 3.88 (3H each, s, two OMe's), 4.14 (2H, q, J = 7 Hz, OCH_2CH_3), 6.76 (3H, s, Ar-H's).

(3S,4S) - (+) - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid ethyl ester* [(+) - **16**]

A colorless oil, $[\alpha]_D^{30} + 26.1°$ (*c* 1.00, EtOH); MS *m/e*: 377 (M^+); IR ($CHCl_3$): 1727 (ester C=O), 1620 cm^{-1} (lactam C=O); NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7 Hz, CCH_2CH_3), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.85 and 3.87 (3H each, s, two OMe's), 4.13 (2H, q, J = 7 Hz, OCH_2CH_3), 6.80 (3H, s, Ar-H's).

(4S,5R) - (−) - 1 - (3,4 - *Dimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid* [(−) - **13**]

A soln of the ester (−)-**12** (2.26 g, 5.99 mmol) in EtOH (18 ml) containing 1 N NaOH aq (9 ml) was kept at room temp for 24 hr. The mixture was concentrated *in vacuo* and H_2O (20 ml) was added to the residue. After having been washed with benzene, the aqueous soln was made acid (pH 1) with conc. HCl aq and extracted with benzene. The benzene extracts were washed with H_2O, dried, and evaporated to leave (−)-**13** (2.01 g, 96%) as a colorless thick oil, $[\alpha]_D^{20} - 1.4°$ (*c* 1.00, EtOH). The IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and ^{13}C NMR ($CDCl_3$) spectra of this oil were identical with those of authentic (±)-**13**.[17]

(3R,4S) - (+) - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 4 - *piperidineethanol* [(+) - **15**]

(i) *Reduction of* (−)-**14**. To a cooled (to 0°), stirred suspension of LAH (30 mg, 0.79 mmol) in dry ether (12 ml) was added dropwise a soln of (−)-**14** (120 mg, 0.32 mmol) in dry ether (12 ml). After the mixture had been treated at reflux with stirring for 6 hr, H_2O (2 drops), 10% NaOH aq (2 drops), and H_2O were successively added with stirring under cooling. Insoluble inorganic materials were removed by filtration and washed with ether. The combined filtrate and washings were dried over K_2CO_3 and evaporated *in vacuo*, leaving (+)-**15** (97 mg, 94%) as colorless, thick oil, $[\alpha]_D^{30} + 8.4°$ (*c* 0.50, EtOH), identical (by comparison of IR and NMR spectra and tlc behavior) with a sample obtained by method (ii).

(ii) *From* (+)-**5**. A stirred mixture of the amino alcohol (+)-**5**[19] (315 mg, 2.0 mmol), 3,4-dimethoxyphenethyl bromide (515 mg, 2.1 mmol), anhyd K_2CO_3 (290 mg, 2.1 mmol), and benzene (8 ml) was refluxed for 8 hr. After cooling, the mixture was stirred with H_2O, and the benzene layer, after separated from the aqueous layer, was extracted with 10% HCl aq. The acid soln was made basic with anhyd K_2CO_3 and extracted with ether. The ether extracts were dried (K_2CO_3) and evaporated *in vacuo* to give (+)-**15** (490 mg, 76%) as a colorless, thick oil, $[\alpha]_D^{30} + 9.1°$ (*c* 2.40, EtOH) [lit.[18] $[\alpha]_D^{22} + 9.0° + 1.26°$ (*c* 2.399, EtOH)]; MS *m/e*: 321 (M^+); IR (film): 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7 Hz, CH_2CH_3), 3.66 (2H, t, J = 6.5 Hz, CH_2CH_2OH), 3.85 and 3.88 (3H each, s, two OMe's), 6.76 (3H, s, Ar-H's).

(3S,4S) - (−) - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 4 - *piperidineethanol* [(−) - **18**]

A soln of (+)-**16** (200 mg, 0.53 mmol) in dry ether (15 ml) was reduced with LAH (55 mg, 1.45 mmol) for 6 hr in a manner similar to that described above for the reduction of (−)-**14** to (+)-**15**. The amino alcohol (−)-**18** was thus produced as a colorless, thick oil (160 mg, 94%), $[\alpha]_D^{30} - 40.1°$ (*c* 1.00, EtOH); MS *m/e*: 321 (M^+). The IR and NMR spectra and the tlc behavior of this oil matched those of (±)-**18**.

(±) - trans - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 4 - *piperidineethanol* [(±) - **18**]

The racemic amino alcohol (±)-**20**,[19] prepared by the LAH reduction of (±)-**19**,[19] was allowed to react with 3,4-dimethoxyphenethyl bromide as described above for (±)-**15** under method (ii). The product (±)-**18**[18] was obtained in 80% yield as a colorless, thick oil, MS *m/e*: 321 (M^+); IR (film): 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7 Hz, CH_2CH_3), 3.56–3.84 (2H, m, CH_2CH_2OH), 3.85 and 3.88 (3H each, s, two OMe's), 6.68–6.88 (3H, m, Ar-H's).

(3S,4S) - (+) - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid* [(+) - **17**]

A soln of (+)-**16** (755 mg, 2.0 mmol) in EtOH (7 ml) containing 1 N NaOH aq (3.5 ml) was kept at 15° for 12 hr. The mixture was then worked up as described above for (−)-**13**, giving (+)-**17** (678 mg, 97%) of m.p. 111–114°. Recrystallisation from AcOEt–hexane (2:1, v/v) yielded an analytical sample as colorless prisms, m.p. 122–124° (Found: C, 65.39; H, 7.77; N, 4.20. $C_{19}H_{27}NO_5$ requires: C, 65.31; H, 7.79; N, 4.01%); $[\alpha]_D^{25} + 20.6°$ (*c* 1.00, EtOH); IR (Nujol): 1712 (CO_2H), 1600 cm^{-1} (lactam

C=O); IR ($CHCl_3$): 1713 (CO_2H), 1620 cm^{-1} (lactam (C=O); NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7 Hz, CH_2CH_3), 2.72–2.98 (2H, m, CH_2CH_2Ar), 3.08–3.30 (2H, m, CH_2CH_2Ar), 3.50–3.72 (2H, m, 6-H's), 3.86 and 3.88 (3H each, s, two OMe's), 6.76 (3H, s, Ar-H's), 10.72 (1H, s, CO_2H).

Esterification of (+)-**17** *to* (+)-**16**

A soln of (+)-**17** (200 mg, 0.57 mmol) in 10% (w/w) ethanolic HCl (12 ml) was kept at 20° for 24 hr. The mixture was evaporated *in vacuo* and the residue was partitioned by extraction with a mixture of H_2O (6 ml) and benzene (15 ml). The benzene extracts were washed successively with 10% Na_2CO_3 aq and H_2O, dried, and concentrated to leave (+)-**16** (200 mg, 93%) as a colorless, thick oil, $[\alpha]_D^{25}$ + 25.6° (*c* 1.00, EtOH), identical (by comparison of IR spectrum) with a sample obtained by the hydrogenolysis of **11**.

Epimerisation of (−)-**14** *to* (+)-**16** *through* (+)-**17**

A soln of (−)-**14** (50 mg, 0.13 mmol) in EtOH (1 ml) containing 2 N NaOH (0.5 ml) was kept at 15° for 12 hr. The mixture was then worked up as described above for (+)-**17**, giving crude (+)-**17** (42 mg, 93%) as a slightly brown solid, m.p. 73–85°. The solid was esterified as described above for the esterification of (+)-**17**, and (+)-**16** was obtained as a pale yellow oil [44 mg, 88% yield from (−)-**14**], $[\alpha]_D^{18}$ + 21° (*c* 0.35, EtOH). Although tlc analysis suggested that this oil still contained a trace amount of the *cis*-ester (−)-**14**, its IR spectrum was superimposable on that of a pure sample of (+)-**16**.

Isomerisation of the cis-*lactam acid* (±)-**13** *to the* trans-*lactam acid* (±)-**21** *or vice versa*

Aliquots (60–80 mg) of (±)-**13**[17,20] or (±)-**21**[21,22] were separately sealed in small ampoules and placed in an oil bath kept at 180° ± 1°. At intervals the ampoules were removed, cooled, and broken, and the relative amounts of a pair of the two isomers in the mixtures were measured by ^{13}C FT NMR spectroscopy as reported previously[19] for a similar isomerisation study of the N-benzyl analogue (±)-**24** or (±)-**26**. In the noise-decoupled ^{13}C NMR spectrum in $CDCl_3$, (±)-**13** exhibited the Me and the methylene C signals of the C-Et group at 11.9 and 20.9 ppm (downfield from internal Me_4Si), whereas (±)-**21**, at 10.7 and 23.2 ppm. For the ^{13}C FT NMR spectroscopic determination, relative heights of the methylene C signals of the isomeric C-Et groups were utilised. The determinations were found to be accurate to ± 1%. The results of the isomerisation study are summarised in the text.

(4R,5R) - (+) - 1 - (3,4 - *Dimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid* [(+) - **21**]

The *cis*-lactam acid (−)-**13** (1.30 g, 3.72 mmol) was placed in a small flask and heated neat in an oil bath kept at 180° ± 1° for 80 min. After cooling, the oily mixture, which was shown to be a 33:67 mixture of (−)-**13** and (+)-**21** by ^{13}C NMR spectroscopic analysis as described above, was triturated with hexane–AcOEt (1:1, v/v) and the insoluble solid [(+)-**21**] that resulted was collected by filtration. The filtrate was evaporated *in vacuo* and the residue was again heated at 180° for 80 min, giving a second crop of (+)-**21**. In a similar manner, a third crop was collected. Recrystallisation of the total amount (1.22 g) of the crude solid, m.p. 104–105°, from hexane–AcOEt (1:1, v/v) yielded (+)-**21** as slightly brown prisms (1.08 g, 83%), m.p. 127–129°. Two more recrystallisations in a similar way afforded an analytical sample as colorless prisms, m.p. 129–130° (Found: C, 65.29; H, 7.75; N, 4.03. $C_{19}H_{27}NO_5$ requires: C, 65.31; H, 7.79; N, 4.01%; $[\alpha]_D^{26}$ + 63.0° (*c* 1.00, EtOH). The IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and ^{13}C NMR ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-**21**.[21,22]

(4R,5R) - (+) - 1 - (3,4 - *Dimethoxyphenethyl*) - 5 - *ethyl* - 2 - *oxo* - 4 - *piperidineacetic acid ethyl ester* [(+) - **22**]

A soln of (+)-**21** (850 mg, 2.43 mmol) in 10% (w/w) ethanolic HCl (30 ml) was kept at 25° for 24 hr. The reaction soln was concentrated *in vacuo* and the residue was partitioned by extraction with a mixture of $CHCl_3$ (50 ml) and H_2O (15 ml). The $CHCl_3$ extracts were washed successively with 10% Na_2CO_3 aq and H_2O, dried, and evaporated to leave a pale brown oil (909 mg). The oil was purified by column chromatography [Al_2O_3 (30 g), AcOEt] to give (+)-**22** (844 mg, 92%) as a colorless oil, $[\alpha]_D^{28}$ + 54.3° (*c* 1.00, EtOH). The IR (film) and NMR ($CDCl_3$) spectra of this oil were identical with those of authentic (±)-**22**.[22]

(3R,4R) - (+) - 1 - (3,4 - *Dimethoxyphenethyl*) - 3 - *ethyl* - 4 - *piperidineethanol* [(+) - **27**]

The lactam ester (+)-**22** was reduced with LAH in a manner similar to that described above for the reduction of (−)-**14** to (+)-**15**, affording (+)-**27** (96% yield) as a colorless, thick oil, $[\alpha]_D^{30}$ + 40.4° (*c* 2.10, EtOH); MS *m/e*: 321 (M^+). The tlc behavior and the IR (film) and NMR ($CDCl_3$) spectra of this sample matched those of (±)-**18** as well as those of (−)-**18** described above.

(2R,3R) - 2 - *Ethoxycarbonyl* - 3 - *ethyl* - 1,2,3,4,6,7 - *hexahydro* - 9,10 - *dimethoxybenzo*[a]*quinolizinium iodide* (**28**)

A soln of (+)-**22** (600 mg, 1.59 mmol) and $POCl_3$ (1.20 g, 7.83 mmol) in dry toluene (6 ml) was refluxed for 1.5 hr. Concentration of the mixture under vacuum left a reddish brown oil, which was dissolved in H_2O (6 ml). The aqueous soln was saturated with KI and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 10% KI aq, dried, and evaporated to leave **28** (735 mg, 95%) as a yellow solid, m.p. 145—151°. Recrystallisation from EtOH–AcOEt (1:4, v/v) gave an analytical sample as minute yellow needles, m.p. 153–154° (Found: C, 51.75; H, 6.18; N, 3.07. $C_{21}H_{30}INO_4$ requires: C, 51.75; H, 6.20; N, 2.87%); UV λ_{max}^{EtOH} 246 nm (ϵ 16100), 304 (9100), 354 (9100). The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-**28**.[22]

(2R,3R) - 2 - *Ethoxycarbonyl* - 3 - *ethyl* - 1,2,3,4,6,7 - *hexahydro* - 9,10 - *dimethoxybenzo*[a]*quinolizinium perchlorate* (**29**)

To a hot soln of **28** (200 mg, 0.41 mmol) in EtOH (5 ml) was added a soln of $AgClO_4$ (93 mg, 0.45 mmol) in EtOH (2 ml). The ppt of AgI that resulted was filtered off while hot and washed with hot EtOH. The filtrate and washings were combined and kept in a refrigerator. The colorless needles that deposited were filtered off and dried to give **29** (166 mg, 88%), m.p. 133–134°. Recrystallisation from EtOH yielded an analytical sample, m.p. 133–134° (Found: C, 54.62; H, 6.59; N, 3.13. $C_{21}H_{30}ClNO_8$ requires: C, 54.84; H, 6.57; N, 3.05%); UV λ_{max}^{EtOH} 246 nm (ϵ 16550), 304 (9250), 354 (9200).

(2R,3R,11*b*S) - (−) - 3 - *Ethyl* - 1,3,4,6,7,11*b* - *hexahydro* - 9,10 - *dimethoxy* - 2H - *benzo*[a]*quinolizine* - 2 - *acetic acid ethyl ester* [(−) - **30**]

A soln of **29** (460 mg, 1.0 mmol) in 90% (v/v) EtOH aq (20 ml) was hydrogenated over Adams catalyst (120 mg) at 1 atm and 18° for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to leave (−)-**30**·$HClO_4$ (462 mg, 100%), m.p. 146–147°, which was dissolved in H_2O (10 ml). The aqueous soln was made basic with anhyd K_2CO_3 and extracted with ether. The ethereal soln was dried (K_2CO_3) and concentrated to leave (−)-**30** (353 mg, 98%) as a faint yellow solid, m.p. 89–90°. Recrystallisation from petroleum ether (b.p. 40–60°) afforded an analytical sample as colorless needles, m.p. 90–91° (lit.[24b] m.p. 89–90°) (Found: C, 70.07; H, 8.49; N, 4.15. $C_{21}H_{31}NO_4$ requires: C, 69.78; H, 8.64; N, 3.87%); $[\alpha]_D^{30}$ − 39.3° (*c* 1.00, EtOH) [lit.[24b] $[\alpha]_D^{23}$ − 39° (*c* 1, EtOH)]. The tlc behavior and the IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of this sample matched those of authentic (±)-**30**.[22]

The perchlorate of (−)-**30**

This was recrystallised from EtOH–AcOEt (1:1, v/v) to colorless scales, m.p. 149–150° (Found: C, 54.89; H, 6.87; N, 3.06. $C_{21}H_{32}ClNO_8$ requires: C, 54.60; H, 6.98; N, 3.03%).

(2S,3R) - 2 - *Ethoxycarbonyl* - 3 - *ethyl* - 1,2,3,4,6,7 - *hexahydro* - 9,10 - *dimethoxybenzo*[a]*quinolizinium iodide* (**31**)

The *cis*-lactam ester (−)-**12** was cyclised with $POCl_3$ and the product was isolated as the iodide salt in a manner similar to that

described above for the *trans* isomer **28**, giving **31** (93% yield) as a pale brown solid, m.p. 114–116°. Recrystallisation from EtOH–AcOEt (1:4, v/v) provided an analytical sample as faintly yellow scales, m.p. 117–119° (Found: C, 51.81; H, 6.25; N, 3.15. $C_{21}H_{30}INO_4$ requires: C, 51.75; H, 6.20; N, 2.87%). The UV (EtOH), IR ($CHCl_3$), and NMR ($CDCl_3$) spectra of this specimen were superimposable on those of authentic (±)-**31**.[17]

(2S,3R) - 2 - *Ethoxycarbonyl* - 3 - *ethyl* - 1,2,3,4,6,7 - *hexahydro* - 9,10 - *dimethoxybenzo*[a]*quinolizinium perchlorate* (**32**)

The iodide **31** was treated with $AgClO_4$ as described above for **29**, and the perchlorate **32** was obtained in 92% yield as minute colorless needles, m.p. 117–118° (Found: C, 54.72; H, 6.44; N, 3.14. $C_{21}H_{30}ClNO_8$ requires: C, 54.85; H, 6.57; N, 3.05%); UV λ_{max}^{EtOH} 246 nm (ε 16100), 304 (9150), 354 (9200).

(2S,3R,11*b*R) - (+) - 3 - *Ethyl* - 1,3,4,6,7,11*b* - *hexahydro* - 9,10 - *dimethoxy* - 2H - *benzo*[a]*quinolizine* - 2 - *acetic acid ethyl ester* [(+) - **33**]

A soln of **32** (1.00 g, 2.17 mmol) in 80% (v/v) EtOH aq (50 ml) was hydrogenated over Adams catalyst (120 mg) at 1 atm and 20° for 45 min. The mixture was worked up as described above for (−)-**30**, but the basic component was extracted with benzene instead of ether, yielding (+)-**33** (720 mg, 92%) as a pale yellow oil, $[\alpha]_D^{30}$ + 107.8° (*c* 1.80, EtOH), which was unstable on exposure to air. The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of this oil were identical with those of authentic (±)-**33**.[17]

The perchlorate of (+)-**33**

This salt was prepared from the free base (+)-**33** by adding an equimolar amount of 70% $HClO_4$ aq. It was recrystallised from AcOEt to give the monohydrate as minute colorless needles, m.p. 120–122° (dried over P_2O_5 at 60° and 3 mmHg for 8 hr) (Found: C, 52.53; H, 6.94; N, 2.83. $C_{21}H_{32}ClNO_8 \cdot H_2O$ requires: C, 52.55; H, 7.13; N, 2.92%).

The hydriodide of (+)-**33**

Equimolar amounts of (+)-**33**·$HClO \cdot H_2O$ and KI were heated in EtOH and the ppt that resulted was filtered off. The filtrate was evaporated *in vacuo* and the residue was recrystallised from EtOH–AcOEt (1:9, v/v) to furnish (+)-**33**·HI as colorless scales, m.p. 195–196° (Found: C, 51.42; H, 6.48; N, 2.87. $C_{21}H_{32}INO_4$ requires: C, 51.54; H, 6.59; N, 2.86%); $[\alpha]_D^{30}$ + 84.4° (*c* 1.00, EtOH).

Epimerisation of the cis-*lactam acid* (−)-**13** *to the* trans-*isomer* (+)-**21** *with boiling* 10% HCl *aq*

A mixture of (−)-**13** (1.58 g, 4.52 mmol) and 10% HCl aq (34 ml) was heated at reflux for 20 hr. After cooling, the mixture was extracted with $CHCl_3$. The $CHCl_3$ soln was washed with H_2O, dried, and evaporated to leave a mixture of (−)-**13** and (+)-**21** as a pale brown gum (1.12 g, 71%), which was dissolved in 10% ethanolic HCl (45 ml). After having been kept at room temp for 24 hr, the ethanolic soln was concentrated and the residue was partitioned by extraction with a mixture of $CHCl_3$ (30 ml) and H_2O (20 ml). The $CHCl_3$ extracts were washed successively with H_2O, 10% Na_2CO_3 aq, and H_2O, dried, and evaporated to leave an oily mixture (1.14 g, 91%) of (−)-**12** and (+)-**22**. A soln of this mixture and $POCl_3$ (2.30 g) in toluene (12 ml) was then refluxed for 1.5 hr, and the mixture was concentrated *in vacuo*. To the residue was added H_2O (15 ml) and the aqueous mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with 10% HCl aq and sat NaCl aq, dried, and evaporated to give a brown gum (1.07 g), which was hydrogenated catalytically as described above for the synthesis of (−)-**30**. The oily mixture (905 mg) of (−)-**30** and (+)-**33** thus formed was then chromatographed on a 108-g Al_2O_3 column using AcOEt–hexane (1:4, v/v) as eluent. Earlier fractions gave (+)-**33** [255 mg, 16% overall yield from (−)-**13**] and later fractions afforded (−)-**30** [452 mg, 28% yield from (−)-**13**]. The two bases were identified with authentic samples by spectral comparison and by converting them into the corresponding perchlorates.

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