Total Synthesis of (±)-Decamine. A Convenient Scheme for the Synthesis of *cis*- and *trans*-Quinolizidine Alkaloids[1a,b]

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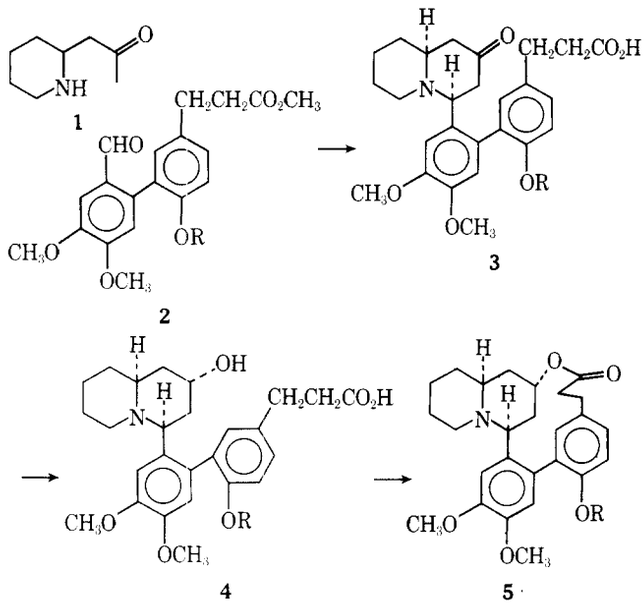
The total synthesis of (±)-decamine, a pentacyclic lythracea alkaloid, is described. The synthesis is based on the stereoselective preparation of *cis*-quinolizidine ketones **6a** and **6b** from isopelletierine and suitably substituted biphenylcarboxaldehydes. Hydrogenation to the thermodynamically less stable α-carbinols was carried out with Pt catalyst in alkaline solution; these were cyclized to the final alkaloids by acid catalysis and in high dilution. A generalized scheme is presented wherein the *cis*-quinolizidine ketone **6a** is epimerized to the trans stereoisomer, thereby acting as precursor to the trans series as well.

Alkaloids from the lythracea family of plants have been known and used in medicine since the early 1600s. Isolation of the first crystalline compounds by Ferris in 1962[2a] resulted in extensive structural studies by Ferris and others[2c,d] that culminated in the recognition, correlation, and classification of over 15 related alkaloids.

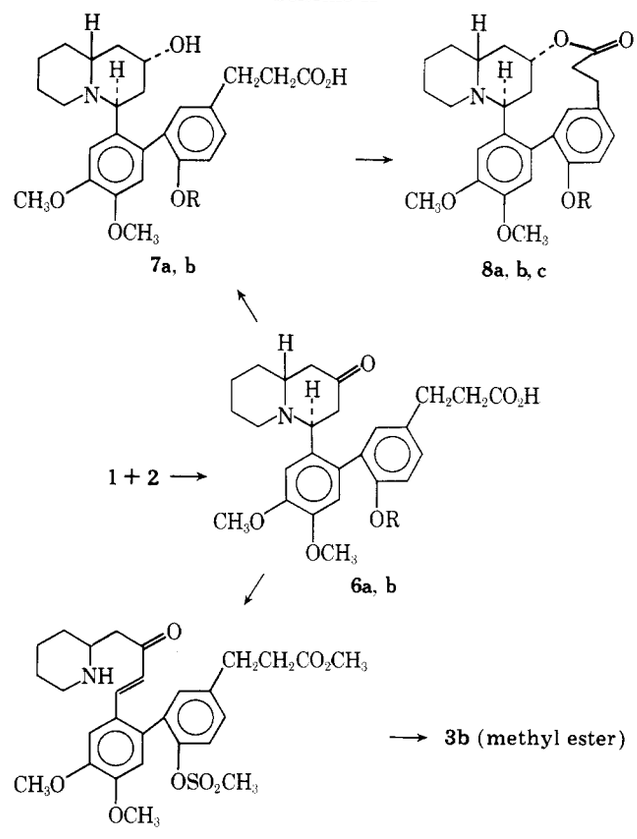
Wrobel and Golebiewski[3a] and Hanaoka et al.[3b] independently announced the total synthesis of (±)-decaline, shortly followed by our own report on the total synthesis of racemic methyldecinine[4a] (**5a**) and decinine (**5b**).[4b] Our general synthetic route for the synthesis of these natural products is shown in Scheme I. Base-catalyzed condensation of the preformed biphenylcarboxaldehydes **2a** and **2b** with isopelletierine gave *trans*-quinolizidine ketone precursors **3a** and **3b**, which were reduced stereoselectively to the desired α-hydroxy acids and cyclized to the desired macrocyclic lactones by high-dilution and acid catalysis. In order to synthesize the related alkaloid decamine, which differs from decinine in the stereochemistry of the quinolizidine moiety only, we had to carry out the alkaline condensation stereoselectively, and under conditions sufficiently mild to prevent the base-induced hydrolysis of the methanesulfonyl protective group in **2b**.

Scheme I



The stereochemistry of the products of the condensation of isopelletierine with aromatic aldehydes depends on the conditions employed. Thus, Matsunaga et al.[5a] obtained a 1:1 mixture of *cis*- and *trans*-quinolizidinones from condensation of **1** with benzaldehyde in aqueous alkaline methanol. In the condensation of **1** with 2-bromoveratraldehyde Hanoaka and co-workers[5b] were able to obtain either the trans product using aqueous methanol or a 3:2 cis:trans mixture by employing aqueous THF for the reaction. In our attempt to obtain *cis*-quinolizidine ketones **6a** and **6b** we examined the effect of temperature and base concentration on the condensation of isopelletierine with biphenylcarboxaldehydes **2a** and **2b** (Scheme II). Predominantly cis product was conveniently obtained at room temperature by the use of weakly alkaline solutions. A mixture of **1** (in the form of its hydrochloride) and **2a** in 30% aqueous ethanol containing 3 equiv of NaOH at room temperature for 5 h gave crystalline keto acid **6a** in 53% yield. The cis stereochemistry about the quinolizidine nucleus was shown by the absence of Bohlmann bands in the solution IR of the methyl ester of **6a** which are present in the IR of the

Scheme II[a]



[a] See text for reagents.

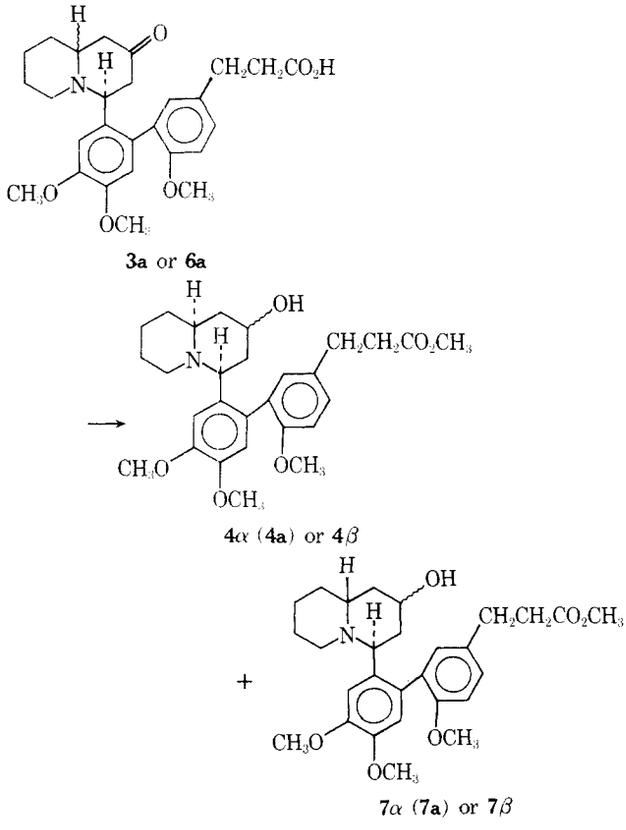
Table I. Reduction Products of Quinolizinones

Starting ketone	Procedure (yield %)	% product distribution			
		4α	4β	7α	7β
3a	a (85)	88	12		
	b (90)	8	92		
	c (85)	95	5		
6a	a (85)	56	6	32	6
	b (90)			47	53
	c (75)			93	7
6b	c (75)			85 (**7b**)	

methyl ester of **3a** and also by the presence of a broad 1 H signal for the benzylic C_4 methine proton at δ 4.10 ppm,[2a] missing from the NMR of **3a**, probably being buried under the methoxy signals. Similar runs with **1** and **2b** gave keto acid **6b**, in 55% yield, with the expected spectral behavior. An examination of the mother liquors (after diazomethane esterification) indicated about 20–25% starting material **2** that could be recycled in the reaction to increase the combined yields of **6a** and **6b** to 65–70% with less than 10% trans product.

$IrCl_4$ reduction of **6a** and alkaline hydrolysis of the resultant carbinol ester, a previously successful procedure in the methyldecinine synthesis,[4a] resulted in the formation of hydroxy acid **7a**, however, only as the minor component. The major product was the methyl decinine precursor **4a**, arising from an acid-catalyzed epimerization of the cis ketone prior to reduction. To circumvent the difficulty of the purification of diastereoisometric compounds **4a** and **7a** alternative methods for the reduction were needed and examined.

Keto acids **3a** and **6a** were reduced with various agents, and the products were esterified by diazomethane and assayed on



the gas chromatograph (Table I). Reduction of **3a** by $NaBH_4$ gave the thermodynamically more stable β-hydroxy compound (**4β**) in a highly stereoselective manner, whereas the analogous **6a** yielded equal amounts of carbinols **7α** and **7β**. The lessening stereoselectivity in favor of the α carbinol encountered with the $IrCl_4$ reductions in the trans vs. the cis series is contrasted with an improved selectivity using $NaBH_4$. Such effect can be interpreted by assuming that whereas the borohydride delivers its hydride onto the sterically less crowded endo face of the carbonyl in the trans series, the bulky $IrCl_4$ uses this site for complexation and the hydride is transferred to the exo, more crowded surface. The cis compounds are more crowded on the α surface resulting in a partial reversal of the stereochemical outcome of the reductions. Pt–acetic acid hydrogenations resulted in complete recovery of the starting materials; however, Pt in weakly alkaline solutions gave smooth conversion to the desired carbinols **4α** and **7α** with a high degree of stereoselectivity. For characterization, **7α** was converted to and purified as the hydrochloride salt of its the *O*-acetyl methyl ester, whose IR shows the presence of ester groups at 1739 and 1724 cm^{-1} and absence of Bohlmann bands characteristic for the trans system.[6] The NMR of this compound is equally instructive. Besides the signals for the various methoxy groups at δ 4.05, 3.80, and 3.60 [s, (1 + 1 + 2) CH_3O, respectively] and the acetyl group at 2.0 ppm, there is also a broad 1 H signal for the carbinol methine proton at 5.10 ppm ($W_{1/2}$ = 8.0 Hz) fully defining the α-axial configuration. The broad 1 H peak for the C_4 benzylic portion at 4.30 ppm is characteristic of the *cis*-quinolizide ring with an aryl substituent in the 4 position.[2a] The high stereoselectivity of these Pt-catalyzed reductions is surprising in view of the opposite behavior of cyclohexanones under identical conditions. The lone pair of electrons on the nitrogen exerts a very pronounced directive effect about the site of hydrogenation by complexation to the catalyst surface. Such an effect, which favors obtaining the axial alcohols, increases as the media for hydrogenation of quinolizidine ketones is changed from acidic to neutral solutions as shown by Aaron et al.[7] in our instance; in alkaline solutions the effect is multifold.

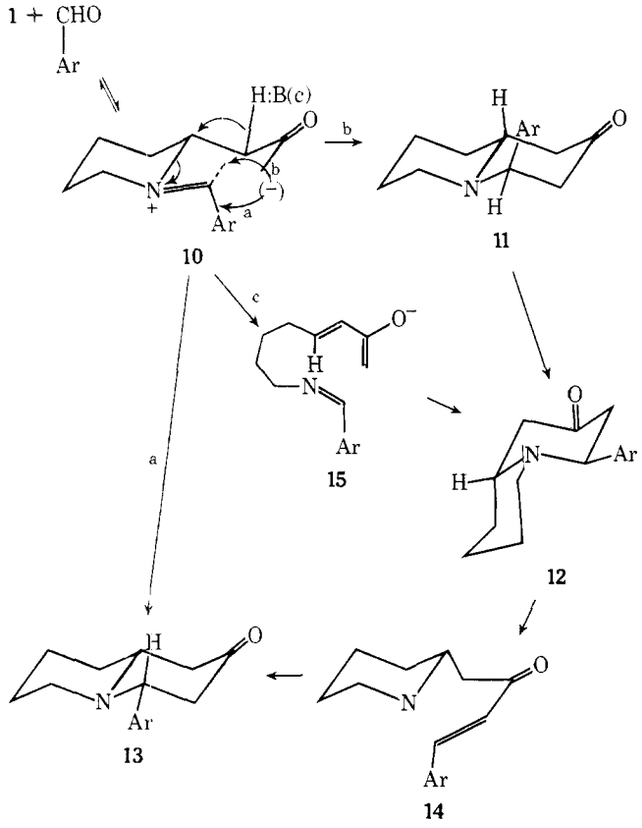
Employing high dilution and *p*-TsOH catalysis cyclization of hydroxy acid **7a** gave (±)-methyldecamine, spectroscopically identical with the methylated natural product. Similar treatment of **7b** yielded the methanesulfonyl derivative of decamine from which **8b** could be easily regenerated by treatment with alcoholic base at room temperature. The product (±)-decamine was identical spectroscopically with natural (−)-decamine. No concurrent hydrolytic opening of the lactone ring was observed during the removal of the methanesulfonyl group.

The successful isolation and purification of cis keto acids **6a** and **6b** enabled us to carry out the total synthesis of decamine and its derivatives economically. The inadvertent acid-catalyzed epimerization of **6b** to **3b** suggested a way to improve on the total synthesis of decinine.[4b] Our previously published synthesis for this compound (Scheme I) suffered from the low yield and difficult purification of trans keto acid **3b**. The yield of trans hydroxy compound **4b**, obtained from the acid-catalyzed epimerization and reduction procedure of **6b** with $IrCl_4$, was already an improvement over our former method; still we wanted to obtain **3b** without the concomitant cis products. We planned to epimerize **6b** by overnight reflux in 1:1 aqueous 3 N HCl–methanol solution, but instead of the expected **3b**, a new product **9** was isolated. The cinnamoyl partial structure was easily deduced for this compound from the NMR spectrum[8a] [AB quartet at δ 7.40 and 6.70 ppm (J_{AB} = 18 Hz)]. The existence of the α,β-unsaturated ketone chromophore could be further seen from bands in the IR (1653 and 1600 cm^{-1}) and UV[8b] (267 and 313 nm) spectra. From this it is apparent that the acid treatment resulted in β-elimination of the tertiary amine giving **9** as product. This unsaturated compound underwent smooth and clean cyclization in 85–90% yield to the trans keto acid ester in refluxing methanol, both supporting the structural assignment and also rendering our epimerization procedure highly successful. The successful

stepwise inversion of **6b** to **3b** supplies a clue for the overall mechanism of reaction.

Hanaoka and co-workers[9] recently studied the base-catalyzed condensation of **1** with 3-hydroxy- and 3-methoxybenzaldehyde. In aqueous alkaline solutions the 3-methoxy compound gave a 6:1 cis to trans product ratio (**12:13**) whereas the 3-hydroxy analogue yielded trans (**13**) almost exclusively. Carrying out the condensation of 3-methoxybenzaldehyde with **1** in alkaline methanol gave primarily the cis product which slowly epimerized to the thermodynamically more stable trans. The authors proposed that both epimers are formed from the common imminium intermediate **10** (Scheme III). The trans product arises by attack of the incipient

Scheme III



carbanion on the α face of the imminium moiety whereas the cis product is the result of β-attack, as shown by pathways a and b, respectively. Hanaoka also suggested that epimerization of **12** proceeds via the intermediate α,β-unsaturated ketone **14,** though no attempt was made to isolate this material.

Our work strongly supports the idea that the cis quinolizidine is the product of kinetic control. The observation that *trans*-**3b** was obtained selectively from α,β-unsaturated ketone **9** under nonequilibrating conditions lends strong support to the inversion pathway suggested by Hanaoka. We find it more difficult to rationalize the selective formation of the cis adduct by the Hanaoka mechanism. If product development followed the suggested pathway, the trans product would predominate because its transition state is a strain-free pseudochair conformation, while the cis product goes through a more strained pseudoboat transition complex.

An alternative mechanism for the generation of the cis product would suggest the primary formation of the imminium intermediate **10,** which would readily undergo a base-assisted retrograde conjugate addition to obtain acyclic Schiff base intermediate **15.** Its concerted or nonconcerted cycloaddition reaction via the enolate would result in the cis compound selectively, as shown by path c in Scheme III.

One additional observation from the experiments of Hanaoka et al. deserves comment. Strong acid (50% HBr) treatment of the *cis*-quinolizidine **12** (Ar = 3-MeOPh) resulted in demethylation exclusively without inversion to the trans product. Quite analogously, when we reacted **6a** in strong acid (concentrated HCl–MeOH, 1:1) none of the α,β-unsaturated ketone was obtained, and only the dimethoxy ketal of **6a** methyl ester was isolated. These experimental findings lend further support for the overall epimerization pathway; the strongly acidic conditions cause protonation of the carbonyl followed by hydration or ketalization, rather than the proposed β-elimination.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 spectrometer and signal positions are listed in δ units downfield from Me_4Si as internal standard. Unless indicated otherwise the NMR were determined in ca. 0.01 M $CDCl_3$ solution at ambient temperature. IR spectra were taken on a Perkin-Elmer Infracord in Nujol mulls. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN-6E spectrometer. Spectral data were collected on the analytical samples. Workup in the usual manner implies chloroform extraction followed by washing the extract with brine, drying it over $MgSO_4$, and evaporating the filtrate to obtain the organic product.

Formation of *cis*-Ketoquinolizidines 6a and 6b. Isopelletierine hydrochloride (0.010 mol) was mixed with an equimolar quantity of the biphenylcarboxaldehyde (0.010 mol) in 10 ml of water and 6 ml of ethanol. The mixture was cooled at ice-bath temperature and granular NaOH (0.03 mol) was added. After dissolution of the base the reaction mixture was allowed to stir at ambient temperature for 3.5–5 h. The solution was diluted with water to 50 ml and extracted with chloroform, discarding the organic extract. The alkaline solution was acidified with dilute HCl to pH 2 and was worked up in the usual manner. Trituration with acetone produced crystalline materials. **2a** yielded **6a** (R = CH_3) in 53% yield, mp 193–194 °C.

Anal. Calcd for $C_{27}H_{33}NO_6$·HCl·H_2O: C, 62.12; H, 6.95; N, 2.68. Found: C, 62.01; H, 6.79; N, 2.54.

Biphenylcarboxaldehyde **2b** in the same reaction yielded **6b** (R = CH_3SO_2), 50%, mp 153–155 °C.

Anal. Calcd for $C_{27}H_{33}NO_8S$·HCl·H_2O: C, 55.40; H, 6.15; N, 2.38. Found: C, 55.71; H, 6.00; N, 2.30.

General Reduction Procedures. A. $IrCl_4$ Reductions.[10] The keto acid (0.010 mol) was refluxed with 1.2 g of $IrCl_4$ (or equivalent recovered material) and 28 ml of trimethyl phosphite in a solution of 210 ml of 2-propanol and 70 ml of water for 24–48 h. The solution was concentrated at reduced pressure to approximately 25 ml and diluted to 150 ml with H_2O. After filtering the aqueous solution was extracted with chloroform. Concentration of the aqueous solution to a viscous oil resulted in recovered catalyst that could be used in subsequent reductions. The organic extract was treated in the usual manner to obtain the hydroxy acids, which are at this stage in the form of isopropyl esters. Refluxing with 5% Na_2CO_3 in MeOH–H_2O (1:1) solutions for 5 h quantitatively saponifies the esters to the acids.

B. $NaBH_4$ Reductions. The keto acid (0.001 mol) was dissolved in 15 ml of MeOH, $NaBH_4$ (1.0 g) was added under N_2, and the reaction mixture was stirred overnight at room temperature. The solution was acidified with dilute HCl, diluted with water, and worked up in the usual manner.

C. General Procedure for Catalytic Reductions. The keto acid (0.001 mol) was dissolved in 1 N NaOH and 50 mg of PtO_2 was added; the solutions were hydrogenated in a Parr shaker at 40–50 psi initial hydrogen pressure for 5–8 h. The catalyst was filtered and the alkaline solution was acidified to pH 2 and worked up in the usual manner.

Hydroxy acids obtained by the general procedures were esterified by treatment with diazomethane (methylene chloride solutions, Diazald diazomethane generator procedure) and were acetylated by the acetic anhydride–pyridine method before assays by GLC. Characterization of hydroxy acids (OAc methyl ester unless otherwise noted) was as follows. **4α:** mp 150–150.5 °C; IR 1740, 1724, 1036 cm^{-1}; NMR ($CDCl_3$) δ 8.3 and 6.65 (s, 2 × 1 H), 7.0 (m, 3 H), 5.2 ($W_{1/2}$ = 9.0 Hz, CHOAc), 4.15, 3.85, and 3.65 (s, 4 CH_3O), 2.0 (s, CH_3CO).

Anal. Calcd for $C_{30}H_{39}NO_7$·HCl·0.25H_2O: C, 63.59; H, 7.30; N, 2.44. Found: C, 63.46; H, 7.20; N, 2.47.

4β: mp 224–225.5 °C; IR 1737, 1054, 1043 cm^{-1}; NMR ($CDCl_3$) δ 8.12 and 6.60 (s, 2 × 1 H), 7.05 (m, 3 H), 4.75 ($W_{1/2}$ = 13 Hz,

CHOAc), 4.1, 3.85, 3.75, and 3.60 (s, 4 CH_3O), 2.02 (s, CH_3CO).

Anal. Calcd for $C_{30}H_{39}NO_7$·HCl: C, 64.10; H, 7.17; N, 2.49. Found: C, 64.07; H, 7.04; N, 2.40.

7α: mp 221–222.5 °C; IR 2380, 1739, 1724, 1041 cm^{-1}; NMR ($CDCl_3$) δ 7.95 and 6.60 (s, 2 × 1 H), 7.0 (m, 3 H), 5.10 ($W_{1/2}$ = 8.0 Hz), 4.05, 3.80, and 3.60 (s, 4 CH_3O), 2.0 (s, CH_3CO).

Anal. Calcd for $C_{30}H_{39}NO_7$·HCl·0.25H_2O: C, 63.66; H, 7.05; N, 2.35. Found: C, 63.59; H, 7.02; N, 2.47.

7b (not converted to the acetate): mp 269–270 °C; IR 3333, 2564, 1739, 1342, 1162 cm^{-1}; NMR ($CDCl_3$) δ 7.9 and 6.8 (s, 2 × 1 H), 7.3 (m, 3 H), 4.0 and 3.85 (s, 2 CH_3O), 2.85 (s, CH_3SO_2).

Anal. Calcd for $C_{27}H_{35}NO_8S$·HCl: C, 56.88; H, 6.36; N, 2.46. Found: C, 56.58; H, 6.37; N, 2.53.

Lactonization Experiment. The hydroxy acid **7a** (0.010 mol) was continuously extracted into a benzene solution (4 l.) containing *p*-toluenesulfonic acid (0.4 g); **7b** was extracted into a 1:1 benzene–chloroform solution of *p*-TsOH. After the acids were completely dissolved (4–7 days) reflux was stopped and the solvent was evaporated at reduced pressure. The crude product was worked up in the usual manner to yield a heavy oil which on trituration with ether produced a solid precipitate, mostly polymeric materials. The volume of the ethereal supernatant solution was reduced to approximately 10 ml and the crystallization of the product was initiated by scratching or addition of petroleum ether.

Compound **7a** yielded (±)-methyldecamine (**8a**, mp 197 °C, 40%): *m/e* 451 (P^+), 436 ($P^+ - CH_3$), 420 ($P^+ - CH_3O$), 376 ($P^+ - CH_3O - CO_2$); IR 1715, 1135, 1036 cm^{-1}; NMR ($CDCl_3$) δ 6.9 and 6.8 (s, 2 × 1 H), 7.2–6.8 (m, 3 H), 5.0 ($W_{1/2}$ = 8.0 Hz), 3.9, 3.82, and 3.70 (s 3 CH_3O)

Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.82; H, 7.60; N, 3.14.

Cyclization of **7b** resulted in 35% yield of **8b**: mp 169–171 °C; IR 1727, 1351, 1111, 1052 cm^{-1}; NMR ($CDCl_3$) δ 7.1 and 7.0 (s, 2 × 1 H), 7.3 (m, 3 H), 5.0 ($W_{1/2}$ = 8.0 Hz), 3.90 and 3.85 (s, 2 CH_3O), 3.0 (s, CH_3SO_2).

Anal. Calcd for $C_{27}H_{33}NO_7S$: C, 62.89; H, 6.45; N, 2.72. Found: C, 62.92; H, 6.46; N, 2.73.

Formation of (±)-Decamine (8c). Methanesulfonyl protected **8b** (0.25 g) was stirred in 10 ml of methanol and 5 ml of water with 0.25 g of NaOH for 6 days at ambient temperature. TLC assay showed that starting material was no longer present and a clear solution was obtained. The methanol was evaporated at reduced pressure, and acidification of the solution with dilute HCl resulted in crystalline (±)-decamine (**8c**) hydrochloride, recrystallized from chloroform–ether: mp 312–314 °C (50% yield); *m/e* 437 (P^+), 420 ($P^+ - OH$), 376 ($P^+ - OH - CO_2$); IR 3171, 2564, 1724, 1136, 1123, 1041 cm^{-1}; NMR ($CDCl_3$) δ 8.8 (s, OH), 7.82 and 6.55 (s, 2 × 1 H), 7.0 (m, 3 H), 5.0 ($W_{1/2}$ = 9.0 Hz), 4.55 (br, 1 H), 3.92 and 3.80 (s, 2 CH_3O).

Anal. Calcd for $C_{26}H_{31}NO_5$·HCl·H_2O: C, 63.47; H, 6.96; N, 2.84. Found: C, 63.69; H, 6.61; N, 2.88.

Epimerization of 6a to 3a. The cis keto acid **6a** (0.5 g) was refluxed in 12 ml of N HCl and 12 ml of methanol for 36 h. The solvent was evaporated and the residue was dissolved in chloroform and washed several times with 5% Na_2CO_3 before drying over $MgSO_4$. Evaporation of the organic solvent yielded an oil whose structure was deduced by NMR, IR, and UV (vide supra). Attempted purification by chromatography (GPC or HPLC) resulted in conversion to trans keto acid **3a**. The oil was taken up in 20 ml of methanol and refluxed for 24 h and the solution (a single spot identical with **3a** by TLC) was evaporated to an oil. Spectroscopically this product was found identical with **3a** described previously.[4a]

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Registry No.—1 HCl, 5984-61-2; **2a**, 53937-18-1; **2b**, 57535-51-0; **3a**, 53375-73-8; **4a** α acetate methyl ester HCl, 60633-93-4; **4a** β acetate methyl ester HCl, 60633-94-5; **6a** HCl, 60633-95-6; **6b** HCl, 60633-96-7; **7a**, 60634-00-6; **7a** acetate methyl ester HCl, 60633-97-8; **7b** HCl, 60633-98-9; **8a**, 60686-42-2; **8b**, 60633-99-0; **8c** HCl, 60686-43-3.

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