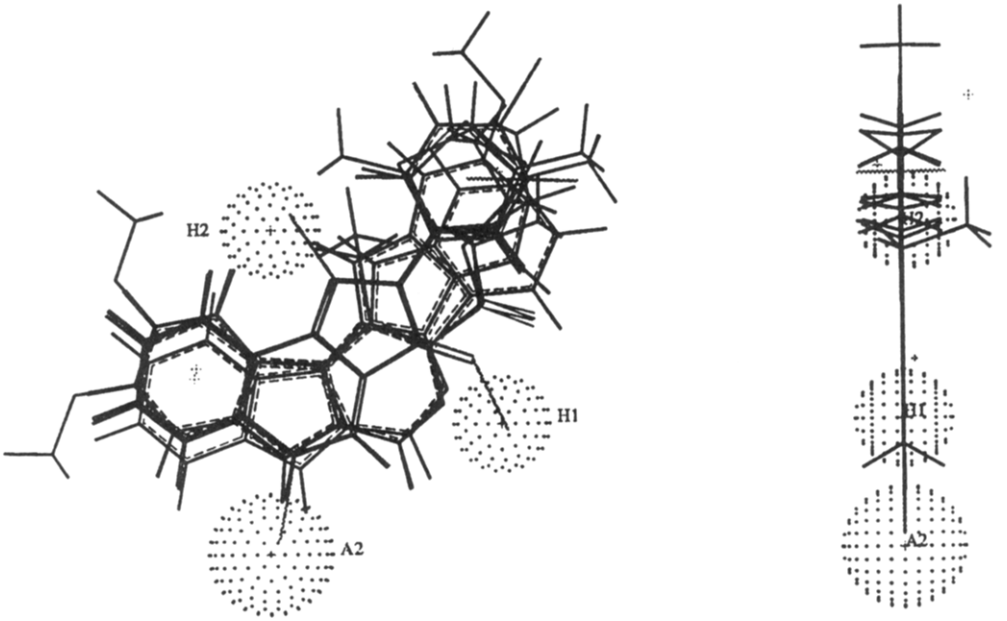


Figure 6. The superposition of 12 inverse agonist ligands at the benzodiazepine binding site (βCCE, DMCM, 3-EBC, 3-propionyl-β-carboline, CGS-8216, 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]diindole, 2-methoxy-7,12-dihydroxypyrido[3,2-*b*:5,4-*b*′]-diindole, 2-thienylpyrazolo[3,4-*c*]quinolin-3-one, 2-(4′-methylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, 3-thienylpyrazolo[3,4-*c*]quinolin-3-one, 3-(5′-methylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, and 3-(4′-methylthienyl)pyrazolo[3,4-*c*]quinolin-3-one). The inverse agonist pharmacophoric descriptors H_1 and H_2 represent hydrogen-bond donor sites on the protein; A_2 represents a hydrogen-bond acceptor site on the protein. The illustration on the right side of the picture (orthographic stereoview) originates from rotation of the pharmacophore 90° to the right.

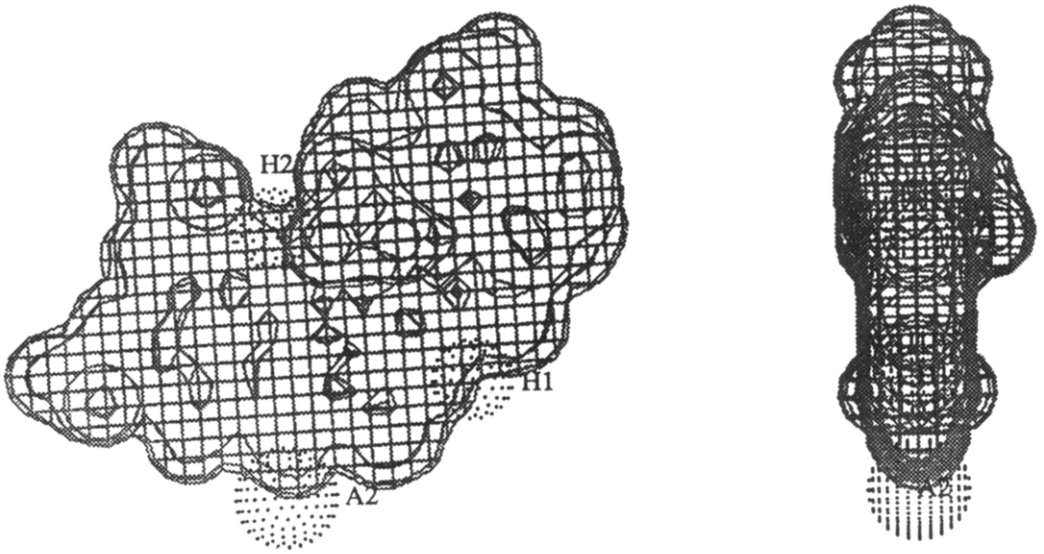
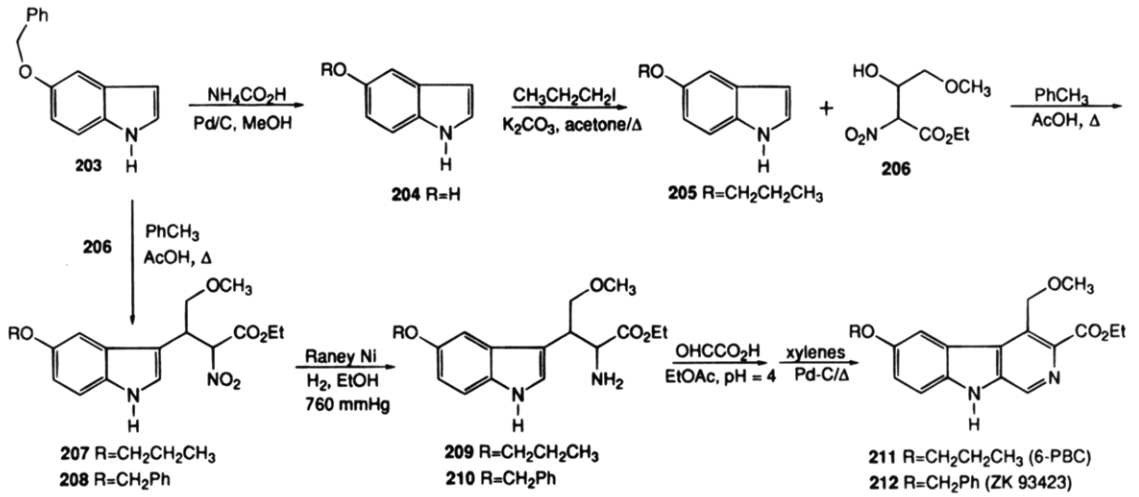


Figure 7. The included volume analysis of 12 inverse agonist ligands at the benzodiazepine binding site.

N(9)−H in a hydrogen-bond interaction of the ligand with a hydrogen-bond acceptor site (A_2) on the receptor was necessary, in contrast to several other pharmacophore models.[44,182−185] In addition, the proposed model required the pyridine N-2 nitrogen atom of a β-carboline or N-5 of a diindole to exhibit hydrogen bond acceptor (N:) properties and interact with a receptor hydrogen bond donating site (H_1) on the protein.[40,186] Lastly, it was proposed there existed a hydrophobic pocket (L_1) in the receptor protein near position 3 of the β-carboline framework. The affinity of various 3-substituted β-carbolines suggested this pocket has a definite length and width.[41,42] It was also noted by Allen et al.[42] that substituents at the 3-position of β-carbolines have a strong influence on both the affinity and type of activity. The synthesis of the long-lived water-soluble partial inverse agonist 3-ethoxy-β-carboline **193** (whose biology was described above) resulted from this modeling.[40−42] With the development of the inverse agonist/antagonist pharmacophore, attention then focused on modeling the agonist pharmacophore of the BzR. It should be noted that controversy existed in the literature as to whether inverse agonists and agonists bound to the same receptor or to different receptor sites.[187,188] Inverse agonists and agonists were treated as separate entities in our work although the common sites of overlap between the two pharmacophores were established from molecular modeling in agreement with the previously reported domain model of Skolnick.[134]

There are a wide variety of compounds which exhibit full agonist activity at the BzR but are structurally unrelated to 1,4-benzodiazepines (e.g.

Scheme 19



Valium). There had only been one β-carboline reported to date[189] which exhibited *full* agonist activity at the BzR, i.e. the β-carboline derivative 6-(benzyloxy)-4-(methoxymethyl)-β-carboline-3-carboxylic acid ethyl ester (ZK 93423, **212**) (Scheme 19). The β-carboline ligands are some of the most difficult to model[190,191] due to the conformational flexibility of substituents located at positions 3, 4, 5, and 6, therefore, the use of ZK 93423 (**212**) was important in establishing the points of electronic interaction necessary for agonist activity. The development of the agonist pharmacophore was carried out in our laboratory by Diaz-Arauzo et al.[191] and then overlapped with the inverse agonist/antagonist model. The strategy employed was analogous to that reported for the inverse agonist/antagonist receptor model and employed 36 different ligands which belonged to 10 different structural families (now 13) and represented 136 different ligands.[44,190,191] The alignment of the agonist ligands and the included volume analysis of these ligands is illustrated in Figures 8 and 9.

The data from the synthetic and computer-assisted analysis of the agonist pharmacophore at the BzR[191] suggested that this site contained two hydrogen bond donating sites (H_1 and H_2), as illustrated in Figure 8. These two sites are located about 6.7 Å from each other. The binding site H_1 is common to both the agonist and inverse agonist pharmacophores, but region H_2 (agonist model, Figure 8) corresponded to the 4-position of β-carbolines or interaction at N-4 of the 1,4-benzodiazepines.[44] With respect to β-carbolines it was believed the oxygen atom at this position was of critical importance for agonists in the β-car-

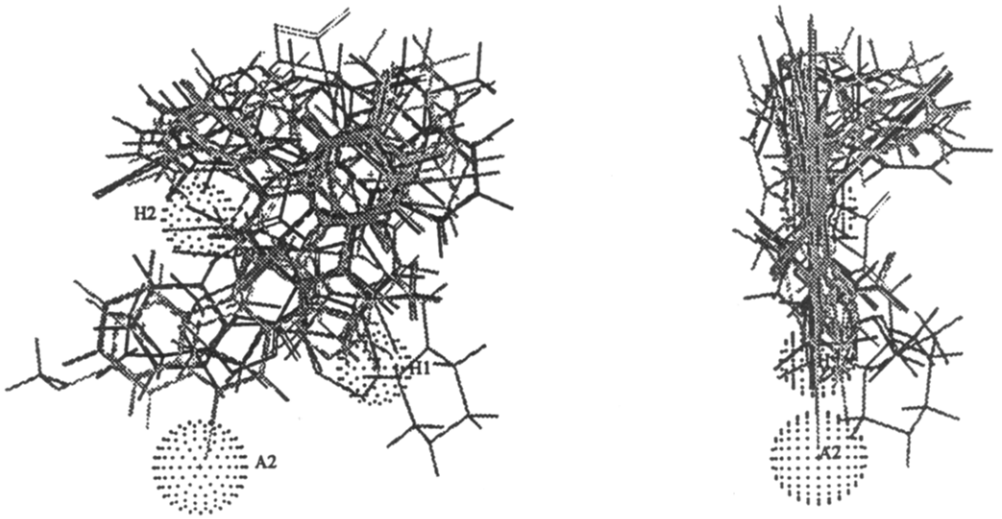


Figure 8. The superposition of 31 agonist ligands to define the agonist pharmacophore at the benzodiazepine binding site (diazepam, flunitrazepam, brotizolam, midazolam, triazolam, norflunitrazepam, 7-aminoflurazepam, 7,2′-dichlorothieno[2,3-*e*][1,4]benzodiazepine, 1-methyl-8-chloro-2′-fluoro-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, 2,9-dichloropyrimido[5,4-*d*][2]benzazepine, 4-methoxy-6-(alkylamino)-3-aryl-1,2,4-triazolo[3,4-*a*]phthalazine, 4-chloro-6-(alkylamino)-3-aryl-1,2,4-triazolo[3,4-*a*]phthalazine, 4-methoxy-6-(alkylamino)-3-aryl-1,2,4-triazolo[3,4-*a*]phthalazine, 4-fluoro-6-(alkylamino)-3-aryl-1,2,4-triazolo[3,4-*a*]phthalazine, 2-benzoyl-5-methoxy-7-ethylimidazo[1,2-*a*]quinoline, 2-benzoyl-5-(methylthio)-6-ethyl-7-methylimidazo[1,2-*c*]pyrimidine, 2-(4′-chlorophenyl)pyrazolo[3,4-*c*]quinolin-3-one, 2-(4′-methoxyphenyl)pyrazolo[3,4-*c*]quinolin-3-one, 2-(2′-methylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, 2-(5′-ethylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, 2-(5′-butylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, 2-(4′,5′-dimethylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, 2-(5′-butylthienyl)pyrazolo[3,4-*c*]quinolin-3-one, ZK 93423, ZK 93426, 6-(benzyloxy)-4-(methoxymethyl)-β-carboline-3-carboxylic acid isopropyl ester, 6-PBC, loprazolam, delorazepam). The agonist pharmacophoric descriptors H_1 and H_2 represent hydrogen-bond donor sites on the protein. The illustration on the right side of the picture (orthographic stereoview) originates from rotation of the pharmacophore 90° to the right.

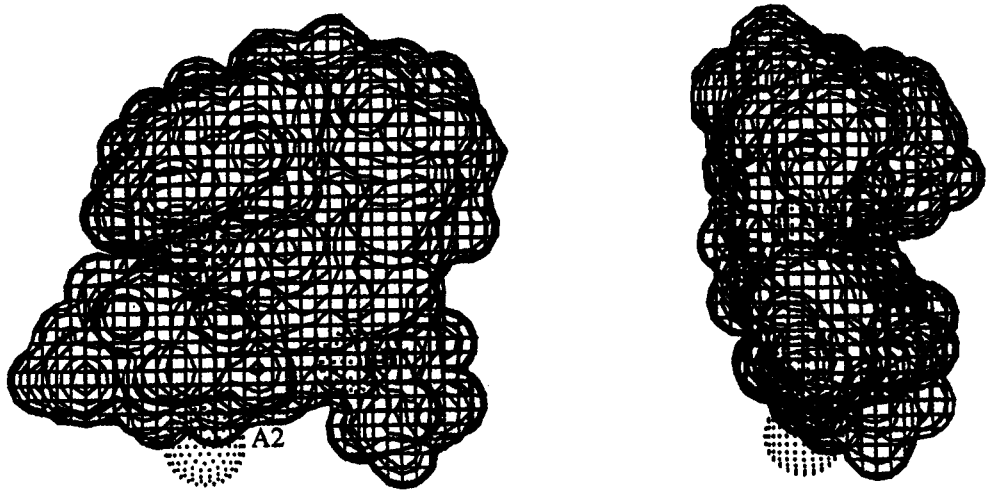


Figure 9. The included volume analysis of 31 agonist ligands at the benzodiazepine binding site.

boline series and directed the ligand into the active site of the agonist receptor region through the formation of a hydrogen bond between the ether oxygen atom at C-4 and H_2 of the receptor protein. In addition there are three areas of lipophilic interaction (L_1,L_2, and L_3). Occupation of the areas L_2/L_3 and interaction at H_1, H_2, and L_1 are important for full agonist activity; full agonist activity appears to require complete occupation of L_2 and L_3. This is in agreement with previous work.[40,41,176,177,182,184–186,192–194]

Substituents which occupy L_3 cannot lie in the same plane as H_1, H_2, and L_1 for they would interfere with the hydrogen bonding protein–ligand interaction at H_2 which would eliminate agonist activity. Areas of negative steric interaction (S_1, S_2, and S_3) between the ligand and receptor-binding protein have also been defined and are illustrated in Figure 10.

With regard to this pharmacophore, it is felt the alignment rule for agonist β-carbolines is different from that which elicit inverse agonist activity. Examination of Figure 11 shows the overlap of the inverse agonist (light-colored area) and agonist (dark-colored area) pharmacophores. It is now clear from molecular graphics that inverse agonists bind to the same domain as agonists.[44,168,195] As illustrated, the inverse agonist pharmacophore is planar while the agonist pharmacophore contains a lipophilic pocket (L_3) out of the plane. It is also apparent that the inverse agonist pharmacophore is considerably smaller in size relative to the agonist receptor/pharmacophore model. As alluded to earlier, it has been proposed that these pharmacophores bind to the same area at the receptor site, but contain different pharmacophoric descriptors in order to elicit the opposite biological response. As evident from the included volumes the interaction at the pharmacophoric descriptors required for agonist activity (H_1, H_2, L_1, L_2, and/or L_3) and inverse agonist activity (H_1, A_2, and L_1) are clearly different although H_1 and L_1 are common descriptors for both types of ligands. Evidence to date suggests that ligands which exhibit full agonist activity (diazepam, ZK 93423, etc.) fully occupy lipophilic regions L_2 and L_3 as well as interacting at L_1, H_1, and H_2. Analysis of limited evidence suggests that the target partial agonists do not fully occupy both L_2 and L_3, but that one or more interactions is diminished in this class of ligands with respect to the

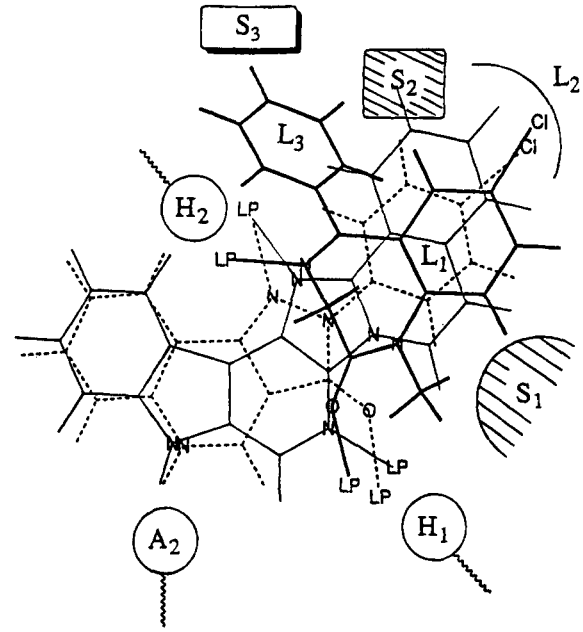


Figure 10. The pyrazolo[3,4-c]quinolin-3-one ligand CGS-9896 (dotted line), diazepam (thick line), and pyridodiindole (thin line) fitted to a schematic representation of the inclusive pharmacophore model for the BzR. The sites H_1 and H_2 designate hydrogen-bond donor sites on the receptor protein while A_2 represents a hydrogen-bond acceptor site. Interaction with the lipophilic pocket L_1, as well as with H_1 and A_2 is required for potent inverse agonist activity. Agonist activity requires interaction with H_1, H_2, L_1, L_2, and/or L_3. Receptor descriptors S_1, S_2, and S_3 are regions of negative steric repulsion.

binding of full agonists. Receptor site selectivity of course plays a critical role in this behavior.

Clinically, there is a need for partial agonists which exhibit anxiolytic/anticonvulsant activity but are devoid of the ataxic/muscle relaxant effects associated with full agonist ligands. As stated earlier, there are only a few β-carboline ligands reported which elicit full agonist activity, and these compounds are the most challenging to model since the multiple rotamers produced by the substituents at positions 3, 4, 5, and 6 present difficulties.[44] In addition, the modeling studies suggested that β-carboline full agonists completely occupied lipophilic pockets L_2 and L_3.[44] On the basis of modeling and the CGS 9895/9896 series it was postulated by Diaz-Arauzo,[191] therefore, that partial occupation of L_3 may result

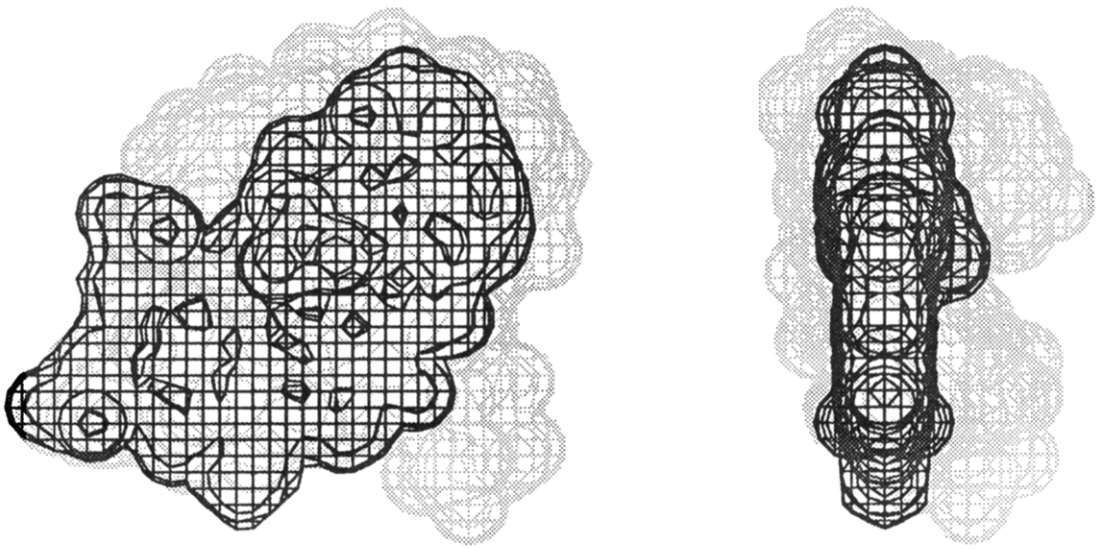


Figure 11. Superposition of the inclusive volumes of inverse agonists (Figure 7) and agonists (Figure 9). The agonist pharmacophore is depicted in gray while that of inverse agonists is the darker region.

in a partial agonist response. As a result of this, the synthesis[190] of a new anxiolytic/anticonvulsant, 6-*n*-propoxy-4-(methoxymethyl)-β-carboline-3-carboxylic acid ethyl ester (6-PBC, **211**), which bound to the BzR with an IC_{50} value of 8.1 nM, was designed. This compound was found to be devoid of the undesired myorelaxant and ataxic effects normally found with full agonist ligands. The synthesis of this compound via the method of Neef et al.[196] is illustrated in Scheme 19.

The 5-(benzyloxy)indole (**203**) was treated with ammonium formate in the presence of a palladium catalyst to provide the 5-hydroxyindole (**204**) in 92% yield. The indole **204** was alkylated with propyl iodide and potassium carbonate in acetone at reflux to furnish 3-(*n*-propoxy)indole (**205**) in excellent yield. A Michael reaction between nitro ester **206** and indole **205** in toluene at reflux yielded the 3,5-disubstituted indole **207**. Reduction of this compound using Raney nickel in ethanol under hydrogen at atmospheric pressure yielded the desired amino compound **209**. The Pictet–Spengler condensation of glyoxylic acid and **209** in ethyl acetate at pH = 4, followed by decarboxylation and subsequent oxidation furnished 6-PBC (**211**). This same procedure had been employed earlier by Neef et al.[196] to prepare the full agonist ZK 93423 (**212**).

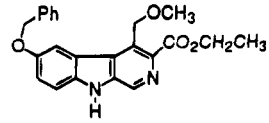
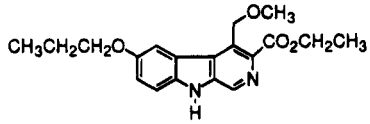
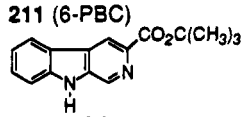
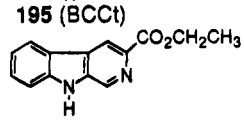
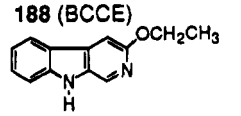
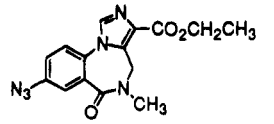
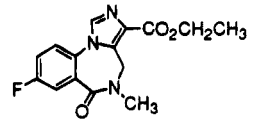
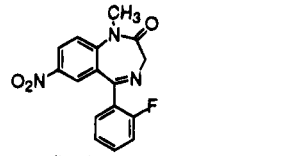
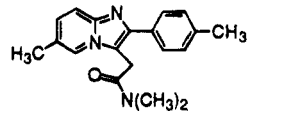
The synthesis and biological activity of **211** has important implications for the development of β-carbolines as partial agonists and anxioselective anxiolytics. The proper lipophilic substituent at position 4 of β-carbolines directs the ligand into the agonist pharmacophore, the alignment of which is clearly different from that for inverse agonists. This new anxiolytic agent exhibited anticonvulsant/anxiolytic activity, but was devoid of the muscle relaxant/ataxic effects often associated with the classical 1,4-benzodiazepines.[190] More importantly, **211** actually antagonized the myorelaxant actions of diazepam, one of the most widely prescribed benzodiazepines currently in use. The design, synthesis, and pharmacological actions of **211**, based on computer-assisted analysis of the agonist pharmacophore, support the validity of this model.

E. Benzodiazepine Receptor Subtype Selectivity

Recently, Zhang et al.[44] have shown with pyrazoloquinolines and imidazobenzodiazepines that the pharmacophoric descriptors H_1, H_2, and L_1 appear to be common to all six recently cloned [ω1, ω1, ω3, ω4, ω5, ω6 (DI)] benzodiazepine receptor sites in agreement with Doble and Martin.[154] The difference between these six major subsites is felt to originate from the size of (or interactions with) the lipophilic pockets, two of which have been designated L_2 and L_3 (see Figures 6–11). Molecular modeling studies using ω1 and ω5 selective ligands suggest that the lipophilic pocket (L_2) in the ω5 site is larger than the analogous pocket in the $Bz_1(\omega 1)$ site. Moreover, Zhang et al. have shown via chemical synthesis and molecular modeling that the lipophilic pocket designated L_3 in the DI (ω6) site is much smaller or nonexistent when compared to the same pocket in the ω1, ω2, ω3, and ω5 sites.[44,197] With these six cloned subtypes (McKernan et al.[145]) it is now possible to pursue the synthesis of ligands selective for one subsite over the other and to correlate the pharmacology with an interaction at that specific subsite. For the purposes of this review, illustrated in Table 12 are some selective β-carbolines, as well as imidazobenzodiazepines (Ro 15-1788 and Ro 15-4513) and their corresponding subsite selectivities.

The receptor subsite binding data for the full agonist β-carboline ZK 93423 (**212**) is given in Table 12. Clearly, there is no selectivity demonstrated between the α1, α2, α3, and α5 BzR subsites for this full agonist. The α4 site is felt to be very similar to the α6 site and is not discussed here.[145] The binding affinity of ZK 93423 at α6, however, is very poor (K_i > 1000 nM). As discussed above, modeling studies suggest this is due to the lack of the lipophilic pocket L_3 at the α6 (DI) site, it is this pocket which would interact with the 6-benzyloxy substituent.[191] This same trend is observed with respect to the affinity of 6-PBC (**211**) at the α6 site (K_i = 1343 nM). Presumably, the 6-propyloxy substituent cannot bind at the diazepam insensitive site [$\alpha 6\beta 2\gamma 2$, (ω6)] for this group would need to occupy L_3. More interest-

Table 12. Receptor Subsite Selectivity Data for Selected BzR Ligands (Nanomolar)

Compound	α1	α2	α3	α5	α6
 **212** (ZK 93423)	4.1	4.2	6	4.5	> 1000
 **211** (6-PBC)	0.49	1.21	2.2	2.39	1343
 **195** (BCCt)	0.72	15	18.9	110.8	>5000
 **188** (BCCE)	1.2	4.9	5.7	26.8	2700
 **193** (3-EBC)	6.43	25.1	ND	826	>1000
 Ro15-4513	3.3	2.6	2.5	0.26	3.8
 Ro15-1788	0.8	0.9	1.05	0.6	148
 flunitrazepam	2.2	2.5	4.5	2.1	>2000
 zolpidem	26.7	156	383	>10,000	>10,000

ingly, 6-PBC (**211**) which is a partial agonist devoid of muscle relaxant activity, binds with a greater selectivity for Bz_1 ($\omega 1$=α1) receptor sites. This is in agreement with the earlier work of Beer and Lippa[153,169] which supports the hypothesis that muscle relaxant activity may arise from interactions at Bz_{II} (Bz_2, Bz_3, and Bz_5) sites.

The three β-carbolines βCCt (**195**), βCCE (**188**), and 3-EBC (**193**) demonstrated α1 selectivity, in fact βCCt (**195**) is the most Bz_1 (α1) selective antagonist (20 fold) reported to date. This now confirms why βCCt **195** antagonized the anxiolytic/anticonvulsant activity of diazepam but not the muscle relaxant or ataxic properties of this agent. Although more data is needed before an accurate correlation can be made, these results coupled with the biological profiles of these ligands, strongly suggest that receptor subsite selectivity and pharmacological action are related. In agreement with Lippa and Beer it appears that Bz_{II} receptors (Bz_2, Bz_3, and perhaps Bz_5) are responsible for the muscle relaxant effects of diazepam rather than the Bz_1 sites.[44]

In conclusion, BzR pharmacology is complicated by the existence of multiple receptor isoforms. The inclusive pharmacophore model (Figures 6–11) for the "diazepam sensitive" (DS) BzR is based upon the weighted average of these receptor subtypes. Numerous β-carbolines, diindoles, 1,4-benzodiazepines, 1,4-benzazepines, triazolobenzodiazepines, imidazobenzodiazepines, and pyrazoloquinolines have been employed to model the inclusive pharmacophore at the benzodiazepine receptor site. In addition, receptor isoforms whose pharmacology resembles that of previously reported BzR-I (Bz_1) and BzR-II (Bz_2, Bz_3,

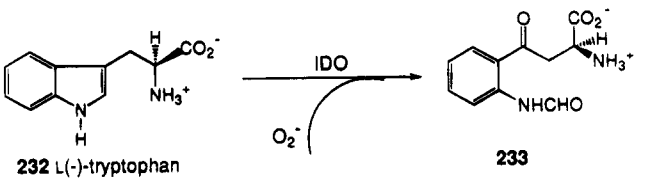
and Bz_5) receptors have been expressed: the type-I BzR was constructed from an $\alpha1\beta2\gamma2$ combination of subunits as described previously while the type-II BzR were composed of $\alpha2\beta2\gamma2$, $\alpha3\beta2\gamma2$, and $\alpha5\beta2\gamma2$ (zolpidem insensitive)[156] receptor isoforms.[198,199] As receptor-selective SAR data is accumulated for each of the cloned receptor isoforms, separate pharmacophore models will need to be developed for each. While these individual models may differ in detail from the inclusive model (inverse agonist/antagonist, and agonist) presented here, these models will nevertheless share many features in common with the inclusive model. The SAR and pharmacophore models which will result from future studies will permit the design of more selective ligands for each receptor subtype and may allow one to decouple the broad spectrum of effects exhibited by the current class of nonselective ligands. An outgrowth of this approach will be new therapeutic opportunities. A direct result of the BzR pharmacophore/receptor model has been the design and synthesis of a new partial agonist,[190] as well as partial inverse agonists.[41] The data obtained from these new ligands will be useful in refining the model and may ultimately lead to better drugs for treatment of anxiety disorders and of other maladies associated with neurotransmission in the CNS.

IV. Indolamine 2,3-Dioxygenase Inhibition in Inflammatory Diseases

Although 3-substituted β-carbolines have been shown to interact at benzodiazepine receptors, a number of related β-carbolines have proven to be effective noncompetitive inhibitors of the indolamine-2,3-dioxygenase (IDO) enzyme system.[200] Furthermore, the most interesting two agents studied to date (3-*n*-butyl-β-carboline and 3-nitro-β-carboline)[40] bind with poor affinity to BzR sites which decreases possible side effects in regard to IDO inhibition.

The metabolism of L-tryptophan (**232**) in mammals proceeds by the serotonin pathway,[201,202] the kynurenine pathway,[201,202] and a third proposed pathway[203–205] which involves the reversible conversion of L-tryptophan (**232**) into indole-3-pyruvic acid and subsequent transformation into kynurenic acid. The initial process in the kynurenine pathway involves the conversion of L-tryptophan **232** and other indoleamines into formylkynurenines by indolamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO). The conversion of tryptophan (**232**) into formylkynurenine (**233**) by IDO is depicted in Scheme 20. The affinity (K_m) of L-tryptophan for IDO is 13 μM.[206] Eventually the kynurenine pathway produces a variety of bioactive metabolites; the most significant of these are kynurenic acid, quinolinic acid (QA) and nicotinamide adenine dinucleotide (NAD). Quinolinic acid has been shown to be present in the mammalian brain, to be an agonist for the excitatory amino acid receptors of the *N*-methyl-D-aspartate (NMDA) receptor ion channel complex and to cause excitotoxic brain lesions when present in high concentrations.[207–209] This overstimulation of NMDA receptors can lead to a variety of neuropsychologic disorders.[207,210–212] Recently, Heyes and co-workers have shown that only macrophage-derived cells and certain liver cells synthesize labeled QA from labeled

Scheme 20



232 L(-)-tryptophan **233**

L-tryptophan following immune stimulation and that macrophages may provide a means for the production of large amounts of quinolinic acid in the brain following inflammation.[213] The activity of later stage enzymes which directly produce QA have been identified in brain tissue. Thus, metabolites from the kynurenine-pathway are manufactured by cells other than the brain and may enter the brain to be later metabolized to quinolinic acid *in vivo*. Kynurenic acid, however, is a noncompetitive agonist which interacts with the same receptor system that is affected by QA but can also cause seizures at high levels.[213,214]

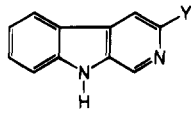
Indolamine 2,3-dioxygenase is a 41 kD, monomeric heme-containing enzyme,[215–220] that utilizes superoxide to cleave the 2,3-double bond of indoleamines.[221–224] A mechanistic model of the conversion of indolamines to formylkynurenines by IDO, analogous to the mechanism of photolytically derived O_2 with tryptophan, has been proposed.[225] Unlike tryptophan 2,3-dioxygenase, an enzyme that is isofunctional to IDO but found only in the liver,[226] IDO is found in a variety of tissues, such as the brain, lung, and small intestine.[227] Furthermore, IDO is induced by interferon-γ;[228–230] consequently, IDO assumes a major role in immunological responses, as well as being a key factor for the *in vivo* production of bioactive metabolites which can be toxic at high levels.

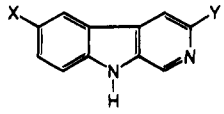
Upon severe infection, large quantities of interferon-γ are produced which subsequently activate IDO to high levels.[231,232] This activation of IDO can lead to aberrant tryptophan metabolism and has been implicated in immunological diseases which affect the central nervous system. It has been demonstrated by Heyes and co-workers that quinolinic acid is produced from L-tryptophan by human macrophages and that the central nervous system could be affected by macrophages which have entered the CNS.[233] Aberrant tryptophan metabolism is characterized by the removal of tryptophan from the amino acid pool and the production of high levels of kynurenine, kynurenic acid and quinolinic acid.[228–230] This condition has been implicated in many inflammatory diseases, including acquired immune deficiency syndrome (AIDS),[234–236] hepatic encephalopathy,[237] polio virus,[238] and others.[239–242]

Norharman (**213**, 91% inhibition of rabbit small intestine IDO, K_i = 120 μM) was shown to function as an uncompetitive inhibitor for IDO,[243] but a noncompetitive mechanism of inhibition for this compound was later established on the basis of kinetic and spectroscopic studies.[244] Moreover, this later work demonstrated that norharman competed with oxygen for the heme–iron site. Several other examples of noncompetitive inhibitors have been discovered which are not β-carbolines.[206,245]

The results of this present study were intended to illustrate some of the structural requirements of the

Table 13. β-Carbolines Evaluated for IDO Inhibition





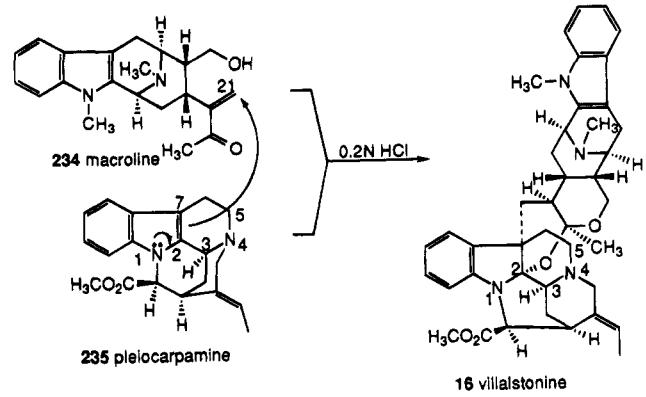
213 Y=H	**220** Y=CO_2t-Bu	**228** X=F; Y=CO_2Me
214 Y=OEt	**221** Y=C(O)*n*-Pr	**229** X=Br; Y=CO_2Me
215 Y=O*n*-Pr	**222** Y=CH_2OH	**230** X=F; Y=CO_2Et
216 Y=OCH_2CH_2OH	**223** Y=*n*-Bu	**231** X=NCS; Y=CO_2Me
217 Y=CO_2H	**224** Y=NH_2	
218 Y=CO_2Me	**225** Y=NCS	
219 Y=CO_2*n*-Pr	**226** Y=NO_2	
	227 Y=OH	

noncompetitive binding site of human monocyte/macrophage IDO for the purpose of developing a potent inhibitor of this enzyme and are presented in Table 13. A series of 3-substituted β-carbolines **213–227** and four 3,6-disubstituted β-carbolines **228–231** were prepared and evaluated for *in vitro* human monocyte/macrophage indolamine 2,3-dioxygenase (IDO) inhibition.[200] Of these, 3-*n*-butyl-β-carboline (**223**, K_i = 3.3 μM) was found to be the most potent inhibitor of IDO reported from any source to date to these authors' knowledge. Substitution of position 6 of 3-(methoxycarbonyl)-β-carboline (**218**, βCCM) with fluoro or isocyanate substituents (K_i = 7.4 and 8.5 μM) furnished derivatives **228** and **231** which were more potent inhibitors of IDO than the parent βCCM (**218**, K_i = 259 μM). The 6-fluoro ethyl ester derivative **230** (K_i = 21.0 μM) was found to be less potent than the methyl ester analog **228**. The inhibition was negated with substitution of position-6 of βCCM (**218**) with bromine. Moderate inhibition was produced by β-carboline-3-carboxylate (**217**, K_i = 40.6 μM) and 3-nitro-β-carboline (**226**, K_i = 37.5 μM). When the 3-substituent of norharman (**213**) was replaced with a polar hydroxyl, amino, hydroxymethyl, or hydroxyethoxy group, only weak inhibition was observed. All of the β-carbolines which were investigated by kinetic methods were found to be noncompetitive or uncompetitive [in the cases of β-carboline-3-carboxylate (**217**) and 3-(hydroxymethyl)-β-carboline (**222**)] inhibitors with respect to the substrate L-tryptophan (**232**). The natural products camalexin and brassilexin (K_i = 5.4 μM) were also found to be noncompetitive inhibitors of IDO and provide important structural leads for further investigations. Both 3-*n*-butyl-β-carboline (**223**) and 3-nitro-β-carboline (**226**) are being evaluated by Heyes et al.[238–241] in *in vivo* models of IDO at the present time.

V. Enantiospecific Total Synthesis of Indole Alkaloids

Bisindole alkaloids comprise a major portion of the macroline/sarpagine class of indole alkaloids and these natural products as a class have been the subject of several reviews, most notably those of Kutney, Lounasmaa, and Cordell.[9,246,247] Bisindoles in general, whether macroline related or not, are a class of alkaloids that present a significant synthetic challenge for the natural products chemist. The biomimetic synthesis of the macroline-related *Alstonia* bisindoles was pioneered by LeQuesne[248] and

Scheme 21[248]



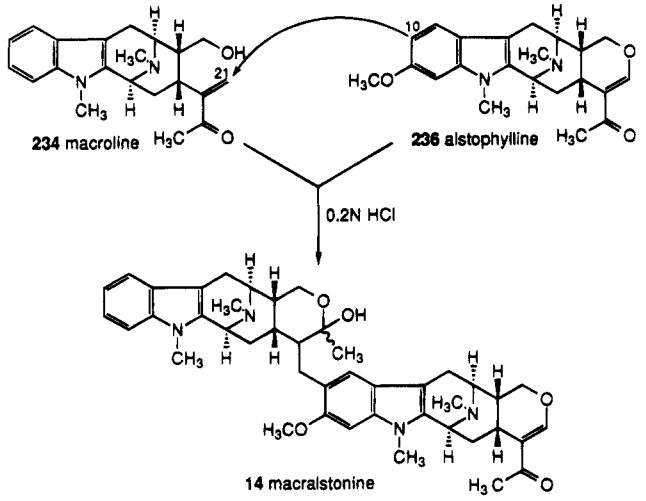
their isolation and structure determination have been reviewed.[24] As alluded to earlier in this review, three of these alkaloids, macralstonine (**14**), macrocarpamine (**15**), and villalstonine (**16**) possess interesting biological activity. As such, these three alkaloids are obvious synthetic targets and progress toward their total synthesis will be presented.

Many of the bisindole alkaloids from *Alstonia* species are comprised of two units directly related to the monomeric derivative macroline, while others originate from the condensation of macroline with another alkaloid. The biomimetic synthesis of *Alstonia* alkaloids involves the Michael addition of a monomeric alkaloid to C-21 of the α, β-unsaturated enone moiety of (+)-macroline (**234**).[248] The biomimetic coupling of macroline (**234**) and pleiocarpamine (**235**) to form villalstonine (**16**) is represented in Scheme 21. The C-7 carbon atom of pleiocarpamine was activated by the lone pair of electrons on the indole nitrogen atom. This activation facilitated the Michael addition to the C-21 enone of macroline (**234**). The iminium ion which formed in this process was then attacked nucleophilically by the oxygen atom of the developing hemiacetal to provide villalstonine (**16**) in a stereospecific coupling process.[248] Since the total synthesis of (+)-macroline (**234**) has been completed and coupled to natural pleiocarpamine (**235**), a partial synthesis of villalstonine (**16**) has recently been completed.[24,249] Macralstonine (**14**), a ring A-oxygenated bisindole, was formed biomimetically by a similar process; however, the Michael addition took place between the C-10 carbon atom of alstophylline (**236**) and C-21 of macroline. Again, hemiketal formation followed the Michael addition and macralstonine **14** resulted (Scheme 22).

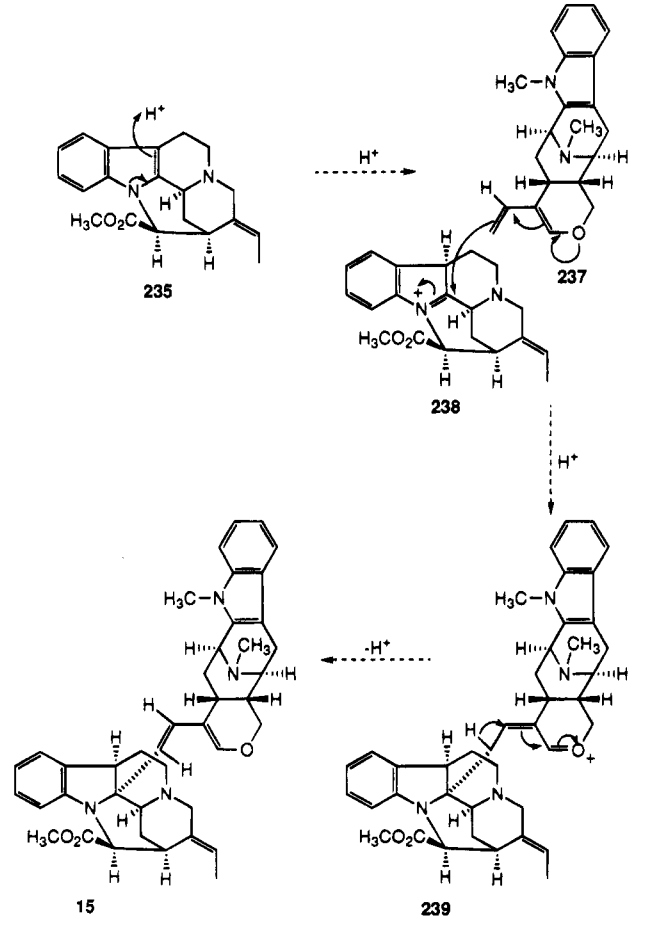
The structure of macrocarpamine (**15**), composed of the subunits of pleiocarpamine (**235**) and an alstonerine derivative **237**, was reported in 1978 by Hesse et al.[250,251] A biomimetic coupling process between pleiocarpamine (**235**) and olefin **237** has been proposed by Hesse to account for the formation of **15** in *Alstonia* species. This process, recently confirmed by Gan in our laboratory, serves as the foundation for the total synthesis of **15** and is depicted in Scheme 23.

The total synthesis of these bisindoles in optically active form therefore requires the enantiospecific preparation of the following monomeric indole alkaloids: macroline, alstophylline, deoxydehydroalston-

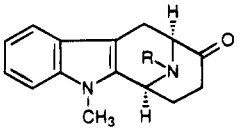
Scheme 22



Scheme 23[250,251]



erine, and pleiocarpamine. The first three of these alkaloids have very similar carbon skeletons; consequently, an ideal approach to these target bases might rest upon the multigram synthesis of a common, optically active intermediate which could be employed for the synthesis of many related natural products. This common intermediate would at the very least contain the requisite tetracyclic ring system which could be readily functionalized for further transformations. The (−)-tetracyclic ketone **240** (Figure 12) was synthesized in 1988 with these goals in mind[45,54,106,252,253] while the racemic compound had been prepared on kilogram scale in the late 1970s.[254]



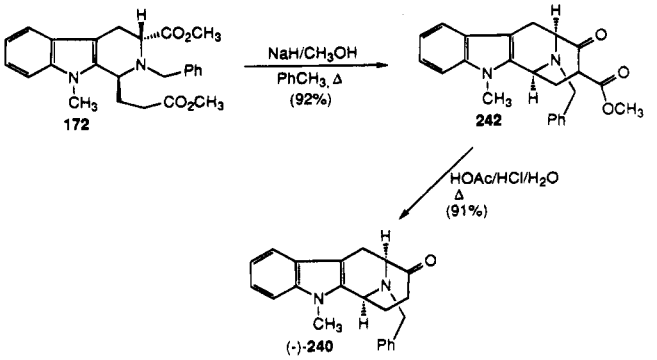
240 R = CH_2Ph
241 R = CH_3

Figure 12. The optically active (−)-tetracyclic ketone.

A. Enantiospecific Synthesis of the (−)-Tetracyclic Ketone

The synthesis of (±)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (**240**) was first reported by Yoneda[45] and was improved by Soerens.[254] The enantiospecific preparation of the tetracyclic ketone **240** in optically active form was developed by Zhang[106,252] and is illustrated in Scheme 24. The synthesis of **240** began with D-(+)-tryptophan since it had been found earlier that the Pictet–Spengler reaction of aldehydes with N_b-benzyl-substituted tryptophan methyl esters exhibited a strong preference for the enantiomerically pure *trans* diester. The 1,3-transfer of chirality from position 3 to position 1 of **172** would impart the correct configuration at C-1 for the synthesis of all the macroline, sarpagine, and ajmaline alkaloids. Hence, as depicted earlier in Scheme 13, methylation of D-(+)-tryptophan **168** was accomplished with sodium in liquid ammonia and methyl iodide in 92% yield. Fischer esterification of the methylated D-(+)-tryptophan gave N_a-methyltryptophan methyl ester (**169**) in 87% yield. The benzylation of the N_b-nitrogen function was carried out without racemization if care was taken to keep the imine intermediate cold during the reduction and to limit the time of reaction (3 h). The tryptophan methyl ester **169** was treated with benzaldehyde at 22 °C, and the imine which resulted was reduced with sodium borohydride (at −5 °C) to provide N_a-methyl-N_b-benzyltryptophan methyl ester **170** (greater than 98% ee) in 88% yield.[252] The Pictet–Spengler condensation of **170** with α-ketoglutaric acid in benzene/dioxane, accompanied by removal of water via a Dean–Stark trap, was followed by esterification in 1% methanolic HCl to afford the required *trans* diester **172** enantiospecifically. In the synthesis of the optically active tetracyclic ketone **240**, the Pictet–Spengler reaction was employed to set the stereochemistry at C-1 of the tetrahydro β-carboline ring system in stereospecific fashion. Yoneda[45] had earlier reported the

Scheme 24



synthesis of a mixture of the racemic diesters **171** and **172** via the Pictet–Spengler reaction. The *cis* isomer **171** was originally reported to be the main constituent[45] but this was later corrected[255] to consist of a mixture of *trans*-**172** and *cis*-**171** diastereomers in a ratio of 5:4, respectively (89.1% yield). In the optically active series, Sakai[255] and co-workers extended the study of the Pictet–Spengler reaction to include the synthesis of (−)-trypargine. Although the synthesis by Sakai et al. was in the N_a-H series, use of the method developed by Ungemach[60] with an N_b-benzyl group provided a remarkable *trans* to *cis* preference.[255] In the N_a-methyl series, however, Zhang[252] observed a 72:28 diastereomeric ratio of *trans*-**172** to *cis*-**171** isomers when N_a-methyl-N_b-benzyltryptophan was treated with methyl 3-formylpropionate under nonacidic aprotic conditions (90% yield). More importantly, there was no racemization at C-3. Under the protic conditions involving α-ketoglutaric acid, Zhang observed almost complete *trans* stereospecificity after esterification (1% methanolic HCl at reflux). The remaining small amount of *cis* isomer had been converted, with no loss of optical activity, into the *trans* diastereomer upon heating in 1% methanolic HCl. Hence, a sequence had been developed to provide the *trans* isomer in high enantiomeric purity even in the N_a-methyl series in the absence of time-consuming separations.

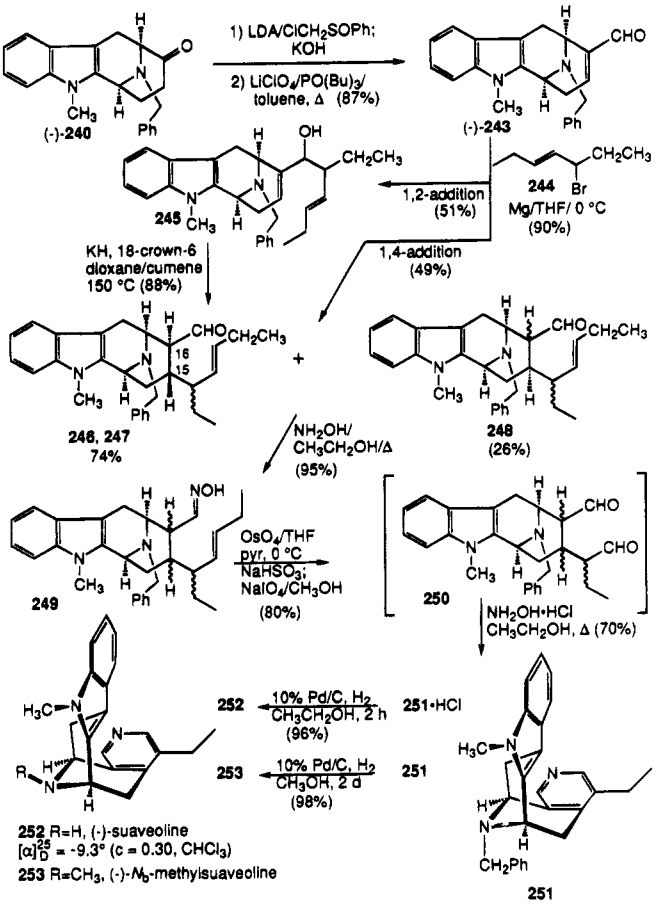
Dieckmann cyclization (Scheme 24) of the *trans* diester **172** afforded the β-ketoester **242** (92%).[252,256] After acid-mediated decarboxylation of **242**, the (−)-tetracyclic ketone **240** was obtained in 91% yield. The enantiomeric purity of this ketone (−)-**240** was shown to be greater than 98% ee by use of both ^{1}H NMR spectroscopy with the chiral shift reagent[112] tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) and by HPLC on a diastereomeric urea derivative of **240**.[256] The utility of this enantiospecific sequence rests on the fact that these reactions can be run on multigram scale to provide the (−)-tetracyclic ketone **240**, which can now be considered a readily available starting material for the synthesis of the macroline, sarpagine, and ajmaline related alkaloids. In addition, D-(+)-tryptophan and L-(−)-tryptophan are both readily available from commercial sources permitting entry into either antipode of the natural products for screening.

B. (−)-Suaveoline

In 1972 Potier et al. isolated suaveoline **252** from the trunk bark of *Rauwolfia suaveolens* S. and reported the specific rotation $[\alpha]^{25}_D = 0° \pm 2°$ for this base. The structure of **252** was elucidated on the basis of mass and proton spectroscopy, as well as a partial synthesis from ajmaline.[257,258] In 1989 Trudell reported the total synthesis of (±)-suaveoline (**252**)[253] and in 1992 Fu completed the first enantiospecific total synthesis of (−)-suaveoline.[259,260] A specific rotation of $[\alpha]^{25}_D = -9.3°$ ($c = 0.30$, $CHCl_3$) was determined for pure **252** in contrast to earlier reports.[257,258]

The total synthesis of (−)-suaveoline (Scheme 25) will be described beginning from (−)-N_a-methyl-N_b-benzyltetracyclic ketone (**240**), the synthesis of which was illustrated in Schemes 13 and 24. Conversion of the carbonyl function of (−)-**240** into the α,

Scheme 25



β-unsaturated aldehyde **243** via the spirooxiranophenyl sulfoxide was accomplished in 87% yield by the method of Trudell[253,261] in the racemic series and of Zhang[106] in the (−)-N_b-methyl series. The pseudosymmetric Grignard reagent, available from 5-bromo-3-heptene (**244**), was then added to the α, β-unsaturated aldehyde **243** at low temperature to provide the products of 1,2- (**245**) and 1,4-addition (**246**–**248**) in a combined yield of 90%. When this sequence was repeated at room temperature, only the product of 1,2-addition **245** was isolated and in high yield (88%). The alcohol **245** was purified and subjected to conditions that promote an oxyanion-Cope rearrangement (150 °C) to furnish the same C-15 functionalized tetracyclic systems **246**, **247**, and **248** obtained from the 1,4-addition in a ratio of 3:2. Although the stereoselectivity in the oxyanion-Cope process was only 3:2 with the preferred attack from the desired bottom face of the C(15)–C(16) olefinic bond, the mixture of aldehydes **246**–**248** could be employed in the synthesis of (−)-suaveoline (**252**). The 1,4-addition of **244** to **243** was unprecedented in these systems and provided the diastereomeric aldehydes **246** and **247** with the ajmaline configuration at C-15 and C-16 in a ratio of 3:1 **246,247/248**. Previous attempts[115,254,262] to effect 1,4-addition to α,β-unsaturated aldehyde **243** had proven unsuccessful; therefore, this example serves as the first case of such an addition in this hindered N_b-benzylazabicyclo[3.3.1]nonane system. Since the configurations of the newly formed stereocenters in aldehydes **246**–**248** will eventually be destroyed, the aldehyde functions of the mixture of **246**–**248** were protected by treatment with hydroxylamine hydrochloride in ethanol at reflux. A diaster-

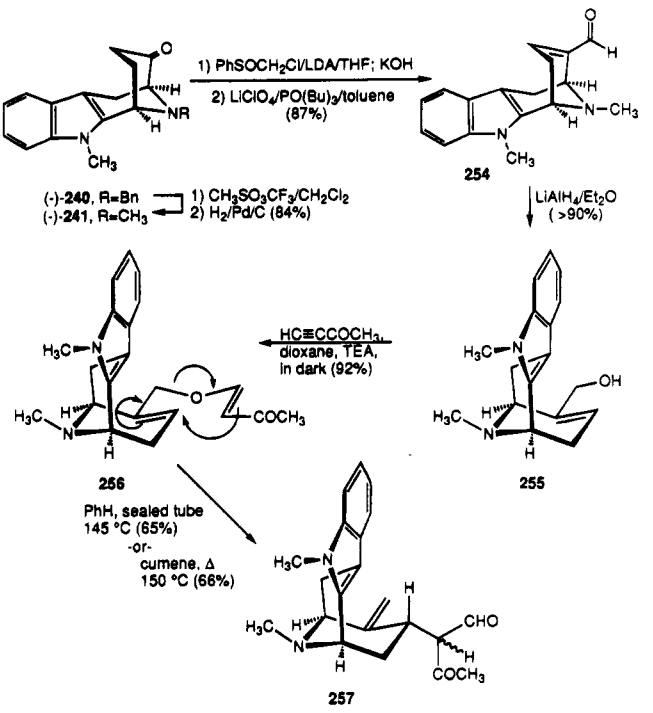
eomeric mixture of oximes represented by **249** was obtained in 95% yield. The mixture of oximes was osmylated and subsequently hydrolyzed reductively with $NaHSO_3$ to provide the desired diol which was subjected directly to the oxidative cleavage sequence ($NaIO_4$). The desired dialdehyde **250** was obtained in 80% overall yield based on recovered starting oxime **249**. The mixture of dialdehydes **250** was cyclized *in situ* with hydroxylamine hydrochloride to provide N_b-benzylsuaveoline (**251**) in 70% yield. When **251** was subjected to the conditions of catalytic debenzylation with excess 10% Pd/C (1.5:1 w/w) and hydrogen in methanol, a 98% yield of (−)-N_b-methylsuaveoline (**253**, $[\alpha]^{25}_D = -89.5°$, $c = 0.35$, $CHCl_3$) was realized in greater than 98% ee. Although the exact mechanism of the benzyl/methyl transformation is still not clear, it provided a simple manner in which to execute a benzyl/methyl transfer in the latter stages of the synthesis. This process can be employed in the preparation of a number of macroline/sarpagine/ajmaline alkaloids.[24,263] Catalytic debenzylation of the hydrochloride salt of (−)-N_b-benzylsuaveoline (**251**) with 10% Pd/C (0.7:1.0 w/w) and hydrogen in ethanol provided a 96% yield of (−)-suaveoline (**252**).[259,260]

This sequence represents the first enantiospecific total synthesis of (−)-suaveoline and provides material upon which an accurate optical rotation could be obtained. Since the intermediates in this route are closely related to those previously reported in the synthesis of (±)-ajmaline, the strategy employed in the macroline series can be extended to alkaloids of the ajmaline family. Later in 1993, Bailey[264] described a formal synthesis of (−)-suaveoline (from L-tryptophan) which rested on the preparation of the optically active N_a-methyl-N_b-benzyl tetracyclic ketone **240**. This (−)-ketone is identical with that reported earlier by Zhang[252] in 1988 and Fu[259] in 1992.

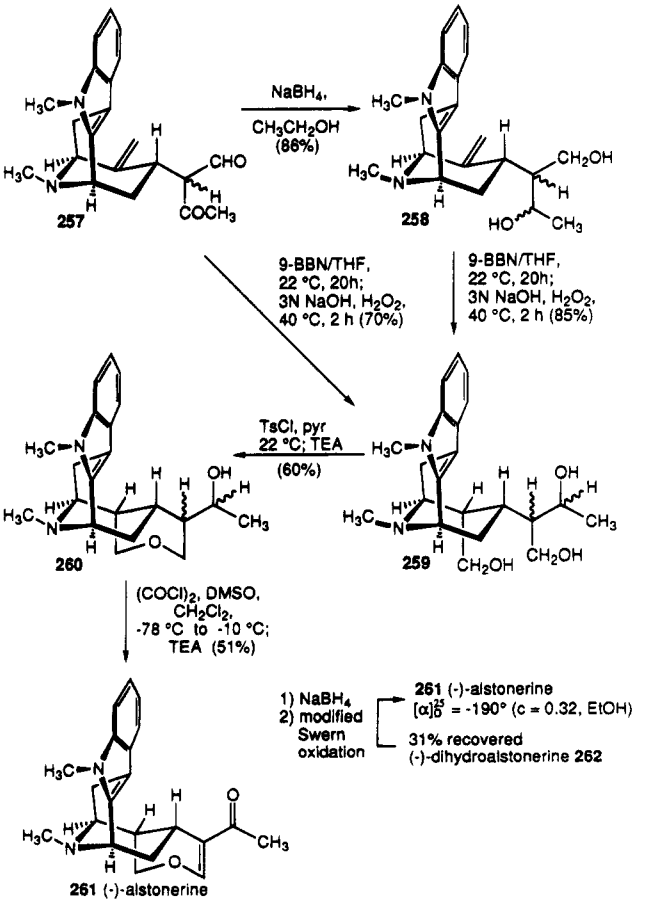
C. (−)-Alstonerine

Alstonerine (**261**) was first isolated from *Alstonia muelleriana* Domin by Elderfield and Gilman[265,266] and its structure was elucidated by LeQuesne et al.[267] The indole alkaloid alstonerine **261** is closely related to the oxindole alkaloid alstonisine (**294**).[268] Zhang[106] reported the synthesis of (−)-alstonerine in 1990 starting from the (−)-tetracyclic ketone **240** which was prepared earlier in enantiospecific fashion.[252,256] The N_b-benzyltetracyclic ketone **240** was methylated with methyl trifluoromethanesulfonate followed by catalytic debenzylation with Pd/C and hydrogen to afford the N_b-methyltetracyclic ketone **241** in high yield (Scheme 26). The ketone **241** was converted into the α,β-unsaturated aldehyde **254** in 80% overall yield using conditions analogous to those reported by Trudell.[253] The α,β-unsaturated aldehyde **254** was then transformed into the allylic alcohol **255** with lithium aluminum hydride in ether at −20 °C. Michael addition to 3-butyn-2-one in the absence of light gave the desired enone **256** in excellent yield. The Claisen rearrangement (**256** to **257**) proceeded via the preferred chair transition state primarily from the bottom face of the double bond to afford the desired β-dicarbonyl compound **257** with a diastereoselectivity in cumene (150 °C) of greater than 4:1 in 82% yield.[106] The β-dicarbonyl compound **257** was then reduced with sodium borohydride to the diol **258** as illustrated in Scheme 27. Hydroboration of the exocyclic methylene function of **258**, with an excess of 9-BBN occurred stereospecifically from the β-face of the double bond and after oxidative workup

Scheme 26



Scheme 27

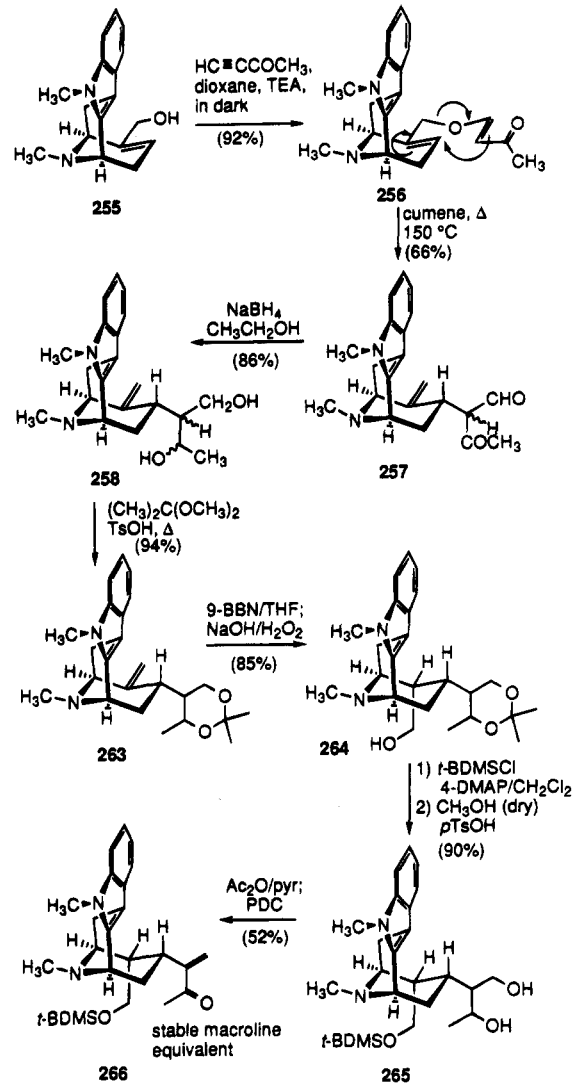


provided the triol **259**. One equivalent of 9-BBN complexed to the N_b-nitrogen function which hindered attack from the bottom face of the double bond and resulted in exclusive hydroboration from the β-face of the exocyclic methylene function. Upon stirring with tosyl chloride (1 equiv) in pyridine followed by treatment with triethylamine, the triol **259** was regioselectively cyclized to the desired monol **260** in 60% yield, accompanied by recovered starting triol **259** (33%). Additional quantities of **260** could be obtained by subjecting the recovered triol **259** to the same tosylation process. The alcohol **260** underwent a modified Swern oxidation to provide (−)-alstonerine (**261**) in 51% yield, accompanied by dihydroalstonerine (**262**, 31%). A proposed mechanism for this transformation has been reported by Bi et al.[24] The dihydroalstonerine intermediate **262** could be recycled to provide additional quantities of **261** by sodium borohydride reduction, the monol of which was subjected to the conditions of the modified Swern oxidation. This procedure may provide a general method for the conversion of hydroxy-substituted tetrahydropyrans into enones which are commonly found in other *Alstonia* alkaloids such as alstophylline (**236**) and alstonisine (**294**). The enantiospecific synthesis of the tetracyclic ketone (−)-**240** coupled with the Claisen rearrangement (C-15) and the hydroboration process (C-16) provided a route of high diastereoselectivity for the enantiospecific synthesis of the macroline/sarpagine alkaloid, (−)-alstonerine **261**. Substitution of the 6-methoxy derivative of tryptophan alkyl ester (**172**) for the parent ester will provide a route to alstophylline (**236**), the monomeric unit required for the synthesis of macralstonine.

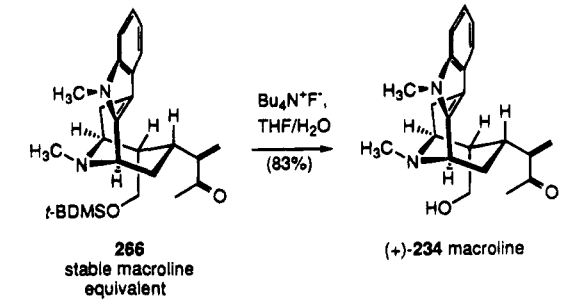
D. (+)-Macroline

The synthesis of (+)-macroline (**234**) has recently been completed (Schemes 28 and 29) in enantiospecific fashion starting with D-(+)-tryptophan.[23,249] The significance of this synthesis becomes apparent when one considers that >70 macroline related alkaloids have been isolated.[24] Macroline is not stable over long periods of time; therefore, the synthesis of the stable macroline equivalent **266** which can be employed for the synthesis of *Alstonia* bisindoles is presented in Scheme 28. The conversion of **266** into (+)-macroline (**234**) follows in Scheme 29. The tetracyclic ketone (−)-**240** was employed for the synthesis of (−)-alstonerine[106] and the required allylic alcohol **255** had been prepared by the route shown in Scheme 26. The synthesis of macroline **234**, as illustrated in Scheme 28, began with the intermediate allylic alcohol **255**. Michael addition of **255** to 3-butyn-2-one in the absence of light provided the enone **256** in excellent yield. The Claisen rearrangement of **256** took place stereoselectively from the desired α-face (4:1) in cumene at 150 °C to afford the same dicarbonyl compound **257** employed for the synthesis of (−)-alstonerine (**261**). Although the stereoselectivity was reported to be 4:1, it may be much higher because the three byproducts formed in this pericyclic event were inseparable, rendering their structure determination difficult at this juncture. Reduction of dicarbonyl compound **257** produced the diol **258**. The diol **258** was converted into

Scheme 28

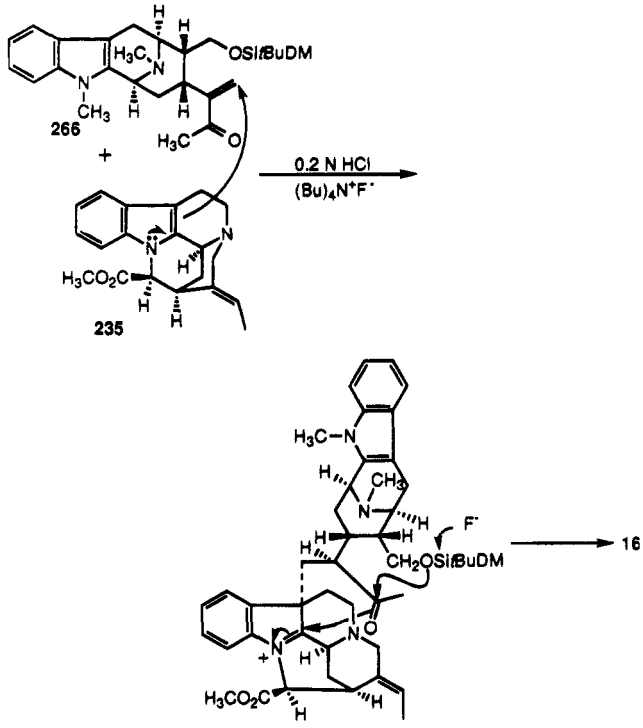


Scheme 29



the triol previously described in Scheme 27; however, attempts to utilize the triol **259** for the synthesis of macroline proved impractical. Consequently, **258** was protected as the acetonide **263** before the hydroboration/oxidation process with 9-BBN/OH^-/H_2O_2 was carried out. Hydroboration of **263** occurred exclusively from the β-face of the C(16−17) olefinic bond, as planned, to provide the desired primary alcohol **264**. The primary hydroxyl moiety of **264** was converted into the *tert*-butyldimethylsilyl ether, after which the acetonide was selectively removed upon stirring this compound with *p*-toluenesulfonic acid in dry methanol under argon. Acetic anhydride was then used to protect the primary alcohol in diol **265**, and the acetate which resulted served as the desired

Scheme 30



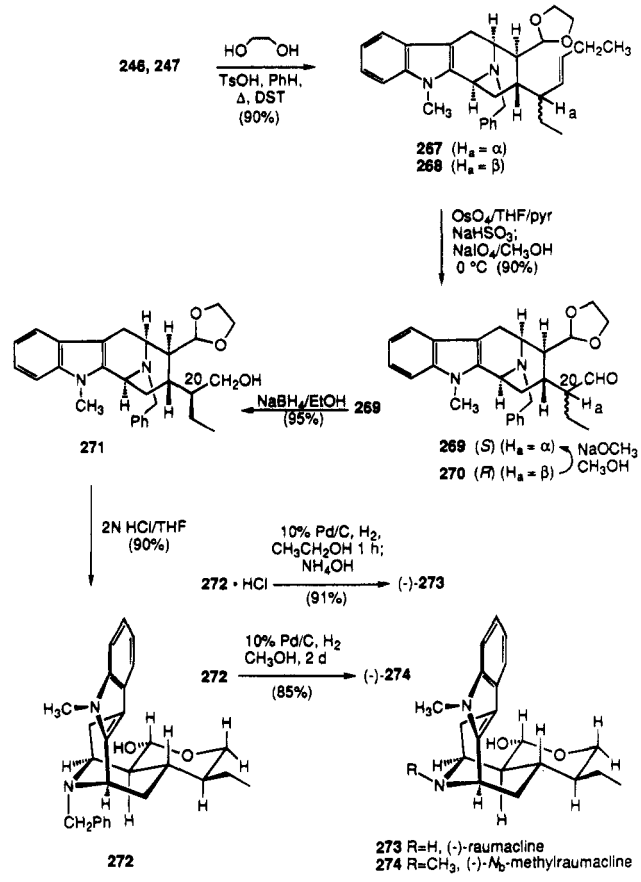
leaving group. This protection of the primary hydroxyl group of **265** was followed by oxidation with pyridinium dichromate (PDC) to provide the stable macroline derivative **266** in a one-pot process. After the oxidation of the secondary alcohol of **265** to the corresponding ketone had occurred, the pyridine present in solution promoted the loss of the β-ketoacetate function to provide the stable macroline enone **266**. When **266** was stirred in THF with tetrabutylammonium fluoride, (+)-macroline (**234**) was obtained (Scheme 29). Macroline is known to cyclize to dihydroalstonerine **262** when exposed to base; therefore, the synthesis of the macroline equivalent **266** was designed to facilitate its use in the synthesis of bisindole alkaloids.

The (−)-tetracyclic ketone **240** has been converted into the macroline equivalent **266** by a series of stereocontrolled steps as described above. When the synthetic macroline equivalent **266** was stirred with plant-derived pleiocarpamine in 0.2 N aqueous hydrochloric acid in the presence of fluoride ion, villalstonine (**16**) was the only observable product, as illustrated in Scheme 30.[250]

E. (−)-Raumacline

Since the complete structure of (+)-ajmaline has been well documented[269−271] and confirmed by X-ray crystallography[272] this commercially available alkaloid has been widely used as a starting material for the preparation of other alkaloids. Stöckigt and Sakai, et al.[273−275] isolated several new alkaloids, termed the raumaclines, from cell cultures of *Rauwolfia serpentina* Benth after feeding experiments with ajmaline. Raumacline (**273**) and N_b-methylraumacline (**274**) were first detected as products of these feeding experiments in 1990. The structures of these alkaloids were elucidated by spectroscopic methods and partial synthesis from ajmaline.[275] Later, Stöckigt et al. isolated[273,274] four more raumacline alkaloids from *Rauwolfia serpentina* Benth cells cultivated in the presence of (+)-ajmaline.

Scheme 31



Soon after the isolation of this new class of alkaloids, Fu[259] completed the total synthesis of (−)-raumacline (**273**) and (−)-N_b-methylraumacline (**274**). The enantiospecific nature of the total synthesis of **273** and **274** is important for several reasons. The relationship between raumacline **273** and ajmaline has now been established chemically by Sakai *et al.*; therefore, entry into other ajmaline alkaloids including the total synthesis of the unnatural antipode (−)-ajmaline can be envisaged. The synthetic route executed by Fu employed the same oxyanion-Cope rearrangement developed for the total synthesis of (−)-suaveoline (**252**)[259] and N_b-methylsuaveoline (**253**).

The formyl group of the mixture of aldehydes **246** and **247** was protected as the ethylene acetal, followed by oxidative cleavage of the double bond to provide two epimeric aldehydes **269** and **270** in excellent yield (Scheme 31) which were separated by flash chromatography. Aldehyde **269** possessed the desired chirality (*S*) at C-20 for the synthesis of (−)-raumacline (**273**) and N_b-methylraumacline (**274**). For this reason the epimer **270** was treated with base and converted into an equilibrium mixture of **269** and **270** (1:1), which was easily separated by flash chromatography on silica gel. The combined (−)-(*S*)-aldehyde **269** was then reduced to the alcohol **271**. This was followed by deprotection of the aldehyde function and cyclization under acidic conditions to provide (−)-N_b-benzylraumacline (**272**). It is worth noting in this last sequence that the formation of **272** from aldehyde **269** was stereospecific. Catalytic

debenzylation of the hydrochloride salt of (−)-**272** in ethanol furnished (−)-raumacline (**273**) in 91% yield. When the base (−)-**273** was subjected to catalytic debenzylation with excess Pd/C and hydrogen in methanol, an 85% yield of (−)-N_b-methylraumacline (**274**) was realized. These two syntheses of (−)-**273** and (−)-**274** and that of (−)-suaveoline (**252**) represent the first enantiospecific synthesis of members of the ajmaline family of indole alkaloids and demonstrate that the strategy employed for the preparation of the macroline related sarpagine alkaloids can be extended to other families of indole alkaloids.

VI. Enantiospecific Synthesis of 5-Methoxy-D-(+)- or L-(−)-tryptophan

Over the past several years the isolation of a number of C-10 ring A-oxygenated indole alkaloids in the macroline/sarpagine series have been reported (Figure 13)[24,276] including 18-hydroxylochnerine (**275**), spegatrine (**276**), lochneram (**277**), 10-methoxyvellosimine (**278**), sarpagine (**279**), lochnerine (**280**), N_a-methylsarpagine (**281**), neosarpagine (**283**), verticillatine (**284**), and 19,20-dehydro-10-methoxytalcarpine (**285**). Interest in the synthesis of N_a-methylsarpagine (**281**) as well as 19,20-dehydro-10-methoxytalcarpine (**285**) has prompted the need for a preparative synthesis of 5-alkoxy-D-(+)-tryptophans via a route which would also provide the L-(−)-enantiomers, if desired. Since, the enantiospecific synthesis of a number of *Alstonia* macroline/sarpagine alkaloids has been demonstrated[24,276] by employing the *trans* 1,3-transfer of chirality during the Pictet–Spengler condensation, the use of D-(+)-tryptophan would provide the natural indole alkaloid while the L-(−) enantiomer would furnish the unnatural antipode for biological screening. Recently, a general method for the enantiospecific synthesis of 5-methoxy-D-(+)-tryptophan (**293**) or the L-(−) optical antipode was completed by Zhang[277] and is illustrated in Scheme 32.

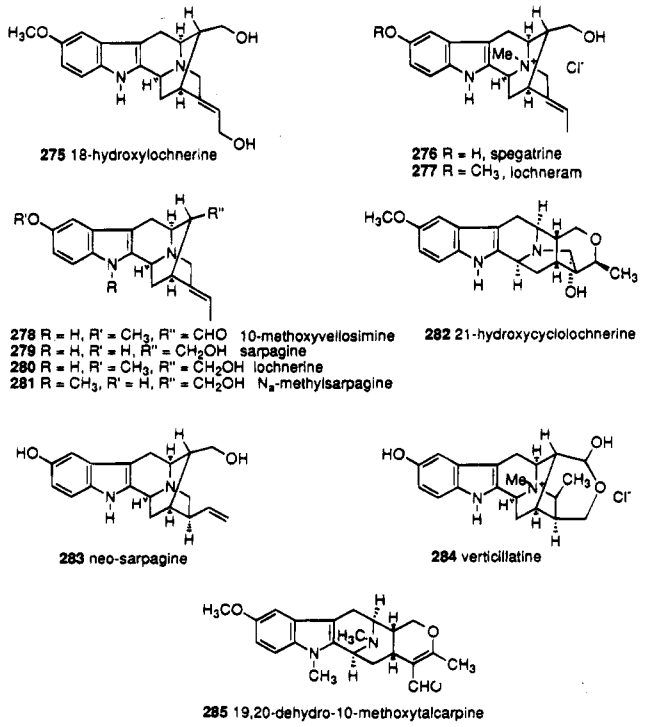
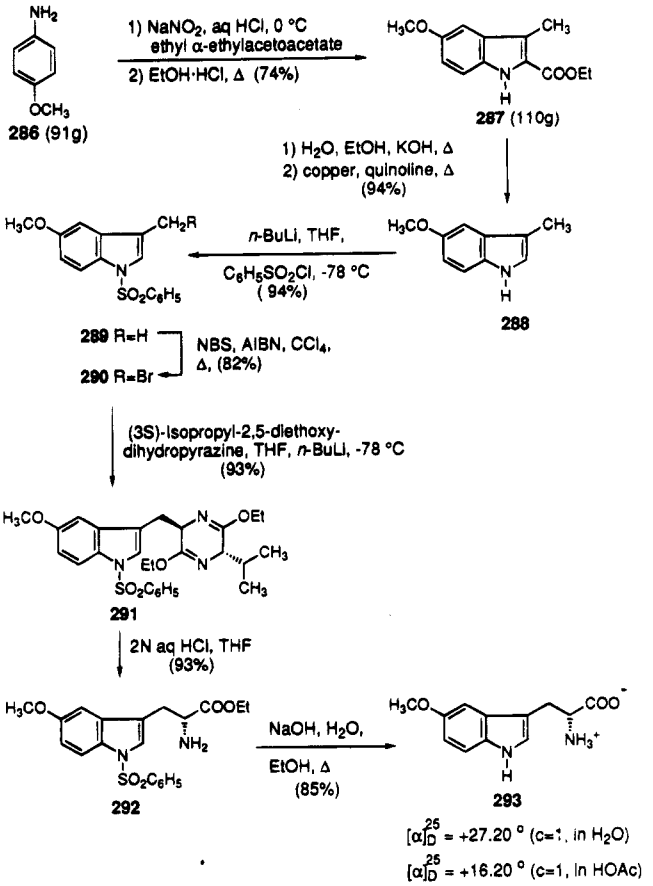


Figure 13. Ring A-oxygenated indole alkaloids.

Scheme 32



In regard to the total synthesis of alstophylline and macralstonine, the preparation of 1-(phenylsulfonyl)-6-methoxy-D-(+)-tryptophan ethyl ester had already been carried out in our laboratories[278] by employing the Schöllkopf chiral auxiliary.[279] The Schöllkopf chiral auxiliary had been chosen for the desired D-(+)-tryptophan would be available from L-valine while the L-(−) enantiomer would originate from D-valine. The success of this sequence rested upon the ability to scale up the first few steps to multihundred gram scale. For this reason, the well-known Fischer indole cyclization,[102] via the thermally mediated [3,3]sigmatropic rearrangement, was chosen as the method by which to generate large quantities of 5-methoxy-3-methylindole (**288**).

Ethyl 5-methoxy-3-methylindole-2-carboxylate (**287**) was prepared on a large scale from *p*-anisidine and ethyl α-ethylacetoacetate by the Fischer indole cyclization via a Japp–Klingman azo-ester intermediate (Scheme 32).[280] This process has been fully explored by Abramovitch and Shapiro as well as reviewed.[95,281] Alkaline hydrolysis of ester **287** and subsequent copper/quinoline-mediated decarboxylation of the carboxylic acid furnished the 5-methoxy-3-methylindole (**288**) in excellent yield. Care must be exercised on decarboxylation of the corresponding acid on a large scale. The best yields were obtained when the carboxylic acid was carefully dried and the decarboxylation was executed at reflux in a well-stirred minimum amount of distilled quinoline (1.5–2 equiv of quinoline with respect to the carboxylic acid). Only a catalytic amount of copper powder was

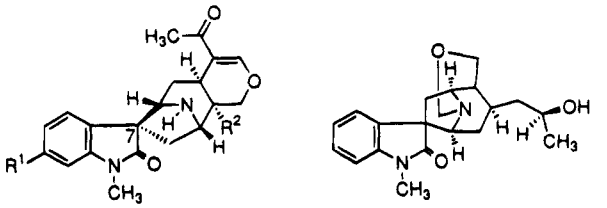
required to ensure yields of **288** in excess of 90%.

In order to employ the Schöllkopf chiral auxiliary in the indole series, protection/deactivation of the indole N(H) group was required. This was accomplished by treatment of indole **288** with *n*-BuLi and benzenesulfonyl chloride in THF at −78 °C to provide sulfonamide **289** in 94% yield.[279,282] The protected indole **289** was then treated with NBS[283] under free radical conditions (AIBN) to afford the protected 3-(bromomethyl)indole **290** in excellent yield. The alkylation of the anion of the Schöllkopf chiral auxiliary derived from L-valine was performed under conditions analogous to those described in the literature[278,282] and afforded the protected tryptophan derivative **291** stereospecifically. The substituted pyrazine group was hydrolyzed under acidic conditions (aqueous 2 N HCl, THF) to provide the desired 1-(phenylsulfonyl)-5-methoxytryptophan ethyl ester (**292**) as the hydrochloride salt. Alkaline hydrolysis of both the 1-phenylsulfonyl protecting group and the ethyl ester moiety furnished 5-methoxy-D-(+)-tryptophan (**293**). Racemization of the chiral center of the amino acid **293** was not observed under the conditions of hydrolysis (8 h) for even prolonged heating under equivalent reaction conditions (OH^-) returned the same amino acid **293** with the identical optical rotation observed on hydrolysis of **293** for only 8 h.

The applicability of this route rests on the ease of execution of each step,[277] moreover the optically active 5-methoxytryptophan was obtained in only five steps from 5-methoxy-3-methylindole (**288**). Recently we reported the enantiospecific synthesis of 6-methoxy-D-(+)-tryptophan[278] which was being employed for the total synthesis of macralstonine as stated. The recent work of Zhang[277] however can be employed to provide 6-methoxy-D-(+)-tryptophan via a much shorter route than the previous sequence.[267,268] In addition, the route by Zhang has been applied to *o*- and *m*-anisidine to provide 7-methoxy-3-methylindole and 6-methoxy-3-methylindole, respectively, in good yields. Attempts to convert these indoles into optically pure 7-methoxy- and 6-methoxytryptophans are currently underway. The sequence by Zhang represents the first synthetic entry into either 5-methoxy-D-(+)- or L-(−)-tryptophan[284,285] and makes these materials available on multigram scale for total synthesis.

VII. Oxindole Alkaloids

The first macroline-related oxindole alkaloid alstonisine (**294**), was isolated from *Alstonia muelleriana* Domin and reported by Elderfield and Gilman (Figure 14).[265,266] The structure of this alkaloid was reported by Nordman,[286] unfortunately an error in transposition of this to paper resulted in an incorrect representation of the structure of alstonisine.[286] The absolute configuration of this base at C-3, C-5, C-15, and C-16 was later determined by Le Quesne et al.[287] when alstonisine (**294**) was biomimetically transformed into talpinine; however, direct confirmation of the stereochemistry at the spirocenter (C-7) has not been reported to date. The establishment of the stereochemistry at the spirocenter C-7 therefore constitutes one of the principal reasons for interest in the enantiospecific total synthesis of alstonisine



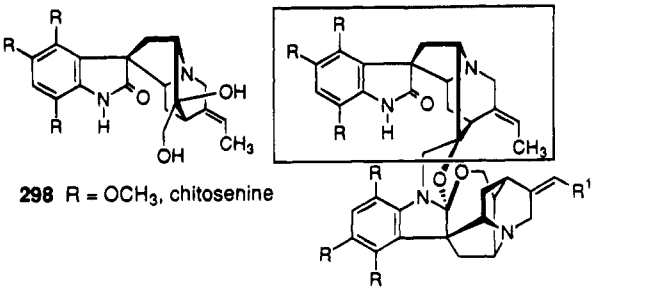
294 $R^1 = R^2 = H$; alstonisine

297 macroxine

295 $R^1 = OCH_3$, $R^2 = H$; N_b-demethylalstophylline oxindole

296 $R^1 = OCH_3$, $R^2 = OH$; 16-hydroxy-N_b-demethylalstophylline oxindole

Figure 14. Macroline-related oxindoles.



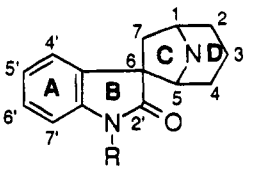
298 R = OCH_3, chitosenine

R = OCH_3

299 $R^1 = CH_2OCH_3$; gardmultine

300 $R^1 = CH_3$; demethoxygardmultine

Figure 15. Oxindoles isolated from *Gardneria multiflora* Makino.



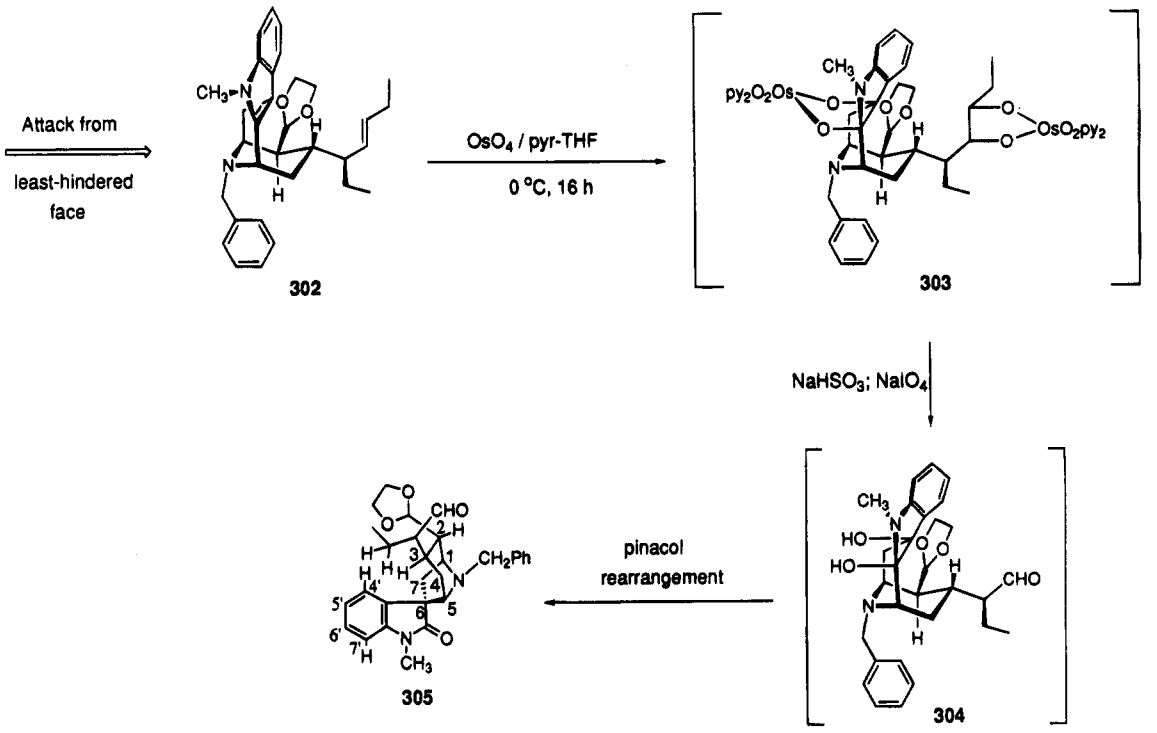
301

Figure 16. The tetracyclic oxindole ring system.

(**294**). Several other macroline-related oxindole alkaloids have recently been isolated from *Alstonia macrophylla* Wall including N_b-demethylalstophylline oxindole (**295**),[288] 16-hydroxy-N_b-demethylalstophylline oxindole (**296**),[289] and macroxine (**297**, Figure 14).[290] The configuration of oxindole alkaloids **295** and **296** at C-7 has been determined by NOE spectroscopic experiments.[288,289] The biological importance of these bases is unclear at this time due to limited amounts of material available for study.

The monomeric base chitosenine (**298**)[291] as well as the bisindoles gardmultine (**299**) and desmethoxygardmultine (**300**)[292] isolated from *Gardneria multiflora* Makino have been shown to exhibit short-lived inhibitory activity *in vivo* of ganglionic transmission in both rats and rabbits (Figure 15).[293] The configuration of the spirocyclic carbon (C-7 in alstonisine **294**) of these oxindoles, however, is opposite to that found in the *Alstonia* oxindoles **294**−**297**. The isolation of alkaloids **298**−**300** in addition to oxindoles **294**−**297** suggests that alkaloids which contain the substructure **301** (Figure 16) may be more prevalent in plants than previously realized. The development of a stereochemically complementary method into

Scheme 33



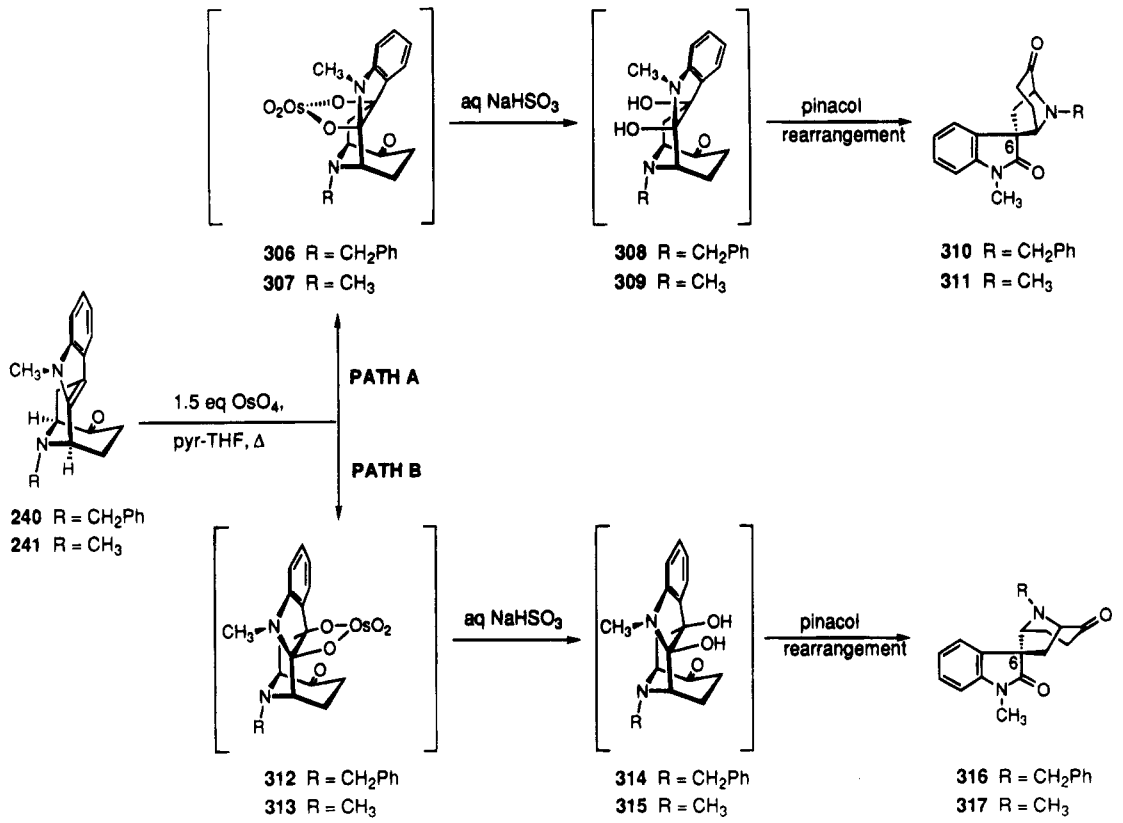
oxindoles related to **301** of either chirality at the spirocyclic carbon would provide material to further the study of these unique oxygenated bases.

Recently Peterson[268] has developed a method to convert N_a-methyltetracyclic ketones into their corresponding oxindoles with a high degree of diastereoselectivity. During the synthesis of (−)-raumacline (**273**),[259] Fu discovered that the treatment of the synthetic N_b-benzyltetracyclic monoketal **302** with osmium tetraoxide in pyridine followed by periodate oxidation provided the oxindole **305**, as illustrated in Scheme 33. This conversion occurred with complete diastereoselectivity with a configuration identical to that proposed for alstonisine **294**. Esmond and Le Quesne had also observed a similar formation of an oxindole during dihydroxylation of a key intermediate during their biomimetic synthesis of macroline.[294] Attack of the osmium tetraoxide was proposed to occur from the less hindered convex face of the indole 2,3-double bond to furnish an intermediate bisosmate ester **303**, as illustrated in Scheme 33. It was believed that the apically positioned acetal group effectively blocked the concave face of the double bond to attack by the OsO_4/pyridine reagent. Conversion of intermediate **303** into the diol-aldehyde **304** and subsequent pinacol rearrangement provided oxindole **305**. The recently developed method of Peterson employing the Sharpless osmylation sequence converts N_a-methyltetracyclic ketone[252] analogs into their corresponding oxindoles with a high degree of diastereoselectivity. These substrates are devoid of a group other than hydrogen situated at either the equatorial position at C-16 or the axial position at C-15 to direct the stereoselectivity. More importantly, this approach provides entry into either spirocyclic oxindole, diastereomeric at C-6 (see Figure 16), from the same (−)-antipode of the tetracyclic ketone **240**.

Optically active (−)-N_b-benzyltetracyclic ketone **240** was treated with osmium tetraoxide in THF at room temperature, followed by reductive workup with aqueous $NaHSO_3$ and flash chromatography, the oxindoles **310** and **316** were produced in a 91:9 ratio in 42% yield (Scheme 34; Table 14). It is believed that the osmium tetraoxide first complexed with the piperidine nitrogen atom of ketone **240** to furnish complex **318** (Figure 17). This complexation was presumably favored due to the axial preference (with respect to the D ring) of the benzyl group. Single-crystal X-ray analysis of an N_b-benzyl tetracyclic derivative indicated that the benzyl group rested in the axial position of the D ring in the crystal.[295] The concomitant complexation of osmium at the equatorial position (with respect to ring D) facilitated intramolecular attack of the osmium reagent to furnish osmate ester **322** (Figure 18) upon heating at reflux. If complexation occurred at the axial position (with respect to the D ring) to give complex **320**, intramolecular delivery of the osmium reagent would be unlikely. The osmate ester **322** was then reduced by sodium bisulfite, and the *cis*-diol **308** which resulted underwent a pinacol rearrangement to furnish oxindole **310** with a 10:1 overall diastereoselectivity. The configuration about the spirocyclic C-6 in oxindole **310** was found to be the same as in alstonisine **294** (C-7) by NMR spectroscopy.[268]

Further evidence for the advent of the complexation/intramolecular delivery of osmium tetraoxide in the previous example was obtained by attempted conversion of N_b-benzoyl ketone **323** into N_b-benzoyloxindole **324** or its diastereomer (Scheme 35). Only the starting ketone **323** was recovered (95% recovery) from this sequence. Clearly, the benzoyl group of substrate **323** was approximately the same size as the benzyl group in ketone **240**. However, the lone pair of electrons of the piperidine nitrogen are

Scheme 34



delocalized into the carbonyl group of the amide function and not readily available to coordinate with osmium tetraoxide. This example demonstrated that neither the complexation of OsO_4 (and subsequent intramolecular oxidation of the indole 2,3-double bond) occurred nor uncomplexed OsO_4 reacted with substrate **323** even from the concave face of the indole double bond at room temperature. Evidently in these systems the OsO_4 was not reactive enough at room temperature to oxidize the indole double bond without previous ligation to a nitrogen atom.

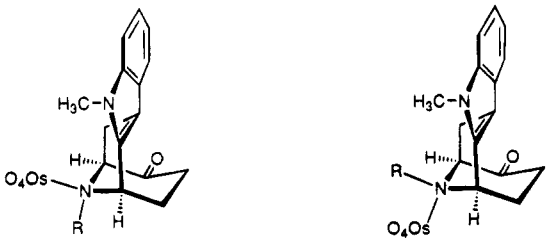


Figure 17. The complexation of osmium tetraoxide to the piperidine nitrogen atom.

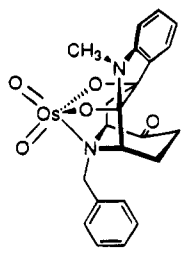
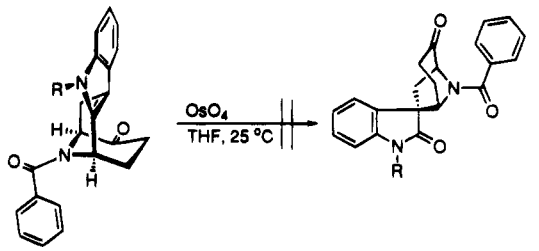


Figure 18. Intermediate osmate ester.

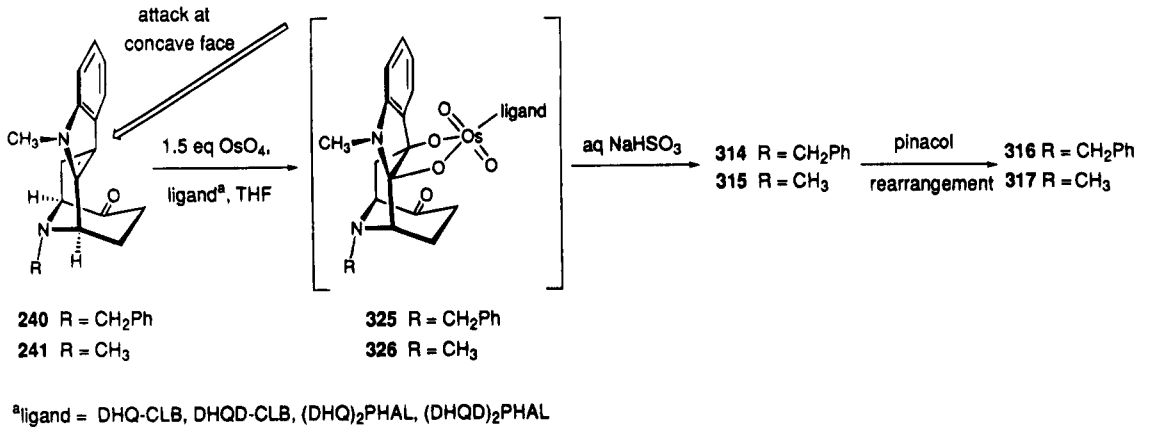
Scheme 35



When a solution of the same (−)-ketone **240** was treated with dihydroquinine 4-chlorobenzoate in THF (Scheme 36, Table 14, entry 2), ketone (−)-**240** was converted into oxindole **316** with 30:1 diastereoselectivity in 91% isolated yield. Employment of the bulky Sharpless phthalazine ligands,[296] $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (Table 14; entries 4 and 5), resulted in reduced facial discrimination. Some matching of configurations between the *Cinchona* derivative and the substrate were necessary to optimize the diastereoselectivity. In the cases immediately above (OsO_4/*Cinchona* derivative) attack of the osmium reagent occurred preferentially from the concave face of the indole 2,3-double bond of substrate **240** to provide osmate ester **325** (Scheme 36). Hydrolysis of ester **325** (aqueous $NaHSO_3$) and subsequent pinacol rearrangement provided oxindole **316**. More importantly, attack of the osmium reagents which contain bulky amino ligands on the indole 2,3-double bond occurred preferentially from the concave face without regard to asymmetry in the pendent ligand.[268]

When N_b-methyl ketone **241** was treated with osmium tetraoxide, osmium tetraoxide/pyridine, or

Scheme 36



[a]ligand = DHQ-CLB, DHQD-CLB, $(DHQ)_2PHAL$, $(DHQD)_2PHAL$

Table 14. Results from the Treatment of Ketones 323, 240, and 241 with Osmium Reagents[a]

entry	ketone	ligand[b]	OsO_4 (equiv)	T (°C)	t (days)	oxindole	yield (%)	**310**:**316**[c]
1	(−)-**240**		1.0	reflux	3	**310**/**316**	42	91:9
2	(−)-**240**	DHQ-CLB	1.5	rt	3	**310**/**316**	91	3:97
3	(−)-**240**	DHQD-CLB	1.5	rt	3	**310**/**316**	77	20:80
4	(−)-**240**	$(DHQ)_2PHAL$	1.5	rt	3	**310**/**316**	81	25:75
5	(−)-**240**	$(DHQD)_2PHAL$	1.5	rt	3	**310**/**316**	82	20:80
6	(±)-**323**		1.0	rt	3	(±)-**324**	0	
7	(±)-**241**		1.0	reflux	3	(±)-**317**	36	0:100
8	(±)-**241**	DHQ-CLB	1.5	rt	3	(±)-**317**	66	0:100

[a] Reactions conducted in THF under a nitrogen atmosphere. [b] Ligands: DHQ-CLB, dihydroquinine 4-chlorobenzoate; DHQD-CLB, dihydroquinidine-4-chlorobenzoate; $(DHQ)_2PHAL$, dihydroquinine 1,4-phthalazinediyl diether; $(DHQD)_2PHAL$, dihydroquinidine 1,4-phthalazinediyl diether. [c] Ratios of diastereomers were obtained by ^1H NMR spectroscopy using a pulse delay of 15 s. The diastereomeric ratios of the mixtures of N_b-benzyl oxindoles **310** to **316** were determined by ^1H NMR spectroscopy (500 MHz, $CDCl_3$) on the purified mixture (flash chromatography) by integration of the N_a-methyl singlets (δ 3.23 for **316** and δ 3.19 for **310**) and confirmed by integration of the H-7α protons (δ 2.54 for **316** and δ 2.91 for **310**). For most reactions the diastereomeric ratios were also determined on the crude product mixtures. No significant difference in the **310**:**316** ratio was observed between crude and purified mixtures.

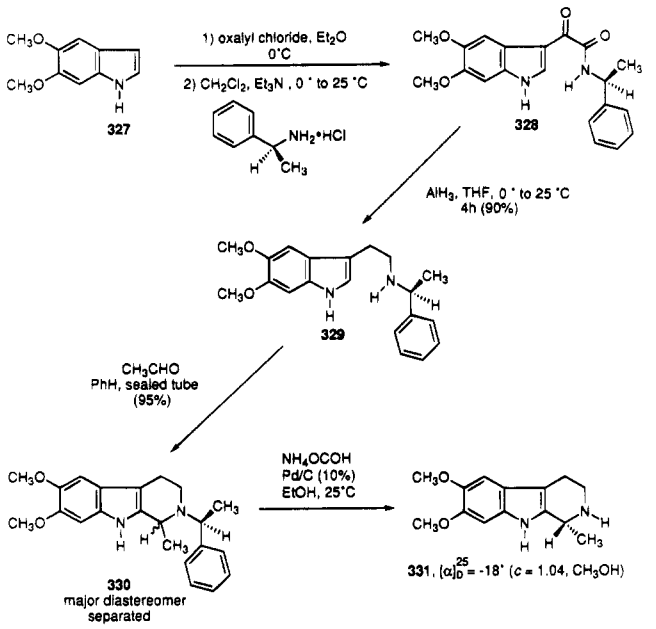
osmium tetraoxide/dihydroquinine 4-chlorobenzoate, only one diastereomer, N_b-methyloxindole **317** was produced and in 36–66% yields (Scheme 36 Table 14, entries 7 and 8). The smaller N_b-methyl substituent in **241** and other macroline-related indoles is believed to preferentially occupy the equatorial position of the D ring.[297] As a result, the ligation and subsequent attack of the osmium reagent on the double bond would be hindered by the N_b-methyl substituent and only osmate ester **313** (or **326** in the case of OsO_4/DHQ-CLB or **321** in the case of OsO_4 alone) and subsequently diol **315** were formed regardless of the osmium reagent. Diol **315** underwent a pinacol rearrangement to furnish spirocylic oxindole **317** with complete diastereoselectivity. The chirality at C-6 of N_b-methyloxindole **317** is identical to that of the spirocyclic carbons present in chitosenine **298**. To date, no previous examples are known in which stereoselective osmylation of the 2,3-double bond of indole alkaloids has been reported to take place in an intramolecular fashion. Stereoselective intramolecular osmylations have, however, been demonstrated for acyclic olefins containing an allylic function that is capable of coordination to osmium.[298,299]

Examination of the results of this study demonstrated that oxindole **310** which is related to alstonisine (**294**) can be prepared with a 10:1 diastereoselectivity from the (−)-N_b-benzyltetracyclic ketone **240** by an intramolecular OsO_4 complexation–control mechanism. An N_b-benzyloxindole related to chitosenine (**298**), which exhibited the opposite configuration to that of alstonisine (**294**) about the spirojuncture (C-7), was also prepared by treatment of (−)-N_b-benzyltetracyclic ketone **240** with osmium tetraoxide reagents that contain bulky amino ligands. From the same optical antipode of tetracyclic ketone (−)-**240** the synthesis of either the *Alstonia* oxindoles or the *Gardneria* and *Voacanga* oxindole alkaloids (diastereomeric at C-7) can be pursued. Furthermore, this approach via the inter- vs intramolecular complexation of osmium reagents may be applicable to the diastereoselective conversion of other classes of indole alkaloids into their respective oxindoles.

VIII. Epimerization in Natural Products by Cleavage Across the Carbon–Nitrogen Bond

The epimerization of the stereocenter at C-1 of tetrahydro β-carbolines by acid catalyzed cleavage across the C(1)–N(2) bond may be more general in scope than was first thought. Reddy has shown that the natural product (−)-1,2,3,4-tetrahydroroeharmine (**331**) can be epimerized to racemic material by stirring with acid. The synthesis of **331** (Scheme 37) began with the treatment of indole **327** with oxalyl chloride in ether which furnished the (5,6-dimethoxyindole-3-glyoxalyl chloride as an insoluble solid. On reaction with *(S)*-α-methylbenzylamine hydrochloride in the presence of excess triethylamine in dichloromethane, glyoxamide **328** was formed in 75% yield.[300] Reduction of both oxygen functions of glyoxamide **328** with AlH_3, generated *in situ* in THF, provided the desired tryptamine **329** in yields ranging from 85 to 90% without racemization of the chiral

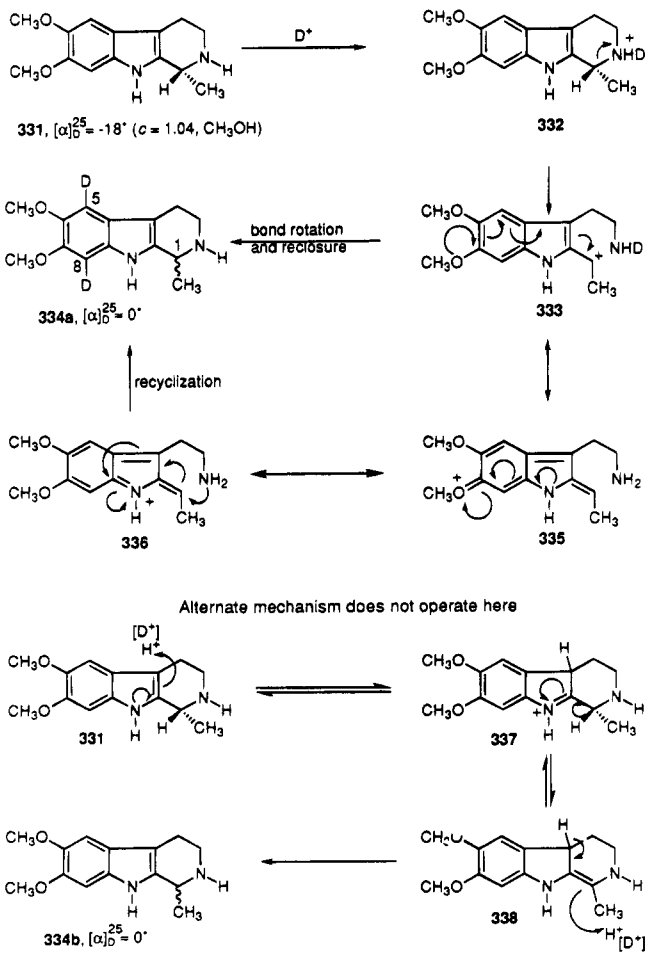
Scheme 37



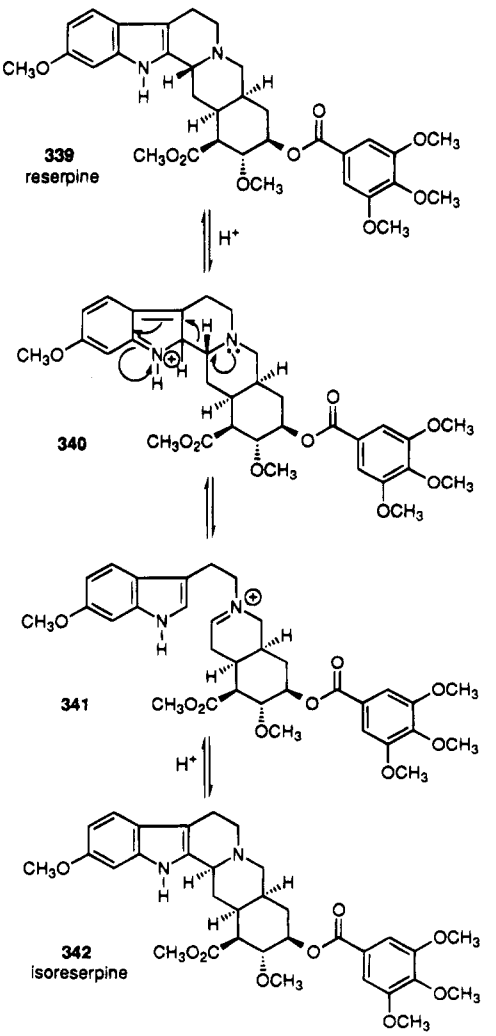
auxiliary. Pictet–Spengler condensation of **329** with acetaldehyde under the nonacidic aprotic conditions furnished 1-methyltetrahydro-β-carboline **330** as a mixture of diastereomers in a ratio of 2:1. Chromatographic separation of the major diastereomer of **330** followed by catalytic transfer hydrogenation provided (Pd/C, NH_4CO_2H, EtOH) (−)-1,2,3,4-tetrahydroroeharmine (**331**), the spectral properties of which were identical to the natural product except for the specific rotation. The specific rotation $[\alpha]^{25}_D$ of synthetic **331** was found to be −18° (c = 1.04, CH_3OH), while that reported for the natural product was −4° (c = 0.12, CH_3OH).[301]

It was believed that (−)-1,2,3,4-tetrahydroroeharmine (**331**) had undergone partial racemization during the acid/base mediated isolation procedure of Gozler et al.[301] To test this hypothesis, optically pure **331** was exposed to deuterated trifluoroacetic acid in dichloromethane at room temperature, as illustrated in Scheme 38. The proton NMR spectrum and the R_f value of the alkaloid which resulted were unchanged; however, the optical rotation of this material was now −0.8°. On the basis of this experiment, it is believed that the mechanism of racemization of **331** occurred as illustrated at the top of Scheme 38. Racemization, we believe has occurred by cleavage across the C(1)–N(2) bond in agreement with previous work from this laboratory. Although deuterium incorporation occurred at C-5 and C-8, no deuterium was found at C-1 of **331**, consequently epimerization could not have occurred by the alternate olefinic protonation mechanism illustrated at the bottom of Scheme 38.

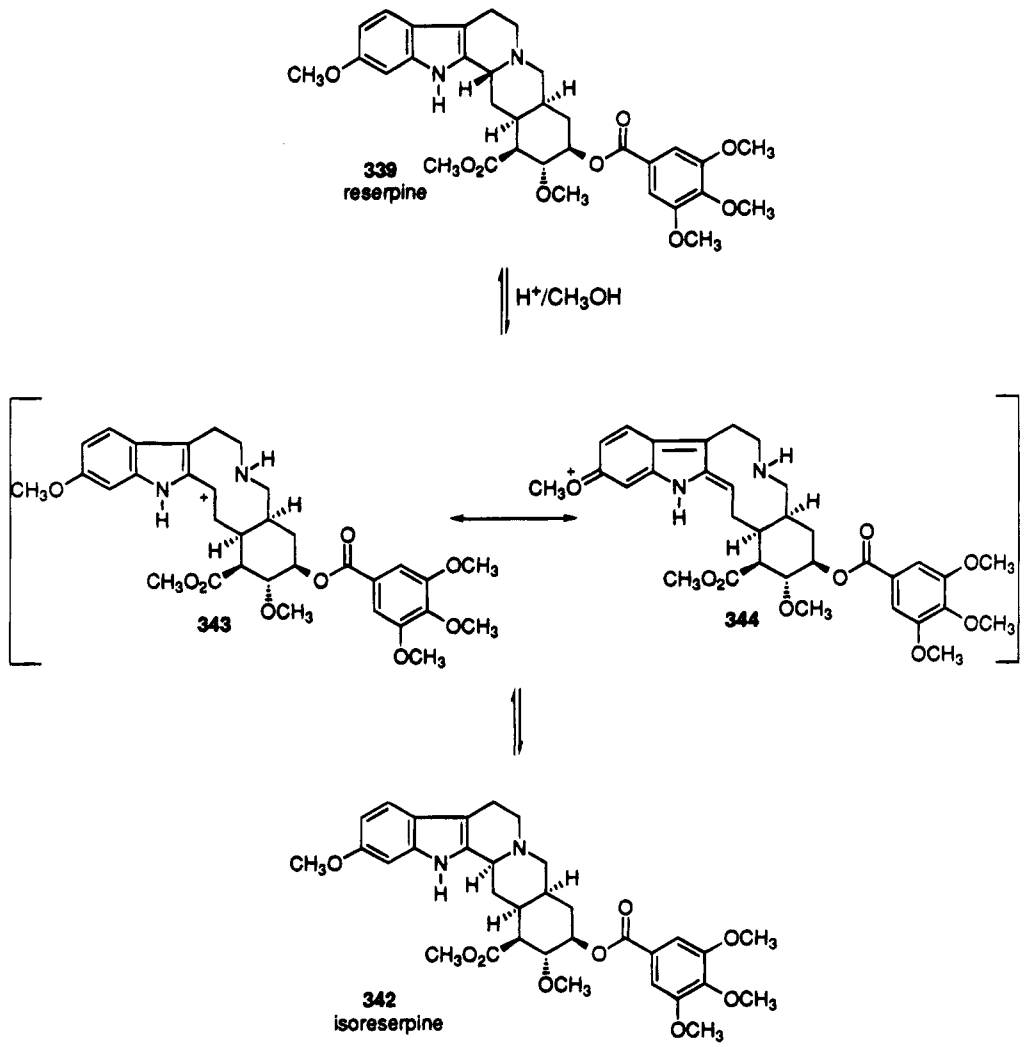
Scheme 38. Cleavage across the C(1)–N(2) Bond



Scheme 39. Previously Proposed Mechanism of Isomerization of Reserpine into Isoreserpine



Scheme 40. Carbocation-Mediated Epimerization of Reserpine into Isoreserpine via C–N Cleavage



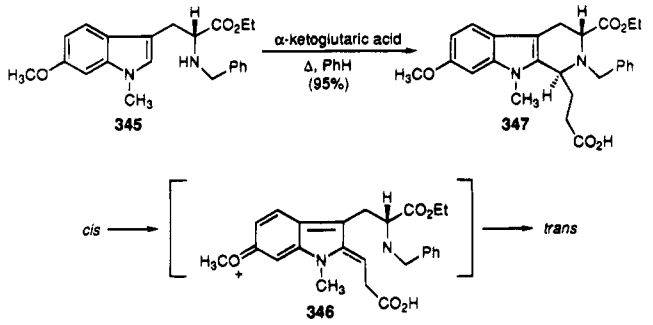
The results observed here are important for all chemists who employ acidic conditions during isolation of *ring A-methoxylated* indole alkaloids. Care must be taken to avoid exposure of these natural products to acid to prevent the opportunity for racemization. In addition, it is strongly believed the racemization of (−)-tetrahydroharmine reported by Brossi[302] occurred in a similar fashion to that depicted in Scheme 38.[300]

The natural product, reserpine (**339**), which was originally isolated from the Indian snake root *Rauwolfia serpentina* Benth,[121,303,304] is the preeminent member of the yohimboid class of indole alkaloids because of its structural complexity coupled with its clinical importance as a hypotensive agent.[305–310] This base also exhibits significant activity as a sedative and tranquilizer.[311] Over the years, reserpine has been the subject of extensive chemical and synthetic investigations.[312–317] It has been reported that the epimerization of reserpine (**339**) to isoreserpine (**342**) can be effected under either acidic or basic conditions, moreover under acidic conditions **342** has been found to predominate over **339** in a ratio of 3.5:1.[318–321] Woodward suggested three possible mechanisms to account for this equilibration[312,313] one of which is similar to that reported by Wenkert and Liu for the epimerization of alloyohimbine to epialloyohimbine.[322] Joule, however, reported that the mechanism involving initial protonation at C-2 followed by reverse Mannich fission of the C(2)–C(3) bond through iminium ion intermediate **341** was responsible for the isomerization between **339** and **342**, as illustrated in Scheme 39.[321]

Observations by Martin[317] during the total synthesis of **339** prompted a reinvestigation of the equilibration in our laboratory. In brief, Martin formed iminium ion **341** by $Hg(OAc)_2$ oxidation of its corresponding dihydro derivative. Cyclization of the iminium ion **341**, proceeded via a half-chair/chair conformation to provide reserpine (**339**) as the major product accompanied by isoreserpine in a ratio of 4.3:1. If iminium ion **341** was indeed an intermediate in the conversion of **339** into **342**, as proposed earlier by Joule[321] then isoreserpine should have been isolated as the major product[321] contrary to the experimental findings of Martin.[317] The Joule intermediate, iminium ion **341**, therefore cannot be the predominant species in the acid-catalyzed isomerization.

The reader will recall that *cis*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline **171** could be converted into the thermodynamically more stable *trans* isomer **172** by bond cleavage across the C(1)–N(2) bond followed by intramolecular recyclization, as discussed above (Scheme 13).[252] Encouraged by these results, reserpine **339** was heated in methanolic hydrogen chloride (1% HCl), under conditions analogous to those employed to convert **171** into **172**. This process

Scheme 41



gave a mixture of isoreserpine (**342**) and reserpine (**339**) with **342** predominating in the product mixture (3:1). Moreover, when isoreserpine (**342**) was heated in methanolic hydrogen chloride it remained the major alkaloid isolated from this equilibration in agreement with its thermodynamic stability.

Upon the basis of the cyclization of **341** reported by Martin,[317] numerous experiments,[111,323] and stereochemical considerations, it was felt that the epimerization of reserpine at C-3 occurred via the pathway outlined in Scheme 40. Protonation of **339** at N-4 followed by ring scission of the C(3)–N(4) bond would afford the carbocation intermediate **343**. This carbocation can then cyclize to furnish isoreserpine (**342**), a thermodynamically more stable molecule with the indole group in an equatorial position relative to ring C.[323] In agreement with the mechanism of cleavage across the C(1)–N(2) bond for the epimerization of *cis*-1,3-disubstituted diastereomers into the *trans* isomers, Hamaker has recently synthesized the key 6-methoxy analog **347** required for the enantiospecific synthesis of alstophylline and macralstonine. When 6-methoxy-N_b-benzyl-D-(+)-tryptophan ethyl ester (**345**) was treated with α-ketoglutaric acid in benzene at reflux only the required *trans* diastereomer **347** was isolated in 95% yield (>98% ee). Presumably the ring A alkoxy group stabilized the intermediate carbocation at C-1 (Scheme 41) permitting the conversion of any *cis* diastereomer so generated into the desired *trans* diastereomer.[324]

IX. Conclusion

The detailed study of the Pictet–Spengler reaction has progressed from the discovery of improved nonacidic aprotic reaction conditions to probing the mechanistic phenomena involved. We have been able to explore the scope of the condensation including the underlying causes for stereospecificity, the mechanism of epimerization of the C-1 carbon atom, and the optimal conditions for effecting highly stereoselective reactions. Although these studies are important, their purpose was to provide a gateway through which to access pharmacologically interesting indole alkaloids.

It is clear that enantiomerically pure N_b-benzyltryptophan alkyl esters can be condensed with aldehydes (acid labile or otherwise) to provide *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines in stereospecific fashion. In those cases in which a small amount of the undesired *cis* diastereomer is formed, addition of excess TFA converts the mixture into the enantiomerically pure *trans* diastereomer. Pictet–

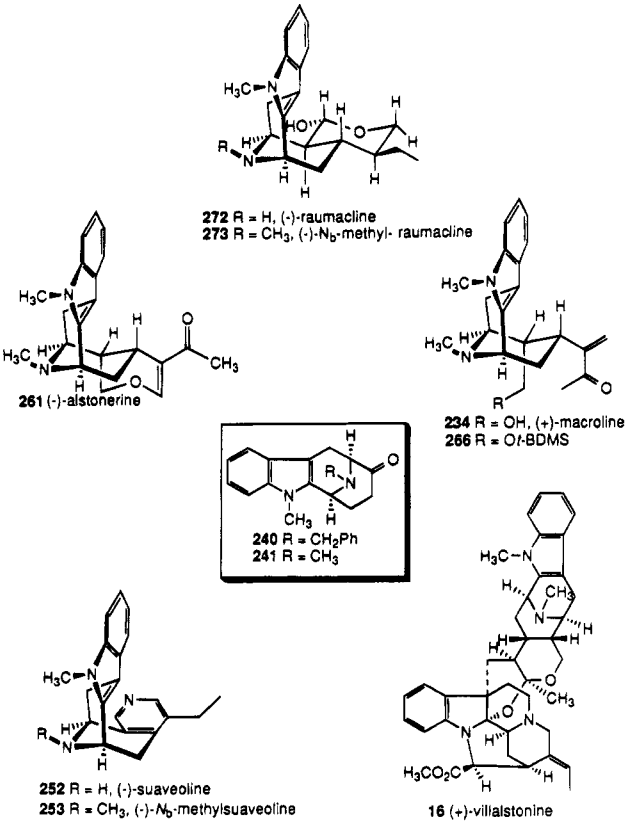


Figure 19. Indole alkaloids prepared from the (−)-tetracyclic ketone.

Spengler reaction of these same aldehydes and esters under acidic conditions should also provide the *trans* isomer with 100% diastereoselectivity, albeit with slightly lower yields.

As such, the enantiospecific synthesis of (−)-alstonerine (**261**) and (+)-macroline **234** have been completed in greater than 98% ee starting from the optically active tetracyclic ketone **240** which had been prepared by an asymmetric Pictet–Spengler reaction. The syntheses of **234** and **261** are the first enantiospecific syntheses of members of the *Alstonia* class of indole alkaloids. Since the three intramolecular reactions (the Pictet–Spengler reaction, the stereocontrolled Dieckmann cyclization, and the Claisen rearrangement) employed in the syntheses provide an intermediate **240** which possessed the same stereochemical configuration at C-3, C-5, and C-15 as those in the macroline, sarpagine, and ajmaline alkaloids with high stereoselectivity, a general approach for the preparation of these alkaloids has been developed (Figure 19). The significance of the synthesis of (+)-macroline (**234**) becomes apparent when one considers that >70 macroline related alkaloids have been isolated and that macroline is known to serve as a biogenetic precursor for many of the bisindole alkaloids as well. Macroline (**234**) is known to cyclize to dihydroalstonerine when exposed to base and is not stable in a vial for long periods of time; therefore, the synthesis of the stable macroline equivalent **266** described herein will obviously facilitate the synthesis of bisindole alkaloids which exhibit greater biological activity than the monomers that constitute them.[24,276] Synthetic (+)-macroline (**234**) has now been coupled stereospecifically with natural pleiocarpamine (**235**) to furnish the antiprotozoal

alkaloid villalstonine (**16**) which contains 11 chiral centers and 11 carbocyclic rings. The macroline intermediate **234** will further provide a means to achieve the total synthesis of other dimeric indole alkaloids in this series.

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