STEREOSPECIFICITY IN THE PICTET-SPENGLER REACTION. ENANTIOSPECIFIC SYNTHESIS OF (6S, 10S)-(−)-5-METHYL-9-OXO-12-BENZYL-6,7,8,9,10,11-HEXAHYDRO-6,10-IMINO-5*H*-CYCLOOCT[*b*]INDOLE, A TEMPLATE FOR PREPARATION OF MACROLINE/SARPAGINE ALKALOIDS

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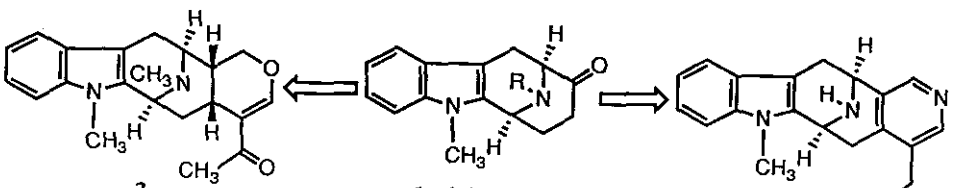
Abstract- The synthesis [from D(+)-tryptophan] of the tetracyclic ketone **[(−)-1b]** was carried out in enantiospecific fashion (>98% ee) *via* the 1,3-transfer of chirality from N_a-methyl, N_b-benzyl tryptophan methyl ester [(+)-**14**] to the *trans* diastereomer [(−)-**4b**] in the Pictet-Spengler reaction. Although the condensation of **14** with aldehyde (**15**) in refluxing benzene generated the tetrahydro ß-carbolines (**4b/5b**) in a kinetic ratio (72:28), epimerization (C-1) of the *cis* diastereomer [(+)-**5b**] into the *trans* isomer [(−)-**4b**] occurred stereospecifically under acidic conditions. Dieckmann cyclization of either the N_a-methyl, N_b-benzyl-*cis*-(+)-**5b** or *trans*-(−)-**4b** diastereomer provided the *cis*-bicyclo[3.3.1]-azanonane system at approximately the same rate, although the ß-keto esters were antipodal, in contrast to results reported in the N_a-benzyl series by Magnus.

Over fifty indole alkaloids isolated from *Alstonia muelleriana*,[1] *Alstonia macrophylla*[2] and other *Alstonia* species possess the basic tetracyclic skeleton (**1**) depicted in Scheme I. During studies directed toward the total synthesis of suaveoline (**2**)[3] and (−)-alstonerine (**3**)[4] the need arose for an enantiospecific synthesis of

(6S,10S)-(−)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole(**1b**). Retrosynthetic bond disconnection from either **2** or **3** in regard to ring E eventually results in the structure of **1** as a key template with regard to the total synthesis of these molecules, as well as for the preparation of a number of other sarpagine/ajmaline alkaloids.[1,2]

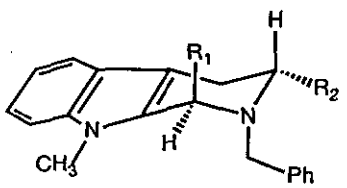
Scheme I



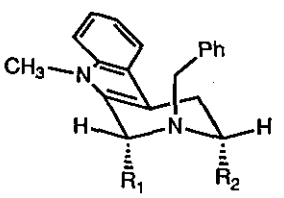
3 2

1a (±), R=CH_2Ph
1b (-), R=CH_2Ph
1c (+), R=CH_2Ph
1d (-), R=CH_3

Yoneda had previously reported the synthesis of (±)-**1a** by the Dieckmann cyclization of the *trans* (**4a**) and *cis* (**5a**)-1,3-disubstituted 1,2,3,4-tetrahydro-ß-carbolines.[5] However, it was later reported[6] that only the *trans* diester [(±)-**4a**] had cyclized to provide the *cis*-fused bicyclo[3.3.1]azanonane skeleton present in **1**, **2**, and **3**.[1,2] In addition, Yoneda suggested that the *cis* diastereomer (**5a**) could not be made to undergo the Dieckmann



(±)-**4a**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3
(-)-**4b**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3
(+)-**4c**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3



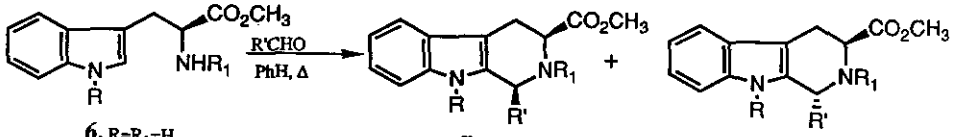
(±)-**5a**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3
(+)-**5b**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3
(-)-**5c**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3

cyclization reportedly due to the formation of an unstable ß−keto ester.[6a] The *trans* diester [(±)-**4a**] had also been converted into **1a** under Dieckmann reaction conditions in our laboratory several years ago.[7] Since the stereochemistry of (±)-**4a** has been rigorously established as *trans* by X-ray crystallography,[6a] clearly an epimerization has occurred to provide the *cis*-fused [3.3.1]bicyclononane system (**1a**). In order to execute an enantiospecific approach to the macroline/sarpagine alkaloids it was necessary to prepare tetrahydro ß-carbolines [**4b**, (*trans*) and **5b**, (*cis*)] in optically pure form and determine whether epimerization occurred at

chiral centers C-1 or C-3 (or both) under Dieckmann reaction conditions required to generate **1**. We wish to report the realization of this objective for the enantiospecific synthesis of *trans* diastereomer [(−)-**4b**] has been completed, moreover (−)-**4b** has been converted into the desired (−)-**3**, enantiospecifically.[4]

Several years ago it was reported that the Pictet-Spengler reaction of tryptophan methyl esters[7] with aldehydes could be executed in nonacidic, aprotic media to provide tetrahydro ß-carbolines (**7** and **8**) in high yield[7] (Scheme II). This media enabled the use of acid-labile aldehydes in the condensation and a number of applications of this process have been reported.[7-10] Of particular interest are the reactions in which methyl 3-formylpropionate or 2-oxoglutaric acid were employed, the yields of tetrahydro ß-carbolines (**4**) and (**5**) were improved from 50% in aqueous media to 80-90% in refluxing benzene.[7,8] Moreover, it was found that incorporation of an N_b-benzyl group into the tryptophan unit resulted in formation of the *trans* (see **4**) diastereomer with high stereoselectivity and often times, stereospecifically (Scheme II). This was illustrated in the racemic series and has now been extended to the optically active series under conditions (H^+) of thermodynamic control.[11,12] The stereospecificity in this process (**6**→**7** + **8**) is dependent upon the size of the aldehyde R′,[11,13] the size of the ester function,[14] as well as the electronic character of the N_b-substituent[13a,b] and this has been reported. The effect of temperature on *cis*-stereoselectivity with **6** when R=R_1=H has been studied by Bailey.[10c]

Scheme II



6, R=R_1=H
or R=CH_3, R_1=H or CH_2Ph
13, R=CH_3, R_1=H

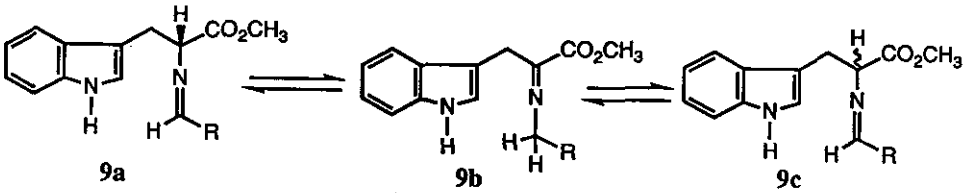
7 **8**

Harrison,[10a] Hino[10b] and Bailey,[10c] however, found that execution of the Pictet-Spengler reaction in aprotic media with optically active tryptophan methyl esters resulted in racemization in varying degrees. Racemization in this series is clearly the result of imine **9a** —> **9b** tautomerization (Scheme III), wherein the optical activity of **9a** is compromised. Since imine (**9a**) is an intermediate in the cyclization it was decided

to increase its electrophilicity *via* use of an N_b-benzyl group (see **10**) in the optical active series.[12]

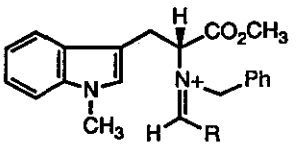
This group would result in a more reactive iminium ion, as well as promoting *trans* stereoselectivity in the condensation.

Scheme III



9a **9b** **9c**

The synthesis of optically active N_a-methyl, N_b-benzyl tryptophan methyl ester (**14**) began with D (+)-tryptophan as illustrated in Scheme IV. The amino acid (**11**) was methylated by stirring in sodium-ammonia followed by addition of methyl iodide to provide the (+)-N_a-methyltryptophan (**12**) in 92% yield.



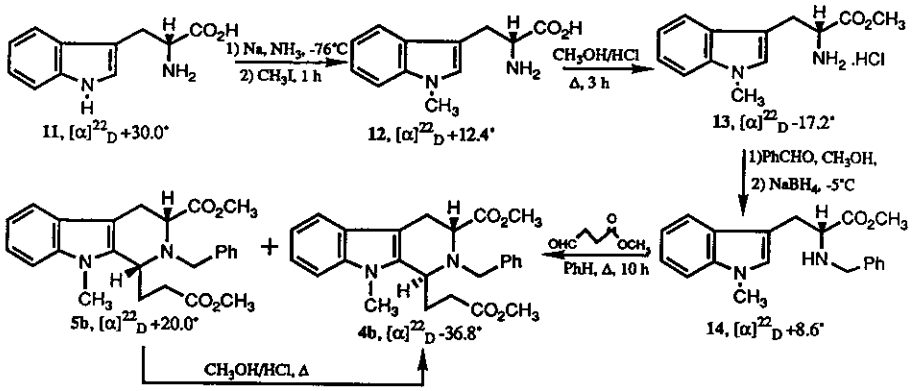
10

Fischer esterification of **12** with methanolic hydrogen chloride gave the methyl ester (**13**) isolated as the hydrochloride salt in greater than 98% ee. The N_a-methyltryptophan methyl ester was converted into the N_a-methyl, N_b-benzyl derivative (**14**) on stirring **13** with benzaldehyde (1.1 eq.) at room temperature (2 h), followed by reduction of the imine which resulted with sodium borohydride at -5°C (3 h). The time and temperature of this process are critical. If the temperature of reduction goes above 0°C, racemization of the chiral center will begin to occur. Moreover, if the initial imine is allowed to stir for more than 1½ hours before reduction, racemization will begin to take place (see Experimental Section for details). The optical purity of the above compounds was found to be greater than 98% ee as determined by ^{1}H-nmr in the presence of the chiral shift reagent, *tris*[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate]europium(III) and by hplc.[15] The nmr method was standardized by admixing the optically active indoles with 3% of the (R/S) material.

Methyl 3-formylpropionate (**15**) required for the Pictet-Spengler reaction was prepared by oxidation (O_3;

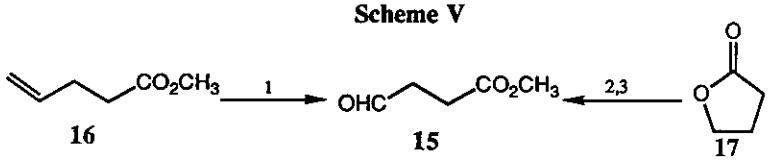
DMS) of methyl 4-pentenoate (**16**) or by acid catalyzed methanolysis of γ-butyrolactone (**17**) followed by PDC oxidation of the alcohol which resulted (Scheme V). The latter procedure proved more economical and

Scheme IV



represented an improvement over the method of Yoneda.[5] The optically active N_a-methyl, N_b-benzyl ester (**14**) was heated with aldehyde (**15**) in refluxing benzene to provide a mixture of the (−)-*trans*-**4b** ($[\alpha]_D^{25}$ -36.8°) and (+)-*cis*-**5b** ($[\alpha]_D^{25}$ + 20.0°) diastereomers in a ratio of 72:28 (81% yield). The *trans* isomer [(−)-**4b**] was shown to be identical spectroscopically (^{1}H-nmr, ^{13}C-nmr, and ir spectroscopy) to the *trans* diastereomer [(±)-**4c**] whose structure was earlier confirmed by single crystal X-ray analysis.[6a] The structures of both **4b** and **5b** were also confirmed by ^{13}C-nmr spectroscopy,[16] as well as by correlation to the isomers reported by Yoneda in the racemic series.[6a] The *trans* **4b** and *cis* **5b** isomers were also obtained in optically active form

Scheme V



1)O_3/ether, -70°C; CH_3OH/CH_3SCH_3; 2) CH_3OH/H_2SO_4, room temperature; 3) PDC/CH_2Cl_2.

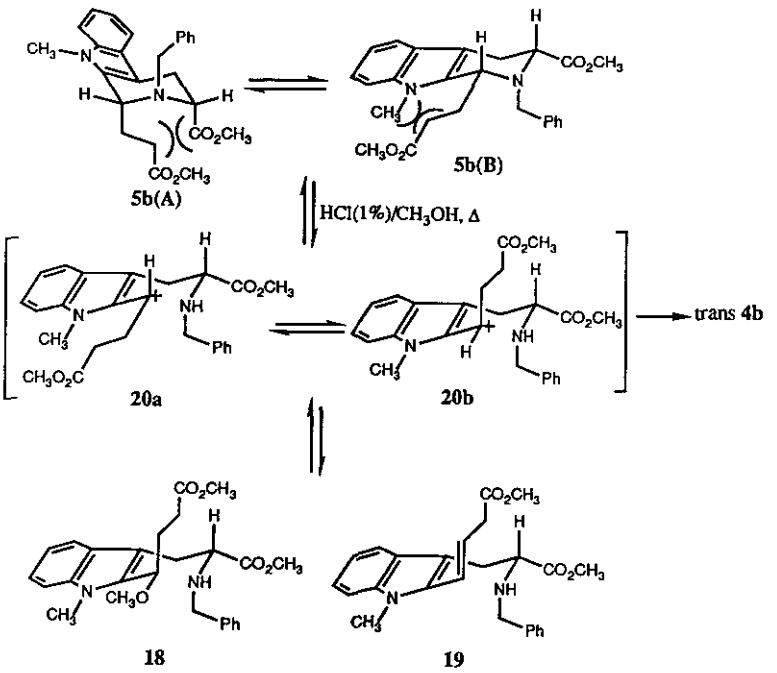
in a ratio of 58:42 when the Pictet-Spengler reaction of **14** was executed with α-ketoglutaric acid (84%) in benzene-dioxane. The origin of this ratio will become clear later (see below).

The enantiomeric purity of both **4b** and **5b** was shown to be at least 98% ee by the chiral shift reagent *tris*-[3-heptofluorpropylhydroxymethylene)-(+)-camphorato]europium(III) and hplc.[15] It is clear that the presence

of the N_b-benzyl group in **10** as suggested, has provided a more reactive iminium ion intermediate and prevented any racemization in this process in aprotic media.[15] This strategy was later employed by Magnus *et al.* in the total synthesis of (+)-koumine.[17]

Earlier it was demonstrated that high *trans* stereoselectivity with aldehydes could be achieved in the Pictet-Spengler reaction either with N_a-H, N_b-benzyl tryptophans[11] or with their N_a-CH_3, N_b-H counterparts.[18] It was surprising that the *trans* stereoselectivity was only 72:28 in the present process, for the effects of the N_a-CH_3 and N_b-benzyl groups evidently are not additive. The reasons for this difference will be reported elsewhere.[19] It was felt, however, that the *trans* diastereomer [(−)-**4b**] was the thermodynamically more stable isomer, for earlier it had been shown that substitution of methyl for hydrogen on the indole N(9)-H of tryptophan provided the *trans* diastereomer often times in stereospecific fashion (see reference 18 for details). When either (−)-**4b** or (+)-**5b** was heated in refluxing benzene, no interconversion between the two diastereomers was observed. It was eventually shown that the reaction of **14** with methyl 3-formylpropionate (**15**) in refluxing benzene provided the ratio of diastereomers based on kinetic control. After numerous experiments[20] it was demonstrated that the *cis* isomer [(+)-**5b**] could be stereospecifically converted into the thermodynamically more stable *trans* diastereomer [(−)-**4b** ($[\alpha]_D^{25°}$ - 36.6°)] simply by heating **5b** in methanolic hydrogen chloride (1%).[12] The yield of this process was greater than 75%. Moreover, the *trans* isomer remained unaffected when heated under the same conditions of methanolic hydrogen chloride; the optical rotation remained -36.6°. The epimerization of (+)-**5b** → (−)-**4b** must have occurred at C-1 (position-1) of the *cis* diastereomer, since **4b** was isolated from this process in >98% ee. If the epimerization of *cis* diastereomer (**5b**) had occurred at C-3, this would have resulted in the formation of the (+)-enantiomer **4c** of **4b** with an expected rotation ($[\alpha]_D^{25°}$ + 36°) equal and opposite to that of (−)-**4b**. At no time was the enantiomer [(+)-**4c**] observed under acidic conditions. Further evidence for the epimerization at C-1 of **4b** under acidic conditions was obtained on isolation of intermediates **18** and **19** from the process (7% yield). Both the methyl ether (**18**) and olefin (**19**) were minor products obtained from the acid-promoted conversion of (+)-**5b** into (−)-**4b**, as illustrated in Scheme VI.

Scheme VI

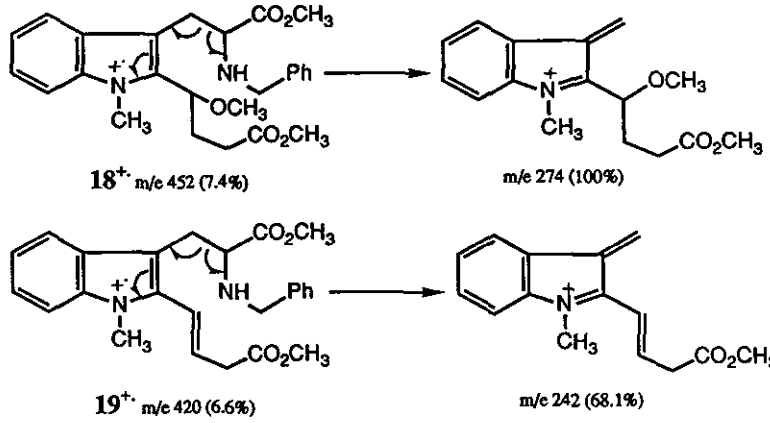


The structures of the methyl ether (**18**) and the olefin (**19**) were deduced from 2D-COSY nmr and mass spectroscopy. The origin of the key fragment ions for both **18** and **19** in the mass spectrometer is depicted in Scheme VII. When **18** and **19** were heated in methanolic hydrogen chloride (1%), analogous to the conditions for conversion of (+)-**5b** into (−)-**4b** , the *trans* isomer (**4b**) was obtained in 75% yield with an optical rotation of -36.6° (>98% ee). No racemization had occurred in the process nor was any of the *cis* diastereomer (**5b**) observed in the reaction mixture (tlc). Clearly, the *trans* isomer (**4b**) is the thermodynamically more stable diastereomer, in large part due to A-strain[21] between the N_a-alkyl function and the substituent at C-1, as reported earlier.[18]

The origin of intermediates (**18**) and (**19**) and the stereospecificity in conversion of **5b** into **4b** can be understood by examination of the intermediates depicted in Scheme VI. In methanolic hydrogen chloride the N_b-nitrogen atom of **5b** is protonated and undergoes ring scission across the C(1)-N(2) bond to generate an ammonium ion represented here by contributors (**20a**) and (**20b**). Bond rotation in **20a** would provide **20b** which undergoes cyclization to provide the *trans* diastereomer [(−)-**4b**]. Capture of the carbocation (**20**) with

methanol or loss of a proton would generate (from **20**) the methyl ether (**18**) and the olefin (**19**), respectively. The driving force for ring scission in (+)-**5b** is relief of the 1,3-diaxial interactions in the preferred conformer [**5b**, (A)] and/or relief of $A^{1,2}$-strain[21] in conformer [**5b**, (B)].

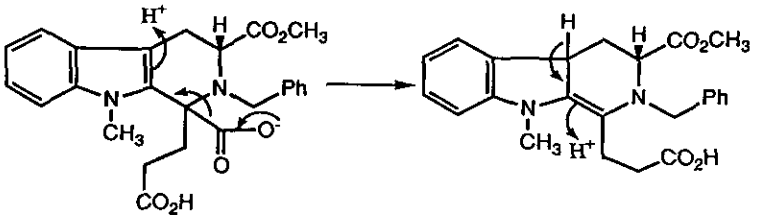
Scheme VII



Although it was surprising initially that **5b** (A) was the preferred conformer in solution, data from the solid state[6a] combined with high resolution proton and carbon-13 nmr spectroscopy supported this observation (see reference 20 for details). The enantiospecific conversion of (1R, 3R)-(+)-*cis* **5b** into (1S,3R)-(−)-*trans* **4b** in methanolic hydrogen chloride has far reaching implications in the indole alkaloid area for generation of chiral intermediate (**20**) *via* any synthetic route will result in the stereospecific generation of the *trans* diastereomer [(−)-**4b**]. Moreover, the facile ring-cleavage across the C(1)-N(2) bond was also employed in the isomerization of reserpine into isoreserpine and permitted the preparation of isoreserpine on multigram scale.[22] Brossi observed the racemization of optically active 1-substituted 1,2,3,4-tetrahydro-ß-carbolines (Harmala alkaloids),[23] presumably, *via* a similar ring scission.

The realization that (+)-**5b** could be converted into (−)-**4b** in greater than 98% ee under mild conditions permitted the use of commercially available 2-ketoglutaric acid in place of methyl 3-formylpropionate in the optically active series. As mentioned, the *trans* stereoselectivity on heating **14** and 2-ketoglutaric acid in refluxing benzene was only 3:2, presumably, because both intermediates (**21**) and (**22**) are involved in the process (Scheme VIII).

Scheme VIII



21 22

The origin of the *cis* and *trans* diastereomers stems from protonation of **22**, rather than from stereocontrol in the Pictet-Spengler reaction. However, execution of the Pictet-Spengler reaction of **14** and 2-ketoglutaric acid in refluxing benzene, followed by treatment in hot methanolic hydrogen chloride (1%), gave the desired (−)-**4b** in >98% ee. Moreover, the condensation of **14** and 2-ketoglutaric acid can be carried out under aqueous acidic conditions to provide (−)-**4b** (>98% ee) directly; albeit, the yield is slightly lower.[24]

Since complete 1,3-transfer of chirality in the Pictet-Spengler reaction had been achieved, the chemical behavior of both **4b** and **5b** was examined under alkaline conditions. The enantiospecific synthesis of the natural antipode (**1b**) of the tetracyclic ketone from D-(+)-tryptophan requires setting the correct chirality at C-1 of **1b** (1,3-transfer of chirality) followed by inversion of the chiral center which remains at C-3. This strategy is based on the stereospecific synthesis of *trans*-1,3-disubstituted ß-carbolines[11,12,18] rather than the less attractive stereoselective synthesis of the *cis* diastereomer.[10c,17a,b] Yoneda had observed that *cis*-(±)-**5c** was converted into the *trans* diastereomer [(±)-**4c**] under conditions of the Dieckmann condensation.[6a] However, the site of epimerization was not rigorously defined since racemic material was employed. Moreover, in a related system, Bailey had reported ring-opening of a 1,3-disubstituted 1,2,3,4-tetrahydro-ß-carboline under alkaline conditions *via* scission across the C(1)-N(2) bond.[23,25] In order to rigorously define the site of epimerization, the *cis* diastereomer [(+)-**5b**] was treated with 2.1 equivalents of sodium hydride in refluxing toluene in the presence of a small amount (1 eq.) of methanol.[6a,20,26] After three hours the reaction was worked up to provide a 78% yield of the *trans* diastereomer [(+)-**4c**]. The optical rotation of which ($[\alpha]_D^{25°}$ + 36.8°) was equal and opposite to (−)-**4b**. The epimerization had occurred only at C-3, moreover, this established that under acidic or alkaline conditions the *trans* diastereomer (**4**) is unequivocally the thermodynamically more stable isomer of the two.[12,18] When the *trans* diastereomer [(−)-**4b**], however,

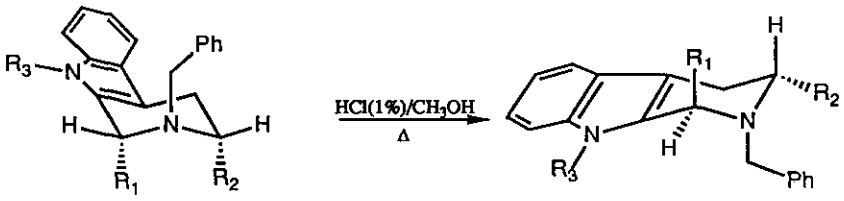
was subjected to the Dieckmann reaction under exactly the same conditions (2.1 eq. NaH, toluene, CH_3OH, Δ, 3 h), the tetracyclic Dieckmann ß-keto ester [(−)-**23**] was isolated in 86% yield. The optical rotation of this enantiomer (**23**) was -161.9° and the material was >98% ee. The failure of the *cis* diastereomer [(+)-**5b**] to undergo the Dieckmann reaction was not unexpected, since Yoneda had been unable to effect cyclization of this diastereomer in the racemic series.[6a] In this regard, when the amount of base was increased to 3.2 equivalents and the reaction held at reflux for 12 hours (+)-**5b** could be converted into the ß-keto ester [(+)-**24**, $[\alpha]_D^{25°}$ + 159.3°] in 82% yield (>98% ee), **24** is the antipode of (−)-**23**. If the equivalents of sodium hydride were increased to 4.2 and that of methanol to 4, the rate of cyclization of *cis*-(+)-**5b** to (+)-**24** could be effected in 3.5 hours (see Experimental for details).

This process constituted the first time the *cis* diastereomer [(+)-**5b**] had been converted into the (+)-keto ester (**24**) consistent with the earlier report of Yoneda[6] for this required excess sodium hydride and methanol to effect the reaction. Recently, however, Magnus *et al.* reported [17a] that the *cis* diester [(+)-**25**] in the N_a-benzyl, N_b-benzyl series cyclized to the ß-keto ester [(+)-**27**] at a much faster rate than the corresponding *trans* isomer [(−)-**26**] cyclized to the antipode [(−)-**28**]. These authors went on to infer that the *cis* diastereomer [(+)-**25**] was thermodynamically more stable than the *trans* isomer [(−)-**26**].[17b]

Since both these results were in direct contrast to those which we had observed in the N_a-methyl, N_b-benzyl series, the reactions in both series were examined. The (+)-*cis*-N_a-benzyl diastereomer [(+)-**25**] and the corresponding (−)-*trans* isomer (**26**) were prepared according to the method of Zhang *et al.*,[12] as described by Magnus.[17]

When (+)-**25** was heated in methanolic hydrogen chloride (1%), it was completely converted (>98% ee) into the (−)-*trans* isomer (**26**). Treatment of (−)-**26** under these conditions returned (−)-**26** unchanged. Furthermore, heating the (+)-*cis* diastereomer (**25**) for one hour, under conditions of the Dieckmann reaction, furnished the (+)-antipode of the *trans* diastereomer (+)-**26** (>98% ee).

Scheme IX



(+)-**5b**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3, R_3=CH_3

(+)-**25**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3, R_3=CH_2Ph

(-)-**4b**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3, R_3=CH_3

(-)-**26**, R_1=$CH_2CH_2CO_2CH_3$ R_2=CO_2CH_3, R_3=CH_2Ph

Clearly, under both acidic or alkaline conditions, the *trans* diastereomer is the more stable diastereomer, thermodynamically.[12,26] This is analogous to the observations reported in the N_a-methyl case.[12] In addition, the equilibration of (+)-**25** into (−)-**26** demonstrates that the stereospecific formation of N_a-benzyl tetracyclic ketone [(−)-**27**] can be achieved negating the need for separation of the two diastereomers.[17a,25] This provides an improved route to koumine[17b] and geissoschizine,[27] as well as the *Alstonia* alkaloids.

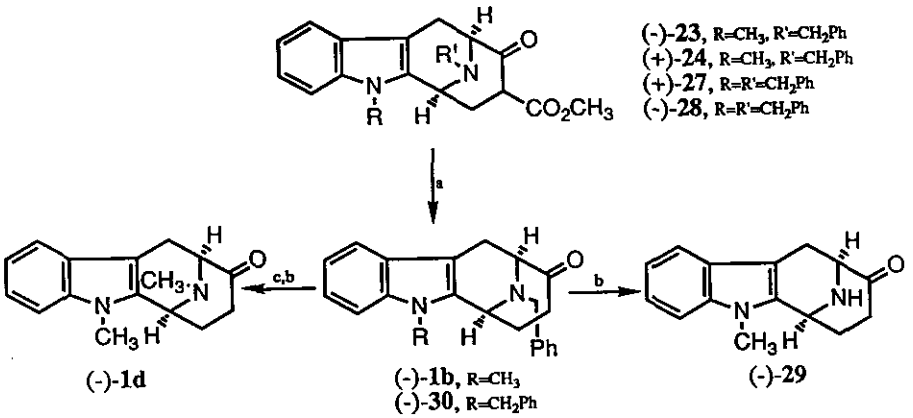
Examination of the results of the Dieckmann reaction in the laboratories of Yoneda,[6] Magnus[17a] and ourselves[12,26] indicated that the rate of cyclization of *cis* or *trans* diastereomers to ß-keto ester depended to some degree on the amount of methanol in the reaction mixture. For this reason the work of Zhang and of Magnus *et al.*[17b] was reinvestigated under the conditions originally employed by Zhang (1 eq. of CH_3OH).[12,26]

When the *trans*(−)-**4b** diastereomer was heated in toluene with 2.1 equivalents of sodium hydride and one equivalent of methanol, cyclization to the ß-keto ester [(−)-**23**] was complete in two hours. When the analogous reaction was run with the *cis* (+)-**5b** diastereomer, the process took three hours to go to completion (tlc/nmr) to provide (+)-**24**. Moreover, when an equimolar mixture of *trans*-(−)-**4b** and *cis*-(+)-**5b** isomers were heated under the same conditions [2.1 eq. NaH, 1 eq. CH_3OH] both diastereomers cyclized at the same rate (see Experimental for details), indicative of the conversion of *cis* (+)-**5b** into (+)-**4c** (*trans* antipode) in the first thirty minutes of heating. As reported earlier,[12,26] the majority of the *cis*-diastereomer had isomerized to the *trans* isomer, which requires re-epimerization to a *cis*-fused system before cyclization.[26] The formation of the (±)-ß-keto ester [**23**/**24**] under these conditions is complete (tlc/nmr) in three hours.

Presumably, the rate of epimerization of *cis*-(+)-**5b** to *trans*-(−)-**4b** is faster than the Dieckmann cyclization of (+)-**5b** to (+)-**24**. This results in the slightly longer reaction times observed for Dieckmann cyclization of **5b** as compared to **4b**. This cyclization, as mentioned, is sensitive to the amount of methanol employed in the process, for both diastereomers provide the ß-ketoester at the same rate when two or more equivalents of methanol were employed. At no time did we observe the Dieckmann cyclization of the *cis* diastereomer [(+)-**5b**] go to completion faster than the *trans*-(−)-isomer (**4b**) underwent the process, in contrast to the results reported by Magnus *et al.* in the N_a-benzyl, N_b-benzyl series.[17a,b]

Attention now turned to comparison of the rates of the Dieckmann cyclization of the *cis* diastereomer (+)-**25** and the *trans* (−)-**26** isomer in the N_a-benzyl, N_b-benzyl series. When the (−)-*trans*-N_a-benzyl diester (**26**) was

Scheme X



(a) HOAc/HCl, Δ; (b) Pd/C, H_2, CH_3CH_2OH; (c) $CH_3SO_3CF_3$, CH_2Cl_2, Δ

heated under the conditions of the Dieckmann reaction [1 eq. **26**, 2 eq. NaH, 1 eq. CH_3OH], analogous to the conditions of Zhang,[12,26] the cyclization was terminated after 1 3/4 hours. At this time the reaction mixture contained 4.3% of the starting *trans* diester [(−)-**26**] and 95.7% of the desired ß-keto ester [(−)-**28**] (see Experimental for details). Execution of the analogous reaction with the (+)-*cis* diester **25** resulted in 100% conversion into the ß-keto ester [(+)-**27**] after 1 3/4 hours. Although the time of completion of either cyclization was almost the same, initially 14.7% of *cis*-(+)-**26** went to ß-keto ester [(+)-**27**], while the remainder was transformed into the *trans* diester [(+)-**26**] which later was converted into ß-keto ester [(+)-**27**]. It is clear that under these conditions a small percentage of the *cis* diastereomer does go to ß-keto ester faster

than the *trans* diastereomer undergoes cyclization, although the overall reaction times are about the same. The full details of this analysis are described in the Experimental Section.

In regard to the reaction time in the presence of two equivalents of methanol, equimolar amounts of the (+)-*cis*-(**25**) and (−)-*trans*-(**26**) diastereomers were admixed and subjected to the Dieckmann cyclization (2 eq. NaH, 2 eq. CH_3OH). The reaction progress was monitored by high resolution nmr *via* a chiral shift reagent. After thirty minutes the (+)-*cis*-diester (**25**) had completely epimerized to the (+)-*trans* diastereomer (**26**) and the racemic mixture which resulted provided ß-keto esters [(+)-**27**] and [(−)-**28**] necessarily at the same rate. Formation of the (±)-ß-keto ester was complete after one hour (see Experimental Section). However, when the analogous reaction with (+)-**25** and (−)-**26** was carried out (2 eq. NaH) in the presence of one equivalent of methanol, a small amount of the *cis*-(+)-**25** could be shown to undergo the Dieckmann reaction prior to cyclization of the *trans* (−)-**26** isomer. As clearly shown in the Experimental Section (hr-nmr, chiral shift reagent[17b]), at time equal to fifteen minutes 10.2% of *cis*-(+)-**25** had cyclized to (+)-**27**, while only 6.5% of the *trans*-(−) diastereomer (**26**) had reacted to provide (−)-**28**. At time equal to thirty minutes the ratio of (−)-**28**:(+)-**27** was 43:57, while after one hour this ratio was 50:50. The Dieckmann cyclization itself was complete after heating for one hour and thirty minutes.

Although a small percentage of the *cis*-isomer underwent the Dieckmann reaction directly, the majority epimerized at C-3 to provide the corresponding *trans* diastereomer. This diastereomer then underwent a re-epimerization as reported earlier from our laboratory,[26] to provide a *cis*-fused intermediate which underwent the Dieckmann cyclization. Although Magnus *et al.*[17b] earlier reported that the *cis* diastereomer cyclized to the ß-keto ester much faster than the corresponding *trans* diastereomer did,[17b] the results presented here with equimolar amounts of (+)-**25**/(−)-**26** clearly do not substantiate that claim.[17b] The earlier report by Magnus[17b] described the rate of cyclization of (+)-**25** and (−)-**26**; however, these reactions were carried out on entirely different scales. Since the rate of the cyclization is dependent upon the amount of methanol present, perhaps, reactions on small scale provide misleading rates.

There can be no doubt as to the validity of the present results under the conditions of Zhang (1 eq. of CH_3OH). Although Magnus has claimed that the *cis* diastereomer in this series undergoes the cyclization at a much faster rate (4 h *vs.* >13 h[17b]), it is clear that both diastereomers undergo the cyclization at about the same rate and is highly dependent on the amount of methanol present.

The ß-keto ester [(−)-**23**] was hydrolyzed and decarboxylated under acidic conditions[5] to provide the (6S,10S)-(−)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole (**1b**) ($[\alpha]_D^{22}$ - 203.4°) in 91% yield. Catalytic debenzylation of **1b** provided the N_b-H analog (−)-**29** ($[\alpha]_D^{22}$ - 116.8°) in excellent yield, as anticipated (Scheme X). Attempts to alkylate **29** with methyl iodide even in refluxing benzene or toluene were unsuccessful. The synthesis of the desired N_b-methyl tetracyclic ketone [(−)-**1d**] was accomplished by methylation of **1b** with methyl triflate, followed by removal of the benzyl group *via* catalytic hydrogenation (Pd/C) in 87% yield (from **1b**).

The maintenance of chirality at C-3 *via* use of the N_b-benzyl group has been demonstrated in the Pictet-Spengler reaction of N_b-benzyl tryptophan methyl esters with **15** in refluxing benzene. Although the kinetic ratio of *trans* (**4b**)/*cis* (**5b**) isomers (72:28) was realized under these conditions, execution of the sequence under conditions of thermodynamic control (H^+/Δ) provided the desired *trans* isomer (**4b**) in stereospecific fashion. The isolation of **18** and **19** in a trapping experiment indicates that the isomerization of the *cis* isomer into the *trans* diastereomer occurs by ring-scission of the C(1)-N(2) bond, followed by recyclization.

The stereospecific, enantiospecific synthesis of tetracyclic templates [(−)-**1b** and (−)-**1d**] *via* the methods described herein has far reaching implications in regard to the synthesis of macroline/sarpagine alkaloids. The stereospecificity of the 1,3-transfer of chirality employed in the synthesis of *trans*-**4b** has been employed in the total synthesis (*via* **1b**) of (−)-alstonerine (**3**).[4] Moreover, the racemic (±)-**1c** has been converted into (±)-suaveoline (**2**) and N_b-methylsuaveoline.[3] The enantiospecific conversion of the N_b-benzyl *cis* diastereomer (**5b**) into the desired **4b** in methanolic hydrogen chloride followed by Dieckmann cyclization to provide (−)-**1b** (>98% ee) alleviates the need to separate the *cis* and *trans* diastereomers available from the

Pictet-Spengler reaction. In addition, the *trans* stereospecificity developed here provides enantio-flexibility for D-(+)-tryptophan will provide (−)-**1b**, while L-(−)-tryptophan will generate the antipode (+)-**1b** (see **1c**), enantiospecifically. The synthesis of (±)-**1b** has been accomplished in seven steps in an overall yield of 53%,[3] while the preparation of the optically active isomer [(−)-**1b**] has been executed on 100 gram scale. Further work is in progress to employ these templates for the synthesis of optically active dimeric indole alkaloids in the *Alstonia* series.

EXPERIMENTAL

Microanalyses were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are reported uncorrected. Proton and carbon nmr spectra were recorded on a Bruker 250 MHz spectrometer or a GE 500 MHz instrument. Infrared spectra were recorded on a Mattson Polaris IR-10400 spectrometer or a Nicolet MX-1 FT-ir spectrophotometer. Mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985B GC-mass spectrophotometer.

All chemicals were purchased from Aldrich Chemical Company unless otherwise noted. The analytical tlc plates used were E. Merck Brinkmann uv active silica gel (Kieselgel 60 F254 on plastic). The tlc plates were visualized under uv light or developed with spray reagents. Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid, or an aqueous solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid. "Chromatography" refers to flash chromatography[28] using 230-400 mesh 60 A silica gel, grade 60 (EM reagent). Methanol was dried by distillation over magnesium metal. Tetrahydrofuran (Baker reagent), benzene (EM reagent) and toluene (EM reagent) were dried by distillation from sodium-benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then distilled over P_2O_5. Dimethyl sulfoxide was dried by distillation under vacuum over CaH_2. Triethylamine and diisopropylamine were dried by distillation over KOH.

D-(+)-N_a-Methyltryptophan 12: A 5 l three neck flask equipped with a mechanical stirrer and dry ice condenser was cooled in a dry ice/acetone bath and filled with liquid ammonia (4 l). Metallic sodium (23 g, 1.0 mol) and $FeCl_3$ (0.65 g, 4 mmol) were added with stirring. After one hour, D-(+)-tryptophan [11 (100 g, 0.49 mol)] was added in one portion to the mixture and the slurry was stirred for 10 min. This treatment was followed by dropwise addition of methyl iodide (92.2 g, 0.65 mol) over a 10 min period, after which stirring was continued for an additional 1 h. The cooling bath was removed and the ammonia allowed to evaporate in the hood for 12 h. The residue which remained was dissolved in hot water (400 ml, 65°C), filtered, and the pH of the filtrate was adjusted to 5 with glacial acetic acid. Precipitation of N_a-methyltryptophan (12) occurred upon cooling. The crude material was crystallized from 68% ethanol-H_2O to provide D-(+)-N_a-methyl tryptophan (98 g, 92%): mp 242-244°C; $[\alpha]_D^{22}$ + 12.4° (c 0.2 in HOAc); ^1H nmr (CD_3COOD) δ 2.03 (s, 3H), 3.47 (m, 1H), 3.79 (s, 3H), 3.80 (m, 1H), 4.45 (m, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.25 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H); mass spectrum (70 ev) m/z 218 (M^+, 4.9); 144 (100). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.06; H, 6.42; N, 12.84. Found: C, 65.59; H 6.44; N, 12.80.

D-(−)-N_a-Methyltryptophan methyl ester HCl 13: D-(+)-N_a-methyltryptophan [12 (95 g)] was dissolved in a freshly saturated solution of methanolic hydrogen chloride (850 ml). The mixture which resulted was heated to reflux for 3.5 h and then allowed to cool to room temperature. The crystalline product which formed upon cooling was collected by filtration and washed with cold ether to provide D-(−)-N_a-methyltryptophan methyl ester HCl [13 (97.6 g, 81%)]: mp 218-219°C; $[\alpha]_D^{22}$ - 17.2°C (c 0.5 in MeOH); ir (KBr) 1740 cm^{-1}; ^1H nmr ($CDCl_3$, free base) δ 1.53 (s, 2H), 3.05 (dd, J = 15 and 6 Hz, 1H), 3.25 (dd, J = 15 and 4 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 3.80 (dd, J = 6 and 4 Hz, 1H), 6.90 (s, 1H), 7.10 (t, J = 8.4 Hz, 1H), 7.20 (t, J = 8.3 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H). Anal. Calcd for $C_{13}H_{17}N_2O_2Cl$: C, 58.05; H, 6.38, N, 10.43. Found: C, 58.20; H, 6.35; N, 10.17.

D-(+)-N_a-Methyl-N_b-benzyltryptophan methyl ester 14: To a solution of D-(−)-N_a-methyltryptophan methyl ester [13 (84.5 g, 0.36 mol)], which was prepared by treatment of the corresponding HCl salt with aq. NH_4OH

(10 %) followed by extraction with CH_2Cl_2, in methanol (500 ml), was added benzaldehyde (42.0 g, 0.40 mol). The solution which resulted was stirred for 2 h at 22°C. The mixture was then cooled in an ice-salt bath to -5°C for 1 h and sodium borohydride (7.0 g, 0.18 mol) was added portionwise over a period of 0.5 h. The solution was allowed to stir for 3 h followed by addition of ice water (7.5 ml), after which the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (1000 ml) and washed with brine (2 x 200 ml). The organic layer was dried (K_2CO_3) and the solvent was removed under reduced pressure to give the free base **14** (90.4 g, 78%). Pure **14** was obtained by flash (wash) column chromatography: $[\alpha]_D^{22}$ + 8.6° (c 1.0 in $CHCl_3$); ir (film) 1725 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.10 (s, 1H), 3.15 (m, 2H), 3.65 (s, 3H), 3.75 (s, 3H), 3.80 (m, 3H), 6.90 (s, 1H), 7.10 (t, J = 8.2 Hz, 1H), 7.25 (m, 7H), 7.55 (d, J = 8.2 Hz, 1H); mass spectrum (CI, CH_4) m/z 323 (M+1, 100). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.82; H, 6.65; N, 8.51.

Methyl-3-formyl-propionate 15: The solution of γ-butyrolactone [**17** (86 g, 1 mol)] and concentrated sulfuric acid (2 g) in methanol (500 ml) was stirred at 22°C for 6 h, after which calcium carbonate (15 g) was added and the mixture which resulted was stirred for an additional 2 h. The reaction mixture was filtered and the solvent was removed under reduced pressure at a temperature of less than 10°C to provide 4-hydroxybutyrate (92 g, 78%). The methanol free residue (55 g, 0.47 mol) was dissolved in dry dichloromethane (150 ml), and the solution which resulted was added to a mixture of pyridinium dichromate (265 g, 0.70 mol) in dry dichloromethane (350 ml). The mixture which resulted was stirred at 22°C for 8 h, and then diluted with dichloromethane (300 ml). The slurry was filtered through a Florisil column to afford the methyl 3-formylpropionate (**15**) which was identical to an authentic sample prepared by the method of Yoneda[5] (38.2 g, 70%).

(1S, 3R)-(−) and (1R, 3R)-(+)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles 4b and 5b: To a solution of D-(+)-N_a-methyl-N_b-benzyltryptophan methyl ester [**14** (90.4 g, 0.31 mol)] in refluxing benzene (500 ml) was added methyl 3-formylpropionate (**15**) dropwise over a period of 0.5 h (44 g, 0.37 mol). The mixture was held at reflux for 10 h with continuous

removal of water *via* a Dean-Stark trap, after which the solvent was removed under reduced pressure to provide an oil. A portion (200 mg) of the crude mixture was employed to determine the ratio of *trans* and *cis* isomers by ^{13}C Nmr spectroscopy[10c] (*trans/cis* = 72/28). The remainder of the material was chromatographed on silica gel (eluent, n-hexane-ethyl acetate, 10:1). The *trans* isomer [(−)-**4b**] had a higher R_f value and was eluted first from the column. It was crystallized from methanol (74.9 g, 58%). The more polar *cis*-(+)-**5b** diastereomer was then obtained and crystallized from ether (30.1 g, 23%).

Trans **4b**: mp 119-120°C [lit.,[6a] (±) mp 145-146°C]; $[\alpha]_D^{22}$ - 36.8° (c 0.95 in CH_3Cl); ir (KBr) 1735 cm^{-1}; ^{13}C Nmr ($CDCl_3$) δ 20.25, 27.90, 29.60, 29.71, 51.26, 52.00, 52.79, 53.32, 56.12, 106.29, 108.90, 118.12, 119.11, 121.32, 126.52, 126.96, 128.14, 129.29, 135.67, 137.46, 139.25, 173.34, 173.87; ^1H Nmr ($CDCl_3$) δ 1.85-2.00 (m, 2H), 2.38 (dt, J = 5.6 and 17.5 Hz, 1H), 2.61 (ddd, J = 5.6, 9.6 and 17.5 Hz, 1H), 3.05 (dd, J = 5.3 and 15.8 Hz, 1H), 3.12 (dd, J = 11.0 and 15.8 Hz, 1H), 3.39-3.81 (AB_q, J = 13.1 Hz, 2H), 3.50 (s, 3H), 3.65 (s, 3H), 3.51 (dd, J = 5.2 and 15.7 Hz, 1H), 3.84 (s, 3H), 4.10 (dd, J = 5.5 and 11.0 Hz, 1H), 7.12-7.40 (m, 8H), 7.60 (d, J = 8 Hz, 1H); mass spectrum (CI, CH_4) m/z 421 (M+1, 100). Anal. Calcd for $C_{25}H_{28}N_{24}$: C, 71.40; H, 6.71; N, 6.67. Found: C, 71.61; H, 6.64; N, 6.57.

Cis-**5b**: mp 115-116°C; $[\alpha]_D^{22}$ + 20° (c 0.96 in CH_3Cl); ir (KBr) 1740 cm^{-1}; ^{13}C Nmr ($CDCl_3$) δ 17.95, 29.10, 29.66, 29.66, 51.30, 51.83, 54.09, 57.44, 61.16, 104.70, 108.79, 118.25, 118.93, 121.28, 126.58, 127.31, 128.36, 129.07, 134.65, 137.49, 138.93, 174.07, 174.25; ^1H Nmr ($CDCl_3$) δ 1.50 (m, 1H), 1.95 (m, 1H), 2.51 (dt, J = 6, 18.0 Hz, 1H), 2.81 (ddd, J = 6, 9.8 and 18.0 Hz, 1H), 3.05 (dd, J = 6.3 and 18.6 Hz, 1H), 3.37 (dd, J = 2.1 and 18.6 Hz, 1H), 3.56 (s, 3H), 3.65 (s, 3H), 3.69 (s, 3H), 3.75 (d, J = 9.5 Hz, 1H), 3.89 (s, 2H), 3.92 (dd, J = 2.1 and 6.3 Hz, 1H), 7.10-7.48 (m, 8H), 7.58 (d, J = 9.4 Hz, 1H); mass spectrum (CI, CH_4) m/z 421 (M+1, 100). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.40; H, 6.71; N, 6.67. Found: C, 71.37; H, 6.54; N, 6.77

Synthesis of (−)-4b and (+)-5b by an Alternative Method: D-(+)-N_a-methyl-N_b-benzyltryptophan [14 (6.6 g, 0.02 mol)] was dissolved in benzene (400 ml) and the solution which resulted was heated to reflux. A solution of 2-oxoglutaric acid (3.3 g, 0.02 mol) in dry dioxane (30 ml) was added dropwise over a 2 h period.

The reaction mixture was held at reflux for 8 h with continuous removal of water *via* a Dean-Stark trap. The solvent was removed under reduced pressure and the residue was dissolved in CH_3OH-CH_2Cl_2 (1/1, 500 ml) and then esterified with ethereal diazomethane at room temperature (4 h). The solvent was removed under reduced pressure to provide a mixture of (−)-**4b** (3.5 g, 49%) and (+)-**5b** (2.5 g, 35%) which were spectrometrically identical with the authentic samples reported above.

The Stability of (−)-4b and (+)-5b in Refluxing Benzene: The *trans* diastereomer [(−)-**4b** (21 mg)] was dissolved in benzene (1 ml) and heated to reflux for 20 h under nitrogen. The solvent was removed under reduced pressure to provide a crude solid which was further purified by crystallization from methanol. The *trans* isomer [(−)-**4b** (17.2 mg)] was obtained and was spectrometrically identical with authentic (−)-**4b** including the optical rotation. The *cis* isomer [(+)-**5b** (21 mg)] was treated similarly and was returned unchanged (16.9 mg). The ^1H nmr, ir, ms, mp and [α] value of **5b** were identical to those of a sample of authentic (+)-**5b**.

Acid Catalyzed Epimerization of (1R, 3R)-(+)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (+)-5b (*cis* isomer) into (1S, 3R)-(−)-4b (*trans* isomer): The *cis* isomer [(+)-**5b** (21 mg)] was dissolved in a solution of methanol (0.23 ml) containing 1% HCl (w/w). The mixture was held at reflux for 6 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue was brought to pH 9 with aqueous ammonia (10%), after which the solution was extracted with $CHCl_3$ (4 x 15 ml). The combined organic layers were dried (K_2CO_3) and the solvent was removed under reduced pressure. Pure (−)-**4b** (15.2 mg, 76%) was obtained after crystallization. This material was spectrometrically identical with an authentic sample of (−)-**4b** including the optical rotation, $[\alpha]_D^{22}$ - 36.6° (c 1.0 in $CHCl_3$). The analogous procedure was employed to scale up the conversion of (+)-**5b** (28 g) into pure (−)-**4b** (22.7 g, 81%) in refluxing methanol (300 ml) containing 1% HCl (w/w). The time of heating was 6 h. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.40; H, 6.71; N, 6.67. Found: C, 70.95; H, 6.55; N, 7.02.

Isolation of 1-Methyl-2-(3-methoxycarbonylpropan-1-methoxy-1-yl)-3-(R)-[1-(benzylamine)-1-(methoxycarbonylethan-2-yl)]indole (18) and 1-Methyl-2-(E)-(3-methoxycarbonylpropyl-1-en-1-yl)-3-(R)-[1-(benzylamine)-1-(methoxycarbonylethan-2-yl)]indole 19: The *cis* isomer [(+)-**5b** (84 mg)] was dissolved in methanol (1 ml) containing 1% HCl (w/w). The mixture was heated to reflux for 1.5 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue was brought to pH 9 with aqueous ammonia (10%), and then extracted with chloroform (4 x 30 ml). The combined organic layers were dried (K_2CO_3) and the solvent was removed under reduced pressure. These two intermediates [**18** and **19** (8.7 mg)] were separated from the *cis* (+)-**5b** (53.3 mg) and the *trans* (−)-**4b** (11.5 mg) diastereomers by flash chromatography. **18**: ^{1}H Nmr ($CDCl_3$) δ 1.89 (m, 1H), 2.05 (m, 1H), 2.30 (m, 1H), 2.40 (m, 1H), 3.05 (s, 3H), 3.57 (s, 3H), 3.64-3.70 (m, 2H), 3.70 (s, 3H), 3.85-3.89 (m, 1H), 3.80-3.89 (m, 2H), 4.55 (dt, J = 5 and 9 Hz 1H), 7.00-7.50 (m, 9H); ms (EI, 15 ev) m/z (relative intensity) 452 (M^+, 7.4), 274 (M^+ - 178, 100) **19**: ^{1}H Nmr ($CDCl_3$) δ 3.29 (dd, J = 8.5 and 18 Hz, 2H), 3.52 (s, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 3.40-3.70 (m, 5H), 6.12 (dd, J = 8.5 and 17 Hz, 1H), 6.57 (d, J = 17 Hz, 1H), 7.00-7.50 (m, 9H); ms (EI, 15 ev) m/z (relative intensity) 420 (M^+, 6.6), 242 (M^+ - 178, 68.1). When **18** and **19** were heated in refluxing methanol containing 1% HCl, the *trans* isomer [(−)-**4b** (5.6 mg)] was isolated and was found to be identical (mp, ms, ir, ^{1}H Nmr and $[\alpha]_D$ with an authentic sample of (−)-**4b** prepared as described above.

(6S, 10S)-(−)-Methyl-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloot[*b*]indole-8-carboxylate (−)-23: A mixture of the *trans* diester [(−)-**4b** (42.0 g, 0.10 mol)] and sodium hydride (5.10 g, 0.21 mol) in dry toluene (650 ml) was heated to reflux under argon after which a solution of dry methanol (4 ml. 0.01 mol) in toluene (16 ml) was added dropwise over 1 h. The mixture was held at reflux for an additional 2 h. Glacial acetic acid (15 ml) was added to the solution, followed by neutralization with a saturated solution of aqueous $NaHCO_3$. The mixture was extracted with toluene (3 x 400 ml) and the combined organic extracts were washed with brine (2 x 200 ml) and dried (K_2CO_3). Removal of the solvent under reduced pressure followed by crystallization of the residue from ethyl acetate provided the ß-keto ester [(−)-**23** (35.2 g, 90.7%)]: mp 149-150°C; $[\alpha]_D^{22}$ = -160.0° (c 1.0, $CHCl_3$); ir (KBr) 1670, 1630 $^{cm-1}$; ^{1}H Nmr ($CDCl_3$) δ 2.29 (d, J = 15.5 Hz, 1H), 2.90 (dd, J = 15.5 and 4.5 Hz, 1H), 2.95 (d, J = 15.8 Hz, 1H), 3.10 (dd,

J = 15.8 and 6.8 Hz, 1H), 3.55 (s, 3H), 3.69 (s, 3H), 3.74 (d, J = 6.8 Hz, 1H), 3.68 (AB_q, J = 11 Hz, 2H), 4.12 (d, J = 4.5 Hz, 1H), 7.05-7.39 (m, 8H), 7.50 (d, J = 8.2 Hz, 1H), 10.89 (s, 1H); ms (CI, CH_4) m/z (relative intensity) 389 (M+1, 100). Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.30; H, 6.23; N, 7.22. Found: C, 74.19; H, 6.23; N, 7.35.

Epimerization of the *cis*-(1R, 3R)-(+)-2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3.4-*b*]indole (+)-5b into the *trans* Diastereomer (1R, 3S)-(+)-4c under Alkaline Conditions: A mixture of the *cis* diester [(+)-**5b** (42 mg, 0.1 mmol)] and sodium hydride (5.1 mg, 0.21 mmol) in dry toluene (0.65 ml) was heated to reflux under argon, after which a solution (0.02 ml) of dry methanol-toluene (1/4, v/v, 1 eq. CH_3OH) was added dropwise over 1 h. The mixture was held at reflux for an additional 2 h. Glacial acetic acid (0.015 ml) was added to the solution, followed by neutralization with saturated aqueous $NaHCO_3$. The mixture was extracted with toluene (3 x 20 ml) and the combined organic extracts were washed with brine (2 x 10 ml) and dried (K_2CO_3). Removal of the solvent under reduced pressure followed by crystallization of the residue from methanol provided the *trans* diastereomer [(+)-**4c** (29.8 mg, 71%)] which was indistinguishable from (−)-**4b** spectrometrically although the optical rotations were opposite in sign. (+)-**4c**: $[\alpha]_D^{22}$ = + 36.8° (c 0.96 in $CHCl_3$).

(6R, 10R)-(+)-Methyl-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imine-5*H*-cyclooct[*b*]indole-8-carboxylate [(+)-24]: A mixture of the *cis* diester [(+)-**5b** (42 mg, 0.1 mmol)] and sodium hydride (7.7 mg, 0.32 mmol) in dry toluene (0.65 ml) was heated to reflux after which a solution (0.02 ml, 0.16 mmol CH_3OH) of dry methanol-toluene (1/2, v/v) was added over a 1 h period. The mixture was held at reflux for an additional 11 h. Glacial acetic acid (0.015 ml) was added to the solution followed by neutralization with saturated aqueous $NaHCO_3$. The mixture was extracted with toluene (3 x 20 ml) and the combined organic extracts were washed with brine (2 x 10 ml) and dried (K_2CO_3). Removal of the solvent under reduced pressure followed by crystallization of the residue from ethyl acetate provided the ß-keto ester [(+)-**24** (31.8 mg, 82%)] which was indistinguishable from (−)-**23** spectrometrically (mp 148-150°C); however, the optical rotation was opposite in sign: $[\alpha]_D^{22}$ + 159.7° (c 1.04, $CHCl_3$). When this reaction was repeated and

quenched with water after being held for one hour at reflux, the *trans* isomer [(+)-**4c**] was obtained as the major product (α_D, tlc). Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.30; H, 6.23; N, 7.22. Found: C, 73.94; H, 6.31; N, 7.01.

The Dieckmann cyclization of the *trans* diester (**4b**) was also carried out at this scale and under these conditions. It was complete within 3h.

Rapid Cyclization of *cis*-(+)-5b to (+)-24 Employing Excess NaH (4.2 eq.) and Methanol (4.0 eq.): A mixture of the *cis* diester [(+)-**5b** (420 mg, 1 mmol)] and sodium hydride (102 mg, 4.2 mmol) in dry toluene (6.5 ml) was heated to reflux after which a solution (0.8 ml) of dry methanol-toluene (1/4, v/v, 4 mmol CH_3OH) was added over a period of 1 h. The mixture was held at reflux until the reaction was complete (additional 2.5 h). Glacial acetic acid (0.2 ml) was added to the solution followed by neutralization with saturated aqueous $NaHCO_3$. The mixture was extracted with toluene (3 x 100 ml) and the combined organic extracts were washed with brine (2 x 40 ml) and dried (K_2CO_3). Removal of the solvent under reduced pressure, followed by flash (wash) column chromatography, gave pure (+)-**24** (314 mg, 81%) which was spectrometrically identical with the authentic sample [(+)-**24**] reported above, including the optical rotation.

Comparison of the Rates of the Dieckmann Cyclization of the *trans*-(1S,3R)-(−)-4b and *cis*-(1R,3R)-(+)-5b 2-Benzyl-3-methoxycarbonyl-1-methoxycarbonylethyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles on Larger Scale: To a mixture of the *trans* diester [(−)-**4b** (1.26 g, 3.0 mmol)] and sodium hydride (153 mg, 6.4 mmol) in toluene (19.5 ml), a solution of dry methanol (3.0 mmol)-toluene (1/4, v/v, 0.6 ml) was added *via* a syringe. The mixture was stirred for 10 min at room temperature, and then heated to reflux. The reaction progress was monitored periodically by tlc. After heating at reflux for 30 min, examination of the tlc indicated the yield of ß-keto ester [(−)-**23**] was approximately 50% accompanied by the *trans* diester [(−)-**4b**]; at 1 h, 90% of the ß-keto ester [(−)-**23**] had formed leaving 10% of the *trans* diester [(−)-**4b**]; at 1.5 h, 95-98% yield of the ß-keto ester [(−)-**23**] was realized accompanied by 2-5% of the *trans* diester [(−)-**4b**]; at 2 h, 100% ß-keto ester [(−)-**23**] was observed. The reaction product [(−)-**23**] was monitored by the same chiral shift

reagent as (−)-**28** (see below). In the presence of the shift reagent, a singlet was observed in the nmr spectrum at 12.52 ppm indicating that the ß-keto ester [(−)-**23**] was optically pure.

To a mixture of the *cis* diester [(+)-**5b** (1.26 g, 3 mmol)] and sodium hydride (153 mg, 6.3 mmol) in dry toluene (19.5 ml), a solution of dry methanol (3 mmol)-toluene (1/4, v/v, 0.6 ml) was added. The mixture was stirred at room temperature for 10 min, and then heated to reflux. The reaction progress was monitored by periodically tlc. After the mixture was heated at reflux for 30 min, examination of the reaction progress by tlc indicated approximately 40% yield of the ß-keto ester [(+)-**24**] accompanied by about 60% of *trans* diester [(+)-**4c**], and a trace of the *cis* diester [(+)-**5b**]; at 1 h, a 60% yield of the ß-keto ester [(+)-**24**] was observed accompanied by 40% of *trans* diester [(+)-**4c**], no *cis* diester [(+)-**5b**] was observed by tlc at this point]. At 1.5 h approximately 75% yield of ß-keto ester [(+)-**24**] was observed with about 25% of the *trans* diester [(+)-**4c**] remaining; at 2 h 90-95% of the ß-keto ester [(+)-**24**] was observed accompanied by about 5-10% of the *trans* diester [(+)-**4c**]; at 2.5 h approximately 98% yield of the ß-keto ester was observed with about 2% of the *trans* diester [(+)−**4c**] remaining; at 3 h 100% of the ß-keto ester [(+)-**24**] was observed. The ß-keto ester was analyzed by a chiral shift reagent.[17b] A singlet was observed in the nmr spectrum at 12.59 ppm indicating the material was optically pure (see below for details).

Dieckmann Cyclization of a Mixture of the *trans*-(−)-4b and *cis*−(+)−5b Diesters with 1. 0 Equivalent of Methanol:[30] To a mixture of the *trans* diester [(−)-**4b** (630 mg, 1.5 mmol)], *cis* diester [(+)-**5b** (630 mg, 1.5 mmol)] and sodium hydride (155 mg, 6.3 mmol) in toluene (19.5 ml), a solution of dry methanol (3 mmol)-toluene (1/4, v/v, 0.6 ml) was added *via* a syringe. The mixture was stirred for 10 min at room temperature, and then heated to reflux. Aliquots of the reaction mixture were withdrawn at 30 min intervals. Chiral shift [S-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol][17b] analysis of each sample was then performed.

time	ß-keto ester	*trans* diester	*cis* diester	ratio of enantiomeric ß-ketoesters (−)-**23**/(+)-**24**
0.5 h	10%	90%	trace	1:1
1 h	50%	50%	0	1:1

time	ß-keto ester	*trans* diester	*cis* diester	ratio of enantiomeric ß-ketoesters (−)-**23**/(+)-**24**
1.5 h	90%	10%	0	1:1
2 h	95%	5%	0	1:1
2.5 h	99%	1%	0	1:1
3 h	100%	0	0	1:1

(6S, 10S)-(−)-5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (−)-1b: The ß-keto ester [(−)-**23** (60.0 g, 0.15 mol)] was heated at reflux for 5 h in a mixture of glacial acetic acid (200 ml), hydrochloric acid (300 ml, conc.) and water (80 ml). After removal of the solvent under reduced pressure, the residue was brought to pH 9 with aqueous NaOH(3N). The mixture which resulted was extracted with CH_2Cl_2 (4 x 250 ml) and the combined organic extracts were washed with saturated NH_4Cl (100 ml), brine (2 x 100 ml) and dried (K_2CO_3). The organic solution was then filtered through a short column of alumina. Removal of the solvent under reduced pressure afforded an oil which crystallized from ethyl acetate to provide the tetracyclic ketone [(−)-**1b** (45 g, 91%)]: mp 142-144°C; $[\alpha]_D^{22}$ -203.4° (c 0.50 in $CHCl_3$); ir (KBr) 1710 cm^{-1}; ^1H Nmr ($CDCl_3$) δ 1.95-2.20 (m, 2H), 2.45 (m, 2H), 2.69 (d, J = 16.2 Hz, 1H), 3.24 (dd, J = 16.2 and 6.3 Hz, 1H), 3.61 (s, 3H), 3.71 (s, 2H), 3.76 (d, J = 6.3 Hz, 1H), 4.05 (t, J = 4.0 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 7.25 (t, J = 8.2 Hz, 1H), 7.30-7.38 (m, 6H), 7.52 (d, 8.2 Hz, 1H); ms (CI, CH_4) m/z (relative intensity) 331 (M+1, 100). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.98; H, 6.75; N, 8.48.

(6S, 10S)-(−)-5-Methyl-9-oxo-H-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (−)-29: The (−)-N_b-benzyltetracyclic ketone [(−)-**1b** (1 g, 3 mmol)] was stirred under an atmosphere of hydrogen gas over Pd/C (100 mg, 10%) in a mixture of ethanol (20 ml, 95%) and HCl (0.7 ml) for 20 h. The reaction slurry was filtered through celite and the solvent was removed under reduced pressure. The residue was brought to pH 8.5 with aqueous ammonia (14%) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with brine (2 x 50 ml) and dried (K_2CO_3). Following the removal of the solvent under reduced pressure, the residue was crystallized from ethyl acetate to afford (−)-**29** (0.37 g, 51%): mp 121-123°C; $[\alpha]_D^{22}$ -116.8° (c 0.50 in $CHCl_3$). The spectral data for **29** were identical to those reported in the literature.[29]

(6S,10S)-(−)-5-Methyl-9-oxo-12-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (−)-1d: The solution of (−)-N_b-benzyltetracyclic ketone [(−)-**1b** (10.0 g, 0.03 mol)] and methyl trifluoromethyl- sulfonate (5.4 g, 0.033 mol) in dry CH_2Cl_2 (100 ml) was heated to reflux under an atmosphere of nitrogen for 8 h. The reaction mixture was diluted with CH_2Cl_2 (700 ml) and washed with saturated aqueous $NaHCO_3$ solution (2 x 100 ml), brine (100 ml) and then dried ($MgSO_4$). The residue (14.1g, 95%) was dissolved in ethanol (200 ml, 95%) and hydrogenated at 1 atm (H_2) over Pd/C (3 g, 10%) until the hydrogen adsorption had ceased (1000 ml). The slurry was filtered through celite and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (800 ml) and washed with saturated $NaHCO_3$ solution (2 x 100 ml), brine (100 ml), and dried (K_2CO_3). After the solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (10 ml) and passed through a wash column (silica gel) after which the residue was crystallized from ethyl acetate to afford (−)-**1d** (6.4 g, 84%): mp 140-141°C; $[\alpha]_D^{22}$ -129.6° (c 0.52 in $CHCl_3$); ^{1}H nmr ($CDCl_3$) δ 1.90-2.08 (m, 2H), 2.30-2.50 (m, 2H), 2.45 (s, 3H), 2.59 (d, J = 16.2 Hz, 1H), 3.17 (dd, J = 16.2 and 7.2 Hz, 1H), 3.57 (d, J = 7.2 Hz, 1H), 3.59 (s, 3H), 4.01 (d, J = 3 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H); ms (CI, CH_4) m/z (relative intensity) 255 (M+1, 100). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.57; H, 7.19; N, 10.98

Acid Catalyzed Epimerization of (+)-*cis*-Methyl 2,9-dibenzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate 25 into (−)-*trans*-Methyl-2,9-dibenzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate 26 Under Acidic Conditions: The *cis* diester [(+)-**25** (38 mg)] was dissolved in methanol (1 ml) containing 1% HCl (w/w). The mixture was heated at reflux for 20 h. The transformation of the *cis* isomer [(+)-**25**] into the *trans* isomer [(−)-**26**] was complete as observed by tlc. After cooling, the mixture was brought to pH 8 with aqueous ammonia (10%) and extracted with CH_2Cl_2 (5 x 20 ml). The combined organic layers were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure. The residue was purified on a short column (wash) of silica gel. The pure (−)-*trans* diester [**26** (22 mg, 57%)] was obtained: mp 145.5-147.0°C (lit.,[17b] 144-145°C); $[\alpha]_D^{24}$ -13.5° (c 1.00, CH_2Cl_2).[17b] The ^{1}H- and ^{13}C-Nmr spectra of the *trans* isomer (**26**) were identical to those reported by

Magnus *et al.*[17b] The diester (**26**) was shown to be >98% ee *via* the methods outlined in reference 17b. The *cis* (+)-**25** and *trans* (−)-**26** isomers in the N_a-benzyl, N_b-benzyl series were prepared according to the method of Zhang,[12] as reported by Magnus.[17b] The stereochemical assignments of **25** and **26** were made *via* the method of Bailey *et al.*,[10c] and compared directly with those reported by Magnus.[17b]

Epimerization of the *cis*-Diester (+)-25 into the *trans* Diester (+)-26 Under Alkaline (Dieckmann) Conditions: To a mixture of the *cis* diester [(+)-**25** (200 mg, 0.404 mmol)], sodium hydride (21.36 mg, 0.89 mmol) in toluene was added methanol (0.04 ml, 1.00 mmol). The mixture was heated to reflux. After 1 h, examination of the reaction mixture by tlc indicated the presence of the *trans* diester [(+)-**26**] and a small amount of the cyclized ß-keto ester [(+)-**27**]. The reaction mixture was quenched with acetic acid after a total time of 78 min. The mixture was separated by flash chromatography to provide the *trans* diester [(+)-**26** (155 mg, 78%)]: mp 150.5-151.0°C (lit.,[17b] 144-145°C); $[\alpha]_D^{24}$ +13.5° (c 1.00, CH_2Cl_2); the ^{1}H- and ^{13}C-Nmr spectra of **26** were identical to those reported by Magnus *et al.*[17b]

Chiral Shift Study of the ß-Keto Ester (+)-27 and (−)-28: The ß-keto ester of (−)-**28** (5 mg) was dissolved in C_6D_6 (0.5 ml) and a ^{1}H Nmr experiment was performed: δ 2.23 (d, J = 15.5 Hz, 1H), 2.72 (dd, J = 15.5 and 5.5 Hz, 1H), 3.10 (d, J = 3.5 Hz, 2H), 3.18 (s, 3H), 3.42 (d, J = 13.5 Hz, 1H), 3.53 (d, J = 13.5 Hz, 1H), 3.81 (t, J = 3.5 Hz, 1H), 3.89 (d, J = 5.5 Hz, 1H), 4.56 (d, J = 17.3 Hz, 1H), 4.63 (d, J = 17.3 Hz, 1H), 6.52-6.56 (m, 2H), 6.83-7.23 (m, 11H), 7.56-7.59 (m, 1H), 12.67 (s, 1H). To this solution was added 10.4 mg of the chiral shift reagent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[17b] A singlet was now observed in the nmr spectrum at 12.60 ppm. The ^{1}H-Nmr spectrum of (+)-**27** (5 mg) was identical to that of (−)-**28**. The chiral shift reagent (10.4 mg) was added to (+)-**27** and a singlet was observed at 12.64 ppm. One-half of the solution from the nmr tube of (+)-**27** (with the chiral shift reagent) was added to the nmr tube containing the solution of (−)-**28** (with the chiral shift reagent). Two peaks were observed in the nmr spectrum of the mixture at 12.63 and 12.60 ppm in about a 1:2 ratio. Equal amounts of both solutions were also admixed and two peaks were observed in the nmr spectrum at 12.63 and 12.60 of equal intensity. This demonstrated that the enol signal of (−)-**28** ß-keto ester generated from the *trans* diester [(−)-**26**] in the presence of the chiral

shift reagent was shifted more upfield than that from (+)-**27**.

Comparison of the Rates of the Dieckmann Cyclization of the *trans*-(1S,3R)-(−)-26 and *cis*-(1R,3R)-(+)-25, Methyl 2,9-dibenzyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionates: To a mixture of the *trans* diester [(−)-**26** (992 mg, 2 mmol)], sodium hydride (106 mg, 4.4 mmol) in toluene (19 ml), was added a solution of 2.0 M methanol in toluene (1 ml, 2 mmol). The mixture was heated to reflux. Aliquots (0.5 ml) of the reaction mixture were withdrawn periodically, neutralized with aq. acetic acid (20%) and extracted with ethyl acetate. The organic phases were concentrated under reduced pressure and the residue analyzed by ^{1}H Nmr spectroscopy (250 MHz) using C_6D_6 as the solvent. The percentages of the *trans* diester [(−)-**26**] and the cyclized ß-keto ester [(−)-**28**] determined from integration of the signals from the mixture are tabulated below:

time	% *trans* diester (−)-**26**	% ß-keto ester (−)-**28**
15 min	100	0
30 min	94.1	5.9
45 min	82.4	17.6
1 h	57.3	42.7
1 h 30 min	17.4	82.6
1 h 45 min	4.3	95.7

The exact same procedure (scale) was carried out with the *cis* diester [(+)-**25**]. At 15 min examination of the reaction mixture by tlc indicated the complete transformation of the *cis* diester [(+)-**25**] into the *trans* diester [(+)-**26**] accompanied by some of the Dieckmann ß-keto ester [(+)-**27**)]. The percentages of the *trans* diester [(+)-**26**] and the ß-keto ester [(+)-**27**] determined by nmr spectroscopy are tabulated below:

time	% *trans* diester (−)-**26**	% ß-keto ester (−)-**28**
15 min	85.3	14.7
30 min	73.4	26.6
45 min	46.7	53.3
1 h	32.2	67.8
1 h 30 min	7.8	92.2
1 h 45 min	0	100

Dieckmann Cyclization of a 50/50 Mixture of *trans*-(−)-26 and *cis*-(+)-25 Diesters Using 2.0 Equivalents of Methanol: To a mixture of the *trans* diester [(−)-**26** (496 mg, 1 mmol)], the *cis* diester [(+)-**25** (496 mg, 1

mmol)], sodium hydride (106 mg, 4.4 mmol) in toluene (19 ml), was added a solution of 4.0 M methanol in toluene (1 ml, 4.0 mmol). This mixture was held at reflux temperature. After 30 min, examination of the reaction progress by tlc indicated the presence of the *trans* diester (**26**) and the cyclized Dieckmann (±)-ß-keto ester. Aliquots (0.5 ml) of the reaction mixture were withdrawn periodically. Each one was worked up and analyzed by ^{1}H-Nmr spectroscopy (250 MHz, C_6D_6) as described in the pervious experiment. Analysis of the product ratios with high resolution nmr and a chiral shift reagent on selected samples gave the ratios of (−)-**28** (from cyclization of (−)-**26**) and (+)-**27** (from cyclization of (+)-**25**).

time	% *trans* diester	% *cis* diester	% ß-keto ester	(−)-**28**/(+)-**27**
30 min	29.3	0	70.7	50:50
45 min	7.0	0	93.0	50:50
1 h	0	0	100	50:50

Dieckmann Cyclization of a Mixture of *trans*-(−)-26 and *cis*-(+)-25 Diesters Using 1.0 Equivalent of Methanol: The above procedure was repeated on the same scale using 2.0 mmol of methanol (2.0 M, 1 ml, 1 eq.).

time	% *trans* diester	% *cis* diester	% ß-keto ester	(−)-**28**/(+)-**27**
15 min	83.3	0	16.7	39:61
30 min	71.5	0	28.5	43:57
1 h	39.1	0	60.9	50:50
1 h 30 min	23.9	0	76.1	

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30. The data in our previous report[26] on the N_a-methyl series did not attempt to compare the rate of cyclization of *cis* and *trans* diastereomers under the same conditions. As clearly stated previously,[26] additional sodium hydride was employed for cyclization of the *cis* diastereomer above that which was required for cyclization of the *trans* isomer (Yoneda's conditions[5,6a]). The rates in that case cannot be compared directly. Magnus *et al.*[17b] claimed that the *cis* isomer required four hours to cyclize, while the corresponding *trans* diastereomer took over thirteen hours to go to completion, presumably under the same conditions.[17a] The discussion of our previous report by Magnus[17b] was erroneous, moreover, in our hands the *cis* and *trans* diesters in the N_a-benzyl series cyclized to completion at about the same rate ($\approx$2 h) rather than the rate earlier reported by Magnus.[17a,b] In addition, in the N_a-methyl series, cyclization of the *trans* diastereomer (2.1 eq. NaH, 1 eq. CH_3OH) always reacted to completion (Dieckmann product) faster under the same conditions than the *cis* isomer did (tlc/nmr); however, the rates (~2 to 3 h) were similar. In the admixed experiment both diastereomers underwent Dieckmann cyclization at the same rate.

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