PICTET-SPENGLER REACTIONS IN APROTIC MEDIA. N_b-BENZYL PROMOTED RETENTION OF OPTICAL ACTIVITY IN THE SYNTHESIS OF AN INDOLO SUBSTITUTED AZABICYCLO[3.3.1]NONANE, A KEY TEMPLATE FOR THE SYNTHESIS OF MACROLINE ALKALOIDS.

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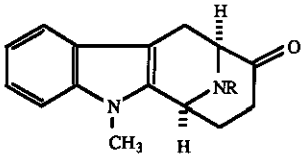
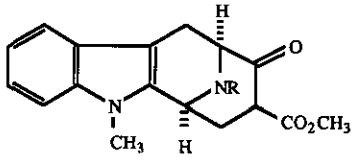
Abstract: The N_b-benzyl group (see **7**) has been employed in the Pictet-Spengler reaction in refluxing benzene to provide complete retention of optical activity in this process. The tetrahydro-β-carbolines **3b** (*trans*) and **4b** (*cis*) were independently converted into the indolo substituted azabicyclo[3.3.1]nonane **1b** and its antipode **1c**, respectively. Consideration of the thermodynamic and kinetic parameters involved in both the Pictet-Spengler and Dieckmann condensations has now permitted the stereospecific synthesis of tetracyclic ketone **2** in high yield and in optically active form.

A number of macroline-related alkaloids have been isolated from *Alstonia macrophylla* wall,[1a-c] *Alstonia muelleriana* Domin[2a-f] and other *Alstonia* species. During studies directed toward the stereospecific synthesis of these macroline alkaloids, the need arose for the preparation of optically active (6S, 10S)-(-)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[6]indole **1**. The template in one approach to these alkaloids.[3]

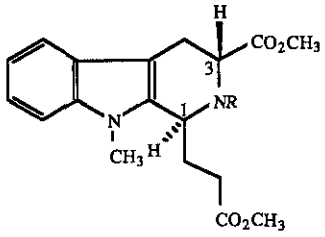


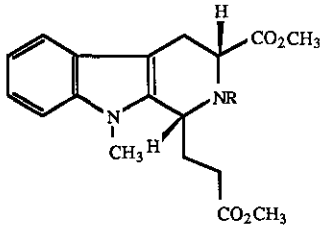
1a (±), R=CH_2Ph
1b (-), R=CH_2Ph
1c (+), R=CH_2Ph



2

Yoneda had previously reported the synthesis of racemic **2** from the Dieckmann cyclization of the (±)-*trans* - and *cis*-1,3-disubstituted1,2,3,4-tetrahydro-β-carbolines **3a** and **4a**[4] but later reported that only the *trans* diastereomer **3a** had cyclized to provide *the cis-fused bicyclo[3.3.1]azanonane skeleton present in* **2**.[5] In addition, Yoneda suggested that the *cis* diastereomer **4a** could not be made to undergo the Dieckmann

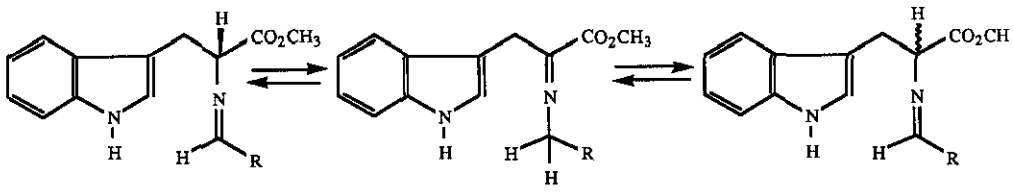




3 a (±) *trans* **4 a** (±) *cis*
3 b (-) optically pure **4 b** (+) optically pure
R=CH_2Ph

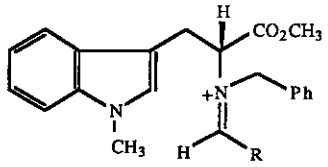
cyclization reportedly due to the formation of an unstable β-ketoester.[5] For a stereocontrolled approach to the macroline alkaloids it was necessary to prepare tetrahydro-β-carbolines **3b** and **4b** in optically pure form and determine whether epimerization occurred at chiral centers -1 or -3 (or both) under Dieckmann reaction conditions required to generate **2**.

Several years ago it was reported that the Pictet-Spengler reaction of tryptophan methyl esters with aldehydes could be executed in nonacidic, aprotic media in high yield.[6] This enabled the use of acid-labile aldehydes such as methyl 3-formyl-propionate in the condensation and a number of applications of this process have been *reported.*[7,8] *Moreover,* it was found that incorporation of an N_b-benzyl group into the tryptophan unit resulted in stereospecific formation of the *trans* (see **3**) isomers in the racemic series[9] and has been recently extended to the optically active series under conditions (H^+) of thermodynamic control.[10] Hino,[11a] Harrison[11b] and Bailey,[11c] 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 **5a** ⇌ **5b** tautomerization



5 a **5 b** **5c** (±)

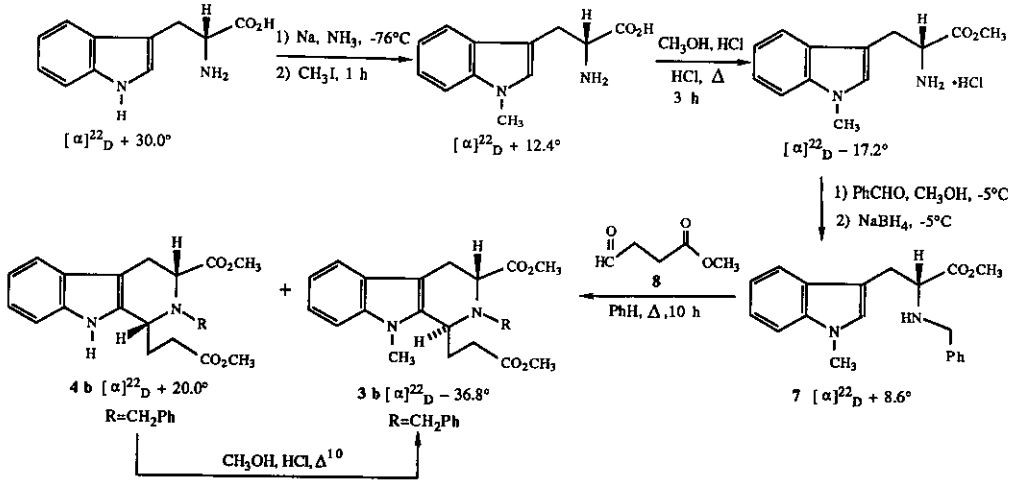
depicted above, wherein the chirality of **5a** is comprised. Since imine **5a** is an intermediate in the cyclization it was decided to increase its electrophilicity *via* use of an N_b-benzyl group (see **6**). This would result in the formation of a more reactive iminium ion. Reaction of optically active N_a-methyl-N_b-benzyltryptophan methyl ester



6

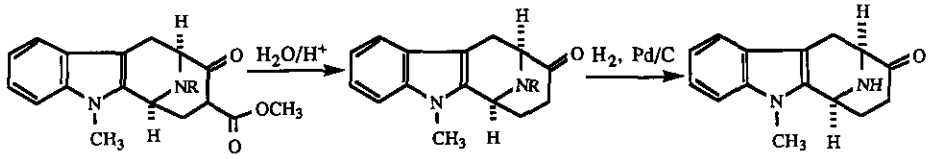
7 (+8.6°) with methyl 3-formylpropionate **8** under conditions of kinetic control (PhH, Δ, 10 h) provided a mixture of the optically pure diastereomers **3b** (-36.8°) and **4b** (+20.0°) in a ratio of 72:28. When the reaction was carried out under conditions of thermodynamic control (H^+, Δ,) as reported,[10] the desired *trans* isomer **3b** was obtained in stereospecific fashion. Moreover, as reported previously optically pure **4b** (*cis*) could be transformed into optically pure **3b** (*trans*) on heating in methanolic hydrogen chloride.[10] Conversion of the *cis* isomer **4b** into the more stable *trans* isomer **3b** under acidic conditions occurs by scisson of the 1-2 (C-N) bond, followed by rotation/recyclization. Intermediates for this process have been isolated.[10] The transformation of D(+)-tryptophan into **3b** and **4b** *via* **7** is outlined in Scheme II.

Scheme II



When treated with sodium hydride in toluene-methanol, analogous to the conditions of Yoneda,[4] the *trans* isomer **3b** was readily cyclized to the desired β-ketoester **2** (Scheme III) in good yield.

Scheme *III*



2 $[\alpha]^{22}_D$-161.9° R=CH_2Ph **1b** $[\alpha]^{22}_D$-203.4° R=CH_2Ph **9** $[\alpha]^{22}_D$-116.8°

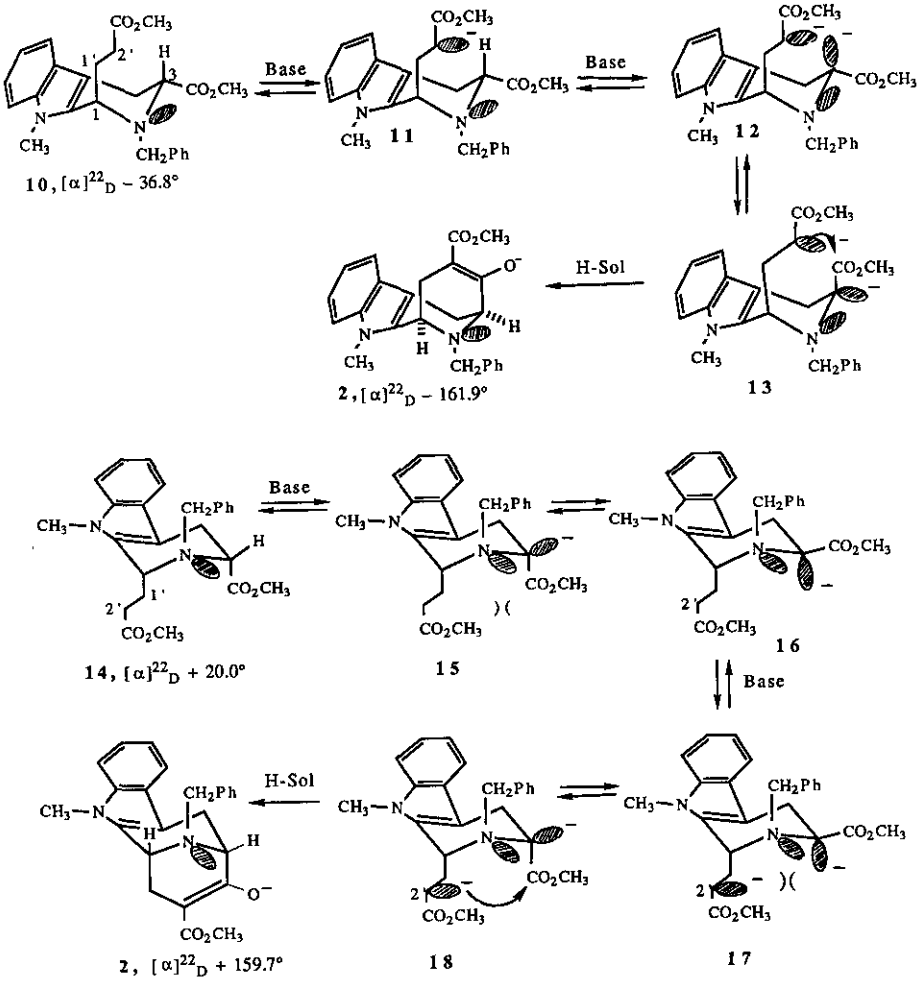
However, the *cis* isomer **4b** could not be coerced to undergo the Dieckmann condensation, but epimerized to the thermodynamically more stable *trans* isomer. This result was unexpected since **4** is *cis*-1,3-disubstituted which should be favorable for cyclization. Yoneda *et al.* had observed similar results with the racemic *cis*-diester **4a** which could not be forced to undergo cyclization despite numerous attempts.[5] However, since the *trans* isomer was converted into the ketoester **2**, the *cis* isomer should also cyclize although it may proceed initially *via* epimerization to the *trans* isomer **3**. When the number of equivalents of sodium hydride was increased to 3 and the reaction mixture was heated for twelve hours, the *cis* isomer **4b** was converted into the antipode of ketoester **2**. The β-ketoester **2** obtained from the *trans* isomer **3b** had an optical rotation of $[\alpha]^{22}_D$-161.9°, whereas the ketoester **2** from the *cis* isomer **4b** exhibited a rotation in the opposite direction $[\alpha]^{22}_D$+159.7°. Moreover, when the *cis* isomer **4b** was converted (NaH) into the *trans* isomer **3**, preceeding cyclization to provide **2**, the optical rotation of that *trans* intermediate was in the positive direction (+36.5°). The optical rotations of **2** and **4b** when compared to their antipodes generated under basic conditions indicated that epimerization had occurred in **3b** and **4b** at position-3. Presumably, the *trans* isomer **3b** undergoes epimerization at position-3, followed by cyclization to provide the *cis*-fused (-)-**2**, while the *cis* isomer **4b** undergoes epimerization to the *trans* diastereomer, followed by reequilibration to the *cis* isomer which then undergoes the Dieckmann cyclization to give the (+)-antipode of **2**. The optical purity of the compounds under study was verified by chiral shift reagents. In particular, the β-ketoester (Scheme III) **2** was decarboxylated under acidic conditions to provide the key tetracyclic ketone (-)-**1b**, followed by catalytic debenzylation to generate (-)-**9**. The optical purity of **9** was confirmed *via* addition of the chiral shift reagent tris-[3-(heptofluoropropylhydroxymethylene)-(+)-camphorato]europium III[17] to a sample afterwhich no splitting was observed. Two sets of signals of **9** were observed in the positive controls, (±)-**9** and 98 (-)-**9**:2 (+)-**9**. The ability to epimerize

position-1 of **4** under acidic conditions[10] and position-3 of **3** under basic conditions has resulted in the stereospecific synthesis of optically pure tetracyclic ketone **1b**.

The unexpected behavior of the *trans* **3b** and *cis* **4b** diastereomers in regard to Dieckmann cyclization is intriguing and presumably can be rationalized on steric and stereoelectronic grounds. Examination of the X-ray crystal structure and nmr spectrum of the *trans* diastereomer[5,13,14] indicates **3b** adopts a conformation in which the substituent at C-1 is axial (to relieve $A^{1,2}$ strain)[15] and the ester group at C-3 is equatorial, whereas the *cis* diastereomer **4b** exists in the diaxial conformation.[5] The N-benzyl group in both diastereomers adopts the axial position to relieve nonbonded interactions. Because the axial hydrogen at C-3 in the *trans* conformer **3b** (see 10, Scheme IV) is sterically hindered,.[16,17] the base ($\bar{O}Me$) first attacks the α-hydrogens located at the 2'-position of **10** to generate anion **11**. Removal of the second proton from **10** (*via* **11**) would generate dianion **12**, the newly formed axial lone pair of electrons of which would presumably prefer to occupy the equatorial position.[18-21] This is due to the 1,2-syn lone-pair, lone-pair repulsion which was also observed by Katritzky *et al.* in the 1,2-diazane system,[22,23] as well as the repulsion between the two anions in **12**. Epimerization of the axial lone pair in **12** to provide **13** would generate the *cis*-fused system required for facile cyclization to **2**. Presumably, stabilization energy gained from the equatorial lone pair of electrons in **13** must compensate for the destabilization effected by the 1,3-diaxial interactions between the substituents located at C-1 and C-3 of **13** when compared to dianion **12**. Cyclization, as described above results in the desired (-) antipode **2**.

In contrast, the equatorial hydrogen atom at C-3 in antipode **4b** (see **14** , Scheme IV) is more accessible to base[16-18] than the corresponding axial hydrogen in **10** and it is removed preferentially to provide equatorial monoanion **15**. Epimerization at position-3 in **15** occurs rapidly to provide the thermodynamically more stable[10] *trans* isomer **16**. However, removal of the second proton (C-2') would now be expected to be difficult (see **16**⇌**17**) since the negative charge will be repelled by the axial anion already generated in conformer **16**. This, presumably, accounts for the vigorous conditions required to convert the *cis* isomer **4b** into (+)-**2**. Examination of the axial anion-anion repulsion in **17** (Scheme IV) clearly illustrates this point. Once the dianion **17** is formed it would be expected to epimerize rapidly to **18** (see also **12**⇌**13**), followed by rapid cyclization to provide the (+) antipode of **2**.

Scheme IV



In summary, the stereochemical outcome of the Pictet-Spengler cyclization of optically pure N_a-methyl-N_b-benzyltryptophan methyl ester **7** with **8** under both kinetic and thermodynamic conditions has been determined. Moreover, the centers of reactivity during the epimerization of 1,3-disubstituted1,2,3,4-tetrahydro-β-carbolines under acidic and basic conditions have been deduced. Combination of these results has permitted the stereospecific synthesis of the azabicyclo[3.3.1]nonane **2** in optically pure form. More importantly, use of the N_b-benzyl group in the Pictet-Spengler reaction in refluxing benzene permitted complete retention of optical activity, in contrast to the racemization reported by Hino,[11a] Harrison[11b] and Bailey[11c] in a related system. Attempts to convert **2** into macroline-related alkaloids will be reported in due course.

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