

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.

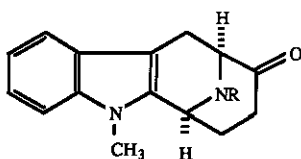
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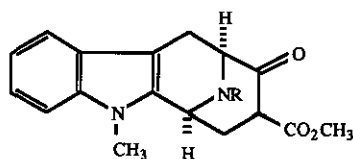
Abstract: The N_b-benzyl group (see 7) has been employed in the Pictet-Spengler reaction in refluxing benzene to provide complete retention of optical activity in this process. The tetrahydro-β-carbolines **3b** (*trans*) and **4b** (*cis*) were independently converted into the indolo substituted azabicyclo[3.3.1]nonane **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

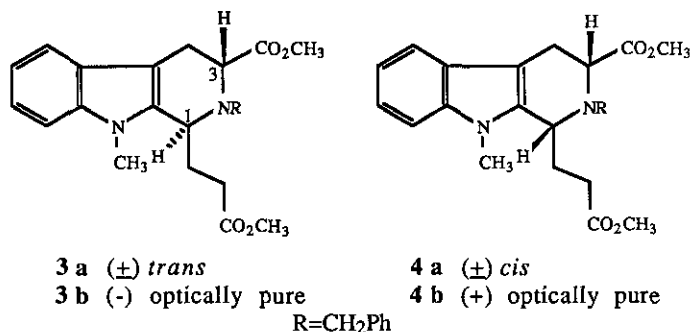


1a (±), R=CH₂Ph
1b (-), R=CH₂Ph
1c (+), R=CH₂Ph



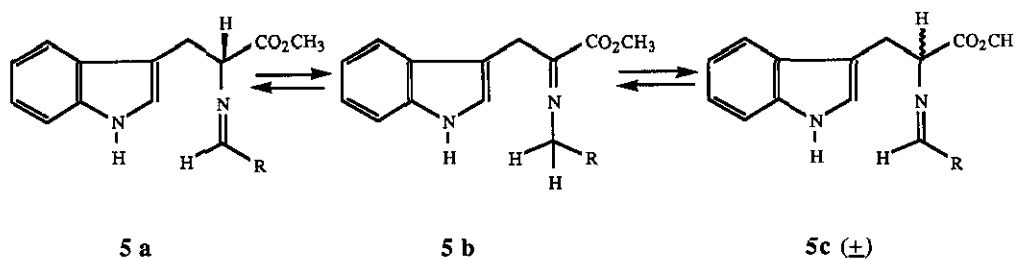
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Yoneda had previously reported the synthesis of racemic **2** from the Dieckmann cyclization of the (\pm)-*trans*- and *cis*-1,3-disubstituted 1,2,3,4-tetrahydro- β -carbolines **3a** and **4a**⁴ but later reported that only the *trans* diastereomer **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

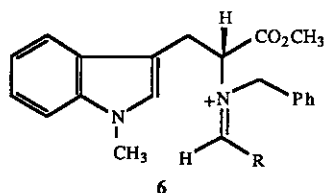


cyclization reportedly due to the formation of an unstable β -ketoester.⁵ For a stereocontrolled approach to the macroline alkaloids it was necessary to prepare tetrahydro- β -carbolines **3b** and **4b** in optically pure form and determine whether epimerization occurred at chiral centers -1 or -3 (or 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-formylpropionate 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*_β-benzyl group into the tryptophan unit resulted in stereospecific formation of the *trans* (see **3**) isomers in the racemic series⁹ 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** \rightleftharpoons **5b** tautomerization

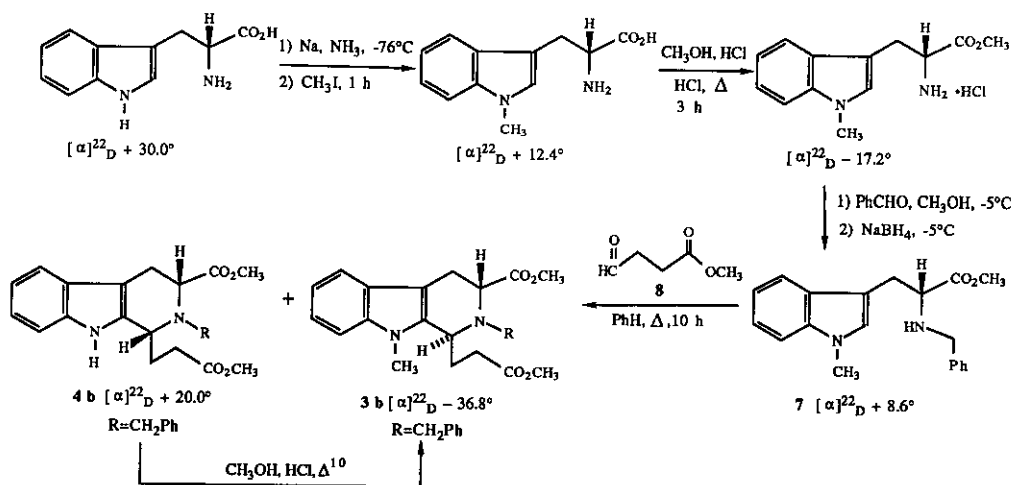


depicted above, wherein the chirality of **5a** is comprised. Since imine **5a** is an intermediate in the cyclization it was decided to increase its electrophilicity *via* use of an N_b -benzyl group (see **6**). This would result in the formation of a more reactive iminium ion. Reaction of optically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



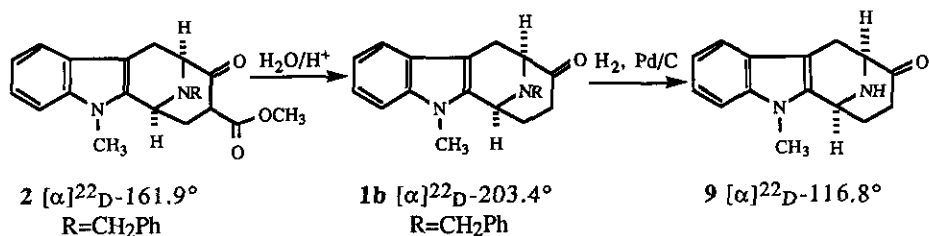
7 (+8.6°) with methyl 3-formylpropionate **8** under conditions of kinetic control (PhH, Δ , 10 h) provided a mixture of the optically pure diastereomers **3b** (-36.8°) and **4b** (+20.0°) in a ratio of 72:28. When the reaction was carried out under conditions of thermodynamic control (H^+ , Δ ,) as 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 scission 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



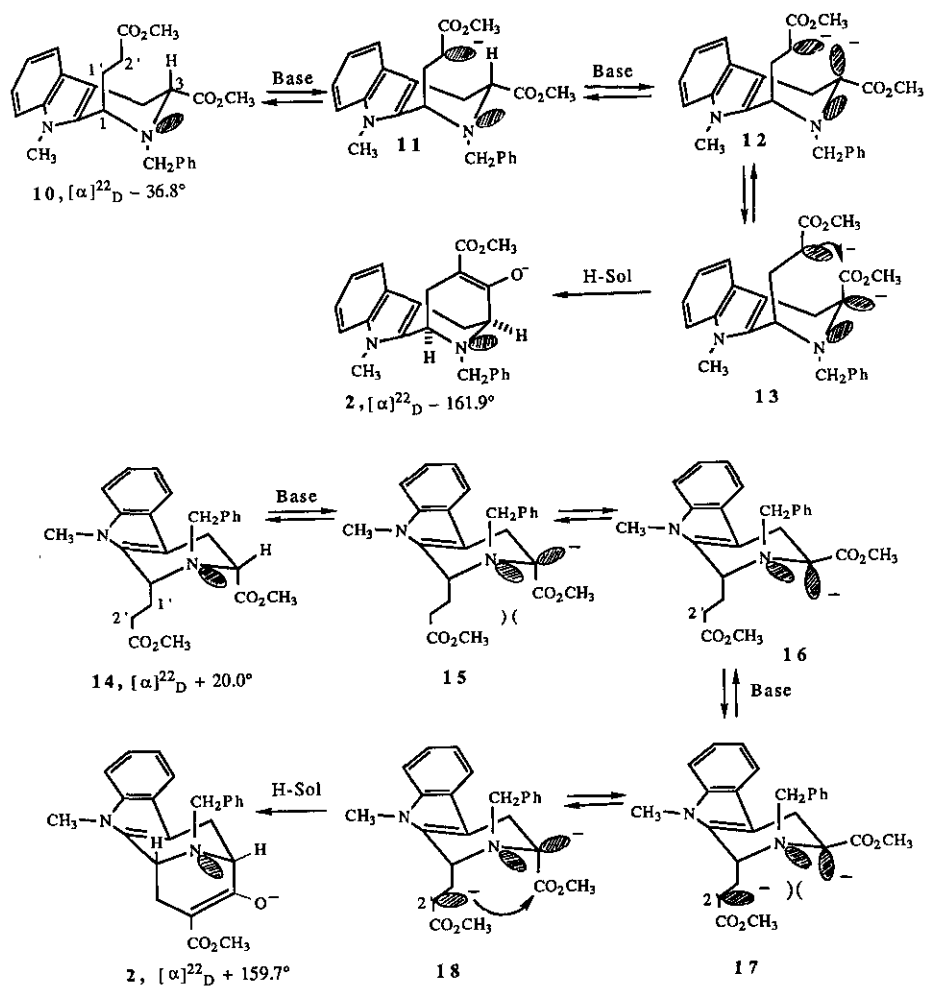
However, the *cis* isomer **4b** could not be coerced to undergo the Dieckmann condensation, but epimerized to the thermodynamically more stable *trans* isomer. This result was unexpected since **4** is *cis*-1,3-disubstituted which should be favorable for cyclization. Yoneda *et al.* had observed similar 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 $[\alpha]_{D}^{22} -161.9^{\circ}$, whereas the ketoester **2** from the *cis* isomer **4b** exhibited a rotation in the opposite direction $[\alpha]_{D}^{22} +159.7^{\circ}$. Moreover, when the *cis* isomer **4b** was converted (NaH) into the *trans* isomer **3**, preceding cyclization to provide **2**, the optical rotation of that *trans* intermediate was in the positive direction ($+36.5^{\circ}$). 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 debenzoylation to generate (-)-**9**. The optical purity of **9** was confirmed *via* addition of the chiral shift reagent tris-[3-(heptofluoropropylhydroxymethylene)-(+)-camphorato]europium III¹⁷ to a sample after which 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 conditions¹⁰ 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 ($\bar{\text{O}}\text{Me}$) 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 base¹⁶⁻¹⁸ 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 stable¹⁰ *trans* isomer **16**. However, removal of the second proton (C-2') would now be expected to be difficult (see **16** \rightleftharpoons **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** \rightleftharpoons **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_2 -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-disubstituted 1,2,3,4-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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