PICTET-SPENGLER REACTIONS IN APROTIC MEDIA. STEREOSPECIFIC CONVERSION OF OPTICALLY ACTIVE CIS-1,3-DISUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLINES INTO THEIR CORRESPONDING TRANS DIASTEREOMERS

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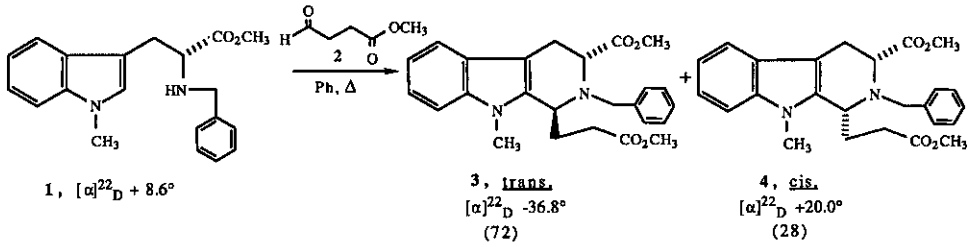
Abstract - The Pictet-Spengler reaction in refluxing benzene of D-(+)-N_a-methyl-N_b-benzyltryptophan methyl ester **1** and methyl 3-formyl-propionate **2**, regioselectively, furnished the trans-1,3-disubstituted-1,2,3,4-tetrahydro-β-carboline **3** (72%) with no detectable racemization at position-3. The optically active cis-diastereomer **4** (28%), which accompanied **3**, was converted (CH_3OH, HCl, Δ) into the trans isomer **3** via the ring-cleaved carbocation intermediate **7**, followed by stereospecific intramolecular cyclization.

During studies[1] directed toward the stereospecific synthesis of macroline-derived alkaloids,[2] the need arose for the preparation of optically active trans-(1S,3R)-methyl-2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-1-propionate **3**. Yoneda had previously reported the synthesis of a mixture of racemic **3** (trans) and **4** (cis),[3] but later reported that the stereochemistry of the major product **3** had been erroneously assigned as 1,3-cis, while the minor product had been incorrectly assigned as the 1,3-trans diastereomer.[4] This difference was resolved and reported.[4] Previously we demonstrated the stereospecific formation of trans-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines via the Pictet-Spengler condensation of N_b-benzyl-tryptophan methyl ester with various aldehydes (cyclohexylcarboxaldehyde, benzaldehyde) in aprotic media.[5] This technique has been subsequently employed by Massiot[6] for the preparation of optically active 1-alkyl-1,2,3,4-tetrahydro-β-carbolines, and by Cava for the synthesis of 6-demethoxyfumitremorgin C.[7] Although there have been reports of racemization during the Pictet-Spengler reaction in aprotic media,[8,9,10] we have now synthesized the trans and cis isomers **3** and **4**,[11] respectively, in high optical purity via the reaction of (D)-N_a-methyl-N_b-benzyltryptophan methyl ester **1**, with **2** in refluxing benzene (Scheme I). This process yielded, regioselectively, the

desired trans isomer **3** ($[\alpha]_D^{22}$-36.8°, $CHCl_3$) accompanied by the cis diastereomer **4** ($[\alpha]_D^{22}$+20°, $CHCl_3$) in 90% yield in a ratio of 72:28 (%). There was no detectable

Scheme I



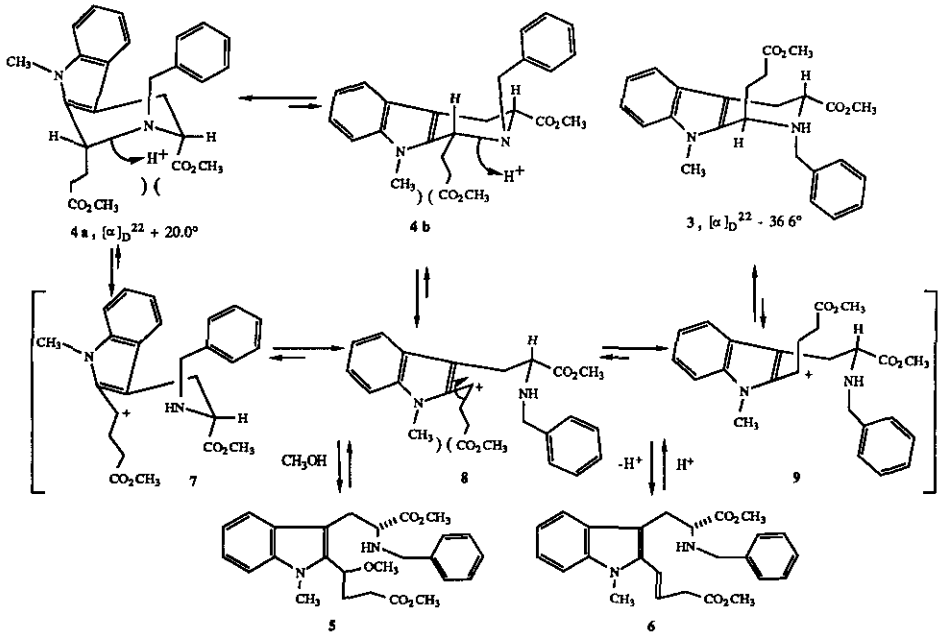
racemization at position-3 of the tetrahydro-β-carboline. The presence of an N_b-benzyl susbstituent provides a highly reactive iminium ion intermediate, consequently the Pictet-Spengler reaction with **2** occurs rapidly without racemization.

Despite the presence of two diastereomers, the separation of **3** from **4** is a tedious process especially for large scale preparations. However, when the Pictet-Spengler reaction of **1** (d,l) with α-ketoglutaric acid or **2** was executed under acidic conditions the trans (d,l)-diastereomer **3** was isolated[1,12a] as the major product, accompanied by only a small amount of **4**.[12b] Apparently, the products of the acid-catalyzed process are formed under thermodynamic control, while the ratio of **3**:**4** in refluxing benzene[13] is regulated by kinetic control.[14] This difference (PhH, Δ) provides a means in which to study this process. When either (-)**3** or (+)**4** was heated in refluxing benzene, no interconversion between the two stereoisomers was observed. It was eventually demonstrated that the cis diastereomer **4** (α_D+20°) could be completely converted into the trans isomer **3** (α_D-36.6°, $CHCl_3$) on heating in refluxing methanol in the presence of 1% HCl. The trans isomer **3** remained unaffected when treated under the analogous conditions. Since the epimerization occurred only at the C-1 position of the cis diastereomer, **4** was converted into the trans isomer (-36.6°) with an optical rotation identical to that of **3** (PhH, Δ; α_D-36.8°) within experimental error. The optical purity of these compounds was verified by the use of ^{1}H-nmr chiral shift reagents. If epimerization of the cis diastereomer had occurred at the C-3 carbon atom (ester) of **4**, it would have resulted in formation of the antipode of **3** with an expected rotation (+36°) equal and opposite to that of **3**. This is contrary to the observed results.

Further evidence for the epimerization of **4** at C-1 to provide **3** was obtained on isolation

of intermediates **5** and **6** (Scheme II). Both the methyl ether **5** and the alkene **6** were minor products obtained from the acid-promoted (CH_3OH, HCl, Δ) conversion of **4** into **3**. The structures of **5** and **6** were confirmed by 2D-COSY nmr and mass spectroscopy.[15] When **5** and **6** were heated in methanolic HCl (1%) both were converted into the optically active trans diastereomer **3** (α_D-36.6°),[16] furthermore, none of the cis isomer **4** was observed or isolated. Based on these experiments, the epimerization of (1R,3R)-(+)-cis **4** to provide (1S,3R)-(-)-trans **3** occurs entirely at C-1 and can be rationalized as illustrated in Scheme II. Under conditions of heat and acid the N_b-nitrogen atom of **4** is protonated, followed by ring cleavage across the 1,2 (C-N) bond to furnish the carbocation **7**. This ion may react either with methanol to give **5** or lose a proton to furnish **6**. Carbocation **7**, which occupies a central position in the equilibrium, may also cyclize via the sterically more favored conformer **9** to furnish the optically active trans diastereomer **3**. The driving force for the ring-scission at C-1 is presumed to result from relief of $A^{(1,2)}$-strain (F. Johnson, Chem. Rev., 1968, **68**, 375) between substitutents (see

Scheme II

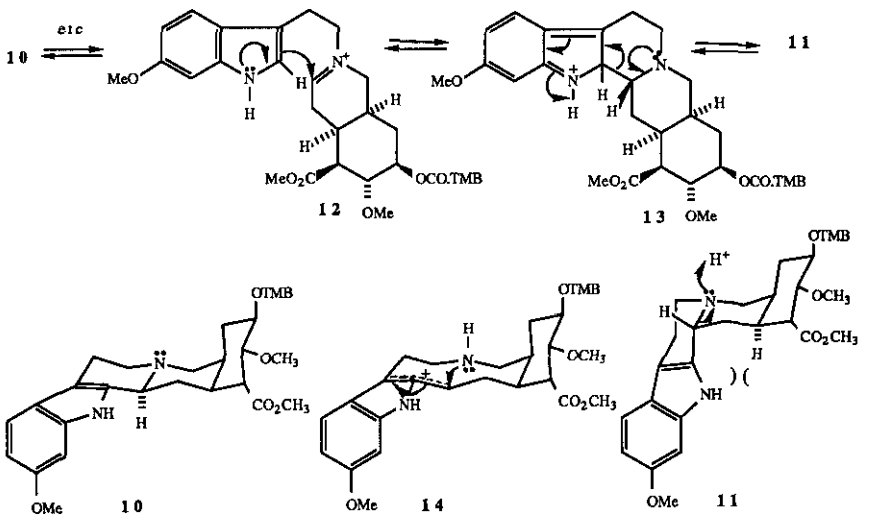


*According to the work of Yoneda, et al. (reference 4), the cis diastereomer **4** exists as the diaxial conformer **4a** in solution in agreement with our work (J. Sandrin, S. Wehrli, J. Cook, unpublished results) via high resolution nmr spectroscopy. However, conformer **4a**, presumably, can flip to conformer **4b** both of which can undergo bond-cleavage across the 1,2-(C-N) bond to provide cations **7** and **8**, respectively. Since **7** can equilibrate to **8**, the conversion of the cis isomer **4** into the trans isomer **3** is shown to occur via cations **7** or **8** and **9**, as illustrated above. Bond rotation around position-1 of cation **8** results in the relief of $A^{(1,2)}$-strain as shown to provide **9** which then cyclizes to give the trans isomer **3**.

8->9) located at C(1) and N(9) in the diequatorial conformer (**4b**) of **4** or the 1,3-diaxial interactions between susbstituents at C(1) and C(3) in the corresponding diaxial conformer **4a**.[4]

This ring-scission process is not only applicable to **4**, but may be important in the interconversion of other natural products.[17] For example, Gaskell and Joule pointed out that isoreserpine **10** which has the indole substituent equatorial to ring-C (Scheme III) was more stable, thermodynamically, than reserpine **11** and 3.5 times more abundant under the conditions of acid-catalyzed equilibration.[18] It was suggested that reserpine **11** reversed to the iminium ion intermediate **12** via **13** and recyclized to provide **10** as the major product.[18] However, Martin et al. recently observed that cyclization of iminium ion **12** yielded reserpine **11** as the major product.[19] It appears that epimerization of **11** to provide **10** must occur by a different mechanism. Because of the conversion of **4** into **3** under acidic conditions, an alternative pathway for the transformation of **11** into **10** (see **14**) may be rationalized as follows: Protonation of reserpine **11** and ring-scission would afford the ring-opened carbocation **14** in order to relieve the 1,3-diaxial interactions in **11** (see Scheme III). The carbocation **14** generated in this process then recyclizes to furnish isoreserpine **10**; a molecule which is more stable, thermodynamically, for the indole group occupies an equatorial position relative to ring-C (see **10**, Scheme III). Studies are underway to employ the ring-scission reaction and the optically active trans diastereomer **3** for the synthesis of indole alkaloids.

Scheme III



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11. **3**: mp 119-120°C; ^{13}C-nmr (250 mHz, $CDCl_3$) 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, 126.96, 128.14, 129.29, 135,67, 137.46, 139.25, 173.34, 173.87. Mass spectrum (CI, CH_4) m/e 421 (M+1); Anal: Calcd for $C_{25}H_{28}N_2C_4$, C, 71.40; H, 6.71; N, 6.67; found C, 71.61; H, 6.64; N, 6.57.

    4: mp 115-116°C; ^{13}C nmr (250 mHz, $CDCl_3$) δ 17.95, 29.10, 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, 137.49, 138.93, 174.07, 174.25; mass spectrum (CI, CH_4) m/e 421 (M+1); Anal: Calcd for $C_{25}H_{28}N_2C_4$, C, 71.40; H, 6.71; N, 6.67; found C, 71.37; H, 6.54; N, 6.77.

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12b. J. Sandrin, L. H. Zhang, and J. M. Cook, unpublished results.

13. D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L Hutchins, M. DiPierro, and J. M. Cook, J. Org. Chem., 1979, **44**, 535.

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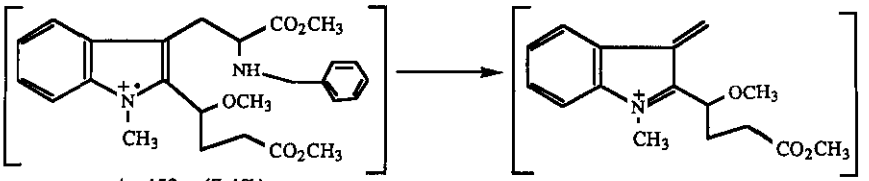
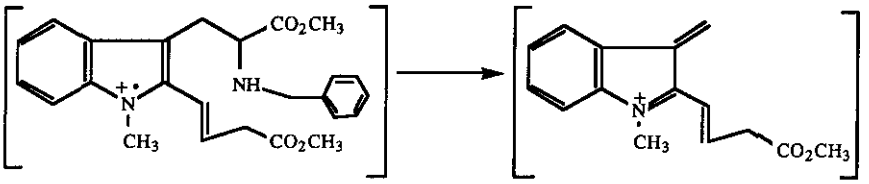
15. **5:** ^1H nmr (250 mHz, $CDCl_3$) σ 1.89 (m, 1H), 2.05 (m, 1H), 2.30 (m, 1H), 2.40 (m, 1H), 4.55 (dt, 1H, J=5 and 9 Hz), 3.05 (s, 3H), 3.50 (s, 3H), 3.57 (s, 3H), 3.70 (s, 3H), 7.00-7.50 (m, 9H); mass spectrum (E.I., 15 eV) relative intensity.



m/e 452 (7.4%) m/e 274 (100%)

6: ^1H nmr (250 mHz, $CDCl_3$) σ 3.29 (dt, 2H, J=8.5 and 18 Hz), 3.52 (s, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 3.40-3.70 (m, 5H), 6.12 (dd, 1H, J=8.5 and 17 Hz), 6.57 (d, 1H, 17 Hz), 7.00-7.50 (m, 9H); mass spectrum (E.I., 15 eV), relative intensity.



m/e 420 (6.6%) m/e 242 (68.1%)

16. The optical purity of these compounds was confirmed by regiospecific conversion into the tetracyclic ketone (see reference 12), followed by catalytic debenzylation. This material was examined by the use of the chiral shift reagent, tris-[3-(heptofluoropropylhydroxymethylene)-(+)-camphorato], europium (III) and high resolution ^1H-nmr spectroscopy (250 mHz). Optimum shifts (splitting) were determined for the racemic material afterwhich the same stoichiometry was employed for the chiral material. To insure the accuracy of the method, the chiral compounds were spiked with 3% d,l material and the spectrum repeated. The chiral shift reagent was obtained from Aldrich Chemical Co. Milwaukee, WI (see Aldrichimica acta, 1972, **5**, 2).

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