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-(+)-
Nα-methyl-Nb-benzyltryptophan methyl ester 1 and methyl 3-
formyl-propionate 2, regioselectively, furnished the trans-1,3-
disubstituted-1,2,3,4-tetrahydro-β-carbon 3 (72%) with no
detectable racemization at position-3. The optically active cis-
diastereomer 4 (28%), which accompanied 3, was converted (CH₃OH,
HCl, Δ) into the trans isomer 3 via the ring-cleaved carbocation
intermediate 7, followed by stereospecific intramolecular cyclization.

During studies¹ 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 Nb-benzyl-
tryptophan methyl ester with various aldehydes (cyclohexylcarboxaldehyde, benzaldehyde) in aprotic media.⁵ This technique has been subsequently employed by
Massiot⁶ 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)-Nα-methyl-Nb-benzyltryptophan methyl ester 1,
with 2 in refluxing benzene (Scheme I). This process yielded, regioselectively, the
desired trans isomer 3 ([α]_D^{22} -36.8°, CHCl_3) accompanied by the cis diastereomer 4 ([α]_D^{22} +20°, CHCl_3) in 90% yield in a ratio of 72:28 (%). There was no detectable racemization at position-3 of the tetrahydro-β-carboline. The presence of an Nb-benzyl substituent 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 as the major product, accompanied by only a small amount of 4. Apparently, the products of the acid-catalyzed process are formed under thermodynamic control, while the ratio of 3:4 in refluxing benzene is regulated by kinetic control. 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 1H-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 (CH₃OH, 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 (αD -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 N₅-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 substituents 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 recylclized 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 recylclizes 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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REFERENCES

11. 3: mp 119-120°C; 13C-nmr (250 mHz, CDCl3) 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 (Cl, CH4) m/e 421 (M+1); Anal: Calcd for C25H28N2C4, C, 71.40; H, 6.71; N, 6.67; found C, 71.61; H, 6.64; N, 6.57.
4: mp 115-116°C; 13C nmr (250 mHz, CDCl3) 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 (Cl, CH₄) m/e 421 (M+1); Anal: Calcd for C₂₅H₂₈N₂C₄, C, 71.40; H, 6.71; N, 6.67; found C, 71.37; H, 6.54; N, 6.77.


15. 5: ¹H nmr (250 mHz, CDCl₃) δ 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.

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 after which the same stoichiometry was employed for the chiral material. To ensure 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).
17. The racemization of optically active 1-substituted Harmala alkaloids may take place via a similar mechanism, A. Brossi, unpublished results. Presented at the 12th Mona Symposium on Natural Products and Medicinal Chemistry, January 4th-8th, Mona, Jamaica, 1988.


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