Evidence for C(1)–N(2) bond scission in the isomerization of *cis*-1,3-disubstituted N_b-benzyl-1,2,3,4-tetrahydro-β-carbolines into their *trans* diastereomers under acidic conditions

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When *cis* diastereomer 13a was stirred in CF_3CO_2D the *trans* isomer 13b was isolated in 90% yield, while treatment of 13a with CF_3CO_2H–$NaBH_4$ provided a mixture of the C(1)–N(2) cleaved product 14 and the *trans* isomer 13b; this provides the best evidence to date that scission of the C(1)–N(2) bond occurs during epimerization of *cis*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines such as 13a into their *trans* isomers 13b.

The Pictet-Spengler reaction has been established as the principal method for the formation of 1,2,3,4-tetrahydro-β-carbolines.[1,2] With the advent of asymmetric control,[1–3] the importance of this method for the stereospecific synthesis of indole alkaloids has rapidly increased. In 1988 Zhang proposed that an intermediate such as **1** (X = H) was involved in the epimerization of *cis*-1,3-disubstituted N_b-benzyl-1,2,3,4-tetrahydro-β-carbolines into their *trans* diastereomers when heated in methanolic hydrogen chloride. Although three potential mechanisms would account for this isomerization, Zhang trapped by-products related to **1** (X = H) in small amounts and converted this mixture under analogous conditions (CH_3OH, 1% HCl, heat) into the *trans* diastereomer exclusively.[3]

The three potential intermediates for this process, depicted in Fig. 1, are related to three different mechanistic pathways investigated earlier by Joule with regard to the isomerization of reserpine into isoreserpine.[4] In 1989 evidence from our laboratory indicated that isomerization of reserpine into isoreserpine took place *via* C(1)–N(2) bond scission related to **1** rather than an iminium ion related to **3**.[5] Experiments with reserpine in CF_3CO_2D pioneered by Joule[4] unequivocally ruled out the intermediacy of an alkenic intermediate related to **2** during the isomerization of reserpine to isoreserpine. Deuterium would have been incorporated at C(1) of the tetrahydro-β-carboline nucleus during regeneration of the 2,3-indole double bond. In fact, in all of the epimerization reactions described here (see below), stirring a *cis*-1,3-disubstituted N_b-benzyltetrahydro-β-carboline in CF_3CO_2D provided the *trans* isomer exclusively with no incorporation of deuterium at C(1). These results rule out an intermediate such as **2** during the process of epimerization.

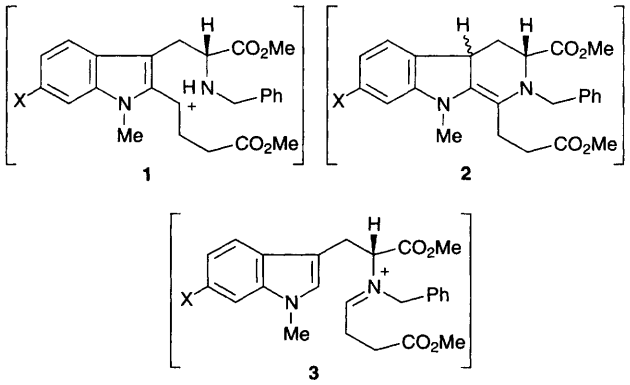
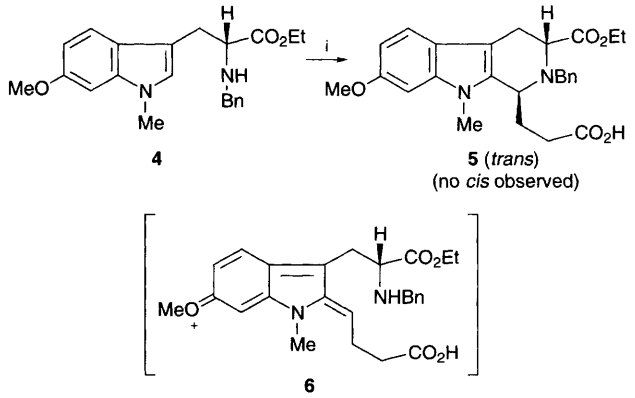


Fig. 1 Potential intermediates

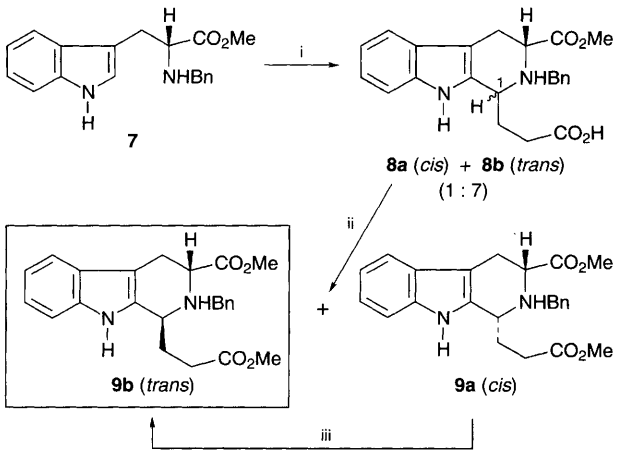
More recently, the optically active 6-methoxy-N_b-benzyltryptophan ethyl ester **4** was heated with a slight excess of α-ketoglutaric acid to provide the *trans* diastereomer **5** exclusively and in excellent yield. The oxonium ion intermediate **6** proposed for this transformation is reminiscent of one of the intermediates proposed earlier for the isomerization of reserpine into isoreserpine.[5] In contrast in the desmethoxy series, N_b-benzyltryptophan methyl ester was earlier heated with α-ketoglutaric acid under similar conditions to furnish a mixture (2:3) of *cis* and *trans* isomers,[3] the former of which was converted exclusively to the *trans* diastereomer on heating under acidic conditions. It is believed that the 6-methoxy group in **4** promoted the conversion of any *cis* isomer so formed to undergo ring opening (*via* **6**) followed by reclosure to the more stable *trans* isomer **5**. This evidence, in agreement with earlier studies with reserpine,[5] although indirect, prompted additional investigation of the mechanism of this isomerization in nonactivated (desmethoxy) tryptophan derivatives.

As outlined in Scheme 2, heating N_b-bentyltryptophan methyl ester **1** with α-ketoglutaric acid gave a mixture of *cis* (**8a**) and *trans* (**8b**) diastereomers in a ratio of 1:7. Conversion of the acids into the corresponding esters was accomplished under neutral conditions to provide the *cis* (**9a**) and *trans* (**9b**) diesters in the N_a–H, N_b–benzyl series. When the *cis* isomer **9a** was stirred at room temperature with 2.4 equiv. of CF_3CO_2H in CH_2Cl_2 for 10 days, the 100% stereoselective formation of the *trans* diastereomer **9b** was realized (90% yield). The optical rotation of *trans* **9b** was identical to that of pure **9b** obtained earlier; epimerization had ocurred only at C(1). When the mixture of *cis* (**9a**) and *trans* (**9b**) isomers was treated under the same conditions, again a 90% yield of the desired *trans* isomer **9b** was realized. The rate of the epimerization could be drastically increased by heating the solution.

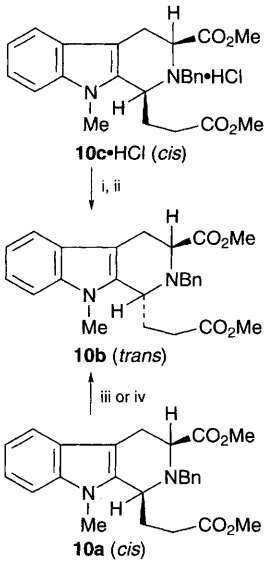
Similar results were observed in CF_3CO_2H–CH_2Cl_2 in the N_a-methyl, N_b-benzyl series. Pictet–Spengler reaction of N_a-methyl-N_b-benzyltryptophan methyl ester with methyl-3-formylpropionate in refluxing benzene furnished a mixture of *cis* (**10a**) and *trans* (**10b**) diastereomers in a ratio of 28:72 in



Scheme 1 *Reagents and conditions*: i, $HO_2CCOCH_2CH_2CO_2H$ (1.05 equiv.), toluene–dioxane, heat, Dean–Stark trap (DST), 85%



Scheme 2 *Reagents and conditions*: i, $HO_2CCOCH_2CH_2CO_2H$ (1.1 equiv.), benzene–dioxane, heat, 3 h, Dean–Stark trap, 85%; ii, CH_2N_2 (1.5 equiv.)–Et_2O, CH_2Cl_2, 0 °C, 1.5 h, 94%; iii, CF_3CO_2H (2.4 equiv.), CH_2Cl_2, room temp., 10 d, complete conversion

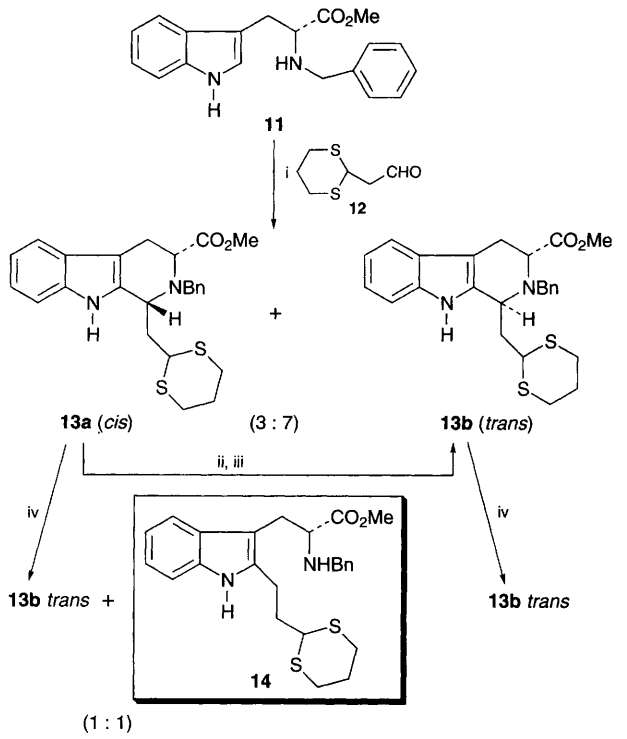


Scheme 3 *Reagents and conditions*: i, CH_2Cl_2, room temp., 18 d, 89%; ii, aq. $NaHCO_3$; iii, CF_3CO_2D, CH_2Cl_2, room temp., 92%; iv, $ZnCl_2$ (4.7 equiv.), $CHCl_3$, heat, 92%

90% yield.[8] When the *cis* isomer **10a** was stirred in CH_2Cl_2–CF_3CO_2D for several days at room temperature, the *trans* isomer **10b** was obtained in optically pure form (92% yield) with no deuterium incorporation at C(1) or C(3). Again, intermediate **2** was unequivocally ruled out, moreover, the mixture [*cis* (**10a**): *trans* (**10b**) 28:72] was converted into optically active *trans* **10b** on heating for 5 h in CF_3CO_2H–CH_2Cl_2.

In order to form intermediate **3** (Fig. 1) in this process, protonation of the indole double bond (the α-carbon atom) must precede iminium ion formation;[4,5] consequently, the *cis* isomer **10a** was heated in dry distilled chloroform (EtOH, HCl free) with anhydrous $ZnCl_2$ (4.6 equiv.). This process provided the *trans* isomer **10b** in 92% yield. Since the solution was devoid of protons, it was felt the Lewis acid promoted the formation of a carbocation intermediate related to **1** and not iminium ion **3**. The control reaction with **10a** in refluxing $CHCl_3$, in the absence of anhydrous $ZnCl_2$, returned only *cis* isomer **10a** in quantitative yield. A similar experiment with the dry hydrochloride salt **10c** of *cis* isomer **10a** gave the *trans* analogue **10b**, again in support of intermediate **1** over **2** or **3**.

Evidence above supported the C(1)–N(2) scission mechanism (see **1**) illustrated in Fig. 1 for this isomerization prompting a similar set of experiments in a different series (Scheme 4).



Scheme 4 *Reagents and conditions*: i, **12**, benzene, heat, Dean–Stark trap, 93%; ii, CF_3CO_2D (2.9 equiv.), CH_2Cl_2, room temp. (no deuterium incorporation in **13b** was observed); iii, CF_3CO_2H (2.1 equiv.), CH_2Cl_2, room temp., 94%; iv, $NaBH_4$, CF_3CO_2H, CH_2Cl_2, room temp.

When optically active N_b-benzyltryptophan methyl ester **11** was heated with aldehyde **12** in refluxing benzene, a mixture of *cis* (**13a**) and *trans* (**13b**) isomers was formed in 90% yield in a ratio of 3:7. When the mixture was stirred in CF_3CO_2D, the *trans* isomer **13b** was formed in high yield, moreover, no deuterium incorporation was observed. Epimerization of **13a** had taken place at C(1), presumably *via* an intermediate analogous to **1** or **3**. The *cis* isomer **13a** was then stirred in CF_3CO_2H in the presence of $NaBH_4$ which furnished a mixture of the reduced intermediate **14** [C(1)–N(2) cleavage] and the *trans* isomer **13b** in approximately equal amounts. No *cis* diastereomer **13a** was observed in this mixture, nor was any product isolated which would correspond to either reduction or hydrolysis of an iminium ion related to that in intermediate **3**. Moreover, when the thermodynamically more stable *trans* isomer **13b** was stirred with CF_3CO_2H–$NaBH_4$ under exactly the same conditions, no ring opening product (**14**) was observed. The failure of *trans* isomer **13b** to provide **14** under these (control) conditions suggests that the origin of **14** (from *cis* isomer **13a**) arises from reduction of a 'carbocation-like' intermediate related to **1** (or the corresponding iminium ion resonance form) and not borane-mediated cleavage of the C(1)–N(2) bond. If the latter event had occurred then the isolation of **14** from *trans* isomer **13b** would have also been expected.

References

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