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A Stereoselective Transformation of Pseudoindoxyls into Oxindoles in a Single Operation

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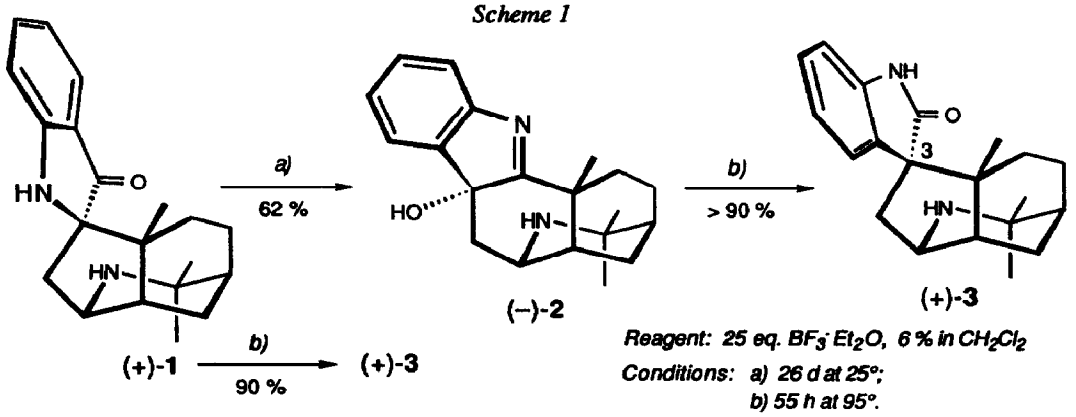
Abstract: The *Aristotelia* alkaloid (+)-aristotelone (**1**), a spiro-pseudoindoxyl derivative, is transformed in over 90 % yield into the oxindole (+)-3-epitasmanine (**3**) upon treatment with hot BF_3·Et_2O in CH_2Cl_2. This intriguing transformation possibly proceeds through the intermediate 3-hydroxyindolenine derivative (-)-serratoline (**2**) which could be isolated when the reaction was run under milder conditions. This rearrangement, for which there is little precedent, is highly stereoselective in that the lactam carbonyl group ends up on the same face of the molecule as the C=O-unit of the starting pseudoindoxyl. That this outcome is due to a kinetic control was demonstrated by showing that the epimeric starting material (–)-**4** furnished exclusively the naturally occurring alkaloid (–)-tasmanine (**5**) under the same reaction conditions.

In connection with work concerned with the total synthesis and with oxidative transformations of certain *Aristotelia* alkaloids [1] we discovered that synthetic (+)-aristotelone (**1**) [2] is slowly transformed into the isomeric compound (-)-serratoline (**2**) when treated with BF_3·Et_2O in CH_2Cl_2 at 25° *(Scheme 1)*. In the crude reaction mixture 2 % of the constitutional isomer (+)-3-epitasmanine (**3**) [2, 3] could also be detected by means of ^{1}H-nmr spectroscopy (characteristic high-field singlet at 0.57 ppm due to the angular methyl group). Additional experiments under more stringent conditions (55 h at 95° in a sealed glass tube) showed that (–)-**2** is transformed into (+)-**3** in virtually quantitative yield, demonstrating that (–)-**2** can serve as a precursor for the latter. Under the same conditions, pseudoindoxyl (+)-**1** furnished the oxindole (+)-**3** in a single operation. [4]

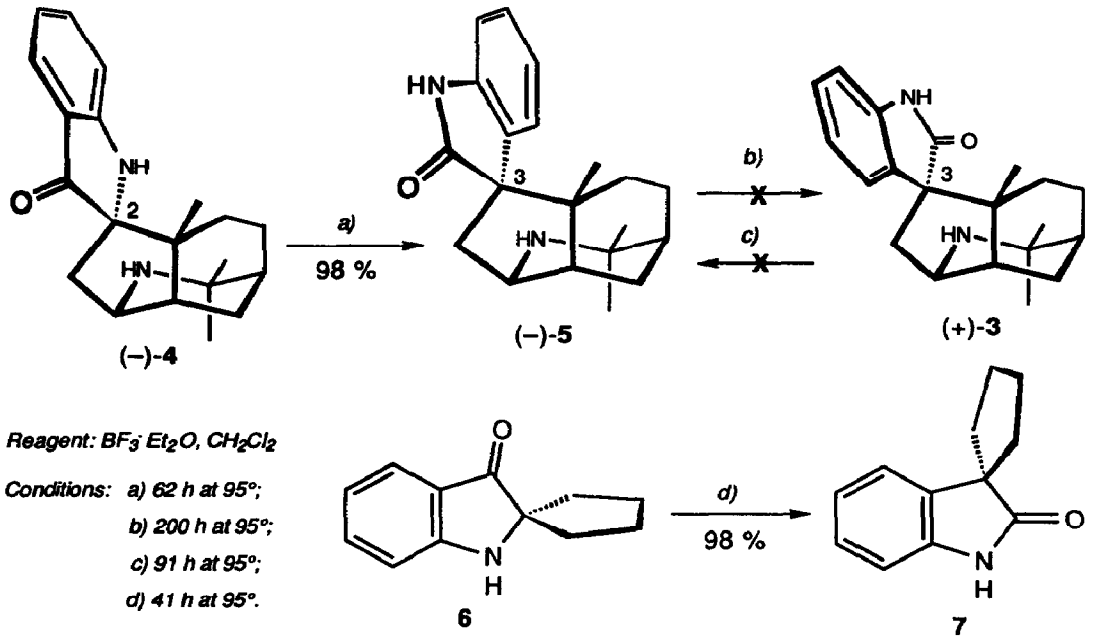
Scheme 1



Reagent: 25 eq. BF_3·Et_2O, 6 % in CH_2Cl_2
Conditions: a) 26 d at 25°;
b) 55 h at 95°.

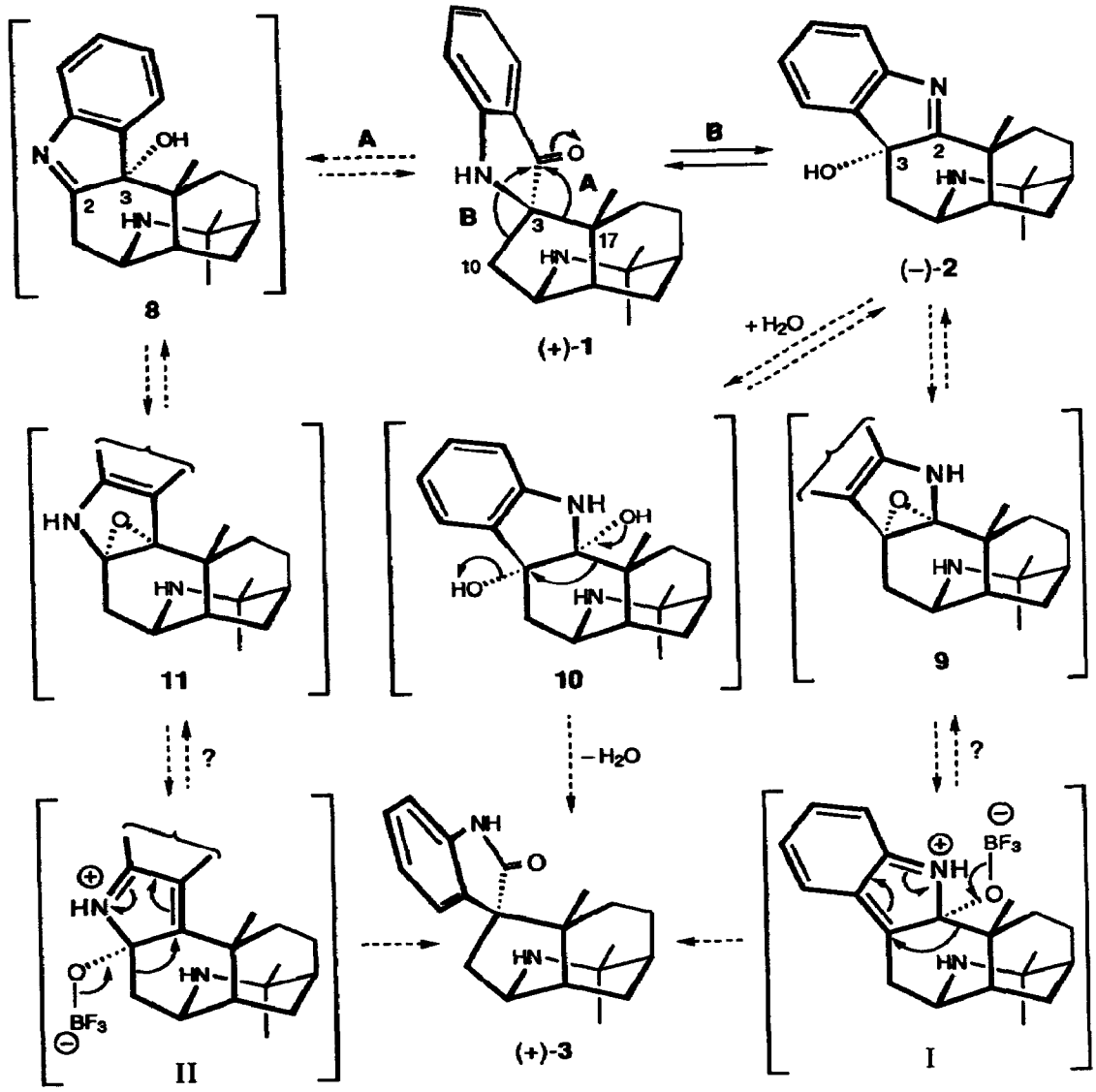
Additional experiments showed that under the above conditions an equilibrium between **1** and **2** is set up, which could be approached starting from both sides. Furthermore, it was shown that the slow formation of the oxindole **3** from either of these precursors is an irreversible process (**3** was recovered absolutely unchanged after exposure to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 95° for 8 days). A control experiment demonstrated that the spiro epimer (–)-tasmanine (**5**) [3] *(Scheme 2)* was also stable under these conditions, thus showing that the exclusive formation of **3** from **1** or **2** is not the result of a subsequent equilibration of the oxindoles **3** and **5**. We corroborated this contention by verifying that the epimeric starting material (–)-2-epiaristotelone (**4**) [2] rearranges stereoselectively (> 95%) into (–)-tasmanine (**5**).

Scheme 2



To the best of our knowledge, the only precedent for the observed double 1,2-migration from carbon to carbon, accompanied by a concomitant 1,2-shift of a carbonyl group in the opposite direction, is represented by an analogous transformation of 2,2-diphenyl-1,2-dihydro-3*H*-indol-3-one into 3,3-diphenyl-1,3-dihydro-2*H*-indol-2-one, which was reported by *Witkop* and *Ek* in 1951.[6,7] Nonetheless, this reaction seemingly is not restricted to that substrate and the *Aristotelia* alkaloids, since under the same conditions, tetrahydrocarbazole pseudoindoxyl (**6**) [8] also rearranged to the corresponding oxindole **7** [9] in virtually quantitative yield.[10] In this experiment, as well as during the transformation (–)-**4** → (–)-**5**, no intermediate 3-hydroxyindolenine derivative could be detected in the reaction mixture, even when the reaction was run under milder conditions (25°C, shorter reaction time). This negative evidence notwithstanding, the first step in the observed rearrangement sequence is most likely represented by a 1,2-shift of a C,C-bond involved in the set-up of the spiro center. In a asymmetric environment, such as in the case of (+)-**1** and (–)-**4**, either of the bonds adjacent to the carbonyl group could migrate to furnish a hydroxyindolenine intermediate belonging to the regular series ((–)-**2**) or to the invert allo-series (**8**) *(Scheme 3)*. [2,13-15] At present, we are unable to decide whether pathway **A** or **B** is followed; **A** is electronically favored, but would lead to an intermediate (**8**), which is known to be much less stable than the alternative (–)-**2**.[16] The next step might well involve either of the epoxides **9** or **11**, as originally proposed by *Witkop*. [6,17] These unstable intermediates can undergo alternative oxirane ring-opening reactions to furnish either their respective precursors **2** and **8**, or the iminium salts **I** and **II**, respectively, both of which are expected to rearrange to the observed final product (+)-**3**. As an alternative, hydrated hydroxyindolenines, such as *cis*-diol **10**, can be considered as possible reactive intermediates.[18,19]

Scheme 3



The rearrangement of (–)-**4** into (–)-**5** most likely proceeds in an analogous fashion, involving either 3-epialloserratoline or 3-episerratoline (the C(3)-epimers of **8** and **2**, respectively) as the first intermediates.The steps that follow would involve the epimeric β-epoxides related to **9** and / or **11**, which one would expect to rearrange stereoselectively to tasmanine (**5**).

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References and Notes

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2. a) R. Güller, H.-J. Borschberg, *Tetrahedron Asymmetry*, **1992**, *3*, 1197;
   b) R. Güller, H.-J. Borschberg, *Helv. Chim. Acta*, **1993**, *76*, 1847;
   c) R. Güller, Dissertation, ETH Zürich, No. 10387 (1993).
3. The spiro epimer (–)-tasmanine (**5**) was isolated from *Aristotelia peduncularis* (R. Kyburz, E. Schöpp, I.R.C. Bick, M. Hesse, *Helv. Chim. Acta*, **1981**, *64*, 2555), as well as from *A. serrata* (M.A. Hai, N.W. Preston, H.-P. Husson, C. Kan-Fan, I.R.C. Bick, *Tetrahedron*, **1984**, *40*, 4359).
   For a recent total synthesis, see ref. [2b]
4. Interestingly, heating of (–)-**2** in the absence of a catalyst, [2] or treatment with hot NaOMe in MeOH, [5] produced the pseudoindoxyl (+)-**1** in 94-98 % yield (no oxindole detectable).
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10. However, several attempts to convert the pseudoindoxyls derived from yohimbine [11] and ibogamine [12] into the corresponding oxindoles were unsuccessful, possibly on electronic grounds in the first case and for steric reasons in the latter.
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17. Similar intermediates have been proposed on various occasions: a) M. Colonna, L. Greci, L. Marchetti, G.D. Andreetti, G. Bocelli, P. Sgarabotto, *J. Chem. Soc., Perkin Trans. 2*, **1976**, 309; b) B. Beitzke, R.R. Schmidt, *Chem. Ber.*, **1985**, *118*, 1726; c) I.A. Cliffe, K. Heatherington, A.C. White, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1975.
18. A similar *cis*-diol has been postulated as intermediate in an OsO_4-mediated oxidative transformation of an indole precursor into the corresponding oxindole derivative: H. Takayama, M. Kitajima, K. Ogata, S.-i. Sakai, *J. Org. Chem.*, **1992**, *57*, 4583. For the isolation of a 1-alkyl-3-aryl-2,3-dihydroxyindolenine, see F. Dallacker, G. Sanders, *Chemiker Zeitung*, **1986**, *110*, 405.
19. Although the presence of water under the given reaction conditions seems unlikely, this variant can not be ruled out since only catalytic amounts of H_2O would be required for the sequence **2** → **10** → **3**.

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