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Solid state isomerisation of atropodiastereomers : A promising method to obtain high diastereomeric ratios.

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Abstract

A series of imides with two chirality axes have been synthesized. Comparatively low activation barriers to isomerisation and, at the same time, high melting points lead to interesting behaviors of these compounds: whereas thermodynamic equilibria of nearly 50:50 diastereomeric ratios were reached rapidly in solution at 110°C, ratios up to 99:1 in favor of one diastereomer have been observed after prolonged heating above the same temperature of the mixture of diastereomers in the solid state. Crystallographic and differential scanning calorimetric (DSC) techniques have been used to support these studies and their interpretation.

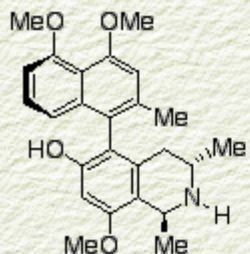
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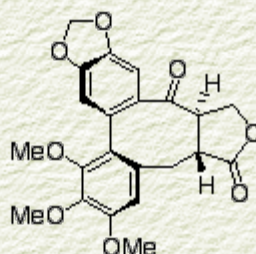
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Introduction

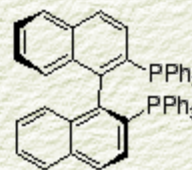
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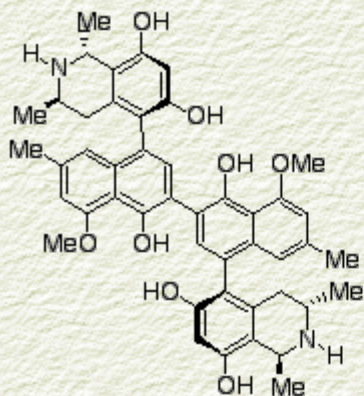
(-)-Ancistrocladine [2]



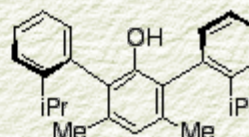
(-)-Steganone [3]



(S)-BINAP [4]



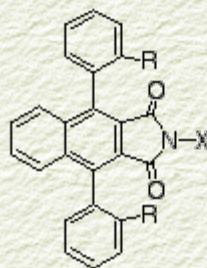
Michelamine A [5]



Chiral auxiliary [6]

Many efforts have been devoted to the development of new methods for the absolute stereochemical control of one stereogenic axis (selective synthesis of one atropenantiomer at the expense of the other) [7].

But, up to now, only little attention has been paid to the relative stereochemical control of two or more stereogenic axes (selective preparation of one atropodiastereomer at the expense of several others). The following represents an original contribution to this topic : high diastereomeric ratios of atropodiastereomers of 1 have been obtained via thermal isomerisation in the solid state.



[1](#), [1a](#), [1b](#), [1c](#), [1d](#),

(Please click on each item to see the corresponding molecule 1, 1a, 1b, 1c, 1d)

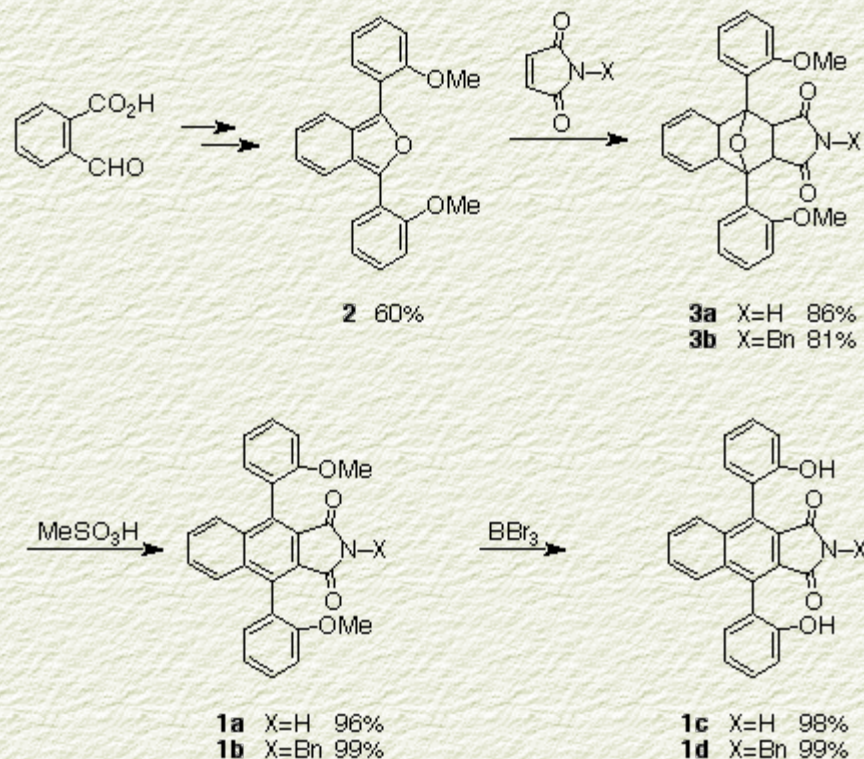
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Synthesis



Scheme 1

The synthesis of compounds **1 a - d** was readily accomplished via isobenzofuran chemistry as depicted on scheme 1. Isobenzofuran **2** was prepared in two steps by standard reactions [8]. Diels-Alder reactions of **2** with maleimide and N-benzylmaleimide proceeded in high yields giving adducts **3a** and **3b** as single diastereomers, presumably with an endo stereochemistry [9]. Aromatisation of the Diels-Alder adducts furnished the target compounds **1a** and **1b** in high yields. Their demethylation with BBr_3 gave **1c** and **1d** nearly quantitatively.

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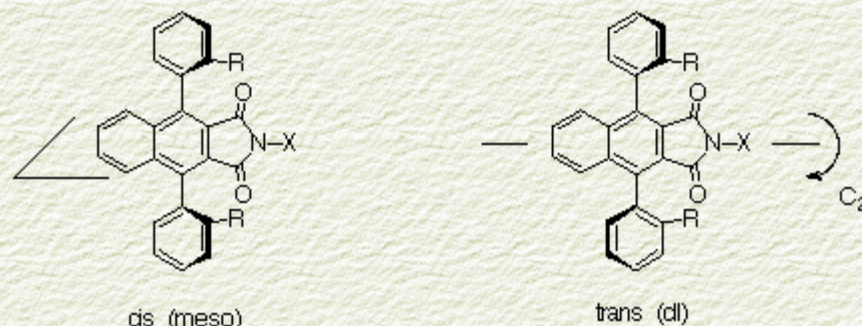
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Stereochemistry, X-ray structures

The presence of two stereogenic axes lead to the existence of two atropodiastereomers : one cis (or meso), achiral and one trans (or dl), chiral.



1 a,b,c,d

Diastereomers of **1a** were separable by crystallization, those of **1b**, **1c** and **1d** by column chromatography. No interconversion was noticed in solution at room temperature after several hours [10]. Attribution of the stereochemistry has been made by chiral HPLC analysis [11] : The trans diastereomer was resolved into its enantiomers, giving two peaks of equal intensities, whereas the achiral cis diastereomer gave only one peak.

This attribution has been confirmed on **1a** by X-ray crystallography: monocrystals of each **1a cis** and **1a trans** have been obtained by slow evaporation of their solutions.

The case of **1a trans** was interesting : while the trans relationship of the two OMe groups is obvious on the structure, it appears that in the crystal the two enantiomers are statistically interchangeable at each molecular site of the lattice, by exchanging the position of the fused benzene ring and of the imide pattern; it crystallises as a pseudoracemate or solid solution of enantiomers, a rather uncommon behavior of chiral compounds in the solid state [12].

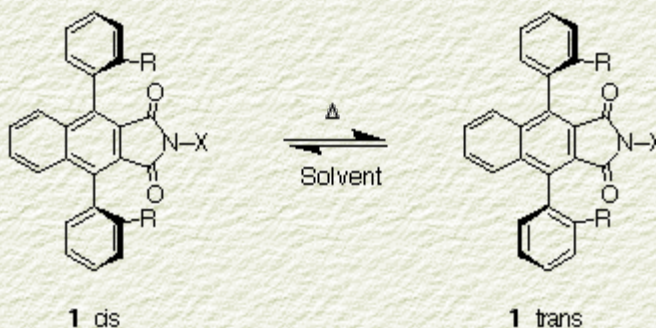
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Isomerisations in solution

Whereas diastereomers of **1a** did not interconvert at room temperature, fast equilibration occurred in refluxing toluene (bp 110°C): after two hours, starting from **1a cis** or **1a trans**, a 45:55 ratio of **1a cis**:**1a trans** was obtained. The same ratio was obtained with **1b**.



Kinetics of isomerisation of **1a** was followed in refluxing iso-propanol (bp 82°C) giving a rate constant $k = 0.17 \text{ h}^{-1}$ ($t_{1/2} = 1.5 \text{ h}$). Solubility problems did not allow the same experiment with **1b** but the atropoisomerisation barrier of **1b** should not be very different from that of **1a**: one can reasonably assume little or no dependence of atropoisomerisation barrier from the nature of the nitrogen substituent X. The nature of the R substituent should have a more pronounced influence : Indeed isomerisation of **1c** (R = OH, X = H) in boiling iso-propanol gave a rate constant of 0.52 h^{-1} ($t_{1/2} = 0.5 \text{ h}$). After equilibration, a **1c cis**:**1c trans** ratio of 50:50 was obtained. Nearly the same data were obtained with **1d**.

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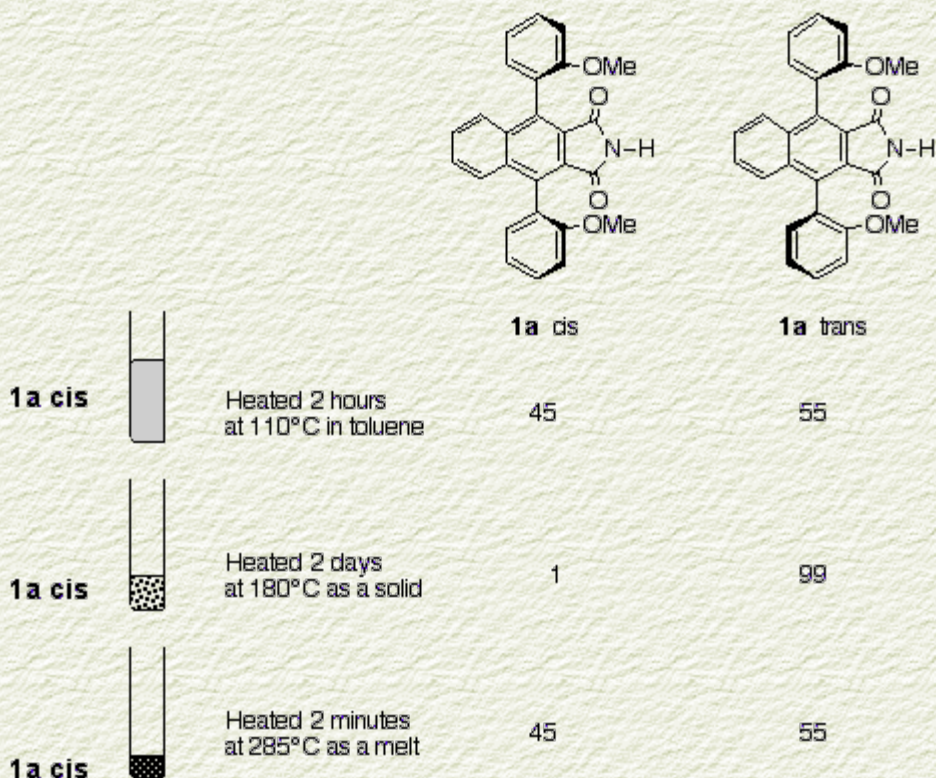
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Isomerisations in the solid state

I. Results :

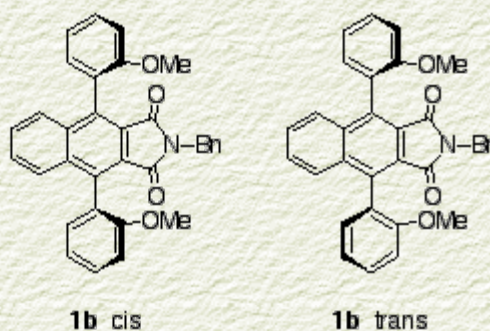
Both diastereomers of **1a** are crystalline solids with high melting point ($> 250^{\circ}\text{C}$). As isomerisation of **1a** was found to be fast in solution above 110°C we became interested in the possibility of performing isomerisations in the solid state. This was possible indeed, but the results were quite unexpected: when a sample of pure **1a cis** as a microcrystallin powder has been heated at 110°C for two hours, small amounts of **1a trans** had formed but the diastereomeric ratio of the sample was far from that of the equilibrium in solution. The isomerisation rate increased as the temperature was raised : a cis:trans ratio of about 70:30 was obtained after one hour at 180°C . Much more surprizing, after one night at 180°C the diastereomeric ratio was 10:90 in favor of the trans isomer , having overtaken the solution equilibrium ratio ! Further heating at 180°C for two days led to almost complete isomerisation of the sample (cis:trans : 1:99). During these experiments no macroscopic changes of the sample, in particular no melting (even partial), were noticed. When the same experiments were performed starting with solid **1a trans** no isomerisation at all was noticed. Heating **1a cis** or **1a trans** up to complete melting ($T > 285^{\circ}\text{C}$) and fast cooling gave the same diastereomeric ratio as that of the solution equilibrium (cis:trans 45:55).



Obviously something interesting happened when **1a** was heated as a crystalline solid. A more thorough study of the crystal behaviour of **1a cis** and **1a trans** was therefore undertaken. Melting points were determined in different conditions. Kofler hot bench gave "instantaneous" melting points of $250 - 252^{\circ}\text{C}$ for **1a cis** and $> 270^{\circ}\text{C}$ (beyond the limits of the apparatus) for **1a trans**. Progressive heating of the samples gave different results : capillary tubes melting point apparatus gave mp $> 270^{\circ}\text{C}$ for both **1a cis** and **1a trans**. Finally DSC (Differential Scanning Calorimetry) studies were undertaken : For **1a trans** the DSC trace at a temperature gradient of $10^{\circ}\text{C}/\text{min}$ gave a sharp heat absorption at the melting point

(281.4°C) with no other noticeable phase transition under this temperature. For **1a cis** a progressive heat absorption occurred within a large temperature interval, followed by a sharp peak with a maximum at 283.6°C. Although complementary studies are necessary such as modification of the temperature gradient, a solid state transformation of **1a cis** seems likely, yielding **1a trans**, in the same crystalline state than that obtained by room temperature crystallization of **1a trans**. This result was further confirmed by [powder X-ray diagram](#) of a sample of **1a cis** isomerized at 180°C for 2 days. It has a very similar diffraction pattern to a [simulated powder X-ray diagram](#), obtained from single crystal X-ray data of **1a trans**.

Interestingly, similar behaviours have been found with other compounds of the series: solution equilibration of **1b** gave a cis:trans ratio of 45:55 whereas solid state heating of this mixture for two days at 180°C gave a 5:95 cis:trans ratio. Products **1c** and **1d** were also isomerisable in the solid state. When the 50:50 cis:trans mixture of **1c** (obtained after solution equilibration) was heated 2 days at 180°C in the solid state a 95:5 ratio was obtained in favor of the cis isomer. Although further experiments are necessary, the same tendency was found for **1d** : solid state isomerisation of a 40:60 cis:trans mixture gave almost pure cis.



Heated 2 hours at 110°C in toluene	45	55
Heated 2 days at 180°C as a solid	5	95

II. Discussion :

The preceding results can be rationalized in the following manner : At room temperature, cis and trans isomers do not interconvert. As true diastereomers, they have physicochemical distinct properties and each of them has his own crystalline form. If the temperature is raised up to a value at which interconversion between the cis and trans form becomes fast, they can no longer be considered as diastereomers but as simple conformers of the same compound. Their crystalline forms should then be considered as polymorphs [13]. In general, at a given temperature and pressure one crystalline form of a given compound is more stable than the other one. There will be a thermodynamic tendency of the metastable crystal to transform into the more stable one. Of course, kinetic factors do not always allow such transformations at significant rates and some special conditions are required for solid to solid transformations to occur [13]. Such conditions are most probably fulfilled in the solid state isomerisations disclosed before. After cooling, conformers again become distinct diastereomers and the diastereomeric ratio is "frozen" at the point it had reached in the solid-solid transformation. Above the melting, ordering is destroyed and equilibration occurs very rapidly. Fast cooling then "freezes" the equilibrium reached in the melted phase.

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Conclusion

The compounds disclosed in this paper combine medium sized atropoisomerisation barriers and high melting points. These features allow atropoisomerisation in solution and in the solid state. The last method, giving diastereomeric ratios of up to 99:1 in favor of one atropodiastereomer, offers new opportunities to the relative stereochemical control of two stereogenic axes. The scope and limitations of this method are now under investigation.

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- [10] Diastereomeric ratios were determined by HPLC on a reversed phase column using MeOH/H₂O mixtures as eluent.
- [11] Determined on a Chiralpak AD column; elution, cyclohexane : i-PrOH (95:5), 1 mL min⁻¹.
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