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β-Oxo-Sulfoxide Rearrangement in the Synthesis of Vindorosine : Study of the Racemization Step

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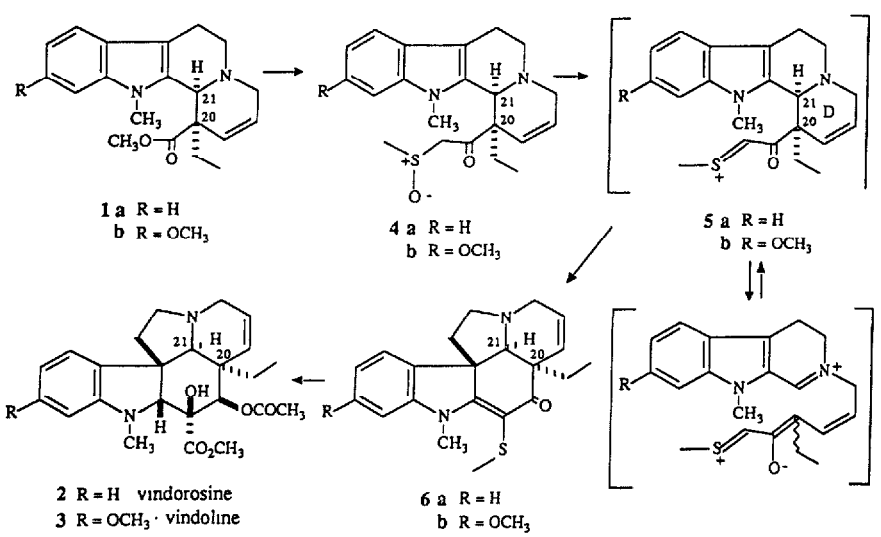
Abstract : The racemization step in the synthesis of Aspidospermane indole alkaloids, through Pummerer promoted skeletal rearrangement of β-oxo-sulfoxides 4, is discussed

The strategy for the synthesis of Aspidospermane indole alkaloids *via* the indolo[2,3-a]quinolizidine **1**, was developed some years ago for the preparation of vindorosine **2** and vindoline **3**.[1,2] This route to the Aspidospermane skeleton involved a rearrangement induced by a Pummerer-type reaction of the β-oxo sulfoxides **4** in the presence of *p*-toluenesulfonic acid (Scheme 1).



Scheme 1

The same reaction scheme was followed with the view of developing an enantioselective synthesis of vindoline **3**. However, the rearrangement step of the assumed optically pure precursor β-oxo-sulfoxide **4b**

gave compound **6b** as a racemic mixture.[3] This result was explained by the opening of the D ring of the intermediate **5b** by an acid-catalyzed reversible retro-Mannich reaction[4] (Scheme 1).

In order to avoid this racemization, we investigated non-acidic mild conditions to perform the skeletal rearrangement of **4a** into the Aspidospermane derivative **6a** Thus, sila-Pummerer reaction of the sulfoxide **4a** with ketenesilylacetals,[5,6] as methylketene ethyl trimethylsilylacetal, and catalytic amount of zinc iodide in acetonitrile at room temperature afforded **6a** in low yield (13%). The yield of **6a** improved when the reaction was carried out in the presence of trialkyl silyl trifluoromethanesulfonate and triethylamine in dichloromethane.[7-10] When triethylamine (1 3 equiv.) and *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf, 1.3 equiv.) were added to a 0.25 M solution of **4a** in dichloromethane at 0°C, the compound **6a** was obtained after 4 hours in 30% yield, together with unreacted **4a** (25%). A new compound was also isolated, in 18% yield, under these conditions and its structural analysis will be published later on.

The enantioselectivity of the mild skeletal rearrangement of **4a** to the Aspidospermane derivative **6a** was studied. The optical resolution of the indolo[2,3-a]quinolizidine **1a** could be achieved by preferential crystallization of L-dibenzoyltartrate of (-) **1a** from methanol.[11] The enantiomeric purity of the corresponding base was assessed by use of chiral shift reagent in NMR : the doubling of the side chain methyl and N-methyl resonances of the racemate (±) **1a** was observed in the presence of tris [3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-praseodymium (III) ($Pr(hfc)_3$).[12] Starting from optically pure indolo[2,3-a]quinolizidine (-) **1a**[11], the same TBDMSOTf induced reaction *via* **4a** afforded **5a** with complete racemization as shown by ^1H NMR. This observation led us to check the optical purity of the β-oxo-sulfoxide **4a** obtained from pure enantiomer (-) **1a**. Unexpectedly, this precursor proved to be racemic as well,[13] indicating that the formation of **4a** is the racemization step in contrast to the previously published conclusions.[3] Furthermore, the greater stability of a β-oxo methylester than a β-oxo-sulfoxide (17-CO-CH_2-CO_2CH_3 instead 17-CO-CH_2-$S(O)CH_3$ in formula **4b**) in preventing the retro-Mannich reaction, observed by P.L. Feldman and H. Rapoport in their synthesis of (-) vindoline,[14] is noteworthy.

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