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Remarkable Stereoelectronic Effect of the Methylenedioxy Phenyl System in the Total Synthesis of Cephalotaxine

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Abstract: Methylenedioxyphenyl unit displays a significant stereoelectronic effect in some key transformations in the total synthesis of cephalotaxine. The ring-strain of methylenedioxy ring may account for some important facile ring-skeleton rearrangements.

Keywords: Stereoelectronic effect, reductive rearrangement, cephalotaxine, total synthesis.

We have recently disclosed[1] two novel approaches for the total synthesis of cephalotaxine (CET), in which one of the key transformation involved a reductive skeletal rearrangement of cyclic amino enone **1b** leading to the designated pentacyclic key intermediate **3b** (65 %) predominately by the action of zinc in hot glacial acetic acid (**Scheme 1**), along with a small amount (< 5 %) of the direct enone reduction product **2b**. Interestingly, in an analogous series of synthesis with 3, 4-dimethoxyphenyl substitution instead of the normal 3, 4-methylenedioxyphenyl, we found that analogous amino enone **1a** gave a product mixture of the desired reductive rearrangement product **3a** and substantial amount of the enone reduction product **2a** in a ratio of about 2 : 1 in a comparable overall yield (*ca.* 60 %) under identical reaction conditions.

It is apparent that the substitution pattern of the phenyl ring in the starting amino enone **1** plays a significant role in this reductive rearrangement reaction. The methylenedioxy group is frequently present in a number of bioactive natural products as a stable catechol-protecting group as in CET. The dramatic stereoelectronic effects of the methylenedioxy group in the synthetic studies of CET have been documented in some cases[2-6]. For example, the Friedel-Crafts cyclization has been often used as an effective approach for the construction of the benzazepine ring system in CET synthesis. A collection of examples in Eqs. 1-4 clearly demonstrated the remarkable stereo electronic effect of the methylenedioxy phenyl compared with the dimethoxyphenyl in terms of the electrophilic reactivity of the substituted phenyl unit, which may result from the geometric constrain of the rigid methylenedioxy ring leading to a comparably less electron donation effect from the oxygen lone-pair into the phenyl π-system[4, 7].

To account for the observed distinctive stereoelectronic effects in **Scheme 1**, it occurred to us that the more electron-rich aryl with 3, 4-dimethoxyphenyl substituent

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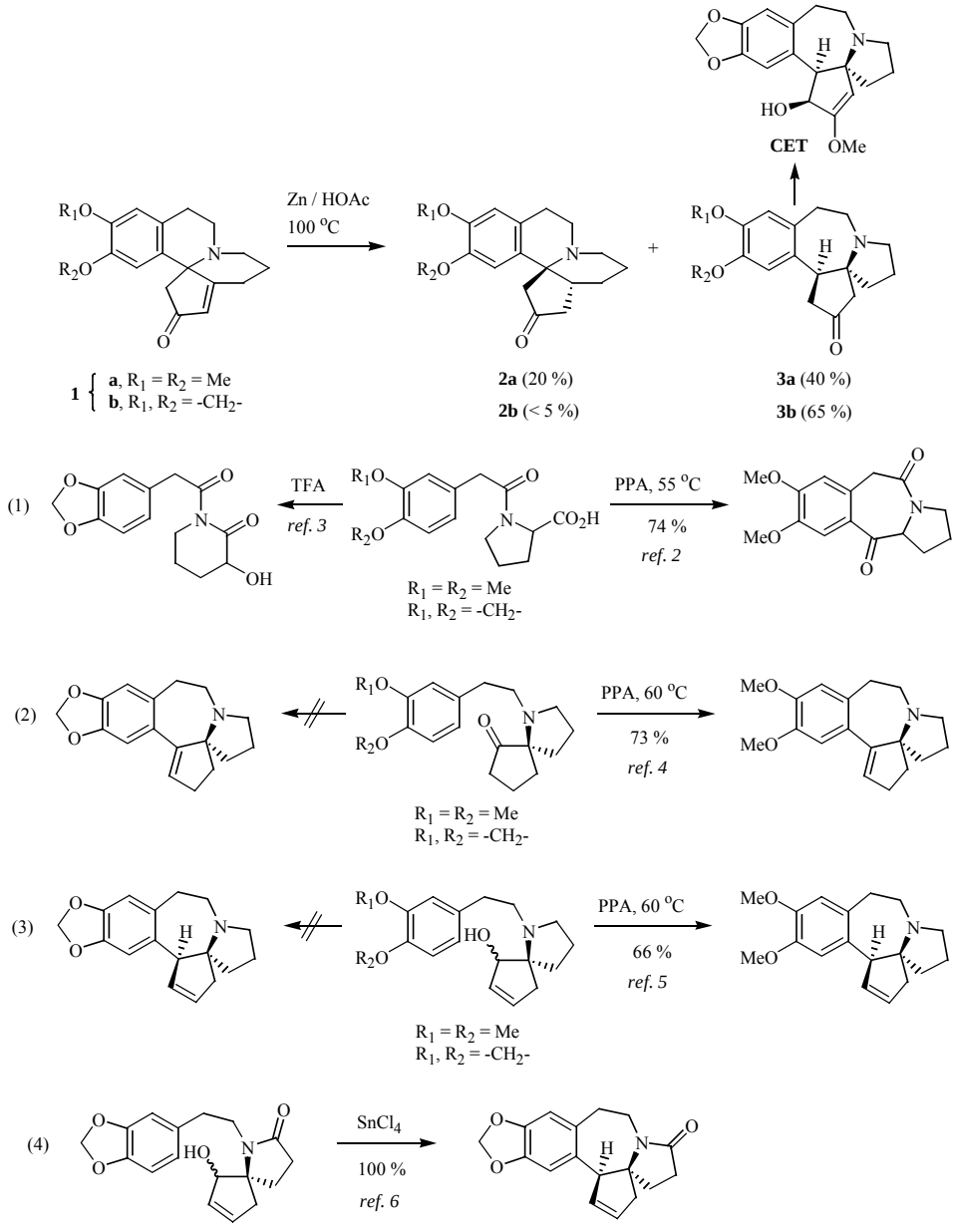
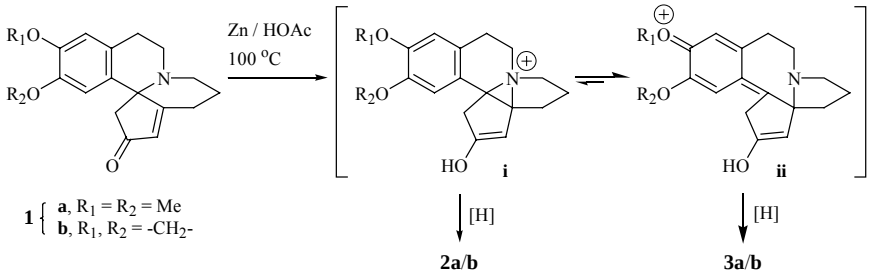
would like to maintain a strained aziridinium intermediate **i** formed by nitrogen lone-pair participating to the enone system (**Scheme 2**), whereas the less electron-rich aryl with 3, 4-methylenedioxy ring substituent tends to rearrange to a less strained ring system with most extended conjugation structure as in **ii**, which would produce the desired reductive rearrangement product predominately. Hydride reduction of the aziridinium intermediate **i** would give direct enone reduction product **2**.

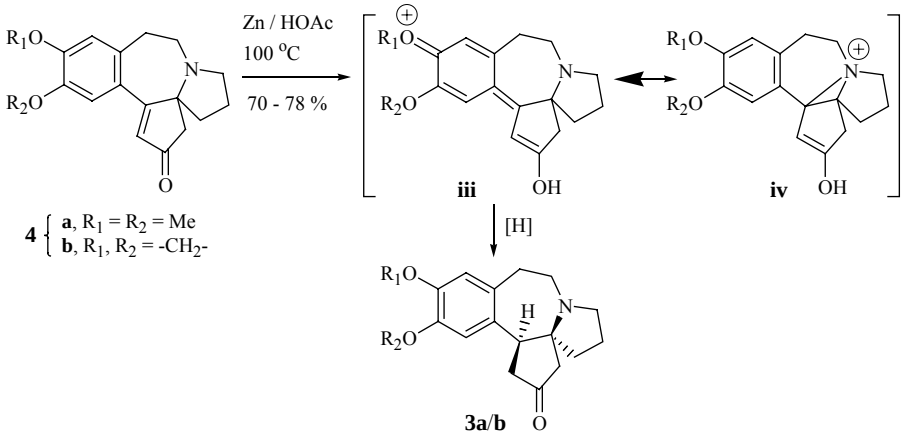
Scheme 1



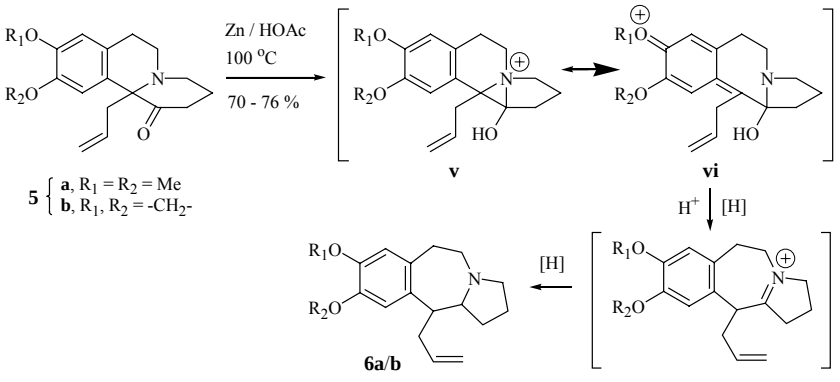
Scheme 2



Scheme 3



Scheme 4



Furthermore, this viewpoint was supported by the zinc-acetic acid reduction of amino enones **4a** or **4b** to the corresponding saturated amino ketone **3** exclusively without any detectable skeletal rearranged product as shown in **Scheme 3**. It is also worthy to note that the more extended conjugating resonance structure **iii** would be much

favorable than isomeric **ii**, and similarly aziridinium enol intermediate **iv** would be a more strained structure than isomeric **i**.

An additional example is the Clemmensen-Clemo-Prelog-Leonard reductive rearrangement[1] of cyclic α-amino ketone **5** providing exclusively the rearranged benzazepine unit in our recently reported CET synthesis regardless the substitution pattern of the phenyl ring. It is evident that this facile skeletal rearrangement was driven by nitrogen lone-pair participating to carbonyl and the subsequent ring-strain releasing toward the resonance structure **vi**.

In conclusion, the significances of the protecting group of catechol unit have been demonstrated in some key transformations in the synthesis of CET, which implies the unique stereoelectronic effect of the methylenedioxy group on the reactivity of the attached phenyl ring as well as the fused ring system. 3, 4-Methylenedioxy is a much better catechol-masking group which arrests the oxygen lone-pair electron from flowing into the phenyl ring system and therefore reducing the electrophilic reactivity of the phenyl ring system. The "ring-strain" or "ring-stress" caused by the methylenedioxy ring unit provides an extra-driving force for a number of synthetically (and perhaps biologically) significant skeletal structure transformations.

Acknowledgments

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