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HIGHLY STEREOSELECTIVE NUCLEOPHILIC ADDITION TO CYCLOPROPYL CARBONYLS: THE FACIAL SELECTIVITY IN THE CYCLOPROPYL KETONES IS OPPOSITE TO THAT IN THE CORRESPONDING ALDEHYDE

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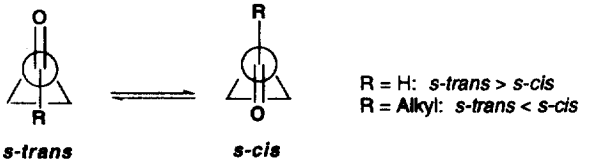
Abstract: Nucleophilic addition reaction of Grignard reagents to cyclopropylcarbaldehyde **4** proceeded highly selectively from the *si*-face to afford **5** in high yield. Although hydride reduction of the corresponding ketone **7** with L-Selectride® also proceeded highly diastereoselectively, the facial selectivity was reversed to give the *re*-face addition product **5**. On the other hand, reduction of **7** with DIBAL-H afforded *si*-face addition product **6** in high yield. The result suggested that these nucleophilic addition reaction proceeded via either the bisected *s-trans* or *s-cis* conformation of the cyclopropane derivatives.

Chemistry of cyclopropane derivatives has been extensively studied because of their biological importance.[1,2,3] Nucleophilic addition reactions of cyclopropyl carbonyls, such as cyclopropylcarbaldehydes or cyclopropyl ketones, are useful in synthetic organic chemistry,[2] especially when the addition reaction proceed stereoselectively. Although a number of the studies have been done,[2] only a few highly stereoselective examples, especially on acyclic cyclopropylcarbonyl derivatives, have been reported.[2a,b]

On the other hand, it has been recognized that cyclopropylcarbaldehydes and cyclopropy ketones preferentially exist in bisected conformations, namely *s-trans* and *s-cis* conformers, due to the characteristic stereo-electronic effects of the cyclopropane ring; the *s-trans* conformer is predominant in cyclopropylcarbaldehydes, conversely, the *s-cis* conformer is predominant in cyclopropyl ketones, as shown in Chart 1.[1a,3] Nucleophilic attacks to the cyclopropyl carbonyl may occur preferentially via these bisected conformations. This is because in the reaction course of the nucleophilic addition reaction, electrons of cyclopropane ring, which can be characterized as a strong π-donor, interact with the antibonding orbital of the incipient bond between the nucleophile and the carbonyl carbon, and this interaction can facilitate the reaction.[4]

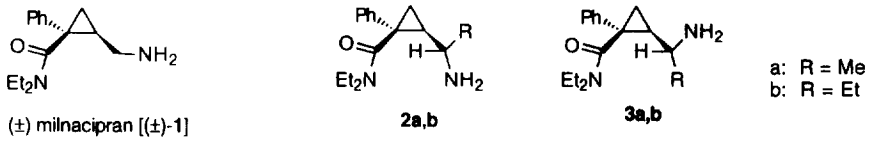
Chart 1



In recent years, we have been engaged in a study on developing novel antagonists of the NMDA (*N*-methyl-D-aspartic acid) receptor, which are expected to be new therapeutic agents for epilepsy, stroke, or ischaemia.[5] We designed several conformationally restricted analogs (CRA) of milnacipran (**1**),[6] namely **2**, **3**, and their enantiomers, as potent NMDA receptor antagonists.[7] During the synthetic study of them, we

found that nucleophilic addition reactions toward both cyclopropylcarbaldehyde **4** and the corresponding ketones **7a,b** proceeded highly stereoselectively, but the facial selectivity was almost completely reversed.

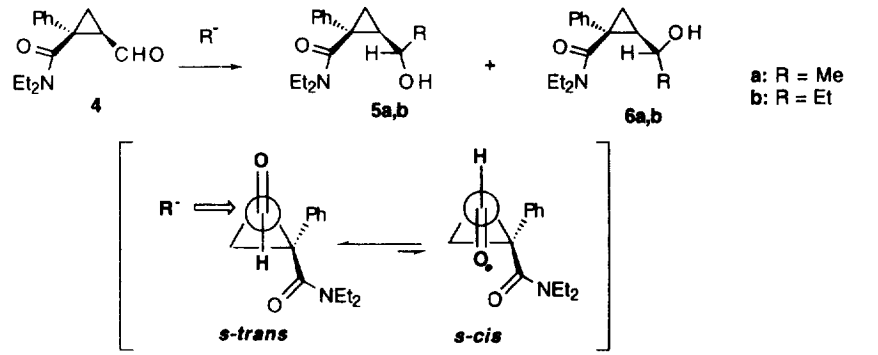
Chart 2



Reaction of cyclopropylcarbaldehyde **4** and MeMgBr (2.5 eq.) at -20 °C in THF gave addition product **5a**[8] highly stereoselectively, which was isolated in 92% yield, with a trace of diastereomer **6a** (**5a**:**6a** = 23:1).[9] Similarly, the reaction of **4** with EtMgBr also proceeded stereoselectively; the corresponding ethyl derivatives **5b** and **6b** were isolated in 90% and 4% yields, respectively.

Cyclopropylcarbaldehydes are thought to exist preferentially in bisected *s-trans* conformation as described above. In fact the X-ray crystallographic analysis of aldehyde **4** (Chart 4)[10] clearly indicates the bisected *s-trans* conformation is preferable. This is the first X-ray crystallographic structure that detects the bisected *s-trans* conformation of cyclopropanecarbaldehyde derivatives. The nucleophilic addition reactions would proceed from the least hindered *si*-face of **4** in the *s-trans* conformation[4] to give **5a** or **5b** diastereoselectively.[11]

Chart 3

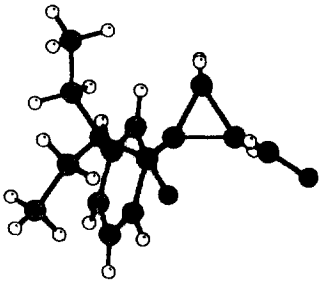


We required both diastereoisomers **5** and **6** to access target compounds **2** and **3**.[12,13] Therefore, stereoselective reduction of ketones **7a** and **7b** was next investigated. Ketones **7a** and **7b** were prepared by PDC oxidation of **5a** and **5b** in CH_2Cl_2, in 94 and 87% yields, respectively. Reduction of **7b** with $NaBH_4$ in MeOH at room temperature afforded the undesired 2'*S*-alcohol **5b** as the major product in 70% yield (**5b**:**6b** = 4:1).[14] When **7b** was treated with L-Selectride® at -78 °C in THF, **5b** was obtained highly selectively (91%, **5b**:**6b** = 50:1[14]). If the conformation of **7b** in the reaction course is similar to that observed by its X-ray crystallographic analysis[15] as shown in Chart 5, the facial selectivity of the addition with these nucleophilic hydride reagents can be explained as the hydride attack occurring from the least hindered face

(*re*-face) to the carbonyl of **7b**. The result is also consistent with the previous reports[1a,3] that cyclopropyl ketones preferentially exist in the bisected *s-cis* conformation.[4]

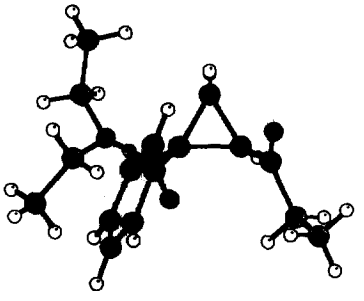
Surprisingly, when **7b** was treated with DIBAL-H in THF at -78 °C desired 2'*R*-alcohol **6b** was obtained highly selectively in 95% yield (**5b**:**6b** = 1:50).[14] Similar desirable result was also obtained in the DIBAL-H reduction of methyl ketone **7a** (yield 90%, **5a**:**6a** = 1:33[14]). When DIBAL-H, which is recognized as an electrophilic reduction reagent for carbonyl groups, is coordinated to the carbonyl of **7**, a conformation like *s-trans* (shown in Chart 6) would be preferred due to the steric repulsion between the two bulky isobutyl and diethylcarbamoyl groups. The hydride attack from the least hindered face (*si*-face) to the intermediate would give the desired product highly selectively. These results showed the stereoselectivity of the hydride reduction almost completely reversed when the reaction was done by a nucleophilic or electrophilic reducing reagent. To our knowledge, only one example on steroid derivatives that showed almost complete reversion of stereoselectivity in hydride reductions[16] similar to our results, has appeared.

Chart 4



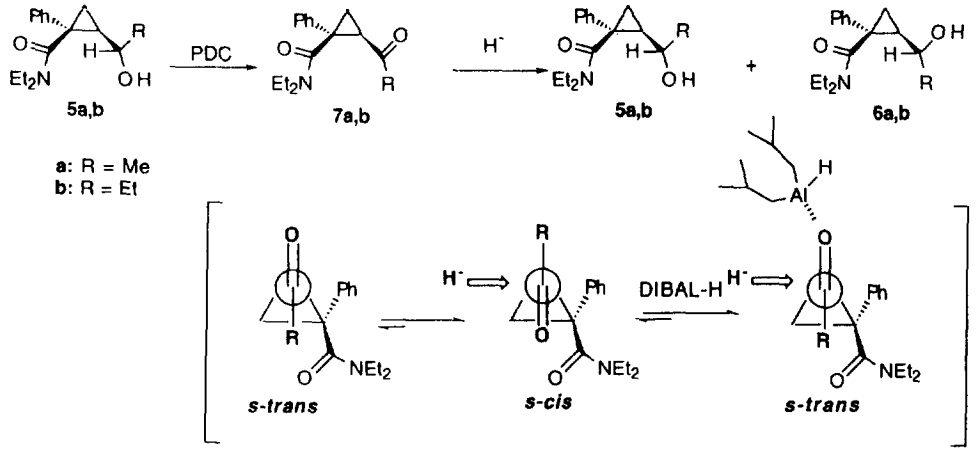
X-ray crystallographic structure of 4

Chart 5



X-ray crystallographic structure of 7b

Chart 6



Cyclopropylcarbaldehydes and cyclopropyl ketones have been thought to exist preferentially in bisected *s-trans* and *s-cis* conformations, respectively, from their theoretical calculations, NMR analyses, or electron diffraction studies.[1a,3] This study would be the first experimental evidence that demonstrates the stereochemical pathways of the nucleophilic attack to the cyclopropyl carbonyl can be determined by the predominant bisected conformation of cyclopropane derivatives[4] which is predictable from the stereoelectronic effect.

Acknowledgment

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4. The reaction pathway of the nucleophilic addition through their bisected conformation would be preferable due to the interaction between the antibonding orbital and electrons of cyclopropane ring which can be explained by Cieplak theory: a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552. b) Cieplak, A. S. ; Tait, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 5875-5876. c) Satoh, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Am. Chem. Soc.* **1995**, *117*, 4279-4287.
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7. Most recently, we found that (±)-milnacipran [(±)-**1**], a clinically useful antidepressant due to inhibiting the re-uptake of serotonin by the nerve terminal in CNS, was a new class of NMDA receptor antagonists. Shuto, S.; Takada, H.; Mochizuki, D.; Tsujita, R.; Hase, Y.; Ono, S.; Shibuya, N.; Matsuda, A. *J. Med. Chem.* **1995**, *38*, 2964-2968.
8. The stereochemisty of **5a** was confirmed from the X-ray crystallograhic analysis of the *O-p*-iodobenzoyl derivative of **5a**.
9. Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Matsuda, A. *Tetrahedron Lett.* submitted.
10. A total of 1174 independent reflections were collected and used for the structure analysis. The final R value was 0.056.
11. The reaction would not proceed via a chelation-controlled pathway, because the stereoselectivity was not changed when the reaction was done in the presence of HMPA (3 mol eq.).
12. Inversion of the configuration of the secondary hydroxyl by nucleophilic substitution reactions was unsuccessful.
13. The target CRA **2a,b** and **3a,b** were synthesized from **5a,b** and **6a,b**, respectively.
14. The ratio of diastereomers produced was confirmed by 500 MHz ^{1}H NMR spectrum of the crude product.
15. A total of 1463 independent reflections were collected and used for the structure analysis. The final R value was 0.059.
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