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# Highly stereoselective addition of Grignard reagents to *C*-cyclopropylnitrone via the bisected *s-trans* conformation. An efficient synthesis of PEDC, a potent NMDA receptor antagonist having a cyclopropane structure

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**Abstract**

An efficient synthesis of PEDC (**1**), a potent NMDA receptor antagonist of a cyclopropane structure, was achieved. The highly stereoselective addition reaction of MeMgBr to *C*-cyclopropylnitrone **2**, via its bisected *s-trans* conformation which can be predicted from the stereo-electronic effects, was developed as the key step. The *s-trans* conformation predominant in *C*-cyclopropynitrone **2** was suggested by NOE experiments. © 2000 Elsevier Science Ltd. All rights reserved.

Stereoselective preparation of biologically important cyclopropane derivatives is of great interest.[1] It is known that α,β-unsaturated cyclopropanes, such as cyclopropylalkenes, -carbaldehydes and -ketones, preferentially exist in bisected *s-trans* or *s-cis* conformation, due to the characteristic stereo-electronic effects of the cyclopropane ring, as shown in Fig. 1a.[1a] We previously showed that nucleophilic attacks of organometallic reagents to the carbonyls adjacent to a cyclopropane occur highly stereoselectively via the bisected conformations.[2,3] In this report, we describe stereoselective addition of Grignard reagent to a *C*-cyclopropylnitrone via its bisected *s-trans* conformation.

In recent years, we have been working to develop novel efficient antagonists of the NMDA (*N*-methyl-D-aspartic acid) receptor, which are expected to be new therapeutic agents for epilepsy, stroke, or ischemia. During our studies, we found 1-phenyl-2-[(*S*)-1-aminoethyl]-*N*,*N*-diethylcyclopropanecarboxamide (**1**) is a new class of potent non-competitive NMDA receptor antagonists.[4] We needed an alternative synthetic method of the large scale preparation of **1** for further biological evaluation.[5]

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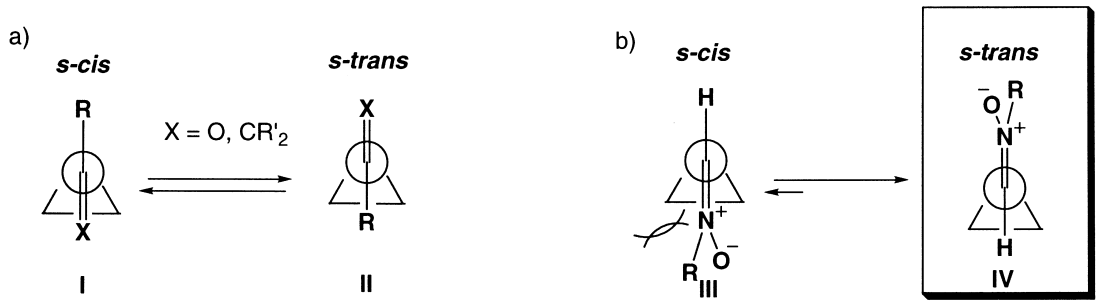
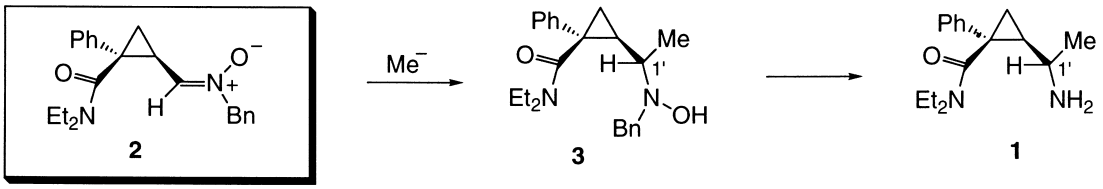



Figure 1.

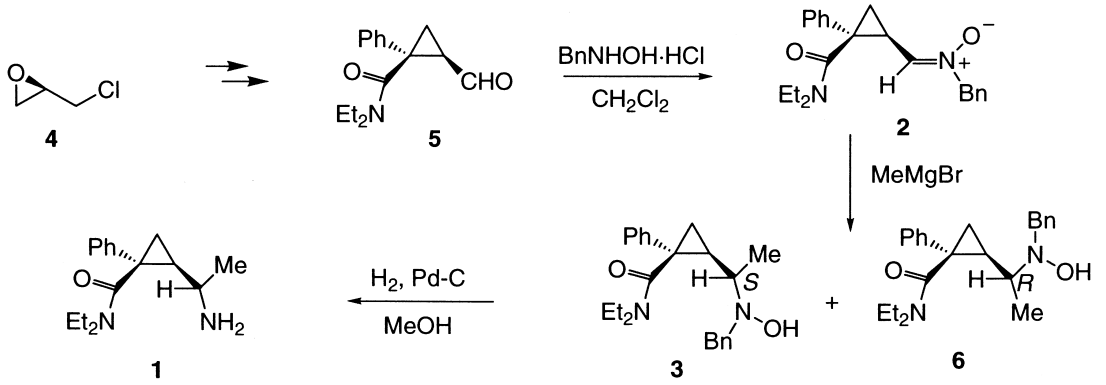
The chelation controlled addition of organometallic reagents to nitrones has been studied extensively, because of its usefulness in the preparation of a variety of asymmetric amines.[6] We planned to develop stereoselective addition to aldonitrones adjacent to a cyclopropane via a non-chelation controlled pathway. We hypothesized that *C*-cyclopropylnitrones should preferentially exist in the bisected conformation, due to the stereoelectronic interaction between the imino moiety and the cyclopropane ring, as in the cyclopropylcarbonyls and the cyclopropylalkenes; the *s-trans* conformer would predominate, due to the steric repulsion of the alkyl substituent at the nitrogen of the nitrone for the cyclopropane ring in the *s-cis* conformation, as shown in Fig. 1b. If this is indeed the case, the stereoselective nucleophilic addition to *C*-cyclopropylnitrones from the least hindered face should occur as in the case of the cyclopropylcarbonyls described above. Thus, we investigated whether the nucleophilic addition of Grignard reagent to the cyclopropylnitrone **2** gives the desired 1′*S*-product **3**, as shown in Scheme 1. Subsequent deprotection would give the target NMDA receptor antagonist **1**.




Scheme 1.

Treatment of the asymmetric cyclopropylcarbaldehyde **5**,[2] which was prepared from (–)-*epi*-chlorohydrin (**4**), with *N*-benzylhydroxyamine hydrochloride in $CH_2Cl_2$ gave quantitatively the *N*-benzyl-*C*-cyclopropylnitrone **2** (Scheme 2).

We wanted to determine whether the bisected *s-trans* conformation would predominate in compound **2** as we had expected, since none of studies on the conformation of *C*-cyclopropylnitrones have been reported. Thus, NOE experiments of **2** in $CDCl_3$ were performed. When the H-1′ was irradiated, very strong NOEs were observed at the H-3 of the cyclopropane (16.5%), which was in the position *trans* to the adjacent 1-phenyl group, and at the benzyl methylene proton (20.0%), as shown in Fig. 2. This NOE study suggests that the molecule would be rigidly restricted in the bisected *s-trans* conformation. As far as we know, this is the first result demonstrating that nitrones adjacent to cyclopropane ring prefer the bisected conformation.[6]




Scheme 2.

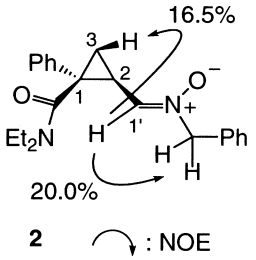



Figure 2.

Based on the results on this conformational analysis, we next investigated addition reactions of MeMgBr on the *C*-cyclopropylnitrone **2**, since Grignard reagents are known to add to nitrones efficiently.[7] The results are summarized in Table 1. The reaction was first carried out with 5 equiv. of the Grignard reagent in THF at –78°C for 2 h to give the addition products, in which the desired 1′-*S* product **3** was produced with high stereoselectivity (*R*:*S* = 5:95), although the yield was unsatisfactory (45%, entry 1). The stereochemistry was confirmed by the conversion of **3** into the final product PEDC (**1**), as described below. The reactions at relatively higher temperatures increased the yield somewhat, but the stereoselectivity decreased (entries 2 and 3). When the reaction was carried out at –78°C for 8 h with $Et_2O$:THF (2:1)[8] as the solvent, it gave the addition products in 83% yield with high stereoselectivity (entry 5, *R*:*S* = 6:94), whereas in a similar reaction in THF alone (entry 4), the yield was only moderate. We next investigated the effect of additives on the reaction with 3 equiv. of MeMgBr in $Et_2O$:THF (entries 7–11). Addition of HMPA, $ZnBr_2$, or TMSCl (entries 7–9) did not improve the yield or the stereoselectivity compared to the reaction without an additive (entry 6). The best result was observed when the reaction was performed with $MgBr_2$ as an additive[7a,b] (entry 10, 81%, *R*:*S* = 2:98). A similar reaction with 2 equiv. of MeMgBr lowered both the yield and stereoselectivity (entry 11).

Thus, a highly stereoselective addition to the nitrone **2** has been developed. The facial selectivity of the addition of the Grignard reagents can be explained as an attack occurring from the least hindered face (*si*-face) on to the imino carbon of **2**, in the bisected *s-trans* conformation **IV**′, to give the desired 1′*S*-product **3** highly stereoselectively, as shown in Fig. 3. This study suggests that

Table 1
The addition reactions of MeBgBr to *C*-cyclopropylnitorone **2**

| Entry | reagent (eq) | solvent | temp, °C | time, h | additive (eq) | yield (**3**+**6**) | ratio [**3** (1'*S*):**6** (1'*R*)][a] |
|---|---|---|---|---|---|---|---|
| 1 | MeMgBr (5) | THF | -78 | 2 | - | 45 | 95:5 |
| 2 | MeMgBr (5) | THF | 0 | 2 | - | 53 | 82:18 |
| 3 | MeMgBr (5) | THF | rt | 2 | - | 56 | 74:26 |
| 4 | MeMgBr (5) | THF | -78 | 8 | - | 56 | 94:6 |
| 5 | MeMgBr (5) | $Et_2O$/THF[b] | -78 | 8 | - | 83 | 94:6 |
| 6 | MeMgBr (3) | $Et_2O$/THF[b] | -78 | 8 | - | 63 | 90:10 |
| 7 | MeMgBr (3) | $Et_2O$/THF[b] | -78 | 8 | HMPA (5) | 32 | 83:17 |
| 8 | MeMgBr (3) | $Et_2O$/THF[b] | -78 | 8 | TMSCl (2) | 88 | 86:14 |
| 9 | MeMgBr (3) | $Et_2O$/THF[b] | -78 | 8 | $ZnBr_2$ (2) | 62 | 87:13 |
| 10 | MeMgBr (3) | $Et_2O$/THF[b] | -78 | 8 | $MgBr_2$ (2) | 81 | 98:2 |
| 11 | MeMgBr (2) | $Et_2O$/THF[b] | -78 | 8 | $MgBr_2$ (2) | 62 | 90:10 |

[a]Determined by $^1$H NMR. [b] $Et_2O$/THF (2:1)

the reaction pathway of the nucleophilic addition to a cyclopropylnitrone probably occurs via the predominant bisected conformation, which can be predicted from stereoelectronic effects. In the course of the nucleophilic addition, the electrons of the cyclopropane ring, which can be characterized as a strong π-donor,[1a] interact with the antibonding orbital of the incipient bond between the nucleophile and the imino carbon of the nitrone **2**. The nucleophilic addition can be facilitated by this interaction, which is maximal when the nitrone is in the bisected conformation. As a result, the reaction should proceed highly stereoselectively.

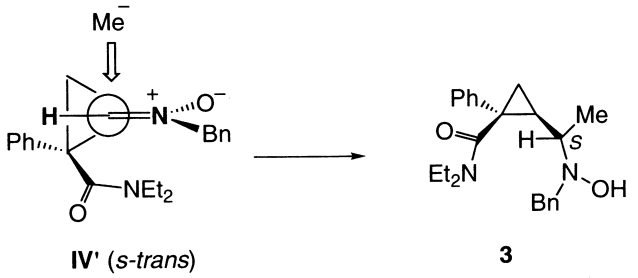



Figure 3.

The *N*-benzyl groups of the 1′*S*-products **3** was readily removed by hydrogenation with Pd–C in MeOH to give the targets **1** in 98% yield.

In summary, we have developed an efficient method for preparing the potent NMDA receptor antagonist PEDC (**1**), and we have demonstrated that the highly stereoselective addition of Grignard reagent to *C*-cyclopropylnitrones would occur via its bisected *s-trans* conformation.

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2. (a) Ono, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 221–224. (b) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamashita, K.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 915–923.
3. Stereoselective hydride reductions of cyclopropylcalbonyls: (a) Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 7245–7247. (b) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1995**, *60*, 2474–2487; and hydroboration of isopropenylcyclopropanes: (c) Cossy, J.; Blanchard, N.; Hamel, C.; Meyer, C. *J. Org. Chem.* **1999**, *64*, 2608–2609, which are likely to be via the bisected conformations, have also been reported.
4. (a) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 641–644. (b) Shuto, S.; Ono, S.; Hase, Y.; Ueno, Y.; Noguchi, T.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1996**, 39, 4844–4852. (c) Shuto, S.; Ono, S.; Imoto, H.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1998**, *41*, 3507–3514. (d) Noguchi, T.; Ishii, K.; Imoto, H.; Otubo, Y.; Shuto, S.; Ono, S.; Matsuda, A.; Yoshii, K. *Synapus* **1999**, *31*, 87–96.
5. The previous method (Ref. 2b) has the disadvantage that: (1) use of a large excess of explosive and toxic $NaN_3$ (Turnbull, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; 1995; Vol 7, pp. 4509–4512) is unsuitable for the large-scale preparation of the compounds; and (2) alkyl groups which can be introduced at the 1′-position are limited, which prevents further structure–activity relationship studies.
6. The X-ray crystallographic structure of the nitrone **2** also demonstrated that it exists in the bisected *s-trans* conformation in the solid state.
7. For examples, see: (a) Ukaji, Y.; Hatanaka, T.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1993**, 1313–1316. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. (c) Merino, P.; Castillo, E.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1725–1729. (d) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, F. *J. Org. Chem.* **1997**, *62*, 5497–5507. (e) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 2371–2374. (f) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301–12322. (f) Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35–46. (f) Dondoni, A. *Synthesis* **1998**, 1681–1706. In these reactions, the facial selectivity has been explained to be via the chelation-controlled pathway.
8. Compound **2** was insoluble in $Et_2O$.