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SYNTHESIS OF (+)- AND (-)-MILNACIPRANS AND THEIR CONFORMATIONALLY RESTRICTED ANALOGS

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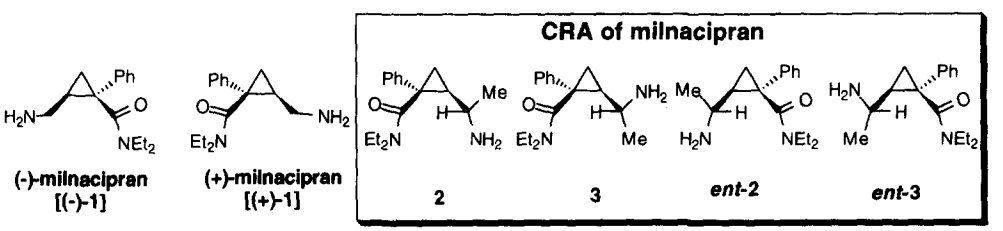
Abstract. Reaction of (*R*)-epichlorohydrin [(*R*)-**5**] and phenylacetonitrile (**6**) in the presence of $NaNH_2$ in benzene gave a cyclopropane derivative which was isolated as lactone **4** [(1*S*,2*R*)-2-oxo-1-phenyl-3-oxabicyclo[3.1.0]hexane] of 96% e.e. in 67% yield, after alkaline hydrolysis of the cyano group. Compound **4** was readily converted to (+)-milnacipran [(+)-**1**], by which the absolute stereochemistry of (+)-**1** was confirmed. (1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminoethyl]-cyclopropane-*N*,*N*-diethylcarboxamindes (**2**), a conformationally restricted analog of **1**, was also synthesized in high enantiomeric purity from **4**. Starting from (*S*)-epichlorohydrin [(*S*)-**5**], their corresponding enantiomers, namely (-)-milnacipran [(-)-**1**] and ***ent*-2**, were also synthesized.

Although NMDA receptor antagonists are effective in experimental models of epilepsy and stroke, the antagonists known so far also have serious behavioral effects and/or are poorly transported to the brain.[1] Therefore, development of other types of efficient NMDA receptor antagonists has been awaited.

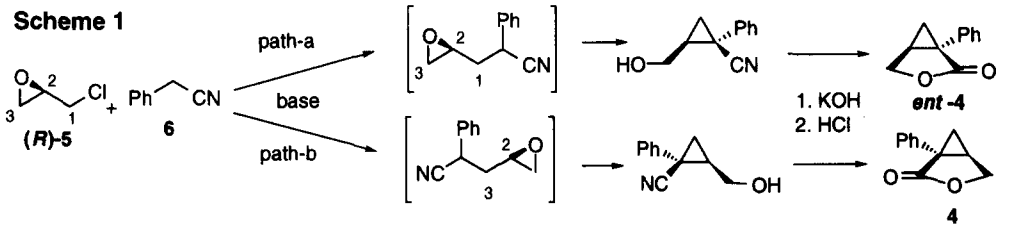
Most recently, we reported that (±)-(*Z*)-2-aminomethyl-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide [(±)-milnacipran, (±)-**1**), known as a clinically efficient antidepressant due to inhibiting the reuptake of serotonin by the nerve terminal in central nervous system,[2] was a new class of NMDA receptor antagonists.[3] We designed conformationally restricted analogs (CRA) of **1**,[4] namely **2**, **3**, and their enantiomers (***ent*-2** and ***ent*-3**), increasing the specific affinity for the NMDA receptor. In this paper we describe highly stereoselective synthesis of (+)- and (-)-milnacipran as well as **2** and ***ent*-2**.



We have developed a convenient synthetic method for (±) milnacipran [(±)-**1**] and its derivatives via racemic lactone (±)-**4**, which was prepared from (±)-epichlorohydrin [(*RS*)-**5**] and phenylacetonitrile (**6**),[5] as the key intermediate.[3] The corresponding optically active lactones **4** and ***ent*-4** were thought to be efficient intermediates for the synthesis of the target compounds. In this reaction, two pathways, path-a and -b, could be considered (Scheme 1). If a nucleophilic attack occurs highly selectively either through path-a or -b, this would provide an efficient method to access both lactone **4** and ***ent*-4** in optically active form, because both (*R*)- and (*S*)-epichlorohydrins are available. Burgess and Ho reported that in a similar reaction with an optically active triflate, nearly all of the optical activity of the triflate was transferred to

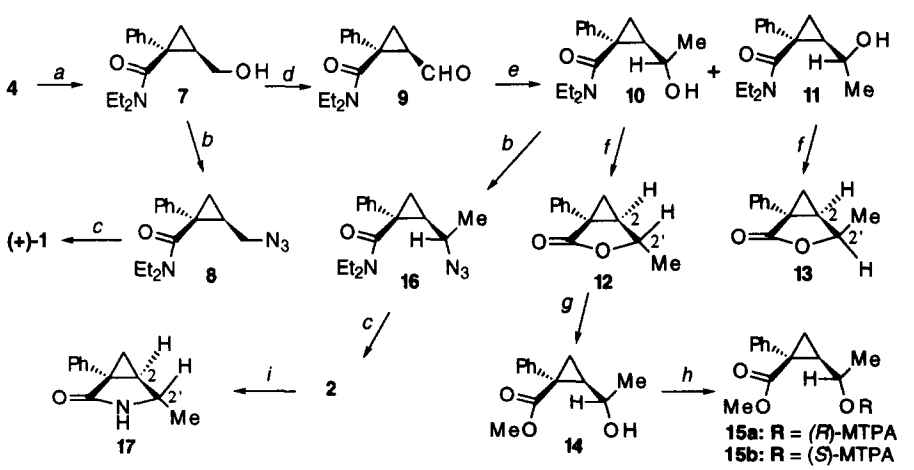
the cyclopropane product through path-a.[6] However, significant instability of the triflate, which would decrease the optical purity, has also been recognized.[7] On the other hand, when chiral epichlorohydrins are used instead of the corresponding triflate in the similar reactions, the reactions proceeded through path-b mainly, while slight decreases of the enantiomeric purity of the product have been observed compared with the reaction with the triflate.[8] However, because both (*R*)-**5** and (*S*)-**5** of high optical purity (>98% e.e.) are commercially available[9] and are significantly stable compared with the corresponding triflate, we selected chiral epichlorohydrines, (*R*)-**5** and (*S*)-**5**, as the synthons and tried to synthesize chiral lactones **4** and ***ent*-4** of high enantiomeric purity.

Scheme 1



We investigated the reaction of (*R*)-**5** and an anion of phenylacetonitrile under various conditions. The resulting cyclopropane product was isolated as lactone **4**, after alkaline hydrolysis of the nitrile group. When the reaction was done with $NaNH_2$, as a base, in benzene at room temperature, the result was the most desirable; (*1S,2R*)-lactone **4** of 96% e.e.[10] was isolated in 67% yield[11] (confirmation of the stereochemistry is described below), which was superior to previous results[6,8] in both the yield and the enantiomeric purity of the product. This indicates that the nucleophile attacks highly selectively at the epoxide through path-b.

Scheme 2

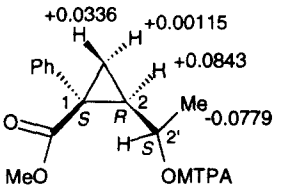


Conditions: a) $LiNH_2$/THF; 87% b) NaN_3, Ph_3P, CBr_4/DMF; **8**, 99%; **16**, 62% c) H_2, Pd-C/MeOH; **1**, 87%; **2**, 97% d) DMSO, oxalyl chloride, then Et_3N/CH_2Cl_2; 96% e) MeMgBr/THF; **10**, 92%; **11**, 3% f) HCl/MeOH; **12**, 63%; **13**, 68% g) i. KOH/MeOH; ii. $TMSCHN_2$/MeOH; 2 steps, 55% h) (*R*)- or (*S*)-MTPACl, DMAP/MeCN; quant. i) i. 6 N HCl; ii. DCC, Et_3N/THF; 2 steps, 65%

Treatment of **4** with $LiNEt_2$ in THF at -78 °C afforded a ring-opening product **7**. From **7**, (+)-milnacipran [(+)-**1**][12] was readily synthesized[13] via azide derivative **8**, according to the method for preparing (±) **1** that has been developed by us (Scheme 2).[3] Similarly, starting from (*S*)-**5**, the corresponding enantiomer (-)-**1** was also synthesized.[12]

Next, synthesis of CRA, **2** and ***ent*-2** from **7** and ***ent*-7**, respectively, was investigated. Swern oxidation of **7** gave aldehyde **9** in high yield. Reaction of **9** and MeMgBr at -20 °C in THF gave addition product **10** highly stereoselectively,[14] which was isolated in 92% yield with a trace of diastereomer **11** (**10**:**11** = 23:1). The absolute stereochemistry was confirmed at this stage by modified Mosher's method.[15]

The absolute stereochemistry was confirmed at this stage by modified Mosher's method.[15] Compound **10** was heated with HCl in MeOH gave lactone **12** in 63% yield.[16] Similarly, the corresponding diastereomer **13** was obtained from **11**. Successive treatment of **12** with NaOH and trimethylsilyldiazomethane in MeOH gave methyl ester **14**, which was then converted to the corresponding *R*- and *S*-MTPA esters (**15a** and **15b**). From $\Delta\delta$ (δ_S -δ_R) values of their ^{1}H NMR spectra, the configuration of the secondary alcohol moiety was identified as *S*. The configuration of the 2-position of the cyclopropane was assigned from the ^{1}H NMR spectra of conformationally rigid lactones **12** and **13**; the coupling constant between H-2 and H-2' of **13** was 4.5 Hz, while the coupling was not observed in **12**. Thus, the stereochemistry of **12** was identified as (1*S*, 2*R*, 2'*S*) and **13** as (1S, 2*R*, 2'*R*).[17] From the result, the absolute stereochemistry of optically active milnaciprans were also confirmed that the configuration of (+)-**1** is as (1*S*, 2*R*) and (-)-**1** as (1*R* 2*S*).



Δδ values (ppm)

Treatment of **10** with $NaN_3/CBr_4/Ph_3P$ system in DMF[18] gave azide derivative **16** with retention of the configuration at the 2'-position (the identification of 2'-configurations is described below). Catalytic hydrogenation of **16** with Pd-C in MeOH gave the target CRA, **2**, in high yield. To confirm the configuration at the 2'-position, **2** was converted to lactam **17** by treatment successively with 6 N HCl and DCC/Et_3N in THF. From the coupling constant between H-2 and H-2' of **17** (2.0 Hz), the 2'-configuration was assigned as *S*.[19]

Starting from (+)-epichlorohydrin [(*s*)-**5**], the corresponding enantiomer, ***ent*-2** was also synthesized.

Although studies on synthesizing optically active cyclopropane derivatives have been extensively done in recent years due to their biological importance, an efficient general method for preparing them of high enantiomeric purity has not been developed.[20] This method with (*R*)- or (*S*)-epichlorohydrin as a synthon for chiral cyclopropanes would be one of the most useful methods; chiral epichlorohydrins are readily available in high optical purity and stable enough, and cyclopropane products of high optical purity can be obtained readily on a large scale[21] as demonstrated in this study.

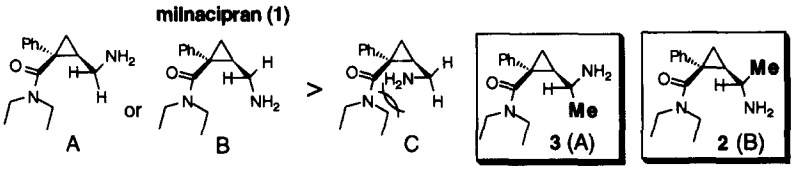
Acknowledgment

We thank to Mr. H. Takada for helpful discussion and Mrs. K. Yamashita for X-ray crystallographic analysis. We also thank to Daiso Co., Ltd. for their gift of chiral epichlorohydrins.

References and Notes

1. Collingridge, G. L. Watkins, J. C.; "The NMDA Receptor", eds, IRL Press at Oxford Univ. Press; Oxford, UK, 1994.
2. a) Brukey, M. *Drugs future* **1986**, *11*, 21-23. b) Moret, C.; Charveron, M.; Finberg, J. P. M.; Cozinier, J.; M. Brukey, M. *Neuropharmacology* **1985**, *24*, 1211-1219.

3. Shuto, S.; Takada, H.; Mochizuki, D.; Tsujita, R.; Hase, Y.; Ono, S.; Shibuya, N.; Matsuda, A. *J. Med. Chem.* **1995**, *38*, 2964-2968.
4. Adjacent substituents on a cyclopropane ring mutually exert steric repulsion quite significantly, because they are fixed in an eclipsed conformation to each other. Consequently, conformations of the substituents on a cyclopropane can be restricted by the steric effect of adjacent substituents. Therefore, depend on the configuration of the alkyl group introduced, the conformation of the aminomethyl moiety which is essential for the activity of (±)-**1**, can be restricted; conformer B would be predominant in **2** and ***ent*-2**, conversely, conformer A would be predominant in **3** and ***ent*-3** as shown here.



5. Mouzin, G.; Cousse, H.; Bonnaud, B. A. *Synthesis* **1978**, 304-305.
6. From a triflate of 92 % e.e., the corresponding cyclopropane derivative of 91% e.e. was synthesized in 50% yield: Burgess, K.; Ho, K-K. *J. Org. Chem.* **1992**, *57*, 5931-5936.
7. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437-475.
8. (a) Reaction of (*S*)-**5** of 88% e.e. and heptynyllithium gave the corresponding epoxide of 76% e.e.: Russell, S. W.; Pabon, H. J. J.. *J. Chem Soc. Perkin 1* **1982**, 545-552. (b) Reaction of (*R*)-**5** and sodium dimethyl malonate gave the corresponding cyclopropane product of 93% e.e. in 36% yield: Pirrung, M. C.; Dunlap. S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301-1310.
9. Available from Daiso Co., Ltd.
10. Enantiomeric purity was measured by HPLC with Chiralcel-OJ column (Daicel Chemical Co., Ltd.).
11. When the other solvents or bases were used, the yield and/or the enantiomeric purity were decreased.
12. (+)-**1**: mp 176-178°C; $[\alpha]_D^{25}$ + 72.8 ° (c 0.95, $CHCl_3$). Anal. calcd for $C_{15}H_{22}N_2O{\cdot}HCl$: C, 63.72; H, 8.14; N, 9.91. Found; C. 63.38; H, 8.16; N, 9.84. (-)-**1**: mp 171-172°C; $[\alpha]_D^{22}$ - 75.1 ° (c 0.99, $CHCl_3$). Anal. calcd for $C_{15}H_{22}N_2O{\cdot}HCl$: C, 63.72; H, 8.14; N, 9.91. Found; C. 63.43; H, 8.15; N, 9.58.
13. Although (+)- and (-)-milnaciprans have been prepared using optical resolution method with (*R*)-1-phenylethylamine, the optical purity was low (75% e.e. and 80% e.e., respectively): Bonnaud, R.; Calmel, R., Patoiseau, J-F.; N'Guyen, N-T.; Cousse, H. *J. Chromatogr.* **1985**, *318*, 398-403.
14. On the facial selectivity of the reaction see: Ono, S.; Shuto, S. Matsuda, A. *Tetrahedron Lett.* in press.
15. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.
16. Successive treatment of **10** with KOH/glycerol and DCC/MeOH also gave **12**.
17. The absolute stereochemistry was also confirmed from the X-ray crystallographic analysis of the corresponding *O-p*-iodobenzoate of **10**.
18. Yamamoto, I.; Sekine, M.; Hata, T. *J. Chem. Soc. Perkin 1* **1983**, 306-310.
19. Similarly, from **11**, which was obtained by stereoselective hydride reduction of the corresponding ketone, **3** was also synthesized (cf. ref. 14). Compound **3** was converted to the corresponding lactam of which $J_{2,2'}$ value was 5.9 Hz.
20. a) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247-1270. b) Wong, H. N. C.; Hon, M-Y.; Tse, C-Y.; Yip, Y-C. *Chem. Rev.*, **1989**, *89*, 165-198.
21. More than 30 g of chiral cyclopropane derivative **4** or ***ent*-4** can be prepared at once.

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