A Synthesis of (–)-*cis*-2-Aminomethylcyclopropanecarboxylic Acid [(–)-CAMP]

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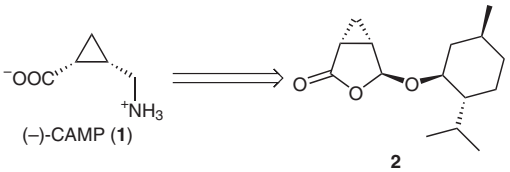
Abstract: An enantioselective synthesis of (–)-*cis*-2-aminomethylcyclopropanecarboxylic acid [(–)-CAMP] has been achieved in 2.5% total yield over ten steps starting from 2-furaldehyde. The synthesis features diastereoselective cyclopropane formation via diazene, followed by oxime formation and the reduction, for construction of the γ-aminobutyric acid (GABA) motif.

Key words: amino acids, cycloaddition, photochemistry, ring contraction, stereoselective synthesis

Inhibitory neurotransmission in the mammalian central nervous system is mediated by γ-aminobutyric acid (GABA) receptors.[1] Deactivation of GABA receptors, for example, by decreasing the concentration of GABA, causes seizures, because of an imbalance to the concentration of excitatory neurotransmitter, glutamate. Decrease of the inhibitory neurotransmission causes not only epilepsy, but also other neuronal disorders such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and drug addiction.[1c] Selective ligands for GABA receptors are thus important as a tool for understanding the biological functions of the receptors, as well as a possible candidate for treatment of such neuronal diseases associated with GABA receptors. In 1980, *cis*-2-aminomethylcyclopropanecarboxylic acid (CAMP) was synthesized in the racemic form and introduced to neurochemistry by Allan et al. as a conformationally restricted analogue of GABA.[2] After twenty years, (+)-CAMP and (–)-CAMP were characterized by the same research group as a full agonist and an antagonist for GABAc receptor, respectively.[3] Because of the intriguingly diverse neuroactivities, several practical methods have been reported to date for the enantioselective synthesis of (+)- and (–)-CAMP. In 1997, Galeazzi et al. reported a ten-step synthesis using phenylethylamine as a chiral auxiliary.[4] Duke et al. employed the resolution of racemic CAMP by esterification with chiral alcohol in 1998.[5] In 2002, Baxendale et al. reported an eight-step synthesis using polymer-supported reagents while the enantiomeric purity was low (90% ee).[6] Rodríguez–Soria et al. achieved a six-step synthesis employing radical reaction in 2008.[7] Some of them[4,5,7] demonstrated the enantioselective synthesis of subgram quantities of CAMP. We also started our own study to develop an easy, practical, and promising synthetic entry that will be capable of producing both enantiomers of CAMP with high enantiomeric purity. Here, we describe our preliminary results to reach the goal.

We decided to employ chiral auxiliary assisted organic synthesis for the preparation of highly enantiopure CAMP that will be used for precise biological studies. In 1994, Feringa's group reported the diastereoselective synthesis of cyclopropane (enantiomer of **2**, see Scheme 1) using L-menthol as a chiral auxiliary.[8] However, they did not isolate the cyclopropane *ent*-**2**, and synthetic details were not described in the paper probably due to the lability of *ent*-**2** and/or the diazene precursor (see below), which causes poor reproducibility. In the present study, we reinvestigated the synthesis of the cyclopropane **2** (Scheme 1) and successfully established the isolation procedure. Eventually, we achieved the synthesis of (–)-CAMP (**1**) by using the cyclopropane **2** as a synthetic intermediate as discussed below.



Scheme 1 Our synthetic plan toward (–)-CAMP (**1**) using D-menthol as a chiral auxiliary

The synthesis started with butenolide **3**, known as (5*S*)-(D-menthyloxy)-2(5*H*)-furanone[9] and readily prepared in 20% yield in two steps from 2-furaldehyde (Scheme 2). 1,3-Dipolar cycloaddition of diazomethane to butenolide **3** proceeded slowly but cleanly in Et_2O at –40 °C over two days to give rise to diazene **4**[10] in 66% isolated yield. The purification was carefully performed by flash column chromatography using neutral silica gel 60N, because diazene **4** was unstable under both acidic and alkaline conditions. Even under neutral conditions, diazene **4** should not be stored and used immediately, since **4** gradually decomposes into a complex mixture. In the 1,3-dipolar cycloaddition, diastereomer of **4** (structure not shown) was also generated in ca. 25% yield as judged from ^{1}H NMR. The structures were determined on the basis of 2D NMR experiments (COSY, NOESY). The selectivity was comparable to that reported by Feringa;[8] however, the present study is the first demonstration that diastereomerically pure diazene **4** is isolated and characterized. The major isomer **4** was then subjected to photoirradiation (high-

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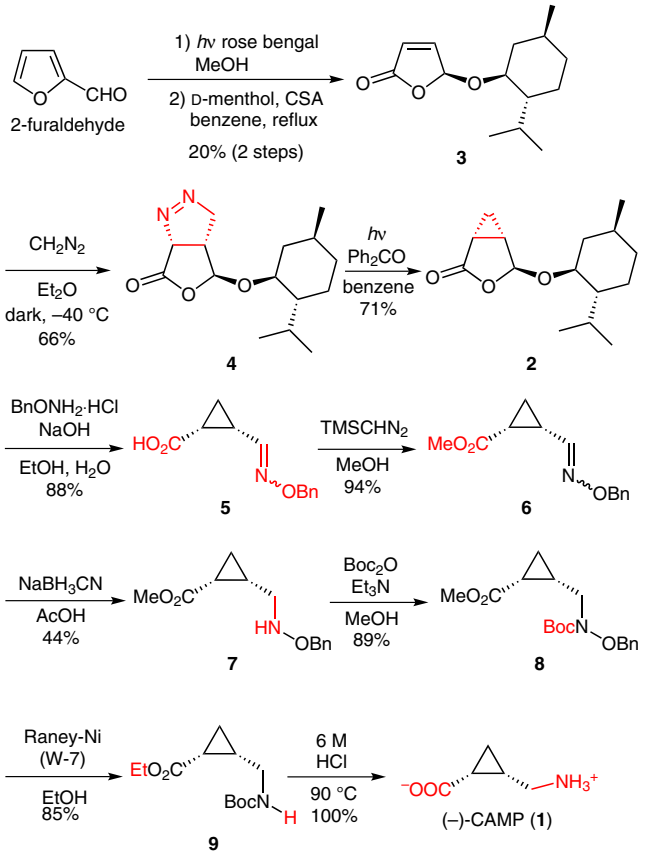
pressure mercury lamp, benzophenone, benzene) to induce cyclopropane formation with concomitant elimination of nitrogen. While small amounts of by-products such as undesired 3-methylbutenolide (structure not shown)[8] were observed, the desired cyclopropane **2**[11] was cleanly provided in 71% yield.



Scheme 2 Ten-step enantioselective synthesis of (–)-CAMP (**1**)

With cyclopropane **2** in hand, we then investigated the introduction of nitrogen functionality. After several experiments, treatment of **2** with benzyloxyamine was found to be convenient, furnishing oxime ether **5** in an excellent yield (88%). After esterification ($TMSCHN_2$), efficient conditions were explored for reduction of the oxime ether to generate amine directly. The earlier attempts were, however, discouraging. For example, hydrogenation (H_2, 10% Pd/C, EtOH)[12] of **6** (and also the precursor **5**) induced cleavage of the cyclopropane ring predominantly. We therefore screened mild conditions, and finally found that stepwise reductions [$NaBH_3CN$, AcOH; Boc_2O, Et_3N; Raney-Ni (W-7, EtOH][13] cleanly realize the desired transformation to furnish *N*-Boc amine **9** in 33% yield. Global deprotection under acidic conditions (6 M hydrochloric acid, 90 °C) successfully delivered the desired (–)-CAMP (**1**) with high enantiomeric purity (100% ee) in quantitative yield.[14] Spectroscopic data including the $[\alpha]_D$ value were in good agreement with those reported.[4–7]

In conclusion, we have successfully developed a new entry for enantioselective synthesis of *cis*-(–)-2-aminomethylcyclopropanecarboxylic acid [(–)-CAMP, **1**] employing *d*-menthol as the chiral auxiliary. Starting from 2-furaldehyde, the synthesis was performed in 2.5% yield over ten steps. In addition to the efficient cyclopropane formation, adoption of hydrophobic and nonvolatile intermediates is apparently worthy of note in our successful synthesis of such a hydrophilic molecule of low molecular weight. Efforts are currently directed toward the large-scale synthesis of the antipode [(+)-CAMP], a potent agonist for GABAc receptor,[3] using *l*-menthol as the chiral auxiliary to prove the synthetic practicality of our methodology. The next challenge also includes successful reduction of oxime ether **5** to deliver (–)-CAMP (**1**) directly without sacrificing the cyclopropane ring, which greatly shortens the synthesis to six steps.

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(10) Spectroscopic data for diazene **4**: $[\alpha]_D^{20.1}$ –57.2 (*c* = 0.94, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 5.05 (d, *J* = 6.8 Hz, 1 H), 4.41 (d, *J* = 2.0 Hz, 1 H), 3.95 (m, 1 H), 3.79 (m, 1 H), 3.35 (td, *J* = 10.6, 4.3 Hz, 1 H), 2.34 (m, 1 H), 1.95 (m, 1 H), 1.70 (m, 1 H), 1.52–1.57 (m, 2 H), 1.25 (m, 1 H), 1.10 (br, 1 H), 0.99–1.01 (m, 6 H), 0.85–0.95 (m, 4 H), 0.69–0.79 (m, 2 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 167.0, 104.3, 93.5, 83.1, 77.7, 48.1, 39.9, 39.1, 34.3, 31.3, 25.7, 23.2, 22.3, 21.0, 15.9.
(11) Spectroscopic data for cyclopropane **2**: $[\alpha]_D^{20.3}$ +137.0 (*c* = 1.07, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.41 (s, 1 H), 3.53 (td, *J* = 10.8, 4.11 Hz, 1 H), 2.01–2.19 (m, 4 H), 1.61–1.66 (m, 2 H), 1.37 (m, 1 H), 1.15–1.25 (m, 2 H), 0.77–1.04 (m, 13 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 99.8, 77.5, 47.7, 40.2, 34.2, 31.4, 25.3, 23.1 (2 ×), 22.1, 20.9, 17.1, 15.6, 11.8.
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(14) A suspension of protected CAMP **9** (13.0 mg, 0.053 mmol) in hydrochloric acid (6 M, 0.200 mL) was stirred at 90 °C for 8 h. The reaction mixture was then concentrated under reduced pressure and subjected to ion-exchange chromatography (Dowex 1-X8, 1.0 × 5 cm, H_2O) to give (–)-CAMP hydrochloride (8.2 mg, 100%) as a colorless solid; $[\alpha]_D^{20.3}$ –35.9 (*c* = 0.50, H_2O). IR (KBr): 3430, 3105, 1706, 1600, 1428, 1194, 861 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 3.08–3.19 (m, 2 H), 1.80 (m 1 H), 1.53 (m, 1 H), 1.20 (m, 1 H), 0.94 (m, 1 H). ^{13}C NMR (100 MHz, D_2O): δ = 176.5, 37.9, 17.7, 17.4, 12.8.

