Chinese Chemical Letters Vol. 13, No. 6, pp 528 – 530, 2002
http://www.imm.ac.cn/journal/ccl/html

Study on the Synthesis of Metabolite of Clausenamide (CM1)

Xing Zhou LI, Ke Mei WU, Dao Fei HUANG, Liang HUANG*

Institute of Materia Medica , Chinese Academy of Medical Sciences & Peking Union Medical College. 1 Xian Nong Tan St. Beijing 100050

Abstract: (+)CM1, (-)CM1 as well as (±)CM1 – the metabolites of clausenamide were synthesized from β-phenyl-(N-*p*-methoxylbenzyl)-ethanol amine through 8 and 6 steps respectively.

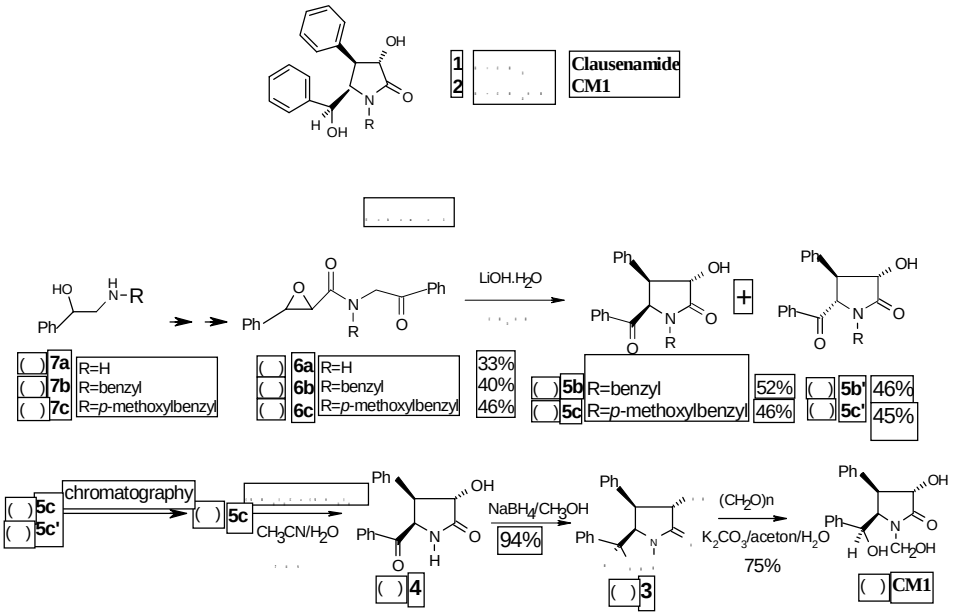
Keywords: Metabolite, clausenamide, intramolecule cyclization, debenzylation, hydroxymethylation.

(-) Clausenamide (**1**) showed strong nootropic action, while its (+) antipode had no such an action. The content of CM1(**2**) in the metabolites of (-)**1** is much higher than that of (+)**1**[1]. For comparing the nootropic activity of enantiomers, (+) and (-) **CM1** were synthesized.

CM1 is the hydroxylated product of the N-methyl group of clausenamide. Oxidation of the C_3-OH and C_6-OH protected clausenamide to introduce the hydroxyl group into the methyl was tried but unsuccessful. Then *de novo* synthesis **CM1** on the basis of synthetic route of clausenamide[2] was designed (as shown in **Scheme 1**) by starting with β-phenyl-ethanol amine **7a** or its N-substituted derivative **7b,c**. **7a-c** were converted to corrospounding epoxide **6a-c** with no trouble[2]. However the intramolecule cyclization of compound **6a** was slow and complicated in the presence of catalytic amount of LiOH in water/methanol. Thus N-benzyl derivative **6b** was prepared. **6b** did cyclize smoothly, gaving **5b** (mp 175-177°C) and **5b′**. But the intented debenzylation of **5b** by different methods, such as catalytic hydrogenolysis, acidic solvolysis[3], Li/NH_3 reduction, and ammonium ceric nitrated (CAN)[4] or t-BuLi/O_2[5] was all failed. *p*-Methoxybenzyl derivative **6c** was thus prepared considering the *p*-methoxybenzyl group is easier to be stripped off than benzyl group. **6c** was cyclized in methanol/ water with 0.2 eq LiOH to give the mixture of **5c** (mp 152-154°C) and **5c′** (mp: 155-157°C). They were separated by chromatography to give pure **5c** and **5c′**. CAN oxidation worked nicely on N-*p*-methoxybenzyl derivative **5c** to give demethyl-clausenamidone **4** which yielded (±) **CM1** (with indentical ^{1}HNMR and Ms as reported [1]) by subsequent reduction and hydroxymethylation[5] as shown in **Scheme 1.**

(-) and (+) **CM1** were prepared through resolution of the intermediate **5c** with N-phthalyl –L-alanine as resolving agent as shown in **Scheme 2**. The esterification of **5c** with N-phthalyl –L-alanine gave a mixture of diasteroisomers **8** and **8′**, which was

very hard to separate. Therefore debenzylation with CAN was carried out first, the neonatal mixture of **9** and **9′** was separated by recrystallization and chromatography. Reduction the ketone with $NaBH_4$ followed by hydrolysis of the ester group with NaOH of **9** or **9′** in one pot separately gave the enantiomerically pure (–) **3** or (+) **3** respectively. Hydromethylation of (–) **3** and (+) **3** yielded the corresponding (-)**CM1** and (+)**CM1** with ee>99% (determined by HPLC with chiral column). The study on the correlation of the sign of rotation with the absolute conformation of (+)**CM1** and (-)**CM1** and their physiological activity is in progress.



Scheme 2

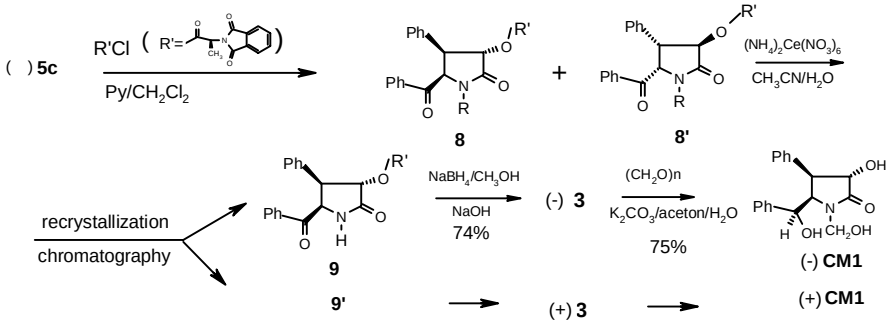


Table 1 the physicochemical constant of (±)**CM1**,(-)**CM1**,(+)**CM1** and (+)**3**, (-)**3**

Compound	melting point	sign of rotation
(±)**CM1**	199~200°C	----------
(-)**CM1**	191~193°C	$[\alpha]_D^{18}$ -119（c, 0.261, CH_3OH）
(+)**CM1**	189~191°C	$[\alpha]_D^{18}$ +117（c, 0.394, CH_3OH）
(-) **3**	203-205°C	$[\alpha]_D^{15}$ -144 (c,0.497, CH_3OH)
(+) **3**	204-207°C	$[\alpha]_D^{15}$ +140 (c,0.419, CH_3OH).

Acknowledgments

This work was supported by the National Natural Science Foundation of China. (No.29790121)

References and Notes

1. Q. Q.YAO, *Chin. J.of Pharmacology and Toxicology*, **1999,** *13* (3), 214.
2. L. HUANG, *Chin. Chem.Lett*., **1994**, *5* (4), 267.
3. J. E Sempl, *J.Am.Chem.Soc*. **1980**, *107*, 7505.
4. M. YAMAURA, *Bull.Chem.Soc.Jap*., **1995**, *58*, 1413.
5. R. M.Willlams, *Tetrahedron Lett*., **1989**, *30* (4), 451.
6. B. Jouglet, *Syn.Comm*, **1995,** *25* (23), 3869.

Received 8 January, 2002