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Study on the Synthesis of Metabolite CM2 of Clausenamide

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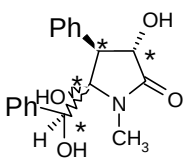
Abstract: Synthesis of the optically active metabolite of clausenamide **CM2** (3, 5-dihydroxy-5-(α-hydroxylbenzyl)-1-methyl-4-benzylpyrrolidin-2-one) from 3-O-acetyl- clausenamide was described.

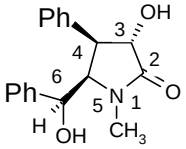
Keywords: Metabolite, clausenamide, dehydration, dihydroxylation, deacylation.

(-) Clausenamide(I) possesses nootropic effect than its (+) isomer[1]. The metabolites of these two optical enantiomers were almost the same, but the content of the metabolites **CM1**(III) and **CM2** (II) of (-) I were much higher than those of (+) I[2]. In order to study the difference of bioactivity between the enantiomers, synthesis of optically active **CM1**(III) and **CM2** (II) has been undertaken. The preparation of **CM1** was reported in the previous paper[3], here the synthesis of **CM2** was described.

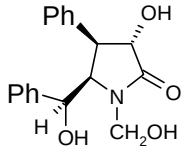
Figure 1



C5-**OH** configuration undefined **CM2** ( )



(-)3S,4R,5R,6S **Clausenamide** ( )
(+)3R,4S,5S,6R **Clausenamide** ( )



3S,4R,5R,6S **CM1** ( )
3R,4S,5S,6R **CM1** ( )

CM2 is the C5 hydroxylated product of of clausenamide (I), the hydroxylation could take place either at the same side (α-face) or at the opposite side (β-face) of the C5-**H** of (-) I. In any case the configuration of C6 should not be touched. But the direct introduction of the tertiary C5-**OH** is not an easy task. Therefore the synthetic route through hydroxylation of $\Delta^{5,6}$ (-) clausenamide (**2**)was designed for preparing the metabolite (-)**CM2** as shown in the **Scheme**.

(-)3-O-acetyl-clausenamide(**1**)(mp 244-246°C, $[\alpha]_D^{14}$ = -167 (c 0.106, $CHCl_3$)) was dehydrated under the condition of $POCl_3$/pyridine[4] at ambient temperature to give **(-)2**

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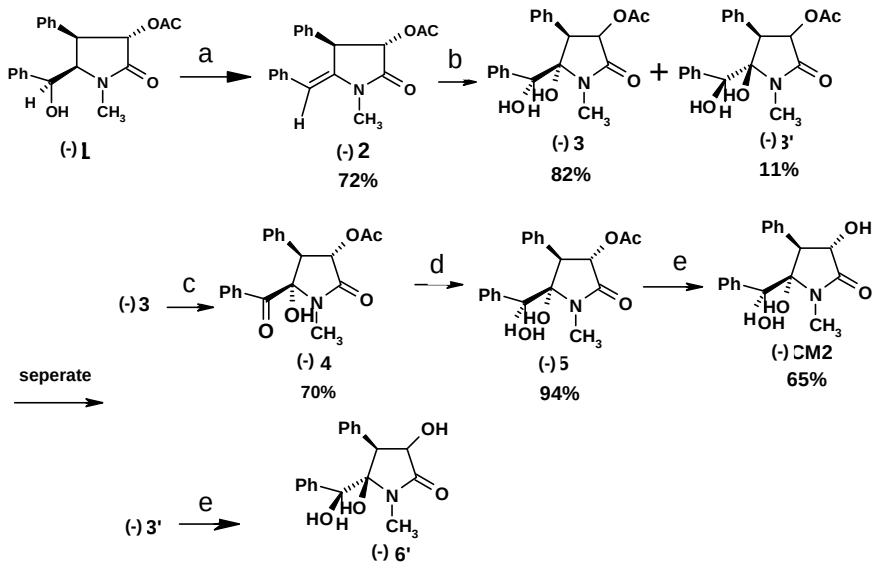
(mp 119-120°C, $[\alpha]_D^{18}$ = -330 (c 0.870, $CHCl_3$)). The NOE-DIFF indicated the double bond is in *trans* form.

Scheme



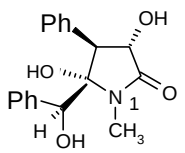
Reagents and conditions: a. $POCl_3$/Py, b. OsO_4/NMO/THF/Acetone, c. DMSO/oxalyl chloride,/ THF/TEA, d. $NaBH_4$/MeOH, e. Sm/I_2/MeOH

Compound **(-) 2** was *cis*-dihydroxylated with OsO_4/NMO to give the main product (-)**3**(mp 125-128°C, $[\alpha]_D^{15}$ = -323 (c 0.346, CH_3OH)) with 82% yield and the minor product (-)**3′**. The NOE effect between the single sharp peak of C5-O**H** (δ, 5.66) and the the double peak of C4-**H** (δ, 3.76) indicated that C5-**OH** being at the same side(*α*-side)of C4-**H**, which means the *cis*-dihydroxylation mainly took place at the less hindered side as shown in **Scheme**. In this way the configuration of C6 was inverted from S as in (-) I to R**.** This most likely is not the right structure. The *β*-face dihydroxylated product(-)**3′** would retained the C6 S configuration and the C5-**OH** was at the *β*-face**.** It was deacylated to give **6′**. However the physical constants and spectral data of which did not coincide with what reported for (-) **CM2**.

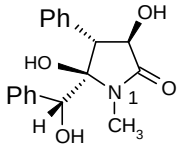
From above experimental results, it is evident that (-)**CM2** has the C5-OH at the α-face with S configuration of C6. This led to try *trans*-dihydroxylation of (-) **2** with various methods, but all were failed. A pathway through oxidation of the C6-**OH** in (-) **3** to ketone (-)**4** and then reduced to hydroxyl group was adopted on the basis of the reduction of (-)ketone of clausenamide [(-)clausenamidon] giving stereospecific S configuration[5] of C6. (-)**3** was oxidized by Swern oxidation to yield α-hydroxylketone (-)**4**(mp 125-128°C, $[\alpha]_D^{14}$ = -310 (c 0.360, $CHCl_3$)) . Reduction of the ketone group of (-)**4** with $NaBH_4$ gave (-)**5** (mp 153-156°C, $[\alpha]_D^{18}$ = -31.9 (c 0.455, CH_3OH)). Under the mild and neutral deacylation condition of Sm/I_2/MeOH[6] an oil was obtained with identical physical constants and spectral data as reported for (-)**CM2** ($[\alpha]_D^{18}$ = 53.6 (c

0.497, CH_3OH）. (+) Clausenamide($[\alpha]_D^{18}$ =+54.1（c 0.475, CH_3OH）) gave the enantiomer (+) **CM2** by the same process. According to the C5-OH substitution, the absolute configurations of (-)**CM2** and (+)**CM2** were assigned as (3S,4S,5S,6S) and (3R, 4R, 5R, 6R) respectively as shown in **Figure 2**.

Figure 2



(-)3S,4S,5S,6S **CM2** **( )**



(+)3R,4R,5R,6R **CM2** **( )**

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