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A concise total synthesis of (−)-dehydroclausenamide utilizing the novel formation of *cis*-epoxide as the key step

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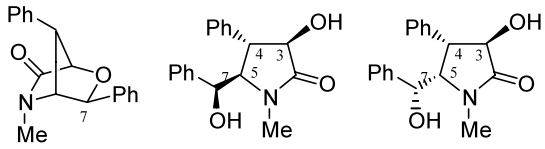
Abstract—The asymmetric total synthesis of (−)-dehydroclausenamide **1** was accomplished through a concise and efficient synthetic route employing as the key step the novel formation of *cis*-epoxy amide **7**, which was resulted from the reaction of starting material **4** bearing an optically pure *erythro* vicinal diol unit with 5*H*-3-oxa-octafluoro pentanesulfonyl fluoride ($HCF_2CF_2OCF_2CF_2SO_2F$) in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU).

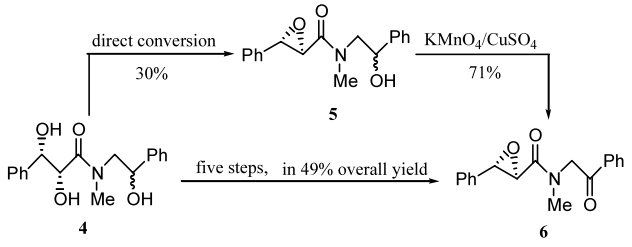
Dehydroclausenamide **1**, neoclausenamide **2** and clausenamide **3** are three major biologically active lactams isolated from aqueous extract of dry leaves of Chinese folk medicine *Clausena lansium*.[1,2] These naturally occurring molecules exhibit a remarkable hepatoprotective effect against chemical toxins, such as carbon tetrachloride and thioacetamide in preliminary animal tests; further investigation showed they have potent anti-amnaesic activity.[2] Their interesting bio-activity and poor availability led to active synthetic activities. In 1987, Hartwig[3] first achieved the total synthesis of (+)-**3**. Since then, Huang,[4] Ikeda[5] and Roberts[6] and our group,[7] respectively, reported the asymmetric total syntheses of (−)-**1**, (+)-**2**, (−)-**3** and (+)-**3**.



1 **2** **3**

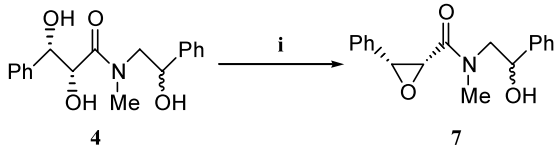
In the course of our synthetic studies toward (+)-**2**, we used amide **4** as an intermediate which can be easily prepared starting from mandelic acid and methyl cinnamate. However, the direct transformation of **4** to *trans*-epoxy amide **5** only resulted in a low yield (30%) (Scheme 1), which led us to devise a longer synthetic route including protection and deprotection steps. Thus, after five consecutive steps, the oxidation product ketone **6** was obtained in 49% overall yield.[7]

In our continued research program concerting fluoroalkanosulfonyl fluoride induced reactions and their application in organic synthesis,[8] we found that fluoro alkanosulfonyl fluorides can conveniently convert some vicinal diols into the corresponding epoxides.[9] When this reaction was applied to optically pure *erythro* vicinal diol unit of amide **4**, a smoothly transformation to the corresponding **7** with the structural feature of *cis*-epoxy amide was achieved in 82.5% yield, while another free hydroxyl group remained intact (Scheme 2).



4 **5** **6**

Scheme 1.



4 **7**

Scheme 2. *Reagents and conditions*: (i) $HCF_2CF_2OCF_2CF_2SO_2F$, DBU, CH_2Cl_2, 0°C, 82.5%.

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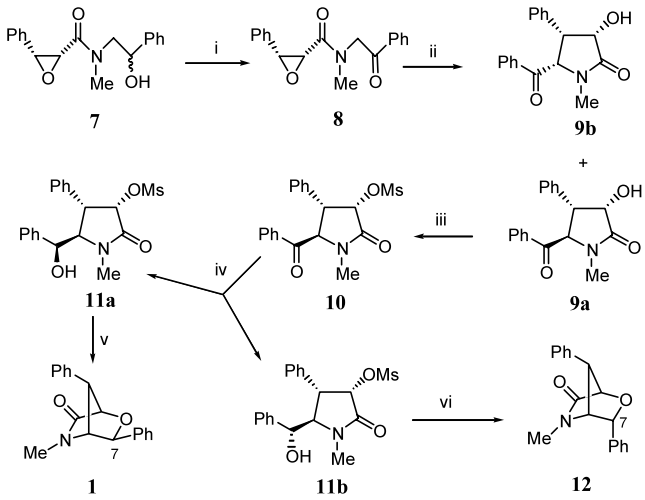

Scheme 3. *Reagents and conditions*: (i) PDC, CH_2Cl_2, rt, 82%; (ii) 1% aq. Me_4NOH, CH_2Cl_2, 40–45°C, 79%; (iii) MsCl, Et_3N, CH_2Cl_2, 0°C, 96%; (iv) $NaBH_4$, THF, rt, for **11a**, 54%, for **11b**, 46%; (v) $KOBu^t$, THF, rt, 100%; (vi) $KOBu^t$, THF, rt, 100%.

Based on this novel result, we then carried out the total synthesis of (−)-**1** with a concise and efficient synthetic route employing **7** as the key intermediate. Herein, we would like to report the results of our study (Scheme 3).

With the key intermediate **7** in hand, we then continued our synthetic sequence (see Scheme 3). The reaction of **7** with pyridinium dichromate (PDC) in CH_2Cl_2 furnished an oxidation product **8** in 82% yield. Subsequent base-catalyzed cyclization of **8** in a biphasic medium (CH_2Cl_2:H_2O 1:1) provided cyclized lactam **9a** as a single product in 79% yield. No undesired C-5 isomer **9b** was formed under this condition. Interestingly, when this reaction was performed in a solution (THF:H_2O 1:1) instead of a biphasic medium (CH_2Cl_2:H_2O 1:1), a mixture of **9a** and **9b** in a ratio of 1.6:1 was produced in a nearly quantitive yield. Treatment of **9a** with methanesulfonyl chloride (MsCl) and Et_3N in CH_2Cl_2 generated **10** in 96% yield. Next, our attention was turned to the reduction of the ketone group at the C-5 side chain of **10**. In the hope to obtian a higher ratio of desired **11a** to unwanted **11b** in the product, bulky reducing agents, such as diisobutylaluminum hydride (DIBAL-H), potassium and lithium tri-*sec*-butylborohydride (K and L-Selectride) were firstly investigated. Unfortunately all attempts were unfruitful. Finally, the reduction of **10** with sodium borohydride offered a 1.2:1 mixture of **11a** and **11b** in a quantitive yield, which can be easily separated through flash chromatography. Cyclization–etherification of **11a** in the presence of potassium *t*-butoxide ($KOBu^t$) as base in anhydrous THF led to a clean formation of (−)-**1** in 100% yield, mp 198–200°C, $[\alpha]_D^{20}$ −92.5° (*c*, 0.18. MeOH). Accordingly, **12**, a C-7 epimer, was afforded under the same conditions from **11b** in 100% yield. The spectroscopic properties of the above obtained (−)-**1** were in good agreement with those previously reported.[1,4]

In conclusion, a concise and highly efficient total synthesis of (−)-**1** was completed in six linear steps and in 27.5% overall yield starting from amide **4**. The key step involved in this synthesis is novel, being mediated by fluoroalkanosulfonyl fluoride transformation of vicinal diols into the corresponding epoxides.

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