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Selective 3- and 6-OH modification of (−)-clausenamide

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Abstract

(−)-Clausenamide is a drug candidate under Phase I clinical trial for treatment of Alzheimer's disease (AD). In order to elucidate the substituent related structure–activity relationship, six one-substituent modified (−)-clausenamide analogues were designed, and four of them, namely 3-*O*-methyl, 6-*O*-methyl, 3-des-hydroxyl and 6-des-hydroxyl analogues were prepared by selective 3- and 6-OH modification of (−)-clausenamide.

Keywords: (−)-Clausenamide; Derivatives; Synthesis; Alzheimer's disease

Racemic clausenamide ((±)-**1**, Fig. 1) is a natural product isolated from aqueous extract of the leaves of *Clausena lansium (Lour) skeels* [1]. The racemate showed remarkable nootropic activity in a number of *in vivo* biological tests, but the *levo* rotatory enantiomer, ((−)-clausenamide **1**, Fig. 1), was eventually found to be the active isomer [2,3]. Presently, this chiral compound is under clinical trial for treatment of Alzheimer's disease. In order to get the insight view of stereochemistry related structure–activity relationship (SAR), all 16 stereoisomers of (−)-**1** were prepared and their biological activities evaluated in an earlier study [4].

As the molecule of (−)-clausenamide is featured not only with the four chiral centers but also with the four substituents: 3-OH, 6-OH, 4-Ph and 6-Ph, it is interesting to find how the presence of these substituents is related to its biological activity. In order to get this question answered, six one-substituent modified (−)-clasuenamide analogues (**2**–**5**, **6** and **7**, Fig. 1) were designed. In this letter, we describe the preparation of compound **2**–**5**, using (−)-clausenamide as starting material since it provides the fastest access to the target molecules in the forms of pure enantiomers.

Compound **2** and **3** are simple mono-*O*-methylated derivatives of (−)-**1**. Because the 3-OH of (−)-**1** is *trans* to both C4 and C5 substituents and less hindered, compound **2** was expected to be prepared by selective 3-*O*-methylation of the starting material. After screening of several commonly used *O*-methylation conditions including MeI/NaH in DMF, MeI/K_2CO_3 in acetone and Me_2SO_4/KOH in toluene/H_2O, reaction under the last biphasic condition was found to give the best result, and (−)-**1** was converted into compound **2** as single product in excellent yield (90%) (Scheme 1). This encouraged us to go one step further to carry out the 3-OH selective protection of (−)-**1** with TBS under classic silylation condition [5], and compound **8** was isolated in 81% yield. Subsequent 6-OH methylation of **8** followed by release of the 3-OH with TBAF afforded compound **3** in 65% yield over two steps (Scheme 1).

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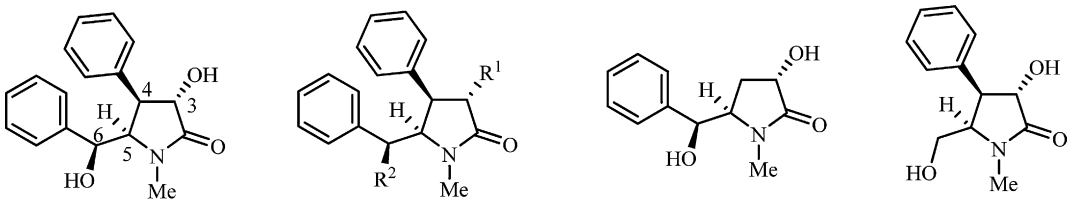
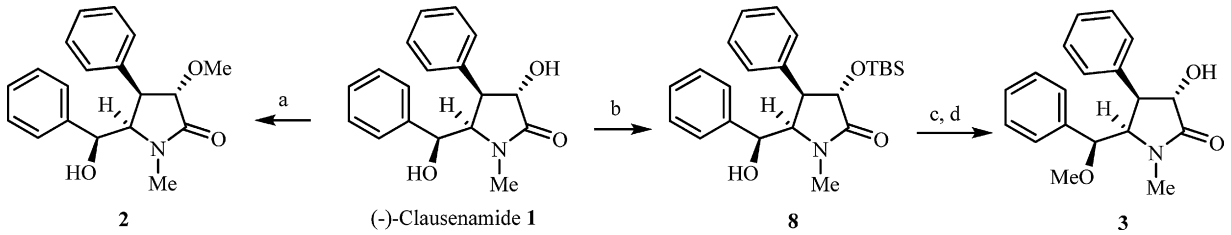


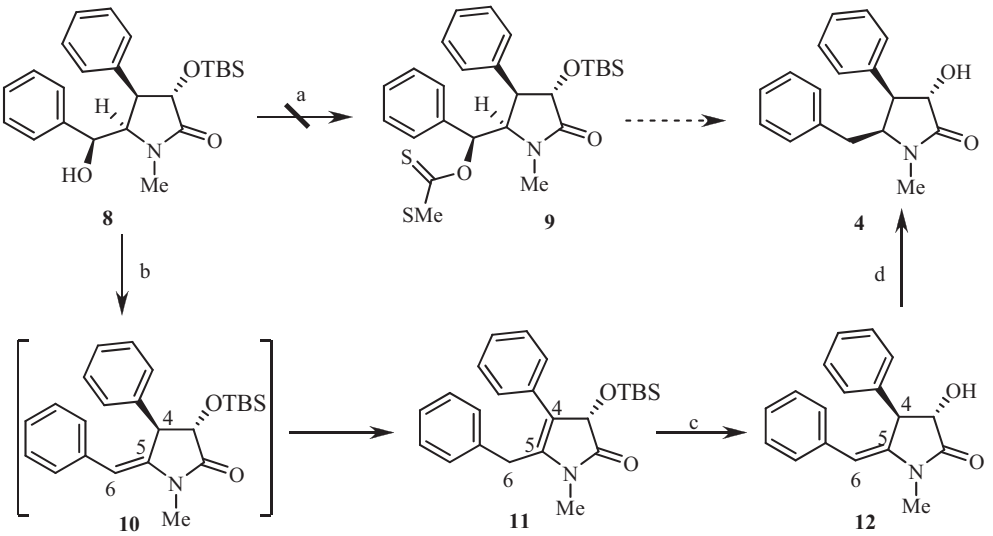
Fig. 1. (−)-Clausenamide and designed derivatives.



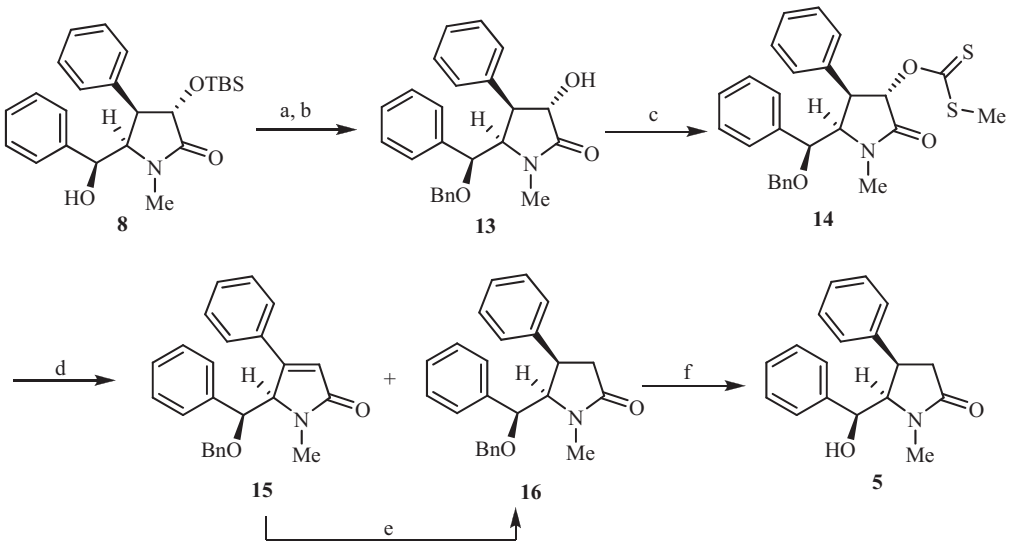
Scheme 1. Synthesis of **2** and **3**. *Reagents and conditions*: (a) Me_2SO_4/KOH in toluene/H_2O; (b) TBSCl/imidazole; (c) MeI/NaH; (d) TBAF.

In our initial plan (Scheme 2), an *S*-methyl xanthate mediate dehydroxylation was designed as the first step to realize the transformation of **8** into compound **4**. Unfortunately, treatment of **8** with CS_2/NaH and MeI failed to give **9**. Therefore, an alternative plan *en route* intermediate **10** was proposed. Compound **8** was thus treated with $POCl_3$/Py, a commonly used dehydration reagent [6], but afforded an unexpected product **11**, which was believed to form from double bond migration of the original elimination product **10** in 87% yield. To our delight, when the TBS group was removed by treatment of **11** with TBAF, the location of C=C double bond switched back to C5–C6 with the restoration of R configuration at C4 [7], and **12** was isolated in 77% yield. With intermediate **12** in hand, a variety of hydrogenation conditions were tested, and the reaction in anhydrous THF with Raney Ni as catalyst was found to give the optimal yield of **4** (74% after crystallization of the crude product from ethyl acetate).

Similar to that of **4**, synthesis of **5** was also started with intermediate **8**, which was first treated with benzyl bromide/NaH to have the 6-OH protected, and then with TBAF to remove the 3-*O*-TBS group to give key intermediate **13** in



Scheme 2. Synthesis of **4**. *Reagents and conditions*: (a) 1—NaH, imidazole; 2—CS_2; 3—MeI; (b) $POCl_3$/Py; (c) TBAF; (d) 10% Pd/C, H_2.



Scheme 3. Synthesis of **5**. *Reagents and conditions*: (a) NaH, BnBr; (b) TBAF; (c) 1—NaH, imidazole; 2—CS_2; 3—MeI; (d) $((n\text{-}Bu)_4N)_2S_2O_8$, HCOONa; (e) T-1 Raney Ni, H_2; (f) 10% Pd/C, H_2.

63% yield over two steps (Scheme 2). Unlike compound **8**, conversion of **13** into the corresponding *S*-methyl xanthate proved to be easy and **14** was isolated in 78% yield. Treatment of *S*-methyl xanthate **14** with sodium formate in the presence of $((n\text{-}Bu)_4N)_2S_2O_8$ as radical initiator [8] afforded an inseparable 1:1 [9] mixture of dehydroxylation product **16** and elimination product **15** in a total yield of 66%. Raney Ni catalyzed hydrogenation of this mixture, during which compound **15** was saturated with the incoming hydrogen atoms attacking the less hindered α face, gave **16** in pure form in 91% yield. Deprotection of 6-OH was then furnished by palladium catalyzed hydrogenolysis of **16** to afford target molecule **5** in 96% yield (Scheme 3).

In conclusion, a small library consists of six one-substituent modified (−)-clausenamide analogues was designed as probe for structure–activity relationship elucidation, and four members possessing retained carbon skeletons were synthesized in optical active form by selective OH modifications using readily available (−)-clausenamide as starting material [10]. It was demonstrated for the first time that the steric hindrance margin between the 3- and 6-OH in the molecule of (−)-clausenamide provided a sufficiently wide open window for manipulation of OH protective groups. Des-hydroxyl modifications to the 6- or 3-OH could then be carried out by adoption of an elimination–hydrogenation sequence or an *S*-methyl xanthate mediated dehydroxylation procedure, respectively. Synthesis of the other two library members, **6** and **7**, as well as the results from biological studies on the nootropic effect of compound **2–7** will be published separately.

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References

[1] M.H. Yang, Y.H. Cao, W.X. Li, et al. Acta Pharmacol. Sin. 22 (1) (1987) 33.
[2] W. Hartwig, L. Born, J. Org. Chem. 52 (1987) 4352.
[3] J.T. Zhang, X.Y. Jiang, Collection of the Academic Papers of Scientific Annual Meeting of Peking Union Medical College, Beijing Medical University & Peking Union Medical College Publishing House, Beijing, 1994, 356.
[4] Z. Feng, X. Li, G. Zheng, et al. Bioorg. Med. Chem. Lett. 19 (8) (2009) 2112.
[5] E.J. Corey, A. Venkateswarlu, J. Am. Chem. Soc. 94 (17) (1972) 6190.
[6] W.G. Dauben, G.A. Boswell, J. Am. Chem. Soc. 83 (24) (1961) 5003.
[7] The trans geometry between 3-OH and 4-Ph was validated by 1H NMR of 12; (S)-(−)-O-actylmandelation of compound 4 was carried out later and only one product was detected by 1H NMR of the reaction mixture, therefore the possible C-3 epimerization could be precluded.

[8] H.S. Park, H.Y. Lee, Y.H. Kim, Org. Lett. 7 (15) (2005) 3187.
[9] The proportions of the two compounds were determined by 1H NMR of the mixture.
[10] Analytical data for compounds **2**–**5**. *Compound **2***: mp: 191.0–191.9 °C; $[\alpha]_D^{20}$ −184.3 (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H), 3.55 (s, 3H), 3.83 (d, 1H, *J* = 9.0 Hz), 3.81 (dd, 1H, *J* = 9.0, 8.7 Hz), 4.15 (dd, 1H, *J* = 4.2, 8.7 Hz), 4.75 (d, 1H, *J* = 4.2 Hz), 6.85–7.37 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.7, 140.9, 135.7, 128.6, 127.6, 127.2, 126.4, 126.3, 77.4, 71.1, 65.2, 57.3, 47.3, 29.5; FT-IR (cm^{-1}): 1681.1; EI-MS (*m*/*z*, %): 312 (M^++1, 2), 204 (100), 176 (100); HRMS (M^++H) calcd. for $C_{19}H_{21}NO_3$ 312.1600, found 312.1590; *Compound **3***: mp: 157.5–58.4 °C; $[\alpha]_D^{20}$ −146.4 (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.71 (s, 3H), 2.77 (s, 3H), 3.55 (dd, 1H, *J* = 11.1, 8.1 Hz), 3.77 (dd, 1H, *J* = 6.3, 11.1 Hz), 4.12 (d, 1H, *J* = 4.2 Hz), 4.25 (dd, 1H, *J* = 4.2, 8.1 Hz), 5.44 (d, 1H, *J* = 6.3 Hz), 6.68–7.38 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.1, 137.1, 136.2, 128.6 × 2, 127.9, 126.6, 82.6, 68.3, 63.7, 55.9, 49.5, 30.6; FT-IR: 1672.6; EI-MS (*m*/*z*, %): 312 (M^+ + 1, 2), 191 (84), 162 (96), 134 (100); HRMS (M^++H) calcd. for $C_{19}H_{21}NO_3$ 312.1600, found 312.1517; *Compound **4***: mp: 143.3–144.0 °C; $[\alpha]_D^{20}$ −267.4 (c 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (dd, 1H, *J* = 8.1, 14.1 Hz), 2.62 (s, 3H), 2.64 (dd, 1H, *J* = 4.2, 14.1 Hz), 3.73 (dd, 1H, *J* = 8.1, 10.8 Hz), 4.04 (ddd, 1H, *J* = 8.1, 8.1, 4.2 Hz), 4.59 (d, 1H, *J* = 10.8 Hz), 6.83–7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 137.6, 135.9, 129.1, 128.8, 128.5, 128.1, 127.4, 126.7, 70.0, 63.0, 51.7, 37.0, 30.3; FT-IR (cm^{-1}): 1763.4, 1603.4; MS (*m*/*z*, %): 281 (M^+, 1), 190 (100), 91 (85); HRMS (M^++H) calcd. for $C_{18}H_{20}NO_2$ 282.1488, found 282.1489; *Compound **5***: mp: 104.5–105.8 °C; $[\alpha]_D^{20}$ −119.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (d, 2H, *J* = 9.9), 2.75 (s, 3H), 3.92 (dd, 1H, *J* = 9.9, 7.8 Hz), 4.15 (dd, 1H, *J* = 5.1, 7.8, 3.9 Hz), 4.73 (d, 1H, *J* = 5.1 Hz), 6.91–7.40 (m, 10H); ^{13}C NMR (100 MHz, CDCl3): δ 174.7, 139.7, 137.0, 128.7, 128.3, 128.27, 127.5, 127.3, 73.7, 68.8, 41.9, 33.7, 30.9; FT-IR (cm^{-1}): 1671.5, 1602.6, 1484.9; FAB-MS (*m*/*z*, %): 282 (M^++1, 100); HRMS (M^+ + 1): calcd. for $C_{18}H_{20}NO_2$ 282.1494, found 282.1501.