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Asymmetric synthesis of pedamide using I_2-induced heterocyclization to construct the skeleton

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Abstract

An alternative approach to synthesize pedamide, a key building block of pederin was described. Iodine-induced asymmetric heterocyclization was used as the key step to construct the skeleton, a tetrahydropyran ring with three chiral centers. Brown's asymmetric allylation and Lewis acid-mediated allylation were investigated to introduce chains and chiral alcohols. Sharpless dihydroxylation decorated the side chain. And high optically pure target was obtained by removing the epimers formed in these reactions on column chromatography.

Keywords: Synthesis; Pedamide; Pederin

As the precursor of the right half of pederin (**1**) [1], pedamide (**2d**) and its analogs have been adopted as the key building block in the synthesis of pederin [2a]. Pedamide has three chiral centers and 2,4-*trans*, 2,6-*trans* substituents on its tetrahydropyran ring (Fig. 1). The unique structure aroused wide interest of organic chemists. In the past decades, many groups reported their work on the synthesis of pedamide **2d** and its analogs by using different heterocyclization reactions to construct the skeleton [2–6], including nucleophilic substitutions of hydroxyl towards

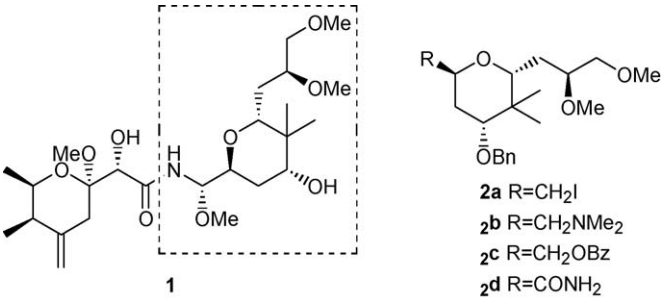

Fig. 1. Pederin.

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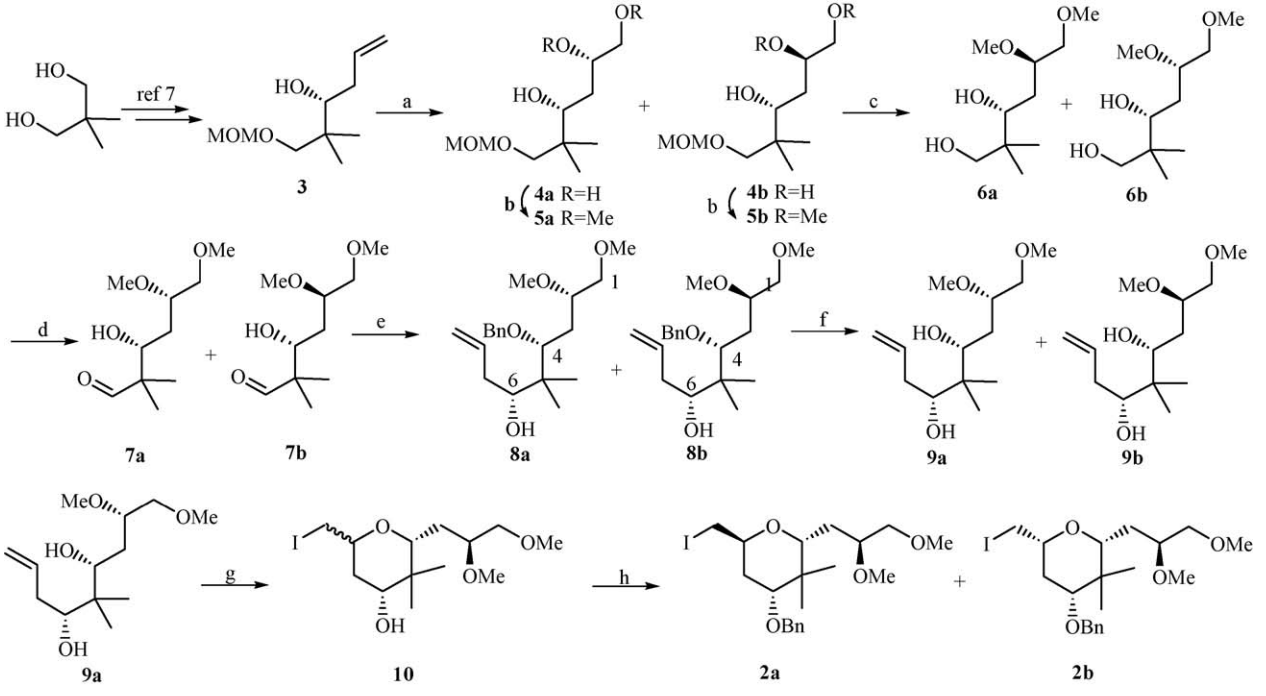


Scheme 1. Reagents and conditions: (a) AD-mix-α, $MeSO_2NH_2$, ^tBuOH, H_2O, r.t., 98%; (b) MeI, NaH, THF, r.t., 94%; (c) HCl (aq. 3 mol/L), MeOH, reflux, 4 h, 92%; (d) DMSO, oxalyl chloride, CH_2Cl_2, −78 °C, 1 h, 97%; (e) TMS-allyl, $SnCl_4$, CH_2Cl_2, −78 °C, 3 h, 62%, *dr* = 2.8:1; (f) Li, NH_3(liquid), Et_2O, −78 °C, 20 min, 96%, *dr* = 1.9:1; (g) I_2, $NaHCO_3$, Et_2O, H_2O, 0 °C, 10 h, 98%; (h) BnBr, NaH, DMF, 0 °C to r.t., 8 h, 90%, *dr* = 4.2:1.

epoxide [2], lactonization [3–4], intramolecular acetalization [5], hetero-Diels-Alder reaction [6a] and cyclization of *N*-acyl enamine [6b].

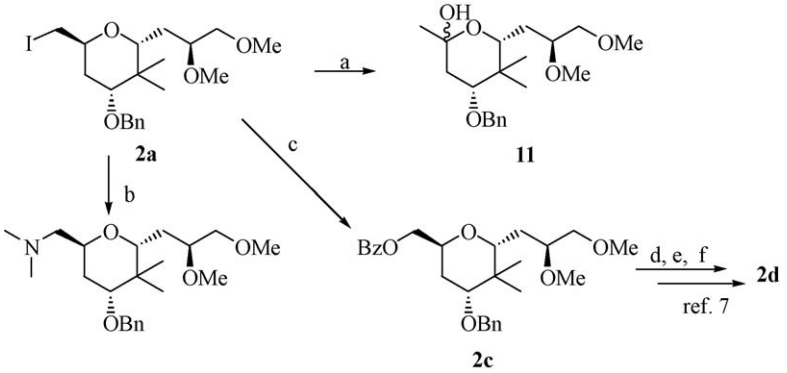
With our efforts toward the synthesis of pedamide, I_2-induced heterocyclization was found to be efficient in the construction of the skeleton of pedamide [7]. Herein an alternative synthetic scheme based on this reaction as key step was described.

The precursor **9a** for the heterocyclization was synthesized from compound **3** (80%ee) which was readily prepared according to our previous method [7]. **3** was dihydroxylated with Sharpless condition [8], followed by protecting hydroxyl group with MeI/NaH to form compound **5**. The dihydroxylation of **3** gave a pair of diastereoisomers **4a** and **4b**, which are not separable on silica gel column and were conducted to the next reaction together without separation and formed a mixture of **5a** and **5b**. Then this mixture was converted to alcohol **6a** and **6b** by removing MOM group in acidic condition. And the mixture of aldehyde **7a** and **7b** was formed in Swern oxidation of the mixture of **6a** and **6b** in high yield. The allylation of the mixture of **7a** and **7b** proceeded in the presence of Ipc_2B-allyl firstly [9]. But it gave a very low conversion and 1.4:1 *dr* ratio. Lewis acid-mediated allylation gave the best diastereoselectivity [10]. The mixture of aldehyde **7a** and **7b** was treated with TMS-allyl under the chelating of $SnCl_4$. The 6*R* diastereoisomer **8a/8b** and their 6*S*-epimers formed in 2.8:1 ratio and 62% total yield. And the 6*S*-epimers could be removed from 6*R*-epimers **8a/8b** on column chromatography. Then the mixture of olefin **8a** and **8b** was treated with Li/NH_3 to remove the Bn group and a mixture of diol **9a/9b** formed in 96% yield. To be excited, the precursor of heterocyclization, compound **9a** was easily separated from its epimer **9b** by silica gel column chromatography. The ratio of **9a** and **9b** is 1.9:1. **9a** has three chiral centers, which will control the selectivity of heterocyclization and the formation of the last chiral center of **2d**.

The cyclization of **9a** proceeded under the induction of I_2 in the presence of $NaHCO_3$ as base in heterogeneous condition to give the desired tetrahydropyran **10** in 98% yields, which was a mixture of 2*R*-**10** and 2*S*-**10** [11]. Hydroxyl group in compound **10** was etherified with BnBr/NaH in DMF to give compound **2a** in 73% yield and its epimer **2b** in 17% yield. They were separated on column chromatography. This also showed that the ratio of 2*R*-**10** and 2*S*-**10** is 73:17. During the cyclization, I_2 coordinated with the double bonds to form a cyclic iodonium ion firstly. And the hydroxyl nucleophilically attacked the cyclic iodonium ion intramolecularly from the opposite position of iodine atom to form the product. This was a strictly anti stereospecific addition when it carried out under basic conditions [12]. It showed good *regio*- and *stereo*-selectivity. No product of four-membered ring was detected. The physical property of **2a** was consistent with those reported in the literature [7,13] (Scheme 1).

In order to convert the iodomethyl side chain to amide part, some oxidative nucleophilic substitutions and hydrolyzations were tried and some analogs of **2d** formed in these reactions. In CH_2Cl_2, *m*-chloro peroxybenzoic acid converted **2a** to alcohol **11** in a moderate yield [14a]. In the presence of NaOH, **2a** reacted with aqueous DMF and yielded **2b** in very high yield [14b]. Compound **11** [15] and **2b** [16] are new compounds (Scheme 2).

Then **2a** was treated with sodium benzoate and NMP, [11b] K_2CO_3/MeOH, Jone's reagent and PyBOP/HOBt/DIPEA/NH_4Cl [3c,17] in turn. The desired compound, amide **2d** formed in very high yield [7]. In this scheme, compound **10** has no protective group at its 4-OH group. So it can be verified at this point to form different derivatives.



Scheme 2. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 0 °C, 2 h, 47%; (b) NaOH (3 mol/L, aq), DMF, 90 °C, 8 h, 89%; (c) BzONa, NMP, 100 °C, 6 h, 93%; (d) K_2CO_3, MeOH, r.t., 4 h, 98%; (e) CrO_3, H_2SO_4, acetone, 0 °C, 2 h; (f) PyBOP, HOBt, DIPEA, NH_4Cl, DMF, r.t., 1.5 h, 83% (two steps).

In summary, an alternative approach toward the asymmetric synthesis of pedamide **2d** was developed in 16 steps with more than 6% overall yield and good stereoselectivity. And several analogs of **2d** were prepared during this process. It is interesting that the epimers formed in the asymmetric reactions could be separated in the subsequent steps by column chromatography. In this synthesis, two reagent-controlled stereoselective reactions and two substrate-controlled asymmetric reactions were adopted. The key step is the diastereoselective iodine-induced hetereocyclization, which is a useful reaction for the formation of multi-substituted tetrahydropyran and will find wide application in the preparation of bioactive products.

Acknowledgment

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References

[1] (a) M.R. Levine, J. Dancis, M. Pavan, R.P. Cox, Pediat. Res. 8 (1974) 606;
(b) J. Piel, D. Butzke, D. Fusetani, D. Hui, M. Platzer, G. Wen, S. Matsunaga, J. Nat. Prod. 68 (2005) 472.
[2] (a) F. Matsuda, M. Tomiyoshi, T. Yanagiya, Matsumoto, Tetrahedron 44 (1988) 7063;
(b) M. Yanagiya, F. Matsuda, K. Hasegawa, T. Matsumoto, Tetrahedron Lett. 23 (1982) 4039;
(c) T. Matsumoto, F. Matsuda, K. Hasagawa, M. Yanagiya, Tetrahedron 40 (1984) 2337.
[3] (a) T. Nakata, S. Nagao, N. Mori, T. Oishi, Tetrahedron Lett. 26 (1985) 6461;
(b) T. Takemura, Y. Nishii, S. Takahashi, J. Kobayashi, T. Nakata, Tetrahedron 58 (2002) 6359.
[4] (a) P. Kocienski, T.M. Willson, J. Chem. Soc. Commun. (1984) 1011;
(b) T.M. Willson, P. Kocienski, K. Jarowicki, K. Isaac, A. Faller, S.F. Campbell, J. Bordner, Tetrahedron 46 (1990) 1757;
(c) T.M. Willson, J.P. Kocienski, K. Jarowicki, K. Isaac, P.M. Hitchcock, A. Faller, S.F. Campbell, Tetrahedron 46 (1990) 1767;
(d) P. Kocienski, K. Jarowicki, S. Marczak, Synthesis (1991) 1191.
[5] R.W. Hoffman, A. Schlapbach, Tetrahedron 48 (1992) 1959.
[6] (a) C.J. John, V.H. Rawal, Angew Chem. Int. Engl. 119 (2007) 6622;
(b) X. Huang, N. Shao, A. Palani, R. Aslanian, A. Buevich, Org. Lett. 9 (2007) 2597.
[7] D. Liu, J. Xue, Z. Xie, L. Wei, X. Zhang, Y. Li, Synlett (2008) 1526.
[8] H.K.C. Michael, S. VanNieuwenhze, K.B. Sharpless, Chem. Rev. 94 (1994) 2483.
[9] P.K. Jadhav, K.S. Bhat, P.T. Perumal, H.C. Brown, J. Org. Chem. 51 (1986) 432.
[10] C.H. Heathcock, S. Kiyooka, T.A. Blumenkopf, J. Org. Chem. 49 (1984) 4214.
[11] (a) L.F. Tietze, C. Schneider, J. Org. Chem. 56 (1991) 2476;
(b) A. Kang, S.Y. Kang, H.W. Choi, C.M. Kim, H.S. Jun, J.H. Younb, Synthesis (2004) 1102.
[12] F.A. Carey, R.J. Sundberg, Advanced Organic Chemistry: Reactions and Synthesis Part B, 4th ed., Plenum, New York, 2002, pp. 200–205.
[13] Data of synthetic **2a**: $[\alpha]D^{20}$-30 (*c* 1.00, $CHCl_3$); IR (film): 3745, 3396, 3063, 3029, 2925, 2873, 1740, 1650, 1542, 1456, 1387, 1334, 1279, 1193, 1097, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.31 (m, 5H, ArH), 4.60 (d, 1H, J = 12.0 Hz, $ArCH_2O$), 4.41 (d, 1H, J = 12.3 Hz, $ArCH_2O$), 3.69 (m, 3H), 3.52 (m, 2H), 3.41 (s, 3H), 3.39 (s, 3H) 3.18 (m, 3H), 1.91 (m, 1H), 1.62 (m, 3H) 0.92 (s, 6H, CMe_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 138.7, 128.3, 127.5, 127.4, 81.8, 77.9, 76.2, 74.1, 72.1, 71.5, 59.2, 56.9, 37.2, 31.3, 29.9, 22.7, 19.7, 10.3; MS (EI) *m/z*: 430, 417, 385, 359, 303, 253, 223, 197, 169, 91.
[14] (a) T.L. Macdonald, N. Narasimhan, L.T. Burka, J. Am. Chem. Soc. 102 (1980) 7760;
(b) M. Numazawa, M. Nagaoka, J. Org. Chem. 47 (1982) 4024.
[15] Data of compound **11**: ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.35 (m, 5H, ArH), 5.47 (s, 1H), 4.68 (d, 1H, J = 11.7 Hz), 4.47 (d, 1H, J = 12.0 Hz), 3.84 (d, 1H, J = 9.6 Hz), 3.53 (m, 2H), 3.47 (m, 2H), 3.39 (m, 7H), 1.96 (d, 1H, J = 14.7 Hz), 1.83 (d, 1H, J = 14.1 Hz), 1.64 (m, 2H), 1.34 (s, 3H, MeCO), 0.93 (s, 3H, CMe_2), 0.89 (s, 3H, CMe_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 137.3, 128.5, 128.1, 127.7, 127.0, 95.7, 83.8, 77.8, 73.1, 72.8, 68.1, 59.2, 56.9, 36.3, 33.8, 29.6, 28.6, 22.8, 19.3; MS (EI): 335, 321, 294, 227, 139, 109, 91; HRMS calcd for $C_{20}H_{32}O_5Na$ ($M + Na^+$) 375.2142, found 375.2136.
[16] Data of compound **2b**: $[\alpha]_{20}^{D}$ −26 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.33 (m, 5H, ArH), 4.62 (d, 1H, J = 11.7 Hz, $ArCH_2O$), 4.40 (d, 1H, J = 11.7 Hz, $ArCH_2O$), 3.64 (t, 1H, J = 6.0 Hz), 3.35 (m, 10H), 3.22 (s, 1H), 2.95 (d, 1H, J = 8.4 Hz, CH_2N), 2.86 (d, 1H, J = 8.4 Hz,CH_2N), 2.73 (s, 6H, NMe_2), 1.72 (m, 1H), 1.59 (m, 3H), 0.86 (s, 3H, CMe_2), 0.84 (s, 3H, CMe_2); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 138.5, 128.3, 127.7, 127.6, 80.8, 78.5, 76.6, 73.9, 71.6, 68.3, 61.6, 59.2, 56.9, 43.9, 37.1, 30.9, 29.6, 29.2, 23.0, 19.5; MS (EI): 379, 364, 348, 334, 318, 288, 121, 91, 58; HRMS calcd for $C_{22}H_{38}NO_4$ ($M + H^+$) 380.2795, found 380.2793.
[17] W. Wang, J.S. McMurray, Tetrahedron Lett. 40 (1999) 2501.