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A stereoselective approach for the total synthesis of (−)-tadanalactam from acetonide-D-glucose

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ABSTRACT

A stereoselective and realistic approach for the total synthesis of naturally occurring δ-lactam (−)-tadanalactam, has been accomplished from the commercially existing acetonide-D-glucose involving Birch reduction, Pinnick oxidation, Staudinger reaction, and hydroboration reactions. Finally benzyl ether deprotection and subsequent oxirane formation using Birch reduction completed the total synthesis of (−)-tadanalactam.

Substituted 2-piperidones (δ-lactam), exhibiting interesting biological activities, are present in numerous natural products such as alkaloids and drugs. Therefore, efficient stereoselective syntheses of functionalized 2-piperidone derivatives are of importance in medicinal chemistry. 2-Piperidone moiety (Fig. 1) is found in 3β,4α-dihydroxy-2-piperidinone (**3**) and 5,6-dihydro-2(1*H*)-pyridinone (**4**) isolated[1] from *Piper longum*, showing a superior anti-HBV activity in vitro, Piperlongumine (PL) alkaloid (**5**) with anti-cancer activity, isolated[2] from the various parts of long pepper, *Piper longum* L. also possesses 2-piperidone in its structure. (3*S*,4*R*)-3,4-dihydroxy-1-(3-phenylpropanoyl)piperidin-2-one (**6**) isolated[3] from *Piper longum*, demonstrated significant activity, with IC_{50} values of 1.80 and 0.21 mM against HBsAg (hepatitis B virus surface antigen) and HBeAg (hepatitis B virus e antigen) correspondingly. Kaousine (**7**) isolated[4] from the aerial part of *Piper capense* L.f (Piperaceae), shows lower antiplasmodial activity. Alkaloids, Piplaroxide (**8**), isolated[5] from *Piper tuberculatum*, 3,4-epoxy-8,9-dihydropiplartine (**9**) isolated[6] from leaves and twigs of *Piper verrucosum*, and 3,4-epoxy-5-pipermethystine (**10**) isolated[7] from roots of the kava shrub (*Piper methysticum*) are all substituted piperidones.

(−)-Tadanalactam, (3α,4α-epoxy-2-piperidone), an antifungal agent, was first isolated from sponge *Tedania ignis* and its chemical and biological characterization was carried out in 1994 by Cardellina et al.[8] In 2007, Lago et al.[9] reported the isolation and characterization of (−)-tadanalactam from the leaves of *Piper crassinervium* (piperaceae). In 2009 Tilve and co-workers[10] reported the total synthesis and stereochemistry of (−)-tadanalactam (**1**) and (+)-tadanalactam (**2**) by following a synthetic route with tandem Oxidation-Wittig reaction and Sharpless asymmetric dihydroxylation as the key steps. In continuation of our research program focused toward the total synthesis of bioactive molecules from inexpensive and readily accessible starting materials,[11] we have established an effective approach utilizing Birch reduction, Pinnick oxidation, Staudinger reaction, hydroboration, and reductive elimination reactions, for the linear stereoselective synthesis of (−)-tadanalactam (**1**), starting from the abundantly available acetonide-D-glucose.

As shown retrosynthetically (Scheme 1), synthesis of (−)-tadanalactam could be accomplished from **18**, via Birch reduction, which in turn could be prepared from **17** by reduction (Staudinger reaction), followed by cyclization. Compound **17** is accessible from **15** via acetonide deprotection, oxidative cleavage, and Pinnick oxidation followed by esterification. Hydroboration of **13** resulted in the primary alcohol, which was then converted into azido compound **15**, by tosylation, followed by nucleophilic substitution reaction. Compound **13** could be achieved from **11** by *O*-benzylation, regioselective acetonide deprotection, oxidative cleavage, and finally reduction.

Our synthesis (Scheme 2) started with acetonide-D-glucose (**11**), which was converted to *O*-benzylated compound by a known protocol.[12,13] Regioselective deprotection of the 5,6 acetonide group in *O*-benzylated compound with 0.8% H_2SO_4 in MeOH for 5 h afforded

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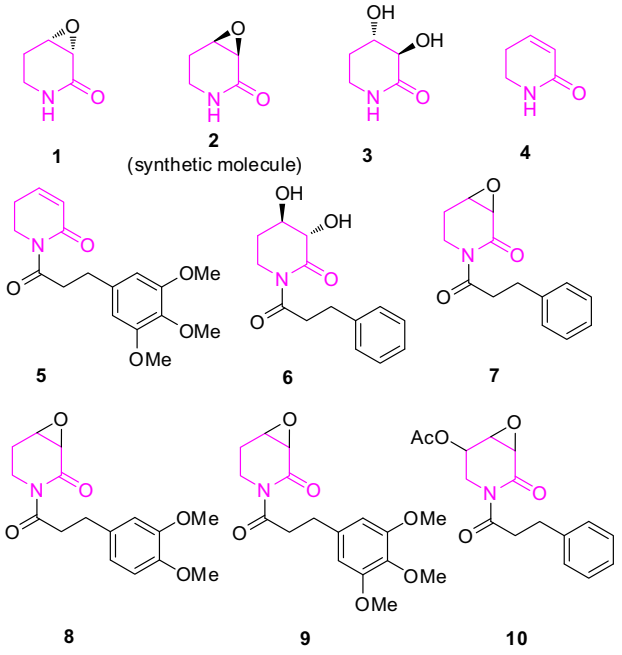
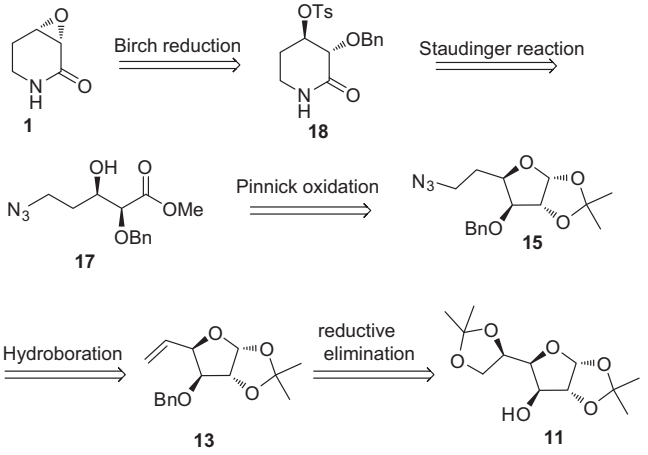
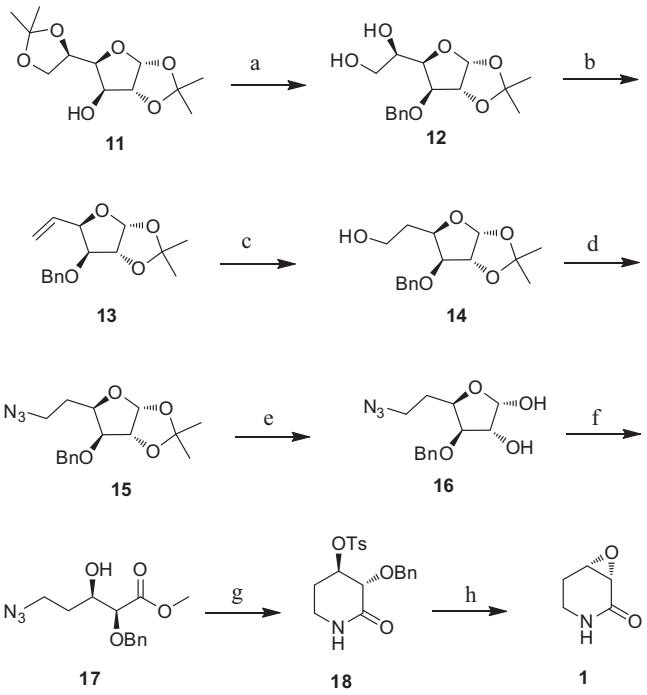


Figure 1. Naturally and synthetically occurring 2-piperidones.

the dihydroxy compound **12** with 95% yield. Reductive elimination[14] of **12** with iodine–PPh_3–imidazole in toluene at reflux conditions for 2 h gave olefin **9** in 86% yield. Compound **9** was subjected to hydroboration[15] using 9-BBN, which resulted in the addition of borane, regioselectively at C-3 position in 4 h, which was immediately subjected to oxidation with H_2O_2 in the presence of 3 N NaOH at rt to provide the primary alcohol **14** in 93% yield. The primary alcohol was converted into the corresponding tosylate with *p*-toluenesulfonyl chloride and catalytic amount of DMAP in pyridine/CH_2Cl_2 to furnish O-tosylated compound, which was then treated with sodium azide in DMF at 60 °C for 12 h to give **15** in 87% yield. Deprotection of 1,2-acetonide in **15** with 4% H_2SO_4 in THF at reflux temperature for 12 h afforded diol **16** in 94% yield. Oxidative cleavage of the diol **16**, with $NaIO_4$ in methanol/water furnished the aldehyde, which was then subjected to oxidation (Pinnick oxidation) using $NaClO_2$ and H_2O_2 in methanol/water for 4 h in the presence of a basic buffer NaH_2PO_4 to afford the acid, which was then



Scheme 1. Retrosynthetic analysis of (−)-tadanalactam.



Scheme 2. Reagents and conditions: (a) (i) Ref. 12 (ii) 0.8% H_2SO_4, MeOH, rt, 8 h, 95%; (b) PPh_3, imidazole, I_2, toluene, reflux, 4 h, 86%; (c) (i) 9-BBN, THF, 0 °C, rt, 4 h. (ii) 3 N NaOH, H_2O_2, rt, 3 h, 93% (for two steps); (d) (i) Ts-Cl, Et_3N, DCM, 0 °C, rt, 2 h. (ii) NaN_3, DMF, 60 °C, 5 h, 87% (for two steps); (e) 4% H_2SO_4, THF, reflux, 6 h, 94%; (f) (i) $NaIO_4$, MeOH/H_2O (2:1), rt, 0.5 h. (ii) $NaClO_2$, NaH_2PO_4, H_2O_2, MeOH/H_2O, 0 °C, rt, 4 h. (iii) $SOCl_2$, MeOH, 0 °C, rt, 12 h (overall 3 steps), 76%; (g) (i) Ts-Cl, Py, DCM, 0 °C, rt, 8 h, (ii) PPh_3, THF:H_2O (8:2), rt, 3 h, (overall 2 steps), 92%; (h) Li/liq. NH_3, −78 °C, 10 min, 78%.

(without further purification) taken up for selective methylation (esterification) in the presence of $SOCl_2$ in methanol for 12 h at room temperature to furnish the ester **17**. Reaction of **17** with *p*-toluenesulfonyl chloride in pyridine and catalytic amount of DMAP produced the tosylate, at this stage, reduction of azide using the Staudinger conditions. That is, treatment with triphenylphosphine in THF/H_2O resulted in one-pot reductive lactonization, to give lactam **18** in 76% yield. Compound **18** was subsequently subjected to deprotection of the benzylether using Li/liq.NH_3 in dry THF (Birch reduction). The ammonia present in the reaction facilitated the oxirane ring formation, thus forming the target molecule (−)-tadanalactam in a single step with 78% yield. The spectroscopic data[16] were in agreement with the recently synthesized structure of (−)-tadanalactam (**1**).[10]

In conclusion, a stereoselective synthesis of (−)-tadanalactam has been achieved from the commercially available acetonide-D-glucose via a high yielding route (34% overall yield) by using Birch reduction, Pinnick oxidation, Staudinger reaction, hydroboration, and reductive elimination reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.115.

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16. *Spectral data for selected compounds:*
(3aR,5R,6S,6aR)-5-(2-azidoethyl)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (**15**):
IR(KBr) ν cm^{-1}: 2926, 2097, 1454, 1075. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.30 (m, 5H, Ar-H), 5.91 (d, J = 3.81 Hz, 1H), 4.71 (d, J = 11.90 Hz, 1H), 4.63 (d, J = 3.96 Hz, 1H), 4.48 (d, J = 11.90 Hz, 1H), 4.23 (m, 1H), 3.81 (d, J = 3.20 Hz, 1H), 3.36 (ddd, J = 1.98, 5.95, 7.62 Hz, 2H), 2.03–2.10 (m, 1H), 1.90–1.81 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 137.3, 128.5, 128.0, 127.7, 111.5, 104.6, 82.2, 82.0, 71.7, 48.5, 27.8, 26.6, 26.1. MS (ESI) m/z: 342 $[M+Na]^+$.
(2S,3R)-methyl5-azido-2-(benzyloxy)-3-hydroxy pentanoate (17).
IR(KBr) ν cm^{-1}: 3445, 2926, 2100, 1747, 1455, 1266, 1129, 750. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.31 (m, 5H, Ar-H), 4.81 (d, J = 11.44 Hz, 1H), 4.45 (d, J = 11.44 Hz, 1H), 4.00 (br s, 1H), 3.88 (d, J = 4.12 Hz, 1H), 3.79 (s, 3H, OCH_3), 3.41 (dd, J = 5.95, 7.47 Hz, 2H), 1.82 (ddd, J = 1.83, 3.96,5.79, 9.76, 1H), 1.73–1.66 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 171.0, 136.5, 128.5, 128.3, 128.2, 80.2, 72.9, 69.6, 52.1, 47.9, 32.4. MS (ESI) m/z: 302 $[M+Na]^+$.
(−)-Tadanalactam (**1**): To a freshly distilled ammonia (3 mL) taken in a 50 mL two-necked round-bottomed flask fitted with a coldfinger condenser were added freshly cut lithium metal pieces (0.015 g, 21.3 mmol) at −78 °C and the resulting gray suspension was stirred for 30 min, then the compound **18** (0.2 g, 5.3 mmol) in anhydrous THF (20 mL) was added and stirred at −78 °C for 10 min. The reaction mixture was quenched with solid NH_4Cl portion wise and then ammonia was allowed to evaporate. Then mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (60–120mesh, MeOH/EtOAc = 0.2:9.8) to afford compound **1** (0.046 g, 78%) as a yellow oil. $[\alpha]_D^{27}$ = −7.21 (*c* 0.162 MeOH) [lit.[10]. $[\alpha]_D^{27}$ −7.6 (*c* 0.130, MeOH)]. IR(KBr) ν cm^{-1}: 3303, 2925, 1684, 1119, 622. ^1H NMR (500 MHz, $CDCl_3$): δ 5.68 (s, 1H, NH), 3.64 (br s, 1H), 3.42 (dd, J = 4.1, 2.4, 1H), 3.36 (dd, J = 12.4, 4.4 Hz, 1H), 3.05 (ddd, J = 12.3, 6.1, 1.4 Hz, 1H), 2.38–2.26 (m, 1H), 2.07 (dd, J = 12.3, 6.1, 1.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 53.0, 50.8, 34.3, 23.5. HRMS (ESI) m/z calcd. for $C_5H_8O_2N$ $[M+H]^+$. 114.0550, found 114.0549.