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A concise synthesis of (+)-pancratistatin using pinitol as a chiral building block

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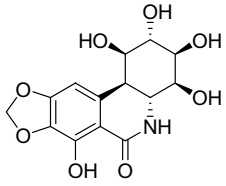
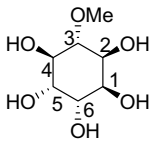
Abstract—A concise approach toward (+)-Pancratistatin has been achieved via 12 steps from pinitol. An ultrasound assisted arylcerium induced ring opening of cyclic sulfate was employed as a key step.

Pancratistatin, isolated in 1984 by Dr. Pettit and co-workers from the native Hawaiian plant *Pancratium Littorale*, is an important member of the amaryllidaceae alkaloids.[1] Pancratistatin exhibits a spectrum of both in vitro and in vivo cancer cell grow the inhibitory activity and antiviral activity.[2] These include, but are not limited to the activity against murine P-5076 ovarian sarcoma and P-388 lymphocytic leukemia. Although the mode of action of Pancratistatin remains mysterious, it is generally believed that Pancratistain and other amaryllidaceae alkaloids are potent inhibitors of the ribosomal peptidyl transferases, which play vital roles in the cell cycle from G_0/G_1 to S phase (Fig. 1).[3]

The promising biological activity and natural paucity has made Pancratistatin an interesting target for total synthesis. Danishefsky's group reported the first total synthesis of racemic Pancratistatin in 1989.[4] In 1995, Hudlicky and co-workers accomplished the first enantioselective synthesis of the natural enantiomer.[5] Since then, numerous research groups around the world have presented their stereoselective synthesis of (+)-Pancratistatin. These include research teams led by Trost and Pulley,[6] Haseltine and co-workers,[7] Magnus and Sebhat,[8] Rigby et al.,[9] and Kim et al.[10] So far, the most effective strategy was developed by Trost and Pulley, who summarized a synthesis in 13 steps with an impressive overall yield of 11%.[6] In 2001, Pettit et al. efforts to modify the abundant alkaloid (+)-Narciclasine resulted in another effective route to (+)-Pancratistatin.[11] Despite the fact that many synthetic methodologies toward (+)-Pancratistatin and its analogues[12] have been successfully developed, the construction of the transfused BC ring system and the stereocontrolled installation of the hydroxyl functions remain to be challenging for synthetic organic chemists. The supply constraint of (+)-Pancratistatin is still a big hurdle for its therapeutic application. Herein, we wish to report a concise synthesis of (+)-Pancratistatin from pinitol.



(+)-Pancratistatin



Pinitol

Figure 1. Structure of (+)-Pancratistatin and Pinitol.

We approached the synthesis of (+)-Pancratistatin by employing a convergent synthetic strategy (Scheme 1). According to our retrosynthetic analysis, the skeleton of the target molecule could be constructed by coupling two segments **1** and **2**.

It is obvious that the contiguous stereogenic centers of the C ring of (+)-Pancratistatin match exactly with those of D-chiral-inositol. Therefore, we started

Keywords: Pancratistatin; Stereoselective synthesis; Pinitol; Cyclic sulfate; Arylcerium.
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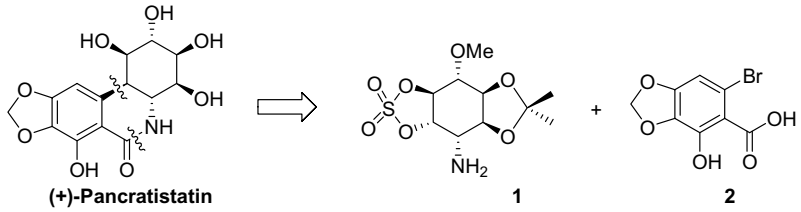


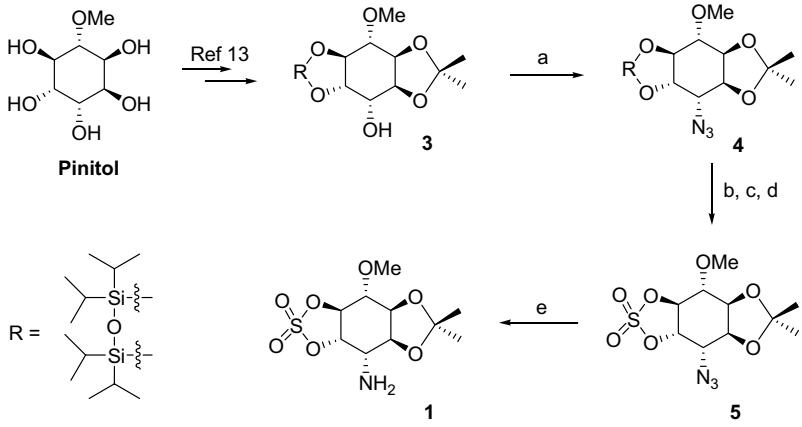
Scheme 1. Retrosynthetic analysis of (+)-Pancratistatin.

constructing the polyhydroxy subunit of (+)-Pancratistatin by employing pinitol as a building block. Using the method reported by Martín-Lomas and co-workers,[13] pinitol was converted to compound **3**. With compound **3** in hand, we investigated the installation of the 6α-NH_2 function by modifying the 6α-OH group. The stereoselective construction of 6α-NH_2 calls for a 6β-azide, which was usually prepared from 6α-hydroxyl inositol derivatives via two steps.[14] As an alternate, we resorted to a one-pot transformation employing a Mitsunobu reversion followed by an azide substitution, which has been recently applied in the synthesis of bile acid dimers by Aher and Pore.[15] Even though the transformation proceeded in a sluggish manner possibly due to steric reasons, the azide **4** was obtained in moderate yield. The silyl function was then removed by TBAF and a cyclic sulfate **5** was installed to minimize the hindrance for the coming coupling as well as the ring opening manipulation. After a Staudinger reduction,[16] the desired free amine **1** was obtained for the coupling reaction (Scheme 2).

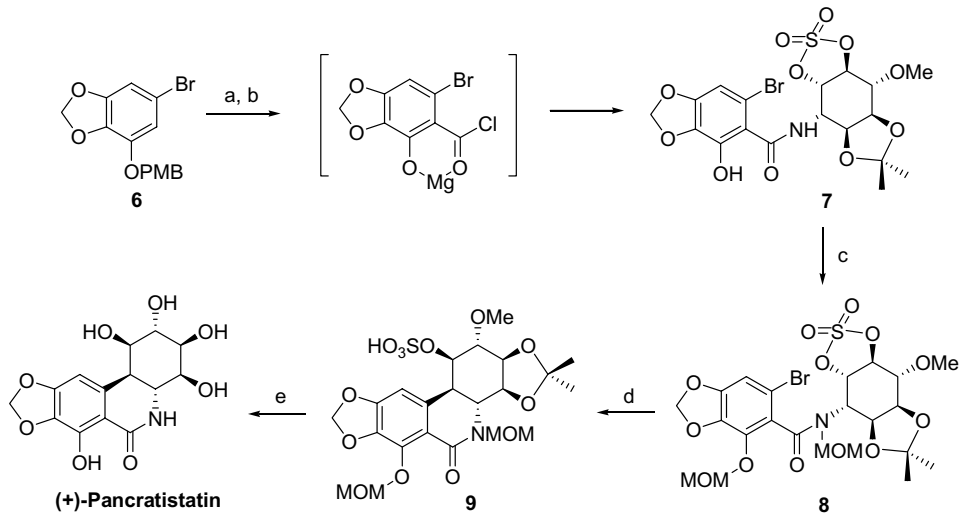
The synthesis of segment **2** was achieved via reactions from compound **6**, which was prepared according to the procedure reported by Coleman and Gurrala.[17] Compound **6** was subjected to an acid promoted PMB deprotection,[18] followed by a one-pot phosgene mediated coupling reaction[19] with **1** to afford amide **7** in moderate yield. MOM protection of both the amide and the free phenol provide **8** as the vital precursor for ring-closure study (Scheme 3).

The cyclic sulfate has been widely used as important intermediates in organic synthesis.[20] Noticing that a nucleophilic ring opening from C5 would constitute a C ring with the exact stereochemistry as that of (+)-Pancratistatin, we explored with great interest the intramolecular nucleophilic ring opening of the cyclic sulfate **8**. It has been reported that cyclic sulfates ring could be opened by diverse nucleophiles like alcohols,[21] azides or amines,[22] thiols,[23] halides,[24] and C-nucleophiles[23] as well. In order to induce the intramolecular cyclization, we initially employed *t*-BuLi to convert the aryl bromide to the corresponding aryl lithium.[23b] Much disappointedly, we found the reaction proceeded in a sluggish manner to give a complex mixture of products. Attempts in transforming the aryl bromide unit to its magnesium bromide[23a] were unrewarding either. We postulated that aryl lithium and aryl magnesium bromide's abilities as strong bases have incurred unexpected reactions such as elimination.[25] Therefore, we tried to resort to much 'softer' nucleophiles. It came to our attention that in addition to aryl lithium and aryl magnesium, other aryl nucleophiles such as aryl cerium,[26] aryl cadmium,[27] aryl lithium cuprates[28] have been widely used in synthetic chemistry. Among them, organocerium compounds were reported to possess the same activity as those of organolithium and organomagnesium agents, but much milder to avoid lots of side reactions.[26] Inspired by these findings, we have all the reasons to hypothesize the possibility of employing appropriate arylcerium to serve as a nucleophile in our cyclic sulfate ring opening.

In order to establish the arylcerium for the ring opening study, we explored the synthetic route as outlined in Scheme 3, compound **8** was treated with equal equivalent *t*-BuLi followed by addition of anhydrous $CeCl_3$ to effect the nucleophilic ring opening.[29] We were very



Scheme 2. Reagents and conditions: (a) (1) PPh_3, DEAD, CH_3SO_3H, CH_2Cl_2, 0 °C to rt; (2) NaN_3, DMF, 60 °C, 72%; (b) TBAF, THF, 0 °C to rt, 100%; (c) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (d) $NaIO_4$, $RuCl_3$, aq CH_3CN, 87% over two steps; (e) PPh_3, aq THF, 0 °C to rt, 94%.



Scheme 3. Reagents and conditions: (a) CH_3CO_2H, 100 °C, 4 h, 97%; (b) $MgBr_2{\cdot}OEt_2$, $COCl_2$, ether, 0 °C, **1**, 64%; (c) K_2CO_3, MOMCl, DMF, rt, 84%; (d) *t*-BuLi, $CeCl_3$, ultrasound, THF, −78 °C to rt, 72%; (e) (1) BBr_3, CH_2Cl_2, −78 to 0 °C, 1 h; (2) MeOH, −78 to 0 °C, 2 h, 52%.

fortunate to obtain the highly desired **9** in 76% after recovering 20% of the starting material **8**. To the best of our knowledge, this is the first ring opening of cyclic sulfate by organocerium. Further optimization led us to find that when the reaction was performed in an ultrasonic bath,[30] the yield was improved with all the compound **8** consumed and the reaction time was shortened as well.[31] After securing the both the skeleton and the stereochemistry of the target, we explored the deprotection of **9**. This proceeded uneventfully, but it is worth mentioning that maintaining the reaction temperature below 0 °C and controlling the reaction time are vital to realize global deprotection without jeopardizing the methylenecatechol unit.[32,10]

In summary, a concise synthesis of (+)-Pancratistatin[33] was accomplished via 12 steps from pinitol and an readily available compound **6** by employing an arylcerium induced ring opening of cyclic sulfate **8** as the key step.

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31. Procedure for the ring opening reaction: A solution of **8** (300 mg, 0.48 mmol) in anhydrous THF (5 mL) was cooled to −78 °C and *t*-BuLi (2.5 M in hexanes, 0.19 mL, 0.48 mmol) was added dropwise. The resulting pale-yellow solution was allowed to stir at the same temperature for 30 min, before a suspension of anhydrous $CeCl_3$ (125 mg) in THF (1 mL)[29] was added. The mixture was stirred at −78 °C for 2 h and allowed to warm up slowly to room temperature. The flask was then placed in an ultrasonic bath (Bransonic 2210) at room temperature. The reaction was monitored by TLC until **8** was fully consumed (approximately 4 h). Saturated aqueous NH_4Cl solution (2 mL) was added and the mixture was extracted with ethyl acetate (15 mL × 3). The organic layer was combined, washed with brine (15 mL × 3) and dried over Na_2SO_4. After concentrating under reduced pressure, the residue was purified by flash column chromatography ($R_f = 0.27$, hexanes/ethyl acetate 2:3) to give **9** (188 mg, 72%) as an off-white solid.
32. For selective cleavage of aryl methylenedioxy group or methyl ether, see: Gerecke, M.; Borer, R.; Brossi, A. *Helv. Chim. Acta* **1976**, *59*, 2551.
33. (+)-Pancratistatin (6.1 mg) was obtained as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.51 (s, 1H), 6.48 (d, $J = 1.0$ Hz, 1H), 6.05 (d, $J = 1.1$ Hz, 1H), 6.02 (d, $J = 1.0$ Hz, 1H), 5.35 (s, 1H), 5.05–5.07 (m, 2H), 4.84 (s, 1H), 4.27 (m, 1H), 3.95 (dd, $J_1 = 7.4$ Hz, $J_2 = 4.0$ Hz, 1H), 3.84 (s, 1H), 3.68–3.72 (m, 2H), 2.95 (d, $J = 11.2$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.82, 152.30, 145.64, 140.01, 131.94, 107.73, 101.95, 97.93, 73.50, 70.42, 70.21, 68.76, 50.68, 29.20.