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PTSA-catalyzed tandem cyclization protocol for the stereoselective total synthesis of obolactone

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ABSTRACT

Stereoselective total synthesis of obolactone by the Brønsted acid (PTSA) mediated tandem cyclization of the appropriately substituted diketone in one-pot in a highly selective and efficient manner is reported.

Recently, pyrone containing natural product, obolactone **1** was isolated by Guéritte and co-workers from *Cryptocarya obovata*.[1] Obolactone **1** is unique in the sense that two dihydropyrones, namely a γ-pyrone and α-pyrone are linked through a methylene bridge thus presenting a rare structural motif. We are interested in the total synthesis of α-pyrone containing natural products due to their structural diversity, substitution pattern on the side-chain, their ubiquitous presence coupled with varied biological activity[2] and reported the synthesis of some 6-alkyl α-pyrone containing natural products earlier.[3] Recently Pan and co-workers reported the first asymmetric total synthesis of **1** via RCM protocol.[4] Attracted by its structural elegance and complexity, we explored alternative strategies that allow far simpler and efficient access to such skeleton containing natural products. Herein we report the stereoselective total synthesis of **1** by the Brønsted acid-mediated tandem cyclization of the diketone **2** in one-pot.

The synthetic strategy envisaged (Scheme 1) stems from a simple logic that a Brønsted acid (PTSA)-mediated tandem cyclization of the appropriately substituted diketone **2** maybe invoked to result in the target **1**. Diketone **2** in turn could be accessed from **3** through oxidation and **3** could be realized from the known alcohol **4** through a series of reactions as enumerated in Scheme 1.

Accordingly, the synthesis (Scheme 1) begins from the commercially available homopropargyl alcohol and its transformation into a known alcohol **4**.[5] Later, **4** was oxidized to aldehyde under Swern conditions and immediately subjected to Keck allylation[6] reaction {(*R*,*R*)-BINOL/Ti(O^iPr)$_4$/allyltributyltin/CH_2Cl_2/−78 °C to −20 °C) to afford homoallyl alcohol **5** in good yield (75%, over two steps) and diastereoselectivity (dr 9:1). The absolute stereochemistry of the newly created stereogenic center was assigned based on Rychnovsky's analogy of the corresponding acetonide **5a**.[7] For instance, the ^{13}C NMR of **5a** revealed the carbon atoms due to the acetonide methyls at δ 19.8 and at δ 30.1 ppm characteristic of the acetonide of a *syn*-1,3-diol moiety. Thus the relative stereochemistry of the newly created stereogenic center was unequivocally assigned as *syn* to the existing one and its absolute stereochemistry as '*R*'.

Having obtained the 1,3-diol **5** that is differently functionalized at both the ends, the free hydroxyl group was protected as its silyl ether under the conventional reaction conditions to afford **6** (90%). Since the terminal olefin present in **6** was conceived as the masked carbonyl group, its dihydroxylation (OsO_4/NMO/acetone/H_2O) and oxidative cleavage ($NaIO_4$/satd $NaHCO_3$/CH_2Cl_2/rt) gave the corresponding aldehyde which on a Wittig olefination reaction[8] {$(CF_3CH_2O)_2POCH_2COOCH_3$/KHMDS/18-Crown-6/THF/−78 °C to rt/12 h} furnished the α,β-unsaturated ester **7** (70%, over three steps) predominantly as the (*Z*)-isomer, as characterized by ^1H and ^{13}C NMR spectroscopy. The coupling constant (J = 11.7 Hz) and the chemical shift values (δ 6.35–6.26 ppm as a multiplet and at δ 5.80 ppm as a doublet) confirmed the (*Z*)-geometry of the olefin. Later the PMB group was deblocked (DDQ/CH_2Cl_2/H_2O/rt/30 min) to afford compound **8** (90%).

The alcohol **8** was oxidized to aldehyde under Swern reaction conditions which on crucial aldol reaction with the in situ generated anion of benzylideneacetone (LHMDS/THF/−78 °C) furnished compound **3** (65%) as a 1:1 diastereomeric mixture. The diastereo-

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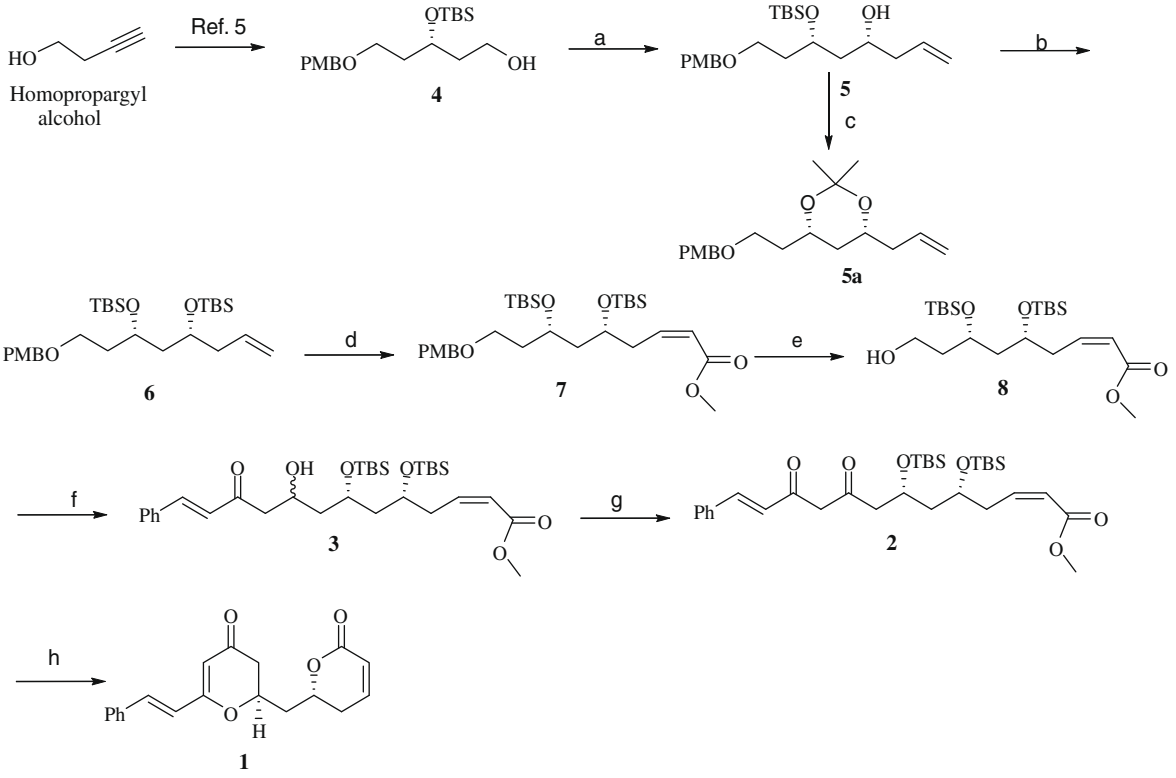

Scheme 1. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 90%, (ii) (*R*,*R*)-BINOL, 4 Å MS, $Ti(O^iPr)_4$, allyltributyltin, CH_2Cl_2, −78 to −20 °C, 12 h, 75%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 3 h, 90%; (c) (i) HF·Py, THF, 0 °C to rt, 12 h, (ii) 2,2-DMP, PPTS, CH_2Cl_2, rt, 2 h, (85% over two steps); (d) (i) OsO_4, NMO, acetone/water (4:1), (ii) $NaIO_4$, satd $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 12 h, (iii) $(CF_3CH_2O)_2POCH_2COOCH_3$, KHMDS, 18-Crown-6, dry THF, −78 °C to rt, 12 h, 70%, (70% over three steps); (e) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C to rt, 30 min, 90%; (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 90%, (ii) benzylideneacetone, LHMDS, dry THF, −78 °C, 2 h, 65%; (g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h, 80%; (h) PTSA, benzene, rt, 4 h, 75%.

meric mixture was taken up for the next reaction without any purification since the alcohol transforms into ketone functionality in the next step. Accordingly, the alcohol was oxidized (DMP/$NaHCO_3$/CH_2Cl_2/0 °C to rt/1 h) to afford the diketone **2** (80%) which was earlier identified as the crucial intermediate. The diketone **2** was characterized by its spectral data. For instance, ^1H NMR spectrum revealed the protons due to characteristic methylene flanked by two ketone groups at δ 3.10–2.90 ppm as a multiplet integrating for one proton while the other proton showed at δ 2.78–2.67 ppm as a multiplet. The same protons were present at δ 2.89–2.64 as a multiplet in compound **3**. Later the tandem PTSA-catalyzed cyclization of **2** to result in **1** was effected by the literature inspired report for the γ-pyrone ring construction.[9] Thus, **2** on exposure to PTSA in benzene at room temperature for 4 h afforded the target natural product **1** (75%) through a multiple reaction set; namely silyl deprotection-tandem ring-closing reactions in an unprecedented single step. The physical and spectroscopic data of synthetic **1** are consistent with the reported values.[10,1,4] The HRMS spectrum displayed the $[M+Na]^+$ 333.1109, calculated 333.1102 for the molecular formula $C_{19}H_{18}O_4Na$.

In conclusion, herein we have described the total synthesis of **1** through a Brønsted acid-mediated tandem cyclization as the key reaction to realize a methylene bridged bis-dihydropyrone ring skeleton in one-pot in a highly efficient manner. This strategy maybe adopted for the synthesis of similar ring-containing natural products.

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Supplementary data

Supplementary data (general procedures and spectral data of the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.133.

References and notes

1. Dumontet, V.; Hung, N. V.; Adeline, M.-T.; Riche, C.; Chiaroni, A.; Sévenet, T.; Guéritte, F. *J. Nat. Prod.* **2004**, *67*, 858.
2. Marco, J. A.; Carda, M.; Murga, J.; Falomir, E. *Tetrahedron* **2007**, *63*, 2929.
3. (a) Radha Krishna, P.; Ramana Reddy, V. V. *Tetrahedron Lett.* **2005**, *46*, 3905; (b) Radha Krishna, P.; Srinivas Reddy, P. *Tetrahedron* **2007**, *63*, 3995; (c) Radha Krishna, P.; Srinivas, R. *Tetrahedron Lett.* **2007**, *48*, 2013; (d) Radha Krishna, P.; Srinivas, R. *Tetrahedron: Asymmetry* **2007**, *18*, 2197.
4. Zhang, J.; Li, Y.; Wang, W.; She, X.; Pan, X. *J. Org. Chem.* **2006**, *71*, 2918.
5. Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245.
6. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
7. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
8. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
9. Wender, P. A.; Koehler, M. F. T.; Sendzik, M. *Org. Lett.* **2003**, *5*, 4549.
10. Please see Supplementary data for the experimental procedures and spectral data.