ORGANIC LETTERS

2011
Vol. 13, No. 24
6532–6535

Total Synthesis of Polygalolide A

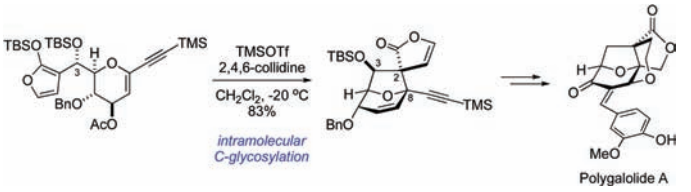
Masaatsu Adachi,*,† Hitomi Yamada,† Minoru Isobe,‡ and Toshio Nishikawa†

Laboratory of Organic Chemistry, Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan, and Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan

madachi@agr.nagoya-u.ac.jp

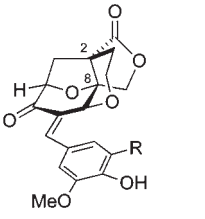
Received October 20, 2011

ABSTRACT



The total synthesis of polygalolide A was accomplished through intramolecular *C*-glycosylation of glucal modified with siloxyfuran. The siloxyfuran group and siloxy substituent at the C-3 position played crucial roles in allowing direct access to the highly substituted oxabicyclo[3.2.1] core skeleton with correct quaternary stereogenic centers.

Polygalolide A (**1**) and B (**2**) were isolated from the roots and stems of the folk medicinal plant *Polygala fallax* Hemsl. (Polygalaceae) by Wei and co-workers in 2003 (Figure 1).[1] These two molecules represent a new type of phenolic compound with a distinctive tetracyclic substructure characterized by a highly substituted oxabicyclo[3.2.1]octanone core skeleton, contiguous quaternary stereogenic centers fused with a γ-lactone, and a six-membered ether. Although details of the biological activity of **1** and **2** have not been reported, their characteristic structures have attracted considerable interest in the fields of organic synthesis and biology. Studying the structures and synthesis of polygalolides may also help to develop general annulation strategies for the construction of oxabicycles.[2] The first total synthesis of polygalolides was reported by Hashimoto and co-workers, who constructed the oxabicyclo[3.2.1]octanone skeleton using 1,3-dipolar cycloaddition of carbonyl ylide and determined the absolute configurations.[3] Snider and Hashimoto also reported the formal total synthesis using [5 + 2] cycloaddition of oxidopyrylium ylide.[4] Here, we report an alternative total synthesis of polygalolide A (**1**) through intramolecular *C*-glycosylation[5] of glucal modified with siloxyfuran.



Polygalolide A, **1** (R = H)
Polygalolide B, **2** (R = OMe)

Figure 1. Structures of Polygalolide A (**1**) and B (**2**).

The retrosynthetic analysis of polygalolide A (**1**) is illustrated in Scheme 1. We planned to synthesize **1** from intermediate **3**, a known synthetic precursor of polygalolides, according to the report of Hashimoto.[3] In our

† Nagoya University.
‡ National Tsing Hua University.

(1) Ma, W.; Wei, X.; Ling, T.; Xie, H.; Zhou, W. *J. Nat. Prod.* **2003**, *66*, 441–443.

(2) For recent reviews on the synthesis of the oxabicyclo scaffold, see: (a) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297–2306. (b) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.—Eur. J.* **2006**, *12*, 3438–3447. (c) López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2007**, *13*, 2172–2178. (d) Singh, V.; Krishna, U. M.; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405–3428.

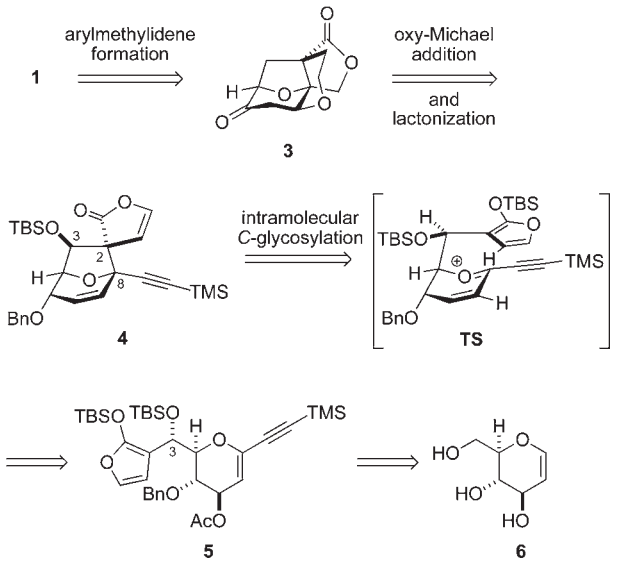
(3) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6532–6535.

(4) Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873–874.

(5) For recent reviews on *C*-glycosylation, see: (a) Meo, P.; Osborn, H. H. I. In *Carbohydrate*; Osborn, H. M. I., Ed.; Academic Press: Amsterdam, 2003; pp 337–384. (b) Nishikawa, T.; Adachi, M.; Isobe, M. In *Glycoscience*, 2nd ed.; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer Verlag: Berlin, Heidelberg, 2008; pp 756–811.

10.1021/ol2028256
Published on Web 11/17/2011

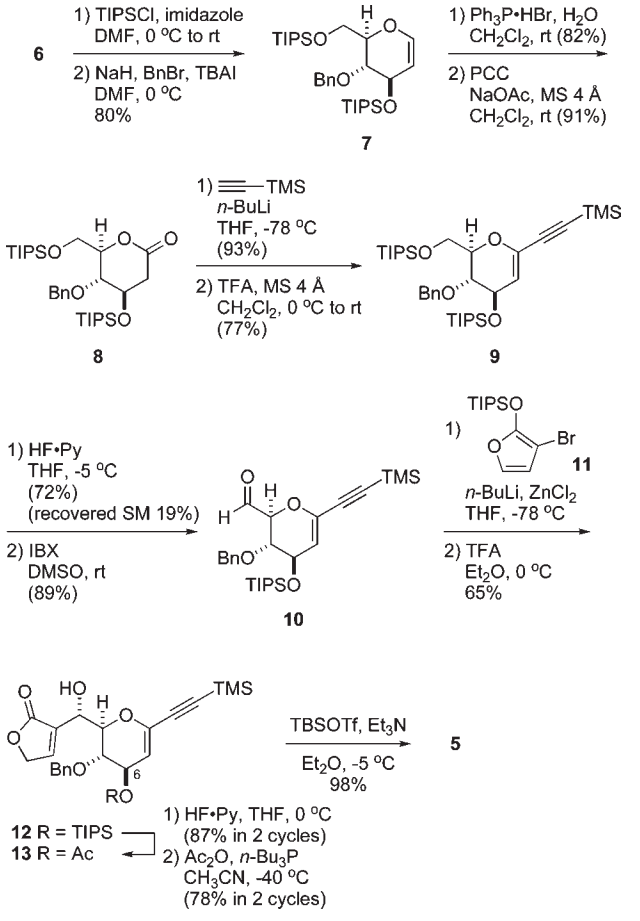
Scheme 1. Retrosynthetic Analysis of Polygalolide A (**1**)



proposed synthesis route, tetracyclic intermediate **3** would be generated via deoxygenation at the C-3 position of the oxabicyclo[3.2.1]octene skeleton of tricyclic spiro compound **4**, followed by oxy-Michael addition and lactonization to an enone intermediate. We envisaged that **4** would be synthesized by intramolecular Ferrier-type *C*-glycosylation as a key step from glucal **5** modified with a ketene silyl acetal and a siloxy substituent at the C-3 position.[6,7] For *C*-glycosylation,[8,9] silicon-based reagents have been widely employed as highly reactive carbon nucleophiles. Here, we selected stable siloxyfuran[8a] as an equivalent of the ketene silyl acetal, with the aim of constructing a quaternary stereogenic center at the C-2 position of **4** and synthesis of an oxabicyclooctene ring system. The siloxy substituent at the C-3 position was expected to control the configuration at the C-2 position as a result of steric hindrance in the transition state, as discussed later. Furthermore, we anticipated that the acetylene moiety of **5** would stabilize an oxocarbenium cation intermediate generated through activation to construct a quaternary stereogenic center at the C-8 position. Precursor **5**, possessing all of the necessary carbon atoms, would be synthesized from a commercially available D-glucal (**6**) by introduction of an acetylene moiety and chelation-controlled addition[10] of a siloxyfuran to aldehyde to establish the C-3 stereogenic center.

The siloxyfuran **5** was first synthesized from D-glucal (**6**) through furanone-substituted glucal **13** (Scheme 2). Silylation of D-glucal (**6**) was followed by benzylation of the remaining secondary alcohol to afford glucal **7**. Following the hydration of **7** with triphenylphosphine hydrobromide in CH_2Cl_2 and H_2O,[11] the resulting hemiacetal was oxidized with PCC to provide lactone **8**. Introduction of an acetylene unit to **8** was performed by the addition of lithium trimethylsilylacetylide and dehydration of the resulting hemiacetal with TFA to furnish alkynylated glucal **9**. After the primary TIPS group was selectively desilylated using pyridine hydrofluoride in THF, oxidation with IBX afforded aldehyde **10**. The addition of lithiosiloxyfuran[12] to **10** in the presence of $ZnCl_2$ proceeded in a highly stereoselective manner with chelation control. Subsequent acid hydrolysis of the unstable adduct gave lactone **12** as a single diastereomer.[13] An acetyl group, a leaving group at the C-6 position required for Ferrier-type *C*-glycosylation, was introduced by deprotection of the TIPS group and regioselective acetylation using Vedejs's procedure.[14] The resulting glucal **13** was treated with TBSOTf and triethylamine in Et_2O to furnish the siloxyfuran **5** in high yield.

Scheme 2. Synthesis of Siloxyfuran **5**, a Precursor for *C*-Glycosylation

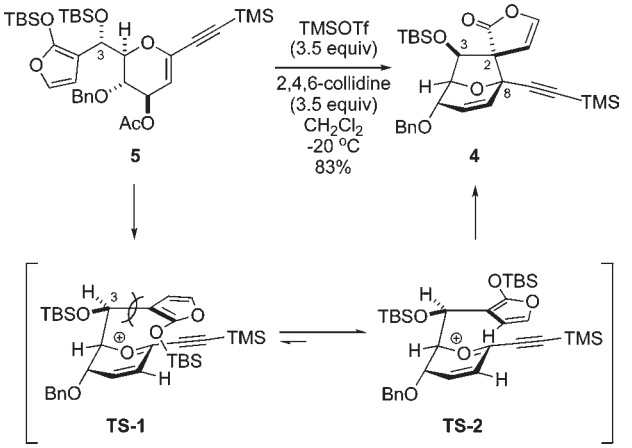


(6) As the methodology for construction of the oxabicyclo[3.2.1] skeleton includes a C–C bond formation at an anomeric position using an oxocarbenium cation generated from glucal derivative **5**, we termed it intramolecular *C*-glycosylation.

(7) For intramolecular *C*-glycosylation via an oxocarbenium cation by using carbohydrate derivatives and related compounds, see: (a) Martin, O. R. *Tetrahedron Lett*. **1985**, *26*, 2055–2058. (b) Stork, G.; Krafft, M. E.; Biller, S. A. *Tetrahedron Lett*. **1987**, *28*, 1035–1038. (c) Araki, Y.; Mokubo, E.; Kobayashi, N.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett*. **1989**, *30*, 1115–1118. (d) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *Carbohydr. Res*. **1990**, *208*, 264–266. (e) Craig, D.; Munasinghe, R. N. *Tetrahedron Lett*. **1992**, *33*, 663–666. (f) Sasmal, P. K.; Maier, M. E. *Org. Lett*. **2002**, *4*, 1271–1274.

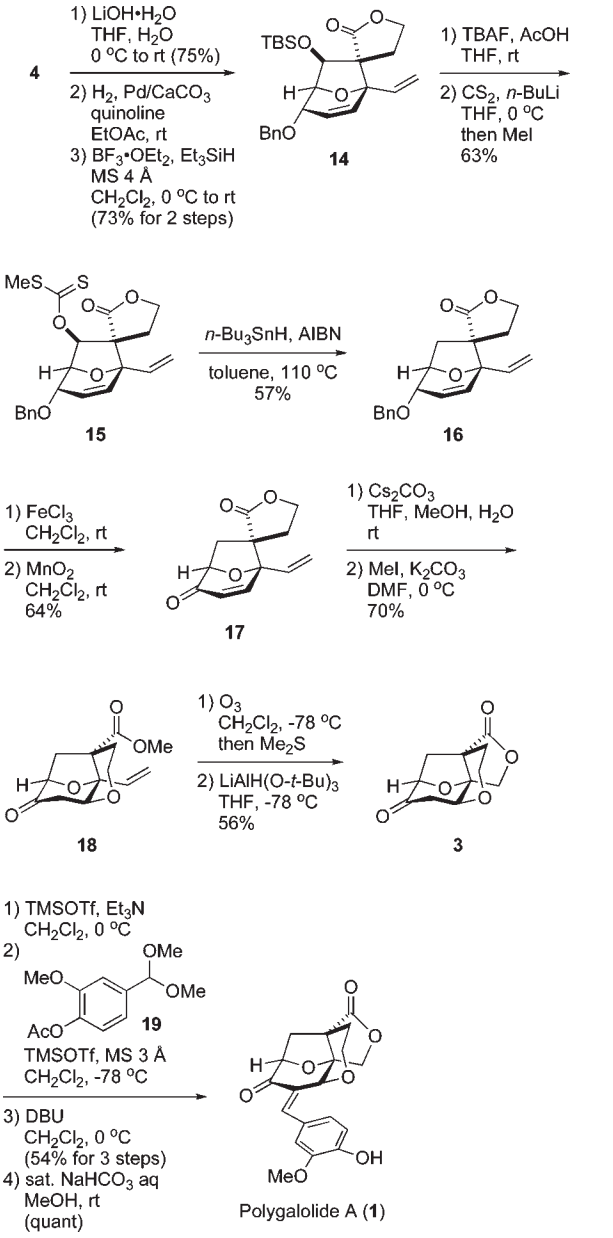
After obtaining siloxyfuran **5**, we next investigated a key intramolecular *C*-glycosylation for the synthesis of oxabicyclo[3.2.1]octene **4** (Scheme 3). Upon treatment of siloxyfuran **5** with a Lewis acid such as $SnCl_4$, $TiCl_4$, or BF_3•OEt_2 in CH_2Cl_2, a complex mixture of products was obtained. After extensive examination, we determined that TMSOTf and 2,4,6-collidine in CH_2Cl_2 at −20 °C was the optimal condition for the intramolecular *C*-glycosylation to give desired oxabicyclo[3.2.1]octene **4** in 83% yield as a single product. The structure of **4** was unambiguously confirmed by X-ray crystallographic analysis.[15]

Scheme 3. Synthesis of Oxabicyclo[3.2.1]octene **4** and Proposed Mechanism for the Intramolecular *C*-Glycosylation



The high stereoselectivity of the intramolecular *C*-glycosylation, as predicted (Scheme 3), is dictated by the effect of the siloxy substituent at the C-3 position. Under the reaction conditions, siloxyfuran **5** would give an oxocarbenium cation intermediate, which has two possible transition states (**TS-1** and **TS-2**) in a cyclization step. Considering allylic 1,3-strain, the *C*-glycosylation proceeds through the more stable **TS-2** with minimum steric hindrance between the two TBS groups to yield product **4** exclusively.

Scheme 4. Total Synthesis of Polygalolide A (**1**)



Next, oxabicyclo[3.2.1]octene **4** was transformed into tetracyclic lactone **3**, as shown in Scheme 4. Hydrolysis of **4** with LiOH gave a hemiacetal, and partial hydrogenation of the desilylated acetylenic moiety with Lindlar's catalyst and subsequent reduction with Et_3SiH and BF_3•OEt_2 in the presence of MS-4 Å afforded spirolactone **14**. At this stage, oxygen functionality at the C-3 position was removed using the Barton−McCombie deoxygenation protocol.[16] Deprotection of the TBS group was followed

(8) (a) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res.* **1987**, *171*, 193–199. (b) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211–6215. (c) Isobe, M.; Phoosaha, W.; Saeeng, R.; Kira, K.; Yenjai, C. *Org. Lett.* **2003**, *5*, 4883–4885. (d) Saeeng, R.; Isobe, M. *Org. Lett.* **2005**, *7*, 1585–1588. (e) Saeeng, R.; Isobe, M. *Chem. Lett.* **2006**, *35*, 552–557.

(9) (a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.* **1993**, *34*, 5757–5760. (b) Tanaka, S.; Isobe, M. *Tetrahedron* **1994**, *50*, 5633–5644. (c) Hamajima, A.; Isobe, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2941–2945.

(10) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **1984**, *23*, 556–569. (b) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.

(11) (a) Koviach, J. L.; Chappell, M. D.; Halcomb, R. L. *J. Org. Chem.* **2001**, *66*, 2318–2326. (b) Bolitt, V.; Mioskowski, C. *J. Org. Chem.* **1990**, *55*, 5812–5813.

(12) Boukouvalas, J.; Marion, O. *Synlett* **2006**, 1511–1514.

(13) Although the stereochemistry of the generated alcohol at the C-3 position was not determined at this stage, the configuration was finally confirmed to be *S* by X-ray crystallographic analysis of oxabicyclo-[3.2.1]octene **4**.

(14) (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358–3359. (b) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286–7288.

(15) CCDC 836367 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585. (b) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329–2338.

by treatment with *n*-BuLi, CS_2, and MeI to give xanthate **15**, which was treated with *n*-Bu_3SnH in the presence of AIBN at 110 °C to furnish alkene **16**. Debenzylation of **16** with $FeCl_3$ and oxidation with MnO_2 gave enone **17**. Upon treatment with Cs_2CO_3 in aqueous THF and MeOH, oxy-Michael addition of the alcohol intermediate resulted in a tricyclic compound. Methylation of the carboxylic acid group with MeI and K_2CO_3 afforded methyl ester **18**. Sequential ozonolysis of the vinyl group and chemoselective reduction of the resulting aldehyde with $LiAlH(O\text{-}t\text{-}Bu)_3$ in the presence of the ketone provided the primary alcohol, which underwent spontaneous lactonization to yield the desired tetracyclic lactone **3**.[3]

Finally, according to Hashimoto's procedure,[3] tetracyclic lactone **3** was transformed into polygalolide A (**1**) by Mukaiyama aldol-type condensation with dimethyl acetal **19**. The spectroscopic data of the synthesized compound were identical to those of natural polygalolide A (**1**) with the exception of optical rotation. The synthetic $[\alpha]_D$ value ($[\alpha]_D^{26} = -491$ ($c = 0.0226$, MeOH)) was also consistent with that of reported data.[3]

In conclusion, we have accomplished the total synthesis of polygalolide A (**1**) starting from D-glucal through intramolecular *C*-glycosylation for the construction of the oxabicyclo[3.2.1] core skeleton. In our distinctive synthesis approach, the siloxyfuran group and siloxy substituent at the C-3 position of **5** played crucial roles in allowing direct access to the highly substituted oxabicyclo[3.2.1] core skeleton with correct quaternary stereogenic centers. This novel and reliable methodology is applicable for the synthesis of polygalolide analogues and natural products containing an oxabicyclo skeleton.

Acknowledgment. This work was financially supported by Grants-in-Aid for Young Scientists (Start-up and B) and a Global COE program from the Japan Society for the Promotion of Science (JSPS), and a SUNBOR GRANT from the Suntory Institute for Bioorganic Research. H.Y. is thankful for the Daiko Foundation Scholarship and Nagoya University Scholarship for outstanding graduate students. We are grateful to Mr. K. Yoza (Bruker AXS) for the X-ray crystallographic analysis. We gratefully acknowledge Prof. S. Hashimoto (Hokkaido University) and Prof. S. Nakamura (Nagoya City University) for providing the spectra of tetracyclic compound **3** and polygalolide A.

Supporting Information Available. Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra for all new compounds, and crystallographic data for **4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.