CHEMISTRY
AN ASIAN JOURNAL
ACES
FULL PAPER

DOI: 10.1002/asia.201300362

Stereocontrolled Total Synthesis of Polygalolide A

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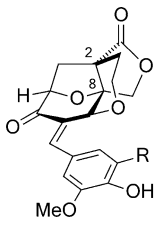
Abstract: The total synthesis of polygalolide A, a secondary metabolite that was isolated from a Chinese medicinal plant, is reported. A key issue in this synthesis was construction of an oxabicyclo[3.2.1] skeleton, which was solved by the development of an intramolecular Ferrier-type C-glycosylation of a glucal with siloxyfuran as an internal nucleophile. The substrate was prepared from D-glucal by the introduction of trimethylsilylacetylene and siloxyfuran groups. Although C-glycosylation did not occur under the conditions found from model experiments, further examination revealed that the combination of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,4,6-collidine successfully afforded the desired product as a single diastereomer. The siloxy group at the C3 position played a crucial role in the stereocontrol of this reaction. The product was further transformed into a tetracyclic compound as follows: The vinyl ether and acetylenic moieties were reduced and the siloxy group was removed with a Barton–McCombie reaction. The construction of the six-membered ether and the γ-lactone provided the tetracyclic compound. Finally, a phenolic moiety was introduced by using a Mukaiyama aldol reaction to furnish polygalolide A.

Keywords: glycosylation · heterocycles · natural products · polygalolides · total synthesis

Introduction

Polygalolides A (**1**) and B (**2**) were isolated by Wei and co-workers in 2003 from the powdered dried roots and stems of the folk medicinal plant *Polygala fallax* Hemsl. (Polygalaceae) and is used as a tonic or as an antihepatitis drug (Scheme 1).[1] Extensive spectroscopic analysis has revealed that these two molecules represent a new type of phenolic compound with a distinctive tetracyclic substructure that is characterized by a highly substituted oxabicyclo-[3.2.1]octanone skeleton, contiguous quaternary stereogenic centers that are fused with a γ-lactone, and a six-membered ether. Although the biological activities of compounds **1** and **2** have not yet been reported, their characteristic structures have attracted considerable interest in the field of organic synthesis. The absolute configuration of the polygalolides was established by their first total synthesis in 2006 by Hashimoto, Nakamura, and co-workers,[2] who constructed the oxabicyclo[3.2.1]octanone skeleton by using an intramolecular 1,3-dipolar cycloaddition of carbonyl ylide. A comparison of the $[\alpha]_D$ values of these synthesized compounds with those of natural polygalolides led them to suggest that these natural products might be biosynthesized in their near-racemic forms. Snider, Hashimoto, and co-workers also reported a formal total synthesis by using the [5+2] cycloaddition of oxidopyrylium ylide as a key step.[3] Herein, we report the full details of our efforts toward the total synthesis of polygalolide A (**1**), through the development of an intramolecular Ferrier-type C-glycosylation of a glucal modified with siloxyfuran as a key step for the construction of the oxabicyclo[3.2.1] structure in this natural product.[4]



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

Scheme 1. Structures of polygalolides A (**1**) and B (**2**).

Results and Discussion

Initial Synthetic Plan for Polygalolide A (1)

We planned to synthesize polygalolide A (**1**) from tetracyclic intermediate **3**, which was employed by Hashimoto, Nakamura, and co-workers in their total synthesis[2] (Scheme 2).

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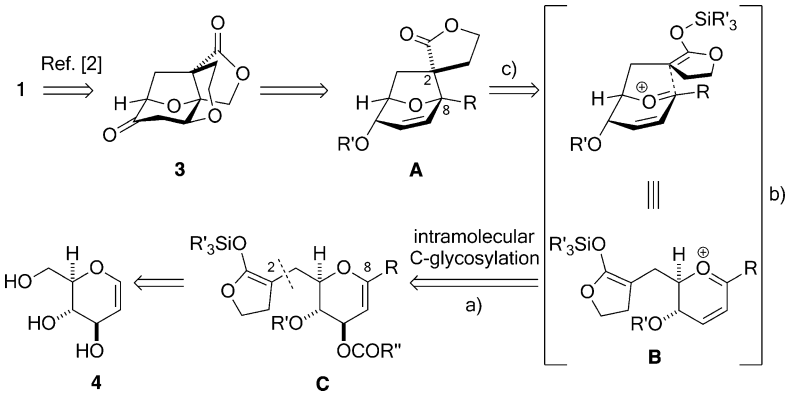
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201300362.



Scheme 2. Retrosynthetic analysis of polygalolide A (**1**).

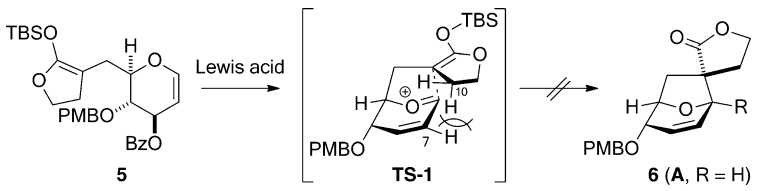
The γ-lactone and six-membered ether moieties in intermediate **3** would be transformed from a tricyclic compound **A** with an oxabicyclo[3.2.1]octene skeleton. We envisaged that compound **A** would be synthesized from glucal derivative **C** through: a) The generation of oxocarbenium ion **B** through Lewis acid-promoted activation of the ester group and migration of the double bond (so-called Ferrier rearrangement); b) partial ring inversion from the $^4C_1$-conformer into the $^1C_4$-conformer; and c) an intramolecular C–C bond-forming reaction (so-called C-glycosylation[5–7]) to yield oxabicyclo[3.2.1]octene **A** in a one-pot manner.[8] The precursor **C**, which possessed a nucleophilic moiety, would be prepared from D-glucal (**4**). Because a few examples of intramolecular C-glycosylation reactions have been reported,[9] we began with a model experiment for examining the feasibility of this synthetic strategy.

Model Experiments for the Construction of the Oxabicyclo[3.2.1]octene Skeleton

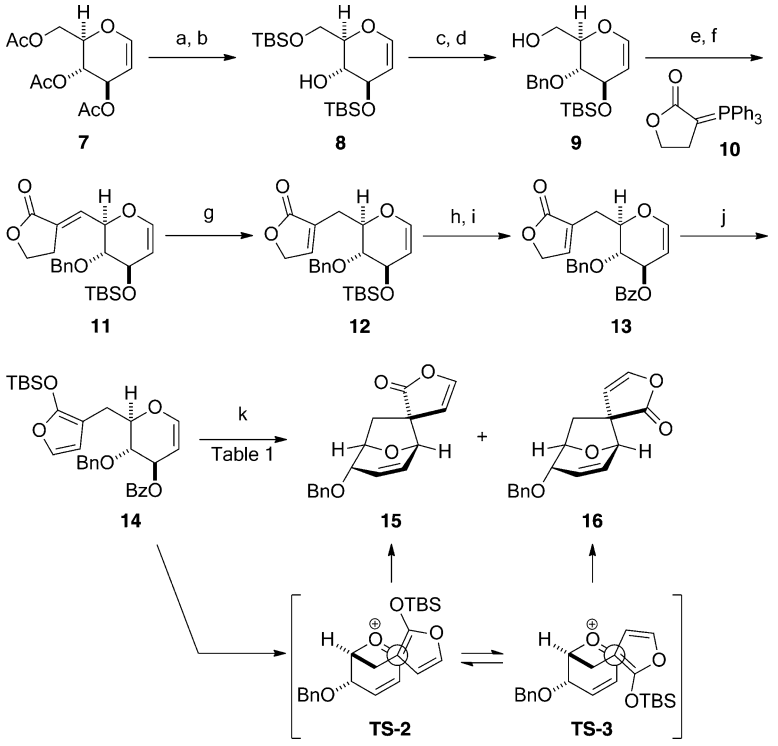
To examine the intramolecular C-glycosylation reaction, γ-butyrolactone-derived silyl enolate **5**[10] was prepared as a model compound without a substituent at the C8 position (**C**; Scheme 2, R = H) and then exposed to conventional conditions for the C-glycosylation reaction. However, all of the attempted intramolecular C-glycosylation reactions with various Lewis acids, such as TMSOTf, $TiCl_4$, and $BF_3{\cdot}OEt_2$, did not give the desired oxabicyclo[3.2.1]octene **6**, but rather a complex mixture of products was afforded, although the oxocarbenium ion was generated through activation of the benzoate (Scheme 3).[11] The lack of success of these C-glycosylation reactions might be explained by steric repulsion between the H7 and H10 atoms in transition state **TS-1** of the resulting oxocarbenium ion. The instability of the ketene silyl acetal moiety under the glycosylation conditions might also be another reason for these unsuccessful results. These analyses led us to design glucal **14**, which possessed a siloxyfuran moiety as an alternative nucleophile (Scheme 4) for the C-glycosylation reaction with the aim of enhancing its stability and minimizing steric hindrance.

A new model precursor **14** was synthesized from tri-*O*-acetyl-D-glucal (**7**), a commercially available starting material (Scheme 4). Deacetylation of compound **7** with NaOMe followed by regioselective silylation of the resulting triol with TBSCl afforded bis-TBS ether **8**. Benzylation of the remaining hydroxy group and selective desilylation of the primary TBS group with hydrogen fluoride pyridine gave alcohol **9**. A γ-lactone unit was introduced by oxidation of the primary alcohol and Wittig reaction of the resulting aldehyde with compound **10** provided lactone **11** in good yield. Isomerization of the olefin was best carried out by treatment with Wilkinson's catalyst and Et_3SiH in toluene to yield the desired furanone **12**. Finally, the TBS ether of compound **12** was transformed into the corresponding benzoate in two steps, including desilylation and benzoylation, under the mild conditions developed by Oriyama and co-workers (BzCl, TMEDA, 0 °C).[12] Treatment of compound **13** with TBSOTf and LHMDS gave siloxyfuran **14**, which was then immediately used in the C-glycosylation reaction without purification because of its instability.

When compound **14** was treated with $SnCl_4$ in the presence of 4 Å M.S. at −78 °C, followed by gradually increasing the reaction temperature to −30 °C, a complex mixture of products was obtained (Table 1, entry 1). The reaction with $ZnCl_2$ solely provided oxabicyclo[3.2.1]octene **16** in 10% overall yield over two steps (Table 1, entry 2). Fortunately, further experimentation led us to find that $TiCl_4$ and $BF_3{\cdot}OEt_2$ were optimal Lewis acids for the production of the oxabicyclo[3.2.1]octene; when compound **14** was treated with 1.5 equivalents of $TiCl_4$, oxabicyclic products **15** and **16** were obtained in 24% and 49% overall yield, respectively, over two steps (Table 1, entry 4).[13] The C-glycosylation reaction with $BF_3{\cdot}OEt_2$ proceeded smoothly to give compounds **15** and **16** in 37% and 38% overall yield, respectively, over two steps (Table 1, entry 5). The reason for the



Scheme 3. Intramolecular Ferrier-type C-glycosylation for the construction of the oxabicyclo[3.2.1] core skeleton of polygalolides.



Scheme 4. Synthesis of model precursor siloxyfuran **14** and oxabicyclo[3.2.1]octene through intramolecular Ferrier-type C-glycosylation. Reagents and conditions: a) NaOMe, MeOH, RT, 0.4 h; b) TBSCl, imidazole, DMF, 0 °C, 11 h, 73 % over 2 steps; c) NaH, BnBr, TBAI, DMF, −5 to 5 °C, 9 h, 92 %; d) HF·Py, THF, 0 °C, 4 h, 74 % in 2 cycles; e) IBX, DMSO, RT, 6 h; f) compound **10**, CH_2Cl_2, 0 °C to RT, 3 h, 79 % over 2 steps; g) [RhCl(PPh_3)$_3$], Et_3SiH, toluene, 60 °C, 1.5 h, 92 %; h) TBAF, AcOH, THF, 0 °C to RT, 22 h, 78 %; i) BzCl, TMEDA, CH_2Cl_2, 0 °C, 0.6 h, 65 %; j) LHMDS, THF, −78 °C, 1 h; then TBSOTf, −20 °C, 1 h; k) see Table 1. Ac = acetyl, TBS = *tert*-butyldimethylsilyl, Bn = benzyl, TBAI = tetrabutylammonium iodide, Py = pyridine, IBX = 2-iodoxybenzoic acid, TBAF = tetrabutylammonium fluoride, Bz = benzoyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, LHMDS = lithium bis(trimethylsilyl)amide, Tf = trifluoromethanesulfonyl, M.S. = molecular sieves.

Table 1. Intramolecular Ferrier-type C-glycosylation of compound **14**.[a]

Entry	Lewis acid	*t* [h]	Yield [%][b]	
			15	**16**
1	$SnCl_4$	4	0	0
2	$ZnCl_2$	13	0	10
3	TMSOTf	4	0	0
4	$TiCl_4$	5	24	49
5	BF_3·OEt_2	4	37	38

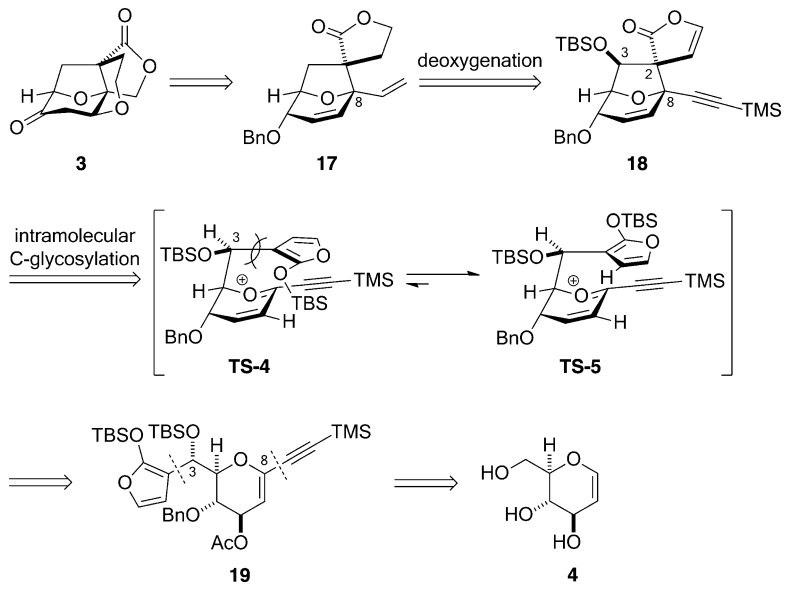
[a] The reaction was performed with a Lewis acid (1.5 equiv) and 4 Å M.S. in CH_2Cl_2 for the indicated time. [b] Yield of isolated product over 2 steps. TMS = trimethylsilyl.

low stereoselectivity of the C-glycosylation reaction might be due to be the small energy difference between two possible transition states, **TS-2** and **TS-3**, which leads to oxabicyclic products **15** and **16**, respectively.

Modified Synthetic Plan for Polygalolide A (1)

With efficient access to the oxabicyclo[3.2.1]octene skeleton secured, the remaining issue was the stereocontrol at the C2 position. We envisaged that the configuration at the C2 position could be controlled by introducing a bulky auxiliary at the C3 position of a precursor for the C-glycosylation reaction. This auxiliary should be easy to prepare and securely remove and it must be compatible with the C-glycosylation conditions. Based on these considerations, we modified our synthetic plan for polygalolide A (**1**), as shown in Scheme 5, and designed a new precursor **19** for the intramolecular C-glycosylation reaction, which possessed a siloxy group at the C3 position with an *S* configuration and an acetylene group at the C8 position. The acetylenic moiety was anticipated to be the synthetic equivalent of a hydroxymethyl group at the C8 position and would stabilize an oxocarbenium ion intermediate. The precursor **19** would be synthesized from a commercially available D-glucal (**4**) by the introduction of the acetylenic and siloxyfuran moieties at the C8 and C2 positions, respectively. In the C-glycosylation of compound **19**, considering unfavorable 1,3-allylic strain between the two siloxy groups in transition state **TS-4**, more-stable transition state **TS-5** would preferentially yield the desired oxabicyclo[3.2.1]octene **18**. In our newly designed synthetic route, compound **18** would be transformed into tricyclic compound **17** by deoxygenation at the C3 position. Construction of six-membered ether and the γ-lactone would afford tetracyclic intermediate **3**.

Siloxyfuran **19**, a precursor for the C-glycosylation, was synthesized from D-glucal (**4**) (Scheme 6). Hydroxy groups at the C3 and C6 positions were protected as TIPS ether and benzylation of the remaining secondary alcohol gave compound **20**. Construction of the ene-yne moiety of compound **24** was achieved in a two-step procedure, that is, the addition of an acetylide to a lactone derivative and subsequent dehydration, as follows: The direct oxidation of compound **20** with pyridinium chlorochromate (PCC)[14] provided the required lactone **22** in 51 % yield, along with a significant amount of byproducts. Thus, the stepwise preparation of compound **22** was examined next. Hydration of compound **20** with triphenylphosphine hydrobromide in CH_2Cl_2 and water[15] gave hemiacetal **21**, which was oxidized with PCC to provide lactone **22** in good overall yield. The addition of lithium trimethylsilylacetylide gave hemiacetal **23** in high yield, however, dehydration of compound **23** did not readily give enyne **24** under conditions with either phospho-



Scheme 5. Modified synthetic plan for polygalolide A (**1**).

rus oxychloride or Burgess reagent because of the steric hindrance around the tertiary alcohol. In contrast, the dehydration of compound **23** with TFA in the presence of 4 Å M.S. proceeded smoothly to furnish compound **24**. After the TIPS group on the primary alcohol was selectively desilylated by using hydrogen fluoride pyridine, oxidation with IBX afforded aldehyde **26**. The addition of lithiosiloxyfuran,[16] as prepared from bromofuran **27** with *n*BuLi, was best carried out in the presence of $ZnCl_2$ to afford adduct **28** as a single product.[17] Because of its instability, the adduct **28** was immediately hydrolyzed with TFA in Et_2O and furanone **29** was isolated in 65% yield over two steps as a single diastereomer.[18] The stereochemical outcome of this addition might be explained as follows: On the pretreatment of compound **26** with $ZnCl_2$, the carbonyl oxygen atom and the ring oxygen atom of the glucal would chelate to the zinc cation and, thus, the nucleophile would approach from the less-hindered side.

An acetyl group was introduced as a leaving group at the C6 position for the intramolecular Ferrier-type C-glycosylation reaction. The TIPS group of compound **29** was deprotected with hydrogen fluoride pyridine in THF to give diol **30** in 87% yield after two cycles. The regioselective acetylation proceeded smoothly under the conditions reported by Vedejs et al.[19] (acetic anhydride in the presence of a catalytic amount of nBu$_3$P at −40 °C) to afford the desired acetate **31** in 78% yield after two cycles.[20] Fortunately, when siloxyfuran **19** was prepared from the resulting acetate **31** by treatment with TBSOTf and Et_3N in dichloromethane, oxabicyclo[3.2.1]octene **18**, the desired product, was incidentally obtained in 16% yield as a single diastereomer. The structure of compound **18** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[21] This unexpected but successful result encouraged us to examine the C-glycosylation conditions from compound **31**; however, the direct synthesis of compound **18** was difficult. Therefore, we would synthesize compound **18** in steps from compound **31** through compound **19**, and the preparation of compound **19** from compound **31** was reexamined. Finally, TBSOTf and Et_3N in Et_2O (instead of dichloromethane) was found to be the optimal conditions, thus giving the desired compound **19** in 98% yield.

According to the conditions developed in the model experiment, the intramolecular C-glycosylation of siloxyfuran **19** was investigated (Table 2). The siloxyfuran **19** was treated with a Lewis acid, such as $TiCl_4$ or $BF_3{\cdot}OEt_2$, in CH_2Cl_2 to give a complex mixture of products (Table 2, entries 1 and 2). Attempted C-glycosylations with other conventional Lewis acids also failed to give the expected oxabicyclic product **18**. These results might be due to instability of the highly functionalized precursor **19**, which possessed the siloxy substituent at the C3 position. Next, the conditions (TBSOTf, Et_3N, in CH_2Cl_2) that were incidentally found for the direct production of compound **18** from acetate **31** were examined in detail for the C-glycosylation reaction. The possibility of TfOH as a "real" activator was excluded by the following experiment: Treatment of compound **19** with TfOH in the presence of Et_3N at −20 °C only provided a small amount of the oxabicyclic product **18** in 11% yield (Table 2, entry 3). After extensive attempts by employing a combination of TBSOTf and Et_3N, we were pleased to find that the exposure of the siloxyfuran **19** to an equimolar ratio of TBSOTf (3.5 equiv) and Et_3N (3.5 equiv)

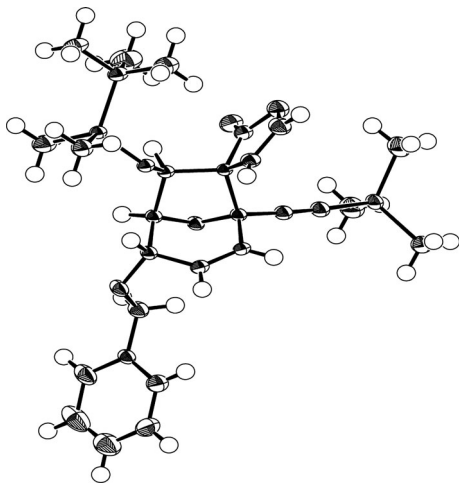
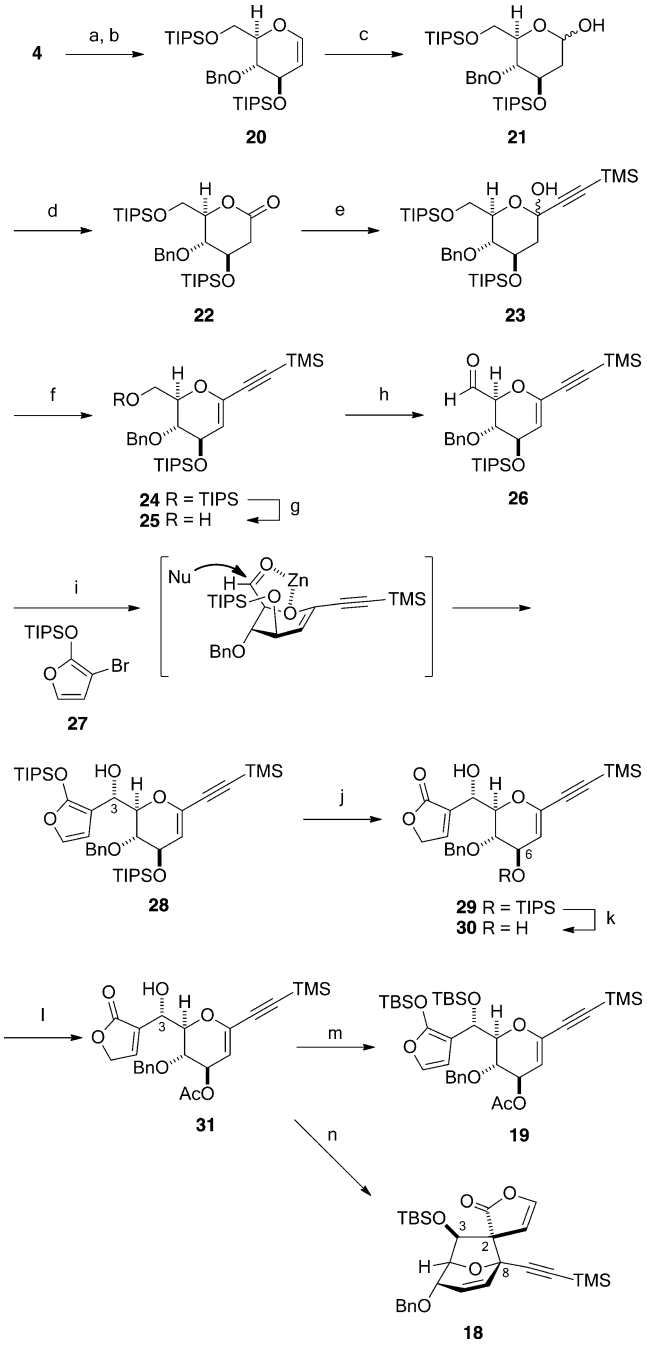
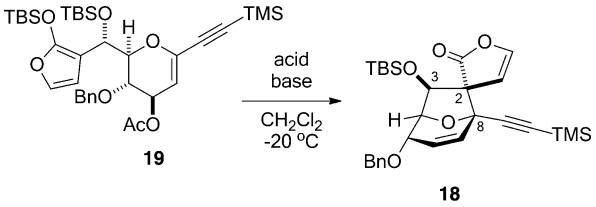


Figure 1. ORTEP of compound **18**.



Scheme 6. Synthesis of siloxyfuran **19** as a precursor for the intramolecular Ferrier-type C-glycosylation reaction. Reagents and conditions: a) TIPSCl, imidazole, DMF, 0 °C to RT, 18 h; b) NaH, BnBr, TBAI, DMF, 0 °C, 2.5 h, 80 % over 2 steps; c) Ph_3P·HBr, CH_2Cl_2/water (37:1), RT, 13.8 h, 82 %; d) PCC, NaOAc, 4 Å M.S., CH_2Cl_2, RT, 1.5 h, 91 %; e) trimethylsilylacetylene, *n*BuLi, THF, −78 °C, 0.8 h, 93 %; f) TFA, 4 Å M.S., CH_2Cl_2, 0 °C to RT, 24 h, 77 %; g) HF·Py, THF, −5 °C, 4.8 h, 72 % (recovered starting material, 19 %); h) IBX, DMSO, RT, 9.6 h, 89 %; i) bromofuran **27**, *n*BuLi, $ZnCl_2$, THF, −78 °C, 1.3 h; j) TFA, Et_2O, 0 °C, 10 h, 65 % over 2 steps; k) HF·Py, THF, 0 °C, 24 h, 87 % in 2 cycles; l) Ac_2O, *n*Bu_3P, MeCN, −40 °C, 11.5 h, 78 % in 2 cycles; m) TBSOTf, Et_3N, Et_2O, −5 °C, 50 min, 98 %; n) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 20 min, 16 %. TIPS = triisopropylsilyl, PCC = pyridinium chlorochromate, TFA = trifluoroacetic acid.

Table 2. Synthesis of oxabicyclo[3.2.1]octene **18** through intramolecular Ferrier-type C-glycosylation.

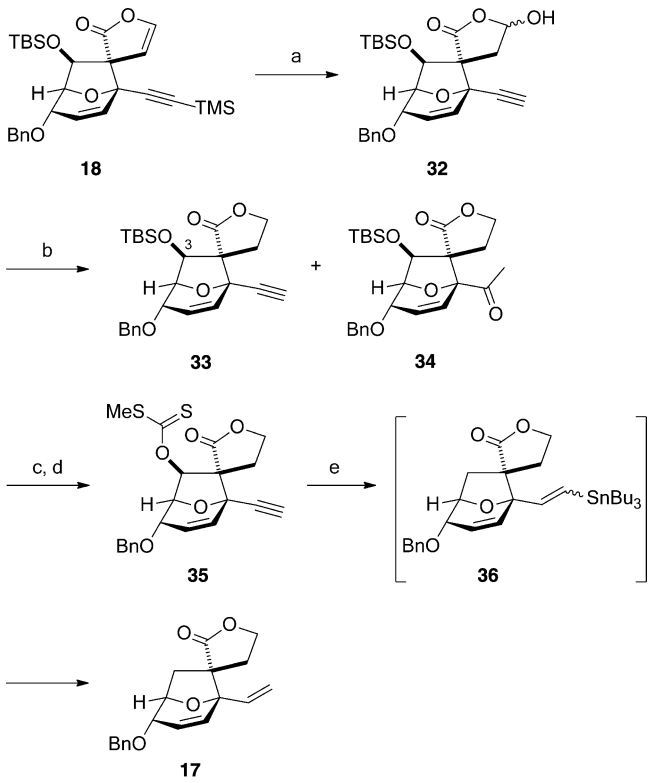


Entry	Acid	Base	Yield [%][c]
1	$TiCl_4$	–	0
2	BF_3·OEt_2	–	0
3[a]	TfOH	Et_3N	11
4[b]	TBSOTf	Et_3N	61
5[b]	TBSOTf	DIEA	59
6[b]	TBSOTf	DTBMP	54
7[b]	TBSOTf	2,4,6-collidine	72
8[b]	TBSOTf	DMAP	0
9[b]	TMSOTf	2,4,6-collidine	83

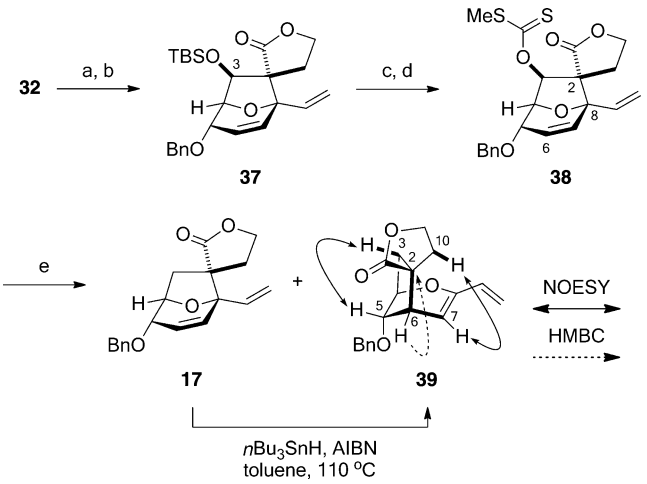
[a] The reaction was performed with TfOH (9.0 equiv) and E_3N (9.0 equiv) in CH_2Cl_2. [b] The reaction was performed with a Lewis acid (3.5 equiv) and a base (3.5 equiv) in CH_2Cl_2. [c] Yield of isolated compound **18**. DIEA = *N*,*N*-diisopropylethylamine, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, DMAP = *N*,*N*-dimethyl-4-aminopyridine.

in CH_2Cl_2 at −20 °C provided compound **18** in 61 % yield as a single diastereomer (Table 2, entry 4). The C-glycosylation of compound **19** also proceeded smoothly in the presence of a base, such as *N*,*N*-diisopropylethylamine (DIEA), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), or 2,4,6-collidine, thus giving oxabicyclic product **18** in good yields (Table 2, entries 5–7). On the other hand, the reaction of siloxyfuran **19** with an equimolar ratio of TBSOTf and *N*,*N*-dimethyl-4-aminopyridine (DMAP) provided a complex mixture of products (Table 2, entry 8). Finally, an equimolar ratio of TMSOTf (3.5 equiv) and 2,4,6-collidine (3.5 equiv) in CH_2Cl_2 at −20 °C were found to be the optimal conditions for the intramolecular C-glycosylation, thus providing compound **18** in 83 % yield as a single diastereomer (Table 2, entry 9). The exclusive production of compound **18** as a single diastereomer indicates a crucial role of the siloxy substituent at the C3 position of compound **19**, as expected. In this C-glycosylation reaction, a silylammonium or silylpyridinium triflate[22] might be generated and serve as an active promoter, which would selectively activate the acetyl group of compound **19**. This developed C-glycosylation reaction allows the gram-scale synthesis of oxabicyclo[3.2.1]octene **18** from acetate **31**.

Next, the oxabicyclo[3.2.1]octene **18** was transformed into tricyclic compound **17**, according to the synthetic plan shown in Scheme 5. Because the direct reduction of the vinyl ether moiety in compound **18** was unsuccessful, its two-step transformation into γ-lactone **33** through hemiacetal **32** was examined (Scheme 7). Hydrolysis of compound **18** with LiOH was followed by reduction of the resulting hemiacetal **32** with Et_3SiH and BF_3·OEt_2[23] in the presence of 4 Å M.S. to give the desired γ-lactone **33** in 43 % yield, along with methyl ketone **34** in 41 % yield as a byproduct. At this stage, the oxygen functionality at the C3 position



Scheme 7. Synthesis of tricyclic spiro compound **17**. Reagents and conditions: a) $LiOH{\cdot}H_2O$, THF/water (3:1), 0 °C to RT, 6.5 h, 75%; b) $BF_3{\cdot}OEt_2$, Et_3SiH, 4 Å M.S., CH_2Cl_2, 0 °C to RT, 2 h, 43% over 2 steps for compound **33**, 41% over 2 steps for compound **34**; c) TBAF, AcOH, THF, 0 °C, 10 min; d) CS_2, *n*BuLi, THF, −10 °C to RT, 1.7 h; then MeI, RT, 1 h, 71% over 2 steps; e) $n Bu_3SnH$, AIBN, toluene, 110 °C, 1 h; then *p*-$TsOH{\cdot}H_2O$, 0 °C to RT, 16 h, 48%. AIBN = 2,2′-azobisisobutyronitrile, Ts = toluenesulfonyl.

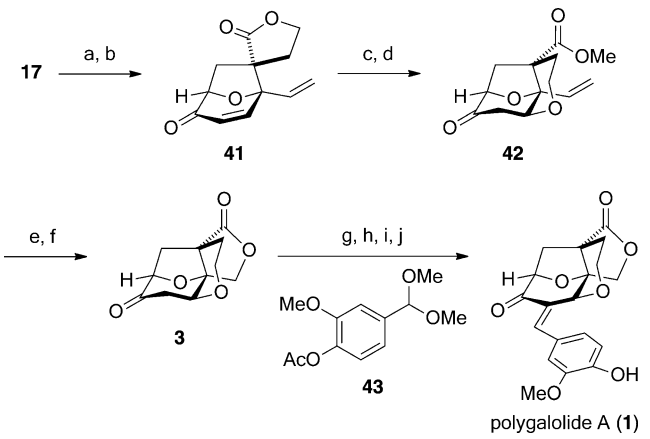


Scheme 8. Alternative synthetic route to tricyclic spiro compound **17**. Reagents and conditions: a) H_2, $Pd/CaCO_3$, quinoline, EtOAc, RT, 30 min; b) $BF_3{\cdot}OEt_2$, Et_3SiH, 4 Å M.S., CH_2Cl_2, 0 °C to RT, 42 h, 73% over 2 steps; c) TBAF, AcOH, THF, 0 °C, 3.5 h; d) CS_2, *n*BuLi, THF, 0 °C, 30 min; then MeI, 0 °C, 10 min, 63% over 2 steps; e) $n Bu_3SnH$, AIBN, toluene, 110 °C, 1 h, 57%.

was removed by using Barton–McCombie deoxygenation.[24] The TBS group was deprotected and then xanthate **35** was prepared by treatment with *n*BuLi, CS_2, and MeI. The deoxygenation of compound **35** with $n Bu_3SnH$ in the presence of AIBN at 110 °C gave vinyl stannane **36**, which was subjected to protodestannylation with *p*-TsOH to furnish the desired spiro compound **17** in 48% yield. This route enabled us to synthesize compound **17**; however, the generation of byproduct **34** could not be completely prevented. Because this result might be due to the presence of the acetylenic moiety adjacent to the hemiacetal, we slightly modified the synthetic route by including a transformation of the acetylenic moiety of compound **32** into an alkene group prior to silane reduction, as described below.

The partial hydrogenation of compound **32** in the presence of Lindlar's catalyst and subsequent reduction with Et_3SiH and $BF_3{\cdot}OEt_2$ afforded alkene **37** in 73% overall yield over two steps without the formation of any byproducts (Scheme 8). According to the above procedure, compound **37** was transformed into xanthate **38** in two steps. Barton–McCombie deoxygenation of compound **38** with $n Bu_3SnH$ in the presence of AIBN (40 mol%) at 110 °C for 1.5 h gave the desired spiro compound **17** in 13% yield, along with diene **39** in 52% yield as a byproduct.[25] Further experiments revealed that the undesired diene **39** was generated from compound **17**; exposure of compound **17** to the same conditions for 1.5 h provided compound **39** in 90% yield as a single diastereomer, whereas this transformation did not occur in the absence of $n Bu_3SnH$ and AIBN. These results indicated that the tributylstannyl radical that was generated from $n Bu_3SnH$ and AIBN might cause the transformation.[26] In fact, the brief exposure of xanthate **38** to a small amount of the stannyl radical was crucial for preventing the production of undesired compound **39**. Finally, $n Bu_3SnH$ in the presence of AIBN (10 mol%) at 110 °C for 1 h were found to be the optimal conditions for the successful deoxygenation to give compound **17** without the formation of compound **39**. As a result, we established an efficient accessible route to spiro compound **17**.

For the total synthesis of polygalolide A (**1**), the next task was the transformation of compound **17** into tetracyclic lactone **3** (Scheme 9). Deprotection of the benzyl group of compound **17** was best achieved by treatment with $FeCl_3$ in CH_2Cl_2 to provide the allylic alcohol,[27] which was oxidized with MnO_2 to give enone **41** in 64% yield over two steps. To construct a six-membered ether by oxy-Michael addition, hydrolysis of the lactone was examined. Basic conditions, such as NaOMe, *t*BuOK, or LiOH, did not provide the oxy-Michael product, even under refluxing conditions. We found that the use of Cs_2CO_3 and MeOH was indispensable for the hydrolysis and oxy-Michael addition reactions; treatment with Cs_2CO_3 in aqueous THF and MeOH at room temperature gave the desired alcohol intermediate, which spontaneously underwent the oxy-Michael addition. The carboxylic acid of the product was treated with MeI and K_2CO_3 to afford methyl ester **42**. Ozonolysis of the vinyl group was followed by chemoselective reduction of the resulting aldehyde in the presence of the ketone with $LiAlH(OtBu)_3$ to



Scheme 9. Total synthesis of polygalolide A (**1**). Reagents and conditions: a) $FeCl_3$, CH_2Cl_2, RT, 30 min; b) MnO_2, CH_2Cl_2, RT, 13 h, 64% over 2 steps; c) Cs_2CO_3, THF/MeOH/water (2:1:1), 0°C, 11 h; d) MeI, K_2CO_3, DMF, 0°C, 6.6 h, 70% over 2 steps; e) O_3, CH_2Cl_2, −78°C, 15 min; then Me_2S; f) $LiAlH(OtBu)_3$, THF, −78°C, 25 min, 56% over 2 steps; g) TMSOTf, Et_3N, CH_2Cl_2, 0°C, 7.5 h; h) dimethyl acetal **43**, TMSOTf, 3 Å M.S., CH_2Cl_2, −78°C, 40 min; i) DBU, CH_2Cl_2, 0°C, 35 min, 54% over 3 steps; j) sat. aq. $NaHCO_3$, MeOH, RT, 21 h, quant. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

provide the primary alcohol, which underwent spontaneous lactonization to yield the desired tetracyclic lactone **3**.[2] Finally, according to the procedure of Hashimoto and co-workers,[2] compound **3** was transformed into polygalolide A (**1**) through Mukaiyama-aldol-type condensation with dimethyl acetal **43** and then deprotection of the acetate. The spectroscopic data of the synthesized compound were identical to those of natural polygalolide A (**1**) with the exception of the value of optical rotation.[1] The synthetic $[\alpha]_D$ value (= −491, c = 0.0226 in MeOH) was also consistent with that reported by Hashimoto and co-workers (= −499.9, c = 0.022 in MeOH).[2]

Conclusions

For the construction of the oxabicyclo[3.2.1] structure, a core skeleton of polygalolide A (**1**), we have developed an intramolecular Ferrier-type C-glycosylation. Initial model experiments of the key reaction of a glucal **14**-modified siloxyfuran as an internal nucleophile led us to find that $TiCl_4$ and $BF_3{\cdot}OEt_2$ were effective Lewis acids, thus giving a mixture of oxabicyclic products **15** and **16** in high yield but with low stereoselectivity. For the total synthesis of polygalolide A (**1**), we modified this intramolecular C-glycosylation reaction to control the configuration at the C2 position. The salient feature of this C-glycosylation reaction was the introduction of a siloxy substituent at the C3 position as a temporary auxiliary into precursor **19**, which was synthesized from D-glucal by the introduction of trimethylsilylacetylene and siloxyfuran groups. Although the optimal conditions in the model experiments did not lead to the C-glycosylation of compound **19**, further examination led us to find that the combination of TMSOTf and 2,4,6-collidine successfully afforded oxabicyclo[3.2.1]octene **18** with the correct quaternary stereogenic centers in 83% yield. The successful production of a single diastereomer indicated that the siloxy group at the C3 position played a crucial role in the stereocontrol of this reaction, as expected. Although several problems were encountered in the transformation of oxabicyclic product **18** into tetracyclic intermediate **3**, we have established a successful route as follows: The vinyl ether and acetylenic moieties in compound **18** were reduced and the oxygen functionality at the C3 position was removed by using Barton–McCombie deoxygenation to provide tricyclic spiro compound **17**. The six-membered ether was constructed by hydrolysis of the lactone moiety and spontaneous oxy-Michael addition. Ozonolysis of the vinyl group was followed by chemoselective reduction of the resulting aldehyde to give tetracyclic intermediate **3**. Finally, a phenolic moiety was introduced by a Mukaiyama aldol reaction to furnish polygalolide A (**1**). This method should be applicable to the synthesis of analogues of polygalolide and natural products that contain an oxabicyclo skeleton.

Experimental Section

For experimental procedures, please see the Supporting Information.

Acknowledgements

This work was financially supported by Grants-in-Aid for Scientific Research, a Global COE program from the Japan Society for the Promotion of Science (JSPS), a Program for Leading Graduate Schools "Integrative Graduate Education and Research in Green Natural Sciences" (MEXT), and a SUNBOR grant from the Suntory Institute for Bioorganic Research. H.Y. is grateful for a Daiko Foundation Scholarship and a Nagoya University Scholarship for outstanding graduate students. We thank Dr. K. Yoza (Bruker AXS) for performing the X-ray crystallographic analysis. We also 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 (**1**).

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[8] Because the construction of the oxabicyclo[3.2.1] skeleton involves C–C bond formation at the anomeric position by using an oxocarbenium ion that is generated from a glycal derivative, we termed it "intramolecular C-glycosylation".

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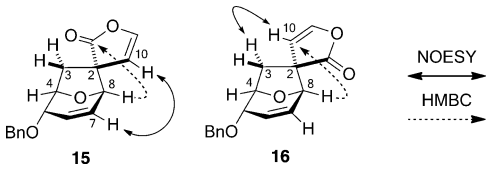
[13] The structures of compounds **15** and **16** were determined by extensive analysis of their NMR spectra. The newly formed C–C bonds were confirmed by HMBC correlation and the configurations at the C2 position of compounds **15** and **16** were determined by NOESY correlation.



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[18] Although the stereochemistry of the generated asymmetric center at the C3 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 **18**.

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[20] On the other hand, selective benzoylation at the C6 position of diol **30** was unsuccessful under the conditions used in the model experiment.

[21] CCDC 836367 (**18**) 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.

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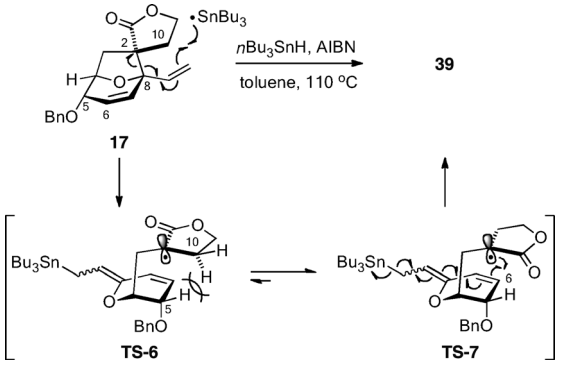
[25] The structure of compound **39** was determined by extensive NMR analysis. The newly formed C–C bond was undoubtedly determined by HMBC correlation between the H6 and C2 atoms. The configuration at the newly generated stereogenic center of the C2 position was determined by NOESY correlations.

[26] The mechanism for the formation of diene **39** is proposed as described below: In the first step, compound **17** reacts with the stannyl radical, followed by the cleavage of a C–C bond to provide an α-carbonyl radical intermediate. In the second step, the stable radical can overlap at the C6 or C8 positions with the π orbital of the diene moiety in the transition state. In this case, the radical C–C bond-forming reaction predominantly proceeds at the C6 position to give the rearranged product **39**. This stereochemical outcome might be explained by steric hindrance at two possible transition states (**TS-6** and **TS-7**). The steric repulsion between the hydrogen atom at the C5 position and the methylene group of the lactone moiety lead to transition state **TS-7**, thus yielding compound **39**.

[27] Deprotection of the benzyl group of compound **17** was problematic: Deprotection with BBr_3 gave a complex mixture of products. When compound **17** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), allylic alcohol was obtained in moderate yield, along with a considerable amount of the starting material **17**, even when an excess of the reagents was employed.



Received: March 19, 2013
Published online: May 13, 2013