OL Organic Letters

pubs.acs.org/OrgLett Letter

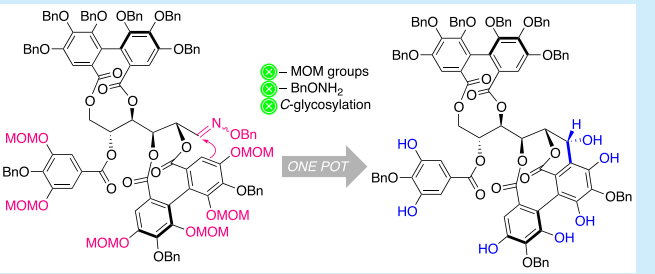
Total Synthesis of Casuarinin

Shinnosuke Wakamori,* Shintaro Matsumoto, Reina Kusuki, Kazutada Ikeuchi, and Hidetoshi Yamada*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00876 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: This study involves the total synthesis of casuarinin, a naturally occurring ellagitannin, in which an open-chain glucose is esterified with two (*S*)-hexahydroxydiphenoyl (HHDP) groups. One HHDP group incorporates a C-glycosidic bond between its benzene ring and the glucose moiety, which was constructed with complete stereoselectivity using a benzyl oxime group that opened the glucopyranose ring and acted as a scaffold for C-glycoside production. This total synthesis enables future structure−activity relationship studies of this compound.



Casuarinin [(1*R*)-**1**] is an ellagitannin originally isolated in 1981 by Okuda and co-workers from the leaves of the drooping she-oak, *Casuarina stricta*.[1] The ubiquitous availability of (1*R*)-**1** has allowed for a variety of investigations to test its biological activities. This compound is typically found to show anti-herpes virus type 2 (HSV-2) activity[2] and antioxidant activity;[3,4] it affects apoptosis and cell cycle progression in the G_0/G_1 phase in human breast cancer cells (MCF-7) and lung cancer cells (A549)[5,6] and blocks NF-κB activation of HaCaT cells.[7,8] However, the relationships between the various bioactivities reported and the structural features of (1*R*)-**1** have been poorly studied.

Casuarinin [(1*R*)-**1**] and its 1-OH epimer, stachyurin [(1*S*)-**1**],[9] consist of an open-chain form of a D-glucose unit with two (*S*)-hexahydroxydiphenoyl (HHDP) groups: one between oxygens 2 and 3 (O-2 and O-3, respectively) and the other between O-4 and O-6 of glucose (Figure 1). The difference between these two HHDP groups is that a benzene ring of the 2,3-*O*-HHDP group notably links to C-1 of the glucose moiety through a *C*-glycosidic bond, as opposed to the usual acyl linkage of the 4,6-*O*-HHDP group. In addition, the benzylic C-1 is a reactive site that allows for the formation of a carbocation, which can generate its analogues, such as oligomers and complexes with a flavan-3-ol unit.[10−12]

Okuda and co-workers proposed the configuration of C-1 to be *S* in (1*R*)-**1** and *R* in (1*S*)-**1** on the basis of the dihedral angles between H-1 and H-2 in the corresponding ^{1}H NMR spectra.[1,9] The axial chirality of the 4,6-*O*-HHDP group in (1*R*)-**1** was determined to be *S* via the release of (*S*)-**2** as a fragment from its pentadecamethylated derivative. In contrast, the (*S*)-axial chirality of another fragment **3** from the same derivative was determined, as well as structures of other ellagitannins, by comparison of the CD and optical rotatory dispersion data.[13] A 1990 study by Nishioka and co-workers contradicted the configuration at C-1 assigned by Okuda's

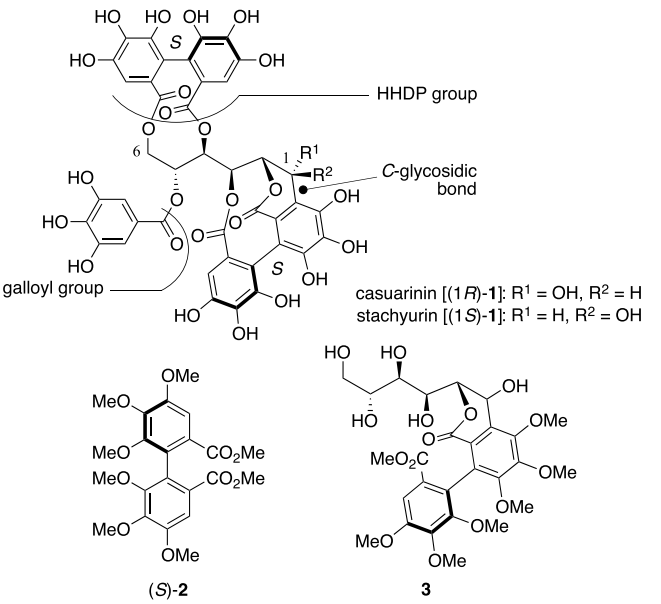


Figure 1. Structures of casuarinin [(1*R*)-**1**], stachyurin [(1*S*)-**1**], and compounds utilized to determine the axial chiralities of (1*R*)-**1** and (1*S*)-**1**.

group, and the presently accepted structures are the (1*R*)-isomer for (1*R*)-**1** and the (1*S*)-isomer for stachyurin (1*S*)-**1**.[14]

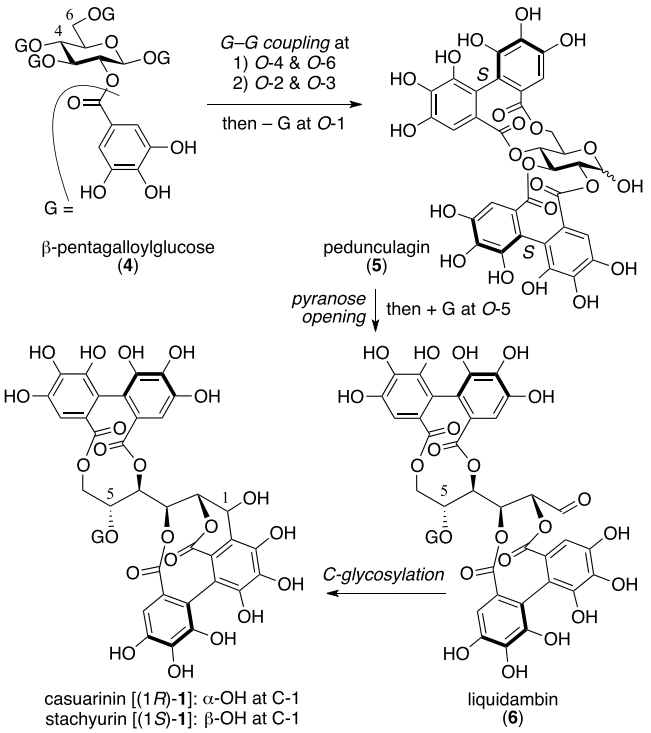
Quideau and co-workers proposed a biosynthetic pathway for the *C*-glycosidic ellagitannins and their analogues (Scheme

Received: March 9, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00876
Org. Lett. XXXX, XXX, XXX−XXX

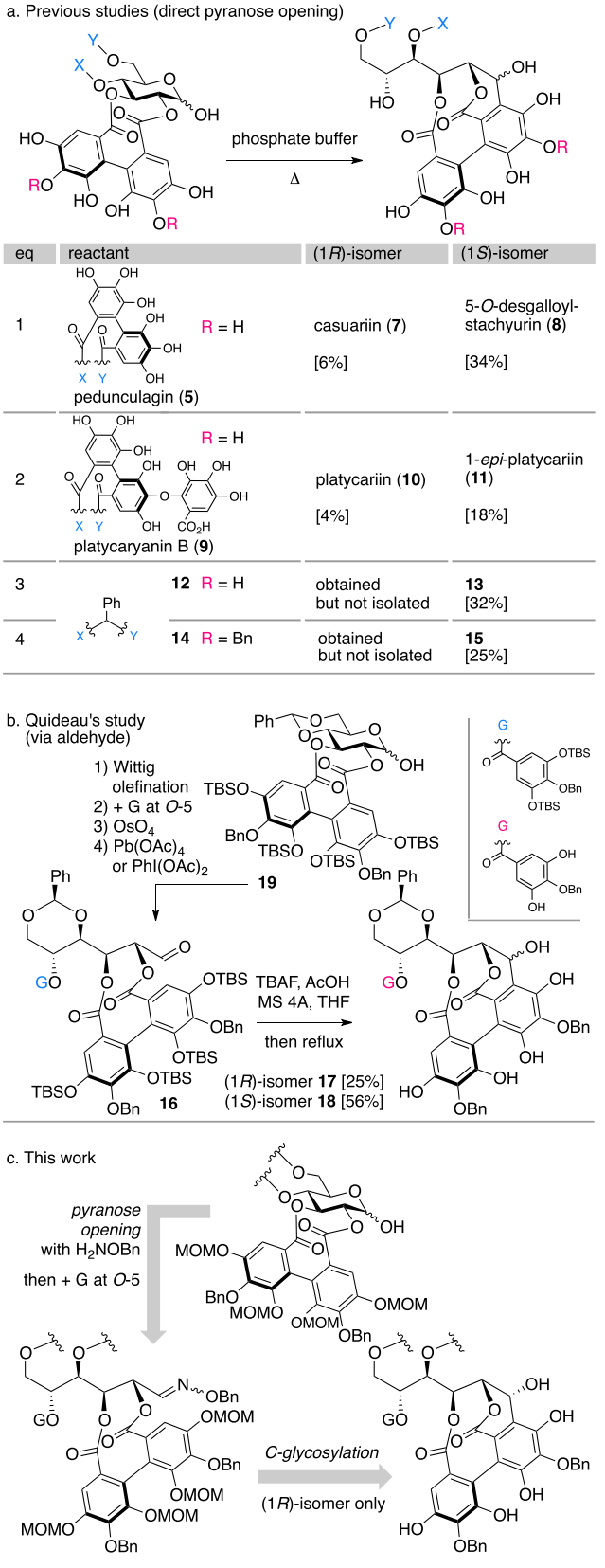
1).[15] Starting from β-pentagalloylglucose (**4**), the galloyl groups between O-4 and O-6, followed by those between O-2 and O-3, oxidatively couple to form the two HHDP groups. Successively, the galloyl group at O-1 is hydrolyzed to produce pedunculagin (**5**).[16,17] Subsequently, the pyranose ring of **5** opens and the newly formed hydroxy group at O-5 is galloylated to generate liquidambin (**6**). Then, *C*-glycosylation takes place between C-1 and the 2,3-*O*-HHDP group to provide (1*R*)-**1** and (1*S*)-**1**. As a result, it is believed that the (*S*)-axial chirality of the 2,3-*O*-HHDP group of both (1*R*)-**1** and (1*S*)-**1** preserves that of **6**.

Scheme 1. Biosynthesis of *C*-Glycosidic Ellagitannins Proposed by Quideau and Co-workers



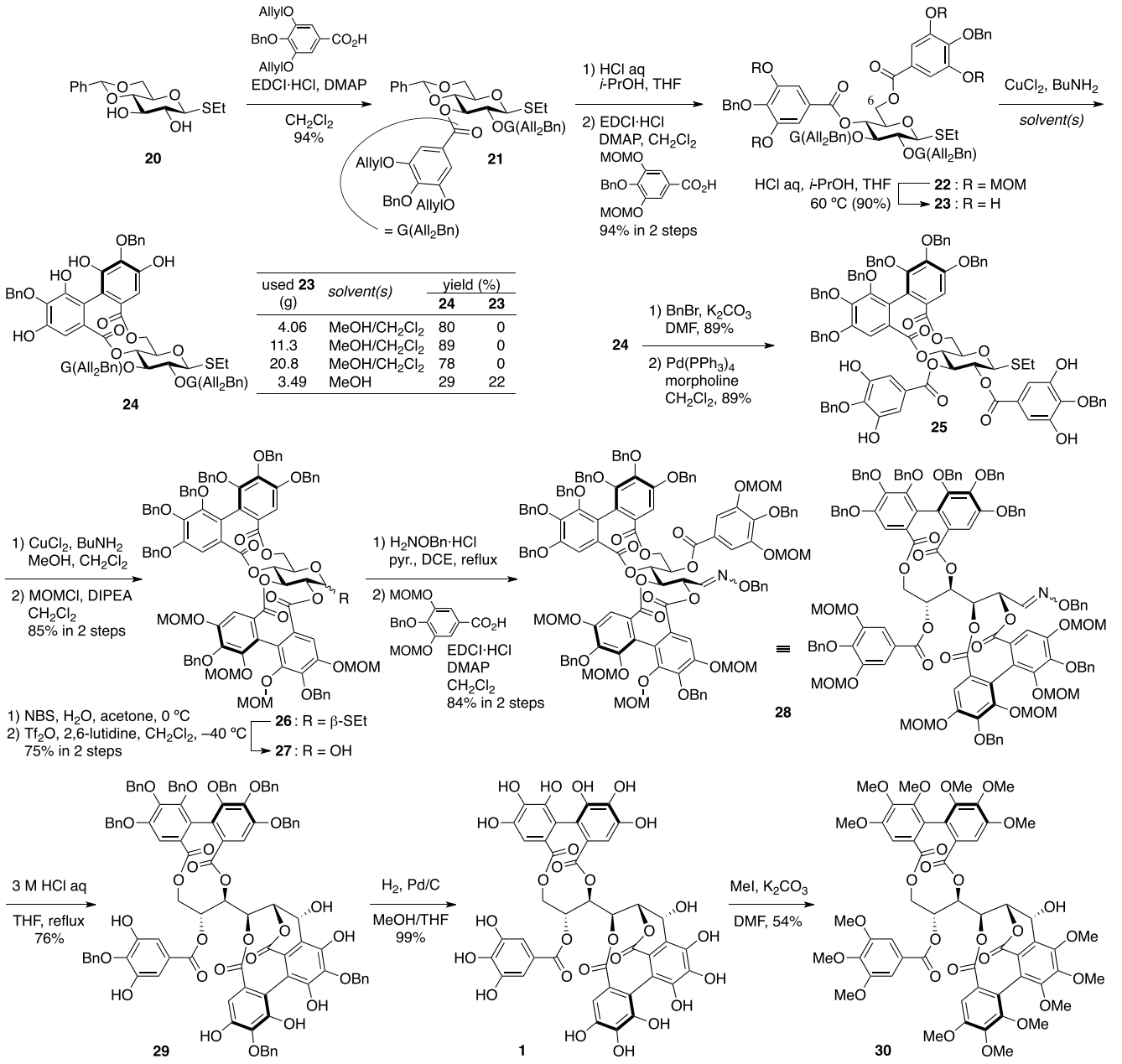
For the construction of the characteristic *C*-glycosidic bond, two kinds of approaches have been developed. Tanaka and co-workers reported the biomimetic direct transformation from pedunculagin (**5**) to casuariin (**7**) and 5-*O*-desgalloylstachyurin (**8**), where the *C*-glycosidic bond was formed by the treatment of **5** with pH 7.5 phosphate buffer (Scheme 2a, eq 1). Under the same reaction conditions, platycaryanin B (**9**) was transformed into platycariin (**10**) and its 1-epimer **11** (Scheme 2a, eq 2).[18] Deffieux, Quideau, and co-workers applied this direct transformation to chemically synthesized **12** to provide *C*-glycoside **13** (Scheme 2a, eq 3).[19] This method was also employed for the transformation of **14** to **15** (Scheme 2a, eq 4), in which the hydroxy groups of the HHDP moiety were partially protected. Although these direct transformations yielded *C*-glycosidic products, the generation of two secondary hydroxy groups might limit the site-selective introduction of the desired galloyl group at O-5. Thus, Quideau and co-workers reported that the fully protected aldehyde **16** was transformed into C-glycosides **17** and **18** in 81% total yield when using tetrabutylammonium fluoride with acetic acid in tetrahydrofuran (Scheme 2b).[20] Although their study improved the yield of *C*-glycosylation, the preparation of **16** from glucopyranose **19** required four chemical conversion steps.

Scheme 2. Previous Methods and Our Strategy for the Construction of the *C*-Glycosidic Bond



https://dx.doi.org/10.1021/acs.orglett.0c00876
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Total Synthesis of Casuarinin [(1*R*)-1]



used **23** (g)	*solvent(s)*	yield (%) **24**	**23**
4.06	MeOH/CH_2Cl_2	80	0
11.3	MeOH/CH_2Cl_2	89	0
20.8	MeOH/CH_2Cl_2	78	0
3.49	MeOH	29	22

We herein describe the total synthesis of casuarinin [(1*R*)-**1**] toward the synthesis of a series of its analogues. In this work, an oxime was successfully used for both opening the glucopyranose ring[21−23] and forming the *C*-glycosidic bond as an electrophile (Scheme 2c). This method led to the efficient synthesis of (1*R*)-**1** along with complete control of the configuration at C-1 to provide the desired (1*R*)-isomer as a single diastereomer.

The key intermediate **28** was synthesized from a known diol **20** (Scheme 3). Acylation of **20**[24] with a gallic acid derivative protected by allyl and benzyl groups[25] yielded **21**. Removal of the benzylidene acetal from **21**, followed by the introduction of two gallic acid derivatives protected with benzyl and methoxymethyl (MOM) groups,[26] furnished **22**. Removal of the MOM groups from **22** gave **23**. The oxidation of **23** with a complex derived from copper(II) chloride and butylamine[26] in a 1/1 (v/v) mixture of methanol and dichloromethane successfully formed the (*S*)-HHDP group between the O-4 and O-6 galloyl groups and provided the desired compound **24** (optimization of this solvent system is described in the next paragraph). Protection of the hydroxyl groups of **24** with benzyl groups, followed by removal of the allyl groups, produced tetraol **25**. Oxidation of **25** in the same solvent system formed the 2,3-*O*-(*S*)-HHDP group. The assignment of (*S*)-axial chirality of both the 4,6-*O*- and 2,3-*O*-HHDP groups was reliable on the basis of the results previously obtained by three different groups.[19,27−31] After MOM protection of the remaining hydroxyl groups, **26** was obtained in 85% yield. *N*-Bromosuccinimide (NBS) oxidation of the ethylthio group in **26** generated the corresponding sulfoxides as a mixture of diastereomers, which were hydrolyzed using trifluoromethanesulfonic (triflic) anhydride in the presence of 2,6-lutidine, transforming the sulfoxides to pyranose **27**.[32] Treatment of **27** with *O*-benzylhydroxylamine hydrochloride in the presence of

https://dx.doi.org/10.1021/acs.orglett.0c00876
Org. Lett. XXXX, XXX, XXX−XXX

pyridine opened the pyranose ring to furnish the corresponding benzyloxime. Subsequently, galloylation of the resulting hydroxy group at C-5 afforded the desired key intermediate **28** as a 92/8 mixture of geometrical isomers.

In the intramolecular oxidative coupling of the galloyl motifs in **23** (Scheme 3), the use of a mixture of methanol and dichloromethane (1/1, v/v) as the solvent system was essential to obtain **24** in satisfactory yield. The reaction employing the mixed solvent system provided **24** in 80% yield when using **23** on a 4.06 g scale. The yield of the reaction was retained when the amount of **23** was increased to 11.3 and 20.8 g (89% and 78% yields, respectively), demonstrating stable reproducibility. In contrast, under the standard reaction conditions using methanol as the solvent,[26] the yield of **24** was 29% and **23** was recovered in 22% yield (details in SI-09). The use of the mixed solvent system was also necessary for the oxidation of **25** due to the low solubility of **25** in methanol alone.

The low reactivity at the anomeric position of **26** was unusual (Scheme 3). Treatment of ethylthio glycoside with NBS in the presence of water commonly results in hydrolysis to provide the corresponding hemiacetal.[33−35] Treatment of **26** with NBS and water, however, gave the corresponding sulfoxides (dr = 50/50). A deactivation process, named the disarming effect, from the four electron-withdrawing acyl bonds at O-2, O-3, O-4, and O-6 may be the cause of the irregularly low reactivity.[36] The use of *m*-chloroperoxybenzoic acid also produced the corresponding sulfoxide; however, the yield was lower than that obtained when using NBS, due to overoxidation to sulfone. An attempt to oxidize the ethylthio group with a combination of *N*-iodosuccinimide and triflic acid resulted in decomposition, and no reaction occurred with silver(I) nitrate.

The final stage of the total synthesis was *C*-glycosylation. The formation of the desired intramolecular carbon−carbon bond between C-1 and the 2,3-*O*-HHDP group was investigated, and the total synthesis of casuarinin [(1*R*)-**1**] was achieved (Scheme 3). For the conversion of **28** to *C*-glucoside **29**, stirring **28** with 3 M hydrochloric acid in tetrahydrofuran under reflux was optimal to obtain **29** in 76% yield as a single diastereomer. This treatment provided a one-pot process for the removal of the MOM groups, the release of benzyloxyamine, and the Friedel−Crafts-type *C*-glycosylation. Because the generated 1-OH was at a benzylic position, its configuration was considered to easily epimerize via the formation of the corresponding carbocation under such highly acidic conditions. Thus, the stereoselectivity of the *C*-glycosylation might arise under thermodynamic control, though the reaction mechanism has not yet been elucidated in detail. Workup procedures, however, impacted the yield of **29**. Direct extraction using ethyl acetate without neutralization of the reaction mixture was important for the reproducible formation of product **29**. When saturated aqueous sodium hydrogen carbonate was used to neutralize the reaction mixture, the yield of **29** was approximately 36−50% (details in SI-17). Finally, (1*R*)-**1** was synthesized by hydrogenolytic debenzylation.

To identify the synthesized (1*R*)-**1** with the natural product, full methylation of the phenolic hydroxy groups was required. The ^{1}H and ^{13}C NMR spectra of the synthesized (1*R*)-**1** were not identical with those reported previously[37] (details in SI-01). Such a trend is frequently observed in ellagitannins because the NMR chemical shifts are sensitive to the measurement conditions and often vary depending on the temperature, concentration, and amount of water contamination. Therefore, all of the phenolic hydroxy groups of the synthesized (1*R*)-**1** were methylated to obtain pentadecamethyl ether **30** (Scheme 3), which eliminated the chemical shift variability, and gave a ^{1}H NMR spectrum that was identical to that reported for **30** derived from natural casuarinin [(1*R*)-**1**] (details in SI-02). Thus, we achieved the total synthesis of (1*R*)-**1**.

In summary, the total synthesis of casuarinin [(1*R*)-**1**] was demonstrated in this study. The novel method presented here utilizing the benzyloxime group was sufficiently effective for the construction of the *C*-glycosidic bond involving pyranose ring opening and Friedel−Crafts-type *C*-glycosylation. The complete stereoselectivity of 1-OH in the *C*-glycosylation step is another significant feature of this synthesis. The proposed synthetic route would enable the preparation of various analogues of (1*R*)-**1**, which can contribute to detailed structure−activity relationship studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00876.

Additional supporting data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Shinnosuke Wakamori − *School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo 669-1337, Japan;* orcid.org/0000-0002-0544-9486; Email: shinnosuke1010@kwansei.ac.jp

Authors

Shintaro Matsumoto − *School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo 669-1337, Japan*

Reina Kusuki − *School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo 669-1337, Japan*

Kazutada Ikeuchi − *School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo 669-1337, Japan;* orcid.org/0000-0001-5343-3502

Hidetoshi Yamada − *School of Science and Technology, Kwansei Gakuin University, Sanda, Hyogo 669-1337, Japan;* orcid.org/0000-0003-2272-319X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00876

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to Emeritus Prof. Shigeo Katsumura (Kwansei Gakuin University) for his help in writing the manuscript. The authors also express thanks to The Ministry of Education, Culture, Sports Science and Technology of Japan for supporting the program for the Strategic Research Foundation at Private Universities (S1311046) and JSPS KAKENHI (Grant JP16H01163 in Middle Molecular Strategy), which partly supported this work. The authors also thank Osaka Synthetic Chemical Laboratories, Inc., for their provision of EDCI·HCl.

DEDICATION

†Deceased on November 23, 2019. This paper is dedicated to the memory of Prof. Dr. Hidetoshi Yamada.

REFERENCES

(1) Okuda, T.; Yoshida, T.; Ashida, M. *Heterocycles* **1981**, *16*, 1681.
(2) Cheng, H.-Y.; Lin, C.-C.; Lin, T.-C. *Antiviral Res.* **2002**, *55*, 447.
(3) Chen, C.-H.; Liu, T.-Z.; Kuo, T.-C.; Lu, F.-J.; Chen, Y.-C.; Chang-Chien, Y.-W.; Lin, C.-C. *Planta Med.* **2004**, *70*, 1022.
(4) Kaneshima, T.; Myoda, T.; Nakata, M.; Fujimori, T.; Toeda, K.; Nishizawa, M. *LWT Food Sci. Technol.* **2016**, *69*, 76.
(5) Kuo, P.-L.; Hsu, Y.-L.; Lin, T.-C.; Chang, J.-K.; Lin, C.-C. *Anti-Cancer Drugs* **2005**, *16*, 409.
(6) Kuo, P.-L.; Hsu, Y.-L.; Lin, T.-C.; Lin, L.-T.; Chang, J.-K.; Lin, C.-C. *Planta Med.* **2005**, *71*, 237.
(7) Kwon, D.-J.; Bae, Y.-S.; Ju, S. M.; Goh, A. R.; Choi, S. Y.; Park, J. *Biochem. Biophys. Res. Commun.* **2011**, *409*, 780.
(8) Kwon, D.-J.; Bae, Y.-S.; Ju, S. M.; Goh, A. R.; Youn, G. S.; Choi, S. Y.; Park, J. *Biochem. Biophys. Res. Commun.* **2012**, *417*, 1254.
(9) Okuda, T.; Yoshida, T.; Ashida, M.; Kazaki, K. *Chem. Pharm. Bull.* **1982**, *30*, 766.
(10) Yoshida, T.; Ito, H.; Yoshimura, M.; Miyashita, K.; Hatano, T. *Phytochemistry* **2008**, *69*, 3070.
(11) Tanaka, T.; Ishida, N.; Ishimatsu, M.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1992**, *40*, 2092.
(12) Yoshida, T.; Nakata, F.; Hosotani, K.; Nitta, A.; Okuda, T. *Chem. Pharm. Bull.* **1992**, *40*, 1727.
(13) Yamada, H.; Wakamori, S.; Hirokane, T.; Ikeuchi, K.; Matsumoto, S. *Molecules* **2018**, *23*, 1901.
(14) Nonaka, G.-I.; Sakai, T.; Tanaka, T.; Mihashi, K.; Nishioka, I. *Chem. Pharm. Bull.* **1990**, *38*, 2151.
(15) Quideau, S.; Varadinova, T.; Karagiozova, D.; Jourdes, M.; Pardon, P.; Baudry, C.; Genova, P.; Diakov, T.; Petrova, R. *Chem. Biodiversity* **2004**, *1*, 247.
(16) Niemetz, R.; Gross, G. G. *Phytochemistry* **2003**, *62*, 301.
(17) Niemetz, R.; Schilling, G.; Gross, G. G. *Chem. Commun.* **2001**, 35.
(18) Tanaka, T.; Kirihara, S.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1993**, *41*, 1708.
(19) Malik, G.; Natangelo, A.; Charris, J.; Pouységu, L.; Manfredini, S.; Cavagnat, D.; Buffeteau, T.; Deffieux, D.; Quideau, S. *Chem. - Eur. J.* **2012**, *18*, 9063.
(20) Richieu, A.; Peixoto, P. A.; Pouységu, L.; Deffieux, D.; Quideau, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13833.
(21) Takahashi, S.; Inoue, H.; Kuzuhara, H. *J. Carbohydr. Chem.* **1995**, *14*, 273.
(22) Blasberger, D.; Green, D.; Carmely, S.; Spector, I.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 459.
(23) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.
(24) Bochkov, A. F.; Dzhein, A. Ch. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1968**, *17*, 168.
(25) Yamaguchi, S.; Ashikaga, Y.; Nishii, K.; Yamada, H. *Org. Lett.* **2012**, *14*, 5928.
(26) Yamada, H.; Nagao, K.; Dokei, K.; Kasai, Y.; Michihata, N. *J. Am. Chem. Soc.* **2008**, *130*, 7566.
(27) Michihata, N.; Kaneko, Y.; Kasai, Y.; Tanigawa, K.; Hirokane, T.; Higasa, S.; Yamada, H. *J. Org. Chem.* **2013**, *78*, 4319.
(28) Hirokane, T.; Ikeuchi, K.; Yamada, H. *Eur. J. Org. Chem.* **2015**, *2015*, 7352.
(29) Takeuchi, H.; Mishiro, K.; Ueda, Y.; Fujimori, Y.; Furuta, T.; Kawabata, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 6177.
(30) Takeuchi, H.; Ueda, Y.; Furuta, T.; Kawabata, T. *Chem. Pharm. Bull.* **2017**, *65*, 25.
(31) Ashibe, S.; Ikeuchi, K.; Kume, Y.; Wakamori, S.; Ueno, Y.; Iwashita, T.; Yamada, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 15402.
(32) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
(33) Bauer, J.; Rademann, J. *J. Am. Chem. Soc.* **2005**, *127*, 7296.
(34) Paul, S.; Jayaraman, N. *Carbohydr. Res.* **2008**, *343*, 453.
(35) Motawia, M. S.; Marcussen, J.; Møller, B. L. *J. Carbohydr. Chem.* **1995**, *14*, 1279.
(36) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.
(37) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, *22*, 1765.

https://dx.doi.org/10.1021/acs.orglett.0c00876
Org. Lett. XXXX, XXX, XXX−XXX