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COMMUNICATION

Synthesis of Diaryl Ether Components of Ellagitannins Using Ortho-quinone with Consonant Mesomeric Effects

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Methods for synthesizing C–O digallate structures, the basic unit of diaryl ether components of natural ellagitannins, are described. In the designed building block derived from gallic acid, consonantly overlapped mesomeric effects enhanced its electrophilicity. This building block demonstrated substantial reactivity to improve synthesis of dehydrodigalloyl, tergalloyl, and valloneoyl groups.

Ellagitannins are a class of natural polyphenols, whose basic structure includes glucose with esterified galloyl and hexahydroxydiphenoyl (HHDP) groups whose contains C–C bond by coupling between galloyl groups (Figure 1).[1] Since glucose contains multiple hydroxy groups, the flexibility of the positions and numbers of the esterified galloyl and HHDP groups impart significant structural diversity.[2] Moreover, the formation of diaryl ether components enhances this diversity because formation of these components oligomerizes monomers.[3] Each diaryl ether component contains a C–O digallate structure with two galloyl groups connected via a C–O bond, the dehydrodigalloyl (DHDG) group being a representative example.[4] Other diaryl ether components, such as tergalloyl and valoneoyl groups,[4] also contain the C–O digallate structure. Oligomeric ellagitannins and their monomers exhibit a variety of biological activities.[5] However, the unavailability of systematically modified analogues from nature has impeded the understanding of their structure-activity relationships. A promising strategy to solve the problem is the customizable syntheses of oligomeric ellagitannins.[3,6]

To date, three methods have been reported for the synthesis of the most basic diaryl ether component, the DHDG group.[7–9] However, only one method[9] enables the syntheses of both tergalloyl and valoneoyl groups. In this method[9], a derivative of gallic acid **1** (Scheme 1) is transformed to the corresponding brominated aldehyde **2**, and then oxidation of the phenolic moiety provides the ortho-(*o*-) quinone monoketal **3**. The *oxa*-Michael addition of a phenolate ion to **3** and simultaneous elimination of bromide forms a C–O bond to afford **4**. Subsequently, **4** requires reductive aromatization to obtain **5** and oxidation of the aldehyde produces the C–O digallate **6**. In this route, relying on the use of bypasses the aldehyde is advantageous for discrimination of the carboxylate moieties of the diaryl ether components. Since the carboxylate moieties are unequally modified in most ellagitannins, as in both the natural products shown in Figure 1,[10] an aldehyde is convenient for constructing unequally esterified carboxylates. Another reason for installing aldehyde in **3** is the unsuccessful *oxa*-Michael addition to the corresponding ester **7**, making the aldehyde indispensable for the successful addition of phenolate. Consequently, the synthetic route demands oxidation-state adjustments of the carboxyl group, the innate

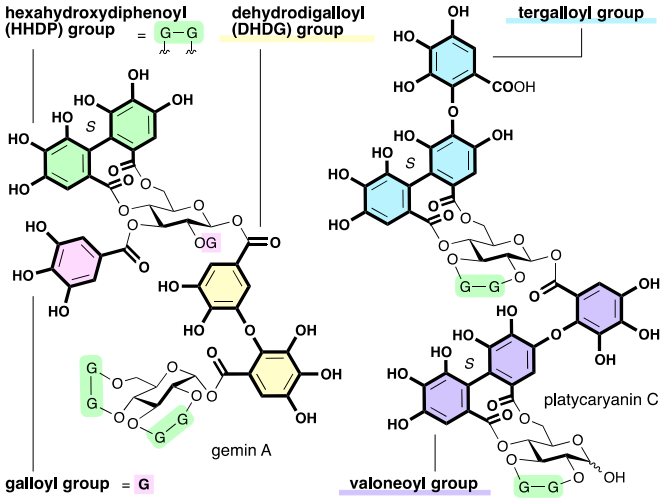

Figure 1. Examples of dimeric natural ellagitannins and diaryl ether-components of ellagitannins

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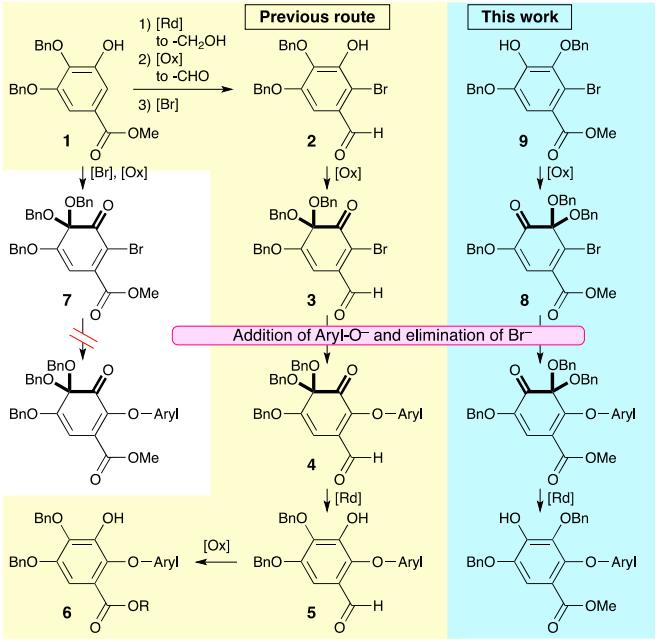
state of galloyl group, aldehyde must be oxidized to a carboxyl group, the increased reactivity of **8** was attributed to the enhanced electrophilicity induced by the mesomeric effects arising from the ketone and ester groups.

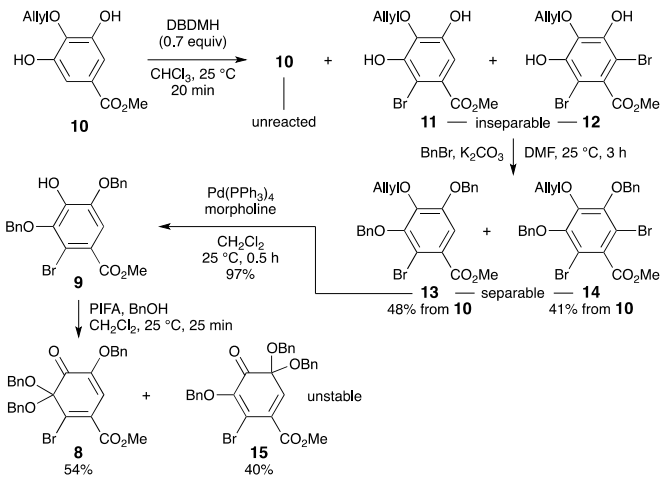


Scheme 1. Comparison of the previous (yellow background) and improved (blue background) methods for synthesizing the C–O digallate structure. [Br]: bromination, [Ox]: oxidation, [Rd]: reduction.

which increases the number of required steps. Herein, we describe a novel building block **8** (Scheme 1, blue background), to remove extra redox steps in the currently used method.

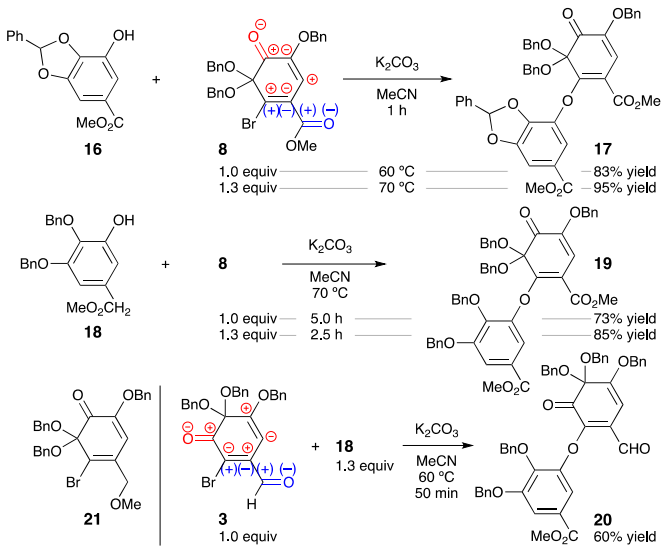
The brominated *o*-quinone monoketal **8** was prepared in four steps from **10**[11] (Scheme 2). Bromination of **10** using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)[12] yielded a mixture of unreacted **10**, monobrominated **11**, and dibrominated **12** (ESI-3). After separation of **10**, benzylation of a mixture of **11** and **12** furnished **13** and **14**, and chromatographic separation provided pure **13** in 48% yield from **10** (ESI-4). Successive removal of the allyl group[13] from **13** generated **9** (ESI-5) and oxidation of the corresponding phenol moiety using phenyliodine bis(trifluoroacetate) (PIFA)[14] in the presence of benzyl alcohol afforded **8** in 54% yield and its regioisomer **15** (40% yield; ESI-6). Isolated **8** was stable in air at 25 °C, while **15** decomposed at the same temperatures.

Consecutive addition of phenolate to **8** and release of bromide via elimination afforded good to excellent yields (Scheme 3). Starting with phenol **16**,[15] reaction of equimolar amounts of **8** in the presence of potassium carbonate in acetonitrile provided **17** in 83% yield (ESI-7), while the use of 1.3 equiv of **8** and the heating to 70 °C improved the yield to 95% (ESI-8). From phenol **18**,[16] in which the hydroxy group was more sterically hindered than in **16**, **19** was obtained in 73% yield with 1.0 equiv of **8** (ESI-9). When 1.3 equiv of **8** was applied, the yield was improved and the reaction time was halved (ESI-10). Comparison of the newly obtained results to those of the previous method utilizing **3**[9] indicated the enhanced reactivity of **8**. In contrast, replacement of the keto-"ester" **8** with keto-"ether" **21** (ESI-11–15) did not produce the corresponding C–O connected compound (ESI-16). Therefore,



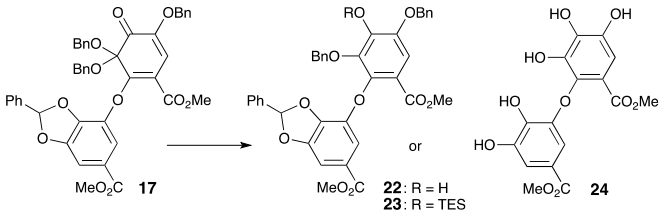
Scheme 2. Preparation of **8**, an improved building block for synthesizing the C–O digallate structure

Reductive aromatization of **17** can be achieved using several methods. Tetrakis(triphenylphosphine)palladium(0)-catalysed reductive aromatization, using triethylsilane as a reductant, is a unique method for preparing the aldehyde type C–O digallate like **20**.[9] Application of this method to **17** afforded the desired compound **22** and the corresponding triethylsilyl ether **23** (Table 1, entry 1; ESI-17), with unreproducible yields of the two compounds. Regardless, the addition of tetrabutylammonium fluoride (TBAF) after completion of the reductive aromatization provided only **22** steadily (Table 1, entry 2; ESI-18). In contrast, the ketone in **17** was selectively reduced by sodium borohydride in methanol (Table 1, entry 3; ESI-19). Alternatively, hydrogenolysis of **17** using a Pearlman catalyst[18] can be used for reductive aromatization to furnish the pentaphenol **24** in excellent yields (Table 1, entry 4; ESI-20). The use of hydrogenolytic benzyl group removal accompanied by reductive aromatization of an aldehyde-equipped *o*-quinone monoketal moiety (**20** for example) is unrealistic in the previous



Scheme 3. The addition/elimination reactions of phenolate ions to **8** and consonant mesomeric effects in **8**. The products **17** and **19** are equipped with the skeleton of the DHDG group.

Table 1. Reductive aromatization of the *o*-quinone monoketal moiety.

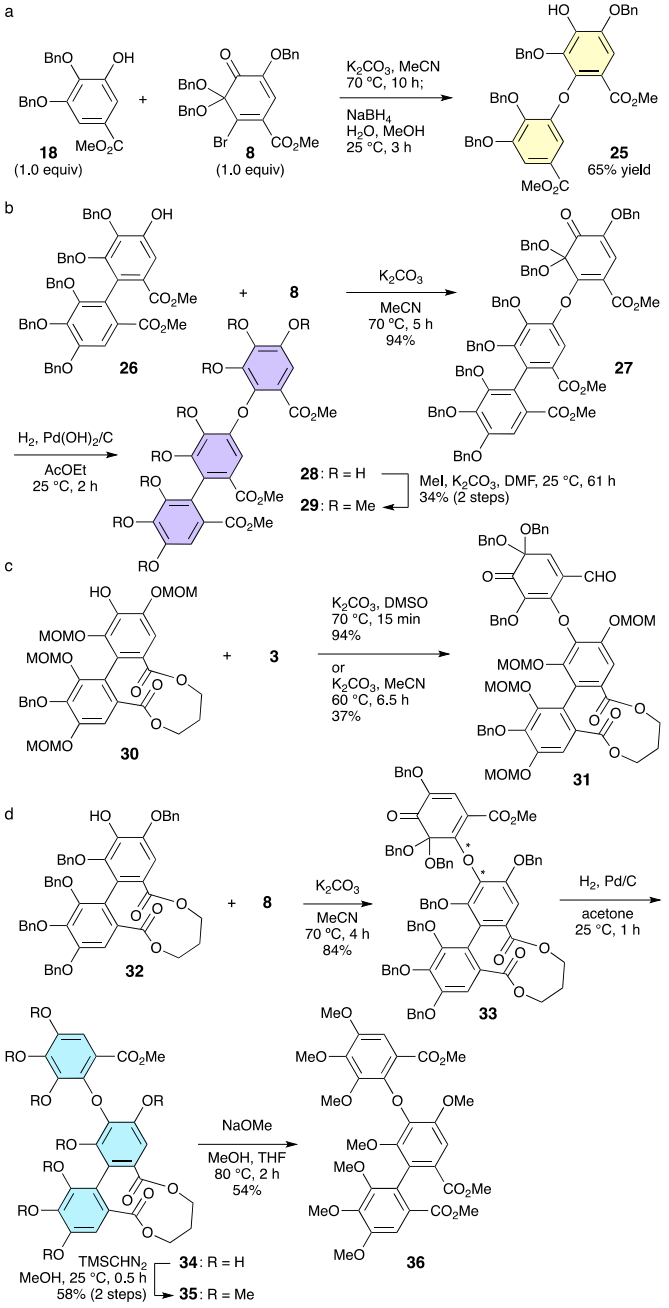


Entry	Reagents	Solvents	Products	Yield (%)
1	$Pd(PPh_3)_4$, Et_3SiH	DMF	**22** **23**	37–83 17–60
2	i) $Pd(PPh_3)_4$, Et_3SiH ii) TBAF (one pot)	DMF THF, DMF	**22**	80
3	i) $NaBH_4$ ii) HCl aq (one pot)	MeOH, Et_2O IPA	**22**	93
4	H_2, $Pd(OH)_2/C$	acetone	**24**	99

method. This is because phenolic hydroxy groups would be generated by the hydrogenolysis, which aldehyde oxidation to the corresponding carboxylic acid is difficult with the hydroxyl groups intact.

The one pot transformation of *oxa*-Michael addition/elimination followed by reductive aromatization was possible without work up process (Scheme 4, a). Specifically, after addition/elimination using **18** and **8**, the directly addition of sodium borohydride to the reaction mixture reduced the quinone monoketal. Subsequent workup with 1 M hydrochloric acid and purification afforded **25** in 65% yield (ESI-21).

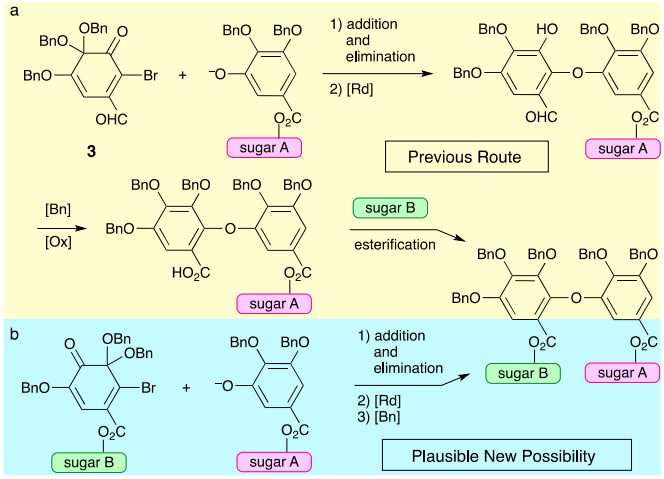
The newly developed method for constructing the C–O digallate structure was applied to valoneoyl and tergalloyl group syntheses. Thus, the use of phenol **26**[9] (Scheme 4, b) as a nucleophile for **8** afforded C–O connected **27** (ESI-22). The structure of **27** was confirmed by transformation to the known **29**[19] via reductive aromatization accompanied by debenzylation and full methylation of the phenolic hydroxy groups (ESI-23). The ^{1}H NMR data of **29** were identical to those derived from the natural product containing the valoneoyl group.[19] Although the previous method allowed for the synthesis of the tergalloyl group using **30** and **3** (Scheme 4, c),[9] two treatments were required to compensate for the low reactivity of **3** and construct the sterically hindered tetra *o*-substituted diaryl ether. The first was the adoption of the methoxymethyl (MOM) as protecting groups of the nucleophilic phenol **30** to reduce steric hindrance around the reaction point. The other was the use of DMSO as the reaction solvent. Acetonitrile is a standard solvent when synthesizing DHDG and valoneoyl groups from **3** thanks to its higher volatility; however, the reaction in acetonitrile decreases the yield of **31** drastically. In contrast, **8** allowed nucleophilic attack of **32** (Scheme 4, d; ESI-24), where the benzyl groups protected the phenols in acetonitrile to furnish C–O connected **33** in 84% yield (ESI-25). The use of trimethylsilyldiazomethane for the methylation of **34** prevented Similes rearrangement, transforming tetra *o*-substituted C–O digallate compound to the corresponding less sterically hindered tri *o*-substituted analogue, as reported by Feldman et al (ESI-26).



Scheme 4. One pot synthesis of the DHDG skeleton and improved synthesis of the valoneoyl and tergalloyl groups.

The improved method for preparing the C–O digallate structure using building block **8** may provide novel routes for ellagitannin syntheses containing diaryl ether components. The previous method requires aldehyde in building block **3** (Scheme 5, a), limiting the pathway to esterification of 'sugar B' after C–O digallate structure formation containing 'sugar A'. The improved method may enable the *oxa*-addition of a phenolate containing 'sugar A' (Scheme 5, b) to a brominated *o*-quinone monoketal derivative furnished with 'sugar B' as a converged synthetic route.

In conclusion, the newly prepared *o*-quinone monoketal **8** was sufficiently stable to be isolated and exhibited high reactivity in the synthesis of the diaryl ether components of



Scheme 5. Possibility convergent synthesis of ellagitannins containing diaryl ether components. [Bn]: benzylation.

ellagitannins. The novel method enabled construction of DHDG, valoneoyl, and tergalloyl skeletons. The high reactivity, i.e. enhanced electrophilicity, of **8** was imparted by the consonantly overlapped mesomeric effects. The advantages of using **8** in the synthesis of the diaryl ether components are: (1) rationalized preparation of the *o*-quinone monoketal key-building block by elimination of the repeated redox steps required in the previously developed method; (2) increased method tolerance for the reductive aromatization of the *o*-quinone monoketal to form the C–O digallate structure; and (3) plausible adoption of a convergent route for ellagitannin synthesis composed of the diaryl ether components. These advantages shorten the synthetic route and expand the number of synthesizable ellagitannins.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) S. Quideau and K. S. Feldman, *Chem. Rev*., 1996, **96**, 475. (b) S. Quideau, D. Deffieux, C. Douat-Casassus and L. Pouységu, *Angew. Chem. Int. Ed*., 2011, **50**, 586. (c) T. Okuda and H. Ito, *Molecules*, 2011, **16**, 2191.

2 (a) O. T. Schmidt and W. Mayer, *Angew. Chem*., 1956, **68**, 103. (b) E. Haslam, in *Plant Polyphenols*, ed. R. W. Hemingway and P. E. Laks, Springer US, New York, 1992, pp. 169–194. (c) E. Haslam, in *Plant Polyphenols 2*, ed. G. G. Gross, R. W. Hemingway and T. Yoshida, Springer US, New York, 1999, pp. 15–40.

3 L. Pouységu, D. Deffieux, G. Malik, A. Natangelo and S. Quideau, *Nat. Prod. Rep*., 2011, **28**, 853.

4 S. Quideau, *Chemistry and biology of ellagitannins—an underestimated class of bioactive plant polyphenols*, World Scientific, Singapore, 2009.

5 (a) K. Fukuchi, H. Sakagami, T. Okuda, T. Hatano, S.-I. Tanuma, K. Kitajima, Y. Inoue, S. Inoue, S. Ichikawa, M. Nonoyama and K. Konno, *Antiviral Res*., 1989, **11**, 285. (b) K.-I. Miyamoto, N. Kishi, R. Koshiura, T. Yoshida, T. Hatano and T. Okuda, *Chem. Pharm. Bull*., 1987, **39**, 814. (c) K.-I. Miyamoto, M. Nomura, M. Sasakura, E. Matsui, R. Koshiura, T. Murayama, T. Furukawa, T. Hatano, T. Yoshida and T. Okuda, *Jpn. J. Cancer Res*., 1993, **84**, 99. (d) T. Yoshida, T. Chou, A. Nitta, K.-I. Miyamoto, R. Koshiura and T. Okuda, *Chem. Pharm. Bull*., 1990, **38**, 1211. (e) T. Okuda, T. Yoshida and T. Hatano, in *Plant Polyphenols*, ed. R. W. Hemingway and P. E. Laks, Springer US, New York, 1992, pp. 539–569.

6 (a) K. S. Feldman, K. Sahasrabudhe, S. Quideau, K. L. Hunter and M. D. Lawlor, in *Plant Polyphenols 2*, ed. G. G. Gross, R. W. Hemingway and T. Yoshida, Springer US, New York, 1999, pp. 101–125. (b) K. S. Feldman, *Phytochemistry*, 2005, **66**, 1984. (c) H. Yamada, T. Hirokane, K. Ikeuchi and S. Wakamori, *Nat. Prod. Commun*., 2017, **12**, 1351.

7 K. S. Feldman, S. Quideau and H. M. Appel, *J. Org. Chem*., 1996, **61**, 6656.

8 K. Shioe, S. Ishikura, Y. Horino and H. Abe, *Chem. Pharm. Bull*., 2013, **61**, 1308.

9 T. Hirokane, Y. Hirata, T. Ishimoto, K. Nishii and H. Yamada, *Nat. Commun*., 2014, **5**, 3478.

10 (a) T. Yoshida and T. Okuda, *J. Chem. Soc. Perkin Trans. 1*, 1985, 315. (b) T. Tanaka, S. Kirihara, G.-I. Nonaka and I. Nishioka, *Chem. Pharm. Bull*., 1993, **41**, 1708.

11 A. W. Freeman, L. A. J. Chrisstoffels and J. M. J. Fréchet, *J. Org. Chem*., 2000, **65**, 7612.

12 (a) R. Aggarwal, R. G. F. Giles, I. R. Green, F. J. Oosthuizen and C. P. Taylor, *Org. Biomol. Chem*. 2005, **3**, 263. (b) A. Alam, Y. Takaguchi, H. Ito, T. Yoshida and S. Tsuboi, *Tetrahedron*, 2005, **61**, 1909.

13 E. Bardaji, J. L. Torres, N. Xaus, P. Clapés, X. Jorba, B. G. de la Torre and G. Valencia, *Synthesis*, 1990, 531.

14 (a) S. Quideau, M. A. Looney, L. Pouységu, S. Ham and D. M. Birney, *Tetrahedron Lett*., 1999, **40**, 615. (b) Z. Gu and A. Zakarian, *Org. Lett*., 2011, **13**, 1080.

15 L. Domon and D. Uguen, *Tetrahedron Lett*., 2000, **41**, 5501.

16 (a) N. Michihata, Y. Kaneko, Y. Kasai, K. Tanigawa, T. Hirokane, S. Higasa and H. Yamada, *J. Org. Chem*., 2013, **78**, 4319. (b) A. J. Pearson and P. R. Bruhn, *J. Org. Chem*., 1991, **56**, 7092.

17 (a) M. G. Dolson, D. K. Jackson, J. S. Swenton, *J. Chem. Soc. Chem. Comm*., 1979, 327. (b) K. C. Mascall and P. A. Jacobi, *Tetrahedron Lett*., 2012, **53**, 1620.

18 W. M. Pearlman, *Tetrahedron Lett*., 1967, **8**, 1663.

19 K. Ishimaru, M. Ishimatsu, G.-I. Nonaka, K. Mihashi, Y. Iwase and I. Nishioka, *Chem. Pharm. Bull*., 1988, **36**, 3319.

20 T. Tanaka, Y. Orii, G.-I. Nonaka, I. Nishioka and I. Kouno, *Phytochemistry*, 1996, **43**, 1345.a