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Synthesis of novel mucic acid 1,4-lactone methyl ester 3-*O*-ferulate related to an extractive component isolated from the peels of *Citrus sudachi*

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ABSTRACT

Synthesis of a new type of mucic acid 1,4-lactone methyl ester 3-*O*-ferulate related to an extractive component isolated from *Citrus sudachi*, and its diastereomer has been achieved by employing stereodivergent dihydroxylation as a key step. The structures of the final products are fully characterized by spectroscopic methods and compared with that of the natural product.

Citrus sudachi Hort. ex Shirai (Rutaceae), called sudachi, is an evergreen tree grown traditionally in the Tokushima prefecture of Japan. In the course of investigating constituents contained in the fruits of *Citrus sudachi*, a variety of flavonoids[1a,b] and limonoids,[1c] such as sudachitin and sudachinoid A, have been isolated (Fig. 1).

Mucic acid 1,4-lactone methyl ester 3-*O*-ferulate **1** has been reported as an unexplored extractive component from the peels of sudachi, whose planar structure with its relative stereochemistry has been determined as shown in Figure 1.[2] The polyoxygenated structure of this natural product, which may possess the real and potential biological properties such as antioxidant and/or antimicrobial effect, has attracted our intense interest from biological and synthetic viewpoints. As part of our continuing investigations in the natural product synthesis based on the chiral pool strategies,[3] we envisioned this molecule as an architecturally sophisticated target for total synthesis. In the present Letter, we report the first total synthesis of **1**, which has made a remarkable finding that the reported structure of this natural product is incorrect.

The synthesis started with the preparation of *C*2 symmetrical amide **2** from L-(+)-tartaric acid according to the literature (Scheme 1).[4] Ring opening alkylation of **2** with allylmagnesium bromide under Barbier conditions afforded the hemiaminal intermediate in an 86% yield.[3c] Reduction of this intermediate with $NaBH_4$ and the following benzoylation provided **3** in a 90% yield over the two steps. This product was subjected to reaction sequences involving OsO_4 dihydroxylation, oxidative cleavage with $NaIO_4$, and oxidative esterification with bromine in aqueous methanol,[5] giving rise to methyl ester **4** in an 89% yield (for 3 steps). Methanolysis of **4** and subsequent mesylation led to C–C double bond formation to afford α,β-unsaturated ester **5** with excellent *E*-selectivity (*E*/*Z* >95/5). The following OsO_4 dihydroxylation proceeded diastereoselectively to furnish **6** as an inseparable mixture of **6a** and **6b** (**6a**/**6b** = 10/1) in a combined yield of 99%.[6,7] Indeed, **6** was readily cyclized upon treatment with pyridinium *p*-toluenesulfonate to form γ-lactone, providing an inseparable 10/1 mixture of **7a** and **7b** through exchange of the protecting groups from Bn to TBS function due to the introduction of a ferulic acid part (67% yield for 4 steps).

Condensation of **7** with TBS-protected ferulic acid **8**[8] in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) gave a diastereomeric mixture, which could be separated by silica gel column chromatography providing **9** as a single isomer. In the next step, exposure of **9** to acidic methanol solution (TsOH or PPTS in MeOH) resulted unexpectedly in the elimination of two TBS groups and concomitant methanolysis to the ring opened product **10** (58% yield) with unidentified side products. Instead, we achieved the deprotection of **9** with $BF_3{\cdot}OEt_2$,[9] producing the target compound **1** (77% yield).[10]

Remarkably, we observed inconstant specific rotations for measurement on the synthetic sample of **1** in MeOH, which could be understood in terms of gradual decomposition to **10**.[11,12] Moreover, significant difference in the ^1H NMR chemical shifts was noticed between the synthetic and original samples; $\Delta\delta = \delta_{synthetic} - \delta_{original} = -0.17$ ppm for H2, $\Delta\delta = -0.13$ ppm for H3 and

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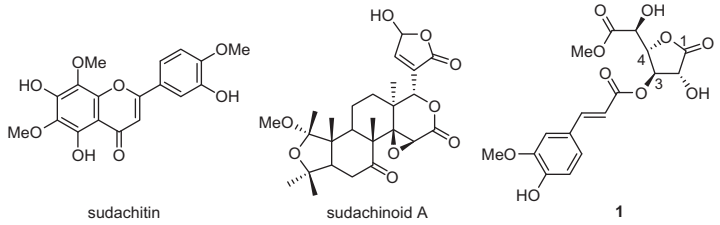
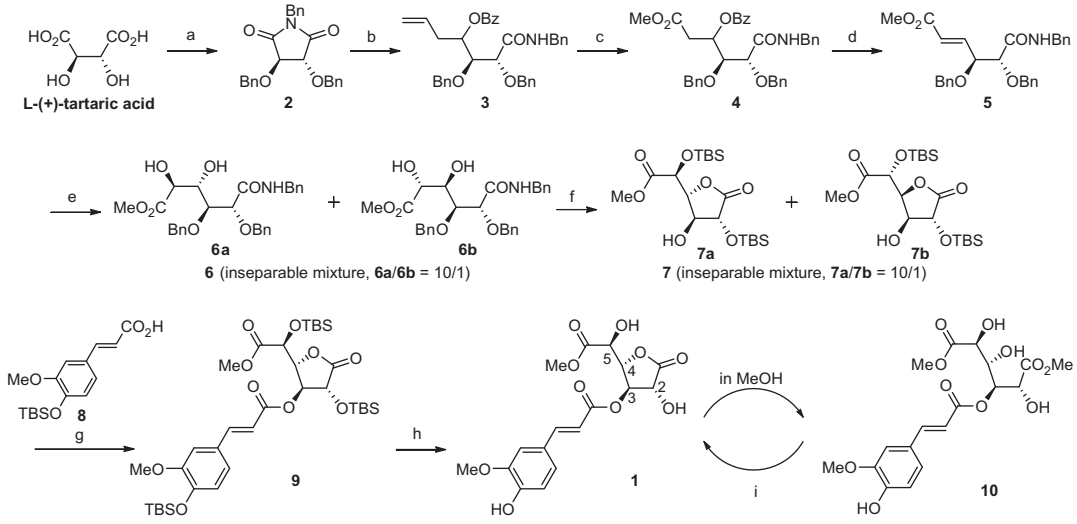


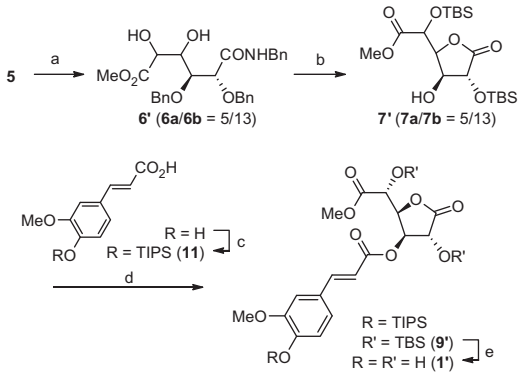
Figure 1. Structures of compounds isolated from *Citrus sudachi*.



Scheme 1. Reagents and conditions: (a) (i) see Ref. 4; (ii) BnBr, Ag_2O, EtOAc; 76%; (b) (i) allyl bromide, Mg, THF, −40–0 °C; 86%; (ii) $NaBH_4$, MeOH; (iii) BzCl, Et_3N, DMAP, CH_2Cl_2; 90% (2 steps); (c) (i) OsO_4, NMO, acetone/H_2O = 2/1; (ii) $NaIO_4$, THF/H_2O = 4/1, 0 °C–rt; (iii) Br_2, MeOH/H_2O = 9/1; 89% (3 steps); (d) (i) K_2CO_3, MeOH, −15 °C; (ii) MsCl, Et_3N, DMAP, $(CH_2Cl)_2$, 0–70 °C; 58% (2 steps); (e) OsO_4, NMO, acetone/H_2O = 2/1; 99%; (f) (i) PPTS, toluene, 80 °C; (ii) TBSCl, imidazole, DMF; 86% (2 steps); (iii) H_2, Pd/C, EtOH; (iv) TBSCl, imidazole, DMF; 78% (2 steps); (g) **8**, EDCI, DMAP, CH_2Cl_2, 0 °C; 72%; (h) $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C; 77% (i) PPTS, 1,4-dioxane, 50 °C; 92%, see Ref. 12.

$\Delta\delta$ = −0.38 ppm for H4.[13] We assume that this clear mismatch in the resonance values would originate from the different stereochemistry.

Thus, we next turned to synthesize its diastereomeric isomer **1′** that would be readily prepared from **6b** by following the above reaction sequences (Scheme 2). In the presence of AD-mix-α (0.2 mol %) and additional $(DHQ)_2PHAL$ (10 mol %), **5** underwent the dihydroxylation with reverse stereoselectivity to provide **6′** as a 5/13 mixture of **6a** and **6b**.[14] Subsequent cyclization of the γ-lactone ring, and exchange of the protecting groups afforded **7′** as a 5/13 mixture of **7a** and **7b** (17% overall yield from **5**). Condensation of **7′** with TIPS-protected ferulic acid **11** provided required diastereomerically pure **9′** in a 35% yield after the chromatographic separation. Finally, deprotection of the silyl groups accomplished the synthesis of **1′** in a 75% yield, however, its ^{1}H NMR chemical shifts proved to be inconsistent again with the reported data.[15]



Scheme 2. Reagents and conditions: (a) AD-mix-α, $(DHQ)_2PHAL$, $MeSO_2NH_2$, *t*-BuOH/H_2O = 1/1; (b) (i) PPTS, toluene, 100 °C; (ii) TBSCl, imidazole, DMF; 29% (3 steps); (iii) H_2, Pd/C, EtOH; (iv) TBSCl, imidazole, DMF; 58% (2 steps); (c) (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (ii) K_2CO_3, THF/H_2O = 1/1; 84% (2 steps); (d) **11**, EDCI, DMAP, CH_2Cl_2, 0 °C; 35%; (e) $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C; 75%.

In summary, we have achieved the first synthesis of a new type of mucic acid 1,4-lactone methyl ester 3-*O*-ferulate **1** and its diastereomer **1′** from commercially available L-(+)-tartaric acid. Comparison of the characterization data for **1** with those reported in the literature has given an indication of the clear inconsistency in the structural assignment, leading to a conclusion that the reported structure of this natural product should be incorrect and the revised form will be described in the near future.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra for synthetic mucic acid 1,4-lactone 6-methyl ester 3-*O*-ferulate and its diastereomer in CD_3OD) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.066.

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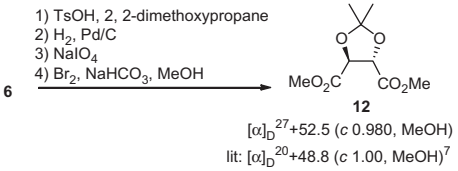
6. The absolute stereochemistry of **6** was determined as follows. After protecting the diol of **6** as an acetonide, α,β-dihydroxyamide was converted to methyl ester **12** via oxidative C–C bond cleavage. Comparison of specific rotation of **12** with the literature data indicated that major isomer of **12** should be dimethyl (+)-2,3-*O*-isopropylidene-D-tartarate. Further analysis on the basis of the spectroscopic data led to a conclusion that the major isomer of **6** should have a 2*S*,3*S* configuration.



$[\alpha]_D^{27}$+52.5 (*c* 0.980, MeOH)
lit: $[\alpha]_D^{20}$+48.8 (*c* 1.00, MeOH)[7]

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10. Characterization data for **1**: R_f = 0.57 (silica gel, hexane/EtOAc = 1/6); $[\alpha]_D^{27}$ +7.87 (*c* 1.22, acetone); IR (KBr) 3422(O–H), 1798 (C=O), 1749 (C=O), 1631 (C=C), 1592 (C=C), 1518 (C=C), 1269 (C–O), 1150 (C–O), 1021 (C–O), 821 (C=C) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.71 (d, *J* = 15.9 Hz, 1H, CH=C*H*), 7.21 (d, *J* = 1.8 Hz, 1H, Ar*H*), 7.10 (dd, *J* = 1.8, 8.1 Hz, 1H, ArH), 6.82 (d, *J* = 8.1 Hz, 1H, Ar*H*), 6.43 (d, *J* = 15.9 Hz, 1H, CH=C*H*), 5.63 (dd, *J* = 6.9, 7.5 Hz, 1H, C*H*), 4.76 (dd, *J* = 2.1, 6.9 Hz, 1H, C*H*), 4.76 (d, *J* = 7.5 Hz, 1H, C*H*), 4.55 (d, *J* = 2.1 Hz, 1H, C*H*), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 174.6 (*C*=O), 173.0 (C=O), 168.4 (*C*=O), 151.2 (*C*), 149.6 (*C*), 148.6 (CH=CH), 127.6 (*C*), 124.6 (*C*H=CH), 116.7 (*C*), 114.2 (*C*), 112.0 (*C*), 81.4 (*C*H), 76.4 (*C*H), 73.4 (*C*H), 70.5 (*C*H), 56.5 (O*C*H_3), 53.0 (O*C*H_3). Anal. calcd for $C_{17}H_{18}O_{10}$: C, 53.41; H, 4.75. Found C, 53.11; H, 5.10.
11. Similar decomposition has been reported for a mucic acid gallate, see: Zhang, Y.-J.; Tanaka, T.; Yang, C.-R.; Kouno, I. *Chem. Pharm. Bull.* **2001**, *49*, 537.
12. We observed that **10** could readily regenerate **1** upon heating with PPTS in 1,4-dioxane.
13. Analogous coupling pattern and coupling constant were observed for these H2–H4 protons.
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15. Characterization data for **1′**: R_f = 0.57 (silica gel, hexane/EtOAc = 1/6); $[\alpha]_D^{27}$ +100 (*c* 1.39, acetone); IR (KBr) 3439 (O–H), 1798 (C=O), 1746 (C=O), 1632 (C=C), 1594 (C=C), 1516 (C=C), 1265 (C–O), 1154 (C–O), 1029 (C–O), 818 (C=C) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.75 (d, *J* = 15.9 Hz, 1H, CH=C*H*), 7.23 (d, *J* = 1.8 Hz, 1H, Ar*H*), 7.13 (dd, *J* = 1.8, 8.1 Hz, 1H, Ar*H*), 6.83 (d, *J* = 8.1 Hz, 1H, Ar*H*), 6.47 (d, *J* = 15.9 Hz, 1H, C*H*=CH), 5.51 (t, *J* = 8.4 Hz, 1H, C*H*), 5.18 (dd, *J* = 1.2, 8.4 Hz, 1H, C*H*), 4.93 (d, *J* = 8.4 Hz, 1H, C*H*), 4.12 (d, *J* = 1.2 Hz, 1H, C*H*), 3.90 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 175.3 (*C*=O), 173.3 (*C*=O), 168.5 (*C*=O), 151.2 (*C*), 149.6 (*C*), 148.8 (*C*H), 127.6 (*C*H), 124.6 (*C*), 116.7 (*C*H), 113.9 (*C*H), 112.0 (*C*H), 78.9 (*C*H), 77.1 (*C*H), 71.1 (*C*H), 69.7 (*C*H), 56.5 (O*C*H_3), 53.1 (O*C*H_3); Anal. calcd for $C_{17}H_{18}O_{10}$: C, 53.41; H, 4.75. Found: C, 53.33, H, 5.15.