



Synthesis of vulpinic acids from dimethyl tartrate

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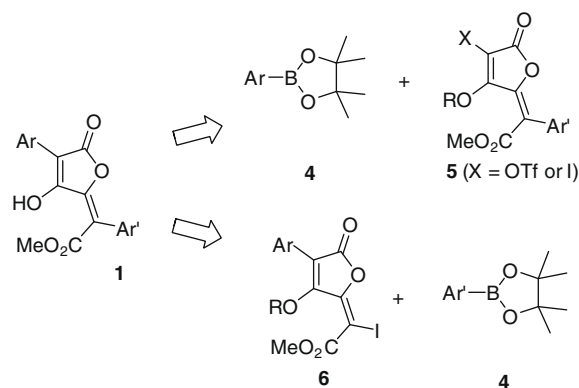
ABSTRACT

A series of vulpinic acids differing by the aryl or heteroaryl groups placed in the ester α -position were prepared by Suzuki–Miyaura cross-coupling involving a common iodide and the corresponding aryl boronates. The preparation of the iodide precursor from (+)-dimethyl L-tartrate required four steps: the esterification of one hydroxyl group, a Dieckmann cyclization allowing the construction of the tetronic acid moiety, a dehydration leading to the installation of the exocyclic double bond and lastly, an *N*-iodo-succinimide-mediated iodation of the alkene obtained.

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Pulvinic acids and the corresponding methyl esters, vulpinic acids, are pigments found in mushrooms and lichens.^{1,2} Antioxidant activities of such compounds were recently shown in a study in our laboratory.^{3,4} In the course of a study aimed at evaluating the properties of various pulvinic acids derivatives, we have developed several routes leading to these compounds.⁵ It was especially interesting to be able to prepare selectively series of compounds in which one of the aryl groups will vary, while the other one would remain unchanged. This would allow evaluating the respective importance of the aryl groups on the activity of the synthesized compounds. Two pathways leading to vulpinic acids **1** are depicted in the Scheme 1. In the first one, already reported,^{5c–e} compounds **1** substituted by various Ar groups were prepared via Suzuki–Miyaura couplings involving several arylboronates **4** and a single alkenyl triflate or iodide **5**. We now report an alternative route leading to unsymmetrical vulpinic acids in which a Suzuki–Miyaura coupling is employed at a late step for the introduction of various aryl and heteroaryl Ar' groups, by combination of arylboronates **4** with a single iodide precursor **6**, in which Ar = 4-methoxyphenyl.

Our initial goal was to prepare alkene **11**, which would be converted to the corresponding iodide. The synthesis of **11** from (+)-dimethyl L-tartrate (**7**) is described in the Scheme 2. Treatment of diol **7** with 4-methoxyphenylacetic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) led to a mixture of monoester **9** and the corresponding diester, which were easily separated by silica gel column chromatography

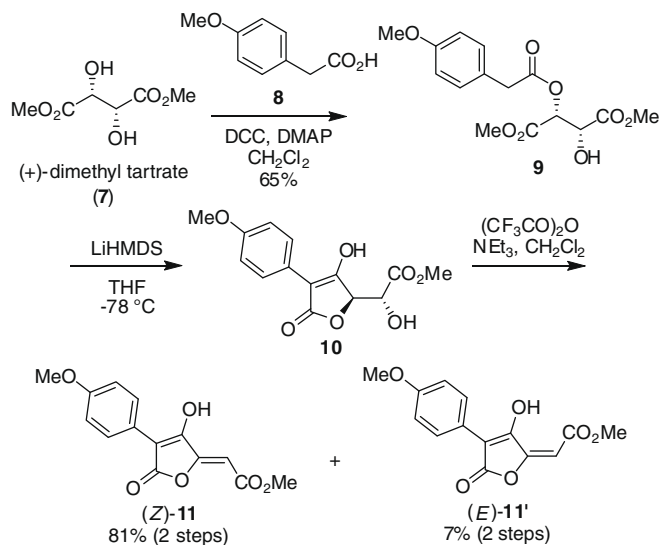


Scheme 1. Routes to vulpinic acids.

and isolated in 65% and 17% yield, respectively. The use of the Lacey version of the Dieckmann condensation for the synthesis of tetronic acids is a well-established method.^{6–8} Brandänge et al. applied this method to the cyclization of the monoacetate derived from dimethyl tartrate.⁹

Accordingly, the cyclization of **9** to tetronic acid **10** was realized by treatment with 3 equiv of lithium hexamethyldisilazide (LiHMDS) in THF at -78°C .¹⁰ The crude tetronic acid was not purified, but directly submitted to dehydrating conditions, leading to a mixture of alkenes (*Z*)-**11** and (*E*)-**11'**, isolated in 81% and 7% overall respective yield from alcohol **9** after silica gel chromatography.¹¹ The two isomers were readily separated, (*E*)-**11'** being distinctly less polar, which may be attributed to a chelation of

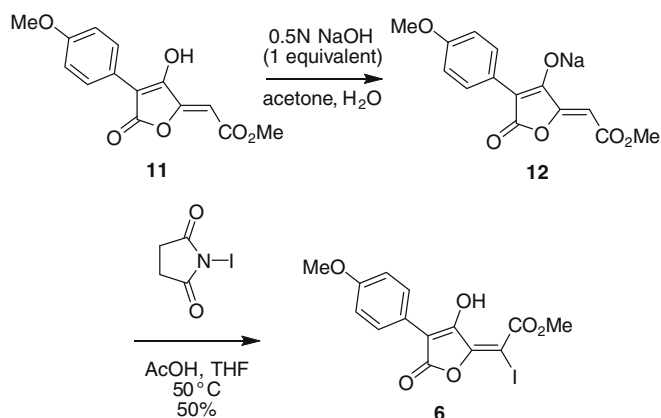
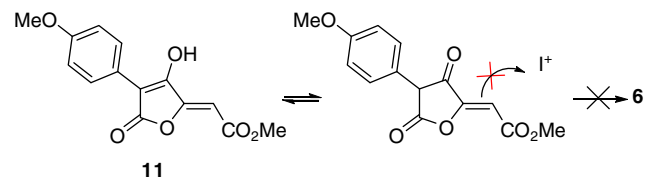
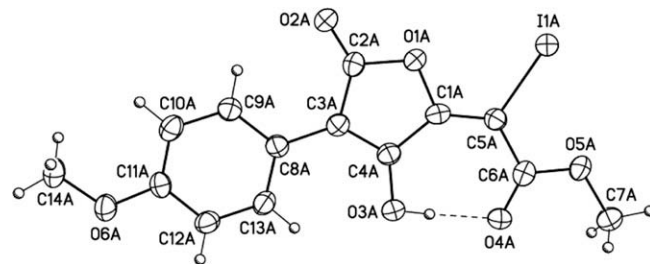
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Scheme 2. Synthesis of alkene **11**.

the hydroxyl group by the ester function in this compound. A strong IR band at 2594 cm^{-1} due to the chelated hydroxyl is observed for (*E*)-**11'**, while a strong IR band at 3524 cm^{-1} due to the nonchelated hydroxyl is observed for (*Z*)-**11**, which is in accordance with previous observations for similar compounds.^{2c} The configuration of the major (*Z*)-isomer was also ascertained on the basis of a single-crystal X-ray diffraction structural study.¹² Only this isomer was then employed in the next step. The synthetic sequence leading to **11** was easily performed on a multi-gram scale.

Attempts to iodinate alkene **11** using several conditions such as *N*-iodosuccinimide in ethanol¹³ or in acetic acid,¹⁴ or I_2/CAN ¹⁵ did not lead to the expected product. A small amount of iodide **6** was identified in a reaction involving the treatment of **11** with *N*-iodosuccinimide in the presence of acetic acid in THF. The reaction conditions were then changed and we eventually showed that iodoalkene **6** could be obtained in 50% yield in a reproducible way, provided that compound **11** was treated with 1 equiv of sodium hydroxide prior to the reaction with *N*-iodosuccinimide (Scheme 3).¹⁶ Thus, the substrate of the reaction was actually compound **12**, in which the enol function was converted to the corresponding sodium enolate.

A hypothesis can then be drawn concerning the lack of reactivity of alkene **11**. In alkene **11**, the enol function is likely to present a significant carbonyl character (Scheme 4). The double bond, which

Scheme 3. Preparation of iodoalkene **6**.Scheme 4. Hypothesis concerning the reactivity of alkene **11**.Figure 1. Molecular structure of iodoalkene **6**.

is also connected to another electron-withdrawing group, the ester function, is thus not nucleophilic enough to react with iodine(I) cation.

A single-crystal X-ray diffraction structural study of iodoalkene **6** allowed establishing the *Z* configuration of the exocyclic double bond (Fig. 1).¹² Thus, the iodination of alkene **11** proceeds with inversion of the double bond configuration. However, due to a change in priority order, both the substrate **11** and the product **6** are (*Z*)-configured. The formation of iodoalkene **6** instead of the corresponding (*E*)-isomer is probably favored because in **6**, the sterically demanding iodine atom is located in a less crowded position.

Suzuki–Miyaura cross-couplings were then carried out using iodoalkene **6** and several aryl- or heteroarylboronates **4** (Scheme 5, Table 1).

The conditions designed by Occhiato et al.,¹⁷ which make use of $\text{PdCl}_2(\text{PPh}_3)_2$ as the catalyst and 2 M Na_2CO_3 as the base, in refluxing THF, were previously employed in related couplings involving iodides such as **5**.^{5d,e} They were applied to the cross-couplings involving iodoalkene **6**, and found to be also convenient in this case. Boronates **4a–h** were thus converted to the corresponding adducts **1a–h** in 50–81% yield.¹⁸ The best yield was obtained from boronate **4a** substituted with a phenyl group (entry 1), which led to the known lichen pigment pinastric acid (**1a**).¹⁵ The physical and spectroscopic data for **1a** are in good agreement with those reported in the literature.^{2g,i,5e,19} Compounds in which the phenyl group is substituted by Cl, CF_3 , or OH were also obtained in good yields

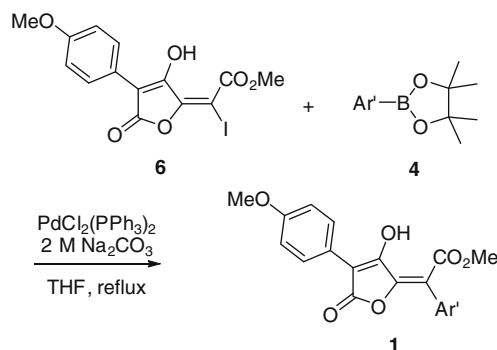








Scheme 5. Synthesis of vulpinic acids **1**.

Table 1
Synthesis of compounds **1a–h**

Entry	Ar'	Boronate	Product	Yield (%)
1		4a	1a	81
2		4b	1b	73
3		4c	1c	60
4		4d	1d	64
5		4e	1e	80
6		4f	1f	50
7		4g	1g	61
8		4h	1h	61

(entries 2–5). As could have been expected, the reaction involving boronate **4f**, in which the phenyl group is substituted in the *para* position by the electron-withdrawing acetyl group was less efficient (entry 6). Compounds **1g** and **1h** derived from heterocyclic boronates **4g** and **4h**, containing a 3-thienyl and a 3-furanyl group, respectively, were also prepared uneventfully (entries 7 and 8). It is worthy of note that these cross-couplings were carried out using iodide **6**, in which the enol function was left unprotected. The antioxidant properties of products **1a–h** are under investigation and will be reported in due course.

In summary, a novel synthetic access to a series of vulpinic acids was developed. In these vulpinic acids, the lactone ring is substituted by a 4-methoxyphenyl group, and they differ by the nature of the aryl or heteroaryl group located in the α -ester position. The approach relied on a convenient preparation of alkene **11** from dimethyl tartrate, involving a Dieckmann condensation, the preparation of iodide **6** under particular conditions, and the use of a Suzuki–Miyaura cross-coupling as the last step. This approach is complementary to the methods that we described previously.

Acknowledgment

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- Synthesis of compound 10**: A solution of LiHMDS (109 mL, 1 M in THF) was added to THF (220 mL) under nitrogen. The solution was cooled to -78°C and then a solution of compound **9** (11.9 g, 36.5 mmol) in THF (120 mL) was added dropwise. The reaction mixture was stirred for 1 h at -78°C and then allowed to warm to room temperature over 2 h. After cooling at 0°C , aqueous 2 N HCl (140 mL) was added. The two layers were separated, and the aqueous layer was extracted with AcOEt (2×200 mL). The combined organic layers were dried (MgSO_4) and filtered. Concentration under vacuum afforded tetronic acid **10** (10.7 g) as a pale yellow solid, which was used directly in the next step. Compound **10**: Mp 179 – 181°C ; TLC: R_f 0.35 (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$); $[\alpha]_D^{20} +132.9$ (c 1.00, MeOH); IR (KBr pellet) ν_{max} : 3324, 3016, 2957, 2843, 2645, 1747, 1696, 1637, 1613, 1517, 1447, 1428, 1391, 1312, 1294, 1259, 1213, 1125, 1032, 992, 832, 628 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6 , δ): 7.87 (d, 2H, $J = 9.0$ Hz, Ar-H), 6.94 (d, 2H, $J = 9.0$ Hz, Ar-H), 5.27 (d, 1H, $J = 1.9$ Hz, $\text{CHO}(\text{O})$), 4.79 (d, 1H, $J = 1.9$ Hz, CHOH), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, acetone- d_6 , δ): 172.4, 172.3, 170.5, 159.6, 129.5 (2C), 123.6, 114.3 (2C), 102.7, 78.6, 69.7, 55.5, 52.9; HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{14}\text{NaO}_7$ $[\text{M}+\text{Na}]^+$ 317.0637, found 317.0633.
- Synthesis of compounds (E)-11', (Z)-11**: A solution of tetronic acid **10** (1.5 g, 5.06 mmol), obtained from the previous reaction, and DMAP (91 mg, 0.253 mmol, 5 mol %) in dry CH_2Cl_2 (45 mL) was cooled to -18°C . Triethylamine (4.23 mL, 30.4 mmol, 6 equiv) was added, then trifluoroacetic anhydride (2.15 mL, 15.2 mmol, 3 equiv) was added dropwise over 15 min. The reaction mixture was allowed to warm to room temperature. After stirring for 16 h, 3 N HCl (15 mL) was added. After stirring for 1 h at room temperature, the two layers were separated, and the aqueous layer was extracted with AcOEt (2×15 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated under vacuum. Silica gel chromatography (90:10, then 50:50, then 30:70 cyclohexane/acetone) afforded alkenes (E)-11' (106 mg, 7%) as a yellow solid and (Z)-11 as an orange solid (1.13 g, 81%). (E)-11': Mp 159 – 160°C ; TLC: R_f 0.7 (1:1 cyclohexane/acetone); IR (KBr pellet) ν_{max} : 3071, 2960, 2923, 2845, 2594, 1780, 1680, 1635, 1604, 1513, 1440, 1353, 1280, 1251, 1188, 1157, 1093, 1042, 927, 833 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 13.15 (s, 1H, OH), 8.11 (d, 2H, $J = 8.6$ Hz, Ar-H), 6.96 (d, 2H, $J = 8.6$ Hz, Ar-H), 5.98 (s, 1H, $=\text{CHCO}_2\text{Me}$), 3.91 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 171.5, 166.6, 159.9, 158.7, 158.2, 129.5 (2C), 121.4, 114.1 (2C), 105.6, 100.2, 55.4, 53.9; HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{12}\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 299.0532, found 299.0542. (Z)-11: Mp 184 – 185°C ; TLC: R_f 0.1 (1:1 cyclohexane/acetone); IR (KBr pellet) ν_{max} : 3524, 3102, 3009, 2954, 2838, 1710, 1665, 1571, 1517, 1436, 1357, 1288, 1219, 1147, 1031, 957, 903, 836, 781, 651, 590 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6 , δ): δ 7.89 (d, 2H, $J = 9.1$ Hz, Ar-H), 7.01 (d, 2H, $J = 9.1$ Hz, Ar-H), 5.91 (s, 1H, $=\text{CHCO}_2\text{Me}$), 3.84 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, acetone- d_6 , δ): 168.1, 164.2, 160.8, 160.5, 153.3, 130.6 (2C), 121.9, 114.8 (2C), 106.0, 95.8, 55.7, 52.1; HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{12}\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 299.0532, found 299.0524.
- Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 717486 for alkene (Z)-11 and CCDC 717485 for iodide **6**. Copies

- of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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