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Flexible synthesis of vulpinic acids from tetronic acid

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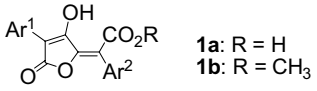
Dedicated to the memory of the late Dr Charles Mioskowski

Abstract—Several vulpinic acids were synthesized in a few steps from a single precursor, the tetronic acid. This commercial compound was converted in a few steps to an iodide. Suzuki–Miyaura cross-couplings involving this common intermediate and various arylboronates allowed to gain access to several vulpinic acids (or methyl pulvinates). Among them, two natural products, vulpinic acid and pinastric acid, were prepared.

Pulvinic acids **1a** and vulpinic acids **1b** are pigments found in lichens and mushrooms, especially in boletes. These compounds display various biological properties.[1] Variegatic acid (3,3′,4,4′-tetrahydroxypulvinic acid) has been shown to have antioxidant properties.[2] Studies in our laboratory have shown that other pulvinic derivatives also have interesting antioxidant activities.[3] Hence, it was of great interest to develop methods allowing to synthesize these compounds or their analogs in an efficient fashion.

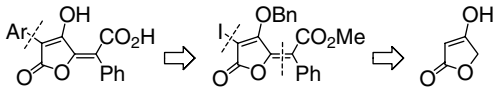


1a,b

Several syntheses of pulvinic acids and vulpinic acids have been described.[4] Recently, we designed an approach to symmetrical pulvinic acids (in which the two aryl groups are identical).[5] An approach leading to non-symmetrical pulvinic compounds which uses a Suzuki–Miyaura cross-coupling as a key step for the introduction of the aryl moiety bonded to the lactone was described by us[6] and by Langer et al.[7] The triflate employed in this coupling was derived from the corresponding enol obtained by cyclocondensation of a 1,3-bis(trimethylsilyloxy)diene with oxalyl chloride.[8] In this Letter, we describe a flexible approach to vulpinic acids which also makes use of a Suzuki–Miyaura cross-coupling as a key step to complete the carbon skeleton of the target compounds (Scheme 1). The two components of the coupling are an arylboronate and an iodide **3**, which are prepared in a few steps from commercially available tetronic acid (**4**).[9]

We chose to introduce an iodine atom on the butenolide because of the known high reactivity of iodides in palladium-mediated cross-couplings.[10]

The preparation of iodide **3** is described in Scheme 2. Tetronic acid was converted to 4-benzyloxy-2(5*H*)-furanone **5** using either a Mitsunobu reaction with benzyl alcohol[11] or an alkylation with benzyl bromide in a basic medium. The latter method was found more convenient on a large scale. The reaction of the anion generated by treatment of **5** with butyllithium at −78 °C in THF with methyl benzoylformate[12] then led to alcohol **6**, obtained as a mixture of diastereomers, which were partially separated by silica gel column chromatography. Several



2 **3** **4**

Scheme 1. Retrosynthetic plan for the synthesis of pulvinic acids from tetronic acid.

Keywords: Natural products; Vulpinic acid; Pulvinic acid; Tetronic acid; Suzuki–Miyaura cross-coupling.
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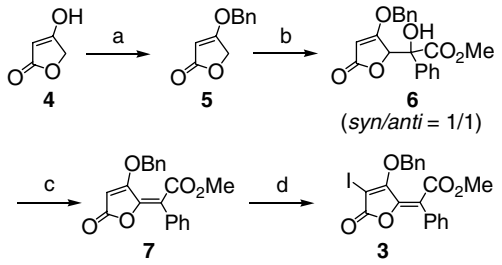


Scheme 2. Synthesis of iodide **3**. Reagents and conditions: (a) K_2CO_3, BnBr, DMF, room temp., 12 h, 75% or BnOH, Ph_3P, DEAD, room temp., 12 h, 85%; (b) (i) *n*-BuLi, THF, −78 °C, 20 min, (ii) methyl benzoylformate, −78 °C to room temp., 12 h, 67%; (c) $(CF_3CO)_2O$, DMAP (cat.), Et_3N, CH_2Cl_2, 4 h, 0 °C, 88%; (d) I_2, CAN, CH_3CN, 40 °C, 4.5 h, 78%.

deshydratation conditions were tested starting from both isomers. Using trifluoroacetic anhydride in the presence of triethylamine and a catalytic amount of DMAP in methylene chloride,[13] both isomers were converted efficiently to alkene **7**. This compound was obtained mainly as a *E*-stereomer, containing 5–10% of the *Z*-stereomer. The two isomers can be distinguished on the basis of the chemical shifts observed in ^{1}H NMR ($CDCl_3$, 400 MHz) for the methyl and the benzylic methylene protons.[14] For example, the signals for the methyl groups appear at 3.45 ppm for the major *E*-isomer and at 3.83 ppm for the minor *Z*-isomer. The difference may be attributable to an anisotropic shielding effect of the benzylic phenyl group on the methyl group of the *E*-isomer. Similar observations were made in the spectra of the compounds **3** and **9a–d** synthesized from **7**. Clear-cut evidence of the *E*-configuration of the major isomer was eventually obtained by comparing the final compounds synthesized from it with the natural products. The selective formation of the *E*-isomer of **7** from alcohol **6** may be attributed to either steric or electronic reasons. A study of the formation of alkenes from various substituted analogs of compound **6** should be necessary to give a rationale concerning the origin of the observed selectivity.

The iodation of compound **7** was performed in good yield with the use of iodine and ammonium cerium(IV) nitrate at 40 °C in acetonitrile.[15] Iodide **3** was thus obtained in four steps from tetronic acid in 39% overall yield.

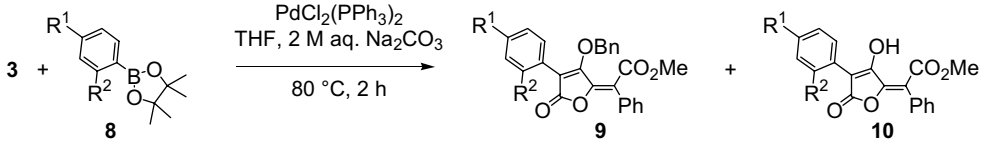
The Suzuki–Miyaura cross-coupling of iodide **3** with several arylboronates **8a–d** was then carried out, under conditions similar to those previously used from the corresponding triflate prepared using a different approach.[6] The catalyst employed was thus $Pd(PPh_3)_2Cl_2$ and the reaction proceeded at reflux for 2 h in a THF/2 M aqueous Na_2CO_3 mixture. The results are summarized in Table 1. The expected adducts **9a–d** were obtained in 55–93% yield after chromatographic purification.[16] In two cases, compounds **10** resulting from a cleavage of the benzyl enol ether function were also obtained (entries 1 and 4). The debenzylation probably occurred after the cross-coupling reaction. We had also observed such debenzylations on some occasions in couplings involving triflates.[6] In compounds **9**, the *Z*-isomer occurred in 6–12%.

Hydrogenolysis of the benzyl protecting groups of compounds **9a–c** was then performed by treatment under hydrogen (1 atm) over palladium on charcoal (Table 2).

Two conditions were employed. The reaction of compound **9a** in methylene chloride led to the corresponding adduct, vulpinic acid **10a** (entry 1). However, the reaction was still incomplete after 48 h. Starting material **9a** was recovered in 16% yield, while **10a** was obtained in 44% yield as pure *E*-isomer, the remaining minor *Z*-isomer being easily removed by chromatography. The spectroscopic data of **10a** are in good agreement with those reported for vulpinic acid in the literature.[4k,7a] Other conditions, which had been previously described by Ramage et al.[4h] for the deprotection of benzylated pulvinic esters, were applied to the other substrates **9b** and **9c**. The reactions, performed in DMF in the presence of hydrochloric acid, lasted for 2.5 h, leading to the expected vulpinic acids **10b** (pinastric acid)[4k,7b,17] and **10c**, obtained after chromatographic purification as pure *E*-isomers in 71% and 68% yield, respectively.[18]

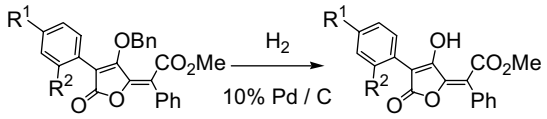
In conclusion, we have developed a practical, flexible approach for the synthesis of vulpinic acids in a few steps from commercially available tetronic acid. It relies on a key Suzuki–Miyaura cross-coupling involving a common intermediate, iodide **3**. Two of the compounds prepared, vulpinic acid and pinastric acid, are natural products. This strategy is currently further developed to gain access to natural pulvinic acids as well as various analogs.

Table 1. Suzuki–Miyaura cross-couplings of iodide **3** with boronates **8**



Entry	Boronate	R^1	R^2	Product	*E*/*Z* ratio in **9**	Yield of **9** (%)	Yield of **10** (%)
1	**8a**	H	H	**9a**	94/6	55	16
2	**8b**	OMe	H	**9b**	91/9	77	—
3	**8c**	H	OH	**9c**	91/9	93	—
4	**8d**	Cl	H	**9d**	88/12	62	31

Table 2. Hydrogenolysis of compounds **9a**–**c**



9 **10**

Entry	Boronate	R^1	R^2	Product	Yield (%)
1	**9a**[a]	H	H	**10a**	44[b]
2	**9b**[c]	OMe	H	**10b**	71
3	**9c**[c]	H	OH	**10c**	68

[a] Reaction in CH_2Cl_2, 48 h.
[b] The starting material was recovered in 16% yield.
[c] Reaction in DMF, containing concentrated HCl, 2.5 h.

Acknowledgment

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16. *Representative procedure for the Suzuki–Miyaura cross-coupling*: All the solvents were degassed. To a solution of iodide **3** (50 mg, 0.108 mmol) in THF (5.5 mL) were added $Pd(PPh_3)_2Cl_2$ (4 mg, 5.4 μmol, 5 mol %), a solution of 4-methoxyphenylboronic acid pinacol ester (37.9 mg, 0.162 mmol, 1.5 equiv) in THF (2 mL), and 2 M aqueous Na_2CO_3 (2.4 mL). The reaction mixture was refluxed for 2 h under argon. After cooling to room temperature, water (5.5 mL) and saturated aqueous NH_4Cl (2 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. Silica gel chromatography (9:1 to 6:4 pentane/AcOEt) afforded **9b** (*E*/*Z* isomers ratio: 91/9) as a yellow solid (37 mg, 77%). Compound **9b**: Mp = 138–139 °C; TLC: $R_f = 0.6$ (7:3 pentane/AcOEt); IR (KBr pellet) $\nu_{max} = 3031$, 2953, 2843, 1776, 1726, 1630, 1602, 1514, 1433, 1292, 1258, 1163, 1045, 941, 833, 759, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.67 (d, $J = 8.7$ Hz, 2H), 7.49 (d, $J = 8.7$ Hz, 2H), 7.42–7.24 (m, 8H), 6.98 (d, $J = 8.7$ Hz, 2H), 4.97 (s, 2H), 3.85 (s, 3H), 3.39 (s, 3H); signal belonging to the *Z*-isomer: δ (minor isomer) = 4.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.1$, 166.8, 160.7, 160.2, 141.6, 134.4, 131.4, 131.2, 129.2, 129.0, 128.7, 128.7, 128.6, 120.7, 116.2, 114.1, 108.7, 75.1, 55.4, 52.4 (two non-identified aromatic CH signals overlap).

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18. *Representative procedure for the hydrogenolysis*: To a suspension of 10% Pd/C (26 mg) and compound **9b** (23 mg, 0.052 mmol) in DMF (2 mL) were added two drops of concentrated HCl. The reaction mixture was placed under a hydrogen atmosphere at 1 atm, under vigorous stirring, for 2.5 h. Hydrogen was replaced by argon, then the suspension was filtered over a short pad of Celite, which was washed with THF. After concentration, ether (20 mL) was added and the organic phase was washed several times with water, dried (Na_2SO_4), filtered and concentrated under vacuum. Silica gel chromatography (9:1 to 1:3 pentane/AcOEt) afforded pinastric acid (**10b**) as a yellow solid (13 mg, 71%). The spectroscopic data agree well with those reported in the literature.[4k,7b,17] Compound **10b**: Mp = 203–205 °C (lit.[4k] 207–209 °C); IR (KBr pellet) ν_{max} = 3745, 3018, 2959, 2841, 2535, 1772, 1674, 1600, 1514, 1493, 1441, 1370, 1308, 1278, 1254, 1189, 1063, 1024, 959, 905, 844, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.9 Hz, 2H), 7.45–7.40 (m, 3H), 7.30–7.25 (m, 2H), 6.98 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 166,1, 159.6, 158.6, 155.0, 132.1, 130.0, 129.4, 128.5, 128.1, 121.6, 115.2, 113.9, 105.3, 55.3, 54.3.