Diastereoselective Synthesis of Functionally Diverse Substituted Pipecolic Acids

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Abstract: The synthesis of *cis*-4-substituted pipecolic acids, 4,5-disubstituted pipecolic acids, and their 6-oxo analogues starting from enantiopure L-aspartic acid is reported. The synthetic strategy involves as key steps, Suzuki–Miyaura and related Pd-mediated couplings, followed by a catalytic hydrogenation with excellent yields and diastereoselectivities. Enolate alkylations provide 4,5-*trans*-oriented functionalization.

Key words: Suzuki–Miyaura coupling, lactam enolate alkylations, arylpiperidine, piperidinone, pipecolic acid

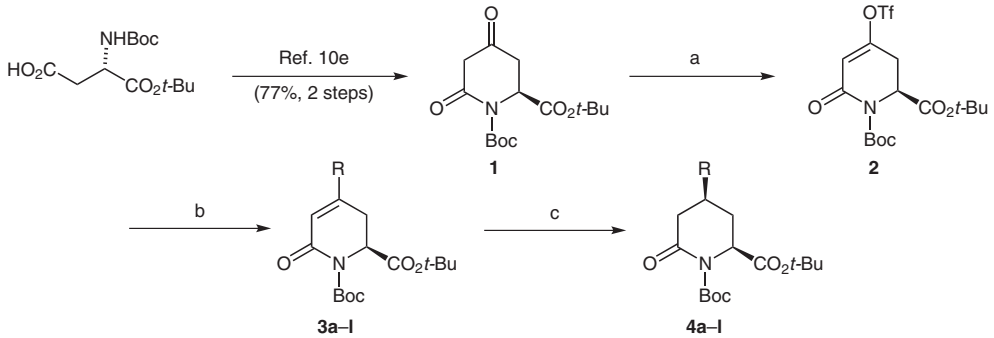
Pipecolic acids are important components of a number of natural products as peptidic subunits,[1] or as embedded substructures.[2] Many applications in medicinal chemistry based on the inclusion of pipecolic acids and their derivatives have been reported.[3] Substituted piperidines, and in particular 4-arylpiperidines, have been extensively used as components of enzyme inhibitors such as paroxetine,[4] as inhibitors of human dopamine transporter,[5] as DPP4 inhibitors,[6] or as CCR2 antagonists.[7]

Although the literature abounds with methods for the synthesis of substituted piperidines[8] and pipecolic acids[9] in enantiomerically pure form, relatively few methods are available for derivatives of 6-oxopipecolic acids such as **4** (Scheme 1).[10] In this paper we report on a practical synthesis of enantiopure substituted pipecolic acids and their 6-oxo analogues starting from the readily available L-aspartic acid.

Treatment of BocO-*tert*-butyl L-aspartate with Meldrum's acid according to Marin[10e] and Murray[11] followed by cyclization and decarboxylation, afforded the 4-oxo derivative **1** in 77% yield over two steps (Scheme 1). Conversion into the enol triflate **2** allowed the application of the Suzuki–Miyaura reaction,[12] and to functionalize at C-4 giving the corresponding 4-substituted 4,5-unsaturated-6-oxopipecolic acid Boc-*t*-Bu esters **3a–l** (Table 1).[13,14] Aryl, olefinic, and heteroaryl boronic acids (Table 1, entries 1–9, 12–14) were found to be excellent reacting partners to **2**. Pyridyl or 2-thiophenyl boronic acids led to lower yields for **3j** and **3k** (entries 10 and 11). While to our best knowledge, no Suzuki reactions have been tested on an enol triflate of a β-dicarbonyl substrate such as **2** with a 3-pyridyl boronic acid or boronate, 2-thienyl boronic acid is known to give lower yields with phenolic triflates.[15]

Suzuki–Miyaura coupling for the methyl **3o** compound also gave a lower yield. This corroborates previous observations with alkylboronic species where better yields were achieved by the use of reactants such as 40 mol% of triphenylarsine.[16] The low reactivity is explained by a difficult transmetalation step between the organoboron species and the Pd intermediate.[17] The use of the more nucleophilic potassium methyltrifluoroborate according to Molander[18] with $PdCl_2(dppf{\cdot}CH_2Cl_2)_2$ improved the yield only moderately up to 40% (Scheme 2).

Catalytic hydrogenation in the presence of Pd/C was highly selective due to the presence of the bulky ester group,



Scheme 1 *Reagents and conditions*: a) DIPEA, Tf_2O, CH_2Cl_2, 0 °C, 30 min; b) $PdCl_2(PPh_3)_4$, 2 M Na_2CO_3, $R^1B(OR^2)_2$, THF, 40 °C 16 h (see Table 1).

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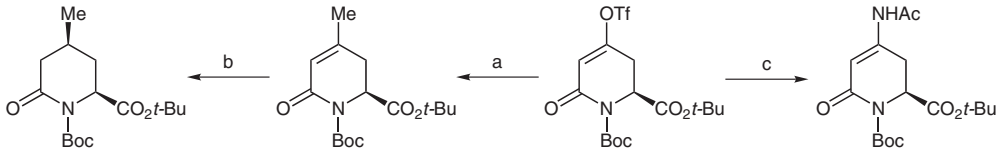


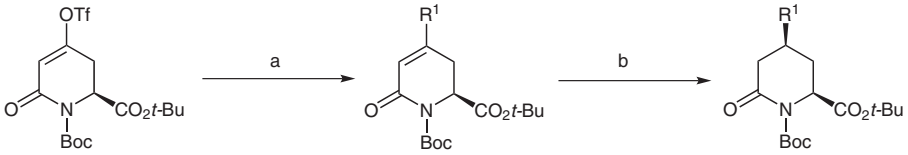
Scheme 2 *Reagents and conditions*: a) $PdCl_2(PPh_3)_2$, 2 M Na_2CO_3, $MeB(OH)_2$, THF, 40 °C, 16 h, 31%, (40% with $MeBF_3K$); b) H_2, Pd/C, EtOAc, 16 h, 69%, de >99%; c) $Pd_2(dba)_3$, Cs_2CO_3, $AcNH_2$, Xantphos, dioxane, 40 °C, 16 h, 44%.

affording the *cis*-substituted products **4a**,**b**,**k**,**o** as confirmed by X-ray structural analysis of **4a** (Figure 1).[14] However, over-reductions occurred for the heteroaryls **4i** and **4j** giving inseparable mixtures (Table 1).

Other types of functionalizations were also possible with the triflate intermediate **2**. Thus, treatment with acetamide in the presence of $Pd_2(dba)_3$ according to Buchwald[19] or Wallace,[20] gave the 4-acetamido analogue **3p** in 44% yield (Scheme 2). To the best of our knowledge, a coupling between an enol triflate and an acetamide has not been described with a 6-oxopipecolic acid core.

The attempted reductive amination of **1** with benzylamine and *p*-anisidine in the presence of $NaBH_4{\cdot}NiCl_2$, $NaBH(OAc)_3$, $NaBH_3CN$, or under high pressure hydrogenation (80 psi) afforded instead the 4-enamino ana-

Table 1 Synthesis of 4-Substituted 4,5-Unsaturated 6-Oxopipecolic Acid Boc-*t*-Bu Esters **3a–l** and Reduction to Compounds **4a–l**



a) $PdCl_2(PPh_3)_4$, 2 M Na_2CO_3, $R^1B(OR^2)_2$, THF, 40 °C 16 h
b) H_2, Pd/C, EtOAc, 2 h

Entry	Aryl	Compound	Yield (%)	Compound	Yield (%)[a]
1	Ph	**3a**	90	**4a**	>98
2	4-$MeOC_6H_4$	**3b**	91	**4b**	90
3	3-$MeOC_6H_4$	**3c**	82	**4c**	94
4	*p*-tolyl	**3d**	84	**4d**	93
5	3-$CHOC_6H_4$	**3e**	82	**4e**	90[c]
6	4-FC_6H_4	**3f**	89	**4f**	>98
7	3-$NO_2C_6H_4$	**3g**	90	**4g**	>98
8	3-CNC_6H_4	**3h**	93	**4h**	86
9	2-furyl	**3i**	86	**4i**	–[d]
10	3-pyridyl	**3j**	58	**4j**	–[d]
11	2-thiophene	**3k**	40	**4k**	40
12	vinyl	**3l**	92	–	–
13	*trans*-styryl	**3m**	84	–	–
14	allyl	**3n**	63	–	–
15	Me	**3o**[b]	31	**4o**	69

[a] In all cases de >98% as determined by ^1H NMR at 400 MHz, see ref. 13, 14.
[b] See Scheme 2.
[c] Yield of alcohol.
[d] Inseparable mixture of partially saturated products.

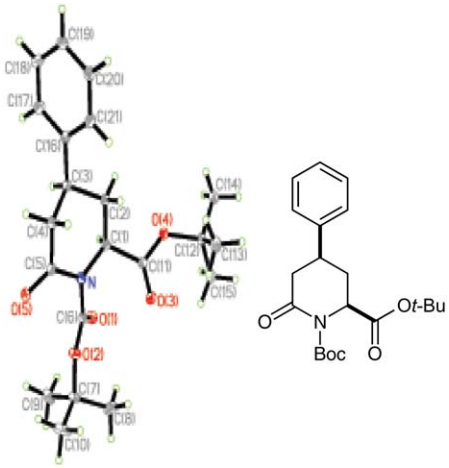
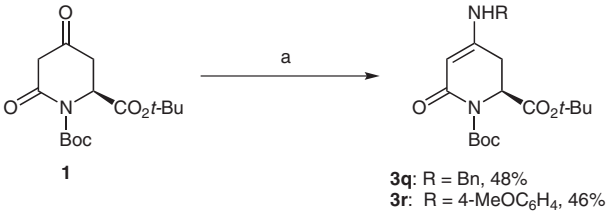


Figure 1 ORTEP of **4a**



Scheme 3 *Reagents and conditions*: a) benzylamine or anisidine, MS, CH_2Cl_2, r.t., 1 h.

logues **3q** and **3r** in modest yields (48% and 46%, respectively; Scheme 3).

Enolate alkylations were also possible for the representative products **4a** and **4c** (Scheme 4).

Thus, treatment of the lithium enolate with electrophiles such as allyl iodide and *m*-methoxybenzyl bromide gave, as expected, the *anti* adducts **5**–**7** with excellent diastereoselectivities.[21] Decarbonylation of the 4-aryl analogues **4a**, **4b**, and **4d** was achieved by reduction with $BH_3{\cdot}SMe_2$ to give the 4-aryl pipecolic esters **8**–**10**.[22] Simultaneous deprotection of the *N*-Boc amine and *tert*-butyl ester was achieved under acidic conditions to afford the hydrochloride salts **11** and **12** with excellent yields.

In summary, we have reported practical methods to access 2,4-*cis*-substituted 6-oxo-pipecolic acids in enantiopure form from a common and readily available precursor Boc-Asp-O*t*-Bu. These functionalized intermediates are useful scaffolds to access a variety of more complex monocyclic and polycyclic compounds of relevance in medicinal chemistry and in natural product synthesis.[23]

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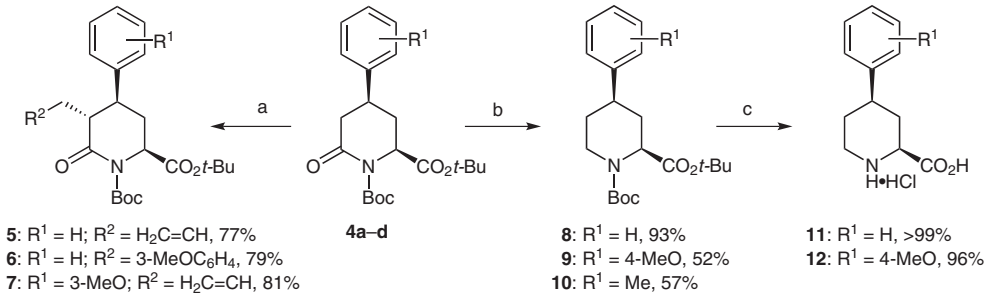

Scheme 4 *Reagents and conditions*: a) LiHMDS, THF, –78 °C, 1 h then allyl iodide or 3-methoxybenzylbromide, –78 °C, 2 h; b) $BH_3{\cdot}SMe_2$, THF, 0 °C then r.t., 16 h; c) HCl 6 M in MeOH, r.t., 3 h.

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(13) **General Procedure for Suzuki–Miyaura Coupling**
Under argon, to a solution of **2** (1 equiv) in THF (0.04 M) were added the boronic acid (1.5 equiv), $(Ph_3P)PdCl_2$ (0.05 equiv) and a 2 M Na_2CO_3 solution (1.5 mL for 0.11 mmol of **2**). The mixture was stirred at 40 °C overnight. The reaction generally turned black at completion. H_2O was added, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography (generally hexane–EtOAc, 8:2).

(14) **Data for Selected Compound: (2*S*,4*S*)-Di-*tert*-butyl 6-Oxo-4-phenylpiperidine-1,2-dicarboxylate (4a)**
From **3a** (119 mg, 0.32 mmol) was obtained **4a** as a white solid (120 mg, 100%); $[\alpha]_D$ –28.6 (*c* 1.04, $CHCl_3$); mp 142.5–147.5 °C. IR (KBr): 2982, 2934, 1731, 1703, 1605, 1495, 1473, 1459, 1392, 1365, 1283, 1270, 1237, 1153, 1135, 1099, 1042, 1029, 1015 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (t, 2 H, *J* = 7.2 Hz), 7.29 (t, 1 H, *J* = 7.4 Hz), 7.21 (d, 2 H, *J* = 7.2 Hz), 4.60 (dd, 1 H, *J* = 10.0, 6.6 Hz), 3.17–3.08 (m, 1 H), 2.85–2.79 (m, 1 H), 2.64 (dd, 1 H, *J* = 16.8, 13.0 Hz), 2.59–2.52 (m, 1 H), 2.03–1.94 (m, 1 H), 1.56 (s, 9 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 169.6, 152.1, 141.7, 128.6, 126.9, 126.1, 83.4, 81.9, 58.7, 41.5, 36.7, 33.4, 27.5 ppm. HRMS: *m/z* calcd for $C_{21}H_{29}NO_5$: 398.20457; found: 398.19487 $[M + Na]^+$.

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(21) **Data for Selected Compound: (2*S*,4*S*,5*R*)-Di-*tert*-butyl 5-Allyl-6-oxo-4-phenylpiperidine-1,2-dicarboxylate (5)**
From **4a** (1.06 g, 2.82 mmol) was obtained **5** as a white solid (904 mg, 77%); $[\alpha]_D$ –133.1 (*c* 1.41, $CHCl_3$); mp 115–117 °C. IR (KBr): 2980, 1728, 1707, 1457, 1366, 1283, 1248, 1225, 1145, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 2 H), 7.28–7.20 (m, 1 H), 7.18–7.08 (m, 2 H), 5.70 (dddd, 1 H, *J* = 17.0, 10.1, 8.6, 5.7 Hz), 4.97 (d, 1 H, *J* = 10.1 Hz), 4.85 (d, 1 H, *J* = 17.1 Hz), 4.47 (dd, 1 H, *J* = 10.3, 6.2 Hz), 2.92 (dt, 1 H, *J* = 11.8, 11.8, 3.9 Hz), 2.73 (td, 1 H, *J* = 11.9, 4.5, 4.5 Hz), 2.66–2.51 (m, 1 H), 2.38 (ddd, 1 H, *J* = 13.7, 6.1, 4.0 Hz), 2.06–1.93 (m, 2 H), 1.51 (s, 9 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 170.1, 152.3, 141.3, 134.0, 128.4, 126.9, 126.7, 117.4, 83.0, 81.6, 58.4, 49.0, 40.5, 33.5, 32.3, 27.4, 27.4 ppm. HRMS: *m/z* calcd for $C_{24}H_{33}NO_5$: 438.23587; found: 438.22464 $[M + Na]^+$.

(22) **Data for Selected Compound: (2*S*,4*R*)-Di-*tert*-butyl 4-Phenylpiperidine-1,2-dicarboxylate (8)**
From **4a** (30 mg, 0.08 mmol) was obtained **8** as a colorless gum (25 mg, 93%); $[\alpha]_D$ –15.6 (*c* 0.95, $CHCl_3$). IR (NaCl): 2976, 1738, 1699, 1602, 1478, 1454, 1393, 1366, 1249, 1150, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (rotamers) = 7.35–7.31 (m, 2 H), 7.26–7.21 (m, 3 H), 4.25–4.21 (m, 1 H), 3.75–3.56 (m, 2 H), 2.88–2.80 (m, 1 H), 2.28–2.22 (m, 1 H), 2.14–2.02 (m, 2 H), 1.87–1.78 (m, 1 H), 1.49 (s, 9 H), 1.42 (s, 9 H). ^{13}C (100 MHz, $CDCl_3$): δ = 171.3, 155.4, 144.6, 128.2, 126.6, 126.0, 80.6, 79.7, 56.1, 37.1, 32.4, 29.8, 28.0, 27.6 ppm. HRMS: *m/z* calcd for $C_{21}H_{31}NO_4$: 361.22531; found: 362.23232 $[M + H]^+$.

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