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Stereocontrolled synthesis of enantiopure diversely functionalized prototypical piperidinone libraries, and constrained analogs of 4-substituted 2-amino adipic acid

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Abstract—Enantiopure 2-substituted 4,5-unsaturated piperidinones were subjected to stereocontrolled nitroalkane additions and the corresponding products were further manipulated to produce 4-aminomethyl derivatives. Diverse substitution led to a set of 4-arylsulfonamides and *O*-carbamates as examples of prototypical piperidinone libraries with two sites of diversity.

Piperidine rings with one or more substituents are abundant in nature, and their stereocontrolled synthesis has been the subject of many reports.[1] Substituted piperidines are key structural elements in compounds possessing CNS activity inhibitors[2] and they are also known enzyme inhibitors.[3,4] The availability of enantiopure 2,4-disubstituted piperidines and their 6-oxo derivatives, with the option to functionally differentiate the appendages would be very useful in the context of spacially defined scaffolds.[5] For example, SB204070, an ester of hydroxymethyl *N*-butylpiperidine was identified as a potent and selective 5-HT_4 receptor antagonist[6] originating from a library of 4-hydroxymethyl piperidines.

Scheme 1 illustrates our synthesis of enantiopure 4-aminomethyl 2-hydroxymethyl-6-oxo piperidines. Thus, 2-hydroxymethyl piperidine **1** readily available via enzymatic resolution[7] or by chemical transformation from L-lysine[8] was protected as the *N*-Boc/OTBDPS derivative, then oxidized to the corresponding 6-oxo derivative. Formation of the α,β-unsaturated lactam **2** proceeded uneventfully in good overall yield. Conjugate addition of nitromethane in the presence of DBU[9] led to an equimolar mixture of the two diastereomers **3** and **4**, which could be easily separated by flash chromatography. The stereochemical assignments were based on NOE measurements and by analogy to a related reaction (see below). Catalytic hydrogenation led to the corresponding 4-aminomethyl analogs **5** and **6**, respectively, which were individually subjected to a three-step sequence involving reaction with arylsulfonyl halides, removal of the TBDPS group, and formation of carbamates with a set of arylisocyanates. Thus, a set of mixed sulfonamide/carbamates corresponding to **7** and **8** and totaling 32 compounds was produced with excellent purities (^{13}C, mass spec., HPLC). Addition of 2-nitropropane to **2** afforded a single adduct **9**, which upon catalytic hydrogenation led to the 4-(2-aminopropyl) analog **10** (Scheme 1).

Treatment of the readily available α,β-unsaturated lactam **12**[10] with nitromethane in DBU gave a 3:1 mixture of the *syn* and *anti* 4-nitromethyl adducts **13** and **14**, respectively, in excellent yield after chromatographic separation (Scheme 2). The structure of the 4-(2-nitropropyl) adduct **15** was ascertained by X-ray crystallography. Removal of the *N*-Boc protective group afforded the 4-nitroalkyl lactams **16** and **17** which were hydrogenated to the corresponding 4-

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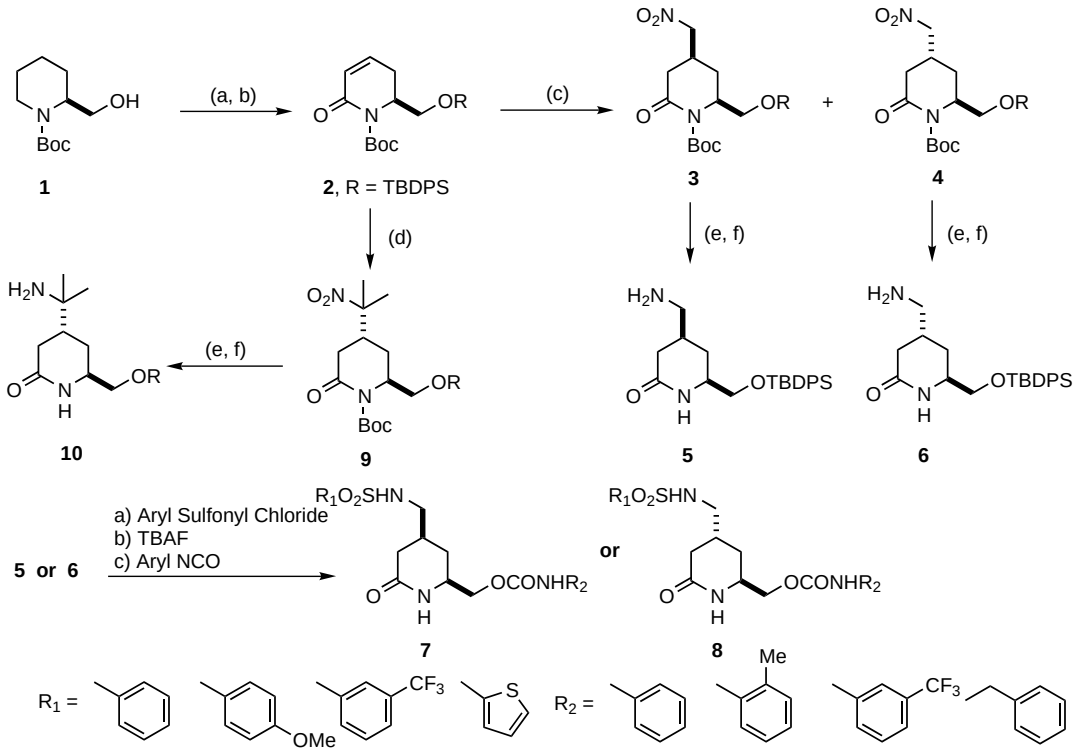
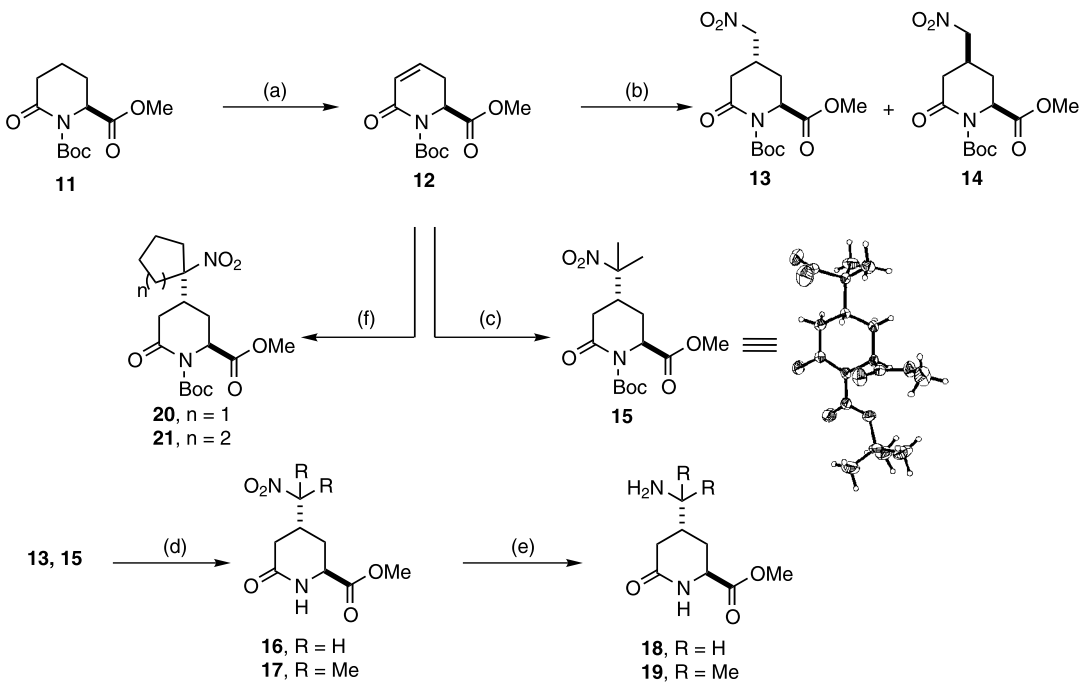


Scheme 1. (a) i. TBDPSCl, DMAP, CH_2Cl_2, ii. $RuO_2{\times}H_2O$, $NaIO_4$, H_2O–EtOAc, 80% (two steps); (b) i. LiHMDS, PhSeBr, THF, ii. H_2O_2, pyridine, CH_2Cl_2, 75% (two steps); (c) CH_3NO_2, DBU, 85%, 1 to 1; (d) 2-nitropropane, DBU, 85%; (e) TFA, CH_2Cl_2, 90%; (f) H_2, Pd–C, MeOH 95%.



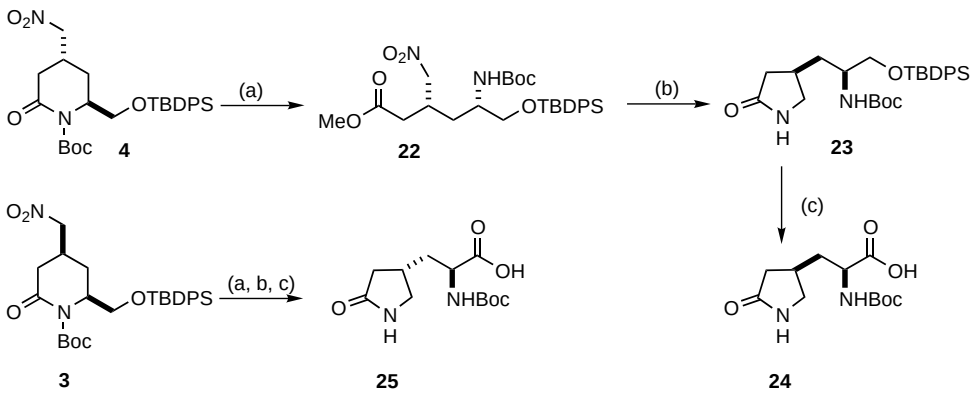
Scheme 2. (a) i. LiHMDS, PhSeBr, THF, ii. H_2O_2, 75% (two steps); (b) CH_3NO_2, DBU, 85%, 3 to 1(*anti* to *syn*); (c) 2-nitropropane, DBU, 85%; (d) TFA, CH_2Cl_2, 90%; (e) H_2, Pd–C, MeOH 95%; (f) nitrocyclohexyl or nitrocyclopentyl, K_2CO_3, MeCN, 65%.

aminoalkyl 6-oxo-2-pipecolate esters **18** and **19**, respectively, in excellent yield. Finally, the Michael additions were also successfully realized with nitrocyclopentane and nitrocyclohexane to give **20** and **21**, respectively, as single isomers. In these cases, the reactions were run in acetonitrile in the presence of potassium carbonate (Scheme 2).

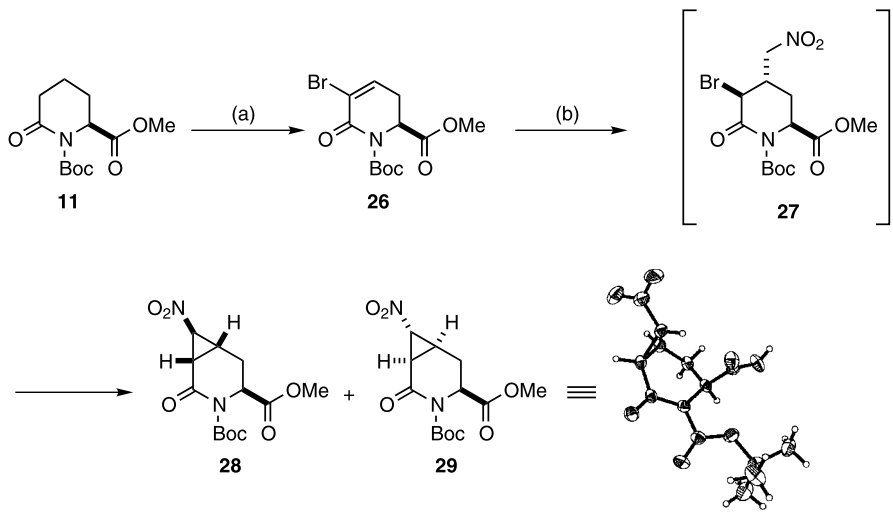
It is surprising that the stereochemical outcome in the reaction of **2** and **12** is different vis-à-vis nitromethane, but not the bulkier homologs. Based on steric factors alone, one would have predicted a lesser amount of the *syn*-isomer **3** compared to **4** (Scheme 1). $A^{1,3}$ strain[11] can play an important role in deciding the conformer population of 2-substituted lactams related **12**, where a pseudoaxial orientation is favored by 5 kcal mol^{-1} in a chair-like conformation.[12] With bulkier nitroalkanes **15**, **20** and **21** are formed quasi exclusively. The X-ray crystal structure of **15** depicts the ester group in an axial orientation (Scheme 2).

When the 4-nitromethyl adduct **4** was subjected to hydrogenation, the rearranged pyrrolidinone **23** was obtained in ~30% yield (Scheme 3). Clearly, this product resulted from an intramolecular attack of the initially formed amino group on the activated lactam carbonyl. A more efficient two-step process was developed whereby, the lactam was first converted to the ester **22**, which upon heating in toluene in the presence of a catalytic quantity of pyridine underwent intramolecular cyclization to **23** in 60% overall yield. Removal of the protective group and oxidation[13] of the primary alcohol to the carboxylic acid gave a β-(3*R*-5-oxo-pyrrolidinyl) L-alanine analog **24**. An analogous sequence led to the 4-*S*-diastereomer **25**. These 3-substituted-5-oxo-pyrrolidines can be considered as constrained analogs of branched L-2-amino adipic acids.[14]

Finally, we prepared a versatile vinylic bromide analog **26** by a sequence of standard reactions, while ensuring the stereochemical integrity of the product. Treatment of **26** with nitromethane as solvent in the presence of DBU led to a 3:1 mixture of *syn* and *anti* 4,5-nitromethano 6-oxo-pipecolates **28** and **29**, respectively (Scheme 4).[15] The minor isomer **29** afforded X-ray quality crystals in which the pseudo axial disposition of the ester group is noteworthy (Scheme 4). It is also of interest that the nitro group in both products **28** and **29**



Scheme 3. (a) NaOMe, THF, 95%; (b) i. H_2, Pd–C, MeOH, ii. toluene, pyridine (cat.) 110°C, 60% (two steps); (c) i. TBAF, THF, ii. TEMPO, $NaClO_2$, NaOCl, MeCN, 35°C, 80%.



Scheme 4. (a) i. LiHMDS, PhSeBr, THF, ii. Br_2, iii. H_2O_2, 65%; (b) CH_3NO_2, DBU, 60%.

adopts an *exo*-orientation vis-à-vis the piperidinone ring.

In conclusion, we have described methodology for the stereocontrolled syntheses of 4-substituted 6-oxo-piperidine-2-carboxylic acids and the corresponding 2-hydroxymethyl analogs.[16] These were used as versatile scaffolds to construct a small library encompassing a 4×4 (or potentially larger) combination of sulfonamides and carbamates. The synthesis of β-(3*R*- and 3*S*-5-oxo-pyrrolidinyl L-alanine could be useful as examples of constrained L-2-amino adipic acids.

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16. Experimental procedures available upon request. Data for selected compounds: **16**: $[\alpha]_D$ +20.0° (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.50 (b, 1H), 4.38–4.37 (d, $J=7.01$ Hz, 2H), 4.24–4.22 (m, 1H), 3.80 (s, 3H), 2.80–2.75 (m, 1H), 2.64–2.57 (m, 1H), 2.33–2.29 (d, $J=13.58$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 171.07(0), 168.95(0), 78.43(−), 52.92(+), 34.18(−), 29.08(+), 27.53(−); HRMS: $C_8H_{12}N_2O_5$. Calcd: 216.0746; found: 217.0820 (m+1). **24**: $[\alpha]_D$ −27.6° (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ (ppm) 4.23–4.26 (dd, $J=15.0$ Hz, 7.2 Hz, 1H), 3.52–3.46 (m, 1H), 3.12–3.08 (dd, $J=6.17$ Hz, 8.90 Hz, 1H), 2.57–2.49 (m, 1H), 2.45–2.38 (dd, $J=8.01$ Hz, 15.37 Hz, 1H), 2.25–2.29 (m, 1H), 1.75–1.78 (m, 1H), 1.45 (m+s, 10H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 177.06(0), 174.72(0), 157.57(0), 70.62(0), 55.86(+), 43.17(−), 40.05(−), 37.04(−), 28.75(+), 23.14(+); HRMS: $C_{12}H_{20}N_2O_5$. Calcd: 272.1372; found: 273.13952 (m+1). **28**: $[\alpha]_D$ −22.3° (*c* 15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$); δ (ppm) 4.76–474 (dd, $J=3.03$ Hz, 1H), 4.44–4.43 (t, $J=2.89$ Hz, 1H), 3.82 (s, 3H), 2.87–2.84 (dd, $J=2.84$ Hz, 9.98 Hz, 1H), 2.76–2.69 (m, 1H), 2.60–2.56 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.20(0), 161.57(0), 149.32(0), 82.29(0), 62.49(+), 54.62, 50.71(+), 26.27(+), 25.29(+), 22.86(−), 20.24(+); HRMS: $C_{13}H_{18}N_2O_7$. Calcd: 314.1114; found: 315.1185 (m+1).