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Synthesis of (2*R*,4*R*)- and (2*S*,4*S*)-4-hydroxypipecolic acid derivatives and (2*S*,4*S*)-(−)-SS20846A

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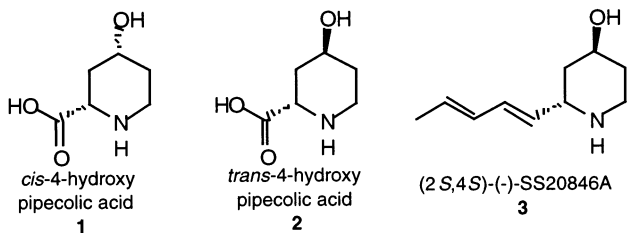
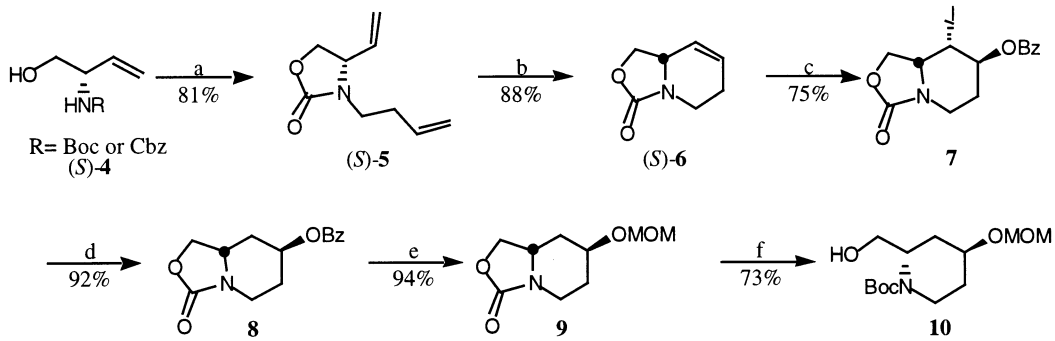
Abstract—Syntheses of protected derivatives of both enantiomers of *trans*-4-hydroxypipecolic acid (**2**) and the natural product (−)-SS20846A (**3**) were accomplished from vinylglycinols. Key transformations involved construction of the piperidine ring via ring-closing metathesis (Grubbs' catalyst) and installation of the 4-hydroxy substituent by Prevost reaction. X-Ray diffraction analyses conclusively established the regio- and stereochemistry of key intermediates. © 2001 Elsevier Science Ltd. All rights reserved.

The enantiopure naturally-occurring 4-hydroxy-2-pipecolic acids **1**[1a] and **2**[1b,c] have been isolated from various green plants.[1] These 4-substituted piperidines constitute important chiral building blocks of biologically active molecules;[2] (2*S*,4*R*)-**1** was utilized in the synthesis of palinavir,[2a] a potent antiviral, and the synthesis of pipecolic acid derivatives is of considerable interest.[3] (−)-SS20846A (**3**) is a 2-alkyl-4-hydroxypiperidine natural product, which has been isolated from *Streptomyces* sp. S20846. This compound has demonstrated antibacterial and anticonvulsant properties. Additionally, *ent*-**3** has shown remarkable DNA binding properties.[4b]

This letter discloses syntheses of both enantiomers of *trans*-4-hydroxypipecolic acid (**2**), the natural product (−)-SS20846A[4,5] (**3**), and *ent*-**3**, in the protected form, from protected derivatives of vinylglycinol [(*R* and *S*)-**4**].[6]



Treatment of compound (*S*)-**4** with NaH in THF resulted in high yields of the corresponding oxazolidinone,[7] which was alkylated with commercially available



Scheme 1. *Reagents and conditions*: (a) i. NaH, THF, ii. NaH, 4-bromo-1-butene, LiI, DMF; (b) Grubbs' catalyst, CH_2Cl_2; (c) I_2, silver benzoate, benzene; (d) Raney Ni, THF/MeOH; (e) i. KCN, MeOH/H_2O (9/1), ii. MOMCl, Hünig's base, CH_2Cl_2; (f) i. 3N NaOH, MeOH/H_2O (9/1), reflux 24 h, ii. Boc_2O, EtOAc.

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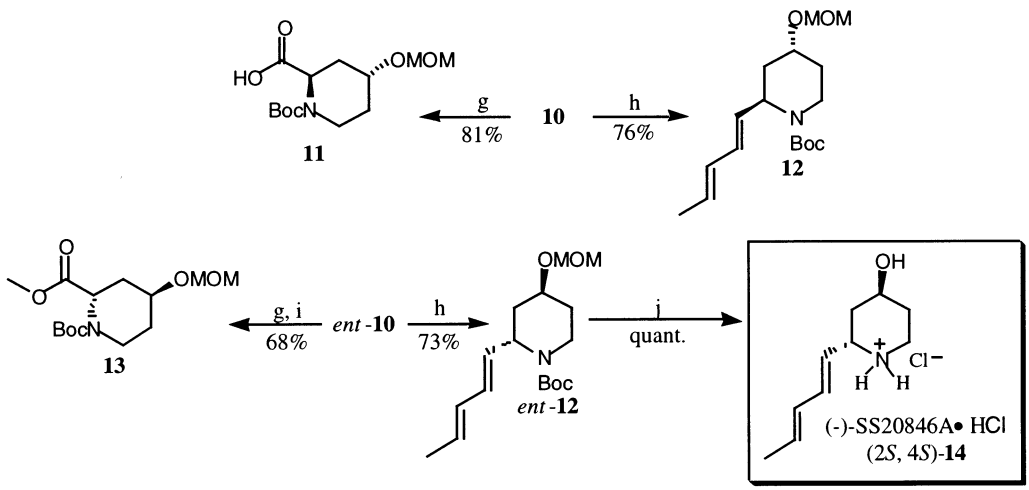

Scheme 2. *Reagents and conditions*: (g) i. Dess–Martin/THF ii. $NaClO_2$, NaH_2PO_4; (h) i. Dess–Martin/CH_2Cl_2 ii. $CH_3CH{=}CH{=}PPh_3$, THF; iii. I_2, benzene, hν, 30 min; (i) CH_2N_2; (j) AcCl/MeOH.

4-bromo-1-butene.[8,9] Alternatively, (*S*)-**5** was synthesized directly from (*S*)-**4** using a one-pot two-step process.[8] Ring-closing metathesis of **5** with Grubbs' catalyst, bis(tricyclohexylphosphine)benzylidineruthenium(IV) dichloride,[10] under standard conditions for 24 h afforded (*S*)-**6** in 88% yield along with a small amount of recovered **5**. Compound (*S*)-**6** when subjected to Prevost reaction conditions afforded **7**. Stereochemistry was unequivocally established by X-ray analysis of **7**.[11] Dehalogenation of **7** with Pd/C proved slow even in the presence of triethylamine. However, Raney nickel afforded **8**[11] successfully in 92% yield. This compound was subjected to protecting group exchange in a one-pot procedure with KCN and MOMCl to afford **9**. NaOH hydrolysis of the oxazolidinone ring of **9** followed by Boc_2O protection of the resultant free amine then afforded the key intermediate **10** (Scheme 1).

The reaction sequence (Scheme 1) was repeated using *R*-**4** to afford *ent*-**10**. Intermediates **10** and *ent*-**10** were oxidized using a two-step Dess–Martin/$NaClO_2$ process[6a] to MOM-protected *trans*-4-hydroxypipecolic acids **11** and *ent*-**11**. The latter was characterized as the methyl ester **13**. The intermediate aldehydes from Dess–Martin oxidation were also subjected to Wittig olefination with $CH_3CH{=}CH{=}PPh_3$[12] to afford compounds **12** as 20/80 mixtures of *E*/*Z* isomers (Scheme 2). Treatment of these mixtures of isomers with I_2/benzene/hν[13] gave an enriched 85/15 mixture of *E*/*Z* isomers. Attempts at removal of the remaining unwanted *Z* isomer by chromatography or through Diels–Alder addition of SO_2[14] were unsuccessful. Full deprotection of *ent*-**12** was accomplished with acetyl chloride in MeOH to afford an 85/15 mixture of *E*/*Z* isomers of (2*S*,4*S*)-(−)-SS20846A hydrochloride in quantitative yield possessing spectral properties and optical rotation in accordance with the literature ($[\alpha]_{22}^{D}$ −9.8 (*c* 0.4, MeOH); lit. for **14**[5b] $[\alpha]_{22}^{D}$ −10.8 (*c* 1.1, MeOH)).[15]

In summary, the chiral building blocks, vinylglycinols [(*R* and *S*)-**4**], were utilized for the synthesis of derivatives of *trans*-4-hydroxypipecolic acids. Key transformations include ring-closing metathesis to construct the piperidine ring and the Prevost reaction to install the 4-hydroxy regio- and stereoselectively as determined by X-ray structural analysis of compounds **7** and **8**. The intermediate **10** was additionally used to synthesize the hydrochloride of the natural product (−)-SS20846A.

Acknowledgements

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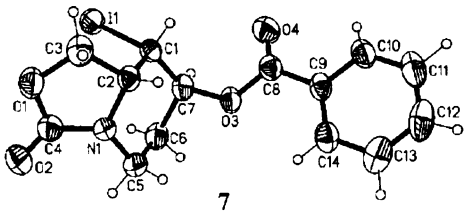

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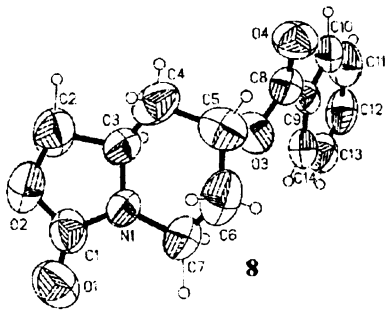

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8. The deprotonation of **4** and alkylation with 4-bromo-1-butene proved extremely problematic. Typically when NaH was used as base a 40% yield of **5** or *ent*-**5** was achieved with a majority of the starting material recovered. The use of *n*-BuLi as base afforded **5** in only 20% yield. Attempts to utilize 4-iodo-1-butene or the triflate of 3-hydroxy-1-butene[9] proved fruitless. Gratifyingly, treatment of the resultant oxazolidinone Na salt with LiI afforded the desired product in high yield.
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15. Selected optical and spectral data: (*S*)-**6** as a clear oil; $[\alpha]_D^{24}$ −123.7 (*c* 1.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.91 (ddd, 1H, J=10.5, 10.5, 5.4 Hz), 5.63 (ddd, 1H J=11.7, 10.5, 1.2 Hz), 4.44 (t_{app}, 1H, J=8.4 Hz), 4.36 (m, 1H), 3.90 (dd, 1H, J=14.1, 7.8 Hz), 3.09–2.99 (m, 2H), 2.42–2.27 (m, 1H), 2.04–1.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 158.02, 127.95, 125.89, 68.10, 52.71, 38.30, 23.64. HRMS (EI) calcd for $C_7H_9NO_2$ 139.0633 (M^+), found 139.0632; *ent*-**7** as white crystals; mp 138–140°C; $[\alpha]_D^{21}$ +50.7 (*c* 1.1, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 8.02 (d, 2H, J=7.2 Hz), 7.62 (t, 1H, J=6.4 Hz), 7.48 (t, 2H, J=7.2 Hz), 5.61 (dt, 1H, J=3.2, 5.6, Hz), 4.52 (bs, 1H), 4.44 (t, 1H, J=8.8 Hz), 4.19 (dd, 1H, J=9.2, 4.8 Hz), 3.95 (dd, 1H, J=14.0, 6.8 Hz), 3.68 (unresolved ddd, 1H, J=16.0, 8.0, 4.8 Hz), 3.34 (ddd, 1H, J=30.0, 13.2, 3.2 Hz), 2.78 (m, 1H), 1.96 (dt_{app}, 1H, J=14.4, 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 165.05, 134.05, 129.88, 129.34, 128.95, 72.14, 69.48, 52.74, 36.47, 31.85, 23.91. HRMS (EI) calcd for $C_{14}H_{14}NO_4$ 260.0922 (M^+–I), found 260.0923; **11** as a clear oil; $[\alpha]_D^{23}$ +22.2 (*c* 0.2, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 8.40–6.80 (bs, 1H), 5.02 & 4.83 (bs overlapping bm, 1H), 4.69 (s, 2H), 4.10 & 3.99 (bd overlapping bd, 1H, J= 12.5, 13.0 Hz), 3.60 (bt_{app}, 1H), 3.37 (s, 3H), 3.07–2.96 (bt overlapping bt, 1H, J=12.0 Hz), 2.52 (bt, 1H, J= 11.0 Hz), 2.16 (s, 1H), 2.09 (bs, 1H), 1.94 (m, 1H), 1.66 (m, 1H), 1.46 & 1.43 (overlapping s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.47b, 156.23, 94.86, 71.29, 55.54, 54.53b, 53.57b, 40.81b, 40.02b, 32.94b, 31.86b, 29.93, 28.52. HRMS (EI) calcd for $C_9H_{15}NO_6$ 233.0899 (M^+–C_4H_8),

found 233.0897; ^{1}H NMR of **14**·HCl (CD_3OD) δ 6.40 (dd, 1H, $J=15.5$, 10.5 Hz), 6.09 (dd, 1H, $J=15.5$, 10.5 Hz), (5.89 unresolved dq, 1H, $J=15.5$, 7 Hz), (5.49 m, 1H), 4.16 (bs, 1H), 4.01 (bt, 1H, $J=8.5$ Hz), 3.38–3.18 (overlapping m, bd, 2H, $J=12.5$ Hz), 1.96–1.76 (overlapping bd, bd, d, d 7H, $J=14.5$, 8.0, 13.5, 11.5 Hz), the *cis*/*trans* isomer displays additional peaks at: δ 6.80 (dd, 1H, $J=10.5$, 4.0 Hz), 6.03 (t_{app}, 1H, $J=11.5$ Hz), 5.68 (m, 1H), 5.60 (dd, 1H, $J=15.5$, 7.5 Hz), 4.09 (bt, 1H); ^{13}C NMR of **14**·HCl (CD_3OD) δ 136.44, 133.24, 130.02, 124.09, 61.15, 52.81, 39.02, 35.62, 28.50, 17.10. HRMS (EI) calcd for $C_{10}H_{17}NO$ 167.1310 (M^+), found 167.1309.