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Versatile chiral synthons for 1,2-diamines: (4*S*,5*S*)- and (4*R*,5*R*)-4,5-dimethoxy-2-imidazolidinones

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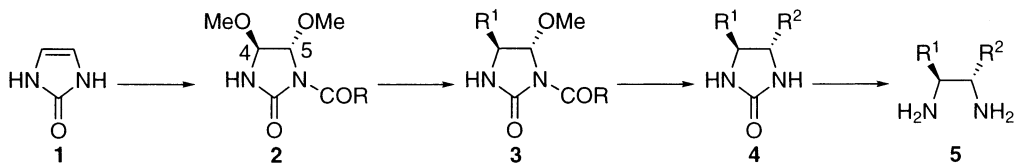
Abstract—(4*S*,5*S*)- and (4*R*,5*R*)-1-Acyl-4,5-dimethoxy-2-imidazolidinone derivatives, which are readily accessible from simple 1,3-dihydro-2-imidazolone heterocycles, represent good candidates for a new class of chiral synthons for use in the preparation of optically active *threo*-diamines such as 2*S*,3*R*- and 3*S*,4*S*-diamino carboxylic acids. © 2001 Elsevier Science Ltd. All rights reserved.

The *vicinal* diamine skeleton is a structural unit found in a substantial number of compounds of biological and medicinal interest,[1] and functions as a chelating ligand for transition metals as well as main group metal complexes.[2] Thus, the use of 1,2-diamines as reliable building blocks in organic synthesis has increased considerably, particularly in the field of catalytic asymmetric synthesis.[1,2] Hence, a versatile route for the chiral synthesis of both unsymmetric and C_2-symmetric 1,2-diamines from simple, unexpensive starting materials would be highly desirable.[3]

The simple heterocycle, 1,3-dihydro-2-imidazolone **1**,[4] which contains *vicinal* amino groups masked with a carbonyl group and an enamine moiety and would be susceptible to various modes of addition reactions, suggests its synthetic potential as a building block for the preparation of 1,2-diamines. In this paper we wish to report on a promising route for an efficient synthesis of optically active 1,2-diamines through the key intermediates, (4*S*,5*S*)- and (4*R*,5*R*)-4,5-dimethoxy-2-imidazolidinones, which are readily accessible from the 2-imidazolone. Both the 4- and 5-methoxy groups on the 2-imidazolidinones **2** may undergo a stepwise and regioselective substitution with organo cuprates, which is fully stereocontrolled by a *vicinal* group, followed by ring opening to give the *threo*-1,2-diamines **5**, as outlined in Scheme 1. It should be noted that the 4-methoxy group is preferentially replaced with organo metals in the presence of Lewis acids, due to the higher stability of acyliminium cation intermediate, which is generated in situ.

Synthesis of (4*S*,5*S*)- and (4*R*,5*R*)-4,5-dimethoxy-2-imidazolidinones (Scheme 2)

The 1,3-diacetyl-2-imidazolone **6**[4] underwent a smooth electrophilic addition of bromine in methylene chloride to give *trans*-4,5-dibromo-2-imidazolidinone **7**, which was methanolyzed to the dimethoxy derivatives in the presence of a tertiary amine. The imidazolidone *rac*-**8** was *N*-acylated with (1*S*,2*R*)-2-methoxy-1-apocamphanecarbonyl chloride (MAC-Cl)[5] followed by deacetylation with Cs_2CO_3 to give the diastereomeric mixture of **9a** and **9b**, of which chromatographic separation on silica gel was unsuccessful. Thus, they were converted to the diastereomeric 1-MAC-4-benzyloxy-5-methoxy derivatives, **10a** and **10b**, by treatment with



Scheme 1.

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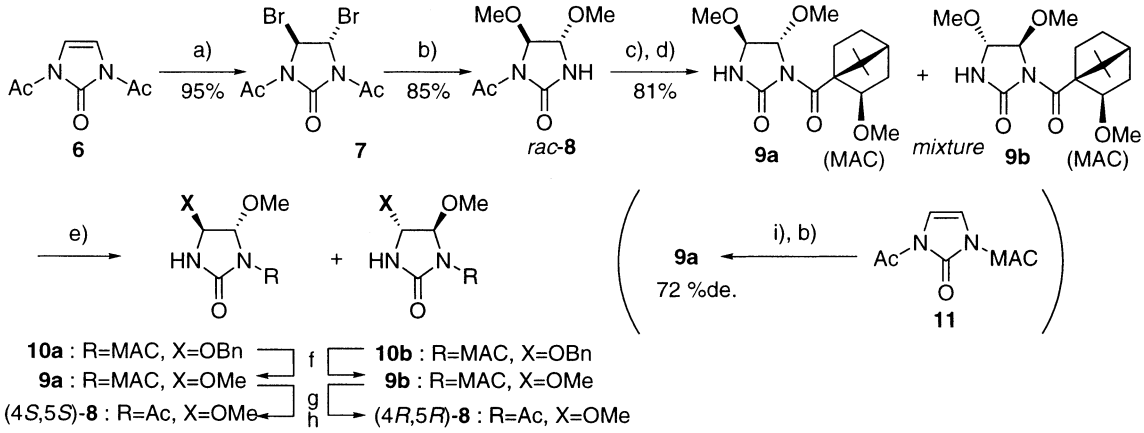


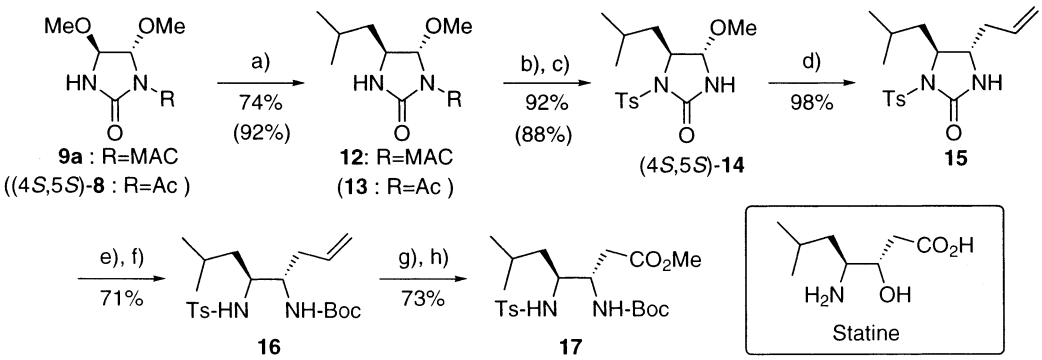
Scheme 2. (a) Br_2, CH_2Cl_2; (b) $^iPr_2NEt$, MeOH; (c) MAC-Cl, NaH, THF; (d) Cs_2CO_3, MeOH, (e) BnOH, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (43% for **10a** and 36% for **10b**); (f) H_2, Pd-black, MeOH; (g) $LiBH_4$, MeOH (87–96%); (h) AcCl, Et_3N, DMAP (82–84%); (i) Br_2, $MeC(OMe)_3$.

$Ph_2CH_2OH/BF_3{\cdot}OEt_2$. The benzyloxy derivatives thus obtained were readily separated by chromatography on silica gel, resulting in the clear-cut separation into the diastereomers **10a** and **10b**,[6] which were reductively debenzylated with H_2/Pd-black in methanol to give quantitative yields of (4*S*,5*S*)- and (4*R*,5*R*)-1-MAC-4,5-dimethoxy-2-imidazolidinones **9a**[7] and **9b**,[7] respectively. On the other hand, treatment of 1-acetyl-3-MAC-2-imidazolone **11** with bromine in trimethyl orthoacetate[8] followed by methanolysis resulted in the diastereoselective formation of **9a** with a moderate selectivity of 72% de. The absolute configuration of diastereomer **9b** was determined by chemical correlation with the authentic (1*R*,1*R*)-1,2-diphenylethylenediamine via its conversion to (4*R*,5*R*)-3-MAC-1-tosyl-4,5-diphenyl-2-imidazolidinone.[9] Subsequent removal of the MAC auxiliary with $LiBH_4$–MeOH, followed by *N*-mono-acetylation, resulted in the smooth formation of 1-acetyl-4,5-dimethoxy-2-imidazolidinones, (4*S*,5*S*)-**8**[10] and (4*R*,5*R*)-**8**,[10] which represent promising chiral synthons for the 1,2-diamines.

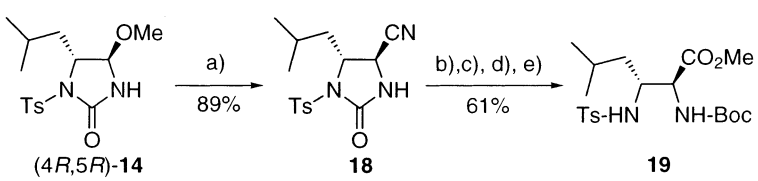
The versatility of the (4*S*,5*S*)- and (4*R*,5*R*)-4,5-dimethoxy derivatives (**8** and **9**) thus obtained was demonstrated by the chiral synthesis of 2,3-diamino and 3,4-diamino carboxylic acids, **17** and **19**, which can be regarded as the diamino analogs of the biologically important amino hydroxy acids, statine[11] and the key component of amastatine,[12] 3-amino-2-hydroxy-5-methylhexanoic acid.

Synthesis of 2,3-and 3,4-diamino acids (Schemes 3 and 4**)**

The (4*S*,5*S*)-1-MAC-4,5-dimethoxy-2-imidazolidinone **9a** was treated with ^{i}BuCu(CN)MgBr/LiCl in the pres-



Scheme 3. (a) $(CH_3)_2CHCH_2MgBr$, CuCN, LiCl, $BF_3{\cdot}OEt_2$, THF; (b) TsCl, BuLi, THF; (c) $PhCH_2SH$, BuLi, THF, (Cs_2CO_3, MeOH for **13**); (d) allylTMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (e) $Ba(OH)_2{\cdot}8H_2O$, EtOH, H_2O; (f) $(Boc)_2O$, Et_3N, CH_2Cl_2; (g) $KMnO_4$, $NaIO_4$, $(CH_3)_2CO$, H_2O; (h) CH_2N_2.



Scheme 4. (a) TMSCN, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (b) HCl, MeOH; (c) $Ba(OH)_2{\cdot}8H_2O$, EtOH, H_2O; (d) $(Boc)_2O$, Et_3N, CH_2Cl_2; (e) CH_2N_2.

ence of $BF_3{\cdot}OEt_2$ at −30°C, resulting in the regioselective replacement of the 4-methoxy group with an isobutyl group with complete retention of configuration. The attack of cuprate toward the acyliminium ion intermediate might be effectively controlled by the *vicinal* methoxy group. Subsequent *N*-sulfonylation with *p*-toluenesulfonyl chloride (Ts-Cl) followed by the removal of the MAC auxiliary with $PhCH_2SLi$ yielded the *N*-Ts derivative (4*S*,5*S*)-**14**. This derivative could also be obtained from compound (4*S*,5*S*)-**8** in yields as given in parenthesis (Scheme 3) by virtually the same procedure as above. Smooth allylation was achieved by treatment with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ to give (4*S*,5*S*)-4-allyl-5-isobutyl-1-tosyl-2-imidazolidinone **15**. The hydrolytic ring-opening with $Ba(OH)_2{\cdot}8H_2O$ followed by *N*-BOC protection yielded the *N*-protected diamine **16**. Oxidative cleavage of the allyl group followed by esterification with diazomethane afforded (3*S*,4*S*)-3-aminodeoxystatine methyl ester **17**,[13] in which the two amino functions were protected with different types of groups.

The (4*R*,5*R*)-2-imidazolidinones, **9b** and (4*R*,5*R*)-**8**, were also successfully employed for the chiral synthesis of (2*S*,3*R*)-2,3-diamino-5-methylhexanoic acid, which represents an amino analog of the key amino acid component of amastatine.

Thus, (4*R*,5*R*)-**14** was converted to (4*S*,5*R*)-4-cyano-5-isobutyl-1-tosyl-2-imidazolidinone **18** by treatment with trimethylsilyl cyanide/$BF_3{\cdot}OEt_2$. Straightforward manipulation including hydrolytic ring-opening and protection gave (2*S*,3*R*)-2,3-diamino-5-methylhexanoic acid **19**[14] in a fully protected form.

The diamino carboxylic acids **17** and **19** thus obtained were thoroughly free from contamination by *erythro*-isomers, as evidenced by spectrographic data. The methodology presented here has applicability to the chiral synthesis of C_2-symmetric 2-imidazolidinone auxiliaries and the 1,2-diamine ligands.

In conclusion, the (4*S*,5*S*)- and (4*R*,5*R*)-1-acyl-4,5-dimethoxy-2-imidazolidinones, which are readily accessible in stable, crystalline forms from the simple heterocycle, 1,3-dihydro-2-imidazolone, represent good candidates for chiral synthons for use in the chiral preparation of synthetically, biologically and medicinally important 1,2-diamines as well as 2-imidazolidinone auxiliaries.[15]

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6. The ratio of R_f values for diastereomers **10a** and **10b** on 0.2 mm silica gel plates (Merck, Kieselgel $60F_{254}$) with the mixture of dichloromethane and ethyl acatate (4:1) as a developing solvent is 1.2.
7. Compound **9a**: mp 84.5–85.0°C (from hexane); $[\alpha]_D^{28}$ −64.8° (*c* 1.00, $CHCl_3$). Compound **9b**: mp 113.5–114.0°C (from hexane); $[\alpha]_D^{31}$ +33.0° (*c* 1.00, $CHCl_3$).
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9. ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, 2H, $J=8.6$ Hz), 7.37–7.38 (m, 3H), 7.26–7.29 (m, 5H), 7.15–7.17 (m, 4H), 5.19 (d, 1H, $J=1.8$ Hz), 5.05 (d, 1H, $J=1.8$ Hz), 4.68 (dd, 1H, $J=4.0$, 7.6 Hz), 3.12 (s, 3H), 2.41 (s, 3H), 2.27–2.38 (m, 1H), 1.59–1.82 (m, 5H), 1.10–1.16 (m, 1H), 1.10 (s, 3H), 0.97 (s, 3H).
10. Compound (4*S*,5*S*)-**8**: mp 61–62°C (from hexane); $[\alpha]_D^{25}$ −68.0° (*c* 1.0, $CHCl_3$). Compound (4*R*,5*R*)-**8**: mp 61–62°C (from hexane); $[\alpha]_D^{25}$ +68.0° (*c* 1.0, $CHCl_3$).
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13. Compound **17**: mp 41.5–42.0°C (from hexane); $[\alpha]_D^{28}$ −40.0° (*c* 0.70, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, 2H, $J=7.9$ Hz), 7.30 (d, 2H, $J=7.9$ Hz), 4.91 (br d, 1H), 4.85 (br d, 1H), 4.06 (m, 1H), 3.69 (s, 3H), 3.48–3.46 (m, 1H), 2.72–2.70 (m, 1H,), 2.55–2.43 (m, 1H), 1.70 (s, 3H), 1.56–1.32 (m, 2H), 1.41 (s, 9H), 0.84–0.78 (m, 1H), 0.69 (d, 3H, $J=6.1$ Hz), 0.65 (d, 3H, $J=6.1$ Hz).
14. Compound **19**: $[\alpha]_D^{25}$ +62.0° (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, 2H, $J=7.9$ Hz), 7.30 (d, 2H, $J=7.9$ Hz), 5.31 (d, 1H, $J=8.5$ Hz), 4.63 (br, 1H), 4.31 (br, 1H), 3.79–3.78 (m, 1H), 3.71 (s, 3H), 2.43 (s, 3H,), 1.55–1.54 (m, 1H), 1.43 (s, 9H), 1.36–1.31 (m, 1H), 1.02–0.99 (m, 1H), 0.77 (d, 3H, $J=6.7$ Hz), 0.68 (d, 3H, $J=6.7$ Hz).
15. Facile conversion of the chiral synthons **8** and **9** into C_2-4,5-disubstituted 2-imidazolidinones and C_2-1,2-diamines will be the subject of a separate paper.