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Tetrahedron Letters 45 (2004) 8073–8077
Tetrahedron Letters

# Enantioselective synthesis of (1*S*,2*S*)-1,2-di-*tert*-butyl and (1*R*,2*R*)-1,2-di-(1-adamantyl)ethylenediamines

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Received 12 March 2004; revised 17 August 2004; accepted 27 August 2004
Available online 17 September 2004

**Abstract**—An enantioselective synthesis of sterically congested 1,2-di-*tert*-butyl and 1,2-di-(1-adamantyl)ethylenediamines has been developed. Thus, diastereomerically pure *trans*-1-apocamphanecarbonyl-4,5-dimethoxy-2-imidazolidinones **6** and **7** were successfully prepared by optical resolution of (±)-*trans*-4,5-dimethoxy-2-imidazolidinone using apocamphanecarbonyl chloride (MAC-Cl) followed by stereospecific and stepwise substitution of the dimethoxyl groups using *tert*-butyl or 1-adamantyl cuprates to provide (4*S*,5*S*)-4,5-di-*tert*-butyl and (4*R*,5*R*)-4,5-di-(1-adamantyl)-2-imidazolidinones **12** and **15**, respectively. Furthermore, *N*-acetyl 4,5-di-*tert*-butyl and 4,5-di-(1-adamantyl)-2-imidazolidinones **16a**,**b** were enantioselectively deacetylated using a catalytic oxazaborolidine system to provide enantiopure 1-*p*-tolylsulfonyl-4,5-di-*tert*-butyl-2-imidazolidinones **12** and **19** and 1-*p*-tolylsulfonyl-4,5-di-(1-adamantyl)-2-imidazolidinones **18** and **20**, respectively. Finally, *N*-*p*-tolylsulfonyl-2-imidazolidinones **12** and **15** were treated with 30 equiv of $Ba(OH)_2{\cdot}8H_2O$ to achieve ring cleavage and to provide (1*S*,2*S*)-1,2-di-*tert*-butylethylenediamine **3** and (1*R*,2*R*)-1,2-di-(1-adamantyl)ethylenediamine **4**.


The vicinal 1,2-diamine functional group represents the structural unit of a number of bioactive compounds such as peptide antibiotics, vitamin H, antitumor agents, and opioid receptor agonists.[1] In addition, 1,2-diamines function as chiral building blocks[2] and bidentate ligands[3] for transition metals in asymmetric synthesis. Many reactions have also been described using these diamines as chiral auxiliaries[2] and as aldehyde protecting groups.[4] Most of these applications generally use the 1,2-diphenylethylenediamine **1** or 1,2-diaminocyclohexane **2** frameworks whose preparations have been fully described (Fig. 1).[5] However, in our projects we were interested in new, congested and benzylic-proton free chiral 1,2-diamines such as 1,2-di-*tert*-butyl ethylenediamine **3** and 1,2-di-(1-adamantyl)ethylenediamine **4**. There are, however, very few methods available for the synthesis of vicinal diamines from readily available starting materials. The addition of Grignard or zinc reagents to the chiral 1,2-bis-imine precursor derived from glyoxal and (*S*)- or (*R*)-methylbenzylamine, followed by hydrogenolysis to remove the phenylethyl group, has been shown to be one of two general methods for preparation of these compounds.[6] The second method involves the coupling of nitriles or *N*-(trimethylsilyl)imines promoted by $NbCl_4(THF)$.[7] These methods suffer from the lack of stepwise additions and hence, yield products usually of $C_2$-symmetric 1,2-diamines. Hence, a versatile route for the chiral synthesis of both unsymmetric and $C_2$-symmetric 1,2-diamines from simple, inexpensive starting materials is highly desirable.

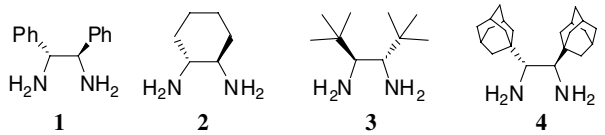


**Figure 1.** $C_2$-symmetric vicinal diamines.

In previous articles[8] we reported that (4*S*,5*S*)- and (4*R*,5*R*)-1-apocamphanecarbonyl-4,5-dimethoxy-2-imidazolidinones (DMIm)[8b] **6** and **7** were good candidates for chiral synthons for use in the synthesis of biologically important 1,2-diamino acids. This strategy was based upon a stereodefined introduction of easily replaceable groups to the 4,5-olefinic moiety of

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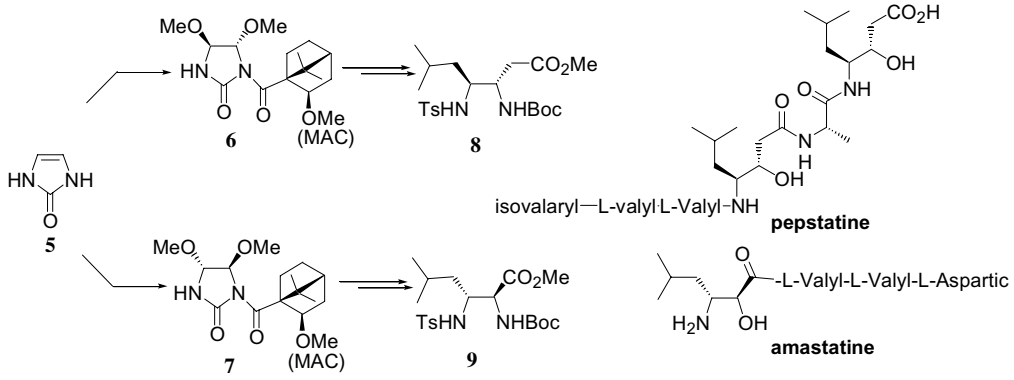
doi:10.1016/j.tetlet.2004.08.164

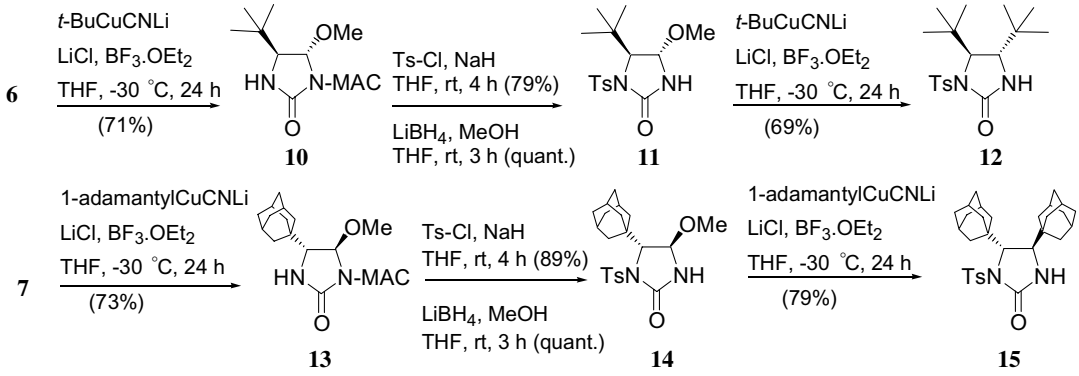
2-imidazolone **5** in the presence of a chiral auxiliary to give versatile chiral synthons, followed by stereospecific and stepwise substitution, to achieve a chiral synthesis of a wide variety of 1,2-diamino acids after hydrolytic cleavage of the imidazolidinone ring. Thus, (4*S*,5*S*)-1-apocamphanecarbonyl-4,5-dimethoxy-2-imidazolidinone **6** was enantioselectively converted into the diamino analogue **8**, the key component of pepstatine, 4-amino-3-hydroxy-6-methylheptanoic acid. Pepastatine has potent pepsin inhibition activity.[9] Furthermore, (4*R*,5*R*)-1-apocamphanecarbonyl-4,5-dimethoxy-2-imidazolidinone **7** was converted into the diamino analogue **9**, the key component of amastatine,[10] 3-amino-2-hydroxy-5-methylhexanoic acid. Amastatine is a potent aminopeptidase A inhibitor (Scheme 1).

In this letter we describe the synthesis of chiral, sterically congested vicinal 1,2-diamines using our well defined, efficient, and stereocontrolled procedures. The diastereomeric pure *trans*-4,5-dimethoxy-1-apocamphanecarbonyl-2-imidazolidinones **6** and **7**, which were prepared from **5**,[11] were treated with *tert*-butyl or 1-adamantyl cuprates (RCu(CN)MgBr/LiCl) in the presence of $BF_3{\cdot}OEt_2$ at −30 °C, to furnish **10** and **13**. The formation of these products can be explained by the *regio*- and *trans*-stereoselective replacement of the methoxyl group with *tert*-butyl or 1-adamantyl groups. The *trans*-attack of cuprate to the acyliminium ion intermediate, which is generated in situ, might be effectively controlled by the vicinal methoxyl group. The subsequent *N*-protection of **10** and **13** with *p*-tolylsulfonyl chloride, followed by the removal of the MAC auxiliary with $LiBH_4$/MeOH yielded *N*-*p*-tolylsulfonyl derivatives **11** and **14**, respectively. Each product was treated with a second equivalent of organocuprate, as described above, to give the sterically congested (4*S*,5*S*)-*trans*-1-*p*-tolylsulfonyl-4,5-di-*tert*-butyl-2-imidazolidinone **12** and (4*R*,5*R*)-*trans*-1-*p*-tolylsulfonyl-4,5-di-(1-adamantyl)-2-imidazolidinone **15** (Scheme 2).

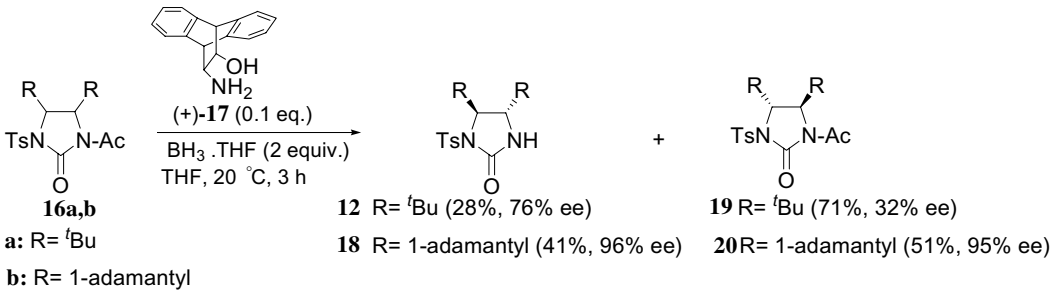
An alternative route towards the congested *trans*-4,5-disubstituted 2-imidazolidinones **12** and **15** was investigated by the kinetic resolution of the *N*-acetyl-derivatives **16a**,**b** in the presence of catalytic amount of oxazaborolidine.[12] The *N*-acetyl-derivatives **16a**,**b** smoothly underwent enantioselective deacetylation on treatment with borane (2 equiv) in the presence of aminoalcohol (+)-**17** (0.1 equiv). The *trans*-4,5-di-(1-adamantyl)-2-imidazolidinone showed promising enantioselective deacetylation with excellent chemical and optical yields. These results might be explained by the high steric bulkiness of the adamantyl compared with the *tert*-butyl moiety. As is clear from Scheme 3, the oxazaborolidine system predominantly deacetylated[12c] the (4*S*,5*S*)-1-acetyl-3-*p*-tosyl-4,5-di-*tert*-butyl-2-imidazolidinone ***SS*-16a** and (4*S*,5*S*)-1-acetyl-3-*p*-tosyl-4,5-




**Scheme 1.** The utility of DMIm for the synthesis of pepstatine and amastatine analogues.




**Scheme 2.** Synthesis of sterically congested 2-imidazolidinones **12** and **15**.




**Scheme 3.** Enantioselective deacetylation of (±)-*trans*-1-acetyl-*p*-tolylsulfonyl-2-imidazolidinones.

di-(1-adamantyl)-2-imidazolidinone ***SS*-16b** (Figs. 2 and 3). The imidazolidinones formed were readily separable by chromatography on silica gel and were purified by recrystallization to give enantiomers **12** and **18**–**20** (Scheme 3). The stereochemistry was determined by comparison with authentic samples obtained as shown in Scheme 2.

The liberation of the chiral diamines depends on hydrolytic ring cleavage of the 2-imidazolidinone using alkali.

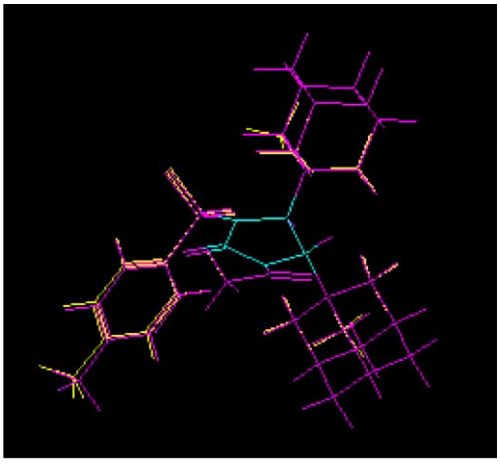


**Figure 2.** Superimposition of the lowest energy conformer of compounds ***SS*-16a** (yellow) and ***SS*-16b** (pink), showing the close match of the 2-imidazolidinone rings (cyan) and slight differences in the *p*-tolylsulfonyl geometry and the significant steric bulkiness of the 1-adamantyl core.

Our trial to liberate the 1,2-diamine from the unprotected *trans*-4,5-di-*tert*-butyl or *trans*-4,5-di-(1-admantyl)-2-imidazolidinones with 30–50 equiv of $Ba(OH)_2 \cdot 8H_2O$ was unsuccessful. However, treatment of the *N*-*p*-tolylsulfonyl-2-imidazolidinones **12** and **15** with 30 equiv of $Ba(OH)_2 \cdot 8H_2O$ in a sealed glass tube at 140 °C for 3 days afforded *N*-*p*-tolylsulfonyl-1,2-diamines **21** and **23**, respectively. The $C_2$-symmetric diamines were obtained either by refluxing **21** or **23** with *p*-tolylsulfonyl chloride in the presence of NaH and THF as solvent to give diprotected amines **22** and **24**[13] or by removal of the *p*-tolylsulfonyl groups by titration with freshly prepared sodium naphthalide solution[14] at −78 °C to give the unprotected diamines **3** and **4**[15] (Scheme 4).

In an attempt to gain a better insight on the molecular structures of the most preferentially deacetylated enantiomers ***SS*-16a** and ***SS*-16b** and the difference in their steric bulkiness, which controls the enantioselective deacetylation according to Scheme 3, conformational analysis of these enantiomers was performed by use of the MM2[16] force field as implemented in Chem3D.[17] The starting atomic coordinates were obtained from the X-ray data of the structurally related molecule; (±)-1-acetyl-4,5-di-*tert*-butyl-2-imidazolidinone.[8c] Full geometry optimization was carried out with semi-empirical AM1[18] as implemented in G98W[19] running on a PC. Calculation of the isopotential molecular surface was performed with Hyperchem 5.1.[20] The most stable conformers of enantiomers ***SS*-16a** and ***SS*-16b** resulting from computational chemistry analysis were superimposed in order to reveal the similarities and differences

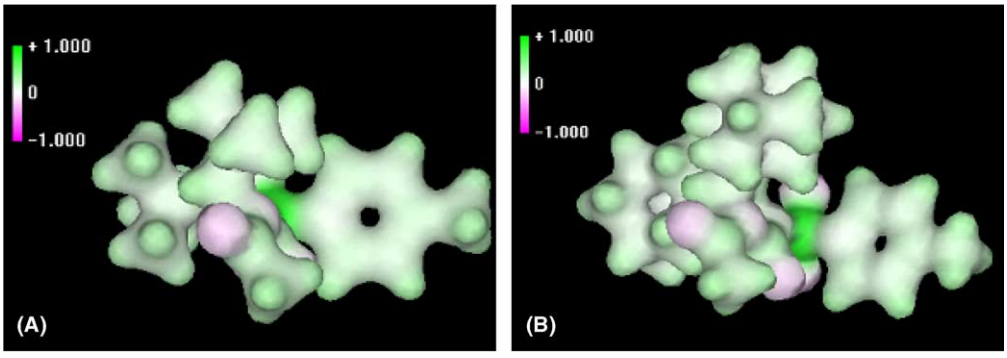
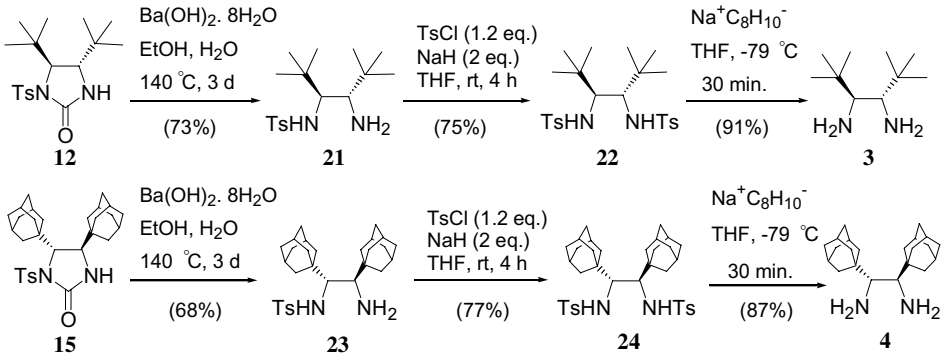



**Figure 3.** Electrostatic potential isosurface of the lowest energy conformer of compounds ***SS*-16a** (left) and ***SS*-16b** (right), negative region colors are pink and positive region colors are green.




**Scheme 4.** Hydrolytic pathway to the vicinal diamines.

in structures (Fig. 2). The strategy of overlay fit was to match two imidazolidinone rings and examine any spatial differences between the atoms of the *tert*-butyl and 1-adamantyl groups. The results showed that atoms of the tosyl groups occupy slightly different spatial positions relative to the plane of the 2-imidazolidinones and closely match the *tert*-butyl and 1-adamantyl groups with RMS values 0.01 Å (Fig. 2). An electrostatic isopotential isosurface was carried out for the lowest energy conformers of ***SS*-16a** and ***SS*-16b**, respectively, to examine the similarity in electronic and conformational properties. Figure 3 presents the electrostatic potentials (ESP) mapped on the isosurface of ***SS*-16a** and ***SS*-16b**, pink colors indicate negative ESP regions and green colors indicate positive ESP regions. Comparison of the ESP of ***SS*-16a** with ***SS*-16b** shows their electronic similarity and steric crowding of the aliphatic cage-like core of the 1-adamantyl moiety compared with that of *tert*-butyl group.

In conclusion, we have successfully developed an efficient synthesis of 1,2-diamino-1,2-di-*tert*-butylethane and of 1,2-diamino-1,2-di-(1-adamantyl)ethane from *trans*-4,5-dimethoxy-2-imidazolidinones by optical resolution using apocamphanecarbonyl chloride (MAC-Cl) or catalytic resolution using an oxazaborolidine. Subsequent stereospecific and stepwise substitution of dimethoxyl groups using *tert*-butyl or 1-adamantyl cuprates and then ring cleavage using 30 equiv of $Ba(OH)_2 \cdot 8H_2O$ to provide chiral 1,2-di-*tert*-butyl and 1,2-di-(1-adamantyl)ethylenediamines, which represent potential precursors for biologically active platinum and palladium complexes.[1a]

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13. Compound (*S*,*S*)-**22**: (75%), mp 193–194 °C (hexane/$CH_2Cl_2$); $[\alpha]_D^{24}$ −40.7 (*c* 1.00, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 7.72–7.70 (d, 4H, $J = 8.5$ Hz), 7.29–7.27 (d, 4H, $J = 8.5$ Hz), 4.46–4.44 (d, 2H, $J = 7.9$ Hz, NH exchangeable with $D_2O$), 3.63–3.61 (d, 2H, $J = 7.9$ Hz), 2.43 (s, 6H), 0.85 (s, 18H); Anal. $C_{24}H_{36}N_2O_4S_2$: calcd CHN: 59.97, 7.55, 5.83, found CHN: 60.00, 7.58, 5.86. Compound (*R*,*R*)-**24**: (77%), mp 210–211 °C (hexane/$CH_2Cl_2$); $[\alpha]_D^{28}$ −9.5 (*c* 1.00, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 7.77–7.76 (d, 4H, $J = 8.6$ Hz), 7.23–7.22 (d,

4H, $J = 8.6$ Hz), 4.89–4.87 (d, 2H, $J = 7.9$ Hz, NH exchangeable with $D_2O$), 3.68–3.66 (d, 2H, $J = 7.9$ Hz), 2.44 (s, 6H), 2.00 (s, 4H), 1.95–1.44 (m, 26H). Anal. $C_{36}H_{48}N_2O_4S_2$: calcd CHN: 67.89, 7.60, 4.40, found CHN: 67.50, 7.78, 4.28.

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15. Compound (*S*,*S*)-**3**: yellow oil (91%); $[\alpha]_D^{26}$ +3.9 (*c* 1.50, $CH_2Cl_2$);[21] $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 3.21 (s, 4H), 2.70 (s, 2H), 0.90 (s, 18H). Compound (*R*,*R*)-**4**: colorless oil (87%); $[\alpha]_D^{29}$ −19.6 (*c* 1.00, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 2.91 (s, 4H), 2.60 (s, 2H), 1.97 (s, 4H), 1.66–1.37 (m, 26H).
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