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Asymmetric Synthesis of Intermediates for Otamixaban and Premafloxacin by the Chiral Ligand-Controlled Asymmetric Conjugate Addition of a Lithium Amide

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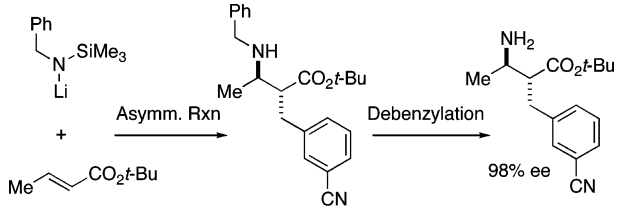

A chiral ligand-controlled conjugate addition reaction of lithium benzyl(trimethylsilyl)amide with *tert*-butyl enoates gave the corresponding lithium enolates that were then treated with electrophiles, giving *anti*-alkylation products with high ee up to 98%. The benzyl group on the amino nitrogen was removed by the oxidation of secondary amines to imines and subsequent transoximation to give 3-aminoalkanoates in good yields. The products are the possible key intermediates of otamixaban and premafloxacin.

Chiral β-amino acids are the established critical skeleton unit of biologically potent peptidic natural products,[1] as well as the medicinally important class of nonpeptidic β-lactams[2] and pharmaceuticals.[3] Among several strategies for the synthesis of chiral β-amino acids,[4] the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carboxylic acid derivatives is one of the most attractive and versatile methods, as has been shown by the reactions using chiral amine nucleophiles,[5,6] chiral enoates,[7] and chiral catalysts.[8] As part of our studies directed toward the development of asymmetric conjugate addition reactions[9,10] of lithiated nucleophiles,[11,12] we have been engaged in the asymmetric conjugate addition of nitrogen nucleophiles to enoates providing chiral β-amino acid equivalents.[13] Our methodology relies on the chiral ligand-mediated asymmetric

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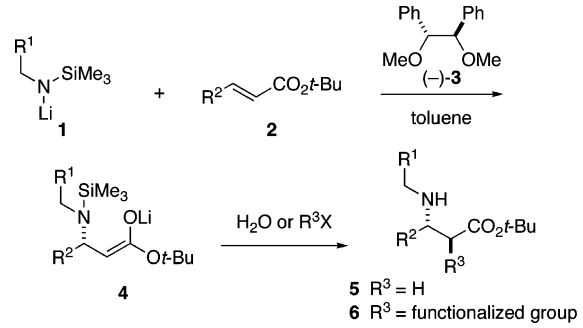
SCHEME 1. Asymmetric Conjugate Amination−Protonation or Alkylation Sequence



conjugate addition[14] of lithium arylmethyl(trimethylsilyl)amides **1** (R^1 = Ar)[15a,b] or allyl(trialkylsilyl)amides **1** (R^1 = CH═CH_2)[15c] to acyclic and cyclic enoates **2**, giving the corresponding *β*-alkylaminoalkanoates **5** in high enantioselectivity by the protonation of enolates **4** (Scheme 1). The potential of this asymmetric conjugate addition lies on the sequential alkylation of enolates **4** to give **6**, because the asymmetric construction of two bonds is possible in a one-pot operation. For visualization of this possibility we selected otamixaban **7**[3bc] and premafloxacin **9**[16] as our targets, because *anti*-3-amino-2-substituted butanoates **8** and **10** are the established synthetic intermediates (Figure 1). Two problems emerged for this purpose. First is the diastereoselective *anti*-alkylation of enolates **4** to give *anti*-**6**. The second is the development of the new methodology for the removal of the *N*-arylmethyl group with cyanobenzyl and allyl groups (R^3) intact in **6**, because hydrogenolysis is the standard protocol for the removal of the *N*-arylmethyl group, which would give undesired reduction products (Scheme 2). We describe herein that the asymmetric conjugate addition of lithium benzyl(trimethylsilyl)amide **1a** (R^1 = Ph) and subsequent alkylation gave enantio- and diastereoselectively *anti*-**6** with extremely high ee. Oxidation of secondary amines **6** to imines **12** and subsequent transoximation successfully gave **13** (Scheme 2). The process provided a short step route to the possible intermediates for otamixaban **7**[3bc] and premafloxacin **9**.[16]

Sequential Conjugate Amination and Alkylation. The advantage of chiral ligand **3**-controlled conjugate addition of a lithium amide **1** to enoates **2** is the formation of reactive lithium enolates **4** with either absolute configuration depending on the use of (−)- or (+)-**3**. The alkylation of an enolate **4** with an electrophile gives 3-benzylamino-2-substituted alkanoates **6** in one pot (Scheme 3).[17] Thus, successive treatment of crotonate **2a** with **1a**-(+)-**3** in toluene at −78 °C for 0.5 h and, after addition of a mixture of HMPA (10 equiv) and THF, with 3-cyanobenzylbromide at −78 °C for 1 h gave a separable mixture of *anti*-**6a** with 98% ee in 84% isolated yield and *syn*-isomer (ee % was not able to be determined) in 15% yield. Treatment of **2a** with **1a**-(−)-**3** and subsequently with allyl bromide gave a 89:11 mixture of *anti*- and *syn*-**6b** (97% ee and 96% ee, vide infra) in quantitative yield. The reaction of cinnamate **2b** was much more *anti*-selective to afford *anti*-**6c** with 92% ee in 97% yield without formation of *syn*-isomer.

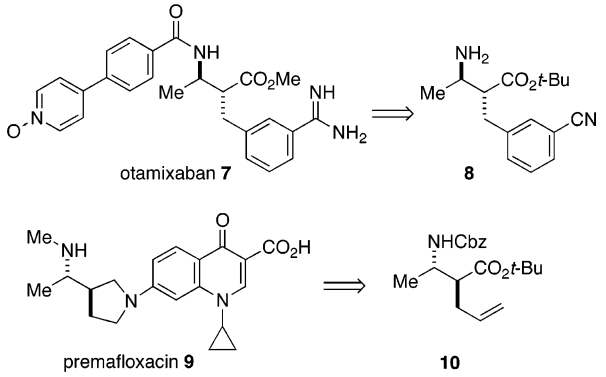
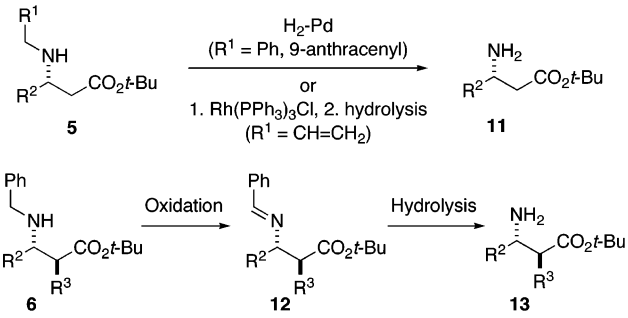


FIGURE 1. Key synthetic intermediates for otamixaban and premafloxacin.

SCHEME 2. Synthesis of Primary Amines by Oxidation and Hydrolysis



The preferential *anti*-alkylation of **4** with an electrophile leads to the plausible model for this diastereoselective alkylation step (Figure 2). Thus, the bottom face approach of an electrophile on a six-membered chelate **A**[18,19] is the preferred axial attack of an electrophile to afford *anti*-**6**. The top-face attack of an electrophile in **A** is unfavorable in the light of equatorial attack as well as steric interference by an pseudoaxial R^2 moiety,

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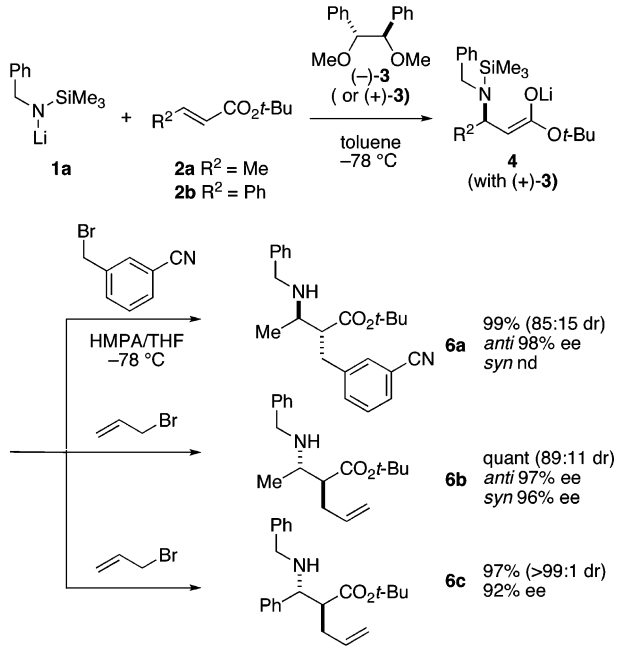
SCHEME 3. Asymmetric Conjugate Amination and Alkylation Giving *anti*-6



suggesting that the bulkiness of R^2 is one of the factors determining diastereoselectivity. Conformation **B** is not the major one because of steric hindrance between R^2 and substituents on the amine nitrogen. This analysis is in accordance with the fact that *anti*-**6c** (R^2 = Ph) was produced in almost perfect *anti*-selectivity, although *anti*-**6a** and *anti*-**6b** (R^2 = Me) were produced in slightly less diastereoselectivity.

Regioselective Oxidation to an Imine and Transoximation for the Removal of a Benzyl Group on the Amine Nitrogen. For the removal of a benzyl group on the nitrogen in **6**, the usual hydrogenolysis protocol is not applicable because of the presence of such sensitive cyanobenzyl or allyl groups. This problem was circumvented by developing regioselective formation of an imine and subsequent transoximation to a primary amine (Scheme 4).[20] N-Chlorination of **5a**, prepared by the protonation of **4**, with NCS in dichloromethane at −20 °C for 0.5 h gave **14** quantitatively. Dehydrochlorination of **14** with DBU[21] in toluene at room temperature for 24 h gave a 92:8 mixture of a desired imine **15** and a undesired enamine **16**. The mixture was then treated with hydroxylamine hydrochloride[22] in aqueous THF at room temperature for 15 min to give a primary amine **11a** in 55% overall yield from **5a**. Regioselective imine formation was greatly improved by treatment with commercially available bulky 6-(dibutylamino)-1,8-diazabicyclo-[5.4.0]undec-7-ene (DBADBU)[23] as a base in toluene to give preferentially **15** in the ratio of 97:3. Transoximation gave **11a**

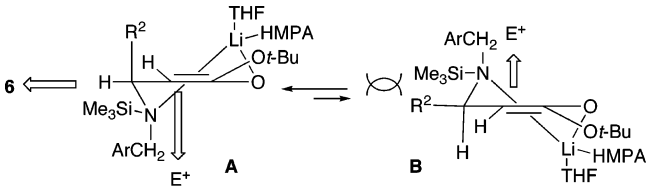
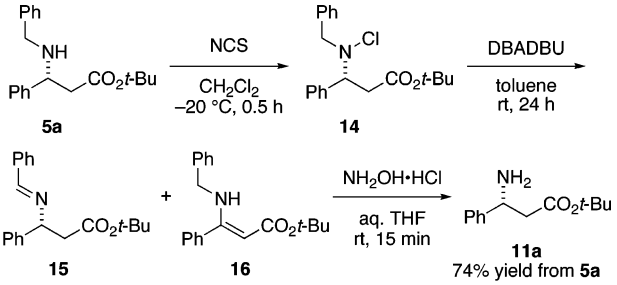
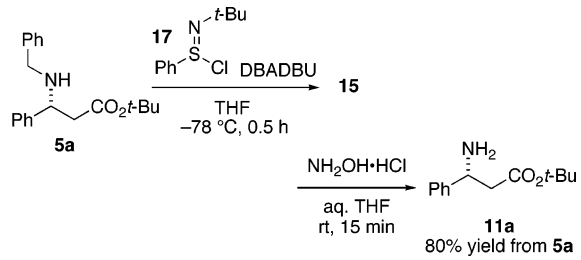


FIGURE 2. Diastereoselective alkylation of enolates **4**.

SCHEME 4. N-Chlorination, Dehydrochlorination, and Transoximation



SCHEME 5. Oxidation and Transoximation



in 74% overall yield. Direct imine formation was also possible by using *N-tert*-butylbenzensulfimidoyl chloride **17**[24] and DBADBU in THF at −78 °C for 0.5 h, and subsequent transoximation gave **11a** in 80% yield (Scheme 5). It is also important to note that no racemization was observed in these transformations of **5a** to **11a**.

Asymmetric Synthesis of Otamixaban and Premafloxacin Key Intermediates. By the chlorination-dehydrochlorination-transoximation protocol for **5a**, *anti*-**6a** was successfully converted to a primary amine **8** in 69% overall yield (Scheme 6). It is also noteworthy that conversion of *anti*-**6a** to **8** was possible in two steps by using **17**-DBU for an imine synthesis and subsequent transoximation giving **8** in 64% yield. The relative and absolute configuration of **8** was unambiguously determined by converting to β-lactam **20**[18] with the established stereochemistry (Scheme 7). Acylation of **8** with **18** gave **19**[3b,c] quantitatively (54% four-step yield from *tert*-butyl crotonate **2a**), the promising synthetic intermediate of otamixaban **7** (Figure 1).

The 89:11 mixture of *anti*- and *syn*-**6b** was treated with NCS to give a chromatographically separable *anti*- and *syn*-*N*-chlorides with 97% and 96% ee in 84% and 6% isolated yields, respectively (Scheme 8). The regioselective dehydrochlorination of *anti*-chloroamine and subsequent transoximation protocol gave the corresponding primary amine, which was then converted to **10** in 58% overall yield. Treatment of an *anti*- and *syn*-mixture of **6b** with **17**-DBADBU and transoximation followed by benzyloxycarbonylation gave a 88:12 mixture of

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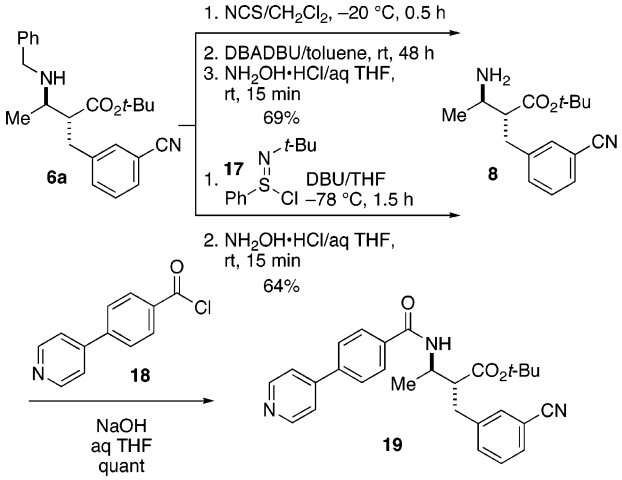
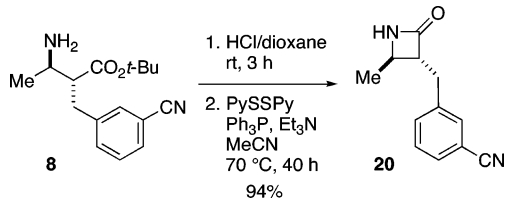
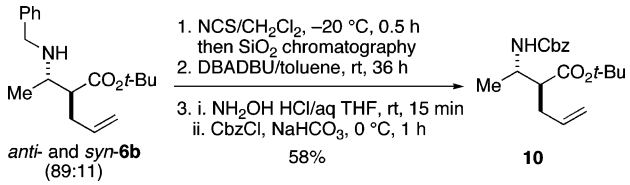
SCHEME 6. Debenzylation of 6a and Acylation Giving 19



SCHEME 7. Confirmation of Stereochemistry of 8



SCHEME 8. Conversion of 6b to 10



anti- and *syn*-**10** in 75% yield. Premafloxacin **9** has been already synthesized starting from **10**.[16]

Sequential treatment of enoates with lithium benzyl(trimethylsilyl)amide in the presence of a chiral diether ligand **3** and then with electrophiles gave preferentially *anti*-3-benzylamino-2-substituted alkanoates with high enantiomeric purity. Oxidation of amines to imines followed by transoximation was developed as a new protocol for the removal of a benzyl group on nitrogen, providing the primary amines with hydrogenation sensitive groups intact. This process was applicable to the short step asymmetric synthesis of the possible key intermediates of the pharmaceuticals otamixaban and premafloxacin.

Experimental Section[25]

(−)-*tert*-Butyl (2*R*,3*R*)-2-(3-Cyanobenzyl)-3-(benzylamino)-butanoate (*anti*-6a). Under Ar atmosphere, to a solution of lithium *N*-benzyl-*N*-trimethylsilylamide (3.0 mmol) and (+)-**3** (873 mg, 3.6 mmol) in toluene (14 mL) was added *tert*-butyl crotonate **2a** (1.0 mmol) at −78 °C, and the mixture was stirred at −78 °C for 0.5 h. After addition of THF (12 mL) and HMPA (1.04 mL, 10 mmol), *m*-cyanobenzylbromide (702 mg, 3.6 mmol) in THF (4 mL) was added, and the whole was stirred at −78 °C for 1 h. After successive addition of saturated ammonium chloride (3.0 mL) and saturated $NaHCO_3$ (10 mL), the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over sodium sulfate. Concentration and silica gel column chromatography (AcOEt/hexane = 1/10−1/4) gave *anti*-**6a** (306 mg, 84%) of $[\alpha]^{25}_D$ −0.8 (*c* 4.82, $CHCl_3$) and *syn*-isomer (55 mg, 15%) of $[\alpha]^{25}_D$ −36.0 (*c* 0.15, $CHCl_3$). The ee of *anti*-**6a** was determined to be 98% ee by ^{1}H NMR (C_6D_6) using (*S*)-(−)-1,1′-bi-2,2′-naphthol as a chiral shift reagent. ^{1}H NMR ($CDCl_3$) δ: 1.16 (3H, d, J = 6.7), 1.31 (9H, s), 1.44 (1H, brs), 2.62 (1H, ddd, J = 5.8, 7.7, 7.7), 2.90 and 2.93 (each 1H, dd, J = 7.7, 13.4), 2.97 (1H, dq, J = 5.8, 6.7), 3.73 and 3.90 (each 1H, d, J = 13.1), 7.24−7.48 (9H, m). ^{13}C NMR ($CDCl_3$) δ: 17.6 (CH_3), 27.9 (CH_3), 33.3 (CH_2), 51.1 (CH_2), 53.5 (CH), 53.8 (CH), 80.8 (C), 112.2(C), 118.9 (C), 127.0 (CH), 128.2 (CH), 128.4 (CH), 129.0 (CH), 129.9 (CH), 132.6 (CH), 133.7 (CH), 140.5 (C), 141.8 (C), 173.1 (C). IR (neat): 3337, 2230, 1720, 1153 cm^{-1}. MS *m*/*z*: 364 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O_2$: C 75.79, H 7.74, N 7.69. Found: C 75.74, H 7.76, N 7.64.

(+)-*tert*-Butyl (2*R*,3*R*)-2-(3-Cyanobenzyl)-3-aminobutanoate (8) by Chlorination, Dehydrochlorination, and Transoximation. A solution of *anti*-**6a** (142 mg, 0.39 mmol) and NCS (156 mg, 1.17 mmol) in methylene chloride (13 mL) was stirred for 0.5 h at −20 °C and was then washed with brine and dried over sodium sulfate. Concentration and silica gel column chromatography (AcOEt/hexane = 1/10) gave a chloroamine (145 mg). The solution of the chloroamine (76 mg, 0.19 mmol) and 6-(dibutylamino)-1,8-diazabicyclo[5.4.0]undec-7-ene (DBADBU**)** (562 mg, 2.0 mmol) in toluene (8 mL) was stirred at room temperature for 48 h, and successively washed with 1 N HCl and brine and dried over sodium sulfate. Concentration gave a crude imine, which was then treated with NH_2OH·HCl (40 mg, 0.57 mmol) in 1 mL of 50% aqueous THF at room temperature for 15 min. After addition of 10% HCl, the whole was washed with AcOEt. The aqueous layer was treated with potassium carbonate until pH 10 and then extracted with ether. The organic layer was dried over potassium carbonate. Concentration and silica gel column chromatography (AcOEt) gave **8** (42 mg) of $[\alpha]^{25}_D$ +35.6 (*c* 1.02, $CHCl_3$) in 69% yield from *anti*-**6a**. ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, d, J = 6.4), 1.30 (9H, s), 1.47 (2H, brs), 2.49 (1H, m), 2.88 (1H, dd, J = 5.7, 13.8), 2.92 (1H, dd, J = 10.7, 13.8), 3.13 (1H, m), 7.36−7.51 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 22.0, 27.9, 35.0, 48.9, 55.8, 81.1, 112.3, 118.9, 129.1, 130.1, 132.6, 133.7, 141.1, 173.0. IR (neat): 3379, 2230, 1717. HRMS *m*/*z*: Calcd for $C_{16}H_{22}N_2O_2$: 274.1681. Found: 274.1679.

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Supporting Information Available: Experimental procedure, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The ^{13}C peak multiplicity assignments were made based on DEPT.