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Asymmetric Synthesis of Maraviroc (UK-427,857)

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Abstract: The asymmetric synthesis of Maraviroc (UK-427,857), a chemochine receptor 5 (CCR-5) receptor antagonist, based on an expeditious organocatalytic enantioselective assembly of the chiral β-amino aldehyde key fragment is presented. The reactions were performed on a gram-scale and allow for the rapid construction of new Maraviroc analogues.

Keywords: β-amino aldehydes; asymmetric catalysis; conjugate additions; Maraviroc; ring-opening

Introduction

Human immunodeficiency virus (HIV) is a pandemic that was first recognized in 1981. In 2008, there were an estimated 33 million people (31–36 million) living with HIV. Among those, 2 million were children younger than 15 years of age. That year HIV caused the death of 2 million people (280,000 children) due to acquired immune deficiency syndrome (AIDS).[1] HIV is a retrovirus that attacks the immune system and targets the white blood cells. The virus enters the host cell *via* the interaction of the viral envelope protein gp 160 and the receptor/coreceptors of the host cell surface. One important coreceptor is the chemochine receptor 5 (CCR-5) which has emerged as a very attractive target for anti-HIV therapy.[2] In this context, Maraviroc **1** developed and discovered by Pfizer is a potent antagonist of the CCR5 receptor.[3] In 2007, Maraviroc became the first and so far only small molecule CCR5 antagonist to be approved by the FDA.

The initial medicinal chemistry synthesis of Maraviroc **1** was based on the employment of the β-amino aldehyde **2c** (Figure 1), which was prepared by reduction of the starting optically pure Boc-protected β-amino acid ester with diisobutylaluminium hydride, as the key chiral building block.[3b] The industrial synthesis of Maraviroc **1** relies on the use of the methyl ester of the Cbz-protected (3*R*)-β-phenylalanine acid,[4] which was prepared in three steps, as the source of chirality for the synthesis. The acid was subsequently transformed to the corresponding key β-amino aldehyde **2a** fragment in three steps. The synthesis of **1** was later modified by instead using β-amino aldehyde **2b**, which was prepared in 6 steps, as the key chiral building block.[4] Maraviroc **1** has also recently been synthesized on a milligram scale.[5] This synthetic route involved a two-step synthesis of the key intermediate **2b** where the first step was an asymmetric allylboration of an acyl imine using a chiral BINOL ligand. However, the acceptor acyl imine is rather unstable and the reaction is sensitive to water. Chiral β-amino aldehydes **2**[6,7] are important synthons for asymmetric synthesis and it should be possible to

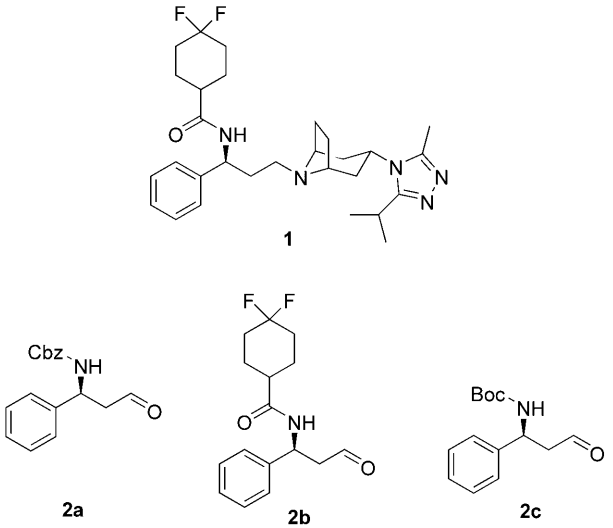
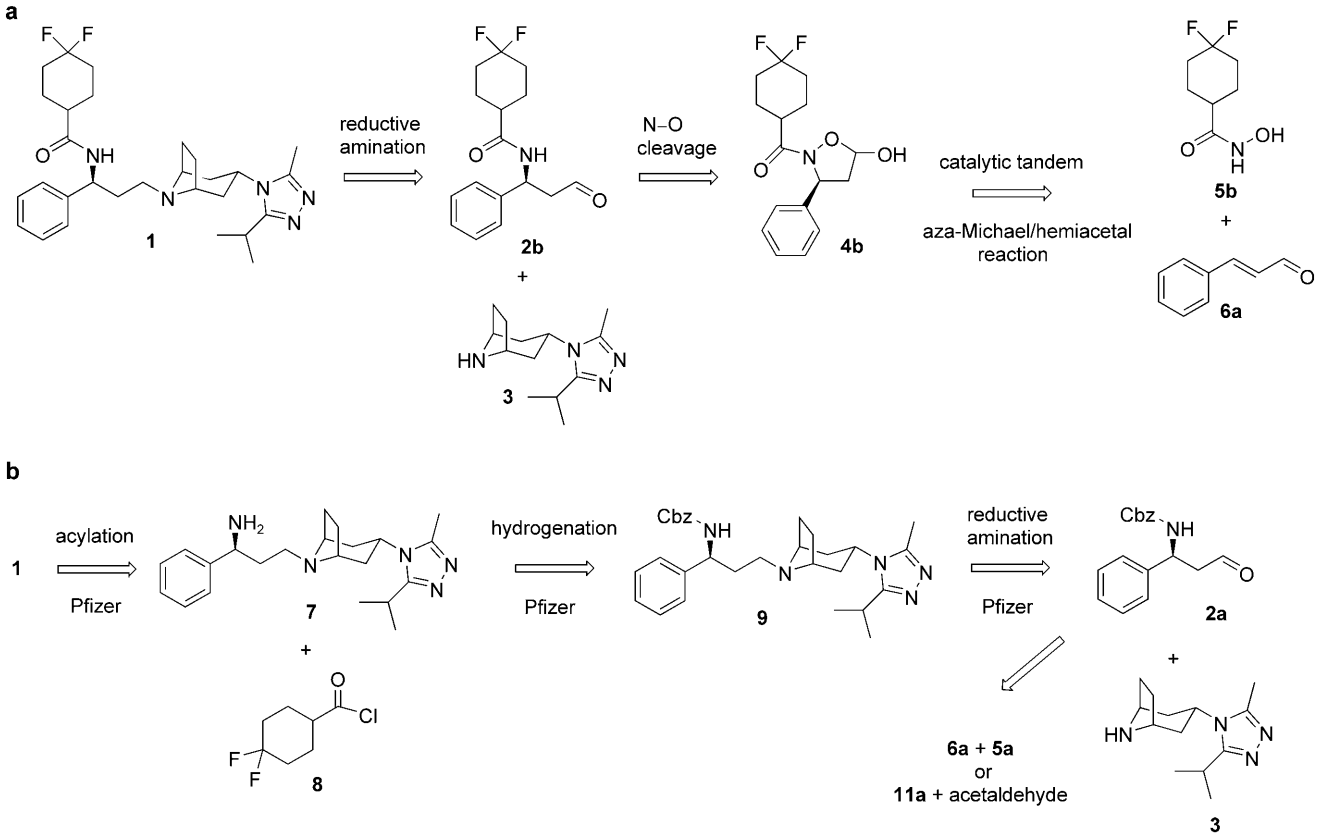


Figure 1. Maraviroc **1** and *N*-acyl-β-amino aldehydes **2a**–**c**.

rapidly implement an amine-catalyzed route into an industrial process. In this context, List[7c] and Maruoka[7e] have developed the enantioselective synthesis of β-amino aldehyde **2c** by organocatalytic Mannich reactions with acetaldehydes as the nucleophile. Based on the importance of finding CCR5 antagonists and our research interest in organocatalysis,[8] we became interested in developing amine-catalyzed enantioselective reactions for the assembly of β-amino aldehydes **2** and subsequent synthesis of Maraviroc and its analogues. Herein, we report the asymmetric synthesis of Maraviroc **1** and its analogues *via* a highly enantioselective synthesis of the key chiral β-amino aldehyde **2** fragments.

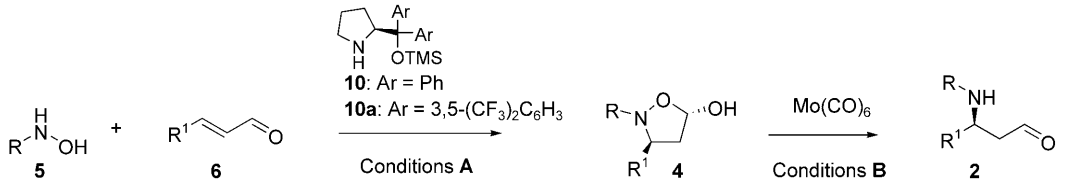
Results and Discussions

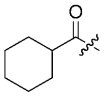
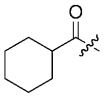
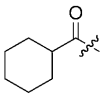
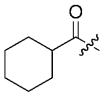
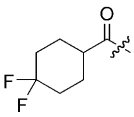
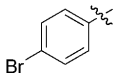
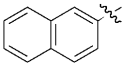
Retrosynthetic analysis suggests that an expeditious route to Maraviroc **1** would be the reductive amination between β-amino aldehyde **2b** and tropane **3** (Scheme 1, **a**). For the asymmetric synthesis of chiral β-amino aldehyde **2b**, we envisioned a two-step protocol involving N–O cleavage of 5-hydroxyisoxazolidine **4b** and catalytic enantioselective tandem aza-Michael/hemiacetal formation[9] between hydroxylamine **5b** and enal **6a**. The previous Pfizer process chemical route[4b] to Maraviroc **1** involved acylation of the chiral amine **7**, which could be obtained by hydrogenation of Cbz-protected amine **9**, with acyl chloride **8**. Reductive amination between Cbz-protected β-amino aldehyde **2a** and tropane **3** is expected to provide access to amine **9** (Scheme 1, **b**). It should be possible to synthesize the chiral aldehyde **2a** by the tandem aza-Michael/hemiacetal formation reaction between hydroxylamine **5a** and cinnamic aldehyde **6a** followed by ring-opening as described (*vide infra*). Another option for the synthesis of aldehyde **2a** would be to use the catalytic Mannich reaction between Cbz-protected aldimine **11a** and acetaldehyde, which has previously been employed using Boc-protected aldimines as substrates (see Table 2).[10] Our efforts began with the development of a two-step asymmetric synthesis of β-amino aldehyde **2** (Table 1). Thus, 5-hydroxyisoxazolidine **4a** (93% yield, 99% *ee*) was first prepared by a catalytic tandem aza-Michael/hemiacetal reaction between cinnamic aldehyde **6a** and Cbz-protected hydroxylamine **5a** using chiral amine **10** (20 mol%) as the catalyst (entry 1). Next, N–O cleavage using $Mo(CO)_6$ as the reducing agent gave the corresponding β-amino aldehyde **2a** in 83% yield and 93% *ee*.[11] Thus, a slight decrease of *ee* occurred during the N–O cleavage. Our two-step reaction sequence was further extended to the synthesis of Boc-protected β-amino



Scheme 1. Retrosynthetic analysis.

Table 1. Asymmetric synthesis of β-amino aldehydes **2**.[a]



Entry	R	R^1	Compound	Conditions A	Yield [%][b]	*ee* [%][c]	Compound	Conditions B	Yield [%][b]	*ee* [%][d]
1	Cbz	Ph	**4a**	A1	93	99	**2a**	B1	83	93
2	Boc	Ph	**4c**	A1	85	n.d.	**2c**	B1	80	93
3		Ph	**4d**	A1	49	89	–	–	–	–
4		Ph	**4d**	A2	91	88	–	–	–	–
5		Ph	**4d**	A3	32 (81)[e]	90	**2d**	B2	68	90
6		Ph	**4d**	A4	25 (75)[e]	91	**2d**	B2	67	90
7		Ph	**4b**	A5	91	80	**2b**	B3	74	80
8		Ph	**4b**	A6	13 (67)[e]	94	**2b**	B3	75	92
9	Boc		**4e**	A1	79	n.d.	**2e**	B2	62	>95
10	Boc		**4f**	A1	77	n.d.	**2f**	B2	56	93

[a] *Conditions:* (A1) A solution of catalyst **10** (20 mol%), cinnamic aldehyde **6a** (0.5 mmol) and protected hydroxycarbamate **5** (0.6 mmol) in $CHCl_3$ (1.0 mL) was stirred at 4 °C for 3 h. (A2) A solution of catalyst **10** (20 mol%), cinnamic aldehyde **6a** (0.5 mmol) and protected hydroxycarbamate **5** (0.6 mmol) in toluene (1.0 mL) was stirred at 4 °C for 16 h. (A3) A solution of catalyst **10** (20 mol%), cinnamic aldehyde **6a** (0.5 mmol) and protected hydroxycarbamate **5** (0.6 mmol) in toluene (1.0 mL) was stirred at 4 °C for 3 h. (A4) A solution of catalyst **10a** (20 mol%), cinnamic aldehyde **6a** (0.5 mmol) and protected hydroxycarbamate **5** (0.6 mmol) in toluene (1.0 mL) was stirred at 4 °C for 120 h. (A5) A solution of catalyst **10** (20 mol%), cinnamic aldehyde **6a** (0.5 mmol) and protected hydroxycarbamate **5** (0.6 mmol) in $CHCl_3$ (1.0 mL) was stirred at 4 °C for 18 h. (A6) A solution of catalyst **10** (20 mol%), cinnamic aldehyde **6a** (0.5 mmol), protected hydroxycarbamate **5** (0.6 mmol) in toluene (1.0 mL) was stirred at −40 °C for 120 h. (B1) $Mo(CO)_6$ (0.48 mmol, 1.2 equiv.) and **4** (0.4 mmol, 1 equiv.) in CH_3CN/H_2O (9:1, 4 mL), reflux for 16 h; (B2) $Mo(CO)_6$ (1.2 equiv.) and **4d** (1 equiv.) in CH_3CN/H_2O (9:1), reflux for 4 h. (B3) $Mo(CO)_6$ (1.2 equiv.) and **4b** (1 equiv.) in CH_3CN/H_2O (9:1), reflux for 2 h.

[b] Yield of pure isolated compound after silica-gel column chromatography.

[c] Determined by chiral phase HPLC analysis of **4**.

[d] Determined by chiral phase HPLC analysis of the corresponding alcohol **2'** after reduction of isolated aldehyde **2** with $NaBH_4$.

[e] The isolated yield is based on recovered starting material.

aldehyde **2c** [68% overall yield (two steps), 93% *ee* (entry 2)].

The tandem reaction between hydroxylamine **5d** and enal **6a** gave the corresponding 5-hydroxyisoxazolidine **4d** in good yields and high *ee*s (entries 3–6). In comparison to the reaction with the carbamate-protected hydroxylamines **5**, the reaction was slower. However, the N–O cleavage was faster in this case

providing the corresponding β-amino aldehyde **2d** within 2 h with 90% *ee* (entries 5 and 6). The chiral pyrrolidine **10**-catalyzed reaction with difluorinated *N*-hydroxylamine **5b** gave the corresponding product **4b** with 80% *ee* (entry 7). However, the enantioselectivity of the tandem reaction was lower in this case as compared to the reaction with hydroxylamine **5d**. Decreasing the temperature to −40 °C improved the *ee* (entry 8). However, the reaction time increased and the conversion and yield were low. Cleavage of the N−O bond of **5b** gave the corresponding key β-amino aldehyde **2b** with 92% *ee* (entry 8). The absolute configuration at the C-3 of **2b** was *S* as established by comparison with the literature data {92% *ee*, $[\alpha]_D^{25}$: −19.3 (*c* 1.0, $CHCl_3$); Lit.[5] $[\alpha]_D^{23}$: −8.2 (*c* 1.0, $CHCl_3$)}. We also performed the two-step reaction using other enals as acceptors and the corresponding aldehydes **2** were isolated with high enantioselectivity (entries 9 and 10). The relative stereochemistry of compounds **4** was established by NOE experiments on **4d** and the coupling constants of the ring protons. The NOE experiments revealed the interaction signal between H^1 and H^{Ar} (Figure 2). Moreover, no interaction between H^1 and H^3 was observed. Thus, their relative stereochemistry was *trans*. With these results in hand, we concluded that the α-anomers of compounds **4** were formed.

In order to find a one-step route to aldehydes **2**, we began to investigate the proline-catalyzed Mannich reaction between *N*-Cbz-protected imines **11** and acetaldehyde (Table 2).

The reactions gave the corresponding aldehydes **2** with high enantioselectivity. For examples, the CBz-protected aldehydes **2** were formed with up to 96% *ee* (entries 1–3). A competing side reaction is the oligomerization of acetaldehyde. As a consequence aldehydes **2** contained a small amount of oligomerization product after silica-gel column chromatography. The employment of syringe pump addition of acetaldehyde did not improve the yield or purity of aldehydes **2**. In order to completely remove the small amount of oligmeric products, aldehydes **2** were converted to the corresponding alcohols **2'** by reduction with $NaBH_4$.

We next embarked on the synthesis of the key tropane **3** as the *p*-TsOH salt *via* literature procedures[3a,4,12–14] (see Supporting Information). Reductive amination with aldehyde **2b** synthesized by our two-step procedure as described (*vide supra*) accomplished the asymmetric synthesis of Maraviroc **1** in 53% overall yield (3 steps) with 80% *ee* and 45% overall yield (3 steps) with 92% *ee*, respectively (Scheme 2). In addition, the absolute configuration of Maraviroc **1** was *S* as determined by comparison with the literature data {80% *ee*, $[\alpha]_D^{25}$: −16.4 (*c* 0.5, $CHCl_3$); Lit.[5] $[\alpha]_D^{23}$: −16.8 (*c* 0.4, $CHCl_3$)}.

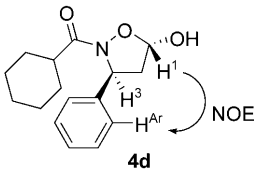
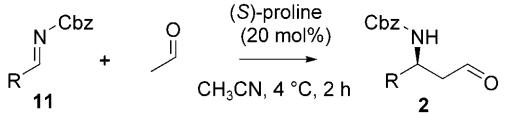


Figure 2. The interactions of the protons of **4d** as determined by NOE experiments.

Table 2. (*S*)-Proline-catalyzed synthesis of aldehyde **2**.[a]

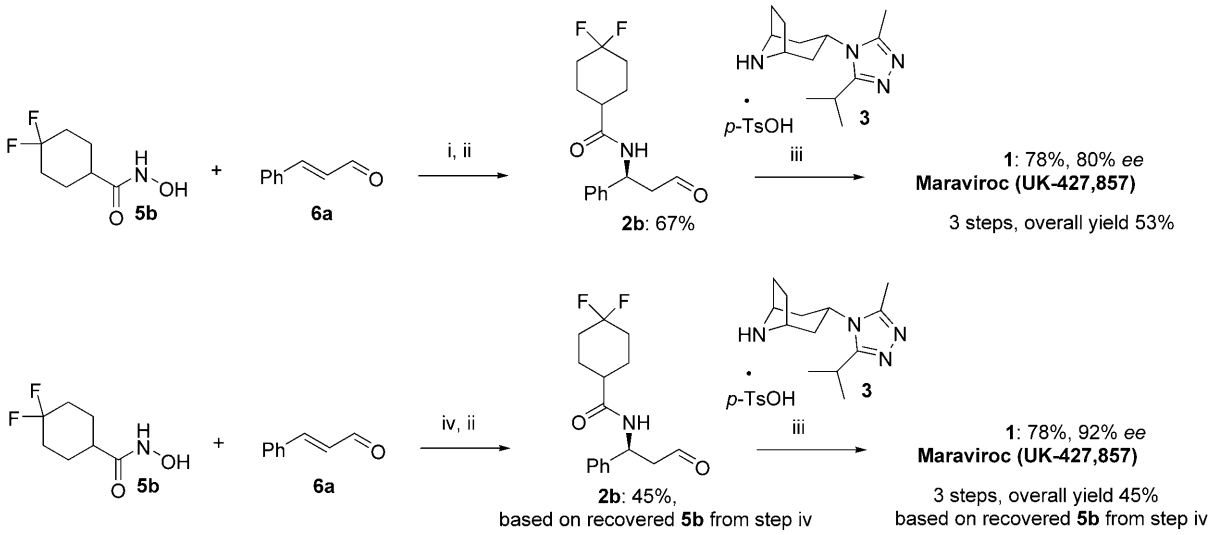


Entry	R	Compound	Yield [%][b]	*ee* [%][c]
1	phenyl	**2a**	22	96
2	4-ClC_6H_4	**2g**	16	91
3	2-naphthyl	**2h**	20	96
4	phenyl[d]	**2i**	28[d]	86[d]

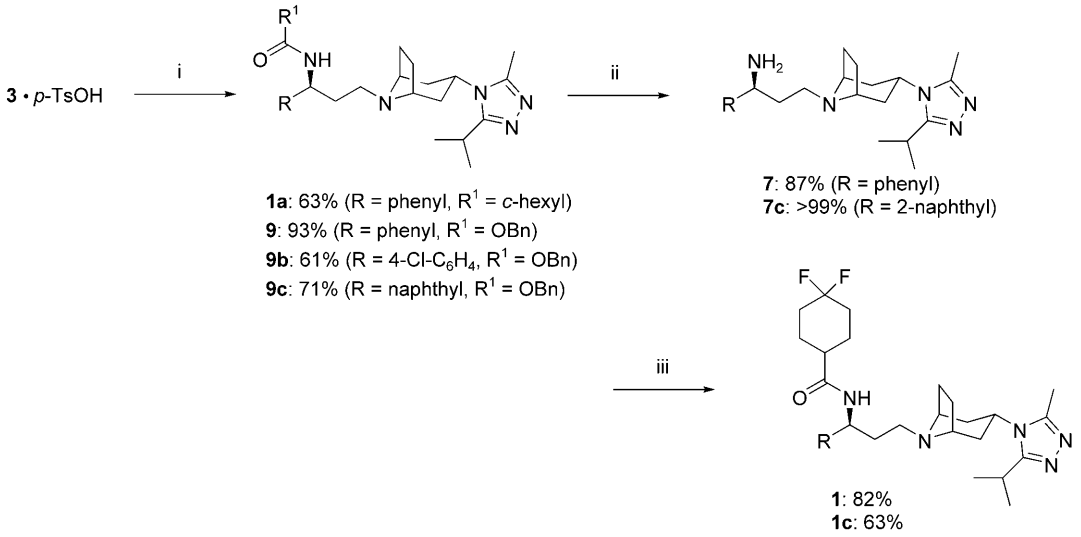
[a] A solution of (*S*)-proline (20 mol%), *N*-Cbz-imine (0.5 mmol) and acetaldehyde (1.5 mmol) was stirred for 2 h at 4 °C in CH_3CN.
[b] Yield of pure isolated alcohol **2'** after silica-gel column chromatography and reduction of the crude aldehyde **2**.
[c] Determined by chiral phase HPLC analysis of the corresponding alcohol **2'** after reduction of isolated aldehyde **2** with $NaBH_4$.
[d] The *N*-benzoylated imine **11d** was used instead of **11**.

Different analogues of Maraviroc **1** were also prepared by our synthetic strategy (Scheme 3). Thus, reductive amination between chiral aldehydes **2** derived by organocatalysis and amine **3** gave the corresponding tropanes **1a** and **9** in high yields. Notably, when using β-amino aldehydes **2g** and **2h** derived by (*S*)-proline catalysis as starting materials, the corresponding pure products **9b** and **9c** were isolated in 61 and 71% yields, respectively. The β-amino aldehyde **2a** obtained by proline catalysis can also be directly used as a starting material for amine **9**. However, it is important that it is completely free from benzaldehyde, which was formed by hydrolysis of imine **11a**, since otherwise protected triazole **16** (see Supporting Information) is also formed. This risk is completely avoided by using pure aldehyde **2a**, which was derived from our two-step reaction sequence, for the reductive amination with **3**. To our delight, the corresponding tropane **9** was isolated in 93% yield.

Removal of the Cbz-protective group by hydrogenation gave the corresponding primary amines **7** and **7c** with up to >99% yield. Acylation of **7** and **7c** with acyl chloride **8** under modified Schotten–Baum conditions (CH_2Cl_2, Na_2CO_3, water) afforded **1** and **1c** in 82 and 63% yields, respectively. The overall yields of **1** *via* aldehyde **2a** derived from the Mannich route or from the aza-Michael/hemiacetal route were 15% (4



Scheme 2. *Conditions:* (i) cat. **10** (20 mol%), $CHCl_3$, 4 °C, 18 h; (ii) **4b**, $Mo(CO)_6$, CH_3CN/H_2O (9:1), reflux, 2 h; (iii) **3**·TsOH, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, room temperature, 1.5 h; (iv) cat. **10** (20 mol%), toluene, −40 °C, 120 h.



Scheme 3. *Conditions:* (i) **2**, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, room temperature, 1.5 h; (ii) $Pd(OH)_2/C$ (10 wt%), MeOH, H_2 (90 psi), room temperature, 16 h; (iii) Na_2CO_3, **8**, CH_2Cl_2-H_2O (3:1), room temperature, 0.5 h.

steps, 96% *ee*) and 51% (5 steps, 93% *ee*), respectively. The absolute configuration of Maraviroc **1** was *S* as determined by comparison with the literature {96% *ee*, $[\alpha]_D^{25}$: −27.4 (*c* 1.0, $CHCl_3$); Lit.[5] $[\alpha]_D^{23}$: −16.8 (*c* 0.4, $CHCl_3$)}. We also showed that the catalytic asymmetric steps can be performed on a gram scale. Thus, the large-scale reaction between cinnamic aldehyde **6a** (31.4 g) and Cbz-protected hydroxylamine **5a** in the presence of catalyst **10** (7 mol%) gave the corresponding 5-hydroxyoxazolidinone **4a** in 91% yield (65 g, 99% *ee*). The (*S*)-proline-catalyzed reaction between acetaldehyde and imine **11a** (10 mmol) was also performed on a 2.5 gram scale giving the corresponding aldehyde **2a** containing some oligomerization product after silica-gel column chromatography. Reduction of **2a** with $NaBH_4$ gave the corresponding pure alcohol **2a′** in 20% yield and 96% *ee*.

Conclusions

In summary, we report an expeditious and practical asymmetric synthesis of Maraviroc **1** and its analogues. The synthetic strategy is based on the rapid assembly of the chiral β-amino aldehyde fragments **2**. The reactions presented herein can be scaled up and are useful for the versatile preparation of new analogues for medicinal chemistry studies.

Experimental Section

Typical Experimental Procedure for the Asymmetric Synthesis of 5-Hydroxyisoxazolidine 4a and 4c

To a stirred solution of catalyst (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (20 mol%) in $CHCl_3$ (1.0 mL) at 4 °C was added cinnamic aldehyde (1.0 equiv., 0.5 mmol) and benzyl hydroxycarbamate (1.2 equiv., 0.6 mmol). The reaction solution was vigorously stirred for 3 h. Next, the reaction mixture was directly loaded upon a silica-gel column and immediate chromatography (pentane:EtOAc = 6:1) furnished the pure products as a thick oil. **4a**: $R_f = 0.21$ (pentane:EtOAc = 4:1); **4c**: $R_f = 0.30$ (pentane:EtOAc = 4:1).

Typical Experimental Procedure for the Asymmetric Synthesis of 5-Hydroxyisoxazolidine 4b

To a stirred solution of catalyst (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine **10** (20 mol%) in $CHCl_3$ (1.0 mL) at 4 °C was added cinnamic aldehyde (1.0 equiv., 0.5 mmol) and *N*-hydroxycyclohexanecarboxamide (1.2 equiv., 0.6 mmol). The reaction solution was vigorously stirred for 18 h. Next, the reaction mixture was directly loaded upon a silica-gel column [29 mm (i.d.), 34 mm (o.d.)] and immediate chromatography (pentane:EtOAc = 3:1) furnished the pure product as a white solid; yield: 142 mg (91%); $R_f = 0.33$ (pentane:EtOAc = 3:1).

Typical Experimental Procedure for the Asymmetric Synthesis of 5-Hydroxyisoxazolidine 4d

To a stirred solution of catalyst (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (20 mol%) in toluene (1.0 mL) at 4 °C was added cinnamic aldehyde (1.0 equiv., 0.5 mmol) and 4,4-difluoro-*N*-hydroxycyclohexanecarboxamide (1.2 equiv., 0.6 mmol). The reaction solution was vigorously stirred for 16 h. Next, the reaction mixture was directly loaded upon a silica-gel column [29 mm (i.d.), 34 mm (o.d.)] and immediate chromatography (pentane:EtOAc = 3:1) furnished the pure product **4d** as a white solid; yield: 125 mg (91%); $R_f = 0.32$ (pentane:EtOAc = 3:1).

Typical Experimental Procedure for the Opening of 4a

To a solution of (*3S*)-benzyl 5-hydroxy-3-phenylisoxazolidine-2-carboxylate **4a** (120 mg, 0.4 mmol) in CH_3CN/H_2O (4.0 mL, 9:1, degassed under nitrogen) was added $Mo(CO)_6$ (1.2 equiv., 0.48 mmol). The reaction solution was vigorously stirred and heated to reflux for 16 h. Next, the crude reaction mixture was filtered through a short column of silica gel (washed by EtOAc). Then solvent was removed and the residue was loaded upon a silica-gel column and immediate chromatography (pentane:EtOAc = 6:1) furnished the pure product **2a** as a white solid; yield: 94 mg (82%); $R_f = 0.45$ (pentane:EtOAc = 3:1).

Typical Experimental Procedure for the Opening of 4c

To a solution of (*3S*)-*tert*-butyl 5-hydroxy-3-phenylisoxazolidine-2-carboxylate **4c** (106 mg, 0.4 mmol) in CH_3CN/H_2O (4.0 mL, 9:1, degassed under nitrogen) was added $Mo(CO)_6$ (1.2 equiv., 0.48 mmol). The reaction was vigorously stirred and heated to reflux for 16 h. Next, the crude reaction mixture was filtered through a short column of silica gel (washed by EtOAc). Then solvent was removed and the residue was loaded upon a silica-gel column and immediate chromatography (pentane:EtOAc = 6:1) furnished the pure product as **2c** a white solid; yield: 80 mg (80%); $R_f = 0.52$ (pentane:EtOAc = 3:1).

Typical Experimental Procedure for the Opening of 4b

To a solution of 4,4-difluorocyclohexyl-[(3*S*)-5-hydroxy-3-phenylisoxazolidin-2-yl]methanone **4b** (0.15 mmol) in CH_3CN/H_2O (1.0 mL, 9:1, degassed under nitrogen) was added $Mo(CO)_6$ (1.2 equiv., 0.18 mmol). The reaction solution was vigorously stirred and heated to reflux for 2 h. Next, the crude reaction mixture was filtered through a short column of silica gel (washed by EtOAc). Then solvent was removed and the residue was loaded upon a silica-gel column [29 mm (i.d.), 34 mm (o.d.)] and immediate chromatography (pentane:EtOAc = 3:1) furnished the pure β-amino aldehyde product **2b** as a white solid; yield: 33 mg (75%); $R_f = 0.44$ (pentane:EtOAc = 2:1).

Typical Experimental Procedure for the Opening of 4d

To a solution of cyclohexyl [(3*S*)-5-hydroxy-3-phenylisoxazolidin-2-yl]methanone **4d** (0.15 mmol) in CH_3CN/H_2O (1.0 mL, 9:1, degassed under nitrogen) was added $Mo(CO)_6$ (1.2 equiv., 0.18 mmol). The reaction solution was vigorously stirred and heated to reflux for 4 h. Next, the crude reaction mixture was filtered through a short column [29 mm (i.d.), 34 mm (o.d.)] of silica gel (washed by EtOAc). Then solvent was removed and the residue was loaded upon a silica-gel column and immediate chromatography (pentane:EtOAc = 3:1) furnished the pure product **2d** as a white solid; yield: 27 mg (68%); $R_f = 0.41$ (pentane:EtOAc = 3:1).

General Experimental Procedure for the Mannich Reaction of Acetaldehyde with *N*-Cbz-Imines

To a stirred solution of catalyst (*S*)-proline (20 mol%) in CH_3CN (2.0 mL) at 4 °C was added the freshly prepared alkyl-*N*-Cbz-imine (1.0 equiv., 0.5 mmol) and acetaldehyde (3 equiv., 1.5 mmol). The reaction was vigorously stirred for 2 h at 4 °C. Next, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The water layer was extracted with CH_2Cl_2. Then the combined organic fractions were dried over Na_2SO_4 and the solvent was removed. The residue was loaded upon a silica-gel column and immediate chromatography (pentane:EtOAc = 6:1) furnished the pure product as a colorless oil.

Typical Experimental Procedure for the Reductive Amination of Aldehydes

To a solution of tosylate salt of amine **3** (157 mg, 0.387 mmol) in CH_2Cl_2 was added the (*S*)-β-aminoaldehydes **2** (0.423 mmol) under an N_2 atmosphere. To the resultant solution acetic acid (10 μL) was added. After that, sodium tri-

acetoxyborohydride (98 mg, 0.464 mmol) was added to the reaction mixture portionwise. The resultant slurry was stirred at ambient temperature for 1.5 h. Then the reaction mixture was treated with H_2O (1 mL) followed by 2 M NaOH (1 mL). The aqueous layer was adjusted to pH 11–12 by addition of 10 M NaOH. The layers were separated and the aqueous phase was reextracted with dichloromethane. The organic fractions were combined, washed with 1 M NaOH and brine, and dried over Na_2SO_4. The solvent was removed. The residue was loaded upon a silica-gel column and immediate chromatography (MeOH:EtOAc = 1:6) furnished the pure products as white solids.

Typical Experimental Procedure for Deprotection

A solution of amine (134 mg) in methanol (3 mL) was added palladium(II) hydroxide monohydrate on carbon (10%) (13 mg, 10 wt%) under an N_2 atmosphere. The resultant slurry was stirred under an atmosphere of hydrogen at 90 psi for 16 h at room temperation. The reaction mixture was filtered through celite and the filter pad was washed with methanol. Then the solvent was removed giving the product **7**; yield: 86 mg (87%).

Typical Experimental Procedure for the Synthesis of Maraviroc and its Analogues by Modified Schotten–Baum Conditions

Amine (0.23 mmol) was dissolved in CH_2Cl_2 (1.5 mL) at room temperature, treated with a solution of saturated aqueous sodium carbonate (1.5 mL) and water (0.5 mL) and the mixture was cooled to 0 °C. 4,4-Difluorocyclohexanecarbonyl chloride (64 mg, 0.35 mmol, 1.5 equiv.) was added to the reaction mixture dropwise at 0 °C and the resultant mixture was stirred for 0.5 h at room temperature. Then the mixture was separated and the aqueous phase was washed with dichloromethane. The combined organic phases were washed with 2 M NaOH followed by water. The organic phase was dried over Na_2SO_4 and the solvent was removed. The residue was loaded upon a silica-gel column and immediate chromatography (MeOH:EtOAc = 1:6) furnished the pure products **1** as white solids; $R_f = 0.52$ (MeOH:EtOAc = 1:1).

Supporting Information

Experimental procedures, full spectroscopic data for all new described compounds, NMR spectra, HPLC traces and HR-mass spectra are available as Supporting Information.

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References

[1] *AIDS Epidemic update*, **2009**, UNAIDS.
[2] a) M. Baba, O. Nishimura, N. Kanzaki, M. Okamoto, H. Sawada, Y. Iizawa, M. Shiraishi, Y. Aramaki, K. Okonogi, K. Meguro, M. Fujino, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 5698; b) R. Kondru, J. Zhang, C. Ji, T. Mirzadegan, D. Rotstein, S. Sankuratri, M. Dioszegi, *Mol. Pharm.* **2008**, *73*, 789; c) J. G. Sodroski, *Cell* **1999**, *99*, 243; d) D. R. Armour, M. J. de Groot, D. A. Price, B. L. C. Stammen, A. Wood, M. Perros, C. Burt, *Chem. Biol. Drug Des.* **2006**, *67*, 305.
[3] a) M. Perros, D. A. Price, B. L. C. Stammen, A. Wood, *PCT Int. Appl.* WO2001090106, **2001**; b) D. A. Price, S. Gayton, M. D. Selby, J. Åhman, S. Haycock-Leandowski, B. L. Stammen, A. Warren, *Tetrahedron Lett.* **2005**, *46*, 5005.
[4] a) J. Åhman, M. Birch, S. J. Haycock-Lewandowski, J. Long, A. Wilder, *Org. Process Res. Dev.* **2008**, *12*, 1104; b) S. J. Haycock-Lewandowski, A. Wilder, J. Åhman, *Org. Process Res. Dev.* **2008**, *12*, 1094.
[5] S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398.
[6] a) D. S. Laitar, J. W. Kramer, B. T. Whiting, E. B. Lobkovsky, G. W. Coates, *Chem. Commun.* **2009**, 5704; b) F. A. Davis, S. M. Szewczyk, *Tetrahedron Lett.* **1998**, *39*, 5951; c) F. A. Davis, M. Song, *Org. Lett.* **2007**, *9*, 2413; d) P. Gizecki, R. Dhal, L. Toupet, G. Dujardin, *Org. Lett.* **2000**, *2*, 585; e) P. Gizecki, R. Dhal, C. Poulard, P. Gosselin, G. Dujardin, *J. Org. Chem.* **2003**, *68*, 4338; f) M. Terada, Y. Toda, *J. Am. Chem. Soc.* **2009**, *131*, 6354; g) D. Limal, A. Quesnel, J.-P. Briand, *Tetrahedron Lett.* **1998**, *39*, 4239; h) M. Rodriguez, A. Heitz, J. Martinez, *Tetrahedron Lett.* **1990**, *31*, 7319; i) P. Gizecki, R. Ait-Youcef, C. Poulard, R. Dhal and G. Dujardin, *Tetrahedron Lett.* **2004**, *45*, 9589.
[7] For amine-catalyzed routes to β-amino aldehydes see: selected reviews: a) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; b) R. Rios, A. Córdova, *Curr. Opin. Drug. Discov.* **2009**, *12*, 824; *via* Mannich reaction: c) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453; d) Y. Hayashi, T. Okano, T. Itoh, T. Urushima, H. Ishikawa, T. Uchimaru, *Angew. Chem.* **2008**, *120*, 9193; *Angew. Chem. Int. Ed.* **2008**, *47*, 9053; e) T. Kano, Y. Yamaguchi, K. Maruoka, *Angew. Chem.* **2009**, *121*, 1870; *Angew. Chem. Int. Ed.* **2009**, *48*, 1838; *via* aza-Michael reaction see: f) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; g) J. Vesely, I. Ibrahem, R. Rios, G. L. Zhao, Y. Xu, Y. Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2193; h) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058.
[8] a) F. Ullah, G.-L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun, A. Córdova, *Chem. Eur. J.* **2009**, *15*, 10013; b) P. Dziedzic, P. Schyman, M. Kullberg, A. Córdova, *Chem. Eur. J.* **2009**, *15*, 4044; c) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Synthesis* **2008**, 1153; d) I. Ibrahem, A. Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2839.
[9] I. Ibrahem. R. Rios, J. Vesely, G. L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849.

[10] In fact, to the best of our knowledge, only the syntheses of Boc- or Bzl-protected β-amino aldehydes **2** are previously described in the literature by chiral amine-catalyzed Mannich reactions using acetaldehyde as the donor. See refs.[7c–e]

[11] a) T. Kudoh, T. Ishikawa, Y. Shimizu, S. Saito, *Org. Lett.* **2003**, *5*, 3875. See also: b) S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. D. Sarlo, *Tetrahedron Lett.* **1990**, *31*, 3351; c) T. B. Nguyen, A. Beauseigneur, A. Martel, R. Dahl, M. Laurent, G. Dujardin, *J. Org. Chem.* **2010**, *75*, 611; d) the N–O cleavage did also work with SmI_2: P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693. However, in this case, aldehyde **2a** and alcohol **2a′** were formed in a 1:1 ratio in 27% combined yield.

[12] a) R. Robinson, *J. Chem. Soc. Trans.* **1917**, *111*, 762; b) S. Archer, T. R. Lewis, M. J. Unser, *J. Am. Chem. Soc.* **1957**, *79*, 4194; c) I. Mergelsberg, G. Werne, *PCT Int. Appl.* WO2006031788, **2008**.

[13] a) D. A. Price, S. Gayton, M. D. Selby, J. Ahman, S. Haycock-Lewandowski, *Synlett* **2005**, 1133; b) D. R. Armour, M. J. de Groot, D. A. Price, B. L. C. Stammen, A. Wood, M. Perros, C. Burt, *Chem. Biol. Drug Des.* **2006**, *67*, 305.

[14] a) A. H. Lewin, G. Sun, L. Fudala, H. Navarro, L.-M. Zhou, P. Popik, A. Faynsteyn, P. Skolnick, *J. Med. Chem.* **1998**, *41*, 988; b) S. Archer, T. R. Lewis, M. J. Unser, *J. Am. Chem. Soc.* **1957**, *79*, 4194.

