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Synthesis and Resolution of 2-(Cyclohexyl-4-(2-quinolylmethoxy)phenyl)methoxyiminopropionic acid, Leukotriene Biosynthesis Inhibitors

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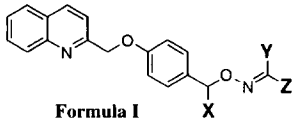
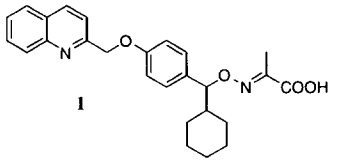
Abstract: The synthesis and resolution of 2-(E)-(cyclohexyl-4-(2-quinolylmethoxy)-phenyl)methoxyiminopropionic acid **1**, a potent leukotriene biosynthesis inhibitor is described. Dibenzoyltartaric acid was used as the chiral auxiliary for the resolution of the hydroxylamine intermediates used in the synthesis. A difficult chromatographic separation was made more practical by changing the order of elution of diastereomers by selection of the natural or unatural tartaric acid auxiliary.

INTRODUCTION

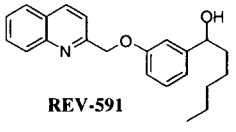
Several inhibitors of leukotriene biosynthesis have demonstrated therapeutic benefit in the treatment of asthma.[1] The 2-quinolylmethoxyphenyl structural motif has proven useful in the design of several leukotriene biosynthesis inhibitors or leukotriene receptor antagonists.[2] Representative examples are: REV-591,[3] L-674,636[4] and BAY X1005.[5] From an extensive investigation of the structure-activity relationships of a series of 2-quinolylmethoxyphenylalkyliminoxy derivatives of the general formula I, we identified the racemate **1** as a promising potent leukotriene inhibitor.[6] This report describes the development of the synthetic routes to access the enantiomers R (-) **1a** and S (+) **1b** required for evaluation of their respective biological properties as leukotriene biosynthesis inhibitors.



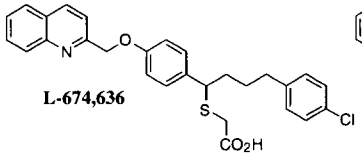
Formula I



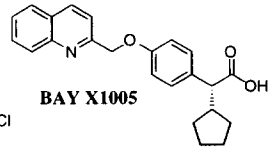
1



REV-591



L-674,636



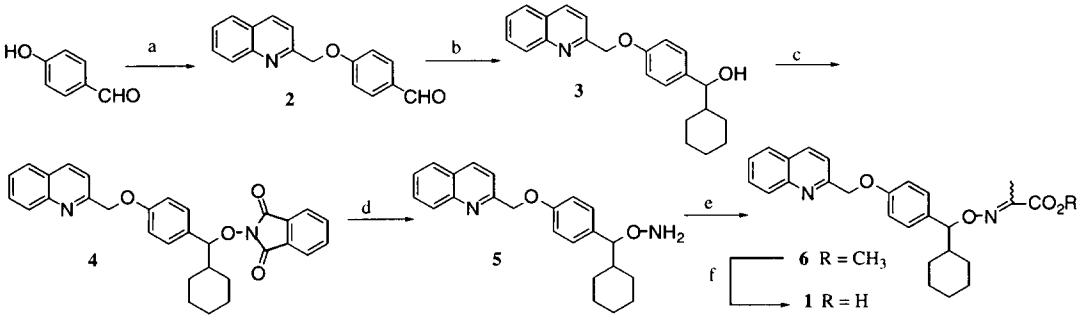
BAY X1005

RESULTS AND DISCUSSION

A general synthetic route was devised for the novel class of leukotriene inhibitors represented by Formula I, as shown in Scheme 1 for the preparation of racemic **1**. Reaction of 4-hydroxybenzaldehyde with 2-chloromethylquinoline in the presence of K_2CO_3 provided the adduct **2** which was reacted with cyclohexyl-magnesium chloride to afford the alcohol intermediate **3** in 70% overall yield. Mitsunobu reaction[7] with *N*-hydroxyphthalimide converted **3** to the corresponding *N*-alkoxyphthalimide **4** that was cleaved with

hydrazine hydrate to provide *O*-alkylhydroxylamine **5** (95% yield for two steps). Reaction of **5** with methyl pyruvate provided the alkoxyiminoester **6** (88% yield) as a mixture of E and Z isomers (48:7) which were separated by column chromatography. Standard hydrolysis provided the desired carboxylic acids, E-**1** and Z-**1**. Fortunately, the major E-oxime isomer **1** was found to provide more potent leukotriene inhibition than the minor Z-isomer.

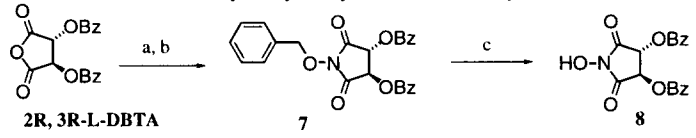
Scheme 1[a] Synthesis of racemic 2-E- and 2-Z-(cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyimino-propionic acid **1**.



[a]Reagents and conditions: a) 2-chloromethylquinoline:HCl, K_2CO_3, DMF, rt, 16 h. b) cyclohexylmagnesium chloride, THF, -78 °C to rt, 12 h. c) PhtNOH, Ph_3P, DEAD, THF, rt, 16 h. d) H_2NNH_2: H_2O, dioxane-EtOH, reflux, 30 min. e) methyl pyruvate, acetic acid, dioxane-MeOH, rt, 12 h. f) NaOH, dioxane-MeOH, rt, 10 h.

We envisioned that application of an appropriate chiral auxiliary to derivatize either the alcohol intermediate **3** or the hydroxylamine intermediate **5** would provide a means to resolve the chiral center via physical separation of diastereomeric derivatives. The method reported for preparation of chiral *O*-tetrahydropyranylhydroxylamine[8] based on the separation of diastereoisomeric *N*-2R,3R-dibenzoyltartaryl derivatives was applied. An improved synthesis of the chiral auxiliary, *N*-hydroxy-2R,3R-dibenzoyltartarimide **8** was achieved from 2R,3R-dibenzoyltartaric acid anhydride[9] (L-DBTA, prepared from natural tartaric acid) by reaction with *O*-benzylhydroxylamine to provide **7** which was subjected to hydrogenolysis to provide pure **8** (Scheme 2). The previously reported synthesis[8] of **8** by direct reaction of L-DBTA with hydroxylamine resulted in contamination with benzoylhydroxamic acid.

Scheme 2.[b] Synthesis of the chiral auxiliary *N*-hydroxy-2R,3R-dibenzoyltartarimide **8**.

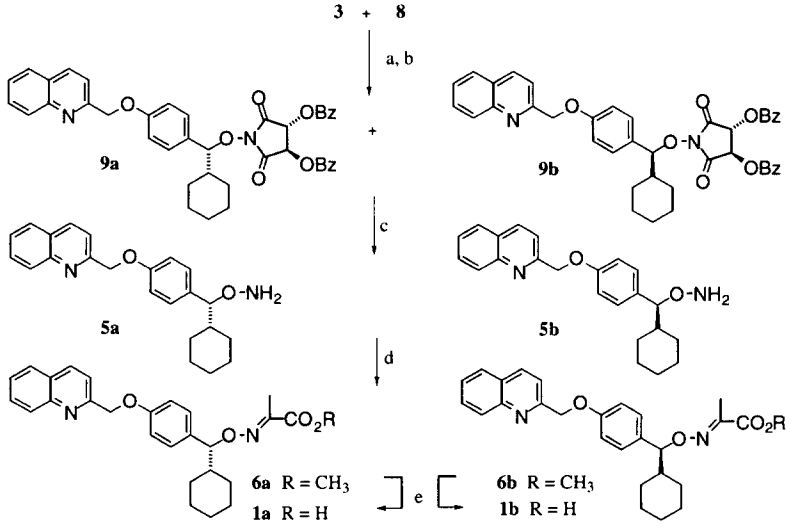


2R, 3R-L-DBTA **7** **8**

[b]Reagents and conditions: a) $C_6H_5CH_2ONH_2$, THF, rt, 12 h. b) $SOCl_2$, $CHCl_3$, O °C to rt, 4 h. c) H_2/10% Pd-C, rt, 5 h.

A Mitsunobu reaction with the chiral auxiliary **8** was applied to the alcohol **3** resulting in the formation of a mixture of diastereoisomeric adducts **9a** and **9b** in 30% yield (Scheme 3). The diastereomers were separated by column chromatography (silica gel, 54:6:40 hexanes-ethyl acetate-dichloromethane) to provide **9a** (17%) and **9b** (11%). Two major side products were identified, bis(*N*-benzoyl-*N*-carboethoxy)hydrazine and *N*-benzoyl-*N*-carboethoxy-*N'*-carboethoxyhydrazine which partially accounted for the low yield of desired adducts due to the instability of the chiral auxiliary **8** under these reaction conditions.

Scheme 3. [c] Resolution of **3** using L-DBTA derivative **8**.



[c]Reagents and conditions: a) Ph_3P, DEAD, THF, rt, 4 h. b) chromatographic separation of diastereoisomers (silica gel, hexanes-EtOAc-CH_2Cl_2 54:6:40); c) H_2NNH_2:H_2O, dioxane-EtOH, reflux, 30 min. d) methyl pyruvate, acetic acid, dioxane-MeOH, rt, 12 h, then chromatographic separation of E- and Z-isomers (silica gel, hexanes-Et_2O 3:1). e) NaOH, dioxane-MeOH, rt, 10 h.

The absolute configurations of the separated diastereomers **9a** and **9b** were tentatively assigned based on the ^1H NMR chemical shifts of the repective methine protons of the L-tartaryl residue. It was previously established[10] that the chemical shift of the L-DBTA derivative of an S-enantiomeric substrate was found downfield relative to that of the R-enantiomeric diastereomer. Thus **9a** (two proton singlet, 5.54 ppm) was assigned the R-configuration and **9b** (two proton singlet, 5.62 ppm) was assigned the S-configuration. The separated diastereomers **9a** and **9b** were individually converted to the corresponding *O*-alkylhydroxylamines **5a** and **5b** and then to the oximes **6a** and **6b** as a mixture of E- and Z-isomers (6:1). The E-isomer of **6a** and **6b** was purified by chromatography (silica gel, 3:1 hexanes-ether). The Z-isomer of both **6a** and **6b** was found to co-elute as a 2:1 mixture contaminated with the *O*-(cyclohexyl-(4-(2-quinolylmethoxy)-phenyl)methyloxime of acetaldehyde. This oxime was probably derived from decarboxylation of the Z-isomer. Since the the Z-isomers were not of interest as leukotriene inhibitors no further effort was made to

avoid this side reaction. The separated E-esters **6a** and **6b** were each hydrolysed with NaOH to provide the two desired carboxylate enantiomers R (-) **1a** and S (+) **1b** (Scheme 3).

To confirm the preliminary assignment of absolute configuration, **1a** was converted into the 3-bromophenylmethylamide derivative **10**. X-ray crystallography of **10** (Figure 1) confirmed the absolute configuration as R and reiterated the utility of the dibenzoyltartaric acid NMR method in assigning absolute configuration.

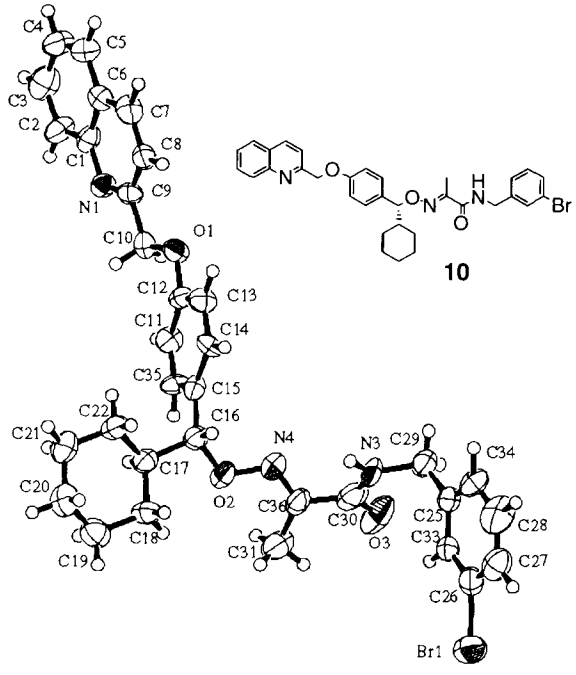
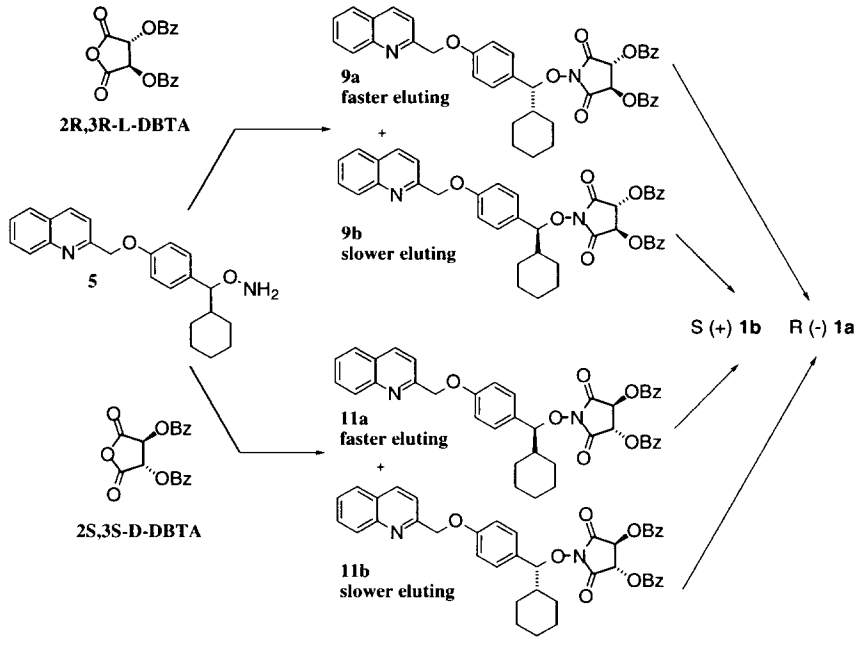


Figure 1. ORTEP structure of **10** obtained by X-ray crystallography.

With conditions for resolution of **1** in hand our attention turned to optimization of the process to secure larger amounts of material for biological testing. The low yields of diastereomers **9a** and **9b** due to the instability of the chiral auxiliary **8** under the Mitsunobu reaction conditions (even at temperatures of 0 to -20 °C), prompted an alternative approach. We investigated the resolution of the racemic *O*-cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methylhydroxylamine **5**. Treatment of **5** with L-DBTA for 25 min followed by cyclization with dicyclohexylcarbodiimide (DCC) in the presence of *N*-hydroxysuccinimide provided an improved yield of diastereomers **9a** + **9b** (65%). The chromatographic separation to provide both compounds in pure form and high recovery was difficult with low pressure silica gel chromatography. However, we found that pure faster eluting diasteromer was readily achieved in good yield providing **9a**, when L-DBTA was employed as the chiral auxiliary. In order to secure pure **9b** by this technique, **5** was derivatized with 2S,3S-D-DBTA (derived from unnatural tartaric acid) to provide the requisite **11a** as the faster eluting diastereomer (Scheme 4). Deprotection of **11a** with hydrazine hydrate followed by oxime formation and ester hydrolysis provided **1b** with the same optical rotation as **1b** prepared from **9b**.

Scheme 4. Resolution of hydroxylamine **5** using L-DBTA and D-DBTA derivatives to control the order of elution to simplify purification of the desired **S (+) 1b** as the faster eluting component.



The inhibitory activity of the compounds against leukotriene biosynthesis was evaluated in intact human neutrophils stimulated with calcium ionophore.[11] The results from dose response inhibition measurements are expressed as the concentration providing 50% inhibition (IC_{50}). Racemic **1** had an IC_{50} = 29 nM, R (-) **1a** had an IC_{50}= 70 nM and S (+) **1b** had an IC_{50} = 15 nM.[12] These results demonstrated a stereochemical preference for the inhibition of leukotriene biosynthesis. The more potent leukotriene inhibitor S (+) **1b** (A-93178) was selected for further pharmacological study as a potential investigational candidate for treatment of leukotriene mediated disorders.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Specific rotations were measured using Perkin Elmer 241 Polarimeter. ^{1}H NMR spectra were recorded using a Nicolet QE-300 (300 MHz) instrument. Mass spectra were obtained with Hewlett Packard HP5985 spectrometer. X-Ray crystallography was taken on a P4 Siemens apparatus with CCD detector. Microanalysis were performed by the Robertson Microlit Laboratories, Inc. in Madison, NJ. Reagents were obtained from Aldrich and Lancaster chemical companies.

Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methanol (3). To a solution of 4-hydroxybenzaldehyde (3.66 g, 30 mmol) and K_2CO_3 (8.24 g, 60 mmol) in DMF (75 mL) was added 2-chloromethylquinoline:HCl (6.42 g, 30 mmol). The mixture was stirred at rt 16 h, poured into water and extracted with ethyl acetate, dried ($MgSO_4$), concentrated *in vacuo* and the residue was chromatographed (silica gel, 2:1 hexanes-ethyl acetate) to afford 4-(2-quinolinylmethoxy)benzaldehyde **2** (5.8 g; 74%) as a white solid. To a solution of **2** (2.63 g, 10

mmol) in THF (50 mL) at -78 °C was added cyclohexylmagnesium chloride (10 mL of a 2 M solution in THF, 20 mmol). The mixture was stirred at rt for 12 h and then quenched with aqueous saturated NH_4Cl (25 mL). The THF was removed *in vacuo*, water was added and the product was extracted with ethyl acetate. The extract was dried ($MgSO_4$), concentrated *in vacuo* and the residue was chromatographed (silica gel, 9:1 methylene chloride-ethyl acetate) to afford **3** (3.3 g, 94%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 1 H), 1.14 (m, 3 H), 1.36 (m, 1 H), 1.62 (m, 3 H), 1.77 (m, 2 H), 2.00 (m, 1 H), 4.30 (d, J = 7 Hz, 1 H), 5.38 (s, 2 H), 6.99 (d, J = 9 Hz, 2 H), 7.21 (d, J = 9 Hz, 2 H), 7.55 (m, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.74 (m, 1 H), 7.83 (m, 1 H), 8.09 (d, J = 8 Hz, 1 H), 8.20 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 348 $(M + H)^+$. Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25; N, 4.03. Found: C, 79.40; H, 7.19; N, 3.93.

(RS)-*O*-Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methylhydroxylamine (5). Triphenylphosphine (5.24 g, 20 mmol) was added to a solution of **3** (4.7 g, 13.5 mmol) and *N*-hydroxyphthalimide (2.28 g, 14 mmol) in THF (100 mL) at ambient temperature followed by dropwise addition of diethylazodicarboxylate (DEAD, 3.2 mL, 20 mmol). The mixture was stirred at rt for 16 h, concentrated *in vacuo*, and the residue was chromatographed (silica gel, 25:1 CH_2Cl_2/EtOAc) to afford *N*-phthaloyl-*O*-cyclohexyl-(4-2-(quinolylmethoxy)phenyl)methylhydroxylamine **4** (6.6 g) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 1 H), 1.31 (m, 6 H), 1.65 (m, 1 H), 1.82 (m, 1 H), 1.99 (m, 1 H), 2.35 (m, 1 H), 5.02 (d, J = 7 Hz, 1 H), 5.33 (s, 2 H), 6.95 (d, J = 9 Hz, 2 H), 7.42 (d, J = 9 Hz, 2 H), 7.54 (m, 1 H), 7.65 (m, 5 H), 7.72 (m, 1 H), 7.83 (m, 1 H), 8.06 (m, 1 H), 8.20 (m, 1 H); MS (DCI/NH_3) m/z 493 $(M + H)^+$.

A mixture of **4** (6.6 g, 13.4 mmol) and hydrazine hydrate (1.5 mL, 30 mmol) in dioxane (20 mL) and ethanol (40 mL) was refluxed for 30 min. and then cooled to rt . Aqueous 10% Na_2CO_3 was added and the mixture was extracted with ethyl acetate, washed with water, brine, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica gel, 2:1 hexanes-EtOAc) to provide **5** (4.64 g, 96%). mp 77-78 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 1 H), 1.10 (m, 6 H), 1.59 (m, 3 H), 1.72 (m, 1 H), 4.12 (d, J = 7 Hz, 1 H), 5.08 (s, 2 H), 5.40 (s, 2 H), 7.02 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.55 (m, 1 H), 7.70 (d, J = 8 Hz, 1 H), 7.75 (m, 1 H), 7.84 (m, 1 H), 8.08 (m, 1 H), 8.20 (d,J = 8 Hz, 1 H); MS (DCI/NH_3) m/z 363 $(M + H)^+$. Anal. Calcd for $C_{23}H_{26}N_2O_2$ x 0.75 H_2O: C, 73.47; H, 7.37; N, 7.45; Found: C, 73.70; H, 7.11; N, 7.95.

(RS) 2-E- and 2-Z-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid (1). A mixture of **5** (1.09 g; 3 mmol), methyl pyruvate (0.3 mL; 3 mmol) and acetic acid (0.18 mL; 3 mmol) in methanol (25 mL), dioxane (20 mL) and water (5 mL) was stirred at rt for 24 h. The organic solvents were removed *in vacuo* and water was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (silica gel, 3:1 hexanes-ethyl acetate) to afford methyl ester **6** (1.18 g) as a oily mixture of E and Z isomers. The mixture was separated by chromatography (silica gel, 3:1 hexanes-ether). **Z-isomer 6** (140 mg, 12%) as an oil. ^1H NMR (300 MHz, DMSO-d_6) δ 0.93 (m, 3 H), 1.08 (m, 2 H), 1.32 (m, 1 H), 1.60 (m, 4 H), 1.68 (m, 1 H), 1.91 (s, 3 H), 3.80 (s, 3 H), 4.73 (d, J = 7 Hz, 1 H), 5.36 (s, 2 H), 7.03 (d, J = 9 Hz, 2 H), 7.14 (d, J = 9 Hz, 2 H), 7.62 (m, 1 H), 7.69 (d, J = 8 Hz, 1 H), 7.78 (m, 1 H), 8.02 (m, 2 H), 8.43 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 447 $(M + H)^+$. Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.49; H, 6.61; N, 5.99. **E-isomer 6** (960 mg, 81%): mp 105-106 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.05 (m, 5 H), 1.33 (m, 1 H), 1.67 (m, 4 H), 1.85 (m, 1 H), 2.03 (s, 3 H), 3.68 (s, 3 H), 4.95 (d, J = 7 Hz, 1 H), 5.36 (s, 2 H), 7.04 (d, J = 9 Hz, 2 H), 7.19 (d, J = 9 Hz, 2

H), 7.63 (m, 1 H), 7.67 (d, J = 8 Hz, 1 H), 7.80 (m, 1 H), 8.00 (m, 2 H), 8.42 (d, J = 8 Hz, 1 H); MS (DCI-NH_3) m/z 447 $(M + H)^+$. Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.45; H, 7.11; N, 6.09.

To a solution of the **Z-isomer 6** (74 mg, 0.17 mmol) in methanol-dioxane (1:2, 12 mL) was added 1N NaOH (1 mL) and the resulting mixture was stirred at rt for 24 h. The solvents were then removed *in vacuo,* the residue was diluted with water and acidified to pH 3 with 10% citric acid. The precipitated solid was filtered, dried *in vacuo* and recrystalllized from ethyl acetate-hexane to provide **Z-1** (65 mg, 88%). mp 142-144 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.07 (m, 5 H), 1.30 (m, 1 H), 1.62 (m, 5 H), 1.87 (s, 3 H), 4.70 (d, J = 7 Hz, 1 H), 5.35 (s, 2 H), 7.02 (d, J = 9 Hz, 2 H), 7.14 (d, J = 9 Hz, 2 H), 7.62 (m, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.80 (m, 1 H), 8.01 (m, 2 H), 8.41 (d, J = 8 Hz, 1 H), 13.56 (br s, 1 H); MS (DCI-NH_3) m/z 433 $(M + H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.99; H, 6.42; N, 6.21.

A solution of the **E-isomer 6** (770 mg, 1.7 mmol) was hydrolyzed by the same method as **Z-isomer 6** to provide 690 mg (94%) of **E-1.** mp 183-184 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.12 (m, 5 H), 1.35 (m, 1 H), 1.67 (m, 4 H), 1.86 (m, 1 H), 1.98 (s, 3 H), 4.92 (d, J = 7 Hz, 1 H), 5.35 (s, 2 H), 7.03 (d, J = 9 Hz, 2 H), 7.17 (d, J = 9 Hz, 2 H), 7.62 (m, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.78 (m, 1 H), 8.00 (m, 2 H), 8.42 (d, J = 8 Hz, 1 H), 13.56 (broad s, 1 H); MS (DCI-NH_3) m/z 433 $(M + H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.90; H, 6.75; N, 6.28.

***N*-Benzyloxy-2R,3R-dibenzoyltartarimide (7).** A solution of *O*-benzylhydroxylamine (prepared from commercially available HCl salt by neutralizing with aqueous saturated $NaHCO_3$ and extraction with ethyl ether, 5.14 g, 44 mmol) in THF (10 mL) was added to a solution of 2R,3R-(L)-dibenzoyltartaric acid anhydride[9] (L-DBTA, 14 g, 40 mmol) in THF (100 mL) and the mixture was stirred at rt for 12 h, then concentrated *in vacuo* and the residue was redissolved in $CHCl_3$ (100 mL). Thionyl chloride (3.65 mL, 50 mmol) was added dropwise to the chloroform solution at 0 °C and the resulting mixture was allowed to warm to rt for 4 h. The mixture was concentrated *in vacuo* and the residue was chromatographed (silica gel, 19:1 CH_2Cl_2-EtOAc) to provide **7** (18.9 g, 95%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 2 H), 5.75 (s, 2 H), 7.46 (m, 7 H), 7.61 (m, 4 H), 8.07 (m, 4 H); MS (DCI-NH_3) m/z 463 $(M + NH_4)^+$.

***N*-Hydroxy-2R,3R-dibenzoyltartarimide (8).** A solution of **7** (18.8 g, 42.2 mmol) in ethyl acetate (250 mL) was hydrogenated at 1 atm over 10% Pd-C (1.9 g) at rt for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo.* The residue was recrystallized from THF-hexane to provide **8** (14 g, 93 %). mp 140 -141 °C; $[\alpha]_D^{23}$ = +161.2 (c = 0.5, THF); ^1H NMR (300 MHz, DMSO-d_6) δ 6.23 (s, 2 H), 7.59 (t, J = 7 Hz, 4 H), 7.74 (m, 2 H), 8.03 (m, 4 H), 11.63 (br s, 1 H); MS (DCI-NH_3) m/z 373 $(M + NH_4)^+$. Anal. Calcd for $C_{18}H_{13}NO_7$ x 0.5 H_2O: C, 59.34; H, 3.87; N, 3.84. Found: C, 59.68; H, 3.55; N, 3.75.

***N*-Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methoxy-2R,3R-dibenzoyltartarimide Diastereomers (9a & 9b).** To a solution of **8** (1.42 g, 4 mmol), **3** (1.4 g, 4 mmol) and triphenylphosphine (1.57 g, 6 mmol) in THF (50 mL) was added dropwise a solution of DEAD (0.96 mL, 6 mmol) in THF (5 mL) and the mixture was stirred at rt for 4 h. The mixture was concentrated *in vacuo* and the residue was chromatographed (silica gel, 38:1 CH_2Cl_2-Et_2O) to provide a crude mixture of diastereomers **9a** and **9b** (1.64 g) contaminated with several impurities. Purification and separation of diastereomers was accomplished by chromatography (silica gel, 54:40:6 hexanes-CH_2Cl_2-EtOAc) to provide **9a** (470 mg) faster eluting diastereomer as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 1 H), 1.27 (m, 5 H), 1.64 (m, 2 H), 1.82 (m, 1 H), 2.04 (m, 1 H), 2.34 (m, 1 H),

5.07 (d, J = 9 Hz, 1 H), 5.40 (s, 2 H), 5.54 (s, 2 H), 7.04 (m, 2 H), 7.43 (m, 6 H), 7.61 (m, 3 H), 7.71 (m, 2 H), 7.80 (m, 1 H), 8.00 (m, 4 H), 8.08 (m, 1 H), 8.18 (d, J = 8 Hz, 1 H); MS (DCI/NH_3) m/z 685 $(M + H)^+$ and **9b** (310 mg) of slower eluting diastereomer : ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 1 H), 1.26 (m, 5 H), 1.65 (m, 2 H), 1.80 (m, 1 H), 2.06 (m, 1 H), 2.32 (m, 1 H), 5.10 (d, J = 9 Hz, 1 H), 5.37 (s, 2 H), 5.62 (s, 2 H), 7.05 (d, J = 9 Hz, 2 H), 7.41 (m, 6 H), 7.55 (m, 3 H), 7.67 (d, J = 8 Hz, 1 H), 7.74 (m, 1 H), 7.83 (m, 1 H), 7.97 (m, 4 H), 8.09 (d, J = 8 Hz, 1 H), 8.16 (d, J = 8 Hz, 1 H); MS (DCI/NH_3) m/z 685 $(M + H)^+$.

(R)-*O*-Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methylhydroxylamine ((R)-5a). A mixture of **9a** (470 mg, 0.68 mmol) and hydrazine hydrate (0.35 mL) in ethanol-dioxane (1:1, 30 mL) was refluxed for 30 min. The mixture was then cooled to rt, treated with aqueous 10% Na_2CO_3 and extracted with ethyl acetate. The organic extract was washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (silica gel, 2:1 hexane-ethyl acetate) to provide **(R)-5a** (200 mg, 80%). mp 105-106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 1 H), 1.12 (m, 4 H), 1.27 (m, 2 H), 1.62 (m, 4 H), 1.74 (m, 1 H), 2.03 (m, 1 H), 4.12 (d, J = 7.50 Hz, 1 H), 5.43 (s, 2 H), 7.03 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.57 (t, J = 7.50 Hz, 1 H), 7.75 (m, 2 H), 7.85 (m, 1 H), 8.16 (d, J = 9 Hz, 1 H), 8.24 (d, J = 9 Hz, 1 H); MS (DCI/NH_3) m/z 363 $(M + H)^+$; Anal. Calcd for $C_{23}H_{26}N_2O_2$ x 0.30 H_2O: C, 75.09; H, 7.29; N, 7.61; Found: C, 74.73; H, 7.39; N, 7.55.

(S)-*O*-(Cyclohexyl-(4-(2-quinolylmethoxy)phenyl))methylhydroxylamine ((S)-5b). The same procedure used for the preparation of **5a** was applied to **9b** to provide **(S)-5b** (70%). The bis-HCl salt was prepared by treating a solution of **(S)-5b** (109 mg, 0.3 mmol) in ether with HCl saturated ether. The solid formed was filtered and dried *in vacuo* to provide **(S)-5b:2HCl** (125 mg, 96%). mp 108 °C (decomp.)

(R)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid methyl ester ((R)-E-6a). To a solution of **5a** (181 mg, 0.5 mmol) in dioxane (15 mL) and methanol (10 mL) was added acetic acid (0.03 mL, 0.5 mmol) and methyl pyruvate (0.06 mL, 0.6 mmol). The mixture was stirred at rt for 12 h and then concentrated *in vacuo*. The residue was chromatographed (silica gel, 3:1 hexane/Et_2O) to provide 25 mg of inseparable 2:1 mixture of **(R)-Z-6a** and (R)-*O*-cyclohexyl-4-(2-quinolylmethoxy)phenylmethyl)oxime of acetaldehyde and 100 mg of **(R)-E-6a.** mp 99-101 °C; $[\alpha]_{D23}$ = -35.0 (c = 0.1, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ 1.10 (m, 6 H), 1.45 (m, 1 H), 1.67 (m, 3 H), 1.86 (m, 1 H), 2.02 (s, 3 H), 3.67 (s, 3 H), 4.95 (d, J = 7 Hz, 1 H), 5.35 (s, 2 H), 7.03 (d, J = 9 Hz, 2 H), 7.18 (d, J = 9 Hz, 2 H), 7.62 (m, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.79 (m, 1 H), 8.00 (t, J = 8 Hz, 2 H), 8.42 (d, J = 8 Hz, 1 H); MS (CDI/NH_3) m/z 447 $(M + H)^+$.

(S)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid methyl ester ((S)-E-6b). The same procedure used for **6a** was applied to provide crude product which was purified by chromatography (silica gel, 3:1 hexane/ether) to afford 20 mg of inseparable 2:1 mixture of **(S)-Z-6b** and (S)-*O*-cyclohexyl-4-(2-quinolylmethoxy)phenylmethyloxime of acetaldehyde and 80 mg of **(S)-E-6b.** mp 96-98 °C; $[\alpha]_{D23}$ = +33.3 (c = 0.15, $CHCl_3$).

(R)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid (R)-E-1a). 1N NaOH (0.2 mL, 0.2 mmol) was added to a solution of **(R)-E-6a** (80 mg, 0.18 mmol) in dioxane (6 mL) and methanol (3 mL) and the mixture was stirred at rt for 10 h. Water (10 mL) was added and the organic solvents were removed *in vacuo*. The aqueous residue was acidified to pH 3 with aqueous 10% citric acid and the precipitated solid was collected by filtration, washed with water and dried *in vacuo*. Recrystallization from ethyl acetate-hexane gave **(R)-E-1a** (60 mg, 76%). mp 179-180 °C; $[\alpha]_{D23}$ = -18.0 (c = 0.1, $CHCl_3$); ^1H

NMR (300 MHz, DMSO-d_6) δ 1.10 (m, 5 H), 1.36 (m, 1 H), 1.66 (m, 4 H), 1.87 (m, 1 H), 2.00 (s, 3 H), 4.92 (d, J = 7 Hz, 1 H), 5.35 (s, 2 H), 7.02 (d, J = 9 Hz, 2 H), 7.18 (d, J = 9 Hz, 2 H), 7.65 (m, 2 H), 7.79 (m, 1 H), 8.00 (t, J = 8 Hz, 2 H), 8.41 (d, J = 8 Hz, 1 H); MS (DCI/NH_3) m/z 433 $(M + H)^+$. Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.98; H, 6.44; N, 6.30.

(S)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid ((S)-E-1b). The same hydrolysis method used for **(R)-E-1a** was applied to **(S)-E-6b.** Recrystallization from ethyl acetate-hexane provided **(S)-E-1b** (35 mg, 88%). mp 179-180 °C; $[\alpha]_{D23}$ = +16.7 (c = 0.15, $CHCl_3$). Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.01; H, 6.49; N, 6.27.

(R)-*O*-Cyclohexyl-(4-(2-quinolylmethoxy)phenyl)methylhydroxylamine ((R)-5a). A mixture of racemic **5** (724 mg, 2 mmol) and 2R, 3R, L-DBTA (714 mg, 2.1 mmol) in anhydrous THF (50 mL) was stirred at rt until complete disappearance of amine by TLC analysis (~25 min). *N*-hydroxysuccinimide (230 mg, 2 mmol) was added followed by dropwise addition of solution of dicyclohexylcarbodiimide (DCC, 433 mg, 2.1 mmol) in THF (10 mL) and the mixture was stirred at rt for 12 h. The precipitated dicyclohexylurea was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed (silica gel, 3:1 hexanes-EtOAc) to provide 950 mg (~65%) of the mixture of diastereoisomers. The mixture was separated by chromatography (silica gel, 54:6:40 hexane-EtOAc-CH_2Cl_2) to provide **9a** (500mg). A solution of **9a** (500mg) and hydrazine hydrate (0.25 mL, 4 mmol) in dioxane-CH_2Cl_2 (2:1, 30 mL) was refluxed for 30 min and the mixture was worked up as previously described to provide **(R)-5a** (225 mg, 85%).

(R)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid (R)-E-1a). The hydroxylamine **(R)-5a** was converted to the oxime of methyl pyruvate as previously described to provide **((R)-E-1a)** (88%). mp 182-183 °C; $[\alpha]_{D23}$ = -17.8 (c = 0.09, $CHCl_3$); Anal. Calcd for $C_{26}H_{28}N_2O_4$ x 0.5 H_2O: C, 70.72; H, 6.62; N, 6.34. Found: C, 70.31; H, 6.24; N, 6.09.

(S)-*N*-Cyclohexyl-4-(2-quinolylmethoxy)phenylmethoxy)-2S,3S-dibenzoyltartarimide (11a). A solution of **5** (253 mg, 0.7 mmol) in THF (30 mL) was reacted with 2S, 3S, D-DBTA (made from unnatural tartaric acid, 340 mg, 1.0 mmol) by the same method as for **9a** above. The crude product was passed through a silica gel column (3:1 hexane-EtOAc) to afford a crude mixture of diastereoisomers (~500 mg). Purification and separation by chromatography (silica gel, 54:6:40 hexane-EtOAc-CH_2Cl_2) provided the faster eluting diastereomer **11a** (240 mg). $[\alpha]_{D23}$ = -265.0 (c = 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 1 H), 1.26 (m, 5 H), 1.62 (m, 2 H), 1.82 (m, 1 H), 2.04 (m, 1 H), 2.36 (m, 1 H), 5.07 (d, J = 9 Hz, 1 H), 5.40 (s, 2 H), 5.55 (s, 2 H), 7.03 (d, J = 9 Hz, 2 H), 7.44 (m, 6 H), 7.53 (m, 1 H), 7.62 (m, 2 H), 7.70 (m, 2 H), 7.81 (m, 1 H), 8.01 (m, 4 H), 8.08 (d, J = 8 Hz, 1 H), 8.20 (d, J = 8 Hz, 1 H) and the slower eluting diastereomer **11b** (150 mg) contaminated with about 25% of **11a**.

(S)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid ((S)-E-1b). The desired material was prepared from **11a** by the previously described methods to provide **(S)-E-1b** (81%).

(S)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid sodium salt To a solution of acid **(S)-E-1b** (1.85 g, 4.28 mmol) in THF (50 mL) was added 1N NaOH (4.28 mL, 4.28 mmol) and the mixture was stirred at rt for 1.5 h, then concentrated *in vacuo* and the residue was triturated with ether. The resulting solid was collected by filtration, washed with ether and dried *in vacuo* to afford **(S)-E-1b Na salt** (1.83 g, 94%). mp 204-218 °C; $[\alpha]_{D25}$ = +9.11 (c = 0.2, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.03 (m, 5 H), 1.36 (m, 1 H), 1.63 (m, 4 H), 1.92 (m, 1 H), 1.96 (s, 3 H), 4.74 (d, J = 7 Hz, 1 H), 5.33 (s, 2 H), 6.99

(d, J = 9 Hz, 2 H), 7.12 (d, J = 9 Hz, 2 H), 7.61 (m, 1 H), 7.67 (d, J = 8 Hz, 1 H), 7.78 (m, 1 H), 8.00 (m, 2 H), 8.40 (d, J = 8 Hz, 1 H); MS (FAB(+)) m/z 455 $(M + H)^+$, 477 $(M + Na)^+$. Anal. Calcd for $C_{26}H_{27}N_2O_4Na$ x 0.75 H_2O: C, 66.72; H, 6.13; N, 5.98. Found: C, 66.47; H, 5.97; N, 5.91.

(R)-2-E-(Cyclohexyl-4-(2-quinolinylmethoxy)phenyl)methoxyiminopropionic acid *N*-(3-bromo)benzylamide (10). To a solution of **R-E-1a** (82 mg, 0.2 mmol), N-hydroxysuccinimide (23 mg, 0.2 mmol), Et_3N (0.03 mL, 0.2 mmol) and 3-bromobenzylamine: HCl (45 mg, 0.2 mmol) in THF (10 mL) at rt was added dropwise a solution of DCC (41.2 mg, 0.2 mmol) in THF (5 mL). The mixture was stirred at rt for 48 h and then concentrated *in vacuo*. The residue was chromatographed (silica gel, 9:1 hexanes-EtOAc) to provide **10** (100mg, 83%). Crystallization from methanol gave crystals suitable for X-ray crystallography. mp 142-143 °C; $[\alpha]_{D^{23}} = +51.2$ (c = 0.125, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ 1.10 (m, 5 H), 1.38 (m, 1 H), 1.66 (m, 3 H), 1.84 (m, 2 H), 1.97 (s, 3 H), 4.27 (t, J = 5 Hz, 2 H), 4.92 (d, J = 7 Hz, 1 H), 5.36 (s, 2 H), 7.04 (d, J = 9 Hz, 2 H), 7.22 (m, 4 H), 7.40 (m, 2 H), 7.62 (m, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.79 (m, 1 H), 8.00 (m, 2 H), 8.42 (m, 2 H); MS (FAB(+)) m/z 600 $(M + H)^+$. Anal. Calcd for $C_{33}H_{34}BrN_3O_3$: C, 66.00; H, 5.71; N, 7.00. Found: C, 65.97; H, 5.74; N, 6.97.

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