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Asymmetric Synthesis of Optically Active Decahydroisoquinolines Useful in HIV-1 Protease Inhibitor Synthesis

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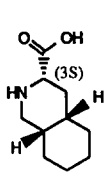
Abstract: An efficient synthesis of amino acid ester **8** is described featuring an asymmetric aza-Diels-Alder reaction of diene **5** and chiral imine **6** which establishes the asymmetry at C-3. Hydrogenation of **7** provides **8** with the desired asymmetry at C-4a and C-8a.

Acquired Immune Deficiency Syndrome (AIDS), a disease of global significance, has spurred worldwide research efforts to combat this disease. The HIV-1 virus, widely believed to be the causative agent for AIDS, contains an essential protease, the HIV-1 protease, required for further viral spread within the host.[2] It is hypothesized that inhibition of the HIV-1 protease will lead to an efficacious treatment for AIDS; consequently, numerous research groups have initiated HIV-1 protease inhibitor programs.[3]

[3S,4aS,8aS]-Decahydro-3-isoquinolinecarboxylic acid (**1**) is a substructure found within HIV-1 protease inhibitors **2**, and **3**[4] that we have recently reported, and within **4**,[5] an inhibitor currently in clinical trials for AIDS. While racemic **1** has been known for many years,[6] only recently have asymmetric syntheses[5c,7] of **1** been reported. We report, herein, an efficient synthesis of ester **8** which features an asymmetric aza-Diels-Alder reaction that establishes the asymmetry at C-3.



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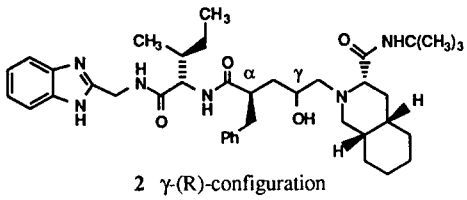
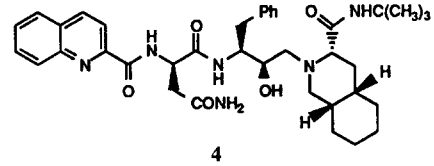


2 γ-(R)-configuration
3 γ-(S)-configuration



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We envisioned that construction of the heterocyclic ring within **1** could be assembled by an asymmetric aza-Diels-Alder reaction utilizing methodology recently reported for related systems.[8] In order to adapt this synthetic protocol to our needs, we required diene **5** and imine **6**[8] containing the (R)-configuration. Cisoid diene **5** has been shown[9] to be an excellent partner in Diels-Alder reactions; therefore, we anticipated no significant problems in our proposed synthetic pathway. Diene **5**, prepared by reported methods (a three step

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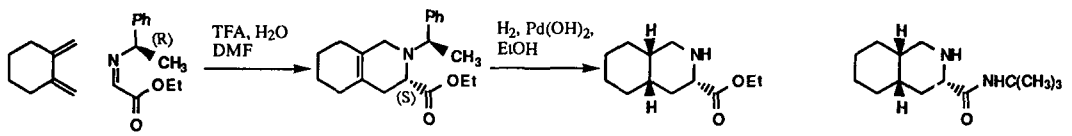
synthesis starting with 1,3,5-trithiane and requiring 1-methyl-1-cyclohexene)[10] was allowed to react with imine **6**[8] in the presence of trifluoroacetic acid (TFA) and water in dimethylformamide (DMF) solution (**Scheme 1**). Aza-Diels-Alder adduct **7** was obtained in 30% yield (crude yield of 45% as a 3:1 mixture of diastereoisomers) after silica gel chromatography ($[\alpha]_D$ 51.7° (c 1.43, MeOH)).[11] The assignment of (S)-configuration to the C-3 carbon atom relies on literature precedent, wherein a related aza-Diels-Alder product was shown by X-ray crystallography to have the (S)-configuration.[8d] It is, of course, obvious that if we had used the (S)-imine we would have obtained adduct **7** with the (R)-configuration at C-3; this experiment was not carried out.

Hydrogenation of **7** with Pearlman's catalyst[8d] gave the desired saturated and deprotected **8** in 45% yield after silica gel chromatography ($[\alpha]_D$ -66.2° (c 0.61, MeOH)). The unexpected volatility of ester **8** may have contributed to the somewhat diminished yield for this transformation. That hydrogenation of the olefin occurred *trans* to the existing ester of **7** was readily verified by nOe experiments.

Scheme 1.



5 **6** **7** **8** **9**

Carboxylic acid ester **8**, or its epimer at C-3, may prove useful as an intermediate in excitatory amino acids (EAA) receptor antagonists.[12] Further, the methyl ester analog of **8** has been previously transformed into amide **9**, an essential intermediate required for the syntheses of HIV-1 protease inhibitors **2**, **3**,[4] and **4**,[5] in a single step by reaction with $(i\text{-Bu})_2\text{AlNHC}(\text{CH}_3)_3$ in tetrahydrofuran (THF) solution.[7d,13] Access to the methyl (or other alkyl) ester analog of **8** should be available by this methodology.

In conclusion, we have demonstrated an efficient asymmetric synthesis of amino ester **8**, a useful intermediate in medicinal chemistry research. The synthesis is quite general in that it allows considerable functionality in the carbocyclic ring (based on the availability of the requisite dienes), the hydrogenation could be carried out with tritiated hydrogen to provide labeled material at non-epimerizable centers, and it should permit the installation of numerous amide side chains based on the availability of the requisite aluminum amides. Additionally, the synthesis is very short, can be carried out in a few weeks, and is amenable to multi-gram quantity scale-up. The use of low pressure hydrogenation in the current synthesis is a significant improvement over prior work.[6,7c] Appropriate choice of the chiral imine dictates the asymmetry at C-3, which in turn controls the asymmetry at C-4a, and C-8a. In addition to the use of these compounds in HIV-1 protease inhibitor synthesis, various stereoisomers and derivatives of **1** have found utility as EAA receptor antagonists,[12] and our synthesis may prove useful in the preparation of these derivatives.

Experimental Section

Melting points were determined on a Mel–Temp apparatus and are uncorrected. Fast atom bombardment (FAB) mass spectra were determined on a VG–ZAB SE mass spectrometer. Electron impact (EI) and chemical ionization (CI) mass spectra were determined on a Finnigan MAT–90 mass spectrometer. IR spectra were recorded on a Nicolet 20SXB FT–IR spectrometer. ^{1}H NMR spectra were determined at 300 MHz, and ^{13}C

NMR spectra were determined at 75 MHz, using a Nicolet QE–300 WB spectrometer; chemical shifts (δ) are in parts per million relative to tetramethylsilane. Apparent couplings are given in hertz. Specific rotations were recorded on a Perkin Elmer 241 Polarimeter. Elemental analyses were performed by Robertson Microlit Laboratories, Inc.; Madison, New Jersey. Unless otherwise noted all reagents and solvents obtained from commercial suppliers were of the highest possible purity and used without further purification. All non–aqueous reactions were performed in dry glassware under an inert atmosphere of dry argon or nitrogen.

Diastereomer ratios were determined by HPLC utilizing a DuPont Zorbax Rx C8 column (5 μm spherical, 4.6 mm x 250 mm) with water/THF/CH_3CN (47/37/16) mobile phase. Approximately 150-300 μg/mL of sample in CH_3CN was prepared; 20 μL of this solution was injected onto the column. Ultraviolet detection (210 nm) was carried out on a Waters Model 486 Tunable Absorbance detector. A Hewlett–Packard LAS 3350 instrument was used for data handling.

[(R)-(1-Phenylethyl)imino]acetic acid ethyl ester (6). A solution of ethyl glyoxylate[14] (5 g, 49 mmol), (R)-(+)-α-methylbenzyl amine (5.93 g, 49 mmol), and toluene was heated at the reflux temperature for 1.5 h. Water was removed from the reaction mixture with the aid of a Dean-Stark trap. The cooled reaction mixture was placed on a rotary evaporator to remove the solvent, leaving the product as an orange oil, 10.05 g (100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (brs, 1H), 7.36-7.33 (m, 5H), 4.60 (q, 1H), 4.34 (q, 2H), 1.62 (d, 3H), 1.34 (t, 3H). Lit.[8d] ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.32 (t, 3H, J = 7.0 Hz), 1.60 (d, 3H, J = 6.9 Hz), 4.31 (q, 2H, J = 7.0 Hz), 4.58 (q, 1H, J = 6.9 Hz), 7.31 (brs, 5H), 7.72 (s, 1H).

[R-(R*,S*)]-1,2,3,4,5,6,7,8-octahydro-2-(1-phenylethyl)-3-isoquinoline carboxylic acid ethyl ester (7). To a round-bottomed flask charged with 1,2-dimethylenecyclohexane[10] (3.16 g, 29.2 mmol) was added a solution of **6** (2.0 g, 9.7 mmol) dissolved in dimethylformamide (7 mL), trifluoroacetic acid (751 μL, 9.7 mmol) and water (1.8 μL, 0.097 mmol). The reaction mixture was stirred at room temperature for 84 h. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (50 mL), and washed with saturated aqueous sodium bicarbonate (200 mL), and brine (200 mL), then dried over anhydrous potassium carbonate. The solvent was removed *in vacuo*, and the residue purified by silica gel chromatography (250 g, elution with 10% ethyl acetate/hexane), followed by further chromatography (150 g, elution with 0.4% ethyl acetate/hexane) to provide the product as a low melting colorless solid 0.919 g (30%): $[\alpha]^{25}_D$ 51.7 (c = 1.43, MeOH); IR (neat) 1722, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.18 (m, 5H), 4.16 (q, J = 7.1 Hz, 2H), 4.06-3.95 (m, 2H), 3.09-2.73 (m, 2H), 2.58-2.23 (m, 2H), 1.96-1.75 (m, 2H), 1.70-1.40 (m, 6H), 1.35 (d, J = 6.6 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.40, 145.87, 128.17, 127.20, 126.86, 126.63, 123.56, 61.79, 59.74, 55.21, 51.06, 33.62, 29.39, 27.15, 22.84, 22.57, 20.74, 14.36 ppm; MS (FAB) m/e 314 (M+H). Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.37; H, 8.51; N, 4.43.

[3S-(3α,4aβ,8aβ)]-1,2,3,4,4a,5,6,7,8,8a-decahydro-3-isoquinolinecarboxylic acid ethyl ester (8). A solution of **7** (1.0 g, 3.19 mmol) dissolved in ethanol (53 mL), and Pearlman's catalyst (997 mg) was placed in a Parr hydrogenator with 45 psi of hydrogen gas for 45 h. The catalyst was removed by filtration through celite, and the filtrate concentrated *in vacuo*, to provide crude product 0.604 g (90%) which

was purified by chromatography on silica gel (75 g; elution with 5% MeOH/$CHCl_3$) to provide product as a colorless oil, 0.303 g (45%): $[\alpha]^{25}_D$ -66.2 (c = 0.61, MeOH); IR (neat) 2923, 2859, 1738, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.18 (q, J = 7.1 Hz, 2H), 3.34-3.29 (m, 1H), 2.89-2.80 (m, 2H), 1.93-1.24 (m, 13H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 173.54, 60.51, 59.34, 51.30, 35.39, 34.38, 31.59, 29.30, 26.20, 24.82, 20.65, 14.07 ppm; MS (FAB) m/e 212 (M+H). Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.50; H, 10.29; N, 6.56.

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