

SYNTHESIS OF (-)-HELIOTRIDANE AND (-)-ISORETRONECANOL VIA DIASTEREOSELECTIVE CONJUGATE ADDITION OF ORGANOCUPRATES TO AN ENOATE DERIVING FROM PROLINE

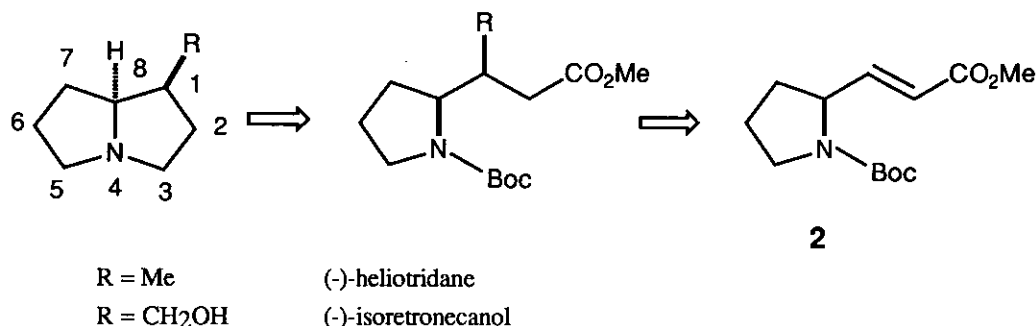
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Abstract - A synthesis of the pyrrolizidine alkaloids (-)-heliotridane and (-)-isoretronecanol and their epimers is described. The key step involves a diastereoselective conjugate addition of organocuprates to (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-[(*E*)-3'-methoxy-3'-oxo-1'-propenyl]pyrrolidine (**2**) deriving from (*S*)-proline.

Pyrrolizidine alkaloids have stimulated a great deal of interest because of their diverse biological activities.¹ The two simplest members of the necine family, isoretronecanol and heliotridane, have been the targets for a large number of syntheses providing either racemic or homochiral material.² The optical active pyrrolizidines have been obtained from building blocks such as proline,^{2a,b} malic acid^{2b} or carbohydrates.^{2c}



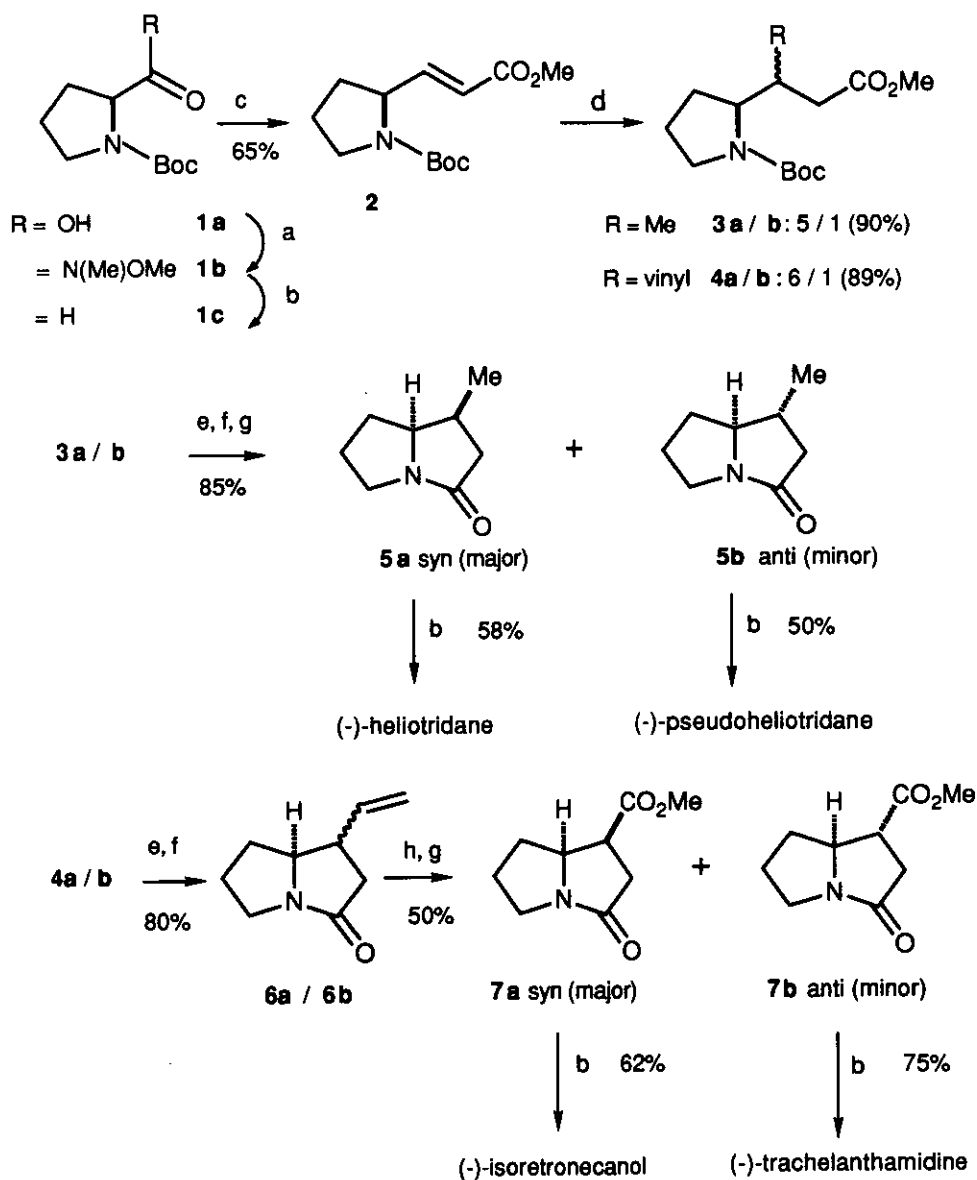
Scheme 1

Following our interest in the conjugate addition of cuprates to vinylogous esters of α amino acids,³ we report herein the synthesis of enantiomerically pure heliotridane and isoretronecanol starting from proline enoate (**2**). We are expecting that the conjugate addition toward **2** will be stereodirected by the *N*-Boc group attached at the chiral center. Indeed it has been recently reported by us⁴ and others^{5,6} that γ -amino- α,β -unsaturated esters underwent stereocontrolled conjugate additions with cuprates.

But in opposition to the corresponding γ -alkoxy related structures where the anti adducts are the major products, the γ -amino group favors the syn adduct.⁷ This reversal in selectivity, not fully understood at the moment,⁸ supports the rationale in our approach to the synthesis of heliotridane and isoretronecanol (Scheme 1).

Compound (**2**) was prepared from (*S*)-Boc-proline via the aldehyde^{9,10} and subsequent reaction with carbomethoxymethylenetriphenylphosphorane in THF at room temperature. The *E* isomer was contaminated with 5 % of the *Z* regioisomer, but as the two isomers are supposed to react similarly during conjugate addition, no purification was performed.³ Enoate (**2**) underwent addition of dimethyl- or divinylcuprates giving the diastereomeric mixture (**3a-b**) and (**4a-b**) respectively. The cuprates were prepared from the magnesium alkyls using CuBr-DMS and the conjugate addition was performed in presence of trimethylsilyl chloride.¹¹ The chemical transformation was completed within 2 h at -30°C. After purification through column chromatography on silica gel, the diastereomeric ratio was determined by ¹H nmr (200 MHz) using the methyl signal of the ester group. In spite of good yields we obtained only moderate diastereomeric excess (**3a-b** : 5/1; **4a-b** : 6/1) but in the expected sense (see below). Attempts to increase the stereoselectivity such as modification in the cuprate preparation, solvent change, stoichiometry or temperature were unsuccessful. Nevertheless we carried over the synthesis, performing the ring closure of the mixture (**3a-b**) or (**4a-b**) to yield the lactams (**5a-b**) and (**6a-b**). After the straightforward hydrolytic cleavage of the Boc group, the cyclisation was achieved using DMAP as catalyst in refluxing pyridine, using other conditions such as triethylamine in toluene or sodium carbonate in water afforded only decomposition of the starting material.¹² At this stage, the diastereomeric lactams (**5a**) and (**5b**) were separated using flash column chromatography. The relative stereochemistry of each isomer was determined by decoupling experiments. For the major isomer (**5a**) the coupling constant for the protons H₁-H₈ was 7.5 Hz corresponding to a dihedral angle of 20° (syn relationship), whereas for the minor isomer (**5b**) the related value was in the range of 2.3 Hz corresponding to a dihedral angle of 120° (anti relationship). These results nicely confirmed our assumption of the syn directing effect of the *N*-Boc group.^{4,5,6} Finally, the isomeric lactams (**5a**) and (**5b**) were reduced by treatment with LiAlH₄ in refluxing ether to (-)-heliotridane and (-)-pseudoheliotridane characterized as their picrates.^{13,14} On the other hand the vinyl group of the mixture of lactams (**6a-b**) were first oxidized to the corresponding carboxylates under Sharpless conditions,¹⁵ followed by diazomethane esterification. For the major isomer (**6a**) the value of the coupling constant for H₁-H₈ was 8.3 Hz, in agreement with a syn relationship.¹⁶ Thus the amide and carboxylate functions were both reduced with LiAlH₄ to obtain (-)-isoretronecanol [α]_D = -75° (c 0.5, EtOH) and (-)-trachelanthamidine [α]_D = -13° (c 0.3, EtOH), identified on the basis of their specific rotation (Scheme 2).^{17,18}

In conclusion, the conjugate addition of dimethyl- and divinylcuprates to enoate (**2**) provided the syn adducts as the major products. The relative and absolute stereochemistry has been established by the synthesis of (-)-



Reagents: a. TEA, pivaloyl chloride and then MeNHOMe; b. LiAlH₄; c. Ph₃P=CHCO₂Me, THF, room temperature; d. R₂CuLi, TMSCl, -30°C; e. HCl, AcOH; f. pyridine, DMAP, reflux; g. flash chromatography; h. Sharpless oxidation, see ref.15, then CH₂N₂.

Scheme 2

heliotridane and (-)-isoretronecanol, and the approach outlined here should be applicable to the synthesis of other pyrrolizidine or indolizidine alkaloids.

EXPERIMENTAL

Ir spectra were recorded on a Pye-Unicam SP3-300S spectrophotometer and ^1H nmr spectra were performed on a Bruker AC 200 (200 MHz) spectrometer using Me_4Si as internal reference. The optical rotation of compounds was measured on a Perkin-Elmer 241 MC polarimeter. Melting points were measured in open capillary tubes using a Gallenkamp apparatus, and are uncorrected. Purifications and separations by column chromatography were performed on silica gel, using the flash chromatography procedure. Ether and THF were distilled from sodium ketyl under argon. Tlc visualization was achieved by spraying with 2% ethanolic phosphomolybdic acid and charring. All reactions were performed under argon.

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-(*N*,*O*-dimethylhydroxyaminocarbonyl)pyrrolidine (1b).

Following the reported procedure,^{9b} a solution of (*S*)-Boc-proline (**1a**) (5 g, 23 mmol) in dichloromethane (70 ml) was cooled at -20°C and triethylamine (3.2 ml, 23 mmol) was added. The temperature was adjusted at -10°C and pivaloyl chloride (2.9 ml, 23 mmol) was added with a syringe. The obtention of the mixed anhydride was checked in Tlc: hexane/AcOEt: 1/1 ($R_f = 0.52$). A solution of *N*,*O*-dimethylhydroxylamine (4.48 g, 46 mmol) in dichloromethane (50 ml) was prepared in the meantime from its hydrochloride, and added at 0°C to the former mixture after filtration of the insoluble material (triethylamine hydrochloride). The mixture was stirred at room temperature for 2 h. Then the organic layer was cooled at 0°C and washed successively with HCl (0.2 N), NaOH (0.2 N), saturated brine and dried with sodium sulfate. Evaporation *in vacuo* of the solvent gave an oil which was purified by chromatography (hexane/AcOEt: 1/2) to afford 5 g (89%, oil) of the title compound (**1b**). ^1H Nmr (200 MHz, CDCl_3) δ 1.40–1.45 (2s, 9H, rotamers), 1.62–2.04 (m, 4H), 3.19 (s, 3H), 3.42–3.54 (m, 2H), 3.71–3.77 (2s, 3H, rotamers), 4.56–4.79 (X part from a ABX, $J_{\text{AX}} + J_{\text{BX}} = 11.5$ Hz).

(*S*)-*N*-*tert*-Butoxycarbonylprolinal (**1c**).

To a suspension of LiAlH_4 (0.97 g, 25.6 mmol, 1.25 eq.) in dry ether (30 ml) at -10°C was added dropwise proline hydroxamate (**1b**) (5.0 g, 20.5 mmol, 1 eq.) in dry ether (30 ml). After stirring 30 min at -10°C , the reaction mixture was quenched by slow addition of H_2O (2 ml) in THF (5 ml). The reaction mixture was filtered, the organic layer was washed with saturated brine, dried and concentrated *in vacuo* by maintaining the water bath temperature below 30°C . The obtained oil, identified as (**1c**) (3.9 g, 96%), was used in the next step without purification.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(*E*)-3'-methoxy-3'-oxo-1'-propenyl]pyrrolidine (**2**).

A mixture of prolinal (**1c**) (3.28 g, 16.5 mmol) and methyl triphenylphosphoranylideneacetate (8.16 g, 27

mmol) in THF (50 ml) was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was taken up in ether and filtered to remove triphenylphosphine oxide. After evaporation *in vacuo*, the residue was purified by chromatography on silica gel (hexane/AcOEt: 3/1) to leave (2) as a clear yellow oil (3.37 g, 80%). ^1H Nmr (200 MHz, CDCl_3) δ 1.42 (s, 9H), 1.71-1.91 (m, 4H), 3.40-3.45 (m, 2H), 3.70 (s, 3H), 4.40 (m, 1H), 5.77-5.85 (d, 1H, $J = 15.5$ Hz), 6.68-6.78 (dd, 1H, $J = 7.5$ and 15.5 Hz). $[\alpha]_D = -70^\circ$ ($c = 1$, CHCl_3). Anal. calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 59.96; H, 8.12; N, 5.51.

(2*S*,3'*R'* and 3'*S*)-*N*-*tert*-Butoxycarbonyl-2-(3'-methoxy-3'-oxo-1'-methylpropyl)pyrrolidine (3a/b).

To a solution of dimethylcuprate (11.7 mmol, 3 eq.) in dry ether (30 ml) prepared from CuI (2.24 g, 11.7 mmol) and MeLi, LiBr complex (15.6 ml, 6 eq., 1.5 M solution in Et_2O) was added at -40°C TMSCl (1.5 ml, 11.7 mmol, 3 eq.) followed by a solution of enoate (2) (1 g, 3.9 mmol, 1 eq.) in dry ether (5 ml). The mixture was stirred at -40°C for 30 min and allowed to reach the room temperature. The reaction was quenched with saturated NH_4Cl and extracted 3 times with ether. The organic layers were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (hexane/AcOEt: 7/1) to give a mixture of (3a/b) as a clear yellow oil (0.94 g, 90 %). ^1H Nmr (200 MHz, CDCl_3) δ 0.87-0.93 (d, $J = 6$ Hz, 3H), 1.46 (s, 9H), 1.64-2.39 (m, 7H), 3.14-3.22 (m, 1H), 3.66 (s, 3H), 3.49-3.77 (m, 2H); minor isomer δ 0.87-0.90 (d, $J = 6$ Hz); 3.63 (s).

(1*S*,2*S*)-2-Methyl-5-azabicyclo[3.3.0]octan-4-one (5a) and (1*S*,2*R*)-2-Methyl-5-azabicyclo[3.3.0]octan-4-one (5b).

A mixture of (3a/b) (0.94 g, 3.5 mmol) in HCl (11 N, 2 ml) and AcOH (6 ml) was stirred at room temperature for 30 min. The solvent was evaporated *in vacuo* and the residue was treated with ether/isopropanol to yield a white solid, which was used in the next step without purification. This solid was heated under reflux in pyridine (10 ml) with a catalytic amount of DMAP for 12 h. The pyridine was evaporated *in vacuo* and the residue was carefully purified by chromatography on silica gel (hexane/AcOEt/MeOH: 2/1/0.1) to obtain the two diastereoisomers: (5a) (347 mg, 84%, oil) was first eluted, followed by (5b) (77 mg, 16%, oil), in a total yield of 85%. Physical data for (5a): ^1H Nmr for (200 MHz, CDCl_3) δ 1.15 (d, 3H, $J = 6.5$ Hz), 1.22-1.49 (m, 1H), 1.96-2.26 (m, 4H), 2.39-2.63 (AB part from ABX, 2H, $J = 8.5$, 10.7 and 15.9 Hz), 2.99-3.11 (m, 1H), 3.45-3.62 (m, 2H). ^{13}C Nmr (50 MHz, CDCl_3) δ 17.5, 26.6, 30.2, 37.5, 40.9, 43.4, 62.6, 175.1. Ms: 139 (M^+), 111, 93, 70, 69, 41. $[\alpha]_D = -52.4^\circ$ ($c = 1$, CHCl_3). Anal. calcd for $\text{C}_8\text{H}_{13}\text{NO}$: C, 69.02; H, 9.41; N, 10.06. Found: C, 68.76; H, 9.75; N, 10.20. Physical data for (5b): ^1H Nmr (200 MHz, CDCl_3) δ 0.95-0.99 (d, 3H, $J = 7.2$ Hz), 1.44-1.76 (m, 2H), 1.97-2.15 (m, 3H), 2.49-2.61 (m, 1H), 2.84-2.97 (A part from ABX, 1H, $J = 8$ and 15 Hz), 3.00-3.13 (m, 1H), 3.45-3.59 (dt, 1H, $J = 7.9$ and 11.4 Hz), 3.91-4.03 (dt, 1H, $J = 9.6$ and 6.5 Hz). ^{13}C Nmr (50 MHz, CDCl_3) δ 15.7, 24.8, 26.7, 29.4, 40.9, 42.8, 64.8, 177.2. $[\alpha]_D = -43.8^\circ$ ($c = 1$, CHCl_3). Anal. calcd for $\text{C}_8\text{H}_{13}\text{NO}$: C, 69.02; H, 9.41; N, 10.06. Found: C, 69.43; H, 9.55; N, 10.20.

(-)-Heliotridane.

A solution of amide (**5a**) (200 mg, 1.4 mmol) in dry THF (4 ml) was slowly added to a stirred suspension of LiAlH_4 (163 mg, 4.3 mmol) in THF (5 ml) at -10°C . After completion of the addition, the reaction mixture was heated at reflux for 2 h. The reaction was quenched by addition of H_2O , filtered and the cake was washed 3 times with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and was concentrated *in vacuo* to yield (-) heliotridane (100 mg, 58%). $[\alpha]_D = -90^\circ$ ($c = 0.5$, EtOH), lit.,¹³ $[\alpha]_D = -90^\circ$ ($c = 0.5$, EtOH).

(-)-Pseudoheliotridane.

The above procedure, performed on (**5b**) (140 mg, 1 mmol) was used for the obtention of (-)-pseudoheliotridane (65 mg, 52%). $[\alpha]_D = -7^\circ$ ($c = 0.5$, EtOH), lit.,¹⁴ $[\alpha]_D = -8.2^\circ$ ($c = 0.5$, EtOH).

(2*S*,3'*R* and 3'*S*)-*N*-tert-Butoxycarbonyl-2-(3'-methoxy-3'-oxo-1'-vinylpropyl)pyrrolidine (4a/b).

To a solution of divinylcuprate (30 mmol, 3 eq.) in THF (50 ml), prepared from $\text{CuBr}\cdot\text{DMS}$ (30 mmol, 3 eq.), LiBr (60 mmol, 6 eq.) and vinylmagnesium bromide (60 mmol, 6 eq.) was added at -40°C a solution of enoate (**2**) (10 mmol, 1 eq.) diluted in THF (10 ml). The mixture was stirred at -40°C for 30 min and allowed to reach the room temperature. The reaction was quenched with saturated NH_4Cl and extracted 3 times with ether. The organic layers were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (hexane/ AcOEt : 6/1) to give (**4a/b**) as a clear oil (2.52 g, 90 %), as mixture of diastereomers. ^1H Nmr (200 MHz, CDCl_3) δ 1.48 (s, 9H), 1.66-1.93 (m, 4H), 2.27-2.40 (m, 4H), 3.15-3.23 (m, 2H), 3.64 (s, 3H), 5.03-5.12 (dd, 2H, $J = 7.6$ and 16.5 Hz), 5.56-5.66 (m, 1H); minor isomer: δ 3.61 (s).

(1*S*,2*S* and 2*R*)-2-Vinyl-5-azabicyclo[3.3.0]octan-4-one (6a/b).

The above procedure for the obtention of (**5a/b**) was used starting from a mixture of (**4a/b**) (2.45 g, 0.9 mmol). The residue was purified by chromatography on silica gel (hexane/ AcOEt/MeOH : 2/1/0.1). (**6a/b**) (oil, 1.21 g, 85%) was obtained as a mixture of diastereomers, used as such in the next step. ^1H Nmr (200 MHz, CDCl_3) δ 1.46-1.75 (m, 2H), 1.90-2.08 (m, 2H), 2.24-2.34 (dd, 1H, $J = 2.9$ and 16.5 Hz), 2.53-2.69 (m, 2H), 2.83-3.11 (m, 2H), 3.49-3.63 (m, 1H), 3.94-4.05 (m, 1H), 5.04-5.13 (m, 2H), 5.64-5.87 (m, 1H).

(1*S*,2*S*)-2-Methoxycarbonyl-5-azabicyclo[3.3.0]octan-4-one (7a) and (1*S*,2*R*)-2-methoxycarbonyl-5-azabicyclo[3.3.0]octan-4-one (7b).

A mixture of (**6a/b**) (0.400 g, 2.64 mmol), NaIO_4 (5.65 g, 26.4 mmol, 10 eq.) and RuCl_3 , H_2O (30 mg, 0.13 mmol, 0.05 eq.) was vigorously stirred in CCl_4 (6 ml), MeCN (6 ml) and H_2O (9 ml) at room temperature for

2 h. The mixture was extracted 3 times with CH_2Cl_2 . The combined organic layers were washed with brine and concentrated *in vacuo*. The residue was treated with CH_2N_2 to afford a clear oil which was purified by a careful chromatography on silica gel (hexane/AcOEt/MeOH: 1/1/0.2) to separate cleanly the diastereoisomers in a total yield of 50 %: (7a) (oil, 210 mg, 90%) and (7b) (oil, 25 mg, 10%). Physical data for (7a): ^1H Nmr (200 MHz, CDCl_3) δ 1.81-2.11 (m, 4H), 2.80-2.84 (d, 2H, $J = 7.9$ Hz), 2.98-3.10 (ddd, 1H, $J = 3.6, 8.7$ and 11.0 Hz), 3.33-3.44 (dt, 1H, $J = 7.9$ and 8.3 Hz), 3.51-3.65 (dt, 1H, $J = 8.0$ and 11.0 Hz), 3.70 (s, 3H), 4.04-4.16 (ddd, 1H, $J = 5.7, 8.3$ and 10.1 Hz). $[\alpha]_D = -137.5^\circ$ ($c = 1.4$, CHCl_3). Anal. calcd for $\text{C}_9\text{H}_{13}\text{NO}_3$: C, 59.00; H, 7.10; N, 7.64. Found: C, 59.35; H, 7.15; N, 7.64. Physical data for (7b): ^1H Nmr (200 MHz, CDCl_3) δ 2.00-2.25 (m, 3H), 2.64-2.81 (m, 1H), 2.91-3.15 (m, 3H), 3.50-3.63 (dt, 1H, $J = 7.8$ and 15.4 Hz), 3.75 (s, 3H), 4.00-4.12 (m, 1H). $[\alpha]_D = -80^\circ$ ($c = 1.5$, CHCl_3). Anal. calcd for $\text{C}_9\text{H}_{13}\text{NO}_3$: C, 59.00; H, 7.10; N, 7.64. Found: C, 59.26; H, 6.67; N, 7.32.

(-)-Isoretronecanol.

To a suspension of LiAlH_4 (38 mg, 0.98 mmol, 3 eq.) in dry THF (3 ml) was added dropwise a solution of (7a) (50 mg, 0.33 mmol, 1 eq.). After refluxing for 4 h, the mixture was cooled at 0°C and H_2O was added carefully. Filtration and evaporation of the solvent *in vacuo* afforded an oil which was purified by chromatography (CHCl_3 , MeOH, triethylamine: 1/1/0.1) to yield (-)-isoretronecanol (28 mg, 60%). $[\alpha]_D = -75^\circ$ ($c = 0.5$, EtOH), lit., $^{17}[\alpha]_D = -78.2^\circ$ ($c = 2$, EtOH).

(-)-Trachelanthamidine.

The above procedure was used starting from (7b) (53 mg, 0.35 mmol) to yield (-)-trachelanthamidine (33 mg, 66%). $[\alpha]_D = -13^\circ$ ($c = 0.3$, EtOH), lit., $^{18}[\alpha]_D = -13.8^\circ$ ($c = 1.2$, EtOH).

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