

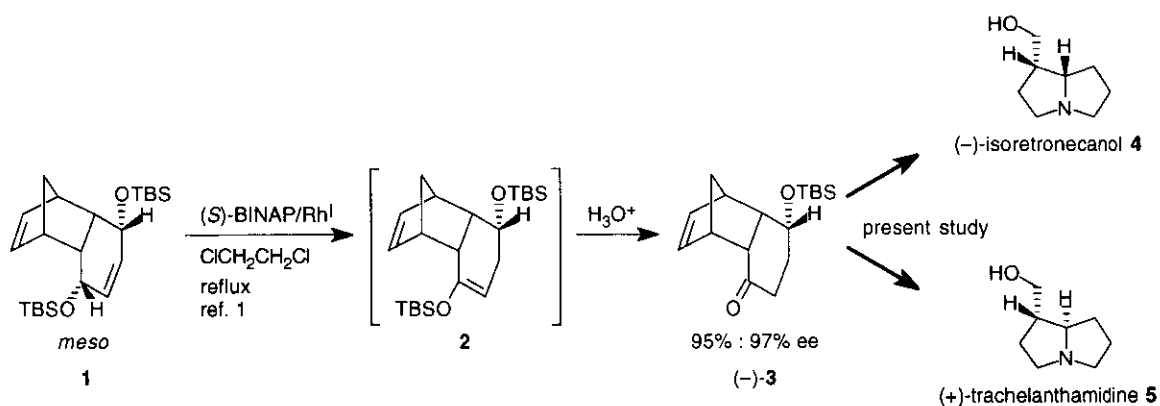
**AN ENANTIO- AND DIASTEREOSELECTIVE SYNTHESIS OF  
(-)-ISORETRONECANOL AND (+)-TRACHELANTHAMIDINE  
FROM A *MESO* PRECURSOR<sup>†</sup>**

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*Abstract* — Two diastereomeric pyrrolizidine alkaloids, (-)-isoretronecanol and (+)-trachelanthamidine, have been synthesized in an enantio- and diastereoselective manner starting from a *meso* precursor via a catalytic asymmetrization.

We found that the *meso*-enediol bis-silyl ether (**1**) rearranged on reflux with a catalytic amount of a chiral BINAP-Rh<sup>I</sup> catalyst in 1,2-dichloroethane to give enantioselectively the silyl enol ether (**2**) which afforded the siloxy ketone (**3**) in high optical purity on hydrolytic workup.<sup>1</sup> In order to exploit the optically active ketone (**3**) as a versatile chiral building block,<sup>2</sup> we attempted diastereoselective conversion of (-)-**3**, obtained in 95% yield with 97% ee using (*S*)-BINAP-Rh<sup>I</sup> catalyst, into two typical diastereomeric pyrrolizidine alkaloids,<sup>3</sup> (-)-isoretronecanol<sup>4</sup> (**4**) and (+)-trachelanthamidine<sup>5</sup> [(+)-laburnine<sup>4a, b</sup>] (**5**), utilizing (-)-**3** as an equivalent of (*R*)-4-hydroxy-2-cyclohexenone<sup>6</sup> (**Scheme 1**). Herein, we report a new enantio- and diastereoselective route to these two alkaloids based on molecular bias and thermal lability of the starting ketone [(-)-**3**].

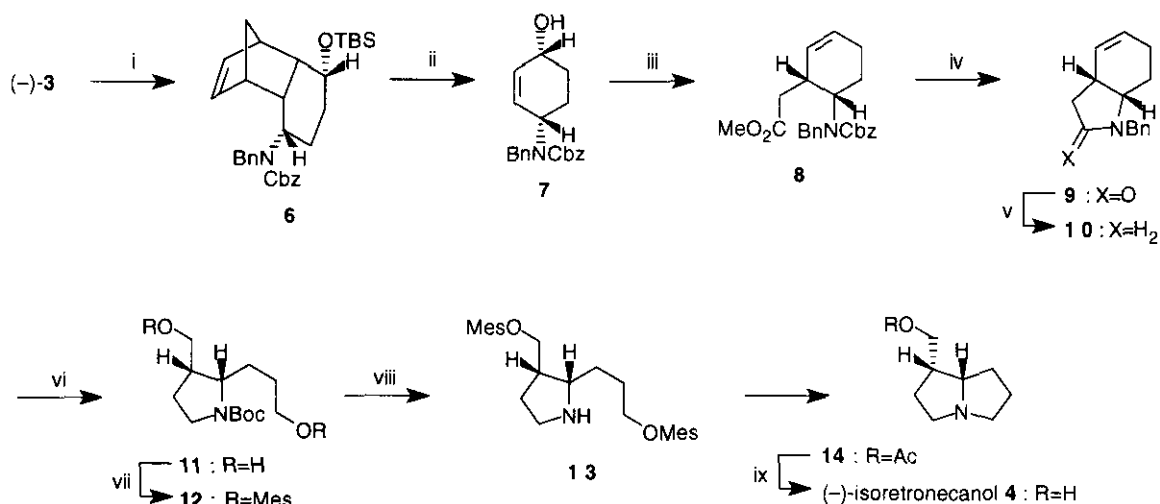


**Scheme 1**

To obtain (-)-isoretronecanol (**4**), (-)-**3** was first transformed into the *endo*-carbamate (**6**), [ $\alpha$ ]<sub>D</sub><sup>25</sup> -27.7° (*c*

<sup>†</sup> Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

1.0,  $\text{CHCl}_3$ ), in 50% overall yield through sequential imine formation, borohydride reduction and carbamoylation.<sup>7</sup> Owing to the biased tricyclic structure, the reduction of the imine intermediate occurred selectively from the convex-face to give a single product having *endo*-1,4-configuration. Thermolysis of **6** in refluxing diphenyl ether in the presence of sodium hydrogen carbonate<sup>8</sup> (20 equiv.) initiated a retro-Diels-Alder reaction with expulsion of cyclopentadiene to furnish the *cis*-4-substituted 2-cyclohexenol (**7**),  $[\alpha]_D^{27} -27.8^\circ$  (*c* 1.4,  $\text{CHCl}_3$ ), in an excellent yield after desilylation. Because the allylic alcohol (**7**) was found to be incompatible with the acid-mediated Johnson-Claisen conditions,<sup>9</sup> **7** was transformed into the *cis*-methyl ester (**8**),  $[\alpha]_D^{30} -110.0^\circ$  (*c* 2.8,  $\text{CHCl}_3$ ), in 72% overall yield *via* vinyl ether formation,<sup>10</sup> Claisen rearrangement,<sup>10</sup> oxidation<sup>11</sup> and esterification. On exposure to boron tribromide<sup>12</sup> followed by treatment with triethylamine, **8** afforded the  $\gamma$ -lactam (**9**),  $[\alpha]_D^{30} -3.5^\circ$  (*c* 1.0,  $\text{CHCl}_3$ ), *via* concurrent debenzoylation, decarboxylation, and cyclization, which was reduced with lithium aluminum hydride in refluxing THF to give rise to the bicyclic amine (**10**),  $[\alpha]_D^{29} +37.7^\circ$  (*c* 1.6,  $\text{CHCl}_3$ ), in 74% overall yield. Transformation of **10** into the target (–)-isoretronecanol (**4**) was found to be unexpectedly difficult. However, the transformation was accomplished through a sequence of 9 steps of reactions. Thus, **10** was first converted into the *cis*-2,3-disubstituted pyrrolidine carbamate (**11**),  $[\alpha]_D^{30} +0.7^\circ$  (*c* 0.4,  $\text{CHCl}_3$ ), in 26% overall yield *via* sequential dihydroxylation, debenzoylation, carbamoylation, and one-pot oxidative cleavage and reduction. Mesylation of **11** gave the dimesylate (**12**) which was exposed with trifluoroacetic acid to give the amino-dimesylate (**13**). The crude **13** was then treated with potassium acetate in DMSO at 80 °C to induce double substitution<sup>4d</sup> to furnish the pyrrolizidine (**14**),  $[\alpha]_D^{30} -42.7^\circ$  (*c* 0.6,  $\text{CHCl}_3$ ). Finally, **14**

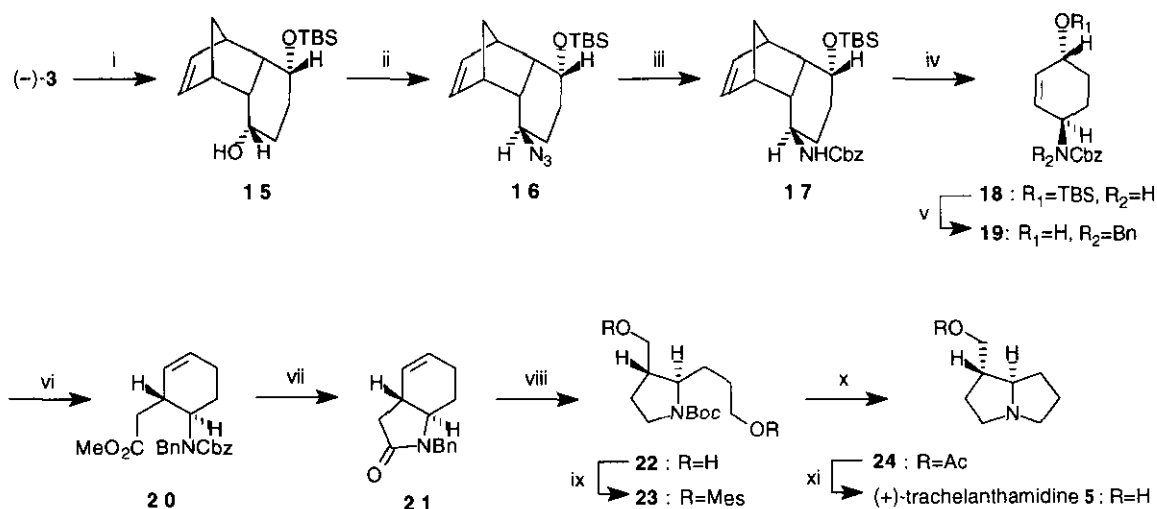


Scheme 2

**Reagents and conditions:** i) (a)  $\text{BnNH}_2$ , then  $\text{NaBH}_4$ , (b)  $\text{Cbz-Cl}$ ,  $\text{NaH}$ , DMF (50%). ii) (a)  $\text{NaHCO}_3$ ,  $\text{Ph}_2\text{O}$ , reflux, (b) TBAF, THF (80%). iii) (a) ethyl vinyl ether,  $\text{Hg}(\text{OAc})_2$ , reflux, (b)  $\text{Ph}_2\text{O}$ , reflux, (c)  $\text{NaClO}_2$ ,  $\text{NaH}_2\text{PO}_4$ , 2-methyl-2-butene, aq. *t*-BuOH, acid workup then  $\text{CH}_2\text{N}_2$  (72%). iv) (a)  $\text{BBR}_3$ ,  $\text{CH}_2\text{Cl}_2$ , (b)  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$  (87%). v)  $\text{LiAlH}_4$ , THF, reflux (85%). vi) (a)  $\text{OsO}_4$  (cat.), NMO, aq. THF, (b)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , MeOH, (c)  $(\text{Boc})_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , (d)  $\text{NaIO}_4$ , aq. THF, then  $\text{NaBH}_4$  (26%). vii)  $\text{Mes-Cl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ . viii) TFA then  $\text{AcOK}$ , DMSO, 80 °C (92% from **11**). ix) 33%  $\text{NH}_4\text{OH}$ , MeOH (84%).

was exposed to ammonium hydroxide to give (-)-isoretronecanol (**4**),  $[\alpha]_D^{29} -74.0^\circ$  ( $c$  0.2, EtOH) [lit.<sup>4n</sup>,  $[\alpha]_D^{27} -77.0^\circ$  ( $c$  0.3, EtOH)], in 77% overall yield from **11** (Scheme 2).

On the other hand, to obtain (+)-trachelanthamidine (**5**), (-)-**3** was first reduced stereoselectively from the convex-face to give the *endo*-alcohol (**15**), mp 128-130 °C,  $[\alpha]_D^{27} +17.2^\circ$  ( $c$  1.0, CHCl<sub>3</sub>), in 85% yield. Treatment of **15** with diphenyl phosphorylazide (DPPA) under Mitsunobu conditions<sup>13</sup> led to generation of the azide (**16**),  $[\alpha]_D^{28} -32.4^\circ$  ( $c$  1.3, CHCl<sub>3</sub>), having *anti*-1,4-configuration with inversion of the stereochemistry. On exposure to triphenylphosphine,<sup>14</sup> followed by carbobenzoxy chloride, **16** gave the secondary carbamate (**17**),  $[\alpha]_D^{32} +8.1^\circ$  ( $c$  0.9, CHCl<sub>3</sub>). Overall yield of **17** from **15** was 36%. Thermolysis of **17** in refluxing diphenyl ether in the presence of sodium hydrogen carbonate<sup>8</sup> afforded the *trans*-4-substituted 2-cyclohexenyl silyl ether (**18**),  $[\alpha]_D^{27} +108.2^\circ$  ( $c$  0.1, CHCl<sub>3</sub>), in 80% yield by the retro-Diels-Alder reaction. On sequential *N*-benzylation and desilylation, **18** gave the cyclohexenol (**19**),  $[\alpha]_D^{29} +91.9^\circ$  ( $c$  1.0, CHCl<sub>3</sub>), in 59% overall yield, which was transformed into the *trans*-methyl ester (**20**),  $[\alpha]_D^{29} -23.3^\circ$  ( $c$  0.5, CHCl<sub>3</sub>), in 59% overall yield *via* a five-step sequence exactly the same as that employed for the preparation of the *cis*-counterpart (**8**) above. Decarbamylation of **20**, followed by treating the resulting amine with DBU in refluxing benzene afforded the  $\gamma$ -lactam (**21**), mp 83-84 °C,  $[\alpha]_D^{30} +119.6^\circ$  ( $c$  0.2, CHCl<sub>3</sub>), in 83% yield. On sequential one-pot ozonolysis- reduction of the olefinic functionality, reduction of the lactam functionality, debenzylation, and carbamylation, **21** furnished the *trans*-2,3-disubstituted pyrrolidine (**22**),  $[\alpha]_D^{31} -40.2^\circ$  ( $c$  0.3, CHCl<sub>3</sub>), in 52% overall yield. Quite similarly as for the *cis*-diastereomer, the *trans*-diol (**22**) was transformed into (+)-trachelanthamidine [(+)-



Scheme 3

**Reagents and conditions:** i) NaBH<sub>4</sub>, MeOH (84%). ii) DPPA, DEAD, PPh<sub>3</sub>, THF (81%). iii) (a) PPh<sub>3</sub>, aq. THF, (b) Cbz-Cl, NaH, DMF (42%). iv) NaHCO<sub>3</sub>, Ph<sub>2</sub>O, reflux (80%). v) (a) BnBr, NaH, DMF, (b) TBAF, THF (59%). vi) (a) ethyl vinyl ether, Hg(OAc)<sub>2</sub>, reflux, (b) Ph<sub>2</sub>O, reflux, (c) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, aq. *t*-BuOH, acid workup then CH<sub>3</sub>N<sub>3</sub>, (59%). vii) (a) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, (b) DBU, benzene, reflux (83%). viii) (a) O<sub>3</sub>, MeOH-CH<sub>2</sub>Cl<sub>2</sub>, then NaBH<sub>4</sub>, (b) LiAlH<sub>4</sub>, THF, reflux, (c) H<sub>2</sub>, Pd(OH)<sub>2</sub>, MeOH, (d) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, (52%). ix) Mes-Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>. x) TFA then AcOK, DMSO, 80 °C (55% from **22**). xi) 33% NH<sub>4</sub>OH-MeOH (84%).

laburnine] (**5**),  $[\alpha]_{\text{D}}^{28} +10.6^{\circ}$  (c 0.2, EtOH) [lit.<sup>4n</sup> for (-)-enantiomer:  $[\alpha]_{\text{D}}^{27} -14.0^{\circ}$  (c 0.5, EtOH)], in 46% overall yield via the dimesylate (**23**) and the acetate (**24**),  $[\alpha]_{\text{D}}^{31} +11.3^{\circ}$  (c 0.2, CHCl<sub>3</sub>), by sequential mesylation, decarbamylation, cyclization<sup>4d</sup> and deacetylation (Scheme 3).

In conclusion, we have developed an enantio- and diastereoselective synthesis of two diastereomeric pyrrolizidine alkaloids, (-)-isoretronecanol (**4**) and (+)-trachelanthamidine (**5**), based on the chemical and stereochemical background of the tricyclic ketone [(-)-**3**] readily accessible in high optical purity from the meso-enediol bis-silyl ether (**1**) by (*S*)-BINAP-Rh<sup>I</sup> catalyzed asymmetric reduction. Thus, our intended utilization of the optically active ketone (**3**) as a chiral equivalent of (*R*)-4-hydroxycyclohexenone was realized as visualized.

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  15. Spectral data of the selected intermediates — **7**: IR (film)  $\nu=3434, 1691 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.45$  (1H, s), 1.75 (4H, m), 4.06 (1H, s), 4.40 (1H, d,  $J=15.9$  Hz), 4.41 (1H, d,  $J=15.9$  Hz), 4.56 (1H, d,  $J=14.7$  Hz), 5.14 (2H, s), 5.66 (1H, d,  $J=9.8$  Hz), 5.86 (1H, m), 7.25 (5H, m), 7.36 (5H, m); HRMS  $m/z=337.1678$ . **9**: IR (film)  $\nu=1684 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.61$  (1H, m), 1.81 (1H, m), 1.93 (2H, m), 2.24 (1H, dd,  $J=7.1, 16.2$  Hz), 2.63 (1H, dd,  $J=9.1, 16.2$  Hz), 2.80 (1H, m), 3.57 (1H, ddd,  $J=3.8, 7.9, 7.9$  Hz), 3.99 (1H, d,  $J=14.8$  Hz), 5.02 (1H, d,  $J=14.8$  Hz), 5.58 (1H, m), 5.78 (1H, m), 7.31 (5H, m); HRMS  $m/z=227.1307$ . **11**: IR (film)  $\nu=3394, 1666 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.50$  (9H, s), 1.70 (5H, m), 1.94 (2H, m), 2.39 (1H, m), 3.36 (2H, m), 3.70 (4H, m), 4.10 (1H, m); HRMS  $m/z=186.1124$ . **14**: IR (film)  $\nu=1738 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.76$  (2H, m), 2.13 (4H, m), 2.22 (3H, s), 2.72 (1H, dt,  $J=6.3, 10.4$  Hz), 2.85 (1H, m), 3.05 (1H, ddd,  $J=2.2, 7.4, 14.3$  Hz), 3.67 (1H, dt,  $J=6.3, 11.8$  Hz), 3.96 (1H, m), 4.08 (1H, dd,  $J=8.2, 11.3$  Hz), 4.25 (1H, dd,  $J=6.3, 11.3$  Hz), 4.36 (1H, dt,  $J=11.8, 7.7$  Hz); HRMS  $m/z=183.1263$ . **19**: IR (film)  $\nu=3434, 1695 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.52$  (3H, m), 2.03 (2H, m), 4.40 (3H, m), 4.80 (1H, m), 5.16 (2H, m), 5.58 (1H, m), 5.82 (1H, m), 7.23 (10H, m); HRMS  $m/z=337.1702$ . **21**: IR (film)  $\nu=1695 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.50$  (1H, m), 2.13 (4H, m), 2.25 (1H, m), 2.55 (1H, m), 3.16 (1H, ddd,  $J=2.5, 12.4, 15.1$  Hz), 4.28 (1H, d,  $J=14.8$  Hz), 4.70 (1H, d,  $J=14.8$  Hz), 5.55 (1H, m), 5.75 (1H, m), 7.28 (5H, m); HRMS  $m/z=227.1337$ . **22**: IR (film)  $\nu=3396, 1670 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.46$  (9H, s), 1.57 (6H, m), 2.06 (2H, m), 3.31 (1H, m), 3.53 (3H, m), 3.75 (3H, m); HRMS  $m/z=259.1798$ . **24**: IR (film)  $\nu=1736 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta=1.82$  (1H, m), 2.05 (3H, s), 2.10 (6H, m), 2.78 (1H, dt,  $J=11.0, 6.0$  Hz), 2.89 (1H, m), 3.60 (1H, dt,  $J=14.3, 7.4$  Hz), 3.89 (1H, m), 4.04 (1H, m), 4.11 (1H, dd,  $J=6.9, 11.5$  Hz), 4.23 (1H, dd,  $J=6.0, 11.5$  Hz); HRMS  $m/z=183.1266$ .