AN ENANTIO- AND DIASTEREOSELECTIVE SYNTHESIS OF (–)-ISORETRONECANOL AND (+)-TRACHELANTHAMIDINE FROM A *MESO* PRECURSOR†

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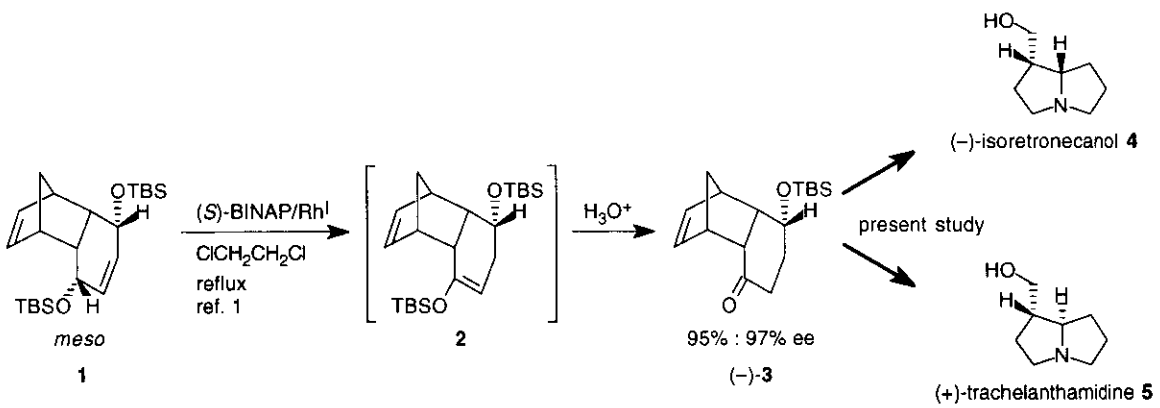
Abstract —— Two diastereomeric pyrrolizidine alkaloids, (–)-isoretronecanol and (+)-trachelanthamidine, have been synthesized in an enantio- and diastereoselective manner starting from a *meso* precursor *via* a catalytic asymmetrization.

We found that the *meso*-enediol bis-silyl ether (**1**) rearranged on reflux with a catalytic amount of a chiral BINAP-Rh^{I} 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.[1] In order to exploit the optically active ketone (**3**) as a versatile chiral building block,[2] we attempted diastereoselective conversion of (–)-**3**, obtained in 95% yield with 97% ee using (*S*)-BINAP-Rh^{I} catalyst, into two typical diastereomeric pyrrolizidine alkaloids,[3] (–)-isoretronecanol[4] (**4**) and (+)-trachelanthamidine[5] [(+)-laburnine[4a, b]] (**5**), utilizing (–)-**3** as an equivalent of (*R*)-4-hydroxy-2-cyclohexenone[6] (**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**].

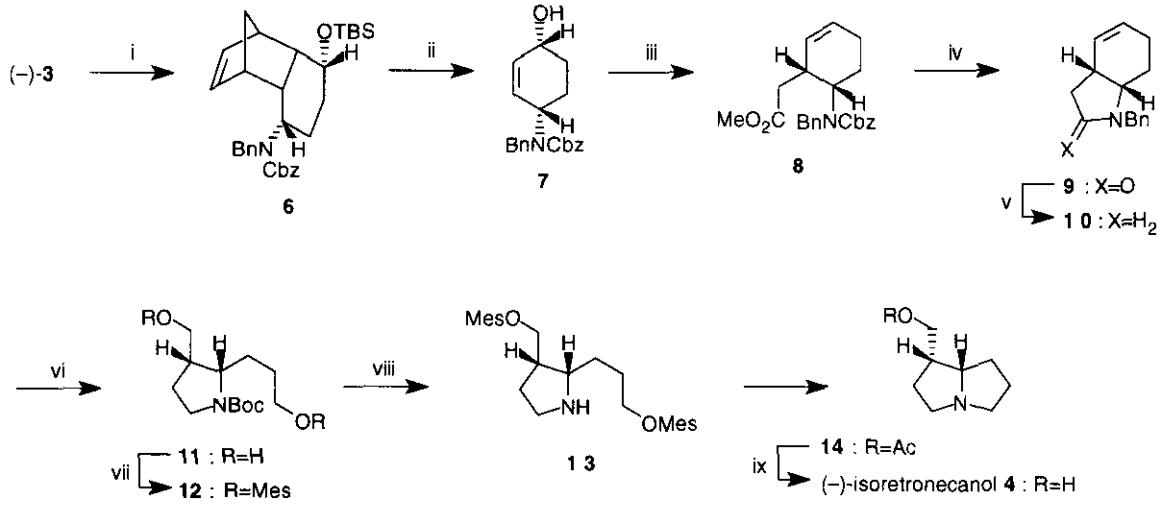


Scheme 1

To obtain (–)-isoretronecanol (**4**), (–)-**3** was first transformed into the *endo*-carbamate (**6**), $[\alpha]_D^{25}$ –27.7° (*c*

† Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

1.0, $CHCl_3$), in 50% overall yield through sequential imine formation, borohydride reduction and carbamoylation.[7] 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[8] (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° (*c* 1.4, $CHCl_3$), in an excellent yield after desilylation. Because the allylic alcohol (**7**) was found to be incompatible with the acid-mediated Johnson-Claisen conditions,[9] **7** was transformed into the *cis*-methyl ester (**8**), $[\alpha]_D^{30}$ –110.0° (*c* 2.8, $CHCl_3$), in 72% overall yield *via* vinyl ether formation,[10] Claisen rearrangement,[10] oxidation[11] and esterification. On exposure to boron tribromide[12] followed by treatment with triethylamine, **8** afforded the γ-lactam (**9**), $[\alpha]_D^{30}$ –3.5° (*c* 1.0, $CHCl_3$), *via* concurrent debenzylation, 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° (*c* 1.6, $CHCl_3$), 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° (*c* 0.4, $CHCl_3$), in 26% overall yield *via* sequential dihydroxylation, debenzylation, 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[4d] to furnish the pyrrolizidine (**14**), $[\alpha]_D^{30}$ –42.7° (*c* 0.6, $CHCl_3$). Finally, **14**

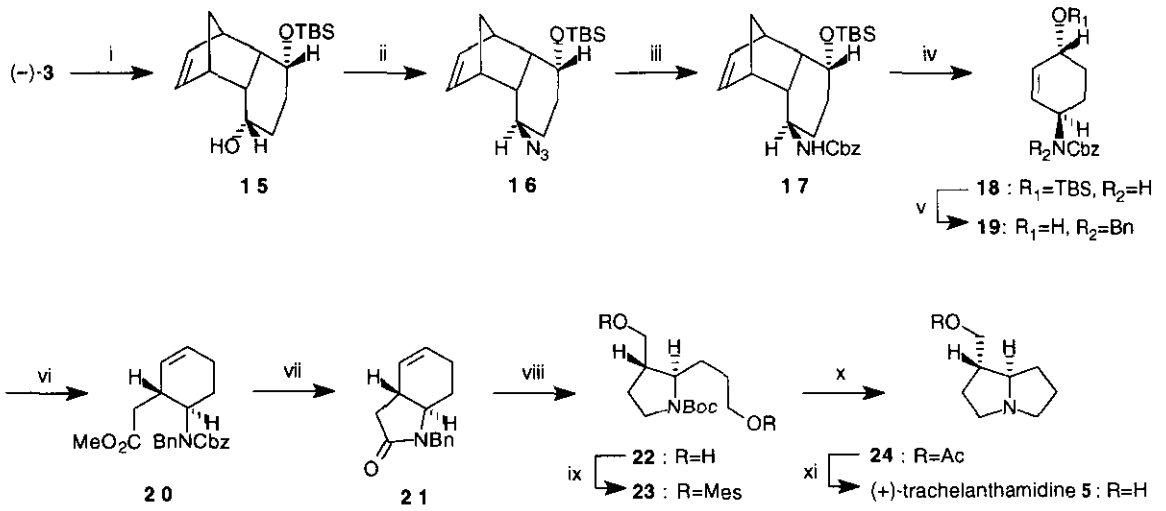


Scheme 2

Reagents and conditions: i) (a) $BnNH_2$ then $NaBH_4$, (b) Cbz-Cl, NaH, DMF (50%). ii) (a) $NaHCO_3$, Ph_2O, reflux, (b) TBAF, THF (80%). iii) (a) ethyl vinyl ether, $Hg(OAc)_2$, reflux, (b) Ph_2O, reflux, (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq. *t*-BuOH, acid workup then CH_2N_2 (72%). iv) (a) BBr_3, CH_2Cl_2, (b) Et_3N, CH_2Cl_2 (87%). v) $LiAlH_4$, THF, reflux (85%). vi) (a) OsO_4 (cat.), NMO, aq. THF, (b) H_2, $Pd(OH)_2$, MeOH, (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, (d) $NaIO_4$, aq. THF, then $NaBH_4$ (26%). vii) Mes-Cl, Et_3N, CH_2Cl_2. viii) TFA then AcOK, DMSO, 80 °C (92% from **11**). ix) 33% NH_4OH, MeOH (84%).

was exposed to ammonium hydroxide to give (–)-isoretronecanol (**4**), $[\alpha]_D^{29}$ –74.0° (*c* 0.2, EtOH) [lit.,[4n]: $[\alpha]_D^{27}$ –77.0° (*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° (*c* 1.0, $CHCl_3$), in 85% yield. Treatment of **15** with diphenyl phosphorylazide (DPPA) under Mitsunobu conditions[13] led to generation of the azide (**16**), $[\alpha]_D^{28}$ –32.4° (*c* 1.3, $CHCl_3$), having *anti*-1,4-configuration with inversion of the stereochemistry. On exposure to triphenylphosphine,[14] followed by carbobenzoxy chloride, **16** gave the secondary carbamate (**17**), $[\alpha]_D^{32}$ +8.1° (*c* 0.9, $CHCl_3$). Overall yield of **17** from **15** was 36%. Thermolysis of **17** in refluxing diphenyl ether in the presence of sodium hydrogen carbonate[8] afforded the *trans*-4-substituted 2-cyclohexenyl silyl ether (**18**), $[\alpha]_D^{27}$ +108.2° (*c* 0.1, $CHCl_3$), 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° (*c* 1.0, $CHCl_3$), in 59% overall yield, which was transformed into the *trans*-methyl ester (**20**), $[\alpha]_D^{29}$ –23.3° (*c* 0.5, $CHCl_3$), in 59% overall yield *via* a five-step sequence exactly the same as that employed for the preparation of the *cis*-counterpart (**8**) above. Decarbamoylation of **20**, followed by treating the resulting amine with DBU in refluxing benzene afforded the γ-lactam (**21**), mp 83-84 °C, $[\alpha]_D^{30}$ +119.6° (*c* 0.2, $CHCl_3$), in 83% yield. On sequential one-pot ozonolysis- reduction of the olefinic functionality, reduction of the lactam functionality, debenzylation, and carbamoylation, **21** furnished the *trans*-2,3-disubstituted pyrrolidine (**22**), $[\alpha]_D^{31}$ –40.2° (*c* 0.3, $CHCl_3$), 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) $NaBH_4$, MeOH (84%). ii) DPPA, DEAD, PPh_3, THF (81%). iii) (a) PPh_3, aq. THF, (b) Cbz-Cl, NaH, DMF (42%). iv) $NaHCO_3$, Ph_2O, reflux (80%). v) (a) BnBr, NaH, DMF, (b) TBAF, THF (59%). vi) (a) ethyl vinyl ether, $Hg(OAc)_2$, reflux, (b) Ph_2O, reflux, (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq. *t*-BuOH, acid workup then CH_2N_2 (59%). vii) (a) BBr_3, CH_2Cl_2, (b) DBU, benzene, reflux (83%). viii) (a) O_3, MeOH-CH_2Cl_2 then $NaBH_4$, (b) $LiAlH_4$, THF, reflux, (c) H_2, $Pd(OH)_2$, MeOH, (d) $(Boc)_2O$, Et_3N, CH_2Cl_2 (52%). ix) Mes-Cl, Et_3N, CH_2Cl_2. x) TFA then AcOK, DMSO, 80 °C (55% from **22**). xi) 33% NH_4OH-MeOH (84%).

laburnine] (**5**), $[\alpha]_D^{28}$ +10.6° (*c* 0.2, EtOH) [lit.[4n] for (–)-enantiomer: $[\alpha]_D^{27}$ –14.0° (*c* 0.5, EtOH)], in 46% overall yield *via* the dimesylate (**23**) and the acetate (**24**), $[\alpha]_D^{31}$ +11.3° (*c* 0.2, $CHCl_3$), by sequential mesylation, decarbamoylation, cyclization[4d] 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^I catalyzed asymmetrization. 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) ν=3434, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=3394, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=3434, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=3396, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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) ν=1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=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.

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