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 asymmetric reaction.

We found that the meso-enediol bis-silyl ether (1) rearranged on reflux with a catalytic amount of a chiral BINAP-Rh¹ 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-Rh¹ catalyst, into two typical diastereomeric pyrrolizidine alkaloids,³ (-)-isoretronecanol⁴ (4) and (+)-trachelanthamidine⁵ [(+)-laburnine⁶ ¹⁷] (5), utilizing (-)-3 as an equivalent of (R)-4-hydroxy-2-cyclohexenone⁶ (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].

To obtain (-)-isoretronecanol (4), (-)-3 was first transformed into the endo-carbamate (6), [α]D²⁵ –27.7° (c

† Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.
1.0, CHCl₃, 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 carbonate⁸ (20 equiv.) initiated a retro-Diels-Alder reaction with expulsion of cyclopentadiene to furnish the cis-4-substituted 2-cyclohexenol (7), [α]D²⁷ −27.8° (c 1.4, CHCl₃), 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), [α]D³⁰ −110.0° (c 2.8, CHCl₃), in 72% overall yield via vinyl ether formation,¹⁰ Claisen rearrangement,¹⁰ oxidation¹¹ and esterification. On exposure to boron tribromide¹² followed by treatment with triethylamine, 8 afforded the γ-lactam (9), [α]D³⁰ +3.5° (c 1.0, CHCl₃), via concurrent debenzylation, decarboxylation, and cyclization, which was reduced with lithium aluminum hydride in refluxing THF to give rise to the bicyclic amine (10), [α]D²⁹ +37.7° (c 1.6, CHCl₃), in 74% overall yield. Transformation of 10 into the target (-)-isoretonecanol (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), [α]D³⁰ +0.7° (c 0.4, CHCl₃), 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 substitution⁴⁰ to furnish the pyrrolizidine (14). [α]D³⁰ −42.7° (c 0.6, CHCl₃). Finally, 14

**Scheme 2**

**Reagents and conditions:** i) (a) BnNH, then NaBH₄, (b) Cbz-Cl, NaH, DMF (50%). ii) (a) NaHCO₃, Ph₂O, reflux, (b) TBAF, THF (80%). iii) (a) ethyl vinyl ether, Hg(OAc)₂, reflux, (b) Ph₂O, reflux, (c) NaClO₃, NaH₂PO₄, 2-methyl-2-butenene, aq. t-BuOH, acid workup then CH₂N₂ (72%). iv) (a) BBr₃, CH₂Cl₂, (b) Et₃N, CH₂Cl₂ (87%). v) LiAlH₄, THF, reflux (85%). vi) (a) OsO₄ (cat.), NMO, aq. THF, (b) H₂, Pd(OH)₂, MeOH, (c) (Boc)₂O, Et₃N, CH₂Cl₂, (d) NaIO₄, aq. THF, then NaBH₄ (26%). vii) Mes-Cl, Et₃N, CH₂Cl₂, viii) TFA then AcOK, DMSO, 80 °C (92% from 11). ix) 33% NH₂OH, MeOH (84%).
was exposed to ammonium hydroxide to give (-)-isoretronecanol (4), \([\alpha]_D^{27} -74.0^\circ\) (c 0.2, EtOH) [lit.\(^{4n}\): \([\alpha]_D^{27} -77.0^\circ\) (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\(_3\)), in 85% yield. Treatment of 15 with diphenyl phosphoryl azide (DPPA) under Mitsunobu conditions\(^{13}\) led to generation of the azide (16), \([\alpha]_D^{38} -32.4^\circ\) (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), \([\alpha]_D^{32} +8.1^\circ\) (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\(^a\) afforded the trans-4-substituted 2-cyclohexenyl silyl ether (18), \([\alpha]_D^{29} +108.2^\circ\) (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), \([\alpha]_D^{29} +91.9^\circ\) (c 1.0, CHCl\(_3\)), in 59% overall yield, which was transformed into the trans-methyl ester (20), \([\alpha]_D^{29} -23.3^\circ\) (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 \(\gamma\)-lactam (21), mp 83-84 °C, \([\alpha]_D^{30} +119.6^\circ\) (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), \([\alpha]_D^{11} -40.2^\circ\) (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\(_2\)O, reflux (80%). v) (a) BnBr, NaH, DMF, (b) TBAF, THF (59%). vi) (a) ethyl vinyl ether, Hg(OAc)\(_2\), reflux, (b) Ph\(_2\)O, reflux, (c) NaClO\(_4\), NaH,PO\(_4\), 2-methyl-2-butene, aq. t-BuOH, acid workup then CH\(_2\)N\(_2\), (59%). vii) (a) BB\(_3\), Cl\(_2\), (b) DBU, benzene, reflux (83%). viii) (a) O\(_3\), MeOH-CH\(_2\)Cl, then NaBH\(_4\), (b) LiAlH\(_4\), THF, reflux, (c) H\(_2\), Pd(OH)\(_2\), MeOH, (d) (Boc)\(_2\)O, Et\(_3\)N, CH\(_2\)Cl\(_2\), (52%). ix) Mes-Cl, Et\(_3\)N, CH\(_2\)Cl\(_2\). x) TFA then AcOK, DMSO, 80 °C (55% from 22). xi) 33% NH\(_4\)OH-MeOH (84%).
laburnine (5), \([\alpha]_D^{28} +10.6^\circ \) (c 0.2, EtOH) [lit.\(^{1n}\) for (−)-enantioner: \([\alpha]_D^{27} -14.0^\circ \) (c 0.5, EtOH)], in 46% overall yield via the dimesylate (23) and the acetate (24), \([\alpha]_D^{31} +11.3^\circ \) (c 0.2, CHCl\(_3\)), by sequential mesylation, decarbamoylation, cyclization\(^{4m}\) and deacetylation (Scheme 3).

In conclusion, we have developed an enantio- and diastereoselective synthesis of two diastereomeric pyrrolizidine alkaloids, (−)-isoretmnecanol (4) and (+)-tmchelanthamidine (5), based on the chemical and stereochemical background of the tricyclic ketone \([\sim\sim-31\) readily accessible in high optical purity from the meso-enediol bis-silyl ether (1) by (S)-BINAP-Rh\(^{\prime}\) catalyzed asymmetrization. Thus, our intended utilization of the optically active ketone (3) as a chiral equivalent of (R)-4-hydroxycyclohexenone was realized as visualized.

REFERENCES


15. Spectral data of the selected intermediates — **7**: IR (film) ν=3434, 1691 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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) v=1684 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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=186.1211.

**14**: IR (film) ν=1738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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) v=1695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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) v=3396, 1670 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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) v=1736 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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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