Removal of the Chiral Inductor from Phenylglycinol-derived Tricyclic Lactams. Unexpected Generation of Chiral trans-Hydrochromene Lactones

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Abstract: In the search for synthetic routes for the preparation of cis- and trans-decahydroquinolin-2-ones, a procedure for the generation of enantiopure trans-hydrochromene lactones, by treatment of (R)-phenylglycinol-derived oxazoloquinolone lactams with Na/liq. NH₃ followed by acidification, has been developed.

Keywords: Decahydroquinoline, debenzylation, lactams, lactones, perhydrochromene, sodium-ammonia.

INTRODUCTION
Chiral aminoalcohol-derived tricyclic lactams have proven to be excellent optically enriched scaffolds for the synthesis of cis-decahydroquinolines (DHQs) and cis- and trans-octahydroindoles.[1-5] In previous work we have reported the enantioselective synthesis of a variety of natural products, such as α-lycorane,[1] Myrioneuron alkaloids,[2] pemiliotxin C,[3] ent-2-epi-pemiliotxin C,[3b] cermizine B,[4] and the marine alkaloids lepadins A-D,[5] from chiral tricyclic lactams, thus demonstrating their value in the field of total synthesis. One of the key steps in the above transformations is the removal of the phenylethanol moiety of the chiral inductor. This is usually accomplished in excellent yield and stereoselectivity in two steps: alane reduction, which brings about the reduction of the lactam carbonyl and the C–O bond of the oxazolidine ring, and catalytic hydrogenation, with concomitant protection by Boc₂O, to promote the reductive cleavage of the benzylic C–N bond. Scheme 1 illustrates the preparation of cis-DHQs 3 and 4 from lactams 1 and 2, respectively.[3a, 6]

Alternatively, the removal of the phenylethanol moiety to give cis-bicyclic lactams (for instance, 5 and 6) has previously been accomplished in the fused 5-5-6-membered and bridged 5-6-7-membered series by cleavage of the oxazolidine C–O bond with a trialkyl- or triarylsilane under acidic conditions, followed by N-debenzylation of the resulting lactam with sodium in liquid ammonia, as outlined in Scheme 2.[1, 7]

We were now interested in exploring procedures for the conversion of the above 5-6-6-membered tricyclic lactams 1 and 2 (A, Figure 1) into cis- and trans-octahydroquinolin-2-ones. The functionalization at the piperidine 2 position may be harnessed for the synthesis of complex DHQ targets.

RESULTS AND DISCUSSION

We were now interested in exploring procedures for the conversion of the above 5-6-6-membered tricyclic lactams 1 and 2 (A, Figure 1) into cis- and trans-octahydroquinolin-2-ones. The functionalization at the piperidine 2 position may be harnessed for the synthesis of complex DHQ targets.
The excellent results obtained by the procedure outlined in Scheme 2 prompted us to use it for the synthesis of cis-decahydroquinolin-2-ones. However, the chemoselective reduction of the oxazolidine ring of 2 required treatment with TiCl₄ (3 equiv) and an excess of triethylsilane (3 equiv) for more than 70 h. Moreover, the reaction took place in moderate yield and low stereoselectivity to give a 5:1 mixture of cis- and trans-isomers 7a and 7b, which could not be separated by column chromatography. The subsequent debenzylation of these isomers with sodium and liquid ammonia afforded a mixture of the corresponding decahydroquinolin-2-ones (87%), from which the cis-isomer 8 could be separated by crystallization. This lactam had previously been converted into the amphibian alkaloid pumiliotoxin C (Scheme 3).

To improve the above results in terms of both chemical yield and stereoselectivity, we developed an alternative procedure leading to cis-decahydroquinolin-2-ones, involving the ruthenium tetroxide oxidation of cis-DHQs. Thus, treatment of cis-DHQ 3 with ruthenium tetroxide gave decahydroquinolin-2-one 10 in excellent yield. A similar oxidation of the methyl substituted tricyclic lactam 4 afforded cis-decahydroquinolin-2-one 9 in high yield (Scheme 4).

Taking into account the transformations depicted in Scheme 1, conversion of tricyclic lactams 1 and 2 into the cis bicyclic lactams 10 and 9 requires three synthetic steps and takes place in 57% and 51% overall yield, respectively.

With a method in hand for the efficient preparation of enantiopure cis-decahydroquinolin-2-ones from chiral tricyclic lactams, the next goal was to set up a procedure for the synthesis of trans isomers.

In view of the reported Et₃SiH-TiCl₄ stereoselective reduction of 8a-hydroperoxy-2-oxoperhydroquinolines (11) to the corresponding trans-decahydroquinolones (12)[9] (Scheme 5), we envisaged an alternative way to remove the chiral inductor. It involves the Na/liq. NH₃-promoted reductive cleavage of the benzyl C—N bond [10] and the subsequent Et₃SiH reduction of the resulting 8a-oxyperhydroquinolone intermediate B, which was expected to provide the desired trans ring junction (i.e. 13).

Scheme 5. Stereoselective generation of trans-decahydroquinolin-2-ones.[9]

However, reduction of lactam 2 with sodium in liquid ammonia under the usual conditions for the N-debenzylation (THF, -33 °C, 1 min; then NH₄Cl and filtration through Celite®), followed by treatment of the resulting crude mixture with Et₃SiH in the presence of TiCl₄ under the conditions used in the preparation of 7, did not afford the expected N-unsubstituted lactam 13. Lactone 14 was isolated in 40% yield instead (Scheme 6). Phenylethanol, arising from the reductive cleavage of the phenylglycinol moiety, was also isolated. Hydroxy acid C was detected by GC/MS (m/z 186) from the crude mixture after the Na/liq. NH₃ reduction, and attempts to purify it by column chromatography (SiO₂) or by acidic work-up resulted in the formation of lactone 14.

Scheme 6. Unexpected generation of a perhydrochromene lactone.
The yield of lactone 14 was improved by omitting the superfluous Et3SiH/TiCl4 treatment and promoting the lactonization of the intermediate hydroxy acid C using concentrated hydrochloric acid (pH = 1-2; see Experimental Section). Under these conditions, enantiopure lactone 14 was obtained in 60% yield (Scheme 7).

**Scheme 7. Conversion of phenylglycinol-derived oxazoloquinolone lactams to trans-hydrochromene lactones.**

Taking into account that we have previously developed a general procedure for the preparation of (R)-phenylglycinol-derived tricyclic lactams, by cyclocondensation of this amino alcohol with appropriate cyclohexanone-derived tricyclic lactams, by cyclocondensation of this amino alcohol with appropriate cyclohexanone -based δ-keto esters,[2-6,12] we envisaged these lactams as general synthetic precursors of enantiopure trans-hydrochromene lactones. Thus, following the above procedure, lactam 15, prepared by desilylation (TBAF) of the corresponding TBDMS derivative,[5b] was satisfactorily converted to enantiopure trans-lactone 16. Similarly, unsaturated lactone 18 and unsubstituted lactone 19 were prepared in acceptable yields from the corresponding tricyclic lactams 17 and 1,[5] respectively. In all cases, the trans ring fusion of the lactone ring was established from the coupling constants of the methine 8a proton.[11] Additionally, the optical purity of lactone 19 was confirmed by its [α]d value, which matched that reported in the literature for this compound.[13]

### CONCLUSION

A convenient procedure for the conversion of tricyclic phenylglycinol-derived oxazoloquinolone lactams to enantiopure trans-hydrochromene lactones, including derivatives bearing an additional stereocenter at the C-5 position, has been developed.

Mechanistic aspects of this unprecedented transformation will be investigated and its scope and application in the synthesis of natural products explored in further studies.

### EXPERIMENTAL SECTION

(4aS,5R,8aR)-1-[(1R)-2-Hydroxy-1-phenylethyl]-5-methyl-2-oxodecahydroquinoline (7): TiCl4 (230 µL, 2.11 mmol) was added to a solution of lactam 2 (200 mg, 0.70 mmol) in anhydrous CH2Cl2 (4 mL) at –78 °C and the mixture was stirred for 30 min. Et3SiH (340 µL, 2.11 mmol) was added and the solution stirred at –78 °C for 45 min. The reaction mixture was allowed to warm to room temperature and stirred for 72 h. Saturated aqueous NaHCO3 was added, and the resulting mixture was extracted with CH2Cl2. The combined organic extracts were washed with brine, dried over anhydrous MgSO4, filtered, and concentrated. Flash chromatography (EtOAc) afforded a mixture (5:1, cis:trans) of lactams 7a and 7b (116 mg, 57%) as a colorless oil: 1H-NMR (400 MHz, CDCl3) δ: 0.99 (d, J = 7.6 Hz, 3H, CH3), 1.23-1.79 (m, 11H, H-7, H-11), 1.81-1.94 (m, 2H, H-7a, H-8), 2.07-2.18 (m, 1H, H-7), 2.53-2.59 (m, 2H, H-6), 3.32 (dt, J = 11.2, 4.3 Hz, 1H, H-11a), 4.04 (dd, J = 11.6, 3 Hz, 1H, H-2), 4.26-4.36 (m, 1H, H-2), 4.57 (dd, J = 6.4, 2.6 Hz, 1H, H-3), 7.26-7.30 (m, 3H, H-Ar), 7.32-7.35 (m, 3H, H-Ar); 13C-NMR (100.6 MHz, CDCl3) δ: 19.0 (CH3), 19.7 (C-10), 22.5 (C-7), 26.1 (C-5), 32.0 (C-6), 33.2 (C-8), 40.1 (C-7a), 57.1 (C-11a), 64.8 (C-2), 66.6 (C-3), 127.2 (CH-0), 127.4 (CH-m), 137.2 (Cq-Ar), 172.0 (NCO); HRMS calcld for [C18H25NO2 + H]+: 288.1598, found 288.195.

(4aS,5R,8aR)-5-Methyl-2-oxodecahydroquinoline (8): Into a three-necked, 100 mL, round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone, NH3 was condensed (30 mL) at –78 °C. Then, a 5:1 mixture of lactams 7a and 7b (400 mg, 1.39 mmol) in anhydrous THF (2 mL) was added and the temperature was raised to –33 °C for 45 min. Sodium metal was added in small portions until the blue color persisted, and the mixture was stirred at –33 °C for 15 min. The reaction was quenched by addition of NH4Cl until the blue color disappeared, and then the mixture was stirred at room temperature for 4 h. The resulting residue was dissolved in water and extracted with CH2Cl2. The combined organic extracts were dried over anhydrous Na2SO4, filtered, and concentrated. Flash chromatography (7:3 hexane-EtOAc to AcOEt) afforded a 5:1 mixture of...
lactam 8 and its trans isomer (202 mg, 87%) as a white solid. Crystallization from AcOEt afforded pure 8 (173 mg, 74%): 1H NMR (400 MHz, CDCl3) δ: 0.93 (d, J = 6.4 Hz, 3H, CH3), 0.99-1.09 (m, 1H), 1.39-1.71 (m, 8H), 2.00-2.10 (m, 1H), 2.26-2.32 (m, 2H), 3.59-3.64 (m, 1H, H-8a), 5.90 (bs, 1H, NH); 13C NMR (100.6 MHz, CDCl3) δ: 19.3 (CH3), 20.0 (CH2), 23.1 (CH3), 27.3 (CH2), 27.6 (CH), 31.8 (CH2), 33.7 (CH2), 39.7 (CH), 52.2 (CH), 172.9 (NCO).

(4aS,5R,8aR)-1-(tert-Butyloxycarbonyl)-5-methyl-2-oxodecahydroquinoline (9): n-BuLi (680 μL of a 1.6 M solution in hexane, 1.09 mmol) was added dropwise to a solution of compound 8 (173 mg, 1.03 mmol) in anhydrous THF (12 mL) at −78 °C. After 30 min, a solution of Boc2O (340 mg, 1.55 mmol) in anhydrous THF (3.1 mL) was added, and the mixture was stirred for 1 h 30 min at −78 °C. Saturated aqueous NH4Cl was added, and mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na2SO4, filtered, and concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded pure lactone.

General Procedure for the Na/liq. NH3 Reduction of Lactams 2, 15, 17, and 1.

Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone, NH3 was condensed (30 mL) at −78 °C. Then, a solution of lactam (1 mmol) in anhydrous THF (5 mL) was added and the temperature was raised to −33 °C. Sodium metal was added in small portions until the blue color persisted, and the mixture was stirred at −33 °C for 30 seconds. The reaction was quenched by addition of NH4Cl until the blue color disappeared, and then the mixture was stirred at room temperature for 4 h. The resulting residue was dissolved with water and CH2Cl2, the two phases were separated, and the organic phase was discarded. The aqueous phase was acidified with concentrated HCl until pH=1-2, and the resulting solution was stirred for 24 h. The aqueous solution was extracted with CH2Cl2, and the combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated to afford the corresponding lactone.

(4aS,5R,8aS)-5-Methyl-2-oxo-octahydrochromene (14): [α]22D = −72.8 (c, 0.5, MeOH); 1H NMR (CDCl3, 400 MHz) δ: 0.97 (d, J = 6.3 Hz, 3H, CH3), 1.02-1.10 (m, 1H), 1.12-1.20 (m, 1H), 1.29-1.55 (m, 3H), 1.63-1.73 (m, 2H), 1.77-1.87 (m, 1H), 2.03-2.16 (m, 2H), 2.45-2.59 (m, 1H, H-3), 2.68 (dd, J = 17.8, 8.1, 4.3 Hz, 1H, H-3), 3.95 (ddd, J = 10.9, 9.9, 4.3 Hz, 1H, H-8a); 13C NMR (CDCl3, 100.6 MHz) δ: 19.0 (CH3), 23.5 (C-7), 23.9 (C-4), 29.6 (C-3), 32.4 (C-8), 34.5 (C-6), 36.3 (C-5), 44.8 (C-4a), 82.9 (C-8a), 171.9 (C-2); HRMS calcd for [C10H16O1 + H+]: 169.1223, found 169.1223.

(4aS,5R,8aS)-5-(5-Hydroxypentyl)-2-oxo-octahydrochromene (16): [α]22D = −61.5 (c, 1.3, MeOH); IR (NaCl): 3429, 1734 cm−1; 1H-NMR (CDCl3, 400 MHz) δ: 0.88-1.61 (m, 14H), 1.78-1.88 (m, 2H), 2.06-2.14 (m, 2H), 2.51 (ddd, J = 17.6, 8.4, 8.2 Hz, 1H, H-3), 2.67 (dd, J = 18.0, 8.2, 4.6 Hz, 1H, H-3), 3.65 (t, J = 6.6 Hz, 2H, H-2'), 3.95 (ddd, J = 10.5, 10.4, 4.2 Hz, 1H, H-8a); 13C NMR (CDCl3, 100.6 MHz) δ: 23.3 (CH3), 23.6 (CH2), 26.0 (CH2), 26.1 (CH2), 29.4 (C-3), 30.7 (CH2), 32.7 (CH2), 32.7 (CH2), 40.9 (C-5), 42.4 (C-4a), 62.9 (C-5'), 82.9 (C-8a), 171.8 (COO); HRMS calcd for [C12H19O3 + H+]: 241.1798, found 241.1798.

(4aS,5R,8aS)-5-Methyl-2-oxo-3,4,4a,7,8,8a-hexahydrochromene (18): [α]22D = −56.4 (c, 1.0, CHCl3); 1H NMR (CDCl3, 400 MHz) δ: 1.51-1.60 (m, 1H), 1.67 (s, 3H, CH3), 1.69-1.79 (m, 1H), 2.06-2.20 (m, 5H), 2.58-2.72 (m, 1H), 2.76 (ddd, J = 18.1, 8.8, 3.5 Hz, 1H, H-4), 2.88 (d, J = 12.4, 9.3, 3.3 Hz, 1H, H-5a), 5.41 (s, 1H); 13C NMR (CDCl3, 100.6 MHz) δ: 19.9 (CH3), 23.5 (CH2), 24.4 (CH3), 28.3 (CH3), 29.9 (CH3), 41.0 (CH), 81.3 (CH), 122.8 (CH), 132.2 (CH), 171.9 (COO); MS (Cl) m/z (%): 166.1, 100 (M+).

(4aR,8aS)-2-Oxooctahydrochromene (19): [α]22D = −39.2 (c, 0.7, MeOH); IR (lit.): −40.5 (c, 0.98, MeOH); 1H-NMR (CDCl3, 400 MHz) δ: 1.00-1.08 (m, 1H), 1.19-1.30 (m, 2H), 1.36-1.54 (m, 3H), 1.67-1.71 (m, 1H), 1.80-1.87 (m, 3H), 2.07-2.10 (m, 1H), 2.46-2.56 (m, 1H), 2.61-2.69 (m, 1H), 3.86 (td, J = 10.2, 4.3 Hz, 1H); 13C NMR (CDCl3, 400 MHz) δ: 24.2 (CH3), 25.2 (CH3), 26.6 (CH2), 29.9 (CH3), 31.2 (CH2), 32.4 (CH2), 38.9 (CH), 83.5 (CH), 171.7 (COO).

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

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