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

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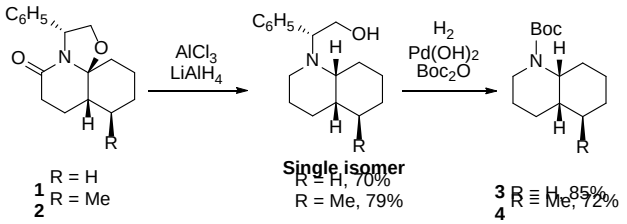
Abstract: In the search for synthetic routes for the preparation of *cis*- and *trans*- decahydroquinolin-2-ones, a procedure for the generation of enantiopure *trans*-hydrochromene lactones, by treatment of (*R*)-phenylglycinol-derived oxazoloquinolone lactams with Na/liq. NH_3 followed by acidification, has been developed.

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

Dedicated to Prof. Miguel Yus on the occasion of his 70th birthday

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] pumiliotoxin C,[3] *ent*-2-*epi*-pumiliotoxin 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 Boc_2O, 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.[5a, 6]



Scheme 1. Stereoselective removal of the chiral inductor to give *cis*-DHQs.

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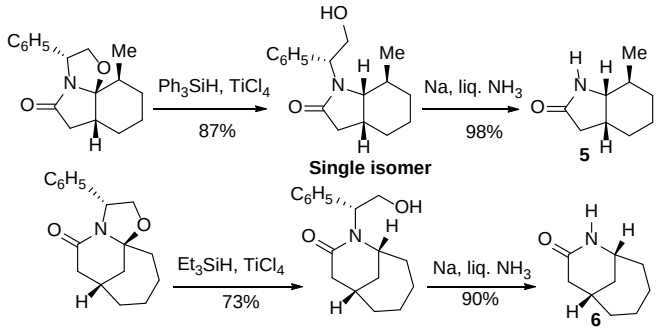
Alternatively, the removal of the phenylethanol moiety to give *cis*-bicyclic lactams (for instance, **5** and **6**) has previously been accomplished in the fused 5-5-6-membered and bridged 5-6-7-membered series by cleavage of the oxazolidine C–O bond with a trialkyl- or triarylsilane under acidic conditions,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



Scheme 2. Generation of *cis*-bicyclic lactams from phenylglycinol-derived tricyclic lactams.

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.

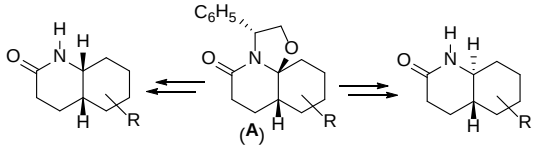


Figure 1. *Cis*- and *trans*-octahydroquinolin-2-ones by from chiral 5-6-6-membered tricyclic lactams.

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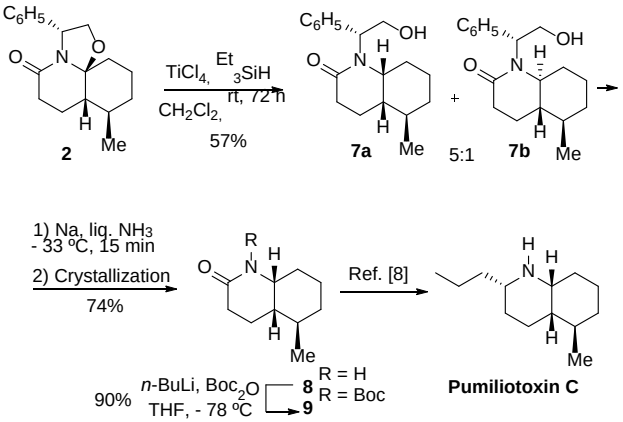
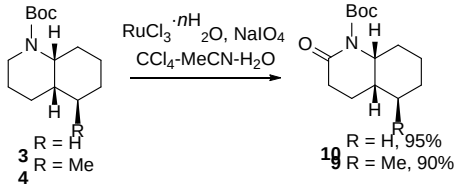
The excellent results obtained by the procedure outlined in Scheme 2 prompted us to use it for the synthesis of *cis*-decahydroquinolin-2-ones. However, the chemoselective reduction of the oxazolidine ring of **2** required treatment with $TiCl_4$ (3 equiv) and an excess of triethylsilane (3 equiv) for 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[8] into the amphibian alkaloid pumiliotoxin C (Scheme 3).



Scheme 3. Access to *cis*-decahydroquinolin-2-ones from 5-6-6-membered tricyclic lactams.

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[5a] (Scheme 4).

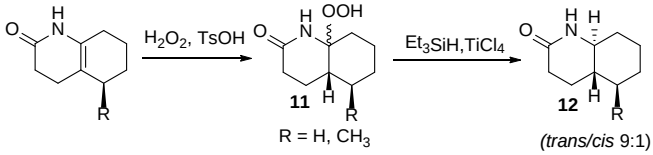


Scheme 4. Oxidation of *cis*-DHQs to *cis*-decahydroquinolin-2-ones

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.

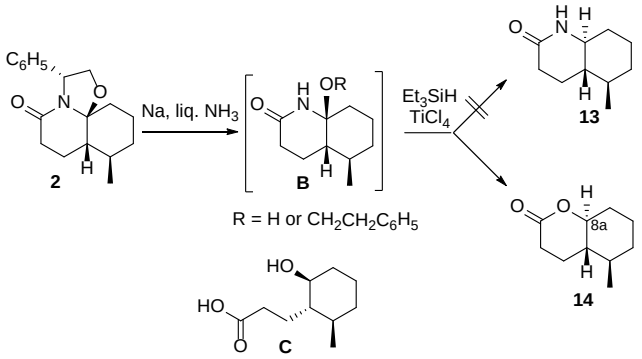
With a method in hand for the efficient preparation of enantiopure *cis*-decahydroquinolin-2-ones from chiral tricyclic lactams, the next goal was to set up a procedure for the synthesis of *trans* isomers.

In view of the reported Et_3SiH-$TiCl_4$ 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. NH_3-promoted reductive cleavage of the benzylic C—N bond [10] and the subsequent Et_3SiH 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 NH_4Cl and filtration through Celite®), followed by treatment of the resulting crude mixture with Et_3SiH in the presence of $TiCl_4$ 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. NH_3 reduction, and attempts to purify it by column chromatography (SiO_2) or by acidic work-up resulted in the formation of lactone **14**.



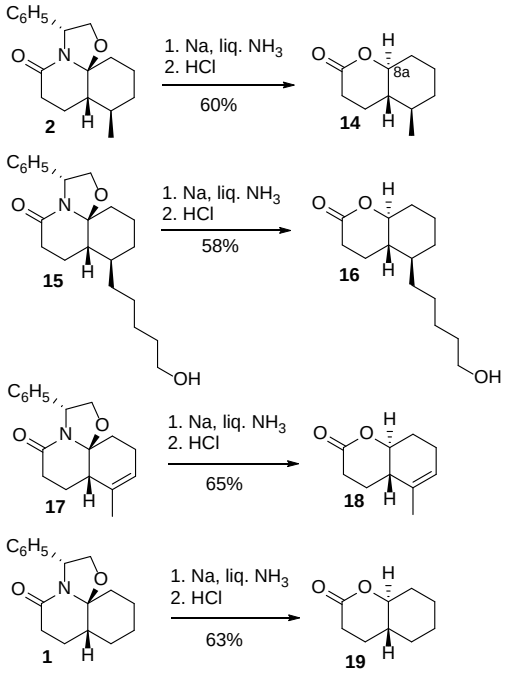
Scheme 6. Unexpected generation of a perhydrochromene lactone.

The above results made evident that the intermediate **B** formed after *N*-debenzylation, before it could undergo the expected $Et_3SiH/TiCl_4$-promoted reduction, is further reduced *in situ* to hydroxy acid **C**, which is converted to lactone **14** under acidic conditions.

The ^1H- and ^{13}C-NMR data of lactone **14** were quite similar to those expected for lactam **13**, except for the

deshielding observed for the proton (δ 3.95 ppm) and carbon (δ 82.8 ppm) at position 8a. The HRMS data confirmed the structural assignment. The *trans* ring fusion of the lactone ring was deduced from the coupling constants (*J* = 10.9, 9.9, and 4.3 Hz) of the methine 8a proton.[11]

The yield of lactone **14** was improved by omitting the superfluous $Et_3SiH/TiCl_4$ 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-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 $[\alpha]_D$ 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

(4a*S*,5*R*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-methyl-2-oxodecahydroquinoline (7): $TiCl_4$ (230 μL, 2.11 mmol) was added to a solution of lactam **2** (200 mg, 0.70 mmol) in anhydrous CH_2Cl_2 (4 mL) at −78 °C and the mixture was stirred for 30 min. Et_3SiH (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 $NaHCO_3$ was added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, 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: ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 0.99 (d, *J* = 7.6 Hz, 3H, CH_3), 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); ^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ*: 19.0 (CH_3), 19.7 (C-10), 22.5 (C-7), 26.1 (C-11), 28.1 (C-9), 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-*o*), 127.4 (CH-*p*), 128.6 (CH-*m*), 137.2 (Cq-Ar), 172.0 (NCO); HRMS calcd for $[C_{18}H_{25}NO_2 + H^+]$: 288.1958, found 288.195.

(4a*S*,5*R*,8a*R*)-5-Methyl-2-oxodecahydroquinoline (8): Into a three-necked, 100 mL, round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone, NH_3 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. 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 NH_4Cl 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 CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, 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%): ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.93 (d, *J* = 6.4 Hz, 3H, CH_3), 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*: 19.3 (CH_3), 20.0 (CH_2), 23.1 (CH_2), 27.3 (CH_2), 27.6 (CH), 31.8 (CH_2), 33.7 (CH_2), 39.7 (CH), 52.2 (CH), 172.9 (NCO).

(4a*S*,5*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-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 Boc_2O (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 NH_4Cl was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography (7:3 hexane–EtOAc) afforded lactam **9** (250 mg, 90%) as a white solid: mp 99–102 °C; $[\alpha]^{23}_D$ = – 23.92 (*c* 1.0, $CHCl_3$); IR (film): 1765, 1712 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.08 (d, *J* = 7.3 Hz, 3H, CH_3), 1.20-1.28 (m, 1H, H-7), 1.45-1.68 (m, 5H, H-4, H-6, H-7, H-8), 1.51 [s, 9H, $C(CH_3)_3$], 1.76-1.93 (m, 3H, H-4a, H-5, H-6), 2.05-2.17 (m, 1H, H-4), 2.39-2.59 (m, 2H, H-3), 4.13-4.21 (m, 1H, H-8a); ^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ*: 19.0 (CH_3), 19.8 (C-7), 23.0 (C-4), 27.2 (C-7), 27.9 [(*C*H_3)$_3$C], 28.7 (C-6), 32.6 (C-5), 33.4 (C-3), 39.3 (C-4a), 54.6 (C-8a), 82.7 [(CH_3)$_3$*C*], 153.3 (CO), 171.4 (C-2); HRMS calcd for [$C_{15}H_{25}NO_3$ + Na^+]: 290.1727, found 290.1723.

(4a*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-2-oxodecahydroquinoline (10): $NaIO_4$ (644 mg, 3.01 mmol) and $RuCl_3 \cdot nH_2O$ (6.3 mg, 0.0301 mmol) were added to a heterogenous solution of **3** (72 mg, 0.301 mmol) in CCl_4–MeCN–H_2O (1.7 mL, 3:3:4) at 0 °C. The mixture was stirred at 0 °C for 5 min and at room temperature for 5 h. Then, EtOAc was added, the resulting mixture was filtered through Celite®, and the filtrate was concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded **10** (72 mg, 95%) as a colorless oil: $[\alpha]^{23}_D$ = + 2.19 (*c* 1.0, MeOH); IR (film): 1765, 1712 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.24-1.55 (m, 5H, H-4, H-5, H-7, H-8), 1.48 (br s, 9H, 3 CH_3), 1.58-1.74 (m, 3H, H-5, H-6), 1.87-1.92 (m, 1H, H-8), 2.02.-2.12 (m, 2H, H-4, H-4a), 2.41-2.58 (m, 2H, H-3), 3.99-4.04 (m, 1H, H-8a); ^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ*: 20.0 (C-7), 21.3 (C-4), 25.1 (C-5), 27.9 [(*C*H_3)$_3$C], 28.2 (C-8), 30.3 (C-6), 33.3 (C-4a), 34.0 (C-3), 58.0 (C-8a), 82.6 [(CH_3)$_3$*C*], 152.8 (CO), 171.2 (C-2); HRMS calcd for [$C_{14}H_{23}NO_3$ + Na^+]: 276.1570, found 276.1574.

General Procedure for the Na/liq. NH_3 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, NH_3 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 NH_4Cl 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 CH_2Cl_2, 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 CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the corresponding lactone.

(4a*S*,5*R*,8a*S*)-5-Methyl-2-oxooctahydrochromene (14): $[\alpha]^{22}_D$ –72.8 (c, 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (d, *J* = 6.3 Hz, 3H, CH_3), 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 (ddd, *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); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 19.0 (CH_3), 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 [$C_{10}H_{16}O_2$ + H^+]: 169.1223, found 169.1223.

(4a*S*,5*R*,8a*S*)-5-(5-Hydroxypentyl)-2-oxooctahydrochromene (16): $[\alpha]^{22}_D$ −61.5 (c, 1.3, MeOH); IR (NaCl): 3429, 1734 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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-5'), 3.95 (ddd, *J* = 10.5, 10.4, 4.2 Hz, 1H, H-8a); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ: 23.3 (CH_2), 23.6 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 29.4 (C-3), 30.7 (CH_2), 32.2 (CH_2), 32.4 (CH_2), 32.7 (CH_2), 40.9 (C-5), 42.9 (C-4a), 62.9 (C-5'), 82.9 (C-8a), 171.8 (COO); HRMS calcd for [$C_{14}H_{24}O_3$ + H^+]: 241.1798, found 241.1798.

(4a*S*,8a*S*)-5-Methyl-2-oxo-3,4,4a,7,8,8a-hexahydrochromene (18): $[\alpha]^{22}_D$ –56.4 (c, 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.51-1.60 (m, 1H), 1.67 (s, 3H, CH_3), 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), 4.14 (ddd, *J* = 12.4, 9.3, 3.3 Hz, 1H), 5.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 19.9 (CH_3), 23.5 (CH_2), 24.4 (CH_2), 28.3 (CH_2), 29.9 (CH_2), 41.0 (CH), 81.3 (CH), 122.8 (CH), 132.2 (CH), 171.9 (COO); MS (CI) m/z (%): 166.1, 100 (M+).

(4a*R*,8a*S*)-2-Oxooctahydrochromene (19): $[\alpha]^{22}_D$ –39.2 (c, 0.7, MeOH) {Lit.[13] –40.5 (c, 0.98, MeOH)}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 400 MHz) δ: 24.2 (CH_2), 25.2 (CH_2), 26.6 (CH_2), 29.9 (CH_2), 31.2 (CH_2), 32.4 (CH_2), 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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