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Solid Support Synthesis of Polysubstituted Tetrahydroquinolines *via* Three-Component Condensation Catalyzed by Yb(OTf)3.

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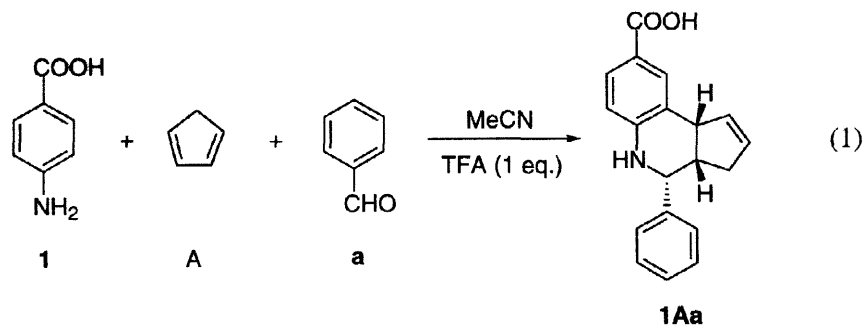
Abstract: Solid support synthesis of polysubstituted tetrahydroquinolines is described. The procedure is based on a three-component condensation involving immobilized derivatives of 4-aminophenylalanine, aldehydes, alkenes and $Yb(OTf)_3$ as a catalyst. The methodology is further expanded to the solid support synthesis of tricyclic tetrahydroquinoline by the concomitant formation of the Schiff base followed by intramolecular trap of the alkene.

Multiple component condensation (MCC) reactions are powerful tools for the fast assembly of polysubstituted molecules, especially when applied to solid support synthesis.[1] Unlike linear libraries, the number of structural analogs generated is dependent only on the number, and availability of inputs in MCC reactions. MCC libraries are synthesized in a single chemical transformation, and thus typically generated in a parallel fashion.

In our continuing effort toward identifying new reaction templates to investigate by solid support methods,[2] we were interested in the versatile synthesis of polysubstituted tetrahydroquinolines (**1Aa**) described by several research groups in the past (eq. 1).[3]



(1)

This approach is based upon the three-component condensation of substituted anilines (**1**) with electron-rich olefins (**A**) and aldehydes (**a**) in the presence of an equimolar amount of TFA in MeCN.[3a] Attempts have been made to expand the scope of this chemistry using heterocyclic amines, as well as various electron-rich olefins.[3,4] Of particular interest is the report by Kobayashi on the succesful application of polymer supported Sc, and Yb catalysts for this three-component condensation.[5] Intrigued by the possibility of utilizing the condensation shown in equation 1 for the synthesis of tetrahydroquinolines on solid support,[6] we chose the aromatic amine input as the anchoring site. This manipulation allowed us to tether the carboxylate directly to the resin and successfully complete the first solid support version of the three-component condensation.[7] To further expand the size, and to

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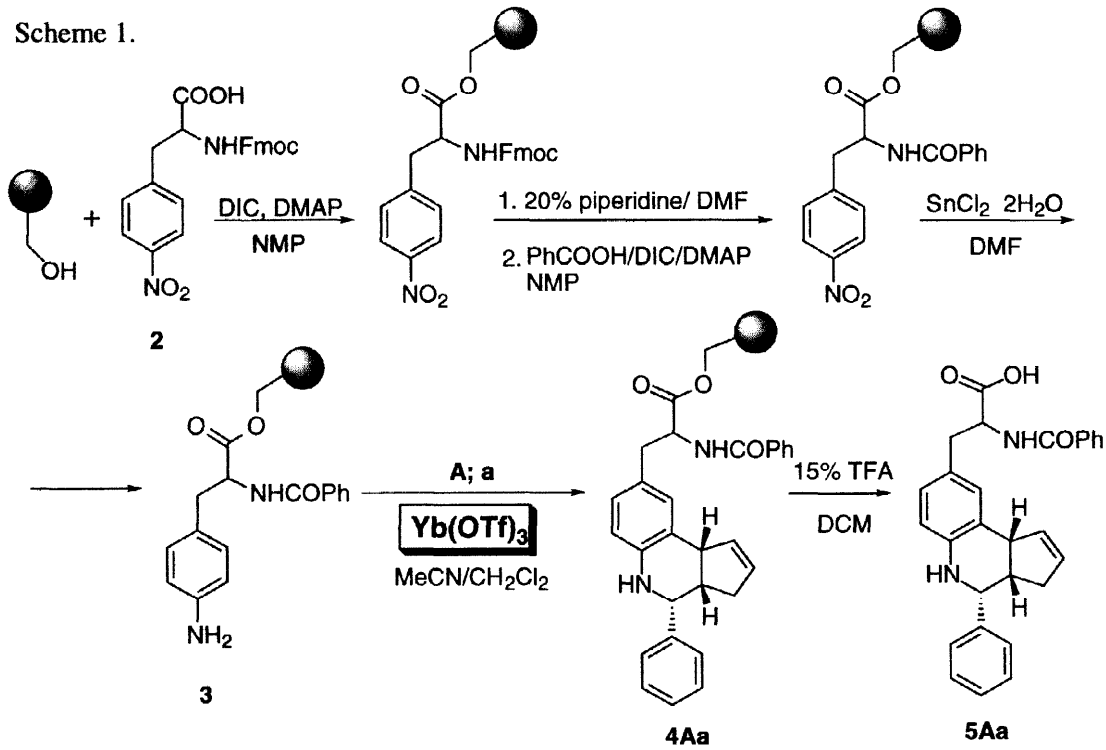
introduce an additional diversity element into the library of tetrahydroquinolines, we selected 4-aminophenylalanine, immobilized on the solid support, as the aromatic amine input (Scheme 1).

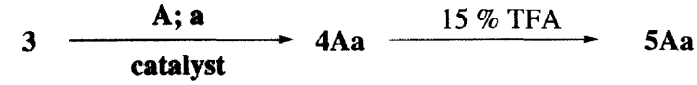
Scheme 1.



Commercially available 4-nitrophenylalanine (**2**) was selected as a convenient precursor for this substrate. Through a standard resin preparation protocol, (**2**) was successfully coupled on to the commercially available Wang resin (loading 0.6 mmol/gram) using DIC/DMAP in DMF at room temperature. Deprotection of the amino group, followed by coupling of benzoic acid and reduction of the nitro group[8] afforded the desired 4-aminophenylalanine derivative (**3**) attached to solid support (0.3 mM/g loading, Scheme 1). Catalysis with TFA (1% in MeCN) of the 3-component condensation of (**3**), (**A**), and (**a**) afforded the desired tetrahydroquinoline (**5Aa**) in only 51% yield (after the treatment of the resin with 15% TFA/CH_2Cl_2).[7] The ^1H NMR analysis of the cleavage product revealed the presence of the nonreacted Schiff base in *ca.* 37% yield. Attempts to incubate the reaction mixtures for longer periods, or to resubject the resin to freshly prepared mixtures of (**A**), and (**a**) in 1% TFA failed to improve the yield of the reaction. Increasing the concentration of TFA from 1% to 3% resulted in the premature cleavage of the nonreacted 4-aminophenylalanine. As a result of the limited yields, a series of Lewis acid catalysts were investigated as alternatives to TFA. The results of these studies are summarized in Table 1. Despite the fact that 1% $BF_3{\cdot}OEt_2$ and 1% $TiCl_4$ were found to be efficient catalysts for this three-component condensation in solution, they failed to produce good yields of the desired tetrahydroquinoline (**5Aa**) on solid support. Anhydrous $InCl_3$ (5% in MeCN) afforded only 34% yield of (**5Aa**).[9] Application of 1% LLB and 0.1 % $Yb(BNP)_3$ did not produce (**5Aa**) even though these catalysts were successfully used for similar cycloadditions.[10] Considerably better results were obtained with 0.1 % solution of $Yb(OTf)_3$ in MeCN.[5] HPLC analysis of the cleaved product (**5Aa**) showed the purity of the desired tetrahydroquinoline to be 88 %. An additional improvement to this procedure was achieved by conducting the solid phase synthesis in a mixture of MeCN/CH_2Cl_2 (2:1), presumably due to the better swelling of the resin in this solvent system. Larger quantities

Table 1.

The effect of the catalyst on the outcome of the three-component condensation.

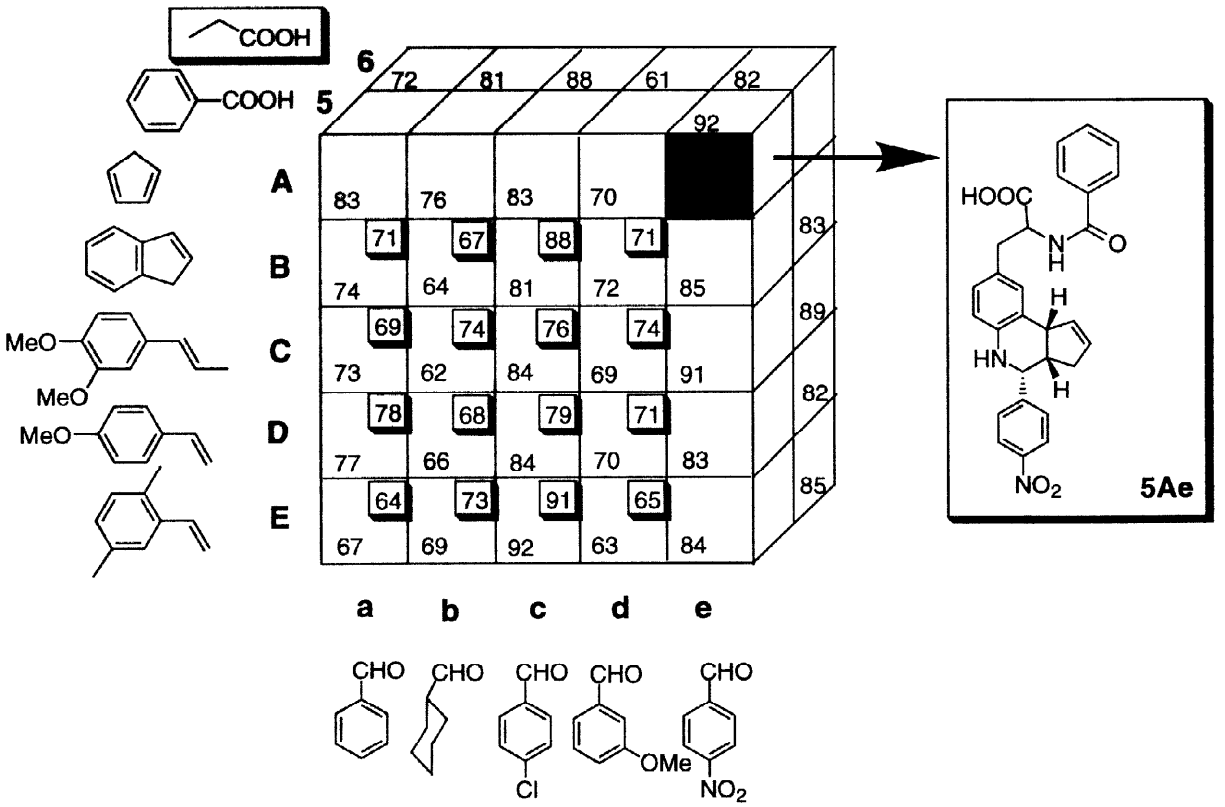


Entry	Catalyst	Solvent	Rxn time, hr.	Yield of product **1Aa** %
1	1% TFA	MeCN	12	51
2	3% TFA	MeCN	6	64
3	1% BF_3OEt_2	CH_2Cl_2	12	54
4	1% $TiCl_4$	CH_2Cl_2	12	34
5	1% *(R)*-LLB	MeCN	48	0
6	0.1 % $Yb(BNP)_3$	MeCN	48	0
7	5% $InCl_3$	MeCN	48	34
8	0.1% $Yb(OTf)_3$	MeCN	24	75
9	0.1 % $Yb(OTf)_3$	MeCN/CH_2Cl_2 2:1	24	83

of CH_2Cl_2 in the reaction solvent resulted in considerably lower yields of (**5Aa**). Several other solvents including DMF, dioxane, THF, and MeOH were inferior to the optimized solvent system.

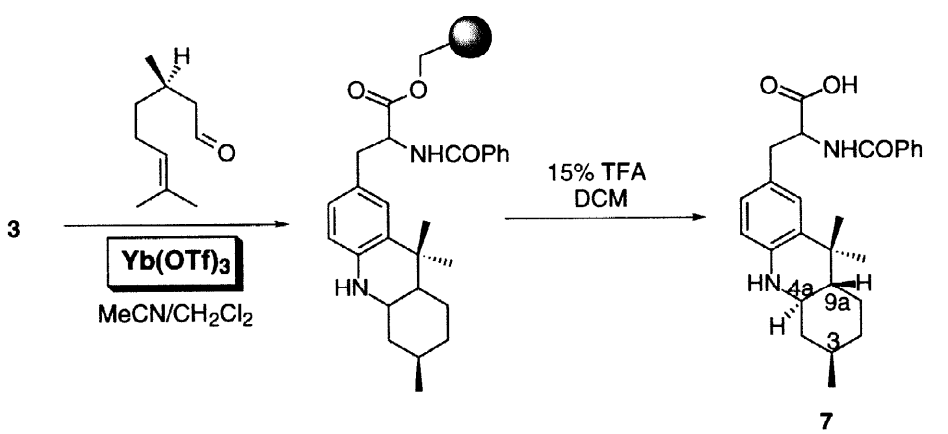
The elaboration of the new reaction conditions for the solid support three-component condensation allowed us to successfully synthesize a library of 50 members (Scheme 2). We found that several new olefins (**C-E**), along with previously reported (**A**), and (**B**)[3,4,5] are efficient entries for this 3CC reaction. The yields of the target tetrahydroquinolines varied from 62 to 91% (based upon 0.3 mM/g loading of the aniline resin **3**). The best yields (76-92%) were achieved with the aldehydes containing electron-withdrawing substituents, and olefinic entries (**A-D**). Since convential reaction conditions (1-3% TFA as a catalyst) led to the polymerization of the olefin **D**, application of $Yb(OTf)_3$ catalyst for the described 3CC with **D** as an olefinic input was especially beneficial. The nature of the carboxylic acid used for the acylation of (**2**) did not affect the yield or purity of tetrahydroquinolines (**5**), and (**6**). Chemical yields (determined based on the 0.3 mM/g loading of the aniline resin **3**, and corresponding to individual compounds characterized by ^1H NMR, LC MS, and HPLC analyses, see

Scheme 2.



Experimental section) are given in Scheme 2. Tetrahydroquinolines (**5**), and (**6**) were isolated as a mixture of diastereomers. The single major impurity detected in the reaction mixtures (^{1}H NMR, HPLC) was the corresponding Schiff base. Primary aldehydes (acetaldehyde and valeraldehyde) afforded only trace amounts of the corresponding tetrahydroquinolines (15-20% by ^{1}H NMR). The reaction mixtures contained significant amount of the nonreacted Schiff base (35-40%) as well as unidentifiable materials.

We extended this methodology to the synthesis of tricyclic tetrahydroquinolines by the concomitant formation of the Schiff base followed by intramolecular trap of the alkene. For example, when the aniline resin (**3**) was allowed to react with *(R)-(+)*-citronellal in the presence of cyclopentadiene (eq. 2) the only product isolated after the cleavage of the resin with TFA was (**7**) in excellent yield (88%) as a single diastereomer. Similar results were



(2)

obtained with other olefinic entries **A-E**. The only isolated product in all cases was **7** (78-89% yield). Product (**7**) was the only compound isolated even when a 10 fold molar excess of (**A**) was added to the reaction mixture. This result suggests that the intramolecular cyclization of the intermediate Schiff base is favored over its reaction with cyclopentadiene.[11] The large vicinal coupling $J_{4a,9a}$ = 10.5 Hz indicated the *trans* ring fusion in (**7**).[11]

In summary, a solid support version of the 3CC reaction to generate tetrahydroquinolines has been developed. Application of the $Yb(OTf)_3$ catalyst for this transformation was found to be more advantageous than the previously reported 1% TFA/MeCN system or various Lewis acids. Several novel olefin inputs have been introduced to enhance the diversity of the library. The efficiency, and versatility of the chemistry described allow access to a large library of polysubstituted tetrahydroquinolines.

Experimental Section

Materials. All solid phase reactions were carried out at room temperature. Reagents were purchased from Aldrich and Acros and used without further purification. Wang resin (loading 0.6 mmol/g) was purchased from Novabiochem and washed with DMF, MeOH, CH_2Cl_2, and MeCN prior to use.

General Methods. All reactions were carried out in Alltech® vessels. Concentration of solutions after workup was performed by reduced pressure rotary evaporation. ^1H NMR spectra were obtained on a Bruker 500 instrument with MeOD and DMSO-d_6 as the solvents. MS analysis (ES and CI modes) was performed on a Perkin Elmer API 165 instrument. HPLC analysis was performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 nm and 254 nm. The column employed was an Ultrasphere C18 cartridge 250mm x 4.6 mm. Solvent system was MeCN/H_2O (.1% TFA added), flow rate 1 mL/min.

General Procedure for Preparing 4-aminophenylalanine on Solid Support. In a standard resin preparation protocol, commercially available (Novabiochem) *N*-Fmoc protected 4-nitrophenylalanine (17.28 g, 40 mM) was dissolved in 500 mL of dry DMF, 5.04 g of DIC (40 mM), and 50 mg of DMAP were added, and the mixture was stirred for 5 min. Wang resin (30g, loading 0.6 mmol/gram) was treated with the mixture, the resulting slurry was agitated for 12 hrs on a Lab-Line orbit shaker, filtered, washed with DMF, MeOH, and CH_2Cl_2. The loading was determined to be 0.5 mmol/g (UV, Fmoc cleavage). The resulting resin (15g) was subjected to 20% solution of piperidine in DMF to remove the Fmoc protective group, washed with DMF, MeOH, CH_2Cl_2, and treated with a solution of 2.44 g (20 mM) of benzoic acid, 2.52 g of DIC (20 mM), and 25 mg of DMAP in 200 mL of dry DMF, or 1.48 g (20 mM) of propionic acid 2.52 g of DIC (20 mM) and 25 mg of DMAP in 200 mL of dry DMF. The resulting *N*-acylated resin (15 g) was washed with DMF, MeOH, CH_2Cl_2, treated with 300 mL of 1.0 M solution of $SnCl_2$•2 H_2O in DMF for 12 hrs, washed thoroughly with DMF (8-9X200 mL), MeOH, and CH_2Cl_2 to afford the desired resin **3** (0.3 mM/g loading as determined by 15% TFA/CH_2Cl_2 cleavage).

General Procedure For Solid Support Synthesis of Tetrahydro-quinolines *via* Three-Component Condensation Catalyzed by $Yb(OTf)_3$: This library was synthesized in parallel under the following reaction conditions: the polymer bound aniline **3** (200 mg of resin per reaction vessel, 0.3 mM/g loading) was treated with 0.5 M solution of aldehyde (300 μL), and 0.5 M solution of alkene (300 μL) in a MeCN/CH_2Cl_2 mixture (2:1 v/v, both solvents were of HPLC grade). A .1% solution of $Yb(OTf)_3$ (400 μL) in the same solvent system was introduced, and the mixture was agitated by bubbling N_2. After 24 hrs, the resulting resin was filtered, washed with DMF, MeOH, CH_2Cl_2, dried in the vacuum oven and treated with a 15%

TFA/CH_2Cl_2 solution (2 mL per reaction vessel) to cleave the target tetrahydroquinoline product. The resulting solution was collected, concentrated under reduced pressure (**attention! efficient liquid N_2 trap**), and the oily residue was triturated with Et_2O to afford the desired product as a solid. All compounds were characterized by ^1H NMR, ESMS, and HPLC analyses.

Selected experimental data:

(3a*R,4*S**,9b*S**)-8-(2-Benzamido-2-carboxyethyl)-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5Aa)**: 21.8 mg (83%); HPLC t_R = 5.93; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d = 2.04 (m, 1H), 2.54 (m, 1H), 3.16 (m, 1H), 3.22 (m, 1H), 3.34 (m, 2H), 4.28 (m, 1H), 4.68 (m, 1H), 5.56 (m,1H), 5.71 (m,1H), 7.12 (m, 1H), 7.21 (m, 1H), 7.37 (s, 1H), 7.40-7.55 (m, 8H), 7.78 (m, 2H); ESI MS *m/z* 439 (M + H^+).

(2*R,3*R**,4*S**)-6-(2-Benzamido-2-carboxyethyl)-2-phenyl-4(3,4-dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline(5Ca)**: 24.1 mg (73%); HPLC t_R = 6.72; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d = 0.75 (d, ^3J (H,H) = 8.0 Hz, 3H), 2.53 (m, 1H), 2.98 (m, 2H), 3.26 (m, 1H), 3.66 (s, 3H), 3.74 (s, 3H), 4.39 (m, 1H), 4.72 (m, 1H), 6.65-6.78 (m, 4H), 7.12 (d, ^3J (H,H) = 7.5 Hz, 1H), 7.23 (d, ^3J(H,H) =7.5 Hz, 1H), 7.44-7.70 (m, 5H); ESI MS *m/z* 551 (M + H^+).

(2*R,3*R**,4*S**)-6-(2-Benzamido-2-carboxyethyl)-2-(4-nitrophenyl)-4-(3,4-dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (5Ce)**: 32.5 mg (91%); HPLC t_R = 6.21; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d = 0.66 (d, ^3J (H,H) = 8.0 Hz, 3H), 2.23 (m, 1H), 2.51 (m, 1H), 3.04 (m, 2H), 3.72 (s, 3H), 3.82 (s, 3H), 4.26 (m, 1H), 4.74 (m, 1H), 6.59-6.78 (m, 3H), 7.32-7.74 (m, 3H), 7.78 (d, ^3J (H,H) = 8.5 Hz, 2H), 8.18 (d, ^3J (H,H) = 8.5 Hz, 2H); ESI MS *m/z* 596 (M + H^+).

***cis*-6-(2-Benzamido-2-carboxyethyl)-2-phenyl-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (5Da)**: 23.7 mg (78%); HPLC t_R = 7.50; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d=1.42 (m, 2H), 1.97 (m, 1H), 2.44 (m, 2H), 3.22 (m, 1H), 4.58 (s, 1H), 6.72 (d, ^3J (H,H)= 8.0 Hz, 2H), 6.81 (d, ^3J (H,H)= 8.0 Hz, 1H), 6.93 (d, ^3J (H,H)= 8.0 Hz, 1H), 7.02 (m, 3H), 7.28-7.55 (m, 5H); ESI MS *m/z* 507 (M + H^+).

(3a*R,4*S**,9b*S**)-8-(2-Carboxy-2-propionamidoethyl)-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (6Aa)**: 16.8 mg (72%); HPLC t_R = 5.77; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d=1.02 (t, ^3J (H,H)= 8.5 Hz, 3H), 2.14 (m, 3H), 2.48 (m, 1H), 2.88 (m, 1H), 3.18 (m, 3H), 4.18 (m, 1H), 4.68 (m, 1H), 5.64 (m, 1H), 5.81 (m, 1H), 7.11 (m, 2H), 7.21 (s, 1H), 7.35-7.45 (m, 5H); ESI MS *m/z* 389(M + H^+).

(3a*R,4*S**,9b*S**)-8-(2-Carboxy-2-propionamidoethyl)-4-cyclohexyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (6Ab)**: 16.9 mg (71%); HPLC t_R = 6.71; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d=0.94 (t, ^3J (H,H)= 8.5 Hz, 3H), 1.12-1.40 (m, 3H), 1.50-2.05 (m, 4H), 2.10 (q, ^3J (H,H)=8.5 Hz, 2H), 2.18 (m, 1H), 2.44 (m, 1H), 2.94 (m, 2H), 3.16 (m, 1H), 3.28 (m, 2H), 3.35 (m, 1H), 3.94 (m, 1H), 4.63 (m, 1H), 5.74 (m, 1H), 5.96 (m, 1H), 7.15-7.30 (m, 3H); ESI MS *m/z* 397 (M + H^+).

(3a*R,4*S**,9b*S**)-8-(2-Carboxy-2-propionamidoethyl)-4-(4-fluorophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (6Ac)**: 21.6 mg (88%); HPLC t_R = 5.82; ^1H NMR (500 MHz, [d_4] MeOH, 25°C, TMS): d=0.98 (t, ^3J (H,H)= 8.5 Hz, 3H), 1.98 (m, 1H), 2.14 (q, ^3J (H,H)= 8.5 Hz, 2H), 2.43 (m, 1H), 2.78 (m, 1H), 3.06 (m 3H), 4.12 (m, 1H), 4.72 (m, 1H), 5.65 (m, 1H), 5.87 (m, 1H), 6.82 (d, ^3J (H,H)= 7.5 Hz, 1H), 6.93 (d, ^3J (H,H)= 7.5 Hz, 1H), 7.19 (m, 2H), 7.21 (s, 1H), 7.43 (m, 2H); ESI MS *m/z* 409 (M + H^+).

(3a*R,4*S**,9b*S**)-8-(2-Carboxy-2-propionamidoethyl)-4-(4-nitrophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (6Ae)**: 21.5 mg (82%); HPLC t_R = 6.94; ^{1}H NMR (500 MHz, [d$_4$] MeOH, 25°C, TMS): d= 1.02 (t, ^3J (H,H)= 8.5 Hz, 3H), 1.86 (m, 1H), 2.19 (q, ^3J (H,H)= 8.5 Hz, 2H), 2.45 (m, 1H), 2.81 (m, 1H), 3.04 (m, 2H), 3.21 (m, 1H), 4.07 (m, 1H), 4.65 (m, 1H), 5.61 (m, 1H), 5.83 (m, 1H), 6.76 (d, ^3J (H,H)= 7.5 Hz, 1H), 6.83 (d, ^3J (H,H)= 7.5 Hz, 1H), 6.94 (s, 1H), 7.75 (d, ^3J (H,H)= 8.5 Hz, 2H), 8.28 (d, ^3J (H,H)= 8.5 Hz, 2H); ESI MS *m/z* 436 (M + H$^+$).

(5a*R,6*S**,11b*R**)-10-(2-Carboxy-2-propionamidoethyl)-6-(4-fluorophenyl)-5a,6,7,11b-tetrahydro-5*H*-indeno[2,3-*c*]quinoline (6Bc)**: 24.2 mg (88%); HPLC t_R = 8.32; ^{1}H NMR (500 MHz, [d$_4$] MeOH, 25°C, TMS): d=0.95 (t, ^3J (H,H)= 8.5 Hz, 3H), 2.11 (d, ^3J (H,H)= 8.5 Hz, 2H), 2.63 (m, 2H), 3.12 (m, 3H), 3.44 (m, 1H), 3.76 (m, 1H), 4.65 (m, 1H), 7.11 (m, 1H), 7.22 (d, ^3J (H,H)= 7.5 Hz, 1H), 7.34 (m, 1H), 7.51 (m, 2H), 7.72 (m, 1H), 7.89 (m, 1H), 8.04 (m, 2H), 8.18 (d, ^3J (H,H)= 7.5 Hz, 2H); ESI MS *m/z* 459 (M + H$^+$).

(2*R,3*R**,4*S**)-6-(2-Carboxy-2-propionamidoethyl)-2-(4-nitrophenyl)-4-(3,4-dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (6Ce)**: 29.3 mg (89%); HPLC t_R = 7.02; ^{1}H NMR (500 MHz, [d$_4$] MeOH, 25°C, TMS): d=0.75 (d, ^3J (H,H)= 8.0 Hz, 3H), 0.98 (t, ^3J (H,H)= 8.5 Hz, 3H), 2.05 (m, 2H), 2.51 (m, 1H), 2.89 (m, 2H), 3.26 (m, 1H), 3.71 (s, 3H), 3.78 (s, 3H), 4.28 (d, ^3J (H,H)= 7.5 Hz, 1H), 4.53 (m, 1H), 6.51 (d, ^3J (H,H)= 8.0 Hz, 1H), 6.65-6.75 (m, 3H), 6.74 (m, 2H), 7.78 (d, ^3J (H,H)= 8.5 Hz, 2H), 8.26 (d, ^3J (H,H)= 8.5 Hz, 2H) ; ESI MS *m/z* 548 (M + H$^+$).

***cis*-6-(2-Carboxy-2-propionamidoethyl)-2-(4-fluorophenyl)-4-(2,5-dimethylphenyl)-1,2,3,4-tetrahydroquinoline (6Ec)**: 25.7 mg (91%); HPLC t_R = 6.13; ^{1}H NMR (500 MHz, [d$_4$] MeOH, 25°C, TMS): d=0.98 (t, ^3J (H,H)= 8.5 Hz, 3H), 2.15 (d, ^3J (H,H)= 8.5 Hz, 2H), 2.72 (m, 1H), 2.84 (m, 2H), 2.92 (m, 1H), 3.11 (m, 2H), 3.16 (s, 3H), 3.18 (s, 3H), 4.64 (m, 1H), 6.84 (s, 1H), 7.13 (s, 1H), 7.32 (d, ^3J (H,H)= 8.0 Hz, 1H), 7.43 (d, ^3J (H,H)= 8.0 Hz, 1H), 7.61 (d, ^3J (H,H)= 7.5 Hz, 1H), 7.76 (d, ^3J (H,H)= 7.5 Hz, 1H), 8.14 (m, 4H); ESI MS *m/z* 471 (M + H$^+$).

***trans*-(3*R*)-7-(2-Benzamido-2-carboxyethyl)-3,9,9-trimethylocta-hydroquinoline (7)**: 22.2 mg (88%); HPLC t_R = 5.84; ^{1}H NMR (500 MHz, [d$_4$] MeOH, 25°C, TMS): d=0.85-1.20 (m, 12H), 1.43 (m, 2H), 1.57 (m, 2H), 1.92 (m, 1H), 2.05 (m, 1H), 2.87 (m, 1H), 3.12 (dd, ^3J (H,H)= 10.5 Hz, ^3J (H,H)= 4.0 Hz, 1H), 4.66 (m, 1H), 6.93-7.18 (m; 2H), 7.36 (m, 2H), 7.44 (m, 2H), 7.71 (m, 2H); ESI MS *m/z* 421 (M + H$^+$).

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