Enantioselective Hydrogenation of β-Keto Esters using Chiral Diphosphine-Ruthenium Complexes: Optimization for Academic and Industrial Purposes and Synthetic Applications

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Abstract: Enantioselective hydrogenation using chiral complexes between atropisomeric diphosphines and ruthenium is a powerful tool for producing chiral compounds. Using a simple and straightforward *in situ* catalyst preparation, the conditions were optimized using molecular hydrogen for both academic and industrial purposes. This led to the best conditions and the lowest catalytic ratio required for the pressure used. Hydrogenation of various β-keto esters was efficiently performed at atmospheric and higher pressures, leading to the use of very low catalyst-substrate ratios up to 1/20,000. Asymmetric hydrogenations were used in key-steps towards the total synthesis of corynomycolic acid, Duloxetine and Fluoxetine.

Keywords: asymmetric catalysis; asymmetric synthesis; Duloxetine; Fluoxetine; hydrogenation; P-ligands; ruthenium

Introduction

Catalyzed hydrogenation and reduction of unsaturated compounds promoted by chiral metal complexes is nowadays a tool of choice for the preparation of enantiomerically enriched and even pure pharmaceuticals or their synthetic intermediates.[1] Homogeneous asymmetric procedures for the preparation of chiral compounds have been successfully applied in academic and industrial[2] syntheses of bioactive molecules and their precursors.

One of the most interesting tools is the enantioselective hydrogenation based on chiral ruthenium-atropisomeric diphosphines complexes. Since the pioneering work of Horner, Knowles,[3] and others on monophosphine ligands, and the breakthrough of C_2-symmetrical chiral ligands used by Kagan et al.,[4] the interest in the development of asymmetric catalytic versions of this reaction led to very powerful systems. The work of Noyori et al. on catalytic asymmetric hydrogenation,[5] as well as asymmetric transfer hydrogenation,[6] with chiral transition metal complexes gave to these reactions a state of the art aura. The importance of this reaction was internationally recognized and ultimately crowned by the Nobel Prize award. The interest for this method and its industrial applications,[7] as well as its ongoing development is still growing due to its huge potential. Several academic syntheses of complex molecules and production of chemicals and pharmaceuticals are now based on catalytic enantioselective hydrogenation procedures,[8] demonstrating the contribution of this reaction to modern organic chemistry.

In our continuing studies[9] on homogeneous hydrogenation over one decade, the objective of actual research in this field is to develop chiral catalysts with the highest catalytic activity. Excellent results were obtained with atropisomeric diphosphine-ruthenium complexes. These catalysts presented very high TON (turnover number), defined as moles of product per mole of catalyst and, for a specific transformation and reaction conditions, very high TOF (turnover frequency), defined as TON per hour or second. Nevertheless, in spite of the high activity reached for some ruthenium based-catalysts, the procedures often suffer from lengthy catalyst preparation and harsh reaction conditions.

In order to increase the efficiency of the asymmetric hydrogenation protocol, as well as its potential use in academic and industrial laboratories, we focused our efforts in developing enantioselective hydrogenation at

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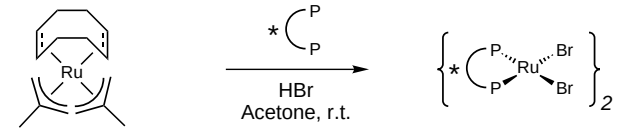
various pressures, trying to find the lowest catalytic ratio of classical diphosphine-ruthenium complexes, under relatively soft conditions. This paper presents our results in this search for improved hydrogenation procedures. The procedures were then used in key-steps for the synthesis of enantiomerically enriched biologically active substances.

Results and Discussion

An Easy Access to Atropisomeric Diphosphino-Ruthenium Catalysts

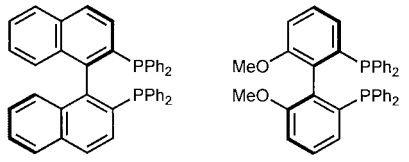
A very efficient dinuclear Ru-catalyst prepared from the polymeric complex $[(cod)RuCl_2]_n$ (cod = cycloocta-1,5-diene) has been described by Ikariya et al.[10] In order to simplify the preparation of catalysts made from atropisomeric diphosphines and ruthenium, a simple and rapid *in situ* procedure[9q] was elaborated a few years ago in our laboratory (Scheme 1). This approach uses the commercially available ruthenium complex $[(cod)Ru(\eta^3\text{-}2\text{-methylallyl})_2]$ (**1**) as a starting material. The catalyst preparation involves a simple treatment of the complex **1** with the selected chiral diphosphine (*P – P) in acetone in the presence of methanolic HBr at room temperature.

This gives quantitatively access within minutes to the corresponding diphosphinehalo-ruthenium species of the general structure $[*(P-P)RuBr_2]_2$. This universal synthetic method allows the production of ruthenium complexes from a wide variety of diphosphines including DIOP,[11] DIPAMP,[12] CHIRAPHOS,[13] BDPP,[14] BIPNOR,[15] BINAP,[16] *Tol*-BINAP,[17] MeO-BIPHEP[18] and more recently cationic *Digm*-BINAP,[19] to quote a few examples. The *in situ* generated chiral



[(cod)Ru(met)$_2$] **1** ***in situ*** *[*(P–P)RuBr$_2$]*

Scheme 1.



(*R*)-BINAP (*R*)-MeO-BIPHEP

(*R*)-**2** (*R*)-**3**

Scheme 2.

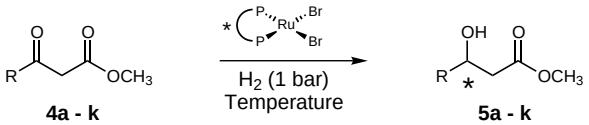
Ru(II)-catalysts have been used by our group[9] and others[20] in very efficient asymmetric hydrogenation reactions of β-keto esters and various substrates both at atmospheric and higher pressures.

For the purpose of this study, we selected the diphosphines BINAP (**2**) and MeO-BIPHEP (**3**), for which the structures of the (*R*)-enantiomers are drawn in Scheme 2.

Asymmetric Hydrogenation at Atmospheric Pressure of Various β-Keto Esters

Chiral β-hydroxy esters are useful building blocks for the synthesis of biologically active compounds and natural products.[21] The importance of preparing enantiomerically pure compounds hardly requires restatement since enantiomers may have different biological activities, sometimes showing no or lower activity or even worst, dramatic toxic side effects. Biological and biotechnological methods have been widely developed and used for this purpose. A major drawback of some of these methodologies is the difficulty to isolate the product from fermentation broths, and which consequently often leads to moderate yields. The use of homogeneous chiral catalysts has some advantages over these bioreactions. The catalyst preparation and use are controlled, the reactions are often fast, and the products can be easily isolated. But most of all, the reaction is tunable, i.e., the catalyst stereochemistry can be selected in order to obtain the desired isomer.

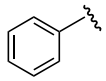
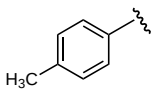
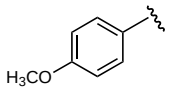
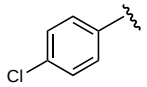
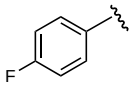
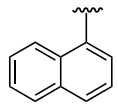
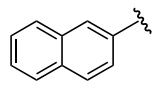
With the goal of finding conditions that can be widely used in laboratories using the simplest available apparatus, we concentrated a part of our studies on hydrogenations at atmospheric pressure. These studies led to a method that can find application in all laboratories without the need for complex equipment. The first efficient transition-metal catalysis that effected highly enantioselective hydrogenation of β-keto esters was reported by Noyori et al.[22] As an example, we previously showed that the asymmetric hydrogenation of β-keto esters under atmospheric pressure[9k, o] could be conducted with 1 to 2 mol % of chiral Ru(II) catalysts. Noyori et al. also reported the BINAP/Ru-catalyzed hydrogenation of β-keto sulfonates at atmospheric pressure.[23] Our method showed a wide scope and was applied to several alkyl- or aryl-substituted β-keto ester hydrogenations, giving access to multigram quantities of the corresponding β-hydroxy esters (Scheme 3) with high enantiomeric excesses.



4a - k **5a - k**

Scheme 3.

Table 1. Asymmetric hydrogenation of β-keto esters **4** at atmospheric pressure.[a]

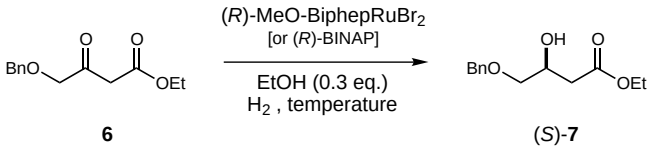
Keto ester	R	Diphosphine[b]	T [°C]	t [h][c]	Hydroxy ester	Yield [%][d]	ee [%][e]
4a	$C_{11}H_{23}$	(*R*)-**2**	50	48	**5a**	100	97 (*R*)
4b	$C_{13}H_{27}$	(*R*)-**2**	50	24	**5b**	100	99 (*R*)
4c	$C_{15}H_{31}$	(*R*)-**2**	50	96	**5c**	100	99 (*R*)
		(*R*)-**3**	40	72		100	97 (*R*)
4d[f]		(*S*)-**3**	50	18	**5d**	90	97 (*R*)
4e		(*R*)-**3**	25	72	**5e**	100	90 (*S*)
4f		(*R*)-**2**	50	20	**5f**	86	90 (*S*)
			65	48		100	77 (*S*)
4g		(*R*)-**3**	60	16	**5g**	84	89 (*S*)
4h		(*R*)-**3**	50	18	**5h**	75	94 (*S*)
			65	48		100	95 (*S*)
4i		(*R*)-**2**	50	24	**5i**	87	89 (*S*)
4j		(*R*)-**3**	50	24	**5j**	80	92 (*S*)
			65	48		100	94 (*S*)
4k		(*R*)-**3**	70	24	**5k**	76	88 (*S*)
			65	48		100	80 (*S*)

[a] 1 mmol scale with MeOH or EtOH (**4d**) as solvent (2 mL).
[b] 2 mol % of the catalyst. **2** = BINAP, **3** = MeO-BIPHEP.
[c] Not optimized.
[d] Yields determined by ^{1}H NMR (300 MHz).
[e] Enantiomeric excesses calculated by GC analysis and/or ^{1}H NMR (300 MHz) with Eu(tfc)$_3$.
[f] Ethyl ester.

Although the reaction can be conducted successfully at room temperature in some cases, the best results were obtained while working at 50 to 70 °C, using the alcohol corresponding to the ester as solvent (Table 1). β-Keto esters bearing fatty side chains (C_{11} to C_{15}, **4a**–**c**) can be quantitatively hydrogenated using either MeO-BIPHEP (**3**) or BINAP (**2**) as the diphosphine ligand (*reaction time not optimized*). Enantiomeric excesses reached in these cases were very high (97 to 99% ee). When the β-keto esters were substituted by aromatic rings, the reaction was not complete below 24 hours (**4d**, **4f**–**i**). Quantitative conversion can generally be reached after 48 hours at 65 °C. Enantiomeric excesses were good for the simple phenyl ring (**4d**, 97% ee) and lower for the *para*-substituted compounds (**4f**–**i**, 77–94% ee) with little influence of the nature of the substituent. Similar results were obtained for isomeric naphthalenic derivatives (**4j**, **k**) with ee in the same average (80–94% ee) for complete transformation. Interestingly, the thienyl-substituted derivative **4e**, had no deleterious effect on the catalysis. The corresponding β-hydroxy ester **5e** was synthesized in 90% ee after 72 hours.

Asymmetric Hydrogenation at Low and Medium Pressures

The main interest in hydrogenation studies is to find the simplest procedure for enantioselective hydrogenation and optimize it for large-scale to batch production. For this purpose, close collaboration between academic and industrial research or process laboratories is mandatory to reach common goals, and to test the reaction conditions in action. The method using atropisomeric



Scheme 4.

phosphines for asymmetric hydrogenation gave us the opportunity to apply this simple and efficient technique in reactions on a large scale, with usual diphosphine ligands. In spite of the good results obtained, the next logical step was to find a way to decrease the amount of catalyst used in this transformation.

A first series of enantioselective hydrogenations were done on a 1 mmol scale in steel autoclaves on a β-keto ester, ethyl 4-benzyloxyacetoacetate **6**. Hydrogenation reactions of β-keto esters were performed using the alcohol corresponding to the ester as solvent and rate-accelerating additive. It was found during this study that a small amount of alcohol in the reaction medium was the way to reach the highest conversion rate. The use of (*S*)-BINAP [(*S*)-**2**], or MeO-BIPHEP [(*S*)-**3**], as ruthenium ligands in the presence of 0.3 equivalents of ethanol in respect to the substrate **6** gave good results for the preparation of ethyl (*S*)-4-benzyloxy-3-hydroxybutyrate **7** as shown in Scheme 4.

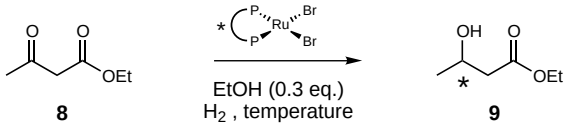
This β-keto ester **6** was hydrogenated in ethyl alcohol as solvent (7 equivalents) with 1 mol % of the catalyst. At 40 °C during 48 h under 4 bar of hydrogen pressure, the alcohol **7** was quantitatively obtained in 97% ee, using (*R*)-BINAP [(*R*)-**2**] as the phosphine (Table 2).

By lowering the amount of ethanol to 0.3 equivalents and S/C = 1000, a similar result was obtained under identical temperature-pressure conditions after 72 h reaction time using (*R*)-MeO-BIPHEP [(*R*)-**3**] as ligand for the catalyst. Reducing the S/C to 3000 under the same conditions led to a moderate conversion (40%) of **6** into the expected product **7**. The transformation was also performed efficiently at S/C = 3000, by increasing the temperature to 80 °C, and operating in a pressure ranging between 6 and 10 bar. When the hydrogenations were arbitrarily stopped after 48 to 80 h, the β-hydroxy ester **7** was quantitatively isolated. In a last run, the catalyst ratio was lowered to 1 to 4000. In this case, quantitative transformation and 96% ee could be reached, if the hydrogenation was conducted for 80 h at 80 °C under 6.5 bar of hydrogen.

These examples led to very good results both in terms of yields and ees of the products, and this under very high substrate-catalyst ratios. As a consequence, this was very promising for exploring other conditions in low catalyst hydrogenation reactions.

In order to test the scope of the reaction, we decided to study a simple model for hydrogenation reactions. Ethyl acetoacetate **8** was selected as a candidate in order to produce the corresponding ethyl 3-hydroxybutyrate **9** (Scheme 5).

The tests were conducted using the BINAP (**2**)-derived catalyst on a 120 mmol (~16 g) scale of β-keto ester **8** (Table 3). At S/C = 1000 under 4 bar of hydrogen at 40 °C, the reaction was complete after 22 h. The β-hydroxy ester **9** was obtained in an enantiomerically pure form. An identical result was obtained with the MeO-BIPHEP (**3**)-based catalyst under the same conditions. At 50 °C, but with S/C = 2000, the same result was obtained when the reaction was stopped after only 9 hours.



Scheme 5.

Table 2. Catalytic asymmetric hydrogenation of ethyl 4-benzyloxyacetoacetate **6**.[a]

Phosphine	S/C	H_2 [bar]	T [°C][b]	t [h][c]	Yield [%][d]	ee **7** [%][e]
(*R*)-**2**[f]	100	4	40	48	100	97 (*S*)
(*R*)-**3**	1000	4	40	72	100	98 (*S*)
(*R*)-**3**	3000	4	40	72	40	97 (*S*)
(*R*)-**3**	3000	6.5	80	80	100	96 (*S*)
(*R*)-**3**	3000	8	80	48	100	98 (*S*)
(*R*)-**3**	3000	10	80	48	100	98 (*S*)
(*R*)-**3**	4000	6.5	80	80	100	96 (*S*)

[a] Ethyl alcohol (0.3 equivalents) was added as an additive.
[b] Temperature of the circulating liquid in the autoclave walls.
[c] Total (arbitrary) time the hydrogenation was conducted.
[d] Determined by ^{1}H NMR (300 MHz).
[e] Measured by HPLC on a Chiralcel OD-H column with hexane/*i*-PrOH (14/86) at 1 mL/min flow, R_t of (*S*)-**7** = 11.2 min, R_t of (*R*)-**7** = 12.8 min.
[f] 7 equivalents of EtOH were used.

Table 3. Large-scale asymmetric hydrogenation of ethyl acetoacetate (**8**) at low catalytic levels.[a]

Phosphine	S/C	H_2 [bar]	T [°C][b]	t [h][c]	Yield [%][d]	*ee* **9** [%][e]
(*R*)-**2**	1000	4	40	22	100	>99 (*R*)
(*S*)-**3**	1000	4	40	22	100	>99 (*S*)
(*R*)-**2**	2000	4	50	9	100	>99 (*R*)
(*S*)-**2**	3000	4	50	18	100	>99 (*S*)
(*S*)-**3**	3000	4	50	24	100	>99 (*S*)
(*S*)-**2**	4000	4	50	24	77	>99 (*S*)
(*S*)-**2**	4000	4	55	65	100	97 (*S*)
(*S*)-**2**	4000	4	70	22	84	96 (*S*)
(*S*)-**2**	6000	4	50	24	28	>99 (*S*)

[a] On a 120 mmol scale (~16 g) with ethyl alcohol (0.3 equivalents) as an additive.
[b] Temperature of the circulating liquid in the autoclave walls.
[c] Total (arbitrary) time the hydrogenation was conducted.
[d] Determined by ^{1}H NMR (300 MHz).
[e] Measured by GC on a Lipodex-A column at 30 °C isothermal at 1 mL/min flow, R_t of **8** = 47 min, R_t of (*S*)-**9** = 49 min, R_t of (*R*)-**9** = 54 min.

In the laboratory, the use of autoclaves to conduct the reaction prevents us from extracting aliquots during its course, the exact reaction time was thus difficult to estimate. This result suggested that the hydrogenation reaction was much more faster than we initially thought. The hydrogenation was then run under the same conditions at S/C = 3000. After 18 h, the same results were obtained (100% yield, >99% ee), with the MeO-BIPHEP (**3**) catalyst, thus demonstrating the efficiency of both catalysts at S/C = 3000.

When using 4 bar of hydrogen at 50 °C and S/C = 4000, a lower conversion of 77% was obtained but in a very high ee after 24 h. A longer reaction time of 65 h gave a quantitative yield of **9** but a lower ee of 97%. Increasing the reaction temperature to 70 °C afforded a better yield (84%) but had a slightly deleterious effect on the ee by lowering it to 96%. When the reaction was carried out at 50 °C and S/C = 6000 during 24 h, **9** was synthesized in 28% yield and 99% ee.

The next step was to try to decrease again the amount of catalyst used. To this purpose, it was obvious that the reaction conditions would have to be harsher in order to obtain good results at very low catalytic levels.

An S/C = 10,000 was first selected to run a test in steel autoclave on a 0.26 mol (34 g) scale of ethyl acetoacetate **8** using (*R*)-BINAP [(*R*)-**2**] as the phosphine. By adjusting the internal hydrogen pressure to 50 bar at room temperature, and conducting the hydrogenation at 80 °C, it was possible to follow the reaction evolution by simply reading the pressure gauge on the autoclave (Table 4).

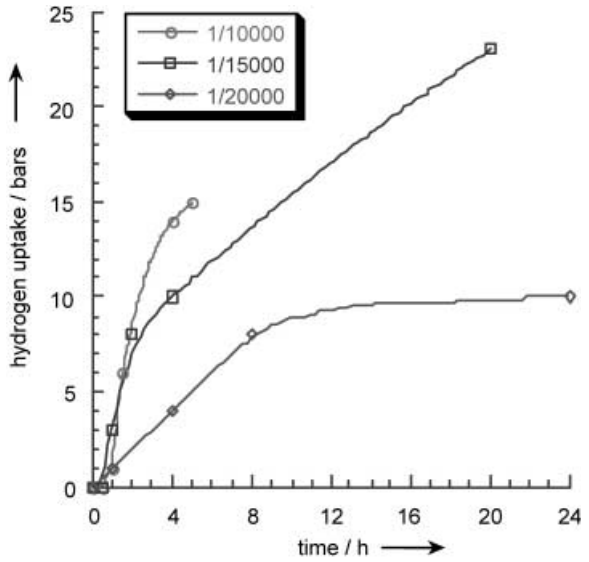
The volume of hydrogen was an indication of the rate and the end of the reaction, after the calculated amount of consumed hydrogen (~15 bar H_2, considering T = 353 K and an autoclave volume of 0.5 L). Under these conditions, the hydrogenation was complete at S/C = 10,000 after 4 to 5 hours, thus generating a TOF of 2000 to 2500 h^{-1} using (*R*)-BinapRuBr$_2$. Ethyl (*R*)-3-hydroxybutyrate **9** was quantitatively obtained in 96% ee. Finally, 100 g of ethyl acetoacetate were hydrogenated under 4 bar of hydrogen pressure in ethanol (0.13% vol.) at 50 °C and S/C = 3000 in 20 hours. The corresponding β-hydroxy ester was isolated in 98% yield and 99% ee.

Table 4. Asymmetric hydrogenation of ethyl acetoacetate **8** at very low catalytic levels.[a]

Phosphine	S/C	T [°C][b]	H_2 [bar][c]	t [h][d]	Yield [%][e]	ee **9** [%][f]
(*R*)-**2**	10,000	25	50	–	–	–
		80	54[g]	0.0	–	–
		80	54	0.5	–	–
		80	50	1.0	–	–
		80	48	1.5	–	–
		80	40	4.0	–	–
		80	39	5.0	100	96 (*R*)
(*R*)-**2**[h]	15,000	25	50	–	–	–
		80	59[g]	0.0	–	–
		80	59	0.5	–	–
		80	56	1.0	–	–
		80	51	1.5	–	–
		80	49	4.0	–	–
		80	30	20.0	93	93 (*R*)
(*R*)-**2**	20,000	25	50	–	–	–
		80	60[g]	0.0	–	–
		80	59	1.0	–	–
		80	59	2.0	–	–
		80	55	4.0	–	–
		80	55	6.0	–	–
		80	52	8.0	–	–
		80	50	24.0	88	91 (*R*)

[a] On a 260 mmol scale (~34 g) with ethyl alcohol (0.3 equivalents) as an additive.
[b] Temperature of the circulating liquid in the autoclave walls.
[c] Observation of the pressure gauge.
[d] Duration of the observation of the pressure.
[e] Determined by ^{1}H NMR (300 MHz).
[f] Measured by GC on a Lipodex-A column at 30 °C isothermal at 1 mL/min flow, R_t of **8** = 47 min, R_t of (*S*)-**9** = 49 min, R_t of (*R*)-**9** = 54 min.
[g] Internal pressure after reaching 80 °C.
[h] On a 390 mmol scale (~51 g).

The same procedure was repeated for S/C = 15,000 and 20,000 and the results of hydrogen consumption, yields and ees are also listed in Table 4. The hydrogenation reaction was much slower at these levels. For the reaction with S/C = 15,000, carried out on a 51 g (0.39 mol) scale, the consumed hydrogen was in the expected range (29 instead of the theoretical 22.5 bar) after 20 h. The hydrogenated product **9** was obtained in 93% yield and ee. While decreasing the catalyst to substrate ratio to S/C = 20,000, on the 34 g scale, 10 bar



Scheme 6.

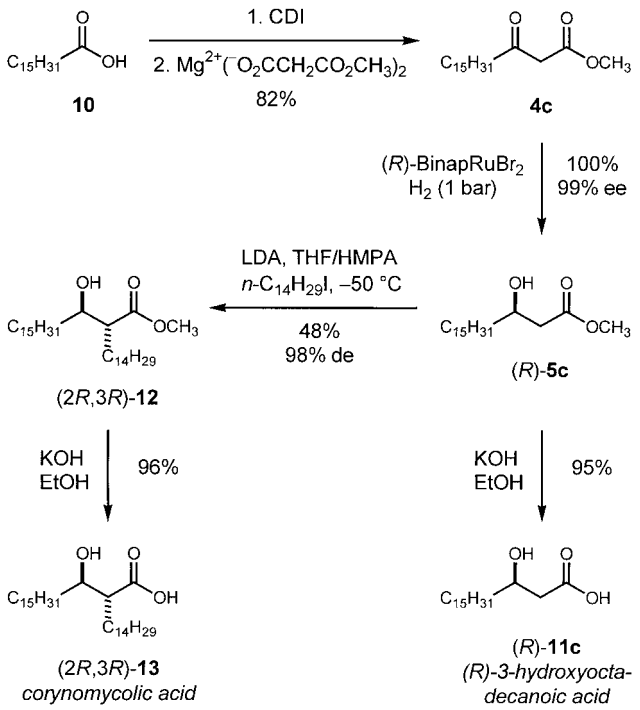
of hydrogen were consumed (instead of the awaited 15 bar) after 24 h. The yield (88%) and the ee (91%) were much lower in this case.

The constant pressure drop allowed us to plot graphics for this hydrogenation reaction at all three low catalytic levels (Scheme 6). The curves display a similar shape at the beginning indicating an initial phase where the pressure was constant, the hydrogenation was only beginning after a certain time varying between 0.5 to 1 hour. Since hydrogen pressure was not constant in the present case, this graph helps to visualize the evolution of the reaction over time. This cannot supply the kinetic information for this reaction, since only the hydrogen pressure can be monitored using the steel autoclave available in the laboratory.

Application to the Enantioselective Synthesis of (+)-(2*R*,3*R*)-Corynomycolic Acid

The synthesis of optically pure long-chain 3-hydroxyalkanoic acids has been of great interest owing to their use as chiral synthons or building blocks.[24] Optically active (+)-(2*R*,3*R*)-corynomycolic acid **13** is a constituent of trehalose diesters of corynomycolic acid isolated from the cell walls of *Corynebacterium* sp. or related organisms which showed significant biological activities.[25]

The racemic acid **13** was prepared previously by a condensation reaction of methyl palmitate,[26] and by an aldol reaction of alkyl ketones or aryl palmitates with palmitaldehyde.[27] Optically active **13** and derivatives were synthesized previously from an optically active epoxide,[28] by asymmetric reduction of 3-oxooctadecanoic acid with fermenting baker's yeast,[29] and by using BINAP-Ru-catalyzed asymmetric hydrogenation of racemic β-ketolactone.[30]



Scheme 7.

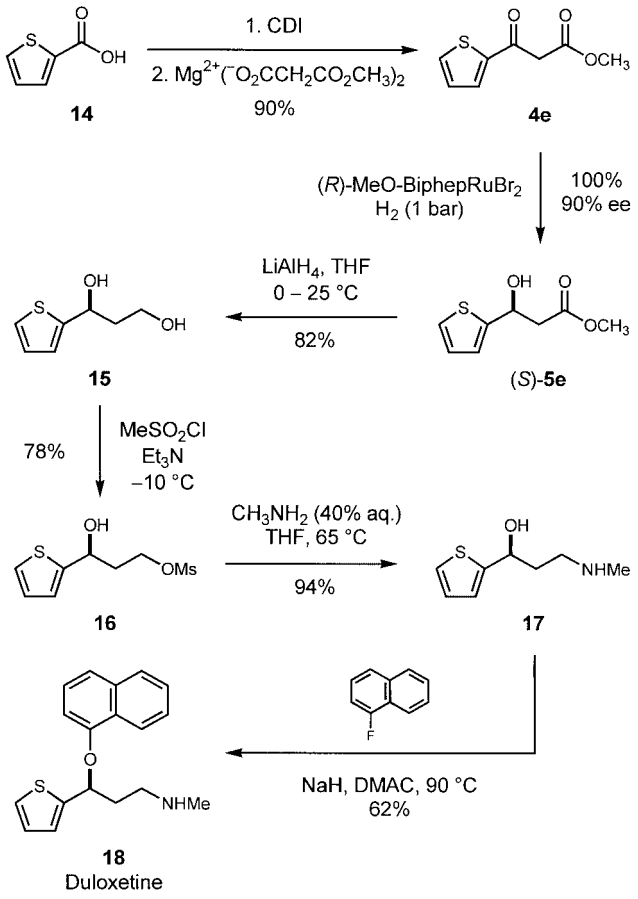
Scheme 7 illustrates our synthetic route to corynomycolic acid **13**. The homologation of palmitic acid **10** was done using Masamune's procedure[31] affording methyl 3-oxooctadecanoate **4c** in 82% yield. The asymmetric hydrogenation of β-keto ester **4c** was carried out at atmospheric pressure, leading quantitatively to **5c** in 99% ee (see Table 1).

The (*R*) configuration of **5c** was determined by comparison with the literature value of the optical rotation. The α-alkylation of **5c** at −50 °C using LDA and *n*-$C_{14}H_{29}Br$ afforded **12** in only 10% yield. When the system LDA/*n*-$C_{14}H_{29}I$/HMPA was used, the product **12** was obtained in 48% yield, in a diastereo- and enantiomerically pure form. The stereochemistry of **12** was assigned as (2*R*,3*R*) based on the steric course of alkylation *via* a rigid cyclic structure, due to the chelation of lithium through the two *O*-anions.[32] Finally, **12** was hydrolyzed by a mixture of aqueous KOH and ethanol at 40 °C for 16 h. Corynomycolic acid **13** was isolated in 96% yield. The optical purity was calculated to be 98% by measuring the specific rotation.

(*R*)-3-Hydroxyoctadecanoic acid **11c**, a fatty acid component of eupassofilin,[33] was also synthesized by saponification using the common intermediate ester **5c**. Treatment of this ester with aqueous KOH in ethanol at 40 °C for 20 h, led to the acid **11c** in 95% yield.

Enantioselective Synthesis of Duloxetine (LY-248686)

Duloxetine (LY-248686), or (*S*)-*N*-methyl-3-(1-naphthoxy)-3-(2-thienyl)propylamine **18**, is a potent inhibitor of the serotonin and norepinephrine uptake carriers. Deeter et al. reported an enantioselective synthesis of Duloxetine **18** from 2-acetylthiophene.[34] The synthesis used an asymmetric reduction of a Mannich base with a 2:1 complex of (2*R*,3*S*)-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol and lithium aluminium hydride as the key step. Duloxetine was obtained in 80–90% yield and enantiomeric excesses ranging between 85 and 88%. A chemo-enzymatic synthesis of Duloxetine has been reported.[35] A key intermediate for the synthesis of (*S*)-Duloxetine has been also synthesized.[36] The introduction of chirality during our synthesis was conveniently controlled by the ruthenium-catalyzed asymmetric hydrogenation of 3-oxo-3-thienyl methylpropanoate **4e** (Scheme 8). The required β-keto ester **4e** was prepared in 90% yield from thiophene-2-carboxylic acid **14** using Masamune's procedure.[31] The β-keto ester **4e** was hydrogenated using (*R*)-MeO-BiphepRuBr$_2$ catalyst affording the corresponding β-hydroxy ester (*S*)-**5e** in quantitative yield and 90% ee. Lithium-aluminium hydride reduction led to the diol **15** (82% yield), which was selectively mesylated at the primary position yielding the monomesylate **16** (78%). Treatment of **16** with methylamine afforded the amine **17** in 94% yield, which was then *O*-alkylated with sodium hydride and fluoronaphthalene to afford Dulotexine **18**, which showed identical properties to the known substance.

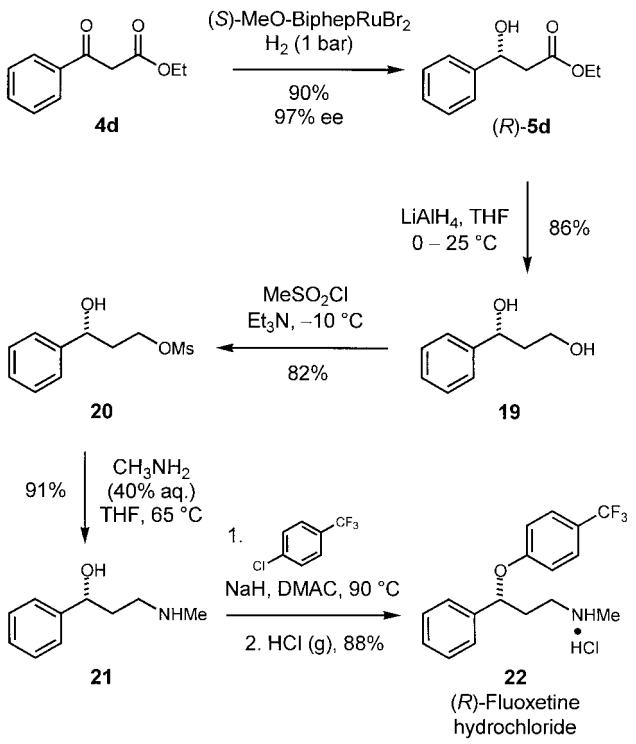


Scheme 8.

Asymmetric Synthesis of (*R*)-Fluoxetine

Fluoxetine or *N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride (**22**) marketed under the trade name Prozac® is a serotonin-uptake inhibitor used as antidepressant but also for treatment of anxiety, alcoholism and bulimia.[37] In view of the different pharmacological activities displayed by each enantiomer, several methods have been reported for the asymmetric synthesis of Fluoxetine[38] and related compounds. Enantioselective hydrogenation (Scheme 9) of methyl 3-oxo-3-phenylpropanoate **4d** catalyzed by the *in situ* generated (*S*)-MeO-BiphepRuBr$_2$ complex was highly efficient at atmospheric pressure leading to multigram quantities of (*R*)-**5d**[22] in 90% yield and 97% ee (see Table 1).

Reduction of the ester function of **5d** with LAH furnished the diol **19** in 86% yield, which was then subjected to mesylation (82% yield). The isolated primary mesylate **20** was treated by methylamine to reach the amine **21** in 91% yield. The sodium alkoxide of



Scheme 9.

21 generated in *N,N*-dimethylacetamide solution using sodium hydride followed by reaction with *p*-trifluoromethylchlorobenzene and hydrochloride salt formation procedure afforded (*R*)-Fluoxetine as its hydrochloride salt **22** in 88% yield. The product **22** was found to be identical to the authentic compound.

Conclusion

In this article, we have presented some of our results on the investigation of asymmetric catalytic hydrogenation reactions using atropisomeric diphosphine/ruthenium complexes. Such complexes can be easily prepared by a fast, soft and straightforward general method that we developed for the *in situ* generation of the catalysts.

Excellent selectivities were conveniently obtained while working at atmospheric pressure for the ruthenium-promoted hydrogenation reaction of β-keto esters. This procedure gives a ready access to enantiomerically pure β-hydroxy esters of various structures, without the need for special equipment. The method can thus be used in any laboratory in order to produce either pure enantiomer of the β-hydroxy ester in multigram quantities.

Using higher pressures and temperatures for the hydrogenation reaction gave us the opportunity to find very efficient conditions for the transformation of β-keto esters. A better procedure was found in which the product was hydrogenated in its neat form, with only traces of a polar protic solvent, usually the alcohol corresponding to the ester. This discovery led to the elaboration of new hydrogenation protocols in which the required quantity of catalyst was greatly reduced. Asymmetric hydrogenation was performed on ethyl acetoacetate, on a large scale (0.26 – 0.39 mol, 34 – 51 g) at S/C of 10,000 to 20,000 with excellent results. The corresponding chiral 3-hydroxybutyrate was quantitatively obtained in only 4 – 5 hours at an S/C = 10,000, resulting in a TOF of 2,000 to 2,500 h^{-1} for this specific transformation. The results obtained here are amongst the best ones that can be reached while working with molecular hydrogen for such a transformation.

The usefulness of this hydrogenation method, using the *in situ* prepared chiral ruthenium catalyst and atmospheric pressure of hydrogen, was clearly demonstrated as the key-step in the syntheses of biologically active substances. Enantioselective synthesis of corynomycolic acid, Duloxetine (LY-248686) and (*R*)-Fluoxetine hydrochloride were conveniently achieved in only a few steps. Asymmetric hydrogenation reactions based on chiral atropisomeric diphosphines as ligands for ruthenium are very important and efficient procedures for the preparation of enantiomerically enriched or pure substrates. This reaction is still nowadays stimulating chemists to design new ligands and find catalysts and procedures to improve the results and the scope of its application. Development of practical asymmetric hydrogenation is thus still highly needed.

Experimental Section

General Remarks

Melting points were determined with an Electrothermal-Engineering-LTD-9026 and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 200 or 400 spectrometer. Spectra were obtained in deuteriated chloroform and chemical shifts are reported in parts per million (ppm) with TMS as an internal reference. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Infrared spectra were taken on a BIO-RAD FTS 6000 spectrometer. Gas chromatography/mass spectrometry (GC/MS) analysis were performed using a Hewlett Packard 5897 system (DB 1701 column) and the ions detected after electron impact (EI) or chemical ionization (CI) at 70 eV. All solvents were freshly distilled, stored under argon and degassed by 3 purge cycles of vacuum/argon at room temperature prior to use. Optical purity (% ee) was determined by GC analysis on Lipodex A column, DB 1701 column [for (*S*)-*O*-acetyllactyl ester], HPLC Chiralcel OD-H or by ^{1}H-NMR spectroscopy in the presence of 10 – 20 mol % (+)-Eu(tfc)$_3$ at 300 MHz.

Synthesis of β-Keto Esters

Procedure A: To a solution of commercially available acid (40 mmol) in dry THF was added under argon over 15 min, 1.1 equivalents (7.13 g, 44 mmol) of 1,1′-carbonyldiimidazole. The mixture was stirred for 10 h at room temperature. The stirring was continued for further 18 h after the addition of 1.1 equivalents of $Mg(OOCH_2COOCH_3)_2$. 1 M HCl was then added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica to furnish the products.

Methyl 3-oxotetradecanoate (**4a**): Yield: 62%; white solid; mp 40 – 41 °C; IR (KBr): ν = 2950 (ν_{CH_3}), 2850 (ν_{CH_2}), 1750 (ν_{COO}), 1710 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR ($CDCl_3$): δ = 3.75 (s, 3H), 3.46 (s, 2H), 2.54 (t, 2H, *J* = 7.3 Hz), 1.57 – 1.65 (m, 2H), 1.27 (m, 22H), 0.89 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ = 202.7, 167.5, 52.1, 48.8, 42.9, 31.7, 29.5, 29.3, 29.2, 28.9, 23.3, 22.5, 13.9; MS (EI): *m/z* = 256 (M^+, 5), 238 (4), 200 (17), 116 (35), 73 (60), 60 (75), 43 (100).

Methyl 3-oxohexadecanoate (**4b**): Yield: 78%; white solid; mp 28 – 30 °C; IR (KBr): ν = 2980 (ν_{CH_3}), 2800 (ν_{CH_2}), 1760(ν_{COO}), 1710 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR ($CDCl_3$): δ = 3,73 (s, 3H), 3.44 (s, 2H), 2.43 (t, 2H, *J* = 7.3 Hz), 1.55 – 1.62 (m, 2H), 1.26 (m, 18H), 0.88 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ = 202.6, 167.5, 52.1, 48.8, 42.9, 31.7, 29.4, 29.2, 29.1, 28.8, 26.1, 22.5, 23.3, 13.9; MS (EI): *m/z* = 284 (M^+, 2), 266 (4), 211 (10), 116 (100), 101 (23), 57 (70), 43 (100).

Procedure B for Methyl 3-(4-Methoxyphenyl)-3-oxopropanoate (4g): Toluene (7 mL) was added dropwise to sodium hydride in mineral oil (60%, 2.5 equivalents, washed twice with hexane). Dimethyl carbonate (2.5 equivalents) was added dropwise and additional distilled toluene (100 mL) was added.

The mixture was heated to reflux and 4-methoxyacetophenone (1 equivalent) in toluene (100 mL) was added dropwise over a period of 2 h. After an additional 0.5 h, the mixture was cooled in ice, diluted with toluene (100 mL), quenched by slow addition of water (100 mL), and acidified with 25% acetic acid until pH 5. The aqueous layer was separated and extracted with ethyl acetate. The combined organic phases were then washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. Concentration provided methyl 3-(4-methoxyphenyl)-3-oxo-propanoate **4g**; yield: 85%; oil; IR (neat): $\nu = 2869$ (ν_{CH_2}), 2954 (ν_{CH_3}), 1747 (ν_{COO}), 1685 cm^{-1} ($\nu_{C=O}$); ^1H NMR ($CDCl_3$): $\delta =$ 7.91 (d, 2H, $J = 7.2$ Hz), 6.94 (d, 2H, $J = 7.2$ Hz), 3.96 (s, 1H), 3.87 (s, 1H), 3.74 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 192.6$, 168.7, 164.5, 132.1, 114.2, 56.1, 53.2, 46.1; MS (70 eV): $m/z = 208$ (M^+, 15), 135 (100), 107 (9.5), 92 (12), 77 (13).

Methyl 3-oxo-3-(2-thienyl)propanoate (**4e**): Yield: 90%; colorless oil; IR (neat): $\nu = 2950$ (ν_{CH_3}), 2850 (ν_{CH_2}), 1750 (ν_{COO}), 1710 cm^{-1} ($\nu_{C=O}$); ^1H NMR ($CDCl_3$): $\delta = 7.74 - 7.68$ (m, 2H), 7.16 – 7.06 (m, 1H), 3.9 (s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 184.7$, 167.3, 143.0, 134.9, 133.3, 129.3, 52.4, 46.0; MS (70 eV): $m/z = 184$ (M^+, 1), 126 (50), 111 (100), 83 (25), 39 (35); MS (CI/ NH_3): $m/z = 202$ (MNH_4^+, 100), 185 (MH^+, 20).

Methyl 3-(4-methylphenyl)-3-oxopropanoate (**4f**): Yield: 85%; colorless oil; IR (neat): $\nu = 2869$ (ν_{CH_2}), 2954 (ν_{CH_3}), 1747 (ν_{COO}), 1685 cm^{-1} ($\nu_{C=O}$) ; ^1H NMR ($CDCl_3$): $\delta = 7.76$ (d, 2H, $J = 7.3$ Hz), 7.34 (d, 2H, $J = 7.3$ Hz), 3.99 (s, 1H), 3.76 (s, 1H), 2.43 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 191.8$, 167.9, 144.6, 133.4, 129.3, 128.5, 52.3, 45.5, 21.5; MS (70 eV): $m/z = 192$ (M^+, 8), 119 (100), 91 (43), 77 (4), 65 (18).

Methyl 3-(4-chlorophenyl)-3-oxopropanoate (**4h**): Yield: 60%; white solid; mp 46 – 48 °C; IR (KBr): $\nu = 2869$ (ν_{CH_2}), 2954 (ν_{CH_3}), 1757 (ν_{COO}), 1657 cm^{-1} ($\nu_{C=O}$); ^1H NMR ($CDCl_3$): $\delta = 7.41 - 7.46$ (m, 4H), 3.98 (s, 1H), 3.8 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 173.2$, 170.1, 131.7, 129.8, 128.7, 127.2, 52.4, 51.4; MS (70 eV): $m/z = 212$ (M^+, 11), 139 (100), 111 (48), 75 (30), 43 (21).

Methyl 3-(4-fluorophenyl)-3-oxopropanoate (**4i**): Yield: 79%; yellow oil; ^1H NMR ($CDCl_3$): $\delta = 7.90 - 8.05$ (m, 1H), 7.09 – 7.20 (m, 1H), 3.95 (s, 2H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 191.2$, 168.2, 164.8, 132.8, 131.7, 116.5, 52.9, 46.0; MS (70 eV): $m/z = 196$ (M^+, 11), 123 (100), 95 (66), 75 (38), 42 (15).

Methyl 3-(1-naphtyl)-3-oxopropanoate (**4j**): Yield: 70%; white solid; mp 60 – 61 °C; IR (KBr): $\nu = 2870$ (ν_{CH_2}), 2960 (ν_{CH_3}), 1755 (ν_{COO}), 1680 cm^{-1} ($\nu_{C=O}$); ^1H NMR ($CDCl_3$): $\delta =$ 7.22 – 8.35 (m, 7H), 4.01 (s, 3H), 3.52 (s, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 195.3$, 168.5, 133.8, 130.8, 128.8, 126.6, 125.8, 124.1, 52.3, 48.3.

Methyl 3-(2-naphtyl)-3-oxopropanoate (**4k**): Yield: 73%; white solid; mp 56 – 58 °C; IR (KBr): $\nu = 2788$ (ν_{CH_2}), 2935 (ν_{CH_3}), 1751 (ν_{COO}), 1667 cm^{-1} ($\nu_{C=O}$); ^1H NMR ($CDCl_3$): $\delta =$ 8.34 – 8.42 (m, 1H), 7.77 – 8.01 (m, 4H), 7.54 – 7.64 (m, 2H), 4.13 (s, 3H), 3.76 (s, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 192.5$, 170.5, 134.8, 132.4, 131.2, 128.9, 126.8, 124.6, 122.6, 51.8, 46.0.

Asymmetric Hydrogenation Reactions

***In situ* Preparation of Dibromodiphosphineruthenium(II) complexes [*(P – P)$RuBr_2]_2$:** (*R*)-BINAP (30 mg, 0.048 mmol) and (Cod)Ru(2-methylallyl)$_2$ (12.8 mg, 0.04 mmol) were placed in a 10 mL Schlenk tube and the vessel was purged with argon. Anhydrous acetone (2 mL degassed by 3 cycles of vacuum/argon at room temperature) were added. To this suspension was added 0.5 mL of a methanolic HBr solution (0.176 M, 8.8 mmol) and the suspension was stirred during 30 min at room temperature. A yellow solid precipitated. Subsequently, the solvent was thoroughly evaporated under vacuum and the catalyst was immediately used.

General Procedure for Hydrogenation Reaction at Atmospheric Pressure: A solution of the β-keto ester **4a** (0.518 g, 2 mmol) or **4d** (4 g, 0.02 mol) was diluted respectively in degassed methanol (4 mL) or ethanol (8 mL). This solution was canulated into a Schlenk tube and degassed by 3 cycles of vacuum/argon. The mixture was added to the *in situ* generated catalyst (2 mol %) in a glass vessel and placed under argon. The argon atmosphere was replaced with 1 atm of hydrogen and the mixture was heated until complete conversion. The solvent was evaporated under vacuum and the β-hydroxy esters were purified on a short pad of silica using a mixture of AcOEt and cyclohexane. Yields were determined by ^1H NMR analysis.

*Methyl (*R*)-3-hydroxytetradecanoate* (**5a**): Yield: 100%; white solid; mp 39 – 40 °C; $[\alpha]_D$: – 18.5 (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3350$ (ν_{OH}), 2950 (ν_{CH_3}), 2850 (ν_{CH_2}), 1745 cm^{-1} (ν_{COO}); ^1H NMR ($CDCl_3$): $\delta = 3.99$ (m, 1H), 3.68 (s, 3H), 3.03 (brs, OH), 2.31 – 2.55 (m, 2H), 1.63 – 1.65 (m, 2H), 1.20 – 1.42 (m, 18H), 0.90 (t, 3H, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 173.5$, 67.9, 52.1, 40.9, 36.4, 31.8, 29.5, 29.2, 25.3, 22.5, 13.9; MS (70 eV): $m/z = 258$ (M^+, 5), 240 (4), 208 (19) , 183 (17), 166 (16), 103 (100), 55 (41), 43 (64).

*Methyl (*R*)-3-hydroxyhexadecanoate* (**5b**): Yield: 100%; white solid; mp 52 – 53 °C; $[\alpha]_D$: – 16.6 (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3500 - 3000$ (ν_{OH}), 2980 (ν_{CH_3}), 2800 (ν_{CH_2}), 1760 – 1740 cm^{-1} (ν_{COO}); ^1H NMR ($CDCl_3$): $\delta = 3.92 - 3.84$ (m, 1H), 3.68 (s, 3H), 2.89 (brs, OH), 2.40-2.60 (m, 2H), 1.69 – 1.76 (m, 2H), 1.28 – 1.49 (m, 22H), 0.90 (t, 3H, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 173.2$, 67.8, 53.2, 41.1, 38.1 31.7, 29.4, 29.1, 22.5, 25.3, 13.9; MS (70 eV): $m/z = 286$ (M^+, 10), 268 (12), 236 (25), 211 (25), 111 (26), 103 (100), 75 (83), 55 (45), 43 (82).

*Methyl (*R*)-3-hydroxyoctadecanoate* (**5c**): Yield: 100%; white solid; mp 55 – 56 °C; $[\alpha]_{D:}$ – 15.5 (*c* 1, $CHCl_3$); IR (KBr): $\nu = 3350$ (ν_{OH}), 2950 (ν_{CH_3}), 2850 (ν_{CH_2}), 1745 cm^{-1} (ν_{COO}); ^1H NMR ($CDCl_3$): $\delta = 3.99$ (m, 1H), 3.71 (s, 3H), 2.89 (s, 1H), 2.46 (m, 2H), 1.44 (m, 2H), 1.25 (m, 26H), 0.87 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 173.4$, 67.9, 51.6, 41.0, 36.4, 31.8, 29.5, 25.4, 22.6, 14.0; MS (70 eV): $m/z = 314$ (M^+, 1), 296 (5), 103 (64), 43 (100).

*Ethyl (*R*)-3-hydroxy-3-phenylpropanoate* (**5d**): Yield: 90%; colorless oil; $[\alpha]_D$: – 52 (*c* 1, $CHCl_3$); IR (neat): $\nu = 3460$ (ν_{OH}), 3040 (ν_{CH_3}), 2970 (ν_{CH_2}), 1716 cm^{-1} (ν_{COO}); ^1H NMR ($CDCl_3$): $\delta = 7.25$ - 7.42 (m, 5H), 5.11 – 5.19 (m, 1H), 4.17 (q, 2H, $J =$ 7.1 Hz), 3.4 (s, 1H, OH), 2.75 (t, 2H), 1.27 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 172.2$, 142.4, 128.4, 127.6, 125.5, 70.2, 60.7, 43.2, 14.0; MS (70 eV): $m/z = 194$ (M^+, 40), 177 (5), 120 (10), 107 (87), 79 (100), 77 (92).

*Methyl (*S*)-3-hydroxy-3-(2-thienyl)propanoate* (**5e**): Yield: 100%; colorless oil; IR (neat): $\nu = 3350$ (ν_{OH}), 2950 (ν_{CH_3}), 2850 (ν_{CH_2}), 1745 cm^{-1} (ν_{COO}); ^1H NMR ($CDCl_3$): $\delta = 7.24 - 7.28$ (m, 1H), 6.95 – 7.01 (m, 2H), 5.38 (t, 1H, $J = 5.2$ Hz), 3.58 (brs, OH), 2.84 (d, 2H, $J = 5.2$ Hz), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 172.1, 146.2, 126.6, 124.7, 123.5, 66.3, 51.8, 42.9; MS (70 eV): $m/z = 186$ (M^+, 40), 113 (100), 85 (60), 45 (22); MS (CI/NH_3): $m/z = 204$ (MNH_4^+, 90), 186 ($MNH_4^+ - H_2O$, 100), 169 ($MH^+ - H_2O$, 10).

Methyl (S)-3-hydroxy-3-(4-methylphenyl)propanoate (**5f**): Yield: 86%; white solid, mp 50–52 °C; $[\alpha]_D$: −22 (*c* 1, $CHCl_3$); IR (KBr): ν = 3350 (ν_{OH}), 1730 (ν_{COO}), 3045 (ν_{CH_3}), 2840 cm^{-1} (ν_{CH_2}); ^1H NMR ($CDCl_3$): δ = 7.28 (d, 2H, *J* = 7.1 Hz), 7.15 (d, 2H, *J* = 7.1 Hz), 5.05–5.13 (m, 1H), 3.70 (s, 3H), 3.15 (d, 1H, *J* = 14 Hz), 2.63–2.80 (m, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 172.6, 144.1, 141.6, 131.6, 126.6, 72.5, 54.1, 43.3, 21.2; MS (70 eV): *m/z* = 194 (M^+, 22), 121 (100), 179 (11), 77 (33), 65 (20).

Methyl (S)-3-hydroxy-3-(4-methoxyphenyl)propanoate (**5g**): Yield: 84%; white solid; mp 29–31 °C; $[\alpha]_D$: −29 (*c* 1, $CHCl_3$); IR (KBr): ν = 3433 (ν_{OH}), 1708 (ν_{COO}), 2912 (ν_{CH_3}), 2850 cm^{-1} (ν_{CH_2}); ^1H NMR ($CDCl_3$): δ = 7.30 (d, 2H, *J* = 7.2 Hz), 6.77 (d, 2H, *J* = 7.2 Hz), 5.02–5.16 (m, 1H), 3.80–3.82 (m, 3H), 3.70 (s, 3H), 2.61–2.78 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 172.7, 159.1, 134.7, 126.9, 113.9, 69.9, 55.3, 51.9, 43.2; MS (70 eV): *m/z* = 210 (M^+, 9), 137 (100), 109 (23), 94 (14), 77 (15).

Methyl (S)-3-(4-chlorophenyl)-3-hydroxypropanoate (**5h**): Yield: 75%; white solid; mp 39–41 °C; $[\alpha]_D$: −18 (*c* 1, EtOH); IR (KBr): ν = 3453 (ν_{OH}), 1717 (ν_{COO}), 2998 (ν_{CH_3}), 2890 cm^{-1} (ν_{CH_2}); ^1H NMR ($CDCl_3$): δ = 7.26–7.23 (m, 4H), 5.08–5.14 (m, 1H), 3.72 (s, 3H), 3.32 (d, 1H, *J* = 2 Hz), 2.70–2.72 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 172.6, 140.8, 134.5, 128.6, 126.9, 69.5, 51.8, 42.8; MS (70 eV): *m/z* = 214 (M^+, 13), 141 (100), 113 (21), 77 (64), 43 (20).

Methyl (S)-3-(4-fluorophenyl)-3-hydroxypropanoate (**5i**): Yield: 87%; colorless oil; ^1H NMR ($CDCl_3$): δ = 7.26–7.36 (m, 1H), 6.98–7.06 (m, 1H), 5.07–5.12 (m, 1H), 3.70 (s, 3H), 3.46 (brs, 1H), 2.78–2.62 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 172.9, 164.3, 138.8, 127.7, 115.5, 70.0, 52.2, 42.6.

Methyl (S)-3-hydroxy-3-(1-naphthyl)propanoate (**5j**): Yield: 80%; white solid; mp 50–52 °C; $[\alpha]_D$: −38 (*c* 1, $CHCl_3$); IR (KBr): ν = 3422 (ν_{OH}), 1751 (ν_{COO}), 2949 (ν_{CH_3}), 2830 cm^{-1} (ν_{CH_2}); ^1H NMR ($CDCl_3$): δ = 7.48–7.87 (m, 7H), 5.30–5.38 (m, 1H), 3.76 (s, 3H), 3.36 (d, 1H, *J* = 2 Hz), 2.79–2.97(m, 2H); ^{13}C NMR ($CDCl_3$): δ = 172.5, 132.9, 123.5, 70.3, 51.8, 43.0; MS (70 eV): *m/z* = 230 (M^+, 99), 157 (100), 129 (83), 77 (16), 43 (21).

Methyl (S)-3-hydroxy-3-(2-naphthyl)propanoate (**5k**): Yield: 76%; white solid; mp 50–52 °C; $[\alpha]_D$: −44.6 (*c* 1, $CHCl_3$); IR (KBr): ν = 3422 (ν_{OH}), 1751 (ν_{COO}), 2949 (ν_{CH_3}), 2830 cm^{-1} (ν_{CH_2}); ^1H NMR ($CDCl_3$): δ = 7.57–8.27 (m, 7 H), 5.22–5.30 (m, 1H), 3.91 (s, 3H), 3.43 (d, 1H, *J* = 8 Hz), 2.88–2.96 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 173.5, 131.9, 123.3, 122.5, 71.3, 52.8, 43.3; MS (70 eV): *m/z* = 230 (M^+, 99), 157 (100), 129 (83), 77 (16), 43 (21).

Synthesis of (+)-(2*R*,3*R*)-Corynomycolic Acid (13)

(*R*)-3-Hydroxyoctadecanoic acid (11c): The β-hydroxy ester **5c** (314 mg, 1 mmol) was dissolved in methanol (10 mL). A 10% aqueous solution of sodium hydroxide (10 mL, excess) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ether and extracted three times with saturated sodium bicarbonate. The ethereal solution was discarded and the combined aqueous extracts were acidified to pH 1 with 3 M HCl and extracted twice with ether and twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to give the corresponding β-hydroxy acid **11c**; yield: 285 mg (95%); white solid; mp 82–83 °C; $[\alpha]_D$: −15.8 (*c* 1, $CHCl_3$); IR (KBr): ν = 3500 (ν_{OH}), 2950 (ν_{CH_3}), 2850 (ν_{CH_2}), 1725 (ν_{COO}), 1250, 1180 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.05 (m, 1H), 2.42–2.66 (m, 2H), 1.45–1.50 (m, 2H), 1.28–1.44 (m, 26H), 0.90 (t, 3H, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 172.6, .66.8, 51.1, 40.6, 36.3, 31.7, 29.5, 29.2, 25.3, 22.5, 13.9; MS (70 eV): *m/z* = 300 (M^+, 3), 282 (5), 264 (8), 222 (8), 89 (100), 71 (53), 43 (57); MS (CI/NH_3): *m/z* = 318 (MNH_4^+, 100).

Methyl (2*R*,3*R*)-3-hydroxy-2-*n*-tetradecyloctadecanoate (12): A solution of lithium diisopropylamide prepared from butyllithium (1.02 mL, 3 eq.) and diisopropylamine (1.02 mL, 3 eq.) was cooled to −78 °C, and β-hydroxy ester **4c** (314 mg, 1 mmol, 1 eq.) was added *via* a cannula as a solution in 10 mL of THF. After 1 h at −78 °C, *n*-$C_{14}H_{29}I$ (810 mg, 2.5 eq.) and $PO(NMe_2)_3$ (0.642 mL, 1.2 eq.) were added *via* a syringe. The mixture was stirred at −40 °C for 1 h then warmed slowly to −20 °C, and stirred at this temperature until TLC analysis showed no trace of starting material. The mixture was treated with saturated $NaHCO_3$, extracted with 25 mL of ether, washed with brine, dried over $MgSO_4$ and solvent was evaporated. The crude product was purified by column chromatography (SiO_2, cyclohexane/AcOEt, 95:5); yield: 245 mg (48%); white solid; mp 60–61 °C; $[\alpha]_D$: +5.7 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ = 3.76 (s, 3H), 3.46 (m, 1H), 2.1–2.55 (m, 1H), 1.22–1.64 (m, 54H), 0.87 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 176.1, 72.2, 51.4, 50.8, 35.6, 31.8, 29.5, 29.2, 27.3, 25.6, 22.6, 14.0; MS (70 eV): *m/z* = 510 (M^+, 1), 492 (4), 437 (10), 313 (25), 284 (30), 270 (60), 59 (40), 43 (100); MS (CI/NH_3): *m/z* = 528 (MNH_4^+, 100), 511 (MH^+, 20).

(+)-(2*R*,3*R*)-Corynomycolic acid (13): In 5 mL of ethanol was dissolved 100 mg (0.196 mmol) of **9** with 2.5 mL of 1 M KOH. The solution was stirred overnight at 40 °C, acidified with hydrochloric acid, and evaporated under reduced pressure. The residue was mixed with water, extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and solvent was evaporated. The crude product was purified by column chromatography (SiO_2, cyclohexane/AcOEt, 60:40); yield: 93 mg (96%); white solid; mp 77–78 °C; $[\alpha]_D$: +7.8 (*c* 1, $CHCl_3$); IR (KBr): ν = 3350 (ν_{OH}), 2950 (ν_{CH_3}), 2850 (ν_{CH_2}), 1745 cm^{-1} (ν_{COO}); ^1H NMR ($CDCl_3$): δ = 3.73 (m, 1H), 2.49–2.45 (m, 1H), 1.15–1.52 (m, 54H), 0.90 (t, 6H); ^{13}C NMR ($CDCl_3$): δ = 179.9, 72.0, 50.8, 35.3, 31.8, 29.5, 29.2, 27.2, 26.8, 25.6, 22.5, 13.9; MS (70 eV): *m/z* = 496 (2), 437 (8), 313 (28), 284 (32), 270 (61), 59 (43), 43 (100); MS (ICI/NH_3): *m/z* = 514 (MNH_4^+, 100), 497 (MH^+, 5).

Asymmetric Synthesis of Duloxetine (LY-248686, 18)

(*S*)-1-(2-Thienyl)propane-1,3-diol (15): Methyl (*S*)-3-hydroxy-3-(2-thienyl)propanoate (**5e**) (1.42 mmol) was dissolved in 10 mL of dry ether and the solution was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (115 mg, 3 mmol, 2.1 eq.) in dry THF under argon. The mixture was allowed to warm to room temperature over 1.5 h and then was quenched by sequential addition of H_2O (0.25 mL), 10% NaOH (0.25 mL), and additional H_2O (0.50 mL). The product was extracted with ether and the organic phase was washed with brine, dried and evaporated. The product was purified by column chromatography (SiO_2, cyclohexane/AcOEt] affording **15**; yield: 183 mg (82%); colorless oil; $[\alpha]_D$: −25 (*c* 1, $CHCl_3$); IR (neat): ν = 3370 (ν_{OH}), 2964 (ν_{CH_3}), 2814 cm^{-1} (ν_{CH_2}); ^1H NMR ($CDCl_3$): δ =

7.25 – 7.28 (m, 1H), 6.95 – 7.01 (m, 2H), 5.20 (t, 1H, $J = 5.2$ Hz), 3.84 – 3.86 (m, 2H), 3,47 (brs, OH), 2,84 (brs, OH), 1.99 – 2.21 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 146.3, 126.5, 124.2, 123.3, 68.5, 59.9, 40.6; MS (70 eV): *m/z* = 158 (M^+, 25), 140 (10), 113 (100), 85 (50) , 45 (23); MS (CI/NH_3): *m/z* = 176 (MNH_4^+, 15), 158 ($MNH_4^+ - H_2O$, 100), 141 ($MH^+ - H_2O$, 10).

(*S*)-3-Hydroxy-3-(2-thienyl)propyl methanesulfonate (16): To a solution of (*S*)-3-(2-thienyl)-propane-1,3-diol **15** (148.5 mg, 0.094 mmol) and triethylamine (2 mL, 0.14 mmol, 1.5 eq.) in ether (30 mL) was added dropwise mesyl chloride (0.17 mmol, 1.1 eq.) under nitrogen at − 10 °C. After stirring at − 10 to 0 °C for 3 h, the mixture was poured into ice/water (30 mL), washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to give **16**; yield: 161 mg (78%); colorless oil; $[\alpha]_D$: − 33 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.23 – 7.28 (m, 1H), 6.93 – 7.01 (m, 2H), 5.05 – 5.14 (m, 1H), 4.51 (dt, 1H, $J = 6.5$ Hz; $J = 10.1$ Hz), 4.22 (dt, 1H, $J = 6.5$ Hz; $J = 10.1$ Hz), 3.10 (brs, OH), 3.05 (s, 3H), 2.18 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 147.3, 126.7, 124.8, 123.9, 66.9, 65.7, 38.1, 37.0; MS (70 eV): *m/z* = 236 (M^+, 20), 219 (4), 140 (40), 113 (89), 86 (100), 79 (50), 45 (60); MS (CI/NH_3): *m/z* = 254 (MNH_4^+, 65), 236 ($MNH_4^+ - H_2O$, 100), 219 ($MH^+ - H_2O$, 20).

(*S*)-*N*-Methyl-3-hydroxy-3-(2-thienyl)propylamine (17): A solution of (*S*)-3-hydroxy-3-(2-thienyl)propyl methanesulfonate **16** (140 mg, 1 mmol) and methylamine (10 mL, 40% in water) in THF (20 mL) was heated at 65 °C for 3 h. After cooling, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, dried with anhydrous potassium carbonate. Concentration to dryness provided the corresponding hydroxyamine **17**; yield: 125 mg (94%); white solid; $[\alpha]_D$: − 12.2 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$): δ = 7.21 – 7.28 (m, 1H), 6.93 – 7.01 (m, 2H), 5.19 – 5.24 (m, 1H), 2.79 – 3.02 (m, 2H), 2.38 (s, 3H), 3.50 (brs, 2H), 1.81 – 2.12 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 149.6, 126.4, 123.5, 122.1, 71.9, 50.1, 36.8, 35.91; MS (70 eV): *m/z* = 171 (M^+, 8), 139 (2), 128 (7), 110 (5), 97 (2), 85 (10), 58 (10), 44 (100); MS (CI/NH_3): *m/z* = 172 (MH^+, 100).

(*S*)-*N*-Methyl-3-(1-naphthoxy)-3-(2-thienyl)propanamine (Duloxetine or LY 248686; 18): To a solution of (*S*)-*N*-methyl-3-hydroxy-3-(2-thienyl)propylamine **17** (58 mg) in dimethylacetamide (5 mL) was added sodium hydride (10 mg, 1.2 eq.) with cooling. The mixture was heated at 50 °C for 1.5 h. An orange solution resulted. To this solution was added 86 mL of 1-fluoronaphthalene (2 eq.), and the mixture was heated at 80 °C for 2.5 h. After cooling and dilution with toluene, the mixture was washed with water, and the aqueous layer was separated and extracted with toluene. The combined toluene solutions were then washed with saturated aqueous sodium bicarbonate and brine and dried over magnesium sulfate. Concentration under vacuum provided **18**; yield: 62%; pale yellow oil; $[\alpha]_D$: + 122 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$): δ = 8.31 (d, 1H, $J = 8$ Hz), 7.93 (d, 1H, $J = 8$ Hz), 7.48 (d, 2H, $J = 8$ Hz), 7.39(d, 1H, $J = 8$ Hz), 7.27 (d, 1H, $J = 8$ Hz), 7.21 (d, 1H, $J = 8$ Hz), 7.05 (d, 1H, $J = 8$ Hz), 6.93 (d, 1H, $J = 8$ Hz), 6.86 (d, 1H, $J = 8$ Hz), 5.77 – 5.80 (m, 1H), 2.81 – 2.85 (m, 2H), 2.44 (s, 3H), 2.43 – 2.46 (m,1H), 2.21 – 2.25 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 142.5, 137.7, 127.3, 126.1, 125.6, 124.4, 122.0, 120.5, 106.9, 74.6, 49.1, 39.8, 34.9; MS (70 eV): *m/z* = 297 (M^+, 5), 187 (20), 154 (58), 110 (23), 97 (10), 84 (13), 77 (8), 58 (16), 44 (100); MS (CI/NH_3): m/z = 298 (MH^+, 100).

Asymmetric Synthesis of (*R*)-Fluoxetine (22)

Ethyl (*R*)-3-hydroxy-3-phenylpropanoate (5d): Yield: 90%; colorless oil; $[\alpha]_D$: − 52 (*c* 1, $CHCl_3$); IR (neat): ν = 3460 (ν_{OH}), 3040 (ν_{CH_3}), 2970 (ν_{CH_2}), 1716 cm^{-1} (ν_{COO}); ^{1}H NMR ($CDCl_3$): δ = 7.25-7.42 (m, 5H), 5.11 – 5.19 (m, 1H), 4.16 (q, 2H, $J = 7.1$ Hz) 3.39 – 3.41 (s, 1H, OH), 2.75 (t, 2H, $J = 7.1$ Hz), 1.27 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): δ = 172.2, 142.4, 128.4, 127.6, 125.5, 70.2, 60.7, 43.2, 14.0; MS (70 eV): *m/z* = 194 (M^+, 40), 177 (5), 120 (10), 107 (87), 79 (100), 77 (92).

(*R*)-1-Phenylpropane-1,3-diol (19): Ethyl-(*R*)-3-hydroxy-3-phenylpropanoate (**5d**) (0.265 g, 1.42 mmol) was dissolved in 10 mL of dry ether and the solution was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (115 mg, 3 mmol, 2.1 eq.) in dry THF under argon. The mixture was allowed to warm to room temperature over 1.5 h and then was quenched by sequential addition of H_2O (0.25 mL), 10% NaOH (0.25 mL), and additional H_2O (0.50 mL). The product was extracted with ether and the organic phase was washed with brine, dried and evaporated. The product was purified by column chromatography (SiO_2, cyclohexane/AcOEt, 50:50) to furnish the diol **19**; yield: 185 mg (86%); colorless oil; $[\alpha]_D$: + 64 (*c* 1, $CHCl_3$); IR (neat): ν = 3320 (ν_{OH}), 3020 (ν_{CH_3}), 2935 (ν_{CH_2}), 1595 cm^{-1} ($\nu_{C=C}$); ^{1}H NMR ($CDCl_3$): δ = 7.15 – 7.40 (m, 5H), 4.73 – 4.91 (m, 1H), 4,16 (brs, OH), 3.58 – 3.74 (m, 2H,), 1.95 – 1.76 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 144.0, 128.1, 127.1, 125.4, 73.1, 60.4, 40.8; MS (70 eV): *m/z* = 152 (28), 133 (10), 107 (60), 91 (7), 79 (100), 77 (90); MS (CI/NH_3): *m/z* = 170 (MNH_4^+, 100), 152 (MH^+, 64).

(*R*)-3-Hydroxy-3-phenylpropyl methanesulfonate (20): To a solution of (*R*)-1-phenylpropane-1,3-diol **19** (150 mg, 0.94 mmol) in ether (30 mL) was added dropwise 2 mL of distilled triethylamine (0.14 mmol, 1.5 eq.) and freshly distilled mesyl chloride (0.17 mmol, 1.1 eq.) under nitrogen at − 10 °C. After stirring at − 10 to 0 °C for 3 h, the mixture was poured into ice water (30 mL), washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to afford **20**; yield: 238 mg (82%); colorless oil; $[\alpha]_D$: + 25 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.25 – 7.42 (m, 5H), 4.79 – 4.88 (m, 1H), 4.19 – 4.29 (m, 1H), 4.38 – 4.46 (m, 1H), 2.94 (s, 3H), 2.85 (brs, OH), 2.06 – 2.15 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 143.4, 128.5, 127.8,125.6, 70.0, 67.1, 38.0, 37.0; MS (70 eV): *m/z* = 230 (M^+, 5), 134 (35), 107 (100), 105 (60), 79 (70), 77 (32).

(*R*)-*N*-Methyl-3-hydroxy-3-phenylpropylamine (21): A solution of (*R*)-3-hydroxy-3-phenylpropyl methanesulfonate **20** (200 mg, 0.64 mmol) and methylamine (20 mL, 40% in water) in THF (50 mL) was heated at 65 °C for 24 h. After cooling, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, dried with anhydrous potassium carbonate. Concentration to dryness provided the corresponding hydroxyamine **21**; yield: 97 mg (91%); pale yellow oil; $[\alpha]_D$: + 34 (*c* 1, $CHCl_3$); IR (KBr): ν = 3280 – 3420 ($\nu_{OH,NH}$), 2945 (ν_{CH_3}), 2840 cm^{-1} (ν_{CH_2}); ^{1}H NMR ($CDCl_3$): δ = 7.21 – 7.43 (m, 5H), 4.91 – 4.97 (m, 1H), 3.71 (brs, 2H), 2.83 – 2.96 (m, 2H), 2.43 (s, 3H), 1.68 – 1.97 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 145.2, 128.0, 125.5, 74.9, 50.4, 37.0, 35.9; MS (70 eV): *m/z* = 165 (M^+, 15), 133 (5), 104 (20), 77 (28), 59 (17), 44 (100), MS (CI/NH_3): *m/z* = 166 (MNH_4^+, 100).

(*R*)-*N*-Methyl-γ-(4-trifluoromethylphenoxy)-3-phenylpropylamine [(*R*)-fluoxetine]: To a solution of (*R*)-*N*-Methyl-3-hydroxy-3-phenylpropylamine (**21**) (61.5 mg, 0.37 mmol) in dimethylacetamide (5 mL) was added sodium hydride

(10.5 mg, 1.2 eq.) with cooling. The mixture was heated at 50 °C for 1.5 h. An orange solution resulted. To this solution was added 68 mL of 1-chloro-4-(trifluoromethyl)benzene (2 eq.), and the mixture was heated at 80 °C for 2.5 h. After cooling and dilution with toluene, the mixture was washed with water, and the aqueous layer was separated and extracted with toluene. The combined toluene solutions were then washed with saturated aqueous sodium bicarbonate and brine and dried over magnesium sulfate. Concentration provided (*R*)-fluoxetine; yield: 62%; pale yellow oil; ^{1}H NMR ($CDCl_3$): δ = 7.28 – 7.37 (m, 5H), 7.45 (d, 2H, *J* = 8 Hz), 6.93 (d, 2Hz, *J* = 8 Hz), 5.29 – 5.36 (m, 1H), 2.76 (t, 2H, *J* = 12 Hz), 1.98 – 2.37 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 160.1, 141.2, 128.7, 128.6, 127.6, 126.5, 125.6, 115.7, 115.6, 78.6, 48.1, 38.6, 36.3; MS (70 eV): *m/z* = 309 (M^+, 38), 13 (10), 162 (15), 104 (20), 91 (16), 77 (25), 44 (100); MS (CI/NH_3): *m/z* = 310 (MNH_4^+, 100).

(*R*)-Fluoxetine hydrochloride (22): (*R*)-Fluoxetine was dissolved in ether and acidified with hydrogen chloride gas (pH 3 – 4). The solution was concentrated to give a solid which was recrystallized from ether/hexane to provide (*R*)-fluoxetine hydrochloride **22**; yield: 80%; white solid; mp 140 °C; $[\alpha]_D$: – 13.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 9.7 (s, 2H), 7.22 – 6.89 (m, 9H), 5.02 – 5.05 (m, 1H), 2.75 (t, 2H, *J* = 10 Hz), 2.41 (s, 3H), 2.18 – 2.23 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 159.1, 139.8, 128.7, 128.5, 126.6, 125.6, 115.8, 77.1, 47.2, 34.5, 33.4; MS (70 eV): *m/z* = 345 (0.5), 309 (M-HCl, 10), 165 (10), 147 (9), 133 (5), 104 (6), 77 (7), 44 (100).

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