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Asymmetric synthesis of ring-fused tetrahydroquinolines using organocatalytic enantioselective conjugate addition and cross-dehydrogenative coupling

Sung Hyuk Gwon, Sung-Gon Kim *

Department of Chemistry, College of Natural Science, Kyonggi University, San 94-6, Iui-dong, Yeongtong-gu, Suwon 443-760, Republic of Korea

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ABSTRACT

Enantioenriched ring-fused tetrahydroquinolines were synthesized by a facile and straightforward process involving the organocatalytic enantioselective conjugate addition reaction of malonates with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde, followed by intramolecular cross-dehydrogenative coupling. Diphenylprolinol TMS ether was used as an organocatalyst in the asymmetric catalytic conjugate addition reaction and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was used as an oxidant in the cross-dehydrogenative coupling (CDC) reaction. The desired ring-fused tetrahydroquinolines were obtained in moderate yields and with high enantioselectivities (up to 97% ee).

1. Introduction

Tetrahydroquinolines are ubiquitous in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[1] Molecules containing the tetrahydroquinoline scaffold exhibit a broad range of bioactivities, such as anti-HIV, antibacterial, antifungal, antimalarial, antitumor, and cardiovascular activities.[2] This scaffold is also present in antioxidants, dyes, and photosensitizers.[3] Due to the importance of these 'privileged' structures, numerous synthetic methods for making tetrahydroquinolines have been reported. Recently, enantioselective synthetic approaches to the generation of chiral tetrahydroquinolines, which mainly rely on the asymmetric hydrogenation of heteroaromatic compounds have been developed.[1d,4] Furthermore, several other methods, such as the nucleophilic addition of imines, organocatalysis, and the Povarov reaction have been disclosed for the construction of chiral tetrahydroquinoline scaffolds.[5] Consequently, the development of an efficient enantioselective synthetic method for generating tetrahydroquinoline scaffolds has attracted our attention. Herein, we report the first example of the asymmetric synthesis of tetrahydroquinoline, especially of ring-fused tetrahydroquinolines, from the organocatalytic enantioselective conjugate addition reaction of malonates with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde, followed by an intramolecular cross-dehydrogenative coupling (CDC) reaction.

The activation of C–H bonds is highly significant in synthetic organic chemistry due to many attendant potential advantages and the possibility of developing new strategies for the synthesis of complex molecules.[6] In recent years, the direct construction of a C–C bond by a simple activation of two C–H bonds has emerged as an attractive and interesting goal in chemistry. This CDC reaction from two C–H bonds allows the use of less functionalized reagents and facilitates fewer synthetic steps to obtain the target molecules.[7]

Asymmetric organocatalysis, which results in better reproducibility and greater operational simplicity than traditional metal catalysis, has also attracted considerable attention over the past decade. In addition, asymmetric organocatalysis is a very promising strategy that provides efficient and environmental friendly access to enantiomerically pure compounds in the synthesis of natural products and biologically active compounds.[8] In particular, organocatalysis has been considered as a highly useful process to replace the role of transition metals in promoting the asymmetric Michael addition reaction, which involves the attack of carbon nucleophiles onto electron-poor double and triple bonds.[9] As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers, we recently developed a novel catalytic asymmetric Michael reaction of *o*-hydroxycinnamaldehydes using an organocatalyst, which afforded enantioenriched chroman derivatives.[10]

With the aim of developing new methodology for producing enantioenriched tetrahydroquinolines, we considered the use of *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde in an organocatalytic asymmetric Michael reaction. In the first step, the reaction of malonates as nucleophiles with this substrate in the presence of an appropriate organocatalyst was assumed to form highly enantioenriched Michael adducts. In the second step,

* Corresponding author. Tel.: +82 31 249 9631; fax: +82 31 249 9639.
E-mail address: sgkim123@kyonggi.ac.kr (S.-G. Kim).

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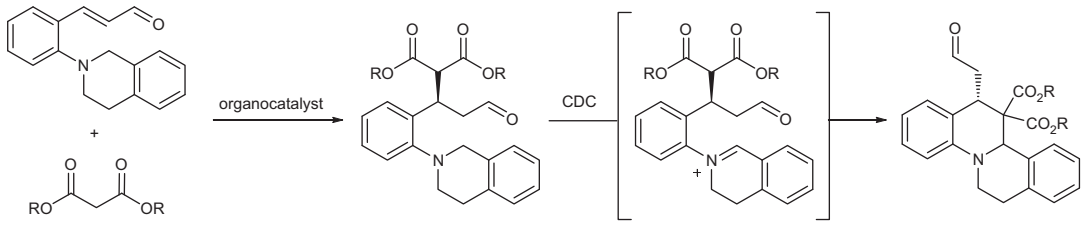


Scheme 1. Asymmetric synthesis of tetrahydroquinolines.

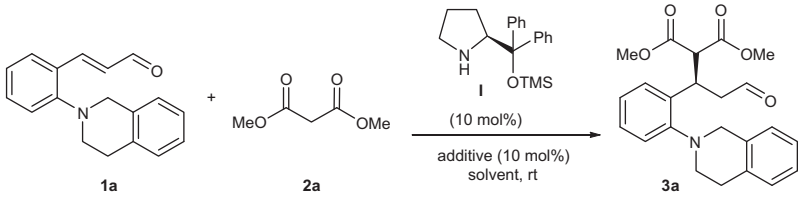
ring-fused tetrahydroquinolines could be obtained through a novel intramolecular oxidative Mannich-type reaction in which the iminium ion intermediate is formed via oxidation (Scheme 1).

2. Results and discussion

Based on our previous results, the α,α-diphenyl-D-prolinol TMS ether catalyst **I**[11] was initially selected as an organocatalyst in the Michael reaction of dimethyl malonates **2a** with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehydes **1a** (Table 1). The reaction was carried out at room temperature in CH_3CN using 10 mol % catalyst **I** with an additive. When benzoic acid was used as the additive, the desired product **3a** was obtained in 38% yield with 59% ee in this Michael reaction (entry 1). The use of sodium acetate as an additive increased the enantioselectivity (87% ee, entry 2). Next, the solvent effect was evaluated for this reaction. The reaction medium had a substantial impact on the conversion efficiency and enantioselective induction. The use of methanol increased the reactivity but decreased the enantioselectivity of this reaction, regardless of the use of additive (entries 3–5). It is notable that polar protic solvents such as MeOH, EtOH, *i*-PrOH, and H_2O are suitable in the organocatalytic conjugate addition reaction of malonates to α,β-unsaturated aldehydes.[10g,12] The best results were obtained by performing the reaction for 72 h in THF without the use of an additive, giving the addition product **3a** in 45% yield and with 95% ee (entry 10). The use of an additive in this reaction did not improve the enantioselectivity (entries 11 and 12). The addition of sodium acetate as a basic additive afforded product **3a** in increased yield but with a slightly decreased enantioselectivity (entry 13).

Having established the optimal reaction conditions for this asymmetric Michael reaction (10 mol % of **I** as the catalyst, in THF at rt), the CDC reaction for generating tetrahydroquinolines was investigated in the next step. Several methods for the intermolecular cross coupling of tertiary amines with nitroalkanes or malonates have been reported. Li developed an oxidative coupling reaction using a combination system comprising CuBr as the catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant.[13] Klussmann also established a copper-catalyzed oxidative coupling reaction using CuCl as a catalyst, acetone or methanol as the solvent, and elemental oxygen as the oxidant.[14] The catalyst-free oxidative coupling reaction using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as an oxidant was developed by Todd,[15] whereas Liang used $PhI(OAc)_2$ as the oxidant.[16] The aforementioned coupling reaction methods were evaluated by performing the current intramolecular oxidative Mannich-type reaction (Table 2). However, no reactions occurred when using the $CuCl_2$/O_2 system, the CuBr/TBHP system, and $PhI(OAc)_2$ (entries 1–5). However, the desired ring-fused tetrahydroquinoline **4a** was obtained in the reaction with DDQ, starting from compound **3a**, although the isolated yield was not satisfactory (entry 6). Attempts were made to optimize the reaction in terms of more sustainable conditions for increasing the yield. By changing the solvent and by using an additive or base, the intramolecular oxidative Mannich-type reaction afforded tetrahydroquinoline **4a** in moderate yield (35% yield); the best reaction conditions involved DDQ

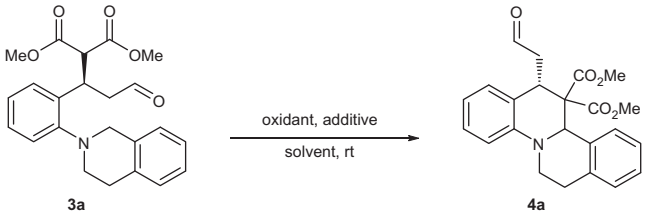
Table 1
Organocatalytic enantioselective conjugate addition reaction of dimethyl malonate **2a** with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde **1a**



Entry	Additive	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	$PhCO_2H$	CH_3CN	26	38	59
2	NaOAC	CH_3CN	72	40	87
3	$PhCO_2H$	MeOH	48	81	35
4	NaOAC	MeOH	48	78	4
5	—	MeOH	48	73	5
6	—	CH_2Cl_2	48	32	39
7	—	$CHCl_3$	48	30	41
8	—	Toluene	48	27	93
9	—	EtOAc	48	41	94
10	—	THF	72	45	95
11	$PhCO_2H$	THF	72	46	91
12	4-$NO_2C_6H_4CO_2H$	THF	72	39	95
13	NaOAC	THF	72	62	89

[a] Yield of isolated product.
[b] Determined by chiral HPLC analysis (Chiralcel AD-H).

Table 2
Intramolecular cross-dehydrogenative coupling reaction of chiral tetrahydroisoquinoline **3a**



3a **4a**

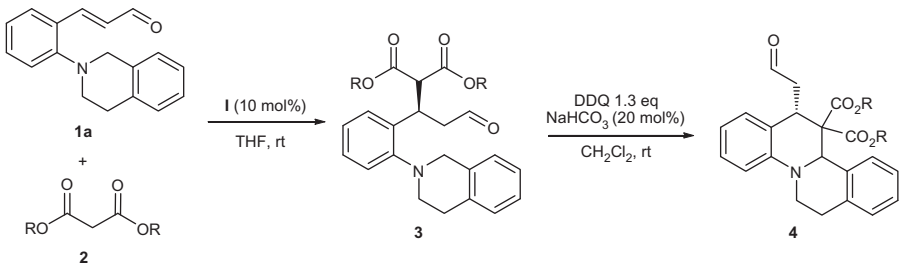
Entry	Oxidant	Additive	Solvent	Time	Yield[a] (%)
1	O_2	$CuCl_2$ (10 mol %)	MeOH	24 h	
2	O_2	$CuCl_2$ (10 mol %)	Acetone	24 h	No rxn
3	tBHP	CuBr (5 mol %)	CH_2Cl_2	48 h	No rxn
4	tBHP	CuBr (5 mol %)	CH_3CN	48 h	No rxn
5[b]	$PhI(OAC)_2$	—	DME	24 h	No rxn
6	DDQ	—	CH_2Cl_2	1 h	14
7	DDQ	—	CH_3CN	3 h	8
8	DDQ	4A MS	EtOAc	30 min	8
9	DDQ	LiOAc (20 mol %)	CH_2Cl_2	30 min	27
10	DDQ	K_2CO_3 (20 mol %)	CH_2Cl_2	30 min	21
11	DDQ	Na_2CO_3 (20 mol %)	CH_2Cl_2	30 min	25
12	DDQ	$NaHCO_3$ (20 mol %)	CH_2Cl_2	30 min	35

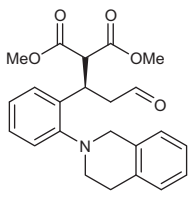
[a] Yield of isolated product.
[b] At 50 °C.

(1.3 equiv) as the oxidant and $NaHCO_3$ (20 mol %) as an additive in CH_2Cl_2 (entry 12).

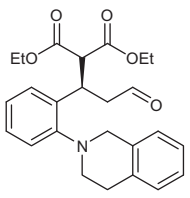
Various malonates **2** were also reacted with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehydes **1a** under the optimized conditions in order to expand the scope of substrates relevant to the organocatalytic asymmetric Michael reaction and intramolecular oxidative Mannich-type reaction for the synthesis of ring-fused tetrahydroquinolines (Table 3). High levels of enantioselectivity (up to 97% ee) were obtained in the first step of the reaction employing malonates. In particular, dibenzyl malonate afforded

Table 3
Asymmetric synthesis of tetrahydroisoquinolines **3** and **4**

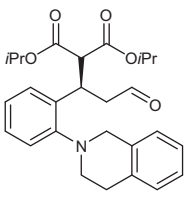




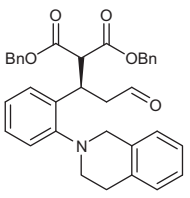
3a (45% yield)
95% ee
72 h



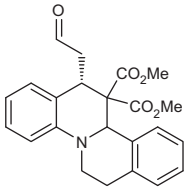
3b (31% yield)
96% ee
72 h



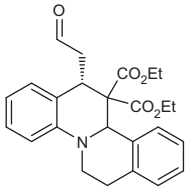
3c (23% yield)
97% ee
5 d



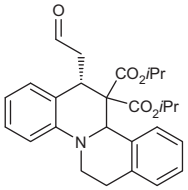
3d (63% yield)
91% ee
72 h



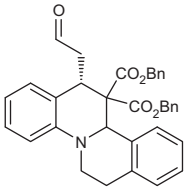
4a (35% yield)
3.8:1 d.r.
30 min



4b (21% yield)
3.2:1 d.r.
30 min



4c (22% yield)
5.2:1 d.r.
30 min



4a (25% yield)
3.7:1 d.r.
30 min

the desired Michael adduct **3d** in good yield and with high enantioselectivity (63% yield, 91% ee). In the intramolecular oxidative Mannich-type reaction, tetrahydroquinolines **4** were synthesized from compounds **3** in moderate yields by utilizing the optimized CDC conditions. The stereoselectivity of tetrahydroquinolines **4** was preserved in this reaction. The absolute configuration of these products was assigned based on previous studies. The reaction of dimethyl malonate **2a** with aromatic α,β-unsaturated aldehydes **1** catalyzed by the same organocatalyst **I** has been reported to give addition products with an (*R*)-configuration.[10g,12] We expected that the absolute configuration of the products of the present reaction can be assigned as the same by analogy.

3. Conclusion

In conclusion, the asymmetric synthesis of ring-fused tetrahydroquinolines was successfully completed based on the organocatalytic enantioselective Michael addition reaction of malonates with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde followed by intramolecular CDC reaction. Diphenylprolinol TMS ether was used as an organocatalyst for the asymmetric catalytic reaction and DDQ was used as an oxidant in this oxidative Mannich-type reaction. An evaluation of the applications of this synthetic methodology for generating enantioenriched tetrahydroquinolines is currently in progress and will be presented in due course.

4. Experimental

4.1. General

Commercial reagents were used without further purification. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. All organic solvents were distilled prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching and anisaldehyde stain.

NMR spectra were recorded on 400 MHz instrument as noted, and were internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm). Enantiomeric excesses were determined on a HPLC instrument using Chiralcel columns as noted.

4.2. General procedure for the organocatalytic asymmetric reaction of malonates with *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde

An amber 2-dram vial equipped with a magnetic stirrer bar containing catalyst **I** (8 mg, 0.025 mmol) and *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde **1a** (66 mg, 0.25 mmol) was charged with THF (0.5 mL) at room temperature. The solution was stirred for 5 min before the addition of malonate **2** (0.30 mmol). The resulting mixture was stirred at a constant temperature until the complete consumption of *o*-*N*-tetrahydroisoquinolinyl-substituted cinnamaldehyde **1a** was observed as determined by TLC. The resulting mixture was directly purified by silica gel chromatography (10% EtOAc/hexanes) to afford the desired compound **3**. The enantiomeric excess was determined by HPLC on a chiral column.

4.2.1. Dimethyl-2-((*R*)-2-formyl-1-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)ethyl)malonate 3a

45% Yield, $[\alpha]_D^{28} = -7.1$ (*c* 0.88, $CHCl_3$), 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 9.63 (s, 1H), 7.09–7.29 (m, 8H), 4.55–4.62 (m, 1H), 4.20 (d, *J* = 14.8 Hz, 1H), 4.08 (d, *J* = 16.4 Hz, 1H), 4.05 (d, *J* = 9.2 Hz, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 3.26 (brs, 2H), 3.09 (brs, 2H), 2.80–2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.7, 168.8, 168.4, 151.6, 136.4, 135.3, 134.3, 128.9, 128.4, 127.6, 126.5, 126.2, 125.7, 125.4, 122.7, 60.4, 55.5, 52.6, 52.4, 51.5, 47.2, 34.5, 29.9; HRMS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{25}NO_5$: 395.1733. Found: 395.1737; HPLC (Chiralcel AD-H, 10% EtOH/hexanes, 1.0 mL/min, flow, λ = 220 nm); t_{minor} = 17.9 min, t_{major} = 19.2 min.

4.2.2. Diethyl-2-((*R*)-2-formyl-1-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)ethyl)malonate 3b

31% Yield, $[\alpha]_D^{28} = -0.7$ (*c* 0.51, $CHCl_3$), 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 9.63 (s, 1H), 7.10–7.28 (m, 8H), 4.50–4.58 (m, 1H), 4.11–4.24 (m, 3H), 3.98–4.05 (m, 4H), 3.27 (brd, *J* = 17.2 Hz, 2H), 3.09 (brs, 2H), 2.78–2.92 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.8, 168.4, 168.0, 151.6, 136.5, 135.3, 134.3, 128.9, 128.3, 127.8, 126.5, 126.2, 125.7, 125.3, 122.5, 61.6, 61.4, 55.8, 55.5, 51.5, 47.4, 34.5, 29.9, 14.0, 13.8; HRMS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{29}NO_5$: 423.2046. Found: 423.2042; HPLC (Chiralcel AD-H, 10% EtOH/hexanes, 1.0 mL/min, flow, λ = 220 nm); t_{major} = 15.3 min, t_{minor} = 16.7 min.

4.2.3. Diisopropyl-2-((*R*)-2-formyl-1-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)ethyl)malonate 3c

23% Yield, $[\alpha]_D^{28} = -7.3$ (*c* 0.95, $CHCl_3$), 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 9.62 (s, 1H), 7.10–7.28 (m, 8H), 5.05 (septet, *J* = 6.4 Hz, 1H), 4.87 (septet, *J* = 6.4 Hz, 1H), 4.23 (d, *J* = 15.2 Hz, 1H), 4.05 (d, *J* = 14.8 Hz, 1H), 3.94 (d, *J* = 9.6 Hz, 1H), 3.19–3.38 (m, 2H), 3.09 (brs, 2H), 2.73–2.91 (m, 2H), 1.22 (dd, *J* = 6.4, 8.8 Hz, 6H), 1.06 (dd, *J* = 6.4, 16.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.9, 167.9, 167.6, 151.5, 136.6, 135.3, 134.3, 128.9, 128.3, 127.9, 126.4, 126.2, 125.7, 125.2, 122.4, 69.1, 68.9, 56.1, 55.5, 51.4, 47.7, 34.4, 29.7, 21.7, 21.6, 21.5, 21.4; HRMS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{33}NO_5$: 451.2359. Found: 451.2357; HPLC (Chiralcel AD-H, 10% EtOH/hexanes, 1.0 mL/min, flow, λ = 220 nm); t_{major} = 15.6 min, t_{minor} = 17.5 min.

4.2.4. Dibenzyl-2-((*R*)-2-formyl-1-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)ethyl)malonate 3d

63% Yield, $[\alpha]_D^{26} = +3.8$ (*c* 0.69, $CHCl_3$), 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 9.55 (s, 1H), 7.00–7.39 (m, 18H), 5.13 (dd, *J* = 12.0, 21.6 Hz, 2H), 4.97 (s, 2H), 4.55–4.62 (m, 1H), 4.15 (d, *J* = 9.2 Hz, 1H), 4.12 (d, *J* = 15.2 Hz, 1H), 3.97 (d, *J* = 16.8 Hz, 1H), 3.19 (brs, 2H), 3.00 (brs, 2H), 2.73–2.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.5, 168.0, 167.7, 151.5, 136.2, 135.3, 135.1, 135.0, 134.3, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.6, 126.5, 126.2, 125.7, 125.4, 122.6, 67.3, 67.2, 55.8, 55.5, 51.4, 47.3, 34.4, 29.8; HRMS (ESI): $[M+H]^+$ Calcd for $C_{35}H_{33}NO_5$: 547.2359. Found: 547.2361; HPLC (Chiralcel AD-H, 10% EtOH/hexanes, 1.0 mL/min, flow, λ = 220 nm); t_{major} = 37.5 min, t_{minor} = 40.8 min.

4.3. General procedure for the intramolecular cross-dehydrogenative coupling reaction using DDQ

To a solution of compound **3** (0.10 mmol) and $NaHCO_3$ (1.7 mg, 0.020 mmol) in CH_2Cl_2 (0.5 mL) was added DDQ (36 mg, 0.13 mmol) at room temperature. After stirring for 30 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried

over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford the desired compound **4**.

4.3.1. (13*R*)-Dimethyl-13-(formylmethyl)-6,7-dihydro-11b*H*-isoquinolino[2,1-*a*]quinoline-12,12(13*H*)-dicarboxylate 4a

35% Yield, $[\alpha]_D^{27} = -72.7$ (*c* 0.10, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) 9.78 (s, 1H), 6.74–7.35 (m, 8H), 4.71 (s, 1H), 4.02–4.13 (m, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.56 (s, 1H), 3.48 (d, J = 15.2 Hz, 2H), 2.91 (d, J = 15.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.2, 168.5, 168.4, 145.5, 135.6, 134.7, 129.7, 128.9, 128.4, 127.0, 126.9, 126.3, 120.1, 118.2, 111.9, 57.2, 53.9, 53.3, 52.8, 52.6, 42.3, 36.1, 29.6; HRMS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{23}NO_5$: 393.1576. Found: 393.1574.

4.3.2. (13*R*)-Diethyl-13-(formylmethyl)-6,7-dihydro-11b*H*-isoquinolino[2,1-*a*]quinoline-12,12(13*H*)-dicarboxylate 4b

21% Yield, $[\alpha]_D^{28} = +22.7$ (*c* 0.14, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) 9.24 (s, 1H), 6.75–7.34 (m, 8H), 4.74 (d, J = 2.0 Hz, 1H), 4.16–4.28 (m, 3H), 3.94–4.09 (m, 4H), 3.47 (s, 1H), 3.06–3.12 (m, 2H), 2.81–2.96 (m, 1H), 1.22–1.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.4, 168.1, 167.9, 145.6, 135.6, 134.8, 129.9, 129.0, 128.3, 126.9, 126.5, 126.2, 122.5, 118.2, 111.8, 61.6, 57.5, 53.9, 53.4, 42.3, 36.0, 29.9, 29.6, 14.1, 14.0; HRMS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{25}NO_5$: 421.1889. Found: 421.1886.

4.3.3. (13*R*)-Diisopropyl-13-(formylmethyl)-6,7-dihydro-11b*H*-isoquinolino[2,1-*a*]quinoline-12,12(13*H*)-dicarboxylate 4c

22% Yield, $[\alpha]_D^{27} = -36.9$ (*c* 0.15, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) 9.24 (s, 1H), 6.72–7.36 (m, 8H), 5.03–5.15 (m, 2H), 4.78 (d, J = 2.8 Hz, 1H), 4.25 (d, J = 7.2 Hz, 1H), 4.01–4.12 (m, 1H), 3.90 (d, J = 8.0 Hz, 1H), 3.48 (t, J = 2.4 Hz, 1H), 3.04–3.14 (m, 2H), 2.85–2.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.2, 167.7, 167.6, 145.5, 135.6, 134.9, 130.1, 128.9, 128.2, 126.9, 126.8, 126.1, 120.5, 118.1, 111.7, 69.4, 69.3, 57.8, 53.9, 53.4, 42.4, 35.8, 29.6, 21.7, 21.6; HRMS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{31}NO_5$: 449.2202. Found: 449.2207.

4.3.4. (13*R*)-Dibenzyl-13-(formylmethyl)-6,7-dihydro-11b*H*-isoquinolino[2,1-*a*]quinoline-12,12(13*H*)-dicarboxylate 4d

25% Yield, $[\alpha]_D^{28} = -26.4$ (*c* 0.16, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) 9.14 (s, 1H), 6.72–7.40 (m, 18H), 5.20 (s, 4H), 4.46 (d, J = 2.4 Hz, 1H), 4.31 (d, J = 7.6 Hz, 1H), 4.09 (d, J = 7.6 Hz, 1H), 3.96–4.01 (m, 1H), 3.33 (t, J = 2.4 Hz, 1H), 2.91–3.03 (m, 2H), 2.80–2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.2, 167.8, 166.3, 135.4, 135.2, 134.6, 129.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2(x2), 128.1, 128.0. 127.7, 126.9, 126.7, 126.1, 120.1, 118.3, 111.9, 67.5, 67.3, 57.4, 53.8, 53.2, 41.6, 35.9, 29.5; HRMS (ESI): $[M+H]^+$ Calcd for $C_{35}H_{31}NO_5$: 545.2202. Found: 545.2205.

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