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# EFFICIENT AND DIASTEREOSELECTIVE SYNTHESIS OF BIS-QUINAZOLINEDIONE DERIVATIVES VIA LOW-VALENT TITANIUM REAGENT

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**Abstract —** An efficient and simple method for the synthesis of chiral benzo[5,6][1,3]oxazino[4,3-*c*]quinoxalinedione and octahydroquinoxalino-[1,2-*c*:4,3-*c*']diquinazolinedione derivatives using 2-hydroxybenzaldehydes (or 2-nitrobenzaldehydes) and chiral cyclohexane-1,2-diamine as the starting materials promoted by low-valent titanium reagent has been described. The structures of all synthesized products were identified by their IR, $^1$H NMR, $^{13}$C NMR and HRMS analysis, and the structure of compound **8b** was confirmed by X-ray diffraction analysis.

Heterocyclic compounds are ubiquitous system in natural products and are considered as privileged structures in drug discovery.[1] Quinazolinones have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals. They are widely used as antibacterial,[2] antidiabetic agents,[3] antitumor,[4] antihypertensive,[5] anti-inflammatory,[6] and protein kinase inhibitors.[7] Moreover, the quinazolinone moiety has been extensively utilized as a druglike scaffold in medicinal chemistry.[8]

There are few methods reported for the synthesis of quinazolinone framework.[9] Only one ring of the product was constructed in these processes. Furthermore, these methods usually required long reaction times (reflux for 2 days),[10] high reaction temperature (150 °C),[11] and using toxic solvents and expensive catalyst.[12] These shortcomings limited the scope of appropriates substrates.

Additionally, the synthesis of bis-quinazolinedione skeleton (Figure 1) is rather scarce. Previously, we have reported the construction of the bis-quinazolinedione analogous framework.[13] However, there is no report for the synthesis of chiral bis-quinazolinedione by far. As our earlier work goes, in this paper, we would like to report a novel access to the construction of the chiral bis-quinazolinedione derivatives.

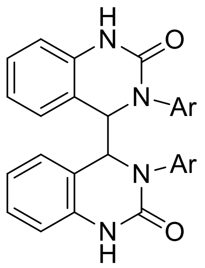
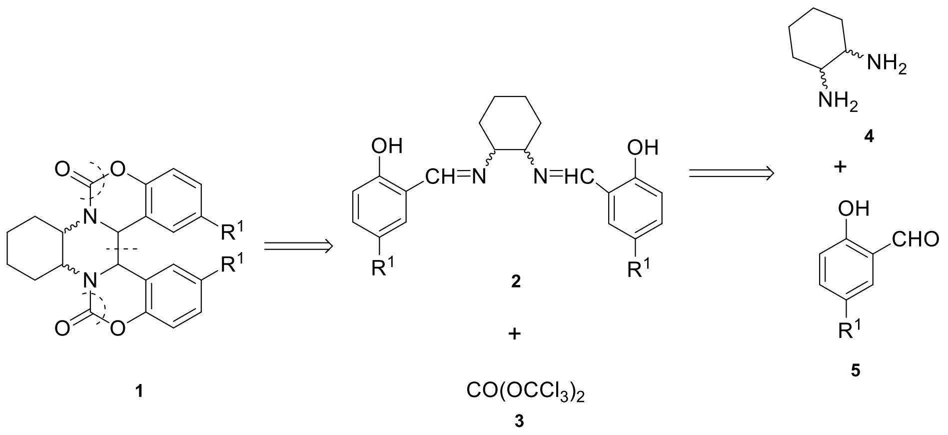


**Figure 1**. Bis-quinazolinedione skeleton

According to our earlier work, the target chiral bis-quinazolinedione derivatives **1**, would be required the reductive coupling of chiral *N*-(2-nitrobenzylidene)aniline derivatives **2** with triphosgene **3** (Scheme 1).[14] Chiral *N*-(2-nitrobenzylidene)aniline can be obtained from corresponding chiral cyclohexane-1,2-diamine **4** and *o*-nitrobenzaldehydes **5**.

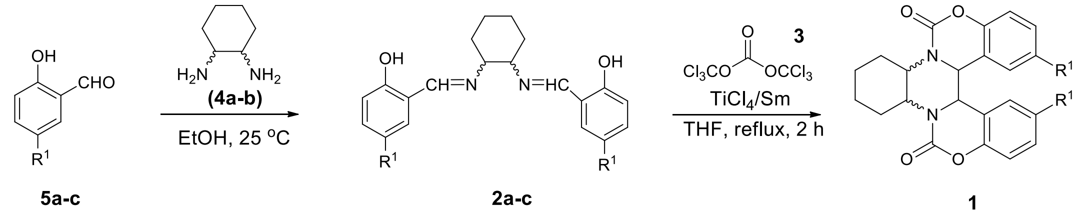


**Scheme 1**. Retrosynthetic pathway for the synthesis of chiral bis-quinazolinediones (**1**)

The starting material chiral diimines derivatives such as ((1*R*,2*R*)-cyclohexane-1,2-diylbis(azanylylidene-)) bis(methanylylidene))diphenol **2a**, are readily obtained from the reaction of salicylaldehyde **5a** with (1*R*,2*R*)-cyclohexane-1,2-diamine **4a** in EtOH at 25 ºC. With compound **2a** in hand, the intramolecular cascade reductive coupling reactions of **2a** together with triphosgene **3** was examined in the presence of four equivalents of $TiCl_4$/Sm as the promoter in THF under reflux for two hours, which gave the desired chiral bis-quinazolinediones derivatives **1a** in 76% yield and > 99.9% *de* after purification of the crude product through the flash column chromatography.

Having established the reaction conditions, we then tested for library construction with substituted salicylaldehydes. The results are summarized in Table 1. It was found there were no remarkable effect of the electronic effect of the substituted groups of salicylaldehydes to the yields and *de*%.

**Table 1.** The synthesis of chiral bis-quinazolinediones derivatives **1**

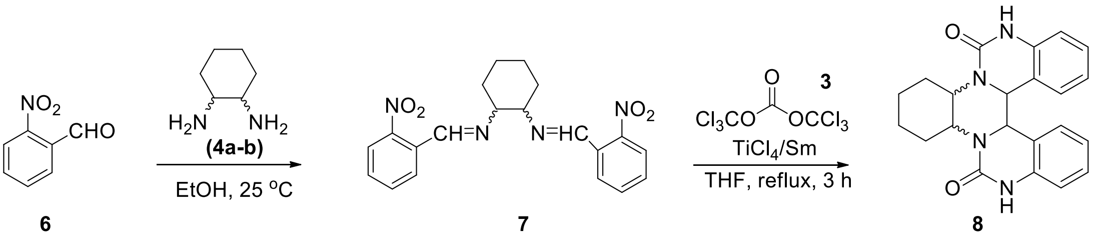


**5a**: $R^1$ = H; **5b**: $R^1$ = 5-Cl; **5c**: $R^1$ = 5-Br 2; **4a**: (1*R*,2*R*)-cyclohexane-1,2-diamine; **4b**: (1*S*,2*S*)-cyclohexane-1,2-diamine

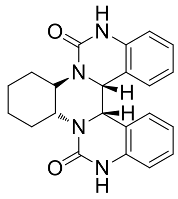
| Entry | Product | 4 | $R^1$ | Yield/% | $[a]^{25}_{D}$ | *de*(%)[a] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **4a** | H | 76 | -142 | > 99.9 |
| 2 | **1b** | **4b** | H | 78 | +145 | > 99.9 |
| 3 | **1c** | **4a** | Cl | 76 | -142 | > 99.9 |
| 4 | **1d** | **4b** | Cl | 71 | +144 | > 99.9 |
| 5 | **1e** | **4a** | Br | 73 | -140 | > 99.9 |
| 6 | **1f** | **4b** | Br | 72 | +143 | > 99.9 |

[a] The *de*'s were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate: 1.0 mL·min$^{-1}$, λ = 245 nm]

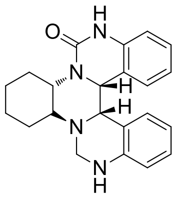
The synthesis of **1** is depicted *N*-(2-nitrobenzylidene)cyclohexane-1,2-diamine derivatives **2** was prepared from *o*-nitrobenzaldehyde **6** and cyclohexane-1,2-diamine **4** in EtOH, which is simple, cheaply priced, and readily available. With compound **1** in hand we then test the reductive coupling of nitro group of the Schiff base **7** and triphosgene to give bis-quinazolinedione derivatives **8**. Due to an additional reduction of the nitro group to the amino group, 8 equiv. of $TiCl_4$/Sm relative to substrate **7** had to be used in this transformation. The results are summarized in Scheme 2.



**4a**: (1*R*,2*R*)-cyclohexane-1,2-diamine; **4b**: (1*S*,2*S*)-cyclohexane-1,2-diamine



**8a** 73% $[a]^{D}_{25}$ -240, *de* > 99.9%[a]



**8b** 72% $[a]^{D}_{25}$ +237, *de* > 99.9%[a]

[a] The *de*'s were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate: 1.0 mL·min$^{-1}$, λ = 245 nm]

**Scheme 2**. The synthesis of chiral bis-quinazolinediones derivatives **8**

The structures of all the products were identified by their IR, $^{1}$H NMR, $^{13}$C NMR and HRMS spectra. The structure of compound **8b** was further confirmed by X-ray diffraction analysis, the EtOH and DMF as solvent used for the recrystallization of **8b**. The molecular structure of the product **8b** is shown in Figure 2.

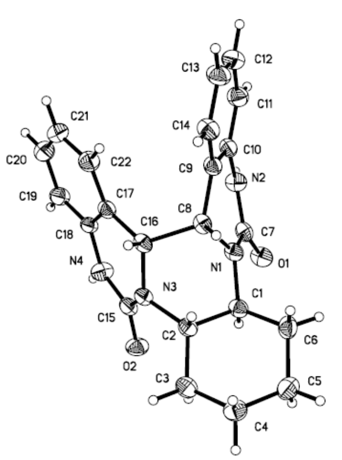
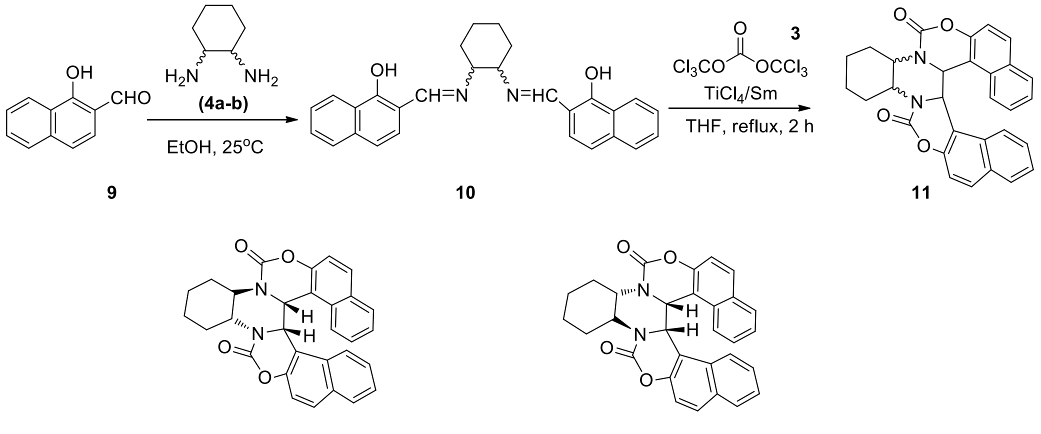


**Figure 2.** The crystal structure of **8b**

To expand the scope of the current method, this effective process was further applied to synthesis of bis-quinazolinediones derivatives **11** through the tandem reductive coupling reaction of triphosgene **3** and diimines **10** resulted from 2-hydroxy-1-naphthaldehyde **9** with cyclohexane-1,2-diamine **4** in the presence of four equivs of $TiCl_4$/Sm in THF under reflux for two hours. The results are shown in Scheme 3.

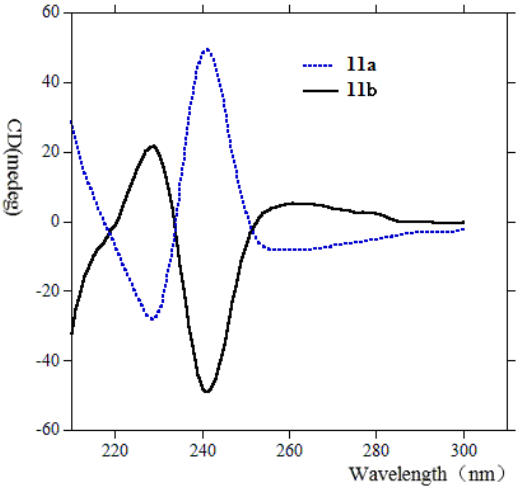


**11a** 85% $[a]^{D}_{25}$ -437, *de* > 99.9%$^{a}$ **11b** 83% $[a]^{D}_{25}$ +434, *de* > 96%$^{a}$

[a] The *de* were determined by HPLC[Daicel Chiralpak AD-H (0.46 cm × 25 cm), hexane/*i*-PrOH (85 : 15), flow rate: 1.0 mL·min$^{-1}$, $\lambda = 210$ nm]

**Scheme 3**. The synthesis of chiral bis-quinazolinediones derivatives **11**

To probe the influence of the chirality on the photophysical behaviour of **11a** and **11b**, the diastereoisomers were subjected to circular dichroism (CD) analysis (Figure 3). This diastereoisomeric pair demonstrated a strong CD effect. The appearance of mirror image CD spectra of **11a** versus **11b** indicates that the optical behaviour is strongly reliant on the chirality of the bis-quinazolinediones derivatives.



Circular dichroism spectra were recorded on Model 410 circular dichroism spectrophotometer at ambient temperature (1.0×$10^{-5}$ mol/L, EtOH)

**Figure 3.** The CD of compounds **11a** and **11b**

In conclusion, a facile and efficient route has been developed for synthesis of complex chiral benzo[5,6][1,3]oxazino[4,3-*c*]quinoxalinedione or octahydroquinoxalino[1,2-*c*:4,3-*c*']diquinazoline-dione derivatives by using *o*-hydroxydiimines or *o*-nitrodiimines and triphosgene as starting materials in the presence of $TiCl_4$/Sm as the reductive coupling reagent. This novel synthetic method provides an easy access to chiral bis-quinazolinedione derivatives. Further exploitation of this method and application of these products are underway.

## EXPERIMENTAL

THF was distilled from sodium-benzophenone just prior to use. Unless otherwise stated, other reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted. Melting points are uncorreted. IR spectra were recorded on a Varian F-1000 spectrometer in KBr with absorptions in $cm^{-1}$. $^1H$ NMR (400 MHz or 300 MHz) and $^{13}C$ NMR (75 MHz or 100 MHz) spectra were recorded on a Bruker DPX-400 MHz spectrometer or Varian Inova-300 MHz and Varian Inova-400 MHz in DMSO-$d_6$ or $CF_3CO_2D$ solution. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from interal standard TMS. High-resolution mass spectra (HRMS) for all the compounds were determined on Micromass GCT-TOF or Bruker MicrOTOF-QII mass spectrometer with ESI resource. X-Ray diffraction analysis was recorded on a Smart-1000 diffractometer. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies 6120 Quadrupole LC/MS.

**Typical experimental procedure for the synthesis of *o*-hydroxydiimines 2a-2c or 10.** To a clear solution of an *o*-hydroxybenzaldehyde **5a-5c** or **9** (6.0 mmol) in 2.0 mL of EtOH was added of 3.0 mmol (1*R*, 2*R*)-cyclohexane-1,2-diamine **4a** or (1*S*, 2*S*)-cyclohexane-1,2-diamine **4b**. The resulting clear reaction mixture was stirred for 4 h at rt to give *o*-hydroxydiimines **2a-2c** or **10** as a yellow precipitate. The solid was filtered, washed with 2.0 mL of EtOH and dried in vacuum.

**Typical experimental procedure for the synthesis of *o*-nitrodiimines 7.** To a clear solution of *o*-nitrobenzaldehyde **6** (6.0 mmol) in 2.0 mL of EtOH was added 3.0 mmol of (1*R*, 2*R*)-cyclohexane-1,2-diamine **4a** or (1*S*, 2*S*)-cyclohexane-1,2-diamine **4b**. The resulting clear reaction mixture was stirred for 4 h at rt to give *o*-nitrodiimines **7** as a yellow precipitate. The solid was filtered, washed with 2.0 mL of EtOH and dried under vacuum.

**Typical experimental procedure for the synthesis chiral bis-quinazolinediones derivatives 1 or 11.** $TiCl_4$ (0.9 mL, 8 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (1.2 g, 8 mmol) in freshly distilled anhydrous THF (10 mL) at rt under $N_2$ atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of *o*-hydroxydiimines **2a-2c** or **10** (2 mmol) and triphosgene **3** (11.8 g, 4 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under $N_2$ atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. After evaporation of the solvent under reduced pressure, the crude products **1** or **11** were purified by the flash column chromatography (PE-acetone = 5:1) to afford the pure product **1** or **11**.

**Typical experimental procedure for the synthesis of chiral bis-quinazolinediones derivatives 8.** $TiCl_4$ (1.8 mL, 16 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (2.4 g, 16 mmol) in freshly distilled anhydrous THF (10 mL) at rt under $N_2$ atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt and a solution of *o*-nitrodiimines **7** (2 mmol) and triphosgene **3** (4 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 3 h under $N_2$ atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous $Na_2SO_4$. After evaporation of the solvent under reduced pressure, the crude products **8** were purified by the flash column chromatography.

**(4*R*,18*R*)-1,2,3,4,4a,18a-Hexahydrobenzo[5,6][1,3]oxazino[3,4-*a*]benzo[5,6][1,3]oxazino[4,3-*c*]quinoxaline-6,17(11b*H*,11c*H*)-dione (1a)** White solid, yield 76%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda = 245$ nm], retention time: t = 6.300 min (retention time RAC $t_1 = 6.299$ min, $t_2 = 6.965$ min); $[\alpha]_D^{25}$ -142 (589 nm, c 0.017, EtOH); IR (KBr): *ν* 3021, 2936, 1729, 1718, 1618, 1595, 1490, 1437, 1421, 1343, 1317, 1277, 1208, 1146, 1113, 1096, 1054, 964, 945, 920, 765, 752, 688 cm$^{-1}$; $^1$H NMR ($CF_3CO_2D$, 400 MHz) $\delta$ (ppm): 7.25-7.24 (m, 1H, ArH), 7.13-7.12 (m, 2H, ArH), 6.96-6.95 (m, 1H, ArH), 6.72-6.57 (m, 3H, ArH), 6.37-6.36 (m, 1H, ArH), 5.29-5.20 (m, 2H, 2 × CH), 4.67-4.65 (m, 1H, CH), 3.27-3.25 (m, 1H, CH), 2.57-2.54 (m, 1H, CH-H), 2.29-2.28 (m, 1H, CH-H), 1.91-1.79 (m, 3H, 3 × CH-H), 1.62-1.28 (m, 3H, 3 × CH-H); $^{13}$C NMR (75 MHz, $CF_3CO_2D$) $\delta$ (ppm): 154.4, 154.2, 148.2, 147.7, 130.5, 129.9, 127.8, 127.1, 127.0, 125.2, 124.0, 116.0, 115.4, 114.4, 114.3, 112.6, 64.7, 63.8, 58.6, 54.4, 29.8, 27.1, 25.3, 23.6; HRMS: *m/z* calcd for $C_{20}H_{21}N_2O_4$ $[M+H]^+$ 377.1501, Found 377.1498.

**(4*S*,18*S*)-1,2,3,4,4a,18a-Hexahydrobenzo[5,6][1,3]oxazino[3,4-*a*]benzo[5,6][1,3]oxazino[4,3-*c*]quinoxaline-6,17(11b*H*,11c*H*)-dione (1b)** White solid, yield 78%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda = 245$ nm], retention time: t = 6.813 min (retention time RAC $t_1 = 6.299$ min, $t_2 = 6.965$ min); $[\alpha]_D^{25}$ +145 (589 nm, c 0.019, EtOH); IR (KBr): *ν* 2936, 1729, 1718, 1618, 1595, 1490, 1437, 1421, 1343, 1317, 1277, 1208, 1146, 1113, 1096, 1054, 964, 945, 920, 765, 752, 688 cm$^{-1}$; $^1$H NMR (DMSO, 400 MHz) $\delta$ (ppm): 7.33-7.25 (m, 2H, ArH), 7.11-7.01 (m, 2H, ArH), 6.90-6.78 (m, 2H, ArH), 6.32-6.30 (m, 1H, ArH), 6.21-6.19 (m, 1H, ArH), 5.49 (s, 1H, CH), 4.97 (s, 1H, CH), 3.96-3.95 (m, 1H, CH), 2.76-2.75 (m, 1H, CH), 2.99-2.96 (m, 1H, CH-H), 2.72-2.71 (m, 1H, CH-H), 1.99-1.95 (m, 1H, CH-H), 1.77-1.76 (m, 2H, 2 ×CH-H), 1.42-1.41 (m, 2H, 2 ×CH-H), 1.22-1.21 (m, 1H, CH-H); $^{13}$C NMR (75 MHz, DMSO) $\delta$ (ppm): 150.3, 149.3, 130.4, 130.3, 128.8, 123.7, 117.6, 115.3, 115.2, 64.8, 63.4, 62.0, 59.8, 32.7, 31.2, 28.6, 25.1; HRMS: *m/z* calcd for $C_{20}H_{21}N_2O_4$ $[M+H]^+$ 377.1501, Found 377.1505.

**(4*R*,18*R*)-10,13-dichloro-1,2,3,4,4a,18a-hexahydrobenzo[5,6][1,3]oxazino[3,4-*a*]benzo[5,6][1,3]oxazino[4,3-*c*]quinoxaline-6,17(11b*H*,11c*H*)-dione (1c)** White solid, yield 76%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda = 245$ nm], retention time: t = 4.382 min (retention time RAC $t_1 = 4.361$ min, $t_2 = 4.716$ min); $[\alpha]_D^{25}$ -142 (589 nm, c 0.019, EtOH); IR (KBr): *ν* 2943, 1725, 1718, 1618, 1595, 1490, 1437, 1423, 1343, 1317, 1273, 1208, 1146, 1115, 1054, 964, 945, 923, 771, 756, 688 cm$^{-1}$; $^1$H NMR ($CF_3CO_2D$, 400 MHz) $\delta$ (ppm): 7.21 (dd, $J_1 = 8.8$ Hz, $J_2 = 1.6$ Hz, 2H, ArH), 6.88 (d, $J = 8.4$ Hz, 2H, ArH), 6.06-6.05 (m, 2H, ArH), 4.57 (s, 2H, 2 × CH), 3.74-3.72 (m, 2H, 2 × CH), 3.98-3.95 (m, 2H, 2 × CH-H), 2.18-2.15 (m, 2H, 2 × CH-H), 1.81-1.79 (m, 2H, 2 × CH-H), 1.26-1.21 (m, 2H, 2 × CH-H); $^1$H

NMR ($CF_3CO_2D$, 75 MHz) *δ* (ppm): 152.8, 146.2, 130.8, 130.3, 127.7, 116.4, 66.6, 66.0, 28.8, 24.1; HRMS: *m/z* calcd for $C_{22}H_{18}Cl_2N_2O_4Na$ $[M+Na]^+$ 467.0541, Found 467.0556.

**(4*S*,18*S*)-10,13-Dichloro-1,2,3,4,4a,18a-hexahydrobenzo[5,6][1,3]oxazino[3,4-*a*]benzo[5,6][1,3]oxazino[4,3-*c*]quinoxaline-6,17(11b*H*,11c*H*)-dione (1d)** White solid, yield 71%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda$ = 245 nm], retention time: t = 4.732 min (retention time RAC $t_1$ = 4.361 min, $t_2$ = 4.716 min); $[\alpha]_D^{25}$ + 144 (589 nm, c 0.017, EtOH); IR (KBr): *v* 2922, 1729, 1718, 1618, 1595, 1453, 1437, 1424, 1343, 1317, 1275, 1208, 1146, 1113, 1096, 1054, 963, 945, 920, 756 cm$^{-1}$; $^1$H NMR ($CF_3COOD$, 400 MHz) *δ* (ppm): 7.19 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz, 2H, ArH), 6.86 (d, *J* = 8.8 Hz, 2H, ArH), 6.05-6.04 (m, 2H, ArH), 4.55 (s, 2H, 2 × CH), 3.73-3.70 (m, 2H, 2 × CH), 3.96-3.94 (m, 2H, 2 × CH-H), 2.17-2.13 (m, 2H, 2 × CH-H), 1.80-1.78 (m, 2H, 2 × CH-H), 1.25-1.22 (m, 2H, 2 ×CH-H); $^1$H NMR ($CF_3COOD$, 75 MHz) *δ* (ppm): 152.8, 146.2, 130.8, 130.3, 127.7, 116.4, 66.6, 65.9, 28.8, 24.1; HRMS: *m/z* calcd for $C_{22}H_{18}Cl_2N_2O_4Na$ $[M+Na]^+$ 467.0541, Found 467.0537.

**(4*R*,18*R*)-10,13-Dibromo-1,2,3,4,4a,18a-hexahydrobenzo[5,6][1,3]oxazino[3,4-*a*]benzo[5,6][1,3]oxazino[4,3-*c*]quinoxaline-6,17(11b*H*,11c*H*)-dione (1e)** White solid, yield 73%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda$ = 245 nm], retention time: t = 5.551 min (retention time RAC $t_1$ = 5.548 min, $t_2$ = 6.727 min); $[\alpha]_D^{25}$ -140 (589 nm, c 0.017 , EtOH); IR (KBr): *v* 2955, 1729, 1718, 1618, 1595, 1490, 1437, 1421, 1343, 1317, 1277, 1212, 1146, 1113, 1095, 1054, 964, 945, 925, 765, 752, 658 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz) *δ* (ppm): 7.55-7.54 (m, 2H, ArH), 7.09-7.08 (m, 2H, ArH), 6.45-6.44 (m, 2H, ArH), 5.02 (s, 2H, 2 × CH), 3.69 (s, 2H, 2 × CH), 2.98-2.97 (m, 2H, 2 × CH-H), 1.98-1.97 (m, 2H, 2 × CH-H), 1.77-1.76 (m, 2H, 2 × CH-H), 1.20-1.19 (m, 2H, 2 × CH-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) *δ* (ppm): 151.5, 150.7, 135.5, 133.6, 121.1, 119.7, 117.1, 66.5, 66.0, 33.3, 30.7, 27.2; HRMS: *m/z* calcd for $C_{22}H_{18}Br_2N_2O_4Na$ $[M+Na]^+$ 554.9531, Found 554.9545.

**(4*S*,18*S*)-10,13-Dibromo-1,2,3,4,4a,18a-hexahydrobenzo[5,6][1,3]oxazino[3,4-*a*]benzo[5,6][1,3]oxazino[4,3-*c*]quinoxaline-6,17(11b*H*,11c*H*)-dione (1f)** White solid, yield 72%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda$ = 245 nm], retention time: t = 6.773 min (retention time RAC $t_1$ = 5.548 min, $t_2$ = 6.727 min); $[\alpha]_D^{25}$ +143 (589 nm, c 0.018, EtOH); IR (KBr): *v* 2953, 1729, 1718, 1618, 1595, 1490, 1433, 1421, 1343, 1317, 1277, 1208, 1146, 1113, 1093, 1054, 964, 945, 923, 734, 731, 681 cm$^{-1}$; $^1$H NMR ($CF_3COOD$-$d_1$, 400 MHz) *δ* (ppm): 6.99-6.94 (m, 4H, ArH), 5.94-5.93 (m, 2H, ArH), 4.67 (s, 2H, 2 × CH), 3.82-3.81 (m, 2H, 2 × CH), 3.05-3.04 (m, 2H, 2 × CH-H), 2.26-2.24 (m, 2H, 2 × CH-H), 1.90-1.89 (m, 2H, 2 × CH-H), 1.38-1.34 (m, 2H, 2 × CH-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) *δ* (ppm):

151.6, 150.3, 132.5, 130.6, 129.5, 120.8, 119.8, 66.5, 66.0, 33.3, 30.7, 27.2; HRMS: *m/z* calcd for $C_{22}H_{18}Br_2N_2O_4Na$ [M+Na]$^+$ 554.9531, Found 554.9531.

**(4*R*,18*R*)-1,2,3,4,4a,11c,16,18a-Octahydroquinoxalino[1,2-*c*:4,3-*c*']diquinazoline-6-17(7*H*,11b*H*)-dione (8a)** White solid, yield 73%; mp > 300°C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda$ = 245 nm], retention time: t = 5.231 min (retention time RAC $t_1$ = 5.234 min, $t_2$ = 6.712 min); $[\alpha]_D^{25}$-240 (589 nm, c 0.019, EtOH); IR (KBr): *ν* 3410, 3321, 3012, 2931, 1729, 1718, 1618, 1595, 1490, 1431, 1421, 1343, 1317, 1217, 1208, 1146, 1113, 1096, 1051, 964, 945, 910, 765, 751, 682 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz) *δ* (ppm): 9.25 (s, 1H, NH), 8.91 (s, 1H, NH), 7.25-7.24 (m, 1H, ArH), 6.97-6.96 (m, 1H, ArH), 6.83-6.82 (m, 2H, ArH), 6.52-6.32 (m, 4H, ArH), 5.21 (s, 1H, CH), 5.07 (s, 1H, CH), 4.65-4.64 (m, 1H, CH), 3.06-3.05 (m, 1H, CH), 2.88-2.60 (m, 2H, 2 × CH-H), 1.76-1.60 (m, 4H, 4 × CH-H), 1.34-1.32 (m, 2H, 2 × CH-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) *δ* (ppm): 159.8, 158.5, 142.7, 142.4, 134.4, 133.8, 133.7, 133.3, 126.0, 124.7, 121.8, 121.2, 118.7, 118.1, 72.2, 67.6, 60.6, 59.2, 37.0, 36.4, 34.0, 31.9, 30.5; HRMS: *m/z* calcd for $C_{22}H_{22}N_4O_2Na$ [M+Na]$^+$ 397.1640, Found 397. 1647.

**(4*S*,18*S*)-1,2,3,4,4a,11c,16,18a-Octahydroquinoxalino[1,2-*c*:4,3-*c*']diquinazoline-6,17(7*H*,11b*H*)-dione (8b)** White solid, yield 72%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak OJ-RH (0.46 cm × 25 cm), MeOH / $H_2O$ (80 : 20), flow rate : 1.0 mL·min$^{-1}$, $\lambda$ = 245 nm], retention time: t = 6.707 min (retention time RAC $t_1$ = 5.234 min, $t_2$ = 6.712 min); $[\alpha]_D^{25}$ + 237 (589 nm, c 0.017, EtOH); IR (KBr): *ν* 3410, 3329, 2936, 1729, 1718, 1618, 1597, 1490, 1437, 1421, 1343, 1317, 1277, 1208, 1145, 1117, 1096, 1054, 964, 945, 970, 767, 752, 678 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz) *δ* (ppm): 9.22 (s, 1H, NH), 8.89 (s, 1H, NH), 7.25 (d, *J* = 7.6 Hz, 1H, ArH), 6.96 (t, *J* =7 .6 Hz, 1H, ArH), 6.85-6.80 (m, 2H, ArH), 6.51 (d, *J*=8.0 Hz, 1H, ArH), 6.41 (d, *J* = 8.0 Hz, 1H, ArH), 6.34-6.28 (m, 2H, ArH), 5.22 (d, *J* = 7.2 Hz, 1H, CH), 5.06 (d, *J* = 7.6 Hz, 1H, CH), 4.68-4.64 (m, 1H, CH), 3.09-3.03 (m, 1H, CH), 2.67-2.58 (m, 1H, CH-H), 2.11-2.10 (m, 1H, CH-H), 1.81-1.74 (m, 2H, 2 × CH-H), 1.62-1.60 (m, 2H, 2 × CH-H), 1.40-1.28 (m, 2H, 2 × CH-H); HRMS: *m/z* calcd for $C_{22}H_{22}N_4O_2Na$ [M+Na]$^+$ 397.1640, Found 397.1649.

**(15*R*,19*R*)-15a,16,17,18,19,19a-Hexahydronaphtho[1',2':5,6][1,3]oxazino[3,4-*a*]naphtho[1',2':5,6][1,3]oxazino[4,3-*c*]quinoxaline-14,21(6c*H*,6d*H*)-dione (11a)** White solid, yield 85%; mp > 300 °C; *de* > 99.9%, the *de* were determined by HPLC [Daicel Chiralpak AD-H, hexane/*i*-PrOH (85 : 15), flow rate: 1.0 mL·min$^{-1}$, $\lambda$ = 210 nm], t = 13.585 (retention time RAC $t_1$ = 13.593 min, $t_2$ = 33.632 min); $[\alpha]_D^{25}$ -437 (589 nm, c 0.020, EtOH); IR (KBr): *ν* 3445, 2931, 2348, 1728, 1450, 1208, 814 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) *δ* (ppm): 7.58 (d, *J* = 8.8 Hz, 2H, ArH), 7.32 (d, *J* = 8.4 Hz, 2H, ArH), 7.14 (d, *J* = 8.8 Hz, 2H, ArH), 6.96-6.89 (m, 4H, ArH), 6.80-6.76 (m, 2H, ArH), 5.81 (s, 2H, 2 × CH), 4.07-4.04 (m, 1H, CH), 3.18-3.15 (m, 1H, CH), 1.98-1.95 (m, 2H, 2 × CH-H), 1.79-1.78 (m, 2H, 2 × CH-H), 1.25-1.15 (m, 3H, 3

× CH-H), 1.78-1.70 (m, 1H, CH); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 150.5, 147.8, 131.2, 129.7, 129.6, 127.9, 126.2, 124.6, 121.3, 115.2, 111.1, 64.1, 62.6, 28.6, 25.3; HRMS: *m/z* calcd for $C_{30}H_{24}N_2O_4Na$ [M+Na]$^+$ 499.1634, Found 499.1637.

**(15*S*,19*S*)-15a,16,17,18,19,19a-Hexahydronaphtho[1',2':5,6][1,3]oxazino[3,4-*a*]naphtho[1',2':5,6][1,3]-oxazino[4,3-*c*]quinoxaline-14,21(6c*H*,6d*H*)-dione (11b)** White solid, yield 83%; mp > 300 °C; *de* 96%, the *de* were determined by HPLC [Daicel Chiralpak AD-H, hexane/*i*-PrOH (85 : 15) , flow rate: 1.0 mL·min$^{-1}$, $\lambda$ = 210 nm]; $t_{major}$ = 13.639, $t_{minor}$ = 32.382 (retention time RAC $t_1$ = 13.593 min, $t_2$ = 33.632 min) $[\alpha]_D^{25}$ +434 (589 nm, c 0.020, EtOH); IR (KBr) $v$: 3455, 2918, 1729, 1453, 1209, 1056, 814, 594 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 7.46 (d, *J* = 8.8 Hz, 2H, ArH), 7.19 (d, *J* = 8.0 Hz, 2H, ArH), 7.01 (d, *J* = 8.8 Hz, 2H, ArH), 6.84-6.77 (m, 4H, ArH), 6.68-6.64 (m, 2H, ArH), 5.69 (s, 2H, 2 × CH), 3.95-3.92 (m, 1H, CH), 3.05-3.03 (m, 1H, CH), 1.87-1.83 (m, 2H, 2 × CH-H) 1.66-1.65 (m, 2H, 2 × CH-H), 1.11-1.04 (m, 3H, 3 × CH-H), 0.88-0.85 (m, 1H, CH-H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 150.5, 147.8, 131.1, 129.7, 129.6, 127.9, 126.2, 124.5, 121.3, 115.2, 111.1, 64.1, 62.6, 28.6, 25.3; HRMS: *m/z* calcd for $C_{30}H_{24}N_2O_4Na$ [M+Na]$^+$ 499.1634, Found 499.1652.

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