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# Application of asymmetric alkylation of malonic diester with phase-transfer catalysis: synthesis of LFA-1 antagonist BIRT-377

Takuya Kanemitsu, Saeka Furukoshi, Michiko Miyazaki, Kazuhiro Nagata, Takashi Itoh *

*School of Pharmacy, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan*

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ABSTRACT

An efficient asymmetric synthesis of LFA-1 antagonist BIRT-377 using enantioselective phase-transfer catalytic alkylation has been developed. The alkylation of α-monosubstituted *tert*-butyl methyl malonate was catalyzed by a quaternary ammonium salt derived from a cinchona alkaloid to obtain the product with a quaternary stereogenic carbon in high yield and with high enantioselectivity. The chiral α,α-disubstituted product thus obtained was transformed into BIRT-377 through alternating chemoselective deprotection of the two ester groups followed by Curtius rearrangement.



## 1. Introduction

Phase-transfer catalysis is regarded as one of the most efficient synthesis methods in organic chemistry, since it is both inexpensive and relatively environmentally benign.[1] The development of asymmetric phase-transfer catalysis has attracted much attention for the construction of quaternary stereogenic carbon centers because the resulting products are versatile precursors for the synthesis of various compounds.[2] The phase-transfer catalytic α-alkylation of carbonyl compounds has been extensively studied, and several powerful methods have been developed.[3] Recently, we have reported one such development for the asymmetric synthesis of malonic esters using cinchona alkaloid derivatives as inexpensive phase-transfer catalysts.[4] This method provides access to α,α-disubstituted malonic diesters containing an all-carbon substituted quaternary stereocenter. The chiral α,α-disubstituted malonic diesters thus obtained have been used to synthesize α,α-disubstituted amino acids. It should be noted that in this transformation, both (*S*)- and (*R*)-α,α-disubstituted amino acids have been prepared from the same stereoisomer using selective de-esterification. Therefore, the chiral α,α-disubstituted malonates are important intermediates in the synthesis of biologically active compounds. Nevertheless, there are few other reports of enantioselective catalytic additions at the α-position of malonates, and few synthetic methods have been disclosed.[5] Over the course of our research on phase-transfer catalysis, we predicted that it would be applicable to the synthesis of BIRT-377 **1**, a lymphocyte function associated antigen-1 (LFA-1) antagonist.

BIRT-377 is an inhibitor of the interaction between LFA-1 and intercellular adhesion molecule-1 (ICAM-1) under cell-cell interactions of the immune system. ICAM-1 and LFA-1 are involved in the binding of lymphocytes to the antigen-presenting cells or to the vascular endothelial cells.[6] In this context, the development of effective synthetic methods for BIRT-377 has attracted much attention for the treatment of inflammatory and immune disorders.[7] Among them, asymmetric syntheses using organocatalysts have afforded promising results. Barbas et al. developed the first catalytic asymmetric synthesis of BIRT-377.[7d] The quaternary stereocenter was constructed through L-proline–tetrazole-catalyzed direct enantioselective α-amination. Maruoka et al. synthesized BIRT-377 through enantioselective phase-transfer alkylation of an alanine-derived Schiff base.[7e,g] Over the course of our studies, we envisioned that an approach to BIRT-377 could be accomplished by the construction of an α,α-disubstituted malonate (Scheme 1). Herein, we report the efficient asymmetric synthesis of BIRT-377 via phase-transfer catalytic alkylation of α-monosubstituted *tert*-butyl methyl malonate in the presence of *N*-(9-anthracenylmethyl)cinchoninium chloride as an inexpensive phase-transfer catalyst.

## 2. Results and discussion

We predicted that both (*R*)- and (*S*)-α,α-disubstituted malonic diesters could be converted into the target molecule through the chemoselective de-esterification of the *tert*-butyl or methyl ester (Scheme 1). *tert*-Butyl and methyl esters are simple protecting groups that can be readily cleaved chemoselectively under acidic and alkaline conditions, respectively. Thus, we initially prepared the *tert*-butyl methyl α-monoalkylated malonates **3** and **4**

* Corresponding author. Tel.: +81 3 3784 8184; fax: +81 3 3784 5982.
*E-mail address:* itoh-t@pharm.showa-u.ac.jp (T. Itoh).

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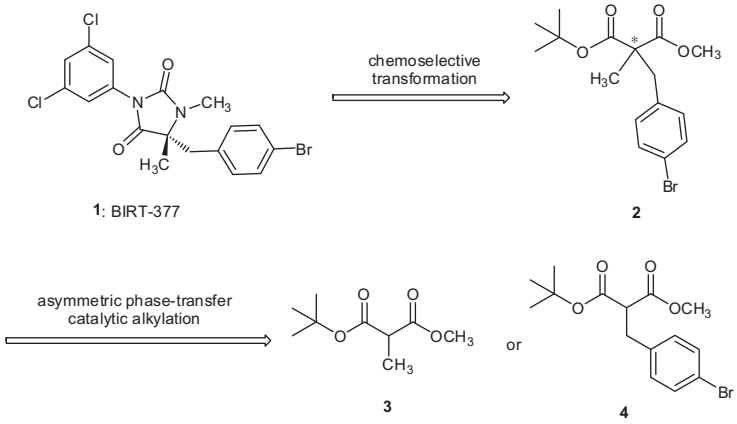
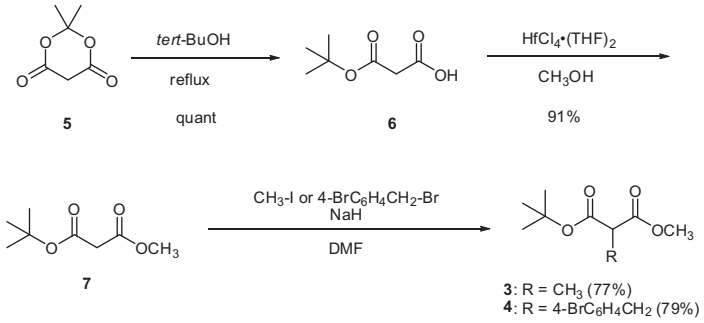


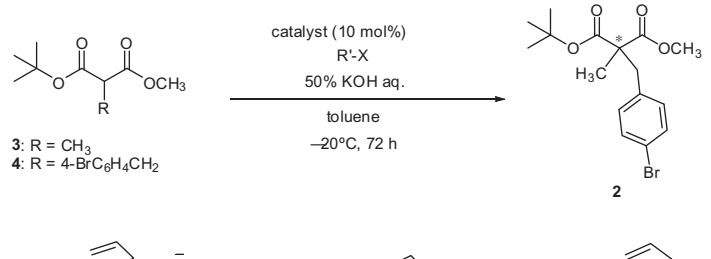

**Scheme 1.** Retrosynthetic analysis of BIRT-377.

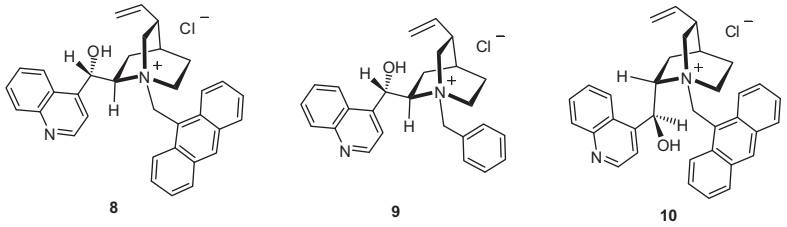



**Scheme 2.** Synthesis of α-monoalkyl *tert*-butyl methyl malonates **3** and **4**.

(Scheme 2). *tert*-Butyl malonate **6** was prepared from Meldrum's acid **5** through solvolysis by *tert*-butanol in quantitative yield. The subsequent esterification was catalyzed by a hafnium(IV) salt[8] to afford *tert*-butyl methyl malonate **7** in 91% yield. Malonate **7** was then alkylated with methyl iodide or 4-bromobenzyl bromide under basic conditions to afford α-monoalkyl *tert*-butyl methyl

**Table 1**
Substrate and catalyst screening for preparation of α,α-dialkyl *tert*-butyl methyl malonate **2**




| Entry[a] | Substrate | Catalyst | R′-X | Yield[b] (%) | ee[c] (%) | Configuration |
|---|---|---|---|---|---|---|
| 1 | **3** | **8** | 4-$BrC_6H_4CH_2$-Br | 94 | 76 | (*S*) |
| 2 | **4** | **8** | $CH_3$-I | 91 | 89 | (*R*) |
| 3 | **4** | **9** | $CH_3$-I | 72 | 27 | (*R*) |
| 4 | **4** | **10** | $CH_3$-I | 79 | 37 | (*S*) |

[a] The reaction was performed with α-monoalkyl *tert*-butyl methyl malonate (**3** or **4**), R′-X, catalyst, and 50% KOH aq at −20 °C for 72 h.
[b] Isolated yields.
[c] Determined by chiral HPLC.

malonates **3** or **4** in 77% or 81% yield, respectively. The α-monoalkyl malonates **3** and **4** were then used as substrates for the asymmetric alkylation reaction in order to evaluate the performance of the catalysts.

In order to obtain the enantioenriched α,α-disubstituted malonic diester **2**, we screened several substrates and catalysts (Table 1). The alkylation of α-methyl malonate **3** or α-4-bromobenzyl malonate **4** was carried out under the phase-transfer conditions previously reported.[4] Malonate **3** or **4** was treated with alkyl halide, 50% KOH, and the representative cinchona alkaloid derivatives **8**–**10** at −20 °C in toluene. α-Methyl malonate **3** with *N*-(9-anthracenylmethyl)cinchoninium chloride **8** afforded α,α-disubstituted malonic diester **2** with the (*S*)-enantiomer in excess in high chemical yield, but the enantioselectivity was unsatisfactory (Table 1, entry 1). In the case of α-4-bromobenzyl malonate **4** using catalyst **8**, the (*R*)-isomer was obtained in high chemical yield with high enantioselectivity (Table 1, entry 2). However, *N*-benzylcinchoninium chloride **9** afforded a moderate chemical yield and low enantioselectivity (Table 1, entry 3). *N*-(9-Anthracenylmethyl) cinchonidinium chloride **10** was also obtained in moderate yield and low enantioselectivity (Table 1, entries 4). As anticipated, catalyst **10**, a pseudo-enantiomer of catalyst **8**, led to the formation of the (*S*)-enantiomer in excess. According to these experiments, the best result was obtained when using a combination of α-4-bromobenzyl malonate **4** as the substrate and compound **8** as the catalyst. Although we have attempted to obtain enantiopure α,α-disubstituted malonic diester **2** by recrystallization, the access was limited in our hands. Thus, we decided to use the 89% ee of α-4-bromophenyl methyl malonate **2** for the asymmetric synthesis of BIRT-377 (Scheme 3).

Next, we investigated the synthetic route to BIRT-377 from **2**. The *tert*-butyl ester of α,α-disubstituted malonic diester **2** was chemoselectively cleaved by TFA to afford carboxylic acid **11** in quantitative yield. Next, a one-pot Curtius rearrangement followed by 3,5-dichloroaniline introduction, accompanied by a ring closure, was accomplished for the synthesis of hydantoin **12** in high yield, i.e., carboxylic acid **11** was converted into the isocyanate through Curtius rearrangement using diphenylphosphoryl azide (DPPA)[9] in the presence of triethylamine, followed by urea formation with 3,5-dichloroaniline and ring closure through an ester-amide exchange reaction to afford hydantoin **12** in 75% yield. Subsequent N-methylation of the hydantoin **12** was carried out with lithium bis(trimethylsilyl)amide and methyl iodide to obtain BIRT-377 **1** in 89% yield. The confirmation of the stereochemistry of **1** was accomplished by comparison of the specific rotation with the literature value.[7g]

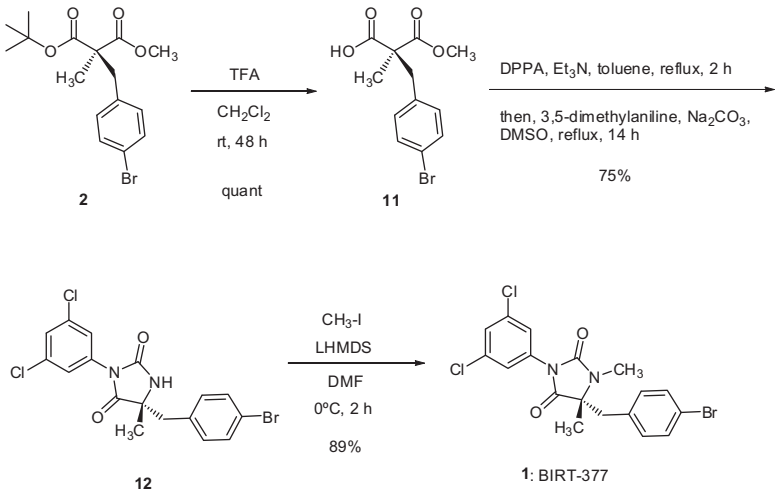
## 3. Conclusion

In conclusion, we have described an efficient asymmetric synthesis of LFA-1 antagonist BIRT-377 using enantioselective phase-transfer catalytic alkylation. Methylation of α-4-bromobenzyl *tert*-butyl methyl malonate in the presence of *N*-(9-anthracenylmethyl)cinchoninium chloride afforded the product with a quaternary stereogenic carbon in high yield and with high enantioselectivity. The α,α-disubstituted product thus obtained was transformed into BIRT-377 through alternating chemoselective transformation of the two ester groups. Over the course of these studies, a one-pot Curtius rearrangement/3,5-dichloroaniline introduction/ring closing method for synthesis of hydantoin was developed.

## 4. Experimental

### 4.1. General

All materials were purchased from commercial suppliers and used without further purification. Progress of the reactions was monitored by thin layer chromatography (TLC) performed on Merck Art. 5715 Kieselgel 60 $F_{254}$/0.25 mm thickness plates. Visualization was accomplished with UV light and cerium sulfate-ammonium molybdate solution followed by heating. Column chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica Gel 60 N (100–210 μm). $^1$H and $^{13}$C NMR spectra were recorded with JEOL JNM AL-400 instrument (400 MHz for $^1$H and 100 MHz for $^{13}$C) or JEOL JMN ECA-500 instrument (500 MHz for $^1$H and 125 MHz for $^{13}$C) in deuterated solvent, using tetramethylsilane ($\delta$ = 0.0 ppm in $^1$H NMR spectra) and $CDCl_3$ ($\delta$ = 77.0 ppm in $^{13}$C NMR spectra) as internal standards. $^1$H data are reported as follows: chemical shift ($\delta$ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet) and coupling constant ($J$ in Hz). Optical rotations were measured on a JASCO P1020 polarimeter operating at the sodium D line at room temperature. Concentration is given in g/100 mL. The HPLC analyses were performed with Shimadzu equipment (210 $\lambda$ absorbance Detector) using Chiralcel OD column with hexane/ethyl alcohol mixture Daicel Chemical Industries, LTD. The HPLC method was calibrated with the corresponding racemic




**Scheme 3.** Synthesis of BIPT-377 1.

mixture. High-resolution mass spectra (HRMS) were measured with JEOL JMS-MS700V using *p*-nitrobenzyl alcohol as a matrix. The known compounds have been identified by comparison of spectral data with those reported. The absolute configurations of the optically active compounds were determined on the basis of the measured specific rotation compared with literature values.

### 4.2. 1-*tert*-Butyl malonate 6

A 200 mL round-bottom flask equipped with a stirring bar was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione **5** (Meldrum's acid, 5.0 g, 34.7 mmol) and *tert*-butyl alcohol (40 mL). The reaction was allowed to stir for 6 h at reflux conditions. The reaction mixture was concentrated in vacuo to afford the desired product **6** (5.56 g, 100%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.51 (br s, $^1$H), 3.35 (s, 2H), 1.42 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.8, 166.3, 81.9, 42.1, 27.9; HR-FAB MS calcd for $C_7H_{13}O_4$ $[M+H]^+$ 161.0814, found 161.0809.

### 4.3. 1-*tert*-Butyl 3-methyl malonate 7

A 200 mL round-bottom flask equipped with a stirring bar was charged with compound **6** (3.0 g, 18.7 mmol) and methyl alcohol (70 mL). To the solution, hafnium(IV) chloride tetrahydrofuran complex (1:2) (88 mg, 0.19 mmol) was added. The reaction was allowed to stir for 2 days at room temperature. To the reaction mixture, brine was added and extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by silica gel column chromatography (hexanes/AcOEt = 50:50) to afford the desired product **7** (3.0 g, 91%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.74 (s, 3H), 3.30 (s, 2H), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 165.8, 82.1, 52.3, 42.7, 27.9; HR-FAB MS calcd for $C_8H_{15}O_4$ $[M+H]^+$ 175.0883, found 175.0875.

### 4.4. 1-*tert*-Butyl 3-methyl 2-methylmalonate 3

A 100 mL round-bottom flask equipped with a stirring bar was charged with compound **7** (1920 mg, 11.0 mmol) and DMF (25 mL). To the solution, sodium hydride (60% oil suspension, 446 mg, 11.0 mmol) was added. The reaction was allowed to stir at 0 °C for 30 h. To the mixture, methyl iodide (670 μL, 11.0 mmol) was added at 0 °C and the mixture was stirred at room temperature for 18 h. To the reaction mixture, $H_2O$ was added, and the mixture was extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by silica gel column chromatography (hexanes/AcOEt = 90:10) to afford the desired product **3** (1597 mg, 77%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.73 (s, 3H), 3.35 (q, $J$ = 7.3 Hz, 1H), 1.46 (s, 9H), 1.38 (d, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.9, 169.2, 81.6, 52.2, 47.0, 27.8, 13.5.

### 4.5. 1-*tert*-Butyl 3-methyl 2-(4-bromobenzyl)malonate 4

A 100 mL round-bottom flask equipped with a stirring bar was charged with compound **7** (1000 mg, 5.8 mmol) and DMF (20 mL). To the solution, sodium hydride (60% oil suspension, 233 mg, 5.8 mmol) was added. The reaction was allowed to stir at 0 °C for 1 h. To the mixture, 4-bromobenzyl bromide (1437 mg, 5.8 mmol) was added at 0 °C and the mixture was stirred at room temperature for 20 h. To the reaction mixture, $H_2O$ was added, and the mixture was extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by silica gel column chromatography (hexanes/AcOEt = 90:10) to afford the desired product **4** (1551 mg, 79%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (d, $J$ = 8.3 Hz, 2H), 7.08 (d, $J$ = 8.3 Hz, 2H), 3.70 (s, 3H), 3.53 (t, $J$ = 7.8 Hz, 1H), 3.13 (d, $J$ = 7.8 Hz, 2H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.4, 167.5, 137.0, 131.5, 130.6, 120.5, 83.2, 54.3, 52.4, 34.0, 27.8; HR-FAB MS calcd for $C_{15}H_{20}BrO_4$ $[M+H]^+$ 343.0545, found 343.0558.

### 4.6. Optimized procedure for asymmetric synthesis of methyl 1-*tert*-butyl 3-methyl 2-(4-bromobenzyl)-2-malonate 2

A 50 mL round-bottom flask equipped with a stirring bar was charged with compound **4** (430 mg, 1.25 mmol), catalyst **8** (65 mg, 0.125 mmol), and toluene (12.5 mL), and the apparatus was cooled to −20 °C. To the mixture, methyl iodide (390 μL, 6.26 mmol) and 50% KOH aq (2.5 mL) were added and the mixture was stirred vigorously at −20 °C for 72 h, after which the reaction mixture was neutralized with 1 M HCl and poured into an extraction funnel. The mixture was extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by silica gel column chromatography (hexanes/AcOEt = 90:10) to afford the desired product **2** (407 mg, 91%) as a white solid. The ee value of the product was determined by chiral-phase HPLC analysis. mp 48–50 °C; $[\alpha]_D^{20}$ = −2.5 (*c* 1.6, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (d, $J$ = 8.5 Hz, 2H), 7.14 (d, $J$ = 8.3 Hz, 2H), 3.72 (s, 3H), 3.17 (d, $J$ = 13.7 Hz, 1H), 3.10 (d, $J$ = 13.9 Hz, 1H), 1.44 (s, 9H), 1.29 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 170.7, 135.4, 131.9, 131.2, 120.9, 81.9, 55.2, 52.3, 40.4, 27.8, 19.7; HR-FAB MS calcd for $C_{16}H_{22}BrO_4$ $[M+H]^+$ 357.0701, found 357.0721; Enantiomeric excess: 89%; HPLC (Daicel Chiralcel OD, hexane/EtOH 500:1, flow rate 0.5 mL/min, λ = 210 nm): major isomer: $t_R$ = 16.0 min; minor isomer: $t_R$ = 17.5 min.

### 4.7. Methyl (*R*)-1-methyl 2-(4-bromobenzyl)-2-malonate 11

A 50 mL round-bottom flask equipped with a stirring bar was charged with compound **2** (300 mg, 0.84 mmol) and $CH_2Cl_2$ (5 mL). To the mixture, TFA (250 μL) was added and the mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo. The remaining residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH/AcOH = 50:50:1) to afford the desired product **11** (253 mg, 100%) as a white solid. mp 86–88 °C; $[\alpha]_D^{22}$ = +0.7 (*c* 3.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.09 (br s, 1H), 7.40 (d, $J$ = 8.3 Hz, 2H), 7.03 (d, $J$ = 8.5 Hz, 2H), 3.76 (s, 3H), 3.26 (d, $J$ = 13.9 Hz, 1H), 3.15 (d, $J$ = 13.9 Hz, 1H), 1.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.3, 171.9, 134.6, 131.8, 131.4, 121.2, 54.7, 52.8, 40.6, 19.8; HR-FAB MS calcd for $C_{12}H_{14}BrO_4$ $[M+H]^+$ 301.0075, found 301.0100.

### 4.8. (*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methylimidazolidine-2,4-dione 12

A 50 mL round-bottom flask equipped with a stirring bar was charged with compound **11** (93 mg, 0.31 mmol) and toluene (6 mL). To the solution, triethylamine (65 μL, 0.47 mmol) and DPPA (100 μL, 0.46 mmol) were added. The reaction was allowed under reflux conditions. After 2 h, 3,5-dichloroaniline (75 mg, 0.46 mmol) was added and the mixture was stirred at reflux for 8 h. To the mixture, $Na_2CO_3$ (66 mg, 0.62 mmol) and DMSO (6 mL) were added and the mixture was stirred at reflux for 6 h. To the reaction mixture, brine was added, and the mixture was extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by silica gel column chromatography (hexanes/AcOEt = 60:40) to afford the desired product **12** (99 mg, 75%) as colorless syrup. $[\alpha]_D^{21}$ = +107.3 (*c* 2.7, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 8.3 Hz, 2H), 7.34 (t, $J$ = 1.8 Hz, 1H), 7.06 (d, $J$ = 8.3 Hz, 2H), 7.01 (d, $J$ = 2.0 Hz, 2H), 5.89 (s, 1H), 3.14 (d, $J$ = 13.7 Hz, 1H), 2.91 (d, $J$ = 13.7 Hz, 1H), 1.61 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.0, 154.0, 135.2, 132.9, 132.7, 131.9,

131.7, 128.5, 124.5, 122.1, 62.5, 43.7, 23.5; HR-FAB MS calcd for $C_{17}H_{14}BrCl_2N_2O_2$ $[M+H]^+$ 426.9616, found 426.9648; enantiomeric excess: 89%; HPLC (Daicel Chiralpak AD-H, hexane/EtOH 9:1, flow rate 1.0 mL/min, $\lambda$ = 210 nm): major isomer: $t_R$ = 11.6 min; minor isomer: $t_R$ = 5.8 min.

### 4.9. (*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1, 5-dimethyl-imidazolidine-2,4-dione 1: BIRT-377

A 50 mL round-bottom flask equipped with a stirring bar was charged with compound **12** (45 mg, 0.11 mmol) and DMF (2 mL). To the solution, LHMDS (1.0 M in THF, 160 μL, 0.16 mmol) was added and the mixture was stirred at 0 °C for 1 h. To the mixture, methyl iodide (13 μL, 0.21 mmol) was added and the reaction was stirred at room temperature. After 2 h, $H_2O$ was added, and the mixture was extracted with $CH_2Cl_2$ (3×), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by silica gel column chromatography (hexanes/$CH_2Cl_2$ = 50:50 → 0:100) to afford the desired product **1** (41 mg, 89%) as colorless syrup; $[\alpha]_D^{21}$ = +115.6 (*c* 1.4, $CHCl_3$) {Ref., $[\alpha]_D^{22}$ = +132.4 (*c* 1.02, $CHCl_3$)[7g]}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42 (d, *J* = 8.5 Hz, 2H), 7.29 (t, *J* = 2.0 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 2.0 Hz, 2H), 3.09 (d, *J* = 14.1 Hz, 1H), 3.06 (s, 3H), 2.97 (d, *J* = 14.1 Hz, 1H), 1.62 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.3, 153.4, 135.0, 133.0, 132.8, 131.8, 131.1, 128.3, 124.5, 122.0, 65.7, 40.7, 25.3, 21.0; HR-FAB MS calcd for $C_{18}H_{16}BrCl_2N_2O_2$ $[M+H]^+$ 440.9772, found 440.9780; enantiomeric excess: 89%; HPLC (Daicel Chiralpak AD-H, hexane/2-PrOH 95:5, flow rate 1.0 mL/min, $\lambda$ = 210 nm): major isomer: $t_R$ = 14.4 min; minor isomer: $t_R$ = 12.0 min.

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