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Stereodivergent synthesis of the LFA-1 antagonist BIRT-377 by porcine liver esterase desymmetrization and Curtius rearrangement†

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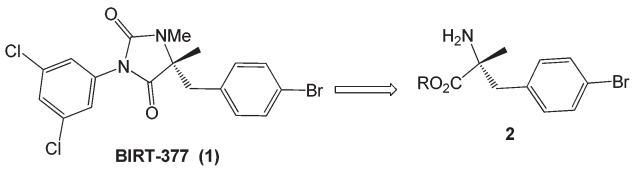
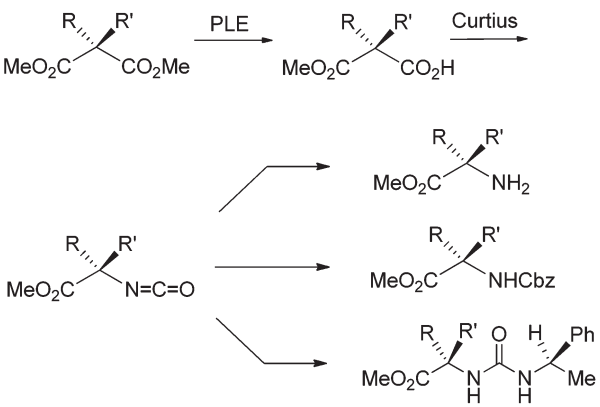
The LFA-1 inhibitor and leukocyte adhesion suppressor BIRT-377 was prepared in high enantiomeric excess by desymmetrization of dimethyl 2-*p*-bromobenzyl-2-methylmalonate, followed by condensation of the resulting carboxylic acid with 3,5-dichloroaniline, saponification of the remaining ester and Curtius rearrangement as the key steps. When Curtius rearrangement preceded the condensation step, (*ent*)-BIRT-377 was similarly obtained in high ee.

Introduction

Binding of the ligand ICAM-1 to the antigen LFA-1 mediates leukocyte adhesion, which is implicated in a number of key immunological processes. The hydantoin BIRT-377 (**1**) suppresses leukocyte adhesion by selectively inhibiting LFA-1, thus providing a potential therapy for certain immune disorders, as well as serving as an anti-inflammatory agent.[1,2] Despite the relative structural simplicity of **1**, the enantioselective formation of its quaternary stereocenter poses a significant challenge.[3] This has been previously addressed by means of chiral oxazolidinone intermediates,[3a,h,k] *via* alkylation of a bislactim derived from D-valine and alanine[3d] and the use of chiral imidazolidinone intermediates.[3g,i,j] Other methods employed chiral phase transfer catalysts in enolate alkylations,[3b,c] a chiral aziridine intermediate[3e] and an organocatalytic amination procedure.[3f] We considered that a possible new approach might be *via* appropriate derivatives of the corresponding α,α-disubstituted amino acid **2** (Scheme 1), since a number of methods are available for the preparation of such compounds.[4] We recently reported[5] that the use of porcine liver esterase (PLE)-mediated desymmetrization of α,α-dialkylated malonate diesters,[6] followed by stereospecific Curtius rearrangement,[7] provides an enantioselective approach to α-quaternary amino acids, as well as their Cbz and urea derivatives (Scheme 2). This method often delivers the products with high enantiomeric excesses and the active site model of PLE proposed by Jones *et al.*,[6b] as well as analogy with previously reported examples,[5,6,8,9] enables the prediction



Scheme 1



Scheme 2

of absolute configuration of the product with a reasonable degree of certainty. However, PLE consists of several isozymes with different activities and substrate specificities.[10] Some variation in the properties of different batches of commercial PLE can therefore be expected if they have nonidentical isozyme composition. The cosolvent also plays an important role in determining the degree of enantioselectivity.[11] An earlier vari-

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ation of this protocol provided a highly enantioselective synthesis of the antiviral agent (−)-virantmycin and its (+)-enantiomer.[9] We now report the application of sequential PLE desymmetrization and Curtius rearrangement to a stereodivergent synthesis of BIRT-377.

Results and discussion

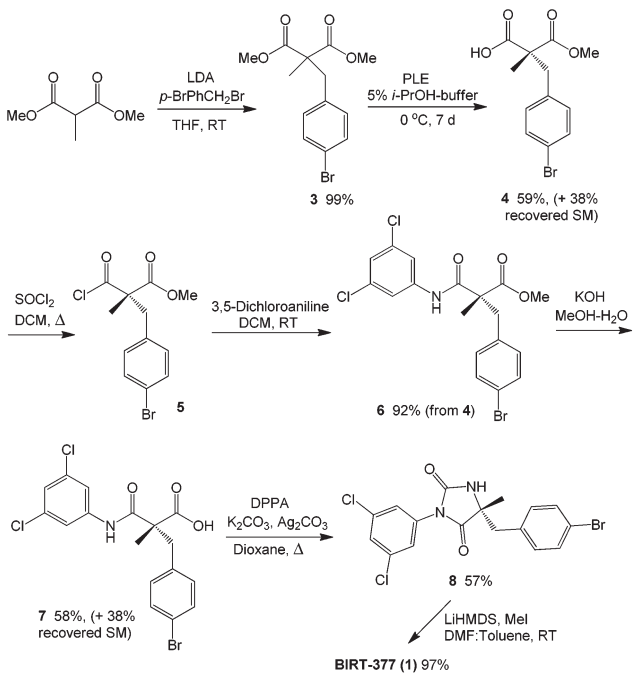
Our synthetic approach to BIRT-377 is shown in Scheme 3. Commercially available dimethyl 2-methylmalonate was alkylated with *p*-bromobenzyl bromide to afford the achiral quaternary malonate diester **3**. In earlier studies, Björkling *et al.*[6f] had observed that dimethyl 2-benzyl-2-methylmalonate afforded a very low ee of only 16% with PLE. However, we later noted that the ee increased considerably to 80% when the 2-benzyl substituent was homologated to the corresponding 2-(2-phenethyl) group.[5] This suggested that the increased size of the phenethyl substituent resulted in tighter binding to the large hydrophobic pocket of PLE in the Jones model.[6b] Similarly, we reasoned that the larger *p*-bromobenzyl substituent of **3**, compared with benzyl, might provide enhanced binding to the enzyme and afford improved enantioselectivity. Thus, desymmetrization of **3** with PLE was investigated under a variety of conditions, but produced only modest enantiomeric excesses of up to 75% of the half-ester **4** (Table 1). In general, the process tolerated a variety of cosolvents at concentrations in the range of 2.5–15% in an aqueous phosphate buffer at pH 8. Similar buffers at pH 7.5 and 7, as well as tris HCl buffer at pH 7.5 gave marginally lower ee values. The highest enantioselectivities were obtained at 0 °C in 5% 2-propanol (ee: 75%; isolated yield: 59%) or in 2.5% *t*-butanol (ee: 73%; isolated yield: 57%) as the cosolvent after 7 days.[12] When the former experiment in 2-propanol was conducted at room temperature for 2 days, the yield increased slightly to 64% and the ee decreased to 70%. These conditions were preferred for larger scale experiments. Enantiomeric excesses of the half-ester **4** were measured by ^{1}H-NMR integration of a solution of the diastereomeric salts formed by mixing the product with an equimolar amount of (*R*)-(+)-α-methylbenzylamine in $CDCl_3$.

The use of THF, acetonitrile or trifluoroethanol afforded lower enantioselectivities, while aqueous ethanol (not shown) provided low yields and very poor enantioselectivities under all conditions studied. The PLE-promoted partial hydrolysis in all solvent combinations typically slowed after the first few days and the unreacted diester was easily recovered and recycled. For example, the product **4** obtained in 5% 2-propanol at 0 °C was accompanied by 38% recovery of starting material, for a mass balance of 97%. A variety of other enzymes was also tested. These included: α-chymotrypsin,[6f,13] as well as lipases from *Thermomyces lanuginosus* (lipolase), *Rhizopus Niveus* and *Pseudomonas Cepacia*.[14,15] All either failed to provide the desired product **4** from diester **3** or afforded significantly lower enantioselectivities.

Table 1 Desymmetrization of α,α-disubstituted malonate diester **3** with PLE

Cosolvent[a] (%)	Temperature[b] (°C)	Time (days)	Yield[c] (%)	ee[d] (%)
i-PrOH 2.5	RT	2	31	64
5	RT	2	64	70
7.5	RT	2	45	68
15	RT	2	47	58
5	0	7	59 (97)[e]	75
5	40	1	49	68
THF 2.5	RT	2	36	50
5	RT	2	39	50
7.5	RT	2	62	44
15	RT	2	15	40
t-BuOH 2.5	RT	2	32	68
5	RT	2	26	64
7.5	RT	2	23	62
10	RT	2	34	60
12.5	RT	2	58	50
15	RT	2	51	46
2.5	0	7	57	73
5	40	1	36	64
MeCN 2.5	RT	2	70	58
5	RT	2	26	50
10	RT	2	55	30
12.5	RT	2	47	20
15	RT	2	68	30
CF_3CH_2OH 2.5	RT	2	43	64
5	RT	2	19	58
12.5	RT	2	SM	—

[a] The cosolvent was mixed with a pH 8 phosphate buffer. [b] RT = room temperature. [c] Isolated yields of half-ester **4** are reported; SM indicates that only starting material was recovered. [d] The enantiomeric excesses (ee) were measured by ^{1}H NMR integration of signals from diastereomers in a $CDCl_3$ solution containing an equimolar amount of (*R*)-(+)-α-methylbenzylamine. [e] The product was accompanied by 38% recovery of starting material; the yield in parentheses is the total mass balance.

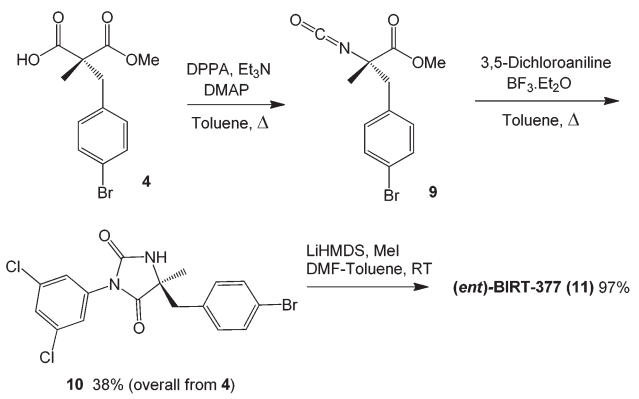


Scheme 3

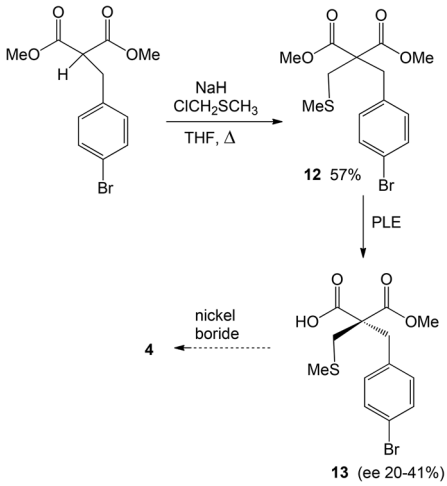
Condensation of the acyl chloride **5**, derived from the half-ester **4**, with 3,5-dichloroaniline produced amide **6** in 92% overall yield (Scheme 3). Saponification of the remaining ester group was followed by Curtius rearrangement. The ester hydrolysis proceeded slowly, presumably due to steric hindrance, and the best results were obtained when the reaction was stopped before completion in order to avoid the accumulation of side products. This afforded 58% of the required carboxylic acid **7**, along with 38% of recovered starting material, for a mass balance of 96%. The Curtius rearrangement was effected by a modification of the Shioiri procedure[16] employing diphenylphosphoryl azide (DPPA) and was conducted under conditions where cyclization of the intermediate isocyanate occurred in the same pot in 57% overall yield. Finally, N-methylation of hydantoin **8** was performed by a literature method[3d,f,k] in essentially quantitative yield. Thus the synthesis of BIRT-377 (**1**) was achieved in seven steps from dimethyl 2-methylmalonate in the overall yield of 17%, or 47% when adjusted for the recovery of starting material in the steps leading to **4** and **7**, but with an ee limited to only 75% in the PLE-mediated desymmetrization step.

The same desymmetrized half-ester **4** was also converted into (*ent*)-BIRT-377 (**11**) by a reversal of the order of steps involving Curtius rearrangement and introduction of the 3,5-dichloroaniline moiety, as shown in Scheme 4. Thus, **4** was first converted to the isocyanate **9**, followed by addition of the aniline and cyclization to **10** in the presence of boron trifluoride etherate. Poorer yields were obtained in the absence of the Lewis acid, with other Lewis acids (*e.g.* CuCl, $EtAlCl_2$, $Tb(OTf)_3$, $LaCl_3$) or in the presence of bases (*e.g.* Et_3N, pyridine, LDA, K_2CO_3) under a variety of conditions. N-Methylation again completed the formation of **11** in three steps from the half-ester **4** in the overall yield of 37%.

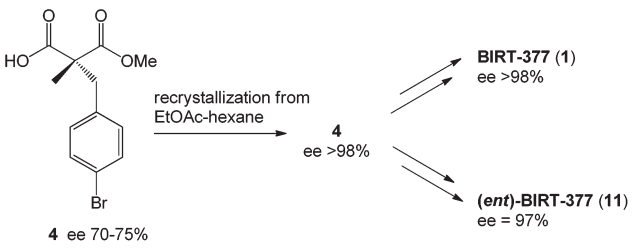
The relatively poor enantioselectivity (maximum ee of 75%) in the formation of **4** prompted further attempts at improvement. We had previously reported[5] that the poor enantioselectivity that had been observed by Björkling *et al.*[6f] in the PLE-mediated desymmetrization of dimethyl 2-benzyl-2-methylmalonate (ee 16%) also improved when the 2-methyl group was increased in size to ethyl (ee 52%) or *n*-propyl



Scheme 4



Scheme 5



Scheme 6

(ee 79%). This may again be attributed to a tighter fit of the latter substituents, in this case into the small hydrophobic binding site of PLE in the Jones model. We therefore prepared the larger 2-methylthiomethyl derivative **12**, with the intention of converting the resulting desymmetrized half-ester **13** to the required methyl derivative **4** by reductive desulfurization with nickel boride[17] (Scheme 5). Unfortunately, **13** was obtained in very poor ee (20–41%) under a variety of conditions.

Finally, we were pleased to discover that one recrystallization of half-ester **4**, obtained from ethyl acetate–hexane produced two crops of an enantiopure product (ee >98%) in which none of the minor enantiomer could be detected by NMR analysis, with a high recovery of 88% of the major enantiomer (see the ESI† for spectra of the recrystallized product and of a racemic sample for comparison, taken in the presence of 1 equiv. of (*R*)-(+)-α-methylbenzylamine). The recrystallized sample of **4** was then converted to BIRT-377 (**1**) and its enantiomer **11** by the same procedures shown in Schemes 3 and 4, respectively, to afford the final products with ees of >98% and 97%, respectively (Scheme 6), as determined by polarimetry and confirmed by HPLC with a chiral column.

Conclusion

In summary, this method provides a concise and stereodivergent synthesis of BIRT-377 and its enantiomer from the same

half-ester intermediate **4**. Although the initial PLE-mediated desymmetrization of **3** produced only a modest enantiomeric excess of at most 75% of **4**, a single recrystallization of this product delivered the half-ester and consequently the final products **1** and **11** in a high state of enantiomeric purity.

Experimental section

General experimental

^{1}H NMR spectra were recorded at 300 or 400 MHz, while ^{13}C spectra were obtained at 76 and 101 MHz, respectively. High resolution mass spectra were obtained using a time of flight (TOF) analyzer with electron impact (EI) ionization or a quadrupole TOF analyzer with electrospray ionization (ESI). Melting points and specific rotations are reported for products derived from recrystallized half-ester **4** with ee of >98%. PLE was obtained from a commercial source as a mixture of isozymes (lyophilized powder; 17 units mg^{-1}).

Dimethyl 2-(4-bromobenzyl)-2-methylmalonate (3). Diisopropylamine (2.43 g, 3.37 mL, 24.1 mmol) was dissolved in 100 mL of dry THF at 0 °C under argon. *n*-Butyllithium (9.62 mL; 2.5 M in hexanes, 24 mmol) was added dropwise over 5 min, followed by dimethyl 2-methylmalonate (3.51 g, 24.0 mmol) over 20 min. The mixture was stirred at room temperature for 1 h and then 1-bromo-4-(bromomethyl) benzene (7.21 g, 28.9 mmol) in 50 mL of dry THF was added by cannula. The mixture was refluxed for 16 h and was then quenched with brine and extracted with diethyl ether. The ether extracts were dried, concentrated *in vacuo* and chromatographed over silica-gel (ethyl acetate–hexanes, 1 : 2) to afford 7.50 g of **2** (99%) as a pale yellow solid; mp 55–56 °C; IR (film) 1733 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 2 H), 6.98 (d, J = 8.4 Hz, 2 H), 3.72 (s, 6 H), 3.17 (s, 2 H), 1.34 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 172.2, 135.2, 132.0, 131.5, 121.2, 54.9, 52.7, 40.8, 19.9; mass spectrum (EI), (*m*/*z*, %) 316 (30, M$^+$, ^{81}Br), 314 (32, M$^+$, ^{79}Br), 256 (89), 254 (91), 196 (22), 194 (22), 171 (100), 169 (98), 115 (51); HRMS (EI) calc'd for $C_{13}H_{15}{}^{81}BrO_4$: 316.0133; found: 316.0124; calc'd for $C_{13}H_{15}{}^{79}BrO_4$: 314.0154; found: 314.0143.

(*R*)-2-(4-Bromobenzyl)-3-methoxy-2-methyl-3-oxopropanoic acid (4). Diester **3** (400 mg, 1.27 mmol) in 4 mL of 2-propanol was added to 76 mL of 0.2 M sodium phosphate buffer (pH 8). PLE (50 mg; lyophilized powder, 17 units mg^{-1}) was dissolved in a minimum amount of the buffer solution and was added to the solution of **3**. The mixture was stirred for 7 d at 0 °C. It was then acidified with 1 M HCl and extracted with dichloromethane. The combined organic fractions were filtered through Celite, dried and then extracted with 1 M KOH. Unreacted starting material **3** (152 mg, 38%) was recovered by evaporation of the organic layer and chromatography over silica-gel (ethyl acetate–hexanes, 1 : 2). The aqueous layer was reacidified with 1 M HCl and extracted with dichloromethane. The combined organic phases were dried and concentrated *in vacuo* to provide **4** (225 mg, 59%) as a pale yellow solid: mp 61–63 °C; IR (film) 3300–2700, 1705 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 11.24 (br s, 1 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.03 (d, J = 8.4 Hz, 2 H), 3.76 (s, 3 H), 3.25 (d, J = 13.7 Hz, 1 H), 3.15 (d, J = 13.7 Hz, 1 H), 1.39 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 177.7, 172.0, 134.8, 132.0, 131.6, 121.4, 54.9, 53.0, 40.8, 19.9; mass spectrum (EI), (*m*/*z*, %) 302 (12, M$^+$, ^{81}Br), 300 (10, M$^+$, ^{79}Br), 256 (22), 254 (20), 171 (100), 169 (98); HRMS (EI) calc'd for $C_{12}H_{13}{}^{81}BrO_4$: 301.9977; found: 301.9991; calc'd for $C_{12}H_{13}{}^{79}BrO_4$: 299.9997; found: 299.9987; ee 75%.

A larger batch of half ester **4** (2.64 g, ee 70%) was prepared similarly in 64% yield, except that the reaction was carried out at room temperature for 2 d. Recrystallization from ethyl acetate–hexane afforded 1.96 g of product in two crops of off-white solid with $[\alpha]_D^{20}$ −5.4 (*c* 3.1, dichloromethane) and $[\alpha]_D^{20}$ −5.4 (*c* 4.6, dichloromethane), respectively, that were combined (88% recovery of the major enantiomer); mp 71–72 °C; ee >98%.

The ees for the above products were measured by integration of well separated benzylic methylene signals in the ^{1}H NMR spectra of equimolar mixtures of **4** and (*R*)-(+)-α-methylbenzylamine in $CDCl_3$.

A racemic sample of **4** was prepared for comparison by dissolving diester **3** (200 mg, 0.635 mmol) in 20 mL of methanol. Potassium hydroxide (355 mg, 6.35 mmol) in 10 mL of water was added and the solution was stirred for 4 h at 16 °C. The mixture was then washed with dichloromethane, acidified with 1 M HCl and extracted with dichloromethane. The combined organic layers were dried and concentrated *in vacuo* to afford the racemic half-ester **4** (162 mg, 85%) as a yellow oil with NMR spectra identical to the sample prepared by hydrolysis with PLE. Racemic half-ester **4** was treated with an equimolar amount of (*R*)-(+)-α-methylbenzylamine in $CDCl_3$ to ensure that the NMR signals were well separated and to correctly identify them in samples of the enantioenriched half-ester by comparison (see the ESI†).

Methyl (*S*)-2-(4-bromobenzyl)-3-chloro-2-methyl-3-oxopropanoate (5). Half-ester **4** (145 mg, 0.482 mmol) and thionyl chloride (294 mg, 180 μL, 2.47 mmol) were refluxed in 50 mL of dichloromethane for 6 h. The mixture was then concentrated *in vacuo* to afford the crude acid chloride **5** as a light brown oil, which was used directly without further purification: IR (film) 1788, 1746 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.27 (crude t, J = 14.6 Hz), 1.45 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 173.2, 169.8, 133.7, 132.0, 131.8, 121.9, 64.7, 53.4, 40.8, 20.1; mass spectrum (EI), (*m*/*z*, %) 320 (12, M$^+$, ^{81}Br), 318 (10, M$^+$, ^{79}Br), 256 (32), 254 (34), 171 (100), 169 (94); HRMS (EI) calc'd for $C_{12}H_{12}{}^{81}Br^{35}ClO_3$: 319.9638; found: 319.9642; calc'd for $C_{12}H_{12}{}^{79}Br^{35}ClO_3$: 317.9658; found: 317.9667.

Methyl (*R*)-2-(4-bromobenzyl)-3-(3,5-dichlorophenylamino)-2-methyl-3-oxopropanoate (6). Acid chloride **5** (215 mg, 0.673 mmol) and 3,5-dichloroaniline (109 mg, 0.673 mmol) were stirred in dichloromethane (5 mL) at room temperature for 14 h. The mixture was washed with saturated $NaHCO_3$ solution, followed by brine and extracted with dichloromethane. The combined organic layers were dried, concentrated *in vacuo* and chromatographed over silica gel (ethyl acetate–hexanes,

1 : 2) to yield **6** (274 mg, 92%) as a pale pink oil: IR (film) 3478, 3388, 1715, 1645 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 9.62 (br s, 1 H), 7.49 (d, J = 1.8 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H), 7.11 (t, J = 1.8 Hz, 1 H), 6.95 (d, J = 8.4 Hz, 2 H) 3.78 (s, 3 H), 3.39 (d, J = 13.5 Hz), 3.08 (d, J = 13.5 Hz), 1.56 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 175.7, 169.3, 139.4, 135.4, 135.2, 131.7, 131.3, 124.6, 121.6, 118.6, 55.5, 53.1, 44.1, 22.2; mass spectrum (EI), (*m*/*z*, %) 445 (18, M^+, ^{81}Br), 443 (16, M^+, ^{79}Br), 256 (36), 254 (32), 225 (38), 223 (42), 171 (98), 169 (100); HRMS (EI) calc'd for $C_{18}H_{16}{}^{81}Br^{35}Cl_2NO_3$: 444.9670; found 444.9673; calc'd for $C_{18}H_{16}{}^{79}Br^{35}Cl_2NO_3$: 442.9691; found: 442.9699; $[\alpha]_D^{20}$ +60.1 (*c* 3.0, dichloromethane).

(*R*)-2-(4-Bromobenzyl)-3-(3,5-dichlorophenylamino)-2-methyl-3-oxopropanoic acid (7). Amide **6** (240 mg, 0.539 mmol) was dissolved in 5 mL of methanol. Potassium hydroxide (302 mg, 5.39 mmol) in 6 mL of water was added and the solution was stirred for 20 h at room temperature. The mixture was then extracted with dichloromethane. The combined organic layers were dried and evaporated *in vacuo* to obtain recovered starting material **6** (91 mg, 38%). The aqueous layer was acidified with 1 M HCl and extracted with ethyl acetate. The combined organic layers were dried and concentrated *in vacuo* to afford half-ester **7** (135 mg, 58%) as a pale pink solid: mp 158–159 °C; IR (solid, attenuated total reflectance) 3700–2900, 3329, 1712, 1655 cm^{-1}; ^1H NMR (300 MHz; CD_3OD) δ 7.58 (d, J = 1.9 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.17 (t, J = 1.9 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 2 H), 3.29 (d, J = 13.6 Hz, 1 H), 3.22 (d, J = 13.6 Hz, 1 H), 1.41 (s, 3 H); ^{13}C NMR (101 MHz; CD_3OD) δ 176.1, 172.4, 141.7, 137.1, 136.0, 133.1, 132.3, 124.9, 121.9, 120.1, 56.9, 42.6, 21.0; mass spectrum (EI), (*m*/*z*, %) 431 (<1, M^+, ^{81}Br), 429 (<1, M^+, ^{79}Br), 387 (33), 199 (56), 197 (53), 171 (100), 169 (90), 161 (74); HRMS (EI) calc'd for $C_{17}H_{14}{}^{81}Br^{35}Cl_2NO_3$: 430.9514; found: 430.9506; calc'd for $C_{17}H_{14}{}^{79}Br^{35}Cl_2NO_3$: 428.9534; found: 428.9554; $[\alpha]_D^{20}$ +83 (*c* 1.9, dichloromethane).

(*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methylimidazolidine-2,4-dione (8). Diphenylphosphoryl azide (99 μL, 126 mg, 0.46 mmol) was added to a mixture of **7** (100 mg, 0.232 mmol), K_2CO_3 (35 mg, 0.25 mmol) and Ag_2CO_3 (64 mg, 0.23 mmol) in dry dioxane (10 mL). The mixture was stirred at room temperature under argon for 1 h, followed by 22 h at reflux. It was washed with 2 M HCl, saturated $NaHCO_3$ and brine. The mixture was extracted with ethyl acetate. The organic layers were combined, dried, concentrated *in vacuo* and chromatographed over silica-gel (ethyl acetate–hexanes, 1 : 2) to afford **8** as a solid foam, (56 mg, 57%); IR (film)) 3276, 1771, 1714 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2 H), 7.35 (t, J = 1.8 Hz, 1 H), 7.15 (broad s, 1 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.97 (d, J = 1.8 Hz, 2 H), 3.13 (d, J = 13.7 Hz, 1 H), 2.89 (d, J = 13.7 Hz, 1 H), 1.60 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 174.2, 155.0, 135.2, 132.9, 132.8, 131.8, 131.7, 128.6, 124.6, 122.0, 62.9, 43.6, 23.4; mass spectrum (EI), (*m*/*z*, %) 428 (18, M^+, ^{81}Br), 426 (12, M^+, ^{79}Br), 259 (23), 257 (32), 171 (100), 169 (94); HRMS (EI) calc'd for $C_{17}H_{13}{}^{81}Br^{35}Cl_2N_2O_2$: 427.9517; found: 427.9521; calc'd for $C_{17}H_{13}{}^{79}Br^{35}Cl_2N_2O_2$: 425.9537; found: 425.9544. $[\alpha]_D^{20}$ +120 (*c* 2.00, dichloromethane); lit.[3d] $[\alpha]_D^{20}$ +121.4 (*c* 1, dichloromethane).

(*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione, BIRT-377 (1). Hydantoin **8** (22 mg, 0.051 mmol) was *N*-methylated by a literature procedure[3d,f,k] to afford **1** (22 mg, 97%); mp 136–137 °C; lit.[3d,e,g,k] mp 135–136 °C; IR (film) 1776, 1724 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2 H), 7.30 (t, J = 1.8 Hz, 1 H), 6.96 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 1.9 Hz, 2 H), 3.11 (d, J = 14.0 Hz), 3.09 (s, 3 H), 2.98 (d, J = 14.0 Hz, 1 H), 1.63 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 173.4, 153.5, 135.1, 133.0, 132.9, 131.9, 131.1, 128.4, 124.5, 122.0, 65.7, 40.8, 25.3, 21.1; mass spectrum (EI), (*m*/*z*, %) 442 (3, M^+, ^{81}Br), 440 (2, M^+, ^{79}Br), (271 (100), 56 (71); HRMS (EI) calc'd for $C_{18}H_{15}{}^{81}Br^{35}Cl_2N_2O_2$: 441.9673; found: 441.9656; calc'd for $C_{18}H_{15}{}^{79}Br^{35}Cl_2N_2O_2$: 439.9694; found: 439.9688. Elemental analysis calc'd for $C_{18}H_{15}BrCl_2N_2O_2$: C, 48.90; H, 3.42; N, 6.34; found: C, 49.09; H, 3.42; N, 6.38. $[\alpha]_D^{20}$ +135 (*c* 1.50, ethanol); lit.[3d] $[\alpha]_D^{25}$ +127.1 (*c* 1, ethanol); lit.[3e] $[\alpha]_D^{25}$ +130.2 (*c* 1, ethanol); lit.[3f] $[\alpha]_D^{25}$ +131.6 (*c* 1.0, ethanol); lit.[3g] $[\alpha]_D^{25}$ +127.3 (*c* 0.78, ethanol); lit.[3k] $[\alpha]_D^{25}$ +134.3 (*c* 1.0, ethanol); ee >98% based on HPLC analysis (Chiralpak AD column; 250 mm × 4.6 mm; 10 μm particle size. Solvent system: isocratic conditions using 95 : 5 hexanes-iPrOH + 10% diethylamine; injection solvent: 9 : 1 hexanes–ethyl acetate. Detector: UV, 254 nm).

Methyl (*S*)-3-(4-bromophenyl)-2-isocyanato-2-methylpropanoate (9). Half-ester **4** (480 mg, 1.59 mmol), diphenylphosphoryl azide (415 mg, 325 μL, 1.51 mmol), triethylamine (177 mg, 254 μL, 1.75 mmol) and 4-(dimethylamino)pyridine (214 mg, 1.75 mmol) were refluxed in toluene (40 mL) for 6 h under argon. The mixture was then washed with saturated $NaHCO_3$ and brine, and extracted with diethyl ether. The combined organic layers were dried, concentrated *in vacuo* to afford the crude isocyanate **9** as a brown oil: IR (film) 2248, 1738 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2 H), 7.05 (d, J = 8.4 Hz, 2 H), 3.78 (s, 3 H), 3.11 (d, J = 13.5 Hz, 1 H), 2.85 (d, J = 13.5 Hz, 1 H), 1.55 (s, 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 173.2, 134.2, 131.8, 131.7, 130.9, 121.8, 65.2, 53.5, 45.7, 29.9, 27.1. The crude product was employed directly in the next step without further purification.

(*S*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methylimidazolidine-2,4-dione (10). Boron trifluoride diethyl etherate (36 μL, 42 mg, 0.30 mmol) was added to a mixture of crude **9** (88 mg, 0.30 mmol) and 3,5-dichloroaniline (48 mg, 0.30 mmol) in dry toluene (15 mL). The mixture was stirred under argon at room temperature for 3 h, followed by reflux for 20 h. The reaction was then quenched with water and extracted with ethyl acetate. The organic layers were dried, concentrated *in vacuo* and chromatographed over silica-gel (ethyl acetate–hexanes, 1 : 2) to afford hydantoin **10** (45 mg, 38% over two steps) as a colourless oil with NMR spectra identical to those of the (*R*)-enantiomer **8**; $[\alpha]_D^{20}$ −119 (*c* 1.30, dichloromethane).

(*S*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione, (*ent*)-BIRT-377 (11). Hydantoin **10** was treated by the same procedure as its enantiomer **8** to afford **11**

in 97% yield, with spectra identical to those of **1**; mp 134–135 °C; $[\alpha]_D^{20}$ −128 (*c* 1.00, ethanol); ee 95% based on specific rotation; 97% based on HPLC analysis performed as for **1**.

Dimethyl 2-(4-bromobenzyl)-2-(methylthiomethyl)malonate (12). Sodium hydride (199 mg, 60% dispersion in mineral oil, 5.0 mmol) was dissolved in dry THF (100 mL) at 0 °C under argon. Commercially available dimethyl 2-(4-bromobenzyl)-malonate (1.00 g, 3.32 mmol) in dry THF (15 mL) was added dropwise and the mixture was stirred for 2 h. Chloromethyl methyl sulfide (818 mg, 8.47 mmol) in THF (2 mL) was added and the mixture was refluxed for 16 h. The reaction was quenched with saturated NH_4Cl solution and the mixture was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed over silica-gel (ethyl acetate–hexanes, 1 : 4) to afford 506 mg (42%) of **12** as a pale yellow oil; IR (film) 1733 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 3.34 (s, 6 H), 3.31 (s, 2 H), 2.92 (s, 2 H), 2.10 (s, 3 H); ^{13}C NMR (400 MHz; $CDCl_3$) δ 170.4, 134.7, 131.71, 131.69, 121.4, 59.4, 52.9, 37.1, 36.7, 17.1; mass spectrum (EI), (*m*/*z*, %) 362 (5, M^+, ^{81}Br), 360 (4, M^+, ^{79}Br), 269 (15), 267 (14), 191 (100), 159 (91); HRMS (EI) calc'd for $C_{14}H_{17}{}^{81}BrO_4S$: 362.0010; found: 362.0008; calc'd for $C_{14}H_{17}{}^{79}BrO_4S$: 360.0031; found: 360.0046.

(*S*)-2-(4-Bromobenzyl)-3-methoxy-2-(methylthiomethyl)-3-oxopropanoic acid (13). Diester **12** (50 mg, 0.14 mmol) in DMSO (2 mL) was added to sodium phosphate buffer (18 mL, pH 8), followed by PLE (7 mg). The mixture was stirred for 2 days at room temperature. It was then acidified with 1 M HCl and extracted with dichloromethane. The organic fractions were filtered through Celite and then extracted with 1 M KOH. The aqueous layer was reacidified with 1 M HCl and extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo.* Flash chromatography over silica-gel (ethyl acetate–hexanes, 1 : 9, containing 1% acetic acid) afforded 32 mg (67%) of **13** as a pale yellow oil; IR (film) 1742, 1700 cm^{-1}; 1H NMR (300 MHz; $CDCl_3$) δ 10.74 (br s, 1 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.03 (d, J = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.35 (d, J = 13.8 Hz, 1 H), 3.24 (d, J = 13.8 Hz, 1 H), 3.04 (d, J = 13.4 Hz, 1 H), 2.96 (d, J = 13.4 Hz, 1 H), 2.14 (s, 3 H); ^{13}C NMR (400 MHz; $CDCl_3$) δ 174.7, 171.5, 134.1, 131.9, 131.5, 121.7, 59.9, 53.3, 38.6, 37.6, 17.1; mass spectrum (EI), (*m*/*z*, %) 348 (2, M^+, ^{81}Br), 346 (2, M^+, ^{79}Br), 256 (35), 254 (37), 196 (48), 194 (52), 115 (100); HRMS (EI) calc'd for $C_{13}H_{15}{}^{81}BrO_4S$: 347.9854; found: 347.9856; calc'd for $C_{13}H_{15}{}^{79}BrO_4S$: 345.9874; found: 345.9866.

The ee was determined to be 20% by integration of well separated methyl and benzylic signals in the ^1H NMR spectrum of an equimolar mixture of **13** and *R*-(+)-α-methylbenzylamine in benzene-d_6. With other cosolvents and additives, the ee was in the range 20–41%.

A racemic sample of **13** was prepared by hydrolysis of **12** with KOH solution, as in the preparation of racemic half-ester **4**. Racemic half-ester **13** was treated with an equimolar amount of (*R*)-(+)-α-methylbenzylamine to ensure that the NMR signals were well separated and to correctly identify them in samples of the enantioenriched half-ester by comparison.

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