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Asymmetric synthesis of (*S*)-1-aminoindan-1,5-dicarboxylic acid and related analogues via intramolecular acylation of enantiopure α,α-disubstituted amino acids

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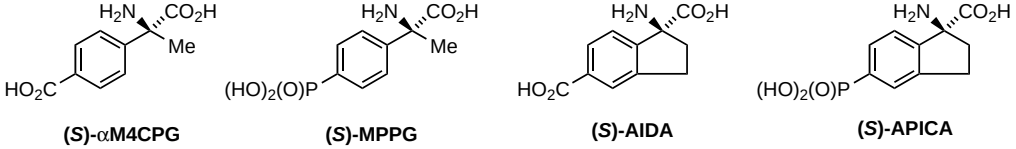
Abstract—α,α-Disubstituted amino acid derivatives are synthesized either by a self-regeneration of stereocenter strategy or using the asymmetric Strecker reaction/alkylation method. Of the four types of substrates tested for intramolecular acylation, those with a 4-alkoxyl group do not react, those with a 4-bromo substituent give lower conversions, while those without a 4-substituent or with a 4-methyl group work well to give the desired cyclization products. Based on these investigations, a new route for preparing (*S*)-1-aminoindan-1,5-dicarboxylic acid (*S*)-AIDA and its analogues was developed. © 2002 Published by Elsevier Science Ltd.

1. Introduction

1-Aminoindan-1,5-dicarboxylic acid (AIDA)[1] and 1-amino-5-phosphenoindan-1-carboxylic acid (APICA)[2] (Scheme 1) are two subtype-selective antagonists for metabotropic glutamate receptors (mGluRs).[3] Both compounds are conformationally constrained analogues of α-methyl-4-carboxyphenglycine (α-M4CPG) or α-methyl-4-phosphonophenglycine (MPPG), two antagonists for mGluRs with lower subtype selectivity.[3] Recently, both racemic AIDA[4] and APICA[5] have become useful pharmaceutical tools in seeking the roles of mGluRs in physiological processes. It was reported that for enantiopure phenylglycine-type mGluRs antagonists that have been tested, only the (*S*)-isomers are antagonists for mGluRs while (*R*)-isomers may be antagonists for other glutamate receptor subtypes,[6,7] which implied that this class of antagonists had marked stereoselective recognition to mGluRs. Thus, an efficient protocol to prepare enantiopure AIDA is highly desirable to investigate the particular role of each enantiomer. The first asymmetric route to (*S*)-AIDA and (*S*)-APICA was developed in our group.[8] However, in the asymmetric Strecker reaction of aryl ketones, which was the key step in that protocol, both conversion rates and diastereoselectivities were unsatisfactory. These drawbacks make it difficult to prepare (*S*)-AIDA or (*S*)-APICA on large scale, which led us to seek an alternative route as described below.

2. Results and discussion

Our new strategy to synthesize these compounds is shown in Scheme 2. The target molecules were expected to be prepared from ketone **A**, which could be obtained



Scheme 1.

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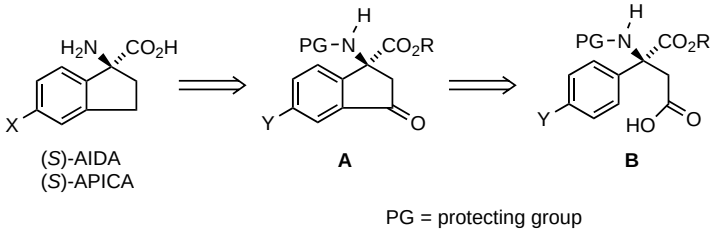


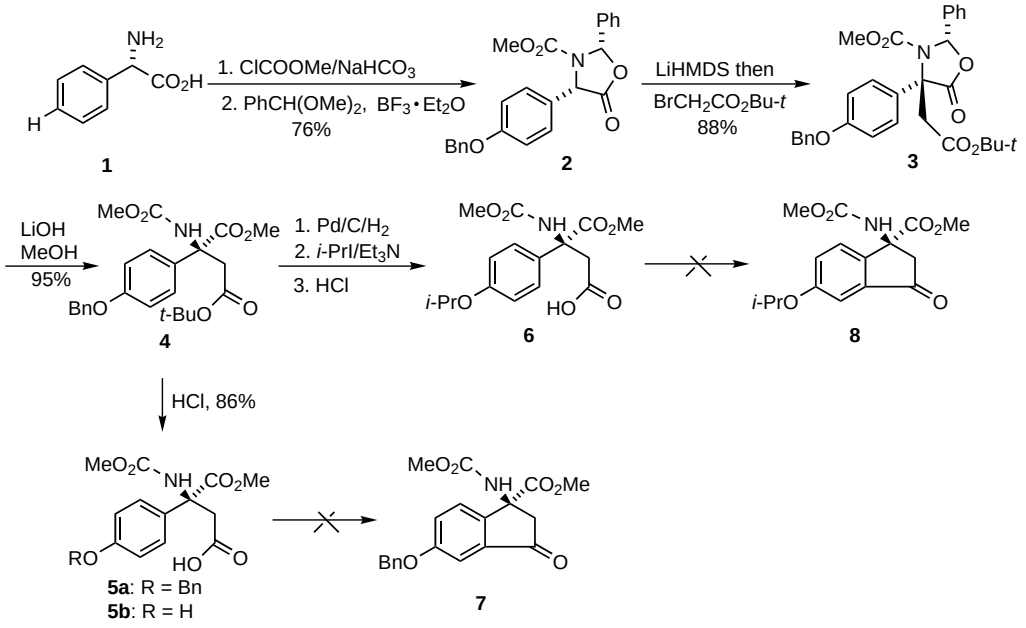
Scheme 2.

by intramolecular acylation of enantiopure α,α-disubstituted amino acid derivative **B**. Obviously, the key problems for this plan were effecting the intramolecular acylation of **B** and how to obtain the desired α,α-disubstituted amino acid derivative **B** in enantiopure form.

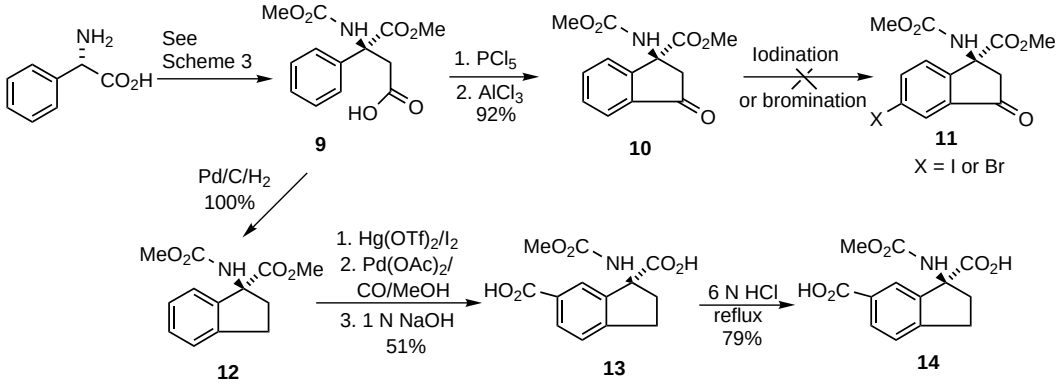
Initially, we planed to prepare the intermediate **B** via the self-regeneration of stereocenter strategy.[9] Accordingly, protection of (*S*)-4-benzoxyphenylglycine **1**[10] with methyl chloroformate afforded the carbamate, which was reacted with benzaldehyde dimethyl acetal in methylene chloride in the presence of boron trifluoride etherate to produce *cis*-oxazolidinone **2** (Scheme 3).[11] Alkylation of **2** with *tert*-butyl bromoacetate provided **3** in 88% yield with over 97% diastereoselectivity. The oxazolidinone ring of **3** was opened by treatment with lithium hydroxide in methanol to give diester **4**. Selective deprotection of **4** with hydrogen chloride in methylene chloride produced acid **5a**. Intramolecular acylation of **5a** was attempted under various conditions such as $PCl_3/AlCl_3$, $(COCl)_2/AlCl_3$, PPA and $(CF_3CO)_2O/H_3PO_4$.[12] Unfortunately no desired cyclization product was obtained after working up. In most cases the starting material or debenzylation product **5b** was isolated. Buckley and Rapoport reported that reducing the amount of catalyst or using sterically bulky alkyl groups was helpful for aryl ether acylation.[13] In order to see if this role worked in our case, we converted the benzyl ether **5a** into *i*-propyl ether **6**. However, using **6** as an intramolecular acylation substrate we still did not get the desired product even when 100 mol% $AlCl_3$ was used.

When they investigated the intramolecular Friedel–Crafts reaction of protected amino acids, McClure and co-workers found that the phenylalanine-derived acid worked for this reaction while the tyrosine-derived analogue could not be applied in this reaction.[14] This stimulated us to use acid **9** (Scheme 4) without the 4-alkoxyl group for the intramolecular acylation. If this reaction worked out, we would be able to obtain the target molecules by introducing a functional group at the 4-position of the benzene ring at a later stage. With this idea in mind, we prepared the acid **9** from (*R*)-phenylglycine using the reaction sequence shown in Scheme 3. This time acylation through the acyl chloride or the *N*-carboxyanhydride worked very well to afford the cyclized product **10** in 92% yield.

Direct iodination or bromination of **10** using $I_2/Hg(OTf)_2$,[15] $I_2/PhI(OAc)_2$[16] or $Br_2/AgOCOCF_3$[17] was attempted, but under these conditions only the starting material was recovered. Thus, we had to move our attention to iodination of the more reactive compound



Scheme 3.

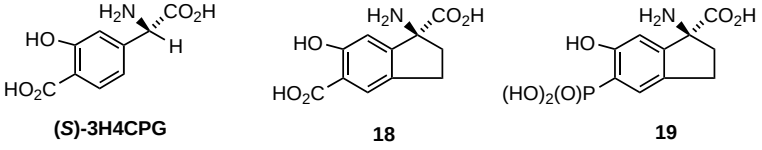


Scheme 4.

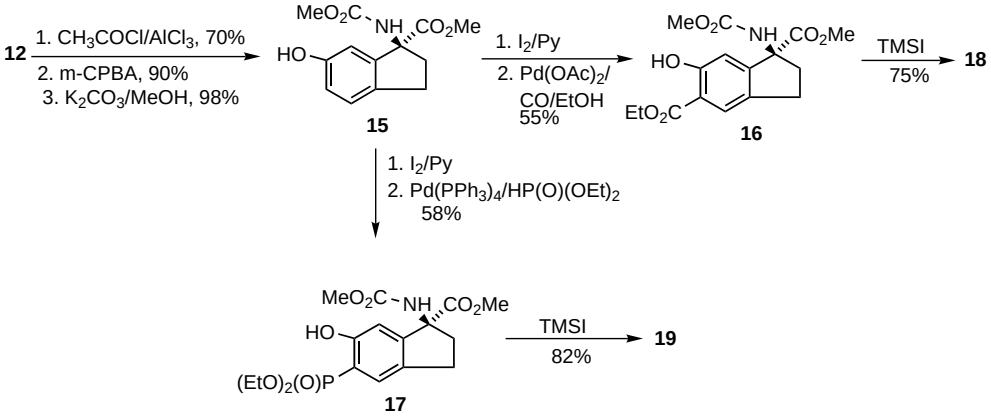
12. When **12** was treated with $I_2/Hg(OTf)_2$ the reaction occurred to give an inseparable mixture of two iodination products in a ratio of about 3/1 as shown by ^1H NMR analysis. This mixture was directly subjected to palladium-catalyzed carbonylation before the two ester groups were hydrolyzed. The major isomer in the resultant mixture was carefully purified by column chromatography to provide the diacid **13**. Deprotection of **13** then gave amino acid **14**. By comparing the ^1H NMR data with those reported,[1] we were disappointed to find that this product was 1-aminoindan-1,6-dicarboxylic acid instead of the desired 1,5-diacid, (*S*)-AIDA, which indicated that iodination of **12** took place mainly at the 6-position. This observation can be explained as follows: the 1-*N* moiety might coordinate with Hg(II) to make the 1-NCO_2Me group electron-deficient, which, together with the 1-methyl ester group make the 1-quarternary carbon a strongly electron-withdrawing group, thereby giving the observed orientation of iodination.

Inspired by the above observation, we realized that if we completed the acylation on **12** and then converted the ketone moiety to a phenol by Baeyer–Villiger oxidation,[18] we would be able to introduce an orientation-directing group onto the benzene ring and thereby effect the desired iodination. If this idea worked out, we could prepare the two conformationally constrained analogues, **18** and **19** of (*S*)-3-hydroxy-4-carboxyphenylglycine ((*S*)-3H4CPG), another known mGluR modulator (Scheme 5). Thus, treatment of **12** with acetyl chloride catalyzed by $AlCl_3$ followed by oxidation with *m*-CPBA and subsequent hydrolysis with K_2CO_3/MeOH provided phenol **15**. Iodination of **15** with I_2/Py afforded an iodide, which was directly subjected to palladium-catalyzed carbonylation or phosphonation to produce **16** or **17**. Deprotection of **16** or **17** with TMSI gave **18** or **19**, respectively (Scheme 6).

The successful acylation of **12** encouraged us to try using a similar acid with a suitable substituent at the 4-position of the benzene ring to access the target



Scheme 5.

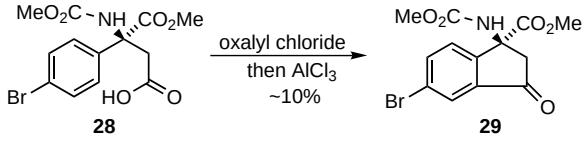


Scheme 6.

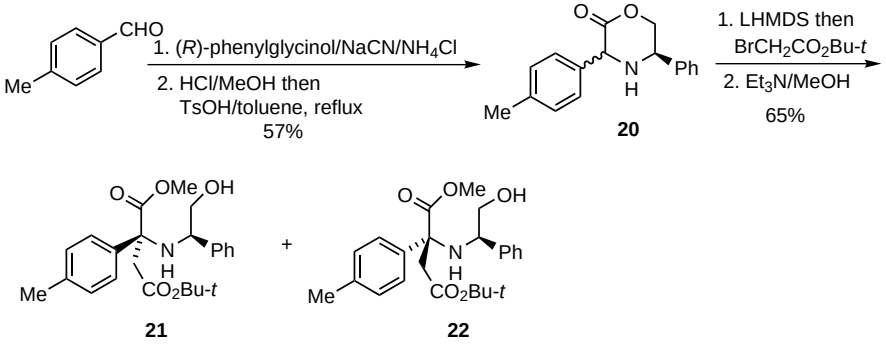
molecules. This time we chose our own method to assemble the intramolecular acylation precursor. This method is based on alkylation of the product from asymmetric Strecker reaction of an aldehyde.[19] As outlined in Scheme 7, asymmetric Strecker reaction of 4-methylbenzaldehyde followed by esterification and lactonization provided lactone **20**. Alkylation of **20** with *tert*-butyl bromoacetate followed by opening of the lactone ring with Et_3N/MeOH delivered two diastereomers **21** and **22** in a ratio of 4/1. Although we had observed that if the amino group was masked as NBn the diastereoselectivity could be improved greatly,[19] this strategy could not be used in this case because benzylation of **20** failed.

With **21** in hand, we finally found a useful route to (*S*)-AIDA as shown in Scheme 8. Removal of the chiral auxiliary of **21** was achieved by oxidation with $Pb(OAc)_4$ followed by protection of the resulting amine with methyl chloroformate to produce the acid **23**. Intramolecular acylation worked again to give **24** and subsequent bromination of **24** with NBS yielded the dibromide **25** in high yield,[20] which was transformed into diester **26** in three steps: (1) treatment of **25** with Ag_2O to provide the aldehyde; (2) oxidation of the aldehyde generated with $AgNO_3$/NaOH to give the acid;[21] and (3) esterification of the acid with MeI/K_2CO_3 in DMF to afford **26**. Finally, reduction of ketone **26** by Pd/C-catalyzed hydrogenation provided **27**, which was heated in refluxing in 6N aqueous HCl to remove all protecting groups, giving crude (*S*)-AIDA as its hydrochloride salt. Treatment of this salt with propylene oxide furnished free (*S*)-AIDA.

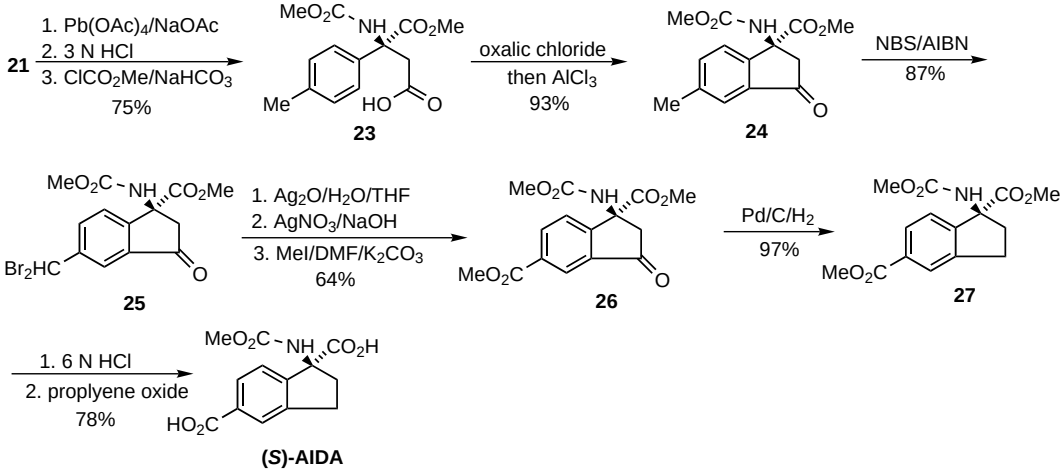
It is notable that we also prepared acid **28** with a 4-bromo group using a similar procedure for preparing **23**. When this compound was subjected to intramolecular acylation, less than 10% conversion was observed (Scheme 9). Prolonging the reaction time or increasing the reaction temperature gave decomposition products. Taking this result and the above observations together, we conclude that the acylation of structure **B**-type compounds is heavily dependent on the nature of the 4-substitutent of the benzene ring.



Scheme 9.



Scheme 7.



Scheme 8.

3. Conclusion

In brief, we have developed a new strategy to access (*S*)-AIDA and related analogues using intramolecular acylation of suitable α,α-disubstituted amino acid derivatives as a key step. The results presented here are not only useful for synthesizing these mGluR modulators, but also of benefit for related amino acid chemistry.

4. Experimental

4.1. (2*R*,4*S*)-2-Phenyl-4-((4-phenylmethoxy)phenyl)-5-oxo-3-oxazolidinine-carboxylic acid, methyl ester, 2

A suspension of (*S*)-4-benzoxyphenylglycine (20 g, 77.8 mmol), $NaHCO_3$ (13.0 g, 155.6 mmol) in water (120 mL) and chloroform (20 mL) was treated with methyl chloroformate (12.0 mL, 155.6 mmol) in a dropwise manner. The solution was stirred for 24 h and 1N aq. HCl was added to adjust the pH to 4. The mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated to yield a crude solid residue. The residue was dissolved in dry methylene chloride (400 mL) and treated with benzaldehyde dimethyl acetal (11.8 mL, 85.6 mmol) and boron trifluoride etherate (40.7 mL, 331.6 mmol) by syringe at 0°C. The mixture was stirred for 2 h at the same temperature and satd aq. $NaHCO_3$ (100 mL) was added to quench the reaction. The aq. layer was separated and extracted with methylene chloride. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed to afford **2** (23.6 g, 76%). $[\alpha]_D^{20}=+68$ (*c* 2.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.25 (m, 12H), 7.05 (d, $J=8.5$ Hz, 2H), 6.75 (s, 1H), 5.40 (s, 1H), 5.10 (s, 2H), 3.50 (s, 3H); MS *m*/*z* 403 (M^+); HRMS found *m*/*z* 403.1412 (M^+); $C_{24}H_{21}NO_5$ requires 403.1421.

4.2. (2*R*,4*S*)-[2-Phenyl-3-(methoxycarbonyl)amino-4-(4-phenylmethoxy)phenyloxazolidin-4-yl]acetic acid, *tert*-butyl ester, 3

A solution of **2** (2.0 g, 6.7 mmol) in anhydrous THF (100 mL) was cooled to −78°C and treated with KHMDS (1 M in THF, 7.4 mL, 7.4 mmol) at −78°C under an argon atmosphere. The mixture was stirred for 30 min and *tert*-butyl bromoacetate (1.4 g, 7.4 mmol) was added by syringe. The reaction mixture was stirred for 2 h and allowed to warm to room temperature. The mixture was partitioned between ethyl acetate and water and separated, the organic layer was washed with brine and dried over $MgSO_4$. After the solvent was evaporated, the residual oil was purified by flash chromatography to afford **3** as colorless oil (2.4 g, 88%). $[\alpha]_D^{20}=-9.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.40 (m, 12H), 7.05 (d, $J=9.0$ Hz, 2H), 6.80 (s, 1H), 5.20 (s, 2H), 3.81 (s, 3H), 3.54–3.31 (m, 2H), 1.62 (s, 9H); MS *m*/*z* 517 (M^+). Anal. calcd for $C_{30}H_{31}NO_7$: C, 69.63; H, 6.00; N, 2.71. Found: C, 69.34; H, 6.06; N, 2.57%.

4.3. (*S*)-2-(Methoxycarbonyl)amino-2-(4-phenylmethoxy)phenylsuccinic acid, 1-methyl ester, 4-*tert*-butyl ester, 4

To a solution of **3** (4.6 g, 8.9 mmol) in MeOH (160 mL) was added 4N LiOH (4.5 mL). The resultant mixture was stirred at room temperature for 24 h and concentrated via rotavapor. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$. The solvent was evaporated and the residual oil was chromatographed to afford **4** as a colorless oil (3.8 g, 95%). $[\alpha]_D^{20}=+19.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 7H), 6.90 (d, $J=7.8$ Hz, 2H), 6.50 (s, 1H), 5.01 (s, 2H), 3.75 (d, $J=15.6$ Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.51 (d, $J=15.6$ Hz, 1H), 1.43 (s, 9H); MS *m*/*z* 443 (M^+). Anal. calcd for $C_{24}H_{29}NO_7$: C, 65.01; H, 6.55; N, 3.16. Found: C, 64.83; H, 6.61; N, 2.98%.

4.4. (*S*)-2-(Methoxycarbonyl)amino-2-(4-phenylmethoxy)phenylsuccinic acid, 1-methyl ester, 5a

To a solution of **4** (2.34 g, 5.28 mmol) in methylene chloride (100 mL) was introduced gaseous hydrochloride until no more starting material was detected by TLC. After the solvent was evaporated, the residual oil was chromatographed to afford **5** (1.76 g, 86%). $[\alpha]_D^{20}=+32.8$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.30 (m, 7H), 6.90 (d, $J=8.9$ Hz, 2H), 6.50 (s, 1H), 5.05 (s, 2H), 3.95 (d, $J=15.9$ Hz, 1H), 3.70 (s, 3H), 3.65 (d, $J=15.9$ Hz, 1H), 3.62 (s, 3H); MS *m*/*z* 387 (M^+); HRMS found *m*/*z* 387.1310 (M^+); $C_{20}H_{21}NO_7$ requires 387.1319.

4.5. (*S*)-2-(Methoxycarbonyl)amino-2-phenylsuccinic acid, 1-methyl ester, 9

Following the procedure for preparing **5a** from (*S*)-4-benzoxyphenylglycine, acid **9** was prepared from (*S*)-phenylglycine. $[\alpha]_D^{20}=+31.3$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.27 (m, 5H), 6.60 (s, 1H), 4.00 (d, $J=17.0$ Hz, 1H), 3.71 (s, 3H), 3.69 (d, $J=17.0$ Hz, 1H), 3.61 (s, 3H); MS *m*/*z* 282 (M^++H^+); HRMS found *m*/*z* 281.0916 (M^+); $C_{13}H_{15}NO_6$ requires 281.0899.

4.6. (*S*)-1-(Methoxycarbonyl)amino-3-oxoindan-1-carboxylic acid, methyl ester, 10

To a solution of **9** (9.8 g, 35.6 mmol) in anhydrous ether (120 mL) was added PCl_5 (7.4 g, 35.6 mmol) in three portions at 0°C. After the addition the solution was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was dissolved in dry methylene chloride (100 mL). This solution was added dropwise to a suspension of $AlCl_3$ (14.2 g, 106.8 mmol) in methylene chloride (120 mL). The resultant mixture was stirred for 2 h at room temperature before pouring into 1N aq. HCl (100 mL) at 0°C to quench the reaction. The organic layer was separated and the aq. layer was extracted with methylene chloride. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The resid-

ual solid was recrystallized from hexane/ethyl acetate to afford 8.3 g (91%) of **10** as a white crystal. Mp 67°C; $[\alpha]_D^{20}=+188.4$ (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, $J=7.6$ Hz, 1H), 7.63 (t, $J=7.6$ Hz, 1H), 7.53 (d, $J=7.6$ Hz, 1H), 7.51 (t, $J=7.5$ Hz, 1H), 6.18 (br s, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.44 (d, $J=18.5$ Hz, 1H), 3.17 (d, $J=18.1$ Hz, 1H); MS m/z 263 (M^+); HRMS found m/z 263.0802 (M^+); $C_{13}H_{13}NO_5$ requires 263.0794.

4.7. (*S*)-1-(Methoxycarbonyl)aminoindan-1-carboxylic acid, methyl ester, 12

A suspension of **10** (5.0 g, 19.0 mmol), 10% Pd/C (0.5 g) in methanol (100 mL) and 25% aq. HCl (13 mL) was hydrogenated at atmospheric pressure and room temperature for 6 h. The Pd/C was removed by filtration and the filtrate was diluted with water (50 mL) and evaporated via rotavapor to remove methanol. Extractive work-up with ether, followed by chromatography afforded **12** (4.45 g, 94%). $[\alpha]_D^{20}=+118.6$ (c 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.18 (m, 4H), 5.66 (br s, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.14–2.99 (m, 3H), 2.45 (m, 1H); MS m/z 250 (M^++H^+); HRMS found m/z 249.1020 (M^+); $C_{13}H_{15}NO_4$ requires 249.1001.

4.8. (*S*)-1-(Methoxycarbonyl)aminoindan-1,6-dicarboxylic acid, 13

To a mixture of **12** (1.0 g, 4.0 mmol) and $Hg(OTf)_2$ (2.0 g, 4.0 mmol) in methylene chloride (5 mL) was added dropwise a solution of iodine (1.0 g, 4.0 mmol) in methylene chloride (5 mL). The resultant solution was stirred for 24 h at room temperature and partitioned between ethyl acetate and water. The organic layer was washed with aq. Na_2SO_3, aq. KI, and brine, respectively. After drying over Na_2SO_4, the organic phase was concentrated and chromatographed to afford a mixture of iodides, which was dissolved in DMF (10 mL) and EtOH (10 mL). To this solution was added Et_3N (4.1 mL, 29.3 mmol), dppp (60 mg, 0.15 mmol) and $Pd(OAc)_2$ (33 mg, 0.15 mmol). The resulting solution was bubbled with CO and heated at 60°C for 2 h. The mixture was cooled and poured into water (50 mL) and then extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated. The residue was dissolved in MeOH (10 mL) and treated with 1N KOH (5 mL). The resultant mixture was stirred for 2 h and 1N aq. HCl was added to adjust the mixture to pH 2. Extractive work-up with ether, followed by chromatography afforded **13** (569 mg, 51%). $[\alpha]_D^{20}=+124.1$ (c 0.11, $CHCl_3$); ^1H NMR (300 MHz, CD_3SOCD_3) δ 8.04 (s, 1H), 7.99 (s, 1H), 7.85 (d, $J=8.0$ Hz, 1H), 7.36 (d, $J=7.9$ Hz, 1H), 3.51 (s, 3H), 2.97 (m, 2H), 2.77 (m, 1H), 2.24 (m, 1H); MS m/z 280 (M^++H^+); HRMS found m/z 279.0756 (M^+); $C_{13}H_{13}NO_6$ requires 297.0745.

4.9. (*S*)-1-Aminoindan-1,6-dicarboxylic acid, 14

A mixture of **13** (100 mg, 0.36 mmol) in 6N aq. HCl (3 mL) in a sealed tube was heated at 100°C for 24 h. The cooled solution was concentrated to dryness and the residue was dissolved in ethanol (1 mL). To this solution was added propylene oxide (0.5 mL). The resultant precipitate was filtered, washed with ethanol and dried in vacuo to afford **14** (63 mg, 79%). $[\alpha]_D^{20}=+81$ (c 0.13, H_2O); ^1H NMR (300 MHz, D_2O) δ 8.02 (d, $J=7.8$ Hz, 1H), 7.99 (s, 1H), 7.48 (d, $J=7.8$ Hz, 1H), 3.22 (t, $J=6.0$ Hz, 1H), 2.88 (dt, $J=14.1$, 7.1 Hz, 2H), 2.42 (dt, $J=14.2$, 7.1 Hz, 1H); MS (ESI) m/z 221 (M^+).

4.10. (*S*)-6-Hydroxy-1-(methoxycarbonyl)aminoindan-1-carboxylic acid, methyl ester, 15

To a mixture of **12** (1.42 g, 5.7 mmol) in carbon disulfide (20 mL) was added $AlCl_3$ (3.0 g, 22.8 mmol) and acetyl chloride (0.5 mL, 6.8 mmol) at 0°C. The reaction mixture was stirred at room temperature for 12 h and poured into ice-water (20 mL). Extractive work-up with ether, followed by chromatography afforded the acylation product (1.2 g, 70%), which was dissolved in chloroform (20 mL). To this solution was added *m*-CPBA (50%, 2.5 g, 7.3 mmol). The resultant solution was heated under reflux for 24 h in the dark, and then partitioned between ethyl acetate and satd aq. Na_2SO_3. The organic extract was concentrated and the residue was dissolved in MeOH (20 mL) and 10% aq. K_2CO_3 (10 mL) was added at 0°C. The resultant mixture was stirred for 1 h at 0°C and then acidified with 1N aq. HCl. Extractive work-up with ether followed by chromatography afforded **15** (0.95 g, 63% overall yield for three steps). $[\alpha]_D^{20}=+45.5$ (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.18 (m, 4H), 5.66 (br s, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.14–2.99 (m, 3H), 2.45 (m, 1H), 7.09 (d, $J=8.3$ Hz, 1H), 6.77–6.74 (m, 2H), 5.72 (br s, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.02–2.99 (m, 3H), 2.55–2.38 (m, 1H); MS m/z 265 (M^+); HRMS found m/z 265.0950 (M^+); $C_{13}H_{15}NO_5$ requires 265.0922.

4.11. (*S*)-6-Hydroxy-1-(methoxycarbonyl)aminoindan-1,5-dicarboxylic acid, dimethyl ester, 16

To a solution of **15** (63 mg, 0.24 mmol) in dioxane (1.2 mL) was added pyridine (0.2 mL) and iodine (73 mg, 0.28 mmol). The resultant mixture was heated under reflux for 24 h and then the cooled solution was partitioned between ethyl acetate and water. The organic extract was dried over Na_2SO_4 and concentrated to afford crude iodide, which was dissolved in DMF (2 mL) and ethanol (2 mL). To this solution was added triethylamine (0.5 mL), dppp (10 mg, 0.024 mmol) and $Pd(OAc)_2$ (6 mg, 0.024 mmol), the mixture was bubbled with CO and heated at 60°C for 2 h. The mixture was cooled and partitioned between ethyl acetate and water. The organic extract was dried over Na_2SO_4 and concentrated and the residue was chromatographed to afford **16** (44 mg, 55%). $[\alpha]_D^{20}=+116.3$ (c 0.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.75 (s, 1H), 6.86 (s, 1H), 5.89 (br s, 1H), 4.42 (q, $J=6.5$ Hz, 2H), 3.73 (s, 3H), 3.65 (s, 3H), 3.05 (t, $J=6.9$ Hz, 2H), 2.90 (dt, $J=14.6$, 6.8 Hz, 1H), 2.55 (m, 1H), 1.30 (t, $J=6.9$ Hz, 3H); MS m/z 337 (M^+); HRMS found m/z 337.1152 (M^+); $C_{16}H_{19}NO_7$ requires 337.1160.

4.12. (*S*)-6-Hydroxy-5-diethylphosphono-1-(methoxycarbonyl)aminoindan-1-carboxylic acid, methyl ester, 17

To a solution of **15** (101 mg, 0.38 mmol) in 2 mL of dioxane were added 0.3 mL of pyridine and iodine (117 mg, 0.45 mmol). The resultant mixture was refluxed for 24 h and then the cooled solution was partitioned between ethyl acetate and water. The organic extract was dried over Na_2SO_4 and concentrated to afford crude iodide, which was dissolved in 3 mL of triethylamine. To this solution were added diethyl phosphite (58 μL, 0.44 mmol) and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) under a nitrogen atmosphere. The resultant mixture was heated at 100°C in a sealed tube for 24 h before it was partitioned between ethyl acetate and water. The organic extract was dried over Na_2SO_4 and concentrated, the residue was chromatographed to afford 88 mg (58%) of **17**. $[\alpha]_D^{20}=+103.9$ (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.24 (d, $J=14.1$ Hz, 1H), 6.88 (d, $J=5.9$ Hz, 1H); 5.74 (br s, 1H), 4.18–3.98 (m, 4H), 3.72 (s, 3H), 3.65 (s, 3H), 3.05–2.97 (m, 3H), 2.55–2.45 (m, 1H), 1.30 (t, $J=6.9$ Hz, 6H); MS *m*/*z* 401 (M^+); HRMS found *m*/*z* 401.1239 (M^+); $C_{17}H_{24}NPO_8$ requires 401.1240.

4.13. (*S*)-6-Hydroxy-1-aminoindan-1,5-dicarboxylic acid, 18

To a solution of **16** (25 mg, 0.074 mmol) in acetonitrile (3 mL) under argon was added TMSI (53 μL, 0.37 mmol). The reaction mixture was heated at 50°C for 24 h and then concentrated. The residue was dissolved in distilled water (2 mL) and washed with ethyl acetate. The aq. layer was concentrated and the residue was purified with Dowex-50W eluting with water to afford **18** (14 mg, 75%). $[\alpha]_D^{20}=+87.2$ (*c* 0.1, 6N aq. HCl); ^1H NMR (300 MHz, D_2O) δ 7.53 (s, 1H), 6.81 (s, 1H), 2.93 (t, $J=6.9$ Hz, 2H), 2.76 (dt, $J=14.1$, 6.9 Hz, 1H), 2.28 (dt, $J=14.1$, 7.0 Hz, 1H); MS (ESI) *m*/*z* 238 (M^++H^+).

4.14. (*S*)-6-Hydroxy-5-phosphono-1-aminoindan-1-carboxylic acid, 19

Following the same procedure for preparing **18** from **16**, **19** was obtained from **17** in 82% yield. $[\alpha]_D^{20}=+76.3$ (*c* 0.1, 6N aq. HCl); ^1H NMR (300 MHz, D_2O) δ 7.50 (d, $J=14.3$ Hz, 1H), 6.83 (d, $J=6.1$ Hz, 1H), 2.95 (t, $J=7.1$ Hz, 2H), 2.79 (dt, $J=14.5$, 7.0 Hz, 1H), 2.28 (dt, $J=14.5$, 7.0 Hz, 1H); MS (ESI) *m*/*z* 274 (M^++H^+).

4.15. (3*R*,5*R*)-3-(4-Methylphenyl)-5-phenyl-2-morpholinone and (3*S*,5*R*)-3-(4-methylphenyl)-5-phenyl-2-morpholinone, 20

To a solution of 4-methylbenzaldehyde (12.0 g, 100 mmol), (*R*)-phenylglycinol (15.1 g, 110 mmol), ammonium chloride (7.0 g, 130 mmol) in methanol (75 mL) and water (75 mL) was added sodium cyanide (4.9 g, 100 mmol) with cooling by ice-water. The solution was stirred at room temperature for 8 h before MeOH was evaporated in vacuo. The aq. phase was extracted three times with ethyl acetate. The combined organic extract was washed with brine and dried over Na_2SO_4. After the solvent had been evaporated in vacuo, the residue was dissolved in satd methanolic hydrochloride (50 mL). The resultant solution was stirred overnight and then evaporated in vacuo. The residue was dissolved in water and the solution was neutralized with aq. sodium bicarbonate until pH 8. Extractive work-up with ether followed by chromatography gave the corresponding amino ester, which was dissolved in toluene (2000 mL). After it was added TsOH (0.86 g, 5 mmol), the solution was refluxed for 24 h under argon. The solvent was evaporated and the residue was purified by chromatography to give 15.2 g (57%) of **20** as a mixture of two diastereomers. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.20 (m, 9H), 5.02 (s, 1H), 5.53–4.39 (m, 3H), 2.36 (s, 1H); MS *m*/*z* 268 (M^++H^+).

4.16. (*S*)-2-((*R*)-2-Hydroxy-1-phenylethylamino)-2-(4-methylphenyl)succinic acid 4-*tert*-butyl ester, 1-methyl ester, 21 and (*R*)-2-((*R*)-2-hydroxy-1-phenylethylamino)-2-(4-methylphenyl)succinic acid 4-*tert*-butyl ester, 1-methyl ester, 22

A solution of **20** (10.0 g, 37.5 mmol) in 1/1 *n*-hexane/THF (250 mL) was cooled to −78°C under argon. To this solution was added LHMDS (1.0 M in THF, 45 mL, 45.0 mmol) over 30 min. Stirring was continued for 1 h at the same temperature and a solution of *tert*-butyl bromoacetate (8.4 g, 43.1 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred at −78°C for 12 h before satd aq. ammonium chloride (100 mL) was added to quench the reaction. The mixture was partitioned between ethyl acetate and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to give the alkylation products (9.85 g, 69%).

A solution of the above products (9.5 g, 24.9 mmol) and triethylamine (10 mL) in methanol (200 mL) was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed to afford **21** (4.41 g, 76% yield based on 57% conversion), **22** (1.15 g, 20% yield based on 57% conversion), together with starting material (4.12 g). **21**: $[\alpha]_D^{18}=-2.6$ (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (m, 3H), 6.98 (d, $J=8.4$ Hz, 2H), 6.94–6.87 (m, 4H), 3.62 (s, 3H), 3.51 (m, 1H), 3.46 (d, $J=6.6$ Hz, 2H), 3.38 (m, 1H), 3.25 (d, $J=14.9$ Hz, 1H), 3.18 (d, $J=15.1$ Hz, 1H), 2.26 (s, 3H), 1.48 (s, 9H); MS *m*/*z* 414 (M^++H^+); HRMS found *m*/*z* 413.2212 (M^+); $C_{24}H_{31}NO_5$ requires 413.2202. **22**: $[\alpha]_D^{18}=+23.5$ (*c* 2.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.19 (m, 3H), 7.17 (d, $J=8.5$ Hz, 2H), 7.11–7.07 (m, 4H), 5.30 (s, 1H), 3.62–3.55 (m, 2H), 3.51–3.42 (m, 4H), 3.18 (d, $J=16.2$ Hz, 1H), 3.16 (m, 1H), 2.74 (d, $J=16.4$ Hz, 1H), 2.31 (s, 3H), 1.31 (s, 9H); MS *m*/*z* 414 (M^++H^+); HRMS found *m*/*z* 382.2012 (M^+−OMe); $C_{23}H_{28}NO_4$ requires 282.2018.

4.17. (*S*)-2-(Methoxycarbonyl)amino-2-(4-methylphenyl)succinic acid, 1-methyl ester, 23

To a solution of **21** (3.0 g, 7.3 mmol) in 1/1 MeOH/CH_2Cl_2 (150 mL) were added NaOAc (1.9 g, 23.1

mmol), $Pb(OAc)_4$ (4.9 g, 11.0 mmol) at 0°C. The mixture was stirred at 0°C for 30 min, filtered through silica gel. The filtrate was evaporated in vacuo and the residue was dissolved in THF (30 mL). To this solution was added 3N aq. HCl (50 mL) and the mixture stirred for 2 h. After the solvent was evaporated in vacuo, the residue was dissolved in water (30 mL). The solution was cooled to 0°C and $NaHCO_3$ (2.5 g, 29.2 mmol) was added. To this mixture methyl chloroformate (1.4 g, 14.6 mmol) was added dropwise. The mixture was stirred at room temperature overnight and then acidified with 1N aq. HCl to pH 3. The solution was extracted three times with chloroform, the combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, the residue was purified by chromatography to afford 1.62 g (75%) of **23**. $[\alpha]_D^{18}=+12.0$ (*c* 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, $J=8.1$ Hz, 2H), 7.18 (d, $J=8.1$ Hz, 2H), 6.59 (s, 1H), 3.97 (d, $J=16.7$ Hz, 1H), 3.71–3.62 (m, 1H), 3.70 (s, 3H), 3.61 (s, 3H), 2.34 (s, 3H); MS *m*/*z* 294 (M^+-H^+); HRMS found *m*/*z* 250.1085 (M^+-CO_2); $C_{13}H_{17}NO_4$ requires 250.1079.

4.18. (*S*)-1-(Methoxycarbonyl)amino-5-methyl-3-oxoindan-1-carboxylic acid methyl ester, 24

To a solution of **23** (1.5 g, 5.1 mmol) in ether (10 mL) was added oxalyl chloride (0.7 g, 6.0 mmol) at 0°C. A drop of DMF was added and the solution was stirred at 0°C for 0.5 h. The solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL). To this solution was added a suspension of anhydrous aluminum chloride (3.1 g, 22.9 mmol) in CH_2Cl_2 (200 mL) at 0°C. The mixture was stirred for 12 h at room temperature before it was poured onto a mixture of ice (about 80 g) and 3N aq. HCl (150 mL). The organic layer was separated and washed with brine, dried over Na_2SO_4. After removal of solvent the residue was purified by chromatography to afford **24** (1.3 g, 93%). $[\alpha]_D^{18}=+78$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.45 (d, $J=8.0$ Hz, 1H), 7.25 (d, $J=8.0$ Hz, 1H), 6.10 (br s, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.45 (d, $J=18.0$ Hz, 1H), 3.16 (d, $J=18.0$ Hz, 1H), 2.42 (s, 3H); MS *m*/*z* 278 (M^++H^+); HRMS found *m*/*z* 277.0943 (M^+); $C_{14}H_{15}NO_5$ requires 277.1013.

4.19. (*S*)-1-(Methoxycarbonyl)amino-5-dibromomethyl-3-oxoindan-1-carboxylic acid methyl ester, 25

To a refluxing solution of **24** (1.0 g, 3.6 mmol) in CCl_4 (70 mL) were sequentially added NBS (0.71 g, 4.0 mmol) and AIBN (30 mg). The solution was stirred under reflux for 0.5 h, and further NBS (0.71 g, 4.0 mmol) was added. Stirring was continued for 3.5 h at the same temperature and the solvent was evaporated in vacuo. The residue was purified by chromatography to afford **25** (1.4 g, 87%). $[\alpha]_D^{18}=+51$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.94 (d, $J=8.1$ Hz, 1H), 7.58 (d, $J=8.0$ Hz, 1H), 6.69 (s, 1H), 6.23 (br s, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.43 (d, $J=18.4$ Hz, 1H), 3.27 (d, $J=18.4$ Hz, 1H); MS *m*/*z* 434 (M^+, ^{81}Br). Anal. calcd for $C_{14}H_{13}Br_2NO_5$: C, 38.65; H, 3.01; N, 3.22. Found: C, 38.22; H, 3.05; N, 3.23%.

4.20. (*S*)-1-(Methoxycarbonyl)amino-3-oxoindan-1,5-dicarboxylic acid, dimethyl ester, 26

To a solution of **25** (1.25 g, 2.89 mmol) in THF (30 mL) and H_2O (20 mL) was added freshly prepared Ag_2O (1.07 g, 4.62 mmol). The mixture was stirred at room temperature for 12 h and filtered. The filtrate was evaporated in vacuo and the residue was dissolved in MeOH (10 mL) for use in the next synthetic step.

To a solution of silver nitrate (2.46 g, 14.47 mmol) in H_2O (20 mL) was added a solution of NaOH (1.16 g, 29.00 mmol) in H_2O (15 mL) dropwise. The mixture was stirred for 20 min and the above methanolic solution was added with ice-water cooling. Stirring was continued until the reaction was complete (monitored by TLC). The mixture was filtered and the filtrate was acidified with 1N aq. HCl to give pH 1. The solution was extracted six times with chloroform and the combined organic extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, the residue was dissolved in DMF (30 mL). To this solution were sequentially added K_2CO_3 (0.75 g, 7.09 mmol) and MeI (0.81 g, 5.70 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated in vacuo and the residue was suspended in ethyl acetate and then washed with water and brine. The organic extract was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to afford **26** (591 mg, 64%). $[\alpha]_D^{18}=+87.4$ (*c* 2.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.35 (dd, $J=8.0$, 1.6 Hz, 1H), 7.60 (d, $J=8.2$ Hz, 1H), 6.32 (br s, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 3.17 (t, $J=7.4$ Hz, 2H), 2.95 (dt, $J=13.0$, 7.4 Hz, 1H), 2.55 (m, 1H); MS *m*/*z* 322 (M^++H^+); HRMS found *m*/*z* 290.0627 (M^+–OMe); $C_{14}H_{12}NO_6$ requires 290.0665.

4.21. (*S*)-1-(Methoxycarbonyl)amino-3-indan-1,5-dicarboxylic acid, dimethyl ester, 27

A suspension of **26** (500 mg, 1.56 mmol), 50 mg of 10% Pd/C in 20 mL of MeOH was stirred under H_2 (10 atm) at 30°C for 8 h. The catalyst was removed by filtration and the filtrate was concentrated, the residue was purified by chromatography to afford product **27** (463 mg, 97%). $[\alpha]_D^{18}=+44.8$ (*c* 3.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.90 (d, $J=8.4$ Hz, 1H), 7.33 (d, $J=8.2$ Hz, 1H), 5.82 (br s, 1H), 3.90 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 3.15 (t, $J=7.4$ Hz, 2H), 2.95 (dt, $J=13.0$, 7.4 Hz, 1H), 2.55 (m, 1H); MS *m*/*z* 276 (M^+–OMe); HRMS found *m*/*z* 276.0893 (M^+–OMe); $C_{14}H_{14}NO_5$ requires 276.0872.

4.22. (*S*)-1-Amino-3-indan-1,5-dicarboxylic acid, (*S*)-AIDA

In a sealed tube were placed **27** (400 mg, 1.3 mmol) and 6N aq. HCl (15 mL). The mixture was heated to 130°C with stirring for 24 h. The solvent was evaporated in vacuo and the residue was dissolved in EtOH (50 mL). To this solution propylene oxide (5 mL) was added with stirring and the resultant solution was heated to 60°C. The mixture was stirred for 30 min. The white

precipitate was collected by suction filtration and recrystallized from distilled water to afford (*S*)-AIDA (225 mg, 78%). $[\alpha]_D^{20}=+83.5$ (*c* 0.9, 6N aq. HCl) [lit.[8] $[\alpha]_D^{20}=+86.3$ (*c* 0.8, 6N aq. HCl)]; ^{1}H NMR (300 MHz, D_2O) δ 7.98 (s, 1H), 7.91 (d, $J=8.1$ Hz, 1H), 7.48 (d, $J=8.0$ Hz, 1H), 3.23 (t, $J=7.2$ Hz, 2H), 2.89 (dt, $J=14.4$, 7.2 Hz, 1H), 2.43 (dt, $J=14.4$, 7.3 Hz, 1H); MS (ESI) m/z 221 (M^+).

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