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PAPER

Construction of the biaryl-part of vancomycin aglycon *via* atropo-diastereoselective Suzuki–Miyaura coupling†

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An atropo-diastereoselective synthesis with dr up to 98/2 towards the biaryl subunit of vancomycin based on the use of enantiopure β-hydroxysulfoxide derivatives as novel chiral auxiliary is reported.

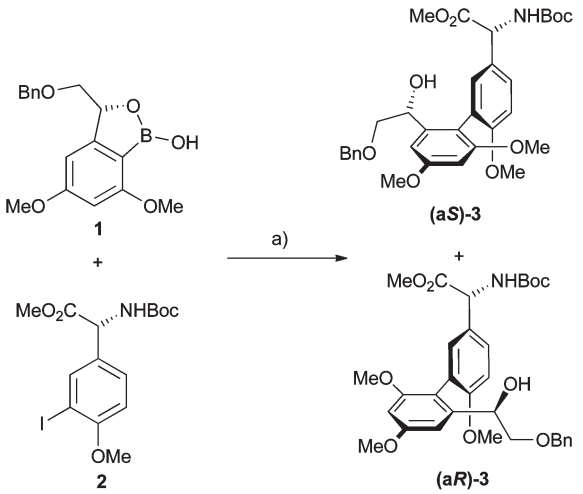
Introduction

The discovery of penicillin[1] as a drug to treat infectious diseases followed by the development of several other antibacterial agents marked a milestone in the fight of humankind against bacteria. However, these antibacterial drugs saved millions of lives but were not able to tame bacteria after all. In contrast, this war led to the emergence of newer and even more dangerous bacterial strains, which responded defiantly against a variety of known antibiotics.

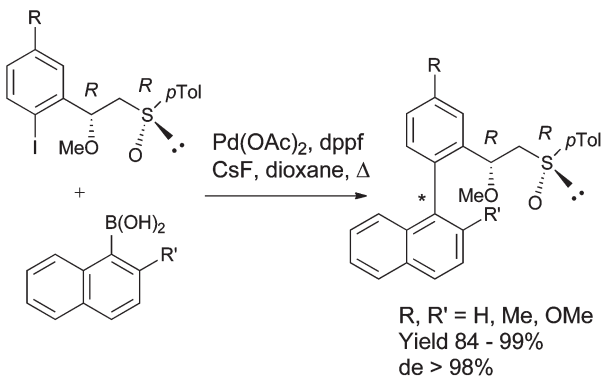
For several decades vancomycin, a prominent member of the glycopeptide class of antibacterial agents,[2] proved to be a drug of "last resort", used only after treatment with other antibiotics had failed. Due to its medical importance and intriguing mode of action[3] in combination with its unusual molecular architecture[4] vancomycin was and still is a fascinating target for synthetic organic chemists. During the last decades numerous studies towards the total synthesis of vancomycin were published.[5–14] Especially the synthesis of the AB biaryl ring system of vancomycin proved to be a highly challenging task.

Nicolaou and co-workers achieved the formation of the vancomycin biaryl ring system utilising a stereocontrolled Suzuki–Miyaura coupling reaction of boronic acid **1** and aryl iodide **2**, which was derived from *p*-hydroxyphenylglycine.[15] The stereochemical outcome of the coupling reaction is controlled by the benzylic stereogenic center of the boronic acid building block **1** (see Scheme 1).

Recently, we published a methodology for an atropo-diastereoselective Suzuki–Miyaura coupling reaction, using enantiopure β-hydroxysulfoxide derivatives as novel chiral auxiliaries (Scheme 2).[16] The advantages of sulfoxides are the possibility to get them in an enantiomerically pure form and that they can be easily converted into a multitude of synthetically valuable functional groups (either by desulfurization, the Pummerer reaction



Scheme 1 (a) $Pd(Ph_3P)_4$, Na_2CO_3, toluene–MeOH–H_2O (10 : 1 : 0.5), 4 h, 90 °C, 84% (a*S*/a*R* = 2 : 1).



Scheme 2 Atropo-diastereoselective Suzuki–Miyaura coupling reaction using enantiopure β-hydroxysulfoxide derivatives as novel chiral auxiliaries.

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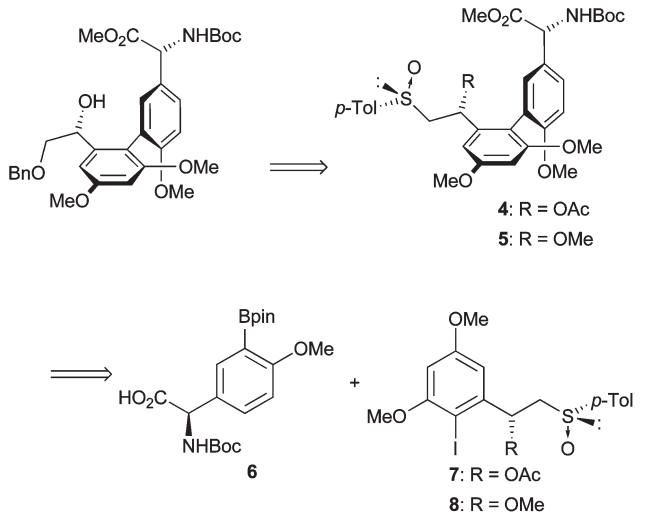
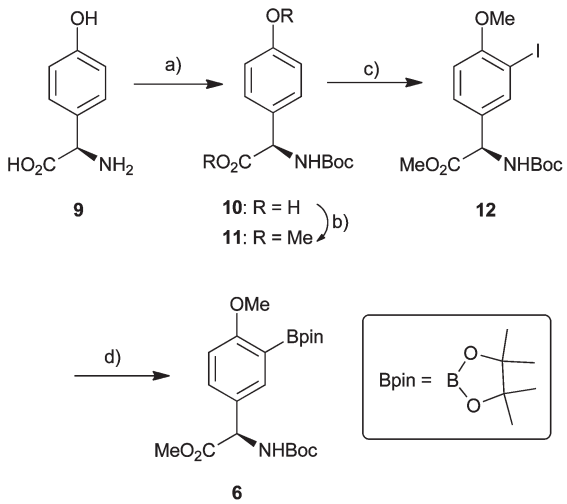
†Electronic supplementary information (ESI) available: ^{1}H-NMR spectra and X-ray data of compounds **(a*S*)-4**, **(a*S*)-5**. CCDC reference numbers 871940 and 871941. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25373a



Scheme 3 Retrosynthetic approach to Nicolaou's synthon using enantiopure β-hydroxysulfoxide derivatives as chiral auxiliaries.



Scheme 4 (a) Boc_2O, NaOH, H_2O–dioxane 2 : 1, 4 h, 20 °C, 99%; (b) K_2CO_3, MeI, acetone, 16 h, 50 °C, 99%; (c) I_2, AgTFA, $CHCl_3$, 15 h, 20 °C, 91%; (d) HBpin, 2-(dicyclohexylphosphino)-biphenyl, $Pd(OAc)_2$, NEt_3, dioxane, 30 min, 85 °C, 69%.

or by sulfoxide/metal interconversion followed by trapping with one of the numerous electrophiles).[17]

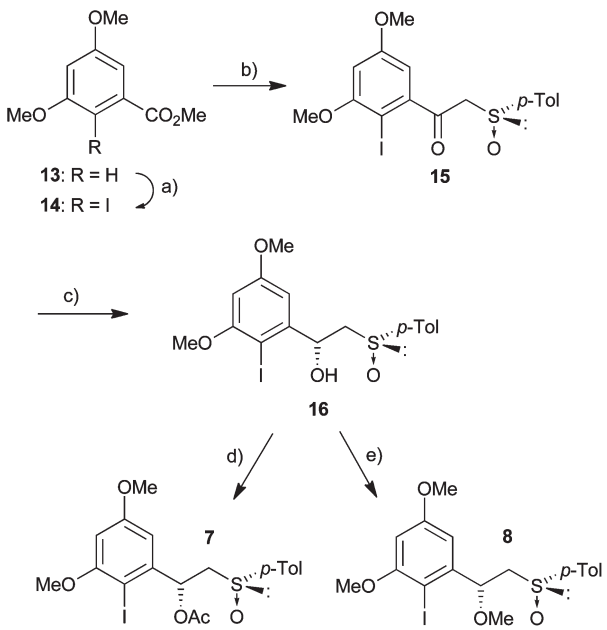
The excellent diastereoselectivities that we have observed in the formation of the biaryl axis prompted us to investigate if the developed method would also be applicable for the preparation of the biaryl synthon **3**, which Nicolaou used in his total synthesis of vancomycin.

From a retrosynthetic point of view boronic ester **6** and aryl iodides **7** and **8** represent suitable building blocks for the envisaged synthesis of Nicolaou's synthon (see Scheme 3).

Results and discussion

Boronic ester **6** was synthesized as summarized in Scheme 4. Protection of the amino group of commercially available D-4-hydroxyphenylglycine (**9**) with Boc_2O in the presence of sodium hydroxide furnished derivative **10** (99% yield), which upon treatment with potassium carbonate and methyl iodide led to fully protected compound **11** in 99% yield. Subsequent iodination of compound **11** with iodine in the presence of silver trifluoroacetate gave iodide **12** in an excellent yield of 91%. It is known that α-amino acid derivatives, particularly those of phenylglycine, can suffer significant racemization when they are submitted to reaction conditions that are considered to be typical for Suzuki–Miyaura couplings (*e.g.* basic conditions, prolonged reaction times at elevated temperatures).[18] In conclusion, the palladium catalyzed coupling of iodide **12** with pinacolborane had to be conducted under very mild conditions to avoid any unwanted racemization. Therefore, iodide **12** was reacted with pinacolborane in the presence of 2-(dicyclohexylphosphino)-biphenyl,[19] palladium acetate and triethylamine at 85 °C for 30 min to yield boronic ester **6** (69% yield). Using dppf as ligand[20] or DPEPhos[21] gave respectively 32 and 38% yields.

Aryl iodides **7** and **8** were prepared as shown in Scheme 5. Commercially available methyl 3,5-dimethoxybenzoate (**13**) was reacted with iodine in the presence of silver trifluoroacetate to

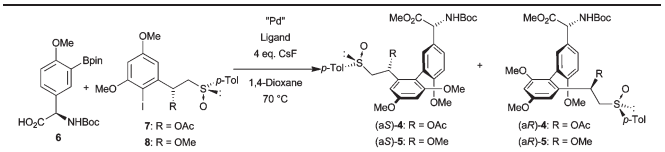


Scheme 5 (a) I_2, AgTFA, $CHCl_3$, 2 h, 20 °C, 65% (89% based on recovered starting material); b) LDA, (+)-(*R*)-methyl *p*-tolylsulfoxide, THF, 12 h, −15–20 °C, 80%; (c) $ZnBr_2$, DIBAL, THF, 5 h, −78–20 °C, 90%, de > 98%; (d) Ac_2O, pyridine, 2 h, 20 °C, 98%; (e) NaH, MeI, DMF, 40 min, −20 °C, 91%.

deliver iodide **14** (65% yield, 89% based on recovered starting material). β-Keto sulfoxide **15** was prepared by the conversion of iodide **14** with (+)-(*R*)-methyl *p*-tolylsulfoxide, which was deprotonated using a freshly prepared lithium diisopropylamide solution (80% yield).

Subsequent diastereoselective reduction of β-keto sulfoxide **15** with diisobutylaluminium hydride in the presence of

Table 1 Atropo-diastereoselective Suzuki–Miyaura coupling



Entry	Reagents	"Pd"/ligand[a]	Time [h]	Yield[b] [%]	dr [a*S*/a*R*][c]
1[d]	**6** + **7** (2 : 1)	$Pd(OAc)_2$/dppf	55	54	90 : 10
2[e]	**6** + **7** (2 : 1)	$Pd(OAc)_2$/dppf	2	51	>98 : 2
3[e]	**6** + **7** (2 : 1)	$Pd(OAc)_2$/S-Phos	2	65	>98 : 2
4[e]	**6** + **7** (2 : 1)	$Pd_2(dba)_3$/S-Phos	2	69	>98 : 2
5[e]	**6** + **8** (2 : 1)	$Pd(OAc)_2$/dppf	2	53	85 : 15
6[e]	**6** + **8** (2 : 1)	$Pd(OAc)_2$/S-Phos	2	68	85 : 15
7[e]	**6** + **8** (2 : 1)	$Pd_2(dba)_3$/S-Phos	2	71	85 : 15

[a] 10 mol% "Pd" are used; in the case of dppf 15 mol% are used; in the case of S-Phos 20 mol% are used. [b] Combined yield (a*S* and a*R*). [c] Determined by NMR. [d] Anhydrous dioxane. [e] Wet dioxane.

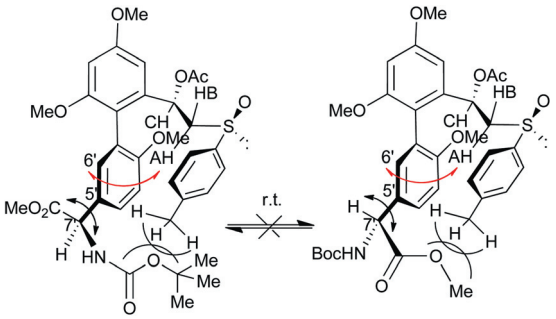


Fig. 1 Conformational rotamers of the biaryl **(a*S*)-4**.

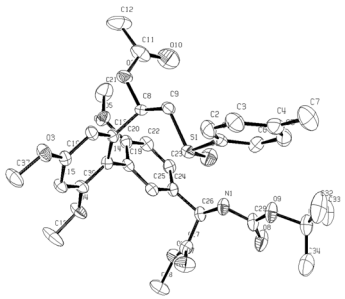


Fig. 2 X-ray crystal structure of the biaryl **(a*S*)-4**.

zinc bromide is known to provide the [2(*R*),S(*R*)]-β-hydroxysulfoxide **16** in which the OH group is *syn* to the bulky substituent of the sulfoxide.[22] In this case **16** was obtained in a yield of 90% with an excellent diastereoselectivity of de > 98%. To complete the synthesis of the building blocks, acetate **7** and methyl ether **8** were prepared by conversion of alcohol **16** with acetic anhydride in pyridine (98% yield) and methyl iodide in the presence of sodium hydride (91% yield), respectively.

With the boronic acid derivative **6** and the two iodide building blocks **7** and **8** in hand, the next step to achieve in the reaction sequence towards Nicolaou's synthon **3** was the Suzuki–Miyaura coupling to form biaryls **4** and **5**, respectively. Thus, in a first test boronic ester **6** and iodide **7** bearing an acetoxy substituent at the side-chain (in order to make the deprotection easier) entered smoothly into a Suzuki–Miyaura coupling reaction [Pd-$(OAc)_2$, dppf, CsF, 1,4-dioxane, 70 °C, 55 h] to afford a 90/10 mixture of atropoisomers **(a*S*)-4** and **(a*R*)-4** in 54% combined yield (Table 1, entry 1). Surprisingly, when we performed the reaction in wet dioxane, we obtained the coupling product in 2 h reaction time and an excellent diastereoselectivity. No trace of the other diastereoisomer was detectable in the ^{1}H and ^{13}C NMR spectra (Table 1, entry 2). An explanation could be the formation of CsOH by reaction of CsF with water which accelerates the reaction and thus avoids racemization due to shorter reaction times (2 h compared to 55 h). The exchange of dppf as the ligand by S-Phos raised the yield to 65% (Table 1, entry 3). A further improvement of the yield (69%) was achieved by using $Pd_2(dba)_3$ instead of $Pd(OAc)_2$ as the palladium source (Table 1, entry 4). Under these conditions only one atropoisomer **(a*S*)-4** has been observed.

In the ^{1}H NMR two sets of signals can be detected, corresponding to conformational rotamers around the aminoester moiety (Fig. 1). These rotamers are stable at room temperature due to steric hindrance between the aminoester and *p*-tolyl substituents.

The absolute configuration of the major atropoisomer **(a*S*)-4** has been confirmed by single crystal X-ray analysis (see Fig. 2).‡

In our previous studies on the atropo-diastereomeric Suzuki–Miyaura coupling we had already realized a strong influence of the substituent at the C-2 side-chain position. Therefore, we employed next the methoxy compound **8**. In wet dioxane the yields increased also in this case when changing from $Pd(OAc)_2$/dppf (53%, Table 1 entry 5), over S-Phos (68%, Table 1 entry 6) to $Pd_2(dba)_3$/S-Phos (71%, Table 1 entry 7). We noticed also a slightly decrease of diastereoselectivity (dr 85/15). Once again the absolute configuration of the major atropoisomer **(a*S*)-5** has been confirmed by single crystal X-ray analysis (see Fig. 3).‡

Conclusions

In the present work we developed an atropo-diastereoselective approach to the biaryl subunit of vancomycin based on the use of enantiopure β-hydroxysulfoxide as chiral auxiliaries during

‡ Crystal data: for **(a*S*)-4**: $C_{34}H_{41}NO_{10}S$, M = 655.74, orthorhombic, a = 9.5048(3) Å, b = 18.9754(6) Å, c = 19.2401(7) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 3470.1(2) Å^3, T = 296(2) K, space group $P2_12_12_1$, Z = 4, MoKα, 15 051 reflections measured, 5726 independent reflections (R_{int} = 0.0412). The final R_1 values were 0.0714 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1969 ($I > 2\sigma(I)$). The final R_1 values were 0.0804 (all data). The final w$R(F^2)$ values were 0.2074 (all data).

For **(a*S*)-5**: $C_{33}H_{41}NO_9S$, M = 627.73, monoclinic, a = 10.6718(5) Å, b = 11.6816(6) Å, c = 14.2167(7) Å, α = 90.00°, β = 111.9350(10)°, γ = 90.00°, V = 1644.01(14) Å^3, T = 173(2) K, space group $P2_1$, Z = 2, MoKα, 17 874 reflections measured, 6187 independent reflections (R_{int} = 0.0157). The final R_1 values were 0.0268 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.0666 ($I > 2\sigma(I)$). The final R_1 values were 0.0296 (all data). The final w$R(F^2)$ values were 0.0686 (all data).

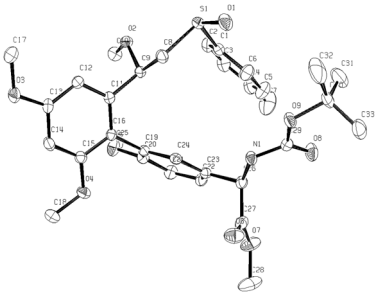


Fig. 3 X-ray crystal structure of the biaryl **(a*S*)-5**.

the Suzuki–Miyaura coupling reaction. The absolute stereochemistry of the major atropoisomers has been confirmed by single crystal X-ray analysis.

Experimental section

General

Starting materials, if commercial, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of argon, using appropriate glassware. Et_2O and THF were dried by distillation from sodium after the characteristic blue color of sodium diphenyl ketyl (benzophenone–sodium "radical–anion") had been found to persist. Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. If no reduced pressure is specified, boiling ranges (b.p.) refer to ordinary atmosphere conditions (725 ± 25 Torr). Melting ranges (m.p.) given were found to be reproducible after recrystallization, unless stated otherwise ("decomp."), and are uncorrected. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica-gel (60-F254). Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 63–210 μm.

Methyl [a*S*,1*R*,7′*R*,(S)*R*]-*tert*-butoxycarbonylamino-{6-[1-acetoxy-2-(4-tolylsulfinyl)-ethyl]-2,4,2′-trimethoxy-biphenyl-5′-yl}acetate (4)

A solution of iodide **7** (100.0 mg, 0.204 mmol) and the catalytic system (Pd-catalyst and ligand, see Table 1) in dioxane (3.0 ml) is stirred at 20 °C for 1 h. A second solution is prepared from boronic ester **6** (172.5 mg, 0.409 mmol, 2 eq.) and CsF (124.4 mg, 0.820 mmol, 4 eq.) in dioxane (3.0 ml) and stirred for 30 min at 20 °C before the first solution is added *via* syringe. The reaction mixture is heated to 70 °C for 2 h, quenched by the addition of H_2O and extracted with CH_2Cl_2. The solvent is evaporated and the crude product is purified by column chromatography (cyclohexane–EtOAc = 4 : 1) to yield (a*S*)-**4** and (a*R*)-**4** as colorless solids.

(a*S*)-**4** (major) : (a*R*)-**4** (minor) = 90 : 10

(a*S*)-4: 1st rotamer. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.42 (9H, s, *t*Bu), 1.96 (3H, s, Ac), 2.40 (3H, s, $CH_3{}^{pTol}$), 2.98 (2H, AB, J_{AB} = 13.3 Hz, J_{AX} = 9.3 Hz, J_{BX} = 4.1 Hz, $\Delta\nu$ = 99 Hz, CH_2), 3.64 (3H, s, $OMe^{Ar\text{-}2}$), 3.66 (3H, s, $OMe^{Ar\text{-}2'}$), 3.73 (3H, s, CO_2Me), 3.85 (3H. s, $OMe^{Ar\text{-}4}$), 5.21 (1H, d, J = 8.0 Hz, C*H*(NHBoc)), 5.82 (1H, X, J_{AX} = 9.3 Hz, J_{BX} = 4.1 Hz, C*H*(OAc)), 6.13 (1H, d, J = 8.0 Hz, NH), 6.48 (1H, d J = 2.3 Hz, $H^{Ar\text{-}3}$), 6.63 (1H, d, J = 2.3 Hz, $H^{Ar\text{-}5}$), 6.82 (1H, d, J = 8.5 Hz, $H^{Ar\text{-}3'}$), 7.03 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}6'}$), 7.25 (4H, A_2B_2, J_{AB} = 8.1 Hz, $\Delta\nu$ = 28 Hz, H^{pTol}), 7.32 (1H, m, $H^{Ar\text{-}4'}$); Anal. calcd for $C_{34}H_{41}NO_{10}S$: C, 62.28; H, 6.30. Found: C, 62.29; H, 6.31%.

(a*S*)-4: 2nd rotamer. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.44 (9H, s, *t*Bu), 2.05 (3H, s, Ac), 2.42 (3H, s, $CH_3{}^{pTol}$), 2.97 (2H, AB, J_{AB} = 13.4 Hz, J_{AX} = 10.5 Hz, J_{BX} = 3.0 Hz, $\Delta\nu$ = 129 Hz, CH_2), 3.63 (3H, s, $OMe^{Ar\text{-}2}$), 3.66 (3H, s, $OMe^{Ar\text{-}2'}$), 3.77 (3H, s, CO_2Me), 3.84 (3H. s, $OMe^{Ar\text{-}4}$), 5.29 (1H, d, J = 7.2 Hz, C*H*(NHBoc)), 5.52 (1H, d, J = 7.2 Hz, NH), 5.78 (1H, X, J_{AX} = 10.5 Hz, J_{BX} = 3.0 Hz, C*H*(OAc)), 6.47 (1H, d J = 2.4 Hz, $H^{Ar\text{-}3}$), 6.64 (1H, d, J = 2.4 Hz, $H^{Ar\text{-}5}$), 6.79 (1H, d, J = 8.7 Hz, $H^{Ar\text{-}3'}$), 6.93 (1H, d, J = 1.9 Hz, $H^{Ar\text{-}6'}$), 7.26 (4H, A_2B_2, J_{AB} = 8.1 Hz, $\Delta\nu$ = 21 Hz, H^{pTol}), 7.26 (1H, m, $H^{Ar\text{-}4'}$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 20.9 (OAc), 21.4 ($CH_3{}^{pTol}$), 28.3 (C(CH_3)$_3$), 52.6 (OMe), 55.3 (OMe), 55.5 (OMe), 55.8 (OMe), 57.0 (*C*H(NHBoc)CO_2Me), 62.9 (CH_2), 68.0 (CH), 80.0 (*C*(CH_3)$_3$), 98.8 (CH^{Ar}), 102.0 (CH^{Ar}), 111.2 (CH^{Ar}), 117.4 (C^{Ar}), 124.1 (CH^{pTol}), 128.1 (CH^{Ar}), 130.0 (CH^{pTol}), 131.4 (CH^{Ar}), 139.4 (C^{Ar}), 140.0 (C^{Ar}), 141.3 (C^{Ar}), 141.3 (C^{Ar}), 155.0 (C^{Ar}), 156.5 (C^{Ar}), 158.2 (C^{Ar}), 159.9 (C^{Ar}), 160.5 (C═O), 169.8 (C═O), 171.9 (C═O); Anal. calcd for $C_{34}H_{41}NO_{10}S$: C, 62.28; H, 6.30. Found: C, 62.26; H, 6.28%.

(a*R*)-4: 1st rotamer. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.44 (9H, s, *t*Bu), 2.06 (3H, s, OAc), 2.44 (3H, s, $CH_3{}^{pTol}$), 3.12 (2H, AB d′ABX, J_{AB} = 13.3 Hz, J_{AX} = 11.3 Hz, J_{BX} = 2.3 Hz, $\Delta\nu$ = 175 Hz, CH_2), 3.49 (3H, s, $OMe^{Ar\text{-}2}$), 3.61 (3H, s, $OMe^{Ar\text{-}2'}$), 3.71 (3H, s, CO_2Me), 3.83 (3H, s, $OMe^{Ar\text{-}4}$), 5.29 (1H, d large, J = 7.0 Hz, C*H*(NHBoc)), 5.44 (1H, d large, J = 7.0 Hz, NH), 5.51 (1H, X d′ABX, J_{AX} = 11.3 Hz, J_{BX} = 2.3 Hz, C*H*(OAc)), 6.43 (1H, d, J = 2.2 Hz, $H^{Ar\text{-}3}$), 6.58 (1H, d, J = 8.2 Hz, $H^{Ar\text{-}3'}$), 6.59 (1H, d, J = 2.2 Hz, $H^{Ar\text{-}5}$), 7.06 (1H, s large, $H^{Ar\text{-}6'}$), 7.20 (4H, A_2B_2, J_{AB} = 8.02 Hz, $\Delta\nu$ = 37 Hz, H^{pTol}), 7.53 (1H, m, $H^{Ar\text{-}4'}$).

(a*R*)-4: 2nd rotamer. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.47 (9H, s, *t*Bu), 2.03 (3H, s, OAc), 2.42 (3H, s, $CH_3{}^{pTol}$), 3.14 (2H, AB d′ABX, J_{AB} = 13.3 Hz, J_{AX} = 11.3 Hz, J_{BX} = 2.3 Hz, $\Delta\nu$ = 212 Hz, CH_2), 3.50 (3H, s, $OMe^{Ar\text{-}2}$), 3.61 (3H, s, $OMe^{Ar\text{-}2'}$), 3.80 (3H, s, CO_2Me), 3.84 (3H, s, $OMe^{Ar\text{-}4}$), 5.22 (1H, d large, J = 7.0 Hz, C*H*(NHBoc)), 5.50 (1H, d large, J = 7.0 Hz, NH), 5.86 (1H, X d′ABX, J_{AX} = 11.3 Hz, J_{BX} = 2.3 Hz, C*H*(OAc)), 6.43 (1H, d, J = 2.2 Hz, $H^{Ar\text{-}3}$), 6.58 (1H, d, J = 8.2 Hz, $H^{Ar\text{-}3'}$), 6.59 (1H, d, J = 2.2 Hz, $H^{Ar\text{-}5}$), 7.00 (1H, s large, $H^{Ar\text{-}6'}$), 7.22 (4H, A_2B_2, J_{AB} = 11.7 Hz, $\Delta\nu$ = 27 Hz, H^{pTol}), 7.71 (1H, m, $H^{Ar\text{-}4'}$).

Methyl [a*S*,1*R*,7′*R*,(S)*R*]-*tert*-butoxycarbonylamino-{2,4,2′-trimethoxy-6-[1-methoxy-2-(4-tolylsulfinyl)-ethyl]-biphenyl-5′-yl}acetate (5)

A solution of iodide **8** (94.4 mg, 0.204 mmol) and the catalytic system (Pd-catalyst and ligand, see Table 1) in dioxane (3.0 ml) is stirred at 20 °C for 1 h. A second solution is prepared from boronic ester **6** (172.5 mg, 0.409 mmol, 2 eq.) and CsF (124.4 mg, 0.820 mmol, 4 eq.) in dioxane (3.0 ml) and stirred for 30 min at 20 °C before the first solution is added *via* syringe. The reaction mixture is heated to 70 °C for 2 h, quenched by the addition of H_2O and extracted with CH_2Cl_2. The solvent is evaporated and the crude product is purified by column chromatography (cyclohexane–EtOAc 4 : 1) to yield (a*S*)-**5** and (a*R*)-**5** as colorless solids.

(a*S*)-**5** (major) : (a*R*)-**5** (minor) = 85 : 15

(a*S*)-5. M.p. 140–142 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.43 (9H, s, *t*Bu), 2.41 (3H, s, $CH_3{}^{pTol}$), 3.05 (3H, s, OMe), 3.30 (2H, AB, J_{AB} = 12.6 Hz, J_{AX} = 9.3 Hz, J_{BX} = 4.5 Hz, $\Delta\nu$ = 219 Hz, CH_2), 3.51 (3H, s, OMe), 3.62 (3H, s, OMe), 3.70 (1H, X, J_{AX} = 9.3 Hz, J_{BX} = 4.5 Hz, C*H*(OMe)), 3.76 (3H, s, OMe), 3.84 (3H, s, OMe), 5.26 (1H, d, J = 7.0 Hz, C*H*(NHBoc)), 6.22 (1H, d, J = 7.0 Hz, NH), 6.46 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}3}$), 6.66 (1H, d, J = 8.5 Hz, $H^{Ar\text{-}3'}$), 6.68 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}5}$), 7.01 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}6'}$), 7.19 (4H, A_2B_2, J_{AB} = 7.9 Hz, $\Delta\nu$ = 26 Hz, H^{pTol}), 7.33 (1H, dd, J = 8.5, 2.5 Hz, $H^{Ar\text{-}4'}$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.4 ($CH_3{}^{pTol}$), 28.3 (C(CH_3)$_3$), 52.5 (OMe), 54.9 (OMe), 55.4 (OMe), 55.6 (OMe), 56.2 (OMe), 57.1 (C*H*(NHBoc)CO_2Me), 64.0 (CH_2), 75.5 (*C*H(OMe)), 79.8 (*C*(CH_3)$_3$), 98.5 (CH^{Ar}), 100.9 (CH^{Ar}), 110.6 (CH^{Ar}), 118.6 (C^{Ar}), 124.1 (C^{Ar}), 124.2 (CH^{pTol}), 128.2 (CH^{Ar}), 128.5 (C^{Ar}), 129.7 (CH^{pTol}), 131.7 (CH^{Ar}), 139.4 (C^{Ar}), 140.2 (C^{Ar}), 141.1 (C^{Ar}), 155.2 (C^{Ar}), 155.8 (C^{Ar}), 156.0 (C^{Ar}), 160.8 (C═O), 172.0 (C═O); IR (neat): ν 3340 (NH), 2957, 1740 (C═O), 1706 (C═O), 1602, 1523, 1505, 1490, 1463, 1342, 1264, 1201, 1161, 1069, 1054, 1035, 983, 934, 809; $[\alpha]_{20}^{D}$ = −76.4 (c = 1, $CHCl_3$); Anal. calcd for $C_{33}H_{41}NO_9S$: C, 63.14; H, 6.58. Found: C, 63.16; H, 6.57%.

(a*R*)-5. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.44 (9H, s, *t*Bu), 2.43 (3H, s, $CH_3{}^{pTol}$), 3.06 (3H, s, OMe), 3.43 (2H, AB, J_{AB} = 10.5 Hz, J_{AX} = 3.2 Hz, J_{BX} = 12.6 Hz, CH_2), 3.49 (3H, s, OMe), 3.63 (3H, s, OMe), 3.77 (1H, X, m, C*H*(OMe)), 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 5.34 (1H, d, J = 7.5 Hz, C*H*(NHBoc)), 5.59 (1H, d, J = 7.5 Hz, NH), 6.45 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}3}$), 6.63 (1H, d, J = 8.5 Hz, $H^{Ar\text{-}3'}$), 6.69 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}5}$), 6.89 (1H, d, J = 2.5 Hz, $H^{Ar\text{-}6'}$), 7.20 (4H, A_2B_2, J_{AB} = 8.5 Hz, H^{pTol}), 7.31 (1H, dd, J = 8.5, 2.5 Hz, $H^{Ar\text{-}4'}$); Anal. calcd for $C_{33}H_{41}NO_9S$: C, 63.14; H, 6.58. Found: C, 63.10; H, 6.52%.

Methyl (−)-(2*R*)-*tert*-butoxycarbonylamino-[4-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]acetate (6)

To a solution of iodide **12** (6.0 g, 14.2 mmol) and 2-(dicyclohexylphosphino)-biphenyl (987 mg, 2.8 mmol) in dry 1,4-dioxane (80 ml) are added $Pd(OAc)_2$ (180 mg, 0.7 mmol) and NEt_3 (7.9 ml, 56.8 mmol). The resulting solution is degassed and pinacolborane (6.1 ml, 42.6 mmol) is added *via* syringe over 15 min. The reaction mixture is heated to 85 °C for 30 min (color changes from light yellow to dark green), quenched by the addition of a saturated aqueous NH_4Cl-solution (150 ml) and extracted with ethyl acetate (4 × 200 ml). The crude product can be purified either by column chromatography (cyclohexane–EtOAc = 9 : 1–3 : 7) or by crystallization from cyclohexane. Yield: 4.18 g (9.7 mmol, 69%) colorless solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.35 (12H, s, CH_3 pinacol), 1.43 (9H, s, CH_3 Boc), 3.71 (3H, s, OCH_3), 3.82 (3H, s, CO_2CH_3), 5.23 (1H, bs, CH), 5.40 (1H, bs, NH), 6.82 (1H, d, J = 8.7 Hz, $H^{Ar\text{-}5}$), 7.37 (1H, dd, J = 8.7, 2.3 Hz, $H^{Ar\text{-}6}$), 7.62 (1H, d, J = 2.3 Hz, $H^{Ar\text{-}2}$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.8 (2 × CH_3 pinacol), 28.3 (CH_3 Boc), 52.5 (CO_2CH_3), 55.9 (OCH_3), 57.1 (CH), 74.8 (*C*(CH_3) Boc), 83.6 (*C*(CH_3) pinacol), 110.8 ($CH^{Ar\text{-}5}$), 128.1 ($C^{Ar\text{-}1}$), 131.4 ($CH^{Ar\text{-}6}$), 135.4 ($CH^{Ar\text{-}2}$), 154.8 ($C^{Ar\text{-}4}$), 164.2 (CO_2*t*Bu), 171.9 (CO_2Me); ^{11}B-NMR ($CDCl_3$, 128 MHz): δ 34,07; IR (neat): ν 3360 (NH), 2978, 1747 (C═O), 1713 (C═O), 1606, 1495, 1422, 1371, 1349, 1253, 1144, 1074, 1028, 966, 857; $[\alpha]_{20}^{D}$ = −76.9 (c = 0.7, $CHCl_3$); Anal. calcd for $C_{21}H_{32}BNO_7$: C, 59.87; H, 7.66. Found: C, 59.84; H, 7.65%.

(+)-[1*R*,(S)*R*]-1-(2-Iodo-3,5-dimethoxyphenyl)-2-(4-tolylsulfinyl)-ethyl acetate (7)

To a solution of β-hydroxy-sulfoxide **16** (2.11 g, 4.7 mmol) in pyridine (20 ml) is added acetic anhydride (0.5 ml) and the mixture is stirred for 2 h at ambient temperature. A saturated aqueous solution of NH_4Cl is added and the mixture is extracted with ethyl acetate. The combined organic phases are dried over $MgSO_4$, filtered and evaporated. The crude product is purified by column chromatography (Et_2O–cyclohexane 4 : 1). Yield: 2.25 g (4.6 mmol, 98%) colorless solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.13 (3H, s, OAc), 2.42 (3H, s, $CH_3{}^{pTol}$), 3.25 (2H, AB, J_{AB} = 13.6 Hz, J_{AX} = 10 Hz, J_{BX} = 3.0 Hz, $\Delta\nu$ = 30 Hz, CH_2), 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 6.20 (1H, X, J_{AX} = 10 Hz, J_{BX} = 3.0 Hz, CH), 6.35 (1H, d, J = 2.6 Hz, H^{Ar}), 6.59 (1H, d, J = 2.6 Hz, H^{Ar}), 7.49 (4H, A_2B_2, J_{AB} = 8.1 Hz, $\Delta\nu$ = 74 Hz, H^{pTol}); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 20.9 (OAc), 21.5 ($CH3^{pTol}$), 55.6 (OMe), 56.5 (OMe), 62.6 (CH_2), 74.4 (CH), 77.8 ($C^{Ar\text{-}2}$), 98.4 ($CH^{Ar\text{-}4}$), 104.0 ($CH^{Ar\text{-}6}$), 124.6 (CH^{pTol}), 130.1 (CH^{pTol}), 140.4 ($C^{pTol\text{-}1}$), 142.0 ($C^{pTol\text{-}4}$), 142.8 ($C^{Ar\text{-}1}$), 158.9 ($C^{Ar\text{-}5}$), 161.6 ($C^{Ar\text{-}3}$), 169.3 (CO); IR (neat): ν 2938, 1743 (C═O), 1579, 1452, 1431, 1371, 1350, 1319, 1221, 1202, 1160, 1079, 1035, 1010, 984, 927, 836, 808; $[\alpha]_{20}^{D}$ = +45.6 (c = 1.05, $CHCl_3$); Anal. calcd for $C_{19}H_{21}IO_5S$: C, 46.73; H, 4.33. Found: C, 46.74; H, 4.33%.

(−)-[1*R*,(S)*R*]-2-Iodo-3,5-dimethoxy-1-[1-methoxy-2-(4-tolylsulfinyl)-ethyl]benzene (8)

NaH (37.6 mg, 0.94 mmol, 60% in paraffin) is washed with hexane, filtered and dried *in vacuo* before a solution of β-hydroxy-sulfoxide **16** (350 mg, 0.78 mmol) in anhydrous DMF (6.0 ml) is added at −20 °C. The reaction mixture is stirred for 10 min before MeI (0.1 ml, 1.57 mmol) is added drop wise *via* syringe. After 30 min at −20 °C saturated aqueous NH_4Cl-solution is added and the mixture is extracted with Et_2O. The combined organic phases are dried over $MgSO_4$, filtered and

evaporated. The crude product is purified by column chromatography (Et_2O). Yield: 329.0 mg (0.72 mmol, 91%) colorless solid. M.p. 110–112 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.44 (3H, s, CH_3^{pTol}), 3.14 (2H, AB, J_{AB} = 13.0 Hz, J_{AX} = 3.0 Hz, J_{BX} = 10.4 Hz, $\Delta\nu$ = 68 Hz, CH_2), 3.17 (3H, s, OMe), 3.81 (3H, s, $OMe^{Ar\text{-}5}$), 3.83 (3H, s, $OMe^{Ar\text{-}3}$), 4.49 (1H, X, J_{AX} = 3.0 Hz, J_{BX} = 10.4 Hz, C*H*(OMe)), 6.37 (1H, d, J = 2.7 Hz, $H^{Ar\text{-}6}$), 6.69 (1H, d, J = 2.7 Hz, $H^{Ar\text{-}4}$), 7.42 (4H, A_2B_2, J_{AB} = 7.9 Hz, $\Delta\nu$ = 91 Hz, H^{pTol}); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.5 (CH_3^{pTol}), 55.6 ($OMe^{Ar\text{-}5}$), 56.4 ($OMe^{Ar\text{-}3}$), 57.0 (OMe), 63.5 (CH_2), 79.0 ($C^{Ar\text{-}2}$), 82.5 (*C*H(OMe)), 99.0 (CH^{Ar}), 103.4 (CH^{Ar}), 125.0 (CH^{pTol}), 130.0 (CH^{pTol}), 142.0 ($C^{pTol\text{-}1}$), 143.2 ($C^{pTol\text{-}4}$), 152.9 ($C^{Ar\text{-}1}$), 158.7 ($C^{Ar\text{-}3}$), 161.9 ($C^{Ar\text{-}5}$); IR (neat): ν 2940, 1591, 1573, 1456, 1429, 1317, 1218, 1152, 1109, 1069, 1035, 1026, 1010, 979, 930, 859, 807, 765; $[\alpha]_{20}^{D}$ = −14.5 (c = 1.0, $CHCl_3$); Anal. calcd for $C_{18}H_{21}IO_4S$: C, 46.97; H, 4.60. Found: C, 46.94; H, 4.62%.

Methyl 2-iodo-3,5-dimethoxybenzoate (14)

A solution of iodine (5.18 g, 20.4 mmol) in chloroform (200 ml) is added drop wise to a stirred solution of methyl 3,5-dimethoxybenzoate **13** (4.0 g, 20.4 mmol) in chloroform (50 ml) containing suspended silver trifluoroacetate (4.51 g, 20.4 mmol). After the addition the precipitated silver iodide is collected by filtration and washed with dichloromethane. The combined filtrates are washed with water (100 ml), saturated aqueous $Na_2S_2O_3$ (2 × 100 ml) and brine (100 ml). The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated. The crude product is purified by column chromatography (cyclohexane–EtOAc 5 : 1). Yield: 4.3 g (13.3 mmol, 65%, 89% based on recovered starting material) colorless solid. M.p. 68–72 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.82 (3H, d, J = 1.1 Hz, OMe), 3.87 (3H, d, J = 1.1 Hz, OMe), 3.93 (3H, d, J = 1.1 Hz, CO_2Me), 6.52 (1H, dd, J = 2.6, 1.1 Hz, H^{Ar}), 6.80 (1H, dd, J = 2.6, 1.1 Hz, H^{Ar}); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 52.6 (OCH_3), 55.7 (OCH_3), 56.6 (CO_2CH_3), 75.7 ($C^{Ar\text{-}2}$), 101.3 (CH^{Ar}), 138.9 ($C^{Ar\text{-}1}$), 159.4 (C^{Ar}-OMe), 160.9 (C^{Ar}-OMe), 168.0 (CO_2CH_3); IR (neat): ν 2952, 1719 (C═O), 1576, 1453, 1442, 1428, 1330, 1240, 1211, 1150, 1070, 1051, 1012, 881, 848, 816, 781, 754; Anal. calcd for $C_{10}H_{11}IO_4$: C, 37.29; H, 3.44. Found: C, 37.35; H, 3.49%.

(+)-[(S)*R*]-1-(2-Iodo-3,5-dimethoxyphenyl)-2-(4-tolylsulfinyl)-ethanone (15)

To a solution of diisopropylamine (1.9 ml, 13.6 mmol) in anhydrous THF (60 ml) is added a solution of *n*-BuLi (9.0 ml, 13.6 mmol, 1.6 M in hexane) at −15 °C. After completion of the addition the reaction mixture is kept at −15 °C for a further 30 min before it is warmed to 0 °C. A solution of (+)-(*R*)-methyl *p*-tolylsulfoxide (2.1 g, 13.6 mmol) in dry THF (60 ml) is slowly added using a cannula and the mixture is stirred for an additional 30 min. Then the prepared mixture is slowly transferred *via* cannula to a solution of ester **14** (2.2 g, 6.8 mmol) in THF (60 ml) at 0 °C. After completion of the addition the reaction mixture is allowed to warm to ambient temperature and stirred for 12 h. A saturated aqueous solution of NH_4Cl (150 ml) is added, the mixture is acidified (pH ∼ 2) with 10% H_2SO_4 and the phases are separated. The aqueous phase is extracted with ethyl acetate (2 × 150 ml). The combined organic phases are washed with brine (150 ml), dried over $MgSO_4$, filtered and evaporated. The crude product is purified by column chromatography (cyclohexane–EtOAc 2 : 3). Yield: 2.38 g (5.4 mmol, 80%) light yellow solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.40 (3H, s, CH_3^{pTol}), 3.77 (3H, s, $OMe^{Ar\text{-}5}$), 3.85 (3H, s, $OMe^{Ar\text{-}3}$), 4.43 (2H, AB, J = 14.1 Hz, $\Delta\nu$ = 43 Hz, CH_2), 6.35 (1H, d, J = 2.6 Hz, $H^{Ar\text{-}6}$), 6.46 (1H, d, J = 2.6 Hz, $H^{Ar\text{-}4}$), 7.45 (4H, A_2B_2, J_{AB} = 8.0 Hz, $\Delta\nu$ = 83 Hz, H^{pTol}); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.4 (CH_3^{pTol}), 55.7 ($OMe^{Ar\text{-}5}$), 56.6 ($OMe^{Ar\text{-}3}$), 68.7 (CH_2), 72.3 ($C^{Ar\text{-}2}$), 101.1 (CH^{Ar}), 104.9 (CH^{Ar}), 124.5 (CH^{pTol}), 130.1 (CH^{pTol}), 142.2 ($C^{Ar\text{-}3}$), 142.2 ($C^{pTol\text{-}1}$), 142.2 ($C^{pTol\text{-}4}$), 158.9 ($C^{Ar\text{-}3}$), 161.4 ($C^{Ar\text{-}5}$), 196.3 (CO); IR (neat): ν 2948, 1692 (C═O), 1585, 1447, 1411, 1334, 1290, 1205, 1171, 1150, 1076, 1029, 1007, 937, 850, 806, 815, 774; $[\alpha]_{20}^{D}$ = +122.0 (c = 1.0, $CHCl_3$); Anal. calcd for $C_{17}H_{17}IO_4S$: C, 45.96; H, 3.86. Found: C, 45.91; H, 3.79%.

(−)-[1*R*,(S)*R*]-1-(2-Iodo-3,5-dimethoxyphenyl)-2-(4-tolylsulfinyl)-ethanol (16)

To flame dried $ZnBr_2$ (3.6 g, 15.6 mmol) is added a solution of β-ketosulfoxide **15** (2.32 g, 5.2 mmol) in dry THF (100 ml) at 0 °C. The reaction mixture is stirred at 0 °C for 15 min before it is cooled to −78 °C. Then a solution of DIBAL (10.4 ml, 10.4 mmol, 1 M in toluene) is added at −78 °C and the mixture is stirred for 5 h. A saturated aqueous solution of disodium tartrate is added, the phases are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are dried over $MgSO_4$, filtered and evaporated. The crude product is purified by column chromatography (EtOAc–CH_2Cl_2 1 : 4). Yield: 2.11 g (4.7 mmol, 90%) colorless solid. M.p. 58–62 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.41 (3H, s, CH_3^{pTol}), 3.01 (2H, AB, J_{AB} = 13.2 Hz, J_{AX} = 10.0 Hz, J_{BX} = 1.5 Hz, $\Delta\nu$ = 89 Hz, CH_2), 3.81 (3H, s, $OMe^{Ar\text{-}5}$), 3.84 (3H, s, $OMe^{Ar\text{-}3}$), 5.69 (1H, X, J_{AX} = 10.0 Hz, J_{BX} = 1.5 Hz, C*H*(OH)), 6.37 (1H, d, J = 2.8 Hz, $H^{Ar\text{-}6}$), 6.90 (1H, d, J = 2.8 Hz, $H^{Ar\text{-}4}$), 7.45 (4H, A_2B_2, J_{AB} = 8.3 Hz, $\Delta\nu$ = 73 Hz, H^{pTol}); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.4 (CH_3^{pTol}), 55.6 ($OMe^{Ar\text{-}5}$), 56.5 ($OMe^{Ar\text{-}3}$), 62.3 (CH_2), 75.2 (CH(OH)), 77.6 ($C^{Ar\text{-}2}$-I), 98.9 (CH^{Ar}), 103.8 (CH^{Ar}), 123.9 (CH^{pTol}), 130.2 (CH^{pTol}), 140.4 ($C^{pTol\text{-}1}$), 142.2 ($C^{pTol\text{-}4}$), 145.8 ($C^{Ar\text{-}1}$), 158.5 ($C^{Ar\text{-}3}$), 161.6 ($C^{Ar\text{-}5}$); IR (neat): ν 3270 (OH), 2937, 1578, 1450, 1427, 1413, 1316, 1214, 1197, 1156, 1066, 1008, 989, 807; $[\alpha]_{20}^{D}$ = −52.8 (c = 1.0, $CHCl_3$); Anal. calcd for $C_{17}H_{19}IO_4S$: C, 45.75; H, 4.29. Found: C, 46.04; H, 4.35%.

N-(*tert*-Butyloxycarbonyl)-D-(4-hydroxyphenyl)-glycine (10)

To a solution of NaOH (0.72 g, 18.0 mmol) in H_2O–dioxane 2 : 1 (54.0 ml) are added D-(4-hydroxyphenyl)-glycine **9** (3.0 g, 18.0 mmol) and a solution of Boc_2O (4.29 g, 19.7 mmol) in dioxane (18.0 ml) and the reaction mixture is stirred for 4 h at ambient temperature. The dioxane is evaporated and the remaining aqueous phase is washed with a small amount of Et_2O. Then the aqueous phase is acidified with $KHSO_4$ (pH ∼ 2–3) and

extracted with ethyl acetate. The combined organic phases are dried over $MgSO_4$, filtered and evaporated. The resulting residue is taken up in $CHCl_3$ and the solvent is evaporated to give a white powder, which can be used for the next reaction step without any further purification. Yield: 4.8 g (17.95 mmol, 99%) colorless powder. M.p. 205 °C decomp. (Lit. 199 °C).[5f] ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.37 (9H, s, *t*Bu), 6.94 (1H, d, J = 7.5 Hz, C*H*(CO_2H)NHBoc), 6.93 (4H, A_2B_2, J_{AB} = 8.5 Hz, $\Delta\nu$ = 140 Hz, H^{Ar}), 7.37 (1H, d, J = 7.5 Hz, N*H*Boc), 9.42 (1H, bs, OH), 12.58 (1H, bs, CO_2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.1 ($CO_2C(CH_3)_3$), 57.0 (*C*H(CO_2H)NHBoc), 79.1 ($CO_2C(CH_3)_3$), 115.0 (CH^{Ar}), 127.4 ($C^{Ar\text{-}1}$), 128.8 (CH^{Ar}), 155.0 ($C^{Ar\text{-}4}$-OH), 156.9 (CO_2H), 172.6 ($CO_2C(CH_3)_3$); $[\alpha]_{20}^{D}$ = −130.9 (c = 1.24, EtOH), Lit.[5f] $[\alpha]_{20}^{D}$ = 130.0 (c = 1.08, EtOH).

N-(*tert*-Butyloxycarbonyl)-D-(4-methoxyphenyl)-glycine methyl ester (11)

To a solution of **10** (8.0 g, 29.9 mmol) in acetone (150 ml) are added K_2CO_3 (16.55 g, 119.7 mmol) and MeI (5.59 ml, 89.8 mmol) and the mixture is heated to reflux for 16 h. After cooling to ambient temperature the reaction mixture is filtered over a pad of celite, which is afterwards washed with Et_2O. The organic phase is washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product is purified by column chromatography (Et_2O–cyclohexane 2 : 1). Yield: 8.8 g (29.8 mmol, 99%) colorless solid. M.p. 70–75 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.34 (9H, s, *t*Bu), 3.63 (3H, s, OMe), 3.71 (3H, s, OMe), 5.17 (1H, bd, J = 7.1 Hz, CH), 5.40 (1H, bd, J = 7.1 Hz, NH), 6.99 (4H, A_2B_2, J_{AB} = 8.7 Hz, $\Delta\nu$ = 121 Hz, H^{Ar}); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.3 (*t*Bu), 52.6 (OMe), 55.3 (CO_2CH_3), 57.0 (CH), 80.1 ($C(CH_3)_3$), 114.3 (CH^{Ar}), 128.4 (CH^{Ar}), 129.0(C^{Ar}), 154.8 (C^{Ar}), 159.6 (CO_2Me), 171.9 (CO_2*t*Bu); IR (neat): ν 3369 (NH), 2979, 1741 (C═O), 1697 (C═O), 1511, 1341, 1250, 1214, 1157, 1052, 1028, 980, 894, 832; $[\alpha]_{20}^{D}$ = −106.3 (c = 1.1, $CHCl_3$); Anal. calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17. Found: C, 60.86; H, 6.99%.

N-(*tert*-Butyloxycarbonyl)-D-(3-iodo-4-methoxyphenyl)-glycine methyl ester (12)

To a solution of **11** (1.0 g, 3.39 mmol) in $CHCl_3$ (7.0 ml) is added silver trifluoroacetate (1.65 g, 7.45 mmol) followed by iodine (1.03 g, 4.06 mmol) and the reaction mixture is stirred for 15 h at ambient temperature. The mixture is diluted with Et_2O and filtered over a pad of celite, which is washed afterwards with Et_2O. The organic phase is washed with a saturated aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered and evaporated. The crude product is purified by column chromatography (CH_2Cl_2). Yield: 1.3 g (3.09 mmol, 91%) colorless solid. M. p. 91–93 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.42 (9H, s, *t*Bu), 3.72 (3H, s, OMe), 3.86 (3H, s, OMe), 5.20 (1H, bd, J = 7.2 Hz, CH), 5.54 (1H, bd, J = 7.2 Hz, NH), 6.77 (1H, d, J = 8.5 Hz, $H^{Ar\text{-}5}$), 7.31 (1H, dd, J = 8.5, 2.2 Hz, $H^{Ar\text{-}6}$), 7.74 (1H, d, J = 2.2 Hz, $H^{Ar\text{-}2}$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.2 (*t*Bu), 52.8 (OMe), 56.3 (CH), 56.4 (CO_2CH_3), 80.3 ($C(CH_3)_3$), 86.3 (C^{Ar}), 110.9 (CH^{Ar}), 128.5 (CH^{Ar}), 131.1 (C^{Ar}), 137.9 (CH^{Ar}), 154.7 (C^{Ar}), 158.2 (CO_2Me), 171.4 (CO_2*t*Bu); IR (neat): ν 3369 (NH), 2979, 1741 (C═O), 1697(C═O), 1511, 1341, 1250, 1214, 1157, 1052, 1028, 980, 894, 832; $[\alpha]_{20}^{D}$ = −80.5 (c = 1.6, $CHCl_3$); Anal. calcd for $C_{15}H_{20}INO_5$: C, 42.77; H, 4.79. Found: C, 42.62; H, 4.71%.

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Notes and references

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