# Enantioselective Synthesis of the Pyrrolidine Core of Endothelin Antagonist ABT-627 (Atrasentan) via 1,2-Oxazines

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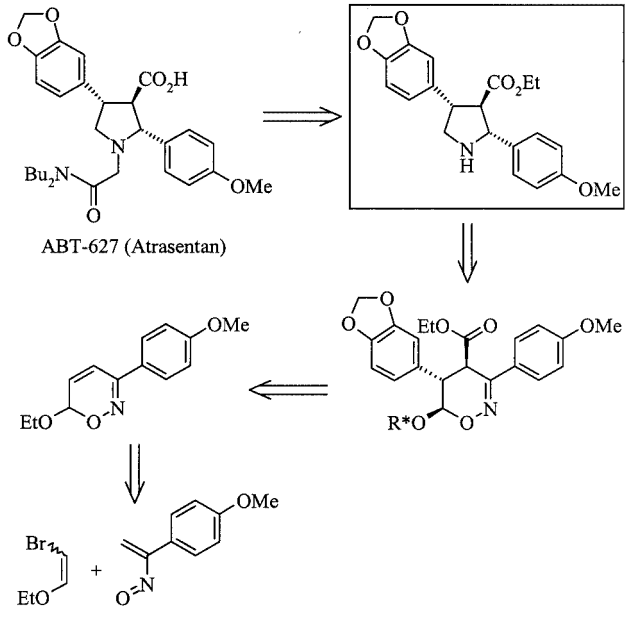
Diastereoselective syntheses of the pyrrolidine core **6a** of the endothelin antagonist ABT-627 (Atrasentan) either as a racemic mixture or as an enantiopure compound are presented. The crucial steps of these syntheses utilized the highly diastereoselective conjugate addition of 1,3-benzodioxol-5-yllithium to racemic 6*H*-1,2-oxazine **3** or enantiopure 6*H*-1,2-oxazines **7** or **8**, followed by trapping with ethyl cyanoformate (Mander's reagent). The resulting 5,6-dihydro-4*H*-1,2-oxazines were transformed into the 2,3,4-trisubstituted pyrrolidine **6a**.


## Introduction

Endothelins (ET-1, ET-2, and ET-3) constitute a family of bicyclic peptides, each containing 21 amino acids, which are potent vasoconstrictors and potent mitogens.[1] ET-1, produced primarily by endothelial cells, has been implicated as a contributing factor in many diseases. Two subtypes of human endothelin receptors ($ET_A$ and $ET_B$) exist, and it is apparent from many studies that most of the actions of ET-1 associated with pathological conditions are mediated by $ET_A$ receptors, while the $ET_B$ receptors may mediate some beneficial effects.[2] Animal models and human studies have suggested that ET receptor antagonists may have beneficial effects in the treatment of a number of different diseases, such as heart failure, pulmonary hypertension, renal failure, asthma, and as a therapeutic agent for cancers.[3] Selective blocking of the $ET_A$ receptor subtype may be advantageous in the treatment of these diseases. In 1996 a novel class of non-peptide endothelin receptor antagonists containing a substituted pyrrolidine ring was discovered at Abbott Laboratories.[4] ABT-627 (Atrasentan, Scheme 1) is highly potent and selective for the $ET_A$ receptor subtype. In the following years, structure-activity studies were carried out to increase the selectivity, binding affinity and metabolic stability of ABT-627 by modification of the substituents on the pyrrolidine ring.[2−5] Recent results demonstrate that the selectivity and the metabolic stability can be improved by variation of the substituents on the aromatic rings.[3] Meanwhile, phase III clinical trials with Atrasentan for the treatment of prostate cancer are in progress and phase II trials for the treatment of other cancers are planned.[6]




Scheme 1. Retrosynthetic analysis of endothelin antagonist ABT-627 (Atrasentan)

In the initial synthesis of ABT-627, the construction of the pyrrolidine ring involves a Michael reaction between ethyl (4-methoxybenzoyl)acetate and 3,4-(methylenedioxy)-2′-nitrostyrene, followed by a reduction.[4] The disadvantages of this method are poor diastereoselectivity and resolution of the enantiomers at a late stage, either by treatment of the carboxylic acid with a chiral oxazolidine and separation of the resulting diastereomers by chromatography, or by generation of a chiral salt and separation of the diastereomers by crystallisation. Wittenberger[7] and Pfau[8] have developed enantioselective syntheses with the use of a valine-derived oxazolidinone or of methylbenzylamine as chiral auxiliaries. The pyrrolidine ring is formed either by a

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ring-contraction of a 1,2-oxazine, prepared by diastereoselective cyclization, or by a method similar to the original synthesis, but now with employment of an enantioselective Michael-type reaction.

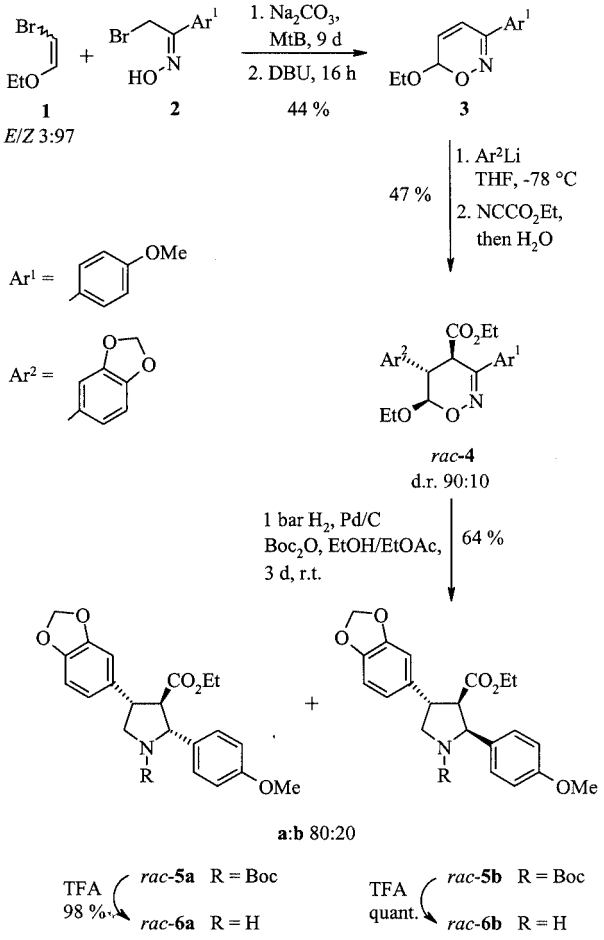
Retrosynthetic analysis (Scheme 1) shows that the pyrrolidine core of ABT-627 should also be available through hydrogenolysis of a suitably substituted 1,2-oxazine, which should be accessible from conjugate addition between 1,3-benzodioxol-5-yllithium or an equivalent and a 6*H*-1,2-oxazine, followed by trapping of the intermediate with a carboxylating electrophile. In the key step, a hetero-Diels–Alder reaction of an α-nitroso alkene should provide the required 6*H*-1,2-oxazine. Conjugate additions of reactive organolithium compounds and trapping of the intermediates with electrophiles has proved to be an highly efficient and diastereoselective process, affording 4,5-*trans*/5,6-*trans*-diastereomers either in large excess or exclusively.[9,10] Introduction of chiral alkoxy groups at 6*H*-1,2-oxazine permits the synthesis of enantiopure 1,2-oxazines and products derived from them.[11]

## Results and Discussion

### Synthesis of the Racemic Pyrrolidine

We first examined the viability of the anticipated route by a synthesis of *rac*-**6a**. This 2,3,4-trisubstituted pyrrolidine was prepared starting from 1-bromo-2-ethoxyethene (**1**) and α-bromo-(*p*-methoxy)acetophenonoxime (**2**, Scheme 2). Addition of sodium carbonate to the reaction mixture causes a nitroso alkene to be formed in situ, and this undergoes a hetero-Diels–Alder reaction to yield a 5-bromo-substituted 4*H*-1,2-oxazine. Its treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished 6*H*-1,2-oxazine **3** in 44% yield. Unfortunately, all attempts to improve the efficiency of this reaction were unsuccessful: neither the use of a larger excess of the dienophile, in order to avoid side reactions of the reactive nitroso alkene, nor modifications of the reaction conditions [different solvents ($CH_2Cl_2$ or aqueous solution of LiCl), enhanced pressure or temperature] had a positive effect. The relatively low yield of the cycloaddition in relation to the reactions of other nitroso alkenes, such as 1-alkoxycarbonyl- or 1-phenyl-substituted nitroso alkenes,[12] may be explained by the electron-donating effect of the methoxy substituent, which makes the transient nitroso alkene (derived from **2**) an inferior heterodiene for a Diels–Alder reaction with inverse electron demand.

Addition of 1,3-benzodioxol-5-yllithium to 6*H*-1,2-oxazine **3** and trapping of the resulting intermediate with ethyl cyanoformate (Mander's reagent[13]) provided 1,2-oxazine *rac*-**4** in moderate yield but with good diastereoselectivity (*d. r.* 90:10). In accordance with previous results,[10] confirmed by NMR spectroscopy, the configuration of the major isomer was assigned as 4,5-*trans*/5,6-*trans* and that of the minor isomer 4,5-*cis*/5,6-*trans*. This recorded diastereomeric ratio probably represents the equilibrium. For crude *rac*-**4** a ratio of 44:56 was recorded, which was apparently changed by column chromatography due to the acid-catalysed equilibration. This behaviour has been discussed earlier and is only relevant for 4-alkoxycarbonyl-substituted 1,2-oxazines.[10]




Scheme 2. Synthesis 2,3,4-trisubstituted pyrrolidines *rac*-**6a** and *rac*-**6b**

The transformation of 1,2-oxazines into pyrrolidines by cleavage of the N–O bond with catalytically activated hydrogen is a well known process.[14] Hydrogenolysis of *rac*-**4** with Pd/C as catalyst in the presence of $Boc_2O$ gave the protected pyrrolidine *rac*-**5** in 64% yield as a mixture of diastereomers (80:20), which were easily separated by HPLC. The mechanism of this multi-step, one-pot process involves a reductive cleavage of the N–O bond, fragmentation of the resulting semiacetal, reduction of the C=N bond, recyclisation, and final reduction of the resulting cyclic imine intermediate to afford the isolated pyrrolidine derivative. In previous studies[15] it was shown that addition of $Boc_2O$ to the reaction mixture prevents the cleavage of the benzylic C–N bond of the pyrrolidine produced. This acylating additive also results in a cleaner reaction and facilitates purification of products.

The configurations of pyrrolidines *rac*-**5a** and *rac*-**5b** were assigned after cleavage of the protecting group with trifluoroacetic acid (TFA). Comparison with the known 2,3-*trans*/3,4-*trans*-substituted pyrrolidine[4] and NOE measurements revealed that the major isomer has the desired 2,3-

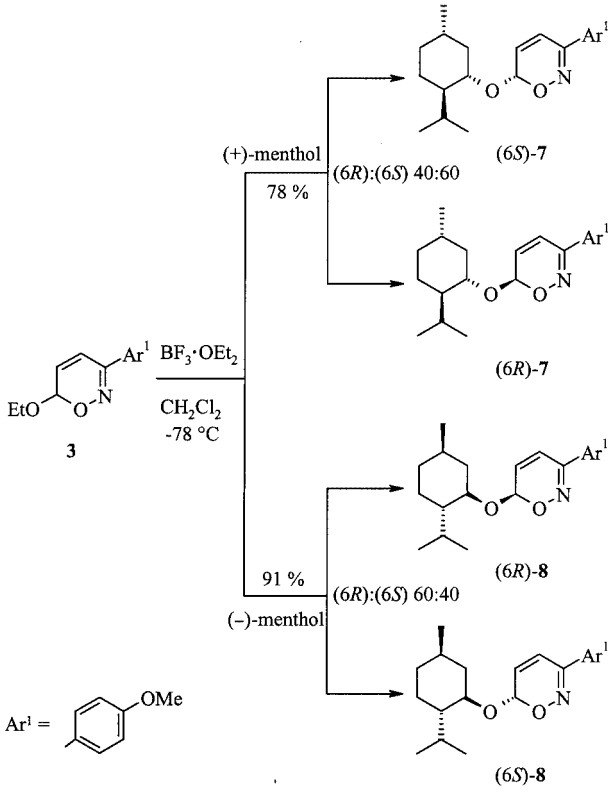
*trans*/3,4-*trans* configuration, while the minor isomer is the 2,3-*cis*/3,4-*trans* product. The transformation of pyrrolidine *rac*-**6a** into ABT-627 by *N*-alkylation and subsequent ester hydrolysis was described previously.[4]

### Synthesis of Enantiopure Pyrrolidine

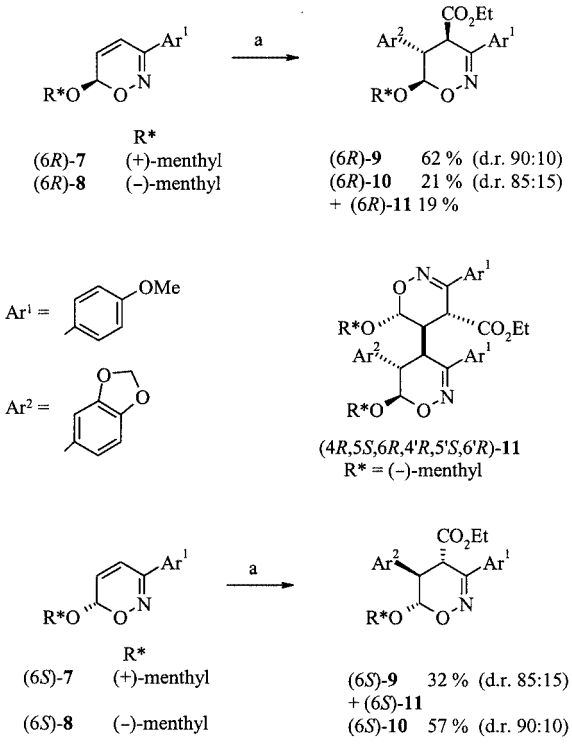
The synthesis of enantiopure precursor (2*R*,3*R*,4*S*)-**6a** was also achieved with 6*H*-1,2-oxazine **3** as starting material. In a previous publication[11] we reported the synthesis of related enantiopure 6*H*-1,2-oxazines by Lewis acid-catalysed exchange of the 6-ethoxy group with (−)-menthol employed as chiral auxiliary. Treatment of **3** with either (+)-menthol or (−)-menthol furnished the expected pairs of two diastereomers (*d. r.* 60:40). With (+)-menthol and **3**, (6*S*)-**7** is the slightly favoured diastereomer, whereas (6*R*)-**8** is formed predominantly with (−)-menthol (Scheme 3). The diastereomers can easily be separated by flash chromatography or HPLC. On treatment of a pure compound with catalytic amounts of acid the 60:40 mixture of isomers is formed again, which in principle provides the opportunity to recycle the undesired diastereomer.

Addition of 1,3-benzodioxol-5-yllithium to compounds **7** and **8**, followed by trapping with ethyl cyanoformate, yielded the desired compounds **9** and **10** with good diastereoselectivities (Scheme 4). Remarkably, the enantiomers (6*R*)-**8** and (6*S*)-**7** are much less reactive towards the addition of an aryllithium compound than the enantiomers (6*R*)-**7** and (6*S*)-**8**, reflected both in lower yields and the formation of side product **11**, apparently generated by addition of the lithiated intermediate to a second 6*H*-1,2-oxazine. In general, the 6*H*-1,2-oxazines were added to an excess of the organolithium reagent (2.2 equiv.) over a period of 35 to 60 min in order to avoid this side reaction. For the reaction of (6*S*)-**7** we therefore increased the addition time (120 min) and the excess of the organolithium reagent (5 equiv.), but the yield of (6*S*)-**9** was only slightly improved and the formation of **11** could not be prevented. These experiments clearly reveal that enantiomers (6*R*)-**7** and (6*S*)-**8** are the compounds with matching configurations for efficient attack of (bulky) aryllithium species, whereas their diastereomers (6*S*)-**7** and (6*R*)-**8** apparently have mismatched configurations. As a consequence, the preferred pathway to 1,2-oxazine with the required 6*R* configuration uses (+)-menthol as chiral auxiliary. The stereochemistry of diastereomerically pure side product **11** was not established, but a 4*R*,5*S*,6*R* configuration in both 1,2-oxazine rings of this "dimer" is most likely for mechanistic reasons.

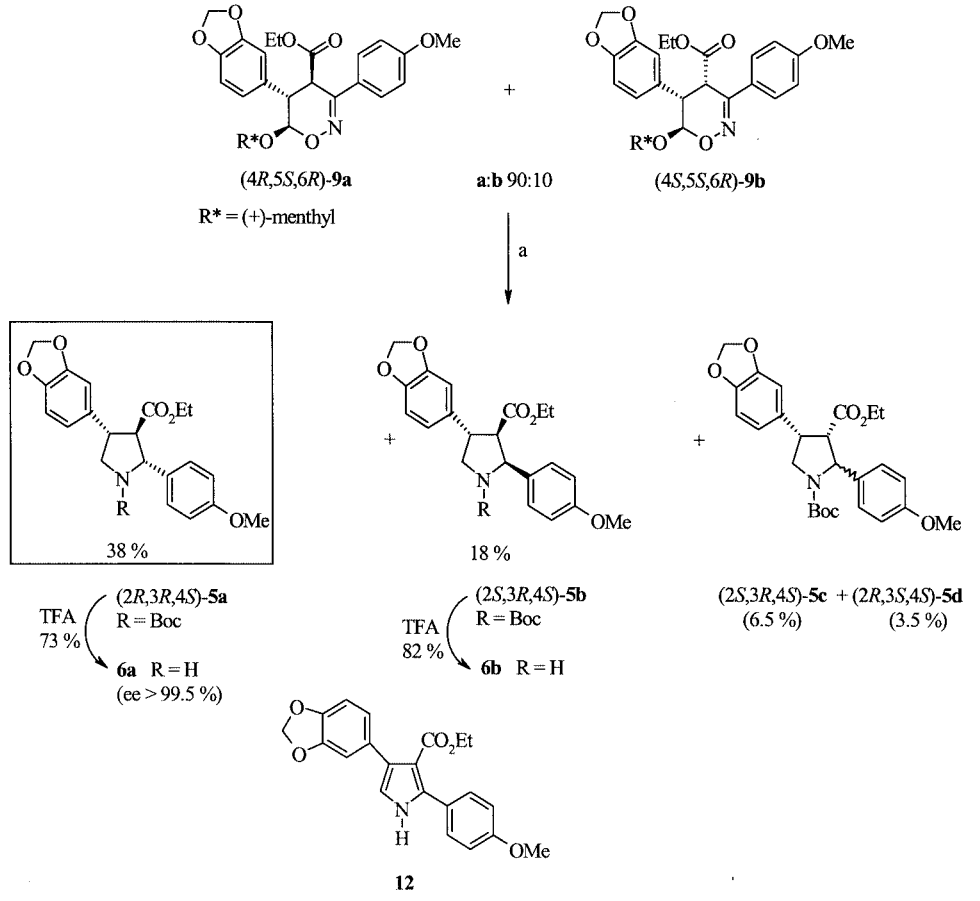
The hydrogenolysis of 1,2-oxazine (6*R*)-**9** was first carried out under conditions as successfully applied to *rac*-**4** (Scheme 2). However, no conversion was observed on use either of Pd/C or of $Pd(OH)_2$/C at atmospheric pressure, or when higher pressure (50−60 bar) was employed. In all cases the starting material was recovered unchanged. Finally, an excess of Raney nickel (ca. 1 g Raney Ni per mmol




Scheme 3. Synthesis of 6-menthyloxysubstituted 6*H*-1,2-oxazines **7** and **8**




Scheme 4. Conjugated addition of 1,3-benzodioxol-5-yllithium to 6-menthyloxy-substituted 6*H*-1,2-oxazines **7** and **8**; (a) 1. $LiAr^2$, THF, −78 °C, 2. $NCCO_2Et$, −78 °C, then EtOH

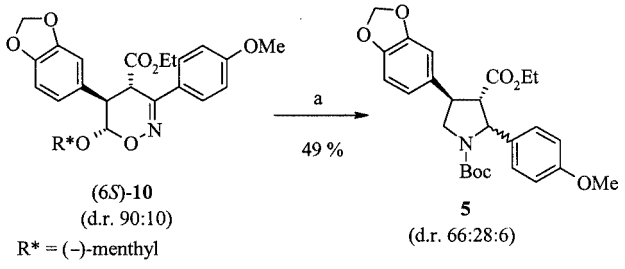



Scheme 5. Hydrogenolysis of **9**; (a) 70 bar $H_2$, Raney nickel, $Boc_2O$, EtOH/EtOAc

of 1,2-oxazine) under 50−70 bar of hydrogen in the presence of $Boc_2O$ provided the desired pyrrolidines **5**. Interestingly, a reaction employing lower amounts of Raney nickel (ca. 0.5 g per mmol 1,2-oxazine) furnished pyrrole **12** as major component (24%) accompanied by only small quantities of pyrrolidine **5** (7%) (Scheme 5). These experiments show that the reductive cleavage of the N−O bond of 1,2-oxazine **9** is strongly hampered by the bulky 6-menthyloxy group. With Raney nickel the N−O bond is cleaved, but the subsequent reduction of the imine bond is relatively slow. If this imine cyclizes, after elimination of menthol and hydrogen shift, pyrrole **12** is finally formed. Only if this imine is reduced before cyclization can pyrrolidine **6** be formed. An excess of Raney nickel apparently helps to direct the reaction of this pathway.

Thus, hydrogenolysis of (6*R*)-**9** and (6*S*)-**10** (mixture of diastereomers **a**/**b** = 90:10) under these conditions afforded pyrrolidines **5** as mixtures of diastereomers, which could be separated by HPLC (Schemes 5 and 6). Standard deprotection of **5a** and **5b** with trifluoroacetic acid finally provided pyrrolidines **6a** and **6b** in good yields. The enantiomeric excess of our target compound (2*R*,3*R*,4*S*)-**6a** was determined by transformation into the Mosher amide and HPLC comparison with this corresponding amide derived from *rac*-**6a**.

In both hydrogenolysis reactions (Schemes 5 and 6) the 2,3-*trans*/3,4-*trans* diastereomers moderately predominate. The configurations of isomers **5c** and **5d** were assigned by



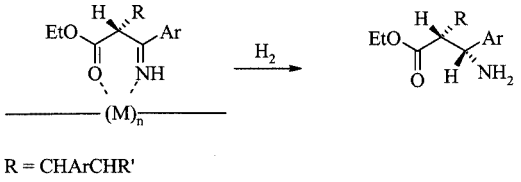

Scheme 6. Hydrogenolysis of **10**; (a) 50−60 bar $H_2$, Raney nickel, $Boc_2O$, EtOH/EtOAc, 22 h

comparison of the chemical shifts of the protons at C-3. Because of the ring current of the vicinal aromatic rings at C-2 and C-4 the signal of the 2,3-*trans* compound is shifted to higher field [3-$H_{trans}$ δ = 3.30−3.17 (m); 3-$H_{cis}$ δ = 3.48 ($m_c$)].

The formation of the 2,3-*trans* products in moderate excess (*dr*, 70:30) may be interpreted in terms of a chelation mechanism in which complexation of the carbonyl and the imine group with the catalyst surface after N−O cleavage of **9** results in a fixed conformation. The subsequent reduction of the imine unit occurs opposite to the bulky group R (representing the residue of the intermediate), as illustrated in

Scheme 7, to provide the observed major diastereomers. We admit that this interpretation is speculative.




Scheme 7. Proposed chelation mechanism for the reduction of imine intermediates during hydrogenolysis of 5,6-dihydro-4*H*-1,2-oxazines

## Conclusion

In summary, we have described a fairly short new method for the synthesis of enantiopure 2,3,4-trisubstituted pyrrolidines through the use of cheap and commercially available auxiliaries and reagents. The core of endothelin antagonist **5a** was prepared in five steps: (i) hetero-Diels–Alder-reaction with a 1-aryl-nitrosoalkene generated in situ, (ii) exchange of the ethoxy group by (+)- or (−)-menthyloxy, followed by separation of the diastereomers, (iii) conjugated addition, (iv) hydrogenolysis, and (v) deprotection of the pyrrolidine. Unfortunately, the overall efficiency of our auxiliary-based method is diminished by the necessity to separate the diastereomers formed. On the other hand, this method makes both enantiomers available and it is in principle highly flexible with respect to substituents at C-2 and C-4 of the pyrrolidine ring, while the ethoxycarbonyl group at C-3 may also be substituted by other moieties introduced in the conjugate addition (step iii). Thus, many analogues of ABT-627 should be available by our route.

## Experimental Section

**General:** Unless otherwise stated, all reactions were performed under argon atmosphere in flame-dried flasks by addition of the components by syringe. All solvents were dried by standard procedures. $^1$H and $^{13}$C NMR spectra were recorded on Bruker instruments (AC, 500, WH 270, AC 250) in $CDCl_3$ or $C_6D_6$ solution. The chemical shifts are given relative to the TMS or to the $CDCl_3$ signal ($\delta_H$ = 7.27, $\delta_C$ = 77.0). Higher order NMR spectra were approximately interpreted as first-order spectra if possible. Missing signals of minor isomers are hidden by signals of major isomers, or could not be unambiguously identified due to low intensity. IR spectra were measured with a Nicolet 5 SXC FT-IR spectrometer. The MS and HRMS spectra were recorded with a Varian MAT 711 instrument. Neutral aluminium oxide (activity III, Fluka/Merck) or silica gel (0.040–0.063 mm, Fluka) were used for column chromatography. Nucleosil 50-5 (Macherey & Nagel) was used for HPLC. Melting points (uncorrected) were measured with a Thermovar melting point microscope from Reichert. Optical rotations were determined with Perkin–Elmer 241 polarimeter at 20 °C. Starting materials **1**[16] and **2**[17] were prepared by literature procedures. All other chemicals were commercially available and were used as received.

**6-Ethoxy-3-(*p*-methoxyphenyl)-6*H*-1,2-oxazine (3):** α-Bromo-(*p*-methoxy)acetophenonoxime (**2**, 2.47 g, 10.1 mmol) and 1-bromo-2-ethoxyethene (**1**, 15.1 g, 100 mmol) were dissolved in *tert*-butyl methyl ether (MtB) (200 mL) and dichloromethane (50 mL). To start the reaction, freshly ground sodium carbonate (6.40 g, 60.0 mmol) was added, and the reaction mixture was stirred for 9 days at room temp., another portion of sodium carbonate (6.40 g, 60.0 mmol) being added after 3 days. The suspension was filtered through a pad of Celite to remove inorganic salts. The resulting filtrate was treated with DBU (2.40 mL, 15.9 mmol) and the mixture was stirred for 16 h at room temp. The solution was then washed with water (3 ×) and dried with $Na_2SO_4$. The solvent was removed in vacuo, and the excess of **1** was distilled off by Kugelrohr distillation. The residue was purified by column chromatography (aluminium oxide, *n*-hexane/ethyl acetate, 4:1) to yield 1,2-oxazine **3** (1.03 g, 44%) as a colourless solid (m.p. 31–33 °C). $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 9.2 Hz, 2 H, Ar), 6.94 (d, *J* = 9.6 Hz, 2 H, Ar), 6.59 (d, *J* = 9.8 Hz, 1 H, 4-H), 6.41 (dd, *J* = 4.4, 9.8 Hz, 1 H, 5-H), 5.59 (d, *J* = 4.4 Hz, 1 H, 6-H), 4.00, 3.69 (2 dq, *J* = 7.1, 9.6 Hz, 2 H, $OCH_2$), 3.84 (s, 3 H, $OCH_3$), 1.23 (t, *J* = 7.1 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ = 160.9 (s, *C*$OCH_3$), 153.5 (s, C=N), 127.4 (d, Ar), 126.4 (d, C-5), 126.2 (s, Ar), 116.2 (d, C-4), 114.0 (d, Ar), 91.7 (d, C-6), 64.0 (t, $OCH_2$), 55.3 (q, $OCH_3$), 15.0 (q, $CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3070–2840 $cm^{-1}$ (C–H), 1610 (C=N). $C_{13}H_{15}NO_3$ (233.3) calcd. C 66.94, H 6.31, N 6.00; found C 66.86, H 6.43, N 5.83.

**General Procedure A (Addition of 1,3-Benzodioxol-5-yllithium to 1,2-Oxazines 3, 7, and 8):** *tert*-Butyllithium (1.5 M solution in pentane, 4.4 equiv.) was added at −78 °C to a solution of 5-bromo-1,3-benzodioxole (2.2 equiv.) in THF (5 mL/mmol of 1,2-oxazine). After the mixture had been stirred for 30 min, a solution of 1,2-oxazine (1.0 equiv.) in THF (10 mL/mmol of 1,2-oxazine) was added (addition time see below) and the mixture was stirred at −78 °C. Ethyl cyanoformate was then added, and the mixture was stirred at −78 °C. Water or ethanol was added and the mixture was allowed to warm to room temp. After addition of sat. aqueous ammonium chloride solution (10 mL/mmol of 1,2-oxazine) the mixture was extracted with diethyl ether (2 × 20 mL/mmol of 1,2-oxazine), the combined extracts were dried ($Na_2SO_4$), and the solvent was removed in vacuo. The crude product was purified by column chromatography (neutral aluminium oxide).

***t*-5-(1,3-Benzodioxol-5-yl)-*c*-6-ethoxy-*r*-4-ethoxycarbonyl-3-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine (*rac*-4):** According to General Procedure A, a solution of 1,3-benzodioxol-5-yllithium was prepared from 5-bromo-1,3-benzodioxole (442 mg, 2.20 mmol) and *tert*-butyllithium (2.9 mL, 4.4 mmol). 1,2-Oxazine **3** (233 mg, 1.00 mmol) was added to this solution over a period of 60 min. After the mixture had been stirred for an additional 15 min, ethyl cyanoformate (0.30 mL, 3.10 mmol) was added and the reaction mixture was stirred for 60 min. Water (1 mL) was then added, and the mixture was allowed to warm to room temp. The crude product (*dr*, 44:56) was purified by column chromatography (*n*-hexane/ethyl acetate, 6:1) to yield 1,2-oxazine *rac*-**4** (264 mg, 62%, *dr* 90:10) as a yellowish solid, together with the starting material **3** (30 mg, 13%). 1,2-Oxazine *rac*-**4** was recrystallized from *n*-hexane/ethyl acetate to provide diastereomerically pure product (202 mg, 47%) as colourless crystals (m.p. 127–128 °C). $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.61–7.57 (m, 2 H, Ph), 6.92–6.89 (m, 2 H, Ph), 6.78–6.74 (m, 3 H, Ph), 5.92 (s, 2 H, $OCH_2O$), 5.28* (d, *J* = 3.4 Hz, 0.1 H, 6-H), 5.10 (d, *J* = 2.4 Hz, 0.9 H, 6-H), 4.25–3.80 (m, 4 H, $OCH_2$, 5-H), 3.82 (s, 3 H, $OCH_3$), 3.64 (d, *J* = 2.0 Hz, 1 H, 4-H), 3.70–3.53 (m, 1 H, $OCH_2$), 1.15 (t, *J* = 7.1 Hz, 3 H, $CH_3$), 1.11 (t, *J* = 7.3 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 169.6 (s, C=O), 160.7 (s, *C*$OCH_3$), 152.8 (s, C=N),

148.1, 146.9, 132.4, 128.6 (4 s, Ar), 127.2, 113.8 (2 d, 3-Ar), 122.6*, 121.0, 108.5, 108.1, 108.0* (5 d, Ar), 101.1 (t, $OCH_2O$), 98.3*, 97.7 (2 d, C-6), 64.2*, 63.5, 61.5, 60.9* (4 t, $OCH_2$), 55.3 ($OCH_3$), 42.5*, 42.3, 42.0*, 41.1 (4 d, C-4, C-5), 15.0*, 14.8, 13.8, 13.5* (4 q, $CH_3$) ppm, * signals of 3,4-*cis* isomer. IR (KBr): $\tilde{\nu}$ = 2980−2840 $cm^{-1}$ (C−H), 1730 (C=O), 1610 (C=N). $C_{23}H_{25}NO_7$ (427.5): calcd. C 64.62, H 5.89, N 3.28; found C 64.40, H 5.79, N 3.23.

**Ethyl 4-(1,3-Benzodioxol-5-yl)-*N*-*tert*-butoxycarbonyl-2-(4-methoxyphenyl)pyrrolidine-3-carboxylate (*rac*-5):** A suspension of Pd (10%)/C (50 mg) in ethanol (8 mL) was saturated with hydrogen. 1,2-Oxazine *rac*-**4** (220 mg, 0.515 mmol) and di-*tert*-butyl dicarbonate (120 mg, 0.550 mmol) dissolved in ethyl acetate (8 mL) were added, and the mixture was stirred under hydrogen at atmospheric pressure and room temp. for 3 days. The suspension was then filtered through Celite, eluting with ethyl acetate. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography ($SiO_2$, *n*-hexane/ethyl acetate, 4:1) to yield a mixture of isomers (**5a/5b** 80:20). Separation of the obtained isomers by HPLC (solvent: *n*-hexane + 15% ethyl acetate) yielded *rac*-**5a** (81 mg), a mixture of **5a/5b** (80:20, 51 mg), and *rac*-**5b** (23 mg, total yield 64%) as colourless oils.

***rac*-5a:** $^1$H NMR (500 MHz, $CDCl_3$, 320 K): δ = 7.14, 6.83 (2 d, *J* = 8.7 Hz, 2 H, 2 H, 2-Ar), 6.72−6.67 (m, 3 H, 4-Ar), 5.87 (s, 2 H, $OCH_2O$), 4.97 (d, *J* = 8.5 Hz, 1 H, 2-H), 4.20 ($m_c$, 1 H, 5-H), 4.03 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 3.77 (s, 3 H, $OCH_3$), 3.60−3.51 (m, 2 H, 4-H, 5-H), 3.04 ($m_c$, 1 H, 3-H), 1.22 [br. s, 9 H, $C(CH_3)_3$], 1.06 (t, *J* = 7.2 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ = 171.6 (s, C=O), 158.6 (s, *C*$OCH_3$), 153.9 (s, C=O), 147.8, 146.7, 133.3, 131.3 (4 s, Ar), 126.8, 126.5*, 120.7, 114.0*, 113.6, 108.3, 107.4 (7 d, Ar), 101.0 (t, $OCH_2O$), 79.7 [s, *C*$(CH_3)_3$], 64.7 (d, C-2), 61.3 (d, C-3), 60.8 (t, $OCH_2$), 55.1 (q, $OCH_3$), 53.8 (t, C-5), 47.2 (d, C-4), 27.9 [q, C(*C*$H_3)_3$], 14.0 (q, $CH_3$) ppm, * signals of rotamer. IR (film): $\tilde{\nu}$ = 2980−2930 $cm^{-1}$ (C−H), 1730, 1695 (C=O). $C_{26}H_{31}NO_7$ (469.2): calcd. C 66.51, H 6.65, N 2.98; found C 66.55, H 6.57, N 2.68.

***rac*-5b:** $^1$H NMR (500 MHz, $CDCl_3$, 320 K): δ = 7.09, 6.81 (2 d, *J* = 8.9 Hz, 2 H, 2 H, 2-Ar), 6.76−6.70 (m, 3 H, 4-Ar), 5.89 (s, 2 H, $OCH_2O$), 5.23 (br. s, 1 H, 2-H), 4.12 (t, *J* = 10.0 Hz, 1 H, 5-H), 3.87 (dt, *J* = 9.4, 11.4 Hz, 1 H, 4-H), 3.77 (s, 3 H, $OCH_3$), 3.73 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 3.50 (t, *J* ≈ 11 Hz, 1 H, 5-H), 3.46 (dd, *J* = 8.7, 11.4 Hz, 1 H, 3-H), 1.27 [br. s, 9 H, $C(CH_3)_3$], 0.96 (t, *J* = 7.1 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 169.2 (s, C=O), 159.0 (s, *C*$OCH_3$), 153.8 (s, C=O), 147.9, 146.7, 132.7, 132.4* (3 s, Ar), 127.7, 121.0, 113.6*, 113.3, 108.4, 108.0 (6 d, Ar), 101.0 (t, $OCH_2O$), 79.8 [s, *C*$(CH_3)_3$], 62.7 (d, C-2), 60.5 (t, $OCH_2$), 56.7, 55.7* (2 d, C-3), 55.2 (q, $OCH_3$), 53.7*, 52.9 (2 t, C-5), 43.1*, 42.3 (2 d, C-4), 28.2 [q, C(*C*$H_3)_3$], 13.8 (2 q, $CH_3$) ppm, * signals of a rotamer. IR (film): $\tilde{\nu}$ = 2980−2840 $cm^{-1}$ (C−H), 1740, 1695 (C=O), 1610, 1585, 1250, 1180, 1040.

**Mixture of Isomers:** MS (EI, 80 eV): *m*/*z* (%) = 469 (5) [$M^+$], 412 (33) [$M^+ - C_4H_9$], 368 (100) [$M^+ - C_5H_9O_2$], 352 (17), 180 (34), 148 (58), 136 (31), 121 (9). HRMS (EI, 80 eV) $C_{26}H_{31}NO_7$: calcd. 469.2101; found 469.2120.

**General Procedure B (Deprotection of *tert*-Butyl Carbamates):** Pyrrolidine **5** was dissolved in $CH_2Cl_2$, and TFA was added at 0 °C. The mixture was stirred at room temp. and satd. sodium hydrogen carbonate solution was then added. The mixture was diluted with $CH_2Cl_2$ and washed with brine. The organic phase was dried ($Na_2SO_4$), and the solvent was evaporated in vacuo.

**Ethyl *c*-4-(1,3-Benzodioxol-5-yl)-*r*-2-(4-methoxyphenyl)pyrrolidine-*t*-3-carboxylate (*rac*-6a):** According to General Procedure B, pyrrolidine *rac*-**5a** (60 mg, 0.127 mmol), dissolved in TFA (1 mL), was stirred for 1 h. After the aqueous workup, *rac*-**6a** (46 mg, 98%) was obtained as a spectroscopically pure compound. Column chromatography ($SiO_2$, *n*-hexane/ethyl acetate, 1:2) yielded *rac*-**6a** (14 mg, 30%) as a colourless oil. $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.8 Hz, 2 H, Ar), 6.82−6.65 (m, 5 H, Ar), 5.91 (s, 2 H, $OCH_2O$), 4.45 (d, *J* = 8.8 Hz, 1 H, 2-H), 4.04−3.88 (m, 2 H, $OCH_2$), 3.73 (s, 3 H, $OCH_3$), 3.73−3.44 (m, 2 H, 4-H, 5-H), 3.18 (dd, *J* = 6.3, 9.9 Hz, 1 H, 5-H), 2.88 (t, *J* = 8.8 Hz, 1 H, 3-H), 1.97 (br.s, 1 H, NH), 1.09 (t, *J* = 7.0 Hz, 3 H, $CH_3$) ppm. The analytical data are in accordance with those given in ref.[8].

**Ethyl *t*-4-(1,3-Benzodioxol-5-yl)-*r*-2-(4-methoxyphenyl)pyrrolidine-*t*-3-carboxylate (*rac*-6b):** According to General Procedure B, pyrrolidine *rac*-**5b** (20 mg, 0.043 mmol), dissolved in TFA (1 mL), was stirred for 1 h. After the aqueous workup, *rac*-**6b** (16 mg, quant., colourless oil) was obtained as a spectroscopically pure compound. $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.8 Hz, 2 H, Ar), 6.92−6.70 (m, 5 H, Ar), 5.91 (s, 2 H, $OCH_2O$), 4.66 (d, *J* = 8.8 Hz, 1 H, 2-H), 4.80−3.52 (m, 4 H, $OCH_2$, 4-H, 5-H), 3.77 (s, 3 H, $OCH_3$), 3.26 (dd, *J* = 7.4, 8.8 Hz, 1 H, 5-H), 3.01 ($m_c$, 1 H, 3-H), 0.80 (t, *J* = 7.0 Hz, 3 H, $CH_3$).

**General Procedure C (Preparation of 6-Menthyloxy-6*H*-1,2-oxazines 7−8):** $BF_3{\cdot}OEt_2$ (2 equiv.) was added at −78 °C to a solution of 1,2-oxazine **3** in $CH_2Cl_2$ (20 mL/mmol). After the mixture had been stirred for 30 min, (+)- or (−)-menthol (3 equiv.) was added and the solution was allowed to warm to room temp. The reaction mixture was stirred for 24 h, water (5 mL/mmol) was then added, the phases were separated, the organic layer was dried ($Na_2SO_4$), and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (neutral aluminium oxide, *n*-hexane/ethyl acetate, 8:1). The diastereomers were separated by HPLC (*n*-hexane +5% ethyl acetate).

**6-[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyloxy]-3-(*p*-methoxyphenyl)-6*H*-1,2-oxazine (7):** According to General Procedure C, (+)-menthol (2.08 g, 13.3 mmol) was added to a solution of $BF_3{\cdot}OEt_2$ (1.11 mL, 8.86 mmol) and 1,2-oxazine **3** (1.03 g, 4.43 mmol). Purification of the crude product by chromatography provided 1,2-oxazine **7** [1.19 g, 78%, (6*S*)/(6*R*) = 60:40]. Separation of the diastereomers by HPLC yielded (6*R*)-**7** (433 mg, 28%) as colourless crystals (m.p. 147−149 °C) and (6*S*)-**7** (681 mg, 45%) as colourless crystals (m.p. 107−108 °C).

**[(6*R*)-7]:** $[\alpha]_D^{20}$ = −56.4 (*c* = 1.34, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.66, 6.94 (2 d, *J* = 8.8 Hz, 2 H, 2 H, Ar), 6.58 (d, *J* = 10.0 Hz, 1 H, 4-H), 6.41 (dd, *J* = 4.4, 10.0 Hz, 1 H, 5-H), 5.62 (d, *J* = 4.4 Hz, 1 H, 6-H), 3.84 (s, 3 H, $OCH_3$), 3.61 (dt, *J* = 4.2, 10.5 Hz, 1 H, 1′-H), 2.28 ($m_c$, 1 H, 2′-H), 2.15−2.05 [m, 1 H, C*H*$(CH_3)_2$], 1.65−0.83 (m, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), 0.91 (d, *J* = 7.4 Hz, 3 H, 5′-$CH_3$), 0.90, 0.83 [2 d, *J* = 6.6 Hz, 6 H, CH(C*H*$_3)_2$] ppm. $^{13}$C NMR (67.9 MHz, $CDCl_3$): δ = 160.9 (s, *C*$OCH_3$), 153.3 (s, C=N), 127.5 (d, Ar), 126.6 (s, Ar), 126.0 (d, C-5), 116.2 (d, C-4), 114.1 (d, Ar), 93.0 (d, C-6), 79.7 (d, C-1′), 55.3 (q, $OCH_3$), 48.5 (d, C-2′), 42.2 (t, C-6′), 34.3 (t, C-4′), 31.7 (d, C-5′), 25.6 [d, *C*H$(CH_3)_2$], 23.2 (t, C-3′), 22.1 (q, 5′-$CH_3$), 21.1, 16.3 [2 q, CH(*C*$H_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3075−2850 $cm^{-1}$ (C−H), 1610, 1580 (C=C, C=N). $C_{21}H_{29}NO_3$ (343.5): calcd. C 73.44, H 8.51, N 4.08; found C 73.34, H 8.38, N 4.03.

**[(6*S*)-7]:** $[\alpha]_D^{20}$ = +94.8 (*c* = 1.11, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.61, 6.92 (2 d, *J* = 8.8 Hz, 2 H, 2 H, Ar), 6.57 (d, *J* = 9.6 Hz, 1 H, 4-H), 6.34 (dd, *J* = 4.4, 9.6 Hz, 1 H, 5-H), 5.72

(d, $J$ = 4.4 Hz, 1 H, 6-H), 3.86−3.75 (m, 1 H, 1′-H), 3.82 (s, 3 H, $OCH_3$), 2.16−2.11 (m, 1 H, 2′-H), 2.00−1.94 [m, 1 H, C$H$($CH_3$)$_2$], 1.67−0.78 (m, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), 0.92 (d, $J$ = 6.6 Hz, 3 H, 5′-$CH_3$), 0.80, 0.78 [2 d, $J$ = 6.6 Hz, 6 H, CH(C$H_3$)$_2$] ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 160.8 (s, $C$OCH$_3$), 153.5 (s, C=N), 127.3 (d, Ar), 126.6 (s, Ar), 126.5 (d, C-5), 116.1 (d, C-4), 114.1 (d, Ar), 88.0 (d, C-6), 74.8 (d, C-1′), 55.3 (t, $OCH_3$), 48.1 (d, C-2′), 40.2 (t, C-6′), 34.5 (t, C-4′), 31.4 (d, C-5′), 25.2 [d, $C$H($CH_3$)$_2$], 23.4 (t, C-3′), 22.6 (q, 5′-$CH_3$), 20.8, 15.9 [2 q, CH($C$H$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 2950−2865 cm$^{-1}$ (C−H), 1610, 1580 (C=C, C=N). $C_{21}H_{29}NO_3$ (343.5): calcd. C 73.44, H 8.51, N 4.08; found C 73.39, H 8.24, N 4.09.

**6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]-3-(*p*-methoxyphenyl)-6*H*-1,2-oxazine (8):** According to General Procedure C, (−)-menthol (1.19 g, 7.68 mmol) was added to a solution of $BF_3$·$OEt_2$ (0.64 mL, 5.21 mmol) and 1,2-oxazine **3** (597 mg, 2.56 mmol). Purification of the crude product by chromatography provided 1,2-oxazine **8** [801 mg, 91%, (6*R*)/(6*S*) = 60:40]. Separation of the diastereomers by HPLC yielded (6*S*)-**8** (259 mg, 29%) as colourless crystals (m.p. 145−146 °C) and (6*R*)-**8** (459 mg, 52%) as colourless crystals (m.p. 105−107 °C).

**[(6*S*)-8]:** $[\alpha]_D^{20}$ = +56.2 ($c$ = 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.66, 6.94 (2 d, $J$ = 8.8 Hz, 2 H, 2 H, Ar), 6.58 (d, $J$ = 10.0 Hz, 1 H, 4-H), 6.41 (dd, $J$ = 4.8, 10.0 Hz, 1 H, 5-H), 5.62 (d, $J$ = 4.8 Hz, 1 H, 6-H), 3.84 (s, 3 H, $OCH_3$), 3.61 (dt, $J$ = 4.4, 10.7 Hz, 1 H, 1′-H), 2.28 ($m_c$, 1 H, 2′-H), 2.15−2.05 [m, 1 H, C$H$($CH_3$)$_2$], 1.65−0.83 (m, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), 0.91 (d, $J$ = 7.4 Hz, 3 H, 5′-$CH_3$), 0.90, 0.83 [2 d, $J$ = 6.6 Hz, 6 H, CH(C$H_3$)$_2$] ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 160.9 (s, $C$OCH$_3$), 153.3 (s, C=N), 127.5 (d, Ar), 126.6 (s, Ar), 126.0 (d, C-5), 116.2 (d, C-4), 114.1 (d, Ar), 93.0 (d, C-6), 79.8 (d, C-1′), 55.3 (q, $OCH_3$), 48.5 (d, C-2′), 42.3 (t, C-6′), 34.4 (t, C-4′), 31.7 (d, C-5′), 25.7 [d, $C$H($CH_3$)$_2$], 23.3 (t, C-3′), 22.1 (q, 5′-$CH_3$), 21.1, 16.3 [2 q, CH($C$H$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3075−2850 cm$^{-1}$ (C−H), 1610, 1580 (C=C, C=N). $C_{21}H_{29}NO_3$ (343.5): calcd. C 73.44, H 8.51, N 4.08; found C 73.28, H 8.37, N 3.98.

**[(6*R*)-8]:** $[\alpha]_D^{20}$ = −93.8 ($c$ = 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.63, 6.92 (2 d, $J$ = 8.8 Hz, 2 H, 2 H, Ar), 6.57 (d, $J$ = 9.6 Hz, 1 H, 4-H), 6.34 (dd, $J$ = 4.4, 9.6 Hz, 1 H, 5-H), 5.72 (d, $J$ = 4.4 Hz, 1 H, 6-H), 3.86−3.75 (m, 1 H, 1′-H), 3.82 (s, 3 H, $OCH_3$), 2.16−2.11 (m, 1 H, 2′-H), 2.00−1.94 [m, 1 H, C$H$($CH_3$)$_2$], 1.67−0.78 (m, 7 H, 3′-H, 4′-H, 5′-H, 6′-H), 0.92 (d, $J$ = 6.6 Hz, 3 H, 5′-$CH_3$), 0.80, 0.78 [2 d, $J$ = 6.6 Hz, 6 H, CH(C$H_3$)$_2$] ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 160.9 (s, $C$OCH$_3$), 153.5 (s, C=N), 127.3 (d, Ar), 126.6 (s, Ar), 126.5 (d, C-5), 116.1 (d, C-4), 114.1 (d, Ar), 88.1 (d, C-6), 74.8 (d, C-1′), 55.3 (t, $OCH_3$), 48.1 (d, C-2′), 40.2 (t, C-6′), 34.5 (t, C-4′), 31.4 (d, C-5′), 25.2 [d, $C$H($CH_3$)$_2$], 23.5 (t, C-3′), 22.6 (q, 5′-$CH_3$), 20.8, 16.0 [2 q, CH($C$H$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 2950−2840 cm$^{-1}$ (C-H), 1610, 1580 (C=C, C=N). $C_{21}H_{29}NO_3$ (343.5): calcd. C 73.44, H 8.51, N 4.08; found C 73.48, H 8.42, N 4.02.

**Ethyl (6*R*)-5-(1,3-Benzodioxol-5-yl)-6-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy]-3-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine-4-carboxylate [(6*R*)-9]:** According to General Procedure A, a solution of 1,3-benzodioxol-5-yllithium was prepared from 5-bromo-1,3-benzodioxole (738 mg, 3.67 mmol) and *tert*-butyllithium (4.9 mL, 7.3 mmol). 1,2-Oxazine (6*R*)-**7** (573 mg, 1.67 mmol) was added to this solution over a period of 45 min. After the mixture had additionally been stirred for 30 min, ethyl cyanoformate (0.49 mL, 5.01 mmol) was added, and the reaction mixture was stirred for 60 min. Ethanol (0.8 mL) was then added and the mixture was allowed to warm to room temp. The crude product was purified by column chromatography (*n*-hexane/ethyl acetate, 8:1) to give 1,2-oxazine (6*R*)-**9** (559 mg, 62%, 4,5-*trans*/4,5-*cis* = 90:10) as a colourless oil. The major isomer was isolated by HPLC (*n*-hexane + 10% ethyl acetate) {$[\alpha]_D^{20}$ = +75.6 ($c$ = 0.93, $CHCl_3$)}. $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.58, 6.90 (2 d, $J$ = 8.8 Hz, 2 H, 2 H, 3-Ar), 6.78−6.75 (m, 3 H, 5-Ar), 5.93 (s, 2 H, $OCH_2O$), 5.36* (d, $J$ = 5.1 Hz, 0.1 H, 6-H), 5.07 (d, $J$ = 3.7 Hz, 0.9 H, 6-H), 4.19* (d, $J$ = 7.4 Hz, 0.1 H, 4-H), 4.15−3.80 (m, 2 H, $OCH_2$), 3.83 (s, 3 H, $OCH_3$), 3.83−3.80 (m, 1 H, 5-H), 3.70 (d, $J$ = 3.7 Hz, 0.9 H, 4-H), 3.48 (dt, $J$ = 4.4, 10.3 Hz, 1 H, 1′-H), 2.30−2.22 (m, 1 H, 2′-H), 1.90−0.65 [m, 10 H, 3′-H, 4′-H, 5′-H, 6′-H, contains at 1.09 (t, $J$ = 7.0 Hz, $CH_3$)], 0.90, 0.67 (2 d, $J$ = 6.6 Hz, 3 H each, $CH_3$), 0.83 (d, $J$ = 7.4 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (67.9 MHz, $CDCl_3$): δ = 169.4 (s, C=O), 160.7 (s, $C$OMe), 152.9 (s, C=N), 148.0, 146.9, 132.4, 128.4 (4 s, Ar), 127.3, 127.1*, 121.1, 113.8, 109.9*, 108.4, 108.1 107.6* (8 d, Ar), 101.0 (t, $OCH_2O$), 100.1, 99.7* (2 d, C-6), 80.7*, 80.6 (2 d, C-1′), 61.3 (t, $OCH_2$), 55.3, 55.0* (2 q, $OCH_3$), 48.8 (d, C-2′), 43.2 (d, C-5), 42.9*, 42.7 (2 d, C-4), 42.6 (t, C-6′), 34.3 (t, C-4′), 31.6 (d, C-5′), 25.3 (d, 2′-CH), 23.0 (t, C-3′), 22.2 (q, 5′-$CH_3$), 21.1, 21.0*, 16.0, 13.8 (4 q, $CH_3$) ppm, * signals of 4,5-*cis*-isomer. IR (film): $\tilde{\nu}$ = 2955−2870 cm$^{-1}$ (C−H), 1735 (C=O). $C_{31}H_{39}NO_7$ (537.6): calcd. C 69.25, H 7.31, N 2.61; found C 69.12, H 7.37, N 2.61.

**Ethyl (6*R*)-5-(1,3-Benzodioxol-5-yl)-6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]-3-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine-4-carboxylate [(6*R*)-10]:** According to General Procedure A, a solution of 1,3-benzodioxol-5-yllithium was prepared from 5-bromo-1,3-benzodioxole (222 mg, 2.10 mmol) and *tert*-butyllithium (1.7 mL, 2.2 mmol). 1,2-Oxazine (6*R*)-**8** (172 mg, 0.501 mmol) was added to this solution over a period of 35 min. After the mixture had been stirred for an additional 30 min, ethyl cyanoformate (0.15 mL, 1.53 mmol) was added and the reaction mixture was stirred for 60 min. Ethanol (0.3 mL) was then added and the mixture was allowed to warm to room temp. The crude product was purified by column chromatography (*n*-hexane/ethyl acetate, 8:1) to give 1,2-oxazine (6*R*)-**10** (56 mg, 21%, 4,5-*trans*/4,5-*cis* = 85:15) as a colourless oil and a mixture of bis-1,2-oxazine (6*R*)-**11** and ethyl benzodioxole-5-carboxylate (53 mg, calcd. yield of (6*R*)-**11** 19%). Bis-1,2-oxazine (6*R*)-**11** (yellowish solid, m.p. 72−79 °C) was purified by HPLC (*n*-hexane + 10% ethyl acetate). (6*R*)-**10:** $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.50, 6.87 (2 d, $J$ = 8.8 Hz, 2 H, 2 H, 3-Ar), 6.77−6.70 (m, 3 H, 5-Ar), 5.89 (s, 2 H, $OCH_2O$), 5.38* (d, $J$ = 2.9 Hz, 0.15 H, 6-H), 5.16 (d, $J$ = 2.2 Hz, 0.85 H, 6-H), 4.18−4.05 (m, 1 H, $OCH_2$), 3.89−3.77 (m, 2 H, $OCH_2$, 5-H), 3.80 (s, 3 H, $OCH_3$), 3.64 (dt, $J$ = 3.7, 10.7 Hz, 1 H, 1′-H), 3.61 (d, $J$ = 2.2 Hz, 1 H, 4-H), 2.17−1.94 (m, 1 H, 2′-H), 1.64−0.73 [m, 10 H, 3′-H, 4′-H, 5′-H, 6′-H, contains at 0.99 (t, $J$ = 7.0 Hz, $CH_3$)], 0.87, 0.82 (2 d, $J$ = 6.6 Hz, 3 H each, $CH_3$), 0.81 (d, $J$ = 7.4 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (67.9 MHz, $CDCl_3$): δ = 169.1 (s, C=O), 160.6 (s, $C$OMe), 154.7*, 153.0 (2 s, C=N), 148.1, 147.6*, 147.0*, 146.9, 133.1, 130.1*, 129.2, 128.5* (8 s, Ar), 127.2, 126.9*, 122.8*, 121.0, 113.8, 109.1*, 108.4, 108.2, 107.8* (9 d, Ar), 101.0 (t, $OCH_2O$), 95.0, 93.5* (2 d, C-6), 80.5, 74.2* (2 d, C-1′), 61.3, 60.3* (2 t, $OCH_2$), 55.3 (q, $OCH_3$), 48.0*, 47.8 (2 d, C-2′), 42.7, 42.6* (2 d, C-5), 41.2, 41.0* (2 d, C-4), 40.2 (t, C-6′), 34.4*, 34.3 (2 t, C-4′), 31.4, 31.2* (2 d, C-5′), 25.5*, 24.4 (2 d, 2′-CH), 23.0*, 22.6 (2 t, C-3′), 22.3 (q, 5′-$CH_3$), 21.3, 21.0*, 15.5*, 15.4, 13.7, 13.5* (6 q, $CH_3$) ppm, * signals of 4,5-*cis*-isomer. IR (film): $\tilde{\nu}$ = 3055−2870 cm$^{-1}$ (C−H), 1735 (C=O), 1610 (C=N). MS (EI, 80 eV): $m/z$ (%) = 537 (5) [M$^+$], 398 (7), 382 (12) 366 (14), 353 (22), 220 (100). HRMS (EI, 80 eV) $C_{31}H_{39}NO_7$: calcd. 537.2727; found 537.2748.

**Ethyl 5-(1,3-Benzodioxol-5-yl)-6,6′-bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]-3,3′-bis(4-methoxyphenyl)-5,6,5′,6′-tetrahydro-4*H*,4*H*′-[4,5′]bi-1,2-oxazinyl-4′-carboxylate [(6*R*)-11]:** $[\alpha]_D^{20}$ = +2.8 (*c* = 1.01, $CHCl_3$). $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.70, 7.63, (2 d, *J* = 8.8 Hz, 2 H, 2 H, Ar), 6.92 (t, *J* = 8.8 Hz, 4 H, Ar), 6.71−6.60 (m, 3 H, Ar), 5.90 (s, 2 H, $OCH_2O$), 4.71 (d, *J* = 5.2 Hz, 1 H, 6′-H), 4.67 (d, *J* = 7.4 Hz, 1 H, 6-H), 4.08 (d, *J* = 1.5 Hz, 1 H, 4′-H), 4.03−3.90, 3.81−3.73 (2 m, 1 H each, $OCH_2$), 3.84, 3.83 (2 s, 3 H each, $OCH_3$), 3.59 (dt, *J* = 3.9, 10.7 Hz, 1 H, 1′′-H), 3.47 (dt, *J* = 4.4, 10.3 Hz, 1 H, 1′′-H), 3.30 ($m_c$, 1 H, 4-H), 3.24−3.19 (m, 1 H, 5′-H), 3.16 (dd, *J* = 3.3, 7.4 Hz, 1 H, 5-H), 2.28−2.17, 2.12−2.02 (2 m, 1 H each, 2′′-H), 1.62−0.63, 0.47−0.32 (m, 35 H, CH, $CH_2$, $CH_3$) ppm. $^{13}$C NMR (67.9 MHz, $CDCl_3$): δ = 168.6 (s, C=O), 161.3, 160.9 (2 s, *C*OMe), 165.4, 159.1, 147.9, 146.6, 135.0, 127.9 (6 s, C=N, Ar), 128.1, 127.8, 121.4, 114.1, 113.8, 108.5, 108.3 (7 d, Ar), 101.0 (t, $OCH_2O$), 100.6, 95.4 (2 d, C-6), 77.5, 76.2 (2 d, C-1′′), 61.3 (t, $OCH_2$), 55.2 (q, $OCH_3$), 47.8, 47.5, 43.3, 42.3 (4 d, C-4, C-5), 39.8, 39.3 (2 t, C-6′), 34.3 (t, C-4′), 31.2, 31.1 (2 d, C-5′), 25.2, 24.9 (2 d, 2′-CH), 23.0, 22.9 (2 t, C-3′′), 22.1, 22.0, 21.1, 21.0, 15.9, 13.6 (6 q, $CH_3$) ppm. IR (KBr): ṽ = 2925−2870 $cm^{-1}$ (C−H), 1740 (C=O), 1610 (C=N). MS (EI, 80 eV): *m*/*z* (%) = 880 (3) [$M^+$], 741 (6), 709 (37), 571 (25), 401 (64), 379 (100), 306 (41), 280 (67), 270 (54), 246 (93), 149 (71). HRMS (EI, 80 eV) $C_{52}H_{68}N_2O_{10}$: calcd. 880.4874; found 880.4854.

**Ethyl (6*S*)-5-(1,3-Benzodioxol-5-yl)-6-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy]-3-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine-4-carboxylate [(6*S*)-9]:** According to General Procedure A, a solution of 1,3-benzodioxol-5-yllithium was prepared from 5-bromo-1,3-benzodioxole (901 mg, 4.48 mmol) and *tert*-butyllithium (6.0 mL, 9.0 mmol). 1,2-Oxazine (6*S*)-**7** (308 mg, 0.897 mmol) was added to this solution over a period of 120 min. After addition of ethyl cyanoformate (0.54 mL, 5.51 mmol) the reaction mixture was stirred for 60 min. Ethanol (1.0 mL) was then added and the mixture was allowed to warm to room temp. The $^1$H NMR spectrum shows a mixture of (6*S*)-**9** and (6*S*)-**11** (70:30). Purification by column chromatography (*n*-hexane/ethyl acetate, 8:1) yielded 1,2-oxazine (6*S*)-**7** (154 mg, 32%, 4,5-*trans*/4,5-*cis* = 85:15) as a colourless oil. Bis-1,2-oxazine (6*S*)-**11** was not isolated in this experiment. **(6*S*)-9**: $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.52, 6.90 (2 d, *J* = 8.8 Hz, 2 H each, 3-Ar), 6.80−6.72 (m, 3 H, 5-Ar), 5.92 (s, 2 H, $OCH_2O$), 5.40* (d, *J* = 2.9 Hz, 0.15 H, 6-H), 5.20 (d, *J* = 2.2 Hz, 0.85 H, 6-H), 4.29−4.09 (m, 1 H, $OCH_2$), 3.92−3.81 (m, 2 H, $OCH_2$, 5-H), 3.82 (s, 3 H, $OCH_3$), 3.67 (dt, *J* = 3.7, 10.7 Hz, 1 H, 1′-H), 3.64 (d, *J* = 2.2 Hz, 1 H, 4-H), 2.22−2.01 (m, 1 H, 2′-H), 1.66−0.76 [m, 10 H, 3′-H, 4′-H, 5′-H, 6′-H, contains at 1.02 (t, *J* = 7.4 Hz, $CH_3$)], 0.89, 0.85 (2 d, *J* = 6.6 Hz, 3 H each, $CH_3$), 0.83 (d, *J* = 7.4 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (67.9 MHz, $CDCl_3$): δ = 169.1 (s, C=O), 160.6 (s, *C*OMe), 153.0 (s, C=N), 148.0, 146.8, 133.1, 129.2 (4 s, Ar), 127.2, 126.9*, 122.9*, 121.0, 113.7, 109.9*, 108.4, 108.2, 107.6* (9 d, Ar), 101.0 (t, $OCH_2O$), 94.9, 93.5* (2 d, C-6), 74.2* (d, C-1′), 61.3, 60.8* (2 t, $OCH_2$), 55.3 (q, $OCH_3$), 48.0*, 47.8 (2 d, C-2′), 42.8, 42.6* (2 d, C-5), 41.2, 41.0 (2 d, C-4), 40.2 (t, C-6′), 34.4*, 34.3 (2 t, C-4′), 31.4, 31.2* (2 d, C-5′), 25.5*, 24.4 (2 d, 2′-CH), 23.0*, 22.6 (2 t, C-3′), 22.3 (q, 5′-$CH_3$), 21.3, 21.0*, 15.3, 13.7 (4 q, $CH_3$) ppm, * signals of 4,5-*cis* isomer.

**Ethyl (6*S*)-5-(1,3-Benzodioxol-5-yl)-6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]-3-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine-4-carboxylate [(6*S*)-10]:** According to General Procedure A, a solution of 1,3-benzodioxol-5-yllithium was prepared from 5-bromo-1,3-benzodioxole (442 mg, 2.20 mmol) and *tert*-butyllithium (2.9 mL, 4.4 mmol). 1,2-Oxazine (6*S*)-**8** (343 mg, 1.00 mmol) was added to this solution over a period of 60 min. After the mixture had additionally been stirred for 15 min, ethyl cyanoformate (0.30 mL, 3.10 mmol) was added and the reaction mixture was stirred for 60 min. Ethanol (0.3 mL) was then added and the mixture was allowed to warm to room temp. The crude product was purified by column chromatography (*n*-hexane/ethyl acetate, 10:1) to give 1,2-oxazine (6*S*)-**10** (306 mg, 57%, 4,5-*trans*/4,5-*cis* = 90:10) as a colourless oil. The major isomer was isolated by HPLC (*n*-hexane + 10% ethyl acetate) {$[\alpha]_D^{20}$ = −69.6 (*c* = 0.79, $CHCl_3$)}. $^1$H NMR (270 MHz, $CDCl_3$): δ = 7.60, 6.91 (2 d, *J* = 9.0 Hz, 2 H, 2 H, 3-Ar), 6.78−6.75 (m, 3 H, 5-Ar), 5.91 (s, 2 H, $OCH_2O$), 5.36* (d, *J* = 5.2 Hz, 0.1 H, 6-H), 5.07 (d, *J* = 3.7 Hz, 0.9 H, 6-H), 4.20−3.90 (m, 2 H, $OCH_2$), 3.81 (s, 2.7 H, $OCH_3$), 3.79* (s, 0.3 H, $OCH_3$), 3.81−3.79 (m, 1 H, 5-H), 3.73* (d, *J* = 6.6 Hz, 0.1 H, 4-H), 3.70 (d, *J* = 2.9 Hz, 0.9 H, 4-H), 3.48 (dt, *J* = 4.3, 10.8 Hz, 1 H, 1′-H), 2.29−2.24 (m, 1 H, 2′-H), 1.90−0.65 (m, 10 H, 3′-H, 4′-H, 5′-H, 6′-H, contains at 1.08 (t, *J* = 7.3 Hz, $CH_3$)], 0.90, 0.82 (2 d, *J* = 6.9 Hz, 3 H each, $CH_3$), 0.68 (d, *J* = 7.7 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (67.9 MHz, $CDCl_3$): δ = 169.3 (s, C=O), 160.7 (s, *C*OMe), 152.9 (s, C=N), 148.0, 146.9, 132.4, 128.4 (4 s, Ar), 127.3, 127.1*, 122.6*, 121.1, 113.8, 109.3*, 108.4, 108.0*, 108.1 (9 d, Ar), 101.0 (t, $OCH_2O$), 100.1, 99.7* (2 d, C-6), 80.7*, 80.5 (2 d, C-1′), 61.3, 61.0* (2 t, $OCH_2$), 55.3 (q, $OCH_3$), 48.8, 48.6* (2 d, C-2′), 43.2, 43.0* (2 d, C-5), 42.9*, 42.7 (2 d, C-4), 42.6 (t, C-6′), 34.3 (t, C-4′), 31.6 (d, C-5′), 25.3 (d, 2′-CH), 23.0 (t, C-3′), 22.2 (q, 5′-$CH_3$), 21.1, 16.0, 13.8*, 13.6 (4 q, $CH_3$) ppm, * signals of 4,5-*cis*-isomer. IR (film): ṽ = 2955−2870 $cm^{-1}$ (C-H), 1735 (C=O). $C_{31}H_{39}NO_7$ (537.6): calcd. C 69.25, H 7.31; N 2.61; found C 68.78, H 7.22, N 2.32.

**General Procedure D (Hydrogenolysis of 1,2-Oxazines under Pressure):** 1,2-Oxazine and di-*tert*-butyl dicarbonate were dissolved in ethyl acetate and added to a suspension of Raney nickel (50% in water, Acros) in dry ethanol. The reaction mixture was stirred in an autoclave under hydrogen pressure (times and pressures given below) at room temp. The suspension was then filtered through Celite, eluting with ethyl acetate. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography.

**Hydrogenolysis of (6*R*)-9:** According to General Procedure D, 1,2-oxazine (6*R*)-**9** (488 mg, 0.908 mmol, *dr* 90:10), di-*tert*-butyl dicarbonate (250 mg, 1.13 mmol) and Raney nickel (≈ 1 g) in ethanol/ethyl acetate (1:1, 30 mL) were stirred under hydrogen pressure (≈ 70 bar) for 3 days. The crude product was purified by column chromatography ($SiO_2$, *n*-hexane/ethyl acetate, 4:1) to yield a mixture of isomers (*dr*, 60:24:10:6). Separation of the isomers by HPLC (*n*-hexane + 3% 2-propanol) provided (2*R*,3*R*,4*S*)-**5a** (161 mg, 38%) and (2*S*,3*R*,4*S*)-**5b** (75 mg, 18%) as colourless oils, (2*S*,3*S*,4*S*)-**5c** (28 mg, 6.5%) as a colourless solid (m.p. 115−122 °C) and (2*R*,3*S*,4*S*)-**5d** (15 mg, 3.5%) as a colourless solid (m.p. 130−138 °C).

**(2*R*,3*R*,4*S*)-5a:** $[\alpha]_D^{20}$ = −4.4 (*c* = 0.84, $CHCl_3$). $^1$H NMR (500 MHz, $C_6D_6$, 351 K): δ = 7.21 (d, *J* = 8.5 Hz, 2 H, 3-Ar), 6.80−6.77 (m, 2 H, 3-Ar), 6.66 (d, *J* = 1.6 Hz, 1 H, 5-Ar), 6.54 (d, *J* = 7.9 Hz, 1 H, 5-Ar), 6.50 (dd, *J* = 1.6, 7.9 Hz, 1 H, 5-Ar), 5.34, 5.33 (2 d, *J* = 1.5 Hz, 2 H, $OCH_2O$), 5.21 (br. d, *J* = 8.8 Hz, 1 H, 2-H), 4.26 ($m_c$, 1 H, 5-H), 3.77 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 3.51 ($m_c$, 1 H, 5-H), 3.44 (dt, *J* = 7.3, 11.3 Hz, 1 H, 4-H), 3.14 (dd, *J* = 8.8, 11.3 Hz, 1 H, 3-H), 1.29 (s, 9 H, $CH_3$), 0.73 (t, *J* = 7.1 Hz, 3 H, $CH_3$) ppm. $^{13}$C NMR (125 MHz, $C_6D_6$, 351 K): δ = 171.6 (s, C=O), 159.6 (s, *C*$OCH_3$), 153.9 (s, C=O), 148.5, 147.4, 136.2, 132.5 (4 s, Ar), 127.4, 121.8, 114.4, 108.6, 108.1 (5 d, Ar), 101.0 (t,

$OCH_2O$), 79.2 [s, $C(CH_3)_3$], 65.5 (d, C-2), 61.9 (d, C-3), 60.6 (t, $OCH_2$), 54.9 (q, $OCH_3$), 54.8 (t, C-5), 47.9 (d, C-4), 28.3 [q, $C(CH_3)_3$], 14.0 (q, $CH_3$) ppm. IR (film): $\tilde{\nu}$ = 2975−2835 $cm^{-1}$ (C−H), 1730, 1695 (C=O). $C_{26}H_{31}NO_7$ (469.2): calcd. C 66.45, H 6.66, N 2.98; found C 66.37, H 6.58, N 2.86.

**(2*S*,3*R*,4*S*)-5b:** $[\alpha]_D^{20}$ = +49.8 (*c* = 0.84, $CHCl_3$). $^1H$ NMR (500 MHz, $C_6D_6$, 351 K): δ = 7.15−7.14, 6.77−6.75 (2 m, 2 H each, Ar), 6.65−6.64 (m, 1 H, Ar), 6.55−6.53 (m, 2 H, Ar), 5.32 (s, 2 H, $OCH_2O$), 5.32−5.30 (br. s, 1 H, 2-H), 4.15 ($m_c$, 1 H, 5-H), 3.92 (q, *J* = 10.2 Hz, 1 H, 4-H), 3.57, 3.53 (2 dq, *J* = 7.1, 10.9 Hz, 2 H, $OCH_2$), 3.47 (t, *J* = 10.7 Hz, 1 H, 5-H), 3.32 (s, 3 H, $OCH_3$), 3.32−3.28 (m, 1 H, 3-H), 1.34 (br. s, 9 H, $CH_3$), 0.69 (t, *J* = 7.1 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (125.8 MHz, $C_6D_6$, 351 K): δ = 168.9 (s, C=O), 159.7 (s, $COCH_3$), 153.7 (s, C=O), 148.5, 147.2, 133.7 (3 s, Ar), 128.4, 128.0, 121.3, 113.9, 108.5, 108.4 (s, 5 d, Ar), 101.0 (t, $OCH_2O$), 79.2 [s, $C(CH_3)_3$], 63.4 (d, C-2), 60.3 (t, $OCH_2$), 56.8 (d, C-3), 54.8 (q, $OCH_3$), 53.7 (t, C-5), 43.2 (d, C-4), 28.4 [q, $C(CH_3)_3$], 13.8 (q, $CH_3$) ppm. IR (film): $\tilde{\nu}$ = 2980−2900 $cm^{-1}$ (C−H), 1740, 1695 (C=O), 1610 (C=C). MS (EI, 80 eV): *m*/*z* (%) = 469 (18) [$M^+$], 412 (21) [$M^+ - C_4H_9$], 368 (87) [$M^+$ − Boc], 180 (39), 148 (63), 136 (43), 121 (18), 57 (100) [$C_4H_9^+$]. HRMS (EI, 80 eV) $C_{26}H_{31}NO_2$: calcd. 469.2101; found 469.2143.

**(2*S*,3*S*,4*S*)-5c:** $[\alpha]_D^{20}$ = +23.9 (*c* = 0.95, $CHCl_3$). $^1H$ NMR (270 MHz, $CDCl_3$): δ = 7.19 ($m_c$, 2 H, Ar), 6.87 (d, *J* = 8.8 Hz, 2 H, Ar), 6.72−6.60 (m, 3 H, Ar), 5.93 (s, 2 H, $OCH_2O$), 5.26−5.01 (m, 1 H, 2-H), 4.03−3.88, 3.72−3.64 (2 m, 5 H, $OCH_2$, 4-H, 5-H), 3.80 (s, 3 H, $OCH_3$), 3.30−3.17 (m, 1 H, 3-H), 1.48*, 1.22 [2 s, 9 H, $C(CH_3)_3$], 1.05 (t, *J* = 7.0 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (67.2 MHz, $CDCl_3$): δ = 166.1 (s, C=O), 158.7 (s, $COCH_3$), 154.3 (s, C=O), 147.7, 146.6, 135.3 (3 s, Ar), 126.9, 120.6, 113.7, 108.1, 107.9 (5 d, Ar), 100.9 (t, $OCH_2O$), 79.8 [s, $C(CH_3)_3$], 61.1, 59.0 (2 d, C-2, C-3), 60.5 (t, $OCH_2$), 55.2 (q, $OCH_3$), 51.5 (t, C-5), 44.0 (d, C-4), 29.6*, 28.1 [2 q, $C(CH_3)_3$], 13.9 (q, $CH_3$) ppm, * signals of rotamer. IR (KBr): $\tilde{\nu}$ = 2985−2875 $cm^{-1}$ (C−H), 1720, 1700 (C=O). MS (EI, 80 eV): *m*/*z* (%) = 469 (10) [$M^+$], 413 (26) ($M^+ - C_4H_8$], 368 (100) [$M^+$ − Boc], 148 (45), 57 (65) [$C_4H_9^+$].

**(2*R*,3*S*,4*S*)-5d:** $^1H$ NMR (270 MHz, $CDCl_3$): δ = 7.16, 6.80 (2 d, *J* = 8.8 Hz, 2 H, 2 H, 2-Ar), 6.75−6.66 (m, 3 H, Ar), 5.92 (s, 2 H, $OCH_2O$), 5.26−5.24* (m, 0.36 H, 2-H), 5.15 (d, *J* = 7.4 Hz, 0.64 H, 2-H), 4.36−4.03, 3.70−3.59, 355−3.48 (3 m, 6 H, $OCH_2$, 3-H, 4-H, 5-H), 3.78 (s, 3 H, $OCH_3$), 1.47*, 1.14 [2 s, 9 H, $C(CH_3)_3$], 0.74 (t, *J* = 7.0 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (67.2 MHz, $CDCl_3$): δ = 169.9 (s, C=O), 158.5 (s, $COCH_3$), 154.5 (s, C=O), 147.6, 146.3, 131.7, 131.1 (4 s, Ar), 127.5, 120.3, 112.9, 108.1, 107.9 (5 d, Ar), 100.9 (t, $OCH_2O$), 79.6 [s, $C(CH_3)_3$], 63.9, 56.5 (2 d, C-2, C-3), 59.9 (t, $OCH_2$), 55.2 (q, $OCH_3$), 50.0 (t, C-5), 44.5 (d, C-4), 28.4*, 27.9 [2 q, $C(CH_3)_3$], 13.6 (q, $CH_3$) ppm, * signals of rotamer. MS (EI, 80 eV): *m*/*z* (%) = 469 (13) [$M^+$], 413 (30) [$M^+ - C_4H_8$], 368 (100) [$M^+$ − Boc], 148 (67).

**Deprotection of (2*R*,3*R*,4*S*)-5a:** According to General Procedure B, protected pyrrolidine (2*R*,3*R*,4*S*)-**5a** (161 mg, 0.340 mmol) was dissolved in $CH_2Cl_2$ (2 mL), and TFA (2 mL) was added. The mixture was stirred for 3 h. Column chromatography ($SiO_2$, *n*-hexane/ethyl acetate, 15:85) yielded (2*R*,3*R*,4*S*)-**6a** (92 mg, 73%) as a colourless oil. $[\alpha]_D^{20}$ = +57.7 (*c* = 0.98, $CHCl_3$)* [ref[8]: +57.7 (*c* = 7.68, EtOH)], * Because of the poor solubility of the compound in EtOH we used $CHCl_3$ as solvent. $^1H$ NMR (270 MHz, $CDCl_3$): δ = 7.36, 6.88 (2 d, *J* = 8.8 Hz, 2 H, 2 H, 2-Ar), 6.82 (s, 1 H, 4-Ar), 6.73 (s, 2 H, 4-Ar), 5.92 (s, 2 H, $OCH_2O$), 4.47 (d, *J* = 8.6 Hz, 1 H, 2-H), 4.06 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 3.80 (s, 3 H, $OCH_3$), 3.68−3.51 (m, 2 H, 4-H, 5-H), 3.20 (dd, *J* = 6.6, 10.3 Hz, 1 H, 5-H), 2.90 (t, *J* = 8.6 Hz, 1 H, 3-H), 2.16 (br. s, 1 H, NH), 1.11 (t, *J* = 7.1 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (67.9 MHz, $CDCl_3$): δ = 173.8 (s, C=O), 158.9 (s, $COCH_3$), 147.8, 146.2, 136.4, 134.3 (4 s, Ar), 127.7, 120.4, 113.9, 108.2, 107.5 (5 d, Ar), 100.9 (t, $OCH_2O$), 66.7 (d, C-2), 61.4, 60.6 (2 t, C-5, $OCH_2$), 55.3, 54.6, 50.6 (q, 2 d, $OCH_3$, C-3, C-4), 14.2 (q, $CH_3$) ppm. MS (EI, 80 eV): *m*/*z* (%) = 369 (36) [$M^+$], 340 (13), 324 (13), 221 (4), 149 (100). $C_{21}H_{23}NO_5$ (369.4): calcd. C 68.28, H 6.28, N 3.79; found C 67.88, H 6.19, N 3.79. The analytical data are in accordance with those given in ref.[8]

**Deprotection of (2*R*,3*R*,4*S*)-5b:** According to General Procedure B, the protected pyrrolidine (2*S*,3*R*,4*S*)-**5b** [31 mg, 0.066 mmol, contains 10% of 2*R* diastereomer)] was dissolved in $CH_2Cl_2$ (1 mL), and TFA (1 mL) was added. The mixture was stirred for 5 h. After aqueous workup (2*S*,3*R*,4*S*)-**6b** (20 mg, 82%) was obtained as a colourless oil. $^1H$ NMR (270 MHz, $CDCl_3$): δ = 7.25, 6.85 (2 d, *J* = 8.8 Hz, 2 H, 2 H, 2-Ar), 6.78−6.75 (m, 3 H, 4-Ar), 4.66 (d, *J* = 8.8 Hz, 1 H, 2-H), 3.79 (s, 3 H, $CH_3$), 3.80−3.57 (m, 4 H, $OCH_2$, 4-H, 5-H), 3.27 (dd, *J* = 7.4, 8.8 Hz, 1 H, 5-H), 3.02 ($m_c$, 1 H, 3-H), 2.33 (br. s, 1 H, NH), 0.83 (t, *J* = 7.4 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (67.9 MHz, $CDCl_3$): δ = 172.9 (s, C=O), 158.9 (s, $COCH_3$), 147.8, 146.3, 135.7, 131.9 (4 s, Ar), 128.2, 120.5, 113.4, 108.3, 107.7 (5 d, Ar), 100.9 (t, $OCH_2O$), 65.9 (d, C-2), 60.3 (t, $OCH_2$), 58.2 (t, C-5), 55.3 (q, $OCH_3$), 48.7 (d, C-4), 13.7 (q, $CH_3$) ppm.

**4-(1,3-Benzodioxol-5-yl)-3-ethoxycarbonyl-2-(4-methoxyphenyl)-pyrrole (12):** According to General Procedure D, 1,2-oxazine (6*R*)-**9** (493 mg, 0.917 mmol, *dr* 90:10), di-*tert*-butyl dicarbonate (300 mg, 1.38 mmol) and Raney nickel (≈ 400 mg) in ethanol/ethyl acetate (1:1, 20 mL) were stirred under hydrogen pressure (≈ 50 bar) for 3 days. Purification by column chromatography ($SiO_2$, *n*-hexane/ethyl acetate, 4:1) yielded pyrrolidine **5** (31 mg, 7%, mixture of isomers) and pyrrole **12** (82 mg, 24%) as colourless solids (m.p. 122−123 °C).

**Pyrrole 12:** $^1H$ NMR (250 MHz, $CDCl_3$): δ = 8.41 (br. s, 1 H, NH), 7.46 (d, *J* = 8.8 Hz, 2 H, Ar), 6.94−6.78 (m, 5 H, Ar), 6.69 (d, *J* = 2.2 Hz, 1 H, 5-H), 5.95 (s, 2 H, $OCH_2O$), 4.07 (q, *J* = 7.0 Hz, 2 H, $OCH_2$), 3.83 (s, 3 H, $OCH_3$), 1.04 (t, *J* = 7.0 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (67.9 MHz, $CDCl_3$): δ = 164.6 (s, C=O), 159.5 (s, $COCH_3$), 147.0, 146.2, 137.0, 129.5, 127.4, 124.9 (6 s, Ar, C-2, C-3, C-4), 130.1, 122.2, 116.6, 113.6, 109.9, 107.7 (6 d, Ar, C-5), 100.8 (t, $OCH_2O$), 59.7 (t, $OCH_2$), 55.3 (q, $OCH_3$), 13.8 (q, $CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3300 $cm^{-1}$ (N−H), 1680, 1670 (C=O). $C_{21}H_{19}NO_5$ (365.4): calcd. C 69.03, H 5.24, N 3.83; found C 68.88, H 5.30, N 3.77.

**Hydrogenolysis of (6*S*)-10:** According to General Procedure D, 1,2-oxazine (6*S*)-**10** (244 mg, 0.455 mmol, *dr* 90:10), di-*tert*-butyl dicarbonate (119 mg, 0.545 mmol) and Raney nickel (≈ 200 mg) in ethanol/ethyl acetate (1:1, 20 mL) were stirred under hydrogen pressure (50−60 bar) for 22 h. The crude product was purified by column chromatography ($SiO_2$, *n*-hexane/ethyl acetate, 4:1). Separation of the isomers by HPLC (*n*-hexane + 20% ethyl acetate) yielded (2*S*,3*S*,4*R*)-**5a** (68 mg, 31%), (2*R*,3*S*,4*R*)-**5b** (31 mg, 14%) and a third isomer of **5** (9 mg, 4%) with unknown configuration, as colourless oils.

**(2*S*,3*S*,4*R*)-5a:** $[\alpha]_D^{20}$ = +4.3 (*c* = 0.49, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$, 323 K): δ = 7.16, 6.85 (2 d, *J* = 8.6 Hz, 2 H each, 2-Ar), 6.75−6.70 (m, 3 H, 4-Ar), 5.91 (s, 2 H, $OCH_2O$), 4.96 (br. s, 1 H, 2-H), 4.22 ($m_c$, 1 H, 5-H), 4.04 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 3.79 (s, 3 H, $OCH_3$), 3.62−3.54 (m, 2 H, 4-H, 5-H), 3.05 ($m_c$, 1 H, 3-H), 1.20 [br. s, 9 H, $C(CH_3)_3$], 1.07 (t, *J* = 7.1 Hz, 3 H, $CH_3$) ppm. $^{13}C$ NMR (125.8 MHz, $CDCl_3$, 323 K): δ = 171.7

(s, C=O), 158.9 (s, *C*OCH$_3$), 153.9 (s, C=O), 148.0, 146.9, 135.5, 131.7 (4 s, Ar), 126.8, 120.7, 113.6, 108.4, 107.5 (5 d, Ar), 101.0 (t, OCH$_2$O), 79.7 [s, *C*(CH$_3$)$_3$], 64.8 (d, C-2), 61.4 (d, C-3), 60.8 (t, OCH$_2$), 55.3 (q, OCH$_3$), 54.1 (t, C-5), 47.4 (d, C-4), 28.1 [q, C(*C*H$_3$)$_3$], 14.1 (q, CH$_3$) ppm. MS (EI, 80 eV): *m*/*z* (%) = 469 (10) [M$^+$], 412 (27) [M$^+$ − C$_4$H$_9$], 368 (100) [M$^+$ − Boc], 352 (12), 180 (25), 148 (35), 136 (28), 57 (22). HRMS (EI, 80 eV) $C_{26}H_{31}NO_7$: calcd. 469.2101; found 469.2142.

**(2*R*,3*S*,4*R*)-5b:** $^1$H NMR (500 MHz, CDCl$_3$, 323 K): δ = 7.10−7.09 (m, 2 H, 2-Ar), 6.82 (d, *J* = 8.7 Hz, 2 H, 2-Ar), 6.77−6.71 (m, 3 H, 4-Ar), 5.91 (s, 2 H, OCH$_2$O), 5.31*, 5.20 (2 br. s, 1 H, 2-H), 4.14 (m$_c$, 1 H, 5-H), 3.88 (dt, *J* = 8.9, 11.3 Hz, 1 H, 4-H), 3.78 (s, 3 H, OCH$_3$), 3.74 (q, *J* = 7.1 Hz, 2 H, OCH$_2$), 3.53−3.46 (m, 2 H, 3-H, 5-H), 1.26*, 1.21 [2 br. s, 9 H, C(CH$_3$)$_3$], 0.98 (t, *J* = 7.1 Hz, 3 H, CH$_3$) ppm. $^{13}$C NMR (125.8 MHz, CDCl$_3$, 323 K): δ = 169.2 (s, C=O), 159.1 (s, *C*OCH$_3$), 153.8 (s, C=O), 147.9, 146.7, 132.9 (3 s, Ar), 127.8, 121.0, 113.5, 108.4, 108.0 (5 d, Ar), 101.0 (t, OCH$_2$O), 79.8 [s, *C*(CH$_3$)$_3$], 62.8 (d, C-2), 60.5 (t, OCH$_2$), 56.9 (d, C-3), 55.2 (q, OCH$_3$), 53.0 (t, C-5), 43.1*, 42.5 (2 d, C-4), 28.2 [q, C(*C*H$_3$)$_3$], 13.8 (q, CH$_3$) ppm, * signals of rotamer. MS (EI, 80 eV): *m*/*z* (%) = 469 (3) [M$^+$], 412 (4) [M$^+$ − C$_4$H$_9$], 368 (16) [M$^+$ − Boc], 284 (6), 148 (14), 57 (35). HRMS (EI, 80 eV) $C_{26}H_{31}NO_7$: calcd. 469.2101; found 469.2144.

**Third isomer of 5:** $^1$H NMR (500 MHz, CDCl$_3$, 323 K): δ = 7.18, 6.86 (2 d, *J* = 8.6 Hz, 2 H, 2 H, 2-Ar), 6.73−6.60 (m, 3 H, 4-Ar), 5.91 (s, 2 H, OCH$_2$O), 5.14 (d, *J* = 8.5 Hz, 1 H, 2-H), 4.05−3.96 (m, 2 H, 5-H, 4-H), 3.93 (q, *J* = 7.1 Hz, 2 H, OCH$_2$), 3.80 (s, 3 H, OCH$_3$), 3.68−3.58 (m, 1 H, 5-H), 3.21 (m$_c$, 1 H, 3-H), 1.22 [br. s, 9 H, C(CH$_3$)$_3$], 1.06 (t, *J* = 7.2 Hz, 3 H, CH$_3$) ppm.

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