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ORIGINAL ARTICLE

A refined synthesis of enantiomerically pure 2-aminocyclobutanecarboxylic acids

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Abstract The synthesis of enantiomerically pure 2-aminocyclobutanecarboxylic acids has been refined to improve both the efficiency and the simplicity. These improvements provide a shorter and easier access to the racemic *cis*-cyclobutane β-amino acid core. Derivatization of this material with a chiral non-racemic oxazolidin-2-one allows easy diastereoisomeric separation and presents the advantage of allowing the non-destructive cleavage of the chiral auxiliary either by hydrolysis or by ammonolysis, thus providing an efficacious access to N-protected derivatives of all four stereoisomers of Boc-2-aminocyclobutanecarboxylic acid.

Keywords 2-Aminocyclobutanecarboxylic acids · Photochemical [2 + 2] cycloaddition · Chiral resolution · Epimerization · Oxazolidin-2-one

Introduction

There is an increasing demand for synthetic access to cyclic β-amino acids. Some of these compounds are in themselves bestowed with biological activity, while others are considered to be useful tools for the preparation of peptidomimetics, and for the construction of molecular architectures exhibiting strong self-organization (Fülöp 2001; Fülöp et al. 2006; Kuhl et al. 2005; Kiss et al. 2009). In the area of foldamer science, oligomers of *trans*-2-aminocyclohexanecarboxylic acid (*trans*-ACHC) are known to adopt a 14-helix conformation (Appella et al. 1999a; Hetényi et al. 2005) while oligomers of *trans*-2-aminocyclopentanecarboxylic (*trans*-ACPC) adopt a 12-helix conformation (Appella et al. 1997, 1999b); in contrast, oligomers of *cis*-2-aminocyclopentanecarboxylic (*cis*-ACPC) adopt a strand-like structure (Martinek et al. 2002).

Mixed β-peptides in which ACHC or ACPC has been combined with other β-amino acids may retain a propensity for regular folding (Pomerantz et al. 2008; Hetényi et al. 2009b; Dutot et al. 2008; Chakraborty and Diederichsen 2005; Raguse et al. 2002), and some of these materials display promising biological activities (English et al. 2006; Karlsson et al. 2006; Imamura et al. 2009). Similarly, a variety of helical structure types have been demonstrated for mixed α/β-peptides with heterogeneous backbones in which ACHC or ACPC has been combined with α-amino acids (Lee et al. 2009; Horne and Gellman 2008), and an innovative stereochemical patterning approach to helix design with such building blocks has been proposed (Mándity et al. 2009).

Progress in this developing area has inspired studies of more elaborate bicyclic β-amino acids, in order to widen the range of building blocks for helical manifolds (Mándity et al. 2010; Hetényi et al. 2009a; Chandrasekhar et al. 2006). Small ring β-amino acids should make a logical contribution to the field; the corpus of work is noticeably less extensive however. One important factor which has to be confronted is the intrinsic instability of the building blocks. Indeed, 2-aminocyclopropanecarboxylic acid does not exist, because the vicinal push–pull substituent system facilitates rapid and irreversible ring opening (Gnad and Reiser 2003; Mangelinckx and De Kimpe 2003). Nevertheless, peptides have been made which incorporate

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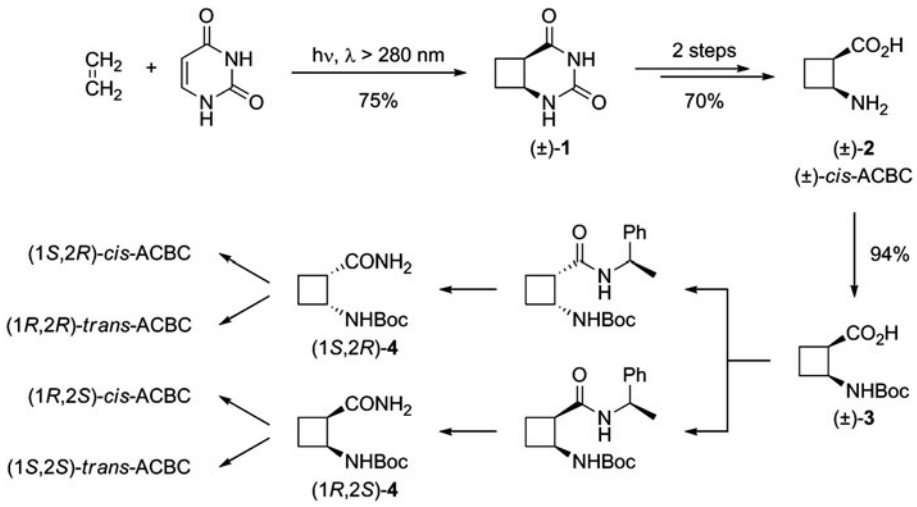


Scheme 1 The established access to enantiopure *cis*- and *trans*-ACBCs

2-aminocyclopropanecarboxylic acids bearing an extra carboxylic acid function at C1 (Godier-Marc et al. 1997) or at C3 (D'Elia et al. 2008; Urman et al. 2007; Koglin et al. 2003), and these materials are stable provided the nitrogen atom remains part of an amide function. Stable helical conformations were observed in mixed α/β-peptides which incorporate C3-substituted *cis*-2-aminocyclopropanecarboxylic acid residues (De Pol et al. 2004).

Recently, it has emerged that 2-aminocyclobutanecarboxylic acids (ACBC) also serve as building blocks for β-peptides with regular structural patterns. Homo-oligomers of *cis*-ACBC adopt strand-type conformations, stabilized by a succession of localized six-membered ring hydrogen bonds, and these oligomers undergo self-assembly to furnish nanofibrils or gels (Rúa et al. 2007; Torres et al. 2010). Dipeptides incorporating *trans*-ACBC appear to adopt eight-membered hydrogen bond rings (Torres et al. 2009), while longer oligomers adopt a 12-helix conformation both in solution and in the solid state (Fernandes et al. 2010).

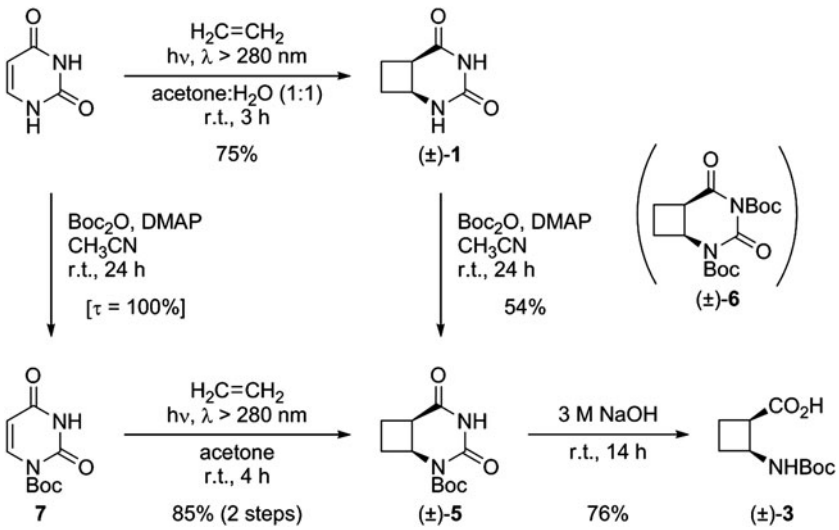
As a part of a program aimed at the discovery of new foldamers constructed from four-membered ring β-amino acids, a rapid and scalable access to enantiomerically pure *cis*- and *trans*-ACBCs was required. Prior to our own contributions in the area, there were only two stereoselective syntheses of this β-amino acid core; taking the lead from earlier work using racemic material (Kennewell et al. 1982), enantiomerically pure *cis*-ACBC was prepared by the groups of Ortuño (Martín-Vilà et al. 1998, 2000) and Bolm (Bolm et al. 2003) via enantioselective desymmetrization of a *meso*-1,2-cyclobutanedicarboxylic acid derivative. About 10 years ago, we began studies on an alternative route to the ACBC core, using the [2 + 2] photocycloaddition reaction of ethylene with uracil as the key step for the construction of the 4-membered ring. After validating the approach for the synthesis of racemic *cis*-ACBC (Aitken et al. 2002), we extended its use to prepare substituted ACBCs (Gauzy et al. 2006), and also described an adaptation using a chiral uracil derivative which provided both *cis*- and *trans*-ACBC in enantiomerically pure form (Gauzy et al. 2004; Fernandes et al. 2007). Subsequently, using racemic *cis*-ACBC as the entry point, a procedure was described which allows access to all four ACBC stereoisomers (Fernandes et al. 2009) (Scheme 1). This approach involves a resolution step via chiral derivatization, and an efficient *cis*-to-*trans* epimerization protocol.

While the above-described procedure provides a satisfactory entry to ACBC stereoisomers, a critical inspection of the synthesis reveals that it suffers from three drawbacks which render it less practical for large-scale preparation (Scheme 1). The first inconvenience is that the preparation of the key intermediate, racemic Boc-*cis*-ACBC, (±)-**3**, is obtained from the free amino acid form of *cis*-ACBC, (±)-**2**, which has an inherent limited stability due to a push–pull substituent effect which promotes ring opening (Aitken et al. 2004). The second difficulty is associated with the low solubility of the intermediate diastereomeric α-methylbenzylamides, which renders their chromatographic separation fastidious. The third discommodity is that the chiral auxiliary used for the resolution process, (*R*)-α-methylbenzylamine, is destroyed during the transformation to enantiopure amides **4**, and thus cannot be recycled (Scheme 1).

Results and discussion

We began our refinements of the [2 + 2] cycloaddition strategy by reconsidering the access to racemic Boc-*cis*-ACBC (±)-**3** without recourse to the free amino acid **2**. This objective implied the introduction of the Boc

Scheme 2 A short access to racemic Boc-*cis*-ACBC



protecting group earlier in the sequence, and indeed we felt that this feature would have the added advantage of facilitating the controlled cleavage of the dihydropyrimidinone moiety. We first studied the introduction of a Boc group at the N1 position of the photocycloadduct **1**, which was obtained from uracil and ethylene as described previously (Aitken et al. 2002). The selective protection of **1** proved to be rather troublesome, because the requisite compound **5** was often accompanied by a significant amount of the bis-Boc compound **6**. The formation of this by-product was suppressed when cycloadduct **1** was treated with a stoichiometric amount of Boc_2O in the presence of 10% of DMAP using acetonitrile as a solvent, to give 54% of compound **5** (Scheme 2). An alternative route to compound **5** consisted of employing N^1-Boc-uracil **7** in the [2 + 2] cycloaddition reaction with ethylene. N^1-Boc-uracil **7** was obtained by regioselective derivatization according to the procedure developed by Jaime-Figueroa et al. (2001) and used without purification in the photocycloaddition reaction with ethylene (Scheme 2), using a 400 W mercury lamp in a reactor fitted with a Pyrex filter, which provides a 280 nm wavelength cutoff. Using this tandem operation, compound (±)-**5** was obtained in 85% yield from uracil.

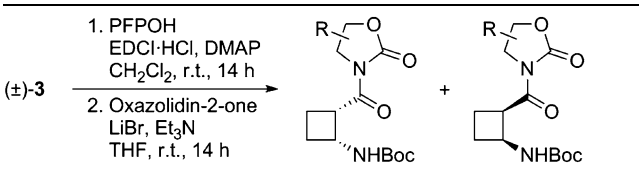
The Boc group on the N1 position enhances the leaving group character of this nitrogen center, which was expected to promote cleavage of the N1–C2 bond. Gratifyingly, treatment of compound (±)-**5** with 3 M aqueous NaOH at room temperature induced the smooth cleavage of both N3–C4 and N1–C2 bonds in a single operation to produce Boc-*cis*-ACBC (±)-**3** in 76% (Scheme 2). By conducting this reaction at room temperature, the risk of partial base-mediated epimerization at C1 is avoided. This constitutes the shortest and the most efficient access to (±)-**3** described to date; the previous synthesis, proceeding via the free amino acid (Scheme 1), required four steps (49% yield from uracil).

We next reinvestigated the resolution procedure with the objective of making it amenable to larger scale preparation. Our intention was to identify a chiral resolving agent which, as well as its separation potential, fulfilled two additional criteria: first, it should not be consumed or destroyed during the procedure (allowing recycling) and second, its controlled cleavage should be possible using conditions which provide either the *cis*-Boc-amino acid **3** or the *cis*-Boc-amino amide **4**. The reason for requiring easy access to this latter derivative is its privileged status as the appropriate precursor for entry to the *trans*-ACBC amino acid series as indicated above (Scheme 1) (Fernandes et al. 2009).

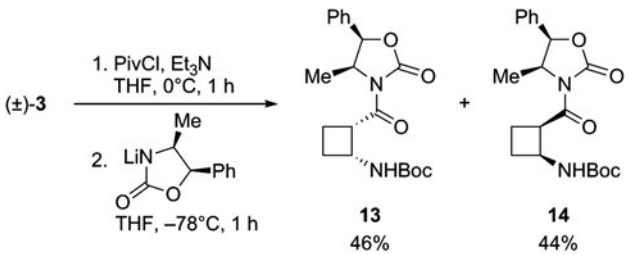
Chiral oxazolidin-2-ones appeared as good chiral resolving agent candidates, likely to meet these two requirements, so we investigated a selection of such compounds. In small-scale reactions (0.1 mmol), a selection of known chiral oxazolidin-2-ones **8**–**12** (Bégis et al. 2009; Tussetschläger et al. 2007; Ahmed et al. 2002) was prepared and coupled to (±)-**3** via its pentafluorophenyl ester (Moser et al. 2008) in order to evaluate the feasibility of diastereomeric separation by chromatography (Table 1). The use of (*S*)-4-benzyl- or (*R*)-4-phenyloxazolidin-2-ones (**8** and **9**, entries 1 and 2) did not provide any diastereomeric separation. The more polar (*S*)-4-(*p*-methoxybenzyl)- (**10**, entry 3) or (*S*)-4-(*p*-nitrobenzyl)oxazolidin-2-ones (**11**, entry 4) allowed diastereomeric separation, but only with difficulty. Finally, the use of oxazolidin-2-one **12** derived from (1*R*,2*S*)-norephedrine (entry 5) gave superior results allowing a clean separation of the two diastereoisomers.

A careful analysis of the reaction mixtures in the above-screening experiments revealed that a partial endocyclic

Table 1 Screening of oxazolidin-2-ones as resolving agent



Entry	Oxazolidin-2-one	Separation
1	**8**	No
2	**9**	No
3	**10**	Difficult
4	**11**	Difficult
5	**12**	Efficient



Scheme 3 Chiral resolution using (1*R*,2*S*)-norephedrine derived oxazolidin-2-one **12**

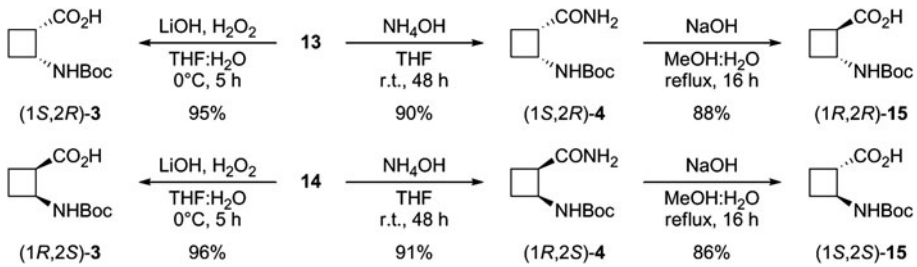
hydrolysis of the oxazolidin-2-one moiety in the products had occurred. For preparative work, therefore, the coupling conditions were modified: we decided to activate the acid as a mixed anhydride using pivaloyl chloride, and introduce the oxazolidin-2-one as its lithium salt. Using these conditions, the coupling of Boc-*cis*-amino acid (±)-**3** to oxazolidin-2-one **12** provided cleanly a mixture of the two diastereoisomers **13** and **14**. These derivatives were easily separated by chromatography and isolated in 46 and 44% yield, respectively (Scheme 3).

The controlled cleavage of the oxazolidin-2-one moiety was vital to the success of this resolution protocol. While the removal of the exocyclic acyl component from an *N*-acyloxazolidin-2-one by hydrolysis is well documented (Ager et al. 1996 and references therein), only a few examples are reported for acyl group removal by ammonolysis (Commerçon and Paris 1991; Chibale and Warren 1995; Boger et al. 1998; Zou et al. 2002). In the first instance, each compound **13** and **14** was treated with lithium hydroperoxide in aqueous THF to produce the two enantiopure compounds Boc-*cis*-ACBC (1*S*,2*R*)-**3** and (1*R*,2*S*)-**3** in 95 and 96%, respectively, without epimerization (Scheme 4). The chiral oxazolidin-2-one **12** was recovered easily at the end of these procedures. In our quest to prepare the Boc-*cis*-amino amide derivatives from the same intermediates **13** and **14**, we were pleased to find that a biphasic mixture of aqueous ammonia and THF allowed a clean and complete cleavage of the oxazolidin-2-one auxiliary. An attempt to perform this transformation using an ammonia solution in ethanol gave a sluggish reaction, and some unidentified secondary products were observed. Using the aqueous ammonia–THF procedure, the *cis*-amides (1*S*,2*R*)-**4** and (1*R*,2*S*)-**4** were obtained in 90 and 91% yield, respectively (Scheme 4). Once again, the chiral oxazolidin-2-one **12** was recovered efficiently in these operations. Treatment of these amides with aqueous NaOH in refluxing MeOH provided access to each of the enantiomers of Boc-*trans*-ACBC, (1*R*,2*R*)-**15** and (1*S*,2*S*)-**15**, in good yields.

Conclusion

In summary, we have reinvestigated and improved the synthesis of 2-aminocyclobutanecarboxylic acids to make it more suitable for routine larger scale preparations. The problems associated with the formation of unprotected *cis*-ACBC as a synthetic intermediate were circumvented, and the use of an oxazolidin-2-one as chiral resolving agent provides a

Scheme 4 Access to all stereoisomers of Boc-ACBC



welcome combination of clean separation with directed non-destructive cleavage, to facilitate access to N-protected derivatives of both *cis*- and *trans*-ACBC on gram scale.

Experimental

General remarks

All reagents and solvents were of commercial grade and were used without further purification, except as follows. Dichloromethane was dried over activated alumina and THF was distilled from sodium/benzophenone. (4*S*,5*R*)-4-Methyl-5-phenyl-1,3-oxazolidin-2-one was prepared from (1*R*,2*S*)-norephedrine according to a literature procedure (Bégis et al. 2009) and had $[\alpha]_D^{24}$ −168 (*c* 1.20, $CHCl_3$) {lit. $[\alpha]_D^{20}$ −170 (*c* 1.20, $CHCl_3$)}.

Flash chromatography was performed with SDS silica gel (35–70 μm). Analytical thin-layer chromatography was performed with 0.25 mm commercial silica gel plates (EMD, Silica Gel $60F_{254}$). TLC plates were visualized by UV fluorescence at 254 nm and then revealed using a phosphomolybdic acid solution (10% in EtOH) or a ninhydrin solution (0.3% in *n*-BuOH). Retention factors (R_f) are given for such analyses. Melting points were obtained in open capillary tubes and are uncorrected.

Optical rotations were measured using a 10 cm quartz cell. Values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature *T*, using solutions of concentration (*c*) in units of g 100 mL^{-1}. Samples for Fourier-transform infrared spectroscopy (IR) were prepared by the dispersion of the solid in a KBr disc. Maximum absorbances (*v*) are given in cm^{-1}.

Nuclear magnetic resonance (NMR) data were acquired on a spectrometer operating at 360 MHz for ^1H and at 90 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm with respect to tetramethylsilane ($\delta = 0$ ppm). Splitting patterns for ^1H NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), broad singlet (bs) or m (multiplet). High-resolution mass spectrometry (HRMS) data were recorded using electrospray ionization either in positive or negative mode (ESI+ or ESI−).

cis-(1-*t*-Butyloxycarbonyl)2,4-diazabicyclo[4.2.0]octane-3,5-dione [(±)-**5**]

To a suspension of uracil (3.36 g, 30 mmol, 1 equiv.) in acetonitrile (150 mL) was added Boc_2O (6.55 g, 30 mmol, 1 equiv.) and DMAP (37 mg, 0.3 mmol, 0.01 equiv.). The mixture was stirred overnight at room temperature, then the solvent was removed under reduced pressure to give the crude Boc-uracil **7** (6.49 g, $\tau = 100\%$) as a white solid which was used directly in the next step without purification. A solution of this crude Boc-uracil in acetone (1 L) was placed in a cylindrical water-cooled reactor, degassed with an argon stream for 30 min, and then saturated with ethylene for 30 min. The solution was then irradiated for 4 h with a 400 W medium-pressure mercury lamp fitted with a Pyrex filter while ethylene was bubbled through. The solution was then evaporated under reduced pressure. Flash chromatography of the residue (*c*-C_6H_{12}/EtOAc = 70/30) gave the cycloadduct (±)-**5** (6.14 g, 85% over 2 steps) as a white solid.

Mp 143°C; R_f 0.16 (*c*-C_6H_{12}/EtOAc); IR (KBr) *v* 3,383, 3,234, 2,984, 1,785, 1,733, and 1,704 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.10–2.40 (m, 3H), 2.50 (m, 1H), 3.34 (m, 1H), 4.74 (m, 1H), 7.58 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.5, 28.0, 30.3, 39.5, 49.0, 84.3, 148.7, 150.7, 172.2; HRMS (ESI+) Calcd for $C_{11}H_{16}N_2NaO_4$ $[M + Na]^+$: 263.1002, found 263.1000; Anal. Calcd for $C_{11}H_{16}N_2O_4$ C, 54.99; H, 6.71; N, 11.66. Found C, 55.05; H, 6.81; N, 11.74.

cis-(2-*t*-Butyloxycarbonylamino)cyclobutanecarboxylic acid [(±)-**3**]

Cycloadduct (±)-**5** (6.13 g, 25.5 mmol) was treated with a 0.5 M aqueous NaOH solution (255 mL) for 8 h at room temperature. The solution was cooled to 0°C and solid NaOH (25.5 g, 63.8 mmol, 25 eq.) was added portionwise. The mixture was stirred for 14 h at room temperature, then was cooled to 0°C and acidified slowly with concentrated HCl to pH 1. The aqueous phase was extracted with EtOAc (5 × 75 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the Boc-amino acid (±)-**3** (4.15 g, 76%) as a white solid. Mp 170–172°C. The spectral data were identical to those reported previously (Fernandes et al. 2007).

Chiral derivatization with (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one

To a cold (−78°C) solution of Boc-amino acid (±)-**3** (2.69 g, 12.5 mmol, 1 equiv.) and Et_3N (2.09 mL, 15.0 mmol, 1.2 equiv.) in dry THF (125 mL) was added dropwise pivaloyl chloride (1.61 mL, 13.1 mmol, 1.05 equiv.). The mixture was stirred for 1 h at 0°C to form the mixed anhydride, then cooled to −78°C. In a separate flask, a cold (ca. −40°C) solution of (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one **12** (2.21 g, 12.5 mmol, 1 equiv.) in THF (60 mL) was treated with *n*-BuLi (1.6 M solution in hexanes, 7.81 mL, 12.5 mmol, 1 equiv.) and stirred for 5 min. The resulting solution was added by rapid cannulation to the cooled (−78°C) solution of the mixed anhydride. Residual metalated oxazolidinone was taken up by rinsing

with dry THF (2 × 5 mL), and added to the cooled reaction mixture; this latter was stirred for 1 h at −78°C. After warming to 0°C, the mixture was treated with saturated $NaHCO_3$ (30 mL), and the THF was removed under reduce pressure. The aqueous phase was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic phases were washed successively with saturated $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography of the residue (EtOAc/petroleum ether = 15/85) gave the diastereoisomers **13** (2.15 g, 46%) and **14** (2.04 g, 44%) as white solids.

(4*S*,5*R*)-*N*-[(1*S*,2*R*)-2-(*t*-Butyloxycarbonylamino) cyclobutanecarbonyl]-4-methyl-5-phenyl-3-oxazolidin-2-one (**13**)

Mp 126°C; R_f 0.57 (EtOAc/petroleum ether = 85/15); $[\alpha]_D^{24}$ +59 (*c* 0.50, $CHCl_3$); IR (KBr) *v* 3,435, 2,983, 1,784, 1,710, 1,683, 1,504, 1,385, 1,368, and 1,346 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.92 (d, 3H, J_3 = 6.8 Hz), 1.45 (s, 9H), 2.01–2.11 (m, 2H), 2.17 (m, 1H), 2.41 (m, 1H), 4.55 (bs, 2H), 4.72 (quint, 1H, J_3 = 6.5 Hz), 5.45 (bs, 1H), 5.64 (d, 1H, J_3 = 7.2 Hz), 7.29 (d, 2H, J_3 = 7.0 Hz), 7.35–7.45 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.6, 19.3, 28.4, 28.7, 44.9, 47.7, 55.0, 79.1, 79.3, 125.7, 128.8, 133.5, 152.6, 155.0, 173.1; HRMS (ESI+) Calcd for $C_{20}H_{26}N_2NaO_5$ $[M + Na]^+$: 397.1734, found 397.1721.

(4*S*,5*R*)-*N*-[(1*R*,2*S*)-2-(*t*-Butyloxycarbonylamino) cyclobutanecarbonyl]-4-methyl-5-phenyl-3-oxazolidin-2-one (**14**)

Mp 102°C; R_f 0.40 (EtOAc/petroleum ether = 85/15); $[\alpha]_D^{24}$ −71 (*c* 0.50, $CHCl_3$); IR (KBr) *v* 3,373, 2,974, 1,783, 1,718, 1,677, 1,512, 1,392, 1,365, and 1,346 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.92 (d, 3H, J_3 = 6.6 Hz), 1.41 (s, 9H), 2.00–2.19 (m, 3H), 2.41 (m, 1H), 4.57 (bs, 1H), 4.64 (t, 1H, J_3 = 8.0 Hz), 4.80 (quint, 1H, J_3 = 6.8 Hz), 5.37 (bs, 1H), 5.65 (d, 1H, J_3 = 7.4 Hz), 7.29 (d, 2H, J_3 = 6.9 Hz), 7.34–7.45 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.8, 18.9, 28.4, 28.3, 45.0, 47.3, 54.7, 78.9, 79.4, 125.7, 128.8, 128.9, 133.5, 152.4, 154.6, 173.5; HRMS (ESI+) Calcd for $C_{20}H_{26}N_2NaO_5$ $[M + Na]^+$: 397.1734, found 397.1723.

(1*S*,2*R*)-(2-*t*-Butyloxycarbonylamino) cyclobutanecarboxylic acid [(1*S*,2*R*)-**3**]

To an ice-cold solution of compound **13** (1.87 g, 5.0 mmol, 1 equiv.) in a 1:4 mixture of water and THF (125 mL) was added a 35% w/w solution of H_2O_2 (2.6 mL, 30.0 mmol, 6 equiv.). The resulting mixture was stirred for 5 min at 0°C, then a solution of LiOH (240 mg, 10.0 mmol, 2 equiv.) in water (30 mL) was added. The mixture was stirred for 5 h at 0°C then 1 M Na_2SO_3 (50 mL) and saturated $NaHCO_3$ (50 mL) were added successively. THF was removed under reduced pressure and the aqueous residue was washed with CH_2Cl_2 (4 × 30 mL) to remove the chiral auxiliary. The aqueous phase was acidified to pH 1 with concentrated HCl and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the Boc-amino acid (1*S*,2*R*)-**3** (1.02 g, 95%) as a white solid. Mp 116–118°C; $[\alpha]_D^{26}$ +64 (*c* 0.93, $CHCl_3$); $[\alpha]_D^{23}$ +127 (*c* 0.92, EtOH). The spectral data were identical to those reported previously (Fernandes et al. 2007).

(1*R*,2*S*)-(2-*t*-Butyloxycarbonylamino) cyclobutanecarboxylic acid [(1*R*,2*S*)-**3**]

To an ice-cold solution of compound **14** (1.81 g, 4.8 mmol, 1 equiv.) in a 1:4 mixture of water and THF (120 mL) was added a 35% w/w solution of H_2O_2 (2.5 mL, 29.0 mmol, 6 equiv.). The resulting mixture was stirred for 5 min at 0°C, then a solution of LiOH (231 mg, 9.7 mmol, 2 equiv.) in water (30 mL) was added. The mixture was stirred for 5 h at 0°C then 1 M Na_2SO_3 (50 mL) and saturated $NaHCO_3$ (50 mL) were added successively. THF was removed under reduced pressure and the aqueous residue was washed with CH_2Cl_2 (4 × 30 mL) to remove the chiral auxiliary. The aqueous phase was acidified to pH 1 with concentrated HCl and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the Boc-amino acid (1*R*,2*S*)-**3** (993 mg, 96%) as a white solid. Mp 116–118°C; $[\alpha]_D^{26}$ −64 (*c* 0.88, $CHCl_3$); $[\alpha]_D^{24}$ −127 (*c* 0.89, EtOH). The spectral data were identical to those reported previously (Fernandes et al. 2007).

(1*S*,2*R*)-(2-*t*-Butyloxycarbonylamino) cyclobutanecarboxamide [(1*S*,2*R*)-**4**]

To a solution of compound **13** (2.48 g, 6.6 mmol) in THF (130 mL) was added aqueous ammonia (25% w/w solution, 66 mL). The resulting mixture was stirred for 48 h at room temperature. Solvents were removed under reduced pressure. Flash chromatography of the residue (EtOAc/*c*-C_6H_{12} = 50/50) gave the Boc-amino amide (1*S*,2*R*)-**4** (1.28 g, 90%) as a white solid. Mp 170°C (dec.); $[\alpha]_D^{27}$ +133 (*c* 0.51, $CHCl_3$). The spectral data were identical to those reported previously (Fernandes et al. 2009).

(1*R*,2*S*)-(2-*t*-Butyloxycarbonylamino) cyclobutanecarboxamide [(1*R*,2*S*)-**4**]

To a solution of compound **14** (1.65 g, 4.4 mmol) in THF (88 mL) was added aqueous ammonia (25% w/w solution,

44 mL). The resulting mixture was stirred for 48 h at room temperature. Solvents were removed under reduced pressure. Flash chromatography of the residue (EtOAc/c-C_6H_{12} = 50/50) gave the Boc-amino amide (1*R*,2*S*)-**4** (865 mg, 91%) as a white solid. Mp 170°C (dec.); $[\alpha]_D^{27}$ −133 (*c* 0.53, $CHCl_3$). The spectral data were identical to those reported previously (Fernandes et al. 2009).

Recovery of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**12**)

Washings obtained during the work-up of the hydrolysis of compound **13** or **14** were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give oxazolidin-2-one **12** (>95%) as a white solid. The oxazolidin-2-one was purified by a quick flash chromatography (EtOAc/CH_2Cl_2 = 30/70) before being reused in the coupling reaction with Boc-amino acid (±)-**3**.

Appropriate fractions obtained during the chromatographic purification of Boc-amino amide (1*S*,2*R*)-**4** or (1*R*,2*S*)-**4**, prepared by ammonolysis of compound **13** or **14**, respectively, were collected and evaporated under reduce pressure to give the oxazolidin-2-one **12** (>90%) as a white solid.

Recovered material from either protocol had $[\alpha]_D^{24}$ −168 (*c* 1.20, $CHCl_3$) and the spectral data were identical to those reported previously (Bégis et al. 2009).

(1*R*,2*R*)-(2-*t*- Butyloxycarbonylamino) cyclobutanecarboxylic acid [(1*R*,2*R*)-**15**]

To a solution of Boc-amino amide (1*S*,2*R*)-**4** (1.14 g, 5.3 mmol) in MeOH (210 mL) was added 6 M aqueous NaOH (70 mL). The resulting mixture was refluxed for 16 h. Methanol was removed under reduced pressure. The aqueous residue was diluted with water (70 mL) and washed with CH_2Cl_2 (3 × 40 mL). The aqueous phase was then cooled to 0°C and acidified slowly with concentrated HCl to pH 1. The aqueous phase was extracted with EtOAc (4 × 75 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude Boc-amino acid was dissolved in EtOH and treated with decolorizing charcoal to give the Boc-amino acid (1*R*,2*R*)-**15** (1.01 g, 88%) as a white solid. Mp 104–105°C (dec.); $[\alpha]_D^{23}$ +11 (*c* 0.50, $CHCl_3$); $[\alpha]_D^{25}$ −23 (*c* 0.53, EtOH). The spectral data were identical to those reported previously (Fernandes et al. 2009).

(1*S*,2*S*)-(2-*t*-Butyloxycarbonylamino) cyclobutanecarboxylic acid [(1*S*,2*S*)-**15**]

To a solution of Boc-amino amide (1*R*,2*S*)-**4** (0.86 g, 4.0 mmol) in MeOH (165 mL) was added 6 M aqueous NaOH (55 mL). The resulting mixture was refluxed for 16 h. Methanol was removed under reduced pressure. The aqueous residue was diluted with water (55 mL) and washed with CH_2Cl_2 (3 × 30 mL). The aqueous phase was then cooled to 0°C and acidified slowly with concentrated HCl to pH 1. The aqueous phase was extracted with EtOAc (4 × 60 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude Boc-amino acid was dissolved in EtOH and treated with decolorizing charcoal to give the Boc-amino acid (1*S*,2*S*)-**15** (0.74 g, 86%) as a white solid. Mp 104–105°C (dec.); $[\alpha]_D^{24}$ −11 (*c* 0.51, $CHCl_3$); $[\alpha]_D^{25}$ +23 (*c* 0.59, EtOH). The spectral data were identical to those reported previously (Fernandes et al. 2009).

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Conflict of interest None.

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