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Synthesis of enantiopure 7-azanorbornane proline–α-amino acid chimeras by highly efficient HPLC resolution of a phenylalanine analogue

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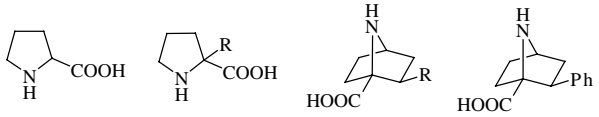
Abstract—The enantiomerically pure conformationally constrained prolines, (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-2-phenyl-7-azabicyclo [2.2.1]heptane-1-carboxylic acid hydrochlorides, which are proline–phenylalanine chimeras, have been separately obtained by resolution of a key intermediate using chiral high performance liquid chromatography. The efficiency of the chromatographic resolution provides a general methodology for the preparation of both enantiomers of a broad variety of proline–α-amino acid chimeras with a 7-azanorbornane skeleton in enantiomerically pure form.

1. Introduction

The introduction of conformational constraints constitutes one of the most promising approaches to the construction of peptide analogues of pharmaceutical interest.[1–4] Furthermore, it has become a useful tool for the elucidation of biologically active conformations[1,5] by providing information about the spatial requirements for optimal interaction with the receptor.[5–7]

Several β-substituted prolines (Fig. 1) have been synthesised to serve as amino acid chimeras in which the functional groups of the amino acid side-chain are combined with the conformational restrictions characteristic of the cyclic amino acid residue.[8] Replacement of the natural amino acids in peptides with such proline–α-amino acid chimeras has led to a better understanding of the bioactive conformations of cholecystokinin,[9–11] angiotensin II,[12,13] bradykinin,[14] and opioide peptides.[15–17] Also, β-alkylproline analogues have served for the development of enzyme inhibitors,[17–19] as well as peptidomimetics exhibiting improved bioactivity and greater metabolic stability.[12–17]



Pro **Pro-α-Aminoacid chimeras** **Pro-Phe chimera**

R = amino acid side chain

Figure 1. Structure of some proline analogues.

The proline analogues containing a 7-azabicyclo[2.2.1]heptane structure (Fig. 1) constitute a distinct class of aminoacids due to their extra conformational restriction. Hence, the benefits of the parent compound (R = H), as a replacement for proline in a boroarginine thrombin inhibitor[20] and as starting material in the synthesis of a new class of HIV-1 protease inhibitor,[21] have already been established.

At present, there are a few examples on the asymmetric synthesis of prolines with a 7-azanorbornane skeleton.[22–27] On the other hand, the literature reports only one resolution procedure to obtain separately both enantiomers of an azabicyclic β-hydroxyproline.[28] This strategy consists of the formation of diastereomers and subsequent separation by crystallisation, which involves the introduction of additional synthetic steps to the pathway towards the final products.

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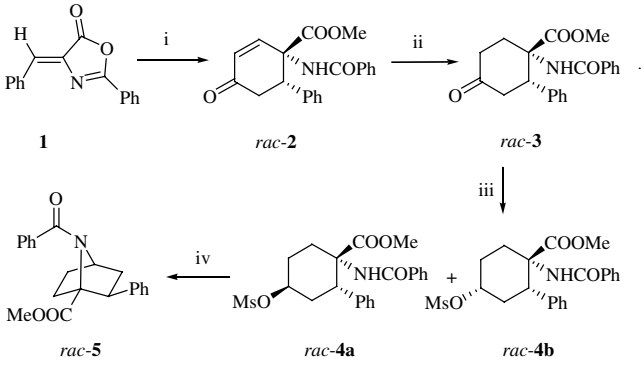
Our main objective herein is the development of a highly efficient and facile resolution method for an azanorbornane proline–phenylalanine chimera analogue in order to facilitate the synthesis of a wide variety of α-amino acid chimeras with 7-azabicyclo[2.2.1]heptane skeleton in enantiomerically pure form. To this end we have used chiral high performance liquid chromatography (HPLC), since we have already shown the efficacy of this methodology for resolving racemic mixtures of other constrained phenylalanine analogues.[29–32] The incorporation of some of these analogues,[33–37] such as 1-amino-2-phenylcyclopropanecarboxylic acid (c_3Phe), 1-amino-2-phenylcyclohexanecarboxylic acid (c_6Phe) and 1-amino-2,3-diphenylcyclopropanecarboxylic acid ($c_3$diPhe), into model peptides has allowed the exploration of structural properties.

2. Results and discussion

Initially the multigram scale synthesis of the racemic proline–phenylalanine chimera derivative, *rac*-**5**, was performed according to a modified literature procedure (Scheme 1).[38,39] Thus, the Diels–Alder reaction of Danishefsky's diene and a C-4 unsaturated oxazolone derived from benzaldehyde, (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone **1**, followed by hydrolysis of the adduct mixture and subsequent elimination of the methoxy group with oxazolone ring opening led to *rac*-**2** in 81% overall yield. Heterogeneous hydrogenation of the double bond of enone *rac*-**2**, by using 20% $Pd(OH)_2/C$ instead of the originally reported catalyst Pd/C, afforded ketone *rac*-**3** in 95% yield. Reduction of *rac*-**3** with L-selectride® (lithium tri-*sec*-butylborohydride) provided preferentially the *axial* alcohol (stereoselectivity ratio: 63:37). Then, the mixture of alcohols was transformed into the corresponding methanesulfonate derivatives, *rac*-**4a** and *rac*-**4b** in 71% combined yield from *rac*-**3**, by treatment with methanesulfonyl chloride in triethylamine. In order to prepare the bicyclic product *rac*-**5**, the base-promoted internal nucleophilic displacement of the methanesulfonate group on *rac*-**4a** was achieved by treatment of the mixture of *rac*-**4a** and *rac*-**4b** with NaH in DMF, instead of potassium *tert*-butoxide in THF as previously reported.[38,39] Finally, the separation of the product *rac*-**5** from the non-cyclisable methanesulfonate *rac*-**4b** was easily achieved by column chromatography.

In this way, the synthesis was accomplished on a multigram scale and ca. 5 g of a racemic mixture of *rac*-**5** could be obtained from oxazolone **1** in seven steps in 27% overall yield.



Scheme 1. Synthesis of 7-azabicyclo[2.2.1]heptane analogue of phenylalanine *rac*-**5**. Reagents and conditions: (i) (a) Danishefsky's diene, toluene, reflux, (b) 0.005 N HCl/THF (1:4), (c) DBU, MeOH, 0 °C (81% from **1**); (ii) H_2, 20% $Pd(OH)_2/C$, CH_2Cl_2, rt (95%); (iii) (a) L-selectride®, THF, −78 °C, (b) MsCl, Et_3N, CH_2Cl_2, rt (71% from *rac*-**3**); (iv) NaH, DMF, −78 °C, then column chromatography (49% from *rac*-**4a**+*rac*-**4b**).

2.1. HPLC resolution of *rac*-5

Once the synthesis of the racemic compound *rac*-**5** had been achieved, we undertook the preparation of this product in enantiomerically pure form by HPLC resolution using a chiral stationary phase. Specifically, a non-commercial polysaccharide-derived support consisting of mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose covalently attached to allylsilica gel was used.[40,41] The excellent chiral discrimination exhibited by this stationary phase towards a variety of compounds[40] together with its high chemical stability, make it especially suitable for resolutions on a preparative scale. The efficiency of this system has actually been demonstrated in the preparative enantioseparations of various phenylalanine surrogates.[29–32]

The resolution of *rac*-**5** was initially investigated on an analytical scale (eluent: 95:5 *n*-hexane/2-propanol, $k'_1 = 1.77$, $\alpha = 1.70$, $R_s = 3.04$). From these satisfactory results, the optimal separation conditions were determined by adding a certain amount of chloroform to the eluent to enhance the solubility of the compound. The extension of the analytical conditions to the preparative scale proved extremely efficient, resulting in a baseline separation of both enantiomers (see Fig. 2). Working on repetitive injection mode, 1.2 g of racemate were injected onto a 150 × 20 mm ID column with a total time of 4–5 h

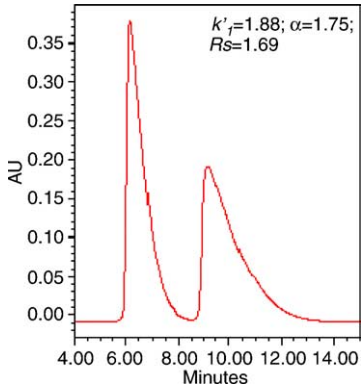


Figure 2. HPLC preparative resolution of *rac*-**5**. Column: 150 × 20 mm ID, eluent: *n*-hexane/chloroform/2-propanol (93:2:5), flow rate: 18 mL min^{-1}. UV detection at 270 nm. Injection of 50 mg of *rac*-**5** in 0.2 mL of dichloromethane. See Section 4.2 for definition of the chromatographic parameters.

to complete the process. Valley–valley collection of the eluting peaks afforded the enantiomerically pure first eluted enantiomer. The second collected enantiomer was obtained in a 99:1 enantiomeric ratio. After recrystallisation of the last enantiomer from ethyl acetate a >99.9:0.1 enantiopurity was achieved. Thus, the resolution of 1.2 g of *rac*-**5** finally resulted in 1.037 g of enantiomerically pure material (ca. 517 and 520 mg of the first and second eluted enantiomer, respectively). The enantiomeric excess of the resolved enantiomers was assessed at analytical level, and the assignment of their absolute configurations was carried out by means of the incorporation of the separated enantiomers into dipeptide derivatives, as described below.

2.2. Assignment of absolute configurations

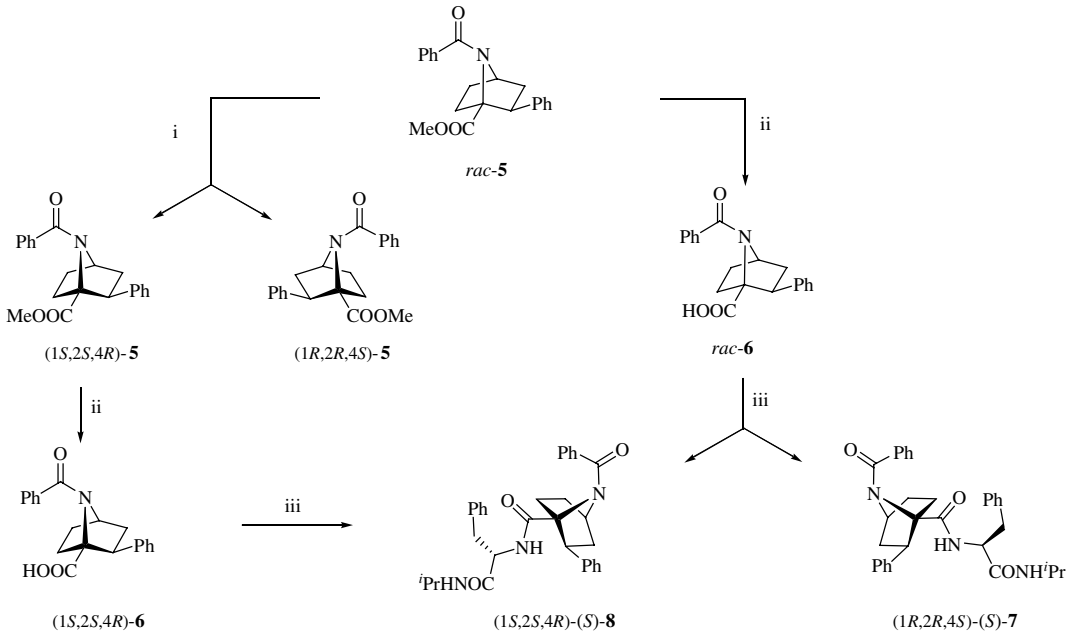
The assignment of absolute configuration was performed by X-ray diffraction analysis of a single crystal obtained from a solution of one of the diastereomeric dipeptides resulting from the coupling of the racemic mixture with an L-phenylalanine derivative. Obrecht et al. had described phenylalanine cyclohexylamide as a very convenient auxiliary for the efficient assignment of the absolute configurations of α,α-disubstituted amino acids.[42,43] According to this approach, we coupled the racemic mixture of the 7-azanorbornane proline *rac*-**5** with this enantiomerically pure L-phenylalanine analogue. However, all the attempts to obtain a suitable crystal to perform single crystal X-ray analysis, from either of the two resulting diastereomeric dipeptides, failed.

With this result in mind, a different phenylalanine derivative was selected for coupling to the racemic 7-azanorbornane proline (Scheme 2). The saponification of *rac*-**5** using potassium hydroxide in methanol led to the corresponding acid *rac*-**6** in 97% yield. The subsequent coupling of this racemic mixture with enantiomerically pure L-phenylalanine isopropylamide using the reagent designed by Castro et al.,[44] (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexaflurophosphate (BOP), provided a mixture of two diastereomeric dipeptide derivatives **7** and **8** in 98% combined yield. After complete separation of the dipeptides by column chromatography, both compounds were individually characterised. A crystal suitable for X-ray crystallography was finally obtained for **8**, the second chromatographic component.

Hence, the absolute configuration of the proline analogue contained in the dipeptide **8** could be unquestionably determined by X-ray diffraction analysis of a crystal, easily obtained by slow evaporation from a solution in dichloromethane/*n*-hexane. The known (*S*) configuration for the phenylalanine residue allowed the determination of the absolute configuration of the azabicyclic residue as (1*S*,2*S*,4*R*).[45]

Independently, the firstly eluting enantiomer of **5** was also coupled with L-phenylalanine isopropylamide under the conditions previously developed for the racemic material (Scheme 2). Comparison of the spectroscopic data of this dipeptide analogue with those obtained for compound **8**, which had provided the suitable single crystal for the X-ray diffraction analysis, allowed the identification of this enantiomer as the one bearing the same (1*S*,2*S*,4*R*) absolute configuration of the azabicyclic residue contained in peptide **8**.

Great interest has been focused on dipeptide **8** since the X-ray diffraction analysis[45] has revealed that, in the solid state, this constrained peptide containing the



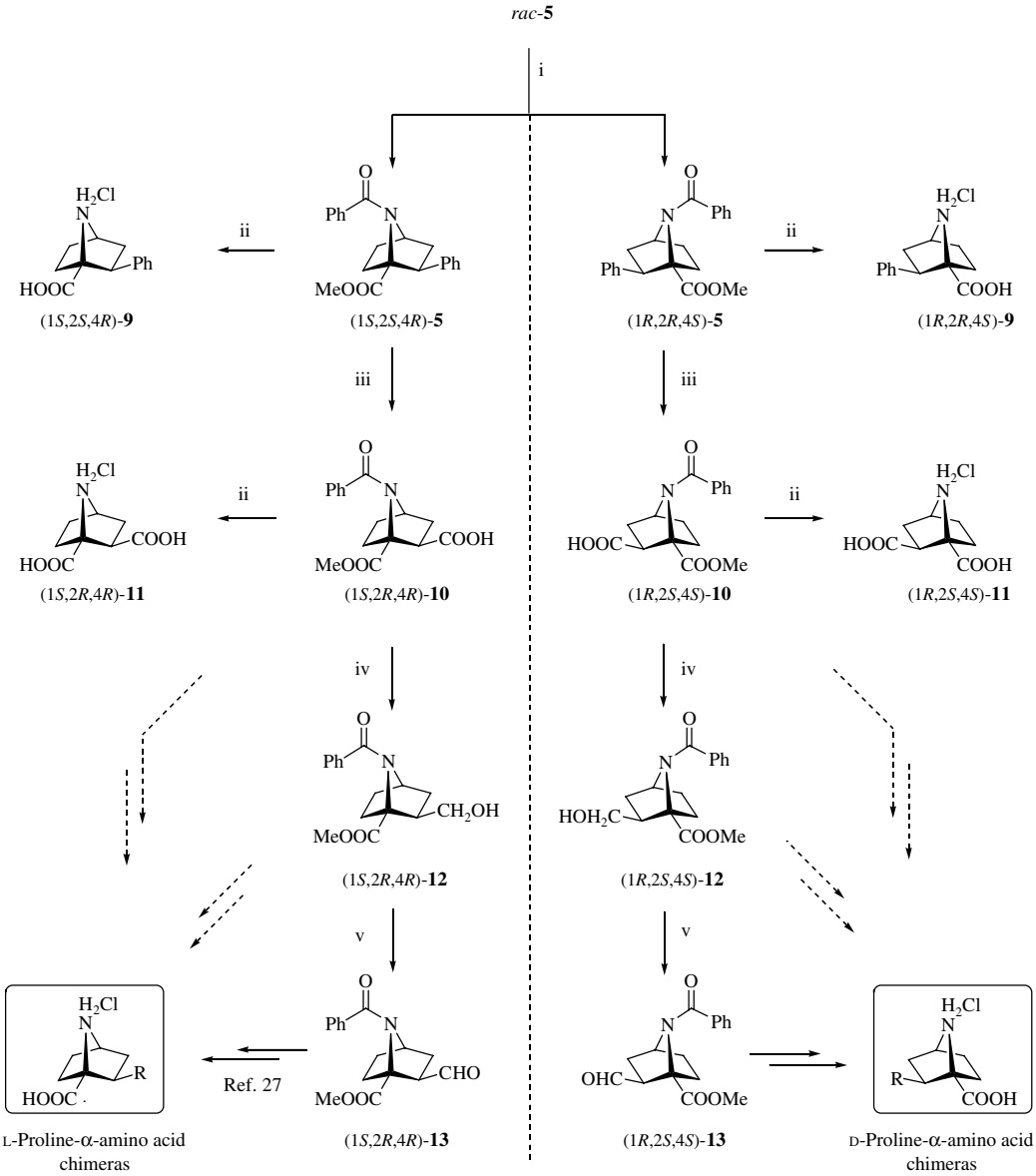
Scheme 2. Resolution of *rac*-**5** and assignment of the absolute configurations. Reagents and conditions: (i) HPLC resolution; (ii) KOH, MeOH, reflux (97%); (iii) (a) Et_3N, BOP, L-phenylalanine isopropylamide hydrochloride, CH_3CN, then column chromatography (98%).

azanorbornane proline adopts a type Iβ-turn whereas the analogous dipeptide sequence incorporating L-proline has been shown to accommodate a βII-turn disposition. As we recently have described, attractive interactions involving the central NH group and either the aromatic rings or the pyramidalised bicyclic nitrogen seem to play a role in the stabilisation of the observed βI-turn conformation.

2.3. Synthesis of proline–α-amino acid chimeras in enantiomerically pure form

After HPLC resolution of *rac*-**5**, the isolated enantiomers were subjected to hydrolysis. A small quantity of each enantiomer, (1*S*,2*S*,4*R*) and (1*R*,2*R*,4*S*)-**5**, was separately treated with aqueous 6 N HCl under reflux to provide the enantiomerically pure proline–phenylalanine chimeras (1*S*,2*S*,4*R*)-**9** and (1*R*,2*R*,4*S*)-**9** both in quantitative yield (Scheme 3). The resulting amino acids, which may be also considered to be (2*S*,3*S*) and (2*R*,3*R*)-3-phenylproline analogues, were fully characterised.

The synthesis of the proline–aspartic acid chimeras was also embarked upon (Scheme 3). Oxidative cleavage of the phenyl substituent on the azabicyclic ring of (1*S*,2*S*,4*R*)-**5** and (1*R*,2*R*,4*S*)-**5** proceeded in 45% yield and led to the intermediates (1*S*,2*R*,4*R*)-**10** and (1*R*,2*S*,4*S*)-**10**. Treatment of each enantiomer with aqueous 6 M HCl under reflux supplied the enantiomerically pure (2*S*,3*R*) and (2*R*,3*S*)-3-carboxyproline ana-



Scheme 3. Synthetic route to enantiomerically pure 7-azanorbornane proline–α-amino acid chimeras. Reagents and conditions: (i) HPLC resolution; (ii) 6 N HCl, reflux (⩾95%); (iii) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$, rt (45%); (iv) (a) Et_3N, IBCF, THF, −15 °C, (b) $NaBH_4$, H_2O, −15 °C then rt (88%); (v) Dess–Martin periodinane reagent, CH_2Cl_2, rt (80%).

logues, (1*S*,2*R*,4*R*)-**11** and (1*R*,2*S*,4*S*)-**11**, in quantitative yield. The determinations of the specific rotations for the enantiomers (1*S*,2*R*,4*R*)-**10** and (1*S*,2*R*,4*R*)-**11** supplied further confirmation of the absolute stereochemistry, since these values agree with the corresponding data for the same compounds previously obtained by asymmetric synthesis.[46,47]

Carboxylic acids (1*S*,2*R*,4*R*)-**10** and (1*R*,2*S*,4*S*)-**10** constitute key intermediates for the preparation of a wide variety of other enantiomerically pure proline–α-amino acid chimeras, either directly, thanks to the versatility of the acidic group, or by transformation into other synthetically flexible functions, such as a hydroxyl or formyl groups.

Thus, the reduction of the acid to the alcohol was performed for both enantiomers, (1*S*,2*R*,4*R*)-**10** and (1*R*,2*S*,4*S*)-**10**. The procedure involving the acyl chloride intermediate was unsuccessful, but the mixed anhydride method led to excellent results (Scheme 3). Separate treatment of (1*S*,2*R*,4*R*)-**10** and (1*R*,2*S*,4*S*)-**10** with *N*-methylmorpholine (NMM) and isobutylchloroformate and subsequent addition of $NaBH_4$ over the resulting anhydrides supplied the enantiomerically pure alcohols (1*S*,2*R*,4*R*)-**12** and (1*R*,2*S*,4*S*)-**12** in 88% yield. The utility of this β hydroxymethyl function to achieve the synthesis of new azabicyclic prolines is under current investigation.

Finally, the oxidation of the hydroxyl group was easily carried out after selecting the best oxidation conditions by testing the racemic mixture of alcohols. Treatment of racemic **12** with chromium trioxide resulted in low yields (69%). On the other hand, a 70:30 mixture of the β-formyl derivative **13** and its C-2 epimer was obtained in a 97% combined yield when the alcohol **12** was treated under Swern conditions with oxalyl choride (1.5 equiv), Et_3N (5 equiv) and DMSO (4.5 equiv) in dry dichloromethane. The best results on this oxidation reaction were obtained by using the Dess–Martin reagent.[48,49] In this case, the process took place in high yield and without any epimerisation detectable in the crude reaction mixture. So, the separate oxidation of the alcohols (1*S*,2*R*,4*R*)-**12** and (1*R*,2*S*,4*S*)-**12** using the Dess–Martin periodinane in dry dichloromethane gave rise to the enantiopure aldehydes (1*S*,2*R*,4*R*)-**13** and (1*R*,2*S*,4*S*)-**13**, respectively, in 80% yield. It is noteworthy that the formyl derivative (1*S*,2*R*,4*R*)-**13** has recently proved to be a versatile synthetic intermediate in the preparation of a wide variety of azabicyclic prolines β-substituted through olefination processes.[27]

3. Conclusion

The high efficacy of the HPLC resolution has provided the enantiomerically pure enantiomers of a constrained proline–phenylalanine chimera and a proline–aspartic acid chimera with a 7-azabicyclo[2.2.1]heptane skeleton. We have also shown the possibility of extending this methodology to the preparation of other proline–α-amino acid chimeras in enantiomerically pure form via the β-formyl derivative, as we have recently described, or by means of the corresponding β-carboxylic or β-hydroxymethyl derivatives, which are presently under investigation.

Therefore, the methodology described herein constitutes an efficient strategy that supplies both enantiomers of a very special kind of amino acid where the rigidity provided by the azabicyclic skeleton and a β-substituent, which mimics the α-amino acid side chain, are combined. These proline–α-amino acid chimeras are new surrogates to be incorporated into peptides whose structural and biological study shed light upon the nature of the effects induced by this type of conformational restriction and the influence of the absolute configurations of the stereogenic centres.

4. Experimental

4.1. General

Melting points were determined using a Büchi SMP-20 apparatus. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 apparatus at room temperature, using the residual solvent signal as the internal standard; chemical shifts (δ) are quoted in ppm, and coupling constants (J) are measured in hertz. Optical rotations were measured in a cell with a 10 cm pathlength at 25 °C using a JASCO P-1020 polarimeter. Elemental analyses were carried out on a Perkin–Elmer 200 C, H, N, S analyser. TLC was performed on Polygram® sil G/UV_{254} precoated silica gel polyester plates and products were visualised under UV light (254 nm), ninhydrin, anisaldehyde or phosphomolybdic acid developers. Column chromatography was performed using silica gel (Kieselgel 60). (*Z*)-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone **1** was prepared by condensation of hippuric acid (benzoylglycine) and benzaldehyde in the presence of anhydrous sodium acetate and acetic anhydride.[38,39]

4.2. High performance liquid chromatography

HPLC was carried out on a system equipped with a Waters 600-E pump and a Waters 991 photodiode array detector. The preparation of the chiral stationary phase, consisting of mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose covalently attached to allylsilica gel, has been already described.[40,41] The solvents used as mobile phases were of spectral grade. The HPLC analytical assays were carried out on a 150×4.6 mm ID column with an eluent flow rate of 1.0 mL min^{-1} and UV monitoring at 220 nm. The capacity (k') k'_1 1.77, selectivity (α) 1.70 and resolution (R_s) 3.04 factors are defined as follows: $k' = (t_r - t_0)/t_0$, $\alpha = k'_2/k'_1$,

$R_s = (t_2 - t_1)/[(w_{1/2})_2 + (w_{1/2})_1]$, where subscripts 1 and 2 refer to the first and second eluted enantiomer, respectively, t_r ($r = 1, 2$) are their retention times, and $(w_{1/2})_1$ and $(w_{1/2})_2$ denote their half high peak widths; t_0 is the dead time. The preparative resolution of *rac*-**5** was carried out on a 150×20 mm ID column. A mixture of *n*-hexane/chloroform/2-propanol (93:2:5) was used as the eluent, at a flow rate of 18 mL min^{-1}. UV detection was performed at 270 nm.

4.3. Preparation of methyl (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-*N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, (1*S*,2*S*,4*R*)-5 and (1*R*,2*R*,4*S*)-5

4.3.1. Synthesis of methyl *N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, *rac*-5. The synthesis of the racemic mixture was basically carried out according to the procedure previously reported in the literature.[38,39] The main modification was introduced into the last step concerning the transformation of *rac*-**4a** into azabicylclic *rac*-**5**. For this purpose, a solution of the mixture of both methanesulfonates, *rac*-**4a** and *rac*-**4b**, (13.5 g, 31.3 mmol) in dry DMF (200 mL) was added to a suspension of NaH (1.54 g, 64.2 mmol) in dry DMF (150 mL) at −78 °C under an argon atmosphere. After stirring at this temperature for 30 min, the mixture was allowed to warm up to room temperature and stirring was maintained at this temperature for an additional 2 h. Saturated aqueous NH_4Cl was added and, after stirring for a further 15 min, the solution was extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with water (150 mL) and saturated brine (2×100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuo. Column chromatography of the resulting residue, using dichloromethane/ethyl acetate (7:3) as eluent, provided compound *rac*-**5** (5.11 g, 15.2 mmol) in 49% yield.

The whole procedure for the synthesis of *rac*-**5** was performed in a multigram scale. Therefore, starting from 14.0 g (56.5 mmol) of the oxazolone **1**, 5.11 g (15.2 mmol) of a racemic mixture of compound *rac*-**5** could be obtained through seven steps in 27% overall yield.

4.3.2. Resolution of *rac*-5. HPLC resolution of *rac*-**5** (1.2 g) dissolved in dichloromethane (4.8 mL) was carried out by successive injections of 0.2 mL on a 150×20 mm ID column filled with 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose bonded on allylsilica gel and using a 93:2:5 mixture of *n*-hexane/chloroform/2-propanol as the eluent (flow rate 18 mL min^{-1}). A total of 24 injections were required with one injection being performed every 10 min. Three separate fractions were collected. Evaporation of the first fraction provided 517 mg of the enantiopure first eluted enantiomer (1*S*,2*S*,4*R*)-**5**. The third fraction was further submitted to recrystallisation from ethyl acetate in order to reach a higher purity. This procedure supplied 520 mg of the last eluted enantiomer (1*R*,2*R*,4*S*)-**5**, also in enantiomeric pure form. The second fraction collected (55 mg) contained a 37:63 mixture of the first and the second eluted enantiomers, (1*S*,2*S*,4*R*)-**5**/(1*R*,2*R*,4*S*)-**5**.

Spectroscopic data for both (1*S*,2*S*,4*R*)-**5** and (1*R*,2*R*,4*S*)-**5** were the same as those described in the literature for *rac*-**5**.[38]

(1*S*,2*S*,4*R*)-**5**: Mp 185–186 °C. $[\alpha]_D = +52.9$ (*c* 1.0, $CHCl_3$)

(1*R*,2*R*,4*S*)-**5**: Mp 186–187 °C. $[\alpha]_D = -52.5$ (*c* 1.0, $CHCl_3$)

4.4. Synthesis of *N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid, 6

4.4.1. *rac*-*N*-Benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid, *rac*-6. A 2 N solution of KOH in methanol (12 mL) was added to *rac*-**5** (300 mg, 0.9 mmol) and the reaction mixture was stirred at 40 °C for 7 h. After evaporation of the solvent, the remaining residue was redissolved in water and followed by addition of 2 N HCl until pH 2. Then, compound *rac*-**6** precipitated as a white solid that was separated by filtration (277 mg, 0.86 mmol, 97% yield). IR (KBr) ν (cm^{-1}): 3100–2800, 2275, 1892, 1712, 1534, 1447; ^1H NMR ($CDCl_3$) δ (ppm): 16.00 (br s, 1H); 7.62–7.48 (m, 5 H); 7.37–7.21 (m, 5H); 4.50–4.47 (m, 1H); 3.57 (dd, 1H, $J = 7.3$ Hz, $J = 6.9$ Hz); 2.51–2.35 (m, 2H); 2.17–2.10 (m, 2H); 2.04–1.88 (m, 1H); 1.74–1.65 (m, 1H). ^{13}C NMR ($CDCl_3$) (ppm): 170.1, 168.9, 134.5, 131.5, 128.9, 128.8, 127.6, 127.6, 126.9, 78.4, 62.2, 52.9, 37.9, 36.3, 28.2. Anal. Calcd for $C_{20}H_{19}NO_3$: C: 74.75, H: 5.96, N: 4.36; found C: 74.70, H: 6.01, N: 4.34.

4.4.2. (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-*N*-Benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid, (1*S*,2*S*,4*R*)-6 and (1*R*,2*R*,4*S*)-6. An identical procedure to that described above was used for the conversion of (1*S*,2*S*,4*R*)-**5** or (1*R*,2*R*,4*S*)-**5** (100 mg, 0.29 mmol) into (1*S*,2*S*,4*R*)-**6** or (1*R*,2*R*,4*S*)-**6**, respectively (86.2 mg, 0.27 mmol, 91% yield). Spectroscopic data were identical to those reported for *rac*-**6**.

(1*S*,2*S*,4*R*)-**6**: Mp 168 °C. $[\alpha]_D = +82.6$ (*c* 0.5, $CHCl_3$)

(1*R*,2*R*,4*S*)-**6**: Mp 168 °C. $[\alpha]_D = -80.5$ (*c* 0.5, $CHCl_3$)

4.5. Synthesis of *N*-benzoyl-2-phenyl-7-azabicyclo-[2.2.1]heptane-1-carbonyl-(*S*)-*N*′-isopropylphenylalaninamide, (1*R*,2*R*,4*S*)-(*S*)-7 and (1*S*,2*S*,4*R*)-(*S*)-8

L-Phenylalanine isopropylamide hydrochloride (77.4 mg, 0.32 mmol), triethylamine (48.6 mg, 0.48 mmol) and the coupling reagent BOP, (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexaflurophosphate, (71 mg, 0.16 mmol) were added to a solution of *N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]hepta-ne-1-carboxylic acid *rac*-**6** (50 mg, 0.16 mmol) in acetonitrile

(4 mL). The mixture was stirred for 30 h at room temperature. After the completion of the reaction, the solvent was removed under vacuum and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The organic layer was washed with two more portions of water (2×10 mL) and, then, dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to give a residue containing the diastereomeric dipeptide analogues. They were fully separated by silica gel column chromatography, eluting with ethyl acetate/*n*-hexane (8:2), which provided 40.6 and 38.8 mg of (1*R*,2*R*,4*S*)-(*S*)-**7** and (1*S*,2*S*,4*R*)-(*S*)-**8**, respectively, in 98% combined yield (79.4 mg, 0.16 mmol).

(1*R*,2*R*,*4S*)-(*S*)-**7**: White solid. Mp 162–163 °C. $[\alpha]_D = -44.7$ (*c* 0.36, $CHCl_3$). IR (nujol) ν (cm^{-1}): 3346–3208, 1661, 1643. ^1H NMR ($CDCl_3$) δ (ppm): 7.75–7.72 (m, 2H); 7.60–7.48 (m, 3H); 7.24–7.12 (m, 8H); 7.09–7.02 (m, 3H); 5.17 (d, 1H, $J = 7.7$ Hz); 4.36 (dd, 1H, $J = 4.8$ Hz, $J = 4.8$ Hz); 4.21 (dd, 1H, $J = 13.9$ Hz, $J = 7.3$ Hz), 3.79 (m, 1H); 3.30 (dd, 1H, $J = 9.2$ Hz, $J = 5.5$ Hz); 3.01 (dd, 1H, $J = 13.6$ Hz, $J = 6.2$ Hz); 2.91 (dd, 1H, $J = 13.6$ Hz, $J = 7.3$ Hz); 2.29–2.17 (m, 2H); 2.10–1.99 (m, 2H); 1.76–1.53 (m, 2H); 0.95 (d, 3H, $J = 6.6$ Hz); 0.85 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.2, 169.2, 168.8, 142.8, 137.5, 135.5, 131.6, 129.5, 128.6, 128.6, 128.3, 128.2, 128.1, 127.1, 126.5, 75.4, 63.0, 54.9, 53.1, 41.2, 38.8, 37.7, 32.7, 30.1, 22.3, 22.1. Anal. Calcd for $C_{32}H_{35}N_3O_3$: C: 75.41, H: 6.92, N: 8.25; found C: 75.30, H: 6.90, N: 8.35.

(1*S*,2*S*,*4R*)-(*S*)-**8**: White solid. Mp 157 °C. $[\alpha]_D = +92.6$ (*c* 0.5, $CHCl_3$). IR (nujol) ν (cm^{-1}): 3429, 3325, 1676, 1660, 1639. ^1H NMR ($CDCl_3$) δ (ppm): 7.70–7.67 (m, 2H); 7.54–7.50 (m, 1H); 7.49–7.28 (m, 7H); 6.94–6.88 (m, 2H); 6.83–6.74 (m, 2H); 5.42 (d, 1H, $J = 6.8$ Hz); 4.39 (m, 1H); 3.94–3.82 (m, 2H); 3.37 (dd, 1H, $J = 9.5$ Hz, $J = 5.1$ Hz), 2.84 (dd, 1H, $J = 13.6$ Hz, $J = 3.4$ Hz); 2.57–2.49 (m, 1H); 2.44–2.34 (m, 1H); 2.16–1.99 (m, 2H); 1.76–1.69 (dd, 1H, $J = 13.6$ Hz, $J = 6.1$ Hz); 1.66–1.57 (m, 2H); 1.02 (d, 3H, $J = 6.6$ Hz); 0.85 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.3, 169.3, 168.2, 142.0, 135.8, 134.5, 132.2, 129.0, 128.7, 128.5, 128.4, 128.1, 127.6, 126.6, 75.1, 64.2, 53.5, 53.2, 41.2, 36.2, 35.9, 31.1, 29.8, 22.2, 21.9. Anal. Calcd for $C_{32}H_{35}N_3O_3$: C 75.41, H 6.92, N 8.25; found C 75.48, H 6.85, N 8.30.

An identical procedure to that described above was applied to transform (1*S*,2*S*,4*R*)-**6** (50 mg, 0.15 mmol) into (1*S*,2*S*,4*R*)-(*S*)-**8**, which was obtained in 98% yield (78 mg, 0.15 mmol). The spectroscopic data were the same as described above.

4.6. Synthesis of (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride, (1*S*,2*S*,4*R*)-9 and (1*R*,2*R*,4*S*)-9

Aqueous 6 N HCl (15 mL) was added to the amido esters (1*S*,2*S*,4*R*)-**5** or (1*R*,2*R*,4*S*)-**5** (100 mg, 0.3 mmol) and the mixture was heated under reflux for 48 h. The solvent was, then, evaporated under vacuum and the residue dissolved in water (30 mL). The solution was extracted with dichloromethane (3×20 mL) and the separated aqueous phase was evaporated to dryness. Total removal of water was achieved by final lyophilisation. This procedure gave the amino acid hydrochlorides (1*S*,2*S*,4*R*)-**9** or (1*R*,2*R*,4*S*)-**9**, respectively, in 95% yield (72 mg, 0.28 mmol). IR (nujol) (cm^{-1}): 3500–2500, 1737, 1603. ^1H NMR (D_2O) δ (ppm): 7.48–7.26 (m, 5 H); 4.43 (dd, 1H, $J = 4.2$ Hz, $J = 4.2$ Hz); 3.69 (dd, 1H, $J = 9.2$ Hz, $J = 6.6$ Hz); 2.52 (dd, 1H, $J = 13.9$ Hz, $J = 9.2$ Hz); 2.40–2.15 (m, 4H); 2.12–1.97 (m, 1H). ^{13}C NMR (D_2O) δ (ppm): 173.3, 141.1, 131.4, 130.6, 130.4, 79.6, 60.6, 51.1, 39.3, 34.1, 28.7.

(1*S*,2*S*,4*R*)-**9**: White solid. Mp dec. $[\alpha]_D = -23.8$ (*c* 0.5, H_2O)

(1*R*,2*R*,4*S*)-**9**: White solid. Mp dec. $[\alpha]_D = +23.6$ (*c* 0.5, H_2O)

4.7. Preparation of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid hydrochloride, (1*S*,2*R*,4*R*)-11 and (1*R*,2*S*,4*S*)-11

4.7.1. Synthesis of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-*N*-benzoyl-1-carbomethoxy-7-azabicyclo[2.2.1]heptane-2-carboxylic acid, (1*S*,2*R*,4*R*)-10 and (1*R*,2*S*,4*S*)-10. $NaIO_4$ (3.8 g, 17.8 mmol) was added to a stirred solution of (1*S*,2*S*,4*R*)-**5** or (1*R*,2*R*,4*S*)-**5** (300 mg, 0.89 mmol) in 31.5 mL of a 1:1:1.5 mixture of acetonitrile/carbon tetrachloride/water. The resulting two-phase solution was treated with $RuCl_3$ (4 mg, 0.02 mmol) and stirred at this temperature for 1 d. Water was added (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (5×20 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography using *n*-hexane/ethyl acetate (1:1) and 2% of acetic acid on silica gel supplied the corresponding carboxylic acid (1*S*,2*R*,4*R*)-**10** or (1*R*,2*S*,4*S*)-**10** in 45% yield (121 mg, 0.4 mmol). The spectroscopic data for each enantiomer were the same as described in the literature for (1*S*,2*R*,4*R*)-**10**.[26]

(1*S*,2*R*,4*R*)-**10**: Mp 169 °C. $[\alpha]_D = -18.8$ (*c* 0.5, $CHCl_3$); $[\alpha]_D = -24.1$ (*c* 0.2, MeOH)[46]

(1*R*,2*S*,4*S*)-**10**: Mp 170 °C. $[\alpha]_D = +19.9$ (*c* 0.5, $CHCl_3$); $[\alpha]_D = +22.3$ (*c* 0.2, MeOH)

4.7.2. Synthesis of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid hydrochloride, (1*S*,2*R*,4*R*)-11 and (1*R*,2*S*,4*S*)-11. Aqueous 6 N HCl (15 mL) was added to the amido esters (1*S*,2*R*,4*R*)-**10** or (1*R*,2*S*,4*S*)-**10** (60 mg, 0.2 mmol) and the mixture was heated under reflux for 32 h. After the reaction was complete the solvent was evaporated under vacuum and the residue dissolved in water (30 mL). The solution was extracted with dichloromethane (3×20 mL) and the separated aqueous phase was evaporated to dryness.

Total removal of water was achieved by final lyophilisation. This procedure provided the corresponding amino acid hydrochlorides (1*S*,2*R*,4*R*)-**11** or (1*R*,2*S*,4*S*)-**11** in quantitative yield (44 mg, 0.2 mmol). The spectroscopic data for each enantiomer were the same as described in the literature for (1*S*,2*R*,4*R*)-**11**.[26]

(1*S*,2*R*,4*R*)-**11**: Mp dec. $[\alpha]_D = -28.0$ (*c* 0.20, H_2O)[47]

(1*R*,2*S*,4*S*)-**11**: Mp dec. $[\alpha]_D = +27.3$ (*c* 0.20, H_2O)

4.8. Preparation of methyl (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, (1*S*,2*R*,4*R*)-12 and (1*R*,2*S*,4*S*)-12

To a cold (−17 °C) solution of carboxylic acid (1*S*,2*R*,4*R*)-**10** or (1*R*,2*S*,4*S*)-**10** (100 mg, 0.33 mmol) in THF (2 mL), were successively added dropwise a solution of *n*-methylmorpholine (36.7 mg, 0.36 mmol) in THF (0.5 mL) and a solution of isobutylchloroformate (IBCF) (45 mg, 0.33 mmol) in THF (0.5 mL). After 10 min, a solution of $NaBH_4$ (38 mg, 0.99 mmol) in water (1 mL) was added at once and the reaction mixture is allowed to reach room temperature along 15 min. Then, water was added (10 mL) and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The resulting crude was purified by column chromatography, using as eluent ethyl acetate/dichloromethane (85:15), and the alcohols (1*S*,2*R*,4*R*)-**12** or (1*R*,2*S*,4*S*)-**12** were respectively obtained in 88% yield (84 mg, 0.29 mmol). IR (neat) ν (cm^{-1}): 3444, 1742, 1645. ^1H NMR ($CDCl_3$) δ (ppm): 7.71–7.65 (m, 2H); 7.53–7.45 (m, 1H); 7.45–7.36 (m, 2H); 4,23 (dd, 1H, $J = 5.1$ Hz, $J = 4.4$ Hz); 3,85 (s, 3H); 3.63–3.07 (m, 2H); 2,92 (dd, 1H, $J = 7.3$ Hz, $J = 6.2$ Hz); 2.43 (m, 1H); 2.29–2.17 (m, 1H); 2.00–1.88 (m, 1H); 1.88–1.68 (m, 3H); 1.59–1.46 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.4, 171.61, 134.4, 128.7, 128.3, 69.3, 63.8, 61.5, 52.5, 48.6, 33.7, 31.7, 30.5.

(1*S*,2*R*,4*R*)-**12**: Mp 91–93 °C. $[\alpha]_D = -40.7$ (*c* 1.0, $CHCl_3$)

(1*R*,2*S*,4*S*)-**12**: oil. $[\alpha]_D = +39.3$ (*c* 1.0, $CHCl_3$)

4.9. Preparation of methyl (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, (1*S*,2*R*,4*R*)-13 and (1*R*,2*S*,4*S*)-13

A solution of the alcohol (1*S*, 2*R*,4*R*)-**12** or (1*R*,2*S*,4*S*)-**12** (300 mg, 1.04 mmol) in dry dichloromethane (6 mL) was added dropwise to a stirred solution of the Dess–Martin periodinane, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, (399 mg, 0.94 mmol) in dry dichloromethane. After 20 min the homogeneous solution was diluted with 100 mL of dichloromethane and washed with a saturated aqueous solution of $NaHCO_3$ containing $Na_2S_2O_3$ (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. Removal of the solvent under vacuum followed by column chromatography, using as eluent ethyl acetate/*n*-hexane (6:4), gave pure aldehyde (1*S*,2*R*,4*R*)-**13** or (1*R*,2*S*,4*S*)-**13**, respectively, in 80% yield (238 mg, 0.83 mmol). The spectroscopic data for each enantiomer were identical to those described in the literature for (1*S*,2*R*,4*R*)-**13**.[26]

(1*S*,2*R*,4*R*)-**13**: Mp 108 °C. $[\alpha]_D = -7.1$ (*c* 1.0, $CHCl_3$) [lit.[27] mp 110 °C. $[\alpha]_D = -7.6$ (*c* 1, $CHCl_3$)]

(1*R*,2*S*,4*S*)-**13**: Mp 108 °C. $[\alpha]_D = +7.1$ (*c* 1.0, $CHCl_3$)

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References and notes

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46. NOTE: New polarimetry measurements on two different samples of (1*S*,2*R*,4*R*)-**10**, prepared following the procedure described in Ref. 26, led to the following values: $[\alpha]_D = -18.8$ (*c* 0.5, $CHCl_3$); $[\alpha]_D = -24.2$ (*c* 0.2, MeOH). Polarimetry data on these new samples are completely different from the one that we previously described in 26 and perfectly agree with the values obtained for samples of (1*S*,2*R*,4*R*)-**10** prepared according to the resolution procedure described in this report [$[\alpha]_D = -18.8$ (*c* 0.5, $CHCl_3$); $[\alpha]_D = -24.1$ (*c* 0.2, MeOH)].
47. NOTE: New polarimetry measurements on two different samples of (1*S*,2*R*,4*R*)-**11**, prepared according to the asymmetric procedure described in Ref. 26, led to the following value: $[\alpha]_D = -27.4$ (*c* 0.2, H_2O). Polarimetry data for these new samples are different from the one that we previously described in 26 and agree with the value obtained for the samples of (1*S*,2*R*,4*R*)-**11** prepared according to the resolution procedure described in this report [$[\alpha]_D = -28.0$ (*c* 0.2, H_2O)].
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