Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: *Asymmetry* 18 (2007) 635–644
Tetrahedron: *Asymmetry*

Quinine-mediated parallel kinetic resolution of racemic cyclic anhydride: stereoselective synthesis, relative and absolute configuration of novel alicyclic β-amino acids

Zdenko Hameršak,[a,*] Marin Roje,[a] Amir Avdagić[b,†] and Vitomir Šunjić[b]

[a]*Department of Organic Chemistry and Biochemistry, Rudjer Bošković Institute, PO Box 180, 10002 Zagreb, Croatia*
[b]*GSK Research Centre Zagreb, Prilaz baruna Filipovića 29, 10000 Zagreb, Croatia*

Received 23 January 2007; accepted 19 February 2007

Abstract—Four *endo*-isomers of (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid (+)-**1** (Icofungipen) have been prepared in enantiomerically pure form. Three *endo*-isomers were obtained by quinine-mediated kinetic resolution of a racemic anhydride, followed by Curtius rearrangement. The fourth isomer was obtained by an *exo–endo* isomerization of (+)-**1**. The assignment of the absolute configuration is based either on the Cotton effect in the CD spectra or in correlation to already known structures.

1. Introduction

β-Amino acids are certainly of less importance than their α-analogues, but they do exhibit interesting biological activity and are present in peptides and different heterocycles.[1] While less explored alicyclic β-amino acids have been found to be useful chiral auxiliaries and building blocks, some exhibit pharmacological activity.[2] (1*R*,2*S*)-2-Aminocyclopentanecarboxylic acid (cispentacin)[3] and (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid (+)-**1** (Icofungipen)[4] are antifungals; cispentacin is also a component of the antibiotic amipurimicyn.[2] The efficient asymmetric synthesis of (+)-**1** and cispentacine was developed based on quinine-mediated enantioselective alcoholysis (desymmetrization) of *meso*-anhydrides.[5,6] Chan and Deng[7] recently accomplished the successful parallel kinetic resolution (PKR) of racemic succinic anhydrides using a modified cinchona alkaloid. This finding prompted our attempts to prepare enantiomerically pure structural isomers of **1** with an endocyclic double bond (**2**–**5**) (Fig. 1).

Conceptually, all the enantiomerically pure structural isomers can be made via the parallel kinetic resolution of *rac*-**7** by intervention of the same chiral auxiliary, quinine.

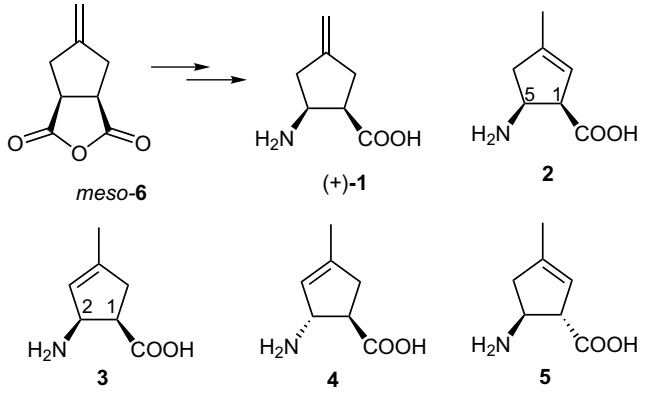


Figure 1.

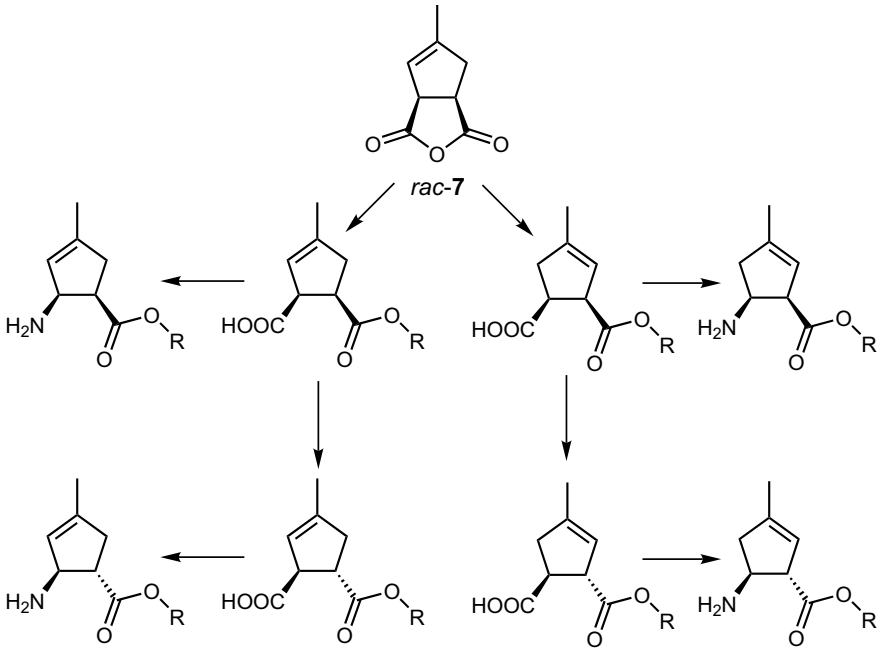
Our first objective was to attain high enantioselectivity with low regio-selectivity in the solvolysis of *rac*-**7**, producing two structurally isomeric, enantiomerically enriched *cis*-products. Their epimerization at the α-C atom to a carboxyalkyl group is expected to afford the subsequent structural isomers, which are the more stable *trans*-products (Scheme 1).

2. Results and discussion

Since the tendency of the exocyclic double bond in the five- and six-membered rings is to migrate into the ring,[8] we

* Corresponding author. Tel.: +3851 4571 300; fax: +3851 4680 108; e-mail: hamer@irb.hr
† Present address: PLIVA R&D Institute, Prilaz baruna Filipovića 29, 10000 Zagreb, Croatia.

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.02.019



Scheme 1.

began the synthesis by preparing *rac*-**7** from *meso*-**6**, available from *rac*-**8**, an intermediate in the preparation of (+)-**1**. In refluxing toluene, catalyzed by *p*-TsOH, *meso*-**6** was isomerized in 87% yield into *rac*-**7** (Scheme 2). The kinetic resolution of *rac*-**7** was completed by alcoholysis with *trans*-cinnamyl alcohol in the presence of quinine at −15 °C. This approach resulted with a 30:70 mixture of monoesters **9** and **10** (determined by NMR or by HPLC on Chiralpak AD). This mixture appeared to be inseparable by either crystallization (oily) or chromatography. The preparative HPLC separation of the **9/10** mixture on a Chiralpak AD column followed by analysis on Chiralpak AS showed 97% ee for **9**; using a Chiralcel OD, 42% ee for **10** was determined.

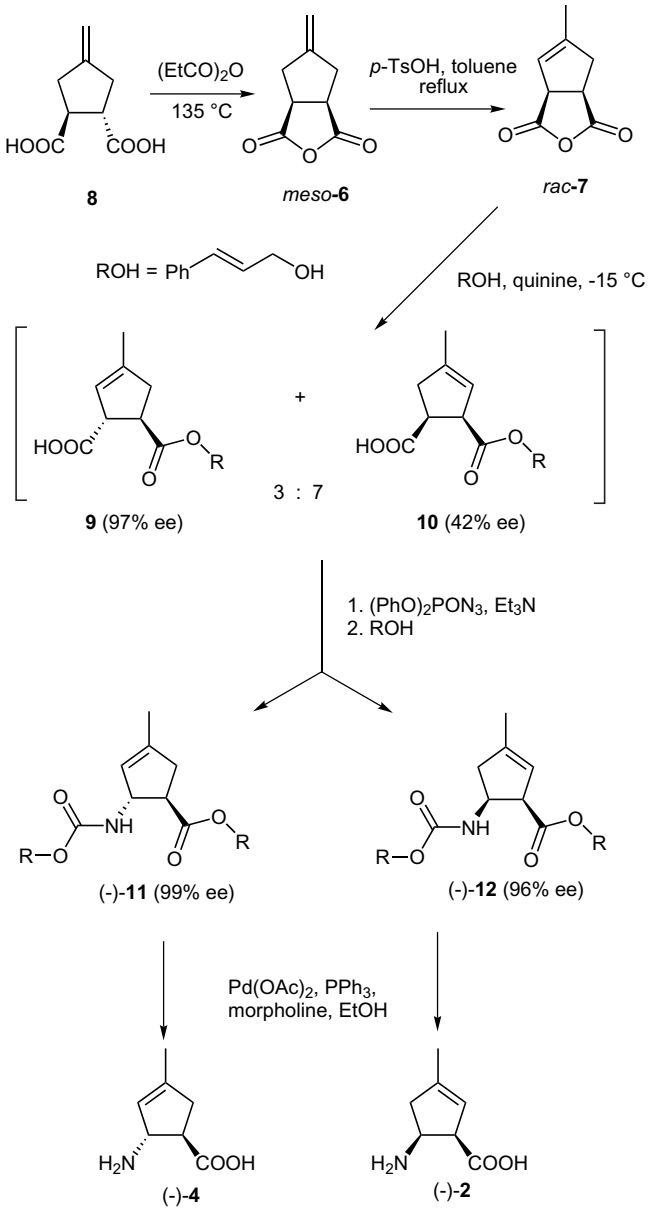
To confirm the *cis*-configuration of **9** and **10**, the mixture of monoesters was converted to dicarboxylic acids **13** and **14** (Scheme 3). However, NMR spectra revealed the existence of two diastereomers in the same 3:7 ratio, suggesting that one dicarboxylic acid had a *trans*-configuration. In order to define the carboxylic acid with a *trans*-configuration pure *cis*-dicarboxylic acid **14** was prepared via hydrolysis of *rac*-**7**, while *trans*-dicarboxylic acid **13** was obtained by isomerization of *trans*-acid **8**. ^{1}H NMR coupling constants between the C(1) and C(2) protons were found to be 9 Hz for the *cis*-derivative and 7 Hz for the *trans*-derivative. Comparison of NMR data revealed that monoester **9** had *trans*-configuration.

Next, the influence of the base catalyst and reaction conditions on the unusual epimerization on the pathway to *trans*-**9** from *rac*-**7** was examined (Table 1). We found both to have only minor effects on the **9/10** ratio (entries 3–5). Even when the reaction was performed without base (entry 6) the same, ca. 30:70 ratio, was obtained. At a lower temperature (entry 2), conversion was not complete after 8 h, but the enantiopuritiy of *cis*-monoester **10** was higher (75% ee).

However, the enantiopurity of *trans*-monoester **9** remained consistently high. Bolm studied the quinine-mediated opening of *meso*-anhydrides with various alcohols and found that in all cases, the monoesters with an (*R*)-configuration on the C-atom bearing an ester group were preferably formed in high ee's.[5] The formation of *trans*-monoester **9** can be explained by the mechanism shown in Scheme 4. The preferred opening of the (1*R*,2*S*)-enantiomer of **7** leads to (1*R*,2*S*)-**10** as the major enantiomer, with an (*R*)-configuration on the C-atom bearing the cinnamoyl ester group, while the less reactive (1*S*,2*R*) enantiomer of **7** produced the minor enantiomer (1*S*,2*R*)-**10**.

To explain the formation of *trans*-**9**, a keto–enol equilibrium at one stereogenic centre could be considered. Although Rappoport[9] has shown theoretically and experimentally that enols of carboxylic acid anhydrides are unlikely, and we also have not detected the enol form of **7** using NMR, we propose the formation of *trans*-**9** via an undetectable quantity of the enol form **7a** in the equilibrium with the dicarbonyl form. The enol form **7a** is stabilized by conjugation and is opened towards (1*R*,2*R*)-**9**, in accordance with Bolm[5] and others findings,[10] with simultaneous epimerization at the second chiral centre.

In the next step, the **9/10** monoester mixture was converted into the protected β-amino acid esters by Curtius rearrangement using diphenyl phosphoryl azide and triethylamine. This was followed by reaction of the intermediate isocyanate with cinnamyl alcohol in refluxing toluene (Scheme 2). Crystallization of the crude product from EtOH/hexane (1:1) afforded an **11/12** mixture (3:7) in 70% yield. Pure (−)-**12** (96% ee) was obtained upon two



Scheme 2.

recrystallizations from abs EtOH in 21% yield, while two recrystallizations of the mother liquor material, enriched in **11** from EtOH/hexane (1:14), afforded 97% pure (−)-**11** (99% ee) in 10% yield.

In the last step, protective groups in (−)-**11** and (−)-**12** were removed by the transallylation of morpholine as a nucleophile in refluxing ethanol. The reaction was catalyzed with palladium acetate–triphenyl phosphine. The precipitated products were crystallized from aqueous ethanol yielding β-amino acids (−)-**2** and (−)-**4** in 65% and 70% yield, respectively.

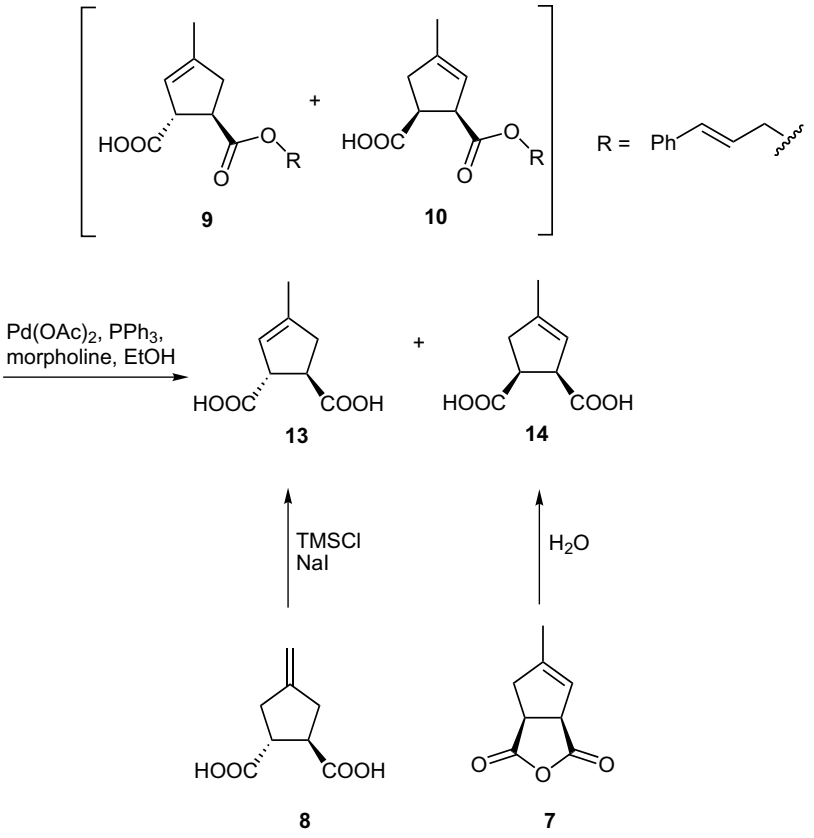
trans-β-Amino acid (+)-**5** was prepared by starting from amino protected ester (−)-**12** (Scheme 5). Base-catalyzed hydrolysis of the ester group with potassium hydroxide in aqueous methanol was accompanied with almost complete epimerization at C(1). A small amount (less than 5%) of non-epimerized product was removed by chromatography on silica gel, producing pure (+)-**15** in 75% yield. Deprotection was performed as described for **11**/**12** to obtain pure (+)-**5** in 62% yield.

For the determination of the absolute configuration, enantiomerically pure *cis* isomers (+)-**3** and (−)-**2** were also prepared according to the published procedure (Scheme 6).[11] The exocyclic double bond of (+)-**1** (99.5% ee) was shifted to the *endo* position in the presence of TMSCl/NaI in acetonitrile, and two structural isomers were converted, without separation, to fmoc-derivatives (+)-**16** and (−)-**17**; according to HPLC a 65:35 mixture was obtained. Crystallization from EtOAc/hexane (1:2) afforded (+)-**16** in 35% yield, while (−)-**17** was obtained as a dicyclohexylamine salt from the mother liquor in 5% yield. Amino acids (−)-**2** and (+)-**3** were isolated upon deprotection by morpholine in 86% and 78% yield, respectively.

For all four enantiomers of *endo*-β-amino acids **2**–**5**, the specific rotation sign was determined; the sign was negative for **2** and **4** and positive for **3** and **5**. The absolute configuration of (−)-**2** and (+)-**3** was (1*R*,5*S*) and (1*R*,2*S*), respectively; both are chemically correlated to (+)-**1** (Scheme 6), whose (1*R*,2*S*)-absolute configuration was straightforward to determine.[5] In order to obtain information about the absolute configurations of the two remaining *endo*-compounds, CD spectra of all isomers were recorded (Fig. 2).

The CD spectra of (−)-**2** and (+)-**5** exhibit the most intensive and nearly enantiomorphic curves in the region of the electronic transitions of the C=C and C=O double bonds with a small (5–7 nm) shift of the two maxima in the spectrum of (−)-**2** to the longer wavelengths. Interestingly, the CD of (+)-**1** is less intense than that of any other *endo*-isomer by an order of magnitude, indicating a nearly parallel position of the transition moments in the two chromophores, C=C and C=O. It was repeatedly shown that the absolute configuration of chiral compounds with a C=C bond at the allylic position[12] could be determined from the CD, based on exciton coupling with the second chromophore distant from the olefin chromophore. Although compounds (−)-**2** and (+)-**5** comprised such homoconjugated, twisted chromophores, and exhibit strong CDs of the opposite sign, we hesitated to use them in an attempt to assign absolute configuration. In order to reliably assign the absolute configuration of (−)-**4** and (+)-**5**, using (−)-**2** as the control, the CD spectra were run of their respective bis-cinnamoyl derivatives (−)-**11** and (−)-**12** (Figs. 3 and 4).

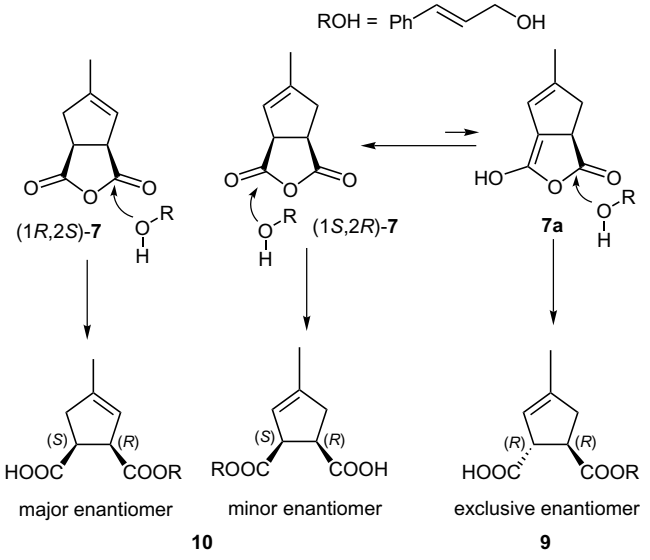
These compounds consist of two independent, degenerate cinnamate chromophores as well as double-bond chromophore.[13] Their CD spectra are therefore dominated by two Cotton effects at longer wavelengths, ca. 253–260 nm, due to the ^1L_a transitions of two chromophores. The second Cotton effect is due to the coupling of ^1B_b transitions at the shorter wavelength, ca. 193–199 nm. Since the olefinic chromophore is also asymmetrically perturbed by substituents and/or the skeletal strain of the double bond, overlap of additional Cotton effects complicates the CD



Scheme 3.

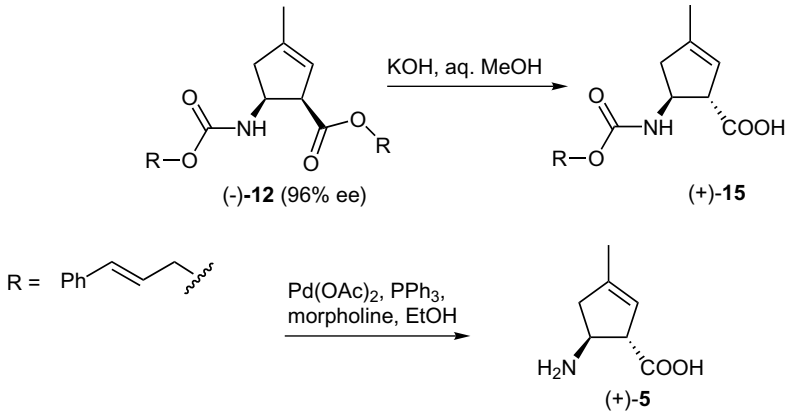
Table 1. Influence of base and conditions on the opening of anhydride **7**

Entry	Base (equimolar)	Conditions	*cis*/*trans* Ratio (% ee)	Yield (%)
1	Quinine	Toluene, −15 °C, 8 h	67(42):33(97)	98
2	Quinine	Toluene/CCl_4 (1:1), −50 °C, 8 h	77(75):23(98)	60
3	Quinine	Toluene, rt, 3 h	66(40):34(96)	96
4	Triethylamine	Toluene, rt, 2 h	79(*rac*):21(*rac*)	98
5	Pyridine	Toluene, rt, 6 h	75(*rac*):25(*rac*)	90
6	Without base	Toluene, 80 °C, overnight	72(*rac*):28(*rac*)	70

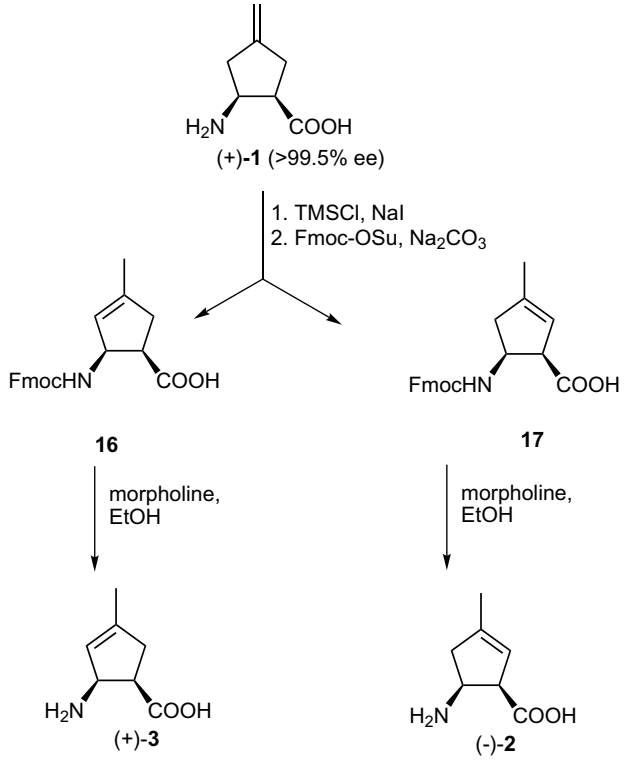


Scheme 4.

curve of the double bond chromophore. The cinnamate conformation is corroborated by MM2 calculations for (−)-**11** (dihedral angle −169°) and (−)-**12** (dihedral angle +28°). These calculations indicated the most stable conformations and consequently indicated the positions of the electric transition moments, which greatly simplified the application of exciton coupling (EC). The weak EC of the two cinnamate chromophores in the CD spectra of (−)-**11** and (−)-**12** is expected because of the small value of the dihedral angle between them. For *trans*-relative configuration in (−)-**11**, the exciton chirality is not affected by conformational change as much as it is by *cis*-oriented chromophoric units in (−)-**12**. As shown in Figure 3, the 253 nm negative Cotton effect in the CD spectra of (−)-**11** reflects a negative chirality between two cinnamate chromophores on C(1) and C(2) revealing (1*R*,2*R*)-absolute configuration. In the case of compound (−)-**12**, the 259 nm positive cinnamate Cotton effect reflects a positive chirality between two cinnamate chromophores on C(1) and C(5)[13] and also shows (1*R*,5*S*) absolute configuration.



Scheme 5.



Scheme 6.

Since no bond breaking occurs from (−)-**11** and (−)-**12** to (−)-**4** and (−)-**2**, respectively, the targeted β-amino acids possess the same absolute configuration as determined by CD for their precursors. Finally, the absolute configuration (1*S*,5*S*) of (+)-**5** is defined by its chemical correlation to (1*R*,5*S*)-(−)-**12**, in which the configuration at C(1) is inverted, going from a *cis*- to *trans*-isomer (Scheme 5).

3. Conclusion

In conclusion, we have synthesized and determined the absolute configuration of four enantiomerically pure *endo*-isomers of Icofungipen, a cyclic β-amino acid with a broad-of spectrum antifungal activity. The key step of the synthesis was the quinine-mediated parallel kinetic resolution of anhydride *rac*-**7** during which an interesting *cis–trans* isomerization was observed, allowing access to new β-amino acid building blocks with defined chirality.

4. Experimental

4.1. General

Mps were determined on an Electrothermal 9100 apparatus in open capillaries and are not corrected. Optical rotations were measured using the Optical Activity AA-10 automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 300 and AV 600 spectrometers, IR spectra on a Bruker ABB Bomen instrument, and CD spectra on a JASCO-810 spectropolarimeter at 25 °C. For chemical purity determination and monitoring of the progress of the reactions, HP 5890 GC and HP 1090 HPLC chromatographs were used. Compounds (+)-**1**, **6** and **8** were obtained from PLIVA d.d., while all other reagents and solvents were purchased from commercial sources and were used without purification.

4.2. 5-Methyl-4,6a-dihydro-3a*H*-cyclopenta[*c*]furan-1,3-dione 7

p-TsOH·H_2O (1.0 g) was suspended in toluene (300 mL). After H_2O had been azeotropically removed, anhydride **6** (20.0 g, 131.5 mmol) was added and refluxed for 4 h. The cooled solution was filtered, evaporated and distilled on Kugelrohr apparatus (125 °C/0.5 mm Hg). Yield: 17.5 g (87%), GC purity 99% (HP-17 column). Mp 49.5–51.5 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.81$ (s, 3H), 2.75 (d, $J = 17.4$ Hz, 1H), 2.89 (dd, $J = 17.5$ Hz, 10.2 Hz, 1H), 3.74 (dd, $J = 10.0$ Hz, 8.3 Hz, 1H), 4.08 (d, $J = 7.7$ Hz, 1H), 5.36 (s, 1H). ^{13}C NMR ($CDCl_3$): 15.48, 39.89, 43.87, 53.12, 118.56, 144.63, 171.52, 174.71.

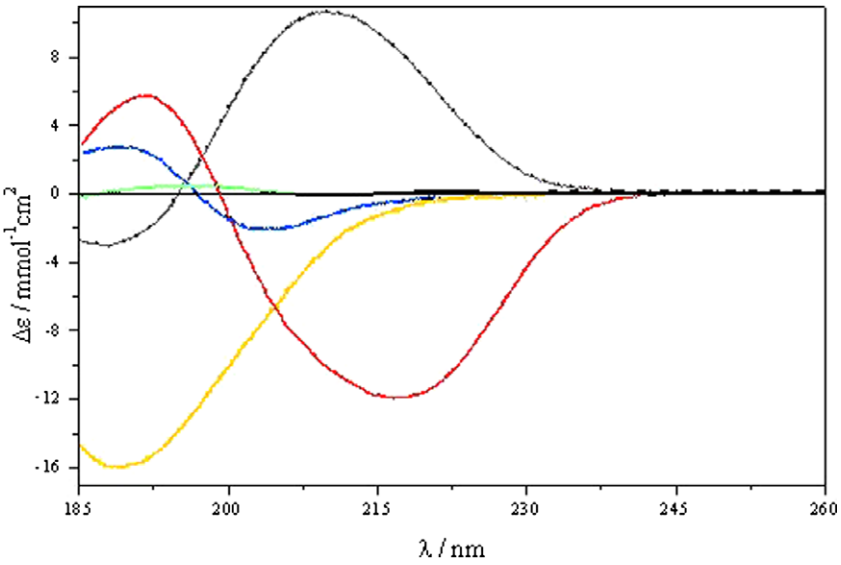


Figure 2. CD spectra of (+)-**1** (——), (−)-**2** (——), (+)-**3** (——), (−)-**4** (——) and (+)-**5** (——) in H_2O.

4.3. (1*R*,2*R*)-4-Methyl-2-(3-phenyl-allyloxycarbonylamino)-cyclopent-3-enecarboxylic acid 9 and (1*S*,5*R*)-3-methyl-5-(3-phenyl-allyloxycarbonylamino)-cyclopent-2-enecarboxylic acid 10

Quinine (36.0 g, 110 mmol) was suspended in toluene (400 mL) followed by anhydride **8** (17.0 g, 111 mmol) and *trans*-cinnamyl alcohol (22.4 g, 168 mmol). The reaction mixture was stirred at −15 °C for 8 h. The toluene solution was then washed with 1 M HCl (2 × 150 mL), H_2O, and extracted with 2% K_2CO_3 (1 × 400, 2 × 200 mL). The aqueous extracts were washed with EtOAc, and acidified to pH 2 with dil HCl. The product was extracted with CH_2Cl_2 to afford 31.5 g (98%, yellowish oil) of a 3:7 **9/10** mixture, which was used in the next step without further purification.

For chiral HPLC analysis, the **9/10** mixture was purified on a short silica gel column and separated on Chiralpak AD (18% EtOH, 0.4% AcOH, hexane to 100%, 254 nm). The same mobile phase was used for the analysis of collected **9** on Chiralpak AS and **10** on Chiralcel OD to reveal 97% ee for **9** and 42% ee for **10**.

4.4. (−)-(1*R*,2*R*)-4-Methyl-2-(3-phenyl-allyloxycarbonyl-amino)-cyclopent-3-enecarboxylic acid 3-phenyl-allyl ester 11 and (−)-(1*R*,5*S*)-3-methyl-5-(3-phenyl-allyloxycarbonylamino)-cyclopent-2-enecarboxylic acid 3-phenyl-allyl ester 12

A solution of a **9/10** mixture (31.3 g, 109 mmol), triethylamine (15.0 mL, 109 mmol), and diphenyl phosphoryl azide (23.0 mL, 109 mmol) in dry toluene (230 mL) was stirred for 2 h at rt and then for 1 h at 90 °C. The solution of *trans*-cinnamyl alcohol (16.5 g, 125 mmol) in toluene (20 mL) was added and the reaction mixture was then heated at reflux overnight. To the cooled solution EtOAc (300 mL) was added and washed with satd $NaHCO_3$. The solvent was evaporated and the crude product mixture was dissolved by heating in 500 mL of EtOH/hexane (1:1) together with about 1 g of active charcoal. After 30 min of heating, the warm solution was filtered and left to crystallize at 4 °C for 24 h. The precipitate was collected on a filter to afford 30.5 g (70%) of **11/12** (30:70, Nucleosil 100-5 RP18, 50–100% MeOH in 20 min at 254 nm). After two recrystallizations from abs EtOH 9.0 g (21%) of **12**, which was 98% pure by HPLC (96% ee; Chiralpak AD, 22% EtOH, 0.4% AcOH, hexane to 100%), was obtained. The mother liquor after the first crystallization was evaporated (16.8 g of **11/12** 60:40 mixture) and crystallized twice from EtOH/hexane (1:14) to yield 4.2 g (10%) of **11** (97% pure, 99% ee). By recycling the mother liquors and crystallization from a solvent mixture depending on the ratio of isomers, practically all of the material could be separated, although with much lower ee of **12**.

Compound **11**: mp 115.0–116.5 °C; $[\alpha]_D^{25} = -101$ (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 1.74$ (s, 3H), 2.50–2.70 (m, 2H), 2.90–3.05 (m, 1H), 4.60–5.10 (m, 5H), 5.24 (s, 1H), 6.20–6.30 (m, 2H), 6.55–6.70 (m, 2H), 7.20–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$): $\delta = 16.21$, 19.20, 51.37, 61.22, 65.24, 123.13, 123.75, 126.43, 126.48, 127.77, 12783, 128.41, 133.44, 133.86, 136.19, 142.51, 155.26, 174.03. IR (KBr): 3306, 3025, 2936, 1721, 1687, 1538, 1246, 1169, 967, 742, 691 cm^{-1}. Anal. Calcd. for $C_{26}H_{27}NO_4$ (417.50): C, 74.80; H, 6.52; N, 3.35. Found: C, 74.37; H, 6.77; N, 3.68.

Compound **12**: mp 135.5–137.0 °C; $[\alpha]_D^{25} = -129$ (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 1.76$ (s, 3H), 2.35–2.45 (m, 1H), 2.50–2.60 (m, 1H), 3.68 (d, $J = 5.5$ Hz, 1H), 4.55–4.75 (m, 5H), 5.34 (s, 1H), 5.61 (d, $J = 10$ Hz, 1H), 6.15–6.35 (m, 2H), 6.55–6.65 (m, 2H), 7.20–7.40 (m, 10H).

^{13}C NMR ($CDCl_3$): $\delta = 16.78$, 42.66, 52.69, 53.30, 65.04, 65.23, 121.31, 122.78, 123.76, 126.41, 126.47, 127.73, 127.90, 128.39, 128.40, 133,31, 134.12, 136.01, 136.19, 143.53, 158,67, 172.51. IR (KBr): 3347, 3031, 2928, 2851, 1725, 1687, 1527, 1260, 1171, 1030, 951, 745, 683 cm^{-1}. Anal. Calcd for $C_{26}H_{27}NO_4$ (417.50): C, 74.80; H, 6.52; N, 3.35. Found: C, 74.49; H, 6.34; N, 3.20.

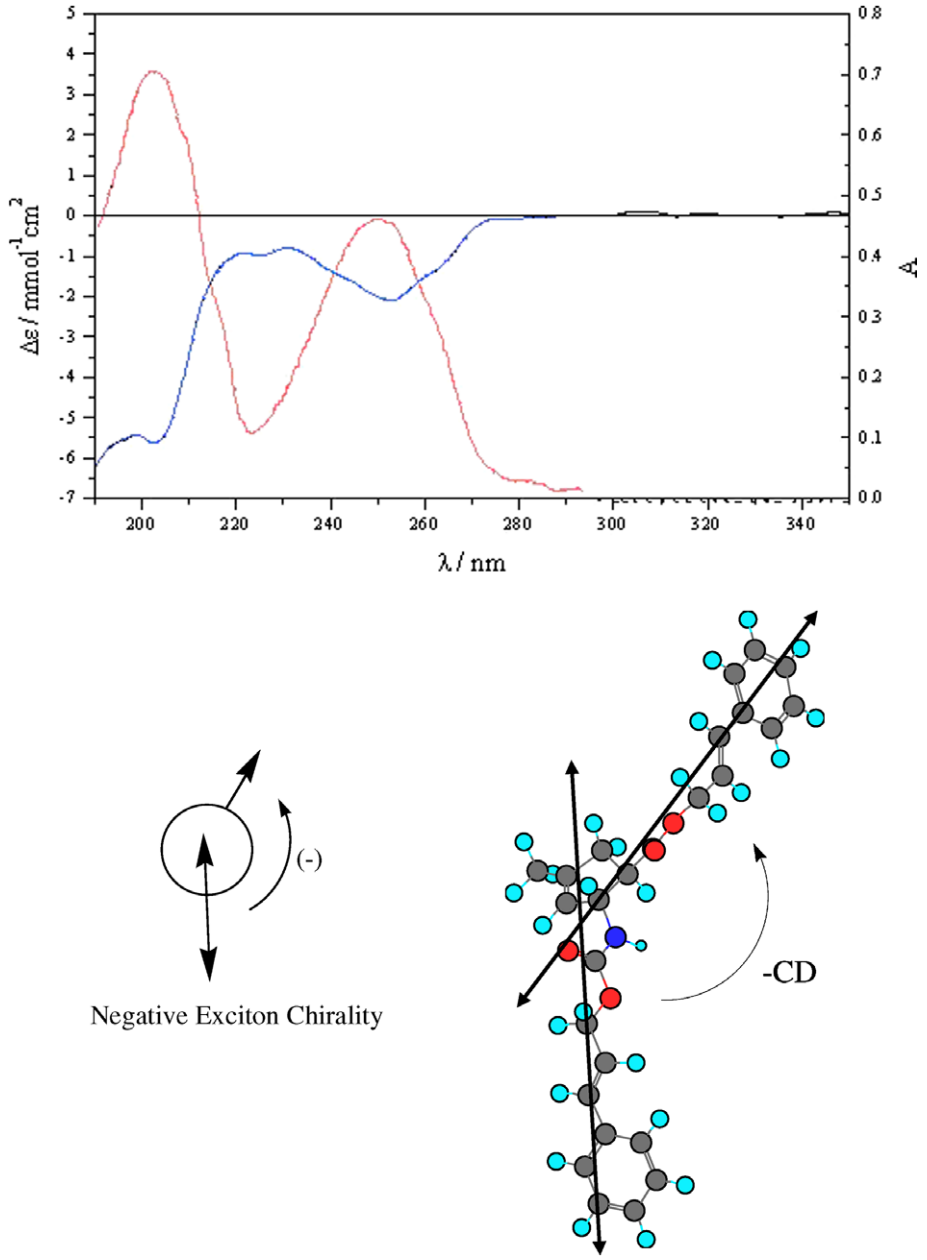


Figure 3. CD (——) and UV (——) spectra of (−)-**11** in MeCN.

4.5. (+)-(1*S*,5*S*)-3-Methyl-5-(3-phenyl-allyloxycarbonyl-amino)-cyclopent-2-enecarboxylic acid 15

To a suspension of **12** (96% ee) (1.5 g, 3.6 mmol) in MeOH (30 mL) and H_2O (20 mL), KOH (1.0 g) was added and stirred at 50 °C for 2 h. H_2O (30 mL) was added, the solution washed with EtOAc, acidified with dil HCl to pH 2 and extracted with EtOAc. The crude product was purified on silica gel using diisopropyl ether/toluene/AcOH (60:30:0.3). Yield: 0.81 g (75%); mp 125–127 °C; $[\alpha]_D^{25} = +46$ (*c* 1, CH_2Cl_2). ^1H NMR ($CDCl_3$): $\delta = 1.74$ (s, 3H), 2.17 (d, $J = 16$ Hz, 1H), 2.86 (dd, $J = 16$ Hz, 7 Hz, 1H), 3.49 (s, 1H), 4.52 (s, 1H), 4.72 (s, 2H), 5,18 (d, $J = 6$ Hz, 1H), 5.34 (s, 1H), 6.24–6.30 (m, 1H), 6.63 (d, $J = 16$ Hz, 1H), 7.24–7.40 (m, 5H), 10.4 (br s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 16.50$, 43.79, 54.54, 58.68, 65.88, 120.78, 123.44, 126.64, 128.04, 128.59, 134.09, 136.25, 141.58, 156.41, 177.17. IR (KBr): 3323, 3063, 2918, 1686, 1541, 1275, 1229, 972, 694 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65. Found: C, 67.38; H, 6.11; N, 4.98.

4.6. (−)-(1*R*,5*S*)-5-Amino-3-methyl-cyclopent-2-enecarboxylic acid 2

To a suspension of **12** (5.0 g; 12 mmol), Ph_3P (32 mg; 0.12 mmol) and morpholine (2.6 mL; 30 mmol) in 25 mL of abs EtOH, $Pd(OAc)_2$ (~2 mg) was added. The reaction

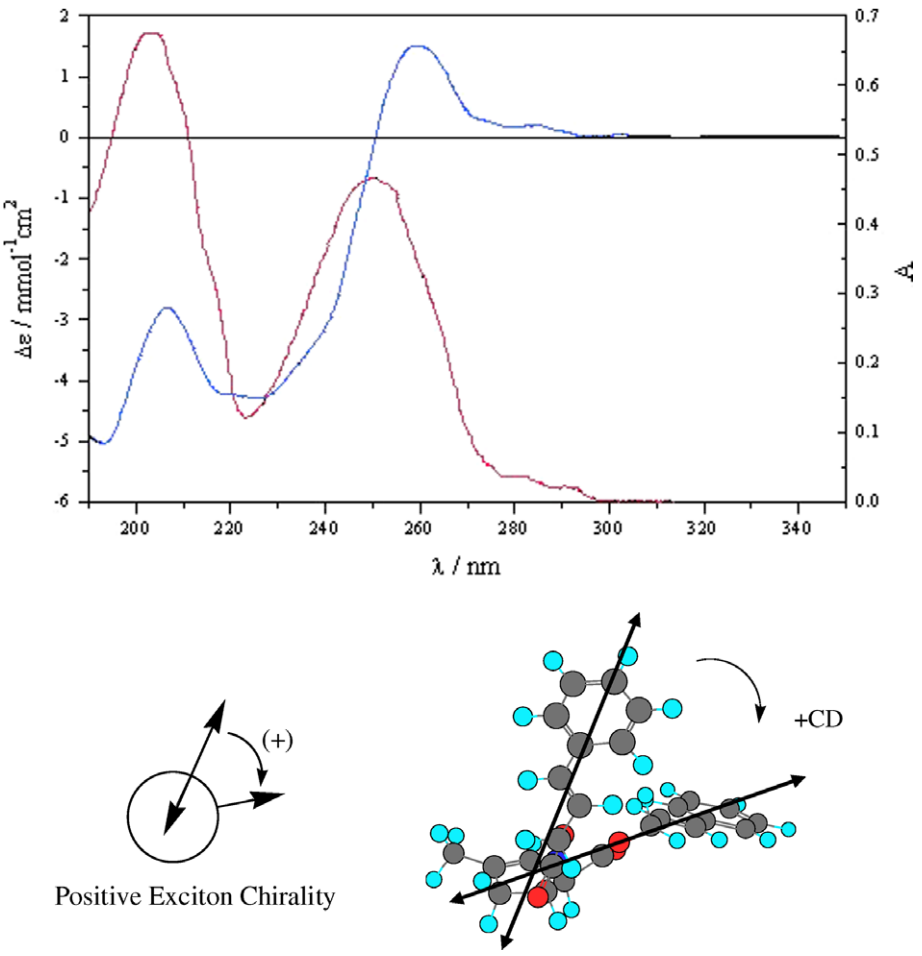


Figure 4. CD (——) and UV (——) spectra of (−)-**12** in MeCN.

mixture was refluxed for 2 h, cooled and left to crystallizing for 2 h at rt. The precipitate was filtered out, washed with EtOH on a filter and recrystallized from 90% EtOH to yield 1.11 g (65%) of 97% pure **2** (Nucleosil 100-5 RP18, 10% aqueous MeOH, 1% H_3PO_4 at 206 nm for 10 min; then gradient to 100% MeOH in 15 min at 254 nm); mp 190 °C (lit.[14] 190 °C); $[\alpha]_D^{25} = -115$ (*c* 1, H_2O). ^{1}H NMR (D_2O): $\delta = 1.68$ (d, $J = 1$ Hz, 3H), 2.61 (dd, $J = 16$ Hz, 4 Hz, 1H), 2.61 (dd, $J = 16.5$ Hz, 7.5 Hz, 1H), 3.51–3.58 (m, 1H), 3.88–3.96 (m, 1H), 5.37 (d, $J = 1.5$ Hz, 1H). ^{13}C NMR (D_2O): $\delta = 16.50$, 40.09, 52.37, 52.45, 123.66, 141.12, 179.69. IR (KBr): 3438, 3052, 2946, 2183, 1654, 1552, 1506, 1393, 1176, 834 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: 59.20; H, 7.67; N, 9.63.

4.7. (−)-(1*R*,2*R*)-2-Amino-4-methyl-cyclopent-3-enecarboxylic acid 4

The reaction was performed as described for **3**. Starting from 6.0 g of **11**, 1.45 g (70%) of 98% pure **4** was obtained. Mp 220 °C; $[\alpha]_D^{25} = -180$ (*c* 0.6, H_2O). ^{1}H NMR (D_2O): $\delta = 1.70$ (s, 3H), 2.37 (dd, $J = 16.5$ Hz, 4.0 Hz, 1H), 2.65–2.90 (m, 2H), 4.39 (s, 1H), 5.27 (s, 1H). ^{13}C NMR (D_2O): $\delta = 15.66$, 40.67, 50.46, 61.10, 119.36, 149.21, 181.23. IR (KBr): 3437, 3049, 2922, 2088, 1656, 1561, 1387, 1272, 780 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: 59.23; H, 7.87; N, 9.73.

4.8. (+)-(1*S*,5*S*)-5-Amino-3-methyl-cyclopent-2-enecarboxylic acid 5

The reaction was performed as described for **3**. Starting from 750 mg of **13** of 160 mg (62%) of **5** was obtained. Mp 224 °C, $[\alpha]_D^{25} = +216$ (*c* 0.8, H_2O). ^{1}H NMR (D_2O): $\delta = 1.74$ (s, 3H), 2.28 (d, $J = 16.5$ Hz, 1H), 2.88 (dd, $J = 16.5$ Hz, 7 Hz, 1H), 3.39 (s, 1H), 4.06–4.09 (m, 1H), 5.37 (s, 1H). ^{13}C NMR (D_2O): $\delta = 16.13$, 41.83, 54.54, 59.87, 122.90, 140.76, 180.46. IR (KBr): 3421, 2964, 2932, 1634, 1574, 1606, 1393, 1213, 743 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.39; H, 7.56; N, 10.11.

4.9. (±)-*trans*-4-Methyl-cyclopent-3-ene-1,2-dicarboxylic acid 13

A mixture of NaI (1.0 g 6.5 mmol) and TMSCl (4.5 mL, 9.3 mmol) in acetonitrile (50 mL) was stirred at rt for 30 min. *trans*-Dicarboxylic acid **8** (1.0 g, 5.8 mmol) was

added and stirred for 5 h at 75 °C. Upon cooling to rt, 20 mL of H_2O was added, and most of the solvent evaporated. EtOAc extraction afforded an oily product, which was recrystallized from EtOH/hexane to obtain 450 mg (45%) of pure **13**. Mp 133–135 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.75$ (s, 3H), 2.62 (dd, $J = 16.5$ Hz, 7 Hz, 1H), 2.72 (dd, $J = 16.5$ Hz, 8 Hz, 1H), 3.60 (dt, $J = 9$ Hz, 7 Hz, 1H), 4.00 (dq, $J = 7$ Hz, 1.5 Hz, 1H), 5.36 (s, 1H), 11.8 (br s, 2H). ^{13}C NMR ($CDCl_3$): 16.19, 39.89, 44.79, 53.56, 120.73, 141.99, 179.71, 180.80. IR (KBr): 3020, 2921, 1708, 1444, 1427, 1291, 1271, 1226, 942 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$ (170.16): C, 56.47; H, 5.92; Found: C, 56.78; H, 5.70.

4.10. (±)-*cis*-4-Methyl-cyclopent-3-ene-1,2-dicarboxylic acid 14

Anhydride **7** (300 mg, 2 mmol) was suspended in H_2O (20 mL) and stirred at 60 °C for 1 h. The clear solution was extracted with EtOAc to give 330 mg (97%) of pure product. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.79$ (s, 3H), 2.48 (dd, $J = 16$ Hz, 9 Hz, 1H), 2.93 (dd, $J = 16$ Hz, 9 Hz, 1H), 3.46 (psq, $J = 9$ Hz, 1H), 3.79 (d, $J = 9$ Hz, 1H), 5.35 (s, 1H), 11.6 (br s, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 16.68$, 37.98, 46.59, 53.12, 120.72, 145.07, 180.34, 180.56. IR (KBr): 3068, 2943, 2916, 1703, 1414, 1320, 1230, 813 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$ (170.16): C, 56.47; H, 5.92; Found: C, 56.29; H, 5.66.

4.11. (+)-(1*R*,2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonyl-amino)-4-methyl-cyclopent-3-enecarboxylic acid 16

A mixture of NaI (4.0 g 26 mmol) and TMSCl (4.5 mL, 35 mmol) in acetonitrile (200 mL) was stirred at rt for 30 min, (+)-**1** (4.0 g, 28 mmol) was added and stirred overnight at 75 °C. Upon cooling to rt, 2 mL of H_2O was added and most of the solvent was evaporated in vacuum. The residue was dissolved in H_2O (100 mL) and washed with CH_2Cl_2 (5 × 50 mL). To the aqueous solution, Na_2CO_3 (15 g) was added, followed by the portionwise addition of a dioxane solution of 9-fluorenylmethyl-succinimidylcarbonate (9.5 g, 28 mmol) at 0 °C. The reaction mixture was stirred at rt for 6 h, after which H_2O (100 mL) was added and the aqueous solution was washed with diisopropyl ether (3 × 50 mL). The aqueous solution was acidified to pH 2 with dil HCl and extracted with diisopropyl ether. The crude product contained a 65/35 ratio of **16**/**17** (determined by HPLC; Nucleosil 100-5, 3% EtOH in CH_2Cl_2), and was recrystallized 3 times from EtOAc/hexane (1:2) to afford 3.44 g (35%) of **16**, 96% HPLC purity. Mp 144–146 °C; $[\alpha]_D^{25} = +78$ (*c* 1, CH_2Cl_2). ^{1}H NMR (DMSO-d_6): $\delta = 1.73$ (s, 3H), 2.17–2.26 (m, 1H), 2.70–2.79 (m, 1H), 3.22–3.36 (m, 2H), 4.10–4.25 (m, 2H), 4.80–4.95 (m, 1H), 5.21 (s, 1H), 7.28–7.92 (m, 8H), 12.05 (br s, 1H). ^{13}C NMR (DMSO-d_6): $\delta = 16.90$, 37.85, 47.15, 47.67, 50.04, 66.06, 120.49, 120.51, 124.02, 125.84, 126.07, 127.53, 128.05, 128.07, 141.14, 143.14, 144.19, 144.55, 155.81, 173.68. IR (KBr): 3423, 3305, 3269, 2926, 1711, 1655, 1412, 1350, 1213, 1054, 740 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_4$ (363.41): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.43; H, 5.55; N, 3.72.

4.12. (−)-(1*R*,5*S*)-5-(9*H*-Fluoren-9-ylmethoxycarbonyl-amino)-3-methyl-cyclopent-2-enecarboxylic acid 17

The first mother liquor obtained after the crystallization of **16** was evaporated, containing 1.85 g (5 mmol) of **16**/**17** (40/60 ratio). The residue was dissolved in 100 mL CH_2Cl_2/hexane (3:7) and treated with dicyclohexylamine (0.60 mL, 3.6 mmol). The precipitated salt was collected on a filter, suspended in CH_2Cl_2 and the free acid liberated with dil HCl. This procedure was repeated with 1 equiv of dicyclohexylamine calculated on the quantity of **17** in the mixture to obtain 0.46 g (5%) of **17,** which was 97% pure. Mp 61–63 °C; $[\alpha]_D^{25} = -91$ (*c* 1, CH_2Cl_2). ^{1}H NMR (DMSO-d_6): $\delta = 1.73$ (s, 3H), 2.41 (d, $J = 7$ Hz, 2H), 3.52 (d, $J = 7$ Hz, 1H), 4.12–4.48 (m, 4H), 5.21 (s, 1H), 7.28–7.92 (m, 8H), 12.0 (br s, 1H). ^{13}C NMR (DMSO-d_6): $\delta = 17.20$, 41.71, 47.14, 53.48, 54.36, 66.08, 120.52, 122.62, 125.75, 126.69, 127.54, 127.58, 128.08, 141.11, 141.15, 142.58, 144.20, 144.45, 156.14, 173.76. IR (KBr): 3408, 3313, 3063, 2935, 1715, 1512, 1450, 1344, 1230, 741 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_4$ (363.41): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.91; H, 5.52; N, 3.48.

4.13. (+)-(1*R*,2*S*)-2-Amino-4-methyl-cyclopent-3-enecarboxylic acid 3

A solution of **16** (3.3 g; 9.1 mmol) and morpholine (1.3 mL, 15 mmol) in 40 mL of abs. EtOH was refluxed for 3 h. The solvent was evaporated; H_2O (50 mL) was added and washed with hexane (3 × 50 mL). The aqueous solution was concentrated and passed through a short column of Amberlite XAD-16. Evaporation of the eluate afforded 1.18 g of the crude product, which was recrystallized from 94% EtOH. Yield: 1.01 g (78%), HPLC purity 96% (Nucleosil 100-5 RP18, 10% aqueous MeOH, 1% H_3PO_4, at 206 nm for 10 min; then gradient to 100% MeOH in 15 min at 254 nm). Mp 219–220 °C (lit.[14] 221 °C); $[\alpha]_D^{25} = +65$ (*c* 0.8, H_2O). ^{1}H NMR (D_2O): $\delta = 1.72$ (s, 3H), 2.51 (d, $J = 8$ Hz, 2H), 3.25 (psq, $J = 8$ Hz, 1H), 4.15 (d, $J = 8$ Hz, 1H), 5.38 (s, 1H). ^{13}C NMR (D_2O): $\delta = 16.74$, 39.32, 47.30, 57.54, 120.79, 151.41, 180.37. IR (KBr): 3429, 3138, 2911, 1649, 1625, 1563, 1398, 1282, 1175, 986, 798 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.25; H, 8.05; N, 9.76.

4.14. (−)-(1*R*,5*S*)-5-Amino-3-methyl-cyclopent-2-enecarboxylic acid 2

The reaction was performed as described for **3**. Starting from 330 mg of **17** of 110 mg (86%) of 97% pure **2** was obtained. Mp 189–190 °C (lit.[14] 190 °C); $[\alpha]_D^{25} = -115$ (*c* 1, H_2O). ^{1}H NMR (D_2O): $\delta = 1.68$ (d, $J = 1$ Hz, 3H), 2.61 (dd, $J = 16$ Hz, 4 Hz, 1H), 2.61 (dd, $J = 16.5$ Hz, 7.5 Hz, 1H), 3.51–3.58 (m, 1H), 3.88–3.96 (m, 1H), 5.37 (d, $J = 1.5$ Hz, 1H). ^{13}C NMR (D_2O): $\delta = 16.50$, 40.09, 52.37, 52.45, 123.66, 141.12, 179.69. IR (KBr): 3438, 3052, 2946, 2183, 1654, 1552, 1506, 1393, 1176, 834 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.35; H, 7.98; N, 9.73.

Acknowledgment

The authors wish to thank Mr. D. Žiher, from PLIVA Structure and Analysis Department, for recording the CD spectra.

References

1. (a) Juaristi, E. *Enantioselective Synthesis of β-Amino Acids*; John Wiley & Sons: Canada, 1997; pp 45–61; (b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117–128.
2. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204.
3. (a) Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749–1755; (b) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756–1762; (c) Iwamoto, T.; Tsuii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H.; Kawabata, K.; Inamoto, Y.; Sakane, K. *J. Antibiot.* **1990**, *43*, 1–7; (d) Kawabata, K.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiot.* **1990**, *43*, 513–518.
4. Sordera, L. A.; Castaner, J.; Bozzo, J. *Drugs Future* **2002**, *27*, 1049.
5. Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberg, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.
6. Mittendorf, J.; Benet-Bucholz, J.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, 136–140.
7. (a) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302–11303; (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965–2984.
8. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; John Wiley & Sons: New York, 2001; pp 770–771.
9. Rappoport, Z.; Lei, Y. X.; Yamataka, H. *Helv. Chim. Acta* **2001**, *84*, 1405–1431.
10. Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131–3134.
11. Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H.-K.; Schmidt, A.; Schönfeld, W. *Biorg. Med. Chem. Lett.* **2003**, *13*, 433–436.
12. (a) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590–5591; (b) Rosini, C.; Giacomelli, G.; Salvadori, P. *J. Org. Chem.* **1984**, *49*, 3394–3395; (c) Skowronek, P.; Gawronski, J. *Tetrahedron Lett.* **2000**, *41*, 2975–2977; (d) Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *Tetrahedron: Asymmetry* **2002**, *13*, 1013–1016.
13. Nakanishi, K.; Berova, N.; Woody, R. W. *Circular Dichroism, Principles and Applications*, 2nd ed.; Wiley-VCH: New York, 2000; pp 337–376.
14. Mittendorf, J.; Kunisch, F.; Plempel, M. Ger. Offen. DE 4217776, 1993; *Chem. Abstr.* **1994**, *121*, 83988.