Tetrahedron: *Asymmetry* 19 (2008) 2856–2860

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Novel functionalized cispentacin derivatives. Synthesis of 1,2,3-triazole-substituted 2-aminocyclopentanecarboxylate stereoisomers

Loránd Kiss [a], Enikő Forró [a], Reijo Sillanpää [c], Ferenc Fülöp [a,b,*]

[a] *Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[b] *Research Group of Stereochemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[c] *Department of Chemistry, University of Jyväskylä, FIN-40351, Jyväskylä, Finland*

ARTICLE INFO

*Article history:*
Received 15 October 2008
Accepted 21 November 2008
Available online 24 January 2009

ABSTRACT

Four 1,2,3-triazole-substituted ethyl 2-amino-3-hydroxycyclopentanecarboxylate diastereomers (3,4-disubstituted cispentacins) with a cyclopentane skeleton were prepared in enantiomerically pure form from racemic β-lactam **7** via enzymatic ring opening, epoxidation and selective ring opening of the oxirane ring with sodium azide. The formation of the 1,2,3-triazole ring system involved click chemistry: 1,3-dipolar cycloaddition of the corresponding 4-substituted azidocarboxylates with diethyl acetylenedicarboxylate.



## 1. Introduction

Alicyclic β-amino acids have attracted great interest in recent years as a consequence of their pharmacological potential.[1] The naturally occurring (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin), an antifungal antibiotic, is one of the most important members of this class of compounds. Many cyclic, conformationally restricted, β-amino acids have been used as building blocks in the synthesis of peptides.[2] Cispentacins functionalized with alkyl groups in positions 3 and 5 have been systematically synthesized in enantiomerically pure form in recent years by Davies et al.[3]

The cycloaddition of azides and alkynes is a useful and convenient method for the preparation of 1,2,3-triazoles.[4] Organic azides play a very important role in click chemistry, when they are submitted to 1,3-dipolar cycloaddition with different dipolarophiles, forming triazoles or triazolines. 1,2,3-Triazoles are known to be powerful pharmacophores (Fig. 1). They are potential targets for drug discovery as they exhibit a broad scale of biological properties such as antiviral, antibacterial, antiepileptic and antiallergic activities.[5] Triazole-modified analogues of antiviral agents such as zanamivir **1** have been described and prepared via the azide-alkyne cycloaddition click chemistry procedure.[6] The triazole skeleton is a component of several nucleosides or carbanucleosides with antiviral, anti-HIV or cytostatic activities.[7,8] The 1,2,3-triazole analogue **2** of neplanocin A, for example, exhibits antiviral activity.[9] The 1,2,4-triazole ring is the key element of the antiviral agent ribavirin **3** and its carbanucleoside equivalent **4**,[10] which also exerts a powerful antiviral activity.

A number of carbocyclic 1,2,3-triazoloribavirin analogues (**5** and **6** Fig. 1) have recently been described as bioactive compounds.[7d,11]

Our present goal was the preparation of 1,2,3-triazole-functionalized cispentacin derivatives by a 'click chemistry' strategy, starting from azido-substituted β-aminocyclopentanecarboxylates.

## 2. Results and discussion

We recently prepared 4-azido-functionalized stereoisomers of cispentacin in enantiomerically pure form from racemic β-lactam **7**.[12,13] We have resolved racemic 6-azabicyclo[3.2.0]hept-3-en-7-one (±)-**7** through Lipolase-catalyzed enantioselective ring opening with $H_2O$ (1 equiv) in diisopropyl ether at 60 °C.[13] However, in accordance with the effort to develop nature-friendly[14] routes to enantiopure products, our earlier method was improved, and *tert*-butyl methyl ether was used instead of diisopropyl ether.

The functionalization process was based on the diastereoselective epoxidation of lactam **7** with opposite selectivities, when two different epoxy-amino ester diastereomers **10** and **11** were obtained and then submitted to oxirane ring opening with $NaN_3$, furnishing the corresponding azido ester derivatives regioselectively. Transformation of β-lactam (−)-**8** led to azido ester enantiomers (−)-**12** and (−)-**13**, while β-amino acid (+)-**9** was converted to azido derivatives (−)-**14** and (−)-**15** (Scheme 1).

The symmetrical ethyl acetylenedicarboxylate was chosen as the alkyne source. Azido esters (−)-**12** and (−)-**13** derived from β-lactam (−)-**8** were treated with the acetylene diester in refluxing EtOH for 6 h, the 1,3-dipolar reaction afforded the triazolo amino esters (+)-**16** and (+)-**17** in 77% and 71% yield, respectively (Scheme 2). The enantiomeric excesses (ee) of (+)-**16** and (+)-**17** were determined by means of chiral HPLC and were found to be ee > 98% in both cases.

The change of solvent resulted in high selectivity and high enantiopurity of both lactam and amino acid enantiomers (ee = 99% and 98%, respectively).

* Corresponding author. Tel.: +36 62 545 562; fax: +36 62 545705.
*E-mail address:* fulop@pharm.u-szeged.hu (F. Fülöp).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.11.035

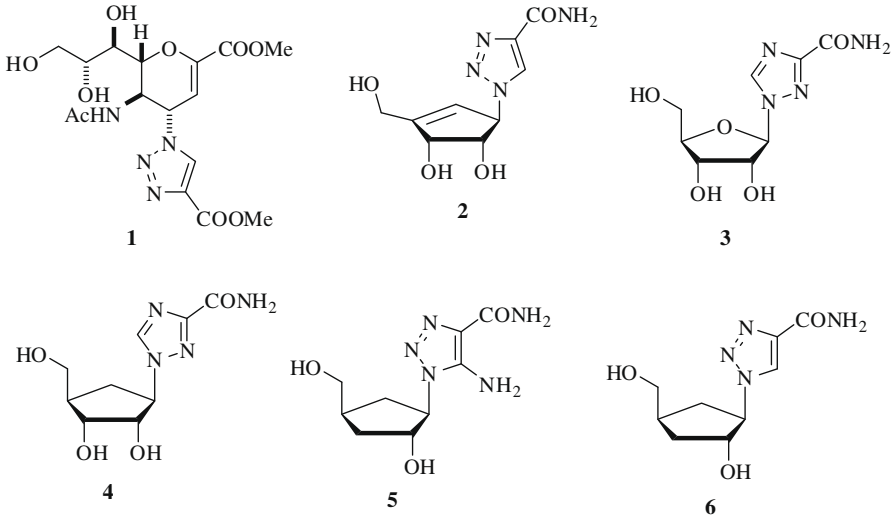
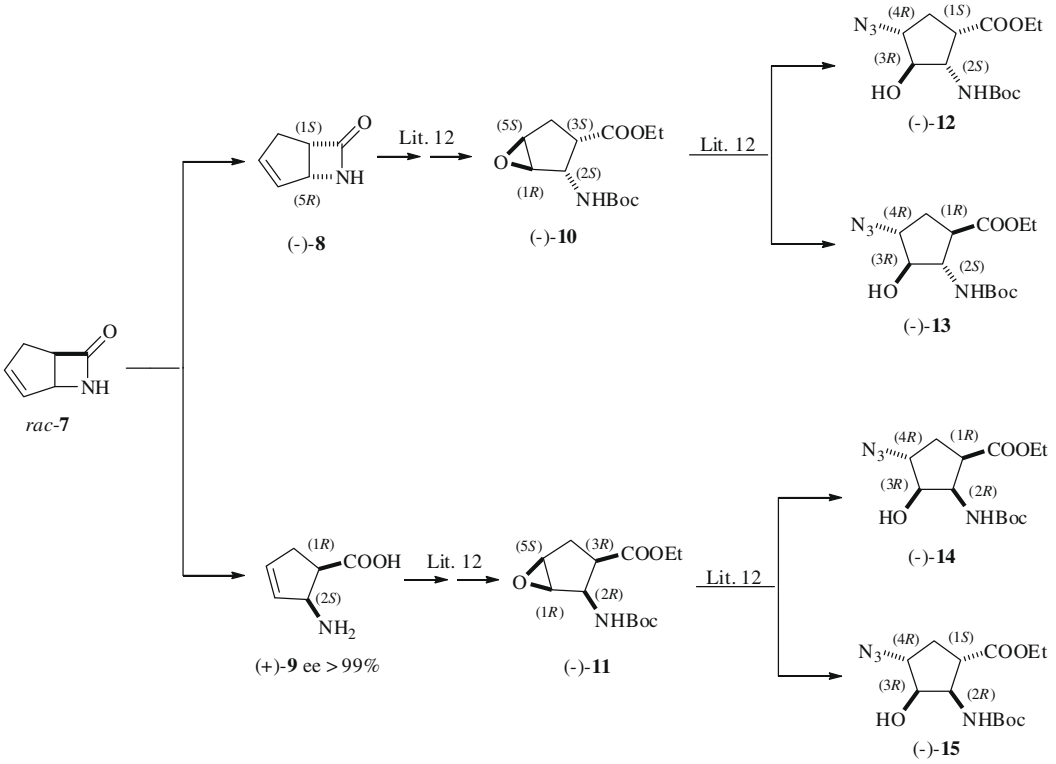
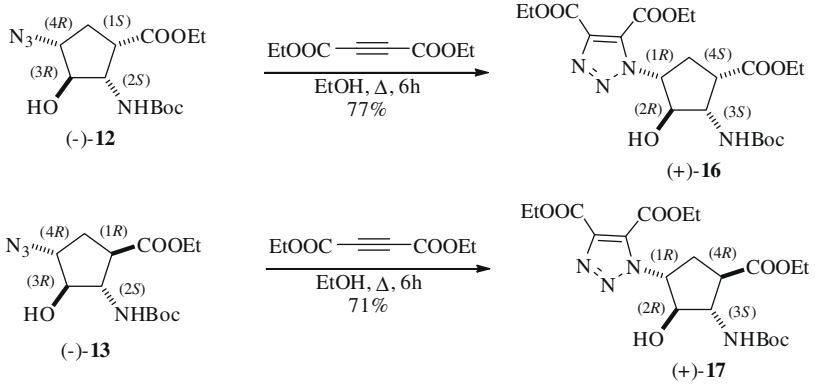


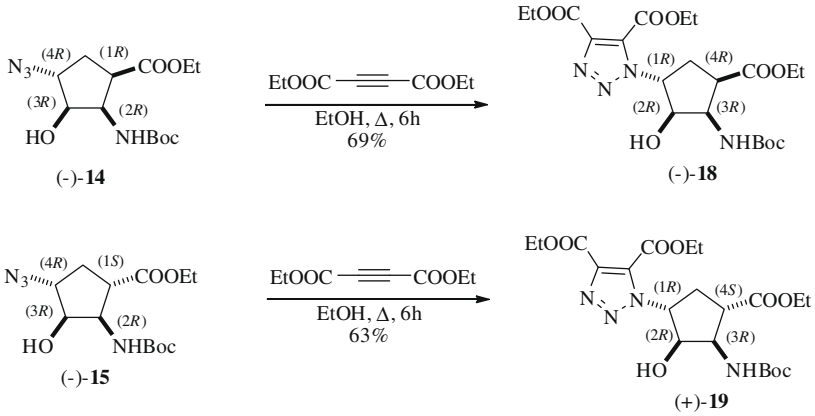

**Figure 1.** Some bioactive triazoles.




**Scheme 1.** Synthesis of β-lactam (−)-**8** and β-amino acid (+)-**9** enantiomers and azido esters (−)-**12**, (−)-**13**, (−)-**14** and (−)-**15**.




**Scheme 2.** Synthesis of triazole-substituted β-amino ester stereoisomers (+)-**16** and (+)-**17**.




**Scheme 3.** Synthesis of triazole-substituted β-amino ester stereoisomers (−)-**18** and (+)-**19**.

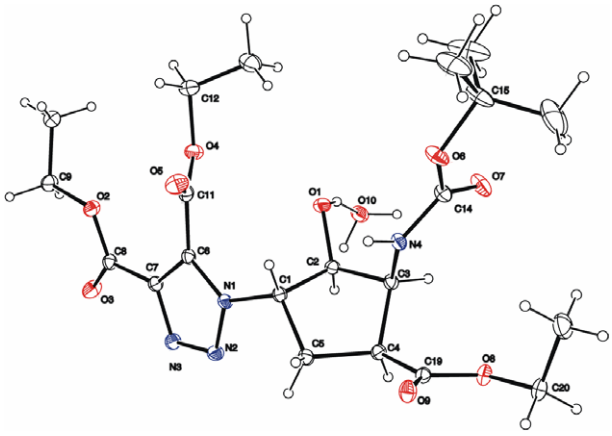



**Figure 2.** ORTEP diagram of compound **18**·$H_2O$.

The azido esters (−)-**14** and (−)-**15** derived from β-amino acid (+)-**9** were reacted with ethyl acetylenedicarboxylate in refluxing EtOH for 6 h in a similar way to that described above, which resulted in two new triazole-substituted stereoisomers, (−)-**18** and (+)-**19**, in 69% and 63% yields (Scheme 3 and Fig. 1). The enantiomeric excess of (−)-**18** was determined by chiral HPLC and that of (+)-**19** by chiral GC; both were found to be ee > 98%.

Figure 2 depicts the solid-state structure of 18 $H_2O$, which confirms the expected structural features of 18 (the X-ray recording was made on the racemic compound since the preliminary experiments were always performed with racemic substances).

## 3. Conclusions

In conclusion, four stereoisomers of 4-triazolo-substituted 2-aminocyclopentanecarboxylates were efficiently prepared in enantiomerically pure form via a 1,3-dipolar cycloaddition azide-alkyne 'click-chemistry' procedure. The triazole-substituted β-aminoesters prepared are highly functionalized cispentacin derivatives, which may be regarded as interesting precursors for new triazole carbonucleosides.

## 4. Experimental

### 4.1. Materials and methods

The chemicals were purchased from Aldrich or Fluka. Melting points were determined with a Kofler apparatus. $^1$H NMR and $^{13}$C NMR and 2D spectra were recorded in DMSO or $CDCl_3$, on a Bruker DRX 400 spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. The IR spectra were recorded on a Perkin–Elmer Spektrum 100 FT-IR spectrometer. The mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer.

### 4.2. Gram-scale resolution of 7-azabicyclo[4.2.0]oct-3-en-8-one, (±)-7

Racemic **7** (4 g, 36.64 mmol) was dissolved in *tert*-butyl methyl ether (80 mL). Lipolase (4 g, 50 mg/mL) and water (0.64 mL, 36.64 mmol) were added, and the mixture was shaken in an incubator shaker at 60 °C for 4 h. The reaction was stopped by filtering off the enzyme at 50% conversion. The solvent was evaporated off and the residual (1*S*,5*R*)-**8** crystallized out [1.88 g, 47%; $[\alpha]_D^{25} = -34.1$ (*c* 0.3; $CHCl_3$); mp 74–75 °C, ee 99%]. The filtered-off enzyme was washed with distilled water (3 × 20 mL), and the water was evaporated off, yielding the crystalline β-amino acid (1*R*,2*S*)-**9** [2.21 g, 48%; $[\alpha]_D^{25} = +96.9$ (*c* 0.3; $H_2O$); mp > 240 °C; ee = 98%]. All the analytical data for (−)-**8** and (+)-**9** are in accordance with literature data.[13]

### 4.3. General procedure for the synthesis of triazolo β-amino esters (+)-16, (+)-17, (−)-18 and (+)-19

To a solution of azido ester (−)-**12** or (−)-**13** or (−)-**14** or (−)-**15** (200 mg, 0.64 mmol) in EtOH (10 mL), ethyl acetylenedicarboxylate (109 mg, 0.64 mmol) was added and the mixture was stirred at reflux for 6 h. The mixture was then concentrated under reduced pressure and crystallized from a mixture of *n*-hexane–EtOAc or purified by column chromatography on silica gel (*n*-hexane–EtOAc).

#### 4.3.1. Diethyl 1-[(1*R*,2*R*,3*S*,4*S*)-3-(*tert*-butoxycarbonyl-amino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (+)-16

A white solid, mp 122–125 °C, yield 77%, $[\alpha]_D^{25} = +64.5$ (*c* 0.66, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.29 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.38 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.40 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.42 (s, 9H, $CH_3$), 2.65–2.77 (m, 2H, $CH_2$) 3.26–3.34 (m, 1H, H-4), 3.48 (br s, 1H, O-H), 4.16–4.26 (m, 3H, $OCH_2$ and H-3), 4.37–4.49 (m, 4H, 2 × $OCH_2$), 4.60–4.66 (m, 1H, H-2), 4.99–5.10 (m, 1H, H-1), 5.71 (br s, 1H, N–H); $^{13}$C NMR (DMSO, 400 MHz): $\delta$ = 13.6, 13.9, 14.0, 27.9, 29.0, 42.0, 55.8, 60.2, 61.4, 62.9, 63.5, 77.1, 77.8, 132.0, 138.3, 155.2, 158.3, 159.6, 171.9; MS: (ESI) *m/z* = 507 (M+Na);

IR(KBr): $\nu_{max}$ 3366, 2978, 1708, 1535; Anal. Calcd for $C_{21}H_{32}N_4O_9$: C, 52.06; H, 6.66; N, 11.56. Found: C, 51.72; H, 6.98; N, 11.14.

#### 4.3.2. Diethyl 1-[(1*R*,2*R*,3*S*,4*R*)-3-(*tert*-butoxycarbonylamino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (+)-17

A white solid, mp 132–134 °C, yield 71%, $[\alpha]_D^{25} = +13$ (*c* 0.63, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.30 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.40 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.41 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.44 (s, 9H, $CH_3$), 2.59–2.67 (m, 1H, $CH_2$), 2.68–2.76 (m, 1H, $CH_2$), 3.12–3.18 (m, 1H, H-4), 3.92–3.99 (m, 1H, H-3), 4.17–4.27 (m, 2H, $OCH_2$), 4.37–4.51 (m, 5H, 2 × $OCH_2$ and H-2), 4.77 (br s, 1H, O-H), 5.15–5.22 (m, 1H, H-1), 5.23 (br s, 1H, N–H); $^{13}$C NMR (DMSO, 400 MHz): $\delta$ = 14.5, 14.7, 14.8, 29.0, 29.6, 44.8, 59.2, 61.3, 62.3, 63.8, 64.1, 77.2, 79.0, 156.0, 158.6, 160.2, 162.4, 164.3, 174.3; MS: (ESI) *m/z* = 507 (M+Na); IR(KBr): $\nu_{max}$ 3400, 2981, 1736, 1709, 1524; Anal. Calcd for $C_{21}H_{32}N_4O_9$: C, 52.06; H, 6.66; N, 11.56. Found: C, 51.70; H, 6.99; N, 11.11.

#### 4.3.3. Diethyl 1-[(1*R*,2*R*,3*R*,4*R*)-3-(*tert*-butoxycarbonyl-amino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (−)-18

A white solid, mp 62–65 °C, yield 69%, $[\alpha]_D^{25} = -18.1$ (*c* 0.6, EtOH). $^1$H NMR (DMSO, 400 MHz): $\delta$ = 1.17 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.29 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.36 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.38 (s, 9H, $CH_3$), 1.96–2.10 (m, 1H, $CH_2$), 2.72–2.81 (m, 1H, $CH_2$), 3.37–3.43 (m, 1H, H-4), 3.97–4.10 (m, 2H, $OCH_2$), 4.26–4.38 (m, 2H, $OCH_2$), 4.38–4.46 (m, 3H, $OCH_2$ and H-3), 4.52–4.59 (m, 1H, H-2), 5.12–5.20 (m, 1H, H-1), 5.52 (br s, 1H, O–H), 6.79 (br s, 1H, N–H); $^{13}$C NMR (DMSO, 400 MHz): $\delta$ = 13.6, 13.9, 14.0, 28.2, 29.0, 43.6, 55.1, 60.0, 61.3, 63.0, 64.5, 76.2, 77.8, 132.2, 138.0, 155.3, 158.4, 159.5, 171.1; MS: (ESI) *m/z* = 991 (2 × M+Na); IR(KBr): $\nu_{max}$ 3356, 2979, 1722, 1708, 1544; Anal. Calcd for $C_{21}H_{32}N_4O_9$: C, 52.06; H, 6.66; N, 11.56. Found: C, 51.77; H, 6.93; N, 11.12.

#### 4.3.4. Diethyl 1-[(1*R*,2*R*,3*R*,4*S*)-3-(*tert*-butoxycarbonyl-amino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (+)-19

A colourless oil, yield 63%, $[\alpha]_D^{25} = +26.2$ (*c* 0.38, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.28 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.38 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.41 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.44 (s, 9H, $CH_3$), 2.61–2.69 (m, 2H, $CH_2$), 3.03–3.14 (m, 1H, H-4), 3.74 (br s, 1H, O-H), 4.14–4.24 (m, 2H, $OCH_2$), 4.35–4.50 (m, 5H, 2 × $OCH_2$ and H-2), 4.61–6.66 (m, 1H, H-2), 5.08–5.14 (m, 1H, H-1), 5.23 (br s, 1H, N–H); $^{13}$C NMR (DMSO, 400 MHz): $\delta$ = 13.6, 13.8, 13.9, 28.1, 30.7, 45.7, 54.9, 60.4, 61.4, 64.5, 65.0, 74.9, 77.9, 131.4, 138.7, 155.0, 158.2, 159.6, 172.9. MS: (ESI) *m/z* = 991 (2 × M+Na); IR(KBr): $\nu_{max}$ 3396, 2983, 1733, 1516; Anal. Calcd for $C_{21}H_{32}N_4O_9$: C, 52.06; H, 6.66; N, 11.56. Found: C, 51.80; H, 7.01; N, 11.19.

### 4.4. Determinations of the enantiomeric excesses of 16–19, separation of the enantiomers

Racemic **16** was derivatized with benzoyl chloride and the product was separated by HPLC. A sample (2 mg) was dissolved in $CH_2Cl_2$ (200 μL), and benzoyl chloride (10 μL) and $Et_3N$ (30 μL) were added. After 10 min, MeOH (20 μL) was added, after which the mixture was kept at 25 °C for 10 min, and next evaporated to dryness. The residue was dissolved in *n*-hexane/isopropanol 97/3 (2 mL), filtered and injected. Retention times (min) [Chiralcel OD-H column (manufactured by Daicel), eluent: *n*-hexane/isopropanol 97/3, flow rate: 0.5 mL/min, room temperature, detection at 205 nm]: 58.9 min and 82.3 min.

Racemic **17** (1 mg) was dissolved in EtOH (1 mL) and separated by HPLC. Retention times (min) [Chiralpak IA column (manufactured by Daicel), eluent: *n*-hexane/ethanol 90/10, flow rate: 0.5 mL/min, room temperature, detection at 205 nm]: 42.7 min and 65.0 min.

Racemic **18** (1 mg) was dissolved in $CH_3CN$ (1 mL) and separated by HPLC. Retention times (min) [Chiralcel OD-RH column (manufactured by Daicel), eluent: $H_2O/CH_3CN$ 70/30, flow rate: 0.4 mL/min, room temperature, detection at 205 nm]: 49.3 and 53.8.

Racemic **19** was derivatized with *N*,*O*-bis-(trimethylsilyl)trifluoroacetamide (BSTFA) and separated by GC. A sample (2 mg) was dissolved in $CH_2Cl_2$ (100 μL), BSTFA (10 μL) was added, the mixture was kept at 25 °C for 20 min, and thereafter injected. Retention times (min) [Chirasil-L-Val column (manufactured by Chrompack), 130 °C for 20 min → 160 °C, temperature rise: 5 °C/min; 140 kPa]: 44.5 and 45.5.

X-ray crystallographic study of **18**·$H_2O$: Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized Mo K radiation ($\lambda$ = 0.71073 Å) as reported earlier.[15]

The structure was solved by direct methods by use of the SHELXS-97 program[16] and full-matrix, least-squares refinements on $F^2$ were performed by use of the SHELXL-97 program16. The CH hydrogen atoms were included at fixed distances with the fixed displacement parameters from their host atoms. The OH and NH hydrogen atoms were refined isotropically with the fixed displacement parameters. The deposition number CCDC 704876 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

## Acknowledgment

We are grateful to the Hungarian Research Foundation (OTKA Nos. F67970 and T049407) for financial support.

## References

1. (a) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181; (b) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629; (c) Miller, J. A.; Nguyen, S. T. *Mini-Rev. Org. Chem.* **2005**, *2*, 343; (d) Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H.-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433; (e) Hamersak, Z.; Roje, M.; Avdagic, A.; Sunjic, V. *Tetrahedron: Asymmetry* **2007**, *18*, 635; (f). *Chem. Rev.* **2001**, *101*, 3893; (g) Yang, D.; Zhang, D.-W.; Hao, Y.; Wu, Y.-D.; Luo, S.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 6719; (h) Rathore, N.; Gellman, S. H.; Pablo, J. J. *Biophys. J.* **2006**, *91*, 3425.
2. (a) Woll, M. G.; Fisk, D. *J. Am. Chem. Soc.* **2002**, *124*, 12447; (b) Cheng, R. P.; Gellman, S. H.; De Grado, W. F. *Chem. Rev.* **2001**, *101*, 3219; (c) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11516; (d) Porter, E. A.; Wang, X.; Schmitt, M. A.; Gellman, S. H. *Org. Lett.* **2002**, *4*, 3317; (e) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173; (f) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323; (g) Martinek, T. A.; Tóth, G. K.; Vass, E.; Hollósi, M.; Fülöp, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 1718; (h) Hetényi, A.; Mándity, I. M.; Martinek, T. A.; Tóth, G. K.; Fülöp, F. *J. Am. Chem. Soc.* **2005**, *127*, 547; (i) Martinek, T. A.; Fülöp, F. *Eur. J. Biochem.* **2003**, *270*, 3657.
3. (a) Abraham, E.; Davies, S. G.; Docherty, A. J.; Ling, K. B.; Roberts, P. M.; Russel, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 1356; (b) Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. S.; Withey, J. M. *Org. Biomol. Chem.* **2003**, *1*, 3698; (c) Davies, S. G.; Garner, A. C.; Long, M. J. C.; Morrison, R. M.; Roberts, P. M.; Savory, E. D.; Smith, A. S.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2005**, *3*, 2762; (d) Urones, J. G.; Garrido, N. M.; Diez, D.; Hammoumi, M. M. E.; Dominguez, S. H.; Casaseca, J. A.; Davies, S. G. *Org. Biomol. Chem.* **2004**, *2*, 364; (e) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.
4. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596; (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004; (c) Lutz, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2; (d) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249.
5. (a) Im, C.; Maiti, S. N.; Micetich, R. G.; Daneshtalab, M.; Atchison, K.; Philips, O. A. *J. Antibiot.* **1994**, *47*, 1030; (b) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camaraza, M. *J. Antiv. Chem. Chemother.* **1998**, *9*, 481; (c)

Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953; (d) Naud, J.; Lemke, C.; Goudreau, N.; Beaulieu, E.; White, P. D.; Brunet, M. L.; Forgione, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3400; (e) Whiting, M.; Mudoon, J.; Lin, Y. C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1435; (f) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053.

6. Li, J.; Zheng, M.; Tang, W.; He, P. L.; Zhu, W.; Li, T.; Zuo, J. P.; Liu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5009.
7. (a) Broggi, J.; Diez-Gonzalez, S.; Petersen, J. L.; Berteina-Raboin, S.; Nolan, S. P.; Agrofoglio, L. A. *Synthesis* **2008**, 141; (b) Broggi, J.; Joubert, N.; Aucagne, V.; Berteina-Raboin, S.; Diez-Gonzalez, S.; Nolan, S.; Topalis, D.; Deville-Bonne, D.; Balzarini, J.; Neyts, J.; Andrei, G.; Snoeck, R.; Agrofoglio, L. A. *Nucleosides, Nucleotides, Nucleic Acids* **2007**, *26*, 1391; (c) Broggi, J.; Joubert, N.; Aucagne, V.; Zevaco, T.; Berteina-Raboin, S.; Nolan, S. P.; Agrofoglio, L. A. *Nucleosides, Nucleotides, Nucleic Acids* **2007**, *26*, 779; (d) Perez-Castro, I.; Caamano, O.; Fernandez, F.; Garcia, M. D.; Lopez, C.; De Clercq, E. *Org. Biomol. Chem.* **2007**, *5*, 3805; (e) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.
8. (a) Li, W.; Xia, Y.; Fan, Z.; Qu, F.; Wu, Q.; Peng, L. *Tetrahedron Lett.* **2008**, *49*, 2804; (b) Zhu, R.; Wang, M.; Xia, Y.; Qu, F.; Neyts, J.; Peng, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3321; (c) Lazrek, H. B.; Taourite, M.; Oulih, T.; Barascut, J. L.; Imbach, J. L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 1949.
9. Cho, J. H.; Bernard, D. L.; Sidwell, R. W.; Kern, E. R.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1140.
10. Kuang, R.; Ganguly, A. K.; Chan, T. M.; Pramanik, B. N.; Blythin, D. J.; McPhail, A. T.; Saksena, A. K. *Tetrahedron Lett.* **2000**, *41*, 9575.
11. Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R. F.; Agrofoglio, L. A. *Bioorg. Med. Chem.* **2003**, *11*, 3633.
12. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2007**, *72*, 8786.
13. Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2875.
14. Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31.
15. Kanizsai, I.; Szakonyi, Z.; Sillanpää, R.; D'Hooghe, M.; De Kimpe, N.; Fülöp, F. *Tetrahedron: Asymmetry* **2006**, *17*, 2857.
16. Sheldrick, G. M. SHELX-97; University of Göttingen: Germany, 1997.