# Synthesis and stereochemistry of azeto[2,1-*a*]isoquinolin-2-one derivatives

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**Dedicated to Professor Gábor Bernáth on the occasion of his 70th birthday**

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**Abstract**

Azeto[2,1-*a*]isoquinolin-2-one derivatives **3-7** were prepared by the reaction of dihydroisoquinoline **1a** or **1b** with the corresponding acid chloride **2a-c** in the presence of triethylamine. Alternatively, **4** was obtained by the reaction of **1a** and phenoxyacetic acid **2d** in the presence of phosphoryl chloride.

**Keywords:** β-Lactam, isoquinoline, stereochemistry

## Introduction

Since the discovery of non-classical β-lactam antibiotics, the synthesis of compounds containing the β-lactam moiety has been a subject of intense study by a number of research groups.[1] More recently, β-lactams have also been found to be versatile intermediates of non-proteogenic amino acids, peptides, peptide turn mimetics,[2] taxoid antitumour agents,[3] heterocycles[4] and other types of compounds of biological interest.[5-7]

Although many methods are known for the construction of β-lactam rings, the Staudinger reaction is still the most frequently used and is considered to be the most effective method. In the standard reaction, ketenes formed by the dehydrohalogenation of acid chlorides containing an α-hydrogen are added to an imine in the presence of a base. A number of modified versions of this reaction have been developed, in which differently activated acids are used as ketene sources instead of acid chlorides, and the mechanism and stereochemistry of β-lactam formation have been studied extensively.[1,8-10]

By means of the above cycloaddition reactions, a great number of azeto[2,1-*a*]isoquinolin-2-one derivatives of synthetic and pharmacological interest have been prepared. However, the stereochemistry and transformations of these azetidinone derivatives have been investigated in only a few cases.[11]

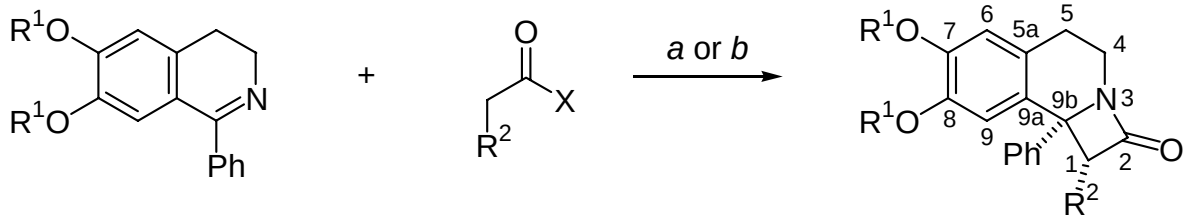
As a continuation of our investigations into the structure of azeto[2,1-*a*]isoquinolines,[12-15] the present work aimed at the preparation and structure analysis of different azeto[2,1-*a*]-isoquinolin-2-ones.

## Results and Discussion

### Chemistry

In the course of the Staudinger ketene-imine cycloaddition, acetic acid derivatives containing electron-withdrawing substituents (alkoxy, aryloxy, phthalimido or halo) in the α position have served as appropriate sources for the generation of ketenes.[1] Phenylacetic acid derivatives have been employed successfully for the preparation of bi- or tricyclic 2-azetidinones in only a few cases.[16-20] Occasionally, low yields are obtained[21] or the reaction does not lead to the expected β-lactam.[22]

The reaction of dihydroisoquinoline **1a** or **1b** in dichloromethane with phenylacetyl chloride **2a** failed in the presence of triethylamine at room temperature. When the reaction was carried out in refluxing toluene, azeto[2,1-*a*]isoquinolin-2-one derivatives **3** and **5** were obtained in good yields. Similarly, **4, 6** and **7** were prepared by the reaction of dihydroisoquinoline **1a** or **1b** with the corresponding acid chloride **2b** or **2c**. Alternatively, **4** was prepared by the reaction of **1a** and phenoxyacetic acid **2d** via the acid chloride generated *in situ* in the presence of $POCl_3$ (Scheme 1)[23].




**1a** $R^1$ = Me
**1b** $R^1$ = Et

**2a** $R^2$ = Ph, X = Cl
**2b** $R^2$ = OPh, X = Cl
**2c** $R^2$ = NPhth, X = Cl
**2d** $R^2$ = OPh, X = OH

**3** $R^1$ = Me, $R^2$ = Ph
**4** $R^1$ = Me, $R^2$ = OPh
**5** $R^1$ = Et, $R^2$ = Ph
**6** $R^1$ = Et, $R^2$ = OPh
**7** $R^1$ = Et, $R^2$ = NPhth

**Scheme 1.** Conditions: (a) 2 equiv. $Et_3N$, toluene, Δ; (b) 1 equiv. $POCl_3$, 2 equiv. $Et_3N$, $CH_2Cl_2$, r.t.

**NMR spectroscopy**

The relative configurations and the predominant conformation of the azetoisoquinoline skeleton were investigated with the aid of standard NMR spectroscopic methods. The studied compounds exhibited similar spectral parameter patterns, and therefore the discussion holds for all the compounds reported here, unless otherwise stated. The scalar coupling patterns for protons H-4 and H-5 reveal a rigid *trans*-diaxial arrangement for H-5*ax* and H-4*ax* (Table 1). At the same time, NOESY cross-peaks can be observed from the H-2′, H-6′ protons of Ph-9b to H-5*ax* and H-4*eq*, which proves the spatial assignment of the signals (Figure 1).

**Table 1.** Characteristic vicinal coupling constants

| Cmpd. | $^3J$(5*ax*,4*ax*) Hz | $^3J$(5*ax*,4*eq*) Hz | $^3J$(5*eq*,4*eq*) Hz | $^3J$(5*eq*,4*ax*) Hz |
|---|---|---|---|---|
| **3** | 11.8 | 7.6 | 2.3 | 6.3 |
| **4** | 10.6 | 7.6 | 3.0 | 6.3 |
| **5** | 11.8 | 7.4 | 1.5 | 6.1 |
| **6** | 10.8 | 7.5 | 2.8 | 6.2 |
| **7** | 11.8 | 6.1 | 2.0 | 6.0 |

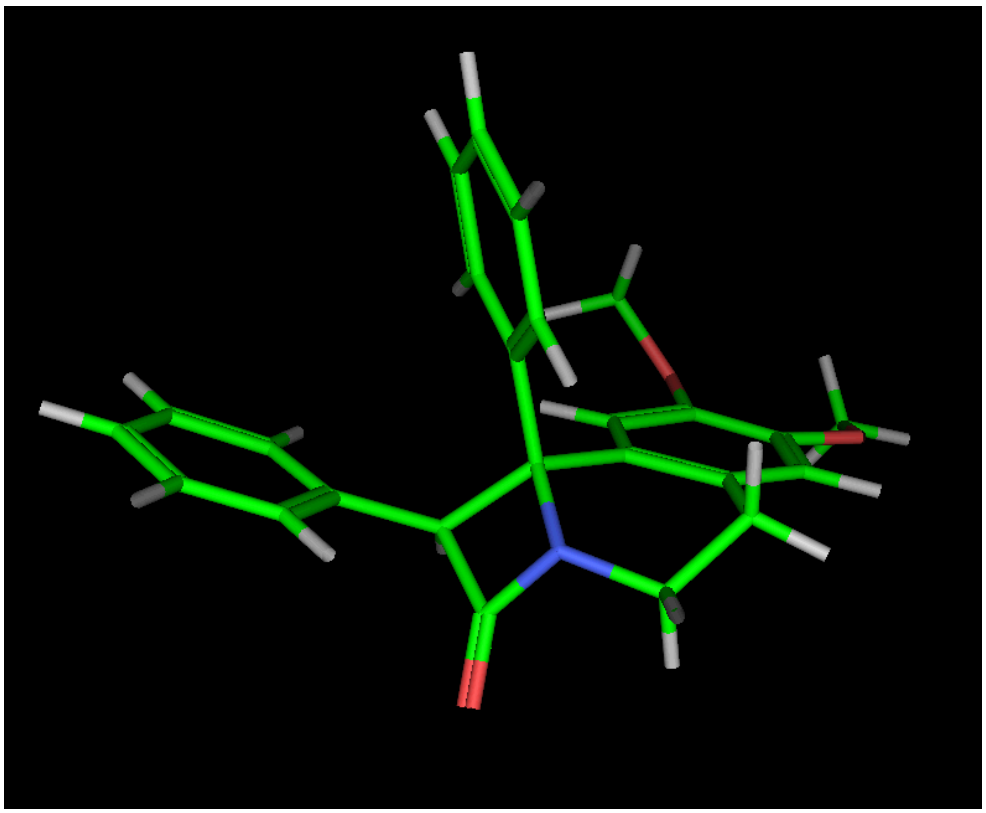


**Figure 1.** 3D structure of **3**, determined by NMR spectroscopy and Merck molecular force field calculations.

The hardly detectable NOE interactions between H-2′, H-6′ protons of Ph-9b and H-1 suggest a *cis* relative configuration for Ph-9b and $R^2$, although this observation cannot be regarded as an unambiguous proof for this assumption. It is interesting that, in derivative **7**, the aromatic protons of the phthalimido group at 7.70 and 7.63 ppm exhibit chemical exchange broadening at ambient temperature, presumably caused by hindered rotation, which supports the *cis* relative configuration on C-9b and C-1 (Figure 2). At 328 K, the broadening decreases so that the multiplet pattern is observable.

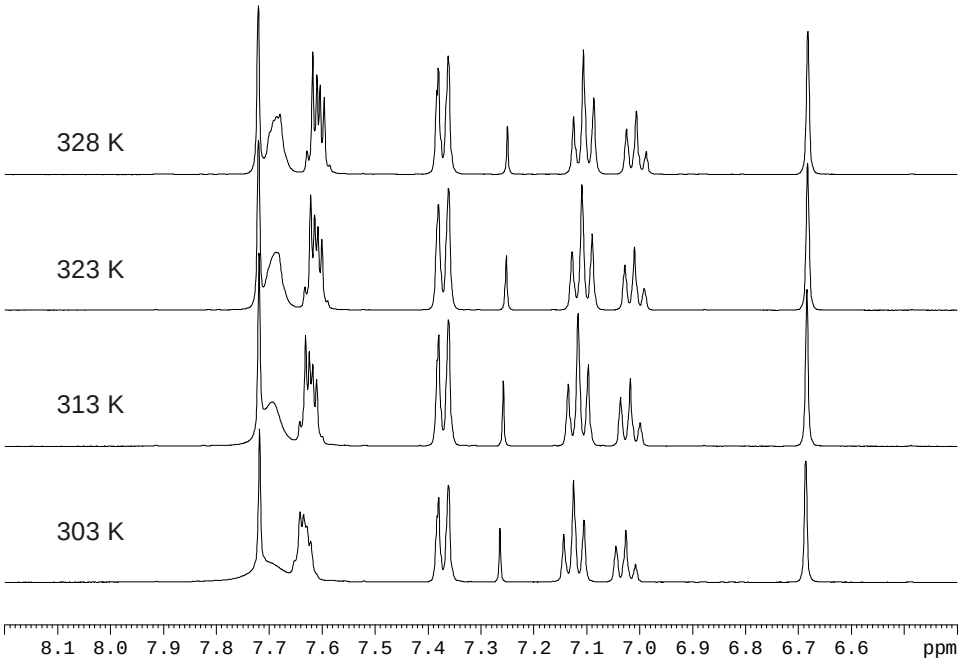



**Figure 2.** Temperature-dependent signal broadening in the $^1$H NMR spectrum of **7**.

## Experimental Section

**General Procedures.** Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel $60F_{254}$ plates were used for TLC: the eluent was toluene:methanol 4:1. 6,7-Dimethoxy-1-phenyl- and 6,7-diethoxy-1-phenyl-3,4-dihydroisoquinoline (**1a** and **1b**) were prepared by standard Bischler-Napieralski cyclization of *N*-benzoylhomoveratrylamine and *N*-benzoyl-2-(3,4-diethoxyphenyl)ethylamine.[24] Phthalylglycyl chloride was prepared from phthalyl-glycine and thionyl chloride.[25]

The $^1$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes, at room temperature, on a Bruker MSL-500 spectrometer at 400.13 ($^1$H) and 100.61 ($^{13}$C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The MS spectra were run on a Finnigan TSQ 7000 mass spectrometer (Finnigan MAT Ltd, San Jose, USA) equipped

with an atmospheric pressure chemical ionization source (APCI). Samples (dissolved in MeOH) were introduced to the ion source with direct injection method using a HPLC pump. APCI ion source conditions were as follows: temperature 450 ºC; current 5 mikroA, nebulizer gas: nitrogen; solvent: 1:1 volume ratio of water:methanol, 0.5% acetic acid; flow rate: 0.2 ml/min.

**General procedure for the preparation of azetoisoquinolines (3-7) (Method A).** To a stirred solution of 1-phenyl-6,7-dimethoxy- or 1-phenyl-6,7-diethoxy-3,4-dihydroisoquinoline **1a** or **1b** (10 mmol) in anhydrous toluene (30 mL), triethylamine (2.8 mL, 20 mmol) was added. The solution was refluxed and the appropriate acid chloride derivative 2a-c (20 mmol) in anhydrous toluene (50 mL) was added dropwise during 3 h under reflux. The reaction mixture was then cooled and extracted with 5% $Na_2CO_3$ solution (20 mL), 5% HCl (20 mL) and brine (20 mL), and the organic layer was dried with $Na_2SO_4$. After evaporation the residue was taken up in diisopropyl ether, and the crystalline product was filtered off and recrystallized.

**(1*R**,9b*R**)-7,8-Dimethoxy-1,9b-diphenyl-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]isoquinolin-2-one (3).** Mp 183-184 ºC (from diisopropyl ether–ethyl acetate), yield 58%. Anal. Calcd. for $C_{25}H_{23}NO_3$ (385.46): C, 77.90; H, 6.01; N, 3.63. Found: C, 77.69; H, 5.92; N, 3.74%. $\delta_H$ ($CDCl_3$) 2.64 (1H, ddd, *J* = 7.6, 11.8, 15.1 Hz, *H-5ax*), 2.78 (1H, ddd, *J* = 2.3, 6.3, 15.1 Hz, H-5*eq*), 3.72 (1H, ddd, *J* = 2.3, 7.6, 11.3 Hz, H-4*eq*), 3.83 (1H, ddd, *J* = 6.3, 11.3, 11.8 Hz, H-4*ax*), 3.88 (3H, s, OMe), 4.05 (3H, s, OMe), 4.91 (1H, s, H-1), 6.70 (1H, s, H-6), 6.99-7.12 (8H, m, Ph-1 and H-3′, H-4′, H-5′ Ph-9b), 7.14 (2H, d, *J* = 7.0 Hz, H-2′, H-6′ Ph-9b), 7.21 (1H, s, H-9). $\delta_C$ ($CDCl_3$) δ 26.92, 39.62, 56.48, 57.00, 66.58, 68.30, 110.58, 112.42, 127.37, 127.44, 127.59, 127.87, 128.14, 128.62, 129.36, 133.36, 133.43, 138.95, 148.36, 148.83, 170.29. MS (APCI): *m*/*z* 386 $[M+H]^+$ (100%).

**(1*R**,9b*R**)-7,8-Dimethoxy-1-phenoxy-9b-phenyl-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]isoquinolin-2-one (4).** Mp 173-175 ºC (from diisopropyl ether–ethyl acetate): yield 86 %. Anal. Calcd. for $C_{25}H_{23}NO_4$ (401.45): C, 74.79; H, 5.77; N, 3.49. Found: C, 74.72; H, 5.70; N, 3.52%. $^1$H NMR ($CDCl_3$) $\delta_H$ 2.61 (1H, ddd, *J* = 7.6, 10.6, 15.6 Hz, H-5*ax*), 2.78 (1H, ddd, *J* = 3.0, 6.3, 15.6 Hz, H-5*eq*), 3.60 (1H, ddd, *J* = 3.0, 7.6, 11.8 Hz, H-4*eq*), 3.83 (1H, ddd, *J* = 6.3, 10.6, 11.8 Hz, H-4*ax*), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 5.49 (1H, s, H-1), 6.70 (1H, s, H-6), 6.86 (2H, d, *J* = 8.4 Hz, H-2′, H-6′ OPh-1), 6.87 (1H, s, H-9), 6.97 (1H, t, *J* = 7.40 Hz, H-4′ OPh-1), 7.21 (2H, t, *J* = 7.6 Hz, H-3′, H-5′ OPh-1), 7.29-7.36 (3H, m, H-3′, H-4′, H-5′ Ph-9b), 7.38 (2H, d, *J* = 7.0 Hz, H-2′, H-6′ Ph-9b). $^{13}$C-NMR ($CDCl_3$) $\delta_C$ 26.98, 38.84, 56.70, 56.97, 67.78, 89.10, 110.31, 112.72, 117.63, 123.28, 127.90, 128.59, 128.62, 128.69, 130.06, 130.80, 138.00, 148.49, 149.39, 157.93, 167.27. MS (APCI): *m*/*z* 402 $[M+H]^+$ (100%).

**(1*R**,9b*R**)-7,8-Diethoxy-1,9b-diphenyl-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]isoquinolin-2-one (5).** Mp 163-166 ºC (from diisopropyl ether–ethyl acetate), yield 56%. Anal. Calcd. for $C_{27}H_{27}NO_3$ (413.51): C, 78.42; H, 6.58; N, 3.39. Found: C, 78.15; H, 6.52; N, 3.44%. $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.45 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathit{H_3}$), 1.53 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathit{H_3}$), 2.64 (1H, ddd, *J* = 7.4, 11.8, 15.1 Hz, H-5*ax*), 2.75 (1H, ddd, *J* = 1.5, 6.1, 15.1 Hz, H-5*eq*), 3.70 (1H, ddd, *J* = 1.5, 7.4, 11.2 Hz, H-4*eq*), 3.83 (1H, ddd, *J* = 6.1, 11.2, 11.8 Hz, H-4*ax*), 4.05-4.12 (2H, m,

OC*H*$_2$CH$_3$), 4.24 (2H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 4.89 (1H, s, H-1), 6.70 (1H, s, H-6), 7.00-7.12 (8H, m, Ph-1 and H-3′, H-4′, H-5′ Ph-9b), 7.14 (2H, d, *J* = 7.08 Hz, H-2′, H-6′ Ph-9b), 7.24 (1H, s, H-9). $^{13}$C-NMR (CDCl$_3$) $\delta_C$ 15.29, 15.45, 26.89, 39.63, 65.15, 66.15, 66.57, 68.33, 113.65, 114.49, 127.36 (3C), 127.54, 128.09, 128.23, 128.58, 129.37, 133.47 (2C), 139.00, 147.92, 149.16, 170.37. MS (APCI): *m*/*z* 414 [M+H]$^+$ (100%).

**(1*R**,9b*R**)-7,8-Diethoxy-1-phenoxy-9b-phenyl-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]isoquinolin-2-one (6).** Mp 117-120 ºC (from diisopropyl ether), yield 74%. Anal. Calcd. for $C_{27}H_{27}NO_4$ (429.51): C, 75.50; H, 6.34; N, 3.26. Found: C, 75.56; H, 6.54; N, 3.32%. $^1$H-NMR (CDCl$_3$) $\delta_H$ 1.42-1.47 (6H, m, OCH$_2$C*H*$_3$), 2.59 (1H, ddd, *J* = 7.5, 10.8, 15.5 Hz, H-5*ax*), 2.75 (1H, ddd, *J* = 2.8, 6.2, 15.5 Hz, H-5*eq*), 3.59 (1H, ddd, *J* = 2.8, 7.5, 11.7 Hz, H-4*eq*), 3.74 (1H, ddd, *J* = 6.2, 10.8, 11.7 Hz, H-4*ax*), 4.03-4.11 (4H, m, OC*H*$_2$CH$_3$), 5.47 (1H, s, H-1), 6.70 (1H, s, H-6), 6.85 (2H, d, *J* = 7.9 Hz, H-2′, H-6′ OPh-1), 6.91 (1H, s, H-9), 6.97 (1H, t, *J* = 7.4 Hz, H-4′ OPh-1), 7.20 (2H, t, *J* = 7.60 Hz, H-3′, H-5′ OPh-1), 7.29-7.35 (3H, m, H-3′, H-4′, H-5′ Ph-9b), 7.38 (2H, d, *J* = 5.80 Hz, H-2′, H-6′ Ph-9b). $^{13}$C-NMR (CDCl$_3$) $\delta_C$ 15.25, 26.71, 38.64, 65.15, 65.60, 67.82, 88.87, 112.59, 114.57, 117.33, 122.95, 127.83, 128.25, 128.32, 128.40, 129.77, 130.69, 137.80, 147.86, 149.05, 157.71, 167.11. MS (APCI): *m*/*z* 430 [M+H]$^+$ (100%).

**(1*R**,9b*R**)-7,8-Diethoxy-9b-phenyl-1-phthalimido-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]isoquinolin-2-one (7).** Mp 226-230 ºC (from methanol–chloroform), yield 68%. Anal. Calcd. for $C_{29}H_{26}N_2O_5$ (482.53): C, 72.18; H, 5.43; N, 5.81. Found: C, 72.64; H, 5.27; N, 5.93%. $^1$H-NMR (CDCl$_3$) $\delta_H$ 1.45 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.60 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 2.68-275 (2H, m, H-5), 3.80 (1H, dt, *J* = 6.0, 11.83 Hz, H-4*ax*), 3.89 (1H, ddd, *J* = 2.0, 6.1, 11.3 Hz, H-4*eq*), 4.04-4.12 (2H, m, OC*H*$_2$CH$_3$), 4.36 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 5.52 (1H, s, H-1), 6.69 (1H, s, H-6), 7.03 (1H, t, *J* = 7.3 Hz, H-4′ Ph-9b), 7.13 (2H, t, *J* = 7.8 Hz, H-3′, H-5′ Ph-9b), 7.38 (2H, t, *J* = 7.3 Hz, H-2′, H-6′ Ph-9b), 7.63-7.72 (4H, bm, PhtN), 7.72 (1H, s, H-9). $^{13}$C-NMR (CDCl$_3$) $\delta_C$ 15.23, 15.26, 26.73, 40.17, 65.57, 65.95, 67.97, 112.88, 115.07, 123.66, 127.21, 127.47, 127.96, 128.42, 131.88, 132.24, 134.40, 137.48, 148.81, 149.15, 165.02. MS (APCI): *m*/*z* 483 [M+H]$^+$ (100%).

**(1*R**,9b*R**)-7,8-Dimethoxy-1-phenoxy-9b-phenyl-1,4,5,9b-tetrahydro-2*H*-azeto[2,1-*a*]isoquinolin-2-one (4) (Method B).** To a stirred solution of 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline **1a** (2.67 g, 10 mmol) in anhydrous dichloromethane (30 mL), triethylamine (2.8 mL, 20 mmol) and phenoxyacetic acid (1.67 g, 11 mmol) were added. The solution was kept at 10-15 ºC and $POCl_3$ (0.93 mL, 10 mmol) in anhydrous dichloromethane (50 mL) was added dropwise during 3 h. The mixture was then allowed to warm up to room temperature, left overnight and next extracted with 5% $Na_2CO_3$ solution (20 mL), 5% HCl and brine (20 mL); the organic layer was dried with $Na_2SO_4$. After evaporation, the residue was taken up in diisopropyl ether, and the crystalline product was filtered off and recrystallized.

Yield 78%. The physical and spectroscopic data on the product were identical to those of the product prepared by Method A.

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## References

1. Gómez-Gallego, M.; Mancheno, M. J.; Sierre, M. A. *Tetrahedron* **2000**, *56*, 5743.
2. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.
3. Bacchi, S.; Bongini, A.; Pannuzio, M.; Villa, M. *Synlett* **1998**, 843.
4. Fülöp, F.; Bernáth, G.; Pihlaja, K. *Adv. Heterocyclic Chem.* **1998**, *69*, 349.
5. Rosenblum, S. B.; Huynh, T.; Alfonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973.
6. Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; LePlante, S. R.; Guse, I.; Ogilive, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M., Cordingley, M. G.; Déziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965.
7. Banik, B. K.; Becker, F. F. *Tetrahedron Lett.* **2000**, *41*, 6551.
8. Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron: Asymmetry* **2002**, *13*, 905.
9. Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12.
10. Banik, I.; Hackfeld, L.; Banik, B. K. *Heterocycles* **2003**, *59*, 505.
11. Fülöp, F.; Bernáth, G. *Curr. Org. Chem.* **1999**, *3*, 1.
12. Fülöp, F.; Kóbor, J.; Bernáth, G.; Sohár, P. *Bio-Organic Heterocycles* Elsevier Science Ltd., Amsterdam, 1986, p. 155.
13. Bernáth, G.; Kóbor, J.; Fülöp, F.; Sohár, P.; Argay, G.; Kálmán, A. *Tetrahedron* **1986**, *42*, 5139.
14. Bernáth, G.; Fülöp, F.; Árva, J.; Kóbor, J.; Sohár, P. *J. Heterocyclic Chem.* **1991**, *28*, 353.
15. Kóbor, J.; Fülöp, F.; Bernáth, G.; Sohár, P. *Tetrahedron* **1987**, *43*, 1887.
16. Bose, A. K.; Amin, S. G.; Kapur, J. C.; Manhas, M. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2193.
17. Fodor, L.; Szabó, J.; Sohár, P. *Tetrahedron* **1981**, *37*, 963.
18. Sohár, P.; Fodor, L.; Szabó, J.; Bernáth, G. *Tetrahedron* **1984**, *40*, 4387.
19. Allman, R.; Debaerdemaeker, T.; Kiehl, Georges; Luttringer, J-P.; Tschamber, T.; Wolff, G.; Streith, J. *Liebigs Ann. Chem.* **1983**, 1361.
20. Sharma, S. D.; Mehra, U.; Kaur, V. *Ind. J. Chem.* **1987**, *26*, 776.
21. Lal, B.; Bhedi, D. N.; Gidwani, R. M.; Sankar, C. *Tetrahedron* **1994**, *50*, 9167.
22. Hatam, M.; Köpper, S.; Martens, J. *Heterocycles* **1996**, *43*, 675.
23. The compounds studied were racemates. In Scheme 1 only one enantiomer is shown..
24. Zhao, B.-X.; Yu, Y.; Eguchi, S. *Org. Prep. Proc. Int.* **1997**, *29*, 185.
25. Golding, B. T.; Hall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1305.