EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201301378

Atropisomerism in 3,4,5-Tri-(2-methoxyphenyl)-2,6-lutidine

Piotr Roszkowski,[a] Dariusz Błachut,[b] Jan K. Maurin,[c,d] Magdalena Woźnica,[e] Jadwiga Frelek,[e] Franciszek Pluciński,[c] and Zbigniew Czarnocki*[a]

Keywords: Amines / Atropisomerism / Cross-coupling / Palladium / Circular dichroism

Suzuki reaction of tribromo-2,6-lutidine with (2-methoxyphenyl)boronic acid gave 3,4,5-tris(2-methoxyphenyl)-2,6-lutidine in the form of a mixture of three atropisomers that were stable at room temperature. Each isomer was isolated and fully characterized, including by X-ray structure determination. One of the isomers, being a racemic mixture, was separated into individual enantiomers by using semipreparative chiral HPLC. Their absolute stereochemistry was initially assigned on the basis of computational calculation of the CD spectra and finally confirmed by X-ray analysis.

Introduction

Restricted rotation about single bonds can give rise to the formation of atropisomers due to the presence of a stereogenic axis.[1] Depending on the size of the aryl substituent, such a stereogenic axis may generate conformationally mobile or conformationally stable atropisomers. Their relatively slow interconversion (by convention having a half life of more than 1000 s) allows isolation of the particular isomers,[2,3] and this phenomenon may have important implications for medicinal chemistry.[4] Many biologically active compounds exist in the form of stable atropisomers, including (–)-steganone, (+)-gossypol, and vancomycin as selected examples.[5] In general organic chemistry, atropisomeric phosphorus ligands have found widespread application in metal catalysis.[6] Among them, several effective organocatalysts bear an axially chiral BINOL scaffold.[7] In a majority of cases, atropisomerism is generated by the presence of sterically demanding substituents placed at the *ortho* position of the aryl moiety, thus causing restricted rotation around the aryl–aryl bonds. The steric hindrance introduced by the substituents together with the geometry of the planar framework of the molecule defines the conformational or configurational stability of atropisomers, which may be studied with various physical methods, including variable-temperature NMR spectroscopy,[8] other kinetic NMR methods, and dynamic GC and HPLC analysis.[9,10] The intriguing diversity and the unique structural, electronic, and photoelectronic properties of axially chiral biaryls and polyaryls of various stereochemical stability has led to their use in a variety of applications.[11] Studies on systems having parallel-stacked aryl groups has provided valuable information on intramolecular weak yet attractive π–π interactions between aromatic rings, which is of particular importance in molecular recognition, for example in biological systems.[12] An interesting example of weak alkyl–alkyl attractive interactions was also observed in stereolabile atropisomers of hindered terphenyl hydrocarbons.[13] Low-temperature NMR analysis of polyarylobenzenes and pentaarylopyridines revealed the presence of conformational stereoisomers that rapidly interconvert at room temperature.[14]

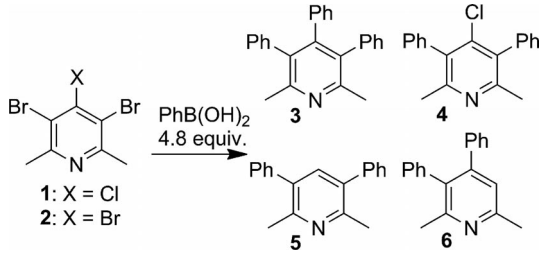
In this communication we report on the synthesis, isolation, and comprehensive characterization of stereoisomers derived from restricted rotation around the aryl–aryl bond in 3,4,5-tris(2-methoxyphenyl)-2,6-lutidine, which is a forensically relevant pyridine derivative.

Results and Discussion

In a continuation of our long-lasting study on heterocyclic impurities present in amphetamine analogues synthesized by the Leuckart method,[15–17] we needed to access a variety of 3,4,5-triaryl-2,6-dimethylpyridine derivatives. Initial screening was performed to find the optimum catalyst, solvent, and base for the cross-coupling of 3,5-dibromo-4-chloro-2,6-dimethylpyridine (**1**) and 3,4,5-tribromo-2,6-pyridine (**2**) with phenylboronic acid. Attempted synthesis of 3,4,5-triphenyl-2,6-lutidine (**3**) by the cross-coupling of **1** with a large excess of phenylboronic acid (4.8 mol) under conventional conditions {[$PdCl_2(PPh_3)_2$], Na_2CO_3, toluene/

[a] Faculty of Chemistry, University of Warsaw,
Pasteura 1, 02-093 Warsaw, Poland
E-mail: czarnoz@chem.uw.edu.pl
http://www.pchzn.chem.uw.edu.pl/
[b] Forensic Laboratory, Internal Security Agency,
1 Sierpnia 30A, 02-134 Warsaw, Poland
[c] National Medicines Institute,
Chełmska 30/34, 00-725 Warsaw, Poland
[d] National Centre for Nuclear Research,
05-400 Otwock-Świerk, Poland
[e] Institute of Organic Chemistry of the Polish Academy of Sciences,
Kasprzaka 44/52, 01-224 Warsaw, Poland
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301378.

H_2O/EtOH, 80 °C, 24 h}, gave a mixture of products, among which chlorodiphenyllutidine **4** was detected as a main component. Similar results, but with a small excess of **3**, were observed when S-Phos/$Pd(OAc)_2$ was used as catalyst. However, when 1,1′-bis(diphenylphosphino)ferrocene {$[PdCl_2(dppf)]\cdot CH_2Cl_2$} in dioxane was used in conjunction with K_3PO_4 as base (Conditions B), compound **4** was formed as a main product, with only a small amount of **3** and traces of diphenylpyridines **5** and **6** (Scheme 1, Table 1). It should be noted that cross-coupling with the 1,1′-bis(diphenylphosphino)ferrocene-based catalytic system may be useful in the construction of 3,5-diaryl(Ar^1)-4-aryl(Ar^2)-substituted 2,6-lutidines with mixed substitution pattern. The usefulness of this ligand in the regioselective arylation of polyhalogenated thiophenes,[18] pyridines,[19] quinolines,[20] isoquinolines,[21] pyrimidines,[22] and 2(1*H*)-pyrazinones[23] has already been demonstrated.



Scheme 1. The Suzuki coupling between halogenated 2,6-lutidines and phenylboronic acid.

Tribromo-2,6-lutidine **2** proved to be a much better starting material with which to complete the triphenylation reaction. Both Conditions A and C were suitable for the preparation of the desired triphenyl derivative **3**, giving 85 and 96% yield, respectively. By monitoring the course of the reaction by GC–MS analysis, it was found that full conversion of tribromo-2,6-lutidine **2** into **3** was achieved in less than 1 h.

Having established suitable conditions for the synthesis of a series of 3,4,5-triaryl-2,6-lutidines, we initially prepared 3,4,5-tris(2-methoxyphenyl)-2,6-lutidine (**7**). TLC analysis of the reaction mixture revealed the presence of three components with MS spectra identical to that of compound **7**. Careful gradient-elution column chromatography allowed the separation of individual components and an estimation of their proportion (**7a**/**7b**/**7c** = 8:42:50). Each compound was then subjected to spectral and single-crystal X-ray diffraction analysis, which proved their diastereomeric relationship (Figure 1). It should be noted that the X-ray structure of racemic compound **7b** was obtained from its hydrochloride salt (for ORTEP diagrams see the Supporting Information).

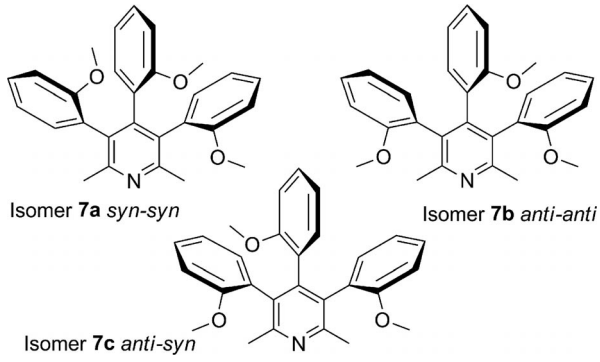


Figure 1. Structures of stereoisomers of 3,4,5-tris(2-methoxyphenyl)-2,6-lutidine (**7**) determined by X-ray analysis.

Racemic compound **7b** was then analyzed with HPLC on a chiral stationary phase, and the results indicated the presence of enantiomeric atropisomers. The circular dichroism (CD) chromatogram recorded at 245 nm exhibited two peaks with opposite sign, as expected (Figure 2a). Moreover, the full CD spectra recorded in acetonitrile for both enantiomers eluted from the HPLC column presented an excellent mirror-image relationship (Figure 2b). To establish their absolute configuration, we initially explored the possibility of resolving racemic **7b** into individual enantiomers by using chiral acids, but – despite intense experimentation – all attempts to induce preferential crystallization proved unsuccessful. Thus, the semipreparative HPLC technique was used to obtain pure enantiomers of **7b**.

Unfortunately, at this stage of research, neither the free bases nor their derivatives (salts or *N*-oxides) formed crystals that were suitable for X-ray diffraction. Therefore, their absolute stereochemistry had to be established by computational methods.

It is now commonly accepted that chiroptical methods combined with quantum chemical calculations is a very powerful approach for elucidating the stereochemistry of

Table 1. Optimization of the synthesis of triphenyllutidine **3**.

Entry	Substrate	Conditions[a]	Conversion [%]	Yield [%][b,c]			
				3	**4**	**5**	**6**
1	**1**	A	ca. 100	44	50	5	ca. 1
2	**1**	B	ca. 100	5	93	ca. 2	trace
3	**1**	C	ca. 100	48	42	9	ca. 1
4	**2**	A	ca. 100	85	–	12	3
5	**2**	B	ca. 100	67	–	26	7
6	**2**	C[d]	ca. 100	96	–	3	trace

[a] Conditions A: $[PdCl_2(PPh_3)_2]$ (8%), Na_2CO_3 (9 equiv.), toluene/H_2O/EtOH (10:2:1), 80 °C, 24 h; Conditions B: $[PdCl_2(dppf)]CH_2Cl_2$ (7%), K_3PO_4 (9 equiv.), dioxane, 90 °C, 24 h; Conditions C: $Pd(OAc)_2$ (3%), S-Phos (5%), K_3PO_4 (9 equiv.), toluene, 90 °C, 24 h. [b] Yield determined by GC–MS analysis. [c] Pyridines **3**–**6** were identified on the basis of GC–MS analysis and comparison with retention data and mass spectra recorded for the previously synthesized pure compounds.[15,16] [d] Full conversion of **2** into **3** was obtained after 1 h.

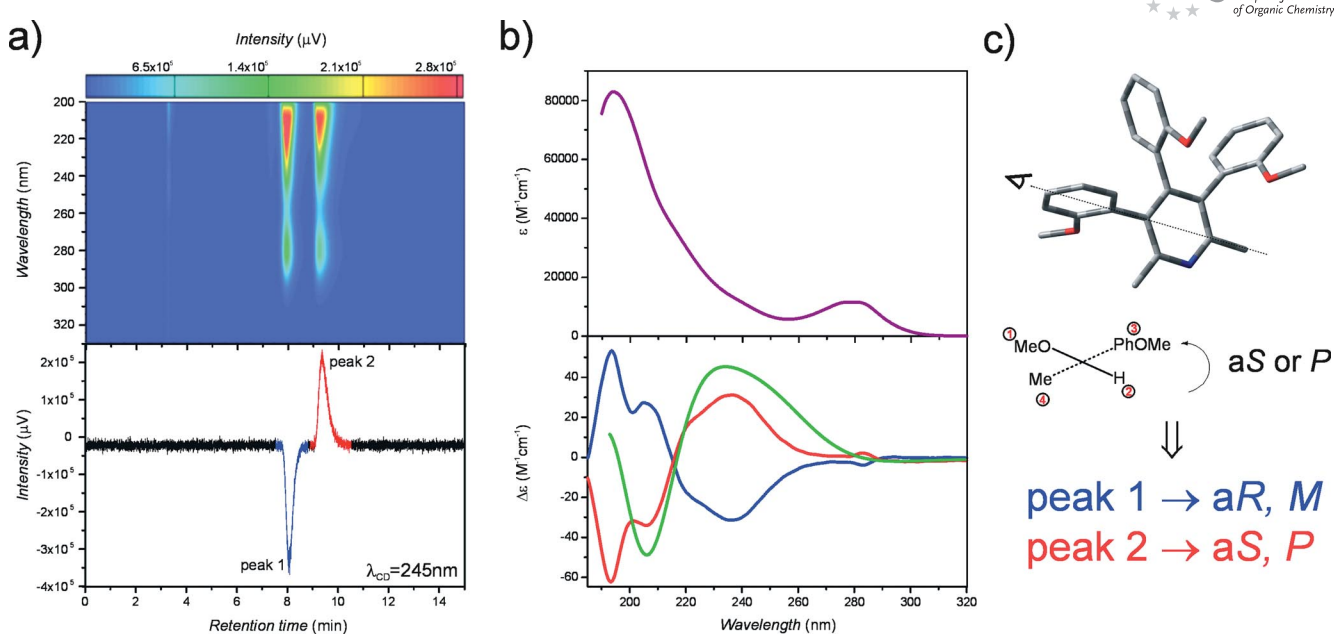


Figure 2. (a) PDA (top) and CD (bottom) chromatograms of a racemic mixture of **7b** on chiral Chiralcel OD-H column (*i*PrOH/hexane, 5:95; flow 1 mL/min). (b) UV spectrum of racemic **7b** (top) and CD spectrum of arbitrarily selected atropisomer (*P*) of **7b** calculated at the B3LYP/TZVP level of theory (green) compared to the CD spectra of Peak 1 (blue) and Peak 2 (red) recorded in acetonitrile (bottom). (c) Calculated structure of (*P*)-**7b** and absolute configuration assignment of studied atropisomers of **7b**.

chiral, nonracemic molecules with a high degree of confidence.[24–26] Because a fundamental prerequisite for the computational calculation of CD spectra is the knowledge of all CD-relevant conformers, our study started with conformational analysis by using HyperChem[27] software and the MM+ force field for an arbitrarily selected (*P*) atropisomer of **7b**. In the energy range of 6 kcal/mol, only one conformer was found, which was subsequently reoptimized by using the Gaussian program package[28] with the B3LYP hybrid functional, TZVP basis set, and the PCM solvent model for acetonitrile. The rotational strength was calculated at the same B3LYP/TZVP level of theory with the PCM solvent model. The CD spectrum was simulated by overlapping Gaussian functions for each transition by using the SpecDis program.[29] As can be seen in Figure 2b, the calculated ECD spectrum is in a good agreement with the experimental data for Peak 2. As a conclusion, the absolute configuration of Peak 1 of **7b** was assigned as (*M*), whereas Peak 2 was assigned (*P*).

Fortunately, our continuous efforts to find an appropriate solvent system for crystallization of optically pure compound **7b** eventually proved successful, and we were able to establish the absolute configuration with X-ray crystallography for both enantiomers. The results were fully consistent with those obtained by using the computational method discussed above (for ORTEP diagrams see the Supporting Information).

During the crystallization experiments with compounds **7a**–**c** we observed their slow interconversion at elevated temperature. To further explore the thermal stability of these atropisomers, we first calculated their energies by using the quantum chemical DFT (B3LYP) method with 6-31G* function basis with Spartan software.[30] For **7a**–**c** these energies were similar, having values of –856524.9, –856520.1, and –856520.4 kcal/mol, respectively. Therefore, the composition of the mixture observed during the thermal atropisomerization process is probably determined by kinetic factors. It was reasonable to assume that the conformational interconversion of atropisomers preferentially takes place in the most unstable form, **7a**, in which the rotation by 180° of the aromatic ring at position 3 or 5 in the pyridine nucleus brings about the formation of **7b**. Subsequent rotation of the opposite ring transforms **7b** into **7c**.

The energy barrier for the first rotation was initially estimated by quantum chemical methods. The rotation range was divided into ten steps and for each step the energy of the molecule was calculated after prior geometry optimization. These calculations were performed by Spartan software at the DFT B3LYP (6-31G*) level of theory. For both conformational conversions, i.e., **7a** into **7b** and **7b** into **7c**, the calculated rotation barriers were equal to 17.0 kcal/mol. The energy barriers for atropisomerization were also investigated experimentally by NMR spectroscopic analysis performed on compound **7a** in dimethyl sulfoxide (DMSO) solution at 100 °C. The resonances of the methoxy groups in compounds **7a**–**c** were observed in kinetic, time-depended ^{1}H NMR spectra (Figure 3).

From these spectra a relationship between the mole fractions of the particular isomers and the time of heating was drawn. The collected data allowed the determination of a kinetic model of the conversion of **7a** into **7b** and **7c** as consecutive, equilibrium processes and, consequently, allowed the respective rate constants and energy barriers to be calculated as $\Delta G^{\neq}_{\mathbf{7a–7b}}$ = 26.8 kcal/mol and $\Delta G^{\neq}_{\mathbf{7b–7c}}$ =

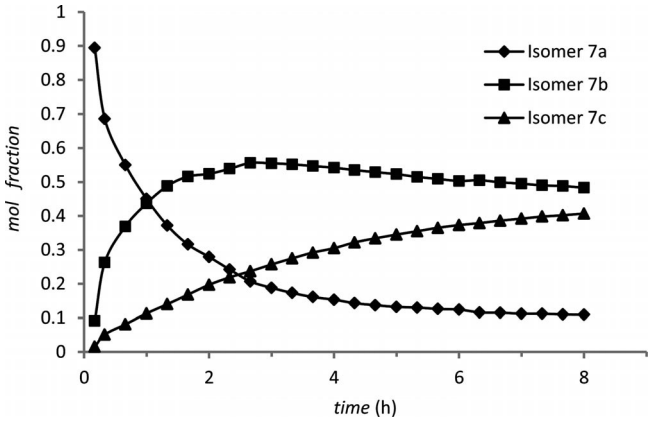


Figure 3. Graphical representation of kinetic, time-dependent ^{1}H NMR analysis of **7a** (100 °C).

27.5 kcal/mol (see the Supporting Information, which also contains VT NMR results).[31]

Conclusions

We found that the Suzuki reaction of tribromo-2,6-lutidine **2** with (2-methoxyphenyl)boronic acid gave 3,4,5-tris(2-methoxyphenyl)-2,6-lutidine in the form of a mixture of three atropisomers **7a**–**c**, which were stable at room temperature. Each isomer was isolated and fully characterized, including X-ray structure determination. Isomer **7b**, being a racemic mixture, was separated into individual enantiomers with semipreparative chiral HPLC. Their absolute stereochemistry was initially assigned on the basis of computed CD spectra and finally confirmed by X-ray analysis. Thermal interconversion of atropisomers was studied with time-dependent NMR and dynamic HPLC analyses, which were supported by quantum chemical methods. The results of the temperature-dependent product distribution may be of interest in forensic chemistry, because it allows an estimation of the "thermal history" of a seized sample.

Experimental Section

General: All reagents were purchased from commercial suppliers and used without further purification. Both 3,5-dibromo-2,6-dimethylpyrid-4-one (**2**) and 3,5-dibromo-4-chloro-2,6-dimethylpyridine (**1**) were prepared according to described methods.[15,16] The NMR spectra were recorded with a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H and at 125 MHz for ^{13}C nuclei; the spectra were measured in $CDCl_3$ or [D_6]DMSO and are given as δ values (in ppm) relative to TMS. Mass spectra were collected with Quatro LC Micromass and LCT Micromass TOF HiRes instruments. Optical rotation was measured with a Perkin–Elmer 247 MC polarimeter. Melting points were determined with a Boetius hot-plate microscope and are uncorrected. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized by using UV light or iodine vapor. Column chromatography was carried out at atmospheric pressure by using Silica Gel 60 (230–400 mesh, Merck) with mixtures of hexane/ethyl acetate as eluent. The single-crystal X-ray measurements were performed with an Oxford Diffraction Excalibur R CCD κ-axis diffractometer by using monochromatic Cu-K_α radiation. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine structures using SHELXS97 and SHELXL97 programs.[32]

3,4,5-Tribromo-2,6-dimethylpyridine (2): A mixture of 3,5-dibromo-2,6-dimethylpyrid-4-one (1.5 g, 5.3 mmol) and phosphorus tribromide (7.3 g, 25.5 mmol) was heated (oil bath) at 180 °C for 1 h. After cooling, the excess of phosphorus tribromide was destroyed by the addition of crushed ice (ca. 100 g). The resulting mixture was neutralized with solid $NaHCO_3$, extracted with dichloromethane (3× 15 mL), and the combined extracts were dried with $MgSO_4$. The organic extract was concentrated at 40 °C under a stream of dry nitrogen to give crude 3,4,5-tribromopyridine **2** (1.45 g) as yellow solid. The product was crystallized from EtOH to give **2** (1.12 g, 61%) as white crystals; m.p. 147–148 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.69 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.7, 138.6, 121.9, 26.8 ppm. HRMS (ESI): calcd. for $C_7H_7Br_3$ [M + H]$^+$ 343.8108; found 343.8105.

3,4,5-Tris(2-methoxyphenyl)-2,6-lutidine (7): According to Conditions C, a vigorously stirred mixture of 3,4,5-tribromo-2,6-dimethylpyridine (**2**; 350 mg, 1.02 mmol), (2-methoxyphenyl)boronic acid (730 mg, 4.9 mmol), $Pd(OAc)_2$ (7.5 mg, 3%mmol), S-Phos (21 mg, 5%mmol) and anhydrous K_3PO_4 (1.9 g, 9 equiv. mol) in toluene (14 mL) was heated (oil bath) at 90 °C under nitrogen for 1 h. After cooling, the solvent was evaporated under vacuum, and the residue was reconstituted with water (25 mL) and extracted with dichloromethane (2× 10 mL). The combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. Atropoisomers **7a**–**c** were isolated from the reaction mixture by gradient-elution column chromatography on silica gel (EtOAc/hexane, 0–25%). HRMS (ESI): calcd. for $C_{28}H_{28}NO_3$ [M + H]$^+$ 426.2069; found 426.2082.

(*syn*,*syn*)-3,4,5-Tris(2-methoxyphenyl)-2,6-lutidine (7a): Colorless solid; m.p. 171–173 °C. ^{1}H NMR (500 MHz, DMSO): δ = 7.12–7.08 (m, 2 H), 6.86–6.81 (m, 5 H), 6.70–6.66 (m, 3 H), 6.44–6.40 (m, 2 H), 3.54 (s, 6 H), 3.24 (s, 3 H), 2.21 (s, 6 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 156.4, 155.8, 153.7, 146.4, 131.5, 131.4, 130.3, 128.3, 127.8, 127.0, 126.6, 119.2, 118.0, 110.3, 109.2, 54.6, 54.0, 23.0 ppm.

(*anti*,*anti*)-(*aR*,*aS*)-3,4,5-Tris(2-methoxyphenyl)-2,6-lutidine (7b): Colorless solid; m.p. 164–166 °C. ^{1}H NMR (500 MHz, DMSO): δ = 7.12–7.08 (m, 2 H), 6.89–6.80 (m, 4 H), 6.70–6.60 (m, 4 H), 6.49–6.44 (m, 2 H), 3.67 (d, J = 5 Hz, 6 H), 3.32 (s, 3 H), 2.18 (d, J = 15 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 156.5, 156.2, 155.5, 153.8, 153.8, 146.4, 131.3, 130.2, 130.2, 129.9, 129.9, 128.5, 128.2, 128.1, 127.7, 127.2, 126.8, 119.8, 119.2, 118.6, 110.4, 110.2, 109.6, 55.0, 54.8, 54.4, 22.8, 22.7 ppm.

(*aR*)-7b: Colorless solid; m.p. 163–164 °C; $[a]_D^{23}$ = –72.1 (c = 1; CH_2Cl_2).

(*aS*)-7b: Colorless solid; m.p. 164–165 °C; $[a]_D^{23}$ = +71.8 (c = 1; CH_2Cl_2).

(*anti*,*syn*)-3,4,5-Tris(2-methoxyphenyl)-2,6-lutidine (7c): Colorless solid; m.p. 176–178 °C. ^{1}H NMR (500 MHz, DMSO): δ = 7.12–7.08 (m, 2 H), 6.92 (dd, J = 7.5, 2.0 Hz, 2 H), 6.85–6.73 (m, 5 H), 6.61 (dd, J = 7.5, 2.0 Hz, 1 H), 6.50–6.45 (m, 2 H), 3.61 (s, 6 H), 3.50 (s, 3 H), 2.16 (s, 6 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 156.0, 155.2, 153.6, 146.6, 130.2, 129.8, 128.6, 128.4, 128.2, 127.6, 127.3, 119.6, 118.5, 110.4, 109.4, 54.9, 54.6, 22.7 ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for all new compounds and ORTEP diagrams.

Acknowledgments

We acknowledge financial support from the National Science Center in the form of grant 2012/05/B/ST5/00713. Computing time at the Interdisciplinary Centre for Mathematical and Computational Modeling (ICM) of University of Warsaw was financed from grant G32-15. We also cordially thank Mrs. Krystyna Wojtasiewicz for her valuable technical assistance.

[1] R. Kuhn, *Moleculare Asymmetrie in Stereochemie* (Ed.: K. Frendenberg), Franz Deutike, Leipzig – Wien, **1993**, pp. 803–824.

[2] M. Oki, *Top. Stereochem.* **1983**, *14*, 1–81.

[3] G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

[4] J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem.* **2009**, *121*, 6516; *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401.

[5] P. G. Cozzi, E. Emmer, A. Gualandi, *Angew. Chem.* **2011**, *123*, 3931; *Angew. Chem. Int. Ed.* **2011**, *50*, 3847–3849.

[6] K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry, M. Yamanaka, *Synlett* **2002**, 1561–1578.

[7] a) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–898; b) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539–4549.

[8] a) D. Casarini, L. Lunazzi, A. Mazzanti, *Eur. J. Org. Chem.* **2010**, 2035–2056; b) N. Bogdan, I. Grosu, G. Benoit, L. Toupet, Y. Ramondenc, E. Condamine, I. S. Dumitrescu, G. Ple, *Org. Lett.* **2006**, *8*, 2619–2622.

[9] a) C. Wolf, *Chem. Soc. Rev.* **2005**, *34*, 595–608; b) L. D′Acqarica, F. Gasparrini, M. Pierini, C. Villani, G. Zappia, *J. Sep. Sci.* **2006**, *29*, 1508–1516; c) F. Piron, N. Vanthuyne, B. Joulin, J.-V. Naubron, C. Cismas, A. Terec, R. A. Varga, C. Roussel, J. Roncali, I. Grosu, *J. Org. Chem.* **2009**, *74*, 9062–9070.

[10] O. Trapp, G. Schoetz, V. Schurig, *Chirality* **2001**, *13*, 403–414.

[11] a) Z. Dominguez, H. Dang, M. J. Strouse, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **2002**, *124*, 7719–7727; b) L. J. Charbonniere, R. Ziessel, M. Montalti, L. Prodi, N. Zaccheroni, C. Boehme, G. Wipff, *J. Am. Chem. Soc.* **2002**, *124*, 7779–7788; c) R. Rathore, M. I. Deselnicu, C. L. Burns, *J. Am. Chem. Soc.* **2002**, *124*, 14832–14833; d) R. Noyori, *Adv. Synth. Catal.* **2003**, *345*, 15–32; e) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155–3212; f) K. Aikawa, K. Mikami, *Angew. Chem.* **2003**, *115*, 5616; *Angew. Chem. Int. Ed.* **2003**, *42*, 5458–5461; g) J. Clayden, A. Lund, L. Vallverdu, M. Helliwell, *Nature* **2004**, *431*, 966–971; h) M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3019; *Angew. Chem. Int. Ed.* **2005**, *44*, 2959–2962; i) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269–279; j) G. Bringmann, H. Scharl, K. Maksimenka, K. Radacki, H. Braunschweig, P. Wich, C. Schmuck, *Eur. J. Org. Chem.* **2006**, 4349–4361; k) E. M. Obrien, B. J. Morgan, M. C. Kozlowski, *Angew. Chem.* **2008**, *120*, 6983; *Angew. Chem. Int. Ed.* **2008**, *47*, 6877–6880.

[12] E. Masashi, K. Yamaguchi, I. Shinohara, F. Ito, Y. Yoshitake, K. Harano, *Tetrahedron* **2010**, *66*, 898–903.

[13] L. Lunazzi, A. Mazzanti, M. Minzoni, J. E. Anderson, *Org. Lett.* **2005**, *7*, 1291–1294.

[14] a) D. Gust, M. W. Fagan, *J. Org. Chem.* **1980**, *45*, 2511–2512; b) A. Patton, J. Wang Dirks, D. Gust, *J. Org. Chem.* **1979**, *44*, 4749–4752.

[15] D. Błachut, K. Wojtasiewicz, Z. Czarnocki, *Forensic Sci. Int.* **2005**, *152*, 157–173.

[16] D. Błachut, Z. Czarnocki, K. Wojtasiewicz, *Synthesis* **2006**, 2855–2864.

[17] D. Błachut, J. Szawkało, Z. Czarnocki, *Synthesis* **2011**, 3496–3506.

[18] W. F. Fobare, W. R. Solvibile, A. J. Robichaud, M. S. Malamas, E. Manas, J. Turner, Y. Hu, E. Wagner, R. Chopra, R. Cowling, G. Jin, J. Bard, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5353–5356.

[19] a) J. Liu, T. Jan, L. Guo, T. Atanasova, R. P. Nargund, *Tetrahedron Lett.* **2009**, *50*, 5228–5230; b) W. P. Blackaby, J. R. Atack, F. Bromidge, J. L. Castro, S. C. Goodacre, D. J. Hallett, R. T. Lewis, G. R. Marshall, A. Pike, A. J. Smith, L. J. Street, D. F. D. Tattersall, K. A. Wafford, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1175–1179.

[20] a) A. V. Tsvetkov, G. V. Latyshev, N. V. Lukashev, I. P. Beletskaya, *Tetrahedron Lett.* **2002**, *43*, 7267–7270; b) M. B. Nolt, Z. Zhao, S. E. Wolkenberg, *Tetrahedron Lett.* **2008**, *49*, 3137–3141.

[21] H. Yang, *Tetrahedron Lett.* **2009**, *50*, 3081–3083.

[22] a) G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424–8429; b) S. C. Ceide, A. G. Montalban, *Tetrahedron Lett.* **2006**, *47*, 4415–4418.

[23] R. Azzam, W. M. De Borggraeve, F. Compernelle, G. J. Hoonaert, *Tetrahedron* **2005**, *61*, 3953–3962.

[24] N. Berova, L. Di Bari, G. Pescitelli, *Chem. Soc. Rev.* **2007**, *36*, 914–931.

[25] G. Bringmann, T. Bruhn, K. Maksimenka, Y. Hemberger, *Eur. J. Org. Chem.* **2009**, 2717–2727.

[26] J. Autschbach, *Chirality* **2009**, *21*, E116–E152.

[27] *HyperChem(TM) Professional 8.0*, Hypercube, Inc., Gainesville, FL.

[28] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery *Jr,* J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, Revision B.01, Gaussian, Inc., Wallingford, CT, **2010**.

[29] T. Bruhn, A. Schaumlöffel, Y. Hemberger, G. Bringmann, *SpecDis version 1.60*, University of Würzburg, Germany, **2012**.

[30] *Spartan ’08 software*, Wavefunction, Inc., Irvine, USA, **2008**.

[31] M. W. Ghosn, C. Wolf, *J. Org. Chem.* **2011**, *76*, 3888–3897.

[32] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.

Received: September 11, 2013
Published Online: November 12, 2013

