The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2021**, part ii, 0-0

to be inserted by editorial office

Synthesis of terminal alkynes based on (1*S*,3*R*,4*R*)- and (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane

Franz Steppeler,[a] Marcin Górecki,[b] and Elżbieta Wojaczyńska*[a]

[a]*Faculty of Chemistry, Wrocław University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50 370 Wrocław, Poland*

[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka St. 44/52, 01 224 Warsaw, Poland*

Email: elzbieta.wojaczynska@pwr.edu.pl

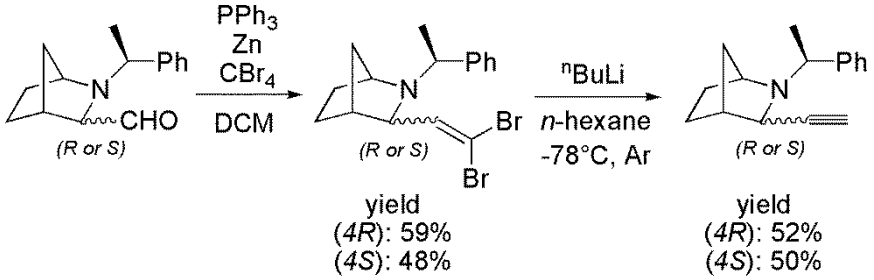
Dedicated to Professor Zbigniew Czarnocki

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

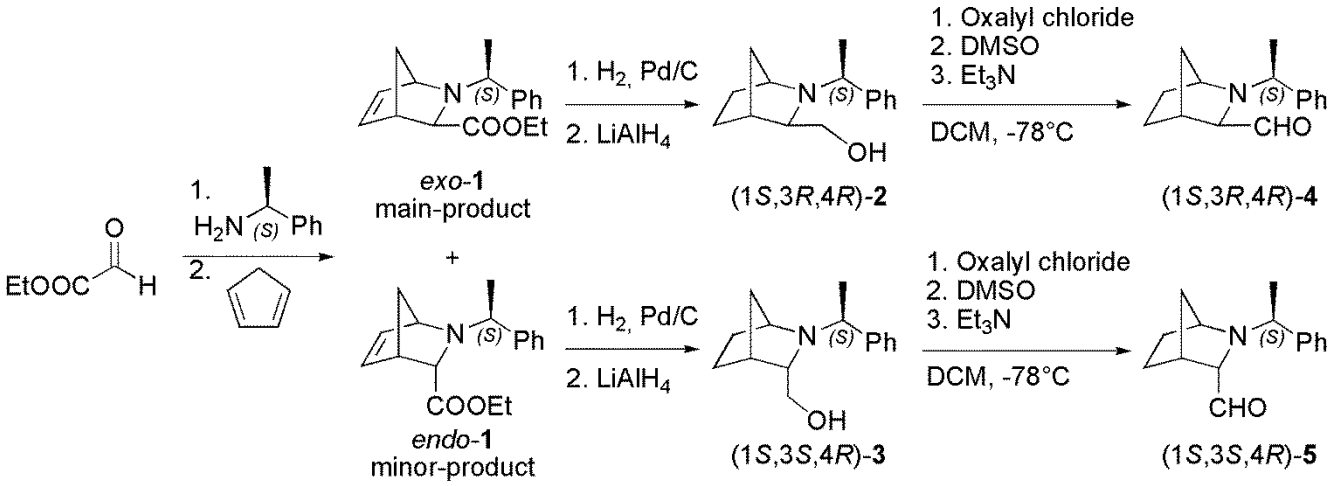
Two approaches to terminal alkynes based on the enantiomerically pure epimers (1*S*,3*R*,4*R*)- and (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane aldehydes were established: i) a non-Wittig route through a dichloroalkene intermediate; and, ii) a Corey-Fuchs approach via dibromoalkene. Among various organometallic reagents tested, the use of *n*-butyllithium was efficient. The resulting alkynes were fully characterized, and one epimer was used in a click chemistry triazole synthesis. For one of the products containing a bulky *N*-Boc-proline substituent, the existence of atropisomers was observed. The absolute stereochemistry was determined by electronic circular dichroism spectroscopy (ECD) and optical rotation supported by quantum chemical simulations.



Keywords: Alkyne, 2-azabicycloalkanes, chiroptical methods, Corey-Fuchs synthesis, CuAAC

Introduction

Nitrogen-containing heterocycles exhibit a broad spectrum of biological activities. 2-Azabicycloalkanes have various applications as rigid analogues of piperidine alkaloids, prolines, azepanes and precursors of chiral substituted cyclopentanes.[1] Over the past decades, continuous progress has been made in the exploration of intrinsically chiral 2-azanorbornane (2-azabicyclo[2.2.1]heptane) scaffold. A convenient method for its synthesis in enantiomerically pure form was first described by the three groups of Stella,[2,3] Bailey[4] and Waldmann[5] in 1990/1991 using chiral imines, and later preparations on gram or even kilogram scale were reported.[6,7] Two products, the major *exo*-**1** and minor *endo*-**1** epimers can be separated, and epimeric enantiopure alcohols, (1*S*,3*R*,4*R*)-**2** and (1*S*,3*S*,4*R*)-**3**, can be obtained in a two-step synthesis from the Diels-Alder cycloadducts (Scheme 1).[8,9] These derivatives have been often used as convenient starting materials for further preparations. In particular, Swern oxidation of alcohols leads to the corresponding aldehydes (1*S*,3*R*,4*R*)-**4** and (1*S*,3*S*,4*R*)-**5**.[10]



Scheme 1. Diels-Alder reaction and modification of 2-azabicycloalkane scaffold.

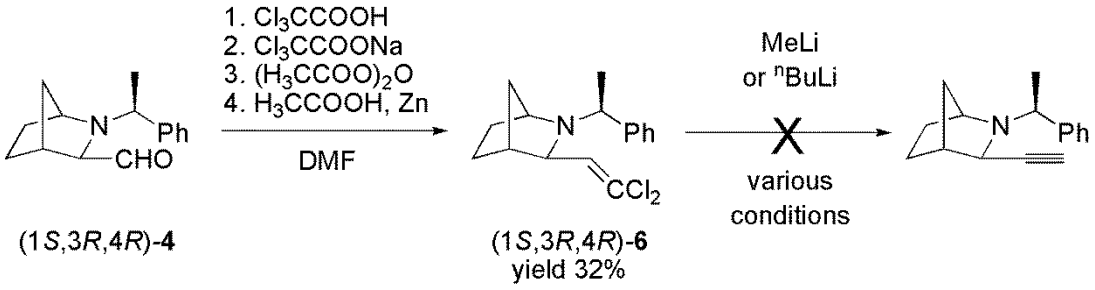
Herein, we focus on the preparation of terminal alkynes based on 2-azanorbornane scaffold using two approaches, non-Wittig and Wittig-type Corey-Fuchs syntheses. The application of the prepared enantiopure compound in a CuAAC click reaction will also be presented.

Results and Discussion

To further explore 2-azanorbornanes in click reactions, we decided to investigate two possible methods of introducing terminal alkyne function into this chiral scaffold. Epimeric enantiopure aldehydes, (1*S*,3*R*,4*R*)-**4** and (1*S*,3*S*,4*R*)-**5**, were chosen as precursors in these preparations. The two tested strategies rely on the formation of dihaloalkene intermediates which were supposed to undergo elimination with strong bases, such as organolithium compounds.

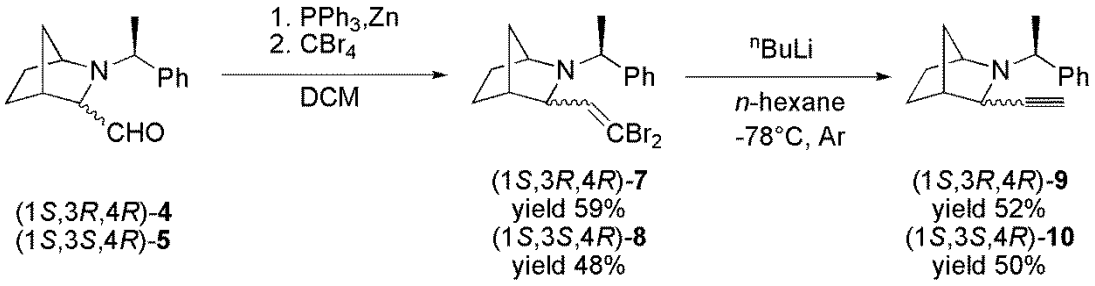
Firstly, we attempted a non-Wittig approach (Scheme 2), using trichloroacetic acid and sodium trichloroacetate as sources of halogen atoms. The advantage of this route lies in the fact that the reaction is carried out without phosphorous derivatives offering lower toxicity of the reaction mixture and of impurities as compared to Wittig-type reactions.[11,12] The reaction of aldehyde **4** gave the dichloroalkene (1*S*,3*R*,4*R*)-**6** in a

moderate yield (32%) (Scheme 2). In the next step, the dichloroalkene **6** was subjected to elimination conditions. Several organolithium bases and conditions were tried, including the recommended methyllithium or *n*-butyllithium and temperatures in the range between -78°C and room temperature, as well as different reaction times. However, all attempts failed and the desired alkyne was not formed and the substrate could be recovered.



Scheme 2. Non-Wittig synthesis of dichloroalkene and unsuccessful synthesis of alkyne.

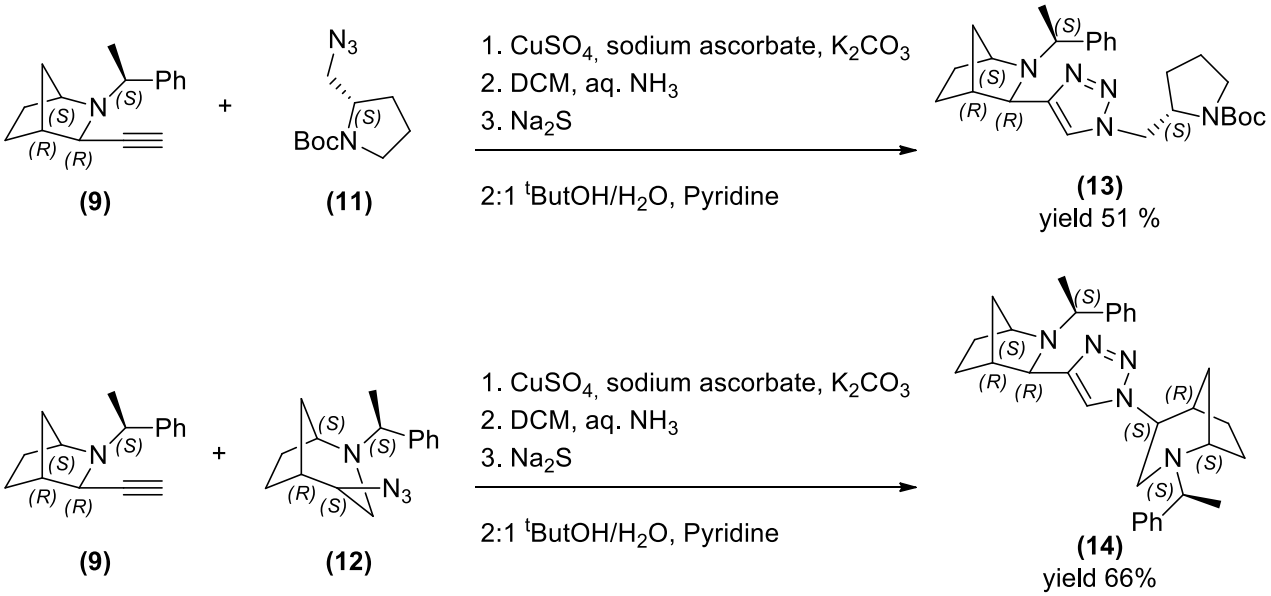
As we thought that dibromoalkenes should be more reactive, in our second approach a Wittig-type Corey-Fuchs reaction pathway was attempted with triphenylphosphine and CBr_4 as a source of bromine atoms (Scheme 3). In our hands, this protocol resulted in higher outcomes of the intermediate dibromoalkenes (1*S*,3*R*,4*R*)-**7** (59%) and (1*S*,3*S*,4*R*)-**8** (48%) which were isolated and characterized. Moreover, we also succeeded in the subsequent elimination performed at -78 °C in *n*-hexane with the *n*-butyllithium as base. Enantiopure terminal alkynes (1*S*,3*R*,4*R*)-**9** and (1*S*,3*S*,4*R*)-**10** were isolated in moderate yield (52 and 50%, respectively).



Scheme 3. Wittig-type (Corey-Fuchs) synthesis of dibromoalkenes **7**, **8** and elimination to terminal alkynes **9**, **10**.

The alkyne (1*S*,3*R*,4*R*)-**9** was used in two CuAAC click-reactions[13,14] with azide compounds, (*S*)-*tert*-butyl 2-(azidomethyl)pyrrolidine-1-carboxylate **11**[15] and another 2-azabicycloalkane derivative formerly obtained in our laboratory, (1*S*,4*S*,5*R*)-4-azido-2-[(*S*)-1-phenylethyl]-2-azabicyclo[3.2.1]octane **12**.[16] The applied CuAAC-conditions were formerly used for click reactions of bicyclic *Cinchona* alkaloids.[17,18] The reactions proceeded smoothly leading exclusively to 1,4-disubstituted 1,2,3-triazoles **13** (51%) and **14** (66%), with the full retention of configurations of all stereocenters (Scheme 4). However, it has to be mentioned, that triazole **13** exists as an equilibrium mixture of two atropisomers in ca. 2:1 ratio, originating from the *tert*-butyloxycarbonyl protecting group at the amine. It is manifested by doubling all resonances in ^{13}C NMR spectrum measured at 298 K, and a broadening of ^{1}H NMR peaks at this temperature. Lowering the temperature resulted in slowing down the exchange and sharpening the resonances (see Supporting Information). The mixture could not be

resolved by chromatography under the conditions tested. The atropisomerism arises from the hindered rotation around the bond connecting the five-membered ring.



Scheme 4. CuAAC reactions of alkyne (1*S*,3*R*,4*R*)-(**9**) with two selected azides.

Attempts to grow crystals suitable for the X-ray measurement of compound **13** were partially successful. From the platelets received, only a model of structure was obtained with a R parameter of 24%. However, the model supported our configuration assignments (Supporting Information, Figure S19). To further confirm the absolute stereochemistry of compound **13** we used chiroptical methods. The absolute configuration was determined by carrying out the experimental study (electronic circular dichroism spectroscopy and optical rotation) supported by quantum chemical simulations. Such approach in stereochemical analysis of chiral compounds has been already recognized to be substantially useful, effective, and steadfast for various chiral molecules, and in many cases it is the complementary part of spectral analysis.[19–25]

In **Figure 1** the measured ECD/UV spectra of compound **13** in hexane solution are presented (black line). As can be seen, in the measurement range there are two ECD bands: a minimum at 215 nm, maximum with well-developed fine structure centered at 262 nm, and one shoulder at *ca.* 227 nm.

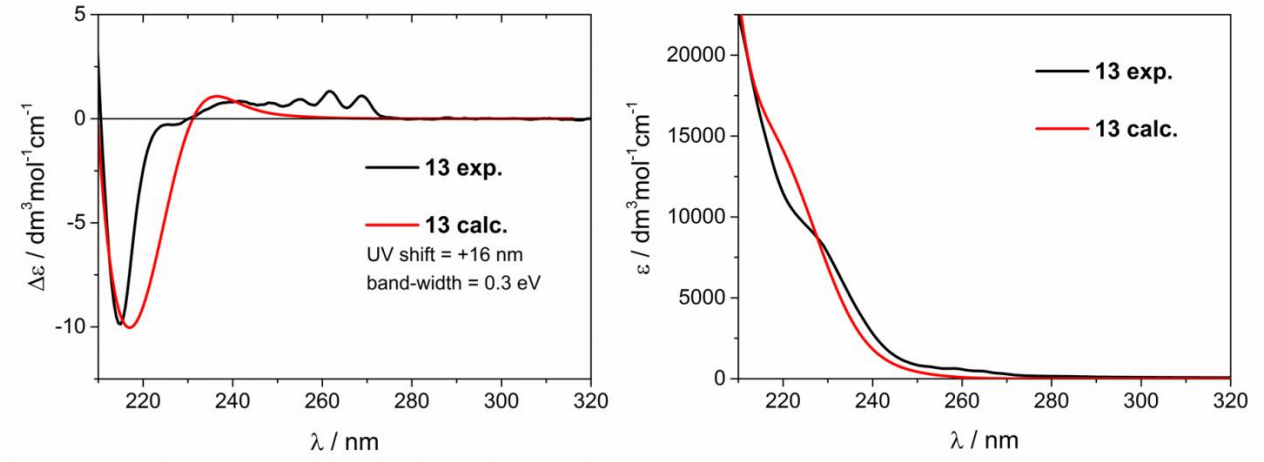


Figure 1. Experimental ECD (left) and UV (right) spectra of compound **13** recorded in hexane at room temperature (black lines) confronted with TDDFT simulations performed at the CAM-B3LYP/def2-TZVP level of theory (red lines). Enantiomeric Similarity Index for calculated curve equals 0.875.

TD-DFT simulations of ECD spectra were preceded by a thorough conformational analysis at the molecular mechanic level and further re-optimization of the subsequent structures at the DFT level (see experimental part for details). Finally, 6 conformers within the range of 1.5 kcal/mol were identified. The 3 most abundant ones cover more than *ca.* 83% of all conformers in solution equilibrium (Figure 2). They show variations both in conformation of the pyrrolidine ring (**Conf. 13a** *vs.* **Conf. 13b**) and in arrangement of the triazole moiety (conf. **13a/13b** vs. conf. **13c**).

As can be seen in Figure 1, the calculated ECD/UV spectra are in good agreement with the experimental ones. However, some incompatibility is visible in the range of 245-275 nm. This is owed to the nature of ^1L_b aromatic band which makes TD-DFT calculations problematic without considering vibronic effects.[26]

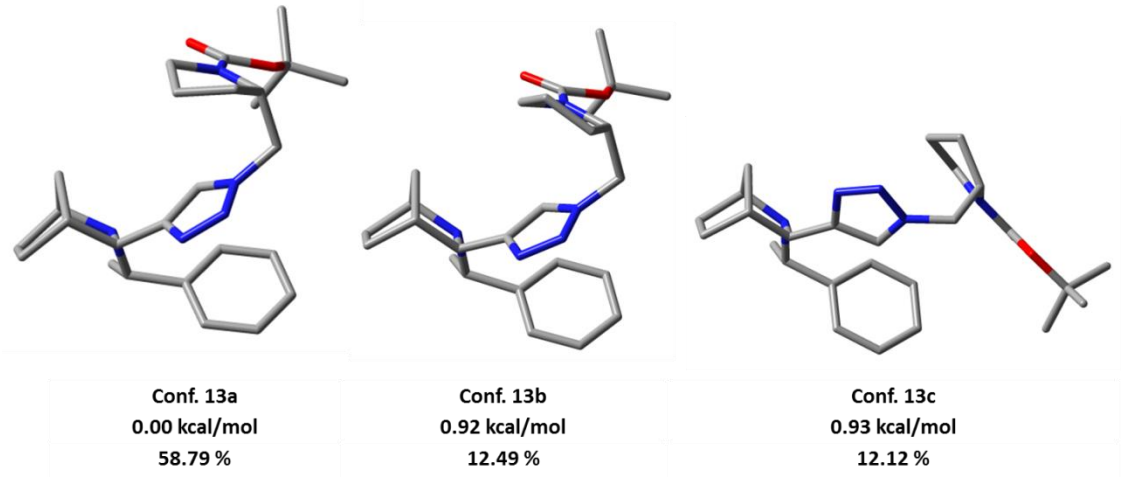


Figure 2. Structures of most abundant conformers of compound **13** (conf. **13a–13c**) calculated at the ωB97X-D/6-311+G(d,p) level of theory with their relative energy (given in kcal/mol) and populations in equlibrium calculated at 298 K. Hydrogen atoms are omitted for clarity.

To independently confirm a conformational equilibrium, TD-DFT calculations of optical rotation ($[\alpha]_D$) at the wavelength of 589 nm were carried out for the same set of conformers. Such complementary approach[27] is considered as a good practice in assigning the absolute configuration, in particular for floppy molecules.[21,28] As can be seen in Table 1, the simulated $[\alpha]_D$ shows the same sign as the experimental data, regardless of the functionals and basis sets used (B3LYP *vs.* CAM-B3LYP or aug-cc-pVDZ *vs.* def2-TZVP).

Table 1. Experimental $[\alpha]_D$ value for compound **13** recorded in CH_2Cl_2 (c = 0.23 g/100 cm^3) at 298 K and simulated ones.

$[\alpha]_D$ /deg cm^2 g^{-1}				
Experiment in CH_2Cl_2	TD-DFT Boltzmann-weighted value			
	CAM-B3LYP/aug-cc-pVDZ/PCM(CH_2Cl_2)	CAM-B3LYP/def2-TZVP/PCM(CH_2Cl_2)	B3LYP/aug-cc-pVDZ /PCM for CH_2Cl_2	B3LYP/def2-TZVP/PCM(CH_2Cl_2)
+45	+27	+23	+29	+25

Furthermore, we noticed that for conformers **13a** and **13b** the sign of $[\alpha]_D$ is positive (very close to the experimental value and does not depend on the level of theory used), while for **13c** its value is always negative (Supplementary Information, Table S1).

Calculations were also performed for the epimer of compound **13** (***epi*-13**) differing by the configuration at C-3 (Supplementary Information, Fig. S21, Tables S2-S4). The obtained results showed, however, that the calculated sign of $[\alpha]_D$ is opposite to the experimental one (negative), and calculated ECD spectrum exhibits lower factor of enantiomeric similarity index (ESI) determined by SpecDis (Δ=0.845), in respect to compound **13** for which this factor equals 0.875.[29]

To sum up, such analysis supports an aforementioned configurational assignment, regardless the amplitude of the $[\alpha]_D$. Another important point to note is that in the equilibrium one can distinguish two main atropisomers divided by different arrangement of the substituted triazole group (Figure 2), namely conformers **13a**/**13b** and conformer **13c**. The calculated energy barrier at the B3LYP/6-311+G(d,p) level of theory for the transformation from one into another, *i.e.* by rotating around C3-triazole bond amounts 6.4 kcal/mol.

Conclusions

A route towards terminal alkynes based on the intrinsically chiral 2-azanorbornane scaffold was developed. From the two proposed routes, the one proceeding via dibromoalkenes yielded two epimeric enantiomerically pure terminal alkynes. Alkyne (1*S*,3*R*,4*R*)-**6** was successfully applied in two CuAAC click-chemistry reactions. This result, together with the possible use of 2-azabicyloalkane-derived azides (*e.g.* **12**) opens the route to a variety of 1,2,3-triazoles based on an intrinsically chiral bicyclic backbone. The results of combined experimental and theoretical analysis of chiroptical data of compound **13** allowed the effective assignment of its three-dimensional structure.

Experimental Section

General. Preparative methods. For the chromatographic separation silica gel 60 (70-230 mesh) was used, and thin layer chromatography was carried out on silica gel 60 precoated plates. Analytical measurements. The NMR spectra were recorded on Jeol 400yh and Bruker Avance II 600 instruments. The measurements were conducted at 298 K. The spectra were calibrated using residual solvent signals. Infrared spectra in the range of 500 – 4000 cm^{-1} were recorded using a Perkin Elmer 2000 FTIR spectrophotometer. High resolution mass spectra were collected using a Waters LCT Premier XE TOF instrument with electrospray ionization. Melting points were determined on the Schmelzpunkt Bestimmer Apotec apparatus using the standard open capillary. The optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ECD spectra measurement was carried out using a Jasco J-815 spectrometer (Tokyo, Japan) at room temperature using spectroscopic grade hexane in quartz cells (0.0033 mol/dm^3) with a path length of 0.1 and 0.02 cm. ECD spectra were measured using a scanning speed of 100 nm/min, a step size of 0.2 nm, a band-width of 1 nm, a response time of 0.5 seconds, and an accumulation of 5 scans. The spectra were background-corrected using solvent recorded under the same conditions.

CCDC-2020530 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Aldehydes **4** and **5** were synthesized using the formerly described method.[10] Azide **12** was prepared as described previously.[16]

(1*S*,3*R*,4*R*)-3-(2,2-Dichlorovinyl)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (6). To a solution of aldehyde **4** (1.295 g, 5.65 mmol) and trichloroacetic acid (1.41 g, 8.6 mmol) in DMF (37 mL) stirred at room temperature, sodium trichloroacetate (1.57 g, 8.5 mmol) was added portionwise. After 2 h when the CO_2 evolution was finished, the solution was cooled to 0 °C and acetic anhydride (1.07 mL, 11.3 mmol) was added dropwise. The reaction mixture was stirred for 1 h to reach room temperature. Then, concentrated acetic acid (5.3 mL) and zinc powder (0.80 g, 12.2 mmol) were added. The reaction mixture was stirred at 60 °C overnight. After cooling to room temperature, the reaction mixture was extracted with *n*-hexane, washed with water and the crude product was recrystallized to give the *title compound* **6** as colorless needles (421 mg, 27%). Mp 129-135 °C (*n*-hexane/EtOAc), $[\alpha]_D^{25}$= -12.5 (*c* 0.48, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (d, 3H, *J* 6.5 Hz), 1.31-1.41 (m, 3H), 1.56-1.66 (m, 1H), 1.71 (dt, 1H, *J* 9.7, 1.8 Hz), 1.93-2.00 (m, 1H), 2.04-2.07 (m, 1H), 2.70 (d, 1H, *J* 8.3 Hz), 3.50 (q, 1H, *J* 6.5 Hz), 3.64 (s, 1H), 5.41 (d, 1H, *J* 8.3 Hz), 7.17-7.24 (m, 2H), 7.26-7.28 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 23.2, 29.4, 36.2, 43.8, 58.5, 60.9, 68.1, 117.1, 127.3, 128.0, 128.1, 135.0, 145.1. IR (KBr): 545, 660, 697, 760, 835, 884, 955, 1080, 1099, 1164, 1188, 1311, 1365, 1445, 1455, 1490, 1613, 2876, 2959, 3065 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{16}H_{20}NCl_2)^+$ 296.0973; found 296.0970.

(1*S*,3*R*,4*R*)-3-(2,2-Dibromovinyl)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (7). To a stirred solution of zinc (1.18 g, 18.0 mmol) in dry DCM (50 mL) under argon atmosphere triphenylphosphine (4.70 g, 17.9 mmol) was added in one portion. The reaction mixture was cooled to 0 °C using an ice bath and a solution of carbon tetrabromide (3.18 g, 9.6 mmol) in DCM (7 mL) was introduced dropwise. To this reaction mixture a solution of aldehyde **4** (1.02 g, 4.5 mmol) in DCM (10 mL) was then added dropwise and the mixture was left to reach room temperature and stirred for 21 h. The solution was extracted with DCM (3×), washed with brine and the combined organic phases were dried ($MgSO_4$). The crude product obtained after removal of solvent was chromatographed on silica (*n*-hexane/EtOAc, 5:1 v/v) to give the *title compound* **7** as red crystals (1.00 g, 58%). Mp 133-138 °C (*n*-hexane/EtOAc), $[\alpha]_D^{25}$= +7.7 (*c* 0.52, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (d, 3H, *J* 6.5 Hz), 1.35-1.44 (m, 3H), 1.63-1.69 (m, 1H), 1.76 (dt, 1H, *J* 9.7, 1.8 Hz), 1.98-2.04 (m, 1H), 2.11-2.13 (m, 1H), 2.65 (d, 1H, *J* 7.9 Hz), 3.55 (q, 1H, *J* 6.5 Hz), 3.69 (s, 1H), 5.99 (d, 1H, *J* 7.9 Hz), 7.24-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 23.0, 29.4, 36.2, 43.6, 58.4, 60.8, 71.0, 85.4, 127.3, 128.0, 128.1, 143.5, 145.0. IR (KBr): 546, 697, 746, 857, 942, 1079, 1094, 1162, 1188, 1310, 1364, 1453, 1490, 1604, 2870, 2968, 3024, 3064 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{16}H_{20}NBr_2)^+$ 383.9962; found 383.9960.

(1*S*,3*S*,4*R*)-3-(2,2-Dibromovinyl)-2-[(S)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (8). To a stirred solution of zinc (0.89 g, 13.6 mmol) in dry DCM (30 mL) under argon atmosphere triphenylphosphine (3.55 g, 13.6 mmol) was added in one portion. The reaction mixture was cooled to 0 °C using an ice bath and then a solution of carbon tetrabromide (2.28 g, 6.8 mmol) in DCM (5 mL) was added dropwise. Aldehyde **4** (780 mg, 3.4 mmol) in DCM (10 mL) was then added dropwise and the reaction mixture was left to reach room temperature and stirred for 21 h. The solution was extracted with DCM (3×), washed with brine and the combined organic phases were dried ($MgSO_4$). The crude product obtained after removal of solvent was chromatographed on silica (*n*-hexane/EtOAc, 5:1 v/v) to give the *title compound* **8** as a solidifying red oil (632 mg, 48%). $[\alpha]_D^{25}$= +5.4 (c=0.61, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05-1.11 (m, 1H), 1.13 (d, 1H, *J* 9.4 Hz), 1.23 (d, 3H, *J* 6.5 Hz), 1.35-1.42 (m, 1H), 1.57 (tt, 1H, *J* 12.3, 4.4 Hz), 1.68 (dt, 1H, *J* 9.6, 1.9 Hz), 1.80-1.89 (m, 1H), 2.24-2.28 (m, 1H), 2.89 (d, 1H, *J* 7.6 Hz), 2.98 (s, 1H), 3.61 (q, 1H, *J* 6.4 Hz), 6.6 (d, 1H, *J* 7.6 Hz), 7.18-7.24 (m, 1H), 7.26-7.33 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.5, 24.5, 29.4, 36.3, 44.5, 59.1, 60.1, 69.8, 85.4, 126.6, 127.4, 128.4, 144.9,

145.9. IR (KBr): 541, 703, 747, 757, 770, 791, 858, 954, 1016, 1079, 1162, 1191, 1304, 1453, 1491, 1604, 2870, 2963, 3027, 3063 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{16}H_{20}NBr_2)^+$ 383.9962; found 383.9965.

(1*S*,3*R*,4*R*)-3-Ethynyl-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (9). To a mechanically stirred solution of dibromoalkene **7** (1.00 g, 3.5 mmol) in *n*-hexane (90 mL) at -78 °C a 2.5-M solution of *n*-buthyllithium in *n*-hexane (3.5 mL, 8.8 mmol) was added. After 3.5 hours the cooling bath was removed and the reaction mixture was allowed to reach 0 °C. The reaction mixture was extracted with *n*-hexane, washed with water and the combined organic layers were dried ($MgSO_4$). The solvent was removed and the crude product was chromatographed on silica (*n*-hexane/EtOAc, 90:10 v/v) to give the *title compound* **9** as a colorless oil (413 mg, 52%). $[\alpha]_D^{25}$= +7.0 (c 1.06, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23-1.29 (m, 1H), 1.31 (d, 3H, *J* 6.5 Hz), 1.33-1.41 (m, 2H), 1.58-1.66 (m, 1H), 1.87 (d, 1H, *J* 2.0 Hz), 1.94-2.01 (m, 1H), 2.07 (dt, 1H, *J* 9.8, 1.9 Hz), 2.30-2.33 (m, 1H), 2.66 (s, 1H), 3.48 (q, 1H, *J* 6.5 Hz), 3.67 (s, 1H), 7.20-7.29 (m, 3H), 7.39-7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.7, 23.3, 28.3, 36.8, 45.2, 58.5, 59.2, 61.7, 68.9, 86.8, 127.2, 128.0, 128.5, 144.8. IR (film): 630, 699, 760, 830, 1024, 1058, 1164, 1303, 1370, 1454, 1493, 2871, 2972, 3307 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{16}H_{20}N)^+$ 226.1596; found 226.1595.

(1*S*,3*S*,4*R*)-3-Ethynyl-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane (10). To a mechanically stirred solution of dibromoalkene **7** (558 mg, 2 mmol) in *n*-hexane (60 mL) at -78 °C, a 2.5 M solution of *n*-buthyllithium in *n*-hexane (2.5 mL, 5 mmol) was added. After 3 hours the cooling bath was removed and the reaction mixture was allowed to reach 0 °C. The reaction mixture was extracted with *n*-hexane, washed with water and the combined organic layers were dried ($MgSO_4$). The solvent was removed and the crude product was chromatographed on silica (*n*-hexane/EtOAc, 90:10 v/v) to give the *title compound* **10** as a yellowish solid (220 mg, (50%). mp 72-75 °C (*n*-hexane/EtOAc), $[\alpha]_D^{25}$= +5.6 (c 1.04, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08 (tdd, 1H, *J* 12.7, 4.7, 2.7 Hz), 1.20 (d, 1H, *J* 9.1 Hz), 1.25-1.33 (m, 1H), 1.43 (d, 3H, *J* 6.4 Hz), 1.55 (tt, 1H, *J* 12.4, 4.4 Hz), 1.75-1.85 (m, 1H), 1.95 (dt, 1H, *J* 9.5, 1.9 Hz), 2.31 (d, 1H, *J* 2.1 Hz), 2.44-2.47 (m, 1H), 2.86 (d, 1H, *J* 1.9 Hz), 3.02 (s, 1H), 3.56 (q, 1H, *J* 6.4 Hz), 7.18-7.23 (m, 1H), 7.26-7.31 (m, 2H), 7.34-7.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 24.7, 28.8, 36.8, 45.7, 58.4, 58.9, 61.3, 69.5, 88.1, 126.9, 127.6, 128.3, 145.4. IR (film): 701, 766, 828, 1028, 1079, 1114, 1162, 1304, 1373, 1453, 1491, 2871, 2972, 3307 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{16}H_{20}N)^+$ 226.1596; found 226.1589.

(2*S*)-*tert*-Butyl 2-[(4-{(1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-3-yl}-1*H*-1,2,3-triazol-1-yl)-methyl]pyrrolidine-1-carboxylate (13). To a stirred solution of alkyne **9** (0.11 g, 0.5 mmol) and azide **11** (0.11 g, 0.5 mmol) in *t*-butanol (2 mL) and water (1 mL), copper(II) sulfate pentahydrate (0.03 g, 0.1 mmol), sodium ascorbate (0.05 g, 0.25 mmol) and anhydrous potassium carbonate (0.06 g, 0.4 mmol) were subsequently added. After stirring for 3 days at room temperature, DCM (2.5 mL) and aqueous 30% NH_3 (0.25 mL) were added to the reaction mixture. The solution was stirred overnight, and then copper was precipitated using sodium sulfide nonahydrate (0.1 mL) and filtered through a pad of celite. The solvent was removed and the crude product purified using column chromatography on silica gel (*n*-hexane/EtOAc, 75:25 v/v) to give the *title compound* **13** as a yellow solid (115 mg, 51%). Mp 134-135 °C (*n*-hexane/Et_2O), $[\alpha]_D^{25}$= +44.8 (*c* 0.23, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 600 MHz, 283 K): δ 1.26 (dd, 1H, *J* 25.4, 9.6 Hz), 1.35 (dd, 3H, *J* 17.0, 6.5 Hz), 1.39-1.51 (m, 3H), 1.54 (d, 9H, *J* 22.9 Hz), 1.61-1.75 (m, 5H), 1.79-1.91 (m, 1H), 2.01-2.08 (m, 1H), 2.23 (dd, 1H, *J* 48.2 Hz, 3.3 Hz), 3.08-3.34 (m, 2H), 3.32 (d, 1H, *J* 12.9 Hz), 3.55 (q, 1H, *J* 6.5 Hz), 3.71 (d, 1H, *J* 24.1 Hz), 3.78-3.92 (m, 1H), 3.03-3.33 (m, 2H), 6.97-7.05 (m, 3H), 7.15-7.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz, 283 K): δ 22.3, 22.4, 22.5, 22.6, 23.3, 28.0, 28.6, 28.6, 28.7, 28.9, 29.1, 35.1, 35.5, 44.9, 45.1, 46.7, 47.0, 50.7, 51.8, 57.2, 57.2, 58.5, 58.7, 61.2, 61.3, 65.1, 65.2, 79.9, 80.2, 121.7, 122.6, 126.8, 127.6, 127.6, 128.4, 128.5, 145.0, 145.4, 153.5, 153.9, 154.2,

154.7. IR (KBr): 545, 699, 762, 1051, 1118, 1174, 1365, 1397, 1455, 1697, 2770, 2869, 2931, 1968, 3426 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{26}H_{38}N_5O_2)^+$ 452.3026; found 452.3026.

(1*S*,4*S*,5*R*)-2-[(*S*)-1-Phenylethyl]-4-(4-{(1*S*,3*S*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-3-yl}-1*H*-1,2,3-triazol-1-yl)-2-azabicyclo[3.2.1]octane (14). To a stirred solution of alkyne **9** (0.13 g, 0.6 mmol) and azide **12** (0.15 g, 0.6 mmol) in *t*-butanol (2 mL) and water (1 mL), copper(II) sulfate pentahydrate (0.03 g, 0.1 mmol), sodium ascorbate (0.05 g, 0.25 mmol) and anhydrous potassium carbonate (0.06 g, 0.4 mmol) were subsequently added. After stirring for 3 days at room temperature, DCM (2.5 mL) and aqueous 30% NH_3 (0.25 mL) were added to the reaction mixture. The solution was stirred overnight, and then copper was precipitated using sodium sulfide nonahydrate (0.1 mL) and filtered through a pad of celite. The solvent was removed and the crude product purified using column chromatography on silica gel (*n*-hexane/EtOAc, 75:25 v/v) to give the *title compound* **14** as an orange oil (177 mg, 66%). $[\alpha]_D^{25}$= 127.4 (*c* 0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21-1.28 (m, 2H), 1.41 (d, 3H, *J* 6.5 Hz), 1.44 (d, 3H, *J* 6.7 Hz), 1.43-1.54 (m, 4H), 1.62-1.70 (m, 2H), 1.74-1.95 (m, 3H), 2.07-2.16 (m, 2H), 2.46 (dd, 1H, *J* 13.6, 4.6 Hz), 2.51 -2.59 (m, 2H), 3.32 (s, 1H), 3.33 (q, 1H, *J* 6.6 Hz), 3.61 (q, 1H, *J* 6.5 Hz), 3.78-3.83 (m, 2H), 4.17 (t, 1H, *J* 4.2 Hz), 6.91-7.02 (m, 3H), 7.08-7.25 (m, 2H), 7.26-7.42 (m, 5H), 7.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 21.6, 22.7, 23.0, 27.3, 28.9, 33.8, 35.3, 40.2, 45.3, 48.1, 55.9, 58.6, 59.2, 61.4, 63.0, 65.3, 121.6, 126.7, 127.3, 127.4, 127.8, 128.2, 128.7, 145.3, 145.4, 152.4. IR (KBr): 546, 701, 761, 1042, 1104, 1133, 1165, 1210, 1258, 1348, 1359, 1453, 1492, 2788, 2868, 2967, 3435 cm^{-1}. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $(C_{31}H_{40}N_5)^+$ 482.3280; found 482.3280.

Computational Details. Conformational analysis and TD-DFT simulations.

The conformational search was carried out using CONFLEX 7[30–32] software with the MMFF94s force field within 10 kcal/mol energy window. Next, all structures were submitted to the Gaussian 16 (version C.01) for DFT re-optimization at the ωB97X-D/6-311+G(d,p) level of theory. All conformers were confirmed to contain no imaginary frequencies. The final 6 structures within 1.5 kcal/mol energy window were selected for subsequent simulations of ECD spectra and $[\alpha]$ value at 589 nm. The final chiroptical data were Boltzmann averaged (T = 293 K) according to the population percentages of individual conformers based on the relative SCF energies. ECD/UV spectra were simulated at the CAM-B3LYP/def2-TZVP and ωB97X-D/6-311+g(d,p) level of theory without consideration of solvent model. The obtained results are similar, so only the results from the CAM-B3LYP/def2-TZVP level were considered. The UV correction was applied according the experimental data. To predict $[\alpha]_D$ values, calculations were made for the same group of 6 conformers as ECD, using the following levels of theory: CAM-B3LYP/aug-cc-pVDZ, CAM-B3LYP/def2-TZVP, B3LYP/aug-cc-pVDZ and B3LYP/def2-TZVP, using PCM model for CH_2Cl_2.

Acknowledgements

We gratefully acknowledge financing from the National Science Centre (NCN) Poland (Grant Harmonia No. 2018/30/M/ST5/00401). M.G. thanks the Wroclaw Centre for Networking and Supercomputing (WCSS) for the computational support. The authors also thank Dr. Karolina Kamińska (Wrocław University of Science and Technology) for the provision of (*S*)-*tert*-butyl 2-(azidomethyl)pyrrolidine-1-carboxylate and helpful discussions. Dr. Marek Daszkiewicz (Institute of Low Temperature and Structure Research, Polish Academy of Sciences, Wrocław) is kindly acknowledged for X-ray measurements.

Supplementary Material

All reaction conditions for the attempted eliminations of dichloroalkene (1*S*,3*R*,4*R*)-**6** to alkyne (1*S*,3*R*,4*R*)-**9**, copies of all ^{1}H and ^{13}C NMR spectra of all products, HRMS spectra of compounds **13** and **14**, basic crystallographic data of **13**, simulated $[\alpha]_D$ values of all conformers and ECD spectrum for ***epi*-13**, Cartesian coordinates for all individual conformers of calculated structures are also available in the supplementary material.

References

1. Wojaczyńska, E.; Wojaczyński, J.; Kleniewska, K.; Dorsz, M.; Olszewski, T. K. *Org. Biomol. Chem.* **2015**, *13*, 6116–6148. http://dx.doi.org/10.1039/c5ob00173k
2. Stella, L.; Abraham, H.; Feneau-Dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603–2606. http://dx.doi.org/10.1016/0040-4039(90)80136-A
3. Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707–9718. http://dx.doi.org/10.1016/S0040-4020(01)81187-X
4. Bailey, P. D.; Wilsona, R. D.; Brownb, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337–1340.
5. Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045–1048. http://dx.doi.org/10.1002/jlac.1991199101180
6. Ekegren, J. K.; Modin, S. A.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **2002**, *13*, 447–449. http://dx.doi.org/10.1016/S0957-4166(02)00127-1
7. Hashimoto, N.; Yasuda, H.; Hayashi, M.; Tanabe, Y. *Org. Process Res. Dev.* **2005**, *9*, 105–109. http://dx.doi.org/10.1021/op049828m
8. Alonso, D. A.; Bertilsson, S. K.; Johnsson, S. Y.; Nordin, S. J. M.; Södergren, M. J.; Andersson, P. G. *J. Org. Chem.* **1999**, *64*, 2276–2280. http://dx.doi.org/10.1021/jo981838w
9. Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391–1401. http://dx.doi.org/10.1016/S0957-4166(97)00118-3
10. Brandt, P.; Hedberg, C.; Lawonn, K.; Pinho, P.; Andersson, P. G. *Chem. - Eur. J.* **1999**, *5*, 1692–1699. http://dx.doi.org/10.1002/(SICI)1521-3765(19990604)5:6<1692::AID-CHEM1692>3.0.CO;2-M
11. Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435–3438. http://dx.doi.org/10.1016/S0040-4039(00)92656-X
12. Wang, Z.; Campagna, S.; Xu, G.; Pierce, M. E.; Fortunak, J. M.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 4007–4009. http://dx.doi.org/10.1016/S0040-4039(00)00547-5
13. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. http://dx.doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
14. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. http://dx.doi.org/10.1021/JO011148J

15. Slaitas, A.; Yeheskiely, E. *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 1377–1379. http://dx.doi.org/10.1081/NCN-100002559
16. Wojaczyńska, E.; Turowska-Tyrk, I.; Skarzewski, J. *Tetrahedron* **2012**, *68*, 7848–7854. http://dx.doi.org/10.1016/j.tet.2012.07.028
17. Kacprzak, K.; Gierczyk, B. *Tetrahedron: Asymmetry* **2010**, *21*, 2740–2745. http://dx.doi.org/10.1016/j.tetasy.2010.10.023
18. Boratyński, P. J.; Kowalczyk, R. *J. Org. Chem.* **2016**, *81*, 8029–8034. http://dx.doi.org/10.1021/acs.joc.6b01403
19. Woznica, M.; Kowalska, P.; Lysek, R.; Masnyk, M.; Gorecki, M.; Kwit, M.; Furche, F.; Frelek, J. *Curr. Org. Chem.* **2010**, *14*, 1022–1036. http://dx.doi.org/10.2174/138527210791130497
20. Kołodziejska, R.; Górecki, M.; Frelek, J.; Dramiński, M. *Tetrahedron: Asymmetry* **2012**, *23*, 683–689. http://dx.doi.org/10.1016/j.tetasy.2012.05.003
21. Szwed, K.; Górecki, M.; Frelek, J.; Asztemborska, M. *Chromatographia* **2013**, *76*, 1603–1611. http://dx.doi.org/10.1007/s10337-013-2538-z
22. Avula, S. K.; Hussain, H.; Csuk, R.; Sommerwerk, S.; Liebing, P.; Górecki, M.; Pescitelli, G.; Al-Rawahi, A.; Ur Rehman, N.; Green, I. R.; Al-Harrasi, A. *Tetrahedron: Asymmetry* **2016**, *27*, 829–833. http://dx.doi.org/10.1016/j.tetasy.2016.07.007
23. Górecki, M.; Roszkowski, P.; Błachut, D.; Maurin, J. K.; Budzianowski, A.; Frelek, J.; Czarnocki, Z. *Eur. J. Org. Chem.* **2016**, *2016*, 2966–2971. http://dx.doi.org/10.1002/ejoc.201600456
24. Górecki, M.; Groszek, G.; Frelek, J. *Chirality* **2017**, *29*, 589–598. http://dx.doi.org/10.1002/chir.22736
25. Rehman, N. U.; Hussain, H.; Al-Shidhani, S.; Kumar Avula, S.; Abbas, G.; Muhammad, A.; Anwar, U.; Orecki, De Gennaro Pescitelli, M. G.; Al-Harrasi, A. *RSC Adv.* **2017**, *7*, 42357–42362. http://dx.doi.org/10.1039/c7ra07351h
26. Pescitelli, G.; Barone, V.; Di Bari, L.; Rizzo, A.; Santoro, F. *J. Org. Chem.* **2013**, *78*, 7398–7405. http://dx.doi.org/10.1021/jo401112v
27. Mándi, A.; Kurtán, T. *Nat. Prod. Rep.* 2019, *36*, 889–918. http://dx.doi.org/10.1039/c9np00002j
28. Santoro, E.; Mazzeo, G.; Marsico, G.; Masi, M.; Longhi, G.; Superchi, S.; Evidente, A.; Abbate, S. *Molecules* **2019**, *24*, 3022. http://dx.doi.org/10.3390/molecules24173022
29. Bruhn, T.; Schaumlöffel, A.; Hemberger, Y.; Bringmann, G. *SpecDis Version 1.71, Würzburg, Germany: University of Würzburg*; 2012.
30. Conflex Corp. 2012.
31. Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950–8951. http://dx.doi.org/10.1021/ja00206a046.
32. Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187–198. http://dx.doi.org/10.1039/p29930000187.