https://dx.doi.org/10.21577/0103-5053.20220124

J. Braz. Chem. Soc., Vol. 34, No. 4, 502-516, 2023

Article

Three-Component Betti Condensation for Synthesis of Aminomethylnaphthols Incorporating Deoxy-isoequilenine Scaffold-Absolute Configuration and Application

Irena Zagranyarska,[a] Kalina Kostova,[a] Krasimira Dikova,[a] Boris Shivachev[b] and Vladimir Dimitrov[*,a]

[a]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev 9, 1113 Sofia, Bulgaria*

[b]*Institute of Mineralogy and Crystallography "Acad. Ivan Kostov", Bulgarian Academy of Sciences, Acad. G. Bonchev 107, 1113 Sofia, Bulgaria*

Chiral aminomethylnaphthols have been prepared highly diastereoselective by means of three-component "Betti condensation", using steroidal 2-naphthol analogue, synthesized from estrone. The use of 2-methoxybenzaldehyde or 2-pyridinecarboxaldehyde as aldehyde component and (*S*)-(–)-1-phenylethan-1-amine or (*S*)-(–)-1-(naphthalen-2-yl)ethan-1-amine, as chiral non-racemic amine component providing the diastereoselectivity, allowed the synthesis of structurally diverse aminomethylnaphthols. The latter easily form 1,3-dihydronaphthoxazines through reaction with formaldehyde. The absolute configurations of the new aminomethylnaphthols synthesized have been determined through advanced nuclear magnetic resonance (NMR) experiments and confirmed by X-ray crystallography. The chiral steroidal aminomethylnaphthols obtained as pure diastereoisomers have been evaluated as pre-catalysts in the enantioselective addition of diethylzinc to aldehydes with enantioselectivities of up to 97% enantiomeric excess (*ee*).

Keywords: Betti condensation, chiral ligands, NOESY spectra, absolute configuration, enantioselectivity

Introduction

In the modern organic synthesis, the preparation of enantiomerically pure products is of general importance due to their applications in medicinal chemistry and in catalytic enantioselective processes. The so-called "Betti condensation" (three-component condensation first studied by Mario Betti[1] leading to 1-(α-aminobenzyl)-2-naphthol, referred to as "Betti base") offers practicable approach for the synthesis of aminobenzylnaphthols.[1] The Betti reaction is one of the early examples of a multicomponent reaction (MCR). It is necessary to emphasize that MCR have become in recent years an indispensable tool for synthesis of multifunctional compounds with diverse fields of application (comprehensive review articles have been recently published).[2-4] The interest in this easy to perform reaction has been awakened by Naso and co-workers[5,6] who synthesized new "Betti base" analogues, realizing efficient resolution into enantiomers with defined configuration[5] and applied them as valuable catalyst in the enantioselective addition of diethylzinc to arylaldehydes (enantioselectivity up to 99% *ee*).[6] In a further development, the use of commercial available chiral non-racemic amines within the three-component condensation resulted in highly diastereoselective synthesis of chiral 1,3-aminobenzylnaphthols with excellent properties as ligands for enantioselective organozinc additions to aldehydes.[7-10] A new synthetic pathway of enantiomerically pure Betti bases has recently been described involving Zr-mediated reduction of chiral pyrrolidine-2-ones to cyclic imines and their further reaction with phenolic derivatives.[11] The scope of the current knowledge on the synthesis and application of aminobenzylnaphthols has recently been demonstrated in review articles.[12-17] In most cases, various chiral amines are used in combination with different aldehydes to prepare chiral non-racemic aminobenzylnaphthols.[7-9,18,19] As a third component 2-naphthol is commonly used in the condensation reaction. Recently we have described the utilization of 2,3-, 2,6- and 1,5-dihydroxynaphthalenes[10] and the use of deoxy-isoequilenine as a new steroidal

*e-mail: vladimir.dimitrov@orgchm.bas.bg
Editor handled this article: Brenno A. D. Neto (Associate)

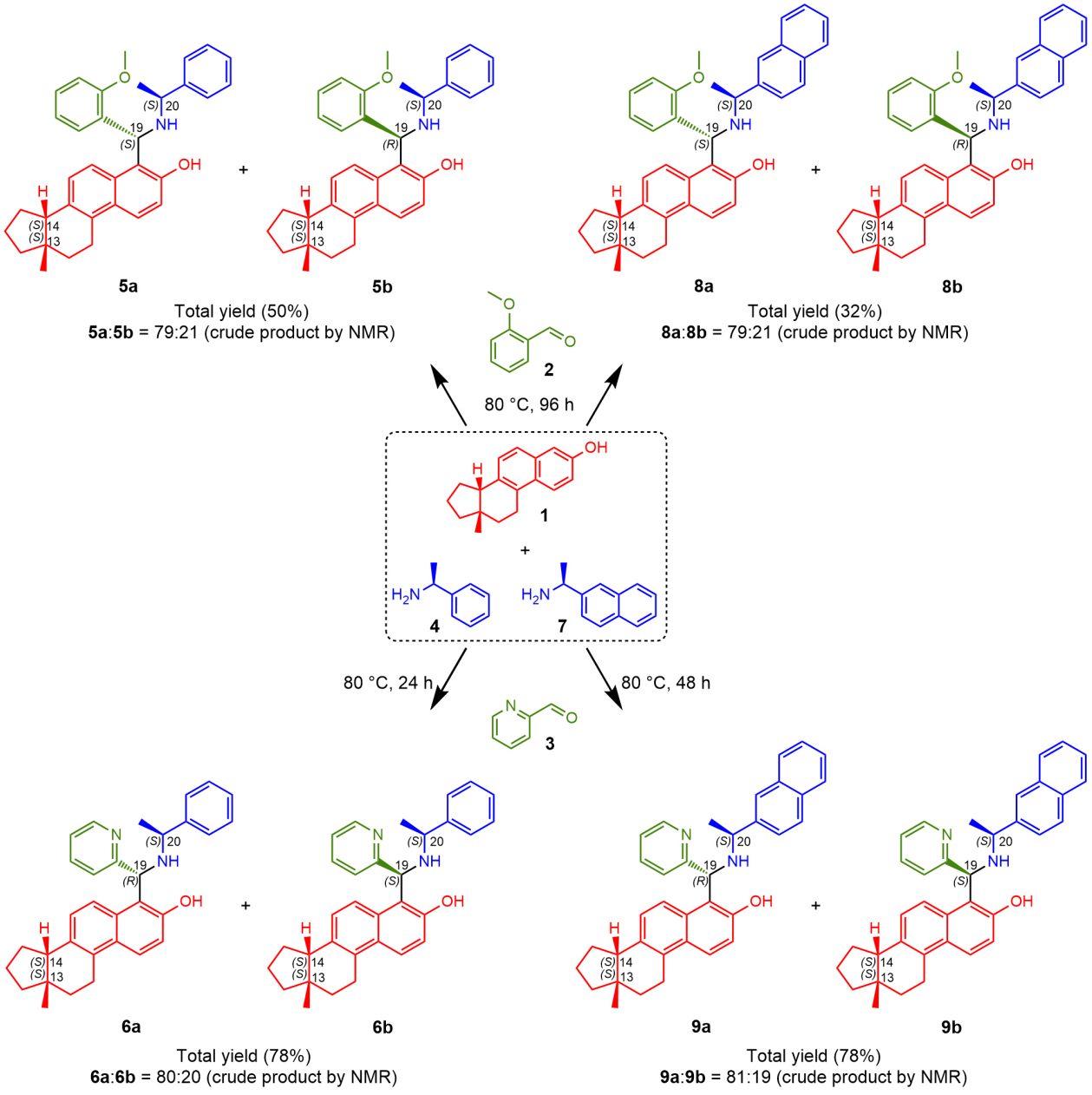
2-naphthol analogue,[20] in condensation reactions with aromatic aldehydes and (*S*)-(−)-1-phenylethan-1-amine. The aminobenzylnaphthols thus synthesized were formed with high diastereoselectivity.

In the current work, we aimed to study the ability of 2-methoxybenzaldehyde (**2**) and 2-pyridinecarboxaldehyde (**3**) to efficiently perform the three component condensation with (*S*)-(−)-1-phenylethan-1-amine (**4**), (*S*)-(−)-1-(naphthalen-2-yl)ethan-1-amine (**7**) and deoxy-isoequilenine (**1**). The diastereoselectivity of the reactions and the configuration of the newly formed stereogenic centers were of particular interest. The capability of the targeted compounds to serve as chiral auxiliaries was evaluated within the model reaction of enantioselective addition of diethylzinc to aldehydes.

Results and Discussion

Synthesis of aminomethylnaphthols by three component condensation

The synthetic approach for the condensation is focused on application of deoxy-isoequilenine (**1**) as 2-naphthol component (Scheme 1), since the utility of this chiral



Scheme 1. Three component condensation of deoxy-isoequilenine (**1**), aromatic aldehydes **2** and **3**, and amines **4** and **7** (the numbering of the C-atoms is tentative and applied for the assignment of nuclear magnetic resonance (NMR) signals and is introduced in the Supplementary Information (SI) section).

compound has been recently demonstrated.[20] The choice of 2-methoxybenzaldehyde (**2**) and 2-pyridinecarboxaldehyde (**3**) is motivated by the presence of additional heteroatom in the corresponding structure, which could bring advantage within the planned catalytic applications.

The readily available chiral amines (*S*)-(–)-1-phenylethan-1-amine (**4**) and (*S*)-(–)-1-(naphthalen-2-yl)ethan-1-amine (**7**) are the corresponding amine components to induce diastereoselectivity in the condensation reaction leading to aminomethylnaphthols **5**, **6**, **8** and **9** (Scheme 1). It should be noted that in all reactions the use of solvent was not necessary and the condensations were performed by simply mixing the three components and heating them. The yields of the aminomethylnaphthols got worse when using of solvents (tetrahydrofuran (THF) or EtOH). The condensation reactions performed with 2-methoxybenzaldehyde (**2**), naphthol **1** and amines **4** or **7**, respectively at 80 °C, were slow with an optimized duration of 96 h to obtain acceptable yields of compounds **5** (50%) and **8** (32%). The diastereoselectivity determined by ^{1}H nuclear magnetic resonance (NMR) spectroscopy of the crude reaction mixtures for the formation of both compounds **5a/5b** and **8a/8b** was high (79:21) in favor of the corresponding *S*,*S*-diastereoisomer (in the following the configuration description refer to the atoms C-19 and C-20; compare Schemes 1 and 2, and for configuration determination Figure 1). Noteworthy, the diastereoisomeric ratio within **5** and **8** formed was always the same regardless of the reaction time (the condensation was evaluated in the range between 24 and 96 h). The individual diastereoisomers could be isolated in pure form by column chromatography in the yields, given as follows (*S*,*S*)-**5a** (47%), (*R*,*S*)-**5b** (3%), (*S*,*S*)-**8a** (26%) and (*R*,*S*)-**8b** (6%). It should be noted that the isolation of the diastereoisomers **5a** and **5b**, **8a** and **8b** in pure form required several column chromatographies due to their close Rf value.

The condensations of 2-pyridinecarboxaldehyde (**3**) with **1** and amines **4** and **7** was high yielding (78% in both cases), respectively, providing compounds **6** and **9** within shorter reaction times (Scheme 1). The diastereoselectivities observed by ^{1}H NMR spectroscopy of the crude reaction mixtures were similar, **6a/6b** = 80:20 and **9a/9b** = 81:19. The predominantly formed **6a-** and **9a-**diastereoisomers showed the same sense of chirality, compared with compounds **5a** and **8a**, for the newly formed stereogenic center at C-19 (the same relative space arrangement of substituents attached to C-19), although according the Cahn, Ingold, Prelog (CIP) convention the configuration is determined as *R* for both **6a** and **9a**. The individual diastereoisomers were isolated in pure form by means of column chromatography realizing the yields, as follows (*R*,*S*)-**6a** (61%), (*S*,*S*)-**6b** (17%), (*R*,*S*)-**9a** (69%) and (*S*,*S*)-**9b** (9%). Also, in this case, due to the close Rf values of the diastereoisomers **6a** and **6b**, **9a** and **9b** the use of several column chromatographies is required to isolate them in pure form.

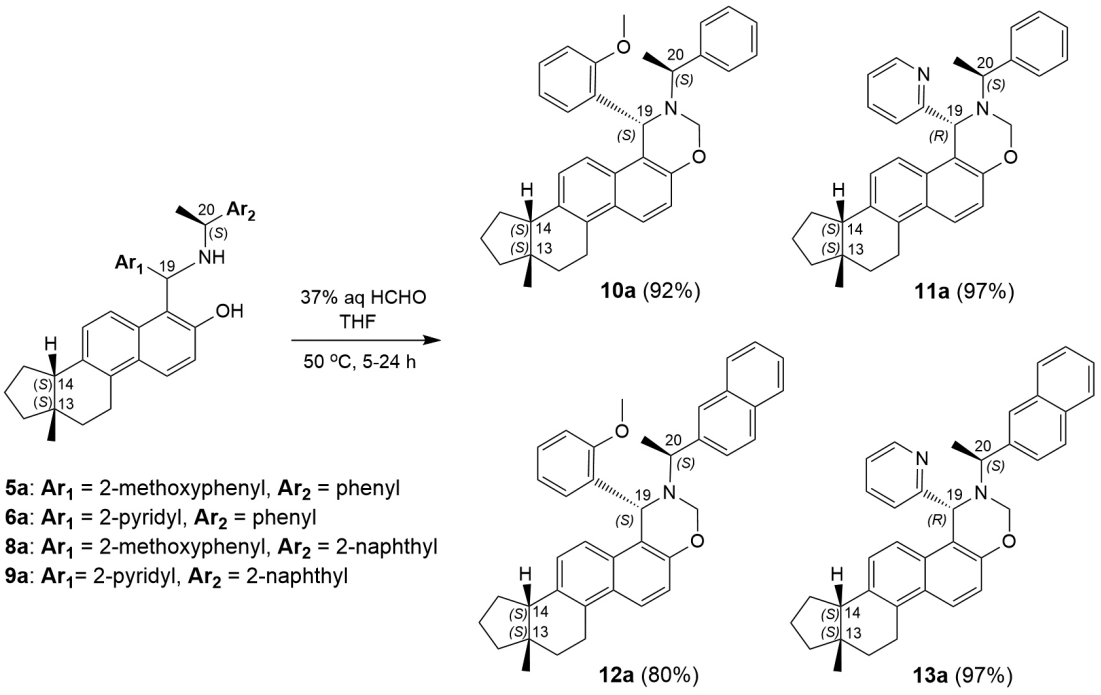
It is important to note that the defined configuration of the corresponding chiral amine applied in the condensation reaction allows to predict the configuration of the predominantly formed diastereoisomer (e.g., the *S*-configured amines **4** and **7** produce predominantly **5a** and **8a** with (*S*)-C-19 configuration. The situation in the case of compounds **6a** and **9a** is similar, however, due to the CIP rules the descriptor for stereogenic center C-19 is formally (*R*). The predictable diastereoselectivity, emphasized also in previous articles,[10,21] is a significant advantage intrinsically connected with the mechanism of the reaction which has been discussed in recent studies.[22]

Synthesis of the corresponding 1,3-dihydronaphthoxazines

The aminomethylnaphthols **5a**, **6a**, **8a** and **9a** were further used in the course of the very efficient reaction with aqueous formaldehyde to provide the corresponding 1,3-dihydronaphthoxazines (Scheme 2). The reactions were performed by gently heating the reactants in THF solution for several hours. The isolation of 1,3-dihydronaphthoxazines **10a**-**13a** occurred in high yields by column chromatography. One reason for the synthesis of these compounds is the systematic generation in recent years of a library containing critical mass of structurally diverse aminomethylnaphthols and the corresponding 1,3-dihydronaphthoxazines for evaluation of the possible biological activity.[23-27] The main reason for the synthesis of compounds **10a**-**13a** in the present study is to analyze and compare the NMR data of the prepared aminomethylnaphthols and their 1,3-dihydronaphthoxazines in order to establish the relative configuration of the newly formed stereogenic center at C-19. The introduction of the pro-stereogenic methylene group between the N- and O-atom leading to **10a**-**13a** is a convenient synthetic method that does not affect the existing stereogenic centers. The methylene-bridge caused reduction of the conformational flexibility within the dihydronaphthoxazine structures providing the opportunity to attain proper information about the space position of substituents attached to C-19 relative to each other by means of NMR experiments.

Structure determination

The configuration determination of the aminomethyl-naphthols **5a/5b**, **6a/6b**, **8a** and **9a/9b** was of particular



Scheme 2. Synthesis of 1,3-dihydronaphthoxazines **10a**, **11a**, **12a** and **13a**.

interest and was performed using NMR experiments. The ^{1}H and ^{13}C signals of the compounds were assigned by means of 1D and 2D spectra (distortionless enhancement by polarization transfer (DEPT), heteronuclear single quantum correlation (HSQC), heteronuclear multiple bond correlation (HMBC) and nuclear overhauser effect spectroscopy (NOESY)). The implementation of the NOESY data was the approach applied[10,20,22] to obtain extensive information about the proton neighborhood around the newly formed stereogenic center at C-19. The data attained permitted elucidation of the relative arrangement of the fragments within the molecules (Figure 1) in respect of the C-19 stereogenic center. Consequently, by using this basic approach the relative configurations of newly formed stereogenic centers in the studied compounds could be determined. Taking into account the known absolute configuration of the fragments originating from (*S*)-(–)-1-phenylethan-1-amine (**4**) or (*S*)-(–)-1-(naphthalen-2-yl)ethan-1-amine (**7**), the absolute configuration at C-19 for the respective compound was deduced.

In the NOESY spectra of **5a**, **6a**, **8a** and **9a**, similar proton proximities could be observed for the relative positions of the steroidal naphthyl fragment, the (*S*)-(–)-1-phenylethan-1-amine or (*S*)-(–)-1-(naphthalen-2-yl)ethan-1-amine and the corresponding *ortho*-methoxyphenyl or 2-pyridyl parts of the structures. The most important proton interactions are indicated by means of arrows in Figure 1. The proton at C-19 is in close proximity to the following nuclei: the *peri*-proton from the steroidal naphthyl fragment, the C-20 methine proton and an *ortho*-proton of the phenyl moiety for all **a**-diastereoisomers (**5a**, **6a**, **8a** and **9a**), as well as, the NH proton for **5a** and **6a**, and the *ortho*-naphthyl proton for **8a** and **9a**. It is important to note that the OH protons for all **a**-diastereoisomers are involved in strong intramolecular O–H···N hydrogen bonding, confirmed by the singlets with the following δ-values in ppm: 13.75 (**5a**), 13.28 (**6a**), 13.71 (**8a**) and 13.24 (**9a**). The data are consistent with the conformations presented and the configurations are strongly supported by the NOESY data obtained for the corresponding 1,3-dihydronaphthoxazines **10a**-**13a** (Figure 1). The CH_2-bridge between the O- and N-atoms generate a conformationally rigid structure, providing additional arguments for a reliable configuration elucidation. Complementary information for the proximity of the H_a and H_b protons of the CH_2-bridge relative to the methyl group attached to C-20 and/or to the *ortho*-protons of the methoxyphenyl moiety additionally supports the configuration of the C-19 stereogenic center as presented in Figure 1.

Furthermore, the NOESY data for the minor diastereoisomers **5b**, **6b** and **9b** indicating the opposite configuration of C-19 could be considered as additional proof for validity of the NMR approach presented above for configuration determination. The discussion of the NOESY spectra of **8b** was abandoned due to the presence of impurities and possible adulteration of the interpretation.

The conformations of the aminomethylnaphthols presented in Figure 1 require some comments. It seems that

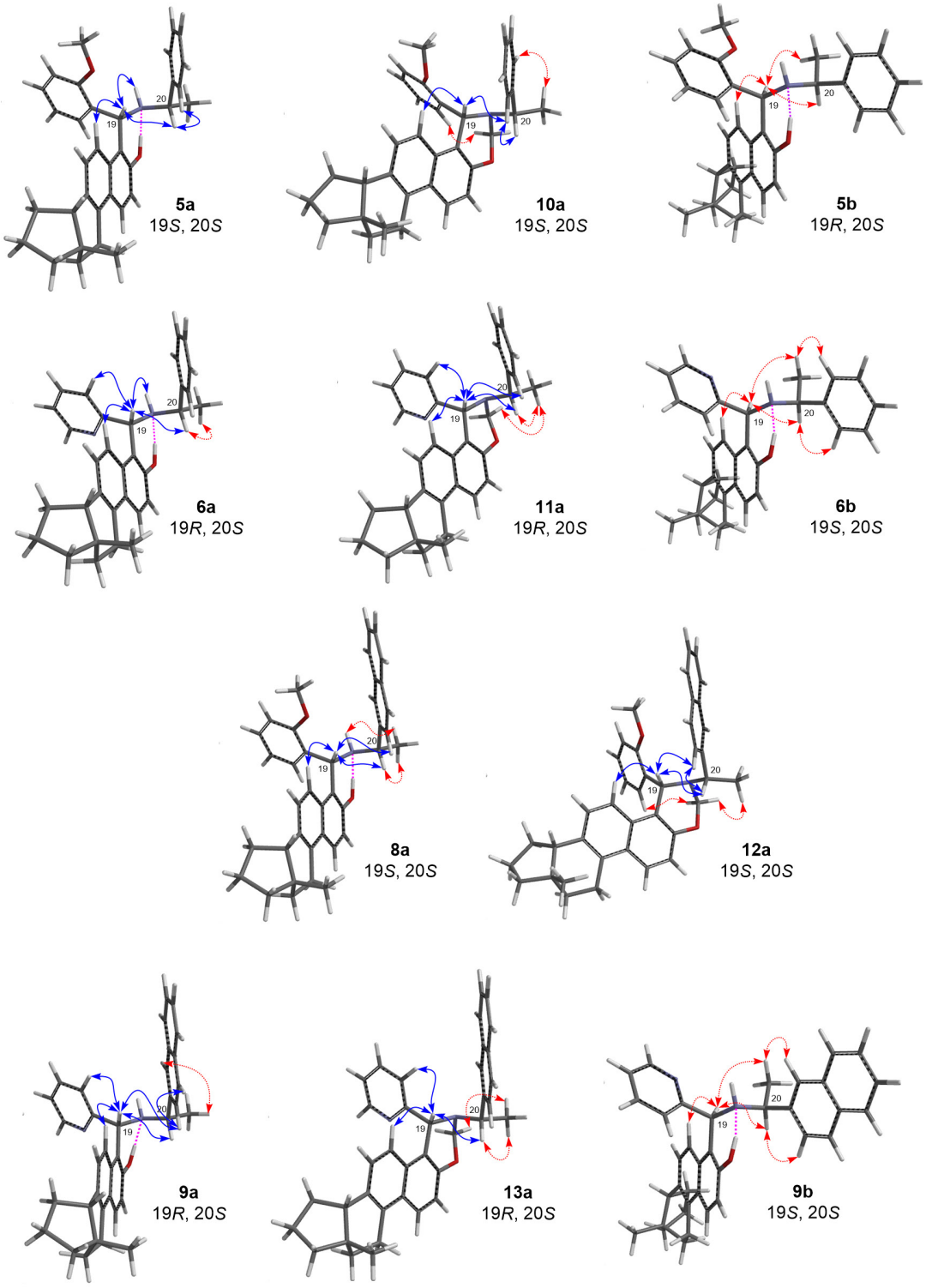


Figure 1. Main proton proximities of compounds **5a/5b**, **6a/6b**, **8a**, **9a/9b** and **10a-13a**, observed in the NOESY spectra (images with arbitrary molecular conformations were created using Spartan for Windows;[28] blue arrows present proton proximities formally in front of C-19, whereas the red ones behind it).

the hydrogen bonding observed within **5a**, **6a**, **8a** and **9a** has a significant impact on the most favored conformations thus providing reliable NOESY data for configuration determination. The NOESY data strongly support comparable conformations of the **a**-diastereoisomers (**5a**, **6a**, **8a** and **9a**) with the corresponding dihydronaphthoxazines (**10a**-**13a**), where the CH_2-bridge force the molecules to adopt a conformationally rigid structure. The strong hydrogen bonding observed in the case of compound **5a**, **6a**, **8a** and **9a** could be considered as formed in the course

of the condensation reaction, which mechanism has been discussed in previous articles.[21,22]

Single-crystal X-ray structure analyses were performed to precisely assign the structures of compounds **5a** and **11a** (suitable crystals were obtained by slow evaporation from ethanol). The absolute configurations of compounds **5a** (*S* for C-19) and **11a** (*R* for C-19) were independently and unequivocally confirmed by single-crystal X-ray structure analyses (see Experimental section). Consequently, the NMR approach for the determination of the configuration, which is presented in Figure 1, is fully confirmed by the results of the X-ray crystallography. Views of the molecules are shown in Figure 2 and the data collection, and refinement parameters are given in the Supplementary Information (SI) section. The values for the bond lengths and bond angles in **5a** and **11a** do not deviate significantly from the observed within similar structures of previously synthesized compounds.[10,20,22]

Compound **5a** crystallizes in $P2_12_12_1$ and the only molecule present in the asymmetric unit exhibits a disorder over two positions for the cyclopentane ring of the steroidal fragment (major component of 75%) (Figure 2). An intramolecular hydrogen bond O1–H1···N1 (2.585 Å) supports the relative orientation of the aromatic moieties around the C-19 center. Compound **11a** crystallizes in the hexagonal $P6_1$ space group as hydrate.

For the crystal structure to fully accommodate the water molecule, disorder over two position is observed (major component of 75%). Interestingly, the water molecules do not show close contacts with the molecule of **11a**. There is an interaction between the water molecules forming chains propagating along the *c* axis (Figure 3).

Application of aminomethylnaphthols as chiral ligands in enantioselective addition of diethylzinc to aldehydes

The newly synthesized compounds **5a**, **6a**, **8a** and **9a** were evaluated as pre-catalysts (3 mol%) in the enantioselective addition of diethylzinc (Et_2Zn) to various aldehydes (Table 1) by following a standard procedure.[10,20,22,29,30]

The reactions catalyzed by the aminomethylnaphthols proceeded in the range of moderate to very good yields. The reaction times varied from 22 to 72 h. The best enantioselectivities were realized by using compound **5a** as ligand. The addition of Et_2Zn to 2-methoxybenzaldehyde and 2-naphthaldehyde occurred with enantioselectivity of 90 and 97%, respectively (entries 2 and 5). The reactions with 2,4,6-trimethylbenzaldehyde and 2,6-dichlorobenzaldehyde using **5a** could also be considered as acceptable, 73% *ee* and 81% *ee*, respectively (entries 3 and 7). Compounds **6a**, **8a** and **9a** applied as ligands provided low to moderate enantioselectivity apart from **8a** realizing with three of the aldehydes (entries 13, 15 and 17) enantioselectivities near the 77%. Notably, the enantioselectivities obtained with benzaldehyde were low with all ligands applied. Interestingly, comparing the enantioselectivity provided by ligand **5a** by using 2-methoxybenzaldehyde and 2-naphthaldehyde (90 and 97% *ee*, respectively), there is a dramatic decrease of asymmetric induction in the case of **6a** with the same aldehydes (3 and 26% *ee*, respectively). It should be noted that ligands **5a** and **8a** delivered products possessing *R*-configuration whereas compounds **6a** and **9a** the *S*-configured substituted 1-aryl-1-propanols. These results indicate a possible role of the pyridyl fragment

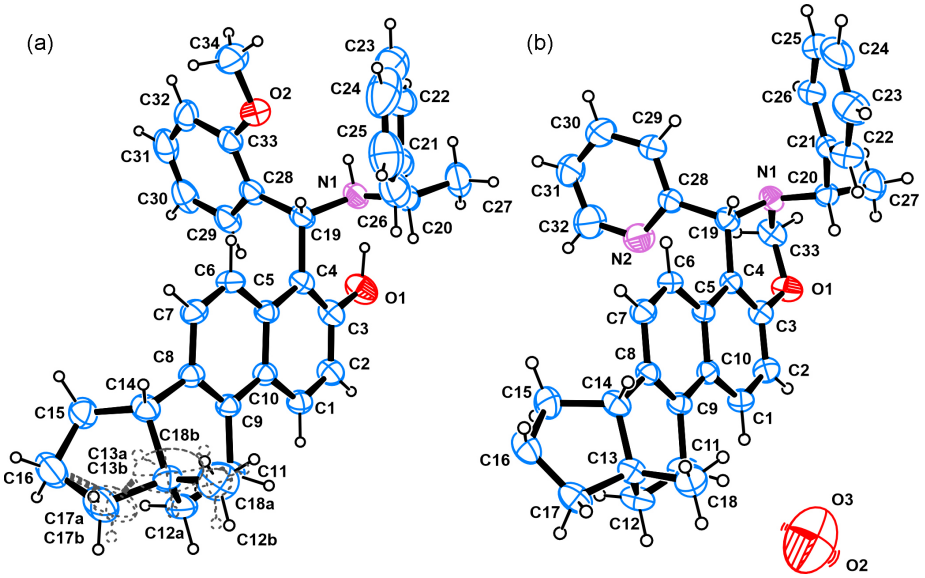


Figure 2. Atomic displacement ellipsoid plots of the molecular structures present in the asymmetric units of (a) (19*S*,20*S*)-**5a** and (b) (19*R*,20*S*)-**11a**. Atomic displacement parameters (ADP) are drawn at the 50% probability level. Hydrogen atoms are shown as spheres with arbitrary radii.

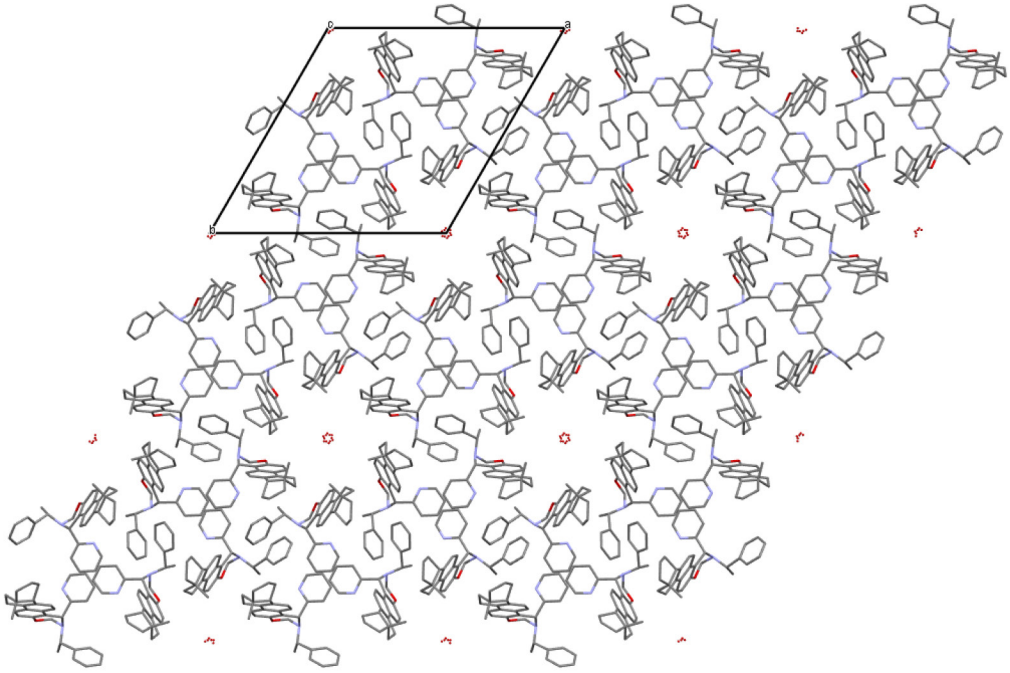
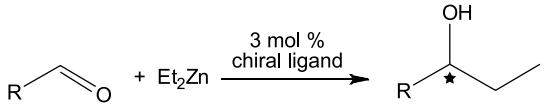


Figure 3. Three-dimensional view of **11a** showing the water neighborhood along the *c* axis.

Table 1. Enantioselective addition of Et_2Zn to aldehydes catalyzed by ligands **5a**, **6a**, **8a** and **9a**



entry	Aldehyde	Ligand	Yield[a] / %	*ee* (config.)[b] / %
1	benzaldehyde	**5a**	34	33 (*R*)[c]
2	2-methoxybenzaldehyde	**5a**	99	90 (*R*)[c]
3	2,4,6-trimethylbenzaldehyde	**5a**	65	73 (unknown)[d]
4	cinnamaldehyde	**5a**	90	56 (*R*)[d]
5	2-naphthaldehyde	**5a**	88	97 (*R*)[c]
6	4-chlorobenzaldehyde	**5a**	39	33 (*R*)[c]
7	2,6-dichlorobenzaldehyde	**5a**	88	81 (unknown)[d]
8	benzaldehyde	**6a**	25	20 (*S*)[c]
9	2-methoxybenzaldehyde	**6a**	93	3 (*S*)[c]
10	cinnamaldehyde	**6a**	52	1 (*S*)[d]
11	2-naphthaldehyde	**6a**	63	26 (*S*)[c]
12	benzaldehyde	**8a**	45	22 (*R*)[c]
13	2-methoxybenzaldehyde	**8a**	50	77 (*R*)[c]
14	cinnamaldehyde	**8a**	57	64 (*R*)[d]
15	2-naphthaldehyde	**8a**	59	76 (*R*)[c]
16	4-chlorobenzaldehyde	**8a**	38	27 (*R*)[c]
17	2,6-dichlorobenzaldehyde	**8a**	90	72 (unknown)[d]
18	benzaldehyde	**9a**	69	24 (*S*)[c]
19	2-methoxybenzaldehyde	**9a**	47	7 (*S*)[c]
20	2-naphthaldehyde	**9a**	51	26 (*S*)[c]

[a]Yield of isolated pure products after column chromatography; [b]the configuration was determined by comparison of the measured specific rotation with literature data; [c]enantiomeric excess (*ee*) was determined by GC (see SI section); [d]enantiomeric excess was determined by HPLC (see SI section); unknown configuration, since no literature data about the specific rotation available.

providing additional coordination site within the active catalyst. In the established mechanistic model, described by Noyori and Kitamura,[30] for the addition of Et_2Zn to aldehydes catalyzed by chiral aminoalcohols, the addition reaction takes place within a transition complex formed by the actually catalyst (aminoalkoxy-Zn-Et intermediate formed *in situ*), Et_2Zn and the corresponding aldehyde. An additional coordinating N-atom (of the pyridyl fragment), as in the case of ligands **6a** and **9a** can significantly influence the stereochemistry within the transition complex and consequently also the outcome of the addition reaction.

Conclusions

The three-component condensation of deoxy-isoequilenine with 2-methoxybenzaldehyde or 2-pyridinecarboxaldehyde as aldehyde component, and (*S*)-(–)-1-phenylethan-1-amine or (*S*)-(–)-1-(naphthalen-2-yl)ethan-1-amine as amine component, has been efficiently applied for the highly diastereoselective synthesis of functionalized aminomethylnaphthols. The diastereoselectivity was induced by the readily available chiral amines applied, which makes the approach economically relevant. The significant advantage of this reaction was the opportunity to predict the configuration of the newly generated stereogenic center, which is directly dependent on the configuration of the amine component in the condensation. The absolute configuration of the newly formed stereogenic center within the synthesized compounds was determined by applying an effective approach based on NMR NOESY experiments. This approach was validated by corresponding X-ray crystal-structure determinations. The aminomethylnaphthols were evaluated as pre-catalysts in the enantioselective addition of Et_2Zn to aldehydes, providing secondary alcohols with up to 97% enantioselectivity.

Experimental

General information

Reagents were commercial grade and used without further purification (2-methoxybenzaldehyde, 2-pyridinecarboxaldehyde, (*S*)-(–)-1-phenylethan-1-amine, (*S*)-(–)-1-(naphthalene-2-yl)ethan-1-amine and 37% aq solution of formaldehyde, Sigma-Aldrich, supplier FOT LTD, Sofia, Bulgaria). The reactions with Et_2Zn (1 mol L^{-1} solution in hexane, Sigma-Aldrich, supplier FOT LTD, Sofia, Bulgaria) were carried out in flame-dried Schlenk flasks under an argon atmosphere. The toluene (high-performance liquid chromatography (HPLC) grade, Sigma-Aldrich, supplier FOT LTD, Sofia, Bulgaria) for the enantioselective organozinc additions was dried by refluxing over $LiAlH_4$ and distilled under an argon atmosphere. Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with Merck Kieselgel 60 F_{254} 0.25 mm (Merck, supplier FOT LTD, Sofia, Bulgaria). Flash column chromatography was carried out using silica gel 60 230-400 mesh, (Merck, supplier FOT LTD, Sofia, Bulgaria). Solvents: petroleum ether (PE), methyl *tert*-butyl ether (MTBE) and tetrahydrofuran (THF) (Sigma-Aldrich, supplier FOT LTD, Sofia, Bulgaria). The melting points of the compounds were determined by using BOETIUS, type PHMK 05, manufacturer VEB Kombinat NAGEMA, Dresden, East Germany, (uncorrected). Optical rotation $[\alpha]_D^{25}$ measurements were obtained using a PerkinElmer 241 polarimeter, supplier PerkinElmer, Vienna, Austria. The NMR spectra were recorded at ambient temperature (298 K) on a Bruker Avance II+ 600 (600 MHz for ^{1}H NMR, 150 MHz for ^{13}C NMR) spectrometer, manufacturer Brucker BioSpin GmbH, Rheinstetten, Germany, with tetramethylsilane (TMS) as internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (*J*, Hz), and identification.

The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, HSQC, HMBC, and NOESY experiments. All assignments marked with an asterisk are tentative. Mass spectra (ESI-MS) were recorded on an API QSTAR PULSAR I spectrometer (AB Sciex LLC, Framingham, USA), and reported in *m/z* with relative intensities (%) in parentheses. High performance liquid chromatography (HPLC) separations were performed with an Agilent 1100 System (supplier T.E.A.M. Ltd.-CAG, Sofia, Bulgaria) fitted with a diode array detector and a manual injector with a 20 μL injection loop. Gas chromatography (GC) was performed with a Shimadzu GC-17A (supplier Shimadzu Handelsgesellschaft mbH Korneuburg, branch Sofia, Bulgaria). Elemental analyses were performed by Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences. Crystallographic measurements and data collection of compounds **5a** and **11a** were performed on an SupernovaDual diffractometer equipped with an Atlas CCD detector using micro-focus Mo Kα radiation (λ = 0.71073 Å) at 290 K (Oxford Diffraction/ Agilent Technologies UK Ltd, Yarnton, England). The determinations of the unit cell parameters, data collection and reduction were performed with Crysalis-Pro software.[31] The structures were solved by direct methods ShelxS[32] and

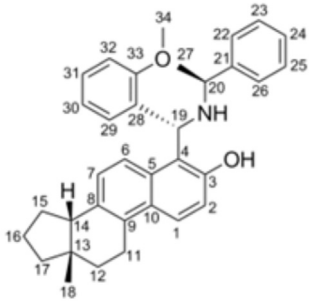
refined by the full-matrix least-squares method with the ShelxL-2013 programs.[32] All non-hydrogen atoms, were located successfully from Fourier maps and were refined anisotropically. Hydrogen atoms on C and N atoms were generated geometrically and their positional parameters were refined with C—H = 0.9600, N—H = 0.9300 Å with Uiso(H) = 1.2Ueq (C or N). Most important crystallographic and refinement indicators are listed in Table S1 (see SI section).

General procedure for the synthesis of aminomethylnaphthols[7,10,20,22]

A mixture of the steroidal naphthol **1** (1 equiv), (*S*)-(−)-1-phenylethan-1-amine (**4**) or (*S*)-(−)-1-(naphthalene-2-yl)ethan-1-amine (**7**) (1.3 equiv) and 2-methoxybenzaldehyde (**2**) or 2-pyridinecarboxaldehyde (**3**) (1.2 equiv) was heated at 80 °C for a period up to 96 h. The crude mixture was chromatographed twice to isolate the corresponding compounds in pure form.

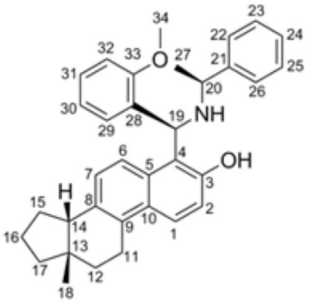
(13*S*,14*S*)-4-((2-Methoxyphenyl)(((*S*)-1-phenylethyl)amino)methyl)-13-methyl-12,13,14,15,16,17-hexahydro-11*H*-cyclopenta[*a*]phenanthren-3-ol (**5**)

According to the general procedure a mixture of **1** (0.292 g, 1.157 mmol), (*S*)-(−)-1-phenylethan-1-amine (**4**) (0.182 g, 0.19 mL, 1.504 mmol) and 2-methoxybenzaldehyde (**2**) (0.189 g, 1.388 mmol) was heated for 96 h. After column chromatography (eluent PE:acetone = 20:1) 0.054 g (18%) of the starting compound **1**, 0.265 g (47%) of the major diastereoisomer (*S*,*S*)-**5a** and 0.017 g (3%) of the minor diastereoisomer (*R*,*S*)-**5b** were isolated. The total yield of **5** is 50%.



Data of (19*S*,20*S*)-**5a**

mp 146-149 °C (colorless crystals); $[\alpha]_D^{25}$ = +197.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (s, 3H, H-C(18)), 1.46 (d, 3H, *J* 6.8 Hz, H-C(27)), 1.49-1.54 (m, 1H, H-C(15)), 1.56-1.69 (m, 5H, H-C(12), H-C(16), H-C(17)), 1.78 (ddd, 1H, *J* 13.1, 11.1, 5.7 Hz, H-C(12)), 2.12-2.18 (m, 1H, H-C(15)), 2.45 (br s, 1H, NH), 2.68 (t, 1H, *J* 9.1 Hz, H-C(14)), 3.02 (ddd, 1H, *J* 16.8, 11.0, 5.7 Hz, H-C(11)), 3.15 (ddd, 1H, *J* 16.9, 5.3, 4.1 Hz, H-C(11)), 3.69 (s, 3H, H-C(34)), 3.88 (q, 1H, *J* 6.2 Hz, H-C(20)), 5.87 (s, 1H, H-C(19)), 6.69 (td, 1H, *J* 7.6, 0.9 Hz, H-C(30)), 6.81 (dd, 1H, *J* 8.2, 0.7 Hz, H-C(32)), 6.93 (dd, 1H, *J* 7.7, 1.6 Hz, H-C(29)), 6.99 (d, 1H, *J* 8.9 Hz, H-C(7)), 7.13-7.16 (m, 1H, H-C(31)), 7.18 (d, 1H, *J* 8.8 Hz, H-C(6)), 7.21-7.24 (m, 3H, H-C(22), H-C(26), H-C(2)), 7.31-7.34 (m, 1H, H-C(24)), 7.35-7.38 (m, 2H, H-C(23), H-C(25)), 7.97 (d, 1H, *J* 9.1 Hz, H-C(1)), 13.75 (br s, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.6 (q, C(27)), 23.0 (t, C(16)), 23.4 (t, C(11)), 26.0 (q, C(18)), 31.8 (t, C(12)), 35.5 (t, C(15)), 39.3 (s, C(13)), 40.8 (t, C(17)), 50.5 (d, C(14)), 54.6 (d, C(19)), 55.1 (q, C(34)), 57.0 (d, C(20)), 110.4 (d, C(32)), 114.0 (s, (C_{ar})), 119.2 (d, C(2)), 119.5 (d, C(6)), 121.2 (d, C(30)), 124.8 (d, C(1)), 127.2 (s, (C_{ar})), 127.4 (2d, C(22), C(26)), 127.64 (d, (C_{ar})), 128.4 (2d, C(23), C(25)), 128.7 (s, (C_{ar})), 129.2 (d, C(31)), 129.3 (d, C(7)), 129.7 (d, C(29)), 130.5 (s, (C_{ar})), 131.3 (s, (C_{ar})), 134.2 (s, (C_{ar})), 143.3 (s, (C_{ar})), 156.5 (s, (C_{ar})), 157.2 (s, (C_{ar})); MS (ESI) *m/z*, 492 ($[M + H]^+$, 5), 371 (100), 275 (7), 265 (47), 169 (5); anal. calcd. for $C_{34}H_{37}NO_2$: C 83.06, H 7.59, N 2.85, found: C 82.93, H 7.63, N 2.69.

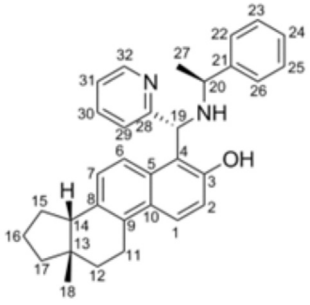


Data of (19*R*,20*S*)-**5b**

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (s, 3H, H-C(18)), 1.61 (d, 3H, *J* 6.6 Hz, H-C(27)), 1.57-1.83 (m, 6H, H-C(12), H-C(15), H-C(16), H-C(17)), 1.80 (ddd, 1H, *J* 12.9, 11.5, 5.6 Hz, H-C(12)), 2.22-2.28 (m, 1H, H-C(15)), 2.66 (dd, 1H, *J* 9.2, 8.8 Hz, H-C(14)), 3.01 (ddd, 1H, *J* 16.9, 11.1, 5.7 Hz, H-C(11)), 3.14 (ddd, 1H, *J* 17.0, 5.2, 4.0 Hz, H-C(11)), 3.93 (q, 1H, *J* 6.5 Hz, H-C(20)), 4.02 (s, 3H, H-C(34)), 6.42 (s, 1H, H-C(19)), 6.74 (t, 1H, *J* 7.3 Hz, H-C(30)), 6.94 (d, 1H, *J* 7.9 Hz, H-C(32)), 7.02 (dd, 1H, *J* 7.7, 1.4 Hz, H-C(29)), 7.10 (d, 1H, *J* 8.8 Hz, H-C(7)), 7.16 (d, 1H, *J* 9.2 Hz, H-C(2)), 7.19-7.23 (m, 2H, H-C(31), H-C(24)), 7.26-7.30 (m, 4H, H-C(22), H-C(26), H-C(23), H-C(25)), 7.50 (d, 1H, *J* 8.9 Hz, H-C(6)), 7.93 (d, 1H, *J* 9.2 Hz, H-C(1)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.0 (q, C(27)), 23.0 (t, C(16)), 23.5 (t, C(11)), 25.9 (q, C(18)), 31.8 (t, C(12)), 35.8 (t, C(15)), 39.4 (s, C(13)), 41.0 (t, C(17)), 50.6 (d, C(14)), 54.1 (d, C(19)), 55.4 (d, C(20)), 55.6 (q, C(34)), 110.5 (d, C(32)), 113.8 (s, (C_{ar})), 119.4 (d, C(6)), 119.5 (d, C(2)), 121.4 (d, C(30)), 124.8 (d, C(1)), 126.5* (2d, C(23), C(25)), 127.2 (d, C(24)), 127.3 (s, (C_{ar})), 128.6 (s, (C_{ar})), 128.7* (2d, C(22), C(26)), 129.3 (d, C(7)), 129.4 (d, C(31)), 129.8 (d, C(29)), 130.8 (s, (C_{ar})), 131.4 (s, (C_{ar})), 134.2 (s, (C_{ar})), 144.2 (s, (C_{ar})), 156.4 (s, (C_{ar})), 157.0 (s, (C_{ar})).

(13*S*,14*S*)-13-Methyl-4-((((*S*)-1-phenylethyl)amino)(pyridin-2-yl)methyl)-12,13,14,15,16,17-hexa-hydro-11*H*-cyclopenta[*a*]phenanthren-3-ol (**6**)

According to the general procedure a mixture of **1** (0.290 g, 1.149 mmol), (*S*)-(–)-1-phenylethan-1-amine (**4**) (0.181 g, 0.19 mL, 1.494 mmol) and 2-pyridinecarboxaldehyde (**3**) (0.148 g, 0.13 mL, 1.379 mmol) was heated for 24 h. After column chromatography (eluent PE:acetone:ammonia = 10:0.5:0.01) 0.322 g (61%) of the major diastereoisomer (*R*,*S*)-**6a** and 0.089 g (17%) of the minor diastereoisomer (*S*,*S*)-**6b** were isolated. The total yield of **6** is 78%.

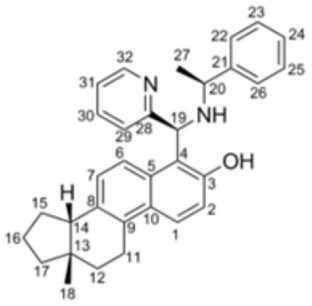


Data of (19*R*,20*S*)-**6a**

mp 80-84 °C (colorless crystals); $[\alpha]_D^{25}$ = –20.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.10 (s, 3H, H-C(18)), 1.52 (d, 3H, *J* 6.8 Hz, H-C(27)), 1.57-1.75 (m, 6H, H-C(15), H-C(12), H-C(16), H-C(17)), 1.83 (ddd, 1H, *J* 13.0, 11.2, 5.7 Hz, H-C(12)), 2.20-2.25 (m, 1H, H-C(15)), 2.72 (dd, 1H, *J* 9.1, 9.0 Hz, H-C(14)), 3.04 (ddd, 1H, *J* 16.9, 11.0, 5.7 Hz, H-C(11)), 3.18 (ddd, 1H, *J* 17.0, 5.2, 4.1 Hz, H-C(11)), 3.90 (q, 1H, *J* 6.6 Hz, H-C(20)), 4.24 (br s, 1H, NH), 5.54 (s, 1H, H-C(19)), 6.65 (d, 1H, *J* 8.0 Hz, H-C(29)), 7.05 (d, 1H, *J* 8.8 Hz, H-C(7)), 7.08 (dd, 1H, *J* 7.2, 5.1 Hz, H-C(31)), 7.18 (d, 1H, *J* 9.1 Hz, H-C(2)), 7.26-7.30 (m, 4H, H-C(6), H-C(22), H-C(26), H-C(24)), 7.33-7.36 (m, 3H, H-C(30), H-C(23), H-C(25)), 7.99 (d, 1H, *J* 9.2 Hz, H-C(1)), 8.57 (dd, 1H, *J* 4.8, 0.8 Hz, H-C(32)), 13.28 (br s, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.0 (t, C(16)), 23.4 (t, C(11)), 23.9 (q, C(27)), 25.9 (q, C(18)), 31.8 (t, C(12)), 35.6 (t, C(15)), 39.4 (s, C(13)), 40.9 (t, C(17)), 50.5 (d, C(14)), 55.6 (d, C(20)), 58.9 (d, C(19)), 114.3 (s, (C_{ar})), 119.3 (d, C(6)), 119.5 (d, C(2)), 122.1 (d, C(29)), 122.4 (d, C(31)), 125.1 (d, C(1)), 127.0 (2d, C(22), C(26)), 127.1 (s, (C_{ar})), 127.6 (d, C(24)), 128.9 (2d, C(23), C(25)), 129.7 (d, C(7)), 130.7 (s, (C_{ar})), 132.2 (s, (C_{ar})), 134.4 (s, (C_{ar})), 136.9 (d, C(30)), 143.5 (s, (C_{ar})), 148.7 (d, C(32)), 156.7 (s, (C_{ar})), 159.6 (s, (C_{ar})); MS (ESI) *m/z*, 463 ([M + H]$^+$, 33), 342 (100); anal. calcd. for $C_{32}H_{34}N_2O$: C 83.08, H 7.41, N 6.06, found: C 83.45, H 7.76, N 6.34.

Data of (19*S*,20*R*)-**6b**

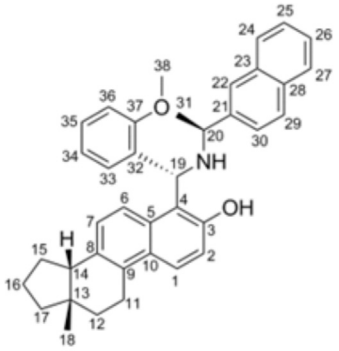
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (s, 3H, H-C(18)), 1.61 (d, 3H, *J* 6.6 Hz, H-C(27)), 1.59-1.77 (m, 6H, H-C(12), H-C(15), H-C(16), H-C(17)), 1.83 (ddd, 1H, *J* 13.0, 11.2, 5.7 Hz, H-C(12)), 2.26-2.32 (m, 1H, H-C(15)), 2.73 (dd, 1H,



J 9.2, 8.8 Hz, H-C(14)), 3.04 (ddd, 1H, *J* 16.9, 11.8, 5.7 Hz, H-C(11)), 3.16 (ddd, 1H, *J* 17.0, 5.3, 4.0 Hz, H-C(11)), 3.94 (q, 1H, *J* 6.6 Hz, H-C(20)), 6.06 (s, 1H, H-C(19)), 6.85 (d, 1H, *J* 8.0 Hz, H-C(29)), 7.14 (d, 1H, *J* 9.2 Hz, H-C(2)), 7.14 (m, 1H, H-C(31)), 7.19 (d, 1H, *J* 8.8 Hz, H-C(7)), 7.19-7.22 (m, 1H, H-C(24)), 7.27-7.30 (m, 2H, H-C(23), H-C(25)), 7.31-7.33 (m, 2H, H-C(22), H-C(26)), 7.44 (td, 1H, *J* 7.7, 1.8 Hz, H-C(30)), 7.69 (d, 1H, *J* 8.8 Hz, H-C(6)), 7.95 (d, 1H, *J* 9.2 Hz, H-C(1)), 8.60-8.61 (m, 1H, H-C(32)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.3 (q, C(27)), 23.0 (t, C(16)), 23.5 (t, C(11)), 25.9 (q, C(18)), 31.8 (t, C(12)), 35.8 (t, C(15)), 39.4 (s, C(13)), 40.9 (t, C(17)), 50.6 (d, C(14)), 54.7 (d, C(20)), 59.6 (d, C(19)), 114.1 (s, (C_{ar})), 119.1 (d, C(6)), 119.7 (d, C(2)), 122.4 (d, C(29)), 122.6 (d, C(31)), 125.2 (d, C(1)), 126.8 (2d, C(22), C(26)), 127.2 (s, (C_{ar})), 127.4 (d, C(24)), 128.7 (2d, C(23), C(25)), 129.7 (d, C(7)), 131.0 (s, (C_{ar})), 132.0 (s, (C_{ar})), 134.5 (s, (C_{ar})), 137.3 (d, C(30)), 144.0 (s, (C_{ar})), 148.9 (d, C(32)), 156.3 (s, (C_{ar})), 159.8 (s, (C_{ar})).

(13*S*,14*S*)-4-((2-Methoxyphenyl)(((*S*)-1-(naphthalen-2-yl)ethyl)amino)methyl)-13-methyl-12,13,14,15,16,17-hexahydro-11*H*-cyclopenta[*a*]phenanthren-3-ol (**8**)

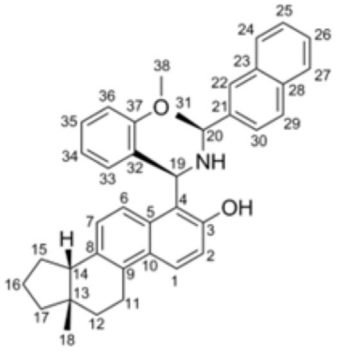
According to the general procedure a mixture of **1** (0.312 g, 1.236 mmol), (*S*)-(–)-1-(naphthalene-2-yl)ethan-1-amine (**7**) (0.275 g, 1.607 mmol) and 2-methoxybenzaldehyde (**2**) (0.202 g, 1.483 mmol) was heated for 96 h. After column chromatography (eluent PE:acetone:ammonia = 20:1:0.05) 0.138 g (44%) of the starting deoxy-isoequilenine (**1**), 0.174 g (26%) of the major diastereoisomer (*S*,*S*)-**8a** and 0.042 g (6%) of the minor diastereoisomer (*R*,*S*)-**8b** were isolated. The total yield of **8** is 32%.



Data of (19*S*,20*S*)-**8a**

mp 101-104 °C (colorless crystals); $[\alpha]_D^{25}$ = +159 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.11 (s, 3H, H-C(18)), 1.47-1.69 (m, 6H, H-C(12), H-C(15), H-C(16), H-C(17)),

1.55 (d, 3H, *J* 6.9 Hz, H-C(31)), 1.79 (ddd, 1H, *J* 13.1, 11.2, 5.7 Hz, H-C(12)), 2.11-2.17 (m, 1H, H-C(15)), 2.58 (br s, 1H, NH), 2.69 (t, 1H, *J* 9.1 Hz, H-C(14)), 3.05 (ddd, 1H, *J* 16.8, 11.0, 5.7 Hz, H-C(11)), 3.17 (ddd, 1H, *J* 16.9, 5.3, 4.0 Hz, H-C(11)), 3.55 (s, 3H, H-C(38)), 4.00-4.06 (m, 1H, H-C(20)), 5.91 (s, 1H, H-C(19)), 6.69 (td, 1H, *J* 7.7, 0.8 Hz, H-C(33)), 6.77 (d, 1H, *J* 8.2 Hz, H-C(36)), 6.93 (d, 1H, *J* 8.8 Hz, H-C(7)), 6.95 (dd, 1H, *J* 7.7, 1.6 Hz, H-C(35)), 7.13 (d, 1H, *J* 8.9 Hz, H-C(6)), 7.12-7.15 (m, 1H, H-C(34)), 7.26 (d, 1H, *J* 9.2 Hz, H-C(2)), 7.42 (dd, 1H, *J* 8.4, 1.7 Hz, H-C(30)), 7.47-7.51 (m, 2H, H-C(25), H-C(26)), 7.57 (s, 1H, H-C(22)), 7.72-7.74 (m, 1H, H-C(24)), 7.87-7.90 (m, 2H, H-C(27), H-C(29)), 8.00 (d, 1H, *J* 9.2 Hz, H-C(1)), 13.71 (s, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.7 (q, C(31)), 23.0 (t, C(16)), 23.4 (t, C(11)), 26.0 (q, C(18)), 31.9 (t, C(12)), 35.5 (t, C(15)), 39.4 (s, C(13)), 40.9 (t, C(17)), 50.5 (d, C(14)), 54.5 (d, C(19)), 55.1 (q, C(38)), 56.9 (d, C(20)), 110.3 (d, C(36)), 114.0 (s, (C_{ar})), 119.2 (d, C(2)), 119.6 (d, C(6)), 121.2 (d, C(33)), 124.9 (d, C(1)), 124.9 (d, C(30)), 125.9* (d, C(25)), 126.3* (d, C(26)), 126.7 (d, C(22)), 127.3 (s, (C_{ar})), 127.8 (d, C(25)), 128.0 (d, C(24)), 128.2 (d, C(29)), 128.5 (s, (C_{ar})), 129.2 (d, C(34)), 129.3 (d, C(7)), 129.8 (d, C(35)), 130.5 (s, (C_{ar})), 131.4 (s, (C_{ar})), 133.1 (s, (C_{ar})), 133.4 (s, (C_{ar})), 134.2 (s, (C_{ar})), 140.4 (s, (C_{ar})), 156.5 (s, (C_{ar})), 157.2 (s, (C_{ar})); MS (ESI) *m/z*, 542 ([M + H]$^+$, 43), 408 (21), 371 (100), 275 (20), 265 (75); anal. calcd. for $C_{38}H_{39}NO_2$: C 84.25, H 7.26, N 2.59, found: C 84.43, H 7.05, N 2.41.

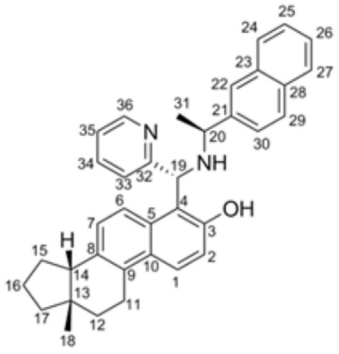


Data of (19*R*,20*S*)-**8b**

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.03 (s, 3H, H-C(18)), 1.69 (d, 3H, *J* 6.6 Hz, H-C(27)), 1.54-1.80 (m, 7H, H-C(12), H-C(15), H-C(16), H-C(17)), 2.22-2.29 (m, 1H, H-C(15)), 2.66 (t, 1H, *J* 9.1 Hz, H-C(14)), 2.98 (ddd, 1H, *J* 16.9, 11.5, 5.7 Hz, H-C(11)), 3.09 (ddd, 1H, *J* 16.6, 5.5, 3.8 Hz, H-C(11)), 4.00 (s, 3H, H-C(38)), 4.11 (q, 1H, H-C(20)), 6.44 (s, 1H, H-C(19)), 6.75 (t, 1H, *J* 7.5 Hz, H-C_{ar}), 6.95 (d, 1H, *J* 8.2 Hz, H-C_{ar}), 7.05 (dd, 1H, *J* 7.7, 1.4 Hz, H-C_{ar}), 7.10 (d, 1H, *J* 8.8 Hz, H-C(7)), 7.12 (d, *J* = 9.2 Hz, 1H, H-C(2)), 7.21-7.22 (m, 2H, H-C(31), H-C(24)), 7.39-7.42 (m, 2H, H-C_{ar}), 7.51 (d, 1H, *J* 9.0 Hz, H-C(6)), 7.66 (s, 1H, H-C(22)), 7.70-7.73 (m, 1H, H-C_{ar}), 7.74-7.77 (m, 2H, H-C_{ar}), 7.85-7.90 (m, 1H, H-C_{ar}), 13.37 (br s, 1H, OH).

(13*S*,14*S*)-13-Methyl-4-((((*S*)-1-(naphthalen-2-yl)ethyl)amino)(pyridin-2-yl)methyl)-12,13,14,15,16,17-hexahydro-11*H*-cyclopenta[*a*]phenanthren-3-ol (**9**)

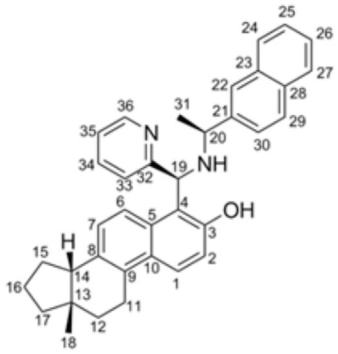
According to the general procedure a mixture of **1** (0.168 g, 0.666 mmol), (*S*)-(–)-1-(naphthalene-2-yl)ethan-1-amine (**7**) (0.148 g, 0.866 mmol) and 2-pyridinecarboxaldehyde (**3**) (0.085 g, 0.076 mL, 0.799 mmol) was heated for 48 h. After column chromatography (eluent PE:acetone:ammonia = 20:1:0.01) 0.011 g (7%) of the starting deoxy-isoequilenine (**1**), 0.236 g (69%) of the major diastereoisomer (*R*,*S*)-**9a** and 0.030 g (9%) of the minor diastereoisomer (*S*,*S*)-**9b** were isolated. The total yield of **9** is 78%.



Data of (19*R*,20*S*)-**9a**

mp 97-101 °C (colorless crystals); $[\alpha]_D^{25}$ = –18 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.13 (s, 3H, H-C(18)), 1.55-1.74 (m, 6H, H-C(15), H-C(12), H-C(16), H-C(17)), 1.61 (d, 3H, *J* 6.8 Hz, H-C(31)), 1.84 (ddd, 1H, *J* 13.0, 11.2, 5.7 Hz, H-C(12)), 2.20 (ddd, 1H, *J* 13.0, 8.1, 3.9 Hz, H-C(15)), 2.72 (t, 1H, *J* 9.1 Hz, H-C(14)), 3.06 (ddd, 1H, *J* 16.9, 11.1, 5.7 Hz, H-C(11)), 3.19 (ddd, 1H, *J* 16.9, 5.4, 3.8 Hz, H-C(11)), 4.06 (q, 1H, *J* 6.8 Hz, H-C(20)), 4.33 (br s, 1H, NH), 5.58 (s, 1H, H-C(19)), 6.64 (d, 1H, *J* 8.0 Hz, H-C(33)), 6.97 (d, 1H, *J* 8.8 Hz, H-C(7)), 7.08 (dd, 1H, *J* 7.2, 0.5 Hz, H-C(35)), 7.20 (d, 1H, *J* 9.1 Hz, H-C(2)), 7.21 (d, 1H, *J* 8.8 Hz, H-C(6)), 7.34 (td, 1H, *J* 7.8, 1.8 Hz, H-C(34)), 7.46-7.49 (m, 2H, H-C(25), H-C(26)), 7.51 (dd, 1H, *J* 8.5, 1.7 Hz, H-C(30)), 7.62 (s, 1H, H-C(22)), 7.71-7.73 (m, 1H, H-C(24)), 7.83-7.86 (m, 1H, H-C(27)), 7.88 (d, 1H, *J* 8.5 Hz, H-C(29)), 8.01 (d, 1H, *J* 9.1 Hz, H-C(1)), 8.57 (ddd, 1H, *J* 4.9, 1.6, 0.8 Hz, H-C(36)), 13.24 (br s, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.0 (t, C(16)), 23.5 (t, C(11)), 23.7 (q, C(31)), 25.9 (q, C(18)), 31.8 (t, C(12)), 35.6 (t, C(15)), 39.4 (s, C(13)), 40.9 (t, C(17)), 50.5 (d, C(14)), 55.6 (d, C(20)), 58.9 (d, C(19)), 114.5 (s, (C_{ar})), 119.4 (d, C(6)), 119.6 (d, C(2)), 122.1 (d, C(33)), 122.4 (d, C(35)), 124.4 (d, C(30)), 125.2 (d, C(1)), 125.9* (d, C(26)), 126.3* (d, C(25)), 126.5 (d, C(22)), 127.1 (s, (C_{ar})), 127.8 (d, C(27)), 128.1 (d, C(24)), 129.0 (d, C(29)), 129.7 (d, C(7)), 130.7 (s, (C_{ar})), 132.3 (s, (C_{ar})), 133.1 (s, (C_{ar})), 133.5 (s, (C_{ar})), 134.5 (s, (C_{ar})), 137.0 (d, C(4)), 140.7 (s, (C_{ar})), 148.6 (d, C(36)), 156.7 (s, (C_{ar})), 159.5 (s, (C_{ar}));

MS (ESI) *m/z*, 513 ([M + H]$^+$, 48), 342 (100); anal. calcd. for $C_{36}H_{36}N_2O$: C 84.34, H 7.08, N 5.46, found: C 84.01, H 7.37, N 5.35.



Data of (19*S*,20*S*)-**9b**

mp 110-114 °C (colorless crystals); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (s, 3H, H-C(18)), 1.51-1.83 (m, 7H, H-C(15), H-C(12), H-C(16), H-C(17)), 1.70 (d, 3H, *J* 6.6 Hz, H-C(27)), 2.30 (ddd, 1H, *J* 12.4, 8.0, 3.9 Hz, H-C(15)), 2.71 (t, 1H, *J* 9.1 Hz, H-C(14)), 2.98 (ddd, 1H, *J* 16.8, 10.9, 5.6 Hz, H-C(11)), 3.04-3.08 (m, 1H, H-C(11)), 4.13 (q, 1H, *J* 6.6 Hz, H-C(20)), 6.06 (s, 1H, H-C(19)), 6.85 (d, 1H, *J* 8.0 Hz, H-C(33)), 7.06 (d, 1H, *J* 9.1 Hz, H-C(2)), 7.14 (dd, 1H, *J* 7.2, 5.0 Hz, H-C(35)), 7.17 (d, 1H, *J* 8.7 Hz, H-C(7)), 7.37-7.40 (m, 2H, H-C(24), H-C(25*)), 7.41-7.46 (m, 2H, H-C(30), H-C(34)), 7.66-7.68 (m, 3H, H-C(6), H-C(22), H-C(26*)), 7.72 (d, 1H, *J* 8.6 Hz, H-C(29)), 7.74 (dd, 1H, *J* 9.4, 2.3 Hz, H-C_{ar}), 7.85 (d, 1H, *J* 9.16 Hz, H-C_{ar}), 8.61-8.62 (m, 1H, H-C(36)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.7 (q, C-27), 23.0 (t, C-16), 23.4 (t, C-11), 25.9 (q, C-18), 31.8 (t, C-12), 35.7 (t, C-15), 39.4 (s, C-13), 40.9 (t, C-17), 50.5 (d, C-14), 55.5 (d, C-20), 59.9 (d, C-19), 114.6 (s, (C_{ar})), 119.1 (d, (C_{ar})), 119.7 (d, C-2), 122.4 (d, C-33), 122.7 (d, C-35), 125.1 (d, C-1), 125.2 (d, (C_{ar})), 125.3 (d, (C_{ar})), 125.7 (d, (C_{ar})), 126.0 (d, (C_{ar})), 127.2 (s, (C_{ar})), 127.6 (d, (C_{ar})), 128.0 (d, (C_{ar})), 128.3 (d, (C_{ar})), 129.7 (d, C-7), 131.0 (s, (C_{ar})), 131.9 (s, (C_{ar})), 132.9 (s, (C_{ar})), 133.3 (s, (C_{ar})), 134.4 (s, (C_{ar})), 137.3 (d, (C_{ar})), 141.1 (s, (C_{ar})), 148.9 (d, C-36), 156.1 (s, (C_{ar})), 159.8 (s, (C_{ar})).

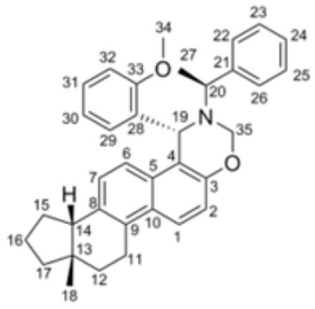
General procedure for the enantioselective addition of diethylzinc to aldehydes

To a solution of the corresponding ligand **5a**, **6a**, **8a** and **9a** (3 mol% based on the aldehyde used in the reaction) in dry toluene (4 mL) Et_2Zn (1.7 equiv of 1 mol L^{-1} solution in hexane) was added dropwise at 0 °C. The mixture was stirred for 30 min at 0 °C and then the corresponding aldehyde (1 equiv) was added at –20 °C. The reaction was stirred and allowed to warm up to 20 °C, and monitored by TLC (PE/Et_2O = 4:1) until the aldehyde was consumed. The mixture was quenched (aq NH_4Cl), extracted with Et_2O (3 × 20 mL), and dried. After evaporation of the solvent, the crude product was purified by column chromatography (eluent PE/Et_2O = 20:1). The enantiomeric excess of the obtained secondary alcohols was determined by GC or HPLC with chiral columns. Conditions for determination of enantiomeric excess are described in the SI section.

General procedure for the synthesis of 1,3-dihydronaphthoxazines

To a solution of the chiral aminomethylnaphthols **5a**, **6a**, **8a** and **9a** (0.200 mmol) in THF (4 mL) 37% aq solution of formaldehyde (calculated to provide 2 equiv of formaldehyde) was added. The reaction mixture was stirred at 50 °C for 5 h for the formation of compounds **5a** and **6a**, and 24 h for the compounds **8a** and **9a**. After evaporation of the solvent the crude product was chromatographed (eluent PE to PE/acetone = 20:1 for compound **10a**; eluent PE to PE/MTBE = 10:1 for compound **11a**; eluent PE/MTBE = 15:1 for compounds **12a** and **13a**).

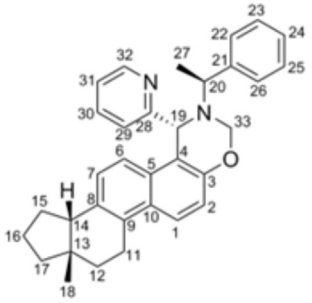
(1*S*,8a*S*,11a*S*)-1-(2-Methoxyphenyl)-8a-methyl-2-((*S*)-1-phenylethyl)-1,2,3,7,8,8a,9,10,11,11a-decahydrocyclopenta[7,8]phenanthro[1,2-*e*][1,3]oxazine (**10a**)



According to the general procedure **10a** was isolated in 92% yield. mp 103-106 °C (colorless crystals); $[\alpha]_D^{25}$ = +204 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (s, 3H, H-C(18)), 1.52 (d, 3H, *J* 6.7 Hz, H-C(27)), 1.48-1.70 (m, 6H, H-C(12), H-C(15), H-C(16), H-C(17)), 1.80 (ddd, 1H, *J* 13.0, 11.3, 5.7 Hz, H-C(12)), 2.10-2.17 (m, 1H, H-C(15)), 2.66 (t, 1H, *J* 9.1 Hz, H-C(14)), 3.02 (ddd, 1H, *J* 16.9, 11.2, 5.7 Hz, H-C(11)), 3.14 (ddd, 1H, *J* 17.0, 5.4, 3.6 Hz, H-C(11)), 3.63 (s, 3H, H-C(34)), 4.10 (q, 1H, *J* 6.7 Hz, H-C(20)), 4.99 (dd, 1H, *J* 10.8, 1.7 Hz, H-C(35)), 5.12 (d, 1H, *J* 10.8 Hz, H-C(35)), 5.68 (s, 1H, H-C(19)), 6.66 (td, 1H, *J* 7.5, 0.9 Hz, H-C(30)), 6.80 (dd, 1H, *J* 7.6, 1.6 Hz, H-C(29)), 6.86 (dd, 1H, *J* 8.2, 0.8 Hz, H-C(32)), 6.90 (d, 1H, *J* 8.7 Hz, H-C(6)), 6.94 (d, 1H, *J* 8.7 Hz, H-C(7)), 7.13 (d, 1H, *J* 9.2 Hz, H-C(2)), 7.17 (td, 1H, *J* 8.2, 1.7 Hz, H-C(31)), 7.27-7.30 (m, 1H, H-C(24)), 7.31-7.34 (m, 4H, H-C(22), H-C(26), H-C(23), H-C(25)), 7.92 (d, 1H, *J* 9.2, H-C(1)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.7 (q, C-27), 22.9 (t, C-16), 23.3 (t, C-11), 25.8 (q, C-18), 31.7 (t, C-12), 35.5 (t, C-15), 39.3 (s, C-13), 41.0 (t, C-17), 50.6 (d, C-14), 52.5 (d, C-19), 54.9 (q, C-34), 60.2 (d, C-20), 75.2 (t, C-35), 110.3 (d, C-32), 113.7 (s, C_{ar}), 117.7 (d, C-2), 119.8 (d, C-30), 120.5 (d, C-6), 124.0 (d, C-1), 127.1 (d, C-24), 127.7 (s, C_{ar}), 128.0* (2d, C-22,

C-26), 128.5* (2d, C-23, C-25), 128.6 (d, C-31), 129.5 (d, C-7), 130.5 (s, C_{ar}), 130.9 (s, C_{ar}), 131.4 (s, C_{ar}), 131.5 (d, C-29), 134.8 (s, C_{ar}), 144.6 (s, C_{ar}), 152.3 (s, C_{ar}), 156.9 (s, C_{ar}); MS (ESI) *m/z*, 504 ($[M + H]^+$, 3), 371 (100), 265 (6).

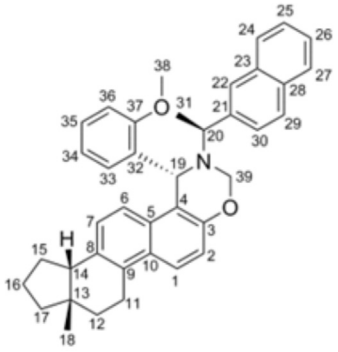
(1*R*,8a*S*,11a*S*)-8a-Methyl-2-((*S*)-1-phenylethyl)-1-(pyridin-2-yl)-1,2,3,7,8,8a,9,10,11,11a-deca-hydrocyclopenta[7,8]phenanthro[1,2-*e*][1,3]oxazine (**11a**)



According to the general procedure **11a** was isolated in 97% yield. mp 150-154 °C (colorless crystals); $[\alpha]_D^{25}$ = +206 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (s, 3H, H-C(18)), 1.53 (d, 3H, *J* 6.6 Hz, H-C(27)), 1.47-1.70 (m, 6H, H-C(12), H-C(15), H-C(16), H-C(17)), 1.77 (ddd, 1H, *J* 13.1, 11.2, 5.7 Hz, H-C(12)), 2.10-2.15 (m, 1H, H-C(15)), 2.64 (t, 1H, *J* 9.1 Hz, H-C(14)), 3.01 (ddd, 1H, *J* 16.9, 11.1, 5.7 Hz, H-C(11)), 3.12 (ddd, 1H, *J* 17.0, 5.5, 3.8 Hz, H-C(11)), 4.07 (q, 1H, *J* 6.6 Hz, H-C(20)), 5.11 (dd, 1H, *J* 10.7, 1.8 Hz, H-C(33)), 5.21 (d, 1H, *J* 10.7 Hz, H-C(33)), 5.30 (s, 1H, H-C(19)), 6.84 (d, 1H, *J* 8.7 Hz, H-C(6)), 6.89 (d, 1H, *J* 8.7 Hz, H-C(7)), 7.03 (d, 1H, *J* 7.9 Hz, H-C(29)), 7.09 (ddd, 1H, *J* 7.4, 4.9, 0.9 Hz, H-C(31)), 7.17 (d, 1H, *J* 9.3 Hz, H-C(2)), 7.29-7.32 (m, 1H, H-C(24)), 7.35-7.37 (m, 2H, H-C(23), H-C(25)), 7.42-7.43 (m, 2H, H-C(22), H-C(26)), 7.56 (td, 1H, *J* 7.7, 1.8 Hz, H-C(30)), 7.93 (d, 1H, *J* 9.3 Hz, H-C(1)), 8.50 (dd, 1H, *J* 4.8, 0.9 Hz, H-C(32)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.9 (q, C-27), 22.9 (t, C-16), 23.3 (t, C-11), 25.8 (q, C-18), 31.7 (t, C-12), 35.5 (t, C-15), 39.3 (s, C-13), 40.9 (t, C-17), 50.6 (d, C-14), 59.7 (d, C-20), 59.9 (d, C-19), 74.3 (t, C-33), 112.7 (s, C_{ar}), 117.9 (d, C-2), 120.5 (d, C-6), 122.1 (d, C-31), 123.9 (d, C-29), 124.3 (d, C-1), 127.5 (d, C-24), 127.8 (s, C_{ar}), 128.0 (2d, C-22, C-26), 128.6 (2d, C-23, C-25), 129.3 (d, C-7), 130.8 (s, C_{ar}), 131.1 (s, C_{ar}), 134.8 (s, C_{ar}), 136.4 (d, C-30), 145.3 (s, C_{ar}), 149.5 (d, C-32), 152.1 (s, C_{ar}), 162.49 (s, C_{ar}); MS (ESI) *m/z*, 475 ($[M + H]^+$, 18), 342 (100).

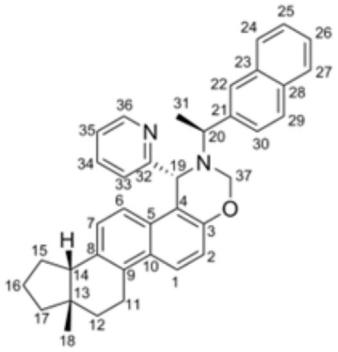
(1*S*,8a*S*,11a*S*)-1-(2-Methoxyphenyl)-8a-methyl-2-((*S*)-1-(naphthalen-2-yl)ethyl)-1,2,3,7,8,8a,9,10,11,11a-deca-hydrocyclopenta[7,8]-phenanthro[1,2-*e*][1,3]oxazine (**12a**)

According to the general procedure **12a** was isolated in 80% yield. mp 85-88 °C (colorless crystals); $[\alpha]_D^{25}$ = +161 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (s, 3H, H-C(18)), 1.47-1.53 (m, 1H, H-C(15)), 1.58-1.68 (m, 5H, H-C(12), H-C(16), H-C(17)), 1.60 (d, 3H, *J* 6.7 Hz, H-C(31)), 1.79 (ddd, 1H, *J* 13.1, 11.3, 5.7 Hz,



H-C(12)), 2.12 (ddd, 1H, *J* 13.0, 8.5, 4.1 Hz, H-C(15)), 2.66 (t, 1H, *J* 9.1 Hz, H-C(14)), 3.03 (ddd, 1H, *J* 17.0, 11.2, 5.7 Hz, H-C(11)), 3.15 (ddd, 1H, *J* 16.9, 5.6, 3.6 Hz, H-C(11)), 3.40 (s, 3H, H-C(38)), 4.26 (q, 1H, *J* 6.7 Hz, H-C(20)), 5.04 (dd, 1H, *J* 10.8, 1.7 Hz, H-C(39)), 5.16 (d, 1H, *J* 10.6 Hz, H-C(39)), 5.75 (s, 1H, H-C(19)), 6.66 (td, 1H, *J* 7.5, 1.0 Hz, H-C(34)), 6.81 (dd, 1H, *J* 7.6, 1.7 Hz, H-C(33)), 6.82 (dd, 1H, *J* 8.3, 1.0 Hz, H-C(36)), 6.86 (d, 1H, *J* 8.7 Hz, H-C(6)), 6.92 (d, 1H, *J* 8.7 Hz, H-C(7)), 7.15 (d, 1H, *J* 9.2 Hz, H-C(2)), 7.16 (dd, 1H, *J* 8.1, 1.7 Hz, H-C(35)), 7.43-7.47 (m, 2H, H-C(25), H-C(26)), 7.56 (dd, 1H, *J* 8.5, 1.7 Hz, H-C(30)), 7.71 (s, 1H, H-C(22)), 7.75-7.76* (m, 1H, H-C(24)), 7.82 (d, 1H, *J* 8.5 Hz, H-C(29)), 7.84-7.86* (m, 1H, H-C(27)), 7.93 (d, 1H, *J* 9.2 Hz, H-C(1)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8 (q, C-27), 22.9 (t, C-16), 23.3 (t, C-11), 25.8 (q, C-18), 31.7 (t, C-12), 35.5 (t, C-15), 39.4 (s, C-13), 41.0 (t, C-17), 50.6 (d, C-14), 52.6 (d, C-19), 54.8 (q, C-38), 60.4 (d, C-20), 74.2 (t, C-39), 110.2 (d, C-36), 113.7 (d, C_{ar}), 117.7 (d, C-2), 119.8 (d, C-34), 120.5 (d, C-6), 124.0 (d, C-1), 125.6 (d, C-25), 125.8 (d, C-26), 126.8 (d, C-22), 127.2 (d, C_{ar}), 127.4 (d, C_{ar}), 127.6 (d, C-30), 127.7 (d, C-29), 128.1 (d, C-27), 128.7 (d, C-35), 129.5 (d, C-7), 130.5 (d, C_{ar}), 130.9 (d, C_{ar}), 131.4 (d, C-33), 131.5 (d, C_{ar}), 133.0 (d, C_{ar}), 133.4 (d, C_{ar}), 134.9 (d, C_{ar}), 142.3 (d, C_{ar}), 152.3 (d, C_{ar}), 156.9 (d, C_{ar}); MS (ESI) *m/z*, 554 ($[M + H]^+$, 11), 371 (46), 339 (45), 155 (100).

(1*R*,8a*S*,11a*S*)-8a-Methyl-2-((*S*)-1-(naphthalen-2-yl)ethyl)-1-(pyridin-2-yl)-1,2,3,7,8,8a,9,10,11,11a-decahydrocyclopenta[7,8]phenanthro[1,2-*e*][1,3]oxazine (**13a**)



According to the general procedure **13a** was isolated in 97% yield. mp 101-104 °C (colorless crystals); $[\alpha]_D^{25}$ = +216 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (s, 3H, H-C(18)), 1.45-1.51 (m, 1H, H-C(15)), 1.55-1.69 (m, 5H, H-C(12), H-C(16), H-C(17)), 1.60 (d, 3H, *J* 6.6 Hz, H-C(31)), 1.76 (ddd, 1H, *J* 13.1, 11.3, 5.8 Hz, H-C(12)), 2.07-2.13

(m, 1H, H-C(15)), 2.62 (dd, 1H, *J* 9.2, 9.1 Hz, H-C(14)), 3.02 (ddd, 1H, *J* 17.0, 11.1, 5.7 Hz, H-C(11)), 3.13 (dd, 1H, *J* 17.0, 5.4, 3.9 Hz, H-C(11)), 4.25 (q, 1H, *J* 6.6 Hz, H-C(20)), 5.17 (dd, 1H, *J* 10.6, 1.7 Hz, H-C(37)), 5.27 (d, 1H, *J* 10.6 Hz, H-C(37)), 5.37 (s, 1H, H-C(19)), 6.78 (d, 1H, *J* 8.7 Hz, H-C(6)), 6.84 (dd, 1H, *J* 8.8 Hz, H-C(7)), 7.01 (d, 1H, *J* 7.9 Hz, H-C(33)), 7.09 (ddd, 1H, *J* 7.4, 4.9, 0.8 Hz, H-C(35)), 7.19 (d, 1H, *J* 9.3 Hz, H-C(2)), 7.45-7.49 (m, 2H, H-C_{ar}), 7.53 (dt, 1H, *J* 7.7, 1.8 Hz, H-C(34)), 7.65 (dd, 1H, *J* 8.5, 1.6 Hz, H-C(30)), 7.76-7.79 (m, 1H, H-C_{ar}), 7.84 (s, 1H, H-C(22)), 7.86-7.89 (m, 1H, H-C_{ar}), 7.89 (d, 1H, *J* 8.5 Hz, H-C(29)), 7.94 (d, 1H, *J* 9.3 Hz, H-C(1)), 8.50 (dd, 1H, *J* 4.8, 0.9 Hz, H-C(36)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.0 (q, C-27), 22.9 (t, C-11), 23.3 (t, C-16), 25.8 (q, C-18), 31.7 (t, C-12), 35.5 (t, C-15), 39.3 (s, C-13), 40.9 (t, C-17), 50.5 (d, C-14), 59.9 (d, C-20), 60.0 (d, C-19), 74.3 (t, C-37), 112.7 (s, C_{ar}), 118.0 (d, C-2), 120.6 (d, C-6), 122.1 (d, C-35), 123.9 (d, C-33), 124.4 (d, C-1), 125.8 (d, C_{ar}), 126.1 (d, C_{ar}), 126.2 (d, C-30), 126.7 (d, C-22), 127.7 (s, C_{ar}), 127.9 (d, C_{ar}), 128.1 (d, C_{ar}), 128.4 (d, C-29), 129.3 (d, C-7), 130.7 (s, C_{ar}), 131.1 (s, C_{ar}), 133.2 (s, C_{ar}), 133.6 (s, C_{ar}), 134.9 (s, C_{ar}), 136.4 (d, C-34), 142.8 (d, C_{ar}), 149.5 (s, C-36), 152.2 (s, C_{ar}), 162.4 (s, C_{ar}); MS (ESI) *m/z*, 525 ([M + H]$^+$, 3), 353 (5), 344 (25), 183 (20), 155 (100), 145 (21), 60 (60).

Supplementary Information

Crystallographic data (excluding structure factors) for the structures in this work were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-2095267 (**5a**), and 2095266 (**11a**). Copies of the data can be obtained, free of charge, via https://www.ccdc.cam.ac.uk/structures/.

Supplementary data (NMR spectra of the synthesized compounds, crystal structures data and conditions for the determination of enantiomeric excess (GC or HPLC)) are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

This work was supported by Operational Program "Science and Education for Smart Growth" 2014-2020, co-financed by European Union through the European Structural and Investment Funds, Grant BG05M2OP001-1.002-0012.

The application of the equipment of INFRAMAT-project, part of the Bulgarian National Roadmap for Research Infrastructures, supported by Bulgarian Ministry of Education and Science is greatly acknowledged.

References

1. Betti, M.; *Gazz. Chim. Ital.* **1900**, *30 II*, 310.
2. Rodrigues, M. O.; Eberlin, M. N.; Neto, B. A. D.; *Chem. Rec.* **2021**, *21*, 2762. [Crossref]
3. Graebin, C. S.; Ribeiro, F. V.; Rogério, K. R.; Kummerle, A. E.; *Curr. Org. Synth.* **2019**, *16*, 855. [Crossref]
4. Insuasty, D.; Castillo, J.; Becerra, D.; Rojas, H.; Abonia, R.; *Molecules* **2020**, *25*, 505. [Crossref]
5. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F.; *Tetrahedron: Asymmetry* **1998**, *9*, 3667. [Crossref]
6. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P.; *Tetrahedron* **1999**, *55*, 14685. [Crossref]
7. Palmieri, G.; *Tetrahedron: Asymmetry* **2000**, *11*, 3361. [Crossref]
8. Cimarelli, C.; Palmieri, G.; Volpini, E.; *Tetrahedron: Asymmetry* **2002**, *13*, 2417. [Crossref]
9. Szatmári, I.; Sillanpää, R.; Fülöp, F.; *Tetrahedron: Asymmetry* **2008**, *19*, 612. [Crossref]
10. Marinova, M.; Kostova, K.; Tzvetkova, P.; Tavlinova-Kirilova, M.; Chimov, A.; Nikolova, R.; Shivachev, B.; Dimitrov, V.; *Tetrahedron: Asymmetry* **2013**, *24*, 1453. [Crossref]
11. Speich, E.; Banfi, L.; Moni, L.; Riva, R.; Rocca, V.; Basso, A.; *Chem. Heterocycl. Compd.* **2018**, *54*, 329. [Crossref]
12. Szatmári, I.; Fülöp, F.; *Curr. Org. Synth.* **2004**, *1*, 155. [Crossref]
13. Cimarelli, C.; Palmieri, G.; *Chirality* **2009**, *21*, 218. [Crossref]
14. Cardellicchio, C.; Capozzi, M. A. M.; Naso, F.; *Tetrahedron: Asymmetry* **2010**, *21*, 507. [Crossref]
15. Szatmári, I.; Fülöp, F.; *Tetrahedron* **2013**, *69*, 1255. [Crossref]
16. Olyaei, A.; Sadeghpour, M.; *RSC Adv.* **2019**, *9*, 18467. [Crossref]
17. Iftikhar, R.; Kamran, M.; Iftikhar, A.; Parveen, S.; Naeem, N.; Jamil, N.; *Mol. Diversity* **2022**. [Crossref]
18. Liu, D.-X.; Zhang, L.-C.; Wang, Q.; Da, C.-S.; Xin, Z.-Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C.; *Org. Lett.* **2001**, *3*, 2733. [Crossref]
19. Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C.; *J. Org. Chem.* **2003**, *68*, 1589. [Crossref]
20. Zagranyarska, I.; Kostova, K.; Zagranyarski, Y.; Nikolova, R.; Shivachev, B.; Dimitrov, V.; *Mol. Diversity* **2020**, *24*, 1343. [Crossref]
21. Cardellicchio, C.; Capozzi, M. A. M.; Alvarez-Larena, A.; Piniella, J. F.; Capitelli, F.; *CrystEngComm* **2012**, *14*, 3972. [Crossref]
22. Dikova, K.; Kostova, K.; Simova, S.; Linden, A.; Chimov, A.; Dimitrov, V.; *Polyhedron* **2019**, *165*, 177. [Crossref]
23. Gyémánt, N.; Engi, H.; Schelz, Z.; Szatmári, I.; Tóth, D.; Fülöp, F.; Molnár, J.; de Witte, P. A. M.; *Br. J. Cancer* **2010**, *103*, 178. [Crossref]
24. Yadav, Y.; MacLean, E. D.; Bhattacharyya, A.; Parmar, V. S.; Balzarini, J.; Barden, C. J.; Too, C. K. L.; Jha, A.; *Eur. J. Med. Chem.* **2011**, *46*, 3858. [Crossref]

25. Capozzi, M. A. M.; Cardellicchio, C.; *Tetrahedron: Asymmetry* **2017**, *28*, 1792. [Crossref]
26. Capozzi, M. A. M.; Cardellicchio, C.; Magaletti, A.; Bevilacqua, A.; Perricone, M.; Corbo, M. R.; *Molecules* **2014**, *19*, 5219. [Crossref]
27. Ankit, L.; Bijoy, P. M.; Mahendra, N.; *Curr. Org. Chem.* **2021**, *25*, 133. [Crossref]
28. *Spartan'08*, version 1.2.0; Wavefunction, Inc., USA, 2008. [Link] accessed in September 2022
29. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R.; *J. Am. Chem. Soc.* **1986**, *108*, 6071. [Crossref]
30. Noyori, R.; Kitamura, M.; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. [Crossref]
31. *CrysAlis PRO*, Agilent Technologies, UK Ltd, Yarnton, England, 2011.
32. Sheldrick, G. M.; *Acta Crystallogr., Sect. A: Found. Adv.* **2008**, *64*, 112. [Crossref]

Submitted: August 17, 2022
Published online: September 28, 2022