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Resolution, absolute configuration, and synthetic transformations of 7-amino-tetrahydroindazolones

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ABSTRACT

The chiral resolution of 7-amino-1-aryl-4,5,6,7-tetrahydro-indazol-4-ones was achieved via salt formation with *O,O′*-dibenzoyl tartaric acid. The transformation of enantiomerically enriched 7-amino-THIs into their corresponding azides proceeds with no decrease in their ee's. A comparison of the X-ray structures of the racemic and enantiopure forms of the title compounds explains the rather large melting point differences between both the series. The enantiopure azides obtained from the corresponding 7-amino-THIs were employed in copper-catalyzed Huisgen 1,3-dipolar cycloaddition reactions with various alkynes. The use of enantiomerically enriched THI scaffolds is demonstrated by the preparation of diastereomerically pure products when the former are conjugated with alkynes arising from natural sources.

1. Introduction

Since the first report on their synthesis in 1903, tetrahydroindazoles **2** (THIs)[1] as a subclass of pyrazoles **1** have caught the interest of organic and medicinal chemists (Fig. 1). Indeed, the molecular scaffold of THIs consists of both, a planar pyrazole unit and a C_4-tether, which is built from tetrahedral carbons. Such a skeleton helps to diversify the vectors of pharmacophore orientation in 3D space. As a consequence, the tetrahydroindazole core can be found in many biologically active compounds. By modifying the substituents, the applications of THIs can range from herbicides[2] to novel antituberculosis agents.[3]

As a result, even a short survey of the literature data shows a vivid renaissance in the field of THIs. Thus, compounds containing the latter scaffold were very recently reported to be useful corticotropin releasing factor (CRF) receptor antagonists.[4] Down-regulation of increased endogenous levels of CRF is applicable in the treatment of several gastrointestinal disorders, major depressive disorders, and dementia of Alzheimer's type. Cognitive abilities can also be improved by tetrahydroindazolones of general structure **2a**.[5] The same type of compounds also possesses antitumor activity while being less toxic than other available antitumor drugs. On the other hand, compounds **2b** are known for their selectivity toward GABA-A α 5 receptors and are useful for enhancing cognition.[6] More recently, other THI-3-carboxamides have been found to regulate the mitotic motor protein Eg5.[7] The specific inhibition of the latter prevents uncontrollable division of malignant cells. Furthermore, THIs **2c** were shown to be active against various carcinomas.[8] Compounds with the general formula **2d** are potent inhibitors of Heat-Shock Protein 90.[9] Additionally, 5-amino-4,5,6,7-tetrahydroindazoles possess dopaminergic activity[10] and THI-substituted 3,5-dihydroxy-6-heptenoic acids have shown HMG-CoA reductase inhibiting activity with IC_{50} = 3.0 nM.[11] Very recently, THIs have also been documented as farnesoid-X-receptor modulators that found use in prevention or treatment of high LDL cholesterol levels.[12] Other potential uses of THIs include inhibition of bacterial type II topoisomerases[13] and mimicking of the heterobicyclic P_1-arginine side-chain. The latter observation led to the discovery of thrombin inhibitors.[14] In addition, cannabinoid modulators[15] and compounds *en route* to the selective and drug-like ligands for the opioid σ1 receptor[16] have been documented within the tetrahydroindazole series.

The aforementioned list of possible applications of tetrahydroindazoles/tetrahydroindazolones is not a comprehensive one. Nevertheless, it is rather clear why structural[17] and synthetic interest in the field of differently substituted 4,5,6,7-THIs has continued.[18] Recently, the orthogonal and regioselective synthesis of *N*-alkyl-3-substituted tetrahydroindazolones has been reported.[19] Fluorine containing THIs have also been described.[20] Several processes toward tetrahydroindazole derivatives under microwave irradiation have been documented. These include Diels–Alder reactions,[21] as well as syntheses starting from enaminoketones.[22] Claramunt, Lopez et al.[23] have studied the synthesis and particularly the tautomeric equilibrium of tetrahydroindazolones. Various tetrahydroindazol-3-yl alanine derivatives[24] as well as novel THI-based chiral auxiliaries[25] have been obtained over the last decade. Enantiomerically enriched tetrahydroindazole derivatives have been obtained from (5*R*)-dihydrocarvone,[26] and also from (−)-menthone[27] and have been used in the formation of transition metal complexes. The analogues of the latter have been applied, for example, in asymmetric allylic alkylations.[28]

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Recently, we have reported a straightforward synthesis of racemic 7-(4-alkyl/aryl-[1,2,3]triazol-1-yl)-1-aryl-4,5,6,7-tetrahydro-1*H*-indazol-4-ones.[29] These molecular scaffolds are interesting in terms of medicinal chemistry. In order to use this approach for conjugation with compounds from natural sources (carbohydrates, peptides, etc.) and/or oligomerization, enantiopure forms of 1-aryl-7-azido-4,5,6,7-tetrahydro-1*H*-indazol-4-ones are required. Hence, we herein report a full account on the synthesis of enantiomerically enriched amines **3** (Fig. 1), their transformation into their corresponding azides and X-ray studies of both series of compounds. The use of such enantiomerically pure building blocks is demonstrated by their reactions with various monosaccharide derivatives: diastereomerically pure THI–sugar conjugates were obtained.

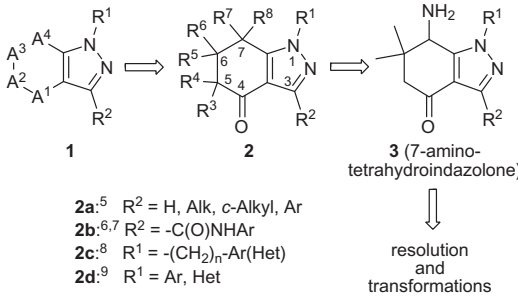
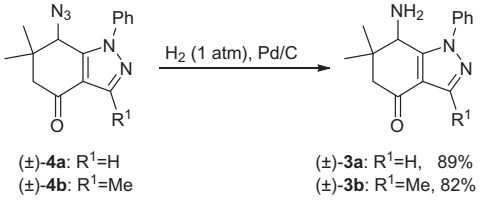


Figure 1. Generalized scaffolds of tetrahydroindazolones.

2. Results and discussions

2.1. Synthesis and absolute configuration of chiral 7-amino-tetrahydroindazolones

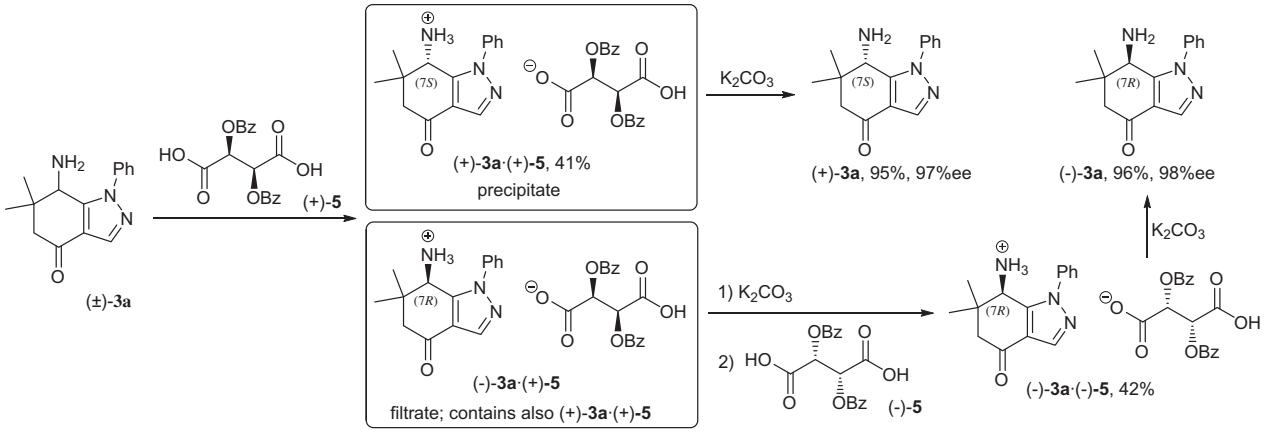
The target amines (±)-**3a**,**b** were obtained from the corresponding azides (±)-**4a**,**b**[30] via catalytic reduction over Pd/C (Scheme 1). It is interesting to note that earlier attempts used $SnCl_2$ as a reducing agent which lead to partial formation of 7-chloroderivatives.



Scheme 1. Catalytic hydrogenation of racemic 7-azidotetrahydroindazolones.

With racemic amines (±)-**3a**,**b** in hand, we turned our attention to their resolution into single enantiomers. Several commercially available chiral acids including mandelic acid, α-methoxy-α-phenylacetic acid, camphorsulfonic acid, tartaric acid, and *O*,*O*′-dibenzoyl tartaric acid were attempted. Thus, camphorsulfonic acid provided well-formed crystals of diastereomerically pure salt albeit in a low isolated yield. Tartaric acid showed certain positive results but mandelic acid and its 2-*O*-methylderivative did not produce solid salts. From the aforementioned group of chiral acids *O*,*O*′-dibenzoyl tartaric acid proved to be the best. Enantiomeric excesses of (+)-**3a** (97% ee) and (−)-**3a** (98% ee) were determined by direct measurement using HPLC with *Pirkle type* stationary phase. The enantiomeric purity of **3a** can be increased up to 99.5% by simple crystallization. On the other hand, the ee's of (+)-**3b** and (−)-**3b** after resolution were 92% and 93%, respectively. The experimental procedure of the chiral resolution consists of mixing the racemic 7-amino-tetrahydroindazolone **3a** or **3b** with 1 equiv of the appropriate enantiomer of *O*,*O*′-dibenzoyl tartaric acid in methanol in order to form the acidic salt of type **3**·**5** (Scheme 2). It was empirically observed that when (+)-(2*S*,3*S*)-di-*O*,*O*′-dibenzoyl tartaric acid (+)-**5** (D-form) was used, salt (+)-**3a**·(+)-**5** crystallized preferably in the presence of its diastereoisomer (−)-**3a**·(+)-**5**. Thus, enantiomerically enriched amine (+)-**3a** was obtained by treating the former with potassium carbonate solution. Similarly, the filtrate containing mainly diastereoisomer (−)-**3a**·(+)-**5** was also treated with potassium carbonate solution in order to obtain the enantiomerically enriched form of amine (−)-**3a**. The latter was then treated with (−)-(2*R*,3*R*)-di-*O*,*O*′-dibenzoyl tartaric acid (−)-**5** (L-form) and after salt formation, crystallization, and basic work-up produced the complementary form of enantiopure amine (−)-**3a**.

The absolute configuration of chirally homogeneous amine (+)-**3a** was established by single crystal X-ray studies of its derivative (−)-**6** obtained in the reaction with commercially available (1*S*)-(−)-camphanic chloride (Scheme 5). An identical route was used to prove independently the absolute configuration of (−)-**3a**. In the case of (+)-**3b** and (−)-**3b** (Scheme 3) we did not succeed in obtaining a crystalline material which would combine the newly formed amine moiety and a chiral auxiliary. However, X-ray studies of imine (−)-**7** obtained from (+)-**3b** with 78% yield demonstrated anomalous-dispersion effects of the relatively heavy bromine atom and thus allowed us to determine the absolute configuration within the **3b** series (Scheme 6). As expected, it kept the same empirical rule: the salt of general formula (+)-**3**·(+)-**5** preferably crystallizes in the presence of (−)-**3**·(+)-**5** while the salt of general formula (−)-**3**·(−)-**5** preferably crystallizes in the presence of (+)-**3**·(−)-**5**.



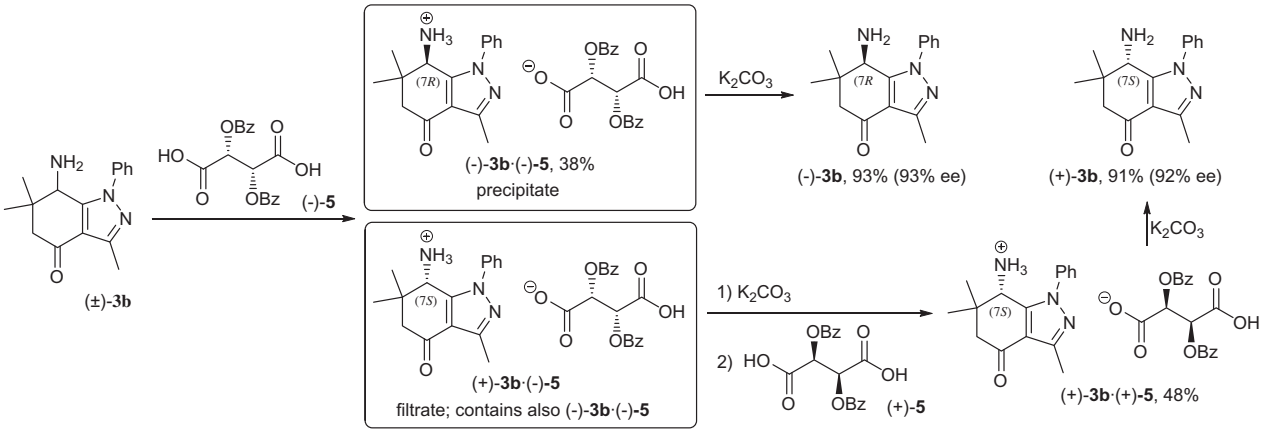
Scheme 2. Resolution of 7-amino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one **3a**.

2.2. Synthetic transformations of enantiomerically pure 7-amino-tetrahydroindazolones

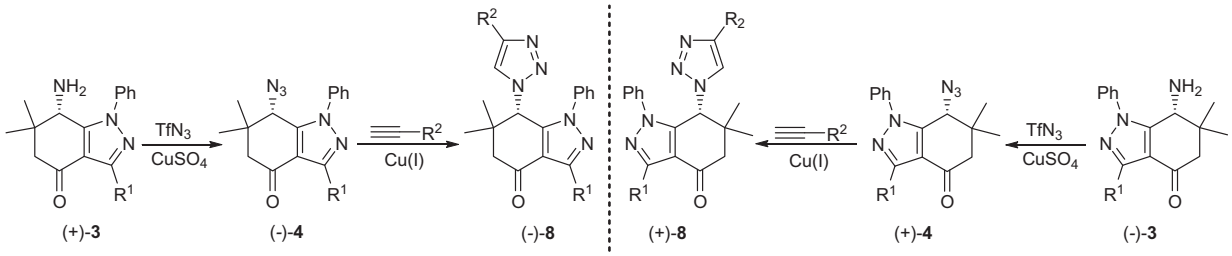
Newly obtained enantiomerically enriched amines **3** were transformed into the corresponding azides by a diazo transfer system consisting of trifluoromethanesulfonyl azide and a catalytic amount of $CuSO_4 \cdot 5H_2O$ (Scheme 4).[31] The isolated yields of enantiomerically pure azides range from 83% to 91%. With azides **4** in the hand, we proceeded to further functionalize the tetrahydroindazolone scaffold via CuAAC reactions.[32] Thus, we prepared triazoles **8a–c** reported earlier,[29] albeit in enantiomerically enriched form (Scheme 4, Table 1). This was achieved by mixing the corresponding azides with either phenylacetylene or propargylic alcohol in the presence of Cu^+ generating Cu^0/Cu^{2+} redox system at +40 °C. The expected 7-triazolyl-tetrahydroindazolones were obtained in moderate to good yields. One can acknowledge that the overall yields in the sequence *chiral amine → chiral azide → chiral triazole* are satisfactory; additionally, no decrease in ee's was observed (Table 1). Moreover, within the triazole series one can easily improve the enantiomeric purity by recrystallization. Next, we turned our attention to a dimerization experiment (Scheme 7) and obtained (+)-**8d** in 40% yield as a single diastereoisomer.

Sugar–heterocycle conjugates have attracted scientific interest for many decades. The most prominent examples are known from nucleoside analogues as antiviral and anticancer drugs. As a result, since the discovery of an efficient and regioselective 1,4-disubstituted 1,2,3-triazole synthesis, the field of carbohydrate–triazole conjugates has become particularly attractive.[33] Hence, the logical development of the field of sugar–heterocycle conjugates involves a conjugation of a heterocycle of choice with a carbohydrate scaffold via a triazole linker.[34] It has been shown that such an arrangement can improve biological targeting abilities.[35]

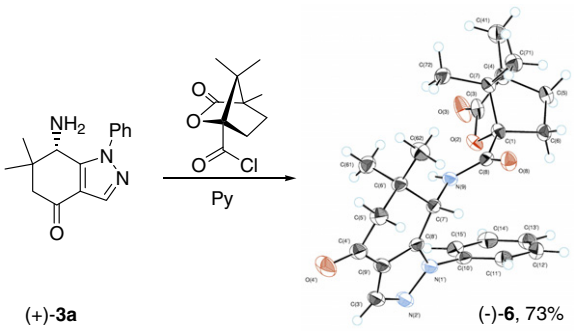
In this context we proceeded to conjugate our scaffolds to three different carbohydrate skeletons via a triazole linker. Thus, the use of propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **9**[36] and azides (+)-**4a** and (−)-**4a** resulted in the (7*R*)-conjugate (−)-**8e**



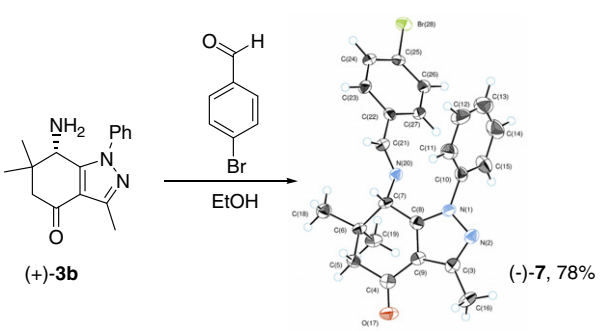
Scheme 3. Resolution of 7-amino-3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one **3b**.



Scheme 4. Synthesis of enantiomerically pure 7-triazolyl-tetrahydroindazolones.



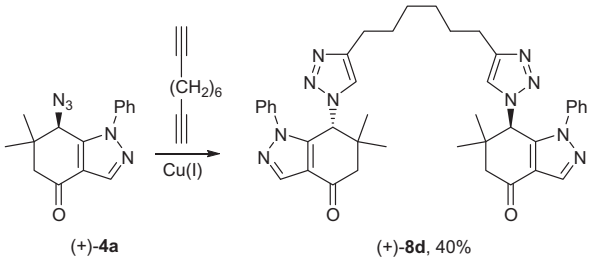
Scheme 5. Synthesis and X-ray analysis of camphanic amide (−)-**6**.



Scheme 6. Synthesis and X-ray analysis of imine (−)-**7**.

Table 1
Synthesis of enantiomerically pure 7-triazolyl-tetrahydroindazolones

Entry	Amine **3**	R^1	Azide **4**, yield%	Alkyne, R^2	Triazole **8**, yield (ee)
1	(+)-**3a**	H	(−)-**4a**, 91%	Ph	(−)-**8a**, 76% (98%)
2				CH_2OH	(−)-**8b**, 60% (>99%)
3	(−)-**3a**	H	(+)-**4a**, 91%	Ph	(+)-**8a**, 80% (98%)
4				CH_2OH	(+)-**8b**, 58% (>99%)
5	(+)-**3b**	Me	(−)-**4b**, 89%	Ph	(−)-**8c**, 48% (>99%)
6	(−)-**3b**	Me	(+)-**4b**, 83%	Ph	(+)-**8c**, 50% (>99%)



Scheme 7. Synthesis of THI dimer (+)-**8d** with an extended bis-triazole-linker.

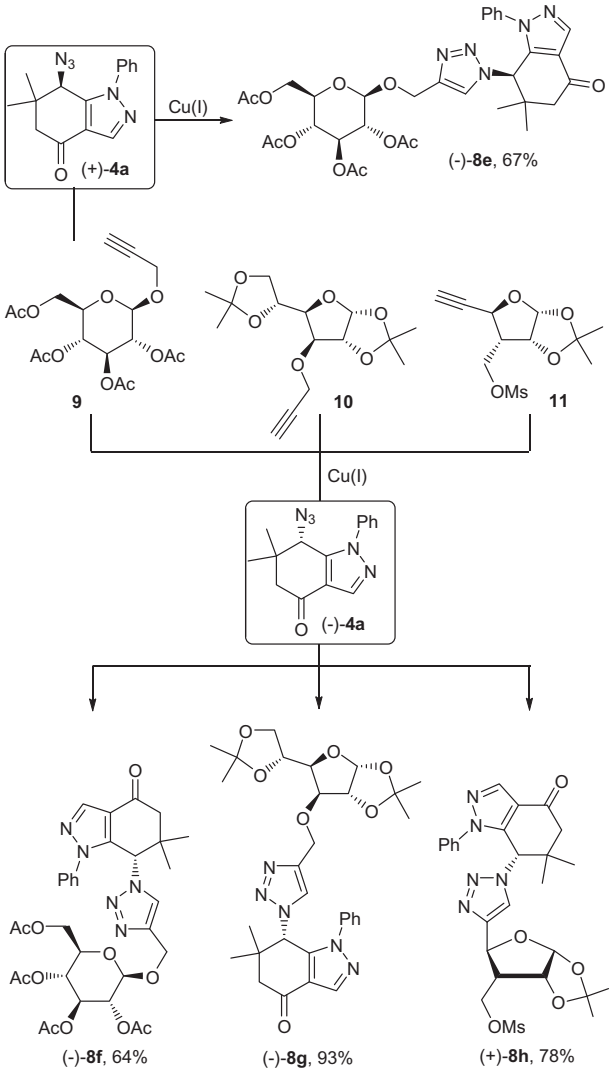
and (7*S*)-conjugate (−)-**8f** in 67% and 64% yield, respectively (Scheme 8). In another experiment, (−)-**4a** was treated with protected 3-*O*-propynyl glucose **10**[37] to produce (−)-**8g** in 93% yield. Finally, an interesting L-nucleoside-like structure (+)-**8h** was obtained by coupling azide (−)-**4a** with alkynyl sugar **11**.[38]

All sugar–tetrahydroindazole conjugates **8e**–**h** were obtained as pure diasteroisomers in good to excellent isolated yields.

2.3. X-ray crystallographic analysis

The structures of the racemic and enantiopure forms of **3a** were established by X-ray structure analysis. Figure 2 illustrates the packing diagram of chirally homogeneous molecule (−)-**3a** crystals. The molecular packing in the axial orthorhombic crystal lattice (space group is $P2_12_12_1$) is characterized by the weak intermolecular hydrogen bonds of NH···O and NH···N types (see Fig. 1). The lengths of these bonds are equal 3.140(2)Å (N–H···O = 169°, H···O = 2.22 Å) and 3.191(2)Å (N–H···N = 149°, H···N = 2.35 Å). The racemic compound (±)-**3a** is crystallized in the planaxial monoclinic lattice (space group is $P2_1/n$). The molecular packing of this compound is shown in Figure 3. In the crystal structure there are moderate intermolecular hydrogen bonds of NH···O type with N···O length 3.075(2)Å (N–H···O = 148°, H···O = 2.18 Å). The molecular chains along crystallographic direction [1 0 1] form in the crystals by means of these bonds. The racemic compound is significantly more dense (D_{calcd} = 1.303 g/cm^3) than the enantiopure crystals (D_{calcd} = 1.263 g/cm^3) notwithstanding the higher temperature of X-ray analysis for the racemic form. Usually the crystal lattice energy is higher for a more dense form; therefore, it should be concluded that the crystal structure for the racemic compound is energetically more stable than the one for the homochiral form. It explains the relatively high melting point (166–167 °C) of the racemic compound in comparison with the pure enantiomer (128–129 °C).

The chiral compound (−)-**4a** gives axial monoclinic crystals (space group is $P2_1$). The peculiarity of these crystals is the following: in the asymmetric unit of the crystal structure there are two independent molecules, which are connected by a center of pseudoinversion (Figure 4). The coordinates of the pseudoinversion centers are (0.5, 0.187, 0.25). The projection of the crystal structure is given on Figure 5. It can be assumed that this structure and centrosymmetric crystal structure of racemic compound (±)-**4a** are pseudoisomorphous to each other. Although suitable samples for



Scheme 8. Synthesis of THI–carbohydrate conjugates.

single crystal X-ray analysis of the racemic compound (±)-**4a** were not obtained, the debyegram is similar to the powder pattern of the pure enantiomer (−)-**4a**, which is theoretically simulated from the obtained crystal structure. Figure 6 gives these powder patterns. Thus, the racemate (±)-**4a** most probably crystallizes in the monoclinic lattice (space group $P2_1/c$) giving molecular packing near to that represented in Figure 5. Normally compounds with such crystal structures form solid solutions on the whole area of composition variation. This fact can explain the relatively near melting point of the pure enantiomer (−)-**4a** (79–80 °C) and the corresponding racemate (±)-**4a** (100–101 °C). For unambiguous confirmation of the structure and absolute configuration the single crystals of (−)-**6** and (−)-**7** were examined by X-ray analysis.

The presence of the bromine atom in structure (−)-**7** provided significant anomalous-dispersion; the crystal structure full matrix least squares refinement using all independent diffraction reflection with Friedel pairs gave the value of Flack's *x* parameter 0.03(2). This allowed us to determine the absolute configuration of the crystal as the expected values are 0 (within 3 esd's) for the correct structure and +1 for the inverted absolute structure.[39]

All of investigated structures are characterized by almost isolated double bonds in tetrahydroindazolone systems. Table 2 lists the principal bond lengths in the studied molecules. These values show the weak conjugation in the molecular structures.

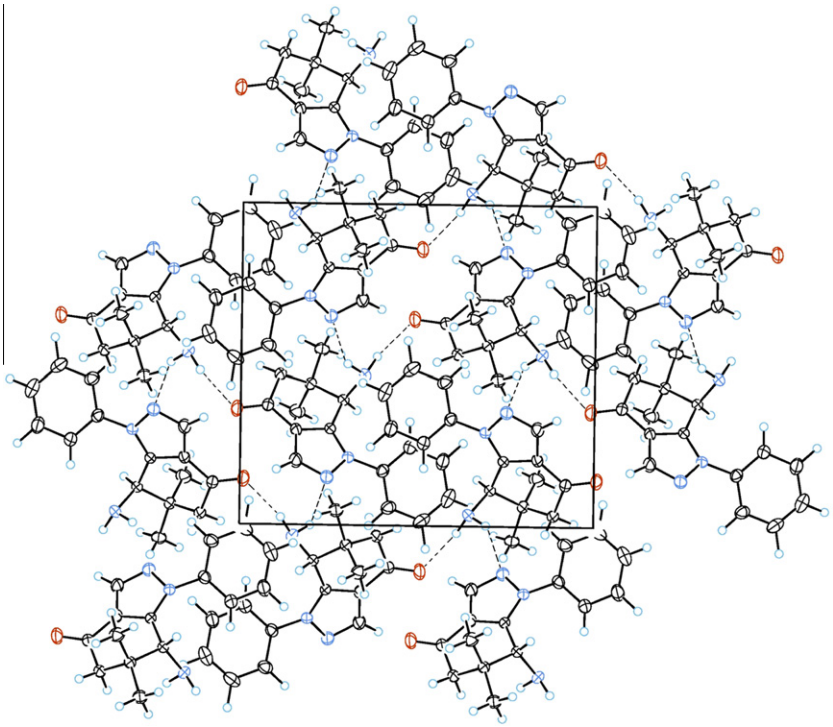


Figure 2. Projection of the crystal structure of (−)-**3a** down the crystallographic *a* axis.

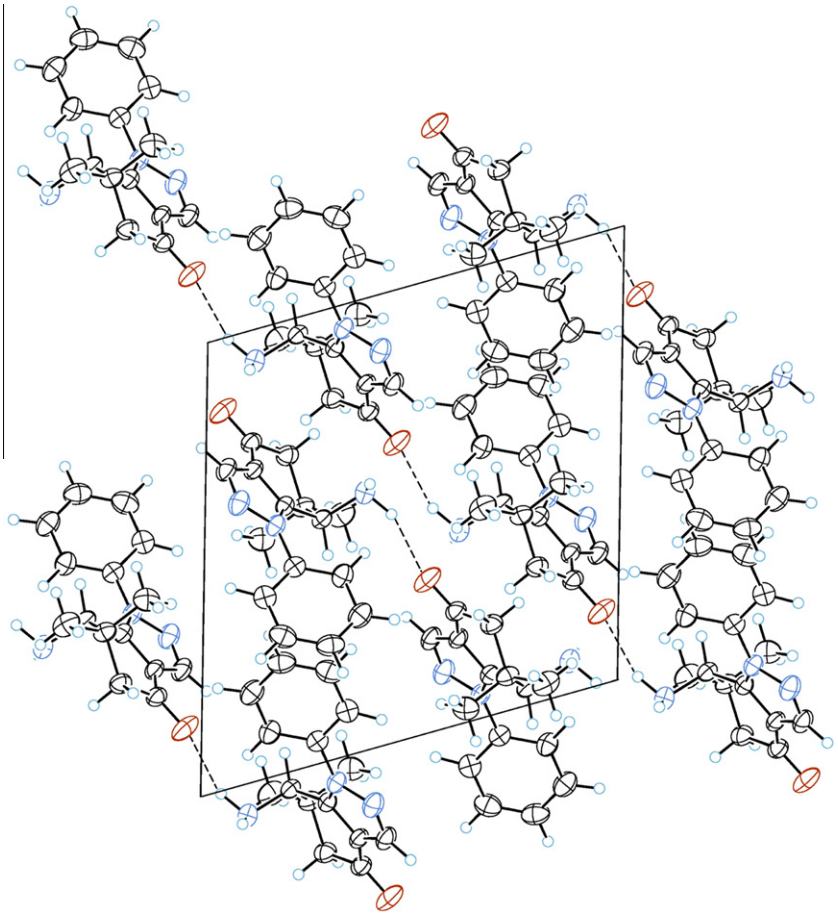


Figure 3. Projection of the crystal structure of (±)-**3a** down the monoclinic axis.

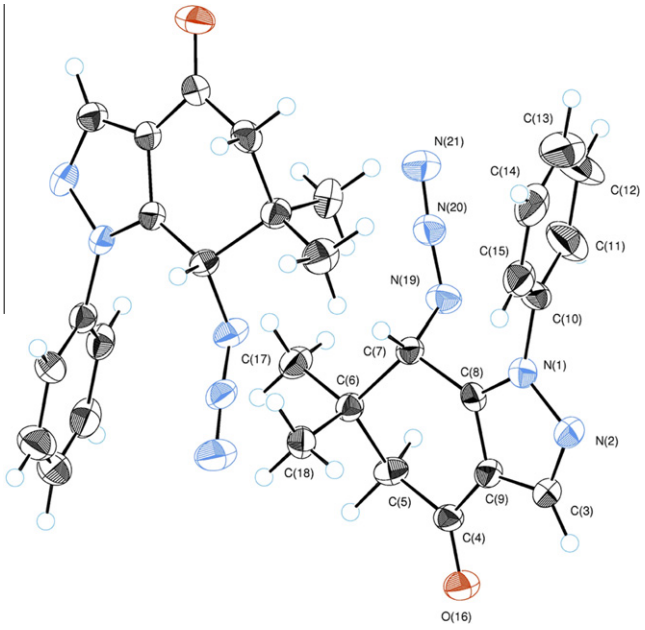


Figure 4. Asymmetric unit of the enantiopure azide (−)-**4a**.

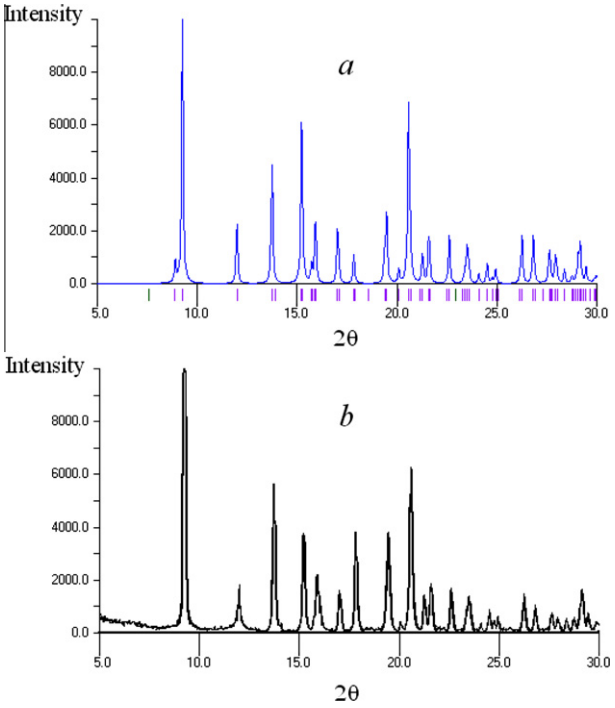


Figure 6. Calculated diffraction pattern (*a*) from single crystal data of the enantiomerically pure azide (−)-**4a** and diffraction pattern (*b*) of the racemate (±)-**4a** obtained on the powder diffractometer.

3. Conclusion

A practical method for the resolution of 7-amino-1-aryl-4,5,6,7-tetrahydro-indazol-4-ones has been achieved via salt formation with either enantiomer of *O,O′*-dibenzoyl tartaric acid. Further chemical transformations of enantiomerically pure 7-amino-THIs are possible without erosion of their ee's. The aforementioned enantiomerically pure heterocycles can be successfully conjugated to different sugar-derived scaffolds in order to produce carbohydrate–tetrahydroindazole conjugates. This might open up possibilities to study the biological targeting of the aforementioned structures, and thus might qualitatively elevate the level of biological activity research of tetrahydroindazoles as pharmacophores in the future.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded at 200, 300 or 400 MHz and at 100 or 75 MHz, respectively. The proton signals for residual non-deuterated solvents (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6) and carbon signals (δ 77.1 for $CDCl_3$ and δ 39.5 for DMSO-d_6) were used as an internal references for ^{1}H and ^{13}C NMR spectra, respectively. Coupling constants are reported in Hertz. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. Yields refer to chromatographically and spectroscopically homogeneous materials. GC–MS (EI: 70 eV) analyses where appropriate were done on HP-5; 5% phenylmethylsiloxane column (30 m, 250 μm, 0,25 μm); He carrier gas; flow rate 1 mL/min; temperature regime: 100 °C hold 3 min; increase rate 50 °C/min until 250 °C, hold 1 min; increase rate 100 °C/min until 310 °C, hold 15 min. Injection volume: 1 μL (*c* 1 mg/mL; $CHCl_3$).

4.1. (±)-7-Amino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (±)-3a

To a solution of (±)-**4a** (10.0 g, 35.5 mmol) in EtOH (150 mL) and THF (50 mL) was added 10% Pd/C (0.8 g, 8 wt %) and gaseous H_2

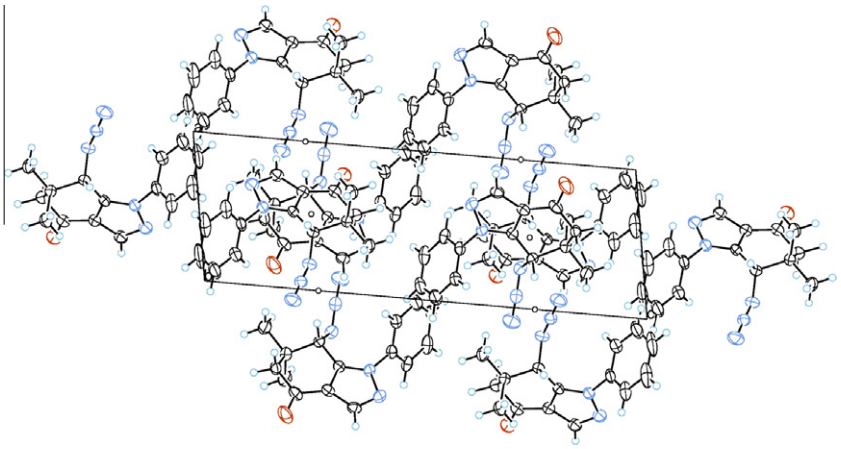


Figure 5. Projection of the crystal structure of (−)-**4a** down the monoclinic axis, showing the centers of pseudoinversion.

Table 2
The principal bond lengths (Å) in tetrahydroindazolones **3**–**6**

Bond	Compound (−)-**3a**	Compound (±)-**3a**	Compound (−)-**4a**	Compound (−)-**6**	Compound (−)-**7**
N(1)–N(2)	1.384(2)	1.383(2)	1.385(5)	1.372(3)	1.390(7)
N(1)–C(8)	1.362(3)	1.359(3)	1.349(5)	1.368(3)	1.337(8)
N(2)–C(3)	1.326(3)	1.319(3)	1.335(6)	1.327(3)	1.329(8)
C(3)–C(9)	1.408(3)	1.407(3)	1.400(6)	1.400(3)	1.419(9)
C(4)–C(9)	1.457(3)	1.456(3)	1.455(6)	1.461(3)	1.467(9)
C(4)–O	1.225(2)	1.228(3)	1.224(5)	1.213(3)	1.235(7)
C(8)–C(9)	1.385(3)	1.380(3)	1.365(5)	1.387(3)	1.371(8)

was passed through the resulting reaction mixture for 2 h (TLC control). The catalyst was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was crystallized from hexane/$CHCl_3$ yielding (±)-**3b** (8.07 g, 89%) as beige crystals. Mp 166–167 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ, ppm: 8.04 (s, 1H, H–C(3)), 7.85–7.80 (m, 2H, H–C(Ph)), 7.57–7.45 (m, 3H, H–C(Ph)), 3.76 (s, 1H, H–C(7)), 2.72, 2.22 (2d, AB syst., 2H, ^2J = 16.6 Hz, H–C(5)), 1.42 (br s, 2H, H_2N–C(7)), 1.14, 1.00 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 192.4, 150.9, 138.8, 137.9, 129.4, 128.5, 124.2, 118.5, 53.0, 46.9, 39.4, 26.3, 25.4. IR (KBr) ν_{max}, cm^{-1}: 3360, 3330, 3060, 2970, 2890, 2875, 1675, 1600, 1540, 1495, 1480, 1400, 1230, 1080, 1060, 1045, 970, 910. GH-MS(EI): t_R = 8.09 min; mass calcd for $C_{15}H_{17}N_3O$ 255.1; found 255.1. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.62; H, 6.74; N, 16.48.

4.2. (±)-7-Amino-3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (±)-3b

To a solution of (±)-**4b** (8.00 g, 27.1 mmol) in EtOH (100 mL) and THF (20 mL) was added 10% Pd/C (0.8 g, 10 wt %) and gaseous H_2 was passed through the resulting reaction mixture for 2 h (TLC control). The catalyst was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was dried in vacuo for 24 h yielding (±)-**3b** (5.97 g, 82%) of as an amorphous powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ, ppm: 7.77 (d, 2H, ^3J = 8.0 Hz, H–C(Ph)), 7.49 (t, 2H, ^3J = 8.0 Hz, H–C(Ph)), 7.42 (t, 1H, ^3J = 8.0 Hz, H–C(Ph)), 3.71 (s, 1H, H–C(7)), 2.69 (d, AB syst., 1H, ^2J = 17.0 Hz, Ha-C(5)), 2.53 (s, 3H, H_3C–C(3)), 2.19 (d, AB syst., 1H, ^2J = 17.0 Hz, Hb-C(5)), 1.41 (bs, 2H, H_2N–C(7)), 1.12, 1.00 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ, ppm: 193.1, 151.8, 149.5, 138.9, 129.4, 128.3, 124.3, 115.7, 53.2, 47.4, 39.4, 26.4, 25.5, 13.3. IR (film) ν_{max}, cm^{-1}: 3385, 3315, 3055, 2960, 2870, 1670, 1650, 1600, 1540, 1505, 1585, 1440, 1405, 1370, 1290, 1130, 1100, 1070, 1045, 950, 925, 905. GH-MS(EI): t_R = 8.13 min; mass calcd for $C_{16}H_{19}N_3O$ 269.2; found 269.1. Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 70.53; H, 7.39; N, 15.38.

4.3. (7*S*)-6,6-Dimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-7-yl-ammonium (2*S*,3*S*)-2,3-bis-benzoyloxy-3-carboxy-propionate (+)-3a·(+)-5 and (7*R*)-6,6-dimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-7-yl-ammonium (2*R*,3*R*)-2,3-bis-benzoyloxy-3-carboxy-propionate (−)-3a·(−)-5

A solution of (+)-**5** (4.77 g, 13.3 mmol) in abs EtOH (10 mL) was added to a solution of (±)-**3a** (3.40 g, 13.3 mmol) in abs EtOH (15 mL) at ambient temperature. The resulting reaction mixture was stirred at ambient temperature for 5 days. The crude salt was filtered, washed on the filter with abs EtOH (2 mL), and crystallized from abs EtOH yielding (+)-**3b**·(+)-**5** (3.34 g, 41%). Mp 204–205 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ, ppm: 8.08 (s, 1H, H–C(3)), 8.00 (d, 4H, ^3J = 7.0 Hz, H–C(Ph)), 7.85 (d, 2H, ^3J = 7.4 Hz, H–C(Ph)), 7.70 (t, 2H, ^3J = 7.4 Hz, H–C(Ph)), 7.59–7.55 (m, 6H, H–C(Ph)), 7.48 (t, 1H, ^3J = 7.4 Hz, H–C(Phr)), 5.80 (s, 2H, H–C(2′,3′)), 3.97 (s, 1H, H–C(7)), 2.94, 2.07 (2d, AB syst., 2H, ^2J = 17.6 Hz, H–C(5)), 1.10, 0.89 (2s, 6H, H_3C–C(6)). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ, ppm: 191.6, 167.4, 164.7, 149.0, 138.4, 137.4, 133.8, 129.3, 129.2, 128.8, 128.7, 128.3, 124.0, 118.8, 71.8, 51.2, 46.2, 38.8, 25.9, 25.1. IR (KBr) ν_{max}, cm^{-1}: 3425, 3150, 3070, 2965, 2640, 1725, 1700, 1685, 1600, 1545, 1505, 1270, 1120, 1070, 1025, 970.

The filtrate from above was evaporated to dryness yielding a mixture of salts (+)-**3a**·(+)-**5** and (−)-**3a**·(+)-**5**. The latter was poured into a vigorously stirred mixture consisting of 10% aqueous solution of K_2CO_3 (100 mL) and $CHCl_3$ (50 mL). The resulting mixture was stirred for 30 min and the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layer was sequentially washed with 10% aqueous solution of K_2CO_3 (30 mL) and saturated aqueous solution of NaCl (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue after drying in vacuo yielded partially enantiomerically enriched amine (−)-**3a** (2.11 g, 91% HPLC purity). The latter was dissolved in abs EtOH (10 mL) and treated with a solution of (−)-**5** (2.69 g, 7.5 mmol, 1 equiv to pure amine **3a**) in abs EtOH (8 mL). The resulting mixture was stirred at ambient temperature for 6 h, filtered, and washed on the filter with abs EtOH (2 mL). The residue was crystallized from abs EtOH yielding (−)-**3b**·(−)-**5** (3.41 g, 42%). Mp 204–205 °C. ^{1}H and ^{13}C NMR data identical to (+)-**3b**·(+)-**5**.

4.4. (+)-(7*S*)-7-Amino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-3a

Salt (+)-**3a**·(+)-**5** (3.34 g, 5.44 mmol) was poured into a vigorously stirred mixture consisting of 10% aqueous solution of K_2CO_3 (70 mL) and $CHCl_3$ (40 mL). The resulting mixture was stirred for 30 min and the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layer was sequentially washed with 10% aqueous solution of K_2CO_3 (30 mL) and saturated aqueous solution of NaCl (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue after drying in vacuo yielded enantiomerically enriched amine (+)-**3a** (1.32 g, 95%, 97% ee). Crystallization of an analytical sample of (+)-**3a** from hexane/$CHCl_3$ increased the ee up to 99.5%. $[\alpha]_D^{22} = 26$ (*c* 2.3, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.41; H, 6.71; N, 16.52. Other analytical data of (+)-**3a** are identical to those of (±)-**3a**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(−)-**3a**] = 8.44 min; t_R[(+)-**3a**] = 9.34 min. Eluent system: hexanes/dioxane = 2:1 in isocratic mode; flow rate 0.8 mL/min; UV detector at 254 nm.

4.5. (−)-(7*R*)-7-Amino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-3a

Salt (−)-**3a**·(−)-**5** (3.41 g, 5.56 mmol) was poured into a vigorously stirred mixture consisting of 10% aqueous solution of

K_2CO_3 (70 mL) and $CHCl_3$ (40 mL). The resulting mixture was stirred for 30 min and the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layer was sequentially washed with 10% aqueous solution of K_2CO_3 (30 mL) and saturated aqueous solution of NaCl (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue after drying in vacuo yielded enantiomerically enriched amine (−)-**3a** (1.36 g, 96%, 98% ee). Crystallization of an analytical sample of (−)-**3a** from hexanes/$CHCl_3$ increased ee up to 99.5%. ($[\alpha]_D^{22} = -26$ (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.50; H, 6.89; N, 16.28. Other analytical data of (−)-**3a** are identical to those of (±)-**3a**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(−)-**3a**] = 8.44 min; t_R[(+)-**3a**] = 9.34 min. Eluent system: hexanes/dioxane = 2:1 in isocratic mode; flow rate 0.8 mL/min; UV detector at 254 nm.

4.6. (7*R*)-3,6,6-Trimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-7-yl-ammonium (2*R*,3*R*)-2,3-bis-benzoyloxy-3-carboxy-propionate (−)-3b·(−)-5 and (7*S*)-3,6,6-trimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-7-yl-ammonium (2*S*,3*S*)-2,3-bis-benzoyloxy-3-carboxy-propionate (+)-3b·(+)-5

A solution of (−)-**5** (4.87 g, 13.6 mmol) in abs EtOH (10 mL) was added to a solution of (±)-**3b** (3.66 g, 13.6 mmol) in abs EtOH (15 mL) at ambient temperature. The resulting reaction mixture was stirred at ambient temperature for 5 days. The crude salt was filtered, washed on the filter with abs EtOH (2 mL), and crystallized from abs EtOH yielding (−)-**3b**·(−)-**5** (2.65 g, 31%). Mp 175–177 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ, ppm: 8.00 (d, 4H, ^3J = 7.5 Hz, H–C(Ph)), 7.87 (d, 2H, ^3J = 7.9 Hz, H–C(Ph)), 7.71 (t, 2H, ^3J = 7.9 Hz, H–C(Ph)), 7.60–7.53 (m, 6H, H–C(Ph)), 7.46 (t, 1H, ^3J = 7.3 Hz, H–C(Ph)), 5.81 (s, 2H, H–C(2′,3′)), 3.80 (s, 1H, H–C(7)), 2.88 (d, AB syst., 1H, ^2J = 17.0 Hz, Ha-C(5)), 2.41 (s, 3H, H_3C–C(3)), 2.01 (d, AB syst., 1H, ^2J = 17.0 Hz, Hb-C(5)), 1.08, 0.88 (2s, 6H, H_3C–C(6)). ^{13}C NMR (DMSO$_{d3}$, 75 MHz) δ, ppm: 192.6, 167.5, 164.8, 149.8, 148.0, 138.5, 133.9, 129.4, 129.3, 129.0, 128.9, 128.1, 124.0, 115.8, 71.7, 51.6, 46.6, 38.9, 26.0, 25.3, 13.1. IR (KBr) ν_{max}, cm^{-1}: 3430, 3140, 3070, 2970, 2655, 2600, 1725, 1670, 1600, 1490, 1265, 1180, 1120, 1070, 1030, 955, 905. Anal. Calcd for $C_{34}H_{33}N_3O_9$: C, 65.06; H, 5.30; N, 6.69. Found: C, 65.33; H, 5.14; N, 6.51.

The filtrate from the above was evaporated to dryness yielding a mixture of salts (−)-**3b**·(−)-**5** and (+)-**3b**·(−)-**5**. The latter was poured into a vigorously stirred mixture consisting of 10% aqueous solution of K_2CO_3 (100 mL) and $CHCl_3$ (50 mL). The resulting mixture was stirred for 30 min and the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layer was sequentially washed with a 10% aqueous solution of K_2CO_3 (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue after drying in vacuo yielded partially enantiomerically enriched amine (+)-**3b** (2.82 g, 87% HPLC purity). The latter was dissolved in abs EtOH (15 mL) and treated with solution of (+)-**5** (3.26 g, 9.1 mmol, 1 equiv to pure amine **3b**) in abs EtOH (10 mL). The resulting mixture was stirred at ambient temperature for 4 h, filtered, and washed on the filter with abs EtOH (2 mL). The residue was crystallized from abs EtOH yielding (+)-**3b**·(+)-**5** (3.73 g, 44%). Mp 177–178 °C. ^{1}H and ^{13}C NMR data identical to (−)-**3b**·(−)-**5**. Anal. Calcd for $C_{34}H_{33}N_3O_9$: C, 65.06; H, 5.30; N, 6.69. Found: C, 64.75; H, 5.20; N, 6.56.

The filtrate from (+)-**3b**·(+)-**5** was basified and extracted with $CHCl_3$ as described above. This resulted in a recovery of virtually racemic amine (±)-**3b** (0.98 g, 91% HPLC purity). The latter was treated sequentially with (−)-**5** and (+)-**5** as described above. This produced an additional portion of salt (−)-**3b**·(−)-**5** (0.60 g, 7%) and salt (+)-**3b**·(+)-**5** (0.35 g, 4%). Thus, the total yield of salts (−)-**3b**·(−)-**5** and (+)-**3b**·(+)-**5** were 38% and 48%, respectively.

4.7. (−)-(7*R*)-7-Amino-3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-3b

Salt (−)-**3b**·(−)-**5** (2.65 g, 4.2 mmol) was poured into a vigorously stirred mixture consisting of 10% aqueous solution of K_2CO_3 (50 mL) and $CHCl_3$ (30 mL). The resulting mixture was stirred for 30 min after which the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The combined organic layer was sequentially washed with 10% aqueous solution of K_2CO_3 (30 mL) and saturated aqueous solution of NaCl (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue after drying in vacuo yielded enantiomerically enriched amine (−)-**3b** (1.05 g, 93%, 93% ee). $[\alpha]_D^{20} = -19.6$ (*c* 6.6, $CHCl_3$). HRMS (TOF-ESI) calcd for $[C_{16}H_{19}N_3O+H]^+$ 270.1606; found 270.1581. Other analytical data of (−)-**3b** are identical to those of (±)-**3b**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(−)-**3b**] = 16.90 min; t_R[(+)-**3b**] = 18.35 min. Eluent system: hexanes/THF/MeCN = 85.2:14.2:0.5 in isocratic mode; flow rate 1 mL/min; UV detector at 254 nm.

4.8. (+)-(7*S*)-7-Amino-3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-3b

Salt (+)-**3b**·(+)-**5** (3.73 g, 5.94 mmol) was poured into a vigorously stirred mixture consisting of 10% aqueous solution of K_2CO_3 (70 mL) and $CHCl_3$ (40 mL). The resulting mixture was stirred for 30 min after which the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layer was sequentially washed with a 10% aqueous solution of K_2CO_3 (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue after drying in vacuo yielded enantiomerically enriched amine (+)-**3b** (1.46 g, 91%, 92% ee). $[\alpha]_D^{20} = +19.8$ (*c* 6.8, $CHCl_3$). HRMS (TOF-ESI) calcd for $[C_{16}H_{19}N_3O+H]^+$ 270.1606; found 270.1617. Other analytical data of (+)-**3b** are identical to those of (±)-**3b**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(−)-**3b**] = 16.90 min; t_R[(+)-**3b**] = 18.35 min. Eluent system: hexanes/THF/MeCN = 85.2:14.2:0.5 in isocratic mode; flow rate 1 mL/min; UV detector at 254 nm.

4.9. Camphanic amide (−)-6

(1*S*)-(−)-Camphanic chloride (0.216 g, 1.00 mmol) was added to a solution of (+)-**3a** (0.12 g, 0.47 mmol) and a catalytic amount of DMAP (6 mg, 10 mol %) in abs pyridine (5 mL) at −15 °C. The resulting reaction mixture was allowed to reach ambient temperature and stirred for 22 h. Then it was diluted with Et_2O (50 mL) and successively washed with saturated aqueous solution of $CuSO_4$ (4 × 15 mL), saturated aqueous solution of $NaHCO_3$ (3 × 20 mL), and brine (15 mL). The resulting organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from ethanol to provide amide (−)-**6** (0.15 g, 73%). Mp 198–199 °C, $[\alpha]_D^{20} = -27$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ, ppm: 8.06 (s, 1H, H–C(3)), 7.53–7.37 (m, 5H, H–C(Ph)), 6.42 (d, 1H, ^3J = 9.5 Hz, HN–C(7)), 5.45 (d, 1H, ^3J = 9.5 Hz, H–C(7)), 2.53, 2.44 (2d, AB syst., 2H, ^2J = 16.9 Hz, H–C(5)), 2.09, 2.18, 1.54, 1.19 (4ddd, 1H, ^2J = 13.2 Hz, ^3J = 10.8 Hz, ^3J = 4.4 Hz, H–C(camph)), 1.18, 1.06, 1.05, 1.04, 0.89 (5s, 15H, H_3C–C(6), H_3C–C(camph)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 191.6, 177.7, 166.6, 146.3, 138.5, 137.9, 129.4, 129.0, 124.6, 120.2, 92.1, 55.1, 53.8, 49.7, 49.6, 39.9, 30.2, 28.8, 27.0, 24.3. 16.8, 16.7, 9.5. IR (KBr) ν_{max}, cm^{-1}: 3415, 2970, 2930, 2895, 1800, 1690, 1675,

1540, 1515, 1480. Anal. Calcd for $C_{25}H_{29}N_3O_4$: C, 68.95; H, 6.71; N, 9.65. Found: C, 68.73; H, 6.73; N, 9.53.

4.10. (−)-(7*S*)-7-[(4-Bromo-benzylidene)-amino]-3,6,6-trimethyl-1-phenyl-1,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-7

4-Bromo-benzaldehyde (0.09 g, 0.5 mmol) was added to a solution of (+)-**3b** (0.13 g, 0.5 mmol) in EtOH (3 mL). The resulting reaction mixture was refluxed for 4 h, and then it was cooled to +5 °C, and triturated with brine. The resulting precipitate was filtered and washed on the filter with water. The filter cake was dried until a constant mass and recrystallized from hexane/EtOAc mixture. Yield of (−)-**7**: 0.17 g (78%). Mp 107–108 °C, $[\alpha]_D^{20} = -54$ (*c* 4.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 7.57 (s, 1H, HC = NC(3)), 7.47 (d, 2H, ^3J = 8.5 Hz, H–C(*p*-Br–C_6H_4)), 7.42–7.39 (m, 3H, H–C(Ph)), 7.37 (d, 2H, ^3J = 8.5 Hz, H–C(*p*-Br–C_6H_4)), 7.30–7.26 (m, 2H, H–C(Ph)), 4.18 (s, 1H, H–C(7)), 2.95 (d, AB syst., ^2J = 16.4 Hz, Ha-C(5)), 2.56 (s, 3H, H_3C–C(3)), 2.25 (d, AB syst., ^2J = 16.9 Hz, Hb-C(5)), 1.12, 0.96 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 193.7, 161.3, 149.4, 148.9, 138.4, 134.1, 131.9, 129.7, 129.3, 129.1, 126.0, 125.9, 116.3, 70.5, 49.1, 39.9, 26.5, 26.3, 13.4. IR (KBr) ν_{max}, cm^{-1}: 2970, 2940, 1675, 1640, 1590, 1490, 1445, 1375, 1070, 1010. GH-MS(EI): t_R = 9.67 min; mass calcd for $C_{23}H_{22}{}^{79}BrN_3O$ 435.1; found 435.0. Anal. Calcd for $C_{23}H_{22}BrN_3O$: C, 63.31; H, 5.08; N, 9.63. Found: C, 63.33; H, 5.02; N, 9.60. Analogously, (−)-**3b** provided (+)-**6** (75%). $[\alpha]_D^{20} = 53$ (*c* 2.6, $CHCl_3$). GH-MS(EI): t_R = 9.70 min; mass calcd for $C_{23}H_{22}{}^{79}BrN_3O$ 435.1; found 435.0.?>

4.11. (−)-(7*S*)-7-Azido-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-4a

General procedure for diazo transfer: First, a fresh solution of TfN_3 was prepared by intensive 2 h stirring of a biphasic system consisting of NaN_3 (1.99 g, 30.54 mmol, 6 equiv) and Tf_2O (2.57 mL, 15.27 mmol, 3 equiv) in water (7 mL) and CH_2Cl_2 (7 mL) at 0 °C. The organic layer was then separated and the aqueous phase was extracted once with CH_2Cl_2 (6 mL). The combined organic layer (~13 mL) was washed with saturated aqueous solution of $NaHCO_3$ (3 mL) and thus was ready for the diazo transfer reaction. The above mentioned solution of TfN_3 was added at ambient temperature to a suspension of amine (+)-**3a** (1.30 g, 5.09 mmol, 1 equiv), $CuSO_4{\cdot}5H_2O$ (25 mg, 0.10 mmol, 2 mol %), and $NaHCO_3$ (0.37 g, 4.40 mmol, 0.87 equiv) in water (13 mL). The resulting reaction mixture was diluted with methanol (~45 mL) until it became homogeneous. Next, it was stirred for 24 h at ambient temperature. Organic solvents were evaporated at reduced pressure and after the addition of brine (20 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was crystallized from hexanes/$CHCl_3$ providing (−)-**4a** (1.31 g, 91%). Mp 79–80 °C, $[\alpha]_D^{20} = -95$ (*c* 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 8.10 (s, 1H, H–C(3)), 7.58–7.51 (m, 5H, H–C(Ph)), 4.26 (s, 1H, H–C(7)), 2.74, 2.28 (2d, AB syst., 2H, ^2J = 17.0 Hz, H–C(5)), 1.26, 1.06 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 191.4, 145.3 (2C), 138.1, 129.8, 129.4, 124.9, 119.4, 61.5, 47.8, 40.9, 26.3, 26.1. IR (KBr) ν_{max}, cm^{-1}: 2980, 2870, 2100, 1680, 1650, 1600, 1540, 1505, 1460, 1320, 1250, 1125, 1060, 1020. HRMS (TOF-ESI) calcd for $[C_{15}H_{15}N_5O+H]^+$ 282.1355; found 282.1348. Enantiomeric excess of (−)-**4a**/(+)-**4a** was not determined by HPLC as no separation between enantiomers was observed on the available columns. Further transformation of (−)-**4a** to the corresponding triazoles showed the conservation of the enantiomeric purity.

4.12. (+)-(7*R*)-7-Azido-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-4a

Product (+)-**4a** was prepared according to general procedure of the diazo transfer. Thus, (−)-**3a** (1.41 g, 5.52 mmol) provided (+)-**4a** (1.41 g, 91%). Mp 79–80 °C, $[\alpha]_D^{20} = 94$ (*c* 1.7, $CHCl_3$). Other analytical data of (+)-**4a** are identical to those of (−)-**4a** described above.

4.13. (−)-(7*S*)-7-Azido-3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-4b

Product (−)-**4b** was prepared according to the general procedure of diazo transfer. Thus, (+)-**3b** (1.14 g, 4.23 mmol) provided (−)-**4b** as a yellowish oil, which was dissolved in toluene/EtOAc (1:2) mixture (20 mL) and passed through a pad of silica gel. Evaporation of filtrate gave (−)-**4b** (1.11 g, 89%). $[\alpha]_D^{20} = -86$ (*c* 2.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ, ppm: 7.58–7.48 (m, 5H, H–C(Ph)), 4.22 (s, 1H, H–C(7)), 2.72 (d, AB syst., 1H, ^2J = 17.2 Hz, Ha-C(5)), 2.56 (s, 3H, H_3C–C(3)), 2.24 (d, AB syst., 1H, ^2J = 17.2 Hz, Hb-C(5)), 1.24, 1.06 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 192.2, 149.7, 145.8, 138.1, 129.7, 129.2, 124.9, 116.5, 61.7, 48.1, 40.8, 26.3, 26.2, 13.3. IR (film) ν_{max}, cm^{-1}: 2980, 2965, 2945, 2870, 2100, 1665, 1595, 1555, 1500, 1440, 1335, 1234, 1045, 905. HRMS (TOF-ESI) calcd for $[C_{16}H_{17}N_5O+H]^+$ 296.1511; found 296.1497. Enantiomeric excess of (−)-**4b**/(+)-**4b** was not determined by HPLC as no separation between the enantiomers was observed on the available columns. Further transformation of (−)-**4b** to the corresponding triazoles showed the conservation of enantiomeric purity.

4.14. (+)-(7*R*)-7-Azido-3,6,6-trimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-4b

Product (+)-**4b** was prepared according to the general procedure of diazo transfer. Thus, (−)-**3b** (1.00 g, 3.71 mmol) provided (+)-**4b** as a yellowish oil, which was dissolved in toluene/EtOAc (1:2) mixture (20 mL) and passed through a pad of silica gel. Evaporation of the filtrate gave (+)-**4b** (0.91 g, 83%). $[\alpha]_D^{20} = 84$ (*c* 2.4, $CHCl_3$). Other analytical data of (+)-**4b** are identical to those of (−)-**4b**.

4.15. (−)-(7*S*)-6,6-Dimethyl-1-phenyl-7-(4-phenyl-[1,2,3]-triazol-1-yl)-4,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-8a

General procedure I of triazole formation: To a solution of azide (−)-**4a** (0.14 g, 0.50 mmol, 1.0 equiv) and phenylacetylene (60 μL, 0.55 mmol, 1.1 equiv) in 2-butanol (4.0 mL) and water (2.0 mL) were added $CuSO_4{\cdot}5H_2O$ (19 mg, 0.075 mmol, 0.15 equiv) and Cu powder (100 mg) at ambient temperature. The resulting mixture was stirred at 40 °C for 8 h, cooled to ambient temperature, and ethyl acetate (30 mL) was added. The resulting suspension was filtered and the filtrate was evaporated under reduced pressure. The residue consisted of chromatographically homogeneous (GC–MS) triazole (−)-**8a**, which after crystallization from hexane/EtOAc mixture provided analytically pure (−)-**8a** (0.13 g, 76%). Mp 181–182 °C, $[\alpha]_D^{20} = -39$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ, ppm: 8.22 (s, 1H, H–C(3)), 7.76 (dd, 2H, ^3J = 7.8 Hz, ^4J = 2.3 Hz, Ar), 7.48 (s, 1H, H–C(5′)), 7.45–7.35 (m, 6H, Ar), 7.02 (dd, 2H, ^3J = 7.8 Hz, ^4J = 2.3 Hz, Ar), 5.64 (s, 1H, H–C(7)), 2.85, 2.43 (2d, 2H, AB syst., ^2J = 17.2 Hz, H–C(5)), 1.25, 0.94 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ, ppm: 190.9, 148.1, 143.2, 138.3, 137.4, 129.6, 129.6, 129.5, 128.9, 128.6, 125.7, 124.4, 120.6, 118.7, 60.8, 48.0, 40.1, 27.1, 25.9. IR (KBr) ν_{max}, cm^{-1}: 3125, 2970, 1685, 1500, 1475, 1230, 970, 765, 695. Anal. Calcd for $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.26. Found: C, 71.82; H, 5.40; N, 18.30. Enantiomeric excess was determined by HPLC [Pirkle

covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8a**] = 19.59 min; t_R[(−)-**8a**] = 23.02 min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.7 mL/min; UV detector at 254 nm.

4.16. (+)-(7*R*)-6,6-Dimethyl-1-phenyl-7-(4-phenyl-[1,2,3]triazol-1-yl)-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-8a

Product (+)-**7a** was prepared according to the general procedure I of triazole formation. Yield 80%. Mp 179–180 °C, $[\alpha]_D^{20} = +40$ (*c* 1.0, $CHCl_3$). Other analytical data of (+)-**8a** are identical to those of (−)-**8a**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8a**] = 19.59 min; t_R[(−)-**8a**] = 23.02 min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.7 mL/min; UV detector at 254 nm.

4.17. (−)-(7*S*)-7-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-6,6-dimethyl-1-phenyl-4,5,6,7-tetra-hydro-1*H*-indazol-4-one (−)-8b

Product (−)-**8b** was prepared according to the general procedure I of triazole formation by using propargyl alcohol instead of phenylacetylene. Yield 60%. Mp 219–221 °C, $[\alpha]_D^{20} = -54$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ, ppm: 8.18 (s, 1H, H–C(3)), 7.42–7.37 (m, 3H, Ar), 7.30 (s, 1H, H–C(5′)), 7.00–6.95 (m, 2H, Ar), 5.60 (s, 1H, H–C(7)), 4.75 (d, 2H, ^3J = 5.5 Hz, HOCH_2–C(4′)), 2.78, 2.40 (2d, 2H, AB syst., ^2J = 17.2 Hz, H–C(5)), 2.33 (t, 1H, ^3J = 5.5 Hz, *H*OCH_2–C(4′)), 1.21, 0.87 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ, ppm: 191.3, 148.4, 143.3, 138.2 (2C), 137.2, 129.5, 124.3, 121.5, 120.4, 60.6, 55.7, 47.8, 40.0, 26.9, 25.6. IR (KBr) ν_{max}, cm^{-1}: 3420, 3130, 2965, 2875, 1660, 1505, 1395, 1225, 1030. Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76. Found: C, 64.39; H, 5.51; N, 20.53. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8b**] = 32.31 min; t_R[(−)-**8b**] = 35.38 min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.7 mL/min; UV detector at 254 nm.

4.18. (+)-(7*R*)-7-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-6,6-dimethyl-1-phenyl-4,5,6,7-tetra-hydro-1*H*-indazol-4-one (+)-8b

Product (+)-**8b** was prepared analogously to product (−)-**8b**. Yield 58%. Mp 218–219 °C, $[\alpha]_D^{20} = +57$ (*c* 1.0, $CHCl_3$). Other analytical data of (+)-**8b** are identical to those of (−)-**8b**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8b**] = 32.31 min; t_R[(−)-**8b**] = 35.38 min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.7 mL/min; UV detector at 254 nm.

4.19. (−)-(7*S*)-3,6,6-Trimethyl-1-phenyl-7-(4-phenyl-[1,2,3]-triazol-1-yl)-4,5,6,7-tetrahydro-1*H*-indazol-4-one (−)-8c

Product (−)-**8c** was prepared according to the general procedure I of triazole formation by using (−)-**4b** instead of (−)-**4a**. Yield 48%. Mp 128–129 °C (EtOAc/hexanes), $[\alpha]_D^{20} = -52$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ, ppm: 7.80–7.75 (m, 2H, Ar), 7.50 (s, 1H, H–C(5′)), 7.46–7.34 (m, 6H, Ar), 7.02–6.97 (m, 2H, Ar), 5.60 (s, 1H, H–C(7)), 2.82 (d, 1H, AB syst., ^2J = 17.2 Hz, Ha-C(5)), 2.64 (s, 3H, H_3C–C(3)), 2.40 (d, 1H, AB syst., ^2J = 17.2 Hz, Hb-C(5)), 1.24, 0.92 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ, ppm: 191.7, 150.0, 148.0, 143.7, 137.4, 129.7, 129.5, 129.3, 128.8, 128.5, 125.7, 124.3, 118.7, 117.7, 61.1, 48.3, 40.0, 27.1, 25.9, 13.4. IR (KBr) ν_{max}, cm^{-1}: 2970, 1680, 1600, 1555, 1510, 1490, 1040, 765, 695. Anal. Calcd for $C_{24}H_{23}N_5O$: C, 72.52.08; H, 5.83; N, 17.62. Found: C, 72.15; H, 5.76; N, 17.65. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8c**] = 16.63 min; t_R[(−)-**8c**] = 19.26 min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.7 mL/min; UV detector at 254 nm.

4.20. (+)-(7*R*)-3,6,6-Trimethyl-1-phenyl-7-(4-phenyl-[1,2,3]-triazol-1-yl)-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-8c

Product (+)-**8c** was prepared analogously to product (−)-**8c**. Yield 50%. Mp 128–129 °C (EtOAc/hexanes), $[\alpha]_D^{20} = +52$ (*c* 1.0, $CHCl_3$). Other analytical data of (+)-**7c** are identical to those of (−)-**8c**. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8c**] = 16.63 min; t_R[(−)-**7c**] = 19.26 min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.7 mL/min; UV detector at 254 nm.

4.21. (+)-(7*R*,7′*R*)-7,7′-(4,4′-(Hexane-1,6-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl))bis(6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazol-4-one (+)-8d

The title compound was prepared by the same procedure as that described for the preparation of (+)-**8a**, using 2 equiv of (+)-**4a** and 1,9-decadiyne instead of phenylacetylene. Reaction temperature 40 °C, reaction time 55 h. Yield 40%. Mp 174–175 °C (EtOAc/hexanes), $[\alpha]_D^{20} = +56$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ, ppm: 8.17 (s, 2H, H–C(3)), 7.42–7.35 (m, 6H, H–C(Ar)), 7.02 (s, 2H, H–C(5′)), 6.99–6.92 (m, 4H, H–C(Ar)), 5.55 (s, 2H, H–C(7)), 2.78 (d, 2H, AB syst., ^2J = 17.1 Hz, Ha-C(5)), 2.63 (t, 4H, ^3J = 7.7 Hz, H–C(1″), H–C(6″)), 2.38 (d, 2H, AB syst., ^2J = 17.1 Hz, Hb-C(5)), 1.66–1.52 (m, 4H, H–C(2″), H–C(5″)), 1.36–1.28 (m, 4H, H–C(3″), H–C(4″)), 1.20, 0.85 (2s, 12H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ, ppm: 190.9, 148.6, 143.3, 138.2, 137.5, 129.5, 129.4, 124.2, 120.5, 120.0, 60.5, 48.0, 40.0, 29.0, 28.6, 27.0, 25.8, 25.3. IR (KBr) ν_{max}, cm^{-1}: 3130, 2935, 2855, 1690, 1550, 1505, 1225, 970, 765, 695. Anal. Calcd for $C_{40}H_{44}N_{10}O_2$: C, 68.94; H, 6.36; N, 20.10. Found: C, 68.98; H, 6.37; N, 20.11. Enantiomeric excess was determined by HPLC [Pirkle covalent (*R*,*R*)-Whelk-O1]: t_R[(+)-**8d**] = 18.18 min; t_R[(−)-**8d**] = 20.66 min; t_R[**8d**$_{meso}$] = 19.36 -min. Eluent system: hexanes/dioxane = 3:1 in isocratic mode; flow rate 0.8 mL/min; UV detector at 254 nm.

4.22. β-Glucopyranose-(7*R*)-THI conjugate (−)-8e

General procedure II of triazole formation: To a vigorously stirred solution of glucose derivative **9** (0.19 g, 0.5 mmol) and (+)-**4a** (0.14 g, 0.5 mmol) in acetone (5 mL) was added $CuSO_4{\cdot}5H_2O$ (10 mg, 0.04 mmol) solution in water (0.5 mL) followed by sodium ascorbate (10 mg, 0,05 mmol) solution in water (0.5 mL) at ambient temperature. The resulting reaction mixture was stirred for 22 h at ambient temperature, then it was diluted with brine (15 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/toluene = 3:2). Yield 0.22 g (67%). $[\alpha]_D^{20} = -1$ (*c* 5.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 8.18 (s, 1H, H–C(3)), 7.44–7.37 (m, 3H, Ar), 7.31 (s, 1H, H–C(5′)), 6.97–6.92 (m, 2H, Ar), 5.54 (s, 1H, H–C(7)), 5.19 (dd, 1H, ^3J = 9.4, 9.2 Hz, H–C(3_{gluc})), 5.09 (dd, 1H, ^3J = 9.8, 9.4 Hz, H–C(4_{gluc})), 4.99 (dd, 1H, ^3J = 7.9, 9.2 Hz, H–C(2_{gluc})), 4.87, 4.76 (2d, AB syst., 2H, ^2J = 12.6 Hz, H_2C–O–C(1_{gluc})), 4.63 (d, 1H, ^3J = 7.9, H–C(1_{gluc})), 4.25 (dd, AB syst., 1H, ^2J = 12.4, ^3J = 4.5 Hz, Ha-C(6_{gluc})), 4.12 (dd, AB syst., 1H, ^2J = 12.4, ^3J = 2.3 Hz, Hb-C(6_{gluc})), 3.71 (ddd, 1H, ^3J = 9.8, 4.5, 2.3 Hz, H–C(5_{gluc})), 2.79, 2.37 (2d, AB syst., 2H, ^2J = 17.1 Hz, H–C(5)), 2.06, 2.02, 1.99, 1.96 (4s, 12H, AcO-C(2,3,4,6_{gluc})), 1.21, 0.85 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 190.8, 170.6, 170.2, 169.4, 169.3, 144.7, 143.0, 138.3, 137.4, 129.7, 129.6, 124.4, 122.4, 120.6, 100.0, 72.6, 72.0,

71.1, 68.2, 62.6, 61.7, 60.8, 47.9, 40.1, 27.1, 25.9, 20.7, 20.6, 20.5 (2C). IR (film) ν_{max}, cm^{-1}: 3140, 3075, 2970, 2880, 1755, 1685, 1600, 1555, 1505, 1475, 1435, 1375, 1230, 1045, 970, 905. HRMS (TOF-ESI) calcd for $[C_{32}H_{37}N_5O_{11}+H]^+$ 668.2568; found 668.2581.

4.23. β-Glucopyranose-(7*S*)-THI conjugate (−)-8f

Product (−)-**8f** was prepared according to the general procedure II of triazole formation by using (−)-**4a** instead of (+)-**4a**. Yield 64%. $[\alpha]_D^{20} = -42$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 8.17 (s, 1H, H–C(3)), 7.54–7.38 (m, 3H, Ar), 7.30 (s, 1H, H–C(5′)), 6.97–6.94 (m, 2H, Ar), 5.55 (s, 1H, H–C(7)), 5.18 (t, 1H, ^3J = 9.4 Hz, H–C(3_{gluc})), 5.07 (dd, 1H, ^3J = 9.8, 9.4 Hz, H–C(4_{gluc})), 4.98 (dd, 1H, ^3J = 7.9, 9.4 Hz, H–C(2_{gluc})), 4.87, 4.77 (2d, AB syst., 2H, ^2J = 12.8 Hz, H_2C–O–C(1_{gluc})), 4.60 (d, 1H, ^3J = 7.9, H–C(1_{gluc})), 4.29 (dd, AB syst., 1H, ^2J = 12.4, ^3J = 4.5 Hz, Ha-C(6_{gluc})), 4.10 (dd, AB syst., 1H, ^2J = 12.4, ^3J = 2.3 Hz, Hb-C(6_{gluc})), 3.71 (ddd, 1H, ^3J = 9.8, 4.5, 2.3 Hz, H–C(5_{gluc})), 2.80, 2.34 (2d, AB syst., 2H, ^2J = 17.3 Hz, H–C(5)), 2.06, 2.02, 1.98, 1.89 (4s, 12H, AcO-C(2,3,4,6_{gluc})), 1.22, 0.85 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz, +55 °C) δ, ppm: 190.4, 170.4, 170.0, 169.2, 169.0, 144.9, 143.3, 138.3, 137.8, 129.7, 129.6, 124.6, 122.3, 120.8, 100.2, 72.9, 72.3, 71.5, 68.7, 62.7, 62.0, 61.1, 48.2, 40.1, 27.2, 25.9, 20.6, 20.5, 20.4 (2C). IR (film) ν_{max}, cm^{-1}: 3135, 2970, 2880, 1760, 1685, 1600, 1555, 1505, 1475, 1435, 1375, 1225, 1040, 970, 905. HRMS (TOF-ESI) calcd for $[C_{32}H_{37}N_5O_{11}+H]^+$ 668.2568; found 668.2595.

4.24. α-Glucofuranose-(7*S*)-THI conjugate (−)-8g

Product (−)-**8g** was prepared according to the general procedure II of triazole formation by using glucose derivative **10** instead of **9** and (−)-**4a** instead of (+)-**4a**. Yield 93%. $[\alpha]_D^{20} = -41$ (*c* 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 8.19 (s, 1H, H–C(3)), 7.41–7.37 (m, 4H, H–C(5′), Ar), 7.01–6.96 (m, 2H, Ar), 5.86 (d, 1H, ^3J = 3.7 Hz, H–C(1_{gluc})), 5.60 (s, 1H, H–C(7)), 4.78, 4.69 (2d, 2H, AB syst., 2H, ^2J = 12.8 Hz, H_2C–O–C(3_{gluc})), 4.56 (d, 1H, ^3J = 3.7 Hz, H–C(2_{gluc})), 4.23 (dt, 1H, ^3J = 8.1 Hz, ^3J = 5.5 Hz, H–C(5_{gluc})), 4.08–4.03 (m, 2H, H–C(4_{gluc}), H–C($6a_{gluc}$)), 3.98 (dd, 1H, AB syst., ^2J = 8.7 Hz, ^3J = 5.5 Hz, H–C($6b_{gluc}$)), 3.94 (d, 1H, ^3J = 3.2 Hz, H–C(3_{gluc})), 2.80, 2.44 (2d, AB syst., 2H, ^2J = 17.2 Hz, H–C(5)), 1.49, 1.36, 1.31, 1.26 (4s, 12H, H_3C–C–O–C(1_{gluc} and 5_{gluc})), 1.22, 0.87 (2s, 6H, H_3C–C(6)), ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 190.9, 145.2, 143.0, 138.3, 137.4, 129.5, 128.8, 128.4, 128.4, 124.3, 121.9, 120.5, 111.8, 109.1, 105.1, 82.4, 81.7, 80.9, 78.9, 72.1, 67.3, 63.7, 60.9, 48.1, 40.1, 27.1, 26.8, 26.1, 25.6, 25.3. IR (film) ν_{max}, cm^{-1}: 3130, 3095, 2980, 2940, 2905, 2880, 1680, 1595, 1555, 1504, 1375, 1220, 1075, 1040, 1025. HRMS (TOF-ESI) calcd for $[C_{30}H_{37}N_5O_7+H]^+$ 580.2771; found 580.2751.

4.25. C-Nucleoside-like conjugate (+)-8h

Product (+)-**8h** was prepared according to the general procedure II of triazole formation by using monosaccharide **11** instead of **9** and (−)-**4a** instead of (+)-**4a**. Yield 78%. $[\alpha]_D^{20} = +27$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 8.17 (s, 1H, H–C(3)), 7.44–7.39 (m, 3H, Ar), 7.33 (s, 1H, H–C(5′)), 6.98–6.94 (m, 2H, Ar), 5.94 (d, 1H, ^3J = 3.6 Hz, H–C(1_{sug})), 5.58 (s, 1H, H–C(7)), 4.96 (d, 1H, ^3J = 10.5 Hz, H–C(4_{sug})), 4.85 (dd, 1H, ^3J = 4.1, 3.6 Hz, H–C(2_{sug})), 4.51 (dd, AB syst., 1H, ^2J = 10.2, ^3J = 9.9 Hz, CH_2–C(3_{sug})), 4.40 dd, AB syst., 1H, ^2J = 10.2, ^3J = 5.5 Hz, CH_2–C(3_{sug})), 2.98 (s, 3H, H_3CSO_2-CH_2–C(3_{sug})), 2.77 (d, AB syst., 1H, ^2J = 17.3 Hz, Ha-C(5)), 2.66 (dddd, 1H, ^3J = 10.5, 9.9, 5.5, 4.1 Hz, H–C(3_{sug})), 2.39 (d, AB syst., 1H, ^2J = 17.3 Hz, Hb-C(5)), 1.55, 1.36 (2s, 6H, H_3C–C–O–C(1_{sug})), 1.21, 0.86 (2s, 6H, H_3C–C(6)). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 198.8, 146.1, 143.0, 138.3, 137.4, 129.7 (2C), 124.4, 121.6, 120.6, 112.5, 105.0, 79.8, 72.9, 65.5, 60.9, 50.0, 47.9, 40.1, 37.1, 27.1, 26.6, 26.2, 25.9. IR (film) ν_{max}, cm^{-1}: 3125, 2985, 1675, 1505, 1355, 1170, 1095, 1035, 990, 960. HRMS (TOF-ESI) calcd for $[C_{26}H_{31}N_5O_7S+H]^+$ 558.2022; found 558.2047.

X-ray powder analysis of a polycrystalline sample of the racemic compound **4** was carried out on an X-ray powder diffractometer Rigaku Ultima IV. All measurements of single crystal X-ray analysis were made on a Bruker-Nonius KappaCCD imaging plate area detector with graphite monochromated MoK radiation (λ = 0.71073 Å). The structures were solved by direct methods with SIR-94 and SIR-97 and refined by full matrix least squares with SHELXL-97 and MAXUS software package. Crystal data are follows:

4.26. Homochiral compound (−)-3a

(CCDC-766065): $C_{15}H_{17}N_3O$, FW = 255.32, orthorhombic, $P2_12_12_1$ (No. 19), colorless prism, *a* = 8.4365(2)Å, *b* = 12.0165(4)Å, *c* = 13.2480(4)Å, *V* = 1343.05(7)Å^3, *T* = 173 K, *Z* = 4, D_{calcd} = 1.263 g/cm^3, μ = 0.082 mm^{-1}, *R* = 0.0468.

4.27. Racemic compound (±)-3

(CCDC-766066): $C_{15}H_{17}N_3O$, FW = 255.32, monoclinic, $P2_1/n$ (No. 14), colorless prism, *a* = 12.3477(9)Å, *b* = 8.4775(7)Å, *c* = 12.9711(9)Å, β = 106.580(4)°, *V* = 1301.3(2)Å^3, *T* = 223 K, *Z* = 4, D_{calcd} = 1.303 g/cm^3, μ = 0.084 mm^{-1}, *R* = 0.0643.

4.28. Homochiral compound (−)-4a

(CCDC-766067): $C_{15}H_{17}N_3O$, FW = 281.32, monoclinic, $P2_1$ (No. 4), colorless prism, *a* = 6.5261(2)Å, *b* = 11.6327(5)Å, *c* = 19.3520(9)Å, β = 99.365(2)°, *V* = 1449.6(1)Å^3, *T* = 173 K, *Z* = 4, D_{calcd} = 1.289 g/cm^3, μ = 0.090 mm^{-1}, *R* = 0.0555.

4.29. Compound (−)-6

(CCDC-764782): $C_{25}H_{29}N_3O_4$, FW = 435.52, orthorhombic, $P2_12_12_1$ (No. 19), colorless prism, *a* = 6.3197(1)Å, *b* = 11.9939(2)Å, *c* = 29.4468(6)Å, *V* = 2232.00(7)Å^3, *T* = 173 K, *Z* = 4, D_{calcd} = 1.296 g/cm^3, μ = 0.080 mm^{-1}, *R* = 0.0440.

4.30. Compound (−)-7

(CCDC-764781): $C_{23}H_{22}BrN_3O$, FW = 436.35, orthorhombic, $P2_12_12_1$ (No. 19), colorless plate, *a* = 6.0806(2)Å, *b* = 16.4672(5)Å, *c* = 20.2648(7)Å, *V* = 2029.1(1)Å^3, *T* = 173 K, *Z* = 4, D_{calcd} = 1.428 g/cm^3, μ = 2.044 mm^{-1}, *R* = 0.0671.

For further details, see crystallographic data for these compounds deposited with the Cambridge Crystallographic Data Centre as Supplementary publications of corresponding CCDC numbers. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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