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Synthesis and applications of *exo N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)benzamides as NMR solvating agents for the chiral discrimination of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphates and α-substituted acids

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ABSTRACT

A series of *exo N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)benzamides were prepared from (*R*)-isobornyl amine and screened as chiral solvating agents to discriminate the isomers of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphates by ^{31}P NMR analysis. A linear relationship between the experimental and calculated enantiomeric purity was established indicating the potential use of the system to determine the ee for samples of this acid of unknown enantiomeric purity. The amides were also screened for chiral discrimination of some α-substituted acids by ^{19}F NMR analysis.

1. Introduction

The synthesis and study of chiral molecules is a well-established and expanding area of modern chemistry. The importance of a wide range of chiral molecules is not merely restricted to bioactive molecules such as pharmaceuticals, chemicals inducing flavors, and fragrances, but also covers many other areas of molecular recognition and material science. Moreover, the activity is often linked to the chiral information and absolute conformation of the optically active compounds. Hence it is important to unambiguously establish detailed chiral information, enantiomeric purity, and absolute configuration. This has necessitated the need for quick, accurate, and reliable techniques to establish the ratio of the enantiomers in chiral samples. More commonly used contemporary techniques for such measurements are based on chromatographic[1] separations such as GC and HPLC, but their success mainly depends on the competence and selectivity of the chiral stationary phases of the columns. More spectroscopic techniques, such as mass spectrometry,[2] IR, UV, and fluorescence spectroscopy,[3] circular dichroism, and electrophoresis[4] have been developed to determine the enantiomeric purity of molecules. Among these other methods, NMR spectroscopy has emerged as an advantageous technique for the fast and accurate determination of the ratio of enantiomers.[5] The two enantiomers of the chiral sample show the same signals in the NMR and cannot be recognized in an achiral environment of the NMR spectroscopy. Hence, some modifications are required to distinguish between the signals in this technique. The enantiomers which typically appear as identical signals in the NMR spectra when converted into diastereomers, show resolved spectroscopic patterns. Converting the analyte sample to diastereomers can carried out in two ways, by forming covalent bonds with chiral derivatizing agents[6] or alternatively by forming temporary supramolecular interactions with chiral solvating (or complexing) agents.[7] One such routinely used technique involves the in situ preparation of diastereomeric lanthanide chelate complexes.[8] However, there are some inherent problems such as the broadening of signals, low solubility in NMR solvents, and their high cost. The second option is probably simpler, and more practical and hence has been investigated considerably in recent years. In the case of chiral solvating agents, the temporary formation of diastereomers with enantiomerically pure reagents results in non-equivalence of the chemical shifts of the protons of the two enantiomers of the analyte.[9] This technique of using chiral solvating agents has distinct advantages of simplicity, more accurate analysis against the derivatization process with chiral derivatizing agents, and it is non-destructive due to weak non-covalent interactions. Such intermolecular supramolecular interactions include dipole–dipole, charge transfer, van der Waals, π–π stacking, and the formation of H-bonding. A variety of compounds such as

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amines, amides, lactams, carboxylic acids, and cyclodextrins with suitable coordination sites and orientations have been developed to effectively function as chiral solvating agents. The success of this technique depends on the adequate combination of these interactions between the two partners of the complex. Hence, even though a large number of chiral solvating agents are available, there is a need to design more molecules, which can be readily prepared in enantiomerically pure form, while they may be easily modified to suit the particular requirement.

The chiral amide of 3,5-dinitro benzoic acid **1a** reported by Kagan et al. is one of the earliest and well-studied chiral solvating agents for efficiently discriminating between several types of molecules by NMR analysis.[10] This is a simple molecule with basic functional units present to enable hydrogen-bonding and π–π interactions with substrates for tight complex formations under NMR conditions. These types of compounds were first developed by Pirkle et al. for the Whelk-O type materials for separation of chiral compounds on HPLC columns.[11] Over the years, a few more derivatives of Kagan's amide have been explored with good success in the molecular recognition of chiral compounds (Chart 1).[12] The range of chiral analytes successfully screened with these chiral solvating agents include amides[12c] sulfoxides,[10b,d] multifunctional *tert*-alcohols,[12d] and phosphine oxides.[10c]

The widely accepted mode of interaction between the chiral solvating agent and analyte molecule involves hydrogen bonding, N–H···O=X (X = C or S of analyte), and the π–π interaction between the aromatic units.[12d] In one case, a cleft like conformation is created by perpendicularly arranged dinitro benzoyl and the naphthalene rings in case of **1b**;[12c] similar types of explanations are offered for the other derivatives **1c** and **1d**.[13] The proposed interactions were also corroborated by up-field and down-field shifts of appropriate examples in the ^{1}H NMR experiments. Recently we have presented our results with a modified Kagan type amide **1e** and demonstrated its slightly superior chiral solvating ability for a variety of substrates.[14] We have an ongoing interest in developing chiral solvating agents suitable for a variety of analytes[15] and herein we report another molecule. The derivatives of Kagan's amide mentioned in Chart 1 have a similar feature of having aromatic systems on the both arms of the amide functionality, although not directly attached in case of **1d**. Herein we report an amide of chiral isobornyl amine with various aromatic acid counterparts and discuss their suitability as chiral solvating agents in some chiral analytes.

2. Result and discussions

The synthesis of modified amides is based on using chiral isobornyl amine **2**, which is a readily available material. The rigid bicyclic framework of isobornyl amine with three stereogenic centers will provide the steric bulk for chiral molecular recognition during the NMR analysis, although it may not offer π–π interactions from both the sides of the amide unit. A series of such amides **4a**–**4h** were synthesized by simple condensation of isobornyl amine **2** and suitable acid chlorides **3** in the presence of a triethylamine as base (Scheme 1).

All of the amide derivatives of **4** were purified by column chromatography, crystallization, and characterized by the usual spectroscopic and analytical tools. The 3,5-dinitro derivative **4f** was also characterized by its single crystal X-ray analysis (Fig. 1).[16] The molecule is crystallized in the $P2_12_12_1$ space group, and two molecules are held together by hydrogen bonding between NH–C=O···H–N–CO with the bond length of 2.114 Å.

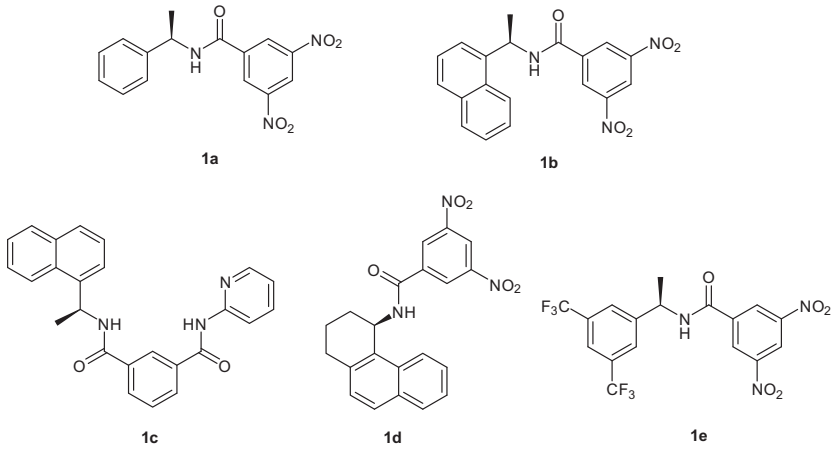
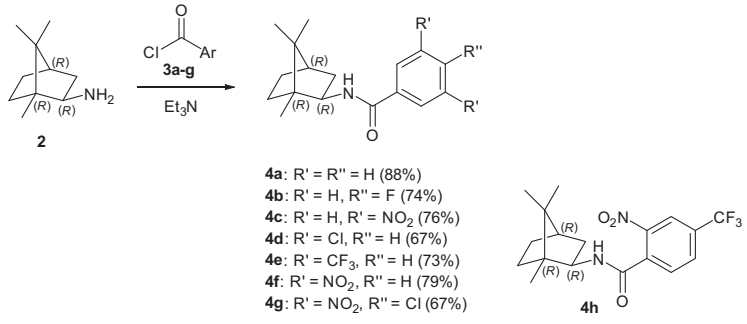


Chart 1. Kagan's amide **1a** and its analogues.



Scheme 1. Synthesis of isobornyl derived amides.

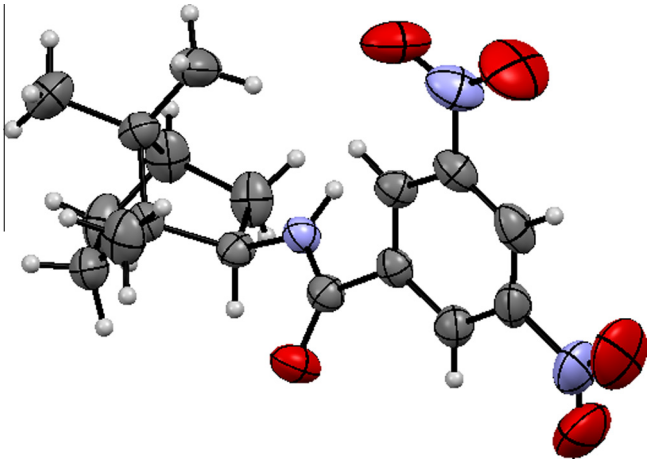
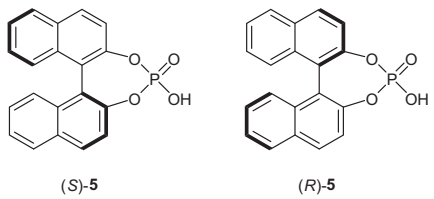


Figure 1. ORTEP diagram of **4f**.

Catalytic asymmetric synthesis is one of the most efficient techniques employed to generate a large amount of chiral material using a small quantity of chiral catalysts. Recently chiral Brønsted acids, such as phosphoric acid derivatives 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **5** (BINPA) and its derivatives, have found wide use as chiral catalysts. Many reactions have been developed to generate a stereogenic center in an enantioselective manner using this class of catalyst.[17] For successful applications in asymmetric reactions, the acid catalysts need to be of enantiomerically pure form and hence it was necessary to develop a tool for the quick and accurate determination of its enantiomeric purity (Chart 2).

The enantiomeric purity of acid **5** and similar compounds can be determined by various techniques, but a very efficient, non-destructive, quick, and reliable one has recently been developed using nuclear magnetic resonance (NMR) spectroscopy. Usually ^{1}H NMR analysis is used to detect the signals separated by in situ chiral discrimination caused by supramolecular interactions between chiral solvating agent and the analyte. In some cases other nuclei such as ^{13}C, ^{19}F, ^{31}P, ^{77}Se, and even ^{195}Pt have been used as the probe to detect the ratio of isomers.[14] There are a few reports on the development and use of some chiral solvating agents to determine the composition of isomers of **5**, an important catalyst by ^{31}P NMR analysis.[18] Although Kagan's amide **1a** has been used as a probe to resolve the signals of compounds containing phosphorus by ^{31}P NMR,[10c,12a] there are no reports on its use for the analysis of **5**. The present set of chiral solvating agents, **4a**–**4h**, was systematically screened to determine their efficiency to discriminate between the isomers of **5** by recording the separation of signals by the ^{31}P NMR analysis. The initial experiment of recording ^{31}P NMR of racemic **5** with modified Kagan's amide **4f** in $CDCl_3$ resulted in small shift of the signal, but no split was observed (Table 1). The shift of the signal from the original position was recorded as induced chemical shift ($\Delta\delta$) while the difference in the two split signals due to recognition of analyte by chiral solvating agents is referred to as a chemical shift non-equivalence ($\Delta\Delta\delta$). The neutral nature of chiral solvating agent **4f** to abstract the acidic hydrogen of **5** is probably responsible for the inefficiency of the chiral discrimination. For similar studies, the use of an external base to assist in the abstraction of this proton for subsequent ionic interactions with a molecule of chiral solvating agents is available in the literature.[9l] Hence, we investigated a few organic bases with the present chiral solvating agent **4f** and the effect was measured (Table 1). Initially triethyl amine was scanned where a slightly larger shift was detected but failed to observe any discrimination. However, when stronger bases were screened, a significant shift was observed, but more importantly the chiral discrimination was also seen. Among the bases, DABCO and pyridine showed good resolution in the ^{31}P signal of the two isomers of **5**, while DMAP showed the best discrimination. The effectiveness of a base for this behavior is due to combined effect of the presence of the aromatic ring to offer π–π interaction as well as its basicity (p*K*a).[19]



(*S*)-**5** (*R*)-**5**

Chart 2. Enantiomers of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate **5**.

Table 1
Effect of base of the recognition of (±)-**5** with chiral solvating agent **4f**[a]

No	Base	Induced chemical shift ($\Delta\delta$)[b]	Chemical shift non-equivalence ($\Delta\Delta\delta$)[b]
1	—	0.05	—[c]
2	Triethyl amine	−1.45	—[c]
3	DBU	−0.45	0.030
4	DABCO	0.32	0.166
5	Pyridine	0.44	0.140
6	DMAP	0.66	0.303

[a] All ^{31}P NMR spectra run at 20 mmol in $CDCl_3$ in a ratio of (±)-**5**/chiral solvating agents **4f**/base (1:2:1).
[b] In ppm.
[c] Not observed.

The proposed intermediate involves three components, that is, the chiral solvating agent, the deprotonated ion of **5,** and protonated base.[9l,m] Hence, we further investigated the ratio of the three species participating in the possible mode of interactions (Table 2). Marginally better parameters were observed when higher amounts of base and chiral solvating agent were used. Similar observations in the case of thiourea based chiral solvating agents were reported for enhanced selectivity with higher amounts of reagent.[20]

Table 2
Composition of DMAP, to chiral solvating agent **4f** and analyte[a]

No	Base	Chiral solvating agent	(±)-**5**	$\Delta\delta$[b]	$\Delta\Delta\delta$[b]
1	1	1	1	1.050	0.262
2	1	2	1	0.660	0.303
3	2	2	1	0.563	0.299
4	1	3	1	0.265	0.266

[a] All ^{31}P NMR spectra run at 20 mmol in $CDCl_3$.
[b] In ppm.

Having established the efficacy of DMAP to be a more suitable base for the present analysis we further scanned the rest of the chiral solvating agent molecules (Table 3). In all cases, the shift

Table 3
Screening chiral solvating agents for recognition of (±)-**5**[a]

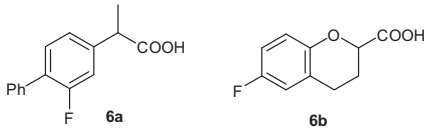
No	Chiral solvating agents **4**	Induced chemical shift ($\Delta\delta$)[b]	Chemical shift non-equivalence ($\Delta\Delta\delta$)[b]
1	**4a**	1.77	—[c]
2	**4b**	1.77	—[c]
3	**4c**	1.57	0.013
4	**4d**	1.70	—[c]
5	**4e**	1.13	—[c]
6	**4f**	0.66	0.303
7	**4g**	0.82	0.251
8	**4h**	1.33	0.020

[a] All ^{31}P NMR spectra run at 20 mmol in $CDCl_3$ in the ratio of (±)-**5**/chiral solvating agents **4f**/DMAP (1:2:1).
[b] In ppm.
[c] Not observed.

in the signal ($\Delta\delta$) was considerable but the chiral discrimination was observed in the case **4c**, **4f,** and **4g**. These three derivatives have a strong electron withdrawing nitro group attached on the acid component of the amides. The beneficial effect of the presence of 3,5-dinitro functionality for effective interactions has also been observed in earlier studies,[10d,12c,14] however, the structurally similar **4d** and **4e** were not suitable to resolve the signals of **5**. We also prepared **4g** with a 3,5-dinitro-4-chloro unit and scanned for chiral solvating agent activity. This was found to be effective with reasonably good results, but with a slightly lower value of chemical shift non- equivalence compared to **4f**. The presence of the slightly larger chlorine atom might contribute to the steric crowding and nullifying the electronic effects. Structurally different **4h**, but with two strongly electron withdrawing groups was also effective but to a lesser degree when compared to dinitro derivative **4f**.

The ability of the chiral discrimination of the present chiral solvating agents was further studied in order to establish the linear relationship between the observed and actual values of ee for establishing its practical utility as a chiral solvating agent (Fig. 2). The observed ee values were found to be within the acceptable limits of the actual values, which confirm the accuracy and consistency of the analysis.

The use of chiral solvating agents for determining the enantiomeric purity by ^{1}H NMR analysis is emerging as a useful tool and hence we decided to scan different types of analytes to prove its wider applicability. Hence we further scanned **4f**, the most promising of the present chiral solvating agents, for α-substituted acids since they form an important class of chiral compounds. The importance of chiral drugs in medicinal chemistry is a well established phenomenon. Herein we scanned **4f** for a few chiral drugs and drug intermediates. Non steroidal anti-inflammatory agents such as flurbiprofen **6a**, are important chiral drugs.[21] We also extended our study with the analysis of **6b**, an intermediate of Nebivolol, a β-blocker agent.[22] Herein we observed the separation of signals in the ^{19}F NMR in the case of **6a** and **6b**, when spectra



Δδ = 1.16
ΔΔδ = 0.01

Δδ = 2.24
ΔΔδ = 0.01

Chart 3. Structures of fluorine containing analytes with $\Delta\delta$ and $\Delta\delta\delta$ values of ^{19}F NMR with **4f** (2.0 equiv) and DMAP (1.0 equiv) in $CDCl_3$ (20 mmol).

were recorded with **4f** (2.0 equiv) and DMAP (1.0 equiv). The separation of signals for the fluorine atom and its shift area is presented in Chart 3.

3. Conclusion

Herein we have synthesized a series of chiral *exo*-(1*R*,2*R*,4*R*)-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)benzamides from (*R*)-isobornyl amine and screened them as chiral solvating agents to determine the ratio of isomers of 1,1′-binaphthyl-2,2′-diyl hydrogen phosphates by ^{31}P NMR analysis. The chiral solvating agent was also screened to discriminate between the signals of a few α-functionalized acids in ^{19}F NMR analysis. Conditions were also standardized for the quantitative determination of the ratio of enantiomers in the controlled experiment, which opens up possibilities for this technique to be used for the determination of the ee of unknown samples of these analytes.

4. Experimental

4.1. General

Thin layer chromatography was performed on silica gel plates quoted on aluminim sheets. The spots were visualized under UV

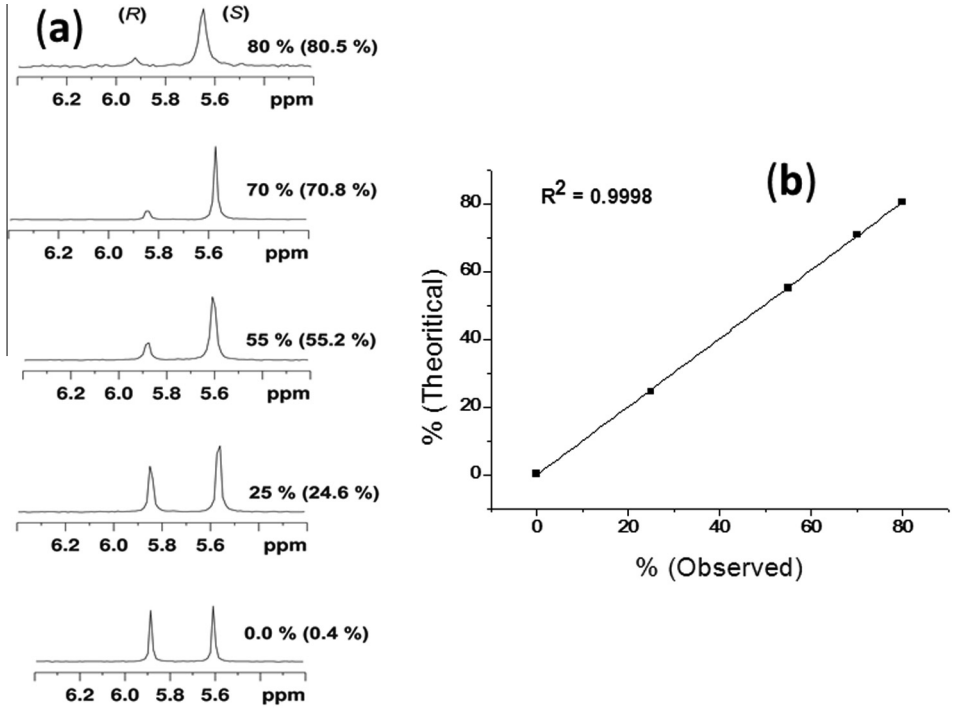


Figure 2. (a) Selected region of ^{31}P NMR spectra of scalemic mixture of **5** in the presence of **4f**; values in parenthesis indicate the observed ee; (b) its correlation between theoretical and observed % ee values.

light or with iodine vapor. All compounds were purified by column chromatography on silica gel (60–120 mesh). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. NMR Spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 376 MHz for ^{19}F NMR, and 162 MHz for ^{31}P NMR) with $CDCl_3$ as the solvent and TMS as the internal standard. Single crystal X-ray diffraction data was collected Xcalibur, Eos, Gemini diffractometer. Mass spectra were recorded on GCMS instrument in the direct injection EI-mode. IR Spectra were recorded as KBr pallets and specific optical rotations were measured on JACSO P-2000 polarimeter. Melting points were recorded in Thiele's tube using paraffin oil and are uncorrected.

4.2. General procedure for the synthesis of amide 4

In a dry round bottom flask, a solution of (−)-*iso*-bornyl amine (0.40 g, 2.7 mmol) dissolved in dry chloroform (5 mL) was mixed with triethyl amine (0.35 mL, 2.7 mmol). The mixture was allowed to cool (0 °C) and then charged with a solution of appropriate acid chloride (1.0 equiv) dissolved in chloroform (in 30 min). The reaction mixture was stirred at room temperature for 4 h after which the solvent was evaporated, and the residue was washed with sodium bicarbonate, and extracted with dichloromethane (3 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under the reduced pressure. The crude product was purified by short column chromatography over silica gel (50% ethyl acetate–petroleum ether).

4.2.1. *N*-((1*R*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)-benzamide 4a

Yield 88%; mp = 101 °C $[\alpha]_D^{28} = -70.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.94 (s, 3H), 1.10 (s, 3H), 1.21–1.27 (m, 1H), 1.36–1.42 (m, 1H), 1.60–1.83 (m, 4H), 1.95–1.99 (m, 1H), 4.10–4.16 (m, 1H), 6.09–6.08 (d, J = 6.8 Hz,1H), 7.43–7.53 (m, 3H), 7.71–7.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.3, 20.4, 35.9, 39.2, 44.9, 47.2, 48.8, 57.2, 126.7 (2C), 128.6 (2C), 131.3, 135.3, 166.8. IR (KBr): υ 3327, 2953, 1643, 1577, 1390, 1286, 1077, 1028, 713 cm^{-1}. HRMS:(ESI+) *m*/*z* calculated for $C_{17}H_{23}NO$ 258.1858 $[M+H]^+$. Found: 258.1858.

4.2.2. 4-Flouro-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)benzamide 4b

Yield 74%; mp = 90 °C $[\alpha]_D^{28} = -7.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (s, 3H), 0.93 (s, 3H), 1.20 (s, 3H), 1.21–1.26 (m, 1H), 1.35–1.41 (m, 1H), 1.60–1.83 (m, 4H), 1.95–2.00 (m, 1H), 4.01–4.14 (m, 1H), 6.01–6.02 (d, J = 7.2 Hz, 1H), 7.10–7.14 (m, 2H), 7.71–7.75 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −108.61. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.3, 20.4, 35.9, 39.2, 44.9, 47.2, 48.8, 57.2, 115.2 (2C) (d, J_{C-F} = 21 Hz), 128.8 (2C) (d, J_{C-F} = 8.8 Hz), 131.2 (d, J_{C-F} = 3.2 Hz), 163.3 (d, J_{C-F} = 250 Hz), 165.7. IR (KBr): υ 3310, 2952, 1635, 149, 1307, 1228, 846 cm^{-1}. HRMS:(ESI+) *m*/*z* calculated for $C_{17}H_{22}FNO$ 276.1764 $[M+H]^+$. Found: 276.1761.

4.2.3. 4-Nitro-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)benzamide 4c

Yield 76%; mp = 148 °C $[\alpha]_D^{28} = -73.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.94 (s, 3H), 1.02 (s, 3H), 1.23–1.27 (m, 1H), 1.35–1.42 (m, 1H), 1.66–1.86 (m, 4H), 1.96–2.02 (m, 1H), 4.12–4.14 (m, 1H), 6.09–6.11 (d, 1H), 7.10–7.14 (d, J = 8.8 Hz, 2H), 8.28–8.30 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.3, 20.4, 26.9, 35.8, 39.1, 44.9, 47.2, 48.9, 57.6, 123.9 (2C), 127.9 (2C), 140.7, 149.4, 164.8. IR (KBr): υ 3411, 2953, 1669, 1598, 1350, 11108, 869, 726 cm^{-1}. HRMS:(ESI+) *m*/*z* calculated for $C_{17}H_{22}N_2O_3$ 303.1709 $[M+H]^+$. Found: 303.1715.

4.2.4. 3,5-Dichloro-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)benzamide 4d

Yield 67%; mp = 176 °C $[\alpha]_D^{28} = -16.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.93 (s, 3H), 1.01 (s, 3H), 1.23–1.27 (m, 1H), 1.38–1.43 (m, 1H), 1.61–1.85 (m, 4H), 1.95–2.00 (m, 1H), 4.10–4.171 (m, 1H), 5.95–6.97 (d, 7.6 Hz, 1H), 7.48–7.49 (t, J = 3.6 Hz, 1H), 7.55–7.56 (d, J = 1.6 Hz. 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.2, 20.4, 26.9, 35.8, 38.9, 44.9, 47.2, 48.9, 57.5, 125.4 (3C), 131.1, 135.4, 138.1, 164.3. IR (KBr): υ 3285, 2953, 1634, 1536, 1287, 1080, 806, 707, 671 cm^{-1}. HRMS:(ESI+) *m*/*z* calculated for $C_{17}H_{21}Cl_2NO$ 326.1078 $[M+H]^+$. Found: 326.1086.

4.2.5. 3,5-Bis(triflouromethyl)-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-yl)benzamide 4e

Yield 73%; mp = 179–180 °C $[\alpha]_D^{28} = -44.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.95 (s, 3H), 1.03 (s, 3H), 1.23–1.27 (m, 1H), 1.38–1.43 (m, 1H), 1.63–1.86 (m, 4H), 1.97–2.00 (m, 1H), 4.11–4.17 (m, 1H), 6.07–6.09 (d, 5.4 Hz, 1H), 8.01 (s, 1H), 8.13 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 20.2, 20.3, 26.9, 35.8, 38.8, 44.9, 47.2, 49.0, 57.8, 118.8 (q, J_{C-F} = 270 Hz), 124.7 (sep, J_{C-F} = 4 Hz), 127.01, 131.6 (q, J_{C-F} = 34 Hz), 137.2, 164.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.88. IR (KBr): υ 3288, 2955, 1635, 1539, 1388, 1192, 1080, 861, 707 cm^{-1}. HRMS: (ESI+) *m*/*z* calculated for $C_{19}H_{21}F_6NO$ 394.1606 $[M+H]^+$. Found: 394.1603.

4.2.6. 3,5-Dinitro-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)benzamide 4f

Yield 79%; mp = 174 °C $[\alpha]_D^{28} = -62.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.94 (s, 3H), 1.1 (s, 3H), 1.21–1.2 (m, 1H), 1.21–1.3–1.40 (m, 1H), 1.63–1.87 (m, 4H), 1.95–1.98 (m,1H), 4.12–4.17 (m, 1H), 6.28–6.30 (d, J = 6.8 Hz, 1H), 8.85–8.86 (d, J = 2.0 Hz, 2H), 9.13–9.14 (t, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.2, 20.4, 26.9, 35.8, 38.8, 44.8, 47.2, 49.2, 58.2, 120.9(2C), 126.9(2C), 138.5, 148.8, 162.3. IR (KBr): υ 3333, 3101, 2953, 1643, 1537, 1347, 1347, 1028, 726 cm^{-1}. HRMS:(ESI+) *m*/*z* calculated for $C_{17}H_{21}N_3O_5$ 348.1559 $[M+H]^+$. Found: 348.1578.

4.2.7. 4-Chloro-3,5-dinitro-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)benzamide 4g

Yield 67%; mp = 155 °C $[\alpha]_D^{28} = -58.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.93 (s, 3H), 1.01 (s, 3H), 1.23–1.27 (m, 1H), 1.34–1.40 (m, 1H), 1.63–1.88 (m, 4H), 1.96–2.02 (m, 1H), 4.08–4.14 (m, 1H), 6.07–6.09 (d, 8.0 Hz, 1H), 8.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.2, 20.5, 26.9, 35.8, 38.9, 44.8, 47.3, 49.1, 58.2, 123.0, 125.8 (2C), 149.6(2C), 161.4. IR (KBr): υ 3352, 2958, 1643, 1547, 1347, 1063, 744 cm^{-1}. HRMS: (ESI+) *m*/*z* calculated for $C_{17}H_{20}ClN_3NaO_5$ 404.0984. Found: 404.0980.

4.2.8. 4-Trifluoromethyl-2-nitro-*N*-((1*R*,2*R*,4*R*)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-yl)benzamide 4h

Yield 70%; mp = 150 °C $[\alpha]_D^{28} = -42.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (s, 3H), 0.91 (s, 3H), .99 (s, 3H), 1.20–1.26 (m, 1H), 1.35–1.41 (m, 1H), 1.65–1.84 (m, 4H), 1.99–12.04 (m, 1H), 4.07–4.13 (m, 1H), 5.79–5.81(d, 8.4 Hz, 1H), 7.65–7.67 (d, J = 8.0 Hz, 1H), 7.93–7.95 (dd, J = 8.0 Hz, 1.2 Hz), 8.33 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.08. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 20.2 (2C), 26.9, 36.0, 36.9, 44.8, 47.2, 48.8, 57.8, 118.0 (q J_{C-F} = 271 Hz), 121.7 (q J_{C-F} = 4.0 Hz)), 129.7, 130.2 (q J_{C-F} = 3.8 Hz) 132.3 (q J_{C-F} = 34 Hz), 136.3, 146.4, 164.5. IR (KBr): υ 3292, 2956, 1636, 1544, 1325, 1148, 908 cm^{-1}. HRMS: (ESI+) *m*/*z* calculated for $C_{18}H_{21}F_3N_2O_4$ 371.1583 $[M+H]^+$. Found: 371.1639.

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