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Stereoselective syntheses of pinane-based 1,3-diamines and their application as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde

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ABSTRACT

A library of 1,3-difunctionalized pinane derivatives was synthesized and applied as chiral catalysts in the addition of diethylzinc to benzaldehyde. The key intermediate β-lactam **2** was prepared regio- and stereoselectively from (−)-apopinene **1**. The treatment of **2** with di-*tert*-butyl dicarbonate afforded *N*-Boc β-lactam **3**, while acid-catalyzed ring opening of **2** resulted in amino acid **4**. Nucleophilic ring opening of **3** with dimethylamine, followed by deprotection and benzylation, furnished β-amino amides **5**, **8**, and **11**, which were transformed in two steps into the corresponding *N*-tosyldiamines **7**, **10**, and **13**, respectively. Since the use of other amines, such as diethylamine, to study the influence of dialkyl substitution was unsuccessful, an alternative synthetic route was applied. Amidation of tosylated β-amino acid **14** furnished amides **15**–**25**. Reduction of **15**, **16**, **19**, **20**, and **24** resulted in *N*-tosyl diamines **26**–**30**. The β-amino amides and N-tosylated diamines were used as chiral ligands in the enantioselective alkylation of benzaldehyde with diethylzinc, resulting in (*R*)- and (*S*)-1-phenyl-1-propanol. The (*R*)-enantiomer was predominant except when **17**, **22**, **23**, and **25** were used as ligands, in which case the opposite stereochemistry was observed. The best ee values (up to 83%) were obtained when **17**, **20**, **23**, and **25** were used as catalysts.

1. Introduction

Over the past several decades, carbon–carbon bond formation has become an intensively examined topic. Among the enantioselective transformations investigated, the alkylation of aldehydes with diethylzinc has proven to be a useful prototype reaction, providing a good opportunity for the comparison of a wide range of catalysts.[1]

Since Oguni and Omi reported the first enantioselective addition of diethylzinc to benzaldehyde catalyzed by a 1,2-difunctionalized chiral ligand, a great number of catalysts have been developed.[2] Following a breakthrough in asymmetric catalysis, it became a challenge to synthesize chiral ligands from natural compounds. Among a variety of methods, the incorporation of chirality into ligands was achieved by using naturally-occurring, enantiomerically pure terpenes as starting materials. Several diamines and amino alcohols obtained from chiral terpenes, such as (+)-pulegone, fenchone–camphor, and limonene, have been found to be effective chiral promoters for various chemical transformations.[3] It is believed that a chiral catalyst with uniform chirality affords only one enantiomer of the product. However, the application of chiral catalysts derived from natural products has the limitation that in some cases only one enantiomer of the starting material is available. Recent reports have demonstrated the possibility of accessing both enantiomers of a product by using the same chiral promoter. Hirose et al. observed the switching of enantioselectivity by exchanging the positions of the amine and sulfonamide groups in ligands with the same chirality.[4]

Although many types of 1,2-difunctionalized chiral auxiliaries have already been tested in enantioselective reactions, the use of 1,3-difunctionalized ligands is less well explored.[5] While amino alcohols are the most commonly employed catalysts in the alkylation of aldehydes, diamines have received less attention, despite the usefulness of such ligands. Asami et al. have successfully applied aromatic 1,2-diamines in the model reaction of diethylzinc addition to benzaldehyde.[6] Hirose et al. achieved higher selectivity by applying 1,3-amino sulfonamides, where the highly acidic proton of the sulfonamido group was necessary for effective catalytic activity.[4]

We previously reported on the transformation of enantiomerically pure monoterpenes such as α-pinene, apopinene, myrtenal, and (+)-3-carene into β-amino acid derivatives, for example, 1,3-amino alcohols and diamines. These 1,2-disubstituted, 1,3-difunctional chiral synthons were successfully applied as catalysts in the enantioselective synthesis of secondary alcohols.[7]

Herein our aim was to synthesize a library of 1,3-diamines from (−)-apopinene and evaluate them as catalysts in the asymmetric addition of diethylzinc to benzaldehyde.

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The conformationally constrained pinane ring system was chosen because better chiral induction was expected. Our previous results led us to expect that the disadvantages of the 2-methyl substituent in the pinane derivatives could be reduced by applying *apo* derivatives. Additionally, both (−)- and (+)-apopinene are available from commercial sources via one or two-step syntheses, but we have only applied (−)-apopinene as the starting material.[8]

2. Results and discussion

2.1. Syntheses of pinane-based tosylated diamines and amides

The syntheses of **3** and **4** were performed by using literature methods starting from commercially available (−)-myrtenal via (−)-apopinene **1** (Fig. 1).[8] The cycloaddition of chlorosulfonyl isocyanate (CSI) proceeded highly regio- and stereospecifically (as revealed by NMR and GC studies on the crude product **2**), resulting in only β-lactam **2**. The *N*-Boc β-lactam **3** was obtained from **2** by treatment with di-*tert*-butyl dicarbonate, while the transformation of **2** into amino acid **4** was achieved with aqueous HCl.

β-Lactam **3** was readily converted into derivatives bearing an *N*,*N*-dimethylamino and a sulfonamido group (Scheme 1). β-Lactam **3** underwent nucleophilic ring opening with dimethylamine to give amide **5** in good yield, either in aqueous or ethanolic solution. Reduction of **5** with $LiAlH_4$ furnished 1,3-diamine **6**. Sulfonation of the secondary amino group in **6** with *p*-toluenesulfonyl chloride resulted in the tosylated 1,3-diamine **7** in a good yield. Deprotection of **5** with 5% aqueous HCl gave **8**, which served as the starting material for the synthesis of additional tosylated diamines and amides. Sulfonation of the primary amino group in **8** led to tosylated *N*,*N*-dimethylamide **9**. Amide **12** was obtained through two different routes: the primary amino group in **8** was transformed into a secondary one by reductive amination, resulting in **11**, which was followed by tosylation; *N*-benzylation of **9** gave **12** in higher yield. The transformation of **9** and **12** into tosylated 1,3-diamines **10** and **13** was accomplished by reduction with $LiAlH_4$.

The attempted ring opening of lactam **3** with diethylamine was unsuccessful, probably because of steric hindrance. Efforts to re-

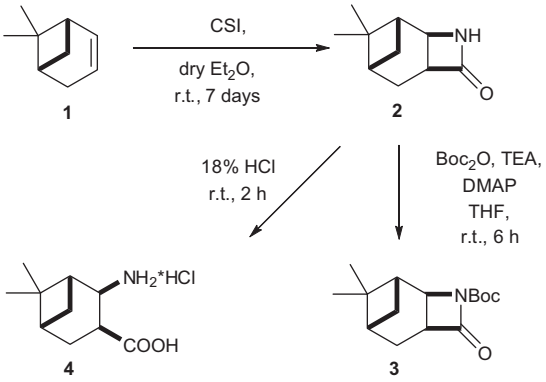
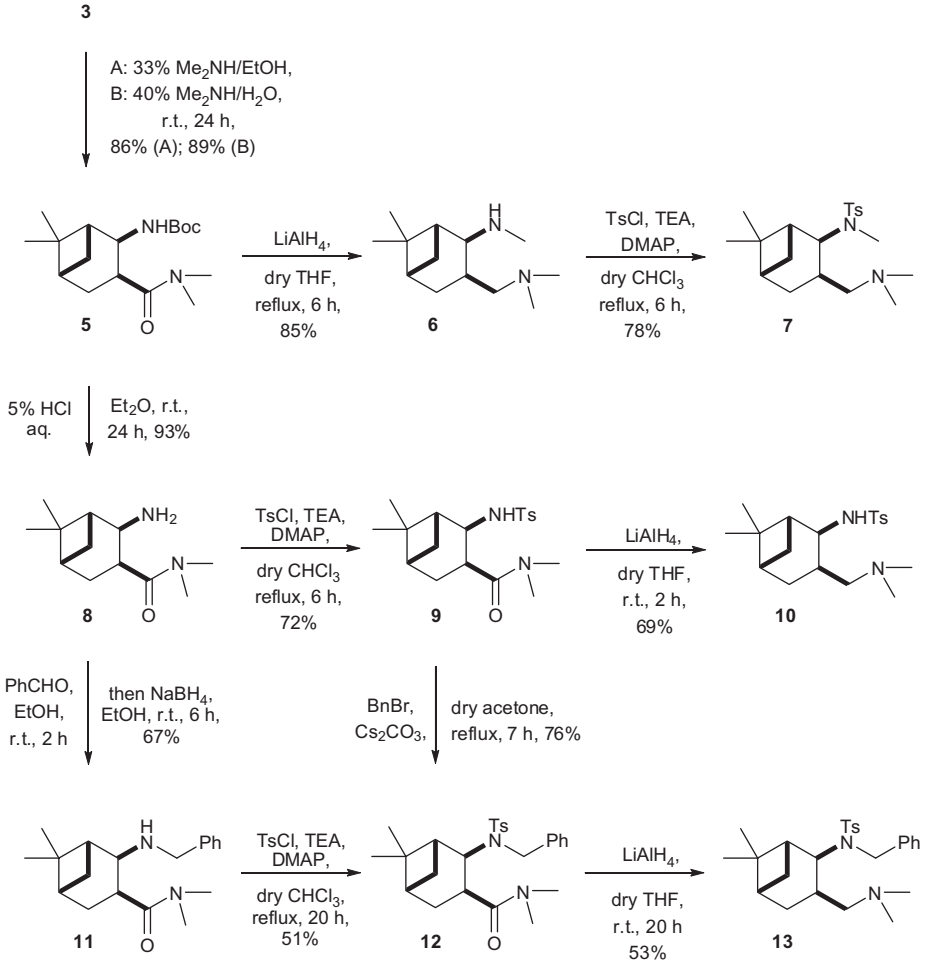


Figure 1. Transformation of a β-lactam into **3** and **4**.



Scheme 1. Syntheses of pinane-type tosylated diamines and amides.

duce amides **8** and **11** to diamines with a primary and secondary amino functionality were also unsuccessful. The starting material could not be recovered; an inseparable mixture of amine-type compounds was obtained. In order to extend the library of desired ligands, an alternative pathway was devised for the syntheses of **15**–**30** (Scheme 2).

In two or three reaction steps, β-amino acid **4** was converted into tosylated primary, secondary, or tertiary amides **15**–**25** and tosylated tertiary amines **26**–**30**. The sulfonation of **4** afforded tosylated amino acid **14**, which underwent amidation via the acid chloride to give **15**–**25**. β-Amino amides **15**–**19** and **21**–**24** were prepared under reflux conditions, but in the syntheses of **20** and **25**, microwave activation was necessary. Reduction of amides **15**, **16**, **19**, **20**, and **24** with $LiAlH_4$ resulted in tertiary 1,3-diamines **26**–**30**, whereas the attempted reductions of **17**, **18**, **21**–**23**, and **25** to secondary or primary amines were unsuccessful with only an inseparable mixture of amine-type compounds being obtained.

2.2. Application of tosylated diamines and amides as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde

The application of sulfonated diamines **7**, **9**, **10**, **12**, **13**, **15**–**25**, and **26**–**30** as catalysts in the ethylation of benzaldehyde resulted in 1-phenyl-1-propanol enantiomers **32** and **33** (Scheme 3).

The enantiomeric purity of the secondary alcohol obtained was determined by GC on a Chirasil-DEX CB column, according to the literature.[9] Catalysts **7**, **9**, **10**, **12**, **13**, **15**–**25**, and **26**–**30** were applied in a 10% molar ratio and the reactions were carried out in *n*-hexane at room temperature. The results are presented in Table 1.

When diamines **7**, **10**, and **13** were applied as chiral ligands in the addition of diethylzinc to benzaldehyde, low to moderate enantioselectivities were achieved. The asymmetric induction was similarly weak when amides **9** and **12** were used. The formation of the (*R*)-enantiomer **33** was predominant in each case.

Following the introduction of a methyl group, or even a bulkier benzyl group onto the sulfonamido moiety **7** and **13**, weak catalytic activity was observed. The enantioselectivity was higher when ligands **9** and **10** were applied, which revealed that the acidic proton on the sulfonamide nitrogen was necessary for a reasonable level of catalytic activity.

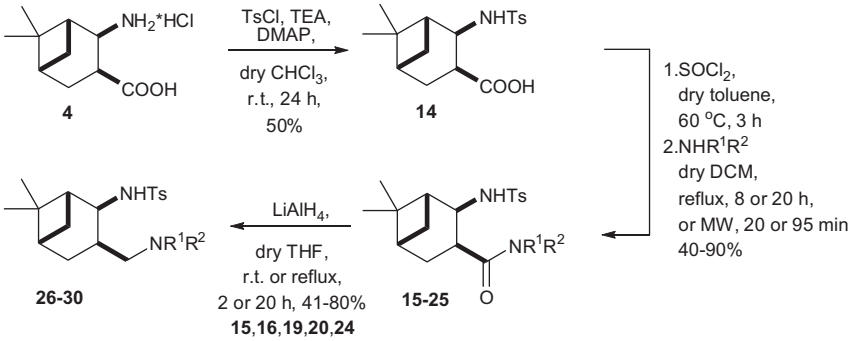
These results encouraged us to investigate the effect of substituents on the aminomethyl or amido group on the stereoselectivity of the alkylation of benzaldehyde by using chiral auxiliaries **15**–**30**.

Chiral ligands bearing a tertiary amide function **15**, **16**, **19**, **20**, and **24** furnished products in low to moderate ee, with (*R*)-selectivity. The highest asymmetric induction was achieved when *N*-benzyl-*N*-methyl derivative **20** was used (ee 65%). Chiral ligand **18** hardly influenced the selectivity at all, probably because of the absence of a substituent on the primary amide group.

Catalysts **17**, **22**, **23**, and **25**, containing a secondary amide group, resulted in the best ee values, while the direction of the enantioselectivity turned from (*R*) to (*S*). A marked increase in the enantioselectivity was observed with the *N*-phenyl derivative **25** (ee 83%).

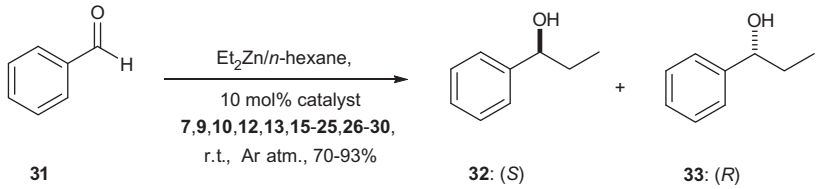
However, when a new asymmetric center was introduced by utilizing (*R*)- and (*S*)-1-phenylethylamine, the catalytic effects of **21** and **22** proved to be unsatisfactory, probably because of the greater steric hindrance of the substituent. When diamines **26**–**30** were explored as chiral auxiliaries in the addition of diethylzinc to benzaldehyde, lower ee values were obtained.

When compared with previously reported applications of monoterpene-based 1,3-aminoalcohols[5c,7a] or sulfonated diamines,[4a] the present *N*-tosyldiamines have less influence on the stereoselectivity of the model reaction. Somewhat higher ee values were obtained when tosylated amino amides were applied. To the best of our knowledge, this is the first example of the use of β-amino amides as catalysts in the reaction of diethylzinc with aldehydes.



15 and **26**: $R^1 = R^2 = Et$; **16** and **27**: $R^1R^2 = (CH_2)_4$; **17**: $R^1 = H$, $R^2 = Bn$;
18: $R^1 = R^2 = H$; **19** and **28**: $R^1 = Me$, $R^2 = Bn$; **20** and **29**: $R^1 = Me$, $R^2 = Ph$;
21: $R^1 = H$, $R^2 = CH(Me)Ph$ (*R*); **22**: $R^1 = H$, $R^2 = CH(Me)Ph$ (*S*);
23: $R^1 = H$, $R^2 = Me$; **24** and **30**: $R^1R^2 = (CH_2)_5$; **25**: $R^1 = H$, $R^2 = Ph$

Scheme 2. Synthesis of derivatives **15**–**30**.



Scheme 3. Catalyzed addition of diethylzinc to benzaldehyde.

Table 1
Addition of diethylzinc to benzaldehyde, catalyzed by various types of 1,3-diamines and β-amino amides

Entry	Catalyst (10 mol %)	Yield[a] (%)	ee[b] (%)	Configuration of the major product[c]
1	**7**	89	5	(*R*)
2	**9**	90	35	(*R*)
3	**10**	81	38	(*R*)
4	**12**	83	6	(*R*)
5	**13**	88	8	(*R*)
6	**15**	79	48	(*R*)
7	**16**	82	30	(*R*)
8	**17**	80	76	(*S*)
9	**18**	93	27	(*R*)
10	**19**	77	32	(*R*)
11	**20**	75	65	(*R*)
12	**21**	80	23	(*R*)
13	**22**	86	14	(*S*)
14	**23**	75	63	(*S*)
15	**24**	78	36	(*R*)
16	**25**	90	83	(*S*)
17	**26**	85	29	(*R*)
18	**27**	92	6	(*S*)
19	**28**	74	26	(*R*)
20	**29**	70	10	(*R*)
21	**30**	72	5	(*R*)

[a] Yields after silica column chromatography.
[b] Determined on the crude product by GC (Chirasil-DEX CB column).
[c] Determined by comparing the GC analysis t_R and the specific rotation with literature data.[9]

3. Conclusions

In conclusion we have developed a library of new chiral pinane-based sulfonated diamines and β-amino amides **7**, **9**, **10**, **12**, **13**, **15**–**25**, and **26**–**30** and successfully applied them as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde, affording optically active secondary alcohols. Significantly higher enantioselectivities were observed when secondary amides were used as compared with primary, tertiary amides, and tertiary diamines. Ligands with a uniform absolute configuration showed switching of the enantioselectivity, when the substituents on the amide function were exchanged. Primary and tertiary amides or tertiary diamines preferred the formation of (*R*)-1-phenyl-1-propanol, while chiral auxiliaries bearing a secondary amide group gave the (*S*)-enantiomer as the main product.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz, δ = 0 (TMS)), in the solvents indicated. Chemical shifts are expressed in ppm (δ) relative to TMS as an internal reference. *J* values are given in Hz. Elemental analyses were performed on a Perkin–Elmer 2400 Elemental Analyzer.

GC measurements were made on a Perkin–Elmer Autosystem XL GC, consisting of a Flame Ionization Detector and a Turbochrom Workstation data system (Perkin–Elmer Corporation Norwalk, USA). The column used for the direct separation of enantiomers was a Chirasil-DEX CB column (2500 × 0.25 mm I.D.).

Microwave (MW) experiments were carried out in a CEM Discover SP MW reactor. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F254-precoated TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied.

Compounds **1**–**4** were prepared according to literature methods, and were identical with those reported therein.[8]

4.2. Preparation of *tert*-butyl(1*R*,2*R*,3*S*,5*R*)-3-(dimethylcarbamoyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-ylcarbamate 5

A: *N*-Boc β-lactam **3** (5.00 g, 18.84 mmol) was dissolved in a 33% solution of Me_2NH in dry EtOH (250 mL). After stirring for 24 h at room temperature, the solvent was evaporated off.

B: *N*-Boc β-lactam **3** (5.00 g, 18.84 mmol) was dissolved in Et_2O (5 mL), and a 40% solution of Me_2NH in H_2O (150 mL) was then added. After stirring for 24 h at room temperature, the solvent was evaporated off.

The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 4:1), resulting in **5** as a white crystalline product. Yield: 86% (*A*) (5.02 g); yield: 89% (*B*) (5.19 g); a white solid; mp: 77–80 °C; $[\alpha]_D^{20} = +31$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.95 (s, 3H), 1.22 (s, 3H), 1.39 (s, 9H), 1.63 (d, 1H, *J* = 11.0 Hz), 1.85–1.93 (m, 3H), 2.11–2.17 (m, 1H), 2.23–2.28 (m, 1H), 2.95 (s, 3H), 3.07 (s, 3H), 3.59 (dt, 1H, *J* = 4.4, 10.5 Hz), 4.40 (t, 1H, *J* = 10.3 Hz), 5.15 (d, 1H, *J* = 10.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.6, 24.9, 26.4, 28.5, 29.0, 34.8, 36.3, 38.2, 39.08, 39.7, 46.9, 48.5, 79.1, 155.2, 175.4. Anal. Calcd for $C_{17}H_{30}N_2O_3$ (310.43): C, 65.77; H, 9.74; N, 9.02%. Found: C, 65.52; H, 9.89; N, 9.10%.

4.3. Method A: general procedure for reduction of amides

To a stirred suspension of $LiAlH_4$ (0.09 g, 2.5 mmol in the synthesis of **10**, **13**, **26**, **27**, **29**, and **30**, or 0.18 g, 5 mmol, in the syntheses of **6** and **28**) in dry THF (10 mL), a solution of amides **5**, **9**, **12**, **15**, **16**, **19**, **20**, or **24** (1 mmol) in dry THF (10 mL) was added at 0 °C. The reaction mixture was stirred for 2 h for **10**, **26**, **27**, and **30** or 20 h for **13** and **29** at room temperature or at reflux for 6 h for **6** and **28**, monitored by TLC, and a mixture of H_2O (0.5 mL) and THF (25 mL) was then added dropwise with cooling. The inorganic material was filtered off and washed with THF. The filtrate was dried (Na_2SO_4) and evaporated to dryness. The crude products were purified by column chromatography on silica gel or recrystallized.

4.3.1. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-((dimethylamino)methyl)-*N*,6,6-trimethylbicyclo[3.1.1]heptan-2-amine 6

Compound **6** was prepared from **5** according to *Method A*. The product obtained was used as a crude material in the next step.

A colorless oil, yield 85% (0.18 g); $[\alpha]_D^{20} = -132$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 (s, 3H), 1.18 (d, 1H, *J* = 9.3 Hz), 1.22 (s, 3H), 1.28–1.34 (m, 1H), 1.84–1.89 (m, 2H), 1.99–2.10 (m, 3H), 2.19 (s, 6H), 2.25 (s, 3H), 2.34–2.44 (m, 1H), 2.81 (t, 1H, *J* = 11.0 Hz), 3.03–3.06 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.8, 26.6, 27.4, 28.2, 30.4, 33.3, 35.0, 37.8, 41.3, 44.1, 45.3, 60.5, 66.3. Anal. Calcd for $C_{13}H_{26}N_2$ (210.36): C, 74.23; H, 12.46; N, 13.32%. Found: C, 74.09; H, 12.57; N, 13.37%.

4.3.2. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-3-((dimethylamino) methyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-methyl benzenesulfonamide 10

Compound **10** was prepared from **9** according to *Method A*. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:1). A white solid, yield 69% (0.24 g); mp: 126–129 °C; $[\alpha]_D^{20} = -5$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.78 (s, 3H), 1.17 (s, 3H), 1.22–1.27 (m, 2H), 1.82–1.86 (m, 1H), 1.97–2.06 (m, 3H), 2.16 (s, 7H), 2.30–2.35 (m, 1H), 2.41 (s, 3H), 2.80–2.87 (m, 1H), 3.60 (d, 1H, *J* = 9.7 Hz), 7.27 (d, 2H, *J* = 8.5 Hz), 7.70 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.6, 25.0, 25.4, 26.5, 31.9, 37.7, 40.1, 44.4, 45.8, 54.8, 67.0, 127.2, 129.4, 137.8, 142.7. Anal. Calcd for $C_{20}H_{32}N_2O_2S$ (350.52): C, 65.10; H, 8.63; N, 7.99; S, 9.15%. Found: C, 65.27; H, 8.59; N, 7.83 S, 9.09%.

4.3.3. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-3-((diethylamino) methyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-methyl benzenesulfonamide 26

Compound **26** was prepared from **15** according to *Method A*. The crude product was purified by column chromatography on silica gel (DCM/MeOH = 9:1). A white solid, yield 80% (0.30 g); mp: 99–101 °C; $[\alpha]_D^{20} = -24$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.79 (s, 3H), 1.04 (t, 6H, *J* = 7.1 Hz), 1.16 (s, 3H), 1.20–1.28 (m, 2H), 1.57 (s, 1H), 1.82–1.86 (m, 1H), 1.97–2.04 (m, 2H), 2.20–2.41 (m, 8H), 2.62–2.70 (m, 2H), 2.84 (t, 1H, *J* = 13.1 Hz), 3.65 (d, 1H, *J* = 10.0 Hz), 7.26 (d, 2H, *J* = 8.4 Hz), 7.69 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 10.6, 20.3, 21.6, 24.8, 25.1, 26.6, 32.2, 37.7, 40.2, 45.3, 45.6, 54.9, 60.4, 127.2, 129.4, 138.6, 142.5. Anal. Calcd for $C_{21}H_{34}N_2O_2S$ (378.57): C, 66.63; H, 9.05; N, 7.40; S, 8.47%. Found: C, 66.59; H, 9.10; N, 7.43; S, 8.40%.

4.3.4. Preparation of *N*-benzyl-*N*-((1*R*,2*R*,3*S*,5*R*)-3-((dimethyl amino)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-methylbenzenesulfonamide 13

Compound **13** was prepared from **12** according to *Method A*. The crude product was purified by column chromatography on silica gel (DCM/MeOH = 19:1). A colorless oil, yield 53% (0.23 g); $[\alpha]_D^{20} = +37$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.82 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.25–1.29 (m, 1H), 1.65–1.68 (m, 1H), 1.83–1.91 (m, 4H), 2.07 (s, 6H), 2.12–2.18 (m, 1H), 2.33–2.40 (m, 5H), 4.20 (d, 1H, *J* = 16.1 Hz), 4.40 (d, 1H, *J* = 10.0 Hz), 4.50 (d, 1H, *J* = 16.1 Hz), 7.21–7.27 (m, 5H), 7.33–7.36 (m, 2H), 7.56 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.5, 21.5, 26.4, 26.9, 29.3, 30.7, 39.8, 40.3, 45.6, 45.8, 50.1, 59.3, 66.6, 127.1, 127.5, 128.2, 129.3, 129.6, 137.9, 138.1, 143.0. Anal. Calcd for $C_{26}H_{36}N_2O_2S$ (440.64): C, 70.87; H, 8.23; N, 6.36; S, 7.28%. Found: C, 70.90; H, 8.17; N, 6.72; S, 7.10%.

4.3.5. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-3-(pyrro lidin-1-ylmethyl)bicyclo[3.1.1]heptan-2-yl)-4-methylbenzene sulfonamide 27

Compound **27** was prepared from **16** according to *Method A*. The crude product was purified by column chromatography on silica gel (DCM/MeOH = 9:1). A white solid, yield 78% (0.29 g); mp: 114–116 °C; $[\alpha]_D^{20} = -20$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.79 (s, 3H), 1.18 (s, 3H), 1.25–1.31 (m, 2H), 1.78–1.85 (m, 5H), 1.99–2.08 (m, 2H), 2.13–2.18 (m, 2H), 2.35–2.49 (m, 8H), 3.09–3.16 (m, 1H), 3.62 (d, 1H, *J* = 10.2 Hz), 7.27 (d, 2H, *J* = 8.8 Hz), 7.69 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.6, 23.6, 25.0, 26.5, 26.9, 32.0, 37.8, 40.1, 45.8, 53.0, 54.9, 63.4, 127.2, 129.4, 137.8, 142.7. Anal. Calcd for $C_{21}H_{32}N_2O_2S$ (376.56): C, 66.98; H, 8.57; N, 7.44; S, 8.52%. Found: C, 66.87; H, 8.52; N, 7.56; S, 8.59%.

4.3.6. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-3-((benzyl(methyl) amino)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-methylbenzenesulfonamide 28

Compound **28** was prepared from **19** according to *Method A*. The crude product was purified by column chromatography on silica gel (DCM/MeOH = 19:1). A white solid, yield 60% (0.25 g); mp: 102–105 °C; $[\alpha]_D^{20} = +12$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.79 (s, 3H), 1.16–1.20 (s, 4H), 1.24–1.28 (m, 1H), 1.57 (s, 1H), 1.82–1.86 (m, 1H), 1.98–2.05 (m, 5H), 2.12–2.16 (m, 1H), 2.26–2.35 (m, 2H), 2.38 (s, 3H), 2.98 (t, 1H, *J* = 12.7 Hz), 3.39 (d, 1H, *J* = 12.7 Hz), 3.60 (d, 1H, *J* = 12.7 Hz), 3.64 (d, 1H, *J* = 12.7 Hz), 7.18 (d, 2H, *J* = 8.2 Hz), 7.28–7.32 (m, 1H), 7.36–7.42 (m, 4H), 7.62 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.5, 25.1, 25.4, 26.5, 32.1, 37.7, 39.8, 40.1, 45.6, 54.8, 62.9, 65.3, 127.2, 127.7, 128.6, 129.3, 129.7, 137.2, 137.9, 142.6. Anal. Calcd for $C_{25}H_{34}N_2O_2S$ (426.61): C, 70.3; H, 8.03; N, 6.57; S, 7.52%. Found: C, 70.30; H, 8.07; N, 6.55; S, 7.63%.

4.3.7. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-3-((methyl (phenyl)amino)methyl)bicyclo[3.1.1]heptan-2-yl)-4-methyl benzenesulfonamide 29

Compound **29** was prepared from **20** according to *Method A*. The crude product was recrystallized from *n*-hexane–*i*Pr_2O. A white solid, yield 41% (0.17 g); mp: 164–166 °C; $[\alpha]_D^{20} = +17$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.80 (s, 3H), 0.86 (s, 1H), 1.07–1.10 (m, 4H), 1.56–1.66 (m, 1H), 1.79 (s, 1H), 1.86–1.91 (m, 1H), 2.10–2.15 (m, 1H), 2.42 (m, 3H), 2.57–2.62 (m, 1H), 2.86 (s, 3H), 3.08 (t, 1H, *J* = 10.6 Hz), 3.59–3.67 (m, 1H), 3.87–3.93 (m, 1H), 5.34 (d, 1H, *J* = 6.9 Hz), 6.67–6.74 (m, 3H), 7.20 (t, 2H, *J* = 7.7 Hz), 7.29 (d, 2H, *J* = 8.1 Hz), 7.74 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.7, 21.6, 26.1, 26.3, 28.1, 31.2, 33.2, 38.5, 40.1, 40.6, 47.9, 54.2, 54.7, 59.2, 65.3, 113.8, 117.4, 127.1, 129.3, 129.8, 136.9, 142.6, 148.8. Anal. Calcd for $C_{24}H_{32}N_2O_2S$ (412.59): C, 69.87; H, 7.82; N, 6.79; S, 7.77%. Found: C, 69.82; H, 7.85; N, 6.75; S, 7.80%.

4.3.8. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-3-(piperidin -1-ylmethyl)bicyclo[3.1.1]heptan-2-yl)-4-methylbenzene sulfonamide 30

Compound **30** was prepared from **24** according to *Method A*. The crude product was purified by column chromatography on silica gel (DCM/MeOH = 9:1). A white solid, yield 78% (0.30 g); mp: 125–130 °C; $[\alpha]_D^{20} = -29$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.77 (s, 3H), 1.15 (s, 3H), 1.20–1.28 (m, 3H), 1.41–1.48 (m, 3H), 1.53–1.70 (m, 4H), 1.81–1.86 (m, 1H), 1.96–2.03 (m, 2H), 2.13 (dd, 1H, *J* = 4.5, 12.8 Hz), 2.26–2.34 (m, 4H), 2.42 (s, 3H), 2.45–2.54 (m, 1H), 2.80 (t, 1H, *J* = 12.8 Hz), 3.64 (d, 1H, *J* = 9.6 Hz), 7.26 (d, 2H, *J* = 8.1 Hz), 7.72 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.3, 21.7, 24.4, 24.5, 25.0, 25.9, 26.6, 31.9, 37.7, 40.3, 45.2, 53.7, 54.8, 66.8, 127.3, 129.4, quaternary C at 138.0 and 142.2 was detected from HMBC. Anal. Calcd for $C_{22}H_{34}N_2O_2S$ (390.58): C, 67.65; H, 8.77; N, 7.17; S, 8.21%. Found: C, 67.59; H, 8.80; N, 7.21; S, 8.14%.

4.4. Method B: synthesis of sulfonamides 7, 9 and 12

To a solution of **6**, **8**, or **11** (1 mmol), TEA (0.12 g, 1.2 mmol), and DMAP (0.01 g, 0.1 mmol) in $CHCl_3$ (10 mL), tosyl chloride (0.21 g, 1.1 mmol) was added at 0 °C. The mixture was refluxed for 9 h

for **7** and **9** or 20 h for **12**. After completion of the tosylation (as indicated by TLC), the reaction was quenched by the addition of 1 M aqueous NaOH (5 mL), and the organic layer was washed with 1 M aqueous NaOH (2 × 10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography on silica gel, or by recrystallization.

4.4.1. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-3-((dimethylamino) methyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-*N*,4-dimethyl benzenesulfonamide 7

Compound **7** was prepared from **6** according to *Method B*. The crude product was recrystallized from *n*-hexane. A yellow solid, yield 78% (0.28 g); mp: 85–87 °C; $[\alpha]_D^{20} = +121$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.85 (s, 3H), 1.09 (s, 3H), 1.27 (d, 1H, *J* = 10.4 Hz), 1.27–1.34 (m, 1H), 1.86–1.93 (m, 3H), 2.13–2.19 (m, 1H), 2.25 (s, 6H), 2.40–2.44 (m, 5H), 2.62–2.65 (m, 1H), 2.74 (s, 3H), 4.37–4.39 (m, 1H), 7.28 (d, 2H, *J* = 8.8 Hz), 7.63 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.6, 21.5, 26.3, 26.8, 29.5, 31.3, 32.5, 40.0, 40.2, 44.5, 45.8, 56.8, 65.4, 126.9, 129.6, 136.6, 143.1. Anal. Calcd for $C_{20}H_{32}N_2O_2S$ (364.55): C, 65.89; H, 8.85; N, 7.68; S, 8.80%. Found: C, 65.93; H, 8.75; N, 7.75 S, 8.71%.

4.4.2. Preparation of (1*R*,2*R*,3*S*,5*R*)-*N*,*N*,6,6-tetramethyl-2-(4-methylphenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxamide 9

Compound **9** was prepared from **8** according to *Method B*. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 2:1). A white solid, yield 72% (0.26 g); mp: 161–164 °C; $[\alpha]_D^{20} = +21$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.87 (s, 3H), 1.15 (s, 3H), 1.74–1.79 (m, 2H), 1.84–1.88 (m, 1H), 1.92–2.01 (m, 2H), 2.04–2.10 (m, 1H), 2.41 (s, 3H), 2.80 (s, 3H), 2.85 (s, 3H), 3.31–3.38 (m, 1H), 4.00–4.03 (m, 1H), 6.16 (s, 1H), 7.25–7.28 (m, 2H), 7.67–7.69 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4, 21.5, 24.4, 26.2, 29.6, 33.3, 36.13, 37.7, 39.1, 39.3, 47.4, 52.4, 126.9, 129.6, 139.4, 142.9, 175.5. Anal. Calcd for $C_{19}H_{28}N_2O_3S$ (364.50): C, 62.61; H, 7.74; N, 7.69; S, 8.80%. Found: C, 62.23; H, 7.94; N, 7.84; S, 8.98%.

4.4.3. Preparation of (1*R*,2*R*,3*S*,5*R*)-2-(*N*-benzyl-4-methyl phenylsulfonamido)-*N*,*N*,6,6-tetramethylbicyclo [3.1.1] heptane-3-carboxamide 12

To a suspension of Cs_2CO_3 (2.75 g, 8.45 mmol) in dry acetone (25 mL), a solution of **9** (0.5 g, 1.37 mmol) in dry acetone (25 mL) was added and the mixture was stirred vigorously for 30 min at room temperature. Benzyl bromide (0.35 g, 2.05 mmol) was then added and the mixture was refluxed for 7 h. The inorganic part was filtered off and washed several times with acetone. The combined filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 2:1). A colorless oil, yield 76% (0.47 g); *Method B*: yield 51% (0.23 g); $[\alpha]_D^{20} = -69$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.90 (s, 3H), 1.13 (s, 3H), 1.60 (t, 1H, *J* = 5.4 Hz), 1.84–1.88 (m, 1H), 1.92–1.98 (m, 1H), 2.07–2.11 (m, 1H), 2.15–2.21 (m, 1H), 2.34 (s, 3H), 2.54 (d, 1H, *J* = 9.9 Hz), 2.90 (s, 3H), 3.26 (s, 3H), 3.76 (dt, 1H, *J* = 2.5, 10.2 Hz), 4.50 (s, 2H), 4.68 (d, 1H, *J* = 10.2 Hz), 7.06–7.13 (m, 7H), 7.30 (d, 2H, *J* = 8.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.3, 21.4, 25.8, 26.5, 29.5, 35.5, 36.5, 38.6, 38.8, 40.8, 44.8, 50.0, 58.5, 126.7, 127.0, 127.7, 128.8, 129.1, 137.9, 138.3, 142.7, 175.1. Anal. Calcd for $C_{26}H_{34}N_2O_3S$ (454.62): C, 68.69; H, 7.54; N, 6.16; S, 7.05%. Found: C, 68.54; H, 7.60; N, 6.21; S, 7.00%.

4.5. Preparation of (1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-2-(4-methyl phenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxylic acid 14

To a solution of **4** (0.22 g, 1 mmol) and TEA (0.30 g, 3 mmol) in DCM (10 mL), tosyl chloride (0.21 g, 1.1 mmol) was added at 0 °C, and the mixture was stirred for 24 h at room temperature. After completion of the tosylation (as indicated by TLC), the organic layer was washed with 5% aqueous HCl (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1 followed by *n*-hexane/EtOAc = 1:1). A white solid, yield 50% (0.16 g); mp: 127–130 °C; $[\alpha]_D^{20} = -55$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.72 (d, 1H, *J* = 10.8 Hz), 0.83 (s, 3H), 1.25 (s, 3H), 1.79–1.91 (m, 3H), 2.09–2.14 (m, 1H), 2.44 (s, 3H), 2.48–2.52 (m, 1H), 3.34- 3.38 (m, 1H), 4.46–4.48 (m, 1H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.85 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.9, 21.8, 23.9, 25.0, 26.7, 39.3, 40.7, 42.4, 44.0, 59.3, 127.5, 129.9, 136.0, 145.0, 168.4. Anal. Calcd for $C_{17}H_{23}NO_4S$ (337.43): C, 60.51; H, 6.87; N, 4.15; S, 9.50%. Found: C, 60.45; H, 6.90; N, 4.20; S, 9.41%.

4.6. Preparation of (1*R*,2*R*,3*S*,5*R*)-2-amino-*N*,*N*,6,6-tetramethyl bicyclo[3.1.1]heptane-3-carboxamide 8

To a stirred solution of *N*-Boc amide **5** (5.0 g, 16 mmol) in Et_2O (50 mL), 5% aqueous HCl (250 mL) was added. The reaction mixture was stirred vigorously for 24 h at room temperature and then evaporated to dryness. The solid product obtained was dissolved in H_2O, and the solution was made alkaline with 15% aqueous KOH and extracted with DCM (3 × 100 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to dryness. The product obtained was used as crude material in the next step. A yellow solid, yield 93% (3.12 g); mp: 68–74 °C; $[\alpha]_D^{20} = -12$ (*c* 0.125, MeOH); ^{1}H NMR (400.6 MHz, $CDCl_3$): δ = 0.90 (s, 3H), 1.22 (s, 3H), 1.40 (s, 2H), 1.59 (d, 1H, *J* = 10.2 Hz), 1.80–1.86 (m, 2H), 1.90–1.94 (m, 1H), 2.06–2.12 (m, 1H), 2.29–2.34 (m, 1H), 2.97 (s, 3H), 3.09 (s, 3H), 3.42–3.51 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.5, 24.8, 26.8, 29.2, 39.0, 36.0, 36.2, 37.8, 40.5, 50.2, 50.6, 180.7. Anal. Calcd for $C_{12}H_{22}N_2O$ (210.32): C, 68.53; H, 10.54; N, 13.32%. Found: C, 68.22; H, 10.79; N, 13.40%.

4.7. Preparation of (1*R*,2*R*,3*S*,5*R*)-2-(benzylamino)-*N*,*N*,6,6-tetramethylbicyclo[3.1.1]heptane-3-carboxamide 11

To a solution of **8** (0.21 g, 1 mmol) in dry EtOH (10 mL), benzaldehyde (0.11 g, 1.05 mmol) was added and the mixture was stirred at room temperature. After 2 h, the solvent was removed under reduced pressure, the residue was dissolved in dry EtOH (10 mL), $NaBH_4$ (0.08 g, 2.00 mmol) was added, and the solution was stirred for 24 h at room temperature. The solvent was then evaporated off and the residue was dissolved in H_2O (10 mL) and extracted with DCM (3 × 15 mL). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:1). A colorless oil, yield 67% (0.20 g); $[\alpha]_D^{20} = -29$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.89 (s, 3H), 1.26 (s, 3H), 1.65 (d, 1H, *J* = 11.2 Hz), 1.80–1.87 (m, 1H), 1.91–1.96 (m, 1H), 2.06–2.11 (m, 1H), 2.20–2.24 (m, 1H), 2.33 (dt, 1H, *J* = 3.6; 13.2 Hz), 2.97 (s, 3H), 2.98 (s, 3H), 3.30 (d, 1H, *J* = 10.6 Hz), 3.50 (dt, 1H, *J* = 3.9, 10.4 Hz), 3.54 (d, 1H, *J* = 13.2 Hz), 3.79 (d, 1H, *J* = 13.2 Hz), 7.17–7.26 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.5, 24.8, 26.8, 29.1, 35.7, 36.1, 38.0, 38.8, 40.3, 43.6, 51.3, 56.0, 126.8, 128.2, 141.1, 176.4. Anal. Calcd for $C_{19}H_{28}N_2O$ (300.44): C, 75.96; H, 9.39; N, 9.32%. Found: C, 75.77; H, 9.50; N, 9.37%.

4.8. Method C: general procedure for the amidation

At first, *N*-tosyl amino acid **14** (0.50 g, 1.48 mmol) in dry toluene (15 mL) was transformed into the acid chloride by the addition of $SOCl_2$ (0.41 g, 3.44 mmol). The mixture was stirred for 3 h at 60 °C and then evaporated to dryness. The residue was dissolved in DCM (15 mL), the appropriate amine (3 equiv in the syntheses of **21** and **22**, or 10 equiv in the synthesis of **15**–**17**, **19** and **24**) was added, and the mixture was refluxed for 8 h for **15**–**17**, **19,** and **24** or 20 h for **21** and **22**. In the case of **18**, NH_3 gas was introduced into the reaction mixture, which was stirred for 5 h at room temperature. In the synthesis of **23**, a 40% solution of $MeNH_2$ in H_2O (5 mL) was added to the reaction mixture, which was then stirred for 20 h at room temperature. The mixture was then evaporated to dryness and the crude product was purified by column chromatography or recrystallized.

4.8.1. Preparation of (1*R*,2*R*,3*S*,5*R*)-*N*,*N*-diethyl-6,6-dimethyl-2-(4-methylphenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxamide 15

Compound **15** was prepared according to *Method C*, and purified by column chromatography on silica gel (*n*-hexane/EtOAc = 3:1). A white solid, yield 66% (0.38 g); mp: 88–90 °C; $[\alpha]_D^{20} = +15$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 1.07 (t, 3H, *J* = 7.2 Hz), 1.14 (s overlapped with t, 6H, *J* = 6.7 Hz), 1.68–1.71 (m, 1H), 1.82–1.88 (m, 2H), 1.96–1.99 (m, 2H), 2.02–2.08 (m, 1H), 2.40 (m, 3H), 3.04–3.13 (m, 1H), 3.22–3.44 (m, 4H), 3.99 (t, 1H, *J* = 10.9 Hz), 6.02 (d, 1H, *J* = 10.2 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.1, 15.0, 20.4, 21.6, 24.3, 26.3, 30.4, 33.5, 39.0, 39.4, 41.4, 42.8, 47.1, 52.4, 126.9, 129.6, 139.4, 142.9, 174.7. Anal. Calcd for $C_{21}H_{32}N_2O_3S$ (392.56): C, 64.25; H, 8.22; N, 7.14; S, 8.17%. Found: C, 64.13; H, 8.26; N, 7.19; S, 8.10%.

4.8.2. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-3-(pyrrolidine-1-carbonyl)bicyclo[3.1.1]heptan-2-yl)-4-methylbenzenesulfonamide 16

Compound **16** was prepared according to *Method C*, and purified by column chromatography on silica gel (*n*-hexane/EtOAc = 3:1). A white solid, yield 72% (0.41 g); mp: 183–185 °C; $[\alpha]_D^{20} = +12$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 1.15 (s, 3H), 1.59 (s, 1H), 1.73–1.88 (m, 7H), 1.95–1.99 (m, 2H), 2.03–2.10 (m, 1H), 2.40 (m, 3H), 3.16–3.31 (m, 3H), 3.38 (t, 1H, *J* = 6.9 Hz), 4.04 (t, 1H, *J* = 9.2 Hz), 6.19 (d, 1H, *J* = 10.0 Hz), 7.25 (d, 2H, *J* = 8.5 Hz), 7.68 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4, 21.6, 24.4, 24.5, 26.0, 26.2, 29.4, 35.8, 39.1, 39.3, 46.1, 46.8, 47.3, 52.4, 126.8, 129.6, 139.5, 142.7, 173.8. Anal. Calcd for $C_{21}H_{30}N_2O_3S$ (390.54): C, 64.58; H, 7.74; N, 7.17; S, 8.21%. Found: C, 64.50; H, 7.78; N, 7.29; S, 8.42%.

4.8.3. Preparation of (1*R*,2*R*,3*S*,5*R*)-*N*-benzyl-6,6-dimethyl-2-(4-methylphenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxamide 17

Compound **17** was prepared according to *Method C* and purified by column chromatography on silica gel (*n*-hexane/EtOAc = 3:1). A white solid, yield 85% (0.53 g); mp: 165–167 °C; $[\alpha]_D^{20} = +70$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.79 (s, 3H), 1.13 (s, 3H), 1.58 (s, 1H), 1.63–1.66 (m, 1H), 1.82–1.88 (m, 2H), 1.97 (t, 1H, *J* = 11.9 Hz), 2.06–2.14 (m, 2H), 2.39 (s, 3H), 2.91 (dt, 1H, *J* = 3.5, 10.5 Hz), 3.99 (t, 1H, *J* = 9.8 Hz), 4.19 (dd, 1H, *J* = 4.5, 14.8 Hz), 4.57 (dd, 1H, *J* = 6.5, 14.8 Hz), 5.54 (d, 1H, *J* = 10.0 Hz), 5.81 (s, 1H), 7.23–7.36 (m, 7H), 7.68 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.6, 24.4, 26.1, 29.3, 39.1, 39.3, 40.5, 44.3, 46.7, 52.7, 126.8, 127.7, 128.1, 128.8, 129.6, 137.9, 139.1, 143.1, 174.8. Anal. Calcd for $C_{24}H_{30}N_2O_3S$ (426.57): C, 67.58; H, 7.09; N, 6.57; S, 7.52%. Found: C, 67.45; H, 7.14; N, 6.70; S, 7.41%.

4.8.4. Preparation of (1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-2-(4-methylphenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxamide 18

Compound **18** was prepared according to *Method C*, and purified by column chromatography on silica gel (*n*-hexane/EtOAc = 2:1). A white solid, yield 66% (0.32 g); mp: 198–221 °C; $[\alpha]_D^{20} = +13$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.76 (s, 3H), 1.08 (s, 3H), 1.49–1.52 (m, 1H), 1.83–1.90 (m, 3H), 2.04–2.10 (m, 1H), 2.22–2.27 (m, 1H), 2.41 (s, 3H), 3.04 (dt, 1H, *J* = 2.8, 10.6 Hz), 3.94 (t, 1H, *J* = 10.6 Hz), 5.72 (s, 1H), 6.57 (s, 1H), 7.26 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 1H, *J* = 10.5 Hz), 7.72 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.5, 24.1, 26.1, 27.8, 39.0, 39.3, 40.1, 46.2, 52.6, 126.9, 129.6, 138.9, 143.0, 178.1. Anal. Calcd for $C_{17}H_{24}N_2O_3S$ (336.45): C, 60.69; H, 7.19; N, 8.33; S, 9.53%. Found: C, 60.45; H, 7.31; N, 8.21; S, 9.40%.

4.8.5. Preparation of (1*R*,2*R*,3*S*,5*R*)-*N*-benzyl-*N*,6,6-trimethyl-2-(4-methylphenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxamide 19

Compound **19** was prepared according to *Method C*, and purified by column chromatography on silica gel (*n*-hexane/EtOAc = 3:1). A white solid, yield 87% (0.56 g); mp: 101–103 °C; $[\alpha]_D^{20} = -3$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$, 2 rotamers): δ = 0.76 (s, 2H, minor), 0.86 (s, 3H, major), 1.11 (s, 2H, minor), 1.15 (s, 3H, major), 1.25 (t, 1H, *J* = 7.15 Hz, minor), 1.66–1.69 (m, 1H, minor), 1.73–1.76 (m, 1H, major), 1.81–1.91 (m, 1H, major/minor), 1.97–1.99 (m, 1H, major/minor), 2.02–2.11 (m, 3H, major/minor), 2.41 (s, 3H, major), 2.43 (s, 2H, minor), 2.77 (s, 3H, major), 2.94 (s, 2H, minor), 3.41 (dt, 1H, *J* = 4.2, 10.02 Hz), 3.50 (dt, 1H, *J* = 4.2, 10.0 Hz), 4.00–4.06 (m, 2H, major), 4.09–4.20 (m, 2H, minor), 4.68 (d, 1H, *J* = 17.4 Hz, minor), 4.85 (d, 1H, *J* = 14.5 Hz), 5.70 (d, 1H, *J* = 10.4 Hz), 6.16 (d, 1H, *J* = 10.4 Hz), 7.11 (d, 1H, *J* = 7.9 Hz, minor), 7.21 (d, 2H, *J* = 7.9 Hz, major), 7.25–7.36 (m, 10H, major/minor), 7.66 (d, 2H, *J* = 7.9 Hz, major), 7.70 (d, 1H, *J* = 7.9 Hz, minor). ^{13}C NMR (100.6 MHz, $CDCl_3$, 2 rotamers): δ = 20.3, 21.6, 24.3, 24.4, 26.2, 26.3, 29.8, 30.1, 33.6, 34.2, 34.9, 35.3, 39.3, 47.0, 47.1, 51.5, 52.3, 52.4, 54.0, 126.3, 126.8, 127.0, 127.5, 127.7, 128. 2, 128.8, 129.0, 129.6, 129.7, 139.9, 137.2, 142.9, 175.8, 175.9. Anal. Calcd for $C_{25}H_{32}N_2O_3S$ (440.60): C, 68.15; H, 7.32; N, 6.36; S, 7.28%. Found: C, 68.23; H, 7.21; N, 6.50; S, 7.37%.

4.8.6. Preparation of (1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-2-(4-methylphenylsulfonamido)-*N*-((*R*)-1-phenylethyl)bicyclo[3.1.1]heptane-3-carboxamide 21

Compound **21** was prepared with 3 equiv (0.54 g, 4.44 mmol) of (*R*)-1-phenylethylamine according to *Method C*, and recrystallized from *n*-hexane. A white solid, yield 78% (0.51 g); mp: 153–155 °C; $[\alpha]_D^{20} = +108$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.77 (s, 3H), 1.09 (s, 3H), 1.54 (d, 4H, *J* = 6.1 Hz), 1.78–1.85 (m, 2H), 1.88–1.95 (m, 1H), 2.01–2.10 (m, 2H), 2.42 (s, 3H), 2.95 (dt, 1H, *J* = 3.4, 10.3 Hz), 3.96 (t, 1H, *J* = 10.0 Hz), 5.02–5.09 (m, 1H), 5.48 (d, 1H, *J* = 10.7 Hz), 5.95 (d, 1H, *J* = 7.4 Hz), 7.23–7.35 (m, 7H), 7.70 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.1, 21.6, 21.9, 24.2, 26.1, 29.0, 39.0, 39.2, 40.4, 46.5, 49.7, 52.6, 126.2, 126.8, 127.4, 128.8, 129.7, 138.9, 143.1, 143.6, 173.9. Anal. Calcd for $C_{25}H_{32}N_2O_3S$ (440.60): C, 68.15; H, 7.32; N, 6.36; S, 7.28%. Found: C, 68.23; H, 7.16; N, 6.32; S, 7.50%.

4.8.7. Preparation of (1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-2-(4-methylphenylsulfonamido)-*N*-((*S*)-1-phenylethyl)bicyclo[3.1.1]heptane-3-carboxamide 22

Compound **22** was prepared with 3 equiv (0.54 g, 4.44 mmol) of (*S*)-1-phenylethylamine according to *Method C*, and recrystallized from *n*-hexane. A white solid, yield 85% (0.55 g); mp: 141–143 °C; $[\alpha]_D^{20} = -6$ (*c* 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.77 (s, 3H), 1.11 (s, 3H), 1.49 (d, 3H, *J* = 6.9 Hz), 1.58–1.62 (m, 1H), 1.83–1.89 (m, 2H), 2.01–2.07 (m, 3H), 2.31 (s, 3H), 2.79–2.85

(m, 1H), 3.89 (t, 1H, J = 9.1 Hz), 5.01–5.08 (m, 1H), 5.73–5.77 (m, 2H), 7.08 (d, 2H, J = 8.3 Hz), 7.28–7.33 (m, 1H), 7.38–7.40 (m, 4H), 7.58 (d, 2H, J = 8.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.0, 21.5, 21.7, 24.2, 26.1, 29.9, 39.1, 39.2, 39.9, 46.5, 49.8, 52.3, 126.7, 126.9, 127.6, 128.9, 129.5, 138.7, 142.5, 142.9, 174.3. Anal. Calcd for $C_{25}H_{32}N_2O_3S$ (440.60): C, 68.15; H, 7.32; N, 6.36; S, 7.28%. Found: C, 68.07; H, 7.48; N, 6.30; S, 7.20%.

4.8.8. Preparation of (1*R*,2*R*,3*S*,5*R*)-*N*,6,6-trimethyl-2-(4-methyl phenylsulfonamido)bicyclo[3.1.1]heptane-3-carboxamide 23

Compound **23** was prepared according to *Method C*, and recrystallized from *n*-hexane. A white solid, yield 90% (0.46 g); mp: 164–166 °C; $[\alpha]_D^{20} = +67$ (c 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.81 (s, 3H), 1.13 (s, 3H), 1.65–1.68 (m, 1H), 1.79 (d, 1H, J = 10.5 Hz) 1.84–1.88 (m, 1H), 1.91–1.97 (m, 1H), 2.05–2.11 (m, 2H), 2.41 (s, 3H), 2.73 (d, 3H, J = 4.6 Hz), 2.89 (dt, 1H, J = 3.6, 10.0 Hz), 3.98 (t, 1H, J = 10.3 Hz), 5.50–5.57 (m, 2H), 7.26 (d, 2H, J = 8.3 Hz), 7.68 (d, 2H, J = 8.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.6, 24.3, 26.1, 29.7, 29.1, 39.1, 39.5, 40.3, 46.9, 52.6, 126.8, 129.6, 138.8, 142.7, 175.7. Anal. Calcd for $C_{18}H_{26}N_2O_3S$ (350.48): C, 61.69; H, 7.48; N, 7.99; S, 9.15%. Found: C, 61.51; H, 7.55; N, 7.80; S, 9.30%.

4.8.9. Preparation of *N*-((1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-3-(piperi dine-1-carbonyl)bicyclo[3.1.1]heptan-2-yl)-4-methylbenzene sulfonamide 24

Compound **24** was prepared according to *Method C*, and recrystallized from *n*-hexane. A white solid, yield 89% (0.53 g); mp: 157–160 °C; $[\alpha]_D^{20} = +21$ (c 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 1.14 (s, 3H), 1.41–1.63 (m, 6H), 1.74–1.79 (m, 2H), 1.84–2.08 (m, 4H), 2.41 (s, 3H), 3.07–3.13 (m, 1H), 3.19–3.26 (m, 1H), 3.31–3.37 (m, 2H), 3.67–3.73 (m, 1H), 4.01 (t, 1H, J = 10.0 Hz), 6.42 (d, 1H, J = 10.0 Hz), 7.25 (d, 2H, J = 8.6 Hz), 7.67 (d, 2H, J = 8.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4, 21.6, 24.4, 24.7, 25.6, 26.3, 26.5, 30.2, 32.6, 39.2, 39.5, 43.3, 47.4, 47.5, 52.7, 126.9, 129.6, 139.8, 142.7, 173.8. Anal. Calcd for $C_{22}H_{32}N_2O_3S$ (404.57): C, 65.31; H, 7.97; N, 6.92; S, 7.93%. Found: C, 65.52; H, 7.76; N, 7.13; S, 7.69%.

4.9. Method D: microwave-assisted synthesis of amides

N-Tosyl amino acid **14** (0.50 g, 1.48 mmol) in dry toluene (15 mL) was transformed into the acid chloride by the addition of $SOCl_2$ (0.41 g, 3.44 mmol). The mixture was stirred for 3 h at 60 °C and then evaporated to dryness. To the residue thus obtained, the appropriate amine (10 equiv) was added and the reaction mixture was heated in a CEM Discover SP MW reactor. In the case of **20**, the mixture was irradiated at 200 W for 20 min at 150 °C, while for **25** the reaction mixture was irradiated at 200 W for 95 min at 110 °C.

4.9.1. Preparation of (1*R*,2*R*,3*S*,5*R*)-*N*,6,6-trimethyl-2-(4-methyl phenylsulfonamido)-*N*-phenylbicyclo[3.1.1]heptane-3-carboxamide 20

Compound **20** was prepared according to *Method D*. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1, then 3:1). A white solid, yield 69% (0.43 g); mp: 117–119 °C; $[\alpha]_D^{20} = -39$ (c 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.54 (s, 3H), 1.07 (s, 3H), 1.68–1.81 (m, 4H), 1.91–1.96 (m, 1H), 2.03–2.08 (m, 1H), 2.42 (s, 3H), 3.18 (s, 1H), 3.22 (s, 3H), 3.75 (t, 1H, J = 10.2 Hz), 6.14 (d, 1H, J = 9.7 Hz), 6.91–6.93 (m, 2H), 7.28–7.36(m, 5H), 7.72 (d, 2H, J = 8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.2, 21.6, 24.7, 26.4, 30.7, 34.6, 37.8, 39.3, 47.2, 52.3, 127.0, 127.3, 128.0, 129.6, 129.9, 139.6, 143.0, 144.1, 175.4. Anal. Calcd for $C_{24}H_{30}N_2O_3S$ (426.57): C, 67.58; H, 7.09; N, 6.57; S, 7.52%. Found: C, 67.47; H, 7.15; N, 6.65; S, 7.60%.

4.9.2. Preparation of (1*R*,2*R*,3*S*,5*R*)-6,6-dimethyl-2-(4-methyl phenylsulfonamido)-*N*-phenylbicyclo[3.1.1]heptane-3-carboxamide 25

Compound **25** was prepared according to *Method D*. The crude product was recrystallized from *n*-hexane. A white solid, yield 40% (0.24 g); mp: 218–220 °C; $[\alpha]_D^{20} = +97$ (c 0.125, MeOH); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.84 (s, 3H), 1.15 (s, 3H), 1.66–1.77 (m, 3H), 1.91 (s, 1H), 2.02 (t, 1H, J = 11.3 Hz), 2.09–2.14 (m, 1H), 2.20–2.24 (m, 1H), 2.32 (s, 3H), 3.04 (dt, 1H, J = 3.2, 10.3 Hz), 4.06 (t, 1H, J = 8.4 Hz), 5.53 (d, 1H, J = 10.1 Hz), 7.09–7.13 (m, 3H), 7.25–7.32 (m, 2H), 7.45 (t, 2H, J = 8.1 Hz), 7.63 (t, 2H, J = 8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.3, 21.6, 24.4, 26.1, 29.2, 39.1, 39.3, 41.3, 47.1, 52.7, 120.3, 124.6, 126.9, 129.0, 129.7, 137.9, 138.5, 143.1, 173.2. Anal. Calcd for $C_{23}H_{28}N_2O_3S$ (440.60): C, 66.96; H, 6.84; N, 6.79; S, 7.77%. Found: C, 66.87; H, 6.80; N, 6.72; S, 7.81%.

4.10. General procedure for the reactions of benzaldehyde with diethylzinc in the presence of chiral catalyst 7, 9, 10, or 12–30

To the respective catalyst (0.1 mmol) **7**, **9**, **10**, or **12**–**30**, a 1 M solution of Et_2Zn in *n*-hexane (3 mL, 3 mmol) was added under an Ar atmosphere at room temperature. The reaction mixture was stirred for 25 min at room temperature, and then benzaldehyde (0.10 g, 1 mmol) was added, followed by stirring at room temperature for a further 20 h. The reaction was quenched with saturated NH_4Cl solution (15 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with H_2O (10 mL), dried (Na_2SO_4), and evaporated under vacuum. The crude secondary alcohols obtained were purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). The enantiomeric excess and absolute configuration of the resulting material were determined by chiral GC, using a chiral stationary phase (Chirasil-Dex CB column) at 90 °C for 1-phenyl-1-propanol **32** and **33** [t_{R1} = 23.2 min for the (*S*)-isomer, t_{R2} = 24.1 min for the (*R*)-isomer].[9] The sign of the specific rotation of each product was also measured.

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