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Synthesis M. Raji et al. Special Topic

Stereoselective Synthesis and Applications of Pinane-Based Chiral 1,4-Amino Alcohol Derivatives

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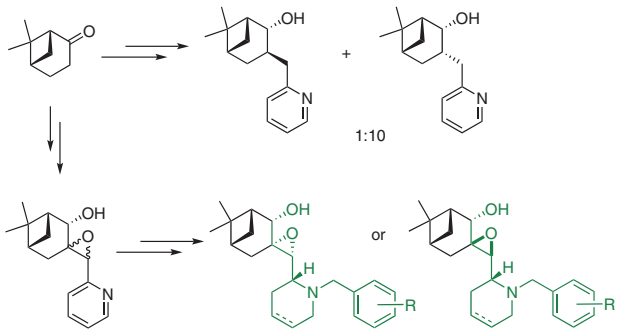

Expressed cytotoxic activity was observed on MDA-MB-231, MCF-7, and A2780 human cancer cell lines

■■*Nomenclature: The term 'α,β-unsaturated alcohol' was changed to '2,3-unsaturated alcohol', since α and β refer to the positions adjacent to a* ***functional group****. For ketones, the functional group is carbonyl, i.e. C=O, so that the α group is the carbon adjacent to C=O. However, for alcohol, the functional group is OH, so that the carbon directly attached to OH is the α group. Thus, an 'α,β-unsaturated alcohol' would be –CH=CHOH, i.e. a vinyl alcohol, whereas the alcohols dealt with in this paper are allylic alcohols, i.e. actually 'β,γ-unsaturated alcohols'. For a ketone, on the other hand, an 'α,β-unsaturated ketone would be –CH=CH–CO–. OK?*■■

■■*Experimental section: please check the elemental composition given with the HRMS data, since there consistently appears to be around 2H atoms too many, even for "[M + 1]", which is "[M + H*$^+$*]?*■■

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Abstract A new library of pinane-based 1,4-amino alcohols was synthesised and utilised as chiral ligands in enantioselective diethylzinc addition to benzaldehyde. Aldol condensation of (+)-nopinone, derived from (–)-β-pinene, with 2-pyridinecarboxaldehyde gave the key intermediate α,β-unsaturated ketone, which was transformed in diastereoselective reduction, followed by hydrogenation, resulting in 1,4-amino alcohols. On the other hand, epoxidation of the α,β-unsaturated ketone, followed by reduction and then hydrogenation of the pyridine ring, afforded a mixture of 4-amino-2,3-epoxy-1-ols. Stereoselective hydride reduction of the epoxy ketone and subsequent condensation of the resulting products with substituted benzyl bromides provided quaternary ammonium salts, which were subjected to hydride reduction and then hydrogenation, affording 4-amino-2,3-epoxy-1-ol derivatives containing an *N*-benzylpiperidine moiety. The inhibition of nucleophile-initiated opening of the oxirane ring was interpreted by a systematic series of comparative Hartree–Fock modelling study using the 6-31+G(d,p) basis set. The antiproliferative activities of 4-amino-2,3-epoxy-1-ol derivatives were examined, and structure–activity relationships were studied from the aspects of the stereochemistry of the oxirane ring, saturation, and substituent effects on the piperidine ring system.

Key words β-pinene, 1,4-amino alcohols, diethylzinc, tetrahydropyridine, antiproliferative

The development of stereoselective methods for the synthesis of biologically active molecules or privileged structural motifs, which can serve as useful building blocks, constitutes an important, yet challenging task in modern organic synthesis.[1] An apparent trend within this research area is related to the use of chiral asymmetric organocatalysts as an effective tool to control stereochemical reaction outcomes.[2,3]

Amino alcohols, such as 1,2-[4] and 1,3-amino alcohols,[5] have been used extensively in asymmetric synthesis as chiral ligands and auxiliaries. Among these, the enantioselective addition of diethylzinc to aldehydes, catalysed by chiral amino alcohols, initiated by Oguni and Omi using (*S*)-leucinol, has attracted considerable attention.[6] However, there are only a few examples of 1,4-amino alcohols, derived from monoterpenes such as (+)-camphor,[7–14] (–)-fenchone,[8,10,13,14] norbornene,[15] and (–)-menthone,[16] used successfully as chiral catalysts with high catalytic activity. Furthermore, the 1,4-amino alcohol moiety represents a privileged structural motif widely distributed in biologically relevant molecules in the life-science industry, including terfenadine[17] and ibutilide.[18]

During efforts to design and synthesise new and inexpensive chiral ligands for catalytic enantioselective reactions, we decided to prepare new pinane-derived 1,4-amino alcohol derivatives, bearing the pinane skeleton, starting from commercially available (–)-β-pinene, and to then apply them as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde. Apart from chemical application, we also wanted to study the antiproliferative activity of 1,4-amino alcohol derivatives on multiple cancer cell lines.

The synthesis of key intermediate (+)-nopinone (**2**), prepared from (–)-β-pinene by using $RuCl_3$ and $NaIO_4$, was previously reported (Scheme 1).[19–22] Diastereoselective aldol condensation of 2-pyridinecarboxaldehyde with (+)-nopinone (**2**) under alkaline conditions provided α,β-unsaturat-

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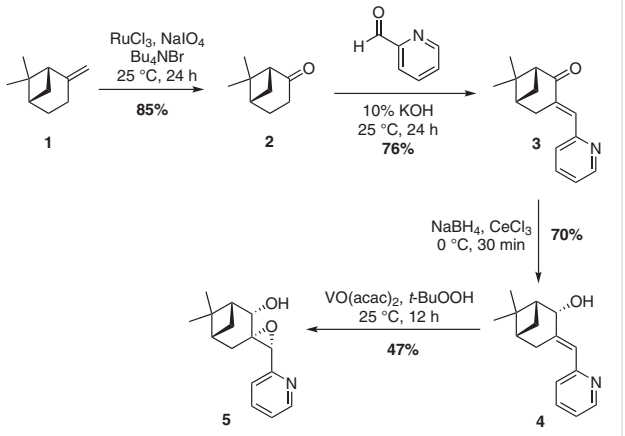
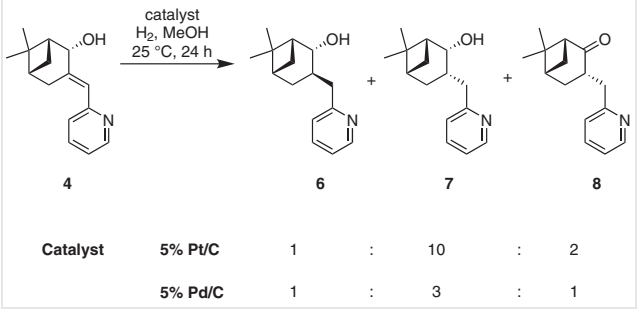
ed ketone **3** in 74% yield■■*76% in Sch 1?*■■. Subsequent reduction of **3** with $NaBH_4$ in the presence of $CeCl_3$ led to the formation of compound **4** in high yield and stereoselectivity. Epoxidation of **4** with *t*-BuOOH in anhydrous toluene in the presence of $VO(acac)_2$ as catalyst gave **5** in moderate yield (Scheme 1).



Scheme 1 Preparation of 2,3-unsaturated alcohol **4** and 2,3-epoxy 1,4-amino alcohol **5**

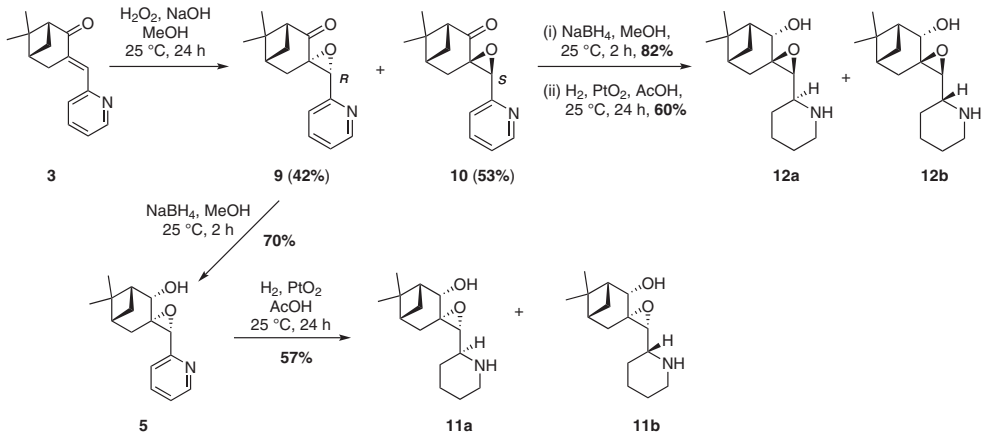
Regioselective catalytic hydrogenation of 2,3-unsaturated amino alcohol **4** gave a mixture of **6** and **7** (Scheme 2). Our results demonstrated that reduction of carbon–carbon double bonds led to di-*endo*■■*OK?*■■ amino alcohol **7** as the main product. Obviously, the addition of hydrogens can take place from both the *Re* and the *Si* side. Interestingly, the ratio of **6** and **7** depends on the catalyst. In the presence 5% Pt/C as catalyst, compound **7** was formed as the major product (dr 10:1 by NMR determination). In turn, the ratio of the two products was found to be 3:1 when 5% Pd/C was used (Scheme 2). Apart from the desired products, compound **8** was also isolated as a minor component. The formation of **8** from **4** could be explained by a metal-catalysed abstraction of hydrogen *gem* to the hydroxyl to afford the corresponding allylic radical. This intermediate would evolve to an enol by isomerisation and fixation of hydrogen, followed by an enol–keto tautomerisation, leading finally to **8**.[23]



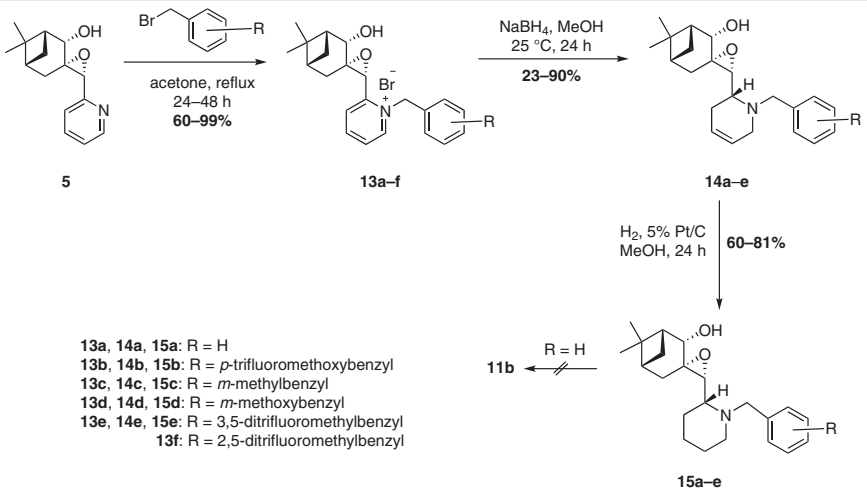
Scheme 2 Hydrogenation of 2,3-unsaturated amino alcohol **4**

To expand the family of ligands, α,β-saturated ketone **3** was first subjected to epoxidation by using H_2O_2 under alkaline conditions, providing the corresponding epoxides **9** and **10** in excellent yields (Scheme 3). Subsequent hydride reduction of epoxide **9** with $NaBH_4$ in MeOH led to the formation of **5** with high diastereoselectivity. It is probably due to the steric hindrance from the two methyl groups on the pinane system that the hydride could only approach the carbonyl carbon from the *Si* side.[24] When ring opening of epoxide **5** was attempted with different reductants, such as L-Selectride and $LiAlH_4$ or by applying epoxide hydrolysis under acidic or alkaline conditions, the opening process failed.

In our next experiment, amino alcohol **5** was subjected to catalytic hydrogenation using Adam's catalyst in glacial acetic acid (Scheme 3).[7] Both epimers **11a** and **11b** of the expected piperidine product were formed in almost equal amounts (dr 1:1). Unfortunately, efforts to separate these



Scheme 3 Preparation of 4-amino-2,3-epoxy-1-ols **11a**,**b** and **12a**,**b**



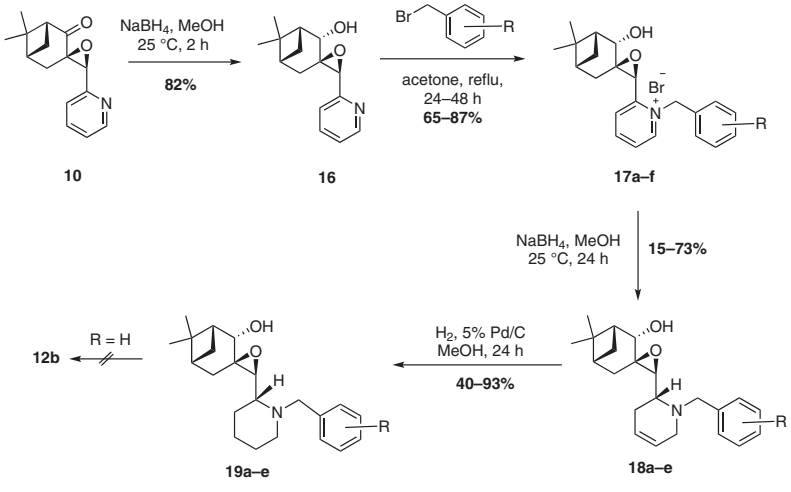
Scheme 4 Synthesis of 4-amino-2,3-epoxy-1-ol derivatives **15a–e**

diastereomers proved to be unsuccessful. Compound **10** underwent similar reactions providing a mixture of **12a** and **12b** (Scheme 3).

To overcome the obstacles in chromatographic separation, another reductive route to **11b** was attempted (Scheme 4). Quaternary ammonium salts **13a–f■■*'g' changed to 'f' – OK?*■■** were easily synthesised by heating **5** under reflux with benzyl bromide derivatives in acetone.[25] Then the products (**13a–f■■*OK?*■■**) were subjected to hydride reduction with $NaBH_4$ to provide **14a–e■■*'g' changed to 'e' – OK?*■■**.[26] Subsequent hydrogenation of **14a–e■■*OK?*■■** in methanol, catalysed by 5% Pd/C afforded **15a–e■■*OK?*■■** (Scheme 4). Our attempts to convert **15a** into **11b** failed, despite increased reaction time, temperature, or pressure. Similar to the case of epoxide **5**, ring opening of **15a** also failed.

In the same manner, as described above (Scheme 4), ketone **10** was reduced to amino alcohol **16** in good yield (Scheme 5). Compound **16** was then transformed into isomers **19a–e■■*'e' not 'g' – OK?*■■**.[27]

To rationalise the resistance of the epoxide ring during the nucleophile-initiated opening reaction, we selected **14a** and **18a** as suitable models for detailed structural analysis. First, with the combined use of high-resolution ^1H and ^{13}C NMR methods, we determined their relative configurations, which are also influenced by the conformational chirality introduced by the tetrahydropyridine ring (Figure 1).



Scheme 5 Synthesis of 4-amino-2,3-epoxy-1-ol derivatives **19a–e**

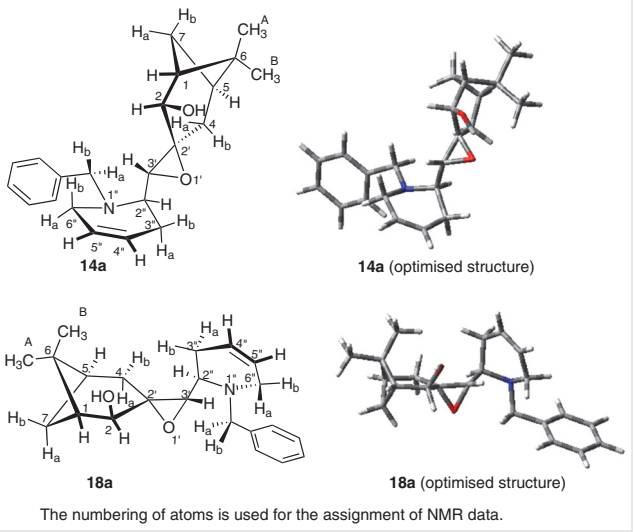


Figure 1 Stereostructures of **14a** and **18a** established by NMR methods and geometry optimisation at the HF-6-31+G(d,p) level of theory (atom numbering used for assignment of ^{1}H and ^{13}C NMR data)

With special focus on the relative configuration of the chiral scaffolds having multiple stereocenters and on the conformation of the tetrahydropyridine ring with the favoured spatial orientations of its substituents, the stereostructures of **14a** and **18a** in DMSO-d_6 were established by ^{1}H and ^{13}C NMR methods (Figure 1). The complete assignment of the ^{1}H and ^{13}C NMR signals was made on the basis of homonuclear $^{1}H/^{1}H$- and the heteronuclear $^{1}H/^{13}C$ correlations revealed by 2D-COSY, HMQC, and HMBC spectra. ROESY experiments were carried out to disclose the spatial proximity of the skeletal protons. Accordingly, in both compounds, characteristic ROE correlations were detected between proton pairs H-2/H-3′, H-3′/H-3_b″, H-3′/H-6_b″, and H-4_b/H-2″, referring to the relative configuration of epoxide stereogenic centres C-2′ and C-3′ and to the axial position of the C-2″–C-3′ bond on the tetrahydropyridine ring with conformational chirality '*P*'. This view is supported by the near antiperiplanar relative position of H-3′ and H-2″ in both compounds, as indicated by the coupling constant with characteristic splits discernible in the following signals: d (J = 8.8 Hz for H-3′) and dt (J = 8.8 Hz and 5.8 Hz for H-2″)

Again, in both compounds, the *endo* orientation of the OH group in the pinane residue is indicated by the ROE value detected between skeletal protons H-2 and H-7_a. On the other hand, the *exo* orientation of the epoxide oxygen in **18a** is reflected in the position of the H-7_a doublet signal shifted downfield by 0.25 ppm relative to that discernible in the ^{1}H NMR spectrum of **14a** (1.09 ppm for **18a** and 0.84 ppm for **14a**). The deshielding effect of the epoxide oxygen on the proximal protons is also manifested in the spectacular difference in the chemical shifts of the OH signals. The relative *cis* position of the OH group and epoxide oxygen in **18a** is confirmed by an epoxide-induced downfield shift of the OH signal compared to that of the same signal measured for **14a** (4.91 ppm for **18a** and 4.00 ppm for **14a**). In **18a**, this significant deshielding effect on the OH proton is obviously exerted by the intramolecular hydrogen bond with the proximal Z²de■■*correct?*■■ oxygen with an interatomic H···O distance of 2.02 Å, as found in the optimised structure of this molecule (Figure 1).

The experimentally established structures presented above were used as input for geometry optimisation carried out by the Hartree–Fock method[28] using the 6-31+G(d,p) basis set.[29] With particular focus on delocalisation around the epoxide region, we performed analysis of the molecular orbitals on the optimised structures of the activated O-protonated cations **14a-H⁺** and **18a-H⁺**. It was found that, in both models, the relevant part of the LUMO on the opposite side of the epoxide oxygen is 'buried' in the 'hole' of the highly crowded molecular architecture and, therefore, it is hardly accessible to any nucleophilic species including a water molecule. Moreover, the electrophilicity of **18a-H⁺** might be further decreased by a donor–acceptor interaction between the oxygen atom of the OH group and the electron-deficient C-2′ atom in the epoxide residue as shown by HOMO-14 (Figure 2).

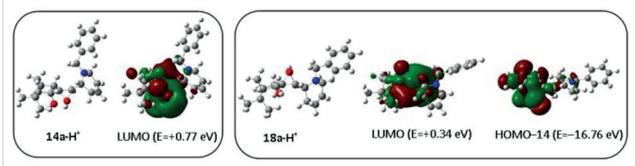
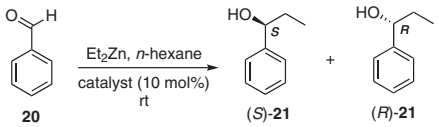


Figure 2 Selected molecular orbitals of O-protonated cations of **14a** and **18a** (**14a-H⁺** and **18a-H⁺**, respectively), accounting for the resistance of the nucleophile-initiated opening of the epoxide ring

The enantioselective addition reaction of diethylzinc to benzaldehyde **20** catalysed by 1,4-amino alcohol derivatives was performed (Scheme 6).[7–9,15] The reaction was carried out in anhydrous *n*-hexane in the presence of a chiral catalyst (10 mol%) at room temperature. After the appropriate time, the reaction mixture was quenched and the product, 1-phenylpropan-1-ol (**21**) was isolated by extraction and purified by column chromatography over silica gel. Its ee value was determined by GC on a CHIRASIL-DEX CB column.[30,31]



Scheme 6 Model reaction for enantioselective catalysis

Low to moderate enantioselectivity was observed (Supporting Information, SI, Table S1). When chiral 1,4-amino alcohols **5** and **6** were examined as catalysts, the addition reaction proceeded with good yield (87%)■■*92% and 85% in Table S1?*■■ and both gave approximately 25% ee■■*9% and 23% ee in Table S1?*■■ of the same (*R*)-**21** with benzaldehyde as substrate. The maximum value of 33% ee was obtained with *N*-benzyl-substituted 4-amino-2,3-epoxy-1-ol **14a**. In the case of chiral ligands **16**, **15a**, and **18a**, the reactions also proceeded with good chemical yield (83–88%■■*86–90% in Table S1?*■■), but low ee values (around 20%) of 1-phenylpropan-1-ol with *R*-configuration were obtained.

Since the epoxide moieties were able to form covalent bonds between the putative target proteins and the inhibitor, irreversible inhibition of the molecular target took place.[32] Moreover, it was found in the literature that although (–)-isopulegol benzyl epoxides had inert properties in chemical transformations,[33] they could act as antiproliferative alkylating agents.[34] Consequently, the antiproliferative activity of our compounds was examined. The in vitro cytotoxic activities of the prepared 4-amino-2,3-epoxide-1-ol analogues were also investigated against a panel of human malignant cell lines isolated from cervical (SiHA and HeLa), breast (MCF7 and MDA-MB-231), and ovary (A2780) cancers (Figure 3 and SI, Table S2).

Figure 3 Antiproliferative properties of selected pinane analogues

Concerning the pharmacological activities of the tested pinane analogues, compounds containing the heteroaromatic pyridine ring (**5**, **13a**, and **17a**) exhibited no considerable antiproliferative action against the utilised human cancer cell lines. Full saturation of the pyridine ring (**15a**, **15d**, **19a** and **19d**) resulted in a similar negligible or modest activities eliciting 30–50% cell growth inhibition at higher concentration (30 μM). Partial saturation, on the other hand, resulted in molecules eliciting substantial activities, which were comparable to those obtained by the reference agent cisplatin. The *trans* orientation of the epoxy function seems to be preferred, especially in the case of **14c** and **18c**. Substituents of the benzyl ring on the tetrahydropyridine function do not seem to determine the activity of the obtained analogue, but non-substituted compounds elicited relatively low activity against the ovarian cancer cell line, with the exception of **18a** (Figure 3).

In conclusion, starting from (–)-β-pinene, a new family of pinane-derived 1,4-amino alcohols was obtained, which exhibited only moderate chiral induction in the model reaction of the addition of Et_2Zn to benzaldehyde with *R*-selectivity.[35–38] The resistance of the oxirane ring during the nucleophile-initiated opening reaction was interpreted by a systematic series of comparative Hartree–Fock modelling using the 6-31+G(d,p) basis set. The results of this study can also account for the failed catalytic debenzylation reaction of *N*-benzyl derivatives. The resulting 4-tetrahydropyridin 2,3-epoxy-1-ols exert markedly antiproliferative action on a panel of human cancer cell lines. The in vitro pharmacological studies have clearly shown that the 1,4-amino alcohol function together with the oxirane and tetrahydropyridine ring systems seem to be essential for reliable antiproliferative activity. The stereochemistry of the oxirane ring and the N-substituents on the trahydropyridine function have no influence on the antiproliferative effect.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 (500 and 125 MHz, respectively). Chemical shifts (δ) are expressed in ppm relative to TMS as internal reference (δ = 0). 2D-COSY, ROESY, HSQC, and HMBC spectra were obtained using the standard Bruker pulse programs. Microanalyses were performed on a Perkin–Elmer 2400 elemental analyser. GC measurements were made on a Perkin-Elmer Autosystem KL GC consisting of a flame ionisation detector and a Turbochrom Workstation data system (Perkin-Elmer Corporation, Norwalk, USA). The separation of *O*-acetyl derivatives of enantiomers was carried out on a CHIRASIL-DEX CB column (2500 × 0.265 mm I.D). HRMS flow injection analysis was performed with a Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap mass spectrometer coupled to a Waters Acquity I-Class UPLC™. Optical rotations were determined on 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 calculations were carried out by using the Gaussian 09 software package.[39] The optimised structures are available from the authors. (–)-β-Pinene (**1**) is available commercially from Merck. All chemicals and solvents were used as supplied. THF and toluene were dried over Na wire. (+)-Nopinone (**2**) was prepared according to literature procedures, and all

spectroscopic data were similar to those described therein.[20] ^{1}H-, ^{13}C-, COSY, HSQC, HMBC, and NOESY NMR spectra of new compounds are available in the SI.

(1*R*,5*R*,*E*)-6,6-Dimethyl-3-(pyridin-2-ylmethylene)bicyclo[3.1.1]heptan-2-one (3)

To a 10% aq KOH solution (1.0 mL), (+)-nopinone (**2**; 100 mg, 0.72 mmol) and 2-pyridinecarboxaldehyde (82 mg, 0.77 mmol) were added. The resulting mixture was stirred at rt for 24 h, and then extracted with Et_2O (3 × 30 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude oily product was purified by chromatography (silica gel, *n*-hexane/EtOAc, 4:1).

Yield: 121 mg (76%); colorless oil; $[\alpha]_D^{20}$ –1.0 (*c* 0.145, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.53 (d, *J* = 9.43■■*correct?*■■ Hz, 1 H, H-7), 2.34 (m, 1 H, H-6), 2.63 (m, 1 H, H-7), 2.72 (t, *J* = 5.5 Hz, 1 H, H-1), 3.18–3.36 (m, 2 H, CH_2), 7.18 (m, 1 H, H-3′), 7.45 (d, *J* = 7.9 Hz, 1 H, ArH), 7.65 (m, 1 H, ArH), 7.69 (m, 1 H, ArH), 8.70 (d, *J* = 4.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 26.2, 27.6, 31.5, 39.4, 40.9, 56.2, 122.3, 127.1, 132.8, 136.0, 137.0, 149.5, 155.5, 203.6.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}NO$■■*H*$_{17}$*?*■■: 228.1388; found: 228.1381.

(1*R*,2*S*,5*R*,*E*)-6,6-Dimethyl-3-(pyridin-2-ylmethylene)bicyclo[3.1.1]heptan-2-ol (4)

Solid $CeCl_3{\cdot}7H_2O$ (163 mg, 0.46 mmol) was added to an ice-cooled solution of **3** (106 mg, 0.46 mmol) in MeOH (2 mL). The reaction mixture was stirred in an ice bath for 30 min before $NaBH_4$ (17 mg, 0.46 mmol) was slowly added to the mixture. Stirring was continued for 30 min at 0 °C. When the reaction was complete, the mixture was evaporated under reduced pressure, and then mixed with brine (10 mL); the product was extracted with Et_2O (3 × 30 mL). The combined organic phase was washed with 3.5% aq HCl solution (10 mL) and dried (Na_2SO_4). Evaporation of the solvent under vacuum afforded pure product **4** without the need for further purification.

Yield: 75 mg (70%); white powder; mp 110–114 °C; $[\alpha]_D^{20}$ +26 (*c* 0.142, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 10.4 Hz, 1 H, H-7), 1.05 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 2.06–2.07 (m, 2 H, H-5), 2.20 (m, 1 H, H-1), 2.36 (m, 1 H, H-7), 2.97–3.27 (m, 2 H, CH_2), 4.66 (s, 1 H, H-2), 6.90 (s, 1 H, H-3′), 7.08 (m, 1 H, ArH), 7.31 (d, *J* = 8.2 Hz, 1 H, ArH), 7.63 (m, 1 H, ArH), 8.62 (d, *J* = 4.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 26.9, 29.4, 34.4, 37.8, 39.5, 46.6, 76.9, 120.8, 124.2, 128.3, 135.9, 146.6, 149.1, 156.8.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{21}NO$■■*H*$_{19}$*?*■■: 230.1545; found: 230.1537.

Hydrogenation of 4, 14a–e, and 18a–e over Pd/C■■check Pd vs Pt: Sch 2: best result Pt/C, Sch 4: Pt/C, but Sch 5: Pd/C?■■; General Procedure

A suspension of 5% Pd/C■■*Pd or Pt?*■■ (50 mg) in MeOH (10 mL) was added to a solution of **4**, **14a–e**, or **18a–e** (0.87 mmol) in MeOH (5 mL). The mixture was stirred under a hydrogen atmosphere at 25 °C for 24 h, and the resulting mixture was filtered through a Celite pad. The filtrate was evaporated to dryness, and the products were separated by column chromatography (silica gel).

(1*R*,2*R*,3*R*,5*S*)-6,6-Dimethyl-3-(pyridin-2-ylmethyl)bicyclo[3.1.1]heptan-2-ol (6)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); yield: 30 mg (15 %); yellow oil; $[\alpha]_D^{20}$ +23 (*c* 0.067, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 10.0 Hz, 1 H, H-7), 1.15 (s, 3 H, CH_3), 1.23–1.28 (m, 4 H, CH_3, H-7), 1.46 (m, 1 H, H-4), 1.97 (m, 1 H, H-5), 2.15 (m, 1 H, H-1), 2.28–2.33 (m, 2 H, H-4, H-7), 2.65 (m, 1 H, H-3), 3.02–3.04 (m, 2 H, CH_2), 3.93 (m, 1 H, H-2), 7.14 (m, 1 H, ArH), 7.21 (d, *J* = 7.8 Hz, 1 H, ArH), 7.62 (t, *J* = 7.5 Hz, 1 H, ArH), 8.49 (d, *J* = 3.8 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.5, 30.0, 34.2, 37.6, 37.7, 41.8, 47.6, 48.1, 79.9, 121.2, 123.9, 136.6, 148.2, 160.8.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{23}NO$■■*H*$_{21}$*?*■■: 232.1701; found: 232.1690.

(1*R*,2*R*,3*S*,5*S*)-6,6-Dimethyl-3-(pyridin-2-ylmethyl)bicyclo[3.1.1]heptan-2-ol (7)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); yield: 90 mg (45 %); yellow oil; $[\alpha]_D^{20}$ –29 (*c* 0.222, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (s, 3 H, CH_3), 1.20–1.26 (m, 4 H, CH_3, H-7), 1.72 (m, 1 H, H-6), 1.94 (m, 1 H, H-3), 2.03 (m, 1 H, H-4), 2.13 (m, 1 H, H-7), 2.27 (m, 1 H, H-1), 2.39 (m, 1 H, H-3), 2.65 (m, 1 H, H-3′), 3.30 (m, 1 H, H-3′), 4.14 (m, 1 H, H-1), 7.16 (m, 1 H, ArH), 7.22(m, 1 H, ArH), 7.66 (m, 1 H, ArH), 8.45 (m, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.0, 25.2, 27.64, 32.9, 36.1, 38.6, 39.3, 41.3, 46.8, 71.9, 121.3, 123.5, 137.5, 148.0, 161.6.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{23}NO$: 232.1701; found: 232.1690.

(1*R*,3*S*,5*S*)-6,6-Dimethyl-3-(pyridin-2-ylmethyl)bicyclo[3.1.1]heptan-2-one (8)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); yield: 30 mg (15 %); yellow oil; $[\alpha]_D^{20}$ –41 (*c* 0.417, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.60 (m, 1 H, H-4), 1.76 (d, *J* = 10.7 Hz, 1 H, H-7), 2.13–2.22 (m, 2 H, H-4, H-5), 2.45 (m, 1 H, H-7), 2.61–2.67 (m, 2 H, H-1, H-3′), 3.27 (m, 1 H, H-3), 3.61 (m, 1 H, H-3′), 7.11 (m, 1 H, ArH), 7.22 (m, 1 H, ArH), 7.59 (m, 1 H, ArH), 8.52 (m, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 25.3, 26.3, 28.7, 37.8, 40.8, 42.7, 43.2, 57.6, 121.2, 123.8, 136.4, 149.0, 160.3, 215.3.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{21}NO$: 230.1545; found: 230.1534.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-3′-[(*R*)-1-Benzylpiperidin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (15a)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.7; yield: 208 mg (70%); yellow oil; $[\alpha]_D^{20}$ –21 (*c* 0.122, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 10.6 Hz, 1 H, H-7), 1.11 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.31 (m, 1 H, H-4″), 1.46–1.55 (m, 3 H, CH_2, H-3″), 1.73–1.77 (m, 2 H, H-4″, H-3″), 1.90 (m, 1 H, H-6″), 1.98–2.06 (m, 3 H, H-2″, H-5, H-4), 2.22 (m, 1 H, H-4), 2.27 (m, 1 H, H-1), 2.40 (m, 1 H, H-7), 2.69 (d, *J* = 3.7 Hz, 1 H, OH), 2.82 (m, 1 H, H-6″), 3.03 (d, *J* = 8.1 Hz, 1 H, H-3′), 3.23 (d, *J* = 14.3 Hz, 1 H, NCH_2),4.02 (m, 1 H, H-2), 4.35 (d, *J* = 13.7 Hz, 1 H, NCH_2), 7.21 (t, *J* = 7.2 Hz, 1 H, ArH), 7.29 (t, *J* = 7.4 Hz, 2 H, ArH), 7.37 (d, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 23.5, 25.4, 27.2, 27.7, 29.4, 32.9, 37.2, 40.7, 46.5, 52.1, 57.1, 59.5, 61.6, 66.8, 73.7, 126.6, 128.0, 128.9.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{33}NO_2$: 342.2433; found: 342.2427.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-6,6-Dimethyl-3′-{(*R*)-1-[4-(trifluoromethoxy)benzyl]piperidin-2-yl}spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (15b)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.6; yield: 329 mg (89%); yellow oil; $[\alpha]_D^{20}$ –10 (*c* 0.152, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (d, 1 H, H-7), 1.10 (s, 3 H, CH_3), 1.26–1.34 (m, 4 H, CH_3, H-5″), 1.47–1.57 (m, 3 H, CH_2, H-3″), 1.73–1.78 (m, 2 H, H-5″, H-3″), 1.91 (m, 1 H, H-6″), 1.97–2.06 (m, 3 H, H-2″, H-5, H-4), 2.22 (m, 1 H, H-4), 2.27 (m, 1 H, H-2), 2.41 (m, 1 H, H-7), 2.68 (s, 1 H, OH), 2.77 (m, 1 H, H-6″), 3.01 (d, *J* = 8.1 Hz, 1 H, H-3′), 3.24 (d, *J* = 14.2 Hz, 1 H, NCH_2), 4.03 (s, 1 H, H-2), 4.33 (d, *J* = 13.5 Hz, 1 H, NCH_2), 7.14 (d, 2 H, ArH), 7.40 (d, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 22.7, 23.4, 25.4, 27.2, 27.7, 29.5, 32.9, 34.0, 37.2, 40.5, 40.6, 46.5, 52.1, 57.1, 58.6, 61.5, 66.7, 73.6, 120.6, 120.7 (q, $^1J_{C\text{-}F}$ = 255.1 Hz), 130.0, 134.4, 148.0.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –57.8.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{32}F_3NO_3$: 426.2256; found: 426.2242.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-6,6-Dimethyl-3′-[(*R*)-1-(3-methylbenzyl)piperidin-2-yl]spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (15c)

Column chromatography (silica gel, *n*-hexane/EtOAc, 2:1); R_f= 0.45; yield: 185 mg (60%); yellow solid; mp 94–96 °C; $[\alpha]_D^{20}$ –24 (*c* 0.132, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 10.7 Hz, 1 H, H-7)1.11 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.31 (m, 1 H, H-4″), 1.45–1.55 (m, 3 H, CH_2, H-5″), 1.72–1.77 (m, 2 H, H-4″, H-5″), 1.87 (m, 1 H, H-6″), 1.98–2.05 (m, 3 H, H-2″, H-5, H-4), 2.22 (m, 1 H, H-4), 2.27 (m, 1 H, H-2″), 2.34 (s, 3 H, CH_3), 2.40 (m, 1 H, H-7), 2.73 (m, 1 H, OH), 2.82 (m, 1 H, H-6″), 3.02 (d, *J* = 8.2 Hz, 1 H, H-3′), 3.17 (d, *J* = 13.5 Hz, 1 H, NCH_2), 4.04 (s, 1 H, H-2), 4.32 (d, *J* = 13.8 Hz, 1 H, NCH_2), 7.03 (m, 1 H, ArH), 7.14–7.19 (m, 3 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 21.4, 23.5, 25.4, 27.2, 27.7, 29.4, 32.9, 37.2, 40.7, 46.4, 52.1, 57.0, 59.5, 61.7, 66.9, 73.6, 126.1, 127.4, 127.9, 129.8, 137.6, 139.2.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{35}NO_2$: 356.2590; found: 356.2575.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-3′-[(*R*)-1-(3-Methoxybenzyl)piperidin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (15d)

Yield: 197 mg (61%); yellow oil; R_f = 0.42 (*n*-hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ –18 (*c* 0.125, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.9 (d, *J* = 10.4 Hz, 1 H, H-7), 1.10 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.30(m, 1 H, H-4″), 1.44–1.56 (m, 3 H, CH_2, H-3″), 1.72–1.77 (m, 2 H, H-4″, H-3″), 1.90 (m, 1 H, H-6″), 1.98–2.06 (m, 3 H, H-2″, H-5, H-4), 2.22 (m, 1 H, H-4), 2.27 (m, 1 H, H-1), 2.40 (m, 1 H, H-7), 2.72 (s, 1 H, OH), 2.83 (m, 1 H, H-6″), 3.02 (d, *J* = 8.5 Hz, 1 H, H-3′), 3.23 (d, *J* = 13.5 Hz, 1 H, NCH_2), 3.80 (s, 3 H, CH_3), 4.03 (s, 1 H, H-2), 4.31 (d, *J* = 13.5 Hz, 1 H, NCH_2), 6.77 (m, 1 H, ArH), 6.95 (d, *J* = 7.3 Hz, 1 H, ArH), 6.98 (s, 1 H, ArH), 7.20 (t, *J* = 7.7 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 23.5, 25.5, 27.2, 27.7, 29.4, 32.9, 37.2, 40.6, 46.4, 52.1, 55.1, 57.0, 59.4, 61.5, 66.8, 73.6, 112.1, 114.3, 121.3, 128.9, 141.1, 159.5.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{35}NO_3$: 372.2539; found: 372.2524.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-3′-{(*R*)-1-[3,5-Bis(trifluoromethyl)benzyl]piperidin-2-yl}-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (15e)

Column chromatography (silica gel, *n*-hexane/EtOAc, 4:1); R_f = 0.3; yield: 336 mg (81%); yellow oil; $[\alpha]_D^{20}$ –13 (*c* 0.122, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 10.6 Hz, 1 H, H-7), 1.10 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.33 (m, 1 H H-4″), 1.49–1.55 (m, 2 H, CH_2), 1.58 (m, 1 H, H-3″), 1.74–1.79 (m, 2 H, H-4″, H-3″), 1.95–2.10 (m, 4 H, H-6″, H-2″, H-5, H-4), 2.19 (m, 1 H, H-4), 2.27 (m, 1 H, H-1), 2.41 (m, 1 H, H-7), 2.60 (s, 1 H, OH), 2.76 (m, 1 H, H-6″), 2.99 (d, *J* = 8.4 Hz, 1 H, H-3′), 3.49 (d, *J* = 14.9 Hz, 1 H, NCH_2), 4.02 (s, 1 H, H-2), 4.36 (d, *J* = 14.6 Hz, 1 H, NCH_2), 7.74 (s, 1 H, ArH), 7.87 (s, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 23.1, 25.4, 27.2, 27.6, 29.5, 29.6, 32.9, 37.1, 40.7, 46.6, 52.3, 57.3, 58.5, 60.8, 66.1, 73.6, 120.7, 123.4 (q, $^1J_{C\text{-}F}$ = 273.0 Hz), 128.8, 131.3 (q, $^2J_{C\text{-}F}$ = 33.2 Hz), 142.2.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –62.7

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{31}F_6NO_2$: 478.2181; found: 478.2170.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-3′-[(*R*)-1-Benzylpiperidin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (19a)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.7; yield: 178 mg (60%); yellow solid; mp 96–99 °C; $[\alpha]_D^{20}$ +87 (*c* 0.130, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.33 (d, *J*= 10.2 Hz, 1 H, H-7), 1.43–1.63 (m, 3 H, CH_2, H-5″), 1.75–1.83 (m, 3 H, H-4, H-5″, H-7), 1.91 (m, 1 H, H-6″), 2.01–2.06 (m, 2 H, H-3′, H-5), 2.19 (m, 1 H, H-1), 2.35 (m, 1 H, H-7), 2.40 (m, 1 H, H-4), 2.82 (m, 1 H, H-6″), 3.24 (d, *J* = 13.8 Hz, 1 H, NCH_2), 3.31 (d, *J* = 8.2 Hz, 1 H, H-3′), 3.85 (d, *J* = 4.0 Hz, 1 H, H-2), 4.38 (d, *J* = 13.9 Hz, 1 H, NCH_2), 7.20 (t, *J* = 7.2 Hz, 1 H, ArH), 7.28 (t, *J* = 7.5 Hz, 2 H, ArH), 7.37 (d, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8, 23.6, 25.6, 26.8, 26.9, 28.4, 33.0, 37.1, 40.2, 46.7, 52.0, 59.5, 59.9, 61.9, 80.5, 126.4, 127.9, 129.0, 139.7.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{33}NO_2$: 342.2433; found: 342.2427.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-6,6-Dimethyl-3′-{(*R*)-1-[4-(trifluoromethoxy)benzyl]piperidin-2-yl}spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (19b)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.6; yield: 137 mg (37%); yellow solid; mp 96–99 °C; $[\alpha]_D^{20}$ +70 (*c* 0.142, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.32 (d, *J* = 10.4 Hz, 1 H, H-7), 1.47–1.62 (m, 3 H, CH_2, H-5″), 1.71–1.82 (m, 3 H, H-4, H-5″, H-7), 1.92 (m, 1 H, H-6″), 2.01–2.06 (m, 2 H, H-3′, H-5), 2.20 (m, 1 H, H-1), 2.34–2.41 (m, 2 H, H-7, H-4), 2.79 (m, 1 H, H-6″), 3.25 (d, *J* = 13.6 Hz, 1 H, NCH_2), 3.29 (d, *J* = 8.4 Hz, 1 H, H-3′), 3.85 (d, *J* = 3.9 Hz, 1 H, H-2), 4.35 (d, *J* = 14.4 Hz, 1 H, NCH_2), 7.13 (d, *J* = 8.1 Hz, 2 H, ArH), 7.40 (d, *J* = 8.1 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5, 25.5, 26.9, 28.4, 33.0, 37.0, 52.0, 58.6, 60.0, 76.7, 77.0, 77.2, 138.4, 147.9.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –57.8.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{32}F_3NO_3$: 426.2256; found: 426.2245.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-6,6-Dimethyl-3′-[(*R*)-1-(3-methylbenzyl)piperidin-2-yl]spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (19c)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.4; yield: 287 mg (93%); yellow oil; $[\alpha]_D^{20}$ +102 (*c* 0.112, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.33 (d, *J* = 10.6 Hz, 1 H, H-7), 1.42–1.63 (m, 3 H, CH_2, H-5″), 1.75–1.84 (m, 3 H, H-4, H-5″, H-7), 1.88 (m, 1 H, H-6″), 1.99–2.05 (m, 2 H, H-3′, H-5), 2.20 (m, 1 H, H-1), 2.33–2.38(m, 4 H, CH_3, H-7), 2.40 (m, 1 H, H-4), 2.83 (m, 1 H, H-6″), 3.18 (d, *J* = 13.6 Hz, 1 H, NCH_2), 3.31 (d, *J* = 8.1 Hz, 1 H, H-3′), 3.86 (d, *J* = 4.2 Hz, 1 H, H-2), 4.36 (d, *J* = 13.6 Hz, 1 H, NCH_2), 7.02–7.03 (m, 1 H, ArH), 7.16–7.19 (m, 3 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 22.8, 23.6, 25.5, 26.8, 26.9, 28.4, 33.0, 37.0, 40.0, 46.6, 52.0, 59.5, 59.9, 62.0, 62.1, 80.5, 126.2, 127.3, 127.8, 129.8, 137.5, 139.4.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{35}NO_2$: 356.2590; found: 356.2576.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-3′-[(*R*)-1-(3-Methoxybenzyl)piperidin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (19d)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.4; yield: 223 mg (69%); yellow oil; $[\alpha]_D^{20}$ +89 (*c* 0.120, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.32 (d, *J* = 10.5 Hz, 1 H, H-7), 1.49–1.56 (m, 2 H, CH_2), 1.61 (m, 1 H, H-5″), 1.75–1.83 (m, 3 H, H-4, H-5″, H-7), 1.93 (m, 1 H, H-6″), 2.03–2.06 (m, 2 H, H-3′, H-5), 2.20 (m, 1 H, H-1), 2.33–2.42 (m, 2 H, H-4, H-7), 2.85 (m, 1 H, H-6″), 3.27 (d, *J* = 13.7 Hz, 1 H, NCH_2), 3.34 (d, J = 8.0 Hz, 1 H, H-3′), 3.80 (s, 3 H, CH_3), 3.86 (d, *J* = 3.9 Hz, 1 H, H-2), 4.36 (d, *J* = 13.7 Hz, 1 H, NCH_2), 6.77 (m, 1 H, ArH), 6.96 (d, *J* = 7.3 Hz, 1 H, ArH), 6.99 (s, 1 H, ArH), 7.20 (t, *J* = 7.7 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8, 23.5, 25.4, 26.8, 26.9, 28.3, 33.0, 37.0, 40.0, 46.6, 52.0, 55.1, 59.3, 60.0, 61.7, 62.0, 80.4, 112.2, 114.5, 121.5, 128.9, 159.5

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{35}NO_3$: 372.2539; found: 372.2528.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-3′-{(*R*)-1-[3,5-Bis(trifluoromethyl)benzyl]piperidin-2-yl}-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (19e)

Column chromatography (silica gel, *n*-hexane/EtOAc, 4:1); R_f = 0.5; yield: 166 mg (40%); yellow oil; $[\alpha]_D^{20}$ +62 (*c* 0.160, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.31 (d, *J* = 10.8 Hz, 2 H, H-7), 1.51–1.62 (m, 3 H, CH_2, H-5″), 1.77–1.84 (m, 3 H, H-4, H-5″, H-7), 1.98–2.08 (m, 3 H, H-3′, H-5, H-6″), 2.21 (m, 1 H, H-1), 2.35–2.40 (m, 2 H, H-4, H-7), 2.75 (m, 1 H, H-6″), 3.29 (d, *J* = 8.5 Hz, 1 H, H-3′), 3.43 (d, *J* = 15.3 Hz, 1 H, NCH_2), 3.84 (d, *J* = 3.5 Hz, 1 H, H-2), 4.43 (d, *J* = 14.8 Hz, 1 H, NCH_2), 7.73 (s, 1 H, ArH), 7.87 (s, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 23.3, 25.5, 26.8, 26.9, 28.4, 29.6, 32.9, 37.0, 40.1, 46.8, 52.3, 58.4, 60.0, 61.3, 61.5, 80.4, 120.6, 121.3 (q, $^1J_{C-F}$ = 274.4 Hz), 128.7 (q, $^3J_{C-F}$ = 3.3 Hz), 131.0 (q, $^4J_{C-F}$ = 33.0 Hz).

^{19}F NMR (471 MHz, DMSO-d_6): δ = –62.7.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{31}F_6NO_2$: 478.2181; found: 478.2172.

Epoxidation of α,β-Unsaturated Amino Ketone 3

Amino ketone **3** (200 mg, 0.88 mmol) was dissolved in MeOH (5.0 mL) and stirred for 15 min at 0 °C before 30% H_2O_2 (160 µL) and 6 M NaOH (64 µL) were added. The mixture was then stirred for 24 h at 25 °C. Et_2O (3 × 30 mL) was used for extraction, H_2O (30 mL) for washing, and Na_2SO_4 for drying. The solvent was evaporated under reduced pressure and the residue was separated by chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.46 (**9**) and 0.64 (**10**).

(1*R*,3*R*,3′*R*,5*R*)-6,6-Dimethyl-3′-(pyridin-2-yl)spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-one (9)

Yield: 90 mg (42%); white solid; mp 72–74 °C; $[\alpha]_D^{20}$ +206 (*c* 0.137, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.64 (d, *J* = 10.2 Hz, 1 H, H-7), 1.76 (m, 1 H, H-4), 2.07 (m, 1 H, H-4), 2.20 (m, 1 H, H-5), 2.55 (m, 1 H, H-7), 2.77 (t, *J* = 5.3 Hz, 1 H, H-1), 4.38 (s, 1 H, H-3′), 7.25–7.28 (m, 2 H, ArH), 7.72 (m, 1 H, ArH), 8.62 (d, J = 4.7 Hz, 1H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 25.6, 25.9, 27.3, 40.0, 42.9, 56.5, 61.6, 65.3, 121.4, 123.1, 136.3, 149.6, 154.5, 208.3.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{19}NO_2$: 244.1338; found: 244.1333.

(1*R*,3*S*,3′*S*,5*R*)-6,6-Dimethyl-3′-(pyridin-2-yl)spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-one (10)

Yield: 113 mg (53%); white solid; mp 68–70 °C; $[\alpha]_D^{20}$ –237 (*c* 0.127, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.9 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.78 (d, J = 10.7 Hz, 1 H, H-7), 1.82 (m, 1 H, H-4), 1.98 (m, 1 H, H-4), 2.25 (m, 1 H, H-5), 2.75–2.82 (m, 2 H, H-7, H-2), 4.62 (s, 1 H, H-3′), 7.24 (m, 1 H, ArH), 7.30 (d, *J* = 7.5 Hz, 1 H, ArH), 7.70 (m, 1 H, ArH), 8.61 (d, J = 4.1 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 25.9, 28.2, 28.9, 40.3, 40.4, 57.5, 60.5, 63.4, 121.1, 123.0, 136.2, 149.5, 155.0, 207.3.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{19}NO_2$: 244.1338; found: 244.1330.

Hydride Reduction; General Procedure

$NaBH_4$ (31.2 mg, 0.82 mmol) was slowly added to a solution of **9** or **10** (100 mg, 0.41 mmol) in MeOH (5 mL). After stirring for 2 h at 0 °C, the mixture was evaporated under reduced pressure. The residue was diluted with H_2O (20 mL) and subsequently extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried (Na_2SO_4), concentrated under reduced pressure, and then purified by column chromatography (silica gel).

(1*R*,2*S*,3*R*,3′*R*,5*R*)-6,6-Dimethyl-3′-(pyridin-2-yl)spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (5)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.57; yield: 70 mg (70%); white solid; mp 72–75 °C; $[\alpha]_D^{20}$ +63 (*c* 0.125, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 10.2 Hz, 1 H, H-7), 1.16 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.72 (m, 1 H, H-4), 1.92 (m, 1 H, H-5), 1.97 (m, 1 H, H-4), 2.30–2.38 (m, 2 H, H-1, H-7), 2.77 (s, 1 H, OH), 4.20 (s, 1 H, H-3′), 4.29 (s, 1 H, H-2), 7.23 (m, 1 H, ArH), 7.31 (d, *J* = 7.6 Hz, 1 H, ArH), 7.70 (m, 1 H, ArH), 8.60 (d, *J* = 4.7 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 27.1, 29.0, 32.2, 37.3, 40.4, 46.4, 62.2, 66.0, 73.7, 120.8, 122.8, 136.3, 149.3, 155.3.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{21}NO_2$: 246.1494; found: 246.1488.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-6,6-Dimethyl-3′-(pyridin-2-yl)spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (16)

Column chromatography (silica gel, *n*-hexane/EtOAc, 1:1); R_f = 0.45; yield: 82 mg (82%); colourless oil; $[\alpha]_D^{20}$ –41 (*c* 0.190, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.68–1.81 (m, 2 H, CH_2), 1.93 (m, 1 H, H-5), 2.24 (m, 1 H, OH), 2.33 (m, 1 H, H-1), 2.40 (m, 1 H, H-7), 4.12 (m, 1 H, H-3′), 4.66 (s, 1 H, H-2), 7.21 (m, 1 H, ArH), 7.28 (d, *J* = 7.8 Hz, 1 H,ArH), 7.68 (m, 1 H, ArH), 8.60 (d, *J* = 4.6 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 26.5, 28.7, 32.3, 37.0, 40.4, 47.5, 61.8, 65.5, 78.8, 121.0, 122.5, 136.2, 149.0, 156.4.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{21}NO_2$: 246.1494; found: 246.1487.

Catalytic Hydrogenation of 5 and 16 over Adam's Catalyst; General Procedure

A solution of **5** or **16** (50 mg, 0.2 mmol) in glacial acetic acid (0.6 mL) was placed under a hydrogen atmosphere in the presence of PtO_2 (10 mg). After the mixture had stirred for 24 h at rt, the catalyst was filtered off through Celite, and 10% aq NaOH solution (10 mL) was added to the reaction mixture. The solution was then extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4, and evaporated under reduced pressure to afford the **11a**/**11b** or **12a**/**12b** mixture, respectively. Unfortunately, efforts to separate these diastereomers proved to be unsuccessful. The product ratio of the mixture was deduced by using the ^{1}H NMR data of the crude products showing the CH–OH doublets at δ = 3.64 and 3.77; this allowed the determination of dr 1:1 for **11a**,**b**. Similar doublets at δ = 3.98 and 4.24 indicated the dr 10:7 for **12a**,**b**.

Quaternisation of the Pyridine Ring; General Procedure

To a solution of **5** or **16** (100 mg, 0.41 mmol) in acetone (2 mL), the substituted benzyl bromide (0.82 mmol) was added. The obtained solution was stirred at 60 °C and the reaction was followed by TLC. When the reaction was complete (24–48 h), the precipitate formed after cooling was filtered through a glass filter and washed with EtOAc to provide **13a**–**f**■■*'g' now 'f' – OK?*■■ or **17a**–**f**■■*'g' not 'f' – OK?*■■ as white, crystalline solids.

1-Benzyl-2-[(1*R*,2*S*,3*R*,3′*R*,5*R*)-2-hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]pyridin-1-ium Bromide (13a)

Yield: 102 mg (60%); white solid; mp 203–205 °C; $[\alpha]_D^{20}$ +64 (*c* 0.130, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = –0.14 (d, *J* = 11.5 Hz, 1 H, H-7), 1.02 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.21 (m, 1 H, H-4), 1.66–1.73 (m, 2 H, H-5, H-4), 1.90 (m, 1 H, H-7), 1.98 (m, 1 H, H-7), 3.74 (d, *J* = 2.3 Hz, 2 H■■*OK?*■■, H-1, OH), 4.62 (s, 1 H, H-3′), 5.98 (d, *J* = 15.8 Hz, 1 H, CH_2), 6.12 (d, *J* = 15.8 Hz, 1 H, CH_2), 7.25 (d, *J* = 7.5 Hz, 2 H, ArH), 7.39–7.46 (m, 3 H, ArH), 8.04 (d, *J* = 7.8 Hz, 1 H, ArH), 8.21 (m, 1 H, ArH), 8.66 (t, *J* = 7.8 Hz, 1 H, ArH), 9.28 (d, *J* = 5.9 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.6, 27.4, 28.9, 32.2, 37.1, 40.1, 47.1, 59.2, 61.0, 65.5, 72.2, 127.1, 127.4, 129.5, 129.8, 134.0, 146.5, 148.0, 152.7.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{27}NO_2$: 336.1967; found: 336.1964.

2-[(1*R*,2*S*,3*R*,3′*R*,5*R*)-2-Hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]-1-[4-(trifluoromethoxy)benzyl]pyridin-1-ium Bromide■■*OK?*■■ (13b)

Yield: 170 mg (83%); white solid; mp 180–184 °C; $[\alpha]_D^{20}$ –48 (*c* 0.152, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = –0.15 (d, *J* = 10.0 Hz, 1 H, H-7), 1.02 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.23 (m, 1 H, H-4), 1.67–1.75 (m, 2 H, H-4, H-5), 1.91 (m, 1 H, H-1), 2.00 (m, 1 H, H-7), 3.74 (s, 1 H, H-3′), 4.64–4.66 (m, 2 H, H-2, OH), 6.02 (d, *J* = 15.8 Hz, 1 H, CH_2), 6.19 (d, *J* = 15.8 Hz, 1 H, CH_2), 7.41–7.46 (m, 4 H, ArH), 8.05 (d, *J* = 7.5 Hz, 1 H, ArH), 8.23 (t, *J* = 6.3 Hz, 1H, ArH), 8.68 (t, *J* = 7.7 Hz, 1 H, ArH), 9.29 (d, *J* = 5.9 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.8, 32.3, 37.1, 40.1, 47.0, 59.2, 60.1, 65.5, 72.2, 120.4 (q, $^1J_{C\text{-}F}$ = 255.4 Hz), 122.3, 127.1, 127.5, 129.7, 133.4, 146.6, 148.1, 149.1, 152.7.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –56.89.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{26}F_3NO_3$: 420.1787; found: 420.1781.

2-[(1*R*,2*S*,3*R*,3′*R*,5*R*)-2-Hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]-1-(3-methylbenzyl)pyridin-1-ium Bromide (13c)

Yield: 148 mg (84%); white solid; mp 211–213 °C; $[\alpha]_D^{20}$ –69 (*c* 0.137, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = –0.15 (d, *J* = 10.5 Hz, 1 H, H-7), 1.01 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.19 (d, 1 H, H-4), 1.67–1.73 (m, 2 H, H-4), 1.90 (m, 1 H, H-5), 2.00 (m, 1 H, H-1), 2.26 (s, 3 H, CH_3), 3.73 (m, 1 H, H-2), 4.64–4.65 (m, 2 H, H-3′, OH), 5.96 (d, *J* = 15.8 Hz, 1 H, CH_2), 6.07 (d, *J* = 15.8 Hz, 1 H, CH_2), 7.04–7.05 (m, 2 H, ArH), 7.20 (d, *J* = 7.3 Hz, 1 H, ArH), 7.33 (t, *J* = 7.5 Hz, 1H, ArH), 8.03 (d, *J* = 7.8 Hz, 1H, ArH), 8.21 (t, *J* = 6.4 Hz, 1 H, ArH), 8.66 (t, *J* = 7.8 Hz, 1 H, ArH), 9.29 (d, *J* = 6.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.2, 21.6, 27.4, 28.8, 32.3, 37.2, 40.1, 47.1, 59.2, 61.0, 65.5, 72.1, 124.5, 127.0, 127.4, 127.9, 129.7, 130.2, 134.0, 139.3, 146.4, 148.0, 152.7.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{29}NO_2$: 350.2120; found: 350.2115.

2-[(1*R*,2*S*,3*R*,3′*R*,5*R*)-2-Hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]-1-(4-methoxybenzyl)pyridin-1-ium Bromide (13d)

Yield: 163 mg (89%); white solid; mp 199–201 °C; $[\alpha]_D^{20}$ –75 (*c* 0.120, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = –0.06 (d, *J* = 10.3 Hz, 1H, H-7), 1.02 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.21 (m, 1 H, H-4), 1.67–1.71 (m, 2 H, H-4, H-5), 1.92 (m, 1 H, H-1), 2.02 (m, 1 H, H-7), 3.73 (s, 3 H, CH_3), 3.77 (m, 1 H, H-5), 4.64–4.65 (m, 2 H, H-3′, OH), 5.96 (d, *J* = 15.8 Hz, 1 H, CH_2), 6.08 (d, *J* = 15.8 Hz, 1 H, CH_2), 6.73 (d, *J* = 7.7 Hz, 1 H, ArH), 6.89 (s, 1 H, ArH), 6.96 (m, 1 H, ArH), 7.34 (t, *J* = 8.1 Hz, 1 H, ArH), 8.03 (d, *J* = 8.1 Hz, 1 H, ArH), 8.20 (t, *J* = 6.5 Hz, 1 H, ArH), 8.66 (t, *J* = 7.6 Hz, 1 H, ArH), 9.28 (d, *J* = 6.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.6, 27.4, 28.9, 32.3, 37.1, 40.1, 47.1, 55.8, 59.2, 65.5, 72.1, 113.6, 114.8, 119.3, 127.0, 127.4, 131.0, 135.4, 146.5, 148.0, 152.7, 160.3

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{29}NO_3$: 366.2069; found: 366.2065.

1-[3,5-Bis(trifluoromethyl)benzyl]-2-[(1*R*,2*S*,3*R*,3′*R*,5*R*)-2-hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]pyridin-1-ium Bromide■■*OK?*■■ (13e)

Yield: 220 mg (97%); white solid; mp 205–209 °C; $[\alpha]_D^{20}$ –47 (*c* 0.145, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = –0.34 (d, *J* = 11.2 Hz, 1 H, H-7), 1.02 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.26 (m, 1 H, H-4), 1.67 (m, 1 H, H-4), 1.73 (m, 1 H, H-1), 1.91 (m, 1 H, H-7), 2.01 (m, 1 H, H-5), 3.75 (m, 1 H, H-2), 4.64 (d, *J* = 4.3 Hz, 1 H, OH), 4.69 (s, 1 H, H-3′), 6.15 (d, *J* = 16.5 Hz, 1 H, CH_2), 6.27 (d, *J* = 15.7 Hz, 1 H, CH_2), 8.05 (d, *J* = 6.9 Hz, 1 H, ArH), 8.14 (s, 2 H, ArH), 8.20–8.21 (m, 2 H, ArH), 8.67 (t, *J* = 7.6 Hz, 1 H, ArH), 9.23 (d, *J* = 5.6 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 27.3, 28.7, 32.4, 37.2, 46.8, 59.4, 59.6, 65.4, 72.3, 123.4 (q, $^1J_{C\text{-}F}$ = 272.8 Hz), 123.7, 127.1, 127.7, 129.6, 131.6 (q, $^4J_{C\text{-}F}$ = 32.9 Hz), 137.0, 146.8, 148.3, 152.7.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –61.32.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{25}F_6NO_2$: 472.1711; found: 472.1701.

1-[2,5-Bis(trifluoromethyl)benzyl]-2-[(1*R*,2*S*,3*R*,3′*R*,5*R*)-2-hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]pyridin-1-ium Bromide■■*OK?*■■ (13f)

Yield: 224 mg (99%); white solid; mp 150–155 °C; $[\alpha]_D^{20}$ –17 (*c* 0.125, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = –0.05 (d, *J* = 10.3 Hz, 1H, H-7), 1.03 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.45 (m, 1 H, H-4), 1.75 (m, 1 H, H-4), 1.80 (m, 1 H, H-5), 1.95 (m, 1 H, H-1), 2.11 (m, 1 H, H-7), 3.71 (m, 1 H, H-2), 4.43 (s, 1 H, H-3′), 4.79 (d, *J* = 4.6 Hz, 1 H, OH), 6.29 (s, 2 H, H-2), 7.38 (s, 1 H, ArH), 8.11–8.15 (m, 2 H, ArH), 8.23–8.25 (m, 2 H, ArH), 8.75 (t, *J* = 8.1 Hz, 1 H, ArH), 9.13 (d, *J* = 5.8 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.6, 27.3, 28.9, 31.1, 32.3, 37.1, 40.1, 47.0, 57.4, 59.5, 65.6, 72.7, 123.3 (q, $^1J_{C\text{-}F}$ = 273.2 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 274.7 Hz), 126.3 (q, $^3J_{C\text{-}F}$ = 3.1 Hz), 127.4, 127.7 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 128.0, 129.2 (q, $^3J_{C\text{-}F}$ = 5.3 Hz), 130.6, 130.8, 133.0, 134.2 (q, $^3J_{C\text{-}F}$ = 31.5 Hz).

^{19}F NMR (471 MHz, DMSO-d_6): δ = –59.4, –61.9.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{25}F_6NO_2$: 472.1711; found: 472.1699.

1-Benzyl-2-[(1*R*,2*S*,3*S*,3′*S*,5*R*)-2-hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]pyridin-1-ium Bromide■■*OK?*■■ (17a)

Yield: 138 mg (81%); white solid; mp 190–193 °C; $[\alpha]_D^{20}$ +65 (*c* 0.140, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.92 (s, 3 H, CH_3), 1.18 (d, *J* = 11.0 Hz, 1 H, H-7), 1.20 (s, 3 H, CH_3), 1.62 (m, 1 H, H-4), 1.91 (m, 1 H, H-5), 2.00 (d, *J* = 15.0 Hz, 1 H, H-4), 2.15 (m, 1 H, H-1), 2.36 (m, 1 H, H-7), 3.89 (m, 1 H, H-2), 4.70 (s, 1 H, H-3′), 5.68 (d, *J* = 4.2 Hz, 1 H, OH), 5.94 (d, *J* = 15.2 Hz, 1 H, CH_2), 6.06 (d, *J* = 15.2 Hz, 1 H, CH_2), 7.36–7.37 (m, 2 H, ArH), 7.43–7.48 (m, 3 H, ArH), 8.01 (d, *J* = 8.0 Hz, 1 H, ArH), 8.17 (t, *J* = 6.7 Hz, 1 H, ArH), 8.66 (t, *J* = 7.9 Hz, 1 H, ArH), 9.13 (d, *J* = 5.8 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.1, 27.2, 27.3, 32.0, 37.2, 39.8, 46.5, 56.7, 68.8, 78.0, 126.9, 127.7, 128.4, 129.7, 129.8, 146.7, 152.5.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{27}NO_2$: 336.1964; found: 336.1956.

2-[(1*R*,2*S*,3*S*,3′*S*,5*R*)-2-Hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]-1-(4-(trifluoromethoxy)benzyl]pyridin-1-ium Bromide■■*OK?*■■ (17b)

Yield: 178 mg (87%); white solid; mp 142–145 °C; $[\alpha]_D^{20}$ +49 (*c* 0.127, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.84 (s, 3 H, CH_3), 1.15 (d, *J* = 9.0 Hz, 1 H, H-7), 1.19 (s, 3 H, CH_3), 1.61 (m, 1 H, H-4), 1.90 (m, 1 H, H-4), 1.97 (m, 1 H, H-5), 2.13 (m, 1 H, H-1), 2.34 (m, 1 H, H-7), 3.87 (s, 1 H, H-3′), 4.69(s, 1 H, H-2), 5.64(s, 1 H, OH), 5.96(d, *J* = 15.3 Hz, 1 H, CH_2), 6.09 (d, *J* = 15.3 Hz, 1 H, CH_2), 7.44–7.49 (m, 4 H, ArH), 8.02 (d, *J* = 7.9 Hz, 1 H, ArH), 8.18 (t, *J* = 6.8 Hz, 1 H, ArH), 8.67 (t, *J* = 7.8 Hz, 1 H, ArH), 9.15 (d, *J* = 5.9 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.0, 27.1, 27.2, 31.9, 37.2, 39.7, 46.4, 56.6, 59.1, 68.8, 78.0, 122.2, 127.0, 127.8, 129.7, 130.4, 132.4, 146.8, 147.5, 149.2, 152.6.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{26}F_3NO_3$: 420.1787; found: 420.1791.

2-[(1*R*,2*S*,3*S*,3′*S*,5*R*)-2-Hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]-1-(3-methylbenzyl)pyridin-1-ium Bromide■■*OK?*■■ (17c)

Yield: 115 mg (65%); white solid; mp 174–176 °C; $[\alpha]_D^{20}$ +59 (*c* 0.120, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.93 (s, 3 H, CH_3), 1.18 (d, *J* = 10.5 Hz, 1 H, H-7), 1.21 (s, 3 H, CH_3), 1.62 (m, 1 H, H-4), 1.92 (m, 1 H, H-5), 1.98 (m, 1 H, H-4), 2.15 (m, 1 H, H-1), 2.31 (s, 3 H, CH_3), 2.36 (m, 1 H, H-7), 3.89 (t, *J* = 4.3 Hz, 1 H, H-2), 4.72 (s, 1 H, H-3′), 5.65 (d, *J* = 4.6 Hz, 1 H, OH), 5.90 (d, *J* = 15.2 Hz, 1 H, CH_2), 6.01 (d, *J* = 5.2 Hz, 1 H, CH_2), 7.14 (d, *J* = 7.7 Hz, 1 H, ArH), 7.20 (s, 1 H, ArH), 7.25 (d, *J* = 7.3 Hz, 1 H, ArH), 7.34 (t, *J* = 7.6 Hz, 1 H, ArH), 8.00 (d, *J* = 7.6 Hz, 1 H, ArH), 8.15 (m, 1 H, ArH), 8.65 (t, *J* = 7.8 Hz, 1 H, ArH), 9.10 (d, *J* = 6.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.3, 23.1, 27.2, 27.3, 32.0, 37.2, 39.8, 46.6, 56.7, 59.9, 68.8, 78.0, 125.4, 126.8, 127.7, 128.9, 129.7, 130.3, 132.9, 139.3, 146.6, 147.2, 152.5.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{29}NO_2$: 350.2120; found: 350.2117.

2-[(1*R*,2*S*,3*S*,3′*S*,5*R*)-2-Hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]-1-(3-methoxybenzyl)pyridin-1-ium Bromide■■*OK?*■■ (17d)

Yield: 119 mg (65%); white solid; mp 166–168 °C; $[\alpha]_D^{20}$ +76 (*c* 0.137, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.92 (s, 3 H, CH_3), 1.17 (d, *J* = 10.6 Hz, 1 H, H-7), 1.21 (s, 3 H, CH_3), 1.59 (m, 1 H, H-4), 1.91 (m, 1 H, H-5), 1.98 (m, 1 H, H-4), 2.15 (m, 1 H, H-1), 2.36 (m, 1 H, H-7), 3.76 (s, 3 H, CH_3), 3.89 (t, *J* = 4.0 Hz, 1 H, H-2), 4.71 (s, 1 H, H-3′), 5.67 (d, *J* = 4.3 Hz, 1 H, OH), 5.90 (d, J = 15.0 Hz, 1 H, CH_2), 6.01 (d, *J* = 15.0 Hz, 1 H, CH_2), 6.86 (d, *J* = 7.7 Hz, 1 H, ArH), 6.97 (s, 1 H, ArH), 7.01 (m, 1 H, ArH), 7.37 (t, *J* = 7.8 Hz, 1 H, ArH) 7.99 (m, 1 H, ArH), 816 (m, 1 H, ArH), 8.65 (m, 1 H, ArH), 9.12 (d, *J* = 5.5 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.1, 27.2, 27.3, 31.9, 37.2, 39.7, 46.5, 55.7, 56.7, 59.7, 68.7, 78.0, 114.4, 115.1, 120.2, 126.8, 127.7, 131.0, 134.3, 146.7, 147.3, 152.5, 160.3.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{29}NO_3$: 366.2069; found: 366.2065.

1-[3,5-Bis(trifluoromethyl)benzyl]-2-[(1*R*,2*S*,3*S*,3′*S*,5*R*)-2-hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]pyridin-1-ium Bromide■■*OK?*■■ (17e)

Yield: 165 mg (73%); white solid; mp 153–157 °C; $[\alpha]_D^{20}$ +52 (*c* 0.150, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.70 (s, 3 H, CH_3), 1.13–1.18 (m, 4 H, CH_3, H-7), 1.62 (m, 1 H, H-4), 1.88–1.94 (m, 2 H, H-4, H-5), 2.12 (m, 1 H, H-1), 2.34 (m, 1 H, H-7), 3.85 (t, *J* = 4.1 Hz, 1 H, H-2), 4.78 (s, 1 H, H-3′), 5.53 (d, *J* = 4.3 Hz, 1 H, OH), 6.10 (d, *J* = 16.0 Hz, 1 H, CH_2), 6.24 (d, *J* = 16.0 Hz, 1 H, CH_2), 8.02 (d, *J* = 8.1 Hz, 1 H, ArH), 8.09 (s, 2 H, ArH), 8.16–8.20 (m, 2 H, ArH), 8.68 (t, *J* = 7.8 Hz, 1 H, ArH), 9.20 (d, *J* = 6.1 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.8, 27.0, 27.2, 31.8, 37.1, 39.7, 46.2, 56.6, 58.9, 68.8, 78.2, 123.5 (q, $^1J_{C-F}$ = 272.6 Hz), 123.6 (q, $^3J_{C-F}$ = 2.9 Hz), 127.1, 127.8, 129.8, 131.3 (q, $^2J_{C-F}$ = 33.4 Hz), 135.9, 146.9, 147.8, 153.0.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –61.19.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{25}F_6NO_2$: 472.1711; found: 472.1700.

1-[2,5-Bis(trifluoromethyl)benzyl]-2-[(1*R*,2*S*,3*S*,3′*S*,5*R*)-2-hydroxy-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-3′-yl]pyridin-1-ium Bromide■■*OK?*■■ (17f)

Yield: 158 mg (70%); white solid; mp 158–161 °C; $[\alpha]_D^{20}$ +44 (*c* 0.145, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.80 (s, 3 H, CH_3), 1.16 (m, 1 H, H-7), 1.18 (s, 3 H, CH_3), 1.64 (m, 1 H, H-4), 1.90 (m, 1 H, H-4), 1.99 (m, 1 H, H-5), 2.10 (m, 1 H, H-1), 2.34 (m, 1 H, H-7), 3.82 (t, *J* = 4.1 Hz, 1 H, H-2), 4.69 (s, 1 H, H-3′), 5.47 (d, *J* = 4.4 Hz, 1 H, OH), 4.21 (d, *J* = 16.7 Hz, 1 H, CH_2), 6.31 (d, *J* = 16.7 Hz, 1 H, CH_2), 7.34 (s, 1 H, ArH), 8.10–8.12 (m, 2 H, ArH), 8.16–8.21 (m, 2 H, ArH), 8.73 (t, *J* = 8.0 Hz, ArH), 1H, 9.00 (d, *J* = 6.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.8, 27.1, 27.2, 31.8, 32.5, 37.1, 39.7, 46.2, 56.5, 56.7, 69.1, 77.9, 124.7, 125.9 (q, $^3J_{C-F}$ = 3.2 Hz), 127.1, 127.6 (q, $^4J_{C-F}$ = 4.3 Hz), 127.9, 129.2 (q, $^3J_{C-F}$ = 4.9 Hz), 132.6, 147.4, 147.6, 153.4.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –61.7, –59.3.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{25}F_6NO_2$: 472.1711; found: 472.1698.

Hydride Reduction of Quaternary Ammonium Salts 13a–e and 17a–e; General Procedure

To a solution of **13a–e** or **17a–e** (0.23 mmol) in MeOH (6 mL) at –10 °C was added $NaBH_4$ (45.4 mg, 1.2 mmol). The reaction mixture was stirred at rt for 24–48 h (indicated by TLC), and then quenched with water (5 mL) and 20% aq NaOH (5 mL) with stirring for an additional 15 min. After diluting the mixture with water (10 mL), the obtained mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc).

(1*R*,2*S*,3*R*,3′*R*,5*R*)-3′-[(*R*)-1-Benzyl-1,2,3,6-tetrahydropyridin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (14a)

Column chromatography (silica gel, *n*-hexane/EtOAc, 4:1); R_f = 0.4; yield: 70 mg (90%); yellow solid; mp 77–80 °C; $[\alpha]_D^{20}$ +1 (*c* 0.125, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.84 (d, *J* = 10.3 Hz, 1 H, H-7_a), 1.01 (s, 3 H, CH_3^B), 1.16 (s, 3 H, CH_3^A), 1.75 (dd, *J* = 14.5 Hz and 4.3 Hz, 1 H, H-4_a), 1.89 (br~s, 1 H, H-5), 1.98–2.04 (overlapping m, 3 H, H-1, H-4_b and H-3″$_b$), 2.19–2.28 (overlapping m, 2 H, H-7_b and H-3″$_a$), 2.35 (td, *J* = 8.8 Hz and 5.8 Hz, 1 H, H-2″), 2.76 (br d, *J* = ~14 Hz, 1 H, H-6″$_a$), 3.03 (br d, *J* = ~14 Hz, 1 H, H-6″$_b$), 2.97 (d, *J* = 8.8 Hz, 1 H, H-3′), 3.44 (d, *J* = 13.6 Hz, 1 H, NC*H*$_a$H$_b$), 3.89 (t, *J* = 4.0 Hz, 1 H, H-2), 4.00 (d, *J* = 4.0 Hz, 1 H,, OH), 4.08 (d, *J* = 13.6 Hz, 1 H, NCH$_a$*H*$_b$), 5.61 (m, 1 H, H-5″), 5.66 (m, 1 H, H-4″), 7.18 (tt, *J* = 7.3 Hz and 2.1 Hz, 1 H, PhH-4), 7.27 (t, *J* = 7.3 Hz, 2 H, PhH-3,5), 7.29 (br d, *J* = ~7 Hz, 2 H, PhH-2,6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.2 (CH_3^B), 27.6 (CH_3^A), 27.9 (C-3″), 29.5 (C-7), 33.0 (C-4), 37.3 (C-6), 40.8 (C-5), 47.1 (C-1), 50.0 (C-6″), 56.8 (C-2″), 56.7 (C-2′), 59.5 (NCH_2), 63.2 (C-3′), 73.7 (C-2), 123.5 (C-4″), 125.6 (C-5″), 127.2 (PhC-4), 128.6 (PhC-3,5), 129.1 (PhC-2,6), 139.7 (PhC-1).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{30}NO_2$: 340.2277; found: 340.2273.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-6,6-Dimethyl-3′-{(*R*)-1-[4-(trifluoromethoxy)benzyl]-1,2,3,6-tetrahydropyridin-2-yl}spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (14b)

Column chromatography (silica gel, *n*-hexane/EtOAc, 2:1); R_f = 0.58; yield: 44 mg (45%); yellow solid; mp 90–93 °C; $[\alpha]_D^{20}$ +25 (*c* 0.125, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (m, 1 H, H-7), 1.11 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.92 (m, 1 H, H-4), 2.01 (m, 1 H, H-5), 2.07 (m, 1 H, H-3″), 2.13 (m, 1 H, H-4), 2.27 (m, 1 H, H-1), 2.37–2.44 (m, 2 H, H-7, H-3″), 2.55 (m, 1 H, H-2″), 2.73 (s, 1 H, OH), 2.98 (m, 1 H, H-6″), 3.17 (d, *J* = 8.8 Hz, 1 H, H-3′), 3.21 (m, 1 H, H-6″), 3.66 (d, *J*= 13.4 Hz, 1 H, NCH_2), 4.02 (m, 1 H, H-2), 4.09 (d, *J* = 13.4 Hz, 1 H, NCH_2), 5.67–5.74 (m, 2 H, H-4″, H-5″), 7.14 (d, *J* = 8.2 Hz, 2 H, ArH), 7.41 (d, *J* = 8.2 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 21.1, 27.2, 27.7, 29.6, 32.8, 37.1, 40.6, 46.5, 49.6, 55.8, 56.8, 58.8, 63.6, 73.5, 120.4 (q, $^1J_{C-F}$ = 254.3 Hz), 120.6, 122.7, 125.4, 130.2, 137.8, 148.1.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –57.7.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{30}F_3NO_3$: 424.2100; found: 424.2092.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-6,6-Dimethyl-3′-[(*R*)-1-(3-methylbenzyl)-1,2,3,6-tetrahydropyridin-2-yl]spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (14c)

Column chromatography (silica gel, *n*-hexane/EtOAc, 2:1); R_f = 0.63; yield: 54 mg (66%); yellow solid; mp 118–122 °C; $[\alpha]_D^{20}$ +12 (*c* 0.130, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 10.0 Hz, 1 H, H-7), 1.12 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.95 (m, 1 H, H-4), 2.00–2.09 (m, 2 H, H-5, H-3″), 2.14 (m, 1 H, H-4), 2.27 (m, 1 H, H-1), 2.33 (s, 3 H, CH_3), 2.36–2.43 (m, 2 H, H-7, H-3″), 2.54 (m, 1 H, H-2″), 2.78 (s, 1 H, OH), 2.96 (m, 1 H, H-6″), 3.18 (d, *J* = 8.9 Hz, 1 H, H-3′), 3.22 (m, 1 H, H-6″), 3.58 (d, *J* = 13.1 Hz, 1 H, NCH_2), 4.02 (s, 1 H, H-2), 4.09 (d, *J* = 13.1 Hz, 1 H, NCH_2), 5.67–5.73 (m, 2 H, H-4″, H-5″), 7.04 (m, 1 H, ArH), 7.18–7.19 (m, 2 H, ArH), 7.22 (s, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 21.3, 27.2, 27.7, 29.6, 32.8, 37.1, 40.6, 46.5, 49.7, 55.9, 56.7, 59.6, 63.8, 73.5, 122.7, 125.6, 126.2, 127.6, 128.0, 129.7, 129.9, 137.7, 138.8.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{33}NO_2$: 354.2433; found: 354.2420.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-3′-[(*R*)-1-(3-Methoxybenzyl)-1,2,3,6-tetrahydropyridin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (14d)

Column chromatography (silica gel, *n*-hexane/EtOAc, 2:1); R_f = 0.5; yield: 52 mg (61%); yellow oil; $[\alpha]_D^{20}$ +10 (*c* 0.132, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 10.4 Hz, 1 H, H-7), 1.11 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.94 (m, 1 H, H-4), 2.00–2.09 (m, 2 H, H-5, H-3″), 2.13 (m, 1 H, H-4), 2.27 (m, 1 H, H-1), 2.37–2.43 (m, 2 H, H-7, H-3″), 2.56 (m, 1 H, H-2″), 2.77 (s, 1 H, OH), 2.98 (m, 1 H, H-6″), 3.18 (d, *J* = 9.1 Hz, 1 H, H-3′), 3.24 (m, 1 H, H-6″), 3.63 (d, *J* = 13.2 Hz, 1 H, NCH_2), 3.80 (s, 3 H, CH_3), 4.02 (s, 1 H, H-2), 4.09 (d, *J* = 13.2 Hz, 1 H, NCH_2), 5.67–5.73 (m, 2 H, H-5″, H-4″), 6.78 (m, 1 H, ArH), 6.97–6.98 (m, 2 H, ArH), 7.21 (t, *J* = 8.0 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 27.2, 27.7, 29.6, 32.8, 37.1, 40.6, 46.5, 49.6, 55.2, 55.8, 56.7, 59.6, 63.8, 73.5, 112.5, 114.3, 121.4, 122.6, 125.6, 129.0, 140.7, 159.6.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{33}NO_3$: 370.2382; found: 370.2372.

(1*R*,2*S*,3*R*,3′*R*,5*R*)-3′-{(*R*)-1-[3,5-Bis(trifluoromethyl)benzyl]-1,2,3,6-tetrahydropyridin-2-yl}-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (14e)

Column chromatography (silica gel, *n*-hexane/EtOAc 4:1); R_f = 0.3; yield: 25 mg (23%); yellow oil; $[\alpha]_D^{20}$ +2 (*c* 0.107, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 10.8 Hz, 1 H, H-7), 1.11 (s, 3 H, CH_3), 1.25–1.26 (m, 4 H, H-4, CH_3), 1.87 (m, 1 H, H-5), 2.01 (m, 1 H, H-3″), 2.08 (m, 1 H, H-4), 2.26 (m, 1 H, H-1), 2.38–2.43 (m, 2 H, H-7, H-3″), 2.53 (m, 1 H, H-2″), 2.66 (s, 1 H, OH), 3.09 (m, 1 H, H-6″), 3.18 (d, *J* = 9.3 Hz, 1 H,H-3′), 3.28 (m, 1 H, H-6″), 3.87 (d, *J* = 13.6 Hz, 1 H, NCH_2), 4.00 (s, 1 H, H-2), 4.13 (d, *J* = 14.2 Hz, 1 H, NCH_2), 5.70–5.76 (m, 2 H, H-5″, H-4″), 7.75 (s, 1 H, ArH), 7.89 (s, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 27.2, 27.6, 29.6, 29.7, 32.8, 37.1, 40.6, 46.7, 49.7, 54.8, 56.8, 58.6, 63.0, 73.5, 120.9, 122.8, 125.0, 129.1, 131.3, 141.9.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –62.9

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{24}H_{29}F_6NO_2$: 476.2024; found: 476.2017.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-3′-[(*R*)-1-Benzyl-1,2,3,6-tetrahydropyridin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (18a)

Column chromatography (silica gel, *n*-hexane/EtOAc, 4:1); R_f = 0.3; yield: 18 mg (23%); yellow oil; $[\alpha]_D^{20}$ +64 (*c* 0.132, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.94 (s, 3 H, CH_3^B), 1.09 (d, *J* = 10.3 Hz, 1 H, H-7_a), 1.16 (s, 3 H, CH_3^A), 1.58 (dd, *J* = 14.5 Hz and 4.3 Hz, 1 H, H-4_a), 1.89 (br~s, 1 H, H-5), 2.00 (qa, *J* = 5.1 Hz, 1 H, H-1), 2.03 (m, 1 H, H-3″$_b$), 2.18–2.21 (overlapping m, 2 H, H-4_b and H-7_b), 2.27 (m, 1 H, H-3″$_a$), 2.36 (td, *J* = 8.8 Hz and 5.8 Hz, 1 H, H-2″), 2.78 (br d, *J* = ~14 Hz, 1 H, H-6″$_a$), 3.08 (br d, *J* = ~14 Hz, 1 H, H-6″$_b$), 3.31 (d, *J* = 8.8 Hz, 1 H H-3′), 3.44 (d, *J* = 13.6 Hz, 1 H, NC*H*$_a$H$_b$), 3.62 (d, *J* = 3.8 Hz, 1 H, H-2), 4.02 (d, *J* = 13.6 Hz, 1 H, NCH$_a$*H*$_b$), 4.91 (br s, 1 H, OH), 5.61 (m, 1 H, H-5″), 5.67 (m, 1 H, H-4″), 7.18 (tt, *J* = 7.3 Hz and 2.1 Hz, 1 H, PhH-4), 7.25 (t, *J* = 7.3 Hz, 2 H, PhH-3,5), 7.28 (br d, *J* = ~7 Hz, 2H, PhH-2,6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.2 (CH_3^B), 27.3 (two coalesced lines, CH_3^A and C-7), 28.5 (C-3″), 33.2 (C-4), 37.1 (C-6), 40.2 (coalesced with the 3rd line of the solvent septet, C-5), 46.8 (C-1), 49.9 (C-6″), 56.2 (C-2″), 59.2 (C-3′), 59.4 (NCH_2), 60.3 (C-2′), 78.6 (C-2), 123.6 (C-4″), 125.6 (C-5″), 127.2 (PhC-4), 128.6 (PhC-3,5), 129.1 (PhC-2,6), 139.8 (PhC-1).

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{22}H_{30}NO_2$: 340.2277; found: 340.2270.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-6,6-Dimethyl-3′-{(*R*)-1-[4-(trifluoromethoxy)benzyl]-1,2,3,6-tetrahydropyridin-2-yl}spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (18b)

Column chromatography (silica gel, *n*-hexane/EtOAc, 2:1); R_f = 0.6; yield: 24 mg (25%); yellow solid; mp 84–86 °C; $[\alpha]_D^{20}$ +35 (*c* 0.075, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (s, 3 H, CH_3), 1.25–1.31 (m, 4 H, CH_3, H-7), 1.76 (m, 1 H, H-4), 2.02 (m, 1 H, H-5), 2.18–2.22 (m, 2 H, H-1, H-3″), 2.30–2.43 (m, 3 H, H-3″, H-7, H-4), 2.51 (m, 1 H, H-2″), 2.95 (m, 1 H, H-6″), 3.24 (m, 1 H, H-3′), 3.46 (d, *J* = 8.9 Hz, 1 H, H-6″), 3.62 (d, *J* = 13.5 Hz, 1 H, NCH_2), 3.88 (d, *J* = 3.8 Hz, 1 H, H-2), 4.16 (d, *J* = 13.3 Hz, 1 H, NCH_2), 5.68–5.77 (m, 2 H, H-4″, H-5″), 7.14 (d, *J* = 8.2 Hz, 2 H, ArH), 7.42 (d, *J* = 8.8 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 26.7, 27.1, 28.4, 32.8, 36.9, 40.0, 46.8, 49.7, 56.5, 58.7, 59.2, 59.8, 80.2, 120.6, 123.1, 125.3, 130.2, 138.1, 148.1

^{19}F NMR (471 MHz, DMSO-d_6): δ = –57.8.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{30}F_3NO_3$: 424.2100; found: 424.2091.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-6,6-Dimethyl-3′-[(*R*)-1-(3-methylbenzyl)-1,2,3,6-tetrahydropyridin-2-yl]spiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (18c)

Column chromatography (silica gel, *n*-hexane/EtOAc, 2:1); R_f = 0.4; yield: 59 mg (73%); yellow oil; $[\alpha]_D^{20}$ +56 (*c* 0.137, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.32 (d, *J* = 10.4 Hz, 1 H, H-7), 1.79 (m, 1 H, H-4), 2.03 (m, 1 H, H-5), 2.19–2.24 (m, 2 H, H-1, H-3″), 2.33 (s, 3 H, CH_3), 2.34–2.43 (m, 3 H, H-4, H-3″, H-7), 2.48–2.52 (m, 1 H, H-2″), 2.92 (m, 1 H, H-6″), 3.24 (m, 1 H, H-6″), 3.47 (d, *J* = 8.5 Hz, 1 H, H-3′), 3.54 (d, *J* = 12.2 Hz, 1 H, NCH_2), 3.89 (d, *J* = 4.2 Hz, 1 H, H-2), 4.17 (d, *J* = 13.2 Hz, 1 H, NCH_2), 5.67–5.76 (m, 2 H, H-5″, H-4″), 7.03–7.04 (m, 1 H, ArH), 7.18 (d, *J* = 4.7 Hz, 2 H, ArH), 7.12 (s, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 22.7, 26.7, 27.0, 28.4, 32.9, 37.0, 40.0, 46.8, 49.8, 56.8, 59.5, 59.6, 59.8, 80.2, 123.0, 125.5, 126.2, 127.5, 127.9, 129.8, 137.6, 139.1.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{33}NO_2$: 354.2433; found: 354.2422.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-3′-[(*R*)-1-(3-Methoxybenzyl)-1,2,3,6-tetrahydropyridin-2-yl]-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (18d)

Column chromatography (silica gel, *n*-hexane/EtOAc 1:1); R_f = 0.6; yield: 48 mg (50%); yellow solid; mp 79–82 °C; $[\alpha]_D^{20}$ +48 (*c* 0.100, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.31 (d, *J* = 10.6 Hz, 1 H, H-7), 1.78 (m, 1 H, H-4), 2.03 (m, 1 H, H-5), 2.19 (m, 2 H, H-1, H-3″), 2.31–2.43 (m, 3 H, H-4, H-3″, H-7), 2.51 (m, 1 H, H-2″), 2.94 (m, 1 H, H-6″), 3.25 (m, 1 H, H-6″), 3.46 (d, *J* = 8.9 Hz, 1 H, H-3′), 3.59 (d, *J* = 13.3 Hz, 1 H, NCH_2), 3.79 (s, 3 H, CH_3), 3.88 (d, *J* = 3.9 Hz, 1 H, H-2), 4.16 (d, *J* = 13.4 Hz, 1 H, NCH_2), 5.67–5.76 (m, 2 H, H-5″, H-4″), 6.77 (m, 1 H, ArH), 6.97–6.99 (m, 2 H, ArH), 7.20 (t, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 26.7, 27.0, 28.4, 32.9, 37.0, 40.0, 46.8, 49.8, 55.2, 56.6, 59.4, 59.6, 59.7, 80.2, 112.4, 114.3, 121.4, 122.9, 125.5, 129.0, 141.0, 159.5.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{23}H_{33}NO_3$: 370.2382; found: 370.2370.

(1*R*,2*S*,3*S*,3′*S*,5*R*)-3′-{(*R*)-1-[3,5-bis(trifluoromethyl)benzyl]-1,2,3,6-tetrahydropyridin-2-yl}-6,6-dimethylspiro(bicyclo[3.1.1]heptane-3,2′-oxiran)-2-ol (18e)

Column chromatography (silica gel, *n*-hexane/EtOAc, 4:1); R_f = 0.75; yield: 16 mg (15%); yellow oil; $[\alpha]_D^{20}$ +44 (*c* 0.100, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.28–1.31 (m, 4 H, CH_3, H-7), 1.71 (m, 1 H, H-4), 2.02 (m, 1 H, H-5), 2.15–2.21 (m, 2 H, H-7, H-3″), 2.29 (m, 1 H, H-2″), 2.34–2.44 (m, 2 H, H-4, H-3″), 2.50 (m, 1 H, H-2″), 3.02 (m, 1 H, H-6″), 3.27+ (m, 1 H, H-6″), 3.45 (d, *J* = 9.3 Hz, 1 H, H-3′), 3.80 (d, *J*= 14.3 Hz, 1 H, NCH_2), 3.87 (d, *J* = 4.0 Hz, 1 H, H-2), 4.21 (d, *J* = 13.9 Hz, 1 H, NCH_2), 5.69–5.79 (m, 2 H, H-4″, H-5″), 7.74 (s, 1 H, ArH), 7.87 (s, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6, 26.7, 27.1, 28.3, 29.6, 32.8, 36.9, 40.0, 46.9, 49.9, 55.9, 58.6, 58.9, 59.8, 80.1, 120.9, 123.1, 124.9, 129.0, 121.5.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –62.7.

HRMS (ESI): *m*/*z* [M + 1]$^+$ for $C_{24}H_{29}F_6NO_2$: 476.2024; found: 476.2015.

Reaction of Benzaldehyde with Diethylzinc in the Presence of a Chiral Catalyst; General Procedure

A 1 M solution of Et_2Zn in *n*-hexane (3 mL, 3 mmol) was added to the catalyst (0.1 mmol) under an argon atmosphere at rt. The solution was stirred for 25 min at rt, and then benzaldehyde (1 mmol) was added. After stirring at rt for a further 20 h, the reaction mixture was quenched with saturated aq NH_4Cl solution (15 mL), and then 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 alcohol products obtained were purified by flash column chromatography (*n*-hexane/EtOAc, 4:1). The ee and absolute configuration of the resulting materials were determined (comparing with literature data) by chiral GC on a CHIRASIL-DEX CB column after O-acetylation in an AcO_2/DMPA/pyridine system.

Determination of Antiproliferative Properties

The human cancer cell lines isolated from cervical adenocarcinoma (HeLa and SiHa), breast cancer (MCF7 and MDA-MB-231), and ovarian cancer (A2780) were purchased from the European Collection of Cell Cultures (Salisbury, UK). The cells were maintained in Minimum Essential Medium (MEM) supplemented with fetal calf serum (10%), non-essential amino acids (1%) and penicillin-streptomycin (1%) at 37 °C in a humidified atmosphere containing 5% CO_2. All media and supplements for these experiments were obtained from Lonza Group Ltd. (Basel, Switzerland). The antiproliferative properties of the prepared compounds were determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay.[40] Briefly, cells were seeded into 96 well plates (5000 cells/well) and incubated with the tested compounds at 10 and 30 μM under cell-culturing conditions for 72 h. Then MTT solution (5 mg/mL) was added to each sample, which was then incubated for a further 4 h. The formazan crystals precipitated were dissolved in 100 μL dimethyl sulfoxide, and the absorbance was measured at 545 nm with a microplate reader (BMG Labtech, Ortenberg, Germany). Two independent experiments were performed with five wells for each one of the conditions. Cisplatin (Ebewe GmbH, Unterach, Austria), a clinically used anticancer agent, was used as a reference agent. Calculations were performed by means of the GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA, USA).

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719887.

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