Stereoselective Synthesis of 4-Substituted 4-Hydroxypiperidines via Epoxidation–Ring Opening of 4-Methylenepiperidines

Victoria A. McKay, Sarah J. Thompson, Phuong Minh Tran, Kirsten J. Goodall, Margaret A. Brimble, David Barker*

Department of Chemistry, The University of Auckland, 23 Symonds St, Auckland, New Zealand
Fax +64(9)3737422; E-mail: d.barker@auckland.ac.nz

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Abstract: Reaction of 9-methylene-3-azabicyclo[3.3.1]nonanes with trifluoroperacetic acid results in stereoselective epoxidation to give the *syn*-epoxide. Intermolecular hydrogen bonding between the protonated tertiary amine and the peracid is responsible for the high levels of stereoselectivity.

Key words: stereoselective epoxidation, homoallylic epoxidation, bicyclic amines, 4-hydroxypiperidines

4-Hydroxypiperidines are a common structural motif found in many bioactive drugs, such as the antidiarrhoeal loperamide (**1**), the schizophrenia medication haloperidol and benztropine (**2**), a drug used in the treatment of Parkinson's disease (Figure 1). Compounds with this motif have also recently been reported to act as histamine[1] and chemokine CCR5[2] receptor antagonists, to inhibit serine hydrolases[3] and to target opioid receptors.[4] 4-Hydroxypiperidines have also been used in the stereospecific synthesis of 4-phenyl- and 4-alkylpiperidines, where the configuration of the 4-hydroxy group is important in defining the stereochemistry in the desired nonhydroxy product.[5]

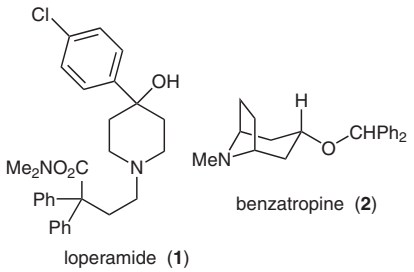
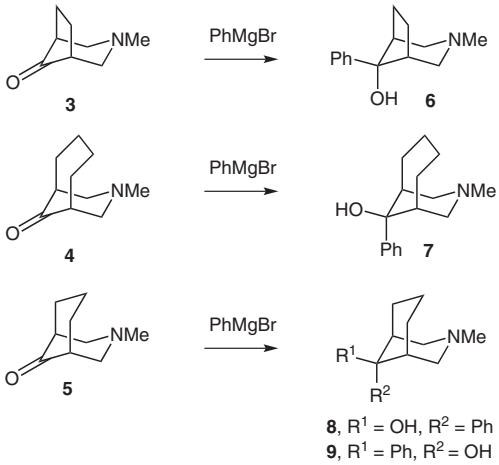


Figure 1 Drugs containing a 4-hydroxypiperidine motif

In general, 4-substituted 4-hydroxypiperidines are prepared from the nucleophilic addition of an organometallic reagent (e.g., a Grignard reagent) onto a 4-ketopiperidine (4-piperidone). Regardless of whether the 4-ketopiperidine is found in a mono- or bicyclic ring system, these additions invariably lead to mixtures of diastereomers being produced.[6] Additions to azabicyclic ketones **3**–**5** are known to be controlled by steric effects; thus piperidone **3**, with a fused five-membered ring, affords addition products **6** (example given using PhMgBr) with the 4-hydroxy group *syn* to the piperidine ring (Scheme 1).[7] Conversely piperidone **4**, with a fused seven-membered ring gives only *anti* products **7**. Piperidone **5**, however, with a fused six-membered ring, gives mixtures of both *syn*- and *anti*-alcohols **8** and **9** with the major isomer alcohol **8** resulting from attack over the less hindered face. We herein report a method for the stereoselective synthesis of 4-substituted 4-hydroxypiperidines via a stereoselective epoxidation–ring-opening protocol.



Scheme 1 Products from nucleophilic addition to bicyclic 4-piperidones[7]

The synthesis began by preparing substituted 4-piperidones via the Lewis acid catalysed double-Mannich reaction of benzyl bisaminol ether **10** with acylic[8] **11** and cyclic[9] **12**–**14** β-keto esters. Using 1.5 equivalents of both $MeSiCl_3$ and aminol ether **10** gave monocyclic piperidone **16** in 82% yield, whilst differently ring-sized azabicycles **17**, **18**, and **19** were generated in 81%, 97% and 99% yields, respectively (Scheme 2). These piperidones **16**–**19** then underwent Wittig olefination[10] using methyl triphenylphosphonium bromide to give 4-methylene piperidines **20**–**23** in 70–83% yields. It is noteworthy that the ^{1}H NMR showed the configuration of monocyclic alkene **20** to have an axial ester, the same as that found in the starting ketone **16**.[8]

We began our epoxidation study on 3-azabicyclo[3.3.1]nonane **22**, as this 6,6-ring system is found in a number of neurally active natural alkaloids[11] and keto derivates such as **18** are known to react nonspecifically with

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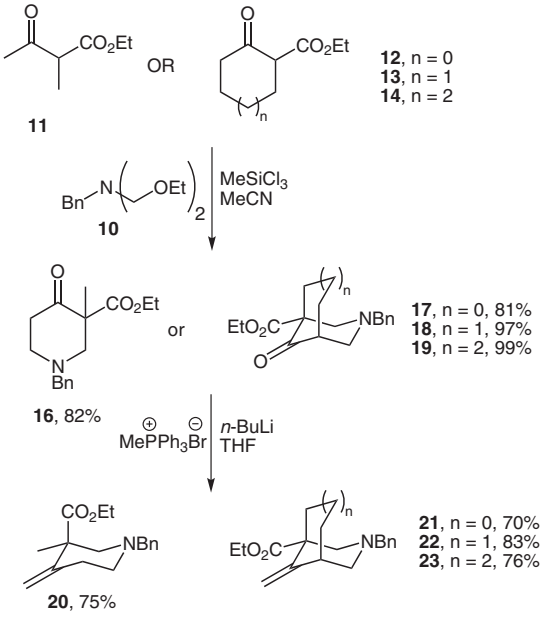
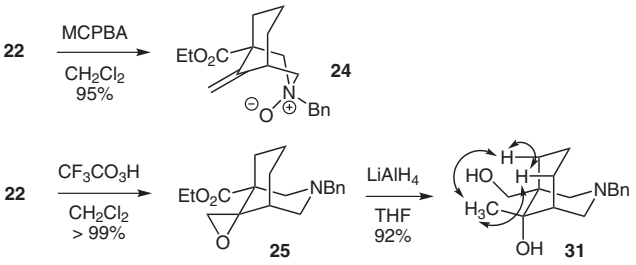
nucleophiles.[6,7] Firstly, the use of *meta*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 was attempted, and after one hour of reaction this resulted in exclusive formation of methylene *N*-oxide **24** in 95% yield. When *N*-oxide **24** was further reacted with additional MCPBA no epoxidation of the methylene group was observed, even after extended reaction times.[12]



Scheme 2 Synthesis of 4-methylenepiperidines

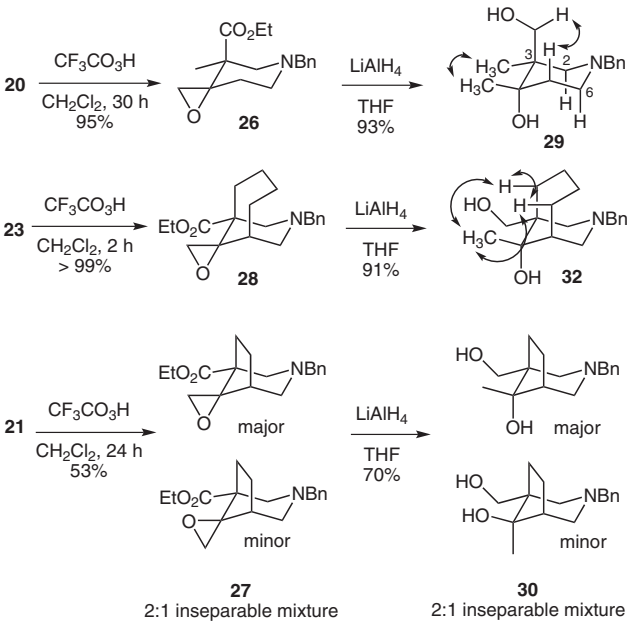
In an attempt to avoid this N-oxidation, the MCPBA reaction was repeated with the addition of trifluoroacetic acid (TFA), a reagent combination which has been previously used for alkene epoxidation in alkaloid systems.[13] Unfortunately, only a complex mixture of products was obtained. Replacing the TFA with AcOH or by using the preformed HCl salt of bicycle **22** produced a similar complex mixture. Quick et al.[14] reported similar results in their attempts to use MCPBA to oxidize an alkene within a quinolizidine, with either the *N*-oxide or mixtures being produced. They noted that the use of trifluoroperactic acid was successful in generating the desired epoxide. When the published conditions were used upon alkene **22**, a single epoxide product **25** was obtained in low yield with no signs of N-oxidation. Optimisation of the conditions using five equivalents of trifluoroperacetic acid in CH_2Cl_2 at 0 °C for two hours resulted in quantitative formation of epoxide **25** (Scheme 3).[15]

Epoxidation of alkene **23** occurred in a similar time frame as the reaction of **22**, giving a single epoxide product **28** again in quantitative yield (Scheme 4). The epoxidation of monocyclic alkene **20** gave a single epoxide **26** in 95% yield; however, the reaction required at least 30 hours to go to completion. Similarly, epoxidation of alkene **21** under the same conditions took 24 hours before the starting material was completely consumed but, in this case, gave an inseparable 2:1 mixture of epoxides **27** in 53% yield.[16]



Scheme 3 Peracid oxidation of alkene **22** and conversion of epoxide **25** to diol **31**, with key NOE correlations shown

Analysis of the ^{1}H NMR 2D NOESY spectra of epoxides **25**–**28** showed no interactions between the methylene group on the epoxide and protons elsewhere in the molecule. To determine the stereochemistry, it was therefore decided to open the epoxide ring to form a tertiary alcohol. In previous work on 9-alkyl-9-hydroxy-3-azabicyclo[3.3.1]nonanes we have observed strong NOE interactions between the 9-alkyl substituent and the protons in the bicyclic ring structure.[6a] The stereochemistry of the 9-hydroxy group can also be determined by examination of the ^{13}C NMR data. This is due to the γ-gauche effect the 9-OH has on the chemical shift of the carbons in the bicyclic ring structure that are *syn* to the hydroxy group.[17] Ring opening was effected by lithium aluminium hydride reduction of epoxides **25**–**28** to give diols **29**–**32** in 70–93% yield.

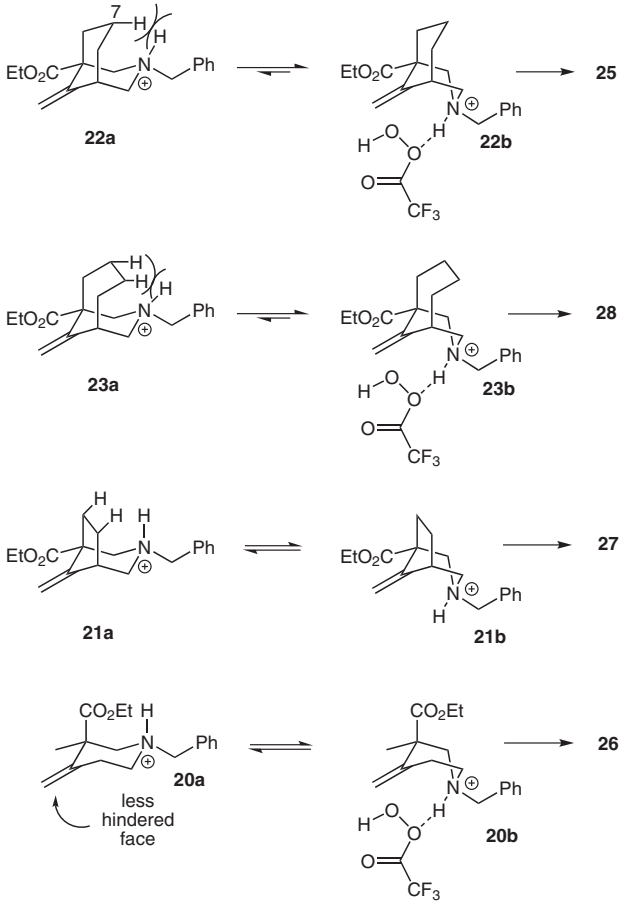


Scheme 4 Synthesis of epoxides **26**–**28** and diols **29**, **30**, and **32**, showing key NOE correlations used for stereochemical determination

Examination of the NMR spectra of diols **31** and **32** showed NOE interactions between the chiral methyl group and the spatially adjacent protons on the carbocyclic ring of the bicyclic system, confirming the orientation between the tertiary alcohol and amine to be *syn* (Schemes 3 and 4). The diastereomers of diol **30** were not

separable, however, NMR analysis again showed the major diastereomer to have the same *syn* orientation as diols **31** and **32**. The stereochemistry of piperidine diol **29** was determined by a combination of NMR experiments and by comparison with similar piperidine diols.[8] In the ^{1}H NMR 2D NOESY spectrum, strong NOE cross peaks were observed between the protons of 3-methylenehydroxy group and the axial H5 and also between the 3- and 4-methyl groups, whilst the downfield shift of the axial H2 and H6 protons showed their close spatial arrangement with the 4-OH group.

With the stereochemistry of alcohols **29**–**32** and therefore epoxides **25**–**28** determined, we were able to rationalise the stereoselective nature of the epoxidation. For the reaction of bicyclic alkene **22**, in which the epoxidation was fast and completely selective, we theorised that under the acidic conditions formation of an ammonium salt **22a** would ensue. Due to steric interaction between the now quaternary amine and the axial H7 of the salt **22a**, the preferred structure would change from the normal chair–chair[17] conformation to a chair–boat **22b** (Scheme 5).

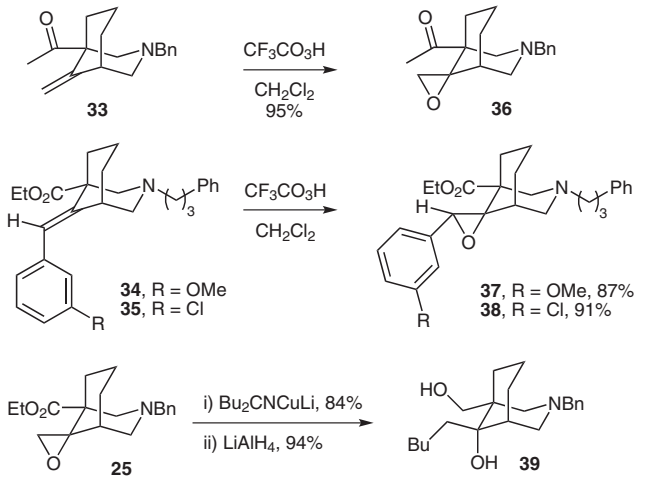


Scheme 5 Proposed ring conformations resulting in *syn*-epoxidation

In this conformation hydrogen bonding between the N–H and the peracid can occur, placing the reactive oxygen of the peracid in a favourable position directly above one face of the alkene. Under these circumstances we would expect epoxidation to be rapid and selective, exactly what was observed experimentally. Protonation of the amine in alkene **23** also results in unfavourable steric interactions between the quaternary amine **23a** and the protons on the carbocyclic ring. A chair-to-boat ring flip of the piperidine ring results in the similar conformation **23b** where the peracid is directed to one face of the alkene. In the case of alkene **21**, the protonated psuedo-chair in amine **21a** has far less steric interactions with the carbocyclic ring and would not be expected to undergo such a rapid ring flip to form a boat-shaped conformer **21b** as alkenes **22** and **23**. It would appear that ring flip does occur, however, slowly, as the predominant epoxide is *syn* to the nitrogen in the piperidine ring. The slow reaction may, however, allow epoxidation to occur from the carbocyclic face.

In the case of monocyclic piperidine alkene **20** epoxidation could occur by a hydrogen bonded mechanism or steric interactions only, with the axial ester group blocking the bottom face of the alkene. Either case results in the same product, as a ring flip from chair **20a** to boat **20b** would also favour the attack from the face opposite the ester.

To explore the selectivity of the epoxidation further, we attempted the reaction on keto alkene **33**, where Baeyer–Villiger oxidation is a competing process, as well as styrenes[18] **34** and **35** (Scheme 6). In all cases the reaction was rapid and, again, completely selective, giving *syn*-epoxides **36**–**38** in 87–95% yields.[19] In a preliminary exploration of the utility of theses epoxides in the synthesis of other 4-hydroxy 4-substituted piperidines, epoxide **25** was reacted specifically at the epoxide with lithium dibutylcyanocuprate to afford a tertiary alcohol-ester (Scheme 6), which was reduced to give diol **39** in 79% overall yield over the two steps.[20]



Scheme 6 Synthesis of epoxides **36**–**38** and diol **39**

In summary, the epoxidation of 4-methylenepiperidines in constrained systems with trifluoroperacetic acid is stereoselective, allowing access to 4-substituted 4-hydroxypiperidines in a stereodefined manner. In particular, azabicyclic ketones of the types **4** and **5** can be converted into

4-hydroxypiperidines with opposite stereochemistry to that given by nucleophilic addition to the ketone itself.

Acknowledgment

We wish to thank the University of Auckland, in particular Staff Research Fund (#3607881), for financial assistance with the project.

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(12) After a 48 h reaction >80% *N*-oxide **24** was returned with the remaining material being unidentified decomposition products.
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(15) **General Procedure for the Epoxidation of 4-Methylenepiperidines**
Trifluoroacetic anhydride (6 equiv) was added dropwise to a stirred solution of 30% w/w H_2O_2 (5 equiv) in CH_2Cl_2 (1 mL/mmol alkene) at 0 °C. The solution was stirred for 1 h prior to the dropwise addition of a solution of 4-methylenepiperidine (1 equiv) in CH_2Cl_2 (1 mL/mmol alkene). The mixture was allowed to warm to r.t. and stirred for a further 4 h. The reaction was then quenched by careful additon of sat. aq $NaHCO_3$ and stirred until cessation of bubbles occurred. The volatiles were then removed in vacuo and the resultant aqueous solution extracted with EtOAc (2 × 20 mL). The combined organic phase were washed with sat. aq $NaHCO_3$, H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to afford the crude product, which was purified by flash chromatography.
Synthesis of Alcohol 39 from Epoxide 25
n-BuLi (1.6 M in hexanes, 0.6 mL, 0.95mmol) was added dropwise to a suspension of copper cyanide (43 mg, 0.48 mmol) in THF (0.5 mL) at –78 °C. The suspension was allowed to warm to 0 °C and stirred for 30 min, cooled to –78 °C followed by dropwise addition of epoxide **25** in THF (0.5 mL). The solution was stirred for a further 15 min and quenched with a 9:1 mixture of sat. aq NH_4Cl and aq NH_4OH and concentrated in vacuo. The residue was dissolved in EtOAc, washed with sat. aq NH_4Cl, H_2O and brine, then dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (5:1, hexanes–EtOAc; R_f = 0.7) to afford an alcohol (0.38 g, 89%) which was reduced with $LiAlH_4$ (58 mg, 2.2 mmol) in THF (2 mL) at 0 °C. After stirring for 15 min the reaction, was quenched with sat. aq Na_2SO_4 and filtered through Celite and the solvent removed in vacuo. The residue was dissolved in EtOAc, washed with H_2O and brine, then dried ($MgSO_4$) and concentrated in vacuo to yield crude product which was purified by flash chromatography (5:1, hexanes–EtOAc; R_f = 0.2) to give diol **39** (0.3g, 92%).
(16) **Spectroscopic Data for Selected Products**
Ethyl (1*R,2′*S**,5*R**)-3-Benzyl-3-azaspiro[bicyclo-[3.3.1]nonane-9,2′-oxirane]-1-carboxylate (25)**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.26–1.31 (1 H, m, 5-H), 1.56–1.64 (1 H, m, 7_A-H), 1.77–2.01 (3 H, m, 8_A-H, 6-CH_2), 2.24 (1 H, ddt, *J* = 13.5, 6.6, 2.1 Hz, 8_B-H), 2.51 (1 H, d, *J* = 3.0 Hz, 4_A-H), 2.55 (1 H, d, *J* = 4.8 Hz, $2'_A$-H), 2.87 (3 H, m, 7_B-H, 2_A-H, 4_B-H), 3.05 (1 H, d, *J* = 11.7 Hz, 2_B-H), 3.18 (1 H, d, *J* = 4.8 Hz, $2'_B$-H), 3.43 (1 H, d, *J* = 13.5 Hz, $PhCH_A$), 3.53 (1 H, d, *J* = 13.5 Hz, $PhCH_B$), 4.06 (2 H, dq, *J* = 7.2, 1.5 Hz, OCH_2CH_3), 7.23–7.35 (5 H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 21.0 (C-7), 31.1 (C-6), 34.8 (C-8), 38.5 (C-5), 46.9 (C-1), 52.91 (C-2′), 56.3 (C-4), 58.5 (C-2), 60.7 (OCH_2CH_3), 62.2 (C-9), 63.3 ($PhCH_2$), 126.8 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 138.4 (ArC), 172.5 (C=O). ESI-MS: *m/z* (%) = 316 (100) [M^+], 338 (20) [MNa^+]. MS: *m/z* calcd for $C_{19}H_{26}NO_3$: 316.1907 [$M]^+$; found: 316.1912.
Ethyl (1*R,2′*S**,6*R**)-8-Benzyl-8-azaspiro[bicyclo-[4.3.1]decane-10,2′-oxirane]-1-carboxylate (28)**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.41–1.51 (1 H, m, 6-H, 6-CH_2), 1.56–1.77 (5 H, m, 2_A-H, 5-H_2, 3-CH_2), 1.92–2.16 (3 H, m, 4-CH_2, 2_B-H), 2.47 (2 H, dd, *J* = 11.1, 4.5 Hz, 7_A-H), 2.52 (1 H, d, *J* = 4.8 Hz, $2'_A$-H), 2.64 (1 H, td, *J* = 12.0, 0.9 Hz, 7_B-H), 2.71 (2 H, m, 9-CH_2), 3.31 (1 H, d, *J* = 4.8 Hz, $2'_B$-H), 3.53 (2 H, s, $PhCH_2$), 4.06 (2 H, q, *J* = 7.2 Hz, OCH_2CH_3), 7.25–7.38 (5 H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 26.4 (C-5), 26.5 (C-4), 33.0 (C-3), 35.8 (C-2), 42.2 (C-6), 50.1 (C-1), 51.6 (C-2′), 57.8 (C-7), 58.7 (C-10), 60.4 (C-9), 60.6 (OCH_2CH_3), 63.5 ($PhCH_2$), 127.0 (ArCH), 128.2 (ArCH), 129.1 (ArCH), 138.9 (ArC), 173.6 (C=O). ESI-MS: *m/z* (%) = 330 (100) [M^+], 352 (22) [MNa^+]. MS: *m/z* calcd for $C_{20}H_{27}NO_3$: 330.2064 [M^+]; found 330.2074.

(1*S,5*R**,9*S**)-3-Benzyl-1-(hydroxymethyl)-9-methyl-3-azabicyclo[3.3.1]nonan-9-ol (29)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.32 (1 H, m, 7_A-H), 1.35 (3 H, s, 9-CH_3) 1.42–1.58 (3 H, m, 6-CH_2, 8_A-H), 1.67–1.79 (2 H, m, 5-H, 8_B-H), 2.30–2.47 (3 H, m, 2_A-H, 4_A-H, 7_B-H), 2.93 (1 H, dd, *J* = 10.8, 2.4 Hz, 4_B-H), 3.10–3.18 (3 H, m, C*H*$_A$OH, 2_B-H, OH), 3.41 (1 H, d, *J* = 13.2 Hz, PhC*H*$_A$), 3.58 (1 H, d, *J* = 13.2 Hz, PhC*H*$_B$), 3.80 (1 H, d, *J* = 11.1, 2.4 Hz, C*H*$_B$OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 (C-6), 22.1 (C9-*C*H_3), 28.3 (C-8), 32.0 (C-7), 39.0 (C-1), 41.4 (C-5), 54.2 (C-4), 57.1 (C-2), 62.8 (Ph*C*H_2), 70.0 (CH_2OH), 74.0 (C-9), 127.0 (ArCH), 128.3 (ArCH), 128.7 (ArCH), 138.7 (ArC). ESI-MS: *m/z* (%) = 276 (100) [MH^+]. MS: *m/z* calcd for $C_{17}H_{26}NO_2$: 276.1958 [MH^+]; found: 276.1941.

(1*S,6*R**,10*S**)-8-Benzyl-1-(hydroxymethyl)-10-methyl-8-azabicyclo[4.3.1]decan-10-ol (32)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.60 (7 H, m, 6-H, 5-CH_2, 4-CH_2, 3-CH_2), 1.42 (3 H, s, 10-CH_3) 2.08–2.15 (2 H, m, 2-CH_2), 2.24 (1 H, dd, *J* = 11.1, 1.0 Hz, 9_A-H), 2.42 (1 H, dd, *J* = 11.4, 1.0 Hz, 7_A-H), 2.78 (1 H, dd, *J* = 11.4, 6.3 Hz, 7_B-H), 3.16–3.24 (3 H, m, C*H*$_A$OH, 9_B-H, OH), 3.39 (1 H, d, *J* = 13.2 Hz, PhC*H*$_A$), 3.56 (1 H, d, *J* = 13.2 Hz, PhC*H*$_B$), 3.89 (1 H, d, *J* = 11.1, 2.4 Hz, C*H*$_B$OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.16 (C10-*C*H_3), 25.2, 25.3, 29.6, and 35.5 (C-2, C-3, C-4, C-5), 44.1 (C-1), 46.3 (C-6), 56.5 (C-7), 59.0 (C-9) 63.3 (Ph*C*H_2), 70.3 (CH_2OH), 77.9 (C-10), 127.0 (ArCH), 128.2 (ArCH), 128.9 (ArCH), 138.7 (ArC). ESI-MS: *m/z* (%) = 290 (100) [MH^+], 272 (5) [M – OH]. MS: *m/z* calcd for $C_{18}H_{28}NO_2$: 290.2115 [MH^+]; found: 290.2105.

1-{(1*R,2'*S**,5*R**)-3-Benzyl-3-azaspiro[bicyclo-[3.3.1]nonane-9,2'-oxirane]-1-yl}ethanone (36)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.29 (1 H, m, 5-H), 1.62 (1 H, m, 7_A-H), 1.74–1.83 (2 H, m, 8_A-H, 6_A-H), 1.92 (1 H, m, 6_B-H), 2.09 (3 H, s, O=CCH_3), 2.18 (1 H, m, 8_B-H), 2.54 (1 H, d, *J* = 4.2 Hz, $2'_A$-H), 2.63 (1 H, m, 4_B-H), 2.69 (1 H, d, *J* = 4.2 Hz, $2'_B$-H), 2.83 (1 H, m 7_B-H), 2.90 (1 H, d, *J* = 11.4 Hz, 4_B-H), 2.94–3.00 (2 H, m, 2-CH_2), 3.50 (2 H, s, Ph*C*H_2), 7.23–7.34 (5 H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (C-7), 29.5 (O=C*C*H_3), 31.1 (C-6), 33.1 (C-8), 38.6 (C-5), 51.1 (C-1), 52.3 (C-2′), 56.6 (C-4), 59.2 (C-2), 62.7 (C-9), 63.5 (Ph*C*H_2), 127.0 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 138.7 (ArC), 209.9 (C=O). ESI-MS: *m/z* (%) = 285 (100) [M^+]. MS: *m/z* calcd for $C_{18}H_{23}NO_2$: 285.1728 [M^+]; found: 285.1728.

(1*S,5*R**,9*S**)-3-Benzyl-1-(hydroxymethyl)-9-pentyl-3-azabicyclo[3.3.1]nonan-9-ol (39)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86–0.94 [4 H, m, $(CH_2)_4CH_3$, $CH_2CH_A(CH_2)_2CH_3$), 1.15–1.60 [10 H, m, 6-CH_2, 8_A-H, $CH_2(CH_2)_3CH_3$, $CH_2CH_B(CH_2)_2CH_3$, $(CH_2)_2CH_2CH_2CH_3$, $(CH_2)_3CH_2CH_3$], 1.81–1.90 (2 H, m, 5-H, 8_B-H), 2.34 (1 H, d, *J* = 10.8 Hz, C*H*$_A$OH), 2.36–2.52 (3 H, m, 4_A-H, 7_A-H, OH), 2.50 (1 H, dd, *J* = 11.0 Hz, 2_A-H), 2.85 (1 H, dd, *J* = 11.4, 2.1 Hz, 4_B-H), 3.04 (1 H, d, *J* = 10.8 Hz, C*H*$_B$OH), 3.12 (1 H, dd, *J* = 11.4, 2.1 Hz 2_B-H), 3.38 (1 H, d, *J* = 13.2, PhC*H*$_A$), 3.54 (1 H, d, *J* = 13.2 Hz, PhC*H*$_B$), 7.19–7.28 (5 H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 [$(CH_2)_4CH_3$], 18.7 (C-7), 21.5 [$CH_2(CH_2)_3CH_3$], 22.7 [$CH_2CH_2(CH_2)_2CH_3$], 27.8 (C-6), 31.7 [$(CH_2)_2CH_2CH_2CH_3$], 32.5 [$(CH_2)_3CH_2CH_3$], 32.5 (C-8), 35.9 (C-5), 40.9 (C-1), 54.3 (C-4), 57.3 (C-2), 62.9 (Ph*C*H_2), 69.4 (CH_2OH), 76.0 (C-9), 126.8 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 139.0 (ArC). ESI-MS: *m/z* (%) = 332 (100) [MH^+]. MS: *m/z* calcd for $C_{21}H_{34}NO_2$: 332.2584 [MH^+]; found: 332.2590.

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(19) The stereochemistry was again determined by analysis of the ring-opened tertiary alcohols.

(20) Diols such as **29**, **32**, and **39** can be esterified selectively in high yields at the primary alcohol.