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Convergent and Selective Synthesis of Pyrrolidinones, Piperidinones, Dihydropyridinones and Pyridinols from a Common Intermediate – Potential Precursors of Bioactive Products

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Dedicated to Oleg Kulinkovich on the occasion of his 60th birthday

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Titanium-mediated cyclopropanation of natural and unnatural β-amino acid derivatives provides azabicyclo[3.1.0]hexan-1-ols as mixtures of diastereomers that are separable by silica-gel chromatography. Depending on the ring cleavage procedure employed, these compounds lead efficiently to diverse intermediates for the synthesis of pharmaceuticals. Thus, depending on the experimental conditions, basic treatment can furnish racemic pyrrolidinones as a mixture of diastereomers and piperidinones. In contrast, the synthesis of optically active dihydropyridinones was achieved through a one-pot $FeCl_3$/AcONa reaction or performed by using bis(*sym*-collidine)iodine hexafluorophosphate. Furthermore, whereas the palladium-mediated hydrogenolysis of these dihydropyridinones furnished both chiral piperidinones and original pyridinols, a Ce^{IV}-promoted radical process yielded chiral tricyclic piperidinones.

Introduction

The synthesis of a large number of bioactive products or intermediates for pharmacologically important compounds containing an N-heterocycle in their structure constantly requires new methodologies, combining both high performance reactions and efficient protocols. Recently, we reported that azabicyclo[3.1.0]hexan-1-ols **1a**–**f** constitute particularly interesting building blocks for the preparation of dihydropyridinones, piperidinones and pyrrolidinones, potentially endowed with wide-ranging biological properties.[1] Indeed, as depicted in Figure 1, whereas azabicyclo[3.1.0]-hexan-1-ol **1f** (R = Ph) has been used as a precursor for the synthesis of NK1 antagonist **A**,[2] enone **2**,[3] for example, could give dihydropyridinone **B**, an inhibitor of χ-secretase.[4] Likewise, piperidone C, a useful intermediate in the synthesis of compounds that possess pharmacological activity,[5] possibly elaborated from dihydropyridinone **2f**, or

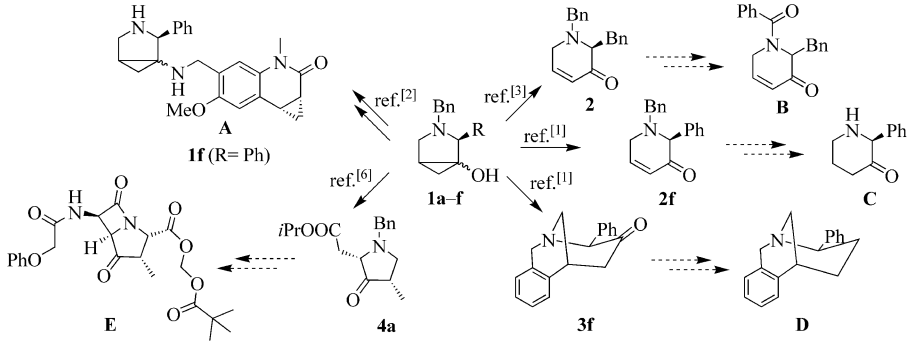

Figure 1. Azabicyclo[3.1.0]hexan-1-ols: possible applications in the synthesis of bioactive products.

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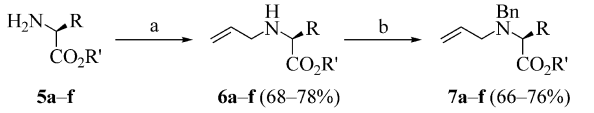
azocine **D**, an inhibitor of biogenic amine transporters,[6] may be accessible from piperidinone **3f** and pyrrolidinone **4a**[7] is a potential precursor of carbapen **E**.[8] Intermediates **2**, **2f**, **3f** and **4a** were obtained from common precursors **1**

(R = benzyl, phenyl, $CH_2COOiPr$, respectively) by applying carefully selected reaction conditions. These protocols represent a powerful and versatile application in the synthesis of amino acid derivatives.

Results and Discussion

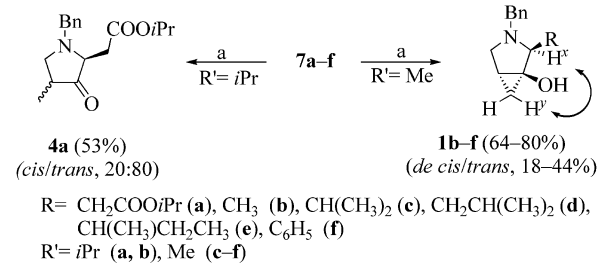
Synthesis of Azabicyclo[3.1.0]hexan-1-ols

Starting compounds **1a**–**f** were readily prepared from commercially available amino esters **5a**–**f** or after esterification of the corresponding amino acids [aspartic acid (**a**), alanine (**b**), valine (**c**), leucine (**d**), isoleucine (**e**), phenylglycine (**f**)]. After *N*-allylation,[9] esters **6a**–**f** were benzylated[10] to furnish expected diprotected amines **7a**–**f** (Scheme 1). Inversion of the order of the allylation and benzylation steps, under the same conditions, gave amino esters **7a**–**f** in lower or comparable yields.



Scheme 1. (a) Allyl bromide, $Li(OH)\cdot H_2O$, MS 4 Å, DMF, 20 °C; (b) benzyl bromide, K_2CO_3, DMF, 20 °C.

ω-Alkenoic esters **7a**–**f** underwent an intramolecular Kulinkovich reaction[11] to afford the required azabicyclo[3.1.0]-hexan-1-ols **1b**–**f**. An exception occurred in the case of the aspartic acid derivative, where a further spontaneous ring opening took place to give pyrrolidinone **4a** as an inseparable mixture of diastereomers[7] (Scheme 2).



Scheme 2. (a) $Ti(OiPr)_4$ (0.1 equiv.), *i*PrMgBr (5 equiv.), THF/Et_2O, 20 °C.

In most cases, the chiral bicyclic cyclopropanols were sufficiently pure to be engaged in further reactions. However, most diastereomers could be separated chromatographically on silica gel to be characterized individually. The relative *cis* and *trans* configurations of each diastereomer **1b**–**f** were assigned by observation of a nOe effect between the H^x and H^y hydrogens in the *cis* isomers and confirmed by X-ray crystal structure analysis for compounds *trans*-**1d** and *cis*-**1e**, respectively (Figure 2).

Synthesis of Racemic Pyrrolidinones and Piperidinones

Surprisingly, azabicyclo[3.1.0]hexan-1-ols **1b**–**f** were very resistant to treatment with harsh acidic conditions (HCl, MeOH, 12 h, reflux). In contrast, in accordance with the previous observations reported by Patel *et al.*[12] concerning ring opening of fused bicyclo[3.1.0]hexanols, treatment of azabicyclo[3.1.0]hexan-1-ols **1b**–**f** with potassium hydroxide in refluxing methanol led rapidly to a chromatographically separable mixture of pyrrolidinones **4b**–**f** and piperidinones **8b**–**f** (Scheme 3). The base-mediated cleavage of the cyclopropane moiety of these heterocycles (by fragmentation paths *x* or *y*) took place with racemization, as, for example, an inseparable mixture of four diastereomers was observed in the case of isoleucine derivative **4d**. Likewise, piperidinones **8b**–**f** presented no optical activity, probably as a result of base-promoted epimerization.

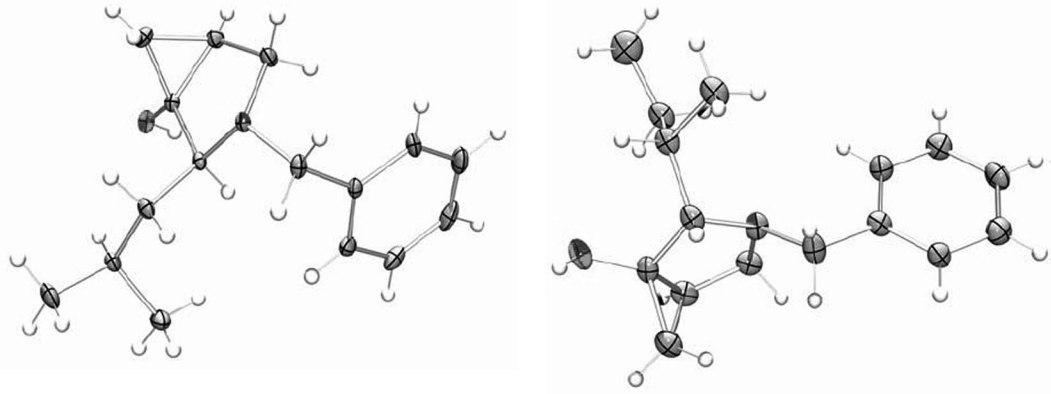
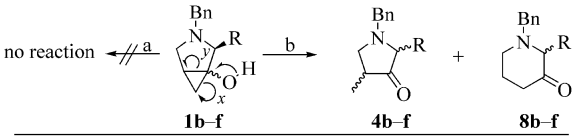


Figure 2. ORTEP plot of X-ray crystal structure of *trans*-**1d** and *cis*-**1e**.



1b–f **4b–f** **8b–f**

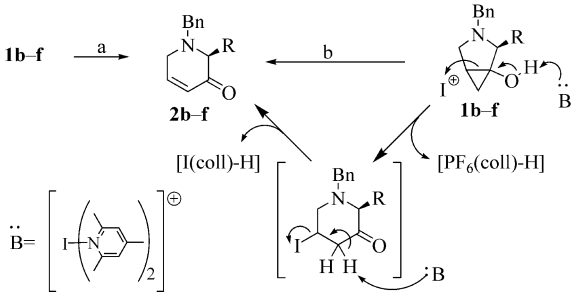
	R	Yield [%]	Ratio (*cis*/*trans*)	
b	CH_3	76	72 (24:76)	28
c	$CH(CH_3)_2$	89	61 (20:80)	39
d	$CH_2CH(CH_3)_2$	83	66 (18:82)	34
e	$CH(CH_3)CH_2CH_3$	86	63[a]	37[b]
f	C_6H_5	92	75 (24:76)	25

[a] A mixture of four inseparable and unattributed diastereomers in a 47:27:18:8 ratio. [b] A 50:50 mixture of diastereomers.

Scheme 3. (a) 2.4 M HCl in MeOH, 80 °C, 12 h; (b) KOH (2.5 equiv.), MeOH, 80 °C, 10 min.

Synthesis of Chiral Dihydropyridinones

The two-step ferric chloride/sodium acetate procedure, used for the first time by Saegusa[13] in the synthesis of cyclohexenones from bicyclo[3.1.0]hexan-1-ol, was also successfully applied in the synthesis of dihydropyridinone **2**.[14] We achieved the ring cleavage–dehydrochlorination steps in a one-pot reaction without isolation of the β-chloro ketone intermediate, while preserving the integrity of the stereogenic carbon centre. Treatment of **1b–f** with the basic and electrophilic bis(*sym*-collidine)bromine hexafluorophosphate, which is known to oxidize primary, secondary and even *p*-methoxybenzyl alcohols,[15] was ineffective. However, we were delighted to find that treatment with the ambiphilic iodo parent bis(*sym*-collidine)IPF_6[16] in dichloromethane afforded chiral dihydropyridinones **2b–f** directly according to an addition–elimination process as depicted in Scheme 4.



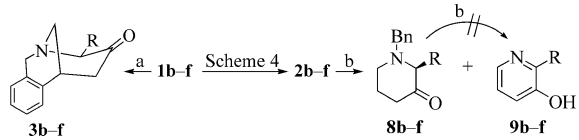
	R	Yield [%]	
		Procedure a	Procedure b
b	CH_3	76	73
c	R =$CH(CH_3)_2$	89	71
d	R =$CH_2CH(CH_3)_2$	83	78
e	R =$CH(CH_3)CH_2CH_3$	86	72
f	R =C_6H_5	92	40[a]

[a] Plus 37% of unexpected product **4f**.

Scheme 4. (a) $FeCl_3$, Et_2O, 0 °C, 3 h, then AcONa, MeOH, 20 °C; (b) bis(*sym*-collidine)IPF_6, CH_2Cl_2, 20 °C.

Synthesis of Chiral Piperidinones and Pyridinols

The oxidation of cyclopropanols **1b–f** was accomplished by using cerium ammonium nitrate to furnish chiral tricyclic piperidinones **3b–f** by an internal radical process as previously reported.[1] Hydrogenation of chiral dihydropyridinones **2b–f** was performed by using palladium hydroxide as a catalyst and was monitored by TLC until complete disappearance of the starting material was observed. After 20 h, a separable mixture of chiral piperidinones **8b–f** was obtained as the major products arising from chemoselective double bond reduction. Pyridinols **9b–f** resulting from a monodebenzylation–aromatization process were also obtained (Scheme 5). This formation of these latter products is unprecedented. Furthermore, exposure of piperidinones **8b–f** to the same reaction conditions [H_2, cat. $Pd(OH)_2/C$] left these materials unchanged; no trace of pyridinols **9b–f** was detected.



3b–f **8b–f** **9b–f**

	R	Yield [%]	Ratio (**8b–f**/**9b–f**)	
b	CH_3	74	81	19
c	$CH(CH_3)_2$	76	63	37
d	$CH_2CH(CH_3)_2$	83	70	30
e	$CH(CH_3)CH_2CH_3$	82	65	35
f	C_6H_5	84	81	19

Scheme 5. (a) CAN, CH_3CN/H_2O (4:1), 0 °C, 30 min; (b) H_2, 20% $Pd(OH)_2/C$, AcOEt, 20 °C.

Conclusions

We have presented the concise preparation and some new applications of azabicyclo[3.1.0]hexan-1-ols. These compounds constitute very efficient intermediates for the synthesis of bioactive products involving readily available starting materials and inexpensive reagents, and the methodology of the sequence is quite simple.

Experimental Section

General Remarks: Melting points (uncorrected) were determined with a Büchi B-545 apparatus. Polarimetric measurements were performed with a Perkin–Elmer 241 polarimeter. FTIR spectra were recorded with a Perkin–Elmer spectrophotometer (Spectrum One). ^1H NMR spectra were measured with a Bruker DPX 250 (250 MHz), AV 360 (360 MHz) or AM 300 (300 MHz) spectrometer and $CHCl_3$ (δ = 7.27 ppm) was used as an internal standard. ^{13}C NMR were measured with a Bruker DPX 250 (62.9 MHz), AV 360 (90.6 MHz) or AM 300 (75.5 MHz) spectrometer and chemical shifts are reported relative to the resonance of the solvent ($CDCl_3$; δ = 77 ppm). The DEPT-135 pulse was used for the determination of signal types. MS (electronic impact or chemical ionization) was recorded with a Nermag R-10 instrument coupled with a OK1 DP 125 gas chromatographer. Relative percentages are shown in brackets. High-resolution mass spectra were recorded with a Finningan MAT 95S (electronic impact or electrospray). Elemental analyses were performed with a Perkin–Elmer 240C analyzer by the Service of Microanalyse, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette (France). Solvents were dried according to standard pro-

cedures. All reactions requiring anhydrous conditions were performed under an atmosphere of argon.

General Procedure for the *N*-Allylation Reaction: Molecular sieves (4 Å, 15 g), lithium hydroxide monohydrate (2.54 g, 58.4 mmol) and allylbromide (2.75 mL, 58.4 mmol) were successively added under an atmosphere of argon at 20 °C to a solution of the hydrochloride salts of methyl or isopropyl amino esters **5a**–**f** (26.5 mmol) in DMF (70 mL). After stirring for 12 h, the mixture was diluted with diethyl ether (80 mL) and quenched by the addition of H_2O (35 mL). The mixture was then filtered through Celite, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried with magnesium sulfate and concentrated. The crude residue was purified by flash chromatography on silica gel (dichloromethane/diethyl ether, 85:15) to afford *N*-allyl amino esters **6a**–**f**.

Diisopropyl *N*-Allyl-L-aspartate (6a): Yellow oil. Yield: 68%. $[\alpha]_D^{20}$ = –18 (c = 2, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.90–5.80 (m, 1 H), 5.30–5.00 (m, 4 H), 3.60 (t, ^3J = 6.8 Hz, 1 H), 3.34 (dd, ^2J = 13.7 Hz, ^3J = 6.1 Hz, 1 H), 3.19 (dd, ^2J = 13.7 Hz, ^3J = 6.1 Hz, 1 H), 2.70 (dd, ^2J = 15.8 Hz, ^3J = 6.8 Hz, 1 H), 2.60 (dd, ^2J = 15.8 Hz, ^3J = 6.8 Hz, 1 H), 1.85 (br. s, 1 H), 1.26 (d, ^3J = 6.1 Hz, 6 H), 1.23 (d, ^3J = 6.1 Hz, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.1, 170.3, 136.2, 116.4, 68.6, 68.1, 57.0, 50.6, 38.5, 21.8 ppm. IR (neat): $\tilde{\nu}$ = 3339, 2981, 2937, 1732, 1644 cm^{-1}. MS (EI): *m*/*z* (%) = 257 (3) $[M]^{+\cdot}$, 170 (100), 156 (29), 114 (17), 68 (31), 56 (26), 43 (20), 41 (24). HRMS (ESI+): calcd. for $C_{13}H_{23}NO_4Na$ 280.15190; found 280.15275.

Isopropyl *N*-Allyl-L-alaninate (6b): Yellow oil. Yield: 72%. $[\alpha]_D^{20}$ = –47 (c = 1, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.93–5.82 (m, 1 H), 5.20 (dd, ^3J = 17.3 Hz, ^2J = 1.4 Hz, 1 H), 5.15 (dd, ^3J = 10.3 Hz, ^2J = 1.4 Hz, 1 H), 5.15–5.03 (m, 1 H), 3.31 (q, ^3J = 7.0 Hz, 1 H), 3.27 (dd, ^2J = 13.7 Hz, ^3J = 6.1 Hz, 1 H), 3.15 (dd, ^2J = 13.7 Hz, ^3J = 6.1 Hz, 1 H), 1.62 (br. s, 1 H), 1.31 (d, ^3J = 6.2 Hz, 3 H), 1.30 (d, ^3J = 7.0 Hz, 3 H), 1.28 (d, ^3J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 174.9, 136.2, 116.0, 67.7, 55.7, 50.3, 21.7, 21.6, 18.9 ppm. IR (neat): $\tilde{\nu}$ = 3334, 3079, 2980, 2936, 1730, 1644 cm^{-1}. MS (EI): *m*/*z* (%) = 171 (2) $[M]^{+\cdot}$, 84 (100), 41 (25). HRMS (ESI+): calcd. for $C_9H_{17}NO_2Na$ 194.11520; found 194.11472.

Methyl *N*-Allyl-L-valinate (6c): Colourless liquid. Yield: 71%. $[\alpha]_D^{20}$ = –74 (c = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.83–5.70 (m, 1 H), 5.11 (dd, ^3J = 17.3 Hz, ^2J = 1.7 Hz, 1 H), 5.01 (dd, ^3J = 10.2 Hz, ^2J = 1.7 Hz, 1 H), 3.67 (s, 3 H), 3.21 (dd, ^2J = 13.7 Hz, ^3J = 5.8 Hz, 1 H), 2.99 (dd, ^2J = 13.7 Hz, ^3J = 5.8 Hz, 1 H), 2.96 (d, ^3J = 6.0 Hz, 1 H), 1.97–1.80 (m, 1 H), 1.68 (br. s, 1 H), 0.88 (d, ^3J = 6.8 Hz, 3 H), 0.87 (d, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 175.6, 136.6, 116.1, 66.3, 51.3, 51.2, 31.6, 19.1, 18.6 ppm. IR (neat): $\tilde{\nu}$ = 3334, 3080, 2980, 2962, 1736, 1644 cm^{-1}. MS (EI): *m*/*z* (%) = 171 (2) $[M]^{+\cdot}$, 127 (55), 112 (100), 70 (12), 67 (36), 56 (23), 41 (57). $C_9H_{17}NO_2$ (171.24): calcd. C 63.13, H 10.01, N 8.18; found C 62.76, H 9.95, N 8.06.

Methyl *N*-Allyl-L-leucinate (6d): Colourless liquid. Yield: 75%. $[\alpha]_D^{20}$ = –48 (c = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.96–5.80 (m, 1 H), 5.20 (dd, ^3J = 17.2 Hz, ^2J = 1.7 Hz, 1 H), 5.11 (dd, ^3J = 10.3 Hz, ^2J = 1.7 Hz, 1 H), 3.75 (s, 3 H), 3.33 (t, ^3J = 7.2 Hz, 1 H), 3.26 (dd, ^2J = 13.5 Hz, ^3J = 6.3 Hz, 1 H), 3.11 (dd, ^2J = 13.5 Hz, ^3J = 6.3 Hz, 1 H), 1.77–1.69 (m, 1 H), 1.68 (br. s, 1 H), 1.52–1.46 (m, 2 H), 0.95 (d, ^3J = 6.3 Hz, 3 H), 0.92 (d, ^3J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 176.3, 136.3, 116.1, 58.9, 51.4, 50.7, 42.8, 24.8, 22.6, 22.2 ppm. IR (neat): $\tilde{\nu}$ = 3336, 3079, 2956, 2870, 1738, 1644 cm^{-1}. MS (EI): *m*/*z* (%) = 185 (5) $[M]^{+\cdot}$, 128 (12), 126 (100), 84 (10), 70 (26), 56 (13), 41 (30). $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.61, H 10.11, N 7.41.

Methyl *N*-Allyl-L-isoleucinate (6e): Colourless liquid. Yield: 68%. $[\alpha]_D^{20}$ = –15 (c = 1, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.90–5.80 (m, 1 H), 5.27 (dd, ^3J = 16.9 Hz, ^2J = 1.4 Hz, 1 H), 5.18 (dd, ^3J = 10.2 Hz, ^2J = 1.4 Hz, 1 H), 3.73 (s, 3 H), 3.27 (dd, ^2J = 14.0 Hz, ^3J = 6.1 Hz, 1 H), 3.11 (d, ^3J = 6.1 Hz, 1 H), 2.99 (dd, ^2J = 14.0 Hz, ^3J = 6.1 Hz, 1 H), 1.64 (br. s, 1 H), 1.58–1.53 (m, 1 H), 1.23–1.16 (m, 2 H), 0.93 (d, ^3J = 8.3 Hz, 3 H), 0.92 (t, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 169.7, 138.6, 116.2, 65.1, 51.2, 51.1, 38.4, 25.6, 15.5, 11.4 ppm. IR (neat): $\tilde{\nu}$ = 3337, 3080, 2964, 2877, 1736, 1644 cm^{-1}. MS (EI): *m*/*z* (%) = 185 (2) $[M]^{+\cdot}$, 128 (71), 126 (100), 68 (28), 40 (10). $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.41, H 10.43, N 7.21.

Methyl (2*S*)-(Allylamino)(phenyl)acetate (6f): Colourless liquid. Yield: 78%. $[\alpha]_D^{20}$ = –112 (c = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.37 (m, 5 H), 5.92–5.85 (m, 1 H), 5.21 (dd, ^3J = 17.3 Hz, ^2J = 1.1 Hz, 1 H), 5.15 (dd, ^3J = 10.3 Hz, ^2J = 1.1 Hz, 1 H), 4.43 (s, 1 H), 3.72 (s, 3 H), 3.22 (d, ^3J = 6.3 Hz, 2 H), 2.09 (br. s, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.5, 139.9, 136.1, 128.7, 127.5, 127.2, 116.7, 64.4, 52.2, 50.1 ppm. IR (neat): $\tilde{\nu}$ = 3340, 3030, 2979, 2841, 1736, 1644, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 205 (3) $[M]^{+\cdot}$, 186 (100), 103 (17), 91 (24), 77 (10), 41 (43). $C_{10}H_{19}NO_2$ (205.25): calcd. C 70.22, H 7.37, N 6.82; found C 69.85, H 7.26, N 6.65.

General Procedure for the *N*-Benzylation Reaction: Potassium carbonate (4.25 g, 30.8 mmol) and benzyl bromide (7.26 g, 60 mmol) were added successively under an atmosphere of argon at 20 °C to a solution of *N*-allyl amino esters **6a**–**f** (14 mmol) in DMF (40 mL). After stirring for 30 h, the reaction mixture was quenched by the addition of H_2O (20 mL), diluted with diethyl ether (60 mL) and filtered through Celite. After extraction of the aqueous phase with diethyl ether (3 × 50 mL), the combined organic layer was washed with brine (50 mL), dried with magnesium sulfate and concentrated. The crude residue was purified by flash chromatography on silica gel (dichloromethane/diethyl ether, 95: 5) to afford *N*-allyl *N*-benzyl amino esters **7a**–**f**.

Isopropyl *N*-Allyl-*N*-benzyl-L-alaninate (7b): Colourless liquid. Yield: 71%. $[\alpha]_D^{20}$ = –137 (c = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5 H), 5.87–5.74 (m, 1 H), 5.24 (dd, ^3J = 17.0 Hz, ^2J = 1.2 Hz, 1 H), 5.10 (dd, ^3J = 10.1 Hz, ^2J = 1.2 Hz, 1 H), 5.11–5.05 (m, 1 H), 3.77 (AB system, δ_{vAB} = 65.0 Hz, J = 14.0 Hz, 2 H), 3.54 (q, ^3J = 7.0 Hz, 1 H), 3.28 (dd, ^2J = 14.3 Hz, ^3J = 7.2 Hz, 1 H), 3.15 (dd, ^2J = 14.3 Hz, ^3J = 7.2 Hz, 1 H), 1.29 (d, ^3J = 6.3 Hz, 6 H), 1.27 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.3, 140.3, 136.8, 128.6, 128.2, 126.8, 117.0, 67.6, 57.0, 54.3, 53.6, 22.0, 21.2, 15.3 ppm. IR (neat): $\tilde{\nu}$ = 3440, 3079, 2980, 2879, 1732, 1642, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 261 (6) $[M]^{+\cdot}$, 175 (12), 174 (100), 131 (10), 91 (97). $C_{16}H_{23}NO_2$ (261.36): calcd. C 73.53, H 8.87; N 5.36; found C 73.18, H 8.73, N 4.98.

Methyl *N*-Allyl-*N*-benzyl-L-valinate (7c): Colourless liquid. Yield: 69%. $[\alpha]_D^{20}$ = –219 (c = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5 H), 5.85–5.77 (m, 1 H), 5.15 (dd, ^3J = 17.3 Hz, ^2J = 1.4 Hz, 1 H), 5.01 (dd, ^3J = 10.3 Hz, ^2J = 1.4 Hz, 1 H), 3.89 (AB system, δ_{vAB} = 80.0 Hz, J = 14.4 Hz, 2 H), 3.75 (s, 3 H), 3.41 (dd, ^2J = 14.1 Hz, ^3J = 4.8 Hz, 1 H), 3.32 (d, ^2J = 14.1 Hz, 1 H), 2.94 (d, ^3J = 10.4 Hz, 1 H), 2.15–2.08 (m, 1 H), 1.01 (d, ^3J = 6.5 Hz, 3 H), 0.86 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.8, 136.6, 133.2, 128.7, 128.2, 127.9, 117.2, 68.6, 54.4, 51.2, 50.6, 27.5, 19.9, 19.6 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2961, 2872, 1732, 1642, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 261 (63) $[M]^{+\cdot}$,

234 (40), 218 (17), 202 (46), 91 (100), 40 (10). HRMS (ESI+): calcd. for $C_{16}H_{23}NO_2Na$ 284.16210; found 284.16302.

Methyl *N*-Allyl-*N*-benzyl-L-leucinate (7d): Colourless liquid. Yield: 73%. $[a]_D^{20}$ = –127 (*c* = 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 5.88–5.75 (m, 1 H), 5.25 (dd, ^3J = 17.0 Hz, ^2J = 1.2 Hz, 1 H), 5.11 (dd, ^3J = 10.2 Hz, ^2J = 1.2 Hz, 1 H), 3.74 (s, 3 H), 3.69 (AB system, δ_{vAB} = 123.0 Hz, *J* = 14.4 Hz, 2 H), 3.50 (t, ^3J = 6.3 Hz, 1 H), 3.33 (dd, ^2J = 14.4 Hz, ^3J = 7.2 Hz, 1 H), 3.06 (dd, ^2J = 14.4 Hz, ^3J = 7.2 Hz, 1 H), 1.77–1.74 (m, 1 H), 1.67–1.60 (m, 2 H), 0.92 (d, ^3J = 6.5 Hz, 3 H), 0.86 (d, ^3J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 174.0, 140.3, 136.7, 128.7, 128.2, 126.8, 117.0, 59.5, 54.3, 53.6, 50.9, 38.8, 24.5, 23.2, 21.8 ppm. IR (neat): $\tilde{\nu}$ = 3029, 2954, 2869, 1735, 1642, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 275 (4) $[M]^{+\cdot}$, 217 (17), 216 (100), 90 (93). $C_{17}H_{25}NO_2$ (263.38): calcd. C 74.14, H 9.15, N 5.09; found C 73.78, H 9.21, N 4.88.

Methyl *N*-Allyl-*N*-benzyl-L-isoleucinate (7e): Colourless liquid. Yield: 66%. $[a]_D^{20}$ = –150 (*c* = 1, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 5 H), 5.89–5.81 (m, 1 H), 5.27 (dd, ^3J = 16.9 Hz, ^2J = 1.0 Hz, 1 H), 5.11 (dd, ^3J = 10.1 Hz, ^2J = 1.0 Hz, 1 H), 3.74 (s, 3 H), 3.73 (AB system, δ_{vAB} = 248.4 Hz, *J* = 14.4 Hz, 2 H), 3.46 (dd, ^2J = 14.4 Hz, ^3J = 8.3 Hz, 1 H), 3.12 (d, ^3J = 10.8 Hz, 1 H), 2.93 (dd, ^2J = 14.4 Hz, ^3J = 8.3 Hz, 1 H), 2.00–1.90 (m, 1 H), 1.23–1.17 (m, 2 H), 0.93 (d, ^3J = 8.3 Hz, 3 H), 0.90 (t, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.7, 139.8, 136.6, 128.7, 128.2, 126.8, 117.3, 66.9, 54.5, 53.6, 50.5, 38.2, 24.8, 15.9, 11.8 ppm. IR (neat): $\tilde{\nu}$ = 3064, 2964, 2877, 1732, 1642, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 275 (5) $[M]^{+\cdot}$, 218 (11), 216 (22), 91 (100), 41 (12). $C_{17}H_{25}NO_2$ (275.39): calcd. C 74.14, H 9.15, N 5.09; found C 73.91, H 9.04, N 4.73.

Methyl (2*S*)-[Allyl(benzyl)amino](phenyl)acetate (7f): Yellow oil. Yield: 76%. $[a]_D^{20}$ = –47 (*c* = 0.1, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 10 H), 5.90–5.79 (m, 1 H), 5.18 (dd, ^3J = 17.3 Hz, ^2J = 1.8 Hz, 1 H), 5.14 (dd, ^3J = 10.9 Hz, ^2J = 1.8 Hz, 1 H), 4.68 (s, 1 H), 3.76 (s, 3 H), 3.76 (AB system, δ_{vAB} = 15.0 Hz, *J* = 12.7 Hz, 2 H), 3.22 (d, ^3J = 6.1 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.7, 139.7, 136.9, 135.9, 128.7, 128.5, 128.2, 128.0, 117.8, 67.1, 54.2, 53.2, 51.5 ppm. IR (neat): $\tilde{\nu}$ = 3064, 2950, 2842, 1727, 1641, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 295 (5) $[M]^{+\cdot}$, 236 (41), 91 (100). HRMS (ESI+): calcd. for $C_{19}H_{21}NO_2Na$ 318.14650; found 318.14723.

General Procedure for the Cyclopropanation Reaction: An ethereal solution of isopropylmagnesium bromide (1.7 M, 12.6 mL, 21.5 mmol) was added under an atmosphere of argon at 20 °C over a period of 4 h to a solution of amino esters **7a**–**f** (4.3 mmol) and titanium isopropoxide (0.13 mL, 0.43 mmol) in anhydrous THF/Et_2O (1:1, 30 mL). After additional stirring for 1 h, the mixture was poured into a cold aqueous H_2SO_4 solution (1 M, 10 mL). The white precipitate was filtered through a plug of Celite and washed with diethyl ether (50 mL), and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried with magnesium sulfate and concentrated; the residue was sufficiently pure to be used without further purification in the next step. However, some diastereomers could be separated and characterized after flash chromatography on silica gel (petroleum ether/ethyl acetate,70:30).

3-Benzyl-2-methyl-3-azabicyclo[3.1.0]hexan-1-ol (1b): Separable *cis* and *trans* diastereomers. Yield: 64%; *cis*/*trans*, 68:32. Data for (1*S*,2*S*,5*R*)-*cis*-**1b**: Pale yellow oil. $[a]_D^{20}$ = +156 (*c* = 0.6, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.17–7.07 (m, 5 H), 3.67 (AB system, $\delta_{v\alpha}B$ = 32.4 Hz, *J* = 13.6 Hz, 2 H), 3.23 (q, ^3J = 6.4 Hz, 1 H), 2.81 (dd, ^2J = 8.7 Hz, ^3J = 3.8 Hz, 1 H), 2.70 (br. s, 1 H), 2;52 (d, ^2J = 8.7 Hz, 1 H), 1.50–1.46 (m, 1 H), 1.29 (t, $^{2,3}J$ = 4.5 Hz, 1 H), 1.12 (d, ^3J = 6.4 Hz, 3 H), 0.95 (dd, ^3J = 8.8 Hz, ^2J = 4.5 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.6, 128.5, 128.3, 126.9, 64.6, 59.6, 54.6, 51.5, 22.9, 18.2, 10.1 ppm. IR (neat): $\tilde{\nu}$ = 3334, 3030, 2966, 2893, 2796, 1604 cm^{-1}. MS (EI): *m*/*z* (%) = 203 (2) $[M]^{+\cdot}$, 175 (23), 91 (100), 65 (12). HRMS (EI): calcd. for $C_{16}H_{23}NO$ 203.1386; found 203.1379. Data for (1*R*,2*S*,5*S*)-*trans*-**1b**: Colourless oil. $[a]_D^{20}$ = +50 (*c* = 0.5, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.20–7.06 (m, 5 H), 3.61 (AB system, δ_{vAB} = 226.8 Hz, *J* = 13.4 Hz, 2 H), 2.76 (q, ^3J = 6.4 Hz, 1 H), 2.71 (d, ^2J = 8.8 Hz, 1 H), 2.47 (dd, ^2J = 8.8 Hz, ^3J = 3.8 Hz, 1 H), 2.41 (br. s, 1 H), 1.43–1.38 (m, 1 H), 1.22 (d, ^3J = 6.4 Hz, 3 H), 1.04 (t, $^{2,3}J$ = 4.7 Hz, 1 H), 0.71 (dd, ^3J = 9.0 Hz, ^2J = 4.7 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 138.5, 129.0, 128.2, 127.0, 64.8, 61.8, 56.5, 53.4, 21.3, 14.1, 12.8 ppm. IR (neat): $\tilde{\nu}$ = 3353, 3028, 2965, 2898, 1604 cm^{-1}. MS (EI): *m*/*z* (%) = 203 (4) $[M]^{+\cdot}$, 175 (14), 160 (75), 132 (13), 91 (100), 65 (22). $C_{13}H_{17}NO$ (203.28): calcd. C 76.81, H 8.43, N 6.89; found C 76.68, H 8.66, N 6.44.

3-Benzyl-2-isopropyl-3-azabicyclo[3.1.0]hexan-1-ol (1c): Inseparable mixture of *cis* and *trans* diastereomers. Pale yellow oil. Yield: 75%; *cis*/*trans*, 72:28. IR (neat): $\tilde{\nu}$ = 3369, 3027, 2958, 1603 cm^{-1}. HRMS (ESI+): calcd. for $C_{15}H_{21}NO_2H$ 232.1696; found 232.1702. Data for (1*S*,2*S*,5*R*)-*cis*-**1c**: ^1H NMR (360 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 5 H), 3.80 (AB system, $\delta_{v\alpha}B$ = 46.8 Hz, *J* = 14.4 Hz, 2 H), 3.29 (dd, ^2J = 10.8 Hz, ^3J = 4.0 Hz, 1 H), 3.07 (d, ^3J = 2.2 Hz, 1 H), 2.95 (br. s, 1 H), 2.28 (d, ^2J = 10.8 Hz, 1 H), 2.20–2.16 (m, 1 H), 1.59–1.54 (m, 1 H), 1.10 (dd, ^2J = 9.0 Hz, ^3J = 4.7 Hz, 1 H), 1.05 (d, ^3J = 6.7 Hz, 3 H), 1.03 (d, ^3J = 6.7 Hz, 3 H), 0.4 (t, $^{2,3}J$ = 4.7 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 141.2, 128.7, 128.2, 126.8, 73.9, 62.6, 55.5, 55.4, 30.9, 26.5, 20.7, 19.9, 17.5 ppm. MS (EI): *m*/*z* (%) = 231 (2) $[M]^{+\cdot}$, 188 (17), 90 (100). Data for (1*R*,2*S*,5*S*)-*trans*-**1c**: ^1H NMR (360 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 3.60 (AB system, $\delta_{v\alpha}B$ = 309.6 Hz, *J* = 13.3 Hz, 2 H), 2.75 (d, ^3J = 2.5 Hz, 1 H), 2.69 (d, ^2J = 9.0 Hz, 1 H), 2.40 (dd, ^2J = 9.0 Hz, ^3J = 3.6 Hz, 1 H), 2.19–2.15 (m, 1 H), 1.29 (d, ^3J = 7.2 Hz, 3 H), 1.28 (br. s, 1 H), 1.24 (t, $^{2,3}J$ = 4.3 Hz, 1 H), 1.14–1.10 (m, 1 H), 1.13 (d, ^3J = 7.2 Hz, 3 H), 0.89 (dd, ^3J = 9.0, ^2J = 4.3 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.4, 128.6, 127.5, 126.8, 70.6, 64.7, 57.3, 54.0, 28.5, 20.7, 19.7, 17.8, 15.5 ppm. MS (EI): *m*/*z* (%) = 231 ($M^{+\cdot}$, 4), 188 (17), 160 (41), 90 (100), 84 (10), 64 (11).

3-Benzyl-2-(2-methylpropyl)-3-azabicyclo[3.1.0]hexan-1-ol (1d): Separable *cis* and *trans* diastereomers. Yield: 80%; *cis*/*trans*, 64:36. Data for (1*S*,2*S*,5*R*)-*cis*-**1d**: White solid. M.p. 125 °C. $[a]_D^{20}$ = +35 (*c* = 0.5, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 3.68 (AB system, $\delta_{v\alpha}B$ = 52.2 Hz, *J* = 13.7 Hz, 2 H), 3.02 (dd, ^2J = 10.1 Hz, ^3J = 4.0 Hz, 1 H), 2.96 (dd, ^2J = 6.9 Hz, ^3J = 5.4 Hz, 1 H), 2.27 (d, ^2J = 10.1 Hz, 1 H), 2.07 (br. s, 1 H), 1.98–1.84 (m, 1 H), 1.74–1.64 (m, 1 H), 1.52–1.38 (m, 2 H), 1.29 (t, $^{2,3}J$ = 7.2 Hz, 1 H), 1.10 (dd, ^2J = 9.0 Hz, ^3J = 4.7 Hz, 1 H), 0.96 (d, ^3J = 6.5 Hz, 3 H), 0.93 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.6, 128.5, 128.2, 126.8, 65.3, 60.8, 57.3, 53.4, 37.1, 25.9, 24.5, 23.2, 22.9, 21.8 ppm. IR (neat): $\tilde{\nu}$ = 3340, 2955, 2870, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 245 (2) $[M]^{+\cdot}$, 188 (100), 91 (52). $C_{16}H_{23}NO$ (245.36): calcd. C 78.32, H 9.45, N 5.71; found C 78.27, H 9.41, N 5.63. Data for (1*R*,2*S*,5*S*)-*trans*-**1d**: Deliquescent white solid. $[a]_D^{20}$ = +109 (*c* = 1, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 5 H), 3.62 (AB system, $\delta_{v\alpha}B$ = 262.8 Hz, *J* = 13.3 Hz, 2 H), 2.87 (dd, ^2J = 7.9 Hz, ^3J = 3.2 Hz, 1 H), 2.70 (d, ^2J = 9.0 Hz, 1 H), 2.46 (dd, ^2J = 9.0 Hz, ^3J = 4.0 Hz, 1 H), 2.07 (br. s, 1 H), 2.06–1.98 (m, 1 H), 1.60–1.52 (m, 2 H), 1.37–1.34 (m, 1 H), 1.06 (t, $^{2,3}J$ = 4.8 Hz, 1 H), 1.03 (d, ^3J = 6.5 Hz, 3 H), 1.02 (d, ^3J = 6.5 Hz, 3 H), 0.80 (dd, ^2J = 9.0 Hz, ^3J = 4.8 Hz, 1 H) ppm.

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.2, 128.7, 128.1, 126.8, 67.7, 64.3, 57.0, 53.6, 40.4, 25.6, 24.6, 22.7, 22.2, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 3340, 2955, 2798, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 245 (4) $[M]^{+\cdot}$, 189 (16), 188 (100), 91 (52). HRMS (EI): calcd. for $C_{16}H_{23}NO$ 245.17740; found 245.17717.

3-Benzyl-2-[(1*S*)-1-methylpropyl]-3-azabicyclo [3.1.0] hexan-1-ol (1e): Inseparable mixture of *cis* and *trans* diastereomers. Deliquescent white solid. Yield: 79%; *cis*/*trans*, 71:29. IR (neat): $\tilde{\nu}$ = 3028, 2927, 2793, 1603 cm^{-1}. Data for (1*S*,2*S*,5*R*)-*cis*-**1e**: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 5 H), 3.79 (AB system, $\delta_{\nu\alpha}$B = 50.4 Hz, *J* = 14.4 Hz, 2 H), 3.25 (dd, ^2J = 10.5 Hz, ^3J = 3.6 Hz, 1 H), 3.09 (d, ^3J = 2.2 Hz, 1 H), 2.28 (d, ^2J = 10.5 Hz, 1 H), 1.89–1.85 (m, 1 H), 1.58–1.53 (m, 1 H), 1.45–1.39 (m, 2 H), 1.28 (br. s, 1 H), 1.10 (dd, ^2J = 9.0 Hz, ^3J = 4.7 Hz, 1 H), 1.05 (d, ^3J = 6.8 Hz, 3 H), 0.97 (t, ^3J = 7.2 Hz, 3 H), 0.45 (t, $^{2,3}J$ = 4.7 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 138.9, 128.2, 128.1, 126.7, 73.6, 64.5, 61.7, 55.1, 38.2, 28.0, 24.5, 19.9, 15.7, 12.6 ppm. MS (EI): *m*/*z* (%) = 245 (3) $[M]^{+\cdot}$, 187 (22), 90 (100), 65 (10). HRMS (EI): calcd. for $C_{16}H_{23}NO$ 245.1852; found 245.1850. Data for (1*R*,2*S*,5*S*)-*trans*-**1e**: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H), 3.59 (AB system, $\delta_{\nu\alpha}$B = 320.4 Hz, *J* = 13.3 Hz, 2 H), 2.82 (d, ^3J = 2.9 Hz, 1 H), 2.69 (d, ^2J = 9.0 Hz, 1 H), 2.39 (dd, ^2J = 9.0 Hz, ^3J = 4.0 Hz, 1 H), 1.87–1.83 (m, 1 H), 1.65–1.55 (m, 2 H), 1.47–1.43 (m, 1 H), 1.28 (br. s, 1 H), 1.12 (d, ^3J = 8.7 Hz, 3 H), 1.05 (t, ^3J = 8.6 Hz, 3 H), 0.89 (dd, ^2J = 9.0 Hz, ^3J = 5.0 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 137.8, 128.5, 127.9, 126.6, 69.6, 60.9, 57.1, 53.9, 36.0, 26.7, 19.6, 15.7, 14.6, 13.2 ppm. MS (EI) *m*/*z* (%) = 245 (4) $[M]^{+\cdot}$, 206 (34), 187 (14), 160 (31), 90 (100), 65 (11), 40 (21). HRMS (EI): calcd. for $C_{16}H_{23}NO$ 245.1852; found 245.1853.

Potassium Hydroxide Promoted Ring Cleavage: Dry potassium hydroxide (70 mg, 1.25 mmol) was added to a solution of azabicyclo[3.1.0]hexane-1-ols **1b**–**f** (0.5 mmol) in anhydrous methanol (5 mL), and the mixture was heated at reflux for 10 min. After cooling, the solvent was evaporated and the residue was diluted with diethyl ether (10 mL) and water (2 mL). After extraction of the aqueous phase with diethyl ether (3 × 5 mL), the combined organic layer was washed with brine (3 mL), dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 90:10) to furnish pyrrolidinones **4b**–**f** as an inseparable mixture of diastereomers and piperidinones **8b**–**f**.

***cis*- and *trans*-1-Benzyl-2,4-dimethylpyrrolidin-3-one (4b):** Inseparable mixture of *cis* and *trans* diastereomers. Colourless liquid. Yield: 55%; *cis*/*trans*, 24:76. IR (neat): $\tilde{\nu}$ = 3082, 3032, 2932, 1715, 1604 cm^{-1}. $C_{13}H_{17}NO$ (203.28): calcd. C 76.81, H 8.43, N 6.89; found C 76.45, H 8.34, N 6.71. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 10 H, *cis* + *trans*), 3.75 (AB system, $\delta_{\nu\alpha}$B = 197.4 Hz, *J* = 13.2 Hz, 2 H, *cis*), 3.73 (AB system, $\delta_{\nu\alpha}$B = 226.2 Hz, *J* = 12.9 Hz, 2 H, *trans*), 3.32 (dd, ^2J = 9.0 Hz, ^3J = 4.5 Hz, 1 H, *trans*), 2.81 (dd, ^2J = 9.6 Hz, ^3J = 2.1 Hz, 1 H, *cis*), 2.74 (q, ^3J = 6.3 Hz, 1 H, *cis*), 2.64 (m, 1 H, *cis*), 2.59 (q, ^3J = 6.6 Hz, 1 H, *trans*), 2.44–2.36 (m, 2 H, *cis* + *trans*), 2.02 (dd, ^2J = 10.8 Hz, ^3J = 9.0 Hz, 1 H, *trans*), 1.29 (d, ^3J = 6.6 Hz, 3 H, *trans*), 1.24 (d, ^3J = 6.3 Hz, 3 H, *cis*), 1.17 (d, ^3J = 7.5 Hz, 3 H, *cis*), 1.09 (d, ^3J = 7.2 Hz, 3 H, *trans*) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 211.9 (*cis*), 210.9 (*trans*), 137.7 (*cis*), 137.4 (*trans*), 129.2 (*cis* + *trans*), 128.4 (*cis* + *trans*), 127.4 (*trans*), 127.2 (*cis*), 65.6 (*trans*), 65.1 (*cis*), 58.6 (*trans*), 57.9 (*cis*), 57.2 (*trans*), 56.1 (*cis*), 41.9 (*trans*), 40.9 (*cis*), 15.9 (*cis*), 14.8 (*trans*), 14.0 (*cis*), 11.9 (*trans*) ppm. MS (EI, *cis*), *m*/*z* (%) = 203 (2) $[M]^{+\cdot}$, 175 (53), 132 (11), 91 (100). MS (EI, *trans*), *m*/*z* (%) = 203 (2) $[M]^{+\cdot}$, 175 (52), 132 (10), 91 (100).

1-Benzyl-2-methylpiperidin-3-one (8b): Yellow oil. Yield: 21%. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.23 (m, 5 H), 3.61 (AB system, $\delta_{\nu\alpha}$B = 47.5 Hz, *J* = 13.7 Hz, 2 H), 3.48 (q, ^3J = 6.7 Hz, 1 H), 3.20 (td, ^2J = 12.5 Hz, ^3J = 4.4 Hz, 1 H), 2.72 (td, ^2J = 15.1 Hz, ^3J = 6.1 Hz, 1 H), 2.58–2.21 (m, 2 H), 2.39–2.01 (m, 2 H), 1.21 (d, ^3J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 207.1, 139.9, 128.7, 128.4, 127.6, 61.9, 58.9, 49.2, 38.3, 23.3, 10.3 ppm. IR (neat): $\tilde{\nu}$ = 3086, 3036, 2938, 1718, 1600 cm^{-1}. MS (EI): *m*/*z* (%) = 203 (6) $[M]^{+\cdot}$, 194 (11), 104 (30), 92 (100), 65 (10). HRMS (EI): calcd. for $C_{13}H_{17}NO$ 203.13570; found 203.13558.

***cis*- and *trans*-1-Benzyl-2-isopropyl-4-methylpyrrolidin-3-one (4c):** Inseparable mixture of *cis* and *trans* diastereomers. Colourless liquid. Yield: 54%; *cis*/*trans*, 20:80. IR (neat): $\tilde{\nu}$ = 3081, 3031, 2934, 1711 1603 cm^{-1}. $C_{15}H_{21}NO$ (231.33): calcd. C 77.88, H 9.15, N 6.05; found C 77.51, H 8.96, N 5.92. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 10 H, *cis* + *trans*), 3.72 (AB system, $\delta_{\nu AB}$ = 292.0 Hz, *J* = 13.3 Hz, 2 H, *cis*), 3.71 (AB system, $\delta_{\nu\alpha}$B = 304.6 Hz, *J* = 13.3 Hz, 2 H, *trans*), 3.38–3.28 (m, 1 H, *trans*), 2.83 (dd, ^2J = 10.1 Hz, ^3J = 2.5 Hz, 1 H, *cis*), 2.66 (d, ^3J = 2.9 Hz, 1 H, *cis*), 2.60–2.55 (m, 2 H, *trans*), 2.35–2.26 (m, 2 H, *cis* + *trans*), 2.14–2.06 (m, 2 H, *cis* + *trans*), 1.97 (dd, ^2J = 11.5 Hz, ^3J = 9.0 Hz, 1 H, *trans*), 1.15 (d, ^3J = 7.2 Hz, 3 H, *trans*), 1.14–1.07 (m, 9 H, *cis*), 1.03 (d, 3 H, ^3J = 7.2 Hz, *trans*), 1.02 (d, ^3J = 7.2 Hz, 3 H, *trans*) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 218.7 (*cis*), 218.1 (*trans*), 140.8 (*cis*), 138.3 (*trans*), 128.8 (*cis* + *trans*), 128.6 (*cis*), 128.3 (*cis* + *trans*), 127.2 (*trans*), 74.3 (*cis*), 74.0 (*cis*), 59.2 (*trans*), 57.0 (*cis*), 51.2 (*trans*), 49.4 (*cis*), 33.9 (*cis*), 31.7 (*trans*), 29.0 (*cis*), 27.2 (*trans*), 19.1 (*trans*), 18.9 (*cis*), 18.0 (*trans*), 17.8 (*cis*) ppm. MS (EI, *cis*), *m*/*z* (%) = 231 (2) $[M]^{+\cdot}$, 203 (28), 188 (35), 91 (100). MS (EI, *trans*), *m*/*z* (%) = 231 (2) $[M]^{+\cdot}$, 203 (17), 188 (32), 91 (100).

1-Benzyl-2-isopropylpiperidin-3-one (8c): Yellow oil. Yield: 35%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H), 3.75 (AB system, $\delta_{\nu\alpha}$B = 27.0 Hz, *J* = 13.6 Hz, 2 H), 3.23 (td, ^2J = 14.4 Hz, ^3J = 3.3 Hz, 1 H), 2.71 (dt, ^2J = 15.3 Hz, ^3J = 4.5 Hz, 1 H), 2.60–2.51 (m, 2 H), 2.50 (d, ^3J = 9.3 Hz, 1 H), 2.40–2.29 (m, 2 H), 2.03–1.96 (m, 1 H), 1.04 (d, ^3J = 6.6 Hz, 3 H), 0.79 (d, ^3J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 214.8, 139.1, 128.7, 128.3, 127.1, 77.2, 57.3, 44.2, 38.6, 27.2, 25.6, 20.0, 19.2 ppm. IR (neat): $\tilde{\nu}$ = 3086, 3028, 2935, 1711, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 231 (5) $[M]^{+\cdot}$, 203 (14), 188 (35), 174 (14), 160 (70), 91 (100), 84 (11). HRMS (EI): calcd. for $C_{15}H_{21}NO$ 231.16960; found 231.16936.

***cis*- and *trans*-1-Benzyl-2-(2-methylpropyl)-4-methylpyrrolidin-3-one (4d):** Inseparable mixture of *cis* and *trans* diastereomers. Colourless liquid. Yield: 55%; *cis*/*trans*, 18:82. IR (neat): $\tilde{\nu}$ = 3085, 3030, 2930, 1713, 1603 cm^{-1}. $C_{16}H_{23}NO$ (245.36): calcd. C 78.32, H 9.45, N 5.71; found C 77.91, H 9.42, N 5.38. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 10 H, *cis* + *trans*), 3.76 (AB system, $\delta_{\nu AB}$ = 201.2 Hz, *J* = 13.3 Hz, 2 H, *cis*), 3.71 (AB system, $\delta_{\nu\alpha}$B = 235.2 Hz, *J* = 13.3 Hz, 2 H, *trans*), 3.33 (t, ^3J = 8.3 Hz, 1 H, *trans*), 2.85 (dd, ^2J = 9.8 Hz, ^3J = 2.5 Hz, 1 H, *cis*), 2.74 (t, ^3J = 5.5 Hz, 1 H, *cis*), 2.63–2.56 (m, 2 H, *trans*), 2.52–2.20 (m, 3 H, *cis* + *trans*), 2.06–1.90 (m, 1 H, *cis*), 1.95 (dd, ^2J = 11.3 Hz, ^3J = 9.0 Hz, 1 H, *trans*), 1.78–1.49 (m, 4 H, *cis* + *trans*), 1.19 (m, 18 H, *cis* + *trans*) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 217.3 (*cis*), 216.2 (*trans*), 137.8 (*cis*), 137.6 (*trans*), 129.0 (*trans*), 128.7 (*cis*), 128.6 (*trans*), 128.4 (*cis*), 127.3 (*trans*), 127.2 (*cis*), 68.7 (*cis*), 68.5 (*cis*), 58.8 (*trans*), 58.7 (*cis*), 57.2 (*trans*), 56.1 (*cis*), 42.3 (*trans*), 40.8 (*cis*), 38.4 (*trans*), 37.2 (*cis*), 25.8 (*cis*), 25.2 (*trans*), 24.9 (*trans*), 23.7 (*cis*), 22.9 (*cis*), 22.7 (*trans*), 22.5 (*cis*) ppm. MS (EI, *cis*), *m*/*z* (%) = 245 (1) $[M]^{+\cdot}$, 176 (100), 91 (98). MS (EI, *trans*), *m*/*z* (%) = 245 (2) $[M]^{+\cdot}$, 217 (22), 202 (28), 174 (23), 160 (100), 146 (51), 91 (76).

1-Benzyl-2-(2-methylpropyl)piperidin-3-one (8d): Yellow oil. Yield: 28%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 5 H), 3.73

(AB system, δ_{vAB} = 27.0 Hz, J = 13.7 Hz, 2 H), 3.18 (t, ^3J = 6.5 Hz, 1 H), 3.07 (td, ^2J = 13.6 Hz, ^3J = 4.0 Hz, 1 H), 2.69 (td, ^2J = 13.7 Hz, ^3J = 4.3 Hz, 1 H), 2.61–2.49 (m, 2 H), 2.42–2.34 (m, 2 H), 2.17–1.93 (m, 1 H), 1.73–1.48 (m, 2 H), 0.90 (d, ^3J = 6.3 Hz, 3 H), 0.84 (d, ^3J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 207.6, 139.1, 128.9, 128.4, 127.5, 68.5, 56.9, 45.1, 37.5, 36.1, 24.9, 23.8, 22.7, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 3077, 3030, 2957, 1713, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 245 (4) $[M]^{+\cdot}$, 217 (22), 202 (26), 174 (25), 160 (100), 91 (73). HRMS (ESI+): calcd. for $C_{16}H_{24}NOH$ 246.18520; found 246.18534.

***cis*- and *trans*-1-Benzyl-2-[(1*S*)-1-methylpropyl]-4-methylpyrrolidin-3-one (4e):** Inseparable mixture of *cis* and *trans* diastereomers. Colourless liquid. Yield: 54%; 47(P^1):27(P^2):18(P^3):8(P^4) (unattributed). IR (neat): $\tilde{\nu}$ = 3084, 3031, 2934, 1713, 1603 cm^{-1}. MS (EI, *cis*): *m*/*z* (%) = 245 (X) $[M]^{+\cdot}$, 176 (100), 91 (98). MS (EI, *trans*): *m*/*z* (%) = 245 (X) $[M]^{+\cdot}$, 217 (22), 202 (28), 174 (23), 160 (100), 146 (51), 91 (76). $C_{16}H_{23}NO$ (245.36): calcd. C 78.32, H 9.45, N 5.71; found C 77.91, H 9.32, N 5.42. Colourless liquid. Yield: 55%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 20 H), 3.76 (AB system, δ_{vAB} = 156.6 Hz, J = 14.1 Hz, 2 H, P^4), 3.75 (AB system, δ_{vAB} = 233.2 Hz, J = 13.5 Hz, 2 H, P^3), 3.73 (AB system, δ_{vAB} = 260.8 Hz, J = 12.9 Hz, 2 H, P^2), 3.72 (AB system, $\delta_{v\alpha}$B = 256.5 Hz, J = 13.8 Hz, 2 H, P^1), 3.36–3.33 (m, 2 H), 2.87–2.50 (m, 8 H), 2.37–2.24 (m, 4 H), 2.20–1.54 (m, 14 H), 1.20–0.80 (m, 36 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 218.2 (P^1), 216.7 (P^4), 214.3. (P^3), 211.9 (P^2), 138.5 (P^3), 138.4 (P^2), 138.3 (P^1), 138.1 (P^4), 128.8–127.1 (P^1, P^2, P^3, P^4), 74.2 (P^4), 74.0 (P^2), 73.6 (P^3), 73.2 (P^1), 59.7 (P^4), 59.6 (P^2), 59.0 (P^1), 58.9 (P^3), 57.3 (P^2), 57.1 (P^1), 56.4 (P^4), 56.3 (P^3), 43.8 (P^1), 43.6 (P^2), 41.3 (P^3), 41.0 (P^4), 36.6 (P^2), 36.0 (P^1, P^3), 35.2 (P^4), 25.9 (P^1, P^3), 25.8 (P^4), 25.6 (P^2), 15.7 (P^2), 15.6 (P^4), 15.4 (P^3), 15.2 (P^1), 12.7 (P^2, P^3), 12.6 (P^4), 12.5 (P^1), 11.2 (P^2, P^4), 11.1 (P^1, P^3) ppm. MS (EI, P^1): *m*/*z* (%) = 245 (0.8) $[M]^{+\cdot}$, 217 (22), 203 (23), 188 (49), 91 (100). MS (EI, P^2): *m*/*z* (%) = 245 (0.6) $[M]^{+\cdot}$, 217 (23), 188 (53), 147 (11), 91 (100). MS (EI, P^3): *m*/*z* (%) = 245 (0.5) $[M]^{+\cdot}$, 217 (20), 188 (48), 91 (100). MS (EI, P^4): *m*/*z* (%) = 245 (0.6) $[M]^{+\cdot}$, 217 (20), 188 (43), 147 (11), 91 (100).

1-Benzyl-2-[(1*S*)-1-methylpropyl]piperidin-3-one (8e): Inseparable mixture of diastereomers. Yellow oil. Yield: 32%; 50:50 mixture. IR (neat): $\tilde{\nu}$ = 3086, 3029, 2961, 1707, 1601 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 10 H), 3.75 (AB system, $\delta_{v\alpha}$B = 29.7 Hz, J = 13.5 Hz, 2 H), 3.74 (AB system, $\delta_{v\alpha}$B = 24.6 Hz, J = 13.5 Hz, 2 H), 3.40–3.29 (m, 2 H), 2.87–2.54 (m, 6 H), 2.73 (d, ^3J = 10.4 Hz, 1 H, diast. 1), 2.69 (d, ^3J = 11.2 Hz, 1 H, diast. 2), 2.43–2.32 (m, 4 H, diast. 1 + diast. 2), 2.13–2.04 (m, 2 H, diast. 1 + diast. 2), 1.87–1.76 (m, 4 H, diast. 1, diast. 2), 1.05 (t, ^3J = 7.4 Hz, 3 H, diast. 1), 0.88 (d, ^3J = 7.2 Hz, 3 H, diast. 1), 0.82 (t, ^3J = 7.6 Hz, 3 H, diast. 2), 0.77 (d, ^3J = 6.6 Hz, 3 H, diast. 2) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 214.8 (diast. 1), 214.7 (diast. 2), 139.0 (diast. 1), 138.9 (diast. 2), 128.8 (diast. 1), 128.7(diast. 2), 128.2 (diast. 1, diast. 2), 127.2 (diast. 1), 127.1 (diast. 2), 75.9 (diast. 2), 75.3 (diast. 1), 57.4 (diast. 1), 57.3 (diast. 2), 44.1 (diast. 1, diast. 2), 38.6 (diast. 2), 38.5 (diast. 1), 33.9 (diast. 2), 33.1 (diast. 1), 25.9 (diast. 2), 25.4 (diast. 1), 25.7 (diast. 2), 25.3 (diast. 1), 15.7 (diast. 2), 15.2 (diast. 1), 11.2 (diast. 2), 10.4 (diast. 1) ppm. MS (EI, diast. 1): *m*/*z* (%) = 245 (5) $[M]^{+\cdot}$, 217 (22), 188 (23), 160 (81), 91 (100). MS (EI, diast. 2): *m*/*z* (%) = 245 (5) $[M]^{+\cdot}$, 217 (19), 188 (60), 160 (72), 91 (100). HRMS (ESI+): calcd. for $C_{16}H_{24}NOH$ 246.18520; found 246.18429.

***cis*- and *trans*-1-Benzyl-2-phenyl-4-methylpyrrolidin-3-one (4f):** Inseparable mixture of *cis* and *trans* diastereomers. Colourless liquid. Yield: 69%; *cis*/*trans*, 24:76. IR (neat): $\tilde{\nu}$ = 3062, 3030, 2932, 1715, 1604 cm^{-1}. $C_{18}H_{19}NO$ (265.35): calcd. C 81.47, H 7.22, N 5.28; found C 81.11, H 7.19, N 4.91. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 20 H, *cis, trans*), 3.69 (AB system, $\delta_{v\alpha}$B = 213.0 Hz, J = 13.2 Hz, 2 H, *cis*), 3.69 (s, 1 H, *cis*), 3.68 (AB system, $\delta_{v\alpha}$B = 222.0 Hz, J = 12.9 Hz, 2 H, *trans*), 3.63 (s, 1 H, *trans*), 3.50 (t, $^{2,3}J$ = 8.7 Hz, 1 H, *trans*), 3.03 (d, ^2J = 9.3 Hz, 1 H, *cis*), 2.71 (dd, ^2J = 9.3 Hz, ^3J = 6.6 Hz,1 H, *cis*), 2.64–2.52 (m, 2 H, *cis, trans*), 2.20 (t, $^{2,3}J$ = 9.3 Hz, 1 H, *trans*), 1.28 (d, ^3J = 7.5 Hz, 3 H, *cis*), 1.14 (d, ^3J = 6.9 Hz, 3 H, *trans*) ppm. ^{13}C ppm NMR (62.9 MHz, $CDCl_3$): δ = 215.4 (*cis*), 214.6 (*trans*), 140.3 (*cis*), 140.1 (*trans*), 129.8–127.2 (*cis, trans*), 75.2 (*trans*), 74.8 (*cis*), 58.1 (*trans*), 57.9 (*cis*), 56.1 (*trans*), 55.5 (*cis*), 42.7 (*trans*), 41.4 (*cis*), 16.6 (*cis*), 11.7 (*trans*) ppm. MS (EI, *cis*), *m*/*z* (%) = 265 (2) $[M]^{+\cdot}$, 237 (54), 194 (43), 91 (100). MS (EI, *trans*), *m*/*z* (%) = 265 (3) $[M]^{+\cdot}$, 236 (33), 194 (33), 91 (100).

1-Benzyl-2-phenylpiperidin-3-one (8f): White solid. M.p. 62 °C. Yield: 23%. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.48–7.29 (m, 10 H), 3.96 (s, 1 H), 3.64 (AB system, $\delta_{v\alpha}$B = 47.5 Hz, J = 13.8 Hz, 2 H), 3.15 (td, ^2J = 12.3 Hz, ^3J = 4.5 Hz, 1 H), 2.72 (td, ^2J = 14.8 Hz, ^3J = 6.0 Hz, 1 H), 2.52–2.36 (m, 2 H), 2.36–2.02 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 206.4, 141.1, 140.1, 128.9, 128.7, 128.6, 128.5, 127.9, 127.6, 77.5, 59.3, 49.1, 38.2, 23.4 ppm. IR (neat): $\tilde{\nu}$ = 3085, 3028, 2953, 1715, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 265 (5) $[M]^{+\cdot}$, 237 (45), 194 (21), 160 (59), 146 (24), 118 (47), 104 (12), 91 (100), 65 (13). $C_{18}H_{19}NO$ (265.35): calcd. C 81.47, H 7.22, N 5.28; found C 81.41, H 7.19, N 5.22.

Synthesis of Dihydropyridinones

Method A: Promoted Ferric Chloride Ring Cleavage and Subsequent Basic Elimination: A solution of azabicyclo[3.1.0]hexane-1-ols **1b**–**f** (0.5 mmol) as a mixture of diastereomers in diethyl ether (1 mL) was added dropwise at 0 °C under an atmosphere of argon to a suspension of anhydrous $FeCl_3$ (0.18 g, 1.1 mmol) in diethyl ether (2 mL). After stirring for 3 h at this temperature, the mixture was diluted with freshly distilled methanol (2 mL) and anhydrous sodium acetate (205 mg, 5 mmol) was added in one portion. The reaction was warmed to 20 °C, stirred for 24 h and then evaporated to give a crude residue that was dissolved in ethyl acetate (5 mL) and filtered through Celite. The organic phase was then washed with brine (1 mL), dried with magnesium sulfate and concentrated. Flash chromatography on silica gel (dichloromethane/diethyl ether, 90:10) afforded the chiral dihydropyridinones **2b**–**f**.

Method B: Bis(*sym*-collidine)iodine Hexafluorophosphate: Bis(*sym*-collidine)iodine hexafluorophosphate (0.5 g, 1.5 mmol) was added at 20 °C over a period of 1 h to a solution of azabicyclo[3.1.0]hexane-1-ols **1b**–**f** (0.5 mmol) as a mixture of diastereomers in dichloromethane (2 mL). After stirring for an additional period of 0.5 h, the crude solution was evaporated and directly chromatographed on silica gel (petroleum ether/diethyl ether, 75:25) to give the chiral dihydropyridinones **2b**–**f**.

(2*S*)-1-Benzyl-2-methyl-1,6-dihydropyridin-3(2*H*)-one (2b): Yellow oil. Yield: 76 (A), 73% (B). $[\alpha]_D^{20}$ = +17 (c = 0.1, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5 H), 6.91 (ddd, ^3J = 10.1 Hz, ^3J = 6.8 Hz, ^3J = 4.0 Hz, 1 H), 6.07 (dd, ^3J = 10.1 Hz, ^4J = 2.5 Hz, 1 H), 3.77 (AB system, $\delta_{v\alpha}$B = 39.6 Hz, J = 13.3 Hz, 2 H), 3.45 (ddd, ^2J = 19.8 Hz, ^3J = 4.0 Hz, ^4J = 2.5 Hz, 1 H), 3.44 (q, ^3J = 6.8 Hz, 1 H), 3.32 (ddd, ^2J = 19.8 Hz, ^3J = 4.0 Hz, ^4J = 2.5 Hz, 1 H), 1.25 (d, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 199.2, 147.2, 133.2, 129.7, 128.2, 127.5, 126.7, 62.6, 57.5, 47.3, 10.1 ppm. IR (neat): $\tilde{\nu}$ = 2931, 1684, 1633, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 201 (12) $[M]^{+\cdot}$, 110 (30), 92 (100), 68 (12). HRMS (EI): calcd. for $C_{13}H_{15}NO$ 201.1148; found 201.1141.

(2*S*)-1-Benzyl-2-isopropyl-1,6-dihydropyridin-3(2*H*)-one (2c): Yellow oil. Yield: 89 (A), 71% (B). $[\alpha]_D^{20}$ = +288 (c = 0.1, CH_2Cl_2). ^{1}H

NMR (360 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 5 H), 6.70 (ddd, ^3J = 10.1 Hz, ^3J = 4.3 Hz, ^3J = 1.8 Hz, 1 H), 6.04 (dd, ^3J = 10.1 Hz, ^4J = 2.5 Hz, 1 H), 3.81 (AB system, $\delta_{v\alpha}$B = 28.8 Hz, J = 13.3 Hz, 2 H), 3.67 (dd, ^2J = 20.5 Hz, ^3J = 4.3 Hz, 1 H), 3.22 (dd, ^2J = 20.5 Hz, ^3J = 4.3 Hz, 1 H), 2.69 (d, ^3J = 10.1 Hz, 1 H), 2.04–1.97 (m, 1 H), 1.15 (d, ^3J = 6.5 Hz, 3 H), 0.84 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 200.1, 144.3, 136.8, 128.6, 128.4, 127.2, 127.1, 74.4, 59.0, 46.0, 37.5, 21.2, 19.6 ppm. IR (neat): $\tilde{\nu}$ = 3029, 2960, 1678, 1628, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 229 (2) $[M]^{+\cdot}$, 186 (49), 92 (100). HRMS (ESI+): calcd. for $C_{15}H_{19}NONa$ 252.1359; found 252.1362.

(2*S*)-1-Benzyl-2-(2-methylpropyl)-1,6-dihydropyridin-3(2*H*)-one (2d): Yellow oil. Yield: 83 (A), 78% (B). $[\alpha]_D^{20}$ = +86 (c = 0.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 6.81 (ddd, ^3J = 10.2 Hz, ^3J = 4.5 Hz, ^3J = 2.1 Hz, 1 H), 6.06 (ddd, ^3J = 10.2 Hz, ^4J = 2.1 Hz, ^4J = 0.9 Hz, 1 H), 3.78 (AB system, $\delta_{v\alpha}$B = 21.0 Hz, J = 13.2 Hz, 2 H), 3.58 (ddd, ^2J = 20.1 Hz, ^3J = 2.1 Hz, ^4J = 0.9 Hz, 1 H), 3.32 (t, ^3J = 7.8 Hz, 1 H), 3.24 (ddd, ^2J = 20.1 Hz, ^3J = 2.1 Hz, ^4J = 0.9 Hz, 1 H), 1.84–1.70 (m, 1 H), 1.45–1.27 (m, 2 H), 0.94 (d, ^3J = 6.6 Hz, 3 H), 0.87 (d, ^3J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 199.9, 145.5, 128.9, 128.7, 128.4, 127.3, 126.9, 65.7, 58.0, 46.3, 35.6, 24.8, 22.8, 22.4. IR (neat): $\tilde{\nu}$ = 3029, 2955, 1682, 1637, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 243 (2) $[M]^{+\cdot}$, 186 (20), 176 (23), 152 (10), 132 (12), 91 (100), 67 (11), 65 (13). HRMS (ESI+): calcd. for $C_{16}H_{21}NONa$ 266.1515; found 266.1518.

(2*S*)-1-Benzyl-2-[(1*S*)-1-methylpropyl]-1,6-dihydropyridin-3(2*H*)-one (2e): Yellow oil. Yield: 86 (A), 72% (B). $[\alpha]_D^{20}$ = +332 (c = 0.025, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 6.71 (ddd, ^3J = 10.4 Hz, ^3J = 4.0 Hz, ^3J = 1.8 Hz, 1 H), 6.05 (dd, ^3J = 10.4 Hz, ^4J = 2.5 Hz, 1 H), 3.77 (AB system, $\delta_{v\alpha}$B = 46.8 Hz, J = 13.3 Hz, 2 H), 3.71 (ddd, ^2J = 20.5 Hz, ^3J = 4.0 Hz, ^3J = 2.5 Hz, 1 H), 3.22 (ddd, ^2J = 20.5 Hz, ^3J = 4.0 Hz, ^4J = 2.5 Hz, 1 H), 2.82 (d, ^3J = 10.1 Hz, 1 H), 1.94–1.81 (m, 1 H), 1.37–1.27 (m, 2 H), 0.90 (t, ^3J = 7.6 Hz, 3 H), 0.84 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 200.5, 144.3, 136.6, 128.6, 128.4, 127.2, 127.1, 72.5, 59.0, 45.9, 33.1, 26.5, 15.6, 10.4 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2965, 1678, 1634, 1603 cm^{-1}. MS (EI): *m*/*z* (%) = 243 (3) $[M]^{+\cdot}$, 186 (61), 91 (100). HRMS (ESI+): calcd. for $C_{16}H_{21}NONa$ 266.1515; found 266.1515.

Cerium Ammonium Promoted Nitrate Ring Cleavage: A solution of $Ce(NH_3)_3NH_4$ (0.548 g, 1 mmol) in acetonitrile (4 mL) was added at 0 °C over 5 min to a solution of azabicyclo[3.1.0]hexane-1-ols **4b**–**f** (0.5 mmol) in acetonitrile/water (2:1, 6 mL). After stirring for 30 min at this temperature, a saturated sodium hydrogencarbonate solution was added until complete neutralization (pH 7, about 3 mL). The mixture was then diluted with diethyl ether (30 mL) and filtered through Celite, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phase was washed with brine (5 mL), dried with magnesium sulfate and concentrated. Flash chromatography on silica gel (dichloromethane/diethyl ether, 90:10) furnished chiral tricyclopiperidinones **3b**–**f**.

(3*S*,6*S*)-3-Methyl-5,6-dihydro-1*H*-2,6-methano-2-benzazocin-4-one (3b): Yellow oil. Yield: 74%. $[\alpha]_D^{20}$ = +2 (c = 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–6.96 (m, 4 H), 4.20 (AB system, $\delta_{v\alpha}$B = 195.0 Hz, J = 13.4 Hz, 2 H), 3.50 (AB system, $\delta_{v\alpha}$B = 144.0 Hz, J = 13.4 Hz, 2 H), 3.28 (q, ^3J = 7.0 Hz, 1 H), 3.27 (m, 1 H), 2.96 (dd, ^2J = 15.0 Hz, ^2J = 4.5 Hz, 1 H), 2.44 (d, ^2J = 15.0 Hz, 1 H), 1.44 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 214.2, 138.0, 132.8, 128.5, 127.3, 127.1, 126.2, 69.2, 57.9, 45.6, 45.3, 35.9, 17.9 ppm. IR (neat): $\tilde{\nu}$ = 3021, 2937, 1710, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 201 (15) $[M]^{+\cdot}$, 173 (100), 172 (23), 158 (23), 145 (11), 131 (52), 117 (20), 91 (16), 56 (62). HRMS (ESI+): calcd. for $C_{13}H_{15}NOH$ 202.12260; found 202.12273.

(3*S*,6*S*)-3-Isopropyl-5,6-dihydro-1*H*-2,6-methano-2-benzazocin-4-one (3c): Yellow oil. Yield: 68%. $[\alpha]_D^{20}$ = +6 (c = 0.1, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.39–6.95 (m, 4 H), 4.17 (AB system, $\delta_{v\alpha}$B = 266.4 Hz, J = 17.6 Hz, 2 H), 3.42 (AB system, $\delta_{v\alpha}$B = 162.0 Hz, J = 13.7 Hz, 2 H), 3.30 (m, 1 H), 2.87 (dd, ^2J = 14.0 Hz, ^2J = 4.7 Hz, 1 H), 2.58 (d, ^3J = 5.8 Hz, 1 H), 2.40 (d, ^2J = 14.0 Hz, 1 H), 2.11–1.98 (m, 1 H), 1.14 (d, ^3J = 6.5 Hz, 3 H), 0.84 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 201.3, 131.2, 128.9, 128.7, 128.3, 127.5, 124.3, 80.8, 58.2, 47.1, 46.1, 37.7, 29.7, 20.6, 19.3 ppm. IR (neat): $\tilde{\nu}$ = 2962, 2930, 1708, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 229 (6) $[M]^{+\cdot}$, 201 (32), 187 (10), 186 (100), 130 (21), 115 (32), 91 (15), 84 (15), 56 (13), 41 (11). HRMS (ESI+): calcd. for $C_{15}H_{19}NOH$ 230.15390; found 230.15472.

(3*S*,6*S*)-3-Isobutyl-5,6-dihydro-1*H*-2,6-methano-2-benzazocin-4-one (3d): Yellow oil. Yield: 88%. $[\alpha]_D^{20}$ = –55 (c = 0.5, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.39–7.13 (m, 4 H), 4.72 (AB system, $\delta_{v\alpha}$B = 216.0 Hz, J = 16.6 Hz, 2 H), 4.04 (AB system, $\delta_{v\alpha}$B = 136.8 Hz, J = 13.3 Hz, 2 H), 3.84 (t, ^3J = 5.8 Hz, 1 H), 3.72 (m, 1 H), 3.14 (dd, ^2J = 15.5 Hz, ^3J = 4.3 Hz, 1 H), 2.63 (d, ^2J = 15.5 Hz, 1 H), 2.04–2.00 (m, 2 H), 1.27–1.21 (m, 1 H), 0.99 (d, ^3J = 6.1 Hz, 3 H), 0.97 (d, ^3J = 6.1 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 200.4, 133.5, 129.8, 129.1, 128.4, 127.9, 123.9, 76.2, 56.7, 46.5, 44.3, 38.2, 32.4, 24.6, 22.9, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 2964, 2874, 1732, 1602 cm^{-1}. MS (EI): *m*/*z* (%) = 243 (8) $[M]^{+\cdot}$, 215 (27), 200 (26), 172 (100), 159 (14), 131 (13), 117 (12), 115 (23), 56 (10), 42 (17). HRMS (ESI+): calcd. for $C_{16}H_{21}NOH$ 244.16960; found 244.16986.

(3*S*,6*S*)-3-[(1*S*)-1-Methylpropyl]-5,6-dihydro-1*H*-2,6-methano-2-benzazocin-4-one (3e): Yellow oil. Yield: 73%. $[\alpha]_D^{20}$ = +15 (c = 0.1, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.28–6.94 (m, 4 H), 4.16 (AB system, $\delta_{v\alpha}$B = 270.0 Hz, J = 17.6 Hz, 2 H), 3.84 (d, ^3J = 10.1 Hz, 1 H), 3.41 (AB system, δ_{vAB} = 169.2 Hz, J = 14.0 Hz, 2 H), 3.30 (m, 1 H), 2.87 (dd, ^2J = 14.0 Hz, ^2J = 4.7 Hz, 1 H), 2.63 (d, ^2J = 14.0 Hz, 1 H), 2.11–1.98 (m, 1 H), 1.91–1.86 (m, 2 H), 0.95 (t, ^3J = 7.2 Hz, 3 H), 0.91 (d, ^3J = 8.1 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 202.7, 133.3, 129.6, 129.4, 128.7, 127.6, 123.7, 72.2, 58.4, 47.5, 46.2, 33.4, 32.4, 26.1, 15.7, 10.8 ppm. IR (neat): $\tilde{\nu}$ = 2964, 2876, 1712, 1604 cm^{-1}. MS (EI): *m*/*z* (%) = 243 (5) $[M]^{+\cdot}$, 216 (34), 200 (34), 186 (100), 158 (17), 131 (22), 115 (31), 41 (14). HRMS (ESI+): calcd. for $C_{16}H_{21}NOH$ 244.16960; found 244.16975.

Palladium Hydroxide Promoted Hydrogenation: Palladium hydroxide on charcoal (20%, 3 mg) was added at 20 °C to a solution of dihydropyridinones **2b**–**f** (0.2 mmol) in ethyl acetate (5 mL). After stirring at this temperature, the reaction was complete within 20 h, as monitored by TLC, and the mixture was then filtered through Celite. After concentration, the residue was purified by flash chromatography on silica gel (dichloromethane/diethyl ether, 90:10) to furnish a separable mixture of chiral piperidinones **8b**–**f** and pyridinols **9b**–**f**.

(2*S*)-8b: Yield: 60%. $[\alpha]_D^{20}$ = +5 (c = 0.1, CH_2Cl_2).

(2*S*)-8c: Yield: 48%. $[\alpha]_D^{20}$ = +2 (c = 0.1, CH_2Cl_2).

(2*S*)-8d: Yield: 58%. $[\alpha]_D^{20}$ = +3 (c = 0.2, CH_2Cl_2).

(2*S*)-8e: Yield: 53%. $[\alpha]_D^{20}$ = +5 (c = 0.1, CH_2Cl_2).

(2*S*)-8f: Yield: 68%. $[\alpha]_D^{20}$ = +7 (c = 0.8, CH_2Cl_2).

2-Methylpyridin-3-ol (9b): Deliquescent white solid. Yield: 14%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (dd, ^3J = 4.7 Hz, ^4J = 1.2 Hz, 1 H), 7.15 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1 H), 7.06 (dd, ^3J = 8.4 Hz,

^4J = 4.7 Hz, 1 H), 3.05 (br. s, 1 H), 2.53 (m, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 146.3, 144.7, 139.7, 122.4, 122.3, 18.4 ppm. IR (neat): $\tilde{\nu}$ = 3410, 2963, 1580 cm^{-1}. MS (EI): *m*/*z* (%) = 109 (100) $[M]^{+\cdot}$, 81 (10), 80 (46), 49 (7). HRMS (EI): calcd. for C_6H_7NO 109.05220; found 109.05257.

2-Isopropylpyridin-3-ol (9c): Deliquescent white solid. Yield: 28%. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.03 (d, J = 4.5 Hz, 1 H), 7.16 (d, J = 7.9 Hz, 1 H), 7.09 (dd, ^3J = 7.9 Hz, ^4J = 4.5 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.00 (br. s, 1 H), 1.24 (d, J = 8.3 Hz, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 154.3, 150.1, 140.0, 121.5, 121.2, 28.5, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 3415, 2963, 2923, 1577 cm^{-1}. MS (EI): *m*/*z* (%) = 137 (14) $[M]^{+\cdot}$, 136 (27), 122 (100), 122 (73), 109 (80), 104 (13). HRMS (EI): calcd. for $C_8H_{11}NO$ 137.07570; found 137.07571.

2-Isobutylpyridin-3-ol (9d): Deliquescent white solid. Yield: 25%. ^{1}H NMR (360 MHz, CD_3OD): δ = 7.91 (dd, ^3J = 4.7 Hz, ^4J = 1.3 Hz, 1 H), 7.16 (dd, ^3J = 8.3 Hz, ^4J = 1.3 Hz, 1 H), 7.07 (dd, ^3J = 8.3 Hz, ^4J = 4.7 Hz, 1 H), 2.68 (d, J = 7.6 Hz, 2 H), 2.14–2.03 (m, 1 H), 0.93 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 152.5, 149.4, 138.1, 122.3, 122.2, 40.4, 27.9, 21.4 ppm. IR (neat): $\tilde{\nu}$ = 3433, 2963, 2923, 1577 cm^{-1}. MS (EI): *m*/*z* (%) = 151 (4) $[M]^{+\cdot}$, 136 (19), 110 (10), 109 (100), 108 (10). HRMS (EI): calcd. for $C_9H_{13}NO$ 151.09920; found 151.09920.

2-[(1*S*)-1methylpropyl]Pyridin-3-ol (9e): Deliquescent white solid. Yield: 29%. ^{1}H NMR (360 MHz, CD_3OD): δ = 7.95 (dd, ^3J = 5.8 Hz, ^4J = 1.8 Hz, 1 H), 7.16 (dd, ^3J = 9.7 Hz, ^4J = 1.8 Hz, 1 H), 7.07 (dd, ^3J = 9.7 Hz, ^4J = 5.8 Hz, 1 H), 3.32–3.25 (m, 1 H), 1.86–1.76 (m, 1 H), 1.66–1.57 (m, 1 H), 1.23 (d, J = 8.3 Hz, 3 H), 0.83 (t, J = 9.0 Hz, 3 H) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 152.1, 150.2, 137.1, 120.5, 120.1, 34.1, 26.6, 16.5, 9.6 ppm. IR (neat): $\tilde{\nu}$ = 3425, 2967, 2930, 1578 cm^{-1}. MS (EI): *m*/*z* (%) = 151 (3) $[M]^{+\cdot}$, 136 (59), 123 (100), 122 (73), 109 (32), 104 (10). HRMS (EI): calcd. for $C_9H_{13}NO$ 151.09930; found 151.09978.

2-Phenylpyridin-3-ol (9f): Deliquescent white solid. Yield: 16%. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.24 (d, J = 4.5 Hz, ^4J = 1.5 Hz, 1 H), 7.85 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1 H), 7.41–7.34 (m, 5 H), 7.09 (dd, ^3J = 8.0 Hz, ^4J = 4.5 Hz, 1 H), 2.89 (br. s, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 153.3, 152.1, 137.7, 137.2, 128.9, 128.8, 128.5, 128.1, 121.6, 120.3 ppm. IR (neat): $\tilde{\nu}$ = 3417, 2960, 2927, 1602, 1586 cm^{-1}. MS (EI): *m*/*z* (%) = 171 (5) $[M]^{+\cdot}$, 170 (13), 148 (23), 136 (12), 123 (16), 122 (100), 120 (17), 109 (60). HRMS (EI): calcd. for $C_{11}H_9NO$ 171.06840; found 171.06836.

The data of products **4a** and **7a** are reported in ref.[7]

The data of products *cis*-**1f**, *trans*-**1f**, **2f** and **3f** are reported in ref.[1]

CCDC-669937 (for *trans*-**1d**) and -669938 (for *cis*-**1e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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