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Stereoselective syntheses and transformations of chiral 1,3-aminoalcohols and 1,3-diols derived from nopinone

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ABSTRACT

A library of 1,3-difunctionalized pinane derivatives were synthesized and applied as chiral catalysts in the addition of diethylzinc to benzaldehyde. 1,3-Aminoalcohol **6a** was prepared from (−)-nopinone 2 via stereoselective Mannich condensation and reduction of the resulting β-amino ketone **4**. The key aminoalcohol **6a** was transformed into primary, secondary and tertiary substituted aminoalcohols in order to study the effect of the substituent on catalytic activity. Starting from (−)-nopinone, *cis*- and *trans*-β-hydroxy esters **15** and **16** were prepared in a two-step stereoselective synthesis. Reduction of the hydroxy esters resulted in pinane-based 1,3-diols, while hydrolysis of the esters, followed by DCC-mediated amidation and subsequent reduction, led to *cis*- and *trans*-*N*-benzyl-1,3-aminoalcohols **8** and **23**. *trans*-*N*-Benzyl-1,3-aminoalcohol **8** was also prepared by selective mono-debenzylation of **6a** via a continuous-flow process in an H-Cube® system. The resulting aminoalcohols and diols were applied as chiral catalysts in the reaction of diethylzinc and benzaldehyde.

1. Introduction

In recent decades, natural chiral terpenes, including (+)-pulegone,[1–3] α- and β-pinene[4–6] and fenchone-camphor,[7–9] have proven to be excellent sources for the synthesis of various 1,2- and 1,3-difunctional synthons, such as 1,2- and 1,3-aminoalcohols, which have been applied as useful starting materials in the stereoselective synthesis of compounds of pharmacological interest. They have also served as chiral ligands and auxiliaries in enantioselective transformations.[10–12]

The conversion of enantiomerically pure α-pinene and 3-carene into β-amino acid derivatives such as 1,3-aminoalcohols has recently been reported.[6,13,14] These synthons have been applied as chiral auxiliaries in the enantioselective synthesis of secondary alcohols or pharmacons, for example, esomeprasol or chiral sulfoxides.[15–19]

In addition to their use in enantioselective catalysis, 1,3-aminoalcohols are good starting points for the synthesis of various heterocyclic ring systems such as 1,3-oxazines, 1,3-thiazines or 1,4-oxazepams.[11,20,21]

In recent years, we have devised novel pathways to synthesize new monoterpene-based chiral β-lactams and β-amino acid derivatives derived from (−)- and (+)-apopinene and myrtenic acid.[6,13,14,22–25] It emerged that monoterpene-based 1,3-aminoalcohols prepared from the aforementioned β-amino acid derivatives are excellent building blocks for the synthesis of various 1,3-heterocycles, for example 2-imino-1,3-oxazines, which possess marked anti-cancer activity.[26]

Herein our aim was to synthesize a library of pinane-based chiral 1,3-difunctional synthons such as 1,3-aminoalcohols, β-hydroxy esters and 1,3-diols by starting from (−)-nopinone, prepared from commercially available (−)-β-pinene. We also planned to develop a selective, partial debenzylation method in a flow hydrogenation mesoreactor (H-Cube®) over a supported Pd catalyst and to evaluate the resulting synthons as catalysts in the asymmetric addition of Et_2Zn to benzaldehyde.

2. Results and discussion

2.1. Syntheses of pinane-based 1,3-aminoalcohols and 1,3-diols

The key 1,3-aminoalcohol **6a** was synthesized from (−)-nopinone **2**, prepared from commercially available (−)-β-pinene **1** by a modification of a literature method.[27,28] Compound **2** was converted into a Mannich base with the diastereomeric ratios presented in Table 1. Condensation of **2** with dimethylamine hydrochloride led to an inseparable diastereomeric mixture **3a**,[29] whereas when dibenzylamine hydrochloride or (*R*)-*N*-benzyl-α-methylbenzylamine

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Table 1
Synthesis of amino ketones **3**–**5** via Mannich condensation

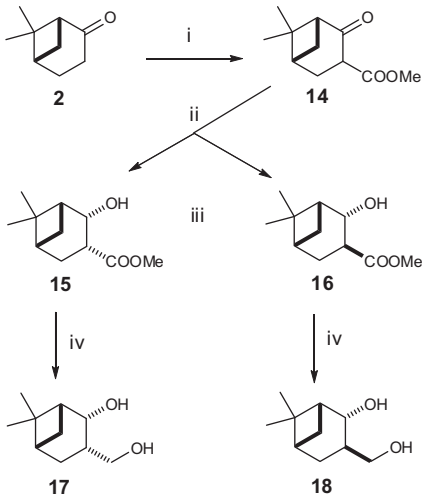
Product	R^1	R^2	Yield (%)	dr (**a**/**b**)
3	Me	Me	81	85:15
4	Bn	Bn	66	100:0
5	(*R*)-CH(Me)Ph	Bn	25	100:0

hydrochloride was applied, the reaction proceeded highly stereoselectively, resulting in the formation of **4a** and **5a** as single diastereoisomers, although in the case of **5a** the yield was dramatically lower (25%) (Scheme 1).

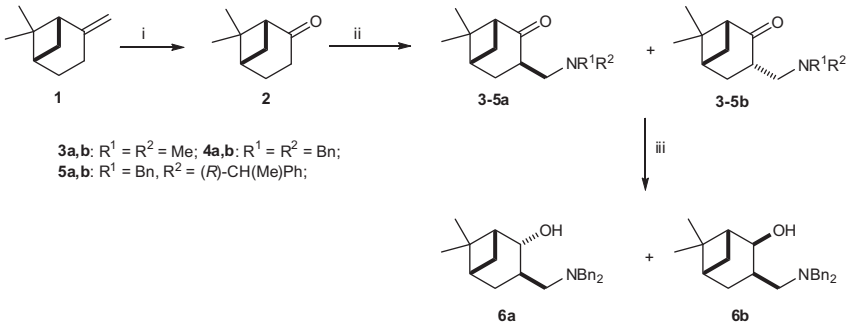
The reduction of aminoketone **4a** with LAH under mild conditions resulted exclusively in the formation of *trans*-1,3-aminoalcohol **6a**. The relative configuration of the stereogenic centres at the 2- and 3-positions was determined by NOESY measurement.

Debenzylation of **6a** led to the key primary aminoalcohol **7**. Starting from **7**, secondary and tertiary aminoalcohols **8**–**12** were then synthesized (Scheme 2). Reductive alkylation of **7** with benzaldehyde, salicylaldehyde or acetone furnished *N*-monosubstituted derivatives **8**–**10**. Ring closure of **9**, followed by LAH reduction, led to *N*-benzyl-*N*-methyl derivative **11**. Similar ring closure of 2′-hydroxybenzyl-substituted compound **9** with formaldehyde took place regioselectively, resulting in *N*-substituted 1,3-benzoxazine **12** as the only product. In order incorporate the secondary alcohol functional group, **6a** was subjected to O-alkylation with benzyl bromide and NaH, giving **13** in acceptable yield.

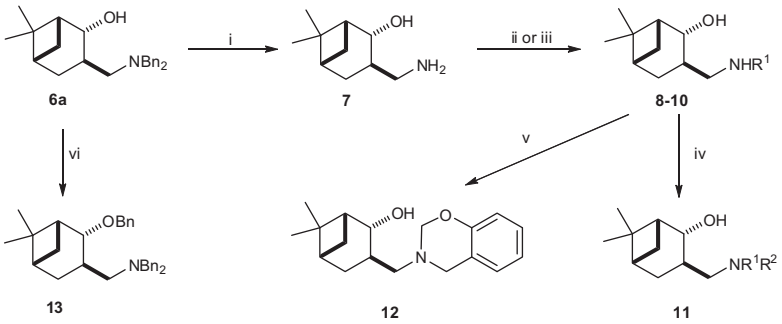
Since alicyclic and bicyclic β-hydroxy esters and 1,3-diols might serve as chiral catalysts or could be used as starting materials for the synthesis of more complex 1,3-heterocycles,[30,31] we decided on the preparation and transformation of some pinane-based β-hydroxy esters and 1,3-diols starting from (−)-nopinone **2**. The synthesis of β-keto ester **14** followed the literature method.[32] Subsequent reduction of **14** with $NaBH_4$ resulted in *cis*-β-hydroxy ester **15** in a highly stereospecific reaction (*cis*/*trans* = 95:5; Scheme 3). Under alkaline conditions, **15** underwent fast and complete isomerization at the carboxylic function, resulting in the *trans*-counterpart **16** in an excellent yield. The relative configuration of the stereogenic centres at the 2- and 3-positions was determined by



Scheme 3. Reagents and conditions: (i) $CO(OMe)_2$, NaH, 68%; (ii) $NaBH_4$, MeOH, 0 °C, 92% (**15**:**16** = 95:5); (iii) NaOMe, MeOH, rt, 3 h, 90%; (iv) LAH, THF, rt, 1 h, 60–78%.



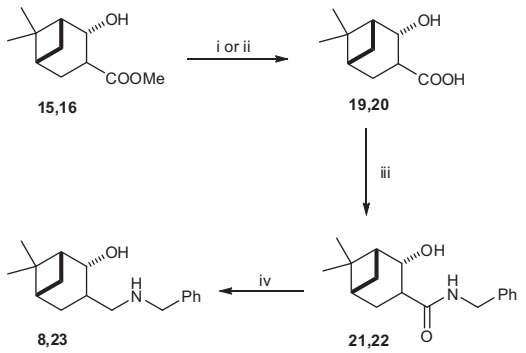
Scheme 1. Reagents and conditions: (i) 2 equiv $NaIO_4$, cat. TBAB, cat. $RuCl_3$, EtOAc/H_2O, rt, 24 h, 85%; (ii) 1.18 equiv $(CH_2O)_n$, 1.08 equiv of amine hydrochloride, dry EtOH, reflux, 1.5 h, 25–66%; (iii) $R^1 = R^2$ = Bn, 4 equiv LAH, THF, rt, 1.5 h, 85%.



Scheme 2. Reagents and conditions: (i) 10% Pd/C, MeOH, 1 atm H_2, rt, 12 h, 79%; (ii) 1 equiv PhCHO (**8**) or 2′-HOC_6H_4CHO (**9**), dry EtOH, rt, 2 h, then 3 equiv $NaBH_4$, dry EtOH, rt, 1 h, 47–95%; (iii) dry acetone, rt, 2 h, then 3 equiv $NaBH_4$, dry EtOH, rt, 1 h, 53%; (iv) R^1 = Bn, CH_2O/H_2O, rt, 1 h, then 3 equiv LAH, THF, reflux, 3 h, 65%, (v) R^1 = 2′-$HOC_6H_4CH_2$, CH_2O/H_2O, rt, 1 h, 62%; (vi) BnBr, NaH, THF, reflux, 15 h, 88%.

NOESY measurements. Reduction of the *cis*- and *trans*-hydroxy esters gave the corresponding pinane-based 1,3-diols **17** and **18**.

Starting from **15** and **16**, an alternative synthesis of *N*-benzyl-substituted 1,3-aminoalcohol **8** and its *cis*-analogue **23** was devised (Scheme 4). Alkaline hydrolysis of **16** with LiOH resulted in the formation of *trans*-β-hydroxy acid **20**. In view of the rapid isomerization under alkaline conditions, the *cis*-analogue **19** was prepared in an acidic medium. Compounds **19** and **20** were successfully converted into amides **21** and **22** with benzylamine in the presence of DCC. Upon reduction of the amides with LAH, *cis*- and *trans*-1,3-aminoalcohols **23** and **8** were obtained.



Scheme 4. Reagents and conditions: (i) **15**, 10% HCl/H_2O, Et_2O, rt, 48 h, 65%; (ii) **16**, 10% $LiOH/H_2O$, Et_2O, rt, 6 h, 85%; (iii) DCC, $BnNH_2$, DCM, 0 °C to rt, 1 h, 27–45%; (iv) LAH, THF, reflux, 2 h, 57–74%.

2.2. Selective synthesis of 8 in a flow hydrogenation mesoreactor (H-Cube®)

Heterogeneous catalytic hydrogenations can gain significant benefit from continuous-flow (CF) processing, due to the greatly enhanced heat and mass transfer, and improved mixing properties.[33–35] Thus, the synthesis of **8** was attempted in a dedicated flow hydrogenation mesoreactor (H-Cube®), and an effective methodology was developed for selective partial N-debenzylation over a supported Pd catalyst. The H_2 gas was produced by the electrolytic decomposition of deionized water; the pyrophoric hydrogenation catalyst was encompassed in a stainless steel cartridge.[36] These features allow for improved operational safety and simplicity compared with the traditional batch process. The flow setup allowed the rapid screening of the reaction conditions, with an excellent level of control over the most important parameters that determine the product selectivity.[37,38] The H-Cube® system was operated in 'Full H_2' mode to deliver the total amount of H_2 produced to the reaction zone. Aliquots of the reaction mixture containing 1 mg mL^{-1} solution of **6a** in MeOH/AcOH = 99:1 were pumped continuously through the system, and the most important reaction parameters were systematically fine-tuned to obtain high conversion and selective secondary amine formation.

Since Pd/C is commonly used when debenzylations are performed in batch reactors, this was our initial choice of catalyst (10% Pd/C).[39] When a flow rate of 1 mL min^{-1} was maintained at 80 °C, quantitative conversion was achieved, but no secondary amine was obtained, with **7** being formed selectively (Table 2, entry 1). When the temperature was lowered to 50 °C, the desired secondary amine became detectable in the reaction mixture (entry 2); at room temperature it was formed in a satisfactory ratio of 81%, while the conversion remained quantitative (entry 3). The adjustment of the flow rate is related to fine-tuning of the residence time on the catalyst bed. We therefore attempted to improve the selectivity of the N-debenzylation as a function of the flow rate. It was found that at a flow rate of 1.5 mL min^{-1}, the proportion of **8** formed increased slightly (85%), but at the expense of conversion (92%, entry 4). It was demonstrated that the longer the residence time, the higher the formation of the primary amine **7**, since **8** was obtained in a proportion of only 73% at a flow rate of 0.5 mL min^{-1} (entry 5). In spite of the above results, we were not totally satisfied, since the Pd/C catalyst deactivated rapidly: a conversion of only 39% was achieved after 2 h of continuous use under the conditions shown in Table 2, entry 3. This was probably due to irreversible adsorption of the substrate or the product(s) onto the catalyst carrier. We therefore changed the catalyst to 5% $Pd/BaSO_4$, with which the formation of the target secondary amine **8** was exclusive at room temperature with a flow rate of 1 mL min^{-1}, with a high conversion of 91% being achieved (entry 6). Indeed, $Pd/BaSO_4$ also proved to be a better choice in terms of reusability, as a conversion of 59% was detected after 2 h of continuous use (Scheme 5).

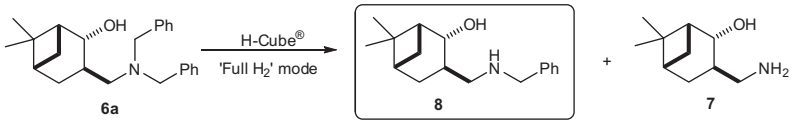
2.3. Application of pinane-based 1,3-aminoalcohols and diols as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde

The application of the prepared 1,3-aminoalcohols **6a–13** and **23**, 1,3-diols **17** and **18** and amides **21** and **22** as catalysts in the

Table 2
Selective synthesis of **8** in a flow hydrogenation mesoreactor

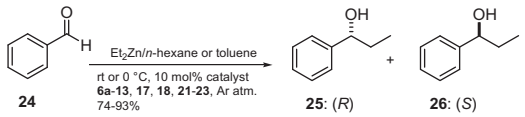
Entry	Catalyst	*T* (°C)	Flow rate[a] (mL min^{-1})	Conversion[b] (%)	Selectivity[b] (%)	
					8	**7**
1	10% Pd/C	80	1	Quantitative	0	100
2	10% Pd/C	50	1	Quantitative	23	77
3	10% Pd/C	rt	1	Quantitative	81	19
4	10% Pd/C	rt	1.5	92	85	15
5	10% Pd/C	rt	0.5	Quantitative	73	27
6	5% $Pd/BaSO_4$	rt	1	91	100	0

[a] $c_{\text{compd } 8}$ = 1 mg mL^{-1} in MeOH/AcOH = 99:1.
[b] Determined by ^1H NMR spectroscopic analysis of the crude material.



Scheme 5.

ethylation of benzaldehyde resulted in the formation of 1-phenyl-1-propanol enantiomers **25** and **26** (Scheme 6).



Scheme 6. Catalysed addition of diethylzinc to benzaldehyde.

The enantiomeric purity of the secondary alcohol obtained was determined by GC on a Chirasil-DEX CB column, according to a literature method.[40,41] Catalysts were applied in a 10% molar ratio and the reactions were carried out in *n*-hexane or toluene at room temperature or 0 °C. The results are presented in Table 3.

In the addition of Et_2Zn in *n*-hexane solution to benzaldehyde, low enantioselectivities were achieved in each case. The stereoselectivity was not improved either by changing the solvent to toluene or by applying a lower temperature. The asymmetric induction was similarly weak when diols **17** and **18** or amides **21** and **22** were used. The formation of the (*S*)-enantiomer **26** was predominant in most cases.

We presume that the low catalytic activity observed was due to the high steric hindrance of the *endo*-hydroxy group at the 2-position, caused by the dimethylmethylene bridge of the pinane ring system.

3. Conclusions

In conclusion, we have developed a library of new chiral pinane-based 1,3-aminoalcohols, 1,3-diols and β-hydroxy amides (**7**–**13**, **17**, **18**, and **21**–**23**). A selective, partial debenzylation method was achieved in a flow hydrogenation mesoreactor over a supported Pd catalyst. From a catalytic aspect, our results revealed that (probably because of the appreciable steric influence of the bicyclic ring system) a stable transition state could not be formed in the reactions of the applied catalysts and Et_2Zn, and their catalytic activity was therefore lower compared with other monoterpene-based 1,3-difunctional catalysts.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz, $\delta = 0$ (TMS)), in the solvents indicated. Chemical shifts are expressed in ppm (δ) relative to TMS as an internal reference. *J* values are given in Hz. Elemental analyses were performed on a Perkin-Elmer 2400 Elemental Analyzer. GC measurements were made on a Perkin-Elmer Autosystem XL GC, consisting of a Flame Ionization Detector and a Turbochrom Workstation data system (Perkin-Elmer Corporation Norwalk, USA). The column used for the direct separation of enantiomers was a Chirasil-DEX CB column (2500 × 0.25 mm I.D.). Optical rotations were obtained with a Perkin-Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F254-precoated TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied.

CF experiments were performed with the H-Cube® (Thales Nano) flow system combined with a built-in electrolytic cell. Compounds **3** and **14** were prepared according to literature methods, and were identical with the products reported therein.[29,32] The configurations of the new stereogenic centres in **6a**, **8**, **16** and **18** were determined in NOESY experiments, based on the observation of NOE effects between H-C(2) and H-C-7 and also between H-C(3) and Me-C(6). Similarly, NOE effects were observed between H-C(2) and H-C(7) and also between H-C(3) and H-C(7) in the cases of **15**, **17** and **23**.

4.1.1. Modified method for the preparation of nopinone 2

To a solution of (−)-β-pinene **1** (10.20 g, 74.9 mmol) in H_2O (200 mL) and EtOAc (200 mL), $RuCl_3$ (0.2 g, 0.96 mmol), $NaIO_4$ (34.5 g, 0.16 mol) and TBAB (0.6 g, 1.9 mmol) were added. The mixture was stirred for 24 h at room temperature. The organic and aqueous phases were separated and the aqueous phase was extracted with EtOAc (2 × 150 mL) The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product obtained was purified by vacuum distillation (8.80 g, 85%). All of the physical and chemical properties of **2** were identical with those reported in the literature.[42]

Table 3
Addition of diethylzinc to benzaldehyde, catalysed by various types of 1,3-aminoalcohols, 1,3-diols and β-hydroxy amides

Entry	Catalyst (10 mol %)	Solvent	*T*	Yield[a] (%)	ee[b] (%)	Config. of major product[c]
1	**6a**	*n*-Hexane	rt	84	16	(*S*)
2	**6a**	*n*-Hexane	0 °C	82	8	(*S*)
3	**6a**	Toluene	rt	85	3	(*R*)
4	**6a**	Toluene	0 °C	80	4	(*R*)
5	**7**	*n*-Hexane	rt	78	14	(*S*)
6	**8**	*n*-Hexane	rt	87	13	(*S*)
7	**9**	*n*-Hexane	rt	82	9	(*R*)
8	**10**	*n*-Hexane	rt	86	6	(*R*)
9	**11**	*n*-Hexane	rt	81	2	(*S*)
10	**12**	*n*-Hexane	rt	83	6	(*S*)
11	**13**	*n*-Hexane	rt	86	8	(*S*)
12	**17**	*n*-Hexane	rt	86	13	(*S*)
13	**18**	*n*-Hexane	rt	88	14	(*S*)
14	**21**	*n*-Hexane	rt	80	18	(*S*)
15	**22**	*n*-Hexane	rt	81	26	(*S*)
16	**22**	Toluene	rt	80	16	(*S*)
17	**23**	*n*-Hexane	rt	74	4	(*S*)

[a] Yields after silica column chromatography.
[b] Determined on the crude product by GC (Chirasil-DEX CB column).
[c] Determined by comparing the GC analysis t_R and the specific rotation with the literature data.[40,41]

4.1.2. General procedure for the preparation of amino ketones 4a and 5a

To a solution of (+)-nopinone **2** (2.76 g, 20.0 mmol) in dry EtOH (8.0 mL), paraformaldehyde (0.71 g, 23.6 mmol) and then dibenzylamine hydrochloride or (*R*)-*N*-benzyl-1-phenylethylamine hydrochloride (21.5 mmol) were added and the mixture was refluxed for 1.5 h. The solvent was evaporated off and the residue was dissolved in CH_2Cl_2 (200 mL). The solution was washed with 5% aqueous KOH (150 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1).

4.1.2.1. (1*R*,3*R*,5*R*)-3-Dibenzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-one 4a. Compound **4a**: 4.98 g (66%); white crystals; mp: 145–147 °C; $[\alpha]_D^{20}$ = +118 (*c* 0.177, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.82 (3H, s), 0.99 (1H, d, *J* = 10.9 Hz), 1.27 (3H, s), 1.97–2.01 (2H, m), 1.84–1.91 (1H, m), 2.10–2.16 (1H, m), 2.30–2.38 (1H, m), 2.47 (1H, t, *J* = 5.3 Hz), 2.59 (1H, dd, *J* = 11.4, 22.2 Hz), 2.61–2.69 (1H, m), 2.84 (1H, dd, *J* = 4.1, 10.9 Hz), 3.34 (2H, d, *J* = 13.4 Hz), 3.83 (2H, d, *J* = 13.3 Hz), 7.19–7.38 (10H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.4, 25.9, 26.2, 27.1, 40.4, 43.0, 58.7, 58.8, 60.0, 127.4, 128.6, 129.4, 139.9, 215.8. Anal. Calcd for $C_{24}H_{29}NO$ (347.49): C, 82.95; H, 8.41; N, 4.03. Found: C, 82.75; H, 8.47; N, 4.12.

4.1.2.2. (1*R*,3*R*,5*R*)-3-{[*N*-Benzyl-*N*-((*R*)-1-phenylethyl)amino]methyl}-6,6-dimethylbicyclo[3.1.1]heptan-2-one 5a. Compound **5a**: 1.05 g (29%); a colourless oil; $[\alpha]_D^{20}$ = +89 (*c* 0.18, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.77 (3H, s), 1.14 (1H, d, *J* = 10.7 Hz), 1.28 (3H, s), 1.43 (3H, d, *J* = 7.0 Hz), 1.85–1.93 (1H, m), 1.99–2.07 (1H, m), 2.14–2.20 (1H, m), 2.36–2.53 (3H, m), 2.66 (1H, t, *J* = 12.4 Hz), 2.81 (1H, dd, *J* = 5.3, 12.5 Hz), 3.40 (1H, d, *J* = 14.2 Hz), 3.75 (2H, d, *J* = 14.2 Hz), 3.85–3.93 (1H, m), 7.19–7.38 (10H, m). Anal. Calcd for $C_{25}H_{31}NO$ (361.52): C, 83.06; H, 8.64; N, 3.87. Found: C, 83.17; H, 8.47; N, 3.99.

4.1.3. (1*R*,2*S*,3*R*,5*R*)-3-Dibenzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 6a

To a slurry of $LiAlH_4$ (2.5 g, 65.9 mmol) in THF (150 mL), compound **4a** (5.0 g, 14.4 mmol) in THF (150 mL) was added dropwise at room temperature. After stirring for 1.5 h (the reduction was monitored by means of TLC), the mixture was decomposed with H_2O (12.5 g) in THF (100 mL) under ice cooling. The inorganic material was filtered off and washed with THF. Drying (Na_2SO_4) and evaporation gave the crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). **6a**: 4.25 g (85%); white crystals; mp: 52–54 °C; $[\alpha]_D^{20}$ = +39 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.35 (1H, d, *J* = 10.2 Hz), 1.07 (3H, s), 1.20 (3H, s), 1.15–1.23 (1H, m), 1.84–1.91 (1H, m), 1.96–2.09 (2H, m), 2.12–2.20 (1H, m), 2.23–2.34 (1H, m), 2.38 (1H, dd, *J* = 5.6, 12.1 Hz), 2.48 (1H, dd, *J* = 10.3, 12.2 Hz), 3.41 (1H, d, *J* = 13.2 Hz), 3.60 (1H, dd, *J* = 2.7, 4.9 Hz), 3.82 (1H, d, *J* = 13.2 Hz), 7.21–7.37 (10H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.8, 28.2, 30.8, 31.3, 37.5, 38.3, 42.1, 48.4, 59.4, 63.5, 79.9, 127.5, 128.7, 129.5, 139.5. Anal. Calcd for $C_{24}H_{31}NO$ (349.51): C, 82.47; H, 8.94; N, 4.01. Found: C, 82.25; H, 8.90; N, 4.09.

4.1.4. (1*R*,2*S*,3*R*,5*R*)-3-Aminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 7

To a suspension of palladium-on-carbon (10% Pd, 0.3 g) in MeOH (100 mL), compound **6a** (2.00 g, 5.7 mmol) was added and the mixture was stirred under an H_2 atmosphere at room temperature and normal pressure. When the reaction was completed (as monitored by TLC, 12 h), the mixture was filtered through a Celite pad and the solution was evaporated to dryness, resulting in the formation of primary aminoalcohol **7** in high purity (based on NMR measurement). **7**: 0.90 g (93%); pale-orange crystals; $[\alpha]_D^{20}$ = +39 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.65 (1H, d, *J* = 10.1 Hz), 1.10 (3H, s), 1.24 (3H, s), 1.28 (1H, ddd, *J* = 2.1, 5.6, 12.3 Hz), 1.92–2.31 (5H, m), 2.68 (1H, dd, *J* = 6,5, 12.3 Hz), 2.80 (1H, dd, *J* = 6.5, 12.3 Hz), 3.82–3.88 (1H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.7, 28.0, 30.1, 31.3, 38.2, 41.8, 42.6, 48.8, 51.1, 78.9. Anal. Calcd for $C_{10}H_{19}NO$ (169.26): C, 70.96; H, 11.31; N, 8.28. Found: C, 70.84; H, 11.26; N, 8.30.

4.1.5. (1*R*,2*S*,3*R*,5*R*)-3-Benzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 8

Method A: To a solution of **7** (1.95 g, 11.5 mmol) in dry EtOH (200 mL), benzaldehyde (1.23 g, 11.6 mmol) was added in one portion, and the solution was stirred at room temperature for 1 h and then evaporated to dryness. The residual product was dissolved in dry EtOH (200 mL) and stirred for a further 1 h. Next, $NaBH_4$ (1.30 g, 34.4 mmol) was added in small portions to the mixture under ice cooling. After stirring for 1 h, the mixture was evaporated to dryness, and the residue was dissolved in H_2O and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography on silica gel (toluene/EtOH = 4:1)

Method B: To a slurry of $LiAlH_4$ (88 mg, 2.32 mmol) in freshly distilled THF (10 mL), **21** (200 mg, 0.73 mmol) in freshly distilled THF (15 mL) was added dropwise at room temperature. The mixture was then refluxed for 2 h (the reduction was monitored by means of TLC), and the mixture was decomposed with H_2O (0.2 g) in THF (3 mL) under ice cooling. The inorganic material was filtered off, washed with THF, dried (Na_2SO_4), filtered and evaporated to dryness. The residue was dissolved in Et_2O and extracted with 5% aqueous HCl solution (4 × 10 mL). The aqueous layer was basified with 10% KOH solution and extracted with CH_2Cl_2 (4 × 20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. **10**: Method A: 1.41 g (47%), Method B: 0.14 g (74%); white crystals; mp: 76–78 °C; $[\alpha]_D^{20}$ = +40 (*c* 0.24, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.63 (1H, d, *J* = 10.1 Hz), 1.11 (3H, s), 1.24 (3H, s), 1.22–1.32 (1H, m), 1.90–1.96 (1H, m), 2.05–2.19 (4H, m), 2.24–2.32 (1H, m), 2.76 (1H, dd, *J* = 5.1, 11.2 Hz), 2.54 (1H, dd, *J* = 9.8, 11.2 Hz), 3.83 (2H, dd, *J* = 7.2, 13.0 Hz), 3.85–3.89 (1H, m), 7.22–7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.7, 28.2, 30.9, 31.5, 38.3, 40.4, 42.0, 48.8, 54.6, 58.8, 80.3, 127.4, 128.5, 128.8, 140.7. Anal. Calcd for $C_{17}H_{25}NO$ (259.39): C, 78.72; H, 9.71; N, 5.40. Found: C, 78.91; H, 9.65; N, 5.30.

4.1.6. (1*R*,2*S*,3*R*,5*R*)-3-(2-Hydroxybenzylaminomethyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 9

To a solution of **7** (0.20 g, 1.18 mmol) in dry EtOH (20 mL), salicylaldehyde (126 μL, 1.18 mmol) was added. The mixture was stirred for 1 h at room temperature and then evaporated to dryness. The residue was dissolved in dry EtOH (20 mL), the solution was stirred for 30 min, and $NaBH_4$ (0.13 g, 3.44 mmol) was then added cautiously in small portions. The mixture was stirred for 12 h at room temperature. The solvent was then removed and the residue obtained was dissolved in H_2O and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (toluene/EtOH = 4:1). **9**: 0.31 g (95%); a yellow oil; $[\alpha]_D^{20}$ = +66 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.65 (1H, d, *J* = 10.4 Hz), 0.86 (1H, d, *J* = 6.6 Hz), 1.09 (3H, s), 1.24 (3H, s), 1.34 (1H, dd, *J* = 2.5, 7.5 Hz), 1.92–1.99 (1H, m), 2.03–2.09 (1H. m), 2.16–2.32 (3H, m), 2.74 (2H, d, *J* = 7.1 Hz), 3.87 (1H. t, *J* = 3.3 Hz), 4.04 (2H, dd, *J* = 13.9, 17.1 Hz), 6.78 (1H, dt, *J* = 1.2, 7.3 Hz), 6.86 (1H, d, *J* = 8.10), 7.01 (1H, d, *J* = 7.5 Hz), 7.17 (1H, dt, *J* = 7.6, 1.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6, 27.8, 29.9, 31.6, 38.0, 38.8, 41.6, 49.2,

53.0, 57.9, 78.9, 116.8, 119.4, 122.6, 128.8, 129.2, 158.4. Anal. Calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.09. Found: C, 73.87; H, 9.23; N, 5.17.

4.1.7. (1*R*,2*S*,3*R*,5*R*)-3-Isopropylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 10

A solution of **7** (0.3 g, 1.77 mmol) in dry acetone (25 mL) was stirred for 1 h at room temperature and then evaporated to dryness. The residue was dissolved in dry EtOH (25 mL), and $NaBH_4$ (0.20 g, 5.29 mmol) was added cautiously in small portions. The mixture was stirred for 12 h at room temperature. The solvent was then removed and the residue was dissolved in H_2O and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 1:2). **10**: 0.20 g (53%); yellow crystals; mp 54–57 °C; $[\alpha]_D^{20}$ = +104 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.65 (1H, d, *J* = 10.2 Hz), 1.08 (6H, d, *J* = 6.3 Hz), 1.11 (3H, s), 1.24 (3H, s) 1.25–1.31 (1H, m), 1.91–2.19 (5H, m), 2.26–2.33 (1H, m), 2.50 (1H, t, *J* = 10.7 Hz), 2.77 (1H, dd, *J* = 5.1, 11.1 Hz), 2.79–2.86 (1H, m), 3.85 (1H, dd, *J* = 2.7, 4.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6, 23.3, 23.5, 28.2, 31.1, 31.6, 38.2, 40.7, 42.0, 48.6, 49.4, 56.7, 80.4. Anal. Calcd for $C_{13}H_{25}NO$ (211.34): C, 73.66 H; 11.92 N; 6.63. Found: C, 73.89 H; 11.69 N; 6.48.

4.1.8. (1*R*,2*S*,3*R*,5*R*)-3-(*N*-Benzyl-*N*-methylaminomethyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 11

To a solution of compound **8** (2.27 g, 8.8 mmol) in Et_2O (20 mL), 33% aqueous CH_2O solution (60 mL) was added, and the mixture was stirred for 1 h at room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product obtained was flashed on a thin silica gel column (*n*-hexane/EtOAc = 4:1), evaporated to dryness and then used without further purification. To a slurry of $LiAlH_4$ (1.14 g, 30.0 mmol) in THF (80 mL), the crude product (5.00 g, 6.6 mmol) in THF (70 mL) was added dropwise at room temperature. After refluxing for 8 h (the reduction was monitored by means of TLC), the mixture was cooled and the $LiAlH_4$ was decomposed with H_2O (2.5 g) in THF (50 mL) under ice cooling. The inorganic material was filtered off and washed with THF. Drying (Na_2SO_4) and evaporation gave the crude product, which was purified as the hydrochloride salt. **11**: 1.57 g (65%); white crystals; mp: 146–150 °C; $[\alpha]_D^{20}$ = +23 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm), two rotamers in a 1:1 ratio were observed: 0.56 (1H, d, *J* = 10.0 Hz), 0.59 (1H, d, *J* = 10.0 Hz), 1.04 (3H, s), 1.05 (3H, s), 1.19 (3H, s), 1.28–1.36 (1H, m), 1.85–2.01 (2H, m), 2.13–2.26 (2H, m), 2.50–2.54 (1H, m), 2.70 (3H, s), 2.76 (3H, s), 2.93–3.21 (2H, m), 3.72–3.81 (1H, m), 4.10 (1H, br s), 4.23–4.56 (2H, m), 7.40–7.70 (5H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.2, 28.3, 28.4, 29.8, 30.0, 32.0, 32.8, 34.7, 34.9, 37.9, 41.5, 41.6, 48.7, 48.8, 52.0, 59.3, 59.8, 63.5, 63.7, 76.2, 76.4, 129.5, 129.8, 130.4, 130.7, 132.3, 132.4, 138.0. Anal. Calcd for $C_{18}H_{27}ClNO$ (309.87): C, 69.77; H, 9.11; N, 4.40. Found: C, 69.89; H, 9.35; N, 4.25.

4.1.9. (1*R*,2*S*,3*R*,5*R*)-3-[(2*H*-Benz[*e*][1,3]oxazin-3(4*H*)-yl)methyl]-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 12

To a solution of **9** (0.20 g, 0.73 mmol) in Et_2O (5 mL), 33% aqueous CH_2O solution (6 mL) was added and the mixture was stirred for 1 h at room temperature. The mixture then was basified with 10% cold aqueous KOH (pH = 10). The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with saturated NaCl solution (3 × 30 mL), then dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). **12**: 0.13 g (62%); a yellow oil; $[\alpha]_D^{20}$ = +58 (*c* 0.260, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.66 (1H, d, *J* = 10.2), 1.12 (3H, s), 1.19–1.27 (4H, m), 1.91–1.96 (1H, m), 2.06–2.15 (2H, m), 2.23–2.33 (2H, m), 2.61 (1H, t, *J* = 12.2 Hz), 2.91 (1H, dd, *J* = 5.9, 12.2 Hz), 3.96 (1H, br s), 4.06 (2H, br s), 4.81–5.04 (2H, m), 6.78 (1H, d, *J* = 8.1 Hz), 6.87 (1H, t, *J* = 7.6 Hz), 6.96 (1H, d, *J* = 7.5 Hz), 7.11 (1H, t, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.7, 28.0, 30.5, 31.2, 38.0, 38.3, 42.0, 48.5, 50.8, 61.3, 79.9, 83.6, 116.8, 120.4, 120.9, 128.0, 128.1, 154.5. Anal. Calcd for $C_{18}H_{25}NO_2$ (287.40): C, 75.22; H, 8.77; N, 4.87. Found: C, 74.91; H, 8.89; N, 5.00.

4.1.10. *N*,*N*-Dibenzyl-1-((1*R*,2*S*,3*R*,5*R*)-2-benzyloxy-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)methanamine 13

A solution of **6a** (0.48 g, 1.37 mmol) in freshly distilled THF (12 mL) was added to a suspension of NaH (60% in mineral oil, 350 mg, 8.8 mmol) in freshly distilled THF (3 mL) under an Ar atmosphere. A solution of benzyl bromide (176 μL, 1.48 mmol) was then added. The mixture was stirred for 15 h at reflux temperature, after which H_2O (3 mL) was added dropwise. The THF was evaporated off and the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 19:1). Isolated compound **13**: 0.53 g (88%); a colourless oil; $[\alpha]_D^{20}$ = +171 (*c* 0.255, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.40 (1H, dd, *J* = 10.0 Hz), 1.06 (3H, s), 1.17 (3H, s), 1.40–1.50 (1H, m), 1.85–1.91 (1H, m), 2.06–2.20 (2H, m), 2.22–2.51 (4H, m), 3.42 (1H, t, *J* = 3.6 Hz), 3.56 (4H, dd, *J* = 13.5, 52.5 Hz), 4.50 (2H, dd, *J* = 11.8, 52.7 Hz), 7.16–7.37 (15 H, m).^{13}C NMR ($CDCl_3$) δ (ppm): 22.7, 27.7, 28.3, 31.5, 34.9, 38.1, 42.0, 43.9, 58.6, 63.9, 70.6, 85.6, 127.1, 127.4, 127.7, 128.4, 128.5, 129.5, 139.9. Anal. Calcd for $C_{30}H_{34}NO$ (424.60): C, 84.86; H, 8.07; N, 3.30. Found: C, 85.02; H, 8.00; N, 3.22.

4.1.11. Stereoselective reduction of oxoester 14

A solution of compound **14** (6.00 g, 30.6 mmol) in MeOH (400 mL) was cooled to 0 °C, and $NaBH_4$ (3.48 g, 92.0 mmol) was added in small portions. The mixture was stirred for 1 h at 0 °C (the reaction was monitored by means of TLC), after which 5% aqueous HCl was then added (40 mL) and the MeOH was evaporated off at room temperature. Next, cold H_2O was added and the mixture was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product obtained was purified by column chromatography on silica gel to give compounds **15** and **16** (*n*-hexane/EtOAc = 4:1).

4.1.11.1. (1*R*,2*S*,3*R*,5*R*)-Methyl 2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate 15. Compound **15**: 5.15 g (85%); a yellow oil; $[\alpha]_D^{20}$ = −10 (*c* 0.240, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.00 (3H, s), 1.15 (3H, s), 1.17 (1H, d, *J* = 10.1 Hz), 1.75–1.90 (2H, m), 2.00–2.13 (2H, m), 2,32 (1H, dd, *J* = 9.0, 12.3 Hz), 3.25 (1H, dd, *J* = 9.0, 17.8 Hz), 3.59 (3H, s), 4.39–4.45 (1H, m), 4.84 (1H, d, *J* = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.5, 26.5, 26.9, 28.5, 38.9, 40.3, 48.0, 51.8, 71.9, 174.1. Anal. Calcd for $C_{11}H_{18}O_3$ (198.26): C, 66.64; H, 9.15. Found: C, 66.76; H, 9.12.

4.1.11.2. (1*R*,2*S*,3*S*,5*R*)-Methyl 2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate 16. Compound **16**: 0.18 g (3%); white crystals; mp: 29–30 °C; $[\alpha]_D^{20}$ = +50 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.78 (1H, d, *J* = 10.1 Hz), 1.01 (3H, s), 1.19 (3H, s), 1.75–1.83 (1H, m), 1.85–1.92 (1H, m), 1.94–1.99 (1H, m), 2.15–2.28 (2H, m), 2.76–2.85 (1H, m), 3.64 (3H, s), 4.16–4.22 (1H, m), 4.93 (1H, d, *J* = 4.1 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.0, 28.2, 28.8, 30.1, 37.5, 41.9, 44.7, 48.2, 52.5, 74.3, 177.8. Anal. Calcd for $C_{11}H_{18}O_3$ (198.26): C, 66.64; H, 9.15. Found: C, 66.78; H 9.01.

4.1.12. Isomerization of 15 to 16

Compound **15** (0.54 g, 2.7 mmol) was dissolved in dry MeOH (10 mL) and the solution was added to a solution of Na (0.013 g, 0.57 mmol) in dry MeOH (10 mL). The mixture was stirred at room temperature for 3 h (the reaction was monitored be means of TLC). The solution was evaporated down to 10 mL, and Et_2O (80 mL) was then added. The mixture was extracted with ice-cold H_2O (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product obtained was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). **16**: 0.46 g (85%).

4.1.13. (1*R*,2*S*,3*S*,5*R*)-3-Hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 17

To a slurry of $LiAlH_4$ (0.34 g, 9.0 mmol) in THF (30 mL), compound **15** (0.89 g, 4.5 mmol) in THF (20 mL) was added dropwise at room temperature. After stirring for 1 h (the reduction was monitored by means of TLC), the mixture was decomposed with H_2O (1.0 g) in THF (20 mL) under ice cooling. The inorganic material was filtered off and washed with THF. Drying (Na_2SO_4) and evaporation led to the crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1). Isolated compound **17**: 0.60 g (78%); white crystals; mp: 30–31 °C; $[\alpha]_D^{20}$ = +27 (*c* 0.235, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.96 (3H, s), 1.15 (3H, s), 1.18 (1H, d, *J* = 9.1 Hz), 1.48 (1H, dd, *J* = 9.2, 12.5 Hz), 1.79–1.90 (2H, m), 2.00–2.10 (2H, m), 2.20–2.32 (1H, m), 3.42 (1H, dt, *J* = 6.2, 10.3 Hz), 3.64–3.71 (1H, m), 4.19–4.29 (3H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.6, 26.0, 28.6, 29.4, 35.6, 38.9, 41.2, 48.1, 63.6, 72.5. Anal. Calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66. Found: C, 70.75; H, 10.51.

4.1.14. (1*R*,2*S*,3*R*,5*R*)-3-Hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 18

To a slurry of $LiAlH_4$ (0.85 g, 22.4 mmol) in THF (60 mL), compound **16** (2.23 g, 11.3 mmol) in THF (25 mL) was added dropwise at room temperature. After stirring for 1 h (the reduction was monitored by means of TLC), the mixture was decomposed with H_2O (2.4 g) in THF (25 mL) under ice cooling. The inorganic material was filtered off and washed with THF. Drying (Na_2SO_4) and evaporation led to the crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1). **18**: 1.14 g (60%); white crystals; mp: 32–35 °C; $[\alpha]_D^{20}$ = +47 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.69 (1H, d, *J* = 9.9 Hz), 1.02 (3H, s), 1.17 (3H, s), 1.48 (1H, dd, *J* = 2.8, 8.5 Hz), 1.81–2.02 (4H, m), 2.07–2.15 (1H, m), 3.29 (1H, dt, *J* = 6.2, 9.9 Hz), 3.45 (1H, dt, *J* = 4.6, 9.8 Hz), 3.61–3.67 (1H, m), 4.45–4.53 (3H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.1, 28.4, 29.1, 30.3, 38.1, 41.8, 41.9, 48.6, 67.5, 74.9. Anal. Calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66. Found: C, 70.23; H, 10.86.

4.1.15. (1*R*,2*S*,3*R*,5*R*)-2-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 19

To a solution of **15** (100 mg, 0.5 mmol) in Et_2O (5 mL), 10% aqueous HCl (5 mL) was added. The mixture was stirred vigorously for 3 days at room temperature (the reaction was monitored by means of TLC). The aqueous layer was then extracted with Et_2O (3 × 30 mL). The combined organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. **19**: 60 mg (65%); white crystals; mp: 59–62 °C $[\alpha]_D^{20}$ = +2 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.09 (3H, s), 1.18 (1H, d, *J* = 10.0 Hz), 1.24 (3H, s), 1.98–2.11 (2H, m), 2.21–2.31 (2H, m), 2.37–2.46 (1H, m), 3.31 (1H, dd, *J* = 9.4, 18.0 Hz), 4.63 (1H, dd, *J* = 4.5, 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.7, 26.3, 26.9, 27.8, 38.7, 40.4, 46.9, 72.9, 179.7. Anal. Calcd for $C_{10}H_{16}O_3$ (184.23): C, 65.19; H, 8.75. Found: C, 65.37; H, 8.52.

4.1.16. (1*R*,2*S*,3*S*,5*R*)-2-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 20

To a solution of **16** (0.50 g, 2.52 mmol) in THF (20 mL), H_2O (20 mL) and $LiOH{\cdot}H_2O$ (0.21 g, 5.00 mmol) were added. The mixture was stirred for 1 h at room temperature (the reaction was monitored by means of TLC). The solution was acidified (pH = 2) with 10% aqueous HCl, and then extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. **20**: 0.39 g (85%); white crystals; mp: 93–96 °C; $[\alpha]_D^{20}$ = +57 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84 (1H, d, *J* = 10.3 Hz), 1.10 (3H, s), 1.26 (3H, s), 1.98–2.18 (3H, m), 2.25–2.37 (2H, m), 3.05 (1H, m), 4.42 (1H, dd, *J* = 3.0, 4.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6, 27.8, 28.9, 29.5, 37.6, 41.0, 44.9, 47.9, 75.9, 182.1. Anal. Calcd for $C_{10}H_{16}O_3$ (184.23): C, 65.19; H, 8.75. Found: C, 65.03; H, 8.91.

4.1.17. (1*R*,2*S*,3*S*,5*R*)-*N*-Benzyl-2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxamide 21

A solution of **20** (1.19 g, 6.46 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C, and DCC was added (1.33 g, 6.46 mmol). The mixture was stirred for 1 h at 0 °C, after which benzylamine (0.8 mL, 7.3 mmol) was added. When the reaction was complete (monitored by means of TLC, 1 h), the mixture was washed with saturated $NaHCO_3$ solution (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:1). **21**: 0.80 g (45%); white crystals; 103–106 °C; $[\alpha]_D^{20}$ = +47 (*c* 0.265, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.95 (1H, d, *J* = 10.3 Hz), 1.09 (3H, s), 1.26 (3H, s), 1.99–2.08 (2H, m), 2.08–2.17 (1H, m), 2.18–2.25 (1H, m), 2.27–2.34 (1H, m), 2.77–2.85 (1H, m), 4.26 (1H, dd, *J* = 2.8, 5.1 Hz), 4.42–4.54 (2H, m), 6.23 (1H, br s), 7.27–7.37 (5H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6, 25.6, 25.9, 27.9, 28.2, 29.7, 37.7, 41.1, 44.1, 45.8, 48.7, 77.3, 127.8, 128.0, 129.0, 138.9, 176.1. Anal. Calcd for $C_{17}H_{23}NO_2$ (273.37): C, 74.69; H, 8.48; N, 5.12. Found: C, 74.33; H, 8.57; N, 5.21.

4.1.18. (1*R*,2*S*,3R,5*R*)-*N*-Benzyl-2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxamide 22

A solution of **19** (0.25 g, 1,36 mmol) in dry CH_2Cl_2 (15 mL) was cooled to 0 °C, and DCC was added (0.28 g, 1.36 mmol). The mixture was stirred for 1 h at 0 °C, after which benzylamine (163 μL, 1.48 mmol) was added. When the reaction was complete (monitored by means of TLC, 1 h), the mixture was washed with saturated $NaHCO_3$ solution (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 2:1). **22**: 95 mg (27%); white crystals; 97–100 °C; $[\alpha]_D^{20}$ = −10 (*c* 0.250, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.16 (3H, s), 1.19 (1H, d, *J* = 10.4 Hz), 1.23 (3H, s), 1.98–2.04 (1H, m), 2.05–2.14 (1H, m), 2.18–2.31 (3H, m), 3.09 (1H, dd, *J* = 9.3, 17.6 Hz), 4.51 (2H, d, *J* = 4.8 Hz), 4.56 (1H, dd, *J* = 4.8, 7.9 Hz), 6.12 (1H, br s), 7.27–7.34 (5H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.5, 25.9, 27.9, 28.8, 38.8, 40.0, 40.7, 43.9, 47.0, 73.0, 127.9, 128.1, 129.1, 138.4, 174.9. Anal. Calcd for $C_{17}H_{23}NO_2$ (273.37): C, 74.69; H, 8.48; N, 5.12. Found: C, 74.81; H, 8.39; N, 5.14.

4.1.19. (1*R*,2*S*,3*S*,5*R*)-3-Benzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol 23

To a slurry of $LiAlH_4$ (176 mg, 4.6 mmol) in freshly distilled THF (10 mL), **22** (0.40 g, 1.54 mmol) in freshly distilled THF (15 mL) was added dropwise at room temperature. The mixture was refluxed for 2 h (the reduction was monitored by means of TLC), after which the mixture was then decomposed with H_2O (0.2 g) in THF (3 mL) under ice cooling. The inorganic material was filtered off and washed with THF, and the filtrate was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography on silica gel (toluene/ethanol = 4:1). **23**: 0.26 g, (57%); white crystals; 36–39 °C; $[\alpha]_D^{20}$ = +46 (*c* 0.255, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.03 (3H, s), 1.16 (1H, d, *J* = 10.0 Hz), 1.21 (3H, s), 1.28 (1H, d, *J* = 14.1 Hz), 1.43–1.53 (1H, m), 1.84–1.95 (2H, m), 2.12–2.20 (1H, m), 2.21–2.28 (1H, m),

2.30–2.41 (1H, m), 2.79–2.93 (2H, m), 3.81 (2H, s), 4.41 (1H, dd, J = 4.7, 8.0 Hz), 7.27–7.36 (5H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 22,7, 25.7, 27.8, 30.2, 32.3, 38.5, 41.2, 46.7, 51.7, 54.1, 73.6, 127.3, 128.3, 128.7, 139.9. Anal. Calcd for $C_{17}H_{25}NO$ (259.39): C, 78.72; H, 9.71; N, 5.40. Found: C, 78.65; H, 9.84; N, 5.36.

4.1.20. General procedure for the reaction of aldehydes with diethylzinc in the presence of chiral catalyst

To the respective catalyst (0.1 mmol), 1 M Et_2Zn in *n*-hexane solution (3 mL, 3 mmol) was added under an Ar atmosphere at room temperature. The reaction was stirred for 25 min at room temperature or 0 °C (see Table 3), and benzaldehyde (1 mmol) was then added to the solution, with subsequent stirring at room temperature or 0 °C (see Table 3) for a further 20 h. The reaction was quenched with saturated NH_4Cl solution (15 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with H_2O (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The crude secondary alcohols obtained were purified by flash column chromatography (*n*-hexane/EtOAc = 4:1). The ee and absolute configuration of the resulting material were determined by chiral GC, using a chiral stationary phase (Chirasil-Dex CB column) at 90 °C.[40,41]

4.1.21. Selective synthesis of 8 in a flow hydrogenation mesoreactor

For the CF reactions, the catalyst cartridge (internal dimensions: 30 mm × 4 mm) was filled with 100 mg of the appropriate hydrogenation catalyst (see Table 2). For small-scale test reactions, 10 mg of **6a** were dissolved in 10 mL of MeOH/AcOH = 99:1. The solution was homogenized by sonication, and then pumped through the H-Cube® reactor under the selected conditions. Between the two reactions, the catalyst bed was washed for 5 min with MeOH/AcOH = 99:1 at a flow rate of 1 mL min^{-1}. The crude product was checked by TLC with a mixture of toluene/EtOH = 4:1 as eluent, and the solvent was evaporated off under vacuum. After dissolution in EtOAc, the mixture was washed with 5% KOH solution, then dried over Na_2SO_4 and finally evaporated. The products were identified by ^{1}H NMR as **7** and **8**.

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