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Synthesis of New Chiral Schiff Bases from (+)-2-Carene

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Abstract—New chiral Schiff bases were synthesized through tricyclic 2-azetidinones as key intermediate products which were obtained by reaction of (+)-2-carene with chlorosulfonyl isocyanate.

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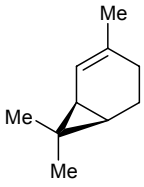
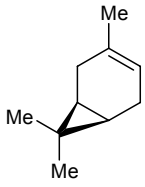
During the past decades optically active monoterpenes were increasingly used as starting compounds for the synthesis of chiral reagents and unique synthons for asymmetric synthesis [1]. Among optically active monoterpenes used in stereoselective syntheses, including asymmetric metal complex catalysis, an important place is occupied by 2- and 3-carenes (**I**, **II**) [2].



I

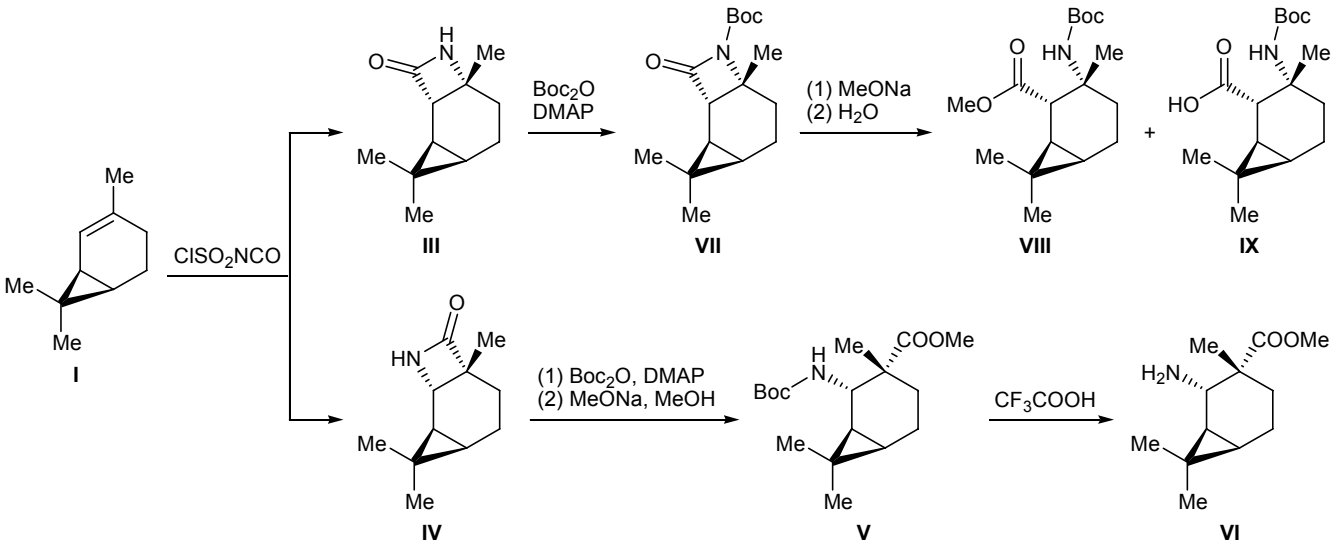


II

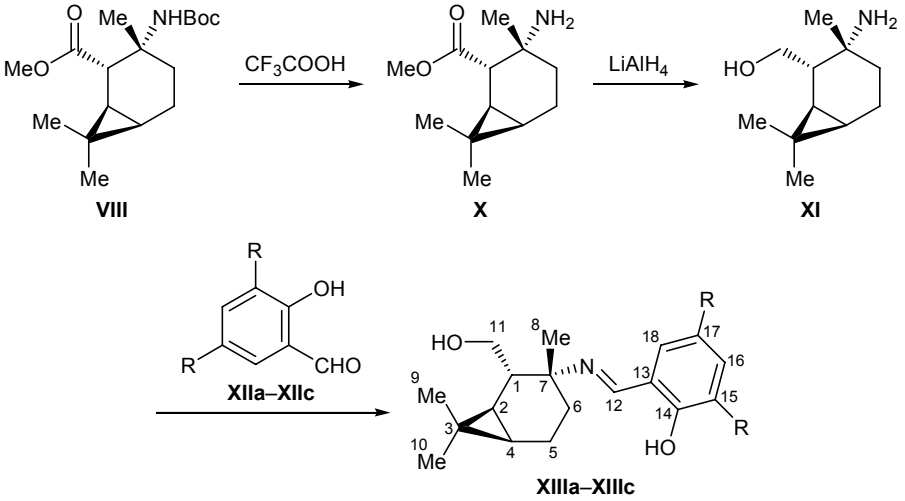
For example, ligands obtained from 3-carene (**II**) ensured vanadium-catalyzed oxidation of prochiral sulfides into optically active sulfoxides [3, 4], palladium-catalyzed asymmetric allylation [5], and addition of diethylzinc to aromatic aldehydes [6, 7].

We recently [8] found that the reaction of (+)-2-carene (**I**) with chlorosulfonyl isocyanate gives a mixture of lactams **III** and **IV** at a ratio of 1 : 1.6 (Scheme 1). Compounds **III** and **IV** were isolated as individual substances by fractional crystallization from hexane. Treatment of lactam **IV** with Boc_2O and subsequent methanolysis afforded compound **V**. By acid hydrolysis of the amide group in **V** we obtained optically active β-amino acid methyl ester **VI**. Likewise, the reaction of **III** with Boc_2O gave afforded compound **VII**. Unlike ester **V**, its isomer **VIII** readily underwent hydrolysis to acid **IX** under basic conditions even in the presence of a small amount of water.

Scheme 1.



Scheme 2.



R = *t*-Bu (**a**), H (**b**), O_2N (**c**).

Depending on the time of contact with water upon treatment of the reaction mixture, either a mixture of ester **VIII** and acid **IX** or substituted amino acid **IX** alone was formed.

Taking into account close position of the newly formed asymmetric centers to the cyclopropane ring, the resulting chiral β-amino acids are promising from the viewpoint of their application in asymmetric synthesis. In fact, it is known that chiral ligands derived from 2-carene are superior to analogous ligands derived from 3-carene (**II**) or α-pinene in the magnitude of asymmetric induction in the synthesis of *syn*-aldols and asymmetric allylboration [9, 10].

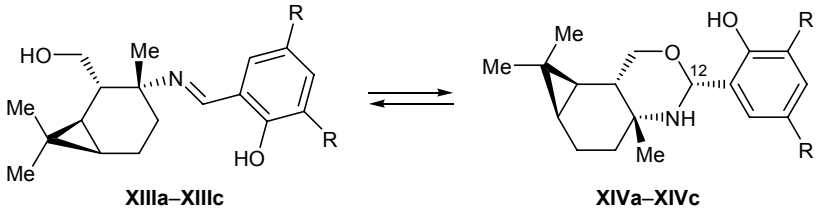
The goal of the present work was to synthesize on the basis of (+)-2-carene (**I**) new compounds, mostly those of the salicylaldehyde imine series, which can be used as chiral ligands in asymmetric metal complex catalysis, specifically in vanadium-catalyzed oxidation of sulfides to sulfoxides.

In order to obtain Schiff bases from salicylaldehyde and its derivatives it was necessary to synthesize terpenoids containing a primary amino group. We found that the use of trifluoroacetic acid instead of water for the decomposition of sodium methoxide after methanolysis of compound **VII** resulted in smooth formation of 95% of *N*-Boc-protected amino ester **VIII**. Interestingly, the reaction mixture contained no hydrolysis product of the amide group, whereas subsequent keeping of compound **VIII** in CH_2Cl_2 in the presence of trifluoroacetic acid gave 97% of amino ester **X** (Scheme 2). The reduction of **X** with $LiAlH_4$ afforded target amino alcohol **XI** in quantitative yield.

As aldehyde component we selected 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**XIIa**), salicylaldehyde (**XIIb**), and 2-hydroxy-3,5-dinitrobenzaldehyde (**XIIc**), taking into account that ligands obtained from the same aldehydes and α-pinene or 3-carene (**II**) turned out to be the most efficient in vanadium-catalyzed asymmetric oxidation of sulfides [3, 4, 11]. The reaction of **XI** with aldehydes **XIIa**–**XIIc** smoothly afforded the corresponding salicylaldehyde imines **XIIIa**–**XIIIc** (Scheme 2).

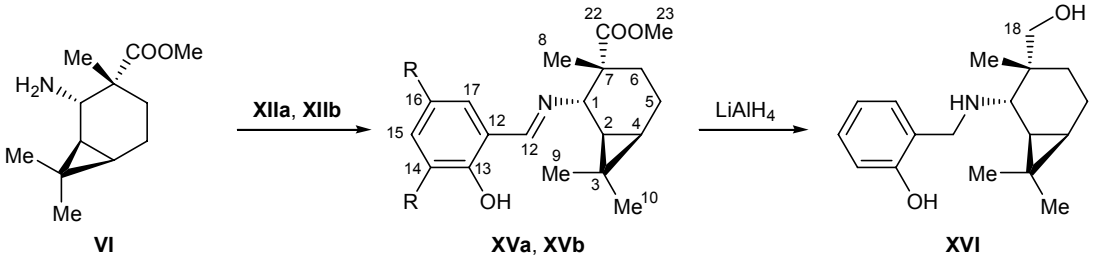
It was reported previously [4, 11] that some Schiff bases derived from monoterpenoids can exist in part as tricyclic benzoxazine structures. According to the ^{1}H NMR data, compounds **XIIIa** and **XIIIb** were

Scheme 3.



R = *t*-Bu (**a**), H (**b**), O_2N (**c**).

Scheme 4.



XII, **XV**, R = *t*-Bu (**a**), H (**b**).

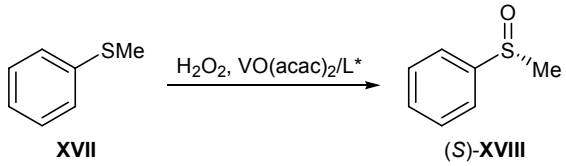
mixtures with the corresponding tricyclic isomers **XIVa** and **XIVb** at ratios of 1:0.4 (**a**) and 1:0.3 (**b**) (Scheme 3). The presence of benzoxazine **XIVc** in addition to structure **XIIIc** in $CDCl_3$ solution (**XIIIc**:**XIVc** ~1:0.1) followed from the ^{1}H NMR spectrum which contained a signal at δ 5.92 ppm assignable to 12-H; however, most signals of **XIVc** in the ^{1}H and ^{13}C NMR spectra could not be identified because of its low concentration. The configuration of C^{12} in molecule **XIVb** was determined with the aid of quantum-chemical calculations. Preliminary conformational analysis of the (12*R*)- and (12*S*)-diastereoisomers of **XIVb**, as well as of Schiff base **XIIIb** revealed, respectively, 29, 31, and 42 stable conformations. The energy of the most stable (12*R*)-conformer of **XIVb** is lower by 6.1 kcal/mol than the energy of the most stable (12*S*)-conformer. Moreover, steric arrangement of substituents in eight most stable conformers of Schiff base **XIIIb** is favorable for cyclization with formation of (12*R*)-diastereoisomer, whereas the most stable conformer suitable for the formation of (12*S*)-diastereoisomer has an energy higher by 1.9 kcal/mol. The mean-square deviations of the calculated NMR chemical shifts of the (12*R*)-diastereoisomer from the experimental values were $\Delta\delta$ = 0.16 ppm (^{1}H) and $\Delta\delta_C$ = 2.8 ppm (^{13}C) against $\Delta\delta$ = 0.26 and $\Delta\delta_C$ = 3.2 ppm for the (12*S*)-configuration. Thus the calculations showed that both thermodynamic and conformational control of the cyclization of Schiff base **XIIIb** should favor formation of tricyclic product with (*R*)-configuration of the C^{12} atom, and the calculated chemical shifts of the (12*R*)-diastereoisomer are better consistent with the experimental ones. Therefore, we can conclude with high probability that compound **XIVb** has just (12*R*)-configuration. The (12*R*)-diastereoisomer of **XIVa** is also appreciably more stable than its (12*S*)-isomer (by 3.5 kcal/mol). Furthermore, the ^{1}H and ^{13}C NMR spectra of **XIVa** are similar to those of **XIVb**, so that the former can also be assigned (12*R*)-configuration.

We previously found that electron-withdrawing substituents in the aromatic ring favor oxazine ring closure in salicylaldehyde imines derived from α-pinene [11]. By contrast, increased concentration of the oxazine structure was observed for analogous ligands derived from 3-carene (**II**) if donor groups were present in the aromatic ring [4]. Obviously, ligands **XIVa**–**XIVc** obtained from 2-carene (**I**) display the same relation between electronic effect of substituents in the benzene ring and the fraction of tricyclic isomer as that found for the ligands based on 3-carene (**II**).

The reduction of compound **VI** with $LiAlH_4$ unexpectedly led to the formation of a complex mixture of products which contained no primary amino group. Therefore, amino ester **VI** was used as starting material for the synthesis of new ligands. By reaction of **VI** with salicylaldehydes **XIIa** and **XIIb** we obtained Schiff bases **XVa** and **XVb**, and the subsequent reduction of **XVb** with $LiAlH_4$ gave compound **XVI** (Scheme 4).

Compounds **XIIIa**–**XIIIc**, **XVa**, **XVb**, and **XVI** were tested as ligands in the asymmetric oxidation of methylsulfanylbenzene (**XVII**) in the presence of $VO(acac)_2$ (Scheme 5). Sulfide **XVII** was used previously as model substrate in the oxidation in the presence of ligands synthesized from 3-carene (**II**) [4] and α-pinene [11]. Taking into account the data of [4, 11], 70% hydrogen peroxide was selected as oxidant, and methylene chloride, as solvent.

Scheme 5.

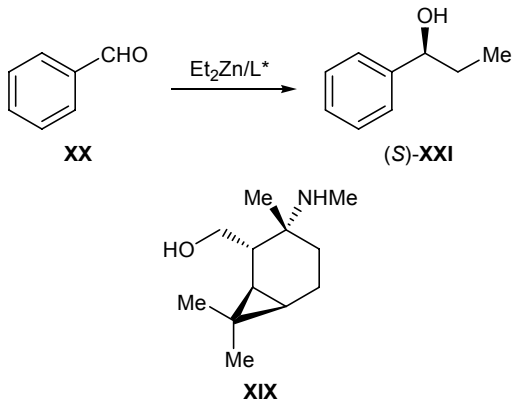


The oxidation with ligand **XIIIa** gave sulfoxide (*S*)-**XVIII** with a small enantiomeric excess (*ee* 8%).

In going to less sterically hindered ligand **XIIIb**, the *ee* value decreased to 4%. The oxidation of **XVII** in the presence of $VO(acac)_2$ and dinitro-substituted ligand **XIIIc** resulted in the formation of (*R*)-**XVIII** as the major stereoisomer, but the *ee* value was also poor (8%). Weak asymmetric induction was also observed in the vanadium-catalyzed oxidation of sulfide **XVII** using ligands **XVa**, **XVb**, and **XVI**; in these cases, the *ee* values did not exceed 6%.

Enantioselective catalytic addition of organometallic reagents, in particular of diethylzinc, to aldehydes is one of the most effective methods for the synthesis of optically active secondary alcohols [12, 13]. We examined enantioselective addition of diethylzinc to benzaldehyde (**XX**) (Scheme 6) in the presence of compound **XVI** and amino alcohol **XIX** which was synthesized by us previously [8] by reduction of a mixture of compounds **VIII** and **IX** with $LiAlH_4$. The results are given in table.

Scheme 6.



The use of compound **XVI** turned out to be ineffective: the reaction was slow, the conversion of benzaldehyde **XX** was as low as 9%, and the product, 1-phenylpropan-1-ol (**XXI**), was almost racemic. The reaction in the presence of amino alcohol **XIX** was characterized by higher conversion and enantioselectivity, and the *ee* value of (*S*)-**XXI** was 29%.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 and AV-400 spectrometers at 500.13 and 400.13 MHz for ^1H and 125.76 and 100.61 MHz for ^{13}C, respectively, from solutions in $CDCl_3$–CCl_4, (~1 : 1 by volume); the residual proton and carbon signals of the solvent were used as reference (δ 7.24, δ_C 76.90 ppm). The structure of the products was determined by NMR spectroscopy with the aid of ^1H–^1H double resonance, ^{13}C *J*-modulation (JMOD; off-resonance decoupling from protons), and two-dimensional ^{13}C–^1H correlation (C–H COSY, direct C–H couplings, $^1J_{CH}$ = 160 Hz) techniques. The high-resolution mass spectra were obtained on a DFS Thermo Scientific spectrometer (USA) (total ion scanning, 0–500 amu, electron impact, 70 eV; direct sample admission into the ion source). The specific optical rotations were measured on a polAAr 3005 polarimeter.

Asymmetric addition of diethylzinc to benzaldehyde (**XX**) in the presence of ligands **XVI** and **XIX**[a]

Ligand no.	Conversion, %	Yield of **XXI**,[b] %	*ee*,[c] %
XVI	9	79	2 (*R*)
XIX	53	77	29 (*S*)

[a] Molar ratio **XX**–$ZnEt_2$–ligand 1 : 1.1 : 0.1; temperature 0°C.
[b] Calculated on the reacted benzaldehyde (**XX**).
[c] Enantiomeric excess of **XXI** was determined by GC–MS using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of **XXI** with published data.

Chirospecific GC–MS analysis was performed on a 6890N gas chromatograph coupled with a 5973 INERT mass selective detector (Agilent, USA) [Cyclosil-B capillary column, 30 m × 0.32 mm × 0.25 μm; oven temperature programming from 50°C (2 min) to 220°C (5 min) at a rate of 2 deg/min; injector and interface temperature 250°C; carrier gas helium, flow rate 2 ml/min, split ratio 99 : 1; amu range 9–500; sample volume 1 μl]. The purity of the initial compounds and final products was checked by GLC on an Agilent 7820A instrument (USA) equipped with a flame-ionization detector and an HP-5 30-m quartz capillary column (carrier gas helium).

Conformational analysis of diastereoisomers of compounds **XIIIb**, **XIVb**, and **XIVa** was performed according to the procedure described in [14]. Geometric parameters of all conformers were optimized in terms of the density functional theory (DFT) using PBE functional [15] and L1 basis set (Λ01 [16], an analog cc-pVDZ); PRIRODA software [17]. The NMR chemical shifts were calculated by the GIAO/DFT/PBE method (L22 basis set, Λ22, an analog of cc-pCVTZ; PRIRODA software). Visualizations of the optimized structures, as well as their Cartesian coordinates and calculated chemical shifts, are available at *http://limor1.nioch.nsc.ru/quant/conformers/carenes/*.

Quantum-chemical calculations were performed at the Information and Calculation Center of the Novosibirsk State University (*http://www.nusc.ru/*).

Compounds **VI** {$[\alpha]_D^{24}$ = –21.2° (*c* = 1.2, $CHCl_3$)} and **VIII** {$[\alpha]_D^{23}$ = –34.7° (*c* = 0.2, $CHCl_3$)} were synthesized from (+)-2-carene (**I**) according to the procedure described in [8].

Methyl (1*R*,2*S*,3*R*,6*R*)-3-amino-3,7,7-trimethylbicyclo[4.1.0]heptane-2-carboxylate (X). A solution of 0.500 g (1.60 mmol) of compound **VIII** in 30 ml of anhydrous methylene chloride was cooled to 0°C, 1.5 ml of trifluoroacetic acid was added, and the mixture was stirred for 2.5 h at 0°C, neutralized with a saturated aqueous solution of $NaHCO_3$, and extracted with methylene chloride. The extract was dried over Na_2SO_4, and the solvent was distilled off. Yield 0.330 g (97%). The ^{1}H NMR spectrum of the product coincided with that given in [8].

{(1*R*,2*S*,3*R*,6*R*)-3-Amino-3,7,7-trimethylbicyclo[4.1.0]heptan-2-yl}methanol (XI). A solution of 0.166 g (0.79 mmol) of compound **X** in 30 ml of anhydrous tetrahydrofuran was cooled to 0°C, a suspension of 0.100 g (2.63 mmol) of $LiAlH_4$ in 5 ml of anhydrous THF was added dropwise under stirring, and the mixture was heated for 2 h under reflux. The mixture was then treated with water until hydrogen no longer evolved, and the precipitate was filtered off and washed with diethyl ether. Yield 0.144 g (100%), $[\alpha]_D^{29}$ = –23.06° (*c* = 0.72, $CHCl_3$), mp 69.3°C. ^{1}H NMR spectrum, δ, ppm: 0.61 d.d (4-H, $J_{4,2}$ = 9.0, $J_{4,5\text{-}ax}$ = 8.2 Hz), 0.85 m (1-H), 0.87 s (C^9H_3), 0.96 d.d (2-H, $J_{2,4}$ = 9.0, $J_{2,1}$ = 5.2 Hz), 1.01 s ($C^{10}H_3$), 0.98–1.12 m (2H, 6-H), 1.14 s (C^8H_3), 1.63 d.d.d.d (5-H_{eq}, ^2J = 15.0, $J_{5\text{-}eq,6\text{-}ax}$ = 7.6, $J_{5\text{-}eq,6\text{-}eq}$ = 1.0, $J_{5\text{-}eq,4}$ = 1.0 Hz), 1.84 d.d.d.d (5-H_{ax}, ^2J = 15.0, $J_{5\text{-}ax,6\text{-}ax}$ = 11.8, $J_{5\text{-}ax,4}$ = 8.2, $J_{5\text{-}ax,6\text{-}eq}$ = 8.2 Hz), 3.53 d.d (11-H, ^2J = 11.0, $J_{11,1}$ = 2.4 Hz), 4.22 d.d (11′-H, ^2J = 11.0, $J_{11',1}$ = 2.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 39.58 d (C^1), 21.20 d (C^2), 17.22 s (C^3), 18.36 d (C^4), 15.40 t (C^5), 39.01 t (C^6), 50.74 s (C^7), 27.18 q (C^8), 15.19 q (C^9), 29.10 q (C^{10}), 65.02 t (C^{11}). Found: *m*/*z* 183.1614 $[M]^+$. $C_{11}H_{21}NO$. Calculated: *M* 183.1618.

2,4-Di-*tert*-butyl-6-{(1*R*,2*S*,3*R*,6*R*)-2-hydroxymethyl-3,7,7-trimethylbicyclo[4.1.0]heptan-3-yliminomethyl}phenol (XIIIa). A solution of 0.040 g of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**XIIa**) in 5 ml of methanol was added dropwise under stirring to a solution of 0.073 g of compound **XI** in 4 ml of anhydrous methanol. The mixture was stirred for 2 days at room temperature, the solvent was distilled off, and the residue was subjected to column chromatography on silica gel using hexane–triethylamine (1%)–chloroform (0 to 100%; gradient elution) as eluent. Yield 0.058 g (85%), $[\alpha]_D^{21}$ +6.11° (*c* = 0.36, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.56 d.d (2-H, $J_{2,4}$ = 9.4, $J_{2,1}$ = 5.1 Hz), 0.80 d.d.d (4-H, $J_{4,2}$ = 9.4, $J_{4,5\text{-}ax}$ = 8.1, $J_{4,5\text{-}eq}$ = 1.0 Hz), 1.03 s (C^9H_3), 1.11 s ($C^{10}H_3$), 1.30 s (17-*t*-Bu), 1.33 s (C^8H_3), 1.28–1.37 m (6-H_{ax}), 1.40–1.47 m (1-H), 1.43 s (15-*t*-Bu), 1.51 d.d.d (6-H_{eq}, ^2J = 14.0, $J_{6\text{-}eq,5\text{-}ax}$ = 8.1, $J_{6\text{-}eq,5\text{-}eq}$ = 1.5 Hz), 1.54 d.d.d.d (5-H_{eq}, ^2J = 14.8, $J_{5\text{-}eq,6\text{-}ax}$ = 7.2, $J_{5\text{-}eq,6\text{-}eq}$ = 1.5, $J_{5\text{-}eq,4}$ = 1.0 Hz), 1.91 d.d.d.d (5-H_{ax}, ^2J = 14.8, $J_{5\text{-}ax,6\text{-}ax}$ = 11.7, $J_{5\text{-}ax,4}$ = 8.1, $J_{5\text{-}ax,6\text{-}eq}$ = 8.1 Hz), 3.63 d.d (11-H, ^2J = 10.5, $J_{11,1}$ = 7.6 Hz), 3.87 d.d (11′-H, ^2J = 10.5, $J_{11',1}$ = 5.4 Hz), 7.03 d (18-H, $J_{18,16}$ = 2.4 Hz), 7.32 d (16-H, $J_{16,18}$ = 2.4 Hz), 8.34 s (12-H), 14.20 br.s (14-OH). ^{13}C NMR spectrum, δ_C, ppm: 44.47 d (C^1), 23.25 d (C^2), 17.55 s (C^3), 19.82 d (C^4), 15.91 t (C^5), 38.68 t (C^6), 58.68 s (C^7), 24.73 q (C^8), 15.87 q (C^9), 29.04 q (C^{10}), 65.00 t (C^{11}), 162.56 d (C^{12}), 118.14 s (C^{13}), 158.49 s (C^{14}), 136.84 s (C^{15}), 126.49 d (C^{16}), 139.44 s (C^{17}), 125.89 d (C^{18}), 35.14 s (C^{19}), 34.14 s (C^{20}), 29.56 q (3C, C^{21}), 31.65 q (3C, C^{22}). Found: *m*/*z* 399.3131 $[M]^+$. $C_{26}H_{41}NO_2$. Calculated: *M* 399.3132.

Tautomer **XIVa**. ^{1}H NMR spectrum, δ, ppm: 0.69 d.d.d (4-H, $J_{4,2}$ = 9.3, $J_{4,5\text{-}ax}$ = 7.5, $J_{4,5\text{-}eq}$ = 1.0 Hz), 0.85 d.d (2-H, $J_{2,4}$ = 9.3, $J_{2,1}$ = 3.8 Hz), 0.97 s (C^9H_3), 1.06 s ($C^{10}H_3$), 1.07–1.21 m (1-H, 6-H), 1.30 s (17-*t*-Bu), 1.39 s (C^8H_3, 15-*t*-Bu), 1.40–1.46 m (6′-H), 1.59 d.d.m (5-H_{eq}, ^2J = 14.8, $J_{5\text{-}eq,6'}$ = 7.2 Hz), 1.78 m (5-H_{ax}), 4.00 d.d (11-H, ^2J = 11.4, $J_{11,1}$ = 1.5 Hz), 4.39 d.d (11′-H, ^2J = 11.4, $J_{11',1}$ = 2.2 Hz), 5.45 s (12-H), 7.21 d and 7.25 d (16-H, 18-H, $J_{16,18}$ = 2.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 33.65 d (C^1), 22.97 d (C^2), 16.93 s (C^3), 18.88 d (C^4), 14.59 t (C^5), 36.08 t (C^6), 48.20 s (C^7), 24.46 q (C^8), 15.50 q (C^9), 29.62 q (C^{10}), 69.63 t (C^{11}), 81.32 d (C^{12}), 123.85 s (C^{13}), 151.98 s (C^{14}), 135.80 s (C^{15}), 123.53 d and 120.63 d (C^{16}, C^{18}), 140.36 s (C^{17}), 35.14 s (C^{19}), 35.03 s (C^{20}), 29.84 q (3C, C^{21}), 31.85 q (3C, C^{22}).

2-{(1*R*,2*S*,3*R*,6*R*)-2-Hydroxymethyl-3,7,7-trimethylbicyclo[4.1.0]heptan-3-yliminomethyl}phenol (XIIIb). A solution of 0.038 g of 2-hydroxybenzaldehyde (**XIIb**) in 5 ml of methanol was added dropwise under stirring to a solution of 0.108 g of compound **XI** in 4 ml of anhydrous methanol, and the mixture was stirred for 3 days at room temperature. The solvent was distilled off, and the residue was purified by column chromatography on silica gel using hexane–triethylamine (1%)–chloroform (0 to 100%; gradient elution) as eluent. Yield 0.089 g (73%),

$[\alpha]_D^{21}$ = +1.85° (*c* = 1.3, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.51 d.d (2-H, $J_{2,4}$ = 9.2, $J_{2,1}$ = 5.1 Hz), 0.82 d.d.d (4-H, $J_{4,2}$ = 9.2, $J_{4,5\text{-}ax}$ = 8.2, $J_{4,5\text{-}eq}$ = 1.0 Hz), 1.01 s (C^9H_3), 1.08 s ($C^{10}H_3$), 1.33 s (C^8H_3), 1.29–1.47 m (3H, 6-H, 1-H), 1.57 d.d.d.d (5-H_{eq}, ^2J = 14.8, $J_{5\text{-}eq,6\text{-}ax}$ = 7.3, $J_{5\text{-}eq,4}$ = 1.0, $J_{5\text{-eq},6\text{-}eq}$ = 1.0 Hz), 1.90 d.d.d.d (5-H_{ax}, ^2J = 14.8, $J_{5\text{-}ax,6\text{-}ax}$ = 11.9, $J_{5\text{-}ax,4}$ = 8.2, $J_{5\text{-}ax,6\text{-}eq}$ = 8.2 Hz), 3.54 d.d (11-H, ^2J = 10.3, $J_{11,1}$ = 7.2 Hz), 3.77 d.d (11′-H, ^2J = 10.3, $J_{11',1}$ = 5.6 Hz), 6.79 d.d.d (17-H, $J_{17,16}$ = 7.5, $J_{17,18}$ = 7.5, $J_{17,15}$ = 1.1 Hz), 6.78 d.d (15-H, $J_{15,16}$ = 8.1, $J_{15,17}$ = 1.1 Hz), 7.19 d.d (18-H, $J_{18,17}$ = 7.5, $J_{18,16}$ = 1.6 Hz), 7.24 d.d.d (16-H, $J_{16,15}$ = 8.1, $J_{16,17}$ = 7.5, $J_{16,18}$ = 1.6 Hz), 8.30 s (12-H), 14.4 br.s (14-OH). ^{13}C NMR spectrum, δ_C, ppm: 44.24 d (C^1), 23.05 d (C^2), 17.56 s (C^3), 19.58 d (C^4), 15.82 t (C^5), 38.95 t (C^6), 58.75 s (C^7), 23.92 q (C^8), 15.77 q (C^9), 28.94 q (C^{10}), 64.77 t (C^{11}), 161.16 d (C^{12}), 118.83 s (C^{13}), 162.24 s (C^{14}), 117.49 d (C^{15}), 132.11 d (C^{16}), 117.84 d (C^{17}), 131.21 d (C^{18}). Found: *m*/*z* 287.1884 $[M]^+$. $C_{18}H_{25}O_2N$. Calculated: *M* 287.1880.

Tautomer **XIVb**. ^{1}H NMR spectrum, δ, ppm: 0.68 d.d.d (4-H, $J_{4,2}$ = 9.2, $J_{4,5\text{-}ax}$ = 7.5, $J_{4,5\text{-}eq}$ = 1.0 Hz), 0.81 d.d (2-H, $J_{2,4}$ = 9.2, $J_{2,1}$ = 3.8 Hz), 0.96 s (C^9H_3), 1.04 s ($C^{10}H_3$), 1.10 m (1-H), 1.19 m (6-H_{eq}), 1.36 s (C^8H_3), 1.39 m (6-H_{ax}), 1.59 d.d.d.d (5-H_{eq}, ^2J = 15.0, $J_{5\text{-}eq,6\text{-}ax}$ = 7.3, $J_{5\text{-}eq,6\text{-}eq}$ = 1.8, $J_{5\text{-}eq,4}$ = 1.0 Hz), 1.78 d.d.d.d (5-H_{ax}, ^2J = 15.0, $J_{5\text{-}ax,6\text{-}ax}$ = 12.2, $J_{5a,4}$ = 7.5, $J_{5\text{-}ax,6\text{-}eq}$ = 7.5 Hz), 3.97 d.d (11-H, ^2J = 11.4, $J_{11,1}$ = 1.7 Hz), 4.38 d.d (11′-H, ^2J = 11.4, $J_{11',1}$ = 2.2 Hz), 5.47 s (12-H), 6.76–6.81 m (15-H, 17-H), 7.14 d.d.d (16-H, $J_{16,15}$ = 8.1, $J_{16,17}$ = 7.5, $J_{16,18}$ = 1.6 Hz), 7.31 br.d (18-H, $J_{18,17}$ = 7.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 33.54 d (C^1), 22.91 d (C^2), 16.89 s (C^3), 18.72 d (C^4), 14.52 t (C^5), 35.98 t (C^6), 48.10 s (C^7), 24.31 q (C^8), 15.42 q (C^9), 29.52 q (C^{10}), 69.56 t (C^{11}), 81.26 d (C^{12}), 124.13 s (C^{13}), 155.54 s (C^{14}), 116.52 d (C^{15}), 129.45 d (C^{16}), 119.07 d (C^{17}), 126.31 d (C^{18}).

2-{(1*R*,2*S*,3*R*,6*R*)-2-Hydroxymethyl-3,7,7-trimethylbicyclo[4.1.0]heptan-3-yliminomethyl}-4,6-dinitrophenol (XIIIc). A solution of 0.099 g of 3,5-dinitrosalicylaldehyde (**XIIc**) in 5 ml of methanol was added dropwise under stirring to a solution of 0.121 g of compound **XI** in 4 ml of anhydrous methanol. The mixture was stirred for 2 days at room temperature, the solvent was distilled off, and the residue was recrystallized from diethyl ether with addition of hexane. Yield 0.157 g (89%), $[\alpha]_D^{21}$ = +7.5° (*c* = 0.31, $CHCl_3$), mp 60.4°C. ^{1}H NMR spectrum, δ, ppm ($CDCl_3$–acetone-d_6): 0.80 d.d (2-H, $J_{2,4}$ = 8.8, $J_{2,1}$ = 6.1 Hz), 0.89 d.d.d (4-H, $J_{4,2}$ = 8.8, $J_{4,5\text{-}ax}$ = 8.3, $J_{4,5\text{-}eq}$ = 1.0 Hz), 0.94 s (C^9H_3), 1.12 s ($C^{10}H_3$), 1.36–1.47 m (1-H, 6-H_{ax}), 1.58 s (C^8H_3), 1.66 d.d.d.d (5-H_{eq}, ^2J = 15.3, $J_{5\text{-}eq,6\text{-}ax}$ = 7.5, $J_{5\text{-}eq,6\text{-}eq}$ = 1.5, $J_{5\text{-}eq,4}$ = 1.0 Hz), 1.80 br.d.d (6-H_{eq}, ^2J = 14.3, $J_{6\text{-}eq,5\text{-}ax}$ = 8.3 Hz), 1.91 d.d.d.d (5-H_{ax}, ^2J = 15.3, $J_{5\text{-}ax,6\text{-}ax}$ = 11.5, $J_{5\text{-}ax,4}$ = 8.3, $J_{5\text{-}ax,6\text{-}eq}$ = 8.3 Hz), 3.75 d.d (11-H, ^2J = 11.1, $J_{11,1}$ = 4.7 Hz), 3.93 d.d (11′-H, ^2J = 11.1, $J_{11',1}$ = 4.4 Hz), 8.49 d (18-H, $J_{18,16}$ = 3.1 Hz), 8.58 br.s (12-H), 8.80 d (16-H, $J_{16,18}$ = 3.1 Hz), 14.61 br.s (14-OH). ^{13}C NMR spectrum, δ_C, ppm: 42.21 d (C^1), 21.18 d (C^2), 18.05 s (C^3), 18.74 d (C^4), 14.79 t (C^5), 37.01 t (C^6), 60.53 s (C^7), 24.05 q (C^8), 15.26 q (C^9), 28.29 q (C^{10}), 63.02 t (C^{11}), 164.06 d (C^{12}), 117.59 s (C^{13}), 170.74 s (C^{14}), 130.68 s (C^{15}), 127.94 d (C^{16}), 140.73 s (C^{17}), 136.74 d (C^{18}). Found: *m*/*z* 377.1579 $[M]^+$. $C_{18}H_{23}O_6N_3$. Calculated: *M* 377.1581.

Methyl (1*S*,2*S*,3*R*,6*R*)-2-(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-3,7,7-trimethylbicyclo-[4.1.0]heptane-3-carboxylate (XVa). A solution of 0.052 g of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**XIIa**) in 5 ml of methanol was added dropwise under stirring to a solution of 0.052 g of compound **VI** in 4 ml of anhydrous methanol. The mixture was stirred for 7 days at room temperature, the solvent was distilled off, and the residue was purified by column chromatography on silica gel using hexane–triethylamine (1%)–chloroform (0 to 100%; gradient elution) as eluent. Yield 0.095 g (100%), $[\alpha]_D^{26}$ = –67.73° (*c* = 0.43, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.76 d.d.d (4-H, $J_{4,2}$ = 9.4, $J_{4,5\text{-}ax}$ = 8.1, $J_{4,5\text{-}eq}$ = 2.3), 0.98 d.d (2-H, $J_{2,4}$ = 9.4, $J_{2,1}$ = 5.1 Hz), 1.05 s (C^9H_3, $C^{10}H_3$), 1.07 m (6-H_{ax}), 1.09 s (C^8H_3), 1.30 s (16-*t*-Bu), 1.44 s (14-*t*-Bu), 1.47 m (5-H_{eq}), 2.01 m (5-H_{ax}), 2.04 m (6-H_{eq}), 2.66 d.d (1-H, $J_{1,2}$ = 5.1 Hz), 3.75 s (OCH_3), 7.05 d (17-H, $J_{17,15}$ = 2.4 Hz), 7.33 d (15-H, $J_{15,17}$ = 2.4 Hz), 8.27 s (11-H), 13.8 br.s (OH). ^{13}C NMR spectrum, δ_C, ppm: 71.10 d (C^1), 27.48 d (C^2), 18.00 s (C^3), 20.77 d (C^4), 16.47 t (C^5), 34.64 t (C^6), 45.07 s (C^7), 24.15 q (C^8), 15.56 q (C^9), 28.54 q (C^{10}), 165.04 d (C^{11}), 117.74 s (C^{12}), 158.42 s (C^{13}), 136.72 s (C^{14}), 126.62 d (C^{15}), 139.40 s (C^{16}), 125.63 d (C^{17}), 35.07 s (C^{18}), 34.06 s (C^{19}), 29.50 q (3C, C^{20}), 31.57 q (3C, C^{21}), 175.20 s (C^{22}), 51.30 q (C^{23}). Found: *m*/*z* 427.3084 $[M]^+$. $C_{27}H_{41}NO_3$. Calculated: *M* 427.3081.

Methyl (1*S*,2*S*,3*R*,6*R*)-2-(2-hydroxybenzylideneamino)-3,7,7-trimethylbicyclo[4.1.0]heptane-3-carboxylate (XVb). A solution of 0.038 g of 2-hydroxybenzaldehyde **XIIb** in 5 ml of methanol was added to a solution of 0.104 g of compound **VI** in 4 ml of anhy-

drous methanol. The mixture was stirred for 3 days at room temperature, the solvent was distilled off, and the residue was purified by column chromatography on silica gel using hexane–triethylamine (1%)–chloroform (0 to 100%; gradient elution) as eluent. Yield 0.155 g (100%), $[\alpha]_D^{23}$ = –130.77° (*c* = 0.13, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.72 d.d.d (4-H, $J_{4,2}$ = 9.4, $J_{4,5\text{-}ax}$ = 8.3, $J_{4,5\text{-}eq}$ = 2.0 Hz), 0.95 d.d (2-H, $J_{2,4}$ = 9.4, $J_{2,1}$ = 5.1 Hz), 1.01 m (6-H$_{ax}$), 1.02 s (C^9H_3, $C^{10}H_3$), 1.06 s (C^8H_3), 1.49 d.d.d.d (5-H$_{eq}$, ^2J = 14.6, $J_{5\text{-}eq,6\text{-}ax}$ = 7.6, $J_{5\text{-}eq,6\text{-}eq}$ = 2.8, $J_{5\text{-}eq,4}$ = 2.0 Hz), 1.97 d.d.d.d (5-H$_{ax}$, ^2J = 14.6, $J_{5\text{-}ax,6\text{-}ax}$ = 10.3, $J_{5\text{-}ax,6\text{-}eq}$ = 8.3, $J_{5\text{-}ax,4}$ = 8.3 Hz), 2.03 m (6-H$_{eq}$), 2.65 d (1-H, $J_{1,2}$ = 5.1), 3.73 s (OCH_3), 6.80 d.d.d (16-H, $J_{16,15}$ = 7.5, $J_{16,17}$ = 7.5, $J_{16,14}$ = 1.1 Hz), 6.91 d.d.d (14-H, $J_{14,15}$ = 8.1, $J_{14,16}$ = 1.1, $J_{14,17}$ = 0.6 Hz), 7.20 d.d (17-H, $J_{17,16}$ = 7.5, $J_{17,15}$ = 1.6 Hz), 7.25 d.d.d (15-H, $J_{15,14}$ = 8.1, $J_{15,16}$ = 7.5, $J_{15,17}$ = 1.6 Hz), 8.25 s (11-H), 13.54 br.s (OH). ^{13}C NMR spectrum, δ_C, ppm: 70.88 d (C^1), 27.69 d (C^2), 18.13 s (C^3), 20.52 d (C^4), 16.41 t (C^5), 34.67 t (C^6), 45.16 s (C^7), 24.10 q (C^8), 15.59 q (C^9), 28.52 q (C^{10}), 163.93 d (C^{11}), 118.74 s (C^{12}), 161.59 s (C^{13}), 117.26 d (C^{14}), 132.10 d (C^{15}), 118.06 d S^{16}), 131.00 d (C^{17}), 175.02 s (C^{18}), 51.40 q (C^{19}). Found: *m*/*z* 315.1827 $[M]^+$. $C_{19}H_{25}NO_3$. Calculated: *M* 315.1829.

2-{(1*S*,2*S*,3*R*,6*R*)-3-Hydroxymethyl-3,7,7-trimethylbicyclo[4.1.0]heptan-2-ylaminomethyl}-phenol (XVI). A solution of 0.051 g of compound **XVb** in 30 ml of anhydrous THF was cooled to 0°C, a suspension of 0.018 g of $LiAlH_4$ in 5 ml of anhydrous THF was carefully added dropwise under stirring, and the mixture was heated for 2 h under reflux. The mixture was then treated with water until hydrogen no longer evolved, and the precipitate was filtered off and washed with diethyl ether. The product was purified by column chromatography on silica gel (5 g) using hexane–ethyl acetate (0 to 100%; gradient elution) as eluent. Yield 0.047 g (100%), $[\alpha]_D^{26}$ = +0.71° (*c* = 0.27, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.70 d.d (2-H, $J_{2,4}$ = 9.2, $J_{2,1}$ = 5.2 Hz), 0.78 d.d.d (4-H, $J_{4,2}$ = 9.2, $J_{4,5\text{-}ax}$ = 8.3, $J_{4,5\text{-}eq}$ = 2.0 Hz), 0.80 s (C^9H_3), 0.90 m (6-H$_{ax}$), 1.06 s (C^8H_3), 1.10 s ($C^{10}H_3$), 1.32 m (6-H$_{eq}$), 1.38 d.d.d.d (5-H$_{eq}$, ^2J = 14.5, $J_{5eq,6\text{-}ax}$ = 7.6, $J_{5\text{-}eq,6\text{-}eq}$ = 3.0, $J_{5\text{-}eq,4}$ = 2.0 Hz), 1.71 d.d.d.d (5-H$_{ax}$, ^2J = 14.5, $J_{5\text{-}ax,6\text{-}ax}$ = 10.5, $J_{5\text{-}ax,4}$ = 8.3, $J_{5\text{-}ax,6\text{-}eq}$ = 8.3 Hz), 2.15 d (1-H, $J_{1,2}$ = 5.2 Hz), 3.39 d and 4.05 d (1H each, 18-H, ^2J = 11.0 Hz), 3.80 d and 4.24 d (2H, 11-H, ^2J = 13.7 Hz), 6.73 d.d (16-H, $J_{16,15}$ = 7.4, $J_{16,17}$ = 7.4 Hz), 6.85 br.d (14-H, $J_{14,15}$ = 8.0 Hz), 6.97 br.d (17-H, $J_{17,16}$ = 7.4 Hz), 7.13 br.d.d (15-H, $J_{15,14}$ = 8.0, $J_{15,16}$ = 7.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 59.82 d (C^1), 24.84 d (C^2), 17.72 s (C^3), 20.54 d (C^4), 15.31 t (C^5), 34.57 t (C^6), 36.92 s (C^7), 22.91 q (C^8), 15.19 q (C^9), 28.42 q (C^{10}), 49.72 t (C^{11}), 120.97 s (C^{12}), 158.09 s (C^{13}), 116.45 d (C^{14}), 129.26 d (C^{15}), 118.93 d (C^{16}), 129.00 d (C^{17}), 66.81 t (C^{18}). Found: *m*/*z* 289.2035 $[M]^+$. $C_{18}H_{27}NO_2$. Calculated: *M* 289.2036.

Typical procedure for the asymmetric oxidation of methylsulfanylbenzene (XVII). A mixture of 2 mg (8 μmol) of $VO(acac)_2$ and 12 μmol of the corresponding ligand in 2 ml of appropriate anhydrous solvent was stirred until $VO(acac)_2$ dissolved completely (~20 min). A solution of 0.105 g (847 μmol) of methylsulfanylbenzene (**XVII**) in 3 ml of anhydrous solvent was added under stirring, the mixture was cooled if necessary, and 1.06 mmol of oxidant was added. The progress of the reaction was monitored by GLC. When the reaction was complete, the mixture was treated with 10 ml of distilled water, the organic layer was separated, the aqueous layer was extracted with the solvent used (2×5 ml), and the extracts were combined with the organic layer, washed with water (2×10 ml), and dried over $MgSO_4$. The drying agent was filtered off, the solvent was distilled off on a rotary evaporator, and the residue was analyzed by ^{1}H NMR spectroscopy to determine the conversion and product ratio. The enantiomeric excess of compound **XVIII** was determined from the ^{1}H NMR spectra recorded in CCl_4–$CDCl_3$ in the presence of an equal amount (by weight) of (*R*)-(–)-3,5-dinitro-*N*-(1-phenylethyl)benzamide. The absolute configuration was assigned by comparing the sign of the optical rotation of **XVIII** with published data.

Typical procedure for the addition of diethylzinc to benzaldehyde. A 1 M solution of diethylzinc in hexane (from Acros Organics), 3.33 ml (3.33 mmol), was slowly added to a solution of 0.3 mmol of the corresponding ligand in 20 ml of anhydrous hexane. The resulting solution was stirred for 20 min at room temperature, cooled to 0°C, and 0.32 g (3 mmol) of benzaldehyde (**XX**) was added. The mixture was kept for 20 h at 0°C, a saturated solution of ammonium chloride was added, the mixture was stirred for 15 min, the organic phase was separated, and the aqueous phase was extracted with diethyl ether. The extract was combined with the organic phase and dried over Na_2SO_4, the solvent was distilled off, and the residue was purified by column chromatography on silica gel using hexane–ethyl acetate (10 to 50%; gradient elution) as eluent. The *ee* value of 1-phenylpropan-1-ol (**XXI**) was determined by GC–MS using a column with a chiral stationary phase.

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