Synthesis of Enantiomerically Pure 1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-2-ones as Chiral Host Compounds for Enantioselective Photochemical Reactions in Solution

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Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

Abstract: The synthesis of the title compounds is described. As common starting material, 1,5,7-trimethyl-2,4-dioxo-3-azabicyclo[3.3.1]-nonan-7-carboxylic acid chloride (**4**) was employed which is in turn available from *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp's triacid). For the synthesis of the diastereomeric menthyl esters **1** and **2**, the chloride **4** was initially substituted by (–)-menthol and its imide part was subsequently reduced to an amide by consecutive treatment with sodium borohydride and triethylsilane. The enantiomerically pure hosts **3a** and **3b** were obtained from the racemate by resolution of their *N*-menthoxycarbonyl derivatives. The racemic compounds *rac*-**3a** and *rac*-**3b** were prepared from the acid chloride **4** and the *ortho*-hydroxyanilines **9a** and **9b** via amide formation, condensation to the oxazole and reduction. Structural data are provided which prove the absolute configuration of compound *ent*-**3b** and the relative configuration of compound *rac*-**3a**.

Key words: supramolecular chemistry, amides, enantiomeric resolution, reductions, photochemistry

Introduction

In the course of stereoselective organic transformations, a defined spatial arrangement of substituents is required to guarantee the differentiation of stereoheterotopic faces.[2] Ground state conformations often serve as useful models to predict the stereochemical outcome of a reaction. This is the more true if the reacting centre of a molecule is rigidly attached to a bulky substituent.

In a recently launched research project, we planned to differentiate the enantiotopic faces of lactams by hydrogen bonding to a suitable chiral host. The goal was to conduct light-induced reactions within the host-guest complex in a stereoselective fashion. The host was to serve as a non-covalently bound, stoichiometric complexing agent. Previous attempts to achieve enantioselective photochemical reactions in solution by chiral complexing agents had encountered little success.[3] We hoped to overcome the problems associated with the high conformational flexibility of many systems by using a rigid host which offers an easily accessible binding site and which simultaneously exhibits an effective sterically demanding "shield". The requirements for a conceivable host are depicted in Figure 1.

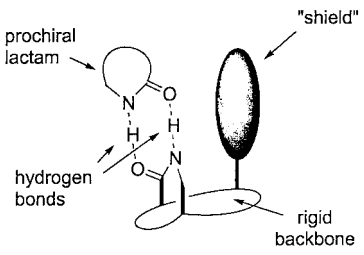

Figure 1 Model of a projected host for the differentiation of enantiotopic faces in prochiral lactams

In essence, the host should consist of three spatially aligned substituents (drawn in bold) and a rigid backbone. One of the most common and easily accessible compounds which offers this spatial alignment is *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp's triacid).[4] Chiral derivatives thereof have been used in molecular recognition studies[5] and have been employed in enantioselective protonation[6] and auxiliary-induced enantioselective C-C-bond forming reactions.[7] Our first target compounds which were conceived to fulfill the requirements provided in Figure 1 were the diastereomeric menthyl esters **1** and **2** (Figure 2). Since they exhibit opposite chirality in the bicyclic lactam part we expected them to behave as if they were enantiomers. In preliminary experiments they proved to be valuable hosts which were superiour to most of the previously used complexing agents.[8] Still, a second generation of host compounds **3** was synthesized whose "shield" was flat and due to its greater diameter more effective (Figure 2). They were prepared in racemic form and subsequently resolved by derivatization.

Unfortunately, host **3a** turned out to be photochemically unstable.[8] Contrary to that, compound **3b** and its enantiomer *ent*-**3b** were stable. They are currently the premier chiral complexing agents in use and induced enantioselectivities up to 98% *ee* in photocycloaddition reactions of prochiral lactams.[9]

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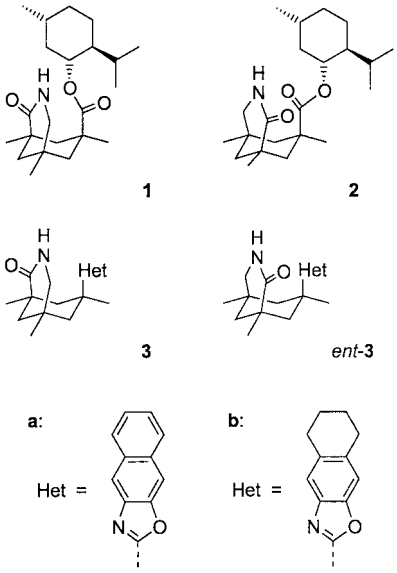


Figure 2 Chiral host compounds **1**, **2**, and **3** synthesized

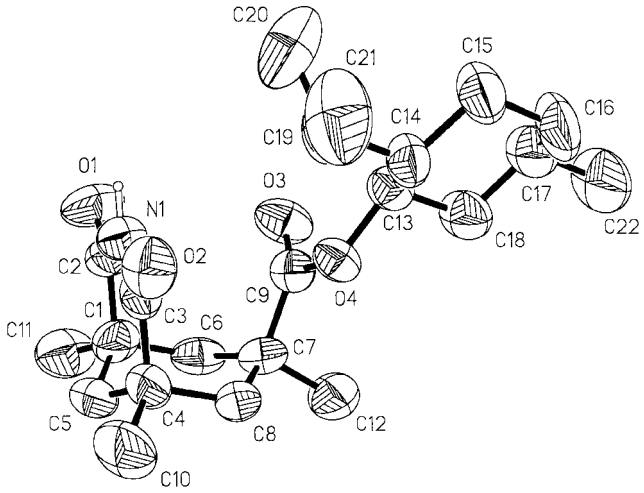


Figure 3 A molecule of compound **5** in the crystal (ORTEP drawing)[11]

In this account we report on the synthesis of the host compounds **1**, **2** and **3**. In addition, structural data are provided which prove the constitution of lactam *rac*-**3a** and the absolute configuration of lactam *ent*-**3b**.

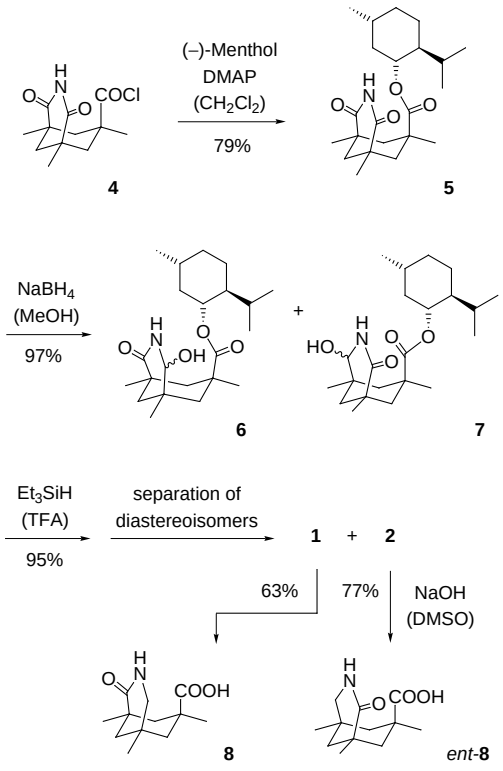
Results and Discussion

*Preparation of the Hosts **1** and **2***: The synthesis of the diastereomeric hosts **1** and **2** is summarized in Scheme 1. It starts with the alkoxydechlorination of the known acid chloride **4**.[7d] The menthyl ester **5** was obtained in 79% yield. Unexpectedly, the reduction of the imide group with sodium borohydride in methanol occurred with considerable regioselectivity. One diastereotopic carbonyl group was reduced with a preference of 4:1. Provided that the major conformer in solution is similar to the solid state conformation depicted in Figure 3,[10] the hydride attack took place at the carbonyl group which is in proximity to the bulky *iso*-propyl group of the menthyl substituent. The more readily accessible carbonyl group is not reduced. In succinimide and maleimide reductions, there is precedence for a similar reaction course. The carbonyl group adjacent to the most substituted carbon is reduced by sodium borohydride with significant regioselectivity.[11] Contrary to that, succinimide[12] and glutarimide[13] reductions which were conducted with di-*iso*-butylaluminum hydride (Dibal-H) or lithium tri(*sec*-butyl)borohydride (L-Selectride) occurred at the carbonyl group remote from the larger ring substituent. Chelation[14] and complexation[15] have been shown to play an important role in the regioselectivity of these reactions. We have not further studied the effect of the counter ion on the regioselectivity of the borohydride reductions nor have we investigated the influence of the reducing agent more closely. To account for the observed regioselectivity we rely on the explanation previously provided for the above-mentioned imide reductions.[11]

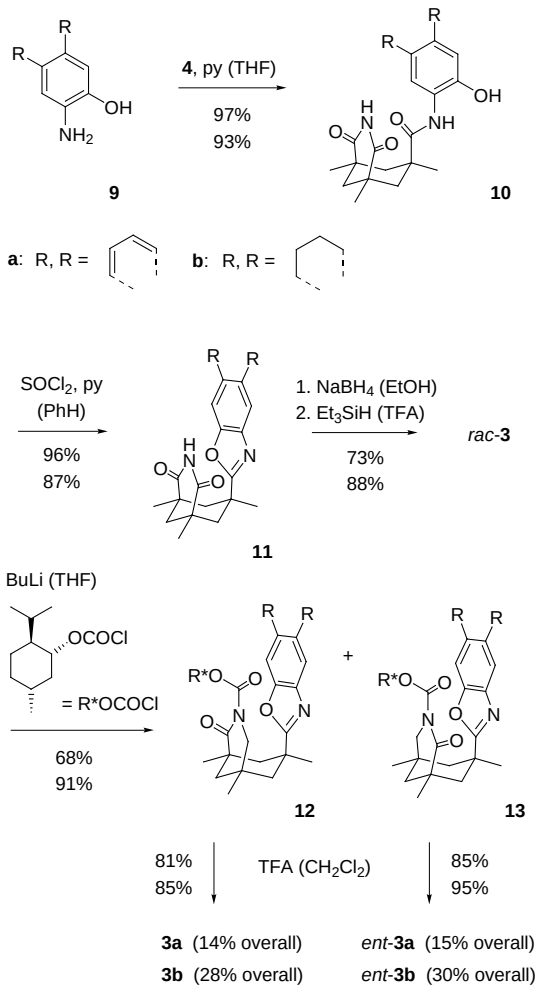
With regard to the facial diastereoselectivity the hydride transfer appears to occur exclusively from one face. As a consequence only two out of four possible diastereoisomers were isolated. Their relative configuration was not assigned. Further reduction of the diastereoisomers **6** and **7** with triethylsilane in trifluoroacetic acid (TFA) yielded the lactams **1** and **2** the ratio of which was identical to the diastereomeric ratio of their precursors. The lactams were separated by flash chromatography. The relative configuration of compound **1** was elucidated by single crystal X-ray crystallography.[9a] As the absolute configuration of the menthyl group is known the X-ray analysis provided the absolute configuration of the 3-azabicyclo[3.3.1]nonan-2-one skeleton. It additionally proved the regioselectivity of the above-mentioned borohydride reduction step.

The saponification of the menthyl esters **1** and **2** was favorably conducted with sodium hydroxide in DMSO (Scheme 1). The acid **8** was obtained from ester **1**. Ester **2** yielded the enantiomeric acid *ent*-**8**. As we considered the acids to be suitable precursors for the synthesis of oxazoles **3** and *ent*-**3** we looked into possible activation methods for the carboxyl group. It turned out that all the methods we successfully employed [$SOCl_2$; oxalyl chloride, DMF (cat.); Yamaguchi procedure] led to racemization. Presumably, the activation facilitates an intramolecular attack of the amide nitrogen atom at the carboxyl group.[16] Potential intermediates formed by this process have a plane of symmetry and consequently yield racemic products.

*Preparation of the Hosts **3***: Due to the facile racemization upon activation of the carboxylic acids **8** and *ent*-**8** the preparation of the oxazoles was attempted via conventional oxazole synthesis and subsequent resolution of the racemic products. The protocol of Rebek, Curran et al. was followed which relies on a resolution via the corresponding *N*-menthoxycarbonyl derivatives.[7d] Starting again



Scheme 1



Scheme 2

with the known acid chloride **4** the aminodechlorination by the corresponding anilines **9a** and **9b**[17] gave the anilides **10** in excellent yields (Scheme 2). In our hands, it proved advantageous to conduct the oxazole formation prior to the reduction of the imide. Consequently, the amides **10** were treated with thionyl chloride to provide the oxazole imides **11**. The reduction sequence ($NaBH_4$, MeOH; Et_3SiH, TFA) previously employed for the related imides **6** and **7** furnished the desired oxazole lactams *rac*-**3**. The resolution proceeded uneventfully and enabled access to the enantiomerically pure hosts **3a**, **3b**, *ent*-**3a** and *ent*-**3b**. Since compounds **3a** and *ent*-**3a** were not photostable their resolution was conducted only once and the yields given in Scheme 2 are not optimized. The synthesis of **3b** and *ent*-**3b** is carried out on a routine basis in our laboratories and proved reproducible. Overall, each enantiomer is obtained in ca. 30% yield from the acid chloride **4**.

The assignment of the absolute configuration of compounds **3** was initially based on the correlation of their specific rotation {**3a**: $[\alpha]_D^{20}$ +42.3 ($c = 1$, CH_2Cl_2); **3b**: $[\alpha]_D^{20}$ +7.4 ($c = 1$, $CHCl_3$)} with the specific rotation of the known dextrorotatory benzoxazole **3c** (R = H) {$[\alpha]_D^{20}$ +7.4 ($c = 2$, $CHCl_3$)} whose absolute configuration had been reported.[7d] Unfortunately, we could not achieve the crystallization of the diastereomeric compounds **12** or **13**. We finally achieved the crystallization of the enantiomerically pure host *ent*-**3b** and of the racemic host *rac*-**3a**.

Crystallographic Studies: With the advent of modern crystallographic techniques and equipment the determination of absolute configuration by anomalous X-ray diffraction experiments has become possible for compounds that do not carry a heavy atom. Due to this development we were able to assign the absolute configuration depicted in Figure 4 to the enantiomerically pure compound *ent*-**3b**.[18] The result is in line with our earlier assignment based on the specific rotation.

Crystals suitable for X-ray analysis were also obtained from the racemic host *rac*-**3a**. The structure depicted in Figure 5 nicely illustrates the two key features of our chiral complexing agent.[19] First, the naphthalene unit acts as a fully planar "shield" which covers the back of the host compound. Secondly, the lactam part of the host binds efficiently to other lactams via hydrogen bonds. In the case shown, host **3a** binds to its sterically complementary enantiomer *ent*-**3a**. If enantiomerically pure host compounds are employed in solution this type of binding is impossible due to severe interactions of the naphthalene backbone. Instead, the photochemical substrate coordinates to the host, a fact which in turn enables the differentiation of the enantiotopic faces.

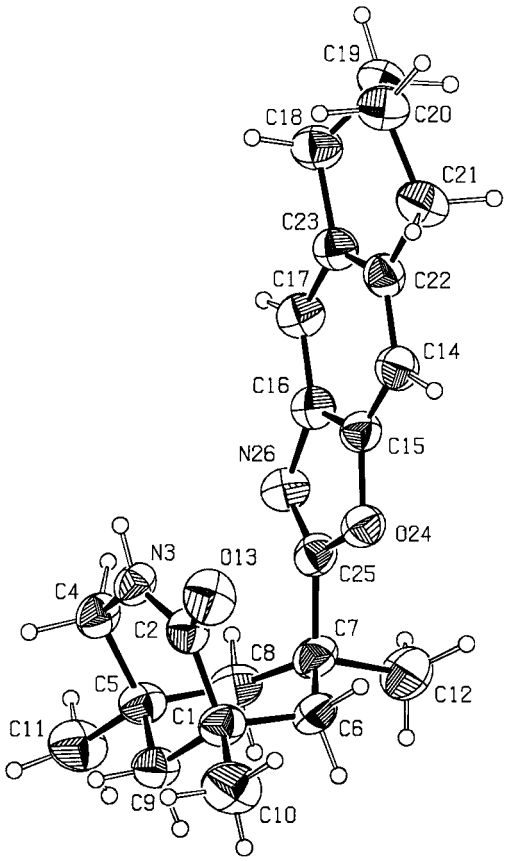


Figure 4 ORTEP drawing of the molecular structure of *ent*-**3b** in the solid state. Thermal ellipsoids are at the 30 % probability level[18]

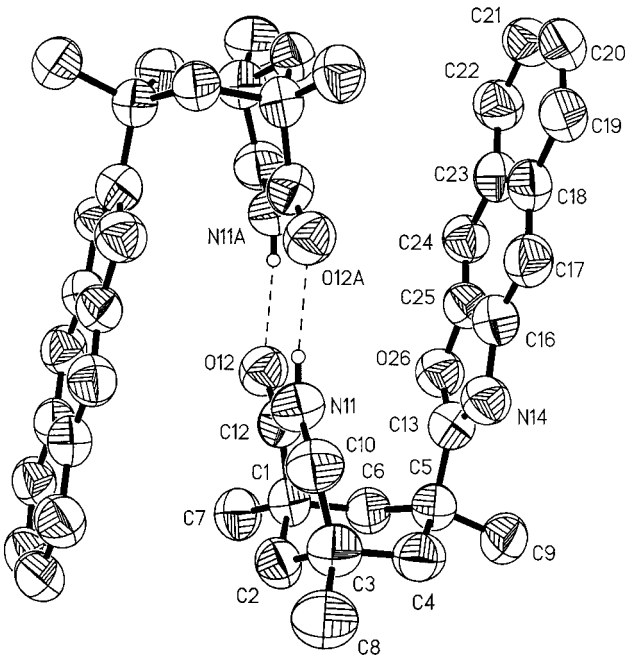


Figure 5 Two molecules of compound **3a** and *ent*-**3a** in the crystal (ORTEP drawing)[19]

Conclusion and Outlook

In summary, we have described the synthesis of the host compounds **1**, **2** and **3**, which are valuable chiral complexing agents used in photochemical transformations. The starting material for all syntheses is the achiral imide **4**, which is readily available from Kemp's triacid. Modifications of the host systems for application in other thermal and photochemical reactions are possible and are projected in the course of further investigations. Results of these studies will be reported in due course.

All reactions involving water-sensitive compounds were carried out in flame-dried glassware with magnetic stirring under Ar. Common solvents (TBME = *t*-BuOMe, Et_2O, P = pentane, CH_2Cl_2, MeOH and EtOH) were distilled prior to use. Anhyd CH_2Cl_2 was distilled from CaH_2, anhyd benzene and THF from Na prior to use. Et_3N was distilled from CaH_2. All other reagents and solvents were used as received. Melting points (uncorrected): Reichert hot bench. IR: Bruker IFS 88 FT-IR or Nicolet 510M FT-IR. MS: Varian CH7 (EI). ^1H and ^{13}C NMR: Bruker ARX-200, Bruker AC-300, Bruker AM-400, Bruker AMX-500, Varian unit plus 600. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent at ambient temperature unless stated otherwise. Chemical shifts are reported relative to TMS as an internal reference. Elemental analysis: Elementar vario EL. Optical rotations: Perkin-Elmer 241, determined at r.t. HPLC: Merck-Hitachi L6200A equipped with an UV spectrometer detector (254 nm). Column: Daicel Chiralcel OD. TLC: Merck aluminum sheets (0.2 mm silica gel 60 F_{254}. Detection: by UV or by coloration with ceric ammonium molybdate (CAM). Flash chromatography:[20] Merck silica gel 60 (230–400 mesh ASTM) (ca 50 g for 1 g of material to be separated).

Imide Ester 5 by Esterification of Acid Chloride 4 with (–)-Menthol

Acid chloride **4**[7d] (17.9 mmol, 4.60 g), (–)-menthol (32.0 mmol, 5.00 g) and *N*,*N*-dimethylaminopyridine (DMAP) (18.0 mmol, 2.20 g) were dissolved in anhyd CH_2Cl_2 (100 mL) and the solution was refluxed. After 24 h another lot of DMAP (2.20 g, 18.0 mmol) was added and after additional 24 h of reflux the solution was allowed to cool to r.t. H_2O (100 mL) and CH_2Cl_2 (400 mL) were added, the layers separated and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with H_2O (25 mL), 1 N HCl (25 mL), sat. aq $NaHCO_3$ solution (25 mL) and brine (25 mL). The combined aqueous layers were extracted with CH_2Cl_2 (100 mL), were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil (9.40 g). Purification of this material by flash chromatography (P–TBME, 3:1) gave a white solid (5.31 g, 79%); R_f 0.14 (P–TBME, 75:25); mp 154°C; $[\alpha]_D^{20}$ –40.6 (c = 1.1, CH_2Cl_2).

IR (KBr): ν = 3212 (m, br, NH), 3098 (m, NH), 2959 (s, CH), 2930 (s, CH), 2872 (s, CH), 1719 (s, C=O), 1696 (vs, C=O), 1462 (m), 1383 (m), 1208 (vs), 1179 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.62 (d, 3 H, ^3J = 7.0 Hz, CH_3CHCH_3), 0.78–0.82 (m, 1 H, $CH_3CHCHHCH_2$), 0.83 (d, 3 H, ^3J = 7.0 Hz, CH_3CHCH_3), 0.86 [d, 3 H, ^3J = 6.6 Hz, $CH_3CH(CH_2)_2$], 0.89–0.96 (m, 2 H, $CO_2CHCHHCH$, CH_3CHCH_2CHH), 1.07 (d, 1 H, ^2J = 14.0 Hz, OCOCCHH), 1.12–1.16 (m, 1 H, OCOCCHH), 1.16 (s, 3 H, CH_3CCO_2), 1.19 (s, 3 H, CH_3CCONH), 1.20 (s, 3 H, CH_3CCONH), 1.31 (d, 1 H, ^2J = 13.3 Hz, NHCOCCHHCCONH), 1.31–1.40 [m, 2 H, $(CH_3)_2CHCH$, $CH_3CH(CH_2)_2$], 1.53–1.65 (m, 2 H, $CH_3CHCHHCHH$), 1.78 [dsep, 1 H, ^3J = 7.0 Hz, ^3J = 2.8 Hz, $(CH_3)_2CH$], 1.87–1.96 (m, 1 H, CO_2CHCHH), 1.92 (d, 1 H, ^2J = 13.3 Hz, NHCOCCHHCCONH), 2.62 (d, 1 H, ^2J = 14.1 Hz,

OCOCC*H*H), 2.68 (d, 1 H, ^2J = 14.0 Hz, OCOCCH*H*), 4.52 (dt, 1 H, ^3J = 10.9 Hz, ^3J = 4.4 Hz, CO_2CH), 7.91 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.3 (q, *C*H_3CHCH$_3$), 20.6 (q, CH$_3$CH*C*H$_3$), 21.8 [q, *C*H_3CH(CH$_2$)$_2$], 22.5 (t, CH$_3$CHCH$_2$*C*H$_2$), 24.1 (q, *C*H_3CCONH), 24.2 (q, *C*H_3CCONH), 25.3 (d, CH$_3$*C*HCH$_3$), 30.8 (q, *C*H_3CO_2), 31.0 [d, CH$_3$*C*H(CH$_2$)$_2$], 33.8 (t, CH$_3$CH*C*H$_2$CH$_2$), 39.1 (t, CO_2CH*C*H$_2$CH), 39.5 (s, *C*CONH), 39.6 (s, *C*CONH), 41.8 (s, OCO*C*CH$_3$), 43.0 (t, OCOC*C*H$_2$), 43.6 (t, OCOCC*H*$_2$), 44.1 (t, *C*H$_2$CCONH), 46.5 (d, (CH$_3$)$_2$CH*C*H), 75.2 (d, CO_2*C*H), 174.2 (s, OCO), 175.7 (s, CONH), 176.1 (s, CONH).

MS (EI, 70 eV): *m/z* (%) = 240 (71), 194 (84), 166 (48), 138 (75), 123 (41), 110 (41), 95 (70), 83 (100), 69 (60), 57 (63), 41 (43).

Anal. Calcd for $C_{22}H_{35}NO_4$ (377.5): C, 69.99; H, 9.34; N, 3.71. Found C, 69.71; H, 9.29; N, 3.60.

N,O-Hemiacetals 6 and 7 by Reduction of Imide 5

Solid $NaBH_4$ (45.0 mmol, 1.70 g) was added in small portions over 2 h to a stirred solution of imide **5** (1.19 mmol, 450 mg) in MeOH (40 mL) at 0 °C. The mixture was stirred overnight (H_2 formation) and poured into cold water (150 mL). A white precipitate formed. After filtration, CH_2Cl_2 (100 mL) was added to the filtrate. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated in vacuo to give a white solid (440 mg, 97%), consisting of two diastereoisomers (dr **6**/**7** = 4:1) which were not separated; R_f 0.39 (P–TBME, 1:3); mp 176 °C.

IR (KBr): ν = 3117 (s, br, NH), 3000 (s, CH), 1723 (s, C=O), 1436 (m), 1404 (m), 1241 (s), 1191 (s), 1164 (s), 1052 cm^{-1} (s).

MS (EI, 70 eV): *m/z* (%) = 379 (0.8) [M$^+$], 362 (0.2) [M$^+$ – OH], 361 (2), 242 (11), 224 (100) [M$^+$ – menthyl], 196 (34) [224 – CO], 168 (20), 123 (40), 95 (22), 83 (42), 69 (20), 55 (31), 41 (21).

Anal. Calcd for $C_{22}H_{37}NO_4$ (379.5): C, 69.62; H, 9.82; N, 3.69. Found C, 69.77; H, 9.60; N, 3.59.

Major Diastereoisomer **6**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.64 (d, 3 H, ^3J = 7.0 Hz, CH$_3$CHC*H*$_3$), 0.83 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$CHCH$_3$), 0.83–0.87 (m, 2 H, CH$_3$CHCH$_2$C*H*HCH, NHCHOHCCH*H*CCO$_2$), 0.88 [d, 3 H, ^3J = 6.6 Hz, C*H*$_3$CH(CH$_2$)$_2$], 0.90–0.96 (m, 1 H, CH$_3$CHC*H*HCH$_2$), 1.00 (s, 3 H, NHCHOHCC*H*$_3$), 1.04–1.13 (m, 2 H, NHCOCCH*H*CCO$_2$, CO_2CHCH*H*), 1.08 (s, 3 H, NHCOCC*H*$_3$), 1.16 (s, 3 H, CH$_3$CCO$_2$), 1.23 (d, 1 H, ^2J = 13.4 Hz, NHCOCC*H*H-CCHOHNH), 1.37–1.40 [m, 1 H, CH$_3$C*H*(CH$_2$)$_2$], 1.40–1.44 [m, 1 H, (CH$_3$)$_2$CHC*H*], 1.57–1.63 (m, 2 H, CH$_3$CHC*H*HCH*H*), 1.71 (d, 1 H, ^2J = 13.4 Hz, NHCOCCH*H*CCHOHNH), 1.80 [dsep, 1 H, ^3J = 7.0 Hz, ^3J = 2.9 Hz, (CH$_3$)$_2$C*H*], 1.93–1.98 (m, 1 H, CO_2CHC*H*H), 2.59 (d, 1 H, ^2J = 14.0 Hz, NHCOCCH*H*CCO$_2$), 2.62 (d, 1 H, ^2J = 15.1 Hz, NHCHOHCC*H*HCCO$_2$), 4.50 (d, 1 H, ^3J = 13.0 Hz, CONHC*H*OH), 4.54 (dt, 1 H, ^3J = 11.0 Hz, ^3J = 4.4 Hz, CO_2CH), 4.84 (d, 1 H, ^3J = 13.0 Hz, CONHCHO*H*), 5.32 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.4 (q, *C*H_3CHCH$_3$), 20.7 (q, CH$_3$CH*C*H$_3$), 21.9 [q, *C*H_3CH(CH$_2$)$_2$], 22.8 (t, CH$_3$CHCH$_2$*C*HH), 24.6 (q, *C*H_3CCONH), 25.7 (d, CH$_3$*C*HCH$_3$), 27.3 (q, *C*H$_3$CCHOHNH), 31.3 [d, CH$_3$*C*H(CH$_2$)$_2$], 31.7 (q, *C*H_3CCO_2), 33.9 (t, CH$_3$CH*C*H$_2$CH$_2$), 35.8 (s, *C*CHOHNH), 38.1 (s, *C*CONH), 38.8 (t, CO_2CH*C*H$_2$CH), 39.6 (t, NHCHOHC*C*HH), 42.7 (s, CH$_3$*C*CO$_2$), 44.5 (t, NHCOCC*H*$_2$CCHOHCNH), 44.7 (t, NHCOCC*H*$_2$), 46.4 [d, (CH$_3$)$_2$CH*C*H], 76.7 (d, CO_2*C*H), 84.9 (d, CHOH), 174.5 (s, OCO), 179.4 (s, *C*ONHCHOH).

Minor Diastereoisomer **7**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.55 (d, 1 H, ^2J = 15.7 Hz, NHCOCCH*H*CCO$_2$), 2.58 (d, 1 H, ^2J = 16.1 Hz, NHCHOHC*H*HCCO$_2$), 4.49 (d, 1 H, ^3J = 13.0 Hz, CONHC*H*OH), 4.57–4.63 (m, 1 H, CO_2CH), 4.79 (d, ^3J = 13.0 Hz, 1 H, CONH-CHO*H*), 5.26 (br s, 1 H, NH). All other ^{1}H NMR signals overlap with signals of the major diastereoisomer **6**.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6 (q, *C*H_3CHCH$_3$), 20.9 (q, CH$_3$CH*C*H$_3$), 21.9 (q, *C*H_3CH(CH$_2$)$_2$), 22.6 (t, CH$_3$CHCH$_2$*C*H$_2$), 24.7 (d, CH$_3$*C*HCH$_3$), 24.8 (q, *C*H_3CCONH), 27.3 (q, *C*H$_3$CCHOHNH), 31.4 [d, CH$_3$*C*H(CH$_2$)$_2$], 32.4 (q, *C*H_3CCO_2), 34.0 (t, CH$_3$CH*C*H$_2$CH$_2$), 35.8 (s, *C*CHOHNH), 38.2 (s, *C*CONH), 39.2 (t, CO_2CH*C*H$_2$CH), 40.0 (t, NHCHOHCC*H*$_2$CCO$_2$), 42.6 (s, CH$_3$*C*CO$_2$), 44.5 (t, NHCOC*C*H$_2$CCHOHNH), 44.8 (t, NHCOCC*H*$_2$), 46.5 [d, (CH$_3$)$_2$CH*C*H], 76.7 (d, CO_2*C*H), 84.9 (d, CHOH), 174.6 (s, OCO), 179.0 (s, *C*ONHCHOH).

Chiral Hosts 1 and 2 by Reduction of *N,O*-Hemiacetals 6 and 7

The mixture of diastereoisomers **6**/**7** (7.24 mmol, 2.75 g) was dissolved in TFA (25 mL) and triethylsilane (9 mL, 6.54 g, 56.2 mmol) was added. The mixture was stirred vigorously at r.t. for 5 h. CH_2Cl_2 (250 mL) and sat. aq $NaHCO_3$ solution (100 mL) were added. Solid $NaHCO_3$ was added until gas formation ceased and the pH value was adjusted to 6–7. The precipitate was filtered off, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil (3.68 g), consisting of the two diastereoisomers. The crude product was purified and separated by flash chromatography (P–TBME, 3:1) to give the diastereoisomers **1** (2.01 g, 76%) and **2** (0.50 g, 19%) as white solids.

(1*R*,5*S*,7*S*)-1,5,7-Trimethyl-2-oxo-3-azabicyclo[3.3.1]-nonan-7-carboxylic Acid Menthyl Ester (**1**)

R_f 0.27 (P–TBME, 1:1); mp 122 °C; $[\alpha]_D^{20}$–14.5 (*c* = 1, CH_2Cl_2).

IR (KBr): ν = 3375 (s, NH), 2959 (s, CH), 2866 (s, CH), 1720 (s, C=O), 1666 (s, C=O), 1486 (m), 1454 (m), 1268 (s), 1188 cm^{-1}(s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.61 (d, 3 H, ^3J = 7.0 Hz, CH$_3$CHC*H*$_3$), 0.76–0.80 (m, 1 H, CH$_3$CHC*H*HCH$_2$CH), 0.79 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$CHCH$_3$), 0.83 [d, 3 H, ^3J = 6.6 Hz, C*H*$_3$CH(CH$_2$)$_2$], 0.89 (s, 3 H, NHCH$_2$CC*H*$_3$), 0.90–0.96 (m, 2 H, CH$_3$CHCH$_2$C*H*H, NHCOCCH*H*CCO$_2$), 0.97 (d, 1 H, ^2J = 13.9 Hz, CONHCH$_2$CCH*H*CCO$_2$), 1.05–1.09 (m, 1 H, CO_2OCHCH*H*), 1.06 (s, 3 H, NHCOCC*H*$_3$), 1.08 (s, 3 H, CH$_3$CCO$_2$), 1.15 (d, 1 H, ^2J = 12.8 Hz, NHCOC*H*HCCHOHNH), 1.30–1.44 (m, 2 H, [CH$_3$)$_2$CHC*H*, CH$_3$C*H*(CH$_2$)$_2$], 1.53–1.59 (m, 2 H, CH$_3$CHC*H*HCH*H*CH), 1.63 (d, 1 H, ^2J = 12.8 Hz, NHCOCCH*H*CCH$_2$NH), 1.82 [dsep, 1 H, ^3J = 6.9 Hz, ^3J = 2.6 Hz, (CH$_3$)$_2$C*H*], 1.85–1.91 (m, 1 H, CO_2CHC*H*H), 2.47 (d, 1 H, ^2J = 14.0 Hz, NHCOCCH*H*CCO$_2$), 2.54 (d, 1 H, ^2J = 13.9 Hz, CONHCH$_2$CC*H*HCCO$_2$), 2.94 (d, 1 H, ^2J = 11.3 Hz, CONHC*H*H), 3.14 (d, 1 H, ^2J = 11.3 Hz, CONHCH*H*), 4.44 (dt, 1H, ^3J = 11.0 Hz, ^3J = 4.3 Hz, CO_2CH), 4.97 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.4 (q, *C*H_3CHCH$_3$), 20.7 (q, CH$_3$CH*C*H$_3$), 21.9 [q, *C*H_3CH(CH$_2$)$_2$], 22.7 (t, CH$_3$CHCH$_2$*C*H$_2$), 24.9 (q, *C*H_3CCONH), 25.6 (d, CH$_3$*C*HCH$_3$), 28.8 (q, *C*H$_3$CCH$_2$NH), 30.3 (s, *C*CH$_2$NH), 31.3 [d, CH$_3$*C*H(CH$_2$)$_2$], 31.6 (q, *C*H$_3$CCO$_2$), 33.9 (t, CH$_3$CH*C*H$_2$CH$_2$), 38.1 (s, *C*CONH), 39.0 (t, CO_2CH*C*H$_2$CH), 42.4 (s, CH$_3$*C*CO$_2$), 44.6 (t, NHCH$_2$C*C*H$_2$), 45.0 (t, NHCOC*C*H$_2$CCH$_2$NH), 46.2 (t, NHCOCC*H*$_2$), 46.4 [d, (CH$_3$)$_2$CH*C*H], 52.9 (t, CONHC*H*$_2$), 75.1 (d, CO_2*C*H), 174.7 (s, OCO), 175.5 (s, CONH).

MS (EI, 70 eV): *m/z* (%) = 363 (26) [M$^+$], 225 (100) [RCO$_2$H$^+$], 208 (14) [M$^+$ – menthyl], 180 (31) [208 – CO], 151 (30), 124 (21), 107 (9), 96 (11), 83 (27), 70 (42), 55 (33).

Anal. Calcd for $C_{22}H_{37}NO_3$ (363.5): C, 72.69; H, 10.26; N, 3.85. Found C, 72.41; H, 10.09; N, 4.13.

(1*S*,5*R*,7*R*)-1,5,7-Trimethyl-2-oxo-3-azabicyclo[3.3.1]-nonan-7-carboxylic Acid Menthyl Ester (**2**)
R_f 0.13 (P–TBME, 1:1); mp 176 °C; $[\alpha]_D^{20}$ −5.4 (*c* = 1, CH_2Cl_2).

IR (KBr): ν = 3208 (m, NH), 3087 (m, NH), 2957 (s, CH), 2928 (s, CH), 1728 (s, C=O), 1673 (s, C=O), 1495 (w), 1458 (w), 1272 (m), 1191 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.64 (d, 3 H, ^3J = 6.4 Hz, C*H*$_3$CHCH$_3$), 0.77–0.79 (m, 1 H, CH$_3$CHCH*H*CH$_2$), 0.80–0.85 [m, 6 H, CH$_3$CHC*H*$_3$, C*H*$_3$CH(CH$_2$)], 0.86–0.88 (m, 1 H, CO$_2$CHCH*H*), 0.91 (s, 3 H, CONHCH$_2$CC*H*$_3$), 0.92–0.96 (m, 2 H, CONHCH$_2$CCH*H*CCO$_2$, CH$_3$CHCH$_2$CH*H*), 1.01–1.03 (m, 1 H, NHCOCCH*H*CCOC), 1.07 (s, 3 H, NHCOCC*H*$_3$), 1.09 (s, 3 H, OCOCCH$_3$), 1.15–1.19 (m, 1 H, NHCOCC*H*HCCH$_2$NH), 1.29–1.37 [m, 1 H, (CH$_3$)$_2$CHC*H*], 1.38–1.45 [m, 1 H, CH$_3$C*H*(CH$_2$)$_2$], 1.58–1.66 (m, 3 H, NHCOCCH*H*CCH$_2$NH, CH$_3$CHC*H*HC*H*H), 1.87–1.95 [m, 2 H, CO$_2$CHC*H*H, (CH$_3$)$_2$C*H*], 2.42 (d, 1 H, ^2J = 14.1 Hz, NHCOCC*H*HCCO$_2$), 2.59 (d, 1 H, ^2J = 13.9 Hz, CONHCH$_2$CC*H*HCCO$_2$), 2.98 (d, 1 H, ^2J = 11.4 Hz, CONHC*H*H), 3.12 (d, 1 H, ^2J = 11.4 Hz, CONHCH*H*), 4.60 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.2 Hz, CO$_2$CH), 5.24 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5 (q, *C*H$_3$CHCH$_3$), 20.8 (q, CH$_3$CH*C*H$_3$), 21.9 [q, *C*H$_3$CH(CH$_2$)$_2$], 22.7 (t, CH$_3$CHCH$_2$*C*H$_2$), 25.0 (q, *C*H$_3$CCONH), 25.0 (d, CH$_3$*C*HCH$_3$), 28.8 (q, *C*H$_3$CCH$_2$NH), 30.3 (s, *C*CH$_2$NH), 31.2 [d, CH$_3$*C*H(CH$_2$)$_2$], 31.7 (q, *C*H$_3$CCO$_2$), 34.1 (t, CH$_3$CH*C*H$_2$CH$_2$), 38.1 (s, *C*CONH), 40.2 (t, CO$_2$CH*C*H$_2$CH), 42.3 (s, CH$_3$*C*CO$_2$), 45.1 (t, NHCOC*C*H$_2$CCH$_2$NH), 45.3 (t, NHCH$_2$C*C*H$_2$), 45.9 (t, NHCOCC*H*$_2$), 47.0 (d, (CH$_3$)$_2$CH*C*H), 52.9 (t, CONH*C*H$_2$), 74.4 (d, CO$_2$*C*H), 174.8 (s, OCO), 175.2 (s, CONH).

MS (EI, 70 eV): *m/z* (%) = 363 (8) [M$^+$], 225 (100) [RCO$_2$H$^+$], 208 (30) [M$^+$ – menthyl], 180 (36) [208 – CO], 151 (27), 123 (23), 107 (12), 95 (18), 83 (22), 70 (26), 55 (27).

Anal. Calcd for $C_{22}H_{37}NO_3$ (363.5): C, 72.69; H, 10.26; N, 3.85. Found C, 72.41; H, 10.50; N, 3.82.

Acids 8 and *ent*-8 by Saponification of the Chiral Hosts 1 and 2
A solution of chiral host **1** (7.43 mmol, 2.70 g) in 2 N NaOH (100 mL) and DMSO (180 mL) was heated under reflux for 4 h and allowed to cool to r.t. H_2O (100 mL) was added, and the mixture was extracted with TBME (100 mL). The layers were separated and the organic layer was discarded. The aqueous layer was adjusted to pH 1 with 1 N HCl and extracted with TBME (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give **8** as a white solid (1.05 g, 63%); mp 250–255 °C; $[\alpha]_D^{20}$ +167 (*c* = 1, CH_2Cl_2).

IR (KBr): ν = 3263 (m, br, NH), 3198 (m, br, NH), 2960 (m, CH), 2929 (m, CH), 1693 (s, C=O), 1629 (m, C=O), 1493 (m), 1458 (m), 1213 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, CH$_3$), 0.91–0.94 (m, 1 H, C*H*H), 1.00 (d, 1 H, ^2J = 13.8 Hz, C*H*H), 1.09 (s, 3 H, CH$_3$), 1.13 (s, 3 H, CH$_3$), 1.16 (d, 1 H, ^2J = 12.8 Hz, CH*H*), 1.63 (d, 1 H, ^2J = 12.8 Hz, CH*H*), 2.36 (d, 1 H, ^2J = 14.1 Hz, CH*H*), 2.60 (d, 1 H, ^2J = 13.8 Hz, CH*H*), 2.96 (d, 1 H, ^2J = 12.1 Hz, CONHC*H*H), 3.18 (d, 1 H, ^2J = 12.1 Hz, CONHCH*H*), 8.57 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3 (q, *C*H$_3$), 29.0 (q, CH$_3$), 30.2 (s, C), 31.2 (q, *C*H$_3$), 38.3 (s, C), 42.4 (s, C), 44.5 (t, CH$_2$), 45.4 (t, CH$_2$), 45.5 (t, CH$_2$), 52.9 (t, CONH*C*H$_2$), 178.7 (s, CO), 181.7 (s, CO).

MS (EI, 70 eV): *m/z* (%) = 252 (46) [M$^+$], 208 (7) [M$^+$ – CO$_2$], 207 (20), 181 (7), 180 (16), 151 (39), 124 (79), 123 (57), 121 (34), 109 (23), 107 (39), 95 (43), 81 (40), 70 (100), 55 (34), 41 (52).

HRMS (EI): $C_{12}H_{19}NO_3$, *m/z* calcd 225.1365, found 225.1363; $C_{11}{}^{13}C_1H_{19}NO_3$, *m/z* calcd 226.1399, found 226.1395.

ent-**8**

The chiral ester **2** (1.10 mmol, 0.40 g) was saponified in analogy to the aforementioned procedure to give a white solid of the acid *ent*-**8** (308 mg, 7%); $[\alpha]_D^{20}$–166 (*c* = 1.98, CH_2Cl_2).

Anilides 10 by Aminodechlorination of the Acid Chloride 4 with the Anilines 9

1,5,7-Trimethyl-2,4-dioxo-3-azabicyclo[3.3.1]-nonan-7-carboxylic Acid (3′-Hydroxynaphthalene-2′-yl)amide (**10a**)
A stirred solution of acid chloride **4** (1.77 mmol, 465 mg) in THF (15 mL) was treated with **9a** (2.25 mmol, 370 mg) and pyridine (0.21 mL, 206 mg, 2.60 mmol). The mixture was heated under reflux for 15 h and evaporated. Without further workup, the crude product was purified by flash chromatography (TBME–P, 1:1 → TBME) to give a white solid (656 mg, 97%); R_f 0.12 (P–TBME, 1:1); mp 264–266 °C.

IR (KBr): ν = 3419 (m, NH), 3197 (m, NH), 2968 (m, CH), 2870 (m, CH), 1730 (s, C=O), 1698 (vs, C=O), 1589 (s), 1240 (m), 1204 cm^{-1} (s).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.13 (s, 6 H, CH$_3$), 1.24 (s, 3 H, CH$_3$), 1.35 (d, 2 H, ^2J = 14.1 Hz, C*H*H), 1.44 (d, 1 H, ^2J = 12.9 Hz, C*H*H), 1.91 (d, 1 H, ^2J = 12.9 Hz, CH*H*), 2.54 (d, 2 H, ^2J = 14.1 Hz, CH*H*), 7.16 (s, 1 H, arom H), 7.26 (virt. t, 1 H, ^3J = 6.6 Hz, arom H), 7.31 (virt. t, 1 H, ^3J = 6.8 Hz, arom H), 7.63 (d, 1 H, ^3J = 7.9 Hz, arom H), 7.69 (d, 1 H, ^3J = 7.9 Hz, arom H), 8.30 (s, 1 H, arom H), 8.59 (s, 1 H, NH), 10.30 (br s, 1 H, OH), 10.41 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.6 (q, 2 C, CH$_3$), 27.0 (s, C), 31.3 (q, CH$_3$), 42.9 (s, 2 C, C), 43.4 (t, 2 C, CH$_2$), 43.5 (t, CH$_2$), 108.8 (d, CH$_{ar}$), 119.1 (d, CH$_{ar}$), 123.4 (d, CH$_{ar}$), 125.1 (d, CH$_{ar}$), 125.8 (d, CH$_{ar}$), 127.3 (d, CH$_{ar}$), 127.9 (s, C$_{ar}$), 128.0 (s, C$_{ar}$), 131.1 (s, C$_{ar}$), 147.6 (s, C$_{ar}$), 173.0 (s, CO), 177.0 (s, 2 C, CO).

MS (EI, 70 eV): *m/z* (%) = 380 (21) [M$^+$], 194 (4) [M$^+$ – CONHArOH], 166 (12), 159 (100) [NH$_2$ArOH$^+$], 110 (27).

Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.4): C, 69.46; H, 6.36; N, 7.36. Found C, 68.93; H, 6.37; N, 7.40.

HRMS (EI): $C_{22}H_{24}N_2O_4$, *m/z* calcd 380.1736, found 380.1733; $C_{21}{}^{13}C_1H_{24}N_2O_4$, *m/z* calcd 381.1769, found 381.1765.

1,5,7-Trimethyl-2,4-dioxo-3-azabicyclo[3.3.1]-nonan-7-carboxylic Acid (3′-Hydroxy-5′,6′,7′,8′-tetrahydronaphthalene-2′-yl) Amide (**10b**)
A solution of **9b**[18] (5.90 mmol, 1.44 g) in THF (60 mL) and pyridine (1.11 mL, 1.09 g, 13.7 mmol) was added to a stirred solution of the acid chloride **4** (4.90 mmol, 1.26 g) in THF (30 mL). The mixture was heated under reflux for 16 h and evaporated. The crude product was dissolved in CH_2Cl_2 (80 mL) and washed with H_2O (2 × 20 mL), 1 N HCl (3 × 20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (TBME–P, 1:1 → TBME) to give a white solid (1.75 g, 93%); R_f 0.13 (P–TBME, 1:1); mp 210 °C.

IR (KBr): ν = 3400 (m, NH), 3182 (m, NH), 2918 (m, CH), 1721 (s, C=O), 1695 (vs, C=O), 1380 (m), 1211 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (s, 6 H, CH$_3$), 1.33 (s, 3 H, CH$_3$), 1.34 (d, 2 H, ^2J = 14.5 Hz, C*H*H), 1.41 (d, 1 H, ^2J = 13.3 Hz, C*H*H), 1.69–1.77 (m, 4 H, ArCH$_2$C*H*$_2$C*H*$_2$), 1.99 (d, 1 H, ^2J = 13.3 Hz, CH*H*), 2.58–2.71 (m, 6 H, ArC*H*$_2$CH$_2$CH$_2$C*H*$_2$, CH*H*), 6.66 (s, 1 H, arom H), 6.80 (s, 1 H, arom H), 7.56, 7.59, 7.93 (br s, 3 H, NH, NH, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.0 (t, ArCH$_2$*C*H$_2$), 23.2 (t, ArCH$_2$*C*H$_2$), 24.2 (q, 2 C, CH$_3$), 28.5 (t, Ar*C*H$_2$), 28.9 (t, Ar*C*H$_2$), 31.8 (q, CH$_3$), 40.1 (s, 2 C, C), 42.9 (s, C), 44.3 (t, 3 C, CH$_2$), 105.0

(s, C_{ar}), 119.5 (d, CH_{ar}), 123.0 (d, CH_{ar}), 129.4 (s, C_{ar}), 136.3 (s, C_{ar}), 146.6 (s, C_{ar}), 173.8 (s, CO), 176.6 (s, 2 C, CO).

MS (EI, 70 eV): *m/z* (%) = 384 (19) [M^+], 163 (100) [$NH_2C_{10}H_{10}OH^+$], 135 (3), 110 (11).

Anal. Calcd for $C_{22}H_{28}N_2O_4$ (384.5): C, 68.73; H, 7.34; N, 7.29. Found C, 68.47; H, 7.21; N, 7.31.

Oxazoles 11 by Cyclization of the 2-Hydroxyanilides 10

1,5,7-Trimethyl-7-(1´-oxa-3´-azacyclopenta[*b*]naphthalene-2´-yl)-3-azabicyclo[3.3.1]nonan-2,4-dione (**11a**)
Under argon, 2-hydroxyanilide **10a** (2.47 mmol, 941 mg) was suspended in benzene (15 mL). Pyridine (1.31 mL, 1.29 g, 16.2 mmol) and $SOCl_2$ (0.94 mL, 1.54 g, 12.9 mmol) were added successively. The mixture was heated under reflux for 2 h, and the solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 (80 mL) and 1 N HCl (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with 1 N HCl (40 mL), sat. aq $NaHCO_3$ solution (40 mL), and brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brownish solid (857 mg, 96%). This material was sufficiently pure for further use. If required it can be purified by flash chromatography (TBME–P, 1:1); R_f 0.55 (P–TBME, 1:3); mp 318–319 °C.

IR (KBr): ν = 3434 (m, NH), 3193 (m, NH), 2966 (m, CH), 1696 (vs, C=O), 1322 (m), 1207 cm^{-1}(s).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.95 (s, 6 H, CH_3), 1.17 (d, 1 H, ^2J = 13.1 Hz, C*H*H), 1.28 (s, 3 H, CH_3), 1.32 (d, 2 H, ^2J = 14.2 Hz, C*H*H), 1.41 (d, 1 H, ^2J = 13.1 Hz, CH*H*), 2.87 (d, 2 H, ^2J = 14.2 Hz, CH*H*), 7.34–7.40 (m, 2 H, arom H), 7.68 (s, 1 H, arom H), 7.69 (br s, 1 H, NH), 7.80 (m, 1 H, arom H), 7.85 (m, 1 H, arom H), 7.89 (s, 1 H, arom H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 24.5 (q, 2 C, CH_3), 32.7 (q, CH_3), 37.9 (s, C), 40.2 (s, 2 C, C), 44.4 (t, CH_2), 44.9 (t, 2 C, CH_2), 106.8 (d, CH_{ar}), 117.5 (d, CH_{ar}), 125.2 (d, CH_{ar}), 125.9 (d, CH_{ar}), 128.5 (d, CH_{ar}), 129.0 (d, CH_{ar}), 131.8 (s, C_{ar}), 132.0 (s, C_{ar}), 141.7 (s, C_{ar}), 149.7 (s, C_{ar}), 172.5 (s, CN), 176.8 (s, 2 C, CO).

MS (EI, 70 eV): *m/z* (%) = 362 (100) [M^+], 210 (22), 169 (14), 141 (4), 107 (7), 81 (3), 55 (3).

HRMS (EI): $C_{22}H_{22}N_2O_3$, *m/z* calcd 362.1630, found 362.1622; $C_{22}{}^{13}C_1H_{22}N_2O_3$, *m/z* calcd 363.1663, found 363.1661.

1,5,7-Trimethyl-7-(5´,6´,7´,8´-tetrahydro-1´-oxa-3´-azacyclopenta[*b*]naphthalene-2´-yl)-3-azabicyclo[3.3.1]nonan-2,4-dione (**11b**)
Under argon, 2-hydroxyanilide **10b** (4.13 mmol, 1.59 g) was suspended in benzene (20 mL), and pyridine (2.17 mL, 2.13 g, 26.9 mmol) and $SOCl_2$ (1.50 mL, 2.45 g, 20.7 mmol) were added. The mixture was heated under reflux for 3 h, and the solvent was removed under reduced pressure. Without further workup the residue was purified by flash chromatography (TBME–P, 1:2 → 2:1) to give a white solid (1.31 g, 87%); R_f 0.27 (P–TBME, 1:1); mp 259 °C.

IR (KBr): ν = 3410 (m, NH), 3182 (m, NH), 2964 (m, CH), 2930 (m, CH), 1702 (s, C=O), 1463 (m), 1377 (m), 1205 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 6 H, CH_3), 1.38 (s, 3 H, CH_3), 1.44–1.49 (m, 3 H, C*H*H), 1.78–1.81 (m, 4 H, $ArCH_2CH_2CH_2$), 1.99 (virt. dt, 1 H, ^2J = 13.3 Hz, ^4J = 2.2 Hz, CH*H*), 2.82–2.88 (m, 4 H, $ArCH_2CH_2CH_2CH_2$), 3.04–3.09 (m, 2H, CH*H*), 7.01 (br s, 1 H, NH), 7.14 (s, 1 H, arom H), 7.31 (s, 1 H, arom H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.0 (t, $ArCH_2CH_2$), 23.1 (t, $ArCH_2CH_2$), 24.5 (q, 2 C, CH_3), 29.7 (t, $ArCH_2$), 30.0 (t, $ArCH_2$), 32.5 (q, CH_3), 37.1 (s, C), 40.0 (s, 2 C, C), 44.5 (t, 2 C, CH_2), 44.7 (t, CH_2), 110.0 (d, CH_{ar}), 119.4 (d, CH_{ar}), 133.6 (s, C_{ar}), 134.6 (s, C_{ar}), 138.9 (s, C_{ar}), 148.6 (s, C_{ar}), 168.5 (s, CN), 175.8 (s, 2 C, CO).

MS (EI, 70 eV): *m/z* (%) = 366 (100) [M^+], 351 (5), 267 (8), 214 (43), 187 (5), 174 (6), 145 (10), 110 (7), 81 (2).

Anal. Calcd for $C_{22}H_{26}N_2O_3$ (366.5): C, 72.11; H, 7.15; N, 7.64. Found C, 71.86; H, 7.02; N, 7.49.

Chiral Hosts *rac*-3 by Reduction of the Oxazole Imides 11; Typical Procedure

1,5,7-Trimethyl-7-(1´-oxa-3´-azacyclopenta[*b*]naphthalene-2´-yl)-3-azabicyclo[3.3.1]nonan-2-one (*rac*-**3a**)
Under argon, oxazole imide **11a** (2.30 mmol, 832 mg) was suspended in anhyd EtOH (200 mL). $NaBH_4$ (92.1 mmol, 3.48 g) was added in small portions over 1 h at r.t., and the suspension was stirred for 15 h. The mixture was poured into cold H_2O (300 mL) and extracted with $CHCl_3$ (250 mL). The layers were separated, and the aqueous layer was extracted with an additional amount of $CHCl_3$ (100 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give a cream colored solid (888 mg). This material was suspended in TFA (8 mL), and triethylsilane (3.0 ml, 2.20 g, 18.6 mmol) was added. The mixture was stirred at r.t. for 4 h. CH_2Cl_2 (100 mL) and sat. aq $NaHCO_3$ solution (40 mL) were added. Solid $NaHCO_3$ was added until gas formation had ceased and a pH value of 6–7 was measured. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (1. TBME–P, 1:1; 2. EtOAc) to give a white solid (582 mg, 73%); R_f 0.08 (P–TBME, 1:1); mp 292–294 °C.

IR (KBr): ν = 3440 (m, NH), 3189 (m, NH), 2985 (m, CH), 2952 (m, CH), 1668 (s, C=O), 1560 (m), 1249 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.09–1.13 (m, 1 H, C*H*H), 1.20–1.30 (m, 2 H, C*H*H, CH*H*), 1.32–1.36 (m, 1 H, C*H*H), 1.33 (s, 3 H, CH_3), 2.77 (d, 1 H, ^2J = 11.0 Hz, NHC*H*H), 2.89 (d, 2 H, ^2J = 13.1 Hz, CH*H*, CH*H*), 3.22 (d, 1 H, ^2J = 11.0 Hz, NHCH*H*), 5.61 (s, 1 H, NH), 7.40–7.46 (m, 2 H, arom H), 7.79 (s, 1 H, arom. H), 7.85–7.88 (m, 1 H, arom H), 7.91–7.93 (m, 1 H, arom H), 8.00 (s, 1 H, arom H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5 (q, CH_3), 29.1 (q, CH_3), 30.5 (s, C), 33.1 (q, CH_3), 37.7 (s, C), 38.0 (s, C), 44.7 (t, CH_2), 45.9 (t, CH_2), 47.0 (t, CH_2), 52.6 (t, NCH_2), 106.3 (d, CH_{ar}), 116.5 (d, CH_{ar}), 124.3 (d, CH_{ar}), 125.0 (d, CH_{ar}), 127.9 (d, CH_{ar}), 128.4 (d, CH_{ar}), 131.1 (s, C_{ar}), 131.2 (s, C_{ar}), 141.4 (s, C_{ar}), 149.3 (s, C_{ar}), 173.4, 174.8 (s, 2 C, CN, CO).

MS (EI, 70 eV): *m/z* (%) = 348 (100) [M^+], 320 (12) [M^+ – CO], 293 (5), 251 (32), 210 (76), 170 (13), 124 (20), 111 (47), 107 (17), 96 (21), 70 (15), 55 (21).

HRMS (EI): $C_{22}H_{24}N_2O_2$, *m/z* calcd 348.1838, found 348.1843; $C_{21}{}^{13}C_1H_{24}N_2O_2$, *m/z* calcd 349.1871, found 349.1865.

1,5,7-Trimethyl-7-(5´,6´,7´,8´-tetrahydro-1´-oxa-3´-azacyclopenta[*b*]naphthalene-2´-yl)-3-azabicyclo[3.3.1]nonan-2-one (*rac*-**3b**)
The reduction of the oxazole imide **11b** (3.55 mmol, 1.30 g) was conducted in analogy to the aforementioned preparation of *rac*-**3a**. The crude product was purified by flash chromatography (TBME–P, 1:1 → 2:1) to give a white solid (1.08 g, 88%); R_f 0.08 (P–TBME, 1:1); mp 228 °C.

IR (KBr): ν = 3448 (s, NH), 3199 (m, NH), 2925 (s, CH), 1674 (vs, C=O), 1556 (m), 1464 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.32–1.35 (m, 2 H, C*H*H), 1.39 (dd, 1 H, ^2J = 14.2 Hz, ^4J = 1.6 Hz, C*H*H), 1.74 (virt. dt, 1 H, ^2J = 12.8 Hz,

^4J = 2.0 Hz, CH*H*), 1.78–1.83 (m, 4 H, ArCH$_2$C*H*$_2$C*H*$_2$), 2.83–2.88 (m, 4 H, ArC*H*$_2$CH$_2$CH$_2$C*H*$_2$), 2.88–2.94 (m, 2 H, CH*H*, NHC*H*H), 2.97 (virt. dt, 1 H, ^2J = 14.1 Hz, ^4J = 1.9 Hz, CH*H*), 3.25 (virt. dt, 1 H, ^2J = 11.4 Hz, ^4J = 2.4 Hz, NHCH*H*), 4.71 (br s, 1 H, NH), 7.18 (s, 1 H, arom H), 7.27 (s, 1 H, arom H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 23.1 (t, ArCH$_2$*C*H$_2$), 23.2 (t, ArCH$_2$*C*H$_2$), 25.1 (q, CH$_3$), 29.1 (q, CH$_3$), 29.8 (t, Ar*C*H$_2$), 30.0 (t, Ar*C*H$_2$), 30.7 (s, C), 33.3 (q, CH$_3$), 37.5 (s, C), 38.4 (s, C), 45.1 (t, CH$_2$), 45.9 (t, CH$_2$), 47.2 (t, CH$_2$), 52.7 (t, NCH$_2$), 110.3 (d, CH$_{ar}$), 118.7 (d, CH$_{ar}$), 133.1 (s, C$_{ar}$), 134.0 (s, C$_{ar}$), 139.2 (s, C$_{ar}$), 148.7 (s, C$_{ar}$), 170.5, 174.8 (s, 2 C, CN, CO).

MS (EI, 70 eV): *m/z* (%) = 352 (64) [M$^+$], 337 (5), 297 (7), 255 (19), 228 (27), 214 (100), 187 (9), 174 (13), 124 (9), 111 (31), 96 (11), 70 (5).

Anal. Calcd for $C_{22}H_{28}N_2O_2$ (352.5): C, 74.97; H, 8.01; N, 7.95. Found C, 74.66; H, 7.81; N, 8.22.

1,5,7-Trimethyl-2-oxo-7-(1´-oxa-3´-azacyclopenta[b]naphthalene-2´-yl)-3-azabicyclo[3.3.1]nonan-3-carboxylic Acid-(–)-menthyl Esters (12a and 13a); Typical Procedure

BuLi (0.69 mL, 1.72 M in hexanes, 1.19 mmol) was added dropwise to a stirred solution of the chiral host *rac*-**3a** (1.08 mmol, 377 mg) in THF (20 mL) at –78 °C. After 0.5 h, (–)-menthyl chloroformate (276 μL, 285 mg, 1.30 mmol) was added dropwise. The mixture was stirred at –78 °C for 45 min and then at 0 °C for 1 h. The reaction was quenched by the addition of sat. aq NH_4Cl solution (2 mL), and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (40 mL) and sat. aq $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (TBME–P, 1:8 → 1:3) to yield **12a** (196 mg, 34%) and **13a** (196 mg, 34%) as white solids.

Less Polar Diastereoisomer: (1*S*,5*S*,7*R*)-**13a**
R_f 0.57 (P–TBME, 1:3); mp 66–69 °C; $[\alpha]_D^{20}$–37.4 (*c* = 1.0, CH_2Cl_2).

IR (KBr): ν = 2957 (s, CH), 2931 (m, CH), 1715 (br, vs, C=O), 1564 (m), 1459 (m), 1264 cm^{-1} (s).

^{1}H NMR (500 MHz, CDCl$_3$): δ = -0.65 (virt. q, 1 H, $^2J \cong {}^3J \cong$ 11.7 Hz, C*H*H-menthyl), 0.10–0.17 (m, 1 H, C*H*H-menthyl), 0.12 (d, 3 H, ^3J = 6.6 Hz, CH$_2$CHC*H*$_3$), 0.52 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$CHCH$_3$), 0.64–0.74 (m, 2 H, C*H*H-menthyl, CH*H*-menthyl), 0.80 (d, 3 H, ^3J = 7.0 Hz, CH$_3$CHC*H*$_3$), 0.80–0.94 (m, 2 H, CH-menthyl, CH-menthyl), 1.16 (s, 3 H, CH$_3$), 1.22–1.27 (m, 1 H, CH*H*-menthyl), 1.29 (s, 3 H, CH$_3$), 1.35 (s, 3 H, CH$_3$), 1.35–1.39 (m, 1 H, CH*H*-menthyl), 1.41 (dd, 1 H, ^2J = 12.9 Hz, ^4J = 2.5 Hz, C*H*H), 1.44 (d, 1 H, ^2J = 14.4 Hz, C*H*H), 1.47 (dd, 1 H, ^2J = 14.4 Hz, ^4J = 1.8 Hz, C*H*H), 1.84 (d, 1 H, ^2J = 12.9 Hz, CH*H*), 1.97 (dsep, 1 H, ^3J = 7.0 Hz, ^3J = 2.9 Hz, CH$_3$C*H*CH$_3$), 3.04 (d, 1 H, ^2J = 14.4 Hz, CH*H*), 3.11 (d, 1 H, ^2J = 14.4 Hz, CH*H*), 3.34 (dd, 1 H, ^2J = 12.4 Hz, ^4J = 1.7 Hz, NHC*H*H), 3.72 (dd, 1 H, ^2J = 12.4 Hz, ^4J = 2.4 Hz, NHCH*H*), 4.00 (virt. dt, 1 H, ^3J = 10.9 Hz, ^3J = 4.3 Hz, CO$_2$C*H*), 7.39–7.45 (m, 2 H, arom H), 7.84 (s, 1 H, arom H), 7.87–7.93 (m, 2 H, arom H), 8.02 (s, 1 H, arom H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 15.5 (q, *C*H$_3$CHCH$_3$), 20.9 (q, CH$_3$CH*C*H$_3$), 21.0 (q, *C*H$_3$CHCH$_2$), 22.4 (t, CH$_2$-menthyl), 24.8 (d, CH$_3$*C*HCH$_3$), 26.3 (q, CH$_3$), 29.4 (q, CH$_3$), 30.6 (d, CH-menthyl), 30.7 (s, C), 33.5 (t, CH$_2$-menthyl), 34.0 (q, CH$_3$), 37.7 (s, C), 38.3 (t, CH$_2$-menthyl), 41.1 (s, C), 44.7 (t, CH$_2$), 45.9 (d, CH-menthyl), 46.1 (t, CH$_2$), 46.5 (t, CH$_2$), 57.8 (t, NCH$_2$), 77.7 (d, NCO$_2$*C*H), 106.4 (d, CH$_{ar}$), 116.7 (d, CH$_{ar}$), 124.5 (d, CH$_{ar}$), 125.2 (d, CH$_{ar}$), 127.9 (d, CH$_{ar}$), 128.5 (d, CH$_{ar}$), 131.3 (s, C$_{ar}$), 131.4 (s, C$_{ar}$), 141.5 (s, C$_{ar}$), 150.0 (s, C$_{ar}$), 154.5 (s, NCO$_2$), 173.3, 173.4 (s, 2 C, CO, CN).

MS (EI, 70 eV): *m/z* (%) = 530 (4) [M$^+$], 348 (100) [MH$^+$ – CO-menthyl], 320 (15) [348 – CO], 251 (10), 210 (39), 170 (17), 111 (28), 83 (74), 69 (41), 55 (37).

HRMS (EI): $C_{33}H_{42}N_2O_4$, *m/z* calcd 530.3145, found 530.3141; $C_{32}{}^{13}C_1H_{42}N_2O_4$, *m/z* calcd 531.3179, found 531.3177.

More Polar Diastereoisomer: (1*R*,5*R*,7*S*)-**12a**
R_f 0.47 (P–TBME, 1:3); mp 73–75 °C; $[\alpha]_D^{20}$–52.8 (*c* = 1.0, CH_2Cl_2).

IR (KBr): ν = 2958 (s, CH), 2930 (m, CH), 1772 (s, C=O), 1712 (s, C=O), 1564 (m), 1458 (m), 1248 cm^{-1} (s).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.24 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$CHCH$_3$), 0.26 (virt. q, 1 H, $^2J \cong {}^3J \cong$ 12.0 Hz, C*H*H-menthyl), 0.45–0.55 (m, 1 H, C*H*H-menthyl), 0.47 (d, 3 H, ^3J = 6.6 Hz, CH$_2$CHC*H*$_3$), 0.60 (d, 3 H, ^3J = 7.0 Hz, CH$_3$CHC*H*$_3$), 0.63–0.68 (m, 1 H, C*H*H-menthyl), 0.90–1.03 (m, 2 H, CH-menthyl, CH-menthyl), 1.05–1.11 (m, 1 H, CH*H*-menthyl), 1.08 (s, 3 H, CH$_3$), 1.24 (s, 3 H, CH$_3$), 1.30 (s, 3 H, CH$_3$), 1.30–1.47 (m, 4 H, C*H*H, C*H*H, CH*H*-menthyl, CH*H*-menthyl), 1.35 (d, 1 H, ^2J = 14.3 Hz, C*H*H), 1.43 (dsep, 1 H, ^3J = 7.0 Hz, ^3J = 2.7 Hz, CH$_3$C*H*CH$_3$), 1.75 (d, 1 H, ^2J = 12.8 Hz, CH*H*), 2.94 (d, 1 H, ^2J = 14.3 Hz, CH*H*), 3.03 (d, 1 H, ^2J = 14.2 Hz, CH*H*), 3.08 (dd, 1 H, ^2J = 12.3 Hz, ^4J = 1.5 Hz, NHC*H*H), 3.79 (dd, 1 H, ^2J = 12.3 Hz, ^4J = 2.2 Hz, NHCH*H*), 3.95 (dt, 1 H, ^3J = 10.9 Hz, ^3J = 4.4 Hz, CO$_2$C*H*), 7.30–7.38 (m, 2 H, arom H), 7.79 (s, 1 H, arom H), 7.79–7.83 (m, 2 H, arom H), 7.94 (s, 1 H, arom H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 15.5 (q, *C*H$_3$CHCH$_3$), 20.6 (q, CH$_3$CH*C*H$_3$), 21.6 (q, *C*H$_3$CHCH$_2$), 22.7 (t, CH$_2$-menthyl), 25.6 (d, CH$_3$*C*HCH$_3$), 26.2 (q, CH$_3$), 29.8 (q, CH$_3$), 30.6 (s, C), 30.8 (d, CH-menthyl), 33.6 (q, CH$_3$), 33.9 (t, CH$_2$-menthyl), 37.7 (s, C), 39.7 (t, CH$_2$-menthyl), 41.0 (s, C), 44.0 (t, CH$_2$), 46.2 (t, CH$_2$), 46.3 (d, CH-menthyl), 47.0 (t, CH$_2$), 57.2 (t, NCH$_2$), 76.6 (d, NCO$_2$*C*H), 106.5 (d, CH$_{ar}$), 116.6 (d, CH$_{ar}$), 124.3 (d, CH$_{ar}$), 125.0 (d, CH$_{ar}$), 128.0 (d, CH$_{ar}$), 128.4 (d, CH$_{ar}$), 131.0 (s, C$_{ar}$), 131.4 (s, C$_{ar}$), 141.2 (s, C$_{ar}$), 149.7 (s, C$_{ar}$), 151.8 (s, NCO$_2$), 172.9, 173.9 (s, 2 C, CO, CN).

MS (EI, 70 eV): *m/z* (%) = 530 (10) [M$^+$], 375 (8), 348 (100) [MH$^+$ – CO-menthyl], 320 (50) [348 – CO], 295 (23), 251 (22), 210 (60), 170 (19), 138 (20), 111 (40), 95 (32), 83 (74), 69 (44), 55 (86).

HRMS (EI): $C_{33}H_{42}N_2O_4$, calcd 530.3145, *m/z* found 530.3139; $C_{32}{}^{13}C_1H_{42}N_2O_4$, *m/z* calcd 531.3179, found 531.3174.

1,5,7-Trimethyl-2-oxo-7-(5´,6´,7´,8´-tetrahydro-1´-oxa-3´-azacyclopenta[*b*]naphthalene-2´-yl)-3-azabicyclo[3.3.1]nonan-3-carboxylic Acid-(–)-menthyl Esters (12b and 13b)

The acylation of chiral host *rac*-**3b** (1.73 mmol, 605 mg) was performed in analogy to the aforementioned procedure and yielded compounds **12b** (421 mg, 46%) and **13b** (419 mg, 45%).

Less Polar Diastereoisomer (1*S*,5*S*,7*R*)-**13b**
R_f 0.53 (P–TBME, 1:1); mp 83 °C; $[\alpha]_D^{20}$–34.7 (*c* = 1.0, CH_2Cl_2).

IR (KBr): ν = 2956 (s, CH), 2931 (m, CH), 2869 (m, CH), 1717 (br, vs, C=O), 1558 (m), 1464 (s), 1265 cm^{-1} (s).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.09 (virt. q, 1 H, $^2J \cong {}^3J \cong$ 11.7 Hz, C*H*H-menthyl), 0.62 (d, 3 H, ^3J = 7.0 Hz, CH$_3$-menthyl), 0.63–0.73 (m, 1 H, C*H*H-menthyl), 0.81 (d, 3 H, ^3J = 6.7 Hz, CH$_3$-menthyl), 0.83–0.91 (m, 1 H, C*H*H-menthyl), 0.89 (d, 3 H, ^3J = 7.1 Hz, CH$_3$-menthyl), 1.03–1.13 (m, 1 H, CH-menthyl), 1.15 (s, 3 H, CH$_3$), 1.19–1.30 (m, 1 H, CH-menthyl), 1.28 (s, 3 H, CH$_3$), 1.29 (s, 3 H, CH$_3$), 1.32–1.38 (m, 1 H, CH*H*-menthyl), 1.40 (d, 2 H, ^2J = 14.2 Hz, C*H*H, C*H*H), 1.44 (d, 1 H, ^2J = 14.7 Hz, C*H*H), 1.53–1.61 (m, 2 H, CH*H*-menthyl, CH*H*-menthyl), 1.75–1.89 (m, 5 H, ArCH$_2$C*H*$_2$C*H*$_2$, CH*H*), 2.00 (dsep, 1 H, ^3J = 7.0 Hz, ^3J = 2.5 Hz, CH$_3$C*H*CH$_3$), 2.86–

2.90 (m, 4 H, ArC*H*$_2$CH$_2$CH$_2$C*H*$_2$), 2.99 (d, 1 H, ^2J = 14.0 Hz, CH*H*), 3.06 (d, 1 H, ^2J = 14.2 Hz, CH*H*), 3.33 (d, 1 H, ^2J = 12.4 Hz, CONC*H*H), 3.67 (dd, 1 H, ^2J = 12.4 Hz, ^4J = 1.8 Hz, CONCH*H*), 4.12 (virt. dt, 1 H, ^3J = 10.9 Hz, ^3J = 4.3 Hz, CO$_2$C*H*), 7.16 (s, 1 H, arom H), 7.28 (s, 1 H, arom H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6 (q, CH_3-menthyl), 20.9 (q, CH_3-menthyl), 22.0 (q, CH_3-menthyl), 22.6 (t, CH_2-menthyl), 23.0 (t, ArCH$_2$*C*H$_2$), 23.1 (t, ArCH$_2$*C*H$_2$), 24.9 (d, (CH$_3$)$_2$*C*H), 26.2 (q, CH_3), 29.5 (q, CH_3), 29.6 (t, Ar*C*H$_2$), 29.9 (t, Ar*C*H$_2$), 30.5 (d, CH-menthyl), 31.0 (s, C), 34.0 (q, CH_3), 34.1 (t, CH_2-menthyl), 37.4 (s, C), 39.1 (t, CH_2-menthyl), 40.9 (s, C), 44.6 (t, CH_2), 46.0 (t, CH_2), 46.1 (d, CH-menthyl), 46.6 (t, CH_2), 57.6 (t, CONCH_2), 77.5 (d, CO$_2$*C*H), 110.0 (d, CH_{ar}), 118.9 (d, CH_{ar}), 132.7 (s, C_{ar}), 133.6 (s, C_{ar}), 139.6 (s, C_{ar}), 149.4 (s, C_{ar}), 154.2 (s, NCO_2), 173.3, 173.4 (s, 2 C, CO, CN).

MS (EI, 70 eV): *m/z* (%) = 534 (4) [M^+], 352 (100) [MH^+ – CO-menthyl], 297 (2), 255 (6), 228 (11), 214 (25), 174 (8), 111 (14), 83 (24), 69 (13), 55 (19).

HRMS (EI): $C_{33}H_{46}N_2O_4$, *m/z* calcd 534.3458, found 534.3454; $C_{32}{}^{13}C_1H_{46}N_2O_4$, *m/z* calcd 535.3491, found 535.3488.

More Polar Diastereoisomer (1*R*,5*R*,7*S*)-**12b**
R_f 0.43 (P–TBME, 1:1); mp 73–76 °C; $[\alpha]_D^{20}$–76.1 (*c* = 1.0, CH_2Cl_2).

IR (KBr): ν = 2955 (s, CH), 2930 (s, CH), 2868 (m, CH), 1772 (s, C=O), 1713 (s, C=O), 1559 (m), 1463 (s), 1263 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.50 (d, 3 H, ^3J = 7.1 Hz, CH_3-menthyl), 0.66 (virt. q, 1 H, $^2J \cong {}^3J \cong$ 11.6 Hz, C*H*H-menthyl), 0.75–0.85 (m, 1 H, C*H*H-menthyl), 0.79 (d, 3 H, ^3J = 7.0 Hz, CH_3-menthyl), 0.87 (d, 3 H, ^3J = 6.6 Hz, CH_3-menthyl), 0.88–0.94 (m, 1 H, C*H*H-menthyl), 1.14 (s, 3 H, CH_3), 1.16–1.24 (m, 1 H, CH-menthyl), 1.26–1.33 (m, 1 H, CH-menthyl), 1.29 (s, 6 H, CH_3, CH_3), 1.37 (dd, 1 H, ^2J = 12.7 Hz, ^4J = 1.8 Hz, C*H*H), 1.38 (d, 1 H, ^2J = 14.1 Hz, C*H*H), 1.41 (d, 1 H, ^2J = 14.4 Hz, C*H*H), 1.52–1.63 (m, 3 H, CH*H*-menthyl, CH*H*-menthyl, CH*H*-menthyl), 1.66 (dsep, 1 H, ^3J = 7.0 Hz, ^3J = 2.6 Hz, CH$_3$C*H*CH$_3$), 1.75–1.84 (m, 5 H, ArCH$_2$C*H*$_2$C*H*$_2$, CH*H*), 2.77–2.89 (m, 4 H, ArC*H*$_2$CH$_2$CH$_2$C*H*$_2$), 2.94 (d, 1 H, ^2J = 14.2 Hz, CH*H*), 3.03 (d, 1 H, ^2J = 14.1 Hz, CH*H*), 3.14 (d, 1 H, ^2J = 12.3 Hz, CONC*H*H), 3.88 (dd, 1 H, ^2J = 12.3 Hz, ^4J = 1.7 Hz, CONCH*H*), 4.22 (virt. dt, 1 H, ^3J = 10.9 Hz, ^3J = 4.3 Hz, CO$_2$C*H*), 7.17 (s, 1 H, arom H), 7.26 (s, 1 H, arom H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.7 (q, CH_3-menthyl), 20.8 (q, CH_3-menthyl), 22.1 (q, CH_3-menthyl), 22.8 (t, CH_2-menthyl), 23.1 (t, ArCH$_2$*C*H$_2$), 23.2 (t, ArCH$_2$*C*H$_2$), 25.6 (d, (CH$_3$)$_2$*C*H), 26.3 (q, CH_3), 29.8 (t, Ar*C*H$_2$), 29.9 (q, CH_3), 30.0 (t, Ar*C*H$_2$), 30.6 (s, C), 31.2 (d, CH-menthyl), 33.7 (q, CH_3), 34.1 (t, CH_2-menthyl), 37.4 (s, C), 40.1 (t, CH_2-menthyl), 41.0 (s, C), 44.0 (t, CH_2), 46.4 (t, CH_2), 46.5 (d, CH-menthyl), 46.9 (t, CH_2), 57.3 (t, CONCH_2), 76.5 (d, CO$_2$*C*H), 110.2 (d, CH_{ar}), 118.8 (d, CH_{ar}), 132.8 (s, C_{ar}), 134.0 (s, C_{ar}), 139.1 (s, C_{ar}), 149.0 (s, C_{ar}), 151.9 (s, NCO_2), 169.8, 174.1 (s, 2 C, CO, CN).

MS (EI, 70 eV): *m/z* (%) = 534 (5) [M^+], 352 (100) [MH^+ – CO-menthyl], 297 (1), 255 (5), 228 (9), 214 (20), 174 (6), 111 (11), 83 (20), 69 (12), 55 (17).

HRMS (EI): $C_{33}H_{46}N_2O_4$, *m/z* calcd 534.3458, found 534.3464; $C_{32}{}^{13}C_1H_{46}N_2O_4$, *m/z* calcd 535.3491, found 535.3499.

Enantiomerically Pure Chiral Hosts 3 by Hydrolysis of the *N*-Menthoxycarbonyl Amides 12 and 13; Typical Procedure

(–)-(1*S*,5*S*,7*R*)-1,5,7-Trimethyl-7-(1′-oxa-3′-azacyclopenta[*b*]-naphthalene-2′-yl)-3-azabicyclo[3.3.1]nonan-2-one (*ent*-**3a**)
N-Menthoxycarbonyl amide **13a** (0.30 mmol, 160 mg) was dissolved in TFA (4 mL) and stirred for 22 h at r.t. The mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), sat. aq $NaHCO_3$ solution (2 × 10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give the chiral acid *ent*-**3a** (65 mg, 62%) and starting material **13a** (36 mg, 23%); $[\alpha]_D^{20}$–44.3 (*c* = 1.0, CH_2Cl_2); HPLC: t_R = 18.6 min (hexane–*iso*-propyl alcohol, 92:8) [265 nm].

(+)-(1*R*,5*R*,7*S*)-1,5,7-Trimethyl-7-(1′-oxa-3′-azacyclopenta[*b*]-naphthalene-2′-yl)-3-azabicyclo[3.3.1]nonan-2-one (**3a**)
The hydrolysis of the *N*-menthoxycarbonyl amide **12a** (0.17 mmol, 90 mg) was performed in analogy to the aforementioned procedure and yielded **3a** (48 mg, 81%); $[\alpha]_D^{20}$ +42.3 (*c* = 0.99, CH_2Cl_2); HPLC: t_R = 22.2 min (hexane–*iso*-propyl alcohol, 92:8) [265 nm].

(–)-(1*S*,5*S*,7*R*)- 1,5,7-Trimethyl-7-(5′,6′,7′,8′-tetrahydro-1′-oxa-3′-azacyclopenta[*b*]naphthalene-2′-yl)-3-azabicyclo[3.3.1]nonan-2-one (*ent*-**3b**)
The hydrolysis of the *N*-menthoxycarbonyl amide **13b** (3.18 mmol, 1.70 g) was performed in analogy to the aforementioned procedure and yielded *ent*-**3b** (1.07 g, 95%);$[\alpha]_D^{20}$–21.9 (*c* = 0.90, CH_2Cl_2); HPLC: t_R = 17.4 min (hexane–*iso*-propyl alcohol, 98:2) [265 nm].

(+)-(1*R*, 5*R*, 7*S*)- 1,5,7-Trimethyl-7-(5′,6′,7′,8′-tetrahydro-1′-oxa-3′-azacyclopenta[*b*]naphthalene-2′-yl)-3-azabicyclo[3.3.1]nonan-2-one (**3b**)
The hydrolysis of the *N*-menthoxycarbonyl amide **12b** (2.66 mmol, 1.42 g) was performed in analogy to the aforementioned procedure and yielded **3b** (795 mg, 85%); $[\alpha]_D^{20}$ +20.5 (*c* = 0.90, CH_2Cl_2); $[\alpha]_D^{20}$ +7.4 (*c* = 1.0, $CHCl_3$); HPLC: t_R = 19.0 min (hexane–*iso*-propyl alcohol, 98:2) [265 nm].

X-Ray Single Crystal Structure Determination of Chiral Host *ent*-**3b** × **1/3H$_2$O**

The measurements were carried out on our standard device (Stoe & Cie. IPDS camera, rotating anode, 173 K, Mo-Kα radiation). During the final refinement cycles we located and refined freely: 1) all hydrogen atoms, 2) a very small disorder of the cyclohexene group with a ratio of 91:9, and 3) a solvent water molecule with a site occupancy factor of 1/3. The hydrogen atoms attached to the atoms involved in the disorder were calculated in ideal positions. The hydrogen atoms bound to the water molecule could be located but not refined. With this knowledge we started with the same crystal a new measurement on our CAD4 diffractometer (sealed tube, 293 K, Cu-Kα radiation, whole sphere). The results fit very well the results of the low temperature measurement. But now the disorder of the cyclohexene group increased to a ratio of 75:25. Flack's parameter now verified the choice of the right enantiomer. Finally, to recheck the results we started a series of psi-scans from 12 Friedel pairs with a significant difference in their intensities. 544 reflections were collected. The R-values calculated from the final model proved the choice of the enantiomer (right handed model: *R*1 = 0.0278, *wR*2 = 0.0721; left handed model: *R*1 = 0.0279, *wR*2 = 0.0775).

X-Ray Single Crystal Structure Determination of Chiral Host *ent*-**3b** × **1/3H$_2$O at 293 K**[19]

Crystal Data: $C_{22}H_{28}N_2O_2$ × 1/3H_2O, M_r = 358.41, orthorhombic, space group $P2_12_12_1$, *a* = 761.83(2), *b* = 1609.20(6), *c* = 1648.87(6) pm, *V* = 2021.4(1)·10^6 pm^3, *Z* = 4, ρ_{calcd} = 1.178 gcm–^{3}, F_{000} = 773.3, λ (Cu Kα) = 154.184 pm, μ = 0.604 mm^{-1}.

Data Collection and Reduction: Crystal size: 0.18 × 0.36 × 0.61 mm, Theta range: 3.84° to 64.97°, Index ranges: –8 ≤ h ≤ 8, –18 ≤ k ≤ 18, –19 ≤ l ≤ 19, Reflections collected: 13177, Independent reflections: 3421 [R_{int} = 0.0366], Absorption correction: DIFABS strategy [$T_{min/max}$ = 0.193/0.663], Refinement method: Full-matrix least-squares on F^2, Data/restraints/parameters: 3421/0/376, Final *R* indi-

ces [I > 2σ(I)]: *R*1 = 0.0306, *wR*2 = 0.0783, GOF on F^2: 1.113, Final *R* indices (all data): *R*1 = 0.0335, *wR*2 = 0.0807, GOF on F^2: 1.113, Extinction parameter: 0.0018(4), Absolute structure parameter: 0.0(2), Largest diff. peak and hole: 0.08 eÅ^{-3} and -0.08 eÅ^{-3}.

Measurement, Computing and Graphics: Measurement device: NONIUS CAD4, Computing cell refinement: CAD4 Operating System [unix version, 1997], Computing data reduction: CADLP (U. Müller et al., 1986), Computing structure solution: SIR92 (Giacovazzo et al., 1994), Computing structure refinement: SHELXL-97 (Sheldrick, 1998), Computing molecular graphic: Platon (Spek, 2000).

X-Ray Single Crystal Structure Determination of Chiral Host *ent*-3b × 1/3H$_2$O at 173 K

Crystal Data: $C_{22}H_{28}N_2O_2 \times 1/3H_2O$, M_r = 358.41, orthorhombic, space group $P2_12_12_1$, *a* = 760.41(8), *b* = 1593.42(11), *c* = 1645.92(11) pm, *V* = 1994.3(3)·10^6 pm^3, *Z* = 4, ρ_{calcd} = 1.194 gcm^{-3}, F_{000} = 773.3, λ (Mo Kα) = 71.073 pm, μ = 0.077 mm^{-1}.

Data Collection and Reduction: Crystal size: 0.18 × 0.36 × 0.61 mm, Theta range: 2.47° to 25.66°, Index ranges: –9 ≤ h ≤ 9, –19 ≤ k ≤ 19, –19 ≤ l ≤ 20, Reflections collected: 17122, Independent reflections: 3756 [R_{int} = 0.0471], Absorption correction: None, Refinement method: Full-matrix least-squares on F^2, Data/restraints/parameters: 3756/0/376, Final *R* indices [I > 2σ(I)]: *R*1 = 0.0305, *wR*2 = 0.0703, GOF on F^2: 1.004, Final *R* indices (all data): *R*1 = 0.0363, *wR*2 = 0.0722, GOF on F^2: 1.004, Extinction parameter: 0.005(3), Absolute structure parameter: 0.2(9), Largest diff. peak and hole: 0.14 eÅ^{-3} and -0.14 eÅ^{-3}.

Measurement, Computing and Graphics: Measurement device: IPDS – 2.8 (STOE & Cie., 1997), Computing cell refinement: IPDS – 2.8 (STOE & Cie., 1997), Computing data reduction: IPDS – 2.8 (STOE & Cie., 1997), Computing structure solution: SIR92 (Giacovazzo et al., 1994), Computing structure refinement: SHELXL-97 (Sheldrick, 1998), Computing molecular graphic: PLATON (Spek, 2000).

Deposition of Data: Crystallographic data (excluding structure factors) for the structures reported here have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-158291 (*ent*-**3b**-293) and no. CCDC-158292 (*ent*-**3b**-173). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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(10) **5**: $C_{22}H_{35}NO_4$; Crystal Data: colorless prism; rhombohedral, *R*3, *a* = *b* = 2822.4(1)pm, *c* = 1526.2(1)pm; *Z* = 6; *R* = 5.16%; GOF = 1.034. Data collection: Data were collected on an Enraf Nonius CAD4 instrument at 293 K employing Cu Kα irradiation (154.178 pm). ω-scan, 6287 reflections (-h, +k, ±l), Θ_{max} = 65°, 5754 independent and 4128 observed reflections [F ≥ 4σ(F)], 521 refined parameters, *wR*2 = 0.1373, residual electron density 0.174 eÅ^{-3}, direct methods, hydrogen atoms calculated. Further details of the crystal structure investigations related to this compound may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ, on quoting the full literature citation (CCDC-157021)

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