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Original article

Epimers of bicyclo[2.2.2]octan-2-ol derivatives with antiprotozoal activity

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Abstract

(2*SR*,6*RS*,7*RS*)-4-Dialkylaminobicyclo[2.2.2]octan-2-ols and several of their esters have shown promising activity against the causative organisms for malaria and sleeping sickness. The base-catalyzed epimerization of the alcohols was carried out by different methods giving their (2*RS*,6*RS*,7*RS*)-isomers. Best results were obtained by the consecutive use of potassium *tert*-butoxide and sodium. The isomeric alcohols were converted to selected esters. All new compounds were tested for their activity against *Trypanosoma brucei rhodesiense* (STIB 900) and a multi-resistant strain of *Plasmodium falciparum*. The antitrypanosomal activity and the cytotoxicity were in general increased. The most active antitrypanosomal agents were the benzoate **8b** and the 4-chlorobenzoate **9b** of the 4-pyrrolidino series. The nicotinate **10a** and the isonicotinate **11a** showed the highest antiplasmodial activities.
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1. Introduction

Malaria is a global health problem killing 2–3 million people every year [1]. In many parts of the world traditional therapeutics have become ineffective against some strains of the causative protozoon, *Plasmodium falciparum*. Since possible resistances have already been demonstrated for the most recently introduced artemisinine derivatives, there is a need for new antimalarials with potency against the multidrug-resistant strains [2–7]. In order to circumvent drug-resistance the structures of the new compounds should be far away from those of the drugs in use.

The circumstances for the treatment of East African sleeping sickness, which is caused by the protozoan parasite *Trypanosoma brucei rhodesiense*, are even worse. If untreated the infection is fatal and every year more than 40 000 people die from the disease [8,9]. For many decades not a single novel drug against this parasite has been developed. At the time of writing there are only three drugs available and patients suffer from their painful application and severe side effects. Moreover, increasing resistance against these drugs has been reported. Therefore, there is an urgent need for new antitrypanosomals [10].

Due to their activity against the causative organisms of malaria tropica and East African trypanosomiasis the synthesis of 4-aminobicyclo[2.2.2]octan-2-ols is of special interest [11]. A large number of ester derivatives have been prepared and some of them have shown promising antiprotozoal activity [12–15]. So far the synthesis has been restricted to compounds with (2*SR*,6*RS*,7*RS*)-configuration, in which the oxygen in ring position 2 is shielded by one of the aromatic rings. This paper deals with the preparation of analogues with reverse configuration in ring position 2 and with the investigation of the resulting changes in antiprotozoal activity. All new compounds

Abbreviations: CC, column chromatography; CH_2Cl_2, dichloromethane; 4-DMAP, 4-dimethylaminopyridine; EtOH, ethanol; HCl, hydrochloric acid; MeOH, methanol; NaOH, sodium hydroxide.

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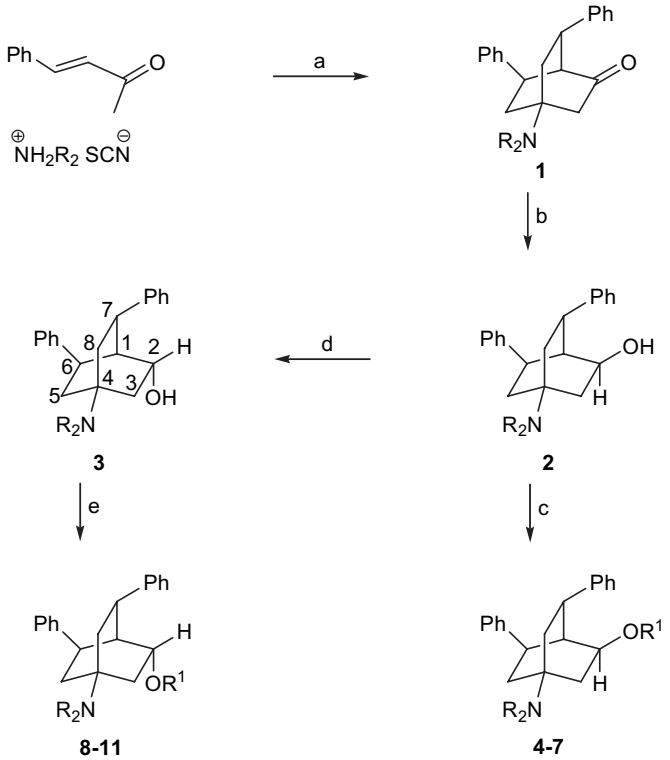
were characterized and tested in vitro for their activities against *T. b. rhodesiense* and the K_1 strain of *P. falciparum* as well as for their cytotoxicity. The results were compared to those of the formerly prepared epimers.

2. Chemistry

Bicyclo[2.2.2]octan-2-ones **1** have been synthesized in a one-pot reaction from acyclic starting material [16]. Their hydrogenation with hydride catalysts gave selectively the (2*SR*,6*RS*,7*RS*)-bicyclo[2.2.2]octan-2-ols **2** [11]. The direct conversion of the ketones **1** to alcohols **3** was attempted by several different methods, such as Meerwein–Ponndorf–Verley reduction. However, compounds **2** always remained the main components in the reaction mixtures. Therefore we focused our efforts towards the epimerization of their stereocenter in ring position 2 (Scheme 1).



Compounds	R^1
1-3	----
4,8	benzoyl
5,9	4-Cl-benzoyl
6,10	nicotinyl
7,11	isonicotinyl

Scheme 1. Preparation of epimeric bicyclo[2.2.2]octanols **2**, **3** and their derivatives **4**–**11**. Reagents and conditions: (a) toluene, 160 °C, 4 h; (b) $LiAlH_4$, ether, rt, 16 h; (c) acyl chloride, pyridine, 140 °C, 16 h or acyl chloride, 4-DMAP, CH_2Cl_2, rt, 16 h or carboxylic acid, 4-DMAP, DCC, CH_2Cl_2, rt, 2 days; (d) methods A–C (Section 6); (e) acyl chloride, 4-DMAP, CH_2Cl_2, rt, 16 h. **1a**–**11a**: NR_2 = dimethylamino, **1b**–**11b**: NR_2 = pyrrolidino, **1c**–**11c**: NR_2 = piperidino.

For the chemical inversion of secondary alcohols several methods have been reported. The most popular chemical reaction is the Mitsunobu inversion [18]. Some of its drawbacks are the labour-intensive preparation and work-up [19]. Moreover, the reaction is S_{N^2} dependent and may fail in the case of sterically hindered alcohols [20,21]. Interestingly that has already been reported for a bicyclo[2.2.2]octane derivative [22].

Since compounds **2** have a slight propensity for elimination in acidic medium, we decided for a base-catalyzed inversion method. The reactions were monitored by TLC and the degree of conversion was determined by means of ^{1}H NMR. The (2*SR*,6*RS*,7*RS*)-bicyclo[2.2.2]octan-2-ols **2** were epimerized to their (2*RS*,6*RS*,7*RS*)-isomers **3** by different methods. When alcohols **2** were heated with equimolar quantities of potassium *tert*-butoxide without solvent for 24 h, 74–88% of compounds **3** were detected in the reaction mixtures (method A). Longer reaction periods did not increase the amount of desired epimer and use of excess alcoholate led to the formation of ring cleavage products. The chromatographic separation of the two epimers required several passages entailing a serious loss of yield. Since compounds **3** were needed for further reactions, we still sought for a method for the quantitative epimerization of compounds **2**. Full stereoinversion was achieved by treatment of **2** with sodium in dry toluene at ambient temperature (method B). Drawbacks of the reaction were the low reaction rate and the formation of a considerable amount of ketones **1** as by-products. However, compounds **1** were easily removed and recovered by column chromatography. Best results were obtained by the consecutive use of potassium *tert*-butoxide and sodium for the inversion of compound **2b** (method C). The reaction period for the quantitative conversion was distinctly shortened. Furthermore, the amount of the afforded ketone **1b** was markedly reduced, indicating that only **2b** was oxidized upon treatment with sodium, whereas **3b** remained unchanged (Table 1).

The new bicyclo-octanols **3** were transformed to epimers of the esters **4**–**7**, which were in general more active than their parent alcohols. Compounds **8**–**11** were yielded by acylation of **3** with acid chlorides using standard procedures.

The structures of compounds **3** were investigated by NMR experiments. The stereoinversion in ring position 2 was confirmed by a NOE from aromatic *ortho*-protons to 2-H and 7-H. The bicyclo-octane skeleton was established by the typical large W-couplings (2–3 Hz) between the protons in ring positions 3, 5 and 8 (Fig. 1).

Table 1
Epimerization of bicyclo-octanols **2**

Method	Epimeric excess of **3** (%)[a]			Formation of **1** (%)[a]		
	3a	**3b**	**3c**	**1a**	**1b**	**1c**
A	48	76	70	n.d.	n.d.	n.d.
B	>96	>96	>96	50	55	75
C		>96			10	

n.d.: not detectable.
[a] Ratios were determined by ^{1}H NMR integration of reaction mixtures.

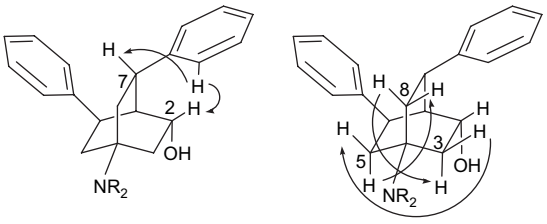


Fig. 1. NOEs and W-couplings for compounds **3**.

3. Antiprotozoal activity

Alcohols **3** and esters **8**–**11** were tested via microplate assays for their activities against the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine) and *T. brucei rhodesiense*. The cytotoxicity was determined with rat skeletal myoblasts (L-6 cells). Melarsoprol and chloroquine were used as standards.

4. Results and discussion

The new alcohols **3** and esters **8**–**11** were tested for their antiprotozoal activities against the K_1 strain of *P. falciparum* and *T. b. rhodesiense* (STIB 900). Their cytotoxicity was determined with rat skeletal myoblasts (L-6 cells).

In order to study the effect of the stereoinversion in ring position 2 on the antiprotozoal potencies and the cytotoxicity of the bicyclo-octyl esters, the results were compared to those of their formerly prepared epimers (Table 2).

In the alcohol series compound **3b** ($IC_{50} = 1.23$ μM) was the most active antiplasmodial of the new bicyclo-octanols, but its activity did not come up to that of **2c** ($IC_{50} = 0.84$ μM). As already observed for their epimers **4**–**7**, most of the esters **8**–**11** were more active than their parent alcohols and some of them even as their epimers. Particularly, the nicotinate **10a** and the isonicotinates **11a** and **11c** ($IC_{50} = 0.49$–0.62 μM) show promising antiplasmodial activity, which is with the exception of **6b** ($IC_{50} = 0.20$ μM) in the range of the most active bicyclo-octyl esters **4**–**7**of the (2*SR*,6*RS*,7*RS*)-series ($IC_{50} = 0.47$–0.66 μM). Obviously the antiplasmodial activity is not significantly influenced by the relative spatial arrangement of phenyl ring in position 7 and acyloxy substituent in those esters.

Most of the new esters **8**–**11** were more active antitrypanosomals than their epimers **4**–**7** indicating the positive contribution of the new configuration in ring position 2. The highest antitrypanosomal activities of the new compounds showed the 4-pyrrolidino-substituted benzoate **8b** ($IC_{50} = 0.96$ μM) and the corresponding 4′-chlorobenzoate **9b** ($IC_{50} = 0.86$ μM). They were far more active than their corresponding epimers **4b** ($IC_{50} = 4.95$ μM) and **5b** ($IC_{50} = 6.27$ μM). However, the nicotinate **6b** ($IC_{50} = 0.62$ μM) remains the most promising antitrypanosomal of this series.

As already observed for the antitrypanosomal activity the stereoinversion caused an unequivocal change of the cytotoxic properties of the esters. Nearly all of the new esters **8**–**11** were more toxic. In contrast the cytotoxic activities of the new alcohols **3** were comparable to those of their epimers **2** or better.

Table 2
In vitro antiprotozoal activities and cytotoxicity of alcohols **2**, **3** and esters **4**–**11** against *Trypanosoma brucei rhodesiense*, *Plasmodium falciparum* K1, and L-6 cells, expressed as IC_{50} (μM)[a,b]

Compound	*P. falciparum* K1[c]	*T. b. rhodesiense*	Cytotoxicity L-6 cells
2a	>15.55	2.95	132.5
2b	2.39	4.26	26.76
2c	0.84	5.34	37.34
3a	13.13	3.64	157.72
3b	1.23	2.53	35.40
3c	2.77	13.14	34.30
4a	2.47	1.53	9.88
4b	4.50	4.95	5.08
4c	0.66	14.99	97.29
5a	0.55	1.06	9.46
5b	0.47	6.27	74.87
5c	0.79	37.58	103.9
6a	1.49	15.94	171.4
6b	0.20	0.62	24.40
6c	0.48	70.94	0.87
7a	1.14	3.16	26.14
7b	0.86	3.49	27.40
7c	0.65	16.92	113.2
8a	1.18	1.12	6.02
8b	0.80	0.96	8.41
8c	0.77	3.12	17.25
9a	1.11	2.04	4.35
9b	0.76	0.86	7.31
9c	1.12	1.76	23.00
10a	0.50	1.52	12.25
10b	2.34	1.07	18.74
10c	n.t.	n.t.	21.31
11a	0.49	1.68	12.53
11b	4.49	1.44	26.92
11c	0.62	3.35	21.32
Mel		0.0039	7.78
Chl	0.12[d]		188.5

n.t.: not tested due to low activity in a pre-screening; chl = chloroquine; mel = melarsoprol.

[a] Values represent the average of four determinations (two determinations of two independent experiments).

[b] Values for esters 4–7 [13–15].

[c] Resistant to chloroquine and pyrimethamine.

[d] Against sensitive *P. falciparum* strains.

5. Conclusion

This paper reports the first synthesis of (2*RS*,6*RS*,7*RS*)-isomers in the bicyclo[2.2.2]octane series. The (2*SR*,6*RS*,7*RS*)-4-dialkylaminobicyclo[2.2.2]octan-2-ols have been isomerized to their (2*RS*,6*RS*,7*RS*)-epimers by several methods. Full conversion of the parent alcohols to a mixture of ketone and epimer and in this way circumvention of the chromatographic separation of the epimers was achieved by treatment with sodium. The highest yields were obtained by the subsequent use of potassium *tert*-butoxide and sodium. Selected esters were prepared from the new alcohols. The antiplasmodial and antitrypanosomal activities of all new compounds were determined and compared to those of the corresponding epimers. Some of the new esters showed good antiprotozoal activities.

The influence on the antiplasmodial activity was not uniform, whereas the antitrypanosomal activity and the cytotoxicity were significantly increased.

6. Experimental

6.1. Instrumentation and chemicals

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer) in KBr discs; frequencies are reported in cm^{-1}. UV/vis: Lambda 17 UV/vis-spectrometer (Perkin Elmer), maxima reported in nm. NMR spectra: Varian UnityInova 400, 5 mm tubes, 25 °C, internal standards: ^1H: TMS [$\delta = 0.00$ ppm], ^{13}C: center of the solvent peak [$\delta = 77.0$ ppm for $CDCl_3$]. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra are reported in ppm, ^1H- and ^{13}C-resonances were assigned using ^1H,^1H- and ^1H, ^{13}C-correlation spectra and are numbered as given in the formulas (br broad, d dublet, dd double dublet, ddd double double dublet, dt double triplet, m multiplet, s singlet, t triplet, td triple dublet). MS: Kratos profile spectrometer. Microanalyses: EA 1108 CHNS–O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna. Materials: column chromatography (CC): silica gel 60 (Merck 70–230 mesh, pore-diameter 60 Å); thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254}, 0.2 mm, 200 × 200 mm); the substances were detected in UV light at 254 nm.

6.2. Syntheses

Ketones **1a–c** were prepared according to reported procedures [11,16], but DMF was replaced as solvent by toluene and the reactions were carried out at 160 °C.

Alcohols **2a–c** were prepared according to reported procedures [11].

6.2.1. General procedures for the synthesis of (2RS,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo [2.2.2]octan-2-ols (**3a–c**)

General method A: a mixture of the bicyclic alcohol **2** and potassium *tert*-butoxide was heated at 200 °C in an argon atmosphere for 24 h. Then 10 ml EtOH and 50 ml H_2O were added and the mixture was shaken five times with a total of 250 ml diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. A sample of the oily residue was measured by ^1H NMR spectroscopy revealing the isomer ratio of the mixture.

General method B: in an argon atmosphere the bicyclic alcohol **2** was dissolved in dry toluene and sodium was added. The mixture was stirred for 1 h at 100 °C and then at room temperature in an argon atmosphere until the sodium was dissolved. A sample was taken and the progress of the reaction was checked by ^1H NMR. If it was incomplete, the procedure was repeated after adding a smaller amount of sodium. The mixture was diluted with CH_2Cl_2 and then it was carefully shaken six times with water. The organic layer was dried with sodium sulfate, filtered and the solvent was removed in vacuo. The residue was purified by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (5:1). The fractions containing the product were combined and the solvent was evaporated.

General method C: the mixture of isomeric alcohols **2** and **3**, which was obtained by method A was dissolved in dry toluene and argon was induced. After the addition of sodium it was treated as outlined in method B.

*6.2.1.1. (2RS,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**3a**). Method A*: compound **2a** (0.40 mmol) and potassium *tert*-butoxide (0.40 mmol) yielded after work-up with 0.2 ml EtOH, 1 ml H_2O and 5 ml diethyl ether an oily residue containing 26% of **2a** and 74% of **3a**.

Method B: in 65 ml dry toluene in a 500 ml round-bottomed flask **2a** (29.6 mmol) and sodium in two portions (56.5 mmol + 21.8 mmol) yielded an oily mixture of **1a** and **3a**. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (5:1) gave 28% of **3a** as a yellowish resin.

IR = 2869, 1601, 1495, 1466, 1447, 1065, 1022, 751, 699; UV (CH_2Cl_2, (log ε)): 268 (2.602), 260 (2.764), 254 (2.740), 231 (3.127); ^1H NMR ($CDCl_3$) $\delta = 1.50$ (ddd, $J = 12.6$, 6.7, 3.0 Hz, 1H, 3-H), 1.67 (ddd, $J = 12.8$, 9.3, 2.7 Hz, 1H, 8-H), 1.78 (ddd, $J = 12.3$, 9.5, 2.6 Hz, 1H, 5-H), 2.00 (d, $J = 2.0$ Hz, 1H, 1-H), 2.02 (ddd, $J = 12.8$, 10.2, 2.9 Hz, 1H, 8-H), 2.14–2.24 (m, 2H, 3-H, 5-H), 2.31 (s, 6H, $N(CH_3)_2$), 3.20 (br, t, $J = 9.8$ Hz, 1H, 7-H), 3.59 (br, t, $J = 9.6$ Hz, 1H, 6-H), 4.23 (ddd, $J = 9.4$, 6.7, 2.0 Hz, 1H, 2-H), 7.14–7.39 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$) $\delta = 31.66$ (C-5), 33.07 (C-8), 34.45 (C-6), 34.70 (C-7), 37.24 (C-3), 38.31 ($N(CH_3)_2$), 45.67 (C-1), 57.11 (C-4), 65.36 (C-2), 126.01, 126.06, 127.33, 127.51, 128.37, 128.42, 143.76, 144.19 (aromatic C); Anal. Calcd. for $C_{22}H_{27}NO$ (321.46): C 82.20, H 8.47, N 4.36; found: C 81.98, H 8.47, N 4.24.

*6.2.1.2. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo [2.2.2]octan-2-ol (**3b**). Method A*: compound **2b** (14.4 mmol) and potassium *tert*-butoxide (14.4 mmol) yielded an oily residue containing 12% of **2b** and 88% of **3b**.

Method B: in 60 ml dry toluene in a 500 ml round-bottomed flask **2b** (10.2 mmol) and sodium in two portions (20.4 mmol + 12.4 mmol) yielded an oily mixture of **1b** and **3b**. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (5:1) gave 36% of **3c** as a yellowish resin.

Method C: in 40 ml dry toluene in a 250 ml round-bottomed flask 12.0 mmol of the mixture of **2b** and **3b**, which was afforded by method A, were treated with two portions of sodium (8.7 mmol + 8.7 mmol) yielding an oily mixture of **1b** and **3b**. Purification by means of column chromatography over silica gel using CH_2Cl_2/MeOH (5:1) as eluent gave 65% of **3b** as a yellowish resin.

IR = 2870, 1601, 1495, 1447, 1064, 1029, 752, 699; UV (CH_2Cl_2, (log ε)): $\lambda = 268$ (2.681), 260 (2.829), 254 (2.838),

230 (3.210); ^{1}H NMR ($CDCl_3$) $\delta = 1.56$ (ddd, $J = 12.8$, 6.0, 2.7 Hz, 1H, 3-H), 1.73–1.82 (m, 5H, 8-H, $(CH_2)_2$), 1.88 (ddd, $J = 12.2$, 9.5, 2.5 Hz, 1H, 5-H), 1.98 (d, $J = 1.9$ Hz, 1H, 1-H), 2.04 (ddd, $J = 12.4$, 10.7, 3.0 Hz, 1H, 8-H), 2.18 (ddd, $J = 12.4$, 9.5, 2.7 Hz, 1H, 5-H), 2.23 (ddd, $J = 12.4$, 9.7, 2.5 Hz, 1H, 3-H), 2.65–2.79 (m, 4H, $N(CH_2)_2$), 3.23 (br, t, $J = 9.7$ Hz, 1H, 7-H), 3.62 (br, t, $J = 9.7$ Hz, 1H, 6-H), 4.24 (ddd, $J = 9.5$, 6.0, 2.0 Hz, 1H, 2-H), 7.14–7.40 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$) $\delta = 23.52$ ($(CH_2)_2$), 32.56 (C-5), 34.01 (C-8), 34.50 (C-6), 34.67 (C-7), 37.88 (C-3), 45.44 ($N(CH_2)_2$), 45.98 (C-1), 55.78 (C-4), 65.28 (C-2), 125.95, 126.00, 127.37, 127.56, 128.32, 128.38, 143.83, 144.27 (aromatic C); Anal. Calcd. for $C_{24}H_{29}NO \cdot 0.7H_2O$ (360.11): C 80.05, H 8.51, N 3.89; found: C 79.90, H 8.25, N 3.85.

*6.2.1.3. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-ol (**3c**). Method A*: compound **2c** (0.84 mmol) and potassium *tert*-butoxide (0.84 mmol) yielded an oily residue containing 15% of **2c** and 85% of **3c**.

Method B: in 75 ml dry toluene in a 500 ml round-bottomed flask **2c** (23.2 mmol) and sodium in portions (48.1 mmol + 13.8 mmol + 4.3 mmol) yielded an oily mixture of **1c** and **3c**. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (5:1) gave 15% of **3c** as a yellowish resin.

IR = 2935, 1603, 1496, 1447, 1153, 1110, 753, 699; UV (MeOH, (log ε)): $\lambda = 259$ (2.984), 210 (4.158); ^{1}H NMR ($CDCl_3$) $\delta = 1.43$–1.50 (m, 2H, CH_2), 1.57–1.66 (m, 4H, $2CH_2$), 1.69 (br, t, $J = 10.9$ Hz, 1H, 8-H), 1.83–1.93 (m, 2H, 3-H, 5-H), 2.10 (td, $J = 10.9$, 1.9 Hz, 1H, 8-H), 2.25 (ddd, $J = 12.9$, 9.7, 2.6 Hz, 1H, 5-H), 2.29 (br, s, 1H, 1-H), 2.39–2.46 (m, 1H, 3-H), 2.51–2.68 (m, 4H, $N(CH_2)_2$), 3.24 (br, t, $J = 9.6$ Hz, 1H, 7-H), 3.66 (br, t, $J = 9.6$ Hz, 1H, 6-H), 4.43 (ddd, $J = 9.3$, 7.3, 1.6 Hz, 1H, 2-H), 7.12–7.41 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$) $\delta = 24.88$ (CH_2), 26.75 ($2CH_2$), 32.22 (C-5), 33.52 (C-8), 35.51 (C-6), 35.66 (C-7), 39.15 (C-3), 46.10 (C-1), 46.86 ($N(CH_2)_2$), 56.57 (C-2), 57.83 (C-4), 126.24, 126.30, 127.09, 127.51, 128.48, 128.55, 143.07, 143.30 (aromatic C); Anal. Calcd. for $C_{25}H_{31}NO \cdot 0.5H_2O$ (370.54): C 81.04, H 8.70, N 3.78; found: C 81.16, H 8.96, N 3.62.

The preparation of esters **4–7** has already been reported in Refs. [13–15].

*6.2.2. General procedure for the synthesis of (2RS,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl esters **8–11***

The bicyclo-octanol **3** and 4-DMAP were dissolved in CH_2Cl_2 and cooled with an ice bath. Under stirring the acyl chloride in 2 ml CH_2Cl_2 was added and argon was induced. After 1 h the ice bath was removed and the solution was stirred over night at room temperature in an argon atmosphere. Then it was carefully shaken five times with water, three times with 1 M NaOH and again washed three times with water, dried over sodium sulfate and filtered. The solvent was removed in vacuo and the residue was purified by means of column chromatography. Alternatively hydrochlorides were afforded by treatment of the acetone solution of the residue with equivalent amounts of a 1 M solution of hydrogen chloride in diethyl ether. The precipitate was sucked off and washed with a mixture of diethyl ether and EtOH.

*6.2.2.1. (2RS,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl benzoate (**8a**).* Compound **3a** (0.71 mmol), benzoyl chloride (1.41 mmol) and 4-DMAP (1.40 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue. Purification by means of column chromatography over silica gel using CH_2Cl_2/MeOH (29:1) as eluent gave 84% of **8a** as a yellowish resin. IR = 2868, 1715, 1601, 1583, 1496, 1274, 1112, 712, 699; UV (CH_2Cl_2, (log ε)): $\lambda = 282$ (2.914), 233 (4.113); ^{1}H NMR ($CDCl_3$) $\delta = 1.71$ (ddd, $J = 13.2$, 5.9, 2.9 Hz, 1H, 3-H), 1.76 (ddd, $J = 12.6$, 9.5, 2.8 Hz, 1H, 8-H), 1.89 (ddd, $J = 12.3$, 9.5, 2.6 Hz, 1H, 5-H), 2.16 (ddd, $J = 12.6$, 10.7, 3.1 Hz, 1H, 8-H), 2.30 (ddd, $J = 12.3$, 10.4, 2.7 Hz, 1H, 5-H), 2.36 (s, 6H, $N(CH_3)_2$), 2.45 (d, $J = 1.9$ Hz, 1H, 1-H), 2.49 (ddd, $J = 13.2$, 9.8, 2.6 Hz, 1H, 3-H), 3.27 (br, t, $J = 9.9$ Hz, 1H, 7-H), 3.70 (br, t, $J = 9.8$ Hz, 1H, 6-H), 5.43 (ddd, $J = 9.8$, 5.9, 1.9 Hz, 1H, 2-H), 7.18–7.58 (m, 13H, Ar-H), 8.06 (d, $J = 8.0$ Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) $\delta = 32.20$ (C-5), 34.34 (C-3, C-8), 34.46 (C-7), 35.69 (C-6), 38.39 ($N(CH_3)_2$), 41.22 (C-1), 56.79 (C-4), 70.41 (C-2), 126.24, 127.18, 127.44, 128.38, 128.54, 128.57, 129.53, 130.43, 132.96, 143.41, 143.53 (aromatic C), 166.10 (COO); Anal. Calcd. for $C_{29}H_{31}NO_2 \cdot 0.5H_2O$ (434.58): C 80.15, H 7.42, N 3.22; found: C 80.25, H 7.53, N 3.16.

*6.2.2.2. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl benzoate (**8b**).* Compound **3b** (0.78 mmol), benzoyl chloride (1.56 mmol) and 4-DMAP (1.56 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue. Purification by means of column chromatography over aluminium oxide eluting with CH_2Cl_2 gave 58% of **8b** as a yellowish resin. IR = 2869, 1715, 1601, 1495, 1449, 1274, 1112, 712, 699; UV (CH_2Cl_2, (log ε)): $\lambda = 281$ (3.088), 233 (4.160); ^{1}H NMR ($CDCl_3$) $\delta = 1.74$–1.88 (m, 6H, 3-H, 8-H, $(CH_2)_2$), 2.00 (br, t, $J = 13.4$ Hz, 1H, 5-H), 2.18 (br, t, $J = 11.4$ Hz, 1H, 8-H), 2.30 (br, t, $J = 13.3$ Hz, 1H, 5-H), 2.42 (d, $J = 2.1$ Hz, 1H, 1-H), 2.52 (br, dd, $J = 12.5$, 9.8 Hz, 1H, 3-H), 2.69–2.83 (m, 4H, $N(CH_2)_2$), 3.29 (t, $J = 10.0$ Hz, 1H, 7-H), 3.73 (t, $J = 9.7$ Hz, 1H, 6-H), 5.43 (ddd, $J = 9.7$, 5.7, 2.1 Hz, 1H, 2-H), 7.19–7.56 (m, 13H, Ar-H), 8.06 (d, $J = 7.6$ Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) $\delta = 23.57$ ($(CH_2)_2$), 33.29 (C-5), 34.39 (C-7), 34.97 (C-3), 35.05 (C-8), 35.73 (C-6), 41.56 (C-1), 45.64 ($N(CH_2)_2$), 55.42 (C-4), 70.42 (C-2), 126.17, 126.19, 127.21, 127.50, 128.36, 128.50, 129.49, 130.46, 132.92, 143.49, 143.59 (aromatic C), 166.08 (COO); Anal. Calcd. for $C_{31}H_{33}NO_2 \cdot 0.5H_2O$ (460.62): C 80.84, H 7.44, N 3.04; found: C 80.99, H 7.42, N 2.88.

*6.2.2.3. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl benzoate (**8c**).* Compound **3c** (0.78 mmol), benzoyl chloride (1.56 mmol) and 4-DMAP (0.16 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue. Purification by

means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (29:1) gave 83% of **8c** as a yellowish resin. IR = 2855, 1716, 1603, 1495, 1451, 1274, 1112, 713, 699; UV (MeOH, (log ε)): λ = 282 (3.122), 228 (4.059), 210 (4.297); ^{1}H NMR ($CDCl_3$) δ = 1.42–1.49 (m, 2H, CH_2), 1.58–1.66 (m, 4H, $2CH_2$), 1.72 (ddd, *J* = 12.7, 6.1, 2.7 Hz, 1H, 3-H), 1.77 (ddd, *J* = 12.5, 9.9, 2.4 Hz, 1H, 8-H), 1.90 (ddd, *J* = 12.4, 9.6, 2.1 Hz, 1H, 5-H), 2.17 (ddd, *J* = 12.5, 9.9, 2.7 Hz, 1H, 8-H), 2.32 (ddd, *J* = 12.4, 9.6, 2.4 Hz, 1H, 5-H), 2.44 (d, *J* = 2.0 Hz, 1H, 1-H), 2.52 (ddd, *J* = 12.7, 9.5, 2.1 Hz, 1H, 3-H), 2.55–2.72 (m, 4H, $N(CH_2)_2$), 3.24 (t, *J* = 9.9 Hz, 1H, 7-H), 3.67 (t, *J* = 9.6 Hz, 1H, 6-H), 5.40 (ddd, *J* = 9.5, 6.1, 2.0 Hz, 1H, 2-H), 7.17–7.58 (m, 13H, Ar-H), 8.05 (d, *J* = 7.2 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ = 24.93 (CH_2), 26.78 ($2CH_2$), 32.60 (C-5), 34.49 (C-7), 34.77 (C-8), 34.94 (C-3), 35.76 (C-6), 41.34 (C-1), 46.82 ($N(CH_2)_2$), 57.36 (C-4), 70.63 (C-2), 126.19, 127.20, 127.46, 128.38, 128.50, 128.53, 129.52, 130.47, 132.94, 143.51, 143.61 (aromatic C), 166.14 (COO). Anal. Calcd. for $C_{32}H_{35}NO_2$ (465.63): C 82.54, H 7.58, N 3.01; found: C 82.58, H 7.74, N 2.86.

*6.2.2.4. (2RS,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 4-chlorobenzoate (**9a**).* Compound **3a** (0.62 mmol), 4-chlorobenzoyl chloride (1.33 mmol) and 4-DMAP (1.34 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (29:1) gave 86% of **9a** as a colourless resin. IR = 2869, 1718, 1593, 1496, 1447, 1272, 1116, 1104, 1091, 759, 699; UV (CH_2Cl_2, (log ε)): λ = 282 (2.907), 241 (4.252); ^{1}H NMR ($CDCl_3$) δ = 1.68 (ddd, *J* = 13.1, 5.9, 3.1 Hz, 1H, 3-H), 1.76 (ddd, *J* = 12.4, 9.6, 2.7 Hz, 1H, 8-H), 1.88 (ddd, *J* = 12.2, 9.4, 2.5 Hz, 1H, 5-H), 2.16 (ddd, *J* = 12.4, 10.6, 3.0 Hz, 1H, 8-H), 2.30 (ddd, *J* = 12.2, 10.7, 2.7 Hz, 1H, 5-H), 2.36 (s, 6H, $N(CH_3)_2$), 2.43 (d, *J* = 2.0 Hz, 1H, 1-H), 2.49 (ddd, *J* = 13.1, 9.6, 2.5 Hz, 1H, 3-H), 3.27 (br, t, *J* = 9.9 Hz, 1H, 7-H), 3.66 (br, t, *J* = 9.6 Hz, 1H, 6-H), 5.41 (ddd, *J* = 9.6, 5.9, 2.0 Hz, 1H, 2-H), 7.18–7.43 (m, 12H, Ar-H), 7.98 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ = 32.24 (C-5), 34.23 (C-8), 34.34 (C-3), 34.48 (C-7), 35.67 (C-6), 38.39 ($N(CH_3)_2$), 41.17 (C-1), 56.84 (C-4), 70.77 (C-2), 126.31, 127.17, 127.40, 128.59, 128.75, 128.86, 130.92, 139.44, 143.30, 143.41 (aromatic C), 165.25 (COO); Anal. Calcd. for $C_{29}H_{30}ClNO_2$ (460.02): C 74.84, H 6.63, N 3.01, Cl 7.62; found: C 74.89, H 6.54, N. 2.97, Cl 7.50.

*6.2.2.5. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 4-chlorobenzoate (**9b**).* Compound **3b** (0.72 mmol), 4-chlorobenzoyl chloride (1.44 mmol) and 4-DMAP (0.11 mmol) in 15 ml dry CH_2Cl_2 yielded a residue. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (29:1) gave 81% of **9b** as a white residue. IR = 2872, 1720, 1595, 1496, 1489, 1448, 1272, 1116, 1104, 1092, 760, 699; UV (CH_2Cl_2, (log ε)): λ = 282 (3.077), 240 (4.282); ^{1}H NMR ($CDCl_3$) δ = 1.74 (ddd, *J* = 13.1, 5.8, 2.7 Hz, 1H, 3-H), 1.76–1.84 (m, 4H, $(CH_2)_2$), 1.84 (ddd, *J* = 13.6, 9.8, 2.6 Hz, 1H, 8-H), 1.99 (ddd, *J* = 13.4, 9.5, 2.3 Hz, 1H, 5-H), 2.17 (ddd, *J* = 13.6, 9.8, 2.7 Hz, 1H, 8-H), 2.30 (ddd, *J* = 13.4, 9.5, 2.6 Hz, 1H, 5-H), 2.41 (d, *J* = 2.3 Hz, 1H, 1-H), 2.51 (ddd, *J* = 13.1, 9.4, 2.3 Hz, 1H, 3-H), 2.69–2.82 (m, 4H, $N(CH_2)_2$), 3.29 (t, *J* = 9.8 Hz, 1H, 7-H), 3.69 (t, *J* = 9.5 Hz, 1H, 6-H), 5.41 (ddd, *J* = 9.4, 5.8, 2.3 Hz, 1H, 2-H), 7.18–7.43 (m, 12H, Ar-H), 7.98 (d, *J* = 8.5 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ = 23.57 ($(CH_2)_2$), 33.32 (C-5), 34.42 (C-7), 34.92 (C-8), 34.99 (C-3), 35.71 (C-6), 41.51 (C-1), 45.49 ($N(CH_2)_2$), 55.43 (C-4), 70.81 (C-2), 126.25, 126.27, 127.22, 127.48, 128.55, 128.75, 128.90, 130.91, 139.41, 143.40, 143.50 (aromatic C), 165.27 (COO); Anal. Calcd. for $C_{31}H_{32}ClNO_2 \cdot 0.3H_2O$ (491.46): C 75.76, H 6.69, N 2.85; found: C 75.68, H 6.64, N 2.86.

*6.2.2.6. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 4-chlorobenzoate (**9c**).* Compound **3c** (0.54 mmol), 4-chlorobenzoyl chloride (1.08 mmol) and 4-DMAP (1.08 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (29:1) gave 89% of **9c** as a yellowish resin. IR = 2851, 1719, 1594, 1496, 1448, 1272, 1114, 1104, 1092, 1015, 756, 759, 699; UV (CH_2Cl_2, (log ε)): λ = 283 (2.923), 241 (4.278); ^{1}H NMR ($CDCl_3$) δ = 1.42–1.50 (m, 2H, CH_2), 1.58–1.66 (m, 4H, $2CH_2$), 1.67–1.74 (m, 1H, 3-H), 1.76 (br, dd, *J* = 12.5, 9.7 Hz, 1H, 8-H), 1.89 (br, dd, *J* = 12.5, 9.5 Hz, 1H, 5-H), 2.16 (br, dd, *J* = 12.1, 9.5 Hz, 1H, 8-H), 2.32 (br, dd, *J* = 12.4, 9.7 1H, 5-H), 2.43 (s, 1H, 1-H), 2.51 (br, dd, *J* = 13.3, 9.1 Hz, 1H, 3-H), 2.54–2.72 (m, 4H, $N(CH_2)_2$), 3.25 (t, *J* = 9.6 Hz, 1H, 7-H), 3.63 (t, *J* = 9.6 Hz, 1H, 6-H), 5.39 (ddd, *J* = 9.1, 6.4, 2.1 Hz, 1H, 2-H), 7.18–7.43 (m, 12H, Ar-H), 7.98 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ = 24.93 (CH_2), 26.80 ($2CH_2$), 32.65 (C-5), 34.51 (C-7), 34.65 (C-8), 34.95 (C-3), 35.75 (C-6), 41.31 (C-1), 46.84 ($N(CH_2)_2$), 57.32 (C-4), 71.01 (C-2), 126.24, 127.18, 127.42, 128.54, 128.74, 128.91, 130.90, 139.40, 143.41, 143.51 (aromatic C), 165.27 (COO); Anal. Calcd. for $C_{32}H_{42}ClNO_2 \cdot 0.2H_2O$ (503.68): C 76.31, H 6.88, N 2.78, Cl 7.04; found: C 76.21, H 6.77, N 2.73, Cl 7.38.

*6.2.2.7. (2RS,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl nicotinate (**10a**).* Compound **3a** (1.26 mmol), nicotinyl chloride (2.52 mmol) and 4-DMAP (0.25 mmol) in 12 ml dry CH_2Cl_2 yielded an oily residue, which was treated with an 1 M ethereal solution of HCl giving 22% of the dihydrochloride of **10a** (22%) as white crystals. Mp: 160–162 °C (HCl: EtOH/diethyl ether). IR = 1730, 1631, 1602, 1496, 1290, 1134, 742, 702, 674; UV (MeOH, (log ε)): λ = 264 (3.663), 210 (4.459); ^{1}H NMR ($CDCl_3$) δ = 1.73 (ddd, *J* = 12.9, 5.9, 3.0 Hz, 1H, 3-H), 1.77 (ddd, *J* = 12.6, 9.6, 2.6 Hz, 1H, 8-H), 1.90 (ddd, *J* = 12.2, 9.5, 2.4 Hz, 1H, 5-H), 2.17 (ddd, *J* = 12.6, 9.6, 3.0 Hz, 1H, 8-H), 2.30 (ddd, *J* = 12.2, 9.5, 2.6 Hz, 1H, 5-H), 2.37 (s, 6H, $N(CH_3)_2$), 2.43 (d, *J* = 2.0 Hz, 1H, 1-H), 2.51 (ddd, *J* = 12.9, 9.6, 2.4 Hz, 1H, 3-H), 3.29 (t, *J* = 9.6 Hz, 1H, 7-H), 3.67 (t, *J* = 9.5 Hz, 1H, 6-H), 5.44 (ddd, *J* = 9.6, 5.9,

2.0 Hz, 1H, 2-H), 7.19–7.41 (m, 11H, 5′-H, Ar-H), 8.30 (d, $J = 7.9$ Hz, 1H, 4′-H), 8.78 (d, $J = 4.4$ Hz, 1H, 6′-H), 9.26 (s, 1H, 2′-H); ^{13}C NMR ($CDCl_3$) $\delta = 32.11$ (C-5), 34.09 (C-8), 34.32 (C-3), 34.41 (C-7), 35.72 (C-6), 38.38 ($N(CH_3)_2$), 41.36 (C-1), 56.84 (C-4), 71.14 (C-2), 123.31 (C-5′), 126.36 (C-3′), 137.00 (C-4′), 150.87 (C-2′), 153.48 (C-6′), 126.33, 127.15, 127.41, 128.59, 143.18, 143.21 (aromatic C), 164.79 (COO); HRMS (base, MALDI) calcd for $C_{28}H_{30}N_2O_2H$: 427.2386, found: 427.2350.

*6.2.2.8. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl nicotinate (**10b**).* Compound **3b** (0.71 mmol), nicotinyl chloride (1.41 mmol) and 4-DMAP (0.14 mmol) in 20 ml dry CH_2Cl_2 yielded a residue. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (19:1) gave 62% of **10b** as a yellowish resin. IR = 2872, 1721, 1591, 1496, 1448, 1281, 1122, 1024, 742, 700; UV (MeOH, (log ε)): $\lambda = 260$ (3.933), 210 (4.521); ^{1}H NMR ($CDCl_3$) $\delta = 1.79$–1.90 (m, 6H, 3-H, 8-H, $(CH_2)_2$), 2.04 (ddd, $J = 13.1$, 9.5, 2.0 Hz, 1H, 5-H), 2.22 (br, dd, $J = 13.0$, 9.7 Hz, 1H, 8-H), 2.33 (br, dd, $J = 13.1$, 9.5 Hz, 1H, 5-H), 2.42 (d, $J = 2.0$ Hz, 1H, 1-H), 2.55 (ddd, $J = 12.9$, 9.7, 2.0 Hz, 1H, 3-H), 2.76–2.86 (m, 4H, $N(CH_2)_2$), 3.32 (t, $J = 9.7$ Hz, 1H, 7-H), 3.71 (t, $J = 9.5$ Hz, 1H, 6-H), 5.45 (ddd, $J = 9.7$, 5.9, 2.0 Hz, 1H, 2-H), 7.19–7.42 (m, 11H, 5′-H, Ar-H), 8.30 (dt, $J = 7.9$, 1.6 Hz, 1H, 4′-H), 8.78 (dd, $J = 4.8$, 1.6 Hz, 1H, 6′-H), 9.26 (dd, $J = 1.5$ Hz, 1H, 2′-H); ^{13}C NMR ($CDCl_3$) $\delta = 23.58$ ($(CH_2)_2$), 33.13 (C-5), 34.31 (C-7), 34.63 (C-8), 34.94 (C-3), 35.73 (C-6), 41.65 (C-1), 45.66 ($N(CH_2)_2$), 56.31 (C-4), 71.02 (C-2), 123.32 (C-5′), 126.25 (C-3′), 137.00 (C-4′), 150.87 (C-2′), 153.50 (C-6′), 126.35, 127.18, 127.47, 128.59, 143.11 (aromatic C), 164.79 (COO); Anal. Calcd. for $C_{30}H_{32}N_2O_2 \cdot 0.7H_2O$ (465.21): C 77.46, H 7.24, N 6.02; found: C 77.63, H 7.03, N 6.06.

*6.2.2.9. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl nicotinate (**10c**).* Compound **3c** (0.79 mmol), nicotinyl chloride (2.20 mmol) and 4-DMAP (0.22 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue, which was treated with an 1 M ethereal solution of HCl giving 34% of the dihydrochloride of **10c** as white crystals. Mp: 169 °C (HCl: EtOH/diethyl ether). IR = 1723, 1636, 1602, 1497, 1295, 1142, 1113, 760, 739, 702, 674; UV (MeOH, (log ε)): $\lambda = 263$ (3.608), 210 (4.360); ^{1}H NMR ($CDCl_3$) $\delta = 1.43$–1.49 (m, 2H, CH_2), 1.57–1.65 (m, 4H, $2CH_2$), 1.69–1.81 (m, 2H, 3-H, 8-H), 1.91 (br, dd, $J = 12.0$, 9.5 Hz, 1H, 5-H), 2.18 (br, dd, $J = 10.8$, 9.3 Hz, 1H, 8-H), 2.32 (br, dd, $J = 12.0$, 9.5 Hz, 1H, 5-H), 2.43 (s, 1H, 1-H), 2.53 (br, t, $J = 12.0$ Hz, 1H, 3-H), 2.55–2.74 (m, 4H, $N(CH_2)_2$), 3.27 (t, $J = 9.3$ Hz, 1H, 7-H), 3.64 (t, $J = 9.5$ Hz, 1H, 6-H), 5.40–5.45 (m, 1H, 2-H), 7.19–7.41 (m, 11H, 5′-H, Ar-H), 8.30 (br, d, $J = 7.8$ Hz, 1H, 4′-H), 8.78 (br, d, $J = 3.4$ Hz, 1H, 6′-H), 9.26 (br, s, 1H, 2′-H); ^{13}C NMR ($CDCl_3$) $\delta = 24.91$ (CH_2), 26.76 ($2CH_2$), 32.54 (C-5), 34.46 (C-7), 34.53 (C-8), 34.93 (C-3), 35.81 (C-6), 41.52 (C-1), 46.83 ($N(CH_2)_2$), 57.35 (C-4), 71.39 (C-2), 123.29 (C-5′), 126.26 (C-3′), 136.97 (C-4′), 150.86 (C-2′), 153.44 (C-6′), 126.29, 127.16, 127.43, 128.54, 143.30, 143.32 (aromatic C), 164.81 (COO). Anal. Calcd. for $C_{31}H_{36}Cl_2N_2O_2 \cdot 1.5H_2O$ (566.57): C 65.72, H 6.94, N 4.94; found: C 65.86, H 7.09, N 4.72.

*6.2.2.10. (2RS,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl isonicotinate (**11a**).* Compound **3a** (0.56 mmol), isonicotinyl chloride (1.12 mmol) and 4-DMAP (0.11 mmol) in 10 ml dry CH_2Cl_2 yielded 29% of pure **11a**. IR = 1725, 1601, 1496, 1281, 1124, 756, 700; UV (MeOH, (log ε)): $\lambda = 267$ (3.500), 211 (4.382); ^{1}H NMR ($CDCl_3$) $\delta = 1.70$ (ddd, $J = 13.2$, 5.8, 2.9 Hz, 1H, 3-H), 1.77 (ddd, $J = 12.4$, 9.3, 2.6 Hz, 1H, 8-H), 1.90 (ddd, $J = 12.2$, 9.4, 2.3 Hz, 1H, 5-H), 2.17 (ddd, $J = 12.4$, 10.2, 2.9 Hz, 1H, 8-H), 2.31 (ddd, $J = 12.2$, 10.2, 2.6 Hz, 1H, 5-H), 2.37 (s, 6H, $N(CH_3)_2$), 2.44 (d, $J = 1.8$ Hz, 1H, 1-H), 2.50 (ddd, $J = 13.2$, 9.7, 2.3 Hz, 1H, 3-H), 3.29 (dd, $J = 10.2$, 9.3 Hz, 1H, 7-H), 3.65 (dd, $J = 10.2$, 9.4 Hz, 1H, 6-H), 5.44 (ddd, $J = 9.7$, 5.8, 1.8 Hz, 1H, 2-H), 7.19–7.39 (m, 10H, Ar-H), 7.85 (d, $J = 6.0$ Hz, 2H, 3′-H, 5′-H), 8.79 (d, $J = 6.4$ Hz, 2H, 2′-H, 6′-H); ^{13}C NMR ($CDCl_3$) $\delta = 32.10$ (C-5), 34.07 (C-8), 34.30 (C-3), 34.44 (C-7), 35.67 (C-6), 38.39 ($N(CH_3)_2$), 41.21 (C-1), 56.83 (C-4), 71.59 (C-2), 122.78 (C-3′, C-5′), 137.55 (C-4′), 150.68 (C-2′, C-6′), 126.38, 126.40, 127.15, 127.38, 128.63, 143.14, 143.21 (aromatic C), 164.67 (COO). Anal. Calcd. for $C_{28}H_{30}N_2O_2 \cdot 0.6H_2O$ (437.37): C 76.89, H 7.19, N 6.40; found: C 76.93, H 7.10, N. 6.27.

*6.2.2.11. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl isonicotinate (**11b**).* Compound **3b** (1.04 mmol), isonicotinyl chloride (2.08 mmol) and 4-DMAP (0.21 mmol) in 20 ml dry CH_2Cl_2 yielded an oily residue. Purification by means of column chromatography over silica gel eluting with CH_2Cl_2/MeOH (19:1) gave 69% of **11b** as a yellowish resin. IR = 2872, 1728, 1602, 1496, 1448, 1281, 1124, 756, 699; UV (MeOH, (log ε)): $\lambda = 269$ (3.578), 211 (4.406); ^{1}H NMR ($CDCl_3$) $\delta = 1.79$ (ddd, $J = 13.2$, 5.9, 2.8 Hz, 1H, 3-H), 1.79–1.84 (m, 4H, $(CH_2)_2$), 1.85 (ddd, $J = 13.2$, 9.9, 2.5 Hz, 1H, 8-H), 2.02 (ddd, $J = 12.8$, 9.5, 2.2 Hz, 1H, 5-H), 2.20 (ddd, $J = 13.2$, 9.9, 2.8 Hz, 1H, 8-H), 2.32 (ddd, $J = 12.8$, 9.5, 2.5 Hz, 1H, 5-H), 2.42 (d, $J = 2.2$ Hz, 1H, 1-H), 2.53 (ddd, $J = 13.2$, 9.5, 2.2 Hz, 1H, 3-H), 2.75–2.84 (m, 4H, $N(CH_2)_2$), 3.32 (t, $J = 9.9$ Hz, 1H, 7-H), 3.69 (t, $J = 9.5$ Hz, 1H, 6-H), 5.44 (ddd, $J = 9.5$, 5.9, 2.2 Hz, 1H, 2-H), 7.19–7.39 (m, 10H, Ar-H), 7.85 (d, $J = 5.9$ Hz, 2H, 3′-H, 5′-H), 8.79 (d, $J = 5.9$ Hz, 2H, 2′-H, 6′-H); ^{13}C NMR ($CDCl_3$) $\delta = 23.57$ ($(CH_2)_2$), 33.23 (C-5), 34.35 (C-7), 34.65 (C-8), 34.93 (C-3), 35.67 (C-6), 41.50 (C-1), 45.57 ($N(CH_2)_2$), 55.68 (C-4), 71.52 (C-2), 122.76 (C-3′, C-5′), 137.55 (C-4′), 150.65 (C-2′, C-6′), 126.35, 126.38, 127.17, 127.43, 128.60, 143.13 (aromatic C), 164.65 (COO). Anal. Calcd. for $C_{30}H_{32}N_2O_2$ (452.59): C 79.61, H 7.13, N 6.19; found: C 79.40, H 7.36, N 6.03.

*6.2.2.12. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl isonicotinate (**11c**).* Compound **3c** (0.87 mmol), isonicotinyl chloride (2.61 mmol) and 4-DMAP

(0.26 mmol) in 10 ml dry CH_2Cl_2 yielded an oily residue, which was treated with an 1 M ethereal solution of HCl giving 48% of the dihydrochloride of **11c** as white crystals. Mp: 180–182 °C (HCl: EtOH/diethyl ether). IR = 1727, 1636, 1611, 1495, 1452, 1287, 1132, 754, 706, 687; UV (MeOH, (log ε)): $\lambda = 269$ (3.461), 211 (4.360); ^{1}H NMR ($CDCl_3$) $\delta = 1.43$–1.50 (m, 2H, CH_2), 1.58–1.66 (m, 4H, $2CH_2$), 1.72 (ddd, $J = 11.9$, 6.0, 2.7 Hz, 1H, 3-H), 1.77 (ddd, $J = 12.2$, 9.7, 2.3 Hz, 1H, 8-H), 1.90 (ddd, $J = 12.4$, 9.5, 2.3 Hz, 1H, 5-H), 2.17 (ddd, $J = 12.2$, 9.0, 2.8 Hz, 1H, 8-H), 2.32 (ddd, $J = 12.4$, 10.3, 2.3 Hz, 1H, 5-H), 2.43 (d, $J = 1.9$ Hz, 1H, 1-H), 2.52 (ddd, $J = 11.9$, 9.9, 2.3 Hz, 1H, 3-H), 2.57–2.74 (m, 4H, $N(CH_2)_2$), 3.26 (br, t, $J = 9.6$ Hz, 1H, 7-H), 3.62 (br, t, $J = 9.7$ Hz, 1H, 6-H), 5.41 (ddd, $J = 9.9$, 6.1, 1.9 Hz, 1H, 2-H), 7.19–7.38 (m, 10H, Ar-H), 7.84 (d, $J = 6.0$ Hz, 2H, 3′-H, 5′-H), 8.78 (d, $J = 6.0$ Hz, 2H, 2′-H, 6′-H); ^{13}C NMR ($CDCl_3$) $\delta = 24.91$ (CH_2), 26.78 ($2CH_2$), 32.63 (C-5), 34.47 (C-7), 34.49 (C-8), 34.88 (C-3), 35.74 (C-6), 41.33 (C-1), 46.84 ($N(CH_2)_2$), 57.31 (C-4), 71.81 (C-2), 122.75 (C-3′, C-5′), 137.59 (C-4′), 150.65 (C-2′, C-6′), 126.30, 126.32, 127.14, 127.38, 128.57, 143.23, 143.30 (aromatic C), 164.66 (COO). Anal. Calcd. for $C_{31}H_{36}Cl_2N_2O_2 \cdot 2H_2O$ (575.58): C 64.69, H 7.00, N 4.87; found: C 64.86, H 7.12, N 4.75.

6.3. Biological tests

Detailed descriptions of the used methodologies have already been published [17].

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References

[1] V.S. Moorthy, M.F. Good, A.S. Hill, Lancet 363 (2004) 150–156.
[2] J.E. Hyde, Microbes Infect. 4 (2002) 165–174.
[3] L. Loutan, Int. J. Antimicrob. Agents 21 (2003) 158–163.
[4] S.R. Meshnick, Int. J. Parasitol. 32 (2002) 1655–1660.
[5] F.C. Tanser, D. le Suer, Int. J. Health Geogr. 1 (2002) 4.
[6] P.A. Winstanley, S.A. Ward, R.W. Snow, Microbes Infect 4 (2002) 157–164.
[7] C. Wongsrichanalai, A.L. Pickard, E.H. Wernsdorfer, S.R. Meshnik, Lancet Infect. Dis. 2 (2002) 209–218.
[8] L.V. Kirchhoff, in: G.L. Mandell, J.E. Benett, R. Dolin (Eds.), Mandell, Douglas, and Benett's Principles and Practice of Infectious Diseases, Churchill Livingstone, Philadelphia, 2000, pp. 2853–2858.
[9] WHO, World Health Report, Statistical Annex; 2004, p. 120.
[10] S. Hoet, F. Opperdoes, R. Brun, J. Quetin-Leclercq, Nat. Prod. Rep. 21 (2004) 353–364.
[11] R. Weis, R. Brun, R. Saf, W. Seebacher, Monatsh. Chem. 134 (2003) 1019–1026.
[12] W. Seebacher, R. Brun, M. Kaiser, R. Saf, R. Weis, Eur. J. Med. Chem. 40 (2005) 888–896.
[13] W. Seebacher, C. Schlapper, R. Brun, M. Kaiser, R. Saf, R. Weis, Eur. J. Pharm. Sci. 24 (2005) 281–289.
[14] W. Seebacher, C. Schlapper, R. Brun, M. Kaiser, R. Saf, R. Weis, Eur. J. Med. Chem. 41 (2006) 970–977.
[15] R. Weis, C. Schlapper, R. Brun, M. Kaiser, W. Seebacher, Eur. J. Pharm. Sci. 28 (2006) 361–368.
[16] R. Weis, K. Schweiger, W. Seebacher, F. Belaj, Tetrahedron 54 (1998) 14015–14022.
[17] W. Seebacher, R. Brun, R. Weis, Eur. J. Pharm. Sci. 21 (2004) 225–233.
[18] S. Chandrasekhar, G. Kulkarni, Tetrahedron: Asymmetry 13 (2002) 615–619.
[19] N.G. Anderson, D.A. Lust, K.A. Colapret, J.H. Simpson, M.F. Malley, J.Z.J. Gougoutas, J. Org. Chem. 61 (1996) 7955–7958.
[20] C. Ahn, P.J. DeShong, J. Org. Chem. 67 (2002) 1754–1759.
[21] R.M. Moriarty, H. Zhuang, R. Penmasta, K. Liu, A.K. Awasthi, S.M. Tuladhar, M.S.C. Rao, V.K. Singh, Tetrahedron Lett. 34 (1993) 8029–8032.
[22] K. Mori, Y. Matsushima, Synthesis 4 (1993) 406–410.