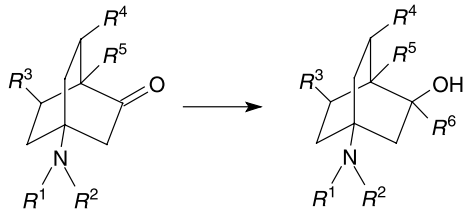
Monatshefte für Chemie (2006)
DOI 10.1007/s00706-006-0455-7

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Graphical Abstract



Monatshefte für Chemie (2006)
DOI 10.1007/s00706-006-0455-7

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Structural Requirements for the Antiprotozoal Activity of 4-Aminobicyclo[2.2.2]octan-2-ols

Werner Seebacher[1,*], **Heinrich Berger**[1], **Marcel Kaiser**[2], **Reto Brun**[2], **Robert Saf**[3], and **Robert Weis**[1]

[1] Institute of Pharmaceutical Sciences, Pharmaceutical Chemistry, Karl-Franzens-University of Graz, A-8010 Graz, Austria
[2] Swiss Tropical Institute, CH-4002 Basel, Switzerland
[3] Institute of Chemical Technology of Organic Materials, Erzherzog-Johann University, A-8010 Graz, Austria

Received January 17, 2006; accepted January 26, 2006
Published online April 5, 2006

Summary. Several 4-aminobicyclo[2.2.2]octan-2-ones and -ols were synthesized using different pathways. The new compounds were investigated for their activity against *Trypanosoma b. rhodesiense*, the causative organism of East African sleeping sickness and *Plasmodium falciparum* the protozoan parasite which causes Malaria tropica. The results are compared to the activities of known compounds and the influence of the substitution of the bicyclo[2.2.2]octane skeleton on the biological activities is discussed.

Keywords. Antiplasmodial activity; Antitrypanosomal activity; Amino alcohols; Cyclizations; Structure-activity relationship.

Introduction

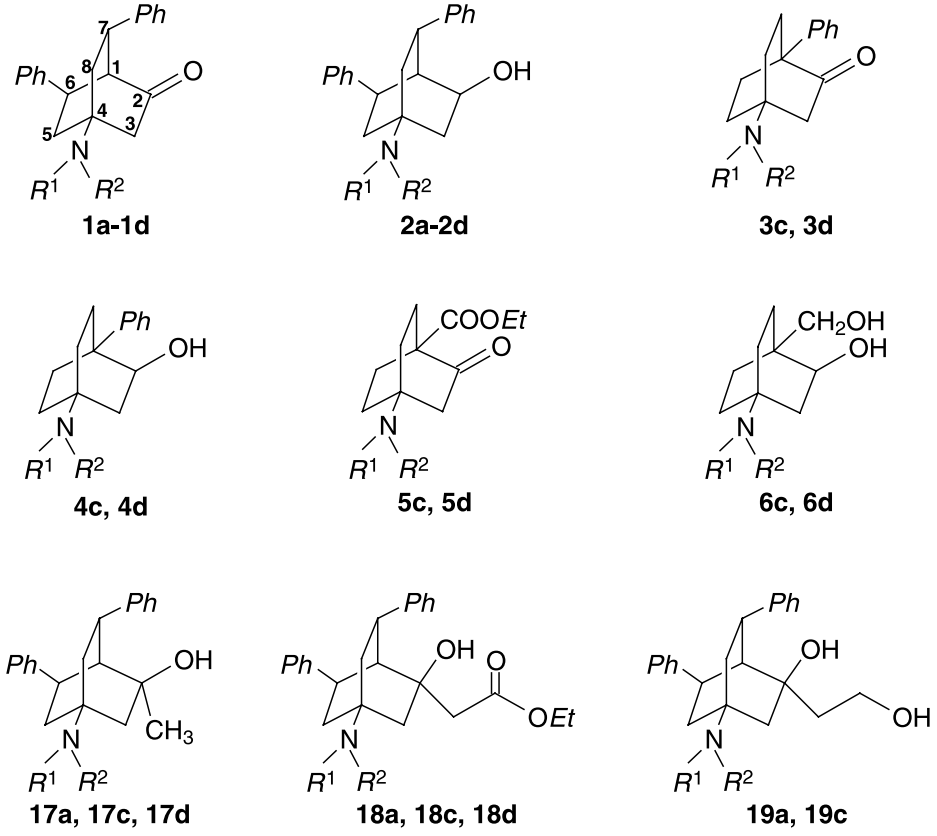
Human African trypanosomiasis is caused by the protozoan parasites *Trypanosoma brucei gambiense* and *T. b. rhodesiense*. About 0.5 million people are infected with African trypanosomiasis in various countries of central Africa. The disease is fatal if untreated and therefore causes 50000 deaths per year [1, 2]. Only four drugs are in use for treatment. Pentamidine and suramine are not able to cross the blood–brain barrier efficiently and therefore, will not cure CNS infections [3], the later stage of trypanosomiasis. Melarsoprol is active against all strains of trypanosomes in all stages, however, encephalopathy, an undesired effect of this drug is usually fatal for up to 5% of the patients [4]. *D*,*L*-α-Difluoromethylornithine

* Corresponding author. E-mail: we.seebacher@uni-graz.at

(Eflornithine®) is used as an alternative to melarsoprol, but unfortunately it is ineffective against *T. b. rhodesiense* [5]. Therefore, new trypanocides with less side effects are in great demand.

Malaria kills 2–3 million people yearly [6]. The main reason that causes malaria deaths to increase is drug resistance in the deadly species of *Plasmodium falciparum* [7]. Wide-spread drug resistance against traditional therapeutics such as chloroquine and the combination sulfadoxine-pyrimethamine which were once highly effective, makes them almost useless in many parts of the world [8, 9]. Since loss of sensibility has been observed even for the most recently introduced artemisinine derivatives [10], there is an urgent need for potent new antimalarial drugs.

Recently, we reported about the biological activities of 4-aminobicyclo[2.2.2]octan-2-ones **1a**–**1d** and -ols **2a**–**2d** [11] (Fig. 1). Those compounds were screened for their potencies against several causative organisms of tropical



a: $R^1 = R^2 = CH_3$
b: $R^1 + R^2 = -(CH_2)_2-O-(CH_2)_2-$
c: $R^1 + R^2 = -(CH_2)_4-$
d: $R^1 + R^2 = -(CH_2)_5-$

Fig. 1. Structure of 4-aminobicyclo[2.2.2.]octane derivatives

diseases and were found to be active against *Trypanosoma brucei rhodesiense* and *Plasmodium falciparum* K_1, a strain which is resistant to chloroquin and pyrimethamine. The next step of our investigations was the variation of the alkyl chains of the amino group, which lead to bicyclic alcohols that partially exhibit enhanced antitrypanosomal and antiplasmodial activities [12].

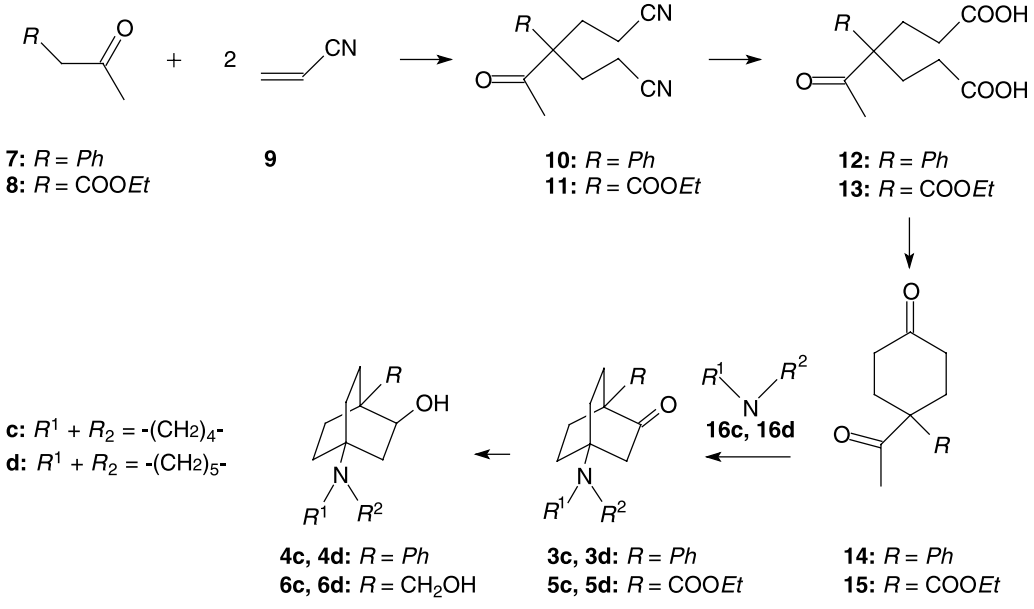
In order to find out if the aromatic substituents contribute to the biological activities of 4-aminobicyclo[2.2.2]octan-2-ones and -ols, we synthesized compounds without and compounds with only one aromatic ring *via* a different sequence of reactions. In addition, the carbinol carbon atom of compounds **2** was further substituted by hydrophilic or lipophilic alkyl chains.

Results and Discussions

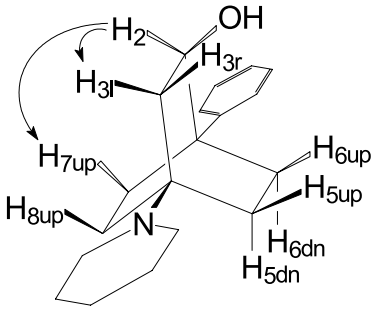
Syntheses

Compounds **3**–**6** which have no phenyl ring in positions 6 and 7 were prepared from phenylacetone (**7**) or ethyl acetoacetate (**8**) and acrylonitrile (**9**) giving 4,4-disubstituted pimelonitriles **10** and **11** [13, 14], which were hydrolized to the corresponding pimelic acids **12** and **13** [14]. Those were cyclized giving 4-acetyl-4-cyclohexanones **14** and **15** [15]. Subsequent reaction with pyrrolidine (**16c**) or piperidine (**16d**) gave bicyclic ketones **3c**, **3d** and **5c**, **5d** in one step in analogy to a reported cyclization [16]. Those were reduced to the corresponding bicyclo[2.2.2]octan-2-ols **4c** and **4d** and diols **6c** and **6d** using $LiAlH_4$ as catalyst (Scheme 1).

The assignment of the signals in the NMR spectra of **4d** was achieved by N*O*E-measurements (ROESY): crosspeaks were observed from 2-H to 7-H_{up} and

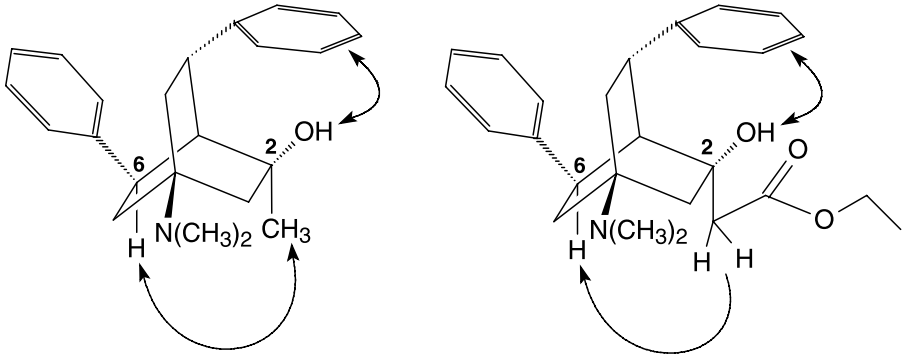


Scheme 1



4d

Fig. 2. N*O*Es observed for **4d**



17a **18a**

Fig. 3. N*O*Es observed for **17a** and **18a**

to 3-H_l (Fig. 2). Additionally, we observed w-couplings in the H,H-COSY spectra from 2-H to 6-H_{dn} and from 6-H_{up} to 7-H_{up}.

The 2,2-disubstituted bicyclo[2.2.2]octan-2-ols **17**–**19** were prepared from ketones **1**. The latter were treated with methyllithium in dry *THF* giving tertiary alcohols **17a**, **17c**, and **17d**. The *Reformatzky* reaction of **1** with ethyl bromoacetate affords esters **18a**, **18c**, and **18d**, which were reduced to their diols **19a** and **19c**. The configuration in postition 2 was determined for **17a** and **18a** *via* N*O*E experiments. For compounds **17a** and **18a** we observed N*O*Es from aromatic protons to the proton of the OH group. Furthermore, the 6-H showed through space interactions to the protons of the 2-methyl group of **17a** and to the corresponding methylene protons of **18a** (Fig. 3). Therefore the configuration is (*2SR*,*6RS*,*7RS*) – **17a** and (*2RS*,*6RS*,*7RS*) – **18a**.

Antiprotozoal Acitivities and Cytotoxicity

All new compounds **3**–**6** and **17**–**19** were tested for their activities against *Trypanosoma b. rhodesiense* and *Plasmodium falciparum* K_1 using *in vitro* microplate assays. Their cytotoxicity was determined using L-6 cells. The results are presented in Table 1.

Table 1. Activities of compounds **1–6** and **17–19** expressed as IC_{50} (μM)[a]

Compd.	*P. falciparum* K_1	*T.b.rhodesiense*	Cytotox. L6-cells
1a	>10.57	9.99	24.57
1b	>11.89	116.3	n.t.
1c	1.19	8.03	26.45
1d	3.95	8.12	46.82
2a	>15.55	2.95	132.5
2b	2.42	20.80	n.t.
2c	2.39	4.26	26.76
2d	0.84	5.34	37.34
3c	7.83	121.80	>334.1
3d	7.31	107.97	>317.6
4c	6.71	124.65	>331.61
4d	5.33	158.12	>315.32
5c	>16.57	>298.20	>298.20
5d	17.90	>322.15	>322.15
6c	>22.19	>399.41	>399.41
6d	>20.89	>376.02	>376.02
17a	1.84	1.54	8.80
17c	2.99	1.57	16.83
17d	4.01	3.73	8.03
18a	4.92	6.22	34.85
18c	3.57	2.11	41.82
18d	3.10	1.92	36.30
19a	7.47	3.42	167.16
19c	6.56	4.05	76.41
chl	0.062		
sur		0.011	
mef			4.3

[a] Values represent the average of four determinations (two determinations of two independent experiments), n.t.: not tested, *chl* = chloroquine, *mef* = mefloquine, *sur* = suramine

Obviously, the antitrypanosomal activity is positively influenced by the presence of aromatic substituents: Compounds **3** and **4** with only one phenyl ring in position 1 show much lower activity than those bearing two phenyl rings in positions 6 and 7 like compounds **1**, **2**, and **17–19**. The non-aromatic compounds **5** and **6** are completely inactive. The insertion of an additional substituent in position 2 of bicyclo[2.2.2]octan-2-ols **2** yielded two exceptional compounds with increased antitrypanosomal activity.

For the antimalarial activity similar results were observed. The compounds with two phenyl rings are in general more active than those without or with only one phenyl ring. Compared to **2a** the dimethylamino compounds **17a**, **18a**, and **19a** showed higher antiplasmodial activity whereas the pyrrolidino- and piperidino-substituted compounds **17c**, **17d**, **18c**, **18d**, and **19c** were less active than their analogues **2c** and **2d**.

Compound **17a** exhibits the highest antitrypanosomal potency of the so far prepared bicyclo[2.2.2]octan-2-ols. Furthermore, it showed good antiplasmodial

activity, but the potency of **2d** was not achieved. Since the replacement of a proton by a simple methyl group causes a dramatical influence on those activities, it seems worth while to synthesize a further series of those bicyclooctanols varying acidity and polarity of the newly inserted substituents.

Conclusion

2-Substituted derivatives of 6,7-diphenylbicyclo[2.2.2]octan-2-ols were prepared. Even small structural variations led to remarkable changes of their antiprotozoal activities and a single new compound has quite good antiplasmodial and promising antitrypanosomal activity.

Several new 6,7-unsubstituted bicyclo[2.2.2]octan-2-ones and -ols were synthesized *via* an alternative pathway. The investigation of their antitrypanosomal and antiplasmodial properties show clearly that the aromatic rings are favourable for those activities. The results of this investigation thus furnish information for further derivatizations of the bicyclo[2.2.2]octane skeleton.

Experimental

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). UV/VIS: Lambda 17 UV/VIS-spectrometer (Perkin Elmer). NMR spectra: Varian Inova 400 (300 K) 5 mm tubes, solvent resonance as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. ^{1}H- and ^{13}C-resonances are numbered as given in the formulae. MS, HR-MS: Kratos profile spectrometer 70 eV electron impact. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their values were in satisfactory agreement with the calculated ones. 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.

The preparation of ketones **1a**–**1d** and alcohols **2a**–**2d** has been reported [11, 17].

*Cyclization to **3c**, **3d** and **5c**, **5d***

The ketone **14** [15] or the ester **15** [16] were dissolved in dry benzene, the secondary amine and *p*-toluenesulfonic acid were added. The mixture was refluxed over night at 120°C at a H_2O separator and cooled to room temperature. The solvent was evaporated and the round bottomed flask containing the residue was connected with a Kugelrohr distillation apparatus and heated to 250°C for 10–20 min. Subsequent distillation *in vacuo* yielded crude products which were further purified.

1-Phenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one (**3c**, $C_{18}H_{23}NO$)

In 75.5 cm^3 benzene 3.39 g **14** (15.67 mmol) reacted with 1.45 g (20.4 mmol) pyrrolidine and 66.5 mg (0.05 mmol) *p*-toluenesulfonic acid to a residue which was recrystallized from ethyl acetate giving 800 mg **3c** (19%) as white needles. Mp 143°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.76$–1.82 (m, $(CH_2)_2$), 1.85–1.92 (m, 5-H, 8-H), 1.93–2.00 (m, 5-H, 8-H), 2.10 (ddd, $J = 13.3$, 10.8, 5.0 Hz, 6-H, 7-H), 2.25 (ddd, $J = 11.0$, 10.7, 4.5 Hz, 6-H, 7-H), 2.54 (s, 3-H), 2.64–2.72 (m, $N(CH_2)_2$), 7.18–7.36 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.53$ ($(CH_2)_2$), 27.99 (C-5, C-8), 29.47 (C-6, C-7), 45.45 (C-3), 45.56 ($N(CH_2)_2$), 49.47 (C-1), 55.88 (C-4), 126.64, 127.22, 127.89 (aromatic C), 140.54 (aromatic C_q), 212.69 (C-2) ppm; IR (KBr): $\bar{\nu} = 2961$, 2870, 2815, 1719, 1500, 1444, 1343, 1182, 1135, 1104, 754, 695 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 232 (2.995) nm; MS (70 eV):

$m/z = 269$ (M^+), 241, 226, 212, 136, 123, 91; HRMS (EI+): calcd. ($C_{18}H_{23}NO$) 269.17796, found 269.17783.

1-Phenyl-4-piperidinobicyclo[2.2.2]octan-2-one (**3d**, $C_{19}H_{25}NO$)
In 30 cm^3 benzene reacted 1.85 g **14** (8.55 mmol) with 947 mg (11.12 mmol) piperidine and 38 mg (0.19 mmol) *p*-toluenesulfonic acid to a residue which was recrystallized from ethyl acetate giving 750 mg **3d** (31%) as white needles. Mp 168°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.42$–1.48 (m, CH_2), 1.57–1.63 (m, $2CH_2$), 1.84 (ddd, $J = 10.8$, 10.4, 5.2 Hz, 5-H, 8-H), 1.96 (ddd, $J = 12.5$, 10.5, 4.2 Hz, 5-H, 8-H), 2.07 (ddd, $J = 13.2$, 10.7, 4.9 Hz, 6-H, 7-H), 2.22 (ddd, $J = 10.8$, 10.7, 4.7 Hz, 6-H, 7-H), 2.51 (s, 3-H), 254–2.57 (m, $N(CH_2)_2$), 7.18–7.35 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.76$ (CH_2), 26.69 ($2CH_2$), 27.26 (C-5, C-8), 29.55 (C-6, C-7), 45.62 (C-3), 46.81 ($N(CH_2)_2$), 49.45 (C-1), 57.76 (C-4), 126.64, 127.21, 127.90 (aromatic C), 140.55 (aromatic C_q), 212.80 (C-2) ppm; IR (KBr): $\bar{\nu} = 2971$, 2930, 2913, 2849, 2808, 1713, 1498, 1450, 1344, 1191, 1116, 1018, 751, 695 cm^{-1}; UV (CH_2Cl_2): λ ($\log\varepsilon$) = 231 (3.088) nm; MS (70 eV): $m/z = 283$ (M^+), 255, 240, 226, 150, 137, 124, 103, 91; HRMS (EI+): calcd. ($C_{19}H_{25}NO$) 283.19361, found 283.19469.

Ethyl 2-oxo-4-pyrrolidinobicyclo[2.2.2]octan-1-carboxylate (**5c**, $C_{15}H_{23}NO_3$)
Pyrrolidine, 18 g (25 mmol), 4.1 g **15** (19.3 mmol), and 40 mg *p*-toluenesulfonic acid in 91 cm^3 dry benzene gave a brownish oil, which was purified using CC (silica gel, ethyl acetate:*Me*OH = 5:1). Subsequent purification by means of CC over basic Al_2O_3 using *Me*OH as eluent gave 2.9 g **5c** (57%) as a brown oil. The hydrochloride was prepared by treatment of a solution of **5c** in CH_2Cl_2 with etheral HCl, subsequent evaporation of the solvents, and crystallization from ethyl acetate. A further crystallization was done from ethanol/ethyl acetate. Mp (HCl) 208°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.1$ Hz, OCH_2CH_3), 1.75–1.89 (m, 5-H, 8-H, $(CH_2)_2$), 1.97 (ddd, $J = 13.9$, 10.8, 5.1 Hz, 6-H, 7-H), 2.27 (ddd, $J = 11.1$, 10.5, 5.5 Hz, 6-H, 7-H), 2.44 (s, 3-H), 2.62–2.66 (m, $N(CH_2)_2$), 4.20 (q, $J = 7.1$ Hz, OCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.05$ (OCH_2CH_3), 23.47 ($(CH_2)_2$), 25.50 (C-6, C-7), 27.07 (C-5, C-8), 44.74 (C-3), 45.53 ($N(CH_2)_2$), 53.63 (C-1), 56.23 (C-4), 60.88 (OCH_2CH_3), 171.44 (COO), 208.98 (C-2) ppm; IR (HCl, KBr): $\bar{\nu} = 2975$, 2881, 2548, 2418, 1740, 1716, 1462, 1365, 1343, 1272, 1083, 1048 cm^{-1}; MS (70 eV): $m/z = 265$ (M^+), 237, 222, 192, 180, 164, 150, 136, 123, 110, 93, 77, 70; HRMS (EI+): calcd. ($C_{15}H_{23}NO_3$) 265.16779, found 265.16651.

Ethyl 2-oxo-4-piperidinobicyclo[2.2.2]octan-1-carboxylate (**5d**, $C_{16}H_{25}NO_3$)
Piperidine, 756 mg (8.88 mmol), 1.45 g **15** (6.83 mmol), and 30 mg *p*-toluenesulfonic acid reacted in 30 cm^3 dry benzene. The product was yielded as yellow oil, which solidified upon cooling. After recrystallization from ethyl acetate 373 mg **5d** (18%) were obtained. Mp 89°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.2$ Hz, OCH_2CH_3), 1.40–1.46 (m, CH_2), 1.54–1.60 (m, $2CH_2$), 1.75 (ddd, $J = 13.2$, 11.1, 5.3 Hz, 5-H, 8-H), 1.82 (ddd, $J = 12.3$, 11.3, 4.5 Hz, 5-H, 8-H), 1.94 (ddd, $J = 13.5$, 10.8, 5.3 Hz, 6-H, 7-H), 2.24 (ddd, $J = 11.2$, 10.6, 4.9 Hz, 6-H, 7-H), 2.41 (s, 3-H), 2.48–2.53 (m, $N(CH_2)_2$), 4.20 (q, $J = 7.2$ Hz, OCH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.06$ (OCH_2CH_3), 24.67 (CH_2), 25.56 (C-6, C-7), 26.37 (C-5, C-8), 26.61 ($2CH_2$), 44.88 (C-3), 46.76 ($N(CH_2)_2$), 53.57 (C-1), 58.07 (C-4), 60.87 (OCH_2CH_3), 171.44 (COO), 209.09 (C-2) ppm; IR (KBr): $\bar{\nu} = 2977$, 2931, 2876, 2855, 2811, 1736, 1715, 1454, 1367, 1344, 1300, 1253, 1192, 1154, 1114, 1062 cm^{-1}; MS (70 eV): $m/z = 279$ (M^+), 251, 236, 206, 194, 178, 164, 150, 137, 124, 93; HRMS (EI+): calcd. ($C_{16}H_{25}NO_3$) 279.18344, found 279.18166.

*Reduction to **4c**, **4d**, **6c**, **6d**, **19a**, and **19c***
The bicyclo[2.2.2]octan-2-ones **3**, **5**, or the acetates **18** were suspended in dry ether and $LiAlH_4$ was added in portions with cooling on an ice bath. After 1 h, the ice bath was removed and the reaction mixture was stirred over night at room temperature. The reaction was quenched cautiously with H_2O under cooling and 2 *N* NaOH was added. The mixture was extracted 5 times with CH_2Cl_2 and the

combined organic layers were washed 2 times with H_2O, dried (Na_2SO_4), and filtered. The solvent was evaporated *in vacuo* giving pure products.

(2RS)-(±)-1-Phenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-ol (**4c**, $C_{18}H_{25}NO$)
In 14 cm^3 dry ether 416 mg **3c** (1.54 mmol) reacted with 176 mg (4.63 mmol) $LiAlH_4$ to 320 mg **4c** (73%). Mp (CH_2Cl_2) 216°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (s, OH), 1.61–1.90 (m, 3-H, 5-H, 6-H, 7-H, 8-H, $(CH_2)_2$), 1.92–2.02 (m, 7-H), 2.17 (ddd, $J = 13.0$, 9.5, 3.2 Hz, 3-H), 2.36–2.45 (m, 6-H), 2.60–2.70 (m, $N(CH_2)_2$), 4.19 (br, d, $J = 7.5$ Hz, 2-H), 7.20–7.38 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.59$ ($(CH_2)_2$), 23.90 (C-6), 26.72 (C-5), 28.68 (C-8), 31.62 (C-7), 37.35 (C-3), 39.69 (C-1), 46.37 ($N(CH_2)_2$), 53.92 (C-4), 73.44 (C-2), 126.35, 126.39, 128.54 (aromatic C), 145.29 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3093$, 2965, 2938, 2866, 2836, 1497, 1455, 1328, 1160, 1133, 1056, 1039, 876, 759, 694 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 232 (3.161) nm; MS (70 eV): $m/z = 271$ (M^+), 226, 139, 123, 111, 91; HRMS (EI+): calcd. ($C_{18}H_{25}NO$) 271.19361, found 271.19321.

(2RS)-(±)-1-Phenyl-4-piperidinobicyclo[2.2.2]octan-2-ol (**4d**, $C_{19}H_{27}NO$)
In 5 cm^3 dry ether 160 mg **3d** (0.56 mmol) reacted with 70 mg (1.84 mmol) $LiAlH_4$ to 150 mg **4d** (94%). Mp (CH_2Cl_2) 206°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (d, $J = 1.8$ Hz, OH), 1.40–1.46 (m, CH_2), 1.55–1.74 (m, 3-H, 5-H, 7-H, 8-H, $2CH_2$), 1.75–1.89 (m, 5-H, 6-H), 1.92–1.99 (m, 7-H), 2.12 (ddd, $J = 13.4$, 9.2, 3.1 Hz, 3-H), 2.33–2.40 (m, 6-H), 2.53–2.55 (m, $N(CH_2)_2$), 4.14 (ddd, $J = 9.2$, 1.8, 1.6 Hz, 2-H), 7.20–7.38 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.13$ (C-6), 24.96 (CH_2), 26.30 (C-5), 26.85 ($2CH_2$), 27.86 (C-8), 31.71 (C-7), 37.01 (C-3), 39.68 (C-1), 46.67 ($N(CH_2)_2$), 55.88 (C-4), 73.59 (C-2), 126.33, 126.39, 128.53 (aromatic C), 145.31 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3158$, 2974, 2937, 2856, 2811, 1496, 1442, 1318, 1148, 1108, 1051, 1034, 1014, 886, 762, 695 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 232 (3.180) nm; MS (70 eV): $m/z = 285$ (M^+), 240, 153, 137, 125, 91; HRMS (EI+): calcd. ($C_{19}H_{27}NO$) 285.20926, found 285.20732.

(2RS)-(±)-1-Hydroxymethyl-4-pyrrolidinobicyclo[2.2.2]octan-2-ol (**6c**, $C_{13}H_{23}NO_2$)
In 5 cm^3 dry ether 500 mg **5c** (1.88 mmol) reacted with 680 mg (18.0 mmol) $LiAlH_4$ to 300 mg **6c** (71%). Mp (CH_2Cl_2) 162°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (ddd, $J = 12.2$, 12.0, 5.8 Hz, 6-H), 1.28 (t, $J = 7.7$ Hz, 7-H), 1.44–1.60 (m, 3-H, 5-H, 8-H), 1.70–1.78 (m, 5-H, $(CH_2)_2$), 1.99 (ddd, $J = 13.3$, 9.2, 2.8 Hz, 3-H), 2.16 (ddd, $J = 12.8$, 10.5, 2.4 Hz, 6-H), 2.60 (br, s, $N(CH_2)_2$), 3.38 (d, $J = 10.5$ Hz, C*H*$_2$OH), 3.47 (d, $J = 10.5$ Hz, C*H*$_2$OH), 3.99 (br, d, $J = 8.7$ Hz, 2-H), 4.07 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.41$ (C-6), 23.46 ($(CH_2)_2$), 26.18 (C-5), 26.47 (C-7), 27.22 (C-8), 35.62 (C-1), 38.42 (C-3), 45.24 ($N(CH_2)_2$), 53.93 (C-4), 70.26 (CH_2OH), 72.96 (C-2) ppm; IR (KBr): $\bar{\nu} = 3423$, 3104, 2946, 2863, 2826, 1462, 1365, 1338, 1153, 1117, 1088, 1045, 1017 cm^{-1}; MS (70 eV): $m/z = 225$ (M^+), 194, 180, 164, 139, 123, 110, 70; HRMS (EI+): calcd. ($C_{13}H_{23}NO_2$) 225.17288, found 225.17287.

(2RS)-(±)-1-Hydroxymethyl-4-piperidinobicyclo[2.2.2]octan-2-ol (**6d**, $C_{14}H_{25}NO_2$)
In 5 cm^3 dry ether 260 mg **5d** (0.93 mmol) reacted with 330 mg (8.69 mmol) $LiAlH_4$ to 200 mg **6d** (90%). Mp (CH_2Cl_2) 143°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (ddd, $J = 12.0$, 11.8, 5.8 Hz, 6-H), 1.27 (t, $J = 7.6$ Hz, 7-H), 1.40–1.62 (m, 3-H, 5-H, 8-H, $3CH_2$), 1.73 (dddd, $J = 13.5$, 10.2, 5.4, 2.8 Hz, 5-H), 1.94 (ddd, $J = 12.4$, 9.7, 2.8 Hz, 3-H), 2.11 (ddd, $J = 13.3$, 10.3, 3.0 Hz, 6-H), 2.49 (br, s, $N(CH_2)_2$), 3.39 (d, $J = 10.2$ Hz, C*H*$_2$OH), 3.47 (s, OH), 3.48 (d, $J = 10.2$ Hz, C*H*$_2$OH), 3.56 (s, OH), 3.98 (br, d, $J = 8.4$ Hz, 2-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.59$ (C-6), 24.82 (CH_2), 25.69 (C-5), 26.52, 26.58 (C-7, C-8, $2CH_2$), 35.66 (C-1), 38.00 (C-3), 46.55 ($N(CH_2)_2$), 53.89 (C-4), 70.13 (CH_2OH), 73.20 (C-2) ppm; IR (KBr): $\bar{\nu} = 3383$, 3185, 2936, 2857, 2813, 2743, 1467, 1450, 1442, 1340, 1302, 1278, 1150, 1103, 1036, 1001, 866, 809 cm^{-1}; MS (70 eV): $m/z = 239$ (M^+), 208, 194, 180, 153, 136, 124, 84; HRMS (EI+): calcd. ($C_{14}H_{25}NO_2$) 239.18853, found 239.19024.

(2SR,6RS,7RS)-(±)-4-Dimethylamino-2-(2-hydroxyethyl)-6,7-diphenyl-bicyclo[2.2.2]octan-2-ol (**19a**, $C_{24}H_{31}NO_2$)

In 5 cm^3 dry ether 260 mg **18a** (0.638 mmol) reacted with 121 mg (3.18 mmol) $LiAlH_4$ to 210 mg **19a** (90%). Mp (ether/petrolether) 137°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.60$ (dd, $J = 13.3$, 2.1 Hz, 3-H), 1.85–1.93 (m, 3-H, 5-H, CH_2CH$_2$OH), 1.97–2.10 (m, 5-H, 8-H, CH_2CH$_2$OH), 2.23 (ddd, $J = 11.9$, 9.9, 2.1 Hz, 8-H), 2.30 (s, OH), 2.36 (s, N$(CH_3)_2$), 2.43 (s, 1-H), 3.08 (br, t, $J = 9.4$ Hz, 6-H), 3.14 (br, t, $J = 9.9$ Hz, 7-H), 3.43 (s, OH), 3.84–3.97 (m, CH$_2$CH_2OH), 7.08–7.39 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.66$ (C-8), 32.58 (C-5), 34.75 (C-7), 38.31 (N$(CH_3)_2$), 38.71 (C-6), 41.18 (C-3), 42.16 (*C*H$_2$CH$_2$OH), 47.49 (C-1), 57.21 (C-4), 59.21 (CH$_2$*C*H$_2$OH), 77.50 (C-2), 125.55 126.29, 126.63, 127.29, 128.24, 128.53 (aromatic C), 143.24, 145.62 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3397$, 3058, 3024, 2995, 2953, 2937, 2874, 2835, 2791, 1600, 1497, 1467, 1447, 1349, 1085, 1062, 1033, 851, 751, 697 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.250) nm; MS (70 eV): $m/z = 365$ (M^+), 320, 276, 260, 184, 173, 157, 112, 91, 85, 70; HRMS (EI+): calcd. ($C_{24}H_{31}NO_2$) 365.23548, found 365.23738.

(2SR,6RS,7RS)-(±)-2-(2-Hydroxyethyl)-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-ol (**19c**, $C_{26}H_{33}NO_2$)

In 5 cm^3 dry ether 230 mg **18c** (0.548 mmol) reacted with 104 mg (2.74 mmol) $LiAlH_4$ to 150 mg **19c** (70%). Mp (petrolether/CH_2Cl_2) 150°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.72$ (br, d, $J = 13.3$ Hz, 3-H), 1.82–2.15 (m, 3-H, 5-H, 8-H, CH_2CH$_2$OH, $(CH_2)_2$), 2.30 (br, t, $J = 10.5$ Hz, 8-H), 2.43 (s, 1-H), 2.70–2.85 (m, N$(CH_2)_2$), 3.10–3.21 (m, 6-H, 7-H), 3.84–4.02 (m, CH$_2$CH_2OH), 7.09–7.42 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.54$ ($(CH_2)_2$), 31.62 (C-8), 33.26 (C-5), 34.60 (C-7), 38.80 (C-6), 42.11 (C-3), 42.36 (*C*H$_2$CH$_2$OH), 45.49 (N$(CH_2)_2$), 48.11 (C-1), 55.81 (C-4), 59.43 (CH$_2$*C*H$_2$OH), 77.94 (C-2), 125.71, 126.32, 126.62, 127.38, 128.40, 128.56 (aromatic C), 143.30, 145.57 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3396$, 3086, 3057, 3022, 2935, 2871, 1600, 1496, 1446, 1351, 1081, 1046, 1032, 752, 697 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.300), 262 (2.905) nm; MS (70 eV): $m/z = 391$ (M^+), 346, 302, 286, 210, 199, 183, 91; HRMS (EI+): calcd. ($C_{26}H_{33}NO_2$) 391.25113, found 391.24900.

*Preparation of **17a**, **17c**, and **17d***

Ketones **2** were dissolved in dry *THF* and cooled to −78°C. An etheral solution of *Me*Li (1.6 *M*) was added dropwise. Stirring was continued over night and the reaction mixture was allowed to warm up to room temperature during this time. After quenching with a saturated solution of NH_4Cl the mixture was extracted 5 times with CH_2Cl_2. The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was purified by use of CC using CH_2Cl_2:*Me*OH = 5:1 as eluent.

(2SR,6RS,7RS)-(±)-4-Dimethylamino-2-methyl-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**17a**, $C_{23}H_{29}NO$)

In 40 cm^3 dry *THF* 1.54 g **1a** (4.82 mmol) reacted with 10.6 cm^3 of an etheral solution of *Me*Li (1.6 *M*) to 200 mg **17a** (12%). Mp (ether/petrolether) 110°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (br, s, OH), 1.44 (s, CH_3), 1.56 (dd, $J = 13.4$, 2.6 Hz, 3-H), 1.82 (dd, $J = 13.4$, 2.6 Hz, 3-H), 1.89 (ddd, $J = 12.1$, 9.6, 2.6 Hz, 5-H), 1.99–2.06 (m, 5-H, 8-H), 2.22 (s, 1-H), 2.25 (ddd, $J = 12.0$, 9.9, 2.1 Hz, 8-H), 2.37 (s, N$(CH_3)_2$), 3.14 (br, t, $J = 9.5$ Hz, 6-H, 7-H), 7.08–7.41 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.23$ (CH_3), 30.47 (C-8), 32.49 (C-5), 35.11 (C-7), 38.38 (N$(CH_3)_2$), 39.31 (C-6), 42.06 (C-3), 49.95 (C-1), 57.34 (C-4), 74.57 (C-2), 125.51 126.23, 126.79, 127.34, 128.23, 128.49 (aromatic C), 143.52, 145.83 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3261$, 3024, 2959, 2924, 2870, 2835, 2793, 1600, 1496, 1446, 1369, 1328, 1212, 1113, 1061, 1038, 938, 750, 699 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.232) nm; MS (70 eV): $m/z = 335$ (M^+), 320, 276, 230, 173, 154, 127, 96, 84, 77; HRMS (EI+): calcd. ($C_{23}H_{29}NO$) 335.22491, found 335.22711.

(2SR,6RS,7RS)-(±)-2-Methyl-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-ol (**17c**, $C_{25}H_{31}NO$)

In 40 cm^3 dry *THF* 1.658 g **1c** (4.80 mmol) reacted with 10.6 cm^3 of an etheral solution of *Me*Li (1.6 *M*) to 350 mg **17c** (20%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (br, s, OH), 1.43 (s, CH_3), 1.67 (br, d, $J = 13.5$ Hz, 3-H), 1.78–1.86 (m, 3-H, $(CH_2)_2$), 1.95–2.10 (m, 5-H, 8-H), 2.21 (s, 1-H), 2.31 (dd, $J = 11.1$, 10.8 Hz, 8-H), 2.72–2.84 (m, $N(CH_2)_2$), 3.13–3.19 (m, 6-H, 7-H), 7.08–7.42 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.52$ ($(CH_2)_2$), 30.21 (CH_3), 31.25 (C-8), 33.21 (C-5), 35.01 (C-7), 39.31 (C-6), 43.06 (C-3), 45.49 ($N(CH_2)_2$), 50.25 (C-1), 56.06 (C-4), 74.56 (C-2), 125.46, 126.19, 126.78, 127.37, 128.20, 128.46 (aromatic C), 143.54, 145.85 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3421$, 3024, 2962, 2870, 2815, 1600, 1495, 1447, 1358, 1333, 1199, 1110, 750, 697 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.260) nm; MS (70 eV): $m/z = 361$ (M^+), 346, 302, 270, 256, 226, 199, 180, 153, 136, 91; HRMS (EI+): calcd. ($C_{25}H_{31}NO$) 361.24056, found 361.24067.

(2SR,6RS,7RS)-(±)-2-Methyl-6,7-diphenyl-4-piperidinobicyclo[2.2.2]octan-2-ol (**17d**, $C_{26}H_{33}NO$)

In 41 cm^3 dry *THF* 1.44 g **1d** (4.00 mmol) reacted with 8.8 cm^3 of an etheral solution of *Me*Li (1.6 *M*) to 280 mg **17d** (19%). Mp (ether/petrolether) 120°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (br, s, OH), 1.43 (s, CH_3), 1.45–1.52 (m, CH_2), 1.61–1.72 (m, 3-H, $2CH_2$), 1.85 (dd, $J = 13.5$, 2.2 Hz, 3-H), 1.94 (ddd, $J = 12.3$, 9.9, 2.4 Hz, 5-H), 2.04–2.12 (m, 5-H, 8-H), 2.24 (s, 1-H), 2.29 (ddd, $J = 12.0$, 9.9, 2.1 Hz, 8-H), 2.62–2.78 (m, $N(CH_2)_2$), 3.13 (br, t, $J = 9.6$ Hz, 6-H, 7-H), 7.09–7.41 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.85$ (CH_2), 26.53 ($2CH_2$), 30.16 (CH_3), 31.11 (C-8), 32.68 (C-5), 35.13 (C-7), 39.31 (C-6), 42.33 (C-3), 46.88 ($N(CH_2)_2$), 49.87 (C-1), 58.50 (C-4), 74.65 (C-2), 125.50, 126.22, 126.77, 127.33, 128.22, 128.47 (aromatic C), 143.46, 145.83 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3448$, 3298, 2974, 2929, 2865, 2799, 1600, 1495, 1445, 1350, 1196, 1154, 1089, 1035, 941, 758, 741, 703, 696 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.290) nm; MS (70 eV): $m/z = 375$ (M^+), 360, 316, 284, 270, 240, 213, 194, 167, 150, 124, 91; HRMS (EI+): calcd. ($C_{26}H_{33}NO$) 375.25621, found 375.25424.

*Reformatzky Reaction to **18a**, **18c**, and **18d***

To 1.68 g activated Zn [18] a few crystals I_2 were added and heated up until evaporation of I_2 was observed. At this moment, the I_2 was removed by a stream of Ar and 8 cm^3 dry *THF* were added. To the stirred mixture, 1.1 cm^3 ethyl bromoacetate (10 mmol) were added dropwise. The mixture was stirred under Ar at room temperature for 2 h. Then it was heated to 50°C and a solution of 4.7 mmol **1a**, **1c**, and **1d** in 50 cm^3 dry *THF* was added within 15 min. The reaction mixture was stirred for 90 min at this temperature and 2.2 cm^3 ethyl bromoacetate (20 mmol) were added dropwise. After 90 min stirring at 50°C it was cooled to room temperature and stirred for 48 h. Then, 20 cm^3 aqua dest. and 20 cm^3 2 *N* H_2SO_4 were added. 2 *N* NaOH was then added cautiously to alkalize the solution. The formed organic layer was separated and the aqueous layer extracted 4 times with ether. The combined organic layers were washed once with H_2O, dried (Na_2SO_4), filtered, and the solvent was evaporated *in vacuo*. The residue was purified by means of CC over silica gel using CH_2Cl_2:*Me*OH = 4:1 as eluent.

(2RS,6RS,7RS)-(±)-Ethyl 2-(4-dimethylamino-2-hydroxy-6,7-diphenyl-bicyclo[2.2.2]oct-2-yl)acetate (**18a**, $C_{26}H_{33}NO_3$)

Product **18a**, 333 mg (17%) was obtained from 1.5 g **1a** (4.7 mmol) as an oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.1$ Hz, CH_3), 1.52 (dd, $J = 13.4$, 1.6 Hz, 3-H), 1.87–1.96 (m, 3-H, 5-H), 2.01–2.11 (m, 5-H, 8-H), 2.27 (ddd, $J = 12.1$, 9.7, 2.3 Hz, 8-H), 2.37 (s, $N(CH_3)_2$), 2.53 (s, 1-H), 2.73 (d, $J = 15.9$ Hz, CH_2COO), 2.81 (d, $J = 15.9$ Hz, CH_2COO), 2.94 (s, OH), 3.06 (br, t, $J = 9.4$ Hz, 6-H), 3.13 (br, t, $J = 9.8$ Hz, 7-H), 4.17 (q, $J = 7.1$ Hz, OCH_2), 7.07–7.38 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.14$ (CH_3), 30.74 (C-8), 32.74 (C-5), 34.92 (C-7), 38.35 ($N(CH_3)_2$), 38.81 (C-6), 41.39 (C-3), 44.56 (CH_2COO), 45.80 (C-1), 57.11 (C-4), 60.68 (OCH_2), 74.42 (C-2), 125.25 126.29, 126.46, 127.29, 128.00, 128.49 (aromatic C), 143.05, 145.76 (aromatic C_q), 172.24 (COOH)

ppm; IR (KBr): $\bar{\nu} = 3510$, 2981, 2948, 2869, 2780, 1719, 1610, 1497, 1464, 1446, 1369, 1333, 1185, 1031, 750, 698 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.169) nm; MS (70 eV): $m/z = 407$ (M^+), 320, 302, 276, 226, 199, 173, 112, 91, 85, 70; HRMS (EI+): calcd. ($C_{26}H_{33}NO_3$) 407.24604, found 407.24308.

(2RS,6RS,7RS)-(±)-Ethyl 2-(2-hydroxy-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)acetate (**18c**, $C_{28}H_{35}NO_3$)

Product **18c**, 350 mg (17%) was obtained from 1.624 g **1c** (4.7 mmol) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.2$ Hz, CH_3), 1.62 (br, d, $J = 12.6$ Hz, 3-H), 1.81 (br, s, $(CH_2)_2$), 1.91 (br, d, $J = 13.7$ Hz, 3-H), 2.03 (br, t, $J = 8.7$ Hz, 5-H), 2.11 (ddd, $J = 11.6$, 9.6, 2.0 Hz, 8-H), 2.33 (br, dd, $J = 10.9$, 10.6 Hz, 8-H), 2.51 (s, 1-H), 2.73 (d, $J = 16.1$ Hz, CH_2COO), 2.82 (d, $J = 16.0$ Hz, CH_2COO), 2.74–2.82 (m, $N(CH_2)_2$), 2.91 (s, OH), 3.09 (br, t, $J = 9.4$ Hz, 6-H), 3.15 (br, t, $J = 9.9$ Hz, 7-H), 4.17 (q, $J = 7.2$ Hz, OCH_2), 7.08–7.39 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.17$ (CH_3), 23.51 ($(CH_2)_2$), 31.52 (C-8), 33.54 (C-5), 34.89 (C-7), 38.87 (C-6), 42.47 (C-3), 44.67 (CH_2COO), 45.48 ($N(CH_2)_2$), 46.22 (C-1), 55.65 (C-4), 60.68 (OCH_2), 74.49 (C-2), 125.22 126.27, 126.51, 127.38, 127.99, 128.49 (aromatic C), 143.18, 145.90 (aromatic C_q), 172.29 (COOH) ppm; IR (KBr): $\bar{\nu} = 3025$, 2963, 2872, 1716, 1601, 1497, 1447, 1369, 1332, 1266, 1189, 1113, 1031, 750, 698 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.215) nm; MS (70 eV): $m/z = 433$ (M^+), 346, 328, 302, 252, 226, 199, 131, 91; HRMS (EI+): calcd. ($C_{28}H_{35}NO_3$) 433.26169, found 433.26297.

(2RS,6RS,7RS)-(±)-Ethyl 2-(2-hydroxy-6,7-diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)acetate (**18d**, $C_{29}H_{37}NO_3$)

Product **18d**, 120 mg (6%) was obtained from 1.633 g **1d** (4.7 mmol) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.2$ Hz, CH_3), 1.45–1.50 (m, CH_2), 1.52 (br, d, $J = 14.7$ Hz, 3-H), 1.58–1.78 (m, $2CH_2$), 1.90–1.96 (m, 3-H, 5-H), 2.02–2.11 (m, 5-H, 8-H), 2.30 (br, t, $J = 10.8$ Hz, 8-H), 2.52 (s, 1-H), 2.56–2.74 (m, $N(CH_2)_2$), 2.71 (d, $J = 16.1$ Hz, CH_2COO), 2.79 (d, $J = 15.7$ Hz, CH_2COO), 2.92 (s, OH), 3.03 (br, t, $J = 9.2$ Hz, 6-H), 3.10 (br, t, $J = 9.7$ Hz, 7-H), 4.16 (q, $J = 7.2$ Hz, OCH_2), 7.07–7.38 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.12$ (CH_3), 24.93 (CH_2), 26.75 ($2CH_2$), 31.50 (C-8), 32.97 (C-5), 34.93 (C-7), 38.83 (C-6), 41.75 (C-3), 44.51 (CH_2COO), 45.88 (C-1), 46.78 ($N(CH_2)_2$), 57.51 (C-4), 60.62 (OCH_2), 74.46 (C-2), 125.15, 126.19, 126.45, 127.30, 127.93, 128.42 (aromatic C), 143.18, 145.93 (aromatic C_q), 172.27 (COOH) ppm; IR (KBr): $\bar{\nu} = 3025$, 2977, 2932, 2853, 2791, 1716, 1601, 1497, 1446, 1370, 1333, 1264, 1189, 1112, 1033, 937, 747, 698 cm^{-1}; UV (CH_2Cl_2): λ (logε) = 230 (3.239) nm; MS (70 eV): $m/z = 447$ (M^+), 360, 342, 316, 266, 240, 213, 131, 91; HRMS (EI+): calcd. ($C_{29}H_{37}NO_3$) 447.27734, found 447.27714.

Antiprotozoal Tests, Cytotoxicity

A detailed description of the microplate assays against *Plasmodium falciparum* K_1 and *Trypanosoma brucei rhodesiense* (STIB900) as well as the examination of the cytotoxicity using L6 cells has been reported [19].

Acknowledgements

This work was supported by the *Fonds zur Förderung der wissenschaftlichen Forschung* (Austrian Science Fund) grant Nr. P-15928.

References

[1] Burri C, Nkunku S, Merolle A, Smith T, Blum J, Brun R (2000) Lancet **355**: 1419

[2] Barrett MP, Burchmore RJS, Stich A, Lazzari JO, Frasch AC, Cazzulo JJ, Krishna S (2003) Lancet **362**: 1469

[3] Jennings FW, Rodgers J, Bradley B, Gettinby G, Kennedy PGE, Murray M (2002) Parasit Int **51**: 381
[4] World Health Organization (1999) Human African Trypanosomiasis Treatment and Drug Resistance Network. Report of the first meeting. Geneva, World Health Organization, 14–15 April 1999, WHO/CDS/CSR/EDC/99.5. WHO: Geneva
[5] Agbo EC, Majiwa PAO, Büscher P, Claassen E, te Pas MFW (2003) Trends in Microbiology **11**: 329
[6] Moorthy VS, Good MF, Hill AS (2004) Lancet **363**: 156
[7] Attaran A, Barnes KI, Curtis C, d' Alessandro U, Fanello CI, Galinski MR, Kokwaro G, Looareesuwan S, Makanga M, Mutabingwa TK, Talisuna A, Trape JF, Watkins WM (2004) Lancet **363**: 240
[8] Loutan L (2003) Int J Antimicrob Agents **21**: 163
[9] Tanser FC, le Suer D (2002) Int J Health Geogr **1**: 4
[10] Meshnick SR (2002) Int J Parasit **32**: 1660
[11] Weis R, Brun R, Saf R, Seebacher W (2003) Monatsh Chem **134**: 1019
[12] Seebacher W, Kaiser M, Brun R, Saf R, Weis R (2005) Monatsh Chem **136**: 625
[13] Adamcik JA, Miklasiewicz EJ (1963) J Org Chem **28**: 336
[14] Bruson HA, Riener TW (1942) J Am Chem Soc **64**: 2850
[15] Colonge J, Vuillemet R (1961) Bull Soc chim Fr: 2235
[16] Ahmed SA, Hickmott PW (1979) J Chem Soc Perkin I: 2180
[17] Weis R, Schweiger K, Seebacher W, Belaj F (1998) Tetrahedron **54**: 14015
[18] Weiss D, Hobe S, Beckert R, Klemm D (1990) J Prak Chem **332**: 367
[19] Seebacher W, Brun R, Weis R (2004) Eur J Pharm Sci **21**: 225