Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 377–383

TETRAHEDRON

Reduction of 6/7-substituted 3-phenyltrop-3-en-2-ones: stereoselectivity and conformational analysis of the products

Anu J. Airaksinen,[a,*] Jarkko Lipsonen,[a] Markku Ahlgren,[b] Pirjo Vainiotalo,[b] Kim A. Bergström,[c] Reino Laatikainen[a] and Jouko Vepsäläinen[a]

[a]*Department of Chemistry, University of Kuopio, POB 1627, FIN-70211 Kuopio, Finland*
[b]*Department of Chemistry, University of Joensuu, POB 111, FIN-80101 Joensuu, Finland*
[c]*MAP Medical Technologies OY, POB 9, FIN-00251 Helsinki, Finland*

Received 15 August 2002; revised 1 November 2002; accepted 21 November 2002

Abstract—Reduction of 6/7-carboethoxy-3-phenyltrop-3-en-2-ones with H_2/Pd/C and $NaBH_4$ was studied in order to find a stereoselective route to the corresponding 3-phenyltropan-2-ones and 2α/2β-hydroxy-3-phenyltropanes. The 6/7-*exo*-carboethoxy-3-phenyltrop-3-en-2-ones were selectively reduced by Pd/C to 3β-phenyltropan-2-ones and 2α-hydroxy-3β-phenyltropanes. The corresponding 2β-hydroxy-3β-phenyl analogues were synthesized using $NaBH_4$, with a yield of 40%. Reduction of 6-*endo*-carboethoxy-3-phenyltrop-3-en-2-one yielded several products. The corresponding 7-*endo*-substituted analogue was selectively reduced with both Pd/C and $NaBH_4$ to 7-*endo*-carboethoxy-3β-phenyltropin-2-one. Analysis of stereochemically important ^{1}H NMR spectroscopy parameters was performed for all the products and used for conformational analysis in solution. X-ray analysis was performed for selected compounds.

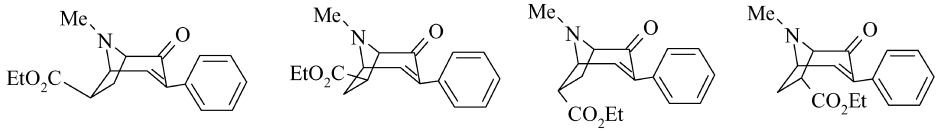
1. Introduction

Phenyltropanes are cocaine analogues, which inhibit reuptake of the monoamine neurotransmitters, dopamine, serotonin and norephineprine. For this reason, their radiolabelled forms have been used in imaging of the monoamine reuptake sites in brain.[1] Phenyltropanes are also under vigorous research because they are potential agents in treatment of cocaine abuse.[2] Tropane structures can be synthesized for example by Diels–Alder reactions.[3] The reaction yields biologically inactive tropenones with a conjugated double bond and a carbonyl group. However, a flexible chair conformation is known to be important for the biological activity of phenyltropanes.[4,5] Binding to the active site is also very sensitive to configuration of the substitution at the tropane ring[6,7] and thus, stereochemically selective synthesis routes are needed.

The reduction of trop-3-en-2-ones, with no substituent at the 3-position, has been previously reported,[8–11] but the stereoselectivity only at the 2-position was studied. In this previous work, it was found that the reduction of 6-*exo*-substituted trop-3-en-2-ones with H_2/Pd/C yielded 2-tropinones with no side products.[8,9] Reduction with $NaBH_4$ yielded 2β-hydroxytrop-3-enes[10] and when followed by H_2/Pd/C reduction, 2β- and 2α-hydroxytropanes.[11] In this work, we explored the influence of the aromatic substituent at the 3-position on the stereoselectivity on both the 2- and 3-positions with $NaBH_4$ and H_2/Pd/C as reducing agents. We also examined the role of the substituent at *endo* or *exo*-position of the ethylene bridge (**1a**–**d**) (Fig. 1).

2. Results

The racemic 6/7-*exo*-carboethoxy-3-phenyltrop-3-en-2-ones (**1a**,**b**) were selectively reduced to the corresponding 3β-phenyltropin-2-ones (**2a**,**b**) by catalytic hydrogenation

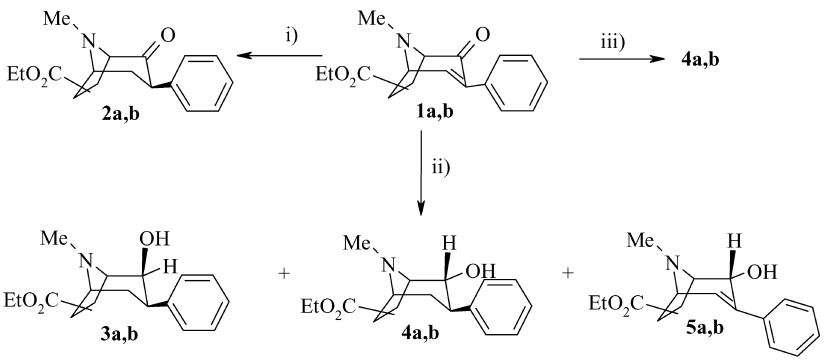


1a **1b** **1c** **1d**

Figure 1. 6/7-Carboethoxy-3-phenyltrop-3-en-2-ones (**1a**–**b**).

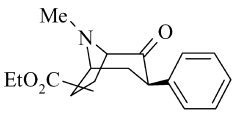
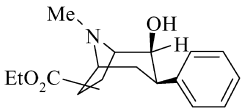
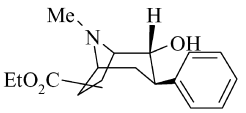
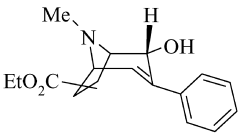
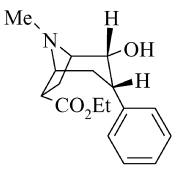
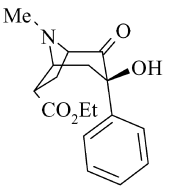
Keywords: reduction; NMR; computer-assisted methods; X-ray crystallography; conformation.
* Corresponding author. Tel.: +358-17-163245; fax: +358-17-163259; e-mail: anu.airaksinen@uku.fi

0040–4020/03/$ - see front matter
PII: S0040-4020(02)01520-X

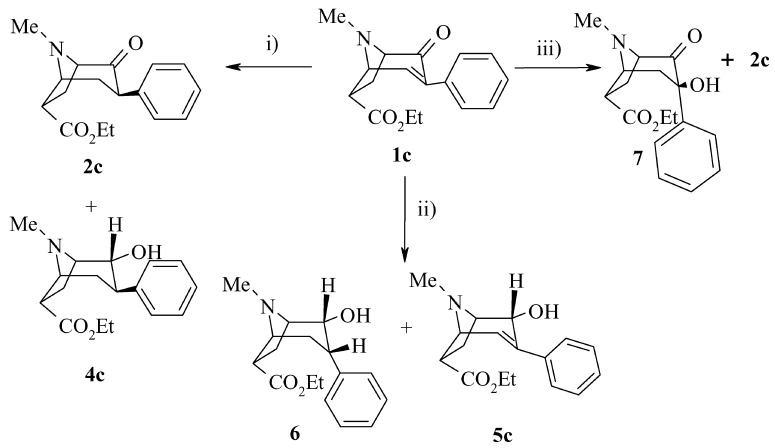


Scheme 1. (i) 5% Pd/C, H_2, MeOH, rt, 25 min; (ii) $NaBH_4$, MeOH, −30°C, 4 h; (iii) 5% Pd/C, H_2, MeOH, 52°C, 17 h. (**a**) 6-*exo*-CO_2Et, (**b**) 7-*exo*-CO_2Et.

Table 1. Reduction of 6/7-*exo*-carboethoxy-3-phenyltrop-3-en-2-ones **1a–d**

Starting material, yield (%)				Conditions	Product
1a	**1b**	**1c**	**1d**		
99	99	–	–	5% Pd/C, H_2, rt, 25 min	**2** 
<1	<1	22	99	5% Pd/C, H_2, 52°C, 17 h	
<1	<1	<1	52	$NaBH_4$, MeOH, −30°C, 4 h	
35	48	<1	<1	$NaBH_4$, MeOH, −30°C, 4 h	**3** 
99	99	58	<1	5% Pd/C, H_2, 52°C, 17 h	**4** 
27	20	<1	<1	$NaBH_4$, MeOH, −30°C, 4 h	
24	32	38	<1	$NaBH_4$, MeOH, −30°C, 4 h	**5** 
<1	<1	62	<1	$NaBH_4$, MeOH, −30°C, 4 h	**6** 
<1	<1	12[a]	<1	5% Pd/C, H_2, 52°C, 1 h	**7** 

[a] 20% of **2c** was also formed.

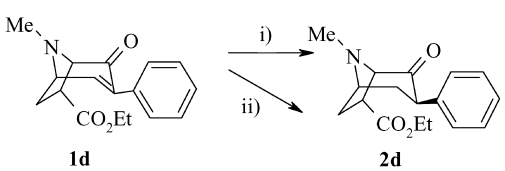


Scheme 2. (i) 5% Pd/C, H_2, MeOH, 52°C, 17 h; (ii) $NaBH_4$, MeOH, −30°C, 4 h; (iii) 5% Pd/C, H_2, MeOH, 52°C, 1 h.

with 5% Pd/C at room temperature in 25 min with quantitative yields (Scheme 1). The corresponding 2α-hydroxy-3β-phenyltropanes (**4a**,**b**) were selectively synthesized at elevated temperature using a prolonged reaction time (17 h) (Table 1). However, sometimes the reaction stopped at the tropinone step, possibly due to poisoning of the catalyst. The same reductions were also made by using 5% Pt/C, without differences in reduction rate. Catalytic hydrogenation of **1a** under 3 bars with 5% Pd/C and at elevated temperature gave the corresponding 2α-hydroxy-3α-phenyltropane. However, the reaction was not reproducible and in most of the cases, the 2α-hydroxy-3β-phenyltropane (**4a**) was the main product.

Reduction with $NaBH_4$ gave 2β-hydroxy-3β-phenyltropanes (**3a**,**b**), but only with moderate yields, 35–48%, and with two side products, the 2α-hydroxyl analogue (**4a**,**b**) and the corresponding intermediate with a double bond (**5a**,**b**), with yields of 20–27% and 24–32%, respectively. The intermediate had the hydroxyl group at the 2-position oriented in the opposite sense to that of tropanes lacking the phenyl group.[10]

In the reductions of 6-*endo*-substituted tropinone (**1c**) less selectivity was observed (Table 1 and Scheme 2). The catalytic hydrogenation with Pd/C for 17 h gave a mixture of the 3β-phenyltropin-2-one (**2c**) and the 2α-hydroxy-3β-phenyl analogue (**4c**), with yields of 22 and 58%, respectively. With the shorter reduction time (1 h) tropinone (**2c**) was formed together with an unexpected side product 3α-hydroxy-3β-phenyltropinone (**7**), which was formed only in these conditions and only for the 6-*endo*-substituted tropinone (**1c**). In the $NaBH_4$ reduction the main product was 2α-hydroxy-3α-phenyltropane (**6**), with yield of 62%. The side product was the unsaturated intermediate (**5c**).



Scheme 3. (i) 5% Pd/C, H_2, MeOH, 52°C, 17 h; (ii) $NaBH_4$, MeOH, −30°C, 4 h.

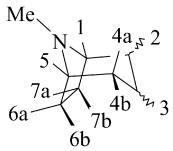
The reduction of unsaturated 7-*endo*-substituted tropinones (**1d**) with both reducing agents gave only 3β-phenyltropinones (**2d**) (Scheme 3). Obviously, the 7-*endo*-substituent induces such a strong steric hindrance to the C(2) carbonyl group that it prevents the reduction. The yield of the tropinone in the $NaBH_4$ reduction was low due to degradation of the tropane ring.

The products were identified by ^1H NMR, 2D-COSY and ^{13}C NMR spectroscopy. The spectral analyses were based on our previous paper.[12] Couplings of the protons 2–4 are very informative not only in determining configuration, but also in conformational analysis of the tropane ring. The compounds **3a** and **b** have couplings of $^3J(2,3)$ around 3 Hz, characteristic for β-substituted tropanes; for the α-substituted compounds **4a**–**c** the $^3J(2,3)$ couplings are 9–10 Hz. The $^3J(3,4a)$ couplings for all these compounds are over 11 Hz indicating that the phenyl group is in the β-position (Table 2). The coupling data correlates well with the calculated values (Table 2) of the chair conformation obtained by using molecular modeling and the Haasnoot equation for the couplings.[13] This suggests that the conformational equilibrium is highly towards a chair form. In addition, X-ray analysis of **3a** showed that the compound is also in the chair conformation in solid state (Fig. 2).

The coupling data of compounds **2a**–**d** do not correspond to any single pure conformer, but a conformer that is between the chair and half-chair conformations. Furthermore, molecular dynamics calculations suggest that the carbon 2–4 moiety is very flexible, with a boat conformation only within one kJ/mol from the energetic minimum. Compound **6** has $^3J(1,2)$, $^3J(3,4a)$ and $^3J(4a,5)$ couplings of 8.6, 6.9 and 9.8 Hz, respectively, indicating that the structure is 2α-hydroxy-3α-phenyl. These values correspond well to the calculated values for the boat conformation. However, our molecular modeling calculations suggest that the half-chair and chair conformations are energetically within ca. 5 kJ/mol from the boat conformation and separated with a very low barrier.

The unsaturated analogues **5a**–**c** have $^3J(1,2)$ and $^3J(4a, 5)$ couplings of over 5 Hz. The dihedral angle is between the angles of boat and chair conformations, leading to the

Table 2. The conformationally and configurationally most important coupling constants (Hz) of the products **2**–**7**. Coupling constants of computationally optimized structures calculated by the Haasnoot equation are in parentheses



	^3J(1,2)	^3J(2,3)	^4J(2,4a)	^4J(2,4b)	^3J(3,4a)	^3J(3,4b)	^4J(3,5)	^3J(4a,5)	^3J(4b,5)	Conf.[a]
2a	–	–	–	–	11.92 (12.00)	8.02 (5.81)	0.94	3.63 (3.72)	2.23 (2.74)	Chair
2b	–	–	–	–	11.70 (11.94)	8.08 (5.94)	0.58	3.71 (3.58)	2.10 (2.84)	Chair
2c	–	–	–	–	11.67 (12.04)	8.27 (5.57)	0.75	3.97 (3.66)	1.98 (2.88)	Chair
2d	–	–	–	–	11.73 (11.88)	8.16 (6.08)	−0.71	3.57 (3.41)	2.29 (2.98)	Chair
3a	4.04 (3.33)	3.19 (3.57)	0.08	1.04	13.01 (12.41)	5.36 (5.62)	0.09	2.96 (3.36)	3.19 (2.75)	Chair[b]
3b	4.08 (3.30)	3.10 (3.47)	0.40	1.06	12.99 (12.31)	5.50 (5.77)	0.83	3.11 (3.32)	3.09 (2.76)	Chair
4a	3.67 (3.86)	9.83 (9.41)	0.69	0.46	12.36 (12.22)	6.02 (5.94)	0.65	2.97 (3.38)	2.96 (2.72)	Chair
4b	3.77 (3.87)	9.77 (9.51)	0.14	0.03	12.57 (12.14)	5.97 (6.07)	0.59	3.05 (3.37)	2.83 (2.71)	Chair
4c	3.59 (3.76)	9.93 (9.42)	0.21	0.47	12.65 (12.19)	6.17 (5.90)	0.32	3.23 (3.50)	2.58 (2.66)	Chair
5a	5.13 (5.68)	–	1.03	–	–	–	–	5.50[c]	–	Half-chair
5b	5.27 (5.67)	–	1.00	–	–	–	–	5.67[c]	–	Half-chair
5c	5.20 (5.70)	–	1.11	–	–	–	–	5.49[c]	–	Half-chair
6	8.58 (8.15)	5.71 (4.42)	1.51	0.57	6.88 (6.78)	12.90 (11.44)	0.88	9.81 (9.32)	2.04 (0.91)	Boat
7	–	–	–	–	–	–	–	9.40 (8.54)	0.94 (0.50)	Boat[b]

The rms values of the spectral analyses (in % of the NH_3 signal=100%) were from 0.15 to 0.50%. Standard deviations of the couplings were from 0.01 to 0.10 Hz.

[a] The main conformation based on the ^{1}H NMR spectra.

[b] Solid state structure determined by the X-ray crystallography.

[c] Not optimized.

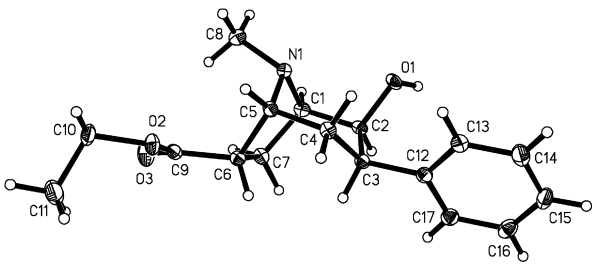


Figure 2. ORTEP presentation of compound **3a**.

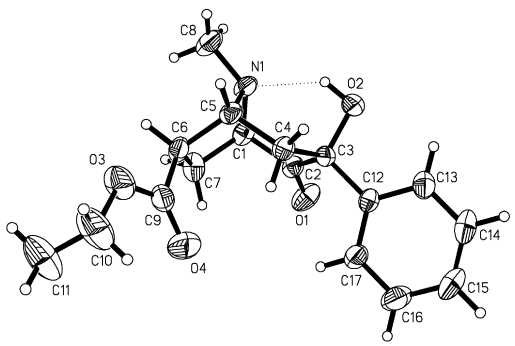


Figure 3. ORTEP presentation of compound **7**.

conclusion that compounds **5a**–**c** are mainly in a half-chair conformation. Although, **5a**–**c** lack the ^3J couplings characteristic for the 2α-hydroxyl compounds, the increased ^4J(2,4a) and ^4J(2,7a) couplings (W-coupling) indicate that the 2-hydroxy group is in the α-position. Furthermore, since the ^4J couplings are very sensitive to the planarity of the pathway,[14] these couplings indicate that the main conformer is almost planar, probably due to the conjugation with the double bond, and, on the basis of modeling, rather rigid, too. The structure of **7** has only a few conformationally informative couplings, making the ^{1}H NMR spectroscopy structural analysis difficult, and thus the structure was derived from the X-ray analysis (Fig. 3). A comparison of the few couplings with the calculated results confirms that the boat conformation is also the main form in solution.

3. Discussion

In catalytic hydrogenations, the direction from which the hydrogen attacks at the reaction center depends on the orientation of the reacting compound on the surface of the catalyst, leading normally to *syn* products.[15] However, in our case the *anti* compounds **4a**–**c** were formed. The hydrogenation of 7-*endo*-substituted **1d**, gave only the partly reduced ketone (**2d**), obviously due to steric hindrance by the substituent at the 7-position. The same effect is observed in hydrogenation of 6-*endo*-substituted **1c**, where the yield of the product **4c** is decreased as compared to the *exo*-substituted tropanes.

In $NaBH_4$ reductions, the nucleophilic reductant normally attacks from the less hindered side of the molecule, leading to hydroxyl group at that side.[15] With our *exo*-substituted starting materials (**1a**,**b**) the main products were alcohols, in which the hydroxyl and phenyl groups are at the β-position (**3a**,**b**). The C(3)–C(4) double bond is reduced probably because it is conjugated to the carbonyl and the phenyl ring. However, the unsaturated side products (**5a**,**b**) were also formed to some extent. With the 6-*endo*-substituted starting material the 2β,3β-analogue was not formed, instead the main product was the 2α,3α-analogue (**6**). The main reason is obviously the steric hindrance of the 6-*endo*-substituent, leading to a boat conformation and thus enabling attack of the reductive nucleophile from the

reverse direction as compared to the *exo*-substituted products.

4. Conclusion

The position of the EtO_2C-substituent at the 6/7-bridge had a decisive role in determining the product of $NaBH_4$ and H_2/Pd/C reductions. The 6/7-*endo*-substituted tropanes (**1b**–**c**) behaved in a totally different way from those having the substituent at the *exo*-position (**1a**–**b**). In addition, it was found that the reduction strengths of both reducing agents were enhanced due to conjugation of the phenyl group at the 3-position, the C(2) carbonyl and the C(3)–C(4) double bond. The 6/7-*exo*- and 7-*endo*-substituted 3β-phenyl-2-tropanones were selectively produced by Pd/C hydrogenation, likewise the 6/7-*exo*-substituted 2α-hydroxy-3β-phenyltropanes. For the 2β-hydroxy-3β-phenyl tropanes no stereoselective route was found. As to the conformational analysis of the products, our results suggest that 2α-hydroxy-3α-phenyl tropane (**6**, pushed by phenyl to the boat conformation) and all the keto-compounds **2a**–**d** and **7**, are very flexible.

5. Experimental

NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 500 MHz NMR spectrometer. TMS was used as internal standard. Preparation and analysis of the spectra were made with PERCHit software.[16] FIDs were multiplied with sin×exp window function, Fourier transformed and base line corrected. The spectra were solved first by the integral transform method, after which the solutions were refined by the total-line shape procedure. Signs of the couplings were ignored, except in geminal couplings and in cases were the sign was essential for good fit. Molecular mechanics calculations were performed using MM+ force field under HyperChem™ software. Starting materials **1a**–**d** were prepared using literature procedures.[3] Reagents in the syntheses were purchased mainly from Aldrich Chemicals and used without further purification. Dry methanol was prepared by refluxing with Mg pieces and iodine. Column chromatography was carried out with Kieselgel 60. Infrared spectra were recorded as liquid film between KBr discs.

5.1. General procedure for the H_2/Pd/C reductions

The starting material (**1a**–**d**, 0.1 g, 0.35 mmol) was dissolved in MeOH (15 mL) and 5% Pd/C (15%, w/w) was added. The reaction mixture was hydrogenated at ambient temperature with vigorous stirring. The mixture was filtered with celite and evaporated to dryness. If further purification was needed, were products separated by column chromatography with EtOAc or EtOAc–MeOH gradient.

5.2. General procedure for the $NaBH_4$ reductions

Starting material (**1a**–**d**, 0.2 g, 0.70 mmol) in dry methanol (18 mL) was added to $NaBH_4$ (0.2 g, 5.12 mmol) in −30°C and stirred for 4 h. Conc. HCl (800 μL) was added carefully and the mixture was allowed to warm to rt, evaporated to dryness and dissolved to water. The mixture was made basic with NH_4OH, extracted with CH_2Cl_2 and evaporated to dryness. The products were separated by column chromatography with EtOAC–TEA 15:1.

5.2.1. 8-Methyl-2-oxo-3-phenyl-8-aza-bicyclo[3.2.1]-octane-6-*exo*-carboxylic acid ethyl ester (2a). From **1a** (204.0 mg, 0.72 mmol). Reaction conditions: 5% Pd/C, H_2, rt, 25 min. Yield 204.5 mg (99%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.29–7.24 (m, 1H), 7.15–7.12 (m, 2H), 4.23 (q, 2H, J=7.1 Hz), 3.83–3.80 (m, H_5, J_{5-4a}=3.6 Hz, J_{5-4b}=2.2 Hz, J_{5-1}=1.0 Hz), 3.60–3.55 (m, H_3, J_{3-4a}=11.9 Hz, J_{3-4b}=8.0 Hz), 3.56 (d, H_1, J_{1-7a}=7.4 Hz), 3.48 (s, 3H), 3.17 (dd, H_{6b}, J_{6b-7b}=9.8 Hz, J_{6b-7a}=5.7 Hz), 2.80–2.72 (m, H_{7a}, J_{7a-b}=−14.3 Hz), 2.52–2.46 (m, H_{4a}, J_{4a-b}=−13.6 Hz), 2.26 (ddd, H_{4b}), 2.20 (dd, H_{7b}), 1.31 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 207.8, 174.4, 138.0, 129.0, 128.6, 127.2, 72.0, 63.8, 61.2, 49.7, 46.7, 39.3, 37.5, 30.6, 14.3. [M+H$^+$] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1597.

5.2.2. 8-Methyl-2-oxo-3-phenyl-8-aza-bicyclo[3.2.1]-octane-7-*exo*-carboxylic acid ethyl ester (2b). From **1b** (53.0 mg, 0.19 mmol). Reaction conditions: 5% Pd/C, H_2, rt, 25 min. Yield 54.0 mg (99%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.31 (m, 2H), 7.28–7.24 (m, 1H), 7.15–7.11 (m, 2H), 4.19 (q, 2H, J=7.1 Hz), 3.81 (s, H_1, J_{1-5}=1.0 Hz, J_{1-7b}=0.9 Hz), 3.57 (dd, H_3, J_{3-4a}=11.7 Hz, J_{3-4b}=8.1 Hz, J_{3-5}=0.6 Hz), 3.55–3.51 (m, H_5, J_{5-6a}=6.9 Hz, J_{5-4a}=3.7 Hz, J_{5-4b}=2.1 Hz), 3.09 (dd, H_{7b}, J_{7b-6b}=9.8 Hz, J_{7b-6a}=5.6 Hz), 2.78–2.72 (m, H_{6a}, J_{6a-b}=−13.6 Hz, J_{6a-4a}=1.4 Hz), 2.52 (s, 3H), 2.46–2.39 (m, H_{4a}, J_{4a-b}=−13.4 Hz), 2.23 (dd, H_{6b}), 2.14 (ddd, H_{4b}), 1.28 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.5, 173.7, 138.0, 129.1, 128.6, 127.3, 74.1, 61.6, 60.6, 49.7, 46.1, 39.5, 38.0, 31.2, 14.2. [M+H$^+$] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1586.

5.2.3. 8-Methyl-2-oxo-3-phenyl-8-aza-bicyclo[3.2.1]-octane-6-*endo*-carboxylic acid ethyl ester (2c). From **1c** (82.0 mg, 0.29 mmol). Reaction conditions: 5% Pd/C, H_2, 52°C, 17 h. The product was purified by column chromatography with EtOAc–MeOH gradient. Yield 19.0 mg (22%) as a yellow oil. IR (cm^{-1}): 3054, 2929, 1726, 1692, 1266, 1192, 738, 703. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.28–7.23 (m, 1H), 7.16–7.12 (m, 2H), 4.25 (q, 2H, J=7.1 Hz), 3.92 (dd, H_3, J_{3-4a}=11.7 Hz, J_{3-4b}=8.3 Hz, J_{3-5}=0.8 Hz), 3.68–3.64 (m, H_5, J_{5-6a}=6.6 Hz, J_{5-4a}=4.0 Hz, J_{5-4b}=2.0 Hz, J_{5-1}=1.0 Hz), 3.59–3.52 (m, H_{6a}, J_{6a-7a}=11.6 Hz, J_{6a-7b}=6.0 Hz, J_{6a-4a}=1.0 Hz), 3.50 (d, H_1, J_{1-7a}=7.7 Hz, J_{1-7b}=1.0 Hz), 2.53 (s, 3H), 2.55–2.46 (m, H_{7a}, J_{7a-b}=−14.5 Hz), 2.48–2.41 (m, H_{7b}), 2.37–2.28 (m, H_{4a}, J_{4a-b}=−14.0 Hz), 2.13 (ddd, H_{4b}), 1.31 (t, 3H). [M+H$^+$] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1586.

5.2.4. 8-Methyl-2-oxo-3-phenyl-8-aza-bicyclo[3.2.1]-octane-7-*endo*-carboxylic acid ethyl ester (2d). From **1d** (30.5 mg, 0.11 mmol). Reaction conditions: 5% Pd/C, H_2, 52°C, 17 h. Yield 32.0 mg (99%) as a yellow wax. From **1d** (100.4 mg, 0.35 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 52.6 mg (52%). IR (cm^{-1}): 3055, 2929, 1727, 1266, 1198, 738, 702. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2H), 7.27–7.22 (m,

1H), 7.14–7.11 (m, 2H), 4.12 (q, 2H, J=7.1 Hz), 3.71 (dd, H_3, J_{3-4a}=11.7 Hz, J_{3-4b}=8.2 Hz), 3.74–3.69 (m, H_1, J_{1-7a}=7.0 Hz, J_{1-5}=1.0 Hz), 3.61–3.55 (m, H_{7a}, J_{7a-6a}=12.1 Hz, J_{7a-6b}=5.9 Hz), 3.48–3.44 (m, H_5, J_{5-6a}=7.1 Hz, J_{5-4a}=3.6 Hz, J_{5-4b}=2.3 Hz), 2.58–2.51 (m, H_{6a}, J_{6a-b}=−13.7 Hz, J_{6a-4a}=1.1 Hz), 2.52 (s, 3H), 2.45–2.39 (m, H_{4a}, J_{4a-b}=−13.2 Hz), 2.41–2.36 (m, H_{6b}), 2.21 (ddd, H_{4b}), 1.20 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.9, 172.6, 138.5, 129.1, 128.5, 127.0, 74.6, 61.3, 60.5, 50.5, 45.3, 40.4, 38.1, 29.5, 14.2. [M+H$^+$] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1586.

5.2.5. 8-Methyl-2βhydroxy-3β-phenyl-8-aza-bicyclo[3.2.1]octane-6-*exo*-carboxylic acid ethyl ester (3a). From **1a** (206.0 mg, 0.72 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 74.6 mg (35%) as a gray solid; mp 122°C. IR (cm^{-1}): 3200, 3055, 2929, 1721, 1461, 1174, 770, 696, 678. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.28–7.26 (m, 2H), 7.23–7.19 (m, 1H), 4.19 (q, 2H, J=7.1 Hz), 3.69–3.67 (m, H_5, J_{5-4a}=3.0 Hz, J_{5-4b}=3.2 Hz, J_{5-1}=1.6 Hz), 3.64 (t, H_2, J_{2-1}=4.0 Hz, J_{2-3}=3.2 Hz, J_{2-4b}=1.0 Hz), 3.39–3.35 (m, H_1, J_{1-7a}=7.3 Hz), 2.92 (dd, H_{6b}, J_{6b-7b}=9.8 Hz, J_{6b-7a}=5.6 Hz), 2.73 (ddd, H_3, J_{3-4a}=13.0 Hz, J_{3-4b}=5.4 Hz), 2.70–2.64 (m, H_{7a}, J_{7a-7b}=−14.2 Hz), 2.31 (s, 3H), 2.21 (td, H_{4a}, J_{4a-4b}=−13.1 Hz), 1.95 (dd, H_{7b}), 1.72 (ddd, H_{4b}), 1.29 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.5, 141.6, 128.3, 128.2, 126.4, 71.7, 69.0, 65.8, 61.0, 45.7, 41.9, 39.2, 34.3, 27.8, 14.3. [M+H$^+$] for $C_{17}H_{23}NO_3$ calcd 290.1751, found 290.1732.

5.2.6. 8-Methyl-2β-hydroxy-3β-phenyl-8-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid ethyl ester (3b). From **1b** (207.0 mg, 0.73 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 100.5 mg (48%) as a yellow wax. IR (cm^{-1}): 3428, 3054, 2942, 1726, 1266, 1192, 738, 704. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.28–7.25 (m, 2H), 7.22–7.18 (m, 1H), 4.19 (q, 2H, J=7.1 Hz), 3.73 (t, H_2, J_{2-1}=4.1 Hz, J_{2-3}=3.1 Hz, J_{2-4b}=1.1 Hz), 3.65–3.62 (m, H_1, J_{1-5}=1.7 Hz, J_{1-7b}=1.1 Hz, J_{1-3}=0.5 Hz), 3.34–3.31 (m, H_5, J_{5-6a}=6.7 Hz, J_{5-4a}=3.1 Hz, J_{5-4b}=3.1 Hz), 2.89 (dd, H_{7b}, J_{7b-6b}=9.6 Hz, J_{7b-6a}=6.0 Hz), 2.73 (ddd, H_3, J_{3-4a}=13.0 Hz, J_{3-4b}=5.5 Hz), 2.68–2.62 (m, H_{6a}, J_{6a-b}=−13.7 Hz, J_{6a-4a}=1.2 Hz), 2.31 (s, 3H), 2.14 (td, H_{4a}, J_{4a-4b}=−13.1 Hz), 1.94 (dd, H_{6b}), 1.58 (ddd, H_{4b}), 1.28 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.9, 141.7, 128.3, 128.2, 126.4, 71.9, 71.6, 62.2, 61.0, 45.8, 41.9, 38.9, 33.7, 28.1, 14.3. [M+H$^+$] for $C_{17}H_{23}NO_3$ calcd 290.1751, found 290.1714.

5.2.7. 8-Methyl-2α-hydroxy-3β-phenyl-8-aza-bicyclo[3.2.1]octane-6-*exo*-carboxylic acid ethyl ester (4a). From **1a** (53.0 mg, 0.19 mmol). Reaction conditions: 5% Pd/C, H_2, 52°C, 17 h. Yield 54.3 mg (99%) as a brown oil. From **1a** (206.0 mg, 0.72 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 55.0 mg (27%). IR (cm^{-1}): 3400, 3053, 2940, 1723, 1264, 1186, 741, 705. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.29–7.26 (m, 2H), 7.24–7.20 (m, 1H), 4.19 (q, 2H, J=7.1 Hz), 3.87 (dd, H_2, J_{2-3}=9.8 Hz, J_{2-1}=3.7 Hz, J_{2-7a}=0.7 Hz, J_{2-4a}=0.7 Hz), 3.62–3.59 (m, H_5, J_{5-4a}=3.0 Hz, J_{5-4b}=3.0 Hz, J_{5-1}=1.2 Hz, J_{5-7b}=0.4 Hz), 3.32–3.29 (m, H_1, J_{1-7a}=6.7 Hz, J_{1-3}=0.7 Hz), 2.83 (dd, H_{6b}, J_{6b-7b}=10.0 Hz, J_{6b-7a}=5.8 Hz), 2.51–2.45 (m, H_{7a}, J_{7a-b}=−14.1 Hz), 2.47–2.41 (m, H_3, J_{3-4a}=12.4 Hz, J_{3-4b}=6.0 Hz), 2.32 (s, 3H), 2.26 (dd, H_{7b}), 1.91 (td, H_{4a}, J_{4a-4b}=−13.4 Hz), 1.76 (ddd, H_{4b}), 1.28 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.5, 141.9, 128.8, 128.3, 127.0, 73.8, 67.5, 65.8, 60.9, 47.0, 44.9, 41.0, 39.0, 25.3, 14.3. [M+H$^+$] for $C_{17}H_{23}NO_3$ calcd 290.1751, found 290.1711.

5.2.8. 8-Methyl-2α-hydroxy-3β-phenyl-8-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid ethyl ester (4b). From **1b** (110.0 mg, 0.39 mmol). Reaction conditions: 5% Pd/C, H_2, 52°C, 17 h. Yield 112.6 mg (99%) as a white solid; mp 129°C. From **1b** (207.0 mg, 0.73 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 42.1 mg (20%). IR (cm^{-1}): 3150, 3063, 2957, 1729, 1205, 1180, 758, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2H), 7.30–7.26 (m, 2H), 7.25–7.20 (m, 1H), 4.19 (q, 2H, J=7.1 Hz), 3.93 (dd, H_2, J_{2-3}=9.8 Hz, J_{2-1}=3.8 Hz), 3.63 (d, H_1, J_{1-5}=1.3 Hz, J_{1-7b}=0.9 Hz), 3.30–3.26 (m, H_5, J_{5-6a}=6.8 Hz, J_{5-4a}=3.1 Hz, J_{5-4b}=2.8 Hz, J_{5-3}=0.6 Hz), 3.20 (dd, H_{7b}, J_{7b-6b}=10.0 Hz, J_{7b-6a}=6.0 Hz), 2.68–2.61 (m, H_{6a}, J_{6a-b}=−13.7 Hz, J_{6a-4a}=1.2 Hz), 2.46–2.40 (m, H_3, J_{3-4a}=12.6 Hz, J_{3-4b}=6.0 Hz), 2.31 (s, 3H), 1.92–1.86 (m, H_{6b}), 1.90–1.84 (m, H_{4a}, J_{4a-b}=−13.4 Hz), 1.65 (ddd, H_{4b}), 1.27 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.8, 141.9, 128.6, 128.1, 127.0, 73.8, 70.7, 62.4, 60.9, 44.7, 42.7, 41.2, 38.6, 29.5, 14.3. [M+H$^+$] for $C_{17}H_{23}NO_3$ calcd 290.1751, found 290.1722.

5.2.9. 8-Methyl-2α-hydroxy-3β-phenyl-8-aza-bicyclo[3.2.1]octane-6-*endo*-carboxylic acid ethyl ester (4c). From **1c** (82.0 mg, 0.29 mmol). Reaction conditions: 5% Pd/C, H_2, 52°C, 17 h. The product was purified by column chromatography with EtOAc–MeOH gradient. Yield 48.5 mg (58%) as a yellow oil. IR (cm^{-1}): 3592, 3436, 3053, 2948, 1727, 1266, 1191, 745, 703. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.28–7.26 (m, 2H), 7.23–7.19 (m, 1H), 4.18 (q, 2H, J=7.1 Hz), 3.98 (dd, H_2, J_{2-3}=9.9 Hz, J_{2-1}=3.6 Hz, J_{2-7a}=0.5 Hz), 3.48–3.42 (m, H_{6a}, J_{6a-7a}=11.9 Hz, J_{6a-7b}=6.1 Hz, J_{6a-5}=6.7 Hz, J_{6a-4a}=0.9 Hz), 3.41–3.38 (m, H_5, J_{5-4a}=3.2 Hz, J_{5-4b}=2.6 Hz, J_{5-1}=1.3 Hz), 3.24 (dd, H_1, J_{1-7a}=7.1 Hz, J_{1-7b}=0.9 Hz), 2.82–2.75 (m, H_3, J_{3-4a}=12.7 Hz, J_{3-4b}=6.2 Hz), 2.53 (dd, H_{7b}, J_{7b-7a}=−14.2 Hz), 2.40 (s, 3H), 2.17–2.10 (m, H_{7a}), 1.90–1.83 (m, H_{4a}, J_{4a-4b}=−14.0 Hz), 1.76 (ddd, H_{4b}), 1.26 (t, 3H).

5.2.10. 8-Methyl-2α-hydroxy-3-phenyl-8-aza-bicyclo[3.2.1]oct-3-ene-6-*exo*-carboxylic acid ethyl ester (5a). From **1a** (206.0 mg, 0.72 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 48.8 mg (24%) as a white wax. IR (cm^{-1}): 3590, 3400, 3053, 2986, 1726, 1265, 740, 706. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.33 (m, 4H), 7.29–7.25 (m, 1H), 6.23 (dd, H_4, J_{4-5}=5.5 Hz, J_{4-2}=1.0 Hz), 5.13 (d, H_2, J_{2-1}=5.1 Hz, J_{2-7a}=0.1 Hz), 4.19 (q, 2H, J=7.1 Hz), 3.85 (d, H_5, J_{5-1}=1.1 Hz), 3.59–3.56 (m, H_1, J_{1-7a}=7.6 Hz), 3.00–2.96 (m, H_{6b}, J_{6b-7b}=9.8 Hz, J_{6b-7a}=3.6 Hz), 2.52–2.47 (m, H_{7b}, J_{7b-a}=−14.2 Hz), 2.52–2.47 (m, H_{7a}), 2.46 (s, 3H), 1.29 (t, 3H). [M+H$^+$] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1605.

5.2.11. 8-Methyl-2α-hydroxy-3-phenyl-8-aza-bicyclo[3.2.1]oct-3-ene-7-*exo*-carboxylic acid ethyl ester (5b). From **1b** (207.0 mg, 0.73 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 67.0 mg (32%) as a yellowish wax. IR (cm^{-1}): 3587, 3053, 2983, 1724, 1266, 738, 704. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 4H), 7.28–7.24 (m, 1H), 6.15 (dd, H_4, J_{4-5}=5.7 Hz, J_{4-2}=1.0 Hz), 5.19 (d, H_2, J_{2-1}=5.3 Hz), 4.17 (q, 2H, J=7.1 Hz), 3.79 (dt, H_1, J_{1-5}=1.6 Hz, J_{1-7b}=1.5 Hz), 3.52 (t, H_5, J_{5-6a}=5.2 Hz), 3.47 (t, H_{7b}, J_{7b-6b}=9.4 Hz, J_{7b-6a}=7.3 Hz), 2.49–2.42 (m, H_{6a}, J_{6a-b}=−12.5 Hz), 2.44 (s, 3H), 2.19 (dd, H_{6b}), 1.26 (t, 3H). [M+H^+] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1605.

5.2.12. 8-Methyl-2α-hydroxy-3-phenyl-8-aza-bicyclo[3.2.1]oct-3-ene-6-*endo*-carboxylic acid ethyl ester (5c). From **1c** (218.0 mg, 0.76 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 83.4 mg (38%) as a yellow oil. IR (cm^{-1}): 3589, 3053, 2984, 1729, 1266, 740, 705. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H), 6.00 (d, H_4, J_{4-5}=5.5 Hz, J_{4-2}=1.1 Hz), 5.18 (d, H_2, J_{2-1}=5.2 Hz, J_{2-7a}=0.9 Hz), 4.20 (q, 2H, J=7.1 Hz), 3.70 (t, H_5, J_{5-6a}=6.0 Hz, J_{5-1}=1.3 Hz), 3.49–3.44 (m, H_{6a}, J_{6a-7a}=10.7 Hz, J_{6a-7b}=6.5 Hz), 3.47–3.43 (m, H_1, J_{1-7a}=7.3 Hz, J_{1-7b}=1.3 Hz), 2.64 (dd, H_{7b}, J_{7b-a}=−14.1 Hz), 2.46 (s, 3H), 2.16–2.08 (m, H_{7a}), 1.31 (t, 3H). [M+H^+] for $C_{17}H_{21}NO_3$ calcd 288.1594, found 288.1605.

5.2.13. 8-Methyl-2α-hydroxy-3α-phenyl-8-aza-bicyclo[3.2.1]octane-6-*endo*-carboxylic acid ethyl ester (6). From **1c** (218.0 mg, 0.76 mmol). Reaction conditions: $NaBH_4$, MeOH, −30°C, 4 h. Yield 135.0 mg (62%) as a white wax. IR (cm^{-1}): 3581, 3449, 3055, 3942, 1726, 1266, 1199, 742, 703. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.23–7.19 (m, 3H), 4.34–4.29 (m, H_2, J_{2-3}=5.7 Hz, J_{2-1}=8.6 Hz, J_{2-7a}=0.7 Hz), 4.22 (q, 2H, J=7.1 Hz), 3.58–3.53 (m, H_5, J_{5-4a}=9.8 Hz, J_{5-6a}=6.0 Hz, J_{5-4b}=2.0 Hz, J_{5-1}=1.8 Hz), 3.45 (t, H_1, J_{1-7a}=7.7 Hz, J_{1-7b}=1.5 Hz), 3.41–3.35 (m, H_{6a}, J_{6a-7a}=11.0 Hz, J_{6a-7b}=6.4 Hz), 3.36–3.30 (m, H_3, J_{3-4a}=6.9 Hz, J_{3-4b}=12.9 Hz), 2.77 (dd, H_{7b}, J_{7b-a}=−14.3 Hz), 2.34 (s, 3H), 2.10–2.03 (m, H_{4a}, J_{4a-4b}=−14.3 Hz), 2.01–1.93 (m, H_{7a}), 1.61–1.54 (m, H_{4b}), 1.29 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.1, 140.2, 129.2, 128.5, 126.7, 71.1, 65.5, 62.5, 60.7, 45.8, 41.1, 39.8, 28.2, 21.1, 14.4. [M+H^+] for $C_{17}H_{23}NO_3$ calcd 290.1751, found 290.1710.

5.2.14. 8-Methyl-2-oxy-3β-hydroxy-3α-phenyl-8-aza-bicyclo[3.2.1]octane-6-*endo*-carboxylic acid ethyl ester (7). From **1c** (110.0 mg, 0.39 mmol). Reaction conditions: 5% Pd/C, H_2, 52°C, 1 h. The product was purified by column chromatography with EtOAc. Yield 14.1 mg (12%) as a yellow wax. IR (cm^{-1}): 3278, 3054, 2985, 1731, 1266, 1195, 739, 703. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.34 (m, 4H), 7.32–7.28 (m, 1H), 4.18 (q, 2H, J=7.1 Hz), 3.84–3.79 (m, H_5, J_{5-4a}=9.4 Hz, J_{5-6a}=6.6 Hz, J_{5-1}=1.9 Hz, J_{5-4b}=0.9 Hz), 3.77 (dt, H_1, J_{1-7a}=8.5 Hz, J_{1-7b}=1.5 Hz), 3.56–3.50 (m, H_{6a}, J_{6a-7a}=11.3 Hz, J_{6a-7b}=6.0 Hz), 2.66–2.58 (m, H_{7a}, J_{7a-7b}=−14.4 Hz), 2.49–2.43 (m, H_{4a}, J_{4a-4b}=−15.7 Hz), 2.45 (s, 3H), 2.37 (dd, H_{7b}), 1.87 (d, H_{4b}), 1.27 (t, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.9, 172.9, 139.6, 128.0, 127.5, 126.5, 76.3, 71.1, 63.0, 61.4, 44.9, 39.8, 39.4, 27.9, 14.4. [M+H^+] for $C_{17}H_{21}NO_4$ calcd 304.1543, found 304.1526.

5.3. Registry

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos CCDC 190367 and 190368. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

Acknowledgements

This work was supported by grants from Kuopio University Hospital (EVO 5114), Technical Development Centre of Finland (TEKES 204/401/98) and Graduate School of Bioorganic Chemistry, Turku, Finland. We thank Mrs Maritta Salminkoski and Mrs Ritva Romppainen for technical assistance.

References

1. Bergström, K. A.; Tupala, E.; Tiihonen, J. *Pharmacol. Toxicol.* **2001**, *88*, 287–293.
2. Singh, S. *Chem. Rev.* **2000**, *100*, 925–1024.
3. Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 503–509.
4. Meltzer, P. C.; Blundell, P.; Huang, H.; Liu, S.; Yong, Y. F.; Madras, B. K. *Bioorg. Med. Chem.* **2000**, *8*, 581–590.
5. Chang, A.-C.; Burgess, J. P.; Mascarella, S. W.; Abraham, P.; Kuhar, M. J.; Carroll, F. I. *J. Med. Chem.* **1997**, *40*, 1247–1251.
6. Abraham, P.; Pitner, J. B.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. *J. Med. Chem.* **1992**, *35*, 141–144.
7. Carroll, F. I.; Lewin, A. O.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883–886.
8. Takahashi, T.; Kitano, K.; Hagi, T.; Nihonmatsu, H.; Koizumi, T. *Chem. Lett.* **1989**, 597–598.
9. Pei, X.-F.; Shen, J.-X. *Heterocycles* **1993**, *36*, 2549–2556.
10. Jung, M. E.; Longmei, Z.; Tangsheng, P.; Huiyan, Z.; Yan, L.; Jingyu, S. *J. Org. Chem.* **1992**, *57*, 3528–3530.
11. Takahashi, T.; Hagi, T.; Kitano, K.; Takeuchi, Y.; Koizumi, T. *Chem. Lett.* **1989**, 593–596.
12. Airaksinen, A. J.; Tuppurainen, K. A.; Lötjönen, S. E.; Niemitz, M.; Yu, M.; Vepsäläinen, J.; Laatikainen, R.; Hiltunen, J.; Bergström, K. A. *Tetrahedron* **1999**, *55*, 10537–10546.
13. Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.
14. Gunther, H. *NMR Spectroscopy, Basic Principles, Concepts, and Applications in Chemistry*; 2nd ed. Wiley: Chichester, 1994.
15. Hudlický, M. *Reductions in Organic Chemistry*; Ellis Horwood Limited: Chichester, 1984.
16. Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson. A* **1996**, *120*, 1–10.