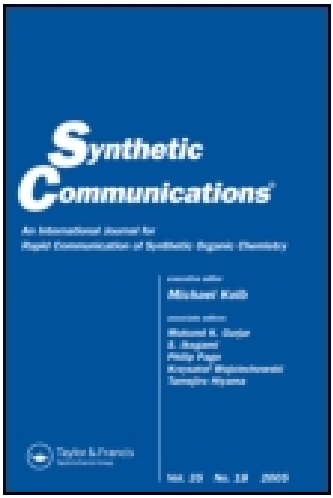

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Improved Synthesis of Methyl 7,7-Ethylenedioxy-3-methyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylate, Intermediate for the Synthesis of Huperzine A Analogues

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IMPROVED SYNTHESIS OF METHYL 7,7-ETHYLENEDIOXY-3-METHYL-9-OXOBICYCLO[3.3.1]NON-3-ENE-1-CARBOXYLATE, INTERMEDIATE FOR THE SYNTHESIS OF HUPERZINE A ANALOGUES

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Abstract: The title compound **4** has been obtained in an improved yield, from **1** via alcohol **2a**, which was dehydrated by pyrolytic *syn*-elimination of its derived thiocarbonate **2c**. A *trans*-configuration of **2a** and its stereoisomer **3a** was established by X-ray diffraction analysis of their mesylates **2b** and **3b**.

In connection with the preparation of analogues of Huperzine A[1] modified at the heterocyclic moiety, as part of a project directed to the synthesis of anticholinesterasic agents for the treatment of Alzheimer's disease[2], we developed a synthesis of ketoester **4** which contains the carbobicyclic skeleton of Huperzine A and the appropriate functional groups. Recently, Kozikowski et al.[3] have published also the synthesis of several analogues of this alkaloid modified at the heterocyclic moiety. In one of these papers[3c], they described a low yield preparation of ketoester **4**, as a key intermediate. This fact, prompted us to publish our improved results about the synthesis of this ketoester, based on the knowledge of the relative configuration of its precursors.

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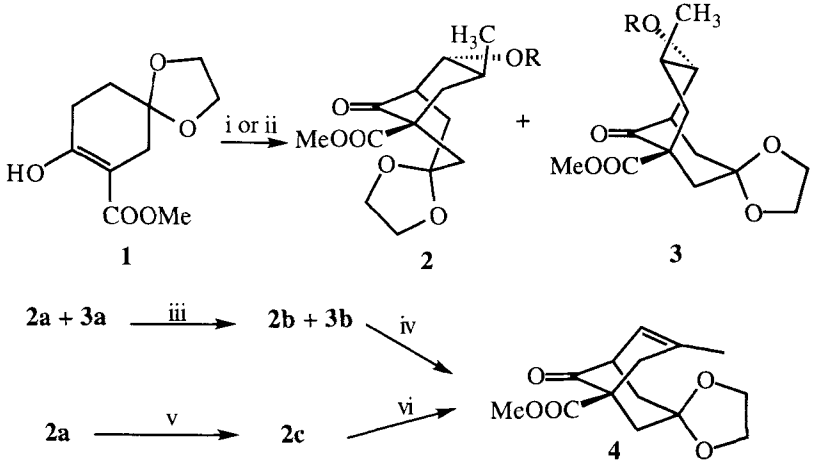

2a, **3a**, R = H; **2b**, **3b**, R = Ms; **2c**, R = C(S)O-C_6H_4-*p*-CH_3

i) methacrolein, TMG, CH_2Cl_2; ii) methacrolein, DBU, acetonitrile; iii) MsCl, Et_3N, DMAP, CH_2Cl_2; iv) DBU, toluene, 160 °C, closed reactor; v) *p*-CH_3-C_6H_4-OC(S)Cl, pyridine; vi) Δ.

Scheme

The described synthesis of ketoester **4** starts from cyclohexane-1,4-dione monoethylene acetal, which was transformed into ketoester **1**. Reaction of **1** with methacrolein catalysed by 1,1,3,3-tetramethylguanidine (TMG) gave a diastereomeric mixture of bicyclic alcohols which was dehydrated by mesylation followed by treatment with 2,4,6-collidine. However, the last step of this synthesis takes place in very low yield (32%) which reduces the global yield of **4** to 25%.

Our synthesis of ketoester **4** (Scheme) starts from the known compound **1**[4], which was prepared in a similar way to that recently described by Kozikowski et al.[3c]. This on reaction with methacrolein under TMG catalysis gave a mixture containing mainly the diastereomeric bicyclic alcohols **2a** and **3a** which could not be separated by column chromatography. Reaction of the above mixture with methanesulfonyl chloride gave a mixture containing the corresponding mesylates **2b** and **3b**, from which pure samples of both compounds were obtained by crystallization from ethyl acetate. The total yield of **2b** and **3b** from **1** was 53%

(30% of **2b** and 23% of **3b**). In contrast, condensation of **1** with methacrolein in the presence of an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[5] gave a product which, after mesylation, afforded essentially pure mesylate **2b**, the presence of **3b** being not observed. The IR, ^{1}H and ^{13}C NMR data of **2b** and **3b** coincide with those described by Kozikowski et al.[3c] for the more and less polar mesylates, respectively, although the melting point observed for **3b** (136-138°C) is slightly greater than that described (128°C). All attempts to transform these mesylates into ketoester **4** gave poor results, the best one (35% yield) was obtained in the reaction of pure **2b** with DBU in toluene at 160 °C in a sealed reactor. This yield is very similar to that described by Kozikowski et al.[3c] for the mixture of mesylates.

X-Ray diffraction analysis of mesylates **2b** and **3b** allowed us to know not only their configuration but also their conformation in the solid state (Figures 1 and 2 and Table 3). In both cases, the mesyloxy and methyl substituents are in a *trans* arrangement and the conformation of the bicyclo[3.3.1]nonane skeleton is *boat-chair*. In compound **2b** the methyl-substituted cyclohexanone ring adopts a *chair* conformation with *equatorial* methyl and mesyloxy substitutents, while the other cyclohexanone ring adopts a *boat* conformation in order to minimize the steric interaction[6]. In contrast, in compound **3b** the methyl-substituted cyclohexanone ring adopts a *boat* conformation with *equatorial* methyl and mesyloxy substitutents, while the other cyclohexanone ring adopts a *chair* conformation since, in this case, no steric interaction between the *endo*-substituents at C3 and C7 can take place.

The configuration of mesylates **2b** and **3b** can explain the low yield of their base-induced eliminations to ketoester **4** since in both cases the 7-H atom and the mesyloxy group cannot adopt a *trans-diaxial* relationship, because they are in a *cis* arrangement. Consequently, a pyrolytic *syn*-elimination reaction would be the method of choice to carry out the dehydration of alcohols **2a** and **3a**.

In practice, the product derived from the reaction of **1** with methacrolein under DBU catalysis containing mainly alcohol **2a** was reacted with O-(*p*-tolyl) chlorothionoformate[7] affording the corresponding thiocarbonate **2c**, which on heating at 250 °C / 0.6 Torr gave a distillate from which pure **4** was isolated after column chromatography in 40% overall yield from **1**. Although the yield of this transformation is medium it is clearly superior to that described[3c] via mesylates **2b** and **3b**.

The 500 MHz ^{1}H and 50.3 MHz ^{13}C NMR spectra of these compounds were fully assigned on the basis of COSY $^{1}H/^{1}H$ and $^{1}H/^{13}C$ experiments (For the

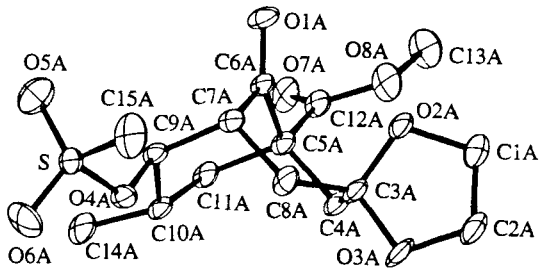

Figure 1. Perspective drawing (ORTEP) of **2b**.

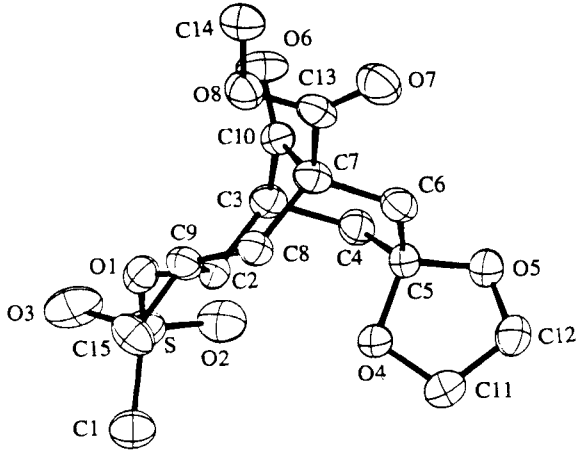

Figure 2. Perspective drawing (ORTEP) of **3b**.

^{1}H NMR chemical shifts and coupling constant values, see Table 1; for the ^{13}C NMR chemical shifts see Table 2). The observed coupling constant values show the conformation of **2b** and **3b** in $CDCl_3$ to be the same found in the solid state. Also, as expected, the preferred conformation of **2c** seems to be the same kind of *boat-chair* as for **2b**. The value of $J_{4\text{-}Hexo,5\text{-}H}$ = 10.5 Hz in compounds **2b** and **2c** is indicative of a *boat* conformation for their ethylenedioxy-substituted rings[8].

Work is in progress to transform ketoester **4** into Huperzine A analogues modified at the heterocyclic moiety.

Table 1. ^{1}H-NMR data of the compounds **2-4**.

	2b	**2c**	**3b**	**4**[a]
2-H$_{endo}$	2.14	2.20	2.09	2.13
J$_{2\text{-}H_{endo},2\text{-}H_{exo}}$	14.0	14.5	14.5	14.5
J$_{2\text{-}H_{endo},4\text{-}H_{endo}}$			4.0	3.5
2-H$_{exo}$	2.87	2.90	2.61	2.70
J$_{2\text{-}H_{exo},4\text{-}H_{exo}}$	3.5	3.5		
4-H$_{endo}$	2.52	2.55	2.50	2.05
J$_{4\text{-}H_{endo},4\text{-}H_{exo}}$	14.0	14.5	14.5	13.5
J$_{4\text{-}H_{endo},5\text{-}H}$	3.0	3.0	2.5	2.0
4-H$_{exo}$	2.15	2.11	2.15	2.19
J$_{4\text{-}H_{exo},5\text{-}H}$	10.5	10.5	5.0	6.0
5-H	3.25	3.38	2.80	2.77
J$_{5\text{-}H,6\text{-}H}$	5.0	5.0	1.5	6.0
6-H	4.38	5.14	5.18	5.32
J$_{6\text{-}H,7\text{-}H}$	10.5	10.5	11.0	
7-H	2.47	2.64	1.67	
J$_{7\text{-}H,8\text{-}H_{endo}}$	5.0		14.0	
J$_{7\text{-}H,8\text{-}H_{exo}}$	13.0		6.0	
J$_{7\text{-}H,7\text{-}CH_3}$	6.0	6.5	6.0	
8-H$_{endo}$	1.97	1.97	2.34	2.56
J$_{8\text{-}H_{endo},8\text{-}H_{exo}}$	14.0		14.0	17.5
8-H$_{exo}$	1.88	1.97	2.52	3.23
O-CH$_2$CH$_2$O-	3.92-4.07	3.90-4.10	3.86, 4.09	3.80, 3.96
O-C$_6$H$_4$C*H*$_3$		2.35		
7-CH$_3$	1.16	1.15	1.11	1.68
CH$_3$SO$_3$	3.01		3.02	
Ar-2(6)-H		6.94		
J$_{2\text{-}H,3\text{-}H}$		8.5		
Ar-3(5)-H		7.18		
COOCH$_3$	3.77	3.78	3.75	3.74

[a] In order to compare these data, compound **4** has been numbered in the same manner used for the rest compounds.

Experimental

Melting points were determined on a Gallenkamp melting-point apparatus, model MFB 595010M. IR spectra were recorded on a FT/IR Perkin-Elmer spectrometer, model 1600. ^{1}H and ^{13}C NMR spectra were taken on Varian VXR 500 and Gemini 200 spectrometers, respectively, always in $CDCl_3$ as solvent. The chemical shifts are given in ppm (δ scale) relative to internal TMS. COSY ^{1}H/^{1}H experiments were performed using standard procedures while COSY ^{1}H/^{13}C were performed using the HMQC sequence with an indirect detection probe. Coupling constants are expressed in Hertz. Mycroanalyses were carried out at the Microanalysis Service of the Centro de Investigación y Desarrollo, CID, Barcelona, Spain.

Table 2. ^{13}C-NMR chemical shifts of compounds **2-4**.

	2b	**2c**[a]	**3b**	**4**[b]
C1	56.4	56.7	55.7	55.9
C2	40.9	41.0	44.2	44.3
C3	104.5	104.7	106.4	106.1
C4	34.4	34.6	39.8	40.8
C5	49.2	46.6	52.7	44.3
C6	85.2	87.6	84.5	121.1
C7	28.6	28.5	32.6	135.3
C8	39.1	39.4	33.8	43.2
C9	205.0	205.4	208.5	209.4
O-CH_2CH_2O-	64.4	64.4	63.5	63.0
	65.4	65.3	64.9	64.8
7-CH_3	17.0	16.9	17.7	22.0
CH_3SO_3	38.6		38.3	
$COOCH_3$	52.8	52.8	52.7	52.3
***C*$OOCH_3$**	171.5	171.7	171.8	171.4

[a] Other absorptions: 151.0 (Ar-C1), 121.3 [Ar-C2(6)], 130.7, [Ar-C3(5)], 136.4 (Ar-C4), 20.9 (Ar-CH_3), 193.8 (CS). [b]See caption [a] of Table 1.

Methyl 3,3-Ethylenedioxy-*endo*-6-(methanesulfonyloxy)-*exo*-7-methyl-9-oxobicyclo[3.3.1]nonane-1-carboxylate 2b and Methyl 3,3-Ethylenedioxy-*exo*-6-(methanesulfonyloxy)-*endo*-7-methyl-9-oxobicyclo[3.3.1]nonane-1-carboxylate 3b: A solution of methacrolein (6.25 g, 89.3 mmol) in anhydrous CH_2Cl_2 (25 ml) was added dropwise to a cooled (-78 °C) solution of compound **1** (5.00 g, 23.4 mmol) and TMG (0.52 g, 4.52 mmol) in anhydrous CH_2Cl_2 (125 ml). The solution was stirred at this temp. for 30 min and then, it was allowed to warm to room temp. and stirring was continued for 2 more hours. The solvent was removed in vacuo and the brown residue (7.45 g) was chromatographed (100 g silica gel, using a mixture of ethyl acetate / methanol in the ratio of 9:1 as eluent) affording a colourless gelatinous product (6.77 g) consisting mainly of alcohols **2a** and **3a**, which was used as such in the next step.

Methanesulfonyl chloride (7.30 ml, 94.0 mmol) was added dropwise with magnetic stirring to a solution of the above product (6.75 g, *ca.* 23.0 mmol), triethylamine (33.2 ml, 240 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (70 mg) in anhydrous CH_2Cl_2 (170 ml) and the mixture was stirred at room temp. for 6 h. The mixture was diluted with CH_2Cl_2 (150 ml), washed with saturated aqueous solution of NH_4Cl (4 x 150 ml) until the aqueous phase remained at pH 5-6. After drying with Na_2SO_4, the solution was concentrated in vacuo to give a brown

Table 3. Experimental data of the X-ray crystal structure determination of mesylates **2b** and **3b**

Compound	**2b**	**3b**
Molecular formula	$C_{15}H_{22}O_8S$	$C_{15}H_{22}O_8S$
Molecular mass	362.39	362.39
Crystal system	triclinic	orthorhombic
Space grup	$P\bar{1}$	$Pbn2_1$
Cell parameters[a]		
a [Å]	18.091	15.787(3)
b [Å]	11.077	14.533(3)
c [Å]	8.927	7.436(2)
α [°]	109.77	90
β [°]	90.52	90
γ [°]	87.50	90
V [Å^3]	1681.8	1706.1(7)
Z	4	4
F(000)	768	768
d(calcd) [Mg m^{-3}]	1.431	1.411
Size of crystal [mm]	0.1 x 0.1 x 0.2	0.4 x 0.4 x 0.8
Measured reflections	9869	1580
Independent reflections	9869	1580
Observed reflections	6528	1242
μ(Mo-*K*α) [mm^{-1}][b]	0.233	0.229
R	0.033	0.048
*R*w	0.083	0.120
Diff. Four. $\Delta\rho_{max}$[c]	0.293	0.3
$\Delta\rho_{min}$[d]	-0.323	-0.2
Refined parameters	435	227
Max. shift / e.s.d.	15.0	0.1

[a] Determined by automatic centering of 25 reflections ($8 \leq \theta \leq 12°$). [b] μ(Mo-*K*α), Linear absorption coefficient. Radiation Mo-*K*α (λ = 0.71069Å). [c] Maximum and [d] minimum peaks in final difference synthesis.

gummy residue (8.0 g), which on crystallization from ethyl acetate (15 ml) gave a yellowish solid (3.63 g), mixture of **2b** and **3b** in a ratio of *ca.* 2:1 (^{13}C-NMR). Concentration of the mother liquors to about 4 ml gave more solid (0.80 g) mixture of **2b** and **3b** in the approximate ratio of 1:6. Global yield of **2b** and **3b** from **1**(4.43 g, 53%), which corresponds to *ca.* 30% of the more polar mesylate **2b** and 23% of the less polar mesylate **3b**. One recrystallization of both solids from ethyl acetate gave the analytical samples of mesylates **2b** and **3b**, respectively. The more

polar mesylate **2b** showed m.p. 177-179 °C (described[3c] 177-179 °C) and the less polar mesylate **3b**, m.p. 136-138 °C (described[3c] 128 °C).

Methyl 7,7-Ethylenedioxy-3-methyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylate 4 and Methyl 3,3-Ethylenedioxy-*exo*-7-methyl-9-oxo-*endo*-6-(*p*-tolyloxythiocarbonyloxy)bicyclo[3.3.1]nonane-1-carboxylate 2c: A solution of methacrolein (34.2 g, 488 mmol) in anhydrous acetonitrile (220 ml) was added dropwise to a stirred solution of **1** (27.5 g, 128 mmol) and DBU (21.5 g, 141 mmol) in anhydrous acetonitrile (500 ml) and the solution was stirred at room temp. for 30 min. The solvent was removed in vacuo to give a reddish residue (58.0 g) which was flash-chromatographed [silica gel 40-60 μm (20 x 8 cm) using a mixture of ethyl acetate / hexane in the ratio of 9:1 as eluent], affording a colourless gelatinous residue (37.7 g) containing mainly alcohol **2a** as it was established by conversion of a sample into the corresponding mesylate as described before.

Part of the above product (36.0 g, ca. 127 mmol) was dissolved in anhydrous pyridine (234 ml), the solution was cooled in an ice-bath and O-(*p*-tolyl) chlorothionoformate (23.0 ml, 149 mmol) was added slowly with stirring. The reddish solution was stirred at room temp. for 3 h, and then, poured onto cold water (700 ml) and the mixture extracted with benzene (4 x 200 ml). The combined organic extracts were washed with aqueous 5% HCl until the aqueous phase remained acidic and then with water (2 x 200 ml) and brine (1 x 200 ml). The dried (Na_2SO_4) solution was concentrated in vacuo affording a dark brown gelatinous residue consisting mainly of thiocarbonate **2c**.

Most of the above residue was pyrolyzed in a rotary microdistillation apparatus at 250 °C / 0.7 Torr to give a yellow oil (27.2 g) consisting mainly of ketoester **4**, *p*-cresol and O,O-bis-(*p*-tolyl) thiocarbonate (^{1}H NMR). This oil was dissolved in CH_2Cl_2 (250 ml), the solution was washed with aqueous solution of 2 N NaOH (3 x 100 ml), dried with Na_2SO_4, and concentrated in vacuo to give a yellow oil consisting of ketoester **4** and O,O-bis-(*p*-tolyl) thiocarbonate (^{1}H NMR). After flash column chromatography [silica gel 40-60 μm (20 x 8 cm column) using a mixture of ethyl acetate / hexane in the ratio of 2:8 as eluent], pure **4** (12.9 g, 40% global yield from **1**) was obtained as a colorless oil, b.p. 190-200 °C / 0.7 Torr.

An analytical sample of **2c** could be obtained after crystallization followed by three recrystallizations of the crude thiocarbonate from ethyl acetate, m.p. 157-159 °C. IR (KBr) ν: 1736 and 1720 (CO st), 1249, 1240 (C=S st).

$C_{22}H_{26}O_7S$ (434.5) Calcd. C 60.81 H 6.04 S 7.38
Found C 60.95 H 6.11 S 7.23

X-ray Crystal-Structure Determinations of **2b** *and* **3b** (Table 3): A prismatic crystal was selected and mounted on a Philips PW-1100 four-circle diffractometer. Unit cell parameters were determined by automatic centering of 25 reflections and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-$K\alpha$ radiation, using w/2θ scan technique. Reflections were measured in the range $2.21 \leq \theta \leq 30.19$ for **2b**, and $3.81 \leq \theta \leq 29.99$ for **3b**, and were assumed as observed by applying the condition $I \geq 2\ \sigma\ (I)$. Three reflections were measured every two hours as orientation and intensity control; significant intensity decay was not observed. Lorentz polarization and extinction but no absorption corrections were made for **2b** and **3b**. The structure was solved by Direct methods using the SHELXS computer program[9] and refined by the full-matrix least-squares method with the SHELX-95 computer program[10]. The function minimized was $\Sigma\ w\ [|F_o|^2 - |F_c|^2]^2$, where $w = [\sigma^2(I) + (0.0627\ P)^2 + 0.0000\ P]^{-1}$ for **2b** and $w = [\sigma^2(I) + (0.1254\ P)^2 + 2.1781\ P]^{-1}$ for **3b**, being $P = (|F_o|^2 + 2|F_c|^2) / 3$ in both cases. f, f' and f'' were taken from International Tables of X-ray Crystallography[11]. The extinction coefficient was 0.026(12) for **2b** and 0.000 for **3b**. A carbon atom of **3b** was located in disordered position, an occupancy factor of 0.5 was assigned according to maximum of Fourier synthesis. The positions of all hydrogen atoms were computed and refined with an overall isotropic temperature factor by using a riding model.

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