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(±)-*anti*-7-Ethyl-1-(4-methoxyphenyl)-5,5,*syn*-8-trimethyl-2-oxabicyclo[2.2.2]-octan-3-one, a bicyclic δ-lactone

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Key indicators

Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.003 Å
R factor = 0.041
wR factor = 0.129
Data-to-parameter ratio = 15.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title bicyclic δ-lactone, $C_{19}H_{26}O_3$, (I), was formed in the reaction of (±)-*cis*-2,6,6-trimethyl-*trans*-3-ethyl-4-oxocyclohexanecarboxylic acid with *p*-methoxyphenylmagnesium bromide, following acidification. The kinetically favored (I) was formed rapidly but reversibly, allowing the thermodynamically favored γ-lactone to be formed and isolated after a longer treatment with acid. The expected corresponding carboxylic acids were not isolable under these conditions. In lactone (I), basically composed of an aromatic ring appended to a [2.2.2] bicyclic system, the O—C(O)—C group is asymmetric, its O—C═O angle being 119.46 (19)° and its O═C—C angle being 127.82 (19)°.

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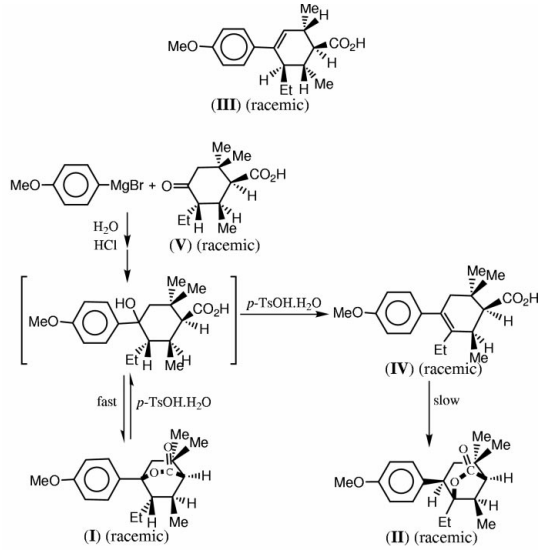
Lactone precursors of prostate therapy agents. I.

Comment

We recently reported the preparation, isolation and unequivocal diastereomer identification of (1*RS*,2*RS*,5*SR*,6*SR*)-2,6-dimethyl-4-(4-methoxyphenyl)-5-ethyl-3-cyclohexene-1-carboxylic acid, (III), and noted that a preliminary study indicated that it definitely inhibits prostate cancer-cell proliferation (Xie *et al.*, 2002*a*).



Further study of (III) and related compounds in prostate therapy is being continued. The preparation and potent *in vivo* estrogenicity of diastereomeric carboxylic acid mixtures of (III), as well as of related (IV), were reported some time ago (Nathan & Hogg, 1956; Crenshaw *et al.*, 1972, 1973, 1974; Dvolaitzky *et al.*, 1974; Fouquey *et al.*, 1975, 1976, 1978). However, single diastereomers and enantiomers apparently were neither isolated nor unequivocally characterized (nor were their estrogen-receptor binding affinities studied; *cf.* Meyers *et al.*, 1988); consequently, the observed biological

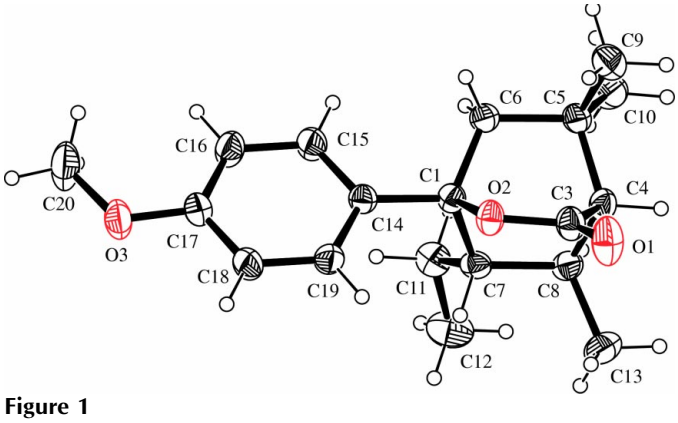


Figure 1
The molecular structure and atom-numbering scheme for (I), with displacement ellipsoids at the 30% probability level.

activities could not be associated with any one absolute structure. Based on our unequivocal characterization of the single diastereomer (III) and our study showing its potential utility in prostate therapy, we decided to prepare and unequivocally characterize diastereomer (IV) and study its biological activity. In this way, we hoped to relate such activity with distereomeric structure.

Having prepared and characterized the required starting material (V) (Xie *et al.*, 2002*b*), we proceeded to convert it into (IV) in a manner similar to our synthesis of (III) (Xie *et al.*, 2002*a*). However, instead of obtaining the expected carboxylic acid, (IV), we obtained the corresponding kinetically favored bicyclic δ-lactone, (I), when the reaction mixture in 3*N* HCl was worked up within several hours. On repeating the reaction but allowing the mixture to remain in the 3*N* HCl for several days before being worked up, the thermodynamically favored isomeric bicyclic γ-lactone, (II), was obtained (Xie *et al.*, 2003). These transformations are illustrated in the Scheme.

The structure and atom numbering of (I) are shown in Fig. 1. Lactone (I) is basically composed of an aromatic ring appended to a [2.2.2] bicyclic system. The O—C(O)—C group is asymmetric, its O—C═O angle being 119.46 (19)° and its O═C—C angle being 127.82 (19)°. The four atoms comprising the lactone moiety, C1/O2/C3/C4, are essentially coplanar, as evidenced by the torsion angle (Table 1), and the least-squares plane of this moiety is nearly perpendicular to the cyclohexane ring, the angle formed being 89.85 (13)°. Selected geometric parameters are presented in Table 1.

Experimental

Compound (I) was prepared by adding a solution of *p*-methoxyphenylmagnesium bromide in tetrahydrofuran (11 ml, 0.5 *M*, 5.5 mmol) dropwise over a period of 30 min to a stirred solution of keto acid (V) (0.207 g, 0.98 mmol; Xie *et al.*, 2002*b*) in tetrahydrofuran (20 ml) which was flushed with argon and maintained in an ice bath. The mixture was stirred in the ice bath for an additional 30 min, then at room temperature for 2 h, and finally under reflux for 30 min. It was acidified with 3*N* HCl and extracted with ether. The extracts were dried and concentrated *in vacuo* to a brown pasty solid, to which benzene (5 ml) and *p*-TsOH·H_2O (0.07 g) were added, and the solution was refluxed for 2 h. The benzene was then removed by evaporation, water was added and the mixture was extracted with ether. Evaporation of the extracts and purification of the residue chromatographically provided a major fraction which crystallized on removal of the solvent; pure (I), m.p. 388–388.8 K (recrystallized, CH_2Cl_2-hexane). This fraction was the most polar, indicating the absence of a carboxylic acid, *e.g.* (IV). IR (neat): 1753 cm^{-1}; NMR ($CDCl_3$), ^1H (300 MHz): δ 0.82 (*t, J* = 7.2 Hz, 3H), 1.10 (*m, J* = 7.2 Hz, 2H), 1.12 (*s*, 3H), 1.15 (*d, J* = 6.6 Hz, 3H), 1.23 (*s*, 3H), 1.35 (*m, J* = 6.3 Hz, 1H), 1.82 (*dd, J* = 13.8 Hz, 1.8 Hz, 1H), 2.08 (*m, J* = 7.2 Hz, 1H), 2.13 (*d, J* = 1.8 Hz, 1H), 2.19 (*d, J* = 13.8 Hz, 1H), 3.81 (*s*, 3H), 6.88 (*d, J* = 8.7 Hz, 2H), 7.29 (*d, J* = 9.0 Hz, 2H); ^{13}C (75 MHz): δ 12.39, 22.85, 24.65, 27.53, 32.02, 32.12, 32.23, 38.80, 53.50, 55.25, 55.83, 88.05, 113.42, 127.13, 133.31 (2C), 159.12 (2C), 175.89.

Crystal data

$C_{19}H_{26}O_3$	D_x = 1.155 Mg m^{-3}
M_r = 302.40	Mo Kα radiation
Monoclinic, *C*2/*c*	Cell parameters from 25 reflections
a = 32.326 (4) Å	θ = 16.1–19.3°
b = 7.1937 (12) Å	μ = 0.08 mm^{-1}
c = 15.4134 (19) Å	*T* = 296 K
β = 104.022 (9)°	Irregular fragment, colorless
V = 3477.5 (9) $Å^3$	0.49 × 0.33 × 0.27 mm
Z = 8	

Data collection

Rigaku AFC-5*S* diffractometer	θ_{max} = 25.1°
ω scans	*h* = 0 → 38
Absorption correction: none	*k* = 0 → 8
3156 measured reflections	*l* = −18 → 17
3098 independent reflections	3 standard reflections
1775 reflections with $I > 2\sigma(I)$	every 100 reflections
R_{int} = 0.012	intensity decay: 0.3%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0578P)^2 + 1.278P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.041	
$wR(F^2)$ = 0.129	
S = 1.02	$(\Delta/\sigma)_{max}$ = 0.001
3098 reflections	$\Delta\rho_{max}$ = 0.13 e $Å^{-3}$
204 parameters	$\Delta\rho_{min}$ = −0.19 e $Å^{-3}$
H-atom parameters constrained	

Table 1
Selected geometric parameters (°).

O1—C3—C4	127.82 (19)	C3—O2—C1	114.24 (14)
O2—C3—C4	112.70 (18)		
C1—O2—C3—C4	2.8 (2)	C6—C1—C14—C15	23.4 (3)
C6—C1—C14—C19	−161.08 (19)		

The rotational orientations of the methyl H atoms were refined by the circular Fourier method available in *SHELXL*97 (Sheldrick, 1997). All H atoms were refined as riding, with C—H distances ranging from 0.93 to 0.98 Å.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1996); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *PROCESS* in *TEXSAN* (Molecular Structure Corporation, 1997); program(s) used to solve structure: *SIR*92 (Burla *et al.*, 1989); program(s) used to refine structure: *LS* in *TEXSAN* and *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *TEXSAN, SHELXL*97 and *PLATON* (Spek, 2000).

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