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2(*S*),6(*R*)-Dimethyl-4-(4-methoxyphenyl)-5(*R*)-ethyl-3-cyclohexene-1(*S*)-carboxylic acid and its enantiomer: potential therapeutic agents for prostate cancer

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Key indicators

Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.004 Å
R factor = 0.041
wR factor = 0.134
Data-to-parameter ratio = 14.6

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

The synthesis, isolation, and definitive diasteriomeric characterization of the racemic title compound, $C_{18}H_{24}O_3$, (I), was accomplished. The two enantiomers are hydrogen bonded through their respective carboxylic acid groups, forming an octagonal bridge. A preliminary study indicates that (I) definitely inhibits prostate cancer-cell proliferation.

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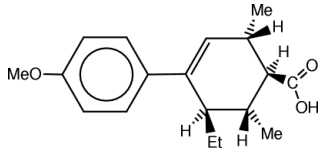
This paper is dedicated to Dr James W. Neckers on the occasion of his 100th birthday.

Comment

In the reported synthesis of (I) by Crenshaw *et al.* (1974), a multitude of isomeric compounds was concurrently formed. Compound (I), with four different asymmetric centers, has eight different diastereomeric isomers, each possessing two enantiomers. Moreover, the synthesis employed also produces related compounds whose double bond is shifted from that in (I), producing three different asymmetric centers, which further increases the number of possible diastereomeric and enantiomeric isomers formed. The Crenshaw group employed a mixture of such isomers in their study of *in vivo* estrogenic activity, thereby leaving unsolved the important question of which compound, diastereomer, and corresponding enantiomer was responsible for the observed activity. Moreover, without doing binding studies, they assumed that these compounds would exhibit correspondingly high estrogen-receptor affinity. However, some years prior to the Crenshaw group's publication, early mouse studies by Terenius (1967, 1968) suggested that 3-methoxy-substituted carboxylic acids, like (−)-3-MeO-bisdehydrodoisynolic and (−)-3-MeO-allenolic acids, exhibit significant *in vivo* estrogenic activity but bind poorly to ER receptors; the corresponding 3-OH acids likewise exhibited high *in vivo* estrogenicity, but showed relatively less reduction in their receptor-binding affinity. Our more recent studies with those carboxylic acids confirmed that dichotomy between *in vivo* activity and binding affinity, although we found a substantially greater differential than did Terenius between the *in vivo* and binding activities of the 3-OH compounds (Meyers *et al.*, 1988, 1997, 2002; Soto *et al.*, 1988; Banz *et al.*, 1998).



(I)

We have now successfully carried out a total synthesis and isolation of racemic (I), affording for the first time the unequivocal characterization of a single diastereomer from the mixture and a study of the biological activity of that diastereomer. We previously reported preparing and char-

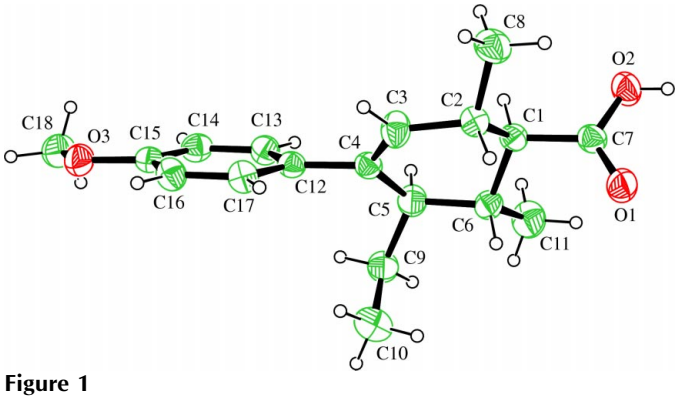


Figure 1
The molecular structure and atom numbering scheme for (I), with displacement ellipsoids at the 30% probablilty level.

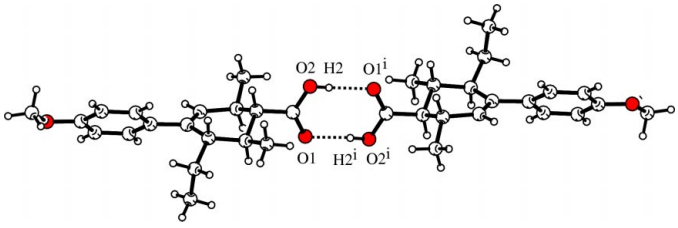


Figure 2
Dimer formation through hydrogen bonding in (I) [symmetry code: (i) $1-x, 1-y, 2-z$].

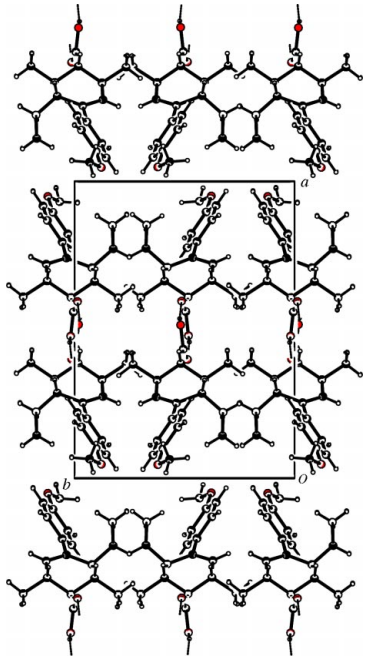


Figure 3
A *c*-axis projection of the molecular packing in (I), showing the layers of dimers.

acterizing only the non-aromatic moiety of a compound related to (I) (Xie *et al.*, 2002). Our preliminary study indicates that racemic (I) definitely inhibits prostate cancer-cell proliferation.

The structure and atom numbering of one enantiomer of (I) are shown in Fig. 1. It is unequivocally 2(*S*),6(*R*)-dimethyl-4-(4-methoxyphenyl)-5(*R*)-ethyl-3-cyclohexene-1(*S*)-carboxylic acid. Fig. 2 shows the two enantiomers of (I) hydrogen bonded with each other *via* their respective carboxyl OH and C=O groups, forming an eight-membered ring. The hydrogen-bond geometry is given in Table 1. The overall packing (Fig. 3) shows layers of these hydrogen-bonded enantiomeric pairs.

Experimental

Compound (I) was synthesized following the general method reported by Crenshaw *et al.* (1974). The intermediates and products were separated from the mixture of formed compounds by column chromatography and recrystallizations. Isolated (I) was recrystallized twice from hexane–ethyl acetate; colorless crystals, m.p. 462–463 K; IR (neat, cm^{-1}): 3420, 2960, 1698; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (*d*, J = 8.7 Hz, 2H), 6.52 (*d*, J = 9.0 Hz, 2H), 5.61 (*s*, 1H), 3.81 (*s*, 3H), 2.50 (*m*, 2H), 2.00 (*m*, 2H), 1.51 (*m*, 2H), 1.12 (*d*, J = 6.0 Hz, 3H), 1.07 (*d*, J = 7.2 Hz, 3H), 0.59 (*t*, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.90, 158.42, 139.80, 134.53, 131.27, 127.41 (2 C), 113.52 (2 C), 55.34, 55.24, 43.70, 33.95, 33.67, 21.44, 20.16, 18.47, 7.70.

Crystal data

$C_{18}H_{24}O_3$
M_r = 288.37
Monoclinic, $P2_1/c$
a = 15.789 (4) Å
b = 11.680 (5) Å
c = 8.7260 (13) Å
β = 92.296 (16)°
V = 1607.9 (8) Å^3
Z = 4
D_x = 1.191 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 7.8–12.4°
μ = 0.08 mm^{-1}
T = 296 K
Plate, colorless
0.49 × 0.40 × 0.07 mm

Data collection

Rigaku AFC-5*S* diffractometer
ω scans
3052 measured reflections
2846 independent reflections
1176 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 25.0°
$h = -18 \rightarrow 18$
$k = -13 \rightarrow 0$
$l = 0 \rightarrow 10$
3 standard reflections
every 100 reflections
intensity decay: 0.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.134
S = 0.98
2846 reflections
195 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.05P)^2 + 0.1653P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O1^{i}	0.82	1.87	2.679 (3)	171

Symmetry code: (i) $1-x, 1-y, 2-z$.

The rotational orientations of the methyl and hydroxyl groups were determined by the circular Fourier refinement method available in *SHELXL*97 (Sheldrick, 1997). All H atoms were treated as riding, with an O—H distance of 0.83 Å and C—H distances in the range 0.93–0.98 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 *for Windows* (Farrugia, 1997) and *PLATON* (Spek, 2000); software used to prepare material for publication: *TEXSAN, SHELXL*97 and *PLATON*.

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