

# Enantioselective total synthesis of polyoxygenated cyclohexanoids: (+)-streptol, *ent*-RKTS-33 and putative '(+)-parasitenone'. Identity of parasitenone with (+)-epoxydon

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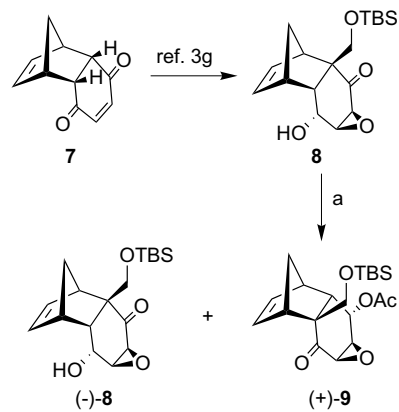
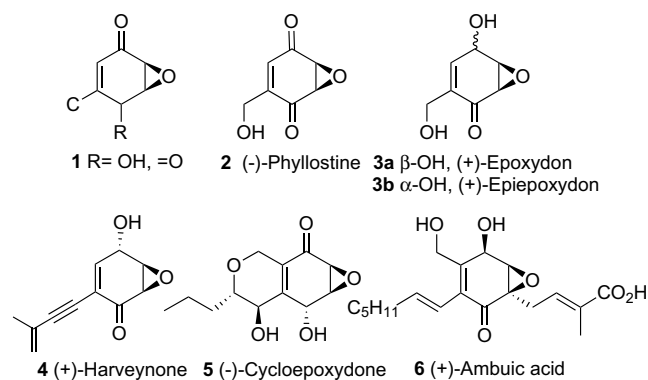
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**Abstract**—Short, simple and enantioselective syntheses of the natural product (+)-streptol, the non-peptide apoptosis inhibitor *ent*-RKTS-33 and the putative structure of 'parasitenone' have been accomplished from the readily available chiral building block. 'Parasitenone' has been shown to be identical with the known natural product epoxydon.

Polyketide natural products, based on the epoxyquinone motif **1**, and exhibiting a wide-ranging biological profile ranging from phytotoxic, anti-fungal, anti-bacterial, anti-tumour and enzyme inhibitory activity, have surfaced regularly from diverse natural sources.<sup>1</sup> The variegated substitution and polyoxygenation pattern displayed by these natural products is amply demonstrated in cyclohexanoid natural products like (–)-phyllostine **2**,<sup>1a</sup> (+)-epoxydon **3a**,<sup>1b</sup> (+)-epiepoxydon **3b**,<sup>1c</sup> (+)-harveynone **4**,<sup>1d</sup> (–)-cycloepoxydon **5**<sup>1e</sup> and (+)-ambuic acid **6**<sup>1f</sup> to name a few. These and related polyoxygenated cyclohexanoid natural products have attracted synthetic interest from several research groups and

many innovative strategies have been devised towards their synthesis.<sup>2</sup> Our group has also been drawn to this arena and we have delineated a simple, general approach to this class of natural products from the readily available Diels–Alder adduct **7** of cyclopentadiene and *p*-benzoquinone (Scheme 1).<sup>3</sup> Recently, an enantioselective version, based on a kinetic enzymatic resolution of intermediate **8**, has also been developed and provided a convenient access to the enantiomerically enriched building blocks (+)-**9** and (–)-**8** (Scheme 1).<sup>3g</sup>

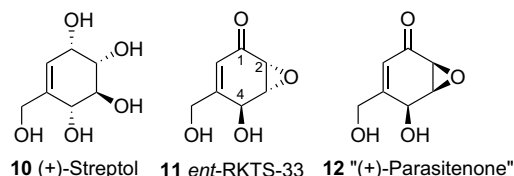
In this letter, we describe the elaboration of the chiral precursor (+)-**9** to the natural product (+)-streptol **10**,



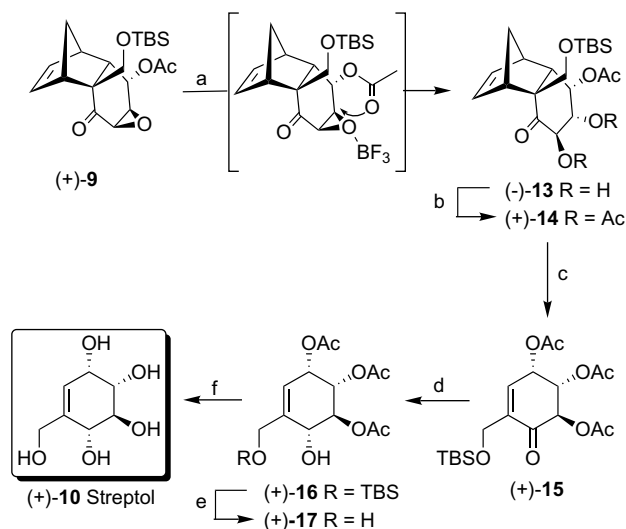
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**Scheme 1.** Reagents and conditions: (a) Lipase PS-D (Amano), vinyl acetate, rt, 28 h, (+)-**9**, 46%, ~99% ee, (–)-**8**, 45%, ~99% ee.

*ent*-RKTS-33 **11** and the putative structure of the recently isolated natural product '(+)-parasitenone' **12**.



(+)-Streptol **10** (also known as valienol) was isolated from a culture of an unidentified *Streptomyces* sp. by Sakuda et al. and shown to inhibit the growth of lettuce seedlings at a concentration above 13 ppm.<sup>4</sup> To date, two syntheses of racemic **10** by Suami et al.<sup>5a</sup> and Block et al.<sup>5b</sup> and of *ent*-**10** by Müller et al.<sup>5c</sup> have been reported. Our synthetic approach to the natural enantiomer (+)-**10** emanated from the chiral tricyclic acetate (+)-**9**, which was subjected to BF<sub>3</sub>·Et<sub>2</sub>O mediated and acetate-assisted regioselective cleavage of the epoxide ring to furnish the *trans*-diol (–)-**13** (Scheme 2).<sup>6,7</sup> The *trans*-diol moiety in (–)-**13** was protected as the diacetate, (+)-**14**. Thermal activation of the tricyclic adduct (+)-**14** induced a facile retro-Diels–Alder reaction, with the elimination of cyclopentadiene, to deliver the enone (+)-**15**. Reduction of the carbonyl functionality in (+)-**15** under Luche conditions<sup>8</sup> was stereoselective and furnished the *endo*-alcohol (+)-**16**.<sup>7</sup> TBS deprotection in (+)-**16** gave (+)-**17** and acetate hydrolysis furnished the natural product, streptol (+)-**10** [ $\alpha_D^{25}$  +91.8 (*c* 0.25, H<sub>2</sub>O); lit.<sup>5c</sup> synthetic *ent*-**10** [ $\alpha_D^{25}$  –92.5 (*c* 0.2, H<sub>2</sub>O)]. The spectral data of our synthetic compound were found to be identical in all respects with those reported for the natural product.<sup>4,7</sup>

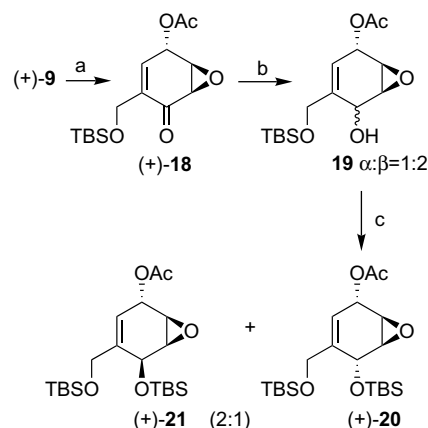


**Scheme 2.** Reagents and conditions: (a) BF<sub>3</sub>·Et<sub>2</sub>O, toluene, 0 °C, 1 h, 62%; (b) Ac<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 2 h, quant.; (c) Ph<sub>2</sub>O, 230 °C, 15 min, 91%; (d) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 0 °C, 80%; (e) 40% HF, pyridine, THF, 0 °C, 83%; (f) NaOMe, MeOH, 96%.

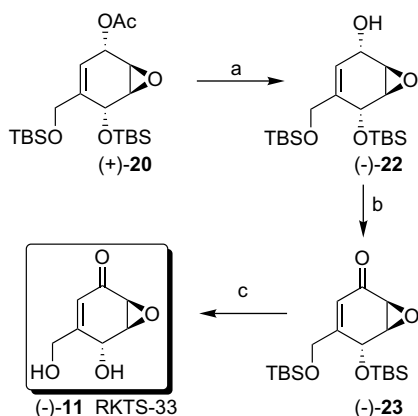
At this juncture, we were drawn to the literature reports dealing with two epimeric polyoxygenated epoxyquinoids. The first one, by Kakeya et al. in 2003, described RKTS-33 *ent*-**11** as a novel non-peptide inhibitor of death-receptor mediated apoptosis.<sup>9</sup> The other report in 2002 by Son et al., recorded the isolation of a new natural product, parasitenone (+)-**12** from the marine algicolous fungus *Apergillus parasiticus* with promising free radical scavenging activity.<sup>10</sup> Interestingly, the two compounds RKTS-33 *ent*-**11** and (+)-parasitenone **12** were found to be epimeric at C4, belonged to opposite enantiomeric series and exhibited very different biological activity. Our chiral building block (+)-**9** appeared to be well poised for elaboration to RKTS-33 **11** and (+)-**12**.

Retro-Diels–Alder reaction of the enantiomerically pure tricyclic acetate (+)-**9** furnished epoxycyclohexenone (+)-**18**,<sup>7</sup> and further 1,2-reduction gave a diastereomeric mixture of alcohols **19a,b** ( $\alpha:\beta = 1:2$ ), in which the  $\beta$ -isomer was the major product (Scheme 3). The epimeric alcohols **19a,b** were converted to their TBS ether derivatives (+)-**20**/(+)-**21**, respectively, and readily separated by column chromatography.<sup>7</sup> The acetate in the  $\alpha$ -isomer (+)-**20** was removed to give alcohol (–)-**22**, which was subsequently oxidized to the enone (–)-**23** (Scheme 4).<sup>7</sup> Finally, TBS deprotection in (–)-**23** furnished RKTS-33 (–)-**11** [ $\alpha_D^{25}$  –275.7 (*c* 0.33, C<sub>2</sub>H<sub>5</sub>OH), whose spectral data were in complete agreement with those reported by Kakeya et al.<sup>7,9</sup>

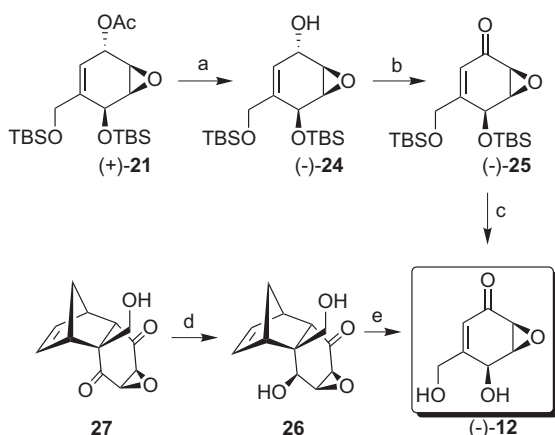
In another sequence, the major  $\beta$ -isomer (+)-**21** was subjected to acetate hydrolysis to give alcohol (–)-**24** (Scheme 5).<sup>7</sup> MnO<sub>2</sub> mediated allylic oxidation of (–)-**24** led to the enone (–)-**25**, which on TBS deprotection furnished the enone diol (–)-**12** corresponding to the structure assigned to the natural product 'parasitenone'.<sup>10</sup> However, the spectral data of our synthetic sample and those reported by Son et al. were a complete mismatch.<sup>11</sup> To confirm further, the stereochemical integrity of our synthetic sample, tricyclic *exo*-alcohol (±)-**26**, prepared by us in a different context from the



**Scheme 3.** Reagents and conditions: (a) Ph<sub>2</sub>O, 230 °C, 10 min, 93%; (b) NaBH<sub>4</sub>, MeOH, –50 °C, 5 min, 87%; (c) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, –10 °C, 83%.



**Scheme 4.** Reagents and conditions: (a) LiOH, MeOH, 0 °C, 30 min, 70%; (b) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h, 83%; (c) 40% HF, CH<sub>3</sub>CN, 0 °C to rt, 3 h, 80%.



**Scheme 5.** Reagents and conditions: (a) LiOH, MeOH, 0 °C, 30 min, 68%; (b) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h, 86%; (c) 40% HF, CH<sub>3</sub>CN, 0 °C to rt, 3 h, 80%; (d) DIBAL-H, THF, -78 °C, 65%; (e) Ph<sub>2</sub>O, 240 °C, 45 min, quant.

tricyclic diketone **27**, was subjected to thermal activation to furnish (±)-**12**, spectroscopically identical with (–)-**12** described above (Scheme 5). Since, the stereostructure of **26** was secured through single crystal X-ray structure analysis,<sup>12</sup> it reconfirmed the stereostructure of our synthetic **12**. These results clearly indicated that the assigned structure of the natural product ‘parasitenone’ was untenable.<sup>10</sup>

Consequently, the question arose as to what is ‘parasitenone’? A critical examination of the spectral data reported for ‘parasitenone’ by Son et al. with other similar epoxyquinone based natural product siblings led us to surmise that ‘parasitenone’ is in fact identical with (+)-epoxydon **3a**.<sup>1b</sup> This was confirmed through a direct spectral (<sup>1</sup>H and <sup>13</sup>C NMR) comparison between (+)-epoxydon **3a** (synthesized earlier by us)<sup>3g</sup> and ‘parasitenone’ in DMSO-*d*<sub>6</sub>.<sup>11</sup> The perfect spectral match between the two led to the inevitable conclusion that the recently isolated natural product from *Apergillus parasiticus*<sup>10</sup> is epoxydon **3a** and not ‘parasitenone’ **12**.

In short, we have utilized the readily available chiral building block (+)-**9** for the first synthesis of the naturally occurring enantiomer of streptol (+)-**10** and RKTS-33 (–)-**11**. A synthesis of the putative structure **12** assigned to the natural product ‘parasitenone’ has shown that its formulation is incorrect. The identity of the natural product ‘parasitenone’ with the known compound (+)-epoxydon **3a** has been firmly established.

## Acknowledgements

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7. All new compounds were fully characterized on the basis of IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass data. Spectral data of selected compounds: (–)-**13** [ $\alpha$ ] $_{\text{D}}^{25}$  –3.4 (*c* 2.34,  $\text{CHCl}_3$ ); IR (neat) 3466, 1742, 1713  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.27 (dd, *J* = 5.1, 2.4 Hz, 1H), 5.97 (dd, *J* = 5.1, 3.0 Hz, 1H), 5.77 (dd, *J* = 9.6, 3.9 Hz, 1H), 4.28 (d, *J* = 9 Hz, 1H), 4.05 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.81 (d, *J* = 12 Hz, 1H), 3.40 (br s, 1H), 3.33 (d, *J* = 9.3 Hz, 1H), 3.00 (s, 1H), 2.92 (dd, *J* = 9.5, 3 Hz, 1H), 2.79 (s, 1H), 2.17 (s,  $\text{CH}_3$ ), 1.52 (1/2 ABq, *J* = 8.7 Hz, 1H), 1.44 (1/2 ABq, *J* = 8.7 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), –0.01 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  214.0, 170.6, 139.7, 133.2, 74.9, 72.2, 69.3, 69.2, 62.3, 50.5, 48.3, 46.6, 46.5, 25.8, 21.2, 18.2, –5.6, –5.7; HRMS (ES) *m/z* calcd for  $\text{C}_{20}\text{H}_{32}\text{O}_6\text{SiNa}$  [ $\text{M}+\text{Na}$ ] $^+$ : 419.1866, found 419.1865; (+)-**18** [ $\alpha$ ] $_{\text{D}}^{25}$  (+)-173 (*c* 1.34,  $\text{CHCl}_3$ ); IR (neat) 1743, 1685  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.61–6.58 (m, 1H), 5.83 (d, 1H, *J* = 4.5 Hz), 4.48 (d, 1H, *J* = 16.5 Hz), 4.23 (td, 1H, *J* = 2.4, 16.1 Hz), 3.74–3.72 (m, 1H), 3.48 (dd, 1H, *J* = 0.6, 3.6 Hz), 2.13 (s, 3H), 0.93 (s, 9H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.7, 169.7, 139.0, 132.6, 64.1, 59.4, 55.2, 52.9, 25.8 (3C), 20.7, 18.3, –5.5 (2C); HRMS (ES) *m/z* calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_5\text{SiNa}$  [ $\text{M}+\text{Na}$ ] $^+$ : 335.1291, found 335.1283; (+)-**10** [ $\alpha$ ] $_{\text{D}}^{25}$  +91.8 (*c* 0.25,  $\text{H}_2\text{O}$ );  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ )  $\delta$  5.70 (d, *J* = 5.4 Hz, 1H), 4.13 (dd, *J* = 5.0 Hz, 1H), 4.09 (d, *J* = 15.6 Hz, 1H), 3.99 (d, *J* = 14.1 Hz, 1H), 3.93 (dd, *J* = 7.7, 0.6 Hz, 1H), 3.55 (dd, *J* = 10.4, 7.7 Hz, 1H), 3.43 (dd, *J* = 10.8, 3.9 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  144.9, 124.9, 75.3, 75.0, 73.4, 68.9, 64.0; (+)-**20** [ $\alpha$ ] $_{\text{D}}^{25}$  +45.2 (*c* 0.31,  $\text{CHCl}_3$ ); IR (neat) 1744  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.68–5.65 (m, 1H), 5.54 (m, 1H), 4.42 (s, 1H), 4.19 (1/2 ABq, *J* = 14.4 Hz, 1H), 4.08 (1/2 ABq, *J* = 14.4 Hz, 1H), 3.30–3.28 (m, 1H), 3.24–3.23 (m, 1H), 2.11 (s, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 139.8, 115.4, 64.4, 63.6, 62.9, 53.4, 51.1, 25.8, 25.7, 21.0, 18.3, 18.0, –4.4, –4.7, –5.3, –5.5; HRMS (ES) *m/z* calcd for  $\text{C}_{21}\text{H}_{40}\text{O}_5\text{Si}_2\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 451.2312, found 451.2329; (+)-**21** [ $\alpha$ ] $_{\text{D}}^{25}$  +45.8 (*c* 1.07,  $\text{CHCl}_3$ ); IR (neat) 1743  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.71–5.69 (m, 1H), 5.58–5.57 (m, 1H), 4.69 (s, 1H), 4.26 (1/2 ABq, *J* = 15 Hz, 1H), 4.17 (1/2 ABq, *J* = 14.6 Hz, 1H), 3.41–3.36 (m, 2H), 2.08 (s, 3H), 0.94 (s, 9H), 0.90 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H), 0.05 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 141.1, 115.5, 66.2, 65.1, 63.0, 54.2, 52.7, 25.9, 25.7, 21.0, 18.3, 18.1, –4.2, –4.9, –5.3, –5.5; HRMS (ES) *m/z* calcd for  $\text{C}_{21}\text{H}_{40}\text{O}_5\text{Si}_2\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 451.2312, found 451.2290; (–)-**11** [ $\alpha$ ] $_{\text{D}}^{25}$  –275.8 (*c* 0.33,  $\text{C}_2\text{H}_5\text{OH}$ ); IR (neat) 3352, 1673  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  6.00 (d, *J* = 1.8 Hz, 1H), 4.54 (s, 1H), 4.47 (1/2 ABq, *J* = 16.8 Hz, 1H), 4.21 (1/2 ABq, *J* = 18.3 Hz, 1H), 3.77 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.36–3.34 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{COCD}_3$ )  $\delta$  194.0, 161.2, 120.1, 63.6, 62.6, 57.7, 53.5; HRMS (ES) *m/z* calcd for  $\text{C}_7\text{H}_8\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 179.0320, found 179.0301; (–)-**12** [ $\alpha$ ] $_{\text{D}}^{25}$  –115.4 (*c* 0.39,  $\text{C}_2\text{H}_5\text{OH}$ );  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  5.82 (dd as t, *J* = 1.8 Hz, 1H), 4.64 (br s, 1H), 4.21 (1/2 ABq, *J* = 18.3 Hz, 1H), 4.09 (1/2 ABq, *J* = 18.3 Hz, 1H), 3.75 (dd, *J* = 4.4, 2.9 Hz, 1H), 3.38 (dd, *J* = 4.2, 2.4 Hz, 1H),  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  193.6, 163.0, 117.2, 64.6, 60.4, 55.3, 53.2; HRMS (ES) *m/z* calcd for  $\text{C}_7\text{H}_8\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ] $^+$ : 179.0320, found 179.0311.
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11. Comparison of the spectral data ( $^{13}\text{C}$  NMR in  $\text{DMSO}-d_6$ ) of natural ‘parasitenone’, 10 synthetic **12** and (+)-epoxydon **3a**.

‘parasitenone’	193.9, 141.4, 133.8, 63.7, 57.3, 54.0, 52.9
Synthetic <b>12</b>	193.6, 163.0, 117.2, 64.6, 60.4, 55.3, 53.2
Epoxydon <b>3a</b>	194.0, 141.4, 133.8, 63.7, 57.6, 54.0, 52.9

12. X-ray data for **26**: X-ray data were collected at 293 K on a BRUKER SMART APEX CCD diffractometer with graphite monochromated  $\text{MoK}\alpha$  radiation ( $\lambda = 0.7107 \text{ \AA}$ ). The structure was solved by direct methods (SIR92). Refinement was done by full-matrix least-squares procedures on  $F^2$  using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically.  $\text{C}_{12}\text{H}_{14}\text{O}_4$ , *MW* = 222.2, colourless crystal, Crystal system: orthorhombic, space group:  $\text{Pbc}_a$ , cell parameters: *a* = 8.415(2)  $\text{ \AA}$ , *b* = 9.020 (2)  $\text{ \AA}$ , *c* = 26.924 (7)  $\text{ \AA}$ , *V* = 2043.63(9)  $\text{ \AA}^3$ , *Z* = 7, *D<sub>c</sub>* = 1.26  $\text{ g cm}^{-3}$ , *F*(000) = 825.9,  $\mu = 0.095 \text{ mm}^{-1}$ . Total number of l.s. parameters = 201, *R*1 = 0.050 for 1747 *F<sub>o</sub>* > 4 sig (*F<sub>o</sub>*) and 0.062 for all 2089 data. *wR*2 = 0.105, GOF = 1.116, restrained GOF = 1.116 for all data. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, UK (CCDC 260720). An ORTEP diagram (with 50% ellipsoidal probability) is shown below.

