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Neo-clerodane diterpenoids from *Croton schiedeanus*

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Dedicated to the memory of Dr. Benedicto del Rey Herrero

Abstract

Two new *neo*-clerodane type furano diterpenoids were isolated from the aerial part of *Croton schiedeanus*, besides the clerodane diterpenes *cis*- and *trans*-dehydrocrotonin, previously isolated from other species of *Croton*. Structural elucidation was achieved on basis of extensive NMR experiments, including X-ray diffraction analysis and molecular mechanics calculations. The previously known flavonoids ayanin and quercetin-3,7-dimethyl ether were also obtained from the extract of this plant.

Keywords: *Croton schiedeanus*; Euphorbiaceae; *Neo*-clerodane diterpenoids; 5β-Hydroxy-*cis*-dehydrocrotonin; (12*R*)-12-Hydroxycascarillone

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1. Introduction

Croton schiedeanus Schlecht is a tree which grows widely in Colombia and is particularly widespread in the Amazonian and Cundinamarca regions, where it is popularly known as ‘‘almizclillo’’, and used as a traditional medicine for the treatment of hypertension (García, 1975; Correa and Bernal, 1992). The genus *Croton* is a rich source of diterpenoids, mainly with clerodane skeleton (Merrit and Ley, 1992).

In this report, we describe the isolation from the aerial part of *Croton schiedeanus,* and the identification of two new *neo*-clerodane diterpenoids: 5β-hydroxy-*cis*-dehydrocrotonin (**1**) and (12*R)*-12-hydroxycascarillone (**2**), and the known *cis*-dehydrocrotonin (**3**) and *trans*-dehydrocrotonin (**4**), previously isolated from other species of *Croton* (Fig. 1). In addition, the flavonoids: ayanin (Malan and Roux, 1979; Agrawal, 1989) and quercetin-3,7-dimethyl ether (Wollenweber et al., 1981; Agrawal, 1989), were also obtained from the same source. Structural elucidation was achieved by spectroscopic measurements including 2D NMR experiments and by comparison with closely related compounds. The stereochemistry was determined by studies of ROESY ^{1}H NMR spectra and assisted by molecular modelling calculations and in the case of compound **1**, it was confirmed by single-crystal X-ray diffraction analysis.

2. Results and discussion

The aerial part was extracted with ethanol and this extract was partitioned between $CHCl_3$ and H_2O. The residue of $CHCl_3$ extract was fractionated with aqueous 4% NaOH yielding an acidic part and a neutral part. The diterpenoids contained in the neutral part were purified using a combination of silica gel and sephadex CC. The diterpenoids **3** and **4**, previously isolated from *Croton cajucara*, were identified as *cis*- and *trans*-dehydrocrotonin by comparison of their chemical and spectral data with literature values (Kubo et al., 1991).

Compound **1**, isolated as a colourless solid, presented a molecular ion ([M$^+$] at *m/z* 330) consistent with the molecular formula $C_{19}H_{22}O_5$. The IR spectrum showed absorptions of hydroxyl (3433 cm^{-1}), γ-lactone (1760 cm^{-1}), α,β-unsaturated carbonyl (1657 cm^{-1}) and furan ring (1498, 874 cm^{-1}) functionalities. The ^{1}H NMR spectrum (see Experimental) suggested a structure

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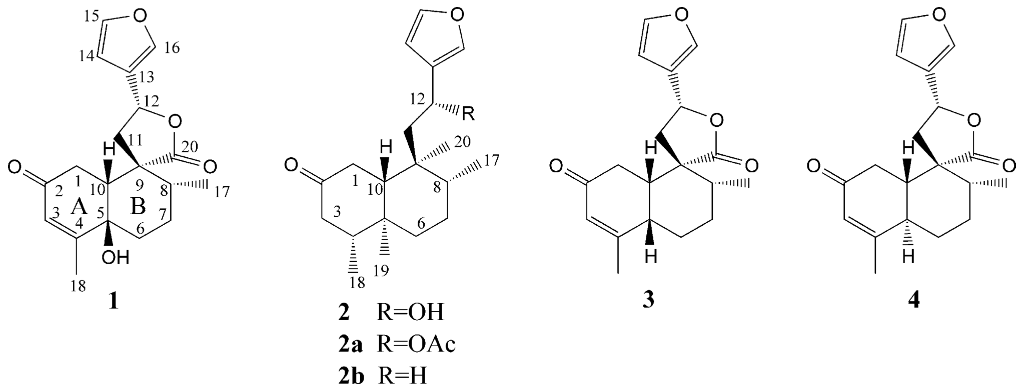


Fig. 1. Structures of compounds isolated from *C. schiedeanus*.

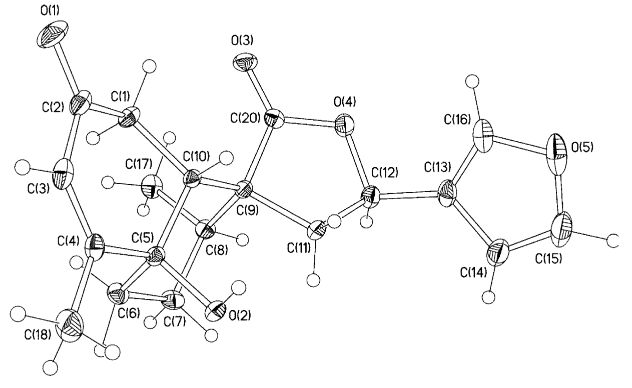


Fig. 2. X-ray molecular structure of compound **1**.

closely related to dehydrocrotonins (DHC), showing signals of secondary (δ 1.15, *d*) and tertiary (δ 2.01, *s*) methyl groups, and β-substituted furan (δ 6.42, 7.43 and 7.47). The most notable difference with the DHC is the absence of signals for H-5, which would indicate that this compound could possess the hydroxyl group at C-5. This proposal was supported by the presence of a signal for a non protonated hydroxylated carbon (δ 72.6) in the ^{13}C NMR spectrum. This spectrum (see Experimental) showed other 18 signals for a β-substituted furan, a spiro-20,12-γ-lactone involving the C-9, C-11, C-12 and C-20 carbons, a C-17 secondary methyl, a C-18 methyl, a ketone function, two olefinic carbons, three methylene groups and two methine groups.

On the basis of ^{1}H–^{1}H COSY and ^{1}H–^{13}C correlation experiments, all proton and ^{13}C signals were unambiguously assigned. Thus, the compound **1** was identified as 5-hydroxydehydrocrotonin. Furthermore, a single-crystal X-ray diffraction of **1** was undertaken in order to determine the stereochemistry at the C-5 asymmetric centre. The ORTEP perspective drawing depicted in Fig. 2, supports the preceding deductions concerning this structure and permits to propose its absolute configuration, showing chair conformations for both ring (A and B), although ring A is distorted due to the presence of a double bond between C-3 and C-4. The hydroxyl group at C-5 and the hydrogen at position C-10 are on the same side of an A/B *cis*-decalin moiety, and **1**, was finally identified as 5β-hydroxy-*cis*-dehydrocrotonin. The crystal structure is stabilized by intermolecular hydrogen bonds (O–H···O) between the tertiary hydroxyl group at C-5 of one molecule and the carbonyl oxygen atom of the ketone at C-2 of another one (Fig. 3). The hydrogen bonds parameters are: O–H···O [O1–O2 = 2.77(4) Å, $H_2O\cdots O1 = 1.89(2)$ Å, $<O1–H_2O\cdots O2> = 172.5(1)°$].

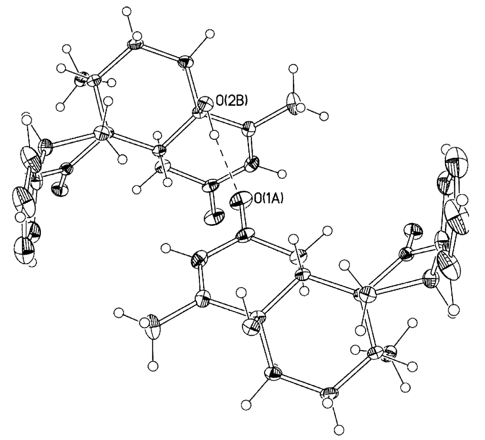


Fig. 3. Intermolecular O···H interaction connecting the molecules of **1** in the crystal.

The second new diterpenoid, **2**, isolated as an oil, gave a molecular ion peak in the mass spectrum at *m*/*z* 341 ($M^+ + 23$, Na), in agreement with the molecular formula $C_{20}H_{30}O_3$. The IR spectrum showed hydroxyl (3413 cm^{-1}), ketone (1712 cm^{-1}) and furan ring (1503, 874 cm^{-1}) absorptions. The ^{1}H NMR presented a number of similarities to that of cascarillone (**2b**), a diterpene which was isolated from cascarilla oil (Iio et al., 1989). The compound **2** showed in ^{1}H NMR (see Experimental) signals of two tertiary (δ 0.61, *s* and 0.70, *s*) and two secondary (δ 0.65, *d*, and 0.72, *d*) methyl groups and β-substituted furan (δ 6.35, 7.18 and 7.28). The main difference between compound **2** and cascarillone (**2b**) was the presence in **2** of a hydroxyl group attached to C-12 (δ 4.71, *d*) instead of the methylene group of cascarillone (**2b**) (δ 2.12, *m*). In agreement with this, acetylation (acetic anhydride/pyridine) of compound **2** yielded a derivative **2a**, whose IR, ^{1}H and ^{13}C (see Experimental) were in accordance with the presence of an acetate group at the C-12 position. Furthermore, structure **2** was also supported by the ^{13}C NMR spectrum. The comparison of the ^{13}C NMR spectra of **2** and **2b** determinates that **2** has an hydroxyl group attached to C-12 (δ 62.8).

The C-12 configuration was resolved by a combination of 2D ROESY data and MM calculations. The use of NOE difference experiments is accepted as a definitive method to determine the C-12 stereochemistry (Jiménez-Barbero, 1993). In our case, the cross peaks observed in the ROESY spectrum between H-12, H-1β and H-10 imply that these protons were in close proximity of one to another, and indicates that the C-12 stereocentre has the *R* configuration. These results are in accordance with the studies made on 12-hydroxylated *neo*-clerodanes (Jimenez-Barbero, 1993) where strong H-12/H-17 and H-12/H-8 NOE's are observed for *S*-type compounds, while clear H-12/H-10 and H-12/H-1β are present for the *R*-type analogues. Examination of the lowest energy conformation of both epimers at C-12 of compound **2** (**2A** and **2B**) (Fig. 4) obtained after a Montecarlo random conformational search (Allinger, 1977; Mohamadi et al., 1990), is in agreement with our findings. The interprotonic distance between H-12 and H-1β, 4.0 Å, measured in the global minimum of **2B** epimer is too large to give an observable ROE effect. Furthermore, in the **2A** epimer lowest energy conformer, the distances are in agreement with the experimental ROE results (Table 1). On the basis of these facts, the structure of compound **2** was established as (12*R)*-12-hydroxycasacarillone.

In previous studies, we have reported the antihypertensive and vasorelaxant activity of the ethanolic extract from *Croton schiedeanus*, as well as the vasorelaxant activity of the neutral fraction partitioned from this extract. Also, we have shown that the antihypertensive and vasorelaxant effects elicited by this Colombian medicinal plant are due to a synergistic activity among the flavonoid and the terpenoid compounds (Guerrero et al., 2002).

In summary, compounds **1** and **2** were isolated from *Croton schiedeanus*, and to our knowledge, this represents the first report of such compounds from a natural source.

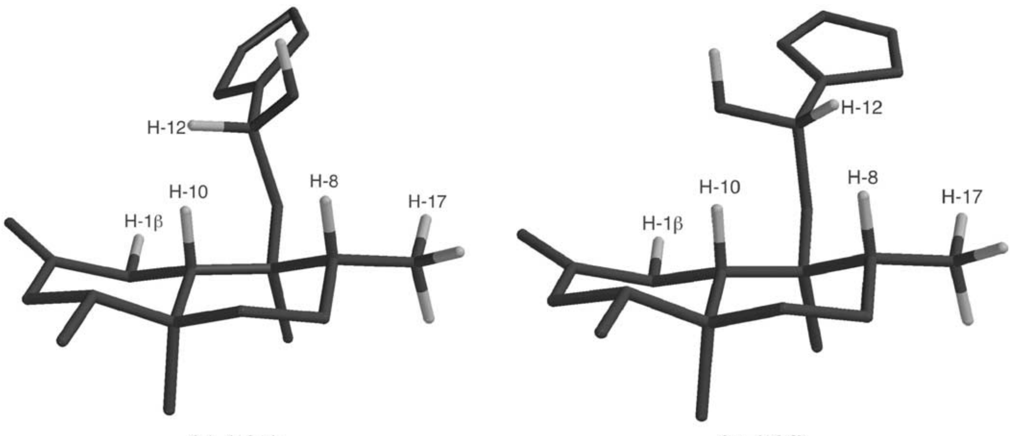
3. Experimental

3.1. General experimental procedures

Melting points were determined on a Büchi 510-K melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR were recorded on Bruker WP 200 SY (200,13 MHz) and Bruker 400 DRX (400 MHz) instruments. Chemical shifts (δ) are given in ppm and TMS as internal standard. Sephadex LH-20 (Fluka, 25–100 μm) and silica gel 60 (Merck, 230–400 mesh) were used for flash chromatography; precoated silica gel plates (Merck, Kieselgel 60 F254, 0.25 mm) were used for TLC analysis. For MS analyses, a VG-TS250 apparatus (70 eV) was used. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

3.2. Plant material

The aerial part of *Croton schiedeanus* Schlecht (Euphorbiaceae) was collected from de region of Tocaima, Cundinamarca, Colombia, in November 1999. Its identity was confirmed by José Luis Fernández and a voucher specimen has been deposited under No. 432164 in the Herbarium of Natural Sciences Institute of National University of Colombia.



2A (12*R*) **2B** (12*S*)

Fig. 4. Low energy conformations of compounds **2A** and **2B**.

Table 1
Relevant interprotonic distances for **2A** and **2B**, according to MM2 calculations

Proton pair	**2A** (12*R*)	**2B** (12*S*)
H1-H12	2.4	4.0
H8-H12	3.4	2.1
H10-H12	2.1	2.1
H17-H12	4.6	3.0

3.3. Extraction and isolation

The dried and milled sample (10 kg) was soaked in 96% EtOH (50 l) at room temperature for 3 days. The EtOH was removed in vacuo to yield a dark residue (160 g), which was partitioned between CHCl$_3$ and H$_2$O to give CHCl$_3$ soluble fraction (90 g). The residue of CHCl$_3$ extract was fractionated with aqueous 4% NaOH yielding two parts: an acid part (18 g) and a neutral part (65 g). The acid part was separated by flash column chromatography, over silica gel, gradient elution with 0–100% EtOAc/hexane afforded 26 fractions. Fractions 12–18 eluting with 20% EtOAc/hexane, yielded ayanin as an amorphous solid, which was purified by crystallization from acetone/MeOH yielding ayanin (0.9 g) as a yellow solid. Fractions 22–26 eluting with 40% EtOAc/hexane, yielded quercetin 3,7-dimethyl ether (0.5 g) as yellow solid powder, which was purified by crystallization from MeOH.

The neutral part was separated by flash column chromatography, over silica gel, gradient elution with 0–100% EtOAc/hexane afforded 68 fractions. Fractions 35–40 eluting with 30% EtOAc/hexane were obtained as an oil after removal of solvents, further purification over Sephadex LH-20 using as eluent MeOH/CH$_2$Cl$_2$/*n*-hexane (1:1:1), to afford **2** (64 mg) followed by **4** (140 mg). From fractions 44-50 using as eluent 50% EtOAc/hexane and purification over Sephadex LH-20 using as eluent MeOH/CH$_2$Cl$_2$/hexane (1:1:1), afforded **3** (480 mg) and **1** (90 mg).

3.4. 5β-Hydroxy-cis-dehydrocrotonin (1)

Colourless needles, mp 182–183 °C (MeOH/ether); [α]$_D$ +14.6° (CHCl$_3$, *c* 0.8). IR ν_{max} (KBr) cm^{-1}: 3433, 1760, 1657, 1498, 1409, 1191, 1042, 874. ^{1}H NMR (CDCl$_3$) δ: 1.15 (3H, *d*, *J*=7.3 Hz, H-17), 1.16 (2H, *m*, H-6), 1.6–1.8 (2H, *m*, H-7), 2.01 (3H, *s*, H-18), 2.02 (1H, *m*, H-8), 2.26 (1H, *m*, H-10), 2.30 (1H, *dd*, *J*=9.5, 13.2 Hz, H-11α), 2.58 (1H, *dd*, *J*=9.5, 17 Hz, H-1α), 2.85 (1H, *dd*, *J*=7.3, 13.8 Hz, H-11β), 3.34 (1H, *dd*, *J*=5.3, 17 Hz, H-1β), 5.33 (1H, *t*, *J*=7.2 Hz, H-12), 5.88 (1H, s, H-3), 6.42 (1H, *br s*, H-14), 7.43 (1H, *s*, H-15), 7.47 (1H, *s*, H-16) (assignments based on COSY and ROESY correlations). ^{13}C NMR (CDCl$_3$): δ 17.2 (C-17), 18.6 (C-18), 25.3 (C-6), 29.6 (C-7), 35.5 (C-8), 37.5 (C-1), 45.7 (C-11), 49.4 (C-10), 50.9 (C-9), 71.1 (C-12), 72.6 (C-5), 108.1 (C-14), 124.6 (C-13), 127.9 (C-3), 139.7 (C-16), 144.1 (C-15), 163.0 (C-4), 176.3 (C-20), 197.0 (C-2) (the assignments based on a ^{1}H, ^{13}C-correlation). EI-MS *m*/*z* (rel. int.%) 330 [M$^+$] (30), 221 (30), 149 (100), 123 (75).

3.5. (12R)-12-Hydroxycascarillone (2)

[α]$_D$ −47.6° (CHCl$_3$, *c* 0.31). IR ν_{max} (CHCl$_3$) cm^{-1}: 3413, 1712, 1698, 1503, 1461, 1129, 874. ^{1}H NMR (C$_6$D$_6$) δ: 0.61 (3H, *s*, H-20), 0.65 (3H, *d*, *J*=6.5 Hz, H-17), 0.70 (3H, *s*, H-19), 0.72 (3H, *d*, *J*=7.3 Hz, H-18), 0.80 and 1.40 (2H, *m*, H-6); 1.29 (1H, *m*, H-10), 1.86 and 1.87 [(1H, *d*, *J*=8.7 Hz) and (1H, *d*, *J*=8.7 Hz) H-11], 1.95 and 2.22 [(1H, *dd*, *J*=14.9 and 13.9 Hz) and (1H, *bd*, *J*=15.1 Hz) H-1], 4.71 (1H, *d*, *J*=8.6 Hz, H-12), 6.35 (1H, *s*, H-14), 7.18 (1H, *s*, H-16), 7.28 (1H, *s*, H-15). ^{1}H NMR (CDCl$_3$) δ: 0.75 (3H, *s*, H-20), 0.78 (3H, *d*, *J*=6.7 Hz, H-17), 0.86 (3H, *d*, *J*=7.3 Hz, H-18), 0.96 (3H, *s*, H-19), 1.10 and 1.59 (2H, *m*, H-6); 1.40 and 1.50 (2H, *m*, H-7), 1.62 (1H, *m*, H-8), 1.80 (1H, *d*, *J*=8.6 Hz, H-11α), 1.88 (1H, *d*, *J*=8.6 Hz, H-11β), 2.00 (1H, *dd*, *J*=2.9, 13.5 Hz, H-10), 2.16 and 2.19 (2H, *m*, H-3), 2.28 (1H, *dd*, *J*=14.2 and 13.9 Hz, H-1α), 2.66 (1H, *dd*, *J*=14.2 and 2.6 Hz H-1β), 4.79 (1H, *t*, *J*=8.4 Hz, H-12), 6.37 (1H, *s*, H-14), 7.34 (1H, *s*, H-16), 7.36 (1H, *s*, H-15) (assignments based on COSY and ROESY correlations). ^{13}C NMR (C$_6$D$_6$): δ 12.2 (C-19), 14.5 (C-18), 15.9 (C-17), 17.0 (C-20), 27.2 (C-7), 36.4 (C-9), 37.0 (C-8), 38.4 (C-6), 39.2 (C-1), 39.6 (C-5), 45.1 (C-4), 45.5 (C-11), 46.1 (C-3), 49.2 (C-10), 62.8 (C-12), 108.7 (C-14), 131.6 (C-13), 138.1 (C-16), 143.0 (C-15), 210.1 (C-2). ^{13}C NMR (CDCl$_3$): δ 12.6 (C-19), 14.7 (C-18), 16.1 (C-17), 17.2 (C-20), 27.1 (C-7), 36.6 (C-9), 37.1 (C-8), 38.4 (C-6), 39.4 (C-1), 39.8 (C-5), 45.0 (C-11), 45.4 (C-4), 46.3 (C-3), 49.4 (C-10), 63.0(C-12), 108.6 (C-14), 131.2 (C-13), 138.3 (C-16), 143.2 (C-15), 212.3 (C-2). (assignments based on a ^{1}H, ^{13}C-correlation). ESI-MS *m*/*z* (rel. int.%) 341 [M+Na]$^+$.

3.6. (12R)-12-Acetoxycascarillone (2a)

^{1}H NMR (CDCl$_3$) δ: 0.75 (3H, *s*, H-20), 0.78 (3H, *d*, *J*=6.7 Hz, H-17), 0.84 (3H, *d*, *J*=6.7 Hz, H-18), 0.94 (3H, *s*, H-19), 1.40 (1H, *m*, H-10), 1.44 (2H, *m*, H-7), 1.64 (1H, *m*, H-8), 1.66 and 2.04 (2H, *m*, H-11), 1.75 (2H, *m*, H-6), 1.96 (*s*, 3H, OCOCH$_3$), 2.07 and 2.15 [(1H, *d*, *J*=7.5 Hz) and (1H, *d*, *J*=9.0 Hz) H-3], 2.27 and 2.63 [(1H, *t*, *J*=14.2 Hz) and (1H, *dd*, *J*=3.2, 14.6 Hz) H-1], 5.89 (1H, *d*, *J*=9.1 Hz, H-12),), 6.32 (1H, *s*, H-14), 7.33 (1H, *s*, H-16), 7.34 (1H, *s*, H-15). (assignments based on COSY and ROESY correlations). ^{13}C NMR (CDCl$_3$): δ 12.5 (C-19), 16.9 (C-20), 21.1

(OCO$\underline{C}H_3$), 14.7 (C-18), 15.9 (C-17), 26.9 (C-7), 36.5 (C-9), 37.1 (C-8), 38.2 (C-6), 39.2 (C-1), 39.9 (C-5), 42.2 (C-11), 45.6 (C-4), 46.2 (C-3), 49.5 (C-10), 64.3 (C-12), 108.4 (C-14), 126.0 (C-13), 139.3 (C-16), 170.0 (O$\underline{C}OCH_3$), 143.1 (C-15), 211.5 (C-2).

3.7. Molecular modelling

Calculations were performed on a Silicon Graphics Indigo computer. Compounds 2A and 2B were built using Macromodel[i] v.4. Conformational analysis of the two compounds was performed by a Monte Carlo random search. All freely rotating bonds were searched with MM2 minimization to a gradient of less than 0.001 kcal/mol. In order to reproduce the experimental NMR conditions, calculations were performed considering chloroform as solvent. MacroModel uses a solvation model which treats the solvent as an analytical continuum starting near the van der Waals surface of the solute.

3.8. X-ray analysis of compound 1

Compound **1**, $C_{19}H_{22}O_5$, crystallizes in orthorhombic space group $P2_12_12_1$, with $Z=4$, and unit cell parameters, $a=6.6380(13)$ Å, $b=10.144(2)$ Å, $c=24.685(5)$ Å, $\alpha=\beta=\delta=90°$.

X-ray diffraction data were collected on a four circle Seifert XRD 3003 SC diffractometer (CuF_α, $\lambda=1.5418$ Å), graphite monochromator, room temperature, ω-2θ scan. The unit cell parameters were determined by least squares refinement on the 2θ values of 25 strong well centred reflections in the range $16° < 2\theta < 40°$. Scattering factors for neutral atoms and anomalous dispersion correction for C and O were taken from "International Tables for X Ray Crystallography" (International Tables for X Ray Crystallography, 1995, Vol C. Dordrecht: Kluwer Academic Publishers). Structure of $C_{19}H_{22}O_5$ was resolved by direct methods and refined in the space group $P2_12_12_1$. Full matrix least-squares refinement with anisotropic thermal parameters for non-H atoms was carried out by minimizing w(Fo^2–Fc^2)^2. Refinement on F^2 for all reflections, weighted R factors (R_w), and all goodness of fit S are based on F^2, while conventional R factors (R) are based on F; R factors based on F^2 are statistically about twice as large those based on F, and R factors based on all data will be even larger. Resulting absolute structure parameter: 0.36 (155).

All calculations were performed using CRYSOM (Martínez-Ripoll and Cano, 1996), software for data collection, XRAY80 (Stewart et al., 1990), for data reduction, SHELXTL™ (Siemens SHELXTL™ version 5.0, Siemens analytical X-ray instruments inc., Madison, WI 53719, 1995) to resolve and refine the structure and to prepare material for publication. Full crystallographic details, have been deposited at the Cambridge Crystallographic Data Centre No. CCDC 188952.

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