Journal of Natural Products
Vol. 58, No. 8, pp. 1270-1273, August 1995

A SHORT ENANTIOSELECTIVE SYNTHESIS OF A BIOLOGICALLY ACTIVE COMPOUND FROM *PERSEA AMERICANA*

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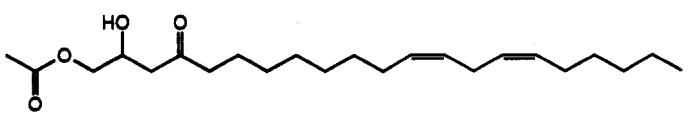
ABSTRACT.—A short synthesis of (2*R*)-(12*Z*,15*Z*)-2-hydroxy-4-oxoheneicosa-12,15-dien-1-yl acetate, a bioactive compound isolated from the avocado plant, *Persea americana*, has been achieved by an enantioselective aldol reaction of 2-acetoxyacetaldehyde with (10*Z*,13*Z*)-nonadeca-10,13-dien-2-one.

The compound, (12Z,15Z)-2-hydroxy-4-oxoheneicosa-12,15-dien-1-yl acetate [**1**], was first reported in 1975 as a component of the leaves of the avocado plant, *Persea americana* P. Mill. (Lauraceae) (1). It was subsequently also identified as a natural antifungal compound present in unripe avocado fruit, the concentration of which decreased during the ripening process (2). Recently, it was determined using laboratory testing with mice that this is the active compound responsible for the earlier reported necrosis of the acinar epithelium of the mammary glands of lactating animals feeding on avocado leaves (3,4).

Although the structure of **1** had been previously established, its absolute stereochemistry was not determined. Our efforts to establish this using the Mosher ester methods (5) were unsuccessful (3). We therefore set out to design a short enantioselective synthetic route to **1** which would provide both enantiomers as well as allow variation of the aliphatic chain and ester group for testing purposes. Coincidentally, but unknown to us, Bull and Carman (6) were also pursuing routes to the synthesis of **1** in order to study its antifungal activity. Their recently reported 11-step synthesis starting from (*S*)-malic acid gave the unnatural *S*-(−)-enantiomer. This paper describes a three-step enantioselective synthesis of (+)-**1** and (−)-**1** and the racemate (±)-**1**.

Compound **1** was synthesized from readily available allyl acetate [**2**] and linoleic acid [**3**]. Ozonolysis of the allyl acetate [**2**] (7) followed by reductive workup with triphenylphosphine produced 2-acetoxyacetaldehyde [**4**] in 85% yield. Treatment of linoleic acid [**3**] with an excess of methyl lithium formed the methyl ketone **5** in 77% yield (8). An enantioselective aldol reaction via enol diisopinocampheylborinates (9) was used for the synthesis of (+)-**1** and (−)-**1**. Commercially available (−)-*B*-chlorodiisopinocampheylborane [(−)-$(Ipc)_2BCl$] was employed for the preparation of enantiomer (+)-**1**. Reaction of **5** with four equivalents of (−)-$(Ipc)_2BCl$ and six equivalents of diisopropylethylamine in dry CH_2Cl_2 at −78° furnished the enol borinate **6** after 5 h. Borinate **6** was reacted with 3 equivalents of aldehyde **4** for 12 h and oxidative workup with H_2O_2 gave the target molecule (+)-**1** in a moderate yield of 54% (Scheme 1).

The racemate (±)-**1** was synthesized by condensation of compounds **4** and **5** with lithium diisopropylamide as base in THF at −78°. Under these conditions



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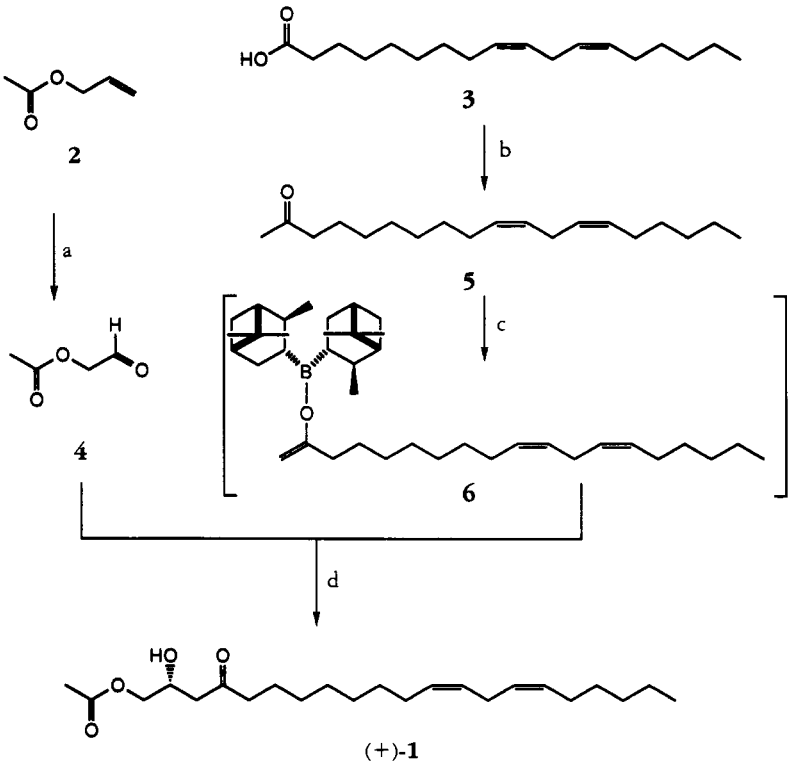

(a) O_3, CH_2Cl_2, −78°, PPh_3, 85%; (b) 4 equivalents MeLi, THF, 0°, 2 h, TMSCl, 77%; (c) 4 equivalents (−)-$(Ipc)_2BCl$, 6 equivalents diisopropylethylamine, CH_2Cl_2, −78°, 5 h; (d) 3 equivalents of **4**, −78°, 1 h, then −15° for 16 h, H_2O_2.

SCHEME 1. Synthetic Scheme for (2*R*)-(12*Z*,15*Z*)-2-hydroxy-4-oxoheneicosa-12,15-dien-1-yl acetate [**1**].

regioselective enolization was observed and the racemic compound (±)-**1** was obtained in 60% yield.

The measured optical rotation of the natural material was $[\alpha]^{20}D$ +10.7° (*c*=1, $CHCl_3$) (3). An $[\alpha]^{20}D$ of +10.2° (*c*=1, $CHCl_3$) was found for the synthetic product, (+)-**1**. Using (+)-$(Ipc)_2BCl$ in place of its (−) form the corresponding enantiomer (−)-**1** was formed in a similar yield and with an $[\alpha]^{20}D$ of −10.3° (*c*=1, $CHCl_3$). From the optical rotation measurements the ee values for (+)-**1** and (−)-**1** could be determined as 95% and 96%, respectively. Additionally, chiral shift ^1H-nmr studies were performed, using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium (III) ($Eu(hfc)_3$) as chiral shift reagent. The diastereotopic protons at C-5 were readily separated using a $4 \cdot 10^{-3}$ M solution of $Eu(hfc)_3$ in $CDCl_3$. Under these conditions the signals for the *R*- and *S*-forms of one of these C-5 protons of (±)-**1** were resolved. Measurement of the relative areas under these signals for the products from the enantioselective synthesis provided values for the enantiomeric excess.

According to Paterson *et al.* (9), aldol reactions of this type are consistent in the sense of asymmetric induction. With (−)-$(Ipc)_2BCl$ as chiral auxiliary an attack on the *re*-face of aldehyde **4** is favored. Hence the reaction of enolate **6** with aldehyde **4** results predominantly in the generation of the *R* configuration for compound **1**, supporting the assignment of the absolute configuration of the natural product as the *R*-enantiomer (6).

The *R* and *S* isomers of **1** were tested

for activity required to induce widespread mammary gland necrosis in lactating mice at the dose of 50–100 mg/kg body weight. The *R* isomer was active but the *S* isomer was inactive even as a high single dose (200 mg/kg). The racemic mixture was less active than the *R* isomer (3).

By using oleic acid in place of linoleic acid [**3**] a more stable analogue of **1** with only one double bond was obtained in similar yields. The biological activity of (+)-15,16-dihydro **1** was the same as that of (+)-**1**, while (−)-15,16-dihydro **1** was inactive.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Boiling points are uncorrected. ^{1}H- and ^{13}C-nmr spectra were recorded in $CDCl_3$ on a Varian Gemini-300 instrument. Where necessary, solvents and reagents were purified and dried according to procedures detailed in Perrin and Armarego (10). Anhydrous solvents were distilled from drying agents directly prior to use. Reactions performed under anhydrous conditions were carried out under a dry Ar atmosphere unless otherwise stated. Flash chromatography was carried out using 230–400 mesh Si gel.

2-ACETOXYACETALDEHYDE [**4**].—Following the literature procedure (7) ozone was passed through a solution of allyl acetate (20 g, 200 mmol) in CH_2Cl_2 (150 ml) at −78°. After the reaction was complete a solution of PPh_3 (52.4 g, 200 mmol) in CH_2Cl_2 (150 ml) was added dropwise at −78° for 3 h and the solution was stirred at room temperature overnight. The CH_2Cl_2 was removed, the residue suspended in Et_2O (75 ml) and left overnight at −15°. After removal of Ph_3PO by filtration and concentration of the filtrate, the residue was distilled to obtain pure **4** (17.4 g, 85%); bp 48° 14 Torr [lit. (7) 93° 70 Torr]; ^{1}H nmr ($CDCl_3$) δ 2.21 (3H, s), 4.69 (2H, s), 9.61 (1H, s).

(10*Z*,13*Z*)-NONADECA-10,13-DIEN-2-ONE [**5**].—A stirred solution of linoleic acid (5.61 g, 20 mmol) in THF (150 ml) was cooled to 0° and treated with methyllithium (80 mmol; 1.4 M in Et_2O). After 2 h at 0° Me_3SiCl (30 ml, 120 mmol) was added. The reaction mixture was allowed to warm to room temperature at which point 1 M HCl (150 ml) was added. After stirring for 1 h the mixture was extracted with Et_2O, the organic layer washed with H_2O and brine, and dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave crude methyl ketone **5**. Flash chromatography (25% Et_2O in *n*-hexane) furnished pure **5** as a colorless oil (4.3 g, 77%); ^{1}H nmr ($CDCl_3$) δ 0.89 (3H, t, J=7.1 Hz), 1.21–1.29 (14H, m), 1.55 (2H, quint., J=7.3 Hz), 2.01 (4H, m), 2.12 (3H, s), 2.40 (2H, t, J=7.3 Hz), 2.76 (2H, t, J=6.6 Hz), 5.26–5.42 (4H, m); ^{13}C nmr ($CDCl_3$) δ 14.11, 22.61, 23.84, 25.64, 27.21 (2C), 29.14, 29.16, 29.34, 29.38, 29.63, 29.86, 31.55, 43.79, 127.91, 128.04, 130.02, 130.18, 209.26.

(12*Z*,15*Z*)-2-HYDROXY-4-OXOHENEICOSA-12,15-DIEN-1-YL ACETATE [(±)-**1**].—The kinetic enolate of **5** was prepared from (10*Z*,13*Z*)-nonadeca-10,13-dien-2-one (1.11 g, 4 mmol) and lithium diisopropylamide (5 mmol) in dry THF at −78°. To this solution freshly distilled 2-acetoxyacetaldehyde (0.51 g, 5 mmol) in THF was added dropwise at the same temperature. After 30 min, the cooling was removed and the solution was immediately neutralized with HOAc (0.3 ml, 5 mmol). Isolation and flash chromatography (30% EtOAc in *n*-hexane) gave pure (±)-**1** (0.92 g, 60%). All spectroscopic data were consistent with those reported for the natural product (1–3).

(2*R*)-(12*Z*,15*Z*)-2-HYDROXY-4-OXOHENEICOSA-12,15-DIEN-1-YL ACETATE [(+)-**1**].—This was prepared by a modification of the method by Paterson *et al.* (9). A solution of (−)-*B*-chlorodiisopinocampheylborane [(−)-$(Ipc)_2BCl$; 1283 mg, 4 mmol] in dry CH_2Cl_2 (20 ml) was cooled to −78° under Ar. Diisopropylethylamine (1.04 ml, 6 mmol) was added dropwise followed by a solution of **5** (557 mg, 2 mmol) in CH_2Cl_2 (5 ml). After 3 h at −78° another 4 mmol of (−)-$(Ipc)_2BCl$ and 6 mmol diisopropylethylamine were added and the reaction mixture was stirred for a further 2 h. After that time freshly distilled **4** (613 mg, 6 mmol) in CH_2Cl_2 (5 ml) was added. The solution was stirred at −78° for 1 h and then left at −15° for 16 h. The reaction mixture was quenched with pH 7 buffer and extracted with Et_2O, and the organic layer dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in MeOH (30 ml) and pH 7 buffer (5 ml), the solution sooled to 0° and 30% H_2O_2 (8 ml) was added. The reaction mixture was stirred for 2 h, then poured into H_2O and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ solution and brine, the organic layer dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (30% EtOAc in *n*-hexane) furnished pure (+)-**1** (396 mg, 52%). Chiral shift experiments with Eu(hfc)$_3$ indicated >90% ee; $[\alpha]^{20}D$ +10.2° (c=1, $CHCl_3$). All other spectroscopic data were consistent with those reported for the natural product (1–3).

(2*S*)-(12*Z*,15*Z*)-2-HYDROXY-4-OXOHENEICOSA-12,15-DIEN-1-YL ACETATE [(−)-**1**].—This compound was synthesized as described for (+)-**1** except that (+)-$(Ipc)_2BCl$ was employed. Chiral

shift experiments indicated >90% ee; $[\alpha]^{20}D$ $-10.3°$ ($c=1$, $CHCl_3$).

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Received 17 January 1995