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SYNTHESIS OF LABELED (10*R*)-JUVENILE HORMONE III BISEPOXIDE, AND ITS PHOTOAFFINITY ANALOG, [12-^{3}H]-(10*R*)-6,7,10,11-BISEPOXYFARNESYL DIAZOACETATE (BEFDA)

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SUMMARY

Radiolabeled optically-active JH III bisepoxide ([^{3}H]-(10*R*)-JHB_3) was synthesized from [12-^{3}H] (10*R*)-JH III using dimethyldioxirane to give an inseparable mixture of diastereomers with the *trans*-6,7-epoxide *syn* or *anti* to the existing 10,11-epoxide. [^{3}H]-(10*R*)-JHB_3 (or the unlabeled material) was converted in three steps to the corresponding (10*R*)-6,7,10,11-bisepoxyfarnesyl diazoacetate (BEFDA), a photoaffinity label for JHB_3 receptors and binding proteins.

Key words: Juvenile hormone bisepoxide, dimethyldioxirane, photoaffinity label, binding protein, tritium

INTRODUCTION

Recent research carried out by Richard *et al.*[1] has shown that JH III bisepoxide (JHB_3) is produced by ring glands from third instar larvae of *Drosophila melanogaster*. The physiological studies have shown also that JHB_3 is produced solely by the corpus allatum portion of the ring gland *in vitro*, and it is a fly juvenile hormone (JH). *In vitro* metabolism of JHB_3 was also investigated using purified mouse liver cytosolic epoxide hydrolase (cEH) and cell fractions from *D. melanogaster*.[2] *In vitro* metabolism of epoxides in insect tissues (*Lymantria dispar*)[3] or in mammalian tissues (rabbit liver)[4] has been shown to be regio- and enantio-selective. For example, the *in vitro* metabolism of the bis epoxide produced four isomers, the epoxy diol, *cis*- and *trans*-tetrahydrofuran-diols and tetraols with unidentified

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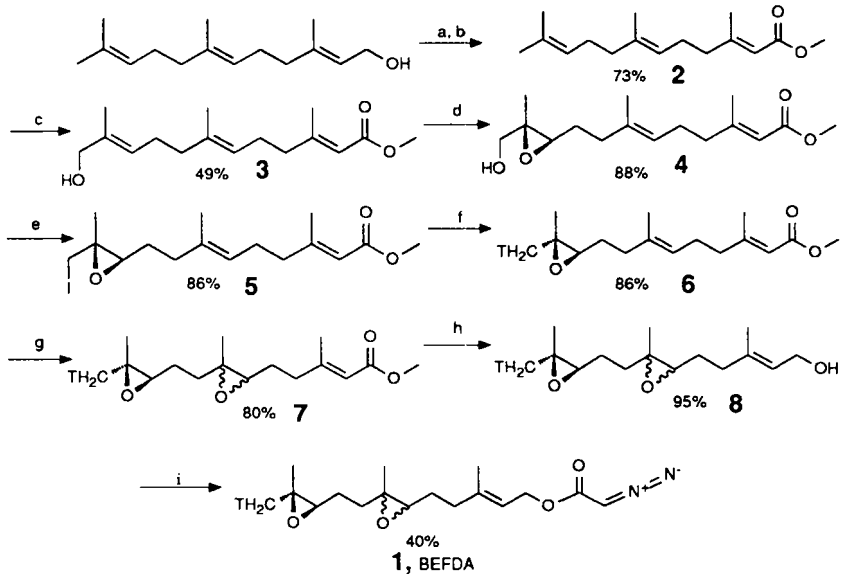
stereochemistry of the centers where the hydroxyl groups are attached.[2,5]

In order to further clarify the physiological role of JHB_3 and to facilitate investigations of the proteins which bind and catabolize this new JH, we prepared the radioactive (10*R*)-bisepoxide[6] and its photoaffinity analog, bisepoxyfarnesyl diazoacetate ([^{3}H]BEFDA). The details of the syntheses are presented below, including improved protocols for the synthesis of (10*R*)-JH III from farnesol.



Scheme I. Synthesis of [^{3}H]BEFDA: T = ^{1}H, unlabeled; T = ^{3}H, radiolabeled. Reagents and conditions: **(a)** MnO_2, hexane, 0 °C, rt; **(b)** MnO_2, KCN, CH_3COOH, CH_3OH; **(c)** SeO_2, *t*-BuOOH, CH_2Cl_2, 0 °C; **(d)** $Ti(OiPr)_4$, (-)-DIPT, TBHP, 4 Å molecular sieves, CH_2Cl_2, -45 °C; **(e)** Ph_3P, imidazole, I_2, Et_2O:CH_3CN (5:3), 0 °C; **(f)** HMPA:THF (3:2), $NaBH_3CN$, rt; **(g)** dimethyldioxirane, acetone, 18-crown-6, CH_2Cl_2, phosphate buffer, pH 7.2; **(h)** DIBAL-H, hexane, -78 °C; **(i)** *p*-$CH_3C_6H_4SO_2NHNCHCOCl$, $C_6H_5N(CH_3)_2$, CH_2Cl_2, 0 °C; then Et_3N, CH_2Cl_2, 0 °C.

Results and Discussion

The synthesis of BEFDA in labeled and unlabeled forms is summarized in Scheme I. For the unlabeled material JH III bisepoxide (7) was prepared using the dimethyldioxirane protocol developed by the Hammock group.[5] In our synthesis, we employed (10*R*)-JH III prepared in our laboratories.[7] As a result, a mixture of two diastereomeric bisepoxides was formed, but these could not be separated chromatographically. Subsequent reduction of the

ester to the allylic alcohol, followed by esterification and diazoacetate formation, gave the unlabeled BEFDA (1). The radiolabeled (10*R*)-JHB_3 was prepared starting with [12-^{3}H] (10*R*)-JH III, with reduction and diazoacetylation as described for the unlabeled material.[7] The bisepoxide was sensitive to acid, and we found that to obtain acceptable yields of diazoacetate 1 from allylic alcohol 8, only 0.9 to 1.0 molar equivalents of the acylating agent could be employed.

The [^{3}H]BEFDA will be employed in photocovalent modification of JHB_3 binding proteins from a variety of insects. In addition, the insect JH epoxide hydratase appears to be a candidate for photoaffinity labeling using this substrate. The results of these experiments will be reported in due course.

MATERIALS AND METHODS

***(E,E)*-3,7,11-Trimethyldodeca-2,6,10-trienal**. A mixture of *trans,trans*-farnesol (2.0 g, 9.0 mmol) and MnO_2 (15 g, 172 mmol, activated, Aldrich) in hexane (100 mL) was stirred at 0 °C for 1 hr. Then, it was warmed to room temperature and stirred for an additional 2 hr. The mixture was filtered and concentrated *in vacuo* to give 1.95 g of crude aldehyde (98% crude yield) which was used in the next step without further purification. R_f = 0.54 in 20% EtOAc:Hex. FT-IR (neat): 2965.8; 2918.6; 2854.5; 1739.4; 1675.5; 1443.8; 1379.4; 1239.9; 1193.9; 1120.9; 1046.3 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 9.92 (d, *J* = 8.09 Hz, 1H); 5.81 (d, *J* = 8.12 Hz, 1H); 5.01 (m, 2H); 2.11 (d, *J* = 1.11 Hz, 3H); 1.89-2.17 (m, 8H); 1.61 (s, 3H); 1.53 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ (ppm): (191.08, 190.82); 163.62; 136.26; 131.17; 127.17; 123.86; 122.22; 40.40; 39.43; 26.40; 25.46; 17.44; 17.28, 15.81.

Methyl *(E,E)*-3,7,11-trimethyldodeca-2,6,10-trienoate (2) : The above aldehyde (1.95 g, 9 mmol) was stirred with a mixture of potassium cyanide (3.0 g), acetic acid (0.8 g), and MnO_2 (16 g) in methanol (200 mL) for 14 hr at room temperature.[8] After filtration through Florisil to remove MnO_2, the solvent was removed under reduced pressure and the residue was diluted with ether, washed (H_2O), dried ($MgSO_4$), concentrated and purified over silica gel (SiO_2) to give 1.63 g of methyl farnesoate 2 as a colorless oil (74% yield). R_f = 0.65 in 20% EtOAc:Hex. FT-IR (neat): 2923.2; 2854.9; 1721.0; 1649.5; 1434.7; 1383.2; 1358.2; 1324.7; 1223.8; 1146.7; 1108.4; 1057.2 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.64 (s, 1H); 5.06 (m, 2H); 3.65 (s, 3H); 2.14 (d, *J* = 1.32 Hz, 3H); 1.86-2.15 (m, 8H); 1.65 (s, 3H); 1.57 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.12; 160.03; 136.03; 131.25; 124.16; 122.81; 115.17; 50.63; 40.84; 39.58; 26.57; 25.84; 25.58; 17.57, 15.89.

Methyl *(E,E,E)*-12-hydroxy-3,7,11-trimethyldodeca-2,6,10-trienoate (3). A suspension of selenium dioxide (111.2 mg, 1.0 mmol) in dry CH_2Cl_2 (5.0 mL) was stirred with *t*-butyl hydroperoxide (90%, 0.45 mL, 4.0 mmol) for 45 min in the dark under nitrogen atmosphere.[9] The resulting solution was cooled to 10 °C using water/ice bath and methyl farnesoate (0.5 g,

2.0 mmol) was added. The mixture was stirred for 3.0 hr, diluted with CH_2Cl_2, washed (sat. $NaHCO_3$), dried ($MgSO_4$), concentrated *in vacuo*, and purified (SiO_2) using hexane: EtOAc as eluent to give the following components in order of elution: (**i**) starting material (63 mg, 13.0%), (**ii**) aldehyde (33 mg, 6.3%): colorless oil, R_f = 0.43 in 20% EtOAc:Hex. FT-IR (neat): 2978.7; 1719.7; 1648.8; 1437.3; 1362.8; 1241.8; 1195.9; 1151.4; 1046.4 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm): 9.30(s, 1H); 6.37 (m, 1H); 5.60 (m, 1H); 5.07 (m, 1H); 3.64 (s, 3H); 2.00-2.40 (m, 8H); 2.15 (s, 3H); 1.73 (s, 3H); 1.62 (s, 3H); (**iii**) secondary alcohol (35 mg, 6.6%): colorless oil, R_f = 0.26 in 20% EtOAc:Hex. FT-IR (neat): 3460.5; 2918.3; 1720.2; 1649.1; 1436.0; 1374.4; 1358.6; 1225.8; 1149.1; 1047.2 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.66 (s, 1H); 5.35 (m, 1H); 5.05 (m, 1H); 3.97 (t, J = 6.53 Hz, 1H); 3.67 (s, 3H); 2.35-2.67 (m, 7H); 2.16 (s, 3H); 1.71 (s, 3H); 1.63 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.12; 159.68; 137.83; 134.77; 124.41; 119.93; 115.30; 76.90; 50.78; 40.44; 34.12; 26.11; 25.41; 18.75, 17.97, 17.90; and (**iv**) desired product **3** (130.2 mg, 40.2%): colorless oil, R_f = 0.17 in 20% EtOAc:Hex. FT-IR (neat): 3430.0; 2919.2; 2856.9; 1739.9; 1719.7; 1648.9; 1435.8; 1373.3; 1358.2; 1325.2; 1226.2; 1147.9; 1046.8 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.66 (s, 1H); 5.36 (t, J = 6.78 Hz, 1H); 5.08 (m, 1H); 3.98 (s, 2H); 3.68 (s, 3H); 1.98-2.23 (m, 8H); 2.15 (d, J = 1.95 Hz, 3H); 1.59 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.15; 160.00; 135.64; 134.67; 125.31; 122.87; 115.05; 68.46; 50.63; 40.67; 39.06; 25.92; 25.65; 18.62, 15.85, 15.77, 13.50.

Methyl *(E,E)*-(10*R*,11*R*)-10,11-epoxy-12-hydroxy-3,7,11-trimethyl-2,6-dodecadienoate (4). To a suspension of 4 Å molecular sieves (activated powder, 120 mg) in dry CH_2Cl_2 stirred at -45 °C under nitrogen atmosphere, were added (-)-diisopropyl tartrate (0.88 mL, 0.1 M solution in CH_2Cl_2), titanium isopropoxide (0.75 mL, 0.1 M solution in CH_2Cl_2) and *t*-butyl hydroperoxide (0.5 mL, 3.0 M solution in isooctane).[10] The mixture was stirred at this temperature for 45 min, then the above allylic alcohol (200 mg, 0.75 mmol) in CH_2Cl_2 was added dropwise. The resulting mixture was stirred at -45 °C for overnight, then, it was warmed to -20 °C and 2.0 mL of 10% tartaric acid solution was added and the mixture was warmed slowly to room temperature. The mixture was poured into saturated Na_2CO_3 solution and extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated *in vacuo*, purified (SiO_2) to give 161 mg of epoxy alcohol **4** as a colorless oil in 76% yield. R_f = 0.15 in 30% EtOAc:Hex. FT-IR (neat): 3458.4; 2929.7; 1718.8; 1649.0; 1435.8; 1348.4; 1358.2; 1325.6; 1225.5; 1147.5; 1044.7 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.61 (s, 1H); 5.08 (m, 1H); 3.62 (s, 3H); 3.51 (m, 2H); 2.94 (t, J = 6.23 Hz, 1H); 1.83-2.41 (m, 8H); 2.10 (d, J = 0.86 Hz, 3H); 1.56 (s, 3H); 1.22 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.12; 159.78; 134.93; 123.51; 115.21; 65.40; 60.96; 59.805; 50.66; 40.61; 36.10; 26.55; 25.67; 18.56, 15.82, 14.07. NMR of the α-methoxy-α-trifluoromethylphenyl acetate revealed an enantiomeric purity of >95%.

Methyl *(E,E)*-(10*R*,11*R*)-10,11-epoxy-12-iodo-3,7,11-trimethyl-2,6-dodecadienoate (5). To a stirred and ice cold solution of the alcohol (60 mg, 0.21 mmol), recrystallized triphenylphosphine (72 mg, 0.27 mmol) and imidazole (20 mg, 0.29 mmol) in acetonitrile:ether

(3 mL:5 mL), was added iodine (76.4 mg, 0.30 mmol). The resulting reddish suspension was stirred for 45 min at 0 °C, then, it was diluted with ether and washed (sat. $Na_2S_2O_3$, sat. $CuSO_4$), dried ($MgSO_4$)[11], concentrated, and purified (SiO_2) to give 72 mg of pure iodide **5** as a colorless oil. R_f = 0.65 in 30% EtOAc:Hex. FT-IR (neat): 2946.6; 1716.6; 1649.5; 1434.4; 1385.0; 1357.8; 1325.5; 1224.8; 1147.0; 1047.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.65 (s, 1H); 5.15 (m, 1H); 3.67 (s, 1H); 3.10 (dd, *J* = 9.28, 45.75 Hz, 2H); 2.83 (t, *J* = 6.20 Hz, 1H); 1.66-2.17 (m, 8H); 2.15 (d, *J* = 1.0 Hz, 3H); 1.61 (s, 3H); 1.43 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.14; 159.74; 134.80; 123.87; 115.36; 66.07; 59.99; 50.77; 40.73; 36.07; 27.50; 25.86; 18.78; 15.98, 13.84.

If allowed to react for over 1 hr, this reaction gave another product identified by ^{1}H and ^{13}C as methyl *(E,E)*-3,7,11-trimethyl-10-hydroxy-2,6,11-dodecatrienoate, R_f = 0.44 in 30% EtOAc:Hex. FT-IR (neat): 3448.8; 2945.0; 2854.0; 1720.4; 1649.6; 1435.8; 1383.9; 1356.1; 1225.3; 1147.5; 1061.5 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.66 (s, 1H); 5.12 (m, 1H); 4.87 (d, *J* = 28.97 Hz, 2H); 4.02 (t, *J* = 6.40 Hz, 1H); 3.67 (s, 3H); 2.15 (d, *J* = 2.91 Hz, 3H); 1.90-2.03 (m, 6H); 1.66 (s, 3H); 1.61 (s, 3H); 1.62 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.20; 159.88; 147.54; 135.83; 123.32; 115.33; 110.91; 75.45; 50.73; 40.81; 35.62; 33.13; 31.56; 25.86; 18.76; 17.59.

Methyl *(E,E)*-(10*R*)-10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienoate (JH III, 6). Iodide **5** (1.0 g, 2.55 mmol) was stirred with $NaBH_3CN$ (1.55 g, 25 mmol) in freshly distilled HMPA (30.0 mL) and dry THF (20 mL) under nitrogen atmosphere for 3 days.[12] Then, 50 mL of 0.1 M solution NaH_2PO_4 was added and the mixture was extracted with pentane and dried ($MgSO_4$). The crude product was purified (SiO_2) to give 0.58 g of a colorless oil (86% yield), R_f = 0.54 in 30% EtOAc:Hex. FT-IR (neat): 2955.3; 2926.0; 1719.3; 1649.5; 1435.0; 1378.2; 1357.9; 1324.2; 1279.1; 1224.2; 1147.1; 1059.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.64 (s, 1H); 5.12 (m, 1H); 3.66 (s, 3H); 2.68 (t, *J* = 6.2 Hz, 1H); 1.60-2.16 (m, 8H); 1.61 (s, 3H); 1.28 (s, 3H); 1.24(s, 3H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 167.15; 159.78; 135.31; 123.45; 115.30; 64.042; 58.206; 50.70; 40.78; 36.30; 27.42; 25.90; 24.84; 18.77; 18.71; 15.99.

Methyl (10*R*)-*(E)*-6,7,10,11-diepoxy-3,7,11-trimethyl-2-dodecenoate (7). A solution of potassium peroxomonosulfate (0.37 mmol) in water (10 mL) was added dropwise (10 min) to a well-stirred biphasic mixture of CH_2Cl_2 (8 mL) and buffered water (pH 7.5, phosphate buffer (4 mL) kept at 0 °C and containing (10*R*)-JH III (100 mg, 0.37 mmol), acetone (4 mL), and 18-crown-6 (100 mg, 0.33 mmol) as the phase-transfer catalyst. During the addition the pH was monitored and kept constant by using a pH-stat (0.5 N KOH).[13,14] The mixture was stirred at 0 °C for two hr. The organic layer was extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*, and purified (SiO_2) to give 47 mg of unreacted JH III (**6**) and 45 mg of the bisepoxide (**7**) in 80% yield based on the reacted JH III. R_f = 0.47 in 40% EtOAc:Hex. FT-IR (neat): 2960.7; 2926.9; 1718.9; 1649.7; 1435.2; 1383.7; 1360.1; 1326.2; 1281.1; 1225.6; 1151.0; 1031.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.68(s, 1H); 3.66 (, 3H); 2.64-2.78

(m, 2H); 2.26 (m, 2H); 2.15 (s, 3H); 1.55-1.78 (m, 6H); 1.28 (s, 3H); 1.25 (s, 3H); 1.24 (s,3H). ^{13}C-NMR ($CDCl_3$): δ (ppm): 166.94; 158.68; (158.64); 115.72; 63.91; (63.74); 62.77; (62.24); 60.50; (60.37); 58.30; (58.23); 50.78; 37.66; (37.53); 35.57; (35.12); 26.70; (26.56); 24.77; (24.51); 18.73; (18.63); 16.70; (16.43).

***(E)*-(10*R*)-6,7,10,11-Diepoxy-3,7,11-trimethyl-2-dodecen-1-ol (8).** To a solution of the above diepoxide (5.0 mg, 17.7 μmol) in hexane (1.5 mL) stirred at -78 °C under argon atmosphere was added DIBAL-H (20 μL, 1.0 M solution in hexane).[7] After stirring for 30 min, the reaction was quenched with EtOAc. Then, $MgSO_4$ was added and the mixture was filtered and concentrated *in vacuo* to give 5 mg which was used in the next step without further purification. R_f = 0.21 in 70% EtOAc:Hex. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.32 (t, J = 6.56 Hz, 1H); 4.01 (d, J = 6.73 Hz, 2H); 2.55-2.65 (m, 2H); 2.06 (m, 2H); 1.47-1.93 (m, 6H); 1.57 (s, 3H); 1.19 (s, 3H); 1.17 (s, 3H); 1.15 (s, 3H).

When performed at 0 °C, the reaction conditions resulted in cleavage of the epoxide in addition to reduction of the ester group. To optimize conditions for the next reaction, the alcohol was obtained from the silyl protected diepoxide in 68% yield by treatment with one equivalent of tetra-*n*-butylammonium fluoride in THF at 0 °C.

***(E)*-(10*R*)-6,7,10,11-Diepoxy-3,7,11-trimethyl-2-dodecenyl diazoacetate (1).** To an ice cold solution of the above crude alcohol (5.0 mg), and *p*-toluenesulfonylhydrazone glyoxylic acid (5.0 mg, 20 μmol) was added *N,N*-dimethylaniline (5.0 μL) in dry CH_2Cl_2 (1.0 mL). The solution was stirred at 0 °C for 30 min, and then triethylamine (5.0 μL) was introduced and the solution was stirred at 0 °C for 30 min and at room temperature for 1 hr. Hexane was added and the precipitate was filtered.[15] The solution was concentrated and purified (SiO_2) to give 2.0 mg of the title compound. R_f = 0.27 in 40% EtOAc:Hex. UV at 244.5 nm, A = 2.881 for c = 4 x 10^{-4} M, ε = 7202.5 in absolute ethanol. ^{1}H-NMR ($CDCl_3$): δ (ppm): 5.32 (t, J = 6.61 Hz, 1H); 4.76 (s,1H); 4.68 (d, J = 7.21 Hz, 2H); 2.64-2.78 (m, 2H); 2.20 (m, 2H); 1.72 (s, 3H); 1.45-1.80 (m, 6H); 1.20 (s, 3H); 1.17 (s, 3H); 1.16 (s, 3H).

[12-^{3}H]-Methyl (10*R*)-(*E*)-6,7,10,11-diepoxy-3,7,11-trimethyl-2-dodecenoate (7, T = ^{3}H). To a mixture of [12-^{3}H] (10*R*)-JH III (6, T = ^{3}H) (4.0 mCi, specific activity 14 Ci/mmol) in CH_2Cl_2 (1.0 mL), acetone (0.5 mL), buffered water (0.5 mL) and 18-crown-6 (2.0 mg, 6.6 μmol) stirred at 0 °C was added potassium peroxomonosulfate (0.3 μmol) in water (0.2 mL). The mixture was stirred for 4 hr at 0 °C before the organic layer was extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified (SiO_2) to give unreacted [12-^{3}H] (10*R*)-JH III (0.6 mCi) and the desired bisepoxide (1.4 mCi) in 41% radiochemical yield (based on the reacted starting material). Autoradiography of TLC plates indicated that the radioactive JH III and JHB III co-migrated with the corresponding radioinert JH III and JHB_3.

[12-^{3}H]-(10*R*)-(*E*)-6,7,10,11-Diepoxy-3,7,11-trimethyl-2-dodecen-1-ol (8, T = ^{3}H). To a solution of the above bisepoxide (0.2 mCi, 14 Ci/mmol) in hexane (0.5 mL) stirred at

-78 °C under argon atmosphere was added DIBAL-H (14 μL, 1.0 mM solution in hexane). After stirring for 1 hr, the reaction was quenched as described for the radioinert alcohol (8). The crude alcohol was used in the next step without further purification.

[12-^{3}H]-(10*R*)-(*E*)-6,7,10,11-Diepoxy-3,7,11-trimethyl-2-dodecenyl diazoacetate (1, T = ^{3}H). To an ice cold solution of the above alcohol in dry CH_2Cl_2 (0.5 mL) and *p*-toluenesulfonylhydrazone glyoxylic acid (1.0 μL, 10 mM solution in CH_2Cl_2) was added *N,N*-dimethylaniline (1.0 μL, 0.1 M solution in CH_2Cl_2). The solution was stirred at 0 °C for 1 hr, and then triethylamine (1.0 μL, 0.1 M solution in CH_2Cl_2) was added and the solution was stirred at 0 °C for 1 hr and at room temperature for 1 hr. Concentration of the solution and purification (SiO_2), followed by TLC-autoradiography gave [^{3}H]BEFDA (150 μCi, 14 Ci/mmol), which co-migrated with the cold BEFDA, in 75% radiochemical yield from [12-^{3}H]-(10*R*)-JH III.

Acknowledgements

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