Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Lucina G. Sánchez [a], Elizabeth N. Castillo [a], Hortensia Maldonado [a], Daniel Chávez [a], Ratnasamy Somanathan [a] & Gerardo Aguirre [a]
[a] Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Tijuana, México
Version of record first published: 25 Jan 2008.

To cite this article: Lucina G. Sánchez , Elizabeth N. Castillo , Hortensia Maldonado , Daniel Chávez , Ratnasamy Somanathan & Gerardo Aguirre (2007): Stereoselective Synthesis of Rubrenoic and nor-Rubrenoic acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:1, 54-71

To link to this article: http://dx.doi.org/10.1080/00397910701649049

Synthetic Communications®, 38: 54–71, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701649049

Stereoselective Synthesis of Rubrenoic and *nor*-Rubrenoic acids

Lucina G. Sánchez, Elizabeth N. Castillo, Hortensia Maldonado, Daniel Chávez, Ratnasamy Somanathan, and Gerardo Aguirre

Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Tijuana, México

Abstract: The total stereoselective synthesis of (*Z*)-rubrenoic I (**1a**), (*Z*)-*nor*-rubrenoic I (**17a**), (*E*)-rubrenoic III (**3b**), and *nor*-(*E*)-rubrenoic III (**30b**) acids was achieved using Suzuki and Stille cross-coupling reactions from readily available starting materials.

Keywords: rubrenoic acid, Suzuki and Stille cross-coupling reaction

INTRODUCTION

Natural products isolated from marine organisms represent a new source of pharmacologically active chemical compounds showing impressive in vitro activities.[1] Rubrenoic acids I–III (**1**–**3**) are unique aromatic unsaturated acids with a hexane or hexene carboxylic acid and a butenyl or butadienyl side chain (Fig. 1). They have been isolated from the marine bacterium *Alteromonas rubra*, and they demonstrated bronchodilator activity.[2]

Rubrenoic acids **1**–**3** possess similar structural features to serpentenes **4**–**5** (Fig. 2), which are polyunsaturated carboxylic acids with 20 carbons.[3,4] They are isolated from *Streptomyces sp.* Tü 3851 and show mild antibacterial activity. *Ortho*-methyl phenyl alkenoic acids are periodically encountered in

Received in the USA June 26, 2007
Address correspondence to Gerardo Aguirre, Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Apdo. Postal 1166, Tijuana 22500, B.C. México. E-mail: lasvid777@yahoo.com.mx or gaguirre@tectijuana.mx

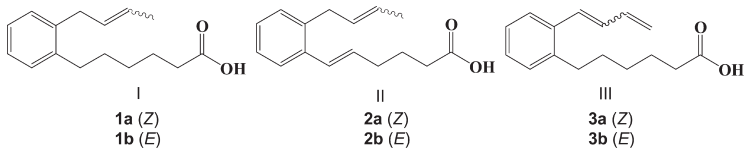


Figure 1. Structure of natural rubrenoic acids I-III (**1**–**3**).

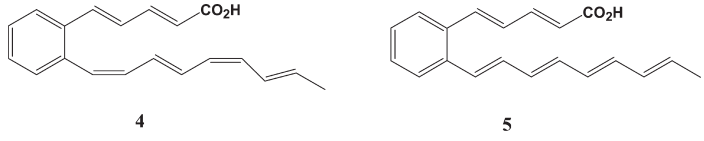


Figure 2. Structures of serpentene (**4**) and all-*trans* serpentene (**5**).

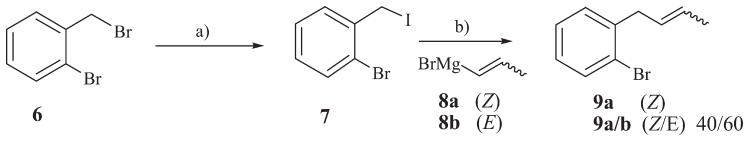
nature: *o*-methylcinnamide (U-77863) from *Streptomyces griseoluteus*[3] inhibits cancer invasion and metastasis;[5] 1-hydroxy-2-hydroxymethyl-3-pent-1-enyl-benzene and 1-hydroxy-2-hydroxymethyl-3-pent-1,3-dienylbenzene, isolated from *deuteromycete*, inhibit both the TPA-induced NF-kB and AP-1.[6] 5-(2-Methylphenyl)-4-pentenoic acid has been isolated from a terrestrial *Streptomycete*,[7] and demetric acid has been isolated from *Streptomyces umbrosus*.[8] Even shorter analogs have been described as acyl groups for the *Streptomyces* peptides WS 9326A[9,10] and RP 1776.[11]

A previous report on the synthesis of **3a**,**b** led to yields of only 5–20%; also, the synthesis of pseudorubrenoic acid led to low yield.[12] The biological activities of these polyunsaturated compounds have not been fully explored because of the lack of appreciable amounts of material. We therefore embarked on a project to develop an efficient general synthetic route to obtain these compounds.

RESULTS AND DISCUSSION

As model compounds, we selected rubrenoic acids I as target molecules to test our general synthetic route (Scheme 1). Commercially available 2-bromobenzyl bromide (**6**) was converted into the 2-bromobenzyl iodide (**7**) and then alkylated with *cis*-vinyl magnesium bromide (**8a**) to give the 1-bromo-2-[(*Z*)-but-2-enyl]-benzene (**9a**) in 77% yield (*E* isomer was not detected by ^{1}H NMR). Interestingly, when compound **7** was alkylated with *trans*-vinyl magnesium bromide (**8b**), a mixture of the isomers **9a**/**b** was obtained in a 40/60 proportion as determined by ^{1}H NMR (integration for benzylic protons).

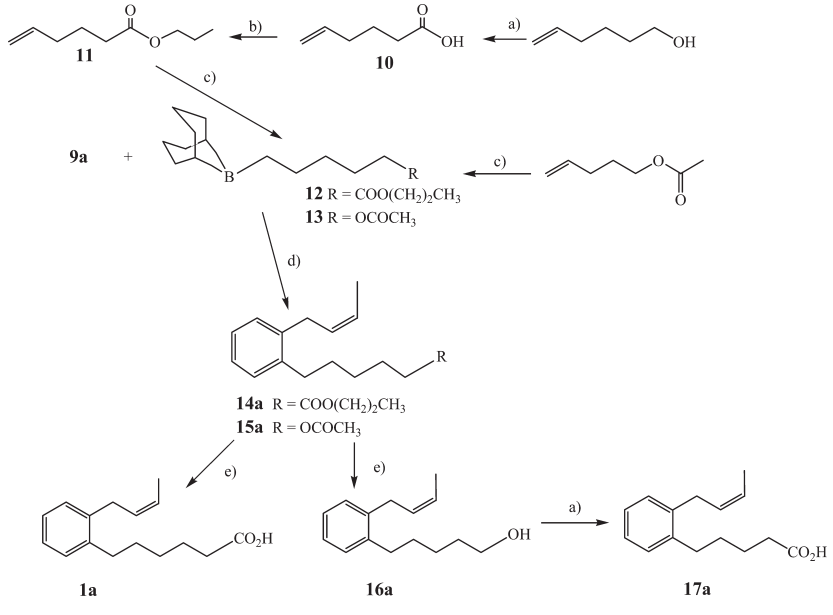
The ortho-hexane carboxylate fragment was prepared[13,14] from 6-(9-borabicyclo [3.3.1] non-9-yl) propyl hexanoate (**12**), which was in turn prepared from commercially available 5-hexen-1-ol followed by oxidation



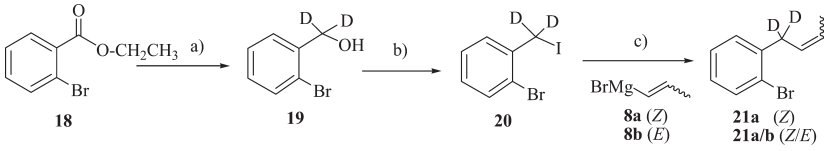
Scheme 1. (a) Nal 2 eq., acetone, room temperature; (b) Cul/THF, −78°C, 0°C to −15°C.

and esterification to propyl hex-5-enoate (**11**). A Suzuki–Miyaura[14] coupling with **9a**, using Pd(dppf)Cl_2 as catalyst, gave 6-(2-(*Z*)-but-2-enyl-phenyl)-hexanoic acid propyl ester (**14a**). Hydrolysis gave (*Z*)-rubrenoic acid I (**1a**) in 19% yield. Similarly, acetic acid 5-(9-borabicyclo [3.3.1] non-9-yl)-pentyl ester (**13**) coupling to **9a** gave *nor*-(*Z*)-rubrenoic acid I (**17a**) in 24% yield with an additional step, Jones's oxidation of the primary alcohol (Scheme 2). For both compounds (**1a, 17a**), the ^{1}H NMR signals for the vinylic protons displayed *cis* stereochemistry ($J = 11.2$ Hz).

To establish unequivocally the stereochemistry on the double bond, we prepared the benzylic-deuterated analogs. Thus, 1-bromo-2-[(*Z*)-1,1-dideutero-but-2-enyl]-benzene (**21a**) was prepared from commercially available ethyl 2-bromobenzoate (**18**), which was reduced with $LiAlD_4$ to (2-bromo-phenyl)-dideutero-methanol (**19**) in 95% yield. Intermediate **19**



Scheme 2. (a) CrO_3, H_2SO_4 1.5 M, acetone; (b) bromine–propane, $NaHCO_3$, DMF; (c) 9-BBN 0.5 M in THF; (d) $CsCO_3$, Ph_3As 10% mol, $PdCl_2$(dppf) 5% mol, DMF–THF–water; (e) LiOH 1 N, CH_3OH/THF (2/3 v/v), reflux.



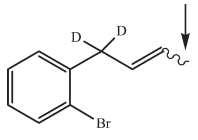
Scheme 3. (a) $LiAlD_4$/THF; (b) $CeCl_3 \cdot 7H_2O$, NaI, acetonitrile; (c) CuI/THF, −78°C, 0°C to −15°C.

was converted to 1-bromo-2-(iodo-dideutero-methyl)-benzene (**20**) and alkylated with *cis*-vinyl magnesium bromide (**8a**) to give 1-bromo-2-[(*Z*)-1, 1-dideutero-but-2-enyl]-benzene (**21a**) in 72% yield. Alkylation was also performed with *trans*-vinyl magnesium bromide (**8b**) then to give 1-bromo-2-[(*Z*/*E*)-1,1-dideutero-but-2-enyl]-benzene (**21a/b**) as a *cis*/*trans* mixture in 72% yield (Scheme 3).

As expected, the ^{1}H NMR spectrum of the deuterated compounds **21a/b** was complex. All the NMR signals appear as a multiplet at 5.55 ppm (both *cis* and *trans* vinylic protons). However, in double resonance using irradiation of the methyl protons, the spectrum simplifies, and it was possible to see the four doublets for the *cis* and *trans* vinylic protons (Table 1). Similarly, decoupling of the vinylic protons resulted in a spectrum with two singlets for the methyls. Integration of the well-separated signals for the allylic methyls (δ_H 1.57 for *cis and* 1.62 *for trans*) indicated a 40:60 ratio for the isomers *Z*/*E*, respectively. This was confirmed by analysis of the gas chromatography/electron impact mass spectrometry (GC/EIMS) chromatogram.

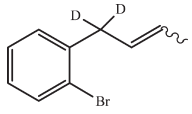
Careful analysis of ^{13}C NMR spectra for compound **21a** and the mixture of compounds **21a/b** showed different signals for the vinylic methyls, δ_C 13.4 corresponding to the *cis* isomer and δ_C 13.6/18.4 for the *cis*/*trans* mixture (Table 2). These results are in agreement with ^{13}C NMR data reported in

Table 1. Partial ^{1}H NMR data of the mixture of 1-bromo-2-[(*E*/*Z*)-1,1-dideutero-but-2-enyl]-benzene (**21a/b**) in a double resonance experiment (200 MHz, $CDCl_3$)



Multiplicity	δ (ppm)	*J* (Hz)	Configuration
d	5.74	9.4	*cis*
d	5.72	16.2	*trans*
d	5.68	15.2	*trans*
d	5.67	7.4	*cis*

Table 2. Partial ^{13}C NMR data of the 1-bromo-2-[(*Z*)-1,1-dideutero-but-2-enyl]-benzene (**21a**) and the mixture of 1-bromo-2-[(*Z*/*E*)-1,1-dideutero-but-2-enyl]-benzene (**21a/b**) (50 MHz, $CDCl_3$)



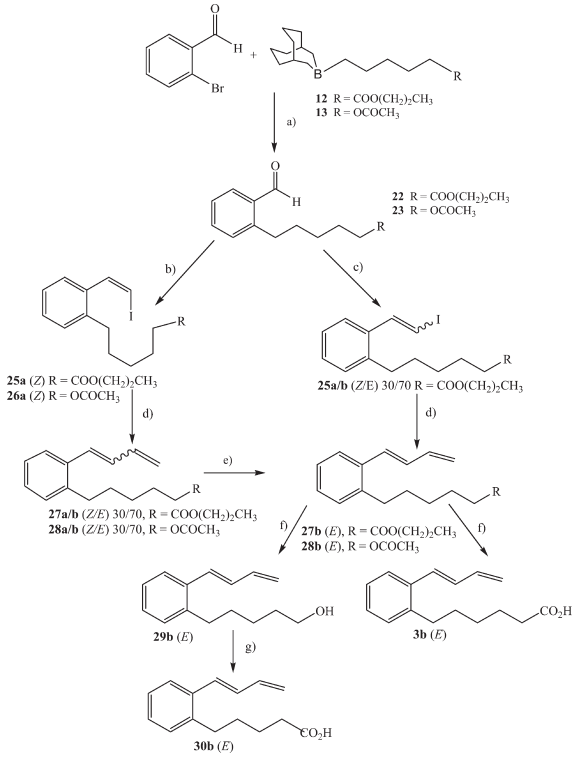
compound	δ (ppm)	Configuration
21a	13.4	*cis*
21a/b	13.6/18.4	*cis*/*trans*

the literature, where the signal for the vinylic methyl in *cis* position is found ca. 5.3 ppm upfield from the *trans*.[15,16]

To obtain rubrenoic acid III (**3**), the general synthetic route described in Scheme 4 was followed. *o*-Bromoenzaldehyde was coupled with 6-(9-borabicyclo [3.3.1] non-9-yl) propyl hexanoate (**12**) using the Suzuki–Miyaura method[14] to give the intermediate propyl 6-(2-formylphenyl) hexanoate (**22**) in 85% yield. The intermediate **22** when treated with triphenyl iodomethyl phosphonium iodide (**24**) gave the 6-[2-*Z*-(2-iodo-vinyl)-phenyl]-hexanoic acid propyl ester (**25a**) in 50% yield.[17] Stille coupling reaction[18] with tributylvinyltin gave the 6-(2-*Z*-buta-1,3-dienyl-phenyl)-hexanoic acid propyl ester (**27a**) in 65% yield. We found than the *cis* compound spontaneously isomerizes in the presence of light to the *trans* isomer 6-(2-*E*-buta-1,3-dienyl-phenyl)-hexanoic acid propyl ester (**27b**). We carried out the Stille coupling reaction in the absence of light, and then immediately analyzed it by high performance liquid chromatography (HPLC). From this, we obtained a mixture of **27a** and **27b** in a ratio of 30/70 (*Z*/*E*), respectively. After few hours under daylight, only the *trans* isomer could be detected in the HPLC. This result is different from a previous work,[3] which reported the separation of both isomers. Finally, hydrolysis of the protecting group gave *E*-rubrenoic acid III (**3b**) in 19% overall yield. On the other hand, when the intermediate **22** was treated under White's conditions,[19] the mixture of *Z*/*E* iodo-alkene **25a/b** was obtained, and only **27b** was recovered after Stille coupling reaction.[18] Thus, only the *E*-rubrenoic acid III (**3b**) could be obtained.

The *nor*-rubrenoic acid III (**30b**) was obtained in a fashion similar to the synthesis of *E*-rubrenoic acid III (**3b**), but in this case hydrolysis of acetic acid 5-(2-*E*-buta-1,3-dienyl-phenyl)-pentyl ester (**28b**) gave 5-(2-*E*-buta-1,3-dienyl-phenyl)-pentan-1-ol (**29b**) in 95% yield. Lastly, Jones's oxidation of **29b** led to the *nor*-*E*-rubrenoic acid III (**30b**) in 22% overall yield (Scheme 4).

In summary, we have developed an efficient synthetic route to (*Z*)-rubrenoic and *nor*-(*Z*)-rubrenoic acids I with overall yields of 19%



Scheme 4. (a) $CsCO_3$, Ph_3As 10% mol, $PdCl_2$(dppf) 5% mol, DMF–THF–water; (b) $Ph_3P^+CH_2I.I^-$ (**24**) NaHMDS 1.0 M, rt, HMPA $-78°C$; (c) $CrCl_2$, CHI_3/THF, 0°C; (d) CuI 10% mol, $Pd(PPh_3)_4$ 5% mol, $[CH_3(CH_2)_3]_3Sn$ $CH{=}CH_2$ rt; (e) CH_2Cl_2, I_2, λ; (f) LiOH 1 N, CH_3OH/THF (2/3 v/v) reflux; (g) CrO_3, H_2SO_4 1.5 M; acetone.

and 24%, respectively. Studies of the butenyl chain with deuterated benzylic positions and double-irradiation NMR experiments corroborated the *cis* stereochemistry in the double bond as well as chemical shifts on ^{13}C NMR. (*E*)-rubrenoic acid and *nor*-(*E*)-rubrenoic acids III were obtained in overall yields of 19% and 22%, respectively. Both the rubrenoic acids and *nor*-rubrenoic acids (I and III) can be synthesized in reasonable amounts for further biological studies. Our stereoselective synthetic methodology also provides a route to other similar polyunsaturated benzene compounds.

EXPERIMENTAL

General Methods

Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin-Elmer

FT-IR 1600 spectrometer. ^{1}H (200-MHz) and ^{13}C NMR (75-MHz) spectra were recorded on a Bruker Avance DPX 300-MHz spectrometer. Spectra were run in $CDCl_3$ with tetramethylsilane (TMS) used as internal standard. Mass spectra were obtained on a Hewlett Packard 5989 MS spectrometer at 70 eV by direct insertion. The high resolution mass spectrometry (HRMS) (FAB^+) data was obtained on a Finnigan MAT-90 instrument, and elementary analyses for carbon and hydrogen were conducted by Galbraith Laboratories, Inc. (Knoxville, TN). Reagents were acquired from Aldrich and used as received: 9-BBN (0.05 M solution in THF), 2-bromobenzyl bromide, benzaldehyde 2-bromine, ethyl 2-bromobenzoate, $PdCl_2$ (dppf), Ph_3As, Cs_2CO_3, NaHMDS (1.0 M solution in THF), hexamethylphosphoramide (HMPA), $Pd(PPh_3)_4$, $CrCl_2$, $LiAlD_4$, 5-hexen-1-ol, *cis*-1-bromo-1-propene, *trans*-1-bromo-1-propene, 1-bromo-propane, and 4-pentenyl acetate.

2-Bromobenzyl Iodide (7)

A solution of 2-bromobenzyl bromide (**6**) (1.00 g, 4.0 mmol) was added dropwise to a solution of sodium iodine (1.20 g, 8.00 mmol) in acetone (40 mL). The mixture was vigorously stirred for 5 min, in which time the mixture turned orange with formation of a white precipitate (NaBr). The reaction was complete in 21 hr. The solid was collected by filtration and washed twice with acetone, and the filtrate was concentrated under reduced pressure, dissolved in water, and extracted with ethyl ether (50 mL). The organic phase was washed with brine, dried under anhydrous $MgSO_4$, and filtered, and solvent was removed under reduced pressure to give an amber color solid (1.12 g, 94%), melting point 42–44°C. IR (KBr): 3065, 2926, 1152, 573 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (1H, dd, $J = 8.2$, 1.8 Hz, Ar); 7.44 (1H, dd, $J = 7.6$, 1.6 Hz, Ar); 7.25 (1H, dt, $J = 7.8$, 1.2 Hz, Ar); 7.12 (1H, dt, $J = 7.6$, 1.8 Hz, Ar); 4.54 (2H, s, -C$\underline{H}_2$-l); ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.6, 130.6, 129.6, 128.0, 124.1, 5.7; m/z (EIMS) 298 M^++2 (8), 296 M^+ (8), 169 (100), 127 (47), 89 (55). Anal. calcd. for C_7H_6BrI: C, 28.31; H, 2.04. Found: C, 28.48; H, 2.22.

cis-Propenyl Magnesium Bromide (**8a**) Grignard Reagent

In a dry Schlenk flask (100 mL), magnesium (0.245 g, 10.10 mmol), and iodine in catalytic amounts were placed under an inert atmosphere in tetrahydrofuran (THF) (50 mL). The solution was stirred for 10 min at room temperature, and then a solution of *cis*-bromo-1-propene was added (1.22 g, 10.10 mmol). The reaction mixture was stirred at reflux temperature for 30 min. The crude product was used in the next step of the procedure.

1-Bromo-2-[(*Z*)-but-2-enyl]-benzene (**9a**)

A suspension of 2-bromobenzyl iodide (**7**) (0.500 g, 1.684 mmol) in THF (40 mL) was treated with copper iodide (0.034 g, 0.178 mmol) under an inert atmosphere at −78°C. Then a solution of Grignard reagent **8a** was added dropwise by syringe. The reaction mixture was stirred for 17 h at −10°C. The reaction was quenched by addition of NH_4Cl (10 mL) and extracted with ethyl ether (3 × 30 mL). The organic layer was washed twice with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (90:10 hexanes–petroleum ether) to give a clear yellow oil product (0.27 g, 77%). IR (film): 3062–3020, 2916–2854, 1468–1441, 1021, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (1H, d, $J = 7.6$ Hz, Ar); 7.23 (2H, m, Ar); 7.06 (1H, dd, $J = 8.2$, 3.4 Hz, Ar); 5.54 (2H, m, -CH_2-C<u>H</u>=C<u>H</u>-CH_3); 3.50 (2H, d, $J = 6.4$ Hz, -C<u>H_2</u>-CH=CH-CH_3); 1.73 (3H, d, $J = 6.0$ Hz, -CH=CH-C<u>H_3</u>); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.4, 132.7, 130.0, 127.5, 127.4, 127.3, 125.8, 124.5, 33.6, 13.0; m/z (EIMS) 212 M^++2 (36), 210 M^+ (37), 131 (93), 116 (100), 91 (57). Anal. calcd. for $C_{10}H_{11}Br$: C, 56.90; H, 5.25. Found: C, 57.02; H, 5.38.

1-Bromo-2-[(*Z*/*E*)-but-2-enyl]-benzene (**9a**/**b**)

This compound was synthesized following the same procedure described for compound **9a** using a solution of Grignard reagent **8b** and compound **7** to give a clear yellow oil product (77%). *Z*/*E* 40:60. IR (film): 3058–3014 (C=C-H); 2918–2854 (C-H); 1467–1438 (-CH_2-); 1024 (Ar-Br); 966 (CH=CH); 747 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.52 (1H, d, $J = 7.6$ Hz, Ar); 7.21 (2H, m, Ar); 7.03 (1H, m, Ar); 5.56 (2H, m, -CH_2-C<u>H</u>=C<u>H</u>-CH_3); 3.50 (2H, d, $J = 6.4$ Hz, -C<u>H_2</u>-CH=CH-); 3.42 (2H,d, $J = 6.4$ Hz, -C<u>H_2</u>-CH=CH-); 1.73 (3H, d, $J = 6.0$ Hz -CH=CH-C<u>H_3</u>). ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.4, 132.7, 130.0, 127.5, 127.4 127.3, 125.8, 124.5, 36.4, 33.6, 19.0, 13.0. m/z (EIMS) 212 M^++2 (36), 210 M^+ (37), 131 (93), 116 (100), 91 (57). Purity determined by GC-EIMS *Z*/*E* 55:37 (92%).

Hex-5-enoic Acid (**10**)

A solution of chromium trioxide (6.250 g, 62.5 mmol) in aqueous 1.5 M sulfuric acid (100 mL, 150 mmol) at 0°C was treated with a solution of 5-hexen-1-ol (1.662 g, 16.6 mmol) in acetone (200 mL) by dropwise addition over 6 h. The reaction was complete in 8 h at 5°C and diluted with ethyl ether (150 mL). The organic phase was washed with a brine solution (3 × 100 mL). The organic phase was concentrated under reduced pressure and dissolved in ethyl ether (100 mL). The solution was washed with 1M NaOH (2 × 75 mL), then washed and acidified with 6 M sulfuric acid (50 mL), and extracted again with ethyl ether (3 × 75 mL). The organic

phase was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (90:10 hexanes–ethyl acetate) to give a colorless liquid (yield, 1.118 g, 60%). IR (film): 3215, 3077, 2936, 1711, 1642, 1245 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 11.2 (1H, bs, COOH); 5.77 (1H, ddt, $J = 17.2$, 10.2, 6.6 Hz, -CH=CH_2); 5.01 (2H, m, -CH=CH_2); 2.36 (2H, t, $J = 7.4$ Hz, -CH_2-COOH); 2.11 (2H, c, $J = 7.0$, 6.6 Hz, =CH-CH_2-CH_2-); 1.73 (2H, q, $J = 7.0$, 6.8 Hz, -CH_2-CH_2-CH_2-); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.9, 137.2, 115.3, 33.3, 32.9, 23.7.

Propyl Hex-5-enoate (**11**)

$NaHCO_3$ (20 eq., 1.68 g) and 1-bromo-propane (10 eq., 0.907 mL) were added to a solution of hex-5-enoic acid (**10**) (0.114 g, 1.0 mmol) in DMF (5 mL). The reaction mixture was stirred at room temperature for 24 h, quenched with water (50 mL), and then extracted with ethyl ether (3 × 50 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and filtered, and solvent was removed under pressure to give a light yellow liquid product (0.1342 g, 86%). IR (film): 3077, 2968, 1736, 1684, 1173 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.78 (1H, ddt, $J = 17.0$, 11.2, 6.6 Hz, CH_2=CH-); 5.01 (1H, dd, $J = 17.2$, 1.6 Hz, CH_2=CH-); 4.97 (1H, dd, $J = 11.2$, 1.2 Hz, CH_2=CH-), 4.03 (2H, t, $J = 6.6$ Hz, -CO_2-CH_2-CH_2-); 2.31 (2H, t, $J = 7.8$ Hz, -CH_2-CO_2-CH_2 -); 2.08 (2H, c, $J = 6.8$, 6.4 Hz, =CH-CH_2-CH_2-); 1.69 (2H, q, $J = 7.0$ Hz, -CH_2-CH_2-CH_2-CO_2-CH_2); 1.65 (2H, sext, $J = 7.4$ Hz, -CH_2-CO_2-CH_2-CH_2-CH_3); 0.94 (3H, t, $J = 7.6$ Hz, -CH_2-CO_2-CH_2-CH_2-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.4, 137.4, 115.0, 65.7, 33.5, 33.0, 24.1, 21.9, 10.4. Anal. calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.29; H, 9.42.

6-(9-Borabicyclo [3.3.1] non-9-yl)-propyl Hexanoate (**12**)

A solution of propyl hex-5-enoate (**11**) (0.569 g, 4.44 mmol) in THF (4 mL) was cooled to 0°C, and a solution of 9-BBN (0.5 M solution in THF, 8.9 mL, 4.44 mmol) was added dropwise during 15 min. The solution was warmed to room temperature and stirred for 4 h. The crude product was used in situ in the Suzuki coupling procedure in the next step.

Acetic Acid 5-(9-Borabicyclo [3.3.1] non-9-yl)-pentyl Ester (**13**)

This compound was synthesized following the same procedure described for compound **12** but using 4-pentenyl acetate. In this reaction, the 9-BBN was added at −10°C for 5 min and stirred at room temperature for 4 h.

General Procedure of the Suzuki–Miyaura Cross-coupling

6-(2-(*Z*)-but-2-enyl-phenyl)-hexanoic Acid Propyl Ester (**14a**)

A suspension of compound **9a** (0.455 g, 2.15 mmol), Cs_2CO_3 (1.26 g, 3.87 mmol, 1.8 eq.), $PdCl_2$ (dppf) (0.078 g, 0.107 mmol, 5% mol), and Ph_3As (0.066 g, 0.215 mmol, 10% mol) in DMF (10 mL) was placed in a dry round-bottom flask (50 mL). The solution was stirred for 5 min, during which time the mixture turned orange. Water (0.46 mL, 25.8 mmol, 12 eq.), and then a solution of compounds **12**/THF (2.58 mmol) were added. The solution was stirred for 5 min, and then more water was added (0.37 mL, 20.64 mmol, 12 eq.). Then the reaction mixture was stirred for 4 h. The reaction was quenched by addition of water (100 mL). After regular extraction with ethyl ether (3 × 50 mL), the organic phase was washed with aqueous 10% HCl solution (1 × 50 mL), 10% NH_4OH (1 × 50 mL), water (2 × 50 mL), and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under vacuum, and the product was purified by flash-column chromatography on silica gel (90:10 petroleum ether–ethyl acetate) to give a light yellow liquid product (0.198 g, 53%). IR (film): 2932, 1735, 1175, 749 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.05 (4H, m, Ar); 5.46 (2H, m, Ar-CH_2-C<u>H</u>=C<u>H</u>-CH_3); 3.95 (2H, t, $J = 7.0$ Hz, -O-C<u>H_2</u>); 3.31 (2H, d, $J = 5.6$ Hz, Ar-C<u>H_2</u>-CH=CH); 2.54 (2H, t, $J = 8.2$ Hz, Ar-C<u>H_2</u>-CH_2-); 2.24 (2H, t, $J = 7.6$ Hz, C<u>H_2</u>-C=O); 1.66 (3H, d, $J = 5.8$ Hz, CH=CH-C<u>H_3</u>); 1.62 (8H, m, -C<u>H_2</u>); 0.86 (3H, t, $J = 7.8$ Hz, CH_2-C<u>H_3</u>); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.8, 140.4, 138.8, 129.2, 129.1, 126.1, 126.1, 124.5, 66.0, 34.6, 32.9, 30.9, 30.6, 29.5, 25.2, 22.3, 13.2, 10.7. Anal. calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.21; H, 9.90.

Acetic Acid 5-(2-But-2-enyl-phenyl)-pentyl Ester (**15a**)

This compound was synthesized following the same procedure described for the Suzuki–Miyaura coupling in compound **14a** using the compounds **9a** and **13** to give a light yellow liquid product (50%). IR (film): 2933–2859 (C-H); 1739 (C=O); 1238 (C-O-C); 1041 (CH-O-CH_2-); 751 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.15 (4H, m, Ar); 5.54 (2H, m, Ar-CH_2-C<u>H</u>=C<u>H</u>-CH_3); 4.08 (2H, t, $J = 4.6$ Hz, -C<u>H_2</u>-O-C=O-CH_3); 3.40 (2H, d, $J = 4.4$ Hz, Ar-C<u>H_2</u>-CH=CH-); 2.64 (2H, t, $J = 5.6$ Hz, Ar-C<u>H_2</u>-CH_2); 2.05 (3H, s, -C=O-C<u>H_3</u>); 1.75 (3H, d, $J = 3.8$ Hz, -CH=CH-C<u>H_3</u>); 1.42 (6H, m, -C<u>H_2</u>-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 139.9, 138.4, 132.5, 130.2, 128.9, 128.8, 125.8, 124.2, 64.3, 32.6, 30.5, 30.3, 28.5, 26.0, 21.0, 12.9. m/z (EIMS): 260 (M^+), 129 (100). Anal. calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.57; H, 9.16.

(*Z*)-Rubrenoic Acid I (**1a**)

Saponification

A solution of 1 N LiOH (0.71 mL) was added to a solution of compound **14a** (0.064 g, 0.22 mmol) in CH_3OH/THF (2/3 v/v) (10 mL), and the reaction mixture was stirred and refluxed for 3 h. Then aqueous 2 N HCl (50 mL) was added, and the product was extracted with ethyl acetate (3 × 30 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and purified by flash column chromatography on silica-gel dichloromethane to give an oily product (0.51 g, 95%). IR (film): 3200, 3075, 2933, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.05 (4H, m, Ar); 5.46 (2H, m, -CH_2-C<u>H</u>=C<u>H</u>-CH_3); 3.31 (2H, d, $J = 5.8$ Hz, Ar-C<u>H_2</u>-CH=CH); 2.55 (2H, t, $J = 8.6$ Hz, Ar-C<u>H_2</u>-CH_2-); 2.30 (2H, t, $J = 6.6$ Hz, -C<u>H_2</u>-COOH); 1.67 (3H, d, $J = 5.8$ Hz, -CH=CH-C<u>H_3</u>); 1.54 (6H, m, -C<u>H_2</u>-); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.1, 140.0, 138.5, 128.8 (3C), 125.8, 125.7, 124.2, 33.4, 32.6, 30.5, 30.3, 29.1, 24.5, 12.9. m/z [HRMS (FAB^+)] calc. for $C_{15}H_{21}O_2$ [M + H] 233.1542. Found: 245.1508. Anal. calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.57; H, 9.13.

5-(2-But-2-enyl-phenyl)-pentan-1-ol (**16a**)

This compound was obtained following the same procedure described for compound **1a** using the compound **15a** to give an oil (63%). IR (film): 3355 (-OH); 2930–2860 (C-H); 1457 (C=C); 1049 (CH-O-CH_2-); 751 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.13 (4H, m, Ar); 5.54 (2H, m, Ar-CH_2-C<u>H</u>=C<u>H</u>-CH_3); 3.64 (2H, t, $J = 6.4$ Hz, -C<u>H_2</u>-OH); 3.39 (2H, d, $J = 6.2$ Hz, Ar-C<u>H_2</u>-CH=CH-); 2.63 (2H, t, $J = 8.0$ Hz, Ar-C<u>H_2</u>-CH_2-); 1.74 (3H, d, $J = 5.2$ Hz, -CH=CH-C<u>H_3</u>); 1.60 (4H, m, -C<u>H_2</u>-CH_2-C<u>H_2</u>-); 1.46 (2H, m, -CH_2-C<u>H_2</u>-CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.7, 139.0, 129.4, 129.3, 129.2, 126.3, 126.2, 124.7, 63.1, 33.1, 32.9, 30.9, 30.5, 26.1, 13.1. m/z (EIMS) 218 M^+ (30) 129 (100). Anal. calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.61; H, 10.28.

nor-(*Z*)-Rubrenoic Acid I (**17a**)

This compound was obtained following the same procedure described for compound **10** using the compound **16a** to give an oily product (73%). IR (film): 3339 (-OH); 3060 (C=C-H); 2922 (C-H); 1708 (COOH); 1411 (-CH_2-); 1285 (C-0); 751 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.16 (4H, m, Ar); 5.49 (2H, m, Ar-CH_2-C<u>H</u>=C<u>H</u>-CH_3); 3.39 (2H, d, $J = 6.4$ Hz, Ar-C<u>H_2</u>-CH=CH-); 2.61 (2H, t, $J = 8.4$ Hz, Ar-C<u>H_2</u>-CH_2); 2.42 (2H, t, $J = 7.0$ Hz, -C<u>H_2</u>-COOH); 1.75 (3H, d, $J = 6.2$ Hz, -CH=CH-C<u>H_3</u>); 1.69 (4H, m, -C<u>H_2</u>-C<u>H_2</u>-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.0, 139.6, 138.5, 128.9, 128.8, 128.1, 125.9, 125.8, 124.3, 33.9, 32.4, 30.3, 24.7, 12.9. m/z

[HRMS (FAB^+)] calc. for $C_{14}H_{19}O_2$ [M + H] 219.1385. Found: 219.1415. Anal. calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.75; H, 8.89.

(2-Bromo-phenyl)-dideutero-methanol (**19**)

A suspension of $LiAlD_4$ (1.08 g, 25.72 mmol) and dry THF (150 mL) was added dropwise to a solution of ethyl 2-bromobenzoate (**18**) (2.94 g, 12.86 mmol) in dry THF (50 mL) at 0°C in a dry round-bottom flask (250 mL). The solution was stirred for 12 h, in which time the mixture turned gray. This was then added dropwise to a solution of 3 M NaOH, which resulted in a white suspension. The solid was collected by filtration, washed twice with ethyl ether, dried under anhydrous $MgSO_4$, and filtered, and solvent was removed under reduced pressure to give a white solid, yield 95%, mp 73–74°C. IR (film): 3332; 3061–3027; 2199–2090; 1227; 666 (C-Br) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.47 (1H, dd, $J = 7.6$, 1.4 Hz, Ar); 7.40 (1H, dd, $J = 7.6$, 1.8 Hz, Ar); 7.31 (1H, td, $J = 7.6$, 1.2 Hz, Ar); 7.09 (1H, td, $J = 7.2$, 1.8 Hz, Ar); 1.99 (1H, bs, -OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.0, 132.7, 129.2, 129.1, 127.7, 122.7.

1-Bromo-2-(iodo-dideutero-methyl)-benzene (**20**)

Compound **19** (0.189 g, 1 mmol) and NaI (0.179 g, 1.2 mmol) in acetonitrile (10 mL) were placed in a dry round-bottom flask (50 mL), to which $CeCl_3 \cdot 7 H_2O$ (0.560 g, 1.5 mmol) was added, and the resulting mixture was stirred for 24 h at reflux. The mixture was diluted with ethylic and treated with 0.5 N HCL (15 mL). The organic layer was separated, and the aqueuos phase was extracted ethylic ether (2 × 20 mL). The combined organic phase was washed with a solution of saturated $NaHCO_3$ and brine, dried under anhydrous $MgSO_4$, and filtered. Solvent was removed under reduced pressure to give an amber-colored solid (72%), mp 39–40°C. IR (film): 3026; 2922; 2172; 548 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.47 (1H, dd, $J = 8.0$, 1.2 Hz, Ar); 7.40 (1H, dd, $J = 7.8$, 2.2 Hz, Ar); 7.25 (1H, td, $J = 7.6$, 1.2 Hz, Ar); 7.09 (1H, td, $J = 7.8$, 1.8 Hz, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.6, 132.6, 129.24, 129.1, 127.7, 122.7, 40.1.

1-Bromo-2-[(*Z*)-1,1-dideutero-but-2-enyl]-benzene (**21a**)

This compound was synthesized following the same procedure described for compound **9a** using a solution of Grignard reagent **8a** and compound **20** to give a yellow oily product (72%). IR (film): 3018; 2196; 745; 653 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 (1H, dt, $J = 7.8$, 0.8 Hz, Ar); 7.17 (1H, td, $J = 4.0$, 0.8 Hz, Ar); 7.15 (2H, m, Ar); 6.98 (1H, dt, $J = 7.4$, 4.8 Hz, 1H, Ar); 5.54 (2H, m, C<u>H</u>═C<u>H</u>); 1.66 (3H, d, $J = 7.8$ Hz, CH═CH-C<u>H</u>$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.0, 132.7, 130.8, 130.1, 127.7, 127.5, 127.3, 125.9, 40.0, 13.4. Purity determined by GC-EIMS, 88%.

1-Bromo-2-[(*Z*/*E*)-1,1-dideutero-but-2-enyl]-benzene (**21a**/**b**)

This compound was synthesized following the same procedure described for compound **9a** using a solution of Grignard reagent **8b** and the compound **20** to give a yellow oil product (72%). *Z*/*E* 40:60. IR (film): 2924; 939; 745; 653 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.52 (2H, m, Ar); 7.19 (4H, m, Ar); 7.05 (2H, m, Ar); 5.55 (4H, m, -Ar-CD_2-C<u>H</u>=C<u>H</u>-CH_3); 1.60 (6H, m, CH=CH-C<u>H</u>$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2, 138.0, 132.9, 132.7, 128.4, 127.9, 127.8, 127.6, 127.5, 126.1, 125.9, 124.5, 124.2, 18.4, 13.6.

Propyl 6-(2-Formylphenyl) Hexanoate (**22**)

This compound was synthesized following the same procedure described for the Suzuki–Miyaura coupling in compound **14a**. The solution of benzaldehyde-2-bromine (0.318 g, 1.72 mmol), Cs_2CO_3 (1.008 g, 3.096 mmol, 1.8 eq.), $PdCl_2$ (dppf) (0.063 g, 0.086 mmol, 5% mol), and Ph_3As (0.053 g, 0.172 mmol, 10 mol) in DMF (10 mL) was stirred with a suspension of 9-BBN-H/THF **12** (2.58 mmol) to give a light yellow liquid product (0.386 g, 85%). IR (film): 2930, 1734, 1696, 1185, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 10.25 (1H, s, Ar-C<u>H</u>O); 7.82 (1H, dd, $J = 7.4$, 1.4 Hz, Ar); 7.49 (1H, td, $J = 7.4$, 1.4 Hz, Ar); 7.35 (1H, td, $J = 7.2$, 1.4 Hz, Ar); 7.25 (1H, d, $J = 7.8$ Hz, Ar); 4.02 (2H, t, $J = 6.8$ Hz, -O-C<u>H</u>$_2$); 3.03 (2H, t, $J = 7.6$ Hz, Ar-C<u>H</u>$_2$); 2.31 (2H, t, $J = 7.8$ Hz, C<u>H</u>$_2$-COO-); 1.65 (6H, m, -C<u>H</u>$_2$-); 1.45 (2H, m, -C<u>H</u>$_2$-); 0.93 (3H, t, $J = 7.6$ Hz, -CH_2-C<u>H</u>$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.9, 173.4, 145.0, 133.4, 133.4, 133.3, 131.6, 130.6, 126.2, 65.7, 34.1, 32.3, 31.8, 28.9, 24.7, 21.9, 10.7. Anal. calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.33; H, 8.57.

Acetic Acid 5-(2-Formyl-phenyl)-pentyl Ester (**23**)

This compound was synthesized following the same procedure described for the Suzuki–Miyaura coupling in compound **22** using compound **13** to give a light yellow liquid product (50%). IR (film): 2933–2859 (C-H); 1736 (C=O); 1697 (C=O); 1241 (C-O-C); 1041 (CH-O-CH_2-); 756 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 10.24 (1H, s, C<u>H</u>O); 7.81 (1H, dd, $J = 7.4$, 1.6 Hz, Ar); 7.50 (1H, td, $J = 7.4$, 1.6 Hz, Ar); 7.36 (1H, td, $J = 7.8$, 1.2 Hz, Ar); 7.26 (1H, dd, $J = 7.4$, 1.2 Hz, Ar); 4.05 (2H, t, $J = 6.6$ Hz, -C<u>H</u>$_2$-O-C=O); 3.04 (2H, t, $J = 8.2$ Hz, Ar-C<u>H</u>$_2$-); 2.40 (2H, t, $J = 6.6$ Hz, C<u>H</u>$_2$-C=O); 2.04 (3H, s, -O = C-C<u>H</u>$_3$); 1.55 (6H, ma, -C<u>H</u>$_2$-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.9, 144.9, 133.4, 133.4, 131.8, 130.7, 126.2, 64.2, 41.6, 32.4, 31.7, 28.4, 27.1, 24.7, 20.9. Anal. calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.92; H, 7.84.

Triphenyl Iodomethyl Phosphonium Iodide (**24**)

Iodoform (4.02 g, 15 mmol) was added to a solution of triphenyl phosphine (5.00 g, 19.06 mmol) in toluene (20 mL). The suspension was stirred at reflux temperature for 16 h. The solvent was removed at reduced pressure, and the product was washed with ethyl ether to give a white solid product (6.45 g, 81%, mp 180–181°C). IR (film): 2910–2845, 1430, 779–682 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (15H, m, -Ar); 4.85 (2H, d, $J = 8.6$ Hz, P-C$\underline{H}_2$-).

6-[2-*Z*-(2-iodo-vinyl)-phenyl]-hexanoic Acid Propyl Ester (**25a**)

A suspension of salt **24** (2.65 g, 5.00 mmol) in THF (5 mL) was added to a solution of NaHMDS 1.0 M (0.917 g, 1.014 mL, 5 mmol). The solution was stirred at room temperature under argon atmosphere. The mixture was stirred for 5 min at −78°C, and then HMPA (1.74 mL, 10 mmol) and a solution of compound **22** (0.262 g, 1 mmol) in THF (1.0 mL) were added. The reaction mixture was maintained at −78°C for 1 h, and then water (5 mL) was added; the product was extracted with ethyl ether (3 × 30 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with a mixture of petroleum ether and dichloromethane to give a light yellow liquid product (0.189 g, 50%). IR (film): 2919, 1733, 1173 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 (1H, d, $J = 8.4$ Hz, Ar-C$\underline{H}$=CH-I); 7.18 (4H, m, Ar); 6.59 (1H, d, $J = 8.4$ Hz, Ar-CH=C$\underline{H}$-I); 3.95 (2H, t, $J = 6.6$ Hz, -O-C$\underline{H}_2$-); 2.47 (2H, t, $J = 8.2$ Hz, Ar-C$\underline{H}_2$-); 2.23 (2H, t, $J = 7.6$ Hz, C$\underline{H}_2$-COO); 1.58 (6H, m, -C$\underline{H}_2$); 1.30 (2H, m, -C$\underline{H}_2$-); 0.86 (3H, t, $J = 7.4$ Hz, CH_2-C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.4, 141.0, 139.0, 137.0, 129.0, 128.7, 128.1, 125.5, 83.8, 65.9, 34.4, 33.4, 30.4, 29.1, 25.0, 22.2, 10.6. Anal. calcd. for $C_{17}H_{23}IO_2$: C, 52.86; H, 6.00. Found: C, 52.92; H, 6.12.

6-[2-*E*/*Z*-(2-Iodo-vinyl)-phenyl]-hexanoic Acid Propyl Ester (**25a**/**b**)

A solution of $CrCl_2$ (0.737 g, 6 mmol) in THF (5 mL) was cooled to 0°C. Then a solution of compound **22** (0.65 g, 1.0 mmol) and CHI_3 (0.787 g, 2.0 mmol) in dry THF (5 mL) was added. The mixture was stirred to room temperature and extracted with ethyl ether (3 × 30 mL); the organic phase was washed, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated to give a yellow liquid product (0.148 g, 52%). IR (film): 3062, 2934, 1732, 1178 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.56 (1H, d, $J = 14.6$ Hz, Ar-C$\underline{H}$=CH-I_{trans}); 7.20 (1H, d, $J = 8.4$ Hz, Ar-C$\underline{H}$=CH-I_{cis}); 7.14 (8H, m, Ar); 6.59 (1H, d, $J = 14.6$ Hz, Ar-CH=C$\underline{H}$-I_{trans}); 6.56 (1H, d, $J = 8.4$ Hz, Ar-CH=C$\underline{H}$-I_{cis}); 3.94 (2H, t, $J = 6.6$ Hz, -O-C$\underline{H}_2$-); 3.93 (2H, t, $J = 6.6$ Hz, -O-C$\underline{H}_2$-); 2.55 (2H, t, $J = 8.2$ Hz, Ar-C$\underline{H}_2$-); 2.45 (2H, t, $J = 8.2$ Hz, Ar-C$\underline{H}_2$-); 2.22 (2H, t, $J = 7.6$ Hz, C$\underline{H}_2$-COO); 2.21 (2H, t,

$J = 7.6$ Hz, -C$\underline{H}_2$-COO); 1.56 (12H, m, -C$\underline{H}_2$-); 1.30 (4H, m, -C$\underline{H}_2$-); 0.85 (6H, t, $J = 7.8$ Hz, -CH$_2$-C$\underline{H}_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.7, 143.2, 139.3, 136.6, 129.6, 128.4, 126.4, 125.4, 126.2, 84.1, 66.1, 34.5, 33.3, 30.9, 29.2, 29.2, 25.1, 22.3, 10.8.

Acetic Acid 5-[2-(*Z*-2-Iodo-vinyl)-phenyl]-pentyl Ester (**26a**)

This compound was synthesized following the same procedure described for the compound **25a** using compound **23** and the salt **24** to give a light yellow liquid product (50%). IR (film): 3062; 2928; 1736; 1204; 753 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19 (1H, d, $J = 8.0$ Hz, Ar-C$\underline{H}$=CH-I); 7.05 (4H, m, Ar); 6.48 (1H, d, $J = 8.4$ Hz, Ar-CH=C$\underline{H}$-I); 3.86 (2H, t, $J = 6.6$ Hz, -O-C$\underline{H}_2$-); 2.37 (2H, t, $J = 7.6$ Hz, Ar-C$\underline{H}_2$-); 1.85 (3H, s, -O-CO-C$\underline{H}_3$); 1.35 (6H, m, -C$\underline{H}_2$-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 140.1, 139.0, 136.7, 129.1, 128.7, 128.5, 125.6, 84.0, 64.6, 33.5, 28.6, 22.2, 21.4. Anal. calcd. for $C_{15}H_{19}IO_2$: C, 50.29; H, 5.35. Found: C, 50.20; H, 5.48.

General Procedure for Stille Coupling

6-(2-*Z*/*E*-Buta-1,3-dienyl-phenyl)-hexanoic Acid Propyl Ester (**27a**/**b**)

Compound **25a** (0.199 g, 0.519 mmol), cooper iodide (0.009 g, 0.051 mmol, 10% mol), Pd $(PPh_3)_4$ (0.030 g, 0.026 mmol. 5% mol), and tributylvinyltin (0.20 mL, 0.214 g, 0.67 mmol) in DMF (5 mL) were dissolved in a Schlenk flask (100 mL) under an inert atmosphere. The reaction mixture was stirred for 21 h at room temperature and quenched with water. The product was extracted with ethyl ether (3×30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the product was purified by flash-column chromatography on silica gel (95:5 ether petroleum–ethyl acetate) to give a light green liquid product (0.096 g, 65%). IR (film): 3023, 2935, 1732, 1177 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (2H, m, Ar); 7.14 (2H, m, Ar); 6.75 (1H, dd, $J = 15.0$, 9.6 Hz, Ar-CH=C$\underline{H}$-); 6.73 (1H, d, $J = 15.0$ Hz, Ar-C$\underline{H}$=CH-); 6.54 (1H, ddd, $J = 17.0$, 9.2, 9.2 Hz, -C$\underline{H}$=CH$_2$); 5.32 (1H, dd, $J = 16.2$, 2.2 Hz, -CH=C$\underline{H}_2$); 5.16 (1H, dd, $J = 10.0$, 2.2 Hz, -CH=C$\underline{H}_2$); 4.02 (2H, t, $J = 6.6$ Hz, -O-C$\underline{H}_2$-); 2.67 (2H, t, $J = 8.0$ Hz, Ar-C$\underline{H}_2$-); 2.30 (2H, t, $J = 7.8$ Hz, -C$\underline{H}_2$-CO); 1.62 (6H, m, -C$\underline{H}_2$-); 1.40 (2H, m, -C$\underline{H}_2$-); 0.95 (3H, t, $J = 7.6$ Hz, CH$_2$-C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.8, 140.1, 137.5, 135.5, 131.0, 130.2, 129.7, 127.6, 126.2, 125.6, 117.5, 66.1, 34.6, 33.4, 31.0, 29.2, 25.2, 22.3, 10.7.

Acetic acid 5-(2*Z*/*E*-Buta-1,3-dienyl-phenyl)-pentyl Ester (**28a**/**b**)

This compound was synthesized following the same procedure described for Stille coupling using the compound **26a** to give a light green liquid product

(0.024 g, 65%). IR (film): 2933–2859 (C-H); 1739 (C═O); 1238 (C-O-C); 1042 (CH-O-CH_2-); 997 (C═C); 751 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.48 (2H, m, Ar); 7.15 (4H, m, Ar-CH═CH-CH═CH_2); 6.96 (1H, dd, $J = 17.6$, 10.6 Hz, Ar-CH═CH-CH═CH_2); 5.64 (1H, dd, $J = 17.0$, 1.6 Hz, -CH═CH_2); 5.28 (1H, dd, $J = 11.0$, 1.2 Hz, -CH═CH_2); 4.04 (2H, m, -CH_2-O-); 2.68 (2H, t, $J = 7.4$, Ar-CH_2-); 2.03 (3H, s, -O═C-CH_3); 1.67 (4H, m, -CH_2-). 1.41 (2H, m, -CH_2-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.2, 139.8, 136.4, 134.6, 133.0, 129.5, 129.0, 127.8, 126.3, 125.8, 115.5, 64.7, 34.6, 31.0, 28.8, 26.2, 21.4. m/z (EIMS) 232 $[M]^+$ (17), 143 (100).

(*E*)-Rubrenoic Acid III (**3b**)

This compound was obtained following the same procedure described for compound **1a** using the compound **27b** to give a liquid product (0.078 g, 95%). IR (film): 3200, 3060, 2960, 1709, 1094–1019 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (2H, m, Ar); 7.15 (m, 4H, Ar-CH═CH-CH═CH_2); 6.96 (1H, dd, $J = 17.6$, 11.0 Hz, Ar-CH═CH-CH═CH_2); 5.62 (1H, dd, $J = 15.8$, 1.4 Hz, Ar-CH═CH-CH═CH_2); 5.27 (1H, dd, $J = 9.4$, 1.4 Hz, Ar-CH═CH-CH═CH_2); 2.67 (2H, t, $J = 8.0$ Hz, Ar-CH_2-CH_2-); 2.34 (2H, t, $J = 7.4$ Hz, -CH_2-C═O-); 1.62 (4H, m, -CH_2-); 1.41 (2H, m, -CH_2-); ^{13}C NMR (50 MHz, $CDCl_3$): δ 180.2, 139.8, 136.3, 134.6, 129.5, 129.4, 127.8, 126.3, 126.2, 125.8, 115.6, 34.3, 33.6, 31.0, 29.2, 24.8. m/z [HRMS (FAB^+)] calc. for $C_{16}H_{21}O_2$ [M + H] 245.1542. Found: 245.1566. Anal. calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.86; H, 8.37.

5-(2-*E*-Buta-1,3-dienyl-phenyl)-pentan-1-ol (**29b**)

This compound was obtained following the same procedure described for compound **1a** using the compound **28b** to give a crystalline liquid product (95%). IR (film): 3345 (-OH); 2932 (C-H); 1451 (C═C); 1048 (CH-O-); 752 (C-H) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.48 (2H, m, Ar); 7.18 (4H, m, Ar-CH═CH-CH═CH_2); 7.00 (1H, dd, $J = 17.2$, 11.0 Hz, Ar-CH═CH-); 5.64 (1H, dd, $J = 17.2$, 1.6 Hz, -CH═CH_2); 5.28 (1H, dd, $J = 11.0$, 1.4 Hz, -CH═CH_2); 3.63 (2H, t, $J = 6.2$ Hz, -CH_2-O-); 2.68 (2H, t, $J = 7.0$ Hz, Ar-CH_2); 1.60 (4H, m, -CH_2-); 1.42 (2H, m, -CH_2-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.4, 134.6, 133.0, 123.0, 129.6 128.9, 128.8, 127.8 126.2, 125.7, 115.4, 63.1, 34.7, 33.7, 31.2, 26.0. Anal. calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.40; H, 9.40.

nor-(*E*)-Rubrenoic Acid III (**30b**)

This compound was obtained following the same procedure described for compound **10** using the compound **29b** to give a liquid product (69%). IR (film): 3224 (-OH); 2934 (C-H); 1709 (COOH) cm^{-1}. ^1H NMR (200 MHz,

$CDCl_3$): δ 7.44 (2H, m, Ar); 7.19 (3H, m, Ar-CH=CH-CH=CH_2); 6.99 (1H, dd, $J = 17.2$, 9.0 Hz, Ar-CH=CH-); 5.64 (1H, dd, $J = 17.2$, 1.4 Hz, -CH=CH_2); 5.29 (1H, dd, $J = 10.8$, 1.4 Hz, -CH=CH_2); 2.81 (2H, t, $J = 7.4$ Hz, Ar-CH_2-); 2.40 (2H, t, $J = 7.4$ Hz, -CH_2-COOH); 1.69 (4H, m, -CH_2-CH_2-). ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.0, 134.6, 133.0, 129.5, 128.9, 128.8, 127.8, 126.4, 126.1, 125.9, 115.6, 34.3, 30.7, 30.2, 24.7. m/z [HRMS (FAB^+)] calc. for $C_{15}H_{19}O_2$ [M + H] 231.1385. Found: 231.1410. Anal. calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.41; H, 8.09.

ACKNOWLEDGMENT

We gratefully acknowledge support for this project from Consejo del Sistema Nacional de Educación Tecnológica (COSNET) 491-02-P (2002) and a graduate fellowship from Consejo Nacional de Ciencia y Tecnología (CONACyT) for L. G. S.

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