Concise Syntheses of the Abyssinones and Discovery of New Inhibitors of Prostate Cancer and MMP-2 Expression

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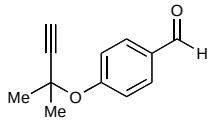
Supporting Information

General Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. Toluene was purified by passage though a bed of activated alumina.[1] Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[2] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration.) Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian INOVA 500 (125 MHz) or INOVA 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Optical rotations were measured on a Perkin Elmer Model 341 Polarimeter with a sodium lamp. CD spectral data was recorded in MeOH on a JASCO J-715 Spectropolarimeter using a 0.5 mm cuvette. Mass spectra were obtained on a Varian 1200 Quadrupole Mass Spectrometer and on a GCMS Model HP6890. CuI was stored in a glove box and used without purification. Thiourea catalysts **I** and **II** were prepared according to the procedure of Hiemstra.[3] $Pd(PPh_3)_4$ was freshly prepared.[4]

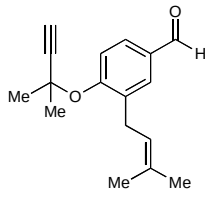
General Procedure for CuI-Catalyzed Etherification



4-(2-methylbut-3-yn-2-yloxy)benzaldehyde (**18**). Prepared using a modified procedure of Bell et al.[5] To a 250 round bottom flask was added 4-hydroxybenzaldehyde (10.0 g, 81.9 mmol), K_2CO_3 (22.7 g, 164 mmol), KI (23.0 g, 139 mmol) and CuI (781 mg, 4.10 mmol). The round bottom flask was purged with N_2 and DMF (50 mL) and 3-chloro-3-methyl-1-butyne (16.5 mL, 147 mmol) were added. The reaction mixture was heated to 65 °C for 2.5 h. After cooling to room temperature, the reaction mixture was taken up in Et_2O, washed three times with 1M NaOH and once with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford aryl

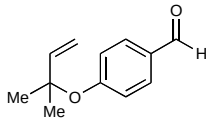
1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996,** 15, (5), 1518-1520.
2. Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals;* 3rd Ed., Pergamon Press, Oxford, **1988**.
3. Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006,** *45*, 929-931.
4. Schlosser, M. *Organometallics in Synthesis: A Manual, 2nd edition*, Wiley, NY, **2004**.
5. Kyogoku, K.; Hatayama, K.; Yokomori, S.; Seki, T.; Tanaka, I. *Agr. Biol. Chem.* **1975**, *39*, 667-672.

propargyl ether **18** (9.48 g, 62%) as a clear orange oil. Analytical data matched those reported in the literature.[6]

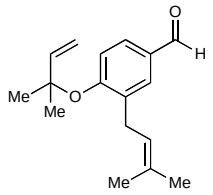


3-(3-methylbut-2-enyl)-4-(2-methylbut-3-yn-2-yloxy)benzaldehyde (**19**). Prepared according to the above procedure using 4-hydroxy-3-(3-methylbut-2-enyl)benzaldehyde (**23**) (5.04 g, 26.5 mmol), K_2CO_3 (7.33 g, 53 mmol), KI (7.49 g, 45.1 mmol), CuI (253 mg, 1.33 mmol) and 3-chloro-3-methyl-1-butyne (5.36 mL, 47.7 mmol) in DMF (20 mL). The residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford the prenylated aryl propargyl ether **19** (3.95 g, 58%) as a golden yellow oil. Analytical data matched those reported in the literature.[5] Previously unreported LRMS (electrospray): Mass calculated for $C_{17}H_{20}O_2$ $[M]^+$ 256, found 256.

General Procedure for Lindlar Reductions



4-(2-methylbut-3-en-2-yloxy)benzaldehyde (**20**). To a flame-dried Parr vessel was added 4-(2-methylbut-3-yn-2-yloxy)benzaldehyde (**18**) (10.9 g, 57.9 mmol) and Lindlar catalyst (2.18 g). The reaction, which was run neat, was subjected to 55 psi for 48 h. The reaction was monitored by thin layer chromatography (10% EtOAc/hexanes). Purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford the aryl allyl ether **20** (9.90 g, 91%) as a clear yellow oil. Analytical data matched those reported in the literature.[7] Mass calculated for $C_{12}H_{14}O_2$ $[M]^+$ 190, found 190.

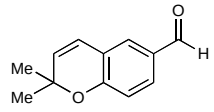


3-(3-methylbut-2-enyl)-4-(2-methylbut-3-en-2-yloxy)benzaldehyde (21). Prepared according to the general procedure using 3-(3-methylbut-2-enyl)-4-(2-methylbut-3-yn-2-yloxy)benzaldehyde (**19**) (4.27 g) and Lindlar catalyst (835 mg) for 32 h. After completion, the reaction mixture was filtered though a short pad of Celite, concentrated *in vacuo*, then filtered through a short pad of silica gel using EtOAc as the eluent to afford the prenylated aryl allyl ether **21** (4.18 g, 97%) as a red-orange oil. Analytical data

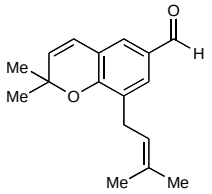
6. Smith, L. R.; Mahoney, N.; Molyneux, R. J. *J. Nat. Prod.* **2003**, *66*, 169-176.
7. Knight, D.W.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1* **1979**, 70-76.

matched those reported in the literature.[5] Mass calculated for $C_{17}H_{22}O_2$ $[M]^+$ 258, found 258.

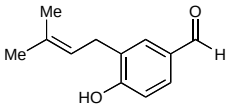
General Procedure for Microwave Irradiation-Induced Claisen Rearrangement



2,2-dimethyl-2*H*-chromene-6-carbaldehyde (**5**). To a 10-20 mL microwave vial was added 4-(2-methylbut-3-yn-2-yloxy)benzaldehyde (**18**) (2.04 g, 10.8 mmol) and toluene (9 mL). The vial was purged with N_2, capped, and heated to 190 °C under microwave irradiation for 25 min with 30 s prestirring, normal absorption. The reaction mixture was taken up in EtOAc and the solvent was concentrated *in vacuo*. Purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford aldehyde **5** (1.96 g, 96%) as a golden yellow oil. Analytical data matched those reported in the literature.[6]



2,2-dimethyl-8-(3-methylbut-2-enyl)-2*H*-chromene-6-carbaldehyde (**22**). Prepared according to the above procedure using 3-(3-methylbut-2-enyl)-4-(2-methylbut-3-yn-2-yloxy)benzaldehyde (**19**) (1.69 g, 6.59 mmol) and toluene (9 mL). Purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford aldehyde **22** (1.53 g, 91%) as a golden yellow oil. Analytical data for **22**: IR (film) 2975, 2920, 1690, 1593, 1373, 1277, 1136 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 6.33 (d, J = 9.8 Hz, 1H), 5.65 (d, J = 9.8 Hz, 1H), 5.27-5.24 (m, 1H), 3.28 (d, J = 7.3 Hz, 2H), 1.72 (s, 3H), 1.71 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 156.5, 133.2, 131.7, 131.1, 130.1, 129.7, 126.4, 122.0, 121.9, 121.0, 78.0, 28.7, 28.3, 26.0, 18.1; Mass calculated for $C_{17}H_{20}O_2$ $[M]^+$ 256, found 256.



4-hydroxy-3-(3-methylbut-2-enyl)benzaldehyde (**23**). Prepared according to the general procedure using a 10-20 mL microwave vial, 4-(2-methylbut-3-en-2-yloxy)benzaldehyde (**20**) (9.81 g) and toluene (16 mL). This reaction was heated to 175 °C under microwave irradiation for 25 min with 30 s prestirring. Purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford the prenylated benzaldehyde **23** (9.06 g, 92%) as a pale yellow solid. Analytical data matched those reported in the literature.[8]

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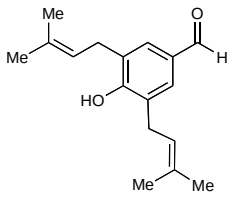
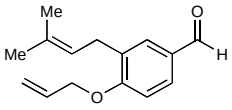
8. Kyogoku, K.; Hatayama, K.; Yokomori, S.; Seki, T.; Tanaka, I. *Agr. Biol. Chem.* **1975**, *39*, 133-138.



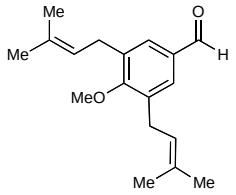
4-hydroxy-3,5-bis(3-methylbut-2-enyl)benzaldehyde (**24**). Prepared according to the general procedure using a 2-5 mL microwave vial, 3-(3-methylbut-2-enyl)-4-(2-methylbut-3-en-2-yloxy)benzaldehyde (**21**) (1.67 g, 6.46 mmol) and toluene (5 mL) under microwave irradiation at 200 °C. Analysis by ^{1}H NMR revealed 15% double bond isomer side product with one prenyl group and one isoprenyl group. Purified by flash column chromatography ($AgNO_3$ impregnated SiO_2,[9] 20% EtOAc/hexanes) to afford the bisprenylated benzaldehyde **24** (1.10 g, 66%) as a yellow solid. Analytical data matched those reported in the literature.[8]

Alkylations of Prenyl Aldehydes



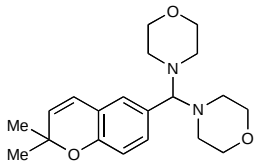
4-(allyloxy)-3-(3-methylbut-2-enyl)benzaldehyde (**25**). To a 25 mL round bottom flask was added 4-hydroxy-3-(3-methylbut-2-enyl)benzaldehyde (**23**) (2.72 g, 14.3 mmol) and K_2CO_3 (2.97 g, 21.5 mmol). The flask was equipped with a reflux condenser and purged with N_2, followed by addition of acetone (15 mL) and allyl bromide (1.86 mL, 21.5 mmol). The reaction was heated to reflux. After 3 h the reaction was stopped and allowed to cool to room temperature. The reaction mixture was diluted with H_2O, extracted three times with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford **25** (3.13 g, 95%) as an orange-brown oil. Analytical data for allyloxy prenyl benzaldehyde **25**: IR (film) 2971, 2916, 2727, 1689, 1593, 1111 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.71-7.63 (m, 2H), 6.92 (d, *J* = 8.79 Hz, 1H), 6.10-6.03 (m, 1H), 5.44 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.33-5.27 (m, 2H), 4.65 (d, *J* = 4.9 Hz, 2H), 3.38 (d, *J* = 7.3 Hz, 2H), 1.76 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 161.6, 133.6, 132.7, 131.4, 130.7, 130.6, 129.9, 121.6, 117.9, 111.3, 69.1, 28.6, 26.0, 18.0; GCMS: Mass calculated for $C_{15}H_{18}O_2$, $[M]^+$, 230. Found 230.

9. Williams, C.M.; Mander, L.N. *Tetrahedron* **2001**, *57*, 425-447.

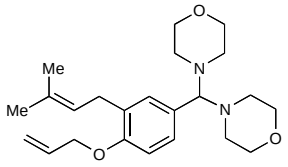


4-methoxy-3,5-bis(3-methylbut-2-enyl)benzaldehyde (**26**). To a 100 mL round bottom flask was added 4-hydroxy-3,5-bis(3-methylbut-2-enyl)benzaldehyde (**24**) (1.10 g, 4.26 mmol) and K_2CO_3 (1.48 g, 10.7 mmol). The flask was equipped with a reflux condenser and purged with N_2, followed by addition of acetone (10 mL) and MeI (668 μL, 10.7 mmol). Reaction was heated to 37 °C for 15 h. After cooling to room temperature, the reaction mixture was taken up in H_2O and extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo* to afford methoxy bis-prenyl benzaldehyde **26** (1.06 g, 91%) as a yellow oil. Analytical data for **26**: IR (film) 2970, 2919, 2589, 1695, 1593, 1439, 1381, 1273, 1119, 1003 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.57 (s, 2H), 5.29 (bs, 2H), 3.79 (s, 3H), 3.40 (d, *J* = 6.77 Hz, 4H), 1.76 (s, 6H), 1.74 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 161.8, 136.0 (2x), 133.5 (2x), 132.9, 129.9 (2x), 122.3 (2x), 61.1, 28.5 (2x), 26.0 (2x), 18.1 (2x); LRMS (electrospray): Mass calculated for $C_{18}H_{24}O_2$, $[M]^+$, 272. Found $[M+H]^+$, 273.

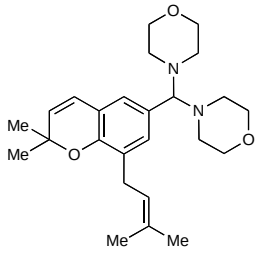
General Procedure to Access Bis-Aminals



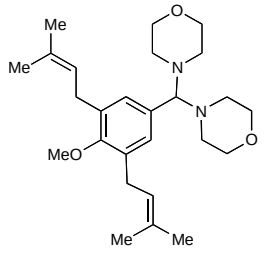
4,4'-((2,2-dimethyl-2*H*-chromen-6-yl)methylene)dimorpholine (**6**). To a 50 mL round bottom flask was added **5** (1.95g, 10.4 mmol), benzene (12 mL) and morpholine (1.82 mL, 20.8 mmol). The flask was equipped with a Dean-Stark trap and water condenser and heated to 110 °C for 23 h. The reaction was monitored by ^1H NMR. The solvent was concentrated *in vacuo* to afford bis-aminal **6** (3.64 g, quantitative yield) as an orange-yellow oil. Analytical data for **6**: IR (film) 2963, 2847, 2810, 1487, 1266, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, *J* = 7.9 Hz, 1H), 6.78 (s, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.60 (d, *J* = 8.9 Hz, 1H), 3.65 (bs, 8H), 3.52 (s, 1H), 2.41 (bs, 8H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 131.0, 129.8, 126.8, 126.6, 122.6, 120.6, 115.7 (2x), 88.9, 76.5 (2x), 67.4 (4x), 49.8 (2x), 28.3 (2x); LRMS (electrospray): Mass calculated for $C_{20}H_{28}N_2O_3$, $[M]^+$, 344 Found $[M+H-C_4H_9NO]^+$, 258.



4,4'-((4-(allyloxy)-3-(3-methylbut-2-enyl)phenyl)methylene)dimorpholine (**27**). Prepared according to the general procedure using **25** (2.98 g, 12.9 mmol), morpholine (2.26 mL, 25.8 mmol, and benzene (26 mL) for 24 h to afford **27** (4.90 g, 98%) as a brown oil. Analytical data for **27**: IR (film) 2959, 2850, 1605, 1496, 1450, 1247, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95-6.94 (m, 2H), 6.78 (d, *J* = 8.60 Hz, 1H), 6.11-6.03 (m, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.30-5.26 (m, 2H), 4.54 (d, *J* = 4.8 Hz, 2H), 3.66 (bs, 8H), 3.56 (s, 1H), 3.34 (d, *J* = 7.1 Hz, 2H), 2.41 (bs, 8H), 1.73 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 133.9, 132.5, 130.3, 129.8, 127.4, 126.3, 122.9, 117.2 (2x), 110.8, 88.9, 69.0 (2x), 67.5 (4x), 49.8 (2x), 29.1, 26.1, 18.1; LRMS (electrospray): Mass calculated for $C_{23}H_{34}N_2O_3$, $[M]^+$, 386. Found $[M+H-C_4H_9NO]^+$ 326.

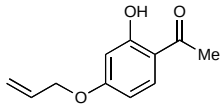


4,4'-((2,2-dimethyl-8-(3-methylbut-2-enyl)-2*H*-chromen-6-yl)methylene)dimorpholine (**28**). Prepared according to the general procedure using 2,2-dimethyl-8-(3-methylbut-2-enyl)-2*H*-chromene-6-carbaldehyde (**22**) (1.67 g, 6.51 mmol), morpholine (1.14 mL, 13.0 mmol) and benzene (15 mL) for 51.5 h to afford **28** (2.61 g, 97%) as an orange-brown oil. Analytical data for bis-aminal **28**: IR (film) 2967, 2916, 2851, 2812, 1690, 1456, 1137, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.64 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.59 (d, *J* = 9.7 Hz, 1H), 5.26 (bs, 1H), 3.66 (bs, 8H), 3.50 (s, 1H) 3.25 (d, *J* = 6.6 Hz, 2H), 2.43 (bs, 8H), 1.72 (s, 6H), 141 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 131.9, 130.7, 130.2, 128.6, 128.5, 125.9, 124.6, 123.2, 123.0, 120.3, 89.0, 76.3 (2x), 67.5 (4x), 49.8 (2x), 28.8, 28.3 (2x), 26.1, 18.2; LRMS (electrospray): Mass calculated for $C_{25}H_{36}N_2O_3$, $[M]^+$, 412. Found $[M+H- C_4H_9NO]^+$, 326.

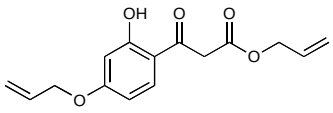


4,4'-((4-methoxy-3,5-bis(3-methylbut-2-enyl)phenyl)methylene)dimorpholine (**29**). Prepared according to the general procedure using 4-hydroxy-3,5-bis(3-methylbut-2-enyl)benzaldehyde (**26**) (1.37 g, 5.03 mmol), benzene (15 mL), and morpholine (0.875 mL, 10.0 mmol) to afford bis-aminal **29** (2.10 g, quantitative yield) as a golden yellow viscous oil. Analytical data for **29**: IR (film) 2962, 2914, 2850, 1693, 1454, 1273, 1117 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2H), 5.26 (bs, 2H), 3.71 (s, 3H), 3.67 (bs, 8H), 3.54 (s, 1H), 3.34 (d, J = 6.59 Hz, 4H), 2.41 (bs, 8H), 1.73 (s, 6H), 1.72 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 134.0 (2x), 132.4 (2x), 129.6, 128.4 (2x), 123.6 (2x), 88.8, 67.5 (4x), 61.1, 49.7 (4x), 28.8 (2x), 26.0 (2x), 18.0 (2x); LRMS (electrospray): Mass calculated for $C_{26}H_{40}N_2O_3$, $[M]^+$, 428. Found, $[M+H- C_4H_9NO]^+$, 342.

General Procedure to Access Allyl β-Ketoester



1-(4-(allyloxy)-2-hydroxyphenyl)ethanone (**30**). To a 500mL round bottom flask was added 2,4-dihydroxyacetophenone (15.2 g, 100 mmol) and K_2CO_3 (14.5 g, 105 mmol). The round bottom flask was equipped with a reflux condenser, purged with N_2, and acetone (200 mL) and allyl bromide (9.09 mL, 105 mmol) were added. The reaction was heated to reflux and stirred for 14 h. After completion, the reaction was allowed to cool to room temperature, filtered, and the solvent was concentrated *in vacuo*. The resulting residue was taken up in EtOAc (100 mL), washed three times with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford allyloxyhydroxyacetophenone (17.7 g, 92%) as a golden yellow oil. Analytical data matched those reported in the literature.[10]

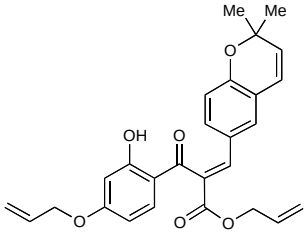


allyl 3-(4-(allyloxy)-2-hydroxyphenyl)-3-oxopropanoate (**31**). Prepared using a modified procedure of Donnelly.[11] To a 250 mL round bottom flask purged with N_2 was added THF (12 mL) and *bis*(trimethylsilyl)amide (2.65 mL, 12.7 mmol). The solution

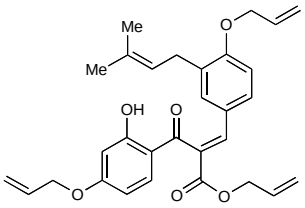
10. Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. *J. Org. Chem*. **2003**, *68*, 5493-5499.
11. Donnelly, D. M. X.; Fitzpatrick, B. M.; Finet, J. P. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1791-1795.

was cooled to –78 °C and *n*-BuLi (7.68 mL, 1.55 M) was added and the solution is warmed to 0 °C for 1 h. The solution was cooled to –78 °C and 1-(4-(allyloxy)-2-hydroxyphenyl)ethanone (**30**) (762 mg, 3.96 mmol) in THF (15 mL) was added dropwise via cannula. This was stirred at –78 °C for 1 h, stirred at –10 °C for 3 h, and cooled to –78 °C. A solution of diallyl carbonate (1.82 mL, 12.7 mmol) in THF (1.5 mL) was added quickly to the reaction mixture and allowed to warm to room temperature overnight. The solution was poured onto a mixture of concentrated HCl (3 mL) and ice (50 g). The mixture was extracted with $CHCl_3$ (3 x 50 mL), washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to afford β-keto ester **31** (776 mg, 75%) as a golden yellow oil. Analytical data for **31**: IR (film) 3460, 3086, 2934, 1740, 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.2 (s, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 6.42 (d, *J* = 1.98 Hz, 1H), 6.38 (s, 1H) 6.00-5.92 (m, 1H), 5.89-5.81 (m, 1H), 5.36 (d, *J* = 17.4 Hz), 5.28-5.25 (m, 2H), 5.18 (d, J = 10.3 Hz, 1H), 4.60 (d, *J* = 5.1 Hz, 2H), 4.50 (d, *J* = 4.36 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 167.1, 165.8, 165.8, 132.3 (2x), 131.8, 118.9, 118.6, 113.4, 108.7, 102.0, 69.3, 66.3, 45.5; LRMS (electrospray): Mass calculated for $C_{15}H_{16}O_5$, $[M]^+$, 276. Found, $[M+H]^+$ 277.

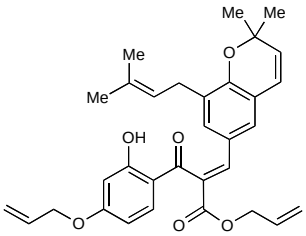
General Procedure for the Preparation of Alkylidene Substrates



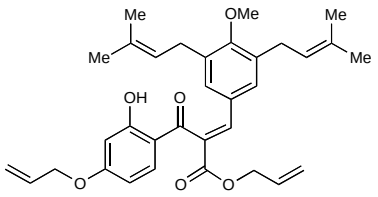
(*E*)-allyl 2-(4-(allyloxy)-2-hydroxyphenylcarbonyl)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enoate (**10**). To a 25 mL round bottom flask was added **31** (512 mg, 1.83 mmol) and **6** (866 mg, 2.51 mmol). The flask was purged with N_2 and toluene (3 mL) and glacial Acetic acid (287 μL, 5.02 mmol) were added. The reaction was allowed to stir at room temp for 1.5 h. The reaction mixture was diluted with EtOAc, washed with water twice and brine once. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purified by flash column chromatography (SiO_2, 5% EtOAc/Hex) to afford **10** (712 mg, 81%, with >95:5 *E:Z* selectivity) as a golden yellow oil. Analytical data for **10**: IR (film) 2974, 2933, 1713, 1616, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.5 (s, 1H), 7.82 (s, 1H), 7.42 (d, *J* = 9.1 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.98 (s, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.46 (s, 1H), 6.34 (d, *J* = 7.53 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 6.03-5.95 (m, 1H), 5.88-5.80 (m, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.7 Hz, 1H), 5.21-5.14 (m, 2H), 4.67 (d, *J* = 3.6 Hz, 2H), 4.53 (d, *J* = 4.8 Hz, 2H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 166.1, 166.0, 165.0, 155.8, 142.9, 134.0, 132.3, 132.2, 131.9, 131.5, 129.2, 126.6, 125.5, 121.8, 121.5, 118.7, 118.2, 117.2, 114.4, 108.9, 102.0, 69.3 (2x), 66.0, 28.6 (2x); LRMS (electrospray): Mass calculated for $C_{27}H_{26}O_6$, $[M]^+$, 446. Found $[M+H]^+$ 447.



(*E*)-allyl 2-(4-(allyloxy)-2-hydroxyphenylcarbonyl)-3-(4-(allyloxy)-3-(3-methylbut-2-enyl)phenyl)prop-2-enoate (**12**). Prepared according to the general procedure using **31** (200 mg, 724 μmol), **27** (354 mg, 916 μmol), toluene (800 μL) and glacial Acetic acid (105 μL). Purified by flash column chromatography (SiO_2, 5% EtOAc/Hex) to afford **12** (257 mg, 73%, with >95:5 *E:Z* selectivity) as a golden yellow oil. Analytical data for **12**: IR (film) 3430, 3084, 2924, 1717, 1620, 1600, 1499, 1243 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.5 (s, 1H), 7.86 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.46 (s, 1H), 6.33 (d, *J* = 8.8 Hz, 1H), 6.04-5.98 (m, 2H), 5.89-5.81 (m, 1H), 5.42-5.36 (m, 2H), 5.32-5.35 (m, 4H), 5.22-5.16 (m, 11H), 5.12 (ap t, *J* = 7.3 Hz, 1H), 4.68 (d, *J* = 4.0 Hz, 2H), 4.55 (d, *J* = 5.1 Hz, 2H), 4.52 (d, *J* = 4.8 Hz, 2H), 3.21 (d, *J* = 7.3 Hz, 2H), 1.71 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 166.0 (2x) , 165.1, 158.7, 143.4, 134.0, 133.9, 133.0, 132.3, 132.0, 131.9, 131.2, 130.6, 126.4, 125.3, 121.3, 118.7, 118.2, 117.7, 114.4, 111.6, 108.8, 102.0, 69.3, 68.9, 65.9, 28.3, 26.0, 17.9; LRMS (electrospray): Mass calculated for $C_{30}H_{32}O_6$, $[M]^+$, 488. Found $[M+H]^+$, 489.

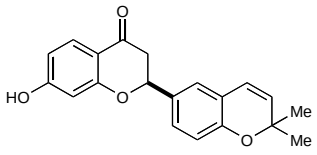


(*E*)-allyl 2-(4-(allyloxy)-2-hydroxyphenylcarbonyl)-3-(2,2-dimethyl-8-(3-methylbut-2-enyl)-2*H*-chromen-6-yl)prop-2-enoate (**11**). Prepared according to the general procedure using **31** (85 mg, 308 μmol), **28** (176 mg, 427 μmol), toluene (1 mL) and glacial Acetic acid (49 μL). Purified by flash column chromatography (SiO_2, 5% EtOAc/Hex) to afford **11** (138 mg, 87%, with >95:5 *E:Z* selectivity) as a golden yellow oil. Analytical data for **11**: IR (film) 2975, 2925, 1713, 1621, 1238, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.5 (s, 1H), 7.81 (s, 1H) 7.42 (d, *J* = 9.2 Hz, 1H), 7.01 (s, 1H), 6.86 (s, 1H), 6.46 (s, 1H), 6.33 (dd, *J* = 7.1, 1.6 Hz, 1H)), 6.17 d, *J* = 9.9 Hz, 1H), 6.05-5.97 (m, 1H), 5.89-5.81 (m, 1H), 5.57 (d, *J* = 9.9, Hz, 1H), 5.41 (d, *J* = 17.7 Hz, 1H), 5.31 (d, *J* = 9.3 Hz, 1H), 5.21-5.15 (m, 2H), 5.08 (ap t, *J* = 7.1 Hz, 1H), 4.68 (d, *J* = 4.0 Hz, 2H), 4.55 (d, *J* = 4.8 Hz, 2H), 3.12 (d, *J* = 7.13 Hz, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 165.9 (2x), 165.0, 153.5, 143.4, 134.0, 133.3, 132.3, 132.1, 131.9, 131.1, 130.0, 127.3, 126.1, 124.9, 122.1, 121.5, 121.0, 118.7, 118.1, 114.4, 108.8, 101.9, 77.4, 69.3, 65.9, 28.5 (2x), 27.9, 25.9, 17.9; LRMS (electrospray): Mass calculated for $C_{32}H_{34}O_6$, $[M]^+$, 514. Found $[M+H]^+$, 515.



(*E*)-allyl 2-(4-(allyloxy)-2-hydroxyphenylcarbonyl)-3-(4-methoxy-3,5-bis(3-methylbut-2-enyl)phenyl)prop-2-enoate (**13**). Prepared according to the general procedure using **31** (536 mg, 1.94 mmol), 4,4'-((4-methoxy-3,5-bis(3-methylbut-2-enyl)phenyl)methylene)dimorpholine (**29**) (1.05 g, 2.45 mmol), glacial Acetic acid (281 μL), and toluene (2 mL) to afford **13** (625 mg, 61%, with >95:5 *E:Z* selectivity) as a yellow oil. Analytical data for **13**: IR (film) 2924, 1713, 1620, 1239 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.6 (s, 1H), 7.85 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.05 (s, 2H), 6.46 (s, 1H), 6.33 (dd, *J* = 8.8, 1.5 Hz, 1H), 6.05-5.97 (m, 1H), 5.89-5.81 (m, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.31 (d, *J* = 10.7 Hz, 1H), 5.21-5.16 (m, 2H), 5.11-5.08 (m, 2H), 4.68 (d, *J* = 4.9 Hz, 2H), 4.56 (d, *J* = 4.4 Hz, 2H), 3.69 (s, 3H), 3.24 (d, *J* = 6.84 Hz, 4H), 1.71 (s, 6H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 165.9 (2x), 164.9, 158.7, 143.4, 135.6 (2x), 134.0, 133.7, 132.3, 131.9, 130.5 (2x), 128.7, 127.9, 122.1 (2x), 118.7, 118.2, 114.4, 108.8, 102.0, 69.3, 66.0, 61.0, 28.2 (2x), 26.0 (2x), 18.0 (2x); LRMS (electrospray): Mass calculated for $C_{33}H_{38}O_6$, $[M]^+$, 530. Found $[M+H]^+$, 531.

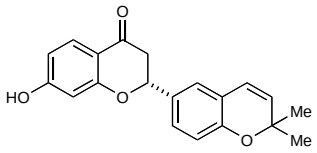
General Cyclization and Decarboxylation/Deprotection Procedure



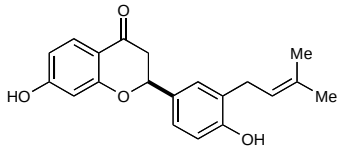
(*S*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one ((***S*)-1**, **(*2S*)-abyssinone I**). To a 10 mL round bottom flask was added **10** (78 mg, 175 μmol), and thiourea catalyst **II** (12 mg, 18 μmol). The flask was purged with N_2, toluene (1.8 mL) was added and the resulting solution was stored at –25 °C. Reaction progress was monitored by reverse phase high performance chromatography. After 40 h, toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***S*)-14** (72 mg) as an amber oil. This oil was used without further purification. To a 10 mL round bottom flask containing a magnetic stirring bar was added (***S*)-14** (73 mg, 164 μmol) and $Pd(PPh_3)_4$ (10 mg, 8 μmol). The flask was purged with N_2 and THF (3 mL), and morpholine (215 μL, 2.46 mmol) were added. Reaction progress was monitored by reverse phase high performance liquid chromatography. After 2 h 15 min, the solution was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford (*S*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one (***S*)-1** (43 mg, 76% over two steps) as a yellow oil in 82% ee. Analytical data for (***S*)-1**: $[\alpha]_D$: –65.0 (MeOH, *c* = 0.38); CD (*c* 0.055 mM, MeOH) $\Delta\varepsilon_{246}$ 2.49, $\Delta\varepsilon_{303}$ –4.02, $\Delta\varepsilon_{343}$ –0.82; IR (film) 3291, 3225, 2972, 2925, 1600, 1493, 1463, 1246, 1123 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.3, 2.0

Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.54 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.33 (d, *J* = 9.8 Hz, 1H), 5.84 (bs, 1H), 5.65 (d, *J* = 9.8 Hz, 1H), 5.35 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.05 (dd, *J* = 17.1, 13.7 Hz, 1H), 2.79 (dd, *J* = 16.6, 2.4 Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 164.2, 164.0, 153.7, 131.6, 130.9, 129.7, 127.5, 124.7, 122.2, 121.7, 116.8, 114.8, 111.2, 103.7, 79.9, 76.9, 44.2, 28.3; LRMS (electrospray): Mass calculated for $C_{20}H_{18}O_4$, $[M]^+$, 322. Found $[M+H]^+$, 323.

(2*R*)-allyl 7-(allyloxy)-2',2'-dimethyl-4-oxo-2,6'-bichroman-3-carboxylate ((*R*)-14). Prepared according to the general procedure using **10** (113 mg, 253 μmol), and thiourea catalyst **I** (9 mg, 14 μmol) and toluene (2.5 mL) stored at –25 °C. After 39 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***R***)-**14** (100 mg, 88%) as an amber oil. This was judged to be greater than 95% pure.

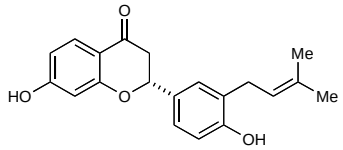


(*R*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one ((***R***)-**1**, **(*2R*)-abyssinone I**). (2*R*)-allyl 7-(allyloxy)-2',2'-dimethyl-4-oxo-2,6'-bichroman-3-carboxylate ((***R***)-**14**), (37 mg, 83 μmol), $Pd(PPh_3)_4$ (4 mg, 4 μmol), morpholine (110 μL, 1.25 mmol) and THF (1 mL) was stirred for 2 h and the solvent was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford (***R***)-**1** (22 mg, 81%) as a yellow oil in 87% ee. Analytical data for (***R***)-**1**: $[\alpha]_D$: +54.5 (MeOH, *c* = 0.44); CD (*c* 0.065mM, MeOH) $\Delta\varepsilon_{245}$ –2.58, $\Delta\varepsilon_{301}$ 6.73, $\Delta\varepsilon_{347}$ 1.71.

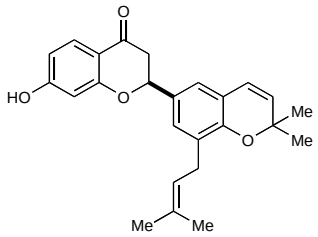


(*S*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one ((***S***)-**2**, **(*2S*)-abyssinone II**). Prepared according to the general procedure using **12** (70 mg, 142 μmol), thiourea catalyst **II** (10 mg, 14 μmol) and toluene (1.4 mL). After 60 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***S***)-**15** (66 mg) as a yellow solid. This solid was used without further purification. (2*S*)-allyl 7-(allyloxy)-2',2'-dimethyl-4-oxo-2,6'-bichroman-3-carboxylate ((***S***)-**15**) (66 mg, 140 μmol), $Pd(PPh_3)_4$ (8 mg, 7 μmol), morpholine (305 μL, 3.5 mmol) and THF (2 mL) was stirred for 2 h 15 min and the solvent was concentrated *in vacuo* to afford (***S***)-**2** (35 mg, 72% over two steps) as a yellow oil in 89% ee. Analytical data for (***S***)-**2**: $[\alpha]_D$: –40.6 (MeOH, c = 0.35); CD (*c* 0.104 mM, MeOH) $\Delta\varepsilon_{243}$ 5.87, $\Delta\varepsilon_{303}$ –8.41, $\Delta\varepsilon_{332}$ 2.96; IR (film) 3309, 2967, 2918, 1655, 1601, 1463, 1251 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.22-7.20 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3, 2.0 Hz, 1H), 6.45 (d, *J* = 2.4

Hz, 1H), 5.93 (bs, 1H), 5.37 (dd, *J* = 13.7, 2.9 Hz, 1H), 5.32 (ap t, *J* = 7.3 Hz, 1H) 3.39 (d, *J* = 7.3 Hz, 2H), 3.06 (dd, *J* = 16.6, 13.5 Hz, 1H), 2.79 (dd, *J* = 16.8, 2.9 Hz, 1H), 1.78 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 164.3, 164.3, 155.1, 135.3, 130.8, 129.7, 128.5, 127.8, 125.9, 121.6, 116.2, 114.7, 111.2, 103.7, 80.0, 44.2, 29.9, 26.1, 18.2; LRMS (electrospray): Mass calculated for $C_{20}H_{20}O_4$, $[M]^+$, 324. Found $[M+H]^+$, 325.

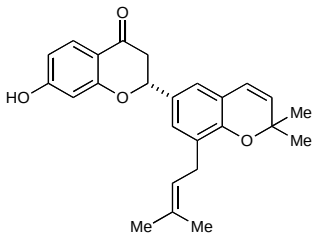


(*R*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one ((***R*)-2**, **(*2R*)-abyssinone II**). Prepared according to the general procedure using (*E*)-allyl 2-(4-(allyloxy)-2-hydroxyphenylcarbonyl)-3-(4-(allyloxy)-3-(3-methylbut-2-enyl)phenyl)prop-2-enoate (**12**) (66 mg, 134 μmol) thiourea catalyst **I** (9 mg, 14 μmol) and toluene (1.3 mL). After 45 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***R*)-15** (66 mg) as a bright yellow solid. This oil was used without further purification. (2*R*)-allyl 7-(allyloxy)-2',2'-dimethyl-4-oxo-2,6'-bichroman-3-carboxylate ((***R*)-15**) (60 mg, 122 μmol), $Pd(PPh_3)_4$ (7 mg, 6 μmol), morpholine (265 μL, 3.05 mmol) and THF (2 mL) was stirred for 2 h 15 min and the solvent was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% to 50% EtOAc/hexanes) to afford (***R*)-2** (20 mg, 61% over two steps) as a yellow oil in 88% ee. Analytical data for (***R*)-2**: $[\alpha]_D$: +36.4 (MeOH, c = 0.39); CD (*c* 0.053 mM, MeOH) $\Delta\varepsilon_{246}$ -1.26, $\Delta\varepsilon_{303}$ 4.55, $\Delta\varepsilon_{334}$ -0.924.

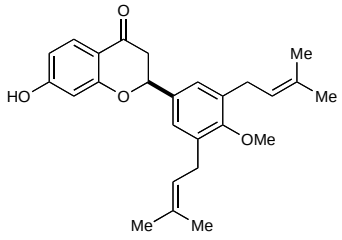


(*S*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one ((***S*)-3, (*2S*)-abyssinone III)**. Prepared according to the general procedure stirring **11** (78 mg, 151 μmol), thiourea catalyst **II** (12 mg, 15.8 μmol) and toluene (1.5 mL). After 84 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***S*)-16** (77 mg) as a yellow oil. This oil was used without further purification. (2*S*)-allyl 7-(allyloxy)-2',2'-dimethyl-4-oxo-2,6'-bichroman-3-carboxylate ((***S*)-16**), (77 mg, 150 μmol), $Pd(PPh_3)_4$ (9 mg, 8 μmol), morpholine (200 μL, 2.25 mmol) and THF (2 mL) was stirred for 2 h 15 min and the solvent was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford (***S*)-3** (41 mg, 70% over two steps) as a yellow oil in 84% ee. Analytical data for (***S*)-3**: $[\alpha]_D$: –57.6 (MeOH, c = 0.34); CD (*c* 0.058 mM, MeOH) $\Delta\varepsilon_{248}$ 3.97, $\Delta\varepsilon_{301}$ –6.20, $\Delta\varepsilon_{347}$ –1.29; IR (film) 3247, 2974, 2928, 1728, 1663, 1605, 1466, 1150 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.79 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 6.14 (bs, 1H), 5.63 (d, *J* = 9.77 Hz, 1H), 5.32 (dd, *J* = 13.2, 2.44 Hz, 1H), 5.27 (ap t, *J* =

7.33 Hz, 1H), 3.28 (d, *J* = 7.3 Hz, 2H), 3.06 (dd, *J* = 17.1, 13.7 Hz, 1H), 2.78 (dd, *J* = 17.1, 2.93 Hz, 1H), 1.73 (s, 6H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 164.4, 164.2, 151.3, 132.6, 131.3, 130.2, 129.8, 129.7, 127.8, 122.5 (3x), 121.4, 114.7, 111.2, 103.7, 80.2, 77.5, 44.2, 28.5, 28.3, 26.1 (2x), 18.1; LRMS (electrospray): Mass calculated for $C_{25}H_{26}O_4$, $[M]^+$, 390. Found $[M+H]^+$, 391.

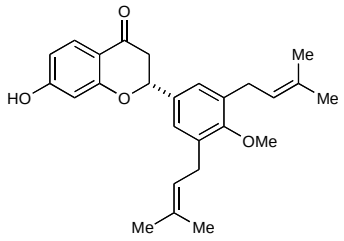


(*R*)-7-hydroxy-2',2'-dimethyl-2,6'-bichroman-4-one ((***R*)-3**, **(*2R*)-abyssinone III**). Prepared according to the general procedure using **11** (53 mg, 103 μmol), thiourea catalyst **I** (7 mg, 10.6 μmol) and toluene (1 mL). After 84 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***R*)-16** (43 mg) as a yellow oil. This oil was used without further purification. (2*R*)-allyl 7-(allyloxy)-2',2'-dimethyl-4-oxo-2,6'-bichroman-3-carboxylate ((***R*)-16**), (46 mg, 89 μmol), $Pd(PPh_3)_4$ (5 mg, 5 μmol), morpholine (115 μL, 1.34 mmol) and THF (1.8 mL) was stirred for 2 h 15 min and the solvent was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford (***R*)-3** (32 mg, 75% over two steps) as a yellow oil in 86% ee. Analytical data for (***R*)-3**: $[\alpha]_D$: +57.9 (MeOH, c = 0.33); CD (*c* 0.058 mM, MeOH) $\Delta\varepsilon_{303}$ 3.38, $\Delta\varepsilon_{343}$ 0.78.



(*S*)-7-hydroxy-2-(4-methoxy-3-(3-methylbut-2-enyl)-5-(4-methylpent-3-enyl)phenyl)chroman-4-one ((***S*)-4**, **(*2S*)-abyssinone IV 4′-OMe)**. Prepared according to the general procedure using **13** (43 mg, 81 μmol), thiourea catalyst **II** (6 mg, 8 μmol) and toluene (800 μL). After 48 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***S*)-17** (33 mg) as a yellow oil. This oil was used without further purification. (2*S*)-allyl 7-(allyloxy)-2-(4-methoxy-3,5-bis(3-methylbut-2-enyl)phenyl)-4-oxochroman-3-carboxylate ((***S*)-17**) (33 mg, 60 μmol), $Pd(PPh_3)_4$ (4 mg, 3 μmol), morpholine (80 μL, 900 μmol) and THF (1.2 mL) was stirred for 2 h and the solvent was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford (***S*)-4** (21 mg, 65% over two steps) as a yellow oil in 94% ee. Analytical data for (***S*)-4**: $[\alpha]_D$: –66.2 (MeOH, *c* = 0.21); CD (*c* 0.21 mM, MeOH) $\Delta\varepsilon_{239}$ 4.67, $\Delta\varepsilon_{288}$ -7.96, $\Delta\varepsilon_{330}$, +2.82; IR (film) 3223, 2968, 2917, 1657, 1601, 1465, 1277 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 1H), 7.12 (s, 2H), 6.58 (dd, *J* = 10.7, 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz,

1H), 5.37 (dd, *J* = 13.2, 2.4 Hz, 1H), 5.28 (ap t, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 3.38 (d, *J* = 7.3 Hz, 4H), 3.08 (dd, *J* = 16.6, 13.7, Hz, 1H), 2.80 (dd, *J* = 16.6, 2.4 Hz, 1H), 1.74 (s, 6H), 1.73 (s, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 164.7, 164.4, 156.7, 135.6, 134.3, 133.2, 129.6, 126.2, 122.8, 114.6, 111.3, 103.7, 80.2, 61.2, 44.2, 28.7, 26.0, 18.2; LRMS (electrospray): Mass calculated for $C_{26}H_{30}O_4$, $[M]^+$, 406. Found $[M+H]^+$, 407.

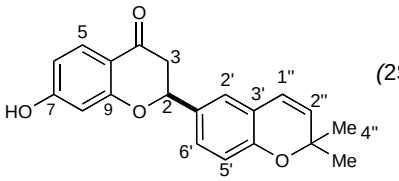


(*R*)-7-hydroxy-2-(4-methoxy-3-(3-methylbut-2-enyl)-5-(4-methylpent-3-enyl)phenyl)chroman-4-one ((***R*)-4, (*2R*)-abyssinone IV 4′-OMe**). Prepared according to the general procedure stirring **13**, (50 mg, 90 μmol), thiourea catalyst **I** (6 mg, 9 μmol) and toluene (1 mL). After 48 h toluene was concentrated *in vacuo* and the resulting residue was run though a short pad of silica gel using 10% EtOAc/hexanes as the eluent to afford (***R*)-17** (39 mg) as a yellow oil. This oil was used without further purification. (2*R*)-allyl 7-(allyloxy)-2-(4-methoxy-3,5-bis(3-methylbut-2-enyl)phenyl)-4-oxochroman-3-carboxylate (***R*)-(17**) (39 mg, 70 μmol), $Pd(PPh_3)_4$ (4 mg, 3.7 μmol), morpholine (90 μL, 1.05 mmol) and THF (1 mL) was stirred for 1.5 h and the solvent was concentrated *in vacuo*. Purified by column chromatography (SiO_2, 30% EtOAc/Hex) to afford (***R*)-4** (23 mg, 65% over two steps) as a yellow oil in 95% ee. Analytical data for (***R*)-4**: $[\alpha]_D$: +63.6 (MeOH, c = 0.225); CD (*c* 0.25 mM, MeOH) $\Delta\varepsilon_{242}$ –1.52, $\Delta\varepsilon_{300}$ 10.5, $\Delta\varepsilon_{345}$ 3.13.

General Procedure for Racemic Cyclizations for HPLC Traces

To a round bottom flask containing a magnetic stirring bar was added the alkylidene compound, 30 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and acetonitrile (0.1 M). The solution was stirred at 23 °C for 5-12 h. Reaction progress was monitored by reverse phase high performance liquid chromatography. After complete cyclization, the reaction was diluted with EtOAc, poured into a separatory funnel and washed with brine three times. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude carboxyflavanone. Purified by flash column chromatography (10% EtOAc/hexanes). To a round bottom flask containing a magnetic stirring bar was added the carboxyflavanone and $Pd(PPh_3)_4$ (5 mol %). The flask was purged with N_2 and THF (0.05 M) and morpholine (15-25 equivalents) were added. The reaction was monitored by reverse phase high performance liquid chromatography. After completion, the solvent was concentrated *in vacuo* to provide the unpurified abyssinones. Purified by flash column chromatography (30% EtOAc/hexanes).

Comparative Analysis of Natural and Synthetic Abyssinones

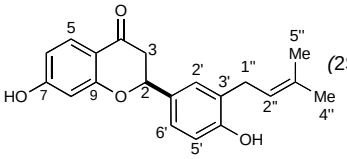


(2S)-abyssinone I

	^{1}H NMR ($CDCl_3$) *J* in Hz		^{13}C NMR ($CDCl_3$)
position	isolated[a]	synthetic	synthetic
2	5.35 (dd, 11.5, 4.1)	5.35 (dd, 13.2, 2.4)	79.9
3_{ax}	2.96 (dd, 16.8, 11.5)	3.05 (dd, 16.7, 13.5)	44.2
3_{eq}	2.75 (dd, 16.8, 4.1)	2.79 (dd, 16.8, 2.4)	-
4	-	-	192.4
5	7.85 (d, 8.4)	7.86 (d, 8.6)	130.9
6	6.52 (dd, 8.4, 2.4)	6.55 (dd, 8.2, 2.0)	111.2
7	-	-	164.2
8	6.44 (d, 2.4)	6.45 (d, 2.5)	103.7
9	-	-	164.0
10	-	-	114.8
1'	-	-	131.6
2'	7.07 (d, 2.2)	7.08 (d, 2.0)	124.7
3'	-	-	121.7
4'	-	-	153.7
5'	6.79 (d, 8.3)	6.81 (d, 8.2)	116.8
6'	7.19 (dd, 8.3, 2.2)	7.18 (dd, 8.2, 2.0)	129.7
1"	6.33 (d, 10)	6.33 (d, 9.9)	122.2
2"	5.64 (d, 10)	5.65 (d, 9.7)	127.5
3"	-	-	76.9
4"	not reported[b]	1.44 (s)	28.3
OH	not reported	5.96 (bs, 1H)	-

optical data	isolated (*S*)	synthetic (*S*)	synthetic (*R*)
CD	332($\Delta\varepsilon$) +2.54, 303($\Delta\varepsilon$) –6.1 (MeOH)	343($\Delta\varepsilon$) –0.82, 303($\Delta\varepsilon$) –4.02 (c 0.055 mM, MeOH)	345($\Delta\varepsilon$) –2.58, 301($\Delta\varepsilon$) +6.73 (c 0.065mM, MeOH)
optical rotation	not reported	$[\alpha]_D$: –65.0 (MeOH, c = 0.38)	$[\alpha]_D$: +54.5 (MeOH, c = 0.44)

[a] Kamat, V. S.; Chuo, F. Y.; Kubo, I.; Nakanishi, K. *Heterocycles* **1981**, *15*, 1163-1170.
[b] ^{13}C NMR spectral data and some ^{1}H signals were not provided in the isolation paper.



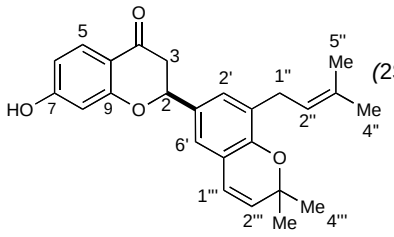
(2S)-abyssinone II

	^{1}H NMR ($CDCl_3$) *J* in Hz			^{1}H NMR (CD_3OD)
position	isolated[a]	synthetic (Naithani)[c]	synthetic (Scheidt)	synthetic (Cushman)[d]
2	5.37 (dd, 12.0, 4.1)	5.36 (dd, 13.4, 2.8)	5.36 (dd, 13.2, 2.9)	5.35 (dd, 13.4, 2.8)
3_{ax}	3.08 (dd, 17.1, 12.0)	3.07 (dd, 13.3, 3.7)	3.06 (dd, 16.6, 13.5)	3.02 (dd, 13.4, 3.7)
3_{eq}	2.75 (dd, 17.1, 4.1)	2.79 (dd, 17, 2.9)	2.79 (dd, 16.8, 2.9)	2.67 (dd, 16.9, 2.9)
4	-	-	-	-
5	7.85 (d, 8.3)	7.84 (d, 8.7)	7.85 (d, 8.8)	7.68 (d, 8.7)
6	6.52 (dd, 8.3, 2.4)	6.56 (dd, 8.7, 2.3)	6.55 (dd, 8.6, 2.0)	6.48 (dd, 8.7, 2.3)
7	-	-	-	-
8	6.45 (d, 2.4)	6.47 (d, 2.3)	6.46 (d, 2.4)	6.33 (d, 2.3)
9	-	-	-	-
10	-	-	-	-
1'	-	-	-	-
2'	7.3-7.1 (m, 2H)	7.19 (m)	7.21-7.20 (m)	7.13 (m)
3'	-	-	-	-
4'	-	-	-	-
5'	6.83 (d, 8.5)	6.84 (d, 8.8)	6.85 (d, 7.9)	6.76 (d, 8.7)
6'	7.3-7.1 (m, 2H)	7.19 (m)	7.21-7.20 (m)	7.13 (m)
1''	not reported[b]	3.37 (d, 7.2)	3.38 (d, 7.0)	3.29 (d, 7.2)
2''	not reported	5.31 (t, 7.2)	5.32 (ap t, 7.3)	5.31 (t, 7.2)
3''	-	-	-	-
4''	not reported	1.75 (s)	1.78 (s)	1.72 (s)
5''	not reported	1.74 (s)	1.78 (s)	1.70 (s)

		^{13}C NMR ($CDCl_3$)		^{13}C NMR (CD_3OD)
position		synthetic (Naithani)[c]	synthetic (Scheidt)	synthetic (Cushman)[d]
2		80.2	80.0	81.1
3_{ax}		44.4	44.2	44.9
3_{eq}		-	-	-
4		192.7	192.7	193.5
5		129.9	129.7	129.8
6		111.3	111.2	111.6
7		164.1	164.3	165.5
8		103.9	103.7	103.8
9		164.4	164.3	166.7
10		115.0	114.7	114.9
1'		135.6	135.3	133.1
2'		128.7	128.5	129.4
3'		127.9	127.8	128.9
4'		155.3	155.1	156.5
5'		116.4	116.2	115.6
6'		126.1	125.9	126.1
1''		30.1	29.9	29.3
2''		121.7	121.6	123.7
3''		131.0	130.8	131.1
4''		26.2	26.1	25.9
5''		18.3	18.2	17.8

optical data	isolated (*S*)	synthetic (*S*)	synthetic (*R*)
CD	273($\Delta\varepsilon$) –10.7[e]	332($\Delta\varepsilon$) +2.96, 303($\Delta\varepsilon$) –8.41 (c 0.104 mM, MeOH)	334($\Delta\varepsilon$) –0.92, 303($\Delta\varepsilon$) +4.55 (c 0.053 mM, MeOH)
optical rotation	not reported	$[\alpha]_D$: –40.6 (MeOH, c = 0.35)	$[\alpha]_D$: +36.4 (MeOH, c = 0.39)

[a] Kamat, V. S.; Chuo, F. Y.; Kubo, I.; Nakanishi, K. *Heterocycles* **1981**, *15*, 1163-1170. [b] ^{13}C NMR spectral data and some ^{1}H signals were not provided in the isolation paper. For racemic syntheses of (±) abyssinone II: [c] Moriarty, R. M.; Grubjesic, S.; Surve, B. C.; Chandersekera, S. N.; Prakash, O.; Naithani, R. *Eur. J. Med. Chem.* **2006**, *41*, 263-267. [d] Maiti, A.; Cuendet, M.; Croy, V. L.; Endringer, D. C.; Pezzuto, J. M.; Cushman, M. *J. Med. Chem.* **2007**, *50*, 2799-2806. [e] Data obtained from private communication with Prof. A. D. Kinghorn from isolation in: Bhat, K. P. L.; Fong, H. H. S.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 1286-1293.

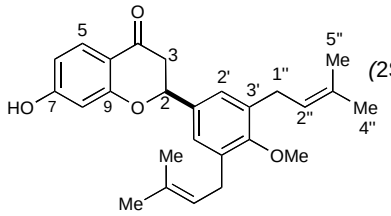


(2S)-abyssinone III

	^{1}H NMR ($CDCl_3$) *J* in Hz		^{13}C NMR ($CDCl_3$)[b]	
position	isolated[a]	synthetic (Scheidt)	isolated	synthetic
2	5.32 (dd, 12.2, 4.1)	5.32 (dd, 13.2, 2.4)	not reported	80.2
3_{ax}	3.08 (dd, 17.1, 12.2)	3.06 (dd, 17.1, 13.7)		44.2
3_{eq}	2.73 (dd, 17.1, 4.1)	2.78 (dd, 17.1, 2.9)		-
4	-	-		192.8
5	7.86 (d, 8.3)	7.85 (d, 8.8)		130.2
6	6.50 (dd, 8.3, 2.4)	6.54 (dd, 8.3, 2.0)		111.2
7	-	-		164.1
8	6.44 (d, 2.4)	6.46 (d, 2.4)		103.7
9	-	-		164.4
10	-	-		114.7
1'	-	-		129.8
2'	6.93 (d, 2.2)	6.94 (d, 1.9)		127.8
3'	-	-		131.3
4'	-	-		151.3
5'	-	-		121.4
6'	7.04 (d, 2.2)	7.04 (d, 2.0)		122.5
1''	not reported[b]	3.28 (d, 7.3)		28.5
2''	not reported	5.27 (br t, 7.3)		122.5
3''	-	-		132.6
4''	not reported	1.73 (s)		28.3
5''	not reported	1.73 (s)		18.2
1'''	6.32 (d, 9.8)	6.31 (d, 9.8)		122.5
2'''	5.62 (d, 9.8)	5.63 (d, 9.8)		129.7
3'''	-	-		77.5
4'''	not reported	1.43 (s)		26.0

optical data	isolated (*S*)	synthetic (*S*)	synthetic (*R*)
CD	330($\Delta\varepsilon$) +0.88, 303($\Delta\varepsilon$) –2.64	347($\Delta\varepsilon$) –1.29, 301($\Delta\varepsilon$) –6.20	343($\Delta\varepsilon$) +0.78, 303($\Delta\varepsilon$) +3.38
optical rotation	not reported	$[a]_D$: –57.6 (MeOH, c = 0.34)	$[a]_D$: +57.9 (MeOH, c = 0.33)

[a] Kamat, V. S.; Chuo, F. Y.; Kubo, I.; Nakanishi, K. *Heterocycles* **1981**, *15*, 1163-1170.
[b] ^{13}C NMR spectral data and some ^{1}H signals were not provided in the isolation paper.



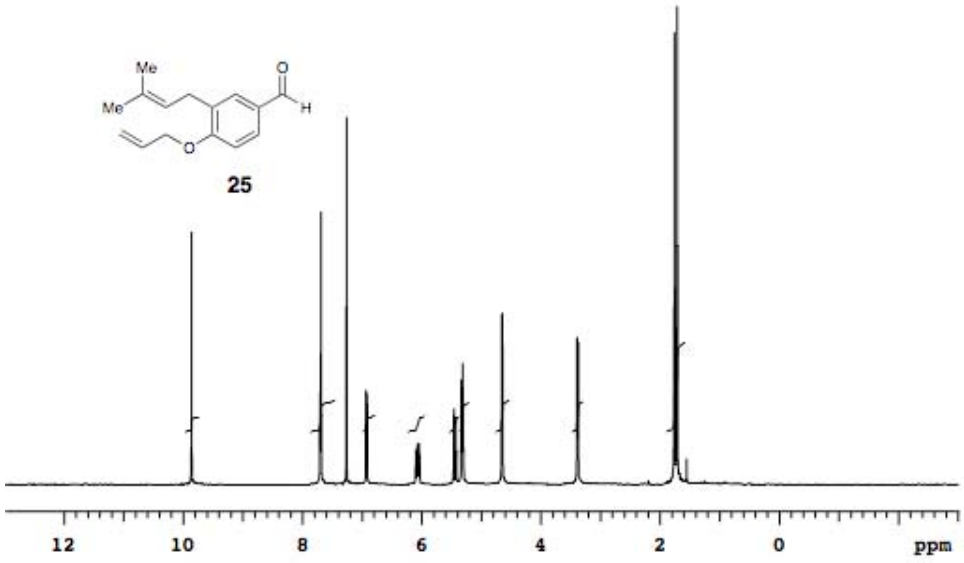
(2S)-abyssinone IV-4'-O-*methyl ether*

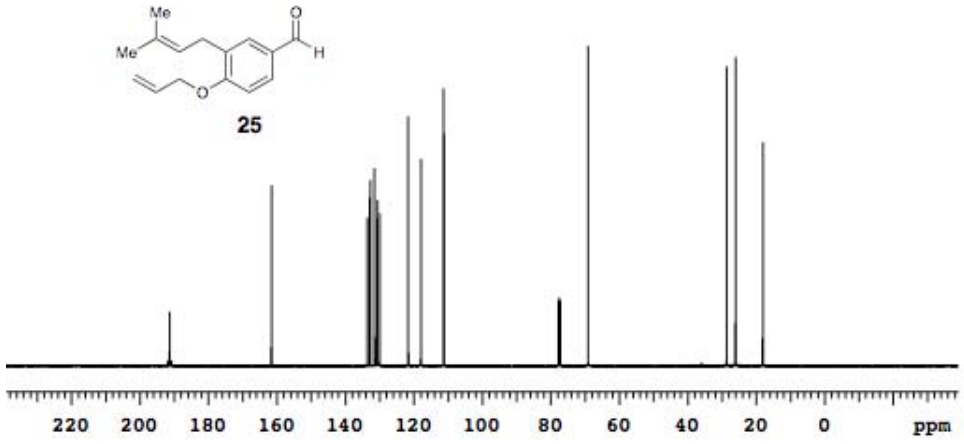
	^{1}H NMR ($CDCl_3$) *J* in Hz		^{13}C NMR ($CDCl_3$)	
position	isolated[a]	synthetic (Scheidt)	isolated[a]	synthetic
2	5.38 (dd, 13.6, 2.8)	5.36 (dd, 13.2, 2.4)	80.2	80.2
3_{ax}	3.06 (dd, 16.8, 13.6)	3.08 (dd, 16.6, 13.7)	44.1	44.2
3_{eq}	2.80 (dd, 16.8, 2.8)	2.80 (dd, 16.6, 2.4)	-	-
4	-	-	191.3	192.7
5	7.87 (d, 8.4)	7.84 (d, 8.8)	129.6	129.6
6	6.54 (dd, 8.4, 2.4)	6.58 (dd, 8.8, 2.0)	110.6	111.3
7	-	-	163.9	164.7
8	6.47 (d, 2.4)	6.50 (d, 2.0)	103.7	103.7
9	-	-	162.8	164.4
10	-	-	115.4	114.6
1'	-	-	134.4	134.3
2'	7.12 (s)	7.12 (s)	126.1	126.2
3'	-	-	135.5	135.6
4'	-	-	156.8	156.7
1''	3.40 (br d, 7.2)	3.38 (d, 7.3)	28.6	28.7
2''	5.30 (m)	5.28 (br t, 6.8)	122.9	122.8
3''	-	-	133.1	133.2
4''	1.76 (br s)	1.74 (s)	26.0	26.0
5''	1.74 (br s)	1.73 (s)	18.1	18.2
OMe	3.76 (s)	3.76 (s)	61.1	61.2

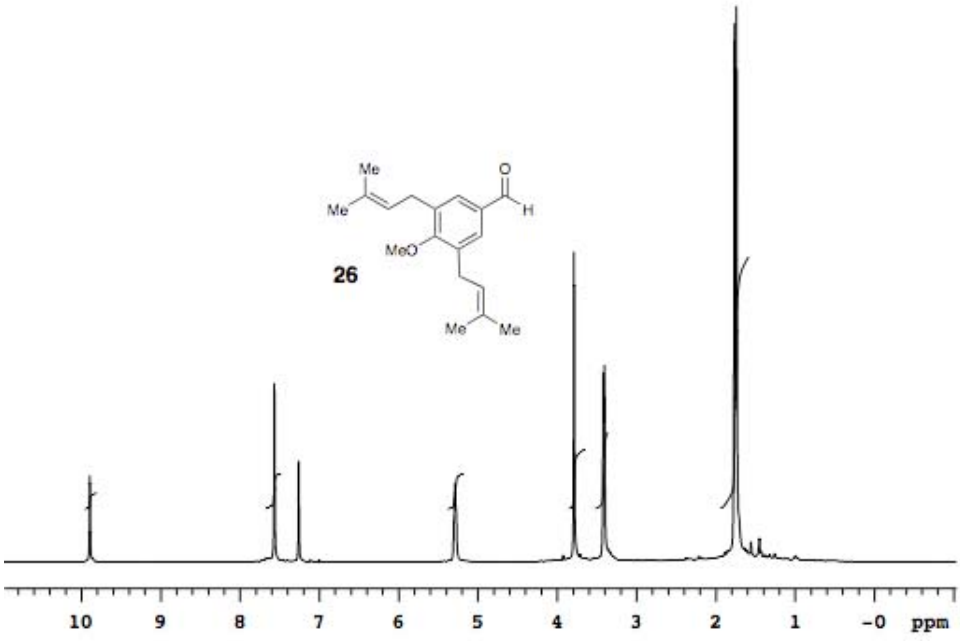
optical data	isolated[a] (*S*)	synthetic (*S*)	synthetic (*R*)
CD	$[\theta]_{330}$ +0.89, $[\theta]_{303}$ –2.64 (c 0.038, MeOH)	330($\Delta\varepsilon$) +2.82, 288($\Delta\varepsilon$) –7.96 (c 0.21 mM, MeOH)	345($\Delta\varepsilon$) +3.13, 300($\Delta\varepsilon$) +10.5 (c 0.25 mM, MeOH)
optical rotation	$[\alpha]_D$: –47.2 (MeOH, c =0.2)	$[\alpha]_D$: –66.2 (MeOH, c = 0.21)	$[\alpha]_D$: +63.6 (MeOH, c = 0.23)

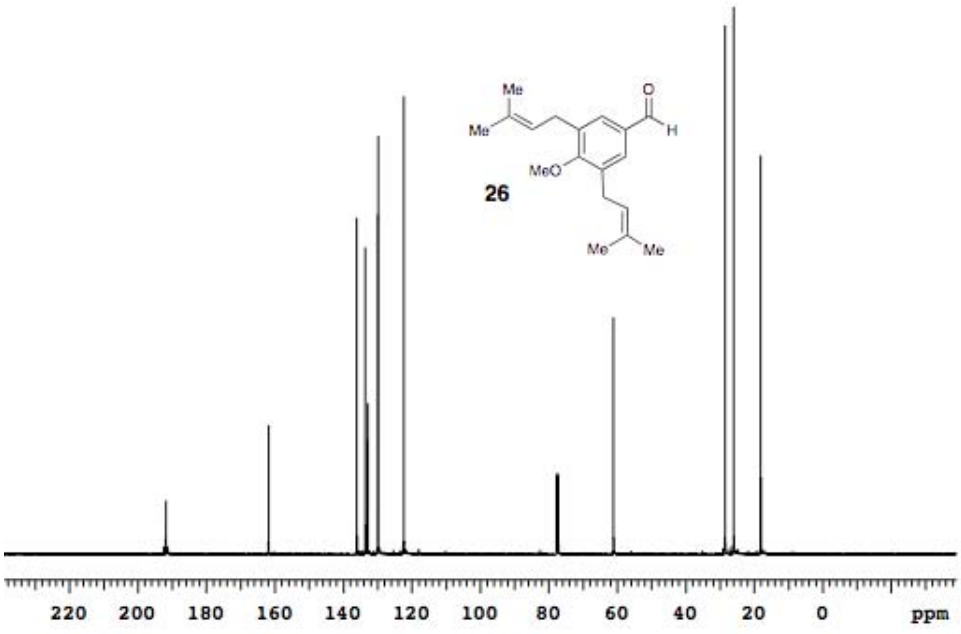
[a] Na, M.; Jang, J.; Njamen, D.; Mbafor, J. T.; Fomum, Z. T.; Kim, B. Y.; Oh, W. K.; Ahn, J. S. *J. Nat. Prod.* **2006**, *69*, 1572-1576.

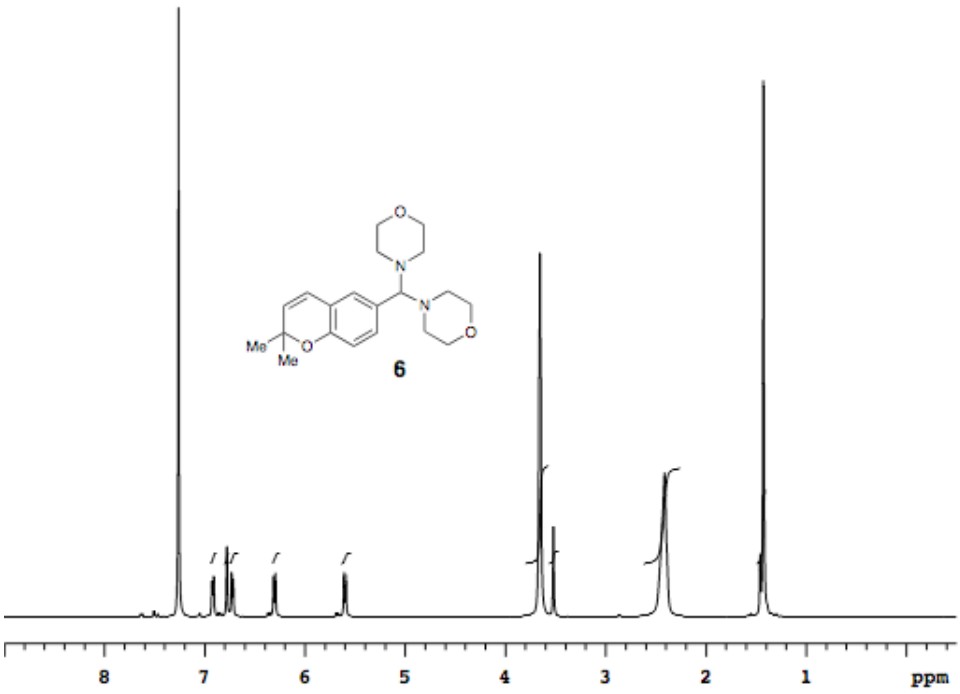
Selected NMR Spectra

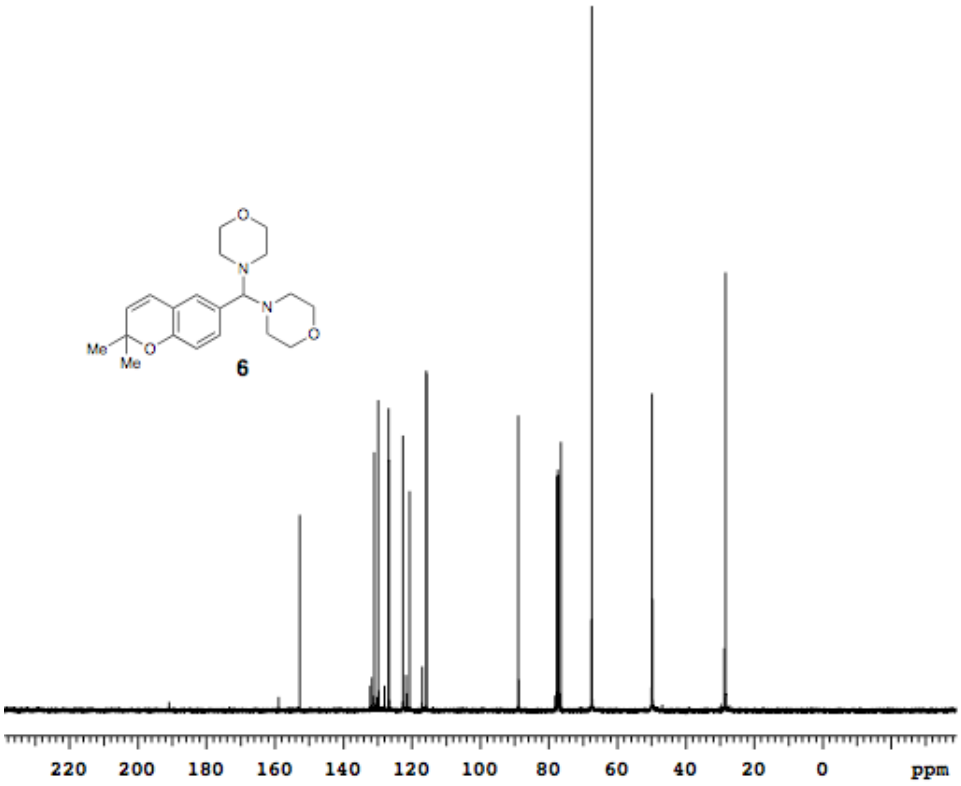


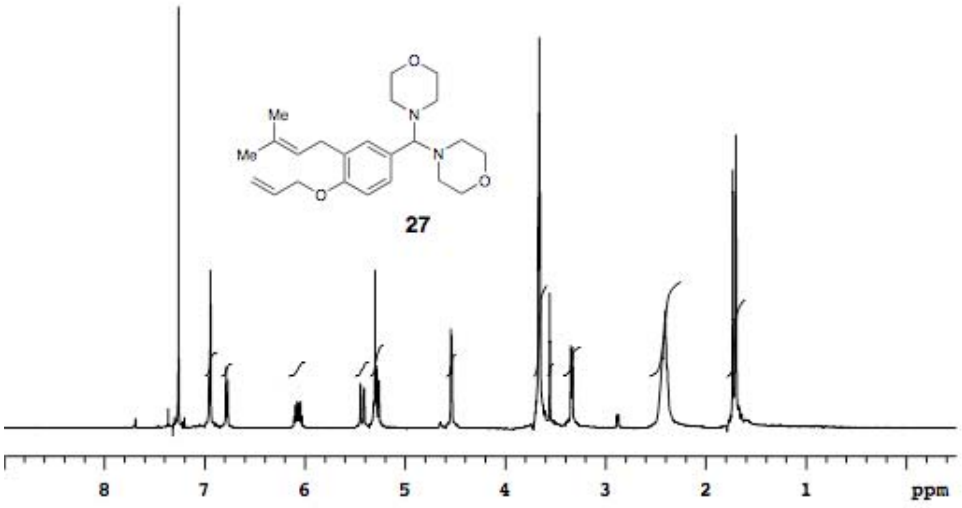


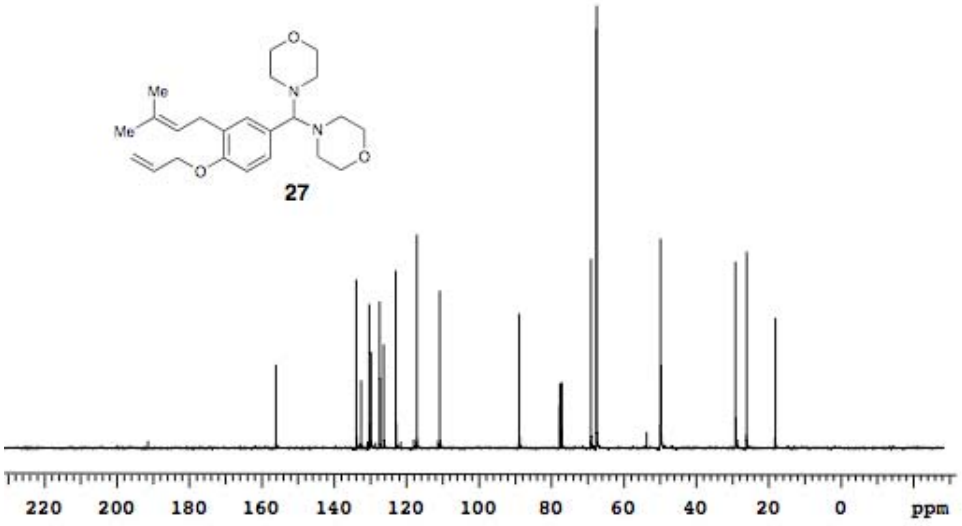

Me
Me
O
H
MeO
26
Me
Me
10
9
8
7
6
5
4
3
2
1
-0
ppm

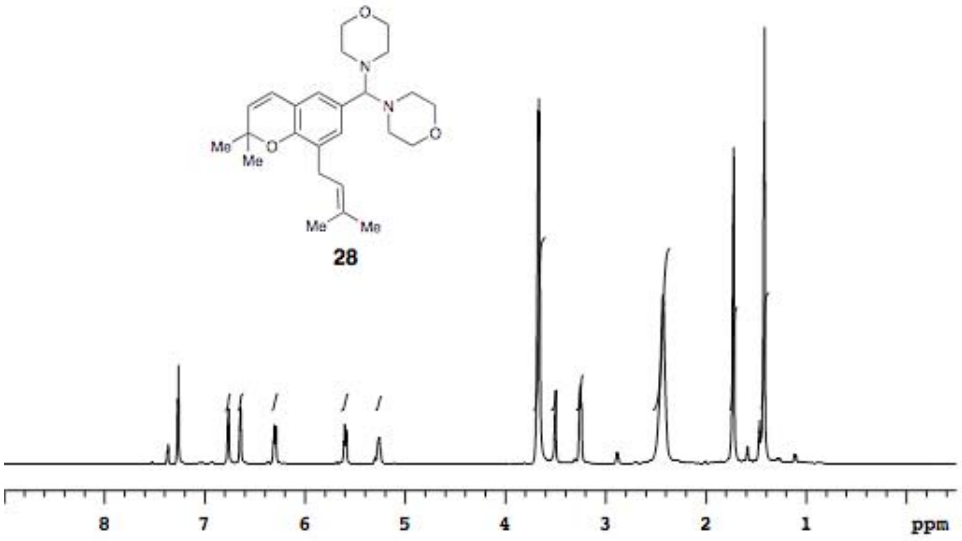

Me
Me
O
H
MeO
26
Me
Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

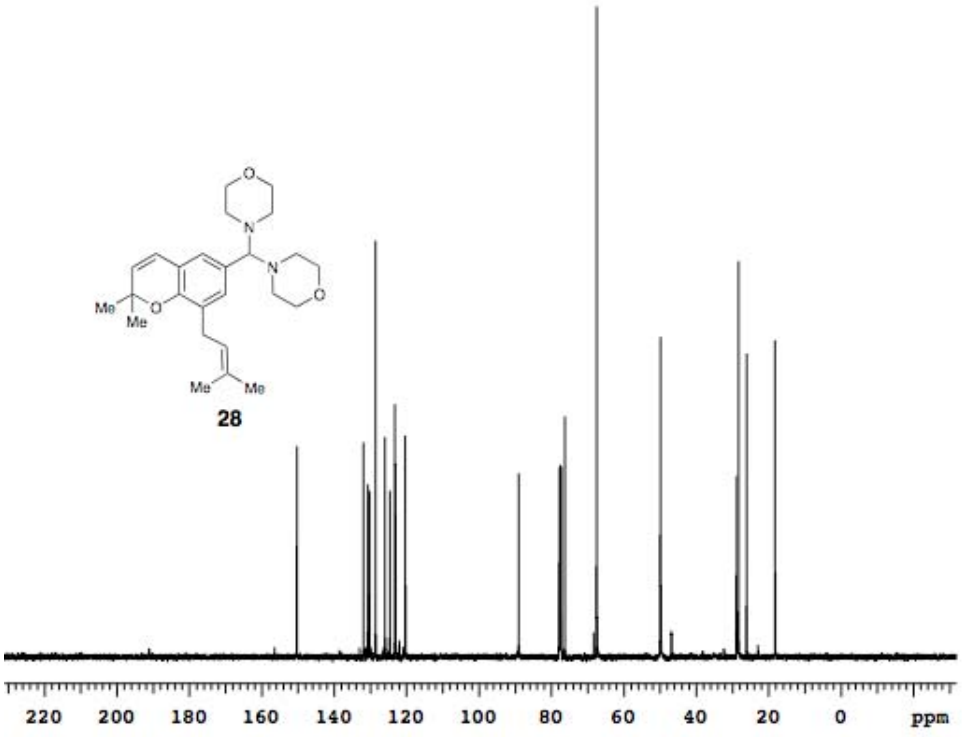

Me
Me
6
8
7
6
5
4
3
2
1
ppm

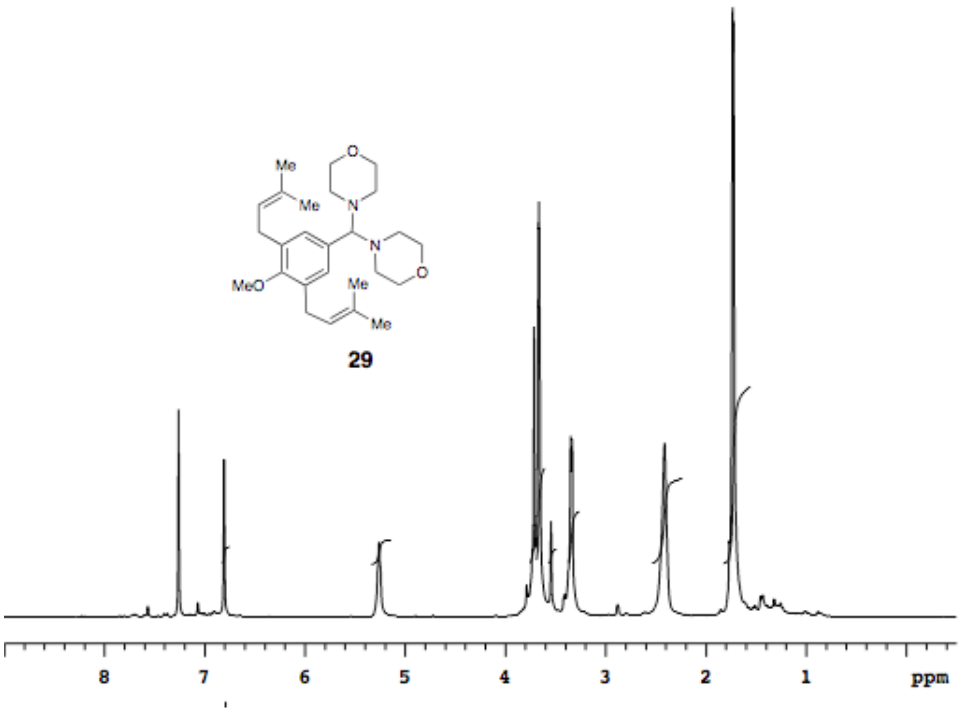

Me
Me
6
220
200
180
160
140
120
100
80
60
40
20
0
ppm

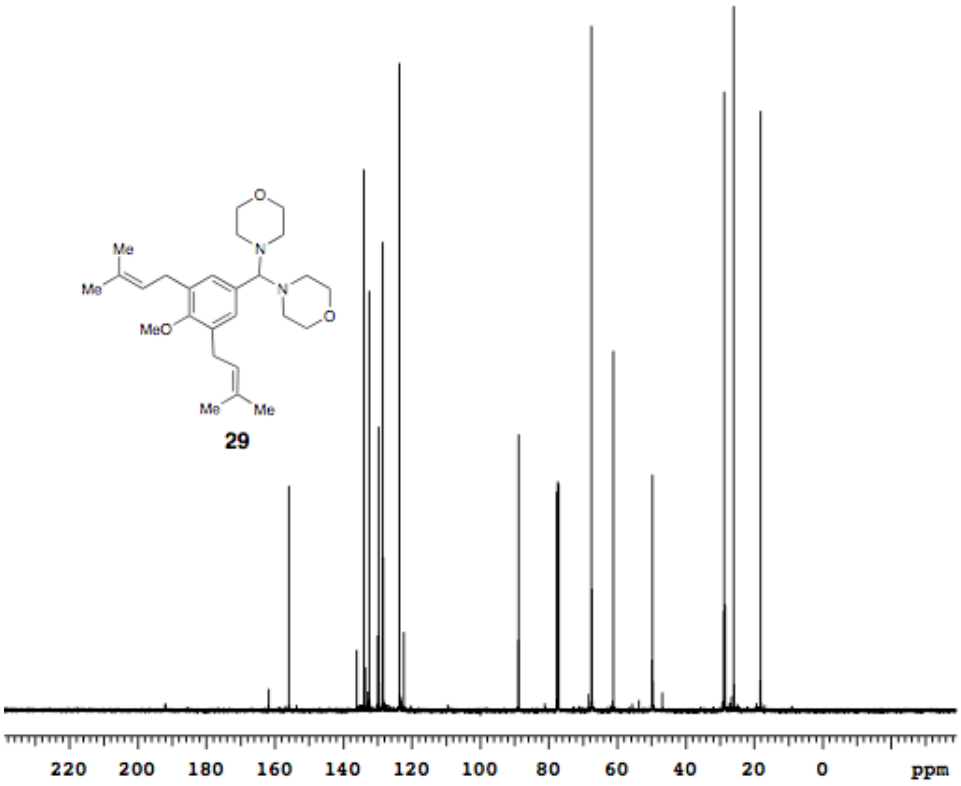

Me
Me
O
N
N
O
O
27
8
7
6
5
4
3
2
1
ppm

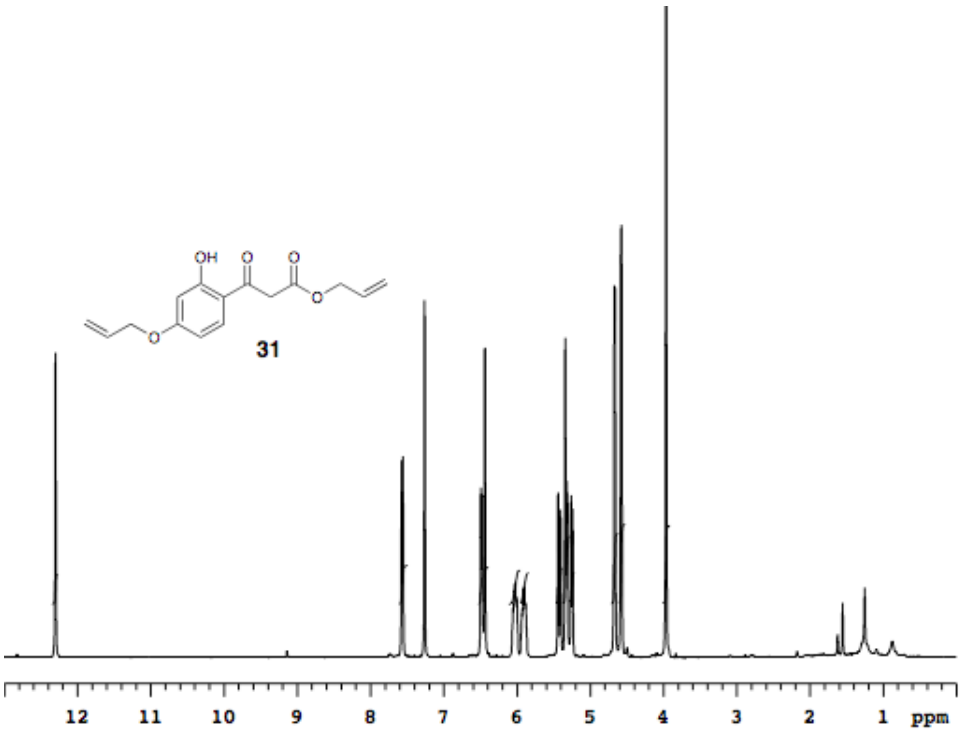

Me
Me
O
N
N
O
O
27
220
200
180
160
140
120
100
80
60
40
20
0
ppm

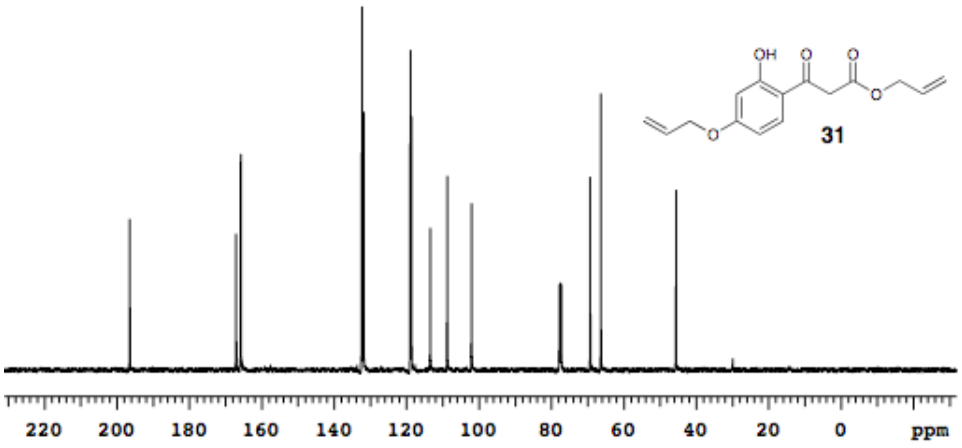

Me
Me
Me
Me
28
8
7
6
5
4
3
2
1
ppm

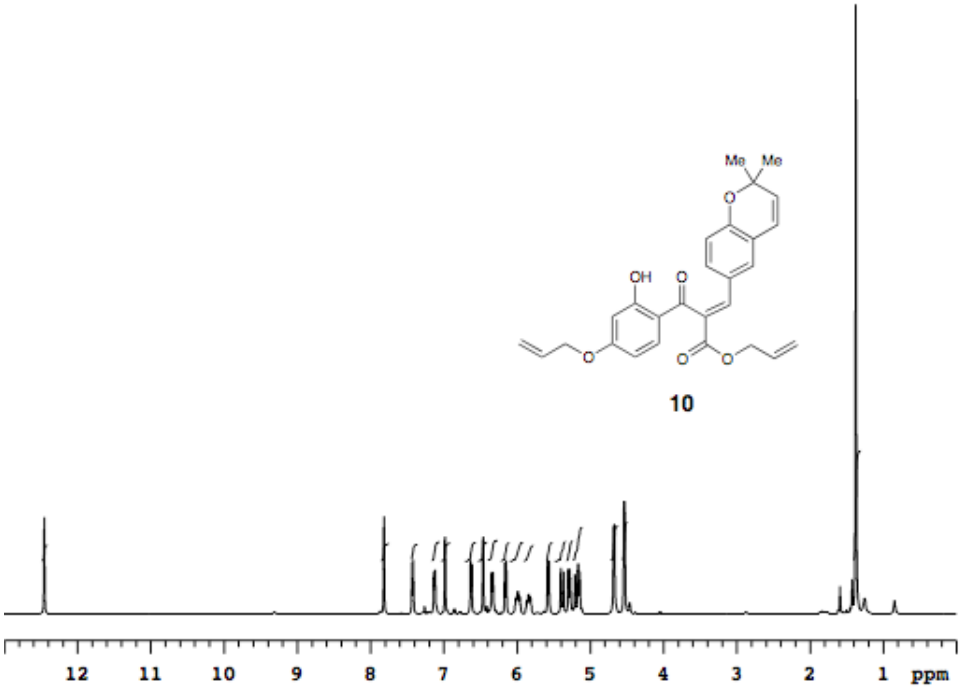

Me
Me
Me
Me
28
220
200
180
160
140
120
100
80
60
40
20
0
ppm

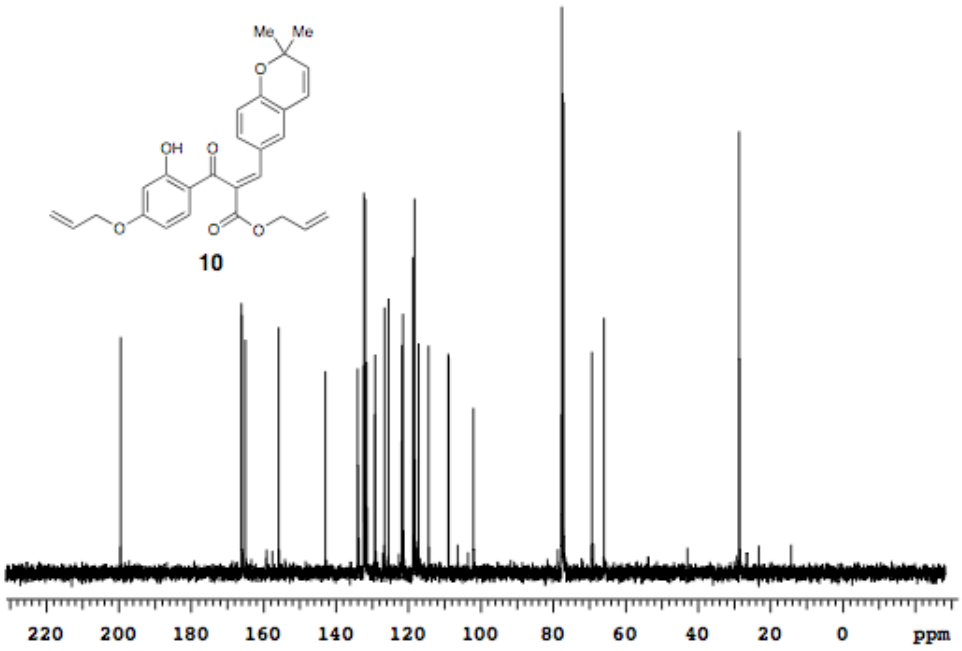

Me
Me
O
N
N
O
MeO
Me
Me
29
8
7
6
5
4
3
2
1
ppm

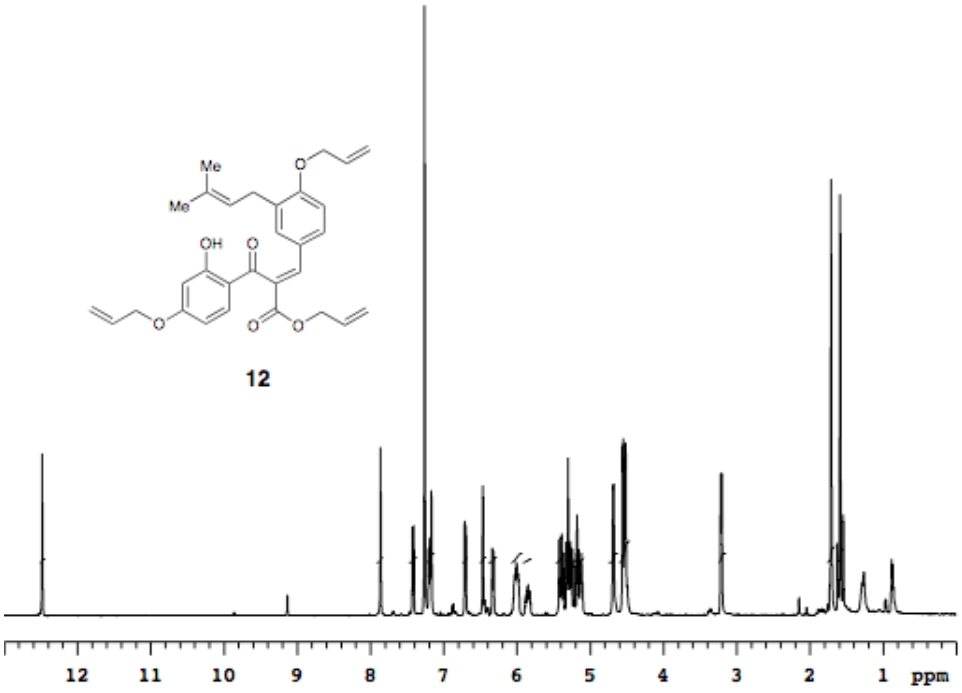

O
N
Me
Me
N
O
MeO
Me
Me
29
220
200
180
160
140
120
100
80
60
40
20
0
ppm

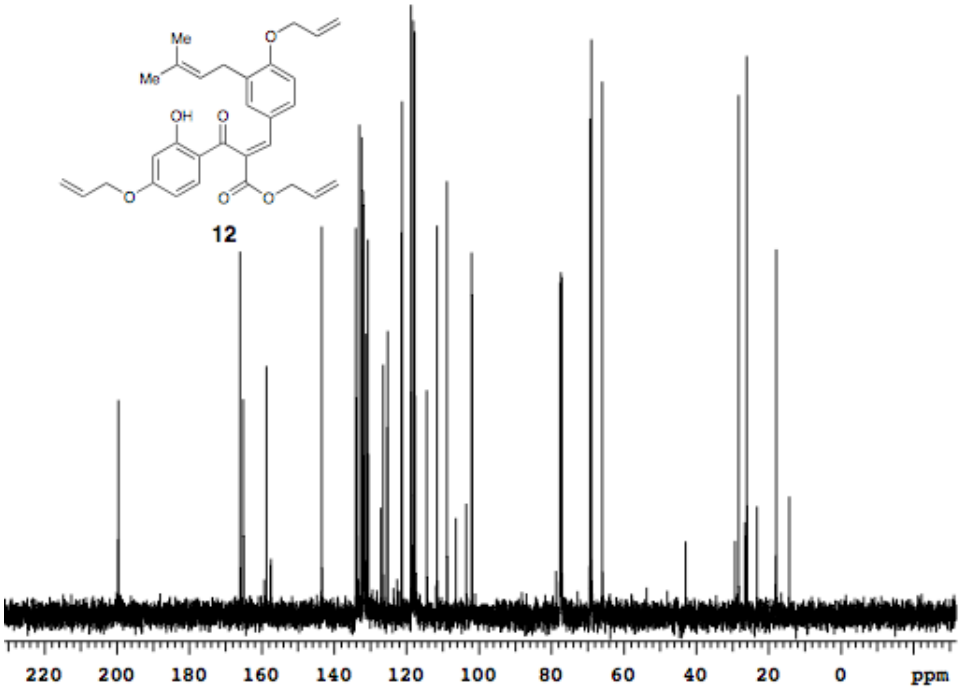

OH
O
O
O
O
31
12
11
10
9
8
7
6
5
4
3
2
1
ppm

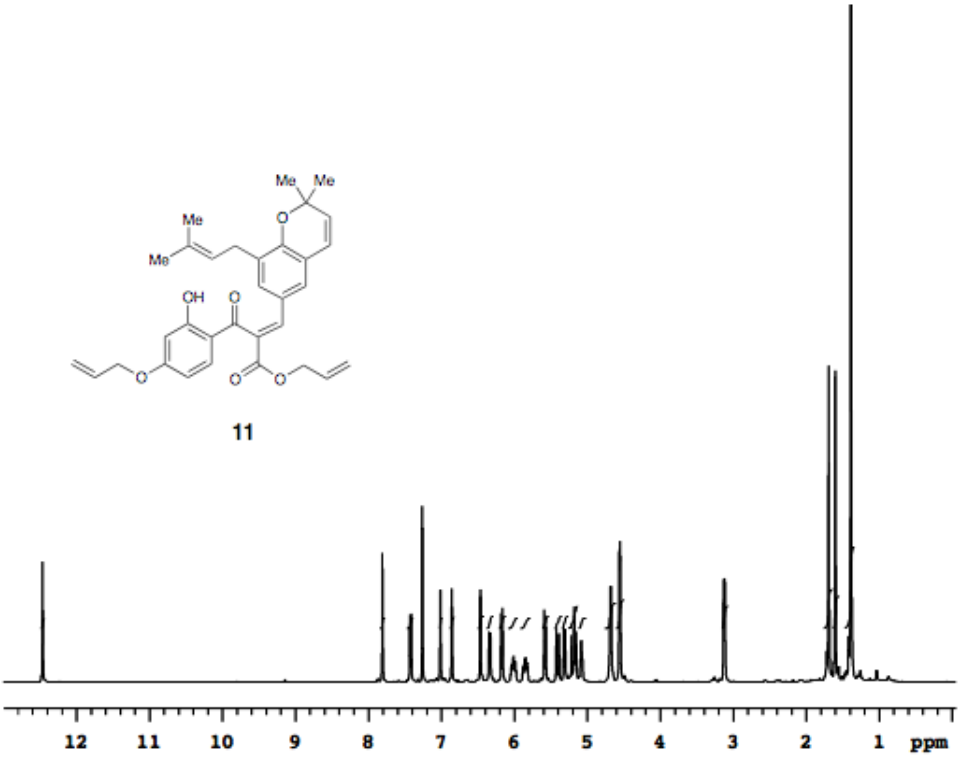

OH
O
O
O
O
31
220
200
180
160
140
120
100
80
60
40
20
0
ppm

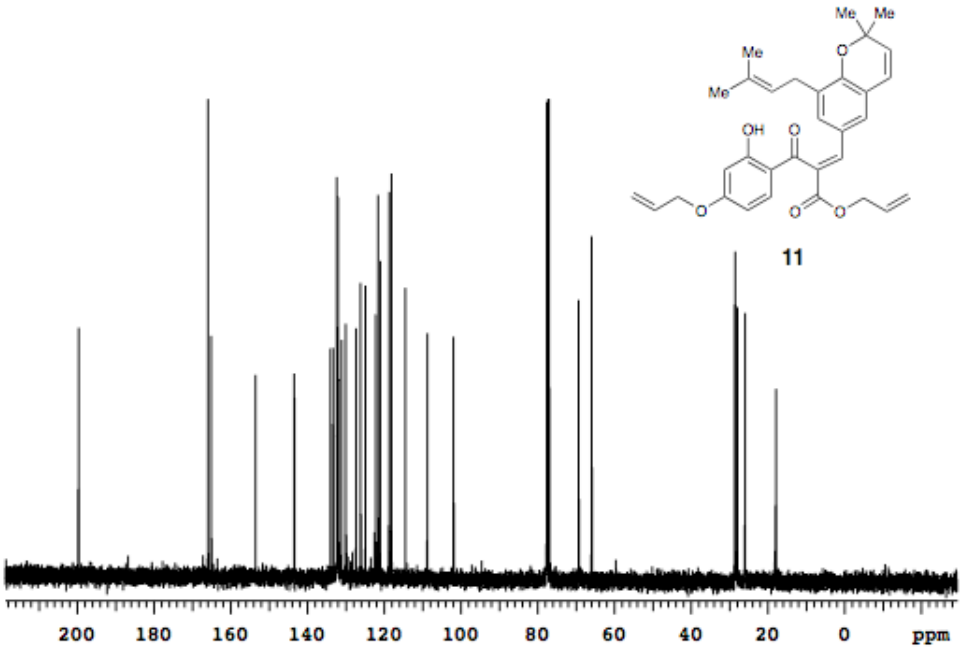

Me
Me
O
OH
O
O
O
O
10
12
11
10
9
8
7
6
5
4
3
2
1
ppm

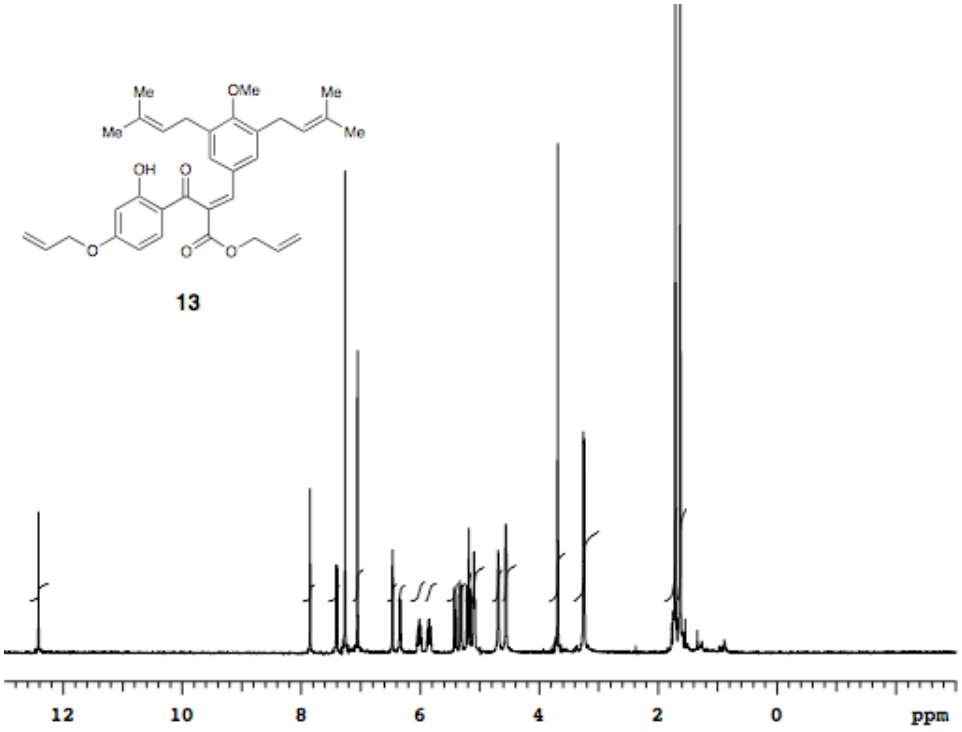

Me
Me
O
OH
O
O
O
O
10
220
200
180
160
140
120
100
80
60
40
20
0
ppm

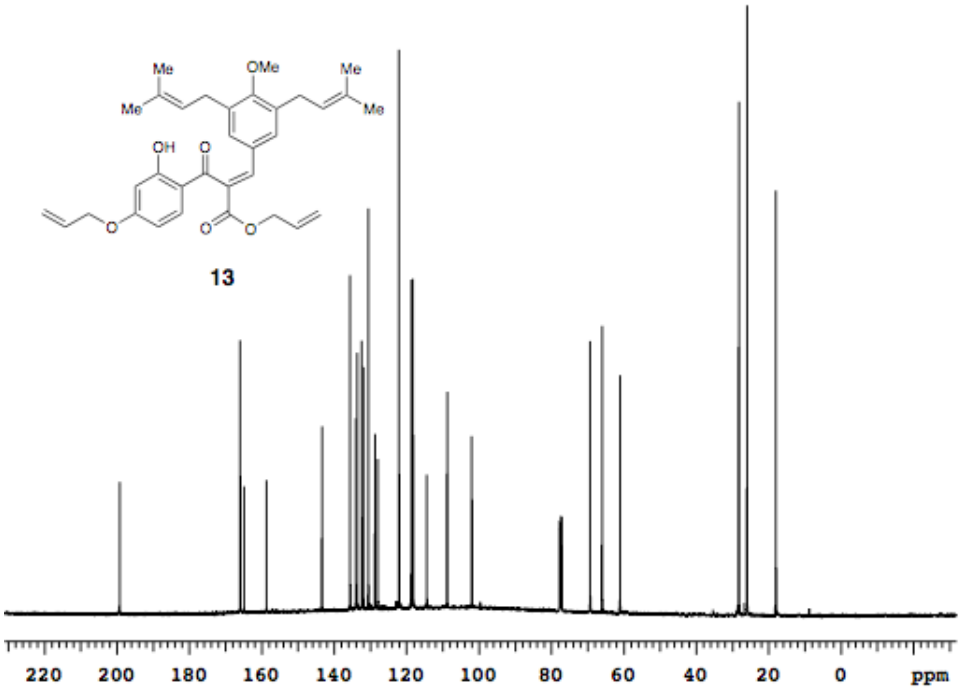

Me
Me
OH
O
O
O
O
O
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

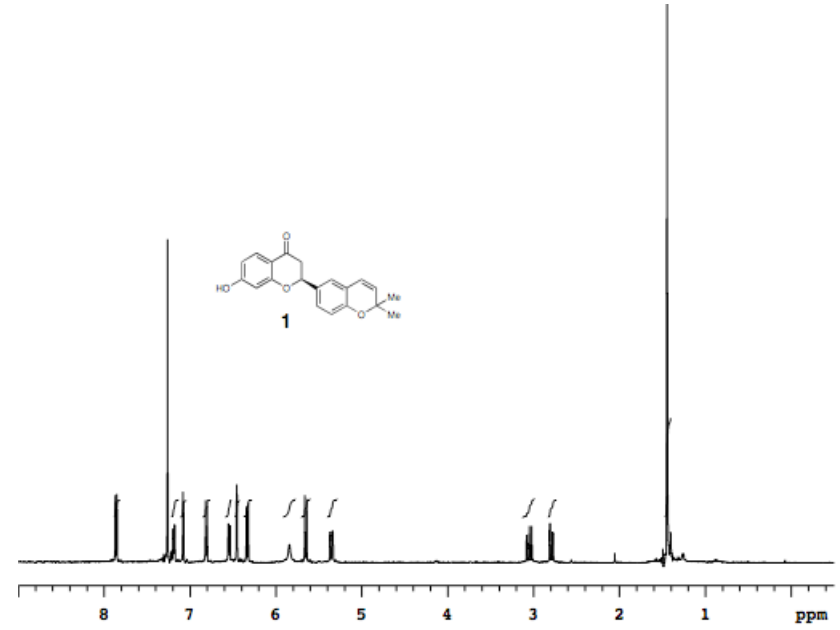

Me
Me
OH
O
O
O
O
O
12
220
200
180
160
140
120
100
80
60
40
20
0
ppm

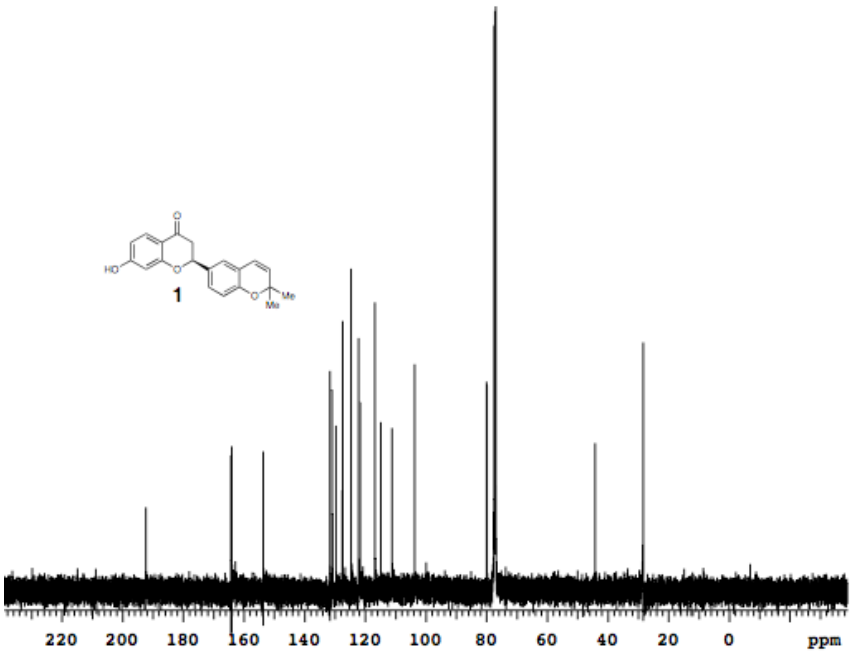

Me
Me
Me
O
Me
OH
O
O
O
O
11
12
11
10
9
8
7
6
5
4
3
2
1
ppm

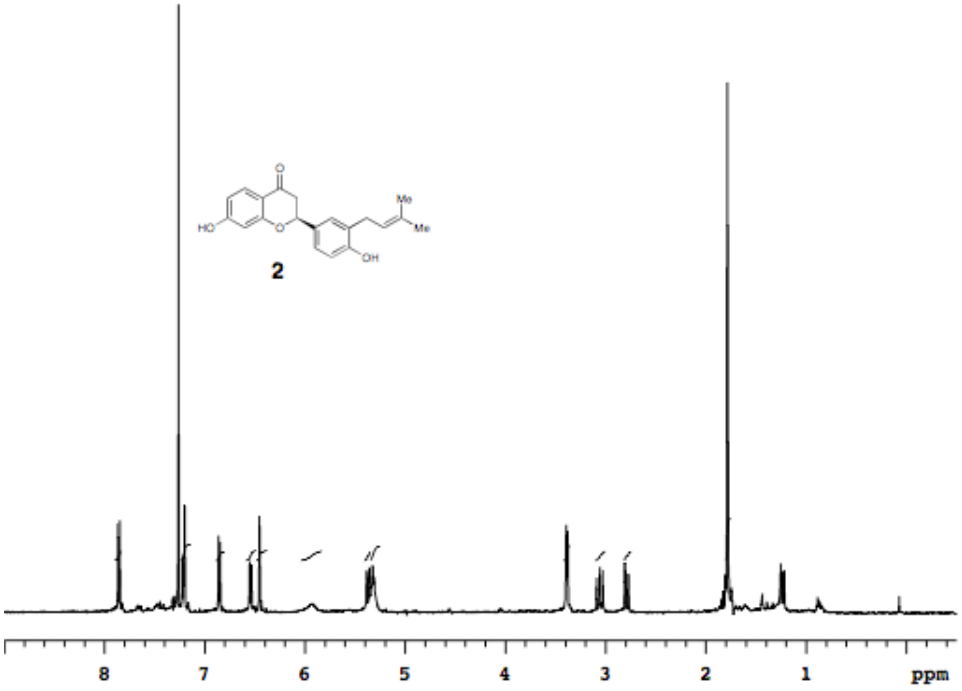

Me
Me
Me
O
Me
OH
O
O
O
O
11
200
180
160
140
120
100
80
60
40
20
0
ppm

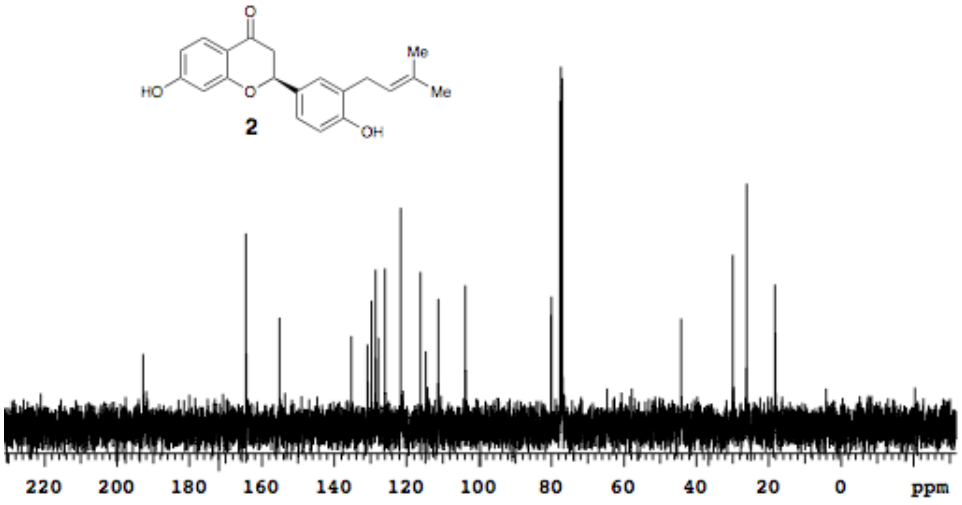

Me
OMe
Me
Me
Me
OH
O
O
O
O
13
12
10
8
6
4
2
0
ppm

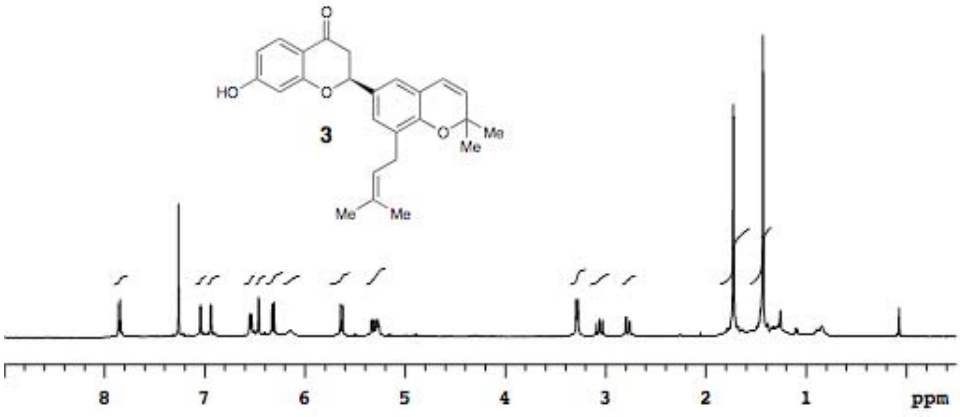

Me
OMe
Me
Me
Me
OH
O
O
O
O
13
220
200
180
160
140
120
100
80
60
40
20
0
ppm

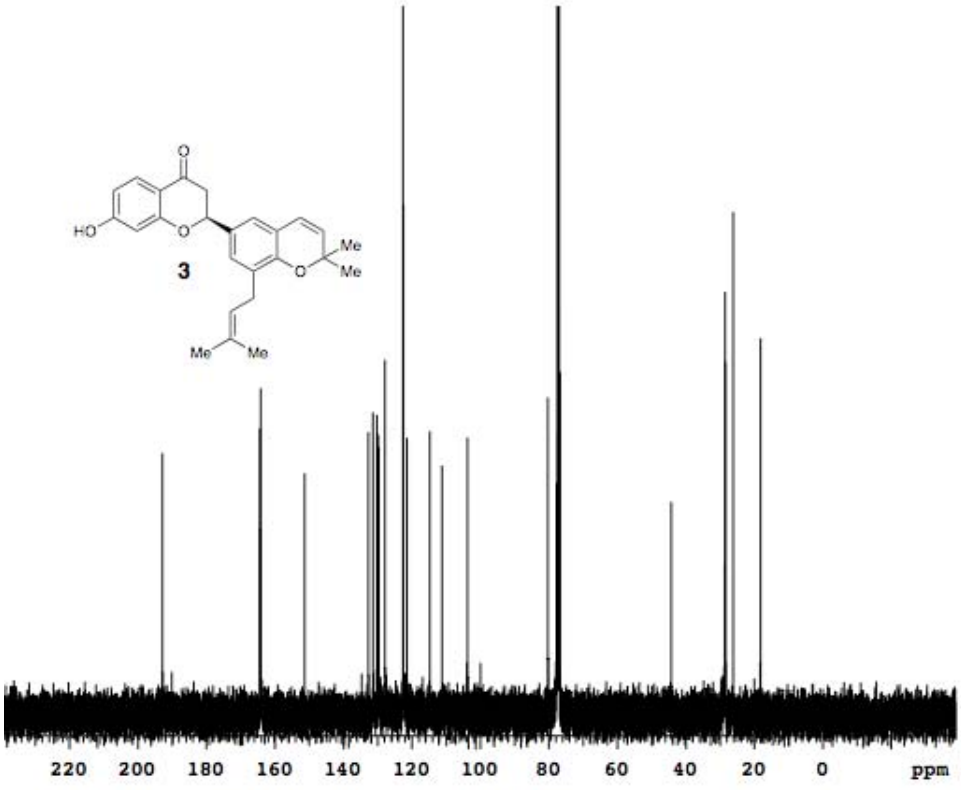

HO
O
O
Me
Me
1
8
7
6
5
4
3
2
1
ppm

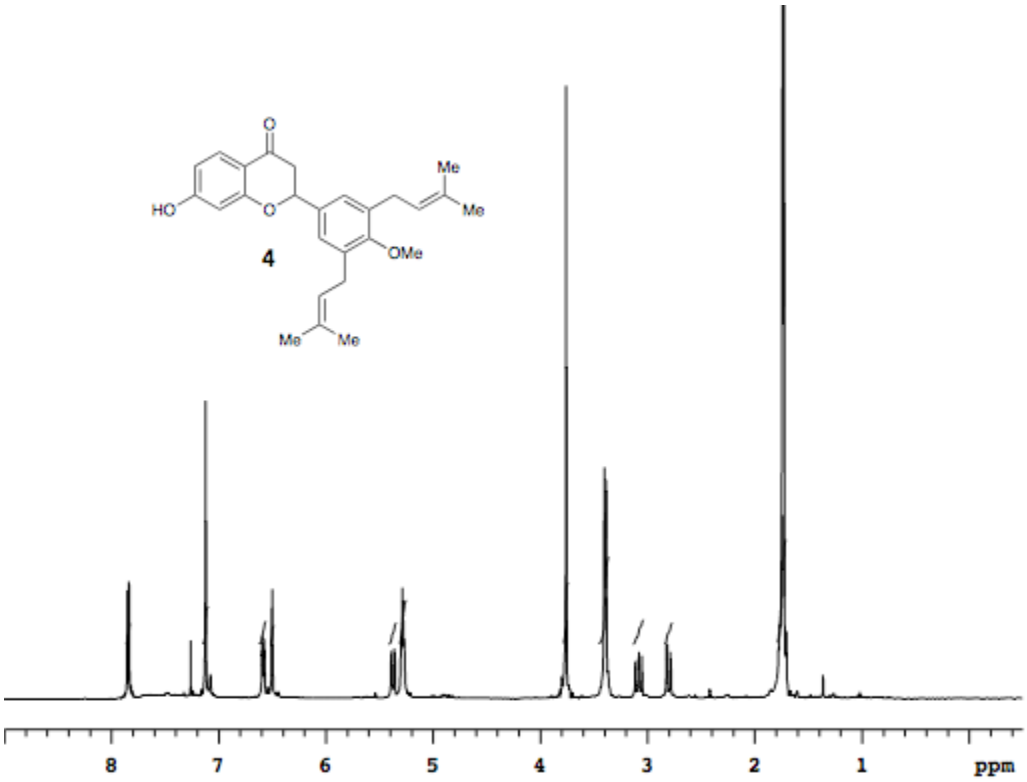

HO
O
O
Me
Me
1
220
200
180
160
140
120
100
80
60
40
20
0
ppm

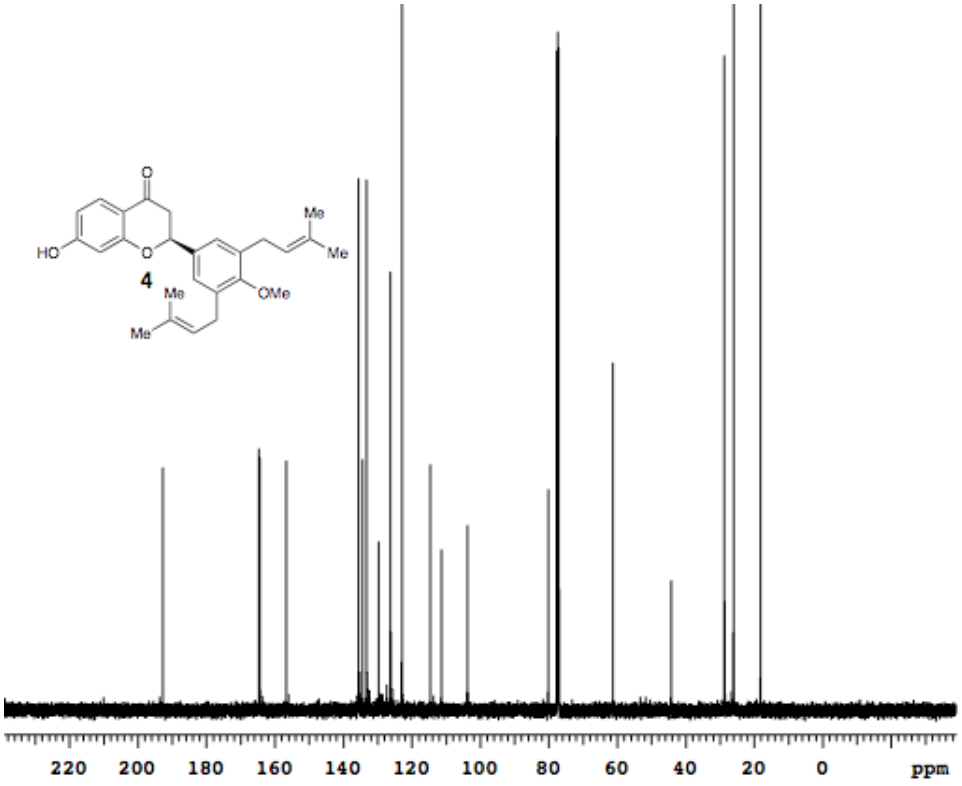

HO
O
O
Me
Me
OH
2
8
7
6
5
4
3
2
1
ppm


HO
O
O
Me
Me
OH
2
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
O
O
O
Me
Me
Me
Me
3
8
7
6
5
4
3
2
1
ppm


HO
O
O
O
Me
Me
Me
Me
3
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HO
O
Me
Me
OMe
4
Me
Me
8
7
6
5
4
3
2
1
ppm


O
HO
O
Me
Me
OMe
4
Me
Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HPLC Traces

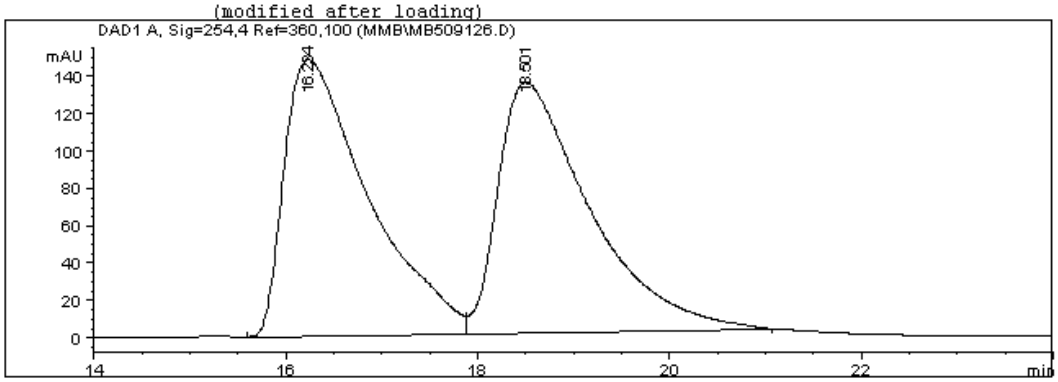
(±)-abyssinone I

HPLC Conditions: 92:8 hexanes:ethanol, 1.0 mL/ min, OD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB509126.D Sample Name: mb5091

abys I rac

```
==================================================================
Injection Date  : 12/28/2007 2:08:04 PM
Sample Name     : mb5091                          Location : Vial 65
Acq. Operator   : mmb
                                                  Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 12/28/2007 2:08:21 PM by mmb
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/7/2008 9:48:10 PM by MMB
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  16.234 PV    0.8904 9004.02539  147.86456  50.1276
   2  18.501 VB    0.9384 8958.17969  134.26581  49.8724

Totals :                  1.79622e4   282.13037

 Results obtained with enhanced integrator!
==================================================================
                        *** End of Report ***
```

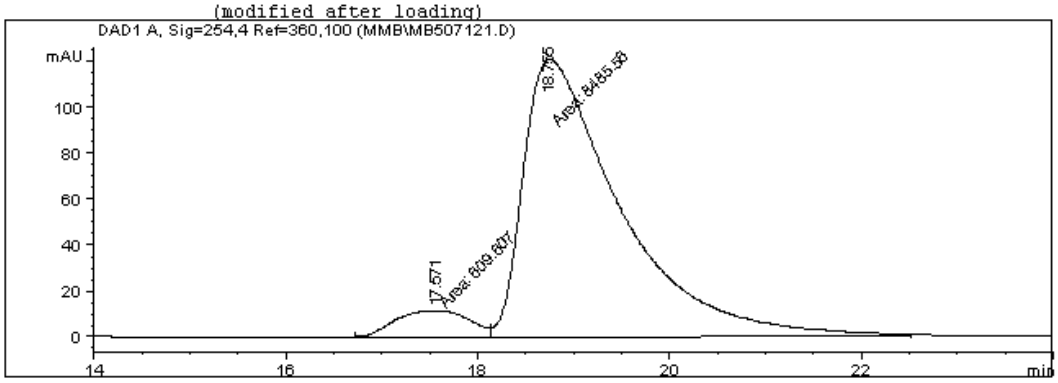
(2*R*)-abyssinone I

HPLC Conditions: 92:8 hexanes:ethanol, 1.0 mL/ min, OD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB507121.D Sample Name: MMB50712

abys I 87% ee?

```
======================================================================
Injection Date  : 1/7/2008 9:15:45 PM
Sample Name     : MMB50712                      Location : Vial 72
Acq. Operator   : MMB
                                               Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/7/2008 9:04:27 PM by MMB
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/7/2008 9:48:10 PM by MMB
                  (modified after loading)
```



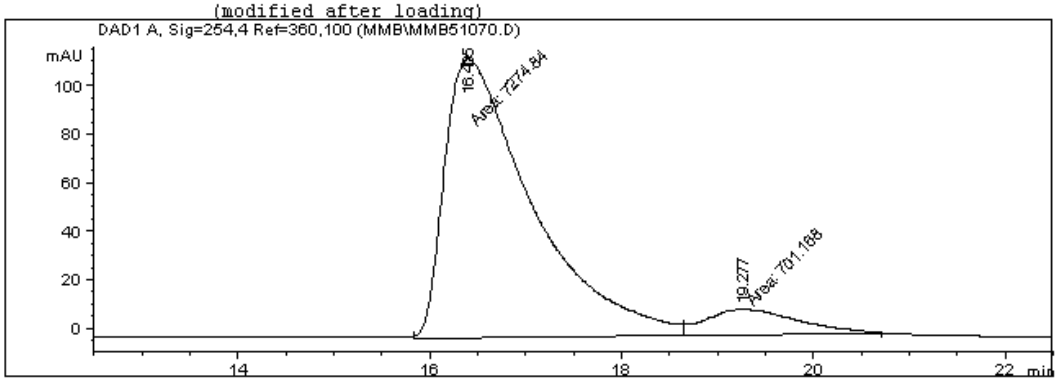

```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  17.571 MM    0.9169  609.60693   11.08076   6.7025
   2  18.755 MM    1.1738 8485.56152  120.48803  93.2975

Totals :                  9095.16846  131.56879

 Results obtained with enhanced integrator!
======================================================================
                        *** End of Report ***
```

(2*S*)-abyssinone I

HPLC Conditions: 92:8 hexanes:ethanol, 1.0 mL/ min, OD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MMB51070.D Sample Name: MMB5107

```
==================================================================
Injection Date  : 1/6/2008 4:10:02 PM
Sample Name     : MMB5107                        Location : Vial 61
Acq. Operator   : MMB
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/6/2008 4:02:34 PM by MMB
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 9:05:03 AM by MMB
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  16.405 MF    1.0578 7274.83740  114.62341  91.2090
   2  19.277 FM    1.1061  701.16803   10.56501   8.7910

Totals :                  7976.00543  125.18842

 Results obtained with enhanced integrator!
==================================================================
                        *** End of Report ***
```

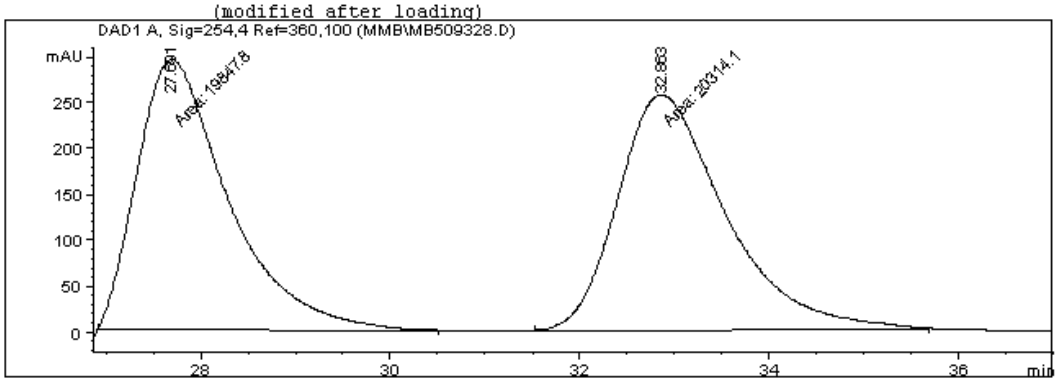
(±)-abyssinone II

HPLC Conditions: 93:6:1 hexanes:isopropanol:ethanol, 1.0 mL/ min, AD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB509328.D Sample Name: racabysII

abys IIrac?

```
======================================================================
Injection Date  : 12/21/2007 2:26:09 PM
Sample Name     : racabysII                      Location : Vial 64
Acq. Operator   : mmb
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 12/21/2007 2:26:28 PM by mmb
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 9:20:46 AM by MMB
                  (modified after loading)
```




```
======================================================================
                          Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.691 MM    1.1225 1.98478e4   294.69852  49.4194
   2  32.863 MM    1.3201 2.03141e4   256.47778  50.5806

Totals :                  4.01619e4   551.17630

 Results obtained with enhanced integrator!
======================================================================
                          *** End of Report ***
```

(2*R*)-abyssinone II

HPLC Conditions: 93:6:1 hexanes:isopropanol:ethanol, 1.0 mL/ min, AD-H Chiralcel column

```
Data File C:\HPCHEM\2\DATA\MMB\MB510201.D                          Sample Name: mb5102

    abys II hiemstra

    ======================================================================
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    Sample Name     : mb5102                          Location : Vial 63
    Acq. Operator   : mmb
                                                     Inj Volume : 5 µl
    Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
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                      (modified after loading)
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    Last changed    : 1/8/2008 9:20:46 AM by MMB
                      (modified after loading)
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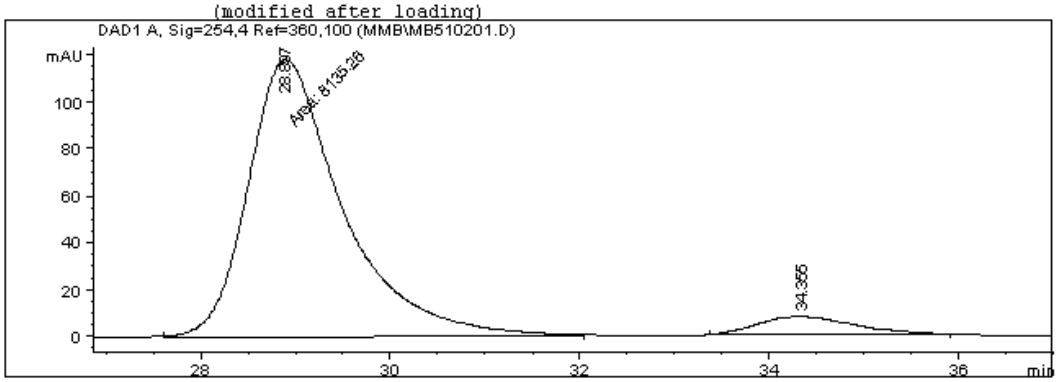


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                              Area Percent Report
    ======================================================================

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    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  28.897 MM    1.1508 8135.26367  117.81593  93.7956
       2  34.355 BB    0.8272  538.12860    7.72010   6.2044

    Totals :                   8673.39227  125.53603

     Results obtained with enhanced integrator!
    ======================================================================
                              *** End of Report ***
```

(2*S*)-abyssinone II

HPLC Conditions: 93:6:1 hexanes:isopropanol:ethanol, 1.0 mL/ min, AD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB509000.D Sample Name: mb5090

abys II

```
==========================================================================
Injection Date  : 12/22/2007 11:29:18 AM
Sample Name     : mb5090                          Location : Vial 61
Acq. Operator   : mmb
                                                  Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 12/22/2007 11:04:42 AM by mmb
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 9:37:19 AM by MMB
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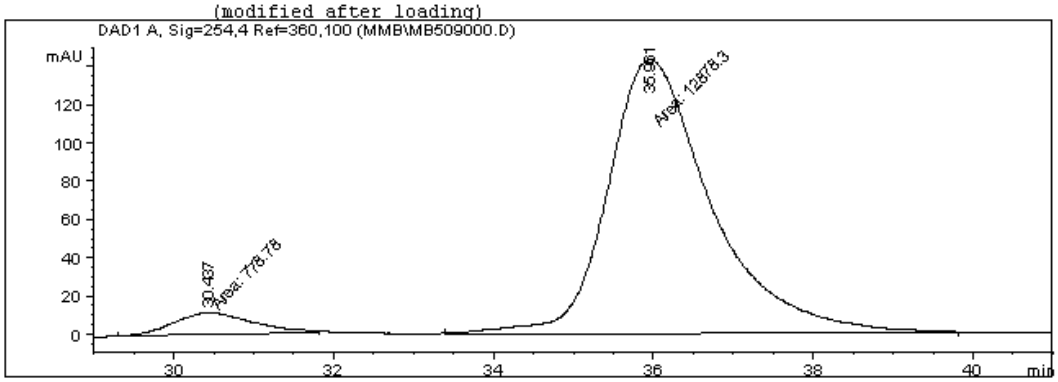



```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.437 MM    1.1602  778.78033   11.18791   5.7024
   2  35.961 MM    1.5009 1.28783e4   143.00276  94.2976

Totals :                  1.36570e4   154.19067

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

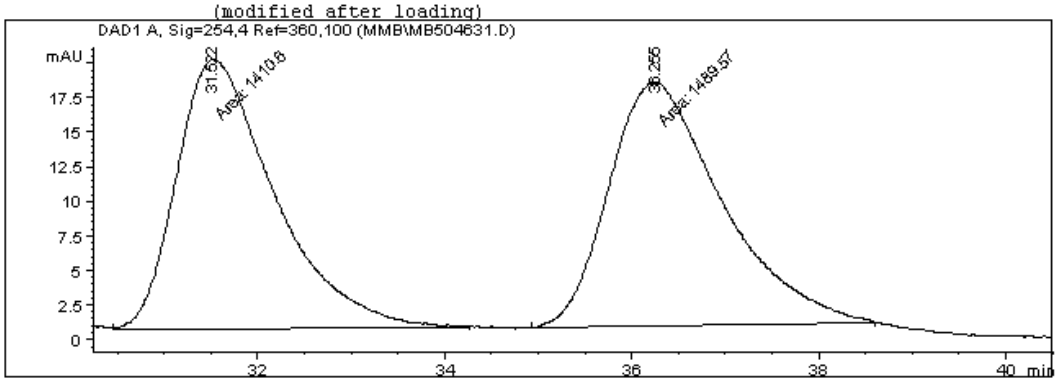
(±)-abyssinone III

HPLC Conditions: 97:3 hexanes:isopropanol, 1.0 mL/ min, AD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB504631.D Sample Name: MMB50463

abys III rac

```
==========================================================================
Injection Date  : 1/8/2008 4:42:58 PM
Sample Name     : MMB50463                        Location : Vial 72
Acq. Operator   : MMB
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 4:43:09 PM by MMB
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 7:42:27 PM by MMB
                  (modified after loading)
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.522 MM    1.2094 1410.60181   19.43979  48.6386
   2  36.255 MM    1.4093 1489.56738   17.61609  51.3614

Totals :                  2900.16919   37.05587

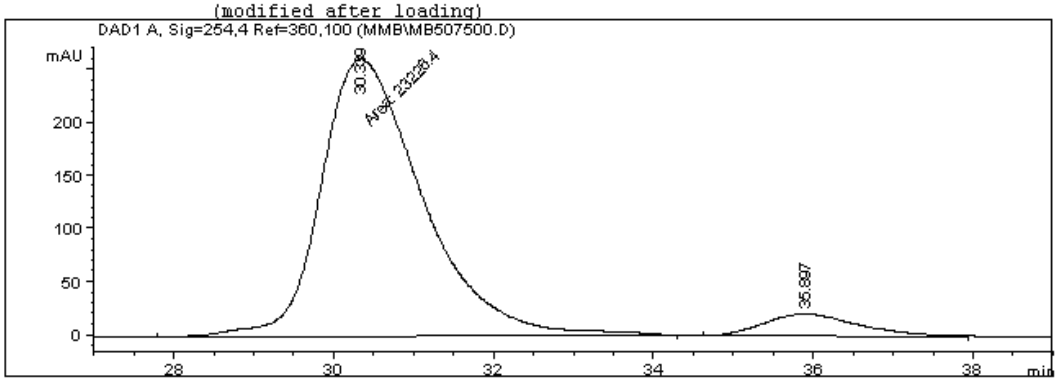
 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

(2*R*)-abyssinone III

HPLC Conditions: 97:3 hexanes:isopropanol, 1.0 mL/ min, AD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB507500.D Sample Name: MB5075

```
==================================================================
Injection Date  : 12/4/2007 12:56:57 PM
Sample Name     : MB5075                          Location : Vial 62
Acq. Operator   : mmb
                                                  Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 12/4/2007 12:54:24 PM by mmb
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 9:45:23 AM by MMB
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.339 MM    1.4817 2.32264e4   261.25299  93.2307
   2  35.897 BB    0.9879 1686.42224   20.62572   6.7693

Totals :                  2.49128e4   281.87871

 Results obtained with enhanced integrator!
==================================================================
                        *** End of Report ***
```

(2*S*)-abyssinone III

HPLC Conditions: 97:3 hexanes:isopropanol, 1.0 mL/ min, AD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB508800.D Sample Name: mmb5088

```
==================================================================
Injection Date  : 12/15/2007 4:46:03 PM
Sample Name     : mmb5088                        Location : Vial 62
Acq. Operator   : mmb
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 12/15/2007 4:43:47 PM by mmb
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 9:56:09 AM by MMB
                  (modified after loading)
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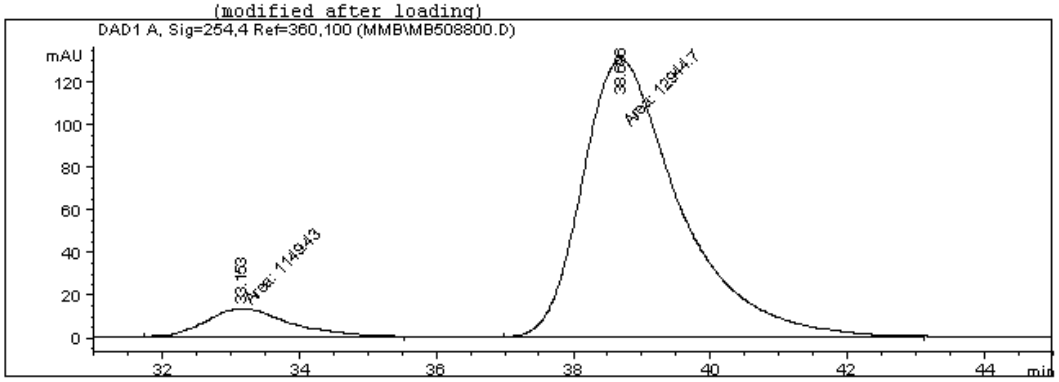



```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  33.153 MM    1.4325 1149.43408   13.37342   8.1554
   2  38.696 MM    1.6549 1.29447e4   130.36363  91.8446

Totals :                  1.4094le4   143.73705

 Results obtained with enhanced integrator!
==================================================================
                          *** End of Report ***
```

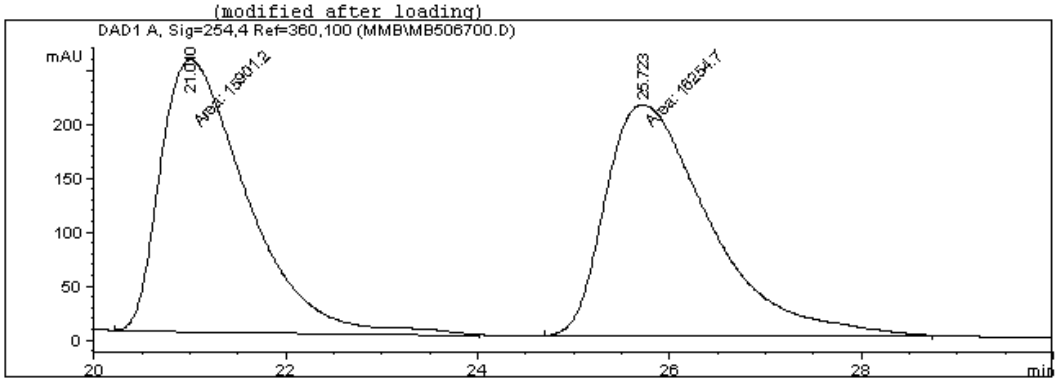
(±)-abyssinone IV 4´-OMe

HPLC Conditions: 95:5 hexanes:isopropanol, 1.0 mL/ min, OD-H Chiralcel column

Data File C:\HPCHEM\2\DATA\MMB\MB506700.D Sample Name: mmb5067

abys IV rac

```
==================================================================
Injection Date  : 1/5/2008 10:20:00 AM
Sample Name     : mmb5067                      Location : Vial 66
Acq. Operator   : mmb
                                              Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/5/2008 10:20:04 AM by mmb
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
Last changed    : 1/8/2008 10:02:25 AM by MMB
                  (modified after loading)
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.010 MM    1.0498 1.59012e4   252.44279  49.4504
   2  25.723 MM    1.2649 1.62547e4   214.17883  50.5496

Totals :                  3.21559e4   466.62163

 Results obtained with enhanced integrator!
==================================================================
                        *** End of Report ***
```

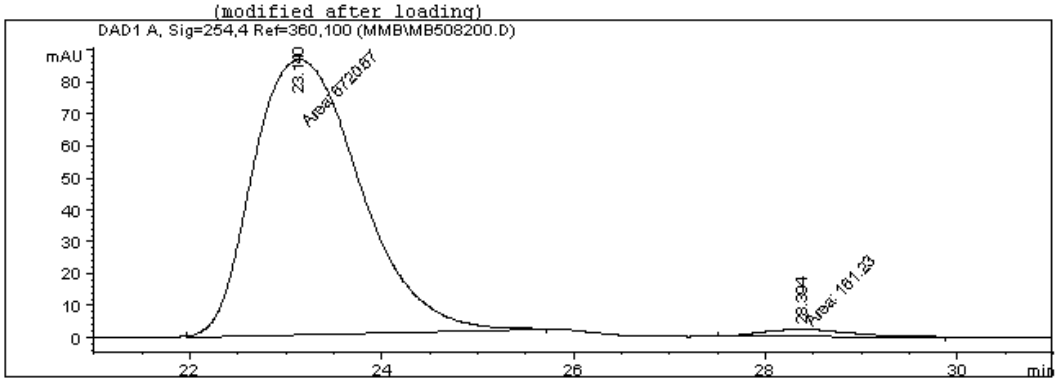
(2*R*)-abyssinone IV 4′-OMe

HPLC Conditions: 95:5 hexanes:isopropanol, 1.0 mL/ min, OD-H Chiralcel column

```
Data File C:\HPCHEM\2\DATA\MMB\MB508200.D                    Sample Name: mb5082

    absyIV0Me

    ======================================================================
    Injection Date  : 12/10/2007 12:00:01 PM
    Sample Name     : mb5082                        Location : Vial 61
    Acq. Operator   : mmb
                                                  Inj Volume : 5 µl
    Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
    Last changed    : 12/10/2007 11:41:29 AM by mmb
                      (modified after loading)
    Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
    Last changed    : 1/8/2008 10:09:03 AM by MMB
                      (modified after loading)
```




```
    ======================================================================
                               Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  23.140 MM    1.3003 6720.66992   86.14075  97.6572
       2  28.394 MM    1.1995  161.23021    2.24027   2.3428

    Totals :                  6881.90013   88.38102

     Results obtained with enhanced integrator!
    ======================================================================
                               *** End of Report ***
```

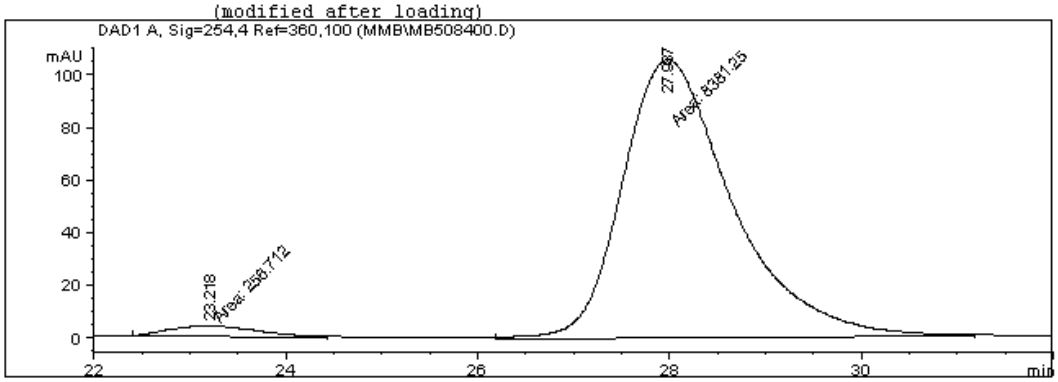
(2*S*)-abyssinone IV 4´-OMe

HPLC Conditions: 95:5 hexanes:isopropanol, 1.0 mL/ min, OD-H Chiralcel column

```
Data File C:\HPCHEM\2\DATA\MMB\MB508400.D                              Sample Name: mb5084

     epi abysIVOMe

    ======================================================================
    Injection Date  : 12/10/2007 1:13:06 PM
    Sample Name     : mb5084                          Location : Vial 63
    Acq. Operator   : mmb
                                                    Inj Volume : 5 µl
    Acq. Method     : C:\HPCHEM\2\METHODS\MMB LC.M
    Last changed    : 12/10/2007 1:14:41 PM by mmb
                      (modified after loading)
    Analysis Method : C:\HPCHEM\2\METHODS\MMB LC.M
    Last changed    : 1/8/2008 10:20:41 AM by MMB
                      (modified after loading)
```




```
    ======================================================================
                               Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  23.218 MM    1.0790  256.71222    3.96525   2.9719
       2  27.987 MM    1.3225 8381.24902  105.62001  97.0281

    Totals :                  8637.96124  109.58526

     Results obtained with enhanced integrator!
    ======================================================================
                               *** End of Report ***
```

General Biological Assay Procedures and Additional Data

Cell culture. PC3-M prostate carcinoma cells were obtained from L. Whitesell (National Cancer Institute, Bethesda, MD) and are a metastatic variant of PC3 cells as described by Kozlowski *et al.*[12] PC3-M cells were grown in Roswell Park Memorial Institute 1640 media (GIBCO/BRL, Gaithersburg, MD) supplemented with 10% FBS (Whittaker, Walkersville, MD), as previously described.[13] Cells were maintained at 37 °C in a humidified atmosphere of 5% carbon dioxide, with media changes occurring three times per week. Cells were also maintained in the exponential growth phase, and routinely certified as mycoplasma free.

MTT (dimethylthiazol-diphenyltetrazolium bromide) growth inhibition assays. Three-day growth inhibition assays were performed in Falcon TC microtiter plates (Becton Dickinson, San Jose, CA) as previously described.[14] First, 800 PC3-M cells per 100 μL of cell culture media were plated into each well and were incubated for 24 hours. The synthetic abyssinones, as well as genistein (LC Laboratories, Woburn, MA; positive control), were suspended in culture media and added to the wells to give a final volume of 200 μL per well. Genistein and all of the synthetic abyssinones were suspended in DMSO (Sigma Chemical, St. Louis, MO) and stored at -20 °C prior to use. The final DMSO concentration did not exceed 0.5% in any experiment. The treated cells were then incubated for an additional 3 days, at which time MTT (dimethylthiazol-diphenyltetrazolium bromide) was added to each well (20 μL of a stock solution containing 5 mg/mL MTT in PBS) and the cells were incubated at 37 °C. Four hours later, the cells were lysed by addition of 200 μL of DMSO to each well, and the optical density at 540 nm was measured on a Bio Tek microplate reader (model EL312E; Bio Tek Instruments, Winooski, VT). Assays were performed in triplicate (N=3) and repeated (N=9), and the average CC_{50} results were used for analysis. For Figure 3A, results are reported as an average CC_{50} value ± SE. A ** indicates a 2-sided t-test p value <0.05. NS indicates a 2-sided t-test p value >0.05.

For t=0 measurements, 800 PC3-M cells per 100 μL of cell culture media were plated into a Falcon TC 96-well plate at the same time as the cells for the three-day assays, as described above. These cells were then allowed to incubate for 20 hours. MTT (20 μL of a stock solution containing 5 mg/mL MTT in PBS) was then added to each well, four hours prior to the addition of the synthetic abyssinones to the remaining plates. After four hours of incubation at 37 °C, these plates were then developed as described and the optical density at 540 nm was measured. The average absorbance value for these untreated cells was then taken to be the t=0 measurement. Preliminary assignments of a cytostatic/cytotoxic mechanism for each compound were made by comparing the absorbance levels at 50 μM (highest dose level) for each abyssinone with the absorbance levels of the untreated controls at t=0. If the three-day absorbance level for the treatment condition was less than or approximately equal to that of the untreated t=0 measurement,

12. Kozlowski, J. M.; Isaiah, J. F.; Campbell, D.; Xu, Z. L.; Kaighn, M. E.; Hart, I. R. *Cancer Res.* **1984**, *44*, 3522-3529.
13. Craft, C. S.; Romero, D.; Vary, C. P. H.; Bergan, R. *Oncogene* **2007**, *26*, 7240-7250.
14. Kyle, E.; Neckers, L.; Takimoto, C.; Curt, G.; Bergan, R. *Mol. Pharmacol.* **1997**, *51*, 197-200.

this was suggestive of a cytotoxic mechanism. Conversely, if the three-day treatment absorbance level was higher than that of the untreated t=0 measurement, then the compound in question was designated as having a cytostatic or combination mechanism. Assays were performed in triplicate (N=3) and repeated (N=4) and average absorbance values were used for analysis. For Figure 3B, values are reported as the average absorbance value ± SE.

Figure S1. Absorbance values for MTT measurements of treated cells (t=72 h) and untreated cells (t=0 and 72 h). (*S*)-Abyssinones III and IV 4′-OMe appear to act through a cytotoxic mechanism, as the absorbance values for these compounds at 72 h is lower than that of the untreated controls at 0 h. All other compounds, including (*R*)-abyssinones III and IV 4′-OMe, appear to act through a cytostatic or combination mechanism to inhibit cell proliferation.

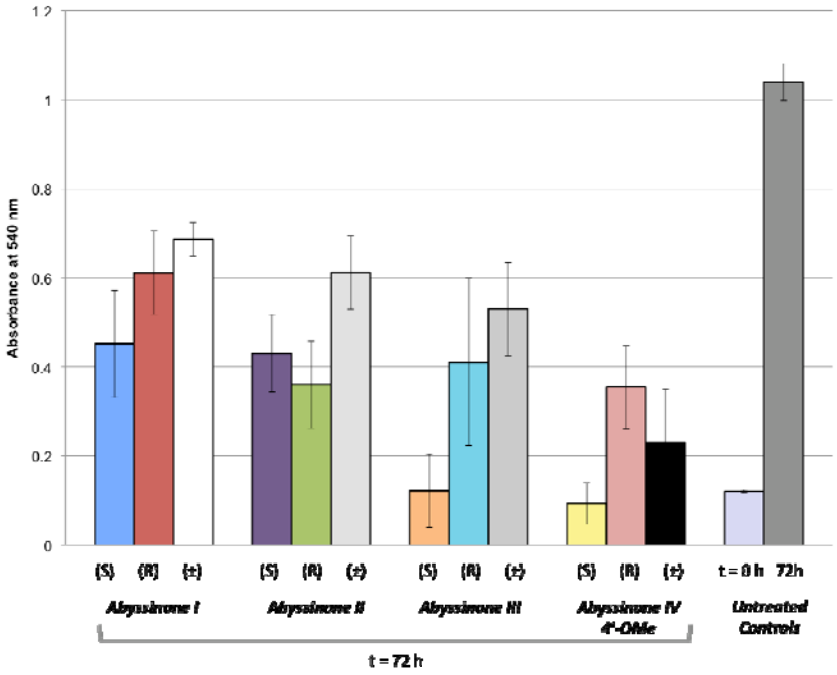


Figure S2. Images of untreated and treated cells at t=0 and t=72 h. (*S*)-Abyssinones III and IV 4′-OMe show significant cytotoxicity when compared to the untreated cells, corroborating the findings in Figure S1.

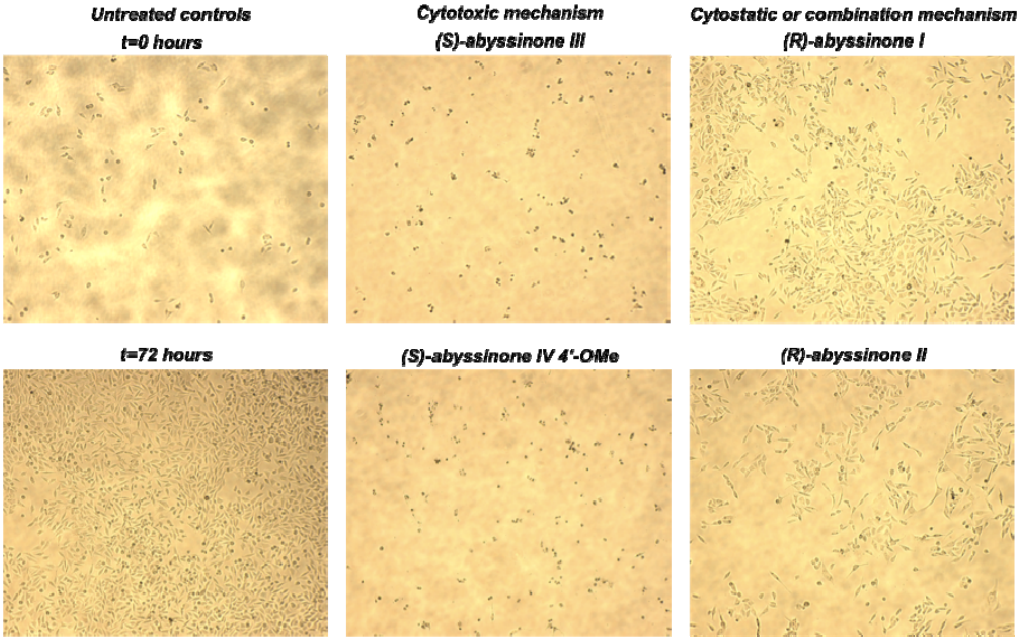
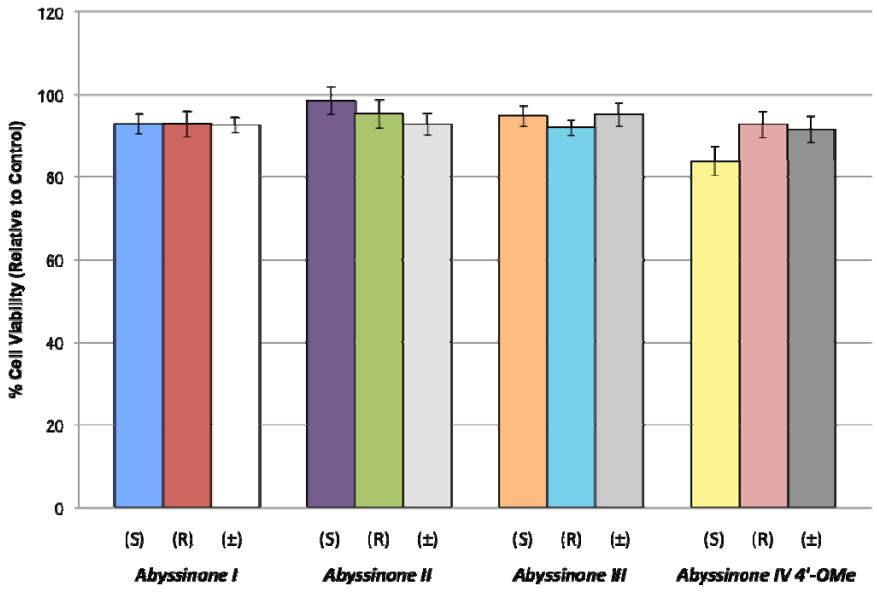


Figure S3. MTT growth inhibition data for treatment with abyssinones at 3 µM. Values are reported as a percentage (mean ± SD) of the untreated control.



Isolation of RNA. Total cellular RNA was isolated from whole cells using the RNeasy Kit (QIAGEN Incorporated, Valencia, CA) per manufacturer's instructions, as described.[15] The quality and quantity of RNA were evaluated by measuring OD 260/280.

Quantitative real-time reverse transcription PCR (qRT-PCR) for MMP-2 expression. Quantitative real-time reverse transcription and quantitative polymerase chain reaction were performed as previously described.[16] To generate the cDNA needed for PCR amplification, 1 μg of RNA was reverse transcribed with TaqMan reverse transcriptase (Applied Biosystems, Foster City, CA) using random hexamers. PCR reactions were then performed with cDNA from the equivalent of 60 ng of RNA in a reaction volume of 20 μL. Reactions were run in replicates of two using a TaqMan Universal PCR kit (Applied Biosystems), with exon-spanning gene-specific sets of two primers and one probe for GAPDH and MMP-2 (assay catalog #s: Hs99999905_m1 and Hs00234422_m1, respectively), and an Applied Biosystems 7500 Real Time Quantitative PCR System workstation. All reactions were repeated in a similar fashion at a separate time, also in replicates of two. For analysis of gene expression, the threshold cycle (Ct) for individual reactions was identified using the Applied Biosystems 7500 Real Time PCR System software. Relative gene expression was calculated using GAPDH for normalization purposes according to the $2^{-\Delta\Delta Ct}$ method. Assays were performed in duplicate (N=2) and repeated (N=3), and the average results were used for analysis. For Figure 4, results are reported as a percentage (mean ± SD) of the untreated control. A * denotes a two-sided t-test p value <0.05, for a comparison between each abyssinone and the untreated control. A ** denotes a one-sided t-test p value <0.05, for a comparison between enantiomers.

15. Craft, C. S.; Xu, L.; Romero, D.; Vary, C. P. H.; Bergan, R. C. *Mol. Pharmacol.* **2008**, *73*, 235-242.
16. Ding, Y.; Xu, L.; Chen, S.; Jovanovic, B. D.; Helenowski, I. B.; Kelly, D. L.; Catalona, W. J.; Yang, X. J.; Pins, M.; Ananthanarayanan, V.; Bergan, R. C. *Prostate Cancer Prostatic Dis.* **2006**, *9*, 379-391,