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Convergent Access to Polycyclic Cyclopentanoids from α,β-Unsaturated Acid Chlorides and Alkynes through a Reductive Coupling, Nazarov Cyclization Sequence

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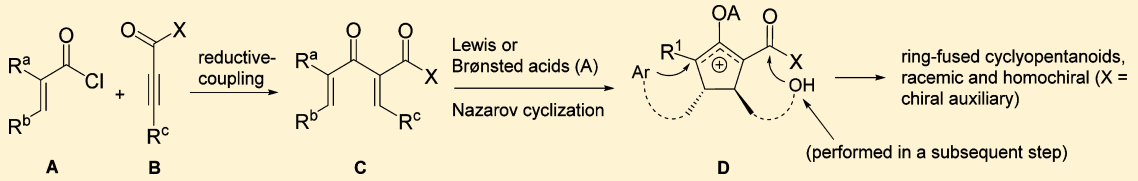
Supporting Information

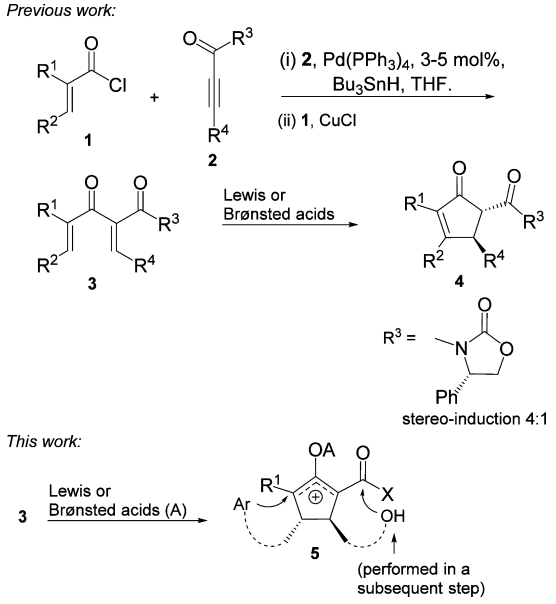


ABSTRACT: Reductive coupling of α,β-unsaturated acid chlorides **A** with alkynoyls **B** provides convergent access to Nazarov cyclization precursors, α-carboxy divinyl ketones **C**. Cyclization of **C** gives an intermediate oxyallyl cation intermediate **D**, which can be trapped with tethered arenes (Ar). The resultant products can be further cyclized through nucleophilic displacement of suitable leaving groups X by tethered OH groups to give lactones (in a subsequent step). Where X is a suitable chiral auxiliary (e.g., oxazolidinone) this strategy affords access to homochiral cyclopentanoids.

In recent years the Nazarov cyclization of divinyl ketones to cyclopentenones has received considerable attention, with significant improvements in methods for achieving enantioselectivity (torquoselectivity) and for trapping reactive intermediates in multistereocenter forming reactions.[1−3] In order to effectively exploit this synthetic versatility, concise and convergent methods for the stereoselective synthesis of divinyl ketones are also required. To this end, we recently described a one-pot, two-stage reductive coupling process composed of a regio- and stereoselective hydrostannylation of alkynoyls **2** followed by Stille-type coupling with α,β-unsaturated acid chlorides **1** to give α-carboxydivinyl ketones **3**, which undergo Nazarov cyclizations to 5-carboxycyclopentenones **4**.[3h] The presence of the α-carbonyl ($R^3C{=}O$) in **3** promotes the regioselective placement of the double bond to the distal side of the cyclopentyl ring in **4**. This carboxy unit can also be used as a linker for labile chiral auxiliaries (R^3 = chiral auxiliaries). Oxazolidinone auxiliaries induce moderate to good levels of stereoinduction upon cyclization **3** → **4** (R^3 = *N*-oxazolidinyl) and enable further enhancement of enantiopurity through ready chromatographic separation of the two diastereomers prior to auxiliary cleavage.[3h] Herein, we describe some useful extensions of this reductive coupling/Nazarov cyclization protocol in the convergent synthesis of ring-fused cyclopentyl systems through trapping of the oxyallyl cation intermediate **5** with tethered electron rich arenes and by nucleophilic displacement of suitable leaving groups X (including X = *N*-oxazolidinyl) with hydroxyl groups (Scheme 1).

We initiated our studies in the racemic series, targeting a dual arene trapping/lactonization process to generate **14** as an example of this convergent approach to multistereocenter-containing polycycles (Scheme 2). Synthesis of **14** commenced with methyl bromotiglate **6**,[4] which was converted to acid

Scheme 1. Reductive Coupling Nazarov Cyclization Sequence



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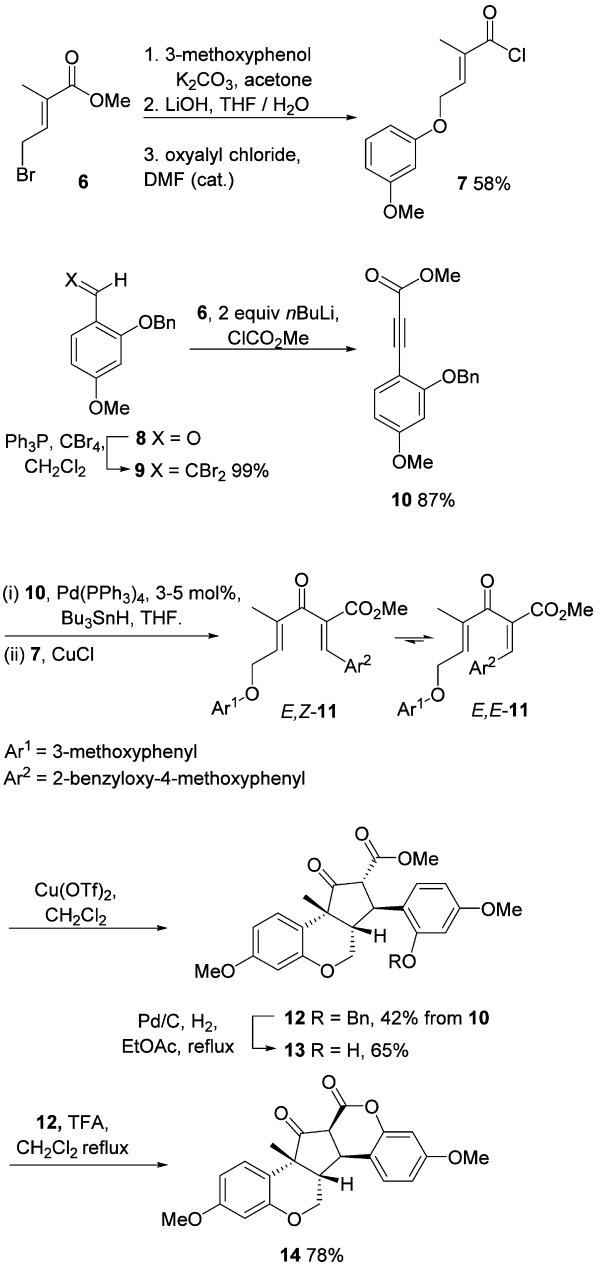
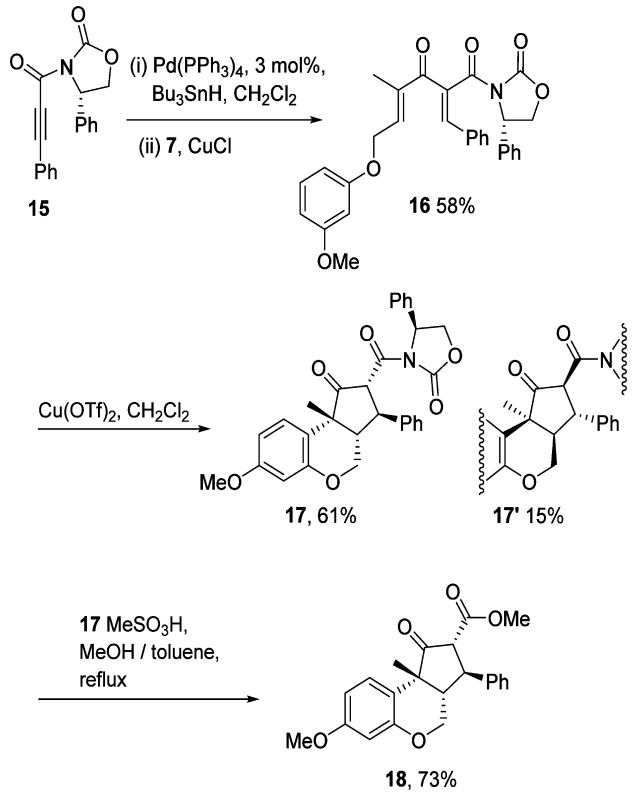
Scheme 2. Synthesis of Polycycle 14



chloride **7** in three steps.[2i] This involved substitution of the bromo group in **6** for 3-methoxyphenol, followed by ester hydrolysis and conversion of the resultant acid to the acid chloride **7** (58% yield from **6**).[2i] Preparation of the propynoyl ester **9** commenced from benzyl protected isovanilin **8**[5] (Scheme 2). Conversion of **8** into the *gem*-dibromostyrene **9** was followed generation of a lithium acetylide (Corey–Fuchs) and addition of methyl chloroformate to give **10** (87%). Reductive coupling of **7** and **10** afforded **11** as a single stereoisomer *E,Z*-**11**, which isomerized completely to the thermodynamic isomer *E,E*-**11** upon chromatography. This material could only be isolated in a semipure form (contained tin byproducts) and was subjected directly to Nazarov cyclization using cupric triflate in dichloromethane to give the cocyclized product **12** (42% overall yield from **10**). Only a single diastereomer of **12** was observed, which was assigned relative stereochemistry depicted (racemic).[6] This stereochemical outcome was rationalized as arriving from conrotation of the Lewis acid activated complex of *E,Z*-**11**. In the presence of the Lewis acid (cupric triflate) the *E,Z*-**11** and *E,E*-**11** isomers are expected to be rapidly interconvertible with cyclization from *E,Z*-**11** complex providing the lowest energy (least congested) transition state.[2y,z] The benzyl ether in **12** was removed by hydrogenolysis to give phenol **13** (63%), which underwent lactonization upon treatment with TFA to provide the *cis*-fused lactone **14** (78%).

We also examined the use of oxazolidinones in enantioselective syntheses of a related ring-fused cyclopentanone **18** (Scheme 3). Thus, *N*-(alkynoyl)oxazolidinone **15**[3h] was

Scheme 3. Asymmetric Synthesis of Polycycle 18



coupled (reductive coupling) to acid chloride **7**, to give divinyl ketone **16** (58%). Unlike the corresponding ester and amides, oxazolidone substituted α-carboxy divinyl ketones thermodynamically favor the *E,Z*-stereochemistry.[3h] Cocyclization of **16** afforded the major diastereomer **17** (61%), which was readily separated from the minor diastereomer **17′** resulting from the opposite sense of conrotation (15%, not shown). X-ray crystal structure analysis of **17** confirmed the predicted sense of induction based on our earlier studies of oxazolidinone controlled Nazarov cyclizations.[3h,7] Refluxing **17** in dry methanol in the presence of $MeSO_3H$ afforded the methyl ester **18** (73%).

We also explored the intramolecular displacement of the oxazolidinone auxiliary in the asymmetric synthesis of the lactone **24** (Scheme 4). The benzyl butynyl ether **19** was converted to **21** using our previously described procedure for the one-pot preparation of *N*-(alkynoyl)oxazolidinones from terminal alkynes.[3h] This involved lithiation of **19** and reaction with carbon dioxide to afford a lithium carboxylate that was in turn converted to a pivaloyl anhydride and reacted with the *N*-

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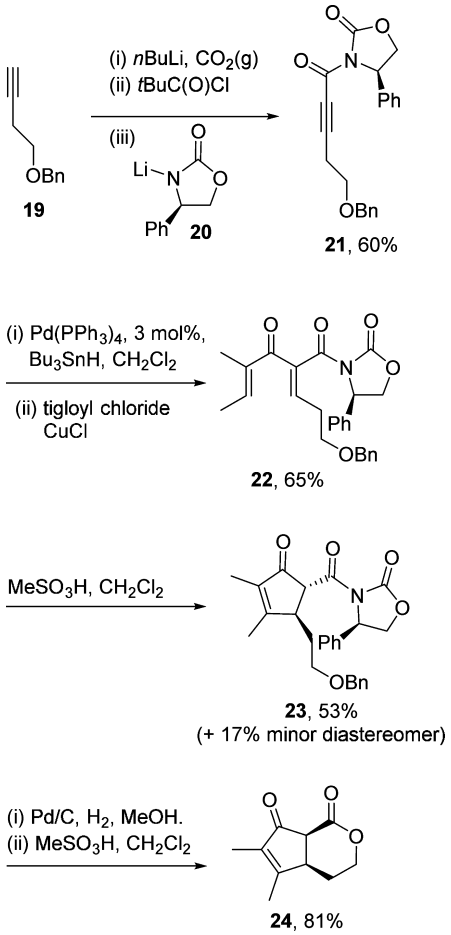
Scheme 4. Asymmetric Synthesis of Lactone 23



lithiated oxazolidinone **20**, giving **21** (60%). This material was coupled to tigloyl chloride (reductive coupling) to give divinyl ketone **22** (65%). Nazarov cyclization of **22** afforded the major diastereomer **23** (53%), which was readily separated from the minor diastereomer (17%, not shown) by column chromatography. The stereochemical assignment of **23** was based on our earlier work (note, alkyl and aryl substituents vicinal to carboxy-oxazolidinone auxiliary undergo Nazarov cyclization with an opposite sense of conrotation).[3h] Sequential hydrogenolysis and treatment with $MeSO_3H$ afforded lactone **24** (81% from **23**). Interestingly, the benzyl ether in **23** was selectively cleaved under these hydrogenation conditions, leaving the enone group in **24** intact and thus available for further synthetic manipulation.

These studies underscore the potential of the two step reductive coupling/Nazarov cyclization protocol to provide convergent access to ring-fused cyclopentanones from readily accessible substrates: α,β-unsaturated acid chlorides and terminal alkynes. This protocol is enhanced by the ready accessibility *N*-(alkynoyl)oxazolidinones from terminal alkynes, which can be utilized in this protocol to provide enantioenriched products through a combination moderate diastereoselection, ready separation of diastereomers, and convenient auxiliary cleavage.

EXPERIMENTAL SECTION

General Methods. All experiments were performed under an anhydrous atmosphere of nitrogen in flame-dried glassware except where indicated. Melting points were recorded with an electrothermal melting point apparatus. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz for proton and 75 MHz for carbon nuclei. All NMR spectra were recorded in (D)chloroform ($CDCl_3$) at 30 °C. The protonicities of the carbon atoms observed in the carbon NMR were determined using J-modulated spin−echo (JMOD) experiments. ^{1}H NMR spectral data are recorded as follows: chemical shift δ (ppm), multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, m_c: centered multiplet, dd: doublet of doublets, dt: doublet of triplets, br: broad), coupling constant(s) (J Hz), and relative integral. ^{13}C NMR spectral data are recorded as δ (ppm) with the protonicity of the carbon given in parentheses. High-resolution mass spectra (HRMS) were recorded on a time-of-flight mass spectrometer fitted with either an electrospray (ESI) or atmospheric pressure ionization (APCI) ion source. Infrared spectra were recorded on a Fourier transform instrument and are given as wavenumbers cm^{-1}. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a commercial solvent purification system (SPS). Thin layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 GF254 plates, and the chromatograms were visualized under a 254 nm UV lamp and/or by treatment with a reagent solution [phosphomolybdic acid/95% ethanol (4 g:100 mL) dip] or anisaldehyde dip (214 mL of EtOH, 8 mL of H_2SO_4, 2.4 mL of AcOH, 5.9 mL of anisaldehyde) followed by heating. Flash column chromatography was performed using silica 40−63 μm.

1,1-Dibromo-2-(2′-benzyloxy-4′-methoxy-phenyl)-ethene ***9***. Carbon tetrabromide (821 mg, 2.48 mmol) was added to a stirred solution of triphenylphosphine (1.3 g, 4.96 mmol) in dichloromethane (15 mL) at 0 °C, and the reaction was allowed to stir for 10 min. To the resultant red/orange solution, 2-benzyloxy-4-methoxy-benzaldehyde **8**[5] (300 mg, 1.24 mmol) was added, and stirring was continued for 15 min. After this the reaction mixture was concentrated under reduced pressure, the residue was subject to flash chromatography on silica-gel (eluted with hexane/dichloromethane 2:1) to provide the product **9** as a clear oil (491 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.42−7.29 (m, 5H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 5.08 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.1 (C), 157.0 (C), 136.5 (C), 132.3 (CH), 129.8 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 117.7 (C), 104.7 (CH), 99.8 (CH), 87.8 (C), 70.4 (CH_2), 55.3 (CH_3); IR (KBr, cm^{-1}) 3030, 2938, 2836, 1607, 1578, 1500, 1458, 1296, 1262, 1197, 1165, 1117, 1038, 866, 835. This material did not provide suitable mass spectral data under ESI conditions.

(2-Benzyloxy-4-methoxy-phenyl)-propynoic acid methyl ester ***10***. *n*-Butyllithium (2.2 mL 2.7 M in hexane, 5.88 mmol,) was added to a stirred solution of the *gem*-dibromostyrene **9** (1.14 g, 2.86 mmol) in dry THF (25 mL) at −78 °C, and the reaction was allowed to warm to rt, stirred for a further 15 min, and then recooled to −78 °C. Methyl chloroformate (0.24 mL, 2.86 mmol) was added, and the reaction was allowed to warm slowly to rt and then quenched with 10% w/v NH_4Cl (aq) (40 mL) and extracted with diethyl ether (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent was removed under a vacuum. The crude residue was purified by silica-gel chromatography (sequential elution with hexane/diethyl ether 9:1, 3:1, and 2:1) to give the product **10** as a white solid (736 mg, 87%): mp = 67−68 °C; ^{1}H NMR ($CDCl_3$) δ 7.52−7.45 (m, 3H), 7.42−7.31 (m, 3H), 6.51−6.46 (m, 2H), 5.18 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.1 (C), 162.3 (C), 154.8 (C), 136.3 (C), 136.0 (CH), 128.5 (CH), 127.8 (CH), 126.7 (CH), 106.0 (CH), 101.8 (C), 100.1 (CH), 84.6 (C), 83.9 (C), 70.3 (CH_2), 55.4 (CH_3), 52.5 (CH_3); IR (KBr, cm^{-1}) 3098, 3021, 2948, 2213, 1703, 1609, 1568, 1505, 1432, 1297, 1209, 1168, 1133, 1034, 999, 834; LRMS (ESI) m/z (%) 314 (M + NH_4^+, 85), 297 (M + H^+, 100), 265 (95); HRMS (ESI) calcd for $C_{18}H_{17}O_4$ (M + H^+) 297.1127, found 297.1110.

rac-3-(2-Benzyloxy-4-methoxyphenyl)-7-methoxy-9b-methyl-1-oxo-1,2,3,3a,4,9b-hexahydrocyclopenta[c]chromene-2-carboxylic acid methyl ester ***12***. Tributyltin hydride (0.341 mL, 1.27 mmol) was added dropwise to a stirred solution of $Pd(PPh_3)_4$ (72 mg 0.063 mmol) and alkyne **10** (450 mg, 1.25 mmol) in THF (5.0 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 30 min. (*E*)-4-

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(3-Methoxyphenoxy)-2-methylbut-2-enoyl chloride **7**[2i] (308.8 mg, 1.28 mmol) and CuCl (118 mg, 1.20 mmol) were then added, and the mixture was stirred at rt for 18 h. After this time the reaction mixture was diluted with ethyl acetate (25 mL), and the resultant solution washed sequentially with 10% w/v NH_4Cl (aq) (20 mL), 2 × 30% w/v KF (aq) (15 mL) and brine (10 mL). The ethyl acetate layer was dried over $MgSO_4$ and concentrated onto silica gel (4 g) under a vacuum. The solid residue was subjected to flash chromatography on silica gel (sequential elution with hexane/ethyl acetate 5:1, 4:1, and 3:1) to afford the crude dienone *E,E*-**11** (372 mg), which was used directly in the next step.

Cupric triflate (500 mg, 1.38 mmol) was added to a stirred solution of crude *E,E*-**11** (372 mg) in dichloromethane (10 mL), and the reaction was stirred at rt for 4 h and then quenched with saturated $NaHCO_3$ (aq) (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed under a vacuum, and the crude residue was purified by flash chromatography on silica-gel (sequential elution with hexane/ethyl acetate 10:1, 5:1 and 2:1) to afford the product **12** as a white solid (263 mg, 42% from **10**): mp = 76−78 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (m_c, 5H), 7.19 (t, J = 8.8 Hz, 2H), 6.58 (d, J = 2.2 Hz, 1H), 6.50−6.46 (m, 2H), 6.38 (m, J = 2.6 Hz, 1H), 5.09−4.98 (m, 2H), 4.06 (dd, J = 11.5, 1.7 Hz, 1H), 3.98 (d, J = 11.1 Hz, 1H), 3.91 (dd, J = 11.5, 1.7 Hz, 1H), 3.84 (t, J = 11.1 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.49 (s, 3H), 2.64 (dt, J = 11.1, 1.5 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.7 (C), 168.5 (C), 160.3 (C), 159.9 (C), 157.6 (C), 154.6 (C), 136.1 (C), 132.2 (CH), 129.6 (CH), 128.7 (CH), 128.2 (CH), 127.6 (CH), 119.2 (C), 112.0 (C), 108.7 (CH), 104.7 (CH), 101.7 (CH), 100.4 (CH), 70.3 (CH_2), 61.6 (CH_2), 58.0 (CH), 55.3 (CH_3), 55.1 (CH_3), 52.1 (CH_3), 48.3 (C), 44.8 (CH), 41.0 (CH), 25.7 (CH_3); IR (KBr, cm^{-1}) 2955, 2926, 2864, 1749, 1730, 1613, 1584, 1503, 1460, 1443, 1379, 1286, 1261, 1196, 1164, 1126, 1034, 912, 834; LRMS (ESI) m/z (%) 520 (M + NH_4^+, 100), 503 (M + H^+, 50); HRMS (ESI) calcd for $C_{30}H_{34}NO_7$ (M + NH_4^+) 520.2335, found 520.2325.

rac-3-(2-Hydroxy-4-methoxyphenyl)-7-methoxy-9b-methyl-1-oxo-1,2,3,3a,4,9b-hexahydrocyclopenta[c]chromene-2-caroxylic acid methyl ester ***13***. A suspension of benzyl-protected substrate **12** (55 mg, 0.11 mmol) and 10% Pd/C (10 mg) in ethyl acetate (2 mL) was stirred under an atmosphere of hydrogen (balloon) at 60 °C for 16 h. After this time the reaction was filtered through Celite, and the solvent was removed under a vacuum to give a crude residue that was purified by silica-gel chromatography (eluent hexane/ethyl acetate 3:1) to afford the product **13** as a clear oil (29 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.49−6.54 (m, 2H), 6.44 (dd, J = 7.5, 2.4 Hz, 2H), 6.39 (br s, 1H), 4.10 (dd, J = 11.4, 1.5 Hz, 1H), 3.99 (dd, J = 11.4, 1.8 Hz, 1H), 3.91−3.75 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 2.56 (d, J = 11.1 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.8 (C), 169.4 (C), 160.0 (2 × C), 155.7 (C), 154.3 (C), 129.6 (CH), 129.2 (CH), 116.7 (C), 111.7 (C), 109.1 (CH), 106.8 (CH), 103.0 (CH), 101.9 (CH), 61.3 (CH_2), 59.3 (CH), 55.2 (2 × CH_3), 52.8 (CH_3), 48.6 (C), 45.4 (CH), 37.4 (CH), 26.2 (CH_3); IR (KBr, cm^{-1}) 3404, 2958, 2929, 1749, 1730, 1616, 1580, 1503, 1441, 1288, 1242, 1199, 1165, 1121, 1033, 836, 799; LRMS (ESI) m/z (%) 430 (M + NH_4^+, 60), 413 (M + H^+, 100); HRMS (ESI) calcd for $C_{23}H_{25}O_7$ (M + H^+) 413.1600, found 413.1599.

rac-3,9-Dimethoxy-13a-methyl-6,6a,6b,12a-tetrahydro-13aH-5,11-dioxadibenzo[a,g]flourene-12,13-dione ***14***. To a stirred solution of phenol **13** (20 mg, 0.049 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL, excess), and the reaction was stirred for 18 h at reflux. After this time the volatile materials were removed by passing a stream of air over the reaction mixture, and the crude residue was purified by flash chromatography on silica-gel (eluent hexane/ethyl acetate 4:1) to give the product **14** as a clear oil (14 mg, 78%): ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.56 (dd, J = 8.8, 2.6 Hz, 1H), 6.42 (d, J = 2.6 Hz, 1H), 4.34 (dd, J = 11.9, 2.2 Hz, 1H), 4.05 (dd, J = 11.9, 1.8 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.61−3.50 (m, 2H), 2.07 (dt, J = 10.5, 2.0 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.8 (C), 161.1 (C), 160.5 (C), 160.2 (C), 154.5 (C), 151.4 (C), 129.9 (CH), 129.7 (CH), 112.5 (C), 112.1 (C), 111.4 (CH), 109.3 (CH), 102.8 (CH), 102.1 (CH), 61.0 (CH_2), 55.7 (CH_3), 55.4 (CH_3), 51.0 (CH), 49.4 (CH), 47.3 (C), 34.9 (CH), 27.0 (CH_3); IR (KBr, cm^{-1}) 2959, 2930, 2840, 1775, 1740, 1617, 1584, 1504, 1443, 1277, 1242, 1157, 1030, 839; LRMS (ESI) m/z (%) 398 (M + H^+, 100), 381 (M + H^+, 20); HRMS (ESI) calcd for $C_{22}H_{21}O_6$ (M + H^+) 381.1338, found 381.1330.

(S)-(2Z,4E)-2-Benzylidene-6-(3″-methoxyphenoxy)-4-methyl-1-(2′-oxo-4′-phenyloxazolidin-3′-yl)-hex-4-ene-1,3-dione ***16***. Tributyltin hydride (0.422 mL, 1.57 mmol) was added dropwise to a stirred solution of $Pd(PPh_3)_4$ (89 mg, 0.077 mmol) and (*S*)-4-phenyl-3-(3-phenylpropioloyl)oxazolidin-2-one **15**[3h] (450 mg, 1.54 mmol) in THF (5.0 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 30 min. (*E*)-4-(3-Methoxyphenoxy)-2-methylbut-2-enoyl chloride **7**[2i] (407.7 mg, 1.69 mmol) and CuCl (152 mg) were then added, and the mixture was stirred at rt for 18 h. After this time the reaction mixture was diluted with ethyl acetate (25 mL), and the resultant solution washed sequentially with 10% w/v NH_4Cl (aq) (20 mL), 2 × 30% w/v KF(aq) (15 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated onto silica (4 g), and the solid residue was subjected to flash chromatography on silica gel (sequential elution with hexane/dichloromethane/diethyl ether 10:10:1 and 5:5:1). The product **16** thus obtained was crystallized by trituration with a 2:1 mixture of hexane and diethyl ether giving a pale yellow solid (453 mg, 58%): mp = 110−111 °C; $[\alpha]^{25}_D$ = +65° (*C* = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.42 (br s, 5H), 7.39 (s, 1H), 7.20 (t, J = 5.4 Hz, 1H), 7.07 (m_c, 5H), 6.63 (t, J = 5.1 Hz, 1H), 6.56−6.49 (m, 3H), 5.55 (dd, J = 8.4, 3.3 Hz, 1H), 4.79 (m_c, 2H), 4.73 (t, J = 8.4 Hz, 1H), 4.36 (dd, J = 9.0, 3.3 Hz, 1H), 3.78 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.9 (C), 165.9 (C), 160.8 (C), 159.4 (C), 152.8 (C), 144.0 (CH), 138.1 (C), 136.6 (CH), 136.2 (C), 134.3 (C), 132.6 (C), 130.3 (CH), 130.0 (CH), 129.6 (CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 126.7 (CH), 106.8 (CH), 106.7 (CH), 101.3 (CH), 70.4 (CH_2), 64.5 (CH_2), 57.3 (CH), 55.2 (CH_3), 13.7 (CH_3); IR (KBr, cm^{-1}) 3063, 2965, 2926, 1788, 1699, 1633, 1614, 1602, 1489, 1450, 1384, 1327, 1265, 1214, 1150, 1119, 1034, 765; LRMS (ESI) m/z (%) 515 (M + NH_4^+, 70), 498 (M + H^+, 35), 335 (100); HRMS (ESI) calcd for $C_{30}H_{28}NO_6$ (M + H^+) 498.1917, found 498.1921.

(4S,2′R,3′S,4′R,9b′R)-3-(7′-Methoxy-9b′-methyl-1′-oxo-3′-phenyl-1′,2′,3′,3a′,4′,9b′-hexahydrocyclopenta[c]chromene-2′-carbonyl)-4-phenyloxazolidin-2-one ***17***. Cupric triflate (363 mg, 1.00 mmol) was added to a stirred solution of **16** (250 mg, 0.502 mmol) in dry dichloromethane (15 mL) at 0 °C, and the reaction was allowed to warm to rt and stirred for 30 h. After this time 5% w/v $NaHCO_3$ (aq) (15 mL) was added, the phases were separated, and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The organic fractions were combined, dried over $MgSO_4$ and concentrated onto silica gel (1 g) under a vacuum. The solid residue was subjected to flash chromatography (elution with hexane/dichloromethane/diethyl ether 20:20:1), which needed to be repeated on a series of mixed fractions in order to achieve complete separation. This afforded the major diastereomer **17** (152 mg, 61%) and the minor diastereomer **17** (38 mg, 15%). Major diastereomer **17**: mp = 160−163 °C; $[\alpha]^{25}_D$ = +189° (*C* = 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37−7.24 (m, 10H), 7.18 (d, J = 8.7 Hz, 1H), 6.37 (dd, J = 8.7, 2.4 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 5.53 (d, J = 12.0 Hz, 1H), 5.24 (dd, J = 9.0, 2.7 Hz, 1H), 4.58 (t, J = 9.0 Hz, 1H), 4.15 (dd, J = 8.7, 2.7 Hz, 1H), 4.05 (d, J = 12.0 Hz, 1H), 3.94 (d, J = 12.0 Hz, 1H), 3.88 (t, J = 12.3 Hz, 1H), 3.71 (s, 3H), 2.27 (d, J = 12.3 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.8 (C), 166.0 (C), 159.8 (C), 154.3 (C), 153.7 (C), 139.0 (C), 137.9 (C), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 125.7 (CH), 112.0 (C), 108.9 (CH), 101.7 (CH), 69.7 (CH_2), 60.8 (CH_2), 59.7 (CH), 57.7 (CH), 55.1 (CH_3), 48.5 (CH), 48.5 (C), 41.5 (CH), 26.6 (CH_3); IR (KBr, cm^{-1}) 3030, 2999, 2910, 2864, 2832, 1763, 1755, 1693, 1611, 1580, 1497, 1461, 1389, 1359, 1309, 1206, 1165, 1113, 1028, 1005, 915, 837, 762; LRMS (ESI) m/z (%) 515 (M + NH_4^+, 100), 498 (M + H^+, 65); HRMS (ESI) calcd for $C_{30}H_{28}NO_6$ (M + H^+) 498.1917, found 498.1903. Minor diastereomer **17**: mp = 190−194 °C; $[\alpha]^{25}_D$ = +45° (*C* = 0.27, $CHCl_3$); ^{1}H NMR

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($CDCl_3$) δ 7.36−7.28 (m, 6H), 7.21−7.11 (m, 3H), 6.84 (dd, J = 8.1, 1.5 Hz, 2H), 6.52 (dd, J = 8.7, 2.7 Hz, 1H), 6.37 (d, J = 2.7 Hz, 1H), 5.61 (d, J = 12.6 Hz, 1H), 5.33 (dd, J = 8.7, 3.3 Hz, 1H), 4.66 (t, J = 8.7 Hz, 1H), 4.13 (dd, J = 8.7, 3.3 Hz, 1H), 4.07 (dd, J = 11.4, 1.8 Hz, 1H), 3.96 (dd, J = 11.4, 1.8 Hz, 1H), 3.82 (t, J = 12.3 Hz, 1H), 3.75 (s, 3H), 2.32 (dt, J = 12.3, 1.8 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.6 (C), 167.2 (C), 159.9 (C), 154.4 (C), 153.6 (C), 138.3 (C), 138.1 (C), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 125.1 (CH), 112.2 (C), 109.1 (CH), 101.8 (CH), 69.8 (CH_2), 60.8 (CH_2), 59.2 (CH), 57.7 (CH), 55.1 (CH_3), 48.8 (CH), 48.5 (C), 43.6 (CH), 26.7 (CH_3); IR (KBr, cm^{-1}) 3061, 3036, 2978, 2916, 2869, 1769, 1751, 1698, 1614, 1580, 1499, 1391, 1316, 1224, 1200, 1167, 1107, 1028, 841, 761; LRMS (ESI) m/z (%) 515 (M + NH_4^+, 60), 498 (M + H^+, 50), 142 (70), 100 (100); HRMS (ESI) calcd for $C_{30}H_{28}NO_6$ (M + H^+) 498.1917, found 498.1921.

(2R,3S,3aR,9bR)-7-Methoxy-9b-methyl-1-oxo-3-phenyl-1,2,3,3a,4,9b-hexahydrocyclopenta[c]chromene-2-carboxylic acid methyl ester ***18***. To a stirred solution of compound **17** (85 mg, 0.171 mmol) in a mixture of dry methanol (4 mL) and toluene (1 mL) was added concentrated sulfuric acid (5 drops), and the reaction heated to reflux for 5 d. After this time the reaction mixture was cooled to rt and quenched with saturated $NaHCO_3$ (aq) (15 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated onto silica gel under reduced pressure. The solid residue was subjected to flash chromatography (sequential elution with hexane/ethyl acetate 9:1 and 4:1) giving the product **18** as a resinous gum (45 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 7.28−7.38 (m, 6H), 6.53 (dd, J = 9.0, 2.7 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 4.10 (dd, J = 11.7, 1.8 Hz, 1H), 3.98 (dd, J = 11.7, 1.8 Hz, 1H), 3.81 (t, J = 11.7 Hz, 1H), 3.78 (s, 3H), 3.60 (d, J = 11.7 Hz, 1H), 3.58 (s, 3H), 2.23 (dt, J = 11.7, 1.8 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.2 (C), 167.9 (C), 160.0 (C), 154.3 (C), 139.0 (C), 129.6 (CH), 128.9 (CH), 127.6 (CH), 127.5 (CH), 111.7 (C), 109.0 (CH), 101.9 (CH), 62.6 (C), 60.8 (CH_2), 60.7 (CH), 55.2 (CH_3), 52.4 (CH_3), 48.6 (CH), 43.0 (CH), 26.4 (CH_3); IR (KBr, cm^{-1}) 2958, 1769, 1729, 1612, 1579, 1497, 1444, 1327, 1239, 1196, 1165, 1032, 927, 838; LRMS (ESI) m/z (%) 384 (M + NH_4^+, 50), 367 (M + H^+, 100); HRMS (ESI) m/z calcd for $C_{22}H_{23}O_5$ (M + H^+) 368.1579, found 368.1577.

(4R)-3-(5′-Benzyloxy-pent-2′-ynoyl)-4-phenyloxazolidin-2-one ***21***. To a stirred solution of the ((but-3-yn-1-yloxy)methyl)benzene **19** (320 mg, 2.0 mmol) in dry THF (6 mL) at −78 °C was added *n*-butyllithium (0.74 mL, 2.7 M in hexanes, 2.0 mmol), and the reaction allowed to warm to rt for 10 min. The solution was recooled to −78 °C, and gaseous carbon dioxide bubbled through the solution for 15 min, and the reaction allowed to warm to rt and stirred for 10 min. After this time N_2 (g) was bubbled through the solution for 5 min to remove excess carbon dioxide. The solution was then cooled to 0 °C, and pivaloyl chloride (0.246 mL, 2.0 mmol) was added. The reaction was allowed to warm to rt and stirred for 1 h before being cooled to −78 °C, at which point a solution of the lithium salt of (*R*)-4-phenyloxazolidin-2-one **20** (1.90 mmol, prepared by addition of 1.90 mmol of *n*-butyllithium to a solution of 1.90 mmol of (*R*)-4-phenyloxazolidin-2-one in 8 mL of THF at −40 °C) was added via cannula at (−40 °C). The resulting reaction was warmed slowly to rt, stirred for 2 h, and then quenched with 10% w/v NH_4Cl (aq) (30 mL) and extracted twice with ethyl acetate (2 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated onto silica gel under a vacuum. The solid residue was subjected to flash chromatography on silica gel (sequential elution with hexane/ethyl acetate 4:1 and 2:1) giving **21** (398 mg, 60%) as a viscous oil: $[\alpha]^{25}_D$ = −10° (*C* = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.28−7.41 (m, 10H), 5.43 (dd, J = 8.7, 3.6 Hz, 1H), 4.68 (t, J = 8.7 Hz, 1H), 4.57 (s, 2H), 4.28 (dd, J = 8.7, 3.6 Hz, 1H), 3.69 (t, J = 6.9 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 152.1 (C), 150.0 (C), 138.3 (C), 137.8 (C), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH) 127.7(CH), 125.9 (CH), 95.2 (C), 74.2 (C), 73.0 (CH_2), 69.8 (CH_2), 67.0 (CH_2), 57.4 (CH), 20.7 (CH_2); IR (KBr, cm^{-1}) 3649, 3562, 3064, 3032, 2916, 2868, 2237, 1790, 1667, 1491, 1455, 1384, 1331, 1202, 1093, 1036, 805; LRMS (ESI) m/z (%) 367 (M + NH_4^+, 100), 350 (M + H^+, 98); HRMS (ESI) calcd for $C_{21}H_{20}NO_4$ (M + H^+) 350.1392, found 350.1370.

(4′R),(2Z,4E)-2-(3″-Benzyloxypropylidene)-4-methyl-1-(2′-oxo-4′-phenyloxazolidin-3′-yl)hex-4-ene-1,3-dione ***22***. Tributyltin hydride (0.125 mL, 0.465 mmol) was added dropwise to a stirred solution of $Pd(PPh_3)_4$ (26 mg 0.023 mmol) and alkyne **21** (160 mg, 0.458 mmol) in THF (1.5 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 30 min. Tigloyl chloride (52 μL, 0.480 mmol) and CuCl (45 mg, 0.458 mmol) were then added, and the mixture was stirred at rt for 18 h. After this time the reaction mixture was diluted with ethyl acetate (10 mL), and the resultant solution washed sequentially with 10% w/v NH_4Cl (aq) (10 mL), 2 × 30% w/v KF (aq) (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated onto silica gel (4 g), and the solid residue was subjected to flash chromatography on silica gel (sequential elution with hexane/ethyl acetate 3:1 and 2:1) giving the product **22** (131 mg, 65%) as a clear resin: $[\alpha]^{25}_D$ = −68° (*C* = 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.28−7.41 (m, 10H), 6.72 (t, J = 7.8 Hz, 1H), 6.57 (q, J = 6.9 Hz, 1H), 5.47 (dd, J = 8.7, 4.5 Hz, 1H), 4.65 (t, J = 8.7 Hz, 1H), 4.47 (s, 2H), 4.22 (dd, J = 8.7, 4.5 Hz, 1H), 3.55 (dt, J = 6.3, 1.5 Hz, 2H), 2.49 (dq, J = 6.3, 2.4 Hz, 2H), 1.86 (s, 3H), 1.81 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 194.6 (C), 165.5 (C), 153.0 (C), 145.8 (CH), 138.5 (C), 138.4 (CH), 138.3 (C), 133.2 (C), 135.4 (C), 129.2 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH) 126.0 (2 x CH), 72.9 (CH_2), 70.5 (CH_2), 68.3 (CH_2), 57.9 (CH), 30.3 (CH_2), 14.5 (CH_3), 12.6 (CH_3); IR (KBr, cm^{-1}) 3545, 3366, 3061, 3033, 2922, 2859, 1785, 1694, 1634, 1454, 1385, 1327, 1278, 1206, 1110, 1080, 919; LRMS (ESI) m/z (%) 451 (M + NH_4^+, 85), 434 (M + H^+, 100), 271 (70); HRMS (ESI) calcd for $C_{26}H_{28}NO_5$ (M + H^+) 434.1967, found 434.1964.

(R)-3-((1R,2R)-2-(2-(Benzyloxy)ethyl)-3,4-dimethyl-5-oxocyclopent-3-ene-1-carbonyl)-4-phenyloxazolidin-2-one ***23***. To an ice-cooled solution of dienone **22** (230 mg, 0.531 mmol) in dry dichloromethane (10 mL) was added $MeSO_3H$ (0.035 mL, 0.53 mmol), and the reaction allowed to warm slowly to rt. After stirring for 5 h TLC analysis revealed complete consumption of the starting material, and the reaction was quenched with saturated $NaHCO_3$ (aq) (15 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (10 mL) dried over $MgSO_4$, and the solvent was removed under reduced pressure to give an oily residue. ^{1}H NMR analysis of this material revealed the presence of **23** and its minor diastereomer in a 3:1 ratio. The crude material was dissolved in dichloromethane and evaporated onto silica gel (1 g) under reduced pressure. The solid residue was subjected to flash chromatography (sequential elution−dichloromethane/hexanes/diethyl ether; 10:10:1, 5:5:1, 5:5:2) to give the major diastereomer **23** as a viscous oil (136 mg, 53%); the minor isomer (17%) was not characterized. Major diastereomer **23**: $[\alpha]^{25}_D$ = +43° (*C* = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.20−7.33 (m, 8H), 7.18 (d, J = 6.0 Hz, 2H), 5.39 (dd, J = 8.7, 2.7 Hz, 1H), 4.99 (d, J = 2.4 Hz, 1H), 4.74 (t, J = 8.7 Hz, 1H), 4.30 (dd, J = 8.7, 2.4 Hz, 1H), 4.20 (m_c, 2H), 3.44−3.51 (m, 1H), 3.34−3.41 (m, 1H), 3.32 (br s, 1H), 2.09−2.19 (m, 1H), 2.01 (s, 3H), 1.69 (s, 3H), 1.53−1.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 200.9 (C), 172.6 (C), 168.4 (C), 153.7 (C), 139.3 (C), 138.1 (C), 134.0 (C), 129.0 (CH), 128.5 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 125.8 (CH), 72.9 (CH_2), 69.8 (CH_2), 68.3 (CH_2), 58.2 (CH), 56.5 (CH), 43.9 (CH), 31.8 (CH_2), 15.1 (CH_3), 8.2 (CH_3); IR (KBr,cm^{-1}) 3646, 3543, 3385, 3032, 2922, 2860, 1784, 1693, 1645, 1452, 1381, 1323, 1240, 1199, 1103, 920, 874; LRMS (ESI) m/z (%) 451 (M + NH_4^+, 25), 434 (M + H^+, 100); HRMS (ESI) calcd for $C_{26}H_{28}NO_5$ (M + H^+) 434.1967, found 434.1968.

(4aR,7aS)-5,6-Dimethyl-3,4,4a,7a-tetrahydrocyclopenta[c]pyran-1,7-dione ***24***. A solution of cyclopentenone **23** (89 mg, 0.205 mmol) and 10% palladium on carbon (10 mg) in ethyl acetate (3 mL) was stirred under an atmosphere of hydrogen at ambient pressure and temperature for 30 h. After this time TLC analysis revealed consumption of the starting material. The reaction mixture was filtered through Celite, and the solvent was removed to give a solid residue (76 mg). The crude material was dissolved in dichloromethane (5 mL), treated with $MeSO_3H$ (2 drops) and allowed to stir overnight. After this time the reaction was quenched with saturated $NaHCO_3$

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(aq) (10 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated onto silica gel (1 g) under reduced pressure. The solid residue was subjected to flash chromatography (sequential elution with hexane/ethyl acetate 1:3 and ethyl acetate) to give the product **24** as a clear oil (30 mg, 81%): $[\alpha]^{25}_D = -167°$ (C = 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.18 (dt, J = 11.4, 3.6 Hz, 1H), 3.89 (dt, J = 11.4, 1.5 Hz, 1H), 3.52 (d, J = 6.9 Hz, 1H), 3.29 (br s, 1H), 2.25 (m_c, 1H), 2.08 (s, 3H), 1.88 (d, J = 14.7 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.2 (C), 168.6 (C), 166.3 (C), 138.3 (C), 63.6 (CH_2), 52.2 (CH), 40.8 (CH), 25.9 (CH_2), 14.8 (CH_3), 8.4 (CH_3); IR (KBr, cm^{-1}) 3466, 3362, 2974, 2897, 1732, 1687, 1643, 1437, 1386, 1329, 1276, 1213, 1188, 1159, 1063, 979, 940, 824, 766; LRMS (ESI) m/z (%) 198 ($M + NH_4^+$, 20), 181 ($M + H^+$, 100); HRMS (ESI) calcd for $C_{10}H_{13}O_3$ ($M + H^+$) 181.0865, found 181.0859.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data for **17** (CIF) and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) This stereochemical assignment is supported by the similar coupling patterns seen in the relevant protons attached to the pyran and cyclopentyl ring systems in the closely related structure **17**, for which an X-ray crystal structure was obtained.

(7) See the Supporting Information.