Benzannulation and hydrocarboxylation methods for the synthesis of a neopentylene-fused analogue of ibuprofen

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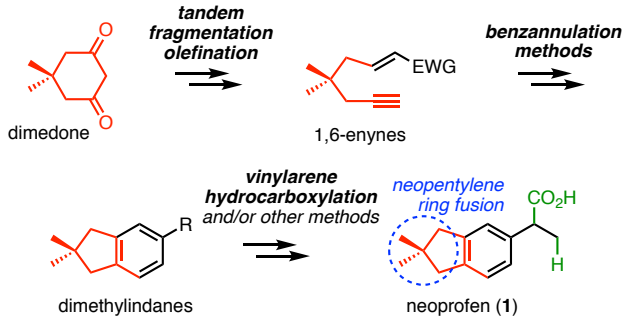
Supporting Information Placeholder



ABSTRACT: Neopentylene ring fusions (ring-fused 4,4-dimethylcyclopentane polycycles) are found in many natural products, but they are largely absent from synthetic compound libraries and focused medicinal chemistry research. Here is reported a synthetic approach to one of the few non-natural product-based target compounds from medicinal chemistry that includes a neopentylene ring fusion: an analogue of ibuprofen referred to herein as "neoprofen". The approach features ring-opening fragmentation reactions of dimedone derivatives coupled with transition metal-catalyzed benzannulation and hydrocarboxylation methods.

As part of a larger medicinal chemistry interest in exploring diverse 3D molecular structural topologies, we recently prepared "neoprofen" (Figure 1, **1**),[1] a known analogue of ibuprofen in which the flexible isobutyl side chain of ibuprofen has been morphed into a compact and rigid neopentylene ring fusion. This compound had previously been prepared in 9 steps from benzaldehyde as part of medicinal chemistry efforts probing the ibuprofen pharmacophore.[2] We reasoned that this strategic ring fusion (and one-atom change in the molecular formula) would impact key pharmacological properties. Molecular docking simulations suggested that neoprofen would not penetrate as deeply into a hydrophobic cavity in the human COX-2 enzyme as does ibuprofen. In initial tests of this hypothesis, we demonstrated that the inhibitory activity of neoprofen in a simple human COX-2 assay is significantly different from that of ibuprofen. As noted in our previous publication,[1] "we anticipate that neopentylene ring-fused structures should have strategic value in molecular pharmacology."

The strategic value of neopentylene ring-fused structures cannot be realized without viable synthetic options for incorporating the neopentylene ring fusion. Neopentylene ring fusions are found in many naturally occurring sesquiterpenes (Figure 2). We developed efficient synthetic routes to alcyopterosins A[3] and O[4] and illudinine,[5] as well as intersected with known

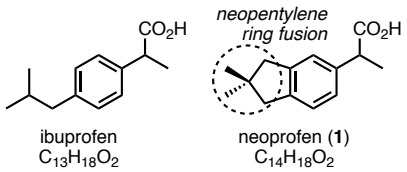


Figure 1. Structures of ibuprofen and neoprofen.

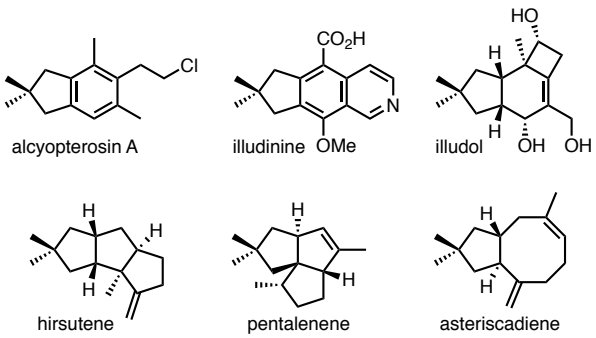


Figure 2. Neopentylene ring fusions in natural products.

routes to hirsutene[6] and illudol[7] to produce streamlined formal syntheses of these compounds.[8] We also noted that

neopentylene ring fusions are largely absent from synthetic compound libraries and medicinal chemistry efforts.[1]

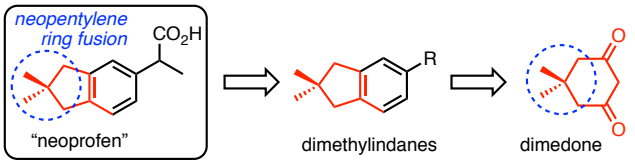
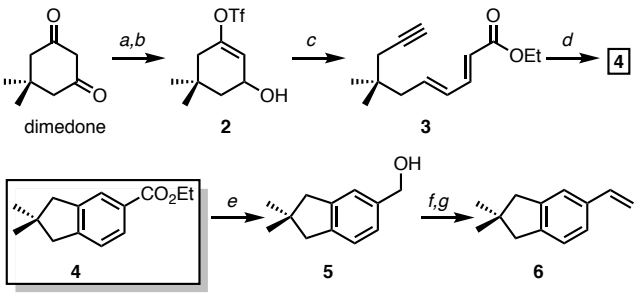


Figure 3. Synthetic strategy to prepare neoprofen from dimedone.

The discrepancy between naturally and synthetically produced neopentylene ring-fused structures reflects limitations in modern methods for chemical synthesis. Therefore, the synthesis of designer targets like neoprofen stands in our minds as an important challenge toward the long-term goal of producing high-value neopentylene ring-fused structures.

Our general approach to this challenge has been to develop ring-opening fragmentation reactions[9,10] that can leverage dimedone (Figure 3) to give rise to bifunctional neopentylene-tethered building blocks for chemical synthesis (e.g., tethered alkynyl ketones,[11,12] 1,6-enynes,[3,5,8] etc.). For example, benzannulation of neopentylene-tethered π-systems can produce dimethylindanes; we reported an oxidative cycloisomerization of dienyne **3** that provides benzoate **4**[13] in 4 steps (ca. 56% overall) from dimedone (Scheme 1), and we produced **4** on a gram-scale in connection with other on-going projects in our lab.[14] Here we report an improved synthesis of neoprofen by this general approach, augmented with critical methodological examination and key innovations in metal-catalyzed benzannulation and hydrocarboxylation reactions (Figure 3).

Scheme 1. Synthesis of neopentylene-fused styrene

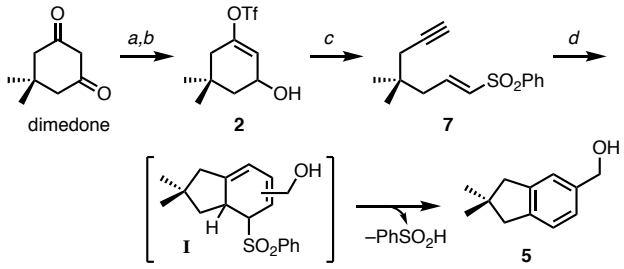


(a) Tf_2O, pyridine, DCM, >95%; (b) DIBAL-H, THF, >95%; (c) LDA, $EtO_2CCH{=}CHCH_2P(O)(OEt)_2$, THF, 81%; (d) 1 mol% $[RhCl(nbd)]_2$, 4 mol% $AgSbF_6$, DCM; DDQ, 77%; (e) DIBAL-H, DCM, 95%; (f) 5 mol% $CuBr_2$, bpy, TEMPO, 10 mol% NMI, CH_3CN, rt, air, 93%; (g) $Ph_3P{=}CH_2$, 86%

For neoprofen, we can now access neopentylene-fused styrene **6** in three simple steps from benzoate **4** — reduction, oxidation, and methylenation (ca. 76% overall, Scheme 1) — from which we envisioned obtaining neoprofen by metal-catalyzed hydrocarboxylation with incorporation of CO_2 (*vide infra*).

Alternatively, we identified a novel benzannulation reaction based on metal-catalyzed [2+2+2] cyclotrimerization methodology, in which 1-sulfonyl-1,6-enyne **7** serves as a surrogate for 4,4-dimethyl-1,6-heptadiyne (**8**). The $Ni(CO)_2(PPh_3)_2$-catalyzed reaction of sulfonyl enyne **7** with propargyl alcohol, with *in situ* elimination of phenylsulfinic acid, provides neopentylene-fused benzyl alcohol **5** in 75% yield (Scheme 2).

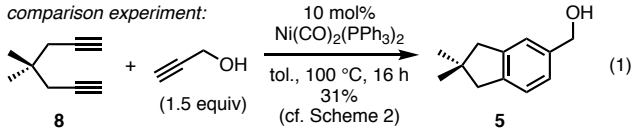
Scheme 2. Synthesis of sulfonyl enyne 7 and tandem cyclotrimerization / elimination with propargyl alcohol



(a) Tf_2O, pyridine, DCM, >95%; (b) DIBAL-H, THF, >95%; (c) PhO_2SCH_2 $P(O)(OEt)_2$, LDA, THF, 93%; (d) 10 mol% $Ni(CO)_2(PPh_3)_2$, 1.5 equiv. $HC{\equiv}CCH_2OH$, toluene, 100 °C, 16 h, 75%

$Ni(CO)_2(PPh_3)_2$ was previously employed for alkyne cyclotrimerization of a neopentylene-tethered 1,6-diyne derived from **8**.[15] Such diynes are difficult to prepare: the synthesis of 1,6-diyne **8** required 6 steps from isophorone,[16] although we recently developed a 4-step alternative from dimedone.[4] Sulfonyl enyne **7** is available in 3 steps (ca. 85% overall) from dimedone (Scheme 2), based on our prior methodology.[8,17] Other neopentylene-tethered sulfonyl enynes are similarly available.

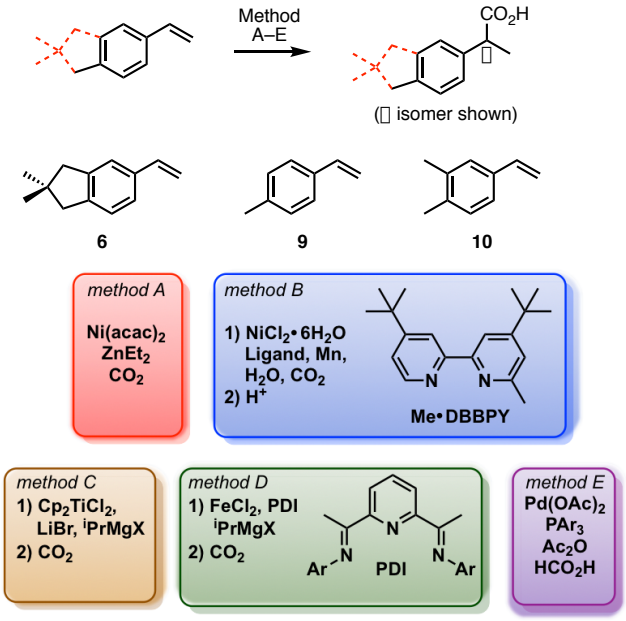
Moreover, the tandem Ni-catalyzed cyclotrimerization / elimination reaction of propargyl alcohol with sulfonyl enyne **7** outperforms the analogous alkyne cyclotrimerization with diyne **8** in preliminary experiments under the same conditions (Eq 1). Vinyl sulfones are generally recognized as versatile functional groups for synthesis[18] and medicinal chemistry.[19] The use of vinyl sulfones as alkyne surrogates for [2+2+2] cycotrimerization is expected to have general utility and is being explored further.[20,21]



Having thus prepared neopentylene styrene **6** by two distinct benzannulation methods (Schemes 1 and 2), we turned our attention to the direct installation of the requisite carboxylic acid functionality by regioselective hydrocarboxylation.[22] We have on-going interests in metal-mediated alkene hydrofunctionalization,[23] including methodologies focused on sustainable chemical synthesis based on earth-abundant metals and/or CO_2 as the C1 source.

We evaluated five one-step hydrocarboxylation methods for converting styrene **6** into neoprofen (**1**), with 4-methylstyrene (**9**) and 3,4-dimethylstyrene (**10**) included as positive controls in most cases (Table 1; see Supporting Information for additional experiments and discussion). Ultimately, Shi's Pd-catalyzed hydrocarboxylation using formic acid as the C1 source (entry 13) provided the best yield of neoprofen **1**. We consistently observed lower yields for hydrocarboxylation of **6** compared with **9** and **10**, underscoring the impact of the neopentylene structural feature and the on-going challenges it presents for chemical synthesis. These findings highlight the need for continued innovation in hydrocarboxylation reactions using CO_2 as the C1 source.

Table 1. Evaluation of Hydrocarboxylation Methodologies

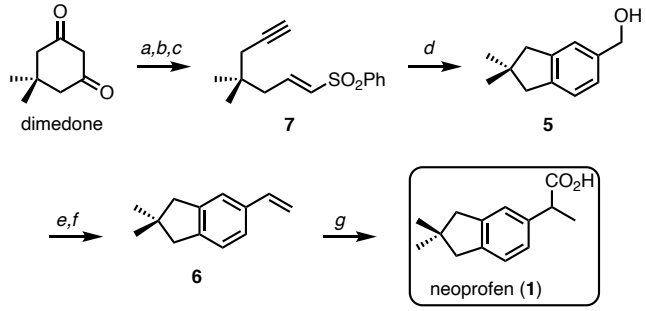


entry	method[a]	substrate	Yield[b] (%)	α:β[c]	Convn[b] (%)
1	A	***6***	***6***	–	***>95***
2		**9**	19	–	>95
3		**10**	6	–	>95
4	B	***6***	***26***	–	***88***
5		**9**	70	–	>95
6		**10**	61	–	>95
7	C	***6***	***14***	***>20:1***	***80***
8		**9**	82	3:1	91
9		**10**	42	2:1	88
10	D	***6***	***50***	***>20:1***	***>95***
11		**9**	94	>20:1	>95
12		**10**	66	>20:1	>95
13	E	***6***	***72***	–	***>95***

[a] Method A: 0.3 M styrene, 10 mol% $Ni(acac)_2$, 20 mol% Cs_2CO_3, 2.5 equiv $ZnEt_2$, CO_2 (1 atm), 16 h, THF, rt, then acid quench; Method B: 0.3 M styrene, 5 mol% $NiCl_2$•$6H_2O$, 5 mol% Me•DBBPY, 4.0 equiv Mn, 9.0 equiv H_2O, CO_2 (1 atm), 48 h, 0–25 °C, then acid quench; Method C: 0.3 M styrene, 5 mol% Cp_2TiCl_2, 1.1 equiv LiBr, 1.1 equiv iPrMgCl, Et_2O, 24 h, 30 °C, then quench CO_2 (1 atm), THF, 2 h, rt, then acid quench; Method D: 0.3 M styrene, 1 mol% $FeCl_2$, 1 mol% PDI, 1.5 equiv iPrMgCl, 1–4 h, rt, then CO_2 (1 atm), 1 h, rt, then acid quench; Method E: 0.3 M styrene, 5 mol% $Pd(OAc)_2$, 20 mol% PAr_3 (Ar = 4-CF_3 C_6H_4), 20 mol% Ac_2O, 3.0 equiv HCO_2H, $PhCH_3$, 80 °C, 48 h. [b] Yield and conversion determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Where no ratio is reported, the α-isomer was the sole identifiable regioisomer.

In conclusion, we report the target-oriented synthesis of neoprofen as a case-study in the broader challenge of crafting neopentylene-fused pharmacophores. Our recent oxidative cycloisomerization methodology[13] provided the initial synthetic entry via benzoate **4**, and we introduce a novel benzannulation — tandem Ni-catalyzed cyclotrimerization / elimination of sulfonyl enyne **7** — as a means of preparing neopentylene-fused arenes (e.g., **5** and **14**). The use of vinyl sulfone as an alkyne surrogate for Ni-catalyzed [2+2+2] cyclotrimerization is expected to be of broader synthetic utility and is the focus of on-going development. We also explored various styrene hydrocarboxylation methods, with the Shi method[22e] providing the highest yield for the neoprofen synthesis, ultimately realizing a 7-step synthesis of neoprofen in 36% overall yield from dimedone (Scheme 3). These findings will inform future work on the synthesis of neopentylene-fused pharmacophores and perhaps of polysubstituted arenes more broadly.

Scheme 3. Tandem cyclotrimerization / elimination of 9



(a) Tf_2O, pyridine, DCM, >95%; (b) DIBAL-H, THF, >95%; (c) PhO_2SCH_2 $P(O)(OEt)_2$, LDA, THF, 93%; (d) 10 mol% $Ni(CO)_2(PPh_3)_2$, 1.5 equiv. HC≡CCH_2OH, toluene, 100 °C, 16 h, 75%; (e) 5 mol% $CuBr_2$, bpy, TEMPO, 10 mol% NMI, CH_3CN, rt, air, 93%; (f) Ph_3P=CH_2, 86%; (g) 5 mol% $Pd(OAc)_2$, 20 mol% PAr_3 (Ar = 4-CF_3 C_6H_4), 20 mol% Ac_2O, 3.0 equiv HCO_2H, $PhCH_3$, 80 °C, 48 h, 72%; 36% overall yield.

EXPERIMENTAL SECTION

General Information. Commercially available compounds were purchased from Alfa Aesar, ACROS, or Sigma–Aldrich and used as received. The solvents were purchased from Fisher Scientific and dried via a Glass Contour solvent purification system. For reactions requiring elevated temperatures, reaction mixtures were heated using heat blocks contoured to the size and shape of the flask. Column chromatography was performed on either a Biotage instrument or on hand-packed silica gel flash columns. Air and moisture sensitive compounds were manipulated under nitrogen using Schlenk technique or in a nitrogen filled glovebox. ^1H and ^{13}C NMR spectra were recorded on JEOL and Agilent 400MHz NMR spectrometers. Deuterated chloroform was purchased from Cambridge Isotope Laboratories. Chemical shifts (δ) are reported in parts per million and referenced to the internal standard, tetramethylsilane (TMS), and/or the residual solvent peaks (e.g., $CHCl_3$). High Resolution Mass Spectrometry (HRMS) data were obtained on a Hybrid Quadrupole-Orbitrap Mass Spectrometer or APCI-Q-TOF.

3-Hydroxy-5,5-dimethylcyclohex-1-en-1-yltrifluoromethanesulfonate (2) (a) To a solution of dimedone (5.0 g, 36 mmol, 1 equiv) in dichloromethane (0.2M) under nitrogen was added pyridine (5.7 mL, 71 mmol, 2 equiv). The mixture was then stirred at -78°C for 10 minutes, then trifluoromethanesulfonic anhydride (6.6 mL, 39 mmol, 1.1 equiv) was added drop wise via syringe. The temperature was maintained for an additional 20 minutes, then warmed to room temperature over 30 minutes. The starting material consumption was monitored via TLC, following this the reaction was quenched with 1M HCl (72 mL). The reaction was extracted 3 times with diethyl ether (3x40 mL). The resulting organic layers were washed with aqueous Na_2CO_3 and water, dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography eluent mixture: 2-5%

EtOAc/Hexane to give the triflate (9.2 g, 34 mmol, 95%), which was used in step (b). The ^{1}H and ^{13}C NMR data were as previously reported.[8]

(b) To a solution of triflate from step (a) (9.2 g, 34 mmol, 1 equiv) in THF (0.25M) at -78°C was slowly added DIBAL-H (1.0M in toluene, 40.6 mL, 41 mmol, 1.2 equiv). The reaction mixture was stirred at -78°C for 10 minutes then warmed to room temperature and stirred for an additional 30 minutes. The reaction was diluted with diethyl ether (100 mL), cooled to 0°C and quenched by the addition of water and 15% NaOH. The mixture was stirred for 15 minutes upon a gel formation, MgSO4 was added and stirred for an additional 15 minutes. Vacuum filtration, rotary evaporation, and column chromatography (eluent mixture: 5-20% EtOAc/Hexanes) gave product **2** (8.8 g, 32.0 mmol, 95%). The ^{1}H and ^{13}C NMR data were as previously reported.[8]

Ethyl (2*E*,4*E*)-7,7-dimethyldeca-2,4-dien-9-ynoate (3) Diisopropylamine (1.1 mL, 7.6 mmol, 2.1 equiv) was added to a flask containing THF (0.1M) under N_2 gas. The flask was cooled to -78°C and kept at this temperature for 15 minutes. To this cooled solution n-BuLi (1.6M in hexanes, 4.8 mL, 2.1 equiv, 7.6 mmol) was added dropwise. The reaction was stirred at -78°C for 15 minutes, warmed to 0°C for 25 minutes and then cooled to -78°C. To the cold reaction, a solution of **2** (1.0 g, 3.6 mmol, 1 equiv) was added slowly followed by addition of ethyl-E-4-(diethoxyphosphoryl)but-2-enoate. The reaction was held at -78°C for an additional 10 minutes, warmed to room temperature slowly, and then heated at 60°C for 2 hours. After consumption of starting material, as confirmed by TLC, the reaction was cooled and quenched with a saturated NH_4Cl solution and a small amount of water to maintain a homogeneous aqueous layer. The product was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated by rotary evaporation. The resulting crude oil was purified by silica gel chromatography using 0-5% eluent mixture of EtOAc/hexanes to give dienyne **3** (655 mg, 81%) as a clear yellow-tinted oil. The ^{1}H and ^{13}C NMR data were as previously reported.[13]

Ethyl-*E*-4-(diethoxyphosphoryl)but-2-enoate The preparation was modified from Greirson et al.[24] *E*-ethyl-4-bromobut-2-enoate (75% assay, 5.33 g , 28 mmol, 1 equiv) was added to triethyl phosphite (4.63 g, 28 mmol, 1.0 equiv) at 120°C and stirred for 1 hour. Distillation of the reaction mixture provided the desired product as a yellow-orange oil (6.1 g, 89%). The ^{1}H and ^{13}C NMR data were as previously reported.[24]

Ethyl 2,2-dimethyl-2,3-dihydro-1*H*-indene-5-carboxylate (4) To a solution of dienyne **3** (500 mg, 2.2 mmol, 1 equiv) in CH_2Cl_2 (0.05M) under N_2 gas, $[RhCl(nbd)]_2$ (10.5 mg, 0.02 mmol, 0.01 equiv) and $AgSbF_6$ (31.2 mg, 0.08 mmol, 0.04 equiv) were added sequentially at room temperature over a period of 30 minutes. DDQ (631 mg, 2.7 mmol, 1.2 equiv) was added after **3** was consumed, as confirmed by TLC, and the resulting mixture was stirred for an additional 2 hours. The reaction was quenched with 5 mL of 15% aqueous NaOH, extracted with CH_2Cl_2 (3 x 10 mL), and concentrated by rotary evaporation. The residue was purified by silica gel chromatography, eluting with 0-10% EtOAc/Hexanes, to give **4** (381 mg, 77%) as a light-yellow oil. The ^{1}H and ^{13}C NMR data were as previously reported.[13]

(2,2-Dimethyl-2,3-dihydro-1*H*-inden-5-yl)methanol (5) — by reduction of ester 4. A solution of ester **4** (627 mg, 2.9 mmol, 1 equiv) in DCM (0.1M) was cooled to -78°C, DIBAL (6.3 mL, 6.3 mmol, 2.2 equiv) was added dropwise, and stirred at constant temperature for 1 hour. Following completion of the reaction, as confirmed by TLC, the solution was warmed to room temperature, quenched with EtOAc (10 mL) and potassium sodium tartrate (Rochelle's salt, 10 mL). The reaction was further diluted with EtOAc and stirred for approximately 2 hours until two clearly separable layers formed. The layers were separated, the organics were extracted with EtOAc (3 x 20 mL), and the combined organic layers were concentrated by rotary evaporation. The residue was purified by silica gel chromatography, eluting with 0-10% EtOAc/hexanes, to produce alcohol **5** as a clear, light-yellow oil (480 mg, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18-7.10 (m, 3H), 5.06 (s, 1H), 4.64 (s,1H), 2.72-2.71 (m, 4H), 1.15 (s, 6H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 143.8, 140.7, 133.4, 132.9, 129.4, 127.6, 81.4, 71.0, 42.7, 34.4, 31.7, 26.8. HRMS (ESI^+) calculated for $C_{12}H_{17}O^+$ $[M+H^+]$ 177.1274; found: 177.1273.

2,2-Dimethyl-5-vinyl-2,3-dihydro-1*H*-indene (6) (a) To a solution of **5** (962 mg, 5.5 mmol, 1 equiv) in acetonitrile (1M) the following were added sequentially, $CuBr_2$ (61 mg, 0.27 mmol, 0.05 equiv in 5.5 mL CH_3CN), 2,2'-bipyridine (43 mg, 0.27 mmol, 0.05 equiv in 5.5 mL CH_3CN), TEMPO (43 mg, 0.27 mmol, 0.05 equiv in 5.5 mL CH_3CN) and NMI (45 mg, 0.55 mmol, 0.05 equiv in 5.5 mL CH_3CN). The reaction was stirred overnight (12-18 hours). Following consumption of the starting material as determined by TLC, the reaction mixture was concentrated by rotary evaporation and purified by silica gel chromatography, eluting 0-5% EtOAc/Hexanes, to give 2,2-dimethyl-2,3-dihydro-1*H*-indene-5-carbaldehyde as a light-yellow oil (882 mg, 93%).[25] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.93 (s, 1H), 7.67-7.61 (m, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 2.77 (s, 2H), 2.70 (d, J =3.6, 2H), 1.15 (s, 6H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 192.5, 151.7, 144.8, 135.3, 129.2, 125.6, 125.3, 48.0, 47.2, 40.7, 28.7. HRMS (ESI^+) calculated for $C_{12}H_{15}O^+$ $[M+H^+]$ 175.1117; found: 175.1115.

(b) A solution of THF (0.1M) and PPh_3MeBr (946 mg, 2.6 mmol, 1.5 equiv) was cooled to -78°C. n-BuLi (1.6M in hexanes, 1.7 mL, 2.7 mmol, 1.6 equiv) was added dropwise and stirred for 30 minutes. The reaction was then warmed to room temperature, stirred for 1 hour and then cooled to -78°C again. The aldehyde from step (a) (302 mg, 1.7 mmol, 1 equiv) was added slowly and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with the addition of EtOAc and water until the mixture became biphasic. The aqueous layer was then extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation Purification by silica gel chromatography, eluting 0-5% EtOAc/Hexanes, gave alkene **6** as a yellow oil (257 mg, 86%).[26] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (s, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.70 (dd, J = 17.6, 10.9 Hz, 1H), 5.73 – 5.65 (m, 1H), 5.16 (d, J = 10.9 Hz, 1H), 2.72 – 2.69 (m, 4H), 1.15 (s, 6H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 144.0, 143.6, 137.3, 135.8, 124.8, 122.3, 112.5, 47.7, 40.4, 28.9. HRMS (ESI^+) calculated for $C_{13}H_{17}^+$ $[M+H^+]$ 173.1325; found: 173.1325.

2-(2,2-Dimethyl-2,3-dihydro-1*H*-inden-5-yl)propanoic acid (1) — by hydrocarboxylation. To a mixture of $Pd(OAc)_2$ (9.8 mg, 0.04 mmol, 0.05 equiv), tris(4-trifluoromethylphenyl)phosphine (81.2 mg, 0.17 mmol, 0.2 equiv), and toluene (0.50 mL, 1M) in a septum-sealed vial (2 dram) was

added via syringe successive solutions of **6** (150 mg, 0.87 mmol, 1 equiv in 0.37 mL toluene), formic acid (99 μL, 2.6 mmol, 3 equiv) and Ac_2O (16 μL, 0.17 mmol, 0.2 equiv) . The septum was removed and the vial sealed with a Teflon cap. The reaction mixture was stirred at 80 °C for 48 hours, cooled to room temperature, diluted with CH_2Cl_2, and transferred into a separatory funnel followed by the addition of 1M NaOH. The mixture was washed with CH_2Cl_2 with vigorous shaking. The aqueous layer was acidified to pH 1-2 with 3M HCl, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to give carboxylic acid **1** as a white solid (136.8 mg, 72%). The ^1H and ^{13}C NMR data were as previously reported.[1]

Diethyl (phenylsulfonyl)methylphosphonate A mixture of chloromethyl phenyl sulfide (2.0 mL, 15 mmol, 1 equiv) and triethyl phosphite (3.1 mL, 18 mmol, 1.2 equiv) was heated at reflux in a 120 °C-bath for 72 hours. The excess reagent was removed via short path distillation (90°C, 12.3 psi) to give a clear, colorless oil (3.1 g, 80%) that was subsequently dissolved in methanol (47.6 mL, 0.25M) and cooled to 0°C. Potassium peroxymonosulfate (10.5 g, 17 mmol, 1.5 equiv) in water (47.6 mL, 0.25M) was added dropwise. The solution was warmed to room temperature and stirred for 18 hours. The solution was filtered and extracted with CH_2Cl_2 (3 x 50 mL), the filtrate was washed with CH_2Cl_2, and the CH_2Cl_2 layers were combined, dried ($MgSO_4$), and concentrated by rotary evaporation to give the phosphonate product as a clear, colorless oil (2.8 g, 81%). The ^1H and ^{13}C NMR data were as previously reported.[27]

(*E*)-4,4-Dimethyl-1-(phenylsulfonyl)-1-hepten-6-yne (7) A 0.1M solution of diisopropylamine (2.2 mL, 15 mmol, 2.1 equiv) in THF was cooled at –78 °C for 15 min, and n-BuLi, (1.6M in hexanes, 9.6 mL, 15 mmol, 2.1 equiv), was added dropwise. The reaction mixture was stirred at –78 °C for 15 minutes, warmed to 0°C for 20 minutes, then re-cooled to –78 °C. A solution of **2** (2.0 g, 7.3 mmol, 1 equiv) in 3 mL THF was added slowly dropwise, followed by diethyl(phenylsulfonyl)-methylphosphonate (2.3 g, 8.0 mmol, 1.1 equiv). The reaction mixture was maintained at –78 °C for an additional 10 minutes, warmed to room temperature, and heated at 60°C for 2 hours. After consumption of the starting material, as confirmed by TLC, the reaction was quenched with a saturated NH_4Cl solution and a small amount of water to maintain a homogeneous aqueous layer. The mixture was extracted with Et_2O, and the organics were washed with brine and concentrated under reduced pressure. The product was purified via silica gel chromatography (0-10% eluent mixture of EtOAc/hexanes) to give **7** as a clear yellow-tinted oil (1.87 g, 93%).[8] ^1H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, J = 8.8 Hz, 2H), 7.63–7.51 (m, 3H), 6.98 (dt, J = 15.7, 8.0 Hz, 1H), 6.36 (d, J = 14.9 Hz, 1H), 2.25 (d, J = 8.8 Hz, 2H), 2.06 (d, J = 2.6 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H), 0.99 (s, 6H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-d) δ 143.7, 140.7, 133.3, 132.9, 129.3, 127.5, 81.3, 70.9, 42.6, 34.4, 31.7, 26.7. HRMS (ESI^+) calculated for $C_{15}H_{17}O_2S^+$ [$M–H^+$] 261.0955; found: 261.0954.

(2,2-Dimethyl-2,3-dihydro-1*H*-inden-5-yl)methanol (5) — by Ni-catalyzed cyclotrimerization with 7. In a glovebox, sulfonyl enyne **7** (21.8 mg, 0.08 mmol, 1 equiv) was weighed into a vial and subsequently dissolved by a solution of $Ni(PPh_3)_2(CO)_2$ (5.3 mg, 0.008 mmol, 0.1 equiv) in 1 mL of dry toluene (0.03M). The vial was sealed by a Teflon-septum cap, removed from the glovebox, connected via inlet syringe to a Schlenk line under N_2 gas, and a solution of propargyl alcohol (7.0 μL, 0.12 mmol, 1.5 equiv) in dry toluene (1.8 mL) was added. The reaction mixture was heated at 100 °C for 16 hours, then cooled to room temperature. The product was purified by silica gel chromatography (eluting 0-10% EtOAc/Hexanes) to produce **5** as a clear, light-yellow oil (11 mg, 75%). The ^1H and ^{13}C NMR data were as reported above for compound **5**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website: Expanded presentation of data and observations from comparison of hydrocarboxylation methods A-D (cf. Table 1) and copies of ^1H and ^{13}C NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was supported by a National Science Foundation (NSF) Career Award (CHE-1752986). We gratefully acknowledge additional support from West Virginia University, the Don and Linda Brodie Fund, and the Eberly Family Foundation. The NMR spectrometer used in this research was acquired through the NSF Major Research Instrumentation (MRI) program (CHE-1228336).

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