JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

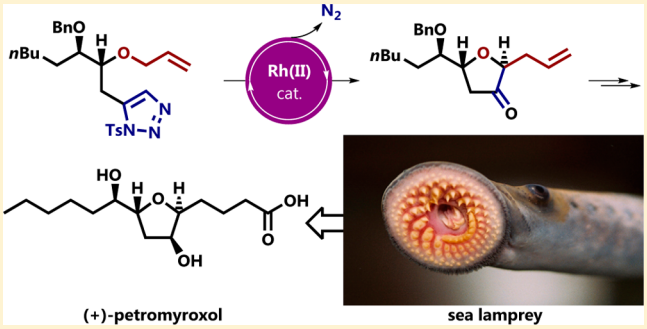
Enantioselective Synthesis of (+)-Petromyroxol, Enabled by Rhodium-Catalyzed Denitrogenation and Rearrangement of a 1-Sulfonyl-1,2,3-Triazole

Alistair Boyer*

School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, U.K.

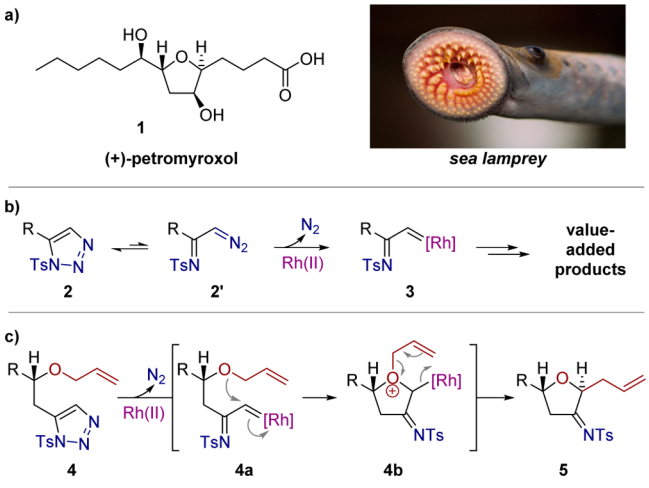
Supporting Information

ABSTRACT: Petromyroxol is a nonracemic mixture of enantiomeric oxylipids isolated from water conditioned with larval sea lamprey. The (+)-antipode exhibits interesting biological properties, but only 1 mg was isolated from >100 000 L of water. Recently, transition-metal-catalyzed denitrogenation of 1-sulfonyl-1,2,3-triazoles has emerged as a powerful strategy for the synthesis of value-added products, including efficient diastereocontrolled construction of tetrahydrofurans. This methodology enabled the rapid development of the first synthesis of (+)-petromyroxol in 9 steps and 20% overall yield from a readily accessible starting material.



Petromyroxols are tetrahydrofuran-containing natural products that were first described in December 2014 (Scheme 1a).[1] They were isolated as a nonracemic 64:36 mixture of (−)/(+) enantiomers, and their structure was deduced by a combination of detailed NMR studies, comparison with known substituted tetrahydrofurans, and Mosher ester analysis. The natural products were isolated from water conditioned with larvae of the sea lamprey, *Petromyrzon marinus* L. The sea lamprey is a parasitic fish that has invaded the Great Lakes and, having no natural predator, has caused serious damage to the fish population, harming the ecosystem and economy of the region.[2] This problem has spurred the investigation of several novel aquatic pest-control strategies, including the study of aquatic pheromones.[3] Importantly, although it is the less-abundant enantiomer, (+)-petromyroxol (**1**) was demonstrated to trigger a significant olfactory response in the sea lamprey.[1] However, the possibility of further study of the biochemistry of (+)-petromyroxol was hampered because only 2.9 mg of the enantiomeric mixture were isolated from over 100 000 L of water.[1]

Scheme 1. Introduction (Photo credit: T. Lawrence, Great Lakes Fishery Commission)



Petromyroxol is a tetrahydrofuran diol from the acetogenin[4] family and one of the vast array of natural compounds that contain a tetrahydrofuran.[5] The prevalence of this fundamental motif has driven the creation of a wide range of innovative and novel methodology for its construction.[6] Recently, this set was expanded to include an efficient stereocontrolled syntheses of substituted THFs, capitalizing on the reactivity of a 1-sulfonyl-1,2,3-triazole (1-ST) motif.[7] Within 1-STs (e.g., **2**, Scheme 1b), the incorporation of a sulfonyl group fine-tunes the reactivity of a 1,2,3-triazole so that, in the presence of a transition metal catalyst, a Dimroth equilibrium can be established (**2**⇌**2′**). The catalyst promotes denitrogenation, forming an α-imino carbenoid **3**. Overall, this strategy has been successfully demonstrated by the transformation of readily accessible building blocks into value-added products.[8] In the case of 1-STs bearing a pendant allyl ether (e.g., **4**), the corresponding carbenoid **4a** can trap an oxygen lone pair to form an oxonium ylide **4b**. The charge is neutralized by [2,3]-sigmatropic rearrangement[9] to form a new C−C bond with high levels of efficiency and stereocontrol.[7]

This manuscript describes the application of this potent approach toward THF construction to the first total synthesis

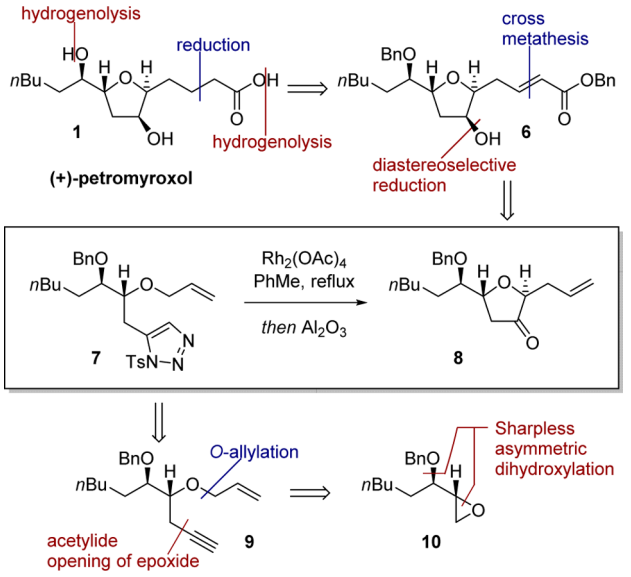
Received: February 19, 2015
Published: April 20, 2015

DOI: 10.1021/acs.joc.5b00399
J. Org. Chem. 2015, 80, 4771−4775

of (+)-petromyroxol. The completion of the synthesis not only confirms the structure of the natural product but also provides valuable access to material required for further investigation of the biology of this fascinating creature.

The keystone to developing a synthesis strategy came with recognition that the central THF motif could be constructed by diastereoselective rhodium-catalyzed denitrogenation and rearrangement of the β-allyloxy-1-ST **7** into a *trans*-2,5-disubstituted dihydrofuran-3-one **8** (Scheme 2).[7a]

Scheme 2. Retrosynthetic Analysis

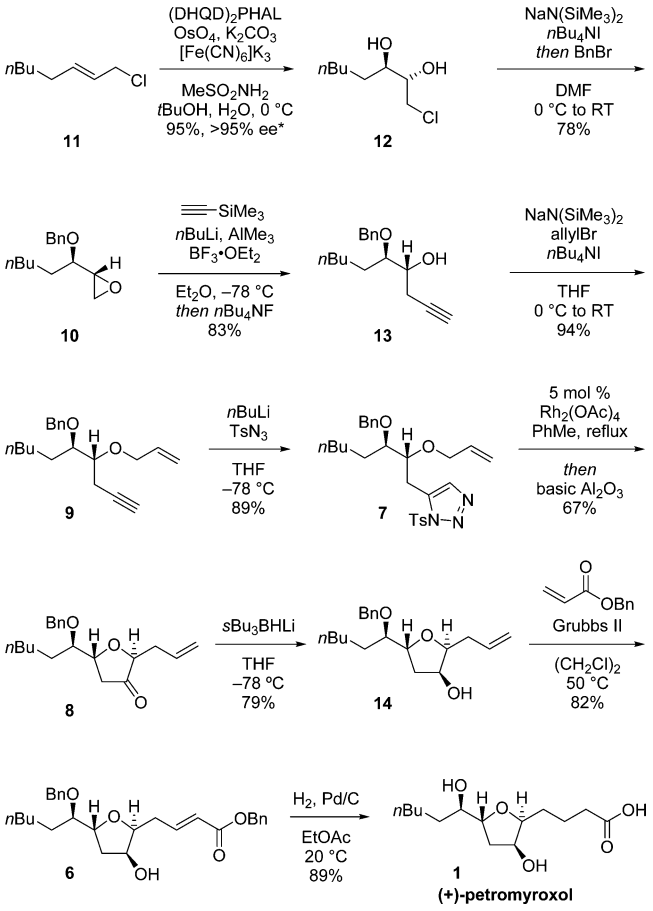


The resulting heterocycle **8** would act as a suitable building block for the remainder of the synthesis, with ketone and allyl groups providing excellent handles for further manipulation. The ketone **8** could be reduced diastereoselectively[10] to give an alcohol with the correct geometry as found in the natural compound. The allyl group would allow introduction of the remaining carbon atom through cross metathesis (**6**). Importantly, the 1-ST substrate **7** for the pivotal transformation would be accessible from the corresponding alkyne **9**, which could in turn come from the *O*-allylation of the product of acetylide epoxide ring opening of appropriately protected 1,2-epoxy-3-octanol **10**.

The synthesis commenced with formation of the requisite epoxide (Scheme 3). Sharpless dihydroxylation[11] of readily accessible *trans*-1-chloro-2-octene (**11**)[12] led to the 1,2-diol **12** with excellent yield (95%) and enantioselectivity (>95% ee).[13] Treatment of the diol **12** with 2 equiv of base followed by benzyl bromide led to tandem epoxide formation−protection of the secondary alcohol (i.e., **10**). The key alkyne motif for 1-ST formation was installed by nucleophilic opening of the epoxide with an aluminum acetylide[14] to give the requisite terminal alkyne (i.e., **13**). Then, the free alcohol was smoothly converted to the allyl ether under standard conditions (**8** → **9**). The triazole motif was installed under anionic conditions by treatment of the terminal alkyne with *n*BuLi followed by TsN_3, resulting in efficient and regioselective formation of the 5-substituted-1-ST **7**.[15]

The conditions developed previously,[7a] namely 5 mol % rhodium(II) acetate in toluene at reflux, were used to promote denitrogenation and rearrangement to form the furanone **8**

Scheme 3. Synthesis



with the desired *trans*-2,5-configuration. In contrast to previous observations,[7a] during this reaction baseline impurities were observed. It is suggested that the unhindered[7b] benzyl ether presents a number of alternative reaction pathways including [1,2]-sigmatropic shift and C−H bond functionalization. However, formation of the five-membered oxonium intermediate species and rearrangement to give the dihydrofuran-3-one was the major pathway giving the heterocyclic scaffold **8** in 67% isolated yield of the desired isomer. The final stereocenter within the target molecule was installed under substrate control, with a hydride delivered opposite to the allyl substituent with >10:1 selectivity (**8** → **14**).[10] Cross-metathesis between the Type I terminal alkene and Type II benzyl acrylate using Grubb's second generation catalyst proceeded in excellent yield accomplishing installation of the one remaining carbon atom (**14** → **6**).[9g,16] Finally, the homologated compound **6** was treated with hydrogen and palladium on carbon to effect concomitant reduction of the alkene and hydrogenolysis of the benzyl ether and benzyl ester to complete the synthesis of (+)-petromyroxol (**1**) in excellent yield. The NMR spectra and optical rotation data were in excellent agreement with those reported for the naturally sourced compound, unambiguously confirming the structure.

Overall, the first enantioselective synthesis of (+)-petromyroxol was completed in only 9 steps with an overall yield of 20% from a readily accessible allylic chloride. The core tetrahydrofuran motif within the natural product was formed by denitrogenation and rearrangement of a 1-ST. This synthesis

DOI: 10.1021/acs.joc.5b00399
J. Org. Chem. 2015, 80, 4771−4775

exemplifies the versatile reactivity of the 1-ST motif as a tool for enabling rapid construction of valuable molecular architecture.

EXPERIMENTAL SECTION

General Considerations. ^{1}H chemical shift data are given in units δ relative to the residual protic solvent where $\delta(CDCl_3)$ = 7.26 ppm, s. ^{13}C chemical shift data were recorded with broad-band proton decoupling and are given in units δ relative to the solvent where $\delta(CDCl_3)$ = 77.0 ppm, t. Peak assignments were made using 2D COSY, HSQC, and HMBC experiments. IR spectra were recorded as thin films using an ATR accessory. Where appropriate, reactions were performed in oven-dried glassware under an an argon atmosphere. Purification was performed using Merck Geduran Si 60 (40−63 μm) silica gel. THF, Et_2O, and toluene were passed through a column of activated alumina under nitrogen before use. Petrol refers to fractions of petroleum ether collected between 40 and 60 °C.

(+)-(*R,R*)-1-Chlorooctane-2,3-diol (12). A suspension of potassium hexacyanoferrate(III) (8.98 g, 27.3 mmol, 4.0 equiv), potassium carbonate (3.77 g, 27.3 mmol, 4.0 equiv), methanesulfonamide (649 mg, 6.8 mmol, 1.0 equiv), $(DHQD)_2PHAL$ (69 mg, 0.09 mmol, 1.3 mol %), and osmium tetroxide (2.5 wt % in *t*BuOH, 0.42 cm^3, 0.04 mmol, 0.6 mol %) in *t*BuOH (25 cm^3) and water (25 cm^3) was stirred at ambient temperature for 0.5 h. The mixture was cooled to 0 °C, and (*E*)-1-chlorooct-2-ene **11**[12] (1.00 g, 6.8 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C for 18 h, and then the reaction was quenched by the addition of sodium sulfite (13.8 g, 109 mmol, 16 equiv) and stirred at ambient temperature for 2 h. The mixture was diluted with water (25 cm^3) and extracted with ethyl acetate (5 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product (main contaminant $MeSO_2NH_2$) was purified by flash column chromatography (gradient from 10 to 20% EtOAc in petrol) to yield the title compound **12** (1.18 g, 95%) as a white crystalline solid. Mp 66−67 °C; $[\alpha]_D^{20}$ +13.3 (*c* 1.5, MeOH); ν_{max} 3310br, 3219br, 2957, 2936, 2861, 1458, and 1126 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 3.71−3.59 (4 H, m, 2 × CH−OH and CH_2Cl), 2.53 (1 H, d, *J* 4.5 Hz, OH), 2.03 (1 H, d, *J* 4.9 Hz, OH), 1.62−1.23 (8 H, m, CH_2) and 0.90 (3 H, t, *J* 6.8 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 73.7 (CH−OH), 71.6 (CH−OH), 47.0 (CH_2Cl), 33.7 (CH_2), 31.7 (CH_2), 25.2 (CH_2), 22.6 (CH_2), and 14.0 (CH_3). The enantiomeric excess (>95% ee) was determined for the subsequent compound **10**. Data consistent with previously reported values.[11c]

(+)-(*R,R*)-3-Benzyloxy-1,2-epoxyoctane (10). Sodium bis(trimethylsilyl)amide (2 M solution in THF, 5.6 cm^3, 11.2 mmol, 2.02 equiv) was added to a solution of diol **12** (1.00 g, 5.6 mmol, 1.0 equiv) and tetrabutylammonium iodide (410 mg, 1.1 mmol, 0.2 equiv) in DMF (50 cm^3) at 0 °C. The mixture was stirred at 0 °C for 1 h, then benzyl bromide (1.3 cm^3, 11.1 mmol, 2.0 equiv) was added, and the mixture was stirred at ambient temperature for 18 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (25 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were washed with aqueous lithium chloride (10 wt %/vol, 50 cm^3) dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient from 1 to 2% EtOAc in petrol) to yield the title compound **10** (1.02 g, 78%) as a colorless oil. $[\alpha]_D^{23}$ +32.2 (*c* 1.6, $CHCl_3$); ν_{max} 2955, 2930, 2859, 1454, 1090, and 1071 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.40−7.26 (5 H, m, Ph), 4.84 (1 H, d, *J* 11.9 Hz, benzyl OCH_A), 4.58 (1 H, d, *J* 11.9 Hz, benzyl OCH_B), 3.08−3.00 (2 H, m, CH−OBn and epoxide CH), 2.78 (1 H, dd, *J* 4.8 and 4.1 Hz, epoxide CH_A), 2.49 (1 H, dd, *J* 4.8 and 2.4 Hz, epoxide CH_B), 1.72−1.18 (8 H, m, CH_2) and 0.88 (3 H, t, *J* 7.1 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 138.7 (Ph), 128.3 (2 × Ph), 127.8 (2 × Ph), 127.4 (Ph), 80.5 (CH−OBn), 71.6 (benzyl OCH_2), 55.1 (epoxide CH), 43.1 (epoxide CH_2), 32.3 (CH_2), 31.8 (CH_2), 25.2 (CH_2), 22.5 (CH_2), and 14.0 (CH_3); *m/z* (ESI-Qq-TOF) 257.1504 ($[M + Na]^+ = C_{15}H_{22}NaO_2^+$ requires 257.1512). The enantiomeric excess was determined to be >95% (Chiralpak AD-H, 0.46Ø × 25 cm, 0.5% *i*PrOH/hexane, 1 cm^3 min^{-1}, 205 nm, major enantiomer t_{ret} = 9.5 min, minor enantiomer t_{ret} = 11.5 min).

(−)-(*R,R*)-5-Benzyloxydec-1-yn-4-ol (13). *n*-Butyllithium (2.2 M solution in hexanes, 2.2 cm^3, 4.9 mmol, 1.3 equiv) was added to a stirred solution of ethynyltrimethylsilane (0.79 cm^3, 5.6 mmol, 1.5 equiv) in diethyl ether (25 cm^3) at −78 °C. The mixture was stirred for 15 min at −78 °C, then trimethylaluminum (2 M in toluene, 2.4 cm^3, 4.9 mmol, 1.3 equiv) was added, and the mixture stirred for 0.5 h at −78 °C and then 0.5 h at −45 °C. The mixture was recooled to −78 °C, and a solution of epoxide **10** (875 mg, 3.7 mmol, 1.0 equiv) in diethyl ether (5 cm^3 with washings) was added followed by $BF_3{\cdot}OEt_2$ (0.51 cm^3, 4.1 mmol, 1.1 equiv) down the cold flask wall. The reaction mixture was stirred for 1 h at −78 °C, and then the reaction was quenched by the addition of methanol (1.5 cm^3). The mixture was allowed to warm to ambient temperature, and saturated aqueous ammonium chloride (30 cm^3) was added. The aqueous layer was extracted with ethyl acetate (2 × 30 cm^3), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was dissolved in THF (30 cm^3), and *n*Bu_4NF (1 M in THF, 7.5 cm^3, 7.5 mmol, 2.0 equiv) was added. The mixture was stirred for 16 h at ambient temperature and then washed with half saturated brine (30 cm^3). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to yield the title compound **13** (807 mg, 83%) as a colorless oil. $[\alpha]_D^{23}$ −40.4 (*c* 1.0, $CHCl_3$); ν_{max} 3451br, 3308, 2951, 2930, 2859, 1454, 1069, and 1028 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.40−7.27 (5 H, m, Ph), 4.68 (1 H, d, *J* 11.3 Hz, benzyl OCH_A), 4.54 (1 H, d, *J* 11.3 Hz, benzyl OCH_B), 3.75 (1 H, dtd, *J* 6.7, 6.3, and 4.1 Hz, CH−OH), 3.56 (1 H, td, *J* 6.1 and 4.1 Hz, CH−OBn), 2.50 (1 H, ddd, *J* 16.8, 6.3, and 2.7 Hz, $CH_AC{\equiv}C$), 2.44 (1 H, ddd, *J* 16.8, 6.3, and 2.7 Hz, $CH_BC{\equiv}C$), 2.39 (1 H, br d, *J* 6.7 Hz, OH), 2.03 (1 H, t, *J* 2.7 Hz, C≡CH), 1.71−1.56 (2 H, m, CH_2), 1.44−1.24 (6 H, m, CH_2) and 0.89 (3 H, t, *J* 6.9 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 138.2 (Ph), 128.5 (2 × Ph), 127.9 (2 × Ph), 127.8 (Ph), 80.9 (C≡C), 80.1 (CH−OBn), 72.6 (benzyl OCH_2), 71.0 (CH−OH), 70.3 (C≡C), 32.0 (CH_2), 30.2 (CH_2), 24.9 (CH_2), 23.8 ($CH_2C{\equiv}C$), 22.6 (CH_2) and 14.0 (CH_3); *m/z* (ESI-Qq-TOF) 283.1681 ($[M + Na]^+ = C_{17}H_{24}NaO_2^+$ requires 283.1669).

(−)-(*R,R*)-4-Allyloxy-5-benzyloxydec-1-yne (9). Sodium bis(trimethylsilyl)amide (1 M solution in THF, 4.1 cm^3, 4.1 mmol, 1.5 equiv), followed by allyl bromide (0.35 cm^3, 4.1 mmol, 1.5 equiv) and tetrabutylammonium iodide (300 mg, 0.8 mmol, 0.3 equiv), was added to a stirred solution of alcohol **13** (705 mg, 2.7 mmol, 1.0 equiv) in DMF (25 cm^3) at 0 °C. The mixture was stirred for 12 h, allowing the mixture to reach ambient temperature, and then the reaction was quenched by the addition of saturated aqueous ammonium chloride (30 cm^3). The mixture was extracted with diethyl ether (3 × 30 cm^3), and the combined organic layers were washed with aqueous lithium chloride (10 wt %/vol, 70 cm^3) dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient from 1 to 2% Et_2O in petrol) to yield the title compound **9** (766 mg, 94%) as a colorless oil. $[\alpha]_D^{23}$ −8.8 (*c* 0.85, $CHCl_3$); ν_{max} 3310, 2953, 2926, 2857, 1454, 1085, and 1074 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.39−7.26 (5 H, m, Ph), 5.93 (1 H, ddt, *J* 17.2, 10.3, and 5.8 Hz, allyl =CH), 5.28 (1 H, ddt, *J* 17.2, 1.6, and 1.4 Hz, allyl $=CH_Z$), 5.18 (1 H, ddt, *J* 10.3, 1.6, and 1.4 Hz, allyl $=CH_E$), 4.65 (1 H, d, *J* 11.4 Hz, benzyl OCH_A), 4.59 (1 H, d, *J* 11.4 Hz, benzyl OCH_B), 4.21 (1 H, ddt, *J* 12.7, 5.8, and 1.4 Hz, allyl OCH_A), 4.08 (1 H, ddt, *J* 12.7, 5.8, and 1.4 Hz, allyl OCH_B), 3.62−3.53 (2 H, m, CH−OBn and CH−Oallyl), 2.57 (1 H, ddd, *J* 17.0, 5.3, and 2.7 Hz, $CH_AC{\equiv}C$), 2.40 (1 H, ddd, *J* 17.0, 6.4, and 2.7 Hz, $CH_BC{\equiv}C$), 1.98 (1 H, t, *J* 2.7 Hz, C≡CH), 1.67−1.19 (8 H, m, CH_2), and 0.88 (3 H, t, *J* 6.9 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 138.7 (Ph), 135.0 (allyl =CH), 128.3 (2 × Ph), 128.0 (2 × Ph), 127.5 (Ph), 117.1 (allyl $=CH_2$), 81.8 (C≡C), 79.7 (CH−OBn), 78.4 (CH−Oallyl), 72.9 (benzyl OCH_2), 71.9 (allyl OCH_2), 69.6 (C≡C), 31.9 (CH_2), 29.8 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 20.3 ($CH_2C{\equiv}C$) and 14.0 (CH_3); *m/z* (ESI-Qq-TOF) 323.1967 ($[M + Na]^+ = C_{20}H_{28}NaO_2^+$ requires 323.1982).

(+)-(*R,R*)-5-(2-Allyloxy-3-benzyloxyoctyl)-1-tosyl-1,2,3-triazole (7). *n*-Butyllithium (2.5 M solution in hexanes, 0.44 cm^3, 1.1

DOI: 10.1021/acs.joc.5b00399
J. Org. Chem. 2015, 80, 4771−4775

mmol, 1.1 equiv) was added to a stirred solution of alkyne **9** (300 mg, 1.0 mmol, 1.0 equiv) in THF (5 cm^3) at −78 °C. The mixture was stirred for 0.5 h at −78 °C, then *p*-toluenesulfonyl azide[17] (1.6 M solution in THF, 0.69 cm^3, 1.1 mmol, 1.1 equiv) was added, and the mixture stirred for 0.5 h at −78 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 cm^3), diluted with ethyl acetate (10 cm^3), and allowed to warm to ambient temperature. The aqueous layer was extracted with ethyl acetate (2 × 10 cm^3), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (rapid: <20 min, <20 fractions, gradient from 10 to 20% EtOAc in petrol) to yield the title compound **7** (442 mg, 89%) as a colorless oil. N.B. When neat, 1-STs can undergo isomerization and decomposition;[15,18] this compound was stored as solution before use. $[\alpha]_D^{21}$ +53.6 (*c* 0.5, $CHCl_3$); ν_{max} 2955, 2930, 2861, 1389, 1196, 1182, and 1086 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.92 (2 H, d, *J* 8.4 Hz, Ts Ar), 7.41−7.28 (8 H, m, Ts Ar, Ph and triazole-H), 5.63 (1 H, ddt, *J* 17.2, 10.3, and 5.8 Hz, allyl =CH), 5.12 (1 H, ddt, *J* 17.2, 1.5, and 1.3 Hz, allyl =CH_Z), 5.08 (1 H, ddt, *J* 10.3, 1.5, and 1.3 Hz, allyl =CH_E), 4.66 (1 H, d, *J* 11.5 Hz, benzyl OCH_A), 4.58 (1 H, d, *J* 11.5 Hz, benzyl OCH_B), 3.91 (1 H, ddt, *J* 12.5, 5.8, and 1.3 Hz, allyl OCH_A), 3.78 (1 H, ddd, *J* 9.7, 4.1, and 3.2 Hz, CH−Oallyl), 3.76 (1 H, ddt, *J* 12.5, 5.8, and 1.3 Hz, allyl OCH_B), 3.51 (1 H, ddd, *J* 8.3, 4.1, and 4.0 Hz, CH−OBn), 3.29 (1 H, ddd, *J* 15.2, 3.2, and 0.5 Hz, CH_A-triazole), 3.02 (1 H, dd, *J* 15.2 and 9.7 Hz, CH_B-triazole), 2.43 (3 H, s, Ts Me), 1.72−1.20 (8 H, m, CH_2), and 0.90 (3 H, t, *J* 7.0 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 146.9 (Ts Ar), 138.4 (Ph), 137.6 (triazole), 134.4 (Ts Ar), 134.2 (allyl =CH), 133.8 (triazole-H), 130.3 (2 × Ts Ar), 128.6 (2 × Ts Ar), 128.4 (2 × Ph), 128.1 (2 × Ph), 127.8 (Ph), 117.5 (allyl =CH_2), 79.1 (CH−OBn), 77.8 (CH−Oallyl), 72.5 (benzyl OCH_2), 71.9 (allyl OCH_2), 31.9 (CH_2), 29.1 (CH_2), 25.8 (CH_2), 25.0 (CH_2−triazole), 22.6 (CH_2), 21.8 (Ts Me) and 14.0 (CH_3); *m*/*z* (ESI-Qq-TOF) 520.2234 ($[M + Na]^+$ = $C_{27}H_{35}N_3NaO_4S^+$ requires 520.2240).

(−)-(2*S*,5*R*)-2-Allyl-5-((*R*)-1-benzyloxyhexyl)dihydrofuran-3-one (8). Rhodium(II) acetate dimer (9 mg, 0.02 mmol, 5 mol %) was added to a stirred solution of 1-tosyl-1,2,3-triazole **7** (210 mg, 0.42 mmol, 1.0 equiv) in toluene (17 cm^3). The reaction mixture was heated under reflux for 0.5 h and then cooled to ambient temperature. Alumina (Basic, pH 9.5, Brockmann activity III, i.e. 6 wt % H_2O, 4.2 g) was added, and the reaction mixture was stirred at ambient temperature for 0.5 h. The mixture was directly purified by flash column chromatography (gradient from 10 to 20% EtOAc in petrol) to give the title compound **8** (89 mg, 67%) as a colorless oil. $[\alpha]_D^{19}$ −89.3 (*c* 1.1, $CHCl_3$); ν_{max} 2953, 2928, 2859, 1757, 1454, and 1071 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.37−7.31 (2 H, m, Ph), 7.31−7.25 (3 H, m, Ph), 5.82 (1 H, ddt, *J* 17.1, 10.2, and 6.9 Hz, allyl =CH), 5.14 (1 H, ddt, *J* 17.1, 1.9, and 1.5 Hz, allyl =CH_Z), 5.10 (1 H, ddt, *J* 10.2, 1.9, and 1.1 Hz, allyl =CH_E), 4.62 (1 H, d, *J* 11.5 Hz, benzyl OCH_A), 4.47 (1 H, d, *J* 11.5 Hz, benzyl OCH_B), 4.44 (1 H, ddd, *J* 8.2, 3.8, and 3.2 Hz, furanone 5-H), 4.13 (1 H, dd, *J* 6.9 and 4.7 Hz, furanone 2-H), 3.33 (1 H, td, *J* 6.6 and 3.2 Hz, CH−OBn), 2.49−2.42 (1 H, m, allyl CH_A), 2.47 (1 H, dd, *J* 17.8 and 8.2 Hz, furanone 4-H_A), 2.34−2.26 (1 H, m, allyl CH_B), 2.31 (1 H, dd, *J* 17.8 and 3.8 Hz, furanone 4-H_B), 1.77−1.64 (2 H, m, CH_2), 1.47−1.24 (6 H, m, CH_2), and 0.90 (3 H, t, *J* 6.9 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 215.6 (C=O), 138.1 (Ph), 133.2 (allyl =CH), 128.4 (2 × Ph), 127.9 (2 × Ph), 127.7 (Ph), 118.0 (allyl =CH_2), 81.8 (CH−OBn), 79.4 (furanone 2-H), 76.1 (furanone 5-H), 72.5 (benzyl OCH_2), 39.4 (furanone 4-H_2), 36.0 (allyl CH_2), 32.0 (CH_2), 30.0 (CH_2), 25.3 (CH_2), 22.6 (CH_2), and 14.0 (CH_3); *m*/*z* (ESI-Qq-TOF) 339.1915 ($[M + Na]^+$ = $C_{20}H_{28}NaO_3^+$ requires 339.1931).

(+)-(2*S*,3*S*,5*R*)-2-Allyl-5-((*R*)-1-benzyloxyhexyl)tetrahydrofuran-3-ol (14). Lithium tri-*sec*-butylborohydride (1 M in THF, 0.47 cm^3, 0.47 mmol, 2.0 equiv) was added to a stirred solution of furan-3-one **8** (75 mg, 0.24 mmol, 1.0 equiv) in THF (2.5 cm^3) at −78 °C. The reaction mixture was stirred for 2.5 h, and the reaction was quenched by the addition of water (0.2 cm^3), H_2O_2 (30 vols, 0.2 cm^3), and NaOH (1 M, 0.02 cm^3) and stirred at ambient temperature for 16 h. Ethyl acetate (5 cm^3) and brine (5 cm^3) were added, and the aqueous layer was extracted with ethyl acetate (2 × 5 cm^3). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by flash column chromatography (gradient from 5% to 10% to 20% EtOAc in petrol) to give a small amount of the undesired diastereoisomer (<1:10) followed by the title compound **14** (60 mg, 79%) as a white solid. Mp 39−41 °C; $[\alpha]_D^{22}$ +18.2 (*c* 0.89, $CHCl_3$); ν_{max} 3437br, 2953, 2930, 2859, 1454, 1090, 1067, and 1028 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.38−7.24 (5 H, m, Ph), 5.88 (1 H, dddd, *J* 17.1, 10.2, 7.5, and 6.5 Hz, allyl =CH), 5.19 (1 H, ddt, *J* 17.1, 1.8, and 1.6 Hz, allyl =CH_Z), 5.09 (1 H, ddt, *J* 10.2, 1.8, and 1.2 Hz, allyl =CH_E), 4.71 (1 H, d, *J* 11.6 Hz, benzyl OCH_A), 4.63 (1 H, d, *J* 11.6 Hz, benzyl OCH_B), 4.33 (1 H, ddd, *J* 9.1, 6.8, and 5.7 Hz, furan 5-H), 4.28−4.23 (1 H, m, furan 3-H), 3.89 (1 H, ddd, *J* 7.2, 7.2, and 2.8 Hz, furan 2-H), 3.32 (1 H, ddd, *J* 7.2, 5.7, and 5.2 Hz, CH−OBn), 2.54−2.35 (2 H, m, allyl CH_2), 1.97 (1 H, ddd, *J* 13.5, 6.8, and 1.4 Hz, furan 7-H_A), 1.92 (1 H, ddd, *J* 13.5, 9.1, and 4.3 Hz, furan 7-H_B), 1.69 (1 H, d, *J* 5.8 Hz, OH), 1.55−1.20 (8 H, m, CH_2) and 0.88 (3 H, t, *J* 7.0 Hz, CH_3); δ_C(101 MHz; $CDCl_3$): 138.9 (Ph), 134.8 (allyl =CH), 128.2 (2 × Ph), 127.9 (2 × Ph), 127.4 (Ph), 117.0 (allyl =CH_2), 81.6 (furan 2-H), 81.0 (CH−OBn), 79.3 (furan 3-H), 72.9 (furan 5-H), 72.7 (benzyl OCH_2), 37.5 (furan 4-H_2), 33.8 (allyl CH_2), 31.9 (CH_2), 30.5 (CH_2), 25.3 (CH_2), 22.6 (CH_2), and 14.0 (CH_3); *m*/*z* (ESI-Qq-TOF) 341.2073 ($[M + Na]^+$ = $C_{20}H_{30}NaO_3^+$ requires 341.2087).

(+)-2,3-Dehydro-1,9-*O*,*O*-dibenzylpetromyroxol (6). A solution of alkene **14** (58 mg, 0.18 mmol, 1.0 equiv) and benzyl acrylate (236 mg, 1.5 mmol, 8.0 equiv) in dichloromethane (3 cm^3) was degassed (bubbling Ar, 5 min), then Grubb's second generation catalyst (15 mg, 0.02 mmol, 10 mol %) was added, and the reaction mixture was stirred at 50 °C. After 2.5 h the reaction was quenched by the addition of methanol (0.1 cm^3) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (25% EtOAc in petrol) to give the title compound **6** (68 mg, 82%) as a colorless oil. $[\alpha]_D^{19}$ +7.4 (*c* 1.0, $CHCl_3$); ν_{max} 3439br, 2951, 2930, 2859, 1721, 1657, 1454, 1377, 1317, 1263, 1163, 1092, 1069, 1042, and 1026 cm^{-1}; δ_H(400 MHz; $CDCl_3$): 7.38−7.23 (10 H, m, Ph), 7.06 (1 H, dt, *J* 15.6 and 7.1 Hz, 3-H), 6.02 (1 H, dt, *J* 15.6 and 1.5 Hz, 2-H), 5.17 (2 H, s, CO_2Bn), 4.67 (1 H, d, *J* 11.6 Hz, 9-OCH_APh), 4.62 (1 H, d, *J* 11.6 Hz, 9-OCH_BPh), 4.32 (1 H, td, *J* 7.9 and 5.6 Hz, 8-H), 4.26 (1 H, ddt, *J* 6.1, 3.0, and 2.8 Hz, 6-H), 3.94 (1 H, td, *J* 6.9 and 3.0 Hz, 5-H), 3.30 (1 H, ddd, *J* 7.1, 5.6, and 5.5 Hz, 9-H), 2.60 (1 H, dddd, *J* 14.7, 7.1, 6.9, and 1.5 Hz, 4-H_A), 2.55 (1 H, dddd, *J* 14.7, 7.1, 6.9, and 1.5 Hz, 4-H_B), 1.95 (2 H, dd, *J* 7.9 and 2.8 Hz, 7-H_2), 1.72 (1 H, d, *J* 6.1 Hz, 6-OH), 1.55−1.20 (8 H, m, 10−13-H_2) and 0.88 (3 H, t, *J* 7.0 Hz, 14-H_3); δ_C(101 MHz; $CDCl_3$): 166.2 (C1), 145.9 (C3), 138.8 (Ph), 136.0 (Ph), 128.5 (2 × Ph), 128.2 (2 × Ph), 128.2 (2 × Ph), 128.1 (Ph), 127.9 (2 × Ph), 127.5 (Ph), 122.9 (C2), 80.9 (C9), 80.7 (C5), 79.4 (C8), 72.8 (C6), 72.7 (benzyl OCH_2), 66.1 (benzyl OCH_2), 37.8 (C7), 32.3 (C4), 31.9 (C10−C13), 30.5 (C10−C13), 25.3 (C10−C13), 22.6 (C10−C13), and 14.0 (C14); *m*/*z* (ESI-Qq-TOF) 475.2442 ($[M + Na]^+$ = $C_{28}H_{36}NaO_5^+$ requires 475.2455).

(+)-Petromyroxol (1). A mixture of benzyl ester **6** (65 mg, 0.14 mmol, 1.0 equiv) and palladium (10 wt % on carbon, 15 mg, 0.01 mmol, 10 mol %) in ethyl acetate (1 cm^3) was evacuated and refilled with hydrogen (3×) and stirred under an atmosphere of hydrogen for 36 h. The reaction vessel was purged, and the crude mixture was purified by flash column chromatography (5% AcOH in EtOAc) to give (+)-petromyroxol **1** (35 mg, 89%) as an amorphous solid. Mp 51−53 °C; $[\alpha]_D^{19}$ +20.5 (*c* 1.7, $CHCl_3$); ν_{max} 3404br, 2952, 2932, 2871, 2860, 1710, 1408, 1292, 1249, 1070, and 1060 cm^{-1}; δ_H(500 MHz; $CDCl_3$): 5.04 (3 H, br, OH), 4.28 (1 H, dd, *J* 4.5 and 2.9 Hz, 6-H), 4.05 (1 H, ddd, *J* 9.3, 6.9, and 6.5 Hz, 8-H), 3.77 (1 H, td, *J* 6.5, 6.5, and 2.9 Hz, 5-H), 3.38 (1 H, ddd, *J* 7.3, 6.9, and 4.0 Hz, 9-H), 2.40 (1 H, dt, *J* 16.3 and 5.9 Hz, 2-H_A), 2.37 (1 H, dt, *J* 16.3 and 5.6 Hz, 2-H_B), 2.02 (1 H, dd, *J* 13.5 and 6.5 Hz, 7-H_A), 1.85 (1 H, ddd, *J* 13.5, 9.3, and 4.5 Hz, 7-H_B), 1.74−1.60 (4 H, m, 3-H_2 and 4-H_2), 1.54−1.46 (1 H, m, 11-H_A), 1.43−1.21 (7 H, m, 10-H_2, 11-H_B, 12-H_2, and 13-H_2) and 0.88 (3 H, t, *J* 6.9 Hz, 14-H_3); δ_C(126 MHz; $CDCl_3$): 178.3 (C1), 82.4 (C5), 80.6 (C8), 74.2 (C9), 73.1 (C6), 37.5 (C7), 33.9 (C2), 33.0 (C10), 31.9 (C12), 28.1 (C4), 25.2 (C11), 22.6 (C13), 21.2 (C3) and 14.0 (C14); *m*/*z* (ESI-Qq-TOF$^+$) 297.1658 ([M +

DOI: 10.1021/acs.joc.5b00399
J. Org. Chem. 2015, 80, 4771−4775

Na]$^+$ = $C_{14}H_{26}NaO_5^+$ requires 297.1672); *m/z* (ESI-Qq-TOF$^-$) 273.1709 ([M − H]$^-$ = $C_{14}H_{25}O_5^-$ requires 273.1707). The NMR peaks were sensitive to sample concentration; data reported for ca. 15 mg·cm^{-3}. Data consistent with those reported for the natural compound;[1] see Supporting Information for further comparison.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR Spectra for compounds **6**−**14**, HPLC chromatogram for compound **10**, TLC data, and a detailed comparison of data collected for natural and synthetic petromyroxol **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: alistair@boyer-research.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The author gratefully acknowledges support from the Ramsay Memorial Fellowships Trust and the University of Glasgow, School of Chemistry as well as valuable discussions with Prof. J. Stephen Clark, Filippo Romiti, and Prof. Weiming Li.

■ REFERENCES

(1) Li, K.; Huertas, M.; Brant, C.; Chung-Davidson, Y.-W.; Bussy, U.; Hoye, T. R.; Li, W. *Org. Lett.* **2014**, *17*, 286−289.

(2) Smith, B. R.; Tibbles, J. J. *Can. J. Fish. Aquat. Sci.* **1980**, *37*, 1780−1801.

(3) (a) Sorensen, P. W.; Fine, J. M.; Dvornikovs, V.; Jeffrey, C. S.; Shao, F.; Wang, J.; Vrieze, L. A.; Anderson, K. R.; Hoye, T. R. *Nat. Chem. Biol.* **2005**, *1*, 324−328. (b) Li, W.; Scott, A. P.; Siefkes, M. J.; Yan, H.; Liu, Q.; Yun, S.-S.; Gage, D. A. *Science* **2002**, *296*, 138−141. (c) Li, K.; Brant, C. O.; Huertas, M.; Hur, S. K.; Li, W. *Org. Lett.* **2013**, *15*, 5924−5927. (d) Li, K.; Brant, C. O.; Siefkes, M. J.; Kruckman, H. G.; Li, W. *PLoS One* **2013**, *8*, e68157. (e) Li, K.; Siefkes, M. J.; Brant, C. O.; Li, W. *Steroids* **2012**, *77*, 806−810.

(4) (a) Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. *Beilstein J. Org. Chem.* **2008**, *4*, 48. (b) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (c) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540.

(5) (a) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567−4610. (b) Zhou, Z.-F.; Menna, M.; Cai, Y.-S.; Guo, Y.-W. *Chem. Rev.* **2015**, *115*, 1543−1596.

(6) (a) Jalce, G.; Franck, X.; Figadère, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537−2581. (b) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261−290.

(7) (a) Boyer, A. *Org. Lett.* **2014**, *16*, 1660−1663. (b) Boyer, A. *Org. Lett.* **2014**, *16*, 5878−5881.

(8) (a) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151−5162. (b) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862−872. (c) Anbarasan, P.; Yadagiri, D.; Rajasekar, S. *Synthesis* **2014**, *46*, 3004−3023. (d) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315.

(9) (a) Kirmse, W.; Kapps, M. *Chem. Ber.* **1968**, *101*, 994−1003. (b) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094−5102. (c) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060−6062. (d) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062−6063. (e) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193−6196. (f) Fu, J.; Shang, H.; Wang, Z.; Chang, L.; Shao, W.; Yang, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4198−4202. (g) Han, M.; Bae, J.; Choi, J.; Tae, J. *Synlett* **2013**, *24*, 2077−2080. (h) Fu, J.; Shen, H.; Chang, Y.; Li, C.; Gong, J.; Yang, Z. *Chem.—Eur. J.* **2014**, *20*, 12881−12888. (i) Clark, J. S.; Hansen, K. E. *Chem.—Eur. J.* **2014**, *20*, 5454−5459. (j) Clark, J. S.; Romiti, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 10072−10075.

(10) (a) Fernández de la Pradilla, R.; Castellanos, A.; Osante, I.; Colomer, I.; Sánchez, M. I. *J. Org. Chem.* **2008**, *74*, 170−181. (b) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'Sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641−2644.

(11) (a) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469−3472. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (c) Zhang, Z.-B.; Wang, Z.-M.; Wang, Y.-X.; Liu, H.-Q.; Lei, G.-X.; Shi, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 53−57.

(12) Glueck, S. M.; Fabian, W. M. F.; Faber, K.; Mayer, S. F. *Chem.—Eur. J.* **2004**, *10*, 3467−3478.

(13) The ee was determined after the next step, for epoxide **10**.

(14) (a) Skrydstrup, T.; Bénéchie, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1990**, *31*, 7145−7148. (b) Fried, J.; Sih, J. C.; Lin, C. H.; Dalven, P. *J. Am. Chem. Soc.* **1972**, *94*, 4343−4345. (c) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745−6754.

(15) (a) Meza-Aviña, M. E.; Patel, M. K.; Lee, C. B.; Dietz, T. J.; Croatt, M. P. *Org. Lett.* **2011**, *13*, 2984−2987. (b) Meza-Aviña, M. E.; Patel, M. K.; Croatt, M. P. *Tetrahedron* **2013**, *69*, 7840−7846.

(16) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(17) Curphey, T. J. *Org. Prep. Proced. Int.* **1981**, *13*, 112−115.

(18) Yamauchi, M.; Miura, T.; Murakami, M. *Heterocycles* **2009**, *80*, 177−181.

DOI: 10.1021/acs.joc.5b00399
J. Org. Chem. 2015, 80, 4771−4775