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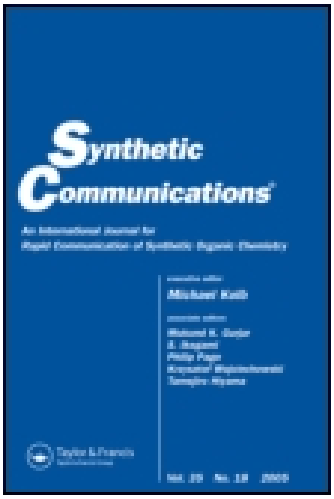

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Large-Scale Preparation of Long-Chain ADMET Synthons

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Accepted author version posted online: 05 May 2014.Published online: 01 Jul 2014.

To cite this article: Nicolas F. Sauty , Hong Li , Lucas Caire da Silva & Kenneth B. Wagener (2014) Large-Scale Preparation of Long-Chain ADMET Synthons, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:16, 2409-2415, DOI: 10.1080/00397911.2014.899606

To link to this article: http://dx.doi.org/10.1080/00397911.2014.899606

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Synthetic Communications®, 44: 2409–2415, 2014
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2014.899606

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LARGE-SCALE PREPARATION OF LONG-CHAIN ADMET SYNTHONS

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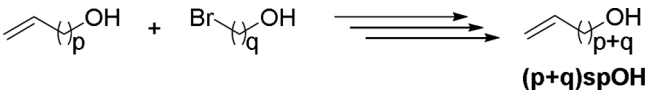
GRAPHICAL ABSTRACT



Abstract *We report a convenient process with minimal purification to produce large quantities of α,ω-alkenyl alcohols. These reagents are indispensable precursors in ADMET chemistry. Icos-19-en-1-ol, nonacos-28-en-1-ol, and octatriacont-37-en-1-ol were produced effortlessly in large quantities (up to 45 g in a single batch) from undec-10-en-1-ol. By extension of the method, any desired methylene run length in the ADMET precursor can be achieved.*

Keywords ADMET; alkenyl synthons; homologation; precision polymers

INTRODUCTION

Acyclic diene metathesis (ADMET) polymerization, first reported in 1991 by the Wagener research group,[1] has been extensively studied since then[2] as a versatile tool to access precision polyolefins.[3–5] These polymers feature a functionality positioned at unequivocal intervals along a polymer chain and display enhanced properties as compared to their random counterparts. For instance, in the precision butyl-branched polyethylene, a linear relationship between the branch frequency and fusion temperature of the polymer was reported.[6]

Precision polyolefins are synthesized from their corresponding symmetrical α,ω-diene monomers. The olefin moiety and the desired number of methylene spacers are in many instances introduced with the use of α,ω-alkenyl bromides[7–9] or with α,ω-alkenyl alcohols.[10] Reducing the functionality frequency along the chain in precision polymers correlates with augmenting the methylene run length in the

Received January 20, 2014.
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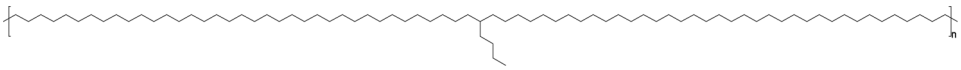

Figure 1. Precision butyl-branched polyethylene with alkyl branch every 75th carbon.

monomer, and therefore in alkenyl synthons. These intermediates are commercially available or can be synthesized[11] for methylene run lengths up to 10; however, no convenient methodology to produce long-chain α,ω-alkenyl synthons has been reported thus far, although there is a synthesis to prepare an α,ω-alkenyl bromide precursor containing 36 methylene spacers, with 4 leading to a butyl branch on every 75th carbon (Fig. 1).

Nonetheless, onerous purification processes were precluded from yielding more than milligrams of the polymer of interest, supplementary work exploiting such lengthy spacers has been pursued. This small-scale limitation has also confined precision polymers to spectral and morphologic characterization only. Larger scales are strongly desired for further analyses and mechanical studies, leading to the evident need for a convenient synthetic route to access ADMET precursors with lengthy spacers in large quantities. This is the object of the research, a result never achieved before. We report a dependable synthesis based on a series of well-established reactions, for an iterative and tunable n-carbon homologation of α,ω-alkenyl alcohols on the multidecagram scale, thereby offering an easy route to alkenyl synthons of any desired methylene run length.

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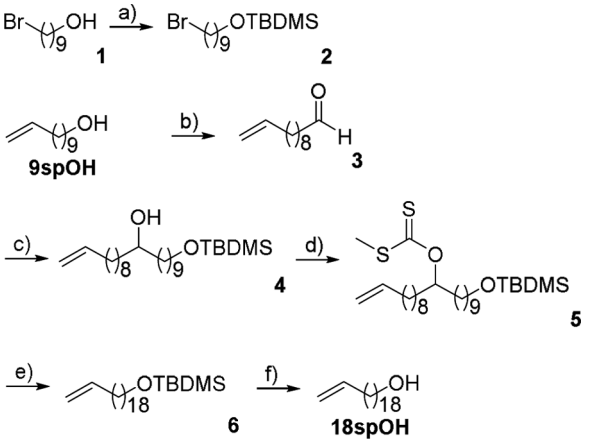
RESULTS AND DISCUSSION

Preparation of nonisomerized alkenyl synthons is paramount in the design of flawless precision polymers. While internal olefins would remain active toward most metathesis catalysts,[12] albeit at a lower conversion rate,[13] an ill-defined material with a statistical distribution of methylene run lengths would result from the use of an isomerized reagent, thereby destroying the precision character. Detectable isomerization by ^{1}H NMR or infrared (IR) inevitably disqualifies any starting material. Commercially available synthons must be tested prior to use as some lots may contain up to 5% isomerized reagent, based on our experience. Our new methodology avoids isomerization completely. The synthesis relies on two building blocks: the parent α,ω-alkenyl alcohol to be homologated by n carbons, and an α,ω-bromoalcohol containing n methylene spacers as a homologation agent. We are interested in synthesizing alkenyl synthons containing 18, 27, and 36 methylene spacers. 9-Bromo-1-nonanol[14] (**1**) is the sole homologation reagent utilized in this report.

The methodology for the homologation of α,ω-alkenyl alcohols is presented in Scheme 1. To simplify our presentation, α,ω-alkenyl alcohols containing X methylene spacers are abbreviated XspOH. Initial investigations were conducted on a gram scale and all the intermediates shown in the sequence were isolated while establishing the methodology. Step-to-step purifications were not necessary.

tert-Butyldimethylsilyl chloride was chosen to protect **1** for its excellent stability in most environments and facile cleavage.[15–18] Following a recently published



Scheme 1. Synthesis of icos-19-en-1-ol. Reagents and conditions: (a) 1-methylimidazole, I_2, TBDMSCl, CH_2Cl_2, rt, 10 min (98%); (b) PCC, CH_2Cl_2, rt, 2 h (90%); (c) (9-((*tert*-butyldimethylsilyl)oxy)nonyl) magnesium bromide, Et_2O, 35 °C, overnight (96%); (d) (i) NaH, imidazole, THF, 0 °C to rt, 2 h; (ii) CS_2, 0 °C to rt, overnight; (iii) MeI, 0 °C to rt, 4 h (93%); (e) TEA, H_3PO_2, AIBN, dioxane, reflux, 3 h (77%); (f) $CuCl_2 \cdot 2H_2O$, acetone/water (95:5), reflux, 2 h (98%).

high-yield protection procedure by Stawinski and coworkers,[19] the corresponding silyl ether **2** was obtained in 98% yield in only 10 min. Batches as large as 150 g could be purified using simple silica plugs. Commercially available aldehyde **3** can shorten the synthesis although lots containing detectable levels of isomerization must be discarded. Compound **3** was also synthesized by oxidation of undec-10-en-1-ol (9spOH) with pyridinium chlorochromate, affording the desired intermediate in 90% yield. Silyl ether **2** was treated with magnesium, and the corresponding Grignard reagent was reacted with the previously prepared aldehyde **3**, affording secondary alcohol **4** in 96% yield. Xanthate **5** was obtained by treatment of **4** with sodium hydride, carbon disulfide, and methyl iodide at 0 °C to attenuate the formation of undesired products.[20] Reductive deoxygenation of the xanthate was first attempted under standard Barton–McCombie conditions,[21] but an unidentified by-product had to be arduously removed from deoxygenated intermediate **6**.

As the occurrence mentioned previously would have most certainly precluded scale up, an alternative deoxygenation procedure was done. Using hypophosphorous acid[22] instead of tributyltin hydride successfully promoted **6** and alleviated our purification concerns. The presence of free radicals may induce olefin isomerization;[23] however, no detectable levels of isomerization by ^{1}H NMR resulted from this reaction. Typically, NMR experiments with concentrated samples (400 μmol/mL $CDCl_3$) and large number of transients (512 or more) enable the detection of low levels isomerization (0.5% and above). Subsequent deprotection of the resulting deoxygenated compound was done by refluxing an acetone–water mixture containing 5 mol% of copper(II) chloride dihydrate, as demonstrated by Tan et al.[24] 18spOH was isolated as white flakes with limited solubility with an overall yield of 59% for the first homologation.

The synthesis was repeated on a large scale with no systematic purification after each step. No systematic purification is key to the success we report herein.

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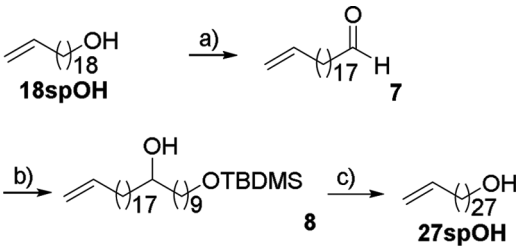

Scheme 2. Synthesis of nonacos-28-en-1-ol. Reagents and conditions: (a) (i) PCC, CH_2Cl_2, reflux, 2 h (88%); (b) crude, (9-((*tert*-butyldimethylsilyl)oxy)nonyl)magnesium bromide, Et_2O, 35 °C, overnight (94%); (c) (i) NaH, imidazole, THF, 0 °C to rt, 2 h; (ii) CS_2, 0 °C to rt, overnight; (iii) MeI, 0 °C to rt, 4 h; (iv) crude, TEA, H_3PO_2, AIBN, dioxane, reflux, 3 h; (v) crude, $CuCl_2 \cdot 2H_2O$, acetone/water (95:5), reflux, 2 h (66%).

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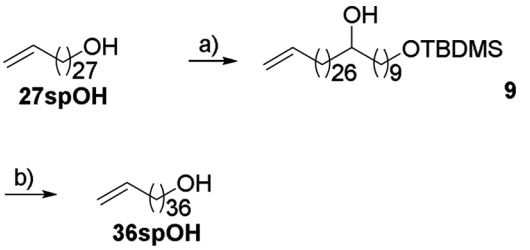
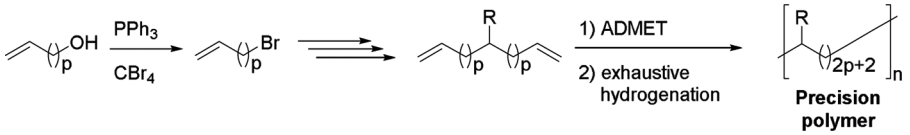
In fact, each subsequent reaction was performed using the crude product of the former, with the exception of **3** and **4**, which were refined by distillation and flash column chromatography respectively. The desired homologated alcohol 18spOH was obtained pure after recrystallization in pentane (about 5 mL pentane per gram of 18spOH). The synthetic sequence afforded approximately 45 g of 18spOH from 45 g of 9spOH, equivalent to an overall 58% yield.

With the intention of producing 27spOH, the synthetic sequence was similarly repeated with limited purifications (Scheme 2). Compounds **7** and **8** were both purified by flash column chromatography, and 27spOH was recrystallized from hexanes. A yield of 20 g of the latter resulted from 26 g of 18spOH, corresponding to 55% overall yield for the second homologation.

Likewise, 36spOH, which in our previous work was especially difficult to make, was produced with only two purification steps (Scheme 3). Purification of **7** was performed by flash column chromatography using near boiling eluent mixtures (50–55 °C) to circumvent the lower solubility of the intermediate. The subsequent xanthate was formed at higher temperatures and reduced concentration as **7** was not soluble in tetrahydrofuran (THF) at 0 °C. As for the deprotection, twice as much solvent (in comparison with the deprotection of **6**) as well as addition of heptane was necessary to solubilize the parent silyl ether of 36spOH. The unprotected alcohol



Scheme 3. Synthesis of octatriacont-37-en-1-ol. Reagents and conditions: (a) (i) PCC, CH_2Cl_2, reflux, 2 h; (ii) crude, (9-((*tert*-butyldimethylsilyl)oxy)nonyl)magnesium bromide, Et_2O, 35 °C, overnight (79%); (b) (i) NaH, imidazole, THF, rt to 40 °C, 2 h; (ii) CS_2, rt, overnight; (iii) MeI, rt, 4 h; (iv) crude, TEA, H_3PO_2, AIBN, dioxane, reflux, 3 h; (v) crude, $CuCl_2 \cdot 2H_2O$, acetone/water/heptane (90:5:5), reflux, 2 h (60%).



Scheme 4. Synthesis of precision polymers from alkenyl alcohols.

precipitated as the reaction proceeded, and fully crystallized as white pure flakes upon cooling of the reaction mixture. Nearly 10 g of 36spOH were obtained from 16 g of 27spOH corresponding to 48% overall yield for the third homologation. The reduced overall yield was attributed to the limited solubility of the intermediates, not to the actual chemistry at hand. In most instances, a diminished conversion of the starting materials was observed. 36spOH was synthesized from 10-undecen-1-ol after three consecutive 9-carbon homologations. Based on our reported yields, 48 g of 36spOH could be prepared from 100 g of 9spOH.

CONCLUSION

To conclude, we report a successful, convenient, and reliable synthetic route to prepare large quantities of lengthy α,ω-alkenyl alcohols without isomerization of the olefin moiety. We effectively prepared alkenyl alcohols containing 18, 27, and 36 methylene units. The alkenyl alcohols can be transformed straightforwardly to their corresponding alkenyl bromides counterparts, building blocks of precision polymers (Scheme 4).

We are convinced that the straightforward and limited number of purifications can indubitably promote a fast production of alkenyl synthons on a much greater scale than we described in this report. Virtually any methylene run length can be accessed by tuning the homologating agent.

EXPERIMENTAL

Icos-19-en-1-ol (18spOH)

In a 1-L, flame-dried, three-necked, round-bottom flask, **4** (97.2 g, 227.8 mmol) and THF (300 mL) were added. The solution was cooled to 0 °C and sodium hydride 60% in mineral oil (15.1 g, 378.1 mmol) was carefully added. After 30 min, the mixture was allowed to slowly warm up to room temperature. After 2 h, the reaction was cooled to 0 °C, and carbon disulfide (52.0 g, 683.2 mmol) was added dropwise. After 3 h, the mixture was allowed to slowly warm to room temperature. Eight h later, the reaction was cooled to 0 °C, and methyl iodide (48.4 g, 341.6 mmol) was added dropwise to the reaction. After 1 h, the reaction was allowed to slowly warm to room temperature, after which the mixture became more viscous. Four h later, the reaction was cooled to 0 °C and was carefully quenched with a saturated ammonium chloride solution. Diethyl ether was added, and aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine and dried over sodium sulfate. Removal of the solvents in vacuo afforded an impure orange oil (124.3 g). Triethylamine (350 mL, 2.51 mol) and a hypophosphorous acid solution in water

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(50% w/v, 150.3 g, 588.7 mmol) were added to a 2-L flask equipped with a condenser containing the impure oil and dioxane (770 mL). The mixture was refluxed and an AIBN solution (7.48 g, 45.55 mmol) in dioxane (100 mL) was added continuously over 4 h. After disappearance of the starting material by thin-layer chromatography (TLC) analysis, the solvents were removed in vacuo, and 100 mL of hexanes were added. The resulting mixture was passed through a silica plug using hexanes/ethyl acetate (98:2) as the mobile phase. The solvents were removed in vacuo, affording a slightly yellow oil (68.4 g). Water (82 mL) and copper(II) chloride dihydrate (1.94 g, 11.39 mmol) were added to a 2-L flask equipped with a condenser containing the yellow oil and acetone (1.6 L). The green mixture was refluxed for 2 h, after which the solvents were removed in vacuo. The resulting solid was dissolved in hexanes, and the solution was filtered over a bed of celite. The solvent was removed in vacuo, and the crude solid was recrystallized in pentane (250 mL), affording 18spOH as pure white flakes (45.3 g, 67% from **4**). Melting point: 56–57 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ (ppm) 5.83 (ddt, $J = 17.0$, 10.2, 6.6 Hz, 1H, vinyl CH), 5.06–4.89 (m, 2H), 3.65 (t, $J = 6.6$ Hz), 2.10–1.99 (m, 2H), 1.73–1.18 (m, 32H); ^{13}C NMR (75 MHz, chloroform-*d*) δ (ppm) 139.5, 114.3, 63.2, 33.0, 32.0, 29.9, 29.9, 29.8, 29.82, 29.80, 29.78, 29.76, 29.73, 29.66, 29.4, 29.2, 26.0; IR $\upsilon_{max} = 3272$, 3079, 2922, 2849, 1647, 1464 cm^{-1}; DART/HRMS: $[M + NH_4]^+$ calculated for $C_{20}H_{40}O$: 314.3417; found: 314.3428. Elemental analysis, calculated: C, 81.01%; H, 13.60%. Found: C, 80.99%; H, 13.73%.

Characterization Data of 27spOH

Melting point: 78–79 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ (ppm) 5.82 (ddt, $J = 17.0$, 10.3, 6.7 Hz, 1H), 5.06–4.88 (m, 2H), 3.65 (t, $J = 6.6$ Hz, 2H), 2.11–1.98 (m, 2H), 1.18–1.62 (m, 50H); ^{13}C NMR (75 MHz, chloroform-*d*) δ (ppm) 139.5, 114.3, 63.3, 34.00, 33.0, 29.93, 29.85, 29.74, 29.66, 29.4, 29.2, 26.0; IR $\upsilon_{max} = 3326$, 3079, 2922, 2846, 1643, 1464 cm^{-1}; DART/HRMS: $[M + NH_4]^+$ calculated for $C_{29}H_{58}O$: 440.4826; found: 440.4831. Elemental analysis: calculated C, 82.39%; H, 13.83%. Found: C, 82.09%; H, 13.70%.

Characterization Data of 36spOH

Melting point: 90–92 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ (ppm) 5.83 (ddt, $J = 17.0$, 10.2, 6.6 Hz, 1H), 5.05–4.86 (m, 2H), 3.65 (t, $J = 6.6$ Hz, 2H), 2.05 (m, 2H), 1.26–1.62 (m, 68H); ^{13}C NMR (125 MHz, chloroform-*d*, 50 °C) δ (ppm) 139.5, 114.3, 63.4, 34.0, 33.1, 29.94, 29.91, 29.86, 29.85, 29.76, 29.70, 29.4, 29.2, 26.0; IR $\upsilon_{max} = 3323$, 3079, 2922, 2849, 1643, 1464 cm^{-1}; DART/HRMS: $[M + NH_4]^+$ calculated for $C_{38}H_{76}O$: 566.6234; found: 566.6232. Elemental analysis calculated: C, 83.13%; H, 13.95%. Found: C, 83.25%; H, 14.05%.

FUNDING

We gratefully acknowledge the National Science Foundation (DMR-1203136) and the Army Research Office (W911NF-13-1-0362) for the financial support of this research.

SUPPORTING INFORMATION

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