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Synthesis of a designed sesquiterpenoid that forms useful composites with peptides and related oligomers

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ABSTRACT

Efficient desymmetrization of isophthalaldehyde allows a scalable asymmetric synthesis of cinnamylated sesquiterpenoid **1**. We have shown that **1** forms useful, property-altered composites with peptides and related oligomers. The current synthesis promises to expand those efforts considerably.

We recently described structure **1** (Fig. 1) as a reagent capable of forming useful composites with peptides and related heteropolymers.[1] In short processing sequences, the molecule is amalgamated with unprotected polyamides in parallel—holding **1** constant and varying the oligomer. This provides us unique collections of complex peptidomimetics (e.g., **5**).[2] As our experiments in this area expand toward being systematic, an ample supply of pure **1** is essential. Herein we describe a preparation to meet those needs.

Our initial synthesis of **1** relied upon copper promoted 1,4-addition of homopropargylic organozinc species **3** to cinnamaldehyde **2**.[1] The resultant trimethylsilyl enol ether was parlayed ((1) PhSeCl; (2) HF/pyridine; (3) $CCl_3C(Me)_2CO_2Cl$, DMAP, pyridine; (4) $NaIO_4$) into isomeric enals **4**. Subsequent chiral imidazolidinone-catalyzed conjugate reduction[3] afforded **1**. In our hands, the conjugate reduction required high catalyst loads to proceed at a useful rate and provided **1** in moderate enantiomeric excess. This was inconvenient because the oily substance **1** could not be further resolved via crystallization.[4] To circumvent these limitations and to provide flexible, scalable access to optically active **1** and congeners, an alternate synthesis was developed.

Commercial isophthaldehyde is desymmetrized[5] via controlled olefination employing (*R*)-(−)phenylglycine derived phosphonoacetyl oxazolidinone **6** (Scheme 1).[6] Adduct **7** is then treated with vinyl magnesium chloride to generate a mixture of diastereoisomeric aryl vinyl carbinols **8**. $MeReO_3$ catalyzed allylic alcohol transposition[7] followed by in situ silylation with TBSCl affords a single isomer of cinnamyl ether **9**. Homopropargylic Grignard reagent **10**[8] is added conjugately to the acrylimide in **9** affording **11** in high yield and diastereomeric excess. After degradation of the silicon groups in **11** with TBAF, the terminal alkyne in **12** participates smoothly in a Sonogashira cross-coupling reaction with methylheptenone derived enol triflate **13**.[9] The resultant dieneyne containing imide **14** is reduced with a twofold excess of (*i*-$Bu)_2AlH$ in toluene to afford aldehyde **15**, from which target **1** is derived via acylation with 2,2,2-trichloro-1,1-dimethylethyl chloroformate.

The above route entails eight linear steps, proceeds in 17% overall yield, and provides **1** in 91% ee.[10,11] It gives access to our target

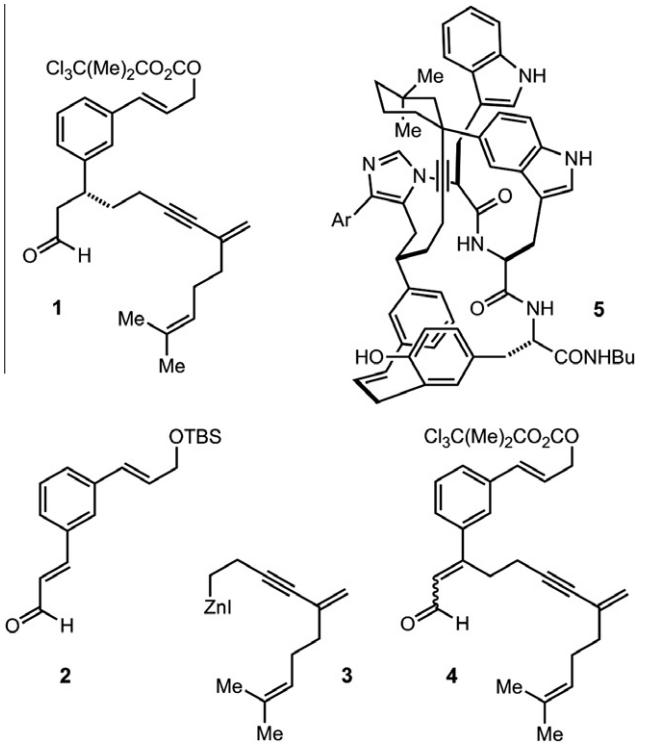

Figure 1. Structure **1** can be incorporated into peptides to generate complex composites such as **5** (Ref. 1). Our initial synthesis of **1** utilized fragments **2** and **3** en route to penultimate intermediate **4**.

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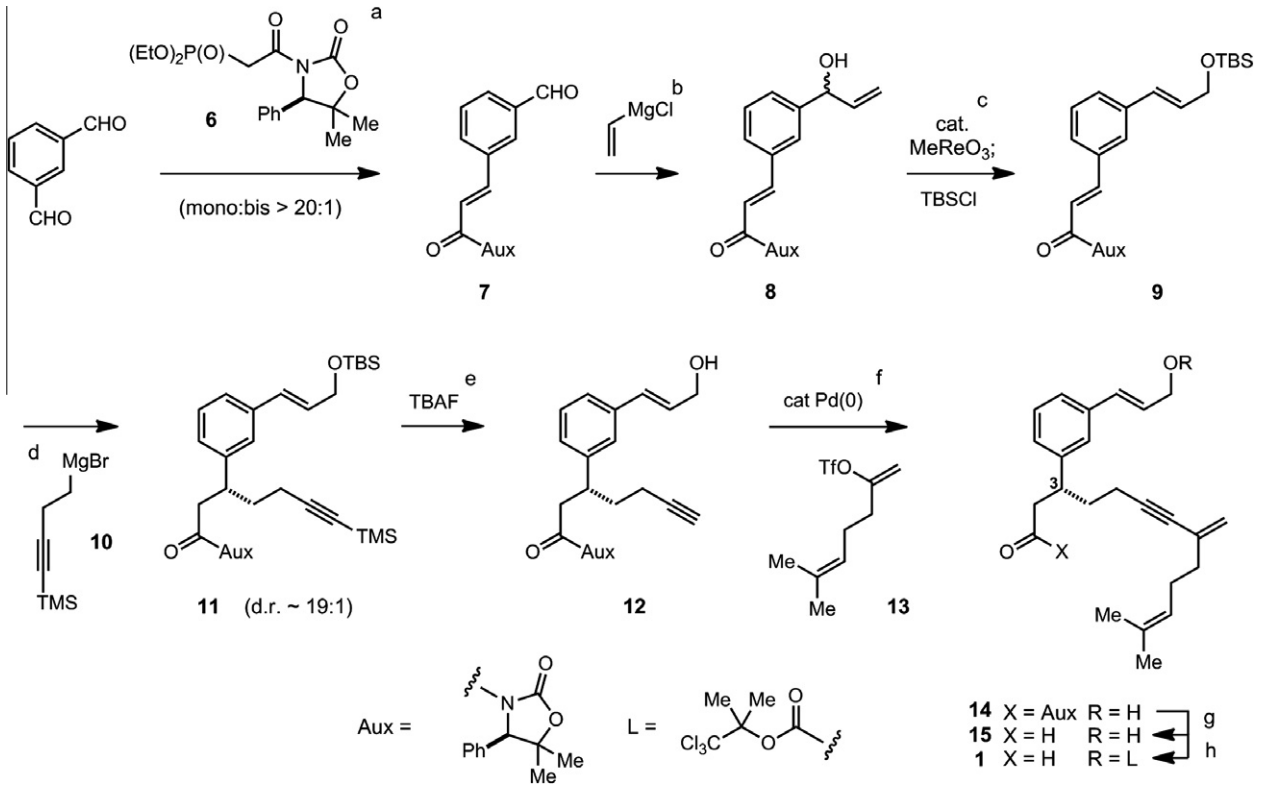

Scheme 1. Reagents and conditions: (a) isophthaladehyde (2 equiv), LiCl, iPr$_2$NEt, MeCN, rt, 48 h (74% from (4*R*)-5,5-dimethyl-4-phenyloxazolidin-2-one); (b) vinylmagnesium chloride, toluene, −78 °C; (c) $MeReO_3$ (3 mol %), toluene, rt, 12 h; TBSCl (1.2 equiv), imidazole, rt, 45 min (79% from **7**); (d) **10** (1.2 equiv), CuI, Me_2S/THF, −40 °C → −20 °C, 96%; (e) TBAF, THF, −10 °C, 1 h, 95%; (f) **13**, $Pd(PPh_3)_2Cl_2$ (2.5 mol %), CuI (5 mol %), iPr$_2$NH, 0 °C → rt, THF,1 h, 61%; (g) (i-Bu)$_2$AlH (3 equiv), toluene, −78 °C; (h) $CCl_3C(Me)_2CO_2Cl$ (1.4 equiv), DMAP, pyridine, DCM, −40 °C, 2 h (52% from **14**).

in multi-gram batches without incident. It has the added benefit of introducing the diene-yne appendage incrementally in two segments, wherein both can be controllably varied in future iterations. Along these lines, we look forward to creating numerous congeners of this novel grafting material.

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Supplementary data

Supplementary data (experimental procedures, characterization data, and NMR spectra for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.083.

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11. Absolute stereochemistry at C-3 in **1** is assigned as *R* by analogy to outcomes in Ref. 6. Material prepared in this work shows $[\alpha]_D^{20}$ = +29.0 (*c* 0.56, $CHCl_3$). This is signed opposite to previously synthesized **1**, which was drawn incorrectly in our previous communication (Ref. 1).