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) CCl₃C(Me)₂CO₂Cl, DMAP, pyridine; (4) NaIO₄) into isomeric enals 4. Subsequent chiral imidazolidinone-catalyzed conjugate reduction3 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 desymmetrized5 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 diastereomeric aryl vinyl carbinols 8. MeReO₃ catalyzed allylic alcohol transposition7 followed by in situ silylation with TBSCl affords a single isomer of cinnamyl ether 9. Subsequent chiral imidazolidinone-catalyzed conjugate reduction3 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.

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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...
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.

References and notes

2. Engaging structure 1 with synthetic WWY in a simple three step reaction sequence (see Ref.1) leads to products such as 5, wherein the composite has restricted conformational mobility, increased stability and solubility and harbors both polar and hydrophobic domains.
4. Reactions of scalemic 1 with enantiopure polyamides generate diastereoisomeric product mixtures which are difficult to separate. This unnecessarily complicates analysis/characterization.
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 [α]D 29.0 (c 0.56, CHCl3). This is signed opposite to previously synthesized 1, which was drawn incorrectly in our previous communication (Ref. 1).