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Constructing Quaternary Stereogenic Centers Using Tertiary Organocuprates and Tertiary Radicals. Total Synthesis of *trans*-Clerodane Natural Products

Daniel S. Müller,[†] Nicholas L. Untiedt,[†] André P. Dieskau, Gregory L. Lackner, and Larry E. Overman*

Department of Chemistry, University of California, Irvine, 1102 Natural Sciences II, Irvine, California 92697-2025, United States

Supporting Information

ABSTRACT: A new concise construction of *trans*-clerodane diterpenoids is reported in which oxacyclic and *trans*-hydronaphthalene fragments are coupled, and the critical C9-quaternary carbon stereocenter formed stereoselectively, by 1,6-addition of a tertiary cuprate or a tertiary carbon radical to β-vinylbutenolide. This strategy is specifically illustrated by total syntheses of (−)-solidagolactone (**4**), (−)-16-hydroxycleroda-3,13-dien-15,16-olide (**5**, PL3), and (−)-annonene (**6**).

The stereoselective construction of quaternary stereocenters is one of the most demanding challenges in organic synthesis.[1] A conceptually straightforward strategy for constructing such carbons is the union of a chiral or prochiral tertiary nucleophile with a carbon-centered electrophile. However, this strategy has been little employed in stereoselective synthesis, in part because of the few methods available for generating nucleophilic tertiary carbons in complex molecules. To address this limitation, we recently showed that structurally elaborate tertiary organocuprates can be formed by reductive lithiation and transmetalation of nitrile precursors and that these nucleophiles add in high yields to appropriate Michael acceptors.[2,3] In extending Okada's pioneering studies,[4] we also reported that a wide variety of tertiary carbon radicals can be generated from precursors containing a *N*-phthalimidoyloxy fragments by visible-light photocatalysis and that these nucleophilic radicals also couple in useful yields with electrophilic alkenes.[5] In the two *cis*-bicyclic ring systems investigated previously, addition reactions of these two classes of tertiary intermediates to electrophilic alkenes remarkably took place with opposite stereoselection (illustrated in the *cis*-perhydropentalene series in Figure 1A,B).[2,5a] To pursue further the utility of trialkyl-tertiary organocuprates and trialkyl-carbon radicals for fragment coupling and to examine stereoselection in other common ring systems, we chose to explore a potentially general construction of *trans*-clerodane diterpenoids in which a tertiary *trans*-octahydronaphthalene cuprate or the corresponding carbon radical would be joined with an oxacyclic side chain electrophile (Figure 1C). *trans*-Clerodanes are a large family of plant diterpenoids exemplified by solidagolactone (**4**),[6] 16-hydroxycleroda-3,13-dien-15,16-olide (**5**, referred to as PL3 or HCD),[7] and annonene (**6**)[8] (Figure 2).[9] A variety of biological activities have been reported for this group of diterpenoids, with their antifeedant activity being widely recognized.[9a] Among the *trans*-clerodane diterpenoids depicted in Figure 2, PL3 is reported to exhibit a particularly broad spectrum of in vitro pharmacological activities including antibacterial,[10] antileishmanial,[11] lipid lowering,[12] antitumor,[13] and antifeedant.[14] Although total syntheses of PL3[15] and annonene[16] have been recorded, a short synthetic route to these diterpenoids is yet to be defined.[17]

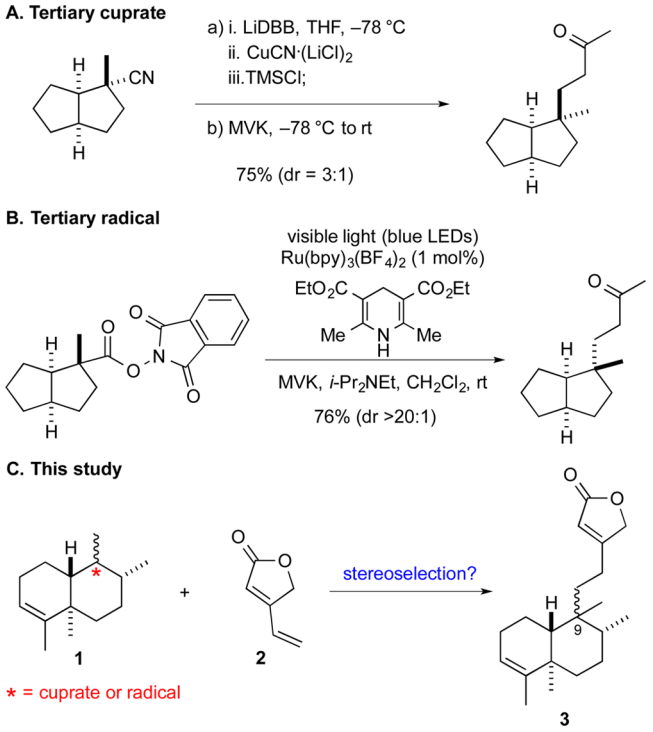

Figure 1. Fragment coupling of: (A) a *cis*-perhydropentalene cuprate with methyl vinyl ketone (MVK), (B) a *cis*-perhydropentalene radical with MVK, and (C) proposed fragment couplings to construct the C9 quaternary stereocenter of *trans*-clerodane diterpenoids. LiDDB = lithium 4,4′-di(*tert*-butyl)biphenylide.

The convergent approach that we pursued envisaged as the pivotal step the 1,6-addition of a *trans*-octahydronaphthalene cuprate or radical **1** to 4-ethenyl-2(5H)furanone (4-vinylbutenolide, **2**),[18] which would yield solidagolactone **4** if this union took place from the equatorial face of the nucleophilic reagent. Oxidation of this intermediate should provide PL3 (**5**), whereas reduction should deliver annonene (**6**). The nucleo-

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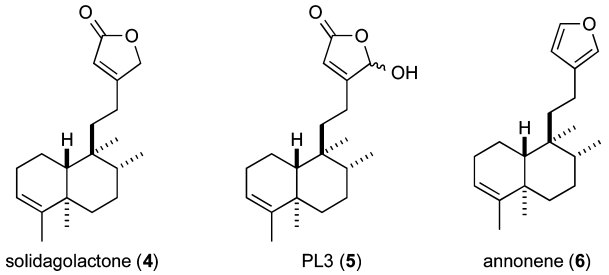
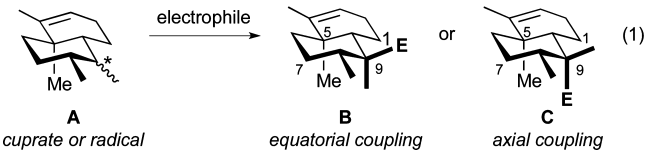


Figure 2. Representative *trans*-clerodane diterpenoids.

philic *trans*-octahydronaphthalene intermediates would arise from a *trans*-decalin ketone prepared in racemic form by Piers in early total syntheses of *trans*-clerodane diterpenoids.[19] 1,6-Additions of carbon nucleophiles to vinylbutenolide **2** have not been reported; however, copper-catalyzed additions of this type to other electron-deficient dienes have considerable precedent.[20] In contrast, 1,6-additions of nucleophilic carbon radicals to dienes are rare,[21] with the one report of the addition of a tertiary radical—adamantyl to methyl sorbate—giving a 1:1 mixture of regioisomeric addition products in low yield.[21a] Stereoselection in forming the C9 quaternary stereocenter in the coupling step would be critical. We anticipated from existing precedent[22] and our studies (Figure 1B) that a tertiary radical would couple stereoselectively from the less-hindered equatorial face (eq 1).

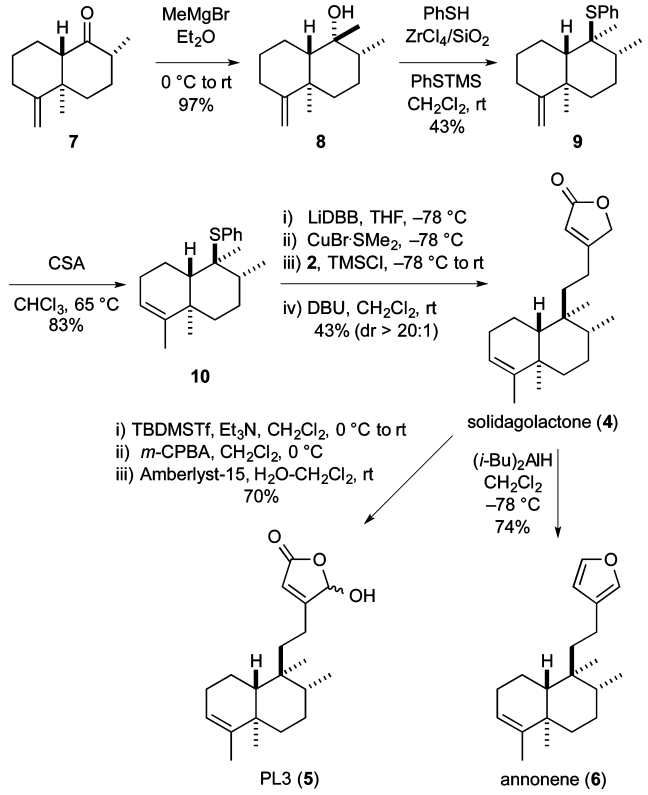


Although our earlier experience suggested that this union might take place from the opposite vector with a cuprate nucleophile, serious destabilizing 1,3-diaxial interactions between the axial C5-methyl substituent and the axial hydrogens at C1 and C7 could well favor equatorial (β-face) coupling with this nucleophile as well (Scheme 1C).

Our exploration of this synthetic approach to *trans*-clerodanes using a cuprate nucleophile was carried out in the racemic series and began with *trans*-decalone **7** (Scheme 1). Accessing the vinylcuprate reagent from a vinylalanate precursor using chemistry recently introduced by Alexakis,[23] decalone **7** was prepared on 0.1 mol scale in three steps and 41% yield from 3-methyl-2-cyclohexenone following the general approach of Piers and Wai.[19,24] Two possibilities for the direct precursor of the cuprate would be a nitrile or a phenylthio derivative.[2,25] As early scouting studies showed that the organolithium progenitor of the cuprate was generated inefficiently from a nitrile antecedent, we turned to a phenylthio precursor. After converting ketone **7** to axial alcohol **8**, we examined a number of conditions for forming the corresponding sulfide.[26] After some experimentation, we found that the method described by Firouzabadi and Iranpoor when modified by including PhSTMS as an additive provided crystalline sulfide **9** in 43% yield.[27] Single-crystal X-ray analysis confirmed that the phenylthio substituent of **9** had been incorporated on the β-face. Exposure of sulfide **9** to camphorsulfonic acid at 65 °C generated *trans*-octahydronaphthalene **10** with high regioisomeric purity (**10**:**9** = 97:3) and 83% yield.

The total syntheses of *trans*-clerodanes **4**–**6** were completed in short order from sulfide **10**. To our delight, generating the

Scheme 1



tertiary cuprate from sulfide **10** by sequential reaction with LiDBB (2 equiv) and $CuBr{\cdot}SMe_2$ (1.1 equiv), and reaction of this intermediate with butenolide **2** in the presence of TMSCl gave the coupled product in ~50% yield as a mixture of double-bond regioisomers. Equilibration of this mixture with DBU delivered (±)-solidagolactone (**4**) in 43% yield over two steps. In contrast to the related coupling carried out in the *cis*-perhydropentalene series (Figure 1A), the new C–C bond of **4** was formed with high selectivity (dr > 20:1) from the less-hindered face. Using slight modifications of reported γ-hydroxybutenolide syntheses,[28] **4** was treated sequentially with *tert*-butyldimethylsilyl triflate/Et_3N, *m*-chloroperbenzoic acid, and aqueous acid to give (±)-PL3 (**5**) in 70% yield. Finally, reduction of **4** with (*i*-Bu)$_2$AlH delivered (±)-annonene (**6**) in 74% yield.[29]

Our initial plan for developing the alternative radical-coupling route to *trans*-clerodane diterpenoids envisaged forming the C9 *trans*-decalin radical from tertiary alcohol **8** using the visible-light photcatalytic method that we had recently described.[5b] However, we were never successful in forming the *N*-phthalimidoyl oxalate derivative of this alcohol, a failure that we attribute to the severe destabilizing 1,3-diaxial interaction with the angular methyl group that would be present in such an intermediate.[30]

We turned to an approach wherein the tertiary radical would be formed from the (*N*-acyloxy)phthalimide derivative of a *trans*-decalin carboxylic acid precursor.[4,5a] In implementing this strategy, we modified the initial conjugate addition step of the Piers synthesis of *trans*-decalones such as **7** to deliver related intermediates in enantioenriched form (Scheme 2). Nickel-catalyzed regioselective hydroalumination of chloroalkyne **11**,[31] followed by catalytic enantioselective conjugate addition of the resulting internal vinylaluminum intermediate to 3-methylcyclohex-2-en-1-one (**12**) using a silver-NHC ligand developed for this purpose by Hoveyda et al. gave 3,3-disubstituted cyclo-

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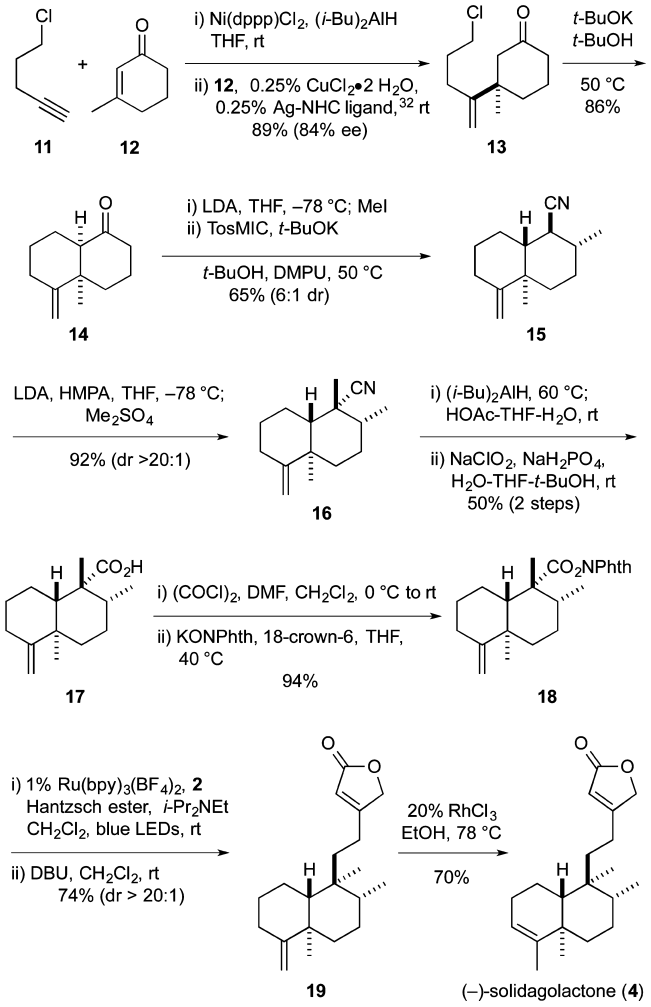
Scheme 2



hexanone **13** in high yield and 84% ee.[32] In scaling this sequence to provide **13** on multigram scale, we discovered that the loading of the Hoveyda copper catalyst could be reduced to 0.25 mol %, making this a notably practical reaction. Using only slight modifications of procedures reported by Piers,[19] chloroketone **13** was cyclized in high yield to decalone **14** (dr = 3:1), which was methylated and converted to nitrile **15**, a 6:1 mixture of nitrile epimers, in 65% yield upon base-promoted reaction with *p*-toluenesulfonylmethyl isocyanide (TosMIC). Methylation of **15** provided tertiary nitrile **16** in high yield as a single diastereoisomer. Undoubtedly reflecting the sterically hindered nature of the axial cyano substituent of this product, we were unable to define conditions for efficient direct hydrolysis of **16** to the corresponding carboxylic acid. With reluctance, we resorted to a two-step redox sequence that delivered decalincarboxylic acid **17** in 50% yield.

The pivotal coupling of the decalin and vinylbutenolide fragments was now readily accomplished. First, carboxylic acid **17** was coupled in 94% yield with *N*-hydroxyphthalimide by way of the acid chloride intermediate. The (*N*-acyloxy)phthalimide product **18**, when exposed at room temperature to visible light, 1 mol % of $Ru(bpy)_3(BF_4)_2$, Hantzsch ester, and i-Pr_2NEt, coupled with vinylbutenolide **2** (1.3 equiv) in high yield to give a mixture of adduct **19** and its β,γ-unsaturated isomers. Exposing this mixture to DBU at room temperature provided clerodane diterpenoid **19**[7d] as a single epimer at the newly formed quaternary stereocenter in 74% yield for the two steps. Isomerization of the double bond of **19** in the presence of catalytic $RhCl_3$ gave (−)-solidagolactone **4**, $[\alpha]^{23}_D$ −26.3° (c = 0.32, $CHCl_3$) in 70% yield. Conversions of (−)-**4** to (−)-PL3 (**5**), $[\alpha]^{23}_D$ −21.4° (c = 0.23, $CHCl_3$), and (−)-annonene (**6**), $[\alpha]^{23}_D$ −28.9° (c = 0.71, $CHCl_3$) were accomplished as in the racemic series.[33]

PL3 (**5**) is reported to show moderate cytotoxicity toward breast, liver, and leukemia cell lines,[13] with a recent study associating its apoptotic activity to inhibition of several histone-modify enzymes.[13c] To further benchmark its anticancer activity, synthetic PL3 was screened against two invasive cancer cell lines: DU145 (human prostate cancer) and A2058 (human melanoma). No significant activity (IC_{50} > 10 μM) was observed.[34]

In conclusion, a new strategy for synthesizing *trans*-clerodane diterpenoids is reported in which side chain and *trans*-decalin (or *trans*-octahydronaphthalene) fragments are coupled by 1,6-addition of a tertiary cuprate or a tertiary carbon radical to vinylbutenolide **2**. Using this approach, stereocontrolled total syntheses of racemic and enantioenriched (−)-solidagolactone (**4**), (−)-PL3 (**5**), and (−)-annonene (**6**) were completed in 7−12 steps from commercially available 3-methylcyclohex-2-enone. An important outcome of this study is the demonstration that the stereochemical complementarity observed previously in constructing quaternary stereocenters using tertiary cuprate and tertiary radical intermediates (Figure 1A,B) is not seen if coupling from one face of the tertiary intermediate is highly favored for steric reasons. We also show for the first time that 1,6-additions of tertiary carbon radicals to electron-deficient dienes can be efficient under conditions useful for the coupling of complex fragments (i.e., using only a 30% excess of the diene component). This step, and the analogous coupling of the cuprate intermediate formed from sulfide **10**, moreover suggests the potential general utility of 1,6-additions to vinylbutenolide **2** for directly introducing the common, and often biologically significant, β-ethanobutenolide fragment into organic molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for new compounds and crystallographic data for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*leoverma@uci.edu

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest

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