Concise synthesis of (–)-cotylenol, a 14-3-3 PPI molecular glue

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ABSTRACT: Small molecules that modulate the 14-3-3 protein-protein interaction (PPI) network represent valuable therapeutics and tool compounds. However, access has been lost to 14-3-3 PPI molecular glues of the cotylenin class, leading to investigations into practical chemical syntheses. Here we report a concise synthesis of (–)-cotylenol via a 10-step entry into the 5-8-5 cotylenin binding region using a convergent fragment coupling and Claisen-ene cascade.

The fusicoccanes comprise a family of 5-8-5 tricyclic diterpenoids produced by phytopathogenic fungi.[1] Their phytotoxic activity originates in modulation of plant 14-3-3 PPIs with phosphoprotein clients.[2,3] Conservation of the 14-3-3 signaling hub across eukaryotes leads the fusicoccane class to exhibit activity in human cells as well, where phenotype depends on selective stabilization (or disruption[4]) of complexes between 14-3-3 and its numerous clients.[5] One important 14-3-3 PPI stabilizer, cotylenin A (**1**),[6] suppresses the self-renewal ability of human chronic myeloid leukemia (CML) cells and significantly decreases levels of the tumorigenic transcription factor c-Myc.[7,8] The mechanism remains unknown. Cotylenin A stabilizes several 14-3-3/client PPIs and a comprehensive understanding of its interactome is absent. Dissection of these interactions may advance the cotylenin chemotype towards therapeutic applications, analogous to the development of novel IMiD molecular glues.[9]

Unfortunately, access to material by isolation has become a substantial barrier to industry and academia alike.[10] Whereas fungal metabolites can be simple to access by fermentation, the producer organism of **1**, a *Cladosporium* species, no longer proliferates in culture, prompting the total synthesis of **1** or reliance on mimics that require multistep semisynthesis (e.g. **2** in 14 steps from fusicoccin A).[11] One total synthesis of cotylenin A has been reported to date (25 steps, 0.15%),[12] along with two syntheses of its aglycon, cotylenol (**3**)[13] (21–32 steps, <1–3.9% yield).[14] Here we report a short synthesis of **3** that may allow us to replenish supplies for the community.

Prior synthetic work by Takeshita and Nakada revealed that assembly of the $\Delta^{1,2}$-alkene with *E*-configuration (e.g. **4**, Figure 1) enabled efficient cyclooctene formation via ene or α-arylation reactions.[12,14] Access to cyclization precursors, however, required 28 and 17 steps, respectively, due to the extreme steric congestion that flanks the alkene. Quick access to the 5-8-5 core with native A- and C-ring functional groups became a top priority, as this region nestles among 14-3-3 helices, whereas the C7-9 bridge binds surface waters.[15] We thought two heavily functionalized, encumbered fragments could be easily assembled if the greatest transition state repulsion occurred in an *intra*-molecular process via scaffold rearrangement. A Claisen reaction would benefit from 1) exothermicity of C=O bond formation to offset this steric repulsion, 2) good models to understand and control product stereocenters using substrate configurations[16] and 3) chemoselectivity.[17] Analysis of Claisen transition states and experimental feedback (SI and Scheme 2) eventually suggested allyl vinyl ether **5** as the required starting material, which could arrive in convergent fashion from prefunctionalized A and C rings.[18]

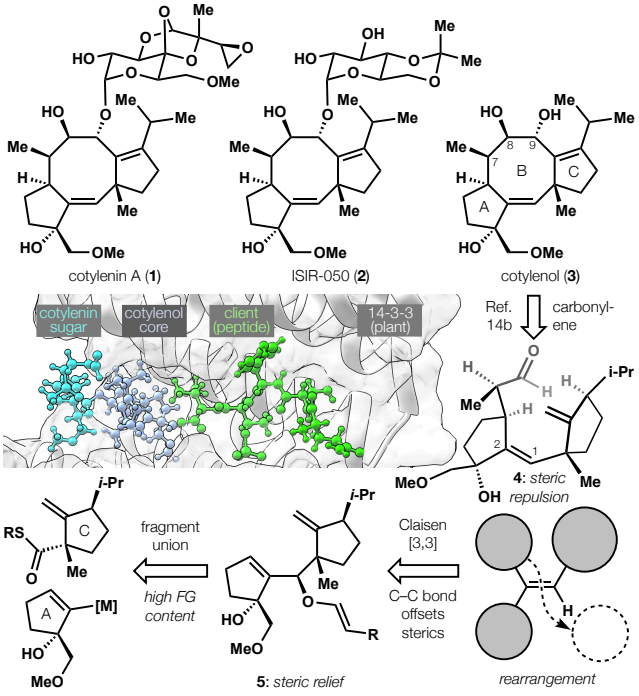
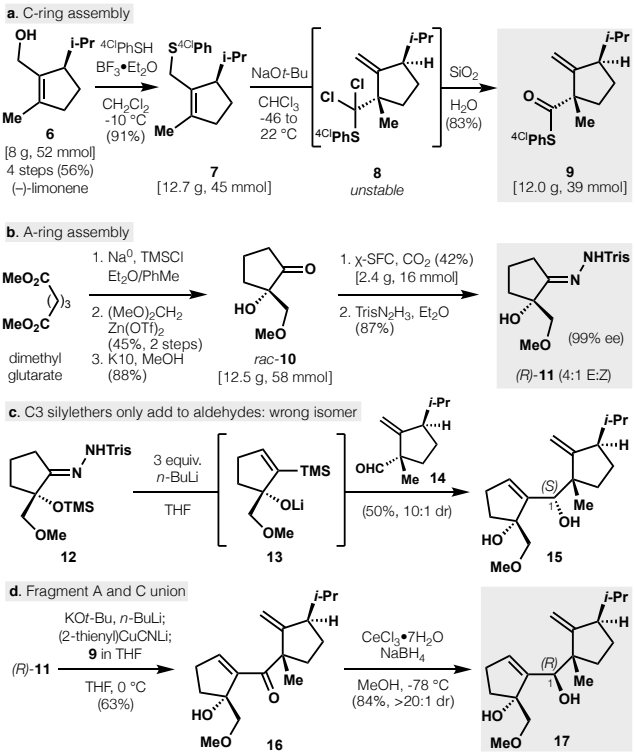


Figure 1. Fusicoccanes like cotylenin A function as molecular glues between 14-3-3 proteins and phosphoprotein clients (from PDB: 3e6y, Ref. 3). Resupply of material might be accomplished by steric rearrangement to enable union of highly functionalized fragments.

Synthetic efforts began with known alcohol **6**, scaled to 50 mmol over 4 steps and 56% yield from (–)-limonene.[19] $BF_3{\cdot}OEt_2$-mediated allylic substitution with 4-chlorothiophenol cleanly afforded thioether **7**. To generate the C-11 quaternary center with an appropriate coupling handle, a [2,3]-Wittig rearrangement of the corresponding sulphonium ylide[20] was effected by generation of dichlorocarbene in the presence of **7** to deliver intermediate **8**, which converted dur-

ing chromatography on hydrated silica gel (78:12 w/w SiO_2/H_2O) to thioester **9** in 83% yield (single diastereomer by ^1H and ^{13}C NMR). Use of sodium *tert*-butoxide in place of potassium base resulted in higher conversions and yields, either via lower rate of alkoxide addition to dichlorocarbene or slower α-elimination resulting in less homodimerization.[21] This route scaled easily: we prepared >10 grams of this functionalized C-ring coupling partner in a single pass.

Preparation of the A-ring began with acyloin cyclization[22] of dimethylglutarate, followed by a $Zn(OTf)_2$-catalyzed Mukaiyama aldol reaction with dimethoxymethane. The *tert*-alkyl silyl ether was cleanly deprotected with Montmorillonite K10 in methanol to ketone *rac*-**10**. Separation of enantiomers by preparative supercritical fluid chromatography (SFC) provided an inexpensive and expedient means to access pure enantiomers (*(R)*- and *(S)*-**10**) to explore downstream chemistry (absolute configuration assigned by derivatization and X-ray crystallography, see SI). Condensation with Tris-$NHNH_2$ produced hydrazone *(R)*-**11** and set the stage for coupling the A and C ring fragments.



Scheme 1. Rapid assembly of A- and C-ring fragments with native functionality preinstalled.

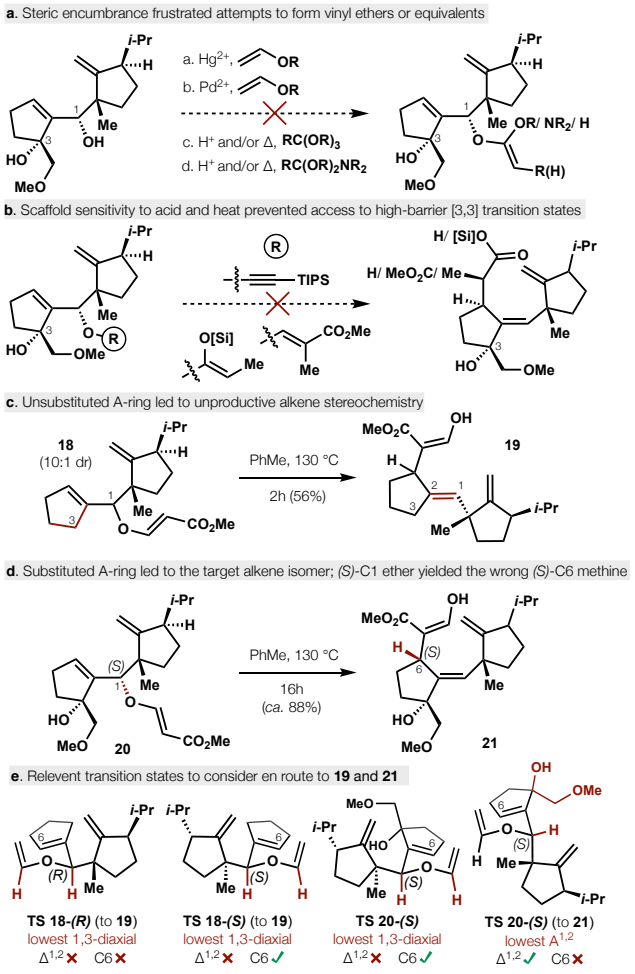
Generation of alkenyl organometallics from A-ring hydrazones proved difficult. Originally, we had protected the C3 alcohol as its silyl ether (**12**, Scheme 1c), but we found that Shapiro reactions consistently resulted in retro-[1,4]-Brook rearrangements to generate a vinyl silane (**13**). Additional *n*-BuLi did not allow reaction of **13** with thioester **9** but did result in engagement of the corresponding carboxaldehyde (**14**, see SI), either via the silate or organolithium, to yield **15**. Unfortunately, major diastereomer **15** was unproductive in the synthesis according to classic Claisen rearrangement models (see Scheme 2 and SI). Attempts to circumvent Brook rearrangement by incubation of unprotected alcohol *(R)*-**11** with >3 equivalents of *n*-BuLi for 1 h at 0 °C were unsuccessful: no **9** was consumed. Transmetallation to copper,[23] however, proved effective. Ultimately, we found that addition of 1 equivalent potassium *tert*-butoxide along with 3 equivalents of *n*-BuLi, followed by subsequent additions of Lipshutz's (2-thienyl)CuCNLi complex[24] and thioester **9** (0.83 equiv.), yielded fragment union product **17** in 63% yield (10% of **9** was recovered). The parent thiophenyl ester gave low yield and conversion, but its 4-chloro analog enhanced performance by analogy to its role in Liebeskind–Srogl coupling.[25]

Luche reduction ($NaBH_4$, $CeCl_3•7H_2O$) at -78 °C then gave diol **17** as a single diastereomer in 84% yield. Reduction of this extremely hindered ketone relied on directing effects from the C3 tertiary alcohol, i.e. C3 silyl ethers prevented reduction, and the C3 epimer (from *(S)*-**11**) delivered the corresponding C1 *(S)* epimer (20:1 dr) under Luche conditions.

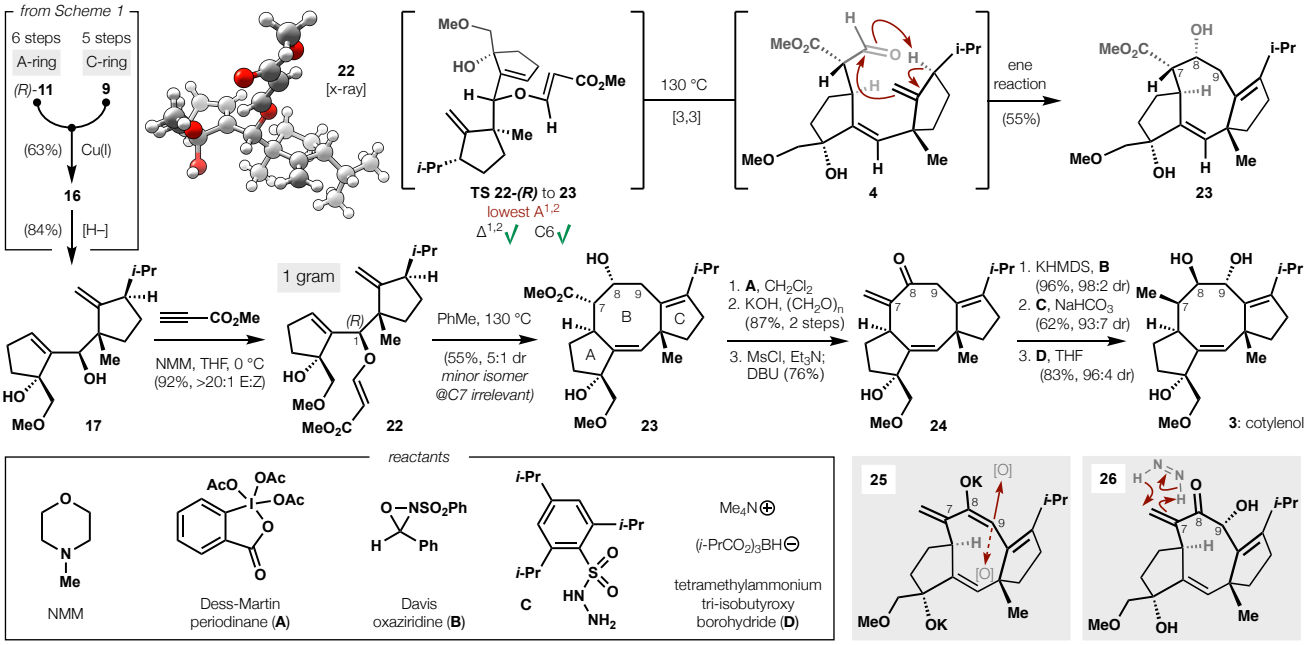
Reliable access to diols **15** and **17** allowed us to explore Claisen rearrangement. Unfortunately, C1 vinyl ether formation was not straightforward. Steric hindrance about the C1 alcohol obstructed reaction with alkenyl electrophiles using palladium or mercury catalysis. High temperature or acid-catalyzed Johnson- and Eschenmoser-Claisen variants caused complex decomposition (Scheme 2a). The limited number of enol and ynol ethers available via Waser's reagent,[26] esterification/silylation or *oxa*-Michael addition did not translate to successful Claisen rearrangements (Scheme 2b), likely due to prohibitively high barriers relative to decomposition pathways.

The allylic, tertiary alcohol at C3 proved especially sensitive to elimination, but its excision was futile: although substrate **18** underwent efficient [3,3]-rearrangement, the product alkene possessed the wrong alkene configuration for cyclization to **3** (Scheme 2c).[27]

Scheme 2. Narrow window of opportunity for Claisen rearrangement.



Scheme 3. Completion of cotylenol (–)-**3** via a stereoselective Claisen-ene cascade cyclization.



Alkene geometry was rationalized by transition states that reduced 1,3-diaxial interactions independent of C1 configuration by placement of the C-ring in a pseudo-equatorial position (see Scheme 2e for transition states). Consistent with this model, fully substituted A-ring **20** led to the targeted alkene geometry, but the incorrect *(S)*-C6 configuration. In this case, repulsion between the C3 position and the C-ring ($A^{1,2}$ strain) forced the C-ring into a pseudo-axial position and led the alkenylether to engage the C6 *si*-face.[16] These data confirmed the necessity of C1 *(R)*-configuration and led us to conclude the alternative alcohol **17** would maintain a pseudo-axial C-ring but access the C6 *re*-face, allowing completion of **3**, assuming the Claisen transition state energy did not exceed the barrier to decomposition pathways like elimination.

As explored in Scheme 1, copper(I)-mediated coupling of rings A and C advanced material quickly to alcohol **17**. Despite the repeated difficulty of forming enol ethers from **17**, we found the combination of *N*-methylmorpholine (NMM) and methyl propiolate to engage the extremely encumbered alcohol with ease at 0 °C in good yield, likely through the alkoxide/enammonium cage pair.[28] The methyl ester was crucial to allow Claisen rearrangement: its absence (Scheme 2b) yielded no product. But polarization imparted by the ester allowed thermal reaction of **22** in silylated glass to provide, to our surprise, the full 5-8-5 ring system **23** via a stereoselective Claisen rearrangement/ ene reaction[14] cascade.[29] C1 *(R)* configuration and A-ring sterics translated cleanly to C6 *(R)* configuration and the requisite *E*-alkene.

A simple sequence then converted **23** to cotylenol (**3**). First, uneventful oxidation of the β-hydroxyester, followed by decarboxylative formaldehyde aldol and elimination yielded enone **24**. Second, introduction of the C7–9 stereocenters required differentiation of the prochiral faces at each carbon. In the long term, stereochemistry and substitution pattern at these positions will likely prove negotiable since this region points toward surface waters on 14-3-3 proteins. In the short term, mechanism of action studies require access to **3** specifically. In contrast to prior syntheses,[12,14] α-hydroxylation of **24** at C9 proved efficient (96%) and highly stereoselective (>20:1 dr), whereas reported oxidations of related cotylenol intermediates delivered mixtures of C9 epimers (2.7–1.5:1).[12,14] We suspected the rigid conformation enforced by the all-sp^2 C7–9 bridge of **25** (the potassium enolate of **24**) allowed reagents to avoid the *i*-Pr substituent but not the bridgehead methyl on the opposite face.[30] Late stage intermediates of prior syntheses possessed pseudo-equatorial methyl groups at C7, which may twist the enolate relative to **25** to expose the internal face. Diimide reduction did not have to contend with either substituent and approached from the exterior face with similarly high dr (93:7). Finally, Nakada's protocol for directed reduction[12] furnished **3** in 83% yield and 96:4 dr without recourse to C3 alcohol protection/ deprotection as used previously.

In conclusion, we have developed the shortest synthesis to date of cotylenol (16 steps, 9% yield from *(R)*-**11**/**9** convergence) by accessing its hindered $\Delta^{1,2}$-alkene via merger of fully functionalized A- and C-rings followed by a Claisen-ene cascade reaction. Steps scale well and we have already saved 1 gram of **22** from these studies with more material en route. The cotylenol and cotylenin A chemotypes are particularly important among 14-3-3 fusicoccanes because, unlike other members, they are no longer available by fermentation. We hope to leverage this synthesis to build a focused library of molecular glues to selectively stabilize partners within the 14-3-3 interactome: for this long-term goal, specific access to **1** or **3** is not crucial, but quick entry to privileged scaffold **23** (10 steps, 11%) may enable extensive exploration of cotylenin chemical space.[31] As seen in crystal structures of **1** and **3** bound to 14-3-3,[3,13] and as suggested by the pharmacology of **2** (Figure 1),[11] the diterpenoid core **3** may play a greater role in binding than the modified sugar motif. However, **1** and **3** hold great value for interrogation of the mechanism behind reduction of c-Myc in CML cells. Whereas multiple aspects of 14-3-3 signaling may be affected, the possibility that **1** enhances c-Myc degradation via 14-3-3-promoted polyubiquitination[32,33] has captured our imagination.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data and structural assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written by R.A.S and T.R.H.

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TOC Graphic: