JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 27 Feb 2019

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

The Total Synthesis of Chalcitrin

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Supporting Information Placeholder

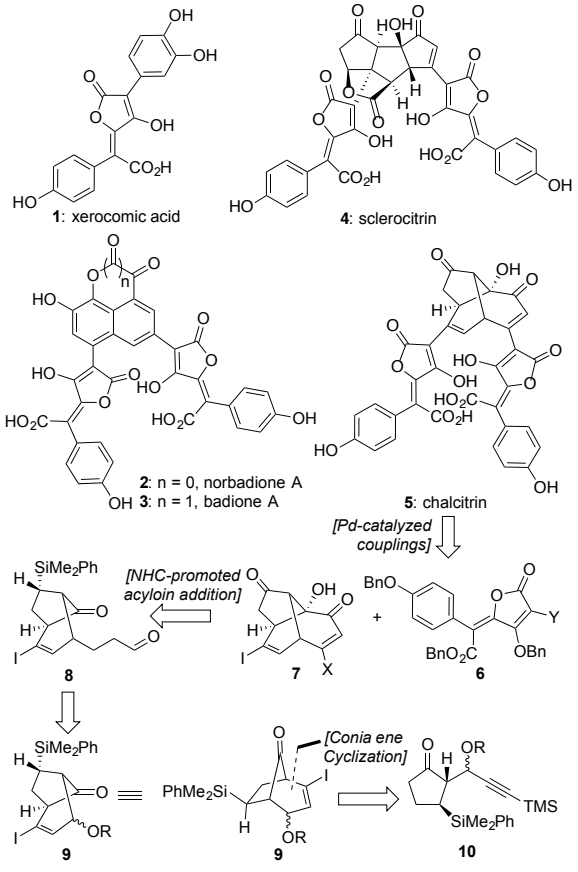
ABSTRACT: The first total synthesis of the yellow pigment chalcitrin, a structurally distinct pulvinic acid dimer obtained from *Chalciporous piperatus,* has been achieved in 17 linear steps from commercially available materials. Key elements of the design include the use of a Au(I)-catalyzed Conia ene reaction and an *N*-heterocyclic carbene-mediated acyloin addition to rapidly fashion its unique polycyclic core, with the two high oxidation state sidechains introduced in a single step via a late-stage double Stille coupling. Of note, many alternate designs based on differential final couplings failed, likely because of the hindered nature of the core. In addition, significant challenges in final natural product characterization in terms of matching NMR spectra were experienced; our studies reveal that the originally characterized material was its carboxylate salt form, not its free acid.

Although Nature generates a vast array of dimeric natural products, there appears to be only a modest number of collections where a single building block has the ability to unite with itself to generate several structurally distinct dimers.[1] One of those rare starting materials is xerocomic acid (**1**, Scheme 1), a highly-oxidized polyphenolic material which is the putative monomeric precursor for norbadione A (**2**), badione A (**3**), sclerocitrin (**4**), and chalcitrin (**5**); that supposition is based on the fact that all of these more complex materials have been co-isolated with xerocomic acid (**1**) from various species of fungi and that dimer concentration relative to **1** tends to increase as the natural sources age.[2,3] The processes proposed for their biogenesis are equally interesting. For example, with **4** and **5**, yellow colored pigments of *Scleroderma citrinum* and *Calciporus piperatus*, respectively, their dearomatized[4] polycyclic cores are surmised to arise from an array of pericyclic ring formations and openings, among other steps.[3] Biologically, their function may be to complex metal ions given that **2** and **3** occur as potassium salts in the producing fungi[2] and norbadione A (**2**) can complex cesium ions better than functionalized monomers; intriguingly, **2** was first isolated from mushroom species in areas of high radioactive ^{137}Cs concentration due to the Chernobyl reactor incident.[5]

Our interest in the collection was piqued principally by chalcitrin (**5**), arguably the rarest dimer of the group given that the others have been obtained in relative large quantities from several sources.[6] By contrast, **5** has only been obtained from *Calciporus piperatus*, with 300 g of fresh fruit bodies affording just 2 mg of chalcitrin (**5**) along with 40 mg of sclerocitrin (**4**); the presence of **5** was also denoted as being strongly dependent on the age and condition of the samples.[3] Our initial synthetic efforts sought biomimetic constructions along the lines of the original Steglich proposals; however, in line with our experiences with other dimeric collections such as those of the resveratrol,[7] rosmarinic acid,[8] and coccinellid classes,[9] we were unable to reduce such strategies to practice. Herein, we document that an alternate, stepwise approach can lead to **5** in 17 linear steps from commercial materials. It features a number of regio- and chemoselective transformations along with a very specific sequence for final sidechain incorporation. Critically, as a result of characterization challenges in its protonated and acidified forms in a variety of solvents, we have determined that chalcitrin was also initially obtained as an alkali metal salt, suggesting that it might also possess distinct metal complexation ability in Nature. Such studies should be readily fueled by these efforts given that ~70 mg of **5** have already been prepared to date in the absence of specific efforts at large-scale synthesis.

Key elements of our overall approach are shown at the bottom of Scheme 1. First, we disconnected the two pulvinic acid sidechains, projecting their incorporation in a final C–C bond formation through some type of Pd-based coupling using tricyclic core **7** and lactone derivative **6**. Whether both couplings could be achieved in tandem or would have to be effected in a stepwise manner was unclear; we left projected flexibility at the positions labeled here as X and Y to address that concern. If successful, a final deprotection of six benzyl ethers would then deliver the target. That particular protecting group was selected based on our past experiences with other polyphenols where rapid and global cleavage proved necessary to enable product isolation where further oxidation and/or decomposition was possible.[7,8] Such concerns arose from the comment above on chalcitrin presence being dependent on sample condition.

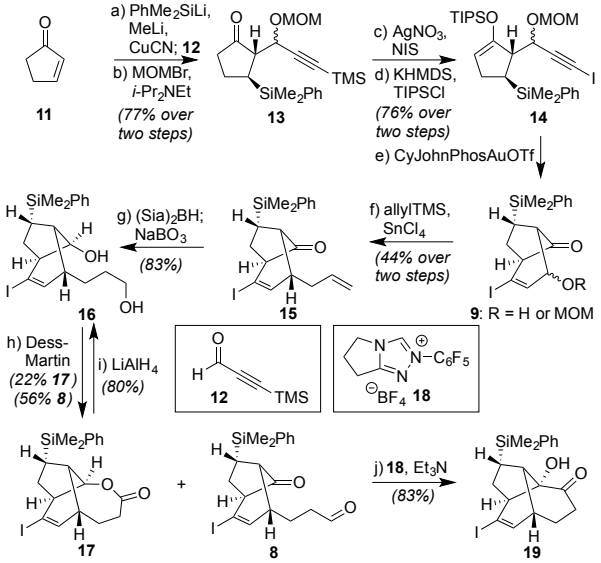
Scheme 1. Selected Structures of Pulvinic Acid Dimers Presumed to Arise from Xerocomic Acid (**1**) and a Retrosynthetic Analysis of Chalcitrin (**5**).



From here, the presence of an α-hydroxy ketone within the tricyclic core of **7** suggested its potential formation via an acyloin addition[10] from **8**. Then, after excision of its alkyl aldehyde sidechain to arrive at **9**, careful consideration of this new architecture, particularly in the second drawn form, suggested that a Conia ene reaction could potentially fashion its bicycle[3.2.1]alkenone from a 1,2-*trans*-difunctionalized cyclopentanone precursor (**10**). This critical step was inspired by Barriault's total synthesis of hyperforin,[11] among several other Conia ene cyclizations[12] such as our own towards the scaparvins.[13] In this design, assuming that the silicon group within **10** would arise via nucleophilic addition onto a precursor α,β-unsaturated ketone, it would then effect all of the stereocontrol in the synthesis, though it ultimately would become a ketone in the final polycyclic core.

Our efforts commenced with forming the full carbon framework of the bridged tricyclic core. Starting from commercially available 2-cyclopentanone (**11**, Scheme 2), a 1,4-addition/aldol reaction with $PhMe_2Si(Me)Cu(CN)Li_2$[14] and trimethylsilyl propynal (**12**) afforded ketone **13** following MOM-protection of the newly formed secondary alcohol. Although this operation produced a 1.45:1 ratio of diastereomers about that new alcohol, this mixture was of no consequence since that center would be ablated later. More significant was that the desired material was formed as a single diastereomer in terms of the chiral centers on the cyclopentane ring. We note that although we have not explicitly performed an asymmetric preparation of this material, the exact same silyl addition followed by trapping with benzaldehyde has been reported by Hoveyda to lead to closely related products in 80% ee.[15] Next, in anticipation of probing the projected Conia ene cyclization, ketone **13** was transformed into **14** in 76% overall yield through iodination of the TMS-protected alkyne using $AgNO_3$ and *N*-iodosuccinimide[16] followed by silyl enol ether formation (KHMDS, TIPSCl). Pleasingly, after extensive screening, we found that the desired Conia ene reaction generating **9** (as a separable mixture of both protected and deprotected alcohols due to the acidic conditions) could indeed be effected using either catalytic JohnPhosAu(NCMe)SbF_6 or CyJohnPhosAuOTf on hundred milligram scale in a 10:1 mixture of toluene/*t*-BuOH. However, on gram scale, only CyJohnPhosAuOTf gave comparable yields. This outcome was fortunate from a cost perspective given that CyJohnPhosAuCl, the precursor to the triflate version, is cheaper than JohnPhosAu(NCMe)SbF_6.[17]

Scheme 2. Gram-Scale Synthesis of the Core Tricycle of Chalcitrin (**5**).[a]

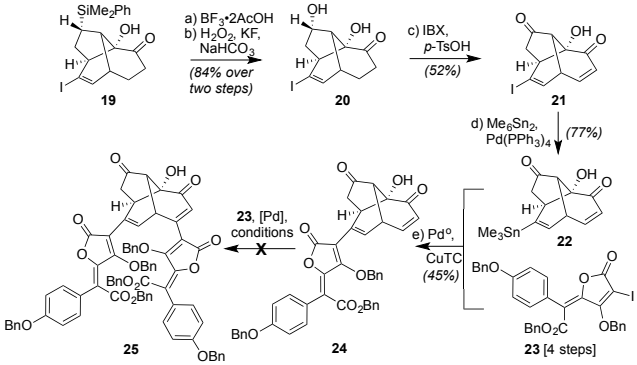


[a]Reagents and conditions: (a) MeLi (1.05 equiv), CuCN (1.1 equiv), THF, -50 °C, 20 min; $PhMe_2SiLi$ (1.1 equiv), -78 °C, 30 min; **11** (1.0 equiv), -78 °C, 30 min, then **12** (1.0 equiv), -78 °C, 30 min, 91%, 1.45:1 dr; (b) *i*-Pr_2NEt (4.3 equiv), MOMBr (3.6 equiv), CH_2Cl_2, 23 °C, 48 h, 85%, 1.6:1 dr; (c) $AgNO_3$ (0.4 equiv), NIS (1.1 equiv), DMF, 23 °C, 6 h, 86%, 1.67:1 dr; (d) TIPSCl (1.3 equiv), KHMDS (1.0 M in THF, 1.3 equiv), THF, -78 °C, 15 min, 88%, 1.6:1 dr; (e) CyJohnPhosAuCl (0.1 equiv), AgOTf (0.095 equiv), toluene/*t*-BuOH = 10:1, 40 °C, 17 h; (f) allyltrimethylsilane (1.21 equiv), $SnCl_4$ (1.2 equiv), 0 °C, 1 h, 44% over two steps; (g) 2-methyl-2-butene (4.5 equiv), BH_3•SMe_2 (2.1 equiv), hexanes, 0 °C, 2 h; **15** (1.0 equiv), 23 °C, 3 h, then $NaBO_3$•H_2O (6.6 equiv), THF/H_2O = 1:1, 23 °C, 8 h; 83%; (h) Dess-Martin periodinane (2.5 equiv), CH_2Cl_2, 23 °C, 2 h, 22% for **17**, 56% for **8**; (i) $LiAlH_4$ (2.4 equiv), CH_2Cl_2, 23 °C, 5 h, 80%; (j) **18** (0.2 equiv), Et_3N (0.2 equiv), THF, 65 °C, 1 h, 83%.

Pressing forward, exposure of **9** (with R = H and OMOM) to a strong Lewis acid in the form of $SnCl_4$ enabled addition of an allyl group to occur onto the intermediate allyl cation with complete regio- and diastereocontrol; this S_N1 substitution process was likely controlled as a result of addition onto the cancave face of **9** with the steric demand of the ketone being less than that of the neighboring C–H group on the bicycle.[18] Subsequent hydroboration of the resultant terminal alkene with $(Sia)_2BH$ and oxidation with $NaBO_3$•H_2O afforded diol **16** in 83% yield in which the ketone was also reduced. Exposure to Dess–Martin periodinane then proved capable of oxidizing its two alcohols into **8**, with a small amount of lactone **17** (22%) formed as well; the latter could be recycled into **16** via reduction using $LiAlH_4$.[19] Finally, treatment of **8** with 20 mol % of *N*-heterocyclic carbene salt **18**[20] in the presence of Et_3N smoothly effected the desired acyloin addition to afford tricycle **19** in 83% yield.[10f]

Our goal now was to incorporate the two sidechains through some variant of Pd-based C–C bond-forming chemistry.[21] In practice, however, this task proved to be highly challenging. Initially, we envisioned an approach in which one of the sidechains would be introduced by a Stille coupling between the stannane variant of the readily synthesized **23**[22] (4 steps from tetronic acid, Scheme 3) and the vinyl iodide motif of **19**; the other sidechain would be added via a Heck reaction between **23** and an enone generated on the right-hand ring of **19**. In practice, however, we were never able to directly form a stannane from iodolactone **23**. As a result, alternate coupling partners were developed by converting **19** into stannane **22** through a two-step Tamao–Fleming oxidation[23] of the alkyl silane, concomitant alcohol oxidation and enone formation using IBX under acidic conditions,[24] and conversion of the alkenyl iodide into a stannane. Critically, while the yield in the step converting **20** to **21** was modest at 52%, in the absence of catalytic *p*-TsOH demonstrably lower yields were obtained with most of the starting material decomposing instead. Pleasingly, the initial coupling between **22** and **23** proceeded smoothly to afford **24** in the presence of $Pd(PPh_3)_4$ and CuTC in 45% yield.[25] Unfortunately, all attempts to advance beyond **24** using a variety of Heck-type additions with **23** failed to deliver **25**. We reason that steric hindrance coupled with the rigidity of the core is the main culprit for this failure given their likely impact on the migratory insertion step.

Scheme 3. Selected Challenges in Sidechain Introduction.[a]

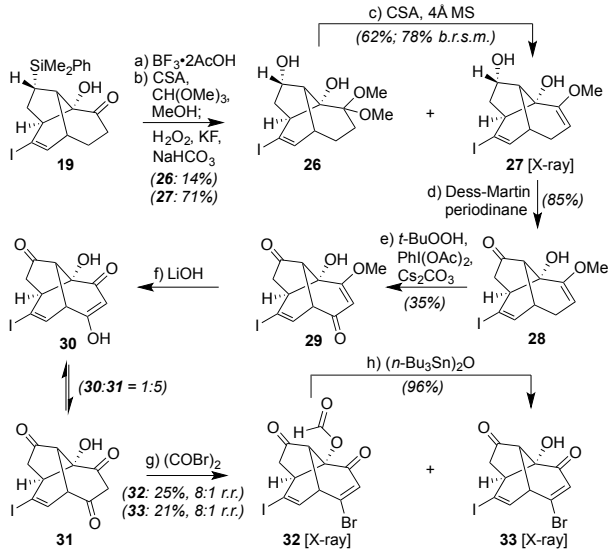


[a]Reagents and conditions: (a) BF_3•2AcOH (4.8 equiv), CH_2Cl_2, 23 °C, 2 h; (b) KF (10 equiv), $NaHCO_3$ (10 equiv), H_2O_2, THF/MeOH = 1:1, 23 °C, 12 h, 84% over two steps; (c) IBX (3.0 equiv), *p*-TsOH•H_2O (0.2 equiv), DMSO, 80 °C, 1 h, 52%; (d) Me_6Sn_2 (1.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF, 60 °C, 1 h, 77% w/grease; (e) **23** (1.2 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuTC (1.5 equiv), NMP, 60 °C, 30 min, 45%.

However, given the successful nature of the initial Stille coupling leading to **24**, we wondered next whether a tandem, double

Stille coupling using **23** could rise to the occasion. As a result, access to compound **33** (Scheme 4) became the synthetic objective, hoping that the vinylogous bromide, as part of an electron-deficient and hindered system, would be capable of also being converted into the requisite stannane and then productively participating in a Stille reaction at the same time as the previously successful left-hand alkenyl stannane. As shown in Scheme 4, access to that key compound was ultimately achieved over several steps via several regio- and chemospecific functionalizations.[26] First, tricycle **19** was converted into methyl enol ether **28** over 3 steps, using CSA to recycle the minor amounts of **26** formed from the initial Tamao–Fleming/ketal formation sequence. From here, subsequent allylic oxidation proved incredibly challenging, with only Yeung's conditions [*t*-BuOOH, $PhI(OAc)_2$, Cs_2CO_3][27] affording sufficient material throughput (35% yield).[28] Next, hydrolysis with LiOH afforded a mixture of **30** and **31** (in a 1:5 ratio) in which the minor enol tautomer favored the indicated and desired orientation, likely due to hydrogen bonding with the neighboring bridgehead tertiary alcohol. Subsequent treatment with $(COBr)_2$ and DMF afforded an ~1:1 mixture of **32** and **33**,[29] structures which were both confirmed by X-ray diffraction. The former could be converted into the latter in near quantitative yield (96%) through treatment with $(n\text{-}Bu_3Sn)_2O$ in hot (80 °C) toluene,[30] thus affording a 45% yield of **33** over three steps from **30**.

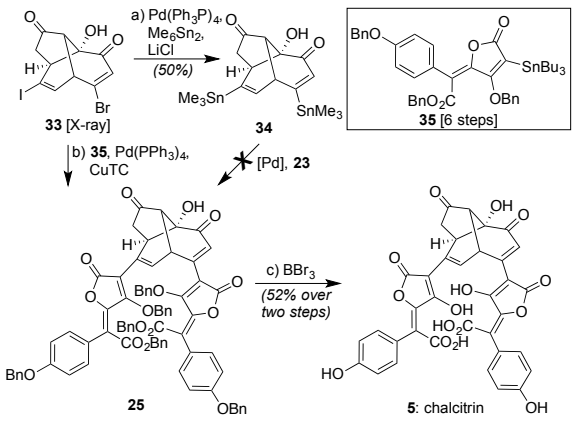
Scheme 4. Synthesis of the Double Vinyl Halide Intermediate (**33**).[a]



[a] Reagents and conditions: (a) BF_3•2AcOH (3.7 equiv), CH_2Cl_2, 23 °C, 2 h; (b) trimethyl orthoformate (7.5 equiv), CSA (0.11 equiv), MeOH, 65 °C, 3 h, then added THF, KF (7.4 equiv), $NaHCO_3$ (7.4 equiv), H_2O_2, 23 °C, 12 h, 14% for **26**, 71% for **27** over two steps; (c) 4Å MS, CSA (0.2 equiv), THF, 23 °C, 12 h, 62% (78% brsm); (d) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 30 min, 85%; (e) 4Å MS, Cs_2CO_3 (9.0 equiv), $PhI(OAc)_2$ (9.0 equiv), *t*-BuOOH (15 equiv), *n*-butyl butyrate/CH_2Cl_2 = 5:2, -15 °C, 36 h, 35%; (f) LiOH•H_2O (5.0 equiv), MeOH/H_2O = 2:1, 80 °C, 3 h; (g) $(COBr)_2$ (1.5 equiv), CH_2Cl_2/DMF = 4:1, 0 to 23 °C, 10 h, 25% for **32**, 21% for **33** over two steps; (h) $(n\text{-}Bu_3Sn)_2O$ (2.0 equiv), toluene, 80 °C, 1 h, 96%; 45% yield of **33** over three steps.

From here, **33** was converted into bis-stannane **34** (Scheme 5) under standard conditions. Unfortunately, attempted coupling with **23** did not succeed in delivering **25**; only decomposition products were observed. As a result, in a final effort, we developed an alternate route to synthesize the stannylated version of **23** (i.e. **35**, 6 steps from tetronic acid, see SI for details), and pleasingly, its union with **33** at both reactive sites could be achieved smoothly using catalytic $Pd(PPh_3)_4$ in the presence of CuTC.[25,31] Subsequent exposure to excess BBr_3 (20 equiv) in CH_2Cl_2 from –78 to –20 °C then effected a smooth deprotection of all six benzyl groups to deliver material in 52% yield over these final two steps which we presumed to be chalcitrin (**5**). As one measure of the overall efficiency of the route, ~70 mg of the final compound was obtained following several runs of different parts of the sequence. Unfortunately, our ^1H and ^{13}C spectra in acetone-d_6 and DMSO-d_6 did not match the values reported for the natural isolate.[32] Given that failure to obtain matching spectra can result from many issues,[12e,33] something we ourselves have recently experienced with other targets,[9b,34] we attempted a number standard alterations such as titrating in acid (TFA) as well as playing with counterions. Nothing afforded identical spectral values[35] until we obtained the sodium dicarboxylate salt by titrating synthetic chalcitrin (**5**) in DMSO-d_6 with NaDMSO-d_6;[33a] as such, we surmise that natural chalcitrin exists in its carboxylate form with alkali metal counterions present. Worth noting is that in its neat and protonated form, chalcitrin (**5**) is not stable under ambient conditions.

Scheme 5. Introduction of the Side-Chains via a Double Stille Coupling and Completion of a 17-Step Total Synthesis of Chalcitrin (**5**).[a]



[a] Reagents and conditions: (a) Me_6Sn_2 (2.5 equiv), LiCl (10.0 equiv), $Pd(Ph_3P)_4$ (0.2 equiv), THF, 60 °C, 30 min, 50% w/grease; (b) **35** (4.3 equiv), $Pd(PPh_3)_4$ (0.2 equiv), CuTC (4.0 equiv), NMP, 60 °C, 1.5 h; (c) BBr_3 (20 equiv), CH_2Cl_2, -78 to -20 °C, 3 h, 52% over two steps.

In conclusion, we have completed the first total synthesis of chalcitrin (**5**) through a route which utilized several effective C–C bond constructions to fashion the core along with a number of regio- and chemoselective transforms to place appropriate functional handles at the two sites needed for sidechain incorporation. Such flexibility proved essential as only one specific variant of the possible Stille coupling partners probed proved successful in achieving the desired transformation, executed here in a highly hindered setting to afford a tandem bond-forming process. Given recent interest in such couplings, many for natural product total synthesis, we anticipate that its success here will provide further inspiration for similar events in other contexts. Finally, the sequence is scalable, having delivered ~35 times the material resources obtained from an initial isolation effort using 300 g of fungi to obtain this intriguing polyphenol.[36]

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of all spectral data, cif files, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Notes: the authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Prof. Wolfgang Steglich (Leibniz Institut für Pflanzenbiochemie) for helpful discussions and kindly providing us with a physical copy of the original ^{13}C NMR spectra and isolation method for chalcitrin (**5**). We also thank Prof. Steglich, Dr. Norbert Arnold, and Dr. Serge Fobofou for supplying a

specimen of *Chalciporus piperatus.* We also thank Dr. Alexander Filatov for obtaining X-ray crystal structures of **27**, **32** and **33** and Dr. Antoni Jurkiewicz and Dr. C. Jin Qin for assistance with NMR and mass spectrometry, respectively. Financial support came from the University of Chicago and a JSPS Research Fellowship for Young Scientists (DC2, to H.F.). As alumni of Lanzhou University, M.Y. and F.Y. wish to dedicate this work to their alma mater on the occasion of its 110th anniversary.

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(32) Spectra in both solvents were taken since while the main text indicated peaks from a sample in DMSO-d_6, the SI section table indicated acetone-d_6 instead, with the latter being the same solvent used to characterize sclerocitrin. Complicating our analysis further was the absence of any physical spectra from the original paper for **5**; pleasingly, several were kindly provided by Prof. Steglich.

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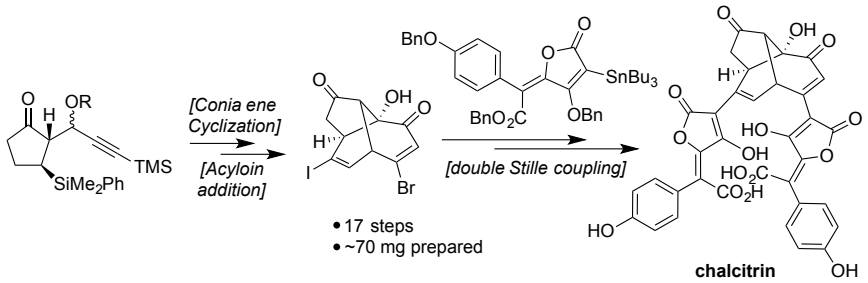
[Conia ene Cyclization]
[Acyloin addition]
[double Stille coupling]
• 17 steps
• ~70 mg prepared
chalcitrin