199 °C. Elemental analysis (%) calcd for $C_{36}H_{48}N_2O$: C 82.39, H 9.22, N 5.34; found: C 80.43, H 9.37, N 5.12; ^{1}H NMR (C_6D_6, 300 MHz, 25 °C, TMS): $\delta = 1.50$ (s, *t*Bu, 18H), 2.23 (s, Me, 18H), 2.36 (s, Me, 3H), 6.49 (s, C=CH, 2H), 6.63 (br s, NCHN, 1H), 6.88 (s, *m*-ArH, 4H), 7.17 (s, ArH, 2H) ppm.

5: **1** (0.30 g, 1.0 mmol) and **3** (0.17 g, 1.0 mmol) were dissolved in toluene (5 mL) by gentle warming. Overnight and at room temperature the resulting solution yielded a crop of orange crystals. First batch yield 0.18 g (38%), mp. 158–162 °C. Elemental analysis (%) calcd for $C_{33}H_{35}N_3$: C 83.68, H 7.45, N 8.87; found: C 82.85, H 7.37, N 8.92; ^{1}H NMR (C_6D_6, 300 MHz, 25 °C, TMS): $\delta = 2.25$ (s, *o*-Me, 12H), 2.26 (s, *p*-Me, 6H), 5.92 (br s, NH, 1H), 6.55 (s, C=CH, 2H), 6.90 (s, *m*-MesH, 4H), 6.96, 7.18, 7.26 (m, ArH, 10H) ppm.

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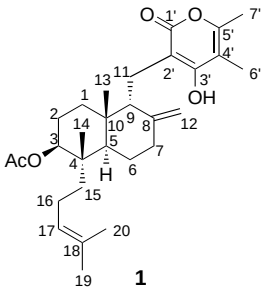
An Efficient Stereoselective Total Synthesis of DL-Sesquicillin, a Glucocorticoid Antagonist**

Fei Zhang and Samuel J. Danishefsky*

Sesquicillin is a C29 isoprenoid-related fermentation product isolated from *Acremonium* sp., strain 132-94.[1] The compound was first identified through screenings directed at the discovery of new agents that inhibit glucocorticoid-induced gene expression in suitably engineered COS-7 cells ($IC_{50} = 0.1–0.5$ μg). In principle, sesquicillin could function as a glucocorticoid antagonist.[2] Also, antihypertensive and bronchospasmolytic properties have been ascribed to sesquicillin in patent disclosures.[3] It is only relatively recently that the gross structure and stereochemistry of sesquicillin have been assigned to be **1**, largely on the basis of detailed NMR spectroscopic measurements. As such, sesquicillin bears a striking resemblance to subglutinols A and B.[4] We hoped that a total synthesis of sesquicillin would allow access to the natural product and its analogues. In this way, we could begin to evaluate the potential of this particular type of glucocorticoid antagonist in projected applications.



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[*] Prof. S. J. Danishefsky, F. Zhang
Department of Chemistry, Columbia University
Havemeyer Hall, New York, NY, 10027 (USA)
E-mail: s-danishefsky@ski.mskcc.org
Prof. S. J. Danishefsky
Laboratory for Bioorganic Chemistry
Sloan–Kettering Institute for Cancer Research
1275 York Avenue, Box 106, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691

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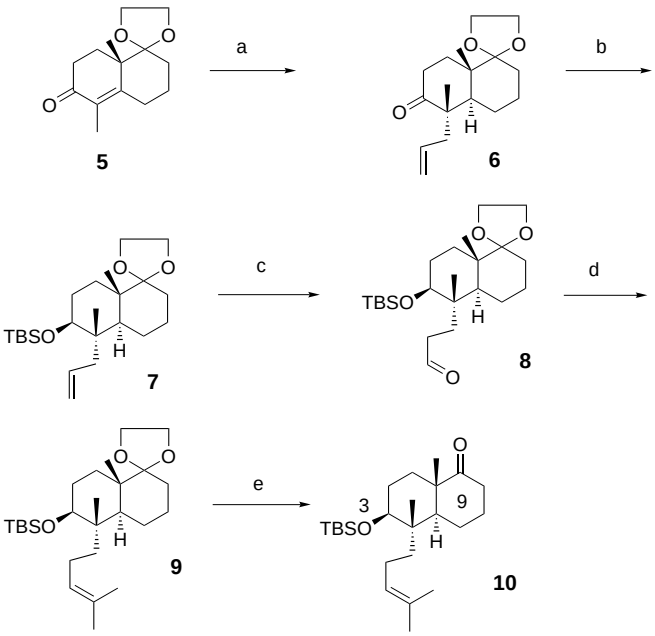
Construction of the AB ring sector of the target system was to follow traditional outlines established in numerous *trans*-decalin-based terpenoid and steroid targets.[5] A serious challenge arises from the need to elaborate a heavily substituted α-pyrone moiety joined to C11, which is axially linked to C9. During these operations, the integrity of the vulnerable *exo* methylene group attached to C8 must be maintained. We hoped to establish the required configuration at C9 relative to the chiral decalin matrix by a [3,3]-sigmatropic bond reorganization originating from suitable derivatization of allylic alcohol **2** (Scheme 1). The rearrangement reaction would produce structure type **4**. It was assumed that in this Claisen-like transformation, the terminal carbon atom (corresponding to C9) would be attacked from its preaxial (i.e. α) face.[6] After the rearrangement, we could broadly consider two perceptions for advancement toward **1** (Scheme 1). Option A: C21 in **4** could at some stage be excised through degradation, leaving C11 as the site for appendage. In this case, C11 must be joined to Cβ (corresponding to 2′) of a linear six-carbon-atom construct, which is further branched at Cγ (corresponding to the ultimate C4′). Option B: C21 would become C2′ of **1** following its interposition between a one-carbon-atom residue (destined to become C1′) and a four-carbon-atom ensemble, branched at its β-carbon atom. Cα of this ensemble eventually becomes C3′ while the β-methyl branch becomes C4′ in **1**.

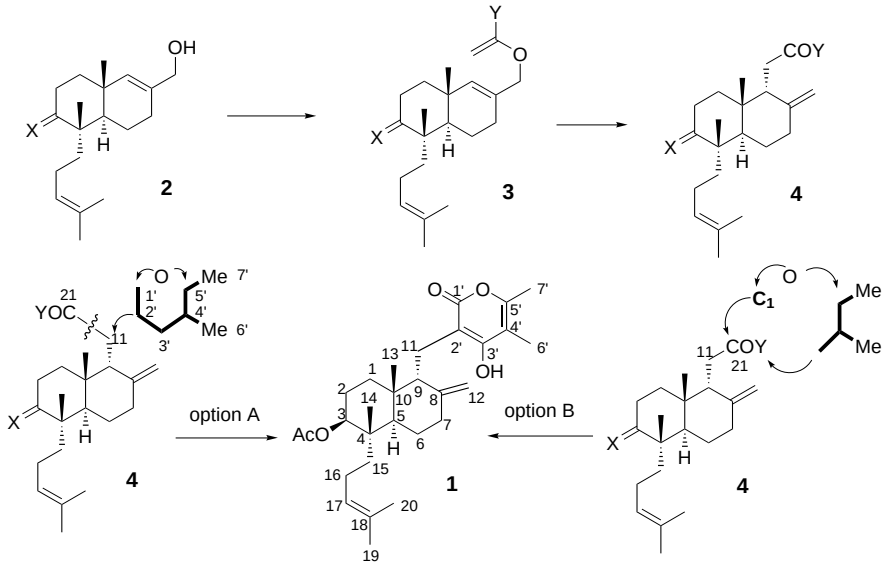
We started with the known ketone **5** (Scheme 2).[7a] The homoprenyl chain was introduced segmentally,[7b] reflecting concerns (based on the results of early probes) about direct alkylation of a C4 enolate with a homoprenyl electrophile. In the event, allylation at C4, which exploited the reductively generated kinetic enolate,[8] gave rise to **6**. Stereospecific reduction of the ketone group and protection of the resulting β-alcohol gave **7**. Chain extension to complete the homoprenyl function proceeded smoothly via aldehyde **8**. Fortunately, PPTS[9] could be used to deprotect the ketal at C9 without reexposure of the alcohol at C3 (see compound **10**, Scheme 2).



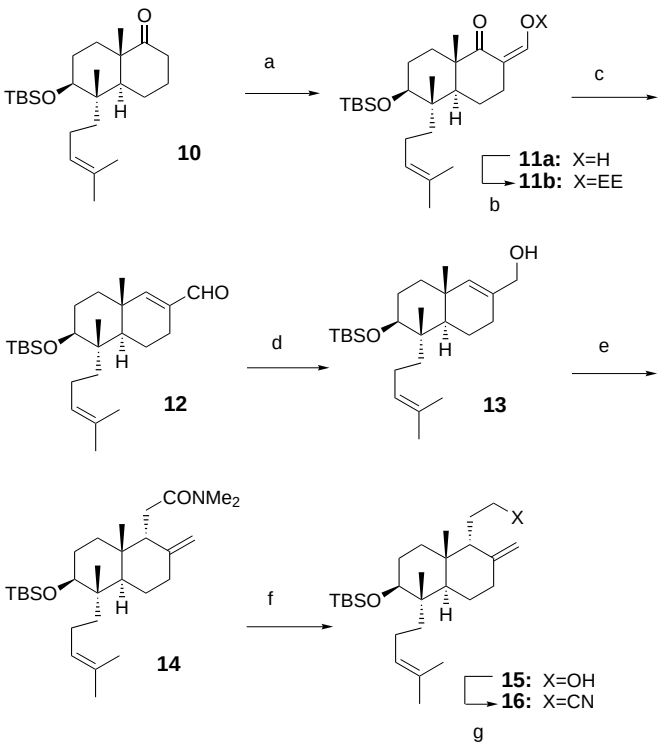
Scheme 2. Reagents and conditions: a) 1. Li/liquid ammonia/THF/*t*BuOH, $-78\,^{\circ}C \rightarrow RT$; 2. allyl bromide (6.25 equiv), 78%; b) 1. $NaBH_4$/EtOH; 2. TBSOTf, 2,6-lutidine, CH_2Cl_2, $-78\,^{\circ}C \rightarrow RT$, 83%; c) 1. $BH_3\cdot$THF, room temperature; 2. $NaOH/H_2O_2$, reflux; 3. PCC, CH_2Cl_2, 56%; d) isopropyltriphenylphosphonium iodide, *t*BuLi, DMSO, 85%; e) PPTS, acetone, reflux, 96%. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; PCC = pyridinium chlorochromate; DMSO = dimethyl sulfoxide; PPTS = pyridinium *p*-toluenesulfonate.

A specific and functional version of the allylic alcohol that corresponds to hypothetical structure **2** (Scheme 1) was constructed along established lines. Following formylation of **10** with ethyl formate,[10] the resulting enol of **11a** was protected through a seldom-used mixed *enol acetalization* protocol (Scheme 3).[11] Reduction of the ketone group of **11b** and acid-induced unmasking of the resulting β-alkoxy allylic alcohol, led to aldehyde **12**. Reduction of the aldehyde function with sodium borohydride afforded **13**, the precursor for the crucial [3,3] sigmatropic rearrangement.

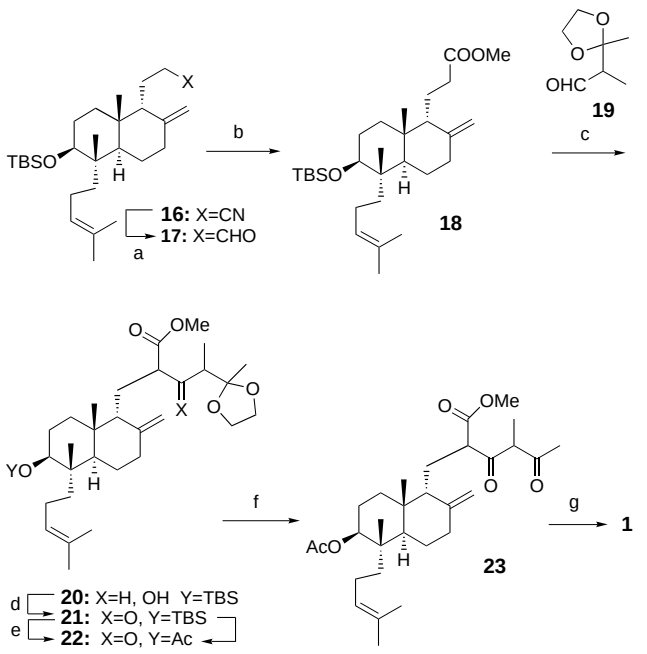
A variety of Claisen-related protocols[12] were screened for the conversion of **13** into a product of the general type **4** (Scheme 1). Of these, the Eschenmoser variation[13] shown below was by far the most effective and delivered **14**, which contains the γ,δ-unsaturated *N*,*N*-dimethylamide function, in high yield with very high stereoselectivity (>20:1). Attempts to convert the dimethylamide function of **14** into the corresponding acid by direct hydrolysis were, as expected, unrewarding. It seems that C21 (structure **4**) is, in fact, quite hindered. The hindrance is probably even greater at C11. We therefore directed our early efforts to reach **1** toward option B. As shown below, this strategy required particular care to maintain the problem-



Scheme 1. Strategic pathway to sesquicillin A.



Scheme 3. Reagents and conditions: a) NaH/THF, ethyl formate, reflux; b) ethyl vinyl ether, H_3PO_4 (cat); c) 1. $NaBH_4$/EtOH; 2. HCl (0.5 N), THF/water, 80% over four steps; d) $NaBH_4$/EtOH, 100%; e) *N*,*N*-dimethyl acetamide dimethyl acetal, *m*-xylene, reflux, 87%; f) superhydride, THF, 99%; g) 1. $MeSO_2Cl$, Et_3N, CH_2Cl_2; 2. NaCN, DMF, 100%. DMF = *N*,*N*-dimethylformamide.



Scheme 4. Reagents and conditions: a) DIBAL-H, hexanes, −78 °C → RT; b) 1. $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O; 2. $TMSCHN_2$, MeOH, benzene, 50% over three steps; c) LDA, **19**, THF, −78 °C, 62%; d) DMP, CH_2Cl_2, 100%; e) 1. HF/CH_3CN; 2. Ac_2O, Et_3N, DMAP, CH_2Cl_2, 83%; f) $[Pd(CH_3CN)_2Cl_2]$, acetone, 97%; g) DBU, benzene, reflux, 61%. DIBAL-H = diisobutylaluminum hydride, TMS = trimethylsilyl, LDA = lithium diisopropylamide, DMP = Dess–Martin periodinane, DMAP = 4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

atic *exo* methylene function in place. The congestion problem was solved through the use of relatively nonbulky reagents. Fortunately, the tertiary amide moiety was converted smoothly into the corresponding alcohol **15** through the use of superhydride. Activation of the alcohol as its mesylate set the stage for chain extension by cyanide displacement (see compound **16**, Scheme 3).

We were unable to devise conditions to reach the C21 acid or ester *directly* from **16**, and again circumspection was required. Reduction of nitrile **16** with DIBAL-H led to the corresponding aldehyde **17** in crude form (Scheme 4). Oxidation and esterification of **17** gave methyl ester **18**. Key to our eventual success was the finding that the ester could be deprotonated with LDA. The resulting C2′ enolate (sesquicillin numbering) did add to the known aldehyde **19** to give **20**.[14] Alcohol **20** was oxidized with the Dess–Martin periodinane[15] to afford **21** as a complex mixture of stereoisomers. Cleavage of the C3 siloxy function[16] generated an alcohol, which was acetylated to give **22**. The total synthesis phase of this project was then completed by treatment of crude **22** with $[Pd(CH_3CN)_2Cl_2]$, and subsequent DBU-induced enol lactonization of **23** to give DL-sesquicillin (**1**). The ^1H and ^{13}C NMR spectra of synthetic and natural sesquicillin[1] were identical. Although the total synthesis reported herein is that of racemic **1**, it would be a straightforward matter to prepare either antipode by starting with enantiomerically pure homogenous **5**.[7a]

We note that the current unoptimized total synthesis of sesquicillin (3.1% overall yield) produces ample amounts of compound for broad-ranging biological studies. It also illustrates the power of the amide acetal version of the Claisen rearrangement (cf. **13** → **14**)[13] and serves to teach, by example, how serious interactive problems of steric hindrance and labile functionality can be overcome.

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