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Total Synthesis of the Reported Structure of Stresgenin B Enabled by the Diastereoselective Cyanation of an Oxocarbenium

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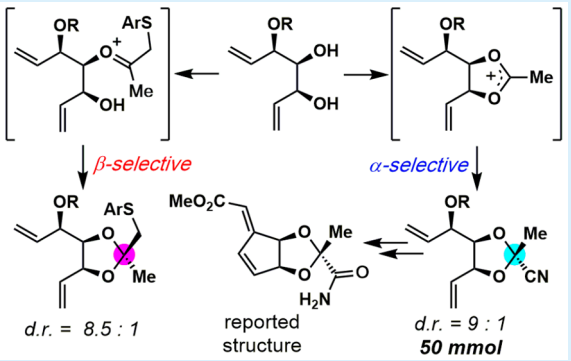
Supporting Information

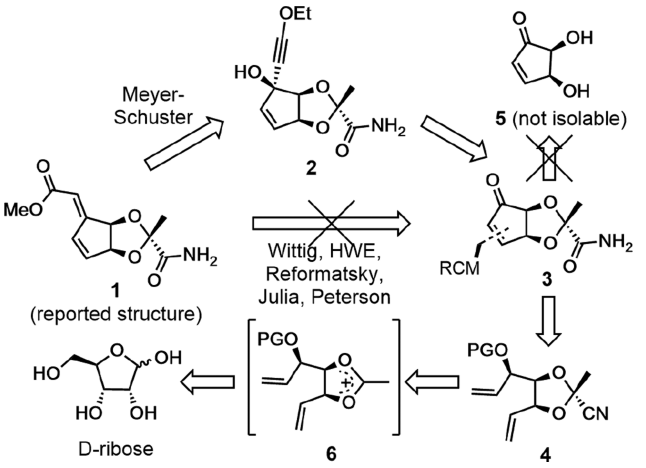
ABSTRACT: We report the first total synthesis of the reported structure of the heat shock protein expression inhibitor stresgenin B. The synthesis features (1) diastereoselective cyanation of an oxocarbenium intermediate en route to the synthetically challenging α-amido dioxolane, (2) Pd-catalyzed hydration of an unstable nitrile, and (3) late-stage Au-catalyzed Meyer–Schuster rearrangement or Ce-mediated Peterson olefination to furnish the exocyclic α,β-unsaturated ester. Our synthetic endeavors allowed us to conclude that the structure of stresgenin B requires revision.



Heat shock proteins (HSPs), such as HSP70 and HSP90, are molecular chaperones that perform various biological processes vital for cell survival. Their overexpression has been implicated in the development, proliferation, and various aspects of the survival of cancer cells—many of their client proteins are oncogenic. HSPs have garnered a tremendous amount of attention from the research community as cancer drug targets (~50 clinical trials as of 2016).[1,2] Most of the clinically studied HSP90 inhibitors bind to the *N*-terminus (ATP-binding site) of the protein. It is known that this mode of inhibition triggers a heat-shock response (HSR) and induces the syntheses of other HSPs (e.g., HSP27, 40 and 70) that also have protective activity toward cancer cells. These limitations reduce the efficacies of the HSP90 inhibitors.[1,2] There are some *C*-terminal inhibitors documented, and they do not trigger a HSR.[2] Nevertheless, targeting the biosynthesis of an HSP, rather than directly targeting the protein, provides a different promising therapeutic approach that might bypass the problem of HSR. In the literature, small molecules that inhibit the biosynthesis of HSPs are very rare (e.g., quercetin).[3] It was discovered that stresgenin B was capable of inhibiting the heat-induced gene expression of the human *HSP70B* promoter driven luciferase in Chinese hamster ovary cells.[3] The IC_{50} of stresgenin B in the *HSP70B* promoter assay was 7.0 μM.[3] Meanwhile, stresgenin B was also found to be cytotoxic against various cancer cell lines with IC_{50} values of 2.6–19.5 μM.[3] The closely related IC_{50} values suggested that the cytotoxicity may be directly correlated with the inhibition of *HSP70B* expression. This natural product also inhibited heat-shock-induced syntheses of HSP72/73, HSP90, and HSP110.[3]

The structure of the natural product was proposed based on UV, ^{1}H and ^{13}C NMR, HMQC, HMBC, and NOESY spectroscopic experiments. It was reported to contain a rare amide-substituted dioxolane (Scheme 1).[3] The absolute stereochemistry was not reported.[4] The prospects of stresgenin B being a lead for development of HSP expression inhibitors, combined with its hitherto unknown mode of action, prompted us to embark on a synthetic project on this molecule. In this paper, we report the first total synthesis of the proposed structure of stresgenin B and its *Z*-isomer to determine that the proposed chemical structure requires revision.

Scheme 1. Reported Structure and Retrosynthetic Analysis of Stresgenin B (1)



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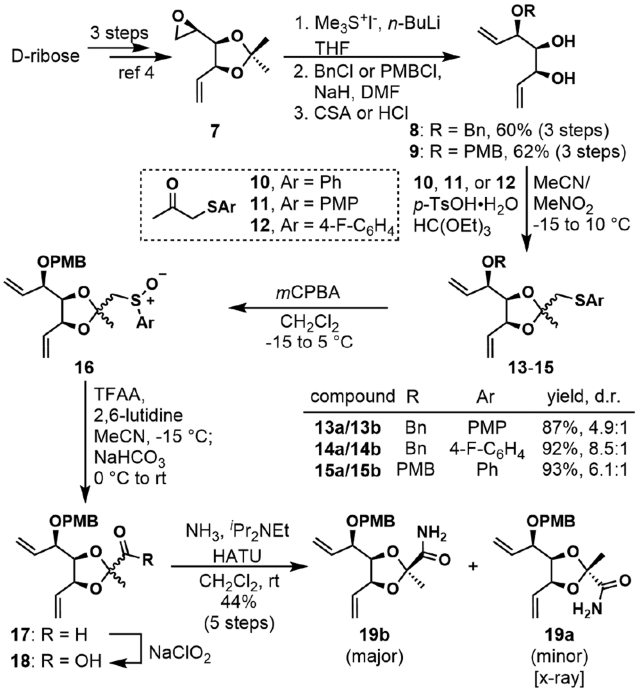
To unambiguously determine the absolute stereoconfiguration of stresgenin B (**1**), we chose a chiral pool synthesis. From our preliminary studies, we found that cyclopentenone **5** was not an accessible intermediate, that the formation of the highly reactive cyclopentenone should be postponed to a late stage, and that the α,β-unsaturated ester was inaccessible via traditional olefination methods. After experimentally evaluating several approaches, we arrived at the synthetic strategy depicted in Scheme 1. Retrosynthetically, the exocyclic α,β-unsaturated ester would be formed by a Meyer−Schuster rearrangement. The primary amide would be derived from an unstable cyanoketal **4**. The nitrile could be installed stereoselectively via a neighboring group directed cyanation of an oxocarbenium intermediate **6**.

We commenced our synthesis from commercially available D-ribose (Scheme 2), and the known epoxide **7** was prepared

Scheme 2. Initial Synthetic Route



in three steps in 53% overall yield.[4] The epoxide was homologated,[4b,c] the product of which was then subjected to protecting group manipulations to give diols **8** and **9** in 60 and 62% yield over three steps, respectively. The direct construction of the α-amidodioxolane functionality proved to be very challenging.[5] The direct condensation of various α-ketoamides and α-ketoesters was futile, notwithstanding the lack of any stereoselectivity. After much exploration, we settled on (phenylthio)acetones **10**−**12** to form the requisite dioxolane (first-generation route, Scheme 2). Reaction conditions were optimized to afford a good dr of up to 8.5:1 (with **12**). At this juncture, we were uncertain of the stereochemical outcome, but it was ascertained by proceeding with the synthetic scheme. We opted to elaborate the thiophenyl handle of **15** as we anticipated facile late-stage PMB deprotection. This sequence allowed us to isolate **19a** as a crystalline solid with the desired stereoconfiguration, unfortunately as the minor isomer (Scheme 2). When we varied the electronics of R and Ar groups systematically (see the SI for additional experiments), the major isomer was the same in all cases. Additionally, the stereoselectivity improved with an electron-poor Ar group but appeared to be independent of the electronics of the R group (Bn or PMB). Taken together, we propose that electrostatic and $\pi-\pi$ interactions are involved. The oxocarbenium **20b** (Figure 1)

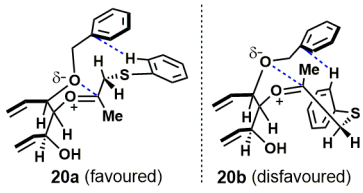
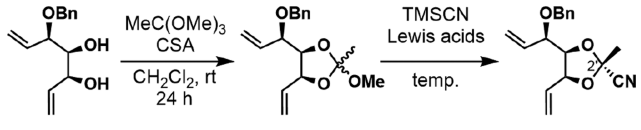


Figure 1. Proposed stereochemical model.

might be more sterically sensitive, keeping the Bn group further from the oxocarbenium, decreasing the electrostatic stabilization. An electron-rich R group (i.e., PMB, see the SI) should have stronger electrostatic attraction that is presumably counterbalanced by weaker $\pi-\pi$ interaction.[6,7]

We then decided to pursue a different strategy that might enable us to both create the dioxolane and reverse the stereoselectivity (Table 1 and Scheme 3). We envisioned that a

Table 1. Optimization of Cyanation



entry	Lewis acid (equiv)	temp (°C)	yield (dr)[b] (%)
1	n-Bu_2BOTf (1.5)	25	dec
2	$Sc(OTf)_3$ (0.20)	25	16 (7.1:1)
3	$TiCl_4$ (1.5)	25	15 (6.9:1)
4	$Yb(OTf)_3 \cdot nH_2O$ (0.20)	25	dec
5	$TiCl_4$ (1.5)	−78	76 (12:1)
6	$AlCl_3$ (1.5)	−78	trace (nd)[c]
7	Et_2AlCl (1.5)	−78	30 (14:1)
8	$SnCl_4$ (1.5)	−78	35 (8:1)
9	$BF_3 \cdot OEt_2$ (1.5)	−78	91 (8.2:1)
10	$BF_3 \cdot OEt_2$ (1.5)	−78 to −20	97 (9:1)[d]

[a]Typical reaction conditions: **8** (0.10 mmol, 1 equiv), $MeC(OMe)_3$ (0.15 mmol, 1.5 equiv), CSA (0.0050 mmol, 0.05 equiv), CH_2Cl_2, rt, then TMSCN (4.0 equiv), Lewis acid (x equiv). [b]Determined by ^1H NMR analysis using mesitylene as external standard. [c]nd = not determined. [d]50 mmol scale, combined isolated yield of diastereomers.

benzyloxy substituent at C-3 (Scheme 3) might undergo neighboring-group participation in a cyclic oxocarbenium ion.[8−10] We sought to generate the oxocarbenium via an orthoester. Diol **8** was treated with $MeC(OMe)_3$ under acidic conditions, and the resulting orthoester **22** was treated with TMSCN and $BF_3 \cdot OEt_2$ to afford cyanoketal **23** (Table 1). Other Lewis acids generally proved to be inferior (entries 1−4 and 6−8). $TiCl_4$ afforded a higher dr (entry 5), but we reasoned the difficulty in workup renders it unsuitable for scale-up purposes.

DFT calculations were undertaken to further understand the factors governing the stereoselectivity of cyanation. We located two transition states, **TS1** and **TS2** (Figure 2A). The distance of 3.16 or 3.30 Å (Figure 2A) between the benzyl ether oxygen

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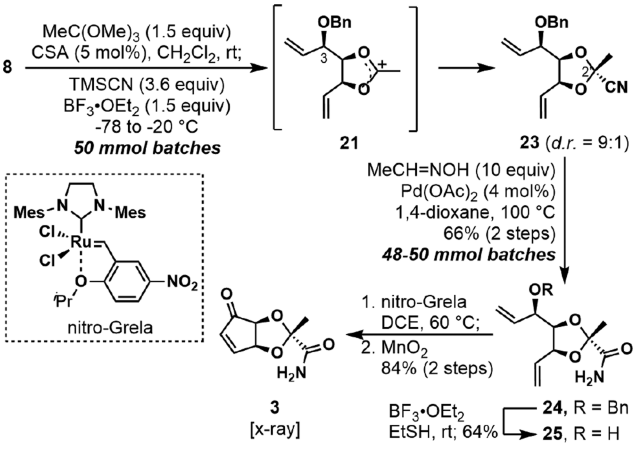
Scheme 3. Second-Generation Synthetic Scheme



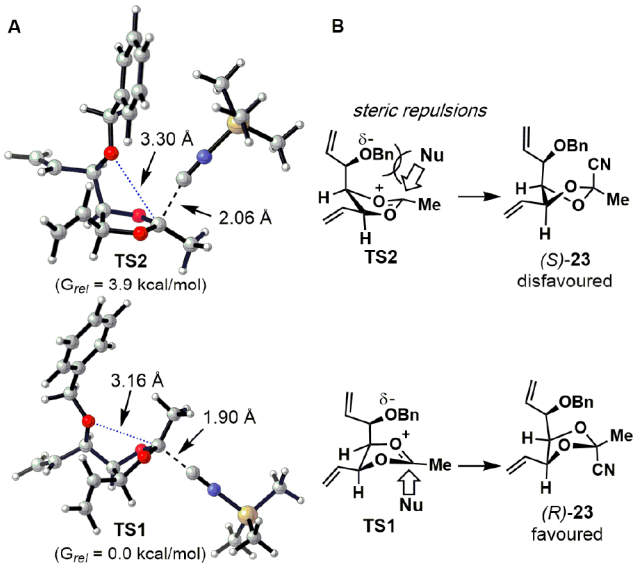


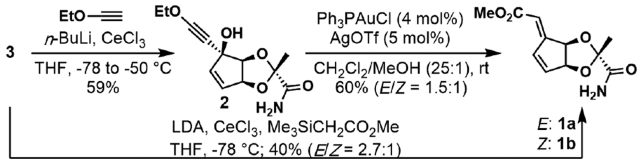
Figure 2. Calculated transition states and proposed stereochemical model. Transition states were computed using M06-2x/6-311++G(d,p)/SMD(dichloromethane)//B3LYP/6-31G(d).

and oxocarbenium suggests that it is a noncovalent interaction, not a formal neighboring-group participation.[8] We attribute the difference in energies of the transition states to a combination of electrostatics and sterics. In **TS2**, the benzyl ether is further away from the oxocarbenium to accommodate the incoming nucleophile, thereby weakening the electrostatic interaction. The stereochemical model is reminiscent of the reports by Woerpel et al. on alkoxy-directed/accelerated nucleophilic additions to acetal-derived oxocarbeniums.[10] In our case, we note that this may be the first example of the use of neighboring-group stabilization as a stereocontrolling factor in a dioxolane derivative synthesis. The conversion of the nitrile to primary amide **24** (Scheme 3) was met with difficulties because of the dioxolane ring opening under widely used reaction conditions, such as alkaline H_2O_2 and Parkins' catalyst,[11] [PtH{$(PMe_2O)_2H$}(PMe_2OH)].

After some trials, we discovered that an anhydrous hydration methodology developed by Chang and Lee using Wilkinson's catalyst, $(Ph_3P)_3RhCl$, provided trace amounts of the desired primary amide **24**.[12] Screening of transition-metal catalysts revealed that $Pd(OAc)_2$ to be the catalyst of choice. This transformation is robust, scalable (up to 50 mmol), and may find broader applications for the conversion of nitriles to primary amides in complex molecules syntheses.[11,12] With **24** in hand, we proceeded to forge the cyclopentenone moiety. Debenzylation was also problematic; the results were either degradation of starting materials or difficult workups and irreproducible yields on larger scales (see the SI for the conditions tested). We found that the rarely employed combination of $BF_3{\cdot}OEt_2$ and EtSH afforded the desired allylic alcohol **25** in 64% yield.[13] Ring-closing metathesis (RCM) using nitro-Grela catalyst[14] was uneventful, and the ensuing oxidation could be performed in a one-pot fashion using MnO_2 to give **3** in 84%.

Preliminary experiments had revealed that the predominant, undesired reactivity of enone **3** was conjugate addition, presumably due to the ring strain of the cyclopentenone moiety. Traditional olefination conditions (e.g., Wittig/Horner–Wadsworth–Emmons, Reformatsky, Julia, Peterson) resulted in either no conversion, conjugate addition, or degradation of starting material under more forcing conditions. We reasoned that a hard and sterically unhindered metal acetylide might preferentially undergo 1,2-addition with **3** (Scheme 4).[15] Thus, we were able to synthesize the

Scheme 4. End-Game of Total Synthesis



propargylic alcohol **2** as a single diastereomer in 59% isolated yield. The propargylic alcohol underwent a smooth Meyer–Schuster rearrangement in excess MeOH to give the reported structure (**1a**) and its *Z* isomer (**1b**), albeit with modest *E*/*Z* selectivity (see the SI for a mechanistic rationale).[16] More conveniently, we also found that Ce-mediated Peterson olefination of ketone **3** could directly afford **1a** and **1b** in 40% combined yield (unoptimized). To our knowledge, this is the first example of a direct olefination using an organocerium enolate.[15] The structure of **1a** was unambiguously confirmed by X-ray analysis.

The ^1H and ^{13}C NMR spectra of both **1a** and **1b** did not match those reported for stresgenin B. In particular, ^{13}C NMR spectrum of **1a** shows striking dissimilarities for the chemical shifts of C2–C5, with differences ranging from 4.5 to 26.0 ppm (see the SI). These differences cannot be accounted by mere stereochemical mis-assignments (i.e., epimers, diastereomers). Furthermore, the coupling constant reported for the olefin C–H's was 9.7 Hz, while those of **1a** and **1b** were 6.0 and 5.6 Hz, respectively. Based on literature surveys and our observations with disubstituted cyclopentene systems, the endocyclic olefin has signature coupling constants of 5.0–6.0 Hz. These strongly suggest the natural product contains a ring structure other than a cyclopentene.[17,18]

We first envisioned two possible constitutional isomers **CS1** and **CS2** (Table 2).[19] Our calculated chemical shifts for C-2 to C-5 suggested the plausibility of a cyclohexadiene motif. Changing the position of the methoxy ester substituent afforded better results for C-2 to C-5 with **CS2** over **CS1**. Therefore, we chose to focus on this constitutional isomer **CS2**. Diastereomeric structure **CS3** gave larger MAD and

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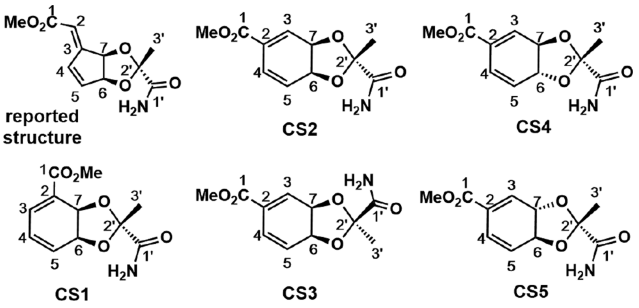
Table 2. Comparison of ^{13}C NMR Data



position	natural	CS1	CS2	CS3	CS4	CS5
O−CH_3	52.2	51.2	51.6	51.4	51.4	51.3
C-1	164.5	166.1	164.2	164.5	164.1	163.8
C-2	130.0	123.3	126.7	125.9	129.0	129.0
C-3	136.2	138.7	137.6	140.4	141.8	141.2
C-4	124.4	120.4	122.8	126.1	131.0	124.4
C-5	129.1	139.8	125.7	125.2	131.2	131.6
C-6	79.2	74.0	69.8	70.0	78.6	78.9
C-7	80.9	68.4	71.2	73.6	80.4	80.1
C-3′	22.1	21.6	21.2	20.3	20.7	21.1
C-2′	109.8	102.1	101.8	104.3	110.8	110.9
C-1′	172.1	169.3	170.1	168.2	175.9	168.3
MAD[a]		5.0	3.7	3.9	2.2	1.6
RMSD[b]		6.2	5.1	4.7	3.0	2.2

[a]MAD = mean absolute deviation. [b]RMSD = root-mean-square deviation. Calculated using GIAO/mPW1PW91/6-311+G(2d,p)/SMD(chloroform)//B3LYP/6-31+G(d,p).[19]

RMSD than **CS2**. The chemical shifts for C-6, C-7, and C-2′ of **CS2** and **CS3** still exhibited large deviations.

We thus wondered whether the dioxolane ring could be trans-fused to the cyclohexadiene (**CS4** and **CS5**). We were initially skeptical as we were not aware of any literature precedence for this trans-fused 6/5-ring system. Despite the lack of literature support, the calculated NMR data of **CS5** showed the lowest MAD and RMSD (^1H NMR: MAD = 0.10 and RMSD = 0.12; see the SI). Moreover, we reasoned that a trans-fused bicycle might be less susceptible to aromatization. Akagawa et al. used the UV−vis spectrum of stresgenin B with a peak at 275 nm as a basis for the presence of a *fully conjugated* dienoate.[3b] However, Figure 5 of the original patent[3a] does not clearly show such a peak. The structure of **CS5** does not support their NOESY correlations. Specifically, the authors reported NOE correlation between ester CH_3 and α-olefin C−H; they assigned this olefin proton to the peak at 7.43 ppm—we believe this to be a mis-assignment—the peak at 7.43 ppm must be due to an olefin C−H conjugated to the ester. If **CS5** is the correct structure, the reported correlation would refer to the ester CH_3 and β-vinyl C−H (position 3, 7.46 ppm). Nevertheless, the calculated average distance between ester CH_3 and β-olefin C−H (conformer 1 of **CS5**) is ∼4.27 Å, indicating that the NOE enhancement might be relatively weak. In addition, the authors reported NOE correlations between the dioxolane methyl group and the peaks at 7.43 and 6.43 ppm; none of our candidate structures can account for these correlations. At this point, without access to the original NOESY experiment data, it is not possible to determine whether these NOE enhancements are significant. While our DFT calculations support **CS5**, other constitutional isomers and diastereomers cannot be fully excluded.

In conclusion, we have accomplished the first total synthesis of the reported structure of stresgenin B. The success of our synthesis hinges upon a benzyloxy neighboring-group-controlled diastereoselective cyanation of a cyclic oxocarbenium ion. We found that by switching to an acyclic oxocarbenium, the diastereoselectivity could be reversed. A notable feature of our work is the presence of a free primary amide through the late-stage of the synthesis. We also investigated plausible structures of stresgenin B via computational methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03219.

Experimental procedures, computational details and characterization data for new compounds (PDF)

Accession Codes

CCDC 1863016−1863019 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839−1862 We note that for constitutional isomer **CS2** there are 2^3 stereoisomers, four of which are NMR-distinguishable diastereomers, corresponding to **CS2**−**CS5**. We also note that for **CS5** the chemical shift for C-3 still has an absolute deviation of 5.0 ppm. We observed similar overestimations when we tested the method on the reported structure, compared to our experimental spectra. We think there is a systematic error of overestimating carbons conjugated (β and δ carbons) to an electron-withdrawing group .

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