Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K

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Abstract: The first total synthesis of heavily oxidized cassane-type diterpenoid neocaesalpin A (**1**) is disclosed. At the heart of the synthesis lies an intermolecular Diels–Alder reaction that rapidly assembles the target framework from commercial materials. A carefully orchestrated sequence of oxidations secured the desired oxygenation pattern. Late-stage release of the characteristic butenolide occurred through a novel mercury(II)-mediated furan oxidation. Successful extension of the route allowed preparation of neocaesalpin AA (**2**) as well as nominal neocaesalpin K (**3**) and suggested structural revision of neocaesalpin K, leading to the hypothesis that the two are likely the same natural product with correct assignment as **2**.

Cassane-type diterpenoids have been isolated from medicinal plants of the genus *Caesalpinia* which comprises approximately 100 species and is commonly found in tropical and subtropical regions.[1] To date, more than 450 cassane-type diterpenoids have been reported, and their biological properties include anti-inflammatory, antimalarial, antitumor, antiviral, antimicrobial, and antioxidant effects.[2] The structural complexity and promising biological activity of cassane-type diterpenoids has been of interest to the synthetic community.[3] Our attention has been drawn on neocaesalpin A (**1,** Figure 1),[4] isolated in 1996 from *Caesalpinia bonduc* (L.), the first cassane-type diterpenoid reported with a butenolide ring. Herein, we disclose the first total synthesis of neocaesalpin A (**1**). Extension of the route allowed synthesis of related neocaesalpin AA (**2**)[5] and nominal neocaesalpin K (**3**).[6]

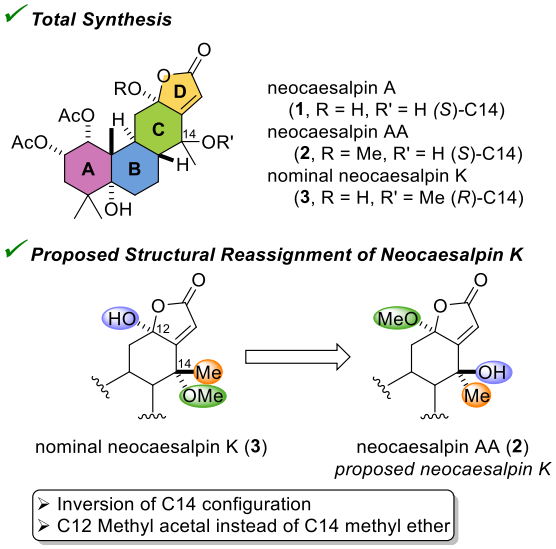
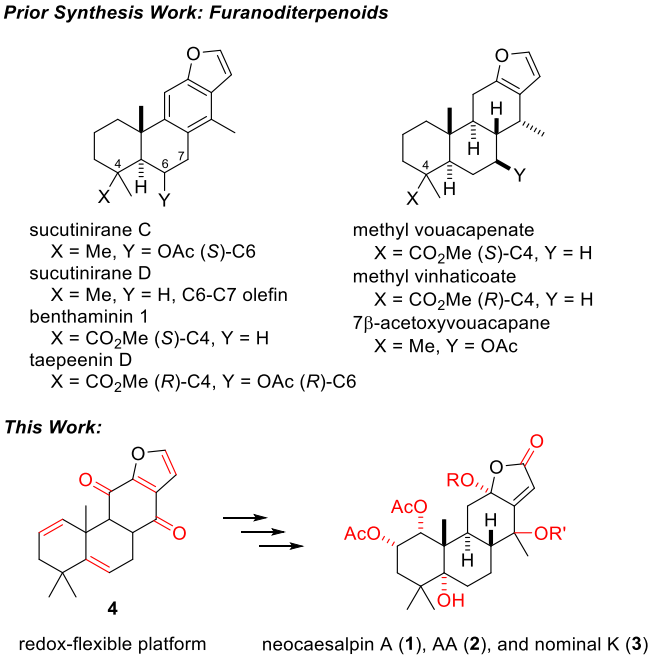


Figure 1. Neocaesalpin A (**1**), AA (**2**), and nominal neocaesalpin K (**3**).

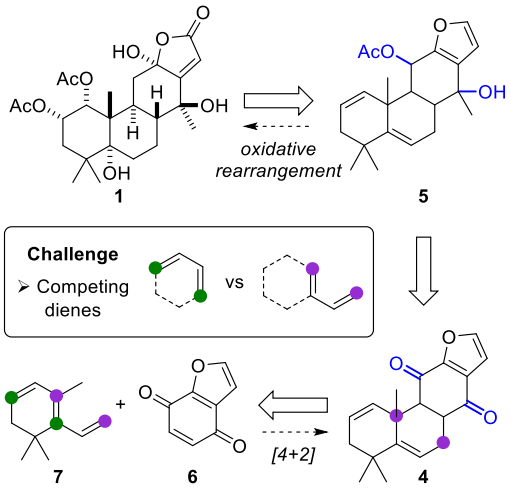
Prior work on cassane-type diterpenoids has generally focused on the family of secondary metabolites with fused benzofurans bearing **A** and **B** rings that are not extensively oxidized unlike the neocaesalpins. This includes the sucutiniranes, benthaminines, and taepeenins as well as representatives with reduced **C** ring, as exemplified by methyl vouacapenate, methyl vinhaticoate, and 7β-acetoxyvouacapane (Scheme 1).[3]

A key feature of the work we describe is to provide access to more extensively oxidized cassanes, such as neocaesalpin A (**1**), AA (**2**), and nominal K (**3**) via key intermediate **4** as a redox-flexible platform. Moreover, we delineate an approach that enables novel late-stage oxidation of a furfuryl acetate under mild conditions to furnish the characteristic butenolide **D** ring. Our work validates the reported assignment for **1** as well as **2** and reveals misassignment of neocaesalpin K (**3**). We posit that neocaesalpin AA and neocaesalpin K may be the same natural product with correct structure as shown for **2**.



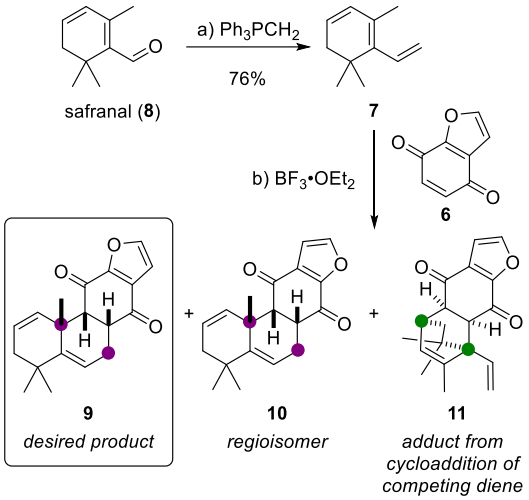
Scheme 1. Prior syntheses of cassane-type diterpenoids and this work.

The retrosynthetic analysis for the route developed in our study is outlined in Scheme 2. Butenolide **D** ring was anticipated to arise from furfuryl acetate **5** via an oxidative rearrangement reaction.[7] Inspection of **5** suggests implementation of a Diels–Alder cycloaddition reaction of furanoquinone **6** and triene **7**. To the best of our knowledge, participation of **7** in Diels-Alder reactions has not been reported. We were cognizant that the use of triene **7** could lead to potential complications from competing [4+2] cycloadditions of two dienes, endocyclic versus exocyclic, with furanoquinone **6**. Thus, we wanted to explore the potential reactivity landscape of **7** to provide access to redox-flexible platform **4**.



Scheme 2. Retrosynthetic analysis of neocaesalpin A (**1**).

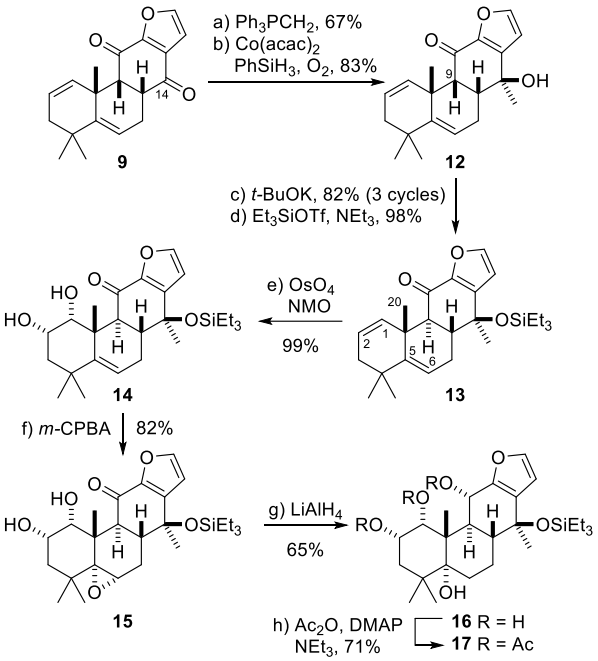
The synthesis of neocaesalpin A (**1**) commenced with preparation of triene **7**. Wittig methenylation of safranal (**8**) in Me_2SO[8] furnished volatile triene **7** in 76% yield (Scheme 3). Triene **7** and furanoquinone **6**[3k, 9] readily underwent cycloaddition in hexafluoroisopropanol (HFIP)[3k, 10] at ambient temperature and in 15 min to form adduct **9** and its regioisomer **10** as an inseparable mixture in combined yield of 51% (**9**:**10** = 8.7:1) along with **11** (33%). The latter resulted from competitive cycloaddition of the endocyclic diene. Further optimization showed that conducting the reaction at −78 °C in presence of BF_3•OEt_2 led to a significant increase in the production of **9** which was formed in combined yield of 85% with regioisomer **10** (**9**:**10** = 6.7:1). Under the improved conditions, only small amounts of adduct **11** (11%) were formed.



Scheme 3. Assembly of the 6−6−6−5 framework from safranal (**8**). Reagents and conditions: a) NaH, Ph_3PMeBr, Me_2SO, rt, 76%, b) BF_3•OEt_2, CH_2Cl_2, −78 °C, 85% (**9**:**10** =6.7:1).

With the full carbocyclic cassane skeleton in hand, we focused on differentiation of the two ketones in **9** (Scheme 4).[3k, 10] Subjecting the inseparable mixture obtained from the cycloaddition reaction to Wittig methenylation led to formation of the C14 methylene which was isolated in 67% yield as a single isomer. Mukaiyama hydration[11] of the resulting exocyclic olefin gave **12** in 83% yield. Subsequently, epimerization of the C9 center in presence of *t*-BuOK afforded a 1.1:1 ratio (^{1}H NMR analysis of unpurified reaction mixture) of *trans*-isomer and *cis*-starting material. Resubjecting recovered starting material **12** to two rounds of epimerization and isolation increased the overall yield of the *trans*-product to 82%. Alcohol silylation with Et_3SiOTf afforded **13** from which subsequent functionalization of the di- and trisubstituted olefins was explored.

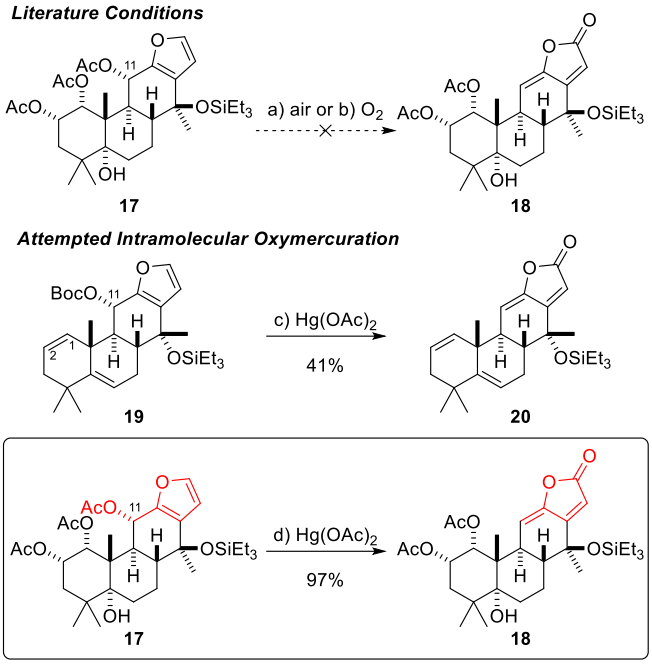
Dihydroxylation employing conditions developed by VanRheenen and Kelly (Upjohn)[12] led exclusively to **14** as a single diastereomer in 99% yield. We hypothesize that formation of the intermediate osmate ester occurs from the more accessible face, opposite the C20 methyl group.[13] As the observed high chemoselectivity in dihydroxylation of the C1-C2 disubstituted olefin would suggest, functionalization of the trisubstituted C5-C6 olefin proved more difficult. Initial attempts were aimed at installing the hindered C5 hydroxy group directly via Mukaiyama hydration. However, the conditions previously employed ($Co(acac)_2$, $PhSiH_3$, O_2, *i*-PrOH) performed poorly, giving the desired hydration product in merely 16% yield. Although residual starting material was recovered (40%), increasing the reaction time did not lead to more product. Further optimization of reaction conditions (catalyst, solvent or additives) did not improve the yield. As an alternative, Prilezhaev epoxidation with *m*-CPBA provided C5-C6 epoxide **15** (82%). Treatment of **15** with $LiAlH_4$ effected epoxide opening and concomitant ketone reduction in 65% yield. Acetylation of tetraol **16** led to furfuryl acetate **17** in 71% yield wherein all but the tertiary alcohol had undergone esterification.



Scheme 4. Synthesis of furfuryl acetate **17**. Reagents and conditions: a) *n*-BuLi, Ph_3PMeBr, THF, −78 °C to rt, 67%; b) $Co(acac)_2$ (20 mol%), $PhSiH_3$, O_2 (1 atm), *i*-PrOH, rt, 83%. c) *t*-BuOK, *t*-BuOH, rt, 50%; d) Et_3SiOTf, NEt_3, CH_2Cl_2, 0 °C, 98%; e) OsO_4 (20 mol%), *N*-methylmorpholine *N*-oxide (NMO), acetone−H_2O (12:1), rt, 99%; f) *m*-CPBA, CH_2Cl_2, rt, 82%; g) $LiAlH_4$, THF, rt to reflux, 65%; h) Ac_2O, 4-dimethylaminopyridine (DMAP), Et_3N, CH_2Cl_2, rt, 71%. acac = acetylacetonate

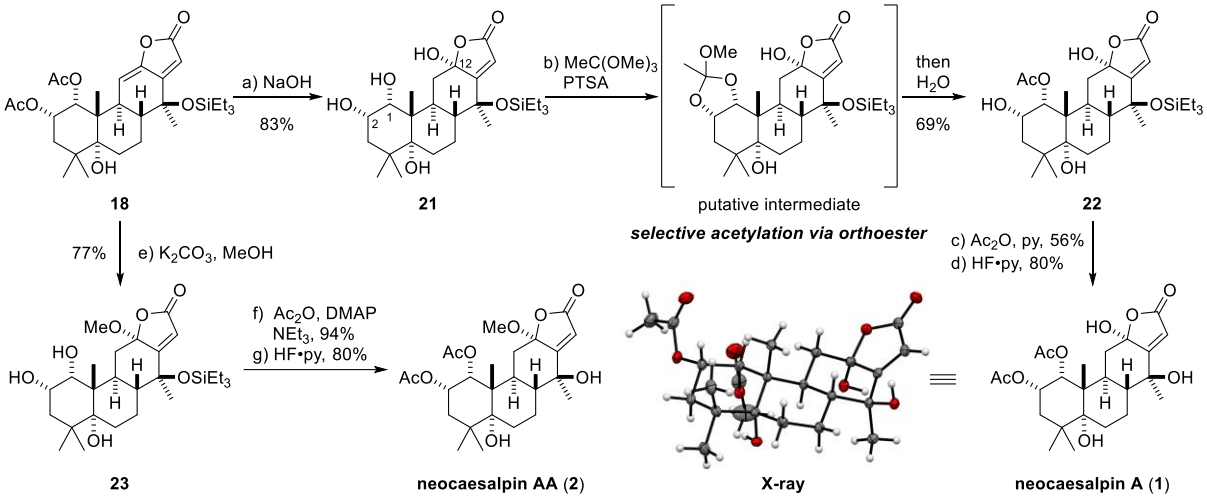
We next proceeded to examine manipulations of ring **D** to access the requisite butenolide. Although the oxidation of furans to γ-hydroxy butenolides is precedented,[14] we intended to specifically exploit the C11 oxidation already present in furfuryl acetate **17** to lead to γ,δ-unsaturated butenolide **18** (Scheme 5). Precedent for the oxidation of furfuryl alcohols/acetates is scarce.[15] The transformation has been reported previously in the synthesis of norneoclerodane diterpenoids, albeit only in 20% yield.[7] Application of the reported conditions (air, $CHCl_3$, rt, 4 days) to furfuryl acetate **17** did not afford butenolide product, even at elevated temperatures (65 °C) and in presence of O_2 atmosphere.

In parallel investigations of showcasing the value of redox-flexible platform **4**, we examined selective C1-C2 alkene functionalization approaches. Inspection of **19** suggested that it might be possible to have neighboring group participation by the pendant Boc alcohol at C11 in intramolecular oxymercuration of the C1-C2 alkene. Treatment of **19** with $Hg(OAc)_2$ in refluxing acetonitrile, however, did not lead to olefin oxymercuration**,** instead we observed oxidation product **20**.[16] Successful oxidation to the γ,δ-unsaturated butenolide product and the fact that the tertiary silyl ether in **19** remained untouched (we had observed its sensitivity to undergo solvolytic cleavage in various experiments), inspired us to examine analogous conditions for furfuryl acetate **17**. Gratifyingly, exposing **17** to $Hg(OAc)_2$ in refluxing acetonitrile afforded butenolide **18** in 97% yield.



Scheme 5. Ring **D** elaboration to access γ,δ-unsaturated butenolide **18**. Reagents and conditions: a) air (1 atm), $CHCl_3$, rt to reflux; b) O_2 (1 atm), $CHCl_3$, rt to reflux; c) $Hg(OAc)_2$, MeCN, rt to reflux, 41%; d) $Hg(OAc)_2$, MeCN, reflux, 97%.

Attempts at hydration of **18** under acidic conditions (aq. HCl) to produce the targeted hemiacetal were not successful. In contrast, treatment of **18** with aqueous NaOH[17] afforded **21** in 83% yield (Scheme 6). We surmise this transformation proceeds via a ring-opened keto carboxylate intermediate. Unfortunately, however, these conditions led to concomitant hydrolysis of the C1 and C2 acetates. Reintroduction of the two acetates at this point was not trivial. Attempts to effect selective acetylation at C1 and C2 by treatment with acetic anhydride, NEt_3, and DMAP revealed that C12 acetylation is fast, furnishing undesired diacetylated (C2 and C12) and triacetylated products. To address this issue, a two-step approach was devised that first targets the C1 and then the C2 hydroxy group selectively.

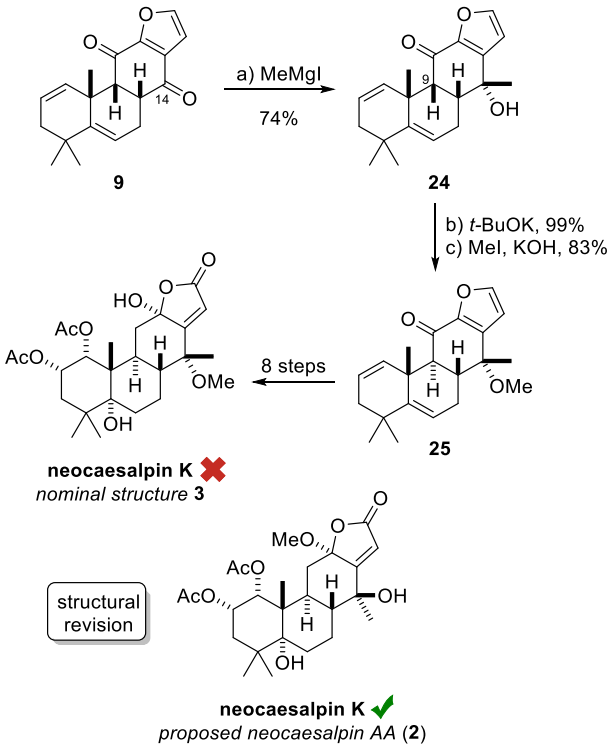


Scheme 6. Completion of the synthesis of neocaesalpin A (**1**) and neocaesalpin AA (**2**). Reagents and conditions: a) 1.2 M aq. NaOH, MeOH−CH_2Cl_2 (5:1), rt, 83%; b) $MeC(OMe)_3$, *para*-toluenesulfonic acid (PTSA, 10 mol%), MeCN, then H_2O, −30 °C to rt, 69%; c) Ac_2O, pyridine, rt, 56%; d) HF•py, THF, rt, 80%; e) K_2CO_3, MeOH, rt, 77%; f) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 94%; g) HF•py, THF, rt, 80%.

In the context of carbohydrate chemistry, regioselective acetylation of various 1,2-diols has been reported via formation of the cyclic orthoester and selective ring opening upon solvolysis.[18] In these studies, preferential opening of the orthoester to the axial acetate has been consistently observed. Consequently, we anticipated that this procedure could produce **22**. Subjecting **21** to $MeC(OMe)_3$/PTSA and subsequent partial hydrolysis furnished desired monoacetate **22** exclusively. Treatment with acetic anhydride/pyridine afforded selective acetylation at C2. Cleavage of the triethylsilyl ether completed the total synthesis of neocaesalpin A (**1**) in 15 steps. The spectral data of synthetic neocaesalpin A (**1**) was in full agreement with that reported in the isolation work (^{1}H NMR, ^{13}C NMR, HRMS).[19]

We then proceeded to access neocaesalpin AA (**2**) from intermediate **18**. Exposure of **18** to methanolic potassium carbonate[7, 20] furnished γ-methoxy butenolide **23**, which as previously observed led to cleavage of the acetate esters. Reintroduction of the C1 and C2 acetates was readily achieved by treatment of **23** with acetic anhydride/DMAP/NEt_3. Final deprotection of the triethylsilyl ether furnished neocaesalpin AA (**2**) in 14 steps, whose spectral characteristics (^{1}H NMR, ^{13}C NMR, HRMS) matched those reported for the natural product.

To further showcase the route, we decided to examine its implementation in the preparation of a related cassane-type diterpenoid. Neocaesalpin K with nominal structure **3** includes inverted configuration (*R*) at C14 and bears a methyl ether instead of a free alcohol (Scheme 7). It is interesting to note that most other butenolide cassane-type diterpenoids feature the (*S*)-C14 configuration as exemplified by neocaesalpin A and AA.[21] The published data employed in the structure elucidation studies of neocaesalpin K did not extend beyond ^{1}H and ^{13}C NMR data in tabular form. Consequently, implementation of a modified synthesis route would provide means to examine and potentially validate the structural assignment.



Scheme 7. Synthesis of nominal neocaesalpin K (**3**) and proposed structural reassignment. Reagents and conditions: a) MeMgI, Et_2O, 0 °C, 74%; b) *t*-BuOK, *t*-BuOH, rt, 99%; c) MeI, KOH, THF, rt, 83%.

In the route to nominal neocaesalpin K, addition of MeMgI to the mixture (**9**/**10**) obtained from the cycloaddition reaction provided tertiary alcohol **24** in 74% yield as a single isomer.[3k, 10] NOE analysis confirmed that tertiary alcohol **24** featured inverted C14 configuration to that observed for the isomeric alcohol product generated from the Mukaiyama hydration reaction (Scheme 4). C9

epimerization of **24** and methylation of the tertiary alcohol provided **25**. Subjecting **25** through a sequence of reactions described for **13** (see supporting information) produced nominal neocaesalpin K (**3**). Unfortunately, neither the ^{1}H nor ^{13}C NMR data of synthetic **3** matched that reported for the natural product. Comparison of the NMR data of neocaesalpin AA (**2**) and reported neocaesalpin K revealed striking similarities. While the tabular ^{13}C NMR shifts of neocaesalpin AA and K are identical, there are discrepancies for the tabular ^{1}H NMR shifts. On the basis of available data,[22] we hypothesize that neocaesalpin AA and K may be the same natural product. The structure reported by the isolation group and validated through synthesis for neocaesalpin AA corresponds to that for neocaesalpin K. In the proposed reassignment of neocaesalpin K we suggest a C12 methyl acetal instead of a C14 methyl ether and inversion of configuration at C14, as shown for neocaesalpin AA (**2**).

In conclusion, we achieved the first total synthesis of neocaesalpin A (**1**). The synthetic approach described provides quick entry to the main target scaffold via an intermolecular Diels–Alder reaction and efficiently sets the complex oxygenation pattern. A novel mercury(II)-mediated oxidation accomplishes butenolide release under mild conditions. Additionally, synthesis of neocaesalpin AA (**2**) and nominal neocaesalpin K (**3**) led to revised assignment of **3** to correspond to that of **2**, suggesting that neocaesalpin K and AA may be the same natural product reported twice with different nominal structures. Efforts to expand the established route to other densely functionalized members of the cassane family are ongoing.

Acknowledgements

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[22] Efforts to contact the isolation team of neocaesalpin K to access NMR spectra were unsuccessful.