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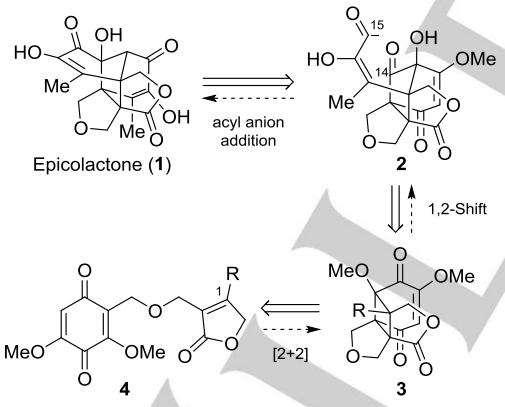
COMMUNICATION

Total Synthesis of Epicolactone

Alberto G. Kravina and Erick M. Carreira*

Abstract: The biologically active and structurally complex secondary metabolite epicolactone is a member of the natural product pool found in cash crop endophytes of the genus *Epicoccum*. By exploiting inherent reactivity, a total synthesis of this highly oxygenated and polycyclic molecule met chemo- and regioselectivity challenges. The key buildup of complexity was accomplished via an intramolecular [2+2] photocycloaddition between a quinone and an electron-deficient diene followed by a cyclobutane ring expansion. The use of a dioxene as an acyl anion equivalent and an intramolecular carbonyl methenylation furnished the natural product.

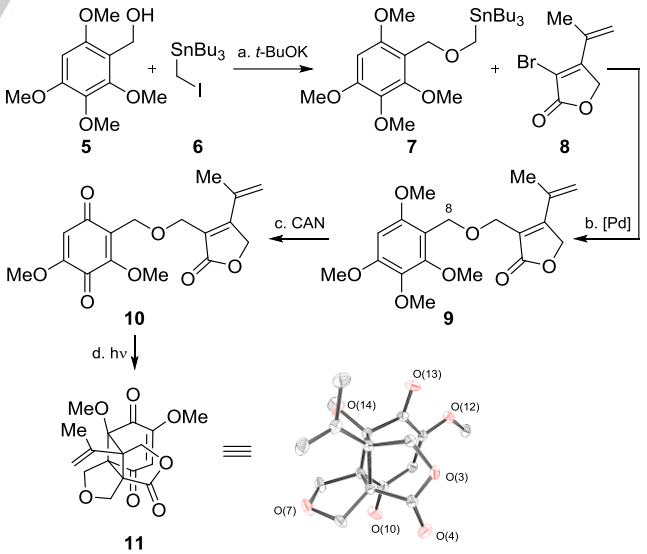
Epicoccum nigrum, a ubiquitous endophytic fungus known to colonize economically important cash crops such as sugarcane[1] and cocoa trees,[2] is a source of biologically active secondary metabolites.[3] Among these, a complex and highly oxygenated caged pentacyclic structure, epicolactone (**1**), was first isolated in 2012.[1] Inspired by the accompanied isolation of speculated biosynthetic precursors from *Epicoccum* caftbo,[2] elegant biomimetic total syntheses of epicolactone[4] and its related analog dibefurin[5] were reported by Trauner and co-workers. Epicolactone's high density of electrophilic and nucleophilic functional groups make it a formidable task for total synthesis. Moreover, given its quasisymmetric nature, a synthesis of this molecule necessitates the development of chemo- and regioselective transformations on a highly hindered molecular scaffold. Herein, we report a total synthesis of epicolactone which addresses these challenges and provides a complementary entry into this structurally intriguing natural product.



Scheme 1. Retrosynthetic analysis of epicolactone (**1**).

The retrosynthetic analysis of epicolactone that guided the route we describe began by disconnecting the carbocycle along the C(14)-C(15) bond (Scheme 1). In the synthetic direction, this requires the addition of an acyl anion synthon to the C(14) ketone in **2**. The structure generated (**2**) suggested an α-ketol or acyloin rearrangement arising from **3**.[6] Finally, a [2+2] photocycloaddition involving electronically similar olefins would expediently assemble cyclobutane **3** from a flat precursor (**4**). This strategy allows for strategic choice of the residue at C(1) in **4** to adapt and tune the reactivity of the unsaturated lactone for the key [2+2] photocycloaddition.

We started the synthesis by combining benzylic alcohol **5** with iodomethyl-tributylstannane (**6**) to give stannane **7** (scheme 2).[7] Cross-coupling of **7** with known bromolactone **8**[8] proceeded with $Pd(PPh_3)_2Cl_2$ as the precatalyst to give adduct **9** in 55% yield despite its tendency to undergo decomposition neat and in solution.[9,10] Subsequently, *p*-quinone **10** had to be obtained preferably over two other *o*-quinone isomers via oxidation of **9**. Avoiding oxidation or elimination at the C(8) methylene of the fragile ether tether proved to be challenging. When a solution of **9** in $MeCN/H_2O$ was exposed to ceric ammonium nitrate in the absence of light with strict control of the reaction time and workup conditions, quinone **10** was obtained as the sole product in 76% yield.[11] With **10** in hand, the feasibility of the key [2+2] photocycloaddition, aimed at assembling the core, could be investigated. Upon irradiation of a benzene solution of **10** with blue LEDs, clean formation of cyclobutane **11** was observed as a single diastereomer in 76% yield. This intramolecular photocycloaddition between a quinone and the internal C–C double bond of an electron deficient diene produced all three quaternary centers of epicolactone in a single step.[12]



Scheme 2. Synthesis of cyclobutane **11**. Reagents and conditions: a) *t*-BuOK (1.2 equiv), DMF, 50 °C, then **6** (1.1 equiv), 78%; b) **8** (1.0 equiv), **7** (3.0 equiv), $Pd(PPh_3)_2Cl_2$ (15 mol%), dioxane, 85 °C, 55%; c) $(NH_4)_2Ce(NO_3)_6$ (2.1 equiv), $MeCN/H_2O$, 25 °C, 76%; d) Blue LED's, PhH, 25 °C, 76%. Intermediate **11** is illustrated as its ORTEP representation with ellipsoids shown at 50% probability. DMF = *N*,*N*-dimethylformamide, CAN = ceric ammonium nitrate.

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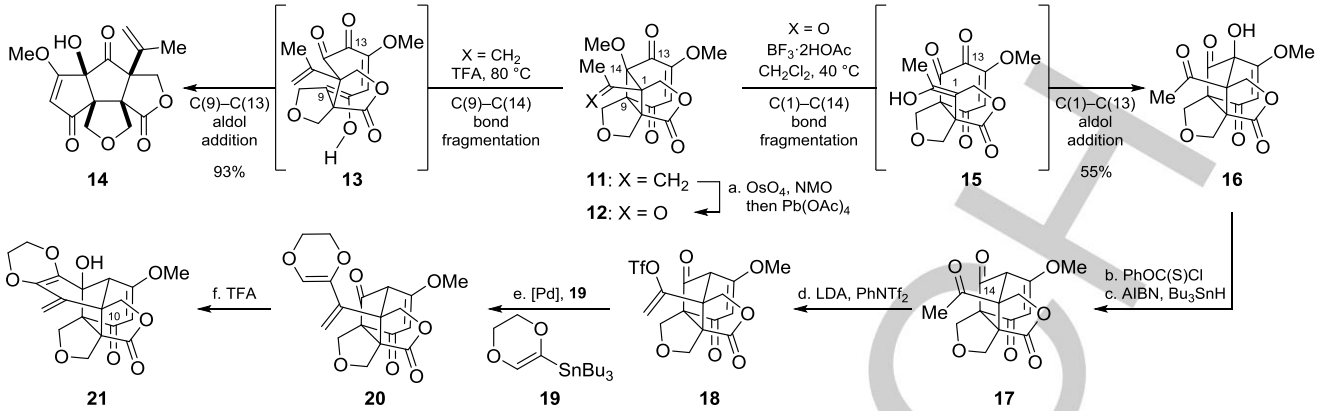

Scheme 3. Cyclobutane expansion via DeMayo fragmentation-aldol addition sequence and synthesis of the cyclic skeleton of epicolactone. Reagents and conditions: a) OsO_4 (30 mol%), NMO (3.0 equiv), CH_2Cl_2, 0 °C to 25 °C, then $Pb(OAc)_4$ (2.5 equiv), CH_2Cl_2, 0 °C, 99% b) *O*-phenyl chlorothionoformate (3.0 equiv), NEt_3 (1.5 equiv), DMAP (5 mol%), 25 °C, 94%; c) AIBN (35 mol%), Bu_3SnH (4.0 equiv), PhMe, 80 °C, 90%; d) LDA (1.05 equiv), **17**, then $PhNTf_2$ (2.4 equiv), THF/HMPA, –78 °C, 51%; e) **19** (5.0 equiv), $Pd(PPh_3)_2Cl_2$ (25 mol%), dioxane, 85 °C, 90%; f) TFA, CH_2Cl_2, 25 °C, quant. NMO = *N*-methylmorpholine *N*-oxide, DMAP = 4-dimethylaminopyridine, AIBN = 2,2'-azobisisobutyronitrile, LDA = lithium diisopropyl amide, THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, TFA = trifluoroacetic acid.

With a robust route that allowed for the preparation of multigram quantities of **11** in hand, we examined the ring expansion required to access the central five-membered ring of epicolactone via the proposed acyloin rearrangement. Such a structural reorganization of the carbon skeleton was observed upon treatment of **11** with refluxing TFA. To our surprise, however, the angularly fused tetracycle **14** was obtained in 93% yield.[13] This product is likely formed by migration of the C(9)-C(14) bond, suggesting that the underlying mechanism for the ring expansion resembles that of a retroaldol-aldol sequence, similar to the DeMayo fragmentation, rather than a concerted 1,2-shift (Scheme 3). Since the carbonyl functionality which promotes this undesired pathway in **11** is part of a vinylogous ester motif, we envisioned that conversion of the 1,1-disubstituted olefin in **11** to the corresponding ketone **12** would facilitate a pathway involving the C(1)-C(14) bond rearrangement to outcompete the undesired C(9)-C(14) counterpart. Exposure of olefin **11** to OsO_4 and NMO in CH_2Cl_2 followed by one-pot oxidative diol cleavage with lead tetraacetate gave ketone **12** in near quantitative yield. Treatment of **12** with TFA or Me_2AlCl analogous to **11** led to quantitative starting material recovery and decomposition, respectively. The use of BF_3-based Lewis acids turned out to be crucial for the successful outcome of the desired retroaldol-aldol sequence. While treatment of **12** with $BF_3{\cdot}OEt_2$ led only to trace amounts of desired product, exposure of **12** to excess $BF_3{\cdot}2HOAc$ in refluxing CH_2Cl_2 produced the ring-expanded cyclopentanol **16** as the sole product in 55% yield.[14],[15] The tertiary alcohol in **16** was subsequently transformed to its *O*-thiocarbonate derivative and subjected to radical deoxygenation to generate **17** in 85% yield over the two steps. Having the central cyclopentane core structure assembled in **17**, we sought to attach a suitable C_2 fragment to its methyl ketone moiety to close left hand side carbocycle of epicolactone. Unfortunately, the selective addition of nucleophiles to the methyl ketone in **17** failed. This was due to the tendency of nucleophiles to add preferentially to the C(14) carbonyl. We hence envisioned differentiating the methyl ketone carbonyl from the other four electrophilic positions in **17** by exploiting its enolizable α-protons.

The formation of enol derivatives of **17** using amine bases and Tf_2O/NfF or employing an established two-step procedure[16] failed. We then turned our attention to the triflation of the alkali metal enolates of **17**. Strict control of the reaction time turned out to be crucial for the successful outcome of the reaction. Employing an almost equimolar quantity of LDA in THF/HMPA followed by trapping of the enolate with $PhNTf_2$ gave triflate **18** in 51% yield. In search of a side chain which could be installed by cross coupling, we speculated that a dioxene such as **20** would enable an intramolecular nucleophilic attack on the C(14) ketone. Its synthesis was effected by coupling known stannane **19**[17] to **18** in 90% yield. It should be noted that the sidechain bears the correct oxidation pattern found in epicolactone. While dioxenes have found use in carbonyl addition reactions through lithiation of the vinylic C–H bond,[18] we found that exposure of **20** to TFA in CH_2Cl_2 led to quantitative formation of hexacycle **21** via an acid-mediated aldol addition. This transformation successfully closed the last carbocycle of epicolactone without revealing its α-hydroxyenone motif. With **21** in hand, we sought to install the methyl group at C(10) via selective addition to the carbonyl of the vinylogous ester in presence of its conjugated position and the χ-lactone. Unfortunately, exposure of **21** to various C_1-organometallic reagents resulted mainly in decomposition of the substrate and/or poor regioselectivities. We speculated that O–H deprotonation by basic organometallic reagents preceded nucleophilic addition to C(10), leading to an unreactive alkoxide. We envisioned that this innate tendency to resist attack by external nucleophiles could be circumvented by employing a silicon tether strategy.[19] Since the tertiary hydroxyl group in **21** is positioned above the plane of the vinylogous ester, we speculated that the C–I bond in silyl ether **22** could be converted into an organometallic nucleophile poised for an intramolecular carbonyl addition (Scheme 4). Upon treatment of **22** with 2.1 equiv of SmI_2 in THF at –78 °C and subsequent acidic workup, clean formation of enone **24** was observed in high yield.[20]

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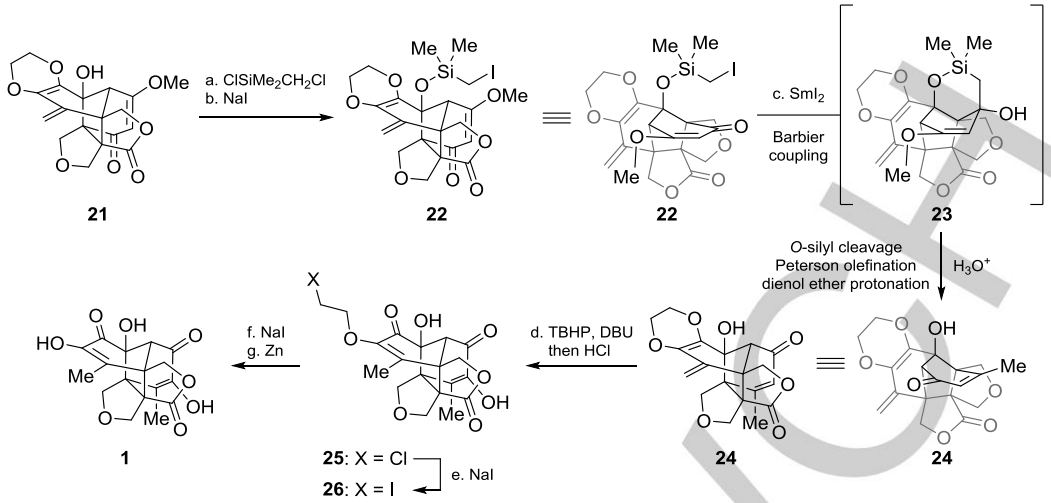

Scheme 4. Completion of the total synthesis of epicolactone. Reagents and conditions: a) (chloromethyl)dimethylchlorosilane (3.0 equiv), NEt_3 (6.0 equiv), DMAP (3 mol%), CH_2Cl_2, 25 °C, 93%; b) NaI (14 equiv), butanone, 80 °C, 82%; c) SmI_2 (2.1 equiv), THF, –78 °C to 25 °C, then aq. HCl, 90%; d) TBHP (1.4 equiv), DBU (1.5 equiv), DCE, 25 °C, then HCl, BuOH, 110 °C, 66%; e) NaI (20 equiv), butanone, 80 °C, 92%; f) Zn (20 equiv), EtOH/HOAc, 55 °C, 93%. TBHP = *tert*-butyl hydroperoxide, DBU = 1,5-diazabicyclo(5.4.0)undec-5-ene, DCE = 1,2-dichloroethane.

The intermediacy of Barbier adduct **23** was proved by working up the reaction under neutral conditions and exposing isolated **23** to TFA/H_2O at 60 °C.[21] With all carbon atoms of epicolactone now installed in **24**, the endphase of the synthesis consisted in transforming the dioxene and enone moieties in **24** to the bis-α-hydroxyenone motif of epicolactone. Selective nucleophilic oxidation of the enone was accomplished with TBHP and DBU. Strictly anhydrous conditions and a slight excess of base were crucial to avoid oxidation of the dioxene. Due to the high instability of the epoxide of enone **24**, direct subjection of the reaction to HCl in BuOH at 110 °C led to chloroethyl ether **25**. With the correct bis-α-oxyenone moieties now in place, formation of the iodoethyl ether **26** (NaI, butanone) and reductive cleavage thereof with zinc in HOAc/EtOH gave synthetic epicolactone. The synthetic material exhibited spectral data identical to those reported its previous isolations[1,2] and total synthesis.[4]

In conclusion, we have developed a robust route for the synthesis of the structurally complex and highly oxygenated natural product epicolactone. An unusual [2+2] photocycloaddition between two electronically similar olefins was employed for the formation of the quaternary centers of the sterically encumbered molecule. A retroaldol-aldol sequence dictated by functional group relationships was employed to synthesize the central cyclopentane embedded in the molecule. In the endphase, an unprecedented acid-catalyzed aldol addition of a dioxene and an intramolecular carbonyl methenylation were developed *en route* to epicolactone. The application of these reactions to the synthesis of other highly caged and oxygenated natural products is subject to further research in our laboratories and will be reported in due course.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: epicolactone • natural products • cycloaddition • ring expansion • acyl anion addition

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[10] The bench-stable *o*-quinone derived from **5** underwent decomposition when exposed to *t*-BuOK and **6** in DMF. See supporting information for details.

[11] Attempts to oxidize **9** with other metal or organic oxidants led only to substrate decomposition or no reaction. Under no circumstance did we observe formation of *o*-quinone isomers of **10**.

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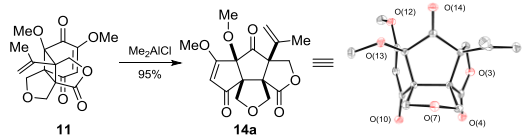

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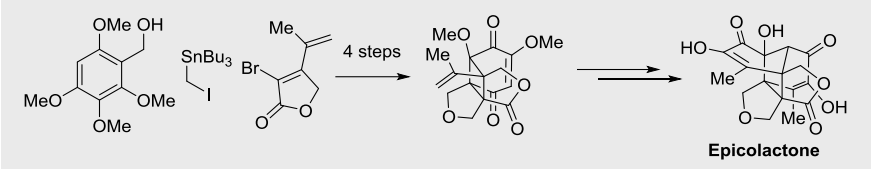

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An Epic Journey: We describe the total synthesis of the structurally complex and biologically active secondary metabolite epicolactone. This synthesis relies on an intramolecular [2+2] photocycloaddition-ring expansion sequence to expediently assemble the core structure. The strategic use of a dioxene and an intramolecular carbonyl methenylation were used as the key C–C bond forming reactions on the highly functionalized and sterically encumbered scaffold.