Organic LETTERS

Letter

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The Discovery of a Novel Route to Highly Substituted α-Tropolones Enables Expedient Entry to the Core of the Gukulenins

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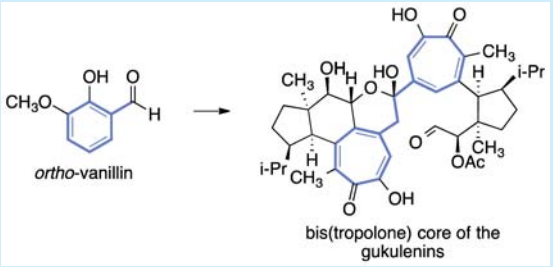
Supporting Information

ABSTRACT: A simple and general method for the synthesis of highly substituted α-tropolone ethers that allows rapid access to the bis(tropolone) core of the antiproliferative metabolites (−)-gukulenins A and F (**3**, **4**) is described. The reaction proceeds by thermolytic opening of *gem*-dibromobicyclo[4.1.0]heptane intermediates, which are readily accessed from simple starting materials. Mechanistic studies suggest the reaction proceeds via an autocatalytic process mediated by methyl hypobromite. This synthetic sequence allows access to a broad array of highly substituted α-tropolones.



Natural α-tropolones are found in hundreds of natural products and have received significant interest from the scientific community due to their unique structural features and manifold therapeutic properties.[1] Of the diverse array of natural products containing the tropolone substructure, none have enjoyed as much attention from synthetic chemists as (−)-colchicine (**1**)[2] and imerubrine (**2**, Figure 1).[3] The

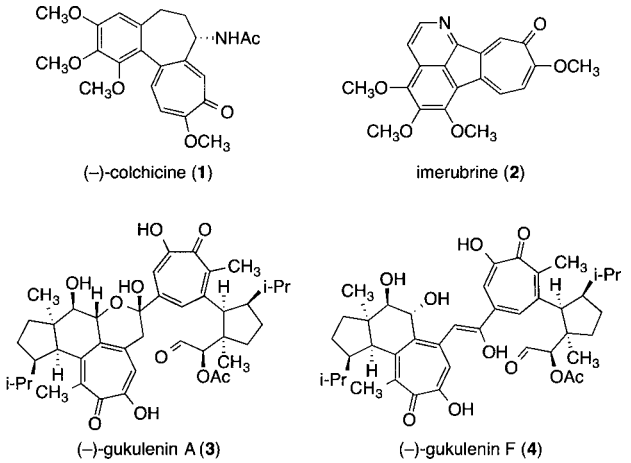


Figure 1. Structures of (−)-colchicine (**1**), imerubrine (**2**), and (−)-gukulenins A and F (**3**, **4**, respectively).

structure of **1** was first proposed in a seminal paper by Dewar,[4] and synthetic studies of **1** and **2** have motivated several methods for the construction of functionalized tropolone skeletons.[5] Selected approaches include 1,3-dipolar cycloaddition reactions,[6] oxidative ring opening of 7-halogenobicyclo[4.1.0]heptane-diols,[7] ring expansion of bicyclo[3.2.0]heptane derivatives,[8] acid-catalyzed rearrangement of bicyclo[4.1.0]heptanols,[9] oxopyrylium cycloadditions,[10] and cycloadditions between tetrabromocyclopropene and furan.[11]

Our interest in methods for tropolone syntheses derive from the pseudodimeric bis(tropolone) natural products (−)-gukulenins A and F (**3** and **4**, respectively), which were recently isolated from the marine sponge *Phorbas gukulensis*.[12] Both **3** and **4** display 50 percent inhibitory potencies in the nanomolar range against various cancer cell lines. We envisioned a synthetic route to **3** and **4** that involves preparation of a C_2-symmetric bis(tropolone) core followed by attachment of the substituted cyclopentyl rings and desymmetrization. As few methods to access 4,6,7-trisubstituted α-tropolones have been reported,[5] we set out to develop a new process. Herein we report the discovery of a simple method that allows access to a broad range of substituted tropolones containing this substitution pattern as well as the core of the targets **3** and **4**.

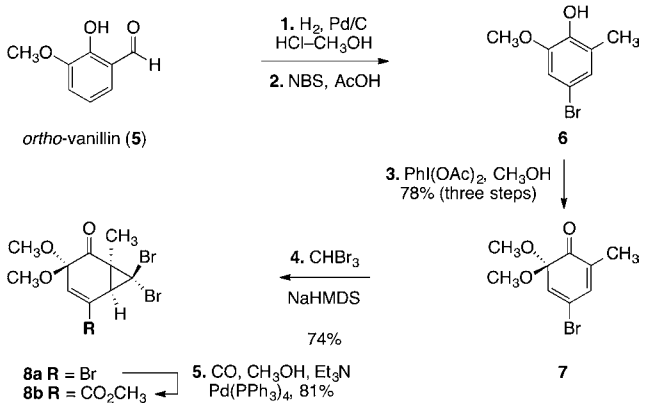
Our tropolone synthesis begins with benzylic reduction and bromination of *ortho*-vanillin (**5**), to provide 4-bromo-2-methoxy-6-methylphenol (**6**, Scheme 1). Oxidation of **6** [bis(acetoxy)iodobenzene, methanol][13] then forms the masked *ortho*-benzoquinone **7** in 78% yield over three steps. Cyclopropanation (bromoform, sodium hexamethyldisilazide) generates the bicyclo[4.1.0]heptane **8a** (74%). Due to the electron-deficient nature of **7**, we believe the formation of **8a** proceeds by the 1,4-addition of a tribromomethyl anion, followed by cyclization,[14] rather than addition of dibromocarbene.[15] The bicyclo[4.1.0]heptane **8a** is a suitable substrate for the ring expansion reaction (vide infra), but in our optimization studies, we employed the more stable carbomethoxy derivative **8b**, which is obtained in 81% yield by palladium-mediated methoxycarbonylation of **8a**.

We envisioned conversion of **8b** to the tropolone **11b** by a cascade comprising 1,2-reduction of the ketone, elimination of methanol (**8b** → **9**), [3,3]-sigmatropic rearrangement (**9** → **10**), and bromide elimination (**10** → **11b**, Scheme 2).

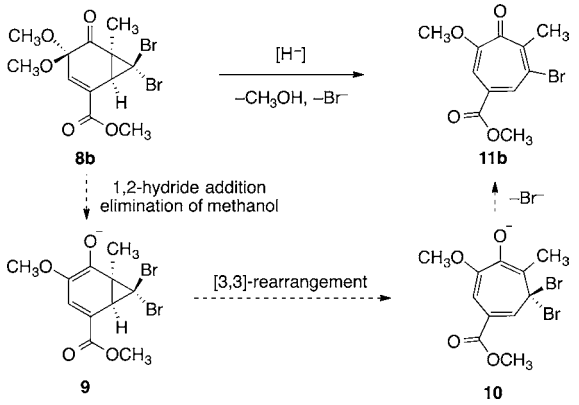
Received: March 22, 2015
Published: April 3, 2015

DOI: 10.1021/acs.orglett.5b00841
Org. Lett. 2015, 17, 2030−2033

Scheme 1. Synthesis of the Bicyclo[4.1.0]heptanes 8a and 8b

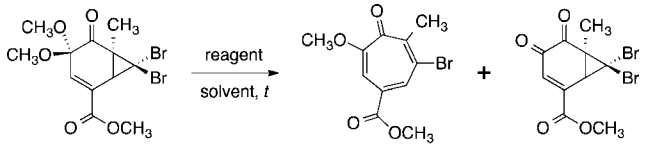


Scheme 2. Original Pathway Conceived for the Conversion of 8b to 11b



Treatment of the bicyclo[4.1.0]heptane **8b** with sodium borohydride in refluxing dioxane resulted primarily in decomposition, though the desired product **11b** was produced in 6% yield (entries 1 and 2, Table 1). An evaluation of a range of hydride sources, solvents, and temperature profiles did not improve the yield of **11b** (data not shown). Moreover, significant variability in the conversion of **8b** in the sodium borohydride−1,4-dioxane system led us to postulate the involvement of alternative mechanistic pathways.

Table 1. Optimization of the Ring Expansion[a]



entry	reagent (equiv)	solvent	t (°C)	conv	yield **11b**	yield **12**
1	$NaBH_4$ (1.1)	dioxane	110	>99%	6%	0%
2	$NaBH_4$ (2.2)	dioxane	110	>99%	6%	0%
3	$BF_3{\cdot}OEt_2$ (1.1)	CH_2Cl_2	23	51%	5%	24%
4	$BF_3{\cdot}OEt_2$ (2.2)	CH_2Cl_2	23	91%	3%	48%
5	Al_2O_3 (0.8)	dioxane	110	>99%	59%	0%
6	$HSnBu_3$ (0.3)	dioxane	110	>99%	61%	9%
7	$HSiEt_3$ (1.0)	dioxane	110	>99%	81%	13%
8	**none**	**THF**	**70**	**>99%**	**86%**	**0%**
9	4 Å MS	THF	70	0%	0%	0%

[a]Yields and conversions determined by ^{1}H NMR spectroscopy against an internal standard or by isolation; see Supporting Information.

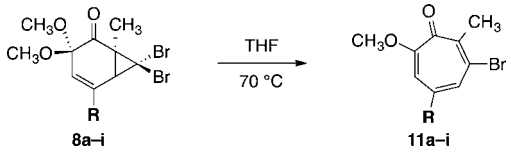
We then considered Lewis acid activation as a means of promoting the reaction; however, treatment of **8b** with boron trifluoride−etherate complex (1.1 or 2.2 equiv, entries 3 and 4, respectively) led predominantly to cleavage of the dimethyl acetal, to produce the α-dicarbonyl **12** in 24% or 48% yield (5% or 3% yield of **11b**). Thermolysis of **8b** in the presence of alumina (introduced to maintain mildly basic reaction conditions) afforded the desired product **11b** in 59% yield, but significant decomposition of the starting material **8b** was still observed (entry 5). As an alternative mechanism we posited that the ring expansion may proceed by generation of a diradical intermediate, as is often proposed in the thermal rearrangement of vinylcyclopropanes.[16] As formal reduction of the substrate is required in the mechanism, tributyltin hydride (entry 6) and triethylsilane (entry 7) were evaluated as hydrogen atom donors. In the presence of either reagent, the yield of the product **11b** was substantial (61% and 81% yield for tributyltin hydride and triethylsilane, respectively) and the α-dicarbonyl **12** was observed as a minor product (9% or 13%). Surprisingly, a control experiment revealed that the rearrangement proceeded smoothly upon heating to 70 °C in tetrahydrofuran alone (86%, entry 8). Addition of 4 Å MS completely inhibited the reaction, which we believe has bearings on the mechanism (entry 9, vide infra).

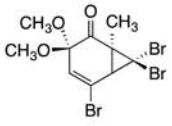
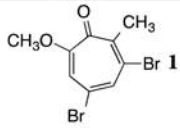
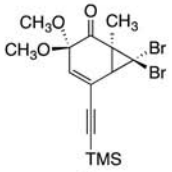
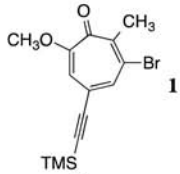
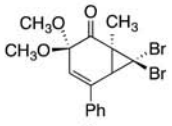
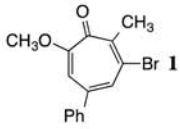
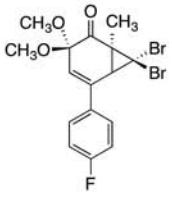
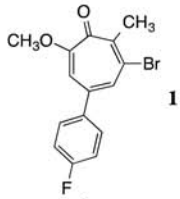
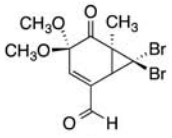
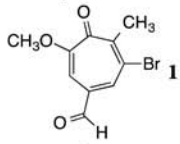
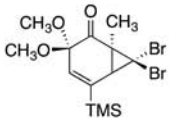
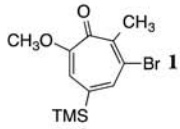
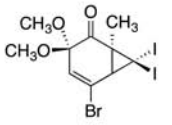
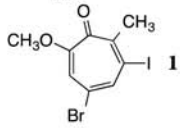
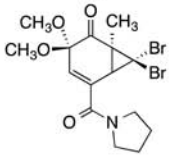
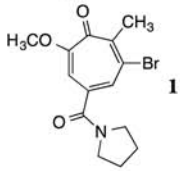
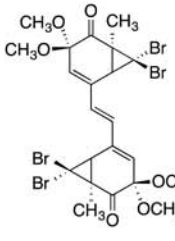
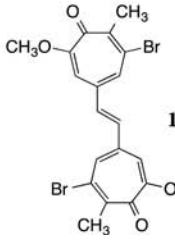
The sequence outlined above provides straightforward access to a broad range of highly substituted tropolone derivatives (Table 2). The substrates **8c−8j** were prepared by site-selective metal-catalyzed functionalization of **8a**.[17] The parent substrate **8a** underwent ring expansion to the dibromotropolone **11a** in 93% yield, and the structure of the product was verified by X-ray analysis (entry 1).[18] The trimethylsilylacetylene derivative **8c** opened smoothly to the alkynyltropolone **11c** in 78% yield (entry 2). Furthermore, the aryl derivatives **8d** and **8e** underwent high-yielding ring expansion (94% each, entries 3 and 4). In these cases, the yields were dramatically improved by the addition of 1 equiv of triphenylphosphine to the reaction mixture. In its absence, competitive bromination of the arene rings was observed. The formyl and silyl derivatives **8f** and **8g** underwent ring expansion in 82% and 83% yield, respectively, to provide the tropolones **11f** and **11g** (entries 5 and 6). Cyclopropanation of **7** with iodoform generated the diiodo cyclopropane **8h**[17] which underwent ring expansion to provide the bromoiodotropolone **12h** in 71% yield. Surprisingly, small amounts of the corresponding 4,6-dibromo- and 4,6-diiodo-tropolones were also produced, potentially by electrophilic transhalogenation of the product. The addition of iodine (1 equiv) was found to suppress formation of these side products (7% and 9% yield of the dibromo- and diiodo-tropolones, respectively). The pyrrolidinyl amide **8i** underwent smooth ring expansion to generate the amide-substituted tropolone **11i** in 83% yield (entry 8). Finally, the bis(dibromocyclopropane) dimer **8j** was prepared in one step from **8a** by Stille coupling with *trans*-1,2-di(tributylstannyl)ethylene (entry 9).[17] This dimeric substrate underwent smooth ring expansion to provide **11j** in 76% yield. The successful synthesis of **11j** establishes a six-step route to the gukulenin skeleton.

The vinyl bromide substituent of the ring expansion products provides a useful handle for further diversification. For example, treatment of **11b** with benzenethiol in the presence of triethylamine induced clean addition−elimination, to provide the sulfide **13** (97%, Scheme 3). Alternatively, Stille coupling of

DOI: 10.1021/acs.orglett.5b00841
Org. Lett. 2015, 17, 2030−2033

Table 2. Thermal Ring Expansion of Bicyclo[4.1.0]heptane Derivatives[a]

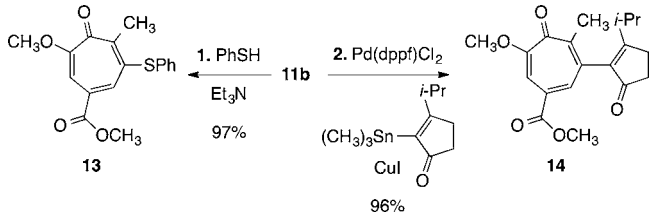


entry	starting material		product		yield[b]
1		**8a**		**11a**	93%
2		**8c**		**11c**	78%
3		**8d**		**11d**	94%[c]
4		**8e**		**11e**	94%[c]
5		**8f**		**11f**	82%
6		**8g**		**11g**	83%
7		**8h**		**11h**	71%[d]
8		**8i**		**11i**	83%
9		**8j**		**11j**	76%

[a]0.18−2.00 mmol scale. [b]Isolated yield after purification by flash-column chromatography. [c]1 equiv of triphenylphosphine was added. [d]1 equiv of iodine was added. Obtained as an inseparable mixture containing the corresponding 4,6-diiodotropolone (9%) and 4,6-dibromotropolone (7%); see Supporting Information.

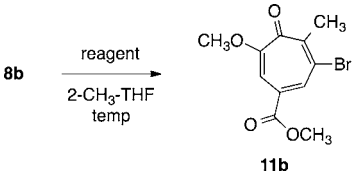
11b with 2-(trimethylstannyl)-3-isopropyl-cyclopent-2-ene-1-one provided the cross-coupling product **14** in 96% yield.

Scheme 3. Functionalization of the Tropolone 11b



Several experiments were conducted to gain insight into the mechanism of this ring expansion. Conducting the ring expansion of **8b** in tetrahydrofuran-d_8 formed the expected product **11b**, without detectable levels of deuterium-atom incorporation (^{1}H NMR analysis). This result would seem to exclude a pathway involving the generation of free radical intermediates and hydrogen atom abstraction from the solvent. In addition, continuous monitoring of this reaction (at 60 °C) at 10 min intervals by ^{1}H NMR spectroscopy revealed a long induction period (ca. 9 h) followed by rapid reaction, with full conversion observed within 10 min and no intermediates detectable by NMR analysis (Figure S1). This suggested to us the possibility of an autocatalytic process, potentially mediated by protic species or methyl hypobromite, the latter of which is formally generated in the transformation of **8b** to **11b**. In accord with this, treatment of **8b** with hydrogen bromide (1.0 equiv) at ambient temperature formed **11b** in 72% yield within 1 h (Scheme 4). To probe for mediation of the reaction by

Scheme 4. Mechanistic Experiments To Evaluate the Role of Acidic and Electrophilic Species in the Ring Opening of 8b



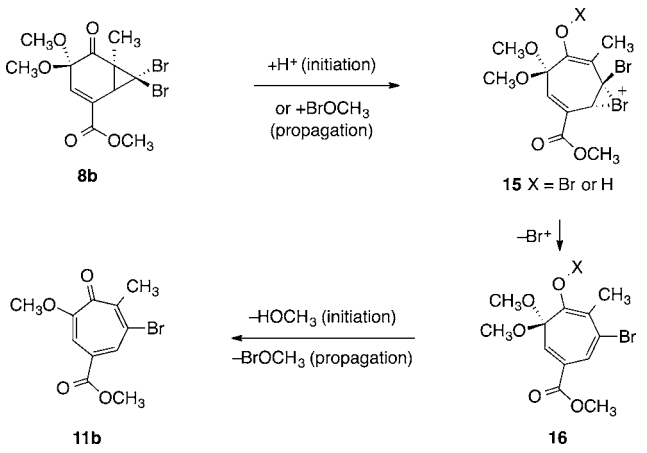
reagent (equiv)	*t*	**11b**
HBr (1.0)	23 °C	72%
$BrOCH_3$ (0.05)	70 °C	>99%
$BrOCH_3$ (1.0)	23 °C	54%

methyl hypobromite, **8b** was treated with 5 mol % methyl hypobromite (generated by the addition of bromine to sodium methoxide)[19] at ambient temperature and immediately warmed to 70 °C. Under these conditions, the ring-expanded product **11b** was obtained in quantitative yield within 10 min. Exposure of **8b** to 1 equiv of methyl hypobromite at ambient temperature provided **11b** in 54% yield, along with unidentified decomposition products.

Based on these data, we suggest the pathway shown in Scheme 5, which shares some similarities to the ring expansion of 2-(dihalomethyl)cyclohexanedienones developed by Barton and co-workers.[7b] *O*-Protonation with concomitant opening of the cyclopropane would provide the bromonium ion **15**. Collapse of the ion by elimination of bromine (the microscopic reverse of electrophilic alkene bromination) would provide the cycloheptatriene **16**. Finally, 1,8-elimination of methanol would afford the ring-expanded product **11b**. The reaction may be initiated by hydrogen-bonding activation of the carbonyl by adventitious water, which is consistent with the observation that 4 Å MS inhibit the reaction. The reaction may be propagated via *O*-bromination by methyl hypobromite, which is

DOI: 10.1021/acs.orglett.5b00841
Org. Lett. 2015, 17, 2030−2033

Scheme 5. Proposed Mechanism for the Ring Expansion of 8b



formed in equimolar quantities with the product. An alternative initiation mechanism involving slow thermolysis of **8b** (to produce the oxyanion corresponding to **15**) may be operative, although this would seem to be inconsistent with the observation that molecular sieves impede the reaction.

In summary, we have discovered a novel ring-expansion reaction that provides access to a broad array of highly substituted α-tropolones in high yield from simple, readily accessible precursors. The reaction sequence establishes a short, six-step route to the bis(tropolone) core of the gukulenins and is likely to be of general utility in the synthesis of highly substituted tropolones.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Camille and Henry Dreyfus Foundation is gratefully acknowledged.

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(2) For reviews, see: (a) Boye, O.; Brossi, A. *Alkaloids (Academic Press)* **1992**, *41*, 125. (b) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230.
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DOI: 10.1021/acs.orglett.5b00841
Org. Lett. 2015, 17, 2030–2033