Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Violaceic Acid and Related Compounds through Aryl Triazene

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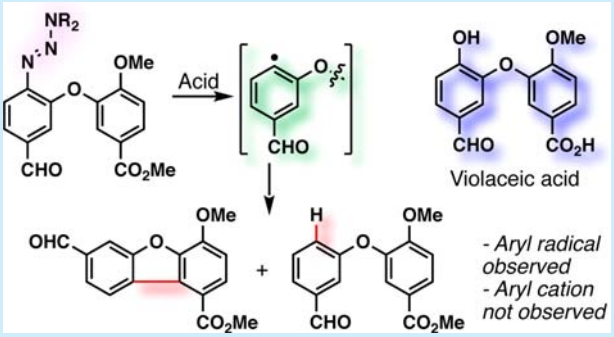
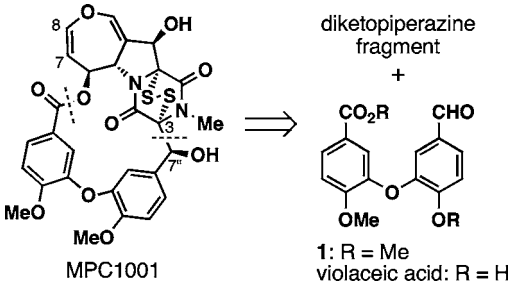
Supporting Information

ABSTRACT: MPC1001 is a potent anticancer natural product that contains a violaceic acid moiety. Herein we report the total synthesis of the natural product violaceic acid and its derivative. In this approach, a triazene-directed Ullman coupling proved to be highly effective. We converted the triazene to a hydroxy group by means of a palladium-catalyzed reaction. Treatment of the triazene with trifluoroacetic acid generated an arenediazonium ion that produced an aryl radical, leading to the protodediazoniation and a tricyclic product.



In 2004, MPC1001 (Scheme 1) was isolated from a fungal strain, *Cladorrhinum* sp. KY4922 (17.6 mg/L of culture broth), found in a soil sample collected in Indonesia.[1] MPC1001 exhibited antimicrobial activities against Gram-positive bacteria in a micromolar range. More significantly, it showed antiproliferative activity against human prostate cancer line DU145 with an IC_{50} value of 9.3 nM.[1]

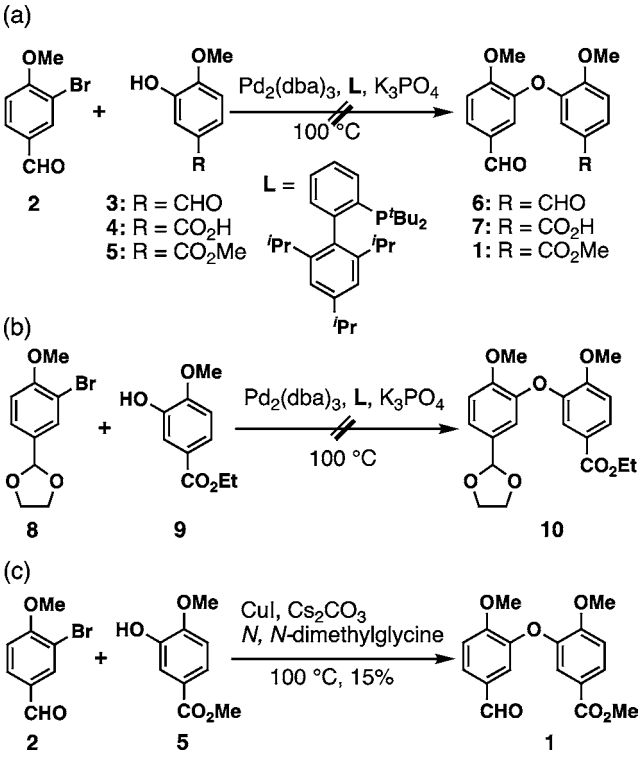
Scheme 1. Structure of MPC1001 and Violaceic Acid



The most convincing evidence for the chemical structure of MPC1001 was the high degree of similarity to emestrin.[2] While the Williams and Clive groups reported fragment syntheses,[3−6] Tokuyama et al. completed the first total synthesis of (+)-MPC1001B.[7] Herein, we wish to report a successful preparation of the aromatic fragment during which another natural product, violaceic acid,[8] was synthesized.

We envisioned that MPC1001 might be assembled by the formations of the ester and C3−C7″ bonds at a late stage of the synthesis, revealing aldehyde **1** as an advanced intermediate (Scheme 1). To facilitate analog synthesis, we desired a convergent approach toward this aromatic fragment, which led us to consider forming a biaryl ether bond by a palladium-catalyzed biaryl ether synthesis.[9] However, as Scheme 2a shows,

Scheme 2. Attempts by Means of the Palladium-Catalyzed Reaction or Ullman Type Reaction



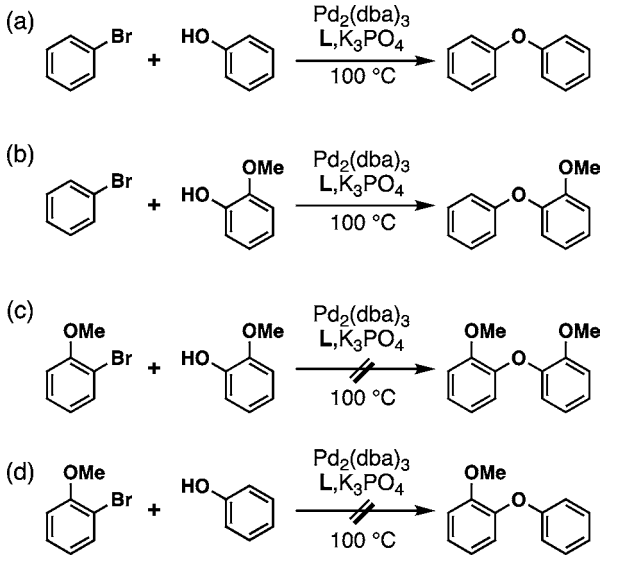
the coupling between aryl bromide **2** and phenols **3**−**5** under the literature conditions ($Pd_2(dba)_3$, **L** (2-di-*tert*-butylphosphi-

Received: January 14, 2017
Published: February 16, 2017

DOI: 10.1021/acs.orglett.7b00141
Org. Lett. 2017, 19, 1116−1119

no-2′,4′,6′-triisopropylbiphenyl), K_3PO_4, 1,4-dioxane−H_2O (1:1), 100 °C)[9] did not produce the desired products **1**, **6**, or **7**, resulting in the recovery of the starting materials. Protection of aldehyde **2** as a cyclic acetal **8** did not enable this coupling (Scheme 2b). Control experiments (Scheme 3)

Scheme 3. Control Experiments for Biaryl Ether Formations



revealed that the methoxy group ortho to the bromine functionality is likely hampering the reaction.[10] When we performed the Ullman coupling using aryl bromide **2** and phenol **5**, using conditions similar to Tokuyama's,[7] biaryl ether **1** could be isolated in only 15% yield (Scheme 2c), which is comparable to their result.

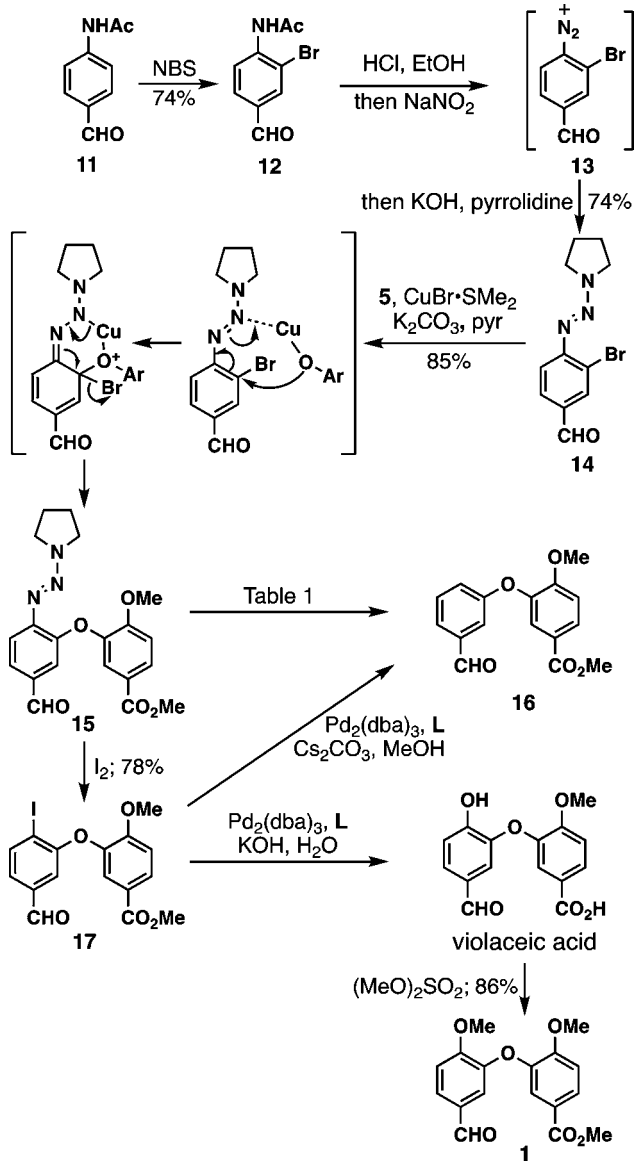
As such, we turned our attention to the triazene approach to improve the synthesis (Scheme 4). The aryl triazene approach was chosen due to the ability of the triazene to activate the ortho-bromide and direct the attack of the alkoxide nucleophile.[11] To exploit this chemistry, we began the synthesis with commercially available *p*-acetamidobenzaldehyde **11**, which was brominated to form aryl bromide **12** in 74% yield.[12] This aryl bromide was converted to triazene **14** in one pot by acid-catalyzed amide ethanolysis, diazonium formation (**13**), and the addition of pyrrolidine.[13] A mixture of triazene **14** and phenol **5** was subjected to CuBr·SMe_2 and K_2CO_3 in MeCN−pyridine (5:1) at 80 °C; to our delight, we were able to obtain the desired biaryl ether **15** in 85% yield in a reproducible manner.

We expected that triazene **15** could be converted to the corresponding methyl ether by an ionic mechanism.[14,15] However, under acidic conditions (5% TFA in MeOH, Table 1, entry 1), we isolated only the reduced arene **16** in 84% yield, which might be formed by a radical mechanism.[16]

In an attempt to trap the putative radical species with O_2, similar conditions were employed under an oxygen atmosphere, which still afforded arene **16** in 88% yield (Table S3, Supporting Information).

When the solvent was CD_3OD[17] (entry 2), the deuterated arene ***d*-16** was obtained in 84% yield, which is consistent with the radical mechanism. Resin-bound sulfonic acid[20] also generated the reduced arene **16** as the sole product (entry 3), indicating that this transformation is not specific with TFA. We hypothesized that a cationic intermediate might be

Scheme 4. Synthesis of Violaceic Acid and Aromatic Fragment 1



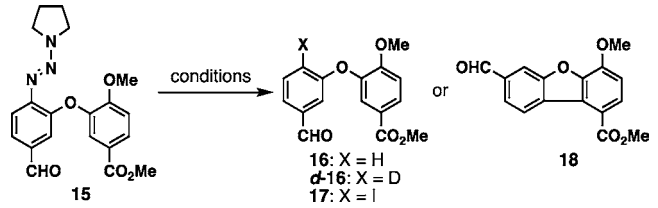
generated and intercepted by MeOH if the treatment of triazene **15** with NIS proceeds by an ionic mechanism. However, this experiment (entry 4) afforded only arene **16** and aryl iodide **17**.

Given the diazonium ion as an intermediate, we speculated that Cohen's method[18] might substitute the triazene moiety with a hydroxy group. However, the treatment of triazene **15** with TFA followed by Cu_2O, $Cu(NO_3)_2$, and $AgNO_3$ (entry 5) also provided arene **16** in 10% yield, with no expected phenol derivative. Changing the solvent from MeOH (entry 1) to MeCN (entry 6) generated benzofuran **18**. Such a Pschorr ring closure[19] may occur through a cationic intermediate,[20] although a radical mechanism is also plausible.[18] We hypothesized that the α-hydrogen of pyrrolidine could be a hydrogen donor toward the putative aryl radical intermediate.[21]

To test this hypothesis, pyrrolidine was added to the reaction (entry 7); the ratio of **16**:**18** increased, indicating that pyrrolidine may indeed be a hydrogen donor. With TEMPO, the overall yield decreased to 5% and the ratio of **16**:**18** remained the same (entry 6 vs entry 8). This result further

DOI: 10.1021/acs.orglett.7b00141
Org. Lett. 2017, 19, 1116−1119

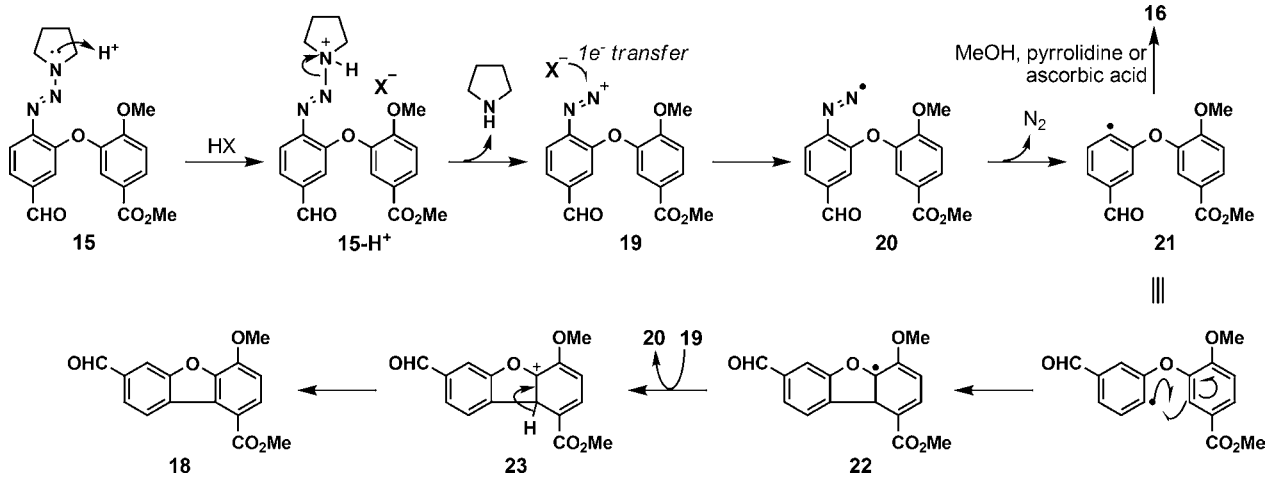
Table 1. Conversion of Triazene 15[a]



entry	acid	additive (equiv)	solvent	temp (°C)	t (h)	yield (%) (**16**:**18**)
1	A	none	MeOH	65	1.5	84 (1:0)
2	A	none	CD_3OD	65	2	84 (***d*-16**) (1:0)
3	B	none	$MeCN/H_2O$	83	2.5	77 (1:0)
4	C	NIS (1) MeOH (20)	MeCN	83	10	26[b]
5	A	Cu(I) (0.9), Cu(II) (30), Ag(I) (30)	CH_2Cl_2; H_2O	0; 23	1; 0.17	10 (1:0)
6[c]	A	none	MeCN	83	4	40 (1:1)
7[c]	A	pyrrolidine (5)	MeCN	83	4	40 (3:1)
8[c]	A	TEMPO (3)	MeCN	83	4	5 (1:1)
9[c]	D	none	MeCN	83	8	54 (3:1)

[a]Acid A = TFA; Acid B = Dowex 5WX8-200; Acid C = no acid; Acid D = Ascorbic acid. [b]Only **16** and **17** were seen in 1:6 ratio. [c]Proportion based on ^{1}H NMR. Cu(I) = Cu_2O; Cu(II) = $Cu(NO_3)_2$; Ag(I) = $AgNO_3$.

Scheme 5. Proposed Mechanism for the Formation of 16 and 18



corroborates with the radical mechanism. When changing the acid from TFA to ascorbic acid, the ratio of **16**:**18** also increased (entry 9). The formation of arene **16** was presumably enhanced by ascorbic acid as a superb H· donor.[22]

Although these results by no means excludes the cation intermediacy, we propose that arene **16** and dibenzofuran **18** are formed through a radical pathway (Scheme 5). In this pathway, after the protonation of triazene **15**, pyrrolidine is lost to form the diazonium ion **19**. Subsequently, a single electron transfer occurs within the ion pair to form radical species **20**.[23,24] The loss of dinitrogen ensues, resulting in the key aryl radical intermediate **21**. This radical species either abstracts a hydrogen atom from pyrrolidine, ascorbic acid, or MeOH to form arene **16** or reacts with the adjacent phenyl ring to form the tricyclic radical **22**. The reduction to form arene **16** becomes a more prominent pathway when a good hydrogen radical donor (e.g., MeOH, pyrrolidine, ascorbic acid) is present in excess. The radical species **22** then reacts with an electron acceptor (e.g., **19**) to form cation **23**, which undergoes aromatization to form dibenzofuran **18**. Arene **16** is produced in a greater proportion due to the rate of hydrogen abstraction of aryl radicals being faster than the rate of Pschorr-type ring closure (5×10^5 M^{-1} s^{-1} vs 1.1×10 M^{-1} s^{-1}).[25,26]

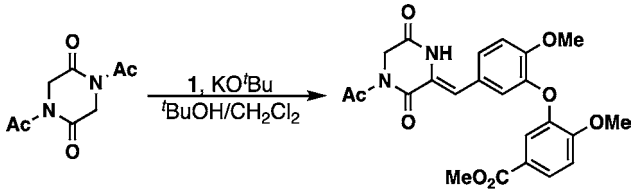
Having failed to directly convert triazene **15** to the corresponding methoxy or hydroxy arene, an alternative approach was pursued for the synthesis of the target molecule **1**; triazene **15** was treated with I_2 in MeCN[27] to form aryl iodide **17** in 78% yield (Scheme 4). When this iodide was treated with $Pd_2(dba)_3$ and Cs_2CO_3 in MeOH, the reduced arene **16** was the major product, presumably through a β-hydride elimination−reductive elimination sequence (i.e., Ar−Pd−OMe → Ar−Pd−H + HCHO → ArH + Pd).[28] As we were also interested in verifying the structure of violaceic acid, we turned our attention to the conversion of the iodide group to a hydroxy group rather than changing the phosphine ligand.[28] Aryl iodide **17** was treated with $Pd_2(dba)_3$, **L**, and KOH in 1,4-dioxane−H_2O (1:1)[8] to synthesize violaceic acid in quantitative yield. This was treated with $(MeO)_2SO_2$ to form methyl ether **1** in 86% yield. Here, the revised structure of violaceic acid[4] was confirmed by chemical synthesis for the first time.

For the next stage of our studies, we performed an aldol reaction[24] between diketopiperazine **24** and aldehyde **1** to

DOI: 10.1021/acs.orglett.7b00141
Org. Lett. 2017, 19, 1116−1119

obtain alkene **25** in 75% yield (Scheme 6, not optimized). An exocyclic olefin may be used for further functionalization to accomplish the total synthesis of MPC1001.[25]

Scheme 6. Aldol Reaction between Aldehyde 1 and Diketopiperazine 24



24 **25**

In summary, we synthesized aldehyde **1** in six steps from aldehyde **11**, featuring a successful application of the triazene approach for biaryl ether formation and the two-step conversion of a triazene to a hydroxy compound. This endeavor also resulted in the total synthesis and structural confirmation of violaceic acid. We also investigated the mechanism that accounts for the formation of arene **16** and dibenzofuran **18**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00141.

Detailed experimental procedures along with analytical and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Cancer Institute (R01 CA120792). J.B. was supported by the Dietrich Arts and Science scholarship from the University of Pittsburgh.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 5 was corrected on February 17, 2017.

DOI: 10.1021/acs.orglett.7b00141
Org. Lett. 2017, 19, 1116−1119