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Synthetic Studies Directed toward Dideoxy Lomaiviticinone Lead to Unexpected 1,2-Oxazepine and Isoxazole Formation

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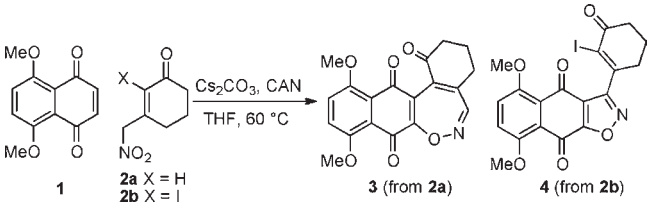
ABSTRACT



In the course of studies directed toward the synthesis of dideoxy lomaiviticinone, 3-(nitromethyl)cyclohexenones 2a (X = H) and 2b (X = I) were prepared. The corresponding enolates were reacted with naphthazarin (1) and unexpectedly afforded 1,2-oxazepine 3 and isoxazole 4, respectively. Rationale for their formation is proposed.

The diazofluorene antitumor antibiotics lomaiviticins A and B[1] have attracted considerable attention from the synthetic community due to their molecular complexity, potent cell cytotoxicity, and scarcity in nature.[2,3] Lomaiviticinone, the aglycone common to lomaiviticin A and B, was recently prepared by an 11-step synthesis reported by Herzon and co-workers.[4] As expected lomaiviticinone prepared by this route was isolated as a rigid polycyclic ring system formed by closure of the C3/C3′ tertiary alcohols onto the neighboring C1/C1′ keto groups (Figure 1). In anticipation of DNA cleavage studies, and simplified synthetic obstacles, we considered it advantageous to access C3/C3′ dideoxy lomaiviticinone, an aglycone with free rotation about the C2−C2′ carbon−carbon bond as found in lomaiviticin A, the more abundant and studied of the two dimeric diazofluorene natural products.

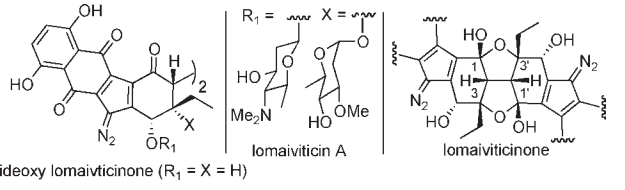


Figure 1. Structure of lomaiviticin A, lomaiviticinone, and dideoxy lomaiviticinone.

In 2008 we reported on the synthesis of the *C*2-symmetric core of dideoxy lomaiviticinone (**3**) starting from (−)-quinic acid.[3c] We planned to advance bis-enone **3** to dideoxy lomaiviticinone starting with conversion of **3** to nitromethylcyclohexenone **2** (X = H or halogen),

(1) He, H.; Ding, W.; Bernan, V.; Richardson, A.; Ireland, C.; Greenstein, M.; Ellestad, G.; Carter, G. *J. Am. Chem. Soc.* **2001**, *123*, 5362–5363.

(2) For a comprehensive review of the lomaiviticins and kinamycins, see: Herzon, S. B.; Woo, C. M. *Nat. Prod. Rep.* **2012**, *29*, 87–118.

(3) Synthetic studies: (a) Nicolaou, K. C.; Denton, R. M.; Lenzen, A.; Edmonds, D. J.; Li, A.; Milburn, R. R.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2076–2081. (b) Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680–1684. (c) Zhang, W.; Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2008**, *10*, 1939–1941. (d) Nicolaou, K. C.; Nold, A. L.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5860–5863. (e) Gholap, S. L.; Woo, C. M.; Ravikumar, P. C.; Herzon, S. B. *Org. Lett.* **2009**, *11*, 4322–4325. (f) Lee, H. G.; Ahn, J. Y.; Lee, A. S.; Shair, M. D. *Chem.—Eur. J.* **2010**, *16*, 13058–13062. (g) Morris, W. J.; Shair, M. D. *Org. Lett.* **2008**, *11*, 9–12. (h) Morris, W. J.; Shair, M. D. *Tetrahedron Lett.* **2010**, *51*, 4310–4312.

(4) (a) Herzon, S. B.; Lu, L.; Woo, C. M.; Gholap, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 7260–7263. (b) Herzon, S. B. *Synlett* **2011**, 2105–2114.

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with the nitro group serving the purposes of methylene activation and as a progenitor to the central diazo group (Figure 2). Given the symmetry of quinone **1**, annulation between **1** and nitro activated cyclohexenone **2** could proceed by one of two orders of bond formation (**a** versus **b**). Herein we describe model studies in anticipation of Michael addition of **2** to quinone **1** (bond **b**). Our investigations started from cyclohexenone led us to discover novel oxidative nitronate mediated [5 + 2] and [3 + 2] quinone annulations.

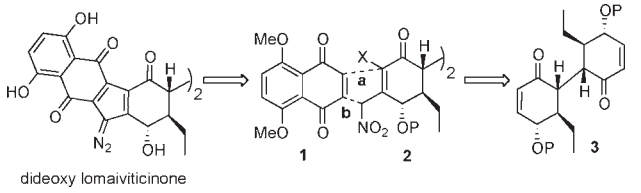
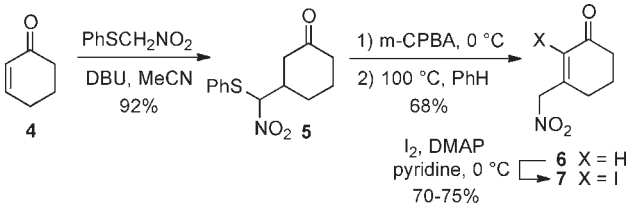


Figure 2. Synthetic strategy leading to dideoxy lomaiviticinone by way of quinone annulation.

Our studies began with an efficient two-step conversion of 2-cyclohexenone (**4**) to 3-(nitromethyl)cyclohexenone starting with the addition of the conjugate base of (phenylthio)nitromethane to **4** (Scheme 1).[5,6] The resulting Michael adduct (**5**) was then oxidized with m-CPBA to the corresponding sulfoxides and immediately heated in refluxing benzene to provide 2-(nitromethyl)cyclohexenone **6**. The α-carbon of enone **6** was then iodinated[7] in anticipation of an intramolecular Heck reaction (bond **a** formation) following formation of bond **b** (Figure 2). Surprisingly, this proved to be the first example of using (phenylthio)nitromethane to introduce a nitromethyl group at the *β*-position of an enone. Historically, (phenylthio)nitromethane has been used primarily in carbonyl additions, alkylations, dipole additions, and ring expansion reactions.[6a,8]

Scheme 1. Preparation 3-(Nitromethyl)cyclohexenones **6** and **7**

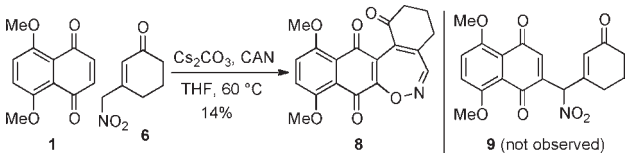


(5) (a) Barrett, A.; Graboski, G.; Russell, M. *J. Org. Chem.* **1985**, *50*, 2603–2605. (b) Bordwell, F.; Bartmess, J. *J. Org. Chem.* **1978**, *43*, 3101–3107.

(6) (a) Boivin, J.; Chauvet, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 4913–4916. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971.

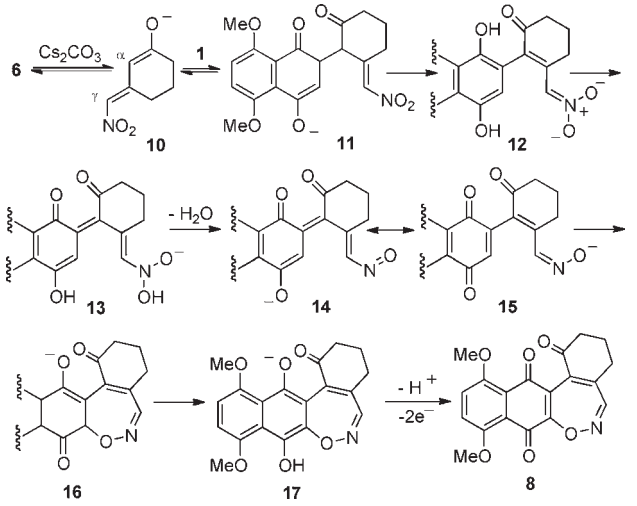
(7) (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917–918.

Scheme 2. Base-Catalyzed Oxidative Addition of Nitrocyclohexenone **6** to Quinone **1**



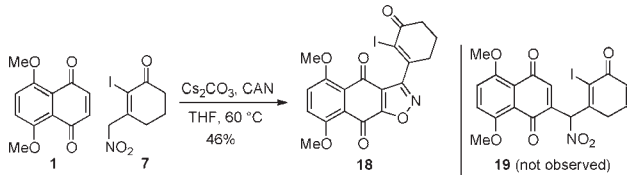
The Michael oxidative addition of enolates to quinones is oftentimes complicated by secondary reactions and electron transfer mediated processes.[9] Nonetheless, we chose to explore the addition of the conjugate base of 3-(nitromethyl)cyclohexenone (**6**) to naphthazarin **1**[10] under oxidative conditions aimed to deliver adduct **9**. After screening a large number of reaction conditions including varying pH and base we eventually isolated an adduct of enone **6** and quinone **1** which, surprisingly, proved not to be **9** but instead [5 + 2] adduct 1,2-oxazepine **8**, albeit isolated in only 14% yield (Scheme 2). The structural assignment of **8** was based on extensive NMR and high-resolution mass spectral analysis. Presented in Scheme 3 is a tentative mechanism for the formation of **8** starting with the addition of **10** to quinone **1**. Tautomerization accompanied by proton transfer results in conversion of **11** to hydroquinone **12**, poised for quinone methide formation (**13**). Loss of a molecule of water then leads to nitroso **14**, equivalent to oxime anion **15** by electron delocalization. Finally, cyclization followed by terminal oxidation accounts for production of 1,2-oxazepine **8**.

Scheme 3. Proposed Base-Catalyzed Oxidative Addition of **6** to Quinone **1** Leading to **8**



(8) (a) Ashwell, M.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron* **1990**, *46*, 7429–7442. (b) Kim, S.; Park, J. H. *Chem. Lett.* **1988**, 1323–1324. (c) Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1988**, 282–283. (d) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1986**, *51*, 1012–1015. (e) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 362–363.

Scheme 4. Base Catalyzed Oxidative Addition of Nitrocyclohexenone **7** to Quinone **1**



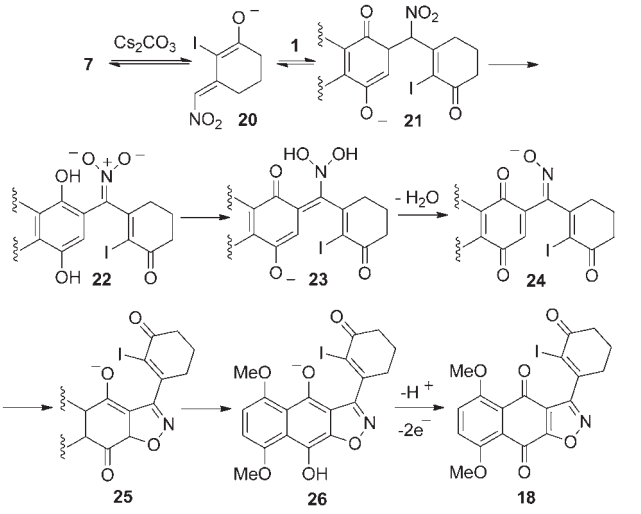
Examination of the reaction pathway leading to undesired quinone **8** (Scheme 3) suggested the desired carbon−carbon bond formation (bond **b**, Scheme 1) could be directed by blocking the α-carbon of dienolate **10** by a halogen atom (cf. **7**, Scheme 5). In this case we anticipated base-catalyzed addition of **7** to naphthazarin **1** under oxidative conditions would afford adduct **19** appropriately functionalized for an intramolecular Heck reaction as demonstrated by Herzon's group.[4] In the event, our plan was once again thwarted leading to a 46% yield of isoxazole quinone **18** without **19** being observed (Scheme 4). In this case the desired carbon−carbon bond formation (**20** + **1**→**21**) was followed by undesired reorganization of oxidation state (**22**→**24**) followed by oxidative cyclization (**24**→**18**) (Scheme 5).

Our failure to effect base-promoted annulation between either cyclohexenone **6** or **7** and quinone **1** can be ascribed to the incompatibility of the nitronate and hydroquinone conjugated systems **12** and **21**. A potential solution to this

(9) (a) Chuang, C.-P.; Wu, Y.-L.; Jiang, M.-C. *Tetrahedron* **1999**, *55*, 11229–11236. (b) Chen, H.-L.; Lin, C.-Y.; Cheng, Y.-C.; Tsai, A.-I.; Chuang, C.-P. *Synthesis* **2005**, 977–985. (c) Tseng, C.-C.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2002**, *58*, 7625–7633. (d) Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1995**, *60*, 5024–5028.

(10) Huot, R.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 838–842.

Scheme 5. Proposed Base-Catalyzed Oxidative Addition of **7** to Quinone **1** Leading to **16**



incompatibility is reduction of the nitro group to a protected amine. This possibility and other approaches to dideoxy lomaiviticinone are under investigation and will be reported in due course.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.