Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 9021–9023

TETRAHEDRON LETTERS

Investigations into arylquinone atropisomers: synthesis and evaluation☆

Umar S. M. Maharoof and Gary A. Sulikowski*

Department of Chemistry, Texas A&M University, PO Box 30012, College Station, TX 77842–3012, USA

Received 2 September 2003; revised 26 September 2003; accepted 29 September 2003

Abstract—An arylquinone capable of existing as two diastereromeric atropisomers was synthesized starting from dibenzofuran. Arylquinone **12** exists as a set of slowly interchanging diastereomeric atropisomers and arylquinone **4** exists as rapidly interchanging atropisomers.

A number of natural products occur as a single atropisomer due to restricted rotation around a carbon–carbon bond. Examples include highly substituted biaryl natural products such as biphyscion (**1**)[1] and the bisquinone bismurrayaquinone A (**2**).[2] In many cases the identification of a natural atropisomer escapes the attention of isolation chemists especially when these are atropenantiomers.[3] While examples of biaryl and bisquinone atropisomers have been reported, no report of the existence of *arylquinone* atropisomers has been communicated in the literature despite their occasional appearance within natural products.[4] One recent example is the class of hibarimicin antitumor antibiotics, that share hibarimicinone (**3**) (Fig. 1) as a common aglycone.[5] The central DE ring system of hibarimicinone incorporates a sterically congested central arylquinone sub-structure suggesting the hibarimicins may exist as single atropisomers. As part of a program directed towards the total synthesis of hibarimicinone we desired, in a preliminary investigation, to evaluate the possibility that arylquinones related to **3** exist as atropisomers. To this end we planned to assemble arylquinone **4** that could exist as a pair of *diastereomeric* atropisomers (**4a** and **4b**), easily distinguished by NMR analysis (Fig. 2). The synthesis and NMR analysis of arylquinone **4** are the subjects of this letter.

Arylquinones have typically been assembled by cross-coupling of a haloquinone and aryl metal reagent, either an arylstannane or arylboronic acid.[6] In the case of congested arylquinones this approach can prove challenging, especially when employing electron rich aryl metal reagents as a coupling partner. We therefore chose to explore an alternative strategy for the synthesis of **4** starting from quinone monoketal **5** (Fig. 3). We anticipated the latter intermediate to be produced from dibenzofuran (**6**) (Scheme 1).

Hydroxylation of dibenzofuran in the C(2) and C(8) positions were achieved by regioselective Friedel–Crafts

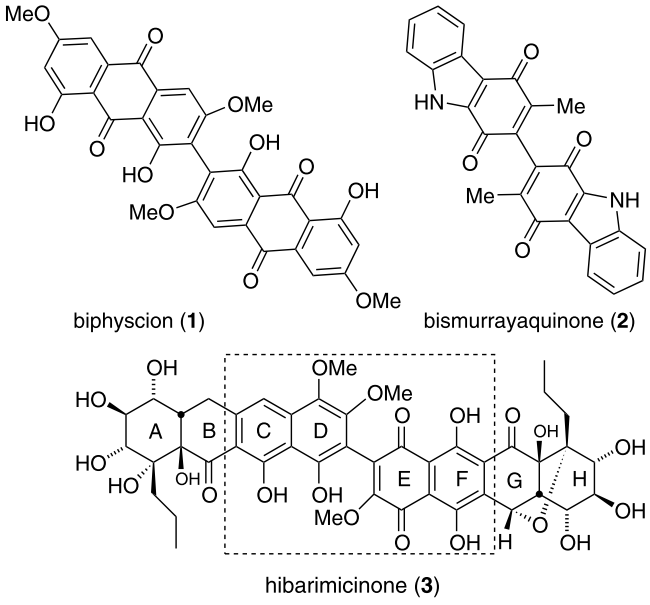


Figure 1.

☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.09.214

* Corresponding author. E-mail: g-sulikowski@tamu.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.214

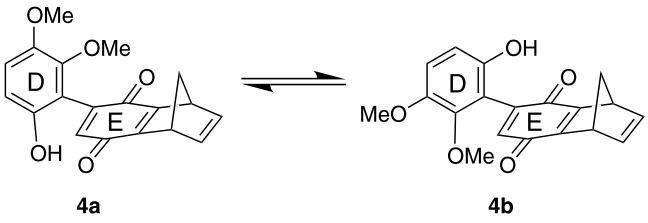


Figure 2.

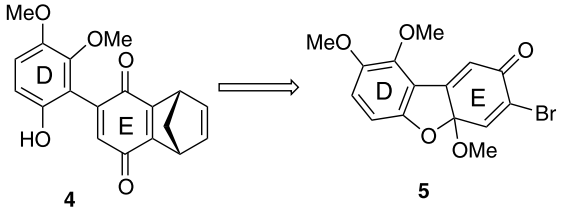
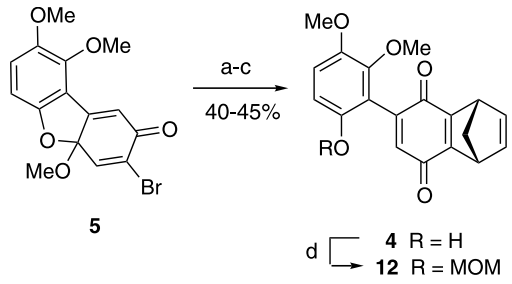


Figure 3.

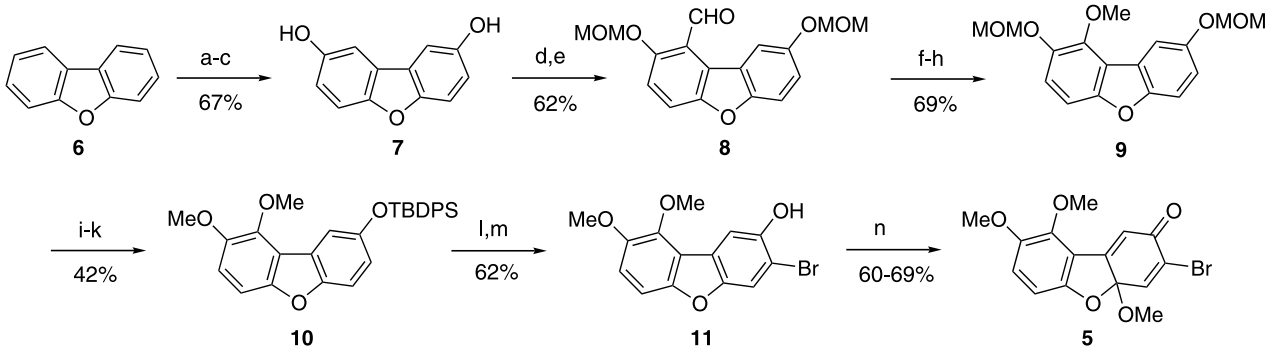
acylation followed by Baeyer–Villiger oxidation and finally reduction to afford bis-phenol **7** in 67% overall yield.[7] Alklyation with MOMCl set the stage for an *ortho*-directed metallation which following quenching of the resulting aryllithium intermediate provided aromatic aldehyde **8**.[8] The aldehyde group was then converted to methyl ether **9** by a standard three-step procedure (1. *m*-CPBA, 2. K_2CO_3, MeOH, and 3. MeI, K_2CO_3). Next, the neighboring MOM ether was exchange for a methyl ether starting with removal of both MOM groups and protection of the less hindered of the two resulting phenolic hydroxyl groups as a *t*-butyldiphenylsilyl ether.[9] The remaining phenol was methylated to provide the desired dimethyl ether **10**. Finally, removal of the silyl protecting group followed by *ortho* bromination[10] gave phenol **11** and oxidation of the latter with (diacetoxyiodo)benzene[11] in methanol provided monoketal **5**.

Monoketal quinone **5** proved to be a very reactive dienophile. For example reaction with cyclopentadiene in toluene occurred at room temperature to provide a single Diels–Alder adduct in 95% yield. Hydrolysis of the latter using lithium tetrafluoroborate in aqueous acetonitrile[12] followed by dehydrobromination provided arylquinone **4**. Interestingly arylquinone **4** appeared as a *single isomer* at room temperature according to both ^1H and ^{13}C NMR analysis, indicating rapid rotation around the aryl-quinone carbon–carbon bond. In contrast, alkylation of **4** with MOMCl gave MOM ether **12** which emerged as an approximately 1:1 mixture of interchanging atropisomers according to NMR analysis. The two conformers failed to coalesce at temperatures as high as 148°C. Furthermore, analysis of **12** by HPLC under various conditions did not lead to separation of atropdiastereoisomers. Taken together, a coalescence temperature greater than 148°C and inseparable atropisomers at room temperature suggests that the barrier to rotation is in the range of 20–25 kcal/mol (Scheme 2).[13]



Scheme 2. *Reagents and conditions*: (a) 1,3-cyclopentadiene, PhMe, 23°C; (b) $LiBF_4$, MeCN (aq.); (c) Et_3N, CH_2Cl_2; (d) MOMCl, *i*-Pr_2NEt, DMF, 60°C.

Steric hindrance alone cannot account for the significant differences in aryl-quinone carbon–carbon bond rotational barriers between phenol **4** and MOM ether **12**. We speculate that the rotational barrier of phenol **4** is significantly lowered due to stabilization of the transition state structure leading to the interconversion of **4a** and **4b** (Fig. 4) by tautomerization to intermediate quinone methide **4c**. In contrast, MOM ether **12** does not have the low energy quinone methide pathway available to assist bond rotation leaving only a higher



Scheme 1. *Reagents and conditions*: (a) AcCl, $AlCl_3$, CH_2Cl_2, 0→23°C; (b) *m*-CPBA, CH_2Cl_2, 50°C; (c) DIBAL, CH_2Cl_2, −78°C; (d) MOMCl, *i*-Pr_2NEt, DMF, 0→23°C; (e) *n*-BuLi, TMEDA, Et_2O, −10°C then DMF; (f) *m*-CPBA, CH_2Cl_2, 23°C; (g) K_2CO_3, MeOH; (h) MeI, K_2CO_3, Me_2CO; (i) HCl, MeOH, 40°C; (j) TBDPSCl, ImH, DMAP, DMF; (k) MeI, K_2CO_3, Me_2CO; (l) TBAF, THF, 0°C; (m) Bu_4NBr_3, CH_2Cl_2, MeOH; (n) $PhI(OAc)_2$, MeOH, 0°C.

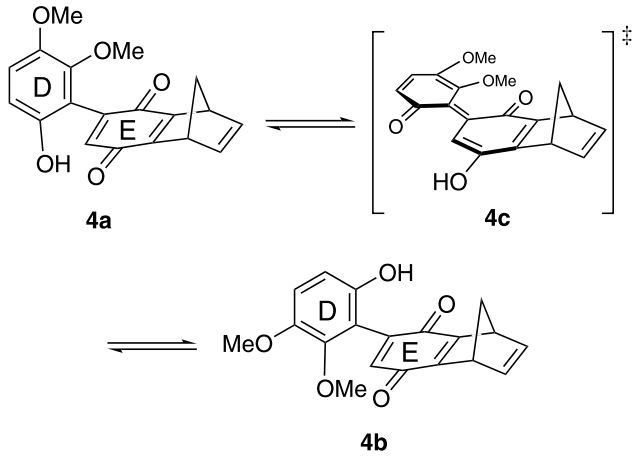


Figure 4.

energy pathway for interchange of conformational isomers.

In conclusion, we have identified for the first time that certain aryl quinones capable of undergoing a tautomeric isomerization to an intermediate quinone methide have unusually low barriers to rotation about central aryl-quinone carbon–carbon bonds. This observation has significant implications in considering the design of synthetic routes leading to natural aryl quinones such as hibarimicin B.

Acknowledgements

We thank the National Institutes of Health (CA59515-06) and The Robert A. Welch Foundation (A-1230) for support of this research. The National Science Foundation (CHE-0077917) is acknowledged for providing funds for the purchase of NMR instrumentation.

References

1. Hauser, F. M.; Gauuan, P. J. F. *Org. Lett*. **1999**, *1*, 671–672.
2. (a) Ito, C.; Thoyama, Y.; Omura, M.; Kajiura, I.; Furukawa, H. *Chem. Pharm. Bull*. **1993**, *41*, 2096–2100; (b) Bringmann, G.; Ledermann, A.; Stahl, M.; Gulden, K. P. *Tetrahedron* **1995**, *51*, 9353–9360.
3. (a) Bringmann, G.; Ledermann, A.; Francois, G. *Heterocycles* **1995**, *40*, 293–300; (b) Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc*. **2001**, *123*, 2703–2711.
4. (a) Fukuyama, Y.; Kiriyama, Y.; Okino, J.; Kodama, M. *Tetrahedron Lett*. **1993**, *34*, 7633–7636; (b) Stack, M. E.; Mazzola, E. P.; Eppley, R. M. *Tetrahedron Lett*. **1979**, 4989–4992.
5. (a) Uehra, Y.; Li, P.-M.; Fukazawa, H.; Mizuno, S.; Nihei, Y.; Nishio, M.; Hanada, M.; Yamamoto, C.; Furumai, T.; Oki, T. *J. Antibiot*. **1993**, *46*, 1306–1308; (b) Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett*. **1996**, *37*, 2785–2788; (c) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 394–401.
6. (a) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett*. **1993**, *34*, 7637–7638; (b) Stagliano, K. W.; Malinakova, H. C. *J. Org. Chem*. **1999**, *64*, 8034–8040.
7. Albrecht, W. L.; Fleming, R. W.; Horgan, S. W.; Mayer, G. D. *J. Med. Chem*. **1977**, *20*, 364–371.
8. Winkle, M. R.; Ronald, R. C. *J. Org. Chem*. **1982**, *47*, 2101–2108.
9. A separable mixture of mono (58%) and bis (29%) silylated products was produced.
10. Kakinami, T.; Urabe, Y.; Hermawan, I.; Yamanishi, H.; Okamoto, T.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 2549–2551.
11. Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891–1896.
12. Lipshutz, B. H.; Harvey, D. F. *Synth. Commun*. **1982**, *12*, 267–277.
13. Oki, M. *The Chemistry of Rotational Isomers*; Springer-Verlag: Berlin, 1993.