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Tetrahedron Letters 45 (2004) 1793–1796
Tetrahedron Letters

Cycloadditions of *o*-quinone dimethides with *p*-quinol derivatives: regiocontrolled formation of anthracyclic ring systems ☆

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Received 2 October 2003; revised 5 December 2003; accepted 5 December 2003

Abstract—Regioselective cycloadditions between the cyclohexadienones **12**–**14** and the *ortho*-quinone dimethide **19**, which is thermally generated from the corresponding 1,3-dihydro-1-methoxy-2,2-dioxide benzo[*c*]thiophene **27**, are reported. The synthetic sequence provides rapid access to highly substituted anthracyclic system and may be of use for construction of the natural product (+)-rishirilide B.

The most obvious disconnection for a synthesis of rishirilide B (**1**) results in the highly oxidized cyclohexenone **4** and the isobenzofuran-4-ol **3** (Fig. 1). Unfortunately, the alcohol functional group present on the isobenzofuran-4-ol **3** would determine the regiochemical outcome of this hypothetical union and lead to the undesired regioisomer **2**.[1] A variety of other natural products containing anthracyclic ring systems pose a similar regiochemical challenge.

Several elegant solutions to this regiochemical dilemma have recently appeared. Hauser and Xu use the isobenzofuranone enolate **5** with the enone **7** to ensure the desired regiochemical outcome of **8** despite the influence of the aryl methoxy residue (Scheme 1).[2] Swenton and co-workers[3] and Baker and co-workers[4] have independently utilized this strategy with the related nitrile **6** in highly efficient syntheses of hydroxypthalides and hongconin, respectively.

However, use of the isobenzofuranone enolates **5** and **6** introduce several problems if applied in the synthesis of **1**. First, erasure of the hydroquinone functionality in **8** requires many synthetic manipulations. Second, the preparation of the methoxy-substituted isobenzofuranone **5** and **6** proves tedious.[5] A recent Suzuki synthesis of these derivatives, which involves an efficient desymmetrization of 2-iodo-resorcinol (Fig. 2), is perhaps the most efficient assembly process leading to enolates **5** and **6**.[6]

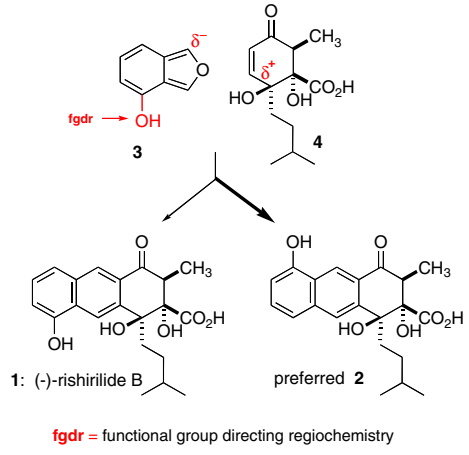
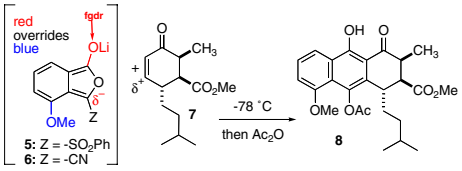


Figure 1. Regiochemical challenge posed by rishirilide B (**1**).



Scheme 1. Hauser assembly of tricycle used in synthesis of rishirilide B (**1**).

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.12.114

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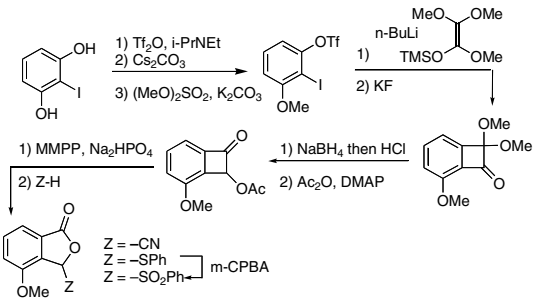
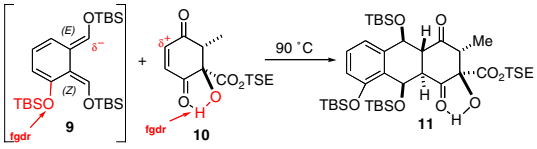


Figure 2. Suzuki synthesis of precursors to furanoenolates **5** and **6**.

Danishefsky and co-workers demonstrated another solution to the regiochemical problem presented by rishirilide B (**1**).[7] In their total synthesis of (−)-(**1**), the (*E*,*Z*)-*o*-quinone dimethide **9** undergoes an *endo* oriented [4+2] cycloaddition with **10**. Because the directing effects of the methide siloxy residues cancel-out, the siloxy substituent on the benzene ring of **9** determines the regiochemical preference with regards to the *o*-quinone dimethide **9**, while an internal hydrogen bond attenuates the electrophilicity and determines the regiochemical preference with regards to the cyclohex-2-ene-1,4-dione **10** (Scheme 2). The cycloaddition between compounds **9** and **10** results almost exclusively in the regioisomer **11**; the methine stereocenter adjacent to the protonated carbonyl most likely arises from a post cycloaddition epimerization.

This elegant strategy, however, is not without problems. The *trans*-substituted cyclobutene precursor to **9** is difficult to prepare and its synthesis results in some of the corresponding *cis*-substituted cyclobutene (Fig. 3). Because cyclobutenes thermally open by a conrotary motion and the fact that only *trans*-substituted cyclobutenes afford geometrically disposed *o*-quinone dimethide capable of cycloaddition,[8] the long route and



Scheme 2. Danishefsky assembly of the rishirilide B core.

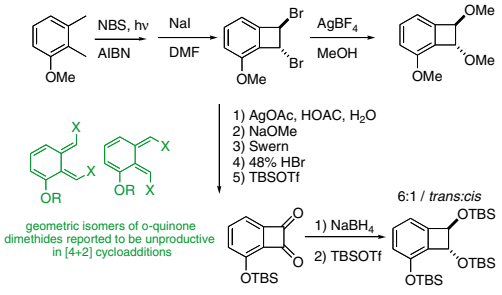
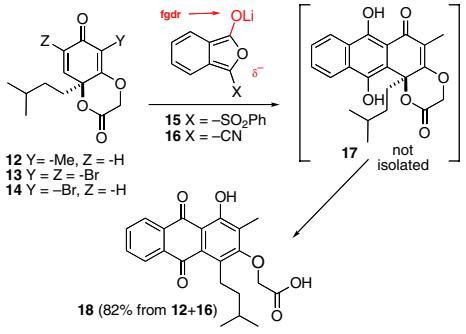


Figure 3. Danishefsky preparation of cyclobutene precursor to **9**.

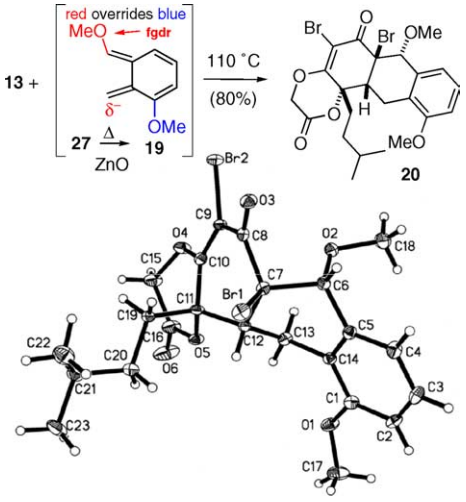
cis-cyclobutene product divert material from the synthetic stream.

With knowledge of the factors responsible for regiochemical control and the difficulty of associated with construction of the prospective coupling partners, we began investigating similar reactions with regards to the novel *p*-quinol derivatives **12**–**14** (Scheme 3). Initially, we were concerned that **12**–**14** might not readily undergo a [4+2] cycloadditions with *o*-quinone dimethides, because similar systems proved sluggish in their cycloadditions.[9] Therefore, we first investigated the reactivity of these *p*-quinol derivatives with the furanoenolates **15** and **16**. While the isobenzofuranone enolate **15** failed to undergo addition to **12**, the less encumbered nitrile derivative **16** participates in the desired Michael–Dieckman process. Instead of the anticipated tautomer **17**, however, the anthraquinone **18** emerges as the sole product. Because this ring forming process destroyed the stereocenter intended to direct the creation of subsequent stereocenters, other annulation reactions were investigated.

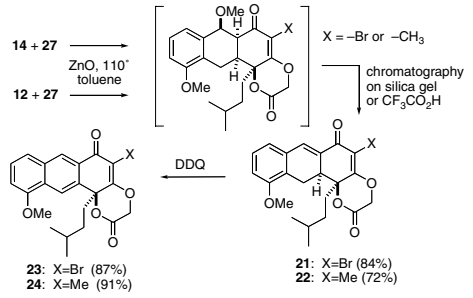
While the combination of **9** and any of our *p*-quinol derivatives **12**–**14** would likely lead to the undesired regiochemistry, we speculated the cycloaddition of the *p*-quinol derivatives **12**–**14** with the unknown *o*-quinone



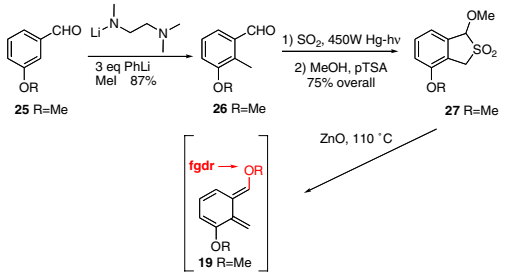
Scheme 3. Anthraquinone emerges upon our addition of **16**–**12**.



Scheme 4. Our revised strategy for rishirilide B core.



Scheme 5. Our cycloadditions of *o*-DM **19** with *p*-quinols **12** and **14**.



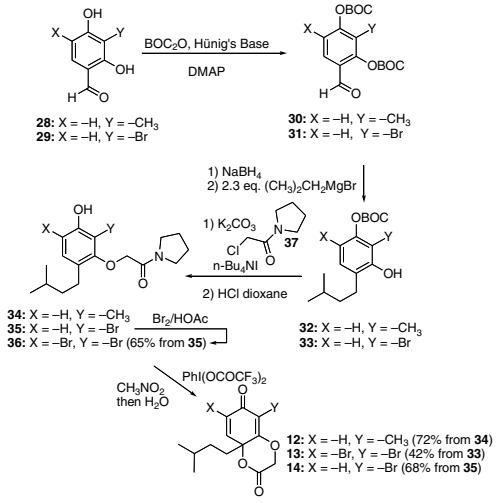
Scheme 6. Our synthesis of the Durst–Charlton type of precursor to **19**.

dimethide **19** might prove fruitful (Scheme 4). The outcome, however, was by no means certain as the directing effects of the methoxy residues in **19** opposed one another. We anticipated that the methide methoxy residue would play a greater role because of its proximity to the reaction sites.

The cycloaddition of the bis-bromide **13**, presumably the most reactive among the three *p*-quinol derivatives, was the first we investigated. Gratifyingly, the reaction between **13** and **19**, which is thermally generated from **27** (Scheme 6), proceeds smoothly and affords **20** in 80% yield (Scheme 4). None of undesired regioisomer is evident upon inspection of the crude NMR spectra for the reaction. The structure of the product **20** was unequivocally established by X-ray analysis.[†] Similar conditions for cycloaddition are almost equally effective with the *p*-quinols **14** and **12** (Scheme 5). These latter two compounds were initially expected to be somewhat less reactive than the bis-bromoenone **13**. Fortunately, both **14** and **12** are smoothly annulated by **19**. However, upon chromatography on silica gel the initial cycloadducts undergo β-elimination of their respective methoxy residues resulting in the corresponding enones, **21** (84% yield) and **22** (72% yield).[‡] To further substantiate the identity of enone **21**, compound **20** is converted into **21** (80% yield) by the addition of PPh_3 in MeOH.[10] Independent treatment of **21** and **22** with DDQ in benzene affords compounds **23** and **24** in 87% and 91% yield, respectively.[11]

When compared with the two previous strategies, several benefits of our approach become apparent. First, an *o*-quinone dimethide masked as a 1,3-dihydro-1-methoxy-2,2-dioxide benzo[*c*]thiophene can be generated under milder conditions (0.5 M in toluene, 1 equiv ZnO, reflux 110 °C).[12] Second, a Durst–Charlton *o*-quinone dimethide is more accessible than **9** or the isobenzofuranone enolates **5** and **6**. As illustrated in Scheme 6, a three-pot method provides the previously unknown *o*-quinone dimethide precursor **27**. The route begins with a Comins process for in situ protection of the commercially available aldehyde **25** followed by subsequent *ortho*- directed aryl lithiation and methylation to afford the benzaldehyde **26** in >87% yield.[13] Photolysis of **26** (0.1 M benzene, 2.5 equiv SO_2, 450 W Hg lamp, 0 °C, 8 h) produces the corresponding hemi-hydrate, which upon addition of MeOH and *p*-TsOH generates **27** in a 75% overall yield. Lastly, because the *o*-quinone dimethide precursor **27** is not a diastereomeric mixture, all of it enters the synthetic stream as **19** leading to **1**.

With regards to the preparation of the *p*-quinol derivatives **12**–**14** were used in this study, these are available in >68% yield by oxidation of the corresponding phenols **34**–**36** [0.01 M in CH_3NO_2, 1.1 equiv of $PhI(OCOCF_3)_2$, 0 °C] (Scheme 7). We find the presence of a substituent larger than a hydrogen atom at the [Y] position in the phenol precursor greatly improves the yields of the dearomatization–lactonization protocol by >20%.[9] The phenols **34**–**36** are constructed from **32** to **33** by introduction of the amide side chain **37** via a Finkelstein procedure and subsequent cleavage of the –OBoc residue by action of aq HCl in dioxane. [14e] Bromination of **35** affords **36**. The phenols **32**–**33** are available from the bis-Boc aldehydes **30**–**31** through a process that involves



Scheme 7. Our synthesis of *p*-quinol derivatives **12**–**14**.

[†] Data for compound **20** has been filed with the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

[‡] The ratio of the adduct containing the methoxy residue and the enone elimination product varies among reactions. However, the former can be transformed into the latter by addition of CF_3COOH upon completion of the cycloaddition.

an *o*-quinone methide intermediate.[14] The benzaldehydes **28** and **29** and amide **37** are known compounds.[15,16]

A method for the enantioselective preparation of compounds resembling **23** and **24** will be reported shortly.[9b] The conversion of these compounds into **1** will be reported in due course.

Supplementary information

Key spectroscopic data and experimental procedures for the construction of **27**, **28**–**37**, **12**–**14**, and **20**–**24** are reported and are available for download.

Acknowledgements

Research Grants from NIH (GM-64831) and UC-AIDS (K00-SB-039) are greatly appreciated.

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