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A Diversity-Oriented Synthesis of Bicyclic *cis*-Dihydroarenediols, *cis*-4-Hydroxyscytalones, and Bicyclic Conduritol Analogues

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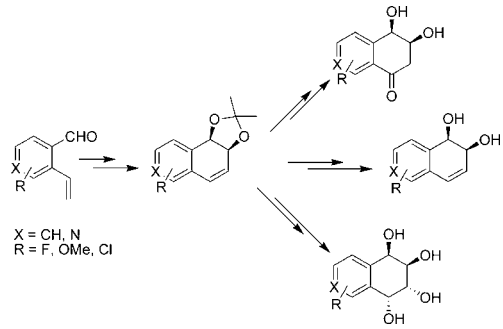
ABSTRACT



A common-intermediate-based enantioselective strategy has been developed aiming at bicyclic arene *cis*-dihydrodiols, *cis*-4-hydroxyscytalones, and bicyclic mimics of conduritol. Key features of this protocol include Barrett's asymmetric hydroxyallylation, ring-closing metathesis (RCM), and completely regioselective Wacker oxidation of internal cyclic olefins.

The chemically sensitive *cis*-keto-diol **1** and corresponding monomethyl ether **2** motifs are present in a host of natural products, some of which show promising biological profiles (Figure 1). Examples of such natural products include the phytotoxic *cis*-6-deoxy-4-hydroxyscytalone (**3a**) and 4-hydroxyscytalone (**3b**),[1] cladosporol (**4**),[2] which shows hyper parasitic activity, and the antiangiogenic chrysanthone A (**5**),[3] to name a few. In view of the absence of any general

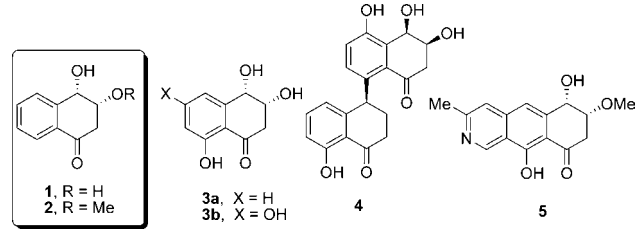


Figure 1. Some bioactive natural products containing *cis*-keto-diol motifs.

methodology for the construction of the common motifs **1** and **2**, it was deemed important to develop one. For this we first targeted the scytalone derivative **3a**,[1] a widely reported secondary metabolite in the literature, as a synthetic exercise toward the array of natural products containing the keto-

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(2) Nasini, G.; Arnone, A.; Assante, G.; Bava, A.; Moricca, S.; Ragazzi, A. *Phytochemistry* **2004**, *65*, 2107.

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diol motif **1**. In addition, the questionable absolute stereochemistry[4a] and conflicting biological profile[4b] of **3a** provided additional impetus to target it in the first place.

Retrosynthetically, a late-stage metal-mediated oxidation of *cis*-dihydroarenediols such as **7** could install the keto functionality in **6** (Figure 2). However, there are only a

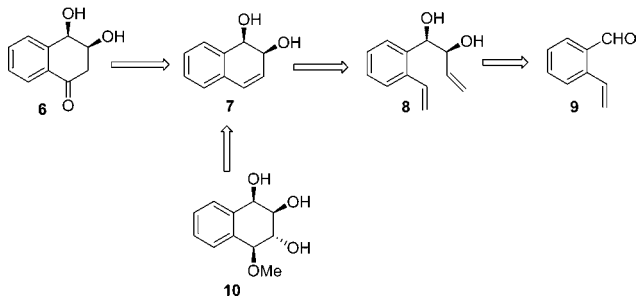
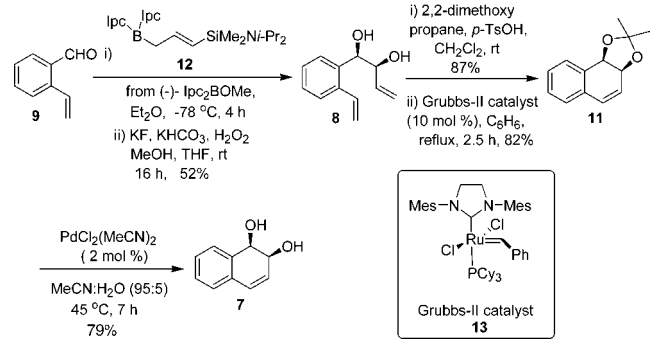


Figure 2. Retrosynthetic analysis.

handful of methods known in the literature for the preparation of bicyclic *cis*-dihydroarenediols, among which the method of choice is undoubtedly the one via chemoenzymatic oxidation pioneered by Gibson[5] in the early 1970s and later developed extensively by the research groups of Boyd,[6] Hudlicky,[7] and others.[8] The applications of *cis*-dihydroarenediols obtained by the enzymatic methodology is prominent in their use as chiral intermediates for natural product synthesis,[9] for designing chiral ligands,[10] and as precursors to conduritol analogues such as **10**,[11] which have some importance in medicinal chemistry. Apart from this and Jerina's early chemical synthesis of the racemic *cis*-dihydrodiol derivative of naphthalene[12] and resolutions thereof,[13] the armamentum of synthetic organic chemists lacks a general and enantiocontrolled method for easy access to *cis*-dihydroarenediols with varied substituents on the aryl ring. In view of this, development of an alternative and flexible route to *cis*-dihydroarenediols, such as **7**, was desirable. To accomplish this task, we envisaged that the systematic use of Barrett's asymmetric hydroxyallylation methodology[14] **9** → **8** followed by RCM **8** → **7** could lead to the desired motifs rapidly. The Barrett methodology was attractive since using either antipode of a chiral auxiliary, such as *B*-methoxydiisopinocampheylborane (Ipc_2BOMe), could give access to different stereoisomers with complete control of regio-, stereo-, and enantioselectivity.

To test this hypothesis, we first attempted the synthesis of the simplest of the bicyclic *cis*-dihydroarenediols, e.g., **7**. Accordingly, the starting *o*-vinylbenzaldehyde **9**[15] was subjected to the aforementioned allylborane methodology. Thus, metalation of allyl(diisopropylamino)dimethylsilane[16] using *n*-butyllithium and TMEDA at 0 °C and sequential reaction of the resultant *E*-lithio derivative with (−)-*B*-methoxydiisopinocampheylborane and BF_3-etherate gave the *E*-reagent **12** (Scheme 1). Addition of *o*-vinylbenzaldehyde **9** at −78 °C gave an intermediate *anti*-*β*-hydroxysilane

Scheme 1. Synthesis of *cis*-1,2-Dihydro-1,2-naphthalenediol



(4) During the course of our work, the controversy regarding the absolute stereochemistry of **3a** was, however, settled by Hernandez-Galan et al.; see: (a) Jimenej-Teja, D.; Daoubi, M.; Collado, I. G.; Hernandez-Galan, R. *Tetrahedron* **2009**, *65*, 3392. (b) For the discussion of the conflicting biological profile of **3a** in a larger context of its racemic synthesis, see: Couche, E.; Fkyerat, A.; Tabacchi, R. *Helv. Chim. Acta* **2009**, *92*, 903.

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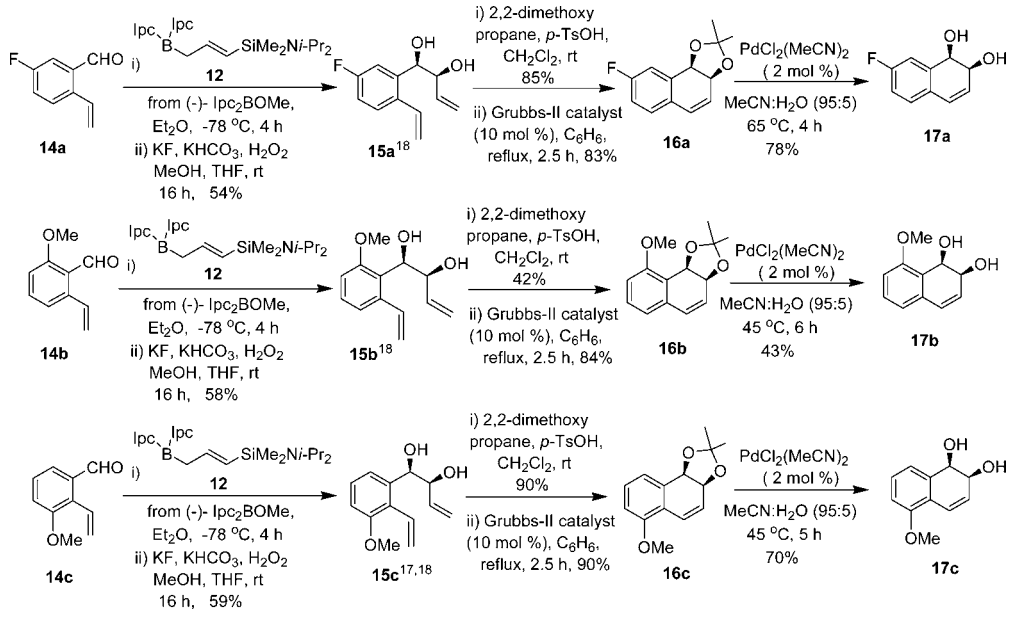
(16) Commercially available from Aldrich.

Scheme 2. Differently Substituted Bicyclic *cis*-Dihydroarenediols



boronate ester which, on oxidative workup with hydrogen peroxide under basic conditions, afforded diol **8** in 52% yield as a single diastereomer (ee = 90%).[17,18]

Unfortunately, our initial attempts to carry out RCM on the free diol **8** failed. This led us to use protecting groups for the *anti*-diol which would be likely to liberate the free diol under nonacidic conditions, which would be essential to prevent possible aromatization. Heating the acetonide-protected diol in benzene at reflux with Grubbs II catalyst **13**[19] gave us the protected *cis*-dihydroxytetrahydronaphthalene **11**.[20] Expectedly, the deprotection step proved most challenging. Attempts were initially made to transform to the *cis*-1,2-dihydrodiol by exposure to Amberlyst 15 in methanol. TLC analysis showed formation of the product alongside naphthols. This failure to isolate the product directed us toward the need for neutral deprotection conditions. Thus, we used Lipshutz's methodology with $PdCl_2(MeCN)_2$ as a catalyst,[21] which ultimately gave our desired product **7**[5] in good yield.

To evaluate the generality of our strategy, we next attempted to access *cis*-dihydroarenediol derivatives that are available in poor yield via the bioconversion pathway. In this regard, we have prepared fluoro-substituted *cis*-dihydroarenediol **17a**[6b] and methoxy-substituted *cis*-dihydroarenediols **17b**[8a,b,e] and **17c**[8a,b,e] along the same route from appropriate *o*-vinyl benzaldehydes **14a**,[22] **14b**,[23] and **14c**[25] in moderate to good overall yields (Scheme 2).

Application of this methodology to heterocyclic analogues would help prove its generality at this stage.

With this end in view, we attempted to prepare *cis*-5,6-dihydroisoquinoline-5,6-diol. However, as the pyridine nitrogen was likely to deactivate the catalyst during RCM,[26] it was both sterically and electronically shielded by putting chlorine atoms[27] adjacent to it. As shown in Scheme 3, this modification allowed successful synthesis of the *cis*-dihydroarenediol **22** in good overall yield from **19**.[28]

After developing a successful new methodology for preparing *cis*-dihydroarenediols, our remaining important goal was to convert them to the corresponding keto-diols. To this end, Wacker oxidation appeared to be a judicious choice. Previous reports[31] suggested that, for cyclic and

(17) Enantiomeric excess (ee) was determined by Mosher ester analysis; see: Davisson, V. J.; Poulter, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 1245.

(18) The relative and absolute configuration of this product is based on Barrett's work[14] and further confirmed by comparison of the sign of optical rotation of its derived *cis*-dihydroarenediol with those in the literature (see the Supporting Information).

(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(20) Orsini, F.; Pelizzoni, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1033.

(21) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

(22) Prepared from commercially available 2-bromo-5-fluorobenzaldehyde by Stille reaction using tributylvinyltin reagent in 94% yield.

(23) Prepared from the corresponding alcohol[24] by oxidation with Collins reagent.

(24) Kumar, V.; Shaw, A. K. *J. Org. Chem.* **2008**, *73*, 7526.

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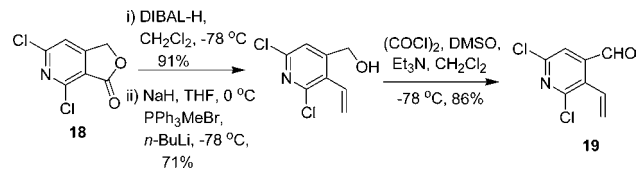
(26) Felpin, F. X.; Girard, S.; Thanh, G. V.; Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305, and references therein.

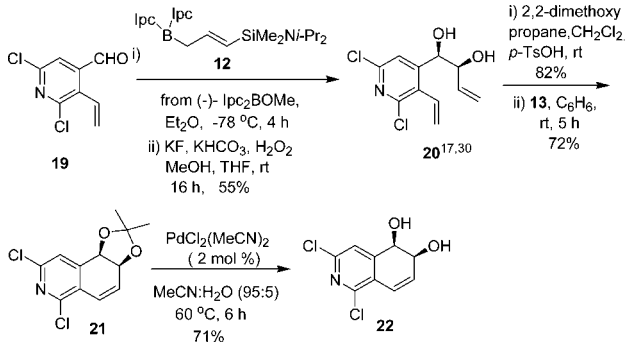
(27) van den Hoogenband, A.; den Hartog, J. A. J.; Faber-Hilhorst, N.; Lange, J. H. M.; Terpstra, J. W. *Tetrahedron Lett.* **2009**, *50*, 5040.

(28) Compound **19** was prepared from the reported lactone **18**[29] in three steps as follows:



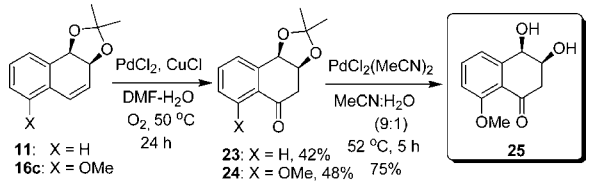
(29) Panda, B.; Basak, S.; Hazra, A.; Sarkar, T. K. *J. Chem. Res.* **2010**, *2010*, 109.

Scheme 3. Heterobicyclic *cis*-Dihydroarenediol



acyclic systems, chelation controls the regioselectivity of Markovnikov-type hydroxypalladation. However, for substituted styrenes *anti*-Markovnikov addition is also reported[32] due to participation of allylic hydrogens. When **11** was exposed to the regular Wacker conditions at 50 °C only **23** was formed, unaccompanied by even traces (TLC) of the other regioisomer (Scheme 4).

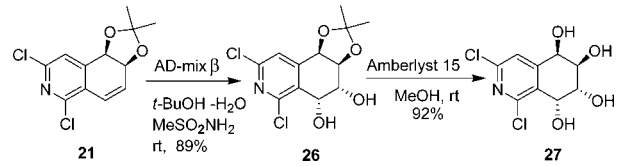
Scheme 4. Regioselective Wacker Oxidation of Internal Cyclic Olefin



A similar reaction was next performed with **16c**. Gratifyingly, only one product **24** was obtained having a keto group at the benzylic position. Removal of the acetonide under the previously mentioned conditions[21] then afforded **25**, which is the phenolic methyl ether of *ent*-**3a**. Clearly, using the antipodal Ipc_2BOMe and replacing the OMe group in **14c** by a suitable silyloxy group coupled with its fluoride-induced cleavage at a later stage could provide the naturally occurring **3a**.

We next examined the preparation of conduritol analogues, and we report here the first chemical synthesis of a heterobicyclic conduritol **27** following the route described in Scheme 5. Thus, Sharpless asymmetric dihydroxylation

Scheme 5. Synthesis of a Heterobicyclic Conduritol Analogue



of **21** followed by deprotection of **26** gave **27** in good overall yield. We expect that this protocol will prove useful for generating libraries of heterobicyclic conduritols for lead discovery in the realm of chemical biology.

In conclusion, we have reported an enantioselective approach for obtaining bicyclic arene *cis*-dihydrodiols, one of which led to the first chemical synthesis of the phenolic methyl ether of *ent*-**3a**. Furthermore, we have shown that this methodology is also applicable to the synthesis of bicyclic conduritol analogues. The generality of this approach serves as a foundation for further efforts toward other keto-diol-containing natural products. Work directed toward this and all other stereoisomers of bicyclic and heterobicyclic conduritols and conduramines is in progress.

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Supporting Information Available: Experimental details and full spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100557F

(30) The relative and absolute configuration of this diol is based on Barrett's work.[14]

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