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Stereoselective *trans*- and *cis*-Dihydroxylations of 2*H*-Pyranyl and Dihydropyridinyl Heterocycles Synthesized from Formal [3 + 3]-Cycloaddition Reactions of α,β-Unsaturated Iminium Ions with 1,3-Dicarbonyl Equivalents†

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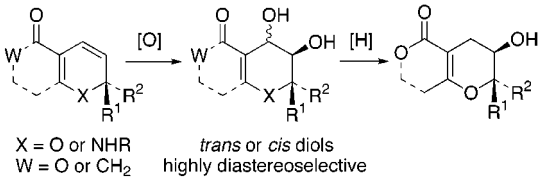
ABSTRACT



We describe here an inherent problem in direct epoxidation of the endocyclic olefin in 2*H*-pyrans fused to 2-pyrones. Such difficulties led to the development of highly stereoselective *trans*- and *cis*-dihydroxylations of these olefinic systems in both 2*H*-pyrans and dihydropyridines fused to a 2-pyrones or a 2-cyclohexenone. Protocols for the removal of the activated allylic hydroxyl group are also reported.

Reactions of α,β-unsaturated iminiums with 1,3-dicarbonyl equivalents constitute a stepwise formal [3 + 3]-cycloaddition[2−4] useful for the synthesis of complex 2*H*-pyranyl and dihydropyridinyl heterocycles [Figure 1].[5−7] These reactions involve a sequence that consists of a Knoevenagel condensation followed by a 6π-electron electrocyclic ring closure[8] and, thus, can be classified as a sequential anionic−pericyclic strategy highly useful for natural product synthesis.[9] The net result of this process is formation of two σ-bonds and a new stereocenter adjacent to the heteroatom. Our work has demonstrated synthetic efficacy of this formal cycloaddition reaction.[5,6] More recently, we have also succeeded

† With the deepest appreciation and respect, this paper is dedicated to Professor Gilbert Stork on the occassion of his 80th birthday.

(1) After the corresponding author, all author names are listed alphabetically.

(2) There are a limited number of examples of metal-mediated [3 + 3]-cycloaddition reactions. For recent reviews, see: (a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

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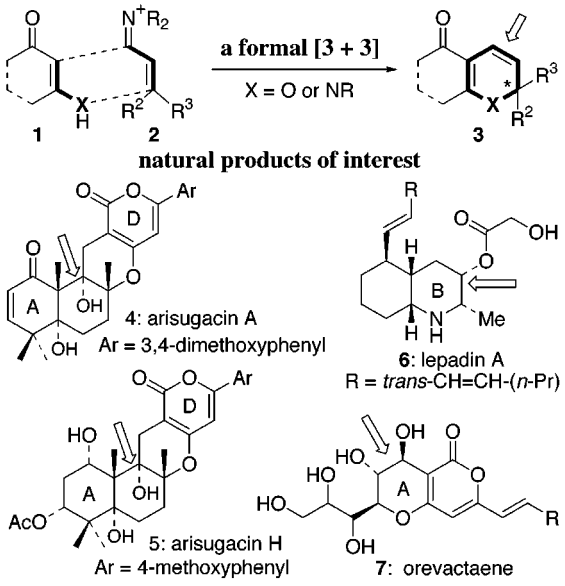


Figure 1.

in designing both stereoselective[5a,6b] and intramolecular variants of this formal cycloaddition.[6a]

Having demonstrated its synthetic feasibility, we have been pursuing applications of this formal [3 + 3]-cycloaddition in the total syntheses of arisugacin A [**4**] and H [**5**],[10−12] lepadin A [**6**],[13] and orevactaene [**7**][14] [Figure 1]. However, to render this formal cycloaddition approach useful in natural product synthesis, an ensuing key transformation would involve oxidation of the endocyclic olefin in the heterocycle **3** to provide the desired hydroxyl functionalities present in **4**−**7**. Despite well-known oxidation chemistry involving analogous endocyclic olefinic systems such as chromenes,[15,16] oxidative transformations involving the endocyclic olefin in 2*H*-pyrans or dihydropyridines such as **3** have been much less explored.[17] We report here our initial success in stereoselective oxidation of this ubiquitous endocyclic olefin.

The unique position of hydroxyl groups in the C-rings of arisugacin A [**4**] and H [**5**] and the B-ring of lepadin A [**6**] prompted us to investigate two approaches [Figure 2]. The

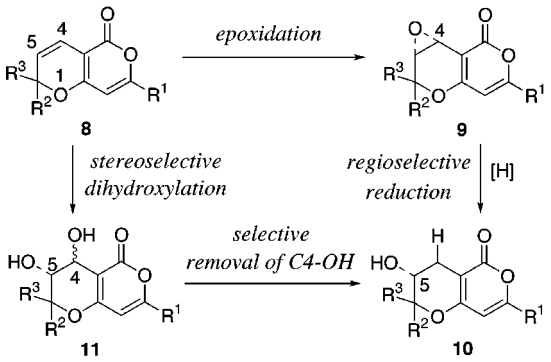
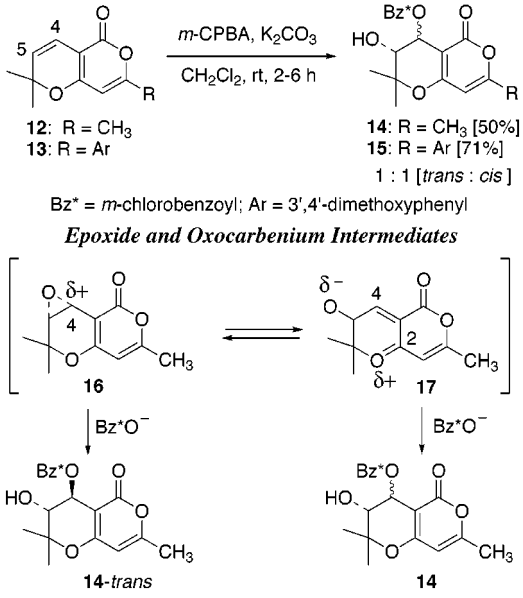


Figure 2.

first one involved the epoxidation of the 2*H*-pyran **8** at C4−C5, followed by a hydride reduction of epoxide **9**, leading to monohydroxylated compound **10**. We had suspected that the hydride would selectively approach toward C4 owing to the activation from the pyranyl oxygen. The second approach involved dihydroxylation of **8** at C4−C5 followed by a selective removal of the C4 hydroxyl group in **10**, which is not well-explored.

As shown in Scheme 1, epoxidation of 2*H*-pyrans **12** and **13** using *m*-CPBA at room temperature in CH_2Cl_2 led to

Scheme 1



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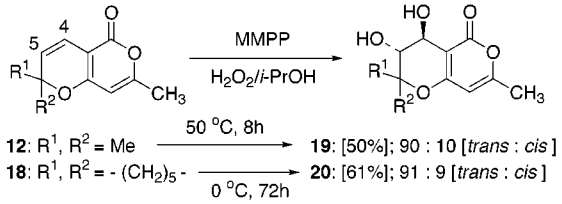
exclusive formation of hydroxyesters **14** and **15**[18] in 50% and 71% yields, respectively, as a 1:1 mixture of *trans* and *cis* isomers. A variety of other conditions [buffered or biphasic conditions] were explored but failed to diminish the addition of the Bz*O [*m*-chlorobenzoyloxy] anion to the initially formed epoxide **16** and/or oxocarbenium intermediate **17** [Scheme 1]. In our hands, epoxide **16** is unstable and undergoes rapid ring opening, especially under acidic conditions, leading to oxocarbenium species **17**. Oxocarbenium species **17** presents minimum stereochemical discrimination toward the incoming Bz*O anion, and thus, both the *trans* and *cis* isomers of **14** or **15** were isolated. It should be noted that the addition of Bz*O anion did occur regioselectively at C4 and not C2. The hydroxyester **14** was unambiguously assigned via a HETCOR experiment where the C4 protons of *trans* and *cis* isomers correlate to ^{13}C chemical shifts with δ values of 65.3 and 68.4 ppm.

Subsequent attempts using reagents such as dimethyldioxirane, in situ reductive trapping of **16** or **17** using $NaCNBH_3$, or attempts to reduce the Bz*O group in **14** or **15** using hydrides such as $NaBH_4$ and $NaCNBH_3$ in the presence of $CeCl_3$ or AcOH were unsuccessful.[19,20] The earlier assertion regarding the activation of C4 in **16** due to the pyranyl oxygen atom appears to be very real as well as extremely problematic in the epoxidation of these particular endocyclic olefins, thereby rendering them very different from those that have been explored in epoxidation studies.[15,16]

We then turned to dihydroxylation protocols to construct the monohydroxylated product **10**. As shown in Scheme 2,

Scheme 2



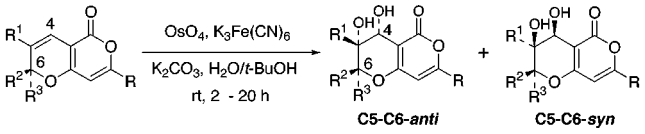
MMPP: magnesium monoperoxyphthalate

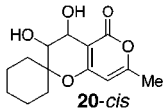
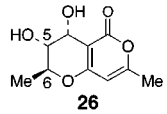
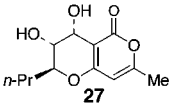
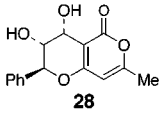
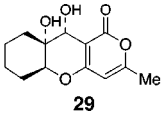
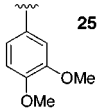
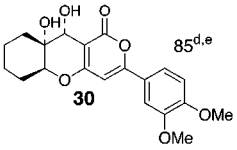
MMPP [magnesium monoperoxyphthalate] epoxidation of **12** and **18**, a more basic protocol, did lead to diols **19** and **20** in 50% and 61% yields, respectively. The relative stereochemistry favored the *trans* isomers with ratios of 90:10 and 91:9 for **19** and **20**, respectively, and *trans* and *cis* isomers are readily separable. The improved stereoselectivity favoring the *trans* isomer may be due to the large excess of H_2O [as a cosolvent] that could efficiently trap out epoxide intermediate **16**.

Attempts to generate an epoxide from *trans* diol **19** via mesylation of either the C4 or C5 hydroxyl group led to epimerization, even in the presence of reducing agents such as $NaCNBH_3/ZnI_2$[21] and $NaBH_4$.[20] However, the ability to stereoselectively construct *trans* diol **19** solidifies an attractive entry for synthesis of orevactaene **7**[14] via the formal [3 + 3]-cycloaddition approach [see Figure 1].

On the other hand, *cis*-dihydroxylation of these endocyclic olefins was quite successful. As shown in Table 1, a range

Table 1



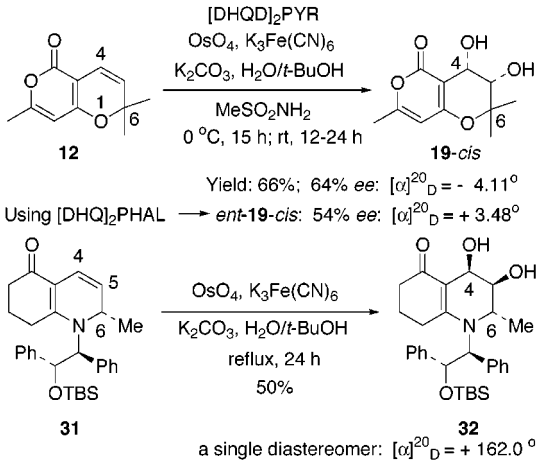
entry	R^1	R^2	R^3	R	start. mat.	*cis*-product[a]	yield[b]	[*anti*:*syn*][c]
1	H	- $CH_2[CH_2]_3CH_2$ -		Me	**18**	 **20**-*cis*	54 %	NA
2	H	Me	H	Me	**21**	 **26**	78	89 : 11
3	H	*n*-Pr	H	Me	**22**	 **27**	75	92 : 8
4	H	Ph	H	Me	**23**	 **28**	73[d]	93 : 7
5	- $CH_2[CH_2]_2CH_2$ -		H	Me	**24**	 **29**	86	≥ 95 : 5
6	- $CH_2[CH_2]_2CH_2$ -		H		**25**	 **30**	85[d,e]	≥ 95 : 5

[a] *Cis* or *trans* is designated for the C4−C5 relative stereochemistry. *Anti* or *syn* is designated for C5−C6 relative stereochemistry. No *trans* products were observed in these reactions due to epimerizations. [b] All yields are isolated yields. [c] All ratios were determined by ^1H NMR and/or ^{13}C NMR. Relative stereochemistry was assigned by NOE experiments. [d] NMO was used and the reaction was carried out in acteone/H_2O. [e] K_3FeCN_6 gave a 74% yield withan *anti*:*syn* ratio of 92:8.

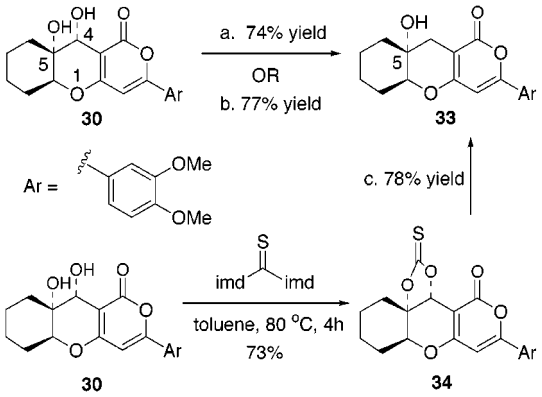
of different substrates [**18**, **21**−**25**] could be *cis*-dihydroxylated in high yields using OsO_4 and K_3FeCN_6 or NMO [entries 4 and 6],[22] and more significantly, diastereoselectivities were very high for reactions of **21**−**25** [entries 2−6]. Given the relatively flat nature of these ring systems [the R^2 substituent actually assumes the pseudoequatorial position for the starting 2*H*-pyrans **21**−**25**], the observed high diastereoselectivity was quite remarkable. The assigned relative stereochemistry of *cis*-diols **20** and **26**−**30** indicates that the approach of OsO_4 still preferred the slightly less hindered face of the olefin.

Given the above success in the *cis*-dihydroxylation, we examined Sharpless' asymmetric dihydroxylation[23] of 2*H*-pyran **12** using $[DHQD]_2PYR$ [two dihydroquinidine ligands linked with pyrimidine] and obtained diol **19**-*cis* in 66% yield (Scheme 3). Formation of the bis-(+)-MTPA ester indicated

Scheme 3



Scheme 4[a]



[a] (a) 5% Pd−C, H_2, Ac_2O [as solvent], rt, 4 h; (b) CF_3COOH, Et_3SiH, CH_2Cl_2, rt, 2 h; (c) AIBN [cat.], *n*-Bu_3SnH [as solvent], 130 °C, sealed tube.

64% ee, which is quite comparable to those reported by Sharpless for asymmetric *cis*-dihydroxylation of chromenes.[23] Likewise, the use of [DHQ]$_2$PHAL [two dihydroquinine ligands linked with phthalazine] led to *ent*-**19**-*cis* in 50% yield with 54% ee. In addition, we found that optically pure dihydropyridine **31** could also undergo *cis*-dihydroxylation, although slower, using OsO_4 and K_3FeCN_6[22] to provide *cis*-diol **32** as a single diastereomer in 50% yield. The relative stereochemistry between C4, C5, and C6 was unambiguously assigned using NOE experiments. This stereoselective *cis*-dihydroxylation protocol provides ocataquinolenone system **31** and offers a potential approach to the AB-ring system of lepadin A [**6**].

With these *cis*-diols in hand, the remaining challenging issue is the ability to selectively remove the C4 hydroxyl group which is not very well-known. This stands as a key transformation for potential total synthesis of relevant natural products **4**−**6** using the formal [3 + 3]-cycloaddition approach.

As shown in Scheme 4, after exploring a variety of different conditions,[24] the C4 hydroxyl group in *cis*-diol **30** was successfully removed to provide the desired monohydroxylated compound **33** in 74% yield by using a hydrogenation protocol in which Ac_2O is used as solvent.[25] The use of alcohol solvents such as MeOH led to isolation of products with the MeO group substituted at C4. While TMSH reduction in TFAA was also feasible,[26] the most reliable protocol that provided **33** in 78% yield has been the two-step sequence consisting of the formation of thiolcarbonate **34** followed by a Barton-type deoxygenation of the more activated allylic hydroxyl group at C4 [Scheme 4].[27]

We have described here highly stereoselective *trans*- and *cis*-dihydroxylations of these olefinic systems in both 2*H*-pyrans and dihydropyridines. This methodology represents a key transformation in constructing various natural products using the formal [3 + 3]-cycloaddition approach. Efforts related to these natural product syntheses are currently underway.

Acknowledgment. R.P.H. thanks the National Institutes of Health [NS38049] and the donors of the Petroleum Research Fund [Type-G].

Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The absolute stereochemistry of **19**-*cis* and *ent*-**19**-*cis* were assigned on the basis of Sharpless' mnemonics, see: Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 6895.

(24) Reductive conditions such as ZnI_2 with $NaCNBH_3$, Ph_3P with $NaCNBH_3$, and $SOCl_2$ followed by DIBAL-H did not provide the desired monohydroxylated products.

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