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STEREOCHEMICAL STUDIES ON THE PREPARATION AND SUBSEQUENT REDUCTIVE CLEAVAGE OF 1,2-DIOXOLANES. APPLICATION TO THE SYNTHESIS OF (±)-YASHABUSHITRIOL.

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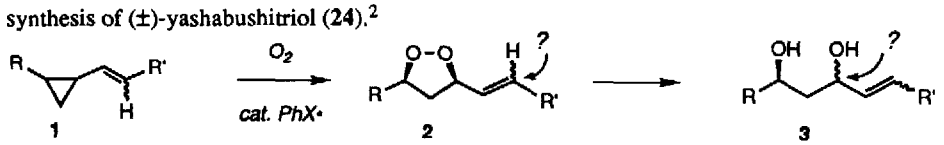
Abstract: (E)-Selective oxygenation of 1,2-disubstituted alkenylcyclopropanes, and subsequent SmI_2 mediated cleavage of the 1,2-dioxolane products with retention of stereochemistry, leads to a concise synthesis of the plant metabolite (±)-yashabushitriol.

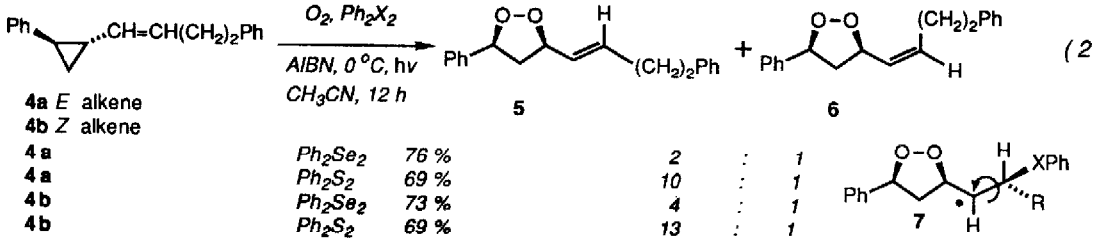
The ready availability of substituted, stereochemically defined 1,2-dioxolane rings via the chalcogen radical catalyzed combination of O_2 with functionalized vinylcyclopropanes may provide access to a wide range of 1,3-diol target structures. Our original efforts in this area documented high levels of stereoselectivity upon formation of the 1,2-dioxolane moiety.[1] However, secondary stereochemical issues, such as the selectivity of alkene formation (*E* vs *Z*) upon oxygenation of 1,2-disubstituted alkenylcyclopropanes (Eq. 1), or the maintenance of stereochemical integrity upon reductive cleavage of the dioxolane ring to afford the 1,3-diol target (**2**→**3**), have not yet been addressed. Herein, we report our preliminary investigations in these areas, and document high levels of stereoselectivity for both issues. The utility of this chemistry in natural product synthesis is further illustrated by application of a (*E*)-alkenyl-1,2-dioxolane species in the concise total synthesis of (±)-yashabushitriol (**24**).[2]



1 **2** **3** (1)

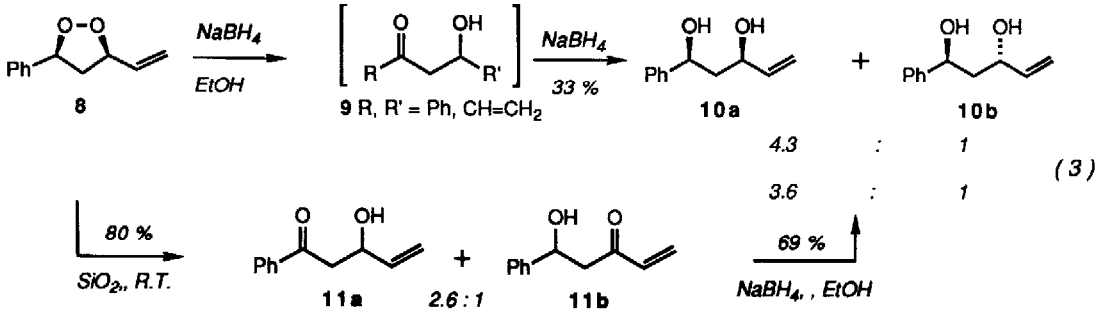
The question of alkene stereoselectivity was probed with both the (*Z*)-alkenylcyclopropane substrate **4b**, prepared by "salt-free" Wittig condensation of trans 2-phenylcyclopropanecarboxaldehyde with $Ph_3P{=}CH(CH_2)_2Ph$ (55%, *Z*/*E* > 10:1), and the (*E*) isomer **4a**, prepared from the same precursors under Schlosser-Wittig[3a] conditions (89%, *E*/*Z* = 2.5:1)[4,3b]. Both phenylthio and phenylseleno radical catalysis were examined, leading to a surprising variance in product alkene selectivity (Eq. 2). Although the yields in all cases were uniformly high and the dioxolane ring was formed with strictly syn stereochemistry[4], phenylthio radical catalysis let to consistently higher *E*/*Z* ratios (10-13:1 with PhS• vs 2-4:1 with PhSe•). Alkene stereoselectivity may be a consequence of kinetic and/or thermodynamic factors. This issue was addressed by resubmitting purified product dioxolanes to reaction conditions. Thus, a sample of strictly (*E*) dioxolane **5** was subjected to reaction with PhS•, and in an independent experiment PhSe•, for 12 h. In both cases, pure (*E*) dioxolane product **5** was recovered (85% and 80% yields, respectively). A similar series of control experiments with partially purified (*Z*)-dioxolane **6** (2.9:1 *Z*:*E*) led to contrasting behavior with the two chalcogens. In the presence of PhSe• (standard reaction conditions, 12 h), the starting dioxolanes could be

recovered unchanged (77%, 2.9:1 *Z:E*). However, the analogous PhS• catalyzed experiment led to alkene equilibration, with a moderate preference for the *E* dioxolane product **5** (12 h, 83%, *E*:Z = 4:1). These results, taken together, argue for a substantial thermodynamically derived preference for *E* alkene with PhS•, and a lesser kinetically derived preference for *E* alkene with PhSe•. A plausible rationalization for this dichotomous behavior can be found in a comparison of the relative rates of competing bond rotation and chalcogen ejection processes from an intermediate **7** (see discussion in reference 1b).



(2)

The reductive cleavage of the O-O bond in endocyclic peroxides can be effected by a variety of reducing agents, including metal hydrides, PR_3, thiourea, and H_2/Pd(C).[5] A competing process that may limit the effectiveness of any particular procedure involves base-mediated isomerization of the 1,2-dioxolane to furnish β-ketoalcohols.[5a,6] Attempted reduction of dioxolane **8**, as a test case, with either PPh_3, PBu_3, thiourea or H_2/Pd(C) resulted in formation of the isomerization products **11a/b** accompanied by only trace amounts (≤10%) of the desired diol **10a**. Reaction of **8** with metal hydrides ($LiAlH_4$[7], $NaBH_4$, Red-Al) gave mixtures of syn and anti 1,3-diol products **10a/b**[4], presumably through putative β-ketoalkoxide intermediates corresponding to **11a/b**. For example, $NaBH_4$ reduction of **8** led to a 4.3:1 ratio of the syn and anti diols **10a** and **10b** (Eq. 3). Controlled decomposition of dioxolane **8** in the absence of hydride provided an authentic sample of the β-ketoalcohols **11a/b**, reduction of which furnished the diols **10a** and **10b** in a ratio similar to that observed in the direct reduction (Eq. 3). Thus, none of the classical 1,2-dioxolane reductive cleavage methods gave satisfactory, reproducible[7] results with the monocyclic 3,5 disubstituted species **8**.

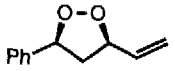
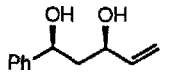
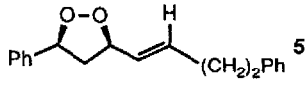
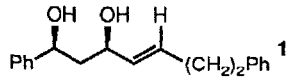
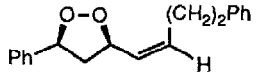
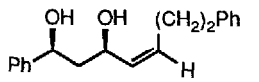
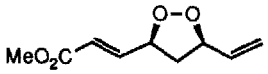
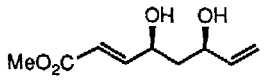
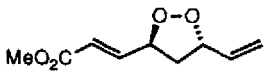
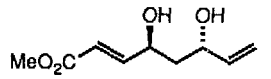
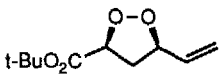
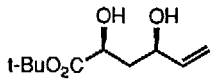
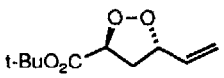
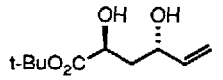


(3)

Fortunately, a survey of single electron reductants led to the discovery that SmI_2•2THF[8] smoothly cleaved the O-O bond of the phenyl-substituted dioxolanes **5-8**, as well as the more base-sensitive

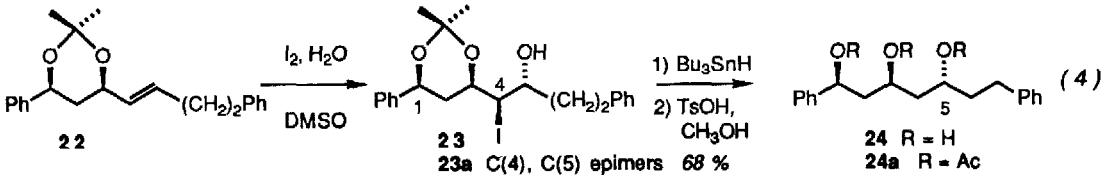
ester-substituted species **12-15** (Table), without intervention of any undesired base-mediated processes. The stereochemistry of the product diols was ascertained by evaluation of the coupling constants of the derived acetonides ($(CH_3O)_2C(CH_3)_2$, PPTS, CH_2CCl_2)[4]. The diols **18-21** displayed no tendency to spontaneously cyclize either to butyrolactone (from **20** or **21**) or to tetrahydrofuran (from **18** or **19**) products.

Table *SmI_2 reduction of 1,2-dioxolanes* *

	**8**		**10a**	*67 %*
	**5**		**16**	*89 %*
	**6**		**17**	*94 %*
	**12**		**18**	*61 %*
	**13**		**19**	*58 %*
	**14**		**20**	*66 %*
	**15**		**21**	*63 %*

** All reductions were carried out with 2.5 eq. SmI_2•THF in THF at -78 °C under an inert atmosphere. All yields refer to isolated, chromatographically pure, spectrally characterized[4] material.*

Acetonide **22**, derived from the (*E*)-alkenyl syn 1,3-diol **16** ($(CH_3O)_2C(CH_3)_2$/PPTS, 92%), could be converted to the plant metabolite (+) yashabushitriol (**24**) in three steps (Eq. 4). Thus, reaction with aqueous iodine led to a mixture of isomeric iodohydrins (**23**: **23a** = 2.6:1, 87%) whose stereochemistry was in accord with the predictions of the model for electrophilic addition to chiral allylic ethers developed by Hehre[9]. The synthetic sample of (+) yashabushitriol (**24**), prepared by reductive deiodination and acetonide hydrolysis of **23**, as well as the derived triacetate **24b** (Ac_2O/pyridine, 70%), exhibited chromatographic and spectral characteristics (TLC, GC, ^1H NMR, ^{13}C NMR, IR, MS, HRMS) indistinguishable from those of the natural material or the triacetate derived therefrom.



(4)

In summary, we have demonstrated that (1) under the appropriate experimental conditions, a high level of *(E)* alkene stereoselectivity accompanies oxygenation of 1,2-disubstituted alkenylcyclopropanes, (2) SmI_2•2THF effects reductive cleavage of 3,5-disubstituted 1,2-dioxolane rings without intervention of competitive isomerization processes, and (3) the natural product yashabushitriol can be efficiently prepared through this vinylcyclopropane/oxygenation methodology. Application of this chemistry to the total synthesis of more structurally complex 1,3 diol-containing natural products is ongoing, and progress will be reported in due course.

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References

1. a) Feldman, K. S.; Simpson, R. E.; Parvez, M.; *J. Am. Chem. Soc.* **1986**, *108*, 1328. b) Feldman, K. S.; Simpson, R. E.; *J. Am. Chem. Soc.* **1989**, *111*, 4878.
2. Hashimoto, T.; Tori, M.; Asakawa, Y.; *Chem. Pharm. Bull.* **1986**, *34*, 1846.
3. a) Schlosser, M.; Christmann, K. F.; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 126. b) For subsequent oxygenations, a pure sample of the *(E)* isomer **4a** was obtained by chromatography on $AgNO_3$-impregnated SiO_2.
4. All new compounds reported herein displayed satisfactory spectral data (^1H NMR, ^{13}C NMR, IR, MS, HRMS).
5. a) For a review of the reduction of endocyclic peroxides, see Balci, M. *Chem Rev.* **1981**, *81*, 91. b) Beckwith, A. L. J.; Wagner, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 7099.
6. Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2501.
7. In our original disclosure of the vinyldioxolane synthesis[1], we reported that $LiAlH_4$ cleanly reduces various syn phenyl-substituted vinyldioxolanes to syn 1,3-diols. Subsequent experiments revealed that even for these relatively robust substrates, the stereochemical integrity of the reduction varied from batch to batch of the $LiAlH_4$ used. In the case of the ester substituted dioxolanes **12-15**, all batches of $LiAlH_4$ resulted in some stereochemical scrambling upon reduction.
8. While this work was in progress, an independent report appeared which described the reductive cleavage of a bicyclic endoperoxide with SmI_2•2THF. Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 736.

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