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Synthesis of Epoxyquinol A and Related Molecules: Probing Chemical Reactivity of Epoxyquinol Dimers and 2*H*-Pyran Precursors

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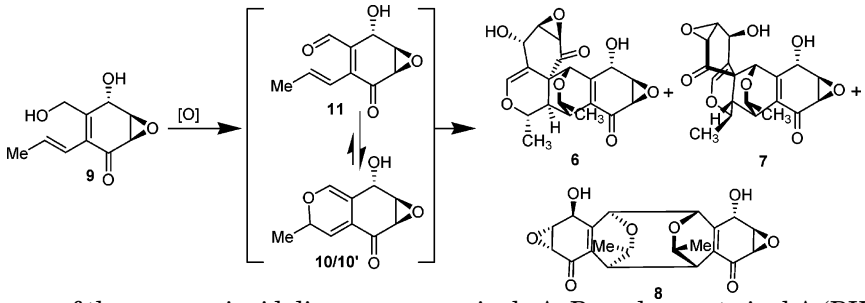
Received May 4, 2005



Total syntheses of the epoxyquinoid dimers, epoxyquinols A, B, and epoxytwinol A (RKB-3564 D), have been accomplished employing [4 + 2] and [4 + 4] dimerization of 2*H*-pyran epoxyquinol monomers. Modifications of 2*H*-pyran precursors have been explored, including alteration of epoxy alcohol and diene stereochemistry. A stable 2*H*-pyran prepared by alteration of the epoxyquinol 2*H*-pyran nucleus was evaluated as a diene in Diels−Alder cycloaddition with reactive dienophiles. Extensive studies for improving the [4 + 4] dimerization of selectively protected 2*H*-pyran monomers to afford the novel epoxyquinoid dimer epoxytwinol A were carried out, and valuable insight regarding competitive [4 + 2] and [4 + 4] dimerization processes has been obtained. In addition, chemical reactivities and structural modifications of epoxyquinol dimers have been evaluated, including [2 + 2] photocycloaddition and [3,3] sigmatropic rearrangement, indicating the possibility for production of novel structural diversity from dimeric epoxyquinoid natural product frameworks.

Introduction

Epoxyquinoids represent a large family of natural products with a wide range of biological activities.[1] The epoxyquinoid family may be divided into two major classes (Figure 1): (1) epoxyquinones,[2] which bear 1,4-diketone functionality on a cyclohexane epoxide ring, and (2) epoxyquinols,[3] compounds wherein at least one of the epoxyketone carbonyl groups is transformed to a secondary or tertiary alcohol. Notably, epoxyquinoid natural products exist in both monomeric (**2**−**4**, Figure 2) and dimeric (**1**, **5**−**8**) forms. The chemical syntheses of complex epoxyquinoid natural products (**1**−**8**) and derivatives,[4] as well as evaluation of their biological properties,[5] have been the subject of considerable investigation in our laboratory.

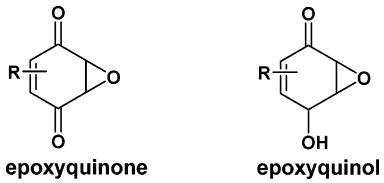


FIGURE 1. General classes of epoxyquinoid natural products.

(1) For a recent review on biological activities and syntheses of cyclohexane epoxides, including epoxyquinoids, see: Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857.

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Published on Web 06/24/2005

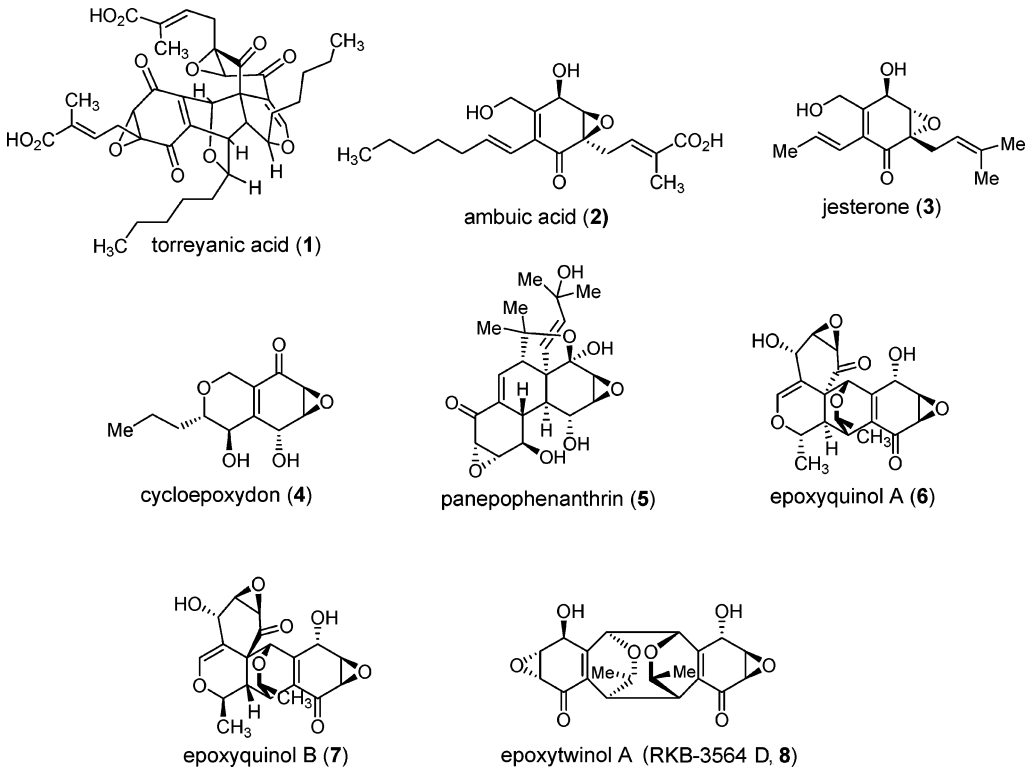

FIGURE 2. Representative epoxyquinoid natural products synthesized in our laboratory.

Recently, the polyketides epoxyquinols A (**6**, Figure 2), B (**7**),[6] and epoxytwinol A (RKB-3564 D, **8**)[7] were isolated by Osada and co-workers and shown to be potent anti-angiogenesis agents.[8] Angiogenesis, the formation of capillary blood vessels from existing blood vessels,[9] occurs in cancer, chronic inflammation, and atherosclerosis.[10] Combined with their novel highly oxygenated, heptacyclic structures and their potential as probes to elucidate the basic biological mechanisms of angiogenesis, the epoxyquinols (**6** and **7**) have attracted immediate attention in the synthetic community,[11] including work in our laboratory directed toward the syntheses of **6**, **7**,[4f] and the related dimer epoxytwinol A (**8**).[4g] In continuation of our studies toward the synthesis of epoxyquinoid natural products[4] and bioactive analogues,[4c,5] herein we present a full account of our syntheses of epoxyquinol dimers **6**−**8**, including efforts to probe the chemical reactivities of both epoxyquinol dimers and 2*H*-pyran precursors.

Synthetic Plan. We recently reported the biomimetic synthesis[12] of torreyanic acid (**1**), which was highlighted by oxidation/oxaelectrocyclization[13]/*endo* Diels−Alder dimerization of an epoxyquinone precursor (Figure 3).[4a,b] Structural inspection indicates significant similarity between the frameworks of the dimeric epoxyquinoid natural products torreyanic acid (**1**) and epoxyquinol A (**6**) (Figure 2).

In contrast to dimer **6**, derived from *endo* [4 + 2] dimerization of diastereomeric 2*H*-pyran monomers, epoxyquinol dimer **7** arises from *exo* Diels−Alder dimerization of two identical epoxyquinol 2*H*-pyran monomers (Figure 4). At the outset of our studies, it was unclear whether monomer **9** would undergo a comparable oxidation/oxaelectrocyclization/Diels−Alder dimerization sequence. Epoxytwinol A (**8**) features a unique 3,8-dioxatricyclo[4,2,2,2^{2,5}]dodeca-9,11-diene ring system, which presumably arises via [4 + 4] cycloaddition of two 2*H*-pyran monomers, **10** or **10′**. NMR analyses of **8** by

(6) Epoxyquinol A: (a) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496. Epoxyquinol B: (b) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.

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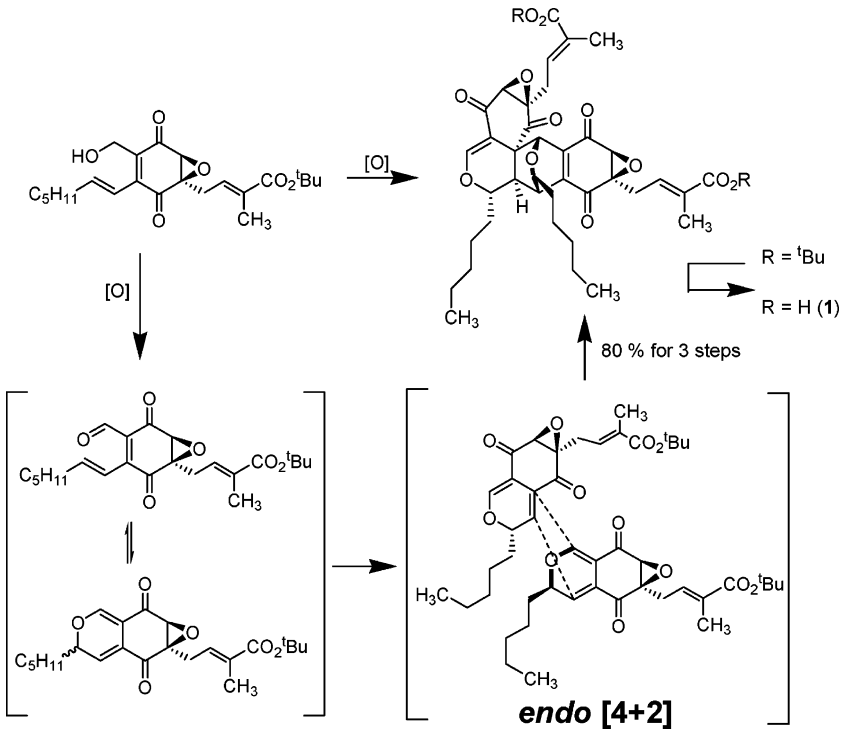


FIGURE 3. Biomimetic synthesis of torreyanic acid.

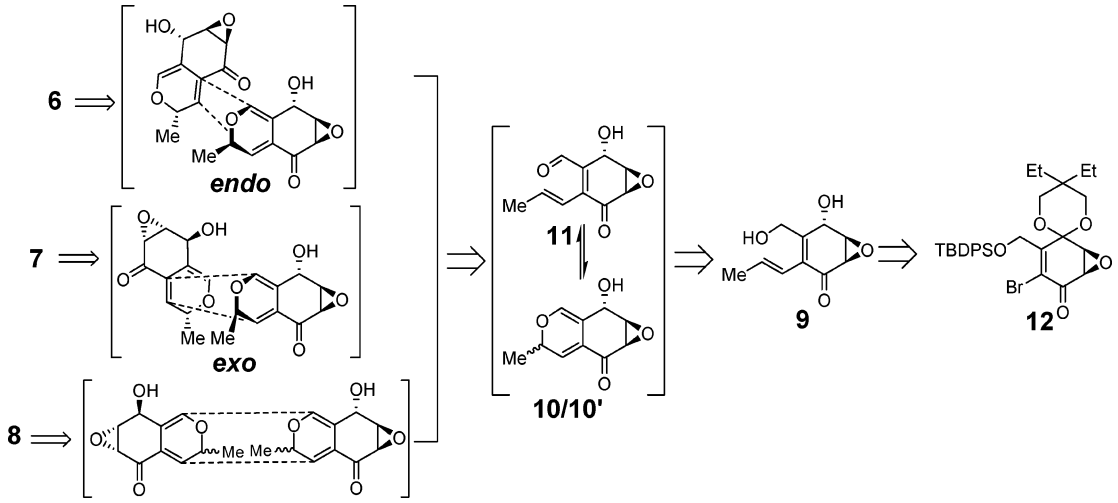


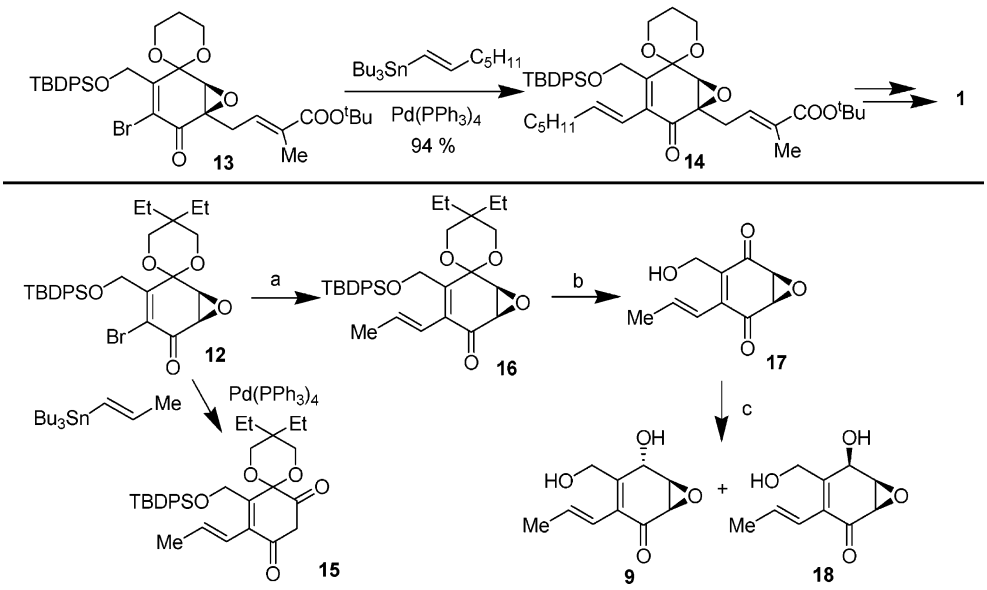
FIGURE 4. Retrosynthetic analysis for epoxyquinols **6**−**8**.

Osada and co-workers[7a,b] showed seven proton and 10 carbon signals, thus indicating a symmetrical structure. However, in the preliminary isolation and characterization efforts,[7a] the relative and absolute stereochemistries of **8** were not assigned. The requisite 2*H*-pyran monomers **10/10′** for the synthesis of dimers **6**−**8** may be derived from selective primary oxidation of **9** followed by 6π-oxaelectrocyclization of the resulting dienal **11**. Epoxyquinol precursor **9** may be prepared from known chiral, nonracemic intermediate **12** prepared during the course of our asymmetric synthesis of (−)-cycloepoxydon (**4**, Figure 2).[4d]

Results and Discussion

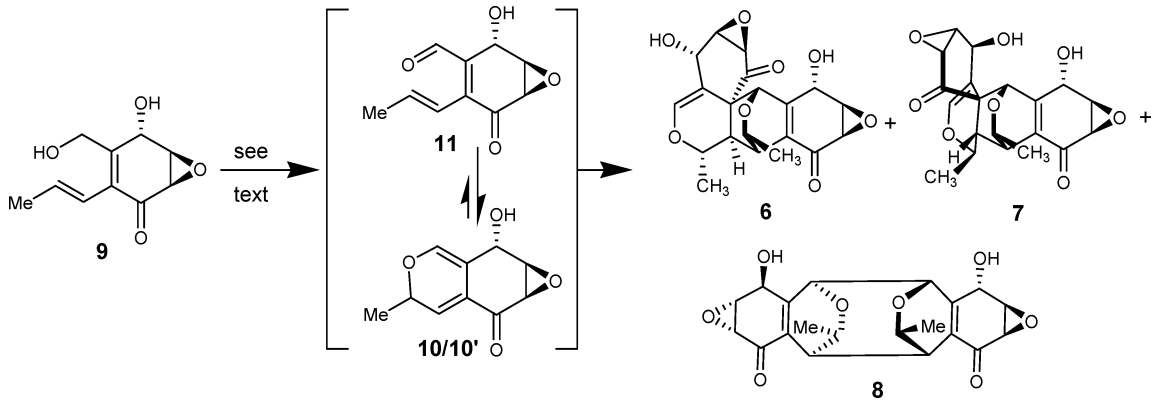
Preparation of Epoxyquinol Monomer 9. Beginning with the advanced epoxy ketone intermediate **12**[4d] (Scheme 1), we planned to install the propenyl side chain using Stille cross-coupling.[14] In our synthesis of torreyanic acid (**1**),[4a,b] we were able to achieve efficient cross-coupling of α-substituted epoxyketone **13** and (*E*)-tributyl-1-heptenylstannane using $Pd(PPh_3)_4$ as catalyst (cf., **13** → **14**, Scheme 1). However, β-diketone **15** was obtained as the major product (65%) when $Pd(PPh_3)_4$ was employed as catalyst for cross-coupling of **12**,[15] indicating that isomerization of the α,β-epoxy ketone to a β-diketone[16] is more facile on epoxy ketone substrates lacking α-substitution. Considering the Lewis basic nature of the PPh_3 ligand, we next employed "ligandless" Stille coupling conditions[17] using Pd_2dba_3 as catalyst, which afforded 70−80% of **16** (48 h, 25 mol % of catalyst). Further improvement using the "accelerating" ligand $AsPh_3$[18] led to efficient production of **16** (5% Pd_2dba_3, 2 h, 98% yield).

SCHEME 1. Preparation of Epoxyquinol Monomer Precursors[a]



[a] Reagents and conditions: (a) (*E*)-tributyl-1-propenylstannane, Pd_2dba_3, $AsPh_3$, $PhCH_3$, 110 °C, 2 h, 98%; (b) 48% HF, CH_3CN, rt, 1 h, 84%; (c) DIBAL-H, THF, −78 °C, 10 min, **9** (72%), **18** (4%).

SCHEME 2. Synthesis of Epoxyquinol Natural Products



Simultaneous deprotection of the cyclic ketal and silyl ether protecting groups of **16** was accomplished using aqueous HF/CH_3CN to afford chiral, nonracemic quinone epoxide **17**. Epoxyquinol monomer **9** and its diastereomer **18** were obtained in an 18:1 ratio from **17** using a regio- and diastereoselective reduction with DIBAL-H.[4f,19]

Synthesis of Epoxyquinols A, B, and RKB-3564 D. With compound **9** in hand, we next examined a number of oxidation conditions. Dess−Martin periodinane and MnO_2 were found to oxidize the secondary alcohol of **9**. Notably, MnO_2 was used to selectively oxidize the primary alcohol in the Hayashi synthesis of epoxyquinols A and B.[11a,b,d,e] In our hands, use of MnO_2 for related oxidations typically resulted in oxidation of the secondary alcohol. We thus turned our attention to tetramethylpiperidine-based nitroxyl radicals,[20] including 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which have been employed in chemoselective oxidation of alcohols.[21] After examining a number of TEMPO-based oxidant systems, we found that the mild condition developed by Semmelhack and co-workers (TEMPO, O_2, CuCl)[22] selectively oxidized primary alcohol **9** without overoxidation to the corresponding carboxylic acid and without detectable oxidation of the secondary alcohol. To our delight, the crude oxidation product (an equilibrium mixture of 90% of **10/10′** and 10% of **11** as determined by ^{1}H NMR) efficiently dimerized in $CDCl_3$ (rt, 30 h) to afford dimers **6** (36%) and **7** (30%) after silica gel chromatography (Scheme 2). Interestingly, we obtained a higher yield of *endo* dimer **6** (55%) and a lesser amount of *exo* dimer **7** (14%) when the crude oxidation products were dimerized in 40% aqueous MeOH. This result is consistent with literature reports on enhancement of *endo* selectivity in

(14) For a review of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React.* **1997**, *50*, 1.
(15) See Supporting Information for further details.
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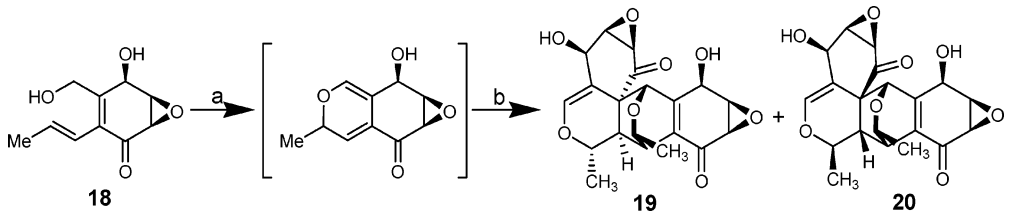
(20) For a review, see: de Nooy, A. E. J.; Besemer, A. C.; Bekkum, H. V. *Synthesis* **1996**, 1153.

TABLE 1. Relative Product Ratios for Dimerization of 10/10′ in Different Solvents[a]

			Relative Product Ratio		
entry	solvent	**10/10′**	epoxyquinol A (**6**)	epoxyquinol B (**7**)	RKB-3564 D (**8**)
1	hexane	ND	10.3	2	1
2	benzene	ND	4	4	1
3	CH_2Cl_2	ND	3.2	3.5	1
4	THF	16	12	5	1
5	DMF	>10	6	5	1
6	MeOH	5.2	4.6	2.8	1
7	MeOH/CH_2Cl_2 (7:100)	2.2	1.6	2.1	1

[a] Relative product ratios determined by ^{1}H NMR analysis (reaction time = 20 h).

SCHEME 3. Dimerization of *syn* Epoxy Alcohol 2*H*-Pyrans[a]



[a] Reagents and conditions: (a) O_2 (1 atm), TEMPO, CuCl, DMF, 1 h; (b) $CDCl_3$, 30 min, **19** (26%), **20** (19%).

Diels−Alder reactions using water.[23] Using the aforementioned dimerization conditions (40% aqueous MeOH), we observed the production of <3% of **8**. In an effort to obtain higher overall yields of **8**, we examined formation of dimers **6**−**8** by systematic evaluation of solvents, as shown in Table 1. These studies indicated that dimerization of **10/10′** in 14:1 of CH_2Cl_2:MeOH provided the highest ratio of [4 + 4] dimer **8** relative to [4 + 2] dimers **6** and **7**. Employing this solvent system, we were able to obtain dimer **8** in an improved overall yield (6−10%). With the synthetic material obtained from these dimerization experiments, we obtained crystals of both **7** and **8** and established their stereochemistries by X-ray crystal structure analysis.[4f,g,15,24] It is noteworthy that both natural products **7** (epoxyquinol B) and **8** (RKB-3564 D) are derived from dimerization of two identical 2*H*-pyrans. In the case of **8**, a C_2-symmetric framework is further supported by ^{1}H NMR analysis.[7] Our structure assignment for dimer **8**[4g] was later corroborated by NMR studies reported by Osada and co-workers.[7b]

Dimerization of a 2*H*-Pyran *syn* Epoxy Alcohol Monomer. During the reduction of quinone epoxide **17** to epoxyquinol **9** (Scheme 1), the diastereomer of **9**, *syn* epoxy alcohol **18**, was also obtained (4%). To further understand the structural requirements for 2*H*-pyran formation and subsequent Diels−Alder dimerization, we next studied the selective oxidation of *syn* epoxyquinol **18**. In the event, using catalytic amounts of CuCl and TEMPO, Semmelhack oxidation[22] of **18** was found to proceed significantly more slowly in comparison to *anti* epoxyquinol **9**. Fortunately, when a stoichiometric amount of CuCl and TEMPO was employed, compound **18** was oxidized smoothly and the resulting intermediate 2*H*-pyran dimerized to afford **19** and **20** (Scheme 3). This result further supports our previously proposed rules for steric demanding effects in the Diels−Alder dimerization of 2*H*-pyran monomers, namely: (i) the methyl groups of the diene and dienophile tend to orient themselves away from one another to avoid steric interactions; and (ii) the dienophile generally approaches the diene *anti* to the epoxide moiety.[4f]

Preparation of a *cis*−*cis* Diene Monomer and its Feasibility as a Precursor to Epoxyquinols A and B. In our synthetic approach to epoxyquinols A and B, oxidation precursor **9** (Scheme 2) possesses a *trans*−*cis* diene moiety. Our earlier computational results on a related epoxyquinone system indicated that a *cis*−*cis* diene may also undergo cyclization to afford a 2*H*-pyran.[4b] We therefore targeted preparation of *cis*−*cis* diene monomer **21** and examined its suitability as a substrate for the oxidation/oxaelectrocyclization/Diels−Alder cascade process (Scheme 4). The preparation of **21** was initiated from epoxy ketone **12**. Stille cross-coupling of **12** with tributyl-1-propynylstannane[25] afforded alkyne **22**, which was converted to *cis*−*cis* diene **23** by Lindlar reduction. After deprotection of the ketal and silyl ether protecting groups of **23**, diastereoselective reduction of the quinone epoxide intermediate using DIBAL-H in THF[19] generated *anti* epoxyquinol **21** (87%). To our delight, 2*H*-pyrans **10/10′** were readily obtained by selective oxidation of **21**. Mehta and co-workers have also reported the tandem oxidation/oxaelectrocyclization/Diels−Alder dimerization of substrate **21** in their synthesis of epoxyquinols A and B.[11f] Interestingly, we observed that the crude reaction mixture contained **10/10′**, *trans*−*cis* dienal **11**, and *cis*−*cis* dienal **24** in an 8:1:1 ratio (^{1}H NMR, $CDCl_3$). For the related oxidation of **9** (Scheme 2), we observed approximately a 9:1 ratio of **10/10′**:**11**, with no detectable

(21) (a) Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177. (b) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L. *J. Org. Chem.* **1996**, *61*, 7452. (c) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974. (d) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041.

(22) (a) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. For a discussion of the reaction mechanism, see: (b) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232.

(23) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365.

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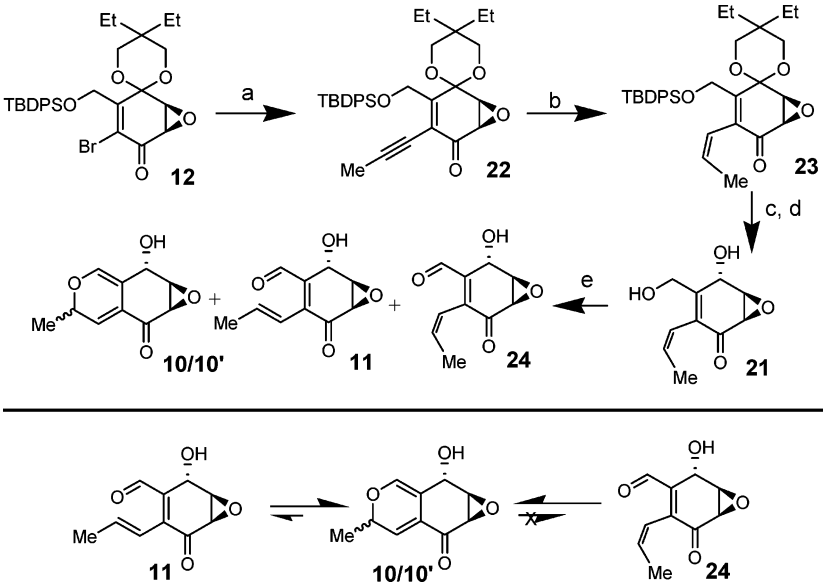
(25) Warner, B. P.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 5822.

SCHEME 4. Preparation and Oxidation/Oxaelectrocyclization of a *cis*−*cis* Diene Precursor[a]



[a] Reagents and conditions: (a) tributyl-1-propynylstannane, Pd_2dba_3·$CHCl_3$, $AsPh_3$, $PhCH_3$, 90 °C, 2 h, 92%; (b) H_2, 5% w/w Pd poisoned with Pb on K_2CO_3, THF, 93%; (c) 48% HF, CH_3CN, rt, 1.5 h, 90%; (d) DIBAL-H, THF, −78 °C, 15 min, 87%; (e) O_2 (1 atm), TEMPO, CuCl, DMF, 1 h.

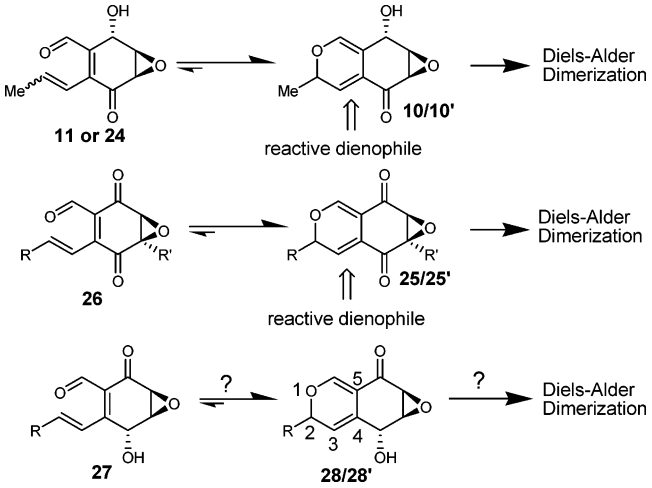
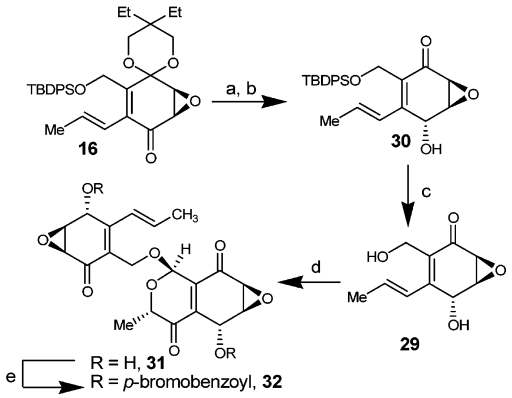


FIGURE 5. Formation and dimerization properties of related 2*H*-pyrans.

amount of **24** in the crude reaction mixture, which indicates a higher activation barrier for retro-6π-electrocyclization of 2*H*-pyrans (**10/10′**) to *cis*−*cis* dienal **24** (Scheme 4). For the related case of epoxyquinone 2*H*-pyrans,[4b] we have calculated the activation barriers from 2*H*-pyrans to dienals and found that there are significantly higher barriers from the 2*H*-pyrans to a *cis*−*cis* dienal (>20 kcal/mol) relative to a *trans*−*cis* dienal (16 kcal/mol).

Preparation and Reactivity of a Stable Isomeric 2*H*-Pyran. During the course of our studies, we discovered the favored valence isomerization[13] of dienals **11** and **24** to 2*H*-pyrans **10/10′**. In our studies directed toward the synthesis of torreyanic acid (**1**, Figure 2),[4a,b] 2*H*-pyran-4,5 diones **25/25′** were also found to be favored relative to the aldehyde valence isomers **26** (Figure 5). Accordingly, we wished to further investigate the equilibrium between isomeric dienal **27** and 2*H*-pyrans **28/28′**, the latter bearing an electron-withdrawing moiety at the 5-position of the 2*H*-pyran.[26] Since both 2*H*-pyrans **10/10′** and **25/25′** bear a reactive dienophile, which is absent in **28/28′**, we reasoned that such 2*H*-pyrans might be unreactive to Diels−Alder dimerization and, therefore, stable for isolation and further transformations. Recently, Hayashi and co-workers reported elegant related studies in which 2*H*-pyrans **10/10′** were used as diene components in [4 + 2] cycloaddition with a number of dienophiles.[11g]

SCHEME 5. Unexpected Formation of a Pseudo-Dimer[a]

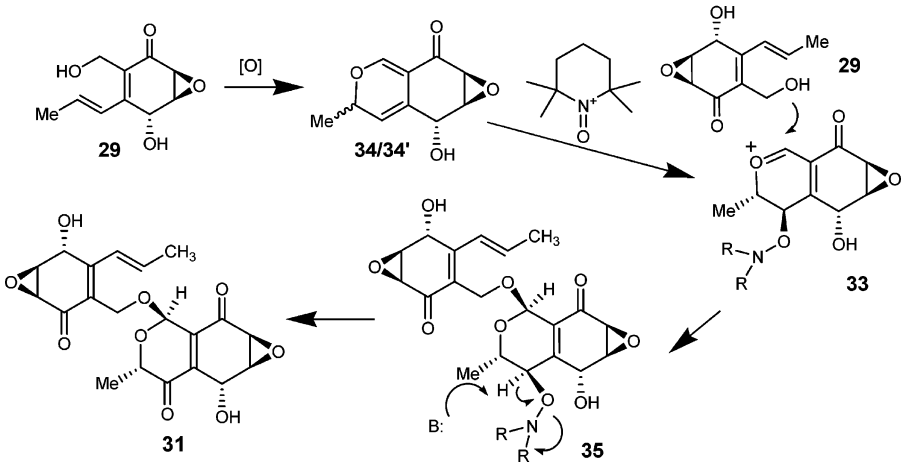


[a] Reagents and conditions: (a) DIBAL-H, THF, −78 °C, 15 min; (b) K-10, CH_2Cl_2, 5 min, 90% for two steps; (c) 48% HF, CH_3CN, rt, 1 h, 77%; (d) O_2 (1 atm), TEMPO, CuCl, DMF, 10 h, 50%; (e) 4-bromobenzoyl chloride, DMAP, Et_3N, CH_2Cl_2, 0 °C, 35 min, 54%.

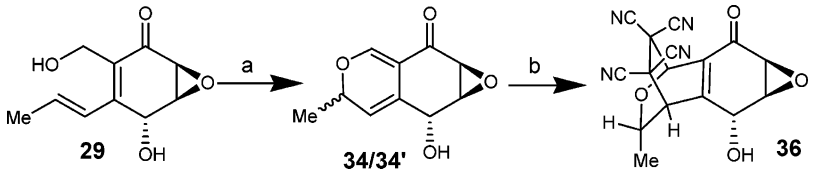
To test this hypothesis, we targeted epoxyquinol **29** (Scheme 5) as a synthetic precursor to regioisomeric 2*H*-pyrans of the general structure **28/28′**. The synthesis began with diastereoselective reduction of epoxy ketone

(26) (a) Gosink, T. A. *J. Org. Chem.* **1974**, *39*, 1942. (b) Ahluwalia, V. K.; Rao, J. S. *Indian J. Chem., Sect. B.* **1989**, *28B*, 81. (c) Moorhoff, C. M. *Synthesis* **1987**, 685.

SCHEME 6. Proposed Mechanism for the Formation of Pseudo-Dimer 31



SCHEME 7. Stable Isomeric 2*H*-Pyran and its Diels–Alder Reaction[a]



[a] Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, 90%; (b) TCNE (3 equiv), 65 °C, $PhCH_3$/THF (1:1), 2 h, 72%.

16 (Scheme 1), followed by hydrolysis of the cyclic ketal using montmorillonite K-10 clay,[27] to afford epoxyquinol **30**, which was converted to **29** by desilylation with aqueous HF. Simultaneous deprotection of the cyclic ketal and silyl ether protecting groups using HF was not applied in this instance due to difficulty in separation of **29** from the hydrolysis product 2,2-diethyl-1,3-propanediol. With alcohol **29** in hand, selective oxidation using Semmelhack's conditions (TEMPO, CuCl, O_2) was first evaluated. Surprisingly, the unusual dimeric product (**31**) was obtained from this reaction. Unambiguous structural assignment was achieved by conversion of **31** into *p*-bromobenzoate **32** followed by single X-ray crystal analysis.[15]

Formation of pseudo-dimer **31** may be rationalized by the general mechanism shown in Scheme 6. Oxonium ion intermediate **33** may be formed by electrophilic attack[28] of the oxoammonium ion (generated by TEMPO/Cu(I))[20] to 2*H*-pyran **34** or **34′**, derived from **29** by oxidation/oxaelectrocyclization. Subsequently, another molecule of **29** may attack **33** to afford acetal intermediate **35**, which may undergo further decomposition[29] to afford pseudo-dimer **31**.

According to the general mechanism proposed in Scheme 6, 2*H*-pyran intermediates **34/34′** are likely a synthetic intermediate. Interestingly, oxidation of **29** using Dess–Martin periodinane (1.1 equiv) afforded epoxyquinoid-fused 2*H*-pyrans **34/34′** in good yield as a 4:1 mixture (1:1 after storage, neat) of diastereomers (Scheme 7). In addition, 2*H*-pyrans **34/34′** were found to be stable compounds, and Diels–Alder dimerization was not observed between these monomers. We next evaluated [4 + 2] reactions between **34/34′** and standard dienophiles, such as 1,4-benzoquinone and *N*-benzylmaleimide, and found that no [4 + 2] cycloaddition occurred up to 80 °C in $PhCH_3$ as solvent. Higher reaction temperatures led to slow decomposition of the 2*H*-pyran. However, **34/34′** did undergo Diels–Alder reaction with the highly reactive dienophile tetracyanoethalene (TCNE, 65 °C)[30] to afford cycloadduct **36** (Scheme 7). In this case, a single diastereomer **36** was isolated in 72% yield, which suggests facile interconversion of the two diastereomeric 2*H*-pyrans **34** and **34′** through a dienal intermediate. The stereochemistry of **36** was confirmed by NOE analysis.[15] It is interesting to note that the secondary alcohol of **34/34′** apparently controls facial selectivity of the Diels–Alder cycloaddition leading to the formation of **36** as a single diastereomer.

Improved Synthesis of Epoxytwinol A (RKB-3564 D) and Dimerization of 2*H*-Pyran Precursors. Even though solvent optimization afforded up to 6–10% yield of **8** from dimerization of **10/10′** in CH_2Cl_2/MeOH (cf., Table 1), we also evaluated other conditions reported in the literature[31] for [4 + 4] cycloaddition of dienes, including photoirradiation and transition metal catalysis,[32] in an attempt to afford a higher yield of **8**. However, in all cases tested, no further improvement was observed. In most reactions, we obtained <10% of **8** from dimer-

(27) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, 1881.

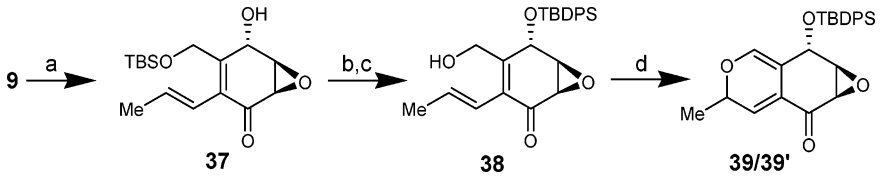
(28) For 1,2-addition of oxoammonium salts to electron-rich olefins, see: Takata, T.; Tsujino, Y.; Nakanishi, S.; Nakamura, K.; Yoshida, E.; Endo, T. *Chem. Lett.* **1999**, 937.

(29) For decomposition of α-(2,2,6,6-tetramethylpiperidinyloxy)-ketone to a *vic*-diketone, see: Liu, Y. C.; Ren, T.; Guo. Q. X. *Chin. J. Chem*. **1996**, *14*, 252.

(30) For Diels–Alder cycloaddition of a 2*H*-pyran and TCNE, see: Fischer, G. W.; Zimmermann, T.; Weissenfels, M. *Z. Chem.* **1981**, *21*, 260.

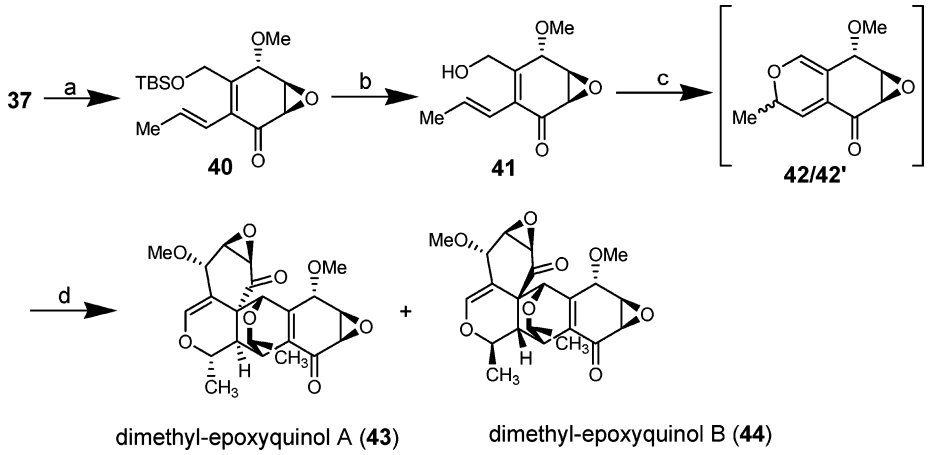
(31) For a review on [4 + 4] cycloaddition, see: Sieburth, S. McN.; Cunard, N. *Tetrahedron* **1996**, *52*, 6251.

SCHEME 8. Synthesis of Stable 2*H*-Pyrans 39/39′[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 1 h, 97%; (b) TBDPSCl, imidazole, DMF, 4 h, 81%; (c) 48% aq HF, CH_3CN, 20 min, 78%; (d) Dess−Martin periodinane, CH_2Cl_2, 30 min, 100%.

SCHEME 9. Synthesis of Dimethyl Epoxyquinols A and B[a]



[a] Reagents and conditions: (a) $Me_3O{\cdot}BF_4$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 3.5 h, 98%; (b) 48% aq HF, CH_3CN, 15 min, 98%; (c) Dess−Martin periodinane, CH_2Cl_2, 30 min; (d) >4 M in EtOAc, 40 h, **43** (36%), **44** (27%).

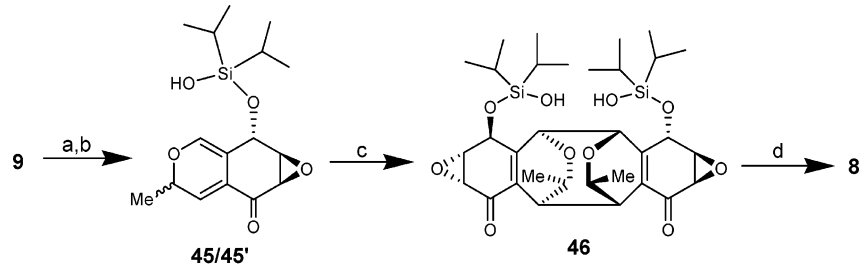
ization of **10/10′** along with significant amounts of **6** and **7** (>60% combined yield) due to the facile [4 + 2] dimerization process. In addition, we found that dimer **8** was not a stable compound and was slowly converted to **7** at room temperature (<5% conversion in $PhCH_3$, 14 h), which suggested that mild conditions are required for effective production of dimer **8**. Considering the predominant generation of **6** and **7** from dimerization of **10/10′**, we reasoned that it may be necessary to block the highly favored [4 + 2] dimerization process. Comparison of the X-ray crystal structures of natural products **6**−**8**[15,24] indicates that the secondary alcohol(s) of **6** and **7** are generally located in more sterically encumbered positions relative to the corresponding alcohols in dimer **8**, which suggested that installation of a bulky protecting group on the secondary alcohol of **10/10′** may block formation of [4 + 2] dimers **6** and **7** and thus favor formation of [4 + 4] dimer **8**. In this regard, *tert*-butyldimethylsilyl ether protection of primary alcohol **9** provided **37**, which was further converted to a bissilyl ether with TBDPSCl/imidazole (Scheme 8). Selective deprotection of the primary *tert*-butyldimethylsilyl ether provided oxidation precursor **38** (62% yield, three steps). In this case, because there is no possibility for oxidation of the secondary alcohol, we employed Dess−Martin periodinane to oxidize **38** to the corresponding 2*H*-pyrans **39/39′** in nearly quantitative yield. As anticipated, Diels−Alder dimerization of **39/39′** did not proceed after several days at room temperature (neat). In addition, the desired [4 + 4] dimerization of **39/39′** did not occur under various conditions as described for **10/10′**, including thermal, transition metal catalysis (Ni(0)), and photoirradiation.[31]

A less sterically encumbered 2*H*-pyran monomer bearing a secondary methyl ether was next prepared, as shown in Scheme 9. Methylation of **37** ($Me_3O{\cdot}BF_4$) cleanly afforded methyl ether **40**, which was desilylated to allylic alcohol **41** using aqueous HF/CH_3CN. Dess−Martin periodinane oxidation of **41** afforded the corresponding 2*H*-pyrans **42/42′**, which were found to be stable when stored at 0 °C for several days. However, in contrast to the report of Hayashi and co-workers,[11e] **42/42′** underwent Diels−Alder dimerization at room temperature slowly (40 h) at high concentration (>4 M in EtOAc) to afford dimethyl epoxyquinol A (**43**) and dimethyl epoxyquinol B (**44**). Combined with our earlier finding of intramolecular hydrogen bonding in the epoxyquinol B X-ray structure,[4f] it is reasonable to suggest that intermolecular hydrogen bonding may promote the Diels−Alder reaction to afford dimers of **6** and **7** as also proposed by Hayashi and co-workers.[11e] However, the ability of 2*H*-pyrans, such as **42/42′**, to dimerize to the epoxyquinol framework indicates that hydrogen bonding is not a strict requirement for Diels−Alder dimerization.

On the basis of the observation that no [4 + 4] dimerization was observed for both secondary alcohol protected monomers (**39/39′** and **42/42′**), we reasoned that the pendant hydroxyl group may somehow facilitate [4 + 4] dimerization. Further experiments indicated that dimerization of **10/10′** occurred during silica gel chromatography with slow elution using 2:1 hexane/EtOAc, leading to improved production of dimer **8** (15%) and suggesting that [4 + 4] dimerization may be promoted

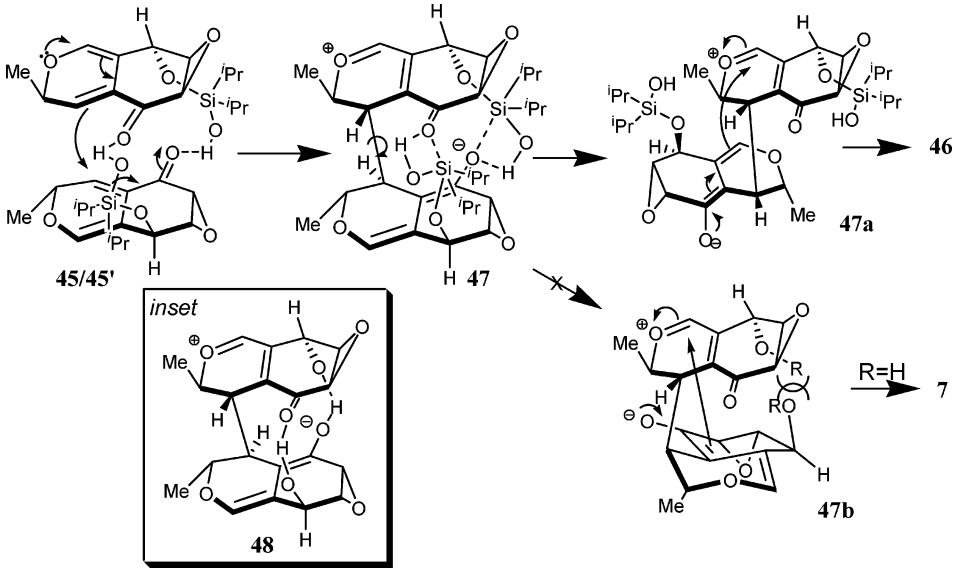
(32) Ni(0): (a) Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. Pd(0): (b) Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951. For a review of transition metal assisted cycloaddition reactions, see: (c) Fruharf, H.-W. *Chem. Rev.* **1997**, *97*, 523.

SCHEME 10. Alkoxysilanol-Facilitated Synthesis of Dimer 8[a]



[a] Reagents and conditions: (a) O_2 (1 atm), TEMPO, CuCl, DMF, 1 h; (b) $^iPr_2SiCl_2$, imidazole, DMF, 15 min, 76% for two steps; (c) neat, 30 h; (d) $Et_3N{\cdot}3HF$, THF, 25 min, 40% for two steps.

SCHEME 11. Mechanistic Proposal



by surface silanols[33] on silica.[34] Combining these considerations, we prepared the novel silanol-protected 2*H*-pyrans **45/45′**. Due to their facile dimerization, 2*H*-pyrans **10/10′** were freshly prepared from **9** and immediately transformed into **45/45′** via a two-step sequence (76%) (Scheme 10). In contrast to TBDPS-protected 2*H*-pyrans **39/39′**, compounds **45/45′** dimerized smoothly (neat, rt, 30 h) to afford [4 + 4] dimer **46** which after silyl deprotection afforded RKB-3564 D in an improved overall yield (40% from 2*H*-pyrans **45/45′**). In this sequence of transformations, no significant amounts of the [4 + 2] dimers epoxyquinols A and B (**6** and **7**) were produced.

[4 + 4] Cycloadditions are electronically forbidden processes[35] and generally require photoirradiation. However, in our studies, ambient light was excluded during the dimerization of **10/10′** or **45/45′**. In addition, we were unable to trap any radical intermediates in the [4 + 4] dimerization of **10/10′** using trapping agents, including TEMPO and Bu_3SnH,[36] thus disfavoring a radical mechanism. Our initial proposal was that the [4 + 4] process of **10/10′** and **45/45′** may proceed through a stepwise mechanism.[4g] A possible silanol-promoted [4 + 4] process for **45/45′** is shown in Scheme 11. Two molecules of **45** or **45′** first approach each other by organization facilitated by two intermolecular hydrogen bonds. Due to the electron-rich nature of the oxygen in the 2*H*-pyran monomer, zwitterionic intermediate **47** may then be generated concurrent with C−C bond formation. By rotation of the newly formed C−C bond, two possible products may be produced. The less sterically demanding conformer **47a** should afford [4 + 4] dimer **46** through attack of a dienolate on the oxonium ion. For R = −Si-(^{i}Pr)$_2$OH, formation of a [4 + 2] dimer precursor to epoxyquinol B (**7**) through arrangement **47b** should be disfavored by steric interactions. However, dimerization of unprotected monomer **10** or **10′** to afford **7** may proceed through transition state as **47b**, which also suggests the

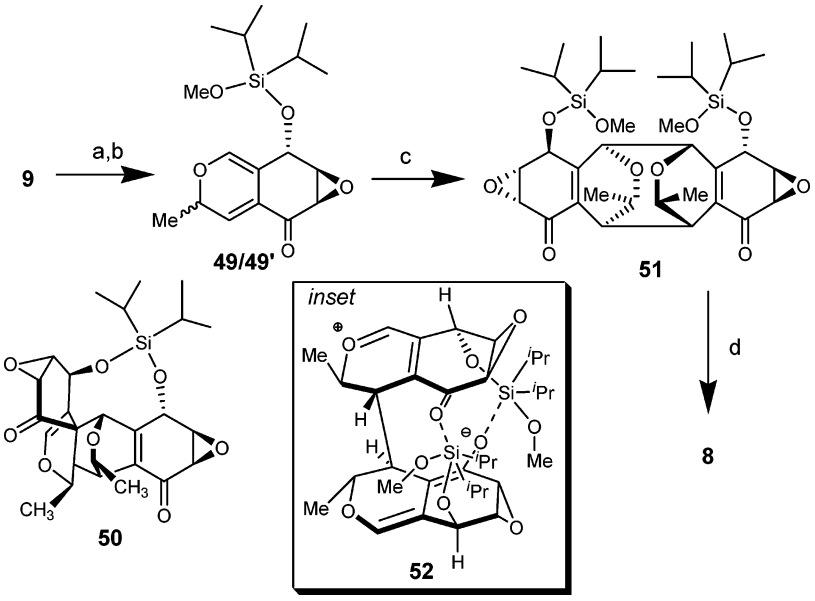
(33) For an excellent review on organosilanols, including hydrogen bonding, see: (a) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147. (b) Chandrasekhar, V.; Boomishankar, R.; Nagendran, S. *Chem. Rev.* **2004**, *104*, 5847. For an aryldialkylsilanol-directed metalation, see: (c) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1993**, *58*, 6314.

(34) For examples of silica gel-promoted cycloaddition, see: (a) Leon, F. M.; Carretero, J. C. *Tetrahedron Lett.* **1991**, *32*, 5405. (b) Wang, W. B.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 763. (c) Posner, G. H.; Carry, J. C.; Lee, J. K.; Bull, D. S.; Dai, H. *Tetrahedron Lett.* **1994**, *35*, 132. (d) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F. *Tetrahedron* **1995**, *51*, 1295. (e) Perez, J. M.; Lopez-Alvarado, P.; Alonso, M. A.; Avendano, C.; Menendez, J. C. *Tetrahedron Lett.* **1996**, *37*, 6955.

(35) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1969. For related [4 + 4] cyclodimerization of 2,3-dihydroisoquinolines, see: (b) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1994**, *35*, 3081. (c) Sugiura, M.; Asai, K.; Hamada, Y.; Hatano, K.; Kurono, Y.; Suezawa, H.; Hirota, M. *Chem. Pharm. Bull.* **1998**, *46*, 1862.

(36) (a) Ding, B.; Bentrude, W. G. *J. Am. Chem. Soc.* **2003**, *125*, 3248. (b) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333.

SCHEME 12. Control Experiment Involving Methoxysilane Synthesis[a]



[a] Reagents and conditions: (a) O_2 (1 atm), TEMPO, CuCl, DMF, 1 h; (b) $^i Pr_2SiCl_2$, imidazole, DMF, 15 min, then quench with methanol, **49/49′** (32.2%), **50** (22%), **45/45′** (20%); (c) neat, 42 h; (d) $Et_3N{\cdot}3HF$, THF, 25 min, 33% for two steps.

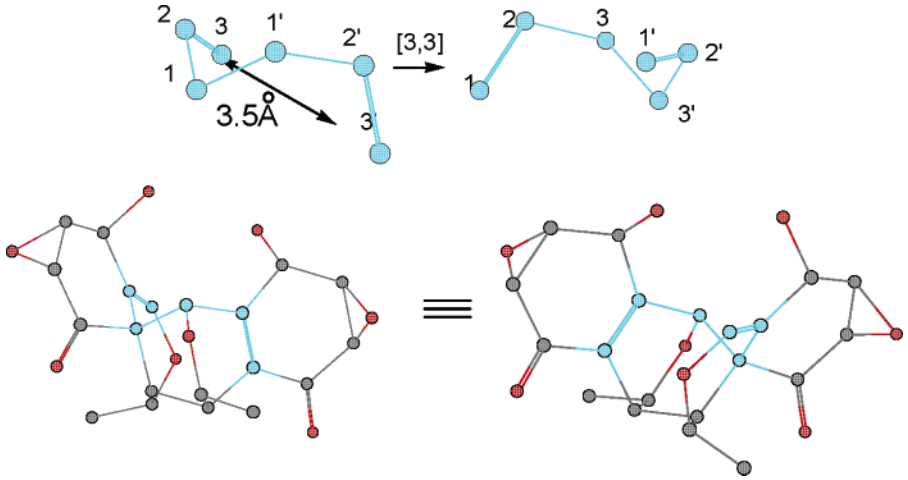


FIGURE 6. Cope-symmetrical framework of epoxyquinol B; [3,3] sigmatropic framework indicated by blue carbon atoms.

possibility of a stepwise mechanism for *exo* [4 + 2] dimer formation.[37]

In the case of **10/10′**, a related stepwise mechanism in the formation of **8** may be imagined involving intermediate **48** (*inset*, Scheme 11). For the 2*H*-pyran silanol monomers, additional interaction between the Si atoms and the oxygen anion and carbonyl oxygen may exist in intermediate **47**[38] due to the electropositive nature of the Si atoms facilitated by two Si−O bonds. Further experiments were conducted to test these assumptions and determine if the silanol moiety was required for hydrogen bonding.[4g] As shown in Scheme 12, replacement of the hydroxyl group of **45/45′** with a methoxy group by quenching the chlorosilane intermediate with methanol instead of water afforded methoxysilanes **49/49′** in 32% isolated yield along with **45/45′** (20%) and **50** (22%). The production of **50** can be explained by intermolecular reaction between one molecule of $^i Pr_2SiCl_2$ with two molecules of **10** followed by *exo* [4 + 2] cycloaddition. A small amount of this side product was also found in the synthesis of **45/45′**.[39] Interestingly, 2*H*-pyrans **49/49′** also dimerized in a similar [4 + 4] fashion to afford **51**, which was further converted to **8** after deprotection. This result suggests the potential relevancy of transition state **52** (*inset*, Scheme 12) in which hydrogen bond organization is not possible.

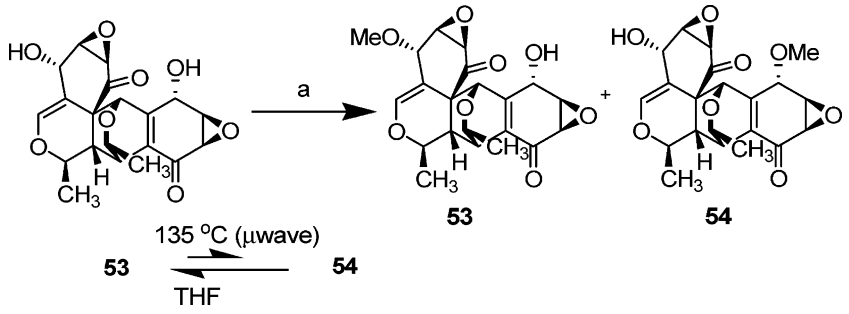
Thus, a number of secondary alcohol derivatives (**39/39′**, **42/42′**, **45/45′**, and **49/49′**) of 2*H*-pyrans **10/10′** have been prepared, and different tendencies for dimerization have been observed. *Steric effects* seem to play a major role for [4 + 2] dimerization, as indicated by comparison

(37) (a) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793. (b) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

(38) For a review on silicon Lewis acid mediated C−C bond formation, see: Dilman, A. D.; Loffe, S. L. *Chem. Rev.* **2003**, *103*, 733.

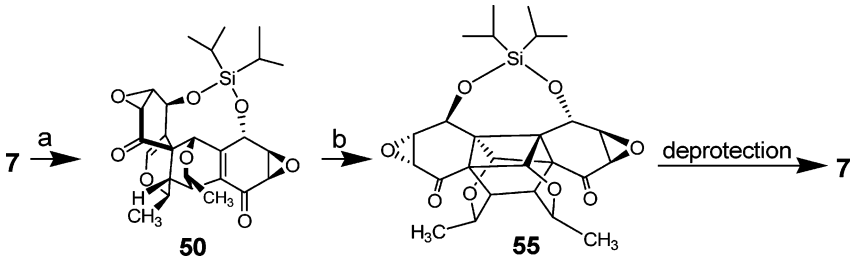
(39) For an efficient synthesis of **50** and related chemistry, see Scheme 14.

SCHEME 13. Experimental Support for the Cope-Symmetrical Framework of Epoxyquinol B[a]



[a] Reagents and conditions: (a) $Me_3O{\cdot}BF_4$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 4 h, **53** (33%), **54** (62%).

SCHEME 14. Unexpected [2 + 2] Photocycloaddition[a]



[a] Reagents and conditions: (a) $^iPr_2SiCl_2$, imidazole, DMF, 3 h, 100%; (b) *hν*, Pyrex, THF, 40 min, 50%.

of the dimerization of **10/10′**, **42/42′**, and **39/39′**. In addition, hydrogen bond organization is not required but may be beneficial for such Diels−Alder dimerization processes. However, for the [4 + 4] dimerization process, hydrogen bond organization as indicated by the dimerization of **10/10′** and **45/45′** or related coordinative interactions[40] as indicated by the dimerization of **49/49′** and **45/45′** may play an important role in addition to steric interactions.

Chemical Reactivity and Structural Modifications of the Epoxyquinols A and B and Epoxytwinol A. In our earlier efforts to explore the chemical diversity of the epoxyquinols,[4f] two unnatural *syn* epoxyquinol dimers were produced by microwave irradiation[41] of epoxyquinol A, while epoxyquinol B was found to be highly stable, presumably due to intramolecular hydrogen bonding. Further examination of the epoxyquinol B structure revealed that this *exo* dimeric product possessed a [3,3] sigmatropic framework and a Cope-symmetrical structure; that is, Cope rearrangement of epoxyquinol B is favored by a carbon 3−3′ distance of 3.5 Å and generates itself (Figure 6).

To further explore the chemical reactivity of the epoxyquinols and evaluate [3,3] Cope rearrangement of the epoxyquinol B core structure, we prepared monomethylated epoxyquinols **53** and **54** (Scheme 13) in order to desymmetrize the sigmatropic framework. To our

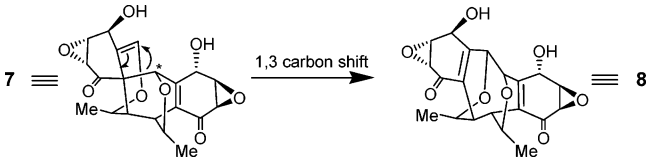
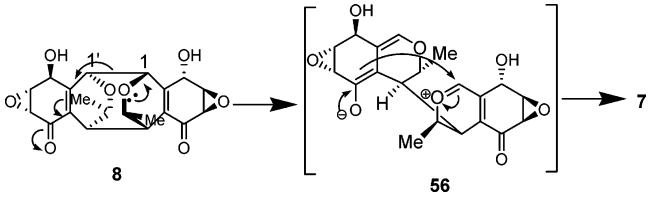


FIGURE 7. Structural relationship between epoxyquinol B (**7**) and epoxytwinol A (**8**).

SCHEME 15



delight, microwave irradiation of either **53** or **54** in THF (140 °C, 300 W, 20 min) afforded a 3:1 mixture of **53/54**, which thus demonstrated the interconversion between the two isomers via [3,3] Cope rearrangement.[42] A retro Diels−Alder mechanism is unlikely since we did not observe other products including epoxyquinol A (**6**), epoxyquinol B (**7**), dimethyl epoxyquinol A (**43**), and dimethyl epoxyquinol B (**44**). However, an alternative stepwise ionic mechanism proposed by Hayashi and coworkers cannot be ruled out.[11g]

Since both dimers of **7** and **8** were obtained from two identical 2*H*-pyrans **10** and a 1,3 carbon shift (retention of stereochemistry)[43] may be used to transform **7** into **8** (Figure 7), we next evaluated photoirradiation of **7**.

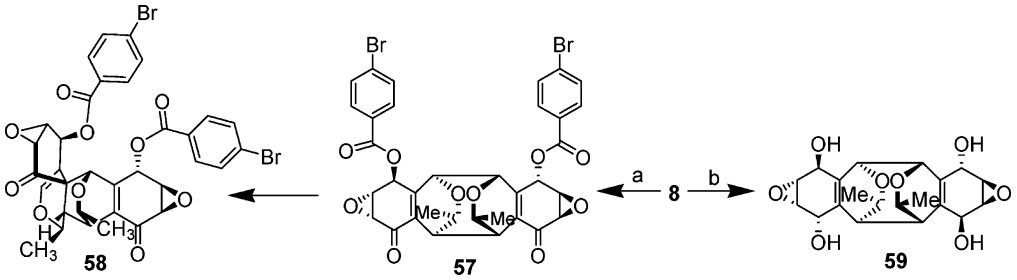
(40) For examples of Si−O coordinative interactions, see: (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res*. **2000**, *33*, 432. (b) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889.

(41) For select examples of microwave irradiation of natural products, see: (a) Salmoria, G. V.; Dall'Oglio, E. L.; Zucco, C. *Synth. Commun*. **1997**, *29*, 4335. (b) Das, B.; Venkataiah, B. *Synth. Commun*. **1999**, *29*, 863. (c) Das, B.; Madhusudhan, P.; Venkataiah, B. *Synth. Commun*. **2000**, *30*, 4001. (d) Das, B.; Venkataiah, B.; Kashinatham, A. *Tetrahedron* **1999**, *55*, 6585. For a recent review of the use of microwave reactions in modern organic synthesis, see: (e) Kappe, C. O. *Angew. Chem., Int. Ed*. **2004**, *43*, 6250.

(42) For an example of a microwave-assisted [3,3] sigmatropic rearrangement (Claisen rearrangement), see: Baxendale, I. R.; Lee, A.-I.; Ley, S. V. *J. Chem. Soc., Perkin Trans.* **2002**, 1850.

(43) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970; p 119.

SCHEME 16. Two Derivatives of Epoxytwinol A[a]

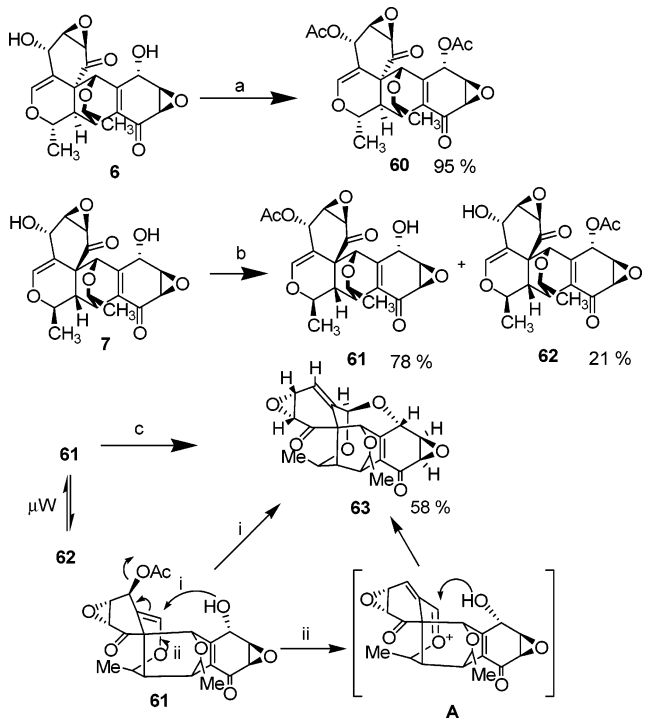


[a] Reagents and conditions: (a) 4-BrC_6H_4COCl, Et_3N, DMAP, CH_2Cl_2, 60 min, 93%; (b) $LiEt_3BH$, THF, −50 to −30 °C, 30 min, 100%.

However, a 1,3 shift failed to occur by UV irradiation of **7** using a 450 W Hanovia lamp (Pyrex filter). During the course of our preparation of 2*H*-pyran alkoxysilanols, we also produced variable amounts of dialkoxysilane **50**. Treatment of epoxyquinol B with $^iPr_2SiCl_2$ (imidazole, DMF) provided efficient access to **50** (Scheme 14). Interestingly, photolysis of **50** afforded the C_2-symmetric photocycloaddition product **55**,[44] which was confirmed by X-ray crystal structural analysis.[15] The propensity of **50** to undergo intramolecular photocycloaddition is consistent with the close proximity between the two olefins in the scaffold of epoxyquinol B as also evident in the previously described [3,3] Cope rearrangement studies (Figure 6 and Scheme 13). Attempted desilylation of **55** ($Et_3N{\cdot}3HF$, TBAF/AcOH) provided **7**, which indicates significant ring strain of the bicyclo[2.2.0]hexane ring system.

In contrast to dimers **6** and **7**, as noted previously, dimer **8** is not a stable compound and is converted slowly to **7** at room temperature in the dark. This rearrangement was found to be faster in polar solvents. For example, at a concentration of 8.6 mM, the conversion of **8** to **7** is 5% in $PhCH_3$, 21% in EtOAc, and 59% in MeOH, respectively, at room temperature (14 h). This solvent effect supports a possible ionic mechanism for the rearrangement, as shown in Scheme 15. Zwitterionic intermediate **56** may be generated by cleavage of the C1−C1′ bond facilitated by the electron-rich pyran oxygen. Additional evidence for the fragility of the C1−C1′ bond was provided by X-ray structure of **8**,[15] which shows a C1−C1′ distance of 1.567 Å, while a typical Csp^3-Csp^3 distance is 1.49−1.54 Å. On the other hand, dimer **8** may be stabilized by two secondary alcohols through delocalization of the electron density of the pyran oxygens by hydrogen bonding. In the X-ray structure of **8**, the distance between the secondary alcohol and pyran oxygen is 3.1−3.3 Å, which may be suitable for weak to moderate intramolecular H-bonding.[45] This hydrogen bond stabilization may also explain the relative instability of **8** in polar solvents. To further support these assumptions and explore the reactivity of **8**, we prepared two derivatives (Scheme 16). It was found that the bisbromobenzoate derivative **57** rearranged to the corresponding epoxyquinol B structure **58** significantly faster than **8** to **7**. For example, at 8.6 mM concentration (rt for 14 h), the conversion of **57** to **58** was 53% in EtOAc compared to

SCHEME 17. Acylation Studies of Epoxyquinols A and B[a]



[a] Reagents and conditions: (a) Ac_2O (3 equiv), Et_3N, DMAP, CH_2Cl_2, 20 min, 95%; (b) Ac_2O (3 equiv), Et_3N, DMAP, CH_2Cl_2, 0 °C, 15 min, **61** (78%), **62** (21%); (c) microwave, 300 W, THF, 150 °C, 15 min, 58%.

21% for **8** to **7**. The fast transformation of **57** to **58** may due to the lack of a secondary alcohol to reduce the electron density of the pyran oxygens. In contrast, tetraol **59**, prepared by diastereoselective reduction of **8**, was a stable compound likely due to the absence of the carbonyl as an electron acceptor, thus eliminating the possibility for fragmentation of **8** to epoxyquinol B **7** (cf., Scheme 15).

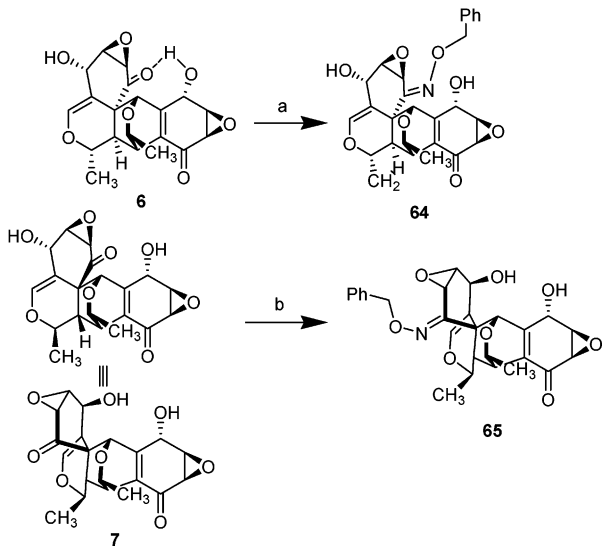
In future work, reporter-tagged versions of the epoxyquinols may be required for molecular target identification.[46] Due to the relative instability of **8**, we choose **6** and **7** for evaluation of derivatization reactions. In principle, there are two functional groups in **6** and **7** that may be modified. The first involves acylation of the

(44) For [2 + 2] cycloaddition of an enone and vinyl ether, see: Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

(45) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.

(46) For use of reporter group-tagged versions of a natural product for identification of molecular targets, see: Adam, G. C.; Vanderwal, C. D.; Sorensen, E. J.; Cravatt, B. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5480.

SCHEME 18. Alkoxyamine Formation[a]



[a] Reagents and conditions: (a) $BnONH_2$, EtOAc, AcOH, 1 h, 100%; (b) $BnONH_2$, EtOAc, AcOH, microwave, 110 °C, 50 min, 68% (93% brsm).

secondary alcohols of **6** and **7** with a functionalized acylating reagent. Alternatively, derivatization of the carbonyl group may be considered. Acylation of epoxyquinol A (**6**) was first conducted, as shown in Scheme 17. Monoacylation of the two secondary alcohols in epoxyquinol A was found to be troublesome. Small amounts of monoacetylated products along with bisacetylated epoxyquinol and recovered starting material were isolated when **6** was treated with 1.2 equiv of Ac_2O. However, diacylation could be conducted smoothly using 3 equiv of Ac_2O to afford bisacetate **60** (95%).

In contrast to epoxyquinol A, monoacylation of epoxyquinol B was found to be facile. Two monoacetates of epoxyquinol B, **61** and **62**, were prepared as shown in Scheme 17. It is interesting to note that when 3 equiv of Ac_2O was employed, only the monoacetates **61** and **62** were isolated without detection of diacetate products. Not surprisingly, **61** and **62** are interconvertable under microwave irradiation (130 °C in THF) due to the facility of [3,3] sigmatropic rearrangement of the epoxyquinol B framework (cf., Scheme 13). To our surprise, the novel caged compound **63** was generated by extended microwave irradiation of either **61** or **62** (150 °C, THF, 300 W). The structure of **63** was determined by X-ray crystal structure analysis.[15] The mechanism for formation of **63** may proceed either through direct intramolecular allylic displacement of **61** (pathway i, Scheme 17) or via formation of an oxonium ion intermediate **A** followed by electrophilic attack (pathway ii, Scheme 17).

Condensation of alkoxyamines with carbonyls is generally an efficient transformation.[47] Considering the different electronic features (one of them is an enone) and stereochemical environments of the two carbonyl groups in epoxyquinols A (**6**) and B (**7**), we anticipated that alkoxyamine formation should be both regio- and stereoselective. In the event, we choose *O*-benzylhydroxyamine as a model for oxime formation. To our delight, efficient condensation was observed between **6** and *O*-benzylhydroxyamine to afford a single oxime diastereomer **64** in quantitative yield (Scheme 18). However, condensation between **7** and *O*-benzylhydroxyamine was found to be sluggish under the same reaction conditions (25% conversion after 20 h), presumably due to the lack of intramolecular H-bonding activation of the carbonyl, as is the case for **6**. However, forcing conditions (microwave, 110 °C, 50 min) afforded a single diastereomeric oxime product **65** in 68% yield (93% based on recovered starting material). The successful synthesis of derivatives **64** and **65** thus sets the stage for the preparation of reporter tag-modified[45] derivatives of epoxyquinols A and B for future molecular target identification studies.

Conclusion

In summary, total syntheses of the angiogenesis inhibitors epoxyquinols A (**6**), B (**7**), and epoxytwinol A (**8**) have been achieved. The relative and absolute stereochemistries of **7** and **8** were confirmed by single-crystal X-ray structure analysis of synthetic materials. Dimerization of a *syn* epoxy alcohol 2*H*-pyran precursor (**18**) further reinforced the rules for the Diels−Alder dimerization of 2*H*-pyrans. A *cis*−*cis* diene-bearing 2*H*-pyran monomer (**21**) was found to be a suitable precursor to epoxyquinols A and B. By alteration of the epoxyquinol 2*H*-pyran nucleus, the stable isomeric 2*H*-pyrans **34/34′** were prepared, and their Diels−Alder reactivity toward reactive dienophiles was evaluated. Extensive studies for improving the [4 + 4] dimerization of selectively protected 2*H*-pyran monomers to afford the novel epoxyquinoid dimer epoxytwinol A were also carried out, which have provided valuable insight regarding competitive [4 + 2] and [4 + 4] dimerization processes. In addition, chemical reactivities and structural modifications of epoxyquinol dimers have been conducted, including [2 + 2] photocycloaddition and [3,3] sigmatropic rearrangement, indicating the possibility for production of novel structural diversity from the natural product frameworks. Continued studies concerning the chemical synthesis of epoxyquinoid natural products and related molecules are currently in progress and will be reported in due course.

Acknowledgment. Financial support from the American Cancer Society (RSG-01-135-01, J.A.P, Jr.) and Bristol Myers-Squibb (Unrestricted Grant in Synthetic Organic Chemistry, J.A.P, Jr.) is gratefully acknowledged. We thank Prof. James Bobbitt (University of Connecticut) for helpful discussions, Ms. Sujata Bardhan (Boston University) for experimental assistance, and Dr. Emil Lobkovsky (Cornell University) for X-ray crystal structure analyses.

Supporting Information Available: Complete experimental procedures and spectral data for all previously unreported compounds described herein, including X-ray crystal structure coordinates for **7**, **8**, **32**, **55**, and **63**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(47) For a review of oxime formation, see: Abele, E.; Lukevics, E. *Org. Prep. Proc. Int.* **2000**, *32*, 235.