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Synthesis of the Epoxyquinol Dimer RKB-3564 D: Utilization of an Alkoxysilanol To Promote [4 + 4] Dimerization

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The novel pentaketide-derived epoxyquinol dimers epoxyquinols A (**1**) and B (**2**)[1] (Figure 1) have drawn significant attention due to their highly oxygenated, heptacyclic structures and potent anti-angiogenic activity. In a previous Communication,[1c] we reported enantioselective syntheses of **1** and **2** by [4 + 2] dimerization of *2H*-pyran monomers. Recently, a closely related natural product, RKB-3564 D (**3**, Figure 1, relative and absolute stereochemistries unassigned) was coisolated with **1** and **2** and also shown to be an angiogenesis inhibitor.[2] Herein, we report the total synthesis of **3** employing an alkoxysilanol protecting group to favor [4 + 4] relative to [4 + 2] dimerization of *2H*-pyran monomers.

The 3,8-dioxatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene structure of dimer **3** suggested [4 + 4] cycloaddition[3] of two identical[4] *2H*-pyrans **4** or **4′** as a retrosynthetic disconnection (Figure 1). A survey of the literature revealed that [4 + 4] cycloadditions have been generally performed using photochemistry, forcing thermal conditions,[3a] and transition metal catalysis.[5] In our initial studies,[1c] we observed <3% of **3** produced with **1** and **2** (>60%) in the dimerization of **4**/**4′**. However, extensive efforts did not significantly improve the yield of **3** due to competitive [4 + 2] dimerization of **4**/**4′**.[6] Even with careful optimization of the solvent[7] (14:1 CH_2Cl_2:MeOH, rt, 50 h) the yield of **3** could only be raised to 6−10%. With the small amount of **3** obtained, we determined its stereochemistry by X-ray crystallography (Figure 2). The absolute configuration of natural RKB-3564 D was determined by comparison of optical rotations.[7]

Inspection of the structures of **2** and **3** reveals that both compounds may be derived from dimerization of two identical *2H*-pyrans **4** and that a 1,3 carbon shift (retention of stereochemistry) may transform **2** into **3**. However, we found that a 1,3 shift failed to occur by UV irradiation of **2** using a 450 W Hanovia lamp (Pyrex filter). Interestingly, photolysis of the derived dialkoxysilane **5** (Scheme 1) unexpectedly afforded the C_2-symmetric photocycloaddition product **6**[8] which was confirmed by X-ray analysis.[7] Attempted desilylation of **6** ($Et_3N{\cdot}3HF$,[9] TBAF/AcOH) provided **2** which indicates that the bicyclo[2.2.0]hexane is prone to retro [2 + 2] cycloaddition to afford the more stable structure **2**.

Since we were unable to rearrange dimer **2** to **3**, we next investigated modifications of *2H*-pyrans **4**/**4′**. X-ray structures of **1**−**3**[7] show that the secondary alcohol(s) of **1** and **2** are generally located in sterically encumbered positions. In contrast, the two hydroxyl groups in **3** are significantly less hindered. We reasoned that installation of a bulky protecting group on the secondary alcohol of **4**/**4′** may block the [4 + 2] process[1g] and favor [4 + 4] dimerization. We thus prepared *2H*-pyran silyl ether **9** from diol **7**,[1c] which was found to be resistant to both [4 + 2] and [4 + 4] dimerization under either thermal or photochemical conditions (Scheme 2). Similarly, related *2H*-pyran monomers, including methyl ether (**10**) and acetate (**11**), did not undergo [4 + 4] dimerization.[10]

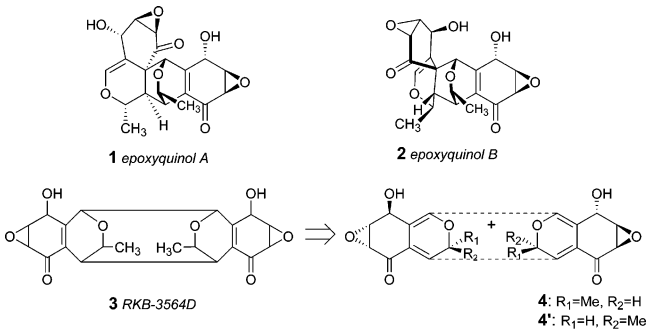


Figure 1. Dimeric epoxyquinol natural products.

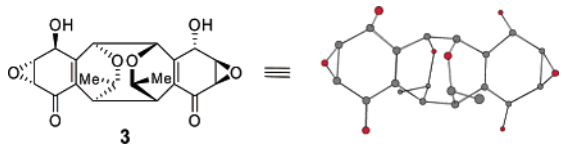
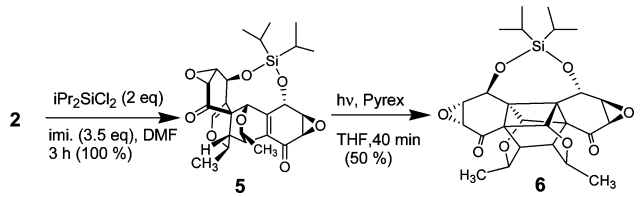
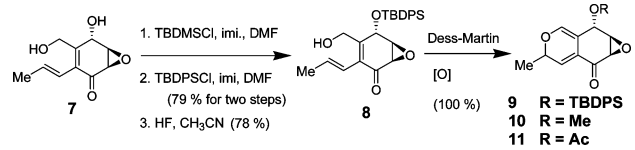


Figure 2. X-ray crystal structure analysis of RKB-3564 D (**3**).

Scheme 1



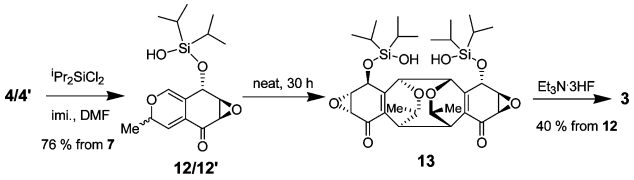
Scheme 2



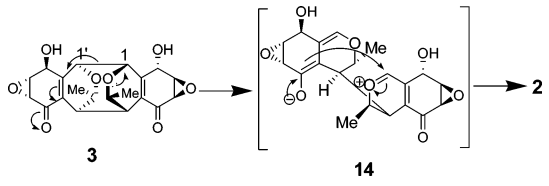
These experiments reinforced the possibility of blocking [4 + 2] dimerization by protection of secondary alcohol of the *2H*-pyran and the apparent requirement of an alcohol to facilitate the [4 + 4] process. Further experiments showed that dimerization of **4**/**4′** occurred during silica gel chromatography (slow elution using 2:1 hexane/EtOAc), leading to improved production of **3** (15%) and suggesting that [4 + 4] dimerization may be promoted by surface silanols on silica. Combining these considerations, we prepared alkoxysilanol **12**/**12′** (Scheme 3) from **4**/**4′**.[11] To our delight, **12**/**12′** underwent smooth cycloaddition to afford [4 + 4] dimer **13** with no evidence of [4 + 2] cycloaddition. After desilylation, **3** was obtained in improved overall yield (30% from **7**). We believe that this is the first use of a dialkylsilanol protecting group to direct the course of a reaction.[12]

10.1021/ja039543+ CCC: $27.50

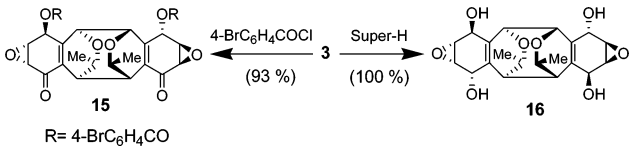
Scheme 3. Alkoxysilanol-Facilitated Synthesis of **3**



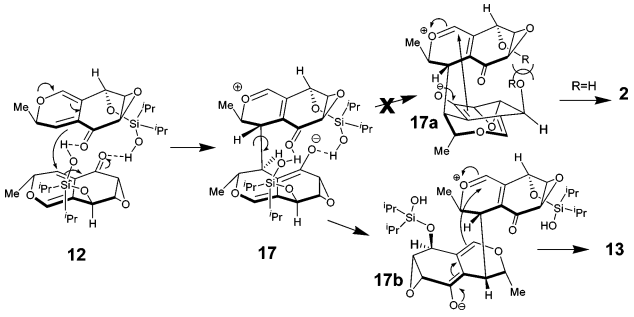
Scheme 4



Scheme 5. RKB-3564 D Derivatives



Scheme 6



We have found that dimer **3** is not stable and is converted to **2** at room temperature in the dark. This rearrangement is faster in polar solvents,[7] suggesting an ionic mechanism (Scheme 4). Zwitterionic intermediate **14** may be generated by cleavage of the C1−C1′ bond facilitated by the electron rich pyran oxygen.[13] On the other hand, dimer **3** may be stabilized by two secondary alcohols through lowered electron density of the pyran oxygens by hydrogen bonding.[14] This may explain the relative instability of **3** in polar solvents. To further support these assumptions, we prepared two derivatives from **3** (Scheme 5). It was found that bis-bromobenzoate derivative **15** rearranged to the corresponding epoxyquinol B structure faster than **3** to **2**[7] presumably due to the lack of secondary alcohols to reduce the electron density of the pyran oxygens. In contrast, tetraol **16** (prepared by diastereoselective reduction of **3**) was a stable compound likely due to the absence of a carbonyl as an electron acceptor.

The previous discussion suggests that [4 + 4] dimerization of **12** may involve a related stepwise, ionic process.[15] Initial C−C bond formation to form zwitterionic intermediate **17** (Scheme 6) may be facilitated by two intermolecular hydrogen bonds.[12a] By rotation of the newly formed C−C bond, two possible products may be produced. Formation of **17a** and the resultant attack of the oxonium ion by the α-carbon of the dienolate may be prohibited by steric interactions between bulky alkoxysilanol substituents. To alleviate steric congestion, formation of **17b** and δ-carbon attack may be favored to afford [4 + 4] dimer **13**. In contrast, dimerization of unprotected monomer **4** to afford **2** may be facilitated by hydrogen bonding through **17a** (R = H).[1g]

In summary, we have developed a strategy for the synthesis of the epoxyquinol dimer RKB-3564 D employing an alkoxysilanol protecting group to redirect the inherently favored [4 + 2] dimerization of *2H*-pyran monomers to a [4 + 4] manifold. Preliminary mechanistic studies suggest that the [4 + 4] dimerization may occur through a stepwise, ionic process. Further studies to examine the scope of the dimerization process and further applications are currently under investigation.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF), including X-ray crystal structure coordinates for **3** and **6**. X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) ^{1}H NMR analysis (ref 2) shows seven proton signals and thus a symmetric structure for RKB-3564 D.

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(6) It was not possible to separate **4** and **4′** as both diastereomers (approximately 1:1) exist in equilibrium with small amount of the corresponding aldehyde and dimerize quickly upon concentration.

(7) Synthetic (+)-**3** was identical to natural (+)-**3** (ref 2) by ^{1}H and ^{13}C NMR, mass spectrum, and $[\alpha]_D$. See Supporting Information for details.

(8) 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.

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(10) In contrast to the results reported in ref 1g, we found that [4 + 2] dimers were formed from *2H*-pyrans **10** and **11** (neat, 40 h).

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(13) The X-ray structure of **3** also shows a C1−C1′ distance of 1.567 Å (typical Csp^3-Csp^3 distance is 1.49 Å − 1.54 Å).

(14) In the X-ray structure of **3**, 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, see Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.

(15) In preliminary studies, we have been unable to trap any radical intermediates in the [4 + 4] process using agents including TEMPO and Bu_3SnH.

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