

Synthesis of *Trans-syn-trans* Fused Bis-Pyrans via *Endo*-Selective Cyclizations of Cyclic Sulfates

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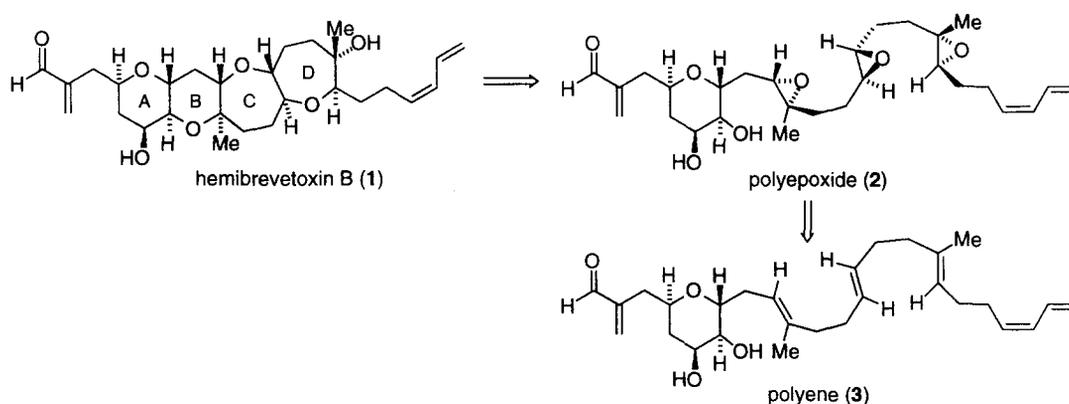
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Abstract: Acid-catalyzed cyclization of hydroxy-cyclic sulfates occurs with *endo*-regioselectivity affording bispyran products from substrates in which the nucleophilic hydroxyl and electrophilic cyclic sulfate groups are 1,2-*trans*-substituted on a cyclic pyran template. This methodology is demonstrated in an enantioselective synthesis of the *trans-syn-trans* fused AB cyclic ether rings of the brevetoxin natural products.

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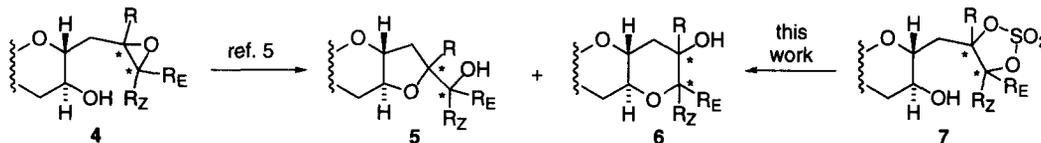
Oxidative cyclization pathways have been hypothesized for the biosynthesis of several classes of cyclic and polycyclic ether natural products.¹ For the brevetoxin-type polycyclic ether structures such as hemibrevetoxin B (**1**),² the repeating *trans-syn-trans* fused polycyclic ether stereochemistry has been proposed to arise from tandem *anti*-cyclization transformation of a polyepoxide arising from enantioselective epoxidation of a polyene precursor.^{1b,c} However, this biosynthetic pathway requires not only enantioselective epoxidation of a polyene such as a hypothetical prebrevetoxin polyene **3**, but also necessitates regioselective *endo*-cyclization of each hydroxyepoxide of polyepoxide **2** (Figure 1).^{3,4}

Figure 1: Proposed biosynthesis of hemibrevetoxin via polyepoxide polycyclization



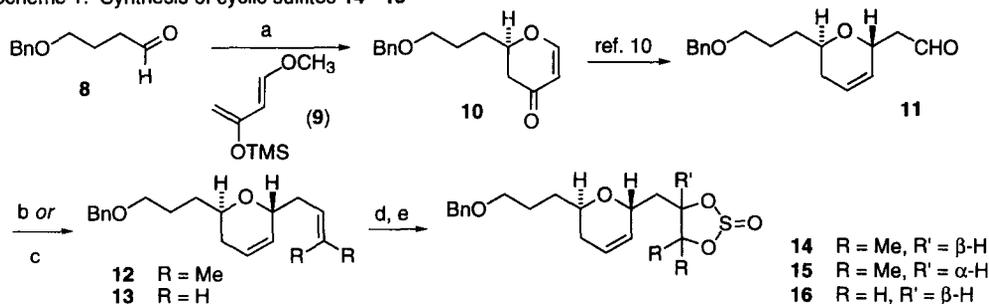
Electrophile-promoted hydroxyalkene cyclizations and acid-catalyzed hydroxyepoxide cycloisomerizations generally proceed via exocyclic pathways (i.e. **4** → **5**, Figure 2) unless carbocation-stabilizing groups are present at R_E and/or R_Z.^{5,6} However, selenium⁷ and tellurium-promoted⁸ *endo*-cyclizations are known for hydroxyalkenes in which hydroxyl and alkene substituents are *trans*-substituted on a monocyclic template, particularly when these cyclizations are conducted under equilibrating reaction conditions rather than "kinetic" or non-equilibrating conditions. Although hydroxyepoxide *endo*-cyclizations are generally disfavored by the early transition state associated with opening of the strained oxirane ring, we hypothesized that the relatively unstrained cyclic sulfate electrophiles⁹ (i.e. **7**) might permit *endo*-cyclization to afford exclusively or predominantly regioisomeric structure **6**. In this communication we describe the first successful examples of this strategy, resulting in the enantioselective synthesis of the AB bis-pyran ring system of the brevetoxin natural products.

Figure 2: *Exo*- vs. *endo*-cyclization pathways



A family of substrates was generated from the monocyclic aldehyde **11**, described in an earlier publication.¹⁰ A significant modification in the preparation of dihydropyrone **10** was enantioselective titanium-BINOL catalyzed cyclocondensation¹¹ of the Kitahara-Danishefsky diene (**9**) with 4-benzyloxybutanal (**8**, Scheme 1), affording dihydropyrone **10** in approximately 95% ee (determined by NMR analysis with the chiral shift reagent Eu(hfc)₃). Wittig reactions of **11** afforded the trisubstituted alkene of **12** and the monosubstituted alkene product **13**. In accordance with previous findings that a similar dihydropyran alkene was resistant to osmium-catalyzed dihydroxylation procedures,¹⁰ we observed regioselective enantioselective dihydroxylation of the acyclic alkene of **12** with both dihydroquinine- and dihydroquinidine-derived phthalazine-linked osmate catalysts (AD-mix- α , 4 : 1 ratio, 70% combined yield; AD-mix- β , 10 : 1 ratio, 77% yield).¹² After separation of diol diastereomers,

Scheme 1: Synthesis of cyclic sulfites **14** - **16**

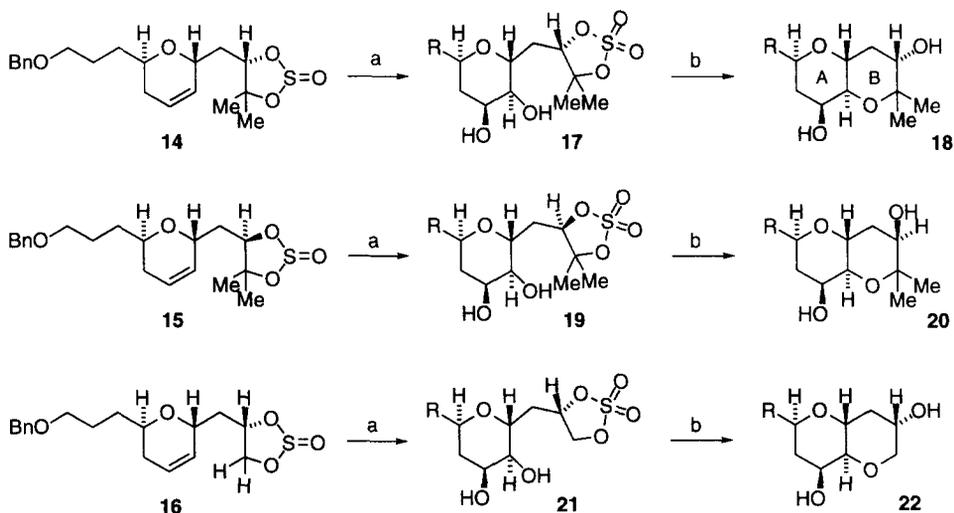


Reagents and Conditions: (a) (*S*)-BINOL / Ti(O-*i*-Pr)₄ / CF₃CO₂H, 4Å MS, Et₂O; then CF₃CO₂H (65% yield, 95% ee). (b) (CH₃)₂CHPPh₃Br / *n*-BuLi, Et₂O, 0°C (40% yield). (c) CH₃PPh₃Br / *n*-BuLi, THF, 0°C (52% yield). (d) AD-mix α or β , CH₃SO₂NH₂, *t*-BuOH : H₂O (1:1), 0°C to 20°C (see text). (e) imidazole / SOCl₂, THF, -20°C to 20°C (95% yield).

the corresponding cyclic sulfites **14** and **15** were formed by reaction with thionyl diimidazole.⁹ Although the monosubstituted alkene **13** was considerably less reactive to enantioselective dihydroxylation catalysts (*AD-mix- α* , 3 : 2 ratio, 35% yield) than was compound **12**, we could also prepare cyclic sulfite **16** by the same route.

Oxidation of the remaining alkene and the cyclic sulfite in compound **14** could be accomplished in a single operation by reaction with ruthenium trichloride and sodium periodate (Scheme 2).¹³ It appears that the alkene of **14** reacted more rapidly than the sulfur atom; furthermore the resulting diol-cyclic sulfate product **17** was relatively unstable and could not be purified by silica gel chromatography. However, heating a solution of crude **17** in acetonitrile in the presence of 1% water (by volume)¹⁴ and a catalytic amount of *p*-toluenesulfonic acid afforded one major bicyclic product **18**.¹⁵ This structure was assigned by acetylation of both alcohols and observation of significant shifts of both carbinol methine ¹H-NMR resonances consistent with the production of two secondary alcohols via endocyclization rather than the tertiary alcohol expected from exocyclization.¹⁶ *Endo*-regioselectivity is not restricted to diastereomer **17** but is also observed upon cyclization of the epimeric cyclic sulfate **19** arising from compound **15**, leading to the bicyclic product **20**. Moreover, cyclic sulfate **21** provided predominantly the endocyclic product **22** (*endo*:*exo* = 4:1), indicating the generality of this endocyclization strategy for C-O bond formation even at primary carbon centers. These results constitute the first examples of pyran (six-membered ring) formation from hydroxy-cyclic sulfate cyclization.

Scheme 2: Endocyclizations of diol-cyclic sulfates **17**, **19**, and **21**



Reagents and Conditions: (a) cat. $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4 , $\text{EtOAc} : \text{CH}_3\text{CN} : \text{H}_2\text{O}$ (3:3:1), 0°C to 20°C , 10 min. (b) cat. *p*-TsOH, 1% H_2O in CH_3CN , reflux 6 h. (**15** - **21**%, two steps).

Current efforts are directed towards tandem oxidative *endo*-cyclizations of polyene substrates analogous to polyene **3** for an eventual synthesis of hemibrevetoxin B (**1**) and other members of this family of natural products.

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- [15] The low yields of products **18**, **20**, and **22** are probably due to a combination of factors. For instance, the ruthenium-catalyzed dihydroxylations of **14** and **16** are estimated to proceed in only ca. 50% yield, in analogy to our earlier experience with similar dihydropyran substrates (ref. 10). Furthermore, compounds **17**, **19**, and **21** are relatively unstable and decompose upon heating in wet acetonitrile in the absence of an acid catalyst. We have not observed any evidence for exocyclization product regioisomers arising from intermediate cyclic sulfates **17** or **19**. We have observed that a simple cyclic sulfate substrate arising from a trisubstituted alkene with a more distant hydroxyl group was observed to undergo pinacol-type dehydration to afford an isopropyl ketone product; X. Guo and F. E. McDonald, unpublished work.
- [16] Characterization data for the diacetate of **18**: IR (film) 1733, 1241 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.35 - 7.28 (5H, m), 5.19 (1H, ddd, $J = 4.7, 3.9, 3.5$ Hz), 5.01 (1H, dd, $J = 6.0, 2.6$ Hz), 4.51 (2H, s), 4.14 (2H, m), 3.97 (1H, d, $J = 3.8$ Hz), 3.50 (2H, m), 2.46 (1H, dt, $J = 13.5, 6.9$ Hz), 2.25 (1H, m), 2.08 (3H, s), 2.05 (3H, s), 1.98 (1H, m), 1.76 - 1.58 (5H, m), 1.25 (3H, s), 1.18 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 170.5, 138.6, 128.4, 127.7, 127.6, 84.6, 83.0, 79.2, 78.8, 76.6, 75.6, 72.9, 70.1, 38.0, 34.3, 32.8, 27.9, 26.4, 22.2, 21.3, 21.1; MS (70eV, EI) 434, 374, 343, 277, 218; HRMS calcd for $\text{C}_{24}\text{H}_{34}\text{O}_7$ 434.2305; found 434.2297.