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LETTERS

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

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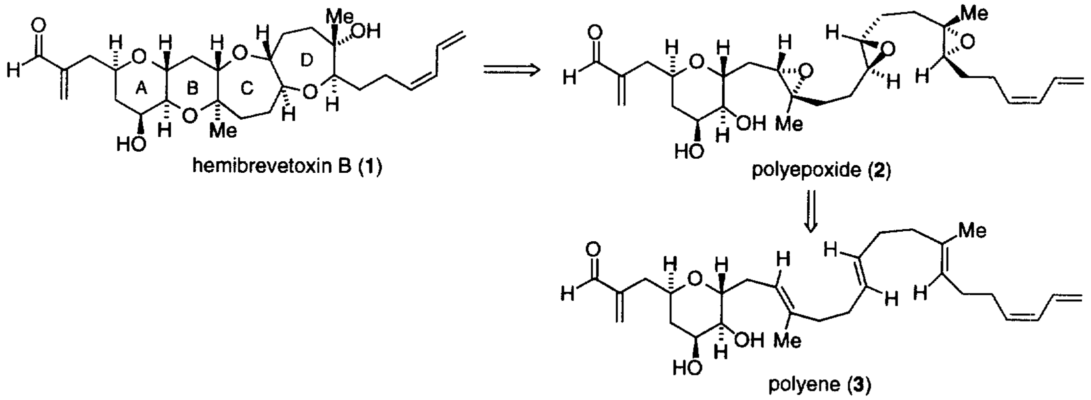
Abstract: Acid-catalyzed cyclization of hydroxy-cyclic sulfates occurs with *endo*-regioselectivity affording bispyran products from substrates in which the nucleophilic hydroxyl and electrophilic cyclic sulfate groups are 1,2-*trans*-substituted on a cyclic pyran template. This methodology is demonstrated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

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



hemibrevetoxin B (**1**)

polyepoxide (**2**)

polyene (**3**)

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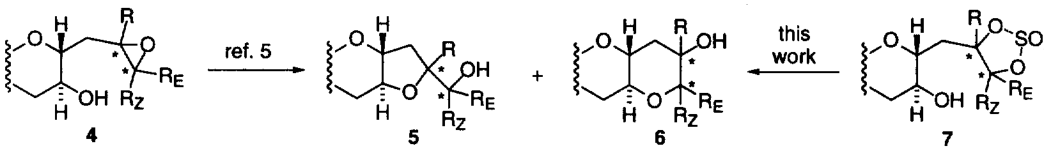
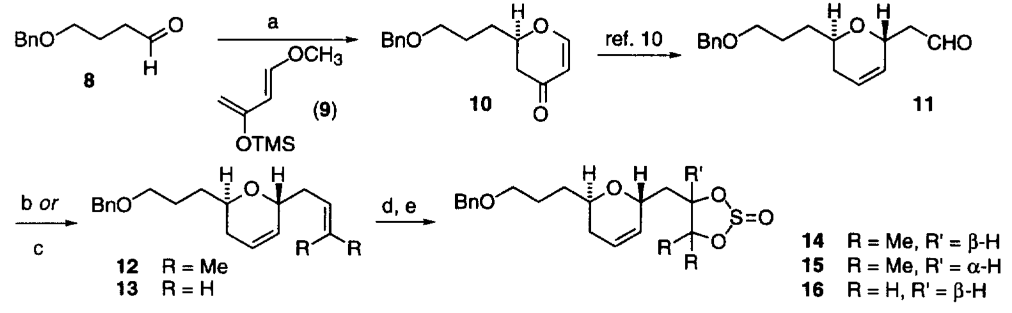
Electrophile-promoted hydroxyalkene cyclizations and acid-catalyzed hydroxyepoxide cycloisomerizations generally proceed via exocyclic pathways (i.e. **4** → **5**, Figure 2) unless carbocation-stabilizing groups are present at R_E and/or R_Z.[5,6] However, selenium[7] and tellurium-promoted[8] *endo*-cyclizations 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 electrophiles[9] (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 cyclocondensation[11] 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**

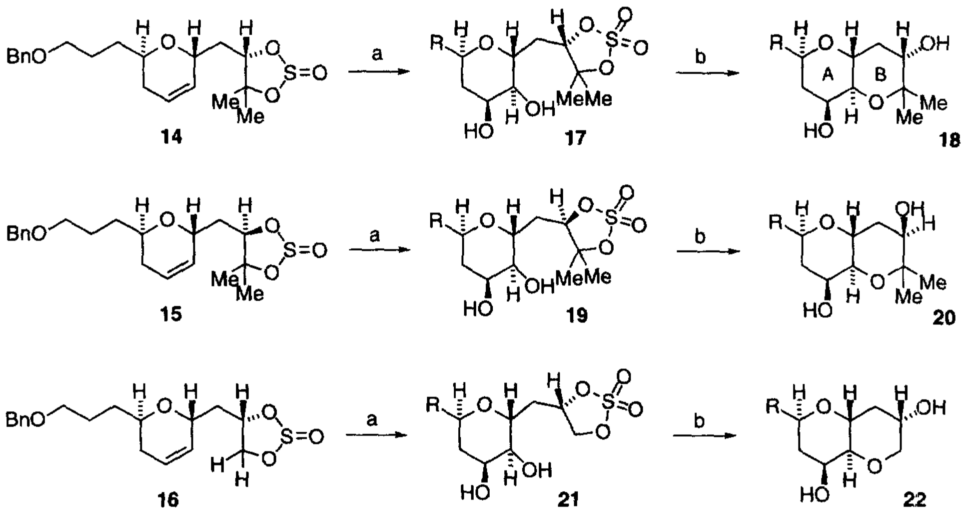


Reagents and Conditions: (a) (*S*)-BINOL / $Ti(O\text{-}i\text{-}Pr)_4$ / CF_3CO_2H, 4Å MS, Et_2O; then CF_3CO_2H (65% yield, 95% ee). (b) $(CH_3)_2CHPPh_3Br$ / *n*-BuLi, Et_2O, 0°C (40% yield). (c) CH_3PPh_3Br / *n*-BuLi, THF, 0°C (52% yield). (d) AD-mix α or β, $CH_3SO_2NH_2$, *t*-BuOH : H_2O (1:1), 0°C to 20°C (see text). (e) imidazole / $SOCl_2$, 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-*alpha*, 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 ^{1}H-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. $RuCl_3 \cdot 3H_2O$, $NaIO_4$, EtOAc : CH_3CN : H_2O (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}; ^{1}H 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 $C_{24}H_{34}O_7$ 434.2305: found 434.2297.