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Total Synthesis of Truncated Brevetoxin B [AFGHIJK]

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Brevetoxin B (1),¹ a member of the "red tide"-associated class of marine neurotoxins,² possesses a striking biological profile as a sodium channel modulator³ and a formidable molecular structure that includes 11 fused rings and 23 stereocenters. Several synthetic methods and schemes have been advanced toward the synthesis of this molecule,^{4,5} but to date, no total synthesis of brevetoxin B (1) or designed analogs have been reported. Herein we report the design and synthesis of a novel version of this compound, truncated brevetoxin B [AFGHIJK] (2), in which all the functionality within the natural compound is present, except for the internal rings BCDE (Figure 1). Such a design was considered important in that it could test the "length hypothesis" of the brevetoxins^{3a,b} and provide useful information about their receptor.^{3c-e}

An attractive bond disconnection across the oxocene ring of 2 revealed two domains (3 and 4) that could be coupled in the synthetic direction *via* a Wittig reaction and cyclized to produce the desired polycyclic framework.

This convergent synthesis began with the construction of intermediates 3 (Scheme 1) and 4 (Scheme 2). Swern oxidation of the alcohol 5⁶ (Scheme 1) followed by addition of MeMgBr and subsequent reoxidation gave rise to ketone 6 in 94% overall yield. After desilylation, the liberated alcohol 7 was converted to the bromoacetate ester 8, which upon exposure to (MeO)₃P at 180 °C afforded the phosphonate 9 in 74% overall yield from 6. A modified Horner-Emmons⁷ reaction was then used for the ring closure of 9 to 10 (88%). Reduction of 10 to the corresponding dihydropyran 12 was achieved by sequential treatment with DIBALH and BF₃·Et₂O/Et₃SiH *via* the intermediacy of lactol

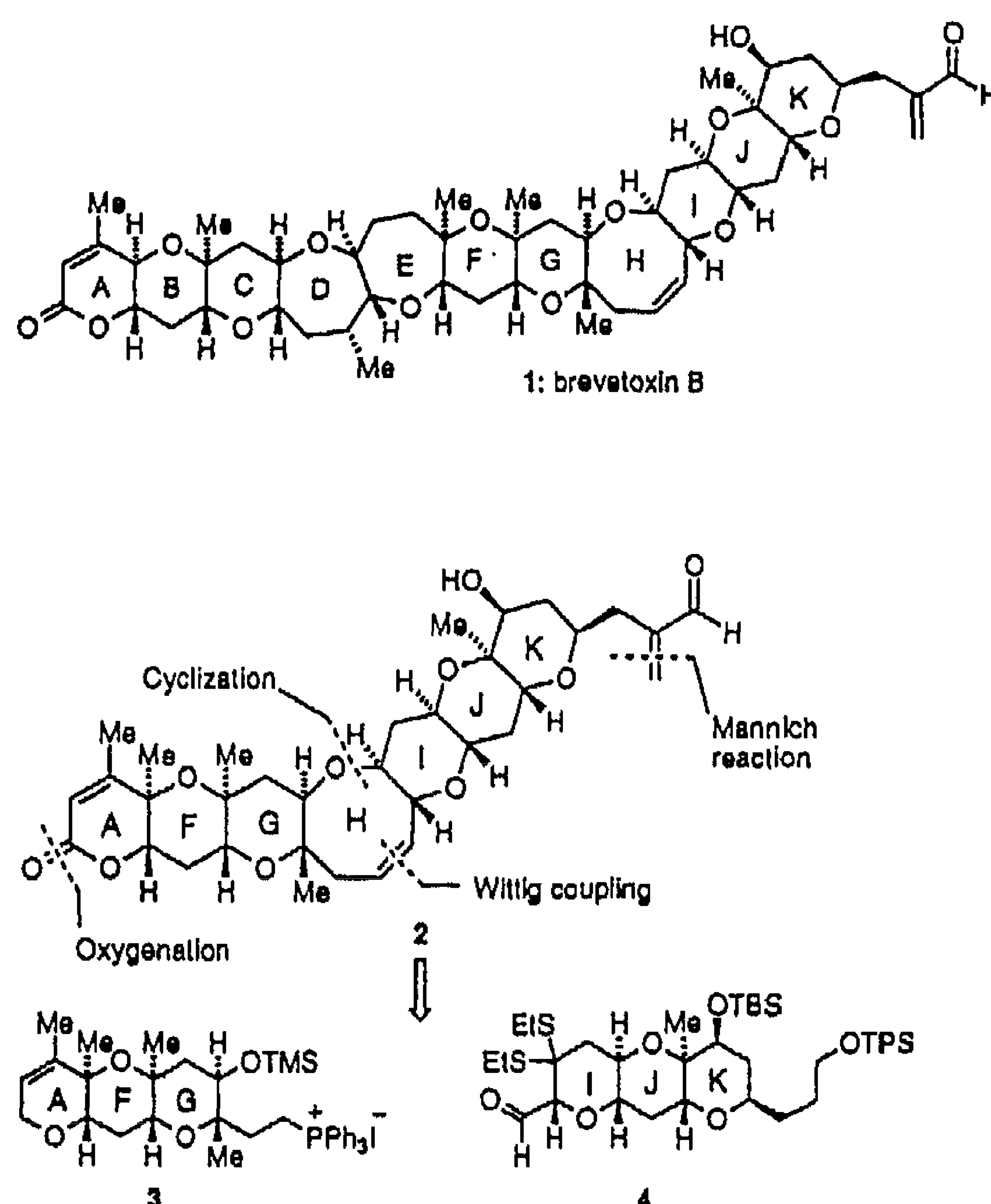
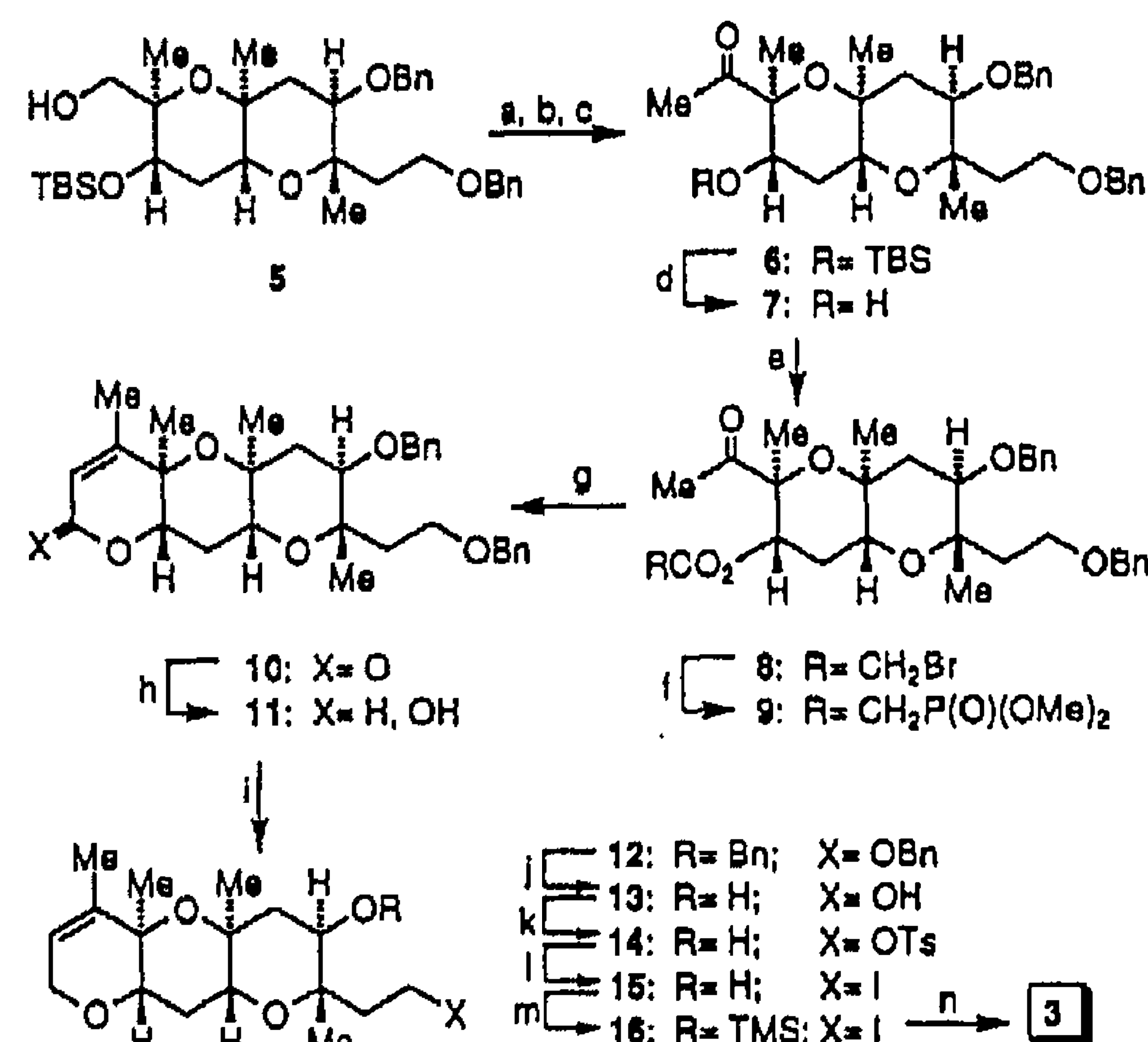


Figure 1. Structure of truncated brevetoxin B [AFGHIJK] (2) and retrosynthetic analysis.

Scheme 1.^a Synthesis of the AFG Ring System 3

^a Reagents and conditions: (a) 2.0 equiv of (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, -78 °C, then 7.0 equiv of Et₃N, 1 h, 100%; (b) 2.0 equiv of MeMgBr, THF, 0 °C, 1 h, 96%; (c) 2.0 equiv of (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, -78 °C, then 7.0 equiv of Et₃N, 1 h, 98%; (d) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; (e) 2.0 equiv of BrCH₂COCl, 4.0 equiv of pyridine, CH₂Cl₂, 0 °C, 5 h, 82%; (f) neat (MeO)₃P, 180 °C (sealed tube), 3 h, 90%; (g) 2.0 equiv of ^tPr₂EtN, 2.0 equiv of LiCl, CH₃CN, 25 °C, 3 h, 88%; (h) 1.5 equiv of DIBALH, CH₂Cl₂, -78 °C, 0.5 h, 98%; (i) 1.0 equiv of BF₃·Et₂O, 5.0 equiv of Et₃SiH, CH₂Cl₂, -10 °C, 0.5 h, 97%; (j) 10.0 equiv of Li, NH₃, THF, -78 °C, 1.5 h, 100%; (k) 1.1 equiv of TsCl, 3.0 equiv of pyridine, CH₂Cl₂, 25 °C, 12 h, 70%; (l) 5.0 equiv of NaI, acetone, 60 °C, 12 h, 83%; (m) 1.5 equiv of TMS-imidazole, CH₂Cl₂, 25 °C, 0.5 h, 100%; (n) 8.0 equiv of PPh₃, CH₃CN, 65 °C, 15 h, 100%. TBS = Si^tBuMe₂, Bn = CH₂Ph, TMS = SiMe₃, TsO = tosylate.

11 (95%). Debenzylation of 12 to the diol 13 followed by selective monotosylation and displacement with NaI of the primary tosylate 14 led to 15 in 58% overall yield. Finally, protection of the secondary alcohol in 15 as a TMS ether and treatment with PPh₃ gave phosphonium salt 3 in quantitative yield.

The construction of aldehyde 4 commenced with diol 17⁸ (Scheme 2), which was first protected as an acetonide and then

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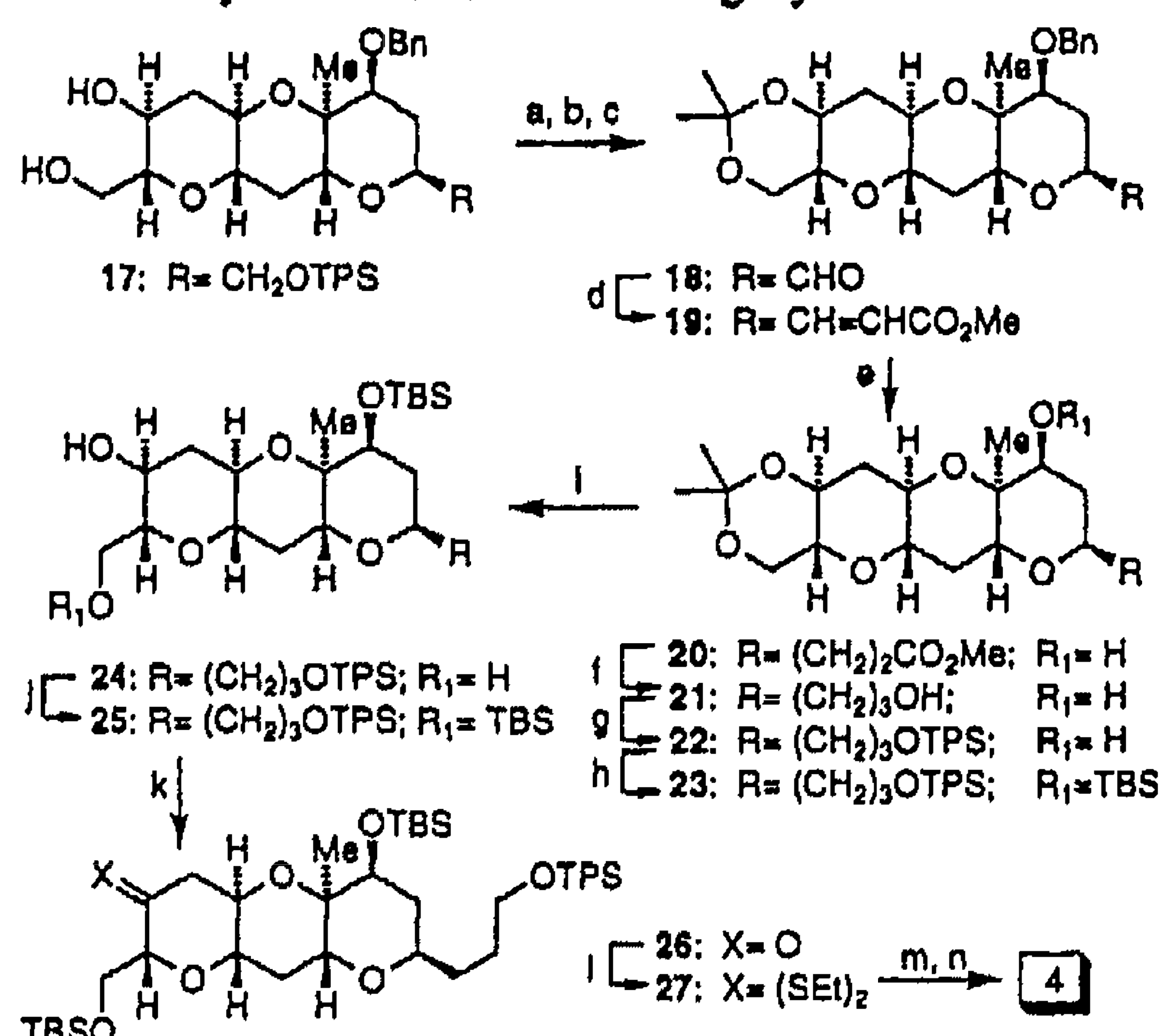
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Scheme 2.^a Synthesis of the IJK Ring System 4

^a Reagents and conditions: (a) 3.0 equiv of $\text{CH}_2=\text{C}(\text{OMe})\text{Me}$, 0.2 equiv of CSA, CH_2Cl_2 , 25 °C, 4 h, 89%; (b) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 97%; (c) 2.0 equiv of $(\text{COCl})_2$, 3.0 equiv of DMSO, CH_2Cl_2 , -78 °C, 0.5 h, then 7.0 equiv of Et_3N , 100%; (d) 2.0 equiv of $\text{Ph}_3\text{P}-\text{CHCO}_2\text{Me}$, CH_2Cl_2 , 25 °C, 5 h, 96% (*E:Z* = 4:1); (e) H_2 , $\text{Pd}(\text{OH})_2$, THF, 25 °C, 40 psi, 14 h, 100%; (f) 2.0 equiv of LiAlH_4 , THF, 25 °C, 4 h, 92%; (g) 1.1 equiv of TPSCl, 2.0 equiv of Et_3N , 0.1 equiv of DMAP, CH_2Cl_2 , 25 °C, 6 h, 95%; (h) 2.0 equiv of TBSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2 , 0 °C, 0.5 h, 100%; (i) 0.2 equiv of CSA, 1:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 0 °C, 2 h, 87%; (j) 1.0 equiv of TBSCl, 2.0 equiv of imidazole, DMF, 0 °C, 1 h, 94%; (k) 1.5 equiv of NMO, 0.02 equiv of TPAP, CH_3CN , 25 °C, 1 h, 96%; (l) 3.0 equiv of EtSH, 1.1 equiv of $\text{Zn}(\text{OTf})_2$, CH_2Cl_2 , 25 °C, 3 h; (m) 0.2 equiv of CSA, MeOH, 25 °C, 1 h, 74% (over two steps); (n) 5.0 equiv of SO_2 -pyridine, 5.0 equiv of Et_3N , 1:1 $\text{CH}_2\text{Cl}_2/\text{DMSO}$, 0 °C, 1.5 h, 92%. TBS = Si^tBuMe_2 , TPS = Si^tBuPh_2 , Bn = CH_2Ph , NMO = 4-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

converted *via* desilylation, oxidation, and a Wittig reaction to the unsaturated ester 19 (*ca.* 4:1 *E:Z* isomers, 83% overall yield) through aldehyde 18. Sequential treatment of 19 with $\text{H}_2/\text{Pd}(\text{OH})_2$ and LiAlH_4 followed by selective silylation of the resulting hydroxyl groups furnished 23 in 87% overall yield. Removal of the acetonide and selective protection of the primary alcohol, followed by oxidation of the secondary alcohol, provided the corresponding ketone 26 in 79% yield. Thioketalization of 26 and hydrolytic cleavage of the primary TBS ether afforded alcohol 27, which was oxidized to the requisite aldehyde 4 (68% overall yield).

Generation of the ylide from 3, followed by reaction with aldehyde 4, produced the *Z*-olefin 28 (Scheme 3) in 57% yield (based on 3). Desilylation of 28, followed by AgClO_4 -induced cyclization and desulfurization,⁹ provided oxocene 29 in 80% overall yield. Oxidation of 29 with PCC gave lactone 30 in 66% yield. Finally desilylation of 30, followed by oxidation and treatment of the resulting aldehyde 31 with Eschenmoser's salt¹⁰ secured, upon desilylation, the targeted 2 in 61% overall yield. X-ray crystallographic analysis of 2 (mp 218 °C, from methanol/petroleum ether) confirmed its structure (see ORTEP drawing, Figure 2).

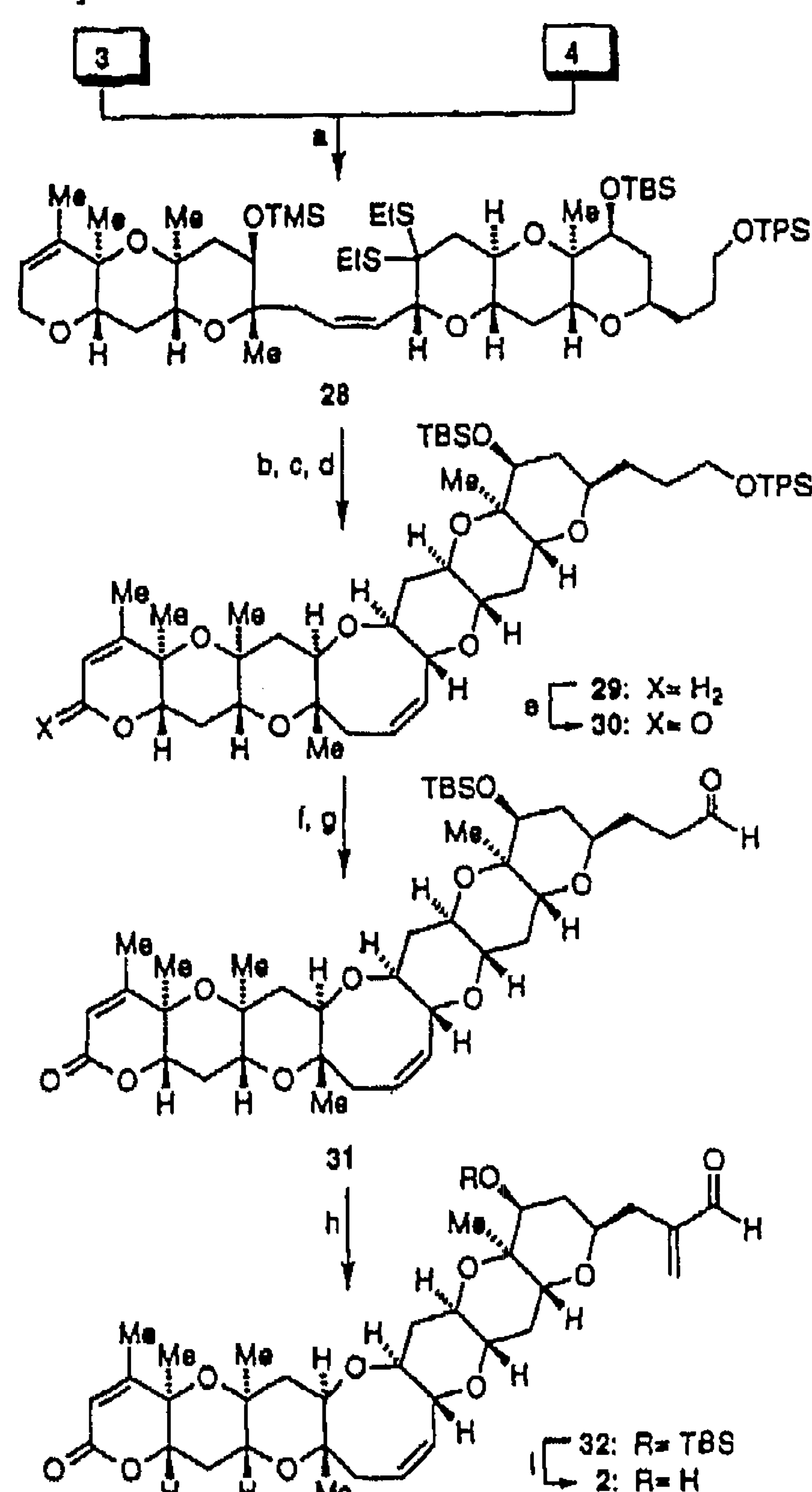
Truncated brevetoxin B [AFGHJK] (2), lacking the BCDE ring segment of the parent compound (1), has a head-to-tail length of 20.4 Å as opposed to *ca.* 30 Å^{1,3a} for 1. Biological studies¹¹ with 2 revealed no binding to the brevetoxin B receptor, supporting the notion that the length of the molecule is crucial for biological activity.^{3a,b} The described chemistry sets the stage for the total synthesis of the natural brevetoxin B (1) and for further chemical biology studies.

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(11) We thank Professor D. G. Baden for these biological studies.

Scheme 3.^a Synthesis of Truncated Brevetoxin B [AFGHJK] 2

^a Reagents and conditions: (a) 1.0 equiv of *n*-BuLi, 2.0 equiv of HMPA, THF, -78 → 25 °C, 1 h, 57%; (b) 0.2 equiv of PPTS, 1:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 25 °C, 1 h, 91%; (c) 4.0 equiv of AgClO_4 , 2.0 equiv of NaHCO_3 , SiO_2 , 4-Å molecular sieves, CH_3NO_2 , 25 °C, 30 h, 90%; (d) 4.0 equiv of Ph_3SnH , 0.1 equiv of AIBN, toluene, 100 °C, 2 h, 98%; (e) 8.0 equiv of PCC, CH_2Cl_2 , 60 °C (sealed tube), 4 h, 66%; (f) 2.0 equiv of TBAF, THF, 25 °C, 13 h, 79%; (g) 3.0 equiv of Dess-Martin periodinane, CH_2Cl_2 , 25 °C, 2 h, 100%; (h) 2.0 equiv of $\text{Me}_2\text{N}=\text{CH}_2^+\text{I}^-$, 20 equiv of Et_3N , CH_2Cl_2 , 25 °C, 12 h, 79%; (i) HF-pyridine, CH_2Cl_2 , 25 °C, 30 min, 97%. TBS = Si^tBuMe_2 , TPS = Si^tBuPh_2 , TMS = SiMe_3 .

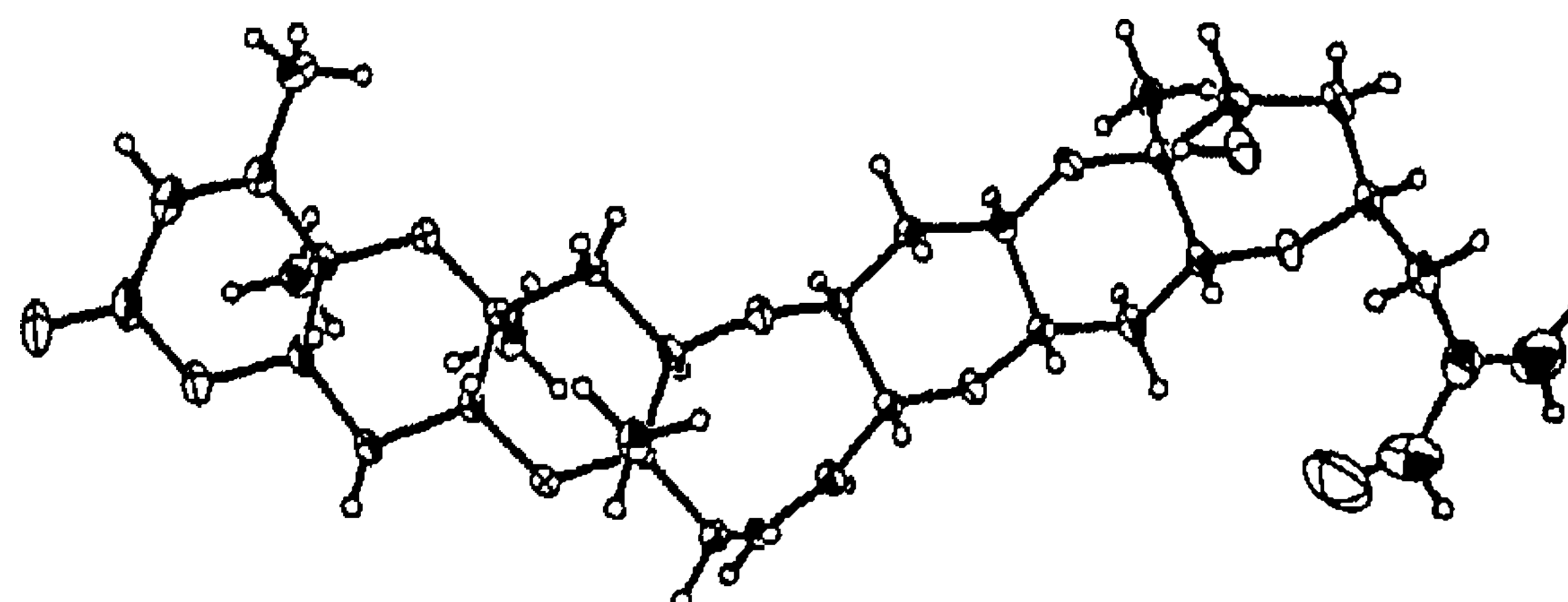


Figure 2. ORTEP drawing of truncated brevetoxin B [AFGHJK] 2.

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Supplementary Material Available: Characterization data for compounds 2 (including X-ray crystallographic parameters), 16, 27–30, and 32 (19 pages); listing of observed and calculated structure factors for 2 (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.