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## Total Synthesis of Brevetoxin B. 1. CDEFG Framework

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With its imposing structure, brevetoxin B (1), produced by *Gymnodinium breve* Davis, stood as a formidable challenge to synthetic chemists since its discovery and structural elucidation in 1981.<sup>1</sup> Brevetoxin's beautifully arranged molecular assembly includes 11 *trans*-fused rings, each containing an oxygen atom, with each fusion consisting of a C-C bond separating two adjacent ring oxygens and with all adjacent substituents flanking the oxygens placed *syn* to each other except on ring K. Its unprecedented architecture, its association with the "red tide" catastrophes,<sup>2</sup> and its potent neurotoxicity and interference with the function of sodium channels attracted serious attention from chemists<sup>3</sup> and biologists<sup>4</sup> alike. We now wish to announce, in this and the following communication,<sup>5</sup> the total synthesis of brevetoxin B (1) in its naturally occurring form.

Figure 1 outlines the strategic bond disconnections and retrosynthetic analysis of 1. The adopted strategy benefited from convergency (oxocene disconnections) and synthetic technologies developed in these laboratories specifically for constructing oxocene<sup>6</sup> and tetrahydropyran<sup>7</sup> systems.

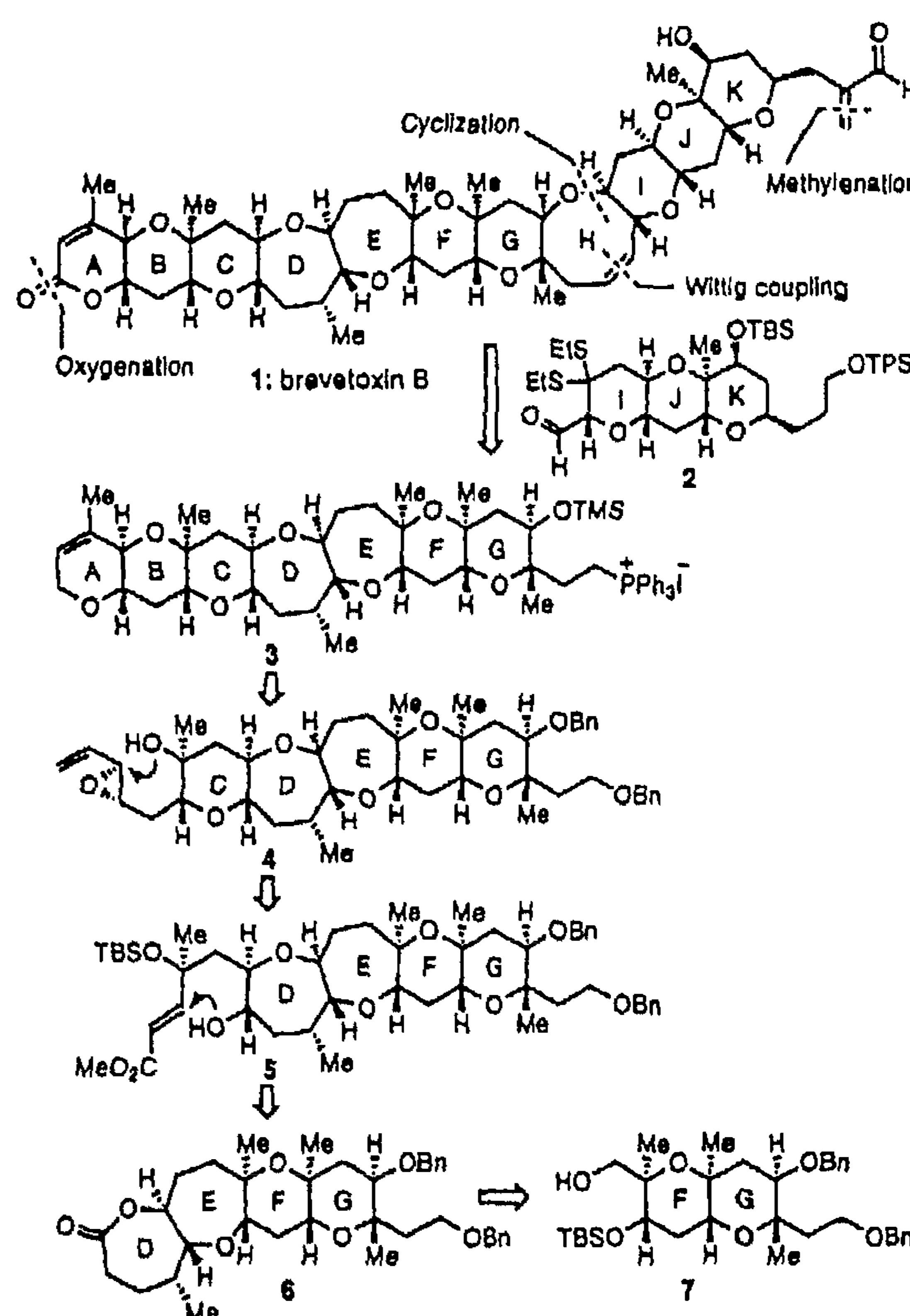


Figure 1. Strategic bond disconnections and retrosynthetic analysis of brevetoxin B (1).

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The construction of the CDEFG framework 4 described herein began with the previously reported intermediate 7 (Scheme 1).<sup>8</sup> Swern oxidation of 7 followed by a Wittig reaction with the appropriate reagent furnished, in 99% overall yield, compound 9 via aldehyde 8. Hydrogenation of 9 and selective, acid-induced monodesilylation gave alcohol 11 via 10 in 97% overall yield. Oxidation of 11 in a sequential fashion using Swern and NaClO<sub>2</sub> conditions resulted in carboxylic acid 12 (97%), which upon desilylation with TBAF led to 13 (91%). Lactonization of hydroxy acid 13 by the Yamaguchi method<sup>9</sup> and enol triflate formation gave 15 via 14 in 84% overall yield. Generation of the higher order cuprate derived from the lithio derivative of iodide 17a<sup>10</sup> and 17b followed by coupling<sup>11</sup> with triflate 15 and partial acid-induced orthoester hydrolysis resulted in formation of 18 via 16 (84% yield over two steps, *ca.* 2.4:1 ratio at C\* in favor of the desired isomer, *vide infra*). Regio- and stereoselective hydroboration of 18 followed by oxidative workup and alkaline hydrolysis furnished hydroxy acid 19 in 73% overall yield. Finally, lactonization<sup>9</sup> of 19 and separation of the C\* epimers afforded pure lactone 6 (60% yield, plus 25% of its C\* methyl epimer), whose structure was determined by X-ray crystallographic analysis (see ORTEP drawing of a derivative<sup>10</sup> of 6, Figure 2).

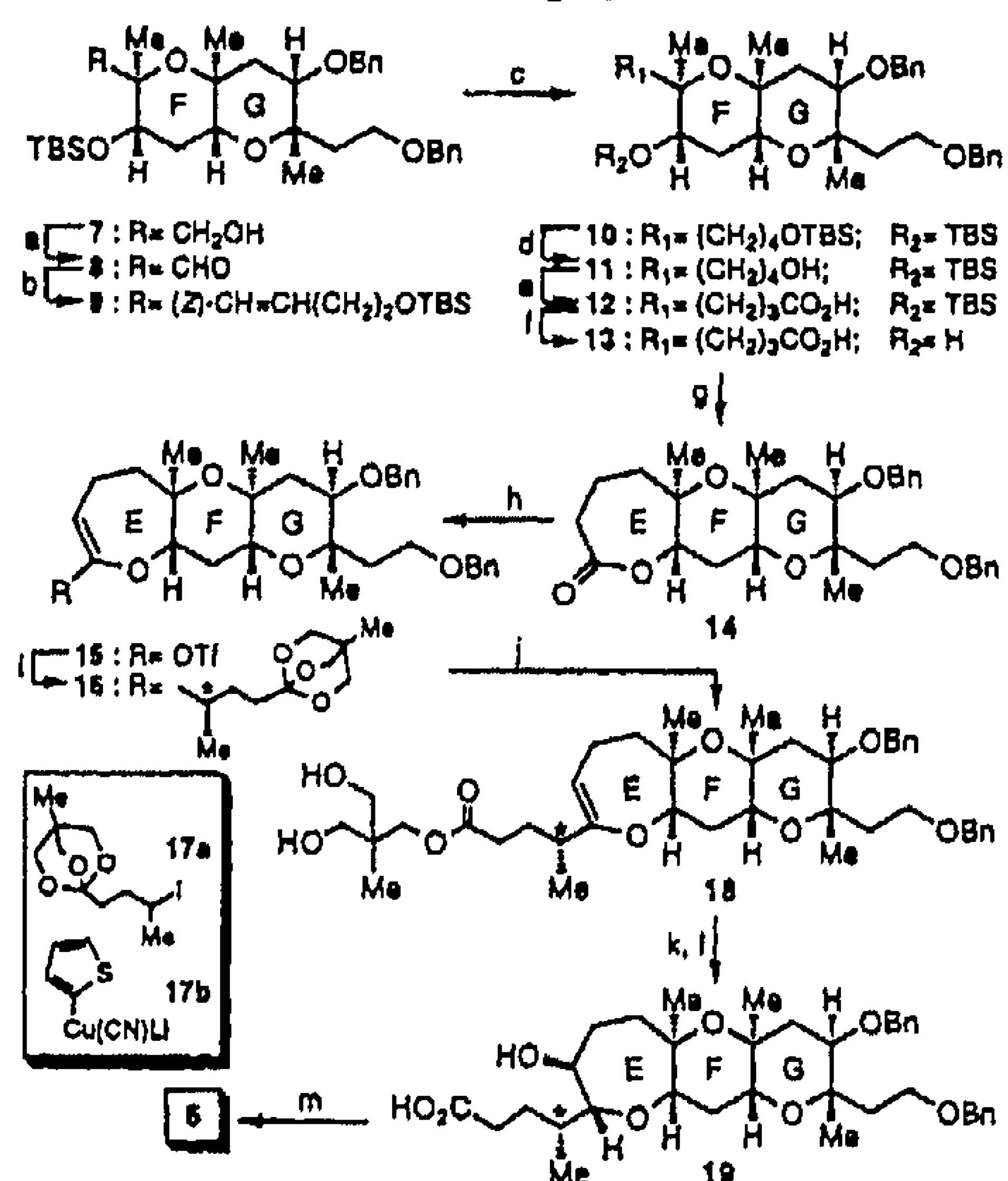
The fusion of the remaining three rings onto the DEFG system 6 to afford the targeted polycyclic framework 4 proceeded as depicted in Scheme 2. Thus, conversion of lactone 6 to its enol triflate (97%) followed by Cr/Ni-mediated coupling<sup>12</sup> with

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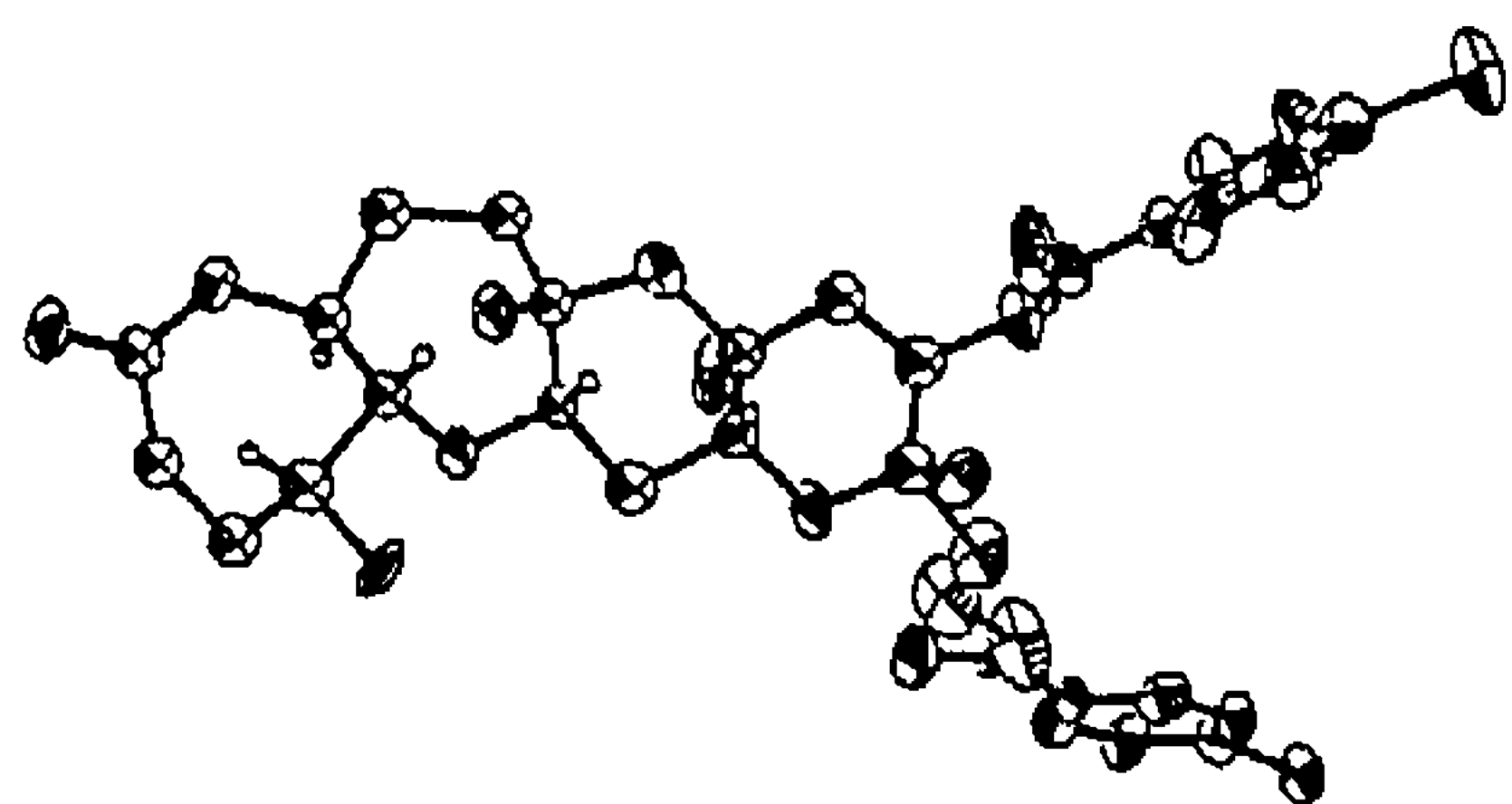
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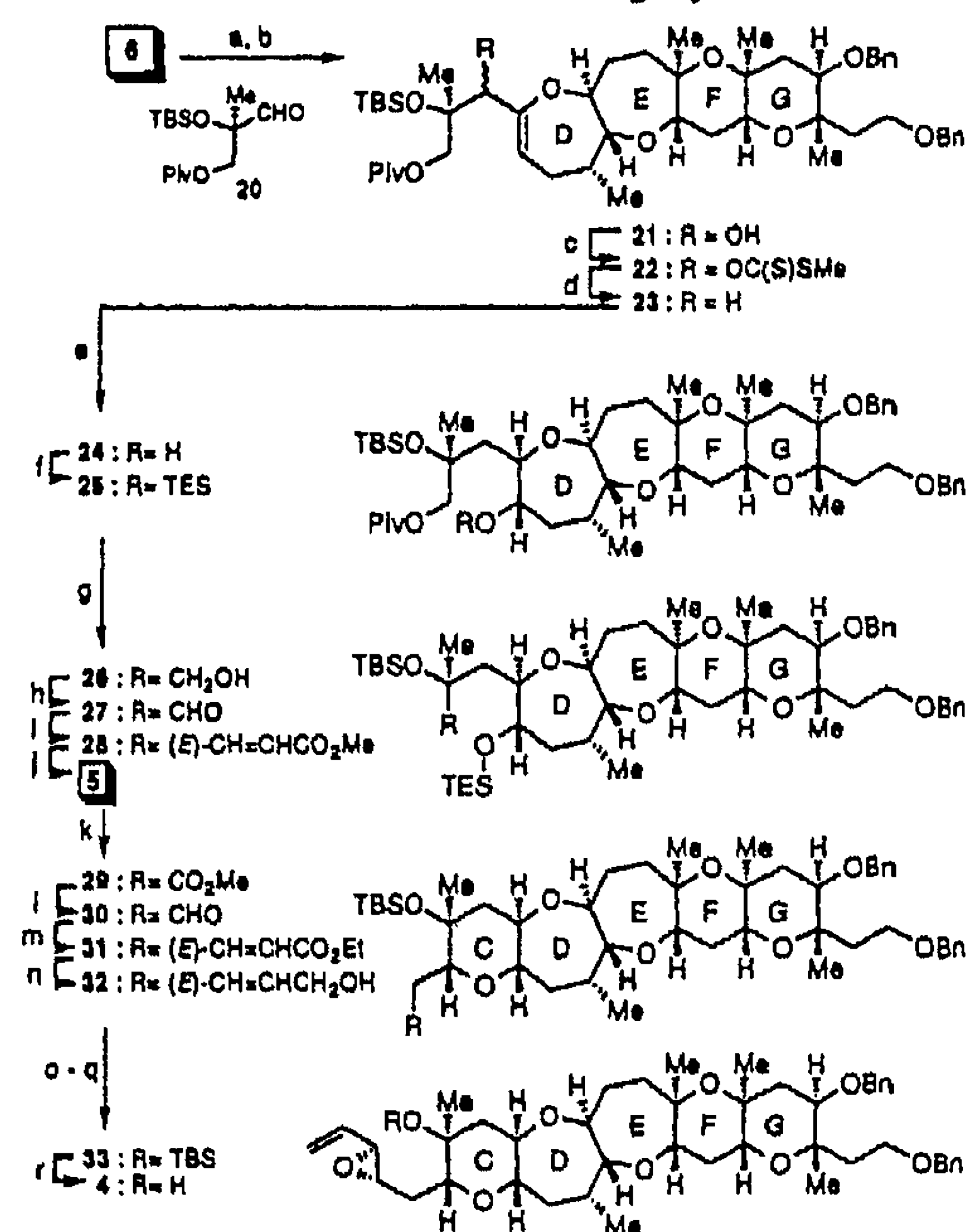
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Scheme 1. Construction of DEFG Ring System 6<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) 2.0 equiv of (COCl)<sub>2</sub>, 3.0 equiv of DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, then 7.0 equiv of Et<sub>3</sub>N, 0.5 h, 100%; (b) 2.0 equiv of TBSO(CH<sub>2</sub>)<sub>3</sub>PPh<sub>3</sub><sup>+</sup>I<sup>-</sup>, 1.5 equiv of NaHMDS, THF, 0 °C, 10 min, then 8, 0.5 h, 99%; (c) H<sub>2</sub>, 0.1 equiv of Pd/C (10%), 0.1 equiv of Na<sub>2</sub>CO<sub>3</sub>, EtOAc, 25 °C, 12 h, 100%; (d) 1.0 equiv of CSA, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), 0 °C 1 h, 97%; (e) 2.0 equiv of (COCl)<sub>2</sub>, 3.0 equiv of DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, then 7.0 equiv of Et<sub>3</sub>N, 0.5 h; 1.5 equiv of NaClO<sub>2</sub>, 2.0 equiv of NaH<sub>2</sub>PO<sub>4</sub>, 2.0 equiv of 2-methyl-2-butene, *t*-BuOH/H<sub>2</sub>O (2:1), 25 °C, 1 h, 97%; (f) 5.0 equiv of TBAF, THF, 65 °C, 8 h, 91%; (g) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et<sub>3</sub>N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (*c* = 0.05 mM), 80 °C, 1 h, 90%; (h) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 2 h, then 1.5 equiv of Tf<sub>2</sub>NPh, -78 → 25 °C, 93%; (i) 6.0 equiv of 17a, 10.0 equiv of *t*-BuLi, Et<sub>2</sub>O, -120 → -78 °C, 0.5 h, then 5.0 equiv of 17b, -78 → 30 °C, 0.5 h, Et<sub>2</sub>O/THF/HMPA (1:1:1), then 15, -78 → 0 °C, 2 h, 84%; (j) 0.3 equiv of PPTS, DME/H<sub>2</sub>O (1:1), 25 °C, 100%; (k) 6.0 equiv of BH<sub>3</sub>·THF, 0 °C, then 25 equiv of 3 N NaOH, 50 equiv of 30% H<sub>2</sub>O<sub>2</sub>, 89%; (l) 2.0 equiv of LiOH, DME/H<sub>2</sub>O (1:1), 25 °C, 82%; (m) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et<sub>3</sub>N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (*c* = 0.05 mM), 80 °C, 1 h, 60% of 6, plus 25% of its C\* epimer (after column chromatography).

Figure 2. ORTEP of the bis(*p*-bromobenzoyl) derivative of 6.

aldehyde 20<sup>10</sup> furnished alcohol 21 (66%, mixture of epimers), which was deoxygenated via xanthate 22 (89%) by the Barton method<sup>13</sup> to afford 23 (67%). Regio- and stereospecific hydration of 23 via hydroboration/oxidation gave alcohol 24 (82%), which was silylated, leading to 25 (96%). A series of reactions involving DIBAL-H-mediated ester cleavage (98%), Dess–Martin oxidation (85%), Horner–Emmons olefination (99%), and acid-induced selective desilylation (100%) afforded α,β-unsaturated ester 5 via 26, 27 and 28. Exposure of 5 to KH led to the formation of the CDEFG ring system 29 in 90%

Scheme 2. Construction of CDEFG Ring System 4<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 2 h, then 1.5 equiv of Tf<sub>2</sub>NPh, -78 → 25 °C, 97%; (b) 6.0 equiv of 20, 6.0 equiv of CrCl<sub>2</sub>, 0.02 equiv of NiCl<sub>2</sub>, DMF, 25 °C, ultrasound, 3 h, 66%; (c) 3.0 equiv of CS<sub>2</sub>, 50.0 equiv of KH (added over 5 h), Et<sub>2</sub>O, then 10.0 equiv of MeI, 25 °C, 89%; (d) 4.0 equiv of *n*-Bu<sub>3</sub>SnH, 0.1 equiv of AIBN, benzene, 80 °C, 67%; (e) 5.0 equiv of BH<sub>3</sub>·THF, -30 °C, then 25 equiv of 3 N NaOH, 50 equiv of 30% H<sub>2</sub>O<sub>2</sub>, 82%; (f) 2.0 equiv of TESOTf, 2.5 equiv of 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, -70 °C, 1 h, 96%; (g) 2.5 equiv of DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 5 min, 98%; (h) 1.7 equiv of Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 2 h, 85%; (i) 2.0 equiv of KHMDS, 0.2 equiv of 18-crown-6, 5.0 equiv of (MeO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Me, THF, 0 °C, 0.5 h then add 27, 3 h, 99%; (j) 1.0 equiv of CSA, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (2:1), 25 °C, 1 h, 100%; (k) 2.0 equiv of KH, THF, 25 °C, 2 h, 90%; (l) 1.3 equiv of DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 min, then 3.0 equiv of MeOH, 97%; (m) 2.0 equiv of Ph<sub>3</sub>PCHCO<sub>2</sub>Et, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 12 h, 98%; (n) 2.5 equiv of DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 h, 96%; (o) 0.2 equiv of Ti(O<sup>*i*</sup>Pr)<sub>4</sub>, 0.2 equiv of (+)-diethyl tartrate, 2.0 equiv of *t*-BuOOH (5 N in decane), CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 5 h, 99%; (p) 5.0 equiv of SO<sub>3</sub>·pyridine, 10 equiv of Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>/DMSO (4:1), 0 °C; (q) 1.2 equiv of NaHMDS, 1.5 equiv of CH<sub>3</sub>PPh<sub>3</sub><sup>+</sup>Br<sup>-</sup>, THF, 25 °C, 1 h, 80% (over two steps); (r) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 100%.

yield via a stereoselective Michael-type reaction.<sup>14</sup> Extension of the ester side chain via DIBAL-H reduction and phosphorane condensation furnished, via aldehyde 30 (97%), the α,β-unsaturated ester 31 (98%), which was reduced to allylic alcohol 32 (96%). Sharpless asymmetric epoxidation<sup>15</sup> of 32 using (+)-DET as the chiral auxiliary gave the corresponding hydroxy epoxide (99% yield), which was further oxidized to the aldehyde and subjected to a Wittig reaction to afford terminal olefin 33 (80% over two steps), and thence hydroxy epoxide 4 upon TBAF-induced desilylation (100%).

The elaboration of 4 to the ABCDEFG framework 3, the coupling of the latter to the IJK system 2 and the completion of the total synthesis of brevetoxin B (1) are described in the following communication.<sup>5,16</sup>

**Acknowledgment.** See following communication.<sup>5</sup>

**Supplementary Material Available:** See following communication.<sup>5</sup>

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(16) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.