Activation of 6-*endo* over 5-*exo* Epoxide Openings. Ring-selective Formation of Tetrahydropyran Systems and Stereocontrolled Synthesis of the ABC Ring Framework of Brevetoxin B

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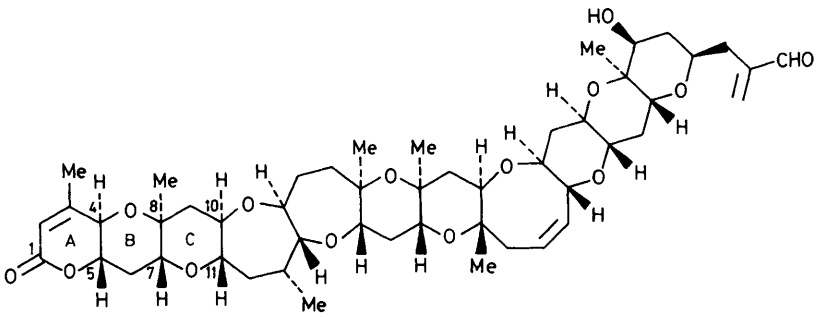
A new synthetic strategy for the regio- and stereo-specific synthesis of tetrahydropyran systems involving 6-*endo* epoxide openings and its application to the construction of the ABC ring system of brevetoxin B are described.

In a programme directed towards the total synthesis of the complex marine toxin brevetoxin B (**1**),[1] currently under way in these laboratories, we needed stereospecific methods for the construction of tetrahydropyran systems. Our present strategy reduces this problem to (a) allylic alcohol formation; (b) epoxidation; and (c) epoxide openings. While for solutions to operations (a) and (b) we could turn to existing methods, a well defined strategy for the regioselective 6-*endo* openings of epoxides by internal nucleophilic oxygen was absent.[2] In this communication we report a stereospecific route to tetrahydropyrans from epoxy-alcohols *via* activation of the 6-*endo* over the usually favoured 5-*exo*[3] modes of epoxide opening and the application of this new technology to the stereocontrolled synthesis of the ABC ring system of brevetoxin B (**1**) in enantiomerically pure form.

Scheme 1 focuses on the present problem and its solution.

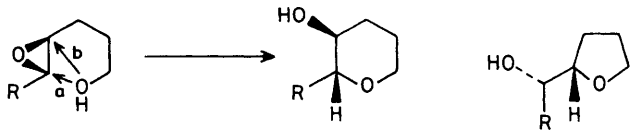


Brevetoxin (1)

Theoretically, the epoxy-alcohol (I) could suffer ring closure (under acidic or basic conditions) *via* a 5-*exo* mode (path **b**) or a 6-*endo* (path **a**) mode of cyclization leading to a tetrahydrofuran or a tetrahydropyran system respectively. When both carbon atoms bonded to oxygen are secondary and the adjacent centres are sp^3 as in case (**2**) conventional considerations suggest the 5-*exo* mode (path **b**) of cyclization as the preferred pathway based mainly on geometric and kinetic constraints. Indeed, experiment confirms this hypothesis, the tetrahydrofuran system (**2b**) being the exclusively observed product (CSA cat., CH_2Cl_2, −20 to 25 °C). The placement of a suitable substituent in group R with the ability to weaken the adjacent C–O bond and/or stabilize an adjacent positive charge was expected to reverse this ring selectivity, favouring the 6-*endo* ring closure and the formation of the tetrahydropyran system. A carbon–carbon π bond, being simple to introduce and useful for further elaboration, was chosen as a 'director functionality,' as seen in Scheme 1. Substrates (**3**), (**4**), and (**5**) were expected to show increasing ability to favour the 6- over the 5-membered ring on electronic grounds. Indeed, (**3**) exhibited partially the expected effect [CSA cat., CH_2Cl_2, −40 to 25 °C, *ca.* 60 : 40 mixture of (**3a**) and (**3b**)] and (**4**) and (**5**) produced, exclusively and in high yield, the corresponding tetrahydropyran systems (**4a**) and (**5a**).† The starting substrates (I) can be prepared by a general, highly efficient strategy and in high enantiomeric purity‡ and the described cyclizations proceed in excellent yields with complete regio- and stereo-control (inversion).§

The potential of this technology for the construction of several of the 6-membered rings of brevetoxin B (**1**) is obvious. Below we demonstrate its applicability in the brevetoxin B project and in complex situations with the synthesis of the key intermediates (**25**) and (**26**) (Scheme 2), containing the ABC ring framework of this target molecule.¶ Reaction of the commercially available tri-*O*-acetyl-D-glucal (**6**) and allyltrimethylsilane in CH_2Cl_2 in the presence of $TiCl_4$[4] at −78 °C yielded, after treatment with potassium carbonate in methanol, the *C*-glycoside diol (**7**) in 95% overall yield and *ca.* 10 : 1 α : β anomeric ratio. Compound (**7**) was then transformed by standard methods to the aldehyde (**10**) *via* the tosylate (**8**) and the nitrile (**9**) in 80% overall yield. Condensation of (**10**) with excess of $Ph_3P{=}CHCO_2Me$ led to the hydroxy-ester (**11**) (86%) which was then smoothly converted into the ketone (**12**) by Swern oxidation.[5] While a number of organometallic reagents (*e.g.* Li, Mg, and Ti) failed to give the desired selectivity, the use of $AlMe_3$ led to remarkable results. Reaction of $AlMe_3$ with (**12**) in 1 : 1 stoicheiometry (CH_2Cl_2, PhMe, −15 °C) proceeded in excellent yield but with a 20 : 1 preference for (**13**) by β-attack, whereas slow addition of (**12**) to excess of $AlMe_3$ (4 equiv.) reversed the preference of attack resulting in a *ca.* 3 : 1 ratio of (**14**) to its epimer [94% total yield from (**11**)] as expected from the elegant studies of Ashby *et al.*[6] Silylation of pure (**14**) followed by reduction (Bu^i_2AlH) of the ester group and Sharpless asymmetric epoxidation[7] led to the epoxide (**15**) (64% overall) which was then oxidized under Swern conditions and treated with Ph_3P–CBr_4[8] to give, after desilylation, the hydroxy-epoxide (**16**) (63% overall yield).

6-*endo*-Cyclization of (**16**) was then smoothly effected by catalytic amounts of CSA (CH_2Cl_2, 25 °C) furnishing the bicyclic system (**17**)** with complete regio- and stereoselectivity as suggested by n.m.r. spectroscopy and subsequently proved by *X*-ray analysis on a more advanced intermediate (*vide infra*). Silylation of (**17**) gave (**18**) (100%) which on treatment with excess of Bu^nLi and MeOCOCl afforded the acetylenic ester (**19**) (78%). The requisite methyl group was stereospecifically delivered by cuprate[9] addition to (**19**) leading to the desired *E* α,β-unsaturated ester (**20**) (75%) which upon exposure to Bu^n_4NF underwent desilylation and concomitant cyclization to give the lactone (**21**) (80% yield).

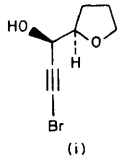


(I) **a**; 6-*endo* **b**; 5-*exo*

Substrate (I)	Product, **a** : **b** ratio[a]	% Yield[b]
(**2**) R = $CH_2CH_2CO_2Me$	0 : 100	94
(**3**) R = *E*-CH=CHCO$_2$Me	60 : 40	96
(**4**) R = CH=CH_2	100 : 0	95
(**5**) R = CH=CBr_2	100 : 0	90

Scheme 1. Ring selectivity in epoxide openings. Conditions: camphorsulphonic acid (CSA) (0.1 equiv.), CH_2Cl_2, −40 to 25 °C. [a] Determined by ^{1}H n.m.r. spectroscopy. [b] Isolated yield.

† Under basic conditions (KOBu^t–Bu^{t}OH; 25 °C) substrate (**4**) afforded a mixture of 6-*endo* and 5-*exo* products [(**4a**) : (**4b**), *ca.* 50 : 50, 85% yield] whereas the dibromovinyl epoxide (**5**) suffered mainly 5-*exo* ring closure with concomitant dehydrobromination leading to the acetylenic bromide (i) accompanied by small amounts of the 6-*endo* product (**5a**) [(i) : (**5a**), *ca.* 95 : 5; 90% yield]. Cyclizations of substrates (**2**) and (**3**) under these conditions were complicated by ester hydrolysis and were not fully explored.



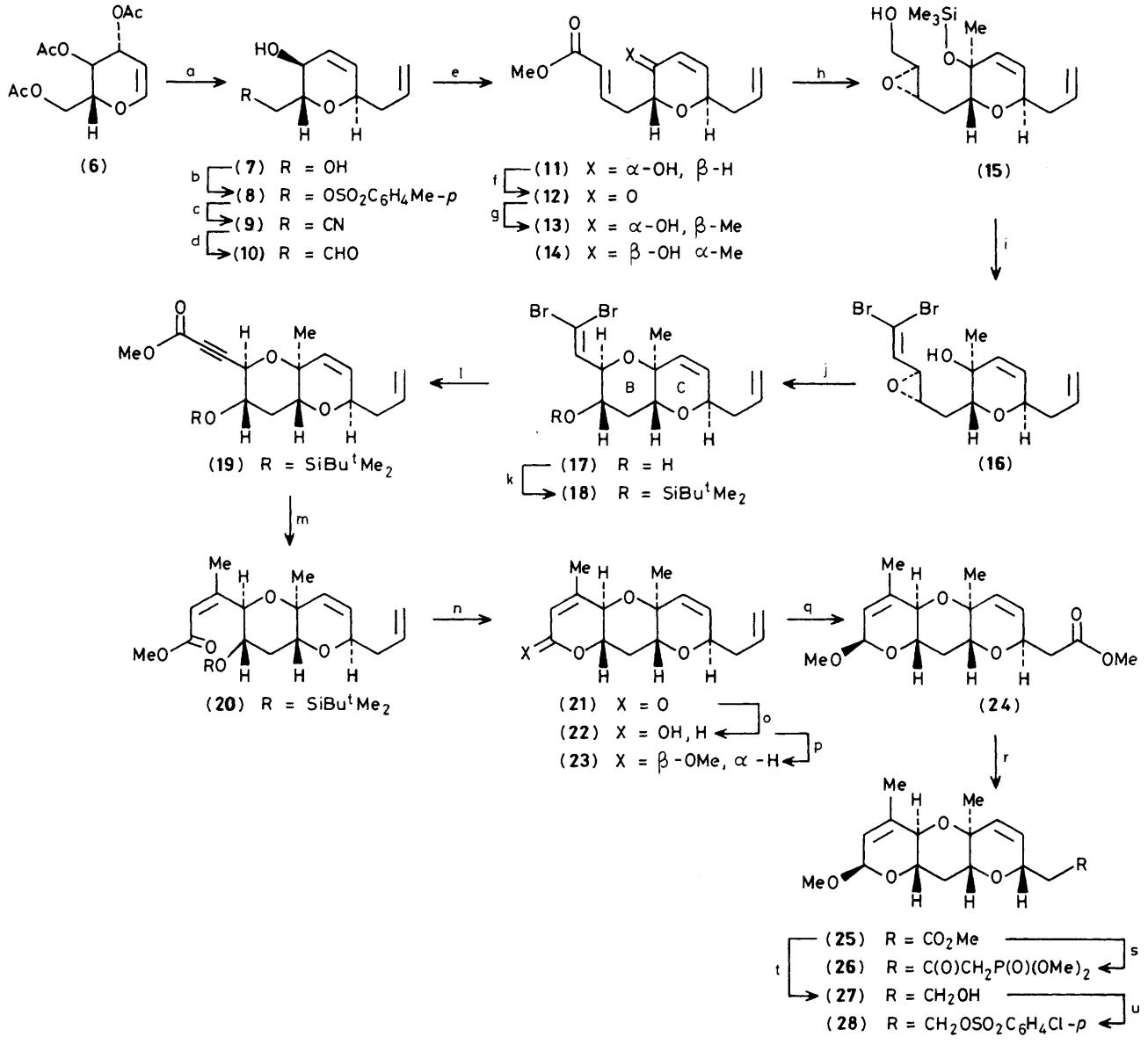
(i)

‡ Substrates (I) [(**3**)—(**5**)] were obtained from pent-4-yn-1-ol in a straightforward manner by (i) silylation (Bu^{t}Me$_2$Si); (ii) hydroxymethylation (Bu^nLi–$[CH_2]_n$O); (iii) RedAl reduction; (iv) Sharpless asymmetric epoxidation;[7] (v) SO_3·pyridine [O]; (vi) Wittig reaction; (vii) desilylation. Compound (**2**) was obtained by diimide reduction of silylated (**3**) followed by step (vii).

§ The structures of the cyclized products were established as follows. (**2b**): γ-lactone formation [*p*-Me$C_6H_4SO_3H$, C_6H_6; i.r. ($CHCl_3$) $\nu_{max.}$ 1775 cm^{-1}; ^{1}H n.m.r. analysis]; (**3a**), (**3b**): MnO_2 oxidation converted (**3b**) into an enone leaving unchanged (**3a**), ^{1}H n.m.r. analysis; (**4a**) and (**5a**) : ^{1}H n.m.r. spectra of the corresponding acetates exhibited a double triplet (*J* 10.0 and 5.0 Hz) for C*H*OAc [δ 4.63 for (**4a**) and 4.68 for (**5a**)] as expected for the tetrahydropyran system.

¶ All new compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials. Product ratios were determined by n.m.r. spectroscopy and/or isolation and are within ± 1% accuracy.

** ^{1}H N.m.r. (250 MHz, $CDCl_3$, brevetoxin B numbering for ring skeleton). (**17**) : δ 6.39 (d, *J* 8.39 Hz, 1H, C*H*=CBr_2), 5.93 (dd, *J* 10.34 and 2.09 Hz, 1H, c-ring –CH=), 5.82 (m, 1H, CH_2CH=CH_2), 5.55 (dd, *J* 10.21 and 2.09 Hz, c-ring –CH=), 5.10 (m, 2H, C=CH_2), 4.25 (m, 1H, H-11), 4.14 (dd, *J* 9.31 and 8.50 Hz, 1H, H-4), 3.58 (m, 1H, H-5) 3.46 (dd, *J* 12.56 and 3.74 Hz, H-7), 2.51—2.11 (m, 1H, CH_2CH=), 2.18 (m, 1H, H-6), 1.85 (d, *J* 4.93 Hz, 1H, OH), 1.70 (ddd, *J* 11.45, 11.44, and 11.45 Hz, 1H, H-6), and 1.30 (s, 3H, Me). (**24**) : δ 5.96 (dd, *J* 10.35 and 1.96 Hz, 1H, c-ring –CH=), 5.54 (dd, *J* 10.25 and 2.04 Hz, 1H, c-ring –CH=), 5.33 (br. s, 1H, A-ring –CH=), 4.81 (br. s, 1H, >C*H*OMe), 4.67 (dd, *J* 10.30 and 10.30 Hz, 1H, H-11), 3.95 (br. d, *J* 12.01 Hz, 1H, H-4), 3.68 (s, 3H, CO_2Me), 3.67—3.51 (m, 1H, H-5), 3.42 (dd, *J* 13.21 and 3.84 Hz, 1H, H-7), 3.36 (s, 3H, OMe), 2.53 (m, 2H, CH_2CO_2Me), 2.12 (m, 1H, H-6), 1.70 (m, 1H, H-6), 1.69 (s, 3H, Me-3), and 1.26 (s, 3H, Me-8).



Scheme 2. Synthesis of the ABC ring system of brevetoxin B. *Reagents and conditions:* (a), i, CH_2=$CHCH_2SiMe_3$ (1.5 equiv.), $TiCl_4$ (1.0 equiv.), CH_2Cl_2, −78 °C (95%, *ca.* 10:1 stereoselectivity), ii, K_2CO_3 (0.1 equiv.), MeOH, 25 °C, 100%; (b), *p*-$MeC_6H_4SO_2Cl$ (1.5 equiv.), pyridine, 0 °C; (c), NaCN (2.0 equiv.), Me_2SO, 70 °C, 87%; (d), Bu^i_2AlH (2.5 equiv.), CH_2Cl_2, −78 °C, 92%; (e), Ph_3P=$CHCO_2Me$ (1.2 equiv.), C_6H_6, 25 °C, 86%; (f), $(COCl)_2$ (1.5 equiv.), Me_2SO (2.0 equiv.), Et_3N (5.0 equiv.), CH_2Cl_2, −78 to 0 °C; (g), $AlMe_3$ (4.0 equiv.), CH_2Cl_2–toluene, −15 °C, 94% overall from (**11**); (**13**):(**14**) *ca.* 3:1; (h), i, 2-trimethylsilylimidazole, CH_2Cl_2, 0—25°C, 100%; ii, Bu^i_2AlH (2.5 equiv.), CH_2Cl_2 −78°C, 87%; iii, Bu^tOOH (4.0 equiv.), $Ti(Pr^iO)_4$ (3.0 equiv.), (+)-diethyl tartrate (4.0 equiv.), CH_2Cl_2, −23 °C, 72%; (i), i, SO_3–pyridine (4.0 equiv.), Et_3N (5.0 equiv.), Me_2SO–CH_2Cl_2 (1:1), 0 °C; ii, CBr_4 (2.0 equiv.), PPh_3 (4.0 equiv.), CH_2Cl_2, −78 °C, 63% overall from (**15**); iii, Bu^n_4NF, tetrahydrofuran (THF), −40 to 0 °C; (j) camphorsulphonic acid (CSA) (0.1 equiv.), CH_2Cl_2, 25 °C, 93% overall from (**16**); (k), Bu^tMe_2SiCl (1.1 equiv.), imidazole (2.2 equiv.), dimethylformamide (DMF), 0 °C, 100%; (l), Bu^nLi (2.2 equiv.), THF, −78 °C, then MeOCOCl (3.0 equiv.), 78%; (m), MeMgCl (6.0 equiv.), CuI (3.0 equiv.), THF, −78 °C, 75%; (n), Bu^n_4NF (1.1 equiv.), THF, 0 °C, 80%; (o), Bu^i_2AlH (1.2 equiv.), CH_2Cl_2, −78 °C, 100%; (p), *p*-$MeC_6H_4SO_3H$ (0.1 equiv.), CH_2Cl_2, 0—25 °C, 91%; (q) $KMnO_4$ (0.1 equiv.), $NaIO_4$ (4.0 equiv.), K_2CO_3 (4.0 equiv.), Bu^tOH–H_2O (1:2), 25 °C, then CH_2N_2, Et_2O–CH_2Cl_2, 0 °C, 84% overall from (**23**); (r), Bu^tOK (0.1 equiv.), C_6H_6, 25 °C, 90%, (**24**):(**25**), *ca.* 1:5; (s), $LiCH_2P(O)(OMe)_2$, THF, −20 °C, 65%; (t), Bu^i_2AlH (2.2 equiv.), CH_2Cl_2, −78 to 25 °C, 95%; (u), *p*-$ClC_6H_4SO_2Cl$ (1.2 equiv.), pyridine, 0—25 °C, 90%.

Reduction (Bu^i_2AlH) of (**21**) followed by methoxy acetal formation (MeOH, *p*-$MeC_6H_4SO_3H$) led to (**23**) (exclusively β-methoxy epimer, 91% overall) *via* the lactol (**22**). Chemoselective oxidative cleavage of the terminal alkene[10] followed by methylation of the resulting carboxylic acid led to the methyl ester (**24**)** (84% overall). As expected, the appendage on ring C was found to be easily epimerizable[11] to its thermodynamically more stable α-isomer under basic conditions, thus serving as a precursor to (**25**) [$KOBu^t$, (**24**):(**25**) *ca.* 1:5, 94% yield] and thence to derivatives (**26**)—(**28**). A preliminary *X*-ray crystal structure determination of the *p*-chlorobenzenesulphonate (**28**) (Scheme 2)

supported the stereochemical assignments for these potential key intermediates of a projected brevetoxin B (**1**) synthesis.

Extension of this strategy to lower and higher ring homologues and the total synthesis of brevetoxin B (**1**) are continuing.

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