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Chemoenzymatic Approach to Tetrodotoxin: Synthesis of Fukuyama's, Alonso's, and Sato's Advanced Intermediates

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Abstract: The advanced intermediates in the syntheses of tetrodotoxin reported by Fukuyama, Alonso, and Sato were prepared. The key steps in the synthesis of the title compounds involved the toluene dioxygenase–mediated dihydroxylation of either iodobenzene or benzyl acetate. The resulting diene diols were transformed to Fukuyama's intermediate in six steps, to Alonso's intermediate in nine steps and to Sato's intermediate in ten steps, respectively.

Tetrodotoxin (**1**), (TTX),[1] Figure 1, was first isolated by Tahara in 1909[2] and eluded precise structural determination for half a century. Following the successful preparation of the toxic principle in analytically pure crystalline form in the early 1950s,[3] a race broke out to elucidate the structure of this marine toxin. In 1964,[4] no fewer than four research groups reported successful elucidation.[5]

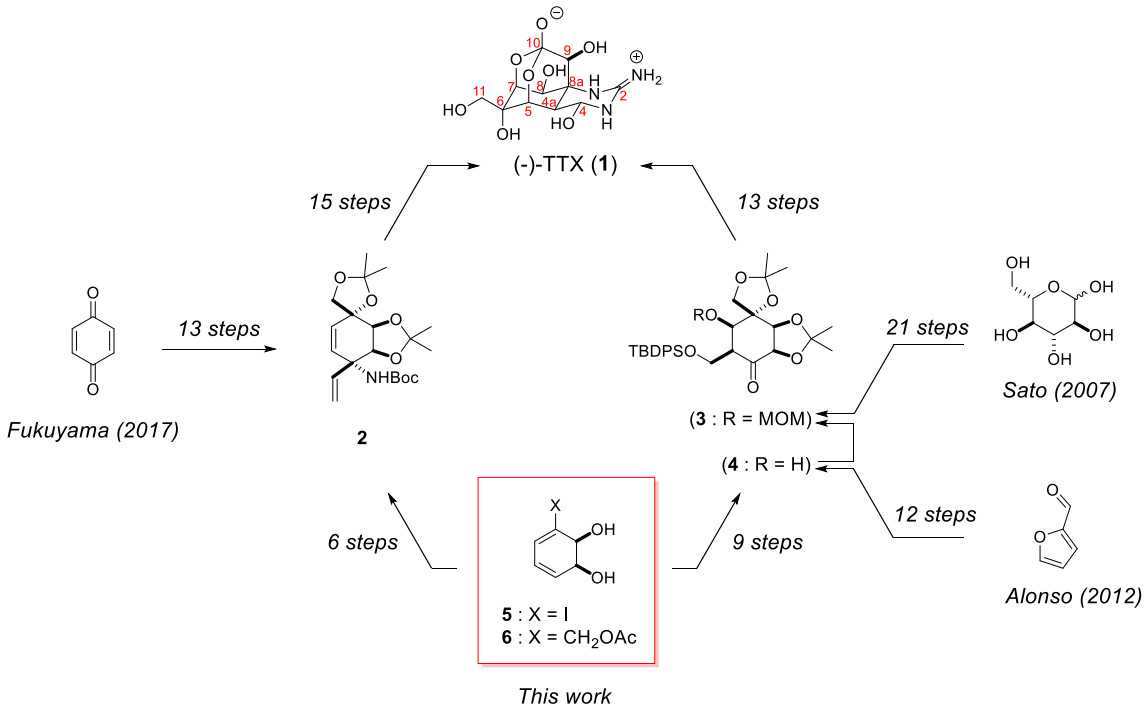

Figure 1. Chemoenzymatic approach to advanced precursors of TTX.

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The structure of TTX contains nine contiguous stereogenic centers in a molecule of only eleven carbons with the molecular weight slightly exceeding 300. The most intriguing structural feature is a dioxaadamantane skeleton with a cyclic guanidine containing a hemiaminal moiety, Figure 1. TTX naturally occurs in several species of pufferfish and some other aquatic animals, but it is believed to be produced by symbiotic bacteria.[6] The toxin is a potent inhibitor of voltage-gated sodium channels (Na_v). At very low dosages it has a potential to treat cancer pain or relieving the symptoms of withdrawal in opiate addicts.[7] The important clinical applications and the intricate structure of TTX have attracted the attention of synthetic community and several syntheses were reported since the attainment of the racemate by Kishi in 1972.[8] The interest in this fascinating molecule continues unabated and many creative total syntheses have been published.[9] Additionally, various approaches to TTX have also been summarized.[10] In this paper, we report a chemoenzymatic synthesis of the title advanced intermediates from diene diols **5** or **6**, Figure 1, obtained by toluene dioxygenase-mediated dihydroxylation of iodobenzene or benzyl acetate, respectively.

Fukyama's synthesis of Boc-protected amine **2** proceeded in 13 steps from benzoquinone (see Scheme 1 in the Appendix of the Supplemental Information Section for detailed description of the synthesis). Alonso's approach started with furfural, which was converted in 12 steps to alcohol **4**, Figure 1 (see Scheme 2 in the Appendix of the Supplemental Information Section for detailed description of the synthesis). Sato prepared the advanced intermediate **3** in 21 steps from *D*-glucose (see Scheme 3 in the Appendix of the Supplemental Information Section for detailed description of the synthesis).

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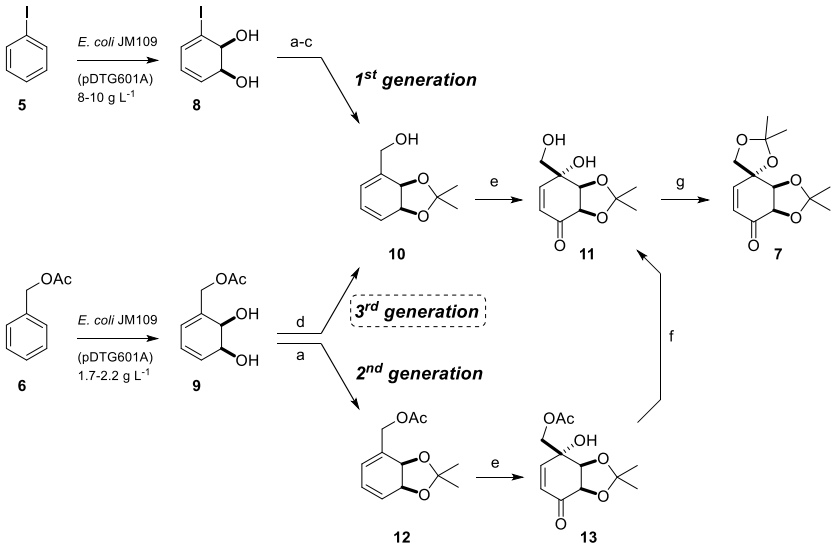
Our approaches to the advanced precursors of TTX shown in Figure 1 share the common intermediate enone **7**, Scheme 1**.** We envisioned access to compounds of this type via enzymatic dihydroxylation of suitable aromatic substrates. This highly regio- and enantioselective dihydroxylation was discovered in 1968 by Gibson[11a] who also later provided a robust recombinant organism, *E. coli* JM109 (pDTG601A), that overexpresses toluene dioxygenase.[11b] The use of this strain in whole-cell fermentations[11c] allows access to large amounts (>20 g/L) of the homochiral diene diols (such as **5** or **6**, Scheme 1) that serve as ideal starting materials for enantioselective synthesis of highly oxygenated targets. To date many examples of efficient chemoenzymatic syntheses of natural products from diols of type **5** have been and continue to be published.[11d-f]



Scheme 1. Synthesis of the key intermediate **7**. a) *p*-TsOH·H_2O, 2,2-DMP, rt; b) $Pd(OAc)_2$, NEt_3, CO (1 atm), MeOH, 40°C; c) DIBAL (neat), benzene : *n*-hexane = 1 : 1, 0 °C; d) *p*-TsOH·H_2O, 2,2-DMP, rt; K_2CO_3, MeOH, rt; e) O_2 (bubbling), TPP, *hv*, CH_2Cl_2; Et_3N, rt (**11**: 46% from **5**, 4 steps; **11**: 68% from **6**, 2 steps; **13**: 42% from **6**, 2 steps); f) LiOH, THF/H_2O, 0°C, 50%; g) *p*-TsOH·H_2O, 2,2-DMP, 50°C, 80%.
Ts = tosyl, DMP = dimethoxypropane, Ac = acyl, DIBAL = diisobutylaluminium hydride, TPP = tetraphenylporphyrin, THF = tetrahydrofuran.

Several generations of approaches to the synthesis of enone **7** were pursued in our group with the most efficient one proceeding in four steps from benzyl acetate **9**. The 1st generation employed iodobenzene **8** as a substrate for chemoenzymatic dihydroxylation by toluene dioxygenase.[11] The resulting iodo diol **5** was converted to the key enone **7** in a five-step sequence. Acetonide protection, palladium catalyzed methoxycarbonylation,[12] and DIBAL reduction produced allylic alcohol **10**. Construction of the tetrasubstituted carbon at C-6 (TTX numbering) was realized through [4+2] hetero-Diels-Alder

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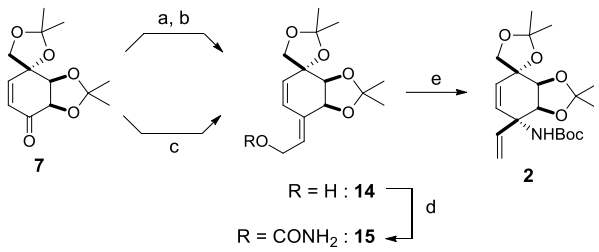
cycloaddition with singlet oxygen followed by Kornblum-DeLaMare rearrangement,[13] utilized recently in our synthesis of pleiogenone.[14] The singlet oxygen cycloaddition took place exclusively from the less sterically hindered face of the diene moiety. The intermediate endo-peroxide was rearranged by means of triethylamine in the same reaction pot to furnish enone **11**. Protection of the diol in **11** provided efficient access to **7** in an overall yield of 36% from diene diol **5**. In the 2nd generation approach we used benzyl acetate **9** as a starting material, as this compound already contains the C-11 hydroxymethyl moiety of TTX. Acetonide protection of the diol in **6** furnished the photooxygenation precursor **12**. Following the cycloaddition of singlet oxygen and the subsequent rearrangement furnished enone **13**, whose deacetylation yielded shorter synthetic route to diol **11** and hence to the key enone **7** (33% overall yield from **6**). Finally, in the 3rd generation approach, we realized that allylic alcohol **10** can be obtained directly from **6** in a one-pot fashion. Thus, acetonide protection of the diol in **6** followed by deacetylation provided rapid access to diene **10**, which was then converted to enone **7** (54% from **6**) in two subsequent synthetic operations as described above.



Scheme 2. Synthesis of Fukuyama's carbamate **2**. a) $TMSCH_2CO_2Et$, LDA, THF, -78 to 0 °C; b) DIBAL, toluene, -78 to 0 °C, 80% (2 steps); c) *n*-BuLi, $Ph_3P^+CH_2CH_2OH\ Br^-$, THF, -30 °C to rt, 64% (*E* : *Z* = 8 : 1); d) $Cl_3CC(O)NCO$, CH_2Cl_2, rt; Et_3N, MeOH, rt, 96%; e) TFAA, *i*-Pr_2NEt, CH_2Cl_2, -78 °C to rt; LiO*t*-Bu, -78 to 0 °C, 56%.
DIBAL = diisobutylaluminium hydride, LDA = lithium diisopropylamide, *t*-Bu = *tert*-butyl, THF = tetrahydrofuran, TMS = trimethylsilyl, Boc = *tert*-butyloxycarbonyl, TFAA = trifluoroacetic anhydride.

With the rapid access to **7** in hand, we turned our attention to the synthesis of Fukuyama's intermediate **2**. Allylic alcohol **14** was accessed in high yields via Peterson olefination/DIBAL reduction sequence and the precursor to rearrangement was prepared through carbamoylation of **14**, as shown in Scheme 2. The allylic alcohol moiety in **14** can also be installed directly on **7** via means of Wittig olefination,[15] albeit in a lower yield. Upon dehydration of **15** with TFAA and Hunig's base,[16] a facile [3,3]-sigmatropic rearrangement took place to yield isocyanate intermediate, which, upon treatment with lithium *tert*-butoxide, furnished Fukuyama's carbamate **2** in 56% yield, Scheme 2, in 6 steps from **6** (*Fukuyama's work*: $[\alpha]_D^{24}$ + 10° (*c* 0.97, $CHCl_3$); *This work*: $[\alpha]_D^{22}$ + 9.8° (*c* 1.0, $CHCl_3$)). Both *E* and *Z* isomers of **14** converge to the same Boc-amine **2**. Fukuyama in his approach to TTX utilized the *Z* isomer of **15** as the rearrangement precursor (see Scheme 1 in the Appendix of the Supplemental Information Section for detailed description of the synthesis).

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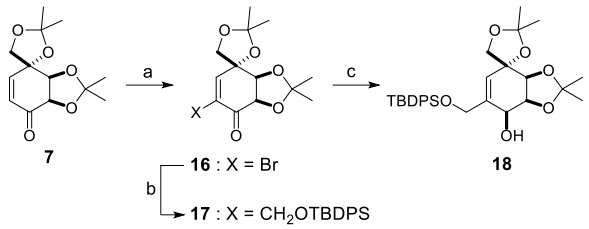
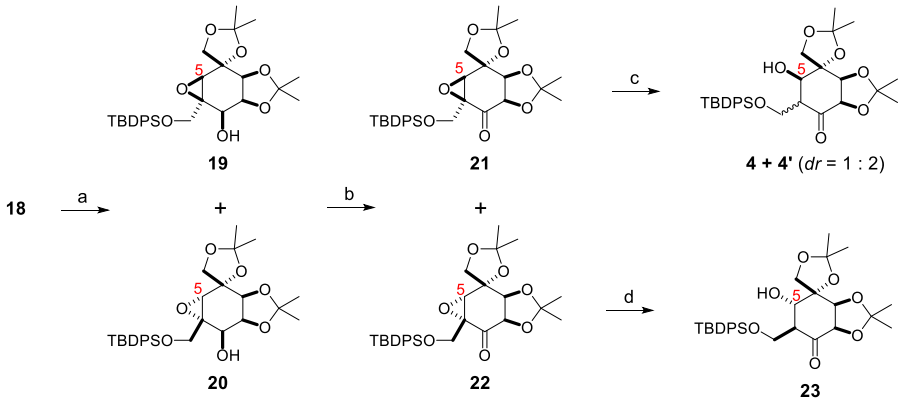
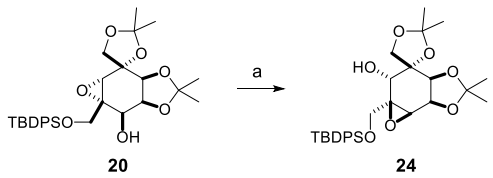
The construction of the key cyclohexanone **3** commenced with the bromination/ dehydrobromination sequence of **7** to furnish the vinyl bromide **16**.[17] Introduction of the C-4 carbon proved possible by utilizing Stille coupling with an oxygenated stannane to provide TBDPS-silyl ether **17**,[18] whose DIBAL reduction gave efficient access to allylic alcohol **18**, Scheme 3. The desired stereochemistry at C-5 of TTX can be accessed through hydroxyl directed epoxidation of **18**. Oxidation of the intermediate epoxy alcohol **19** with IBX provided the α,β-epoxy ketone **21** as a precursor for reductive epoxide opening.[19] Unfortunately, the latter procedure gave **4** and its α-position epimer, **4'**, as an inseparable mixture of diastereomers, Scheme 4. The stereochemistry of the intermediate epoxy alcohol was validated by subjecting the undesired epoxide **20** to a base-promoted Payne rearrangement, Scheme 5.



Scheme 3. Synthesis of allylic alcohol **18**. a) Br_2, CH_2Cl_2, 0°C; Et_3N, 0 °C, 68%; b) $Pd(OAc)_2$, $Bu_3SnCH_2OTBDPS$, 1,4-dioxane, 90 °C, 64%; c) DIBAL, toluene, -78 to 0 °C, 94%.
DIBAL = diisobutylaluminium hydride, TBDPS = *tert*-butyldiphenylsilyl, Bu = butyl, Ac = acyl.



Scheme 4. Reductive epoxide opening approach to **4**. a) *m*CPBA, $CHCl_3$, reflux; b) IBX, EtOAc, reflux, 82% (**21** : **22** = 3 : 7, 2 steps); c) Zn, Cp_2TiCl_2, THF/MeOH, -78 to 0 °C, 20 %; d) Zn, Cp_2TiCl_2, THF/MeOH, 50 °C, 10-30 %.
TBDPS = *tert*-butyldiphenylsilyl, *m*CPBA = *meta*-chloroperbenzoic acid, IBX = 2-iodoxybenzoic acid, Cp = cyclopentadienyl, THF = tetrahydrofuran.



Scheme 5. Payne rearrangement. a) KO*t*-Bu, THF : HO*t*-Bu = 1 : 1, rt, 95%.
THF = tetrahydrofuran, *t*-Bu = *tert*-butyl.

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Clearly, this process requires the *trans* arrangement of the oxirane and hydroxyl functionalities. Moreover, reductive epoxide opening was also performed with keto-epoxide **22**, as shown in Scheme 4, which could not have resulted in inversion of stereochemistry at C-5.

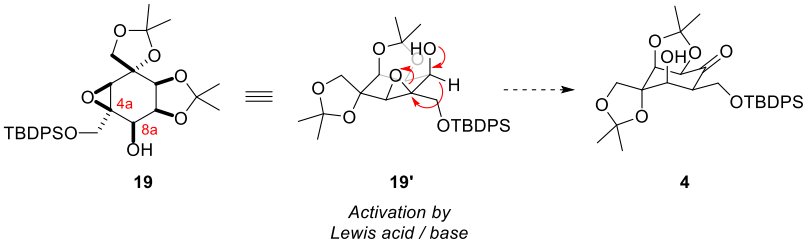


Figure 2. Hydride shift approach.

In considering the problem of the undesired epimer formation, it seemed that a possible solution might involve a suprafacial delivery of a hydrogen by "hydride" migration of an already α-configured hydrogen in **19** in an intramolecular fashion as shown in Figure 2. The key argument in favour of this manoeuvre assumed that it ought to be possible to prompt the rearrangement of **19** to **4** by either Lewis acid activation of the oxirane,[20] or deprotonation of an alcohol, so that the alkoxide would provide the necessary electron push,[21] wherein suprafacial hydride shift of the α-hydrogen from C-8a would deliver it to the desired α-face at C-4a, thereby restoring the carbonyl moiety and producing **4** in a stereospecific fashion. To our disappointment, **19** was completely inert to any kind of Lewis acid or base activation. Assuming that the resident "hydride" lacks the optimal

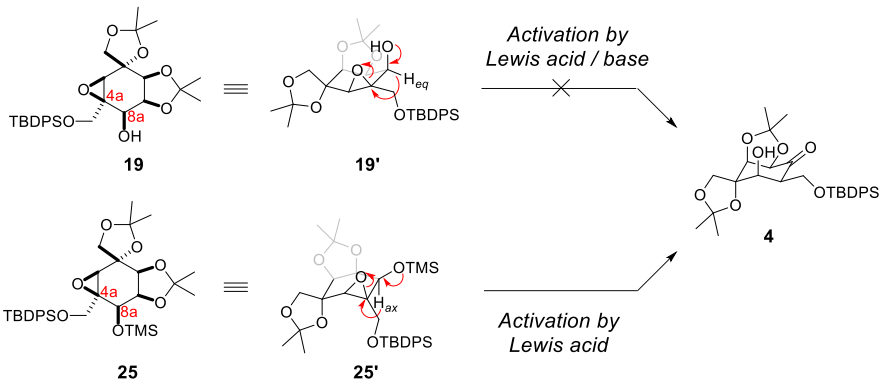
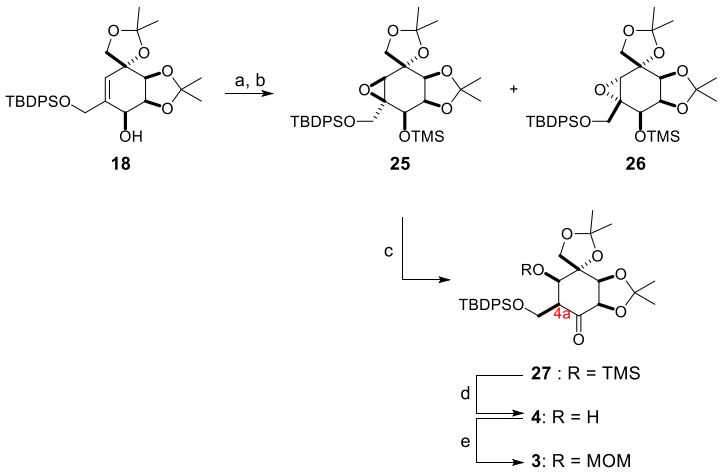


Figure 3. Stereoelectronic arguments.



Scheme 6. Synthesis of Alonso's (**4**) and Sato's (**3**) intermediates. a) *m*CPBA, $CHCl_3$, reflux; b) TMSCl, imidazole, CH_2Cl_2, 85% (**25** : **26** = 3 : 7, 2 steps); c) $TiCl_4$, CH_2Cl_2, -78 °C, 52% (**27** : **4** = 4 : 1); d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 93%; e) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, rt, 79%.
TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, *m*CPBA = *meta*-chloroperbenzoic acid.

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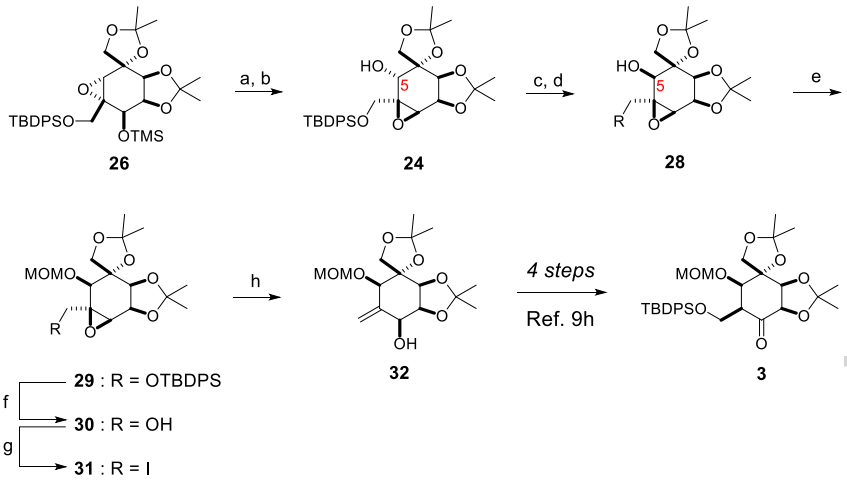
stereoelectronic alignment with the σ*(C–O) of the oxirane, we prepared the TMS ether **25**, from the free alcohol **19**. The introduction of the steric hindrance between the TMS group and the adjacent acetonides forced the resident hydrogen to accommodate pseudoaxial orientation, as shown in Figure 3. Indeed, upon exposure of **25** to $TiCl_4$,[22] the desired hydride shift took place smoothly producing **27** and **4** in 4 : 1 ratio as the major products, with the required stereochemistry at the newly formed C-4a tertiary carbon center, as shown in Scheme 6. Removal of the TMS group in **27** provided the Alonso's intermediate **4** in 49% yield from epoxy silyl ether **25** over two steps. Sato's intermediate **3** (*Sato's work*: $[\alpha]_D^{25}$ - 5.5° (*c* 4.09, $CHCl_3$); *This work*: $[\alpha]_D^{24}$ - 3.5° (*c* 0.44, $CHCl_3$))[23] was then obtained by MOM protection of **4** with dimethoxymethane in the presence of phosphorus(V) oxide. Thus, Sato's intermediate was synthesized in ten steps from **6**.

Finally, the undesired epoxide **26** was also converted to Sato's intermediate as shown in Scheme 7. TMS removal, Payne rearrangement, followed by inversion of stereochemistry at C-5 by oxidation-reduction sequence provided epoxy alcohol **28**. Alkylation of **28** with MOMCl and subsequent cleavage of the silyl ether moiety in **29** furnished primary alcohol **30**. Iodination[24] of **30** and reductive cleavage of the resulting 2,3-epoxyalkyliodide **31** by the sonochemically generated zinc-copper couple[25] gave Sato's allylic alcohol **32** (see Scheme 4 in the Appendix of the Supplemental Information Section for detailed description of the synthesis). This last approach corrected the lack of stereoselectivity in the epoxidation of **18**; both epoxy alcohols **19** and **20** can now be used to access Sato's intermediate.



Scheme 7. The end game: conversion of **26** to Sato's intermediate **32**. a) K_2CO_3, MeOH, rt; b) KO*t*-Bu, THF : HO*t*-Bu = 1 : 1, rt; c) IBX, EtOAc, reflux; d) $NaBH_4$, MeOH, rt, 64% (4 steps); e) NaHMDS, MOMCl, THF, 0 °C to rt, 88%; f) TBAF, THF, rt, 92%; g) I_2, PPh_3, imidazole, CH_2Cl_2, rt, 78%; h) Zn, CuI, EtOH/H_2O/MeOH/THF, sonication, rt, 91%.
THF = tetrahydrofuran, *t*-Bu = *tert*-butyl, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, IBX = 2-iodoxybenzoic acid, HMDS = hexamethyldisilizide, MOM = methoxymethyl, TBAF = tetrabutylammonium fluoride.

In summary, two short chemoenzymatic routes to known advanced intermediates for (–)-TTX are described in this paper and were accomplished in just six and nine steps from **6**, to Fukuyama's and Alonso's intermediates, respectively (these compounds can also be attained from **5**). Alkylation of Alonso's intermediate also formalized the preparation of Sato's ketone **3** in ten steps from benzyl acetate. If our approach were to be used for the completion of (–)-TTX by the known methods the overall step count would be 21 or 22 steps from **6** via Fukuyama's or Sato's intermediate, respectively.

Acknowledgements

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[1] German: "tetrodongift", meaning tetrodon poison. The name was assigned by Tahara (*vide infra*, ref. 2) who pioneered the isolation of the marine toxin.

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