Natural Product Synthesis

DOI: 10.1002/anie.201308502

Total Synthesis of Pectenotoxin-2**

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Abstract: *Pectenotoxin-2 (PTX2) is a shellfish toxin and has a non-anomeric spiroacetal, which is not stabilized by an anomeric effect. The selective construction of the non-anomeric spiroacetal has been a major problem in the synthesis of PTX2. Described herein is the stereoselective total synthesis of PTX2 via the isomerization of anomeric spiroacetal pectenotoxin-2b (PTX2b). The synthesis of PTX2b was achieved by a simple process including sulfone-mediated assembly of spirocyclic and bicyclic acetals and subsequent macrocyclization by ring-closing olefin metathesis. Finally, the selective construction of PTX2 was accomplished by the early termination of a dynamic transition process to equilibrium in the acid-catalyzed isomerization of anomeric PTX2b. [6,6]-Spiroacetal pectenotoxin-2c (PTX2c) was also synthesized from PTX2b. The cytotoxicity assay of the synthetic compounds against HepG2 and Caco2 cancer cells showed a potency of the order: PTX2 ⩾ PTX2b > PTX2c.*

Pectenotoxin-2 (PTX2; **1**; Figure 1), isolated from the Japanese scallop *Patinopecten yessoensis* and the dinoflagellate *Dinophysis fortii* as a diarrhetic shellfish toxin by Yasumoto et al. in the late 1980s,[1] is a unique polyether macrolide consisting of a 34-membered (main chain) lactone, a spiroacetal, a bicyclic acetal, three oxolanes, and a six-membered cyclic acetal. PTX2 has natural congeners having differences in the oxidation state at C43 and in the structures of the spiroacetal (C3–C11), as well as the oxolane/hemiacetal (C32–C38) regions.[1,2] The toxicity of the pectenotoxin congeners (PTXs) is demonstrated by lethality to mice after intraperitoneral injection[1–3] and cytotoxicity to several cancer cell lines,[4] which is attributable to their actin depolymerization ability.[5] The toxicity is reported to correlate with their structures. An increase in the oxidation state at C43 and structural deviations from the spiroacetal consisting of six- and five-membered rings with a 7*R* configuration decreased the toxicity.[6] Thus, PTX2 displayed the strongest toxicity among the congeners.

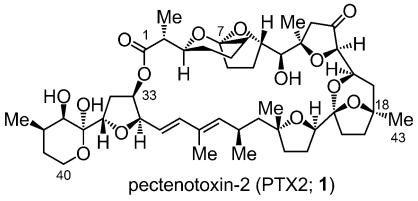
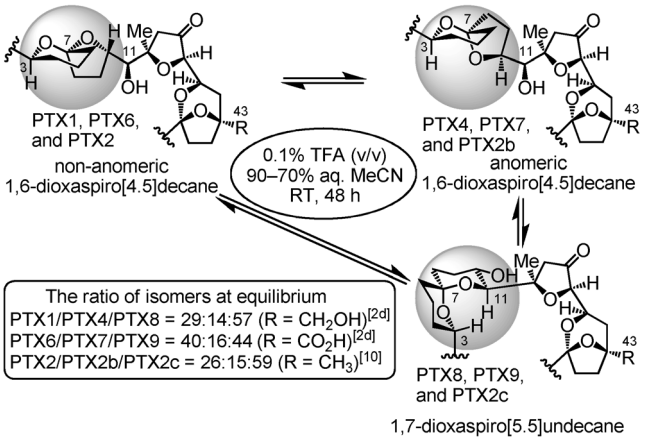


Figure 1. Structure of pectenotoxin-2.

It is notable that the spirocyclic acetal of PTX2, similar to that of PTX1 and PTX6 (Scheme 1), takes a form that is not stabilized by an anomeric effect: the oxygen atom at C7 exocyclic to the oxane ring is in the equatorial position. The unique characteristics of the common non-anomeric[7] spiroacetal moiety of PTX1, PTX2, and PTX6 has attracted the attention of organic chemists and promoted the development of some successful methods for the selective synthesis of non-anomeric spiroacetals, for example, a sequence of stereoselective reductive lithiation and C–C bond formation by Rychnovsky and co-workers,[8] and stereoselective spiroacetalization under carefully controlled kinetic conditions by Pihko and co-workers.[9]



Scheme 1. Reported interconversion between PTX congeners. TFA = trifluoroacetic acid.

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[**] We thank Dr. Eri Fukushi, Mr. Kenji Watanabe (GC-MS & NMR Lab., Faculty of Agriculture, Hokkaido Univ.), Dr. Yasuhiro Kumaki (High-Resolution NMR Lab., Faculty of Science, Hokkaido Univ.), Prof. Keiji Tanino, and Mr. Takahiro Hiramatsu (Faculty of Science, Hokkaido Univ.) for assistance with mass and NMR spectroscopy. We are grateful to Prof. Masayuki Satake (The Univ. of Tokyo) for kindly providing ^{1}H NMR spectra of natural PTX2 and congeners thereof. This work was supported by Grants-in-Aid for Scientific Research from MEXT (Japan).

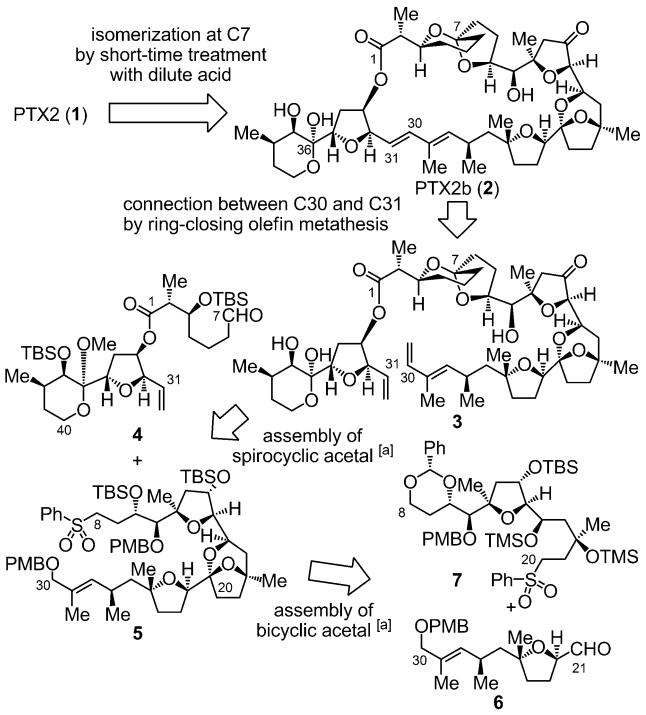
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308502.

Interestingly, Yasumoto et al. reported that upon treatment with a weak acid (0.1% TFA in 90% aqueous acetonitrile) for 48 hours, PTX1 was isomerized to an equilibrium mixture of PTX1, PTX4, and PTX8 in a ratio of 29:14:57, in which PTX4, having a spiroacetal stabilized by an anomeric effect, was a minor component, and PTX8, which had a spiroacetal consisting of two oxanes, was the major component (Scheme 1).[2d] A similar tendency was observed in the isomerization equilibrium between PTX6, PTX7, and PTX9[2d] and also between PTX2, PTX2b, and PTX2c (PTX2b and PTX2c were artifacts, and their structures were tentatively assigned by Suzuki et al. in 2003).[10] The isomerization equilibrium was successfully applied by Evans et al. to form PTX8 from PTX4 using 1% TFA in aqueous acetonitrile, and a ratio of 11:10:79 for PTX1/PTX4/PTX8 was observed for the first total synthesis of PTX4 and PTX8.[11]

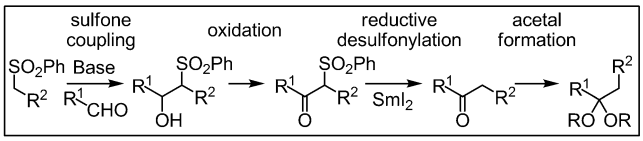
The unique structures and the strong bioactivities of PTXs have prompted many research groups,[8,9,11,12] including our own,[13] to pursue their total syntheses. Although the accessibility to the PTX framework has been proven by the total synthesis of Evans et al.,[11] the problem of the selective total synthesis of the non-anomeric spiroacetal congeners of PTX still remains to be solved. Herein, we describe the total synthesis of non-anomeric spiroacetal PTX2 via the isomerization of anomeric spiroacetal PTX2b. In the isomerization step, the early termination of a dynamic transition process to equilibrium is a key to the selective formation of PTX2.

Our synthetic approach to PTX2 includes acidic isomerization of PTX2b to the target compound at the final stage of the synthesis, where the suppression of the formation of PTX2c was an issue (Scheme 2). To prevent this, the time course of the isomerization of natural PTX2, as reported by Suzuki, provided a clue: PTX2 was rapidly equilibrated with PTX2b in a 3:1 ratio, while the formation of PTX2c was slow.[10] Therefore, if PTX2b is isomerized as a starting material under the same reaction conditions, PTX2 would be generated as a major product in the early stage of the isomerization process, and PTX2c would then increase with decreasing PTX2 and PTX2b, but at a slower rate. Thus, a short-time treatment of PTX2b with dilute TFA was employed as a simple solution for the selective formation of PTX2.

There are three major challenges in the synthesis of PTX2b: a) construction of the macrolactone ring, b) assembly of the anomeric spiroacetal, and c) formation of the bicyclic acetal. We intended to meet the former challenge by applying ring-closing olefin metathesis (RCM)[14] to the double-bond formation between C30 and C31 of triene **3**. The solution of the latter two challenges employed a common reaction sequence including a coupling reaction between sulfone and aldehyde segments, oxidation of the resulting β-hydroxy sulfone to an α-sulfonylketone, reductive desulfonylation, and spirocyclic/bicyclic acetal formation. The reliability of the sequence to form the anomeric spiroacetal was previously demonstrated by Brimble and co-workers in the synthetic studies of PTXs.[12e] Therefore, we employed the sequence for the assembly of **3** from aldehyde **4**[13c] and sulfone **5**. Although the applicability of the sequence to the bicyclic acetal formation was initially unknown, the construction of **5** from



[a] Key Reaction Sequence for the Assembly of Spirocyclic and Bicyclic Acetals

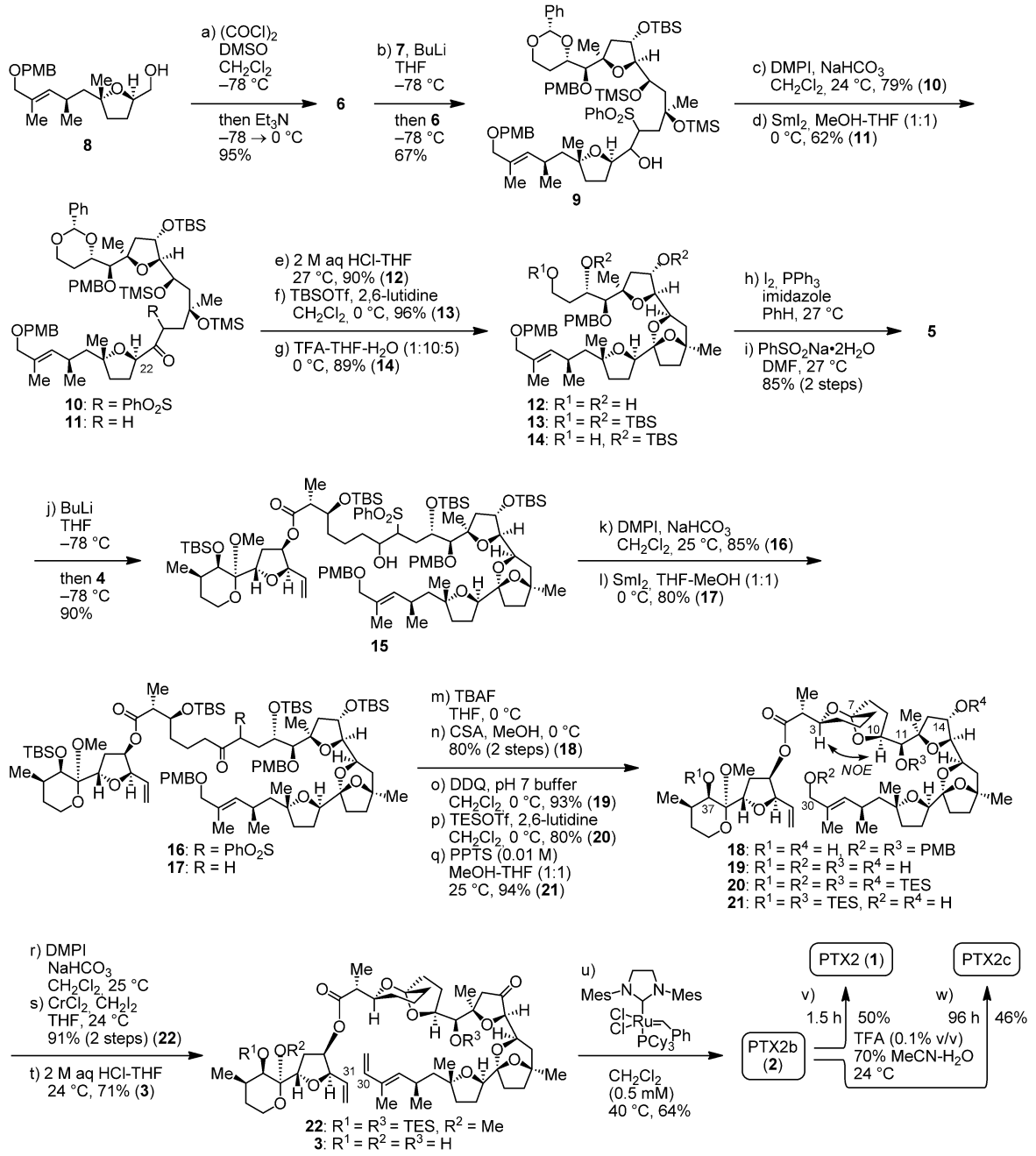


Scheme 2. Retrosynthetic analysis of **1**. PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

aldehyde **6** and sulfone **7**[13e] by the same sequence was planned.

The assembly of **5** was initiated by the connection of **6** with **7** (Scheme 3). Deprotonation of **7** with BuLi and subsequent reaction with **6** (0.77 equiv), prepared from **8**[13d] by Swern oxidation (95%),[15] produced adduct **9** (67% from **8**), which was subjected to Dess–Martin oxidation[16] to give ketone **10** (79%). The phenylsulfonyl group of **10** was detached carefully with SmI_2 under stoichiometric conditions to cleanly produce **11** (62%) without cleavage of the ether bond at C22.[17] The treatment of **11** with 2 M aqueous HCl/THF (1:4) led to the removal of the acetal and silyl protecting groups and the formation of a bicyclic acetal to afford **12** (90%) as a single product. Protection of **12** as a tris(TBS) ether (**13**; 96%) and then selective removal of the primary TBS ether produced alcohol **14** (89%), which was converted into **5** by iodination[18] and subsequent substitution with sodium phenylsulfinate (85% over two steps).

The construction of the anomeric spirocyclic acetal of **3** was also achieved by the sulfone-mediated process from **4** and **5**. The addition of the anion of **5** to **4** (0.53 equiv) afforded adduct **15** (90% from **4**), which was converted into ketone **17** (68% over two steps) by Dess–Martin oxidation and desulfonylation with SmI_2. The formation of a spiroacetal from **17** was performed by a two-step sequence [1) removal of the TBS



Scheme 3. Segment assembly and completion of synthesis. Reagents and conditions: a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min; then Et_3N, −78 °C→0 °C, 20 min, 95%; b) **7**, BuLi, THF, −78 °C, 10 min; then **6**, 10 min, 67%; c) DMPI, $NaHCO_3$, 24 °C, 2 h, 79%; d) SmI_2, MeOH/THF (1:1), 0 °C, 5 min, 62%; e) 2 M aq. HCl/THF (1:4), 27 °C, 15 h, 90%; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 96%; g) TFA/THF/H_2O (1:10:5), 0 °C, 3 h, 89%; h) I_2, PPh_3, imidazole, benzene, 27 °C, 10 min; i) $PhSO_2Na{\cdot}2H_2O$, DMF, 27 °C, 13 h, 85% (2 steps); j) **5**, BuLi, THF, −78 °C, 15 min; then **4**, 20 min, 90%; k) DMPI, $NaHCO_3$, 25 °C, 2 h, 85%; l) SmI_2, MeOH/THF (1:1), 0 °C, 5 min, 80%; m) TBAF, THF, 0 °C, 16 h; n) CSA, MeOH, 0 °C, 2 h, 80% (2 steps); o) DDQ, CH_2Cl_2/pH 7 buffer (10:1), 0 °C, 1 h, 93%; p) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 80%; q) PPTS (0.01 M), MeOH/THF (1:1), 25 °C, 3 h, 94%; r) DMPI, $NaHCO_3$, 25 °C, 3 h; s) $CrCl_2$, CH_2I_2, THF, 24 °C, 15 h, 91% (2 steps); t) 2 M aq. HCl/THF (1:4), 24 °C, 5 h; u) Grubbs' second generation catalyst, CH_2Cl_2 (0.5 mM of **22**), 40 °C, 4 h, 64%; v) TFA (0.1% v/v), 70% MeCN-H_2O, 24 °C, 1.5 h, **1**: 50%, **2**: 18%, PTX2c: 11%; w) TFA (0.1% v/v), 70% MeCN/H_2O, 24 °C, 96 h, **1**: 22%, **2**: 18%, PTX2c: 46%. CSA = 10-camphorsulfonic acid, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide, DMPI = Dess–Martin periodinane, DMSO = dimethyl sulfoxide, Mes = 2,4,6-trimethylphenyl, NOE = nuclear Overhauser effect, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

groups with TBAF, 2) acetal cyclization with CSA] to give anomeric spiroacetal **18** (80% over two steps). The configuration at C7 was confirmed by the presence of an NOE correlation between H3 and H10.[2d]

Next, conversion of **18** into diol **21**, possessing hydroxy groups at C14 and C30 as well as protected oxygen atoms at C11 and C37, was required prior to the installation of a carbonyl group at C14 and a vinyl group at C30. The

PMB groups of **18** were removed with DDQ (93%),[19] and the resulting tetraol **19** was protected as a tetra(TES) ether (**20**; 80%). The sterically less hindered TES ethers at C14 and C30 were selectively cleaved under weak acidic conditions to produce **21** (94%).

Dess–Martin oxidation of **21** followed by Takai olefination[20] selectively afforded ketotriene **22** (91% over two steps). All protecting groups of **22** were removed upon treatment with 2 M aqueous HCl/THF (1:4) to furnish **3** (71%) along with a small amount of a [6,6]-spiroacetal (12%). The RCM of triene **3** with the second-generation Grubbs' catalyst[21] successfully gave PTX2b (**2**) in 64% yield without isomerization of the spiroacetal moiety.

The final isomerization of synthetic PTX2b (**2**) was performed using a 0.1% solution of TFA in 70% MeCN/H_2O at 24 °C. Prior to the preparative scale reaction, the time course of the isomerization of PTX2b was monitored in detail on an approximate 0.1 mg scale by reverse-phase HPLC with UV detection at $\lambda = 235$ nm (Figure 2).[22] As predicted,

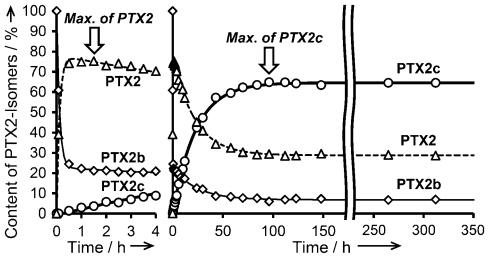


Figure 2. Time course of the isomerization of synthetic PTX2b (**2**) (small-scale experiment).

PTX2b was rapidly isomerized to PTX2 at the initial stage of the isomerization. The content of PTX2 soared from 0% to a maximum of 75% after 1.5 hours, while the content of PTX2b decreased steeply from 100% to 21% in the same period. Then, PTX2 and PTX2b slowly decreased with a gradual increase of PTX2c until 96 hours when the isomerization reached equilibrium and PTX2c was at a maximum of 65% (PTX2/PTX2b/PTX2c = 28:7:65). Thus, in preparative scale isomerization reactions, a 1.5 hour reaction produced **1** as the major component in 50% upon isolation, and a 96 hour reaction led to the isolation of PTX2c (46%).[23]

The synthetic PTX2 (**1**) displayed physical and spectral properties including ^{1}H and ^{13}C NMR, IR, UV, and MS data, as well as optical rotation {$[\alpha]_D^{23} = +15.5$ ($c = 0.050$, MeOH); Ref. [1a]: $[\alpha]_D^{20} = +16.2$ ($c = 0.105$, MeOH)}, identical to the natural product.[1a,2e,f] The structures of synthetic PTX2b and PTX2c were determined by an independent NMR analysis (see the Supporting Information), and the order of elution of the synthetic congeners from HPLC agreed with that of the naturally derived congeners,[10] thereby confirming Suzuki's proposed structures of PTX2b and PTX2c.

The cytotoxicity against human hepatocellular carcinoma cells (HepG2) and human colonic carcinoma cells (Caco2), which was previously examined with natural PTX2 by Sérandour and co-workers,[24] was then investigated with the synthetic compounds. Non-anomeric spiroacetal PTX2 showed the highest IC_{50} value against HepG2/Caco2 growth (3.6/2.6 nmol L^{-1}), while the anomeric spiroacetal PTX2b and [6,6]-spiroacetal PTX2c displayed IC_{50} values of 1.5×10^3/0.56×10^3 and 3.8×10^3/3.6×10^3 nmol L^{-1}, respectively. Thus, the difference in cytotoxicity between spiroacetalic isomers of PTX2 was clarified for the first time, though a similar structure–activity relationship was reported in the mouse lethality of PTX1, PTX4, and PTX8 by Yasumoto.[2d]

In conclusion, the total synthesis of PTX2 (**1**) was achieved through a simple process including sulfone-mediated assembly of bicyclic and anomeric spirocyclic acetals from segments **6**, **7**, and **4**, macrocyclization through RCM to form PTX2b (**2**), and acid-catalyzed isomerization of anomeric spirocyclic acetal **2** to non-anomeric spirocyclic acetal **1** by the early termination of a dynamic transition process to equilibrium. [6,6]-Spiroacetal PTX2c was also synthesized from **2**. The cytotoxicity assay of the synthetic compounds against HepG2 and Caco2 cancer cells showed a potency order of PTX2 ≫ PTX2b > PTX2c.

Received: September 30, 2013
Published online: November 29, 2013

Keywords: isomerization · macrocycles · natural products · spiro compounds · total synthesis

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[22] For the reaction conditions of the isomerization of **2**, see the Supporting Information.
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