Pergamon

Tetrahedron Letters 40 (1999) 5405–5408

TETRAHEDRON LETTERS

Expeditious Tandem-Metathesis Route to the AB-ring Fragment of Ciguatoxin

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Received 9 April 1999; accepted 19 May 1999

Abstract: The AB-ring fragment of ciguatoxin was synthesized in ten steps from tri-*O*-benzyl-D-glucal based on a highly diastereoselective ring-closing metathesis and subsequent cross metathesis.

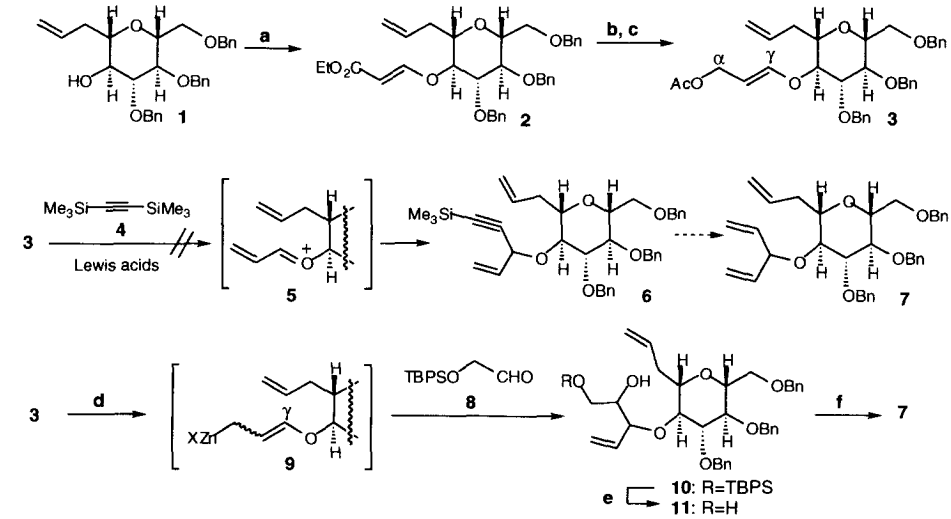
Keyword: Ciguatoxin; Diastereoselective ring-closing metathesis; Cross metathesis; Umpolung of π-allyl palladium

The olefin metathesis reaction has become an important and powerful transformation in organic synthesis.[1,2] In our previous study directed towards the total synthesis of ciguatoxin (CTX1B),[3,4] we established an enantioselective route to the AB-ring fragment.[5] However, this synthesis was linear and lengthy, requiring more than 20 steps from D-glucose. In this paper, we describe a highly diastereoselective ring-closing metathesis[6] and subsequent cross metathesis[7,8] as a rapid and convergent entry to the AB-ring fragment.[9]

The synthesis is initiated with the secondary alcohol (**1**), which is readily available from tri-*O*-benzyl-D-glucal in two steps.[10] Treatment of the alcohol (**1**) with ethyl propiolate in the presence of *N*-methylmorpholine (10 mol%)[11] gave *E*-enol ether (**2**) in 95% yield (Scheme 1). Reduction of **2** with DIBAL-H followed by acetylation gave the γ-alkoxy allylic acetate (**3**) in 95% yield (2 steps). We first attempted to synthesize key intermediate (**7**) *via* a nucleophilic attack of bis-trimethylsilylacetylene (**4**) to an oxocarbenium ion (**5**).[12] The γ-alkoxy allylic acetate (**3**) was treated with **4** (10 eq) in the presence of various Lewis acids ($SnCl_4$, $TiCl_4$, $BF_3{\cdot}Et_2O$, and TMSOTf) in CH_2Cl_2 at low temperatures (from -30 to –5°C). Although no coupled products were obtained, a significant amount of the secondary alcohol (**1**) was recovered in 60-70% yield due to the instability of **5** and poor nucleophilicity of **4**. We then examined the regioselective allylation of **3** utilizing a diethylzinc-mediated umpolung of the π-allyl palladium complex, which was recently developed by Tamaru et al.[13] The allylic acetate (**3**) was treated with $Pd(PPh_3)_4$ (10 mol%), diethylzinc (5 eq), and aldehyde (**8**)[14] (4 eq) in THF. An allylic zinc intermediate (**9**) generated *in situ* was regioselectively reacted with **8** to yield a diastereomeric mixture of γ-adducts (**10**). The mixture was purified after removal of the TBPS group to give diol (**11**) as a diastereomeric mixture in 30% yield from **3**. Deoxygenation of **11** with I_2, PPh_3, and imidazole in toluene afforded an acid-sensitive triene (**7**) in 68% yield.[15]

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01017-5

Scheme 1

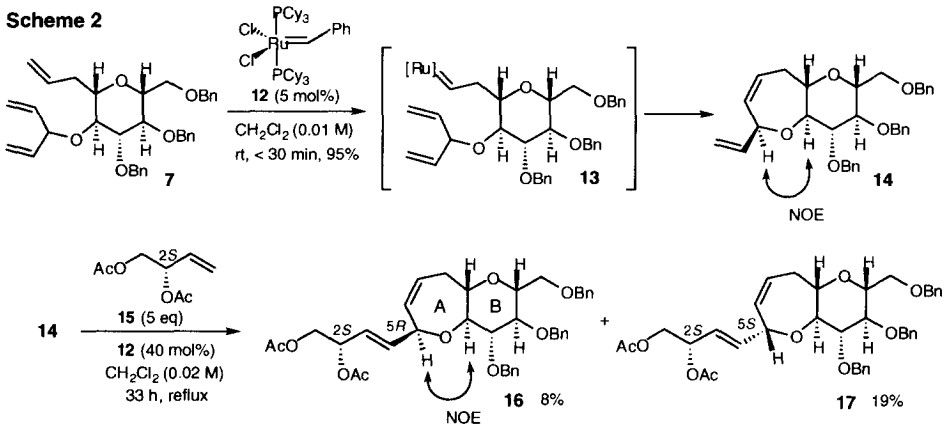


Reagents and conditions: a) ethyl propiolate, *N*-methylmorpholine (10 mol%), CH_2Cl_2, rt, 95%; b) DIBAL-H, CH_2Cl_2, -78°C; c) Ac_2O, pyridine, rt, 95% (2 steps); d) $Pd(PPh_3)_4$ (10 mol%), $ZnEt_2$ (3.5 eq), **8** (4 eq), THF, rt, 60 h; e) TBAF, THF, rt, 30% (2 steps); f) I_2 (6 eq), PPh_3 (5 eq), Imidazole (10 eq), toluene, rt, 16 h, 68%.

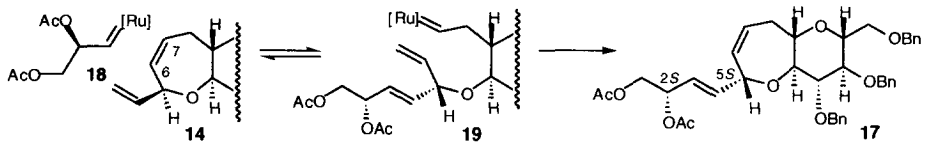
The diastereoselective ring-closing metathesis reaction of **7** using ruthenium catalyst (**12**) (10 mol%) in CH_2Cl_2 (0.015 M) was complete within 30 min to give **14** exclusively in excellent yield (95%) (Scheme 2). The less hindered allylic group of **7** is likely to react rapidly with **12** to form a carbene complex (**13**), which should undergo an equilibrated ring formation with the diastereotopic vinyl groups to yield the most stable (**14**).[6,16] The stereochemistry of **14** was determined by NOE experiments.[17] The final cross-olefin metathesis reaction of **14** with the olefin (**15**)[18] (5 eq) using **12** (40 mol%) proceeded in CH_2Cl_2 (0.02 M) under reflux to give the desired (**16**) together with the C5 epimer (**17**), both of which possess 3,4-(*E*) geometry. Neither the protecting group manipulation of the diol (**15**) nor changing the concentration of **15** increased the chemical yield of this cross-metathesis reaction. A hypothetical reaction pathway to give **17** is shown in Scheme 3. The diene (**14**) may undergo faster ring-opening cross-metathesis[19] with a carbene complex (**18**) at the 6,7-*cis* olefin than at the vinyl group to give **19**, which should form the epimer (**17**).

Thus, the triene (**7**) was synthesized utilizing diethylzinc-mediated umpolung of the π-allyl palladium complex. A highly diastereoselective ring-closing metathesis reaction of **7** was achieved to give the diene (**14**). Although the final cross-metathesis reaction was not improved, we were able to synthesize the AB-ring fragment (**16**) of ciguatoxin in only 8 steps from **1**. Mechanistic investigation of the C5 epimerization process to yield **17** is currently underway in our laboratory.

Scheme 2



Scheme 3



Selected data of **14**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.39 (1H, m, H8), 2.64 (1H, m, H8), 3.19 (1H, td, *J* = 9.0, 4.0 Hz, H9), 3.39 (1H, ddd, *J* = 9.0, 5.0, 2.0 Hz, H13), 3.47 (1H, t, *J* = 9.0 Hz, H12), 3.50 (1H, t, *J* = 9.0 Hz, H10), 3.55 (1H, dd, *J* = 10.5, 5.0 Hz, H14), 3.61 (1H, t, *J* = 9.0 Hz, H11), 3.64 (1H, dd, *J* = 10.5, 2.0 Hz, H14), 4.43 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.47 (1H, d, *J* = 12.5 Hz, CH_2Ph), 4.52 (1H, d, *J* = 12.5 Hz, CH_2Ph), 4.53 (1H, m, H5), 4.69 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.77 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.93 (1H, d, *J* = 11.0 Hz, CH_2Ph), 5.12 (1H, dt, *J* = 10.0, 1.5 Hz, H3), 5.27 (1H, dt, *J* = 17.0, 1.5 Hz, H3), 5.75 (2H, m, H6 and H7), 5.90 (1H, ddd, *J* = 17.0, 10.0, 6.0 Hz, H4), 7.03 (2H, m), 7.19-7.37 (13H, m); ESI-MS, Calcd for $C_{33}H_{36}O_5Na$ ($M+Na^+$) 535.2460, Found 535.2477.

Selected data of **16**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.99 (3H, s, Ac), 2.02 (3H, s, Ac), 2.46 (1H, m, H8), 2.71 (1H, ddd, *J* = 16.0, 8.0, 4.0 Hz, H8), 3.25 (1H, td, *J* = 9.0, 4.0 Hz, H9), 3.46 (1H, ddd, *J* = 9.0, 5.0, 2.0 Hz, H13), 3.56 (1H, t, *J* = 9.0 Hz, H10), 3.56 (1H, t, *J* = 9.0 Hz, H12), 3.63 (1H, dd, *J* = 10.5, 5.0 Hz, H14), 3.67 (1H, t, *J* = 9.0 Hz, H11), 3.71 (1H, dd, *J* = 10.5, 2.0 Hz, H14), 3.99 (1H, dd, *J* = 12.0, 7.5 Hz, H1), 4.18 (1H, dd, *J* = 12.0, 4.0 Hz, H1), 4.51 (1H, d, *J* = 10.5 Hz, CH_2Ph), 4.54 (1H, d, *J* = 12.0 Hz, CH_2Ph), 4.59 (1H, d, *J* = 12.0 Hz, CH_2Ph), 4.62 (1H, m, H5), 4.78 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.83 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.95 (1H, d, *J* = 10.5 Hz, CH_2Ph), 5.51 (1H, m, H2), 5.76 (1H, ddd, *J* = 15.5, 6.5, 1.5 Hz, H3), 5.77 (1H, m, H6), 5.84 (1H, m, H7), 5.92 (1H, ddd, *J* = 15.5, 5.5, 1.0 Hz, H4), 7.18 (2H, m), 7.22-7.38 (13H, m); MALDI-TOFMS, Calcd for $C_{39}H_{44}O_9Na$ ($M+Na^+$) 679.2883, Found 679.3025.

Selected data of **17**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.00 (3H, s, Ac), 2.02 (3H, s, Ac), 2.34 (1H, m, H8), 2.65 (1H, ddd, *J* = 17.5, 7.5, 4.0 Hz, H8), 3.39 (1H, td, *J* = 9.5, 4.0 Hz, H9), 3.44 (1H, m, H13), 3.53 (1H, t, *J* = 9.0 Hz, H12), 3.62 (1H, m, H14), 3.63 (1H, t, *J* = 9.0 Hz, H11), 3.67-3.71 (2H, m, H10 and H14), 4.02 (1H, dd, *J* = 11.5, 6.0 Hz, H1), 4.18 (1H, dd, *J* = 11.5, 3.5 Hz, H1), 4.49 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.53 (1H, d, *J* = 12.0 Hz, CH_2Ph), 4.58 (1H, d, *J* = 12.0 Hz, CH_2Ph), 4.78 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.80 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.89 (1H, m, H5), 4.95 (1H, d, *J* = 11.0 Hz, CH_2Ph), 5.44 (1H, m, H2), 5.67 (1H, m, H6), 5.69 (1H, ddd, *J* = 15.5, 6.0, 1.5 Hz, H3), 5.77 (1H, m, H7), 5.82 (1H, ddd, *J* = 15.5, 5.0, 1.0 Hz, H4), 7.18 (2H, m), 7.22-7.38 (13H, m); MALDI-TOFMS, Calcd for $C_{39}H_{44}O_9Na$ ($M+Na^+$) 679.2883, Found 679.3056.

Acknowledgement

We are grateful to Prof. Yoshinao Tamaru, Nagasaki University for his helpful comments.

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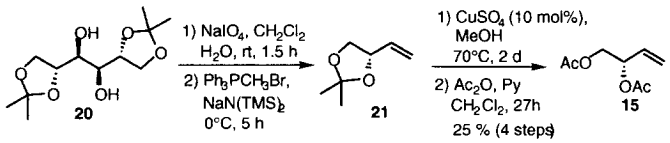
17 The carbon numbering corresponding to that of CTX1B has been used throughout this paper.

18 The olefin (**15**) was synthesized as follows.



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