# Synthesis of JKLM Ring Fragment of Ciguatoxin via Acetylene-Cobalt Strategy

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**Abstract:** A stereoselective synthesis of the JKLM ring fragment has been achieved through a coupling between two segments via heteroconjugate addition, seven-membered ether ring formation mediated by an acetylene cobalt complex and spiroketalization reaction.

**Key words:** acetylene cobalt complex, reductive decomplexation, heteroconjugate addition, medium sized ring, ciguatoxin

Ciguatoxin (CTX) is known as a principal toxin of ciguatera food poisoning caused by carnivorous fishes in the tropical and subtropical sea areas.[1] Several synthetic groups have been studying the total synthesis of CTX (Figure 1).[2,3] We also have endeavored to develop effective methodologies toward the synthesis of ciguatoxin. We have already achieved the syntheses of ABC rings with the side chain,[4] BCDE rings[5] and E′FGH′ rings[6] using acetylene cobalt complex strategy. With regard to right part of ciguatoxin, previously we reported a model study of stereoselective synthesis of the H′IJK ring fragment.[7] In this communication, we report the synthesis of the JKLM ring fragment as the right end of ciguatoxin.

The JKLM-ring fragment **A**, representing C39–C55 portion of ciguatoxin, consists of *trans*-fused tricyclic 6/7/6-membered ether ring and 6/5 spiroketal system. The retrosynthetic analysis for compound **A** is illustrated in Scheme 1. Opening of the terminal spiroketal in compound **A** provides **B** as a synthetic equivalent. The seven-membered ring in **B** would be prepared via acetylene cobalt complex **C**. Opening of the seven-membered ring K in **C** gives compound **D**, which further leads us to the 2 segments **E** and **F** to be coupled between the C46 and C47 bond on the basis of a heteroconjugate addition.[7]

Synthesis of the vinylsulfone **E** began with methyl-α-D-glucopyranoside derivative (Scheme 2). Thus, hydroxyl group at the C2 position in the acetonide **1** was selectively protected by pivaloyl group.[8] Remaining free hydroxyl group was removed under modified Barton conditions[9] to afford compound **2**. The protective groups in **2** were manipulated to provide **3**, which was transformed to lacton **4** via acetolysis, hydrolysis and oxidation of the anomeric position. Addition of allylmagnesium bromide to lactone **4**, followed by Kishi's silane reduction,[10] provided hydropyran system **5** as an exclusive diastereomer. Removal of the pivaloyl group from **5** led to a diol which was converted to **6** through disilylation and selective removal of the silyl group attached to the primary hydroxyl group.[11] Oxidation of the primary alcohol followed by dibromo-olefination of the resulting aldehyde gave the vinyl dibromide[12] which was converted to the thiophenylacetylene **7** by further treatment with *n*-BuLi and $PhSSO_2Ph$. Hydrosilylation of thiophenylacetylene of **7** in the presence of catalytic amount of cobalt complex[13] afforded corresponding vinylsilane with extremely high regioselectivity. Finally, removal of the acetyl group, followed

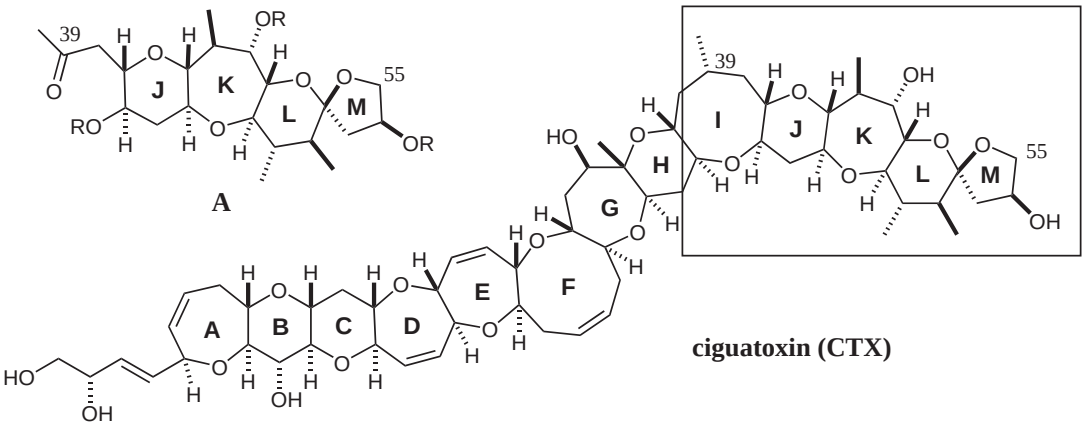


**Figure 1**

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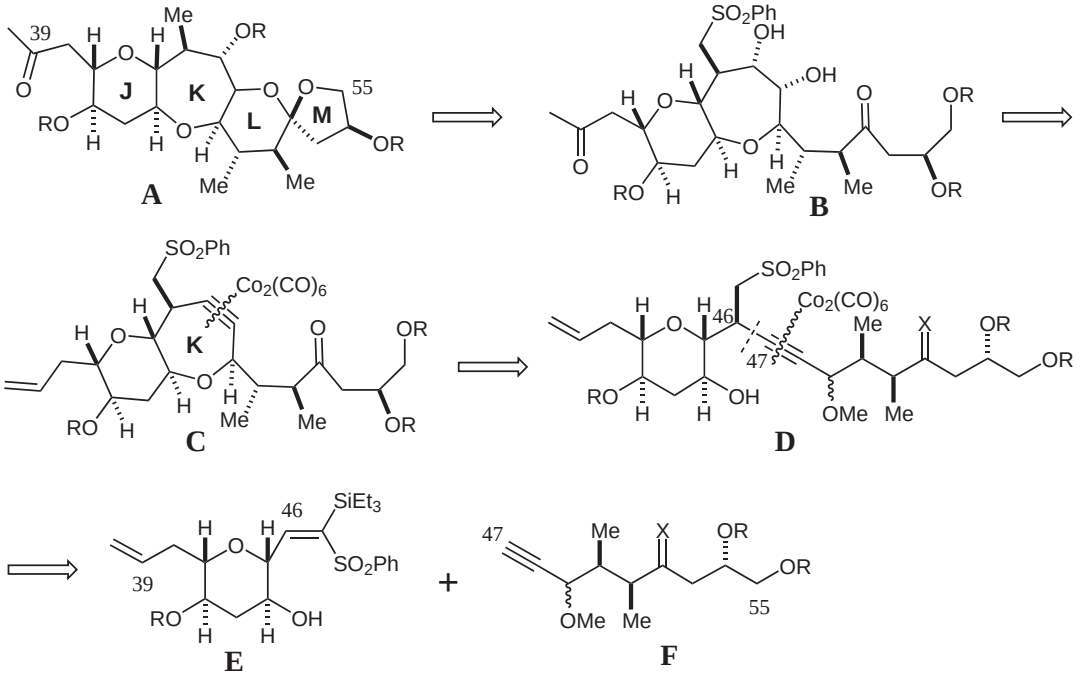
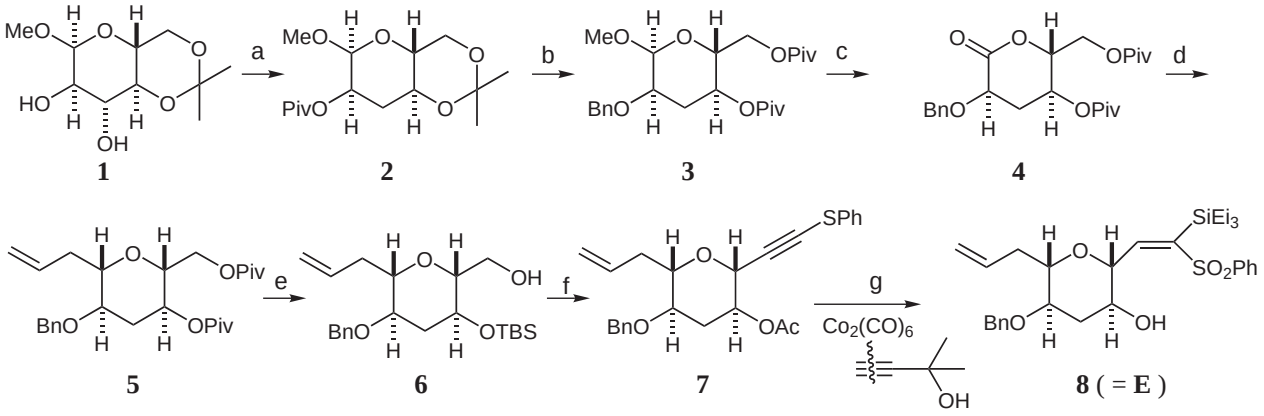


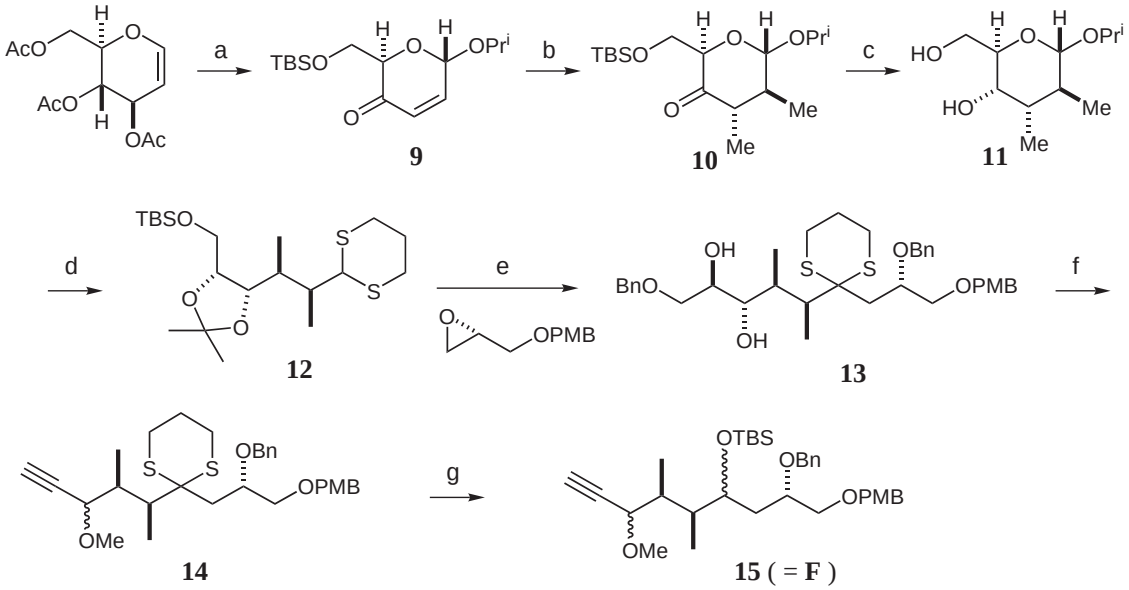
**Scheme 1** Retrosynthetic Analysis of JKLM Segment of CTX

by treatment with *m*-CPBA in the presence of sodium hydrogen phosphate provided the vinyl sulfone **8**.[14]

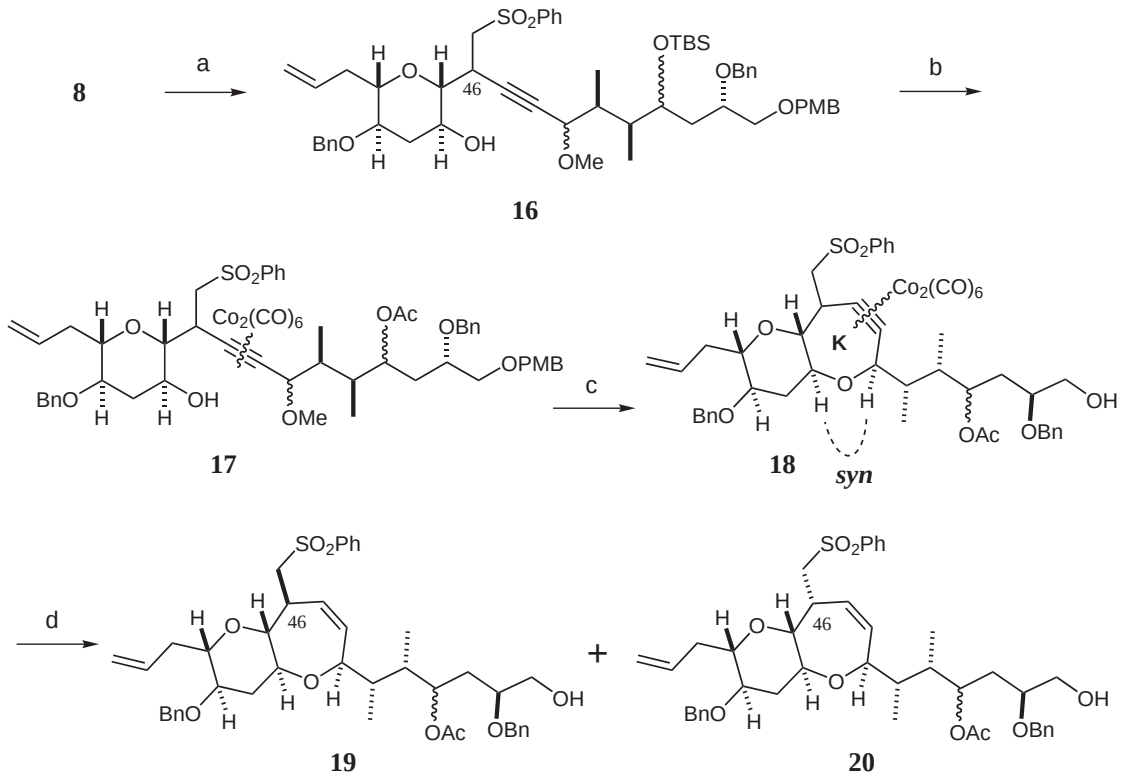
The construction of the other requisite subsegment **F** (in Scheme 1) is shown in Scheme 3. Thus, tri-*O*-acetyl-D-gulcal was converted to the enone **9** by 4-step sequence (O-glycosidation, deacetylation, silylation and oxidation), which could be used in a large scale operation. 1,4-Addition of lithiumdimethyl cuprate to α,β-unsaturated carbonyl of **9**, followed by treatment with MeI in the presence of *N*,*N*-dimethylacetamide as a co-solvent provided **10** as an exclusive diastereomer. The carbonyl group was stereoselectively reduced to the alcohol by $NaBH(OAc)_3$ after the removal of TBS group of **10** to afford the diol **11**. Opening of the pyranose ring of **11** with 1,3-propanedithiol under strongly acidic condition provided open-chain triol compound, which was subsequently protected with TBS and isopropylidene group to give **12**. Coupling reaction of the lithio derivative of dithiane **12** with glycidylmethoxybenzyl ether uneventfully proceeded under mild condition[15] and afforded an alcohol that was protected with benzyl group together with the primary alcohol after desilylation. Subsequent acidic hydrolysis of the acetonide group afforded **13**. Oxidative cleavage of the 1,2-diol of **13** by $Pb(OAc)_4$ provided corresponding aldehyde. The aldehyde was treated with lithium TMS acetylide and



**Scheme 2** *Reagents and conditions*: a) i) Piv-Cl, Py, $CH_2Cl_2$, 68%; ii) thiophosgene, imidazole, $CHCl_3$, toluene, 90 °C; iii) AIBN, $NaH_2PO_2$, 2-methoxy-ethanol, reflux, 87% in 2 steps. b) i) NaOMe, MeOH, 80%; ii) KOH, BnCl; iii) Amberlyst 15E®, MeOH, 86% in 2 steps; iv) Piv-Cl, Py, $CH_2Cl_2$. c) i) $H_2SO_4$, $Ac_2O$, 96% in 2 steps; ii) HCl, DME, $H_2O$, 63%; iii) $Ac_2O$, DMSO, 98%. d) i) $CH_2$=$CHCH_2MgBr$, THF, –78 °C; ii) $Et_3SiH$, $BF_3{\cdot}OEt_2$, $CH_3CN$, –10 °C, 66% in 2 steps. e) i) NaOMe, MeOH, 93%; ii) TBS-Cl, imidazole, DMF; iii) CSA, MeOH, 88% in 2 steps. f) i) $(ClCO)_2$, DMSO, $CH_2Cl_2$; ii) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 91% in 2 steps; iii) n-BuLi, THF, –78 °C to 0 °C, then $PhSSO_2Ph$; iv) TBAF, THF; v) $Ac_2O$, Py, 77% in 3 steps. g) i) $Et_3SiH$, biscobalthexacarbonyl-2-methyl-but-3-yn-2-ol (cat.), $ClCH_2CH_2Cl$; ii) $K_2CO_3$, MeOH; iii) *m*-CPBA, $Na_2HPO_4$, $CH_2Cl_2$, 85% in 3 steps.



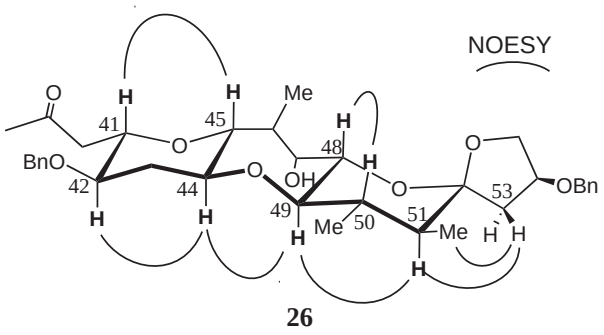

**Scheme 3** *Reagents and conditions*: a) i) *i*-PrOH, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$; ii) $Et_3N$, MeOH, $H_2O$, 84% in 2 steps; iii) TBS-Cl, imidazole, DMF; iv) $Ac_2O$, DMSO, 97% in 2 steps. b) CuI, MeLi, $Et_2O$, 0 °C, then MeI, DMA, 92%. c) i) TBAF, THF, 82%; ii) $NaBH(OAc)_3$, $CH_3CN$, AcOH, 93%. d) i) 1,3-propanedithiol, HCl, $CHCl_3$; ii) TBS-Cl, $Et_3N$, DMAP, $CH_2Cl_2$, 89% in 2 steps; iii) 2,2-dimethoxypropane, PPTS, $CH_2Cl_2$, quant. e) i) (2*S*)-glycidylmethoxybenzyl ether, THF, HMPA, 96%; ii) TBAF, THF; iii) NaH, BnBr, DMF; iv) 80% AcOH, 70% in 3 steps. f) i) $Pb(OAc)_4$, $CH_2Cl_2$, 99%; ii) *n*-BuLi, TMS-acetylene, THF, then MeI; iii) TBAF, THF, 86% in 2 steps. g) i) NCS, $AgNO_3$, 2,4,6-collidine, $CH_3CN$, $H_2O$; ii) $NaBH_4$, MeOH; iii) TBSOTf, Py, $CH_3CN$, 54% in 3 steps.




**Scheme 4** *Reagents and conditions*: a) i) **15**, *n*-BuLi, THF; ii) TBAF, THF, 87% in 2 steps. b) i) ethylvinylether, PPTS, $CH_2Cl_2$, quant.; ii) TBAF, THF, 88%; iii) $Ac_2O$, DMAP, Py; iv) CSA, MeOH, quant. in 2 steps; v) $Co_2(CO)_8$, $CH_2Cl_2$. c) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 93% in 2 steps. d) *bis*-trimethylsilylacetylene, $Bu_3SnH$, toluene, 87% (**19**: 68%, **20**: 19%).

MeI, and then desilylated with TBAF to give the acetylene **14**. Finally, removal of the dithiane group was performed by brief treatment of **14** with *N*-chlorosuccinimide and $AgNO_3$ in wet acetonitrile containing 2,4,6-trimethylpyridine. The unmasked ketone was reduced to an alcohol, which was protected by TBS group to afford the targeted compound **15**.[16]

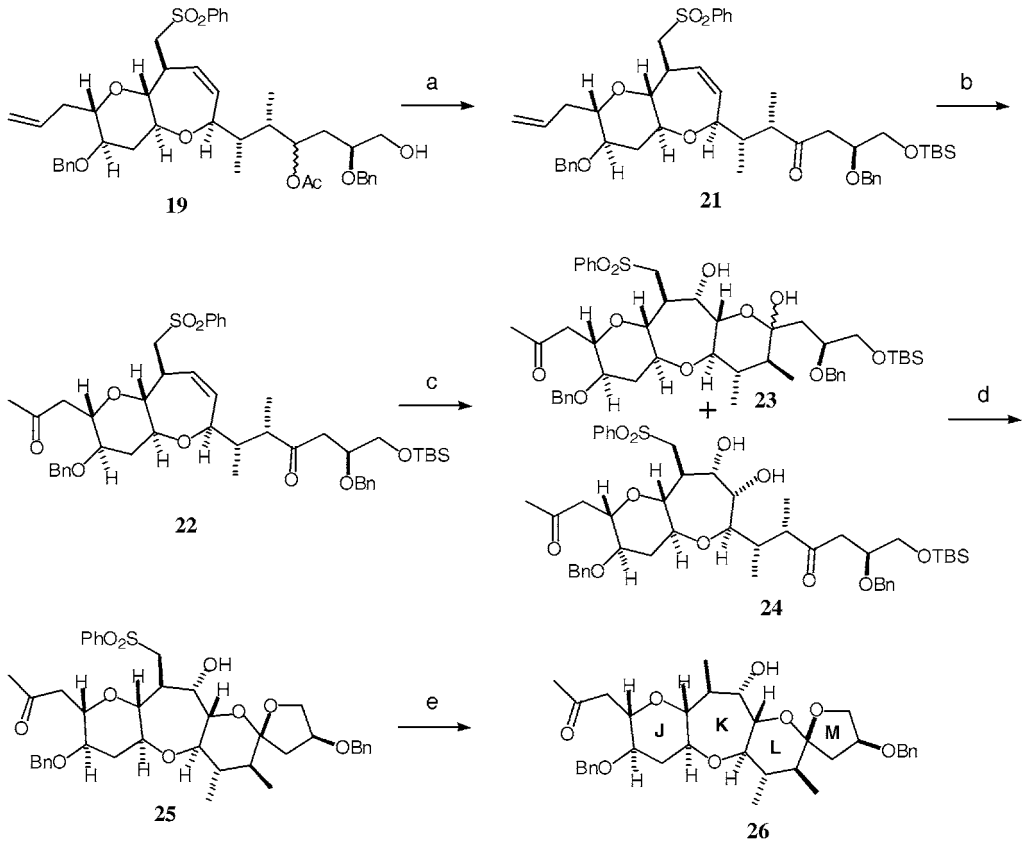
The coupling between **8** and **15** and subsequent K ring cyclization are depicted in Scheme 4. Thus, generation of the lithium acetylide of **15** with *n*-BuLi, followed by addition of **8**, gave a mixture of diastereomeric isomers of **16** (3.6:1 ratio with regard to newly formed C46 asymmetric center). Our previous report of the studies on controlling the stereochemistry of the methyl group in ring K[7a] has shown that the heteroconjugate addition reaction of lithium acetylides and vinyl sulfone with non-protected β-hydroxyl group proceed with extremely high stereoselectivity. The heteroconjugate addition in the present study, however, keeps agreeable stereoselectivity (3.6:1), so we decided to push forward the work of synthesis. TBS group of **16** was exchanged to acetyl group under usual conditions, and then treatment with $Co_2(CO)_8$ in dichloromethane provided the acetylene cobalt complex **17**. Upon treatment of **17** with boron trifluoride etherate, the K ring cyclization took place to afford the bicyclic compound **18** having *syn* stereochemistry. Reductive decomplexation of **18** was conducted with 10 equivalents of $Bu_3SnH$ under heating for 1 hour at 60 °C in toluene[17] in the presence of bis-trimethylsilylacetylene[18] to afford the desired endocyclic olefin **19** and C46-epimer **20** as chromatographically separable products.




**26**

**Figure 2**

The final stage of the synthesis of the JKLM ring fragment is illustrated in Scheme 5. Removal of the acetyl group in **19**, followed by selective protection of the primary alcohol by TBS group and oxidation with IBX,[19] furnished ketone **21**. The terminal olefin in **21** was oxidized to give the methyl ketone **22**. The stereoselective dihydroxylation of the endocyclic olefin in **22** was achieved by Sharpless reagent[20] to afford **23** and **24** as an equilibrium mixture. Desilylation and spiroketalization were conducted with




**19** **21** **22** **23** **24** **25** **26**

**Scheme 5** *Reagents and conditions*: a) i) NaOMe, MeOH; ii) TBSCl, $Et_3N$, DMAP, $CH_2CH_2$, 95% in 2 steps; iii) IBX, DMSO, 97%. b) $PdCl_2$, CuCl, DMF, $H_2O$, $O_2$, 85%. c) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, $H_2O$. d) HF·Py, $CH_3CN$, 72% in 2 steps. e) Na·Hg, $Na_2HPO_4$, MeOH, 82%.

HF·pyridine in acetonitrile to afford the tetracyclic compound **25** as a major product. Finally, reduction with sodium-amalgam in methanol gave desulfonylation product **26**.[21] The stereochemistry of **26** was confirmed from the NOESY experiments and the couplong constants ($J_{44,45}$ = 9.0Hz, $J_{48,49}$ = 9.5Hz) as shown in Figure 2.

We have achieved an efficient synthesis of the JKLM ring fragment based on the convergent strategy. Further studies toward the synthesis of the right part of CTX along this line are now in progress.

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(14) Physical data for **8**. $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.58–0.88 [15 H, m, -Si(C$H_2$C$H_3$)$_3$], 1.47 (1 H, q, *J* = 11.5 Hz, H-43a), 2.16 (1 H, m, allylic), 2.55 (1 H, m, allylic), 2.73 (1 H, dt, *J* = 12.0 Hz, 4.5 Hz, H-43b), 3.01 (1 H, d, *J* = 9.0 Hz, -O*H*), 3.11–3.27 (2 H, m, H-41, 42), 3.34 (1 H, m, H-44), 4.45 (1 H, d, *J* = 11.5 Hz, -OC$H_2$Ph), 4.63 (1 H, d, *J* = 11.5 Hz, -OC$H_2$Ph), 4.68 (1 H, ddd, *J* = 11.5 Hz, 9.5 Hz, 4.5 Hz, H-44), 4.76 (1 H, t, *J* = 9.0 Hz, H-45), 4.97–5.05 (2 H, m, olefinic), 5.68–5.83 (1 H, m, olefinic), 6.40 (1 H, d, *J* = 9.0 Hz, H-46), 7.26–7.40 (5 H, m, aromatic), 7.48–7.63 (3 H, m, aromatic), 7.83–7.90 (2 H, m, aromatic).

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(16) Physical data for **15**. $^1$H NMR ($CDCl_3$, 300M Hz) δ 0.00–0.08 [6 H, m, -Si(C$H_3$)$_2$*t*-Bu], 0.86–1.03 [15 H, m, -Si(C$H_3$)$_2$*t*-Bu, C$H_3$-59, C$H_3$-60], 1.62–1.99 (4 H, m, H-50, 51, 53a, 53b), 2.36–2.45 (1 H, m, H-47), 3.32–3.40 (3 H, m, -OC$H_3$), 3.48–4.06 (5 H, m, H-49, 52, 54, 55a, 55b), 3.83 (3 H, s, -OC$_6$H$_4$OC$H_3$), 4.49–4.76 (4 H, m, -OC$H_2$Ar), 6.90 (2 H, br d, *J* = 8.0 Hz, aromatic), 7.27–7.39 (7 H, m, aromatic).

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(21) Physical data for **26**. IR (KBr) 3447, 2926, 1717, 1636, 1456, 1355, 1077, 1025, 938, 739, 698, 419 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.01 (3 H, δ, *J* = 6.5 Hz, C$H_3$-60), 1.06 (3 H, d, *J* = 6.5 Hz, C$H_3$-59), 1.12 (3 H, d, *J* = 7.5 Hz, C$H_3$-58), 1.40 (1 H, q, *J* = 11.5 Hz, H-43a), 1.48 (1 H, dq, *J* = 11.0 Hz, 6.5 Hz, H-51), 1.61 (1 H, ddq, *J* = 11.0 Hz, 10.0 Hz, 6.5 Hz, H-50), 2.00 (1 H, qdd, *J* = 7.5 Hz, 5.0 Hz, 3.5 Hz, H-46), 2.08 (1 H, dd, *J* = 14.0 Hz, 4.0 Hz, H-53a), 2.13 (1 H, dd, *J* = 14.0 Hz, 6.5 Hz, H-53b), 2.45 (1 H, dd, *J* = 15.5 Hz, 9.0 Hz, H-40a), 2.54 (1 H, dt, *J* = 12.0 Hz, 4.5 Hz, H-43), 2.79 (1 H, dd, *J* = 15.5 Hz, 3.5 Hz, H-40b), 1.61 (1 H, ddq, *J* = 11.0 Hz, 10.0 Hz, 6.5 Hz, H-50), 2.95 (1 H, dd, *J* = 9.5 Hz, 5.0 Hz, H-45), 3.15 (1 H, ddd, *J* = 11.5 Hz, 9.0 Hz, 4.5 Hz, H-42), 3.26 (1 H, t, *J* = 9.5 Hz, H-49), 3.59 (1 H, td, *J* = 9.0 Hz, 3.5 Hz, H-41), 3.62 (1 H, dd, *J* = 9.5 Hz, 2.0 Hz, H-48), 3.65 (1 H, dd, *J* = 3.5 Hz, 2.0 Hz, H-47), 3.69 (1 H, ddd, *J* = 11.5 Hz, 9.5 Hz, 4.5 Hz, H-44), 3.85 (1 H, dd, *J* = 9.5 Hz, 5.0 Hz, H-55a), 3.96 (1 H, dd, *J* = 9.5 Hz, 2.0 Hz, H-55b), 4.26 (1 H, dddd, *J* = 6.5 Hz, 5.0 Hz, 4.0 Hz, 2.0 Hz, H-54), 4.39 (2 H, d, *J* = 11.5 Hz, -OC$H_2$Ph), 4.45 (2 H, d, *J* = 12.0 Hz, -OC$H_2$Ph), 4.47 (2 H, d, *J* = 12.0 Hz, -OC$H_2$Ph), 4.63 (2 H, d, *J* = 11.5 Hz, -OC$H_2$Ph), 7.20–7,37 (10 H, m, aromatic). ESI Q-TOF MS calcd for $C_{35}H_{47}O_8$ 595.327 [M + H]$^+$, found 595.336.