STUDIES TOWARD THE SYNTHESIS OF FURANOCEMBRANE BIPINNATIN J: SYNTHESIS OF A 2,3,5-TRISUBSTITUTED FURFURYL ETHER INTERMEDIATE

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Abstract – Synthesis of 2,3,5-trisubstituted furfuryl ether (**29**), a potential intermediate in a synthetic approach to bipinnatin J, was achieved by a combination of etherification and Stille cross-coupling reaction. Unexpectedly, an intramolecular coupling reaction of **29** proceeded through S_N2' substitution to give 15-membered furfuryl ether (**30**). Formation of γ-butenolide (**34**) was also accomplished by a ruthenium-catalyzed carbonylation of allenic alcohol (**33**).

INTRODUCTION

Marine furanocyclic natural products, such as lophotoxin,[1] bipinnatins,[2] kallolides,[3] and pinnatins,[4] were isolated from gorgonians and soft corals in tropical and temperate seas (Figure 1). Lophotoxin and bipinnatins are members of the lophotoxin family of marine neurotoxins, which block nicotinic acetylcholinergic neurotransmission in autonomic ganglia causing paralysis and asphyxiation.[5] Kallolide A is an antiinflammatory agent with activity comparable to that of indomethacin.[3a] Pinnatins are potent antitumor agents.[4a] Although several total syntheses of furanocembranes (acerosolide and rubifolide) and pseudopteranes (gorgiacerone, kallolides A and B) have been achieved by Paquette *et al.*[6] and Marshall *et al.*,[7] no total synthesis of lophotoxin, bipinnatins, and pinnatins has been achieved yet owing to their structural complexity and lability of furan derivatives.[8]

We have recently reported the stereospecific construction of *anti*- and *syn*-isopropenyl alcohol moieties at the C(2) and C(3) positions of 2,5-bridged furanocycles, such as kalollide A and pinnatin A, employing the [2,3] Wittig rearrangement of cyclic furfuryl ethers.[9] In this regard, we have intended to synthesize furanocembrane bipinnatin J (**1**)[2b] because of its potent biological activity and also structural similarity to
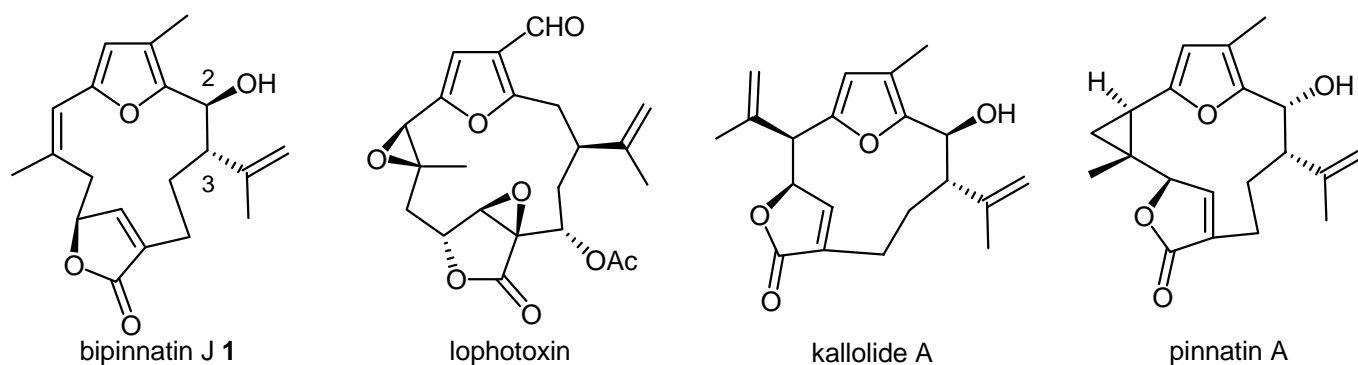
Figure 1.

lophotoxin. Bipinnatin J (**1**) bears three chiral centers with *anti*-homoallylic hydroxy and γ-butenolide moieties, whose stereoselective introduction seems to be a central issue of the synthesis. The retrosynthetic plan is illustrated in Scheme 1. A fundamental premise from the outset was that the γ–butenolide moiety could be introduced in a stereoselective manner late in the synthesis.[7]   Thus, 14-membered furanocycle (**2**) would be postulated as an intermediate. Introduction of the γ-butenolide into furanocycle (**2**) was envisioned to be realized by conversion of propargylic alcohol into allene[10] followed by ruthenium-catalyzed cyclic carbonylation[11] of the corresponding allenic alcohol. *anti*-Homoallylic alcohol (**2**) could be synthesized by Wittig rearrangement of cyclic furfuryl ether (**3**) based on our previous result.[9] Key 17-membered cyclic ether (**3**) could be synthesized by either an intramolecular Nozaki-Hiyama-Kishi reaction[12] of ω–iodoalkynyl aldehyde (**4**) or an intramolecular coupling reaction[13] of ω-alkynylated allylic halide (**5**). We describe here a synthesis of 2,3,5-trisubstituted
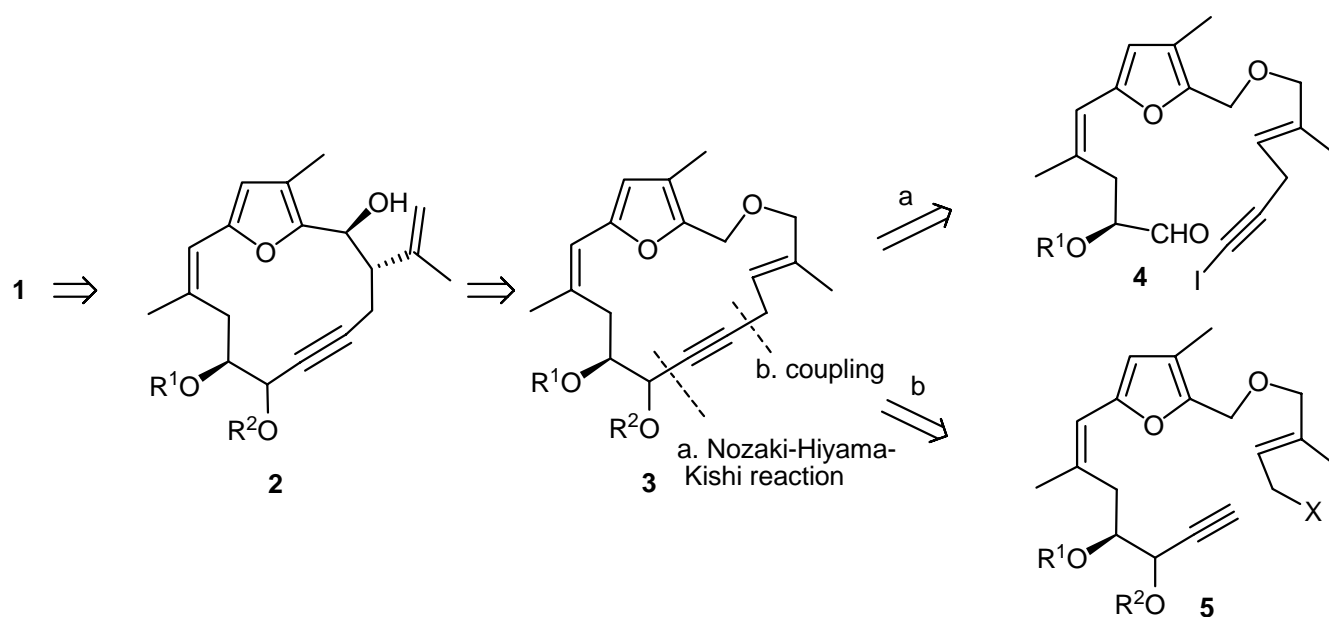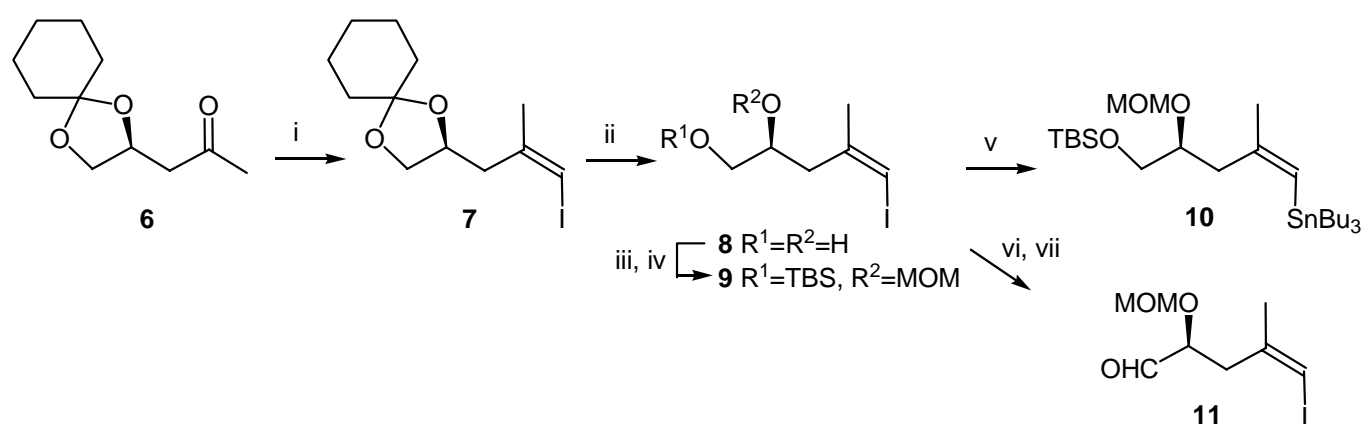

Scheme 1.

furfuryl ether (**29**), a potent intermediate in a synthetic approach to bipinnatin J (**1**), by a Stille coupling between bromofurfuryl ether (**25**) and vinylstannane (**10**) followed by introduction of acetylene moiety. We also demonstrated the stereoselective construction of γ–butenolide moiety using a model compound.

RESULTS AND DISCUSSION

We first prepared chiral segments forthe left parts of intermediates (**4**) and (**5**) from a known chiral ketone (**6**)[14] as shown in Scheme 2. Highly *Z*-selective Wittig iodomethylenation of aldehyde was described by Stork *et al*. and Bestmann *et al*.[15] but there has been no report on that of unsymmetrical ketone to date. Although reaction of **6** with iodomethyltriphenylphosphorane underthe reported condition[15a] gave only a trace of vinyl iodide as a *E/Z* mixture probably due to elimination of β–alkoxy moiety in **6**, the addition of LiBr suppressed side reaction to afford vinyl iodide in 94% yield but in low selectivity (*E/Z*=48/52).[16] The observed LiBr effect might be explained by increasing the reactivity of ketone carbonyl group with coordination of lithium cation.[17] Acid treatment of **7** gave diol (**8**), whose selective protection of primary hydroxy group with TBSCl followed by reaction of secondary hydroxy group with MOMCl furnished **9**. Vinyl iodide (**9**) was further converted into vinylstannane (**10**) by trapping of the lithiated intermediate with tributyltin chloride. Transformation of **9** to α–alkoxy aldehyde (**11**) was carried out by deprotection of silyl moiety and oxidation of the resulting alcohol with sulfurtrioxide-pyridine complex in DMSO (Parikh-Doering oxidation).

Scheme 2. *Reagents and conditions*: (i) ICH$_2$PPh$_3$I (3 equiv.), LiHMDS (3 equiv.), LiBr (6 equiv.), THF-HMPA (10 : 1), -30°C, 1.5 h, 94%, *E/Z*=48/52; (ii) 0.5 M HCl (2.7 equiv.), THF, reflux, 12 h, 97%; (iii) TBSCl (1.6 equiv.), Et$_3$N (2.3 equiv.), DMAP (0.1 equiv.), CH$_2$Cl$_2$, rt, 12 h, 92%; (iv) MOMCl (10 equiv.), *i*-Pr$_2$NEt (28 equiv.), Bu$_4$NI (0.4 equiv.), rt, 21 h, 95%; (v) *t*-BuLi (2.1 equiv.), THF, -78°C, then Bu$_3$SnCl (1.1 equiv.), from −30°C to rt, 1.25 h, 75%; (vi) TBAF (1.2 equiv.), THF, rt, 36 h, 98%; (vii) SO$_3$-pyridine complex (4 equiv.), Et$_3$N (10 equiv.), DMSO (20 equiv.), CH$_2$Cl$_2$, 0°C, 4 h, 76%.

Enyne (**15**), the right part for intermediate (**4**), was prepared as shown in Scheme 3. Stille cross-coupling reaction of vinylstannane (**12**), the silyl ether of a known alcohol,[18] with 3-trimethylsilylpropargyl

bromide gave skipped enyne (**13**) in 67% yield. The use of Ph₃As in place of Ph₃P and DMA ratherthan THF provided improvement in chemical yield.[19] Treatment of **13** with HF in MeCN resulted in selective deprotection to afford allylic alcohol (**14**). Exchanging terminal trimethylsilyl moiety in **13** into bromide was carried out by reaction of NBS and AgNO₃ in acetone to furnish bromoalkyne (**15**).[20]
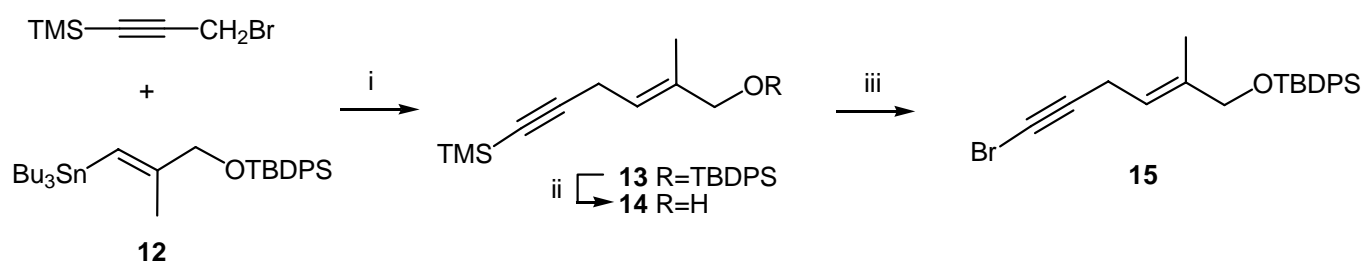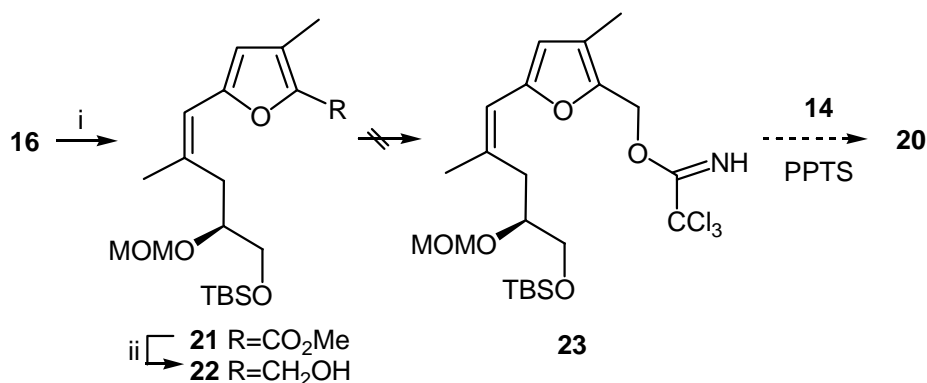
Scheme 3. *Reagents and conditions*: (i) **12** (1 equiv.), 3-trimethylsilylpropargyl bromide (1 equiv.), Pd₂(dba)₃ (5 mol%), Ph₃As (10 mol%), DMA, 110°C, 0.5 h, 67%; (ii) HF (2 equiv.), MeCN, rt, 4 h, 83%; (iii) NBS (1.4 equiv.), AgNO₃ (0.5 equiv.), acetone, rt, 3 h, 89%.

With left and right parts of the intermediates in hand, we examined the synthesis of ω–iodoalkynyl aldehyde (**4**) as follows. (Schemes 4 and 5) Reduction of 5-bromo-3-methylfuroate (**16**)[21] with DIBAL gave relatively unstable furfuryl alcohol (**17**), which was treated with Cl₃CCN and DBU[22] to afford imidate (**18**) in 82% yield (2 steps). Etherification of allylic alcohol (**14**) with **18** was carried out in the presence of PPTS to provide furfuryl ether (**19**) in 76% yield.[23] Unfortunately, attempt to prepare vinylfuran (**20**) using Stille reaction of vinylstannane (**10**) with **19** failed under various conditions.
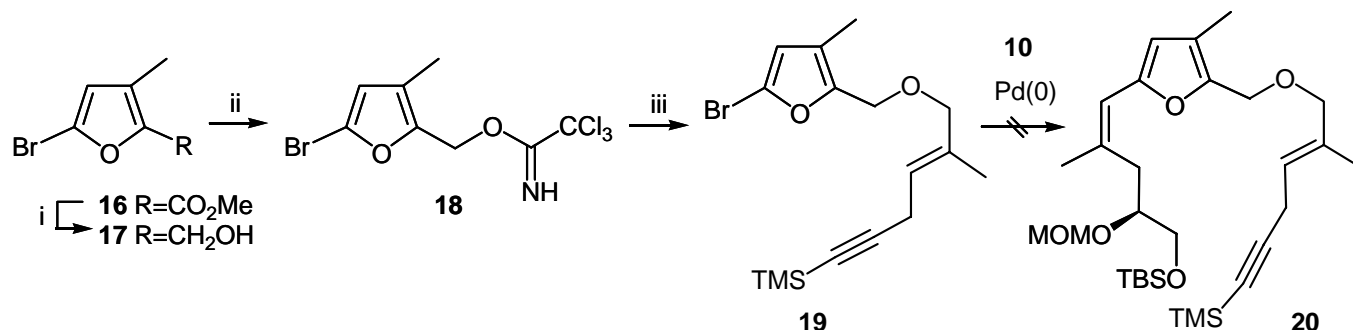
Scheme 4. *Reagents and conditions*: (i) DIBAL (2.2 equiv.), CH₂Cl₂, -78°C, 1 h; (ii) Cl₃CCN (1.3 equiv.), DBU (0.2 equiv.), CH₂Cl₂, 0°C, 20 min, 82% (2 steps); (iii) **14** (1 equiv.), **18** (2 equiv.), PPTS (1 equiv.), CH₂Cl₂, 0°C, 1 h, 76% from **14**

We also tried changing the order of these reactions to obtain **20**. Stille reaction of **10** with bromofuroate (**16**) underwent smoothly to produce vinylfuroate (**21**), whose reduction with DIBAL gave furfuryl

Scheme 5. *Reagents and conditions*: (i) **10** (1 equiv.), **16** (1.1 equiv.), Pd(Ph₃P)₄ (5 mol%), *i*-Pr₂NEt (1.5 equiv.), DMF, 110°C, 3.25 h, 72% from **10**; (ii) DIBAL (2.2 equiv.), CH₂Cl₂, -78°C, 40 min, 91%.

alcohol (**22**). Trichloroacetimidation of **22** did not give **23** owing to its instability. Although this discrepancy in the reactivity toward Stille reaction would not be rationalized, the 1,4-enyne part might disturb the oxidative addition of palladium species by its palladium coordination.

We next examined the synthesis of 17-membered cyclic furfuryl ether (**3**) through ω-alkynylated allylic halide (**5**) as shown in Scheme 6. Etherification of **17** with allylic chloride (**24**), the ethoxyethyl ether of a known alcohol,[24] under usual Williamson reaction condition gave furfuryl ether (**25**) in moderate yield. Stille reaction of **10** with **25** furnished vinylfurfuryl ether (**26**), whose treatment with TBAF followed by Parikh-Doering oxidation of the resulting alcohol provided α–alkoxy aldehyde (**27**). Addition of ethynylmagnesium bromide to **27** gave an inseparable diastereomeric mixture of propargylic alcohol, which was protected as silyl etherto afford **28**. Compound (**28**) was converted to **29**, an important precursor for **3**, by removal of ethoxyethyl moiety followed by chlorination of the resulting allylic alcohol.[25] The stage was now set forthe examination of the ring closure by coupling reaction of ω-alkynylated allylic chloride.[13d] Treatment of **29** with CuI (10 equiv.), NaI (15 equiv.), and Cs₂CO₃ (10 equiv.) in DMF (2.5 mM concentration) at 80°C brought about S_N2' substitution to provide 15-membered cyclic furfuryl ether (**30**) in 45% yield. Since the coupling reaction of copper(I) alkynides with allylic halides has produced preferentially 1,4-enynes, S_N2 products,[13e, 26] we expected S_N2 product (**31**) as a major product ratherthan S_N2' product (**30**) in this reaction. Moreover, semi-empirical MO calculations using the MNDO Hamiltonian have shown 16.4 kcal/mol as the energy difference between the two optimized conformations of 15- and 17-membered model compounds, thus indicating that 17-membered furfuryl ether (**31**) should be thermodynamically more stable than 15-membered ether (**30**) (Figure 2). This observed siteselectivity might be explained by assuming that the participation of the neighboring alkoxy group in furfuryl ether resulted in S_N2' substitution to form three membered oxonium intermediate, which could be attacked at the quaternary carbon by acetylide.
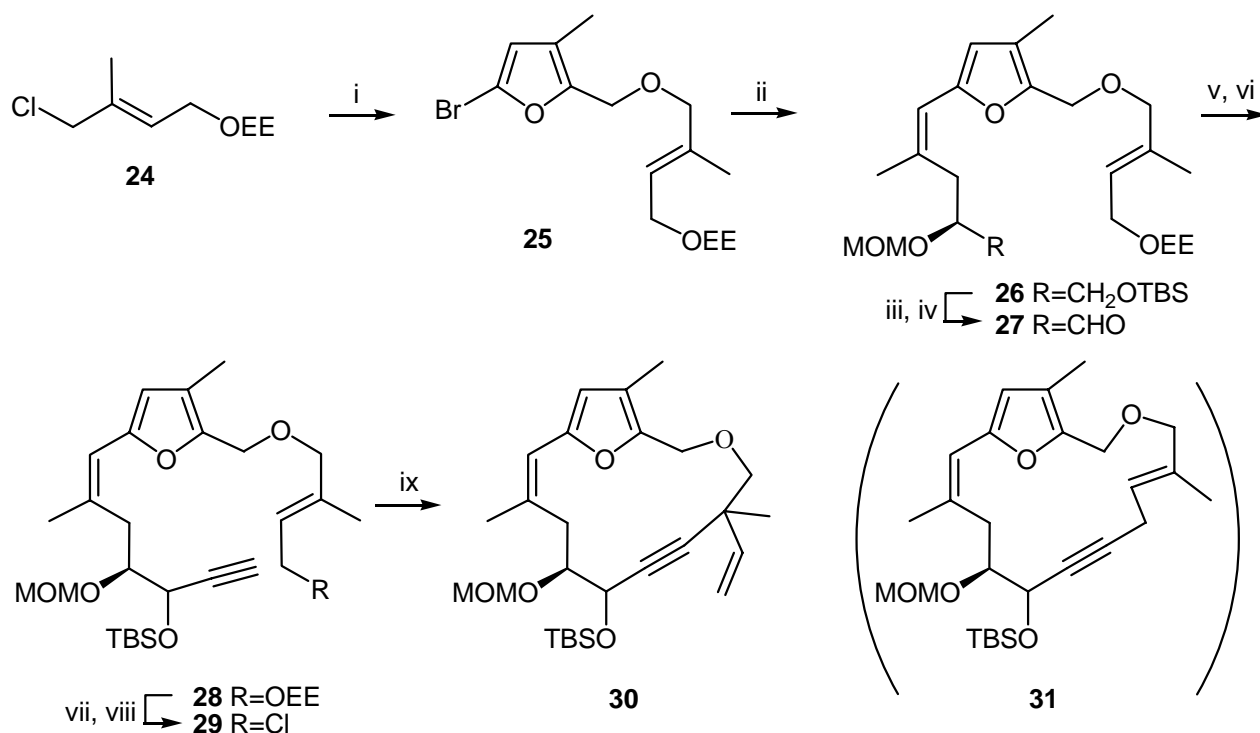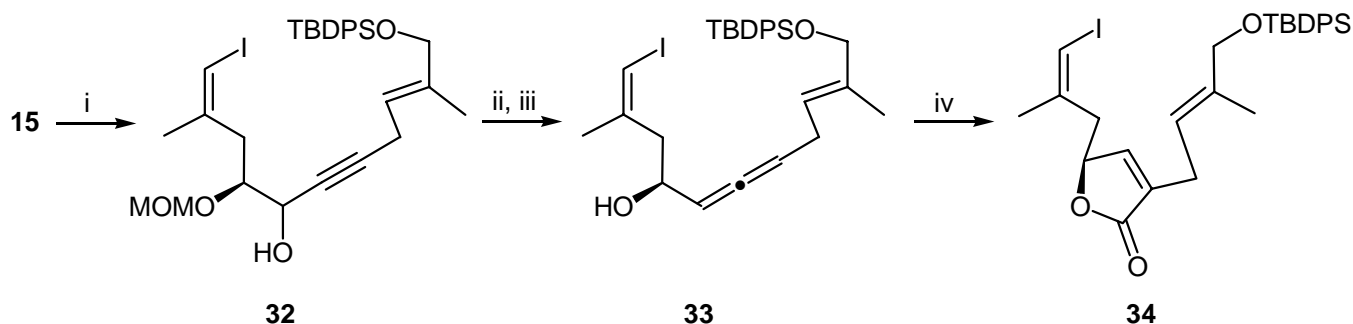
Scheme 6.   *Reagents and conditions*: (i) **17** (1.1 equiv.), NaH (*ca* 50% purity, 1 equiv.), DMF, 0°C, 2 h, 59%; (ii) **10** (1.2 equiv.), Pd$_2$(dba)$_3$ (5 mol%), Ph$_3$As (21 mol%), *i*-Pr$_2$NEt (1.2 equiv.), DMA, 80°C, 2 h, 78%; (iii) TBAF (1.5 equiv.), CH$_2$Cl$_2$, rt, 3 h, 89%; (iv) SO$_3$-pyridine complex (4 equiv.), *i*-Pr$_2$NEt (10 equiv.), DMSO (20 equiv.), CH$_2$Cl$_2$, 0°C, 2 h; (v) ethynylmagnesium bromide (7 equiv.), THF, form -78°C to -20°C, 1 h; (vi) TBSOTf (6 equiv.), 2,6-lutidine (12 equiv.), CH$_2$Cl$_2$, -50°C, 1 h, 55% (3 steps); (vii) 0.5 M HCl (1.5 equiv.), THF, rt, 3 h, 77%; (viii) MsCl (6.5 equiv.), 2,6-lutidine (8.7 equiv.), LiCl (6.2 equiv.), DMF, -5°C, 6 h, 60%; (ix) CuI (10 equiv.), NaI (15 equiv.), Cs$_2$CO$_3$ (10 equiv.), DMF, 80°C, 45%.
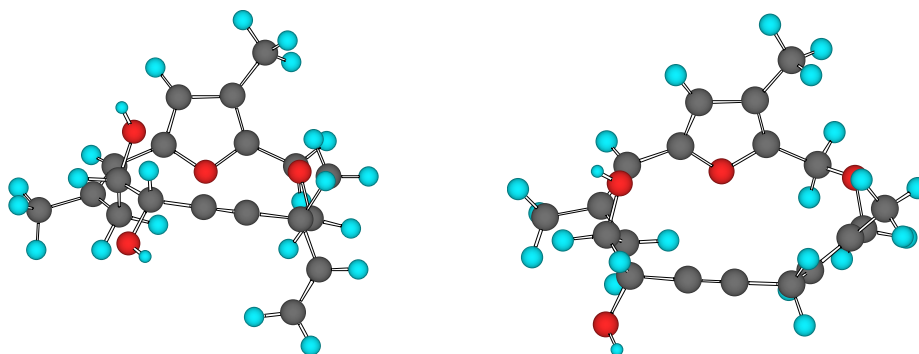
Figure 2.   Conformations of furfuryl ether.   Left:15-membered compound.   Right:17-membered compound.

In view of the synthesis of naturally occurring furanocyclic diterpenes, we then examined the construction of γ-butenolide from propargylic alcohol, such as **2**, using a model compound. (Scheme 7) Reaction of EtMgBr with alkynyl bromide (**15**) followed by the addition of the resulting acetylide to aldehyde (**11**) gave an inseparable mixture of propargylic alcohol (**32**) quantitatively. Compound (**32**) was converted to allenic alcohol (**33**) by the procedure reported by Myers *et al.*[10] and subsequent removal of

methoxymethyl moiety with CBr$_4$ in *i*-PrOH.[27] Ru-catalyzed cyclocarbonylation[11] of **33** was successfully carried out to provide a desired γ–butenolide (**34**) in 66% yield.[28]

Scheme 7. *Reagents and conditions*: (i) **15** (2 equiv.), EtMgBr (2.1 equiv.), THF, 0°C, 15 min, then **11** (1 equiv.), from -78°C to 0°C, 1.5 h, 99%; (ii) Ph$_3$P (5 equiv.), DEAD (5 equiv.), *o*-nitrobenzenesulfonyl hydrazide (5 equiv.), THF, -15°C, 7 h, then from -15°C to rt, 2 h, 51%; (iii) CBr$_4$ (0.2 equiv.), *i*-PrOH, reflux, 3 h, 67%; (iv) Ru$_3$(CO)$_{12}$ (5 mol%), Et$_3$N (3 equiv.), CO (10 atm), 100°C., 119 h, 66%.

In summary, we have achieved the synthesis of a 2,3,5-trisubstituted furfuryl ether, a potent intermediate in a synthetic approach to bipinnatin J, employing a combination of etherification and Stille coupling reaction.   An intramolecular coupling reaction of ω-alkynylated allylic chloride gave unanticipated S$_N$2' product, 15-membered furfuryl ether. We have also demonstrated the stereoselective formation of γ-butenolide from propargylic alcohol. Further synthetic studies toward bipinnatin J are currently under investigation.

ACKNOWLEDGEMENTS

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25. Data for an inseparable mixture (1 : 1) of **29**: IR ν max 1040, 1080, and 1100 cm^{-1}; ^{1}H NMR (CDCl$_3$; 270 MHz) δ 0.14 (6H, s, Si(CH$_3$)$_2$), 0.90 and 0.91 (each 4.5H, each s, C(CH$_3$)$_3$), 1.72 (3H, s, 2"-CCH$_3$), 1.94 (3H, s, 2'-CCH$_3$), 2.00 (3H, s, 3-CCH$_3$), 2.45 (1H, d, *J*=2.1 Hz, 7'-CH), 2.53 and 2.63 (each 0.5H, each dd, *J*=3.5, 13.5 and 2.3, 13.8 Hz, 3'-C*H*H), 2.84 and 2.88 (each 0.5H, each dd, *J*=2.8, 13.5 and 3.8, 13.8 Hz, 3'-CH*H*), 3.31 and 3.32 (each 1.5H, each s, CH$_3$O), 3.76-4.04 (1H, m, 4'-CH), 3.88 (2H, s, 1"-CH$_2$), 4.10 (2H, d, *J*=7.9 Hz, 4"-CH$_2$), 4.35 (2H, s, 2-CCH$_2$), 4.44 and 4.54 (each 0.5H, each dd, *J*=2.1, 3.5 and 2.1, 5.1 Hz, 5'-CH), 4.61 and 4.63 (each 0.5H, each d, each *J*=7.1 Hz, OC*H*HO), 4.71 and 4.79 (each 0.5H, each d, each *J*=6.9 Hz, OCH*H*O), 5.70 (1H, t, *J*=7.9 Hz, 3"-CH), 6.12 (1H, s, CH), 6.29 and 6.30 (each 0.5H, s, CH); ^{13}C NMR (CDCl$_3$; 67.8 MHz) δ -5.0, -4.8, -4.5 (2), 9.9, 10.0, 13.7 (2), 18.1, 18.2, 25.2, 25.5, 25.7 (3), 25.8 (3), 34.3, 35.0, 40.1 (2), 55.7 (2), 61.7, 61.8, 66.0, 66.1, 73.9, 74.1, 74.2 (2), 78.5, 78.7, 82.9 (2), 96.4, 97.1, 110.7, 111.2, 117.0, 117.2, 120.6 (2), 122.4 (2), 135.6, 136.2, 138.7 (2), 145.1, 145.3, 151.8, 151.9; MS (EI): 510 (M$^+$), 512 (M$^+$+2); HRMS (EI): calcd for C$_{27}$H$_{43}$O$_5$ClSi: 510.2568. Found: 510.2573.

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28. Data for **34**: $[\alpha]_D^{23}$ +10.6 ° (c 1.07, CHCl$_3$) ;IR ν max 1110 and 1760 cm^{-1} ; ^{1}H-NMR (CDCl$_3$; 270 MHz) δ 0.95-1.15 (9H, br s, C(CH$_3$)$_3$), 1.60 (3H, s, 4'-CCH$_3$), 1.97 (3H, s, 2''-CCH$_3$), 2.35 (2H, s, 2-CH$_2$), 2.49 (1H, dd, *J*=7.6 and 13.5 Hz, 1'-C*H*H), 2.63 (1H, dd, *J*=5.8 and 13.5 Hz, 1'-CH*H*), 4.05 (2H, s, 5'-CH$_2$), 5.01 (1H, ddd, *J*=0.7, 5.8 and 7.6 Hz, 5-CH), 5.44 (1H, s, 3'-CH), 6.09 (1H, s, 3''-CH), 7.05 (1H, d, *J*=0.7 Hz, 4-CH), 7.25-7.50 (6H, m, Ar), 7.55-7.75 (4H, m, Ar); ^{13}C-NMR (CDCl$_3$: 125.65 MHz) δ 13.6, 19.3, 24.8, 25.1, 25.2, 26.8 (3), 42.4, 68.6, 78.4, 79.4, 122.3, 127.6 (4), 129.6 (2), 133.7 (2), 134.1, 135.5 (4), 142.4, 147.6, 173.3 ; MS (CI): 601 (M+1); HRMS (CI): calcd for C$_{30}$H$_{37}$O$_3$ISi+H : 601.1635. Found ; 601.1609.