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# SYNTHESIS OF THE TRIOXADISPIROKETAL DOMAIN OF SPIRASTRELLOLIDE B

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**Abstract** – Assembly of the trioxadispiroketal domain of the naturally occurring protein serine/threonine phosphatase inhibitor spirastrellolide B via a staged double intramolecular hetero-Michael addition is detailed.

## INTRODUCTION

Spirastrellolides A and B are novel natural products isolated from extracts of the Caribbean marine sponge *Spirastrella coccinea* by Andersen and co-workers.[1] These compounds were originally identified as new sponge-derived antimitotics. Spirastrellolide A methyl ester was shown to exhibit potent antimitotic activities in a cell based assay ($IC_{50}$ 100 ng/mL).[1a] However, unlike most other antimitotic sponge macrolides, the spirastrellolides do not affect tubulin polymerization directly. Instead, the spirastrellolides are potent and relatively selective inhibitors of serine / threonine protein phosphatases (PP2A, $IC_{50}$ = 1 nM; PP1, $IC_{50}$ = 50 nM).[1b] Hence, the bioactivities of the spirastrellolides are similar to those of known protein phosphatase inhibitors, such as okadaic acid[2] and forstriecin,[3] which induce premature entry into mitosis and mitotic arrest.

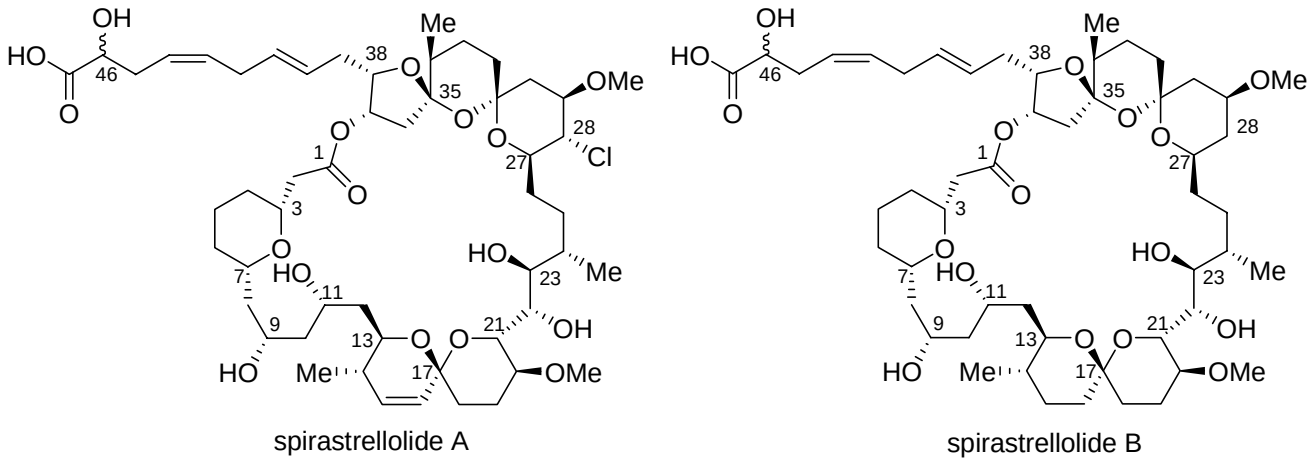
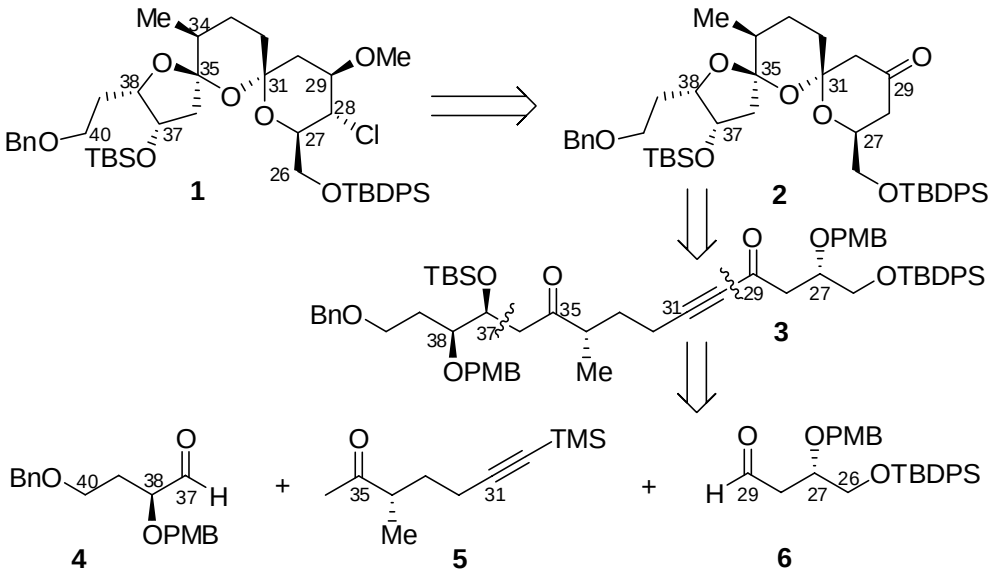



Figure 1. Structures of Spirastrellolides A and B

Despite the initial partial structure and isolation report of spirastrellolide A, it was not until one year later that a revised structural assignment was published, in which a chlorine containing trioxadispiroketal was proposed.[1b] In addition, extensive ROESY studies further supported the initial stereochemical assignments. The relative stereochemistry of the C3-C7, C9-C24, and C27-C38 fragments of spirastrellolide A were assigned; however, the absolute stereochemistry of these three fragments, as well as that of the C46 stereogenic center remained ambiguous.[1] Recently, Andersen and co-workers finalized the core stereochemical assignments of the spirastrellolides based upon X-ray crystallography of a derivative.[1c] Notably, they disclosed that spirastrellolide B is a constitutional isomer of spirastrellolide A that lacks the C28 chlorine and the C15-16 unsaturation, but which apparently retains the complete spectrum and potency of the biological activities of the latter.

A total synthesis of a spirastrellolide has yet to be reported, although several individual fragments have been synthesized.[4] We were initially interested in applying the double-intramolecular hetero-Michael addition (DIHMA) process to the synthesis of the spirastrellolide trioxadispiroketal domain.[4f] This would represent an extension of this synthetic methodology following its success in generating the azaspiracid trioxadispiroketal.[5] Detailed here is a comprehensive accounting of the research leading to the first synthesis of the fully functionalized C26-C40 domain of spirostrellolide B.

## RESULTS AND DISCUSSION

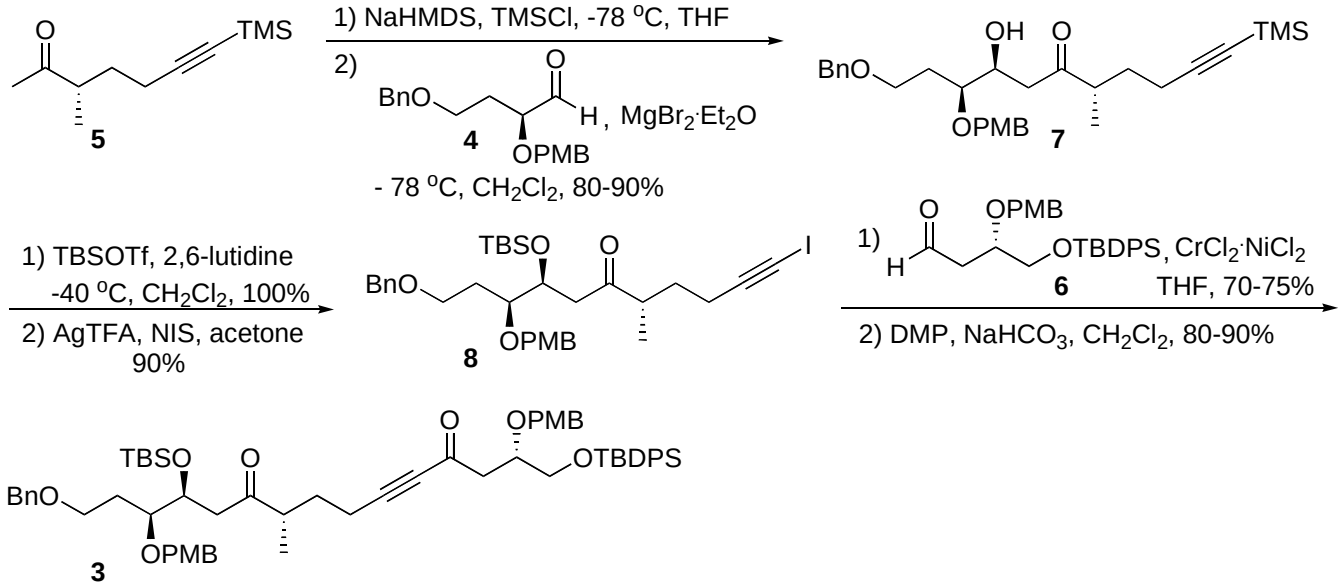



Scheme 1. Retrosynthesis of Spirastrellolide A Trioxadispiroketal

The fully functionalized trioxadispiroketal domain (**1**) of the spirastrellololides was arbitrarily targeted in the absolute configuration that has been recently assigned to the natural products. Establishment of both C31 and C35 spiroketals in (**1**) under thermodynamic control was expected to deliver the natural

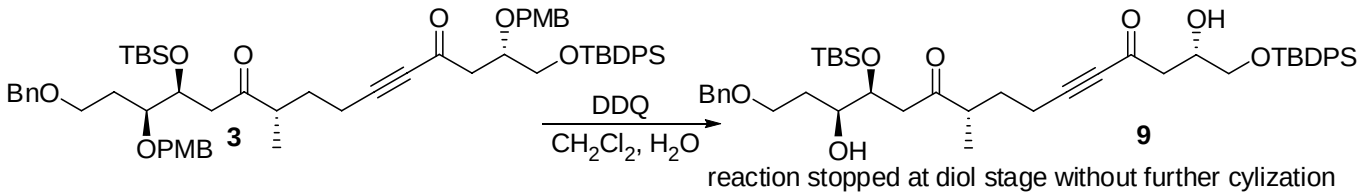
products' configurational and conformational array due to double-anomeric stablization and the predominant equatorial orientation of their appendages. Further, the C28 chlorine atom would be installed at a late stage upon the assembled trioxadispiroketal (**2**) by selective α-keto chlorination. Bis-spiroketal (**2**) would arise from linear ynone (**3**) via a DIHMA process. Ynone (**3**), in turn, would be derived from the C37-C40 aldehyde (**4**), C30-C36 methyl ketone (**5**), and the C26-C29 aldehyde (**6**). These units could be combined sequentially to construct the linear ynone (**3**) by Mukaiyama aldol[6] and Nozaki-Hiyama-Kishi[7] couplings.

The synthesis commenced from 5-hexyn-1-ol, which was converted to methyl ketone (**5**) by known methods.[8] Compound (**5**) was treated with NaHMDS and TMSCl to generate its silyl enol ether, which underwent Mukaiyama chelation controlled aldol reaction[4] with the C37-C40 aldehyde (**4**), that was derived from L-malic acid. $MgBr_2{\cdot}Et_2O$ was essential for the stereoselectivity of this reaction via chelation of oxygen atoms of the PMB ether and the aldehyde carbonyl. This reaction gave greater than a 20:1 diastereomeric ratio favoring in the desired product (**7**) in which generated alcohol was *syn* to the resident PMB ether. Alcohol (**7**) was protected as a TBS ether under mild condition using TBSOTf and 2,6-lutidine. Treatment of silyl protected alkyne with silver trifluoroacetate and *N*-iodosuccinimide successfully produced desired alkynyl iodide (**8**) in excellent yield.[9]



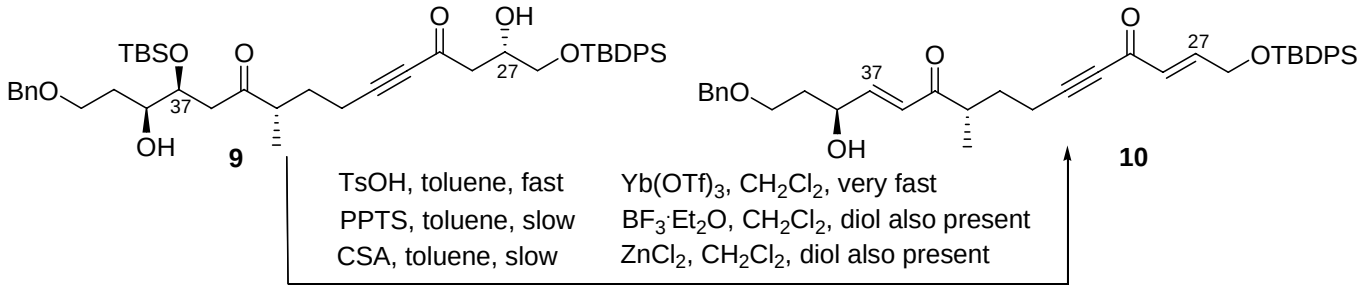

Scheme 2. Synthesis of the Linear Cyclization Precursor

Nozaki-Hiyama-Kishi coupling[7] of the alkynyl iodide (**8**) with L-malic acid-derived C26-C29 aldehyde (**6**) provided the anticipated propargylic alcohol, which was oxidized with Dess-Martin periodinane to ynone (**3**), the linear precursor for subsequent cyclizations.



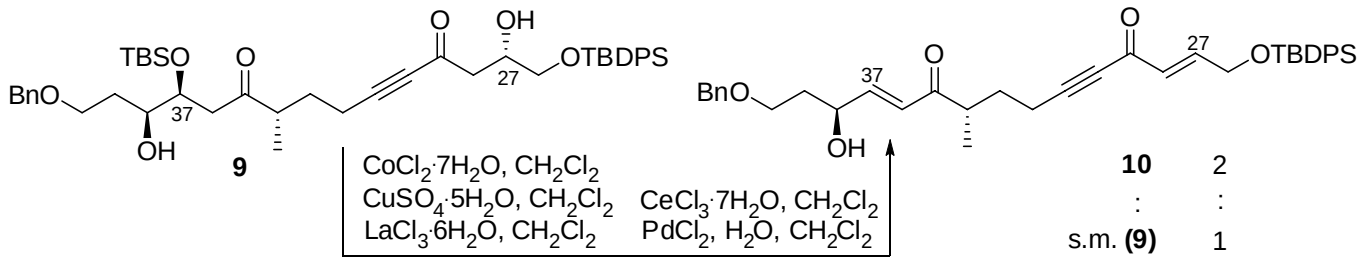

Scheme 3. Attempts to Direct Cyclization

The original hypothesis was that DIHMA cyclization would occur simultaneously upon oxidative cleavage of the bis-PMB ether to free the diol (**9**) under acidic conditions. DDQ in $CH_2Cl_2$ and $H_2O$ was selected first; however, the reaction stopped at the diol stage without further cyclization even after heating or sonication. Attempts to isolate diol (**9**) failed due to its lability to silica gel chromatography. Crude diol (**9**) was submitted to a variety of potential cyclization conditions (Scheme 4).




Scheme 4. Cyclization Attempts under Acidic Conditions

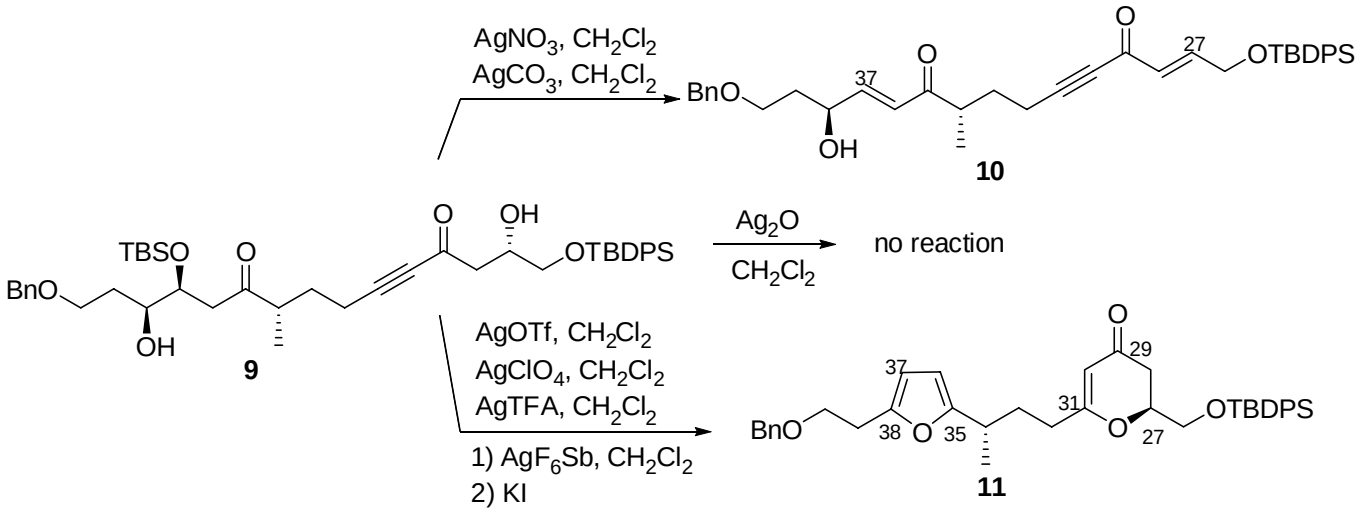
Common organic Brönsted acids were employed first. TsOH in toluene simply led to double β-elimination at the C27 and C37 positions of (**9**) to produce the highly conjugated product (**10**). CSA and PPTS gave the similar results at a much slower reaction rate. Common Lewis acids were tested next. $BF_3{\cdot}Et_2O$, anhydrous $ZnCl_2$, and $Yb(OTf)_3$ all generated the same double elimination product (**10**) from (**9**). $Yb(OTf)_3$ completely converted diol to the elimination product in just several minutes, while there was still some diol (**9**) present under the other two conditions.




Scheme 5. Cyclization Attempts with Hydrated Lewis Acids

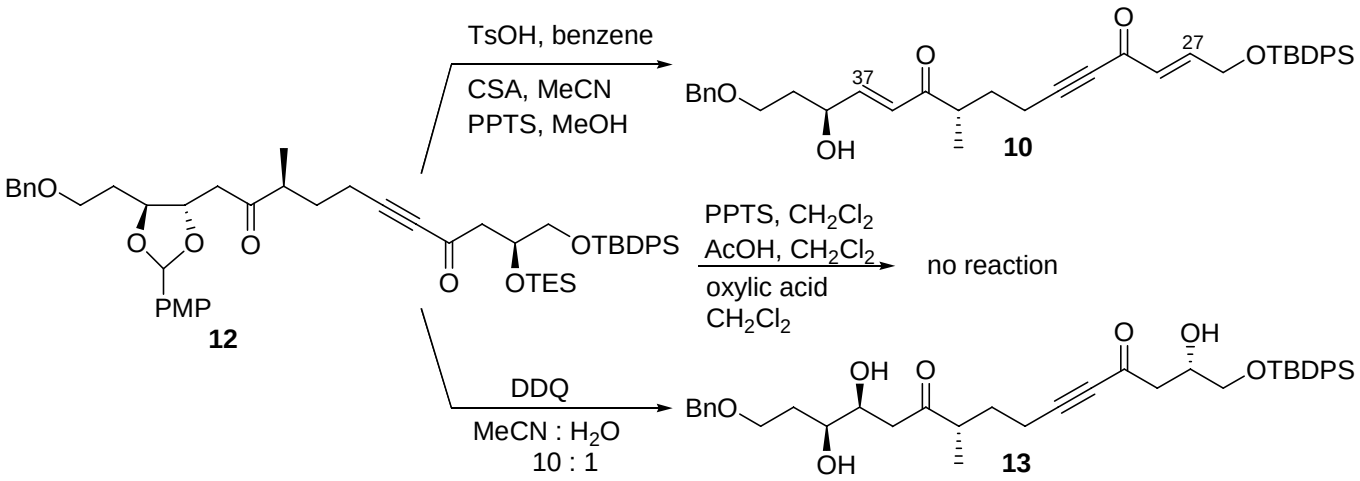
Because dehydration was the major problem in the DIHMA cyclization attempts, introduction of trace amounts of water was hypothesized to decrease the rate of elimination rate versus the rate of cyclization. Several hydrated Lewis acid were surveyed and all of them gave the same result (Scheme 5). The reactions were much slower, and the starting diol (**9**) and the double elimination product (**10**) reached an equilibrium at a ratio of ca. 1 : 2, respectively.

Because attempts at using either Brönsted and Lewis acidic activation of the ynone carbonyl were not fruitful for this particular substrate (**9**), alkyne activation was surveyed next. Various silver salts were utilized as alkyne activation reagents, and the results were mixed. Application of $AgNO_3$ and $Ag_2CO_3$ yielded the double elimination product (**10**), whereas less acidic silver salts like $Ag_2O$ retained mainly diol (**9**) while providing a trace amount of (**10**). More active silver salts gave some promising results. The use of AgOTf, AgTFA and $AgClO_4$ led to one hetero Michael addition at C31, however, β-elimination occurred concurrently to form a furan ring (**11**) at C35-C38. To attenuate the acidity of these more activated silver salts, 2,6-lutidine was added. However, no favorable reactions occurred in the presence of this base.




Scheme 6. Cyclization with Alkyne Activating Silver Salts

In addition to studying various reaction conditions for the cyclization of (**3**) or (**9**), diverse protecting groups on the labile C37 hydroxyl were examined. Instead of a TBS ether, a PMP acetal and a benzyl ether were also surveyed. For generation of a C37,C38 PMP acetal, the C27 hydroxyl was masked as a triethylsilyl ether, which made it possible to simultaneously remove both C27 and C37 protecting groups under acidic conditions. The building blocks of this linear precursor were similar to those used previously; the PMP acetal was installed after Mukaiyama aldol reaction by DDQ oxidation of the α-hydroxyl PMB ether to give (**12**) (Scheme 7).

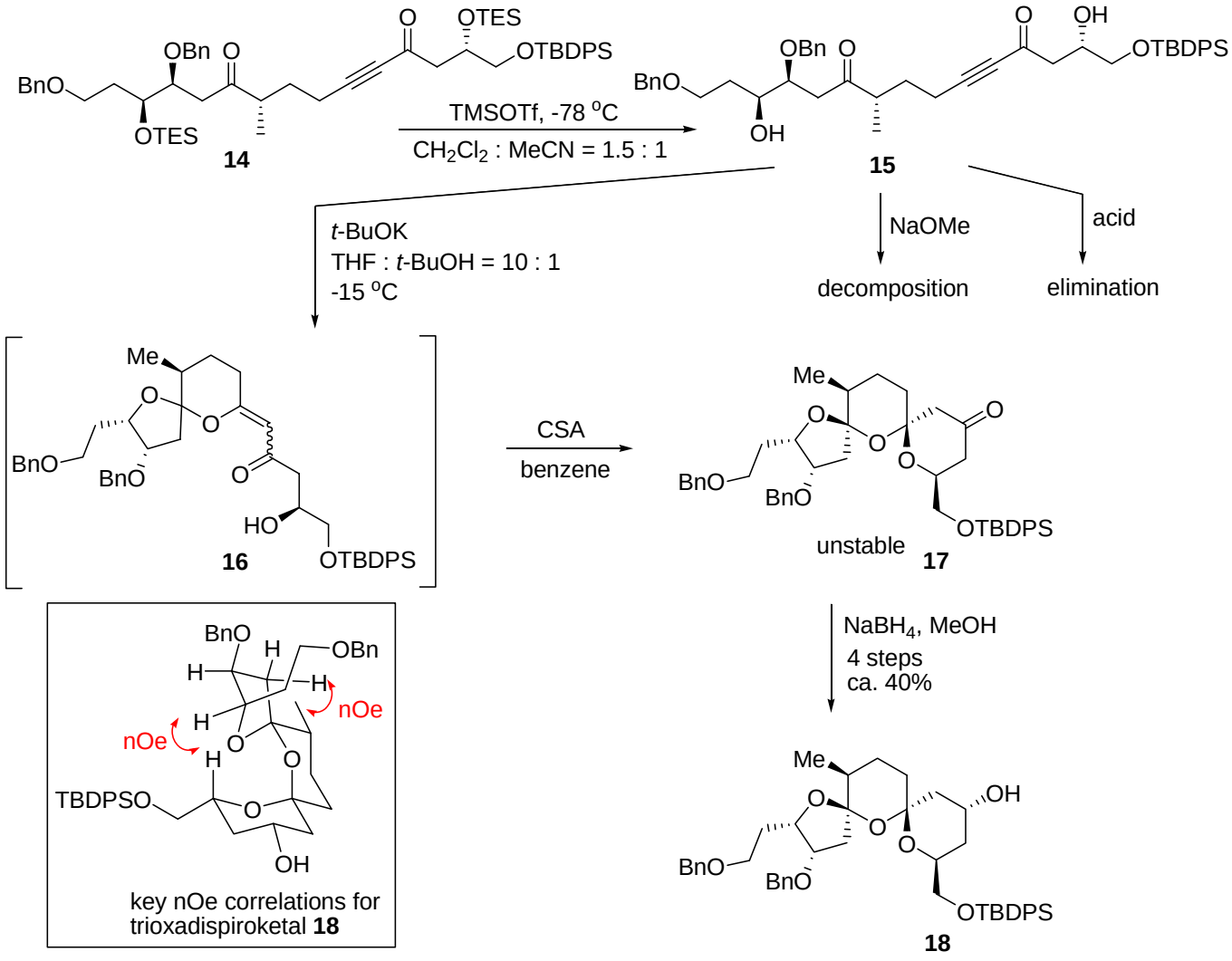



Scheme 7. Cyclization of a PMP Acetal Containing Linear Precursor

The linear substrate (**12**) was subjected to a variety of different Brönsted acids in attempts to induce deprotection-cyclization. The use of TsOH in non-polar solvent quickly led to double β-elimination (**10**), whereas, CSA in $CH_3CN$ gave similar results with much slower reaction rate. Treatment of (**12**) with PPTS in $CH_2Cl_2$ led to very slow loss of protecting groups, but PPTS in methanol quickly led to undesired (**10**). The use of carboxylic acids acetic acid and oxylic acid did not provide any fruitful outcomes. However, an encouraging result occurred when DDQ in $CH_3CN$ and $H_2O$ was used on (**12**). Unlike the previous cases, fully deprotected triol (**13**) could be isolated before β-elimination occurred. But, submission of (**13**) to the DDQ, $CH_3CN$ and $H_2O$ conditions for extended periods only led to an equilibrium between elimination product (**10**) and starting triol (**13**); no conjugate additions were observed.

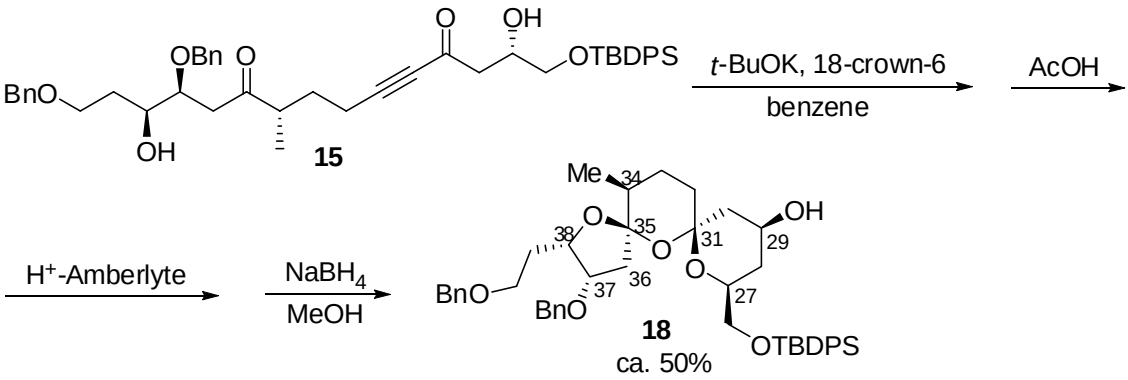
A new linear substrate (**14**, Scheme 8) containing a benzyl ether at C37 and bis-TES ethers at C27 and C38 was examined next. The synthesis of this linear precursor was also similar to the initial sequence leading to (**9**), but the extra protecting group manipulations after the Mukaiyama aldol reaction led to some problems and a diminished overall yield. With this substrate, acidic conditions still gave similar results, but a diol could be isolated after shorter reaction time because of the stability of the benzyl ether. It was apparent that the rates of elimination needed to be suppressed, while the rates of conjugate addition needed to be enhanced, to accomplish the desired trioxadispiroketal formation with this type of labile substrate. Deprotection was accomplished at low temperature in an attempt to reduce the rate of elimination. The use of TMSOTf at -78 ºC in $CH_2Cl_2$ and $CH_3CN$ provided diol (**15**) cleanly in just 5 minutes. Elimination by-products could be generated when the reaction was not carefully quenched with saturated aqueous $NaHCO_3$. In addition, the solvent ratio was significant: less $CH_3CN$ led to more elimination, while too much $CH_3CN$ would lead to freezing of the solvent mixture at -78 ºC.

Because previous studies demonstrated that acidic conditions, as well as attempts at direct alkyne activation did not induce bis-conjugate additions before elimination ensued, basic conditions were attempted with diol (**15**). Treatment of (**15**) with sodium methoxide[10] did not produce any desired product in various solvents; rather, competitive addition of methoxide to the ynone occurred. Alternatively, use of the hindered base potassium *tert*-butoxide at room temperature in THF led to direct decomposition of (**15**). However, lowering the temperature and adding *tert*-butanol to the THF solution induced a single hetero-Michael addition to occur without any elimination to give (**16**), as determined by mass spectrometry using a deuterated methanol exchange experiment. Submission of (**16**) to potassium *tert*-butoxide in THF / *tert*-butanol for longer time did not facilitate a second intramolecular hetero-Michael addition. Enone (**16**) was apparently deactivated by the β-oxygen.




Scheme 8. DIHMA Cyclization of (**15**)

At this juncture, we returned to acidic conditions that might either activate the enone carbonyl directly or convert the enone to a reactive oxocarbenium electrophile, to facilitate the second nucleophilic addition. Hence, intermediate (**16**) was treated with CSA in benzene, which produced the trioxadispiroketal (**17**) together with some undesired elimination by-product. Isolation of (**17**) was challenging due to its instability towards silica gel chromatography; retro hetero-Michael addition occurred readily. Careful monitoring of the reaction process was essential to obtain good yields in the cyclization of (**16**). Exposure of the generated bis-spiroketal (**17**) to prolonged acidic conditions led to either elimination or decomposition. Because isolation and chromatographic purification of cyclized bis-spiroketal (**17**) was not reliable, simple reduction of the C29 ketone provided alcohol (**18**) that could be isolated in moderate yield and fully characterized. A key nOe study showed strong correlations between the C27 and C38 protons of (**18**), which supported the double anomeric stabilized conformation of trioxadispiroketal scaffold. Trioxadispiroketal (**18**) represents the fully functionalized C26-C40 domain of spirastrellolide B in its naturally occurring absolute configuration.



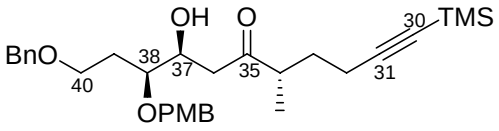

Scheme 9. One-pot DIHMA Cyclization

Subsequently, a telescoped procedure was developed to transform diol (**15**) into trioxadispiroketal (**18**). This involved first treating (**15**) with potassium *tert*-butoxide and 18-crown-6 in benzene, then carefully quenching with acetic acid until the mixture was neutral. The reaction mixture was then passed through a pad of activated proton-Amberlyst ion exchangeable resin, diluted with methanol and reduced with $NaBH_4$ to provide (**18**) in ca. 50% yield, which was a slightly higher yield than was obtained in the stepwise procedure.

In summary, a sequential conjugate addition-based assembly of the spirastrellolide B trioxadispiroketal domain in its natural absolute configuration has been developed. Extension of this synthetic entry to the generation of spirastrellolide B and its analogs and evaluation of their biological activities are ongoing in our laboratories.

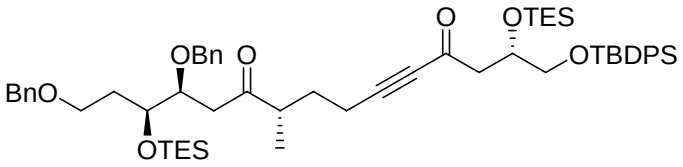
## EXPERIMENTAL

**General:** All air sensitive reactions were carried out under nitrogen or argon in oven dried glassware using standard syringe, cannula and septa techniques. Tetrahydrofuran was distilled from sodium / benzylphenone ketyl under nitrogen. Methylene chloride, benzene, toluene and triethylamine were distilled from calcium hydride under nitrogen. Flash chromatography was performed using Baker Flash silica gel 60 (40 μm). NMR spectra were obtained in $CDCl_3$ and reference to the residual $CDCl_3$ at 7.27 ppm ($^1H$) and 77.0 ppm ($^{13}C$). Optical rotations were obtained using a JASCO DIP-370 digital polarimeter at sodium D line (589 nm) and were reported in concentration of g / 100 mL at 23 $^oC$. Infrared (IR) spectra were obtained using a MIDAC Prospect FT-IR spectrophotometer. High resolution mass spectrometric analyses were performed using a Bruker Biotof II mass spectrometer.



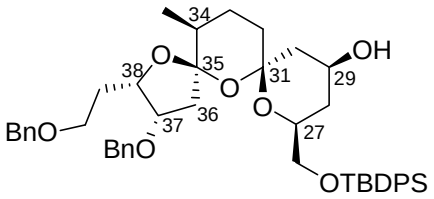

**β-Hydroxyl ketone (7).**

To a solution of $MgBr_2{\cdot}Et_2O$ (937 mg, 5.09 mmol) in $CH_2Cl_2$ (20 mL) at -78 $^oC$ under Ar was added a solution of (*S*)-4-benzyloxy-2-(*p*-methoxybenzyl)oxybutyraldehyde **4** (200 mg, 637 μmol) in $CH_2Cl_2$ via canulate followed by crude silyl enol ether **5b** (524 mg). The mixture was stirred at -78 $^oC$ for 2 h before pH 7 phosphate buffer was added. The resultant mixture was warmed to rt and extracted with $CH_2Cl_2$. The combined organic phase was washed by brine, dried over $Na_2SO_4$, filtered, concentrated and purified by flash chromatography (hexane : EtOAc, 3 : 1, v/v) to give **7** (296 mg, 580 μmol, 91 % yield) as a light yelow oil: $\mathbf{R_f}$ 0.26 (hexane : EtOAc, 3 : 1, v/v); $\mathbf{[\alpha]_D^{23}}$ -6.79 (c 3.68, $CHCl_3$); **IR** (thin film, $\nu_{max}/cm^{-1}$) 3450 (br), 2958, 2934, 2174, 1708, 1612, 1586, 1514, 1456, 1363, 1303, 1249, 1174, 1090, 1036, 843, 759, 699, 638; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.47 (m, 4H), 4.15 (m, 1H), 3.77 (s, 3H), 3.56 (m, 3H), 3.09 (s, 1H), 2.63 (m, 3H), 2.20 (t, *J* = 7.0 Hz, 2H), 1.98 (m, 1H), 1.88 (m, 1H), 1.81 (m, 1H), 1.47 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.15 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.1, 159.3, 138.3, 130.5, 129.7, 128.4, 127.7, 113.8, 106.3, 85.3, 77.6, 73.0, 72.1, 68.7, 66.6, 60.4, 55.2, 45.5, 43.9, 31.0, 30.4, 17.7, 15.9, 14.2, 0.2; **HRMS** calc. for $C_{30}H_{42}NaO_5Si$ $[M + Na]^+$ 533.2699, found 533.2713.



**Ynone (14)**.

To a stirred solution of propargyl alcohol **14b** (33.8 mg, 34.6 μmol) in $CH_2Cl_2$ (10 mL) and *t*-butyl alcohol (1.0 mL), were added $NaHCO_3$ (87.4 mg, 1.04 mmol) and Dess-Martin periodinane (44.3 mg, 104 μmol). The resultant mixture was stirred for 3 h before saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with $CH_2Cl_2$ and the combined organic phase was washed with brine, dried over $Na_2SO_4$, filtered, concentrated and purified by flash chromatography (hexane : EtOAc, 8 : 1, v/v) to give **14** (31.5 mg, 32.3 μmol, 93 % yield) as a colorless oil: $\mathbf{R_f}$ 0.32 (hexane : EtOAc, 6 : 1, v/v); $\mathbf{[\alpha]_D^{23}}$ -10.9 (c 1.38, EtOAc); **IR** (thin film, $\nu_{max}/cm^{-1}$) 2960, 2882, 2215, 1721, 1680, 1461, 1241, 1118, 1013, 738, 700; **$^1$H NMR** (500 MHz, $C_6D_6$) δ 7.75 (m, 6H), 7.29 (m, 4H), 7.15 (m, 10H), 4.57 (s, 2H), 4.56 (m, 1H), 4.36 (s, 2H), 4.27 (m, 1H), 4.20 (m, 1H), 3.77 (m, 1H), 3.61 (m, 1H), 3.56 (m, 2H), 3.05 (d, *J* = 15.5 Hz, 1H), 2.86 (dd, *J* = 7.5, 16.0 Hz, 1H), 2.72 (d, *J* = 17.0 Hz, 1H), 2.56 (dd, *J* = 9.5, 16.5 Hz, 1H), 2.32 (q, *J* = 6.5 Hz, 1H), 2.24 (m, 1H), 1.95 (m, 2H), 1.79 (m, 1H), 1.56 (m, 1H), 1.23 (m, 1H), 1.13 (s, 9H), 0.95 (q, *J* = 7.5 Hz, 18H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.55 (m, 12H); **$^{13}$C NMR** (75 MHz, $C_6D_6$) δ 217.4, 184.5, 138.8, 135.6, 133.2, 129.6, 128.1, 127.7, 127.4, 127.3, 82.1, 78.8, 77.5, 72.5, 72.4, 69.1, 67.9, 67.6, 66.6, 50.9, 45.5, 40.6, 31.4, 30.0, 26.5, 18.9, 16.2, 15.5, 6.6, 4.7; **HRMS** calc. for $C_{58}H_{84}NaO_7Si_3$ $[M + Na]^+$ 999.5423, found 999.5458.




**Trioxadispiroketal (18)**.

To a stirred solution of **14** (5.0 mg, 5.12 μmol) in $CH_2Cl_2$ (3 mL) and $CH_3CN$ (2 mL) at -78 °C under Ar, was added TMSOTf (2.27 mg, 10.2 μmol) very slowly. The resultant mixture was stirred at -78 °C for 5 min before saturated aqueous $NaHCO_3$ was added dropwise. The mixture was allowed to slowly warm to rt while an adequate amount of saturated aqueous $NaHCO_3$ was added to keep the reaction system neutral. The aqueous phase was extracted with ethyl acetate and the combined organic phase was washed with brine, dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (hexane : EtOAc, 4 : 1 to 2 : 1, triethylamine 0.5 %, v/v,) to give a crude diol **15** (3.4 mg, 4.55 μmol, 89 % yield) as a light yellow oil: $\mathbf{R_f}$ 0.17 (hexane : EtOAc, 2 : 1, v/v). Diol **15** (3.4 mg, 4.55 μmol) was dissolved in THF (5 mL) and *t*-butyl alcohol (0.5 mL) and the resultant solution was cooled to -20 °C. Potassium *t*-butoxide (0.3 mg, 2.27 μmol) was added and the mixture was stirred for 20 min before an adequate amount of saturated aqueous $NH_4Cl$ was added to quench and neutralize reaction. The mixture was warm to rt and the aqueous phase was extracted with EtOAc. The combined organic phase was

washed with brine, dried over $Na_2SO_4$, filtered through a pad of 0.5% triethylamine neutralized silica gel to provide crude enone **16** as a yellow oil: $\mathbf{R_f}$ 0.44 (hexane : ethyl acetate, 2 : 1, v/v). Camphorsulfonic acid (< 0.1 mg) was added to the enone **16** solution in benzene (3 mL) and the resultant mixture was stirred at rt until TLC showed no starting material left. $NaBH_4$ (1.0 mg, 26.4 μmol) and MeOH (2 mL) were added to the above solution, and the resultant mixture was stirred for 20 min before an adequate amount of saturated aqueous $NH_4Cl$ was added. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine, dried over $Na_2SO_4$, filtered, concentrated, and purified by 0.5% triethylamine neutralized flash chromatography (hexane : EtOAc, 6 : 1 to 4 : 1, v/v) to give **18** (1.9 mg, 2.53 μmol, 4 steps, 50 %) as a colorless oil: $\mathbf{R_f}$ 0.32 (hexane : EtOAc, 2 : 1, v/v); $\mathbf{[\alpha]_D^{23}}$ 50.0 (c 0.06, EtOAc); **IR** (thin film, $\nu_{max}/cm^{-1}$) 2928, 2864, 2000, 1381, 1118, 668; **$^1$H NMR** (500 MHz, $C_6D_6$) δ 7.90 (d, *J* = 6.5 Hz, 2H), 7.84 (d, *J* = 6.5 Hz, 2H), 7.16 (m, 16H), 4.23 ( d, *J* = 12.0 Hz, 1H), 4,21 (m, 1H), 4.13 (m, 1H), 4.10 (s, 2H), 4.01 (d, *J* = 10.0 Hz, 1H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.90 (m, 1H), 3.84 (dd, *J* = 3.0, 10.5 Hz, 1H), 3.76 (m, 1H), 3.39 (dt, *J* = 2.0, 7.0 Hz, 2H), 2.21 (dq, *J* = 3.5, 13.0 Hz, 1H), 2.06 (m, 2H), 2.01 (d, *J* = 4.5 Hz, 1H), 1.97 (m, 2H), 1.78 (dt, *J* = 13.5, 3.5 Hz, 1H), 1.62 (q, *J* = 12.0 Hz, 1H), 1.51 (m, 1H), 1.40 (dt, *J* = 4.0, 13.0 Hz, 1H), 1.24 (dd, *J* = 3.5, 12.5 Hz, 1H), 1.19 (s, 9H), 1.18 (m, 1H), 1.08 (m, 1H), 0.99 (d, *J* = 6.0 Hz, 3H); **$^{13}$C NMR** (75 MHz, $C_6D_6$) δ 135.9, 135.6, 129.4, 180.1, 89.2, 79.5, 78.6, 72.3, 70.5, 69.3, 67.5, 66.5, 64.5, 46.2, 44.2, 37.4, 36.5, 29.4, 26.6, 23.8, 19.2, 16.3, 0.8; **HRMS** calc. for $C_{46}H_{58}NaO_7Si$ $[M + Na]^+$ 773.3850, found 773.3872.

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