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Facile biomimetic syntheses of the azaspiracid spiroaminal

Son Nguyen, Jianyan Xu and Craig J. Forsyth*

Department of Chemistry, University of Minnesota, 139 Smith Hall, 207 Pleasant Street, SE, Minneapolis, MN 55455, USA

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Abstract—The azaspiracid natural products display a common spiroaminal-containing terminal domain that has inspired the development of two new methods for spiroaminal syntheses—a Staudinger reduction–aza-Wittig process and a double intramolecular hetero-Michael addition. These effective laboratory approaches proceed through imine and enamine intermediates that may reflect transient biogenetic species.

1. Introduction

The azaspiracids are the causative agents of a recently defined class of human poisoning resulting from consumption of tainted shellfish. As such, intense surveillance programs have been established to monitor the occurrence and extent of azaspiracid contamination in edible shellfish. The archetypal member of this novel class of marine toxins, azaspiracid-1 (AZA1, Fig. 1), was reported by Yasumoto and co-workers as an isolate from the cultivated Irish mussel *Mytilus edulis*.[1] Since then, AZA1 has also been found in the dinoflagellate *Protoperidinium crassipes*, which may represent the primary biogenic source of the azaspiracid toxins.[2] Recently, the complete structure of AZA1 was established by a comprehensive total synthesis—correlation effort by the Nicolaou group.[3] To date, five azaspiracids have been isolated and structurally elucidated by extensive NMR analysis and FABMS–MS experiments (AZA1–5),[4] and six others (AZA6–11) have been detected using a combination of liquid chromatography and multi-tandem mass spectrometry (LC–MS^n).[5] Among the 11 known azaspiracids, none show any structural variation within the spiroaminal-terminated C27–C40 domain. Hence, we have focused on developing efficient synthetic entries to this common portion of the natural products to support the generation of an ELISA for environmental monitoring,[6] total syntheses of the natural products, and the laboratory exploration of putative biomimetic pathways.[7] Here, we summarize the development and application of two novel methods for the formation of the common azaspiracid spiroaminal.

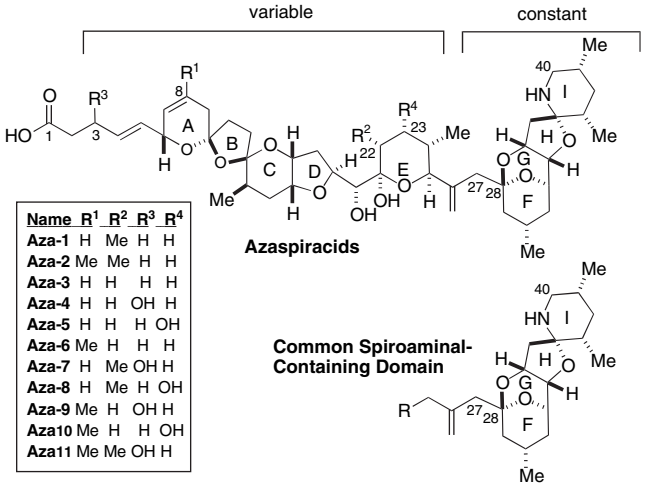

Figure 1. Structures of the azaspiracids and the common spiroaminal-containing domain.

2. Results and discussion

2.1. Synthetic design

Our established route to the dioxabicyclononane system, comprising the C28–C34 F-G rings of the azaspiracids, involves a double intramolecular hetero-Michael addition (DIHMA) upon an ynone.[8] Retrosynthetically, the G ring may be disconnected to enone **1** by a retro-Michael disconnection of the C28 ketal releasing a C34 hydroxyl group (Scheme 1).

A second retro-Michael disconnection of the β-oxyenone reveals dihydroxy ynone **2**, which, in turn may arise via the coupling of a C27 acetylide anion equivalent (**3**) upon a generalized C26 carbonyl derivative. Advanced intermediate **3**

* Corresponding author. Tel.: +1 612 624 0218; fax: +1 612 626 7541; e-mail: forsyth@chem.umn.edu

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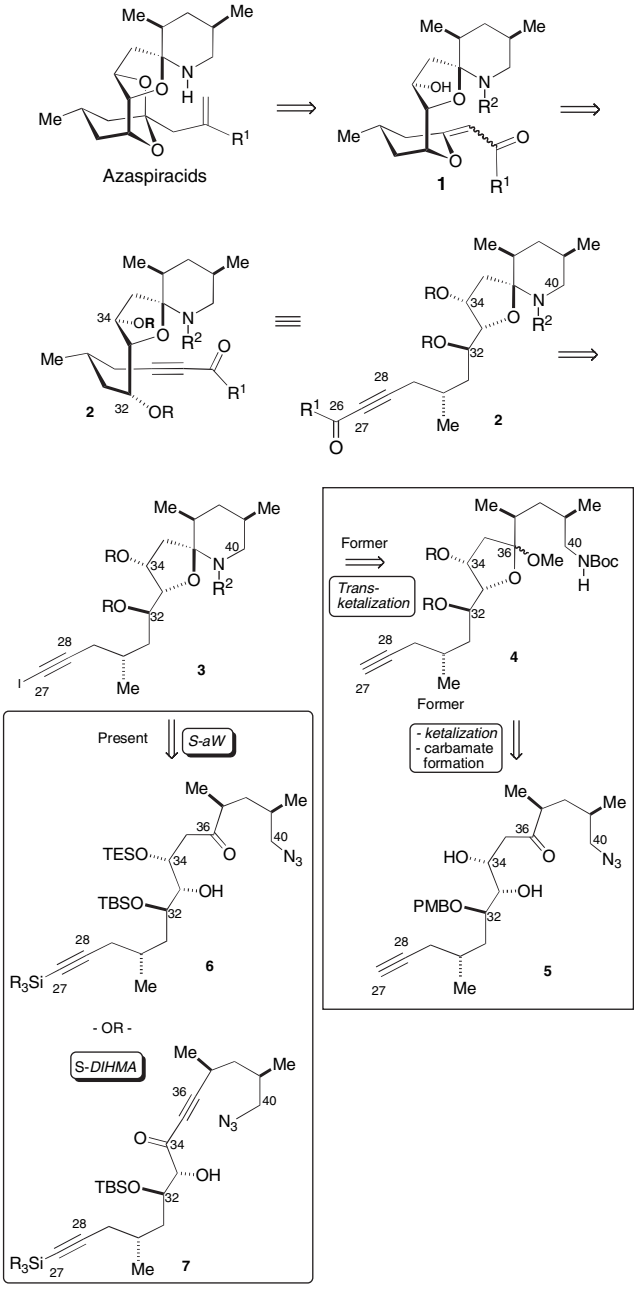
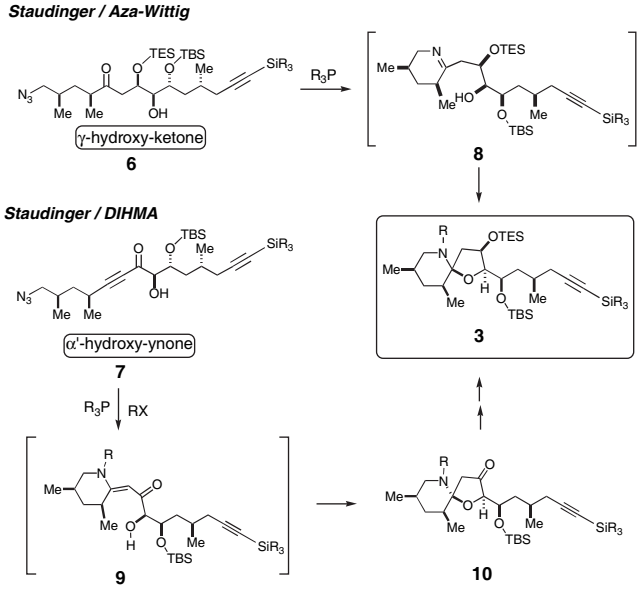


Scheme 1. Retrosynthetic analysis for the C27–C40 fragment.

contains the piperidine–tetrahydrofuran fused spiroaminal (H-I rings) and latent nucleophilic oxygens at C32 and C34 masked as silyl ethers. The previously published assemblies of the azaspiracid spiroaminal moiety used a stepwise sequence of ring-closings.[8–10] These involved the initial formation of the C33–C36 H ring as a cyclic mixed methyl ketal. A C40 terminal azide was then reduced and protected as a carbamate (cf. **4**, Scheme 1). Finally, the spiroaminal was formed by closure of the C36–C40 piperidine I ring upon treatment with a Lewis acid, such as $Yb(OTf)_3$[8,10] or $BF_3\cdot OEt_2$.[9] We have since designed more facile assemblies of spiroaminal **3** from acyclic intermediates γ-hydroxy-δ′-azidoketone **6** or α-hydroxy-α′,β′-ynone **7**.

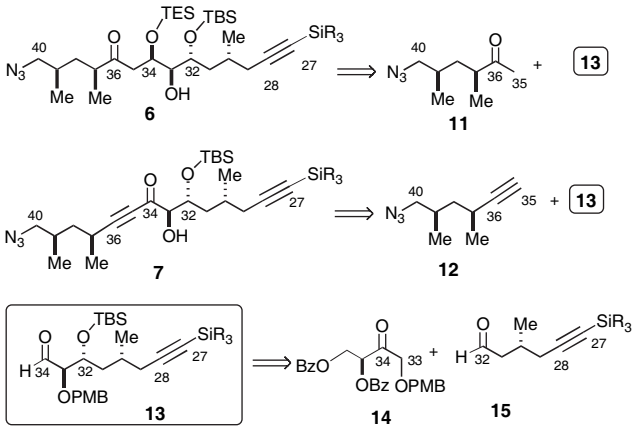
The appropriately functionalized acyclic intermediate **6** would be subjected to Staudinger reduction under anhydrous conditions to induce an intramolecular aza-Wittig reaction (S–aW) to form the I ring as an imine (**8**, Scheme 2), followed by engagement of the tethered hydroxyl group to close the H ring and generate **3**. Both kinetic stereoelectronic and thermodynamic effects should favor the selective formation of the natural products' C36 spiroaminal configuration. Alternatively, liberation of a primary amine by Staudinger reduction of **7** in the presence of a carbamate-forming reagent (RX, Scheme 2) might allow formal successive intramolecular hetero-Michael additions upon the α,β-unsaturated ketone (DIHMA) to ensue. In the latter case, an initial 6-*exo* addition of a carbamate nitrogen upon the ynone would generate a hydroxy-enamine (**9**) that could isomerize to spiroaminal **10**. The residual ketone at C34 of **10** would provide a functional handle for the stereoselective installation of the corresponding silyl ether in **3**. Although Staudinger reactions are unlikely to be involved in the actual biogenesis of spiroaminals, the postulated types of hydroxy-imine or hydroxy-enamine intermediates (**8** and **9**) derived from Staudinger reactions in our laboratory syntheses may well be. Furthermore, these designed Staudinger reaction-initiated cascade sequences should be accessible under essentially neutral reaction conditions that are tolerant of the extensive functionality found in the azaspiracid natural products.



Scheme 2. Two proposed methods for the formation of the azaspiracid spiroaminal.

Retrosynthetically, we maintained the same type of triply convergent approach employed in our previously disclosed synthesis of the acyclic precursor to the azaspiracid C27–C40 domain, but with a few significant changes.[8] Ynones **6** and **7** could be derived from methyl ketone **11** or alkyne **12**, respectively, and the common C34 aldehyde **13** (Scheme 3). A chelation-controlled Mukaiyama aldol reaction was envisioned to join a silyl enol ether derivative of **11** with **13** while simultaneously setting the C33,C34 *syn*-stereochemistry in **6**. Addition of an acetylide nucleophile derived from **12** to aldehyde **13** followed by oxidation and PMB ether cleavage would provide **7**. The common aldehyde **13** arises from a Paterson aldol reaction of a boron enolate obtained from ketone **14** and C32 aldehyde **15**, with subsequent oxidative excision of the benzoyl chiral directing moiety

resident in **14**. Importantly, a chelating α-*p*-methoxybenzyl (PMB) ether was incorporated in aldehyde **13** at the stage of ketone **14** to effect the desired chelation-controlled Mukaiyama reaction. This specific protecting group array would also simplify the functional group manipulations required to enable the late-stage cyclization cascades via either the S–aW or the S–DIHMA processes to form the H-I ring.

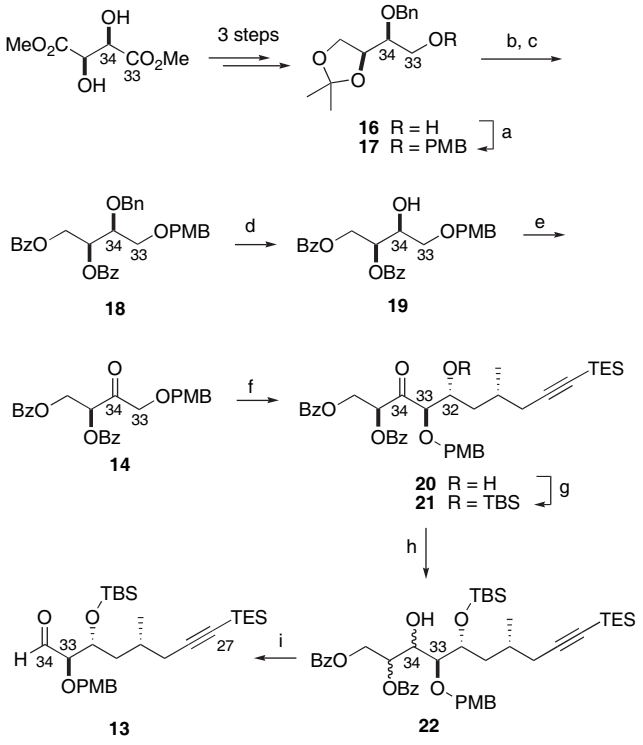


Scheme 3. Key disconnections of ynones **6** and **7**.

2.2. Preparative chemistry

The synthesis of the C27–C34 aldehyde **13** common to both spiroaminal formation strategies began with the preparation of ketone **14**, which ultimately provides only carbons 33 and 34 (Scheme 4). However, **14** also bears the essential α-benzyloxy stereogenic center that defines the absolute stereochemistry of the ensuant C32 and C33 centers via the Paterson boron aldol reaction.[11] Dimethyl D-tartrate was converted into primary alcohol **16** according to the procedure of Ohno.[12] The C32 PMB ether was formed at this stage to generate **17**. Cleavage of the acetonide moiety followed by bis-benzoylation of the resultant diol provided **18**. Selective hydrogenolysis of the benzyl ether of **18** in the presence of the vicinal PMB was accomplished using Pd–$BaSO_4$ in ethyl acetate to yield secondary alcohol **19**. Oxidation of the alcohol then delivered ketone **14** in five steps and 40% overall yield from **16**.

A boron-mediated aldol reaction between ketone **14** and aldehyde **15**[8] following Paterson's procedure[11] proceeded smoothly to afford the desired *syn/anti* product **20** (Scheme 4) in high yield and diastereoselectivity (ds >9:1, by ^{1}H NMR spectroscopy). The anticipated C32,C33 *anti*-relationship was confirmed by the relatively large coupling constant (5 MHz) between C32–H and C33–H. It should be noted that attempts to use the analogous 1,4-bis-(*p*-methoxybenzyl)oxy-3-benzoyl-butanone under the same reaction conditions only resulted in a complicated mixture of inseparable diastereomeric aldol products. The resultant β-hydroxyl group in **20** was protected as a TBS ether to give **21**. Exhaustive reduction of the ketone and the bis-benzoyloxy groups in **21** using $LiAlH_4$ resulted in a low yield of the expected triol. This may be attributed to a net retro-aldol reaction leading to the fragmentation of the oxy-ketone. A stepwise approach was thus pursued. Hence ketone **21** was reduced non-stereoselectively to alcohol **22** using $NaBH_4$. Removal

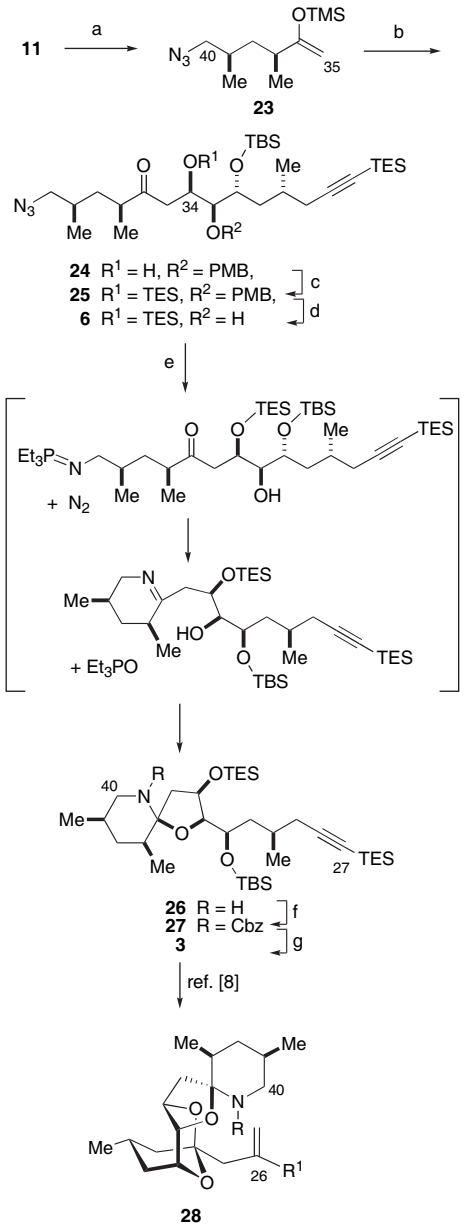


Scheme 4. Synthesis of the C27–C34 aldehyde. a) NaH, PMBCl, TBAI, DMF, THF, 0 °C to rt, 6 h (96%); b) CSA (cat.), MeOH, 30 min; c) BzCl, triethylamine, DMAP, CH_2Cl_2, 14 h (93% from **17**); d) H_2, Pd–$BaSO_4$, EtOAc, 14 h (58%); e) TPAP (cat.), NMO, CH_2Cl_2, 2 h (78%); f) $Chex_2BCl$, triethylamine, 0 °C, 2 h, then **15**, −78 °C, 5 h, (69%); g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min (83%); h) $NaBH_4$, MeOH, 0 °C, 1 h, (92%); i) K_2CO_3, MeOH, 5 h, then AcOH, $NaIO_4$, 30 min (70%).

of both benzoyl groups was then accomplished by treatment of **22** with K_2CO_3 in methanol. Thereafter, the crude triol solution was neutralized with acetic acid and subsequently treated with $NaIO_4$. This one-pot procedure reliably provided the desired C27–C34 aldehyde **13**.

To implement the S–aW spiroaminal formation strategy, methyl ketone **11**[5] (Scheme 3), representing C35–C40 of the azaspiracids, was joined with aldehyde **13** via a chelation-controlled Mukaiyama aldol reaction. (Scheme 5). For this, ketone **11** was converted to the TMS vinyl ether **23** by treatment with NaHMDS followed by TMSCl. Various Lewis acids were screened for the aldol reaction, including $SnCl_4$, $TiCl_4$, $ZnCl_2$, $MgCl_2$, and $MgBr_2\cdot OEt_2$. Among these, $MgBr_2\cdot OEt_2$ best delivered the desired *anti*-Felkin–Anh product **24**. The absolute configuration of (34*R*) in **24** was confirmed by application of the advanced Mosher ester analysis.[13] Silylation of the C34 hydroxy group and removal of the PMB protective group left only the C33 hydroxyl and C36 ketone of **6** free to participate in spiroaminal formation, while the latent nucleophilic terminal nitrogen remained masked as an azide.

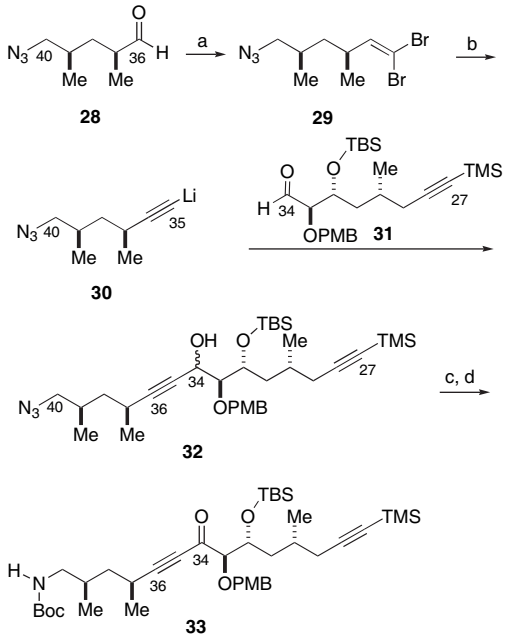
The anticipated spiroaminal moiety in **26** was initially formed in moderate yield upon treatment of azide **6** with *n*-Bu_3P in benzene (Scheme 5). After surveying various conditions it was found that Et_3P in benzene provided better results, reproducibly giving **26** in ca. 75% yield as a ca. 4:1 ratio of C36 epimers. The sequence likely proceeds via reaction of the trialkyphosphine with the azide to generate an



Scheme 5. Spiroaminal assembly via a Staudinger–aza-Wittig process. a) NaHMDS, THF, −78 °C, 15 min, then TMSCl, 1 h (~90%, crude); b) **13**, $MgBr_2 \cdot OEt_2$, CH_2Cl_2, −78 °C to −25 °C, 14 h (66%, 74% borsm); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C (92%); d) DDQ, *t*-BuOH, CH_2Cl_2, H_2O, 2 h, (82%); e) Et_3P, PhH, 6 h (75%); f) CbzCl, K_2CO_3, 4 Å MS, CH_2Cl_2, 14 h (73%); g) AgTFA, NIS, DMF (87%).

iminophosphorane that undergoes an intramolecular aza-Wittig reaction with the C36 ketone to form the six-membered cyclic imine. Addition of the C33 hydroxyl group to the imine completes the cascade. The spiroaminal nitrogen of **26** was converted into the corresponding benzylcarbamate **27** for characterization. ^{1}H NMR experiments, including NOE, firmly established the relative configuration of the C36 spiroaminal center in the major diastereomer as indicated. This result is consistent with either a kinetically controlled pseudoaxial addition of the C33 hydroxyl upon the piperidine imine, or post-addition thermodynamic equilibration, or both.

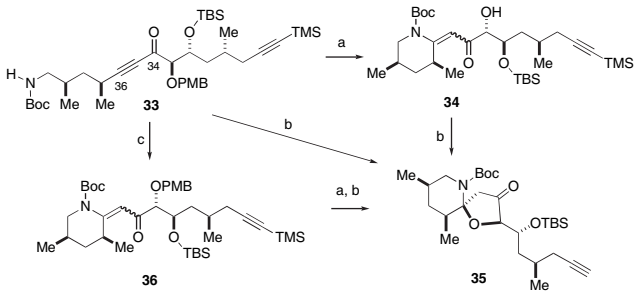
The alternative DIHMA approach to the azaspiracid spiroaminal required the synthesis of a conjugated ynone of type **7** (Scheme 2). For this, δ-azido-aldehyde **28** (Scheme 6) was converted to geminal dibromo-olefin **29** under Corey–Fuchs conditions. Transformation of **29** to the C35–C40 lithium acetylide **30** with *n*-butyllithium allowed addition to C27–C34 aldehyde **31** to generate propargylic alcohols **32**. It was determined that Staudinger reduction and carbamate formation best preceded propargylic alcohol oxidation to yield C27–C40 ynone **33**.



Scheme 6. Assembly of the DIHMA precursor. a) CBr_4, Ph_3P, CH_2Cl_2 (91%); b) *n*-BuLi, THF, −78 °C, then **31** (70%); c) (i) Et_3P, toluene, (ii) BocON, −10 °C to rt (61%); d) MnO_2, pentane (100%).

To parlay carbamate-ynone **33** into the azaspiracid spiroaminal the carbamate nitrogen must conjugatively add to the ynone and the α-keto PMB ether needs to be cleaved so that the liberated C33 secondary hydroxyl group may add to the C34–C36 enone system. An initial attempt to engage in this sequence involved PMB ether cleavage from **33** with DDQ (Scheme 7). Concomitant with removal of the PMB group under the DDQ reaction conditions, however, was the conjugate addition of the carbamate nitrogen upon the ynone to generate hydroxyl enamine **34**. Application of conditions intended to convert the terminal alkynyl silyl group of **34** into the corresponding iodo-alkyne also led to an unanticipated secondary transformation—spiroaminal formation via addition of the C33 hydroxyl upon C36 of the enamine–enone to result in the target **35**. Intramolecular conjugate addition of the carbamate nitrogen of **33** upon the ynone system could also be initiated under the influence of the Lewis acid $MgBr_2 \cdot OEt_2$ to form enone **36**. Thereafter, cleavage of the PMB ether of **36** revealed the C33 hydroxyl, which completed the second conjugate addition to form the spiroaminal. Finally, the direct conversion of C33 PMB ether–ynone **33** into spiroaminal **36** could be accomplished in one operation and moderate yield using AgTFA followed by addition of ethanolic KI. Four functional group transformations are accomplished in this remarkable one-pot process: hetero-Michael addition of the terminal carbamate nitrogen upon the C34–C36 ynone, scission of both C27

terminal alkyne and C33 secondary alcohol protecting groups, and the stereoselective addition of the C33 oxygen upon the C36 center to generate spiroaminal **36**. Presumably, the silver cation activates the internal alkyne towards an initial intramolecular addition of the nitrogen to initiate this cascade.



Scheme 7. Spiroaminal formation via DIHMA. a) DDQ, CH_2Cl_2, *t*-BuOH, pH 7 buffer; b) (i) AgTFA, CH_2Cl_2, (ii) EtOH, H_2O, KI (**33** to **35**=56%). c) $MgBr_2 \cdot OEt_2$, CH_2Cl_2.

3. Conclusion

We have developed two complementary second-generation syntheses of the C27–C40 fragment of the azaspiracids that are both efficient and stereoselective. Both routes utilize a common C27–C34 aldehyde that is assembled with a Paterson aldol reaction to establish the C32 and C33 configurations.

For the Staudinger–aza-Wittig-based assembly of the spiroaminal, the C27–C34 aldehyde was subjected to a chelation-controlled Mukaiyama aldol reaction to set the C34 configuration and provide γ-hydroxy-δ′-azidoketone **6**. Subsequent one-pot formation of the spiroaminal moiety involved treatment with triethylphosphine to initiate the cyclization cascade leading to **26**. Compound **26** represents the fully functionalized C27–C40 azaspiracid intermediate that is amenable to elaboration into the complete F-G-H-I ring domain via our established DIHMA process. The synthetic sequence leading to **27** via the Staudinger–aza-Wittig process started with three simple subunits and was completed in nine linear steps with 11% overall yield.

The complementary DIHMA closure of the azaspiracid spiroaminal required an α-hydroxy-α′,β′-ynone (cf. **7**) that was derived from the C27–C34 aldehyde (**31**) and a C35–C40 acetylide (**30**). The emergent conjugated ynone **33** could also be converted into the corresponding spiroaminal in a one-pot process. In this case, an Ag^+ species initiated the cyclization sequence. Each of these spiroaminal forming processes demonstrated here in the context of the azaspiracids may find broader applications in organic synthesis.

4. Experimental

4.1. General

Unless noted otherwise, all oxygen and moisture-sensitive reactions were executed in oven-dried glassware sealed under a positive pressure of dry argon or nitrogen and moisture-sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. Unless stated otherwise, all commercial reagents were used as received. Organic solvents were dried under nitrogen atmosphere: tetrahydrofuran (THF) and diethyl ether were distilled over Na-benzophenone; CH_2Cl_2, *N*,*N*-di-*iso*-propyl-*N*-ethylamine, and pyridine were distilled from CaH_2. Flash chromatography was performed using Baker Flash silica gel 60 (40 μM); analytical TLC was performed using 0.25 mm EM silica gel 60 F_{254} plates that were visualized by irradiation (254 nm) or by staining (450 mL of 95% ethanol, 25 mL concd. H_2SO_4, 15 mL acetic acid, and 25 mL anisaldehyde). Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. IR spectra were recorded using a Perkin–Elmer 683 infrared spectrophotometer. NMR spectra were obtained using INOVA 500 and 300 MHz Varian instruments. High-resolution mass spectrometric data were obtained using a VG Analytical Sector-Field mass spectrometer.

4.1.1. (2*S*,3*S*)-3-(*O*-Benzyl)-4-(*O*-[*p*-methoxy]benzyl)-1,2,3,4-buaneteteraol-1,2-di-*O*-acetonide (17). To a stirred solution of **16** (2.35 g, 9.32 mmol) in THF (95 mL) at 0 °C was added in portions NaH (1.12 g, 60% in mineral oil, 28 mmol). The suspension was warmed to rt. After 30 min, PMBCl (2.35 mL, 18.6 mmol) and TBAI (0.68 g, 1.9 mmol) were added sequentially. The reaction mixture was stirred for 24 h, cooled to 0 °C, and H_2O (30 mL) was added slowly. The resulting mixture was transferred to a separatory funnel and extracted with diethyl ether (3×70 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (2×30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude residue by silica gel column chromatography (hexanes–ethyl acetate, 10:1 to 5:1, v/v) provided **17** (3.32 g, 8.93 mmol, 96%) as a colorless oil: R_f 0.61 (hexanes–ethyl acetate, 2:1, v/v); $[\alpha]_D^{23}$ −5.8 (*c* 0.63, CH_2Cl_2); IR (thin film): 3063–2840, 1612, 1586, 1513, 1455, 1370, 1301, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.28 (m, 5H), 7.24 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 4.77 (d, *J*=11.4 Hz, 1H), 4.74 (d, *J*=11.4 Hz, 1H), 4.47 (d, *J*=12 Hz, 1H), 4.42 (d, *J*=12 Hz, 1H), 4.26 (q, *J*=9.0 Hz, 1H), 3.97 (dd, *J*=8.4, 6.6 Hz, 1H), 3.81 (s, 3H), 3.72 (dd, *J*=8.4, 7.4 Hz, 1H), 3.64–3.55 (m, 3H), 1.40 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 138.6, 130.2, 129.3, 128.3, 127.9, 127.5, 113.8, 78.4, 76.9, 73.2, 72.9, 70.0, 65.9, 55.3, 26.6, 25.6; HRMS (ESI) calcd for $[C_{22}H_{28}O_5+Na]^+$ 395.1829, found 395.1833.

4.1.2. (2*R*,3*S*)-2-(*O*-Benzyl)-1-(*O*-[*p*-methoxy]benzyl)-1,2,3,4-buaneteteraol (17b). To a stirred solution of **17** (1.00 g, 2.68 mmol) in methanol (26 mL) was added Amberlite (IR 120H^+ C.P., Mallinckrodt; 1.0 g). After the mixture was stirred for 14 h, the resin was removed by filtration. The filtrate was evaporated in vacuo to give **17b** (0.84 g, 2.5 mmol, 94%) as a colorless oil: R_f 0.32 (hexanes–ethyl acetate, 1:1, v/v); $[\alpha]_D^{23}$ +17.6 (*c* 2.13, CH_2Cl_2); IR (thin film): 3417 (br), 3064, 3032, 2933, 2870, 1613, 1587, 1514, 1456, 1365, 1302, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38–7.29 (m, 5H), 7.26 (d, *J*=8.5 Hz, 2H), 6.89 (d, *J*=8.5 Hz, 2H), 4.75 (d, *J*=11.0 Hz, 1H), 4.55 (d, *J*=11.0 Hz, 1H), 4.51 (d, *J*=13.0 Hz, 1H), 4.47 (d, *J*=13.0 Hz, 1H),

3.82 (s, 3H), 3.79 (m, 2H), 3.66 (m, 4H), 2.74 (br d, J=4.5 Hz, 1H), 2.31 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 137.9, 129.7, 129.5, 128.6, 128.0, 113.9, 78.2, 73.3, 72.7, 71.9, 68.9, 63.5, 55.3; MS (ESI) calcd for $[C_{19}H_{24}O_5+Na]^+$ 355.15, found 355.21.

4.1.3. (2*R*,3*S*)-1,2-Dibenzoyl-3-(*O*-benzyl)-4-(*O*-[*p*-methoxy]benzyl)-1,2,3,4-buaneteteraol (18). To a stirred solution of **17b** (0.80 g, 2.4 mmol) in CH_2Cl_2 (24 mL) were added Et_3N (1.33 mL, 9.60 mmol), benzoyl chloride (0.84 mL, 7.2 mmol), and DMAP (29 mg, 0.24 mmol) sequentially. The reaction mixture was stirred for 1.5 h before saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude residue by silica gel column chromatography (hexanes–ethyl acetate, 4:1 to 2:1, v/v) provided **18** (1.18 g, 2.25 mmol, 93%) as a colorless oil: R_f 0.52 (hexanes–ethyl acetate, 2:1, v/v); $[\alpha]_D^{23}$ +3.3 (c 0.92, $CDCl_3$); IR (thin film): 3065, 3033, 2933, 2864, 1782, 1724, 1611, 1586, 1514, 1453, 1368, 1316, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, J=7.1 Hz, 2H), 7.96 (dd, J=7.1 Hz, 2H), 7.56 (m, 2H), 7.41 (m, 4H) 7.36–7.27 (m, 5H), 7.25 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 5.55 (m, 1H), 4.81 (d, J=11.8 Hz, 1H), 4.69 (d, J=11.8 Hz, 1H), 4.66 (d, J=4.2 Hz, 1H), 4.62 (d, J=4.2 Hz, 1H), 4.48 (s, 2H), 4.02 (dd, J=9.9, 5.4 Hz, 1H), 3.79 (s, 3H), 3.72 (d, J=5.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.0, 165.6, 159.0, 137.7, 133.0, 132.9, 129.7, 129.5, 129.3, 128.2, 128.1, 127.8, 127.6, 113.6, 76.3, 73.1, 72.9, 71.3, 68.7, 63.1, 55.1; HRMS (ESI) calcd for $[C_{33}H_{32}O_7+Na]^+$ 563.2041, found 563.2035.

4.1.4. (2*R*,3*S*)-1,2-Dibenzoyl-4-(*O*-[*p*-methoxy]benzyl)-1,2,3,4-buaneteteraol (19). To a solution of **18** (1.00 g, 1.85 mmol) in ethyl acetate (100 mL) was added Pd–$BaSO_4$ (0.2 g, 10% w/w). The mixture was stirred under a H_2 atmosphere (~1 atm) for 6 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 5:1 to 2:1, v/v) to give recovered **18** (0.25 g, 25%) and the product **19** (0.49 g, 1.1 mmol, 58%) as a colorless oil: R_f 0.33 (hexanes–ethyl acetate, 2:1, v/v); $[\alpha]_D^{23}$ −8.7 (c 1.1, $CDCl_3$); IR (thin film): 3489 (br), 3065, 2935, 2865, 1727, 1611, 1586, 1514, 1452, 1361, 1316, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, J=8.7 Hz, 2H), 7.98 (d, J=9.0 Hz, 2H), 7.56 (m, 2H), 7.42 (m, 4H), 7.20 (d, J=8.7 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 5.62 (ddd, J=7.0, 4.5, 4.5 Hz, 1H), 4.71 (dd, J=11.7, 4.5 Hz, 1H), 4.59 (dd, J=11.7, 6.9 Hz, 1H), 4.46 (s, 2H), 4.17 (m, 1H), 3.78 (s, 3H), 3.65 (dd, J=9.9, 4.5 Hz, 1H), 3.59 (dd, J=9.9, 6.3 Hz, 1H), 2.61 (d, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3, 165.9, 159.3, 133.3, 133.2, 129.8, 129.7, 129.5, 128.4, 113.8, 73.3, 72.1, 70.4, 69.6, 63.2, 55.2; MS (ESI) calcd for $[C_{26}H_{26}O_7+Na]^+$ 473.16, found 473.25.

4.1.5. (3*S*)-3,4-Dibenzoyl-4-(*O*-[*p*-methoxy]benzyl)-1,3,4-trihydroxybuanone (14). To a solution of **19** (1.67 g, 3.71 mmol) in CH_2Cl_2 (35 mL) was added 4 Å molecular sieves (0.4 g) and TPAP (65 mg, 0.18 mmol), followed by NMO (0.65 g, 5.6 mmol). After 30 min, the reaction mixture was transferred to a silica gel column and eluted with hexanes–ethyl acetate (9:1 to 4:1 to 2:1, v/v) to provide **14** (1.45 g, 3.24 mmol, 87%) as a colorless oil: R_f 0.37 (hexanes–ethyl acetate, 2:1, v/v); $[\alpha]_D^{23}$ +54.2 (c 0.74, benzene); IR (thin film): 3065, 2956, 2847, 1726, 1611, 1586, 1514, 1452, 1374, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, J=7.5 Hz, 2H), 7.98 (d, J=7.5 Hz, 2H), 7.58 (q, J=7.5 Hz, 2H), 7.44 (q, J=7.5 Hz, 4H), 7.27 (d, J=9.0 Hz, 2H), 6.86 (d, J=9.0 Hz, 2H), 5.89 (t, J=4.0 Hz, 1H), 4.87 (d, J=4.0 Hz, 2H), 4.61 (d, J=12.0 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.38 (d, J=15.0 Hz, 1H), 4.30 (d, J=15.0 Hz, 1H), 3.79 (s, 3H; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.0, 166.0, 165.3, 159.3, 133.7, 133.4, 130.0, 129.7, 128.6, 128.5, 114.0, 102.8, 75.2, 73.4, 73.3, 62.8, 55.3; HRMS (ESI) calcd for $[C_{26}H_{24}O_7+Na]^+$ 471.1420, found 471.1431.

4.1.6. Aldol adduct (20). To a stirred, 0 °C solution of dicyclohexylchloroborane (0.79 mL, 3.6 mmol) and triethylamine (0.63 mL, 4.5 mmol) in diethyl ether (40 mL) was added a solution of **14** (1.34 g, 3.0 mmol) in diethyl ether (2 mL). The initially colorless solution became a yellow suspension. After 2 h, the reaction mixture was cooled to −78 °C, and a solution of **15** (0.49 g, 2.2 mmol) in diethyl ether (3 mL) was added. After 10 min, the reaction mixture was allowed to warm slowly to −25 °C, and stirring was continued at this temperature for 4 h. A solution of pH 7 aqueous phosphate buffer (10 mL), methanol (10 mL), and 30% aqueous H_2O_2 solution (5 mL) were added sequentially. The mixture was allowed to warm to rt and stirred for 1 h before diethyl ether (20 mL) was added. The aqueous phase was separated and extracted with diethyl ether (2×10 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1 to 4:1 to 2:1, v/v) to provide **20** (1.02 g, 1.51 mmol, 69%) as a colorless oil: R_f 0.50 (hexanes–ethyl acetate, 2:1, v/v); $[\alpha]_D^{23}$ +37.5 (c 2.5, CH_2Cl_2); IR (thin film): 3491.8, 2955.9, 2871.4, 2170, 1727, 1613, 1586, 1514, 1453, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, J=7.5 Hz, 2H), 8.01 (d, J=7.5 Hz, 2H), 7.58 (q, J=7.5 Hz, 2H), 7.44 (q, J=7.5 Hz, 4H), 7.27 (d, J=9.0 Hz, 2H), 6.85 (d, J=9.0 Hz, 2H), 5.93 (dd, J=4.5, 3.0 Hz, 1H), 4.89 (m, 2H), 4.63 (d, J=11.5 Hz, 1H), 4.61 (d, 11.5 1H), 4.13 (m, 1H), 4.04 (d, J=5.5 Hz, 1H), 3.77 (s, 3H), 2.90 (d, J=7.5 Hz, 1H) 2.29 (dd, J=12.0, 5.0 Hz, 1H), 2.22 (dd, J=12.0, 6.5 Hz, 1H), 2.00 (m, 1H), 1.64 (ddd, J=14.0, 8.5, 3.5 Hz, 1H), 1.50 (ddd, J=14.0, 1.0, 5.0 Hz), 1.04 (d, J=7.0 Hz, 3H), 0.97 (t, J=7.5 Hz, 9H), 0.56 (q, J=7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.1, 166.4, 166.1, 159.7, 133.9, 133.4, 130.2, 130.0, 129.8, 128.6, 114.0, 106.8, 86.7, 72.8, 69.9, 63.0, 55.9, 38.7, 28.9, 26.1, 20.4, 7.6, 4.6; HRMS (ESI) calcd for $[C_{39}H_{48}O_8Si+Na]^+$ 695.3013, found 695.2990.

4.1.7. TBS ether (21). To a solution of **20** (0.69 g, 1.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added 2,6-lutidine (0.36 mL, 3.1 mmol) and *t*-butyldimethylsilyl triflate (0.47 mL, 2.0 mmol) sequentially. After 1 h, saturated aqueous NH_4Cl (10 mL) was added slowly. The aqueous phase was separated and extracted with diethyl ether (2×10 mL) and the combined organic extracts were washed with

saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 10:1 to 7:1, v/v) to provide **21** (0.66 g, 0.85 mmol, 83%) as a colorless oil: R_f 0.69 (hexanes–ethyl acetate, 2:1, v/v); $[\alpha]_D^{23}$ −15 (*c* 0.97, $CDCl_3$); IR (thin film): 2957, 2923, 2875, 2175, 1725, 1613, 1595, 1512, 1446, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, *J*=8.4 Hz, 2H), 7.99 (d, *J*=8.4 Hz, 2H), 7.57 (m, 2H), 7.43 (m, 4H), 7.29 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H) 6.06 (dd, *J*=5.1, 2.7 Hz, 1H), 4.93 (dd, *J*=12.3, 5.1 Hz, 1H), 4.82 (d, *J*=10.8 Hz, 1H), 4.80 (dd, *J*=12.3, 2.7 Hz, 1H) 4.58 (d, *J*=10.8 Hz, 1H), 4.26 (m, 2H), 3.78 (s, 3H), 2.30 (dd, *J*=16.8, 3.6 Hz, 1H), 2.01 (dd, *J*=16.8, 8.1 Hz, 1H), 1.80 (m, 1H), 1.70–1.60 (m, 2H), 1.03 (d, *J*=6.3 Hz, 3H), 0.98 (t, *J*=7.8 Hz, 9H), 0.91 (s, 9H), 0.56 (q, *J*=7.8 Hz, 6H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 138.6, 130.2, 129.3, 128.3, 127.9, 127.5, 113.8, 78.4, 76.9, 73.2, 72.9, 70.0, 65.9, 55.3, 26.6, 25.6; HRMS (ESI) calcd for $[C_{45}H_{62}O_8Si_2+Na]^+$ 809.3881, found 809.3904.

4.1.8. Alcohol (22). To a stirred, 0 °C solution of **22** (0.80 g, 1.0 mmol) in methanol (11 mL) was slowly added $NaBH_4$ (21 mg, 0.55 mmol). After 1 h, saturated aqueous NH_4Cl (10 mL) was added dropwise and the reaction mixture was allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 10:1 to 7:1, v/v) to provide the corresponding alcohol **22** (0.73 g, 0.93 mmol, 92%, mixture of diastereomers) as a colorless oil: R_f 0.48 (hexanes–ethyl acetate, 5:1, v/v); IR (thin film): 3493, 2954, 2170, 1723, 1611, 1586, 1514, 1454, 1255 cm^{-1}; MS (ESI) calcd for $[C_{45}H_{64}O_8Si_2+Na]^+$ 811.39, found 811.45.

4.1.9. Aldehyde (13). To a solution of **22** (0.73 g, 0.93 mmol) in methanol (5 mL) was added K_2CO_3 (0.74 g, 5.4 mmol). After 5 h, TLC analysis showed complete conversion to triol: HRMS (ESI) calcd for $[C_{31}H_{56}O_6Si_2+K]^+$ 619.3253, found 619.3249. To the solution of triol was slowly added acetic acid (ca. 0.5 mL) to achieve pH 9. $NaIO_4$ (1.14 g, 5.35 mmol) was then added portion-wise. After 4 h, saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (15 mL) were added, and stirring was continued for 15 min. The separated aqueous phase was extracted with CH_2Cl_2 (4×10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1, v/v) to give **13** (3.33 g, 0.65 mmol, 70%) as a colorless oil: R_f 0.58 (hexanes–ethyl acetate, 4:1, v/v); $[\alpha]_D^{23}$ +30.9 (*c* 0.55, $CDCl_3$); IR (thin film): 2956, 2933, 2876, 2172, 1735, 1614, 1587, 1514, 1463, 1379, 1302, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.64 (d, *J*=2.5 Hz, 1H), 7.27 (d, *J*=8.7 Hz, 2H), 6.88 (q, *J*=8.7 Hz, 2H), 4.58 (d, *J*=11.0 Hz, 1H), 4.55 (d, *J*=11.0 Hz, 1H), 4.07 (ddd, *J*=8.0, 6.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.64 (dd, *J*=2.5, 2.5 Hz, 1H) 2.25 (dd, *J*=16.5, 5.0 Hz, 1H), 2.12 (dd, *J*=16.5, 7.0 Hz, 1H), 1.78 (m, 1H), 1.56 (m, 2H), 1.00 (d, *J*=5.0 Hz, 3H), 0.98 (t, *J*=8.0 Hz, 9H), 0.57 (q, *J*=7.5 Hz, 6H), 0.09 (s, 3H), 0.07 (s, 3H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.2, 159.3, 129.5, 129.2, 113.7, 106.0, 86.6, 86.3, 72.3, 72.1, 55.1, 39.8, 28.5, 26.5, 25.7, 19.8, 7.7, 4.4, 0.9, −4.4, −4.9; HRMS (ESI) calcd for $[C_{29}H_{50}O_4Si_2+Na]^+$ 541.3140, found 541.3138.

4.1.10. TMS enol ether (23). To a solution of **11** (0.30 g, 1.8 mmol) in THF (6 mL) at −78 °C was added NaHMDS (2.66 mL, 1 M in THF). After 30 min, trimethylsilyl chloride (0.44 mL, 3.6 mmol) was added. After 1 h, a solution of pH 7 phosphate buffer (6 mL) was added and the reaction mixture was allowed to warm to rt. The separated aqueous phase was extracted with ether, and the ether extract was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation at 20 °C. The residue was passed quickly through a short pad of silica gel with pentane–ether (3:1 v/v). The solvent was removed by rotary evaporation to yield **23** as a pale yellow oil (0.49 g). The product was used for the next step without further purification: R_f 9.0 (hexanes–ethyl acetate, 5:1, v/v); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.01 (d, *J*=0.9 Hz, 1H), 3.96 (s, 1H), 3.17 (dd, *J*=12.0, 6.0 Hz, 1H), 3.08 (dd, *J*=12.0, 6.9 Hz, 1H), 2.19 (m, 1H), 1.75 (m, 1H), 1.58 (ddd, *J*=13.5, 9.6, 4.5 Hz, 1H), 1.02 (d, *J*=6.9 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.19 (d, *J*=9.9 Hz, 9H); IR (thin film): 2963, 2097, 1655, 1624, 1461, 1319, 1253, 1092, 1020 cm^{-1}.

4.1.11. Mukaiyama aldol product (24). To a stirred solution of **23** (0.49 g) and **13** (144 mg, 355 μmol) in CH_2Cl_2 (6 mL) at −78 °C was added a fine powder of $MgBr_2 \cdot OEt_2$ (275 mg, 1.07 mmol). Stirring was continued for 4 h before the reaction flask was placed in a freezer for 14 h. A solution of pH 7 phosphate buffer (10 mL) was added and the temperature was allowed to rise to rt. The aqueous phase was extracted with diethyl ether and the combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1, v/v) to provide **24** (161 mg, 234 μmol, 66%) as a colorless oil: R_f 0.19 (hexanes–ethyl acetate, 5:1, v/v); $[\alpha]_D^{23}$ +25.4 (*c* 0.51, CH_2Cl_2); IR (thin film): 3491, 2962, 2933, 2877, 2170, 2100, 1713, 1614, 1514, 1461, 1380, 1356, 1286, 1251, 1177, 1105, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28 (d, *J*=8.7 Hz, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 4.70 (d, *J*=11.4 Hz, 1H), 4.38 (m, 2H), 4.14 (dd, *J*=6.9, 1.8 Hz, 1H), 3.84 (d, *J*=1.5 Hz, 1H), 3.82 (s, 3H), 3.30 (m, 1H), 3.20 (dd, *J*=12.0, 5.1 Hz, 1H), 3.07 (dd, *J*=12.0, 6.6 Hz, 1H), 2.79 (dd, *J*=17.4, 6.3 Hz, 1H), 2.55 (m, 1H), 2.52 (dd, *J*=17.1, 5.7 Hz, 1H), 2.29 (dd, *J*=16.8, 4.5 Hz, 1H), 2.17 (dd, *J*=16.8, 6.0 Hz, 1H), 1.90–1.55 (m, 6H), 1.07 (d, *J*=7.5 Hz, 3H), 1.04 (d, *J*=6.0 Hz, 3H), 1.00 (t, *J*=7.8 Hz, 9H), 0.93 (d, *J*=7.2 Hz, 3H), 0.91 (s, 9H), 0.59 (q, *J*=7.8 Hz, 6H), 0.15 (s, 3H), 0.12 (s, 3H); MS (ESI) calcd for $[C_{37}H_{65}N_3O_5Si_2+Na]^+$ 710.43, found 710.43.

4.1.12. TES ether (25). To a stirred solution of **10** (32 mg, 47 μmol) in CH_2Cl_2 (1 mL) at −10 °C were added 2,6-lutidine (22 μL, 0.19 mmol) and triethylsilyl triflate (21 μL, 93 μmol). After 30 min, saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. The

residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1, v/v) to provide **25** (35 mg, 43 μmol, 92%) as colorless viscous oil: R_f 0.55 (hexanes–ethyl acetate, 5:1, v/v); $[\alpha]_D^{23}$ +15.4 (*c* 1.4, CH_2Cl_2); IR (thin film): 2957, 2877, 2171, 2098, 1715, 1614, 1514, 1461, 1415, 1380, 1250, 1109, 1071, 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (d, *J*=4.2 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 2H), 4.66 (d, *J*=11.0 Hz, 1H), 4.47 (d, *J*=11.0 Hz, 1H), 4.36 (m, 1H), 3.98 (ddd, *J*=8.5, 4.0, 1.5 Hz, 1H), 3.81 (s, 3H), 3.44 (dd, *J*=5.5, 1.5 Hz, 1H), 3.22 (dd, *J*=11.5, 5.0 Hz, 1H), 3.07 (dd, *J*=11.5, 7.0 Hz, 1H), 2.81 (dd, *J*=17.0, 3.5 Hz, 1H), 2.72 (dd, *J*=17.0, 7.5 Hz, 1H) 2.58 (septet, *J*=7.0 Hz, 1H), 2.30 (dd, *J*=16.5, 3.5 Hz, 1H), 2.04 (dd, *J*=8.0, 16.5 Hz, 1H), 1.88 (m, 1H), 1.79 (ddd, *J*=13.5, 8.5, 6.0 Hz, 1H), 1.66 (m, 1H), 1.48 (ddd, *J*=13.5, 9.0, 4.5 Hz, 1H), 1.07 (d, *J*=7.0 Hz, 3H), 1.04 (d, *J*=6.5 Hz, 3H), 0.99 (t, *J*=8.0 Hz, 9H), 0.93 (d, *J*=7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (t, *J*=8.0 Hz, 9H), 0.58 (q, *J*=8.0 Hz, 6H), 0.54 (q, *J*=4.0 Hz, 6H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.85, 130.85, 128.99, 113.41, 106.70, 92.68, 83.92, 72.74, 71.56, 68.72, 57.58, 55.11, 45.57, 44.30, 39.57, 36.79, 31.23, 28.69, 25.88, 20.26, 17.81, 16.88, 7.39, 6.86, 4.78, 4.48, −3.72, −5.22; HRMS (ESI) calcd for $[C_{43}H_{79}N_3O_5Si_3+Na]^+$ 824.5220, found 824.5234.

4.1.13. Alcohol (6). To a stirred solution of **25** (42 mg, 61 μmol) in CH_2Cl_2 (3 mL) were added aqueous phosphate buffer (0.3 mL, pH 7), *t*-butanol (0.1 mL) and DDQ (42 mg, 0.18 mmol). The reaction mixture turned dark green. After 30 min, saturated aqueous $NaHCO_3$ (3 mL) was added, the mixture was diluted with CH_2Cl_2, and transferred to a separatory funnel. The separated aqueous phase was extracted with CH_2Cl_2 and the combined organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1, v/v) to give **25** (29 mg, 50 μmol, 82%) as a colorless oil: R_f 0.50 (hexanes–ethyl acetate, 5:1, v/v); $[\alpha]_D^{23}$ +6.5 (*c* 0.39, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.30 (dd, *J*=10.2, 5.7 Hz, 1H), 3.77 (dd, *J*=12.0, 6.6 Hz, 1H), 3.35 (dd, *J*=10.2, 5.4 Hz, 1H), 3.24 (dd, *J*=12.0, 5.4 Hz, 1H), 3.12 (dd, *J*=12.0, 6.6 Hz, 1H), 2.80 (dd, *J*=16.5, 5.7 Hz, 1H), 2.61 (dd, *J*=16.5, 5.4 Hz, 1H), 2.47 (d, *J*=6.3 Hz, 1H), 2.32 (dd, *J*=16.8, 3.9 Hz, 1H), 2.09 (dd, *J*=16.8, 7.2 Hz, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 1.69 (m, 1H), 1.53 (t, *J*=6.6 Hz, 1H), 1.10 (d, *J*=6.9 Hz, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 0.99 (t, *J*=7.1 Hz, 9H), 0.96 (t, *J*=7.8 Hz, 9H), 0.90 (s, 9H), 0.64 (q, *J*=7.8 Hz, 6H), 0.57 (d, *J*=7.8 Hz, 6H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz): δ 211.4, 106.7, 82.7, 71.3, 68.1, 57.5, 45.5, 44.5, 38.5, 36.7, 31.2, 29.5, 28.4, 26.3, 25.7, 20.0, 17.8, 16.9, 7.3, 6.7, 4.9, 4.4, 0.8, −4.2, −4.3; IR (thin film): 3551, 2957, 2878, 2172, 2099, 1714, 1613, 1514, 1461, 1414, 1380, 1256, 1102, 1019 cm^{-1}; MS (ESI) calcd for $[C_{35}H_{71}N_3O_4Si_3+Na]^+$ 704.46, found 704.46.

4.1.14. Spiroaminal (26). To a solution of **6** (28 mg, 41 μmol) in toluene was added triethylphosphine (18 μL, 0.12 mmol). After 14 h, solvent was removed under a stream of N_2 (in a hood—stench). The crude product could be used for the next step without purification. For characterization, the residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1, v/v) to yield **26** (19 mg, 30 μmol, 75%, 4:1 mixture of anomers) as a colorless oil: R_f 0.23 (hexanes–ethyl acetate, 5:1, v/v); $[\alpha]_D^{23}$ −10 (*c* 0.40, $CDCl_3$); IR (thin film): 2956, 2878, 2173, 1461, 1415, 1378, 1256, 1017 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz): δ 4.29 (dd, *J*=12.0, 6.5 Hz, 1H), 4.22 (t, *J*=3.5 Hz, 1H), 3.80 (dd, *J*=4.5, 2.5 Hz, 1H), 2.85 (t, *J*=11 Hz, 1H), 2.71 (m, 1H), 2.60 (dd, *J*=16.5, 3.5 Hz, 1H), 2.39 (m, 1H), 2.19 (m, 2H), 2.04 (dd, *J*=13.5, 4.5 Hz, 1H), 1.95 (m, 2H) 1.81 (m, 2H), 1.73 (d, *J*=13.5 Hz, 1H), 1.48 (m, 1H), 1.33 (d, *J*=6.5 Hz, 3H), 1.14 (t, *J*=8.0 Hz, 9H), 1.04 (s, 9H), 0.98 (t, *J*=7 Hz, 9H), 0.89 (d, *J*=6.5 Hz, 3H), 0.85 (d, *J*=7.0 Hz, 3H), 0.29 (s, 6H); HRMS (ESI) calcd for $[C_{35}H_{71}NO_3Si_3+H]^+$ 638.4815, found 638.4834.

4.1.15. Carbamate (27). To a stirred solution of **12** (8 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) were sequentially added powdered 4 Å molecular sieves (30 mg), K_2CO_3 (34 mg, 0.25 mmol, fine powder), and carbobenzyloxy chloride (7.2 μL, 0.05 mmol). After 14 h, the mixture was applied directly onto a silica gel column and eluted with hexanes–ethyl acetate (10:1, v/v). The product collected after evaporation of the solvents by rotary evaporation was placed under high vacuum for 2 h to afford **27** as a colorless oil (7 mg, 9 μmol, 73%, 4:1 mixture of anomers): R_f 0.69 (hexanes–ethyl acetate, 5:1, v/v); $[\alpha]_D^{23}$ +28 (*c* 1.0, CH_2Cl_2); IR (thin film); 2956, 2876, 2171, 1704, 1460, 1396, 1356, 1259, 1174, 1072, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 5.10 (d, *J*=2 Hz, 2H), 4.49 (m, 1H), 4.09 (dd, *J*=8.0, 2.5 Hz, 1H), 3.91 (m, 1H), 3.83 (dt, *J*=9.5, 2.5 Hz, 1H), 3.76 (dd, *J*=13.5, 2.5 Hz, 1H), 3.25 (t, *J*=12.5 Hz, 1H), 2.66 (m, 1H), 2.53 (m, 1H), 2.40 (dd, *J*=16.5, 3.5 Hz, 1H), 1.86 (m, 2H), 1.77 (m, 1H), 1.60 (m, 1H), 1.415 (m, 2H), 1.32 (m, 1H), 1.04 (d, *J*=6 Hz, 3H), 0.99 (t, *J*=5.5 Hz, 9H), 0.94 (t, *J*=8.0 Hz, 9H), 0.91 (s, 9H), 0.80 (d, *J*=6.5 Hz, 3H), 0.77 (d, *J*=7 Hz, 3H), 0.57 (m, 12H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.61, 137.00, 128.48, 127.77, 127.48, 108.42, 95.62, 85.56, 81.82, 72.33, 70.46, 66.50, 59.60, 49.07, 39.54, 38.01, 31.23, 29.87, 26.08, 21.01, 18.73, 16.81, 7.62, 7.13, 4.79, 1.16, −4.14; HRMS (ESI) calcd for $[C_{43}H_{77}NO_5Si_3+Na]^+$ 794.5007, found 794.4999.

4.1.16. Alkynyl iodide (3). To a solution of **27** (5 mg, 6.3 μmol) in DMF (0.3 mL) were added *N*-iodosuccimide (4 mg, 0.09 mmol) and silver trifluoroacetate (1.5 mg, 6.5 μmol). After 10 min, the reaction mixture was diluted with diethyl ether and saturated aqueous $NaHCO_3$ was added. The separated aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 6:1, v/v) to provide **3** (4.3 mg, 87%) as a colorless oil: R_f 0.64 (hexanes–ethyl acetate, 5:1, v/v); $[\alpha]_D^{25}$ +29 (*c* 0.32, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29–7.38 (m, 5H), 5.08 (s, 2H), 4.43–4.50 (m, 1H), 4.09 (dd, *J*=9.0, 4.5 Hz, 1H), 3.83 (dt, *J*=4.5, 2.5 Hz, 1H), 3.75 (dd, *J*=13.5, 3.5 Hz, 1H), 3.22 (dd, *J*=12, 12 Hz, 1H), 2.64 (m, 1H), 2.52 (dd, *J*=16, 12 Hz, 1H), 2.46 (dd, *J*=16.5, 4.5 Hz, 1H), 2.05 (dd, *J*=17.0, 6.0 Hz, 1H), 1.80–1.96 (m, 2H), 1.51–1.59 (m, 2H), 1.2–1.35 (m, 3H), 0.98 (d, *J*=7 Hz, 3H), 0.88–0.91

(m, 9H), 0.80 (d, J=7 Hz, 3H), 0.77 (d, J=7.5 Hz, 3H), 0.55–0.59 (m, 9H), 0.055–0.068 (m, 10H); IR (thin film) 2959 (m), 2929 (m), 2878 (w), 2857 (w), 2361 (m), 1701 (s), 1458 (m), 1397 (m), 1260 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $(C_{37}H_{62}INO_5Si_2+Na)^+$ 806.3109, found 806.3118.

4.1.17. Ynone (33). To a solution of CBr_4 (471 mg, 1.42 mmol) in CH_2Cl_2 (6 mL) at 0 °C under argon was added triphenylphosphine (745 mg, 2.8 mmol). The resulting orange solution was stirred for 30 min before a solution of aldehyde **28** (110 mg, 0.71 mmol) in CH_2Cl_2 (6 mL) was added. After stirring for 10 min, saturated aqueous $NaHCO_3$ (6 mL) was added and the resulting mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes–diethyl ether, 5:1, v/v) to provide dibromide **29** (0.20 g, 0.64 mmol, 91%) as a yellow oil: R_f 0.75 (hexanes–ethyl acetate, 5:1, v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (d, J=9.5 Hz, 1H), 3.16 (d, J=6.0 Hz, 2H), 2.56–2.61 (m, 1H), 1.66–1.70 (m, 1H), 1.42–1.48 (m, 1H), 1.14–1.20 (m, 1H), 1.02 (d, J=7.0 Hz, 3H), 0.98 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 104.8, 58.0, 40.7, 36.0, 31.6, 19.9, 17.6; LRMS (EI) *m/z* calcd for $(C_8H_{13}Br_2N_3–N_2–H)^+$ 280.9, found 280.9.

To a solution of **29** (24 mg, 77 μmol) in THF (0.8 mL) was added *n*-butyllithium (65 μmol, 2.5 M in hexane) at −78 °C. After stirring for 20 min, a solution of aldehyde **31** (15.1 mg, 31 μmol) in THF (0.2 mL) was added. The resulting mixture was warmed slowly to 0 °C over 1 h and stirred for another 30 min at 0 °C before saturated aqueous NH_4Cl (1 mL) was added. The separated aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes–diethyl ether, 10:1, v/v) to afford the alcohol **32** (14.6 mg, 23 μmol, 73%): R_f 0.63 (hexanes–ethyl acetate, 3:1, v/v).

To a solution of **32** (7.2 mg, 11 μmol) in toluene (0.6 mL) under argon was added triethylphosphine (6 mg, 0.05 mmol). The resulting solution was stirred at rt for 50 min and cooled to −20 °C before BocON (7.3 mg, 30 μmol) was added. The reaction mixture was warmed slowly to rt and stirred for 12 h. Ethyl acetate (2 mL) was added and the resulting solution was washed with H_2O (3×1 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes–ethyl acetate, 10:1, v/v) to provide carbamate alcohol **32b** (4.8 mg, 61%): R_f 0.44 (hexanes–ethyl acetate, 3:1, v/v).

Alcohol **32b** (3.8 mg, 5.4 μmol) was dissolved in pentane (0.8 mL) and MnO_2 (21 mg, 0.24 mmol) was added. After stirring for 30 min at rt, the reaction mixture was applied directly to a silica gel column and purified by flash column chromatography (hexanes–diethyl ether, 10:1, v/v) to provide ynone **33** (3.8 mg, 100%): R_f 0.53 (hexanes–ethyl acetate, 3:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J=9.0 Hz, 2H), 6.86 (d, J=9.0 Hz, 2H), 4.63 (d, J=11.5 Hz, 1H), 4.46–4.50 (b, 1H), 4.43 (d, J=11.5 Hz, 1H), 4.13–4.15 (m, 1H), 3.88 (d, J=4.5 Hz, 1H), 3.80 (s, 3H), 2.98–3.06 (m, 1H), 2.90–2.98 (m, 1H), 2.70–2.78 (m, 1H), 2.23 (dd, J=16.5, 4.5 Hz, 1H), 2.05 (dd, J=17.0, 7.0 Hz, 1H), 1.75–1.85 (m, 2H), 1.53–1.62 (m, 3H), 1.43 (s, 9H), 1.22 (d, J=7.0 Hz, 3H), 1.18–1.21 (m, 1H), 0.99 (d, J=7.0 Hz, 3H), 0.89 (d, J=7.0 Hz, 3H), 0.86 (s, 9H), 0.13 (s, 6H), 0.068 (d, J=9.0 Hz, 9H); LRMS *m/z* calcd for $(C_{39}H_{65}INO_6Si_2+Na)^+$ 722.4, found 722.5.

4.1.18. Spiroaminal (35). To a stirred rt solution of ynone **33** (0.5 mg, 0.7 μmol) in CH_2Cl_2 (0.3 mL) was added silver trifluoroacetate (1 mg, 5 μmol). After disappearance of starting material **35** by TLC, ethanol (1 mL) and H_2O (0.5 mL) were added, followed by the addition of KI (2 mg). After stirring for another 5 min, the reaction mixture was applied to a small silica gel column and eluted to afford **38** (0.2 mg, 0.4 μmol, 56%): R_f 0.39 (hexanes–ethyl acetate, 3:1); ^1H NMR (500 MHz, $CDCl_3$) δ 4.48 (d, J=2.0 Hz, 1H), 4.18–4.22 (m, 1H), 3.05–3.08 (m, 1H), 2.85–2.97 (m, 1H), 2.76–2.81 (m, 1H), 2.21 (ddd, J=16.0, 4.5, 2.5 Hz, 1H), 1.98–2.06 (m, 2H), 1.95 (t, J=2.5 Hz, 1H), 1.75–1.85 (m, 1H), 1.63–1.85 (m, 3H), 1.45–1.50 (m, 1H), 1.43 (s, 9H), 1.25–1.27 (m, 1H), 1.02 (d, J=6.5 Hz, 3H), 0.93 (d, J=6.0 Hz, 3H), 0.87–0.90 (m, 12H), 0.11 (d, J=1.5 Hz, 6H). HRMS (ESI) *m/z* calcd for $(C_{18}H_{49}NO_5Si+Na)^+$ 530.3278, found 530.3191.

References and notes

1. Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967–9968.
2. James, K. J.; Moroney, C.; Roden, C.; Satake, M.; Yasumoto, T.; Lehane, M.; Furey, A. *Toxicon* **2003**, *41*, 145–151.
3. Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamada, Y. M. A.; Tang, W.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 4318–4324.
4. (a) Ofuji, K.; Satake, M.; McMahon, T.; Silke, J.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Nat. Toxins* **1999**, *7*, 99–102; (b) Ofuji, K.; Satake, M.; McMahon, T.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 740–742.
5. James, K. J.; Sierra, M. D.; Lehane, M.; Magdalena, A. B.; Furey, A. *Toxicon* **2003**, *41*, 277–283.
6. Nguyen, S.; Xu, J.; Forsyth, C. J. *Abstracts of Papers*, 229th ACS National Meeting, San Diego, CA, United States, March 13–17, 2005; ORGN-330.
7. Aiguade, J.; Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817–820.
8. Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3663–3667.
9. Nicolaou, K. C.; Pihko, P. M.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 1262–1265.
10. Sasaki, M.; Iwamuro, Y.; Nemoto, J.; Oikawa, M. *Tetrahedron Lett.* **2003**, *44*, 6199–6201.
11. Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652.
12. Ohno, M.; Fujita, K.; Nakai, H.; Kobayasi, S.; Inoue, K.; Nojima, S. *Chem. Pharm. Bull.* **1985**, *33*, 572–582.
13. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.