Spiro Compounds

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Gold(I)-Catalyzed Bis-Spiroketalization: Synthesis of the Trioxadispiroketal-Containing A–D Rings of Azaspiracid**

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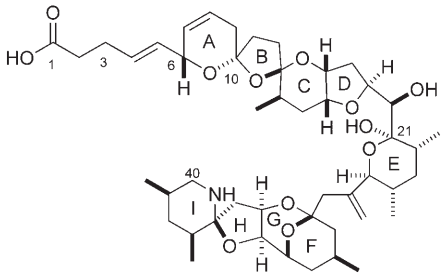
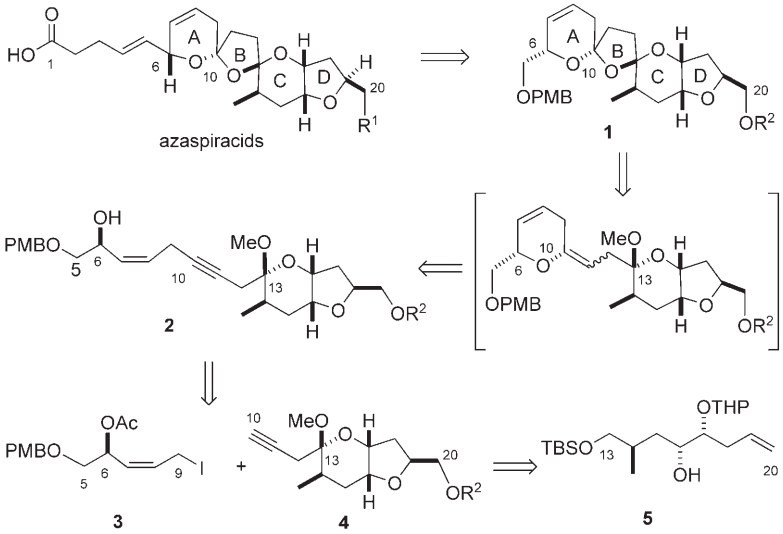
The azaspiracids are a family of marine toxins that were first recognized as being responsible for human poisonings in the Netherlands in 1995.[1] These toxins showed significant acute and chronic effects on the liver, pancreas, thymus, and spleen in mice.[2] Moreover, the azaspiracids have raised concerns over their neurotoxic and tumor-promoting potential.[2] The structure of azaspiracid (**1**, Scheme 1) was originally proposed



Scheme 1. Structure of azaspiracid (**1**).

in 1998[3] and was subsequently revised by Nicolaou et al. in 2004 upon completion of an impressive total synthesis.[4] Herein we report a novel assembly of the trioxadispiroketal-containing A–D domain of azaspiracid which features an unprecedented AuCl-catalyzed[5] bis-spiroketalization and an efficient cobalt-mediated intramolecular etherification, as described by Inoti and Mukaiyama, to close the D ring.[6]

Contrary to the initial structural assignment, the trioxadispiroketal-containing A–D rings of the azaspiracids have been shown to adopt a thermodynamically favored configuration and conformation.[4,7] Thus, it was recognized that assembly of the trioxadispiroketal moiety under equilibrating conditions should favor the delivery of such a system.[4,7,8] By taking advantage of the fact that an alkyne resembles the oxidation state of a ketone (ketal) in its dehydrated form, we previously constructed the azaspiracid C10 spiroketal center through a double intramolecular hetero-Michael addition.[7] However, the geminal bis-hydroxy addition to an alkyne can also be accomplished by Au^{I} or Au^{III} catalysis, without needing conjugation between the alkyne and a carbonyl moiety. This fact was exemplified in the Au^{III}-catalyzed hydration of alkynes,[9] as well as in the conversion of alkynes into methyl enol ethers[9] and dimethyl[9,10] or intramolecularly bridged[11] ketals. An advance in the emergent methodology of homogeneous Au-catalyzed addition to alkynes[5] was targeted in the context of forming the trioxadispiroketal system (**1**, Scheme 2) in the azaspiracid A–D domain.



Scheme 2. Retrosynthetic analysis. PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, THP = tetrahydropyranyl.

We anticipated that an Au^{I}-catalyzed 6-*exo* addition of the C6 hydroxy group of **2** across the C10–C11 alkyne would result in a transient C10–C11 enol ether (Scheme 2). This enol ether could then engage the C13 ketal oxygen atom under protic conditions to form the bis-spiroketal of **1**. The use of an alkyne as a surrogate for a ketone at C10 reduces the likelihood of the C7–C8 alkene isomerizing into the C8–C9 position, which might occur if a ketone was actually present.

Trioxadispiroketalization precursor **2** contains the intact C and D rings with the C13 center at the correct ketal oxidation state as well as the C6 oxygen atom and the *Z* alkene of the A ring in an acyclic chain (Scheme 2). The C5–C9 side chain **3** would be conjoined with bicycle **4** through a copper-mediated alkyne allylation.[12] The latter would be elaborated from hydroxy alkene **5** through the synthesis of the 2,5-*trans*-fused trisubstituted tetrahydrofuran D ring using a cobalt-catalyzed oxyetherification reported by Inoki and Mukaiyama.[6]

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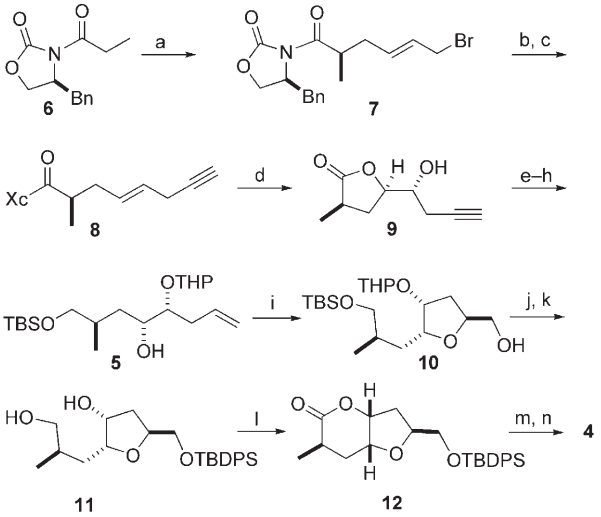
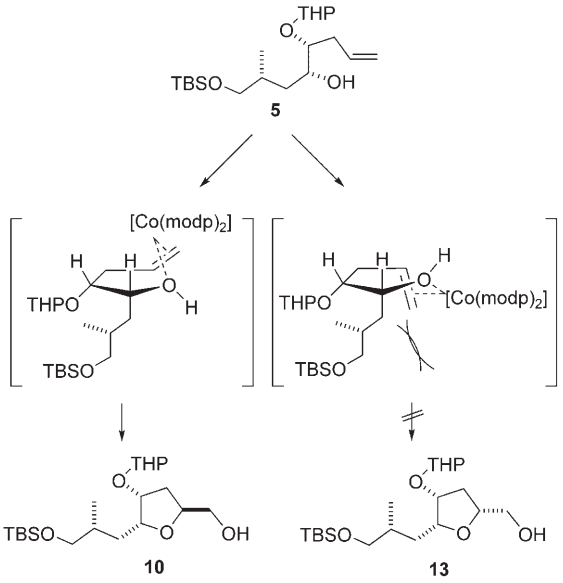
The current empirical exploration commenced with the alkylation of (*S*)-4-benzyl-3-propionyloxazolin-2-one (**6**) with *trans*-1,4-dibromo-2-butene to generate allylic bromide **7** (Scheme 3).[13] Copper-mediated coupling[14] of trimethylsilyl-



Scheme 3. Synthesis of the C and D rings. Reagents and conditions: a) NaHMDS, *trans*-1,4-dibromo-2-butene, −78 °C to −40 °C, THF, 65 %; b) *n*BuLi, CuI, trimethylsilylacetylene, −78 °C to RT; c) TBAF, *p*-TsOH, THF, 87 %, 2 steps; d) AD mix-β, $MeNH_2SO_2$, *t*BuOH/H_2O (1:1), 82 %; e) DHP, PPTS, CH_2Cl_2, 78 %; f) $LiBH_4$, H_2O, Et_2O; g) TBSCl, imidazole, CH_2Cl_2, 73 %, 2 steps; h) H_2, Lindlar catalyst, quinoline, benzene, 99 %; i) $[Co(modp)_2]$ (30 mol %), O_2, *t*BuOOH, 4-Å MS, *i*PrOH, 60 °C, 72 %; j) TBDPSCl, imidazole, CH_2Cl_2, 77 %; k) PPTS, MeOH, 89 %; l) TEMPO, BAIB, CH_2Cl_2, 77 %; m) propargyl bromide, Mg, $HgCl_2$, Et_2O, −78 °C; n) PPTS, MeOH, 73 %. BAIB = [bis-(acetoxy)iodo]benzene, Bn = benzyl, DHP = dihydropyran, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, modp = 1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato, MS = molecular sieves, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy (free radical), Ts = toluene-*p*-sulfonyl, Xc = (*S*)-4-benzyloxazolin-2-one.

acetylene with **7** followed by desilylation afforded enyne **8** in excellent yield. A Sharpless asymmetric dihydroxylation installed the C16 and C17 stereocenters and led to subsequent expulsion of the oxazolidinone to yield lactone **9**.[15] The residual hydroxy group of **9** was converted into a THP acetal. Subsequent reduction of the lactone and selective silylation of the primary hydroxy group, followed by partial hydrogenation of the terminal alkyne, furnished the hydroxy alkene **5**.

Substrate **5** was designed to provide an opportunity to extend the cobalt-catalyzed oxyetherification methodology to the construction of a trisubstituted 2,5-*trans* tetrahydrofuran.[6,16] According to the originally proposed transition state,[6] the additional substituent on the incipient tetrahydrofuran ring would enhance the 2,5-*trans* selectivity by orienting the catalyst to the less sterically hindered face of the terminal alkene (Scheme 4). As anticipated, this reaction occurred smoothly using $[Co(modp)_2]$ as catalyst[6,16] to give exclusively the 2,5-*trans*-substituted tetrahydrofuran **10** in moderate yield. Manipulation of the hydroxy protecting

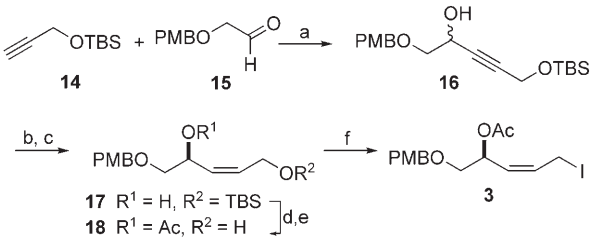


Scheme 4. Alternative modes of Co-catalyzed cyclizations.

groups of **10** gave the diol **11**, which was oxidized to lactone **12** using TEMPO/BAIB.[17] Lactone **12** was treated with propargyl magnesium bromide/mercuric chloride followed by methanol and PPTS to furnish the alkyne ketal **4** (Scheme 3). Intermediate **4** represents the intact azaspiracid D ring appropriately functionalized for elaboration into the fused ABC trioxadispiroketal ring system.

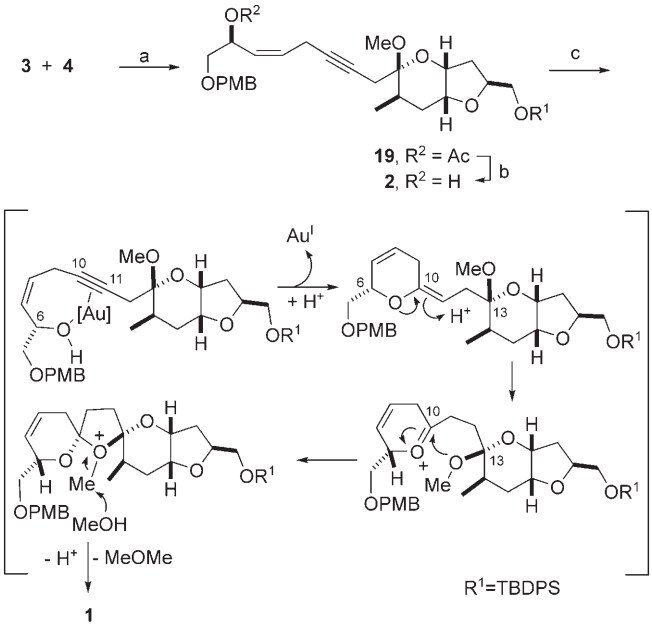
Assembly of the precursor to the A ring began with the addition of the acetylide anion derived from *tert*-butyldimethylsilyl propargyl ether (**14**) to 2-(*p*-methoxybenzyl)oxyacetaldehyde (**15**, Scheme 5). Lindlar reduction of the resultant propargyl alcohol **16** gave a racemic allylic alcohol that could be enantiomerically enriched by either a kinetic resolution utilizing Sharpless asymmetric epoxidation[18] or a Swern oxidation[19]/Corey–Bakshi–Shibata reduction[20] sequence. Both routes provided **17** in high enantioselectivity (≥88 % *ee*). The allylic hydroxy group of **17** was acetylated and the primary silyl ether was cleaved to provide alcohol **18**. Thereafter, alcohol **18** was expeditiously converted into allylic iodide **3**.[21]

The A- and CD-ring precursors **3** and **4** were coupled under mild reaction conditions mediated by CuI/Cs_2CO_3 in



Scheme 5. Synthesis of A-ring precursor **3**. Reagents and conditions: a) *n*BuLi, THF, −78 °C, 85 %; b) H_2, Lindlar catalyst, quinoline, benzene, 100 %; c) $Ti(OiPr)_4$, L-DIPT, *t*BuOOH, 4-Å MS, CH_2Cl_2, −25 °C, 36 h, 39 %; d) AcCl, Py, CH_2Cl_2, 95 %; e) PPTS, MeOH, 87 %; f) I_2, PPh_3, imidazole, CH_2Cl_2, 63 %. L-DIPT = L-diisopropyl tartrate, Py = pyridine.

DMF to give enyne **19** in moderate yield (Scheme 6).[12] The acetate was reductively cleaved to afford the allylic alcohol **2**. To find reliable conditions for the bis-spiroketalization of **2**, a



Scheme 6. Coupling and bis-spiroketalization. Reagents and conditions: a) CuI, Cs_2CO_3, DMF, 46% (89% based on recovered starting material); b) DIBALH, CH_2Cl_2, −78°C, 71%; c) AuCl, PPTS, MeOH, 75%. DIBALH = diisobutylaluminum hydride.

variety of metal salts were screened, including Ag_2O, Ag_2CO_3, AgTFA, $Pd(OAc)_2$, $PdCl_2$, $HgCl_2$, and $Hg(TFA)_2$ (TFA = trifluoroacetate). None of these salts gave satisfactory results. In contrast, we found that enyne **2** was cleanly and quickly converted into the desired bis-spiroketal **1** in good yield using AuCl and PPTS. This process may proceed through an initial associative[10,11] *syn* addition of the C6 hydroxy group and a π-coordinated alkyne–Au^I complex across the alkyne to generate an A-ring enol ether (Scheme 6). Alternatively, a non-associative *anti* oxametalation would generate a geometrically isomeric enol vinyl gold species.[22] In either event, protiodeauration would liberate the catalyst, and protonation of the resultant enol ether at C11 would entice the C13 methoxy oxygen atom to add to C10 and close the B ring. Transfer of the methyl group to a solvent molecule would quench the B-ring oxonium species. NOE studies confirmed that the use of protic solvent and acidic reaction conditions resulted in thermodynamic control over the establishment of the newly formed spiroketal centers at C10 and C13 in **1**.

In summary, a novel and efficient synthesis of the A–D domain of azaspiracid (**1**) has been developed. It features two different catalytic intramolecular oxametalations to assemble the A–D polyether from acyclic precursors. First, a cobalt-catalyzed oxaetherification was used to form the 2,5-*trans*-fused trisubstituted tetrahydrofuran D ring.[6] The kinetic selectivity of this Mukaiyama etherification was augmented by the configurational disposition of the vicinal substituents on the incipient tetrahydrofuran ring. Thereafter, an unprecedented gold(I)-catalyzed bis-spiroketal formation was accomplished using a bridging alkyne as a surrogate for the C10 ketal. This method provided the thermodynamically favored establishment of both of the newly formed spiroketal centers. In addition to demonstrating the use of these metal-mediated intramolecular etherification processes in the context of highly functionalized molecules, this study will support ongoing efforts to develop an efficient synthesis of the azaspiracid natural products.

Experimental Section

AuCl (0.2 mg, 0.9 μmol) and PPTS (0.2 mg, 0.9 μmol) were added to a stirred solution of alcohol **2** (8.0 mg, 11 μmol) in methanol (1 mL) under N_2. After the reaction mixture had been stirred for 20 min, the solvent was removed and the residue purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:1 v/v) to give the bis-spiroketal **1** (5.9 mg, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.62$ (m, 4H), 7.39 (m, 6H), 7.24 (d, $J = 8$ Hz, 2H), 7.26 (d, $J = 9$ Hz, 2H), 5.79 (m, 2H), 4.57 (m, 1H), 4.52 (d, $J = 3.5$ Hz, 2H), 4.33 (m, 1H), 4.23 (m, 1H), 3.91 (m, 1H), 3.80 (s, 3H), 3.76 (dd, $J = 11$, 4 Hz, 1H), 3.66 (dd, $J = 10.5$, 3 Hz, 1H), 3.56 (dd, $J = 10.5$, 4 Hz, 1H), 3.47 (dd, $J = 10$, 5 Hz, 1H), 2.54 (d, $J = 13$ Hz, 1H), 2.29 (m, 1H), 2.20–1.90 (m, 5H), 1.86 (m, 1H), 1.75 (m, 2H), 1.67 (dd, $J = 12$, 7 Hz, 1H), 1.20 (s, 9H), 0.93 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 158.9$, 135.6, 133.6, 129.6, 129.4, 129.2, 127.6, 126.6, 123.7, 113.7, 112.1, 104.8, 78.6, 72.9, 72.3, 72.1, 69.2, 66.3, 55.3, 36.6, 35.7, 35.1, 33.6, 32.2, 31.4, 29.6, 19.3, 16.2 ppm; IR (neat): $\tilde{\nu} = 3070$, 3040, 2956, 2933, 2363, 1652, 1515, 1249, 1111, 808, 705 cm^{-1}; HRMS (ESI): calcd for $C_{41}H_{52}O_7SiNa$ $[M+Na]^+$: 707.3380; found: 707.3389; $[\alpha]_D^{25} = -41$ ($c = 0.5$, $CHCl_3$); $R_f = 0.61$ (hexane/ethyl acetate, 7:3, v/v).

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