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Formal Total Synthesis of Okadaic Acid via Regiocontrolled Gold(I)-Catalyzed Spiroketalizations

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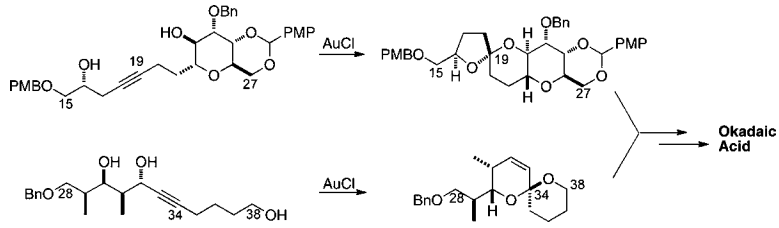
ABSTRACT



Both C19 and C34 spiroketal domains of okadaic acid were assembled using gold(I) chloride catalyzed spiroketalizations, and the two resulting fragments were coupled to give the C15−C38 fragment of okadaic acid, a known intermediate for the total synthesis of this important natural product.

Okadaic acid (OA, **1**, Figure 1) is a polyether natural product originally isolated from the marine sponges *Halichondria okadai* and *H. melanodocia*.[1] The combination of OA's attractive structural features and broad range of biological activities[2−5] has stimulated considerable effort within the synthetic community, culminating in three reported total syntheses of OA[6−8] and one reported total synthesis of the natural product 7-deoxy-okadaic acid.[9]

A common retrosynthetic strategy of the published total syntheses is disconnection of the natural product into three components of comparable complexity. We have continued to refine the fragment syntheses, as well as develop more reliable coupling methods[10] to enhance access to the natural products and analogs. Herein we report some of our recent

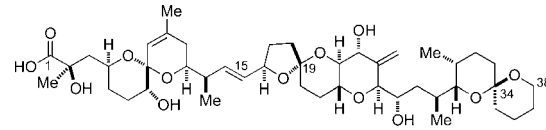


Figure 1. Structure of Okadaic acid.

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efforts in the synthesis of the C15−C38 fragment of OA, which highlights the dual use of Au(I)-catalyzed spiroketalizations.

Transition metal catalyzed spiroketalizations[11−13] have recently emerged as a versatile method for the syntheses of spiroketal moieties of natural products, as exemplified by (+)-broussonetine G,[14] azaspiracid,[15] (+)-spirolaxine methyl ether,[16] and ushikulide A[17] (Figure 2). Compared with the

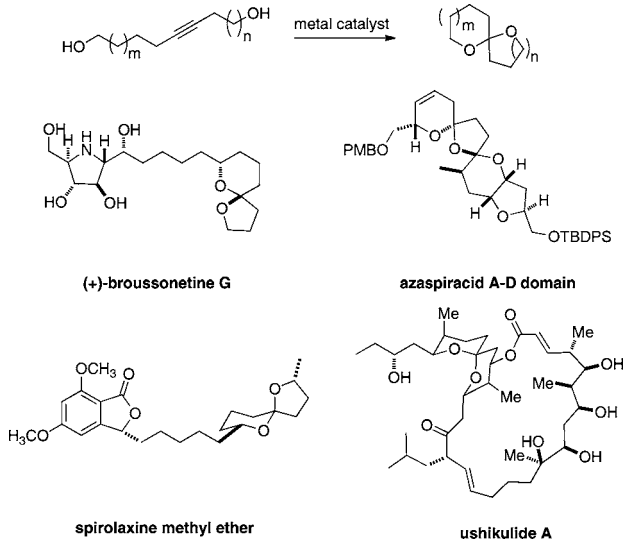


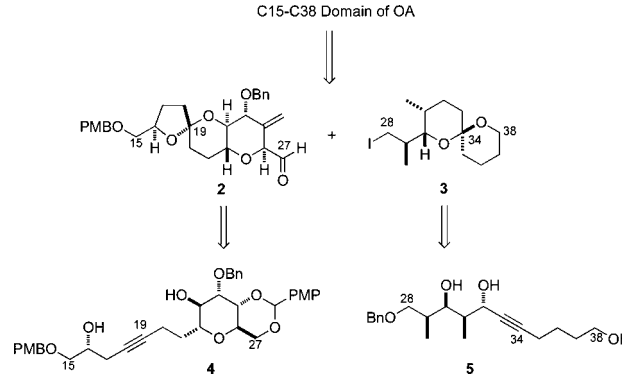
Figure 2. Metal catalyzed spiroketalization used in natural product synthesis.

conventional approach toward spiroketals using acid-catalyzed dehydrative cyclization of dihydroxyl ketones, the use of an alkyne as a dehydrated surrogate for a ketone avoids some potential sensitivity issues associated with highly functionalized ketones.[15,16] With this in mind, we embarked upon the syntheses of the C19 and C34 spiroketals of OA using gold catalysis.

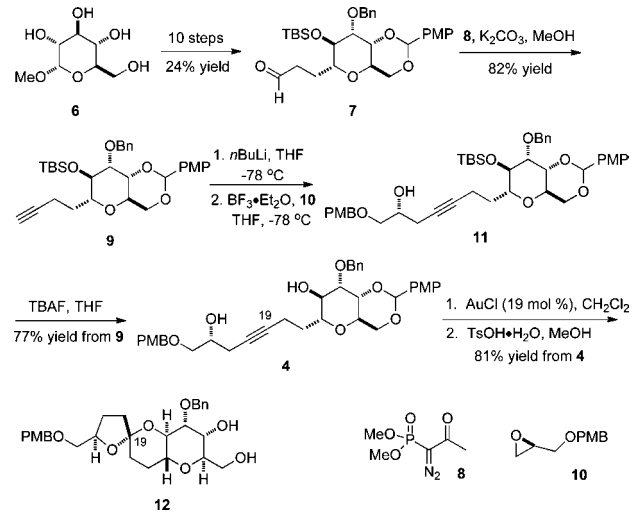
Retrosynthetically, the C15−C38 domain of OA is separated into two fragments: the C27 aldehyde **2** and the C28 iodide **3**, which can be coupled via a derived C28 organometallic species (Scheme 1).[7] The C19 spiroketal in **2** is derived from alkyne **4**, while the synthesis of the C34 spiroketal **3** starts with triol **5**. With the latter 1,3-*anti* triol, the cyclization regioselectivity can be controlled to give the desired 1,7-dioxaspiro[5.5]-undecane system, as recently reported by Aponick et al.[13]

The synthesis of the C19 spiroketal started with known aldehyde **7** (Scheme 2), which was prepared from com-

Scheme 1. Retrosynthesis of the C15−C38 Domain of OA



Scheme 2. Synthesis of C15−C27 Fragment of OA



mercially available methyl-α-D-glucopyranoside **6** in 10 steps.[7b] Treatment of aldehyde **7** with the Bestmann-Ohira reagent (**8**)[18] and K_2CO_3 in methanol afforded terminal alkyne **9** in 82% yield. BF_3-mediated nucleophilic opening[19] of oxirane **10** with the lithium acetylide generated from **9** and *n*BuLi produced alcohol **11** smoothly. Desilylation of **11** with TBAF gave dihydroxyl alkyne **4** as the spiroketalization precursor.

On the basis of previous experience,[10d,15] AuCl was selected as the catalyst for the spiroketalization reaction. Gratifyingly, the desired spiroketal was formed after mixing **4** with a catalytic amount of AuCl in CH_2Cl_2. Any acid cocatalyst was initially avoided here to prevent the removal of the anisylidene protecting group. However, the Lewis acidity of AuCl itself triggered partial removal of the protecting group, but the *in situ* liberated hydroxyl groups did not seem to affect the spiroketalization efficiency.

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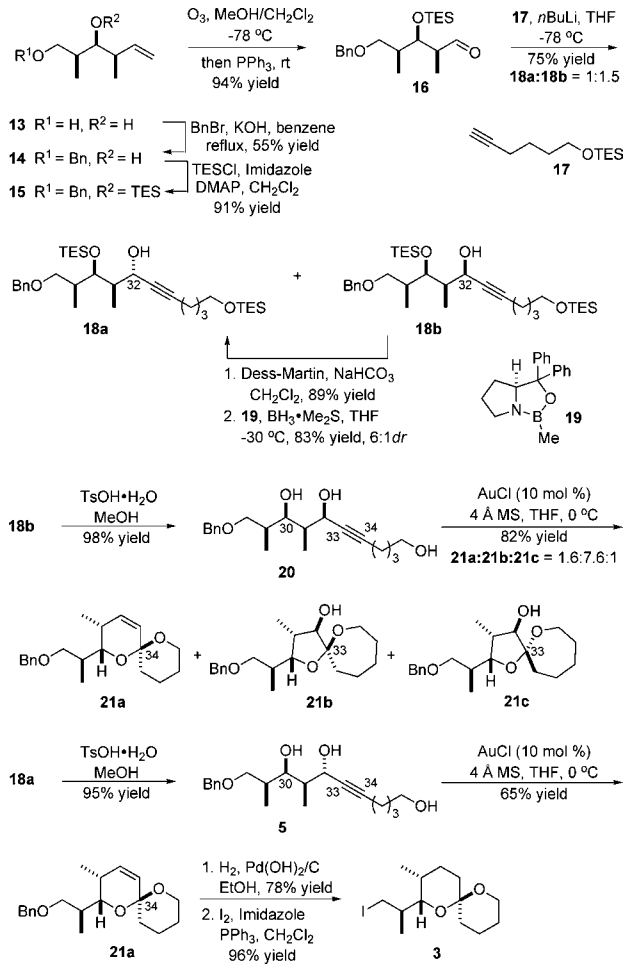
Subsequent addition of TsOH in methanol to the reaction mixture helped to completely remove the anisylidene group to give diol **12** in 81% yield.

The synthesis of the C34 spiroketal began with known diol **13**[7c] (Scheme 3). Selective protection of the primary

Scheme 3. Synthesis of C28−C38 Fragment of OA



hydroxyl group using BnBr and KOH in benzene at reflux[20] gave benzyl ether **14** in 55% yield. The remaining hydroxyl group was protected as triethylsilyl ether **15**. Ozonolysis of **15** yielded aldehyde **16** in 94% yield. Addition of the lithium acetylide derived from alkyne **17** to aldehyde **16** afforded a mixture of epimers at C32 (*anti*:*syn* = 1.0: 1.5). These were separated then treated with TsOH in methanol to generate 1,3-*syn* triol **20** and 1,3-*anti* triol **5** as spiroketalization precursors.

Aponick reported that the relative 1,3-stereochemistry of the propargylic and nucleophilc hydroxyls within triols similar to **20** and **5** influenced the gold catalyzed spiroketalization regioselectivity.[13] Thus, it was of interest to probe the fate of 1,3-*syn* triol **20** versus 1,3-*anti* triol **5** upon gold(I) catalysis. When 1,3-*syn* triol **20** was treated with AuCl, the

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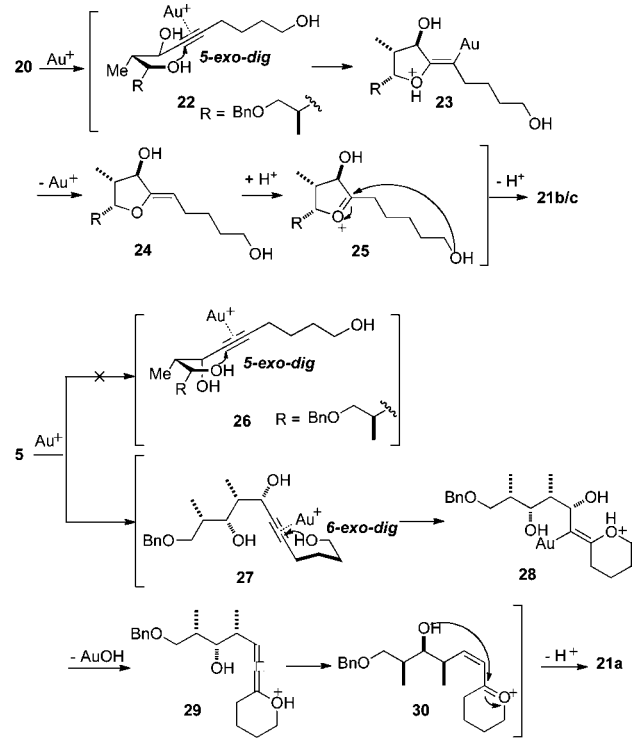
1,6-dioxaspiro[4.6]undecane ring system (33*S*)-**21b** was formed as the major product, followed by the 1,7-dioxaspiro[5.5]undecane ring system (34*S*)-**21a**, and (33*R*)-**21c** in a 7.6:1.6:1.0 ratio, respectively (82% combined yield, Scheme 3). In contrast, the 1,3-*anti* triol **5** gave the unsaturated OA spiroketal **21a** as the exclusive product, albeit in lower yield. The introduction of the alkene into **21a** would be inconsequential en route to **3**. The divergent regioselectivity observed upon cyclization of **20** and **5** is consistent with that reported by Aponick.[13]

These results suggest a kinetic preference for the C30 hydroxyl of 1,3-*syn* triol **20** versus the C30 hydroxyl of 1,3-*anti* triol **5** to participate in initial oxy-auration of the alkyne via 5-*exo* addition at C33 (Scheme 4). The 5-*exo* cyclization

Scheme 4. Proposed Spiroketalization Mechanisms



of **20** would afford an enol ether gold intermediate **23**, protiodeauration of which followed by capture of the primary hydroxyl would lead to spiroketals **21b**/**c**. However, an analogous 5-*exo* cyclization of **5** would proceed via a more sterically hindered all *syn* C30−C32 trisubstituted five membered ring transition state (e.g., **26**, Scheme 4). Alternatively, the primary hydroxyl of **5** likely initiates its spiroketalization via a less encumbered 6-*exo* oxy-auration.

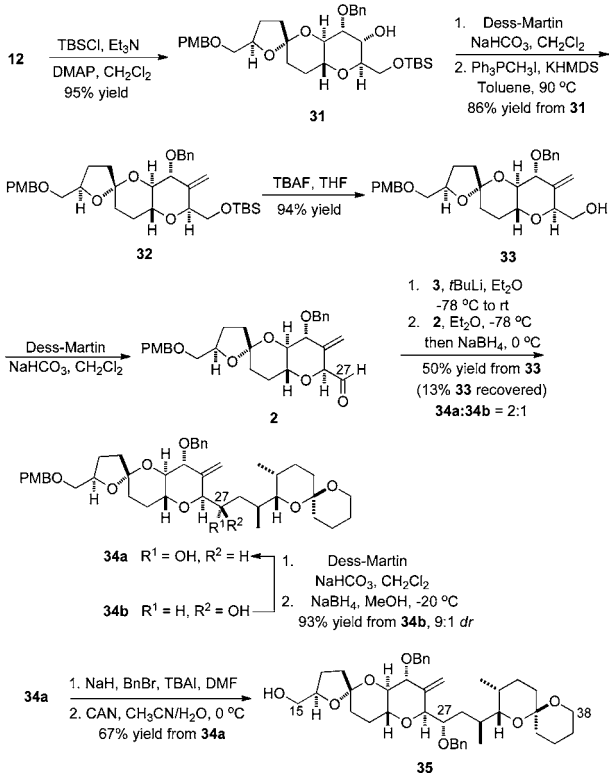
The original C32 propargylic hydroxyl group of **20** is retained in **21b**/**c**, whereas it is eliminated in **21a**. This may reflect a concerted loss of gold hydroxide from an α-hydroxy vinyl gold species (e.g., **28**, Scheme 4), whereas an allylic hydroxy vinyl gold intermediate (e.g., **23**) undergoes simple protiodeauration. Isomerization of the resulting exocyclic allenyl ether intermediate **29** into a vinyl substituted oxac-

arbenium ion (**30**) followed by addition of the C30 hydroxyl would afford **21a**.

Once the dependence of spiroketalization regioselectivity on polyol stereochemistry was confirmed, an initial measure to enhance mass throughput was to convert *syn*-**18b** into *anti*-**18a** (Scheme 3). This was accomplished in a two-step sequence of oxidation/asymmetric reduction.[21] Thus both **18a**/**b** diastereomers converged to spiroketal **21a**. Hydrogenation of **21a** followed by iodination gave **3**.

The next stage was fragment coupling (Scheme 5). Prior to this, the C25 exocyclic alkene of OA was installed. This

Scheme 5. Coupling of C15−C27 and C28−C38 Fragments



was initiated by selective silyl protection of the primary hydroxyl of diol **12**. The resulting secondary alcohol **31** was oxidized to the corresponding ketone then converted into alkene **32** under Wittig conditions. TBAF induced removal of the C27 silyl group gave primary alcohol **33**. This was oxidized into the sensitive β,γ-unsaturated aldehyde **2** using the Dess-Martin periodinane reagent immediately prior to use. Treatment of iodide **3** with *t*BuLi in diethyl ether followed by the addition of aldehyde **2** afforded a mixture of C27 carbinols **34a** and **34b** in 50% combined yield favoring the natural product's configuration (27*S*/27*R* = 2:1). The undesired diastereomer **34b** was converted into **34a** using the traditional oxidation−reduction sequence.[6,7] Thus, **34a** was obtained in 48% combined yield, including stereochemical correction, which is in line with the 52 and 47% yields for coupling and (27*S*) alcohol installation in the other OA total syntheses.[6,8] Protection of the free hydroxyl group at C27 as a benzyl ether followed by removal of the PMB protecting group afforded alcohol **35**, a known intermediate for the total syntheses of OA.[6,8]

In our original approach to OA, the use of an unmodified C28 organolithium species in THF gave the C27−C28 coupled product in poor yield (30−35%), while the major byproduct was the adduct derived from the addition of *t*BuLi to the aldehyde.[7c] As reported in 1997, transmetalation of the organolithium species to an organocerium derivative improved the yields, although the diastereomeric ratio was unfavorable (27*R*/27*S* = 2.5:1.0).[7] In the present case, it was beneficial to use diethyl ether as the bulk solvent and to warm the mixture to room temperature after the lithium−iodine exchange of **3** to decompose any residual *t*BuLi.[22] After the alkyllithium solution was recooled to −78 °C, the addition of aldehyde **2** gave coupled products in yields comparable to those obtained previously with the difficult to handle organocerium reagent (53 vs 50%). However, the diastereoselectivity observed here in forming the C27 carbinol using the organolithium in diethyl ether was favorably reversed (2.5:1 vs 1:2). This may reflect better chelation controlled addition of the C28 organolithium to the C27 aldehyde in diethyl ether than with the organocerium reagent in THF.[7]

In conclusion, the C19 and C34 spiroketals of OA were synthesized using regiocontrolled AuCl catalyzed spiroketalizations of dihydroxy alkynes. The fragments were coupled via C27−C28 bond formation using an improved procedure to afford the C15−C38 domain of OA. Compound **35** can serve as an intermediate in Isobe's and Ley's total syntheses of OA,[6,8] and therefore its preparation here constitutes a formal total synthesis.

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Supporting Information Available: Experimental procedure, characterization data, ^{1}H NMR and ^{13}NMR spectra for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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