Abstract: The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acid nature. In particular, the gold-catalyzed activation of propargylic compounds has progressively emerged in recent years. Some of these gold-catalyzed reactions in alkynes have been optimized and show significant utility in organic synthesis. Thus, apart from significant methodology work, in the meantime gold-catalyzed cyclizations in alkynol derivatives have become an efficient tool in total synthesis. However, there is a lack of specific review articles covering the joined importance of both gold salts and alkynol-based compounds for the synthesis of natural products and derivatives. The aim of this Review is to survey the chemistry of alkynol derivatives under gold-catalyzed cyclization conditions and its utility in total synthesis, concentrating on the advances that have been made in the last decade, and in particular in the last quinquennium.

Keywords: gold catalysis; alkynols; total synthesis; natural products
1. Introduction

Organic synthesis has as one of its major points of interest the study of naturally occurring substances, and this remains both a source of information and an intellectual challenge. Thus, a crucial target for organic chemists is to find the appropriate reaction conditions, allowing functional group compatibility and providing high efficiency and atom economy. During the last years, gold-catalyzed cycloisomerization of alkynol-based systems has emerged as a useful tool in this area, allowing the synthesis of different structures such as furans, dihydrofurans, pyrans, furanones or ketals, among many other heterocyclic systems and naturally occurring structures [1-3].

This overview focuses on the most recent achievements in gold-catalyzed cycloisomerization reactions, for the synthesis of natural products and related compounds. In particular, carbon-carbon and carbon-heteroatom cyclization processes will be considered, paying special attention to reports from the last five years.

2. Cycloisomerization Processes Involving Carbon-Carbon Bond Formation

Gold-catalyzed cycloisomerization reactions involving C–C bond formation have recently emerged as an effective methodology to build hydrocarbon rings. Four, five and six membered cyclic structures, as well as medium sized rings are accessible in good yields and under interesting mild reaction conditions using gold salts and gold complexes. Fused bicyclic compounds can also be produced, leading therefore to an attractive series of natural occurring skeletons.

Benzofurans represent a recurring motif among natural products. Particularly, 2-substituted and 2,7-disubstituted benzofurans and their derivatives are known to show many different biological activities such as antineoplastic, antiviral, antioxidative or anti-inflammatory properties. Although many routes for the preparation of 2-substituted systems have been developed [4,5], 2,7-substituted benzofurans remain almost unexplored (Figure 1) [6-8].
Hashmi et al. have recently proposed an efficient route leading to 7-aryl benzo[b]furans 2 through a gold-catalyzed rearrangement of 3-silyloxy-1,5-enynes [9]. The considerable effort that went into this work, involving a first catalyst screening for substrate 1a and finding the optimal conditions for the dual catalyst system [IPrAuCl]/AgNTf2 is noteworthy. Thus, an easy methodology was performed, using mild conditions, open-air systems and remarkable short reaction times, providing an interesting family of different substituted 7-aryl benzofurans (Scheme 1).

Scheme 1. Gold(I)-catalyzed rearrangement of 3-silyloxy-1,5-enynes.

Reactions conditions: (i) [IPrAuCl]/AgNTf2 (2 mol%), iPrOH (1.1 equiv.), DCM (15 mL/mmol), rt, in air, 1 h.

Approximately a quarter of biologically active known compounds come from fungi, and among their wide range of properties, the antibiotic activity has attracted much interest [10,11]. Guanacastepene A (Figure 2) is extremely active against methicillin-resistant strains of Staphylococcus aureus and vancomycin-resistant E. faecalis, two drug-resistant common pathogens which have generated major concern [12-14].
It has been stated an approach to ring A of guanacastepene, by an unusual gold(I)-catalyzed
cycloisomerization of alkynol-based 1,5-enynes [15]. According to the proposed retrosynthesis, most
of the functionalities present in the natural terpene would be early introduced, while the presence of the
cyclopropyl fused ring could allow the further generation of ring B (Scheme 2).

**Scheme 2.** Retrosynthesis of guanacastepene ring A.

Many 1,5-enynes were tested, and an unexpected pattern of reactivity depending on the substituents
in substrates 4 was found. Thus, the desired bicyclo[3.1.0] system 3 was obtained only when the
reaction was performed with the *syn*-enynes 4a and 4b, yielding 3a and 3b with good conversions and
notable diastereoselectivity. *Anti*-isomers, or any stereochemical change on the starting 1,5-enynes,
resulted in the opposite diastereoselectivity (systems 5), or a dramatic change on the course of the
reaction, leading to alkylidene-cyclopentenes 6, cyclohexadienes 7, or α,β-unsaturated aldehydes 8
(Scheme 3).

Gold-catalyzed isomerization has been also employed in the search of an appropriate route to
(−)-thujopsanone, a derivative of the natural terpene (−)-thujopsene, widely employed in cosmetics [16].
Although the first aim of the authors remained unachieved, and the obtained compound 9 did not
exhibit the appreciated properties of the initial target [17], the chemistry developed merits further
consideration (Scheme 4) [18]. Thus, it was observed that enynol 10 provided the unexpected ether 11
in the presence of different gold catalysts, in amounts similar to those produced by some other metal
salts such as copper or platinum complexes. Interestingly, when the corresponding acetate derivative
12 reacted in the presence of AuCl₃, a tandem cycloisomerization/[1,2]-acyl shift took place, leading to
adduct 13, precursor of the previously mentioned adduct 9, and a close system to (−)-thujopsanone.
Moreover, when the process was tested in the presence of (tBuXPhos)AuNTf₂ as catalyst, an
unprecedented rearrangement/cycloaddition leading to the tricyclic system 14 was reported (Scheme 5).
**Scheme 3.** Divergent reactivity for the gold-catalyzed reaction of 1,5-enynes.

\[
\begin{align*}
&\text{C}_5\text{H}_{11}-\text{Ph} \quad \text{C}_5\text{H}_{11}-\text{Ph} \\
&\quad \text{OH} \quad \text{Bn} \\
\text{4a} \quad &\xrightarrow{i)} \quad \text{3a} \quad 66\% \quad \text{5a} \quad 14\% \\
\text{4b} \quad &\xrightarrow{i)} \quad \text{3b} \quad 54\% \quad \text{6a} \quad 27\% \\
\end{align*}
\]

*Reactivity divergency in 1,5-enynes 4*

\[
\begin{align*}
&\text{R}^3\text{O} \quad \text{C}_5\text{H}_{11} \quad \text{R}^4\text{O} \\
&\quad \text{R}^3 \quad \text{Ph} \quad \text{R}^4 \quad \text{Ph} \\
&\text{4} \quad \xrightarrow{i)} \quad \text{4} \quad \xrightarrow{i)} \quad \text{6b} \quad \text{R}^3=\text{H}, \text{R}^4=\text{H}, \text{R}^5=\text{Me}, 29\% \quad 6c \quad \text{R}^3=\text{Bn}, \text{R}^4=\text{H}, \text{R}^5=\text{Me}, 57\% \\
\end{align*}
\]

From anti-isomer 4

\[
\begin{align*}
5b & \quad \text{R}^3=\text{H}, \text{R}^4=\text{iPr}, \text{R}^5=\text{H}, 70\% \\
5c & \quad \text{R}^3=\text{Bn}, \text{R}^4=\text{iPr}, \text{R}^5=\text{H}, 63\% \\
\end{align*}
\]

**Reaction conditions:** (i) (PPh\(_3\))AuBF\(_4\) (2 mol%), DCM (0.1 M), −20 to −10 °C, 5–15 min.

* Reported yield from a mixture 1:3.3 of the correspondig bicycles 5 and 7.

**Scheme 4.** Projected synthetic route to terpene (−)-thujopsanone.

\[
\begin{align*}
\text{7} \quad \text{R}^1=\text{Ph}, \text{R}^3=\text{Bn}, 33\% & \quad \text{4} \quad \text{8} \quad \text{R}^3=\text{H}, \text{R}^5=\text{H}, 68\% \\
\end{align*}
\]
Scheme 5. Cycloisomerization of enynol 10 and [1,2]-acyl shift rearrangement of acetate 12, respectively.

\[
\text{Catalyst} \quad \text{Yield 11} \\
\left(\text{PPh}_3\right)\text{AuCl}/\text{AgBF}_4 \quad 87\% \\
\left(\text{XPhos}\right)\text{AuNTf}_2 \quad 98\% \\
\text{AuCl}_3 \quad 76\% \\
\text{PtCl}_2 \quad 51\% \\
\left[\text{Cu(CH}_3\text{CN)}_4\right]BF_4 \quad 49\% \\
\]

\[
\text{Catalyst} \quad \text{Yield 13/14} \\
\left(\text{PPh}_3\right)\text{AuNTf}_2 \quad 60\% / 0\% \\
\left(\text{XPhos}\right)\text{AuNTf}_2 \quad 18\% / 0\% \\
\text{AuCl}_3 \quad 78\% / 0\% \\
\text{PtCl}_2 \quad 43\% / 0\% \\
\left[\text{Cu(CH}_3\text{CN)}_4\right]BF_4 \quad 42\% / 0\% \\
\left(\text{tBuXPhos}\right)\text{AuNTf}_2 \quad 9\% / 43\% \\
\]

**Reaction conditions:** (i) cat. (1–5 mol%), DCM, rt, 5 to 120 min; (ii) cat. (1–5 mol%), DCM, rt, 3–24 h; (iii) K$_2$CO$_3$ (1.5 equiv.), MeOH, rt, 20 min.

Gold-catalyzed cycloisomerization methodology has also been applied to the construction of medium sized rings. Allocolchicinoids, presenting a seven membered ring, are structures related to (−)-colchicine, a natural product with important antimitotic activity (Figure 3). Many of these derivatives also show this kind of mitosis arrest, by inhibiting tubulin polymerization [19-21]. N-acetylcolchinol 15, for instance, is described to bind to tubulin more strongly than colchicine itself. Thus, many reports have appeared describing the synthesis of these structures [22-28].

**Figure 3.** Colchicine and allocolchicinoids systems.
Hanna et al. reported the synthesis of derivative 17 [29]. In the proposed sequence, the seven-membered ring is formed by a gold(I)-catalyzed 1,2-O-acyl shift, followed by a cyclopropanation step which leads to the fused three-member ring (Scheme 6). Thus, gold-catalyzed cyclization of alkynol-based systems has also been stated in this work as a useful tool to create medium-sized rings, through an easy methodology providing high yields under mild reaction conditions.

**Scheme 6.** Synthesis of allocolchicinoid 17 and proposed mechanism for the gold-catalyzed cycloisomerization step.

Reaction mechanism

**Reaction conditions:** (i) Cat. A (1 mol%), DCM, rt, 2 h; (ii) K₂CO₃, MeOH, 2.5 h, rt; (iii) THF, −78 °C; (iv) MgSO₄, Toluene, 100 °C; (v) methyl β-nitroacrylate (5.2 equiv.), DCM, rt, 22 h; (vi) DBU (drops), THF, rt, 2 h; (vii) DDQ (1.5 equiv.), DCM, rt, 2 h.
Indole systems are ubiquitous in Nature, appearing in many different alkaloid families. Their wide range of biological activities, and their intriguing chemistry, makes these compounds a target of special interest, and a recurring topic in many studies [30-41]. For instance, the first enantioselective approach to (−)-mersicarpine, an alkaloid isolated from Kopsia plants and exhibiting an unusual tetracyclic structure has been reported. The proposed retrosynthetic analysis included the reaction of an alkynol-based intermediate in the presence of a gold salt, although only the alkyne functional group showed reactivity under these conditions, preserving the hydroxylic group for a further oxidation [42].

More interestingly, the reactivity of alkynol-based systems as formal organic synthons has been also explored in the indole chemistry. It has been established the synthesis of the non-natural skeleton 2,3-indoline-fused cyclobutane through a cascade process, including both C–C and C–O bond formation catalyzed by the same gold salt [43].

On the other hand, Echavarren et al. described in an exhaustive report about inter- and intramolecular gold-catalyzed reaction of alkynes and indoles some examples starting from alkynols and alkynol-based systems. Carbazole-like systems and related structures were therefore achieved (Scheme 7) [44].

**Scheme 7.** Alkynol-based reactivity in indole chemistry.

![Scheme 7](image)

| Reaction | Product 18 | Product 19 | Product 20 | Product 21 |
|----------|------------|------------|------------|------------|
| i) R¹= H, R²= H, R³= H, R⁴= H | cat. B | 64% / 25% / 0% |
| R¹= Me, R²= H, R³= H, R⁴= H | cat. B | 86% / 0% / 0% |
| R¹= Me, R²= H, R³= H, R⁴= H | cat. C | 14% / 27% / 0% |
| R¹= Me, R²= Ph, R³= H, R⁴= H | cat. B | 69% / 17% / 0% |
| R¹= Me, R²= H, R³= Me, R⁴= H | cat. B | 0% / 27% / 36% |
| R¹= H, R²= H, R³= H, R⁴= OMe | cat. B | 89% / 0% / 0% |

**Reaction conditions:** (i) Cat. B or C (5 mol%), DCM, rt, 0.5–48 h; (ii) Cat. B (5 mol%), DCM, rt, 0.2–16 h. (iii) Cat. B (5 mol%), toluene, rt, 9–14 h.
Inspired by the results of the Echevarren group, Liu et al. described the synthesis of dihydrocyclohepta[b]indoles 26 from (Z)-enynols 27 and indole, through an interesting domino sequence including a first gold(0)-catalyzed Friedel-Craft reaction, followed by a hydroarylation step [45]. The resulting products are of considerable interest, as much as they form the key subunits of several alkaloids, like ambiguine, silicine, caulerpin or caulersin. The reported work includes the optimization of the process, by testing different gold salts and solvents, leading to high reaction conversions through mild conditions (Schemes 8 and 9).

**Scheme 8.** Synthesis of dihydrocyclohepta[b]indoles, and related natural structures.

![Scheme 8](image)

**Reaction conditions:** (i) (PPh₃)AuCl/AgSbF₆ (5 mol%), THF, rt, 4–13 h.

3. **Cycloisomerization Processes Involving Carbon-Heteroatom Bond Formation**

Heterocyclic natural occurring motifs such as furans, pyrans or spiroketals can be easily achieved through heterocyclization processes performed on alkynol-based systems. Gold promoted methodologies provide a convenient route to these structures, allowing mild reaction conditions and high yields. Total synthesis and the preparation of related derivatives have been recently described using both C–N and C–O bond formation.

3.1. **Cycloisomerization on Alkynol-Based Systems**

Chromones are natural heterocycles showing a wide range of biological properties. Thus, many strategies like iodocyclizations [46], metal-catalyzed cycloadditions [47], or O-arylation processes [48] have appeared for the synthesis of these oxacyclic systems. Gold catalyzed cycloisomerization of
alkynol based structures 28 have been also stated for the generation of chromones 29 [49]. Interestingly, reaction proceeded with a further migration of group R1, leading to highly functionalized skeletons. Unluckily, only moderate yields were achieved (Scheme 10), inasmuch as isomerization processes competed with the expected Au-based cycloisomerization.

Scheme 9. Proposed reaction mechanism for the tandem gold catalyzed-Friedel-Crafts arylation/hydroarylation process.

Scheme 10. Synthesis of chromones by gold-catalyzed cycloisomerization.

![Diagram](https://via.placeholder.com/150)

**Reaction conditions**: (i) PPh3AuCl (10 mol%)/AgSbF6 (10 mol%), DCE, 50 °C, 0.5 h.

A similar approach has been developed for the synthesis of aurone skeletons [50], natural flavonoids, by an easy three step sequence. Aurones exhibit several biological properties [51-55], and its importance had led to several groups to develop convenient synthetic routes [56-62]. Among them, gold-catalyzed oxycyclization provided the best results, as milder reaction conditions and excellent selectivities, avoiding the formation of flavones as byproducts, were achieved (Scheme 11) [63]. In this case, high yields and complete regioselectivity were obtained.
Scheme 11. Synthesis of aurone skeleton by gold-catalyzed cycloisomerization.

\[
\begin{align*}
\text{Reactor conditions:} & \quad \text{(i) } n\text{-BuLi (1 equiv.), THF, } -78^\circ\text{C to } -40^\circ\text{C, 4 h;} \\
& \quad \text{(ii) AuCl (10 mol%), } K_2CO_3 \text{ (10 mol%), MeCN, rt, 30 h;} \\
& \quad \text{(iii) MnO}_2 \text{ (10 equiv.), DCM, rt, 1 h.}
\end{align*}
\]

Moreover, the present methodology was used for the structural revision of two natural products, (\(Z\))-4'-chloroauroine 30 [64], and (\(Z\))-2'-hydroxyaurone 32 [65], proving that the assumed structures were not the correct ones. Thus, flavonoid systems 30 and 32 could be prepared by the above three step strategy which revealed that their spectral data did not match with the previously reported data of the natural isolated ones. Therefore, the isocumarin 31 and the flavone 33 were prepared and probed as the real structures for these natural products (Figure 4).

Figure 4. New assignment of structures 31 and 33 by comparison with the prepared by the gold catalysis aurone systems 30 and 32.
Trost et al. recently completed the total synthesis of bryostatin 16 [66,67], a structurally complex macrolide which exhibits a wide range of biological activities [68-71]. Focusing on the proposed 26 step sequence (in the longest linear path, and 39 steps as the total), the gold-catalyzed 6-endo-dig oxy cyclization of alkynol 34 to generate the inner dihydropyran cycle D in macrocyclic precursor 35 in 65% yield deserves special attention (Scheme 12).

**Scheme 12.** Gold-based synthesis of dihydropyran ring D in bryostatin total synthesis.

**Reaction conditions:** (i) Pd(OAc)$_2$ (10 mol%), tris(2,6-dimethoxyphenyl)phosphine (10 mol%), benzene, rt; (ii) AuCl(PPh$_3$) (10 mol%), AgSbF$_6$ (10 mol%), DCM/MeCN (4:1), NaHCO$_3$, 0 °C to rt.

(+)-Cephalostatin 1 is another complex macrolide with interesting biological activity. It has been reported to be a promising anticancer agent for the p16 tumor suppressor gene, exhibiting high activity and high selectivity between cancer cells and normal cells [72,73]. Because of the small amounts of cephalostatin available from its natural marine sources, a synthetic approach has emerged as the sole viable tool to provide enough material for biological testing [74-78]. On the other hand, the structural complexity of cephalostatin makes this macrocycle an interesting target to develop new skills in organic synthesis.
Fortner et al. have recently described a total synthesis of cephalostatin, involving the construction of both its eastern and western fragments and their further coupling [79]. Along the high quality chemistry developed for this synthesis, we would like to focus on the dihydrofuran ring E construction on compound 36. Thus, gold-catalyzed cycloisomerization emerge again as a useful methodology to convert alkynol systems in oxacyclic skeletons, crucial and recurring motifs for total synthesis. Moreover, the efficiency of gold catalysis to promote a 5-endo-dig process with an 88% conversion, on what is a hindered internal alkyne 37, deserves special consideration (Scheme 13).

Scheme 13. Synthesis of ring E on the eastern fragment of cephalostatin.

Other natural occurring motifs such as oxazoles and isoxazoles have also been assembled through gold-catalyzed cycloisomerization. Thus, it has been recently established a general method for the synthesis of highly functionalized isoxazoles from alkynyl oxime ethers [80], or an intermolecular alkyne oxidation leading to 2,5-disubstituted oxazoles [81]. Nevertheless, while gold-based alkyne-oxygen cycloisomerization has recently become a hot topic in organic synthesis, only a few examples for alkyne-nitrogen coupling have been described [82-90]. Regarding the synthesis of natural
products and derivatives, Chan et al. have recently described the synthesis of highly substituted indole skeletons [29], from readily available 2-tosylamino-phenylprop-1-yn-3-ols 38 [91]. The reported work shows a versatile approach to these natural occurring motifs, and develops a fascinating study concerning the chemical reactivity of these substrates under gold-catalyzed conditions. Thus, starting in every case from a 5-exo-dig cycloaddition which led to vinyl gold species 39, different reaction pathways were observed depending on the substituent group R1. It was stated that when R1 = aryl, reaction proceeded through a Friedel-Craft process, giving indenyl-fused indoles 40. On the other hand, changing to R1 = H, a protodeauration/1,3-allylic alcohol isomerization took place, leading to indoles 41. The presence of a nucleophile in the reaction media gave place mainly to systems 42, and for R1 = CHR2R3, a more facile protodeauration and dehydratation step delivered systems 43 (Scheme 14).

**Scheme 14.** Indole synthesis from gold-catalyzed cycloisomerization of 2-tosylamino-phenylprop-1-yn-3-ols.

Reaction conditions: (i) AuCl (5 mol%), AgOTf (5 mol%), HMPA (20 mol%), CaSO4 (175 mg/mmol 38), toluene, reflux, 2 h; (ii) AuCl (5 mol%), AgOTf (5 mol%), HMPA (20 mol%), CaSO4 (175 mg/mmol 38), NuH (8 equiv.), toluene, reflux, 2 h.
Another example of gold-based C–N cyclization on alkynol systems for the total synthesis of (+)-andrachcinidine (44) has been established [92]. This natural alkaloid receives its name from its natural source, the beetle *Andrachne aspera*, and it has been shown to be an interesting chemical defense agent [93]. The proposed reaction sequence started with commercial ketal 45, which yielded after six steps the nitrogen-containing alkynol 46. Gold-catalyzed cyclization of 46 provided the piperidine system 47 as a single diastereomer in 89% isolated yield. The reaction mechanism is proposed to follow a first gold-based alkyn hydration providing ketone 48. Methoxy group cleavage would then generate the corresponding α,β-unsaturated system, which could undergo nucleophile addition building the expected 6-membered heterocycle (Scheme 15). It is noteworthy that no competition between nitrogen and oxygen attack was found, which would led to the less favoured 8-membered heterocycle.

**Scheme 15. Synthesis of (+)-andrachcinidine.**

![Synthesis of (+)-andrachcinidine](image)

Reaction conditions: (i) Ph3PAuCl (5 mol%), AgSbF6 (10 mol%), toluene, H2O, 40 °C, 24 h.

3.2. Cycloisomerization on Alkynediol-Based Systems

Ketals are important key structures, and crucial targets in organic synthesis [94-98]. Fused, bicyclic and spiroketals are recurring motifs in natural compounds, and their preparation is a key step in many total syntheses. In particular, spiroketals represent a structural feature of many biomedically relevant natural and non-natural systems [99-102]. Several methods have been developed for the synthesis of
spiroketals, the most common being perhaps the cyclocondensation of ketone diols [103,104]. Nevertheless, gold catalyzed cycloisomerization on alkynediols has emerged as an efficient strategy to build complex ketal systems in just one step, offering specific advantages. For example, Au-catalyzed cycloisomerization of alkynediols are more exothermic, atom economical, and more compatible than ketones under a number of several reaction conditions. Thus, many groups have recently incorporated the present methodology for the synthesis of several natural compounds and derivatives [105-108].

Li et al. have described the preparation of the bisbenzannelated spiroketal core of rubromycins [109]. These natural occurring structures exhibit different biological activities, such as inhibition of DNA polymerase, inhibition of the reverse transcriptase of HIV I, or inhibition of DNA helicase [110-113]. Scheme 16 shows the basic structure motif shared by natural isolated compounds like γ-rubromycin, purpuromycin, or heliquinomycin. According to the described work, easily prepared alkynediols 49 underwent cycloisomerization in the presence of gold catalysis to yield spiroketals 50 with moderate yields, but mainly together with notable amounts of the corresponding benzofuran 51.

Scheme 16. Synthesis of spiroketal motif of rubromycins.

A more effective spiroketalization process was found for the synthesis of cephalosporolides. Concretely, cephalosporolide H 52 is a natural spiroketal isolated from the culture broth of the marine fungus Penicillium sp. This compound presents anti-inflammatory properties by virtue of its inhibitory activity against 3α-hydroxysteroid dehydrogenase [114,115]. Dudley et al. developed a method for cephalosporolide total synthesis based on gold-catalyzed spiroketal generation [116,117]. Starting from pantolactone 53, alkynediol-based system 54 was obtained after a nine step sequence. Gold treatment of 54 yielded the desired structure 55, with an excellent 88% yield. The main inconvenient of the proposed strategy lied on the obtention of 55 as a 1:1 mixture of spiroketal epimers, although further treatment upon zinc chloride chelation provided the expected isomer in 20:1 dr (Scheme 17).
**Scheme 17.** Cephalosporolide H; structure and proposed synthesis.

![Cephalosporolide H](image)

**Reaction conditions:** (i) AuCl (40 mol%), MeOH, rt, 12 h; (ii) ZnCl$_2$ (5 equiv.), MgO (25 equiv.), DCM, rt, 8 h; (iii) TEMPO (1 equiv), PhI(OAc)$_2$ (4.5 equiv.), DCM, rt, 15 h.

Azaspiracid 56 belongs to a family of marine toxins, responsible for human poisoning and diverse chronic effects on liver, pancreas and thymus [118,119]. Its complete structure has been widely studied [120], and several methods for its synthesis have been reported [121,122]. Forsyth et al. have reported the synthesis of the F–I azaspiracid fragment 57 [123]. In particular, we would like to focus on the construction of F and G rings by a one step gold-catalyzed spiroketalization. Alkynediol-based system 58 was obtained by coupling of subunits 59 and 60, prepared from simple precursors. Treatment of 58 with AuCl provided the desired structure 57 with a high 75% yield as a sole isomer. The reaction mechanism is proposed to follow an initial syn addition of the C6 hydroxy group and the π-activated gold-alkyne complex to build ring F. Protodeauration and protonation of the resultant enol ether at C11 would promote the attack of methoxy oxygen to C10, generating therefore ring G (Scheme 18).

Okadaic acid 61 is a complex natural structure isolated from marine sponges [124,125]. Its biological activities [126-128], together with its attractive chemical structure have attracted much interest among organic chemists. In particular, the presence of several spiroketal motifs in this structure makes it a real challenge from the retrosynthetic point of view. An efficient synthesis of the C15-C38 fragment has been reported, based on the high activity and selectivity of AuCl for the synthesis of spiroketals 62 and 63, starting from alkynediols 64 and 66 respectively [129] (Scheme 19).

Bridged-bicyclic ketal has been also produced through gold-catalyzed cycloisomerization of alkynediols. Based on platensimycin structure, a natural inhibitor of microbial fatty acid biosynthesis [130-132], Corey et al. reported the total synthesis of the near-structural mimic 68 [133]. This new structure presents evidence in the literature suggesting excellent antimicrobial properties [134,135]. Thus, easily achieved alkynediol 69 reacted under gold(III) catalysis delivering ketone 70, which contains the tricyclic core of 68, with an excellent 85% yield and >98% ee (Scheme 20). The route to the desired target is completed in just nine steps, providing a facile and quick methodology to the mentioned bioactive structure.
Scheme 18. Synthesis of rings F and G in azaspiracid and reaction mechanism.

Reaction mechanism:

58 \rightarrow \text{[Au]} \rightarrow 58 \quad \text{Au(I)} \quad + \text{H}^+ \quad \rightarrow \quad \text{57 (75%)}

57 \rightarrow \text{MeOMe} \quad \text{MeOH} \quad \text{- H}^+ \quad \text{OMe} \quad \text{MeOH}

Reaction conditions: (i) CuI, Cs$_2$CO$_3$, DMF; (ii) AuCl (10 mol%), PPTS (10 mol%), MeOH, rt, 20 min.
Scheme 19. Synthesis of C15-C27 and C28-C38 fragments of okadaic acid.

Reaction conditions: (i) AuCl (19 mol%), rt, DCM, then TsOH·H₂O, MeOH; (ii) AuCl (10 mol%), 4 Å MS, THF, 0 °C.
Scheme 20. Synthesis of platensimycin-derived structure.

Platensimycin

Corey et al. reported mimic structure 68

TIPS-O
TBS-O

Steps

$\text{HO-OH}$

$\text{HO-OH}$

$\text{HO-OH}$

$i) \quad \text{AuCl}_3 (5 \text{ mol\%}), \text{MeOH}, \text{rt}, 1 \text{ h.}$

4. Conclusions

In this overview we have collected the most recent advances in gold-catalyzed cycloisomerization of alkynol and alkynediol-based systems for the preparation of natural products and derivatives. This type of process has become an established methodology for accessing a large number of both carbocyclic and heterocyclic structures, containing different sized skeletons. Three to seven-membered carbon rings, such as furan, pyrans, piperidines, and different ketal and spiroketal systems are therefore accessible through this strategy. The reactions discussed herein demonstrate the high synthetic potential of alkynol-based compounds undergoing gold catalyzed cyclization. On the other hand, the efficiency of gold salts and gold complexes have been also documented, allowing mild reaction conditions and great functional group compatibility, specially compared to related thermal or basic rearrangements. In addition, the extremely large number of natural bioactive compounds containing these type of structural motifs, readily available through gold-catalyzed conditions, will certainly provide a renewed and continuous topic of investigation in this field.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Hashmi, A.S.K.; Rudolph, M. Gold Catalysis in Total Synthesis. *Chem. Soc. Rev.* 2008, 37, 1766-1775.
2. Fürstner, A. Gold and Platinum Catalysis-A Convenient Tool for Generating Molecular Complexity. *Chem. Soc. Rev.* 2009, 28, 3208-3221.
3. Alcaide, B.; Almendros, P.; Alonso, J.M. Gold Catalyzed Oxyfunctionalization of Alkynols and Alkynediols. *Org. Biomol. Chem.* 2011, 9, 4405-4416.
4. Zeni, G.; Larock, R.C. Synthesis of Heterocycles via Palladium n-Olefin and n-Alkyne Chemistry. *Chem. Rev.* 2004, 104, 2285-2309.
5. Alonso, F.; Beletskaya, I.P.; Yus, M. Transition-Metal-Catalyzed Addition of Heteroatom-Hydrogen Bonds to Alkynes. *Chem. Rev.* 2004, 104, 3079-3159.
6. Michael, P.; Gerd, R.; Theo, S. (Eli Lilly Co.) Imidazole Derivatives for the Treatment of Diabetes, Especially Type II Diabetes. WO Patent 2000078726 A1, 28 December 2000.
7. Tagami, K.; Yoshimura, H.; Nagai, M.; Hibi, S.; Kikuchi, K.; Sato, T.; Okita, M.; Okamoto, Y.; Nagasaka, Y.; Kobayashi, N.; Hida, T.; Tai, K.; Tokuhara, N.; Kobayashi, S. (Eisai Co., Ltd.) Preparation of Fused-ring Carboxylic Acid Compounds as Retinoic Acid Receptor Agonists. WO Patent 9734869 A1, 25 September 1997.
8. Masaki, S.; Mitsunori, K.; Yuhei, M.; Masakuni, K. (Takeda Pharmaceutical) Amide Compound. WO Patent 2010018874 A1, 18 February 2010.
9. Hashmi, A.S.K.; Yang, W.; Rominger, F. Gold(I)-Catalyzed Formation of Benzo[b]furans from 3-Silyloxy-1,5-enynes. *Angew. Chem. Int. Ed.* 2011, 50, 5762-5765.
10. Henkel, T.; Brunne, R.M.; Reichel, F.; Muller, H. Structural Investigation into the Structural Complementarity of Natural Products and Synthetic Compounds. *Angew. Chem. Int. Ed.* 1999, 38, 643-647.
11. Pearce, C. Biologically Active Fungal Metabolites. *Adv. Appl. Microbiol.* 1997, 44, 1-80.
12. For isolation and structural determination of guanacastepene, see: Brady, S.F.; Singh, M.P.; Janso, J.E.; Claridy, J. Guanacastepene, a Fungal-Derived Diterpene Antibiotic with a New Carbon Skeleton. *J. Am. Chem. Soc.* 2000, 122, 2116-2117.
13. For selected studies about the mentioned pathogens, see: Neu, H.C. The Crisis in Antibiotic Resistance. *Science* 1992, 257, 1064-1073.
14. Swartz, M.N. Hospital-Acquired Infections: Diseases with Increasingly Limited Therapies. *Proc. Natl. Acad. Sci. USA* 1994, 91, 2420-2427.
15. Gagosz, F. Unusual Gold(I)-Catalyzed Isomerization of 3-Hydroxylated 1,5-Enynes: Highly Substrate-Dependent Reaction Manifolds. *Org. Lett.* 2005, 7, 4129-4132.
16. Ohloff, G.; Strickler, H.; Willhalm, B.; Borer, C.; Hinder, M. En-Syntheses with Singlet Oxygen. II. Dye-Sensitized Photooxygenation of (∆)-Thujopsene and Stereochemistry of the Prepared Thujopsanols. *Helv. Chim. Acta* 1970, 53, 623-637.
17. Hatsui, T.; Suzuki, N.; Takeshita, H. Dicyanoanthracene-Sensitized Photooxygenation of Thujopsene. *Chem. Lett.* **1985**, *639-642*.
18. Fehr, C.; Vuagnoux, M.; Buzas, A.; Arpagaus, J.; Sommer, H. Gold- and Copper-Catalyzed Cycloisomerizations towards the Synthesis of Thujopsanone-Like Compounds. *Chem. Eur. J.* **2011**, *17*, 6214-6220.
19. Graening, T.; Schmalz, H.-G. Total Synthesis of Colchicine in Comparison: A Journey through 50 Years of Synthetic Organic Chemistry. *Angew. Chem. Int. Ed.* **2004**, *43*, 3230-3256.
20. Boyé, O.; Brossi, A. *The Alkaloids*; Brossi, A., Cordell, G.A., Eds.; Academic Press: New York, NY, USA, 1992; Volume 41, p. 125.
21. Jordan, M.A.; Wilson, L. Microtubules as a Target for Anticancer Drugs. *Nat. Rev. Cancer* **2004**, *4*, 253-265.
22. Vorogushin, A.V.; Wulff, W.D.; Hansen, H.-J. Central-to-Axial Chirality Transfer in the Benzannulation Reaction of Optically Pure Fischer Carbene Complexes in the Synthesis of Allocolchicinoids. *Tetrahedron* **2008**, *64*, 949-968.
23. Besong, G.; Jarowski, K.; Kocienski, P.J.; Sliwinski, E.; Boyle, F.T. Synthesis of (S)-(−)-N-Acetylocolchinol Using Intramolecular Biaryl Oxidative Coupling. *Org. Biomol. Chem.* **2006**, *4*, 2193-2207.
24. Leblanc, M.; Fagnou, K. Allocolchicinoid Synthesis via Direct Arylation. *Org. Lett.* **2005**, *7*, 2849-2852.
25. Büttner, F.; Bergemann, S.; Guénard, D.; Gust, R.; Seitz, G.; Thoret, S. Two Novel Series of Allocolchicinoids with Modified Seven Membered B-Rings: Design, Synthesis, Inhibition of Tubulin Assembly and Citotoxicity. *Bioorg. Med. Chem.* **2005**, *13*, 3497-3511.
26. Wu, T.R.; Chong, J.M. Asymmetric Synthesis of Propargylamines via 3,3’-Disubstituted Binaphtol-Modified Alkynylboronates. *Org. Lett.* **2006**, *8*, 15-18.
27. Vorogushin, A.V.; Predeus, A.V.; Wulff, W.D.; Hansen, H.-J. Diels-Alder Reaction-Aromatization Approach towards Functionalized Ring C Allocolchicinoids. Enantioselective Total Synthesis of (−)-7S-Allocolchicine. *J. Org. Chem.* **2003**, *64*, 5826-5831.
28. For a reported synthesis of 16 see: Boyer, F.-D.; Hanna, I. Synthesis of Allocolchicines Using Sequential Ring-Closing Enyne Methathesis-Diels-Alder Reactions. *Org. Lett.* **2007**, *9*, 715-718.
29. Boyer, F.-D.; Le Goff, X.; Hanna, I. Gold(I)-Catalyzed Cycloisomerization of 1,7- and 1,8-Enynes: Application to the Synthesis of a New Allocolchicinoid. *J. Org. Chem.* **2008**, *74*, 5163-5166.
30. Carbone, M.; Yan, L.; Irace, C.; Mollo, E.; Castelluccio, F.; Di Pascale, A.; Cimino, G.; Santamaria, R.; Guo, Y.-W.; Gavagnin, M. Structure and Cytotoxicity of Phidianidines A and B: First Finding of 1,2,4-Oxadiazole System in a Marine Natural Product. *Org. Lett.* **2011**, *13*, 2516-2519.
31. Sunderhaus, J.D.; Sherman, D.H.; Williams, R.M. Studies on the Biosynthesis of the Stephadin and Notoamide Natural Products: A Stereochemical and Genetic Coundrum. *Israel J. Chem.* **2011**, *51*, 442-452.
32. Wu, M.; Wu, P.; Xie, H.; Wu, G.; Wei, X. Monoterpenoid Indole Alkaloid Mediating DNA Strand Scission from Turpina Arguta. *Planta Medica* **2011**, *77*, 284-286.
33. Ozcelik, B.; Kartal, M.; Orhan, I. Cytotoxicity, Antiviral and Antimicrobial Activities of Alkaloids, Flavonoids and Phenolic Acids. *Pharm. Biol.* **2011**, *49*, 396-402.

34. Yap, W.-S.; Gan, C.-Y.; Low, Y.-Y.; Choo, Y.-M.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. Grandilodines A-C, Biologically Active Indole Alkaloids from Kopsia Grandifolia. *J. Nat. Prod.* **2011**, *74*, 1309-1312.

35. Chung, Y.-M.; Lan, Y.-H.; Hwang, T.-L.; Leu, Y.-L. Anti-Inflammatory and Antioxidant Components from Hygropyza Aristata. *Molecules* **2011**, *16*, 1917-1927.

36. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P.S. Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716-2719.

37. Finlayson, R.; Pearce, A.; Norrie, A.; Page, M.J.; Kaiser, M.; Bourguet-Kondracki, M.-L.; Harper, J.; Webb, V.; Copp, B. Didennidines A and B, Indole Spermidine Alkaloids from the New Zealand Ascidian Didemnum sp. *J. Nat. Prod.* **2011**, *74*, 888-892.

38. Nakadate, S.; Nozawa, K.; Horie, H.; Fuji, Y.; Yaguchi, T. New Type Indole Diterpene, Eujindoles, From Eupenicillium Javanicum. *Heterocycles* **2011**, *83*, 351-356.

39. Ruiz-Sanchis, P.; Savina, S.; Albericio, F.; Alvarez, M. Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]Indole. *Chem. Eur. J.* **2011**, *17*, 1388-1408.

40. Yamada, Y.; Kitajima, M.; Kogure, N.; Wongseripatana, S.; Takayama, H. Seven New Monoterpenoid Indole Alkaloids from Gelsemium Elegans. *Chem. Asian J.* **2011**, *6*, 166-173.

41. Palmisano, G.; Penoni, A.; Sisti, M.; Tiblietti, F.; Tollar, S.; Nicholas, K. Synthesis of Indole Derivatives with Biological Activity by Reactions between Unsaturated Hydrocarbons and N-Aromatic Precursors. *Curr. Org. Chem.* **2010**, *14*, 2409-2441.

42. Nakajima, T.O.; Satoshi, Y.; Fukuyama, T. Total Synthesis of (−)-Mersicarpine. *J. Am. Chem. Soc.* **2010**, *132*, 1236-1237.

43. Zhang, L. Tandem Au-catalyzed 3,3-Rearrangement-[2+2] Cycloadditions of Propargylic Esters: Expeditious Access to Highly Functionalized 2,3-Indoline-Fused Cyclobutanes. *J. Am. Chem. Soc.* **2005**, *127*, 16804-16805.

44. Ferrer, C.; Amijs, C.H.M.; Echavarren, A.M. Intra- and Intermolecular Reactions of Indoles with Alkynes Catalyzed by Gold. *Chem. Eur. J.* **2007**, *13*, 1358-1373.

45. Lu, Y.; Du, X.; Jia, X.; Liu, Y. Gold Catalyzed Intermolecular Reactions of (Z)-Enynols with Indoles for the Construction of Dihydrocyclohepta[b]indole Skeletons through a Cascade Friedel-Crafts/Hydroarylation Sequence. *Adv. Synth. Catal.* **2009**, *351*, 1517-1522.

46. Raffa, G.; Belot, S.; Balme, G.; Monteiro, N. Iodocyclization versus Diiodination in the Reaction of 3-Alkynyl-4-methoxycoumarins with Iodine: Synthesis of 3-Iodofuro[2,3-b]chromones. *Org. Biomol. Chem.* **2011**, *9*, 1474-1478.

47. Wang, L.; Peng, S.; Wang, J. Palladium-Catalyzed Cascade Reactions of Coumarins with Alkynes: Synthesis of Highly Substituted Cyclopentadiene Fused Chromones. *Chem. Commun.* **2011**, *47*, 5422-5424.

48. Zhao, J.; Zhao, Y.; Fu, H. Transition-Metal-Free Intramolecular Ullmann-Type O-Arylation: Synthesis of Chromone Derivatives. *Angew. Chem. Int. Ed.* **2011**, *50*, 3769-3773.

49. Renault, J.; Qian, Z.; Uriac, P.; Goualt, N. Electrophilic Carbon Transfer in Gold Catalysis: Synthesis of Substituted Chromones. *Tetrahedron Lett.* **2011**, *52*, 2476-2479.
50. For a review, see: Boumendjel, A. Aurones: A Subclass of Flavone with Promising Biological Potential. *Curr. Med. Chem.* 2003, 10, 2621-2330.

51. Brooks, C.J.; Watson, D.G. Phytoalexins. *Nat. Prod. Rep.* 1985, 427-459.

52. Morimoto, M.; Fukimoto, H.; Nozoe, T.; Hagiwara, A.; Komai, K. Synthesis and Insect Antifeedant Activity of Aurones against Spodoptera Litura Larvae. *J. Agric. Food. Chem.* 2007, 55, 700-705.

53. Okombi, S.; Rival, D.; Bonnet, S.; Mariotte, A.-M.; Perrier, E.; Boumendjel, A. Discovery of Benzylidenezofuran-3(2H)-one (Aurones) as Inhibitors of Tyrosinase Derived from Human Melanocytes. *J. Med. Chem.* 2006, 49, 329-333.

54. Venkateswarlu, S.; Panchagnula, G.K.; Subbaraju, G.V. Synthesis and Antioxidative Activity of 3',4',6,7-tetrahydroxyaurone, a Metabolite of Biden Frondosa. *Biosci. Biotechnol. Biochem.* 2004, 68, 2183-2185.

55. Auf'mkolk, M.; Koerhle, J.; Hesch, R.D.; Cody, V. Inhibition of Rat Liver Iodothyronine Deiodinase. Interaction of Aurones with the Iodothyronine Ligand-Binding Site. *Biol. Chem.* 1986, 261, 11623-11630.

56. Donnelly, J.A.; Fox, M.J.; Sharma, T.C. α-Halo Ketones. XI Generation of the Wheeler Aurone Synthesis. *Tetrahedron* 1979, 35, 875-879.

57. Bose, G.; Mondal, E.; Khan, A.T.; Bordoloi, M.J. An Environmentally Benign Synthesis of Aurones and Flavones from 2'-Acetoxychalcones using n-Tetrabutylammonium Tribromide. *Tetrahedron Lett.* 2001, 42, 8907-8909.

58. Sekizaki, H. Synthesis of 2-Benzylidene-3(2H)-benzofuran-3-ones (Aurones) by Oxidation of 2'-Hydroxychalcones with Mercury(II) Acetate. *Bull. Chem. Soc. Jpn.* 1988, 61, 1407-1409.

59. Thakkar, K.; Catellani, M.; Chiusoli, G.P. Palladium-catalyzed Synthesis of Aurone from Salicyloyl Chloride and Phenylacetylene. *J. Organomet. Chem.* 1999, 397, 371-373.

60. Atta-ur-Rahman; Choudhary, M.I.; Hayat, S.; Khan, A.; Ahmed, A. Two New Aurones from Marine Brown Alga Spatoglossum Variable. *Chem. Pharm. Bull.* 2001, 49, 105-107.

61. Kobayashi, S.; Miyase, T.; Noguchi, H. Polyphenolic Glycosides and Oligosacharide Multiesters from the Roots of Polygala Dalmaisiana. *J. Nat. Prod.* 2002, 65, 319-328.

62. Trost, B.M.; Dong, G. Total Synthesis of Bryostatin 16 Using a Pd-Catalyzed Diyne Coupling as Macrocyclization Method and Synthesis of C20-epi-Bryostatin 7 as a Potent Anticancer Agent. *J. Am. Chem. Soc.* 2010, 132, 16403-16416.
67. For more information of bryostatin 16, see: Pettit, G.R.; Gao, F.; Blumberg, P.M.; Herald, C.L.; Coll, J.C.; Kamano, Y.; Lewin, N.E.; Schmidt, J.M.; Chapuis, J.-C. Antineoplastic Agents. 340. Isolation and Structural Elucidation of Bryostatins 16-18. J. Nat. Prod. 1996, 59, 286-289.

68. Hale, K.J.; Hummersome, M.G.; Manaviazar, S.; Frigerio, M. The Chemistry and Biology of the Bryostatin Antitumour Macrolides. Nat. Prod. Rep. 2002, 19, 413-453.

69. Newman, D.J.; Cragg, G.M. Marine Natural Products and related Compounds in Clinical and Advanced Preclinical Trials. J. Nat. Prod. 2004, 67, 1216-1238.

70. Hale, K.J.; Manaviazar, S. New Approaches to the Total Synthesis of Bryostatin Antitumor Macrolides. Chem. Asian J. 2010, 5, 704-754.

71. Manaviazar, S.; Hale, K.J. Total Synthesis of Bryostatin 1: A Short Route. Angew. Chem. Int. Ed. 2011, doi:10.1002/anie.201101562

72. Serrano, M. The Tumour Suppressor Protein p16INK4a. Exp. Cell. Res. 1997, 237, 7-13.

73. Pettit, G.R.; Inoue, M.; Kamano, Y.; Herald, D.L.; Arm, C.; Dufresne, C.; Christie, N.D.; Schmidt, J.M.; Doubek, D.L.; Krupa, T.S. Antineoplastic Agent. 174. Isolation and Structure of the Cytostatic Depsipeptide Dolastatin 13 from the Sea Hare Dolabella Auricularia. J. Am. Chem. Soc. 1989, 110, 2006-2007.

74. Jeong, J.U.; Sutton, S.C.; Kim, S.; Fuchs, P.L. Biomimetic Total Syntheses of (+)-Cephalostatin 12, and (+)-Ritterazine K. J. Am. Chem. Soc. 1995, 117, 10157-10158.

75. LaCour, T.G.; Guo, C.; Bhandatu, S.; Fuchs, P.L.; Boyd, M.R. Interphylal Product Splicing: The First Total Syntheses of Cephalostatin 1, the North Hemisphere of Ritterazine G, and the High Active Hybrid Analog, Ritterostatin GN1N. J. Am. Chem. Soc. 1998, 120, 692-707.

76. Jeong, J.U.; Guo, C.; Fuchs, P.L. Synthesis of the South Unit of Cephalostatin. 7. Total Syntheses of (+)-Cephalostatin 7, (+)-Cephalostatin 12, and (+)-Ritterazine K. J. Am. Chem. Soc. 1999, 121, 2071-2084.

77. Kim, S.; Sutton, S.C.; Guo, C.; LaCour, T.G.; Fuchs, P.L. Synthesis of the North 1 Unit of the Cephalostatin Family from Hecogenin Acetate. J. Am. Chem. Soc. 1999, 121, 2056-2070.

78. Lee, S.; Fuchs, P.L. The First Total Synthesis of (Corrected) Ritterazine M. Org. Lett. 2002, 4, 317-318.

79. Fortner, K.C.; Kato, D.; Tanaka, Y.; Shair, M.D. Enantioselective Synthesis of (+)-Cephalostatin 1. J. Am. Chem. Soc. 2010, 132, 275-280.

80. Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. Direct Synthesis of Trisubstituted Isoxazoles through Gold-Catalyzed Domino Reaction of Alkynyl Oxime Ethers. Org. Lett. 2010, 11, 2594-2597.

81. He, W.; Li, C.; Zhang, L. An Efficient [2+2+1] Synthesis of 2,5-Disubstituted Oxazoles via Gold-Catalyzed Intermolecular Alkyne Oxidation. J. Am. Chem. Soc. 2011, 133, 8482-8485.

82. Hashmi, A.S.K.; Schuster, A.M.; Zimmer, M.; Rominger, F. Synthesis of 5-Halo-4H-1,3-oxazine-6-amines by Copper-Mediated Domino Reaction. Chem. Eur. J. 2011, 17, 5511-5515.

83. Gao, X.; Pan, Y.-M.; Li, M.L.; Chen, L.; Zhan, Z.-P. Facile One-Pot Synthesis of Three Different Substituted Thiazoles from Propargylic Alcohols. Org. Biomol. Chem. 2010, 8, 3259-3266.

84. Yoshimatsu, M.; Matsui, M.; Yamamoto, T.; Sawa, A. Convinient Preparation of 4-Arylmethyl- and 4-Hetarylmethyl Thiazoles by Regioselective Cycloaddition Reactions of 3-Sulfanyl- and Selenylpropargylic Alcohols. Tetrahedron Lett. 2010, 66, 7975-7987.
85. Asanuma, Y.; Fujiwara, S.-I.; Shin-Ike, T.; Kambe, N. Selenoimidoylation of Alcohols with Selenium and Isocyanides and its Application to the Synthesis of Selenium-Containing Heterocycles. *J. Org. Chem.* 2004, 69, 4845-4848.

86. Wilckens, K.; Uhlemann, M.; Czekelius, C. Gold-Catalyzed *endo*-Cyclizations of 1,4-Diynes to Seven-Membered Ring Heterocycles. *Chem. Eur. J.* 2009, 15, 13323-13326.

87. Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. Highly Efficient Synthesis of Functionalized Indolizines and Indolizinones by Copper-Catalyzed Cycloisomerization of Propargylic Pyridines. *J. Org. Chem.* 2007, 72, 7783-7786.

88. Bunnelle, E.M.; Smith, C.R.; Lee, S.K.; Singaram, S.W.; Rhodes, A.J.; Sarpong, R. Pt-Catalyzed Cyclization/Migration of Propargylic Alcohols for the Synthesis of 3(2H)-Furanones, Pyrrolones, Indolizines, and Indolizinones. *Tetrahedron Lett.* 2008, 64, 7008-7014.

89. For some examples of non-metal catalyzed cycloisomerizations see: Ji, K.-G.; Zhu, H.-T.; Yang, F.; Shu, X.-Z.; Zhao, S.-C.; Liu, X.-Y.; Shaukat, A.; Liang, Y.-M. A Novel Iodine-Promoted Tandem Cyclization: An Efficient Synthesis of Substituted 3,4-Diiodoheterocyclic Compounds. *Chem. Eur. J.* 2010, 16, 6151-6154.

90. Zang, X.; Teo, W.T.; Chan, S.W.H.; Chan, P.W.H. Brønsted Acid Catalyzed Cyclization of Propargylic Alcohols with Thiocarbonyls. Facile Synthesis of Di- and Trisubstituted Thiazoles. *J. Org. Chem.* 2010, 75, 6290-6293.

91. Kothandaraman, P.; Rao, W.; Foo, S.J.; Chan, P.W.H. Gold-Catalyzed Cycloisomerization Reaction of 2-Tosylamino-phenylprop-1-yn-3-ols via a Versatile Approach for Indole Synthesis. *Angew. Chem. Int. Ed.* 2010, 49, 4619-4623.

92. Jung, H.H.; Floreancig, P.E. Gold-Catalyzed Synthesis of Oxygen- and Nitrogen-Containing Heterocycles from Alkynyl Ethers: Application to the Total Synthesis of Andracchinidine. *J. Org. Chem.* 2007, 72, 7359-7366.

93. Mill, S.; Hootelé, C. Alkaloids of Andracne Aspera. *J. Nat. Prod.* 2000, 63, 762-764.

94. Forsyth, C.J. *Asymmetric Synthesis*, 2nd ed.; Christmann, M., Braese, S., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2008; pp. 271-276.

95. Ballini, R.; Petrini, M. Nitroalkanes as Key Building Blocks for the Synthesis of Heterocyclic Derivatives. *ARKIVOC* 2008, 9, 195-223.

96. Forsyth, C.J. *Asymmetric Synthesis*; Christmann, M., Braese, S., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2007; pp. 256-261.

97. Sherry, B.D.; Maus, L.; Laforteza, B.N.; Toste, D.F. Gold(I)-Catalyzed Synthesis of Dihydropyran-2-ones. *J. Am. Chem. Soc.* 2006, 128, 8132-8133.

98. Alcaide, B.; Almendros, P.; Carrascosa, R.; Torres, M.R. Gold/Acid-Cocatalyzed Regiodivergent Preparation of Bridged Ketals via Direct Bis-Oxycyclization of Alkynyl Acetonides. *Adv. Synth. Catal.* 2010, 352, 1277-1283.

99. Perron, F.; Albizati, K.F. Chemistry of Spiroketals. *Chem. Rev.* 1989, 89, 1617-1661.

100. Aho, J.E.; Pihko, P.M.; Rissa, T.K. Nanometric Spiroketals in Natural Products: Structures, Sources, and Synthetic Strategies. *Chem. Rev.* 2005, 105, 4406-4440.

101. Rama Raju, B.; Saikia, A.K. Asymmetric Synthesis of Naturally Occurring Spiroketals. *Molecules* 2008, 13, 1942-2038.
102. Blunt, J.W.; Copp, B.R.; Hu, W.P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2009**, *26*, 170-244.

103. Brimble, M.A.; Bryant, C.J. Synthesis of the Spiroketal-Containing Anti-Helicobacter Pylori Agents CJ-12,954 and CJ-13,014. *Chem. Commun.* **2006**, 4506-4508.

104. Izquierdo-Cubero, I.; Plaza Lopez-Espinosa, M.T.; Kari, N. Synthesis of Optically Active Chalcogran from L-Sorbose. *Carbohydr. Res.* **1994**, *261*, 231-242.

105. Antoniotti, S.; Genin, E.; Michelet, V.; Genèt, J.-P. Highly Efficient Access to Strained Bicyclic Ketals via Gold-catalyzed Cycloisomerization of Bis-Homopropargylic Diols. *J. Am. Chem. Soc.* **2005**, *127*, 9976-9977.

106. Liu, L.-P.; Hammond, G.B. Highly Efficient and Tunable Synthesis of Dioxabicyclo[4.2.1]Ketals and Tetrahydropyrans via Gold-Catalyzed Cycloisomerization of 2-Alkynyl-1,5-diols. *Org. Lett.* **2009**, *11*, 5090-5092.

107. Liu, B.; De Brabander, J.K. Metal-catalyzed Regioselective Oxy-Functionalization of Internal Alkynes: An Entry into Ketones, Acetals, and Spiroketals. *Org. Lett.* **2006**, *8*, 4907-4910.

108. Hashmi, A.S.K.; Bührle, M.; Wölfe, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. Gold Catalysis: Tandem reactions of Diyne-Diols and External Nucleophiles as an Easy Access to Tricyclic Cage-Like Structures. *Chem. Eur. J.* **2010**, *16*, 9846-9854.

109. Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. Gold-Catalyzed Double Intramolecular Alkyne Hydroalkoxylation: Synthesis of the Bisbenzannulated Spiroketal Core of Rubromycins. *Synlett* **2008**, *6*, 0940-0944.

110. Brockmann, H.; Lenk, W.; Scwantje, G.; Zeeck, A. Robromycins. *Tetrahedron Lett.* **1966**, 3525-3530.

111. Goldman, M.E.; Salituro, G.S.; Bowen, J.A.; Williamson, J.M.; Zink, L.; Scleif, W.A.; Emini, E.A. Inhibition of Human Immunodeficiency Virus-1 reverse Transcriptase Activity by Robromycins: Competitive Interaction at the Template Primer Site. *Mol. Pharmacol.* **1990**, *38*, 20.

112. Trani, A.; Dallanoce, C.; Pranzone, G.; Ripamonti, F.; Goldstein, B.P.; Cibiatti, R. Semisynthetic Derivatives of Purpuromycin as Potential Topical Agents for Vaginal Infections. *J. Med. Chem.* **1997**, *40*, 967-971.

113. Chino, M.; Nishikawa, K.; Umekia, M.; Hayashi, C.; Yamazaki, T.; Tsuchida, T.; Sawa, T.; Hamada, M.; Takeuchi, T. Heliquinomycin, A New Inhibitor of DNA Helicase, Produced by Streptomyces sp. MJ929-SF2. Taxonomy, Production, Isolation, Physicochemical Properties and Biological Activities. *J. Antibiot.* **1996**, *49*, 752.

114. Li, X.; Yao, Y.; Zheng, Y.; Satter, I.; Lin, W. Cephalosporolides H and I, Two Novel Lactones from a Marine-Derived Fungus, Penicillium sp. *Arch. Phram. Res.* **2007**, *30*, 812-815.

115. Penning, T.M. Inhibition of 5β-Dihydrocortisone Reduction in Rat Liver Cytosol: A Rapid Spectrophotometric Screen for Nonsteroidal Antiinflammatory Drug Potency. *Pharm. Sci.* **1985**, *74*, 651-654.

116. Sami, F.; Dudley, G.B. Stereocontrol of 5,5-Spiroketals in the Synthesis of Cephalosporolide H Epimers. *Org. Lett.* **2010**, *12*, 4698-4701.

117. Sami, F.; Dudley, G.B. A Gold-Catalyzed Alkyne-Diol Cycloisomerization for the Synthesis of Oxygenated 5,5-Spiroketals. *Beilstein J. Org. Chem.* **2011**, *7*, 570-577.

118. McMahon, I.; Silke, J. Winter Toxicity of Unknown Aetiology in Mussels. *Harmful Algae News* **1996**, *14*, 2.
119. Ito, E.; Satake, M.; Ofuji, N.; Kurita, N.; McMahon, T.; James, K.; Yasumoto, T. Multiple Organ Damage Caused by a New Toxin Azaspiracid, Isolated from Mussels Produced in Ireland. *Toxicon* **2000**, *38*, 917-930.

120. Satake, M.; Ofuji, K.; Naoki, H.; James, K.J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. Azaspiracid, a New Marine Toxin Having Unique Spiro Ring Assemblies, Isolated from Irish Mussels, *Mytilus Edulis*. *J. Am. Chem. Soc.* **1998**, *120*, 9967-9968.

121. Nicolau, K.C.; Kotifs, T.V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamamda, Y.M.A.; Tang, W.; Frederick, M.O. Structural Revision and Total Synthesis of Azaspiracid-1, part 2: Definition of the ABCD Domain and Total Synthesis. *Angew. Chem. Int. Ed.* **2004**, *43*, 4318-4324.

122. Inoki, S.; Mukaiyama, T. A Convenient Method for the Stereoselective Preparation of trans-(2-Hydroxymethyl)tetrahydrofurans by the Oxidative Cyclization of 5-Hydroxy-1-alkenes with Molecular Oxygen Catalyzed by Cobalt(II) Complex. *Chem. Lett.* **1990**, 67-70.

123. Li, Y.; Zhou, F.; Forsyth, C.J. Gold(I)-Catalyzed Bis-Spiroketalization: Synthesis of the Trioxadispiroketal-Containing A–D Rings of Azaspiracid. *Angew. Chem. Int. Ed.* **2007**, *46*, 279-282.

124. Tachibana, K.; Scheuer, P.J.; Tsukitamni, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schimtz, F.J. Okadaic Acid, A Cytotoxic Polyether from Two Marine Sponges of the Genus Halichondria. *J. Am. Chem. Soc.* **1981**, *103*, 2469-2471.

125. Dounay, A.B.; Forsyth, C.J. Okadaic Acid: The Archetypal Serine/Threonine Protein Phosphatase Inhibitor. *Curr. Med. Chem.* **2002**, *9*, 1939-1980.

126. Scheuer, P. Marine Natural Products Research: A Look into the Dive Bag. *J. Nat. Prod.* **1995**, *58*, 335-343.

127. Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G.K.; Clardy, J. Diarrhetic Shellfish Toxins. *Tetrahedron* **1985**, *41*, 1019-1022.

128. Bialojan, C.; Takai, A. Inhibitory Effect of Marine-Sponge Toxin, Okadaic Acid, on Protein Phosphatases. Specifity and Kinetics. *Biochem. J.* **1988**, *256*, 283-290.

129. Fang, C.; Pang, Y.; Forsyth, C.J. Formal Total Synthesis of Okadaic Acid via Regiocontrolled Gold(I)-Catalyzed Spiroketalizations. *Org. Lett.* **2010**, *12*, 4528-4531.

130. Wang, J.; Soisson, S.M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y.S.; Cummings, R.; *et al.* Platensimycin is a Selective FabF Inhibitor with Potent Antibiotic Properties. *Nature* **2006**, *441*, 358-361.

131. Singh, S.B.; Jayasuriya, H.; Ondeyka, J.G.; Herath, K.B.; Zhang, C.; Zink, D.L.; Tsou, N.N.; Ball, R.G.; Basilio, A.; Genilloud, O.; Diez, M.T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. Isolation, Structure, and Absolute Stereochemistry of Platensimycin, a Broad Spectrum Antibiotic Discovered Using an Antisense Differential Sensitivity Strategy. *J. Am. Chem. Soc.* **2006**, *128*, 11916-11920.

132. Häbich, D.; von Nussbaum, F. Platensimycin, A New Antibiotic and “Superbug Challenger” from Nature. *ChemMedChem* **2006**, *1*, 951-954.

133. Yeung, Y.-Y.; Corey, E.J. A Simple, Efficient, and Enantiocontrolled Synthesis of a Near-Structural Mimic of Platensimycin. *Org. Lett.* **2008**, *17*, 3877-3878.

134. Nicolau, K.C.; Tang, Y.; Wang, Y.; Stepan, A.F.; Li, A.; Montero, A. Total Synthesis and Antibacterial Properties of Carbaplatensimycin. *J. Am. Chem. Soc.* **2007**, *129*, 14850-14851.
135. Nicolau, K.C.; Lister, T.; Denton, R.M.; Montero, A.; Edmons, D.J. Adamantaplatensimycin: A Bioactive Analogue of Platensimycin. Angew. Chem. Int. Ed. 2007, 46, 4712-4714.

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