Tetrahedron 65 (2009) 1871–1879

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cyclization of alkynoic acids with gold catalysts: a surprising dichotomy between Au^{I} and Au^{III}

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ARTICLE INFO

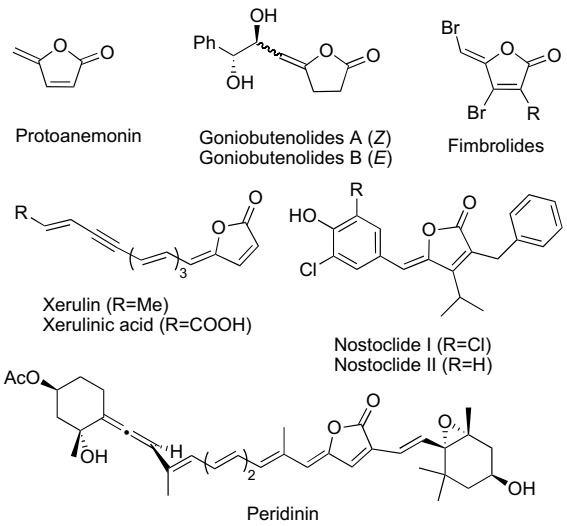
Article history:
Received 28 June 2008
Received in revised form 23 October 2008
Accepted 24 October 2008
Available online 24 December 2008

ABSTRACT

ω-Acetylenic acids, substituted or not at their acetylenic end, could be efficiently cyclized to γ- or δ-alkylidene lactones in the presence of AuCl and K_2CO_3. In contrast $AuCl_3$ led to lactone dimers, probably through cyclization and reductive dimerization. These Au^{I} and Au^{III} catalyzed cyclizations were totally regioselective and most often highly stereoselective.

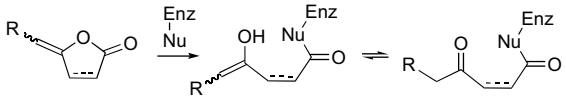
1. Introduction

γ- or δ-Alkylidene lactones constitute a large class of natural products isolated from various natural sources.[1] Their structures could be as simple as protoanemonin,[2] and as complex as peridinin[3] (Scheme 1).



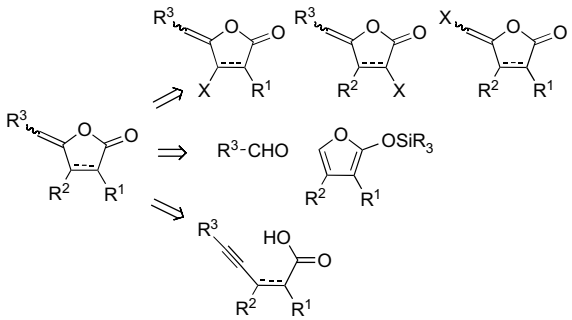
Scheme 1. Some naturally occurring γ- or δ-alkylidene lactones.

Most γ- or δ-alkylidene lactones display interesting biological activities. Their enolester moiety is mainly responsible for antibiotic and cytotoxic activities and they usually act as suicide inhibitors for various enzymes containing nucleophilic group(s) in their active site according to the mechanism depicted in Scheme 2.[4] For example, xerulin and xerulinic acid (Scheme 1) are known to inhibit cholesterol biosynthesis,[5] while bromomethylene furanones such as Fimbrolides[1d] interact with proteins involved in bacteria quorum sensing system.[6] However, recognition processes are also responsible for other biological properties,[7] such as anticancer[8] and anti-HIV[9] activities.



Scheme 2. Mode of action of γ- or δ-alkylidene lactones as suicide inhibitors of enzymes.

Due to these structural and biological interesting properties, several routes towards γ- or δ-alkylidene lactones have been developed over the years.[10,11] These routes could be classified into three main strategy (Scheme 3), i.e., coupling reactions at already



Scheme 3. Routes to alkylidene lactones.

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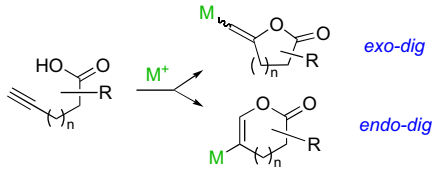
doi:10.1016/j.tet.2008.10.112

formed lactones,[12] condensation reactions[13] and electrophilic lactonization, such as halolactonization.[14]

Among the latter, the metal-catalyzed intramolecular cyclization of ω-alkynoic acids is probably the most convenient and flexible.[15] However, depending on the metal and the conditions, both *exo*- and *endo-dig* cyclization processes could occur, leading to different ring sizes. Moreover, the *exo-dig* pathway could also provide two diastereoisomers at the newly created double bond (Scheme 4).

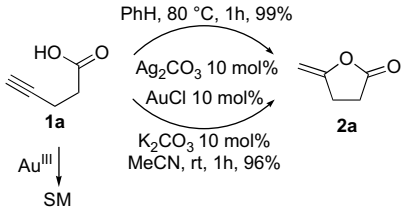


Scheme 4. *endo*- versus *exo-dig* cyclization leading to alkylidene lactones.

Among the metal used for such cyclizations, silver and more recently gold proved to be the most effective as well as the most regioselective.[11,16] In earlier communications, we reported that certain silver[17] and later, gold[18] salts were able to efficiently catalyze the cyclizations of acetylenic acids to γ-methylenene butanolides. We have investigated further the latter, allowing us to achieve efficient alkylidene lactone synthesis. Moreover, we discovered that Au^{I} and Au^{III} catalyzed different reactions depending on the conditions and we presented here the corresponding results.

2. Results and discussion

Our preliminary investigations[18] revealed that gold(I) chloride was the best catalyst for the cyclization of 4-pentynoic acid **1a** to the known γ-methylenene butanolide **2a**, while gold(III) salts left untouched **1a**. However, this cyclization could only be achieved with the help of a catalytic quantity of potassium carbonate (Scheme 5). Solvent screening indicated that this reaction could either be performed in acetonitrile or in THF, while apolar solvents such as benzene or dichloromethane mostly led to recovery of **1a** together with some degradation products. This reaction provided an interesting highly regioselective cyclization, the 5-*exo-dig* addition of a carboxylate ion onto a triple bond, leading exclusively to the butanolide product. The reaction conditions were also smoother than those described some years ago by our group with silver salts (Scheme 5).[17]



Scheme 5. Ag- and Au-catalyzed cyclizations of 4-pentynoic acid.

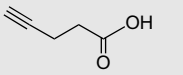
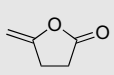
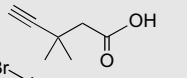
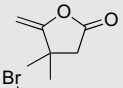
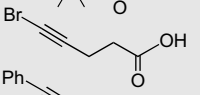
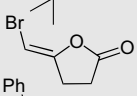
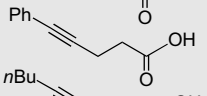
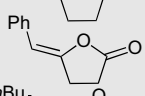
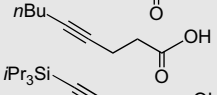
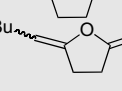
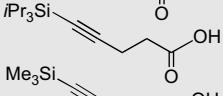
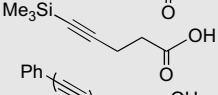
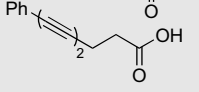
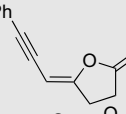
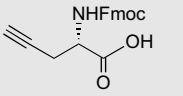
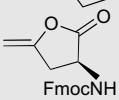
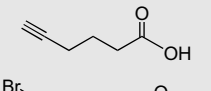
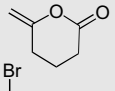
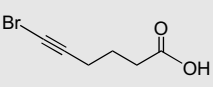
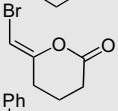
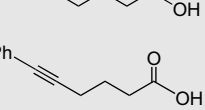
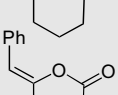
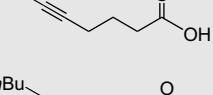
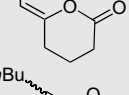
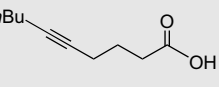
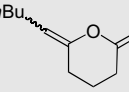
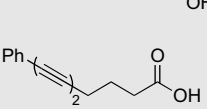
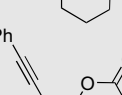
With this new procedure in hand, we then evaluated its scope and limitations, focussing our attention to the regio- and stereoselectivity of this cyclization.

2.1. Cyclization catalyzed with gold chloride

With the hope of benefiting of the Thorpe–Ingold effect,[19,16b,c,e] we selected 3,3-dimethylpent-4-ynoic acid **1b** as starting material. Indeed, the exclusive formation of butanolide **2b** was obtained in high yield upon cyclization but with a yield surprisingly slightly lower than without substituent (Table 1, entry 2 vs 1).

We then moved on to the cyclization of substituted alkynes. 5-Bromopent-4-ynoic acid **1c** was synthesized from 4-pentynoic acid **1a** with *N*-bromosuccinimide and silver nitrate according to the Hofmeister method.[20] Submitted to catalytic amounts of gold chloride and potassium carbonate, **1c** exclusively gave the 5-*exo-dig* product with high stereoselectivity, *Z*-enol ether **2c** being the sole product (Table 1, entry 3). Compound **2c** structure was easily determined by spectroscopic data and comparison with the literature. Indeed, the *Z* isomer exhibited chemical shift at 5.31 ppm for the

Table 1
Au^{I}-catalyzed formation of alkylidene lactones from various acetylenic acids[a]

Entry	Acetylenic acid		Lactone		Yield[b]
1		**1a**		**2a**	96
2		**1b**		**2b**	94
3		**1c**		**2c**	92
4		**1d**		**2d**	94
5		**1e**		**2e**	88[c]
6		**1f**	—	**1f**	0[d]
7		**1g**	—	**1g**	0[d]
8		**1h**		**2h**	75[e]
9		**1i**		**2i**	85
10		**3a**		**4a**	97
11		**3b**		**4b**	98
12		**3c**		**4c**	97
13		**3d**		**4d**	60[f]
14		**3e**		**4e**	Traces[e,g]
15		**5a**		**6a**	25[g]

[a] AuCl (0.1 equiv) and 0.1 equiv of K_2CO_3 in acetonitrile at 20 °C for 2 h unless otherwise stated.
[b] Yield of the pure product after column chromatography.
[c] Isolated as a 1:1 *Z*/*E* mixture.
[d] The starting material was recovered.
[e] The reaction required 2 days.
[f] One of the so-formed stereoisomers seemed unstable.
[g] The reaction required longer time (48 h), leading to decomposition; yield estimated by ^{1}H NMR.

vinylic proton whereas the *E* isomer showed a signal at 6.00 ppm in $CDCl_3$.[21] It is worth noting that *Z*-bromomethylene butanolides could be useful precursors for total syntheses of natural products and of drug-like compounds.[6,22]

Phenyl substituted alkyne **1d** was also synthesized from 4-pentynoic acid **1a** in three steps. Esterification with butanol, followed by Sonogashira coupling with phenyl iodide and saponification provided this alkynoic acid in good overall yield. Upon treatment under our cyclization conditions, **1d** exclusively gave as before 5-*exo*-*dig* product **2d**, as a single stereoisomer (Table 1, entry 4). The *Z* stereochemistry was again proved by spectroscopic comparison with known compounds.[15a] *n*-Butyl substituted alkyne **1e** was prepared from non-4-ynol through alkylation and oxidation of the hydroxyl group according to Jefforg and Wang protocol.[23] To our surprise, acid **1e** gave, after cyclization, an equimolar mixture of *Z*/*E* lactones (Table 1, entry 5) (4.36 and 4.12 ppm for the vinylic proton of the *E* and *Z* isomer in C_6D_6, respectively). Isomerization of the *Z*-enol ether probably occurred during these reaction conditions. It is nevertheless worth noting that the same 1:1 mixture was obtained through cyclization with silver carbonate.[16]

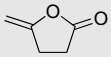
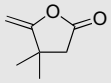
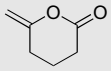
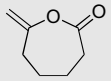
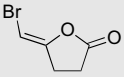
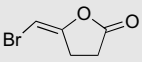
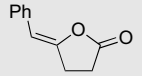
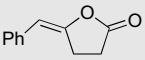
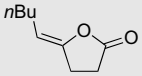
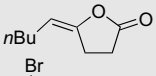
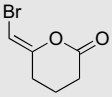
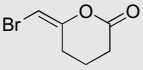
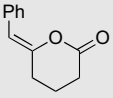
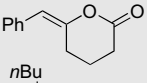
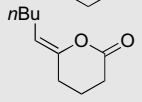
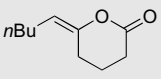
In sharp contrast, silyl protected alkynes **1f–g** did not react in the presence of gold chloride and potassium carbonate, even after prolonged time (Table 1, entries 6 and 7). Since the trimethylsilyl as the voluminous triisopropylsilyl group induced the same negative result, it seemed that bulkiness is not responsible for such lack of reactivity. Silyl groups adjacent to triple bond are known to withdraw electron density from unsaturated bond through d–π conjugation.[24] Therefore, the coordination of such less nucleophilic alkynes to the electrophilic gold ion might be impeded or diminished.

To further expand the scope of this Au^I-catalyzed cyclization, and since the expected compounds exhibit biological properties,[22] we prepared diyne **1h** by Cadiot–Chodkiewic coupling of **1a** with phenyl bromoacetylene.[25] Submitted to gold chloride and potassium carbonate, this diynylacid provided in good yield cyclization product **2h** (Table 1, entry 8). The structural analysis of this compound revealed that only the proximal triple bond was engaged in this cyclization, as expected on entropic and strain basis.

With the same scope enlargement goal, we also investigated the cyclization of the commercially available *N*-protected propargyl glycine **1i**. Here also, a single compound was obtained, the structure of which was clearly established by NMR analysis and through comparison with a recently published side-product (Table 1, entry 9).[26] It is worth noting that this cyclization of alkynyl aminoacid offered a mild and convenient route to compounds known to be suicide inhibitors of various proteases.[27]

In order to evaluate the possible role of the ring size on the *endo*/*exo* selectivity, we studied next the Au^I-catalyzed cyclization of hex-5-ynoic acid derivatives. Treated under our cyclization conditions, simplest hex-5-ynoic acid **3a** gave exclusively *exo*-dig product **4a** in nearly quantitative yield (Table 1, entry 10). With the same methods as before, we prepared a series of substituted hexynoic acids, carrying a bromide, a phenyl or an alkyl and ethynyl chain at the acetylenic end, **3b–e**, respectively. The behaviour of most of these compounds was very similar to those of the substituted pentynoic acids (Table 1, entries 11–13). Indeed, bromoalkyne **3b** and phenylated alkyne **3c** gave exclusively *Z exo* methylene lactones **4b** and **4c** in almost quantitative yields (entries 11 and 12). The *Z* stereoselectivity of these compounds was assigned from the chemical shift of their vinylic proton (see Table 2) and by comparison with known compounds.[15c] The corresponding butyl substituted acetylenic acid **3d** again gave a one to one mixture of *Z* and *E* enol lactones **4d** (entry 13). The ratio was determined by NMR analysis of the crude product (see Table 2). Surprisingly, only the *E* isomer could be isolated, since the *Z* isomer decomposed upon work-up. Similarly to what was observed for **1h**, the cyclization of **3e** proved quite slow, and ynenol lactone **4e** was only produced in trace amount within reasonable reaction time (entry 14).

Table 2
Chemical shift of vinylic protons in various alkylidene lactones

Entry	Lactone		Solvent	δ H-*syn*[a]	δ H-*anti*[a]	Δδ[b]
1		**2a**	$CDCl_3$	4.68	4.27	0.41
2			C_6D_6	4.49	3.76	0.73
3		**2b**	C_6D_6	4.43	3.80	0.63
4		**4a**	$CDCl_3$	4.52	4.25	0.27
5			C_6D_6	4.45	3.82	0.63
6		**6a**	$CDCl_3$	4.82	4.68	0.14
7			C_6D_6	4.50	4.13	0.37
8		**2c**	$CDCl_3$	—	5.31	0.69
9			C_6D_6	—	4.50	0.97
10[15c,21]			$CDCl_3$	6.00	—	0.69
11			C_6D_6	5.47	—	0.97
12		**2d**	$CDCl_3$	—	5.54	0.64
13			C_6D_6	—	4.99	1.12
14[15a]			$CDCl_3$	6.18	—	0.64
15			C_6D_6	6.11	—	1.12
16		**2e**	C_6D_6	—	4.22	0.25
17		**2e**	C_6D_6	4.47	—	0.25
18		**4b**	$CDCl_3$	—	5.32	0.79
19			C_6D_6	—	4.69	1.00
20[15c]			$CDCl_3$	6.11	—	0.79
21			C_6D_6	5.69	—	1.00
22		**4c**	$CDCl_3$	—	5.54	0.78
23			C_6D_6	—	5.06	1.13
24			$CDCl_3$	6.32	—	0.78
25			C_6D_6	6.19	—	1.13
26		**4d**	C_6D_6	—	4.19	0.86
27[36]			$CDCl_3$	5.18	—	—
28		**4d**	C_6D_6	5.05	—	0.86

[a] H-*syn* refers to the vinylic proton facing to the ring oxygen atom and H-*anti* to the other proton.
[b] Difference between the two chemical shifts of each vinylic proton.

For comparison purposes, hept-6-ynoic acid **5a** was also submitted to the Au^I-catalyzed cyclization conditions. However, this acid **5a** did not cyclize cleanly even after a prolonged time, and only 25% of the expected lactone **6a** was detected in the NMR spectra of the crude product (entry 15). Pettily, this compound decomposed upon isolation.

These results revealed that the efficiency of the Au^I-catalyzed cyclization is clearly dependant on the chain length between the acetylenic and the carboxylic parts. Indeed, only 4-pentynoic and 5-hexynoic acid derivatives gave cyclization products in high yields. Interestingly, this Au^I-catalyzed cyclization is highly regio- and

Table 3
Chemical shift differences of vinylic protons in compounds **2a**, **4a** and **6a**

Solvent	Ring size		
	5	6	7
	2a	**4a**	**6a**
$CDCl_3$	0.41	0.27	0.14
C_6D_6	0.73	0.63	0.37

stereoselective, always exclusively yielding the *exo*-dig cyclization product with a *Z* stereochemistry for the bromo and phenyl or alkynyl substituted alkynes.

2.2. Stereochemistry and NMR

With these series of methylene and alkylidene lactones in hand, we observed a strong correlation between some chemical shifts in NMR spectra and compounds' stereochemistry, as well as some tendencies in their variations. Brought together, these correlations could facilitate stereochemical assignments of related compounds. To the best of our knowledge, such correlations were never mentioned before, so we collected our data as well as some relevant literature data in Table 2.

The chemical shifts of the vinylic protons in all methylene lactones are always strongly but differentially influenced by the ring oxygen atom. Indeed, the vinylic hydrogen atoms *syn* to the cyclic oxygen atom (H-*syn*) always exhibit a higher shift than the hydrogen atoms *anti* to the cyclic oxygen (H-*anti*). Electrostatic interactions as well as electronic effects due to one lone pair of the cyclic oxygen atom could be responsible for such a difference.

Moreover, this deshielding effect seems to be dependent on solvent and substitution at the vinylic end but also on ring sizes. The chemical shift difference is larger in apolar solvent (Table 2, entries 2 and 5) than in polar solvent (Table 2, entries 1 and 4; see also Table 3). This difference decreases with ring size increase (Table 2, entry 1 vs 4 vs 6 and 2 vs 5 vs 7; see also Table 3). These data suggest a through space interaction between the *syn* vinylic hydrogen and one lone pair of the cyclic oxygen atom. As ring size increases, more conformational freedom occurs lowering vicinity and contact time between the *syn* vinylic hydrogen and one lone pair of the cyclic oxygen atom.

Whatever the ring size and the solvent, the chemical shift difference seems to increase with the electronic nature of the vinylic substituent (Table 4). The conjugated phenyl group and the electron-withdrawing bromide led to a larger difference (Table 2, entry 1 vs 12–14, 13–15, 22–24, 23–25 and 8–10, 9–11, 18–20, 19–21), while the electron-donating alkyl group tended to lower it, at least in polar solvent (Table 2, entries 16 and 17 vs 2).

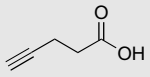
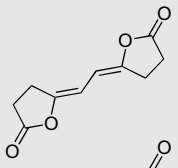
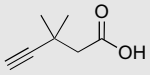
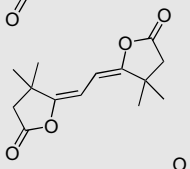
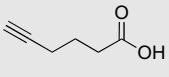
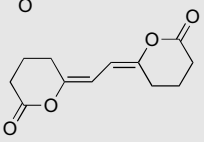
2.3. Cyclization catalyzed with gold trichloride

In our preliminary communication,[18] we showed that gold trichloride could not induce the cyclization of pentynoic acid in the presence or not of potassium carbonate in various solvents. However, we discovered during this study that the order of addition of the reagents played a key role in the outcome of the reaction.

Table 4
Chemical shift differences of vinylic protons in **2e**–**4d**, **2a**–**4a**, **2d**–**4c** and **2c**–**4b**

Ring size	Solvent	*n*-Bu	H	Ph	Br
5	$CDCl_3$	—	0.41	0.64	0.69
5	C_6D_6	0.25	0.73	1.12	0.97
6	$CDCl_3$	—	0.27	0.78	0.79
6	C_6D_6	0.86	0.63	1.13	1.00

Table 5
$AuCl_3/K_2CO_3$-catalyzed formation of dienol lactones from various acetylenic acids[a]

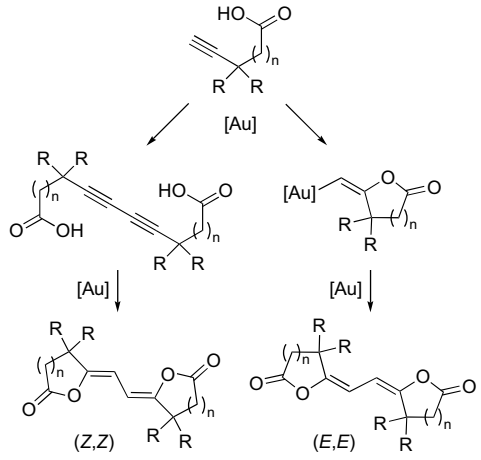
Entry	Acetylenic acid		Lactone		Yield[b]
1		**1a**		**7a**	40
2		**1b**		**7b**	30
3		**3a**		**7c**	25

[a] $AuCl_3$ (0.1 equiv) and 0.1 equiv of K_2CO_3 in acetonitrile at 20 °C for 2 h unless otherwise stated.
[b] Yield of the pure product after column chromatography.

Indeed, when the acetylenic acid is added after having already mixed gold trichloride and potassium carbonate, a new product is formed.

Pent-4-ynoic acid **1a**, 3,3-dimethylpent-4-ynoic acid **1b** and hexyn-5-ynoic acid **3a** were submitted to these conditions and the corresponding new derivatives **7a**–**c** were produced, although in moderate yields (Table 5). NMR data suggested again an enol lactone structure with the typical vinylic carbons around 150 and 97 ppm (see Table 7). However, a single vinylic proton (around 5 ppm) was detected, indicating that substitution occurred at the former terminal acetylenic end. Interestingly, NMR analysis of each crude product revealed the formation of only one stereoisomer. Mass spectra revealed the dimeric nature of these compounds, with observed masses consistently twice the mass of the parent compounds. However, the simplicity of the proton and carbon NMR spectra clearly indicated symmetrical dimers, eliminating one of the three possible structures, i.e., the (*E*,*Z*)-isomer.

Such symmetrical dimers could occur either from a cyclization process similar to the Au^I-catalyzed reaction described above after dimerization of the starting alkyne or from a Au-catalyzed cyclization followed by dimerization of the so-formed organogold species (Scheme 6). It is worth noting that the Au-cyclization of



Scheme 6. Possible pathways for the Au^{III}-catalyzed dimerizations of 4-pentynoic acids.

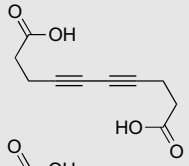
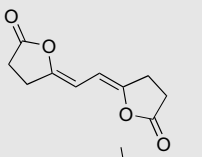
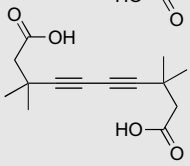
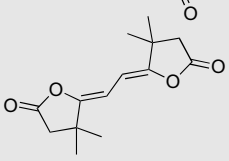
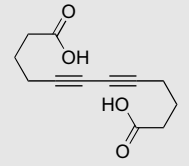
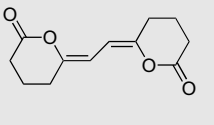
diynes has not been reported before us (see Table 1, entry 8) and the latter seems to be an unprecedented pathway. Nevertheless, a related dimerization process has been proposed to account for side-product formation in Au-catalyzed cyclization of allenols.[28] Dimeric compounds have also been mentioned as minor products in the recent Au-catalyzed synthesis of γ-alkylidene phthalides, although their structures were not clearly established.[16d]

To check the first hypothesis, but also to determine the stereochemistry of compounds **7a–c**, we prepared the corresponding diynyldiacids through conventional Glaser-type homocoupling and submitted them to our Au^{I}-catalyzed cyclization conditions, expecting the formation of the (*Z*,*Z*)-dimers. Thus, acids **1a**, **1b** and **3a** were first esterified with butanol, then dimerized using Glaser protocol. Saponification provided diacids **8a–c** in good yields over three steps. These diacids were then treated with gold chloride and potassium carbonate in acetonitrile and dimeric methylene lactones **9a–c** were isolated, again in moderate yields, especially for those requiring higher temperature due to some degradation. NMR analysis of each crude mixture showed the formation of only one stereoisomer, but different from the ones directly obtained before through Au^{III} catalysis, i.e., **7a–c** (Table 6).

Indeed, these dimers obtained through dimerization and AuCl-catalyzed cyclizations of **8a–c** exhibited vinylic hydrogens resonating at lower field in ^{1}H NMR than dimers issued from the direct $AuCl_3$-cyclizations of acetylenic acids **1a**, **1b** and **3a** (Table 7, entry 2 vs 1, 4 vs 3 and 6 vs 5). Following the trends pointed out in the preceding section, this chemical shift differences suggested that dimers **7a–c** had a proton *syn* to the ring oxygen atom and thus an (*E*,*E*)-stereochemistry and that dimers **9a–c** exhibited the opposite (*Z*,*Z*)-stereochemistry. NOE experiments corroborated these assignments.

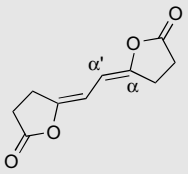
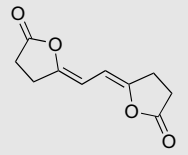
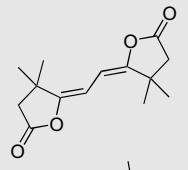
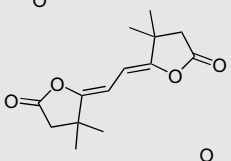
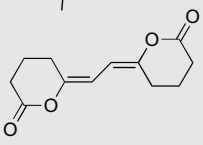
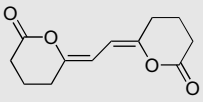
These results showed that the dimerization process initiated by Au^{III} did not involve the formation of diynes as intermediates, but rather relied on the dimerization of an organogold species (Scheme 7). The latter could involve ligand exchange between two organogold intermediates, leading to a diorganogold(III) entity.[28] Reductive elimination of such species would give the corresponding dimer while liberating gold(I). The later step could explain the modest yields observed in this reaction, since half of the starting catalyst is consumed.

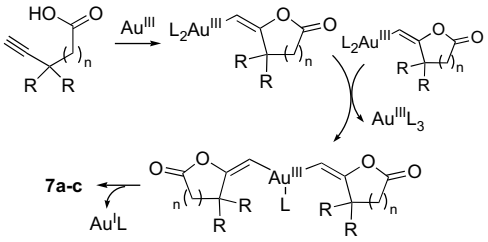
Table 6
Formation of alkylidene lactone dimers through the $AuCl/K_2CO_3$-catalyzed cyclization of diynyldiacids[a]

Entry	Diynylacid		Lactone		Yield[b]
1		**8a**		**9a**	56
2		**8b**		**9b**	18
3		**8c**		**9c**	34

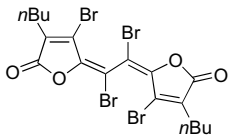
[a] AuCl (0.1 equiv)and 0.1 equiv of K_2CO_3 in acetonitrile at 20 °C for 2 h for **8a**, in refluxing toluene for 24 h for **8b** and **8c**.
[b] Yield of pure product after column chromatography.

Table 7
Chemical shifts of vinylic proton and carbons

Entry	Lactone		Solvent	H-vin	Δδ	α and α′
1		**7a**	CD_3CN	5.75	0.23	158.2 98.5
2		**9a**	CD_3CN	5.52	0.23	148.4 97.1
3		**7b**	$CDCl_3$	5.92	0.34	158.2 98.5
4		**9b**	$CDCl_3$	5.58	0.34	157.6 95.8
5		**7c**	$CDCl_3$	5.78	0.06	150.1 104.2
6		**9c**	$CDCl_3$	5.72	0.06	147.4 101.6



Scheme 7. Possible mechanism for the Au^{III}-catalyzed dimerizations of acetylenic acids.



Scheme 8. Dimeric natural product isolated from the red marine alga *D. elegans*.

This Au^{I}- and Au^{III}-catalyzed synthesis of dimeric lactones offered a unique access to such complex molecules, and allow to stereoselectively obtain either (*E*,*E*)- or (*Z*,*Z*)-isomers.

Interestingly enough, such motif has been detected as natural product in extracts isolated from the red marine alga *Delisea elegans* (Scheme 8).[29] The dienylenol lactone moiety could also act as diene in Diels–Alder reactions.

3. Conclusion

The Au^I-catalyzed cyclizations of γ- and δ-acetylenic acids provided a convenient and rapid access to γ- and δ-alkylidene lactones. Whatever the substitution at the terminal acetylenic end, only the *exo-dig* product was formed in the presence of gold chloride and potassium carbonate. Moreover, except for alkyl substitution, only the *Z* stereoisomer was produced, when the acetylenic end of the starting acetylenic acid was substituted.

In sharp contrast, the treatment of γ- and δ-acetylenic acids with gold trichloride and potassium carbonate offered a direct access to dimeric methylene lactones as a single regio- and stereoisomer of (*E*,*E*)-geometry. Interestingly, the Au^I-catalyzed cyclization of the corresponding diynylacids provided a dimer, again as a single regio- and stereoisomer but with the opposite (*Z*,*Z*)-geometry. Both Au^I-catalyzed cyclization and the Au^{III}-catalyzed dimerization–cyclization are thus complementary.

It is worth noting that such dichotomy in Au^I–Au^{III} catalysis is not so common,[30] and thus enlarges the scope of gold chemistry.[31]

The fact that most of these alkylidene lactones and even the dimeric lactones are natural products or bioactive compounds suggested to develop the present Au^I and Au^{III}-catalyzed cyclizations towards biologically relevant targets. These aspects are now currently explored in our group.

4. Experimental section

4.1. General

Unless otherwise noted, all reagents were obtained commercially and used without further purification. Extracts were dried over $MgSO_4$ or Na_2SO_4 and solvents were removed in vacuo via a rotary evaporator at vacuum pressure. TLC analyses of reaction mixtures were performed on silica gel 60 F_{254} TLC plates, which were visualized through staining with $KMnO_4$, *p*-anisaldehyde, or molybdophosphoric acid/$Ce(SO_4)_2 \cdot 4H_2O$ aqueous or ethanolic solutions. Flash Chromatography (FC) was carried out using silica gel Si 60 (40–63 mm). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer and referenced to $CDCl_3$ (7.26 ppm), CD_3CN (1.94 ppm), C_6D_6 (7.16 ppm) or DMSO-d_6 (2.50 ppm) for proton spectra unless otherwise noted. IR spectra (neat, or KBr) were recorded on FTIR-spectrophotometer Alpha. Mass spectra and high resolution mass spectra were obtained by electrospray (ESI) or electronic impact (EI) method.

4.2. Starting materials

Compounds **1a**, **1i**, **3a** and **5a** are commercially available compounds and they were used as such, unless otherwise noted. Acids **1b**,[32] **1e**,[33] **1f**,[34] **1g**,[31] **1h**,[25] **3d**[30] and **3e**[25] were prepared according to the literature procedures.

4.2.1. 6-Bromohex-5-ynoic acid (*3b*)

To a solution of pent-4-ynoic acid (100 mg, 0.94 mmol) in acetone (5 mL) were added *N*-bromosuccinimide (191 mg, 1.07 mmol) and silver nitrate (15 mg, 1.07 mmol). After stirring at room temperature for 2 h, water (10 mL) was added to the reaction mixture. The aqueous phase was extracted a few times with dichloromethane. The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel to afford **3b** (130 mg, 0.68 mmol, 72%) as a yellow oil. TLC R_f 0.51 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 3175, 2938, 2660, 1701, 1411, 1241, 1154, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (t, J=7.3 Hz, 2H), 2.31 (t, J=7.1 Hz, 2H), 1.84 (quint, J=7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 78.9, 69.3, 32.6, 23.1, 19.0; HRMS: calcd for $C_6H_6^{79}BrLi_2O_2$ $[M+2Li-H]^+$ 202.9871, found 202.9748.

4.2.2. 5-Phenylpent-4-ynoic acid (*1d*)

To a solution of 4-pentynoic acid (200 mg, 2.04 mmol) in dichloromethane (10 mL) were added butanol (0.75 mL, 8.16 mmol, 4 equiv), DMAP (25 mg, 0.20 mmol, 0.1 equiv) and DCC (463 mg, 2.24 mmol, 1.1 equiv). After stirring for 2 h, the so-obtained white suspension was filtrated and concentrated. The residue was chromatographed on silica gel to afford butyl 4-pentynoate (220 mg, 1.43 mmol, 70%) as a colourless oil. TLC R_f 0.7 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 3313, 2959, 2939, 2873, 1736, 1167, 1067, 1028, 633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J=6.6 Hz, 2H), 2.55–2.46 (m, 4H), 1.96 (t, J=2.6 Hz, 1H), 1.60 (m, 2H), 1.36 (m, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 82.5, 68.9, 64.6, 33.4, 30.6, 19.1, 14.4, 13.7; HRMS: calcd for $C_9H_{14}LiO_2$ $[M+Li]^+$ 161.1154, found 161.1043.

To a solution of $Pd(PPh_3)_2Cl_2$ (13 mg, 0.02 mmol) and CuI (7 mg, 0.03 mmol) in anhydrous and degassed Et_3N (3 mL) were added iodobenzene (0.1 mL, 0.9 mmol, 1 equiv) and a solution of butyl pent-4-ynoate (150 mg, 0.97 mmol, 1.1 equiv) in 3 mL of anhydrous acetonitrile. After stirring for 3 h, the reaction mixture was quenched with aqueous 5% NH_4Cl and extracted three times with Et_2O. The organic layers were mixed, dried over Na_2SO_4, filtered and concentrated. Column chromatography afforded butyl 5-phenyl-4-pentynoate (179 mg, 0.78 mmol, 87%) as a colourless oil. TLC R_f 0.4 (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 2959, 2931, 2873, 1733, 1160, 755, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H), 7.29–7.26 (m, 3H), 4.13 (t, J=6.6 Hz, 2H), 2.76–2.71 (m, 2H), 2.65–2.59 (m, 2H), 1.67–1.58 (m, 2H), 1.39–1.35 (m, 2H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 131.6, 128.2, 127.8, 123.5, 88.1, 81.1, 64.6, 43.5, 31.9, 22.7, 19.1, 15.4, 13.7; HRMS: calcd for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1204, found 253.1160.

The ester (170 mg, 0.74 mmol) was treated with aqueous 1 M NaOH (1 mL) in dioxane (5 mL) at room temperature and the reaction mixture was stirred for 4 h. The reaction was quenched with aqueous 1 N HCl (2 mL) and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel to afford **1d** (90 mg, 0.52 mmol, 70%) as a white solid. TLC R_f 0.23 (cyclohexane/EtOAc 40%); mp 107.3 °C; IR (neat) ν_{max} 2919, 2632, 1692, 1632, 1595, 1300, 1210, 1172, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.42–7.37 (m, 2H), 7.31–7.26 (m, 3H), 2.79–2.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 131.6, 128.2, 127.9, 123.4, 87.6, 81.4, 33.5, 15.1; MS (EI) *m*/*z* (%) 174.1 (60, M^+), 146.2 (100), 128.2 (80); HRMS: calcd for $C_{11}H_9O_2$ $[M-H]^-$ 173.0608, found 173.0686.

4.2.3. 5-Bromopent-4-ynoic acid (*1c*)

To a solution of pent-4-ynoic acid (70 mg, 0.71 mmol) in acetone (5 mL) were added *N*-bromosuccinimide (151 mg, 0.85 mmol) and silver nitrate (12 mg, 0.07 mmol). After stirring at room temperature for 2 h, water (10 mL) was added to the reaction mixture. The aqueous phase was extracted a few times with dichloromethane. The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel to afford **1c** (70 mg, 0.4 mmol) as a yellow oil, yield: 55%. TLC R_f 0.59 (cyclohexane/EtOAc 30%); mp 52 °C (lit.[15c,35] 69–72 °C and 78–80 °C); IR (neat) ν_{max} 3255, 3027, 2923, 2850, 1696, 1425, 1355, 1211, 1018, 919 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (dd, J=1.1 and 5.9 Hz, 2H), 2.53 (dd, J=1.1 and 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 77.9, 69.3, 32.9, 15.3; HRMS: calcd for $C_5H_4^{79}BrO_2$ $[M-H]^-$ 174.9400, found 174.9457. Spectroscopic data were consistent with those reported in the literature.

4.2.4. 6-Phenylhex-5-ynoic acid (*3c*)

To a solution of 5-hexynoic acid (200 mg, 1.8 mmol) in dichloromethane (10 mL) were added butanol (0.66 mL, 7.2 mmol, 4 equiv), DMAP (38 mg, 0.18 mmol, 0.1 equiv) and DCC (557 mg, 2.7 mmol, 1.5 equiv). After stirring for 2 h, the so-obtained white

suspension was filtrated and concentrated. The residue was chromatographed on silica gel to afford butyl 5-hexynoate (166 mg, 0.99 mmol, 65%) as a colourless oil. TLC R_f 0.76 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 3297, 2960, 2935, 2874, 1731, 1157, 1064, 1021, 629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J=6.8 Hz, 2H), 2.43 (t, J=7.3 Hz, 2H), 2.25 (td, J=2.75 and 7.1 Hz, 2H), 1.96 (t, J=2.7 Hz, 1H), 1.82 (quint, J=7.3 Hz, 2H), 1.64–1.55 (m, 2H), 1.36 (six, J=7.1 Hz, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 83.3, 69.0, 64.3, 32.9, 30.6, 23.6, 19.1, 17.8, 13.7; HRMS: calcd for $C_{10}H_{16}LiO_2$ $[M+Li]^+$ 175.1310, found 175.1195.

To a solution of $Pd(PPh_3)_2Cl_2$ (11 mg, 0.015 mmol, 0.02 equiv) and CuI (6 mg, 0.03 mmol, 0.04 equiv) in anhydrous and degassed Et_3N (3 mL) were added iodobenzene (0.08 mL, 0.7 mmol, 1 equiv) and a solution of butyl hex-5-ynoate (130 mg, 0.77 mmol, 1.1 equiv) in 3 mL of anhydrous acetonitrile. After stirring for 4 h, the reaction mixture was quenched with aqueous 5% NH_4Cl and extracted three times with Et_2O. The organic layers were mixed, dried over Na_2SO_4, filtered and concentrated. Column chromatography afforded butyl 6-phenyl-5-ynoate (164 mg, 0.67 mmol, 94%) as a colourless oil. TLC R_f 0.60 (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 2958, 2934, 2873, 1731, 1149, 755, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.29–7.26 (m, 3H), 4.08 (t, J=6.6 Hz, 2H), 2.52–2.42 (m, 4H), 1.97–1.82 (m, 2H), 1.6 (quint, J=6.8 Hz, 2H), 1.38 (six, J=7.3 Hz, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 131.6, 128.2, 127.7, 123.7, 88.9, 81.4, 69.1, 64.3, 33.2, 30.7, 24.0, 19.2, 13.7; HRMS: calcd for $C_{16}H_{20}LiO_2$ $[M+Li]^+$ 251.1623, found 251.1630.

The ester (150 mg, 0.61 mmol) was treated with aqueous 1 M NaOH (1 mL) in dioxane (5 mL) at room temperature and the reaction mixture was stirred for 4 h. The reaction was quenched with aqueous 1 N HCl (2 mL) and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed to afford **3c** (87 mg, 0.46 mmol, 75%) as a colourless oil. The physical and spectral data were identical to those described by Curran.[30]

4.3. Typical procedure for the preparation of diyne esters

To a solution of alkynes (1 equiv) in acetonitrile (1 mL/0.1 mmol) at room temperature were added dried and degassed triethylamine (7 equiv), copper iodide (0.03 equiv), $PdCl_2(PPh_3)_2$ (0.03 equiv) and triphenylphosphine (0.03 equiv). After disappearance of the starting material (TLC monitoring), aqueous saturated NH_4Cl and ether were added to the reaction mixture and the resulting layers were separated. After extraction with ether, the combined organic layers were dried over Na_2SO_4, filtrated and concentrated by evaporation. The residue was purified by column chromatography.

4.3.1. Dibutyl deca-4,6-diynedioate

Butyl 4-pentynoate (100 mg, 0.65 mmol) gave diyne (56 mg, 0.18 mmol) as a yellow oil, 56% yield. TLC R_f 0.53 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 2959, 2935, 2973, 1730, 1456, 1147, 1062, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J=6.6 Hz, 2H), 4.09 (t, J=6.6 Hz, 4H), 2.57–2.49 (m, 8H), 1.6 (quint, J=6.9 Hz, 4H), 1.36 (sext, J=7.3 Hz, 4H), 0.92 (t, J=7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 75.7, 65.8, 64.7, 33.0, 30.6, 19.1, 15.2, 13.7; HRMS: calcd for $C_{18}H_{26}LiO_4$ $[M+Li]^+$ 313.1991, found 313.1850.

4.3.2. Dibutyl dodeca-5,7-diynedioate

Butyl 4-hexynoate (280 mg, 1.67 mmol) gave diyne (260 mg, 0.78 mmol) as a colourless oil, 93% yield. TLC R_f 0.7 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 2957, 2922, 2249, 2075, 1687, 1458, 1402, 1230, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J=6.8 Hz, 4H), 2.44 (t, J=7.3 Hz, 4H), 2.33 (t, J=6.8 Hz, 4H), 1.84 (quint, J=7.3 Hz, 4H), 1.66–1.56 (m, 4H), 1.44–1.32 (m, 4H), 0.93 (t, J=7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 76.4, 66.0, 64.4, 33.0, 30.7, 23.5, 19.1, 18.7, 13.7; HRMS: calcd for $C_{20}H_{30}LiO_4$ $[M+Li]^+$ 341.2304, found 341.2102.

4.3.3. Dibutyl 3,3,8,8-tetramethyldeca-4,6-diynedioate

Butyl 3,3-dimethylpent-4-ynoate (200 mg, 1.1 mmol) gave diyne (130 mg, 0.36 mmol) as a colourless oil, 65% yield. TLC R_f 0.7 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 2962, 1730, 1458, 1384, 1187, 1118, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J=6.6 Hz, 4H), 2.44 (s, 4H), 1.65–1.56 (m, 4H), 1.44–1.37 (m, 4H), 1.34 (s, 6H), 0.94 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 83.7, 65.3, 64.4, 46.8, 30.7, 30.4, 28.8, 19.2, 13.8; MS (EI) m/z (%) 362.3 (20, M^+), 146.2 (100); HRMS: calcd for $C_{22}H_{34}LiO_4$ $[M+Li]^+$ 369.2617, found 369.2375.

4.4. Typical procedure for the preparation of diyne acids

To a solution of diester (1 equiv) in dioxane (2.5 mL/mmol) at room temperature was added aqueous NaOH 1 M (2 equiv). After disappearance of the starting material (TLC monitoring), 1 M HCl and ethyl acetate were added to the reaction mixture and the resulting two layers were separated. After extraction with ethyl acetate, the combined organic layers were washed with water, dried over Na_2SO_4, filtrated and concentrated by evaporation. The residue was purified by column chromatography.

4.4.1. Deca-4,6-diynedioic acid (*8a*)

Dibutyl deca-4,6-diynedioate (130 mg, 0.42 mmol) gave diacid (72 mg, 0.37 mmol) as a white solid, 87% yield. TLC R_f 0.3 (cyclohexane/EtOAc 40%); mp 220 °C (dec); IR (neat) ν_{max} 2912, 1689, 1400, 1223 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 2.48–2.43 (m, 8H); ^{13}C NMR (75 MHz, DMSO) δ 173.1, 77.7, 65.7, 32.8.

4.4.2. 3,3,8,8-Tetramethyldeca-4,6-diynedioic acid (*8b*)

Dibutyl 3,3,8,8-tetramethyldeca-4,6-diynedioate (60 mg, 0.166 mmol) gave diacid (27 mg, 0.108 mmol) as a white solid, 67% yield. TLC R_f 0.4 (cyclohexane/EtOAc 40%); mp 157–158 °C; IR (neat) ν_{max} 2951, 1691, 1567, 1428, 1329, 1200, 1045 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 2.44 (s, 2H), 1.32 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 84.3, 64.6, 45.3, 29.8, 28.0.

4.4.3. Dodeca-5,7-diynedioic acid (*8c*)

Dibutyl dodeca-5,7-diynedioate (260 mg, 0.78 mmol) gave diacid (140 mg, 0.63 mmol) as a white solid, 89% yield: TLC R_f 0.36 (cyclohexane/EtOAc 40%); mp 122–123 °C; IR (neat) ν_{max} 2951, 1691, 1567, 1428, 1329, 1200, 1045 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 2.37 (t, J=7.3 Hz, 4H), 2.32 (t, J=7.1 Hz, 4H), 1.76 (quint, J=7.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 76.9, 65.3, 32.1, 23.4, 17.9; HRMS: calcd for $C_{12}H_{13}O_4$ $[M-H]^-$ 221.0819, found 221.0904.

4.5. Cyclization reactions

Products **2a**,[15k] **2h**,[22] **2i**,[26] **4e**[22] and **6a**[15k] are known compounds, exhibiting the same properties as described.

4.6. Typical procedure for the formation of enol lactones from ω-acetylenic acids

To a solution of ω-acetylenic acid (1 equiv) in acetonitrile (3 ml/mmol) at room temperature was added gold chloride (0.1 equiv) and then K_2CO_3 (0.1 equiv). The reaction mixture, initially a white suspension, turned to a dark brown solution within minutes. After disappearance of the starting material (TLC monitoring, usually 2 h), water and dichloromethane were added to the reaction mixture and the resulting two layers were separated. After extraction with dichloromethane, the combined organic layers were dried

over $NaSO_4$. After filtration and solvent evaporation, the crude product was purified by column chromatography when necessary.

*4.6.1. 4,4-Dimethyl-5-methylenedihydrofuran-2(3H)-one (**2b**)*

Following the *general procedure*, **1b** (75 mg, 0.58 mmol) gave **2b** (70 mg, 0.55 mmol, 95%) as a colourless oil. TLC R_f 0.6 (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 2967, 2928, 1801, 1667, 1370, 1196, 1091, 978 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.43 (d, J=2.6 Hz, 1H), 3.80 (d, J=2.6 Hz, 1H), 1.71 (s, 2H), 0.65 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 171.4, 166.0, 84.8, 42.1, 38.1, 30.1; HRMS: 149.0692 ($C_7H_{10}NaO_2$ calcd 149.0578).

*4.6.2. (Z)-5-(Bromomethylene)dihydrofuran-2(3H)-one (**2c**)[21]*

Following the *general procedure*, **1c** (60 mg, 0.34 mmol) gave **2c** (55 mg, 0.32 mmol, 92%) as a yellow oil. TLC R_f 0.8 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 2928, 1808, 1671, 1442, 1328, 1292, 1160, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (t, J=1.7 Hz, 1H), 2.92–2.86 (m, 2H), 2.80–2.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 151.4, 79.4, 28.1, 25.2; HRMS: calcd for $C_5H_5^{79}BrNaO_2$ $[M+Na]^+$ 198.9371, found 198.9436.

*4.6.3. (Z)-5-Benzylidenedihydrofuran-2(3H)-one (**2d**)*

Following the *general procedure*, **1d** (80 mg, 0.46 mmol) gave **2d** (75 mg, 0.43 mmol, 94%) as a white solid. TLC R_f 0.62 (cyclohexane/EtOAc 20%); mp 91 °C; IR (neat) ν_{max} 2922, 1788, 1675, 1443, 1358, 1223, 1176, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J=7.3 and 1.2 Hz, 2H), 7.33 (t, J=7.7 Hz, 2H), 7.20 (tt, J=7.3 and 1.3 Hz, 1H), 5.54 (t, J=1.6 Hz, 1H), 3.05–2.99 (m, 2H), 2.73–2.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 148.1, 133.9, 128.5, 128.3, 126.7, 104.9, 27.0, 26.3; HRMS: calcd for $C_{11}H_{10}NaO_2$ $[M+Na]^+$ 197.0573, found 197.0659.

*4.6.4. (Z and E) 5-Butylidenedihydrofuran-2(3H)-one (**2e**)*

Following the *general procedure*, **1e** (40 mg, 0.26 mmol) gave an inseparable mixture of **2e** (35 mg, 0.23 mmol, 88%) as a colourless oil. TLC R_f 0.70 (cyclohexane/AcOEt 35%); IR (KBr) ν_{max} 1805, 1710, 1240, 1200, 1145, 1100, 1055, 970, 955 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.47 (t large, J=4.2 Hz, 1H, isomer *E*), 4.22 (tt, J=7.2 and 1.5 Hz, 1H, isomer *Z*), 2.23–2.15 (m, 2H), 1.98–1.89 (m, 2H), 1.82–1.75 (m, 1H), 1.62–1.55 (m, 1H), 1.41–1.29 (m, 4H), 0.91 (m, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.6 and 167.4, 153.4 and 147.9, 103.5 and 98.6, 32.3 and 31.7, 28.3 and 28.1, 27.1 and 24.9, 24.3 and 22.2, 21.9 and 18.3, 13.7 and 13.5.

*4.6.5. (Z)-(3-Phenylprop-2-ynylidene)dihydrofuran-2(3H)-one (**2h**)*

Following the *general procedure*, **1h** (100 mg, 0.505 mmol) gave **2h** (75 mg, 0.38 mmol, 75%) as a yellow solid. TLC R_f 0.49 (cyclohexane/EtOAc 50%); mp 85.4 °C; IR (neat) ν_{max} 1801, 1670, 1092, 937 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.42 (m, 2H), 7.33–7.27 (m, 3H), 5.03 (t, J=1.9 Hz, 1H), 2.99–2.94 (m, 2H), 2.76–2.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 158.4, 131.4, 128.3, 128.2, 123.3, 93.6, 85.4, 82.3, 27.4, 25.5; HRMS: calcd for $C_{13}H_{10}NaO_2$ $[M+Na]^+$ 221.0573, found 221.0554.

*4.6.6. 6-Methylenetetrahydro-2H-pyran-2-one (**4a**)[15k]*

Following the *general procedure*, **3a** (50 mg, 0.45 mmol) gave **4a** (49 mg, 0.44 mmol, 97%) as a colourless oil. TLC R_f 0.73 (cyclohexane/EtOAc 20%); IR (KBr) ν_{max} 1767, 1705, 1240, 1215, 1160, 1140, 1050, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.25 (m, 1H), 2.59 (t, J=6.8 Hz, 2H), 2.46 (m, 2H), 1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 156.0, 94.3, 30.9, 27.3, 19.2. Spectroscopic data were consistent with those reported in the literature.

*4.6.7. (Z)-6-(Bromomethylene)tetrahydro-2H-pyran-2-one (**4b**)[21]*

Following the *general procedure*, **3b** (60 mg, 0.32 mmol) gave **4b** (59 mg, 0.31 mmol, 98%) as a yellow solid. TLC R_f 0.65 (cyclohexane/EtOAc 30%); mp 85.4 °C (lit.[ref] 75–76 °C); IR (neat) ν_{max} 2958, 1757, 1649, 1429, 1329, 1259, 1138, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (t, J=1.3 Hz, 1H), 2.68 (t, J=6.8 Hz, 2H), 2.49 (td, J=1.3 and 6.4 Hz, 2H), 1.88 (pent, J=6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 151.1, 84.0, 30.5, 27.1, 18.4; HRMS: calcd for $C_6H_7^{79}BrNaO_2$ $[M+Na]^+$ 212.9522, found 212.9565. Spectroscopic data were consistent with those reported in the literature.

*4.6.8. (Z)-6-Benzylidenetetrahydro-2H-pyran-2-one (**4c**)*

Following the *general procedure*, **3c** acid (70 mg, 0.37 mmol) gave **4c** (68 mg, 0.36 mmol, 97%) as a colourless oil. TLC R_f 0.8 (cyclohexane/EtOAc 30%); IR (neat) ν_{max} 3021, 1759, 1665, 1417, 1326, 1257, 1155, 1042 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.8 (d, J=7.3 Hz, 2H), 7.17–7.22 (m, 2H), 7.03 (t, J=7.3, 1H), 5.12 (s, 1H), 1.93 (t, J=6.8 Hz, 2H), 1.68 (t, J=6.6 Hz, 2H), 0.91 (pent, J=6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 148.5, 134.4, 128.9, 12.0, 126.7, 107.7, 29.9, 27.6, 18.1; HRMS: calcd for $C_{12}H_{12}NaO_2$ $[M+Na]^+$ 211.0735, found 211.0787.

*4.6.9. (E)-6-Butylidenetetrahydro-2H-pyran-2-one (**4d**)*

Following the *general procedure*, **3d** (40 mg, 0.24 mmol) gave a mixture of **4d** (23 mg, 0.14 mmol, 58%) as a colourless oil. TLC R_f 0.58 (pentane/Et_2O 5%); isomer *E*: IR (neat) ν_{max} 2956, 2928, 2857, 1753, 1682, 1222, 1112, 1051 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.05 (t, J=7.9 Hz, 1H), 1.95 (dt, J=6.8 and 2.9 Hz, 2H), 1.74 (t, J=6.6 Hz, 2H), 1.62 (dt, J=7.1 and 7.0 Hz, 1H), 1.12–1.07 (m, 4H), 0.93 (quint, J=6.6 Hz, 2H), 0.78 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 166.9, 148.5, 108.7, 31.8, 30.3, 25.1, 22.0, 21.9, 17.9, 13.7; HRMS: calcd for $C_{10}H_{16}LiO_2$ $[M+Li]^+$ 175.1310, found 175.1312; isomer *E*: spectroscopic data were consistent with those reported by Chapuis et al.[36]

4.7. Typical procedure for dimer formations catalyzed by $AuCl_3$

To a solution of gold trichloride (0.1 equiv) in dry acetonitrile (1 mL/mmol) at room temperature was added K_2CO_3 (0.1 equiv). The reaction mixture was stirred for 1 h and a solution of acetylenic acid (1 equiv) in acetonitrile (1 mL/mmol) was then added dropwise. After disappearance of the starting material (TLC monitoring), water and ethyl acetate were added to the reaction mixture and the resulting two layers were separated. After extraction with ethyl acetate, the combined organic layers were dried over Na_2SO_4. After filtration and solvent evaporation, the crude product was purified by column chromatography.

*4.7.1. (5E,5′E)-5,5′-(Ethane-1,2-diylidene)bis(dihydrofuran-2(3H)-one) (**7a**)*

Pent-4-ynoic acid (100 mg, 1.02 mmol) gave dimer **7a** (40 mg, 0.206 mmol) as a white solid, 40% yield. TLC R_f 0.42 (cyclohexane/EtOAc 30%); mp 147 °C (dec); IR (KBr) ν_{max} 2926, 1788, 1655, 1641, 1438, 1410, 1297, 1264, 1167, 1100 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 5.75 (s, 2H), 2.95–2.89 (m, 4H), 2.71–2.65 (m, 4H); ^{13}C NMR (75 MHz, CD_3CN) δ 175.1, 151.2, 98.3, 27.0, 22.6; MS (EI) *m*/*z* (%) 194.1 (100, M^+); HRMS: calcd for $C_{10}H_{10}LiO_4$ $[M+Li]^+$ 201.0739, found 217.1250.

*4.7.2. (5E,5′E)-5,5′-(Ethane-1,2-diylidene)bis(4,4-dimethyldihydrofuran-2(3H)-one) (**7b**)*

3,3-Dimethylpent-4-ynoic acid (130 mg, 1.03 mmol) gave dimer **7b** (33 mg, 0.132 mmol) as a white solid, 25% yield. TLC R_f 0.41 (cyclohexane/EtOAc 30%); mp 169.1 °C; IR (KBr) ν_{max} 2962, 1781, 1632, 1450, 1275, 1172, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 2H), 2.58 (s, 4H), 1.45 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 158.2, 98.5, 44.8, 38.9, 27.6; HRMS: calcd for $C_{14}H_{19}NaO_4$ $[M+Na]^+$ 273.1103, found 273.1144.

*4.7.3. (6E,6′E)-6,6′-(Ethane-1,2-diylidene)bis(tetrahydro-2H-pyran-2-one) (**7c**)*

Hex-5-ynoic acid (80 mg, 0.72 mmol) gave dimer **7c** (24 mg, 0.206 mmol) as a white solid, 30% yield. TLC R_f 0.60 (cyclohexane/EtOAc 60%); mp 127.6 °C; IR (neat) ν_{max} 2951, 2921, 1791, 1734, 1700, 1216, 1109, 1046, 876 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 2H), 2.63 (t, J=6.6 Hz, 4H), 2.58 (t, J=6.6 Hz, 4H), 1.91 (quint, J=6.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 150.1, 104.2, 30.7, 22.7, 18.0; HRMS: calcd for $C_{12}H_{12}NaO_2$ $[M+Na]^+$ 222.0898, found 222.1189.

4.8. Typical procedure for dimer formations catalyzed by AuCl

See the typical procedure for the formation of enol lactones from ω-acetylenic acids.

*4.8.1. (5Z,5′Z)-5,5′-(Ethane-1,2-diylidene)bis(dihydrofuran-2(3H)-one) (**9a**)*

Deca-4,6-diynedioic acid (60 mg, 0.31 mmol) gave dimer **9a** (34 mg, 0.175 mmol) as a white solid, 56% yield. TLC R_f 0.40 (cyclohexane/EtOAc 30%); mp 214–215 °C (dec); IR (neat) ν_{max} 2935, 1736, 1652, 1440, 1309, 1163, 1090, 919 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 5.52 (s, 2H), 2.89 (t, J=9.0 Hz, 4H), 2.68–2.62 (m, 4H); ^{13}C NMR (75 MHz, CD_3CN) δ 175.1, 148.4, 97.1, 27.2, 24.7; HRMS: calcd for $C_{10}H_{10}NaO_4$ $[M+Na]^+$ 217.0477, found 217.0471.

*4.8.2. (5Z,5′Z)-5,5′-(Ethane-1,2-diylidene)bis(4,4-dimethyldihydrofuran-2(3H)-one) (**9b**)*

3,3,8,8-Tetramethyldeca-4,6-diynedioic acid (40 mg, 0.160 mmol) gave dimer **9b** (7 mg, 0.028 mmol) as a white solid, 18% yield. TLC R_f 0.45 (cyclohexane/EtOAc 30%); mp 171 °C; IR (neat) ν_{max} 2964, 2922, 1788, 1655, 1465, 1386, 1162, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (s, 2H), 2.52 (s, 4H), 1.33 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 157.6, 95.8, 43.1, 39.1, 27.9; HRMS: calcd for $C_{14}H_{19}LiO_{44}$ $[M+Li]^+$ 257.1365, found 257.1409.

*4.8.3. (6Z,6′Z)-6,6′-(Ethane-1,2-diylidene)bis(tetrahydro-2H-pyran-2-one) (**9c**)*

Dodeca-5,7-diynedioic acid (50 mg, 0.16 mmol) gave dimer **9c** (12 mg, 0.054 mmol) as a thick colourless oil, 34% yield. TLC R_f 0.55 (cyclohexane/EtOAc 60%); IR (neat) ν_{max} 2920, 1740, 1701, 1638, 1216, 1121, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (s, 2H), 2.65 (t, J=6.8 Hz, 4H), 2.50 (t, J=6.4 Hz, 4H), 1.87 (quint, J=6.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 147.4, 101.6, 30.7, 27.3, 18.7; HRMS: calcd for $C_{12}H_{14}LiO_4$ $[M+Li]^+$ 229.1052, found 229.1089.

Acknowledgements

The authors thank the CNRS and the French Ministry of Research for financial support. H.H. thanks the Algerian government for fellowship.

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