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Gold-catalyzed bis-cyclization of 1,2-diol- or acetonide-tethered alkynes. Synthesis of β-lactam-bridged acetals: a combined experimental and theoretical study

Benito Alcaide [a,*], Pedro Almendros [b,*], Rocío Carrascosa [a], Ramón López [c], María I. Menéndez [c]

[a] Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain
[b] Instituto de Química Orgánica General, IQOG, Consejo Superior de Investigaciones Científicas, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
[c] Departamento de Química Física y Analítica, Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Asturias, Spain

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ABSTRACT

2-Azetidinone-tethered alkyn-1,2-diols or alkynyl acetonides, readily prepared from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, were used as starting materials for the regio- and diastereospecific catalytic bis-oxycyclization reaction in the presence of a gold/acid binary system. Interestingly, in contrast to the gold-catalyzed reactions of *N*-tethered terminal alkynes, which lead to the corresponding 6,8-dioxabicyclo[3.2.1]octane derivatives (proximal adduct), the reactions of substituted alkynic diols and acetonides under identical conditions gave the 7,9-dioxabicyclo[4.2.1]nonane derivatives (distal adducts) as the sole products, through exclusive 7-*endo*/5-*exo* bis-oxycyclizations by initial attack of the oxygen atom to the external alkyne carbon. Moreover, the mildness of the method allowed the incorporation of a 1,3-diyne moiety as reactive partner, displaying exquisite chemoselectivity toward the internal alkynic moiety. In order to confirm the mechanistic proposal, labeling studies with deuterium oxide have been performed. Besides, density functional calculations were performed to gain insight into the mechanisms of the bis-oxycyclization reactions.

1. Introduction

β-Lactams are not only the most commonly prescribed antibacterial agents,[1] but also exhibit some other biological activities, for which they are considered as enzyme inhibitors,[2] potential chemo- and neurotherapeutic drugs,[3] and gene activation agents.[4] These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest,[5] provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core. In addition, bridged acetals are structural units that are extensively encountered in a number of biologically active natural products, such as attenol, brevicomin, cyclodidemniserinol, frontalin, multistriatin, and pinnatoxin A,[6] and therefore, their stereocontrolled synthesis remains an intensive research area. On the other hand, alkyne chemistry has attracted considerable attention in recent years.[7] In particular, transition metal-catalyzed intramolecular addition of oxygen nucleophiles across a carbon–carbon triple bond is one of the most rapid and convenient methods for the preparation of oxacycles.[8–10] However, regioselectivity problems may be significant (*endo* vs *exo* cyclization). Following our commitment in β-lactams and the synthetic use of metals,[11] in this paper we report a systematic investigation of the gold-catalyzed cyclization of 1,2-diol- or acetonide-tethered alkynes that establishes a regio- and stereocontrolled versatile route to a variety of enantiopure tricyclic β-lactam-bridged acetals. Depending on the nature of the substituent on the alkyne, two different regioselectivities for the addition reactions are observed.[9e,12a] Moreover, the mechanisms of the bis-oxycyclization reactions have additionally been investigated by a theoretical study.

2. Results and discussion

Fig. 1 shows the structures of cyclization precursors. Precursors for the bridged ketal formation, alkynic 1,2-diols **1a**–**e**, **2a**, and **2b**, dialkynic 1,2-diols **3a**–**d**, alkynic acetonides **4a**–**e**, **5a**, and **5b**, and dialkynic acetonides **6a**–**d**, were made starting from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde. Terminal alkynic acetonides **4a** and **5a** were prepared using the ketene-imine cyclization as we

* Corresponding authors. Tel.: +34 91 3944314; fax: +34 91 3944103 (B.A.); tel.: +34 91 5618806; fax: +34 91 5644853 (P.A.); e-mail addresses: alcaideb@quim.ucm.es (B. Alcaide), Palmendros@iqog.csic.es (P. Almendros).

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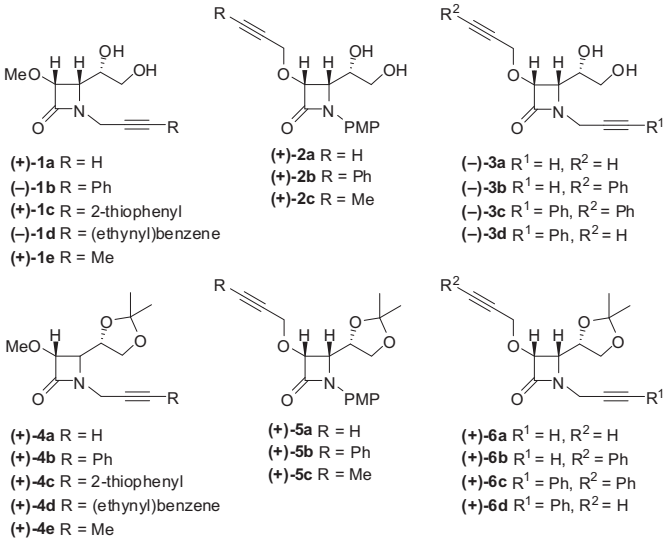
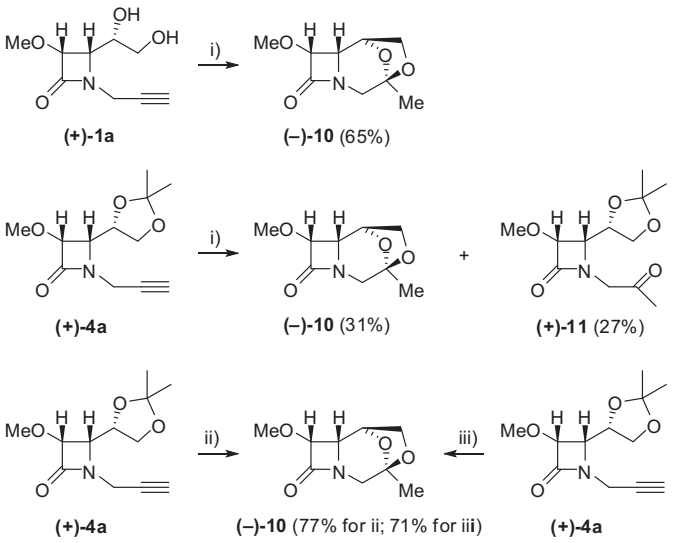


Fig. 1. Structures of alkynic 1,2-diols and alkynic acetonides **1**–**6**. PMP=4-MeOC$_6$H$_4$.

previously described.[13] Terminal alkynes **4a** and **5a** were functionalized as their corresponding aryl alkynes **4b**, **4c**, and **5b** or phenylbuta-1,3-diyne **4d** under Sonogashira or Cadiot–Chodkiewicz conditions (Schemes S1 and S2, see Supplementary data). Methyl-substituted alkynyldioxolane **4e** was prepared through base-promoted *N*-propargylation of the *NH*-β-lactam **7b** with 1-bromobut-2-yne. Starting alkynic acetonide **5c** and dialkynic acetonides **6a**–**d** were prepared from 3-hydroxy-β-lactams **8**[14] using selective transformations of the hydroxylic group together with the Sonogashira protocol (Scheme S3, see Supplementary data). Diols **1**–**3** were prepared from acetonides **4**–**6** through acetonide hydrolysis (Schemes S1–S3, see Supplementary data).

Our investigation began with alkynic diol **1a** as model substrate. Attempts of the cyclization reaction of **1a** using AgOTf, $FeCl_3$, and $[PtCl_2(CH_2{=}CH_2)]_2$ catalysts failed. Nicely, it was found that [AuClPPh$_3$]/AgOTf along with a Brønsted acid (PTSA) at room temperature could be an excellent cooperative catalytic system for this purpose (Scheme 1). However, the conversion to the corresponding tricyclic acetal **10** could not be satisfied with a Lewis acid ($FeCl_3$) in the presence of Au(I)/Ag(I). Taking into account the above success, the more challenging bis-oxycyclization of alkynic acetonide **4a** was tested (Table 1, Scheme 1). To prove this hypothesis, we initially started our investigation by using 2.5 mol % of Au(PPh$_3$)Cl/AgOTf and 10 mol % of PTSA in CH_2Cl_2 at room temperature. To our disappointment, although the reaction gave bridged ketal **10** as the major product, it was obtained together with ketone **11**, arising from alkyne hydration.[15] Gratifyingly, after considerable experimentation, it was found that alkynic acetonide **4a** on exposure to the system [AuClPPh$_3$] (2.5 mol %)/AgOTf (2.5 mol %)/PTSA (10 mol %)/H_2O (100 mol %) in dichloromethane at 80 °C on a sealed tube, directly afforded tricyclic ketal **10** through a regio- and diastereospecific 6-*exo*/5-*exo* bis-oxycyclization (Table 1, Scheme 1). Formation of the undesired ketone **11** was avoided using 100 mol % of water as additive (Scheme 1). Probably, the presence of water favors the hydrolysis of intermediate **25** in the mechanistic proposal of Scheme 6, avoiding alkyne hydration. By contrast to the behavior of alkynic diol **1a**, Brønsted and Lewis acid co-catalysis (PTSA and $FeCl_3$) were equally effective starting from alkynic acetonide **4a**, which may point to two different pathways for the cyclizations of **1a** and **4a**. Besides, the reaction of acetonide **4a** under gold catalysis in the absence of acid additive proceeded to afford the corresponding ketal **10** in just a slightly lower yield (Table 1, Scheme 1). Solvent screening demonstrated that dichloromethane was the best choice in the reaction (Table 1). The use of a more Lewis acidic gold salt ($AuCl_3$) as catalyst alone without PTSA was also tested. Thus, we treated alkynic acetonide **4a** with 5 mol % of $AuCl_3$. However, acetal **10** was obtained in a poor 15% yield.



Scheme 1. Gold catalysis for the bis-cycloetherification of alkynic diol **1a** and alkynic acetonide **4a**. Synthesis of bridged hybrid β-lactam/acetal **10**. Conditions: (i) 2.5 mol % [AuClPPh$_3$], 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, RT, **1a**: 2 h; **4a**: 15 h. (ii) 2.5 mol % [AuClPPh$_3$], 2.5 mol % AgOTf, 10 mol % PTSA or $FeCl_3$, 100 mol % H_2O, CH_2Cl_2, sealed tube, 80 °C, PTSA: 2 h (77% yield); $FeCl_3$: 48 h (50% yield). (iii) 2.5 mol % [AuClPPh$_3$], 2.5 mol % AgOTf, 100 mol % H_2O, CH_2Cl_2, sealed tube, 80 °C, 2 h. PTSA=*p*-Toluenesulfonic acid.

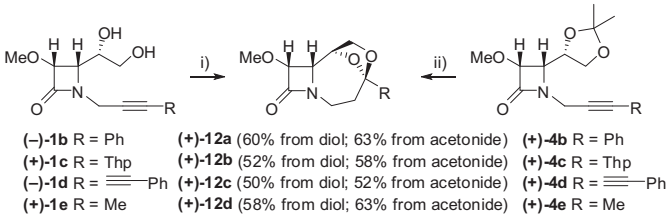
Under the optimized reaction conditions, we investigated the generality of the gold/acid co-catalytic protocol for 1,2-diol- or acetonide-tethered alkynes **1**–**4**. AgOTf cannot be considered a co-catalyst because its action is generally assumed to be restricted to form cationic gold species by anion exchange.[16] The comparative studies of ketals formation with addition of PTSA demonstrated that the presence of the Brønsted acid gives higher yields, acting the acid additive as collaborator but not as a catalyst.[17] Thus, the catalytic system may consist of [Au(OTf)PPh$_3$], generated in situ from [AuClPPh$_3$] and AgOTf. By examining the influence of the R substituents on the alkyne side chain, we found that substrates **1b**–**e** and **4b**–**e** bearing aryl, heteroaryl, alkynyl, or alkyl groups were smoothly transformed into products **12** in reasonable yields (Scheme 2). Worthy of note, in contrast to the gold-catalyzed reactions of terminal alkynic diol **1a** and acetonide **4a**, which lead to the 6,8-dioxabicyclo[3.2.1]octane derivative **10** (proximal adduct), the reactions of substituted alkynic diols **1b**–**e** and acetonides **4b**–**e** under identical conditions gave the 7,9-dioxabicyclo[4.2.1]nonane derivatives **12a**–**d** (distal adducts) as the products, through exclusive 7-*endo*/5-*endo* bis-oxycyclizations by initial attack of the oxygen atom to the external alkyne carbon. Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, some decomposition was observed on sensitive bridged oxacycles **12** during purification by flash chromatography, which may be responsible for the moderate isolated yields. The competition between the initial 6-*exo* and 7-*endo* oxycyclizations is gained by the latter, despite a priori should be energetically more demanding. Thus, the results presented in Schemes 1 and 2 point that there exists a general mode of cyclization, namely the 7-*endo*/5-*endo* bis-oxycyclization, for internal substituted alkynes and the 6-*exo*/5-*endo* mode is preferred for terminal alkynes.[18] The mildness of the method allowed the incorporation of a 1,3-diyne moiety as reactive partner, displaying exquisite chemoselectivity toward the internal alkynic moiety, directing the bis-cycloetherification to

Table 1
Selective bis(cyclization) reaction of alkynic dioxolane **4a** under modified metal-catalyzed conditions[a]

Catalyst (mol %)	Additive (mol %)	Time (h)	Acid (mol %)	*T* (°C)	Solvent	Product	Yield (%)
$[PtCl_2(CH_2{=}CH_2)]_2$ (2.5)	TDMPP (5)	24	—	20	DCM	**10**	—
AgOTf (5)	—	24	—	20	DCM	**10**	—[b]
$FeCl_3$ (10)	—	24	—	20	DCM	**10**	—
$AuCl_3$ (5)	—	14	—	20	DCM	**10**	15
$[AuClPPh_3]$/AgOTf (2.5)	—	15	PTSA (10)	20	DCM	**10**/**11**	31/27
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	2	—	80	DCM	**10**	71
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	48	$FeCl_3$ (10)	80	DCM	**10**	50
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	3	PTSA (10)	80	THF	**10**	64
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	2	PTSA (10)	80	DCE	**10**	75
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	4	PTSA (10)	80	Toluene	**10**	60
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	2	PTSA (10)	80	DCM	**10**	77

PTSA=*p*-Toluenesulfonic acid, TDMPP=tris(2,6 dimethoxyphenyl)phosphine, DCM=dichloromethane, THF=tetrahydrofuran, DCE=1,2-dichloroethane.
[a] Yield of pure, isolated product with correct analytical and spectral data.
[b] Taking into account this result, AgOTf cannot be considered as a co-catalyst because its action is restricted to form the cationic gold species by anion exchange.

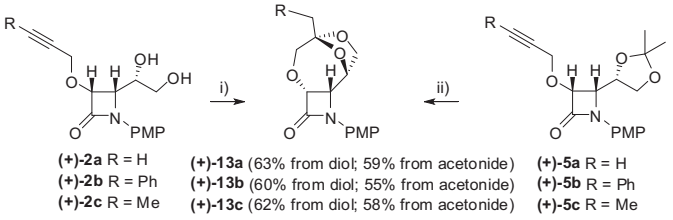
the exclusive formation of tricyclic ketal **12c**. The structure and stereochemistry of the bridged tricycle **12a** were unequivocally established by X-ray crystallographic studies (Fig. S1, see Supplementary data).[19]



Scheme 2. Gold catalysis for the bis-cycloetherification of alkynic diols **1b**–**e** and alkynic acetonides **4b**–**e**. Synthesis of bridged hybrid β-lactam/acetals **12**. Conditions: (i) 2.5 mol % $[AuClPPh_3]$, 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, RT, **1b**: 3 h; **1c**: 3 h; **1d**: 2 h; **1e**: 3 h. (ii) 2.5 mol % $[AuClPPh_3]$, 2.5 mol % AgOTf, 10 mol % PTSA, 100 mol % H_2O, CH_2Cl_2, sealed tube, 80 °C, **4b**: 3 h; **4c**: 3 h; **4d**: 2 h; **4e**: 2 h. PTSA=*p*-Toluenesulfonic acid, Thp=2-thiophenyl.

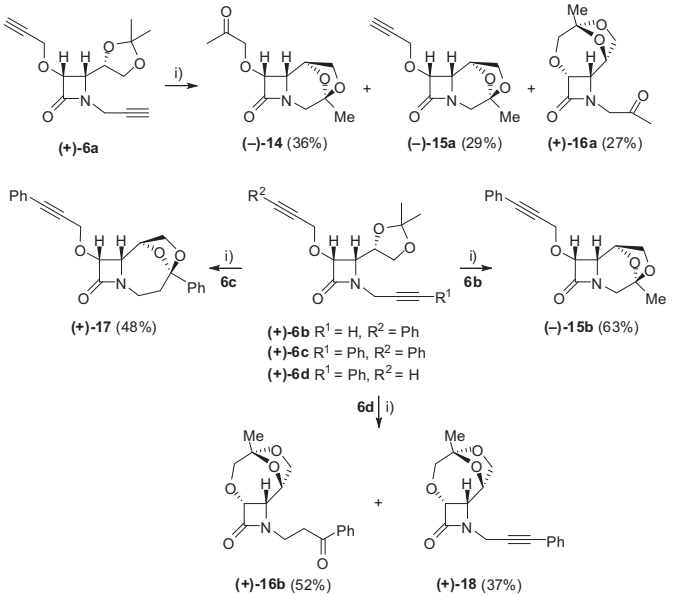
When alkyne substituent was moved from position N1 to C3, as in 3,4-tethered diols **2** and acetonides **5**, they furnished the corresponding bridged ketal systems **13** in fair yields and as only one isomer in their reactions with the gold catalytic system (Scheme 3). Significantly, both substituted and unsubtituted alkynes at the terminal position followed the same regiochemical pattern, yielding proximal adducts as sole bis-cycloetherification reaction products. Although we suspected that the regioselectivity for the substituted alkynic diols **2b** and **2c** and its corresponding dioxolanes **5b** and **5c** would be the same as the previous set of experiments for 1,4-tethered alkynyl derivatives **1** and **4**, we found that in the former case tricyclic acetals **13b** and **13c** (proximal adducts) were obtained as single regio- and diastereomers. Thus, by using a related alkynic diol or acetonide homologue (**2b**, **2c** or **5b**, **5c** vs **1b**, **1e** or **4b**, **4e**), the regioselectivity can be reversed, favoring the 7-*exo*/5-*endo* bis-oxycyclization of the acetonide group toward the internal alkyne carbon (proximal adduct) over the 8-*endo*/5-*endo* bis-oxycyclization toward the external alkyne carbon (distal adduct). The exclusive formation of proximal adducts **13b** and **13c** when the distance between the dioxolane group and the alkyne moiety was increased, would be interpreted by considering the ring size of the intermediates (seven-membered vs eight-membered rings). Probably, the combination of developing ring strain and the requirement to restrict rotations around flexible bonds in the bridged 8,10-dioxabicyclo[5.2.1]decane system ensures unfavorable enthalpic and entropic contributions to ΔG, avoiding its formation.[20]

Upon further exploring the applicability of this bis-cycloetherification reaction, in addition to mono-alkynes, bis-alkynic diols **3** and acetonides **6** were also examined to obtain the



Scheme 3. Gold catalysis for the bis-cycloetherification of alkynic diols **2** and alkynic acetonides **5**. Synthesis of bridged hybrid β-lactam/acetals **13**. Conditions: (i) 2.5 mol % $[AuClPPh_3]$, 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, RT, **2a**: 4 h; **2b**: 5 h; **2c**: 4 h. (ii) 2.5 mol % $[AuClPPh_3]$, 2.5 mol % AgOTf, 10 mol % PTSA, 100 mol % H_2O, CH_2Cl_2, sealed tube, 80 °C, **5a**: 2 h; **5b**: 3 h; **5c**: 3 h. PMP=4-MeOC_6H_4. PTSA=*p*-Toluenesulfonic acid.

corresponding tricyclic acetals, which would be formed by competitive cyclization of the contiguous dioxygenated functionality to one of the two triple bonds catalyzed by gold(I). Thus, we found that the reaction of bis-alkynes **3** and **6** bearing or not phenyl groups at the terminus of the alkyne, also proceeded smoothly to selectively give products **14**–**18** (Scheme 4).[21] During the course of this study, a remarkable substituent effect was discovered: the bis-oxycyclization exclusively occurred at the unsubstituted alkynic



Scheme 4. Gold catalysis for the bis-cycloetherification of bis-alkynic acetonides **6a**–**d**. Synthesis of bridged hybrid β-lactam/acetals **14**–**18**. Conditions: (i) 2.5 mol % $[AuClPPh_3]$, 2.5 mol % AgOTf, 10 mol % PTSA, 100 mol % H_2O, CH_2Cl_2, sealed tube, 80 °C, 3 h. PTSA=*p*-Toluenesulfonic acid.

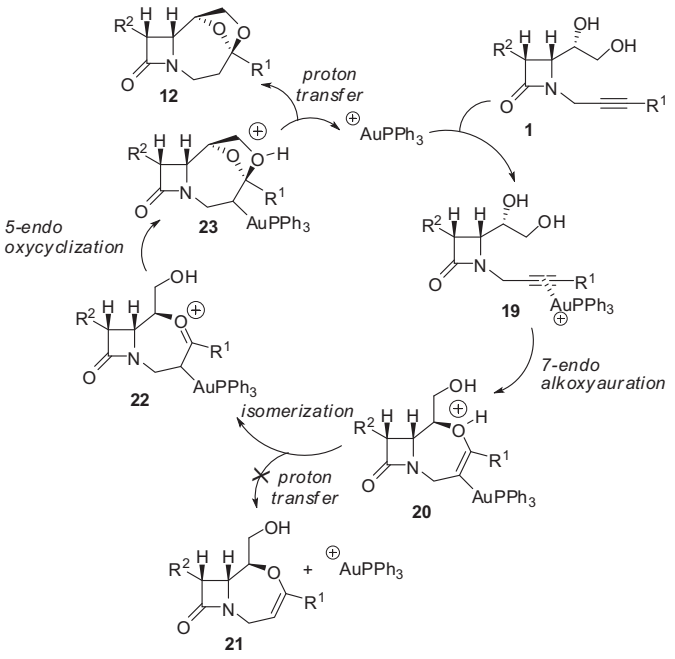
side by treatment of mono-substituted bis-alkynic acetonides **6b** and **6d** under gold/acid co-catalysis. Besides, the bis-hydroalkoxylation of 1,4-tethered bis-alkynic precursors **6b** and **6c** takes place preferentially or solely over the competitive reaction on the corresponding 3,4-tethered moiety. Thus, the chemoselectivity was uniformly high, being possible to direct the tricycle formation by the substitution. In agreement with above results (Schemes 1 and 2), different regioselectivity was observed for non-substituted alkyne **6b** and substituted alkyne **6c**. As can be seen from Scheme 4, tricycles **14**, **16a**, and **16b** bearing a ketonic side-chain were also formed because of further gold-catalyzed hydration of the initially unreacted alkyne moiety.[15] Similar results were obtained using bis-alkynic diols **3a**–**d**.

Bis-cycloetherification of alkynic 1,2-diols **1**–**3**, catalyzed by the gold system was not significantly less effective than was the gold catalysis for the bis-hydroalkoxylation of alkynic acetonides **4**–**6**. Control experiments, however, ruled out the presence of a diol intermediate formed in the gold-catalyzed bis-oxycyclization of alkynic acetonides: diol **1a** did react in dichloromethane at 80 °C on a sealed tube in the presence of [AuClPPh$_3$] (2.5 mol %)/AgOTf (2.5 mol %)/FeCl$_3$ (10 mol %)/H$_2$O (100 mol %) to afford a complex mixture of products, in which the tricyclic acetal **10** was not detected. Besides, no reaction occurred on heating a solution of the above diol in dichloromethane at 80 °C in a sealed tube in the presence of [AuClPPh$_3$] (2.5 mol %)/AgOTf (2.5 mol %)/FeCl$_3$ (10 mol %). The fact that the reaction of acetonide **4a** catalyzed by the π-philic gold complex [Au(OTf)PPh$_3$] alone, in the absence of acid additive, proceeded to afford the corresponding ketal **10**, may also support this order of steps: the acetal attacks the activated alkyne and the resulting oxonium cation then is hydrolyzed.

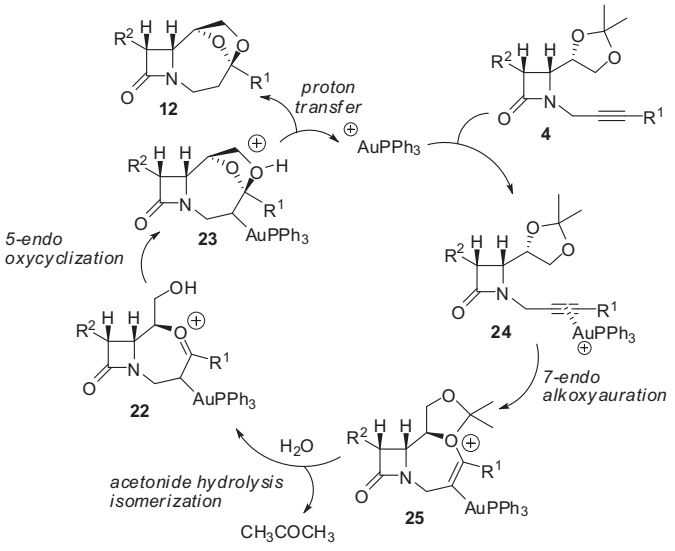
A possible mechanism for the achievement of tricyclic ketals **12** involving a gold-based carbophilic π-acid may proceed through initial η^2-coordination of the metal to the triple bond of alkynic diols **1** leading to intermediates **19**. Next, 7-*endo* alkoxyauration forms intermediates **20**. Vinylmetal species **20** did not evolve through demetalation and proton transfer generating the methylenic oxacycle **21** and releasing the gold catalyst. By contrast, rearrangement of species **20** generates the isomeric metalaoxonium **22**, enhancing the electrophilicity of the unsaturated moiety. Subsequent intramolecular nucleophilic attack of the primary alcohol to the carbonylic-like position from the less hindered face would form complex **23**. Demetalation linked to proton transfer liberates adduct **12** with concomitant regeneration of the Au(I) species (Scheme 5). Triflate assisted proton transfer from intermediates **23** to the final products **12** may also be considered.

A possible pathway for the gold-catalyzed alkynyldioxolane cyclization may initially involve the formation of a π-complex **24** through coordination of the gold salt to the triple bond of alkynyl dioxolanes **1**. Next, 7-*endo* oxymetalation forms enol vinylmetal species **25**. Intermediates **25** did evolve to species **22** through acetonide hydrolysis and further isomerization; thus, enhancing the electrophilicity of the resulting moiety. Subsequent intramolecular nucleophilic attack of the primary alcohol to the electrophilic position would form complex **23**. Demetalation linked to proton transfer liberates adduct **12**,[22] closing the catalytic cycle and releasing the metal catalyst (Scheme 6).

In order to confirm the mechanistic proposal of Scheme 6, we performed labeling studies with deuterium oxide. When alkynyldioxolane **4b** was treated under bis-oxycyclization conditions employing D$_2$O (200 mol %) instead of H$_2$O, adduct **12a** with incorporation of two deuterium atoms at the methylenic group was achieved (Scheme 7). This double deuteration caused both the modification of the peaks at 3.10 and 3.87 ppm, which are the signals of the NC*HH* protons, and the disappearance of the peaks at 1.94 and 2.34 ppm, which are the signals of the NCH$_2$C*HH* protons, on the 7,9-dioxabicyclo[4.2.1]nonane **12a**. Deuterium labeling



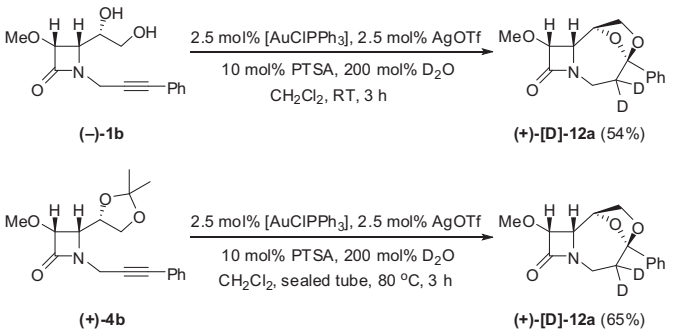
Scheme 5. Mechanistic explanation for the gold-catalyzed bis-cycloetherification of alkynic diols **1**.



Scheme 6. Mechanistic explanation for the gold-catalyzed bis-cycloetherification of alkynic acetonides **4**.

experiment starting from diol **1** was also accomplished, showing a similar trend to, that is, observed starting from acetonide **4** (Scheme 7). The fact that the gold-catalyzed conversion of alkynyldioxolane **4b** into tricycle **12a** in the presence of 2 equiv of D$_2$O afforded double deuterated product [D]-**12a** as judge by ^{1}H NMR spectroscopy and mass spectrometry (see Supplementary data), suggests that deuteration of the double bond in species **25** as well as deuterolysis of the carbon–gold bond in intermediate [D]-**23** have occurred (Scheme S4, see Supplementary data).

Theoretical calculations confirm the mechanistic proposals shown in Schemes 5 and 6 for the gold-catalyzed bis-oxycyclization of 1,2-diol- and acetonide-alkynes (see Computational Methods for details). Figs. 2 and 3 display the Gibbs energy profiles in CH$_2$Cl$_2$ solution for both reactions along with the structure of some relevant intermediates and transition states (TSs), and all the optimized



Scheme 7. Au(I)-catalyzed bis-oxycyclization reactions of alkynyldiol and alkynyldioxolane derivatives **1b** and **4b** in presence of D_2O.

which involves a 1,3-H shift from the oxygen atom to the gold-linked carbon atom of the seven-membered ring, is only energetically accessible thanks to the presence of BSA. When this acid is not present, we located a TS, **TS-20–21′** (49.3 kcal/mol above the intermediate **19**), for a 1,2-H migration from the oxygen atom to the carbon atom bearing the R^1=H substituent. This TS evolves to a minimum energy structure, **21′** (−17.6 kcal/mol relative to isolated reactants), which would not lead to the formation of product **12**. A bis-oxycyclization has happened at **21′**, but the formation of product **12** does not occur because at **21′** both oxygen atoms bond to different C atoms. On the other hand, **21′** is different from structure **21** proposed in Scheme 5. Therefore, our theoretical results clearly show the crucial role played by the Brønsted acid in the bis-oxycyclization of **1**.

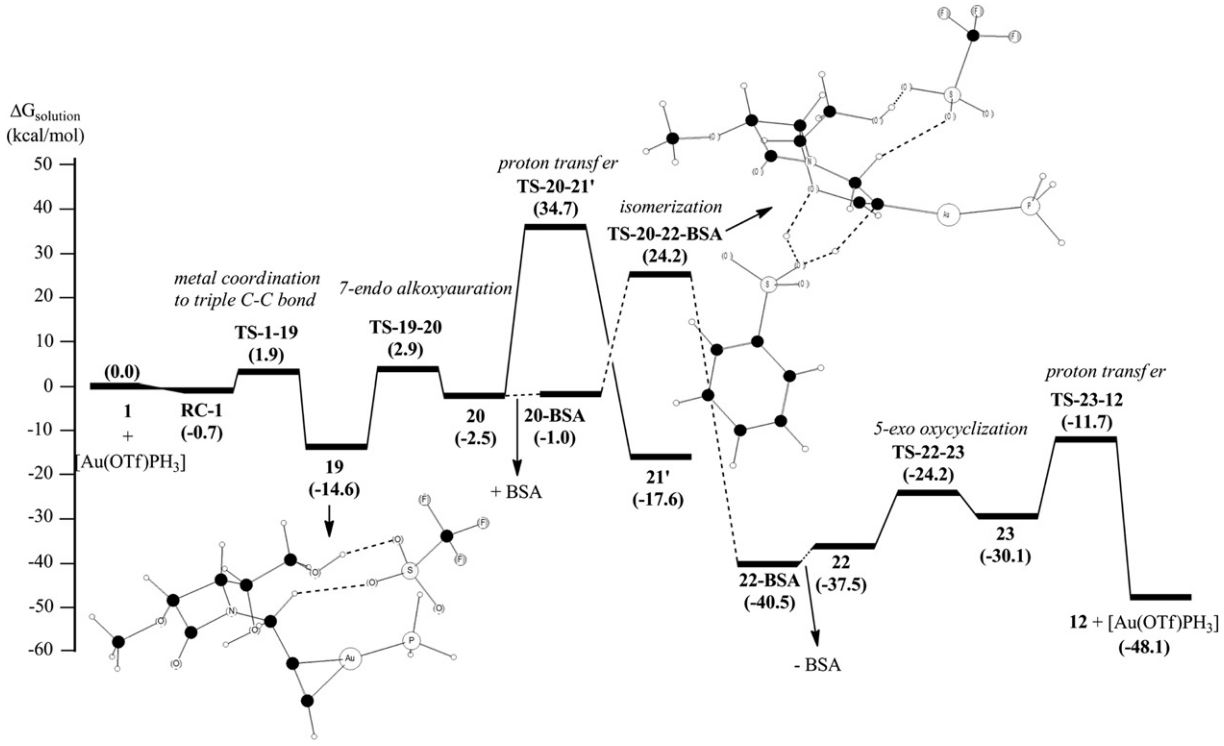


Fig. 2. Gibbs energy profile in CH_2Cl_2 solution obtained for the gold-catalyzed bis-cyclization of the alkynic 1,2-diols **1** at the M06/6−31+G(d) (def2-SVP for Au) theory level. All the energies are referred to the reactants: alkynic 1,2-diol (**1a**)+[Au(OTf)PH_3]+benzenesulfonic acid (BSA).

geometries are collected in the Supplementary data. For the alkynic diol **1**, five reaction steps have been found. The first one, characterized by the TS **TS-1–19** for the Au coordination, presents a small barrier of 1.9 kcal/mol relative to isolated reactants. From this point and along the whole energy profile the triflate anion is clearly separated from the gold(I)-phosphine moiety and from the hot reacting points, so it certainly should not be considered a co-catalyst of the process. At the TSs **TS-19–20** and **TS-22–23** two internal oxycyclizations (7-*endo* and 5-*endo*, respectively) are performed, with energy barriers of 17.5 and 13.3 kcal/mol measured from their corresponding previous intermediates. Opposite to these energetically smooth processes, the most demanding steps are those involving internal rearrangements or proton transfers, **TS-20–22-BSA** and **TS-23–12**, with energy barriers in solution of 38.8 and 28.8 kcal/mol, respectively, from the most stable previous intermediate obtained by us, **19** (14.6 kcal/mol under reactants). **TS-20–22-BSA** corresponds to the rate determining step of the overall reactive process collected in Scheme 5. It is also interesting to note that, **TS-20–22-BSA**, 24.2 kcal/mol above reactants, implies the presence of the Brønsted benzenesulfonic acid (BSA). In effect, according to our theoretical results the passage from **20** to **22**,

For the reaction of alkynic acetonides **4**, the first step is also the gold coordination to the triple C–C bond, characterized by **TS-4–24**, which connects a loose initial complex (2.2 kcal/mol under reactants) with a tighter one (9.8 kcal/mol under reactants). **TS-24–25** performs the first 7-*endo* internal cyclization, with an energy barrier of 13.3 kcal/mol from its previous intermediate, to form the enol vinylmetal species named **25a** in Fig. 3 (1.4 kcal/mol under reactants). Once again the triflate anion is relatively far from both the gold(I)-phosphine moiety and the hot reacting points. No diol intermediates have been theoretically located before the first cyclization along the bis-oxycyclization of **4**,[23] as **24** evolves to the cyclic intermediate **25a**, where one of the C–O bonds in the acetonide ring is elongated. To go step forward along the reaction profile the explicit inclusion of three water molecules is needed, so intermediate **25a** becomes **25b** when those water molecules are added. This addition definitely breaks the acetonide ring and provokes the necessary rearrangements to facilitate the subsequent hydrolysis performed by water molecules. **TS-25–22.1** and **TS-25–22.2** represent the two reaction steps involved in the addition of one water molecule to the system along with the elimination of dimethyl ketone. At **TS-25–22.1** a water molecule is

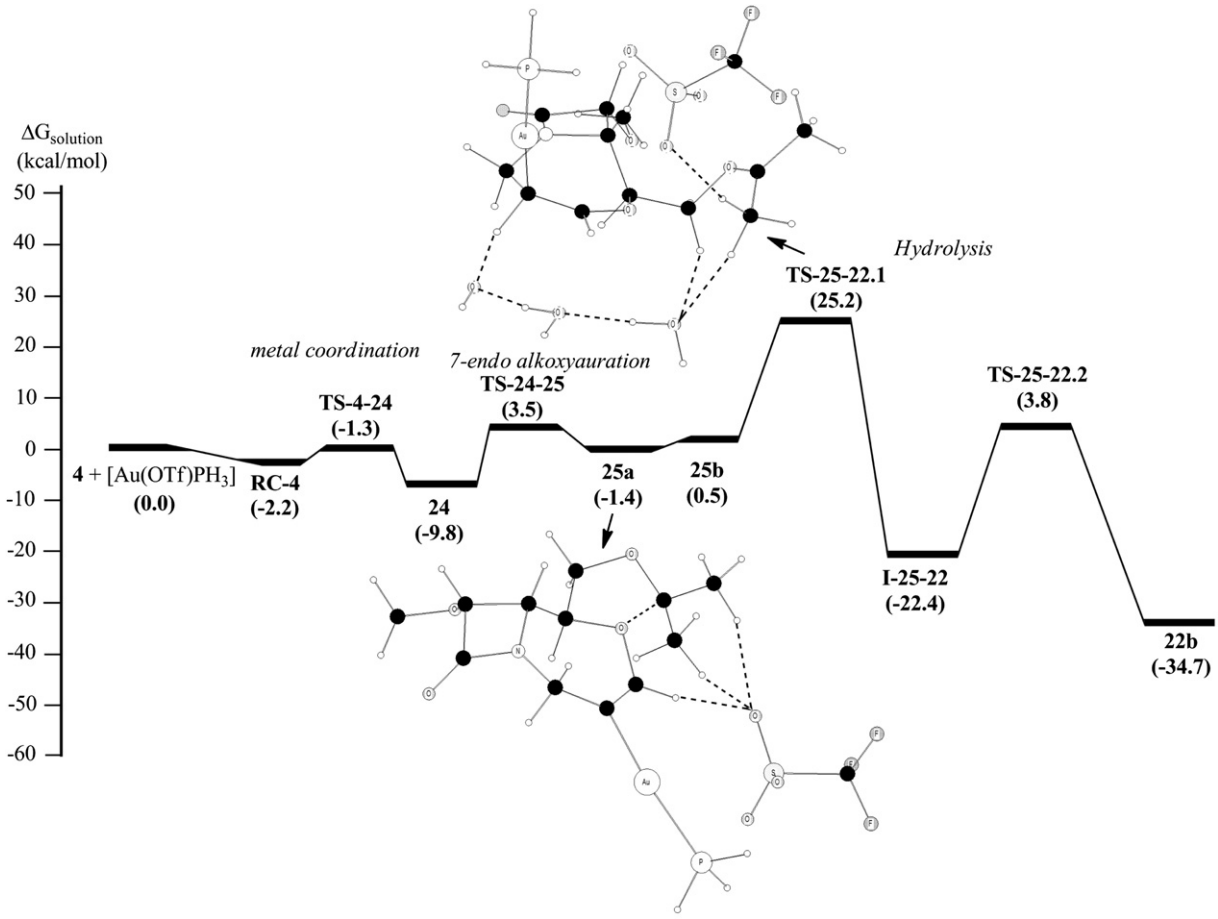


Fig. 3. Gibbs energy profile in CH_2Cl_2 solution obtained for the gold-catalyzed bis-cyclization of the alkynic acetonides **4** at the M06/6–31+G(d) (def2-SVP for Au) theory level. All the energies are referred to the reactants: alkynic acetonide (**4a**)+[Au(OTf)PH_3]+water molecules when necessary.

added to the double bond bearing the gold catalyst and at **TS-25–22.2** an OH^- group bonds to the C atom external to the seven-membered ring, while dimethyl kenote leaves. Between both TSs we located a stable intermediate **I-25–22**, 22.4 kcal/mol under reactants. **TS-25–22.1** and **TS-25–22.2**, are 25.2 and 3.8 kcal/mol over reactants energy, respectively. **TS-25–22.1** corresponds to the rate-limiting step of the overall process shown in Scheme 6 with a value of 35.0 kcal/mol measured from the most stable previous intermediate, **24**. This value is similar to that found for reactant **1**, in accordance with the similar reaction times experimentally observed when **1** is allowed to react in presence of PTSA and **4** in presence of water, as considered in our calculations. **TS-25–22.2** straight yields a water adduct of **22**, **22b** in Fig. 3, without the releasing of the gold catalyst. Eventually, evolution from **22** to the final product **12** goes through the same two final steps as for diol **1**, those described by **TS-22–23** and **TS-23–12**.

3. Conclusions

In conclusion, we have developed efficient catalytic systems based on precious metal salts for the synthesis of a variety of enantiopure tricyclic β-lactam-fused acetals, through regio- and stereocontrolled bis-oxycyclization reactions. The addition of a catalytic amount of PTSA to the gold catalyst improves the cycloketalization acting the acid additive as collaborator. Besides, the mildness of the method allowed the incorporation of a 1,3-diyne moiety as reactive partner, displaying exquisite chemoselectivity toward the internal alkynic moiety. The mechanistic proposal was confirmed by labeling studies with deuterium oxide. Moreover, theoretical calculations are in agreement with the mechanistic explanations.

4. Computational methods

The computational investigation was carried out with the simplified species Au(OTf)PH_3 and benzenesulfonic acid (BSA), which were chosen to mimic the Au(OTf)PPh_3 catalyst and the PTSA Brønsted acid experimentally used, respectively. These simplifications not only minimize the computational time but also make possible computations involving the catalyst and/or the Brønsted acid linked to the alkynic reagents without any significant changes in the obtained theoretical results. In particular, a recent theoretical study on the hydroamination of alkenes catalyzed by gold(I)-phosphine has proved the adequacy of replacing the PPh_3 ligand by the PH_3 one.[24] Besides, the Brønsted acid theoretically employed, BSA, reasonably represents the main features of the experimental one PTSA on the basis of similar p*K*a values.

All the quantum chemical computations were carried out with the Gaussian 09 series of programs.[25] Full geometry optimizations of stable species and TSs were performed in the gas phase by employing the hybrid density functional M06[26] in conjunction with the standard 6–31+G(d) basis set for the non-metal atoms[27] and the def2-SVP pseudopotential for the gold center.[28] This computational scheme is strongly supported by similar theory levels used to investigate related gold-containing systems.[29] Besides, relativistic calculations were done using the Douglas–Kroll–Hess (DKH)

second order scalar relativistic method[30] and the Gaussian nuclear model[31] as implemented in Gaussian 03; finding no significant changes in the relative energies involved in the rate determining energy barrier for the gold-catalyzed bis-cyclization of the alkynic 1,2-diol **1** (see Table S3 in Supplementary data). A similar result could be expected for the acetonide reaction. The nature of the stationary points was verified by analytical harmonic frequency calculations. The intrinsic reaction coordinate (IRC) algorithm was used to check the two minimum energy structures connecting each TS.[32] To take into account condensed-phase effects, single-point calculations were also carried out on the gas-phase optimized geometries using the conductor-like polarizable continuum model (CPCM) with the united atom-Kohm-Sham (UAKS) parametrization.[33] A relative permittivity of 8.93 was assumed in the calculations to simulate dichloromethane as the solvent experimentally used. All energies given in the text correspond to the energy including the effect of the bulk solvent, which was obtained by adding the contribution of the Gibbs energy of solvation to the gas-phase total energies.

5. Experimental section

5.1. General information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in parts per million relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

5.2. Experimental procedures

*5.2.1. Base-promoted reaction between propargylic bromides and hydroxy-β-lactams **8** or **9**. General procedure for the synthesis of propargylic ethers **5c** and **6a–d**.* Tetrabutyl ammonium iodide (31.9 mg, 0.086 mmol), 50% aqueous sodium hydroxide (100 mL), and propargyl bromide, 1-bromobut-2-yne, or (3-bromoprop-1-ynyl)benzene (13.82 mmol), were sequentially added at room temperature to a solution of the appropriate hydroxy-β-lactam **8** or **9** (8.64 mmol) in dichloromethane (100 mL). The reaction was stirred for 15 h and then water was added (50 mL), before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3×50 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures as eluent gave analytically pure compounds **5** or **6**. Spectroscopic and analytical data for some representative forms of **5** or **6** follow.

*5.2.1.1. Propargylic ether (+)-**5c**.* From 253 mg (0.86 mmol) of hydroxy-β-lactam (+)-**8a**, and after chromatography of the residue using ethyl acetate/hexanes (1:2) as eluent gave the propargylic ether (+)-**5c** (240 mg, 81%) as a pale yellow solid. Mp 91–93 °C. $[\alpha]_D$ +18.3 (c 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.62 and 6.83 (d, J=9.0 Hz, each 2H), 4.88 (d, J=5.6 Hz, 1H), 4.36 (s, 3H), 4.25 (dd, J=8.9, 6.8 Hz, 1H), 4.18 (m, 1H), 3.76 (m, 1H), 3.75 (s, 3H), 1.85 (t, J=2.3 Hz, 3H), 1.51 and 1.31 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 164.6, 156.2, 131.0, 119.3, 113.7, 109.5, 83.9, 78.7, 76.9, 73.7, 66.9, 61.6, 59.1, 55.2, 26.5, 24.7, 3.5. IR ($CHCl_3$) ν 1746, 2223 cm^{-1}. HRMS (ESI): calcd for $[C_{19}H_{23}NO_5]^+$ 345.1576, found 345.1571.

*5.2.1.2. Propargylic ether (+)-**6a**.* From 200 mg (0.89 mmol) of hydroxy-β-lactam (−)-**8b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the propargylic ether (+)-**6a** (142 mg, 61%) as a colorless oil. $[\alpha]_D$ +7.5 (c 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.77 (d, J=5.1 Hz, 1H), 4.33 (t, J=2.4 Hz, 2H), 4.29 and 3.86 (dd, J=17.4, 2.5 Hz, each 1H), 4.25 (m, 1H), 4.08 (dd, J=8.9, 6.6 Hz, 1H), 3.80 (m, 1H), 3.71 (dd, J=8.9, 5.0 Hz, 1H), 2.49 (t, J=2.3 Hz, 1H), 2.22 (t, J=2.5 Hz, 1H), 1.42 and 1.29 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.1, 109.6, 79.9, 78.3, 76.6, 76.4, 75.8, 72.1, 66.5, 59.1, 58.4, 30.4, 26.7, 25.0. IR ($CHCl_3$) ν 3310, 1744 cm^{-1}. HRMS (ESI): calcd for $[C_{14}H_{17}NO_4]^+$ 263.1158, found 263.1152.

*5.2.1.3. Propargylic ether (+)-**6b**.* From 134 mg (0.44 mmol) of hydroxy-β-lactam (−)-**9**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the propargylic ether (+)-**6b** (121 mg, 66%) as a yellow oil. $[\alpha]_D$ +7.6 (c 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.34 (m, 2H), 7.28 (m, 3H), 4.84 (d, J=5.3 Hz, 1H), 4.54 and 4.04 (d, J=17.4 Hz, each 1H), 4.53 (s, 2H), 4.31 (m, 1H), 4.10 (dd, J=8.9, 6.6 Hz, 1H), 3.85 and 3.73 (dd, J=9.1, 5.0 Hz, each 1H), 1.42 and 1.28 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.5, 131.7, 131.6, 128.7, 128.4, 128.3, 128.2, 122.4, 122.0, 87.4, 83.8, 83.6, 80.0, 76.7, 66.7, 59.3, 59.2, 31.3, 26.9, 26.1. IR ($CHCl_3$) ν 2190, 1745 cm^{-1}. HRMS (ESI): calcd for $[C_{20}H_{21}NO_4]^+$ 339.1471, found 339.1467.

*5.2.1.4. Propargylic ether (+)-**6c**.* From 99 mg (0.44 mmol) of hydroxy-β-lactam (−)-**8b**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave the propargylic ether (+)-**6c** (96 mg, 64%) as a colorless oil. $[\alpha]_D$ +4.5 (c 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45 (m, 2H), 7.33 (m, 3H), 4.91 (m, 1H), 4.60 (s, 2H), 4.33 (m, 2H), 4.16 (m, 1H), 3.89 (m, 2H), 3.79 (dd, J=8.9, 5.1 Hz, 1H), 2.24 (m, 1H), 1.48 and 1.35 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.5, 131.8, 128.7, 128.3, 122.0, 109.7, 87.4, 83.6, 80.0, 76.8, 76.6, 72.2, 66.7, 59.3, 59.2, 30.5, 26.8, 25.1. IR ($CHCl_3$) ν 3305, 2194, 1745 cm^{-1}. HRMS (ESI): calcd for $[C_{26}H_{25}NO_4]^+$ 415.1784, found 415.1788.

*5.2.1.5. Propargylic ether (+)-**6d**.* From 114 mg (0.38 mmol) of hydroxy-β-lactam (−)-**9**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the propargylic ether (+)-**6d** (71 mg, 55%) as a yellow oil. $[\alpha]_D$ +5.1 (c 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.33 (m, 2H), 7.22 (m, 3H), 4.77 (d, J=5.3 Hz, 1H), 4.53 and 4.04 (d, J=17.5 Hz, each 1H), 4.32 (t, J=2.0 Hz, 1H), 4.28 (m, 1H), 4.07 (m, 1H), 3.85 and 3.71 (dd, J=9.1, 5.0 Hz, each 1H), 2.44 (t, J=2.3 Hz, 1H), 1.43 and 1.28 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.3, 131.7, 128.5, 128.2, 122.4, 109.7, 83.9, 82.1, 79.9, 78.4, 76.6, 75.8, 66.6, 59.1, 58.5, 31.4, 27.0, 25.2. IR ($CHCl_3$) ν 3300, 2190, 1742 cm^{-1}. HRMS (ESI): calcd for $[C_{20}H_{21}NO_4]^+$ 339.1471, found 339.1473.

*5.2.2. Palladium-catalyzed reaction between iodoarenes and terminal alkynes (+)-**4a**, (+)-**5a**, and (−)-**8**. General procedure for the synthesis of aryl-substituted alkynes (+)-**4b**, (+)-**4c**, (+)-**5b**, and (−)-**9**.* $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), CuI (3.8 mg, 0.02 mmol), and triethylamine (60.6 mg, 0.6 mmol) were sequentially added to a solution of the corresponding terminal alkyne **4**, **5**, or **8** (1.0 mmol) and the appropriate iodoarene (1.0 mmol) in acetonitrile (0.8 mL), under argon atmosphere. The reaction mixture was stirred at room temperature. After completion of the reaction as indicated by TLC, the mixture was poured into water (5 mL) and extracted with ethyl acetate (3×5 mL). The organic layer was washed with water (2×10 mL) and brine (2×0 mL), dried over

$MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure aryl-substituted alkynes **4**, **5**, and **9**.

*5.2.2.1. Phenyl-substituted alkyne (+)-**4b**.* From 261 mg (1.09 mmol) of terminal alkyne (+)-**4a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the phenylprop-2-ynyl dioxolane (+)-**4b** (235 mg, 68%) as a pale yellow solid. Mp 83–85 °C. $[\alpha]_D$ +2.3 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.33 (m, 5H), 4.59 and 4.09 (d, *J*=17.3 Hz, each 1H), 4.45 (d, *J*=5.1 Hz, 1H), 4.33 (ddd, *J*=11.5, 6.6, 4.9 Hz, 1H), 4.10 (dd, *J*=8.8, 6.6 Hz, 1H), 3.85 and 3.70 (dd, *J*=9.0, 5.0 Hz, each 1H), 3.52 (s, 3H), 1.48 and 1.34 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.7, 131.6, 128.4, 128.2, 122.4, 109.6, 83.8, 83.1, 82.2, 76.7, 66.6, 59.2, 59.1, 31.2, 26.9, 25.1. IR ($CHCl_3$) ν 1745, 2220 cm^{-1}. HRMS (ESI): calcd for $[C_{18}H_{21}NO_4]^+$ 315.1471, found 315.1468.

*5.2.2.2. 2-Thiophenyl-substituted alkyne (+)-**4c**.* From 250 mg (1.05 mmol) of terminal alkyne (+)-**4a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the 2-thiophenylprop-2-ynyl dioxolane (+)-**4c** (266 mg, 79%) as a pale orange solid. Mp 122–124 °C. $[\alpha]_D$ +1.3 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.21 (dd, *J*=5.1, 1.0 Hz, 1H), 7.15 (dd, *J*=3.7, 1.0 Hz, 1H), 6.92 (dd, *J*=5.1, 3.7 Hz, 1H), 4.58 and 4.09 (d, *J*=17.5 Hz, each 1H), 4.44 (d, *J*=5.1 Hz, 1H), 4.30 (m, 1H), 4.10 (m, 1H), 3.82 and 3.68 (dd, *J*=9.0, 5.1 Hz, each 1H), 3.50 (s, 3H), 1.48 and 1.32 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.6, 132.2, 127.2, 126.8, 122.3, 109.6, 86.2, 83.0, 77.1, 76.6, 66.5, 59.2, 59.1, 31.3, 26.9, 25.1. IR ($CHCl_3$) ν 1744, 2225 cm^{-1}. HRMS (ESI): calcd for $[C_{16}H_{19}NO_4S]^+$ 321.1035, found 321.1029.

*5.2.2.3. Phenyl-substituted alkyne (+)-**5b**.* From 64 mg (0.19 mmol) of terminal alkyne (+)-**5a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave the phenylprop-2-ynyl dioxolane (+)-**5b** (65 mg, 84%) as a yellow oil. $[\alpha]_D$ +8.2 (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.67 and 6.86 (d, *J*=9.0 Hz, each 2H), 7.33 (m, 3H), 5.00 (d, *J*=5.6 Hz, 1H), 4.68 (s, 2H), 4.29 (m, 3H), 3.84 (dd, *J*=8.6, 5.9 Hz, 1H), 3.78 (s, 3H), 1.53 and 1.34 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 164.6, 156.5, 131.8, 131.0, 128.8, 128.3, 119.5, 113.9, 109.7, 87.5, 83.5, 79.0, 77.6, 67.0, 61.8, 59.4, 55.3, 26.7, 24.9. IR ($CHCl_3$) ν 1743, 2222 cm^{-1}. HRMS (ESI): calcd for $[C_{24}H_{25}NO_5]^+$ 407.1733, found 407.1726.

*5.2.2.4. Phenyl-substituted alkyne (−)-**9**.* From 338 mg (1.50 mmol) of terminal alkyne (−)-**8**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave the phenylprop-2-ynyl dioxolane (−)-**9** (261 mg, 58%) as a yellow solid. Mp 144–142 °C. $[\alpha]_D$ −4.3 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.33 (m, 2H), 7.22 (m, 3H), 4.85 (m, 2H), 4.53 and 4.03 (d, *J*=17.5 Hz, each 1H), 4.36 (td, *J*=6.9, 4.5 Hz, 1H), 4.13 (dd, *J*=9.0, 6.9 Hz, 1H), 3.85 (m, 2H), 1.42 and 1.28 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 169.4, 131.6, 128.5, 128.2, 122.2, 109.9, 84.2, 81.7, 75.7, 66.5, 60.2, 31.3, 26.7, 25.0. IR ($CHCl_3$) ν 1742, 2224 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{19}NO_4]^+$ 301.1314, found 301.1310.

5.3. Procedure for the preparation of methyl-substituted alkyne (+)-4e

A solution of the *NH*-β-lactam (+)-(3*R*,4*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-methoxyazetidin-2-one[34] (179 mg, 0.89 mmol) in THF (2 mL) was slowly added to a suspension of sodium hydride (38 mg, 1.98 mmol) in the same solvent (10 mL) at 0 °C. After 1 h stirring at room temperature, the solution was cooled at 0 °C and 1-bromobut-2-yne (131 mg, 0.99 mmol) was added. The reaction was stirred for 12 h and then $NaHCO_3$ (aq satd) was added (1 mL), before being partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (3×10 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes (1:2) as eluent gave 113 mg (50%) of analytically pure compound (+)-**4e** as a pale yellow solid. Mp 133–134 °C. $[\alpha]_D$ +21.4 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.39 (d, *J*=5.1 Hz, 1H), 4.26 (m, 2H), 4.06 (dd, *J*=8.8, 6.6 Hz, 1H), 3.77 (m, 2H), 3.65 (dd, *J*=8.8, 5.1 Hz, 1H), 3.49 (s, 3H), 1.75 (t, *J*=2.4 Hz, 3H), 1.48 and 1.30 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.6, 109.5, 82.9, 79.7, 76.7, 72.1, 66.6, 59.0, 30.8, 26.8, 25.1, 3.2. IR ($CHCl_3$) ν 1744, 2224 cm^{-1}. HRMS (ESI): calcd for $[C_{13}H_{19}NO_4]^+$ 253.1314, found 253.1314.

5.4. Procedure for the synthesis of bromoalkynyl-β-lactam (+)-7a

To a solution of the alkynyl 2-azetidinone (+)-**4a** (0.37 mmol) in acetone (2.5 mL) were added NBS (0.094 g, 0.46 mmol) and silver acetate (0.019 g, 0.11 mmol). The reaction mixture was stirred at room temperature in the dark until disappearance (TLC) of the starting material. The solids were removed by filtration through a Celite pad (washing with ethyl acetate). The combined organic filtrates were washed with water and brine, dried (Na_2SO_4), concentrated under reduced pressure, and then purified by column chromatography eluting with ethyl acetate/hexanes (3/1) to give 95 mg (81%) of analytically pure bromoalkynyl-β-lactam (+)-**7a** as a pale yellow oil.

*5.4.1. Bromoalkynyl-β-lactam (+)-**7a**.* $[\alpha]_D$ +28.2 (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.46 (d, *J*=5.1 Hz, 2H), 4.38 and 3.92 (d, *J*=17.3 Hz, each 1H), 4.30 (m, 1H), 4.11 (dd, *J*=8.8, 6.5 Hz, 1H), 3.80 and 3.70 (dd, *J*=9.0, 5.0 Hz, each 1H), 3.53 (s, 3H), 1.48 and 1.35 (s, each 6H). ^{13}C NMR ($CDCl_3$) δ 166.7, 109.7, 83.1, 76.6, 73.3, 66.7, 59.5, 59.2, 43.7, 31.5, 26.9, 25.1. IR ($CHCl_3$) ν 1742 cm^{-1}. HRMS (ESI): calcd for $[C_{12}H_{16}BrNO_4]^+$ 317.0263, found 317.0270.

5.5. Copper(I) chloride promoted heterocoupling reaction between 2-azetidinone-tethered alkyne (+)-7a and phenylacetylene. Procedure for the synthesis of 1,3-diyne-β-lactam (+)-4d

Few crystals of hydroxylamine hydrochloride, a 70% $EtNH_2$ (0.25 mL) aqueous solution, and CuCl (0.006 mmol, 0.002 equiv) were sequentially added at room temperature to a solution of the alkynyl 2-azetidinone (+)-**7a** (0.36 mmol) in methanol (1.8 mL). Then, phenylacetylene (0.36 mmol) in CH_2Cl_2 (5 mL) was added to the above acetylide suspension cooled at 0 °C. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. The reaction mixture was stirred until disappearance (TLC) of the starting materials. The products were extracted with ethyl acetate (3×5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography eluting with ethyl acetate/hexanes (1/3) to give 118 mg (97%) of analytically pure 1,3-diyne-β-lactam (+)-**4d** as a pale yellow oil.

*5.5.1. 1,3-Diyne-β-lactam (+)-**4d**.* $[\alpha]_D$ +0.78 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.49 (m, 2H), 7.35 (m, 3H), 4.54 and 4.06 (d, *J*=18.0 Hz, each 1H), 4.49 (d, *J*=5.1 Hz, 1H), 4.33 (m, 1H), 4.13 (dd, *J*=9.0, 6.6 Hz, 1H), 3.86 and 3.72 (dd, *J*=9.0, 5.1 Hz, each 1H), 3.55 (s, 3H), 1.52 and 1.37 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.7, 132.6, 129.3, 128.4, 121.3, 109.8, 83.2, 77.3, 76.6, 75.9, 73.3,

68.7, 66.6, 59.5, 59.2, 31.4, 26.9, 25.2. IR ($CHCl_3$) ν 1743, 2195 cm^{-1}. HRMS (ESI): calcd for $[C_{20}H_{21}NO_4]^+$ 339.1471, found 339.1466.

5.6. General procedure for the preparation of 2-azetidinone-tethered alkynic diols 1a–e, 2a, 2b, and 3a–d

To a solution of the corresponding acetonide β-lactam (10 mmol) in THF/water (1:1, 200 mL) was added solid *p*-TsOH·H_2O (12 mmol) in a single portion. The resulting clear solution was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature, and then was neutralized with solid $NaHCO_3$. The mixture was extracted with ethyl acetate (3×40 mL), the organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give diols **1**–**3**. Further purification was not necessary. Spectroscopic and analytical data for some representative forms of **1**–**3** follow.

*5.6.1. Alkynic diol (+)-**1a**.* From 220 mg (0.92 mmol) of dioxolane (+)-**4a**, diol (+)-**1a** (183 mg, quantitative yield) was obtained as a yellow oil. $[\alpha]_D$ +0.2 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.52 (d, *J*=4.9 Hz, 1H), 4.36 (dd, *J*=17.5, 2.5 Hz, 1H), 4.00 (m, 2H), 3.92 (m, 2H), 3.70 (m, 2H), 3.60 (s, 3H), 3.07 and 2.59 (br s, each 1H), 2.31 (t, *J*=2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 167.0, 83.3, 72.8, 70.8, 63.9, 59.5, 58.1, 31.0. IR ($CHCl_3$) ν 3450, 1744, 2180 cm^{-1}. HRMS (ESI): calcd for $[C_9H_{13}NO_4]^+$ 199.0845, found 199.0851.

*5.6.2. Alkynic diol (−)-**1b**.* From 199 mg (0.59 mmol) of dioxolane (+)-**4b**, diol (−)-**1b** (162 mg, quantitative yield) was obtained as colorless solid. Mp 102–104 °C. $[\alpha]_D$ −0.4 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.34 (m, 5H), 4.55 and 4.14 (d, *J*=18.0 Hz, each 1H), 4.49 (d, *J*=4.9 Hz, 1H), 4.01 (m, 1H), 3.96 (dd, *J*=9.5, 4.6 Hz, 1H), 3.71 (m, 2H), 3.57 (s, 3H), 3.21 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 167.1, 131.7, 128.6, 128.3, 122.0, 84.5, 83.3, 81.9, 70.9, 63.9, 59.4, 58.0, 31.8. IR ($CHCl_3$) ν 3445, 1742, 2185 cm^{-1}. HRMS (ESI): calcd for $[C_{15}H_{17}NO_4]^+$ 275.1158, found 275.1162.

*5.6.3. Alkynic diol (+)-**1c**.* From 141 mg (0.44 mmol) of dioxolane (+)-**4c**, diol (+)-**1c** (124 mg, quantitative yield) was obtained as yellow oil. $[\alpha]_D$ +2.3 (*c* 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.22 (dd, *J*=5.1, 1.0 Hz, 1H), 7.18 (dd, *J*=3.7, 1.0 Hz, 1H), 6.93 (dd, *J*=5.1, 3.7 Hz, 1H), 4.57 and 4.15 (d, *J*=17.8 Hz, each 1H), 4.49 (d, *J*=4.9 Hz, 1H), 3.99 (m, 1H), 3.92 (t, *J*=4.9 Hz, 1H), 3.69 (m, 2H), 3.56 (s, 3H), 3.20 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 167.1, 132.5, 127.4, 126.9, 121.9, 86.0, 83.3, 77.7, 71.0, 63.9, 59.4, 58.0, 31.9. IR ($CHCl_3$) ν 3440, 1744, 2180 cm^{-1}. HRMS (ESI): calcd for $[C_{13}H_{15}NO_4S]^+$ 281.0722, found 281.0717.

*5.6.4. Alkynic diol (−)-**1d**.* From 55 mg (0.16 mmol) of dioxolane (+)-**4d**, diol (−)-**1d** (48 mg, quantitative yield) was obtained as yellow oil. $[\alpha]_D$ −1.9 (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.50 (m, 2H), 7.34 (m, 3H), 4.57 (d, *J*=5.1 Hz, 1H), 4.55 and 4.12 (d, *J*=12.2 Hz, each 1H), 4.05 (m, 1H), 3.98 (m, 1H), 3.82 (m, 1H), 3.73 (dd, *J*=6.0, 4.7 Hz, 1H), 3.63 (s, 3H), 2.89 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.8, 132.6, 129.5, 128.4, 83.6, 77.7, 75.5, 73.1, 70.6, 69.2, 64.0, 59.6, 58.3, 32.0. IR ($CHCl_3$) ν 3450, 1743, 2175 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{17}NO_4]^+$ 299.1158, found 299.1166.

*5.6.5. Alkynic diol (+)-**1e**.* From 66 mg (0.16 mmol) of dioxolane (+)-**4e**, diol (+)-**1e** (55 mg, quantitative yield) was obtained as colorless oil. $[\alpha]_D$ +4.6 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.48 (d, *J*=5.1 Hz, 1H), 4.25 and 3.87 (dq, *J*=17.4, 2.3 Hz, each 1H), 3.98 (m, 1H), 3.88 (t, *J*=5.0 Hz, 1H), 3.68 (m, 2H), 3.57 (s, 3H), 3.16 and 2.78 (br s, each 1H), 1.79 (t, *J*=2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 167.0, 83.2, 80.7, 72.0, 71.0, 63.9, 59.4, 58.0, 31.4, 3.3. IR ($CHCl_3$) ν 3454, 1745, 2215 cm^{-1}. HRMS (ESI): calcd for $[C_{10}H_{15}NO_4]^+$ 213.1001, found 213.1009.

*5.6.6. Alkynic diol (+)-**2a**.* From 266 mg (0.80 mmol) of dioxolane (+)-**5a**, diol (+)-**2a** (233 mg, quantitative yield) was obtained as yellow oil. $[\alpha]_D$ +1.0 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.37 and 6.80 (d, *J*=9.0 Hz, each 2H), 4.89 (d, *J*=5.4 Hz, 1H), 4.42 (m, 2H), 4.35 (m, 1H), 4.08 (m, 2H), 3.72 (s, 3H), 3.60 (d, *J*=5.6 Hz, 1H), 3.34 (br s, 2H), 2.57 (t, *J*=2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 164.8, 156.6, 130.6, 119.9, 114.0, 79.5, 78.3, 76.4, 76.3, 71.3, 63.4, 58.9, 55.3. IR ($CHCl_3$) ν 3442, 1744, 2172 cm^{-1}. HRMS (ESI): calcd for $[C_{15}H_{17}NO_5]^+$ 291.1107, found 291.1110.

*5.6.7. Alkynic diol (+)-**2b**.* From 162 mg (0.40 mmol) of dioxolane (+)-**5b**, diol (+)-**2b** (147 mg, quantitative yield) was obtained as colorless oil. $[\alpha]_D$ +14.9 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.39 (m, 7H), 6.82 (d, *J*=9.0 Hz, 2H), 4.99 (d, *J*=5.4 Hz, 1H), 4.66 (d, *J*=2.0 Hz, 2H), 4.39 (t, *J*=4.9 Hz, 1H), 4.17 (m, 1H), 3.73 (s, 3H), 3.65 (d, *J*=5.9 Hz, 2H), 2.96 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 164.9, 156.6, 131.7, 130.7, 128.8, 128.3, 121.8, 120.0, 114.1, 87.8, 83.4, 79.7, 71.4, 63.5, 59.8, 58.4, 55.3. IR ($CHCl_3$) ν 3435, 1745, 2175 cm^{-1}. HRMS (ESI): calcd for $[C_{21}H_{21}NO_5]^+$ 367.1420, found 367.1414.

*5.6.8. Alkynic diol (+)-**2c**.* From 120 mg (0.35 mmol) of dioxolane (+)-**5c**, diol (+)-**2c** (107 mg, quantitative yield) was obtained as colorless oil. $[\alpha]_D$ +36.9 (*c* 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.38 and 6.83 (d, *J*=9.0 Hz, each 2H), 4.96 (d, *J*=5.4 Hz, 1H), 4.42 (m, 3H), 4.18 (m, 1H), 3.76 (s, 3H), 3.75 (m, 1H), 3.64 (d, *J*=6.1 Hz, 1H), 3.12 and 2.68 (br s, each 1H), 1.87 (t, *J*=2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 165.0, 156.6, 130.7, 119.9, 114.1, 84.6, 79.5, 73.7, 71.3, 63.5, 59.7, 58.3, 55.4, 3.6. IR ($CHCl_3$) ν 3435, 1745, 2175 cm^{-1}. HRMS (ESI): calcd for $[C_{16}H_{19}NO_5]^+$ 305.1263, found 305.1257.

*5.6.9. Alkynic diol (−)-**3a**.* From 56 mg (0.21 mmol) of dioxolane (+)-**6a**, diol (−)-**3a** (47 mg, quantitative yield) was obtained as yellow oil. $[\alpha]_D$ −5.5 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.85 (d, *J*=5.0 Hz, 1H), 4.44 (ddd, *J*=23.2, 16.0, 2.3 Hz, 2H), 4.34 (dd, *J*=13.0, 2.5 Hz, 1H), 4.05 (m, 1H), 3.97 (m, 2H), 3.78 (dd, *J*=11.5, 3.7 Hz, 1H), 3.67 (dd, *J*=11.5, 6.1 Hz, 1H), 3.13 and 2.75 (br s, each 1H), 2.55 (t, *J*=2.3 Hz, 1H), 2.32 (t, *J*=2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.6, 80.4, 78.2, 76.8, 76.2, 72.9, 70.9, 63.8, 58.8, 58.2, 30.4, 31.2. IR ($CHCl_3$) ν 3440, 3315, 1745 cm^{-1}. HRMS (ESI): calcd for $[C_{11}H_{13}NO_4]^+$ 223.0845, found 223.0852.

*5.6.10. Alkynic diol (−)-**3b**.* From 32 mg (0.078 mmol) of dioxolane (+)-**6b**, diol (−)-**3b** (29 mg, quantitative yield) was obtained as colorless oil. $[\alpha]_D$ −1.2 (*c* 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45 (m, 4H), 7.33 (m, 6H), 5.00 (d, *J*=5.1 Hz, 1H), 4.73 and 4.66 (d, *J*=16.0 Hz, each 1H), 4.54 and 4.20 (d, *J*=17.0 Hz, each 1H), 4.18 (m, 1H), 4.05 (t, *J*=4.6 Hz, 1H), 3.83 (m, 1H), 2.12 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.6, 131.9, 131.8, 128.9, 128.8, 128.4, 128.3, 122.0, 121.9, 87.9, 84.8, 83.4, 81.8, 80.7, 70.7, 64.0, 59.8, 58.4, 32.0. IR ($CHCl_3$) ν 3434, 2190, 1742 cm^{-1}. HRMS (ESI): calcd for $[C_{23}H_{21}NO_4]^+$ 375.1471, found 375.1468.

*5.6.11. Alkynic diol (−)-**3c**.* From 56 mg (0.17 mmol) of dioxolane (+)-**6c**, diol (−)-**3c** (51 mg, quantitative yield) was obtained as colorless oil; $[\alpha]_D$ −0.4 (*c* 4.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.44 (m, 2H), 7.31 (m, 3H), 4.94 (d, *J*=5.0 Hz, 1H), 4.69 and 4.62 (d, *J*=16.0 Hz, each 1H), 4.37 and 3.97 (dd, *J*=17.7, 2.5 Hz, each 1H), 4.11 (m, 1H), 3.96 (t, *J*=5.0 Hz, 1H), 3.81 (dd, *J*=11.4, 3.8 Hz, 1H), 3.71 (dd, *J*=11.4, 6.2 Hz, 1H), 2.74 (br s, 2H), 2.32 (t, *J*=2.5 Hz, 1H). ^{13}C

NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.8, 131.8, 128.9, 128.4, 121.9, 87.8, 83.4, 80.5, 77.2, 76.8, 72.9, 70.8, 63.9, 59.7, 58.3, 31.1. IR ($CHCl_3$) ν 3442, 3300, 2192, 1740 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{17}NO_4]^+$ 299.1158, found 299.1162.

*5.6.12. Alkynic diol (−)-**3d**.* From 30 mg (0.088 mmol) of dioxolane (+)-**6d**, diol (−)-**3d** (26 mg, quantitative yield) was obtained as colorless oil. $[\alpha]_D$ −1.2 (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.43 (m, 2H), 7.32 (m, 3H), 4.90 (d, *J*=5.0 Hz, 1H), 4.57 and 4.19 (d, *J*=17.7 Hz, each 1H), 4.43 and 4.50 (dd, *J*=16.0, 2.3 Hz, each 1H), 4.12 (m, 1H), 4.03 (t, *J*=5.0 Hz, 1H), 3.83 (dd, *J*=11.4, 4.0 Hz, 1H), 3.77 (dd, *J*=11.4, 6.3 Hz, 1H), 2.54 (t, *J*=2.3 Hz, 1H), 2.18 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.4, 131.8, 128.8, 128.4, 122.0, 84.7, 81.8, 80.6, 78.2, 76.2, 70.7, 64.0, 58.9, 58.2, 32.0. IR ($CHCl_3$) ν 3450, 3294, 2190, 1743 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{17}NO_4]^+$ 299.1158, found 299.1152.

5.7. General procedure for the metal-catalyzed cyclization of alkynyl dioxolanes 4−6 in the presence of water. Preparation of bridged acetals 10, and 12−18

$[AuClPPh_3]$ (0.0093 mmol), AgOTf (0.0093 mmol), *p*-toluenesulfonic acid or $FeCl_3$ (0.037 mmol), and water (0.37 mmol) were sequentially added to a stirred solution of the corresponding alkynyldioxolane **4**–**6** (0.37 mmol) in dichloromethane (0.37 mL). The resulting mixture was heated in a sealed tube at 80 °C until disappearance of the starting material (TLC). The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate was extracted with ethyl acetate (3×5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **10**, and **12**–**18**.

*5.7.1. Tricyclic acetal (−)-**10**.* From 70 mg (0.29 mmol) of alkynyldioxolane (+)-**4a**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave the acetal (−)-**10** (45 mg, 77%) as a colorless oil. $[\alpha]_D$ −1.3 (*c* 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.79 and 4.66 (dd, *J*=4.8, 1.2 Hz, each 1H), 3.84 (m, 3H), 3.65 (s, 3H), 3.53 (m, 1H), 2.98 (dt, *J*=12.9, 0.6 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.8, 104.5, 83.9, 71.0, 69.1, 59.3, 55.4, 51.5, 22.9. IR ($CHCl_3$) ν 1750, 1192, 1042 cm^{-1}. HRMS (ESI): calcd for $[C_9H_{13}NO_4+H]^+$ 200.0923, found 200.0927.

*5.7.2. Tricyclic acetal (+)-**12a**.* From 49 mg (0.16 mmol) of alkynyldioxolane (+)-**4b**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave the acetal (+)-**12a** (26 mg, 63%) as a colorless solid. Mp 150–152 °C. $[\alpha]_D$ +5.0 (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.44 (m, 5H), 4.66 and 4.57 (d, *J*=4.8 Hz, each 1H), 4.09 (m, 1H), 4.01 (dd, *J*=8.1, 4.9 Hz, 1H), 3.87 (ddd, *J*=14.4, 5.4, 1.5 Hz, 1H), 3.79 (d, *J*=4.6 Hz, 1H), 3.63 (s, 3H), 3.10 (ddd, *J*=14.6, 12.0, 4.2 Hz, 1H), 2.34 (ddd, *J*=14.4, 12.2, 5.4 Hz, 1H), 1.94 (ddd, *J*=14.4, 3.9, 1.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 168.2, 142.5, 128.2, 128.1, 124.7, 111.8, 83.5, 72.2, 71.2, 63.0, 59.2, 38.6, 36.5. IR ($CHCl_3$) ν 1748, 1190, 1044 cm^{-1}. HRMS (ESI): calcd for $[C_{15}H_{17}NO_4+H]^+$ 276.1236, found 276.1232.

*5.7.3. Tricyclic acetal (+)-**12b**.* From 118 mg (0.37 mmol) of alkynyldioxolane (+)-**4c**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave the acetal (+)-**12b** (60 mg, 58%) as a colorless solid. Mp 101–103 °C. $[\alpha]_D$ +5.4 (*c* 3.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.23 (dd, *J*=5.0, 1.2 Hz, 1H), 7.09 (dd, *J*=3.7, 1.2 Hz, 1H), 6.95 (dd, *J*=5.0, 3.7 Hz, 1H), 4.72 (d, *J*=5.1 Hz, 1H), 4.55 and 3.77 (d, *J*=4.7 Hz, each 1H), 4.19 (dd, *J*=8.0, 5.1 Hz, 1H), 4.08 (m, 1H), 3.89 (ddd, *J*=14.4, 5.4, 1.2 Hz, 1H), 3.61 (s, 3H), 3.09 (ddd, *J*=14.5, 12.2, 3.9 Hz, 1H), 2.48 (ddd, *J*=14.5, 12.2, 5.4 Hz, 1H), 2.22 (dd, *J*=14.5, 2.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 168.1, 146.0, 126.9, 125.2, 124.2, 109.8, 83.4, 72.5, 71.3, 62.7, 59.3, 37.3, 36.3. IR ($CHCl_3$) ν 1746, 1192, 1045 cm^{-1}. HRMS (ESI): calcd for $[C_{13}H_{15}NO_4S+Na]^+$ 304.0619, found 304.0614.

*5.7.4. Tricyclic acetal (+)-**12c**.* From 104 mg (0.31 mmol) of alkynyldioxolane (+)-**4d**, and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluent gave the acetal (+)-**12c** (48 mg, 52%) as a pale yellow oil. $[\alpha]_D$ +4.1 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45 (m, 2H), 7.33 (m, 3H), 4.71 (d, *J*=5.1 Hz, 1H), 4.54 and 3.75 (d, *J*=4.5 Hz, each 1H), 4.28 (dd, *J*=8.1, 5.1 Hz, 1H), 4.09 (d, *J*=8.1 Hz, 1H), 3.85 (dd, *J*=14.5, 5.2 Hz, 1H), 3.63 (s, 3H), 3.04 (ddd, *J*=14.5, 12.2, 3.7 Hz, 1H), 2.48 (ddd, *J*=14.5, 12.3, 5.3 Hz, 1H), 2.20 (dd, *J*=14.5, 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 168.0, 131.9, 128.9, 128.2, 121.5, 104.8, 86.4, 84.2, 83.5, 72.3, 71.6, 62.6, 59.3, 38.7, 35.9. IR ($CHCl_3$) ν 1745, 1195, 1040 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{17}NO_4+Na]^+$ 322.1055, found 322.1050.

*5.7.5. Tricyclic acetal (+)-**12d**.* From 90 mg (0.36 mmol) of alkynyldioxolane (+)-**4e**, and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluent gave the acetal (+)-**12d** (48 mg, 63%) as a colorless solid. Mp 132–134 °C. $[\alpha]_D$ +5.6 (*c* 3.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.55 (d, *J*=5.4 Hz), 4.49 (d, *J*=4.6 Hz), 4.08 (dd, *J*=7.9, 5.6 Hz, 1H), 3.95 (m, 1H), 3.74 (ddd, *J*=14.5, 5.3, 1.3 Hz, 1H), 3.68 (d, *J*=4.6 Hz, 1H), 3.60 (s, 3H), 2.93 (ddd, *J*=14.5, 12.4, 3.6 Hz, 1H), 2.10 (ddd, *J*=14.4, 12.4, 5.4 Hz, 1H), 1.75 (ddd, *J*=14.2, 3.7, 1.3 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 168.2, 111.9, 83.5, 71.9, 70.7, 62.7, 59.4, 37.2, 36.4, 26.5. IR ($CHCl_3$) ν 1746, 1192, 1042 cm^{-1}. HRMS (ESI): calcd for $[C_{10}H_{14}NO_4+H]^+$ 214.1079, found 214.1085.

*5.7.6. Tricyclic ketal (+)-**13c**.* From 107 mg (0.35 mmol) of alkynyldiol (+)-**2c**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the acetal (+)-**13c** (71 mg, 62%) as a colorless oil. $[\alpha]_D$ +7.7 (*c* 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.31 and 6.89 (d, *J*=9.0 Hz, each 2H), 5.05 (m, 1H), 4.96 (d, *J*=4.5 Hz, 1H), 4.50 (dd, *J*=7.7, 3.7 Hz, 1H), 4.43 (t, *J*=4.7 Hz, 1H), 4.00 (m, 1H), 3.95 and 3.54 (d, *J*=12.4 Hz, each 1H), 3.80 (s, 3H), 1.69 (q, *J*=7.4 Hz, 2H), 0.97 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 161.7, 156.8, 130.0, 118.2, 114.7, 111.9, 83.6, 77.3, 73.0, 65.9, 59.3, 55.5, 26.7, 6.8. IR ($CHCl_3$) ν 1744, 1192, 1041 cm^{-1}. HRMS (ESI): calcd for $[C_{16}H_{19}NO_5+H]^+$ 306.1341, found 306.1348.

*5.7.7. Tricyclic acetal (−)-**15b**.* From 58 mg (0.17 mmol) of alkynyldioxolane (+)-**6b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the acetal (−)-**15b** (32 mg, 63%) as a pale yellow oil. $[\alpha]_D$ −1.8 (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.44 (m, 2H), 7.35 (m, 3H), 5.08 (dd, *J*=4.5, 1.2 Hz, 1H), 4.98 (d, *J*=4.2 Hz, 1H), 4.77 and 4.66 (d, *J*=16.1 Hz, each 1H), 3.81 (m, 3H), 3.60 (d, *J*=4.5 Hz, 1H), 2.99 (dt, *J*=13.0 Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.5, 131.7, 128.9, 128.4, 122.0, 104.3, 87.6, 84.0, 81.3, 71.3, 69.0, 59.6, 56.0, 51.6, 22.9. IR ($CHCl_3$) ν 1752, 1190, 1044 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{17}NO_4+H]^+$ 300.1236, found 300.1215.

*5.7.8. Tricyclic acetal (+)-**17**.* From 85 mg (0.20 mmol) of alkynyldioxolane (+)-**6c**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the acetal (+)-**17** (35 mg, 48%) as a colorless oil. $[\alpha]_D$ +0.3 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.12 (m, 1H), 7.51 (m, 4H), 7.32 (m, 5H), 5.01 (d,

J=4.5 Hz, 1H), 4.89 (d, *J*=4.7 Hz, 1H), 4.77 and 4.66 (d, *J*=16.1 Hz, each 1H), 4.03 (m, 2H), 3.91 and 3.13 (m, each 1H), 3.88 (d, *J*=4.5 Hz, 1H), 2.37 (m, 1H), 1.96 (dd, *J*=14.3, 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 168.0, 142.5, 131.7, 130.2, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 111.8, 87.4, 84.3, 81.0, 72.5, 71.2, 63.5, 59.6, 38.6, 36.7. IR ($CHCl_3$) ν 1746, 1191, 1038 cm^{-1}. HRMS (ESI): calcd for $[C_{23}H_{21}NO_4]^+$ 375.1471, found 375.1457.

5.8. Metal/acid co-catalyzed cyclization of alkynyldioxolane (+)-4a in the absence of water. Preparation of bridged acetal (−)-10 and ketone (+)-11

From 70 mg (0.29 mmol) of alkynyldioxolane (+)-**4a**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent, 18 mg (31%) of the less polar compound (−)-**10** and 20 mg (27%) of the more polar compound (+)-**11** were obtained.

*5.8.1. Ketone (+)-**11**.* Yellow oil. $[\alpha]_D$ +8.5 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.58 (d, *J*=5.1 Hz, 1H), 4.30 (m, 2H), 4.09 (m, 2H), 3.85 (dd, *J*=9.3, 5.1 Hz, 1H), 3.65 (m, 1H), 3.55 (s, 3H), 2.15 (s, 3H), 1.36 and 1.31 (s, each 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 201.6, 167.9, 109.5, 83.3, 76.7, 66.6, 60.6, 59.2, 50.4, 27.2, 26.8, 25.1. IR ($CHCl_3$) ν 1743, 1715 cm^{-1}. HRMS (ESI): calcd for $[C_{12}H_{19}NO_5]^+$ 257.1263, found 257.1259.

5.9. General procedure for the metal/acid co-catalyzed cyclization of alkynyldiols 1–3. Preparation of bridged acetals 10, and 12–18

[AuClPPh$_3$] (0.0093 mmol), AgOTf (0.0093 mmol), and *p*-toluenesulfonic acid (0.037 mmol) were sequentially added to a stirred solution of the corresponding alkynyldiols **1**–**3** (0.37 mmol) in dichloromethane (0.37 mL). The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC), before being filtered through a pack of Celite. The filtrate was extracted with ethyl acetate (3×5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts **10**, and **12**–**18**.

*5.9.1. Tricyclic acetal (+)-**13a**.* From 61 mg (0.21 mmol) of alkynyldiol (+)-**2a**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave the acetal (+)-**13a** (40 mg, 63%) as a yellow solid. Mp 128–130 °C. $[\alpha]_D$ +13.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.31 and 6.89 (d, *J*=9.0 Hz, each 2H), 5.04 (m, 1H), 4.95 (d, *J*=4.4 Hz, 1H), 4.51 (dd, *J*=7.6, 3.7 Hz, 1H), 4.42 (t, *J*=4.6 Hz, 1H), 4.03 (m, 1H), 3.94 (d, *J*=12.5 Hz, 1H), 3.80 (s, 3H), 3.54 (dd, *J*=12.4, 0.7 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 161.6, 156.8, 130.5, 118.2, 114.7, 110.3, 83.5, 77.8, 73.0, 65.9, 59.3, 55.5, 20.5. IR ($CHCl_3$) ν 1747, 1188, 1038 cm^{-1}. HRMS (ESI): calcd for $[C_{15}H_{17}NO_5+Na]^+$ 314.1004, found 314.0999.

*5.9.2. Tricyclic acetal (+)-**13b**.* From 114 mg (0.31 mmol) of alkynyldiol (+)-**2b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the acetal (+)-**13b** (74 mg, 60%) as a colorless oil. $[\alpha]_D$ +3.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.28 (m, 7H), 6.87 (d, *J*=9.0 Hz, 2H), 5.00 (m, 1H), 4.90 (d, *J*=4.6 Hz, 1H), 4.47 (dd, *J*=7.6, 3.7 Hz, 1H), 4.40 (t, *J*=4.6 Hz, 1H), 3.99 and 3.49 (d, *J*=12.2 Hz, each 1H), 3.91 (m, 1H), 3.79 (s, 3H), 3.00 (d, *J*=1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 161.6, 156.8, 134.7, 130.3, 128.8, 128.2, 118.1, 114.7, 111.0, 83.5, 77.2, 73.1, 65.7, 59.2, 55.5, 40.8. IR ($CHCl_3$) ν 1745, 1190, 1040 cm^{-1}. HRMS (ESI): calcd for $[C_{21}H_{21}NO_5+Na]^+$ 390.1317, found 390.1311.

5.10. Metal/acid co-catalyzed cyclization of bis(alkynyl) dioxolane (+)-6a in the presence of water. Preparation of bridged acetals (−)-14, (−)-15a, and (+)-16a

From 65 mg (0.25 mmol) of bis(alkynyl)dioxolane (+)-**6a**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent, 16 mg (29%) of the less polar compound (−)-**15a**, 22 mg (36%) of compound (−)-**14**, and 16 mg (27%) of the more polar compound (+)-**16a** were obtained.

*5.10.1. Tricyclic acetal (−)-**14**.* Pale yellow oil. $[\alpha]_D$ −0.4 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.99 (m, 1H), 4.79 (dd, *J*=4.5, 1.2 Hz, 1H), 4.60 and 4.42 (d, *J*=17.7 Hz, each 1H), 3.89 (m, 2H), 3.80 and 2.99 (d, *J*=13.0 Hz, each 1H), 3.60 (d, *J*=4.7 Hz, 1H), 2.16 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 205.3, 173.3, 104.4, 82.9, 77.2, 71.2, 69.1, 56.0, 51.6, 26.1, 23.0. IR ($CHCl_3$) ν 1747, 1710, 1195, 1044 cm^{-1}. HRMS (ESI): calcd for $[C_{11}H_{15}NO_5+H]^+$ 242.1028, found 242.1023.

*5.10.2. Tricyclic acetal (−)-**15a**.* Colorless oil. $[\alpha]_D$ −1.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 5.00 (dd, *J*=4.5, 1.0 Hz, 1H), 4.90 (d, *J*=4.1 Hz, 1H), 4.56 and 4.46 (dd, *J*=16.1, 2.5 Hz, each 1H), 3.85 (m, 2H), 3.81 and 2.99 (d, *J*=13.0 Hz, each 1H), 3.58 (d, *J*=4.5 Hz, 1H), 2.51 (t, *J*=2.3 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.3, 104.3, 81.1, 78.7, 75.8, 71.2, 69.0, 58.7, 55.8, 51.6, 22.9. IR ($CHCl_3$) ν 3315, 1745, 1192, 1045 cm^{-1}. HRMS (ESI): calcd for $[C_{11}H_{13}NO_4+H]^+$ 224.0923, found 224.0919.

*5.10.3. Tricyclic acetal (+)-**16a**.* Colorless solid. Mp 150–152 °C. $[\alpha]_D$ +6.6 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.91 (d, *J*=4.4 Hz, 1H), 4.67 (m, 1H), 4.32 and 3.91 (d, *J*=18.8 Hz, each 1H), 4.23 (m, 1H), 4.06 (t, *J*=4.4 Hz, 1H), 3.89 and 3.47 (d, *J*=12.5 Hz, each 1H), 2.15 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 201.5, 165.6, 110.0, 84.7, 78.1, 74.1, 66.8, 61.4, 50.8, 27.3, 20.6. IR ($CHCl_3$) ν 1747, 1712, 1192, 1042 cm^{-1}. HRMS (ESI): calcd for $[C_{11}H_{15}NO_5]^+$ 241.0950, found 241.0937.

5.11. Metal/acid co-catalyzed cyclization of bis(alkynyl) dioxolane (+)-6d in the presence of water. Preparation of bridged acetals (+)-16b and (+)-18

From 32 mg (0.096 mmol) of bis(alkynyl)dioxolane (+)-**6d**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent, 11 mg (37%) of the less polar compound (+)-**18** and 16 mg (52%) of the more polar compound (+)-**16b** were obtained.

*5.11.1. Tricyclic acetal (+)-**16b**.* Colorless solid. Mp 123–125 °C. $[\alpha]_D$ +2.7 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.95 (m, 2H), 7.62 (m, 1H), 7.54 (m, 2H), 4.92 (m, 1H), 4.23 (d, *J*=4.4 Hz, 1H), 4.37 (dd, *J*=7.5, 3.6 Hz, 1H), 4.01 (t, *J*=4.4 Hz, 1H), 3.92 (dd, *J*=16.4, 7.5 Hz, 1H), 3.84 and 3.43 (d, *J*=12.6 Hz, each 1H), 3.63 (m, 2H), 3.30 (m, 2H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 197.5, 165.5, 135.9, 133.8, 128.8, 128.0, 110.0, 84.1, 77.8, 73.6, 65.9, 61.0, 37.2, 36.3, 20.6. IR ($CHCl_3$) ν 1743, 1705, 1190, 1040 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{19}NO_5]^+$ 317.1263, found 317.1249.

*5.11.2. Tricyclic acetal (+)-**18**.* Colorless solid. Mp 153–155 °C. $[\alpha]_D$ +11.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.37 (m, 5H), 4.96 (m, 1H), 4.87 (d, *J*=4.2 Hz, 1H), 4.63 (dd, *J*=7.7, 3.6 Hz, 1H), 4.51 and 4.06 (d, *J*=17.8 Hz, each 1H), 4.10 (m, 2H), 3.89 and 3.47 (d, *J*=12.6 Hz, each 1H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 163.9, 131.6, 129.0, 128.5, 121.6, 110.2, 85.1, 84.7, 81.4, 77.8, 73.6,

66.2, 60.1, 31.7, 20.6. IR ($CHCl_3$) ν 2225, 1745, 1190, 1042 cm^{-1}. HRMS (ESI): calcd for $[C_{17}H_{17}NO_4+H]^+$ 300.1236, found 300.1230.

5.12. Procedure for the metal/acid co-catalyzed cyclization of alkynyldioxolane (+)-4b using D_2O instead of H_2O. Preparation of fused acetal (+)-[D]-12a

[AuClPPh$_3$] (0.0063 mmol), AgOTf (0.0063 mmol), *p*-toluenesulfonic acid, and deuterium oxide (0.50 mmol) were sequentially added to a stirred solution of the alkynyldioxolane (+)-**4b** (78 mg, 0.25 mmol) in dichloromethane (0.25 mL). The resulting mixture was heated in a sealed tube at 80 °C for 3 h. The reaction was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate was extracted with ethyl acetate (3×5 mL), and the combined extracts were washed twice with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate (1:2) gave 51 mg (65%) of analytically pure adduct (+)-[D]-**12a**; as a colorless solid. Mp 160–162 °C. $[\alpha]_D$ +7.9 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.57 (m, 2H), 7.32 (m, 3H), 4.67 (d, *J*=4.9 Hz, 1H), 4.57 (d, *J*=4.7 Hz, 1H), 3.87 (ddd, *J*=14.4, 5.4, 1.5 Hz, 1H), 3.79 (d, *J*=4.6 Hz, 1H), 3.63 (s, 3H), 4.05 (m, 2H), 3.87 and 3.10 (d, *J*=14.4 Hz, each 1H), 3.80 (d, *J*=4.7 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 167.7, 142.0, 127.7, 127.6, 124.3, 111.2, 83.0, 71.8, 70.8, 62.5, 58.8, 36.0 (m). IR ($CHCl_3$) ν 1749, 1190, 1045 cm^{-1}. HRMS (ESI): calcd for $[C_{15}H_{15}D_2NO_4+Na]^+$ 300.1181, found 300.1175.

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Supplementary data

Schemes S1–S4, Figures S1–S3, Table S1 and Table S2, ORTEP plot for compound **12a**, computational data, as well as copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.028.

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