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Gold-catalyzed direct cycloketalization of acetonide-tethered alkynes in the presence of water

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ABSTRACT

A methodology for the direct preparation of bridged acetals from acetonide-tethered alkynes under gold catalysis in the presence of water has been developed. The bicyclic ring structures bearing a bridged five-membered ring arise from the regioselective bis-oxycyclization by initial attack of the oxygen atom to the internal alkyne carbon.

1. Introduction

Over the course of the last decade, efforts aimed at maximizing the total efficiency of a given organic transformation have been increased.[1] The use of gold salts has gained a lot of attention in the recent times because of their powerful soft Lewis acidic nature.[2] In particular, the recently developed noble metal activation of alkynes toward simultaneous attack by two contiguous oxygen nucleophiles is an important C–O bond-forming reaction.[3,4] However, these reports involve the use of free hydroxy groups; being missed the direct bis(oxycyclization) sequence of acetonide-tethered alkynes until we merged into this field.[5] In connection with our current research interest in the preparation of biologically relevant heterocycles,[6] we wish to report now details of the direct cycloketalization of acetonide-tethered alkynes to bridged bicyclic acetals, which is carried out using gold catalysis in the presence of water.

2. Results and discussion

Starting substrates, alkynyldioxolanes **1a**–**h**, **2a**–**e**, and **3a**–**d** (Fig. 1) required for our study were prepared from (*R*)-2,3-*O*-isopropylideneglyceraldehyde, from (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol, from (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol, or from 2-*O*-benzyl-D-threitol.

Alkynyldioxolanes **1a**–**h** were prepared as shown in Scheme 1. Alkynyldioxolanes **1a** and **1b** were prepared from (*S*)-(+)-1,2-isopropylideneglycerol through O-propargylation and Sonogashira coupling. Precursors **1c**–**h** were prepared from (*R*)-2,3-*O*-isopropylideneglyceraldehyde via metal-mediated carbonyl-

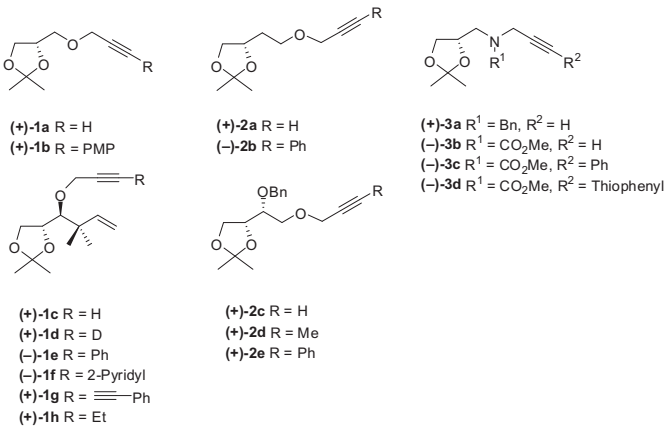

Fig. 1. Structures of cyclization precursors, alkynyldioxolanes **1a**–**h**, **2a**–**e**, and **3a**–**d**. PMP=4-MeOC$_6$H$_4$.

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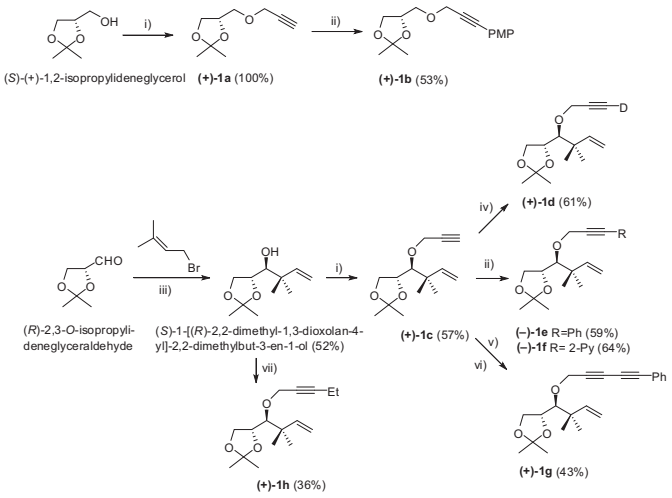
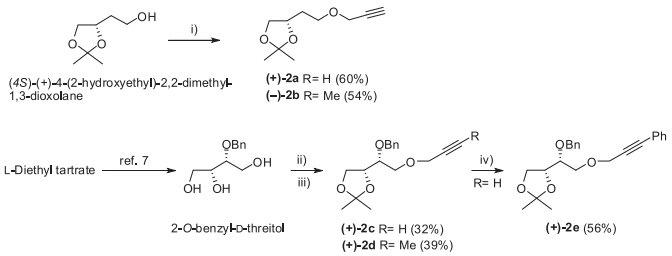
allylation followed by O-propargylation, deuteration, Sonogashira and Cadiot–Chodkiewicz couplings, as appropriate.



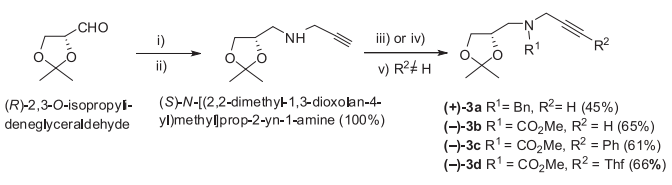
Scheme 1. Reagents and conditions: (i) propargyl bromide, CH_2Cl_2/NaOH (aq 50%), TBAI, RT, 24 h; (ii) 2 mol % CuI, 1 mol % $Pd(PPh_3)_2Cl_2$, ArI, Et_3N, acetonitrile, rt, 15 h; (iii) In, THF/NH_4Cl (aq satd), rt, 15 h; (iv) BuLi, D_2O, THF, −78 °C to rt; (v) NBS, AcOAg, acetone; (vi) phenylacetylene, CuCl, NH_2OH, $EtNH_2$, CH_2Cl_2/MeOH, 0 °C to rt; (vii) 1-bromopent-2-yne, CH_2Cl_2/NaOH (aq 50%), TBAI, rt, 24 h.

Alkynyldioxolanes **2a**–**e** were prepared as shown in Scheme 2. Alkynyldioxolanes **2a** and **2b** were prepared from (4*S*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane through O-propargylation. Precursors **2c**–**e** were prepared from 2-*O*-benzyl-D-threitol[7] via O-isopropylidenation[8] followed by O-propargylation and Sonogashira coupling.



Scheme 2. Reagents and conditions: (i) propargyl bromide or (3-bromoprop-1-ynyl) benzene, CH_2Cl_2/NaOH (aq 50%), TBAI, rt, 24 h; In, THF/NH_4Cl (aq satd), rt, 15 h; (ii) 10 mol % pyridinium *p*-toluenesulfonate, 2,2-dimethoxypropane, rt, 2 h; (iii) propargyl bromide or 1-bromobut-2-yne, NaH, TBAI, THF, rt; (iv) 2 mol % CuI, 1 mol % $Pd(PPh_3)_2Cl_2$, ArI, Et_3N, acetonitrile, rt, 15 h. TBAI=tetrabutylammonium iodide.

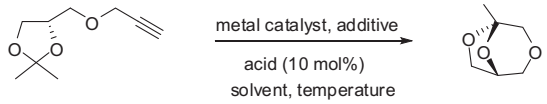
As shown in Scheme 3, alkynyldioxolanes **3a**–**d** were prepared from (*R*)-2,3-*O*-isopropylideneglyceraldehyde through reductive amination followed by protection and Sonogashira coupling, as appropriate.



Scheme 3. Reagents and conditions: (i) propargyl amine, $MgSO_4$, rt, 15 h; (ii) $NaBH_4$, methanol, 0 °C, 30 min; (iii) benzylbromide, K_2CO_3, acetonitrile, rt; (iv) methyl chloroformate, Et_3N, CH_2Cl_2, rt, 2 h; (v) 2 mol % CuI, 1 mol % $Pd(PPh_3)_2Cl_2$, ArI, Et_3N, acetonitrile, rt, 15 h.

Using directly a dioxolane ring instead of the deprotected 1,2-diol moiety as the starting material, would be a significant breakthrough for metal-catalyzed alkyne-cycloketalization in terms of cost-effectiveness. Initial experiments were carried out using alkynyldioxolane **1a** as a model substrate. To optimize the reaction method, different parameters involved in the metal-catalyzed reactions that could affect the formation of the desired product were tested. 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) in CH_2Cl_2 was a competent catalytic system for this purpose (see table).[9,10] Performing the reaction at 80 °C on a sealed tube accelerated the reaction. However, the conversion to the corresponding tricyclic acetal **4a** could not be satisfied in high yield. Solvent screening demonstrated that dichloromethane was the best choice in the reaction. The use of a more Lewis acidic gold salt ($AuCl_3$) as catalyst alone without PTSA was also tested. Thus, we treated alkynic acetonide **1a** with 5 mol % of $AuCl_3$. However, acetal **4a** was obtained in a poor 25% yield. After identifying an appropriate catalyst, we optimized other critical reaction parameters, such as the addition of additives. In particular, the transformation was strongly influenced by the presence of water. Gratifyingly, it was found that alkynic acetonide **1a** 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 bicyclic ketal **4a** through a regio- and diastereoselective bis(oxycyclization) (see Table 1). Probably, the presence of water favors the hydrolysis of intermediate **10** in the mechanistic proposal of Scheme 4. Taking into account that there are only a few gold-catalyzed transformations, which tolerate the presence of water,[11] there would be certain merit using water as an alternative solvent for alkyne-cycloketalization.[12] To test for conditions for the reaction as a suspension in water, we try our optimized catalytic system. Notably, substrate **1a** is completely insoluble in aqueous media. After some experimentation, we observed that the cyclization reaction did not proceed 'on water'. Thus, the use of biphasic water/dichloromethane mixtures was necessary in order to improve the solubility of the substrates; being (4:1 water/dichloromethane) the best solvent system. The presence of a phase transfer agent[13] gave rise to a positive influence on the yield of bridged

Table 1
Selective direct bis(oxycyclization) reaction of acetonide-tethered alkyne **1a** under modified metal-catalyzed conditions[a]

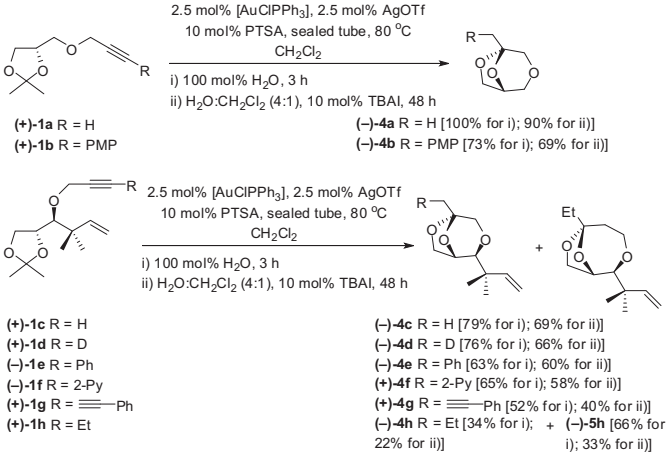


Catalyst (mol %)	Additive (mol %)	*t* (h)	Acid	*T* (°C)	Solvent	Yield (%)
$[PtCl_2(CH_2{=}CH_2)]_2$ (2.5)	TDMPP (5)	24	—	20	DCM	—
AgOTf (5)	—	24	—	20	DCM	—[b]
$FeCl_3$ (10)	—	24	—	20	DCM	—
$AuCl_3$ (5)	—	24	PTSA	80	DCM	25
$[AuClPPh_3]$/AgOTf (2.5)	—	24	PTSA	20	DCM	45
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	3	—	80	DCM	75
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	48	$FeCl_3$	80	DCM	50
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	4	PTSA	80	THF	64
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	3	PTSA	80	DCE	90
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	5	PTSA	80	Toluene	76
$[AuClPPh_3]$/AgOTf (2.5)	TBAI (10)	48	PTSA	80	$4H_2O$: 1DCM	90
$[AuClPPh_3]$/AgOTf (2.5)	H_2O (100)	3	PTSA	80	DCM	100

[a] Yield of pure, isolated product with correct analytical and spectral data. PTSA=*p*-toluenesulfonic acid. TDMPP=tris(2,6-dimethoxyphenyl)phosphine. DCM=dichloromethane. THF=tetrahydrofuran. DCE=1,2-dichloroethane. TBAI=tetrabutylammonium iodide.

[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.[7]

acetal **4a**.[14] The reaction time has a crucial role in the amount of the product obtained: the longer the reaction time, the better the yield, with a best result of 90% at 48 h, because a short reaction time of 2 h leads to a 20% yield.

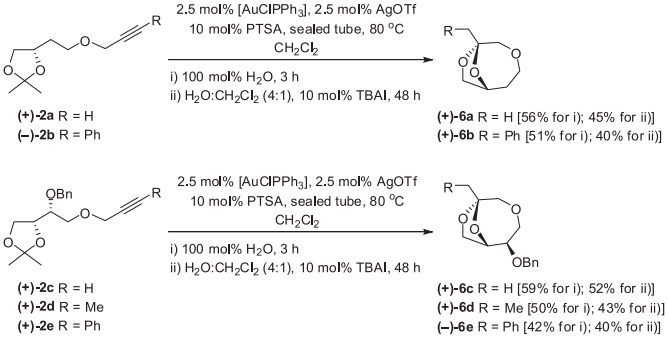


Scheme 4. Preparation of 3,6,8-trioxabicyclo[3.2.1]octanes **4**. PMP=4-MeOC$_6$H$_4$. PTSA=*p*-toluenesulfonic acid. TBAI=tetrabutylammonium iodide.

Having established the optimal reaction conditions, we explored the scope of the methodology by subjecting a range of (prop-2-ynyloxy)methyl-tethered dioxolanes **1b**–**h** to direct alkyne-cycloketalization and the results are shown in Scheme 4. In both cases (addition of 1 equiv of water as well as the presence of large amount of water), the crude reaction mixtures are extremely clean and the acetals are the only products detected. Tolerance toward a variety of substituents (aliphatic, aromatic, and alkynyl groups) on the acetylenic end was demonstrated by obtaining the corresponding enantiopure bridged acetals **4** in good yields. Except for ethyl-substituted alkynyldioxolane **1h**, bicyclic ketals **4** were obtained as single regio- and diastereomers through a 6-*exo*/5-*exo* bis-oxycyclization by initial attack of the oxygen atom to the internal alkyne carbon. The exposure of ethyl-substituted alkyne **1h** to these reactions conditions afforded the 7-*endo*/5-*exo* bis-oxycyclization bridged acetal **5h** as major adduct, being the corresponding 6-*exo*/5-*exo* adduct **4h** the minor component. From these experiments, it can be concluded that this catalytic system in the presence of water enables regioselective control of the intramolecular ketalization reaction between the dioxolane unit and a range of alkynes separated by three atoms. Besides, the method using 1 equiv of water is superior to the method using water as main solvent, in terms of yields and reaction time.

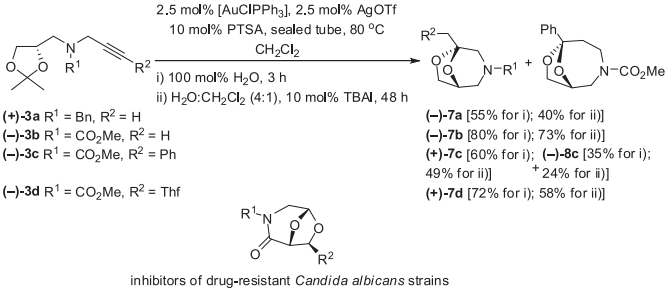
We further examined the scope of this methodology by investigating (prop-2-ynyloxy)ethyl-tethered dioxolanes **2a**–**e**, alkynyldioxolane substrates with a four-atom chain at the junction between the acetonide group and the alkyne. We were pleased to observe that these modifications had little impact on the regiochemical control of the reaction (total regioselectivity was observed in this series). Thus, the increase of the distance between the reactive moieties in one atom favored the 7-*exo*/5-*exo* bis-oxycyclization of the acetonide group toward the internal alkyne carbon, affording proximal adducts **6** (Scheme 5).

Aza-analogues of bridged acetals **4**–**6** have been recently identified as inhibitors of drug-resistant *Candida albicans* strains.[15] Thus, the replacement of the cycloether oxygen for a nitrogen atom was accomplished next. Similar trends to the oxa series were observed under the same gold-catalyzed conditions in the presence of water. Cyclization of aminoalkynes **3a**–**d** possessing a chiral dioxolane ring results in the regio- and stereoselective formation of 6,8-dioxa-3-azabicyclo[3.2.1]octanes **7** (Scheme 6). Bicyclic acetals **7**



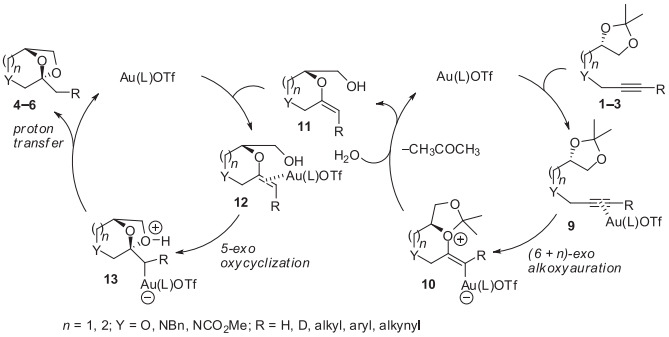
Scheme 5. Preparation of 3,8,9-trioxabicyclo[4.2.1]nonanes **6**. PMP=4-MeOC$_6$H$_4$. PTSA=*p*-toluenesulfonic acid. TBAI=tetrabutylammonium iodide.

were obtained as exclusive reaction products, except for **3c**. Although substitution at the final position of the aminoalkyne had little effect upon the regioselectivity of the reaction, alkynyldioxolane **7c** underwent cycloketalization reaction to afford a mixture of proximal and distal adducts **7c** and **8c**.



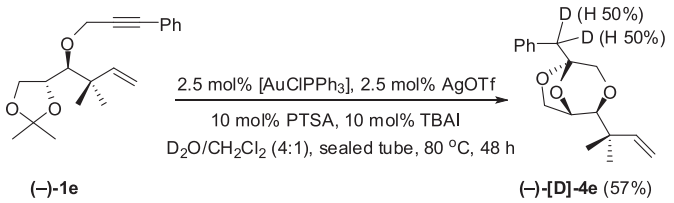
Scheme 6. Preparation of 6,8-dioxa-3-azabicyclo[3.2.1]octanes **7**. Thf=2-thiophenyl. PTSA=*p*-toluenesulfonic acid. TBAI=tetrabutylammonium iodide.

Our proposed mechanism is shown in Scheme 7. Initially, one of the oxygen atoms of the alkynyldioxolanes **1**–**3** attacks through (6+*n*)-*exo* alkoxyauration the gold-activated alkyne **9** to form a vinyl–gold complex **10**, which reacts with water through acetonide hydrolysis and a deauration process, to give intermediate **11** (right circle) and releasing the gold catalyst. The reaction does not stop at this stage; instead methylenic oxacycles **11** can be further cyclized to give the functionalized bridged acetals **4**–**6** (left circle). The second catalytic cycle starts with the coordination of the alkene group by the gold salt, on forming the π-complex **12**, which after 5-*exo* cyclization would form the ate complex **13**. Deauration linked to proton transfer liberates adducts **4**–**6** with concomitant regeneration of the gold catalyst, closing the second catalytic cycle (Scheme 7). Because we had never isolated **11**, it is also possible to think in a Brønsted acid activation of the transient methylenic



Scheme 7. A conceivable mechanistic explanation for the gold-catalyzed bis(oxycyclization) of alkynyldioxolanes **1**–**3**.

intermediate **11**. However, the successful gold-catalyzed cycloketalization reaction of alkynylacetonides in the absence of Brønsted acid additive, may discard this assumption. With the aim of trapping the organometal intermediate to confirm the mechanism of this reaction, we performed deuterium labeling studies with deuterium oxide. When the gold-catalyzed alkyne cycloketalization reaction of substrate **1e** was carried out in presence of D_2O (4 heavy water/1 dichloromethane), adduct **4e** with additional deuterium incorporation (50% D) at the two protons of the benzylic carbon was achieved (Scheme 8). The fact that the gold-catalyzed conversion of alkyne **1e** into bridged acetal **4e** in the presence of D_2O partially afforded double deuterated [D]-**4e**, suggests that deuterolysis of the carbon–gold bonds in species **10** and **13** has occurred.



Scheme 8. Gold-catalyzed bis(oxycyclization) of alkynyldioxolane **1e** in a heavy water medium.

3. Conclusions

In conclusion, we have developed a convenient methodology for the gold-catalyzed direct synthesis of bridged bicyclic acetals from alkynyldioxolanes. The presence of water was beneficial for the transformation. The method using 1 equiv of water is superior to the method using water as main solvent, in terms of yields and reaction time. A conceivable mechanism for the achievement of bridged acetals may imply a regioselective bis-oxycyclization by initial attack of the oxygen atom of the dioxolane moiety to the internal alkyne carbon.

4. Experimental section

4.1. 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, 77.0 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 gram per 100 mL. All commercially available compounds were used without further purification.

4.2. Method A. General procedure for the gold-catalyzed bis(heterocyclization) reaction of alkynyldioxolanes 1, 2, and 3 using 1 equiv of water. Preparation of bridged acetals 4, 5, 6, and 7

[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 alkynyldioxolane **1** (0.37 mmol) in dichloromethane (0.37 mL). The resulting mixture was heated in a sealed tube at 80 °C for 3 h. The reaction mixture was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate was extracted with dichloromethane (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 gave analytically pure adducts. Spectroscopic and analytical data for pure forms of **4**, **5**, **6**, and **7** follow.[16]

4.3. Method B. General procedure for the gold-catalyzed bis(heterocyclization) reaction of alkynyldioxolanes 1, 2, and 3 using water as main solvent. Preparation of bridged acetals 4, 5, 6, and 7

[AuClPPh$_3$] (0.0093 mmol), AgOTf (0.0093 mmol), *p*-toluenesulfonic acid (0.037 mmol), and tetrabutylammonium iodide (0.037 mmol) were sequentially added to a stirred solution of the corresponding alkynyldioxolane **1** (0.37 mmol) in a biphasic water (4 mL)/dichloromethane (1 mL) mixture. The resulting mixture was heated in a sealed tube at 80 °C for 48 h. The reaction mixture was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate was extracted with dichloromethane (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 gave analytically pure adducts. Spectroscopic and analytical data for pure forms of **4**, **5**, **6**, and **7** follow.

*4.3.1. Bicyclic acetal (−)-**4a**.* From 129 mg (0.76 mmol) of alkynyldioxolane (+)-**1a**, and after chromatography of the residue using petroleum ether/diethyl ether (3:1) as eluent gave the ketal (−)-**4a** [method A: 99 mg, 100%; method B: 89 mg, 90%] as a colorless oil; $[\alpha]_D$ −0.5 (*c* 10.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.42 (m, 1H), 4.23 (d, *J*=6.6 Hz, 1H), 3.87 (m, 2H), 3.60 (dd, *J*=11.4, 1.3 Hz, 1H), 3.54 and 3.49 (d, *J*=11.1 Hz, each 1H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=104.9, 74.6, 72.6, 68.5, 67.9, 19.3; IR ($CHCl_3$): ν=2924, 1101, 693 cm^{-1}; HRMS (ES): calcd for $C_6H_{11}O_3$ $[M+H]^+$: 131.0708; found: 131.0705.

*4.3.2. Bicyclic acetal (−)-**4d**.* From 60 mg (0.25 mmol) of alkynyldioxolane (+)-**1c**, and after chromatography of the residue using hexanes/ethyl acetate (7:1) as eluent gave the ketal (−)-**4d** [method A: 38 mg, 76%; method B: 33 mg, 66%] as a yellow oil; $[\alpha]_D$ −0.6 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=5.96 (dd, *J*=17.7, 11.0 Hz, 1H), 5.00 (m, 2H), 4.38 (m, 2H), 3.73 (dd, *J*=7.0, 5.7 Hz, 1H), 3.62 and 3.56 (d, *J*=11.0 Hz, each 1H), 3.53 (s, 1H), 1.33 (t, 2H), 1.07 and 1.06 (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=144.3, 112.3, 104.3, 84.3, 75.6, 74.2, 66.4, 38.8, 24.7, 23.8, 18.6 (t, *J*=19.6 Hz, *C*H_2D); IR ($CHCl_3$): ν=1094, 653 cm^{-1}; HRMS (ES): calcd for $C_{11}H_{18}DO_3$ $[M+H]^+$: 200.1396; found: 200.1391.

*4.3.3. Bicyclic acetal (+)-**4f**.* From 55 mg (0.17 mmol) of alkynyldioxolane (−)-**1f**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave the ketal (+)-**4f** [method A: 30 mg, 65%; method B: 27 mg, 58%] as a colorless oil; $[\alpha]_D$ +0.3 (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=8.54 (d, *J*=3.8 Hz, 1H), 7.62 (td, *J*=7.6, 0.4 Hz, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.16 (m, 1H), 5.94 (dd, *J*=17.7, 11.0 Hz, 1H), 4.97 (m, 2H), 4.40 (m, 2H), 3.68 (m, 1H), 3.71 and 3.63 (d, *J*=11.1 Hz, each 1H), 3.52 (s, 1H), 3.22 and 3.17 (d, *J*=14.0 Hz, each 1H), 1.04 and 1.03 (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=155.6, 148.9, 144.2, 136.3, 124.9, 121.8, 112.3, 105.0, 84.3, 75.7, 73.2, 66.5, 42.2, 38.9, 24.7, 23.8; IR ($CHCl_3$): ν=1179, 1045 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1600; found: 276.1603.

*4.3.4. Bicyclic acetal (+)-**6a**.* From 151 mg (0.82 mmol) of alkynyldioxolane (+)-**2a**, and after chromatography of the residue using petroleum ether/diethyl ether (2:1) as eluent gave the ketal (+)-**6a**

[method A: 66 mg, 56%; method B: 53 mg, 45%] as a colorless oil; $[\alpha]_D$ −0.01 (*c* 2.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.60 (td, *J*=6.9, 2.9 Hz, 1H), 4.11 (t, *J*=7.0 Hz, 1H), 4.04 and 3.69 (ddd, *J*=12.4, 6.1, 3.1 Hz, each 1H), 3.98 (dd, *J*=6.9, 2.9 Hz, 1H), 3.78 and 3.39 (d, *J*=12.4 Hz, each 1H), 2.13 (m, 1H), 1.87 (dddd, *J*=10.2, 6.1, 0.9 Hz, 1H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=110.6, 79.0, 74.2, 73.1, 68.1, 36.7, 21.5; IR ($CHCl_3$): ν=1190 cm^{-1}; HRMS (ES): calcd for $C_7H_{13}O_3$ $[M+H]^+$: 145.0865; found: 145.0868.

*4.3.5. Bicyclic acetal (−)-**7b**.* From 56 mg (0.25 mmol) of alkynyldioxolane (−)-**3b**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave the ketal (−)-**7b** [method A: 37 mg, 80%; method B: 34 mg, 73%] as a colorless oil; $[\alpha]_D$ −0.1 (*c* 1.4 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.46 (m, 1H), 3.85 (m, 3H), 3.77 and 2.92 (d, *J*=5.6 Hz, 1H), 3.69 (s, 3H), 2.92 (d, *J*=12.8 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=159.5, 107.0, 75.9, 71.2, 55.6, 54.9, 49.8, 24.1; IR ($CHCl_3$): ν=1744 cm^{-1}; HRMS (ES): calcd for $C_8H_{14}NO_4$ $[M+H]^+$: 188.0923; found: 188.0924.

4.4. Procedure for the gold-catalyzed cyclization of alkynyldioxolane (−)-1e in a heavy water medium. Preparation of acetal (−)-[D]-4e

$[AuClPPh_3]$ (0.0065 mmol), AgOTf (0.0065 mmol), *p*-toluenesulfonic acid (0.025 mmol), and tetrabutylammonium iodide (0.025 mmol) were sequentially added to a stirred solution of the alkynyldioxolane (−)-**1e** (82 mg, 0.26 mmol) in a biphasic water (0.4 mL)/dichloromethane (0.1 mL) mixture. The resulting mixture was heated in a sealed tube at 80 °C for 48 h. The reaction mixture was allowed to cool to room temperature and filtered through a pack of Celite. The filtrate was extracted with dichloromethane (3×2 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 (10:1) gave 41 mg (57%) of analytically pure adduct (−)-[D]-**4e** as a colorless oil; $[\alpha]_D$ −0.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=7.27 (m, 5H), 5.94 (dd, *J*=17.6, 10.8 Hz, 1H), 4.98 (m, 2H), 4.40 (m, 2H), 3.69 (dd, *J*=7.0, 5.6 Hz, 1H), 3.61 and 3.54 (d, *J*=11.0 Hz, each 1H), 3.51 (s, 1H), 3.02 and 2.92 (d, *J*=14.2 Hz, each 1H), 1.05 and 1.04 (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=144.5, 130.4, 128.4, 127.0, 112.6, 84.6, 77.5, 75.9, 73.4, 66.7, 40.1, 39.1, 25.0, 24.0; IR ($CHCl_3$): ν=1184 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{22}$ DO_3 $[M+H]^+$: 276.1709; found: 276.1705.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.030.

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