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Gold(I)-Catalyzed Cycloisomerization of 1,7- and 1,8-Enynes: Application to the Synthesis of a New Allocolchicinoid

François-Didier Boyer,[†] Xavier Le Goff,[‡] and Issam Hanna*,[§]

Unité de Chimie Biologique, INRA, F-78026 Versailles, France, Laboratoire Hétéroatomes et Coordination, CNRS UMR 7653, and Laboratoire de Synthèse Organique, CNRS UMR 7652, Ecole Polytechnique, F-91128 Palaiseau, France

hanna@poly.polytechnique.fr

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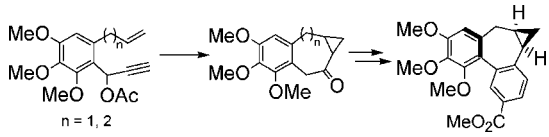


Gold(I)-catalyzed cycloisomerization of 1,7- and 1,8-enyne propargylic acetates afforded cyclopropyl derivatives containing seven- and eight-membered rings, respectively. This reaction was used for the synthesis of a new allocolchicinoid having a cyclopropane ring fused to the B seven-membered ring at the C6−C7 positions.

Cycloisomerization of enynes in the presence of transition-metal catalysts has played an important role in the preparation of a variety of cyclic compounds.[1] In particular, $PtCl_2$- or Au(I)-catalyzed cycloisomerization of enyne substrates bearing an ester group at the propargylic position leads to bicyclic systems with a fused cyclopropane ring, which upon hydrolysis furnishes a cyclopropyl carbonyl derivative (Scheme 1).[2] The overall result of this squeletal rearrangement represents an attractive and less hazardous equivalent to classical diazocarbonyl chemistry.[3] Even at the early stages of development, this methodology has already been applied in the total syntheses of bicyclic sesquiterpenes containing a cyclopropane subunit.[4] However, while rearrangement of 1,5- and 1,6-enynes is well-documented, rare examples are known of such a reaction with 1,7- and 1,8-enyne substrates.[5] We report here that polycyclic compounds in which the cyclopropane ring is fused to seven- and eight-membered rings can be readily obtained by cyclorearrangement of 1,7- and 1,8-enynes, respectively. This methodology was applied to the synthesis of a new class of allocolchicinoids.

SCHEME 1

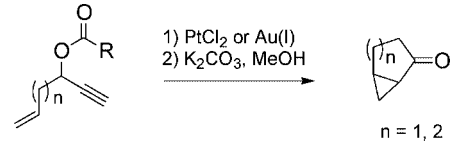
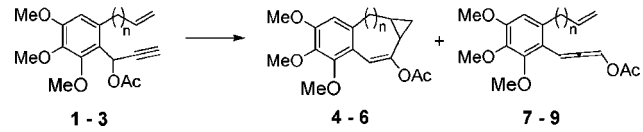
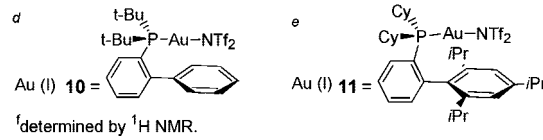


TABLE 1. Gold-Catalyzed Rearrangement of Propargylic Acetates



entry	enyne	catalyst (%),	product (yield)[a]	
1	**1** n = 2	$PtCl_2$ (5%)[b]	**4** (53%)	**7** (7%)
2		Au(I) **10** (1%)[c, d]	**4** (78%)	**7** (8%)
3		Au(I) **11** (1%)[c, e]	**4** (60%)[f]	**7** (16%)
4	**2** n = 1	Au(I) **10** (0.5%)[c, d]	**5** (90%)	**8** (0%)
5	**3** n = 3	Au(I) **10** (4%)[c, d]	**6** (5%)	**9** (32%)

[a]isolated yield. [b]in toluene at 80 °C, 5 h. [c] in dichloromethane at room temperature, 2 h



[f]determined by ^{1}H NMR.

Our work started with enyne propargylic acetate **1** (Table 1).[6] Treatment of **1** with 5% of $PtCl_2$ in toluene at 80 °C for 5 h gave tricyclic enol ester **4** in 53% yield along with allene **7** (7% yield) (Table 1, entry 1). This transformation could be achieved under milder conditions using cationic gold complexes

[†] Unité de Chimie Biologique, INRA.
[‡] Laboratoire Hétéroatomes et Coordination, CNRS.
[§] Laboratoire de Synthèse Organique, CNRS.

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(2) For recent reviews, see: (a) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (b) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350. (c) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. For selected examples, see: (d) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132. (e) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (f) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (g) Marion, N.; de Frémont, P.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048.

(3) For a review, see: Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.

(4) (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. (b) Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *61*, 4793. (c) Fürstner, A.; Hannen, P. *Chem.—Eur. J.* **2006**, *12*, 3006. (d) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901.

(5) For examples of cycloisomerization of 1,7- and 1,8-enynes, see: (a) Moreau, X.; Goddard, J.-P.; Mathieu, B.; Lemière, J.; Lopez-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43. (b) Cabello, N.; Rodriguez, C.; Echavarren, A. M. *Synlett* **2007**, 1753, and ref 2d. (c) For an example of a gold-catalyzed cycloisomerization of 1,9-enyne, see: Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. *Org. Lett.* **2007**, *9*, 2123.

(6) The preparation of propargylic acetates **1** and **3** is described in the Supporting Information.

(7) (a) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133. (b) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614.

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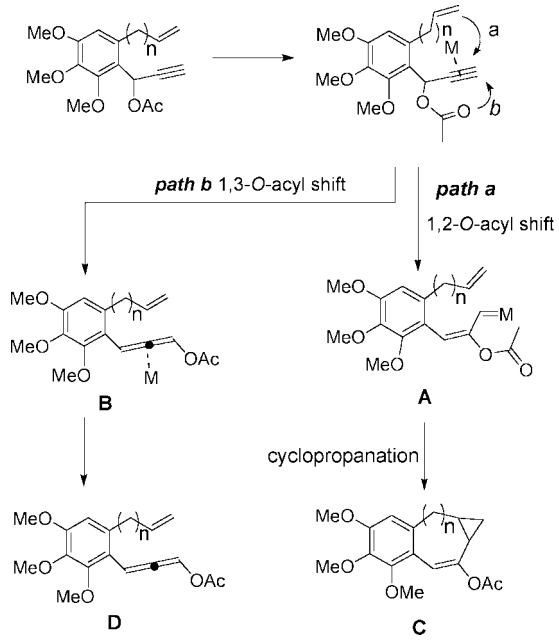
SCHEME 2. Possible Reaction Pathways for Gold-Catalyzed Rearrangement of Propargylic Acetates



bearing the bis(trifluoromethanesulfonyl)imidate moiety.[7] When **1** was treated with the biphenylphosphine-based catalyst **10** (1%) in CH_2Cl_2 at room temperature, **4** was obtained in an improved yield (78%) (Table 1, entry 2). Under these conditions, allene **7** was also isolated in 8% yield. In this skeletal reorganization, enyne **1** was converted into a complex structure in which the cyclopropane ring is fused to the eight-membered ring.[5] The use of the bulkier Au(I) catalyst **11** was found to be synthetically less useful. Thus, treatment of enyne **1** with **11** gave allene acetate **7** (16%), enol acetate **4** (60%), and a mixture of unidentified products (Table 1, entry 3).

We next turned to the preparation of the tricyclic structure **5** containing a seven-membered ring. When propargylic acetate **2** was treated with 0.5% of catalyst **10**, only the product of cycloisomerization **5** was obtained in 90% yield (Table 1, entry 4). In this case, none of allene derivative **8** was isolated. By sharp contrast, 1,9-enyne **3** ($n = 3$)[6] reacted rather sluggishly under the same conditions (entry 5). In fact, to achieve the total conversion of the starting enyne, further amounts of catalyst **10** (4%) were needed. Ultimately, the reaction gave a mixture of products from which allenyl acetate **9** was isolated as the major product in low yield (32%). Only 5% of cyclononane derivative **6** was obtained.

To account for the formation of both enol esters and allenyl acetates, a proposed mechanism is shown in Scheme 2. The acetate group in the polarized metal−alkyne complex initially formed can undergo either 1,2-*O*-acyl shift (*path a*)[8] or 1,3-acyl shift (*path b*) leading to a M-carbene **A** or to an allene **B**, respectively. These complexes are poised for subsequent functionalization: cyclopropanation of **A** leads to the tricyclic derivative **C**, while **B** affords allene acetate **D**.[9] The **D**/**C** ratio strongly depends upon the cyclization efficiency, which is related to ring size. For $n = 1$, ring closure of intermediate **A** occurred

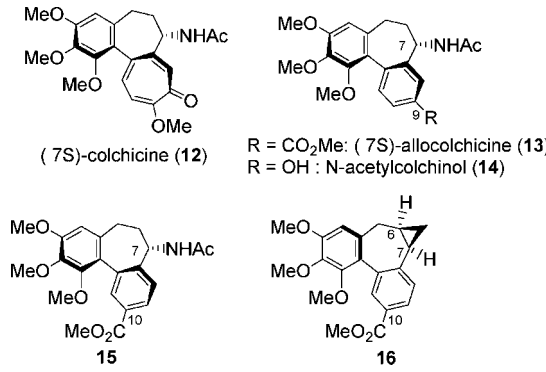


FIGURE 1. Colchicine and allocolchicinoids.

exclusively, leading to the cycloheptyl derivative **5**. For $n = 2$ and 3, the strain incurred in forming eight- and nine-membered rings presumably makes *path a* more difficult, allowing the formation of allenyl acetates **7** and **9**.[10]

We decided next to use the tricyclic structure **5** containig a seven-membered ring for the synthesis of a new class of allocolchicinoids. Allocolchicinoids are analogues of the important antimitotic (−)-colchicine **12**, in which the tropolone ring is replaced by a benzene ring (Figure 1). Like colchicine, some allocolchicinoids also arrest mitosis by inhibiting tubulin polymerization.[11,12] Examples include natural allocolchicine **13**, *N*-acetylcolchinol **14**, and its methyl ether which bind to tubulin more strongly than colchicine itself. Total syntheses of **13** and **14** have been reported, and a number of syntheses of various allocolchicinoids have also been described.[13]

Recently, we described the synthesis of allocolchicine **15**, analogue of **13**, having the ester group at position C10.[14,15] This compound was found to be as active as natural allocolchicine **13**.[16] We report now the synthesis of a new allocolchicinoid **16**, in which the acetamide function in **15** has been replaced by a cyclopropane ring fused to the seven-membered ring at the C6−C7 positions.

The retrosynthetic analysis is outlined in Scheme 3. Thus, the target compound **16** could be prepared by a Diels−Alder/aromatization sequence from diene **17**. This intermediate can be traced back to **18**, which is formed by the Au(I) cycloisomerization reaction of enyne **2**. This precursor was prepared from aldehyde **19**.[15]

As shown in Scheme 4, alkynylation of aldehyde **19** followed by treatment of the resulting hydroxy ester with a catalytic amount of TsOH in CH_2Cl_2 afforded lactone **20** in 61% overall

(8) There is no general agreement on the respective order of 1,2-shift/cyclopropanation. See for examples refs 2c and 4a and references cited therein.

(9) For examples of the formation of allenes as side products, see: Marion, N.; Diez-Gonzalez, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. ref 2c.

(10) Presumably, for the same reasons, 1,4-enynes (Scheme 1, $n = 0$) do not lead to the highly strained [2.1.0]bicyclic system. Instead, 2-cyclopentenones are formed through the Rautenstrauch rearrangement. See: (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950. (b) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802.

(11) For reviews on the synthesis and biological activity of colchicine and allo congeners, see: (a) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230. (b) Boyé, O.; Brossi, A. In *The Alkaloids;* Brossi, A., Cordell, G. A., Eds.; Academic Press: New York, 1992; Vol. 41, p 125, and references therein.

(12) For a review on microtubule-targeted drugs, see: Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253.

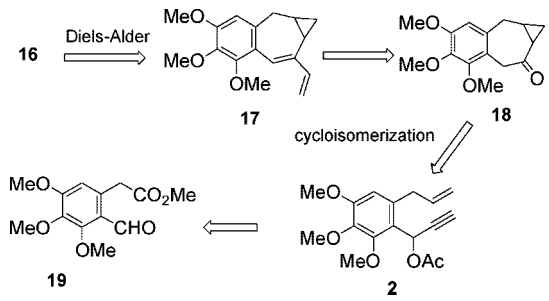
(13) For recent references, see: (a) Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *Tetrahedron* **2008**, *68*, 949. (b) Besong, G.; Jarowski, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem* **2006**, *4*, 2193. (c) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849. (d) Büttner, F.; Bergemann, S.; Guénard, D.; Gust, R.; Seitz, G.; Thoret, S. *Bioorg. Med. Chem.* **2005**, *13*, 3497. (e) Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15. (f) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Org. Chem.* **2003**, *64*, 5826.

(14) The colchicine numbering has been used throughout this paper.

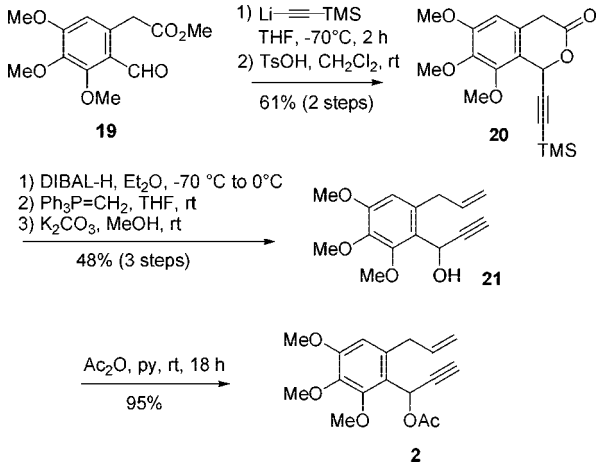
(15) Boyer, F.-D.; Hanna, I. *Org. Lett.* **2007**, *9*, 715.

(16) Boyer, F.-D.; Dubois, J.; Hanna, I. Unpublished work.

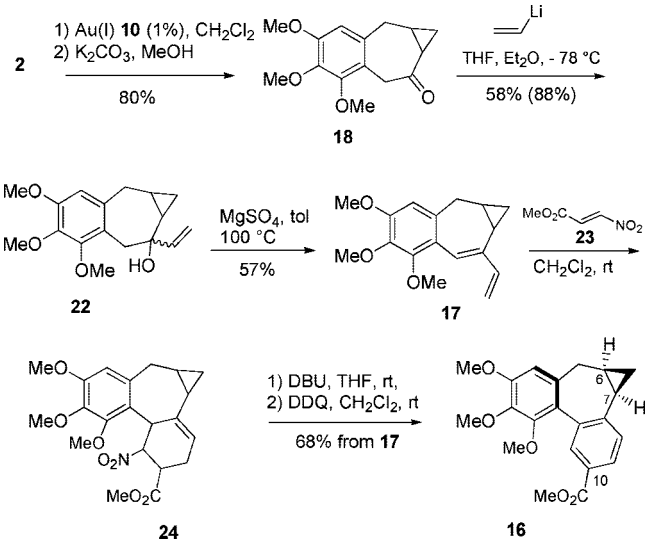
SCHEME 3. Retrosynthetic Analysis



SCHEME 4. Preparation of Enyne 2



SCHEME 5. Synthesis of Allocolchicinoid 16



yield. This product was reduced to the corresponding lactol, which was converted into enyne **21** using a Wittig reaction followed by desilylation of the alkyne moiety. Subsequent acylation of the resulting propargylic alcohol gave **2**.

As seen above, enyne propargylic acetate **2** readily underwent cycloisomerization, affording the tricyclic compound **5** (Table 1) which led after hydrolysis to cyclopropylketone **18** in 80% yield over two steps (Scheme 5). Treatment of this ketone with vinyllithium in ether/THF at −78 °C produced allylic alcohol **22** as a mixture of isomers in 58% yield along with 34% of recovered starting material.[17] When this mixture was heated at 100 °C in toluene in the presence of $MgSO_4$, diene **17** was

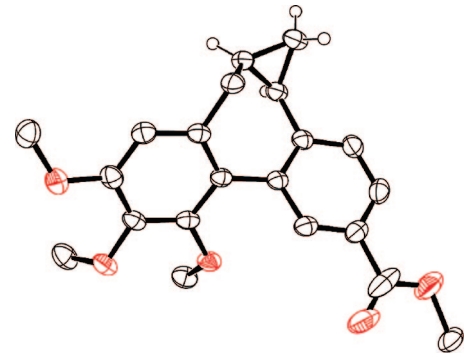


FIGURE 2. ORTEP drawing of compound **16**. Only hydrogen atoms of the cyclopropane ring are shown.

obtained as a white solid in 57% yield. On the basis of the results reported in a previous work,[15] we reasoned that [4 + 2] cycloaddition of methyl β-nitroacrylate **23**[18] to **17** would occur regioselectively, placing the ester group at the desired position. Indeed, **23** readily reacted with diene **17** at *room temperature*, affording cycloadduct **24** in quantitative yield (Scheme 5). The elimination of nitrous acid using DBU and the subsequent aromatization by DDQ furnished allocolchicinoid **16** in 68% overall yield. This tetracyclic structure was assigned on the basis of spectroscopic data, and the relative configuration at C-6 and C-7 was determined by X-ray crystallographic analysis (Figure 2). As allocolchicinoids, this compound displays molecular asymmetry resulting from a noncoplanar arrangement of rings A and C. The X-ray data show that these rings are twisted with a torsion angle of 45°.

In summary, we have achieved the synthesis of a new class of allocolchicinoids using the Au-catalyzed cycloisomerization reaction of 1,7-enyne propargylic acetate for the construction of a seven-membered ring fused to a cyclopropane and a Diels−Alder/aromatization sequence for the elaboration of the aromatic ring C. Compound **16** will be subjected to a tubulin binding assay in order to gain some indication of its ability to function as antimitotic agent, and the results will be reported in due course.

Experimental Section

Cycloisomerization of Enyne 2, Tricyclic Ketone 18: To a solution of enyne propargylic acetate **1** (79 mg, 0.26 mmol) in dry CH_2Cl_2 (1.5 mL) was added Au(I) catalyst **10** (1.5 mg, 0.75 mol %). The mixture was stirred at room temperature for 2 h. After addition of one drop of Et_3N, the solvent was removed. To the solution of the resulting residue in MeOH (3 mL) was added K_2CO_3 (7 mg), and the mixture was stirred for 2.5 h at room temperature. The solvent was removed under reduce pressure, and the residue was submitted to flash chromatography on silica gel (EtOAc/PE 1:4) to give ketone **18** (55 mg, 80% over 2 steps) as a white solid: mp 86−87 °C; ^{1}H NMR δ = 6.55 (s, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.69 (d, J = 13.2 Hz, 1 H), 3.48 (d, J = 13.2 Hz, 1 H), 3.35 (dd, J = 14.8, 6.0 Hz, 1 H), 2.87 (dd, J = 14.8, 7.6 Hz, 1 H), 1.76−1.62 (m, 2 H), 1.35−1.30 (m, 1 H), 1.03 (q, J = 5.6 Hz, 1 H); ^{13}C NMR δ = 204.3 (C), 152.1 (C), 151.7 (C), 141.2 (C), 134.7 (C), 118.6 (C), 108.4 (CH), 61.5 (CH_3), 60.9 (CH_3), 56.0 (CH_3), 38.7 (CH_2), 34.4 (CH_2), 26.9 (CH_2), 20.2 (CH), 15.7

(17) Initial attempts to prepare **22** by treatment of ketone **18** with vinylmagnesium bromide at room temperature led to the desired alcohol in low yield (24%) along with the reduction product of ketone **18**.

(18) Methyl β-nitroacrylate was prepared according to the procedure described by Pritchard et al.: Pritchard, R. G.; Stoodly, R. J.; Yuen, W.-H. *Org. Biomol. Chem.* **2005**, *3*, 162.

(CH_2); IR (CCl_4) ν_{max} 2998, 2937, 2869, 2840, 1740, 1690, 1595 cm^{-1}; EI MS *m/z* (%) 262 ($M^{+\bullet}$) (100), 219 ($M^{+\bullet}$ − Ac) (20); CI MS (NH_3) *m/z* (%) 280 ($M^{+\bullet}$ + 18) (25), 263 ($M^{+\bullet}$ + 1) (100); HMRS (EI) *m/z* calcd for $C_{15}H_{18}O_4$, 262.1205; found, 262.1219.

Cycloadduct 24. A solution of methyl β-nitroacrylate **23** (20 mg, 0.152 mmol, 5.2 equiv) and diene **17** (8 mg, 0.029 mmol) in 0.25 mL of CH_2Cl_2 was stirred at room temperature for 22 h. The volatiles were removed by evaporation under reduced pressure, and the residue was purified by chromatography on silica gel (EtOAc/EP 1:9) to give 12 mg of **24** (0.029 mmol, 100%) as a mixture of diastereoisomers unseparable by chromatography on silica gel. Major isomer: ^{1}H NMR δ = 6.35 (s, 1 H), 5.77−5.75 (m, 1 H), 5.35 (t, J = 3.2 Hz, 1 H), 4.72−4.71 (br s, 1 H), 3.90 (s, 3 H), 3.84 (s, 6 H), 3.82−3.79 (m, 1 H), 3.20 (s, 3 H), 2.53 (dd, J = 14.0, 4.4 Hz, 1 H), 2.41 (dd, J = 14.0, 11.6 Hz, 1 H), 2.16−2.12 (m, 1 H), 1.55−1.48 (m, 1 H), 1.28−1.16 (m, 2 H), 0.84−0.81 (m, 1 H), 0.49 (q, J = 5.2 Hz, 1 H); ^{13}C NMR δ = 171.3 (C), 153.0 (C), 151.7 (C), 140.4 (C), 138.1 (C), 135.5 (C), 124.2 (CH), 122.5 (C), 108.4 (CH), 88.0 (CH), 60.8 (CH_3), 60.7 (CH_3), 55.9 (CH_3), 51.8 (CH_3), 41.1 (CH), 40.9 (CH), 34.9 (CH_2), 23.1 (CH_2), 19.9 (CH), 19.0 (CH), 12.0 (CH_2).

Allocolchicinoid 16. To a solution of **24** (12 mg, 29 μmol) in THF (0.25 mL) was added two drops of DBU. The reaction mixture was stirred for 2 h at room temperature under N_2. The volatiles were removed in vacuo, and the residue was filtered through a thin plug of silica gel (EtOAc/PE 1:9) to give, after solvent evaporation, 10 mg of elimination product. This was dissolved in 0.25 mL of CH_2Cl_2, and DDQ (10 mg, 44 μmol) was added. The solution was stirred for 2 h at room temperature. The solvent was evaporated, and the crude mixture was filtered through a layer of Al_2O_3 to give, after solvent removal, 7 mg of ester **16** (19.7 μmol, 68% from diene **17**) as a colorless oil which crystallized on cooling: mp 105−107 °C. Major atropoisomer: ^{1}H NMR δ = 8.09 (d, J = 2.0 Hz, 1 H), 7.90 (dd, J = 8.0, 2.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 6.61 (s, 1 H), 3.934 (s, 3 H), 3.929 (s, 3 H), 3.91 (s, 3 H), 3.55 (s, 3 H), 3.89 (dd, J = 13.6, 5.2 Hz, 1 H), 2.00−1.92 (m, 2 H), 1.27 (t, J = 3.7 Hz, 1 H), 1.04−1.00 (m, 1 H), 0.50 (q, J = 5.0 Hz, 1 H); ^{13}C NMR δ = 167.3 (C), 152.2 (C), 145.0 (C), 141.1 (C), 137.6 (C), 134.6 (C), 135.3 (C), 133.2 (CH), 132.8 (CH), 127.8 (CH), 127.6 (C), 124.5 (C), 106.7 (CH), 61.1 (CH_3), 61.0 (CH_3), 56.0 (CH_3), 52.0 (CH_3), 36.5 (CH_2), 22.4 (CH), 16.5 (CH), 11.4 (CH_2); IR (CCl_4) ν_{max} 2997, 2933, 2854, 1724, 1596 cm^{-1}; CI MS (NH_3) *m/z* (%) 372 ($M^{\bullet}$ + 18) (100), 355 ($M^{\bullet}$ + 1) (40), 323 (10); HMRS (EI) *m/z* calcd for $C_{21}H_{22}O_5$, 354.1467; found, 354.1453.

Acknowledgment. We are grateful to Dr. F. Gagosz (Ecole Polytechnique) for providing gold catalysts **10** and **11**.

Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray analysis of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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