Natural Products

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Synthesis of (+)-Schisanwilsonene A by Tandem Gold-Catalyzed Cyclization/1,5-Migration/Cyclopropanation**

*Morgane Gaydou, Ricarda E. Miller, Nicolas Delpont, Julien Ceccon, and Antonio M. Echavarren**

(+)-Schisanwilsonene A (**1**) is a carotane-type sesquiterpenoid isolated from the *Schisandra wilsoniana* (Schisandraceae), a medicinal plant indigenous to southern China whose fruits have been used in Chinese folk medicine to treat hepatitis (Figure 1).[1] (+)-Schisanwilsonene A (**1**) shows

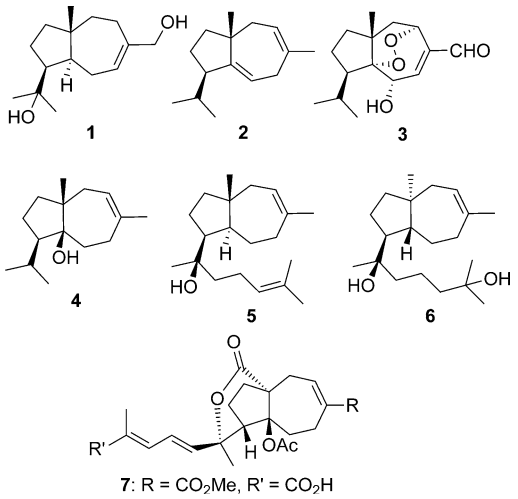

Figure 1. (+)-Schisanwilsonene A (**1**), carota-1,4-diene (**2**), rugosal A (**3**), carotol (**4**), and structurally related diterpenes tormesol (**5**), polasol C (**6**), and pseudolaric acid B (**7**).

antiviral activity inhibiting HBsAg and HBeAg at 50 $\mu g\,mL^{-1}$, with an activity higher than that of lamivudine (2′,3′-dideoxy-3′-thiacytidine, 3TC), a potent reverse transcriptase inhibitor marketed as Zeffix, Heptovir, Epivir, and Epivir-HBV. Other carotanes (also known as daucanes), such as carota-1,4-diene (**2**), rugosal A (**3**), and carotol (**4**) have been isolated from higher plants.[2] These compounds are structurally related to the diterpenes tormesol (**5**), isolated from the plant *Halimium viscosum*,[3,4] and polasol C (**6**) from the marine sponge *Epipolasis* sp.[5] Pseudolaric acid B (**7**) is a member of this family and has attracted much attention because of its antitumor activity.[6] The absolute configurations of carota-1,4-diene (**2**)[7] and carotol (**4**)[8] are known, although sesquiterpenes with the enantiomeric configuration have been isolated from other plant species.[2e]

(+)-Schisanwilsonene A (**1**) and tormesol (**5**) feature a *syn* relationship between the angular Me and the side chain, which is sterically more congested than the *anti* relationship present in polasol C (**6**) and other sphenolobane (tormesane) terpenoids.[9,10]

As part of a program aimed at the synthesis of members of these families of sesquiterpenes and diterpenes, which display significant biological activities,[11] we have targeted (+)-schisanwilsonene A (**1**), whose absolute configuration had not been assigned. Herein we report the first total synthesis of (+)-schisanwilsonene A (**1**) and the assignment of its absolute configuration as shown in Figure 1.

Our synthesis is based on a gold(I)-catalyzed tandem reaction of 1,6-enynes, which are substituted with propargylic alkoxy groups, developed in our group (Scheme 1).[12] Thus, we expected that a cationic gold(I) catalyst would trigger the cyclization of the propargylic alcohol derivative **8** through intermediates **I** and **II** to form the α,β-unsaturated gold carbene **III**, which could then undergo an intermolecular cyclopropanation with alkene **9** to form **10** or **10′**. Selective transformation of one of the diastereotopic alkoxymethylene groups of **10** would then lead to the divinyl cyclopropane **11**, which would undergo a [3,3] sigmatropic rearrangement[13] via $\mathbf{TS_{11\rightarrow 12}}$ to form key the 1,2,3,3a,4,7-hexahydroazulene **12**.[14]

We expected that the bulky CMe_2OR group would dictate the facial selectivity in the cyclopropanation reaction. However, the preferred orientation of the alkene in the approach to **III** was much less evident. This issue was crucial since **10′** would not lead to **12**. DFT calculations (M06 functional)[15] for the cyclopropanation between **III** and 2-methylpropene revealed a modest preference ($\Delta\Delta G^{\ddagger} = 0.4$ kcal mol^{-1}) for the formation of **13** through $\mathbf{TS_{III\rightarrow 13}}$ by a concerted cyclopropanation.[16]

We initially examined an intramolecular strategy in which the alkene was appended to the 1,6-enyne through a silicon tether (Table 1). The siloxanes (±)-**8a**,**b**[17] reacted smoothly with the catalysts **A** and **B** to give the corresponding cyclic (±)-**14a**,**b**, which were immediately treated with HF·py to give (±)-**10a** (Table 1, entries 1–3). The compound (±)-**10a**

[*] M. Gaydou, Dr. R. E. Miller, N. Delpont, Dr. J. Ceccon, Prof. A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
Prof. A. M. Echavarren
Departament de Química Analítica i Química Orgànica
Universitat Rovira i Virgili
C/Marcel·li Domingo s/n, 43007 Tarragona (Spain)
E-mail: aechavarren@iciq.es

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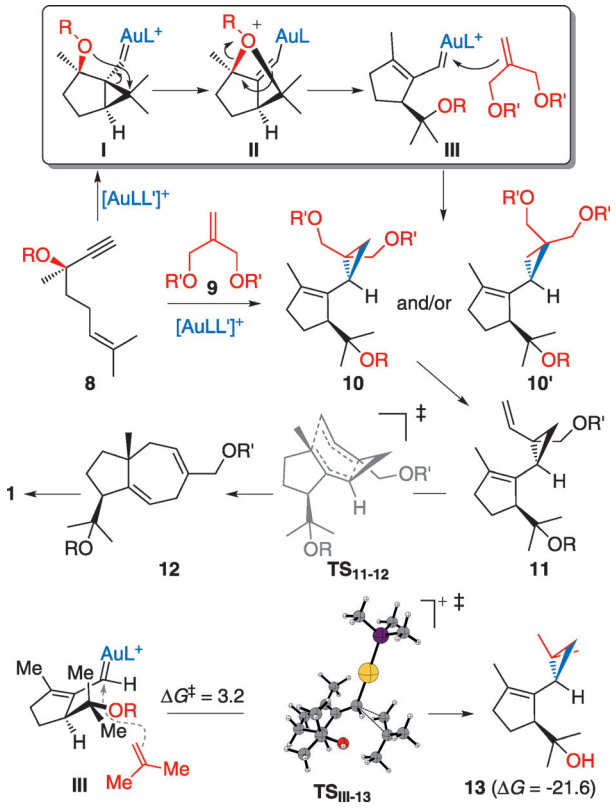


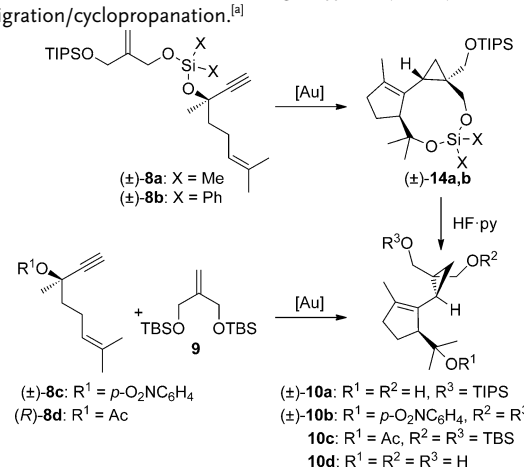
Scheme 1. Gold-catalyzed tandem cyclization/1,5-migration/cyclopropanation for the synthesis of **1**. Energies in kcal mol^{-1}.

was isolated in 40–47% yield as a single crystalline stereoisomer, whose structure was determined by X-ray diffraction (Figure 2a). Although the intramolecular approach leads to the potentially useful synthetic intermediate (±)-**10a**, we also explored the more direct intermolecular reaction using (±)-**8c** having a *p*-nitrophenyl ether as the alkoxy group. Remarkably, reaction of (±)-**8c** with the symmetrically protected 2-methylenepropane-1,3-diol **9** using catalyst **D** led to (±)-**10b** in 78% yield with the same stereochemical outcome as that obtained in the intramolecular reaction.[18]

The substrate **8d** with a propargylic acetate could also be used as a substrate in the tandem cyclization/1,5-migration/cyclopropanation process. Thus, reaction of (*R*)-**8d** (96:4 e.r.)[19] with catalyst **A** led to **10c** in 48–55% yield (up to 2.6 mmol scale) with an e.r. value of 91:9 (Table 1, entry 8). Lower yields were obtained using the catalysts **B** or **D** (Table 1, entries 9 and 10). The relative configuration was confirmed by X-ray diffraction of the crystalline triol **10d** derivative and the absolute configuration was determined on its methyl xanthate (Figures 2b,c).[20]

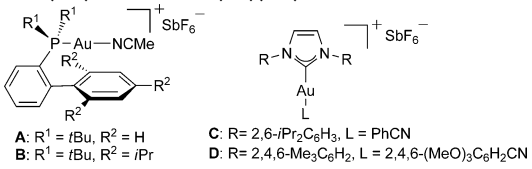
The successful cyclization of **8d** to give **10c** is remarkable since propargyl acetates are prone to undergoing gold(I)-promoted 1,2- or 1,3-migrations in related systems[21,22] (Scheme 2), and could result in racemization.[22g] Indeed, 1,6-enynes with a propargylic acetate react preferentially with gold catalysts by 1,2- or 1,3-acetate migration[23] or by other cycloisomerization pathways.[24] The observed approximate 5% decrease in e.r. from 96:4 to 91:9 can be rationalized by a competitive minor pathway proceeding by 1,2-migration via

Table 1: Intra- and intermolecular gold(I)-catalyzed cyclization/1,5-migration/cyclopropanation.[a]



Entry	Substrate	Catalyst (mol%)	*T* [°C]	**10** Yield [%][b]
1	(±)-**8a**	**A** (5)	0→23	40 (**10a**)
2	(±)-**8b**	**A** (5)	0→23	47 (**10b**)
3	(±)-**8b**	**B** (5)	0	41 (**10b**)
4	(±)-**8b**	**C** (5)	0→23	17 (**10b**)
5	(±)-**8b**	**C** (5)	0	29 (**10b**)
6	(±)-**8b**	**D** (5)	0	26 (**10b**)
7	(±)-**8c**	**D** (2)	23	78 (**10c**)
8	**8d**	**A** (3)	23	48–55 (**10d**)
9	**8d**	**B** (3)	23	22 (**10d**)
10	**8d**	**D** (3)	23	18 (**10d**)

[a] CH_2Cl_2, 30 min. [b] Yield of the isolated product. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.



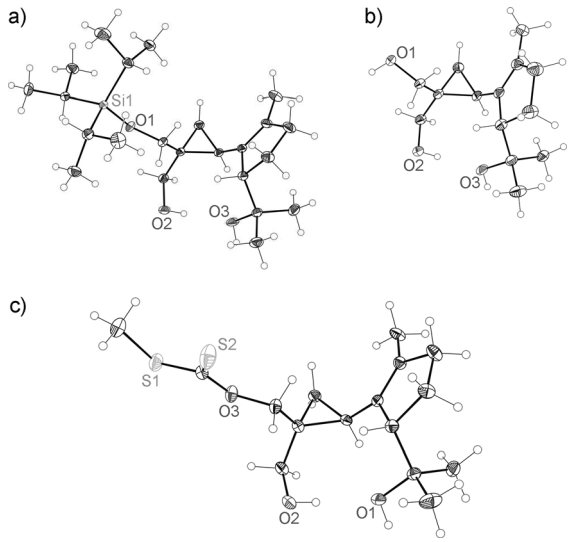
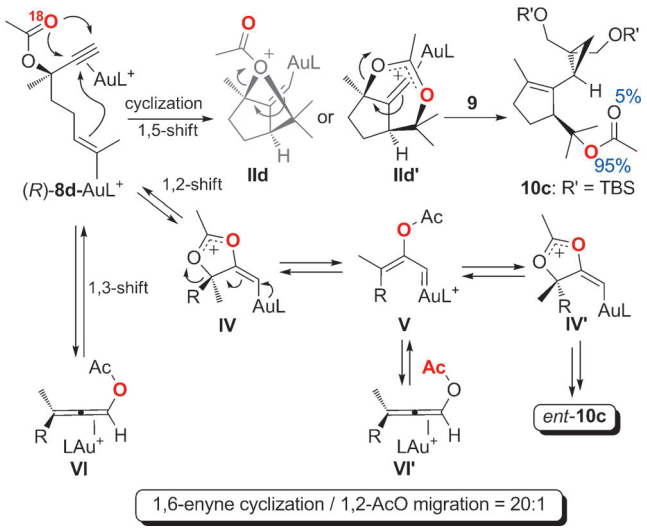
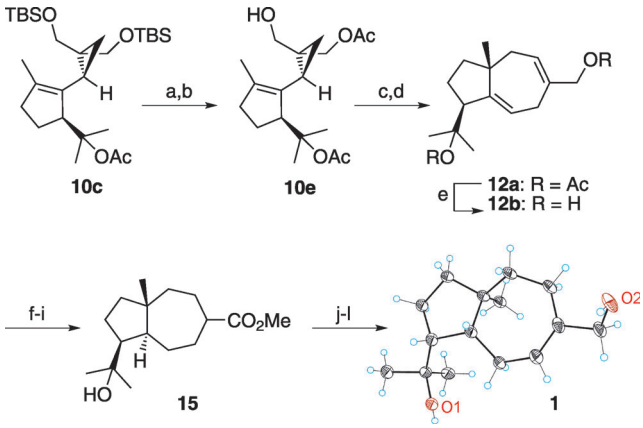


Figure 2. X-ray structures of synthetic intermediates **10a** (a) and **10d** (b) obtained in the intra- and intermolecular approaches, respectively. c) Absolute configuration of the methyl xanthate of **10d**.



Scheme 2. Cyclization/1,5-migration/cyclopropanation leading to **10c** via the intermediate **IId′** with retention of enantiomeric purity versus partial racemization by 1,2-shift of the acetate through **IV**/**V**/**IV′**. The oxygen atom in red refers to the ^{18}O label.



Scheme 3. Synthesis of (+)-schisanwilsonene A (**1**). Reagents and conditions: a) TBAF, THF, 23 °C (81 %); b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C (70 %, 3:1); c) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C; d) Ph_3PCH_3Br, *n*BuLi, THF, −20 °C to 23 °C (83 %, 2 steps); e) $LiAlH_4$, THF, 0 °C to 23 °C (90 %); f) Raney-Ni, H_2 (80 atm), acetone, 63 °C, 60 h (83 %); g) TEMPO, $PhI(OAc)_2$, CH_2Cl_2/H_2O (2:1), 23 °C (55 %); h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH/H_2O (5:1), 23 °C; i) $TMSCHN_2$, toluene/MeOH (1:2), 0 °C (74 %, 2 steps); j) KHMDS, PhSeCl, THF, −78 °C to 0 °C (93 %); k) H_2O_2, CH_2Cl_2, 23 °C (73 %); l) DIBAL, THF, −78 °C to 23 °C (78 %). DIBAL = diisobutylaluminum hydride, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMP = Dess–Martin periodinane, HMDS = hexamethyldisilazide, TBAF = *tert*-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

achiral intermediate **V**. Therefore, in this case, the 1,6-enyne cyclization is approximately 20 times faster than the propargylic acetate migration. We also prepared [^{18}O]-**8d** with the ^{18}O label at the carbonyl group to determine whether the 1,5-migration occurs via the five- (**IId**) or seven-membered ring (**IId′**) intermediates (Scheme 2). The mass spectral data of the resulting acetate **10c** and the triol derivative **10d** revealed that the ^{18}O had been preferentially transferred as the alcohol oxygen atom, and is consistent with a migration proceeding via **IId′**.[25]

The enantioselective synthesis of (+)-schisanwilsonene A (**1**) was completed from **10c** (Scheme 3). After desilylation of **10c**, selective acetylation gave the diacetate **10e** (3:1 ratio). The two acetates were separated by chromatography, and the minor one was recycled. Oxidation of **10e** with DMP and subsequent Wittig methylenation of the aldehyde gave a diene which underwent a [3,3] sigmatropic rearrangement at room temperature to form **12a**. Removal of the acetates with $LiAlH_4$ gave the diol **12b** (90:10 e.r.), a dihydroxy derivative of carota-1,4-diene (**2**). The desired *trans* fusion was established by hydrogenation of **12b** in the presence of Raney nickel, and was followed by oxidation of the primary alcohol and esterification to provide the hydroxy ester **15**. (+)-Schisanwilsonene A (**1**)[26] was finally obtained by selenylation of the potassium enolate of **15**, subsequent elimination of the selenoxide (2–3:1 regioselectivity), and then reduction of the ester.

In summary, we have completed the first enantioselective synthesis of (+)-schisanwilsonene A (**1**) in 13 steps (ca. 4 % overall yield) from the known acetate **8d**. This synthesis establishes the configuration of (+)-schisanwilsonene A as 1*S*,3a*R*,8a*S*. The 1,2,3,3a,4,7-hexahydroazulene skeleton was constructed by a gold(I)-catalyzed reaction and subsequent divinyl cyclopropane rearrangement. We have also found that the intramolecular attack of an alkene to a η^2-alkyne gold(I) complex can be faster than the competing 1,2-acyl migration. In this work, gold(I) orchestrates one of the most complex transformations which has been applied thus far in total synthesis. Extension of this strategy to the synthesis of other terpenoids is underway.

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[25] We found an approximately 5 % scrambling of the ^{18}O label, and can be explained through a double 1,2-shift via **V** to give **VI′**.[22g,i] This result is consistent with the observed approximate 5 % racemization. The equilibration between [^{18}O]-**8d**/AuL^{+} and chiral **VI** by 1,3-shift ([3,3] sigmatropic rearrangement) neither exchanges the ^{18}O label nor leads to racemization.

[26] ^{1}H and ^{13}C NMR data of (+)-**1** is in full accordance with previously reported data. In addition, the relative configuration was confirmed by X-ray diffraction of synthetic (±)-**1**.[20] The optical rotation for the synthetic material, $[\alpha]_D^{25} = +14.8°$ (c = 0.33, MeOH), is lower than that reported $[\alpha]_D^{25} = +52.3°$ (c = 0.02, MeOH). Unfortunately, a sample of natural (+)-**1** was not available anymore from the natural source.[1] HPLC analysis (chiral stationary phase) of synthetic (+)-**1** shows the same enantiomeric ratio (90:10) determined for **12a**, which is also identical, within experimental error, to that found for **10c**. The melting point of the synthetic material (single crystal after recrystallization from cyclohexane/EtOAc) is 143–144 °C (lit[1] 165–168 °C).

