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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[1] (Figure 1). Schisanwilsonene A (**1**) shows antiviral activity inhibiting HBsAg and HBeAg at 50 μg/mL, 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 a marine sponge *Epipolasis* sp.[5] Pseudolaric acid B (**7**) is a member of this family that 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]

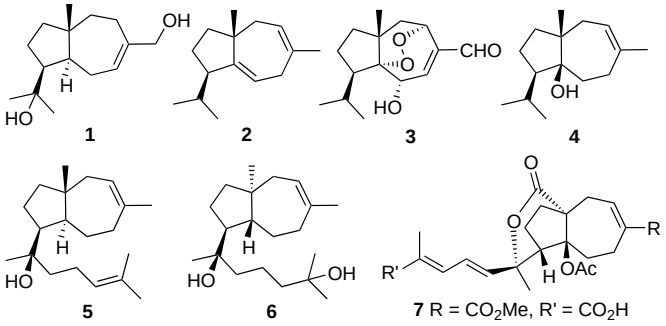

Figure 1. Schisanwilsonene A (**1**), carota-1,4-diene (**2**), rugosal A (**3**), carotol (**4**), and structurally related diterpenes tormesol (**5**), polasol C (**6**), and pseudolaric acid B (**7**).

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

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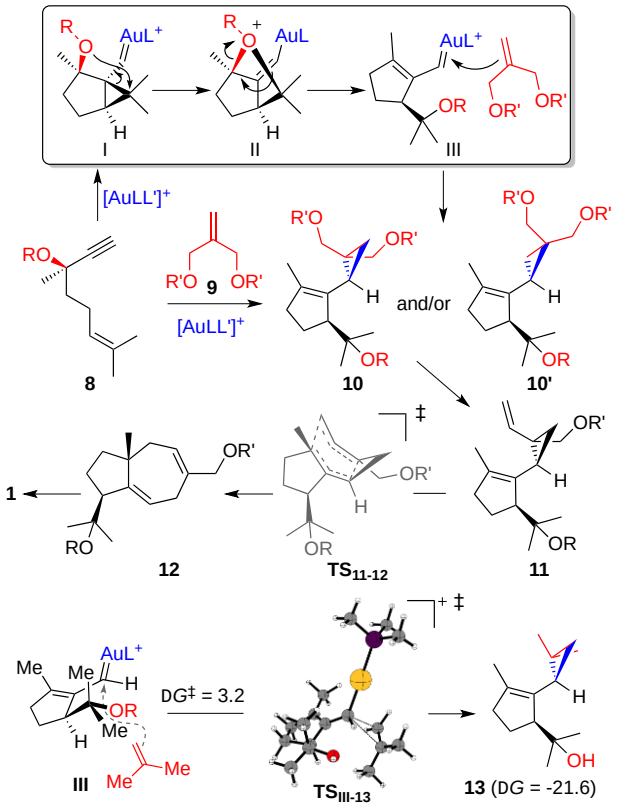
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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

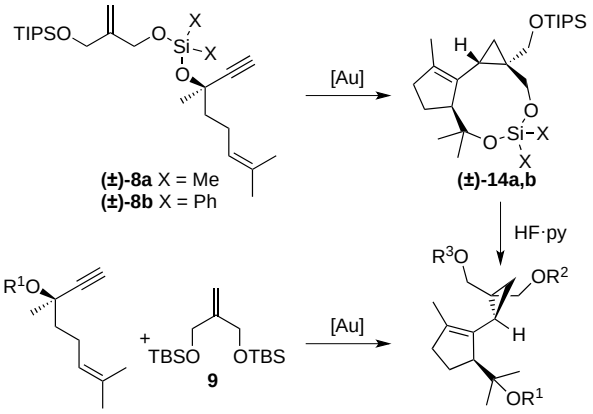
Our synthesis is based on a gold(I)-catalyzed tandem reaction of 1,6-enynes substituted with propargylic alkoxy groups developed in our group (Scheme 1).[12] Thus, we expected that a cationic gold(I) catalyst would trigger the cyclization of propargylic alcohol derivative **8** through intermediates **I** and **II** to form *α,β*-unsaturated gold carbene **III**, which could then undergo an intermolecular cyclopropanation with alkene **9** to form **10** and/or **10'**. Selective transformation of one of the diastereotopic alkoxymethylene groups of **10** would then lead to divinyl cyclopropane **11**, which would undergo a [3,3] sigmatropic rearrangement[13] through **TS11-12** to form key 1,2,3,3a,4,7-hexahydroazulene **12**.[14]



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

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 was a crucial issue, since intermediate **10'** would not lead to **12**. DFT calculations (M06 functional)[15] for the cyclopropanation between gold(I) carbene **III** and 2-methylpropene revealed a modest preference ($\Delta\Delta G^{\ddagger}$ = 0.4 kcal·mol^{-1}) for the formation of **13** through $\mathbf{TS_{III\text{-}13}}$ by a concerted cyclopropanation.[16]

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

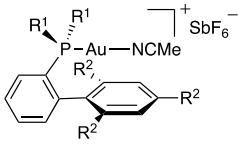


(±)-8c R^1 = *p*-$O_2NC_6H_4$
8d R^1 = Ac

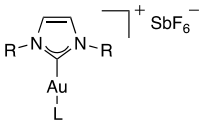
(±)-10a $R^1 = R^2$ = H, R^3 = TIPS
(±)-10b R^1 = *p*-$O_2NC_6H_4$, $R^2 = R^3$ = TBS
10c R^1 = Ac, $R^2 = R^3$ = TBS
10d $R^1 = R^2 = R^3$ = H

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

[a] CH_2Cl_2, 30 min.



A R^1 = *t*Bu, R^2 = H
B R^1 = *t*Bu, R^2 = *i*Pr



C R= 2,6-*i*Pr$_2$C$_6$H$_3$, L = PhCN
D R= 2,4,6-Me$_3$C$_6$H$_2$, L = 2,4,6-(MeO)$_3$C$_6$H$_2$CN

We initially examined an intramolecular strategy in which the alkene was appended to the 1,6-enyne through a silicon tether (Table 1). Siloxanes **(±)-8a**,**b**[17] reacted smoothly with catalysts **A** and **B** to give cyclic **(±)-14a**,**b**, which were immediately treated with HF·py to give **(±)-10a** (Table 1, entries 1-3). Diol **(±)-10a** 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 potentially useful synthetic intermediate **(±)-10a**, we also explored the more direct intermolecular reaction using **(±)-8c** with a *p*-nitrophenyl ether as the alkoxy group. Remarkably, reaction of **(±)-8c** with symmetrically protected 2-methylenepropane-1,3-diol **9** using catalyst **D** led to **(±)-10b** in 78% yield with the same stereochemical outcome obtained in the intramolecular reaction.[18]

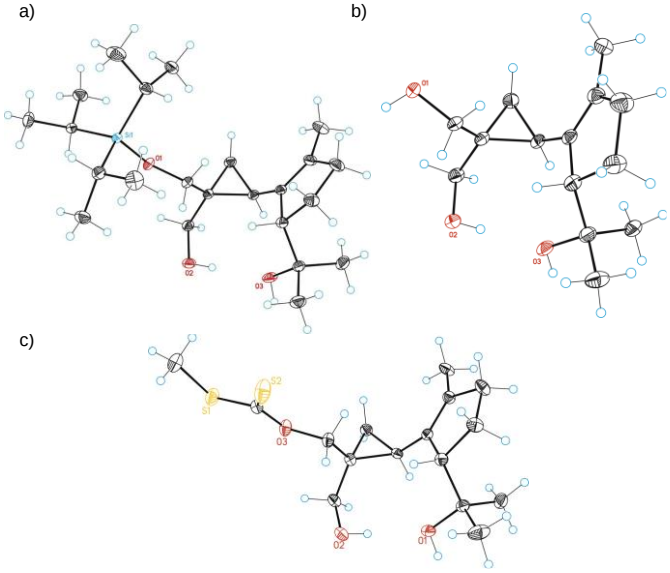
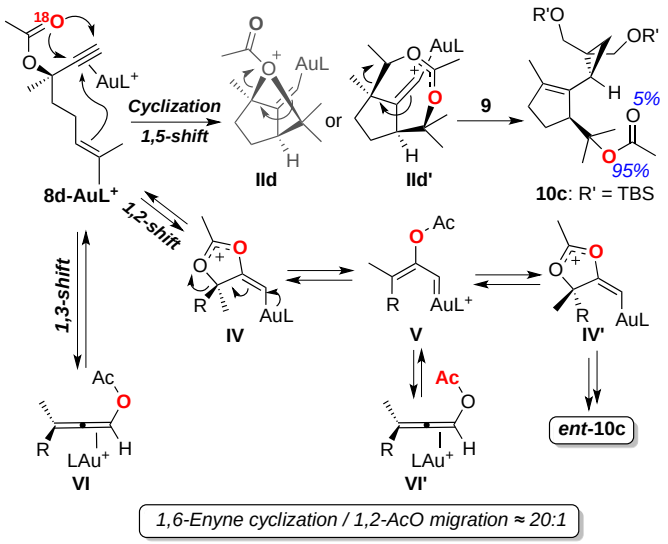


Figure 2. X-Ray structures of synthetic intermediates **10a** (a) and **10d** (b) obtained in the intra- and intermolecular approaches, respectively, and (c) absolute configuration of the methyl xanthate of **10d**.

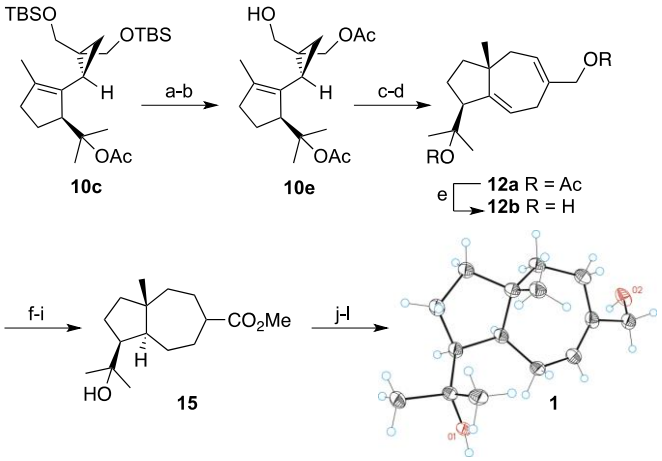
Substrate **8d** with a propargylic acetate could also be used as a substrate in the tandem cyclization/1,5-migration/cyclopropanation process. Thus, reaction of (*R*)-**8d** (96:4 er)[19] with catalyst **A** led to **10c** in 48-55% yield (up to 2.6 mmol scale) with a 91:9 er (Table 1, entry 8). Lower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



Scheme 2 Cyclization/1,5-migration/cyclopropanation leading to **10c** via 8-membered ring intermediate **IId'** with retention of enantiomeric purity vs. partial racemization by 1,2-shift of the acetate through **IV** / **V** / **IV'**. Bold oxygen in red refers to the ^{18}O label.

The successful cyclization of **8d** to give **10c** is remarkable since propargyl acetates are prone to undergo gold(I)-promoted 1,2- or 1,3-migrations in related systems[21,22] (Scheme 2), which 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 *ca.* 5% decrease in er from 96:4 to 91:9 can be rationalized by a competitive minor pathway proceeding by 1,2-migration via achiral intermediate **V**. Therefore, in this case, the 1,6-enyne cyclization is *ca.* 20 times faster than the propargylic acetate migration. We also prepared **^{18}O-8d** with the ^{18}O label at the carbonyl to determine whether the 1,5-migration occurs via 5- or 8-membered ring intermediates **IId** or **IId'** (Scheme 3). The mass spectral data of the resulting acetate **10c** and its triol derivative **10d** revealed that the ^{18}O had been preferentially transferred to the alcoholic oxygen, consistent with a migration proceeding through **IId'**.[25]

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



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, $PhI(OAc)_2$, 2:1 CH_2Cl_2-H_2O, 23 °C (55%); h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, 5:1 *t*BuOH-H_2O, 23 °C; i) $TMSCHN_2$, 1:2 toluene-MeOH, 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%).

In summary, we have completed the first enantioselective synthesis of (+)-schisanwilsonene A (**1**) in 13 steps (*ca.* 4% overall yield) from 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 has been built by a gold(I)-catalyzed reaction, followed by a 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 that has been applied thus far in total synthesis. Extension of this strategy to the synthesis of other terpenoids is underway.

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[14] DFT calculations (B3LYP, 6-31G* (C, H, O, THF solvent) predict a favorable reaction ($\Delta G^{\ddagger}$ = 22.0 kcal·mol^{-1}, ΔG -16.4 kcal·mol^{-1}), in agreement with literature data for other divinyl cyclopropane rearrangements.[13b] See Supporting Information for details.

[15] DFT calculations (M06, 6-31G(d) (C, H, P, O) and SDD (Au), CH_2Cl_2). See Supporting Information for details.

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[17] Siloxanes **(±)-8a-b** were prepared from racemic 3,7-dimethyloct-6-e1-yn-3-ol by sequential reaction with *n*BuLi, the corresponding dichlorosilane, and monosilylated 2-methylenepropane-1,3-diol in 40 and 81% yield, respectively. See Supporting information for details.

[18] The relative configuration of **(±)-10b** was determined by its conversion into (±)-schisanwilsonene A in 13 steps. Details will be reported in the full account of this work.

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

[26] ^1H 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, $[\alpha]_D^{25}$= +14.8º (c 0.33, MeOH), is lower than that reported value $[\alpha]_D^{25}$ = +52.3º (c 0.02, MeOH). Unfortunately, a sample of natural (+)-**1** was not anymore available from the natural source.[1] Chiral HPLC analysis 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 mp of the synthetic material (single crystal after recrystallization from cyclohexane/EtOAc) is 143-144 ºC (lit[1] 165-168 ºC).

Synthesis of (+)-Schisanwilsonene A

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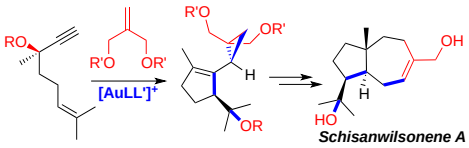

Schisanwilsonene A

The first total synthesis of antiviral schisanwilsonene A has been completed via a fully stereoselective tandem cyclization/1,5-OR migration/ intermolecular cyclopropanation catalyzed by gold.

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