Total Synthesis of Repraesentin F and Configuration Reassignment by a Gold(I)-Catalyzed Cyclization Cascade

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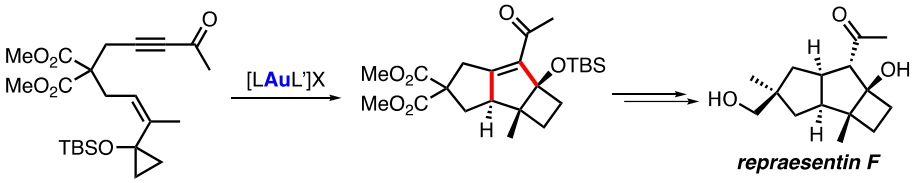
Supporting Information Placeholder



ABSTRACT: The first total synthesis of repraesentin F has been accomplished by a highly diastereoselective gold(I)-catalyzed cyclization cascade as the key step. This cycloisomerization/Prins-type tandem transformation enabled direct access to the atypical tricyclic carbon skeleton of the natural product with the required *syn*/*anti*/*syn* ring fusion. This synthetic effort also allowed reassignment of the relative configuration of repraesentin F and determination of its absolute configuration.

Repraesentin F (**1**) is a protoilludane-related sesquiterpene isolated in 2006 from the fruiting bodies of *Lactarius repraesentaneus*, an endemic fungus of coniferous forests in the mountainous regions of Japan.[1] This sesquiterpene exhibits growth regulation on plants, promoting the radicle elongation of lettuce seedlings 116% at 3.6·10² μM concentration. The most characteristic feature of **1** is its unusual *syn*/*anti*/*syn* decahydrocyclobuta[*a*]pentalene skeleton,[1a] only previously found in the sesquiterpenes sulcatine G (**2**),[2] kelsoene (**3**),[3] and poduran (**4**).[4]

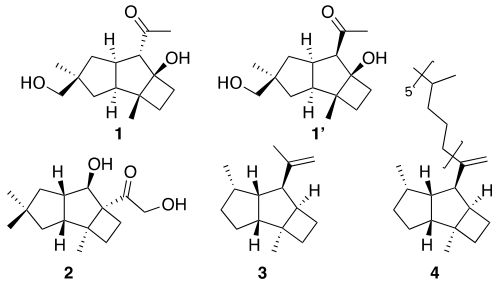
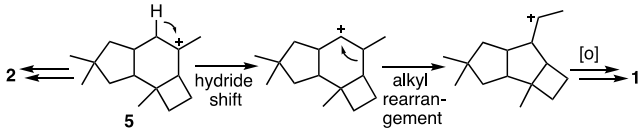


Figure 1. Repraesentin F **1** (corrected, relative configuration), 7-*epi*-repraesentin F **1'** (reported, relative configuration), (+)-sulcatine G (**2**), (+)-kelsoene (**3**), poduran (**4**).

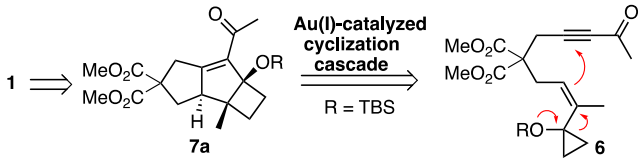
The uncommon tricyclic skeleton of repraesentin F is presumably biosynthesized from a protoilludane intermediate (**5**) that undergoes further rearrangement and oxidation (Scheme 1).[5] Related biosynthethic pathways have been suggested for sulcatine G (**2**),[2] even though both natural products are isolated from different families of fungi.[1a,2] Distinct biosynthetic origins are proposed for kelsoene **3** and poduran **4**.[6]

Scheme 1. Proposed biosynthetic origins for 1 and 2.



Although the syntheses of structurally related sesquiterpenes sulcatine G (**2**)[2] and kelsoene (**3**)[3] have been reported both in racemic[7] and enantiopure[8] forms, there is no total synthesis of repraesentin F reported to date. Furthermore, the absolute configuration of repraesentin F has never been substantiated.

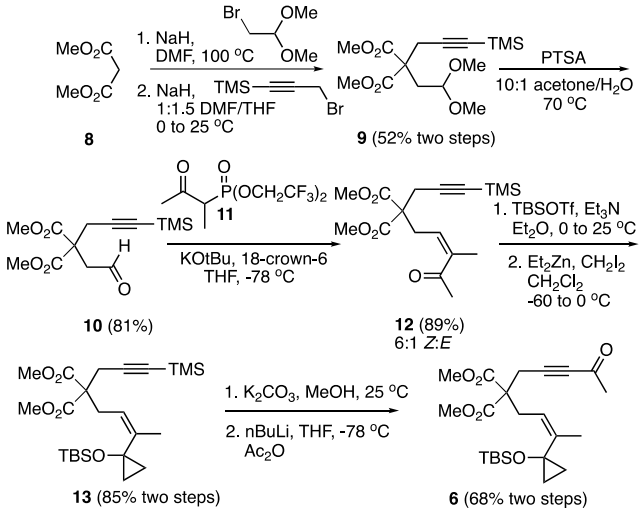
Scheme 2. Retrosynthesis for Repraesentin F



Herein, we report the first total synthesis of repraesentin F (**1**),[9] which leads to the revision of its structure from the originally proposed 7-epimer **1'**[1a] to **1** (Figure 1). Moreover, its absolute configuration was unambiguously assigned after separation of the enantiomers by chiral HPLC and further crystallization of their ferrocenoate ester.[10] Our approach to the construction of the tricyclic scaffold of **1** in a single-step is unparalleled, as it relies on a complex one-pot diastereoselective gold(I)-catalyzed cyclization cascade involving a tandem gold(I)-catalyzed enyne cyclization/ring expansion/Prins cyclization[11] of substrate **6** to efficiently build tricyclic intermediate **7a** (Scheme 2).

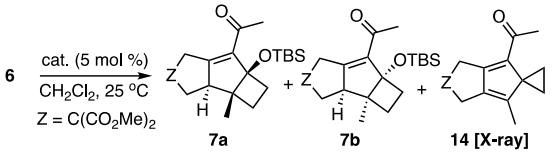
Our synthesis commenced with a double alkylation of dimethyl malonate (**8**) to provide **9** (52%, two steps), which was hydrolyzed under acidic conditions to give aldehyde **10** (81%) (Scheme 3). Alkenylation of aldehyde under the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction using phosphonate **11** provided 1,6-enyne **12** in 89% yield as 6:1 *Z*:*E* isomer mixture. Formation of the TBS enol ether, followed by Simmons-Smith cyclopropanation, led to cyclopropyl enyne **13** (85% yield, two steps). The TMS group was removed with methanolic K_2CO_3 (96%) and the resulting terminal alkyne was then acetylated to give cyclopropyl enyne **6** (68%, two steps, 6:1 *Z*:*E*),

Scheme 3. Preparation of Substituted 1,6-Enyne 6



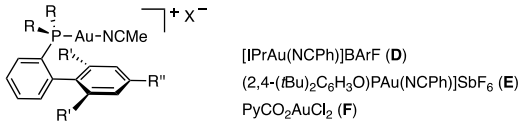
We examined the cascade cyclization of **6** to form tricyclic compound **7a** with the desired *anti* ring fusion. A number of gold(I) complexes, typical Lewis acids, and Brønsted acids were explored as catalysts for the cyclization (Table 1). The use of Lewis acids such as $Sc(OTf)_3$ or $AgSbF_6$ (Table 1, entries 1 and 2) afforded compound **14** as the major product, which originates from **7a** or **7b** by formation of allyl cation **15**, followed by proton-loss and cyclobutane to cyclopropane rearrangement (Scheme 4). The structure of **14** was confirmed by X-ray diffraction. Products **7a** and **7b** were also obtained in low yields, with the formation of the undesired *syn*-fused scaffold **7b** being favored with these catalysts. The formation of desired **7a** was favored when using $ZnCl_2$ or $AgBF_4$ (Table 1, entries 3 and 4), although low yields (16% and 24%, respectively) and moderate diastereoselectivities were obtained. Poor yields of **7a** (27%) were also obtained with $B(C_6F_5)_3$ as the catalyst (Table 1, entry 5). Employing Tf_2NH as Brønsted acid led exclusively to **14** in 53% yield (Table 1, entry 6).

Table 1. Cyclization Cascade of 6 to Give Tricycle 7a

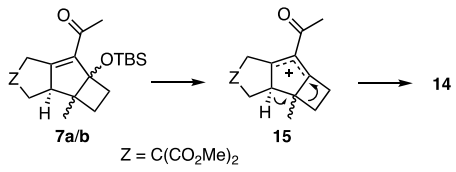


entry	cat.	**7a** yield (%)[a]	ratio **7a**:**7b**	**14** yield (%)[a]
1	$Sc(OTf)_3$	6	1:1.5	42
2	$AgSbF_6$	3	1:3	40
3	$ZnCl_2$	16	1.5:1	0
4	$AgBF_4$	24	1.8:1	10
5[b]	$B(C_6F_5)_3$	27	4.5:1	0
6[c]	Tf_2NH	0	-	53
7	**A**	38 (37)[d]	5.4:1	13
8	**B**	45 (45)[d]	5.6:1	10
9	**C**	52 (61)[d]	7.4:1	0
10	**D**	43	6.1:1	0
11	**E**	24	2.4:1	33
12	**F**	-	-	-
13[e]	**C**	72 (75)[d]	7.2:1	0

[a] Yield determined by ^1H NMR using 1,3,5-tribromobenzene as internal standard. [b] Reaction time 8 h. [c] 2% NMR yield of **7b**. [d] Isolated yield for the mixture **7a** + **7b** in parenthesis. [e] Reaction carried out in Et_2O as solvent, 0.5 mol % catalyst, 40 °C, 8 h.



Scheme 4. Formation of 14 from 7a/b

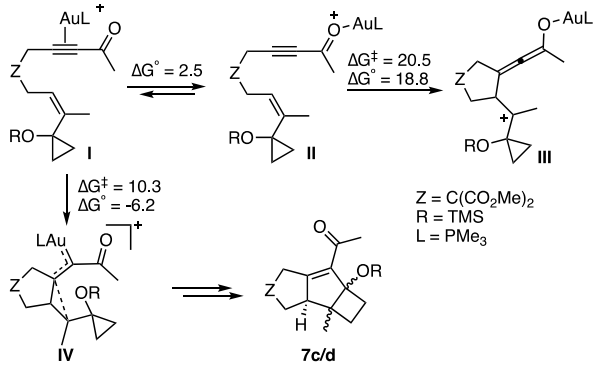


More encouraging results were obtained employing gold(I) catalysis. The use of JohnPhos gold(I) complex **A**, or gold(I) catalyst **B**, both with SbF_6^- as counterion (Table 1, entries 7 and 8), afforded **7a** in 38% and 45% yields in 5.4:1 and 5.6:1 **7a**:**7b** ratios, respectively. In both cases product **14** was observed in 10-13% yields. The use of cationic

gold(I) catalysts **C** and **D** with BArF as counterion was essential to avoid the formation of **14** (Table 1, entries 9 and 10). The best results were obtained with gold(I) complex **C**, which gave **7a** in 52% yield and good 7.4:1 stereoselectivity (Table 1, entry 9). The reaction was optimized by using Et_2O as solvent, lowering the catalyst loading to 0.5 mol % and increasing the temperature to 40 °C (Table 1, entry 13). Under these conditions, complete conversion was achieved, leading to **7a** in 72% yield (7.2:1 stereoselectivity). On the other hand, phosphite gold(I) complex **E** led to **14** as the major product (Table 1, entry 11). Pycolinate gold(III) complex **F** was unreactive in this transformation (Table 1, entry 12). These results illustrate the crucial role of gold(I) catalysts to successfully achieve the demanding cyclization cascade of **6**, leading to **7a** in good yield and diastereoselectivity. Interestingly, when *E*-configured isomer of **6** was subjected to the gold(I)-catalyzed cyclization cascade using the optimized conditions for **6** (entry 13, Table 1), tricyclic compound **7b** was obtained as the major isomer (7:1 ratio) in 30% yield.[12,13]

DFT calculations (B3LYP, 6-31G(d) (C, H, O, P) and SDD (Au), SMD = CH_2Cl_2) were performed to clarify whether the activation of enyne **6** by gold(I) occurs at the alkyne or the keto group. Using a slightly simplified substrate (TMS instead of TBS) and PMe_3 as the phosphine ligand, we found that the complex **I** in which gold(I) is coordinated to the alkyne, is 2.5 kcal·mol^{-1} less stable than the complex **II** with gold(I) coordinated to the keto group (Scheme 5). However, the activation energy for the C–C bond formation from **II** to form **III** ($\Delta G^{\ddagger}$ = 20.5 kcal·mol^{-1}) is much higher than that required for the formation of the distorted cyclopropyl gold(I) carbene-type intermediate **IV** from **I** ($\Delta G^{\ddagger}$ = 10.3 kcal/mol). Accordingly, the reaction initially proceeds by the usual activation of the alkyne by gold(I) as in all other enyne cyclizations.[14]

Scheme 5. Mechanism of the Gold(I)-Catalyzed Enyne Cascade Cyclization[a]

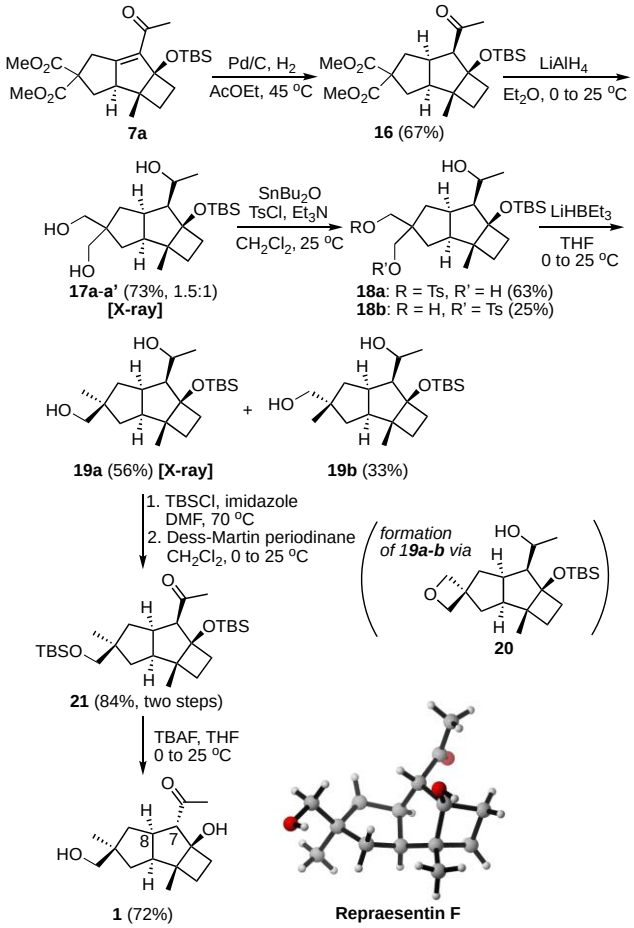


[a] Free energies in kcal·mol^{-1}

Hydrogenation of the tetrasubstituted double bond of **7a** proved to be rather challenging but could be performed employing Pd/C in EtOAc at 45 °C for 4 days (Scheme 6). Under these conditions, **16** was obtained as the major diastereomer in 67% yield. Isomer **7b** turned to be unreactive toward hydrogenation, and was easily separated by chromatography at this stage. Reduction of the keto and malonate groups of **16** with $LiAlH_4$, gave triols **17a-a'** (73%, 1.5:1 *dr*) as an inconsequential 1.5:1 mixture of secondary alcohol epimers. The structures of both epimers were determined by X-ray diffraction. Among the different procedures evaluated for the desymmetrization of 1,3-primary diols, the selective tosylation of primary alcohols catalyzed by Bu_2SnO[15] was the only method that allowed the selective synthesis of monotosylated products **18a** and **18b**. Remarkably, the independent reduction of the primary tosyl groups in **18a** and **18b** with $LiHBEt_3$ gave the same ratio of reduced products **19a** and **19b** (1.7:1). The structure of major isomer **19a** was confirmed by single crystal X-ray diffraction. This reduction actually proceeds *via* the formation of a common oxetane intermediate **20**, which could be isolated at shorter reaction times. The preferential attack of the hydride at the most sterically accessible methylene of oxetane **20** accounts for the formation of **19a**.

Selective protection of the primary alcohol in **19a** with TBSCl followed by oxidation of the secondary alcohol with Dess-Martin periodinane afforded ketone **21** (84% two steps) (Scheme 5). The overall configuration of **21** was assigned by GOESY NMR experiments. Removal of TBS protecting groups with TBAF occurred with concomitant epimerization at the ketone α-position, yielding repraesentin F (**1**) (72%), whose structure was determined by X-ray diffraction. The spectroscopic data of synthetic **1** matched well with those reported for the natural product,[1a] whose structure had been initially proposed to be **1'** (Figure 1) on the basis of the NMR data.[1a]

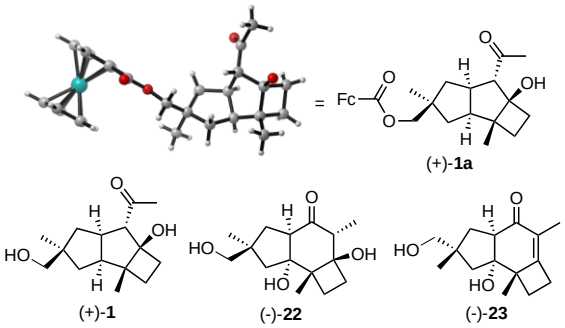
Scheme 6. Synthesis of Repraesentin F (1)



The ready epimerization at C7 under the desilylation reaction conditions was initially puzzling. However, DFT calculations (B3LYP, 6-31G(d) (C, H, O), SMD = CH_2Cl_2) showed that **1** is 4.3 kcal·mol^{-1} more stable than **1'**.[16]

Separation of racemic **1** was performed by preparative chiral HPLC to provide synthetic (+)-**1**, with $[\alpha]_D^{24}$ = +44.8° (c = 0.4, MeOH) matching the optical rotation reported originally for naturally occurring (+)-repraesentin F: $[\alpha]_D^{24}$ = +43° (*c* = 0.34, MeOH).[1a] In order to assign the absolute configuration of natural (+)-**1** by X-ray crystallography, synthetic (+)-**1** was derivatized by esterification of the primary alcohol with ferrocene carboxylic acid[10] to give ferrocene carboxylate (+)-**1a** as an orange solid. Single crystals of high quality were obtained, which allowed the determination of the absolute configuration of (+)-**1a** and by extension of (+)-**1** (Scheme 7). The absolute configuration determined for (+)-**1** was also found in protoilludanes isolated from the same family of fungus (*russulaceae*) such as russujaponol A (**22**),[17] and plorantinone B (**23**),[18] in agreement with the biosynthetic origin of (+)-**1**.[1a,5,19]

Scheme 7. Absolute Configurations of (+)-1a and (+)-1, Protoilludanes (–)-Russujaponol A (22) and (–)-Plorantinone B (23)



In conclusion, we have accomplished the first total synthesis of repraesentin F (**1**) in 16 steps and 2% overall yield. The key step features a diastereoselective gold(I)-catalyzed cyclization cascade that proceeds by the selective activation of the alkyne in a highly functionalized 1,6-enyne leading to the *syn*/*anti*/*syn* decahydrocyclobuta[*a*]pentalene skeleton. The relative and absolute configurations of repraesentin F have been determined by X-ray diffraction. This synthetic study allowed the correction of the previously assigned structure of this natural product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10:1021/XXXXXXX.

All procedures, characterization data for new compounds, and full details on the theoretical calculations including Cartesian coordinates for the calculated structures (PDF)

Accession Codes

CCDC 1859661-1859666 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENTS

We thank Agencia Estatal de Investigación (CTQ2016-75960-P MINECO/AEI/FEDER, UE), AEI-Severo Ochoa Excellence Accreditation 2014-2018 (SEV-2013-0319), the MEC (FPU fellowship to S. F.), the European Research Council (Advanced Grant No. 321066), the AGAUR (2017 SGR 1257), the CERCA Program/Generalitat de Catalunya and the ICIQ Foundation for financial support. We also thank Dr. Tsunashi Kamo (Institute for Agro-Environmental Sciences) for copies of the NMR spectra of repraesentin F, the ICIQ X-ray Diffraction and

Chromatography units, Dr. Tania Jiménez (ICIQ) for preliminary work and Dr. Michael E. Muratore (ICIQ) for helpful discussions.

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(16) Desilylation of **21** with TBAF-HOAc led to deprotection of the primary alcohol with no epimerization C7 (^{13}C NMR: C7 = 64.6, C8 = 47.4, CO = 207.4 ppm, similar to **21**: C7 = 64.7, C8 = 47.5, CO = 207.5 ppm). On the other hand, desilylation of **21** using camphorsulfonic acid led to deprotection of the primary alcohol along with epimerization at C7 (^{13}C NMR: C7 = 71.3, C8 = 43.9, CO = 210.3 ppm similar to **1**: C7 = 69.0, C8 = 42.0, CO = 209.4).[12]

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