MHAT-initiated redox radical cyclization of alkenylsilane enables concise syntheses of (–)-habiterpenol and (+)-2,3-*epi*-habiterpenol

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The concise syntheses of (–)-habiterpenol and (+)-2,3-*epi*-habiterpenol from (3a*R*)-(+)-sclareolide and 6-methoxyindanone in 11 and 12 steps, respectively, were enabled by the regioselective addition of the TMS-indenyl anion and facile stereoselective metal hydride hydrogen atom transter (MHAT)-initiated redox radical cyclization of alkenylsilane.

DNA is constantly damaged by both exogenous and endogenous factors. When a cell is damaged, DNA damage checkpoints are activated and the cell cycle is arrested at the S phase and G1/S and G2/M transitions to enable the cell to repair DNA[1]. However, if the DNA damage checkpoints are abrogated, genetic mutations accumulate, leading to cancer and malignant cell transformation. Normal cells rely on the G1 checkpoint for DNA repair, which is missing in most cancer cells owing to mutations in the tumor suppressor genes p53 and RB. Consequently, DNA repair in cancer cells is more dependent on the G2 checkpoint than the G1 checkpoint[2]. This means that while normal cells can still be repaired through the G1 ch eckpoint when the G2 checkpoint is inhibited, cancer cells lose their DNA repair mechanism, leading to the accumulation of DNA damage and induction of cell death. G2 checkpoint inhibitors are therefore expected to reduce the side effects and enhance the effectiveness of DNA-damaging anticancer agents. Clinical trials of two G2 checkpoint inhibitors, CBP501[3] and AZD7762[4], are currently underway, and they are expected to be effective anticancer agents with a new mechanism of action. In this context, (–)-habiterpenol (**1**)[5], a microbial G2 checkpoint inhibitor, has been isolated from the culture medium of *Phytohabitans* sp. 3787-5 (**Figure 1**). Compound **1** is a potential lead compound for G2 checkpoint inhibitors because it does not exhibit cytotoxicity in bleomycin-induced G2 arrest in Jurkat cells[6]. It contains a phenol moiety in the steroid skeleton with *syn*-fused CD rings and *anti*-fused AB and BC rings. We previously achieved the first total synthesis of **1** through the Ti(III)-mediated stereoselective radical cyclization of epoxide **4**, derived from chiral indenyliodide **2** (13 steps from starting material) and epoxyaldehyde **3**, to construct the *cis*-fused C ring[7] (**Scheme 1**). This enabled the determination of the absolute configuration of **1** and syntheses of 7-*epi*-**1** and some

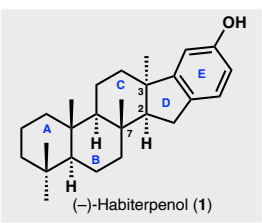
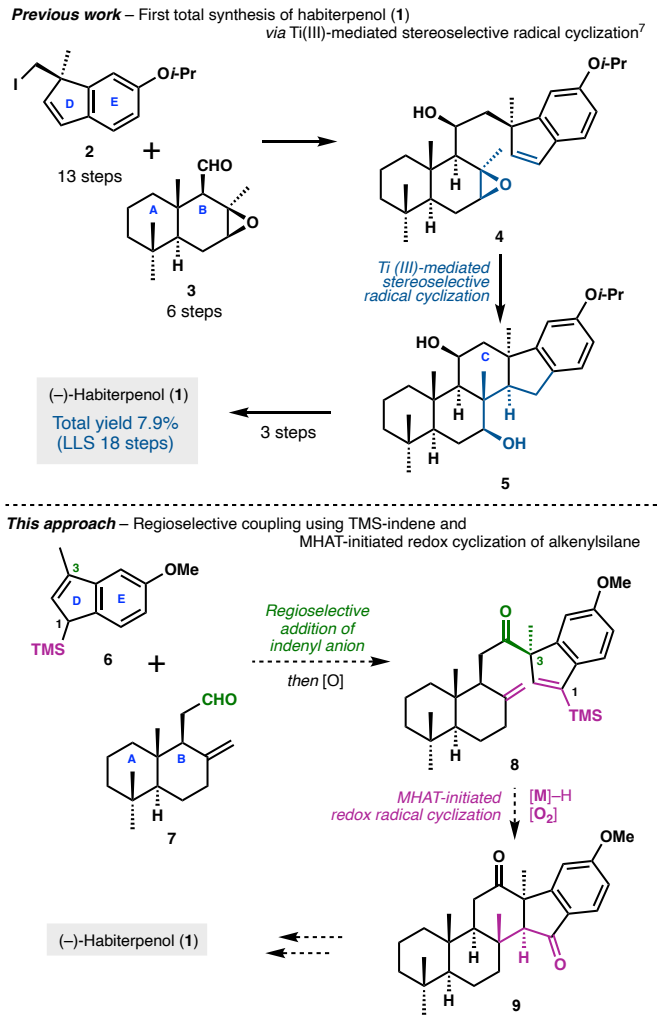


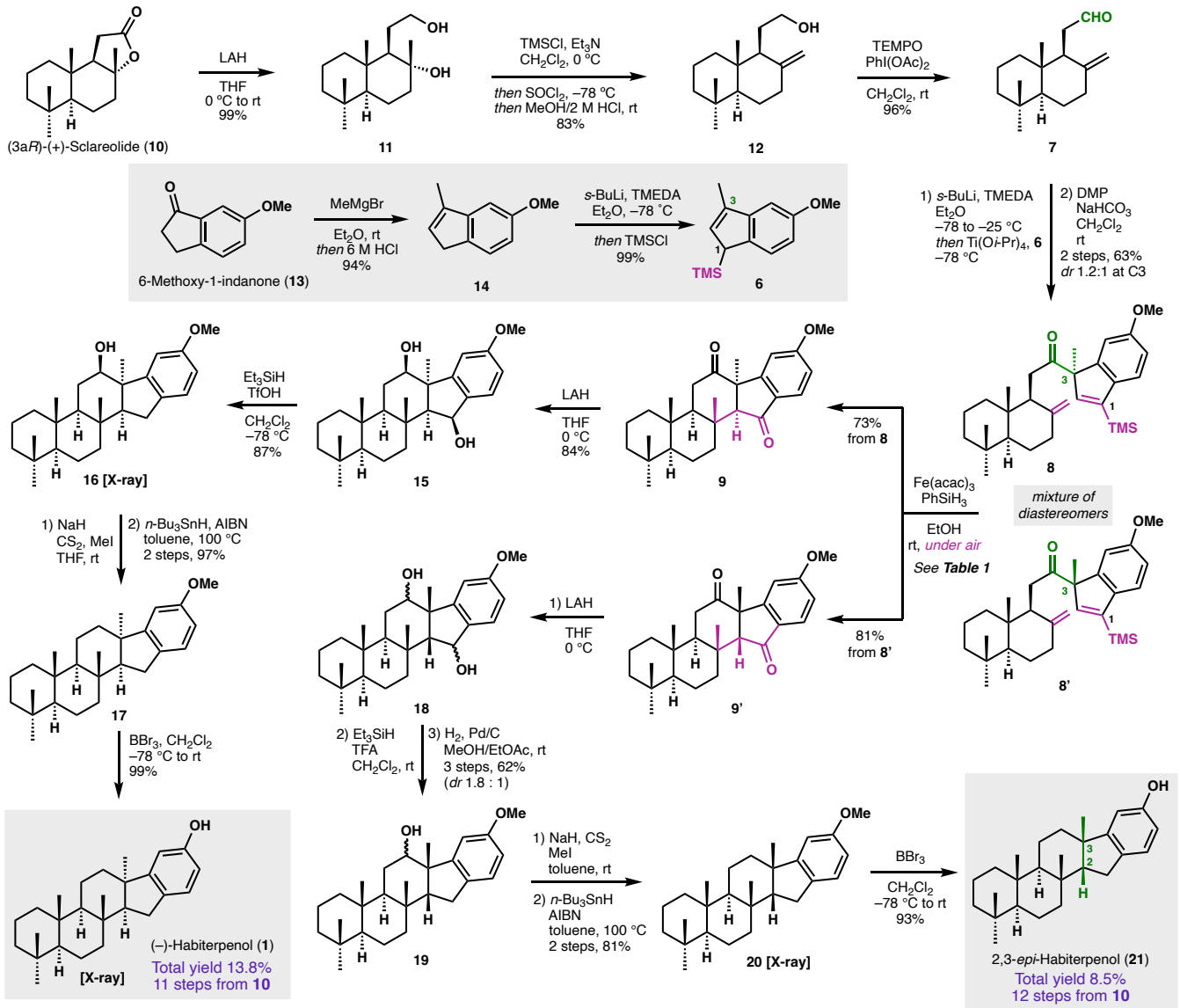
Fig 1. Structure of (–)-habiterpenol (**1**), a G2 checkpoint inhibitor.



Scheme 1 Our previous synthesis of (–)-habiterpenol (**1**), and the summary of this approach.

habiterpenol analogs for a structure–activity relationship (SAR) study[8]. To further improve the synthetic method, we developed a concise route with the key reactions being the coupling of achiral indene **6** (DE-ring unit), which could be easily derived by a few steps, and aldehyde **7** (AB-ring unit)[9] and construction of the C ring through radical cyclization initiated by metal hydride hydrogen atom transfer (MHAT)[10]. Indene **6**, which has a bulky and easily removable TMS group, was used to improve the st ereoselectivity of the coupling reaction with aldehyde **7** to construct the C3 quaternary stereocenter. Furthermore, the MHAT-mediated redox cyclization of alkenylsilane **8** in the presence of oxygen gave the corresponding diketone **9** through the elimination of trimethylsilanol[11]. Diketone **9** was not only easily converted to **1** via the reduction of the two carbonyl groups but was also a highly functional intermediate that could be converted to various derivatives for further SAR studies of **1**. Details of the synthesis are described below.

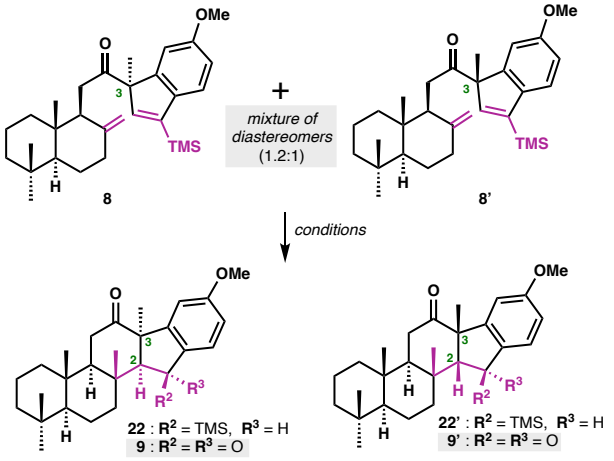
First, the aldehyde and indene units were derived from the starting materials (**Scheme 2**). Reduction of (3a*R*)-(+)-sclareolide (**10**) with $LiAlH_4$ gave diol **11**[12] (99% yield), which was then subjected to the one-pot chemoselective dehydration of the 3˚-alcohol via a TMS-protection/dehydration/TMS-deprotection sequence[13] for the 1˚-alcohol to yield alcohol **12**[14] in 83% yield. Oxidation of **12** with TEMPO gave aldehyde **7** as the AB-ring unit in 96% yield. Meanwhile, TMS-indene **6**, as the DE-ring unit, was derived from 6-methoxyindanone (**13**) by a known procedure[15] to give **14** (94% yield), followed by the introduction of the TMS group in 99% yield. The coupling of aldehyde **7** and the achiral indenyl anion derived from **6** in the presence of TMEDA was attempted to obtain the corresponding secondary alcohols as a diastereomixture. However, their isolation and structural determination proved to be challenging. Dess–Martin periodinane (DMP) oxidation of the coupled compound gave **8** in 63% yield as a diastereomixture (*dr* 1.2:1) without any of the C1-coupled regioisomers. The TMS group of indene **6** was critical to regioselectivity. This was demonstrated by the fact that when indene **14**, which lacked the TMS group, was used, the regioselectivity of the coupling reaction was significantly reduced[16]. Several diastereoselective coupling



Scheme 2 Total syntheses of (–)-habiterpenol (**1**) and 2,3-*epi*-habiterpemol (**21**).

reactions were also attempted[17], although stereoselectivity was not observed[16].

Table 1 Optimization of reaction condition for MHAT-initiated radical cyclization.



entry	reagents and conditions	yield [a]
1	$Mn(dpm)_3$ (30 mol%), $PhSiH_3$ (3 eq.), TBHP (1.5 eq.)	**22**: 28% from **8**
	i-PrOH (0.1 M), rt, under N_2	**22'**: 28% from **8'**
2	$Mn(dpm)_3$ (30 mol%), $PhSiH_3$ (3 eq.)	**22**: 28%, **9**: 23% from **8**
	i-PrOH (0.1 M), rt, *under air*	**22'**: 23%, **9'**: 23% from **8'**
3	$Fe(acac)_3$ (50 mol%), $PhSiH_3$ (3 eq.)	**9**: 73% from **8**
	EtOH (0.1 M), rt, *under air*	**9'**: 81% from **8'**

a) Total yields were calculated based on the ratio of the starting material **8** and **8'**, which was 1.2:1. For details see SI.

After achieving the desired regioselective coupling by introducing a TMS group to the indene unit, we explored the construction of the C ring via MHAT-initiated radical cyclization (**Table 1**). In a preliminary study, we attempted reductive cyclization[10c] using the diastereomixture of **8** and **8'** in the presence of $Mn(dpm)_3$, $PhSiH_3$, and *tert*-butyl hydroperoxide (TBHP) under N_2, which gave **22** and **22'** in low yield (28% each) along with undetected byproducts (entry 1). Although the starting material disappeared, the corresponding benzyl radical generated after cyclization was considered to be excessively resonance stabilized. This made the radical difficult to trap by any hydrogen radical source, leading to the decomposition of the substrate. Therefore, the reaction was conducted under air to capture the radical intermediate using oxygen and obtain the desired diketones **9** (23% yield from **8**) and **9'** (23% yield from **8'**). This reaction also yielded **22** (28% yield from **8**) and **22'** (23% yield from **8'**) (entry 2). Finally, changing the reagents to $Fe(acac)_3$ and $PhSiH_3$[10e,n] enabled the formation of **9** (73% yield from **8**) and **9'** (81% yield from **8'**) without **22** and **22'** (entry 3)[18].

After obtaining diketone **9** via MHAT-initiated redox cyclization of alkenylsilane **8**, the reduction of its two carbonyl groups to complete the total synthesis of **1** was investigated. Several direct reductions of the carbonyl groups were attempted but only complex mixtures were obtained. Therefore, **9** was reduced with $LiAlH_4$ to obtain diol **15** (84% yield), which was subjected to Barton–McCombie deoxygenation. However, the deoxygenation of the corresponding di-xanthate gave a complex mixture. This indicates that the two hydroxyl groups of **15** significantly differ in nature, thereby necessitating their stepwise reduction. The benzylic hydroxyl group of **15** was first reduced with Et_3SiH in the presence of TfOH[19] to obtain **16** (87% yield), whose structure and stereochemistry were determined by X-ray crystallography[20]. The reduction of the remaining hydroxyl group of **16** via a two-step deoxygenation afforded **17** in 97% yield. Finally, the demethylation of **17** gave (–)-habiterpenol (**1**)[20] in 99% yield, and the concise synthesis of **1** was completed in 11 steps from **10** with a total yield of 13.8%.

Next, to expand the SAR study of **1**, 2,3-*epi*-**1** was synthesized from **9'**, which was obtained as a diastereomer of **9** (**Scheme 2**). Compound **9'** was reduced with $LiAlH_4$ to yield diol **18** as a diastereomixture. The benzylic alcohol of diol **18** was then reduced to afford an inseparable mixture of **19** and the corresponding indene. The mixture was then subjected to hydrogenation conditions to obtain **19** as the sole product (62% yield in 2 steps), which was further subjected to Barton–McCombie deoxygenation to afford **20** in 81% yield in 2 steps. The structure and stereochemistry of **20** were determined by X-ray crystallography[20]. Finally, the methyl group of **20** was deprotected to give 2,3-*epi*-habiterpenol (**21**) (93% yield) in 12 steps from **10** with a total yield of 8.5%.

In conclusion, we successfully achieved the concise syntheses of (–)-habiterpenol (**1**) and 2,3-*epi*-habiterpenol (**21**) in 11 and 12 steps, respectively. Notably, introducing a TMS group to the indene unit enabled the complete regioselective coupling of TMS-indene **6** and aldehyde **7**. Moreover, the air-atmospheric, transannular MHAT-initiated redox cyclization of alkenylsilane **8** to construct the C ring of **1** enabled the formation of the corresponding diketone **9**. Currently, we are synthesizing various derivatives from diketones **9** and **9'**, which along with 2,3-*epi*-habiterpenol (**21**), will be investigated for three-dimensional SARs in the future.

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Conflicts of interest

There are no conflicts to declare.

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