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Total synthesis of naturally occurring abietane diterpenoids *via* a late-stage Fe(III)-*b*TAML catalysed Csp^3–H functionalization†

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The synthesis of diverse *trans*-fused decalins, including the abietane diterpenoids scaffold, using an efficient selective oxidation strategy is described. The abietane core was demonstrated to be a versatile scaffold that can be site-selectively functionalized. The utility of this novel oxidation strategy was showcased in a concise total synthesis of six abietane congeners.

Introduction

The use of iron catalyzed reactions to construct complex structures remains a powerful strategy in chemical synthesis.[1] In nature, both heme and nonheme metalloenzymes mediated oxidation of alkanes occurs in excellent selectivity and operate under mild reaction conditions.[2] Inspired by the high catalytic efficiency of the enzymatic model systems, chemists have developed numerous synthetic iron-based complexes for use in C–H bond oxygenation reactions.[3] Despite significant progress, achieving site-selective oxidation of unactivated C(sp^3)–H bonds, which constitute the most prevalent structural motifs in complex natural products, remains a significant challenge. Recent efforts have demonstrated C(sp^3)–H functionalization,[4] including iron-[5,6] and manganese-[7] and copper catalyzed[8] and photochemical,[9] methods that are compatible with diverse C–H substrates as the limiting reagent. Although these transformations can be performed in a stoichiometric fashion by organic peracids,[10] dioxiranes,[11] and oxaziridines,[12] but a catalytic method involving H_2O_2 or O_2 as cheap stoichiometric oxidants is highly desirable.

In this context, abietane diterpenoids are structurally versatile, exhibits tricyclic ring system (Fig. 1) with several stereocenters and a wide grade of oxygenation pattern on the skeleton invites synthetic chemists to be creative and efficient. Majusanic acid D (**1**) and majusanin B (**2**), belongs to a novel class of abietane-type diterpenoids (**3–6**, Fig. 1), that have been isolated in recent years from the roots of *Illicium majus* in 2013.[13] Structurally, they share densely functionalized *trans*-decalin framework. Moreover, the decalin core contains three contiguous stereocenters, two of which are quaternary centers.

Biologically, angustanoic acid E (**6**) demonstrates significant cytotoxicities against five human tumor cells (HCT-8, Bel-7402, BGC-823, A549, and A2780), with IC_{50} value 2.47 ± 0.43 μM.[14] Stimulated by their impressive structures and bioactivities, we initiated a synthesis study of majusanic acid D (**1**) and its derivatives (**2–6**, Fig. 1).

To this end, research in our group along with that in other synthetic groups (*e.g.*, Corey,[15] Alvarez-Manzaneda,[16] Matsumoto,[17] Tada,[18] Burnell,[19] Gonzalez,[20]) focused on the development of new synthetic strategies to access abietane-type diterpenoids. Synthetic challenges include stereoselective installation of three adjacent carbon stereocenters and

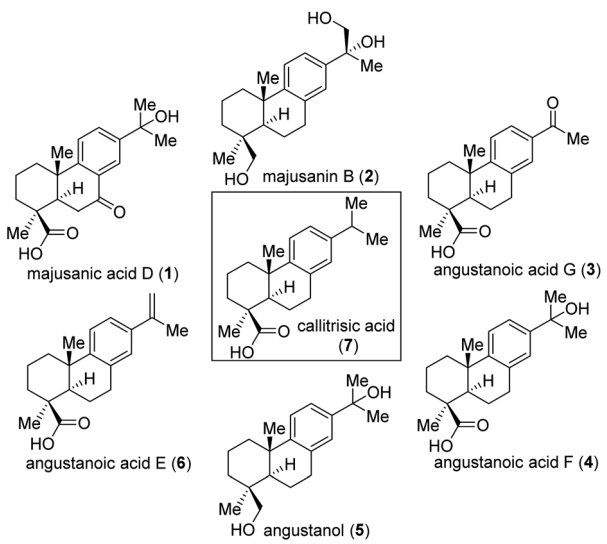

Fig. 1 Representative abietane-diterpenoids.

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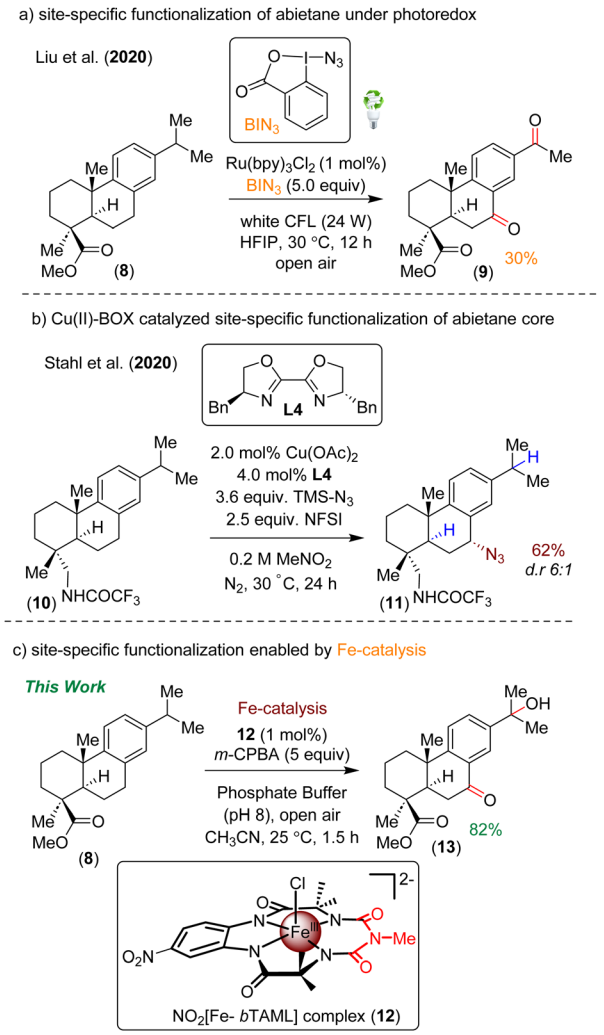
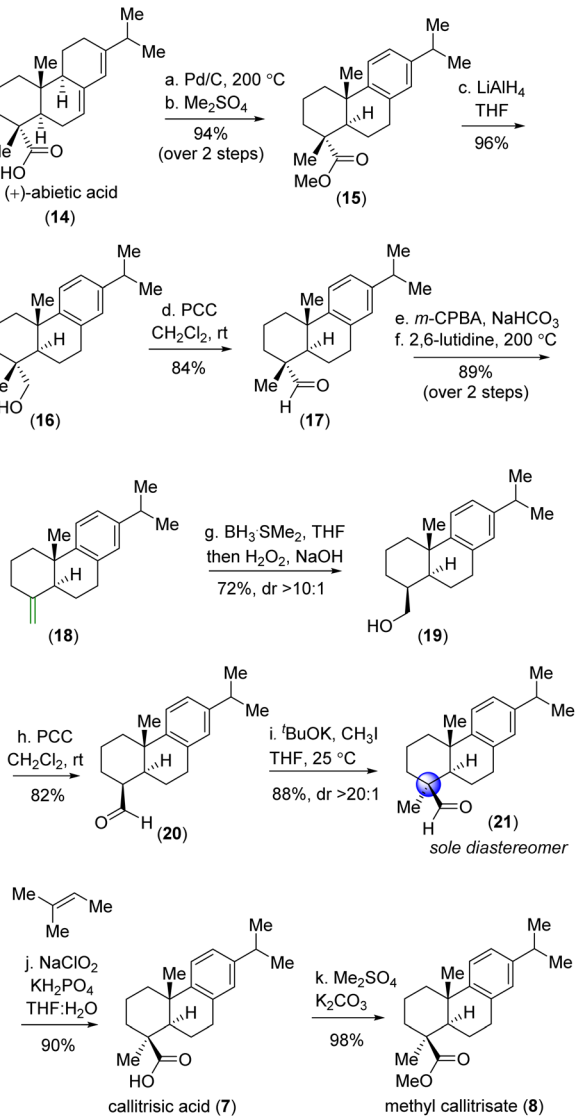


Fig. 2 Site-selective functionalization strategies enabled by versatile reactivity of abietane derivatives.

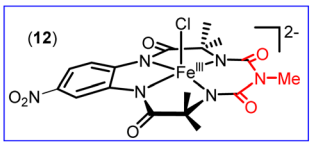
formation of the polyoxygenated moiety. Biosynthetically, the abietane scaffold can be constructed from farnesyl diphosphate (FPP) *via* a cascade polyene cyclization.[21] We envisioned a strategy to advance the abietane scaffold by synthesizing callitrisic acid (7) from abietic acid (**14**) using a modified literature procedure.[22] Then we focused our attention to perform selective oxidation of activated 3 °C–H bonds and activated 2 °C–H bonds *via* NO_2[Fe-*b*-TAML][5] complex (**12**) in the presence of the oxidant *m*-CPBA (Fig. 2c). It is worth mentioning that Matsushita *et al.* has developed Co-catalyzed aerobic benzylic oxidation of 8,11,13-abietatrienes in the presence of *N*-hydroxyphthalimide combined with AIBN derivative and its application in total synthesis of diterpenoids.[23]

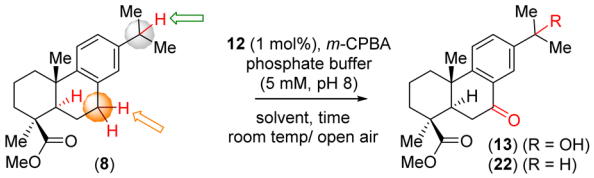
Initially, we wanted to synthesize the core structure of abietane diterpenoids, such as callitrisic acid[22] (7). On the basis of previous reports by two independent groups, Pelletier *et al.* and Alvarez-Manzaneda *et al.*,[24] we have started our synthesis from commercially available (+)-abietic acid (**14**). By subjecting abietic acid to a temperature of 200 °C for a period of 4 hours resulting in the formation of dehydroabietic acid (**14a**) (see ESI†). Subsequently, the resultant product underwent methylation utilizing dimethyl sulfate [$(MeO)_2SO_2$], resulting in the formation of (**15**). The subsequent compound (**15**) was subjected to reduction using $LiAlH_4$, leading to the formation of the primary alcohol (**16**) with a yield of 96%. Treatment of (**16**) with PCC afforded the aldehyde (**17**) which, when treated with *m*-chloroperbenzoic acid, gave the formate (see ESI† for details), which after saponification with refluxing 2,6-lutidine yielded (**18**), whose physical and spectroscopic properties were identical to those reported in the literature.[20b] The C-4 hydroxyl group in (**19**) was installed by treatment of (**18**) with $BH_3{\cdot}SMe_2$ and oxidation of the resultant alkyl borane with H_2O_2 to generate (**19**) regio- and diastereoselectively in 72% yield and its primary alcohol was converted to the corresponding aldehyde (**20**) by PCC oxidation in 82% yield. The C-4 quaternary chiral center was installed by treating aldehyde (**20**) with ^{t}BuOK in THF, and the resultant enolate was reacted with MeI followed by a Pinnick oxidation introduced a carboxylic acid group in callitrisic acid



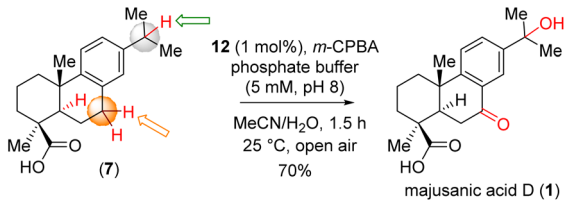
Scheme 1 Synthesis of callitrisic acid (7).

Table 1 Optimization of Fe(III)-*b*TAML Catalysed Csp^3–H oxidation





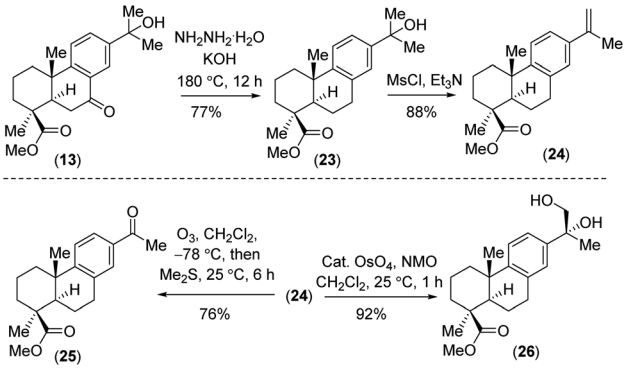
Entry	Solvent	Time (min)	Yield[a,b,c] (%) **13 : 22 : SM**
1	CH_3CN/H_2O (4 : 1)	15	0 : 70:30
2	CH_3CN/H_2O (4 : 1)	30	20 : 57 : 23
3	THF/H_2O (4 : 1)	30	46 : 25 : 29
4	DMF/H_2O (4 : 1)	30	32 : 20 : 48
5[d]	**CH_3CN/H_2O**	**90**	**82 : 0 : 0**
6	CH_3CN/H_2O (2 : 1)	90	75 : 15 : 0
7	DMF/H_2O (2 : 1)	90	61 : 0 : 0
8	H_2O	90	0 : 23 : 77
9	CH_3CN	90	0 : 31 : 69



[a] All reactions were conducted on a 0.2 mmol scale under 1 mol% catalyst. [b] Isolated yield reported after column chromatography. [c] 5 equivalents of *m*CPBA was used. [d] The reaction can be performed conveniently in 100 mg scale.

(7). Subsequently, callitrisic acid (7) was methylated using dimethyl sulfate [$(MeO)_2SO_2$], resulting in the formation of methyl callitrisate (**8**) in 98% yield (Scheme 1).

We then began to evaluate the proposed iron complex catalyzed selective C–H bond oxidation from callitrisic acid methyl ester (**8**). Finally, substrate bearing activated methine and benzylic C–H bonds were explored. We then performed catalytic reaction by introducing *m*-CPBA (5 equiv) *via* a syringe pump at a rate of 100–200 μL h^{-1} into a solution containing (**12**) (1 mol%) and substrate (**8**) (0.2 mmol scale) in an 80% CH_3CN-20% K_2HPO_4 (aq) solvent system (Table 1).[5] Following this protocol for 15 minutes yielded the benzylic ketone intermediate (**22**) with a 70% yield (entry 1, Table 1). Extending the reaction time to 1 hour with ketone (**22**) produced the over-oxidized product (**13**) in an 85% yield (see ESI† for details). Similarly, callitrisic acid methyl ester (**8**) was converted directly to the over-oxidized product (**13**) in 82% yield under the same conditions for 1.5 h (entry 5, Table 1). Notably, the 2° benzylic C–H bonds were observed to be preferentially oxidized over the statistically more significant 3° benzylic C–H bonds.



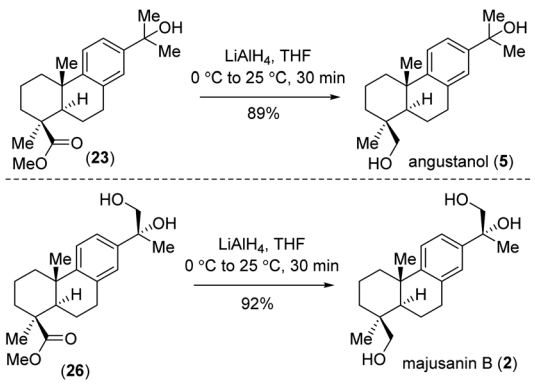
Scheme 2 Synthesis of sesquiterpenoids scaffold.

The ketone formation can be rationalized through a two-step oxidation process of the C–H bond, involving a two-electron transfer mechanism. The second step, specifically the conversion of alcohol to ketone, occurs approximately 100 times faster than the oxidation of alcohol originating from C–H bonds. We posit that the generation of the ketone in the benzylic position of (**22**) can be explained by this mechanism. Taken together, the synthetic utility and versatility of our methodology was successfully showcased, resulting in first asymmetric total synthesis of majusanic acid D (**1**) in significant yield (Scheme 4).

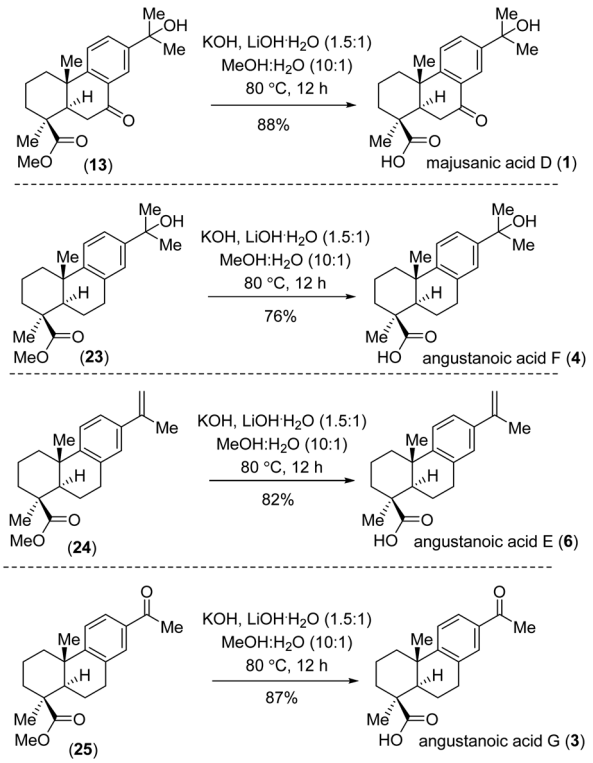
Our next synthetic target was majusanin B (**2**) and its derivatives (**3**–**6**, Fig. 1). With (**13**) in hand, we next explored Wolff–Kishner reduction[25] with hydrazine hydrate ($N_2H_4 \cdot H_2O$) provided the tertiary alcohol in (**23**) in 77% yield, which underwent elimination by reaction with MsCl in the presence of Et_3N in CH_2Cl_2 to give (**24**) in 88% yield.

Subsequent oxidative cleavage of (**24**) with ozonolysis to furnish aromatic acetophenone (**25**) in 76% moderate yield. Dihydroxylation of the olefin group of the styrene derivative in (**24**) with OsO_4/NMO[26] gave diol (**26**) in 92% yield (Scheme 2).

Later, we moved ahead for the collective total synthesis of abietane diterpenoids **1**–**6** shown in Fig. 1. Reduction of (**23**) and (**26**) *via* $LiAlH_4$-reduction ensures the total synthesis of angustanol (**5**) and majusanin B (**2**) (Scheme 3). Lastly, hydrolysis of methyl ester of (**13**), (**23**), (**24**), and (**25**) using LiOH and KOH in hot methanol[27] completed the total synthesis of



Scheme 3 Synthesis of angustanol (**5**) and majusanin B (**2**).



Scheme 4 Majusanic acid D (**1**), angustanoic acid F (**4**), angustanoic acid E (**6**) and angustanoic acid G (**3**).

majusanic acid D (**1**), angustanoic acid F (**4**), angustanoic acid E (**6**) and angustanoic acid G (**3**) respectively (Scheme 4).

Conclusions

We have completed the total syntheses of all known abietane diterpenoids (**1–6**) through a unified strategy inspired by our hypothesis for their biogenesis. Key features of our syntheses include: (1) (+)-callitrisic acid (**7**) synthesis accomplished in 10 steps from abietic acid (**14**) with 32% overall yield, (2) we demonstrate synthetic utility and versatility of Fe-*b*TAML complex catalyzed biomimetic C–H bonds oxidation strategy in the total synthesis of complex natural products.

Data availability

Experimental details and spectral analysis are available free of charge from the ESI† available with this article.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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