# Site-Selective Olefin Functionalization Simplifies the Synthesis of Eudesmane Sesquiterpenes

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**Graphical abstract:**
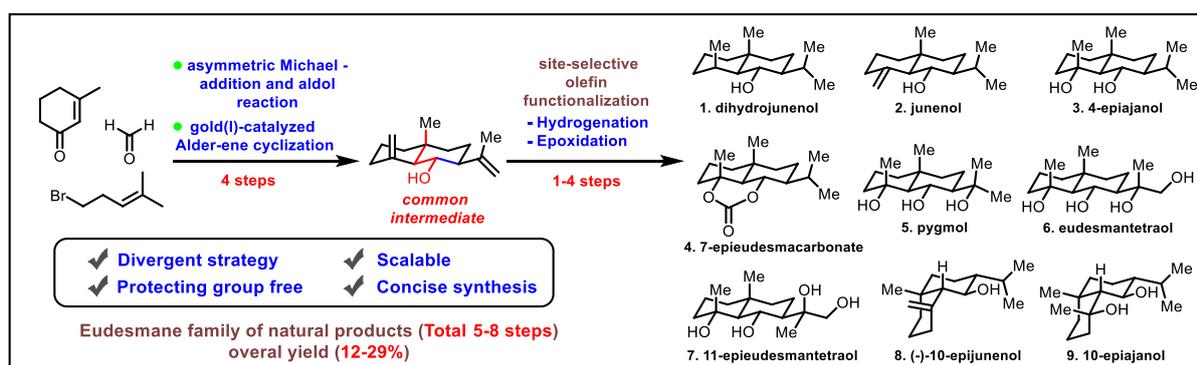
**Abstract:** Late-stage site-specific functionalization of olefins is an underutilized tool in the total synthesis of natural products. Herein, we disclose a short synthesis of oxidized eudesmanes through a site-selective olefin functionalization strategy. To implement this strategy, we synthesized a common intermediate embodying two olefins and hydroxy-carrying eudesmane core *via* an asymmetric tandem Michael addition and Aldol reaction, and Au(I)-catalyzed Alder-ene reaction. The late-stage site-selective olefin hydrogenation and epoxidation techniques were employed for synthesizing nine eudesmane congeners without using protecting groups. This work demonstrates the efficacy of site-selective olefin functionalization strategy in enhancing the accessibility of complex terpenes and their analogs.

Terpenes are a unique class of organic compounds and have played an essential role in unraveling the biology of living organisms due to their unique molecular structures.[1] Nature produces these terpenes in a sophisticated and selective manner through a two-phase approach involving a cyclase phase and an oxidation phase,[2] and site-specific functionalization of C-H bonds or other functional groups.[3] The former approach was explored extensively, and many strategies were developed for achieving complex natural product synthesis;[4] however, the latter approach was rarely investigated in natural product synthesis due to the difficulties that arise while predicting the reactivity of identical functional groups present in the molecule.[5] Nevertheless, such approaches significantly improve the availability of natural products. Even though few strategies were developed based on these approaches,[6] designing such a strategy for
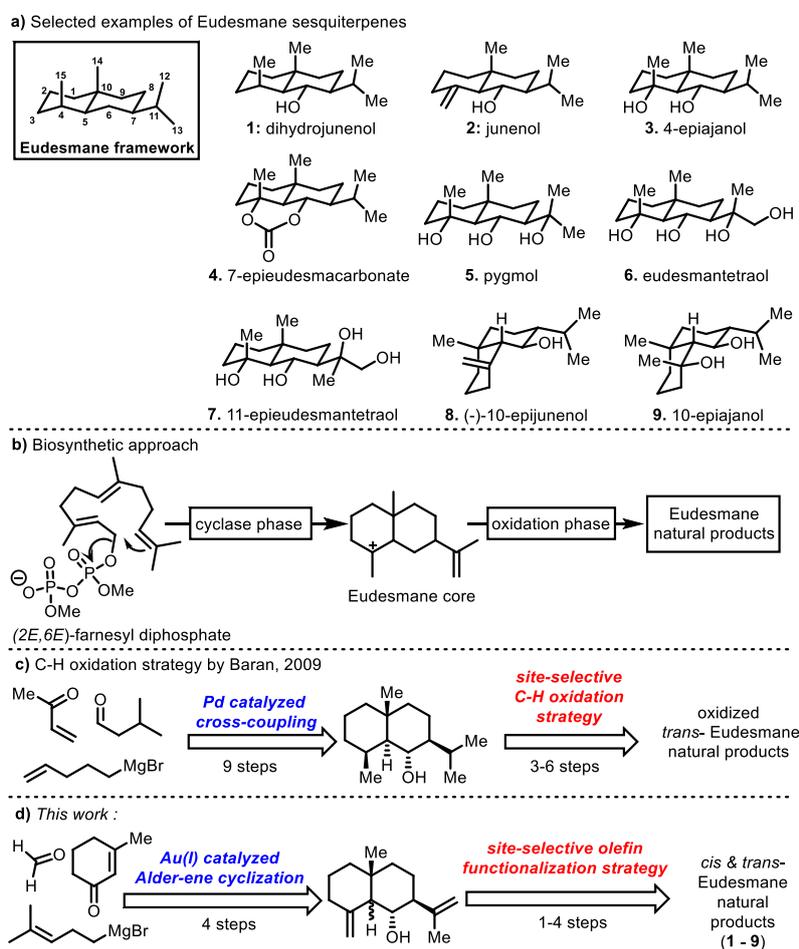


**Figure 1:** a. Chemical structures of dihydrojunenol (**1**), junenol (**2**), 4-epiajanol (**3**), 7-epieudesmacarbonate (**4**), pygmol (**5**), eudesmantetraol (**6**) and 11-epieudesmantetraol (**7**), (-)-10-epijunenol (**8**), 10-epiajanol (**9**); b. Biosynthesis of eudesmanes; c. C-H oxidation strategy by Baran et al.; d. Proposed approach in this work.

synthesizing complex natural products is still a daunting challenge. Considering the challenge, we have taken the eudesmane class of natural products as a case study to showcase the efficiency of site-selective functionalization to access these sesquiterpenes and their congeners.

Eudesmanes are a large class of sesquiterpenes and possess intriguing structures with contiguous chiral centres (Figure 1a) and biological properties.[7] These metabolites are synthesized in nature through a two-phase mechanism. Initially, farnesyl diphosphate undergoes a cyclase phase, resulting in the formation of an eudesmane skeleton. Following this, in the oxidase phase, the eudesmane skeleton undergoes selective C-H oxidations and site-specific olefin functionalization, creating oxidized eudesmanes known as the eudesmanoids with diverse levels of complexity, as illustrated in Figure 1b. Baran and his group developed a ground-breaking C-H oxidation strategy to synthesize *trans*-eudesmanoids, as shown in Figure 1c,[8] which paved the way for efficient synthesis of many complex terpene natural products. In addition, many research groups accomplished the synthesis of various eudesmanes.[9] However, the strategies developed so far require protecting groups and longer synthetic sequences (6 to 15 steps). This necessitated for a more streamlined and robust strategy to access these structurally rigid terpenes. Herein, we report the concise synthesis of nine eudesmane congeners by employing a site-selective olefin functionalization strategy, as shown in Figure 1d.
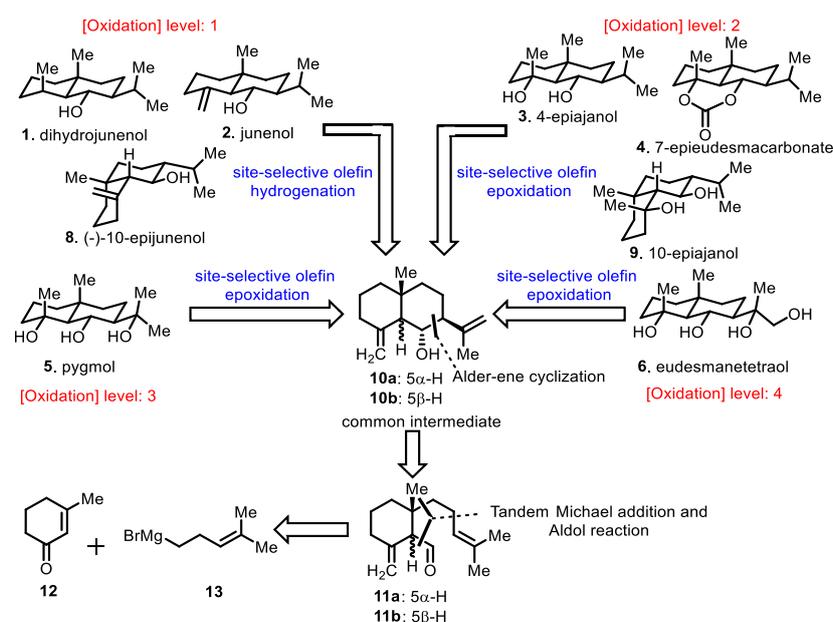


**Scheme 1:** Retrosynthetic analysis of eudesmane terpenes.

Retrosynthetically, we ideated that the oxygen patterns of the eudesmanoids **1**-**9** could be installed by constructing a unified intermediate and subsequently utilizing the existent strategically positioned functionalities for late-stage site-selective functionalization (Figure 2). Therefore, *cis* and *trans* eudesmanoids (**1**-**9**) could be achieved from intermediates **10a,b**, which have four contiguous asymmetric carbon centres and possess two olefin functionalities. We anticipated that the C-6 hydroxy group could trigger the reactivity profile of C-4 and C-11 olefins within the molecule *via* site-selective functionalization, leading to the eudesmanoids. Further, retrosynthetic scission of **10a,b**, at the C6 - C7 bond led to **11a,b** as a potential precursor. In a forward sense, we envisioned an Alder-ene cyclization method to accomplish the C-6 and C-7 bond formation of diene aldehyde **11a,b**. The stereocenters at C-5 and C-10 in **11a,b** could be generated through a one-pot asymmetric Michael addition and Aldol reaction from readily available starting materials **12** and **13.**
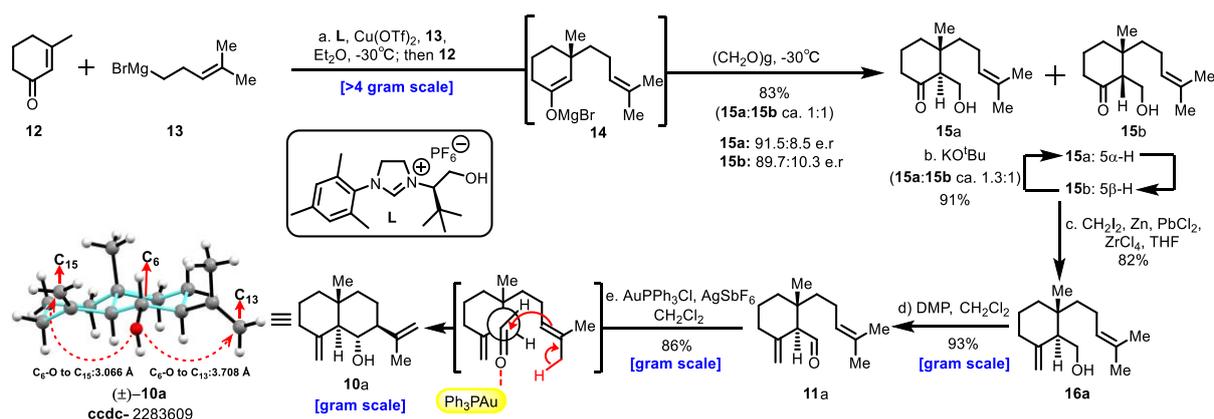


**Scheme 2:** Asymmetric synthesis of common eudesmane intermediate **10a**.

Our synthesis commenced with installing C-2 and C-3 stereocenters on the cyclohexane moiety. This step was efficiently accomplished by employing the Alexakis procedure,[10] which involves Copper-NHC catalyzed 1,4 addition of organomagnesium species to enones. Thus, homoprenyl magnesium bromide **13** was treated with 3-methyl cyclohexenone (**12**) in the presence of Cu(OTf)$_2$ and NHC ligand **L**, resulting in the magnesium enolate **14**, which upon treatment with formaldehyde, afforded chromatographically separable diastereomers **15a** (45%) and **15b** (38%) with good enantioselectivity. The presence of sterically analogous methyl and homoprenyl groups at the quaternary center likely contributed to the poor diastereoselectivity in the reaction. However, additional amounts of **15a** and **15b** were obtained by the

epimerization of the pure diastereomers using *t*BuOK.[11] With multigram quantities of **15a,b** in hand, we first inspected the synthesis of *trans*-eudesmanoids (**1-7**) from **15a**. Firstly, Takai olefination protocol was employed to methylenate the ketone of **15a**, forming olefin **16a** with an 82% yield.[12] Subsequently, the primary alcohol of **16a** was oxidized to **11a** using DMP, setting the stage for the crucial Alder-ene reaction. Although similar ene reactions have been reported in the literature,[13] the Alder-ene cyclization of compound **11a** proved highly challenging due to the substrate's sensitivity caused by the exocyclic olefin. As anticipated, initial explorations involving various thermal conditions, Lewis acids, and metal triflates led to either the decomposition or the formation of multiple products resulting from exocyclic olefin isomerization. Considering the outcome of these results, we shifted towards transition metal catalytic conditions, anticipating the facilitation of the desired transformation. In this regard, the combination of gold and silver catalysts (AuPPh$_3$Cl and AgSbF$_6$) gave gratifying results. A thorough optimization study was conducted by varying the parameters such as catalyst loading, solvent, temperature, etc., enabling the formation of the desired Alder-ene product **10a** with an 86% yield as a single diastereomer (see SI for optimization table). The hallmark of the Alder-ene cyclization lies in its highly organized chair-like transition state geometry that facilitates the stereospecific induction across the decalin system. In addition to its ability to create the vicinal stereochemical relationships in a desired fashion, the application of gold catalysts in the Alder-ene reaction represents a very reliable and powerful tool for constructing these scaffolds. Notably, this step facilitated the regiospecific establishment of a new C-C bond and introduced two stereocenters with excellent stereospecificity, as confirmed by X-ray (SC-XRD) crystal structure analysis.
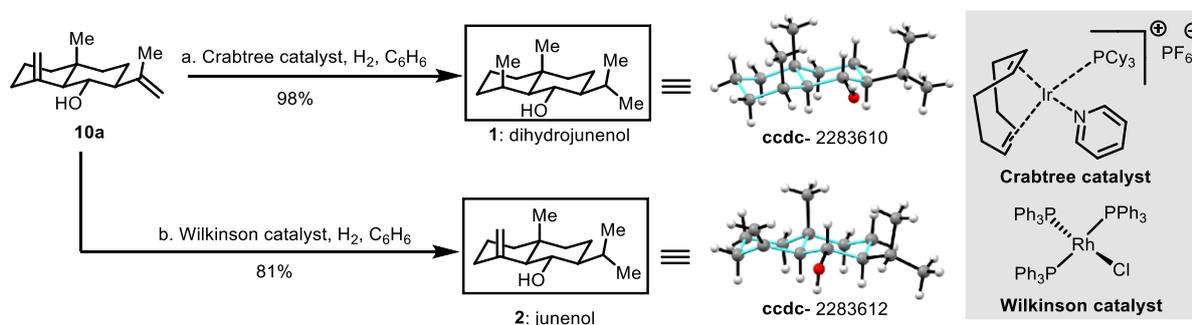


**Scheme 3:** Synthesis of dihydrojunenol (**1**) and junenol (**2**) through site-selective olefin hydrogenation.

After gram-scale synthesis of **10a**, our research endeavours shifted towards the site-selective hydrogenation and epoxidation of the olefins positioned at C-4 and C-11. Site-selective functionalization of complex organic molecules relies on factors encompassing steric hindrance, electronic attributes, and, most notably, the proximity of directing groups. Ascertaining the reactivity of the olefins at C-4 and C-11 posed challenges due to their analogous substitution patterns and spatial remoteness from the C-6 hydroxy functional group. Insights from the X-ray crystal structure analysis of compound **10a** revealed that the hydroxy group at C-6 is slightly closer to the C-4 olefin compared to the C-11 olefin (which is *trans* to the hydroxy group), and the C-11 olefin is more sterically accessible, occupying an equatorial position as shown in scheme 2. Based on this information, we first conducted site-selective hydrogenation of the C-11 olefin using the Crabtree catalyst. Treatment of compound **10a** with the Crabtree catalyst under an H$_2$ atmosphere resulted in the formation of fully hydrogenated dihydrojunenol (**1**) in 98% yield. This observation indicated similar reactivity for both the C-4 and C-11 olefins. Switching to the less reactive Wilkinson catalyst initially provided a selectivity of 1:2 ratio (C-4 hydrogenation versus C-11 hydrogenation). Under the optimized hydrogenation conditions, junenol (**2**) was obtained in 81% yield. The emanation of selectivity mainly relies on the facile coordination of the metal complex with the olefinic counterpart, which is solely driven based on steric. Thereby employing the site-selective olefin hydrogenation strategy dihydrojunenol (**1**) and junenol (**2**) were synthesized in only 5 steps from commercially available starting materials.
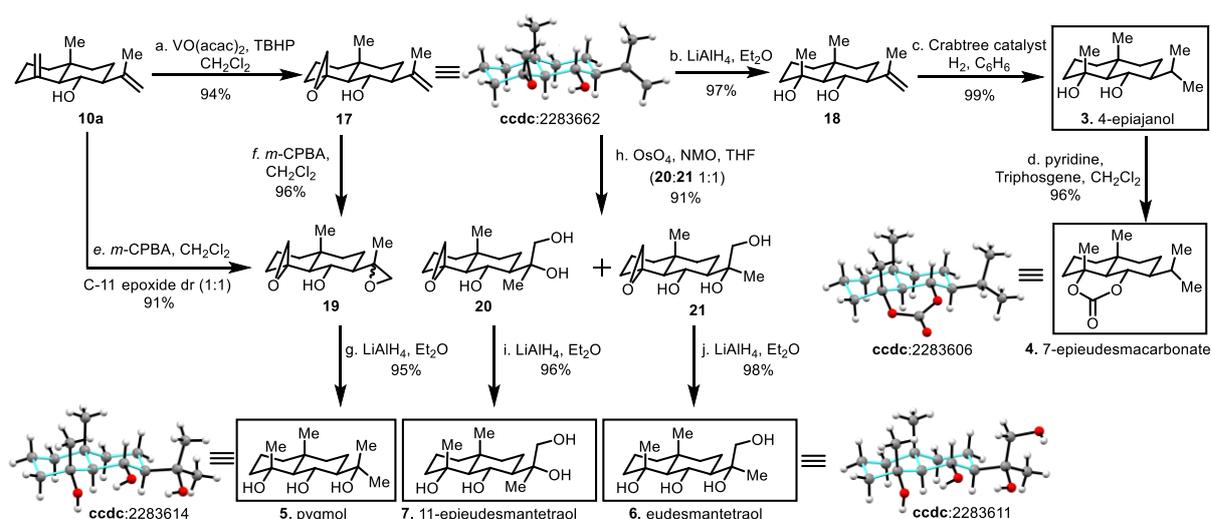
**Scheme 4:** Synthesis of 4-epiajanol (**3**)**,** 7-epieudesmacarbonate (**4**), pygmol (**5**)**,** eudesmantetraol (**6**) and 11-epieudesmantetraol (**7**) through site-specific olefin epoxidation.

Subsequently, our focus shifted towards the site-selective epoxidation of the C-4 olefin, aiming to generate the desired intermediate **17** for synthesizing higher oxidized eudesmanes. Gratifyingly, the C-4 olefin was selectively epoxidized under Sharpless conditions,[14] forming the C-4 epoxide as a single diastereomer in 94% yield.[15] The stereospecific installation of the epoxide on **10a** was mainly maneuvered with the assistance of C-6 hydroxy functionality. Of course, the close proximity of C-4 olefin and proper alignment of the Alcohol-vanadium-peroxide complex were the engineering probes. Surprisingly, prolonged reaction times and increased reagent quantities did not yield diepoxide **19**, indicating the inertness of the C-11 olefin towards Sharpless conditions. Following the crucial site-selective epoxidation reaction, synthesis of oxygenated eudesmanes was aimed by strategically functionalizing monoepoxide **17**. Regiospecific ring opening of the epoxide with $LiAlH_4$,[16] followed by hydrogenation of the C-11 olefin in **18**, provided 4-epiajanol (**3**) in 96% yield (2 steps). Treatment of compound (**3**) with triphosgene afforded the 7-epieudesmacarbonate (**4**) in 96% yield.

The pygmol (**5**) synthesis was approached through two different routes. The first route involved the *m*-CPBA epoxidation of compound **17**, followed by the regioselective opening of the resulting diepoxide **19**. The second route entailed the direct synthesis of compound **19** through the *m*-CPBA epoxidation of the diene in compound **10a**, followed by subsequent epoxide opening reactions. The latter method proved more economical, resulting in a 7-step synthesis of pygmol (**5**) with a yield of 86% (2 steps starting from **10a**). Synthesis of higher oxidized eudesmane family member, eudesmantetraol **6**, was initially targeted through dihydroxylation of compound **18**. However, dihydroxylation of the C-11 olefin in compound **18** under various conditions ($OsO_4$-NMO, $OsO_4$-TMEDA, $I_2$-AgOAc, and Sharpless AD-mix-α and AD-mix-β) failed to provide the diol with desired stereoselectivity, yielding an inseparable mixture of eudesmantetraol (**6**) and 11-epieudesmantetraol (**7**). Nevertheless, the Upjohn dihydroxylation of compound **17** led to the formation of chromatographically separable diol products **20** and **21** with yields of 45% and 46%, respectively. Finally, the regiospecific opening of epoxide in **20** and **21** afforded eudesmantetraol (**6**) and 11-epieudesmantetraol (**7**) with 98% and 96% yields,

respectively. It is noteworthy to mention that the highly oxidized eudesmantetraol (**6**) was synthesized in 7 steps (previous synthesis-15 steps) from 3-methylcyclohexenone (**12**).
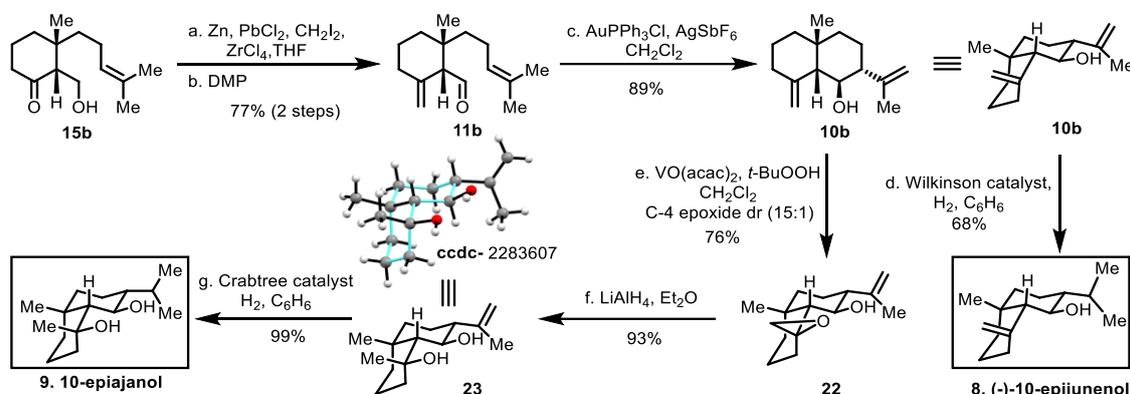


**Scheme 5:** Synthesis of *cis*-eudesmanes (-)-10-epijunenol (**8**) and 10-epiajanol (**9**).

Following the successful construction of higher eudesmanoids containing the *trans*-decalin core, we recognized the crucial role of specific substrate orientation and proximity as the reactivity probe. While many bioactive sesquiterpenoids feature the *cis*-decalin core, their synthesis entails significant challenges due to the scaffold's diversity. Therefore, it was intriguing to investigate the reactivity pattern for the *cis*-eudesmanes. To explore this further, the ene cyclization precursor **11b** was synthesized in gram scale from **15b** by employing similar reaction conditions outlined in Scheme 5. As anticipated, diene aldehyde **11b** displayed a greater inclination to form the *cis*-decalin scaffold **10b** than the *trans*-decalin under Au (I)-catalyzed Alder-ene cyclization conditions. The orientation of the Alder-ene cyclization precursor played a crucial role in the resulting disparity in the reactivities. After successfully creating the intermediate **10b**, the stage was set for exploring the site-selective hydrogenation and epoxidation reactions. The site-selective hydrogenation of intermediate **10b** using Wilkinson's catalyst afforded (-)-10-epijunenol (**8**) in 68% yield. Surprisingly, treatment of **10b** with Sharpless epoxidation conditions delivered the C-4 epoxide **22** in 76% yield. The concave orientation of compound **10b** obstructing the alignment of the vanadium complex might be the probable reason for the reversal in selectivity. Regiospecific opening of epoxide **22** with LiAlH$_4$ afforded diol **23** in 93% yield. The stereochemical outcome of the C-4 quaternary hydroxy center was confirmed using X-ray (SC-XRD) crystal structure analysis. Further hydrogenation of **23** using Crabtree catalyst and H$_2$ gave 10-epiajanol

(**9**) in 99% yield. This study further highlights how minor structural modifications can significantly impact the stereochemical outcomes of chemical reactions.

In summary, we have accomplished the divergent synthesis of the eudesmane class of natural products by employing a site-selective olefin functionalization strategy. The application of asymmetric Cu-NHC catalyzed tandem Michael addition/Aldol reactions and the potentiality of Au(I)-catalysed Alder-ene cyclization reaction was demonstrated for constructing the *cis*/*trans*-decalin framework of eudesmane bearing four consecutive stereocenters with excellent stereospecificity. Further diversification of the eudesmane skeleton through site-selective hydrogenation and epoxidation of olefin functionality led to the concise asymmetric total synthesis of dihydrojunenol (5 steps, 29% overall), junenol (5 steps, 24% overall), 4-epiajanol (7 steps, 27% overall), 7-epieudesmacarbonate (8 steps, 26% overall), pygmol (6 steps, 25% overall), eudesmantetraol (7 steps, 12% overall) and 11-epieudesmantetraol (7 steps, 12% overall), (-)-10-epijunenol (5 steps, 17% overall), 10-epiajanol (7 steps, 18% overall). The presented strategy would facilitate the scalable synthesis of structurally related sesquiterpenes and their analogs, enabling further biological investigations. Further exploration of the site-selective olefin functionalization strategies of higher-order cyclic systems are currently undergoing in our laboratory.

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15.     Notably, the epoxidation of **15a** with *m*-CPBA and Sharpless condition gave a mixture of epoxide products resulting from the epoxidation at both olefins.

16.     Adding $LiAlH_4$ to the etherified solution of **17** gave primary alcohol on C-4, while the reverse addition of **17** to the etherified solution of $LiAlH_4$ gave **18** with desired regiospecificity.

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