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Catalytic Enantioselective Approach to the Eudesmane Sesquiterpenoids: Total Synthesis of (+)-Carissone

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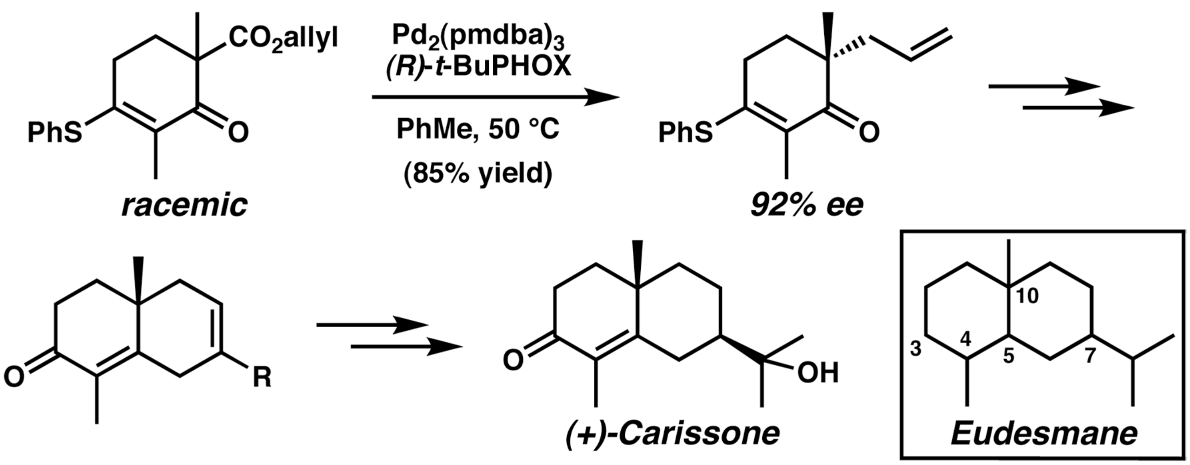
Abstract



A catalytic enantioselective approach to the eudesmane sesquiterpenoids is reported. The strategic use of a palladium-catalyzed enantioselective alkylation of vinylogous ester substrates forged the C(10) all-carbon quaternary center. This key transformation enabled a diastereoselective olefin hydrogenation to create the syn stereochemistry at C(7). The devised synthetic strategy allowed for the preparation of the antibacterial agent (+)-carissone and a formal synthesis of the P/Q-type calcium channel blocker (–)-α-eudesmol.

The flowering plants of the family Asteraceae (Compositae) have many historical uses, including rubber, medicines, edible oils, vegetables, and pesticides.[1] Among these flora are a large number of species that are abundant in structurally diverse sesquiterpenoids, particularly ones that contain the eudesmane skeleton (Figure 1). Over 1000 eudesmanes have been identified from these sources, with their structures diverging based on oxygenation and oxidation patterns within the carbon framework.

This ever-growing[2] class of important secondary metabolites possesses a wide range of biological properties, including plant growth inhibition, insect antifeedant, antibacterial, antifungal, and antitumor activities. Representative eudesmanes include antibacterial agents (+)-carissone (**1**)[3] and (+)-3-oxocostusic acid (**2**),[4] as well as P/Q-type calcium channel blocker (−)-α-eudesmol (**3**)[5] (Figure 1). These examples typify common structural motifs within this class of sesquiterpenoids, including the C(10) all-carbon quaternary stereocenter and

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stereogenic C(7) substituent. The structural similarities and interesting biology associated with this class of molecules has stimulated several synthetic efforts,[6,7,8] most of which employ semi-synthetic or chiral pool strategies. To date, no catalytic asymmetric approaches toward these eudesmanes have been developed. Herein we report an approach[9] that incorporates our recent method for the catalytic asymmetric formation of enantioenriched all-carbon quaternary stereocenters into a general synthetic strategy for this class of sesquiterpenoids.

In devising a strategy for the total synthesis of the eudesmanes, we simplified our target to enone **5**, which has been utilized in the preparation of structures such as **4**,[6d] and itself embodies many features present in various family members (cf. **5** and **1**, **2**) (Figure 2). We envisioned that the stereochemistry of the C(7) substituent could arise by means of the diastereoselective hydrogenation of a substituted cyclohexene (i.e., **6**), the stereochemical outcome of which would be controlled by the C(10) quaternary stereocenter. This cyclohexene could be obtainable from a ring-closing methathesis of triolefin **7**, which would be derived from an appropriately substituted α-quaternary ketone (i.e., **8**). Thus, the key control element in the design of this synthetic strategy is the C(10) quaternary stereocenter,[10] and we therefore sought to develop an efficient and selective means for the preparation of this moiety.

The enantioselective alkylation of ketone enolates is an area of intense investigation in our laboratory.[11] This method has resulted in the preparation of wide range of carbonyl compounds with adjacent quaternary stereocenters with high levels of selectivity and excellent yields, some of which have proved valuable in synthetic endeavors.[12] The application of α-quaternary ketones such as **8** for the devised strategy would require a carbonyl transposition (i.e., **8** → **7**), and we therefore chose to exploit the unique properties of vinylogous esters (i.e., **8** where R^2 = OR) pioneered by Stork and Danheiser[13] for this purpose.

Our initial studies for the asymmetric generation of quaternary stereocenters utilitzing vinylgous ester derivatives focused on enol carbonates due to preliminary investigations[12c,14] that have demonstrated successes for similar substrates. Exposure of allyl enol carbonate **9** to typical reaction conditions consisting of a palladium(0) catalyst and ligand (*S*)-**12**[15] in toluene generated vinylogous ester (+)-**13**, albeit in variable yield and selectivity (Table 1, entry 1). Unfortunately, the instability of **9** impeded further studies as these results were highly dependent on the composition of this enol carbonate.[16] Given the range of substrate possibilities for this transformation,[11d] we next focused on racemic β-ketoester (±)-**10**. Surprisingly, this substrate proved only modestly reactive at 50 °C, producing ketone (+)-**13** in 19% yield and 79% ee (entry 2).[17] Increasing the reaction temperature to 80 °C enabled complete conversion to ketone (+)-**13**, although with slightly reduced selectivity (entry 3). As the lack of reactivity seemed to be a major complication with this substrate, we considered vinylogous thioesters (i.e., (±)-**11**) for their reported activation properties.[14] Indeed, racemic β-ketoester (±)-**11** did prove more reactive and produced ketone (+)-**14** at 50 °C in good yield and 92% ee (entry 4). A screen of solvents revealed that benzene (entry 5) and ethereal solvents (entries 6 and 7) provided similar selectivities to toluene.

With optimal conditions for the preparation of **14**, we sought to demonstrate the feasibility of using this ketone for the total synthesis of (+)-carissone (**1**). Accordingly, racemic β-ketoester (±)-**11** was converted to (−)-**14** in 85% yield[18] and 92% ee using ligand (*R*)-**12**, to correlate with the natural antipode of **1** (Scheme 2). Subsequent conversion of vinylogous thioester (−)-**14** into vinylogous ester (−)-**15** was achieved with sodium methoxide in refluxing methanol. Exposure of the resulting vinylogous ester to the substituted allylmagnesium bromide generated from **16**[19] and magnesium provided enone (−)-**17** in 94% yield. The success of allylmagnesium bromide additions to vinylogous ester (−)-**15** encouraged us to investigate similar reactions of various organometallic reagents with vinylogous thioester (−)-**14**, however, several conditions provided intractable mixtures with no desired products.[20] Nonetheless, ring-closing metathesis of enone (−)-**17** using Grubbs' catalyst **18**[21] efficiently prepared the desired substrate (i.e., (−)-**19**) for the diastereoselective hydrogenation. Gratifyingly, heterogeneous hydrogenation utilizing Rh/Al_2O_3 catalyst[22] in methanol, followed by TBS cleavage, provided alcohol (+)-**20** in good overall yield with excellent diastereoselectivity.[23] This notable transformation generates alcohol (+)-**20** with the C(10) and C(7) stereocenters in the desired syn configuration required for **1**. Conversion of alcohol (+)-**20** to ester (+)-**21** was achieved by a two-step process involving Dess–Martin oxidation,[24] followed by chlorite oxidation[25] with diazomethane workup.

The availability of ester (+)-**21** in the desired configuration enabled preparation of (+)-carissone (**1**) in short order. Diastereoselective reduction of the enone carbonyl under Luche conditions,[26] followed by treatment of the resulting alcohol with methylmagnesium bromide[6m] provided diol (+)-**22**[27] in 71% yield (Scheme 3). The preparation of this diol intersects Aoyama's synthesis (−)-α-eudesmol (**3**)[6e] and represents a formal total synthesis. Furthermore, facile allylic oxidation with manganese dioxide[6a] gave (+)-carissone (**1**), having spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS, optical rotation) identical to that reported for natural **1**.

In summary, we have described the palladium-catalyzed asymmetric alkylation of vinylogous ester substrates and demonstrated the utility of such products in a general synthetic approach for the total synthesis of the eudesmane sesquiterpenoids. Fundamental to this strategy is the use of the resulting C(10) quaternary stereocenter to control the C(7) stereochemistry via a diastereoselective hydrogenation, providing a highly selective and efficient route to the antibacterial agent (+)-carissone (**1**). Studies to understand the interplay between substrate reactivity and selectivity for the asymmetric alkylation of vinylogous ester derivatives, as well as the use of the resulting enantioenriched products in the synthesis of other bioactive natural substances[28] is currently underway.

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16. Enol carbonate **9** was unstable to air, forming complex reaction mixtures that substantially affected yields and selectivities for the alkylation. Aromatic carbonate ***i*** was identified from this mixture. See Supporting Information for more details.

17. The reactivity of β-ketoester (±)-**10** contrasts significantly with that of related derivative (±)-***ii***, which generates ***iii*** in 79% yield and 86% ee under identical conditions.

18. β-ketoester (±)-**11** was recovered in 9% yield.

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22. A variety of homogeneous and heterogeneous catalysts were screened for the hydrogenation of (−)-**19**. Of those that were reactive, most promoted undesired reactivity, including enone reduction and further decomposition. Rh/Al_2O_3 proved to be a mild catalyst at 1 atm H_2 in MeOH for this substrate.

23. The stereochemistry of (+)-**20** was initially verified using NOE correlations. See Supporting Information for details.

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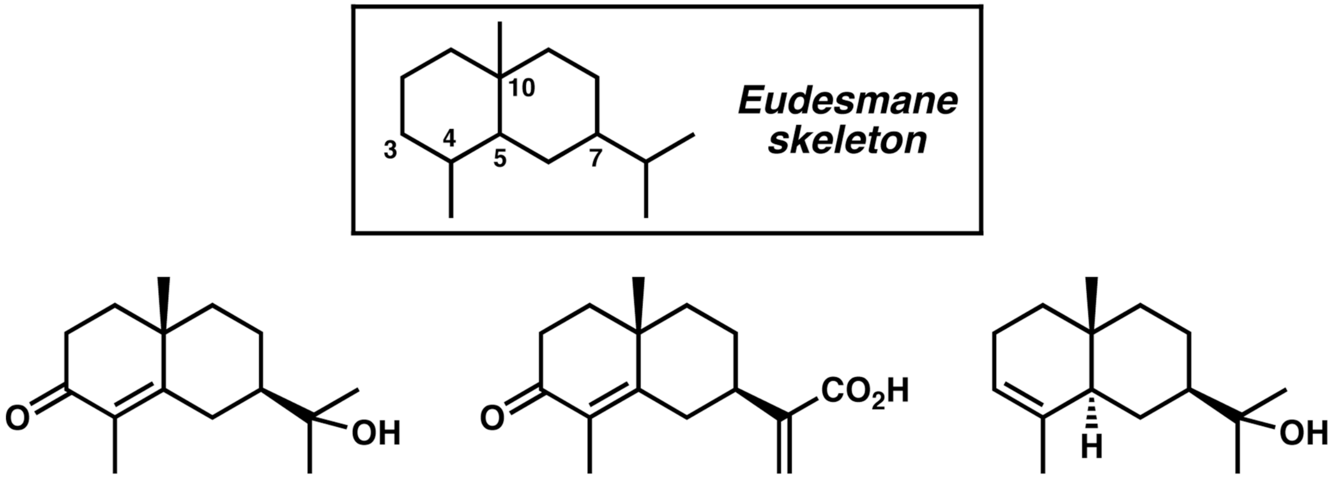
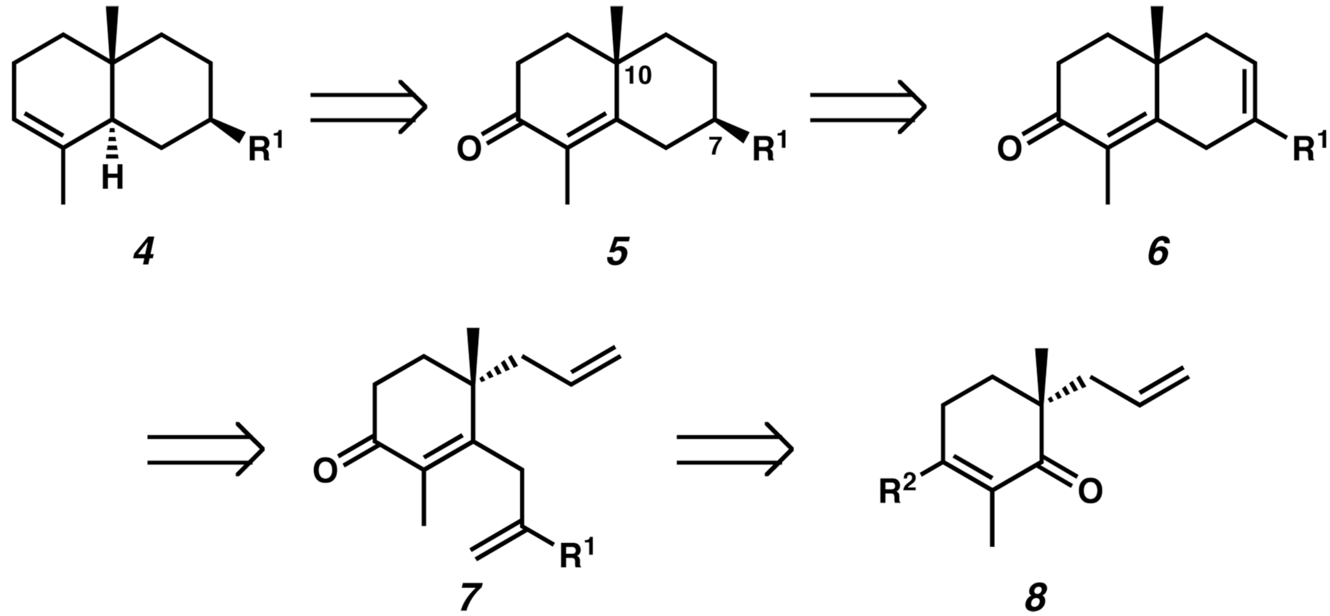
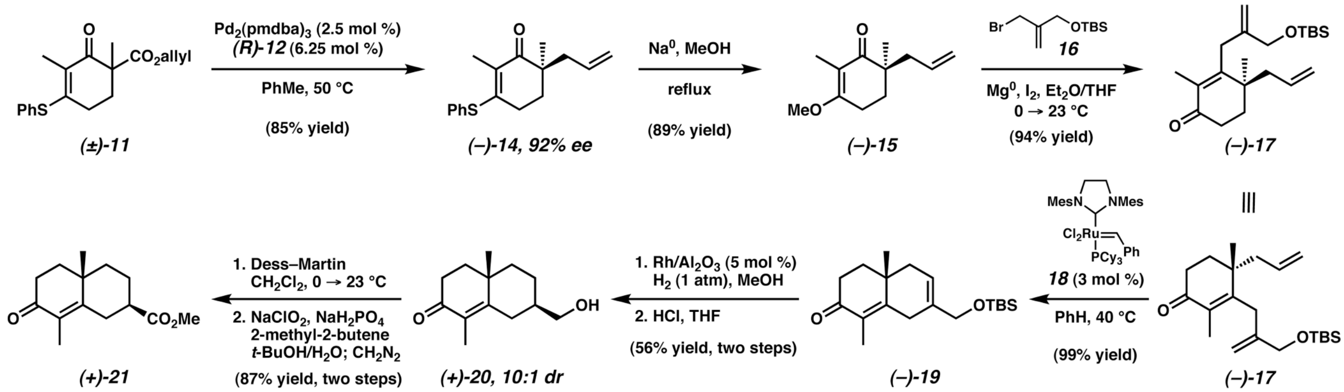


(+)-Carissone (1) (+)-3-Oxocostusic acid (2) (–)-α-Eudesmol (3)

Figure 1.
Representative Eudesmane Sesquiterpenoids

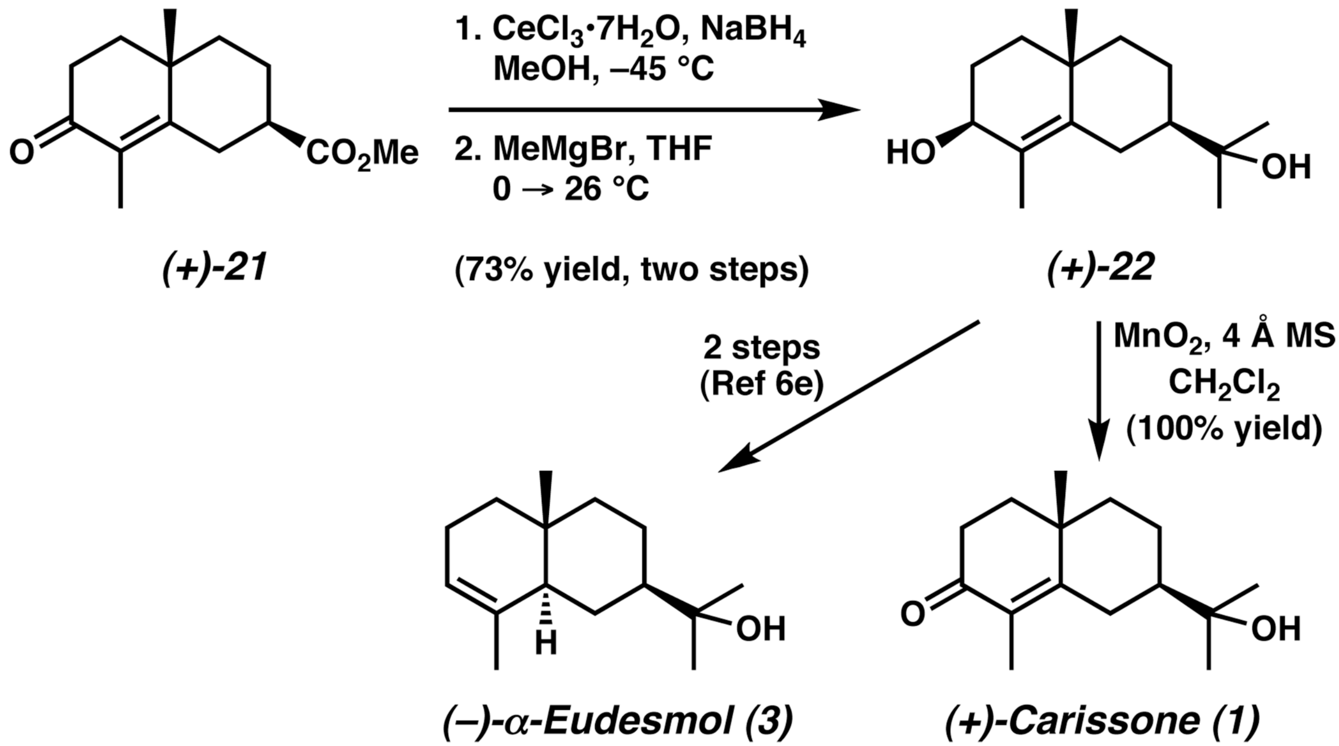


Scheme 1.
Retrosynthetic Analysis of the Eudesmanes



Scheme 2.

Enantioselective Synthesis of the Eudesmane Core



Scheme 3.
End Game for (+)-Carissone (**1**)

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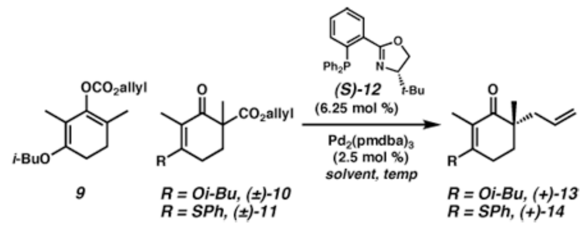
Table 1

Asymmetric Allylation of Vinylogous Ester Derivatives[a]



entry	substrate	solvent	temp (°C)	product	yield[b] (%)	ee[c] (%)
1	**9**	PhMe	25	**13**	22–61	84–88
2	**10**	PhMe	50	**13**	19[d]	79
3	**10**	PhMe	80	**13**	86	75
4	**11**	PhMe	50	**14**	86	92
5	**11**	PhH	50	**14**	61[e]	92
6	**11**	THF	50	**14**	88	92
7	**11**	dioxane	50	**14**	90	91

[a] pmdba = bis(4-methoxybenzylidene)acetone.

[b] Isolated yields.

[c] Enantiomeric excess determined by chiral HPLC or SFC.

[d] β-ketoester (±)-**10** was recovered in 69% yield.

[e] β-ketoester (±)-**11** was recovered in 26% yield.