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Short Access to the Aromadendrane Family: Highly Efficient Stereocontrolled Total Synthesis of (±)-Cyclocolorenone and (±)-α-Gurjunene

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(±)-Cyclocolorenone (**2**), an aromadendrane, was prepared stereoselectively in seven steps in 10.8–12.5% overall yield from the commercially available tropylium cation via key intermediate **6**, which was used as a general and efficient precursor to bicyclo[5.3.0]decane sesquiterpenes. (±)-α-Gurjunene (**3**) was obtained through the efficient deoxygenation of (±)-**2**, constituting therefore the first total synthesis of this natural product in eight steps from the tropylium cation.

Introduction

The first reported member of the aromadendrane family, (+)-aromadendrene [(+)-**1**], which inspired the name of this new group of tricyclic compounds, was isolated by Smith over one century ago by distillation of *Eucalyptus Globulus* essential oil.[1] These sesquiterpenes possessing the bicyclo[5.3.0]decane skeleton represent more than 100 natural compounds.[2] The presence of a *gem*-dimethylcyclopropane ring fused to an hydroazulene ring system at the C-6,7 position is characteristic of this family (representative examples are shown in Figure 1). Although the biological properties of aromadendranes need further study[3] one of them, (–)-macrocarpal A, has shown antibacterial[3b] activity.

(–)-Cyclocolorenone [(–)-**2**] was first isolated in 1958 from *Pseudowintera Colorata*[4] and more recently from *Magnolia grandiflora* bark.[5] Cutler and co-workers[3d] revealed that [(–)-**2**] has phytotoxic, antibacterial, antiviral, and antifungal activities. In 1974, Matsuo and co-workers,[6] and more recently Asakawa and co-workers,[7] isolated (+)-cyclocolorenone [(+)-**2**], which belongs to the *ent*-aromadendrane family. The latter compound has never been assayed for its biological activity. (–)-α-Gurjunene [(–)-**3**] was first isolated in 1958 from *Dipterocarpus Dyeri* (gurjun balsam resin),[8a] the structure of which was determined in 1963[8c] and confirmed, two years later, through a rational correlation with cyclocolorenone by Ourisson and co-workers.[8e] Later, (–)-**3** was isolated in 1973 from *Lansium Anamalayanum*,[8f] then in 1978 from *Helichrysum* species,[8g] and finally in 1987 from *Balsamum Tolutanum*.[8h] As for all most-abundant aromadendrenes, the enantiomeric form (*ent*-aromadendrene) (+)-gurjunene [(+)-**3**] was isolated in 1978 from *Porella* species.[8i] Only a few approaches of this intriguing family of compounds have been reported. One of them uses the photochemical rearrangement outlined by Barton,[9] and another one is based on the thermolysis of an allylidenecyclopropane.[10] Nicholas and co-workers more recently applied their cyclopentannulation reaction to this class of compounds and synthesized (±)-cyclocolorenone (**2**) over 10 steps in 8.9% overall yield from tropone.[11] On our side, we developed an efficient strategy for the construction of hydroazulenone **6** (key intermediate) through a highly selective [2+2] cycloaddition of dichloroketene followed by a regioselective ring expansion with diazomethane and HCl elimination.[12a] This opens access to different natural sesquiterpenes[12] (Scheme 1).

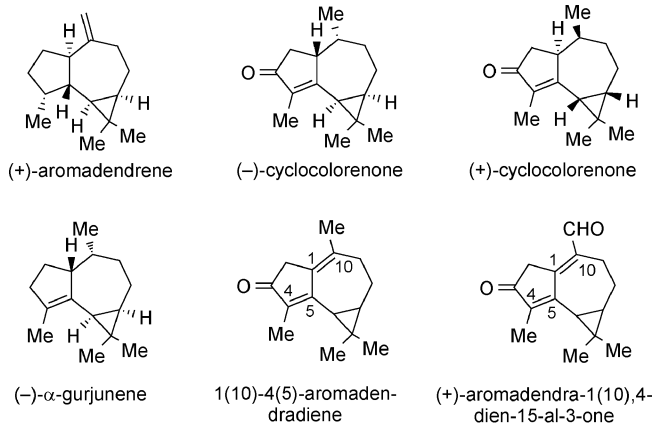

Figure 1. Selected members of aromadendranes.

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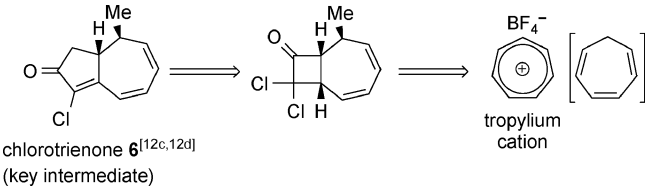
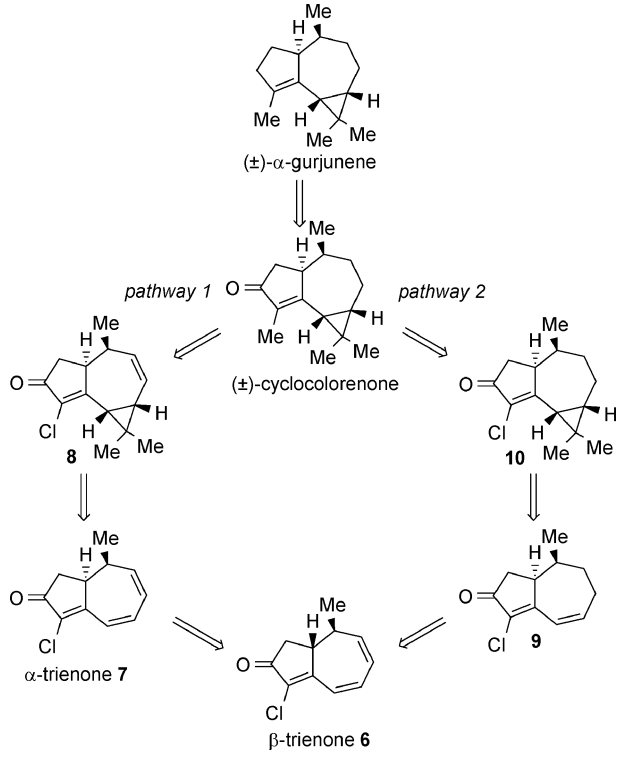


Scheme 1. Synthesis of key intermediate **6** (three steps with 50% overall yield from the tropylium cation, ref.[12c,12d]).

Results and Discussion

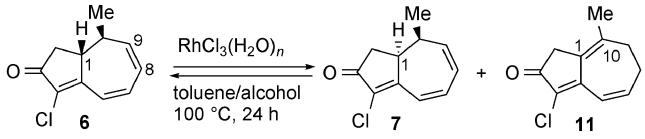
Herein, we propose a new total synthesis of (±)-cyclocolorenone [(+/–)-**2**] and the first total synthesis of (±)-gurjunene [(+/–)-**3**] via [(+/–)-**2**]. Our approach realizes an efficient, versatile, and stereocontrolled access to the aromadendrane family. Our retrosynthetic analysis of cyclocolorenone [(+/–)-**2**] begins with epimerization at the C-1 position of key intermediate **6** (Scheme 2, pathway 1). Molecular models suggested that the relative configuration of C-1 controls that of C-7 upon conjugate addition. Indeed, energy minimizations on β-trienone **6** revealed partial deconjugation of the last double bond at C-8,9 as a consequence of a dihedral angle of 15° of the latter double bond with that at C-6,7.[12a] Similarly, a dihedral angle of 12° was calculated for C-6,7,8,9 of **7**. Selective hydrogenation of **7** was thus expected to occur at C-8,9, and conjugate additions preferentially at C-7. Two retrosynthetic pathways, exploiting these chemical features, were envisaged to synthesize (±)-cyclocolorenone [(+/–)-**2**] (Scheme 2).



Scheme 2. Retrosynthetic analysis.

Attempts to epimerize **6** to **7** with KOH/MeOH[13] led to a complex mixture of products and partial degradation. The best yield of isolated **7** (48%) was obtained (Table 1, Entry 1) in a 1:1 mixture of toluene/ethanol at 100 °C in the presence of $RhCl_3(H_2O)_n$ catalyst[14] (70% yield considering the recovery and recycling of unreacted **6**). Under these conditions, only trace amounts of C-8,9 double-bond migration product **11** were observed, whereas **11** was the major product (55%) in a 5:1 mixture of toluene/ethanol (Table 1, Entry 4).

Table 1. Epimerization at the C-1 position of β-trienone **6** and migration of the C-8,9 double bond.



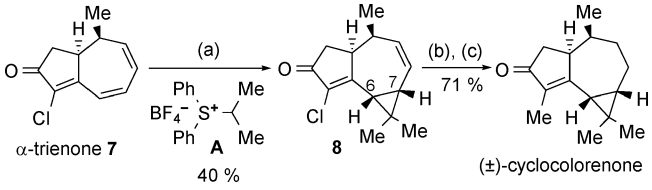
Entry	Toluene/alcohol	β-Trienone **6** [%][a]	α-Trienone **7** [%][a]	Trienone **11** [%][a]
1	1:1 (EtOH)	40	60	Traces[b]
2	0:1 (EtOH)	60	40	0
3	3:1 (EtOH)	30	40	30
4	5:1 (EtOH)	17	28	55
5	10:1 (EtOH)	33	33	34
6	1:1 (MeOH)	50	50	0
7	4:1 (MeOH)	60	40	0

[a] Determined by NMR spectroscopy. [b] <5%.

Our next goal was to introduce the *gem*-dimethylcyclopropane at the C-6,7 positions. Simmons-Smith[15a,15b] cyclopropanation, including also that of Furukawa,[15c] and reaction with 2-diazopropane[15d] applied to substrate **6** did not give the desired tricyclic skeleton. Our attention was turned then to a Michael addition/intramolecular substitution sequence of the sulfur ylide. Applying the conditions outlined by Corey[16] (LDA, CH_2Cl_2/DME, –78→–50 °C) to **7** led only to products of degradation. We reasoned that this failure was due to the ability of **7** to be readily enolized. By screening[17] various bases, solvents, temperature conditions, and Lewis acids,[18] we found that NaHMDS in THF at –110 °C in the presence of $Sc(OTf)_3$ gave the best results. The desired cyclopropane product **8** was isolated in 40% yield. No regio- or stereoisomers could be detected by NMR spectroscopic analysis of the crude reaction mixture.[19] Quantitative hydrogenation with 10% Pd/C followed by Suzuki–Miyaura coupling afforded natural (±)-cyclocolorenone [(+/–)-**2**] in 71% yield (Scheme 3).

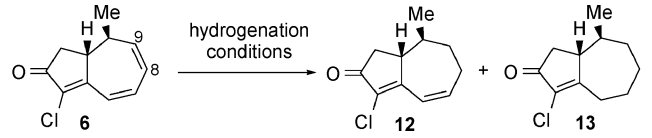
In parallel, we examined the second retrosynthetic pathway of Scheme 2. Assuming that partial deconjugation in trienone **6** would make its catalytic hydrogenation at C-8,9 selective, we explored various reaction conditions (Table 2).

The best results in terms of yield and reproducibility were obtained with 5% Pd/Al_2O_3 as catalyst, with ethyl acetate as solvent, and by controlling the amount of H_2 (syringe addition) as a function of the reaction progress (^1H NMR spectroscopy). We thus obtained 3:1 to 4:1 mixtures



Scheme 3. Synthesis of (±)-cyclocolorenone [(+/–)-**2**] by pathway 1. Reagents and conditions: (a) **A** (1.5 equiv.), NaHMDS (1.65 equiv.), $Sc(OTf)_3$ (cat), THF, –78→10 °C, 40%; (b) H_2, 10% Pd/C, EtOAc, quantitative; (c) $MeB(OH)_2$ (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), dpdb (0.4 equiv.), K_3PO_4 (2 equiv.), toluene, 100 °C, 24 h, 71%. HMDS = 1,1,1,3,3,3-hexamethydisilylazide, dpdb = dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

Table 2. Selective hydrogenation of the C-8,9 double bond in β-trienone **6**.[20]

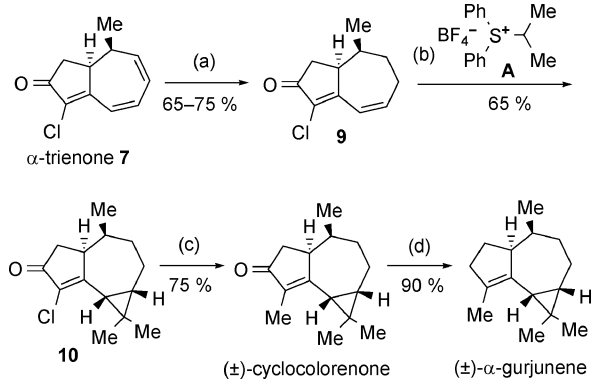


Entry	Hydrogenation conditions	**12**[a]	**13**[a]
1	H_2, 5% Pd/$BaSO_4$, EtOAc	0	1
2	H_2, Pd/$CaCO_3$ (5% Pb), EtOAc[20a]	2–5	1
3	H_2, 5% Pd/Al_2O_3, EtOAc[20b]	3–4	1
4	Et_3SiH, TFA, 50 °C, CH_2Cl_2[20c]	3	2
5	$TsNHNH_2$, NaOAc, Δ, DME/H_2O[20d]	1	1
6	H_2, $(Ph_3P)_3RhCl$, toluene[20e,20f]	2	1
7	Et_3SiH, $(Ph_3P)_3RhCl$, 50 °C, toluene[20g]	1	1
8	$Na_2S_2O_4$, Adogen$_{464}$, $NaHCO_3$, C_6H_6/H_2O[20h]	0	1

[a] Ratio **12**/**13** determined by NMR spectroscopy.

of **12**/**13** (Table 2, Entry 3). These latter compounds were readily separated by column chromatography on silica gel. Dienone **12** was isolated in 65–75% yield and contained trace amounts of isomerized trienone **11**.[21]

α-Dienone **9** was then engaged in the cyclopropanation reaction by using the optimized conditions, and we were pleased to obtain tricyclic compound **10** in 65% yield (95% conversion and complete regio- and stereoselectivity). This higher conversion relative to that obtained for the conversion of **7** into **8** (Scheme 3) can be attributed to the slight difference in p*K*a values corresponding to the side reaction of enolization. Finally, methylation of **10** by applying the Suzuki–Miyaura cross-coupling reaction provided the target (±)-cyclocolorenone [(+/–)-**2**] (m.p. 40 °C).[22] The NMR spectroscopic data of (±)-**2** were identical to those reported in the literature[9a] for the natural product. A final one-step deoxygenation of (±)-**2** with $LiAlH_4$/$AlCl_3$[23] permitted the isolation of (±)-α-gurjunene [(+/–)-**3**] in 90% yield (Scheme 4). The structure of (±)-**3** was deduced from its IR, NMR and LRMS data and was confirmed by showing identical physical constants and spectra to those of (–)-α-gurjunene [(–)-**3**] isolated (by distillation) from *Dipterocarpus Dyeri* (gurjun balsam resin)[8c] and later from different species.[8f,8g,8h]



Scheme 4. Synthesis of (±)-cyclocolorenone [(+/–)-**2**] by pathway 2 and its conversion into (±)-α-gurjunene [(+/–)-**3**]. Reagents and conditions: (a) 5% Pd/Al_2O_3 (cat.), H_2 (1.0–1.5 equiv.), EtOAc, 65–75%; (b) **A** (2 equiv.) NaHMDS (2 equiv.), $Sc(OTf)_3$ (cat), THF, –110→10 °C, 65%; (c) $MeB(OH)_2$ (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), dpdb (0.4 equiv.), K_3PO_4 (2 equiv.), toluene, 100 °C, 20 h, 75%; (d) $AlCl_3$ (27 equiv.) $LiAlH_4$ (6 equiv.), THF, –20 °C, 90%. HMDS = 1,1,1,3,3,3-hexamethydisilylazide, dpdb = dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

Conclusions

In conclusion, we have developed a highly efficient total synthesis of (±)-cyclocolorenone [(+/–)-**2**] that requires only seven steps (10.8–12.5% overall yield) from the tropylium cation. The method exploited the rapid regio- and stereoselective construction of the aromadendrane core that relies upon stereocontrol at the C-1 position of α-trienone **7**. (±)-α-Gurjunene [(±)-**3**] was obtained through the efficient deoxygenation of aromadendrane [(±)-**2**], constituting therefore the first total synthesis of this natural product in eight steps and with 9.7–11.3% overall yield from the tropylium cation. Complementary studies are undergoing in our group to generalize this strategy to other members of this family of natural compounds. More particularly, we plan to open a route to (±)-1(10)-4(5)-aromadendradiene[8h,24] (**4**) and (±)-aromadendra-1(10),4-dien-15-al-3-one[25] (**5**) (Figure 1) thanks to the formation of product **11** from **6** through migration of the C-8,9 double bond to the C-1,10 positions (Table 1).

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for **2**, **3**, **7**–**11**; copies of the ^1H and ^{13}C NMR spectra for **2**, **3**, **7**–**11**.

Acknowledgments

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