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Total Synthesis of (–)-Rotundone and (–)-*epi*-Rotundone from Monoterpene Precursors

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The first total synthesis of (–)-Rotundone **1a** has been accomplished from (*R*)-(+)-Limonene and therefore for the first time from an unrelated monoterpene instead of modifying structurally closely related sesquiterpene precursors such as α-Guaiene **2**. Challenges such as intermediates with stereocenters prone to epimerization by enolization were overcome by designing a *β*-methyl-keto route starting from (*R*)-(+)-Limonene which finally gave (–)-Rotundone **1a** by Nazarov cyclization of precursor **13a**. Diastereomer (–)-*epi*-Rotundone **1b** was separated from (–)-Rotundone **1a** chromatographically. An alternative route from *rac*-Citronellal provided a diastereomer mixture of racemic Nazarov precursor **13** via a TRIP-catalyzed intramolecular aldolization, thus indicating that the Nazarov cyclization precursor **13a** is in principle accessible from *S*-(–)-Citronellal. The 11 step synthesis from (*R*)-(+)-Limonene with ~ 1% overall yield confirmed the absolute stereochemistry of (–)-Rotundone **1a** and provided samples of good olfactory quality.

Keywords: epimerization, (–)-*epi*-Rotundone, enolization, Nazarov reaction, olfactory evaluation, (–)-Rotundone, sesquiterpenes, terpenes, total synthesis, TRIP-catalyzed cyclization.

Introduction. (–)-Rotundone **1a** (Figure 1) is an oxygenated sesquiterpene which has been first identified as a natural sesquiterpenoid in the essential oil from nut grass weed of Japanese origin (*Cyperus rotundus Linné*) by an Indian group which determined its absolute configuration through chemical derivatization and indirect comparision with (–)-α-Guaiene **2**.[1] The absolute configuration of **2** had been determined by Minato through a 10-step-degradation process to *S*-(–)-α-isopropyl-γ-acetobutyric acid,[2] which had been characterized by Wallach en route from (+)-Fenchone to *S*-(–)-isopropylglutaric acid.[3]

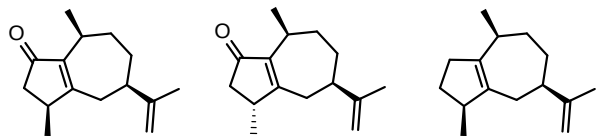


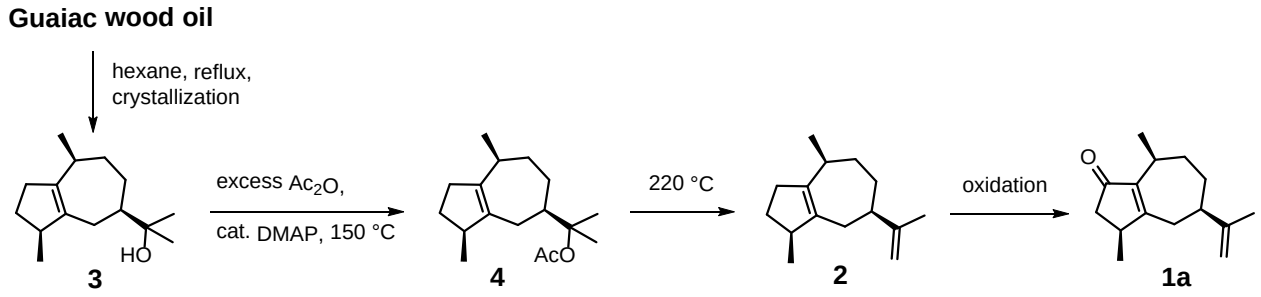
Figure 1. Sesquiterpenes (–)-Rotundone **1a**, (–)-*epi*-Rotundone **1b**, and (–)-α-Guaiene **2**.

In recent times (–)-Rotundone **1a** has been recognized as a unique ingredient for the flavor and fragrance industry, due its rich and diffusive woody, peppery and agarwood like odor[4] at extremely low aroma detection thresholds of only 8 – 16 ng/ L in water and red wine.[5] (–)-Rotundone **1a** has been found as constituent of patchouli oil,[6] Shiraz grape (*Vitis vinifera*), spices (white and black peppers, marjoram, oregano) and oak-aged spirits. Givaudan chemists revealed the significant contribution of (–)-Rotundone to the odor of cypriol oil. [4]

At Hasegawa the olfactory profile of *epi*-Rotundone **1b** was recently explored, and (–)-Rotundone **1a** has been identified in the volatile fraction of *Boswellia sacra* gum resin contributing to the aroma of frankincense. [7] (–)-Rotundone has also been identified as potent odor-active component in the aromas of grapefruit, orange, apple and mango.[8]

(–)-Rotundone **1a** has been prepared from Guaiac wood oil (scheme 1), from which the structurally related precursors (–)-α-Guaiene **2** and (–)-Guaiol **3** are obtained by a tedious and low-yielding extraction.[9,10,11] The allylic oxidation of the sesquiterpene **2** has been effected with iron(III) porphyrins catalysts,[12,13] through electrochemical oxidation,[14] through chromate oxidation or simply by aereal oxida-

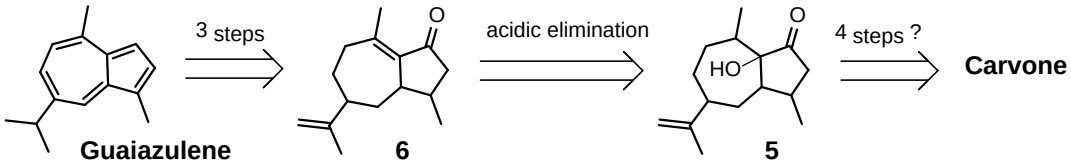
tion.[15] **1a** has been also prepared by Co(II)-catalyzed allylic oxidation of Guaiol-acetate **4** followed by elimination of the acetate,[8] and by photochemical ene oxidation of (–)-α-Guaiene **2** followed by PCC oxidation.[16] All these oxidation procedures give (–)-Rotundone **1a** with low yields and purities, due to the multiple oxidation sites in (–)-α-Guaiene **2**.



Scheme 1. Synthesis of (–)-Rotundone **1a** from (–)-Guaiol **3** obtained from Guaiac wood oil.

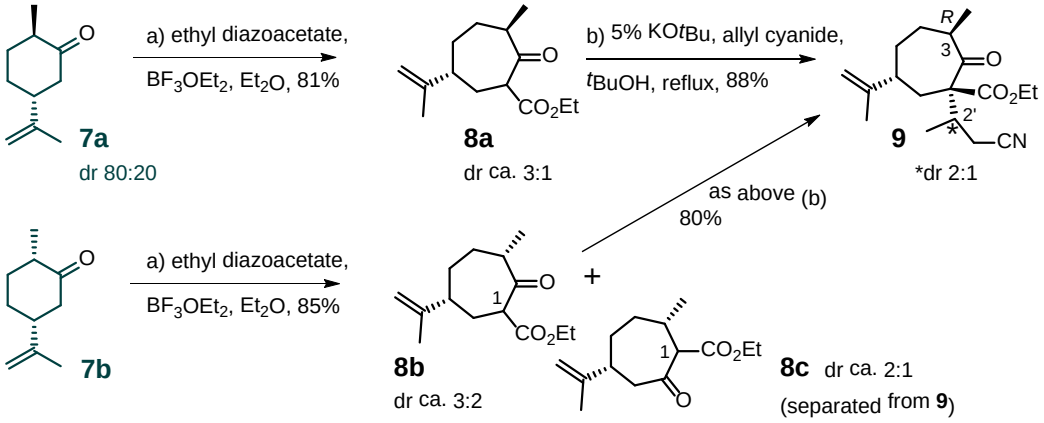
In this context we were interested in a total synthesis of (–)-Rotundone **1a** without using structurally related Guaiene-type precursors **2** – **4**, mainly because the cresolic malodorous off-notes from Guaiac wood oil such as Guaiacol (2-methoxyphenol) are difficult to separate from these intermediates and the final (–)-Rotundone **1a**. Surprisingly, total syntheses of **1a** were unknown at the beginning of our studies, with the next best sequences for the synthesis of *rac*-Guaiol **3** published decades ago.[17,18,19]

Results Shono route. At the beginning of our studies we were interested in a sequence designed by Shono for the synthesis of Guaiazulene,[20] based on earlier work by Sukh Dev.[21,22] This sequence went through the elimination of ketoalcohol **5** to a mixture of Bulnesone **6** isomers (scheme 2). Elimination of **5** under acidic conditions, however, should have been accompagnied by traces of Rotundone isomers **1**. Although such byproducts had not been mentioned in the article, their possible generation stirred our interest because isomer mixtures with low concentrations of powerful olfactory vectors, such as Iso E Super™ for example, have been successfully commercialized.[23] We therefore re-investigated Shono's sequence with the goal to detect and determine the content of the extremely powerful olfactory vector *rac*-**1a** in the mixture of **6** and with the option to optimize the synthesis of Rotundone (–)-**1a** via this or a modified route.



Scheme 2. Retrosynthesis of Guaiazulene from Carvone through acidic elimination of alcohol **5** to α,β-unsaturated ketone **6**.

En route to Bulnesone **6**, precursor **8** was synthesized from dihydrocarvone **7** by diazoacetate insertion (scheme 3). For assignment of the diastereomers of product **8**, the *cis*- and *trans*-isomers of commercially available *rac*-dihydrocarvone **7** were separated by flash chromatograpy.[24] $BF_3(OEt)_2$ promoted diazo acetate insertion into the separated isomers **7a** and **7b** occurred preferentially with migration of the less substituted carbon carbon bond α to the ketone, as known from similar substrates under these conditions.[25,26,27] Whereas diazoacetate insertion into *trans*-dihydrocarvone **7a** gave only one regioisomer (**8a**), *cis*-dihydrocarvone substrate **7b** generated also regioisomer **8c** as byproduct in an (at this stage) inseparable mixture of **8b** and **8c**.

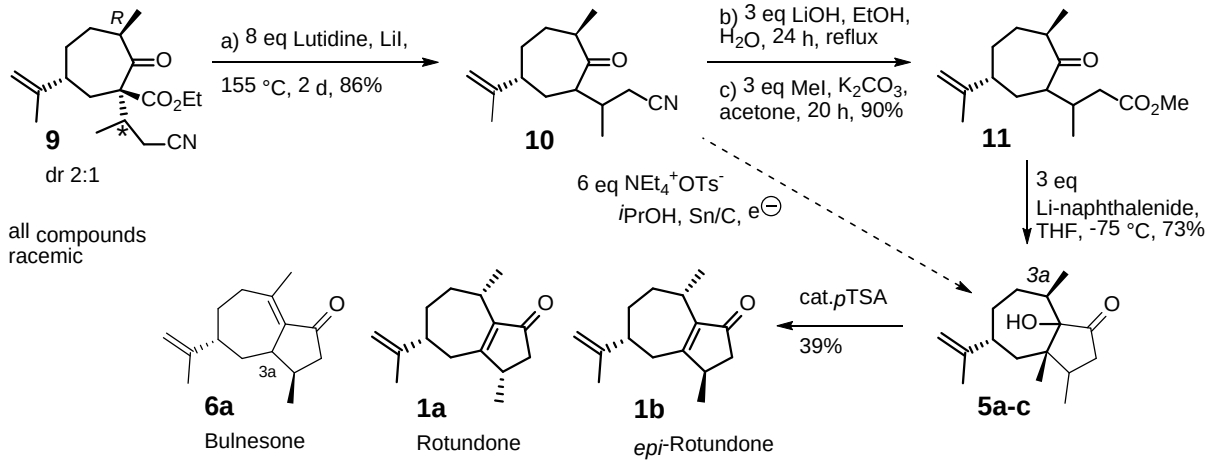


Scheme 3. Diazoacetate insertion into Dihydrocarvone **7**, synthesis of Michael adduct **9**, and separation of regioisomer **8c**.

As Michael addition of **8a** and **8b** to but-2-ene-1-nitrile, generated *in situ* from allyl cyanide, was accompanied by equilibration of the methyl group α to the ketone, adduct **9** was isolated from either *trans*- or *cis*-dihydrocarvone **7a** or **7b** with undesired 7-ring *trans*-configuration at C(3) of **9**. The corre-

sponding 7-ring *cis*-isomer was not detected. Regioisomer **8c** could be separated by distillation and with good purity from nitrile **9**, because only the sterically less hindered α-carbonyl-C(1) in regioisomer **8b** underwent Michael addition to but-2-ene-1-nitrile (from allyl cyanide). The sterically more hindered α-carbonyl-C(1) in regioisomer **8c** did not undergo this reaction.

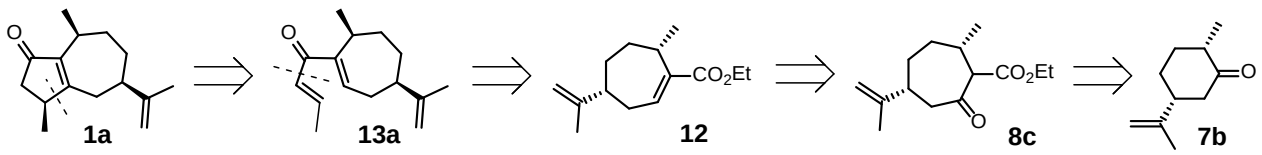
We nevertheless continued the sequence with decarboxylation of *β*-keto ester **9** to ketone **10**, hoping for detection of compounds with desired stereochemistry further downstream of the sequence. Because electrocyclization of mixture **10** to hydroxy-Rotundone mixture **5** gave only poor yields in our hands we went through a detour comprising hydrolysis of nitrile **10** and methylation of the acid followed by acyl-anion cyclization of methylester **11** with Li-naphtalenide (scheme 4), as described for similar transformations.[28] This sequence gave hydroxy-ketone mixture **5a-c** with much better overall yield and purity. The three *3aSR,5RS,8RS*-configurated main diastereomers of **5a-c** were chromatographically separated and their structures assigned by NMR-analysis. Elimination of the hydroxy-ketone mixture **5a-c** with catalytic amounts of acid gave a mixture containing racemic Bulnesone isomer **6a** and racemic Rotundone diastereomers **1a** and **1b** with a regioisomer ratio of 3:1 (for other isomers see the SI). Only the 7-ring-*cis*-configurated Rotundone isomers **1a** and **1b** (diastereomer ratio 2:1) were detected, no other peaks with a Rotundone-like GC-MS-fragmentation pattern.



Scheme 4. Acylanion cyclization of ketoester **11** to hydroxyketones **5a-c** and elimination to a Rotundone / Bulnesone mixture.

The content of *rac*-**1a** in the distilled product mixture was 4% as shown by GC-analysis. The olfactory quality of this mixture was characterized as "similar to Rotundone" by Givaudan perfumers. Sniff-GC revealed that the peak of *rac*-**1a** was the one with an outstanding olfactory intensity.

Nazarov route ex (*R*)-(+)-Limonene. The isolation of regioisomer **8c** (scheme 3) led to the idea of synthesizing (–)-Rotundone **1a** via Nazarov cyclization of ketone **13a.** This ketone was planned to be synthesized by modification of ester **12** which in turn would be available through keto reduction and β-elimination of β-ketoester **8c** (scheme 5). As main advantage of this route it was foreseen that the stereocenter in the β-position to the carbonyl group would be relatively stable against epimerization thus allowing a more stereoselective approach to the final (–)-enantiomer **1a**.

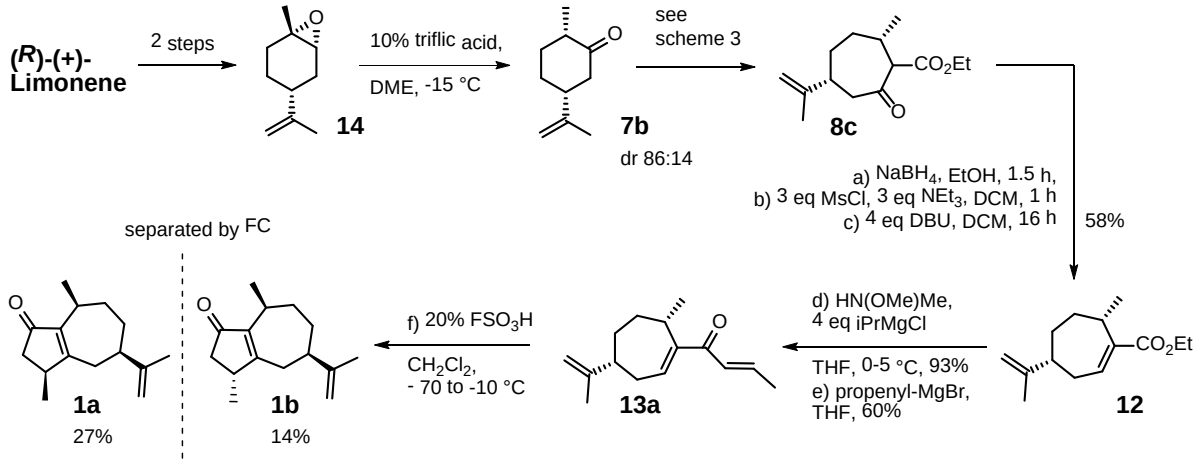


Scheme 5. Retrosynthesis of (–)-Rotundone **1a** via Nazarov cyclization of **13a**, and retrosynthesis of ester **12** from *cis*-dihydrocarvone **7b**.

The first challenge was an enantio- and diastereoselective access to precursor **8c**, which had been separated by distillation and with good purity from racemic nitrile **9** (scheme 3). Larger amounts of *cis*-dihydrocarvone **7b** were therefore prepared from commercially available (*R*)-(+)-Limonene oxide **14** according to Kusumi, using slightly modified conditions (e.g. at lower temperature to avoid *cis*/*trans*-epimerization of the α-methyl group in **7 b**)[29,30] (scheme 6).

With larger amounts of chiral **8c** in hand, reduction of the keto group, mesylation and elimination then gave unsaturated ester **12** as single *cis*-isomer. Weinreb chemistry and addition of 1-propenyl magnesium chloride gave Nazarov precursor **13a** with *cis*-configuration at the 7-ring and an *E*/Z ratio of 87:13 at the propenyl side-chain. Catalytic amounts of fluorosulfonic acid at low temperatures gave a mixture of (–)-Rotundone **1a** and (–)-*epi*-Rotundone **1b** with ca. 40% from cyclization precursor **13a** and 1.1% over all yield from (*R*)-(+)-Limonene through β-keto ester **8c**. Finally, the desired (–)-Rotundone **1a**

was separated chromatographically from its epimer **1b** with good purity and with 0.7% overall yield from (*R*)-(+)-Limonene.

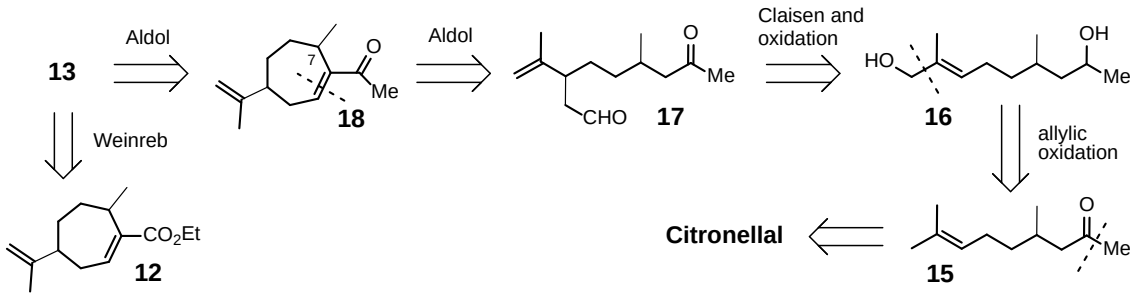


Scheme 6. Synthesis of (–)-Rotundone **1a** and (–)-*epi*-Rotundone **1b** via Nazarov cyclization of **13a** generated from *β*-ketoester **8c**.

Givaudan perfumers describe the **1a** / **1b** mixture (55/35) as woody, dry, camphoraceous, terpenic and tobacco and overall as Rotundone-like and similar to samples obtained by oxidation of α-Guaiene.[12] The separated (–)-*epi*-Rotundone **1b** was analyzed by sniff-GC and described as very weak, corky and woody. A threshold of (–)-*epi*-Rotundone **1b** was not determined because, although base-line separated, Rotundone elutes first under our GC-conditions and would therefore impair the olfactory evaluation of the second peak. A thorough investigation of (–)-*epi*-Rotundone **1b** was recently published,[7] emphasizing the unique organoleptic properties of this compound, although with a > 4000 times higher threshold compared to (–)-Rotundone **1a**. The optical rotation of (–)-Rotundone **1a** was identical with the one of the literature, thus confirming the absolute configuration established by Minato.[2]

Nazarov route ex *rac*-Citronellal. The relatively simple structure of unsaturated ester **12** inspired us to investigate another route via the corresponding methylketone **19** or similarly functionalized analogues (scheme 7). Starting from racemic Citronellal we envisioned to go through selective allylic oxidation, Claisen rearrangement and intramolecular aldol reaction to **19** and to prepare *rac*-**13** for the proof of

concept. Starting from *S*-(-)-Citronellal would have given the desired stereochemistry at least at C(7) of **13** and **19**.



Scheme 7. Retrosynthesis of ketone **19** through intramolecular aldol condensation and Claisen rearrangement starting from Citronellal.

For this purpose ketone 15, prepared from *rac*-Citronellal as described),[31] was selectively oxidized with selenium dioxide,[32,33] and the resulting aldehyde / ketone mixture reduced with $NaBH_4$ to diol **16** (scheme 8). Vinylation,[34] followed by Claisen rearrangement and Pd-catalyzed devinylation,[35] gave a diastereomeric mixture of hydroxy aldehyde, which was oxidized to keto aldehyde **17**. Application of different methods described in the literature for the intramolecular aldolization of 1,5-dicarbonyl compounds (acid and base catalysis, proline)[36,37] gave only poor results if at all (see NaOMe, HCl or proline in table 1). Cyclization of **17** in the presence of aqueous HCl gave rather the undesired compound **19**. Best yields of unsaturated ketone **18** were obtained using 1,1'-binaphthyl-2,2'-diyl hydrogenphosphates (figure 2) as organocatalysts (table 1),[38] which were unprecedented for the intramolecular aldolization to 7-membered ring systems. The intramolecular aldolization of **17** could have been optimized further, however, yields of **18** were sufficient for further transformation.

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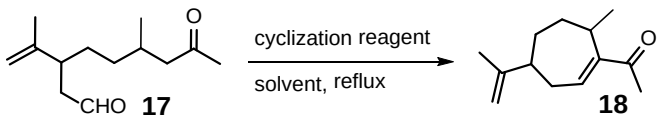
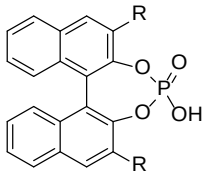
Table 1: Intramolecular aldolization of keto aldehyde **17** to unsaturated ketone **18**.[a]

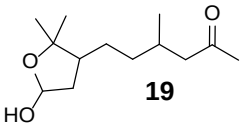


Entry	Cyclization reagent	Equivalents (molar)	Solvent	time (h)	Conversion [b]	Purity (crude) [c]	Yield [d]
1	NaOMe	6	MeOH	5	81	50	12
2	NaOMe	1	MeOH	20	quant	95	5
3	BNHP [e]	0.25	toluene	120	96	35	15
4	(*S*)-TRIP [f]	0.25	toluene	47	97	89	34
5	(*R*)-TRIP [f]	0.25	toluene	46	quant	100	46
6	F-TRIP [g]	0.25	toluene	16	quant	74	45

[a] General reaction conditions: Ketoaldehyde **17** (0.1 – 0.5 g), cyclization reagent, solvent, reflux. [b] Gas chromatography (GC), relative peak area (rpa). [c] GC (rpa) of the crude product. [d] Isolated yield of unsaturated ketone 18 after chromatographical purification. [e] BNHP = 4-hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxa-phosphepine 4-oxide (racemate). [f] TRIP = 3,3′-Bis(2,4,6-triiso-propylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate. [g] F-TRIP = 2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide.

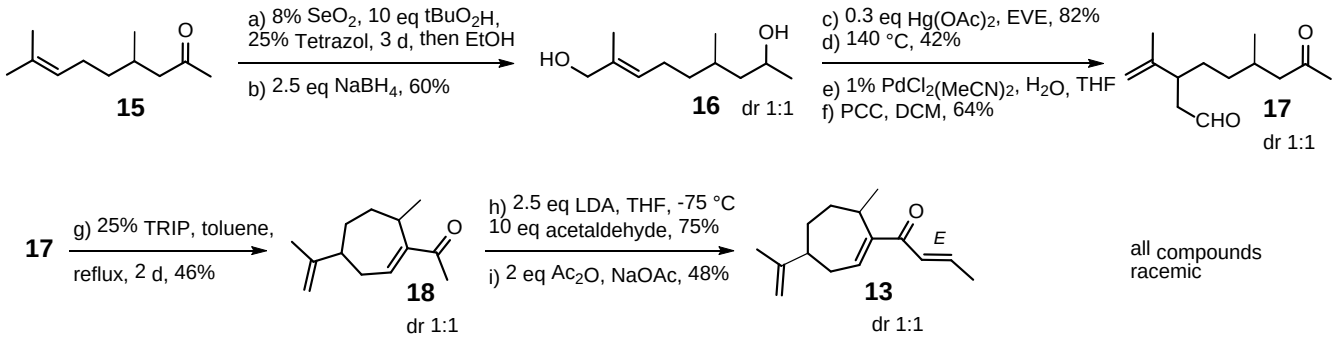


R = H (**BNHP**)
R = 2,4,6-triisopropylphenyl (**TRIP**)
R =3,5-bis(trifluoromethyl)phenyl (**F-TRIP**)



19

For the proof of concept, cyclic ketone **18** was transformed to Nazarov precursor *rac*-**13** (scheme 8) through aldol reaction with acetaldehyde. In contrast to the more valuable *cis*-isomer **13a**, obtained from the (*R*)-(+)-Limonene route (scheme 6), *rac*-**13** was obtained as diasteromeric mixture due to the insufficient stereoselectivity of the Claisen rearrangement. Further optimization of the sequence would use (*S*)-(–)-Citronellal as feedstock and would include diastereoselective construction of the stereocenters in compounds **16** – **18**.



Scheme 8. Synthesis of Nazarov cyclization precursor **13** through an intramolecular aldol reaction of ketoaldehyde **17**.

Conclusion. The total synthesis of (–)-Rotundone **1a** was accomplished from (*R*)-(+)-Limonene in 11 steps with an overall yield of ~ 1%. Challenges were α-methyl carbonyl intermediates, which are instable against enolization and epimerization. Such intermediates were encountered in an alternative sequence adapted from a route to Guaiazulene described by Shono. The use of more stable *β*-methyl carbonyl intermediates provided cyclization precursor **13a** without enolization / epimerization, and a final Nazarov cyclization provided (–)-Rotundone **1a** and (–)-*epi*-Rotundone **1b** which were separated chromatographically. An alternative route from *rac*-Citronellal provided the Nazarov cyclization precursor *rac*-**13** as a mixture of 7-ring diastereomers containing racemic diastereomer **13a**. Starting from (*S*)-(–)-Citronellal this sequence could have been further optimized to produce (–)-Rotundone **1a**. The synthesis from (*R*)-(+)-Limonene confirmed the absolute stereochemistry of (–)-Rotundone **1a** and provided Rotundone samples of good olfactory quality. The total synthesis of (–)-*epi*-Rotundone **1b** has been also achieved for the first time.

All in all new olfactory Rotundone qualities are accessible through these routes, e.g. (a) *rac*- or (–)-Rotundone 4% in a mixture of isomers starting from racemic or (*R*)-(–)-Carvone, (b) pure (-)-Rotundone **1a** starting from (*R*)-(+)-Limonene and (c) *rac* or (–)-Rotundone in a 1:1 diastereomer mixture starting *from rac*- or (*S*)-(–)-Citronellal. Regarding further optimization and upscaling all three se-

quences were considered on the basis of the olfactory qualities of the Rotundone products and the cost structures of each sequence.

Acknowledgements

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Author Contribution Statement

F.R.conceived, performed and partially designed the experiments and analyzed the data in the frame of his master's thesis.[39] F.S. designed the synthetic sequences and wrote the article.

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