

Selective Deoxygenation of Allylic Alcohol: Stereocontrolled Synthesis of Lavandulol

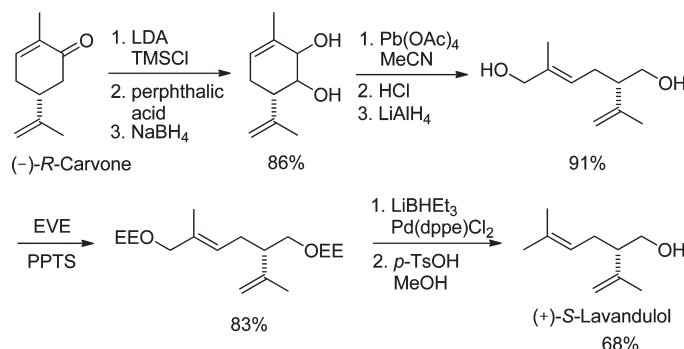
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ABSTRACT



Selective deoxygenation of allylic alcohol can be successfully carried out by the formation of alkoxyalkyl ether (EE or MOM), followed by Pd(dppe)Cl₂-catalyzed reduction with LiBHET₃. (+)-S-Lavandulol has been efficiently synthesized by the application of this protocol to the diol derived from the Pb(OAc)₄-promoted oxidative ring-opening of (-)-R-carvone. This deoxygenation method is general and selective for allylic alcohols.

Lavandulol, the key ingredient of lavender oil and the sex pheromone of the vine mealybug,¹ has an interesting structural feature that arises from the unusual tail-to-tail coupling of dimethylallyl pyrophosphate.² Racemic synthesis of this monoterpene species mainly relied on the regiocontrolled coupling of properly substituted allylic compounds with formaldehyde to produce the homoallylic alcohol, which was mediated by sulfone,³ Ti(IV) or Ce(III),⁴ and Sn(IV),⁵ even though some rearrangement reactions such as Claisen and Prins have found their rare

uses.⁶ Stereoselective synthesis of lavandulol further requires establishing the isopropenyl chiral center, which has drawn much attention from the synthetic organic community. Asymmetric allylation or protonation of senecioic acid derivatives using a chiral auxiliary has been the main repertoire in the enantiomerically pure lavandulol synthesis.⁷ Stereocontrolled synthesis of lavandulol with use of a cyclic template must be the most efficient method since the cheap monoterpene, chiral carvone is readily available. Grob-type fragmentation of the 1,3-diol derivative from (-)-R-carvone has been applied to the synthesis of (+)-S-lavandulol acetate. However, the above strategy suffered from nonselective Bayer–Villiger oxidation in producing the homoallylic alcohol, which instead gave rise to the epoxidation of the electron-rich alkenes.⁸ It was

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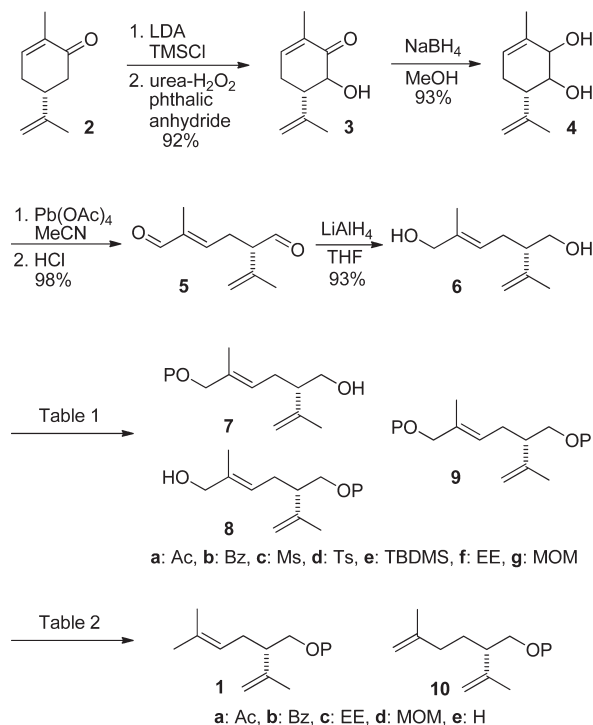
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envisioned, based on our ring-expansion and ring-contraction studies,⁹ that an oxidative ring-opening reaction of the 1,2-diol derived from chiral carvone would perfectly fit into the enantiomeric synthesis of lavandulol utilizing a cyclic template (Scheme 1). The main obstacle in this route seemed to be the selective deoxygenation of allylic alcohol in the presence of homoallylic alcohol. We report herein our efforts to the stereocontrolled synthesis of lavandulol from chiral carvone with the main emphasis on the selective deoxygenation of allylic alcohol.

Scheme 1. Stereocontrolled Synthesis of (+)-*S*-Lavandulol (**1e**) from (–)-*R*-Carvone (**2**)



The cheaper and more abundant (–)-*R*-carvone (**2**) was selected as a starting material for the synthesis of (+)-*S*-lavandulol (**1e**). Direct α' -acetoxylation of (–)-*R*-carvone by Pb(OAc)₄ did not proceed presumably due to the steric effect of the isopropenyl group.¹⁰ Monoperphthalic acid oxidation (urea-H₂O₂, phthalic anhydride) of the TMS enol ether from **2** produced the desired α' -hydroxyketone **3** in 92% yield as a separable 2:1 (β : α -hydroxy) mixture after hydrolytic workup (Scheme 1). Reduction of **3** as a stereoisomeric mixture by NaBH₄ produced 1,2-diol in 93% yield. The mixture of the four stereoisomers of **4** (see the Supporting Information for the ¹H NMR analysis of each isomer)¹¹ was subjected to the oxidative ring-opening reaction by Pb(OAc)₄ to give dial **5** in 98% yield. We demonstrated the importance of the acidic workup (HCl solution) to produce the dial with *E*-alkenyl configuration, which was isomerized from the initially formed dial with *Z*-alkene.^{9b} In fact, oxidative ring-opening of **4** by NaIO₄ without acidic workup exclusively produced the dial with *Z*-alkene (see the Supporting Information for details). Dial

5 was then reduced to diol **6** by LiAlH₄ in 93% yield. Now, the selective deoxygenation at the allylic alcohol from diol **6** would complete the enantiomeric synthesis of (+)-*S*-lavandulol (**1e**), which was far more challenging than what we initially imagined.

Table 1. Protection of the Hydroxyl Groups in Diol **6**

entry	protecting group	reagent (equiv)	product	yield (%)
1	Ac	AcCl (2.5), Et ₃ N (6)	9a	93
2	Bz	BzCl (2.5), Et ₃ N (6)	9b	88
3	Bz	BzCl (1), Et ₃ N (2.5)	7b/9b	40/30
4	Ms	MsCl (1), Et ₃ N (3)	8c	39
5	Ms	MsCl (10), Et ₃ N (6)	8c	64
6	Ts	TsCl (10), pyridine (6)	8d	38
7	TBDMS	TBDMSCl (1), Et ₃ N (2.5)	8e	26
8	TBDMS	TBDMSCl (3), Et ₃ N (6)	9e	81
9	EE ^a	EVE ^b (6), PPTS ^c (0.5)	9f	83
10	MOM	CH ₂ (OMe) ₂ (30), P ₂ O ₅ (3)	9g	69

^a 1-Ethoxyethyl. ^b Ethyl vinyl ether. ^c Pyridinium *p*-toluenesulfonate.

We sought two possibilities for the selective deoxygenation of the allylic alcohol in **6**: first, protection of both hydroxyl groups as acetates and Pd-catalyzed selective reduction of the allylic acetate; second, selective protection of the allylic alcohol as a sulfonate and reduction of the sulfonate. In searching for a selective protection method of the allylic alcohol in the presence of the homoallylic alcohol in diol **6**, various conditions have been tested (Table 1). Protection of both alcohols in **6** with excessive reagents proceeded uneventfully for acetates, benzoates, TBDMS ethers, 1-ethoxyethyl (EE) ethers, and methoxymethyl (MOM) ethers (entries 1–2 and 8–10). Selective protection as a sulfonate was possible only for the homoallylic alcohol, contrary to our hope, even with excessive

Table 2. Reaction Conditions and Results for the Selective Deoxygenation of the Protected Diols **9**

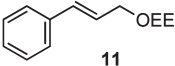
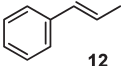
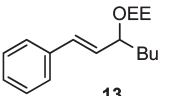
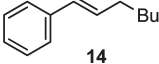
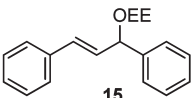
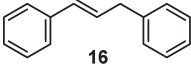
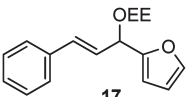
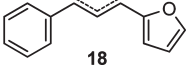
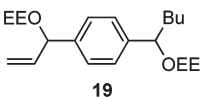
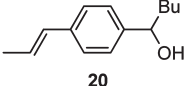
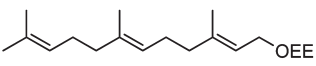
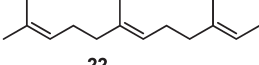
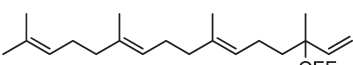
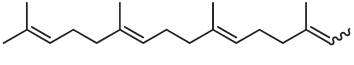
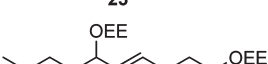
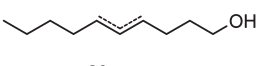
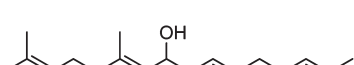
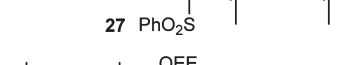
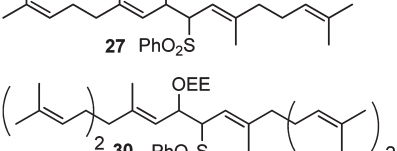
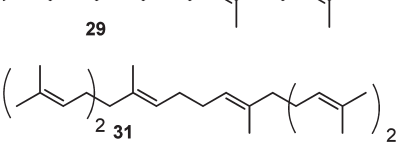
entry	compd	reagent (equiv)	condition	product (%)
1	9a	HCO ₂ H/Et ₃ N (4), Pd(dppe) ₂ Cl ₂ (0.5)	60 °C, 21 h in THF	1a (22)/ 10a (27)
2	9a	NaBH ₃ CN (4), Pd(dppe) ₂ Cl ₂ (0.5)	rt, 5.5 h in THF	1a (38)/ 10a (7)
3	9a	LiBHEt ₃ (3), Pd(dppe) ₂ Cl ₂ (0.3)	rt, 3 h in THF	8a (7)/ 6 (29)
4	9b	NaBH ₃ CN (4), Pd(dppe) ₂ Cl ₂ (0.5)	rt, 10 h in THF	1b (19)
5	9a	Li-naphthalide (10)	0 °C, 0.5 h in THF	6 (42)
6	9a	Na/Hg (20), Na ₂ HPO ₄ (4)	0 °C, 4.5 h in MeOH	6 (68)
7	9a	Li (10), EtNH ₂ (156)	–78 °C, 0.1 h in THF	1e (56)
8	9f	LiBHEt ₃ (3), Pd(dppe) ₂ Cl ₂ (0.2)	80 °C, 10 h in dioxane	1c (68)
9	9g	LiBHEt ₃ (3), Pd(dppe) ₂ Cl ₂ (0.2)	80 °C, 9 h in dioxane	1d (64)

reagents (entries 4–6). The possibility of the selective deoxygenation of the allylic alcohol via sulfonate thus seemed implausible. It is worth mentioning that benzoate protection shows certain preference to the allylic alcohol (entry 3), while TBDMS ether protection still favors the homoallylic alcohol (entry 7) when a stoichiometric reagent is used.

Conditions for the selective deoxygenation at the allylic site of the protected diols **9** were investigated, and the results are summarized in Table 2. Selective reduction of the palladium complex from allylic acetate with a soft hydride nucleophile such as ammonium formate ($\text{HCO}_2\text{H}/\text{Et}_3\text{N}$)

or NaBH_3CN was deteriorated by the formation of the inseparable regioisomeric homoallylic acetate **10a** together with the desired lavandulyl acetate **1a** (entries 1–2).¹² Utilizing a stronger hydride nucleophile (LiBHET_3) facilitated hydrolysis of the acetate groups (entry 3). The π -allyl reduction from dibenzoate **9b** with NaBH_3CN produced only the desired lavandulyl benzoate **1b**, but in a fairly low yield (entry 4). Radical reduction of diacetate **9a** with Li-naphthalide or $\text{Na}(\text{Hg})$ produced diol **6** by the hydrolysis of both acetates (entries 5–6). The condition with Li in EtNH_2 was successful in producing the desired (+)-*S*-lavandulol (56% yield) by selective deoxygenation of allylic

Table 3. Selective Deoxygenation of Allylic Alcohols by the Formation of 1-Ethoxyethyl Ethers^a and Palladium-Catalyzed LiBHET_3 Reaction^b

entry	protected alcohol	yield (%)	reduction product	yield (%)
1		92		81
2		93		96
3		82		82
4		46		90 ^c
5		72		67 ^d
6		99		90
7		99		100 ^e
8		67		61 ^{d,c}
9		95 ^f		69 ^{g,d}
10		95 ^f		60 ^h
11		84 ^f		77 ^h

^a The formation of 1-ethoxyethyl (EE) ether was carried out by the reaction of the corresponding alcohol (1 equiv) with ethyl vinyl ether (3 equiv/–OH) in CH_2Cl_2 in the presence of pyridinium *p*-toluenesulfonate (0.25 equiv/–OH) at 0 °C to room temperature. ^b The mixture of the EE-protected alcohol (1 equiv), $\text{Pd}(\text{dppe})\text{Cl}_2$ (0.05 equiv), and LiBHET_3 (3 equiv) in 1,4-dioxane was heated at 70–80 °C for 3–4 h. ^c A ~1:1 mixture of regioisomers was obtained. ^d The crude reduction product was treated with *p*-TsOH (0.01 equiv) in MeOH at room temperature for 2 h for deprotection of EE. ^e A ~3:1 mixture of stereoisomers was obtained. ^f The overall yield of the coupling between allylic sulfone and unsaturated aldehyde, and the protection of the resulting allylic alcohol. ^g The reduction was carried out at room temperature for 6 h. ^h The reduction was carried out at room temperature for 4 h, and then 70–80 °C for 6 h.

acetate and simultaneous hydrolysis of the homoallylic acetate, as was reported in a related system (entry 7).¹²

Allylic tetrahydropyranyl (THP) ethers are commonly used as a protecting group under basic conditions, but can be regarded as a leaving group in the cross-coupling reaction with organocopper reagents.¹³ The leaving group ability of acetal protecting groups was also demonstrated for 1-ethoxyethyl (EE) ethers in the Cu(I)-mediated coupling reaction with Grignard reagents.¹⁴ We were very happy to find that acetal protecting groups might also be regarded as a good leaving group in the Pd-catalyzed deoxygenation with Super hydride (LiBHET₃), and that it was selective only for allylic alcohols. Diacetals **9f** (EE) and **9g** (MOM) respectively produced the corresponding monoacetal **1c** (68% yield) and **1d** (64% yield) by the Pd-catalyzed deoxygenation with LiBHET₃ (entries 8–9). Acetals from the homoallylic alcohols survived the above deoxygenation condition. (+)-*S*-Lavandulol (**1e**) was obtained quantitatively after deprotection of monoacetal **1c** under catalytic *p*-TsOH in MeOH.

The generality and selectivity of this unprecedented deoxygenation method for allylic alcohol was demonstrated for various compounds (Table 3). The deoxygenation proceeds at the EE-protected allylic alcohol through the π -allyl palladium complex, in which hydride is delivered to the less-hindered site. The reduction is highly regioselective if there is steric bias in the substituents of the π -allyl complex. Either retention (entries 1–2, 6, and 9–11) or complete migration (5 and 7) of the carbon–carbon double bond has occurred. A ~1:1 mixture of regioisomers was obtained when the size of the substituents was comparable (entries 4 and 8). The deoxygenation is selective only for the EE ethers from allylic alcohols, and those from benzylic alcohol and simple alcohol survive

the reaction condition (entries 5 and 8) as was demonstrated in the lavandulol synthesis.

We were curious about any selectivity for desulfonation over deoxygenation in the Pd-catalyzed reduction with LiBHET₃, since the same reagents under milder condition (25 °C instead of 70–80 °C) have been applied to the desulfonation reaction in the sulfone-mediated chain-extension of terpenoids.¹⁵ Compound **27** was prepared by EE-protection of the coupling product between geranyl sulfone and (*E*)-3,7-dimethylocta-2,6-dienal, and was subjected to the desulfonation condition (room temperature for 6 h). Allylic alcohol **28** was exclusively obtained in 69% yield after deprotection of the acetal group, which implicated that sulfone is a better leaving group than EE-ether (entry 9). Both desulfonation and deoxygenation are also possible by sequential elimination at room temperature and then at 70–80 °C (entry 10). Squalene (**31**) can be prepared in 77% yield by this protocol from the EE ether **30** generated by the coupling between (2*E*,6*E*)-farnesyl sulfone and (2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienal (entry 11).

In summary, the stereocontrolled total synthesis of (+)-*S*-lavandulol has been completed in seven steps, 44% overall yield from a readily available (–)-*R*-carvone. This method highlights the oxidative ring-opening of the 1,2-diol derived from the cyclic template and the deoxygenation of the acetal-protected allylic alcohol, which is quite general and selective even in the presence of benzylic or other simple alcohols.

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Supporting Information Available. Experimental procedures, characterization data, and ¹H NMR and ¹³C NMR spectra for all the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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