

trans-2-Tritylcyclohexanol as a Chiral Auxiliary in Permanganate-Mediated Oxidative Cyclization of 2-Methylenehept-5-enoates: Application to the Synthesis of *trans*-(+)-Linalool Oxide

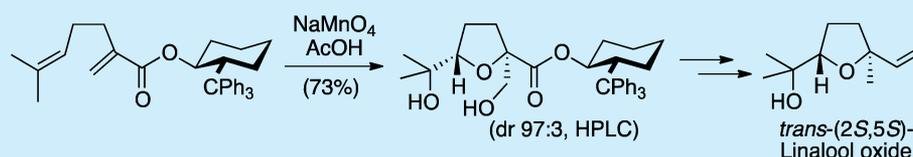
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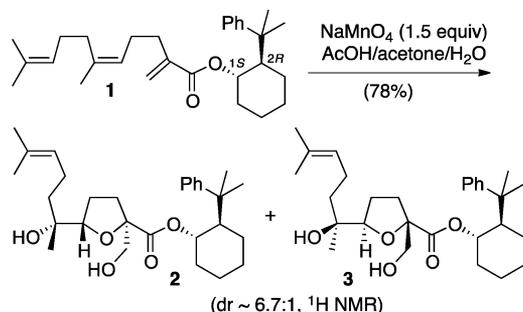
S Supporting Information



ABSTRACT: The permanganate-mediated oxidative cyclization of a series of 2-methylenehept-5-enoates bearing different chiral auxiliaries was investigated, leading to the discovery of *trans*-2-tritylcyclohexanol (TTC) as a highly effective chiral controller for the formation of the 2,5-substituted THF diol product with high diastereoselectivity (dr ~97:3). Chiral resolution of (±)-TTC, prepared in one step from cyclohexene oxide, afforded (–)-(1*S*,2*R*)-TTC (er >99:1), which was applied to the synthesis of (+)-*trans*-(2*S*,5*S*)-linalool oxide.

Chiral auxiliaries based on substituted cyclohexanols continue to find applications in asymmetric synthesis.¹ Since the introduction of 8-phenylmenthol by Corey,² researchers have sought cyclohexanol derivatives that offer improved levels of diastereocontrol and/or can be more readily accessed in enantiomerically pure form.³ We recently applied the (+)-(1*S*,2*R*)-*trans*-2-cumylcyclohexanol ((+)-TCC) auxiliary to the synthesis of the *trans*-THF-containing fragment of the terpenoid natural product eurylene using a selective oxidative monocyclization of a trienoate.⁴ In this context, the TCC auxiliary returned an acceptable level of diastereoselectivity, giving rise to an inseparable mixture of diastereoisomeric oxidative cyclization products **2** and **3** (Scheme 1). The diastereoisomers were separated following conversion to their bis-trimethylsilyl ethers. The regio- and diastereoselectivity

Scheme 1. Stereoselective Oxidative Monocyclization of (1*S*,2*R*)-TCC Trienoate **1⁴**



originates from an initial reaction of permanganate ion with the more electron-poor enoate alkene, followed by cyclization.^{5–7}

In the pursuit of enhanced diastereoselectivity for oxidative cyclizations of structurally related diene systems, some simple modifications to the cyclohexyl auxiliary were considered. Here we report the synthesis and chiral resolution of *trans*-2-(trityl)cyclohexanol (TTC)⁸ and compare its efficacy with several other cyclohexyl derivatives in the context of oxidative cyclization. We also describe a stereoselective synthesis of the *trans*-THF-containing alcohol (+)-*trans*-(2*S*,5*S*)-linalool oxide (furanoid form),⁹ a monoterpenoid present in essential oils, foods, and beverages and used in perfumery.¹⁰

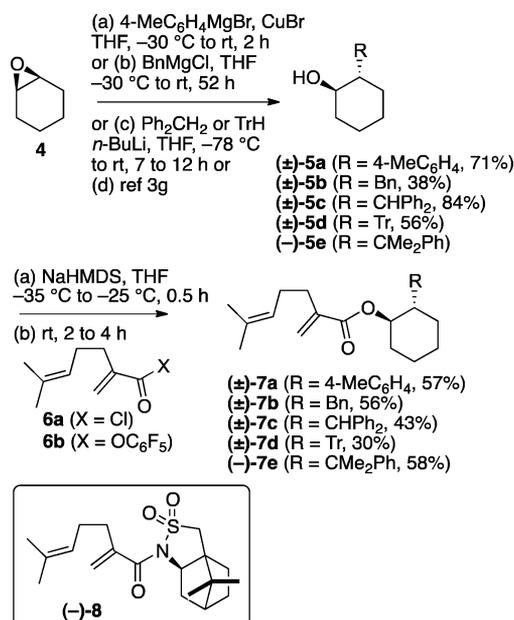
To examine the stereodirecting influence of the 2-cyclohexanol substituent on oxidative cyclization of 6-methyl-2-methylenehept-5-enoates **7a–d**, a number of racemic *trans*-2-substituted cyclohexanols were synthesized by addition of organomagnesium or organolithium reagents to cyclohexene oxide (Scheme 2).¹¹ Subsequent reaction with either 6-methyl-2-methylenehept-5-enoate (6a) or PFP ester **6b** led to the corresponding substituted cyclohexyl esters **7a–d**.¹² For comparative purposes, (1*R*,2*S*)-(–)-TCC and camphor sultam derivatives **7e** and (–)-**8**, respectively, were similarly synthesized.

The 2-substituted cyclohexyl compounds displayed typical NMR spectroscopic data, with the exception of *trans*-2-tritylcyclohexanol ((±)-**5d**) and its derivatives, which exhibited

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Scheme 2. Synthesis of 6-Methyl-2-methylenehept-5-enoic Acid Cyclohexyl Esters 7a–e



significant broadening of signals in the ¹H and ¹³C NMR spectra corresponding to the trityl group, highlighting the increased steric congestion of this system.¹³ Furthermore, the vinylic β proton signals of the enoate 7d displayed upfield shifts (δ 5.14 and 5.20) relative to cyclohexyl esters 7a–c (δ 5.30–5.48 and 5.86–6.12), while the chemical shifts for TTC ester (-)-7e lay in between (δ 5.30 and 5.69) (Table 1). Shielding of

Table 1. Oxidative Cyclization of Cyclohexyl Dienoates 7a–e

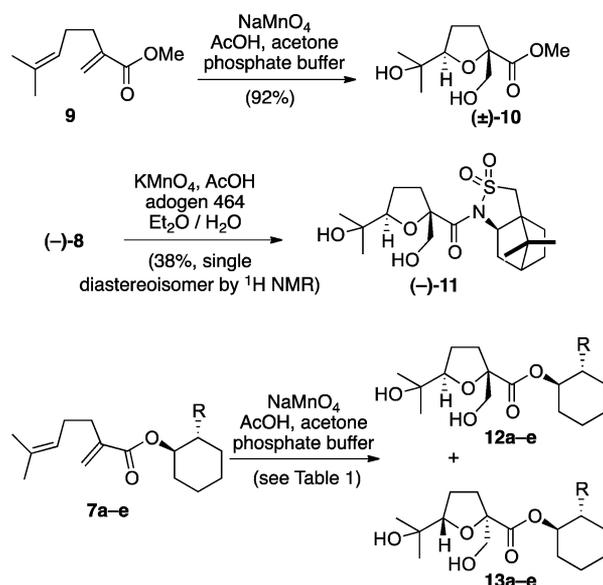
entry	diene	R	yield ^a (12 + 13) (%)	dr (12:13)
1	(±)-7a	4-MeC ₆ H ₄	57 ^b	1:1 ^c
2	(±)-7b	Bn	82 ^b	1.3:1 ^{d,e}
3	(±)-7c	CHPh ₂	99 ^b	1.8:1 ^{d,e}
4	(±)-7d, (±)-TTC	CPh ₃	62 ^b	32.3:1 ^{e,f}
5	(-)-7e, (-)-TTC ^g	CMe ₂ Ph	94	4.2:1 ^{e,h}

^aIsolated unoptimized yields of purified compounds are quoted. ^bRacemic products were obtained. ^cRatio of diastereoisomers estimated from the ¹H NMR spectrum. ^dMajor diastereoisomers 12b and 12c are tentatively assigned by analogy with 12d. ^eRatio of diastereoisomers determined using HPLC. ^fThe relative stereochemistry of the major diastereoisomer 12d was assigned by conversion of (-)-7d to *trans*-(2*S*,5*S*)-linalool oxide (19) described below. ^g97% ee. ^hThe assignment of the major diastereoisomer is described in the Supporting Information.

the β-enoate substituents in a series of 8-arylmenthol crotonates has been cited as support for a favored “stacked” *s-trans* ground-state conformation, which correlated qualitatively with enhanced stereoselectivity.^{3e}

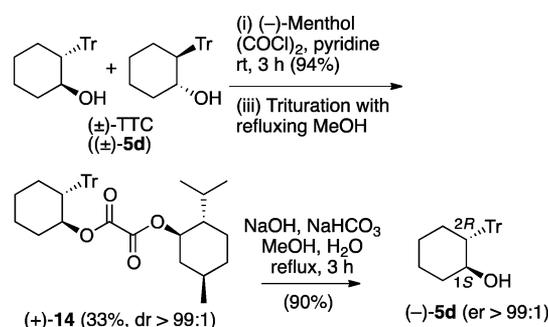
Oxidative cyclization studies commenced with exposure of the methyl ester 9 to permanganate/AcOH, resulting in highly efficient formation of the racemic THF diol 10 in 92% yield (Scheme 3). By contrast, the yield for the oxidative cyclization of the dienoyl (2*R*)-camphorsultam 8 was low (38%), although the product was obtained as a single diastereoisomer (-)-11.¹⁴ Oxidation of cyclohexyl esters 7a–e using KMnO₄ gave diastereoisomeric THF diols 12 and 13 with unoptimized

Scheme 3. Oxidative Cyclization of 6-Methyl-2-methylenehept-5-enoic Acid Derivatives 7a–e, (-)-8, and 9



yields in the range 57–99%, but with markedly different levels of diastereoselection; only the (-)-TTC and (±)-TTC auxiliaries conferred significant levels of stereocontrol upon the cyclization (dr 4.2:1 by ¹H NMR and 97:3 by HPLC, respectively), and only TTC showed very high levels of induction. Assignment of the major diastereoisomers (±)-12d and 12e was ultimately accomplished through the synthesis of *trans*-(2*S*,5*S*)-linalool oxide (19) described below.

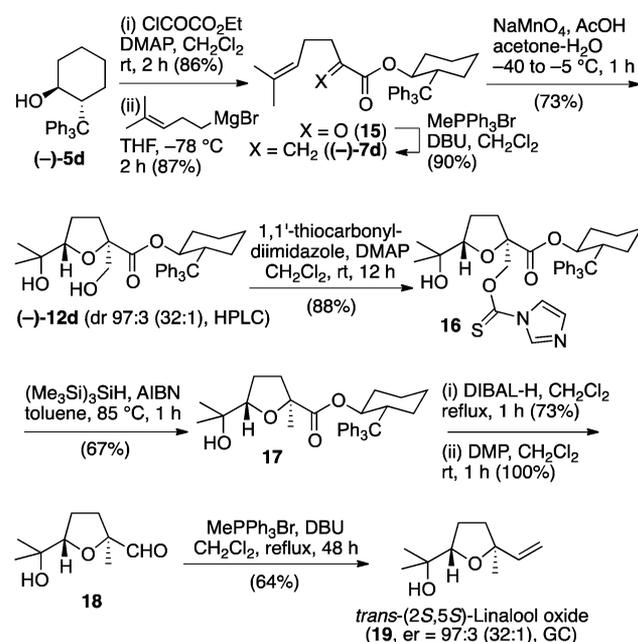
In view of the high level of diastereoselection achieved in the oxidative cyclization of (±)-7d bearing the racemic TTC auxiliary, we wished to develop a chiral resolution of TTC and illustrate its application in a synthesis of the terpenoid natural product (+)-*trans*-(2*S*,5*S*)-linalool oxide (19). Synthesis of (+)-linalool oxide (19) would also allow stereochemical determination of the major diastereoisomer 12d from the oxidative cyclization. Chiral resolution of (±)-TTC was realized on a 95 mmol scale through formation of mixed oxalate esters with (-)-menthol (Scheme 4);^{15,16} the mixture of diastereomeric derivatives was heated in MeOH followed by hot filtration of the sparingly soluble diester (+)-14 with 35% recovery (dr >99:1, HPLC). Hydrolysis of the mixed oxalate ester (+)-14 afforded (-)-5d (24 mmol), which was assigned as the (1*S*,2*R*)-enantiomer using the advanced Mosher ester method.¹⁷ In addition, the (*S*)-Mosher ester derivative proved

Scheme 4. Chiral Resolution of (-)-(1*S*,2*R*)-TTC through Diastereomeric Oxalate Ester formation

amenable to X-ray structural determination, thereby confirming the absolute stereochemistry of (–)-TTC to be (1*S*,2*R*).¹⁸ Overall, this resolution process provides a simple and convenient access to the TTC auxiliary in either enantiomeric form on a multigram scale without the need for chromatographic purification.¹⁹

An improved three-step synthesis of the diene (–)-7*d* was developed starting from reaction of (–)-TTC with ethyl chlorooxoacetate (Scheme 5), followed by selective Grignard

Scheme 5. Synthesis of *trans*-(2*S*,5*S*)-Linalool Oxide (19)



addition to the less hindered ester group and methylation of the resulting α -ketoester 15.²⁰ Oxidative cyclization of dienoate (–)-7*d* on a ~14 mmol scale afforded the THF-diol (–)-12*d* in 73% yield as a 97:3 mixture of diastereoisomers (HPLC), which underwent selective deoxygenation of the primary carbinol group by treatment of the mono thionocarbamate 16 with TTMSS/AIBN in hot toluene.²¹ Although direct reduction of TTC ester 17 to the aldehyde 18 was possible using DIBAL-H, the volatility of the resulting aldehyde complicated its isolation from the reaction mixture. Instead, a two-step reduction-Dess–Martin oxidation protocol was preferred. Pure (–)-TTC was recovered (84%) following the reductive cleavage and chromatographic separation, demonstrating the potential to recycle the auxiliary. The synthesis was completed by methylation of the aldehyde 18 to afford 120 mg of (+)-linalool oxide in 64% isolated yield. The synthetic (+)-linalool oxide (er 97:3, chiral GC) displayed physical and spectroscopic data consistent with reported values for the (+)-(2*S*,5*S*)-enantiomer of linalool oxide (furanoid form).²²

The stereochemical outcome of the reaction may be accounted for by preferential reaction of permanganate ion with the *si*-face of the enoate alkene (Figure 1), with the trityl derivative functioning as a comparatively superior chiral controller to the cumyl group. The observed shielding and significant upfield shift of the alkene protons are also consistent with the depicted ground-state solution conformation.

In conclusion, one-step synthesis and chiral resolution of a sterically encumbered cyclohexyl auxiliary, *trans*-2-tritylcyclo-

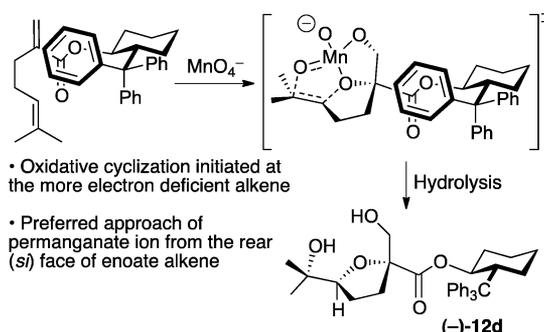


Figure 1. Model for the diastereofacial selectivity observed in the oxidative cyclization of 6-methyl-2-methylenehept-5-enoates.

hexanol (TTC), is reported. It was shown to confer higher levels of diastereofacial selectivity in comparison to other cyclohexyl derivatives studied for the oxidative cyclization of 2-methylenehept-5-enoates and was applied to a stereoselective synthesis of *trans*-(+)-linalool oxide furanoid form. Notably, the reported synthesis illustrates the potential application of permanganate-mediated oxidative cyclization (formally produces 2,5-*cis*-THF-diols) to the synthesis of *trans*-THF systems. Furthermore, TTC may find utility in other auxiliary-controlled diastereoselective processes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, chromatograms, X-ray structures, and copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (14) For details of stereochemical determination by X-ray crystallography, see the Supporting Information.
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