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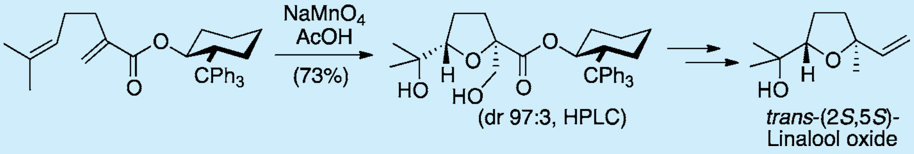
trans-2-Tritylcyclohexanol as a Chiral Auxiliary in Permanganate-Mediated Oxidative Cyclization of 2-Methylenehept-5-enoates: Application to the Synthesis of *trans*-(+)-Linalool Oxide

Ali M. Al Hazmi,[†] Nadeem S. Sheikh,[†,||] Carole J. R. Bataille,[†] Azzam A. M. Al-Hadedi,[†,⊥] Sam V. Watkin,[†] Tim J. Luker,[‡] Nicholas P. Camp,[§] and Richard C. D. Brown*[,†]

[†]Department of Chemistry, The University of Southampton, Highfield, Southampton SO17 1BJ, U.K.
[‡]AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, U.K.
[§]Eli Lilly Research Centre U.K., Erl Wood Manor, Windlesham GU20 6PH, U.K.

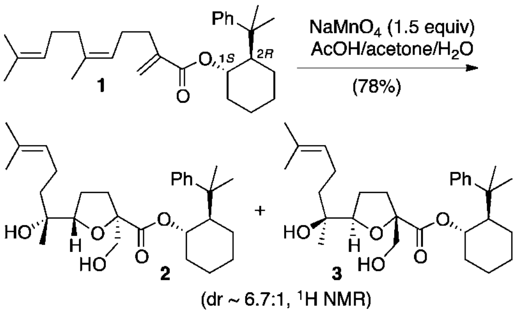
Supporting Information



ABSTRACT: The permanganate-mediated oxidative cyclization of a series of 2-methylenehept-5-eneoates 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 derivates 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 diastereoinduction, 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 originates from an initial reaction of permanganate ion with the more electron-poor enoate alkene, followed by cyclization.[5−7]

Scheme 1. Stereoselective Oxidative Monocyclization of (1*S*,2*R*)-TCC Trienoate 1[4]



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-eneoates **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-eneoyl chloride (**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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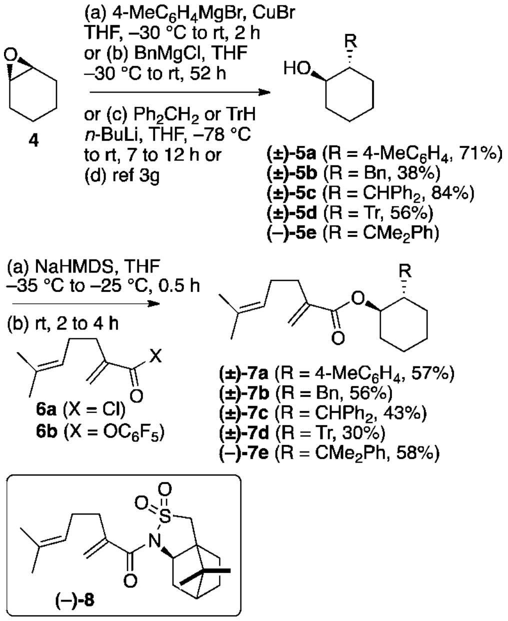
Scheme 2. Synthesis of 6-Methyl-2-methylenehept-5-eneoic Acid Cyclohexyl Esters 7a−e



significant broadening of signals in the ^{1}H and ^{13}C 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 TCC ester (−)-**7e** lay in between (δ 5.30 and 5.69) (Table 1). Shielding of 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]

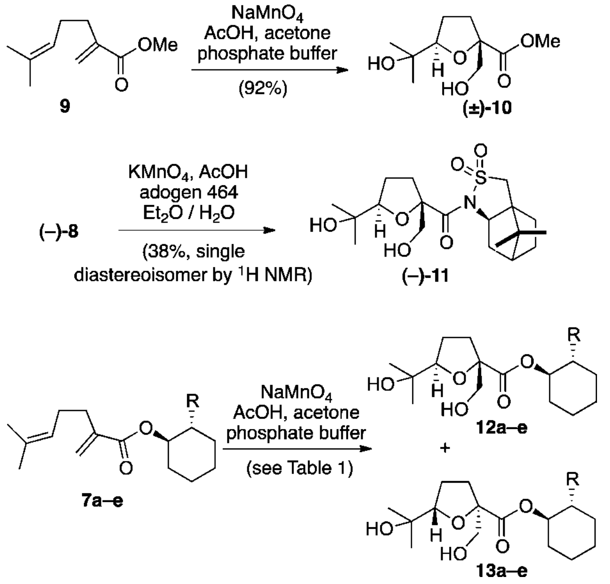
Table 1. Oxidative Cyclization of Cyclohexyl Dienoates 7a−e

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**, (−)-TCC[g]	CMe$_2$Ph	94	4.2:1[c,h]

[a] Isolated unoptimized yields of purified compounds are quoted. [b] Racemic products were obtained. [c] Ratio of diastereoisomers estimated from the ^{1}H NMR spectrum. [d] Major diastereoisomers **12b** and **12c** are tentatively assigned by analogy with **12d**. [e] Ratio of diastereoisomers determined using HPLC. [f] The relative stereochemistry of the major diastereoisomer **12d** was assigned by conversion of (−)-**7d** to *trans*-(2*S*,5*S*)-linalool oxide (**19**) described below. [g] 97% ee. [h] The assignment of the major diastereoisomer is described in the Supporting Information.

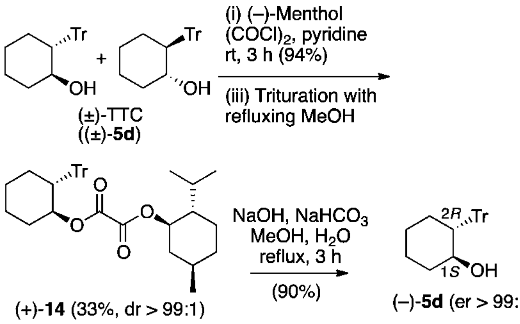
Oxidative cyclization studies commenced with exposure of the methyl ester **9** to permanganate/AcOH, resulting in highly efficient formation of the racemic THF diol **10** in 92% yield (Scheme 3). By contrast, the yield for the oxidative cyclization of the dienoyl (2*R*)-camphorsultam **8** was low (38%), although the product was obtained as a single diastereoisomer (−)-**11**.[14] Oxidation of cyclohexyl esters **7a**−**e** using KMnO$_4$ gave diastereoisomeric THF diols **12** and **13** with unoptimized yields in the range 57−99%, but with markedly different levels of diastereoinduction; only the (−)-TCC and (±)-TTC auxiliaries conferred significant levels of stereocontrol upon the cyclization (dr 4.2:1 by ^{1}H 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.

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



In view of the high level of diastereocontrol achieved in the oxidative cylization 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 (+)-(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

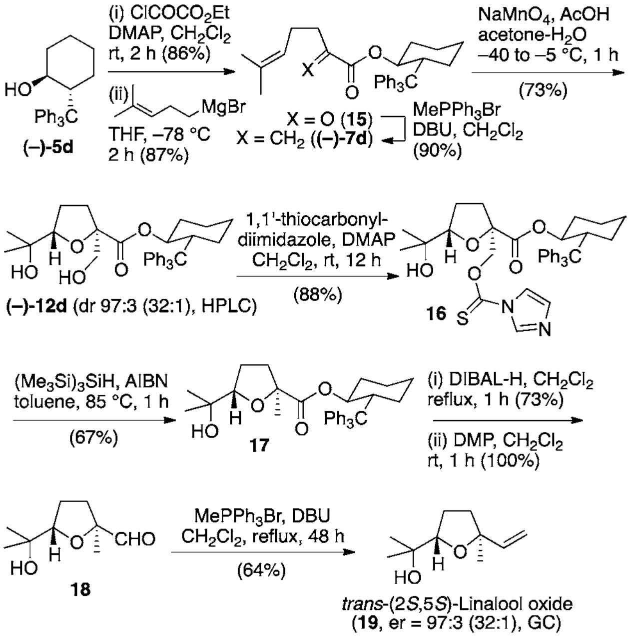
Scheme 4. Chiral Resolution of (−)-(1*S*,2*R*)-TTC through Diastereomeric Oxalate Ester formation



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 (−)-**7d** was developed starting from reaction of (−)-TTC with ethyl chlorooxoacetate (Scheme 5), followed by selective Grignard addition to the less hindered ester group and methylenation of the resulting α-ketoester **15**.[20] Oxidative cyclization of dienoate (−)-**7d** on a ~14 mmol scale afforded the THF-diol (−)-**12d** 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 methylenation 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]

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



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.

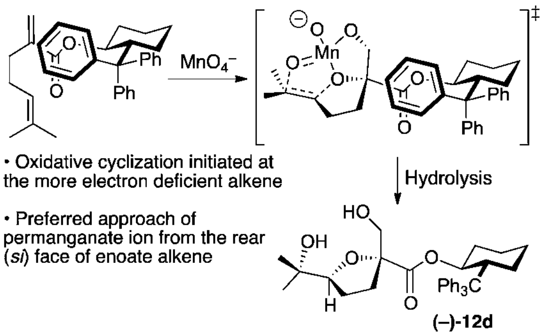


Figure 1. Model for the diastereofacial selectivity observed in the oxidative cyclization of 6-methyl-2-methylenehept-5-eneoates.

In conclusion, one-step synthesis and chiral resolution of a sterically encumbered cyclohexyl auxiliary, *trans*-2-tritylcyclohexanol (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-eneoates and was applied to a stereoselective synthesis of *trans*-(+)-linalool oxide furanoid form. Notably, the reported synthesis illustrates the potential application of permangate-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 ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rcb1@soton.ac.uk.

Present Addresses

[‖]Department of Chemistry, Faculty of Science, King Faisal University, P.O. Box 380, Al-Ahsa 31982, Saudi Arabia.
[⊥]On leave from the Department of Chemistry, College of Science, University of Mosul 41002, Iraq.

Notes

The authors declare no competing financial interest.

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(12) The syntheses of 6-methyl-2-methylenehept-5-eneoyl chloride (**6a**), PFP ester **6b**, dieneoyl camphorsultam **8**, and methyl ester **9** are described in the Supporting Information

(13) Copies of ^{1}H and ^{13}C NMR spectra can be found in the Supporting Information

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

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(22) $[\alpha]_D$ = +7.6 (*c* 0.6, $CHCl_3$, 22 °C) [lit.[9c] +8.33 (*c* 0.6, $CHCl_3$, 20 °C). For (2*R*,5*R*) lit.[9d] −7.45 (*c* 2.54, $CHCl_3$, 20 °C)].