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A three-step enantioselective synthesis of (+)- and (−)- α -thujone†

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The stereocontrolled three-step synthesis of either enantiomer of α -thujone from commercially available 3-methyl-1-butyne is described. The enantioselectivity originates from a Brown crotylation which is then conferred to the all-carbon quaternary center via chirality transfer in a gold-catalyzed cycloisomerization. The route is highly atom economical and requires no protecting groups or redox manipulations.

Thujone is a bicyclic monoterpene natural product that is found in a variety of plants including thuja, cedarleaf, sage, and wormwood. Biosynthetically, thujone is proposed to be generated by an enzyme-mediated reduction of sabinone.¹ It is most notably found in absinthe, a green spirit derived from the essential oil of wormwood. While it was originally believed that thujone was responsible for the psychotropic effects of absinthe, recent studies have disproven this.² The levels of thujone in foodstuffs and beverages is regulated in the European Union, United States, and Canada. Thujone functions as a γ -aminobutyric acid A (GABA_A) receptor antagonist which can cause convulsions at high concentrations.³ Animal studies have demonstrated that (−)- α -thujone **1** is more potent than (+)- β -thujone **2** and the metabolism of the natural product has also been studied.³ (−)- α -Thujone has also been shown to function as a 5-hydroxytryptamine (5-HT₃) receptor antagonist.⁴ 5-HT₃ antagonists are of interest because they can be used to treat nausea associated with chemotherapy, radiation, and withdrawal from drug addiction.⁵ While (−)- α -thujone **1** and (+)- β -thujone **2** are often described in the literature as α -thujone or β -thujone, it has recently been demonstrated that the enantiomers of these stereoisomers, **3** and **4**, are present in Nature as well (Fig. 1).⁶ Since the uncommon stereoisomers have been identified in dietary supplements,⁶ there is a need for a better understanding of the

biological activity of (+)- α -thujone **3** and (−)- β -thujone **4**. An asymmetric synthesis capable of accessing either enantiomer of α -thujone could facilitate further biological study.

Elucidated in 1900 by Semmler,⁷ thujone possesses a bicyclo[3.1.0]hexanone core with three contiguous stereocenters and a quaternary carbon at the cyclopropyl junction. (−)- α -Thujone and (+)- β -thujone are epimeric at the methyl stereocenter. To date, there have been two syntheses of (−)- α -thujone **1** and a racemic synthesis (Scheme 1). There are no syntheses of β -thujone to date. The first synthesis by Oppolzer in 1997 relied on a palladium-catalyzed cycloisomerization of a bis-sulfone enyne to achieve (−)- α -thujone **1** in twelve steps from commercially available starting materials.⁸ Tiefenbacher and coworkers recently reported a six-step diastereoselective synthesis of α -thujone.⁹ This strategy relied on a Simmons-Smith reaction to forge the cyclopropane followed by a regio- and diastereoselective methylation to complete the natural product. The synthesis was rendered asymmetric using an enzymatic kinetic resolution to provide (−)- α -thujone **1** in nine steps from cyclopentadiene. A highlight of this synthesis is the ability to incorporate deuterium as an isotopic label from *d*₆-acetone. The racemic synthesis,

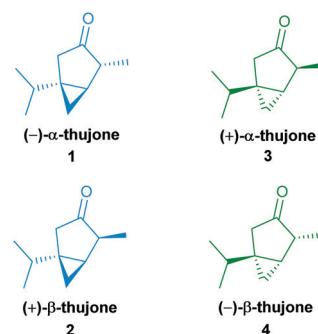
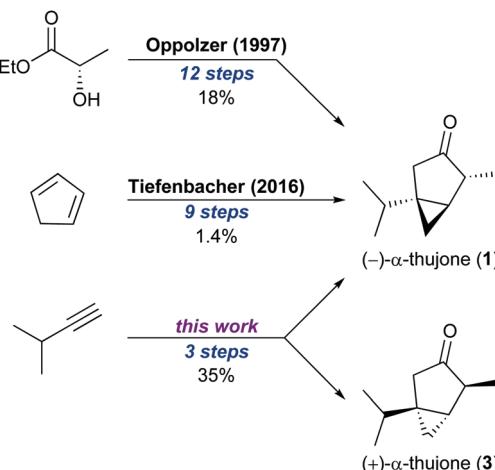
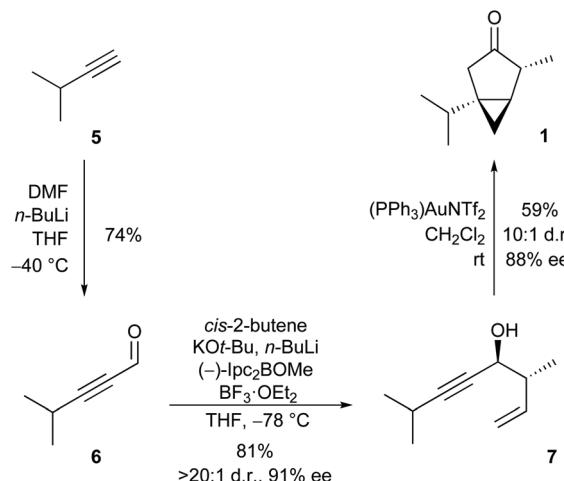


Fig. 1 Structures of the more prevalent stereoisomers, (−)- α -thujone (**1**) and (+)- β -thujone (**2**), in blue and the less prevalent stereoisomers, (+)- α -thujone (**3**) and (−)- β -thujone (**4**), in green.

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Scheme 1 Asymmetric total synthesis of α -thujone.Scheme 2 Three-step synthesis of $(-)\alpha$ -thujone.

reported by our group,⁶ provided a 2 : 1 diastereomeric mixture of the natural product in three steps by employing a platinum-catalyzed cycloisomerization of hydroxylated enynes¹⁰ as the key step.

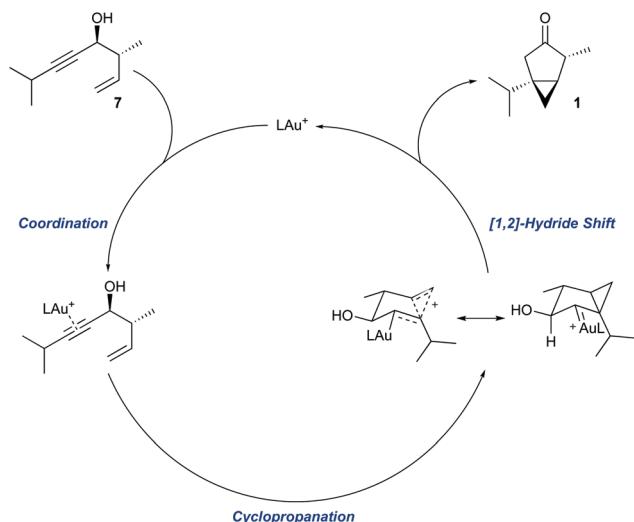
We envisioned that $(-)\alpha$ -thujone **1** could be synthesized asymmetrically *via* an enantioselective crotylation followed by a hydroxylated 1,5-ynal cycloisomerization strategy starting from commercially available 3-methyl-1-butyne **5**. This would accomplish the natural product with no redox manipulations or protecting groups. Our previous racemic synthesis of thujone provided a proof of concept for the cycloisomerization step but inducing asymmetry in the strategy presented several challenges. While asymmetric crotylations are well-established,¹¹ ynals are less common and can provide low enantioselectivities.¹² Additionally, the installation of the key all-carbon quaternary stereocenter would rely on a chirality transfer during the 1,5-ynal cycloisomerization. Transition metal-promoted cycloisomerization of 1,5-enynes has proven to be an effective method for the synthesis of bicyclo[3.1.0]hexan-3-one systems; however, stereoerosion can occur depending on the identity of the substrate.¹³ Additionally, the diastereoselectivity of the transformation can be low depending on the substitution pattern of the homoallylic alcohol.¹⁰

The synthesis commenced with the formylation of 3-methyl-1-butyne **5** with DMF to provide the volatile ynal **6** in 74% yield (Scheme 2). After screening a variety of milder crotylation protocols, a one-pot Brown crotylation of **6** afforded the homoallylic alcohol **7** in 81% yield with high diastereo- and enantioselectivity (>20 : 1 dr, 91% ee). While the yield and diastereoselectivity of other methods were sufficient, achieving high enantioselectivity with the ynal **6** proved challenging. With the requisite chiral alcohol achieved with high stereoselectivity, only the cycloisomerization key step remained to complete the natural product.

The cycloisomerization of hydroxylated enynes to bicyclo[3.1.0]hexanones represents a highly efficient method for building structural complexity. The original report by Fürstner

demonstrates that high levels of stereotransfer from the enantioenriched homoallylic alcohol to the bicyclo[3.1.0]hexanone can occur although the diastereoselectivity was low to moderate.¹⁰ Encouraged by this result, the enyne **7** was exposed to the cycloisomerization conditions of PtCl_2 at 60 °C in toluene which provided 54% yield of thujone with 2 : 1 diastereoselectivity favoring α -thujone. After a screen of conditions with PtCl_2 failed to provide the desired transformation with acceptable levels of diastereoselectivity, we shifted our focus to the more reactive gold catalysts as potential surrogates.

Gold catalysis has been extensively utilized for the related Rautenstrauch rearrangement and various enyne cycloisomerizations from enantioenriched substrates with varying levels of chirality transfer.¹³ While propargyl esters are more common as substrates, gold-catalyzed cycloisomerizations with homoallylic alcohols are known. Gagosz and coworkers reported that commercially available $(\text{Ph}_3\text{P})\text{AuNTf}_2$ can function as a highly active, air-stable catalyst for several rapid and high-yielding enyne cycloisomerizations at ambient temperature.¹⁴ An initial concern with this approach was that the gold(i)-catalyzed isomerization of 3-hydroxylated 1,5-enynes has been shown to be highly substrate-dependent, where cyclohexadienes, α,β -unsaturated aldehydes, and alkylidene cyclopentenes can be generated from the same hydroxylated enyne in varying degrees of selectivity.¹⁵ Gratifyingly, exposing the enyne **7** to catalytic $(\text{Ph}_3\text{P})\text{AuNTf}_2$ for one hour in dichloromethane at room temperature provided $(-)\alpha$ -thujone **1** as a volatile liquid in 59% yield with 10 : 1 dr and 88% ee. $(+)\alpha$ -Thujone **3** was also synthesized using this strategy by employing $(+)-\beta$ -methoxydiisopinocampheylborane to set the stereochemistry in the Brown crotylation step (see the ESI†). $(+)\alpha$ -Thujone **3** was obtained under the same conditions in 63% yield and a 10 : 1 dr and 88% ee. The enantioselectivity was determined by chiral GC-MS and the specific rotation sign matched the reported value for $(-)\alpha$ -thujone **1** and $(+)\alpha$ -thujone **3**. Based on the mechanistic insights provided by



Scheme 3 Plausible mechanism for the gold(I)-catalyzed cycloisomerization.

several groups on metal-catalyzed cycloisomerizations,^{13b,16} a plausible mechanism for the cycloisomerization is provided in Scheme 3. This expeditious route to the natural product will likely provide ample material for biological testing of (+)- α -thujone 3 and the synthesis of thujone metabolites that have previously been reported.^{9,17}

In summary, both enantiomers of α -thujone have been synthesized in a stereoselective fashion from commercially available 3-methyl-1-butyne 5. The atom economical synthesis provided 35% overall yield of the natural product and notably requires no protecting groups or redox manipulations. A benefit of this route is that both enantiomers of β -methoxydiisopinocamphenylborane are commercially available allowing access to the enantioenriched alcohols for the synthesis of (–)- and (+)- α -thujone. The use of $(\text{Ph}_3\text{P})\text{AuNTf}_2$ proved essential for effective chirality transfer in the cycloisomerization step to achieve the natural product in high diastereo- and enantioselectivity. This strategy will likely be amendable to the asymmetric synthesis of other bicyclo[3.1.0]hexanone natural products.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) R. Croteau, *Chem. Rev.*, 1987, **87**, 929; (b) A. J. Foster, D. E. Hall, L. Mortimer, S. Abercromby, R. Gries, G. Gries, J. Bohlmann, J. Russell and J. Mattsson, *Plant Physiol.*, 2013, **161**, 1993.
- (a) D. W. Lachenmeier, J. Emmert, T. Kuballa and G. Sartor, *Forensic Sci. Int.*, 2006, **158**, 1; (b) O. Pelkonen, K. Abass and J. Wiesner, *Regul. Toxicol. Pharmacol.*, 2013, **65**, 100.
- K. M. Höld, N. S. Sirisoma, T. Ikeda, T. Narahashi and J. E. Casida, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 3826.
- T. Deiml, R. Haseneder, W. Ziegglänsberger, G. Rammes, B. Eisensamer, R. Rupprecht and G. Hapfelmeier, *Neuropharmacology*, 2004, **46**, 192.
- (a) G. J. Sanger and P. L. Andrews, *Auton. Neurosci.*, 2006, **129**, 3; (b) A. B. Johnson, *CNS Drugs*, 2004, **18**, 1105.
- J. D. Williams, J. A. Yazarians, C. C. Almeyda, K. A. Anderson and G. R. Boyce, *J. Agric. Food Chem.*, 2016, **64**, 4319.
- F. W. Semmler, *Ber. Dtsch. Chem. Ges.*, 1900, **33**, 275.
- W. Oppolzer, A. Pimm, B. Stammen and W. E. Hume, *Helv. Chim. Acta*, 1997, **80**, 623.
- I. Thamm, J. Richers, M. Rychlik and K. Tiefenbacher, *Chem. Commun.*, 2016, **52**, 11701.
- V. Mamane, T. Gress, H. Krause and A. Fürstner, *J. Am. Chem. Soc.*, 2004, **126**, 8654.
- H.-X. Huo, J. R. Duvall, M.-Y. Huang and R. Hong, *Org. Chem. Front.*, 2014, **1**, 303.
- (a) S. BouzBouz, F. Pradaux, J. Cossy, C. Ferroud and A. Falguières, *Tetrahedron Lett.*, 2000, **41**, 8877; (b) U. Bhakta, E. Sullivan and D. G. Hall, *Tetrahedron*, 2014, **70**, 678; (c) G. A. Brito, F. Della-Felice, G. Luo, A. S. Burns, R. A. Pilli, S. D. Rychnovsky and M. J. Krische, *Org. Lett.*, 2018, **20**, 4144.
- (a) C. Fehr, B. Winter and I. Magpantay, *Chem. – Eur. J.*, 2009, **15**, 9773; (b) N. T. Patel, *Chem. – Asian J.*, 2012, **7**, 2186.
- N. Mézailles, L. Ricard and F. Gagósz, *Org. Lett.*, 2005, **7**, 4133.
- F. Gagósz, *Org. Lett.*, 2005, **7**, 4129.
- J. Marco-Contelles and E. Soriano, *Chem. – Eur. J.*, 2007, **13**, 1350.
- N. S. Sirisoma, K. M. Höld and J. E. Casida, *J. Agric. Food Chem.*, 2001, **49**, 1915.