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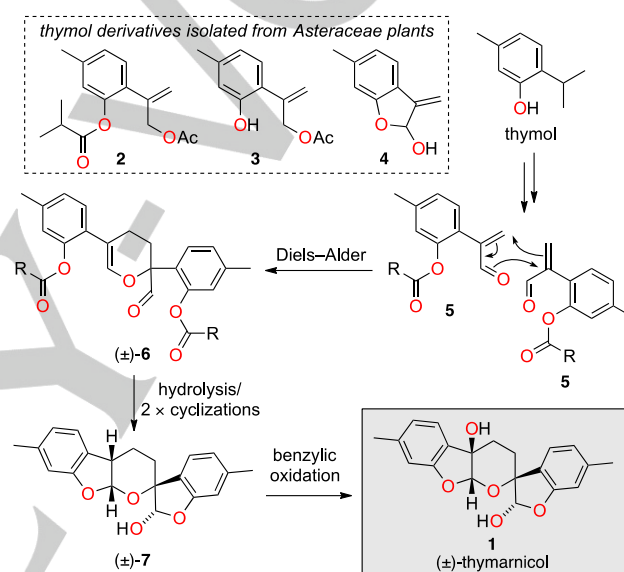
# Total Synthesis of a Dimeric Thymol Derivative Isolated from *Arnica sachalinensis*

Irene De Silvestro,<sup>[a]</sup> Samuel L. Drew,<sup>[b]</sup> Gary S. Nichol<sup>[a]†</sup>, Fernanda Duarte<sup>[a]\*</sup> and Andrew L. Lawrence<sup>[a]\*</sup>

**Abstract:** The total synthesis of a dimeric thymol derivative isolated from *Arnica sachalinensis* has been accomplished in 6 steps. Biomimetic investigations into a biosynthetic hetero-Diels–Alder dimerization, proposed by Passreiter and co-workers, demonstrates the chemical feasibility of this pathway. The Diels–Alder dimerization was found to occur at ambient temperature and the final oxidative cyclization occurs when the substrate is exposed to air and visible light. These results indicate that this natural product is likely the result of spontaneous, *i.e.*, non-enzyme mediated, reactivity.

In 1999, Passreiter and co-workers isolated a racemic thymol derivative (**1**) from the flower-heads of *Arnica sachalinensis* (Asteraceae), a sunflower native to Sakhalin Island off the Pacific Coast of Russia (Scheme 1).<sup>[1]</sup> For ease of discussion within this manuscript, and for future communications, we suggest “thymarnicol” (a portmanteau of thymol and *Arnica*) as a suitable name for this compound (**1**). Preliminary biological testing has revealed thymarnicol (**1**) to have potentially useful antifeedant,<sup>[1a]</sup> phytotoxic,<sup>[2]</sup> and anti-inflammatory<sup>[3]</sup> activity. For its small molecular size thymarnicol (**1**) possesses significant molecular complexity and, despite its dimeric origins, contains no element of symmetry. The dense array of oxygen functionality, and four associated stereogenic centres, at the core of the novel spiro[benzofuran-pyranobenzofuran] framework poses a considerable synthetic challenge. The previous isolation of oxidized and acetylated thymol derivatives from other Asteraceae plants (*e.g.*, **2**, **3** and **4**)<sup>[4]</sup> led Passreiter and co-workers to propose a biosynthetic pathway for thymarnicol (**1**) (Scheme 1).<sup>[1a]</sup> It begins with hetero-Diels–Alder dimerization of an enal-thymol derivative **5** to give dihydropyran **6**.<sup>[5]</sup> Hydrolysis of the phenol ester groups then allows for two cyclizations to form pentacycle **7**, with a final oxidation at the

benzylic-methine position giving thymarnicol (**1**). We decided to embark upon efforts to achieve a concise total synthesis of this complex and compact natural product and to investigate the chemical feasibility of Passreiter’s proposal.



**Scheme 1.** Structure of thymarnicol (**1**) and Passreiter’s proposed biosynthetic pathway. Ac = acetyl.

The synthesis began with Wittig methylenation of commercially available acetophenone **8** to give alkene **9**,<sup>[6]</sup> followed by acetylation using acetic anhydride in pyridine (Scheme 2). Both steps proceeded in excellent yield and could be conducted on multi-gram scales. Oxidation of alkene **10** to enal **11**, using stoichiometric SeO<sub>2</sub>, was done in several smaller batches as the yield was found to decline with scale (see Scheme 2).<sup>[7]</sup> The chemical feasibility of Passreiter’s proposed hetero-Diels–Alder dimerization was quickly established, with enal **11** found to undergo dimerization when stored neat at ambient temperatures (~50% conversion after 5 days). Heating neat samples of enal **11** at 80 °C for 42 h resulted in near quantitative dimerization. The crude dimer was immediately subjected to basic conditions to deprotect the two phenols. This did not give pentacycle **7** (see Scheme 1) but instead gave lactol **12**, the product of just one cyclization (Scheme 2). Interestingly, lactol **12** exists as a mixture of two diastereomers and the ratio between them, determined by analysis of the <sup>1</sup>H NMR spectrum, varies with respect to the solvent (d.r. in CDCl<sub>3</sub> 72:28; CD<sub>3</sub>COCD<sub>3</sub> 78:22), presumably as a result of facile lactol epimerization. It was observed that lactol **12** was unstable; new peaks corresponding to thymarnicol (**1**) could be identified in the

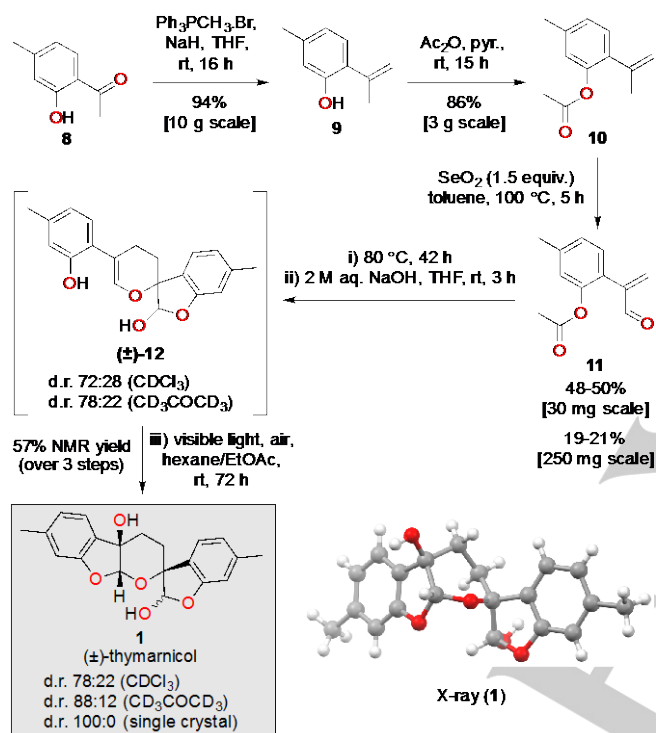
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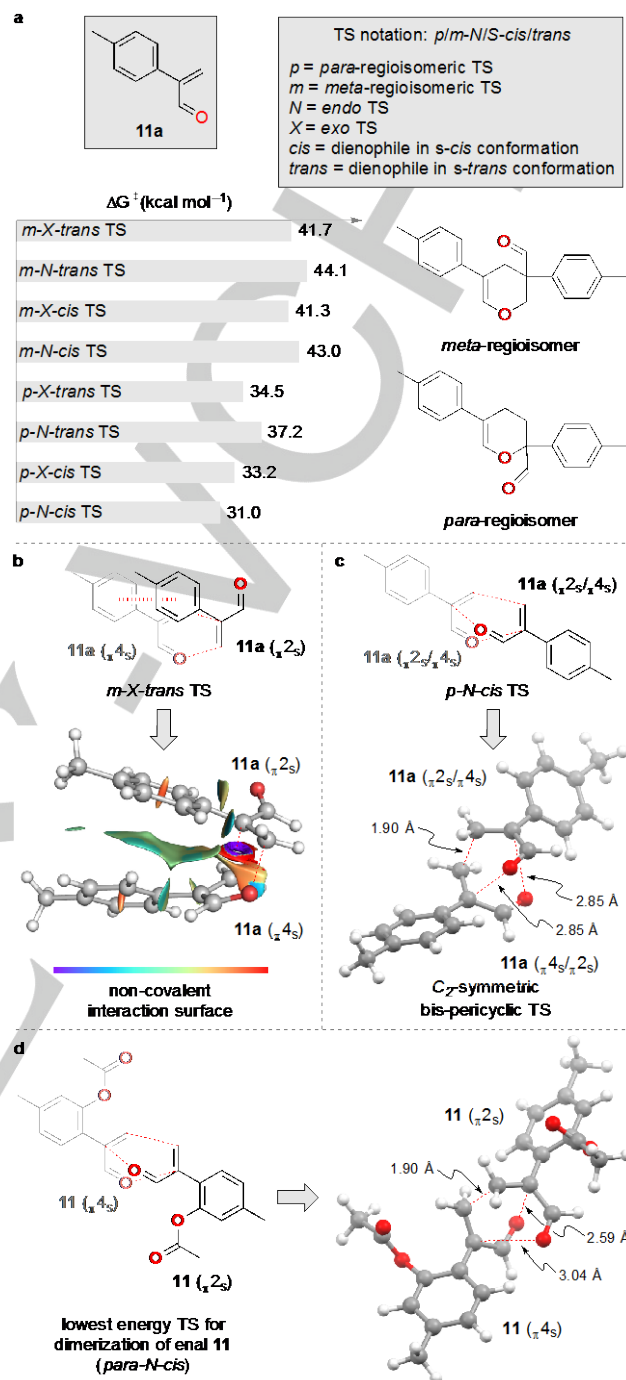
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$^1\text{H}$  NMR spectra of older samples. After careful experimentation we discovered that this fortuitous aerial oxidation was promoted by exposure to visible light.<sup>[8]</sup> Thus, a hexane/EtOAc-solution of crude lactol **12**, open to the atmosphere, was irradiated with visible light from an 11 W compact fluorescent lamp for 72 h. Analysis of the  $^1\text{H}$  NMR spectrum of the resulting product, with inclusion of an internal standard, indicated a remarkable 57% crude yield of the two lactol-epimers of thymarnicol (**1**) over three steps from enal **11**. Work is ongoing in our laboratory to identify other minor products from this aerial oxidation and to interrogate likely mechanisms.<sup>[9]</sup>



**Scheme 2.** Six step synthesis of thymarnicol (**1**). Ac = acetyl.

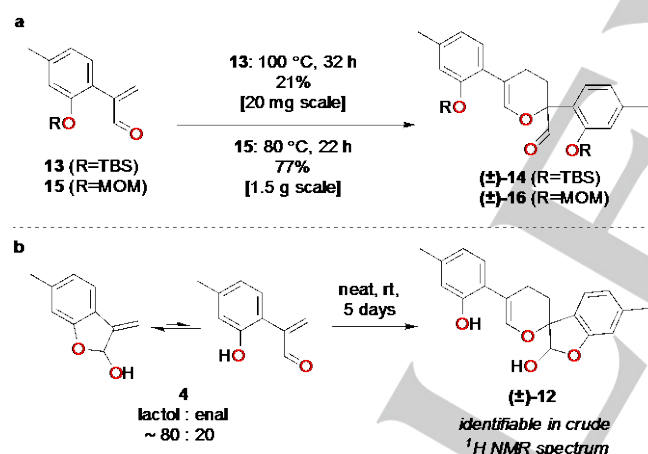
The final three-step sequence, from enal **11** to thymarnicol (**1**), could be conducted on >100 mg scale and without chromatographic purification of intermediates. Column chromatography followed by preparative-HPLC could then be used to access analytically pure samples of thymarnicol (**1**) (40 mg prepared so far), but still as an unavoidable mixture of the two lactol-epimers. Crystallization from acetonitrile resulted in crystals suitable for single crystal X-ray diffraction studies.<sup>[10]</sup> The crystal structure obtained matched that reported for the natural material,<sup>[1b]</sup> consisting of just one lactol-epimer (Scheme 2). Nevertheless, subsequent analysis of these crystals by solution-phase  $^1\text{H}$  NMR spectroscopy showed the presence of both lactol-epimers. It must be concluded that thymarnicol (**1**) is stereodynamic; it exists as a mixture of lactol-epimers in solution but can exist as a single epimer in the solid state. Thus, a six step total synthesis of thymarnicol (**1**) has been achieved, involving the formation of nine new bonds (three C–C, six C–O), three new rings and four new stereogenic centres.



**Scheme 3.** a) Reaction free energies ( $\Delta G^\ddagger_{80^\circ\text{C}}$ ) at the  $\omega\text{B97X-D/6-311++G(d,p)}/\omega\text{B97X-D/6-31+G(d)}$  level of theory for the eight possible transition structures for hetero-Diels–Alder dimerization of model compound **11a**. b) The  $\omega\text{B97X-D/6-31+G(d)}$  optimized structure of the *m-X-trans* TS for model compound **11a**, with a non-covalent interaction surface (green indicates van der Waals/dispersion interactions, blue indicates strong polar interactions and red indicates steric repulsion). c) The  $\omega\text{B97X-D/6-31+G(d)}$  optimized structure of the *p-N-cis* TS for model compound **11a** and for d) enal **11**.

DFT (Density Functional Theory) calculations, at the  $\omega\text{B97X-D/6-31+G(d)}$  level of theory,<sup>[11]</sup> were undertaken to investigate the factors that control the reactivity and regioselectivity of the

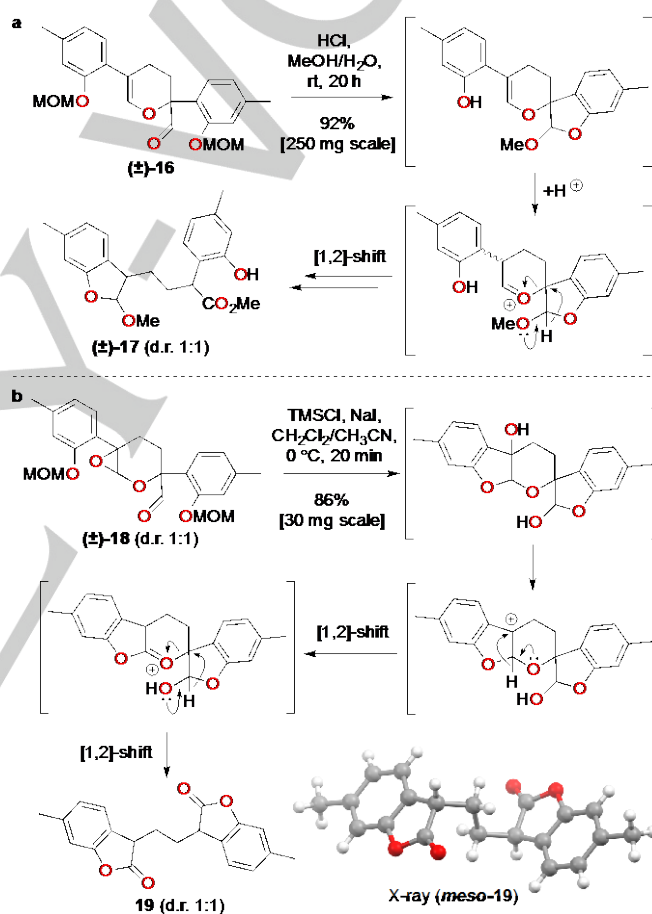
hetero-Diels–Alder dimerization (Scheme 3).<sup>[12]</sup> For a simplified model compound **11a**, bearing no *ortho*-substituent, there are eight distinct transition structures (TSs) possible (Scheme 3a). These TSs are described using a notation where the regiochemical-orientation is *meta* (*m*) or *para* (*p*), the Alder–Stein mode is *endo* (*N*) or *exo* (*X*), and the dienophile adopts either an *s-cis* (*cis*) or *s-trans* (*trans*) conformation. Without exception, the *para*-TSs were found to be significantly lower in energy than the *meta*-TSs due to better orbital overlap and lower distortion penalties (Scheme 3a; see SI for full interaction/distortion analysis).<sup>[13,14]</sup> The unexpected exoselectivity, observed for the majority of the TSs, is due to favourable non-covalent (dispersion) interactions between the two aromatic rings (as shown in Scheme 3b for the *meta-X-trans* TS), which outweighs the higher distortion penalty that normally disfavours *exo*-TSs.<sup>[15]</sup> The lowest energy TS, however, is not *exo*-orientated; the *para-N-cis* TS is a rare example of a  $C_2$ -symmetric bis-pericyclic TS (Scheme 3c).<sup>[16]</sup> In bis-pericyclic TSs the [4+2] and [2+4] cycloaddition pathways have fully merged and thus benefit from three primary orbital interactions. Following the bis-pericyclic TS the pathway then bifurcates to give the degenerate [4+2] and [2+4] cycloadducts. The lowest energy TS for hetero-Diels–Alder dimerization of enal **11** was also found to be a *para-N-cis* TS, which although not  $C_2$ -symmetric still has bis-pericyclic character (Scheme 3d; see SI for full computational details for enal **11**).



**Scheme 4.** a) Hetero-Diels–Alder dimerization of differently protected monomers **13** and **15**. b) Hetero-Diels–Alder dimerization of unprotected monomer **4**. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

Further insights into the origin and reactivity of thymarnicol (**1**) were acquired through other unsuccessful synthetic studies. For example, different phenol protecting groups were investigated (Scheme 4). The TBS (*tert*-butyldimethylsilyl) protected enal **13** underwent a less efficient Diels–Alder dimerization, requiring higher temperatures and resulting in lower yields of dihydropyran **14** (Scheme 4a). Use of the sterically less demanding MOM (methoxymethyl) ether, however, resulted in dimerization occurring at ambient temperature, with a synthetically useful 77% yield of dihydropyran **16** achieved by heating enal **15** at 80 °C for 22 h (Scheme 4a). Unfortunately,

dihydropyran **16** could not be successfully advanced to give thymarnicol (**1**) (*vide infra*). The most interesting precursor to investigate, from a biomimetic perspective, was the unprotected monomer **4**, a known natural product that exists primarily as its lactol isomer (Scheme 4b).<sup>[4b,17]</sup> When compound **4** was stored neat at ambient temperatures multiple new minor peaks appeared in the  $^1\text{H NMR}$  spectrum and the Diels–Alder dimer **12** could be identified amongst these new species. Therefore, an alternative biosynthetic pathway involving dimerization of the natural product **4** is chemically feasible. Synthetically speaking, however, this route was not pursued due to difficulties associated with the preparation and purification of lactol **4** and an apparent lack of selectivity for dimerization.



**Scheme 5.** a) Rearrangement observed during deprotection of MOM-protected dimer **16**. b) Rearrangement observed during deprotection of MOM-protected epoxide **18**. MOM = methoxymethyl, TMS = trimethylsilyl.

The greatest synthetic challenge encountered during our synthetic efforts was the propensity of the thymarnicol-nucleus to undergo acid-promoted rearrangements. For example, attempts to deprotect dimer **16** under standard HCl/MeOH conditions resulted in cleavage of the dihydropyran ring to give dihydrobenzofuran **17** as a mixture of two diastereomers (Scheme 5a).<sup>[18]</sup> Similarly, attempts to cleave the MOM ethers in epoxide **18** led to formation of bis-lactones **19** in high yield



(Scheme 5b).<sup>[10,19]</sup> The predisposed nature of these rearrangements, which presumably occur *via* [1,2]-shift mechanisms (see Scheme 5), leads us to speculate that structures akin to **17** and **19** might be isolated as natural products in the future.<sup>[20]</sup>

In conclusion, through our synthetic efforts we have been able to investigate the chemical feasibility of Passreiter's suggested biosynthetic pathway for thymarnicol (**1**). We have shown that the proposed hetero-Diels–Alder dimerization is plausible, with both acetyl- and MOM- protected systems (**11** and **15**) undergoing spontaneous dimerization at room temperature. We have also provided evidence in support of an alternative biosynthetic pathway involving dimerization of lactol **4**, a known natural product previously isolated from related Asteraceae plants.<sup>[4b]</sup> It was discovered that dihydropyran **12** undergoes the final oxidative cyclization when simply exposed to air and visible light. Therefore, our results indicate that the complexity-generating Diels–Alder dimerization and oxidative cyclization likely proceed without the intervention of enzymes to produce natural thymarnicol (**1**).<sup>[21]</sup>

## Acknowledgements

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**Keywords:** biomimetic synthesis • terpenoids • dimerization • cycloaddition • natural products

- [1] a) C. M. Passreiter, G. Willuhn, H. Weber, K.-J. Schleifer, *Tetrahedron* **1999**, *55*, 2997–3006; b) C. M. Passreiter, H. Weber, D. Bläser, R. Boese, *Tetrahedron* **2002**, *58*, 279–282.
- [2] Thymarnicol (**1**) has also been isolated from *Hofmeisteria schaffneri*, see: A. Peréz-Vasquez, A. Reyes, E. Linares, R. Bye, R. Mata, *J. Nat. Prod.* **2005**, *68*, 959–962.
- [3] Thymarnicol (**1**) has also been isolated from *Eupoatorium cannabinum*, see: J.-J. Chen, Y.-C. Tsai, T.-L. Hwang, T.-C. Wang, *J. Nat. Prod.* **2011**, *74*, 1021–1027.
- [4] a) C. M. Passreiter, U. Matthiesen, G. Willuhn, *Phytochemistry* **1998**, *49*, 777–781; b) F. Bohlman, J. Schulz, U. Bühmann, *Tetrahedron Lett.* **1969**, *53*, 4703–4704; c) F. J. Goomers, *Nematologica* **1972**, *18*, 458–462; d) F. Bohlmann, A. A. Natsu, K. Kerr, *Phytochemistry* **1979**, *18*, 489–490.
- [5] To the best of our knowledge, there have only been two previous reports regarding hetero-Diels–Alder dimerization of 2-aryl- $\alpha,\beta$ -unsaturated aldehydes, and both exhibited the regioselectivity outlined in Passreiter's biosynthetic proposal, see: a) T. Laitalainen, P. Kuronen, A. Hesso, *Org. Prep. Proc. Int.* **1993**, *25*, 597–599; b) H. M. L. Davies, X. Dai, *J. Org. Chem.* **2005**, *70*, 6680–6684.
- [6] J. Ferguson, F. Zeng, H. Alper, *Org. Lett.* **2012**, *14*, 5602–5605.
- [7] The alternative two-step process, involving initial oxidation of alkene **10** to the corresponding allylic alcohol, was thwarted by uncontrollable acetyl migration.
- [8] No oxidation was observed when samples of lactol **12** were exposed to the atmosphere in the dark.
- [9] Inclusion of a photosensitizer (rose bengal) did not lead to any appreciable rate enhancement.
- [10] CCDC 1530569 (**1**) and 1530570 (*meso-9*) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [11] J. D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
- [12] For computational studies on related systems, see: a) Z. Wang, J. S. Hirschi, D. A. Singleton, *Angew. Chem. Int. Ed.* **2009**, *48*, 9156–9159; *Angew. Chem.* **2009**, *121*, 9320–9323; b) L. Toma, P. Quadrelli, P. Caramella, *Tetrahedron Lett.* **2001**, *42*, 731–733; c) V. Bachler, F. Mark *Tetrahedron* **1977**, *33*, 2857–2861; d) P. V. Alston, D. D. Shillady, *J. Org. Chem.* **1974**, *39*, 3402–3406.
- [13] For a description of interaction/distortion analysis, see: a) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10187–10198; b) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647.
- [14] For recent applications of interaction/distortion analysis, see: a) A. Duan, P. Yu, F. Liu, H. Qiu, F. L. Gu, M. P. Doyle, K. N. Houk, *J. Am. Chem. Soc.* **2017**, *139*, 2766–2770; b) B. J. Levandowski, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 16731–16736; c) R. T. Larson, R. P. Pemberton, J. M. Franke, D. J. Tantillo, R. J. Thomson, *J. Am. Chem. Soc.* **2015**, *137*, 11197–11204.
- [15] I. Fernandez, F. M. Bickelhaupt, *J. Comput. Chem.* **2014**, *35*, 371–376.
- [16] For bis-pericyclic Diels–Alder reactions, see: a) T. Wang, T. R. Hoye, *Nat. Chem.* **2015**, *8*, 641–645; b) T. V. Magdesieva, *Russ. Chem. Rev.* **2013**, *82*, 228–247; c) H. Toombs-Ruane, E. L. Pearson, M. N. Paddon-Row, M. S. Sherburn, *Chem. Commun.* **2012**, *48*, 6639–6641; d) M. N. Paddon-Row, M. S. Sherburn, *Chem. Commun.* **2012**, *6*, 832–834; e) D. H. Ess, A. E. Hayden, F.-G. Klamer, K. N. Houk, *J. Org. Chem.* **2008**, *19*, 7586–7592; f) J. B. Thomas, J. R. Waas, M. Harmata, D. A. Singleton, *J. Am. Chem. Soc.* **2008**, *130*, 14544–14555; g) J. Gagnepain, F. Castet, S. Quideau, *Angew. Chem. Int. Ed.* **2007**, *46*, 1533–1535; *Angew. Chem.* **2007**, *119*, 1555–1557; h) N. Celebi-Olcuem, D. H. Ess, V. Aviyente, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 4528–4529; i) P. Quadrelli, S. Romano, L. Toma, P. Caramella, *Tetrahedron Lett.* **2002**, *43*, 8785–8789; j) P. Caramella, P. Quadrelli, L. Toma, *J. Am. Chem. Soc.* **2002**, *124*, 1130–1131.
- [17] For previous syntheses of natural product **4**, see: a) K. J. Divakar, B. D. Kulkarni, A. S. Rao, *Indian J. Chem., Sect B* **1977**, *9*, 849–50; b) A. V. Kalinin, M. A. J. Miah, S. Chattopadhyay, M. Tsukazaki, M. Wicki, T. Nguen, A. L. Coelho, M. Kerr, V. Snieckus, *Synlett* **1997**, 839–841; c) Y. Wang, A. Zhang, *Tetrahedron* **2009**, *34*, 6986–6990.
- [18] T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, **2007**, pp 30–38.
- [19] J. H. Rigby, J. Z. Wilson, *Tetrahedron Lett.* **1984**, *25*, 1429–1432.
- [20] For recent examples of natural product anticipation from biomimetic studies, see: a) D. P. O Malley, K. Li, M. Maue, A. L. Zografos, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775; b) P. Sharma, B. Lygo, W. Lewis, J. E. Moses, *J. Am. Chem. Soc.* **2009**, *131*, 5966–5972; c) M. Gavagnin, E. Mollo, G. Cimino, *Rev. Bras. Farmacogn.* **2015**, *25*, 588–591; d) A. L. Lawrence, R. M. Adlington, J. E. Baldwin, V. Lee, J. A. Kershaw, A. L. Thompson, *Org. Lett.* **2010**, *12*, 1676–1679; e) V. Sofiyev, J.-P. Lumb, M. Volgraf, D. Trauner, *Chem. Eur. J.* **2012**, *18*, 4999–5005; f) H. Shang, J. Liu, R. Bao, Y. Cao, K. Zhao, C. Xiao, B. Zhou, L. Hu, Y. Tang, *Angew. Chem. Int. Ed.* **2014**, *53*, 14494–14498; *Angew. Chem.* **2014**, *126*, 14722–14726; g) S. Strych, G. Journot, R. P. Pemberton, S. C. Wang, D. J. Tantillo, D. Trauner, *Angew. Chem. Int. Ed.* **2015**, *54*, 5079–5083; *Angew. Chem.* **2015**, *127*, 5168–5172; h) P. Ellerbrock, N. Armanino, M. K. Ilg, R. Webster, D. Trauner, *Nat. Chem.* **2015**, *7*, 879–882; i) P. D. Brown, A. L. Lawrence, *Angew. Chem. Int. Ed.* **2016**, *55*, 8421–8425; *Angew. Chem.* **2016**, *128*, 8561–8565.

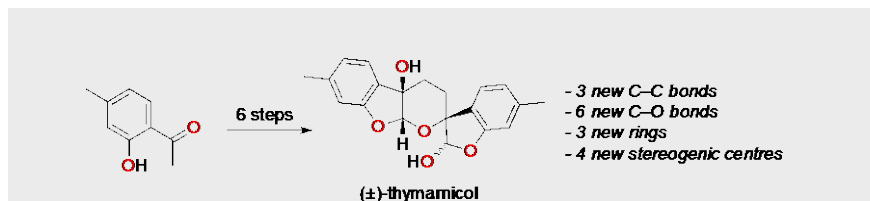
[21] The question of whether thymarnicol (**1**) is an artefact of the extraction/isolation/purification process or is the result of predisposed chemical reactivity, which is useful for the plant, is debatable. Indeed, the division between these two scenarios is difficult to delineate. For relevant discussions, see: a) J. D. Sutherland, J. N. Whitfield,

*Tetrahedron* **1997**, *53*, 11493–11527; b) S. K. Jackson, K.-L. Wu, T. R. Pettus in *Biomimetic Organic Synthesis, Vol. 2* (Eds.: E. Poupon, B. Nay), Wiley-VCH Verlag & Co. KGaA, Weinheim, **2011**, pp. 723–749. c) P. Champy in *Biomimetic Organic Synthesis, Vol. 2* (Eds.: E. Poupon, B. Nay), Wiley-VCH Verlag & Co. KGaA, Weinheim, **2011**, pp. 449–934.

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## COMMUNICATION



Irene De Silvestro, Samuel L. Drew,  
Gary S. Nichol, Fernanda Duarte\* and  
Andrew L. Lawrence\*

Page No. – Page No.

**Total Synthesis of a Dimeric Thymol  
Derivative Isolated from *Arnica  
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**Predisposed reactivity:** The total synthesis of a dimeric thymol derivative isolated from *Arnica sachalinensis* has been accomplished in 6 steps. Biomimetic investigations into a biosynthetic hetero-Diels–Alder dimerization, proposed by Passreiter and co-workers, demonstrates the chemical feasibility of this pathway. The Diels–Alder dimerization was found to occur at ambient temperature and the final oxidative cyclization occurs when the substrate is exposed to air and visible light. These results indicate that this natural product is likely the result of spontaneous, *i.e.*, non-enzyme mediated, reactivity.