A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Isolation and Synthesis of Novel Meroterpenoids from Rhodomyrtus tomentosa: Investigation of a Reactive Enetrione Intermediate

Authors: John Porco, Xu-Jie Qin, Tyler Rauwolf, Pan-Pan Li, Hui Li, James McNeely, Yuan Hua, and Hai-Yang Liu

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201814421
Angew. Chem. 10.1002/ange.201814421

Link to VoR: http://dx.doi.org/10.1002/anie.201814421
http://dx.doi.org/10.1002/ange.201814421

WILEY-VCH

10.1002/anie.201814421

WILEY-VCH

COMMUNICATION

Isolation and Synthesis of Novel Meroterpenoids from *Rhodomyrtus tomentosa*: Investigation of a Reactive Enetrione Intermediate

Xu-Jie Qin,[+] Tyler J. Rauwolf,[+] Pan-Pan Li,[+] Hui Liu, James McNeely, Yan Hua, Hai-Yang Liu,* and John A. Porco, Jr.*

Abstract: Rhodomyrtusials A–C (**5**–**7**), the first examples of triketone-sesquiterpene meroterpenoids featuring a unique 6/5/5/9/4 fused pentacyclic ring system were isolated from *Rhodomyrtus tomentosa*, along with several biogenetically-related dihydropyran isomers (**8**–**11**). Compounds **5**, **6**, and **10** showed acetylcholinesterase (AChE) inhibitory activity. Structures of the isolates were unambiguously established by a combination of spectroscopic data, ECD analysis, and total synthesis. Bioinspired total syntheses of **5**, **7**, and **8**–**11** were achieved in six steps utilizing a reactive enetrione intermediate generated *in situ* from a readily available hydroxy-endoperoxide precursor.

Natural products are an important source for the discovery of new drugs.[1] Species of the Myrtaceae family are rich in structurally intriguing meroterpenoids which possess various bioactivities.[2] Interestingly, many of the natural products derived from these species are derived from a common precursor, syncarpic acid (Figure 1a). Isolates such as callistrilones A–E, have recently attracted interest due to their promising antibacterial activity.[3] Other examples of natural products possessing the *β*-triketone moiety derived from syncarpic acid include rhodomyrtosone A (**2**),[4] tomentodione M (**3**),[5] and myrtucommulone K (**4**).[6] Compound **3** has been shown to reverse multidrug-resistance in MCF-7 and K562 cells,[5] while **4** and analogues possess anti-cancer properties against HEP-G2 and MDA-MB-231 cell lines.[6] The structural diversity found in these natural products, coupled with their diverse biological activities, warrants continued development of new chemistry to access such scaffolds.

A preliminary bioactivity assay of the leaves and stems of *Rhodomyrtus tomentosa* revealed that the petroleum ether (PE) extract showed a significant acetylcholinesterase (AChE) inhibition rate (81%, 500 *μ*g/mL)[7]. Subsequent screening of the title species using a bioassay-guided method led to the isolation of three unprecedented meroterpenoids with a 6/5/5/9/4 pentacyclic ring system, rhodomyrtusials A–C (**5**–**7**), two new biogenetically related isomers, rhotomentodiones A (**8**) and B (**9**), and two known analogues, tomentodiones Q (**10**) and R (**11**) (Figure 1b),[8] all of which possess the syncarpic acid-derived moiety found in **1**–**4**. Herein, we report the structural elucidation, AChE inhibitory activities, and biomimetic total syntheses of these metabolites using a reactive enetrione generated *in situ* from a hydroxy-endoperoxide precursor.

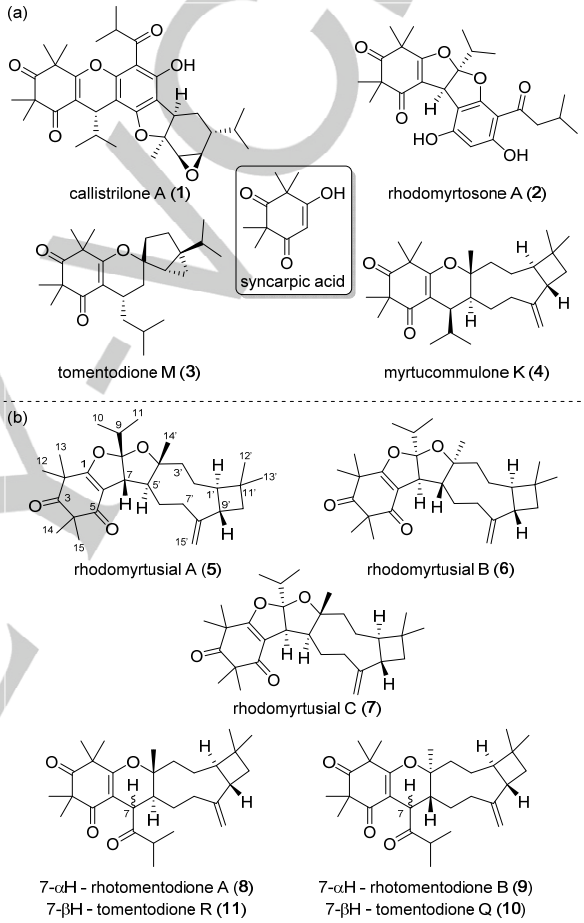


Figure 1. (a) Natural products derived from syncarpic acid; (b) structures of rhodomyrtusials A–C (**5**–**7**), rhotomentodiones A (**8**) and B (**9**), and tomentodiones Q (**10**) and R (**11**).

[a] Dr. X. J. Qin, Mr. Hui Liu, Prof. Dr. H. Y. Liu
State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany,Chinese Academy of Sciences, Kunming 650201 (PR China)
E-mail: haiyangliu@mail.kib.ac.cn
[b] T. J. Rauwolf, Dr. J. McNeely, Prof. Dr. J. A. Porco, Jr
Department of Chemistry, Center for Molecular Discovery (BU-CMD), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215 (United States)
E-mail: porco@bu.edu
[c] P. P. Li, Prof. Dr. Y. Hua
College of Forestry, Southwest Forestry University, Kunming 650224 (PR China)
[+] These authors contributed equally to this work.
Supporting information for this article is given via a link at the end of the document.

Rhodomyrtusial A (**5**) possessed a molecular formula of $C_{30}H_{44}O_4$ with nine indices of hydrogen deficiency (IHDs) based on HRESIMS data. Analysis of the ^{1}H and ^{13}C NMR spectra (Table S1)[7] revealed the presence of seven tertiary and two secondary methyl groups, five methylenes, five methines, five quaternary carbons, two double bonds, and two carbonyl carbons. These functionalities accounted for four out of nine IHDs; the remaining IHDs thus required **5** to have a pentacyclic framework. Structural assignment of **5** was accomplished by analysis of 2D NMR data (Figure S1). HMBC correlations from Me-12/Me-13 to C-1/C-2/C-3 and from Me-14/Me-15 to C-3/C-4/C-5 revealed the presence of a *β*-triketone moiety. The location of an isopentyl group and the construction of one furan ring *via* a 1,8-oxide bridge were determined by HMBC correlations from Me-10/Me-11 to C-8 and H-7 to C-1/C-6/C-9. ^{1}H–^{1}H COSY cross-peaks of H-1′/H-9′/H$_2$-10′ along with HMBC correlations from Me-12′/Me-13′ to C-1′/C-10′/C-11′ delineated a characteristic cyclobutane ring. HMBC correlations from Me-14′ to C-3′/C-4′/C-5′ and H$_2$-15′ to C-7′/C-9′, as well as ^{1}H–^{1}H COSY correlations of H-1′/H$_2$-2′/H$_2$-3′ and H-5′/H$_2$-6′/H$_2$-7′ verified the presence of a caryophyllene unit. The key ^{1}H–^{1}H COSY cross-peaks of H-7/H-5′ verified that the triketone moiety and caryophyllene were connected *via* a C-7–C-5′ bond. The downfield chemical shifts of C-8 (δ_C 127.3) and C-4′ (δ_C 89.7) indicated that an oxygen atom was bridged at C-8 and C-4′ to form an additional furan ring, required to fulfil the last IHD and MS information. ROESY correlations (Figure S1) of H-9′*β*/H-6′a; H-6′a/Me-14′; and Me-14′/H-7′ and H-9′ suggested that these protons were *β*-oriented, whereas H-5′ was assigned as *α*-oriented based on the observed ROESY correlations of H-1′*α*/H-3′a and H-3′a/H-5′. Compared to the calculated ECD curve (Figure S2), the experimental ECD spectrum of **5** with two negative Cotton effects [235 nm (Δ*ε* –0.86) and 306 nm (Δ*ε* –2.72)] and a positive Cotton effect [274 nm (Δ*ε* +8.81)] established its absolute configuration as 7*R*,8*S*,1′*R*,4′*R*,5′*S*,9′*S*.

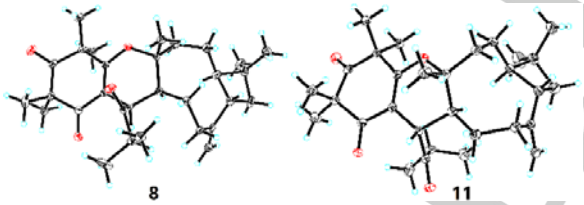


Figure 2. X-ray crystal structures of **8** and **11**.

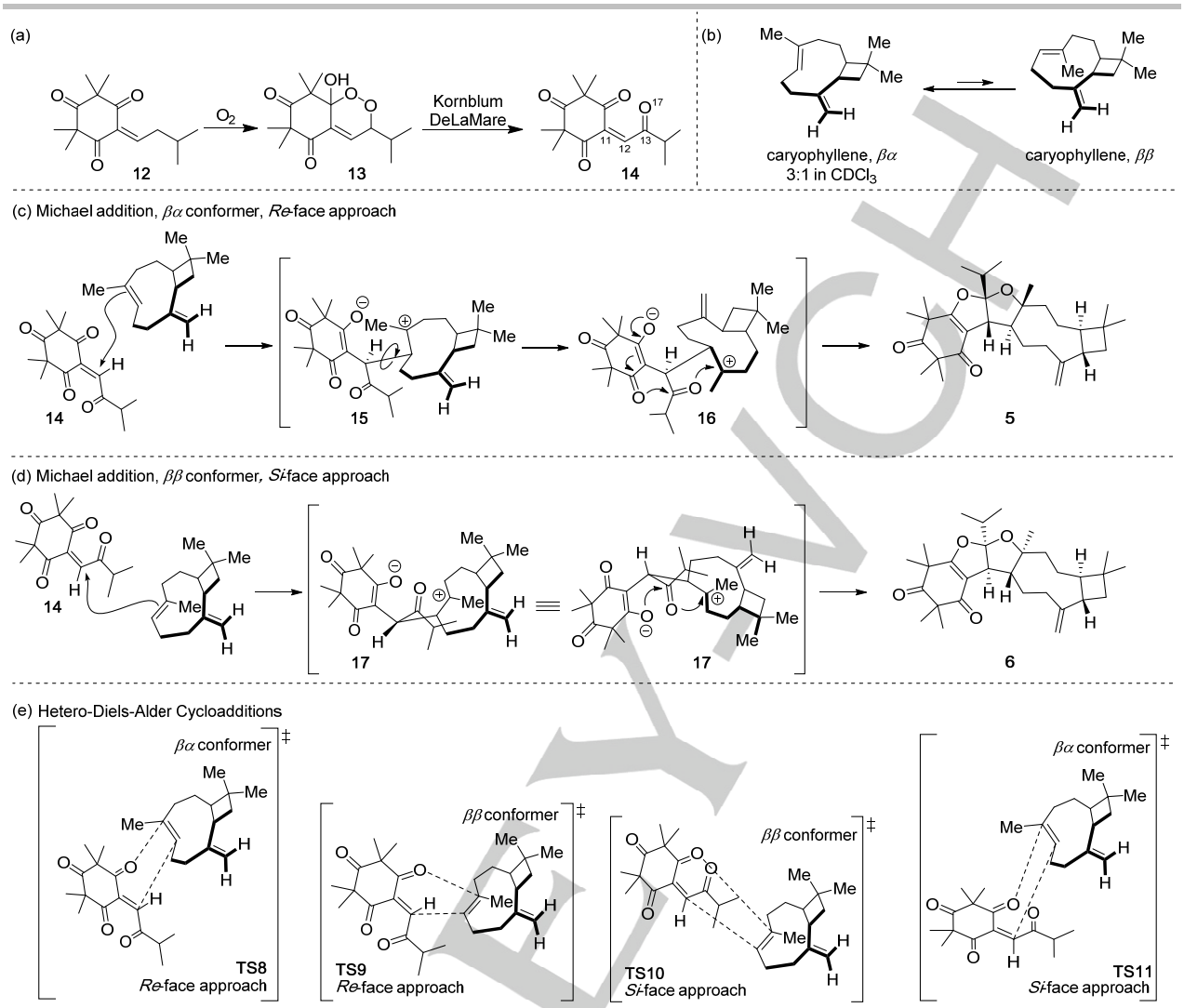
Rhodomyrtusials B (**6**) and C (**7**) possessed the same molecular formula as **5** by HRESIMS data. Comprehensive analysis and comparison of NMR data to **5** (Table S1) revealed that **6** and **7** shared the same planar structure with alternative stereocenters at C-7, C-8, C-4′, and C-5′ (Figure S1). ROESY correlations of H-1′*α*/H-3′a; H-3′a/Me-14′; Me-14′/H-7; and H-7/Me-10 supported H-7, Me-14, and the isopropyl at C-8 were *α*-oriented, whereas H-5′ was *β*-oriented by correlations of H-9′*β*/H-5′ for **6** (Figure S1). For **7**, the observed ROESY correlations of H-1′*α*/H-3′b; H-1′*α*/H-5′; H-5′/H-7; and H-7/Me-10 indicated these groups were *α*-oriented, and the *β*-orientation of Me-14 was established by the ROESY correlations of H-3′a/Me-14′).[7] Absolute configurations of **6** and **7** were defined as 7*S*,8*R*,1′*R*,4′*S*,5′*R*,9′*S* and 7*S*,8*R*,1′*R*,4′*R*,5′*S*,9′*S*, respectively, by comparing experimental and calculated ECD spectra).[7]

In addition to **5**–**7**, two new biogenetically related isomers (**8** and **9**) and two known analogues (**10** and **11**) were identified from *R. tomentosa*. LC-MS analysis indicated that all isolates were present in the cold extract of the title species (Figure S3). The structures and absolute configurations of **8** and **11** were elucidated by spectroscopic data, ECD calculations, and X-ray crystallography.[7] The previously proposed structure and absolute configuration of **11**[8] was confirmed by X-ray crystallography (Figure 2).[9] Furthermore, X-ray analysis of **8** unambiguously determined its absolute configuration as 7*R*,1′*R*,4′*R*,5′*S*,9′*S* (Figure 2).[9] The unambiguous assignment of **8** and analysis of ECD data[7] established the absolute configuration of **10** as 7*S*,1′*R*,4′*S*,5′*R*,9′*S* which is revised from a previously reported structure.[8] Bioactivity assays of the isolates revealed that **5**, **6**, and **10** displayed significant AChE inhibitory activities with IC_{50} values of 8.8, 6.0, and 6.6 *μ*M, respectively. These findings are in good agreement with the AChE inhibitory activity observed from the PE extract.

Proposed biosyntheses of **5**–**11** are shown in Scheme 1. Enetrione (**14**) may serve as a common precursor allowing for access to **5**–**11**. In line with the G-factor series of endoperoxides,[10] alkylidene **12** may undergo autoxidation to afford hydroxy-endoperoxide[4b] (**13**), which may subsequently undergo Kornblum-DeLaMare rearrangement[11] to **14** (Scheme 1a). A DFT model (B3LYP/6-31G**) of **14** (Figure 3) shows a twisted isopropyl ketone (C_{11}-C_{12}-C_{13}-O_{17} = –57.1°) which appears to minimize O-O lone pair interactions.[12] (–)-*Trans*-caryophyllene, a common sesquiterpene, may then react with **14** *via* the more reactive endocyclic double bond[13] in several plausible pathways (Scheme 1c-e, Figure 4) to furnish **5**–**11**. The flexible, nine-membered ring is known to exist in two relevant conformations (*βα*:*ββ* = 3:1) at room temperature (Scheme 1b).[14] In the *βα* conformer, the olefinic methyl group and exocyclic methylene are *trans* with respect to one another. Conversely, the *ββ* conformer is oriented in a *cis* conformation. The assigned configurations of dihydropyrans **8**–**11** indicate both conformers may react with enetrione **14** *via* hetero-Diels Alder (HDA) cycloaddition (Scheme 1e).[15a–k] In contrast stepwise Michael addition[16] of the *βα* conformer of caryophyllene (*re*-face approach Scheme 1c) to **14** may also afford zwitterion **15**, which, after bond-rotation to **16**, may undergo consecutive cyclization to **5**. *Bis*-furan **7** may also be obtained through a similar stepwise Michael addition of the *ββ* conformer (*si*-face approach, Scheme 1d) to **14** may afford intermediate **17**, which can undergo cyclization to **6**. Dihydropyrans **8**–**11** may also be obtained from a stepwise pathway involving zwitterionic intermediates and *bis*-furans **5**–**7** may arise from concerted cycloadditions.

Our synthetic studies began with the synthesis of enetrione (**14**). Despite literature examples reporting syntheses of enetriones,[17] there remains an absence in methodology for the synthesis of cyclic enetriones, presumably due to reactivity of the twisted carbonyl (*cf.* Figure 2). Alkylidene **12** may be synthesized *via* proline-catalyzed condensation of isovaleraldehyde with syncarpic acid.[18] Metal-mediated allylic oxidation attempts[19] on **12** were not fruitful and typically led to

10.1002/anie.201814421



Scheme 1. Proposed biosyntheses of **5**–**11**. (a) Synthesis of enetrione (**14**); (b) conformations of *trans*-caryophyllene; (c) stepwise Michael addition leading to **5**; (d) stepwise Michael addition leading to **6**; (e) Hetero-Diels-Alder (HDA) cycloadditions leading to **8**–**11**.

spontaneous oxidation to endoperoxide **13**. After unsuccessful attempts to obtain **14** *via* Kornblum-DeLaMare rearrangement, we rationalized that the elusive enetrione may be generated *in situ* from **13**. This hydroxy-endoperoxide was previously reported by our group and was obtained as a mixture of diastereomers, albeit in 51% yield.[4b] After experimentation, an improved condition for the synthesis of endoperoxide **13** was identified (Scheme 2a). Subjection of compound **12** to photoenolization conditions[20] (390–720 nm white LEDs) in

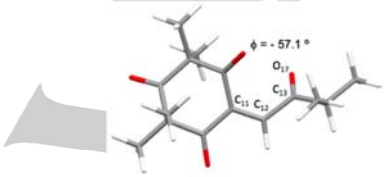
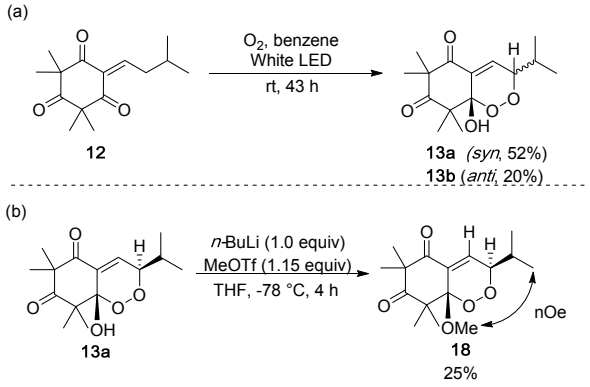


Figure 3. DFT-minimized structure of enetrione **14.**

benzene as solvent and [4+2] cycloaddition with O_2 afforded **13** in 72% combined yield. Exposure of pure **13a** to *O*-methylation conditions[21] afforded endoperoxide **18** in 25% yield (Scheme 2b). Endoperoxide methyl ether (**18**) was characterized by NMR to assign stereochemistry.[7] In particular, a key nOe was observed between the –OMe and isopropyl methyl groups to ascertain *syn* stereochemistry for **13a**. By default, the –OH and isopropyl group in endoperoxide **13b** have an *anti*-relationship.

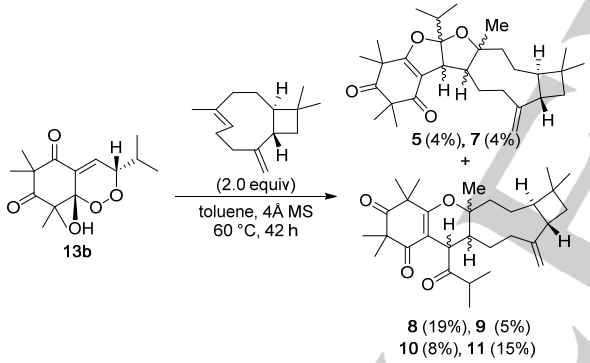
With endoperoxides **13a** and **13b** in hand, we initiated studies towards syntheses of **5**–**11.** Initial reactions of either endoperoxide **13a** or **13b** and *trans*-caryophyllene in polar solvents such as dichloromethane, dichloroethane, nitromethane, trifluoroethanol, and HFIP[15i] were unfruitful. Following conditions reported by Takao and co-workers[21], thermolysis of endoperoxide **13a** in the presence of caryophyllene in toluene at 100 °C afforded **9**, **10**, and **11**, in 10, 10, and 6% yields, respectively. Thermolysis of pure **13b**

10.1002/anie.201814421



Scheme 2. (a) Synthesis of hydroxy-endoperoxides (**13**); (b) Methylation and key nOe for the assignment of **13a** and **13b**.

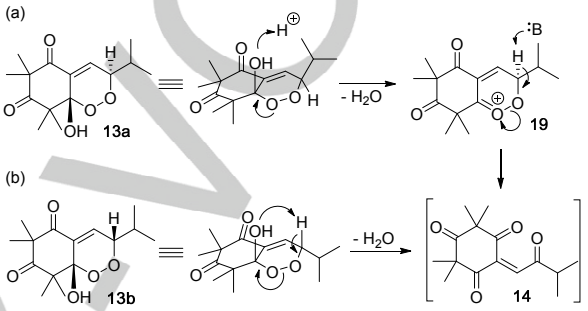
(90 °C, 43 h) without caryophyllene present resulted in a mixture of endoperoxide diastereomers **13a** and **13b** in a 1.5 to 1 ratio.[7] Additionally, thermolysis of **13a** or **13b** in the presence of *trans*-caryophyllene without desiccant at 60 °C gave no conversion to the natural products. These findings led us to evaluate thermolytic conditions with molecular sieves (M.S.) as desiccant.[22] Thermolysis of **13b** in the presence of *trans*-caryophyllene and 4Å M.S. in toluene at 60 °C afforded **5**, **7**, and **8**–**11**, in 4, 4, 19, 5, 8, and 15% yields, respectively (55% combined) after HPLC purification (Scheme 3).[7]



Scheme 3. Synthesis of **5**, **7**, and **8**–**11**.

Interestingly, thermolysis of **13a** with *trans*-caryophyllene and 4Å M.S. resulted in a conversion that was approximately 20% as efficient when the same reaction was run with **13b**.[7] The reaction conditions shown in Scheme 3 produced trace *bis*-furan **6**, but the compound was never successfully isolated. We also considered the use of Lewis and Brønsted acids as catalysts. Utilization of $Ni(ClO_4)_2 \cdot 6\ H_2O$, $Cu(ClO_4)_2 \cdot 6\ H_2O$, $Cu(BF_3)_2 \cdot 6\ H_2O$, and various rare earth metal triflates did not result in product formation. Use of trifluoroacetic acid (TFA) did not afford adducts, likely due to the strength of the acid and the propensity of caryophyllene to rearrange under strongly acidic conditions.[13] Reactions with acetic acid as additive in toluene at 60 °C afforded products **5** and **8**–**11**; however, the results were inconsistent.

Based on our experiments, we propose plausible dehydrative mechanisms for either **13a** or **13b** to produce the reactive enetrione (**14**) *in situ* (Scheme 4). The less reactive endoperoxide (**13a**) may form a cyclic peroxycarbenium[4b, 23] intermediate (**19**) after protonation of the peroxy-ketal and expulsion of water. Deprotonation of the *α*-peroxy methine proton and resulting Kornblum-DeLaMare rearrangement[11] may afford enetrione (**14**, Scheme 4a). We believe that endoperoxide **13b** displays heightened reactivity due to the *syn*-stereochemical relationship of the *α*-peroxy hydroxyl group and the *α*-peroxy methine hydrogen (Scheme 4b).[24] The more reactive endoperoxide (**13b**) may undergo formal, directed Kornblum-DeLaMare rearrangement to afford **14**.[25] This intermediate can then react with caryophyllene to afford compounds **5**–**11**.



Scheme 4. Proposed mechanism for enetrione formation.

We conducted initial DFT calculations (B3LYP/STO-3G) of zwitterionic intermediates **15** and **17** (*vide supra*, Scheme 1c–d) to probe the proposed, stepwise Michael addition pathway. Interestingly, more than half of the conformers converged to product during the optimization process, which led us to investigate concerted pathways *in silico*. Indeed, we successfully located asynchronous, concerted transition states connecting **5** (Figure 4, PBEh-3C, **TS5^c**) and **7** to **14**-*βα* with activation barriers competitive with production of **8**–**11**.[7] A pseudo-concerted transition state connecting **6** and **14**-*ββ* was also located, but the calculated activation barrier was inconsistent with the observed yields. Preliminary quasi-classical trajectory analysis suggests that this is due to a bifurcating potential energy surface (PES).[26] A more extensive computational exploration will be reported in due course.

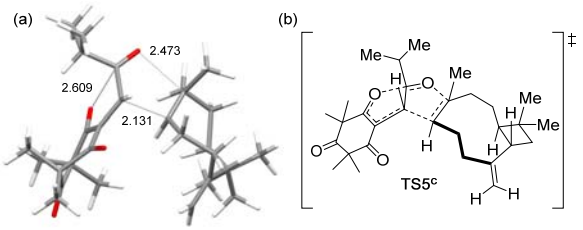
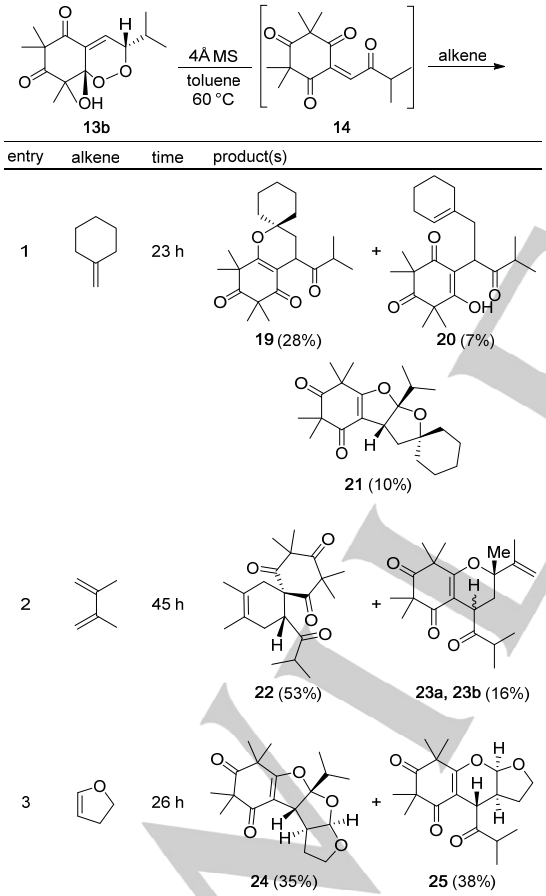


Figure 4. (a) DFT-minimized structure of **TS5^c**; (b) ChemDraw rendition of **TS5^c**.

To better understand the modes of reactivity for **14**, we investigated additional alkene reaction partners (Scheme 5). Reactions involving the 1,1-disubstituted alkene of caryophyllene were not observed (*cf.* Scheme 3). To study

reactivity with 1,1-disubstituted alkenes, methylene cyclohexane was chosen as a simplified reaction partner (Scheme 5, entry 1). In this case, three structurally unique products were obtained in 45% overall yield. Spirocycles **19** and **21** may arise from the concerted cycloaddition pathways previously described; production of **20** demonstrates a new mode of reactivity for enetrione **14** involving an Alder-ene reaction.[27] To further explore the reactivity of **14**, 2,3-dimethylbutadiene was evaluated as a reaction partner (Scheme 5, entry 2). Spirocycle **22** was isolated as the major product in 53% yield, revealing that enetrione **14** also participates in normal demand [4+2] cycloadditions. Dihydropyran diastereomers **23a**/**23b** were also isolated as minor products in 16% yield. This mixture of diastereomers was thermolyzed in toluene (100 °C, 24 h) which resulted in partial conversion to **22**, presumably *via* Claisen rearrangement.[7] Use of the electron-rich reaction partner dihydrofuran (Scheme 5, entry 3) afforded *tris*-furan **24** and dihydropyran **25** in 73% combined yield. These initial studies illustrate four distinct modes of reactivity for enetrione **14** which allow for the synthesis of structurally intriguing small molecules from a common reagent.



Scheme 5. Investigation of alkene reaction partners with enetrione **14.**

In summary, we have isolated the *bis*-furans rhodomyrtusials A–C, three novel triketone-sesquiterpene meroterpenoids featuring a 6/5/5/9/4 pentacyclic ring system as well as four biogenetically related dihydropyran isomers from *R. tomentosa*. Two *bis*-furans and one dihydropyran were found to exhibit AChE inhibitory activities. Six of the seven isolates were synthesized in six steps utilizing a reactive enetrione generated *in situ* from a readily available hydroxy-endoperoxide. Further evaluation of alkene reaction partners identified additional modes of reactivity for the enetrione. Computational studies have identified a valid asynchronous, concerted pathways to *bis*-furan **5** and **7**. Further pharmacological studies, synthesis and biological studies of triketone-sesquiterpene meroterpenoids, and exploration of the reactivity of **14** and related enetriones are currently in progress and will be reported in due course.

Acknowledgements

These studies were funded by the National Natural Science Foundation of China (U1802287 and 31600283), the National Institutes of Health (R35 GM-118173), , Major Bio-Medical Project of Yunnan Province (2018ZF005), Youth Innovation Promotion Association CAS, Key Research and Development Plan of Yunnan Province–Special Project of Science and Technology in Yunnan Province (2017IB007), and Innovation Team of the Ministry of Education (IRT-17R49) and DARPA (W911NF-18-1-0025). We thank Professor Jonathan George (University of Adelaide) for helpful discussions and Thomas Purgett, Dr. Kyle Reichl, and Dr. Wenhan Zhang (BU) for assistance with the manuscript.

Keywords: Myrtaceae • *Rhodomyrtus tomentosa* • total synthesis • caryophyllene • Hetero-Diels-Alder

[1] (a) J. D. Phillipson, 1979, *Trends Pharmacol. Sci.* **1979**, *1*, 36–38; (b) G. M. Cragg, P. G. Grothaus, D. J. Newman, *Chem. Rev.* **2009**, *109*, 3012–3043; (c) B. B. Mishra, V. K. Tiwari, *Eur. J. Med. Chem.* **2011**, *46*, 4769–1807; (d) V. Gogineni, R. F. Schinazi, M. T. Hamann, *Chem. Rev.* **2015**, *115*, 9655–9706; (e) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629–661; (f) M. G. Moloney, *Trends Pharmacol. Sci.* **2016**, *37*, 689–701; (g) S. K. Palanisamy, N. M. Rajendran, A. Marino, *Nat. Prod. Bioprospect.* **2017**, *7*, 1–111; (h) S. E. Kearney et al. *ACS Cent. Sci.* **2018**, *4*, 1727–1741.

[2] (a) S. P. Yang, X. W. Zhang, J. Ai, L. S. Gan, J. B. Xu, Y. Wang, Z. S. Su, L. Wang, J. Din, M. Y. Geng, J. M. Yue, *J. Med. Chem.* **2012**, *55*, 8183–8187; (b) J. Q. Cao, X. J. Huang, Y. T. Li, Y. Wang, L. Wang, R. W. Jiang, W. C. Ye, *Org. Lett.* **2016**, *18*, 120–123; (c) C. J. Li, J. Ma, H. Sun, D. Zhang, D. M. Zhang, *Org. Lett.* **2016**, *18*, 168–171; (d) Y. L. Zhang, C. Chen, X. B. Wang, L. Wu, M H, Yang, J. Luo, C. Zhang, H. B. Sun, J. G. Luo, L. Y. Kong, *Org. Lett.* **2016**, *18*, 4068–4071; (e) L. Q. Hou, C. Guo, J. J. Zhao, Q. W. He, B. B. Zhang, H. Wang, *J. Org. Chem.* **2017**, *82*, 1448–1457; (f) X. J. Qin, M. Y. Feng, H. Liu, W. Ni, T. Rauwolf, J. A. P. Jr., H. Yan, L. He, H. Y. Liu, *Org. Lett.* **2018**, *20*, 5066–5070.

[3] (a) M. J. Cheng, J. Q. Cao, X. Y. Yang, L. P. Zhong, L. J. Hu, X. Lu, B. L. Hou, Y. J. Hu, Y. Wang, X. F. You, L. Wang, W. C. Ye, C. C. Li, *Chem. Sci.* **2018**, *9*, 1488–1495; (b) D. H. Dethe, B. D. Dherange, S. Das, *Org. Lett.* **2018**, *20*, 680–683; (c) Y. H. Guo, Y. H. Zhang, M. X. Xiao, Z. X. Xie, *Org. Lett.* **2018**, *20*, 2509–2512.

[4] (a) A. Hiranrat, W. Mahabusarakam, *Tetrahedron* **2008**, *64*, 11193–11197; (b) A. Gervais, K. E. Lazarski, J. A. Porco, Jr., *J. Org. Chem.* **2015**, *80*, 9584–9591.

[5] X. Zhou, Y. Xia, Y. Zhang, J. Luo, C. Han, H. Zhang, C. Zhang, L. Yang, L. Kong, *Oncotarget*, **2017**, *8*, 101965–101983.

[6] C. Liu, S. Ang, X. Huang, H. Tian, Y. Deng, D. Zhang, Y. Wang, W. Ye, L. Wang, *Org. Lett.* **2016**, *18*, 4004–4007.

[7] See the Supporting Information for complete experimental details.

[8] Y. B. Zhang, W. Li, L. Jiang, L. Yang, N. H. Chen, Z. N. Wu, Y. L. Li, G. C. Wang, *Phytochemistry* **2018**, *153*, 111–119.

[9] CCDC 1853641 (**11**) and CCDC 1855960 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge of charge from the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

[10] (a) C. Givelet, V. Bernat, M. Danel, C. André-Barrès, H. Vial, *Eur. J. Org. Chem.* **2007**, *19*, 3095–3101; (b) V. Bernat, M. Coste, C. André-Barrès, *New J. Chem.* **2009**, *33*, 2380; (c) J. Ruiz, B. Tuccio, R. Lauricella, M. Maynadier, H. Vial, C. André-Barrès, *Tetrahedron* **2013**, *69*, 6709–6720; (d) C. André-Barrès, Y. Carissan, B. Tuccio, *ACS Omega* **2017**, *2*, 5357–5363.

[11] I. A. Yaremenko, V. A. Vil', D. V. Demchuk, A. O. Terent'ev, *Beilstein J. Org. Chem.* **2016**, *12*, 1647–1748.

[12] H. Ito, S. A. MacDonald, C. G. Willson, J. W. Moore, H. M. Gharapetian, J. E. Guillet, *Macromolecules* **1986**, *19*, 1839–1844.

[13] I. G. Collado, J. R. Hanson, A. Macías-Sanchez, J. *Nat. Prod. Rep*. **1998**, *15*, 187, and references cited therein.

[14] H. Shirahama, E. Osawa, B. R. Chhabra, T. Shimokawa, T. Yokono, T. Kanaiwa, T. Amiya, T. Matsumoto, *Tetrahedron Lett.* **1981**, *22*, 1527.

[15] For cycloadditions involving β-caryophyllene, see: A. L. Lawrence, R. M. Adlington, J. E. Baldwin, V. Lee, J. A. Kershaw, A. L. Thompson, *Org. Lett.* **2010**, *12*, 1676–1679; (b) J. T. J. Spence, J. H. George, *Org. Lett.* **2011**, *13*, 5318–5321; (c) K. I. Takao, S. Noguchi, S. Sakamoto, M. Kimura, K. Yoshida, K. I. Tadano, *J. Am. Chem. Soc.* **2015**, *137*, 15971–15977; (d) H. C. Lam, J. T. J. Spence, J. H. George, *Angew. Chem. Int. Ed*. **2016**, *55*, 10368 –10371; (e) Y. L. Zhang, C. Chen, X. B. Wang, L. Wu, M. H. Yang, J. Luo, C. Zhang, H. Bin Sun, J. G. Luo, L. Y. Kong, *Org. Lett.* **2016**, *18*, 4068–4071; (f) H. X. Liu, K. Chen, G. H. Tang, Y. F. Yuan, H. B. Tan, S. X. Qiu, *RSC Adv.* **2016**, *6*, 48231–48236; (g) L. Lv, Y. Li, Y. Zhang, Z. Xie, *Tetrahedron* **2017**, *73*, 3691–3695; (h) J. Q. Hou, C. Guo, J. J. Zhao, Q. W. He, B. B. Zhang, H. Wang, *J. Org. Chem.* **2017**, *82*, 1448–1457; (i) C. G. Newton, D. N. Tran, M. D. Wodrich, N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 13776–13780.; (j) W. L. Zhou, H. B. Tan, S. X. Qiu, G. Y. Chen, H. X. Liu, C. Zheng, *Tet. Lett.* **2017**, *58*, 1817–182; (k) S. J. Ma, J. Yu, D.W. Yan, D. C. Wang, J. M. Gao, Q. Zhang, *Org. Biomol. Chem.* **2018**, *16*, 9454–9460.

[16] (a) S. Onitsuka, H. Nishino, *Tetrahedron* **2003**, *59*, 755–765; (b) M. Gao, Y. Yang, Y. D. Wu, C. Deng, L. P. Cao, X. G. Meng, A. X. Wu, *Org. Lett.* **2010**, *12*, 1856–1859; (c) L. Fan, W. Chen, K. Tang, D. Wu, *Chem. Lett.* **2012**, *41*, 940–942; (d) Y. P. Zhu, Q. Cai, Q. H. Gao, F. C. Jia, M. C. Liu, M. Gao, A. X. Wu, *Tetrahedron* **2013**, *69*, 6392–6398.

[17] H. Tan, H. Liu, L. Zhao, Y. Yuan, B. Li, Y. Jiang, L. Gong, S. Qiu, *Eur. J. Med. Chem.* **2017**, *125*, 492–499.

[18] (a) E. C. Mclaughlin, H. Choi, K. Wang, G. Chiou, M. P. Doyle, *J. Org. Chem.* **2009**, *74*, 730–738; (b) J. Muzart, *Tetrahedron* **1987**, *28*, 4665–4668; (c) R. M. Patel, V. G. Puranik, N. P. Argade, *Org. Biomol. Chem.* **2011**, *9*, 6312–6322; (d) T. K. M. Shing, Y. Y. Yeung, P. L. Su, *Org. Lett.* **2006**, *8*, 3149–3151.

[19] B. B. Snider, Z. Shi, *J. Am. Chem. Soc.* **1992**, *114*, 1790–1800.

[20] V. Bernat, C. André-Barrès, M. Baltas, N. Saffon, H. Vial, *Tetrahedron* **2008**, *64*, 9216–9224.

[21] K. I. Takao, S. Noguchi, S. Sakamoto, M. Kimura, K. Yoshida, K. I. Tadano, *J. Am. Chem. Soc.* **2015**, *137*, 15971–15977.

[22] J. H. Markgraf, D. B Burns, E. W. Greeno, K. J. Leonard, M. D. Miller. *Synthetic Comm.* **1984**, *14*, 647–653.

[23] For cyclic peroxycarbenium ions, see: P. Dussault, X. Liu, *Org. Lett.* **1999**, *1*, 1391–1393.

[24] For 1,4-*syn* elimination, see: R. J. Moss, B. Rickborn, *J. Org. Chem.* **1986**, *51*, 1992–1996.

[25] For an alkoxide-directed Kornblum DeLaMare rearrangement, see: M. J. Palframan, G. Kociok-Kohn, S. E. Lewis, *Chem. Eur. J.* **2012**, *18*, 4766–4774.

[26] (a) Z. Yang, X. Dong, Y. Yu, P. Yu, Y. Li, C. Jamieson, K N. Houk, *J. Am. Chem. Soc.* **2018,** *140* (8), 3061-306; (b) K. K. Kelly, J. S. Hirschi, D. A. Singleton, *J. Am. Chem. Soc.* **2009,** *131* (24), 8382-8383.

[27] H. Liu, W. Zhang, Z. Xu, Y. Chen, H. Tan, S. Qiu, *RSC Adv.*, **2016**, *6*, 25882–25886.

10.1002/anie.201814421

WILEY-VCH

COMMUNICATION

Xu-Jie Qin,[+] Tyler J. Rauwolf,[+] Pan-Pan Li,[+] Hui Liu , James McNeely, Yan Hua, Hai-Yang Liu, and John A. Porco, Jr.**

Page No. – Page No.

Isolation and Synthesis of Novel Meroterpenoids from *Rhodomyrtus tomentosa*: Investigation of a Reactive Enetrione Intermediate

Novel meroterpenoids were isolated from *R. tomentosa* and characterized which led to a hypothesis for their biosynthesis. *In situ* generation of a reactive enetrione in the presence of the sesquiterpene caryophyllene led to efficient chemical syntheses of four of the five meroterpenoids, as well as two biogenetically related cycloadducts, in a biomimetic, six-step sequence. Further evaluation of alkene reaction partners identified additional modes of reactivity for the enetrione reagent.