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Rapid Biomimetic Total Synthesis of (±)-Rossinone B

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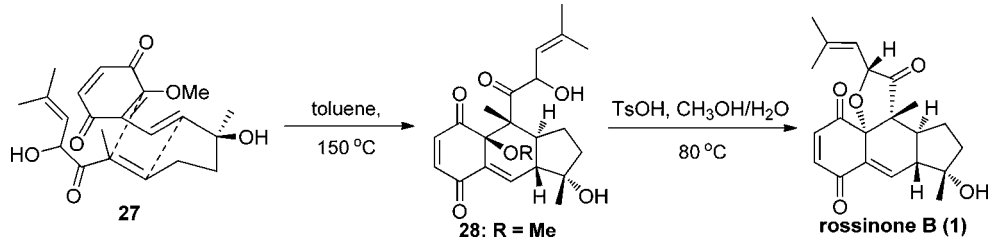
ABSTRACT



A biomimetic total synthesis of (±)-rossinone B has been achieved through a highly efficient strategy featuring a series of rationally designed reactions, including a one-pot allylic rearrangement/oxidation reaction to generate the vinyl quinone 27, an intramolecular vinyl quinone Diels−Alder reaction to construct the linear 6−6−5 tricyclic core of 28, and a double conjugate addition/β-elimination cascade to complete the total synthesis of 1.

Marine organisms have been proven to be invaluable resources for discovery of structurally unique and biologically important natural products.[1] As a paradigmatic example, rossinone B (**1**, Figure 1) was isolated from an Antarctic collection of the ascidian *Aplidium* species by Copp and co-workers in 2009.[2] The preliminary biological investigations have shown that rossinone B exhibited significant biological profiles, including potent antiviral, anti-inflammatory and antileukemic activities. For instance, rossinone B was found to show prominent antiproliferative activity toward the P388 murine leukemia cell-line with low IC_{50} value (0.084 μM).

From a structural point of view, rossinone B possesses a rather novel molecular architecture featured by a linearly fused 6−6−5 ring core, that so far, has only been found in

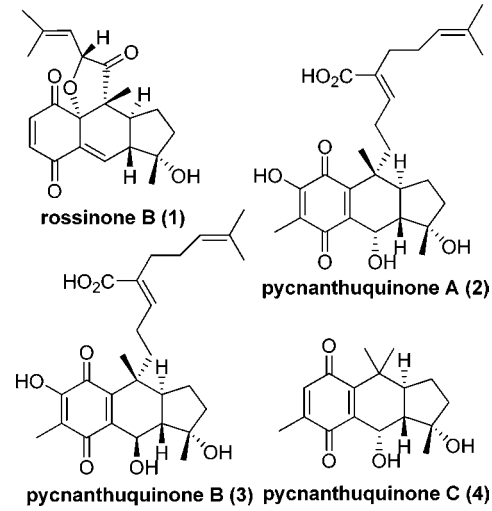


Figure 1. Natural products with 6−6−5 ring core structure.

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(1) (a) Skropeta, D. *Nat. Prod. Rep.* **2008**, *25*, 1131–1166. (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Pep.* **2010**, *27*, 165–237.

(2) Appleton, D. R.; Chuen, C. S.; Berridge, M. V.; Webb, V. L.; Copp, B. R. *J. Org. Chem.* **2009**, *74*, 9195–9198.

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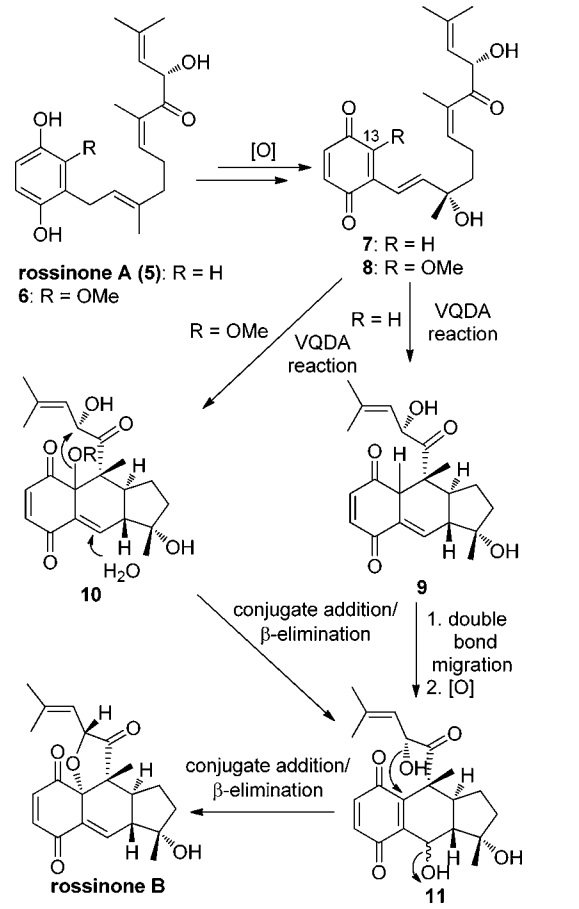
three other natural products, named pycnanthuquinones A (**2**),[3] B (**3**)[3] and C (**4**).[4] Biosynthetically, these natural products are most likely to be derived from the corresponding prenylated hydroquinone derivatives that are usually isolated concomitantly from the natural source. As such, Altena et al. proposed that pycnanthuquinones C was biogenetically produced from a geranyltoluquinol precursor through a cascade cyclization reaction involving a carbocation species.[4] In contrast, Trauner and coworks recently proposed a different biosynthetic mechanism, in which a novel vinyl quinone Diels−Alder (VQDA) reaction was suggested as the key transformation. Notably, this hypothesis has been validated by their elegant work on the biomimetic total synthesis of pycnanthuquinones C.[5]

Attracted by its novel chemical structure, promising biological properties and potentially intriguing biosynthetic pathway, we initiated a program aiming for developing an efficient biomimetic route for synthesis of rossinone B, as well as other members of this family. Herein we report the first total synthesis of (±)-rossinone B by employing a bioinspired intramolecular VQDA reaction as the key reaction.

The proposed biosynthetic pathway[6] coupled with the synthetic plan for rossinone B is depicted in Scheme 1. Rossinone A (**5**), also isolated from the same resource, is believed to be the biosynthetic precursor for rossinone B. Thus, a series of oxidations of **5** leads to vinyl quinone **7**. Then **7** undergoes an intramolecular VQDA reaction to afford the fleeting isoquinone methide intermediate **9**, which spontaneously advances to rossinone B via an isomerization/oxidation/conjugate addition/β-elimination cascade reaction. Notably, although there were sporadic studies on the VQDA reaction,[7−9] its versatile reactivity has been largely unexplored. For instance, the vinyl quinone unit was proven to be an ideal diene partner in the inverse electron-demand Diels−Alder reaction, as shown in the total synthesis of pycnanthuquinones C[5] and halenaquinone.[9a] However, its reactivity in the normal electron-demand Diels−Alder reaction, as in the case of rossinone B, remained uncertain, considering its extremely electron-deficient properties.[10] To overcome this challenge, we envisioned that installing a methoxy group at C-13 (as shown in **8**, Scheme 1) would

Scheme 1. Proposed Biosynthetic Pathway for Rossinone B and Bio-inspired Synthetic Strategy



benefit the practical synthesis by increasing the HOMO energy of the diene partner, and thus facilitating the desired cycloaddition reaction. Moreover, the methoxy group is expected to serve as a leaving group in the following conjugate addition/β-elimination reaction, promoting the transformation from **10** to **11**.

To test the viability of our strategy, a model study was first conducted as shown in Scheme 2. Regioselective metalation of **12**[11] with *n*BuLi at −78 °C followed by addition of aldehyde **13**[12] afforded **14** in 50% yield (82% based on recovered starting material). The synthesis of VQDA reaction precursor **17** was then achieved in a streamlined manner: an acid-promoted 1,3-allylic isomerization[13] converted **14** to the thermodynamically more stable compound **15**, the MOM protection group was then removed under the acidic conditions, and the resulting phenol was immediately oxidized to quinone **17**. Notably, although the aforementioned transformations worked well in a stepwise

(3) Fort, D. M.; Ubillas, R. P.; Mendez, C. D.; Jolad, S. D.; Inman, W. D.; Carney, J. R.; Chen, J. L.; Ianiro, T. T.; Hasbun, C.; Bruening, R. C.; Luo, J.; Reed, M. J.; Iwu, M.; Carlson, T. J.; King, S. R.; Bierer, D. E.; Cooper, R. *J. Org. Chem.* **2000**, *65*, 6534–6539.

(4) Laird, D. W.; Poole, R.; Wikstrom, M.; van Altena, I. A. *J. Nat. Prod.* **2007**, *70*, 671–674.

(5) Löbermann, F.; Mayer, P.; Trauner, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 6199–6202.

(6) We noticed that a similar proposal about the biosynthetic pathway of rossinone B was independently disclosed in ref 5.

(7) (a) Irngartinger, H.; Stadler, B. *Eur. J. Org. Chem.* **1998**, 605–626. (b) Iwamato, H.; Hamada, T. K.; Fujiwara, R. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 575–581.

(8) (a) Noland, W. E.; Kedrowski, B. L. *J. Org. Chem.* **1999**, *64*, 596–603. (b) Kedrowski, B. L.; Noland, W. E. *J. Org. Chem.* **2002**, *67*, 8366–8373.

(9) (a) Kienzler, M. A.; Suseno, S.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 8604–8605. (b) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554–9555.

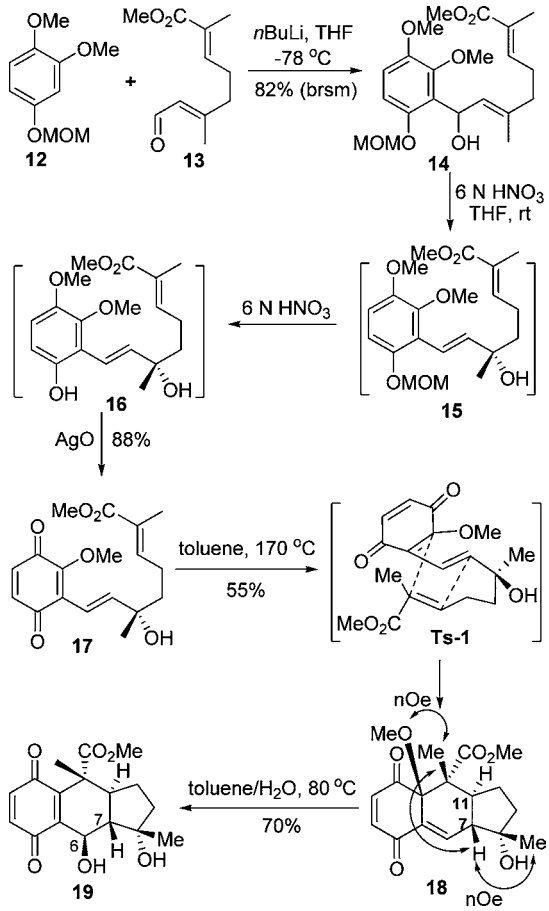
(10) A normal electron-demand VQDA reaction was reported in ref 9b. However, the vinyl quinone unit was embodied in a pyranonaphthoquinone system, making it a relatively special case.

(11) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701–2704.

(12) For preparation of **13**, please see Supporting Information.

(13) Snyder, C. D.; Bondinell, W. E.; Rapoport, H. *J. Org. Chem.* **1971**, *36*, 3951–3960.

Scheme 2. Model Study on VQDA Reaction



manner,[14] the best result was obtained in a one-pot procedure using HNO_3/AgO combination (6 N HNO_3 for 15 min, then AgO for 30 min), providing the desired quinone **17** in 88% over 2 steps.

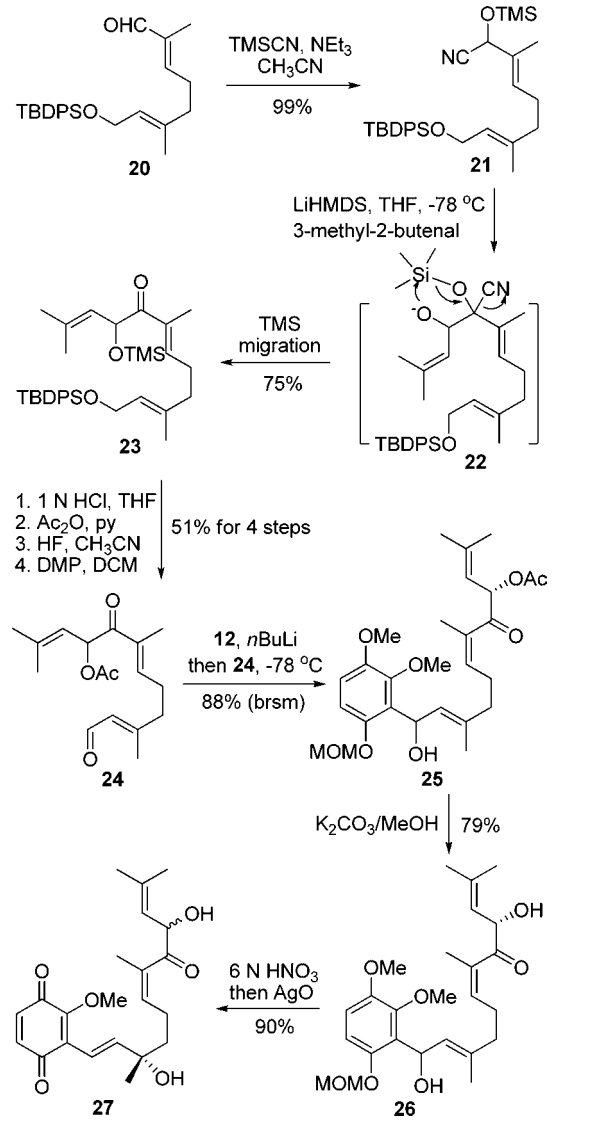
With **17** in hand, we next turned our attention to the intramolecular VQDA reaction. To our delight, the desired reaction proceeded smoothly under thermal condition (170 °C, toluene, sealed tube) to give the tricyclic compound **18** as the only isolatable product in 55% yield. Albeit moderate in yield, the reaction proceeded with high diastereoselectivity, presumably via the endo transition state **Ts-1**, to afford **18** with four consecutive stereocenters established in one operation. The relative stereochemistry of **18** was assigned based on 1D NOE measurement (Scheme 2) and the coupling constant of the characteristic protons.[15] Furthermore, when **18** was heated in a toluene/water mixture at 70 °C, the conjugate addition/β-elimination reaction transpired as expected, to afford **19** as the sole diastereoisomer in 70% yield, and the β-configuration of 6-OH was assigned based on the coupling constant between H-6 and H-7.[16] Notably, **19** shares the same core structure with pycnanthuquinones A (**3**), B (**4**) and C (**5**).

(14) The allylic isomerization product **15** could be isolated, and its structure was fully characterized.

(15) The *trans*-configuration of H-7 and H-11 could be deduced by the coupling constant value between them ($J_{H7\text{-}H11}$ = 12.3 Hz).

Encouraged by success of the model study, we commenced the total synthesis campaign toward rossinone B (**1**). As depicted in Scheme 3, synthesis of **25**, bearing the fully

Scheme 3. Synthesis of Precursor of VQDA Reaction



functionalized side chain, was started with compound **20**.[17] Thus, addition of TMSCN to aldehyde **20** in the presence of Et_3N furnished TMS-protected cyanohydrin **21** in almost quantitative yield.[18] Deprotonation of **21** with LiHMDS at −78 °C, followed by addition of 3-methyl-2-butenal provided the coupled intermediate **22**, which spontaneously underwent a silyl group migration to release the masked ketone, leading to the formation of **23** in 75% yield.[19] The TMS group was

(16) The *trans*-configuration of H-6 and H-7 could be deduced by the coupling constant value between them ($J_{H6\text{-}H7}$ = 9.6 Hz).

(17) The aldehyde **20** was prepared according to the following literature except that TBDPSCl was used instead of TBSCl: Labadie, G. R.; Viswanathan, R.; Poulter, C. D. *J. Org. Chem.* **2007**, *72*, 9291–9297.

(18) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395–405.

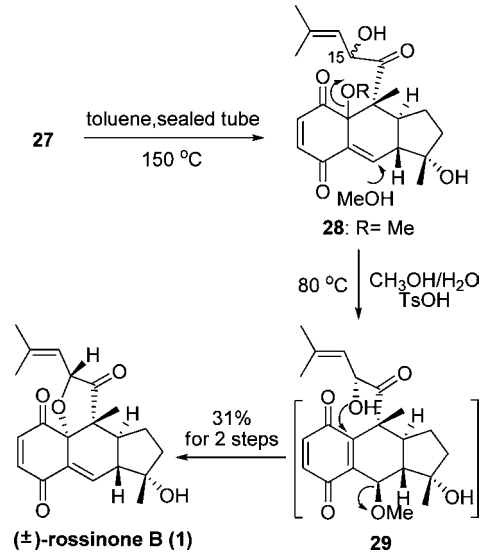
then removed upon treatment with 1 N HCl, and the resulting alcohol was acetylated with Ac_2O/Py. Removal of the TBDPS group with aqueous HF, followed by oxidation with Dess−Martin periodinane gave aldehyde **24** in 51% overall yield from **23**. The next task was to assemble the two fragments **12** and **24**, following the procedure established in our model study. As such, metalation of the MOM-protected phenol **12** with *n*BuLi at −78 °C followed by addition of aldehyde **24** afforded **25** as a 1:1 mixture of inseparable diastereoisomers in 67% yield (88% based on recovered starting material). The acetate was then removed by K_2CO_3/CH_3OH, and the resulting benzylic alcohol **26** was treated with 6 N HNO_3, and then AgO, to furnish vinyl quinone **27** in 71% overall yield.

With **27** in hand, the stage was set to test the key step of our synthesis, the biomimetic intramolecular VQDA reaction. Thus, **27** was heated in toluene (sealed tube, 150 °C) until the characteristic deep brown color of quinone disappeared. However, this reaction, unlike that in the model study, seemed to be somewhat complicated. Preliminary analysis of the crude NMR data showed that two components of the mixture bear very similar NMR spectrum with that of rossinone B, and thus their structures were tentatively assigned as **28**, which represented a mixture of epimers at C-15. Further efforts to obtain pure single isomer for fully structural characterization proved to be fruitless, mainly because of a possible thermodynamic equilibrium observed between the two epimers. In reality, the ratio of epimers at C-15 varied extensively from 12:1 to 1:1 depending on the conditions used (see Supporting Information for details). These interesting phenomena led us to believe that both of the two epimers could be converted to rossinone B in next transformation through the existing equilibrium. This hypothesis was quickly validated by the following experiments. When the mixture of epimeric **28** was heated in CH_3OH/H_2O in presence of TsOH at 80 °C for 12 h, rossinone B was obtained in 31% isolated yield over two steps.[20] Although intermediate **29** was not observed, the transformation from **28** to **1** was believed to proceed through a double conjugate addition/β-elimination cascade reaction (as shown in Scheme 4). The spectroscopic data of synthetic rossinone B (^{1}H and ^{13}C NMR, IR, HRMS) were fully identical with those reported for the naturally occurring product.

(19) (a) Deuchert, K.; Hertenstein, U.; Hünig, S. *Synthesis* **1973**, 777–779. (b) Hünig, S.; Wehner, G. *Synthesis* **1975**, 180. (c) Hünig, S.; Wehner, G. *Synthesis* **1975**, 391–392. (d) Hertenstein, U.; Hünig, S.; Öller, M. *Synthesis* **1976**, 416–417.

(20) The double conjugate addition/β-elimination reaction was first run under the condition used in our model study (H_2O/toluene, 80 °C); however, only epimerization at C-15 was observed.

Scheme 4. Completion of Total Synthesis of Rossinone B



In summary, the first total synthesis of (±)-rossinone B was achieved through a highly efficient biomimetic strategy. It strongly supports the proposal that a novel vinyl quinone Diels−Alder reaction might be involved in the biosynthetic pathway of rossinone B. Further studies on the asymmetric synthesis of **1** and its application to the synthesis of other members of this family as well as their analogs for biological evaluations are undergoing in our laboratory, and will be reported in due course.

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Supporting Information Available: Experimental procedure and characterization data for all of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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