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Total Synthesis of Isofregenedadiol[#]

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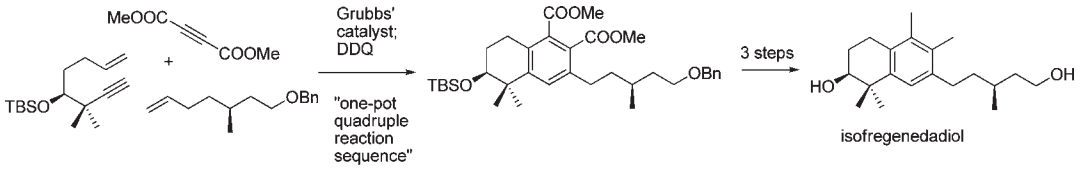
ABSTRACT



The first total synthesis of isofregenedadiol, a bicyclic diterpene isolated from *H. Viscosum*, is reported starting from a D-(−)-pantolactone chiral pool. A one-pot quadruple reaction sequence comprising an enyne ring-closing metathesis/cross-metathesis/Diels−Alder/aromatization for the construction of a target skeleton is the highlight of the present synthesis.

Isofregenedadiol **1** is a tetrahydronaphthalenic diterpenic diol isolated from *Halium Viscosum* (La Fregeneda).[1] This compound's skeleton can be considered as a new kind of rearranged labdane with an aromatized B ring.[2] Although biological activity for this compound was not reported, the related labdanes have shown interesting antibacterial, antifungal, antiprotozoal, and anti-inflammatory activities. The assigned structure and absolute configuration were confirmed through preparation of its diacetate **2** from 7-1abden-3β,15-diol **3** by Marcos et al.[3] An interesting side-chain migration reaction and ring B aromatizations were the key steps in the conversion of labdane **3** to **2** (Figure 1).[3]

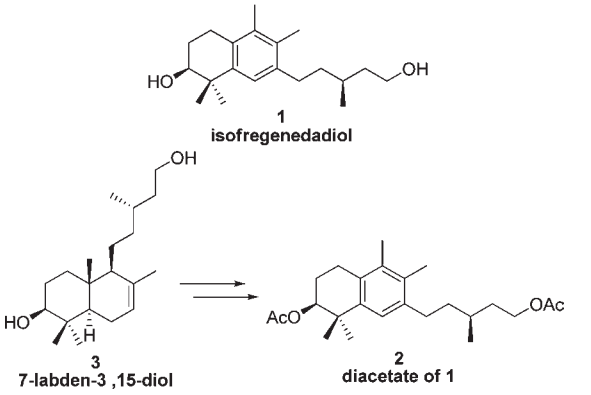


Figure 1. Structures of natural products.

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(4) See previous references from this group where a (−)-pantolactone chiral pool was used in the total synthesis: (a) Reddy, D. S.; Srinivas, G.; Rajesh, B. M.; Kannan, M.; Rajale, T. V.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 6373–6375. (b) Hajare, A.; Datrange, L.; Vyas, S.; Bhuniya, D.; Reddy, D. S. *Tetrahedron Lett.* **2010**, *51*, 5291–5293. (c) Hajare, A.; Ravikumar, V.; Khaleel, S.; Bhuniya, D.; Reddy, D. S. *J. Org. Chem.* **2011**, *76*, 963–966.

(5) Selected references for tandem enyne metathesis/Diels−Alder reactions: (a) Bentz, D.; Laschat, S. *Synthesis* **2000**, *12*, 1766–1773. (b) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Eur. J. Org. Chem.* **2001**, *4*, 787–792. (c) Yang, Y.-K.; Tae, J. *Synlett* **2003**, 2017–2020. (d) Rosillo, M.; Domínguez, G.; Casarrubios, L.; Amador, U.; Pérez-Castells, M. *J. Org. Chem.* **2004**, *69*, 2084–2093. (e) Majumdar, K. C.; Rahaman, H.; Muhuri, S.; Roy, B. *Synlett* **2006**, 466–468. (f) Evanno, L.; Deville, A.; Bodo, B.; Nay, B. *Tetrahedron Lett.* **2007**, *48*, 4331–4333. (g) Ben-Othman, R.; Othman, M.; Coste, S.; Decroix, B. *Tetrahedron* **2008**, *64*, 559–567. (h) Subrahmanyam, A. V.; Palanichamy, K.; Kaliappan, K. P. *Chem.—Eur. J.* **2010**, *16*, 8545–8556.

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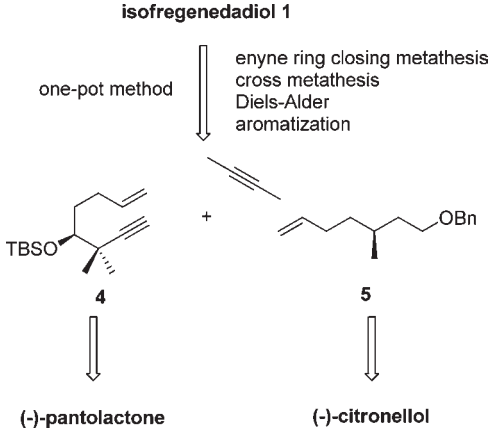
Here, we report the first total synthesis of **1** in an enantiospecific manner starting from D-(−)-pantolactone.[4]

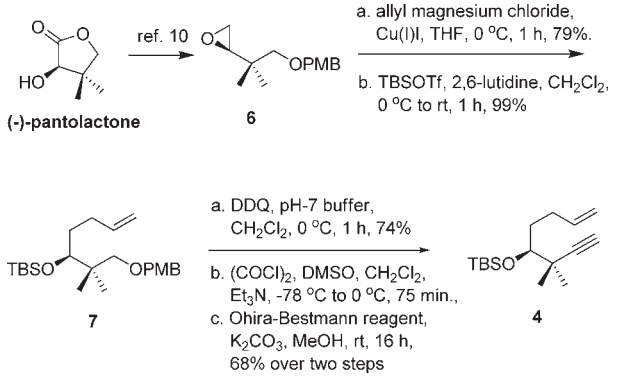
Retrosynthesis is presented in Scheme 1. We envisioned securing the target natural product **1** through a key one-pot quadruple reaction process by combining two metatheses, Diels−Alder and aromatization steps.[5−8] The present four-step one-pot sequence in the synthesis of natural prodcuts is novel. However, tandem enyne metathesis/Diels−Alder have been widely employed in synthesis and the sequence comprising enyne metathesis/cross metathesis/Diels−Alder is less common.[5,6] The synthesis is planned using an appropriate enyne **4**, alkene **5**,[9] and 2-butyne. Enyne **4** and cross-metathesis partner alkene **5** could be prepared from D-(−)-pantolactone and *S*-(−)-citronellol, respectively.

Scheme 1. Retrosynthesis



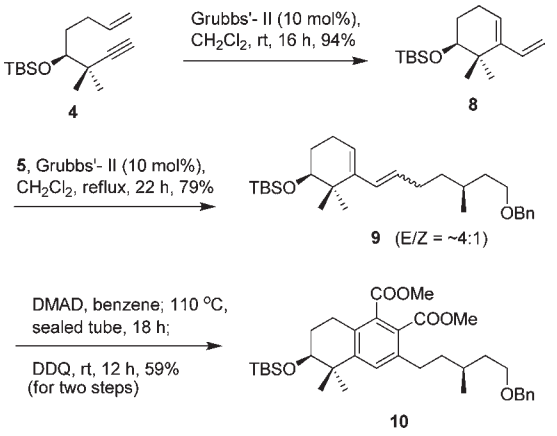
Our synthesis commenced with the preparation of known epoxide **6**[10] from commercially available D-(−)-pantolactone. It was regioselectively opened with an allyl Grignard in the presence of CuI, and the resulting secondary alcohol was protected as TBS ether to furnish compound **7**.[11] Deprotection of the PMB group in **7** and Swern oxidation provided the aldehyde, which was immediately treated with a Bestmann−Ohira reagent[12] to yield the enyne **4** (Scheme 2).

Scheme 2. Synthesis of Key Enyne Precursor **4**



Having the key enyne precursor **4** in hand, initially we have synthesized the isofregenedadiol skeleton in a sequential manner as described in Scheme 3. In the presence of Grubbs' second generation catalyst, enyne **4** underwent RCM to produce diene **8** in 94% yield. The second metathesis (cross) using the same catalyst (5 mol %) and an excess of **5** (∼10 equivalents) under reflux conditions resulted in the desired compound **9**. After a few attempts[13] and replacing 2-butyne with dimethylacetylenedicarboxylate (DMAD), the DA reaction occurred smoothly which was immediately oxidized to **10** in 59% yield over two steps.[14]

Scheme 3. Synthesis of Isofregenedadiol Skeleton through Sequential Method



(6) Selected references for tandem enyne metathesis/cross metathesis/Diels−Alder reactions. (a) Kotha, S.; Halder, S.; Brahmachary, E.; Ganesh, T. *Synlett* **2000**, 853–855. (b) Kotha, S.; Halder, S.; Brahmachary, E. *Tetrahedron* **2002**, *58*, 9203–9208. (c) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439–3442. (d) Park, H.; Hong, Y-L; Kim, Y. B.; Choi, T.-L. *Org. Lett.* **2010**, *12*, 3442–3445.

(7) For selected reviews for synthesis of aromatic compounds using RCM, see: (a) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670. (b) Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743–3782.

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(9) Breitenbach, R.; Chiu, C. K.-F.; Massett, S. S.; Meltz, M.; Murtiashaw, C. W.; Pezzullo, S. L.; Staigers, T. *Tetrahedron: Asymmetry* **1996**, *2*, 435–442.

(10) Brabander, J. D.; Vanhesschet, K.; Vandewalle, M. *Tetrahedron Lett.* **1991**, *32*, 2821–2824.

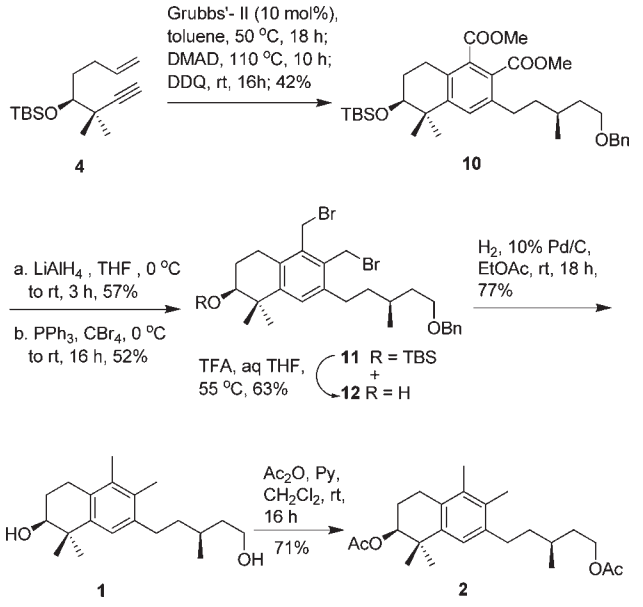
(11) See related references associated with epoxide ring opening reactions: (a) Huynh, C.; Derguini-Boumechal, F.; Linstrumell, G. *Tetrahedron Lett.* **1979**, *17*, 1503–1506. (b) Hirsch, J. A.; Truc, V. C. *J. Org. Chem.* **1986**, *51*, 2218–2227.

(12) Müller, S.; Liepold, B.; Bestmann, H. J. *Synlett* **1996**, 521–522.

(13) Performing the reaction (DA step) with 2-butyne at an elevated temperature in a sealed tube did not produce the desired compound. The low yield in a straightforward DA step with DMAD may be explained by the presence of a *Z*-isomer (∼20% based on NMR); however, we did not recover the unreacted *Z*-isomer.

Having established the scheme in sequential manner, next, we attempted the planned key one-pot quadruple reaction sequence. After a few attempts, one-pot sequence proceeded smoothly to furnish the desired tetrahydronaphthalene derivative **10** in 42% overall yield (Scheme 4). The reaction times are chosen for the addition of subsequent reagents and catalysts based on thin-layer chromatography (tlc) monitoring at each step. In a typical procedure, a mixture of *enyne* **4** (1 mmol) and alkene **5** (8 mmol) was dissolved in toluene, degassed for 10 min in a stream of argon, and then treated with 9 mol % of Grubbs' second generation catalyst in one portion. After being stirred at 50 °C for 12 h, additional amounts of alkene **5** (2 mmol) and catalyst (1 mol %) were added and stirring was continued for 6 h at 50 °C. At this stage, DMAD (2 mmol) was added to the reaction mixture, heated at 110 °C for 10 h, and cooled to room temperature, and DDQ (1.2 mmol) was added and stirring continued at room temperature for 16 h. The reaction mixture was filtered through a plug of Celite pad and washed with dichloromethane. The crude product obtained after the evaporation of solvent was purified by silica gel column chromatography to furnish the desired compound **10** in 42% yield.[15] The diester **10** was transformed to the natural product isofregenedadiol **1** by using $LiAlH_4$ reduction, conversion of the diol to dibromide,[16] and deprotection of the benzyl group (Scheme 4). The spectral data of synthetic isofregenedadiol **1** were compared with those of the natural product and found to be identical. In addition, we have

Scheme 4. Synthesis of Isofregenedadiol and Its Diacetate through One-Pot Quadruple Reaction Process



confirmed the assigned structure without any ambiguity with the help of single crystal X-ray analysis (ORTEP diagram is shown in Figure 2). However, no optical rotation of diol **1** was reported in the literature. To further confirm its absolute configuration, we have prepared the corresponding diacetate **2** and compared the optical rotation with the reported value in the literature.[1]

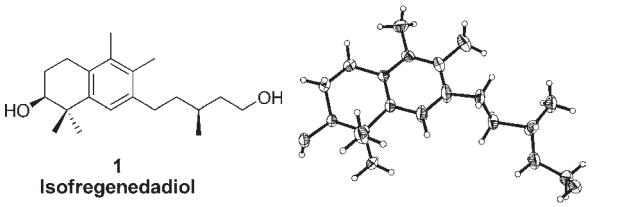
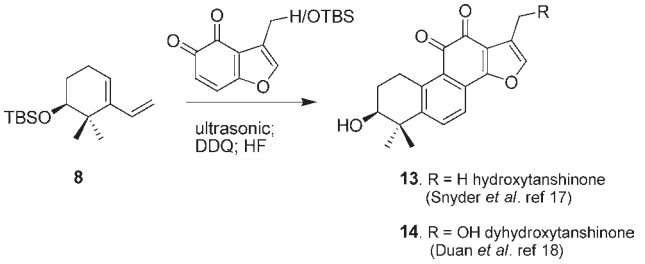


Figure 2. ORTEP diagram of the synthetic isofregenedadiol.

During this process, we have prepared a known intermediate diene **8** as a bonus (Scheme 3). The spectral data (^1H and ^{13}C NMR) of the diene **8** was compared with that of **8** from Snyder's group,[17] and both were found to be identical. Previously, this diene **8** was converted to 3(*S*)-hydroxytanshinone **13** and 3(*S*),17-dihydroxytanshinone **14** through an ultrasound-promoted Diels–Alder cycloaddition with corresponding *o*-quinones followed by removal of the TBS group (Scheme 5).[17,18] Hence our effort can be regarded as formal syntheses of 3(*S*)-dihydroxytanshinone[17] and 3(*S*),17-dihydroxytanshinones.[18] It is noteworthy to mention that the same diene **8** was prepared in racemic form by Marsaioli et al. and utilized for the synthesis of rearranged unsaturated drimane derivatives.[19]

Scheme 5. Formal Synthesis of 3(*S*)-Hydroxytanshinone and 3(*S*),17-Dihydroxytanshinone



In short, we have described the first total synthesis of isofregenedadiol **1**, a bicyclic diterpene using a one-pot

(14) As our main focus is on a tandem one-pot process, we did not attempt further optimization of the scheme at this stage.

(15) The analytical data (^1H, ^{13}C, IR, and MS) of all the products are in good agreement with the proposed structures. Copies of spectra are provided in the Supporting Information.

(16) During the conversion of primary alcohols to corresponding bromides using CBr_4/PPh_3, alcohol **12** was obtained as a major product through deprotection of the OTBS group. See related references: Lee, A. S.-Y.; Yeh, H.-C.; Shie, J.-J. *Tetrahedron Lett.* **1998**, *39*, 5249–5252. Yadav, J. S.; Mishra, R. K. *Tetrahedron Lett.* **2002**, *43*, 5419–5422. The minor product TBS ether **11** converted to **12** by using TFA in aq. THF.

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(18) Zhang, J.; Duan, W.; Cai, J. *Tetrahedron* **2004**, *60*, 1665–1669.

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quadruple reaction sequence. In addition, formal syntheses of two biologically interesting natural products 3(*S*)-hydroxytanshinone **13** and 3(*S*),17-dihydroxytanshinone **14** are claimed through a common intermediate diene **8**.

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Supporting Information Available. Experimental procedures, copies of spectra and spectroscopic data for all new compounds. CIF file of the X-ray crystal structure analysis of isofregenedadiol **1**. This material is available free of charge via the Internet at http://pubs.acs.org.