OL Organic Letters

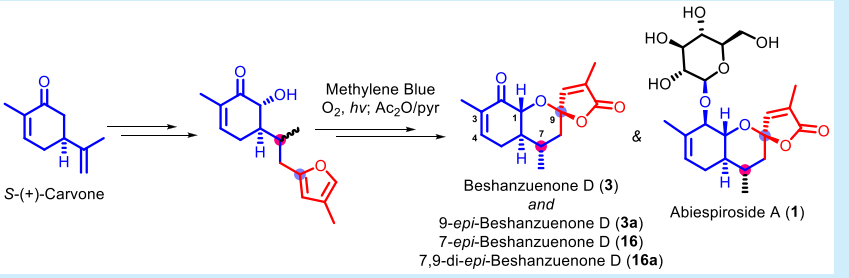
pubs.acs.org/OrgLett Letter

Total Synthesis of Beshanzuenone D and Its Epimers and Abiespiroside A

Balasaheb R. Borade, Ruchi Dixit, and Ravindar Kontham*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03157 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A unified and protecting-group-free six-step total synthesis of bisabolane-type sesquiterpenoid beshanzuenone D and its stereoisomers and abiespiroside A using *S*-(+)-carvone as a common chiral-pool building block is disclosed. This synthetic route features chemoselective allylic chlorination of carvone, Au(I)-catalyzed cycloisomerization induced construction of furan from homopropargylic diol, substrate-controlled selective hydroxylation using Davis-oxaziridine, and dye-sensitized photo-oxidation (through $^1O_2$) of hydroxyalkyl tethered furan to access oxaspirolactone as key transformations. A comprehensive set of NMR data along with DFT calculations, ECD spectra, and optical rotation measurements of the synthesized beshanzuenone D and its epimers were obtained to confirm absolute configurations.

Sesquiterpenoids are a class of immensely diverse natural products emerged from 15-carbon precursors, and they continue to play a remarkable role in synthetic organic chemistry, medicinal chemistry, and drug discovery owing to their broad range of biological activities and diverse structural features.[1] These C-15 sesquiterpenes undergo regio- and stereoselective oxygenation with the aid of P450s (cytochrome P450 monooxygenases), widely present in bacteria, fungi, and plants, and generate diverse natural products with a wide range of biological profile.[2] Inspired by traditional Chinese medicinal applications of plants, in 2010, Zhang and co-workers reported the isolation of abiespiroside A (**1**), an unprecedented oxaspirolactone sesquiterpenoid possessing a 6/6/5 ring system from *Abies delavayi* Franch., trees in the highlands (3300−4000 m high) of the northwest of the Yunnan and southeast of the Tibet provinces of China. They also disclosed its inhibitory properties against LPS-induced NO production in RAW264.7 macrophages, an important therapeutic effect for numerous inflammatory diseases.[3]

Later, in 2016, Hu's research group disclosed the isolation of beshanzuenone C (**2**) and beshanzuenone D (**3**) (oxidized aglycons of abiespiroside A (**1**)) from the shed trunk barks of the plant *Abies beshanzuensis*, which is regarded as one of the 12 critically endangered plant species in the world by the Species Survival Communication (SSC) of the International Union for Conservation of Natural Resources (IUCN) since 1987;[4,5] further, natural products **2** and **3** were assessed for their biological profile and found to significantly inhibit PTP1B (a key target for type-II diabetes and obesity therapy) with IC_{50} values of 16.6 and 10.6 μg/mL, respectively. The structural similarity and identical stereochemical features reveal the close biogenetic relationship between sesquiterpenoids **1**, **2**, and **3** (Figure 1).

Recently, in 2018, the Dai, Adibekian, and Zhang research groups disclosed[6] an elegant synthetic approach for abiespiro-

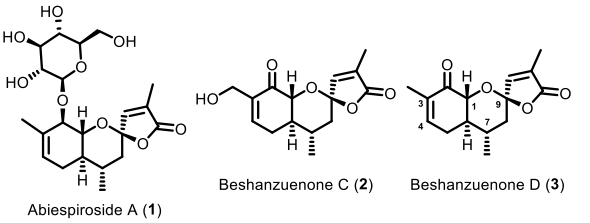


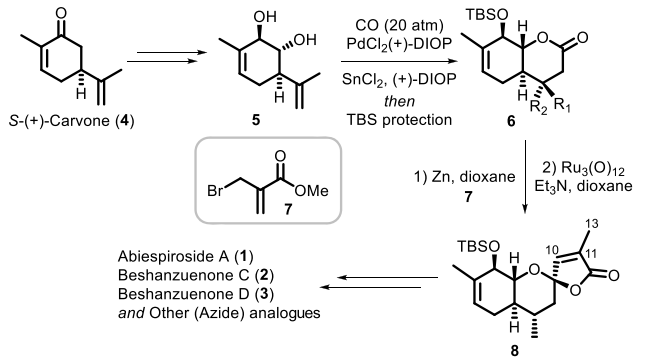
Figure 1. Chemical structures of abiespiroside A (**1**), beshanzuenone C (**2**), and beshanzuenone D (**3**)

Received: September 19, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03157
Org. Lett. XXXX, XXX, XXX−XXX

side A, beshanzueone C and D, and structurally close congeners using their in-house developed Pd-catalyzed hydrocarbonylative lactonization to install the 6/6 fused bicyclic lactone **6** from diol **5** (prepared from *S*-(+)-carvone (**4**)) and the Dreiding–Schmidt reaction employing bromo-ester **7** to construct the 6/5-oxaspirolactone moiety, followed by $Ru_3(CO)_{12}$-mediated *exo* ($\Delta^{11,13}$) to *endo* ($\Delta^{10,11}$) olefin isomerization to deliver advanced intermediate **8** as key steps (Scheme 1). Further, they synthesized and identified an

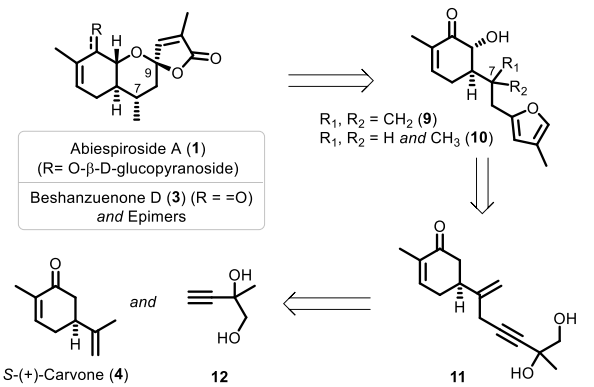
Scheme 1. Previous Synthesis of *Abies* Sesquiterpenoids



analogue as the first covalent and selective SHP2 (Src homology region 2-containing protein tyrosine phosphatase (PTP) 2; a known oncogenic driver) inhibitor, in addition to potential PTP inhibitory activities, with POLE3 (DNA polymerase epsilon subunit 3) identified as one of the cellular targets for these scaffolds with the aid of chemoproteomic studies (Scheme 1).[6] Further to this elegant example of total synthesis, there is an urgent need to develop concise, facile, and practical synthetic routes for these natural products to access in sufficient quantities to carry out comprehensive pharmacological investigations.

In continuation of our interest in the chemistry of oxaspirolactones[7] and total syntheses of biologically active natural products,[8] we embarked on the synthesis of abiespiroside A (**1**) and beshanzuenone D (**3**). In a retrosynthetic analysis (depicted in Scheme 2), we envisioned an approach to access **1**, **3**, and its stereoisomers through dye-sensitized photooxidation-mediated oxaspirolactone construction from hydroxy-cyclohexenone tethered furan precursor **9** or **10** (here, the nascent stereochemistry at C7 and C9 of **1** or **3** would be determined principally by the pre-existing stereocenters on the

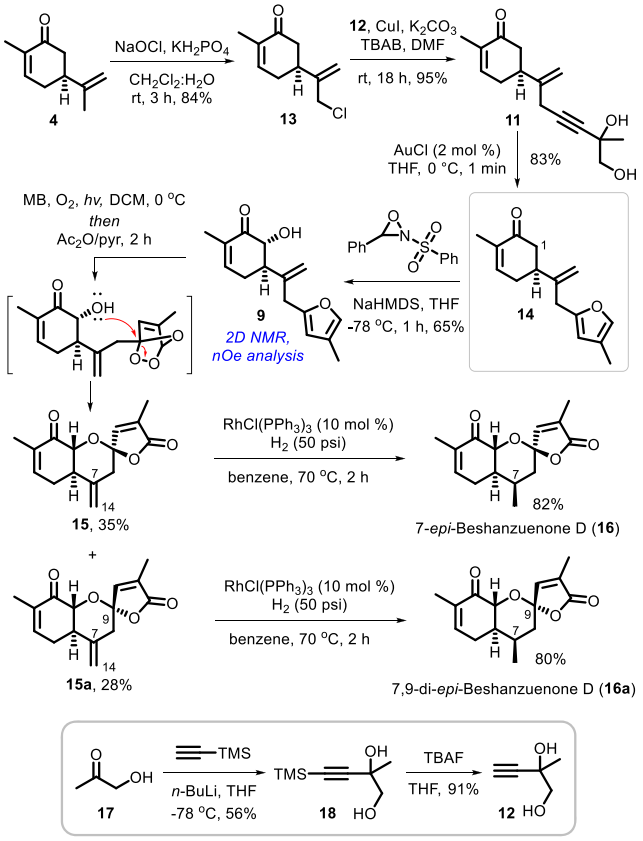
Scheme 2. Retrosynthetic Analysis of *Abies* Sesquiterpenoids 1 and 3 and Epimers



substrates **9** or **10**). Next, the furan intermediate **9** or **10** possessing a methylene or methyl substituent at C7, respectively (beshanzuenone D numbering),[4] would be prepared from propargylic diol **11** through Au-catalyzed dehydrative cycloisomerization. Propargylic diol **11** could readily be synthesized from chiral-pool building block *S*-(+)-carvone (**4**) and known alkyne-diol **12** utilizing an interesting classical sequence of reactions (Scheme 2).

With the general retrosynthetic analysis in hand, we began our study with the synthesis of furan intermediate **14**, which contains a complete carbon skeleton of target natural products **1** and **3** (Scheme 3). Thus, our synthetic efforts were

Scheme 3. Initial Attempt for the Synthesis of *Abies* Sesquiterpenoids



commenced from natural chiral-pool building block *S*-(+)-carvone (**4**), which was subjected to chemoselective allylic chlorination using NaClO and KH_2PO_4 to give intermediate **13** in 84% yield.[9] Subsequent Cu(I)-catalyzed coupling[10] of **13** with propargylic diol **12** (prepared from hydroxyacetone **17** in two steps via **18**)[11] cleanly furnished diol **11** in 95% yield. Next, AuCl-catalyzed dehydrative cycloisomerization of alkyne diol **11** delivered 1,3-disubstituted furan **14** in a good yield of 83% under open-flask conditions.[12] The next task was to introduce the α-hydroxyl functionality at the C1 position of intermediate **14** in which the Davis-oxaziridine[13]-mediated hydroxylation was found to be fruitful and furnished **9** in 65% yield with good diastereoselectivity (*dr*, 9:1; assigned based on 2D NMR and NOE analysis) (Scheme 3).[14]

With a good quantity of furan intermediate **9** in hand, we have proceeded for the construction of 6/6/5 oxaspirolactone precursor **15** or **15a** (Scheme 3). In view of the sensitivity of the α-hydroxyl functionality of **9**, nearly neutral reaction

https://dx.doi.org/10.1021/acs.orglett.0c03157
Org. Lett. XXXX, XXX, XXX–XXX

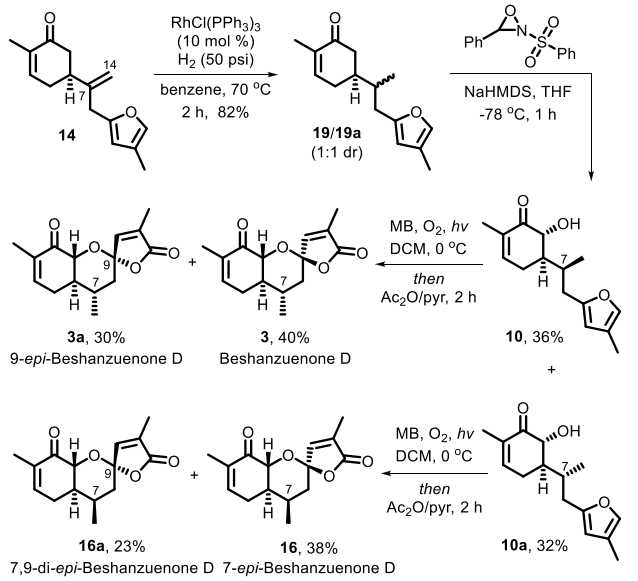
conditions of Mitsunobu's and Vassilikogiannakis's dye-sensitized photo-oxidation of furan were chosen for this endeavor that was known to proceed through [4 + 2]-cycloaddition of singlet oxygen with furan and intramolecular opening of the adduct with the hydroxyl functionality followed by subsequent lactol oxidation steps.[15] Accordingly, hydroxyalkyl furan **9** was treated with methylene blue (MB), oxygen (balloon pressure), and *hv* (visible light, 200 W bulb) followed by Ac_2O in pyridine to get oxaspirolactone **15** and its C9-epimer **15a** in 35 and 28% isolated yield, respectively. We then move forward to the challenging chemoselective $\Delta^{7,14}$ reduction of **15** and **15a** precursors; thus, initially **15** was subjected to hydrogenation using various catalysts (Pd/C, $Pd(OH)_2$/C, and Pt/C) and solvent systems, which resulted in a complex mixture due to nonselective reaction pathways. To our surprise, Wilkinson's reduction[16] of **15** and **15a** using $RhCl(PPh_3)_3$ and H_2 (50 psi) in benzene at 70 °C showed great selectivity but delivered undesired stereoisomeric products 7-*epi*-beshanzuenone D (**16**) and 7,9-di-*epi*-beshanzuenone D (**16a**) in 82 and 80% yield, respectively. This stereochemical outcome could be due to the steric influenced convex facial (α-face) attack of the hydrogenation catalytic system onto the **15** or **15a** (Scheme 3).[14]

Having obtained the undesired (inverse) stereochemistry at the C7-Me group of **16** and **16a**, we decided to slightly alter the synthetic sequence by the reduction of the $\Delta^{7,14}$ at the stage of intermediate **14** instead of advanced tricyclic intermediate **15** and **15a**, that could avoid the restricted single α-facial reduction. Thus, intermediate **14** was reduced using Wilkinson's catalyst under identical conditions employed in Scheme 3, which furnished C7-diastereomers **19** and **19a** in 82% yield as an inseparable mixture. Subsequent α-hydroxylation of the mixture using Davis-oxaziridine delivered diastereomers **10** (36%) and **10a** (32%) with complete substrate controlled stereoselection, which were separated successfully through conventional silica-gel (SiO_2) column chromatography. Next, intermediate **10** was subjected to a photo-oxidation reaction, which delivered beshanzuenone D (**3**) and 9-*epi*-beshanzuenone D (**3a**) in 40 and 30% yield, respectively, whereas precursor **10a** delivered 7-*epi*-beshanzuenone D (**16**) and 7,9-di-*epi*-beshanzuenone D (**16a**) in 38 and 23% yield, respectively. The predominant formation of spiro-epimers **3** and **16** (possessing the β-orientation of lactone ring oxygen) over **3a** and **16a** could be attributed to the stabilization of the oxaspirolactone through an anomeric effect.[17]

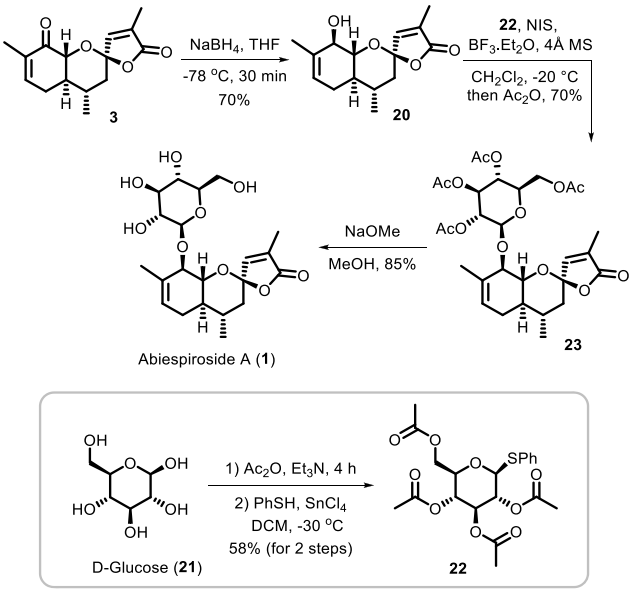
Having successfully completed the synthesis of bashanzuenone D and its epimers (Schemes 3 and 4), we extended our work to access abiespiroside A (**1**) (the β-D-glucopyranoside derivative of beshanzuenone D (**3**)) using a similar strategy to that reported by Davis et al.[6] The selective carbonyl reduction of **3** using $NaBH_4$ in THF at −78 °C gave the hydroxyl intermediate **20** as a single diastereomer. Next, the selective β-glycosylation of alcohol **20** was performed using NIS, BF_3·Et_2O, and known thioglycoside donor **22** (prepared from D-glucose (**21**) in two steps with 58% isolated yield) to furnish the tetra-acetylated glycoside **23** in 70% yield. The global deprotection of acetate groups of **23** using NaOMe in MeOH delivered abiespiroside A (**1**) in 85% yield (Scheme 5).

In order to establish the absolute configurations of **3** and its epimers (**3a**, **16**, and **16a**), initially (+)-beshanzuenone D (**3**) was confirmed through the comparison of ^1H and ^{13}C NMR, HRMS, and optical rotation data with the reported

Scheme 4. Synthesis of Beshanzuenone D (3) and Its Isomers (3a, 16, and 16a)



Scheme 5. Formal Synthesis of Abiespiroside A (1)



literature.[4,6] Furthermore, the ECD spectral (MeOH) data (c = 2.3 × 10^{-3} M (MeOH)) of **3** were also in agreement with that reported in the literature.[4] Interestingly, the ECD spectra of epimer (+)-**16** (possessing the β-orientation of lactone oxygen) show a high degree of similarity with the ECD spectra of **3**, whereas analogues **3a** and **16a** (having the α-orientation of lactone oxygen) displayed distinct ECD curves compared to **3** and **16**, which clearly demonstrates the relation between the stereochemistry at the spiro-center (C9) and ECD absorption (Figure 2).[14]

This unambiguous establishment of the structure of beshanzuenone D (**3**) and the synthetic sequence followed and in turn provided the information about the absolute stereochemistry at C7 of **10**, **10a**, and **3a** (Scheme 4).[14] Consequently, the second congener obtained from intermediate **10** was assigned as 9-*epi*-beshanzuenone D (**3a**) (Scheme 4).[14] The next crucial task was to establish the stereochemistry

https://dx.doi.org/10.1021/acs.orglett.0c03157
Org. Lett. XXXX, XXX, XXX−XXX

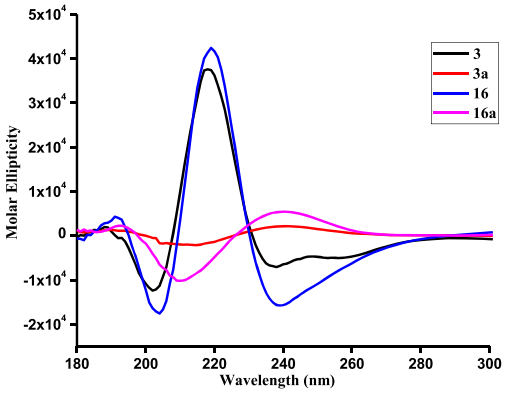


Figure 2. ECD (circular dichroism) spectra (MeOH) of (+)-beshanzuenone D (**3**), (+)-**3a**, (+)-**16**, and (+)-**16a**

at C9 (the spiro stereocenter) of epimers **3a**, **16**, and **16a**. To solve this puzzle, low-energy conformations of **3**, **3a**, **16** and **16a**, and distances between H-1 and ring-C oxygen were obtained through DFT calculations, and in silico chemical shift values for H-1 were further calculated at B3LYP/6-31 level of theory using the GIAO method, which might provide insight into the stereochemical orientation of the lactone ring oxygen (Figure 3).

When the terminal oxygen of the ring-C is β-configured (in **3**), H-1 is in close proximity (2.71 Å) to it and showed δ 4.43 ppm (calcd δ 4.56 ppm) (entry A, Figure 2), whereas, in the spiro-epimer **3a**, ring-C oxygen is in the α-configuration and away from H-1 (3.99 Å); hence, H-1 showed an upfield signal at δ 4.08 ppm (calcd δ 4.29 ppm) (entry B, Figure 2). A similar

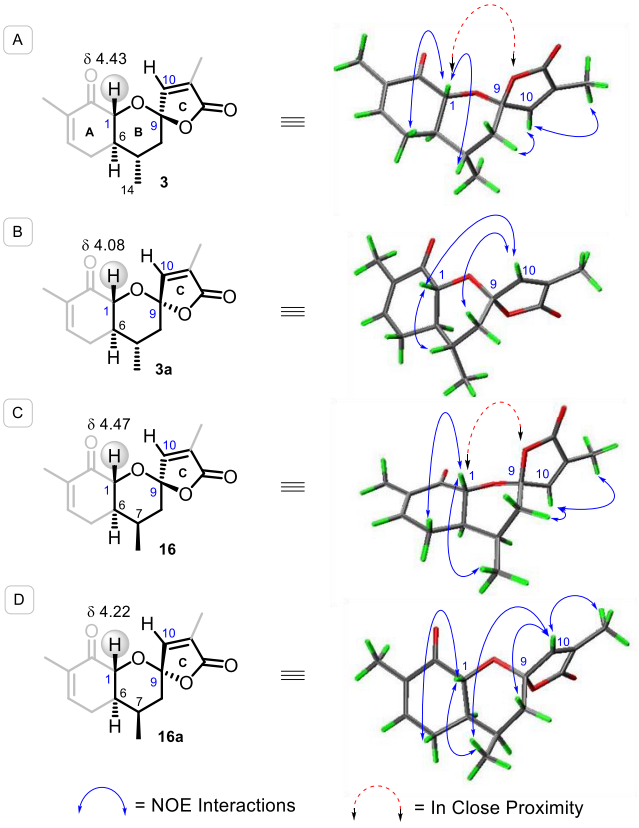


Figure 3. Low energy conformations of **3**, **3a**, **16**, and **16a**; NOE interactions; and NMR analysis.

phenomenon has been noticed for **16** (H-1 showed a downfield signal at δ 4.47 ppm (calcd δ 4.56 ppm) due to the β orientation of ring-C oxygen (entry C, Figure 2)) and **16a** (H-1 showed an upfield signal at δ 4.22 ppm (calcd δ 4.37 ppm) due to the α orientation of ring-C oxygen (entry D, Figure 2)). These downfield changes in chemical shifts are due to the deshielding effect of the nearby electronegative ring-C oxygen atom.[14,20] These observations are in close accordance with that reported for the structural assignment of ritterazines[18] and hippuristanol[8b,19] epimers (Figure 2).[20] These conclusions were further supported by key NOESY correlations of H-1/H-7 and H-8α/H-10 in compound **3**; H-1/H-10, H-1/H-7, and H-8β/H-10 in compound **3a**; H-1/Me-14 and H-8α/H-10 in compound **16**; and H-1/Me-14 and H-8β/H-10 in compound **16a** (Figure 3).[14]

In conclusion, an efficient and unified synthesis of beshanzuenone D and its three epimers has been accomplished from a chiral pool building block *S*-(+)-carvone. This protecting-group-free synthetic route is highly concise with six linear transformations and an overall yield of 7.82, 5.86, 9.64, and 12.35% obtained for **3**, **3a**, **16**, and **16a**, respectively. Furthermore, formal total synthesis of abiespiroside A was also accomplished in a total number of nine steps. This synthetic route would facilitate access to diverse analogues via changing the readily accessible alkyne diol coupling partner (**12**), which in turn generates the library of the furan precursor of the oxaspirolactone skeleton and could help in SAR studies. Absolute configurations of beshanzuenone D (**3**) and its epimers (**3a**, **16**, and **16a**) were established using extensive NMR data, ECD measurements, and DFT calculations. These investigations can assist in the determination of absolute stereochemistry in future isolated natural compounds of this type. The biological activity evaluation of all of these epimers and intermediates is under progress, and the results will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03157.

Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ravindar Kontham − *Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0002-5837-2777; Email: k.ravindar@ncl.res.in, konthamravindar@gmail.com

Authors

Balasaheb R. Borade − *Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Ruchi Dixit − *Physical and Material Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Complete contact information is available at:

https://dx.doi.org/10.1021/acs.orglett.0c03157
Org. Lett. XXXX, XXX, XXX−XXX

https://pubs.acs.org/10.1021/acs.orglett.0c03157

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from CSIR-New Delhi, India (INPROTICS-Pharma and Agro; HCP0011/No.9/1/CS/CIA/2017-MD), is gratefully acknowledged. B.R.B. thanks UGC-India for the award of Senior Research Fellowship (SRF). We thank Dr. Udaya Kiran Marelli, CSIR-NCL, Pune, for 2D NMR support and Prof. H. N. Gopi, IISER-Pune, for ECD analyses.

■ REFERENCES

(1) (a) Degenhardt, J.; Köllner, T. G.; Gershenzon, J. *Phytochemistry* **2009**, *70*, 1621−1637. (b) Ludwiczuk, A.; Skalicka-Wozniak, K.; Georgiev. *Pharmacognosy* **2017**, 233−266. (c) Fraga, B. M. *Nat. Prod. Rep.* **2006**, *23*, 943−972.
(2) Munro, A. W.; Girvan, H. M.; McLean, K. J. *Biochim. Biophys. Acta, Gen. Subj.* **2007**, *1770*, 345−359.
(3) Yang, X.-W.; Li, S.-M.; Li, Y.-L.; Xia, J.-H.; Wu, L.; Shen, Y.-H.; Tian, J.-M.; Wang, N.; Liu, Y.; Zhang, W.-D. *Eur. J. Org. Chem.* **2010**, *2010*, 6531−6534.
(4) Hu, C.-L.; Xiong, J.; Li, J.-Y.; Gao, L.-X.; Wang, W.-X.; Cheng, K.-J.; Yang, G.-X.; Li, J.; Hu, J.-F. *Eur. J. Org. Chem.* **2016**, *2016*, 1832−1835.
(5) (a) Shao, S.; Jin, Z.; Weng, Y. H. *J. Wood Sci.* **2008**, *54*, 81−86.
(6) Davis, D. C.; Hoch, D. G.; Wu, L.; Abegg, D.; Martin, B. S.; Zhang, Z. Y.; Adibekian, A.; Dai, M. *J. Am. Chem. Soc.* **2018**, *140*, 17465−17473.
(7) (a) Thorat, S. S.; Kontham, R. *Org. Biomol. Chem.* **2019**, *17*, 7270−7292. (b) Kambale, D. A.; Thorat, S. S.; Pratapure, M. S.; Gonnade, R. G.; Kontham, R. *Chem. Commun.* **2017**, *53*, 6641−6644.
(8) (a) Thorat, S. S.; Palange, M. N.; Kontham, R. *ACS Omega* **2018**, *3*, 7036−7045. (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem.* **2011**, *76*, 1269−1284. (c) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420−4423.
(9) (a) Zhang, W.; Yao, H.; Yu, J.; Zhang, Z.; Tong, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 4787−4791. (b) Huang, J.; Yang, J. R.; Zhang, J.; Yang, J. *J. Am. Chem. Soc.* **2012**, *134*, 8806−8809.
(10) Joung, S.; Kim, R.; Lee, H. Y. *Org. Lett.* **2017**, *19*, 3903−3906.
(11) Paioti, P. H. S.; Abboud, K. A.; Aponick, A. *ACS Catal.* **2017**, *7*, 2133−2138.
(12) Aponick, A.; Li, C. Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624−4627.
(13) (a) Davis, F. A. *Tetrahedron* **2018**, *74*, 3198−3214. (b) Davis, F. A.; Nadir, U. K.; Kluger, E. W. *J. Chem. Soc., Chem. Commun.* **1977**, *41*, 25−26.
(14) See the Supporting Information for details.
(15) (a) Pavlakos, E.; Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 4556−4559. (b) Fukuda, H.; Takeda, M.; Sato, Y.; Mitsunobu, O. *Synthesis* **1979**, *1979*, 368−370.
(16) (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711. (b) Hussey, A. S.; Takeuchi, Y. *J. Am. Chem. Soc.* **1969**, *91*, 672−675.
(17) (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661. (b) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406−4440.
(18) Phillips, S. T.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6589−6598.
(19) Li, W.; Dang, Y.; Liu, J. O.; Yu, B. *Chem. - Eur. J.* **2009**, *15*, 10356−10359.
(20) Low energy conformations of **3**, **3a**, **16**, and **16a** calculated with DFT at the PBE/TZVP level of theory.

https://dx.doi.org/10.1021/acs.orglett.0c03157
Org. Lett. XXXX, XXX, XXX−XXX