Organic LETTERS

Letter

pubs.acs.org/OrgLett

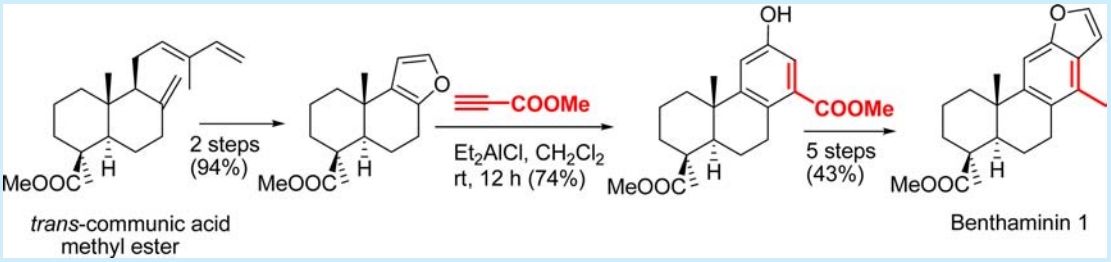
Short Route to Cassane-Type Diterpenoids: Synthesis of the Supposed Structure of Benthaminin 1

Soumicha Mahdjour,[†] Meriem Harche-Kaid,[†] Alí Haidour,[‡] Rachid Chahboun,*[,‡] and Enrique Alvarez-Manzaneda*[,‡]

[†]Laboratory Productions, Plant and Microbial Valuations (LP2VM), Department of Biotechnology, University of Sciences and Technology of Oran Mohamed Boudiaf, BP 1525, EL M'Naouer, Oran, Algeria

[‡]Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain

Supporting Information



ABSTRACT: A short route toward aromatic cassane diterpenes from labdane terpenoids has been developed. In the key step, the aromatic ring with the oxygenated function at C-12 and the characteristic carbon group at C-14 of the target compounds is elaborated via a Diels–Alder/aromatization sequence of a furanosesquiterpene and methyl propiolate. On this basis, the synthesis of the proposed structure of benthaminin 1 from *trans*-communic acid has been achieved. The physical properties of the synthetic compound are somewhat different from those reported for the natural product.

Cassane diterpenes are a group of metabolites that have been isolated in recent years from different species of medicinal plants belonging to the *Caeselpinia* genus, which have aroused great interest because of their biological activity.[1] This family of terpenoids comprises a large number of compounds with a wide structural diversity. Among these compounds, the significant properties of some of those bearing an aromatic C ring have attracted particular attention. Researchers have isolated compounds with a fused furan ring, such as caesalpin D (**1**), which exhibit selective cytotoxic activities against MCF and AGS human cancer cells,[2] the hydroxyfuran **2**, with a potent anti-inflammatory activity,[3] caesaldekarin J (**3**),[4] antibacterial benthaminin 1 (**4**)[5] and benthaminin 3 (**5**),[6] taepeenin D (**6**), with significant Hh/Gli-mediated transcription inhibitory activity and selective cytotoxicity against cancer cells with increased Hh signaling levels, and related compounds (**7**–**10**).[7] In addition, diterpenes with a γ-lactone group, such as taepeenin F (**11**)[7a] and swartziarboreol E (**12**),[8] and a δ-lactone ring, such as antifungal **13**–**16**,[9] have been isolated (Figure 1).

Nevertheless, despite the evident interest in this type of compound, to date, no reports of its synthesis have been published. At first sight, abietic acid (**17**) seems to be an attractive starting material for synthesizing these interesting diterpenes because of its commercial availability, low price, and chemical versatility. This acid has been transformed into terpenes functionalized at C-19;[10] moreover, the carboxylic group on C-4 enables the preparation of terpenoids functionalized on the A ring.[11] Furthermore, B ring functionalization can be easily

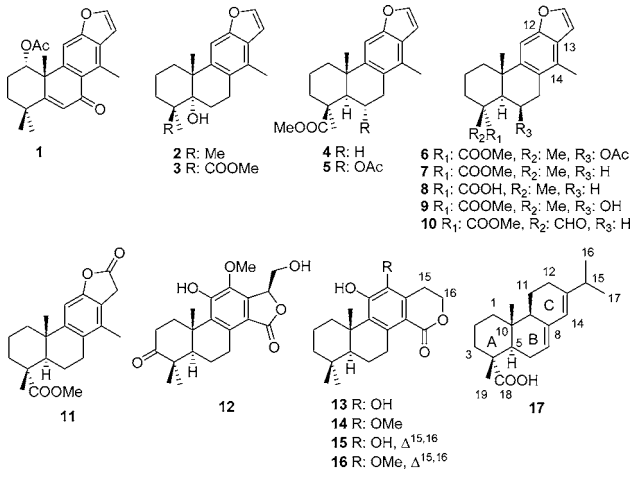


Figure 1. Some aromatic cassane-type diterpenes (**1**–**16**).

achieved after the benzylic oxidation of the corresponding dehydro derivative, dehydroabietic acid.[10,12] The transformation of acid **17** into cassane diterpenes requires appropriate functionalization on the C ring, via electrophilic aromatic substitution of the corresponding dehydroabietic acid derivative. Substitution at C-12 takes place easily.[12b,c,13] In addition,

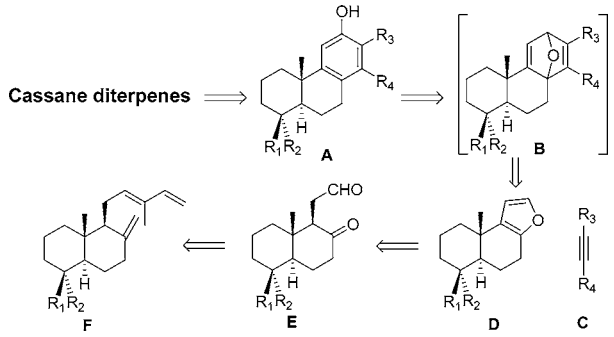
Received: October 20, 2016
Published: November 9, 2016

DOI: 10.1021/acs.orglett.6b03121
Org. Lett. 2016, 18, 5964–5967

deisopropylation under Friedel−Crafts conditions involving *ipso*-substitution at C-13 has been reported;[14] however, substitution at C-14 to introduce the methyl or lactone group characteristic of cassane diterpenes is an arduous task. Recently, Pitsinos et al., as a part of a program to prepare taepeenin D (**6**) and related compounds to explore their medicinal potential, developed a synthetic route from **17**; however, these authors obtained the corresponding 14-demethyl derivative, probably due to the difficulties described above.[15]

Continuing our research into the preparation of bioactive natural products, we focused on the synthesis of cassane-type diterpenes, such as compounds **1**−**16**, from other natural terpenes. To this end, our main objective is to introduce a carbon function at C-14. Scheme 1 shows the planned retrosynthesis.

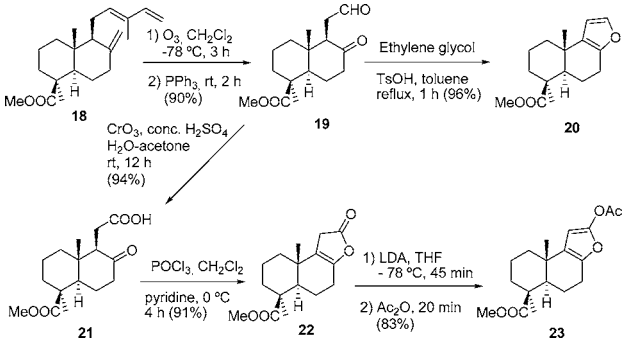
Scheme 1. Retrosynthesis



Phenol **A**, the precursor of the target compounds, is formed after the oxanorbornadiene aromatization of adduct **B**[16] resulting from the Diels−Alder cycloaddition of furanosesquiterpene **D**, which is easily prepared from the labdane diterpene **F**, via ketoaldehyde **E**. A suitable precursor of cassane diterpenes could be prepared utilizing an alkyne **C**, in which R_4 is a carbon group or R_3 is an ester group. In the latter case, the carbon function could be introduced at C-14 after the C−H functionalization *ortho* to the carboxylic acid derived from ester.[17]

The first step was to address the preparation of furanosesquiterpene D. Scheme 2 shows how furans **20** and **23** were obtained from methyl ester **18**, derived from *trans*-communic acid.[18] Ozonolysis of ester **18** gave keto aldehyde **19**, which after treatment with Jones reagent led to keto acid **21**. Reaction of the latter with $POCl_3$ in dichloromethane afforded lactone **22**, which after being treated with LDA and acetic anhydride gave compound **23**. Furanosesquiterpene **20** was obtained from

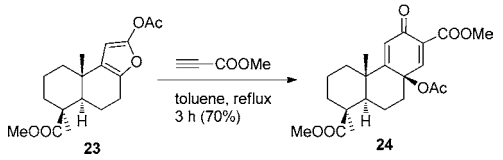
Scheme 2. Syntheses of Furanosesquiterpenes 20 and 23 from Methyl *trans*-Communate (18)



keto aldehyde **19** after a modification of the procedure reported by Imamura et al.,[19] who obtained a diastereoisomer of this compound in low yield after treatment with *p*-toluenesulfonic acid of a keto aldehyde diastereoisomer of **19**, prepared from (−)-*trans*-ozic acid. The low yield of the reported cyclization can be attributed to the instability of this type of keto aldehyde, but it is considerably improved in the presence of ethylene glycol.

Next, the Diels−Alder cycloaddition of furanosesquiterpenes **20** and **23** with methyl propiolate was considered. The substituted furan **23** was expected to undergo regioselective cycloaddition, affording as the major product an *o*-hydroxyester (phenol **A** with R_3 = COOMe and R_4 = H). However, when furan **23** was treated with methyl propiolate in toluene under reflux, the *β*-ketoester **24** was obtained as the sole product (Scheme 3).

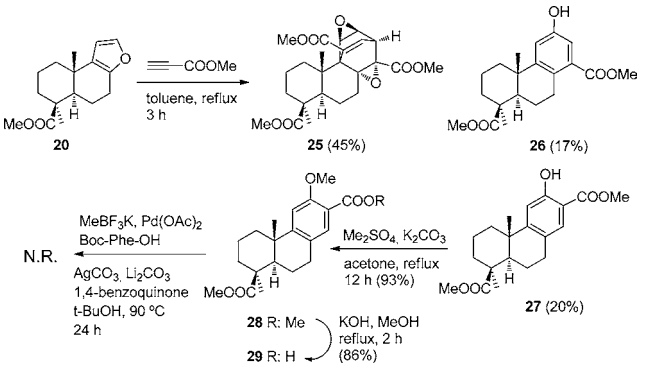
Scheme 3. Diels−Alder Cycloaddition of Furan 23 and Methyl Propiolate



This compound, which could result after the acetyloxy group rearrangement in the intermediate cycloadduct, has a great structural similarity with some abietane hydroxy dienones found in nature, of which it could be a suitable synthetic precursor.[20]

The behavior of furan **20** with methyl propiolate was then investigated. Under the same reaction conditions utilized with the acetoxyfuran **23**, furan **20** afforded a mixture of compounds: the polyoxygenated adduct **25** and the two expected regioisomers hydroxyesters **26** and **27** in an approximate 2.8:1.0:1.2 ratio (Scheme 4).

Scheme 4. Diels−Alder Cycloaddition of Furan 20 and Methyl Propiolate



The structure of compounds **25** and **26** was established on the basis of 1D and 2D NMR experiments (TOCSY, HSQC, HMBC, and NOESY) at 600 and 500 MHz, respectively. X-ray diffraction of hydroxyester **26** was also performed, confirming the *trans* A/B fusion. Ester **27** was investigated as a possible intermediate in the synthesis of cassane diterpenes. To this end, it is transformed into methoxy acid **29**, and this was subjected to the C−H functionalization *ortho* to the carboxylic acid. However, the treatment of *o*-methoxy acid **29** with $MeBF_3K$ in the presence of catalytic $Pd(OAc)_2$ failed to give the desired 14-methyl derivative.[17] Hydroxyester **27** is a precursor of abietane

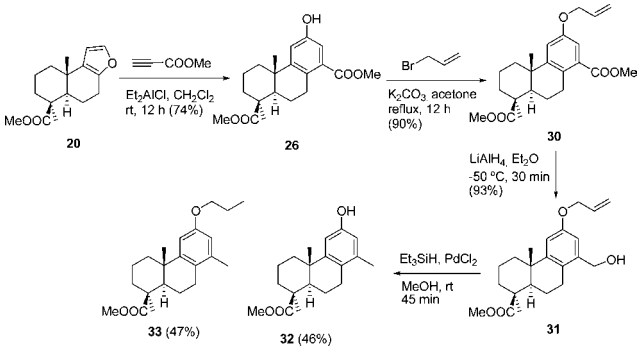
DOI: 10.1021/acs.orglett.6b03121
Org. Lett. 2016, 18, 5964−5967

diterpenes. Its *O*-acetyl derivative has been transformed into sugikurojin A and the cytotoxic 19-hydroxyferruginol.[21]

Hydroxyester **26**, with a carbon function at C-14, is a suitable precursor for synthesizing cassane diterpenes. To obtain this regioisomer more efficiently, we investigated the Diels–Alder cycloaddition of furan **20** with methyl propiolate in the presence of different Lewis acids. Of the Lewis acids investigated ($BF_3 \cdot OEt_2$, $ZnCl_2$, $EtAlCl_2$, Et_2AlCl), 1.5 molar equiv of Et_2AlCl at rt gave the best results, a mixture of hydroxyesters **26** (74%) and **27** (19%).

An initial synthetic approach to cassane diterpene benthaminin 1 (**4**) starting from ester **26**, prepared in good yield from furan **20**, was then undertaken (Scheme 5). The plan was to

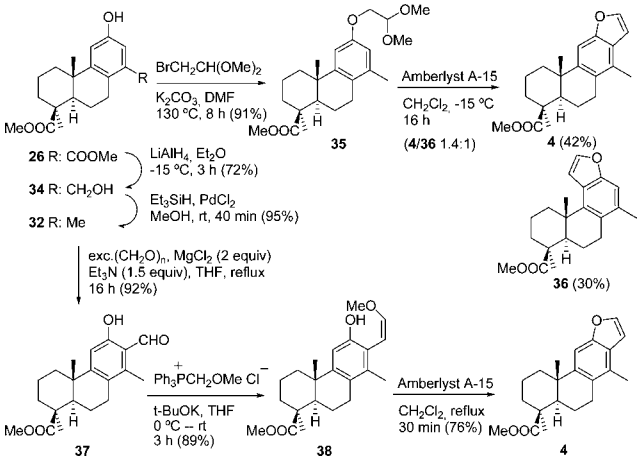
Scheme 5. First Approach to Cassane Diterpene Benthaminin 1 (4) from Furan 20



utilize the allyl group as a protecting group and to construct the furan ring and then to transform the aromatic carboxyl into a methyl group. Treatment of *O*-allyl ester **30** with $LiAlH_4$ at −50 °C gave benzyl alcohol **31**. Unfortunately, further reduction of the hydroxymethyl group with Et_3SiH and $PdCl_2$ also caused the deprotection of the phenolic hydroxyl group and the reduction of the allyl group, affording a 1:1 mixture of phenol **32** and propyl ether **33**.

In view of these results, the synthetic route was modified (Scheme 6). Thus, hydroxyester **26** was first transformed into methyl phenol **32** and then converted into the target compound. The treatment of phenol **32** with bromoacetaldehyde dimethylacetal gave phenoxy acetal **35**, which after acid

Scheme 6. Synthesis of Benthaminin 1 (4) from Hydroxyester 26



treatment led to benthaminin 1 (**4**) and its regioisomer **36**. The relative proportion of both regioisomers depends strongly on the acid employed and on the reaction conditions. Cyclization of acetal **35** in the presence of cationic resin at −15 °C gave the best results, a 1.4:1 mixture of the desired benthaminin 1 (**4**) and its regioisomer **36** in high yield. At higher temperatures, the proportion of regioisomer **36** was increased.

To circumvent the problem of regioselectivity, we explored an alternative route based on an intermolecular electrophilic substitution (Scheme 6). Formylation of phenol **32** afforded the desired aldehyde **37** as the sole product. The location of the formyl group at C-13 was confirmed on the basis of the NOE observed between the aldehyde group and the methyl group at C-14. When aldehyde **37** was treated with Ph_3P = CHOMe, the expected enol ether **38** was obtained, which after being treated with cationic resin afforded the desired benthaminin 1 (**4**) as the sole product in high yield.

A comparison of the ^1H and ^{13}C NMR data of synthetic benthaminin 1 (**4**) and those reported for the natural product showed significant discrepancies, in particular, for the aromatic protons. In the synthetic compound, these appear at δ 7.33 (s, 1H, H-11), 6.71 (br s, 1H, H-15), and 7.51 (d, J = 2.0 Hz, 1H, H-16), whereas the data reported by Dickson et al. for the natural product were δ 6.72 (s, 1H), assigned to H-11, 6.71 (dd, J = 2.0, 0.7 Hz, 1H), assigned to H-15, and 7.26 (d, J = 1.6 Hz, 1H), assigned to H-16.[5] At this point, it is important to highlight that the data of synthetic benthaminin 1 (**4**) are concordant with all those reported for many related compounds. Thus, the aromatic protons for caesaldekarin J (**3**), with a hydroxyl group at C-5, appear at δ 7.35 (s, 1H, H-11), 6.73 (d, J = 2.1 Hz, 1H, H-15), and 7.54 (d, J = 2.1 Hz, 1H, H-16).[4] In a similar way, the ^1H NMR spectra of compounds **2**[3] and **6**–**10**[7] showed a similar pattern for these protons. Benthaminin 3 (**5**),[6] also reported by Dickson et al., showed ^1H NMR data similar to those of natural benthaminin 1 and discordant with those of compounds **2**–**4** and **6**–**10**. The results reported here suggest that revising the structure of the natural compound is necessary.

In summary, a very short route toward aromatic cassane-type diterpenes from labdane terpenoids has been developed. In this way, enantiospecific synthesis of the putative structure of the antibacterial benthaminin 1 (**4**), starting from *trans*-communic acid (**18**), has been achieved. Furthermore, hydroxyester **27** has been previously transformed into abietanes sugikurojin A and the cytotoxic 19-hydroxyferruginol. By means of this strategy, the synthesis of a wide variety of aromatic cassane diterpenes can be undertaken, starting from different labdane diterpenes (**F**, R_1, R_2: COOMe, Me) and taking advantage of the chemical versatility of phenol intermediates, previously utilized in dehydroabietic acid derivatives,[10−12] which makes it feasible to address functionalization on the A, B, and C rings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03121.

X-ray data for compound **26** (CIF)

Experimental procedures, product characterizations and ^1H and ^{13}C NMR spectra for all new compounds, and X-ray crystal structure and crystallographic table for compound **26** (PDF)

DOI: 10.1021/acs.orglett.6b03121
Org. Lett. 2016, 18, 5964–5967

AUTHOR INFORMATION

Corresponding Authors

*E-mail: rachid@ugr.es.
*E-mail: eamr@ugr.es.

ORCID

Enrique Alvarez-Manzaneda: 0000-0002-3659-4475

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the Spanish Ministry of Economy and Competitiveness (Project CTQ2014-56611-R/BQU), the Regional Government of Andalucia (Project P11-CTS-7651) for financial support and assistance provided to the FQM-348 group and the European Commission for the Erasmus Mundus − Al Idrisi predoctoral fellowship granted to S. Mahdjour. This paper is a part of the Ph.D. Thesis of S. Mahdjour.

REFERENCES

(1) For recent reviews on these compounds, see: (a) Dickson, R. A.; Fleischer, T. C.; Houghton, P. J. *Pharmacogn. Commun.* **2011**, *1*, 63−77. (b) Maurya, R.; Ravi, M.; Singh, S.; Yadav, P. P. *Fitoterapia* **2012**, *83*, 272−280. (c) Bao, H.; Zhang, Q.; Ye, Y.; Lin, L. *Phytochem. Rev.* **2016**, DOI: 10.1007/s11101-016-9472-2.

(2) Ma, G.; Yuan, J.; Wu, H.; Cao, L.; Zhang, X.; Xu, L.; Wei, H.; Wu, L.; Zheng, Q.; Li, L.; Zhang, L.; Yang, J.; Xu, X. *J. Nat. Prod.* **2013**, *76*, 1025−1031.

(3) (a) McPherson, D. D.; Che, C.-T.; Cordell, G. A.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S. *Phytochemistry* **1986**, *25*, 167−170. (b) Yodsaoue, O.; Karalai, C.; Ponglimanont, C.; Tewtrakul, S.; Chantrapromma, S. *Tetrahedron* **2011**, *67*, 6838−6846.

(4) Lyder, D. L.; Peter, S. R.; Tinto, W. F.; Bissada, S. M.; McLean, S.; Reynolds, W. F. *J. Nat. Prod.* **1998**, *61*, 1462−1465.

(5) Dickson, R. A.; Houghton, P. J.; Hylands, P. J. *Phytochemistry* **2007**, *68*, 1436−1441.

(6) Dickson, R. A.; Annan, K.; Fleischer, T. C.; Houghton, P. J. *J. Pharmacognosy Nutr. Sc.* **2012**, *2*, 20−25.

(7) (a) Cheenpracha, S.; Srisuwan, R.; Karalai, C.; Ponglimanont, C.; Chantrapromma, S.; Chantrapromma, K.; Fun, H. K.; Anjum, S. Atta-ur-Rahman. *Tetrahedron* **2005**, *61*, 8656−8662. (b) Rifai, Y.; Arai, M. A.; Koyano, T.; Kowithayakorn, T.; Ishibashi, M. *J. Nat. Prod.* **2010**, *73*, 995−997.

(8) Orphelin, B.; Brum-Bousquet, M.; Tillequin, F.; Koch, M.; Moretti, C. *Heterocycles* **1996**, *43*, 173−83.

(9) Favre-Godal, Q.; Dorsaz, S.; Queiroz, E. F.; Marcourt, L.; Ebrahimi, S. N.; Allard, P.-M.; Voinesco, F.; Hamburger, M.; Gupta, M. P.; Gindro, K.; Sanglard, D.; Wolfender, J.-L. *J. Nat. Prod.* **2015**, *78*, 2994−3004.

(10) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Ramos, J. M.; Guardia, J. J.; Messouri, I.; Chayboun, I.; Mansour, A. I.; Dahdouh, A. *Synthesis* **2010**, *2010*, 3493−3503.

(11) (a) Burnell, R. H.; Côte, C.; Theberge, N. *J. Nat. Prod.* **1993**, *56*, 1459−1467. (b) Tapia, R.; Cano, M. J.; Bouanou, H.; Alvarez, E.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *Chem. Commun.* **2013**, *49*, 10257−10259. (c) Tapia, R.; Bouanou, H.; Alvarez, E.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, R. *J. Org. Chem.* **2014**, *79*, 4405−4413.

(12) (a) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. *Tetrahedron Lett.* **2007**, *48*, 989−992. (b) Marcos, I. S.; Beneitez, A.; Castañeda, L.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Synlett* **2007**, *2007*, 1589−1590. (c) Marcos, I. S.; Beneitez, A.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Tetrahedron* **2010**, *66*, 7773−7780. (d) Córdova-Guerrero, I.; San Andrés, L.; Leal-Orozco, A. E.; Padrón, J. M.; Cornejo-Bravo, J. M.; León, F. *Tetrahedron Lett.* **2013**, *54*, 4479−4482.

(13) Cui, Y. M.; Yasutomi, E.; Otani, Y.; Yoshinaga, T.; Ido, K.; Sawada, K.; Ohwada, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5201−5205.

(14) (a) Pelletier, S. W.; Ichinohe, Y.; Herald, D. L. *Tetrahedron Lett.* **1971**, *12*, 4179−4182. (b) Matsumoto, T.; Imai, S.; Yoshinari, T.; Tsuruta, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2401−2407. (c) Burnell, R. H.; Côte, C. *Synth. Commun.* **1988**, *18*, 1753−1756. (d) Burnell, R. H.; Dumont, N.; Théberge, N.; Desfossés, S. *Synth. Commun.* **1992**, *22*, 2571−2578. (e) Baleizao, C.; Pires, N.; Gigante, B.; Curto, M. J. M. *Tetrahedron Lett.* **2004**, *45*, 4375−4377.

(15) Chatzopoulou, M.; Antoniou, A.; Pitsinos, E. N.; Bantzi, M.; Koulocheri, S. D.; Haroutounian, S. A.; Giannis, A. *Org. Lett.* **2014**, *16*, 3344−3347.

(16) For representative examples of the Diels−Alder reaction/aromatization sequence, see: (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088−4096. (b) Moreno, A.; Gómez, M. V.; Vázquez, E.; de la Hoz, A.; Díaz-Ortiz, A.; Prieto, P.; Mayoral, J. A.; Pires, E. *Synlett* **2004**, 1259−1263. (c) Shinohara, H.; Sonoda, M.; Atobe, S.; Masuno, H.; Ogawa, A. *Tetrahedron Lett.* **2011**, *52*, 6238−6241. (d) Mackay, E. G.; Nörret, M.; Wong, L. S.-M.; Louis, I.; Lawrence, A. L.; Willis, A. C.; Sherburn, M. S. *Org. Lett.* **2015**, *17*, 5517−5519. (e) Crockatt, M.; Urbanus, J. H.; Konst, P. M.; De Koning, M. C. PCT Int. Appl. WO2016114668, 2016.

(17) (a) Rosen, R. B.; Simke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, L.-Q.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7317−7320. (b) Fernández, A.; Alvarez, E.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *Chem. Commun.* **2014**, *50*, 13100−13102.

(18) *trans*-Communic acid is a labdane diterpene very abundant in some species of *Juniperus* and *Cupressus*. See: (a) de Pascual, J.; San Feliciano, A.; Miguel del Corral, J. M.; Barrero, A. F. *Phytochemistry* **1983**, *22*, 300−301. (b) Ahond, A.; Carnero, P.; Gastambide, B. *Bull. Soc. Chim. Fr.* **1964**, 348−349.

(19) Giacomini, R. A.; Miranda, P. C. M.; Baptistella, L. H. B.; Imamura, P. M. *Arkivoc* **2003**, 313−322.

(20) (a) Politi, M.; Braca, A.; De Tommasi, N.; Morelli, I.; Manunta, A.; Battinelli, L.; Mazzanti, G. *Planta Med.* **2003**, *69*, 468−470. (b) Guerrero, I. C.; Andrés, L. S.; León, L. G.; Machín, R. P.; Padrón, J. M.; Luis, J. G.; Delgadillo, J. *J. Nat. Prod.* **2006**, *69*, 1803−1805. (c) Gao, Y.- P.; Shen, Y.-H.; Xu, X.-K.; Tian, J.-M.; Zeng, H.-W.; Lin, S.; Liu, C.-M.; Zhang, W.-D. *Phytochem. Lett.* **2014**, *8*, 6−9.

(21) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. *Synlett* **2007**, *2007*, 2425−2429.

DOI: 10.1021/acs.orglett.6b03121
Org. Lett. 2016, 18, 5964−5967