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Bioinspired Total Synthesis of Bolivianine: A Diels–Alder/Intramolecular Hetero-Diels–Alder Cascade Approach

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Supporting Information

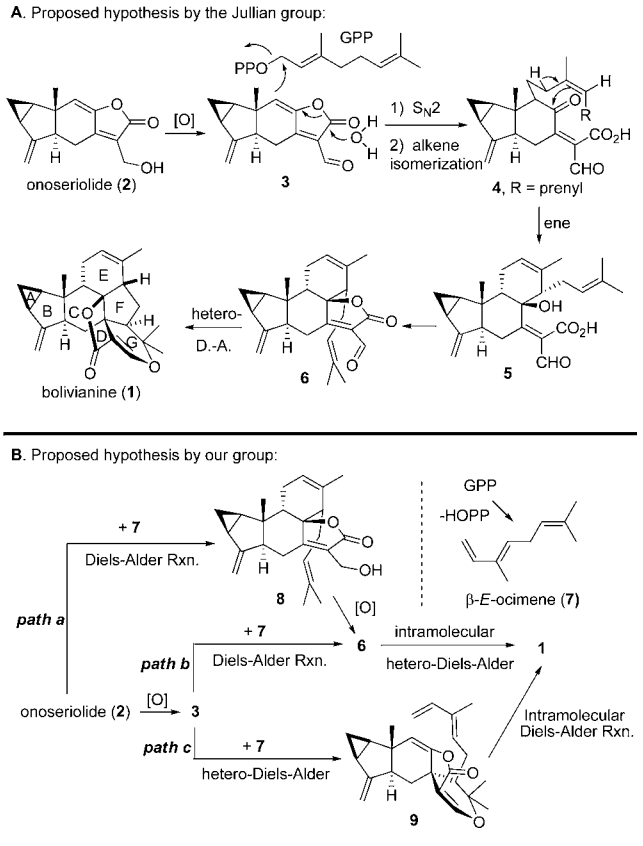
ABSTRACT: We report the first total synthesis of bolivanine in a 14-step pathway involving the synthesis of onoseriolide. Our synthesis features a palladium-catalyzed intramolecular cyclopropanation involving an allylic metal carbene and a Diels–Alder/intramolecular hetero-Diels–Alder cascade, allowing the single-step assembly of a tricyclic system with proper configuration. The synthetic efforts validate our modified biogenetic hypothesis and allow us to confirm the absolute configuration of bolivianine.

In 2007, the structurally complex sesterterpenoid, bolivianine, was isolated by the Jullian group from *Hedyosmum angustifolium* (Chloranthaceae), along with an artifact named isobolivianine.[1] Bolivianine contains a glaring heptacyclic skeleton and nine stereogenic centers. The complexity of this molecule has made it an alluring target for biosynthesis and chemical synthesis target. The Jullian group proposed a hypothesis for its biogenesis. As illustrated in Scheme 1A, the enal **3** could be accessed via allylic oxidation of onoseriolide, a lindenane-type sesquiterpenoid that occurs together with bolivianine in *H. angustifolium*.[2] Simultaneous hydrolysis of **3** and nucleophilic attack on geranylpyrophosphate (GPP), followed by the double bond migration of the geranyl moiety, could generate intermediate **4**. Subsequent ene reaction, lactonization, and finally intramolecular hetero-Diels–Alder cycloaddition could furnish bolivianine.

Some insights from our research group and others led us to consider modifying this hypothesis. We discovered that *β-E*-ocimene (**7**), a natural monoterpene generated from GPP *in vivo*,[3] is also present in *H. angustifolium*.[4] This raised the biosynthetic possibility of constructing ring E of bolivianine through a Diels–Alder cycloaddition between onoseriolide (**2**) or its natural derivative(s) and *β-E*-ocimene (**7**). In fact, researchers have long wondered whether lindenane-type sesquiterpenoid dimers, isolated from the same Chloranthaceae family as bolivianine, could be assembled biosynthetically from the corresponding monomers through Diels–Alder cycloaddition,[5] Indeed, a protracted search for Diels–Alderase led to the discovery of an enzyme that catalyzes [4+2] cycloaddition in the biosynthesis of spinosyn A, based on experimental data[6] and computational modeling.[7]

Based on these insights we chose to pursue a modified biogenetic hypothesis for bolivianine (Scheme 1B). First,

Scheme 1. Hypotheses for Biogenesis of Bolivianine



onoseriolide (**2**) could react with **7** to furnish compound **8**, which could be oxidized *in vivo* to compound **6** and ultimately yield bolivianine (**1**) (path a). Alternatively, initial oxidation of onoseriolide (**2**) could furnish **3**, which could couple with **7** to yield bolivianine (**1**), via either a Diels–Alder/intramolecular hetero-Diels–Alder pathway (DA/IMHDA, path b) or a hetero-Diels–Alder/intramolecular Diels–Alder pathway (HDA/IMDA, path c). Here we report our investigations into these different pathways and describe the total synthesis of onoseriolide and bolivianine.

Inspired by our biogenetic hypothesis (Scheme 1B), we expected that we could achieve sequential cycloadditions using

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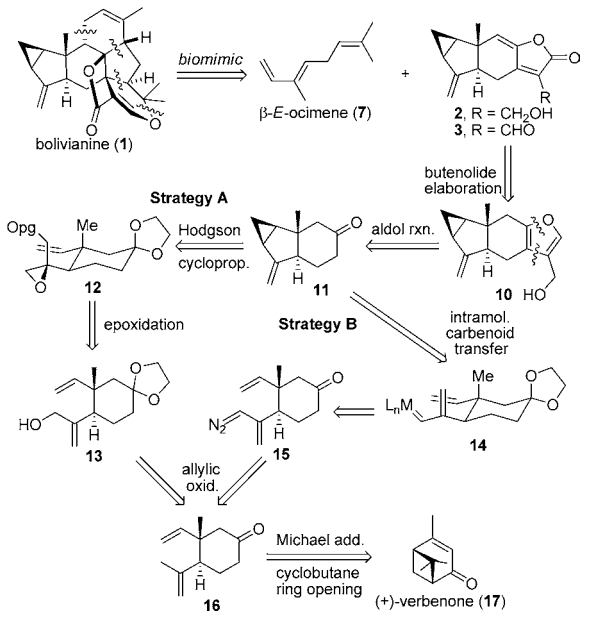
2 or its derivative 3 with 7 at a late stage (Scheme 2).[8] This approach is quite challenging because the desired chemo-, endo-, and diastereoselectivities must be achieved using reactants with different double bonds (2+7 or 3+7). We hypothesized that enantiopure onoseriolide (2) could be obtained from its furan precursor 10,[9] produced from 11 via aldol reaction. Compound 11 could be achieved through Hodgson cyclopropanation from the epoxide 12.[10] The diastereoselective epoxidation of 13 could presumably be controlled by the substrate itself or by a chiral catalyst (strategy A). Alternatively, compound 11 could be generated through metal-catalyzed carbenoid transfer via intermediate 14 (strategy B). Both retrosynthetic strategies point to the allylic oxidation of compound 16. Commercially available (+)-verbenone (17) was thus deduced to be the starting molecule for both strategies.

Scheme 2. Retrosynthetic Analysis



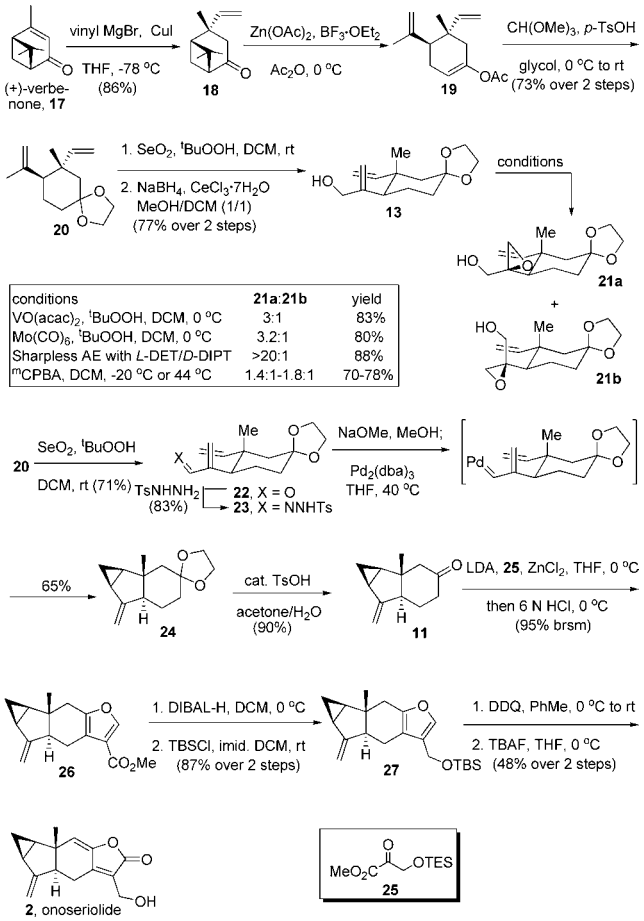
Michael addition to (+)-verbenone using vinyl copper reagent, followed by ring-opening of the cyclobutane, led to the enol acetate 19 (Scheme 3).[11] This was directly transformed to the 1,3-dioxolane 20 in the presence of acid. Allylic oxidation and subsequent Lüche reduction afforded compound 13. The next step, metal-catalyzed selective epoxidation, however, proved problematic. We speculated that if 13 adopted a stable chair conformation during metal catalysis, the equatorial vinyl group could block the approaching peroxide from the α-face of the axial *gem*-substituted double bond, resulting in predominance of the undesired 21a over the desired 21b.[12] To override this unfavorable substrate control, Sharpless asymmetric epoxidation was attempted in an effort to achieve a catalyst-controlled effect. Contrary to our expectations, this led to even worse diastereoselectivity, probably because of the greater bulkiness of the catalyst complex. Although ^{m}CPBA behaved much better, it still gave the desired 21b as the minor product in an unsatisfactory yield.

Armed with our insight into the importance of optimal conformation for the metal-catalyzed epoxidation of 13, we hypothesized that direct intramolecular cyclopropanation via an allylic carbenoid could proceed through this conformation in order to generate 11 (strategy B, Scheme 2). Of the many versatile ways to synthesize diazo compounds,[13] we considered an approach using tosylhydrazone salt to be one of the safest, and so we used it in metal-catalyzed intramolecuar cyclopropanation.[14] After carefully screening reaction conditions, we finally achieved compound 24 as the sole isolable diastereomer in 65% yield. In this approach, an active metal carbene species was generated *in situ* from palladium catalyst and the sodium salt of compound 23 at 40 °C. Direct heating or the use of other metal catalysts led to lower yields. To the best of our knowledge, this is the first successful example of intramolecular cyclopropanation of an allyic diazo compound.

We continued by perfoming acid-catalyzed deprotection to yield compound 11. Treating 11 with the functionalized pyruvate 25,[15] followed by acid-catalyzed furan formation and DIBAL-H reduction, furnished compound 10.[16] Protecting this compound with silyl ether, elaborating the furan ring, and deprotecting proceeded smoothly to yield onoseriolide (2), whose characterization data were in good accord with those reported.[2]

The IMDA reaction with alkylidene-5*H*-furan-2-one has proven extremely useful in natural product synthesis.[17] However, although 5-methylene-2(5*H*)-furanone was proved to be a suitable substrate in the intermolecular Diels–Alder reaction,[18] substituted alkylidene-5*H*-furan-2-ones with dienes often led to unsatisfactory site-, regio-, diastereo-, and *endo*/*exo*-selectivities.[19] To probe the feasibility of biogenetic path a (Scheme 1B), we examined whether 2 and 7 react together.[20]

Scheme 3. Enantioselective Total Synthesis of Onoseriolide



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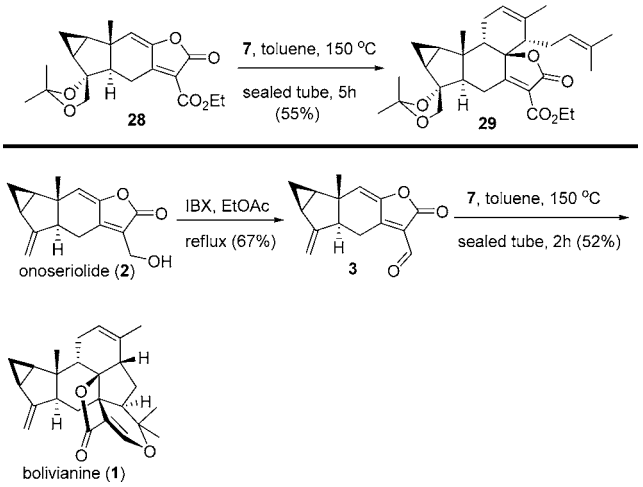
Since β-*E*-ocimene (**7**) is unstable to acid,[21] we focused our attention on the thermal conditions.[22] Unfortunately, we observed no reaction between **2** and **7** even at 150 °C, making us discount the possibility of the corresponding biogenetic pathway (path a, Scheme 1B). So we introduced an alien electron-withdrawing group into the alkylidene-5*H*-furan-2-one segment of onoseriolide (**2**), in order to activate the dienophile by decreasing its LUMO energy. After reaction of compound **28** with **7** in toluene at 150 °C for 5 h,[15] compound **29** formed in 55% yield without other detectable site-, regio-, or diastereoisomers (Scheme 4). The relative configuration of **29** was confirmed by converting it to bolivianine (**1**) in five steps.[15]

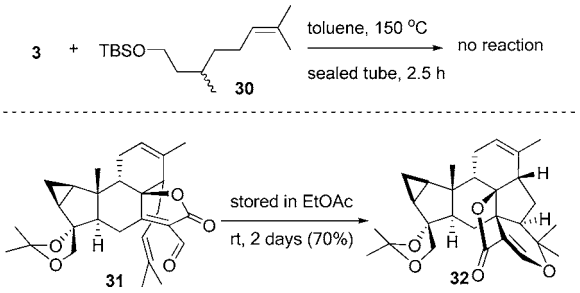
Scheme 4. Bioinspired Synthesis of Bolivianine



This success encouraged us to attempt a DA/IMHDA cascade with **3** and **7**. Compound **3** was prepared by IBX oxidation of **2** and then mixed with β-*E*-ocimene (**7**) in toluene and heated in a sealed tube at 150 °C. This ambitious cascade excitingly delivered bolivianine (**1**) in 52% yield with no other isomers detected (Scheme 4). All characterization data of our synthetic **1** were identical to the reported data, including optical rotation {synthetic **1**, $[\alpha]^{26}_{D}$ −52 (*c* 0.1, $CHCl_3$); natural sample, $[\alpha]^{25}_{D}$ −50 (*c* 0.2, $CHCl_3$)},[1] which confirmed the absolute configuration of bolivianine and its biogenetic correlation with onoseriolide. This one-pot cascade fueled two successful chemical transformations, generating three cycles, four C−C bonds, and five stereogenic centers with excellent selectivities. To the best of our knowledge, such a complex DA/IMHDA cascade has not been exploited before,[23] and it may prove useful in other natural product syntheses.

To gain further insight into the mechanism of the cascade reaction, we treated **3** with the known compound **30** at 150 °C for 2.5 h and observed no reaction (Scheme 5).[24] This allowed us to rule out the possibility of an alternative cascade mechanism initiated by a hetero-Diels−Alder reaction (path c, Scheme 1B). We also found that compound **31** spontaneously turned to compound **32** after standing in ethyl acetate for two days at room temperature,[15] through an IMHDA process. These observations lead us to suggest that the most likely biogenetic route to bolivianene should consist of an initial oxidation of onoseriolide (**2**) to **3**, subsequent Diels−Alder reaction with β-*E*-ocimene (**7**), probably catalyzed *in vivo*

Scheme 5. Probing the Mechanism of the Cascade



by a Diels−Alderase, and spontaneous IMHDA reaction (path b, Scheme 1B).

In conclusion, we completed the first total synthesis of onoseriolide and bolivianine in 12 and 14 steps, respectively, from commercially available (+)-verbenone. Our synthetic strategy involves dexterous assembly of a 3/5/6 skeleton via intramolecular cyclopropanation of an allylic metal carbene intermediate and an ambitious DA/IMHDA cascade to elaborate the EFG tricycle of bolivianine in one pot. Our total synthesis has allowed us to confirm the absolute configuration of bolivianine and provides experimental support for a modified biogenetic pathway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Acebey, L.; Sauvain, M.; Beck, S.; Moulis, C.; Gimenez, A.; Jullian, V. *Org. Lett.* **2007**, *9*, 4693.

(2) (a) Acebey, L.; Jullian, V.; Sereno, D.; Chevalley, S.; Estevez, Y.; Moulis, C.; Beck, S.; Valentin, A.; Gimenez, A.; Sauvain, M. *Planta Med.* **2010**, *76*, 365. (b) Trentin, A. P.; Santos, A. R. S.; Guedes, A.; Pizzolatti, M. G.; Yunes, R. A.; Calixto, J. B. *Planta Med.* **1999**, *65*, 517. (c) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Phytochemistry* **1980**, *19*, 689.

(3) (a) Shimada, T.; Endo, T.; Fujii, H.; Hara, M.; Omura, M. *Plant Sci.* **2005**, *168*, 987. (b) Dudareva, N.; Martin, D.; Kish, C. M.; Kolosova, N.; Gorenstein, N.; Faldt, J.; Miller, B.; Bohlmann, J. *Plant Cell* **2003**, *15*, 1227.

(4) Lorenzo, D.; Loayza, I.; Dellacassa, E. *Flavour Fragr. J.* **2003**, *18*, 32.

(5) Zhan, Z.-J.; Ying, Y.-M.; Ma, L.-F.; Shan, W.-G. *Nat. Prod. Rep.* **2011**, *28*, 594.

(6) Kim, H. J.; Ruszczycky, M. W.; Choi, S.; Liu, Y.; Liu, H. *Nature* **2011**, *473*, 109.

(7) Hess, B. A., Jr.; Smentek, L. *Org. Biomol. Chem.* **2012**, *10*, 7503.

(8) The Diels−Alder reaction has been ubiquitously applied in natural product synthesis. For related seminal reviews, see: (a) Takao,

K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (b) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. For elegant examples, see: (d) Li, C.; Dong, T.; Dian, L.; Zhang, W.; Lei, X. *Chem. Sci.* **2013**, *4*, 1163. (e) Li, C.; Dian, L.; Zhang, W.; Lei, X. *J. Am. Chem. Soc.* **2012**, *134*, 12414. (f) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860. (g) Evans, D. A.; Adams, D. J.; Kwan, E. E. *J. Am. Chem. Soc.* **2012**, *134*, 8162. (h) Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 920. (i) Snyder, S. A.; Wespe, D. A.; von Hof, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 8850. (j) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704. (k) Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8863. (l) Xiao, Q.; Ren, W.-W.; Chen, Z.-X.; Sun, T.-W.; Li, Y.; Ye, Q.-D.; Gong, J.-X.; Meng, F.-K.; You, L.; Liu, Y.-F.; et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 7373. (m) Gong, J.-X.; Lin, G.; Sun, W.-B.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745. (n) Liu, L.-Z.; Han, J.-C.; Yue, G.-Z.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 13608. (o) Sasaki, Y.; Kato, D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 13533. (p) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.

(9) The methyl ether of **10** is linderoxide, a natural sesquiterpenoid, which suggests biosynthetic connections among **2**, **10**, and linderoxide. For the isolation of linderoxide, see: Ishii, H.; Tozyo, T.; Nakamura, M.; Takeda, K. *Tetrahedron* **1968**, *24*, 625.

(10) (a) Yue, G.; Yang, L.; Yuan, C.; Du, B.; Liu, B. *Tetrahedron* **2012**, *68*, 9624. (b) Yue, G.; Yang, L.; Yuan, C.; Jiang, X.; Liu, B. *Org. Lett.* **2011**, *13*, 5406.

(11) Watanabe, M.; Awen, B. Z.; Kato, M. *J. Org. Chem.* **1993**, *58*, 3923.

(12) For the assignment of the configuration of compounds **21a** and **21b**, see ref 10a.

(13) Maas, G. *Angew Chem., Int. Ed.* **2009**, *48*, 8186.

(14) For an elegant review, see: (a) Fulton, J. R.; Aggarwal, V. K.; Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479. For a few examples of intermolecular cyclopropanation of alkenes with allylic tosylhydrazones, see: (b) Barluenga, J.; Quinones, N.; Tomas-Gamasa, M.; Cabal, M.-P. *Eur. J. Org. Chem.* **2012**, 2312. (c) Zhang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 8733. (d) de Meijere, A.; Schulz, T.-J.; Kostikov, R. R.; Graupner, F.; Murr, T.; Bielfeldt, T. *Synthesis* **1991**, 547.

(15) For detailed synthetic information on compounds **25**, **28**, and **31** and the chemical transformations from **29** to **1**, see the Supporting Information.

(16) Direct DDQ oxidation of **10** to onoseriolide (**2**) gave very low yield, presumably because of the free alcohol in **10**.

(17) For examples, see: (a) Niu, D.; Hoye, T. R. *Org. Lett.* **2012**, *14*, 828. (b) Couladouros, E. A.; Bouzas, E. A.; Magos, A. D. *Tetrahedron* **2006**, *62*, 5272. (c) Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6533. (d) Snider, B. B.; Zou, Y. *Org. Lett.* **2005**, *7*, 4939. (e) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691. (f) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.

(18) Alonso, D.; Orti, J.; Branchadell, V.; Oliva, A.; Ortuno, R. M.; Bertran, J.; Font, J. *J. Org. Chem.* **1990**, *55*, 3060.

(19) (a) Dubios, S.; Rodier, F.; Blanc, R.; Rahmani, R.; Heran, V.; Thibonnet, J.; Commeiras, L.; Parrain, J.-L. *Org. Biomol. Chem.* **2012**, *10*, 4712. (b) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135. (c) Branchadell, V.; Font, J.; Oliva, A.; Orti, J.; Ortuno, R. M. *Tetrahedron* **1991**, *47*, 8775. (d) Poss, A. J.; Brodowski, M. H. *Tetrahedron Lett.* **1989**, *30*, 2505.

(20) For preparation of *β-E*-ocimene, see: Cong, H.; Becker, C. F.; Elliott, S. J.; Grinstaff, M. W.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 7514.

(21) Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979.

(22) For the thermal stability of *β-E*-ocimene, see: Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775.

(23) An excellent intramolecular Diels–Alder/intramolecular hetero-Diels–Alder strategy was developed for the total synthesis of (−)-FR182877: (a) Tanaka, N.; Suzuki, T.; Matsumura, T.; Hosoya, Y.; Nakada, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2580. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (c) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.

(24) For the preparation of **30**, see: Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461.