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An efficient synthesis of the guaiane sesquiterpene (−)-isoguaiene by domino metathesis

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Full Research Paper

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Abstract

(−)-Isoguaiene was prepared from (*S*)-citronellal in only 9–10 steps with good overall yields. Either a trienyne or a dienediyne metathesis and highly diastereoselective organocatalytic Michael additions of aldehydes derived from (*S*)-citronellal served as the key transformations.

Introduction

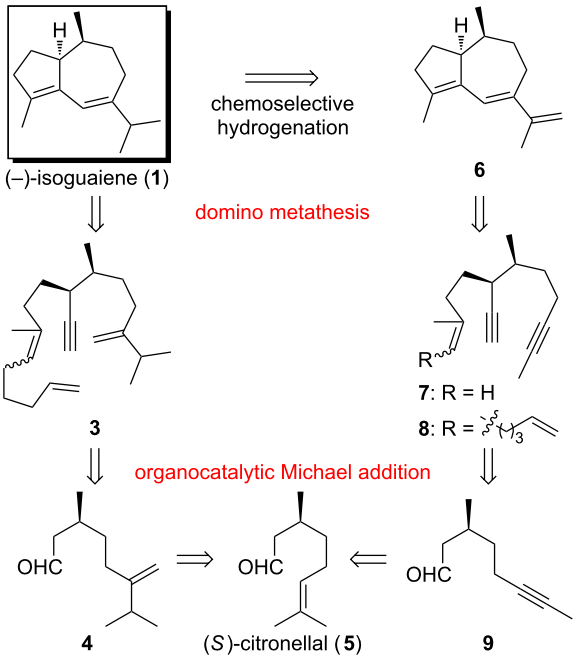
The guaiane sesquiterpene (−)-isoguaiene (**1**) has been isolated from the liverworts *Pellia epiphylla* [1] and *Dumortiera hirsuta* [2] as well as from several *Pimpinella* species [3,4], while the (+)-enantiomer of **1** has been isolated from the roots of *Parthenium hysterophorus* [5]. A recent enantioselective synthesis of (−)-isoguaiene (**1**) from (+)-dihydrocarvone [6] enabled an unambiguous assignment of its absolute configuration as depicted in Figure 1. Due to the structural similarity of **1** and the trisnorsesquiterpene clavukerin A (**2**), we were interested in developing an efficient synthetic access to **1** using a combined organocatalytic/metal-catalyzed strategy related to the one applied to the preparation of **2** [7,8].

(−)-isoguaiene (**1**) (−)-clavukerin A (**2**)

Figure 1: Structures of the sesquiterpene (−)-isoguaiene (**1**) and the trisnorsesquiterpene clavukerin A (**2**).

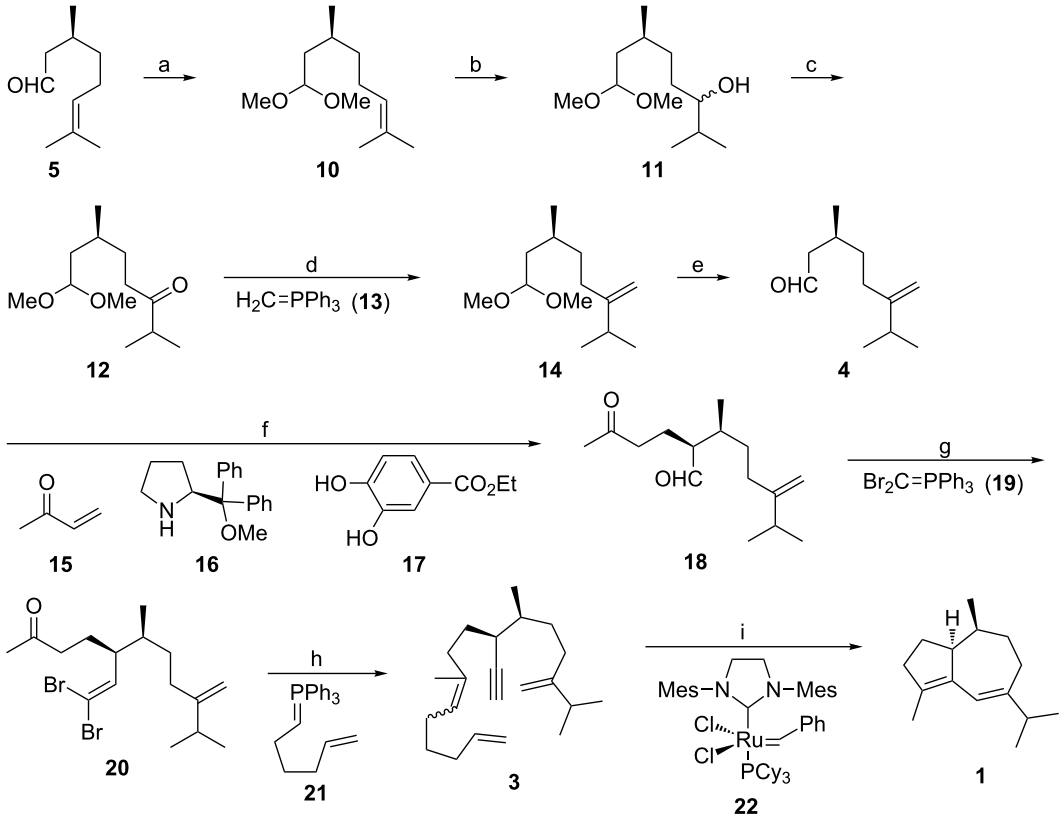
Results and Discussion

As illustrated in Scheme 1, two alternative routes were retrosynthetically devised, both of which feature a domino metathesis event and an organocatalytic Michael addition as the key steps. In closer analogy to our improved synthesis of clavukerin A (**2**) [8], a relay metathesis [9] of trienyne **3** was expected to lead to the hydroazulene **1** selectively. Trienyne **3** was envisioned to result from a stereoselective Michael addition of aldehyde **4** to methyl vinyl ketone [7,8,10] followed by chemoselective elaboration of the two carbonyl functions. Finally, aldehyde **4** was traced back to the commercially available starting material (*S*)-citronellal (**5**). On the other hand, a more rarely used enediyne metathesis [11-14] of compound **7** or its relay surrogate **8** might give rise to the conjugated triene **6**, chemoselective hydrogenation [15] of which would generate the target molecule **1**. Similar to the disconnection of trienyne **3**, the metathesis substrates **7** and **8** can be derived from aldehyde **9**, which is finally also traced back to (*S*)-citronellal (**5**).



Scheme 1: Retrosynthetic analysis for (−)-isoguaiene (**1**).

Scheme 2 illustrates the synthesis of (−)-isoguaiene (**1**) by relay metathesis of trienyne **3**. The unsaturated aldehyde **4** required for the organocatalytic Michael addition was readily prepared in

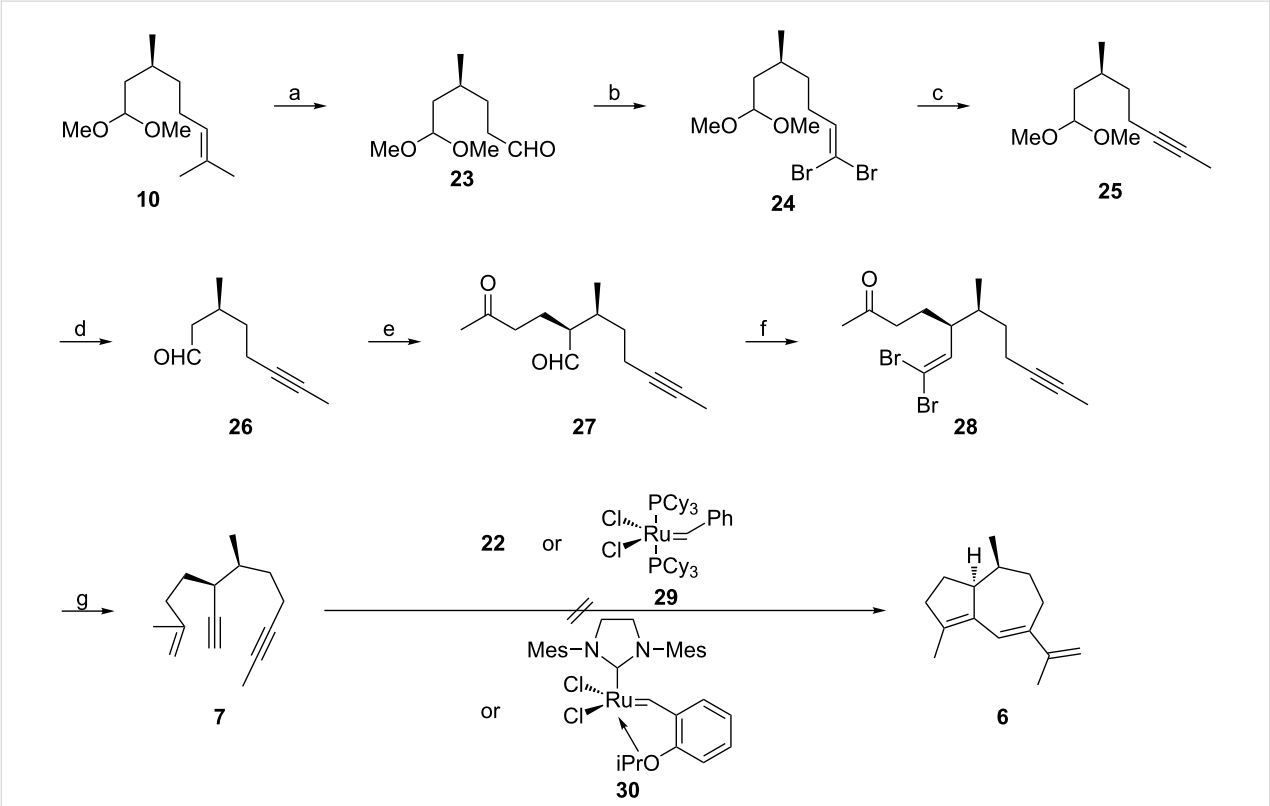


Scheme 2: Synthesis of **1** by relay metathesis of trienyne **3**. a) $HC(OMe)_3$, 4 mol % $LiBF_4$, MeOH, reflux, 80%; b) (i) $BH_3{\cdot}Me_2S$, THF, 0 °C to rt, (ii) 30% H_2O_2, 10% NaOH, 0 °C to rt, 97%; c) 5 mol % TPAP, NMO, CH_2Cl_2, rt, 97%; d) **13**, THF, rt to reflux, 96%; e) 25 mol % TsOH, THF, H_2O, iPrOH, reflux, 92%; f) **15**, 7.5 mol % **16**, 20 mol % **17**, 1 °C, 91%; g) **19**, THF, 0 °C to rt, 84%; h) (i) **21**, THF, −60°C to rt then 50 °C, (ii) BuLi, −78 °C, 76%; i) 30 mol % **22**, benzene, reflux, 51%. TPAP = tetrapropylammonium perruthenate. NMO = *N*-methylmorpholine-*N*-oxide. Ts = *p*-toluenesulfonyl.

five steps commencing with (*S*)-citronellal (**5**). After protection of the aldehyde function as the dimethyl acetal [16-18], hydroboration and oxidative work-up of **10** provided a mixture of epimeric alcohols **11** that was unified by Ley–Griffith oxidation [19] to give ketone **12** [20]. Subsequent Wittig reaction with ylide **13** and acetal cleavage of the resultant olefin **14** delivered aldehyde **4** with considerably higher efficiency compared to the known six-step preparation of *ent*-**4** from (−)-menthone [21]. Asymmetric Michael addition [7,8,10] of aldehyde **4** to methyl vinyl ketone (**15**) proceeded with high catalyst-controlled diastereoselectivity (dr = 23:1) to yield keto aldehyde **18**. Chemoselective dibromoolefination with ylide **19** prepared from dibromomethyltriphenylphosphonium bromide and sodium *tert*-butoxide [22] led to ketone **20** virtually without erosion of the relative configuration (dr = 22:1). After subjecting **20** to carbonyl olefination with unsaturated ylide **21** [8] followed by alkyne generation [23] with butyllithium in a one-pot process, trienyne **3** was obtained as a 1.6:1 mixture of *E* and *Z* olefin isomers. Due to the presence of the isopropyl group at the disubstituted alkene [24] of **3**, 30 mol % of the second generation Grubbs catalyst **22** were required to effect the relay metathesis of **3** to (−)-isoguaiene (**1**) in refluxing benzene in a good yield of 51%.

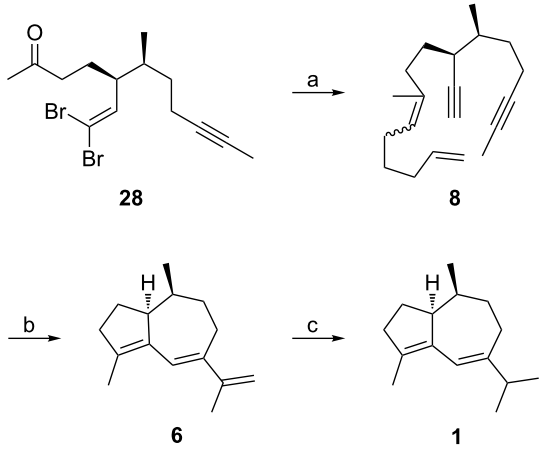
Thus, by application of a domino metathesis strategy featuring trienyne **3**, only 9 steps were needed to secure the guaiane sesquiterpene **1** in 19.7% overall yield starting from (*S*)-citronellal (**5**), which compares favorably with the previous synthesis of **1** from (+)-dihydrocarvone (10 steps, 6.9% overall yield) [6]. Scheme 3 depicts our first attempts to realize an alternative domino metathesis strategy using enediyne **7**.

Ozonolysis of the unsaturated acetal **10** gave aldehyde **23** [17,18] that was subjected to dibromoolefination with ylide **19** as described for the transformation of aldehyde **18**. Use of the preformed ylide **19** led to reproducibly higher yields of **24** in comparison with the application of tetrabromomethane and triphenylphosphine [23]. One-pot alkyne formation and methylation [23] of **24** to furnish **25** and subsequent acetal hydrolysis provided the known aldehyde **26** [25] in very good overall yield. In our hands, the "demethanation" of (*S*)-citronellol to produce the primary alcohol corresponding to aldehyde **26** according to the protocol of Abidi ($NaNO_2$, aqueous AcOH) [26] as a potential shortcut to **26** only proceeded with a maximum yield of 20%. Asymmetric Michael addition of aldehyde **26** to methyl vinyl ketone (**15**) followed immediately by treatment of the resultant unstable keto aldehyde **27** with ylide **19** delivered



Scheme 3: Attempted preparation of **1** by domino metathesis of enediyne **7**. a) (i) O_3, CH_2Cl_2, MeOH, pyridine, −78 °C, (ii) PPh_3, rt, 94%; b) **19**, THF, 0 °C; c) (i) BuLi, −78 °C, (ii) MeI, −78 °C to rt, 92% (2 steps); d) 25 mol % TsOH, THF, H_2O, iPrOH, reflux, 90%; e) **15**, 10 mol % **16**, 20 mol % **17**, 2 °C; f) **19**, THF, 0 °C to rt, 85% (2 steps); g) (i) **13**, THF, rt to reflux, (ii) BuLi, −78 °C, 90%.

dibromo olefin **28** with high diastereocontrol (dr = 19:1). Olefination of ketone **28** with ylide **13** and alkyne formation with butyllithium in a one-pot procedure then gave rise to enediyne **7** in excellent yield. Unfortunately, all attempts to achieve a domino metathesis of **7** to hydroazulene **6** only met with failure. Thus, neither the Grubbs catalysts **22** or **29**, nor the Hoveyda–Blechert catalyst **30** [27,28] in the presence or absence of ethylene effected the desired transformation to triene **6**. As a consequence, we resorted to a relay strategy for enediyne metathesis as well, and the successful execution of this idea is illustrated in Scheme 4.



Scheme 4: Conversion of **28** to **1** by relay metathesis of dienediyne **8**. a) (i) **21**, THF, rt to reflux, (ii) BuLi, −78 °C, 65%; b) 25 mol % **29**, CH_2Cl_2, reflux; c) H_2, 15 mol % $(PPh_3)_3RhCl$, benzene, EtOH, rt, 42% (2 steps).

Similar to the transformation of ketone **20**, the one-pot conversion of ketone **28** by olefination with unsaturated ylide **21** and alkyne formation with butyllithium yielded dienediyne **8** as a 1.3:1 mixture of *E* and *Z* olefin isomers. Gratifyingly, treatment of **8** with 25 mol% of the first generation Grubbs catalyst **29** produced the desired hydroazulene **6** in refluxing dichloromethane. Without purification, the crude sensitive conjugated triene **6** was immediately hydrogenated in the presence of the Wilkinson catalyst [29] to give (−)-isoguaiene (**1**) by chemoselective reduction of only the terminal olefin [15] in satisfactory yield over the 2 steps. Hence, the natural product **1** was available through this domino metathesis strategy featuring dienediyne **8** in 10 steps from (*S*)-citronellal (**5**) in 14.5% overall yield.

Conclusion

In summary, we have accomplished two short and efficient catalytic routes from (*S*)-citronellal (**5**) to the guaiane sesquiterpene (−)-isoguaiene (**1**) using either a trienyne or a dienediyne metathesis and highly diastereoselective organocatalytic Michael additions of aldehydes derived from **5** as the key steps.

Supporting Information

Supporting Information File 1

Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**, **3**, **4**, **7**, **8**, **10**, **12**, **14**, **18**, **20**, **23**–**28**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-83-S1.pdf]

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References

1. Cullmann, F.; Becker, H. *Phytochemistry* **1998,** *47,* 237–245. doi:10.1016/s0031-9422(97)00414-7
2. Saritas, Y.; Bülow, N.; Fricke, C.; König, W. A.; Muhle, H. *Phytochemistry* **1998,** *48,* 1019–1023. doi:10.1016/s0031-9422(97)00484-6
3. Tabanca, N.; Bedir, E.; Ferreira, D.; Slade, D.; Wedge, D. E.; Jacob, M. R.; Khan, S. I.; Kirimer, N.; Baser, K. H. C.; Khan, I. A. *Chem. Biodiversity* **2005,** *2,* 221–232. doi:10.1002/cbdv.200590005
4. Baser, K. H. C.; Tabanca, N.; Kirimer, N.; Bedir, E.; Khan, I. A.; Wedge, D. E. *Pure Appl. Chem.* **2007,** *79,* 539–556. doi:10.1351/pac200779040539
5. Bohlmann, F.; Zdero, C.; Lonitz, M. *Phytochemistry* **1977,** *16,* 575–577. doi:10.1016/0031-9422(77)80018-6
6. Blay, G.; Garcia, B.; Molina, E.; Pedro, J. R. *Org. Lett.* **2005,** *7,* 3291–3294. doi:10.1021/ol0511023
7. Knüppel, S.; Rogachev, V. O.; Metz, P. *Eur. J. Org. Chem.* **2010,** 6145–6148. doi:10.1002/ejoc.201001087
8. Barthel, A.; Kaden, F.; Jäger, A.; Metz, P. *Org. Lett.* **2016,** *18,* 3298–3301. doi:10.1021/acs.orglett.6b01619
9. Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004,** *126,* 10210–10211. doi:10.1021/ja046385t
10. Chi, Y.; Gellman, S. H. *Org. Lett.* **2005,** *7,* 4253–4256. doi:10.1021/ol0517729
11. Banti, D.; North, M. *Tetrahedron Lett.* **2003,** *44,* 8157–8160. doi:10.1016/j.tetlet.2003.09.035
12. Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R.; Schreiber, S. L. *J. Am. Chem. Soc.* **2006,** *128,* 14766–14767. doi:10.1021/ja065724a
13. Yuan, W.; Wei, Y.; Shi, M. *ChemistryOpen* **2013,** *2,* 63–68. doi:10.1002/open.201300002
14. Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998,** *63,* 4291–4298. doi:10.1021/jo972279g
15. Zahel, M.; Wang, Y.; Jäger, A.; Metz, P. *Eur. J. Org. Chem.* **2016,** 5881–5886. doi:10.1002/ejoc.201601197

16. Hamada, N.; Kazahaya, K.; Shimizu, H.; Sato, T. *Synlett* **2004,** 1074–1076. doi:10.1055/s-2004-820038
17. Tietze, L. F.; Denzer, H.; Holdgrün, X.; Neumann, M. *Angew. Chem.* **1987,** *99,* 1309–1310. doi:10.1002/ange.19870991225
Angew. Chem., Int. Ed. **1987**, *26*, 1295-1297. doi:10.1002/anie.198712951
18. Naruse, Y.; Yamamoto, H. *Tetrahedron* **1988,** *44,* 6021–6029. doi:10.1016/s0040-4020(01)89790-8
19. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987,** 1625–1627. doi:10.1039/c39870001625
20. Yarovaya, O. I.; Salomatina, O. V.; Korchagina, D. V.; Polovinka, M. P.; Barkhash, V. A. *Russ. J. Org. Chem.* **2002,** *38,* 1594–1605. doi:10.1023/a:1022501815715
21. Sutherland, A. J.; Sutherland, J. K.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1996,** 349–354. doi:10.1039/p19960000349
22. Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999,** *40,* 8575–8578. doi:10.1016/s0040-4039(99)01830-4
23. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *13,* 3769–3772. doi:10.1016/s0040-4039(01)94157-7
24. Radtke, L.; Willot, M.; Sun, H.; Ziegler, S.; Sauerland, S.; Strohmann, C.; Fröhlich, R.; Habenberger, P.; Waldmann, H.; Christmann, M. *Angew. Chem.* **2011,** *123,* 4084–4088. doi:10.1002/ange.201007790
Angew. Chem., Int. Ed. **2011,** *50,* 3998–4002. doi:10.1002/anie.201007790
25. Gao, P.; Xu, P.-F.; Zhai, H. *J. Org. Chem.* **2009,** *74,* 2592–2593. doi:10.1021/jo900045k
26. Abidi, S. L. *Tetrahedron Lett.* **1986,** *27,* 267–270. doi:10.1016/s0040-4039(00)83993-3
27. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000,** *122,* 8168–8179. doi:10.1021/ja001179g
28. Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000,** *41,* 9973–9976. doi:10.1016/s0040-4039(00)01808-6
29. Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966,** 1711–1732. doi:10.1039/j19660001711

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