

Natural Products Synthesis

International Edition: DOI: 10.1002/anie.201611078
German Edition: DOI: 10.1002/ange.201611078

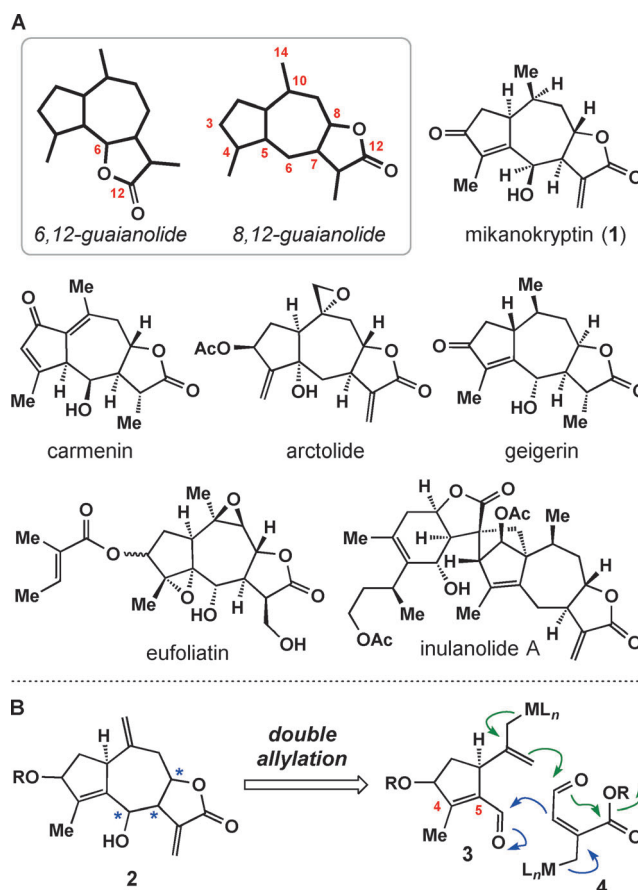
A Double Allylation Strategy for Gram-Scale Guaianolide Production: Total Synthesis of (+)-Mikanokryptin

Xirui Hu, Silong Xu, and Thomas J. Maimone*

Abstract: With over 5000 members isolated to date, sesquiterpene lactones represent a prolific source of medicinal agents with several derivatives in human clinical trials. The guaianolides, a major subset of this group, have been intensely investigated from both medicinal and chemical-synthesis perspectives for decades. To date, the myriad stereochemical permutations presented by this enormous family have precluded the synthesis of many unique members. Herein we report the total synthesis of the *trans*-fused 8,12-guaianolide (+)-mikanokryptin in 10 steps from (+)-carvone. Notably, this synthesis is the first gram-scale total synthesis of a guaianolide natural product.

Sesquiterpene lactones from the *Asteraceae* family of plants represent one of the largest and most biologically significant classes of plant secondary metabolites.^[1] Their presence in both traditional herbal medicine regimes as well as modern human medicine have been extensively documented.^[1,2] In particular, α -methylene- γ -lactone-containing members have strong documented anticancer,^[3] anti-inflammatory,^[4] anthelmintic,^[5] and antimigraine activity.^[6] Multiple members have also been shown to inhibit aspects of the NF- κ B signaling pathway,^[7] a central mediator of the human immune response whose deregulation is noted in inflammatory and autoimmune diseases as well as various human cancers.^[8]

The 5,7-fused bicyclic family of guaianolides is perhaps the flagship subset of sesquiterpene lactone natural products and two major, isomeric subtypes, the 6,12-guaianolides and 8,12-guaianolides, have been isolated (Scheme 1 A). Despite extensive studies on the chemical synthesis of 6,12-guaianolides,^[9] 8,12-guaianolides have received relatively limited attention from the synthetic community.^[10] Mikanokryptin (**1**), isolated in 1975 by Herz and co-workers, belongs to the continually growing family of *trans*-fused 8,12-guaianolides, which are largely unexplored and present stereochemistry patterns not readily addressed by current strategies (Scheme 1 A).^[11] In developing a synthetic route to this family, we viewed a double allylation disconnection as potentially capable of constructing the guaianolide ring system **2** from



Scheme 1. A) Guaianolide ring systems and various members of the 8,12-guaianolide family. B) A double allylation disconnection to access 8,12-guaianolides from simple precursors.

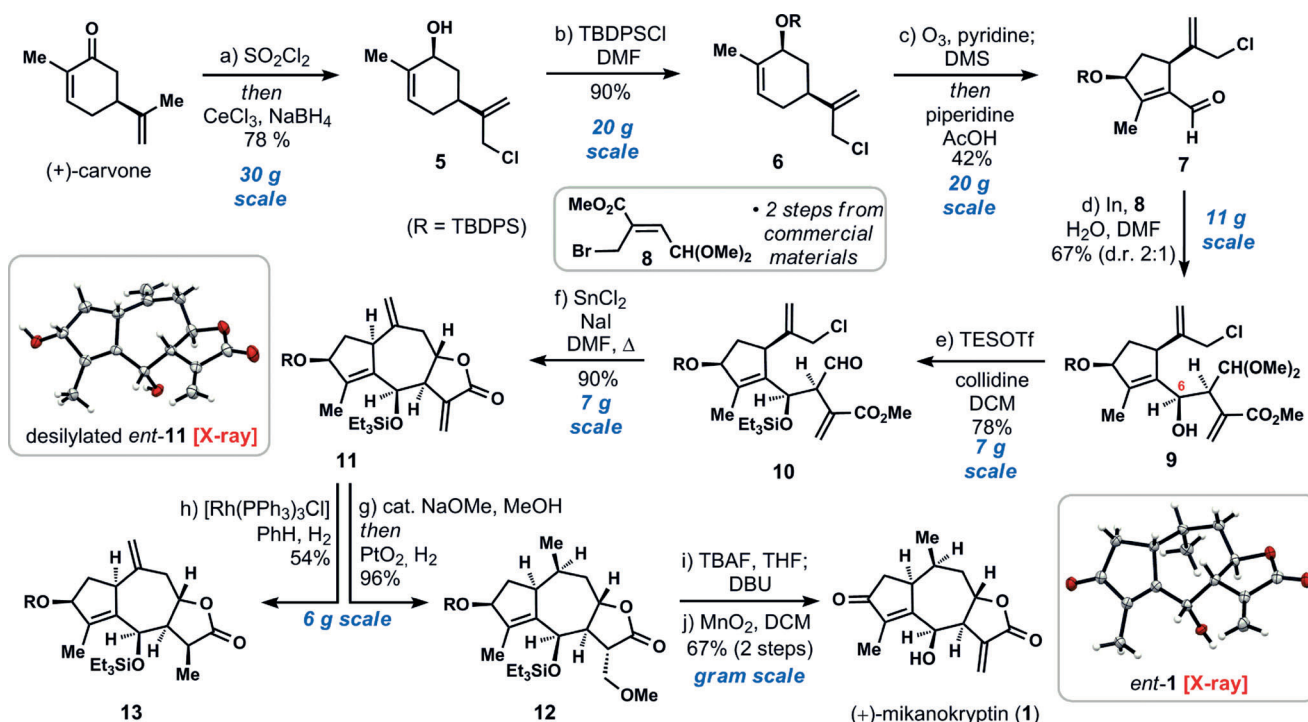
two simple, hypothetical fragments **3** and **4** (Scheme 1 B). Of significant concern to us was the paucity of examples of seven-membered-ring formation by metal-mediated intramolecular Barbier-type allylation relevant to this synthetic problem.^[12,13] Herein we disclose the realization of this plan. Our straightforward total synthesis of **1** is suitable for the formation of multigram quantities of advanced intermediates and a gram of the natural product in a single synthetic pass.

Our studies began with the construction of a precursor to intermediate **3**, for which we turned to the chiral pool of terpenes. For the past several decades, limonene,^[14] isopulegol,^[15] and carvone^[16] have found broad application in the synthesis of guaiane sesquiterpenes, among which carvone is of particular utility for the synthesis of guaianolides with oxidation at C3. Favorskii-type ring contractions have fea-

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under <http://dx.doi.org/10.1002/anie.201611078>.



Scheme 2. Gram-scale total synthesis of (+)-mikanokryptin (**1**). Reagents and conditions: a) carvone (1 equiv), Na_2CO_3 (3 equiv), SO_2Cl_2 (1.2 equiv, added slowly over 2 h), DCM, 0°C , then $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.1 equiv), NaBH_4 (3 equiv), MeOH, 0°C , 1 h, 78%; b) TBDPSCl (1.2 equiv), imidazole (3 equiv), DMAP (0.05 equiv), DMF, room temperature, 8 h, 90%; c) O_3 , pyridine (0.3 equiv), DCM, -78°C , 20–40 min, then DMS (2 equiv), imidazole (3 equiv), DMAP (0.05 equiv), DMF, room temperature, 8 h, then piperidine (0.15 equiv), AcOH (0.2 equiv), 40°C , 16 h, 42%; d) In (1.5 equiv), **7** (1.2 equiv), **8** (1 equiv), H_2O (1 equiv), DMF, room temperature, 8 h, 67%, d.r. 2:1; e) TESOTf (4 equiv), 2,4,6-collidine (6 equiv), DCM, 0°C , 24 h, 78%; f) SnCl_2 (4.5 equiv), NaI (9 equiv), DMF, 60°C , 12 h, 90%; g) NaOMe (0.1 equiv), MeOH, 16 h, then AcOH (0.1 equiv), PtO_2 (0.1 equiv), H_2 (1 atm), 6 h, 96%; h) $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$ (0.1 equiv), H_2 (1 atm), PhH, 1 h, 54%; i) TBAF (3 equiv), THF, room temperature, 24 h; DBU (1.1 equiv), toluene, DCM, Δ , 69%; j) MnO_2 , DCM, room temperature, 16 h, 97%. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DCM = dichloromethane, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide, DMS = dimethyl sulfide, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TESOTf = triethylsilyl trifluoromethanesulfonate, TBAF = tetra-*n*-butylammonium fluoride. All X-ray crystal structures shown were obtained during preliminary studies conducted with (–)-carvone.

tured prominently in this regard, and typical result in cyclopentane-containing building blocks in 5–8 synthetic steps.^[13a,c-g,16a-d] Considering the desire for $\Delta_{4,5}$ unsaturation, we developed a robust three-step protocol from carvone (Scheme 2). The isopropenyl group of carvone was first chlorinated at the allylic position (SO_2Cl_2 , Na_2CO_3), and then directly subjected to the Luche reduction conditions. This one-pot procedure afforded chloro-substituted *cis*-carveol **5** reliably on a 30 g scale in approximately 80% yield. Silylation of **5** with *tert*-butyldiphenylsilyl chloride cleanly provided silyl ether **6** in excellent yield (> 90%). Inspired by previous work with limonene,^[17] ozonolysis of **6** in the presence of catalytic quantities of pyridine (0.3 equiv) resulted in chemoselective cleavage of the trisubstituted olefin under carefully monitored cryogenic conditions.^[18] The sensitive dicarbonyl intermediate thus formed following reductive quenching with dimethyl sulfide underwent intramolecular aldol condensation in the presence of piperidine and acetic acid to afford enal **7** in a one-pot procedure. Large quantities of **7** (ca. 100 g) were readily prepared in our laboratory through this three-step procedure, which is envisioned to serve as the foundation for syntheses of numerous guaianolides with $\Delta_{4,5}$ unsaturation.

With the western fragment completed, we turned toward the first of two allylation reactions. For mikanokryptin (**1**) and

related 8,12-guaianolides (Scheme 1), a *cis* arrangement between the C6 hydroxy group and the neighboring acrylate group is required on the future cycloheptane ring. Although guaianolides with a *trans* arrangement of these groups have been studied (see geigerin, for example, Scheme 1A),^[10b-d] fewer tactics exist to access this pattern and sometimes rely on the inversion or epimerization of a *trans*-configured precursor.^[19] We were pleased to find that allylic bromide **8**, which can be prepared in two steps from commercially available materials on a decagram scale, functioned well in this setting.^[20,21] Under indium-mediated conditions, **8** could be chemoselectively activated in the presence of allylic chloride **7**, and was found to cleanly add to the aldehyde moiety to give **9** (d.r. 2:1 at C6) in 67% yield on a 14 g scale. Allylation protocols based on activation with Cr, Zn, Pd, Cd, Sn, Pb, and Bi were found to be inferior with respect to both yield and diastereoselectivity.^[22] Notably, the incorporation of 1 equivalent of H_2O proved important; without it, slightly lower diastereoselectivity was observed as well as extensive in situ formation of the 6,12-lactone framework. With larger quantities, increased decomposition of **8** was observed. The sensitive homoallylic alcohol **9** and the minor diastereomer were then subjected to the mild deacetalization protocol reported by Fujioka, Kita, and co-workers (TESOTf, 2,4,6-collidine),^[23]

which also silylated the C6 alcohol, thus leading to **10**.^[24] At this stage, the minor diastereomer could also be separated.

With substrate **10** accessible on large scales, we were well-positioned to evaluate the second, seven-membered-ring-forming allylation reaction (Table 1). We commenced our

Table 1: Investigation of metal-mediated allylation conditions for the synthesis of the 5,7,5-fused guaianolide lactone system.

$\text{metal-mediated allylation}$
 $(\text{R} = \text{TBDPS})$

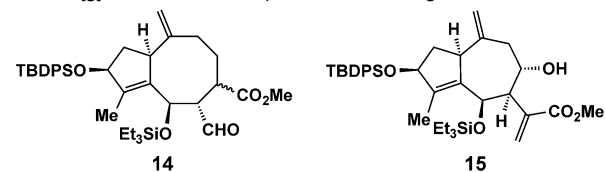
Entry	Conditions ^[a]	Yield [%] ^[b]				rsm ^[c]
		11	14	15		
1	CrCl ₂ , cat. NiCl ₂ , DMF, 60 °C	10 ^[d]	17	–	–	
2	In ⁰ , NaI, DMF, 60 °C	13 ^[e]	–	–	–	
3 ^[f]	NaI; SmI ₂ , HMPA–THF, –78 °C	27 ^[d]	17	–	–	
4 ^[f]	NaI; Zn ⁰ , aq. NH ₄ Cl, THF, rt	0	51	–	–	34
5 ^[f]	NaI; Mg ⁰ , cat. (CH ₂ Br) ₂ , THF, rt	0	–	–	–	
6 ^[f]	NaI; <i>i</i> PrMgCl, THF, 0 °C	0	–	–	–	
7 ^[f]	NaI; SnCl ₂ , DMF, rt	53 ^[e]	–	20	–	9
8 ^[g]	SnCl₂, NaI, DMF, 60 °C	90^[e]	–	–	–	

[a] Reactions were performed on a 30 mg scale unless otherwise stated.

[b] Yield of the isolated product. [c] Recovered starting material.

[d] Diastereomeric ratio: **11**/8-*epi*-**11** 2:1. [e] A single diastereomer was obtained.

[f] The starting material was first treated with NaI in acetone for 8 h. [g] The reaction was performed on a 7 g scale.



investigation by exploring the venerable Nozaki–Hiyama–Kishi (NHK) reaction (entry 1), which has proven efficient in many syntheses of medium-sized rings.^[22a] The desired transformation proceeded in low yield (10%) and with moderate diastereoselectivity (d.r. 2:1). Surprisingly, the major products formed in this reaction were a mixture of two diastereomeric cyclooctanes **14**. This competition (eight- versus seven-membered-ring formation) was also observed under samarium iodide mediated cyclization conditions with an allylic iodide substrate, although in this case the formation of the seven-membered ring to give **11** prevailed slightly (entry 3).^[25] In contrast, indium- and zinc-mediated conditions were more selective for a single product (entries 2 and 4). In the former case, **11** was afforded as a single diastereomer (13%), whereas the latter produced **14** (51%), and recovered **10** (34%). Magnesium-based conditions were ineffective for this transformation (entries 5 and 6). Gratifyingly, tin(II) chloride proved to be a superior reductant.^[22h,26] Finkelstein conversion of **10** into an allylic iodide, followed by SnCl₂-mediated cyclization, afforded synthetically useful quantities of **11** (53%), along with the recovery of **10**, and cycloheptanol **15** (Table 1, entry 7). Notably, only one diastereomer of each

cyclized product was obtained. When all reagents (SnCl₂, NaI, and **10**) were simply mixed together and heated in a single step (entry 8), a remarkably clean reaction ensued at 60 °C to afford **11** in 90% yield as a single diastereomer. Notably, this reaction was performed on a 7 g scale without a depression in yield.

With a six-step, multigram-scale synthesis of the full guaianolide skeleton complete, only redox manipulations were required to complete the target. Chemoselective reduction of the $\Delta_{10,14}$ alkene in **11** proved challenging in the presence of the more reactive α -methylenelactone. In the presence of the Wilkinson catalyst, only the latter was reduced to give **13** (Scheme 2). With PtO₂/H₂, both olefins could be readily hydrogenated. Taking advantage of the high reactivity of the α -methylenelactone toward conjugate addition, we first treated **11** with a catalytic quantity of sodium methoxide (10 mol%) in MeOH, and then reduced the methanol addition product with the Adam catalyst (PtO₂, AcOH, H₂) in near quantitative yield (96%) in the same flask. When attempting the global desilylation of **12** (TBAF, THF), we noticed that a base-mediated retro-conjugate addition of MeOH occurred, thus resulting in a 5:2 mixture of the deprotected conjugated ester and the methanol adduct in 83% yield. When DBU was added to the crude mixture, the reaction could be pushed to completion in favor of the conjugated ester product; thus, the ester was isolated in 69% yield on a gram scale. Finally, the addition of freshly activated MnO₂ provided mikanokryptin (**1**) in near-quantitative yield through highly chemoselective allylic oxidation. Notably, one gram of **1** was synthesized in a single pass from (+)-carvone in 6% overall yield. The absolute configuration of **1** was confirmed as previously reported (synthetic: $[\alpha]_D = +235.0^\circ$, natural: $[\alpha]_D = +264^\circ$ ($c = 0.098$, MeOH)). Moreover, it is envisioned that intermediate **11**, readily accessible in multigram quantities, could serve as a versatile intermediate for the synthesis of guaianolides containing both $\Delta_{4,5}$ and $\Delta_{10,14}$ functionalization.^[27]

In summary, we have completed a short, enantiospecific, gram-scale total synthesis of mikanokryptin, a complex 8,12-guaianolide. Although guaianolides have been the subject of numerous synthetic campaigns, most total synthetic routes to date have produced low-milligram quantities of material.^[28] To the best of our knowledge, this approach represents the first gram-scale, fully synthetic entry into this coveted sesquiterpene family. Two highly robust and scalable allylation processes were critical in processing large quantities of material. Through variations on this strategy, the synthesis of other mikanokryptin-type 8,12-guaianolides should be possible. Such endeavors, in addition to the exploration of alternative reagent-controlled allylation methods to enable the synthesis of all guaianolide stereochemical patterns, are currently under way and will be reported in due course.

Acknowledgements

This research was supported by the NIH (GM116952). T.J.M. is an Alfred P. Sloan Fellow and Cottrell Scholar. Bristol-Myers Squibb, Amgen, and the UC Berkeley Graduate

Division are acknowledged for providing predoctoral fellowships to X.H. S.X. thanks the National Natural Science Foundation of China (No. 21402149) and the Chinese Scholarship Council (CSC) fellowship program. We thank Dr. Hasan Celik and Yujia Tao for NMR spectroscopic assistance and technical assistance, respectively. Dr. Antonio DiPasquale is thanked for X-ray crystallographic analysis, for which support from NIH Shared Instrument Grant S10-RR027172 is acknowledged.

Conflict of interest

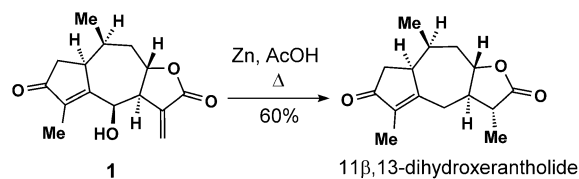
The authors declare no conflict of interest.

Keywords: allylation · guaianolides · natural products · terpenes · total synthesis

- [1] B. Ivanescu, A. Miron, A. Corciova, *J. Anal. Methods Chem.* **2015**, *2015*, 247685.
- [2] a) M. Chadwick, H. Trewin, F. Gawthrop, C. Wagstaff, *Int. J. Mol. Sci.* **2013**, *14*, 12780; b) G. F. Padilla-Gonzalez, F. A. dos Santos, F. B. Da Costa, *Crit. Rev. Plant Sci.* **2016**, *35*, 18.
- [3] a) S. Zhang, Y. K. Won, C. N. Ong, H. M. Shen, *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 239; b) A. Janecka, A. Wyrębska, K. Gach, J. Fichna, T. Janecki, *Drug Discovery Today* **2012**, *17*, 561.
- [4] a) I. Merfort, *Curr. Drug Targets* **2011**, *12*, 1560; b) I. H. Hall, K. H. Lee, C. O. Starnes, Y. Sumida, R. Y. Wu, T. G. Waddell, J. W. Cochran, K. G. Gerhart, *J. Pharm. Sci.* **1979**, *68*, 537.
- [5] a) L. G. Rocha, J. R. Almeida, R. O. Macedo, J. M. Barbosa-Filho, *Phytomedicine* **2005**, *12*, 514; b) H. Fuchino, T. Koide, M. Takahashi, S. Sekita, M. Satake, *Planta Med.* **2001**, *67*, 647.
- [6] a) J. J. Ross, J. T. Arnason, H. C. Birnboim, *Planta Med.* **1999**, *65*, 126; b) R. J. Marles, J. Kaminski, J. T. Arnason, L. Pazos-Sanou, S. Heptinstall, N. H. Fischer, C. W. Crompton, D. G. Kindack, D. V. Awang, *J. Nat. Prod.* **1992**, *55*, 1044.
- [7] B. Siedle, A. J. García-Piñeres, R. Murillo, J. Schulte-Mönting, V. Castro, P. Rüngeler, C. A. Klaas, F. B. Da Costa, W. Kisiel, I. Merfort, *J. Med. Chem.* **2004**, *47*, 6042.
- [8] a) M. R. O. Kreuger, S. Grootjans, M. W. Biavatti, P. Vandenaabee, K. D'Herde, *Anti-Cancer Drugs* **2012**, *23*, 883; b) M. M. Chaturvedi, B. Sung, V. R. Yadav, R. Kannappan, B. B. Aggarwal, *Oncogene* **2011**, *30*, 1615.
- [9] For a recent review of guaianolide syntheses, see: A. Santana, J. M. G. Molinillo, F. A. Macías, *Eur. J. Org. Chem.* **2015**, 2093.
- [10] a) D. H. R. Barton, J. E. D. Levisalles, *J. Chem. Soc.* **1958**, 4518; b) D. H. R. Barton, R. J. Wells, J. T. Pinhey, *J. Chem. Soc.* **1964**, 2518; c) S. Carret, J.-P. Deprés, *Angew. Chem. Int. Ed.* **2007**, *46*, 6870; *Angew. Chem.* **2007**, *119*, 6994; d) G. Valot, J. Garcia, V. Duplan, C. Serba, S. Barluenga, N. Winssinger, *Angew. Chem. Int. Ed.* **2012**, *51*, 5391; *Angew. Chem.* **2012**, *124*, 5487; e) T. S. L. Banchelin, S. Carret, A. Giannini, J.-P. Deprés, *Eur. J. Org. Chem.* **2009**, 3678; f) G. Blay, V. Bargues, L. Cardona, B. Garcia, J. R. Pedro, *J. Org. Chem.* **2000**, *65*, 6703; g) G. Blay, V. V. Bargues, L. Cardona, A. M. Collado, B. Garcia, M. C. Muñoz, J. R. Pedro, *J. Org. Chem.* **2000**, *65*, 2138; h) T. Hirose, N. Miyakoshi, C. Mukai, *J. Org. Chem.* **2008**, *73*, 1061; i) E. E. Anagnostaki, V. P. Demertzidou, A. L. Zografos, *Chem. Commun.* **2015**, 51, 2364.
- [11] a) W. Herz, A. Srinivasan, P. S. Kalyanaraman, *Phytochemistry* **1975**, *14*, 233; b) W. Herz, P. S. Kalyanaraman, *Phytochemistry* **1975**, *14*, 1664; c) W. F. Reynolds, R. G. Enriquez, M. A. Chavez, A. L. Silba, M. A. Martinez, *Can. J. Chem.* **1985**, *63*, 849; d) M. J. Bovill, M. H. P. Guy, G. A. Sim, D. N. J. White, W. Herz, *J. Chem. Soc. Perkin Trans. 2* **1979**, 53.
- [12] a) V. J. Bryan, T. H. Chan, *Tetrahedron Lett.* **1996**, *37*, 5341; b) G. A. Molander, J. B. Etter, P. W. Zinke, *J. Am. Chem. Soc.* **1987**, *109*, 453; c) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1991**, *56*, 4112; d) L. M. Fleury, A. D. Kosal, J. T. Masters, B. L. Ashfeld, *J. Org. Chem.* **2013**, *78*, 253.
- [13] For single allylation events in guaianolide synthesis, see: a) T. G. Elford, D. G. Hall, *J. Am. Chem. Soc.* **2010**, *132*, 1488; b) S. Kalidindi, W. B. Jeong, A. Schall, R. Bandichhor, B. Nosee, O. Reiser, *Angew. Chem. Int. Ed.* **2007**, *46*, 6361; *Angew. Chem.* **2007**, *119*, 6478; c) H. S. Yang, X. X. Qiao, F. Y. Li, H. Ma, L. G. Xie, X. Xu, *Tetrahedron Lett.* **2009**, *50*, 1110; d) H. Yang, Y. Gao, X. Qiao, L. Xie, X. Xu, *Org. Lett.* **2011**, *13*, 3670; e) B. Wen, J. K. Hexum, J. C. Widen, D. A. Harki, K. M. Brummond, *Org. Lett.* **2013**, *15*, 2644; f) S. V. Ley, A. Antonello, E. P. Balskus, D. T. Booth, S. B. Christensen, E. Cleator, H. Gold, K. Hogenauer, U. Hunger, R. M. Myers, S. F. Oliver, O. Simic, M. D. Smith, H. Sohoel, A. J. Woolford, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12073; g) S. P. Andrews, M. Ball, F. Wierschem, E. Cleator, S. Oliver, K. Högenauer, O. Simic, A. Antonello, U. Hüniger, M. D. Smith, S. V. Ley, *Chem. Eur. J.* **2007**, *13*, 5688.
- [14] a) A. Srikrishna, V. H. Pardeshi, G. Satyanarayana, *Tetrahedron: Asymmetry* **2010**, *21*, 746; b) A. Srikrishna, V. H. Pardeshi, *Tetrahedron* **2010**, *66*, 8160; c) E. L. Grimm, J. L. Methot, M. Shamji, *Pure Appl. Chem.* **2003**, *75*, 231.
- [15] M. Zahel, A. Kessberg, P. Metz, *Angew. Chem. Int. Ed.* **2013**, *52*, 5390; *Angew. Chem.* **2013**, *125*, 5500.
- [16] a) E. Lee, J. W. Lim, C. H. Yoon, Y. S. Sung, Y. K. Kim, M. Yun, S. Kim, *J. Am. Chem. Soc.* **1997**, *119*, 8391; b) V. Navickas, D. B. Ushakov, M. E. Maier, M. Strobele, H. J. Meyer, *Org. Lett.* **2010**, *12*, 3418; c) L. Z. Sun, F. Shah, M. A. Helal, Y. S. Wu, Y. Pedduri, A. G. Chittiboyina, J. Gut, P. J. Rosenthal, M. A. Avery, *J. Med. Chem.* **2010**, *53*, 7864; d) T. C. Johnson, M. R. Chin, T. Han, J. P. Shen, T. Rana, D. Siegel, *J. Am. Chem. Soc.* **2016**, *138*, 6068; e) F. L. Manzano, F. M. Guerra, F. J. Moreno-Dorado, Z. D. Jorge, G. M. Massanet, *Org. Lett.* **2006**, *8*, 2879; f) R. Marín-Barrios, A. L. García-Cabeza, F. J. Moreno-Dorado, F. M. Guerra, G. M. Massanet, *J. Org. Chem.* **2014**, *79*, 6501.
- [17] a) A. Srikrishna, N. C. Babu, *Tetrahedron Lett.* **2001**, *42*, 4913; b) D. S. Pisoni, D. B. Silva, R. A. Schenato, M. A. Ceschi, *J. Braz. Chem. Soc.* **2004**, *15*, 652.
- [18] Extensive undesired oxidation of the isopropenyl unit was observed under prolonged reaction times or in the absence of pyridine.
- [19] For examples, see: a) A. E. Greene, M. T. Edgar, *J. Org. Chem.* **1989**, *54*, 1468; b) A. Lauridsen, C. Cornett, T. Vulpus, P. Moldt, S. B. Christensen, *Acta Chem. Scand.* **1996**, *50*, 150; c) A. Barthel, F. Kaden, A. Jäger, P. Metz, *Org. Lett.* **2016**, *18*, 3298.
- [20] For the synthesis of **8**, see the Supporting Information.
- [21] A number of other reagents beside **8** were examined for this transformation (see the Supporting Information for details).
- [22] a) A. Fürstner, *Chem. Rev.* **1999**, *99*, 991; b) Y. Okuda, S. Nakatsukasa, K. Oshima, H. Nozaki, *Chem. Lett.* **1985**, *14*, 481; c) C. Petrier, J. L. Luche, *J. Org. Chem.* **1985**, *50*, 910; d) Y. Gao, X. Wang, L. Sun, L. Xie, X. Xu, *Org. Biomol. Chem.* **2012**, *10*, 3991; e) K. Foo, I. Usui, D. C. G. Götz, E. W. Werner, D. Holte, P. S. Baran, *Angew. Chem. Int. Ed.* **2012**, *51*, 11491; *Angew. Chem.* **2012**, *124*, 11659; f) S. Araki, H. Ito, Y. Butsugan, *J. Organomet. Chem.* **1988**, *347*, 5; g) J. Nokami, T. Tamaoka, H. Ogawa, S. Wakabayashi, *Chem. Lett.* **1986**, *15*, 541; h) P. K. Kalita, P. Phukan, *C. R. Chim.* **2013**, *16*, 1055; i) H. Tanaka, S. Yamashita, T. Hamatani, Y. Ikemoto, S. Torii, *Chem. Lett.* **1986**, *15*, 1611; j) J. Y. Zhou, Y. Jia, G. F. Sun, S. H. Wu, *Synth. Commun.* **1997**, *27*, 1899; k) M. Wada, K. Akiba, *Tetrahedron*

- Lett.* **1985**, 26, 4211; l) S. Araki, H. Ito, N. Katsumura, Y. Butsugan, *J. Organomet. Chem.* **1989**, 369, 291.
- [23] a) H. Fujioka, Y. Sawama, N. Murata, T. Okitsu, O. Kubo, S. Matsuda, Y. Kita, *J. Am. Chem. Soc.* **2004**, 126, 11800; b) H. Fujioka, T. Okitsu, Y. Sawama, N. Murata, R. Li, Y. Kita, *J. Am. Chem. Soc.* **2006**, 128, 5930.
- [24] Common deacetalization conditions with Brønsted acids failed to promote the desired transformation.
- [25] a) G. A. Molander, *Chem. Rev.* **1996**, 96, 307; b) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, 104, 3371; c) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem. Int. Ed.* **2009**, 48, 7140; *Angew. Chem.* **2009**, 121, 7276.
- [26] a) G. P. Boldrini, L. Lodi, E. Tagliavini, C. Tarasco, C. Trombini, A. Umanironchi, *J. Org. Chem.* **1987**, 52, 5447; b) M. K. Chaudhuri, S. K. Dehury, S. Hussain, *Tetrahedron Lett.* **2005**, 46, 6247.
- [27] The treatment of **1** with Zn⁰ in acetic acid at reflux gave 11 β ,13-dihydroxerantholide in 60% yield. This transformation allows access to mikanokryptin-type guaianolides without C6 hydrox-

ylation. 11 β ,13-Dihydroxerantholide has been previously isolated from *Pechuel-Loeschea leibnitziae*: F. Bohlmann, N. Borthakur, *Phytochemistry* **1982**, 21, 1160.



Communications

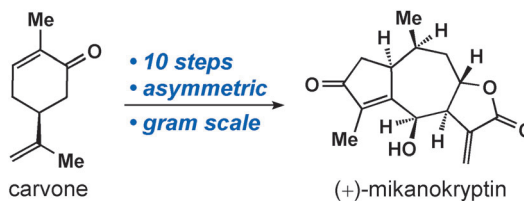


Natural Products Synthesis

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A Double Allylation Strategy for Gram-Scale Guaianolide Production: Total Synthesis of (+)-Mikanokryptin



Can't have too much of a good thing: The myriad stereochemical permutations of the guaianolide sesquiterpene lactones have precluded the synthesis of many unique members. Now a total synthesis of the *trans*-fused 8,12-guaianolide

(+)-mikanokryptin (see scheme) in 10 steps from (+)-carvone has been developed on the basis of two highly robust and scalable allylation processes, which were critical for processing large quantities of material.