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Short Syntheses of (±)-*δ*-Araneosene and Humulene Utilizing a Combination of Four-Component Assembly and Palladium-Mediated Cyclization

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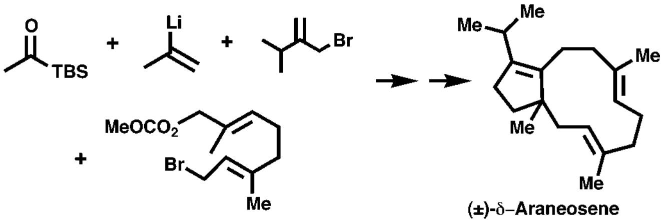
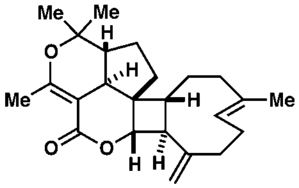
ABSTRACT



The four components shown are assembled in two steps, and the product is converted to araneosene by a short sequence.

The development of simple yet effective syntheses of multiprenyl natural products containing rings in the 9−11 size range continues to present a challenge, especially as more complex members of this class, such as the dollabellane group, are discovered.[1] The research that is described herein originated from methodology developed for the synthesis of the pentacyclic marine natural product antheliolide A,[2] which involved the rapid multicomponent coupling of prenyl units[3] and facile Pd-mediated ring closure.[4] Specifically, this paper describes the incorporation of these operations into new and effective syntheses of (±)-*δ*-araneosene and humulene, each of which contains an eleven-membered ring.



Antheliolide A

The synthesis of (±)-*δ*-araneosene (**1**) is outlined in Scheme 1. The first synthesis of *δ*-araneosene was reported by Mehta and co-workers.[5] A second synthesis was reported by Jenny and Borschberg.[6] In the first step of our synthesis of **1**, methyl *tert*-butyldimethylsilyl ketone was treated with

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[1] For a review, see: Rodriquez, A. D.; Gonzalez, E.; Ramirez, C. *Tetrahedron* **1998**, *54*, 11683.

[2] (a) Green, D.; Carmely, S.; Benayahu, Y.; Kashman, Y. *Tetrahedron Lett.* **1988**, *29*, 1605. (b) Smith, A. B., III; Carrol, P. J.; Kashman, Y.; Green, D. *Tetrahedron Lett.* **1989**, *30*, 3363.

[3] (a) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (b) Corey, E. J.; Lin, S.; Luo, G. *Tetrahedron Lett.* **1997**, *38*, 5771.

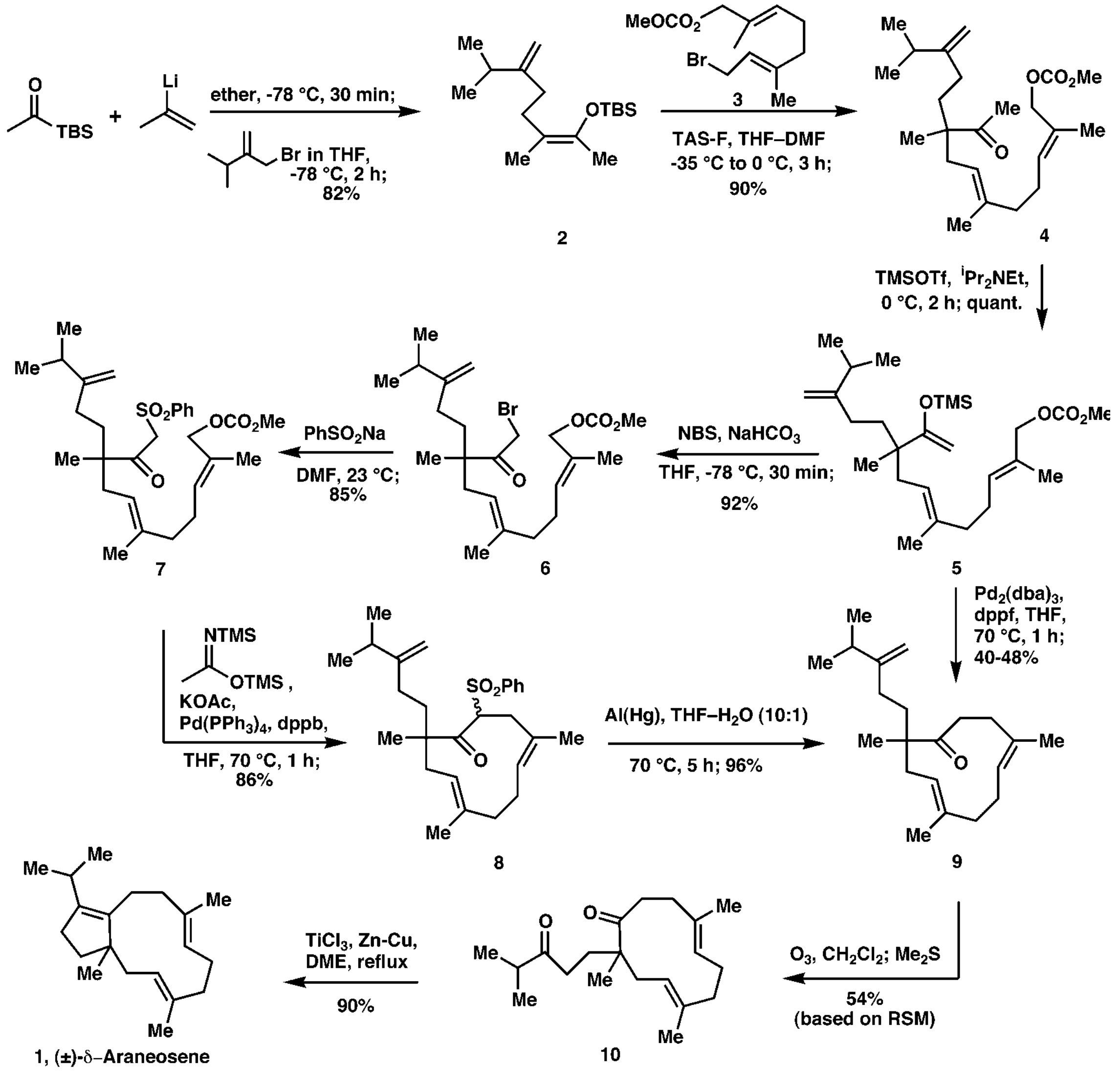
[4] See: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Godleski, S. A. Nucleophiles with Allyl-Metal Complexes. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Chapter 3.3. (c) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (d) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

[5] (a) Mehta, G. *Pure Appl. Chem.* **1990**, *62*, 1263. (b) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765. (c) Mehta, G.; Karra, S. R.; Krishnamurthy, N. *Tetrahedron Lett.* **1994**, *35*, 2761.

[6] Jenny, L.; Borschberg, H.-J. *Helv. Chim. Acta* **1995**, *78*, 715.

10.1021/ol026205p CCC: $22.00

Scheme 1. Synthesis of (±)-δ-Araneosene



2-propenyllithium in ether and then with 2-isopropylallyl bromide in THF to give the (*Z*)-enolsilyl ether **2** (82%). The sequence of reactions that leads to **2** includes (1) carbonyl addition of 2-propenyllithium, (2) Brook rearrangement of Si from C to O, and (3) allylation of the resulting allylic lithium reagent.[3] The silyl ether **2** was then transformed using $(Me_2N)_3S^+Me_3SiF_2^-$ (TAS-F)[7] into the corresponding TAS enolate, which was alkylated with bromide **3**[8] to form the methyl ketone **4** (90%). Thus, all carbons of δ-araneosene were assembled from four readily available components in just two steps in ca. 73% yield. We see no reason the synthesis of **4** cannot be carried out without isolation of **2**, thereby allowing a direct four-component synthesis of **4**. Conversion of methyl ketone **4** into the allylic carbonate/silyl ether **5** was effected in >99% yield using diisopropylethylamine and trimethylsilyl triflate in CH_2Cl_2 solution at 0 °C. Treatment of the allylic carbonate/silyl ether **5** with 10 mol % of Pd−dibenzylidene−acetone complex and bisdiphenylphosphinoferrocene (dppf) in THF at reflux for 1 h effected ring closure to form the 11-membered ketone **9** in 40−48% yield.[9,10] The ketone **9** could also be prepared in somewhat higher yield (ca. 65%) by a longer alternative route through the intermediates **6**, **7**, and **8**.[5,11] Selective ozonolysis of **9** (ca. 0.8 equiv of O_3) afforded the diketone **10**, which was transformed by McMurry cyclization[12] in 90% yield into (±)-δ-araneosene.

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[7] (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1980**, *21*, 2085.

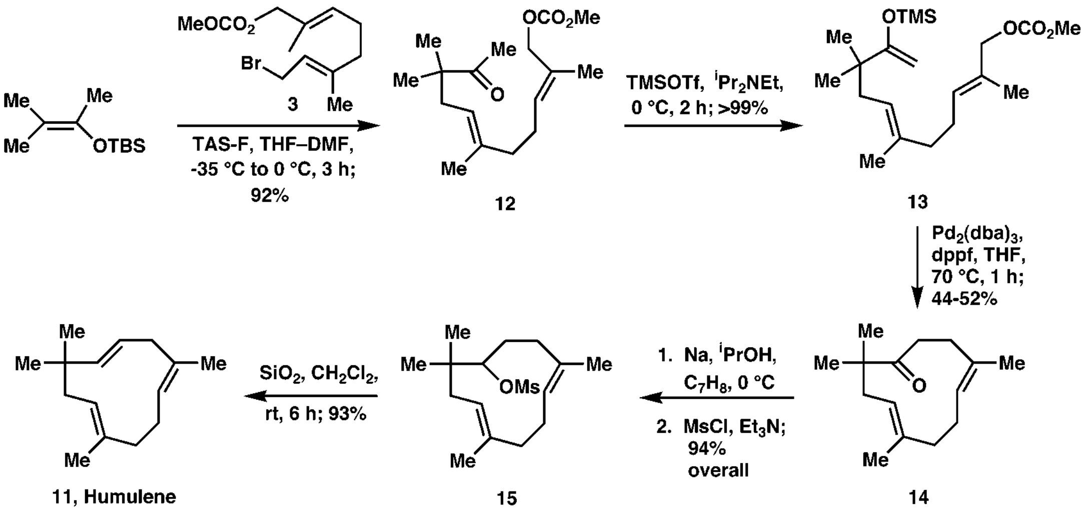
[8] For method of preparation, see Supporting Information.

[9] To the best of our knowledge, the Pd(0)-catalyzed intramolecular allylation using silyl enol ether with allylic carbonate has not been documented before. For an intermolecular version of this type of coupling reaction, see: (a) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325. (b) Tsuji, J.; Takahashi, K.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 4783.

[10] The use of the chelating phosphine ligand dppf retarded β-hydrogen elimination (which gives acyclic diene) relative to ring closure; see (a) Hartwig, J. F.; Driver, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (b) Hartwig, J. F.; Hamann, B. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

[11] For the conversion of **8** to **9**, see: Corey, E. J.; Chaykowsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.

Scheme 2. Synthesis of Humulene



The synthesis of humulene (**11**) was carried out by an approach paralleling that used for araneosene (**1**), as outlined in Scheme 2. Alkylation of the TBS enol ether of methyl isopropyl ketone[13] by **3** afforded the keto carbonate **12** (92%), which could be converted cleanly into the corresponding TMS enol ether **13**. Palladium-mediated cyclization of **13**, as described above for the conversion **5** → **9**, directly generated the required cycloundecadienone **14** in ca. 50% yield. This same compound was produced in ca. 65% yield from **13** by a longer process analogous to the sequence **5** → **8** → **9**. Reduction of ketone **14** to the corresponding secondary alcohol by gradual addition of isopropyl alcohol to a well stirred suspension of sodium sand and **14** in toluene at 0 °C proceeded quantitatively. Reaction of this alcohol with methanesulfonyl chloride and triethylamine in CH_2Cl_2 at −35 °C for 30 min and −20 °C for 30 min gave the mesylate **15** (94% overall from **14**). Elimination of methanesulfonate from **15** occurred upon stirring with silica gel in CH_2Cl_2 at 23 °C for 6 h to produce pure humulene (**11**), identical in all respects with an authentic sample. Of the several reported syntheses of humulene described, this is the simplest and most efficient.[14]

The syntheses of (±)-δ-araneosene and humulene disclosed herein are noteworthy for the simplicity of the C−C bond constructions and cyclization steps, which we believe will prove advantageous in the synthesis of related polyterpenoids.

Acknowledgment. We are grateful to Schering Plough for a Fellowship to T.H.

Supporting Information Available: Experimental procedures for the reaction sequences outlined in Schemes 1 and 2, complete with physical and spectroscopic data for each intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] (a) McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655. (b) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. (c) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.

[13] (a) Ohkata, K.; Mase, M.; Akiba, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1727. (b) This silyl enol ether could also be prepared from methyl *tert*-butyldimethylsilyl ketone and 2-propenyllithium followed by aqueous quench (84% yield) in a manner analogous to the preparation of **2** (Scheme 1).

[14] (a) Corey, E. J.; Hamanaka, E. *J. Am. Chem. Soc.* **1967**, *89*, 2758. (b) Vig, O. P.; Ram, B.; Atwal, K. S.; Bari, S. S. *Ind. J. Chem.* **1976**, *14B*, 855. (c) Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864. (d) McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723. (e) Takahashi, T.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 4695. (f) Corey, E. J.; Daigneault, S.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3675.