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

Tao Hu and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received May 17, 2002

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 units³ and facile Pd-mediated ring closure.⁴ Specifically, this paper describes the incorporation of these operations into new and effective syntheses of (\pm)- δ -araneosene and

10.1021/ol026205p CCC: \$22.00 © 2002 American Chemical Society Published on Web 06/18/2002

humulene, each of which contains an eleven-membered ring.



The synthesis of (\pm) - 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

ORGANIC LETTERS 2002 Vol. 4, No. 14 2441–2443

⁽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,

⁽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.



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 silvl 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 CH₂Cl₂ 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 O₃) afforded the diketone **10**, which was transformed by McMurry cyclization¹² in 90% yield into (\pm) - δ -araneosene.

^{(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.



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 ketone¹³ 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 $5 \rightarrow 9$, 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 $5 \rightarrow 8 \rightarrow 9$. 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 CH₂Cl₂ 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 CH₂Cl₂ 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 (\pm) - 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 polyter-penoids.

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.

OL026205P

^{(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.