Organometallics 1982, *1*, 1243-1244

Silicon in Synthesis. 20. Synthesis of (±)-Hirsutene Using Organosilicon-Mediated Transformations

Philip Magnus*† **and Dominick A. Quagliato**

Department of Chemistry, Indiana University
Bloomington, Indiana 47405

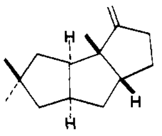
Received May 20, 1982

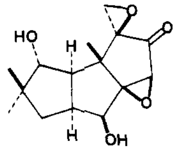
Summary: A total synthesis of the tricyclic sesquiterpene hirsutene is described, where all the key steps use organosilicon mediated reactions.

In recent years a substantial number of sesquiterpene natural products having the linearly fused *cis,anti,cis*-tricyclo[6.3.0.0^{2,6}]undecanoid carbon skeleton have been isolated.[1] This has spurred many interesting syntheses[2] and the more general development of methods for making fused five-membered rings.[3] Our own interest in this area has been to view such structures as platforms upon which to examine new methods in synthesis,[4] in particular those involving organosilicon chemistry.[5]

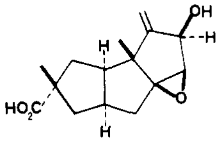
Here we report a short, convergent synthesis of (±)-hirsutene (1), the supposed biogenetic precursor of the antitumor substance coriolin (2), and hirsutic acid (2a) that utilizes a number of organosilicon-mediated steps.

4,4-Dimethylcyclopentenoyl chloride (3)[9] was treated with 1-(trimethylsilyl)-1-(phenylthio)ethylene (4),[6] in the presence of silver tetrafluoroborate at −20 °C in dichloromethane, to give the 4-phenylthio bicyclic enone 5 in 38% yield.[7] Despite extensive experimentation, we have been unable to improve upon this modest yield.[8] Treatment of 5 with methyllithium in ether followed by mercuric ion assisted hydrolysis gave the known bicyclic enone 6 in 93% yield.[10] Not only does the new annulation reaction provide a very short synthesis of 6 in overall yield 33%[10] but also confirms the structure of 5. Although the yield of 5 is modest, the overall conversion of 3 into 6 represents the shortest and highest yielding method for making this compound. Indeed, previous routes to 6 are extremely lengthy and low yielding.[10]

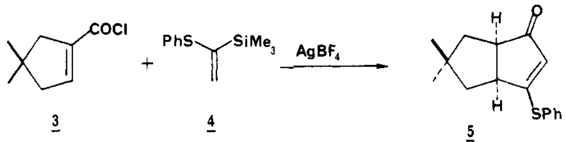

1



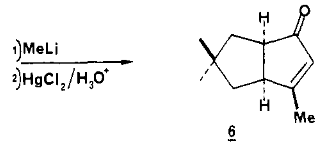
2



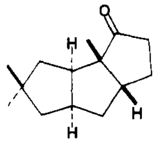
2a



3 + 4 → 5



6



7

Most of the previous syntheses of hirsutene proceed through the known degradation product, the ketone 7, and methenylate this material using the Wittig reaction.[2] Our objective was to add to required four-carbon unit to 6 with the requisite exocyclic methylene group in a single step. To this end, the necessary four-carbon unit 8 is readily available by using organosilicon methodology developed by Boeckman.[11] Treatment of 4-(trimethylsilyl)but-3-yn-1-ol with anhydrous hydrogen bromide gave the vinyl bromide 8, which was converted into the *tert*-butyldimethylsilyl ether 9 by using standard methods.[12] Conversion of 9 into the lithio derivative was achieved by halogen–metal exchange using *t*-BuLi in ether at −100 °C.[13] The corresponding cuprate derivative was formed[14] and treated with the enone 6 to give 10 in 70% yield. No endo addition products were detected.

The −Si-*t*-BuMe$_2$ protecting group, vital to the success of this synthesis, was removed using $Et_3BzN^+Cl^-/KF\cdot 2H_2O$[15] in CH_3CN at 60 °C to give the alcohol 11. Originally we employed an −OMe protecting group, which

---

† Part of this work was carried out at The Ohio State University, Columbus, Ohio 43210

(1) For an extensive compilation of key references see: Little, R. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* 1979, 305. Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* 1980, *102*, 5699.

(2) Syntheses of (±)-hirsutene: Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* 1981, *103*, 2744. Matsumoto, T. *Tetrahedron Lett.* 1976, 2795. Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* 1979, *101*, 6116. Greene, A. E. *Tetrahedron Lett.* 1980, 3059. Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* 1980, *102*, 6351. Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* 1976, 195. Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* 1975, 4377. Biogenetic-like conversion of $\Delta^{7(8)}$-protoilludene to hirsutene: Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* 1978, 1991. Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* 1981, *64*(4), 1347. Stereocontrolled synthesis of (±)-hirsutic acid: Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* 1978, *101*, 1284. Coriolin: Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *Ibid.* 1980, *102*, 2097. Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* 1980, 3587. Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* 1981, 756.

(3) Paquette, L. A. *Top. Current Chem.* 1979, *79*, 43. Eaton, P. E. *Tetrahedron* 1979, *35*, 2189. Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* 1981, *103*, 1604. Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem.* 1980, *45*, 1046 and references therein.

(4) Magnus, P.; Quagliato, D. A. *Organometallics*, preceding paper in this issue.

(5) Cooke, F.; Roy, G.; Magnus, P. *Organometallics* 1982, *1*, 893.

(6) Harirchian, B.; Magnus, P. *J. Chem. Soc., Chem. Commun.* 1977, 522 and the last citation in ref 3.

(7) This yield represents chromatographed, analytically pure material, ref 4 for data.

(8) The major problem with this reaction is the competitive polymerization of the reagent 4 and the formation of phenyl thioesters of 3.

(9) 4,4-Dimethylcyclopentenoyl chloride was made from dimedone and will be described in detail later. 4,4-Dimethylcyclopentene carboxaldehyde is known. Wilson, S. R.; Turner, R. B. *J. Org. Chem.* 1973, *38*, 2870. Magnusson, G.; Thorén, S. *Ibid.* 1973, *38*, 1380.

(10) 4,7,7-Trimethyl-*cis*-bicyclo[3.3.0]oct-3-en-2-one is a well-known compound that has been prepared by a variety of routes: Fex, T.; Froberg, J.; Magnusson, G.; Thorén, S. *J. Org. Chem.* 1976, *41*, 3518. Overall yield 30% through five steps. (This is a very convenient method, especially on a large scale.) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* 1975, 4377. Miyano, K.; Ohfune, Y.; Azuma, S.; Matsumoto, T. *Ibid.* 1974, 1545 (no details on every yield). Paquette, L. A.; Farkas, E.; Galemmo, R. *J. Org. Chem.* 1981, *46*, 5434. Overall yield 18% through eight steps.

(11) Boeckman, R. K., Jr.; Blum, D. M. *J. Org. Chem.* 1974, *39*, 3307.

(12) Ogilvie, K. K. *Can. J. Chem.* 1973, *51*, 3799.

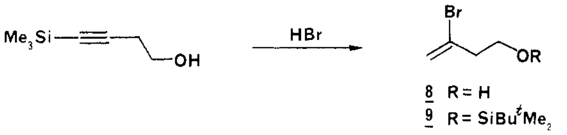
(13) Seebach, D.; Newmann, H. *Ber. Dtsch. Chem.* Ges. 1974, *107*, 847.

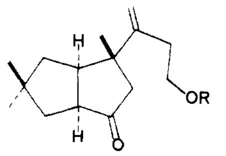
(14) The vinyl bromide 8 (R = MOM) has previously been converted into cuprate derivatives: Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* 1978, *100*, 5565; The most suitable method for converting 9 into a cuprate derivative involved a modification of the Noyori–Hooz methods: Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* 1980, 1247. Hooz, J.; Layton, R. B. *Can. J. Chem.* 1970, *48*, 1626. The 2-vinyl lithio species from 9 in ether was treated with CuI-P(NMe$_2$)$_3$ complex at −78 °C, followed by $BF_3\cdot OEt_2$ (2 equiv), and the enone 6 added. Smith, A. B.; Jerris, P. J. *J. Am. Chem. Soc.* 1981, *103*, 194. Workup gave 10: NMR ($CDCl_3$) δ 0.1 (6 H, s), 0.83 (9 H, s), 0.90 (3 H, s), 1.02 (3 H, s), 1.10 (3 H, s), 2.33 (2 H, *t*, *J* = 8 Hz), 3.68 (2 H, t, *J* = 8 Hz), 4.73 (1 H, s), 4.78 (1 H, s).

(15) Carpino, L. A. *J. Chem. Soc. Chem. Commun.* 1979, 514.

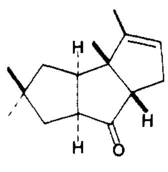
0276-7333/82/2301-1243$01.25/0 © 1982 American Chemical Society

under the conditions required for its removal, caused migration of the exocyclic double bond into the endocyclic position.

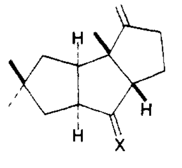




10 R = SiBu^{t}Me$_2$
11 R = H
12 R = SO$_2$C$_6$H$_4$Me-p



13



14 X = O
15 X = OH,H
16 X = OCS$_2$Me, H

The alcohol 11 was converted into the *p*-toluenesulfonate ester 12 in the standard way and treated with lithiohexamethyldisilazane (2.0 equiv) in ether at −78 °C to give the tricyclic ketone 14 (75%).

While there are many methods for directly reducing a ketone to methylene, particularly the Wolff–Kishner reduction and more recent sophistications of this method, the literature indicates that these methods might be expected to proceed in very low yield.[16] The tricyclic ketone 13 was reduced to *endo*-hirsutene in only 8% yield.[16] Consequently, 14 was treated with NaBH$_4$/MeOH to give the alcohol 15 as a mixture of epimers which was converted into its xanthate derivative 16 by treatment with CS$_2$/MeI/NaH/THF.[17] Exposure of 16 to tri-*n*-butyltin hydride in benzene heated at reflux in the presence of AIBN (catalytic) cleanly gave (±)-hirsutene (1) in 65% yield from 14.[18,19]

In summary, all the key steps in this short convergent route to (±)-hirsutene utilize organosilicon chemistry. The number of steps from 3 through to 1 is nine and proceeds in an overall yield of 7%.

Acknowledgment. The National Science Foundation is gratefully thanked for their support of this work (Grant No. CHE 8110674). The National Science Foundation provided funds for the purchase of a Bruker 360 NMR spectrometer. Professor Daniel Little is thanked for IR, NMR, and mass spectra of authentic hirsutene for comparison purposes.

Registry No. **1**, 59433-37-3; **2**, 33404-85-2; **3**, 78064-83-2; **4**, 62762-20-3; **5**, 82494-86-8; **6**, 60064-71-3; **8**, 76334-36-6; **9**, 82511-02-2; **10**, 82511-03-3; **11**, 82511-04-4; **12**, 82511-05-5; **13**, 79897-51-1; **14**, 82511-06-6; **15** isomer 1, 82511-07-7; 15 isomer 2, 82536-00-3; **16** isomer 1, 82511-08-8; 16 isomer 2, 82536-01-4; 4-(trimethylsilyl)but-3-yn-1-ol, 2117-12-6; lithiohexamethyldisilazane, 4039-32-1.

---

(16) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* 1981, *64* (5), 1347.

(17) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* 1981, 743.

(18) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* 1981, *53*, 15 and references therein. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(19) Selected NMR data: 11 (CDCl$_3$), δ 0.87 (3 H, s), 0.97 (3 H, s), 1.08 (3 H, s), 3.00–1.20 (10 H, m), 3.70 (2 h, t, J = 8 Hz), 4.77 (1 H, s), 4.80 (1 H, s); 14, δ 0.92 (3 H, s), 0.98 (3 H, s), 1.10 (3 H, s), 2.90–1.20 (1 H, m), 4.90 (1 H, s), 4.92 (1 H, s); 1 (CDCl$_3$; 360 MHz), δ 0.93 (3 H, s), 0.96 (3 H, s), 1.06 (3 H, s), 1.22 (1 H, m), 1.43 (6 H, m), 1.65 (1 H, m), 1.73 (1 H, m), 2.18 (1 H, m), 2.47 (3 H, m), 4.78 (1 H, s), 4.82 (1 H, s), ^{13}C NMR 23.18, 26.82, 27.24, 29.73, 30.90, 38.62, 40.86, 41.86, 44.25, 48.97, 49.96, 53.43, 55.92, 103.50, 162.76 ppm. All new compounds were completely characterized by NMR, IR, and MS analysis and/or microanalysis.

(Pentaalkylditin)lithiums: Significant Species in Some (Trialkyltin)lithium Preparations

William Kitching,* Henry A. Olszowy, and Gregory M. Drew

Department of Chemistry, University of Queensland Brisbane 4067, Australia

Received April 30, 1982

Summary: (Pentaalkylditin)lithiums are demonstrated to be present in preparations of (trialkyltin)lithium reagents (from the trialkyltin halide and lithium in tetrahydrofuran) by direct observation (^{119}Sn NMR) and alkylation to R$_5$Sn$_2$R′ (R = methyl, *n*-propyl, isopropyl; R′ = cyclohexyl, methyl). Cyclohexylation of (i-C$_3$H$_7$)$_5$Sn$_2$Li proceeds by a free radical route. The R$_5$Sn$_2$Li species are considered to arise by oxidative addition of R$_3$SnLi to R$_2$Sn, formed by R$_3$SnLi $\rightleftharpoons$ R$_2$Sn:RLi, dissociation of which is promoted by R$_6$Sn$_2$ scavenging of RLi.

The reactions of simple (alkyltin)- or (aryltin)lithium reagents usually can be understood in terms of R$_3$SnLi (or some aggregated or solvated assembly) functioning as an electron-transfer reagent, nucleophile, or base.[1–4] However, there are observations,[5–8] mainly with tributyl- and trimethyltin alkali reagents, consistent with the stannylene (R$_2$Sn:) being a significant component of the equilibrium below (eq 1).

$$\mathrm{R_3SnLi} \rightleftharpoons \mathrm{R_2Sn:} + \mathrm{RLi} \qquad (1)$$

An attraction to this proposal is that some R$_3$SnLi have been synthesised by reaction of SnCl$_2$ with 3 equiv of RLi, a procedure[9–11] which could involve the reverse of (1) as the final step. Furthermore, a plausible scheme[8] for the transformation of (CH$_3$)$_3$SnLi to ((CH$_3$)$_3$Sn)$_3$SnLi, which occurs under certain conditions,[11] has eq 1 as the first step followed by oxidative addition of (CH$_3$)$_3$SnLi to (CH$_3$)$_2$Sn yielding (CH$_3$)$_5$Sn$_2$Li. In this communication we wish to describe the characterization of some R$_5$Sn$_2$Li species, the formation of which constitutes very persuasive evidence for the operation of eq 1 and the scheme[8] for (R$_3$Sn)$_3$SnLi formation.

---

(1) Key references are contained in: Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833.

(2) San Filippo, J.; Silbermann, J. *J. Am. Chem. Soc.* **1981**, *103*, 5589.

(3) Kitching, W.; Olszowy, H. A.; Waugh, J.; Doddrell, D. *J. Org. Chem.* **1978**, *43*, 898.

(4) Kitching, W.; Olszowy, H. A.; Harvey, K. *J. Org. Chem.* **1981**, *46*, 2423.

(5) Coates, G. E.; Blake, D.; Tate, J. M. *J. Chem. Soc.* **1961**, 618.

(6) Tamborski, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237.

(7) Wursthorn, K. W.; Kuivila, H. G.; Smith, G. F. *J. Am. Chem. Soc.* **1978**, *100*, 2779.

(8) See also: Quintard, J. P.; Pereyre, M. *Rev. Silicon, Germanium, Tin Lead Compd* **1980**, *4*, 153.

(9) Gilman, H.; Rosenberg, S. D. *J. Am. Chem. Soc.* **1952**, *74*, 531; **1953**, *75*, 2507.

(10) Wittig, G.; Meyer, F. J.; Lange, G. *Justus Liebigs Ann. Chem.* **1951**, *571*, 193.

(11) Wells, W. L.; Brown, T. L. *J. Organomet. Chem.* **1968**, *11*, 271.