Tetrahedron Letters, Vol.27, No.8, pp 905-908, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

FIRST STEREOSPECIFIC SYNTHESIS OF E-γ-BISABOLENE. A METHOD FOR THE CONCURRENT GENERATION OF A RING AND A TETRASUBSTITUTED EXOCYCLIC DOUBLE BOND.

E. J. Corey and William L. Seibel
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

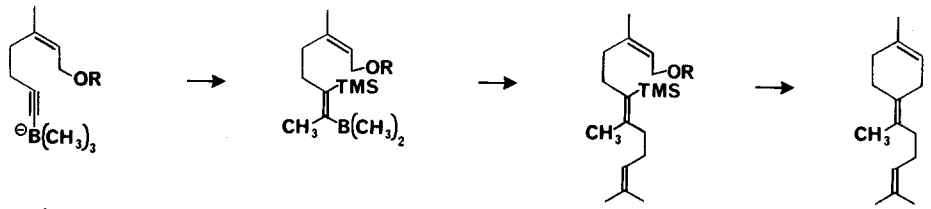
Summary: A short stereospecific synthesis of E-γ-bisabolene (1) from an acyclic acetylenic precursor (either 2 or 6) is described.

E-γ-bisabolene (1)[1] is a long known sesquiterpene which is broadly distributed in nature[2] and of considerable biosynthetic interest as a predecessor of many cyclic and oxygenated terpenoids.[3] This relatively simple substance hitherto has not been synthesized in a stereocontrolled way for lack of a methodology which can generate specifically either an E or Z exocyclic tetrasubstituted olefin.[4] Indeed the stereocontrolled synthesis of exocyclic tetrasubstituted olefins has remained as a classic unsolved general problem. We report herein a stereospecific synthesis of E-γ-bisabolene which involves the concurrent construction of both the tetrasubstituted double bond and the six-membered ring. The synthesis may be carried out from either of two isomeric acetylenic starting materials (2 or 6). Boron, silicon, copper, and titanium reagents are utilized in this relatively short (two-flask) process.

The synthesis of 1 proceeded as follows. Acetylene 2[5] in tetrahydrofuran (THF) solution was deprotonated with n-butyllithium and the resulting lithio acetylide was treated with tris(4-methyl-3-pentenyl)borane[7] to afford the alkynyltrialkylborate 3. Upon addition of trimethylsilyl trifluoromethanesulfonate, 3 was converted to the silylated vinylborane 4. The borane 4 upon successive reaction with n-butyllithium and cuprous iodide was transformed into a dark brown solution of the corresponding vinylcopper reagent which after treatment with triethylphosphite, hexamethylphosphoric triamide and methyl iodide produced the silyl triene 5 isolated in 84% overall yield as a single isomer (by 270 MHz pmr and chromatographic analysis). Desilylation of 5 (tetrabutylammonium fluoride (TBAF), THF, 0°) gave the corresponding alcohol (96% yield) which upon exposure in methylene chloride solution to 1 : 1 titanium tetrachloride-N-methylaniline complex[8] resulted in clean cyclization to E-γ-bisabolene (91% yield, 99.6% E by capillary VPC analysis).[9]

The analogous process for the synthesis of E-γ-bisabolene starting from acetylene 6[10] was accomplished successfully using a modification in the cyclization step. Thus 6 was converted via the lithio derivative to the tris(4-methyl-3-pentenyl)borate which upon treatment with trimethylsilyl trifluoromethanesulfonate afforded stereospecifically vinyl silane 7 in 84% yield. The cyclization of the alcohol corresponding to 7 did not proceed cleanly under a variety of conditions with Lewis acid reagents. However, the required conversion to E-γ-bisabolene was effected by 2-fluoro-N-methylbenzothiazolium trifluoromethanesulfonate[11] in the presence of triethylamine in 85% yield (97.5% purity of 1 by VPC analysis[9]).

In principle the methodology described above should also be applicable to the synthesis of Z-γ-bisabolene (8) from acetylene 2 and trimethylborane according to the following scheme:

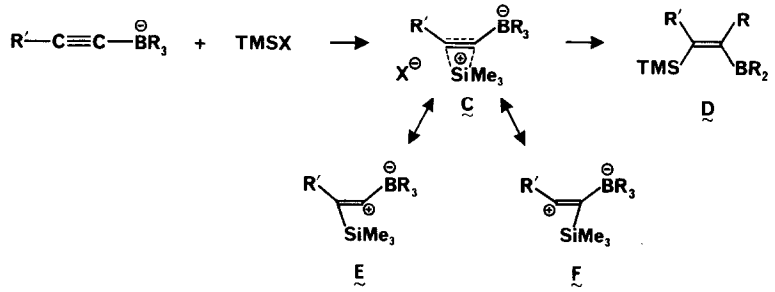


A B 8

However, it was found that the transformation of A to B proceeded in only poor yield. Substitution of trimethylborane as the reagent for acetylenic borate formation by thexyldimethylborane, catechol methylboronate, pinacol methylborate or bis(dimethylamino)methylborane did not lead to improvement. Thus, the extension of the present approach to the synthesis of Z-γ-bisabolene (8) from 2 awaits the development of an effective reagent for geminal methylboronation of acetylenes.

The stereospecific conversion of alkynyl trialkylborates to tetrasubstituted olefins in the acyclic series has previously been reported[12] to follow the stereochemical course shown below:

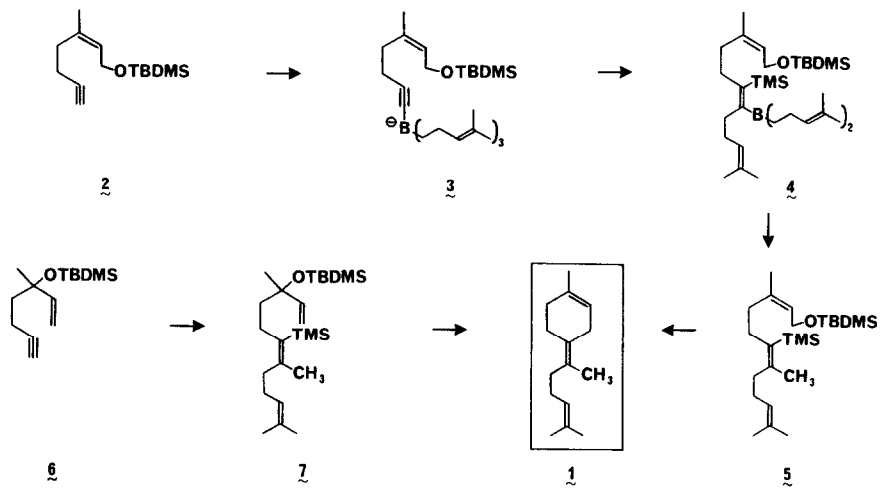
Our data are in accord with the earlier results and also underscore the high stereoselectivity of this process. To our knowledge there has been no satisfactory explanation of this intriguing and useful stereospecificity. Although a definitive mechanistic study is lacking,[13] one attractive possibility is the following:



The key feature of this mechanism is the intermediacy of the unusual silicon bridged species C from which product (D) can be formed stereospecifically by rearrangement of R from boron to carbon (backside to Si). The bridged structure C is a hybrid of canonical forms E (stabilized by α-boron hyperconjugation) and F (stabilized by both β-boron and β-silicon hyperconjugation) and might therefore be unusually favorable.

The following note describes a stereoselective route to Z-γ-bisabolene using a related but different rearrangement with the opposite stereochemical preference.[14] Experimental details are provided.[15]

Vinylsilanes 4 and 7: A solution of 2 or 6 (0.15 M) in THF at -78° was treated with 1 equiv of n-butyllithium. After 5 min, 1.25 equiv of tris(methyl-3-pentenyl)borane was added. After 5 min, 1.25 equiv of $Me_3SiOSO_2CF_3$ was added, and the reaction mixture was maintained at -78° for 6.5 h. After warming to -30°, 1.87 equiv of butyllithium was introduced, imparting a yellow



color over the subsequent 10 min. Addition of 1.05 equiv of cuprous iodide resulted in immediate darkening of the solution. The cuprate formation was allowed to proceed for 10 min, and triethylphosphite (1.3 equiv), hexamethylphosphoric triamide (20% volume) and methyl iodide (3.0 equiv) were added sequentially. The mixture was slowly brought to room temperature and the residual boron compounds were oxidized with 3M sodium hydroxide solution and 30% hydrogen peroxide. Extractive isolation with ether afforded the crude product which was purified via silica gel flash chromatography.

E-γ-Bisabolene from 5: A solution of 6.5 mg (0.059 mmol) of titanium tetrachloride in 1 ml of methylene chloride at -23° was treated with 6.4 μl (0.059 mmol) of N-methylaniline resulting in an opaque blood red mixture. After 20 min, a solution of 10 mg (0.034 mmol) of the alcohol corresponding to 5 in 15 μl of methylene chloride was added dropwise. The reaction mixture was stirred for 1 hr then quenched with 1 ml of water. VPC analysis indicated a 91% yield of E-γ-bisabolene with E:Z ratio of 99.6 : 0.4. E-γ-bisabolene was isolated in 82% yield by careful removal of the solvent. The pmr spectrum so obtained was identical with that of an authentic sample.[9]

E-γ-Bisabolene from 7: A solution of 4.4 mg (0.015 mmol) of the alcohol corresponding to 7 in 50 μl of methylene chloride and 10.5 μl (0.075 mmol) of triethylamine were simultaneously added to a -25° solution of 24 mg (0.075 mmol) of 2-fluoro-N-methylbenzothiazolium trifluoromethanesulfonate and 1.0 μl of hexadecane in 1.2 ml of methylene chloride. The resulting orange solution was stirred at -25° for 6 hr. Analysis by VPC indicated an 85% yield of E-γ-bisabolene with E:Z ratio of 97.5 : 2.5.

References and Notes

1. For nomenclature of bisabolenes see E. Guenther, "The Essential Oils," Vol. 2, p. 84, 1949, D. Van Nostrand Co., Inc. New York.

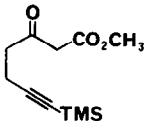
2. (a) F. Bohlmann, K. Knoll, R. King, and H. Robinson, Phytochem., 18, 1997 (1979); (b) P. Simon, ibid., 21, 1299 (1982); (c) F. McEnroe and W. Fenical, Tetrahedron, 34, 1661 (1978); (d) D. J. Faulkner, Nat. Prod. Rep., 1, 251 (1984).

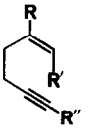
3. (a) D. E. Cane, Tetrahedron, 36, 1109 (1980); (b) P. Anastasis, I. Freer, C. Gilmore, H. Mackie, K. Overton, and S. S. Swanson, Chem. Comm., 268 (1982); (c) W. Parker, J. S. Roberts, and R. Rancage, Quart. Rev. Chem. Soc., 21, 331 (1967).

4. (a) O. P. Vig, B. Ram, C. P. Khera, and J. Chandler, Ind. J. Chem., 8, 955 (1970); (b) D. J. Faulkner and L. E. Wolinsky, J. Org. Chem., 40, 389 (1975); (c) O. P. Vig, S. D. Sharma, P. Kumar, and M. L. Sharma, J. Ind. Chem. Soc., 52, 614 (1975); (d) L. E. Wolinsky, D. J.

Faulkner, J. Finer, and J. Clardy, J. Org. Chem., 41, 697 (1976); (e) S. Sakane, J. Fujiwara, K. Maruoka, and H. Yamamoto, J. Am. Chem. Soc., 105, 6154 (1983).

5. Acetylene 2 was prepared as follows. The dilithio dianion of methylacetoacetate was alkylated with 3-bromo-1-trimethylsilylpropyne (THF, 0°, 5 min) to give 9. Deprotonation of 9 (1.1 equiv KH, 1.1 equiv 18-crown-6, THF, 0°, 20 min) followed by enolate trapping with diphenylchlorophosphate (slow dropwise addition of a -78° solution of 1.5 equiv of phosphate to a -78° solution of anion and reaction for 2 hr at -78°) gave the E phosphate 10. Slow dropwise addition of a precooled (-78°) solution of 10 to a -95° ethereal solution of lithium trimethylferrate[6] (2.7 equiv) cleanly afforded ester 11. Reduction of 11 with diisobutylalumium hydride (3.0 equiv, -78°, CH_2Cl_2) and desilylation (TBAF, 0°, THF, 15 min) produced the alcohol 12 which was silylated (1.3 equiv of TBDMSCl, 1.5 equiv Et_3N, cat. DMAP, CH_2Cl_2, 3 h) to form 2.





9

10 R = $OPO(OC_6H_5)_2$; R' = CO_2CH_3; R'' = TMS

11 R = CH_3; R' = CO_2CH_3; R'' = TMS

12 R = CH_3; R' = CH_2OH; R'' = H

6. E. J. Corey and G. H. Posner, Tetrahedron Letters, 315 (1970).

7. Prepared from the corresponding Grignard reagent and boron trifluoride etherate: (a) M. Julia, S. Julia, and R. Guégan, Bull. Soc. Chim. France, 1072 (1960); (b) R. Lyle, E. DeWitt, and I. Pattison, J. Org. Chem., 21, 61 (1956).

8. T. Saito, A. Itoh, K. Oshima, and H. Nozaki, Tetrahedron Letters, 3519 (1979); Bull. Chem. Soc. Japan, 54, 1456 (1981).

9. Reference samples of E- and Z-γ-bisabolene were prepared as described in ref. 4d.

10. Acetylene 6 was obtained by treatment of a solution of 5-hexyn-2-one (F. Barbot, D. Mesnard, and L. Miginiac, Org. Prep. Proc. Int., 10, 261 (1978)) in ether at 0° with 1.25 equiv of vinylmagnesium bromide, and subsequent silylation (1.4 equiv TBDMSOTf, 1.9 equiv triethylamine, CH_2Cl_2, 5 h, 23°).

11. For a similar use of this reagent see S. Kobayashi, M. Tsutsui, and T. Mukaiyama, Chem. Lett., 1169 (1977).

12. P. Binger and R. Köster, Synthesis, 309 (1973).

13. See, however, A. Pelter, T. W. Bentley, C. R. Harrison, C. Subrahmanyam, and R. J. Laub, J. Chem. Soc. Perkin I, 2419 (1976).

14. E. J. Corey and W. L. Seibel, following paper.

15. This work was assisted financially by the National Science Foundation.

(Received in USA 15 October 1985)