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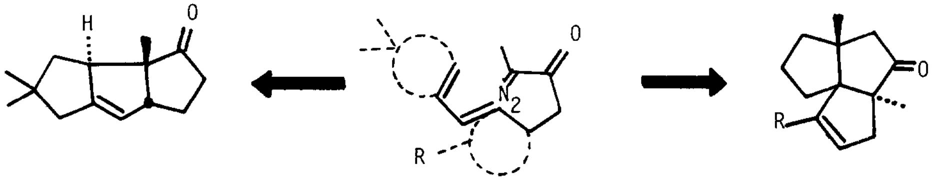
STEREOCONTROLLED TOTAL SYNTHESIS OF ISOCOMENE SESQUITERPENES

Brindaban C. Ranu, Misha Kavka, Leslie A. Higgs and Tomas Hudlicky*[1]

Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061

Abstract: Four isomers of the sesquiterpene isocomene have been synthesized in high yields and in a stereocontrolled fashion from the tricyclic triquinane 1 obtained by the cyclopentene annulation method. Carbon-13 data was obtained for all of the isocomene sesquiterpenes.

The pursuit of a general synthetic methodology for the preparation of linearly and nonlinearly fused triquinanes has led us to the synthesis of ketoester 1.[2,3] This substance has been attained by the cyclopentene annulation of a dienic diazoketone possessing the general structural parameters depicted in i and serving as entry for the construction of either hirsutane[4] or isocomene[2] type sesquiterpenes depending on the endocyclic or exocyclic disposition of the diene moiety.[4] Owing to its reductive and epimerizable capacity the acrylate 1 seemed an ideal precursor for the controlled preparation of all isocomene hydrocarbons. We have therefore prepared α and β isocomenes as well as their unnatural isomers as depicted in Scheme 1.



iii i ii, R = H, CH_3, CO_2R
1, CO_2Et

Hydrogenation of acrylate 1 and a carefully monitored Wittig reaction of the keto ester at room temperature provided olefin 3. This compound was epimerized quantitatively to 4 which could also be produced directly if the Wittig reaction was performed at elevated temperature.[2,5] To prevent epimerization of the labile ester immediate reduction of this functionality with $LiAlH_4$ was carried out and followed by tosylation and displacement to furnish β-epiisocomene 5.[4] Previously reported isomerization of this type of exocyclic olefin was accomplished with p-TsOH in CH_2Cl_2[6] to provide epiisocomene 7 in an overall yield of 51% from 1. Indentical reaction sequence applied to isomerized ester 4 gave β-isocomene 6[6] and isocomene 8[6,7] in the yields of 55% and 51% respectively. Since we had previously reported on the preparation of the corresponding isocomenic acids[2], the synthesis of their methylols and of the parent hydrocarbons constituted the attainment of a general method of synthesis which adequately addressed the provision of all natural products possessing isocomene nucleus and containing at the site of the secondary methyl group any potential oxidation levels between that of a carboxylic acid and a methyl group.

Finally, an additional reason for the synthesis of epiisocomene stemmed not only from our desire to obtain and to tabulate the carbon-13 chemical shift parameters for this substance in comparison to the spectral parameters of isocomene (chemical shifts are indicated in Scheme 1) but also to have a sample on hand as a standard against the outcome of hydrogenation (and eventual conversion to epiisocomene) of ketone 9 which we have prepared in several ways[4,8] and which has been reported to provide isocomene.[9]

Acknowledgments

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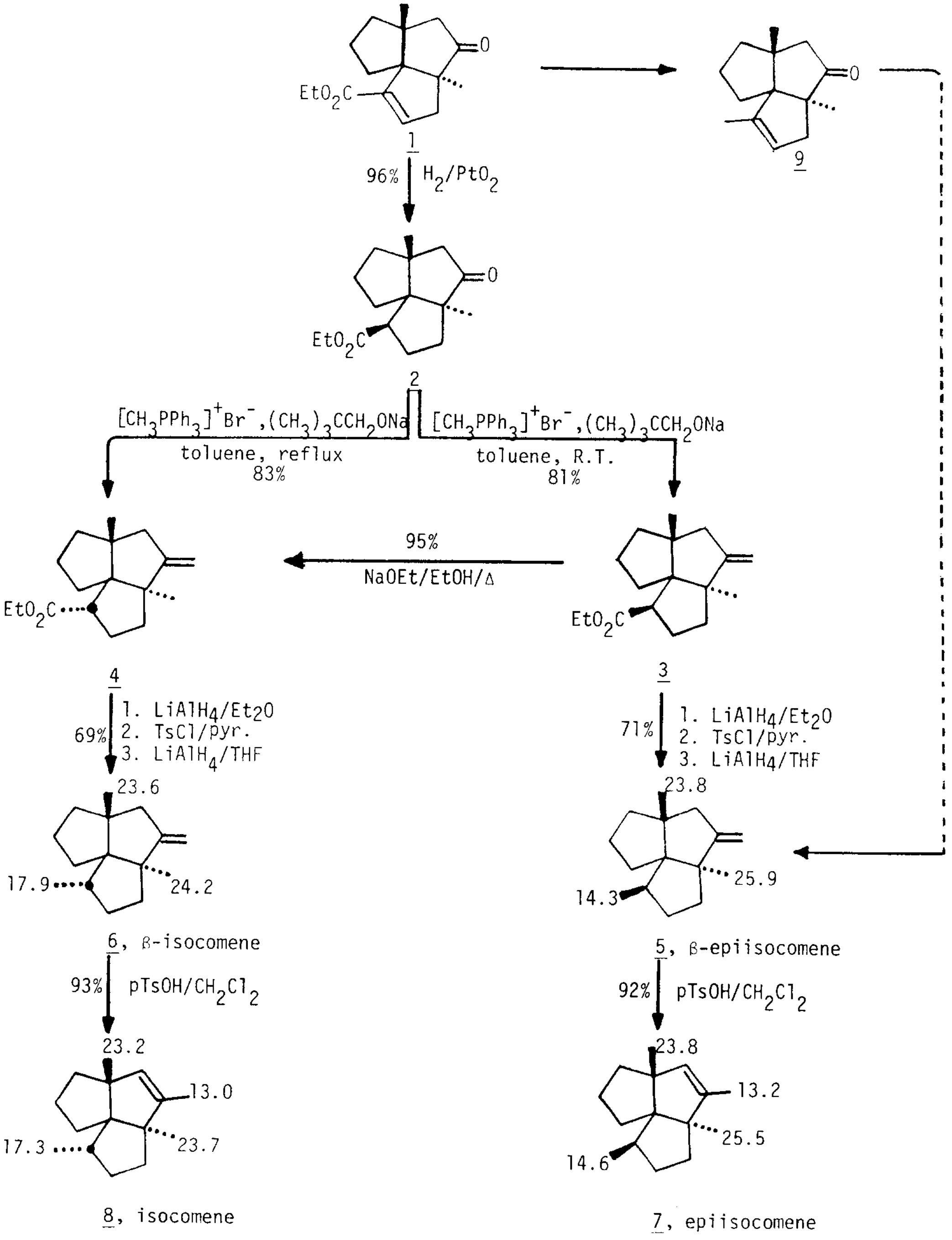
Supplementary Materials Available: Experimental and Spectral data for compounds 3, 4, 5, 6, 7, and 8 may be obtained from the authors.

References

1. Fellow of the Alfred P. Sloan Foundation, 1981-5.
2. R. P. Short, B. C. Ranu, J. M. Revol, T. Hudlicky, J. Org. Chem., 48, 4453 (1983).
3. All new compounds described in this report were fully characterized by ^{1}H-, ^{13}C-NMR, IR and Mass Spectroscopy. Experimental and Spectra data are available from the authors.
4. R. P. Short, L. Rice, T. Hudlicky, unpublished observations: another entry to nonlinear triquianes is provided by the use of ortho-Claisen rearrangement of acetylenic carbinols. Hydroboration/protonation of the resulting enynes provides exocyclic dienes containing alkyl instead of carboxy substituents. Epiisocomene becomes available from ketone 9 by

Scheme 1



^{13}C-NMR shifts are indicated downfield from TMS and upfield from $CDCl_3$(δ= 77.0).

this strategy whereas the synthesis of hirsutene has been reported: T. Hudlicky, T. M. Kutchan, R. S. Wilson, D. T. Mao, *J. Am. Chem. Soc.*, **102**, 6351 (1980).

5. The Wittig reaction [The conditions were adapted from: J. M. Conia and J. Limasset, *Bull. Soc. Chim. Fr.*, **6**, 1936 (1967); see also ref. 6e.] proved to be extremely sensitive to any attempts at scale up. Using 0.001 m of ketone **2** (as reported in ref. 2), **3** was produced in 8.5 hours at R.T. and **4** required 2 hours at reflux. When the scale was doubled, room temperature reaction was much slower and epimerization of **3** to **4** began to compete after 10 hours. On the other hand, at elevated temperature the reaction mixture contained 90% of **3**, 2% of **4** and 8% of **2** after 25 min. After 40 min. this ratio dropped to 60:40 (**4**:**3**). While the conditions are not optimized it appears that better results are obtained at elevated temperature provided the reaction is monitored *extremely* carefully. The esters **3** and **4** and their alcohols are separable by TLC or flash chromatography (see supplementary materials).
6. a, W. Oppolzer, K. Battig, T. Hudlicky, *Tetrahedron*, **37**, 4359 (1981). For other syntheses of isocomene see also: b, W. Oppolzer, K. Battig, T. Hudlicky, *Helv. Chim. Acta*, **62**, 1493 (1979); c, L. A. Paquette, Y. K. Han, *J. Org. Chem.* **44**, 4014 (1979); *J. Am. Chem. Soc.*, **103**, 1835 (1981); d, M. C. Pirrung, *J. Am. Chem. Soc.*, **101**, 7130 (1979); *J. Am. Chem. Soc.* **103**, 82 (1981); e, W. G. Dauben, D. M. Walker, *J. Org. Chem.*, **46**, 1103 (1981); f, P. A. Wender, G. B. Dreyer, *Tetrahedron*, **37**, 4445 (1981); E. Wenkert and T. S. Arrhenius, *J. Am. Chem. Soc.*, **105**, 2030 (1983).
7. Spectral and chromatographic properties of isocomene prepared by the route above were identical (IR, NMR, TLC, G.C.) with those of the sample provided to us by Professor L. A. Paquette.
8. Acrylate **1** was converted to **9** by the following sequence of operations: $(CH_2OH)_2$/pTsOH; $LiAlH_4/Et_2O$; TsCl/Et_3N; $LiAlH_4$/THF; H_3O^+.
9. S. Chatterjee, *J. Chem. Soc. Chem. Comm.*, 620 (1979). This paper reported the hydrogenation of **9** and further conversion to isocomene. These results have been disputed on steric grounds by several groups active in this field (ref. 6e,d). While we do not yet have data for the steric outcome of the hydrogenation of **9**, the hydrogenation of **1** proceeds to the extent of 100% to give the *epi* configuration of the substituent.

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