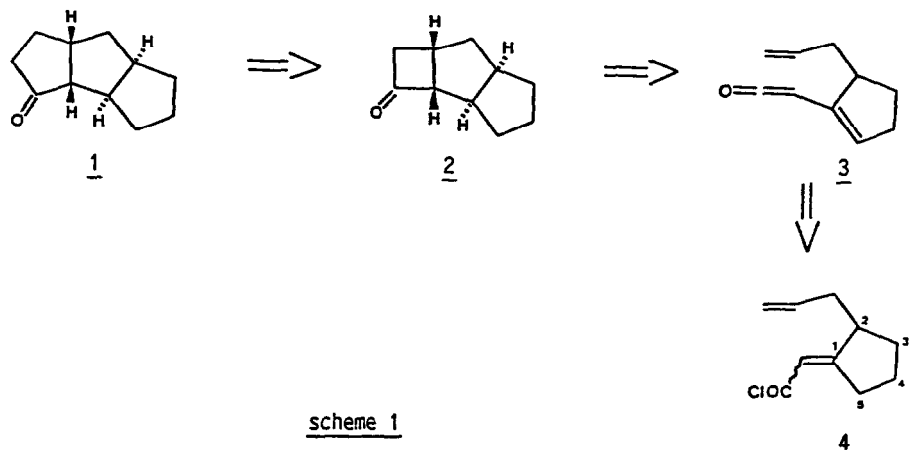
Tetrahedron Letters,Vol.29,No.4,pp 459-462,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

Intramolecular [2+2] cycloadditions of vinylketenes to olefins. Part II. The synthesis of a linear annelated triquinane derivative.

Alain De Mesmaeker, Siem J. Veenstra, Beat Ernst*
Central Research Laboratories, Ciba-Geigy Ltd., CH-4002 Basel, Switzerland.

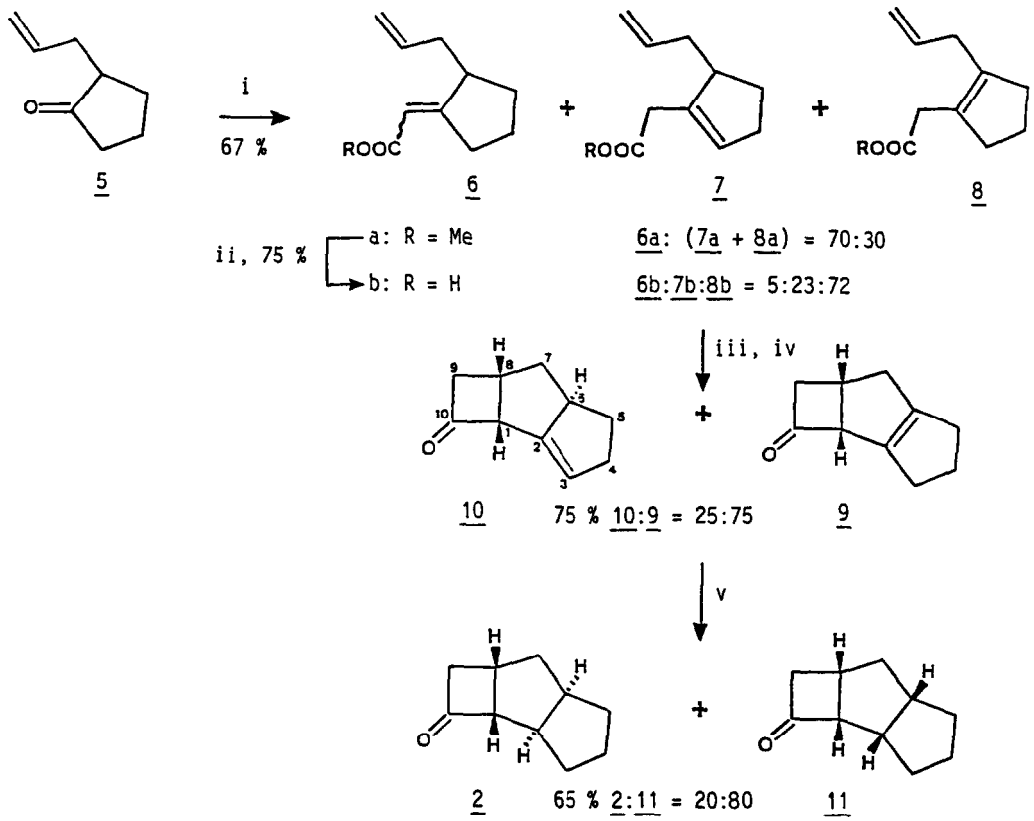
Summary: Regioselective formation of vinylketene 3, followed by its stereoselective intramolecular [2+2] cycloaddition with an olefin, yielded the linear annelated cis-anti-cis triquinane precursor 1.

We have reported previously[1] the synthetic potential of the intramolecular [2+2] cycloaddition of vinylketenes to olefins for the construction of bicyclic cyclobutanones[2]. Here we describe application of this principle to the synthesis of the linear annelated cis-anti-cis-triquinane derivative 1. Triquinanes were intensively studied recently[3], due to their particular structure but also due to the interesting physiological activities of some members of this class of natural products. Although several methods became available, the stereoselective construction of the linear annelated triquinanes with a cis-anti-cis skeleton[3] requires still many steps. We have therefore developed a short, practical and stereoselective synthesis of the model compound 1 based on the retrosynthetic scheme 1.



scheme 1

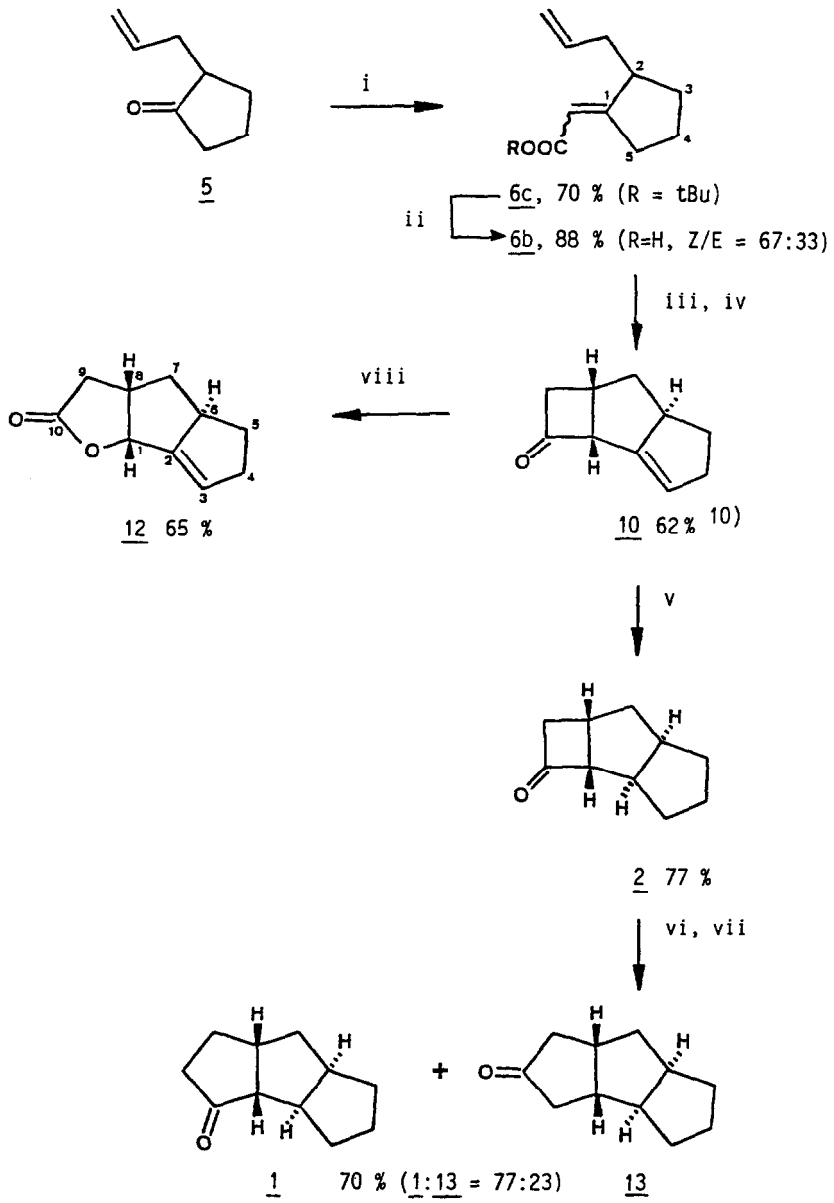
An initial reaction sequence (scheme 2), starting from the allylcyclopentanone 5[4], yielded mainly the undesired cis-syn-cis fused compound 11. Double bond migration into the five membered ring took place during the Horner-Emmons olefination[5] (as much as 30 %) and even more during the alkaline hydrolysis. The β,γ-unsaturated acid 8b was obtained as the major isomer. Conversion of the mixture of 6b, 7b and 8b into the corresponding acid chlorides by treatment with the Ghosez reagent (1-chloro-N,N,2-trimethylpropenylamine[6]), followed by addition of triethylamine yielded the isomeric cyclobutanones 10 (only with the desired stereochemistry in C-6[7a]) and 9.



i = NaH, $(MeO)_2POCH_2COOMe$, DME, 60°C; ii = KOH aq., EtOH, RT; iii = $Me_2C{=}CClNMe_2$, $CHCl_3$, 0°C; iv = NEt_3, $CHCl_3$, RT; v = H_2 (1 atm.), Pd/C, iPrOH, RT.

scheme 2

The selective synthesis of the compound 2 was realized by preventing the above mentioned isomerizations. Peterson olefination of 5 furnished exclusively the α,β-unsaturated esters 6c if the reaction mixture was quenched at -25°C with aqueous NH_4Cl[8]. The hydrolysis of the tert. butylesters 6c was also proceeding without double bond migration (scheme 3). Interestingly, triethylamine abstracted highly selectively ($\geqslant$ 97 %) a proton on C-5 of the acyl chloride 4, giving the intermediate vinylketene 3 which cyclized readily at room temperature to the single epimer 10[7a]. The stereochemistry was verified on the lactone 12[7b]. As expected, the catalytic hydrogenation of the cyclobutanone 10 yielded the cis-anti-cis ring fusion 2. The ketone 1 with the desired triquinane skeleton, was obtained by ring expansion[9].



i = LICA, THF, $Me_3SiCH_2COOtBu$, -78°C, 1 hr ⟶ -25°C, 2 hrs, NH_4Cl aq., -25°C; ii = CF_3COOH, CH_2Cl, RT; iii = $Me_2C{=}CClNMe_2$, $CHCl_3$, 0°C; iv= NEt_3, $CHCl_3$, RT; v = H_2 (1 atm.), Pd/C, THF/AcOH (1:1), RT; vi = $N_2CHCOOEt$, $BF_3.Et_2O$, ether, -30°C ⟶ RT; vii = 4N HCl, AcOH, reflux; viii = AcOH, H_2O_2 aq. (30 %), H_2O, 0°C.

scheme 3

Acknowledgements - The authors thank Miss P. Hoffmann for technical assistance.

References and Notes

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2. For other examples of intramolecular [2+2] cycloaddition of ketenes to olefins see a) ref. cited in 1. b) B.B. Snider, R.A.H.F. Hui, J. Org. Chem., 50, 5167 (1985). c) E. J. Corey, M.C. Desai, T.A. Engler, J. Am. Chem. Soc., 107, 4339 (1985). d) F. Arya, J. Bouquant, J. Chuche, Tetrahedron Lett., 27, 1913 (1986). e) W. Oppolzer, A. Nakao, Tetrahedron Lett., 27, 5471 (1986). f) ref. cited in 1.
3. See for example a) A.E. Greene, M. Luche, A.A. Serra, J. Org. Chem., 50, 3957 (1985). b) P.F. Schuda, J.L. Phillips, T. M. Morgan, J. Org. Chem., 51, 2742 (1986) and references cited therein.
4. The allylcyclopentanone 5 was prepared in three steps from cyclopentanone via allylation of the corresponding dimethylhydrazone (overall yield = 72 %) in analogy with E.J. Corey, D. Enders, Tetrahedron Lett., 3, (1976).
5. For deconjugation of £,$ unsaturated esters during Horner-Emmons and Peterson olefination with ketones see a) S.L. Hartzell, D.F. Sullivan, M.W. Rathke, Tetrahedron Lett., 1403 (1974). b) H. Taguchi, K. Shimoji, H. Yamomoto, H. Nozaki, Bull. Chem. Soc. Jap., 47, 2529 (1974).
6. A. Devos, J. Remion, A. Frisque-Hesbain, A. Colens, L. Ghosez, J.C.S. Chem. Commun., 1180 (1979).
7. a) A single epimer is detected by ^{1}H-NMR and ^{13}C-NMR. Its identity is correlated with ^{1}H-NMR data of compounds 2, 11 and 12. In 2 $^{3}J_{1-2} < 2$Hz: in 11 $^{3}J_{1-2} = 10$ Hz.
   b) The stereochemistry in 12 follows from the coupling constants: $^{3}J_{8-7eq.} \simeq 0$Hz; $^{3}J_{7eq.-6} = 8$ Hz; $^{3}J_{7ax.-6} = 11$ Hz; $^{3}J_{7ax.-8} = 9$ Hz; $^{3}J_{7ax.-7eq.} = 13$ Hz; $^{3}J_{1-8} = 3$ Hz.
8. If the reaction mixture is allowed to reach RT before quenching, deconjugation occurred ($\simeq 10$ %)[5b].
9. For ring expansion of cyclobutanones with ethyldiazo acetate see J.R. Stille, R.H. Grubbs, J. Am. Chem. Soc., 108, 855 (1986) and references cited therein.
10. The isomeric cyclobutanone 9 is detected by ^{1}H-NMR to less than 3 %.

(Received in Germany 26 October 1987)