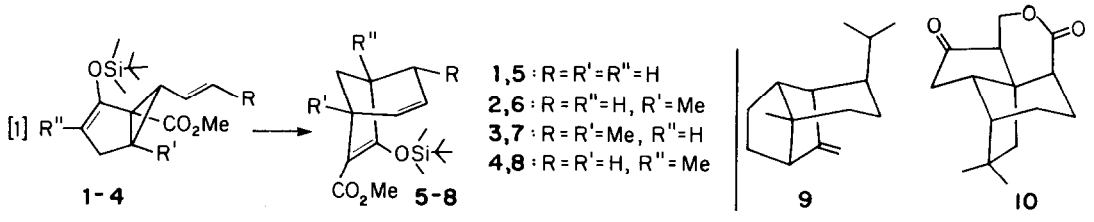
Tetrahedron Letters,Vol.25,No.36,pp 3959-3962,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

THERMAL REARRANGEMENT OF DIVINYLCYCLOPROPANE SYSTEMS. PREPARATION OF FUNCTIONALIZED, STEREOCHEMICALLY DEFINED BICYCLIC AND TRICYCLIC PRODUCTS CONTAINING THE BICYCLO[3.2.1]OCTANE SKELETON

Edward Piers*, Grace L. Jung, and Neil Moss
Department of Chemistry, University of British Columbia
Vancouver, British Columbia, Canada V6T 1Y6

ABSTRACT: A study involving the preparation and thermolysis of substituted 6-exo-(1-alkenyl)bicyclo[3.1.0]hex-2-ene systems (14, 15, 23, 29, 40) shows (a) that C-8 functionalized bicyclo[3.2.1]octa-2,6-dienes can be prepared readily via this methodology (14 → 16; 15 → 17), (b) that the rearrangement reaction is stereospecific even when the 6-(1-alkenyl) group is substituted with a sterically bulky isopropyl group (23 → 24; 29 → 30), and (c) that the method can be extended to include the preparation of tricyclic systems (40 → 41).

A previous report[1] from this laboratory described the synthesis and thermal (Cope) rearrangement of the substituted 6-exo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 1-4 (eq. [1]). This preliminary study demonstrated the potential of the divinylcyclopropane rearrangement of substances such as 1-4 for the preparation of functionalized bicyclo[3.2.1]octa-2,6-dienes (e.g. 5-8). Significantly, the method allowed for the preparation of bicyclo[3.2.1]octane compounds possessing a substituent (R', R") at either bridgehead position and with synthetically useful functional groups on two of the three carbon bridges.

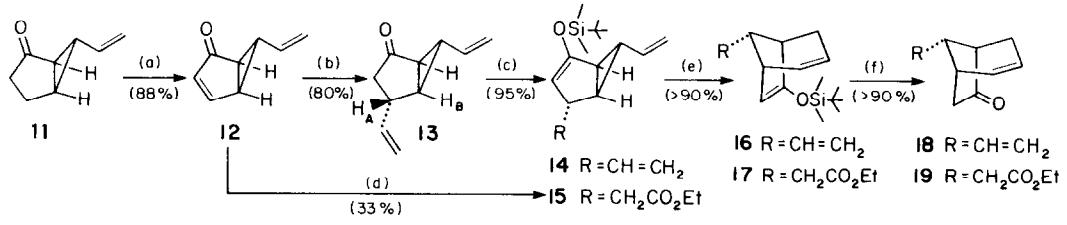


The bicyclo[3.2.1]octane carbon skeleton is a common structural feature of many naturally occurring substances. In fact, the primary motivation for carrying out the above-mentioned study was to develop a general method which would be applicable to the synthesis of natural products containing the bicyclo[3.2.1]octane ring system. In this connection, taking into account the structures of a number of specific target molecules [e.g. sinularene (9)[2], quadrone (10)[3]], it became desirable to extend this investigation in a number of ways. First, it was important to provide for the functionalization of the one-carbon bridge (C-8) of the bicyclo-octadiene product(s). Clearly, this would require the preparation and rearrangement of 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes bearing a suitable functional group at C-4. Second, with respect to the R group on the 6-alkenyl side chain, we wished to determine whether or not the rearrangement was stereospecific. In other words, would rearrangement of geometrically isomeric substrates [R group (E) or (Z) on the 1-alkenyl side chain] give diastereomeric products? The answer to this query was of particular importance for

substrates in which the R group was sterically bulky (e.g. isopropyl). Indeed, for such substrates in which the bulky R group is cis to the cyclopropyl moiety, one might even question the viability of a Cope-like bond reorganization.[4] Third, it was of interest to expand the method to include the preparation of tricyclic products in which an additional ring is appended to the "parent" bicyclo[3.2.1]octane skeleton. We report herein results which pertain to these desired extensions.

Conversion of 6-exo-vinylbicyclo[3.1.0]hexan-2-one (11)[5] into the corresponding enone 12[6] was accomplished readily via known[7] methods (see Scheme 1). Cuprous bromide catalyzed conjugate addition of vinylmagnesium bromide to 12 afforded a single product[8] which, on the basis of steric approach control considerations, was expected to possess the stereochemistry shown in 13. In this stereochemical arrangement, the H_A-H_B dihedral angle is ~ 90° and it was shown by appropriate decoupling experiments that, in the ^1H nmr spectrum of 13, there is no coupling between these two protons. Transformation of the ketone 13 into the enol silyl ether 14 was accomplished via standard reactions.

Although addition (CH_3CN, 55°C)[9] of 1-(tert-butyldimethylsiloxy)-1-ethoxyethene to the enone 12 was clean, the reaction was quite sluggish and produced, after a reaction time of 12 hours, a 33% yield (>95% based on unrecovered 12) of the enol silyl ether 15.

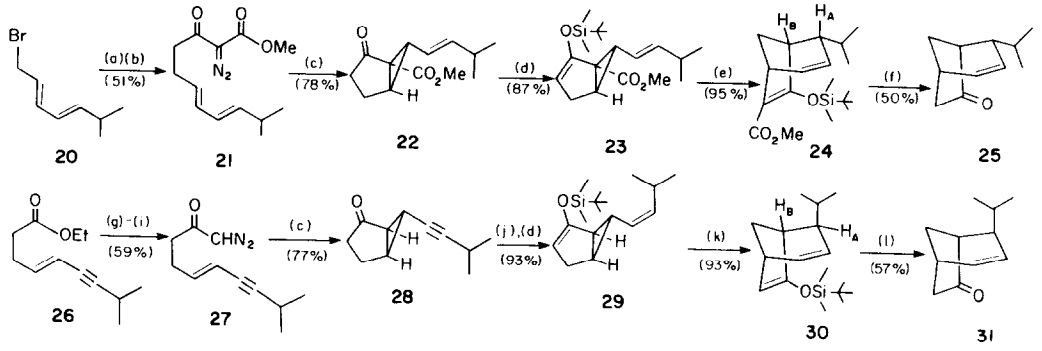


Scheme 1. (a) LDA, THF, -78°C; PhSeCl; H_2O_2, HOAc, THF (b) CH_2=CHMgBr, CuBr•Me_2S, THF, -30°C; NH_4Cl, H_2O (c) LDA, THF, -78°C; t-BuMe_2SiCl, THF-HMPA (d) (t-BuMe_2SiO)(EtO)C=CH_2, MeCN, 55°C (e) 200°C, 2.5 h., C_6H_6 (sealed tube) (f) 1 N HCl, THF, r.t.

Importantly, the thermal rearrangement of substrates 14 and 15 proceeded smoothly and, in each case, a single product (16, 17, respectively) was formed in high yield. Subjection of the latter substances to acid catalyzed hydrolysis provided the bicyclic ketones 18 and 19, respectively. Thus, stereochemically homogeneous functionalization of the C-8 carbon of the bicyclo[3.2.1]octane products can be accomplished readily by means of experimentally convenient reactions.

Alkylation[10] of the dianion of methyl acetoacetate with (E),(E)-1-bromo-6-methylhepta-2,4-diene (20),[11] followed by treatment of the resultant product with p-toluenesulfonyl azide in the presence of triethylamine, gave the diazo keto ester 21 (Scheme 2). Carbenoid ring closure of the latter substance provided the bicyclic ketone 22, which was converted readily into the corresponding enol silyl ether 23.

When hept-1-en-4-yn-3-ol [obtained in 86% yield by reaction of 1-lithio-3-methyl-1-butyne with acrolein (THF, -30°C → r.t.)] was heated (130°C, 40 h.) with triethyl orthoacetate (5 equiv.) in the presence of a catalytic amount of propanoic acid,[12] ethyl (E)-non-4-en-6-ynoate (26) was obtained in 66% yield (Scheme 2). The latter material was converted via standard reactions into the diazoketone 27 which, upon subjection to carbenoid ring closure, was transformed into the bicyclic ketone 28. Hydrogenation of the triple bond in 28 proceeded smoothly and the resultant ketone was converted into the enol silyl ether 29.

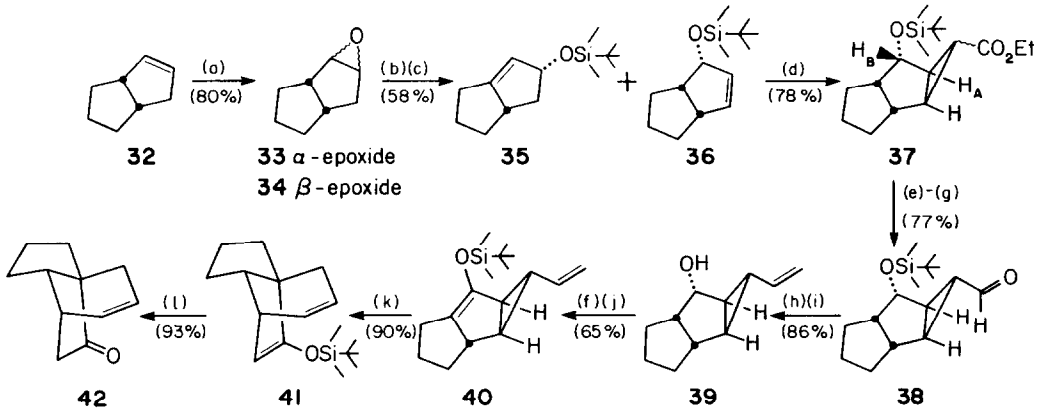


Scheme 2. (a) $[\bar{C}H_2COCHCO_2Me]Na^+Li^+$, THF, r.t.; H_3O^+ (b) p-$MeC_6H_4SO_2N_3$, Et_3N, MeCN, r.t. (c) $Cu(acac)_2$, C_6H_6, reflux (d) LDA, THF, -78°C; t-$BuMe_2SiCl$, THF-HMPA (e) 200°C, 2 h., C_6H_6 (sealed tube) (f) n-Bu_4NF, THF, r.t.; 1 N HCl, THF, reflux (g) KOH, H_2O-MeOH, reflux ; H_3O^+ (h) $(COCl)_2$, hexane, reflux (i) CH_2N_2, Et_2O, 0°C (j) H_2, Lindlar's catalyst, quinoline, pentane (k) 240°C, 4.5 h., C_6H_6 (sealed tube) (l) 1 N HCl, THF, r.t.

It was gratifying to find that thermolysis of the divinylcyclopropanes 23 and 29 provided cleanly, in each case, a single product (24, 30, respectively) in high yield. The fact that these substances are epimeric at the isopropyl-bearing carbon was shown by their ^1H nmr spectra. Suitable decoupling experiments revealed that, in compound 24, the H_A-H_B coupling constant is ~ 5 Hz (dihedral angle ~ 40°), while in 30 there is very weak coupling ($J \leq 1$ Hz) between H_A and H_B (dihedral angle ~ 80°). Treatment of compounds 24 and 30 as indicated in Scheme 2 provided endo-(25) and exo-4-isopropylbicyclo[3.2.1]oct-2-en-6-one (31), respectively. Again, it was clear that these substances were epimeric. Thus, for substrates which contain, on the 6-(1-alkenyl) side chain, bulky substituents, both the viability and stereospecificity of the rearrangement process had been demonstrated.

Treatment of cis-bicyclo[3.3.0]oct-2-ene (32)[13] with N-bromosuccinimide in dimethyl sulfoxide - water,[14] followed by sodium hydroxide, provided a 4:1 mixture of the epoxides 33 and 34[15] (see Scheme 3), which were separated by chromatography. Conversion[16] of 33 into a mixture of the silyl ethers 35 and 36 (1:4, separated by chromatography), followed by $Rh_2(OAc)_4$ catalyzed addition[17] of ethyl diazoacetate to 36, afforded the cyclopropyl esters 37 (mixture of epimers at the ester-bearing carbon). The fact that cyclopropanation had occurred exclusively from the convex side of 36 was shown by the ^1H nmr spectrum of 37. Suitable decoupling experiments disclosed that there is no coupling between H_A and H_B (dihedral angle ~ 90°).

Conversion of 37 into the alcohol 39 (via the aldehyde 38) was accomplished efficiently by way of a sequence of standard reactions. Oxidation of 39 gave the corresponding tricyclic ketone which was transformed into the required enol silyl ether 40. Thermal rearrangement of the latter substance gave mainly one compound, accompanied by a number of minor side-products. Suitable purification of this mixture provided the desired material 41 in excellent yield. Treatment of 41 with tetra-n-butylammonium fluoride gave the tricyclic ketone 42 which, notably, possesses the "parent" carbon skeleton of the anti-tumor sesquiterpenoid quadrone (10).

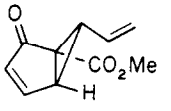


Scheme 3. (a) NBS, DMSO-H_2O, r.t.; NaOH, H_2O, r.t. (b) PhSeNa, EtOH-THF, reflux; H_2O_2, H_2O, reflux (c) t-$BuMe_2SiCl$, imidazole, DMF, r.t. (d) N_2CHCO_2Et, $Rh_2(OAc)_4$ (e) $LiAlH_4$, Et_2O, r.t.; H_2O (f) $C_5H_5N{\cdot}CrO_3{\cdot}HCl$, NaOAc, CH_2Cl_2, r.t. (g) t-BuOK, t-BuOH-THF, r.t. (h) $Ph_3P{=}CH_2$, THF, r.t. (i) n-Bu_4NF, THF, r.t. (j) LDA, THF, -78°C; t-$BuMe_2SiCl$, THF-HMPA (k) 155°C, 5 h., C_6H_6 (sealed tube) (l) n-Bu_4NF, THF, -78°C.

ACKNOWLEDGEMENTS. We gratefully acknowledge (a) the Natural Sciences and Engineering Research Council of Canada for financial support and for Postgraduate Scholarships (to G.L.J. and N.M.) and (b) the Alberta Heritage Scholarship Fund for the Sir James Lougheed Award for Distinction (to N.M.).

REFERENCES AND NOTES

1. E. Piers and E.H. Ruediger, J. Org. Chem., 45, 1725 (1980). 2. C.M. Beechan, C. Djerassi, J.S. Finer, and J. Clardy, Tetrahedron Lett., 2395 (1977); C.M. Beechan, C. Djerassi, and H. Eggert, Tetrahedron, 34, 2503 (1978). 3. R.L. Ranieri and G.J. Calton, Tetrahedron Lett., 499 (1978). 4. For discussions concerning steric factors involved in divinylcyclopropane rearrangements, see E. Piers, H.E. Morton, I. Nagakura, and R.W. Thies, Can. J. Chem., 61, 1226 (1983), and citations therein. 5. T. Hudlicky, F.J. Koszyk, T.M. Kutchan, and J.P. Sheth, J. Org. Chem., 45, 5020 (1980). 6. All compounds reported herein exhibited spectra in accord with structural assignments and gave satisfactory high resolution mass spectrometric molecular mass determinations. 7. H.J. Reich, J.M. Renga, and I.L. Reich, J. Am. Chem. Soc., 97, 5434 (1975). 8. Treatment of the enone i (ref. 1) with cuprate reagents gave complex mixtures of products. 9. Y. Kita, J. Segawa, J. Haruta, H. Yasuda, and Y. Tamura, J. Chem. Soc., Perkin Trans. 1, 1099 (1982). 10. S.N. Huckin and L. Weiler, J. Am. Chem. Soc., 96, 1082 (1974). 11. This bromide was obtained (21% overall yield) from 2-methylpropanal via the following sequence of reactions: $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; i-Bu_2AlH, pentane; pyridinium chlorochromate-on-alumina, CH_2Cl_2; $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; i-Bu_2AlH, pentane; PBr_3-pyridine, Et_2O, 0°C. 12. K.A. Parker and R.W. Kosley, Jr., Tetrahedron Lett., 691 (1975). 13. H.C. Brown and W.J. Hammar, Tetrahedron, 34, 3405 (1978). 14. M. Yamazaki, M. Shibasaki, and I. Ikegami, Chemistry Lett., 1245 (1981). 15. J.K. Whitesell and R.S. Matthews, J. Org. Chem., 42, 3878 (1977). 16. K.B. Sharpless and R.F. Lauer, J. Am. Chem. Soc., 95, 2697 (1973). 17. M.P. Doyle, D. van Leusen, and W.H. Tamblyn, Synthesis, 787 (1981).



i

(Received in USA 13 June 1984)