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VINYL RADICAL CYCLIZATION IN THE SYNTHESIS OF NATURAL PRODUCTS: SEYCHELLENE

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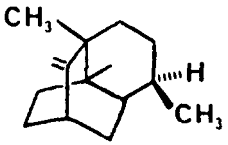
Abstract: The use of vinyl radical cyclization in the simplification of synthesis design is probed with the sesquiterpene seychellene as a target. The construction is particularly effective because of very high stereoselectivity in the alkylation of a 2,2,2-bicyclo-5-octene-2-one system and because of the control offered by the specific location of the double bond in the product of the vinyl radical cyclization.

The defined position occupied by a double bond as a result of vinyl radical cyclization [1] is one of the important advantages of that synthetic process. This is obvious, of course, when the double bond can lead to further regiospecific functionalization. It can also be useful even when the ultimate goal is the corresponding saturated system because of the stereochemical control implicit in the process of hydrogenating the double bond. We illustrate this in the use of the vinyl radical cyclization in the construction of the tricyclic system of seychellene (1), a molecule which has acquired some status as a test system [2] in continuing efforts toward selectivity in synthesis design.



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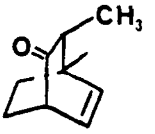
The route we chose was meant to answer two questions: Does alkylation of a 2,2,2-bicyclooctenone such as 2 lead with high stereoselectivity to the stereochemistry shown in 3? Does the vinyl radical cyclization process work well in the formation of a six-membered ring as is present in 1 [3]?



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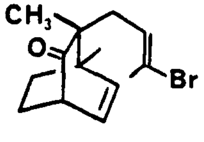

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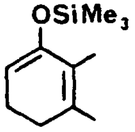

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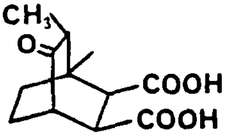

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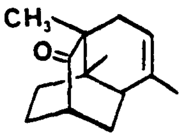
We now show that these questions can be answered in the affirmative. The kinetic lithium enolate of 2,3-dimethylcyclohexenone was trapped as its trimethylsilyl enol ether 4, as described by Jung [2e,i]. Reaction of 4 with 2 equivalents of maleic anhydride in refluxing toluene for 24 hours, followed by hydrolysis in boiling water, gave the crystalline diacid 5, mp 145.3-146° C, in 77% yield [4]. Oxidative decarboxylation with lead tetraacetate in pyridine [5] provided the bicyclooctenone starting material 2[6] in 25% overall yield from 2,3-dimethylcyclohexenone. Alkylation of the lithium enolate of 2 with (E) 1,3-dibromo-2-butene [7] led to the vinyl bromide 3 in 80% yield [8]. This was (PMR, CMR, vpc) very largely a single isomer.

The stereospecificity of the alkylation step is especially notable as it is known that addition of grignard reagents to the parent bicyclooctenone system takes place with only slight selectivity. Whatever its origin (coordination of lithium with the double bond as well as with the oxygen?), it is this selectivity which makes the radical cyclization route a viable one for this type of polycyclic structure.

Treatment of a 0.02M solution of the vinyl bromide 3[9] in benzene with 1.1 equivalent of tributylstannane under reflux (catalytic AIBN; irradiation with a 250 watt sunlamp for 3 hrs) resulted in a 70% yield of norseychellenone 6[10]. Hydrogenation (10% Pd/C in ether; room temperature) gave the expected norseychellanone (7) as the major product (capillary vpc analysis showed the ratio of 7 to its secondary methyl epimer to be 85/15 [11]). The structure of 7, which has previously been converted to seychellene by Piers [2a], was confirmed by comparison with a sample kindly supplied by Professor Piers.



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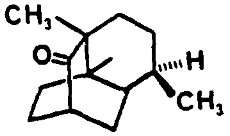

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References and Notes

This paper is contributed in honor of Professor H.H. Wasserman's sixty fifth birthday.

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2. a. E. Piers, R.W. Britton and W. de Waal, J. Am. Chem. Soc., 93, 5113 (1973); Chem. Commun., 1069 (1969); b. K.J. Schmalyl and R.N. Mirrington, Tetrahedron Letters, 3219 (1979); J. Org. Chem., 34, 2358 (1969); c. N. Fukamiya, M. Kato and A. Yoshikoshi, Chem. Commun., 1120 (1971); d. G. Frater, Helv. Chim. Acta, 57, 172 (1974); e. M.E. Jung and C.A. McCombs, J. Am. Chem. Soc., 100, 5207 (1978); f. K. Yamada, Y.

Kyotani, S. Manabe and M. Suzuki, Tetrahedron, 35, 293 (1979); Bull. Soc. Chem. Jap., 51, 3405 (1978); g. M.E. Jung and Y.G. Pan, Tetrahedron Letters, 3127 (1980); h. S.C. Welch, J.M. Gruber, C.Y. Chou, M.R. Wilcott and R. Inners, J. Org. Chem., 46, 2816 (1981); i. M.E. Jung, C.A. McCombs, Y. Takeda and Y.-G. Pan, J. Am. Chem. Soc., 103, 6677 (1981).

3. The work of Jung (refs. 2e and 2i) had already shown that a mixture containing mostly the endocyclic isomer 6 gives predominantly the correct stereochemistry at the secondary methyl center.

4. PMR ($CDCl_3$): 10.55 (2H,bs), 3.6-2.5 (4H,m), 1.06 (3H,d,J=7.5Hz), 1.05 (3H,S); ms (CI-Methane) 241 (M+1), 223 ($-H_2O$). Correct C,H analysis.

5. C.M. Cimarusti and J. Wolinsky, J. Am. Chem. Soc., 90, 113 (1968).

6. Isolated as one pure epimer. PMR: 6.18 (2H,m), 3.10 (1H,m), 1.19 (3H,s), 1.02 (3H,d,J=7.1Hz); ir (film) 1725, 1655, cm-1; ms (EI) 150 (M), 94, 79.

7. Prepared from (2E)-3-bromo-2-butenoic acid (cf W.J. Le Noble, J. Am. Chem. Soc., 83, 3897 (1961) by treatment with a) LAH/THF/3hr reflux; b) $MsCl/NEt_3/CH_2Cl_2/-10^oC$; c) 5 equiv LiBr/THF/room temperature.

8. After flash chromatography (5% ethyl acetate in petroleum ether). PMR: δ 6.13 (2H,m), 5.72 (1H,m), 3.14 (1H,m), 2.14 (3H,bs), 1.15 (3H,s), 1.01 (3H,s); ir (film) 1725, 1645 cm-1; ms (CI-methane) 285, 283 (M+3, M+1), 203 (-HBr).

9. The stereochemistry of the vinyl bromide is irrelevant because of the known high rate of inversion of the intermediate vinyl radical: cf R.W. Fessenden and R.H. Schuler, J. Chem. Phys., 39, 2147 (1963).

10. PMR: δ 5.1 (1H,m), 1.59 (3H,bs), 1.0 (3H,s) .81 (3H,s); ir (film) 1715, 1670 cm-1; ms (EI) 204 (M), 189, 171, 149.

11. The unwanted epimer had the longer retention time.

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