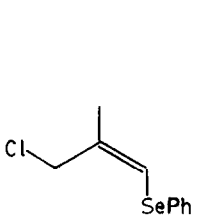
Tetrahedron Letters,Vol.24,No.7,pp 699-702,1983 0040-4039/83/070699-04$03.00/0
Printed in Great Britain

PREPARATION OF 3-CHLORO-2-METHYL-1-SELENOPHENYLPROPENE, A NEW EQUIVALENT OF METHACROLEIN. APPLICATION TO THE REGIOSPECIFIC SYNTHESIS OF A MODEL OF THE SELAGINE RING SYSTEM.

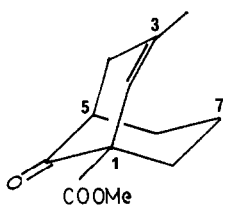
Denis Gravel*, Robert Déziel and Luc Bordeleau
Département de Chimie, Université de Montréal,
C.P. 6210, Succ. A, Montreal, Quebec, H3C 3V1, Canada

Abstract: We report herein the preparation of a new selenium reagent and illustrate one important aspect of its potential usefulness in organic synthesis.

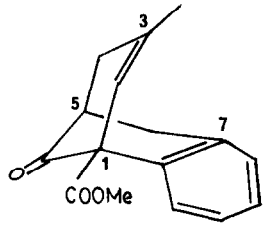
In the present communication we report the preparation of the title compound 1, a new synthetic equivalent of methacrolein, and its application to the regiospecific synthesis of 1-carbomethoxy-3-methyl-9-oxobicyclo[3.3.1]non-2-ene (2) and it 7,8-benzo analog 3, a model of the ring system of the Lycopodium alkaloid selagine 4, via a novel cyclization reaction involving a vinyl selenide.



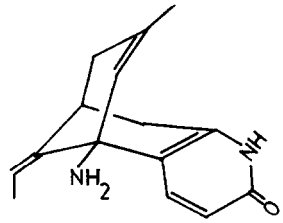
1



2



3



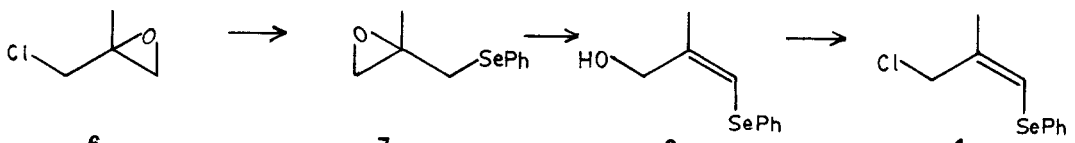
4

Selagine, isolated from Lycopodium selago was shown[1] to have structure 4 where, interestingly, all of the structural features are concentrated on one side of the molecule, which presents an interesting problem of regiochemistry in elaborating a synthetic scheme. Although the 3-ene analog of 2 (and possibly 3) is accessible[2], the first solution to the 2-ene isomer problem was published by Kende[3] who achieved inverse regiochemistry in an elegant manner by using a known methacrolein equivalent, namely: 3-chloro-2-methyl-1-thiophenoxypropene reported by Cohen[4], for the synthesis of model compound 2. In the reported procedure[3], alkylation of the dianion, generated by the Weiler method[5], of 2-carbomethoxycyclohexanone (5) followed by acid catalyzed cyclization of the resulting thioenolether yielded the corresponding thioether which was converted to the sulfoxide and the latter thermolyzed at 150° in collidine for 13 hours to introduce the olefin.

These latter conditions however appeared somewhat harsh for more functionalyzed substrates and we therefore began explorations to prepare the selenium analog of Cohen's reagent[4] in an attempt to provide a milder method of access to these systems. It readily became apparent that an approach modeled on the synthesis of the sulfur analog[4] obtained by chlorination of the allylic phenylthioether precursor was doomed to failure since Sharpless[6] had already reported

that chlorination of allylic phenylselenides by N-chlorosuccinimid leads to the rearranged corresponding allylic chlorides. On the other hand, an alternative approach to the desired reagent could be envisaged via a 3-selenophenyl-2-propen-1-ol precursor where replacement of the allylic hydroxyl group by chloride should be accessible thus avoiding the allylic selenide chlorination impasse. In the event, 2-methyl epichlorohydrin (6) prepared by epoxidation of methallyl chloride with m-chloroperbenzoic acid in dichloromethane, gave upon treatment with 1.0 equivalent of sodium phenylselenide[7] in ethanol at 0°C, followed by warming to 35°C for 1.5 hour, a 93% yield of the corresponding crude 2-methyl-3-selenophenyl-2-propene oxide (7), b.p. 64-66°C, 0.01 torr. The latter, upon treatment with 5 equivalents of sodium hydride[8] in refluxing tetrahydrofuran for 18 hours gave, after distillation, 84% of the pure allylic alcohol: 2-methyl-3-selenophenyl-2-propen-1-ol (8), b.p. 98-100°C, 0.01 torr. Finally, conversion of the allylic alcohol 8 to the desired allylic chloride 1 was effected, without rearrangement, by nucleophilic displacement of the corresponding mesylate generated in situ[9] by treatment with 2.0 equivalents of collidine and 1.5 equivalent of mesyl chloride in dimethyl formamid containing 5.0 equivalents of lithium chloride at 15°C then at room temperature for five hours. The desired allylic chloride: 3-chloro-2-methyl-1-selenophenylpropene (1) was obtained crude as essentially pure Z isomer[10] and in 84% yield (E+Z mixture) after distillation[10], b.p. 82-85°C, 0.01 torr (see Scheme 1)[11].

Scheme 1

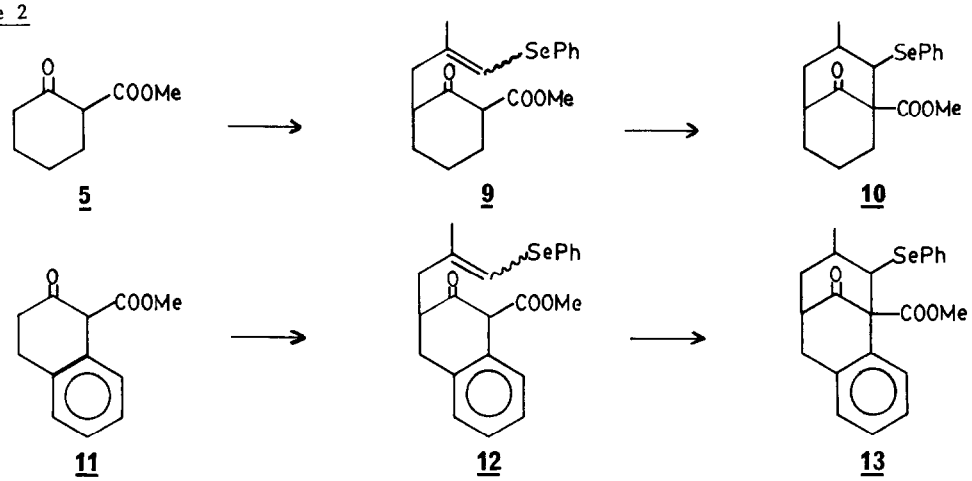


6 7 8 1

As anticipated, the new selenium reagent 1 behaved as its sulfur analog[4] in the Kende sequence[3]. Treatment of the dianion[5] of 2-carbomethoxycyclohexanone (5) with 1.0 equivalent of 3-chloro-2-methyl-1-selenophenylpropene (1) (E+Z mixture) in tetrahydrofuran at 0°C gave, after purification by flash chromatography, a 65% yield of the desired 6-alkylated β-ketoester 9. Cyclization of the latter took place in trifluoroacetic acid[3] at 0°C for 10 hours and was followed by oxidation of the crude selenide 10 with 5.0 equivalents of 30% hydrogen peroxide in dichloromethane at 0°C. Elimination ensued upon letting the solution warm to 25°C and maintaining that temperature for 1.5 hour. The desired known[3] 1-carbomethoxy-3-methyl-9-oxobicyclo[3.3.1]non-2-ene (2) was obtained in 62.5% yield from the alkylated β-ketoester 9, after flash chromatography; its nmr spectrum (400 MHz) was in perfect accord with that reported in the literature[3] (see Scheme 2).

In an analogous manner, treatment of the dianion[5] of α-carbomethoxy-β-tetralone (11) with 1.0 equivalent of the selenium reagent 1 (E+Z mixture) in tetrahydrofuran at 0°C gave, after flash chromatography, a 78% yield of the desired alkylated β-ketoester 12. Cyclization of the latter to the tricyclic precursor 13 was again carried out in trifluoroacetic acid[3] at 0°C but during 24 hours; the desired compound 13 was obtained as a mixture of isomers in 74% yield after flash chromatography. Finally, oxidation to the selenoxide and elimination was achieved by treatment with 10 equivalents of 30% hydrogen peroxide and 5 equivalents of pyridine in

Scheme 2



dichloromethane at 0°C and then heating the intermediate selenoxide in refluxing benzene with 5 equivalents of pyridine for 2 hours; the desired tricyclic ketoester 3, a model of the selagine ring system (4), was obtained in the modest yield of 38% (see however below) after flash chromatography m.p. = 115-116°C (see Scheme 2). The 400 MHz nmr spectrum of 3 corresponds perfectly to the proposed structure and is reported in Table 1.

Table I. 400 MHz pmr spectrum of ketoester 3.

Proton	Multiplicity	Chemical shift	Coupling constants
H_2	d	5.98 ppm	$J_{H_2\ H_{4e}}$ = 1.4 Hz
CH_3	s	1.65 ppm	
H_{4a}	d,d	3.52 ppm	$J_{H_{4a}\ H_{4e}}$ =17 Hz; $J_{H_{4a}\ H_5}$ = 6.3 Hz
H_{4e}	d,d	3.14 ppm	$J_{H_{4a}\ H_{4e}}$ =17 Hz; $J_{H_{4e}\ H_2}$ = 1.4 Hz
H_5	d,d	3.00 ppm	$J_{H_5\ H_{4a}}$ = 6.3 Hz; $J_{H_5\ H_{6a}}$ = 7.5 Hz
H_{6e}	d	2.46 ppm	$J_{H_{6a}\ H_{6e}}$ =18.3 Hz
H_{6a}	d,d	2.86 ppm	$J_{H_{6a}\ H_{6e}}$ =18.3 Hz; $J_{H_{6a}\ H_5}$ = 7.5 Hz
arom (1H)	m	6.84 ppm	
arom (3H)	m	7.20 ppm.	

Two important observations can be made regarding the sequences depicted in Scheme 2: i) cyclization of the vinyl selenide chain in the 7,8-benzo analog 12 requires a longer reaction time than the simpler model 9 which suggests that cyclization may be hampered thus producing a less favorable ratio of isomers for elimination whence the reduced yield of olefin; ii) elimination of the selenoxide in the benzo analog 13 requires conditions more stringent than the simpler model 10 which again suggests hampering by the fused aromatic ring. In order to attempt to correct the problem of stereochemistry in the cyclization of 12 to 13 and thus increase the yield of olefin 3, β-tetralone 11 was alkylated with the pure Z isomer of 1 to give, in comparable yield, the pure Z isomer of 12 which upon cyclization under the usual conditions again gave a mixture of isomers. However, since the desired isomer of 13 for syn elimination of the selenoxide is the trans-diequatorial isomer which should normally be thermodynamically

the more stable and since the reaction should a priori be reversible we therefore attempted an equilibration of the mixture by heating it to reflux (35°C) for 18 hours in a 1:1 mixture of trifluoroacetic acid and dichloromethane. Much to our pleasure, 400 MHz nmr analysis of the product after work up showed a single stereoisomer having the desired trans-diequatorial stereochemistry ($J_{H_2H_3}$ = 11.7 Hz, trans-diaxial). Oxidation of the crude single stereoisomer and elimination of the corresponding selenoxide, as described above, yielded 75% (total and after flash chromatography) of the desired olefin 3.

It therefore stands out that the selenium analog of Cohen's reagent[4] behaves as anticipated with the minor differences that cyclization of the intermediate vinyl selenide is slightly slower and that equilibration of the bicyclic selenide requires a slightly higher temperature.

Finally, it is important to add that the above sequence repeated using the sulfur analog[4] of 1 behaved equally very well yielding only the required trans-diequatorial sulfoxide isomer for elimination but that pyrolysis of the latter under the reported conditions[3] yielded only 40% (after flash chromatography) of the desired olefin 3 thus stressing the advantage of the milder and higher yielding selenium reagent for this sequence. Further work is in progress on these and related systems which will be reported later.

Acknowledgements. This work was supported by grants (to D.G.) and fellowships (to R.D.) from the National Sciences and Engineering Research Council of Canada and the Ministère de l'Éducation du Québec.

References

1. a) Z. Valenta, H. Yoshimura, E.F. Rogers, M. Ternbak and K. Wiesner, Tetrahedron Lett., No. 10, 26 (1960); b) M. Shamma, C.D. Jones and J.A. Weiss, Tetrahedron, 25, 4347 (1969).
2. a) Z. Horii, T. Imanishi, S. Kim, and I. Ninomiya, Chem. Pharm. Bull., 16, 1918 (1968).
3. A.S. Kende and J.A. Schneider, Synthetic Commun., 9, 419 (1979).
4. A.J. Mura, D.A. Bennett, and T. Cohen, Tetrahedron Lett., 4433 (1975).
5. L. Weiler and S. Huckin, J. Am. Chem. Soc., 96, 1082 (1974).
6. T. Hori and K.B. Sharpless, J. Org. Chem., 44, 4208 (1979).
7. K.B. Sharpless and R.F. Lauer, J. Am. Chem.Soc., 95, 2697 (1973).
8. M. Shimizu and I. Kuwajima, J. Org. Chem., 45, 4063 (1980).
9. E.W. Collington and A.I. Meyers, J. Org. Chem., 36, 3044 (1971).
10. On the basis of NOE experiments performed on a Bruker WH-400 instrument.
11. All new compounds reported in this paper have been characterized by mass spectrometry and nmr spectroscopy.

(Received in USA 22 June 1982)