References and Notes

(1) L. N. Mander and J. V. Turner, *J. Org. Chem.*, **38**, 2916 (1973); J. E. Baldwin and J. A. Walker, *Chem. Commun.*, 354 (1972); E. Hunt and B. Lythgoe, *ibid.*, 757 (1972); E. J. Corey and S. W. Walinsky, *J. Amer. Chem. Soc.*, **94**, 8932 (1972).

(2) P. A. Grieco, D. Boxler, and K. Hiroi, *J. Org. Chem.*, **38**, 2572 (1973); V. Rautenstrauch, *Helv. Chim. Acta*, **54**, 739 (1971); J. E. Baldwin, J. DeBernardis, and J. E. Patrick, *Tetrahedron Lett.*, 353 (1970); G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).

(3) G. Andrews and D. A. Evans, *Tetrahedron Lett.*, 5121 (1972).

(4) Allylic sulfoxides have been shown to undergo the [2,3]-sigmatropic rearrangement providing a stereospecific route to trisubstituted olefins: P. A. Grieco, *Chem. Commun.*, 702 (1972); D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1389 (1973); P. A. Grieco and R. S. Finkelhor, *J. Org. Chem.*, **38**, 2245 (1973).

(5) Baldwin has recently demonstrated that α-bromo esters derived from acetylenic alcohols undergo smooth conversion into allenic acids *via* a [3,3]-sigmatropic rearrangement: J. E. Baldwin and J. A. Walker, *Chem. Commun.*, 117 (1973).

(6) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 1038 (1968).

(7) W. Ando, S. Kondo, K. Nakayama, K. Ichibori, H. Kohoda, H. Yamato, I. Imai, S. Nakaido, and T. Migita, *J. Amer. Chem. Soc.*, **94**, 3870 (1972); W. E. Parham and S. H. Groen, *J. Org. Chem.*, **30**, 728 (1965), and **31**, 1694 (1966).

(8) R. W. LaRochelle, B. M. Trost, and L. Krepski, *J. Org. Chem.*, **36**, 1126 (1971), and references cited therein.

(9) W. Ando, S. Kondo, and T. Migita, *Bull. Chem. Soc. Jap.*, **44**, 571 (1971).

(10) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969); E. E. van Tamelen, P. McCurry, and U. Huber, *Proc. Nat. Acad. Sci.*, **68**, 1294 (1971).

(11) Nona-2,3-dien-1-ol was synthesized *via* the reductive elimination ($LiAlH_4$)[12] of the tetrahydropyranyloxy group from 4-tetrahydropyranyloxynona-2-yn-1-ol which was prepared by metalation of the tetrahydropyranyl ether of 1-octyn-3-ol with 1.1 equiv of *n*-BuLi in ether at −78°, followed by treatment with excess paraformaldehyde in tetrahydrofuran (25°).[13]

(12) J. S. Cowie, P. D. Landor, and S. R. Landor, *Chem. Commun.*, 541 (1969).

(13) A. Schaap, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim.*, **84**, 1200 (1965).

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Received October 9, 1973

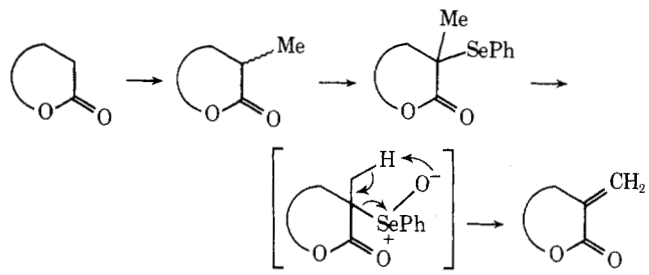
Organoselenium Chemistry. α-Phenylseleno Lactones. A New General Route to the Synthesis of Fused α-Methylene Lactones

Summary: A general high yield "α-methylenation sequence" has been developed for cis- and trans-fused lactone rings employing the reported capabilities of alkylphenyl selenoxides to undergo facile syn elimination at low temperatures.

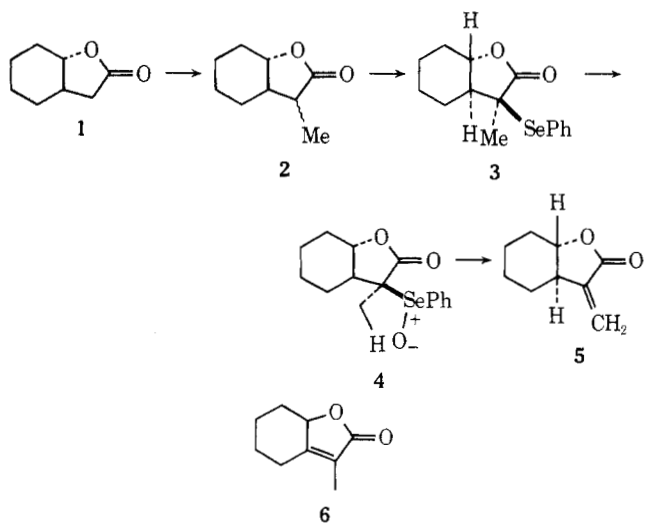
Sir: We report here a general method for the conversion of cis- and trans-fused γ- and δ-lactones into their corresponding α-methylene-γ-butyrolactones and α-methylene-δ-valerolactones which represent structural units found in many naturally occurring cytotoxic sesquiterpenes[1] (*e.g.*, vernolepin[2]). Although the α-methylene lactone structural moiety has been a synthetic objective in several laboratories,[3,4] the number of general approaches[4] remains small.

Our approach requires (a) a method for specific high yield methylation of preformed lactone enolates, (b) a method for stereospecific introduction of an α-phenylseleno substituent (*vide infra*), and (c) a method for specific elimination of the corresponding selenoxide to the exocyclic methylene group (Scheme I). The method is based on the observations by Sharpless[5] and Reich[6] that lithium enolates of ketones, aldehydes, and esters react rapidly and cleanly with phenylselenenyl halides to give α-phenylseleno carbonyl compounds[7] and on the report that alkylphenyl selenoxides readily undergo syn[8] elimination to form olefins.[9]

Scheme I



In the case of the trans-fused γ-butyrolactone **1**, the overall method is illustrated for the conversion of **1** into the *trans*-α-methylene-γ-butyrolactone (**5**), with complete exclusion of the endocyclic isomer **6**. The specific formation of **5** comes about as a result of a stereospecific alkylation of the lactone enolate derived from **2** with diphenyl diselenide[10] which establishes the required anti relationship between the α-phenylseleno substituent and the adjacent methine proton; hence, syn elimination of selenoxide **4** can only lead to **5**.



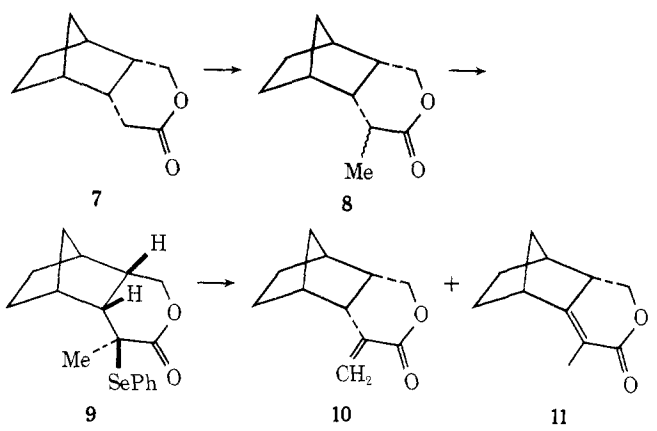
1 2 3 4 5 6

In the conversion of lactones to α-methylene lactones employing the above scheme, the yields of monoalkylated α-methyl lactones are in the range of 90–98%.[12] Similarly, yields for the introduction of the α-phenylseleno group are very high.[11] Formation of the selenoxides is carried out with 30% hydrogen peroxide and results in 90–99% yields of α-methylene lactones. A typical procedure for the conversion of the trans-fused γ-butyrolactone **1** into the trans-fused α-methylene-γ-butyrolactone **5** is as follows. To a solution of 2.4 mmol of lithium diisopropylamide (LDA, prepared from 0.35 ml of diisopropylamine and 1.6 ml of 1.65 *M* butyllithium in hexane under nitrogen at −78°) in 3 ml of anhydrous tetrahydrofuran (THF) was added dropwise over a period of 1 hr, 280 mg (2.0 mmol) of trans-fused lactone **1**[13] in 3 ml of THF. The solution was stirred at −78° for 20 min, 0.15 ml of methyl iodide in 1 ml of THF containing 1 equiv (430 mg) of hexamethylphosphoramide (HMPA) was added rapidly dropwise, and then the mixture was warmed to −40°. The reaction mixture was stirred for 3 hr at −40° and was quenched by the addition of 10% hydrochloric acid. The mixture was diluted with ether and washed with water and saturated sodium chloride solution. There was obtained 310 mg (100%) of crude monoalkylated lactone **2** which was >95% pure by glc analysis.

Introduction of the α-phenylseleno substituent was achieved as follows. The enolate of methylated lactone **2** was prepared as described above by addition of 154 mg (1.0 mmol) of **2** in 1.0 ml of THF to 1.2 mmol of LDA in 3.0 ml of THF. After enolate formation was complete, 377 mg (1.2 mmol) of diphenyl diselenide in 1.0 ml of THF containing 215 mg (1.2 mmol) of HMPA was rapidly added dropwise at −78°. The reaction mixture was stirred at −78° for 40 min, then warmed to −40°, and kept at that temperature for 1.5 hr. The reaction was quenched by the addition of 0.1 *N* HCl solution. Usual work-up afforded yellow crystals which after chromatography on silica gel afforded 264 mg (85%) of the pure α-phenylseleno lactone **3**, mp 124–125°. *Anal.* Calcd for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.86. Found: C, 58.14; H, 5.94.

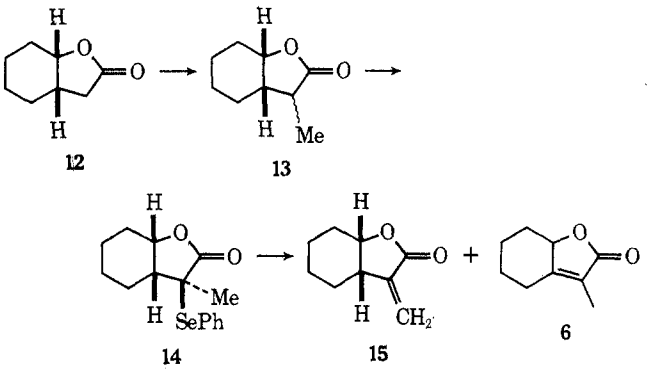
To a solution of the α-phenylseleno lactone **3** (62 mg, 0.2 mmol) in 1.0 ml of THF containing 0.03 ml of acetic acid cooled to 0° was added 0.14 ml of 30% hydrogen peroxide. The reaction was stirred for 30 min at 0°, then poured into cold saturated sodium bicarbonate solution, and extracted with ether. Chromatography of the crude product on silica gel afforded 29 mg (96% yield) of pure trans-fused α-methylene lactone **5**. Its ir [λ_{max} ($CHCl_3$) 5.65 (C=O), 6.00 (C=CH_2) μ] and nmr [δ (CCl_4) 5.95 (d, *J* = 3 Hz, 1 H), 5.30 (d, *J* = 3 Hz, 1 H), 3.9–3.4 (br, 1 H)] were identical with those of a sample of **5** prepared by an alternate procedure.[4a]

The success of the α-methylenation sequence is dependent upon the proper stereochemical relationship between the α-phenylseleno substituent and the proton β to the lactone carbonyl. To achieve the required anti relationship, the introduction of the α substituents must take place with complete stereospecificity. Monoalkylation of the endo δ-lactone **7**[14] proceeded in 95% yield affording lactone **8**. Alkylation of the monomethylated lactone **8** with diphenyl diselenide produced a 62%[12] isolated yield of a pure substance. Spectral data did not allow one to differentiate between the two possible isomeric compounds. However, treatment of **9** with 30% hydrogen peroxide in THF containing a trace of acetic acid resulted in a 3:1 mixture (glc analysis, SE-30) of α-methylene lactone **10**[4c] [λ_{max} ($CHCl_3$) 5.81 (C=O), 6.12 (C=CH_2) μ; nmr (CCl_4) δ 6.11 (t, 1 H), 5.39 (t, 1 H), 4.18 (d, 2 H)] and the corresponding endocyclic double bond isomer **11**, respectively, in 99% isolated yield.



7 8 9 10 11

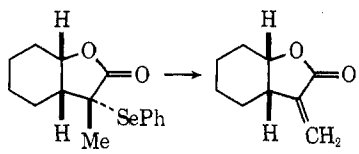
Reaction of the enolate derived from the monomethylated cis-fused lactone **13** (prepared in 90% isolated yield from **12**[15]) with diphenyl diselenide afforded the α-phenylseleno compound **14** (88%) which upon conversion to its selenoxide (30% H_2O_2) produced a 90:10 mixture (glc analysis, SE-30) of endocyclic isomer **6** and cis-fused α-methylene lactone **15**, respectively, in near-quantitative yield.



12 13 14 15 6

In view of the above results, the α-phenylseleno group and the adjacent methine proton in both cases must possess a syn relationship. The obvious way to circumvent formation of the endocyclic isomers (*e.g.*, **6** and **11**) would be to reverse the order of introducing the α-methyl and α-phenylseleno groups maintaining complete stereospecificity during C-alkylation.

α-Phenylselenenylation of cis lactone **12** with diphenyl diselenide employing the general reaction conditions described above, followed by methylation, afforded lactone **16**, free from the isomeric lactone **14**. Employing the usual oxidation procedure, **16** resulted in exclusive formation of the cis-fused α-methylene lactone **15** in very high yield [λ_{max} ($CHCl_3$) 5.69 (C=O), 6.01 (C=CH_2) μ; nmr δ (CCl_4) 5.99 (d, *J* = 2.5 Hz, 1 H), 5.38 (d, *J* = 2.5 Hz, 1 H), 4.40 (q, *J* = 6 Hz, 1 H)].



16 15

This new α-methylenation procedure for the preparation of α-methylene lactones clearly has advantages in terms of yields and mildness of reaction conditions.

Acknowledgment. We thank Professor K. B. Sharpless for helpful suggestions and for informing us of his work prior to publication. We thank Mr. James J. Reap for providing us with lactones **1** and **12**. We thank Eli Lilly and Company and the National Cancer Institute (Public Health Service Research Grant No. R01 CA 13689-02) for generous support of this research.

References and Notes

(1) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); S. M. Kupchan, *Trans. N. Y. Acad. Sci.*, **32**, 85 (1970).

(2) S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969).

(3) (a) E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 230 (1950); (b) E. E. van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, **80**, 3079 (1958); (c) V. B. Piskov, *J. Gen. Chem. USSR*, **30**, 1421 (1960); (d) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965); (e) H. Minato and I. Horibe, *Chem. Commun.*, 531 (1965); (f) A. Löffler, R. D. Pratt, J. Pucknat, G. Gelbard, and A. S. Dreiding, *Chimia*, **23**, 413 (1969); (g) J. Martin, P. C. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970); (h) E. S. Behare and R. B. Miller, *ibid.*, 402 (1970); (i) E. Ohler, K. Reininger, and U. Schmidt, *Angew. Chem. Int. Ed. Engl.*, **9**, 457 (1970); (j) J. W. Patterson and J. E. McMurry, *Chem. Commun.*, 488 (1971); (k) V. R. Tadwalkar and A. S. Rao, *Indian J. Chem.*, **9**, 1416 (1971); (l) L. K. Dalton and B. C. Elmes, *Aust. J. Chem.*, **25**, 625 (1972); (m) A. E. Greene, J. C. Muller, and G. Ourisson, *Tetrahedron Lett.*, 2489, 3375 (1972); (n) K. Yamada, M. Kato, and Y. Hirata, *ibid.*, 2745 (1973); (o) R. C. Ronald, *ibid.*, 3831 (1973); (p) P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, *J. Amer. Chem. Soc.*, **95**, 6848 (1973).

(4) (a) P. A. Grieco and K. Hiroi, *Chem. Commun.*, 1317 (1972); P. A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 1831 (1973); (b) A. D. Har-

mon and C. R. Hutchinson, *ibid.*, 1293 (1973); (c) P. A. Grieco and K. Hiroi, *Chem. Commun.*, 500 (1973).
(5) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, **95,** 6137 (1973).
(6) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Amer. Chem. Soc.*, **95,** 5813 (1973).
(7) A report describing the reaction of phenylselenenyl trifluoroacetates with enol acetates of ketones has appeared [D. L. C. Clive, *Chem. Commun.*, 695 (1973)].
(8) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).
(9) D. N. Jones, D. Mundy, and R. D. Whitehouse, *Chem. Commun.*, 86 (1970); K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **95,** 2697 (1973).
(10) The use of PhSeBr in all the cases examined here gave lower yields (50–70%); use of PhSeSePh gave consistently high yields (85–90%) of α-phenylseleno compounds.[11] For example, reactions of the enolate of methylated lactone **2** with PhSeBr resulted in only a 66% isolated yield of pure **3**, whereas use of PhSeSePh afforded an 85% isolated yield of pure **3**.
(11) With the exception of compound **8**, all yields for the introduction of the α-phenylseleno group from monomethylated lactones are in the range of 85–90%. Reaction of monoethylated lactone **8** with PhSeSePh affords α-phenylseleno compound **9** in yields of 60–65%. Use of PhSeBr results in only 20–25% yields of **9**. Introduction of the phenylseleno substituent on the β surface of the molecule forces the methyl group down, thus resulting in severe steric interactions.
(12) A report describing the alkylation of the enolate of γ-butyrolactone with methyl iodide has appeared [G. H. Posner and G. L. Loomis, *Chem. Commun.*, 892 (1972)]; for other studies on enolates derived from lactones, see ref 3m, 4a, and 4c.
(13) M. S. Newman and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **67,** 233 (1945).
(14) P. A. Grieco and M. Meyers, unpublished results. The synthesis of lactone **7** will be reported in due course.
(15) J. Klein, *J. Amer. Chem. Soc.*, **81,** 3611 (1959).

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Received October 16, 1973