REFERENCES

[1] *E.W. Colvin*, Chem. Soc. Rev. *7*, 15 (1978); *I. Fleming*, Chemistry & Industry *1975*, 449; *P.F. Hudrlik*, J. organometal. Chemistry Library *1*, 127 (1976); *T.-H. Chan*, Accounts chem. Res. *10*, 442 (1977).

[2] a) *W.E. Fristad, T.R. Bailey & L.A. Paquette*, J. org. Chemistry *43*, 1620 (1978); *R.T. Taylor, C.R. Degenhardt, W.P. Melega & L.A. Paquette*, Tetrahedron Letters *1977*, 159; *T.H. Chan, A. Baldassarre & D. Massuda*, Synthesis *1976*, 801; *K. Sachdev*, Tetrahedron Letters *1976*, 4041; b) *J. J. Eisch & G.A. Damasevitz*, J. org. Chemistry *41*, 2214 (1976); *K. Uchida, K. Utimoto & H. Nozaki*, J. org. Chemistry *41*, 2215, 2941 (1976); *R. Köster & L.A. Hagelee*, Synthesis *1976*, 118; *K. Yamamoto, O. Nunokawa & J. Tsuji*, Synthesis *1977*, 721; *H. Westmijze, J. Meijer & P. Vermeer*, Tetrahedron Letters *1977*, 1823; *M. Obayashi, K. Utimoto & H. Nozaki*, Tetrahedron Letters *1977*, 1805.

[3] *D. Seyferth, K.R. Wursthorn & R.E. Mammarella*, J. org. Chemistry *42*, 3104 (1977).

[4] *I. Ojima, M. Kumagai & Y. Miyazawa*, Tetrahedron Letters *1977*, 1385.

[5] *J. Slutsky & H. Kwart*, J. Amer. chem. Soc. *95*, 8678 (1973); *J.-P. Pillot, J. Dunoguès & R. Calas*, Tetrahedron Letters *1976*, 1871.

[6] *M.J. Carter & I. Fleming*, Chem. Commun. *1976*, 679; *I. Fleming & A. Percival*, Chem. Commun. *1976*, 681; *B.-W. Au-Yeung & I. Fleming*, Chem. Commun. *1977*, 79, 81.

[7] *K. Tamao & M. Kumada*, J. organometal. Chemistry *30*, 329 (1971).

[8] *J.F. Biellmann & J.B. Ducep*, Tetrahedron Letters *1968*, 5629; *J.F. Biellmann & D. Schirlin*, Synth. Commun. *8*, 409 (1978).

[9] *M. Kumada, M. Yamaguchi, Y. Yamamoto, J.-I. Nakajima & K. Shiina*, J. org. Chemistry *21*, 1264 (1956); *H. Sakurai, K. Tominaga, T. Watanabe & M. Kumada*, Tetrahedron Letters *1966*, 5493; *M. Ishikawa, M. Kumada & H. Sakurai*, J. organometal. Chemistry *23*, 63 (1970).

[10] *C.D. Hurd & H. Greengard*, J. Amer. chem. Soc. *52*, 3356 (1930).

[11] *K.B. Sharpless & R.F. Lauer*, J. Amer. chem. Soc. *95*, 2697 (1973).

[12] *H.L. Simon, A. Kaufmann & H. Schinz*, Helv. *29*, 1133 (1946).

[13] *T.J. Curphey*, Org. Syntheses *51*, 142 (1971).

[14] *S.L. Stafford & J.D. Baldeschwieler*, J. Amer. chem. Soc. *83*, 4473 (1961); *F.J. Weigert & J.D. Roberts*, J. Amer. chem. Soc. *91*, 4940 (1969).

[15] *I. Fleming & A. Pearce*, Chem. Commun. *1975*, 633.

[16] *K. Utimoto, M. Kitai & H. Nozaki*, Tetrahedron Letters *1975*, 2825.

[17] *A. Hosomi, A. Shirahata & H. Sakurai*, Tetrahedron Letters *1978*, 3043.

292. A New Method for the Construction of Macrolides. Stereoselective Synthesis of (±)-Phoracantholide J

Preliminary communication

by **Martin Petrzilka**

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

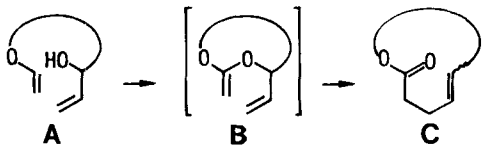
(6.XI.78)

Summary

Starting from 5-chloro-2-pentanone (**1**) the naturally occurring 10-membered lactone phoracantholide J (**8a**) has been synthesized as its racemate in a sequence of six steps *(Scheme 2)*. Salient features of the synthesis include an internal selenium assisted acetal formation (**4**→**5**) and a stereoselective *Claisen* rearrangement (**6**→**7**→**8**). This general synthetic strategy offers an alternative approach towards the construction of macrocyclic lactones.

An effective new version of the ester *Claisen* rearrangement has recently been developed in these laboratories, which allowed the preparation of a series of acyclic γ,δ-unsaturated acids [1] including some naturally occurring ones [2]. The observed regiospecific addition of benzeneselenenyl bromide to enol ethers coupled with the exceptional electrophilicity of this reagent suggested a facile intramolecular variant of this reaction *(Scheme 1)*. Starting from a bifunctional precursor **A** a cyclic ketene

Scheme 1

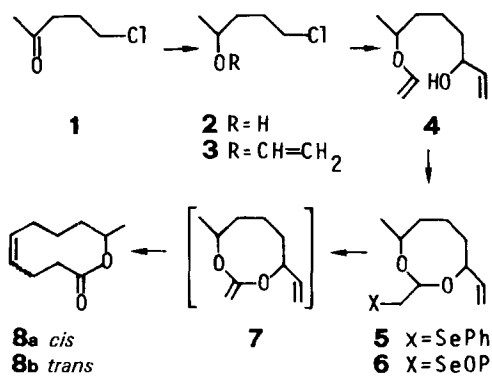


acetal intermediate **B** should be readily accessible which, after *Claisen* rearrangement, would lead to a γ,δ-unsaturated lactone **C**. This contrasts with other variations of the ester *Claisen* rearrangement [3] [4], which have not been applied in this fashion.

The present communication demonstrates the feasibility of this strategy by describing a total synthesis of (±)-phoracantholide J (**8a**)[1]), a major component of the metasternal gland secretion of the eucalypt longicorn *Phoracantha synonyma* [6].

As outlined in *Scheme 2*, a quick assembly of the required cyclization precursor **4** was accomplished starting from commercially available 5-chloro-2-pentanone (**1**). Its reduction with excess $NaBH_4$ in 2-propanol at 0° gave 5-chloro-2-pentanol (**2**; 70%), which upon mercuric acetate (60 mg/10 mmol of **2**) catalyzed vinyl transetherification [7] with ethyl vinyl ether (6 mol-equiv./46 h under reflux) afforded the corresponding *o*-vinyl ether **3**[2]) (45%[3])). Halogen-lithium exchange in **3** using a

Scheme 2



[1]) *Gerlach et al.* have recently prepared this compound by internal esterification of the corresponding hydroxy acid precursor [5].

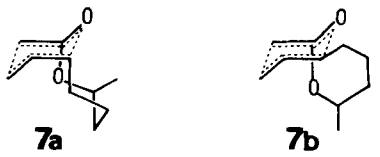
[2]) All new compounds possessed IR., NMR. and mass spectral data consistent with their assigned structures.

[3]) This yield is not optimized.

0.5M solution of lithium naphthalene (2.2 mol-equiv./−70°) [8] in dry THF followed by the addition of freshly distilled acrolein (2.5 mol-equiv.) at −78° furnished, after a non-acidic work-up and chromatography on basic alumina (activity III) with hexane/ether 2:1, the desired allylic alcohol **4**[2]) (64%[3]))[4]). Optimum conditions for the crucial, internal selenium assisted acetal formation consisted in the slow addition of a solution of **4** and *Hünig*'s base[5]) (2.1 mol-equiv.) in dry CH_3CN to a solution of benzeneselenenyl bromide (2 mol-equiv.) at 0° thereby producing the cyclic acetal **5**[2]) as a mixture of diastereoisomers in 71% yield[6]). Although no kinetic data are yet available the result of this remarkably mild and efficient[7]) cyclization process suggests that, of the three possible sites of attack for benzeneselenenyl bromide (two double bonds and the base, see also footnote 5), its regiospecific addition to the enol ether double bond followed by internal nucleophilic attack of the allylic alcohol moiety is preferred.

Finally, subsequent oxidation of **5** using $NaIO_4$ (1.5 mol-equiv.) and $NaHCO_3$ (1.1 mol-equiv.) in $MeOH/H_2O$ 6:1 (30 min/25°) and thermolysis of the resulting selenoxide **6**[2]) in toluene under reflux in the presence of hexylamine (3 mol-equiv.) and dry $MgSO_4$ (2 g/mmol of **6**) for 18 h induced elimination of benzeneselenenic acid to afford, after *Claisen* rearrangement of the intermediate ketene acetal **7**, a 7:2 mixture of **8a**[2]) (phoracantholide J) and **8b**[2])[8]) in 81% yield, identical by spectral and GLC. evidence with two independently prepared samples of **8a** [5] and **8b** [10]. The predominant formation of the naturally occurring *cis*-isomer **8a** over **8b** is not unex-

Scheme 3



7a **7b**

[4]) The corresponding *Grignard* reagent of **3** (1.1 mol-equiv. of Mg/5 h under reflux in THF) equally afforded **4**, albeit in lower yields (30–35%).

[5]) This base was added to trap HBr which is generated simultaneously together with the acid labile acetal **4**. An excess is needed as it is partially consumed by competitively reducing benzeneselenenyl bromide to diphenyldiselenide; for a similar reported case see [9].

[6]) A solution of **4** (0.235 mmol) and *N,N*-diisopropylethylamine (0.493 mmol) in 2 ml of dry CH_3CN (passed through basic alumina, activity I) was added during 30 min to a stirred solution of benzeneselenenyl bromide (0.47 mmol) in 4 ml of dry CH_3CN at 0°, whereby the colour of the mixture changed from dark orange to intensive yellow. After stirring an additional 15 min at 0° the mixture was poured into aq. $NaHCO_3$ solution and extracted with ether. The organic layers were washed with brine, dried over K_2CO_3 and concentrated *in vacuo*. Chromatography on basic alumina (activity III) with hexane (29 mg of diphenyldiselenide recovered) and hexane/ether 8:1 afforded **5**.

[7]) The products of the corresponding bimolecular reaction were not observed.

[8]) A mixture of selenoxide **6** (0.26 mmol), hexylamine (0.78 mmol) and dry $MgSO_4$ (260 mg) in 5 ml of toluene was heated under reflux for 18 h. After filtration the solvent was carefully removed at normal pressure; according to TLC. analysis some of the desired product was lost during this operation owing to its high volatility. Chromatography of the residue on alumina (activity III) with hexane/ether 8:1 followed by bulb-to-bulb distillation (100–130° oven temp./10 Torr) furnished **8a/8b**, separable by GLC. (120°/5% SE-30) or by chromatography on silica gel impregnated with 10% silver nitrate (ether/hexane 2:1).

pected as examination of models of the possible transition states **7a** and **7b**[9]) *(Scheme 3)* reveals, that **7a**, although disposing of an additional 1,3-diaxial interaction, is considerably less strained than **7b**.

The smooth formation of an 8-membered ring[10]) in the key step (**4**→**5**) of the described synthesis coupled with a stereoselective *Claisen* rearrangement (**6**→**7**→**8**) nicely exemplifies the synthetic value of this 'ring growing' process[11]) for the construction of macrocyclic lactones. Further investigations extending this method to the syntheses of lactones of different ring sizes are currently in progress.

I am indebted to Professor *H. Gerlach* and Dr. *H. Malherbe, Ciba-Geigy AG*, Basel, for kindly providing spectra and samples of phoracantholide J (**8a**) and (*E*)-4-decen-9-olide (**8b**). I also wish to thank Mr. *R. Baudat* and Ms. *S. Muralti* for their able experimental assistance, Dr. *R.L. Snowden* for looking through the manuscript and Mr. *J.-P. Saulnier* and Mrs. *F. Klöti* for careful ^{1}H-NMR. and mass spectra measurements.

REFERENCES

[1] *M. Petrzilka*, Helv. *61*, 2286 (1978).
[2] *M. Petrzilka*, unpublished work.
[3] *W.S. Johnson, L. Werthemann, W.R. Barlett, T.J. Brocksom, T. Li, D.J. Faulkner & M.R. Petersen*, J. Amer. chem. Soc. *92*, 741 (1970).
[4] a) *R.T. Arnold & C. Hoffmann*, Synth. Commun. *2*, 27 (1972); b) *R.E. Ireland & R.H. Mueller*, J. Amer. chem. Soc. *94*, 5897 (1972); c) *R.E. Ireland & A.K. Willard*, Tetrahedron Letters *1975*, 3975.
[5] *H. Gerlach, P. Künzler & K. Oertle*, Helv. *61*, 1226 (1978).
[6] *B.P. Moore & M.V. Brown*, Austral. J. Chemistry *29*, 1365 (1976).
[7] *W.H. Watanabe & L.E. Conlon*, J. Amer. chem. Soc. *79*, 2828 (1957).
[8] *C.G. Screttas & M. Micha-Screttas*, J. org. Chemistry *43*, 1069 (1978) and ref. cited therein.
[9] *N. Petragnani & M.D.M. Campos*, Tetrahedron *21*, 13 (1965).
[10] *D. Bellus & R. Malherbe*, Helv. *61*, 3096 (1978).
[11] *H. Hunsdiecker & H. Erlbach*, Chem. Ber. *80*, 129 (1947).
[12] *C. Galli, G. Illuminati, L. Mandolini & P. Tamborra*, J. Amer. chem. Soc. *99*, 2591 (1977).
[13] *M. Stoll & A. Rouvé*, Helv. *18*, 1087 (1935).
[14] For a review on more recent methods see *K.C. Nicolaou*, Tetrahedron *33*, 683 (1977).
[15] *S. Masamune, G.S. Bates & J.W. Corcoran*, Angew. Chem. Int. Ed. Engl. *15*, 585 (1977).

---

9) It is assumed that the *Claisen* rearrangement preferentially proceeds through a chair-like transition state. A third transition state where the two substituents in question would both occupy equatorial positions is, for steric reasons, very unlikely.

10) The yields and cyclization rates of the lactonization of ω-bromo acids [11] [12] and ω-hydroxy acids [13] [14] generally drop to a minimum for the formation of (8–10)-membered rings. For an exception see [5].

11) For the use of this term in this connection see [15].