

Alternative Syntheses of Phoracantholide I (9-Decanolide) from Cyclohexanone and Cycloheptanone

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Foracantolideo I racêmico (**6**) foi sintetizado por quatro caminhos diferentes. A redução (LiAlH_4 ou NaBH_4) do produto de adição de 1-morfolinocicloexeno (**1**) a metil vinil cetona, seguida de hidrólise cuidadosa fornece uma mistura de hemiacetal **2** e éter enólico **3** (em rendimento total de 58-60%), ambos já conhecidos e transformados no foracantolideo I. Na rota alternativa, o hidroperóxido **7**, obtido de hemiacetal **2** (H_2O_2 , H^+), é submetido à expansão de anel (Fe^{+2} , Cu^{+2}) e a proveniente mistura de decanolídeos **8** é hidrogenada (Ra-Ni, H_2), fornecendo o 9-decanolideo (**6**) em 50-60% de rendimento. Em um outro procedimento, 2-alilcicloheptanona (**9**) é hidratada com H_2SO_4 (80%) e a conseqüente mistura de **10** e **11** é transformada no hidroperóxido **15**. Expansão de anel de hidrogenação do produto (**16**), como no caso anterior, fornece o foracantolideo I em 50-60% de rendimento, a partir do composto **9**. Outrossim, a referida lactona pode ser preparada pela desoxigenação de 7-oxo-9-decanolideo (**13**), através de dessulfurização (Ra-Ni) do ditiocetal correspondente. Mas esta rota sofre de péssimos rendimentos (5-25%) na obtenção de cetolactona **13**, seja pela seqüência de nitroação-desoximação ou por ozonólise do éter enólico **11**. Além disso, forma-se um subproduto, junto com a cetolactona **13**, que foi atribuída a estrutura **14**, baseando-se nos seus dados espectrais bem como em outras propriedades já descritas para o composto sintético **14**.

Four different routes for the preparation of the title lactone have been developed. Careful addition of 1-morpholinocyclohexene (**1**) to menthyl vinyl ketone, followed by reduction (LiAlH_4 or NaBH_4) of the adduct and subsequent hydrolysis afford a mixture of the known hemi-ketal **2** and the corresponding enol ether **3** (58-60% total yield), both of which have been converted earlier into phoracantholide I (**6**). Alternatively, the hydroperoxide **7**, derived from hemi-ketal **2** ($\text{H}_2\text{O}_2, \text{H}^+$), is subjected to ring expansion and the resulting mixture of decanolides (**8**) is hydrogenated (Ra-Ni, H_2), obtaining 9-decanolide (**6**) in 50-60% yield. In another procedure, 2-allylcycloheptanone (**9**) is hydrated with 80% H_2SO_4 and the resulting mixture of **10** and **11** is converted into hydroperoxide **15**, which on ring enlargement and subsequent hydrogenation affords the title lactone in 50-60% overall yield from **9**. Alternatively, desulfurization (Ra-Ni) of the dithioketal of 7-keto-9-decanolide (**13**) gives phoracantholide I, but the method suffers from poor yields (5-25%) in the preparation of ketolactone **13**, both by the nitrosation-deoximation sequence and ozonolysis of enol ether **11**. Furthermore, a by-product is formed, along with ketolactone **13**, and has been assigned structure **14**, based on its spectra and other properties already recorded for the synthetic compound (**14**).

Key words: *phoracantholide I; Ring-expansion; 2-allylcycloheptanone; 7-keto-9-decanolide.*

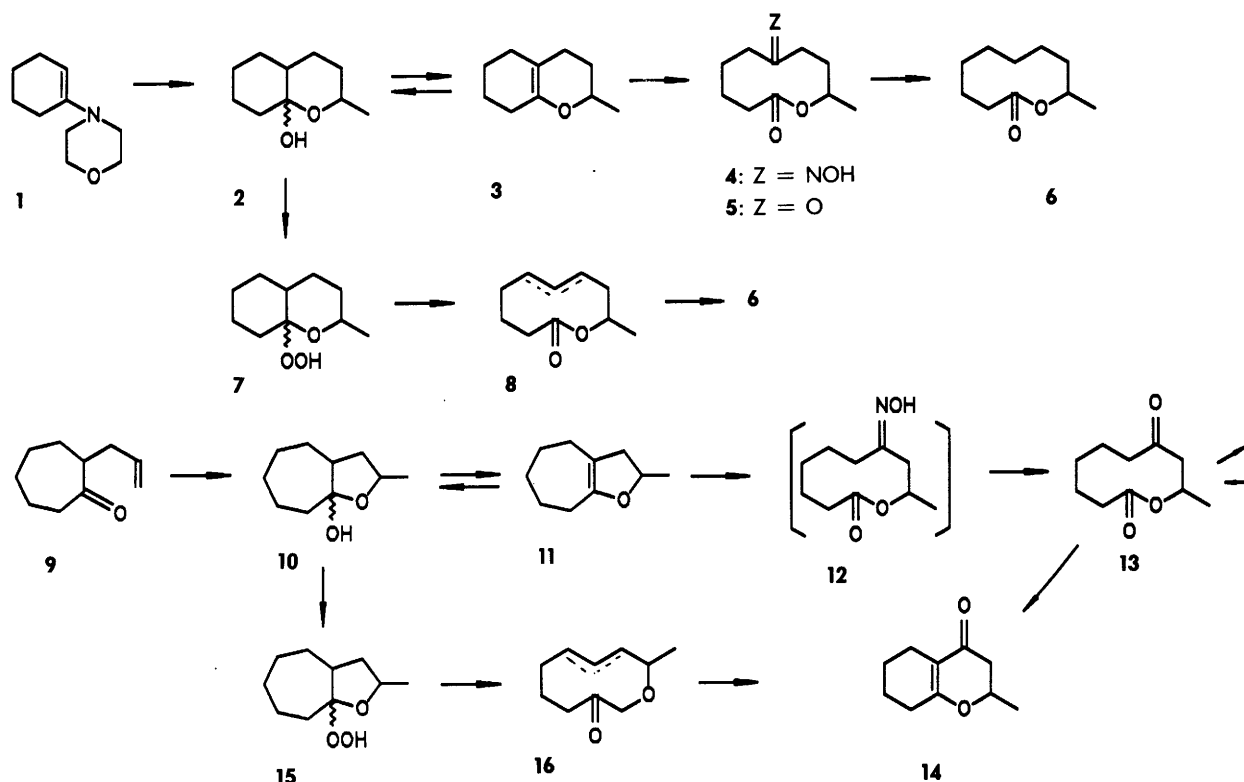
Introduction

Since the isolation of phoracantholide I (**6**) from the defensive secretion of *Phoracantha synonyma*², it has been synthesized by several routes involving either cyclic or acyclic starting materials. Earlier we assembled the 10-membered lactone from cyclohexanone and 4-bromo-1-butene^{3b} and now report some alternative paths starting from both cyclohexanone and cycloheptanone 1 ref. (Scheme).

Aims, Results and Discussion

Our initial objective was to develop an alternative easy preparation of hemi-ketal **2**, which we had already converted into phoracantholide I (**6**)^{3b}. Facile alkylation of enamines with electrophilic olefins attracted our attention due to its high yield and ready availability of enamines⁴. But the reaction of enamines of cyclohexanone with methyl vinyl ketone was known to undergo further cyclization to octalone and the intermediate Michael adduct had not been isolated or intercepted^{4,5}. Nevertheless, we were very much interested in developing this route, because

SCHEME



Reagents: i, $\text{H}_2\text{C}=\text{CHCOCH}_3$; ii, LiAlH_4 or NaBH_4 ; iii, INHCl ; iv, $n\text{-BuONO}$, H_3O^+ ; v, aq. NaHSO_3 or formalin; i, H_2O_2 , H^+ ; vii, $\text{Cu}(\text{OAc})_2$, FeSO_4 ; viii, Ra-Ni , H_2 ; ix, aq. $\text{Hg}(\text{OAc})_2$, followed by NaOH , NaBH_4 ; x, 80% H_2SO_4 ; ix, $\text{HSCH}_2\text{CH}_2\text{SH}$, BF_3 ; xii, Ra-Ni ; xiii, O_3 , followed by Zn , AcOH ; xiv, H^+ or RO^- .

we were also looking for an easy access to higher homologs of enol ether 3, which were needed for the preparation of large-ring ketolactones⁶. After several trials we found out that under carefully controlled conditions the respective adduct from 1-morpholino-1-cycloalkene and alkyl vinyl ketone can be intercepted or even isolated and its keto group reduced selectively with LiAlH_4 or NaBH_4 . Subsequent mild hydrolysis then affords the reduced product, which can be easily dehydrated to the corresponding enol ether. The overall yields are excellent (80-94%) in the cyclododecanone series⁶, but with 1-morpholinocyclohexene (1) and methyl vinyl ketone the solid hemi-ketal 2 is isolated in only 40-45% yield and the mother liquor contains variable quantities of enol ether 3, contaminated with some unidentified minor products (TLC). The liquid portion, after distillation, can be nitrosated according to the established procedure^{3h} to obtain small amounts of oxime 4 or ketolactone 5. This augments (15-18%) the effective total yield of hemi-ketal (2) to 58-60%, which compares very favorably with its earlier preparation (40-45% yield) from 2-ethoxycarbonylcyclohexanone and 4-bromo-1-butene^{3h}.

Searching next for an alternative procedure for converting

hemi-ketal 2 into 9-decanolide (6), we found that it can be changed easily into hydroperoxide 7, in a quantitative yield (H_2O_2 , H^+ , MeOH). Subsequent ring-expansion of 7, can be carried out either by thermolysis⁷ (boiling xylene) or with the help of metal ions (Fe^{+2} Cu^{+2})⁸. The latter method was adopted in our optimized procedure, because it proved to be much easier and cleaner (TLC) than the former option. The resulting mixture of decenolides (8) was hydrogenated (Ra-Ni , H_2) to phoracantholide I (6), identical in all respects (TLC, NMR, IR) with the sample prepared earlier in our laboratories^{3h}. Apart from the simplicity and quick pace of the present transformations, the overall yield (50-60%) of 9-decanolide (6), from compound 2, is far superior to that obtained earlier (30-40%)^{3h}, involving the intermediacy of ketolactone 5.

In another approach, our preliminary attempts were directed to obtain 7-keto-9-decanolide (13) from hemi-ketal 10 and/or enol ether 11. Thus, the crude hemi-ketal 10, obtained by the oxymercuration - demercuration of 2-allylcycloheptanone (9), was subjected to nitrosation, as described for an isomeric compound^{3h}. Although the desired reaction took place (TLC), we were unable to isolate the expected / oximino-lactone 12. Consequently,

the crude reaction product was deoximated by refluxing in aqueous-ethanolic sodium bisulfite (NaHSO_3) or formalin. Laborious fractional crystallization then afforded the desired ketolactone **13** in only 4-18% yield. A by-product was isolated from mother liquor and assigned structure **14**, based on its spectra, further confirmed by comparing its properties with those described for the synthetic compound⁹.

Similarly, ozonolysis of enol ether **11** afforded ketolactone **13** in ~ 25% yield, while the mother liquor revealed the presence of vinylogous lactone **14** (IR: 1670, 1620 cm^{-1}).

As the by product **14** was arising obviously from the transannular acylation of ketolactone **13**, we deliberately provoked this reaction in the mother liquor by refluxing it in chloroform or ethanol, containing small quantity of *p*-toluenesulfonic acid; vinylogous lactone **14** could be isolated rather easily by this procedure.

Attempted deoxygenation of 7-keto-9-decanolide (**13**) through its tosylhydrazone, in the manner described for the isomeric or homologous compounds^{3h,11}, was unsuccessful. In fact, in sharp contrast with the usual easy formation of tosylhydrazones, the desired derivative could not be isolated in the present case. We have also observed similar behaviour in the case of 5-keto-9-decanolide¹², indicating probable side-reactions. However, deoxygenation of ketolactone **13** by desulfurization¹³ of its dithioketal proceeded normally to afford phoracantholide I (**6**).

Due to poor results in the above ketolactone series, we searched for other viable alternatives. Thus, we found that 2-allylcycloheptanone (**9**) can be hydrated rather quickly (10-15min) and economically with 70-90% H_2SO_4 to afford a mixture of hemi-ketal **10** and enol ether **11**, which on small-path distillation gives **11** in 80-90% yield. Furthermore, enol ether **11** or even the crude hydration product can be converted easily ($\text{H}_2\text{O}_2, \text{H}^+$) into hydroperoxide **15**, which on ring-enlargement and subsequent hydrogenation of the resulting decenolides **16**, as described for the previous case, affords 9-decanolide (**6**) in 50-60% overall yield from 2-allylcycloheptanone; this constitutes the most efficient and probably the most economical preparation of racemic phoracantholide I.

In conclusion, four different routes to racemic 9-decanolide or (\pm)-phoracantholide I (**6**) have been developed from cyclohexanone and cycloheptanone, as detailed below in the Experimental part.

Materials and Methods

Reagent grade chemicals, solvents and adsorbents purchased from commercial supplier were used as received, unless indicated otherwise. Petroleum ether, b.p. 30-60°, was used. Organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure on a rotary evaporator. All reactions were monitored by thin layer chromatography (TLC) in the routine manner. IR spectra were recorded on a Perkin Elmer 137 Infracord or 283-B spectrometer. ¹HNMR spectra were registered on Varian A-60D (60 MHz) or EM-390 (90 MHz) spectrometer. Melting points were observed on a Reichert Kofler type hot stage microscope and are uncorrected. All temperatures are expressed in °C. Other specific details are given below in the Experimental part.

Experimental

Preparation of hemi-ketal 2: Freshly distilled methyl vinyl ketone (5.25 g, 75mmol; 6.1 ml) is added to a stirred solution (N_2) of 1-morpholinocyclohexene⁴ (8.35, 50 mmol) in dry benzenel (50ml) and dioxan (12.5 ml), con-

taining acetic acid (3 drops). The reaction mixture, protected from light and moisture, is stirred at room temperature (R.T.) for ~ 30 min and then allowed to rest for 14-16h, when it is slowly heated on a water bath (80-90°) for 2h, followed by a gentle reflux for 2-3h. Low-boiling components are then removed on a rotary evaporator and the residue dissolved in benzene (50ml) is added dropwise (15-20 min) to a well-stirred suspension of LiAlH_4 (760mg, 20 mmol) in anhydrous ether (50ml). A sticky mass usually appears soon after about 1/5 addition and may impede magnetic stirring. However, addition is completed with manual shaking and is followed by a reflux for 2h. The cooled reaction mixture is carefully decomposed with ice chips, acidified (pH ~ 5) with hydrochloric acid (1n, 50ml) and stirred (25-35°) for 16-20H. After adding more hydrochloric acid (2.5N, 5ml), the organic layer is separated and the aqueous portion extracted thrice with ether (3x50ml). Combined organic extract is washed successively with 0.5N hydrochloric acid, water and brine. After drying, the extract is evaporated to ~ 10ml and diluted with petroleum ether. On chilling in a freezer, it affords silky, fine needles (1.2-1.6 g), m. p. 103-105°. Mother liquor gives further crops melting over a wide range (65-100°)¹⁴. Total solid hemi-ketal **2** usually amounts to 3.4-3.9g (40-46% yield).

Final mother liquor on short-path distillation (110-120°/~ 5 torr) furnishes a colorless liquid (2.4-2.7g), which contains appreciable quantities of enol ether **3**, contained with unidentified impurities (TLC, IR, NMR). On nitrosation, in the manner described earlier^{3h}, it gives oximino-lactone **4** and ketolactone **5**, amounting to 14-18% yield with respect to the starting enamine.

The Michael addition product in the above reaction can be isolated by distillation as a pale-yellow, viscous liquid (~ 9g; 76% yield), b.p. 122-130°/0.025 torr or 130-138°/0.15 torr; diagnostic peaks: IR (neat) 1715, 1667, 1117 cm^{-1} ; ¹HNMR (CCl_4) δ 2.09 (s, H_3CCO), 3.67 (~ t $\text{H}_2\text{C-O-CH}_2$). Its reduction and subsequent hydrolysis give results similar to the ones described above for the crude adduct.

The Michael reaction carried out according to Ref. 4 or 5 and its subsequent reduction and hydrolysis conducted under the above conditions gave slightly inferior results.

Reduction of the Michael adduct, *in situ*, with NaBH_4 , followed by usual hydrolysis and work-up also gave inferior results.

Conversion of hemi-ketal 2 into (\pm)-phoracantholide (6):

I - Preparation of hydroperoxide 7: A stirred mixture of hemi-ketal **2** (850 mg, 5 mmol), methanol (10 ml) and hydrogen peroxide (30%; 2.5ml), surrounded by water bath (10-20°), is treated with sulphuric acid (50%; 1 drop), resulting in a complete solution. Stirring is continued for 30 min, when sodium hydroxide (1N, 5ml) is added and the reaction mixture extracted with ethyl acetate (2x25ml). The combined extract is washed with dilute sodium hydroxide and brine (3x20 ml). Drying and evaporation gives a viscous, colorless liquid (940 mg), showing broad and intense absorption in the hydroxyl region.

II - Ring - expansion of hydroperoxide 7 to decenolides 8: The above hydroperoxide (940 mg), dissolved in methanol (75 ml), is treated with cupric acetate monohydrate (1.3g, 6.5 mmol). The reaction mixture is surrounded by tap water and stirred magnetically. After ~ 5 min, ferrous sulphate heptahydrate (1.82 g, 6.5 mmol) is added; there is an immediate reaction and the original bluish-green color changes to dark brown. After stirring for 1 h, excess of methanol is evaporated, the residue dissolved in hydrochloric acid (~ 1N, 20 ml) and the resulting green

solution extracted with ethyl acetate (2x30 ml). The organic extract is washed successively with 1N hydrochloric acid (2x10 ml), saturated sodium bicarbonate (10 ml) and again brine (2x10 ml). Drying and evaporation furnishes a faintly brown liquid (818 mg), with a camphoric smell. TLC examination shows it to be mainly the desired product, contaminated with traces of a slightly higher R_f impurity and a very polar minor spot, almost at the origin. IR (1731 cm⁻¹ and ¹HNMR (δ 1.1 - 1.25, three superimposed doublets due to H₃CCH, and 4.9 - 5.6, complex multiplet due to methine and olefinic CH) also reveal it to be a mixture (8).

III - Reduction of decenolides 8 to 9-decanolide (6): A mixture of the above product (818 mg), methanol (10 ml), Raney Nickel (1 ml of a methanolic suspension)¹⁵ and NaHCO₃ (50 mg) is subjected to hydrogenation (30 p.s.i.) in a Parr apparatus for 3 h. Catalyst is filtered over diatomaceous earth and filtrate evaporated. The resulting liquid containing some sodium bicarbonate is dissolved in petroleum ether and filtered. Evaporation affords a colorless liquid (703 mg), having the characteristic smell of phoracantholide, but still contaminated with some impurities (TLC).

Chromatography over silica gel (10 g), eluted with hexane/EtOAc (0-5%), affords pure 9-decanolide (442 mg), identical in all respects (TLC, IR ¹HNMR) with the sample prepared earlier in our laboratories^{3h}.

Conversion of 2-allylcycloheptanone (9) into 7-oxo-9-decanolide (13): a) Oxymercuration - demercuration of 9 was carried out exactly in the manner described for 2-(3-butenyl) cyclohexanone^{3h}, obtaining the crude product (10) in a quantitative yield: a colorless thick liquid showing strong absorption for OH and only weak band for enol ether 11(1698cm⁻¹).

A solution of the above product (1.7g, 10mmol) in 95% ethanol (3 ml), containing freshly prepared n-butyl nitrite¹⁶ (1.4ml, 1.26g, ~ 12 mmol), was surrounded by tap water and connected to a mercury manometer open at the other end¹⁷. The stirred solution was treated with hydrochloric acid (1N, 0.5 ml), when there was immediately a blue coloration and an exothermic reaction. After stirring for 3-4h, the greenish reaction mixture was taken up in ethyl acetate and washed with water, saturated sodium bicarbonate solution and brine. Drying and evaporation gave a thick, yellowish liquid (1.87g), which gave no crystalline product from MeOH, EtOH, benzene, hexane or their mixtures. Consequently, it was deoximated by refluxing in aqueous ethanolic sodium bisulphite, as described earlier^{3h}. Usual work-up gave a pale-brown liquid (1.37 g), which deposited a colorless solid (136 mg) from petroleum ether. Mother liquor was distilled (110-120°/2 torr) and the distillate (840 mg) after combining with the above solid was crystallised from petroleum ether or 95% ethanol, affording ketolactone 13, as a colorless solid (340 mg; 18.5% yield), m.p. 73-75°
IR (KBr): ν = 1721, 1701, 1245 cm⁻¹.

¹HNMR (CCl₄): δ = 1.35 (d, J 6.5 Hz, CH₃), 1.0 - 2.0 (m, 3 CH₂), 2.0-3.0 (m, having a doublet superimposed at 2.6, 3CH₂), 4.8-5.4 (m, CH).

b) In another experiment, the nitrosation product from hemi-ketal 10 (1.7g) was deoximated by refluxing for 4h in 95% ethanol (5ml), containing formalin (2 ml) and hydrochloric acid (1N, 1 ml). Usual work-up gave a brown liquid (1.3 g), which on short-path distillation furnished a pale-yellow liquid (635 mg). Crystallization from ethanol or petroleum ether or their mixture gave colorless plates of ketolactone 13 (310 mg; 16.8% yield), m.p. 74-75°.

Combined mother liquor (1.3 g) from the above two lots was redistilled and furnished a colorless liquid (935 mg), which on repeated crystallization from petroleum ether afforded colorless needles, m.p. 47-48°, identified as vinylogous lactone 14 (lit. 9, m.p. 46°), based on its spectra.

IR (KBr): ν = 1669, 1618 cm⁻¹.

¹HNMR (CCl₄): δ = 1.43 (d, J 6Hz, CH₃), 1.5 - 2.8 (m, having a doublet superimposed at 2.35, 5 CH₂), 4.2 - 4.7 (m, CH); these values are in accord with those reported earlier⁹.

c-I) Hydration of 9 with H₂SO₄: Ice-cold sulphuric acid (80-90%; 5ml) was added slowly to well-stirred 2-allylcycloheptanone (1.52g, 10 mmol), surrounded by an ice bath. The reaction mixture became brownish (much darker in the case of 90% H₂SO₄) and stirring was continued for 20-30 min, when there was no more starting material (9; TLC). After adding some ice chips, the reaction mixture was taken up in ethyl acetate (60 ml) and washed successively with brine, dilute NaOH and brine. Drying and evaporation gave a slightly yellow liquid (1.6 - 1.7 g), having strong absorption for OH and a weak band for enol ether 11 (~1700 cm⁻¹). Shortpath distillation (110-120°/2-3 torr) furnished a colorless liquid (1.0 - 1.2g), showing absence of OH and a medium intensity absorption for enol ether 11 (1698 cm⁻¹). However, TLC and the methyl and methine region in ¹HNMR (δ :1.1, a minor doublet, 1.3, a major doublet; 4.0 - 5.0, broad multiplet) revealed it to be slightly contaminated enol ether 11. This product was ozonized as described below.

c-II) Ozonolysis of enol ether 11: The above product (760 mg, 5 mmol) dissolved in dichloromethane (50 ml), containing acetic acid (1 ml), was ozonized and worked up according to the established procedure¹⁸, obtaining a yellowish, viscous liquid (740 mg), which on crystallization from ethanol/petroleum ether gave a solid (140 mg). Distillation of mother liquor, followed by crystallization from the above solvent mixture gave a further crop (120 mg), m.p. 72-75°. Total yield = 260 mg (~28%).

Deoxygenation of ketolactone 13 to 9-decanolide (6): Ethanedithiol (0.2 ml, 225 mg, 2.4 mmol) was added to ketolactone 13 (368 mg, 2 mmol) and the resulting solution treated with freshly-distilled boron trifluoride etherate (0.33 ml, 375 mg, 2.64 mmol), which caused an exothermic reaction and yellow coloration. After stirring at room temperature for 16-18h, the low-boiling components were removed under reduced pressure. The residue, dissolved in ether (30 ml), was washed with brine, saturated solution of Na₂CO₃ and brine. Drying and evaporation gave a colorless liquid (520 mg), which was chromatographed over silica gel (20 g), eluted with cyclohexane/ethyl acetate (0-10%). The purified thioketal (441 mg) was refluxed for 20-24h, under strong stirring, in a methanolic suspension of Ra-Ni (20 ml; ~ 12 g)¹⁵. Solids were filtered and washed with a little methanol. After evaporation of solvent, the residue was taken up in ether (20 ml) and washed with brine, saturated NaHCO₃ solution and brine. Drying and evaporation gave a pale-yellow liquid (220 mg), having strong smell of phoracantholide. Chromatographic purification (SiO₂, 10 h; cyclohexane/EtOAc, 0-10%) furnished a pure sample of (±) - phoracantholide I (169 mg; 50% yield), identical in all respects (TLC, IR NMR) with our earlier sample^{3h}.

Purified thioketal can be crystallised to obtain a colorless solid; m.p. 32-34°; IR (neat): ν = 1738, 1270, 1262, 1244, 1162, 1085, 1067 cm⁻¹.

¹HNMR (CDCl₃): δ = 1.37 (d, J 6Hz, CH₃), 1.4-2.6(m, 12H), 3.27 (~s, SCH₂CH₂), 4.95 (m, CH).

Ring expansion of hemi-ketal **10** to decenolides **16**: 2-Allylcycloheptanone (**9**; 1.52 g, 10 mmol) was hydrated with 80% H₂SO₄ as described above (c-I) and resulting crude product was converted into hydroperoxide **15** and subsequently subjected to ring expansion, exactly in the manner described earlier for hemi-ketal **2**, obtaining a yellowish liquid (1.4 g). Similarly, another batch starting with 456 mg (3 mmol) of **9** furnished further amount (400 mg) of crude decenolides **16**. Both lots were combined (1.8 g) and chromatographed over silica gel (15 g). Elution with-hexane gave decenolides **16** (1.059 g; 48.5%), a colorless liquid, homogeneous on TLC; IR (neat) 1732 cm⁻¹; ¹HNMR (CCl₄): δ = 1.23 (d, J 6HZ, CH₃), 1.6-2.5 (m, 5 CH₂), 4.9-5.6 (m, methine and olefinic 3 CH). Further elution with n-hexane/EtOAc (10-20%) furnished a yellow liquid (566 mg; 26%), which was mainly (~80%) the desired decenolides, contaminated with some polar impurities.

Catalytic reduction of the purified decenolides **16** (712 mg) with Ra-Ni, according to the procedure described above for decenolides **8**, gave a slightly yellow liquid (656 mg), which on short-path distillation (110-120°/9-10 torr) furnished pure phoracantholide I (525 mg; 73%), identical in all respects with our earlier samples.

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