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REVERSIBLE DIMETHYLAMINE ADDITION AS A PROTECTING REACTION FOR α,β-UNSATURATED METHYLENE GROUPS OF γ-LACTONES AND ITS REGENERATION BY BASIC ELIMINATION OF QUATERNARY AMMONIUM SALTS

A CONVENIENT SYNTHESIS OF DEHYDROSAUSSUREA LACTONE[a,b]

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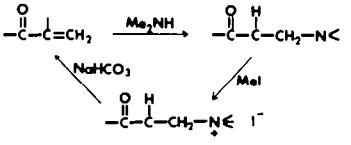
Abstract—The blocking and deblocking sequence pertaining to the α,β-unsaturated methylene γ-lactone unit of costunolide is described. Utilizing this approach a simple and practical synthesis of dehydrosaussurea lactone is reported.

In 1951 Rao and Varma[2] isolated saussurea lactone in an unspecified yield from the essential oil of costus roots, *Saussurea lappa* Clarke, to which structure **1** was assigned by Bhattacharyya *et al.*[3] on the basis of pyrolytic conversion of dihydrocostunolide **2** to a compound identical with saussurea lactone.† However, these authors suggested it to be an artefact arising from **2** probably during distillation of the essential oil which contains a trace amount of dihydrocostunolide.[4] In light of the above proposal it was intriguing to note that there was no parallel report of dehydrosaussurea lactone **3** correspondingly formed from costunolide **4** which constitutes about 15% of the essential oil;‡ thus studies were initiated to examine the lactonic constituents of costus root oil in greater detail.§ Besides being a reference compound in the projected program, a substantial quantity of dehydrosaussurea lactone **3** was needed in connection with our carbocyclization studies.[5] This necessitated the development of a practical synthesis of dehydrosaussurea lactone **3**.[1]

The direct thermolytic conversion of costunolide **4** to dehydrosaussurea lactone **3** studied in this laboratory[1] was not a practical proposition as the overall yields were low due to thermal instability of **3** and **4**. This has been ascribed to the presence of the α,β-unsaturated methylene γ-lactone unit and it was successfully overcome by blocking the α,β-unsaturated methylene group of the γ-lactone moiety with dimethylamine and its subsequent regeneration by mild base treatment of the quaternary ammonium salt; the blocking sequence is depicted in Scheme 1.



Scheme 1.

Addition of dimethylamine to a cold methanolic solution of costunolide **4** yielded the more stable amine adduct **5**[7] which was thermolyzed at 205–210° under an atmosphere of nitrogen for 3–10 min.¶ Guided by the various appropriate signals in the NMR spectrum of the crude thermolysate it was tentatively deduced that it consisted of four compounds:dehydrosaussurea lactone **3** and costunolide **4**, formed through thermal elimination of $-NMe_2$ group from the adducts themselves, i.e. costunolide amine **5** and dehydrosaussurea lactone amine **6**.

Chromatographic purification of these compounds on silica gel column led to extensive secondary reactions (Experimental). The noteworthy observation in this context was the isolation of an extremely polar compound

[a] For a preliminary communication on this work see Ref. 1.

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†To the best of our knowledge, the original specimen of saussurea lactone isolated by Rao and Varma has never been compared with the thermolytic product **1** of dihydrocostunolide **2**. Instead, the specimen with similar physical constants from the personal collection of Sadgopal was utilized in this study.[3] Through the courtesy of Professor Dutta we were able to obtain a small sample of the original saussurea lactone[2] and it has now been found identical (IR and NMR spectra) with **1**, the Cope product of dihydrocostunolide **2**.

‡Despite the thermal instability of **4**, we have been able to demonstrate its partial survival by isolating **4** along with **3** from our thermolytic experiments (Experimental).

§Unpublished results secured by John W. Andrews.

[1]Briefly reported by T.C.J. in connection with another paper presented at the 7th International Symposium on the Chemistry of Natural Products held in Riga, Latvia, U.S.S.R.[6]

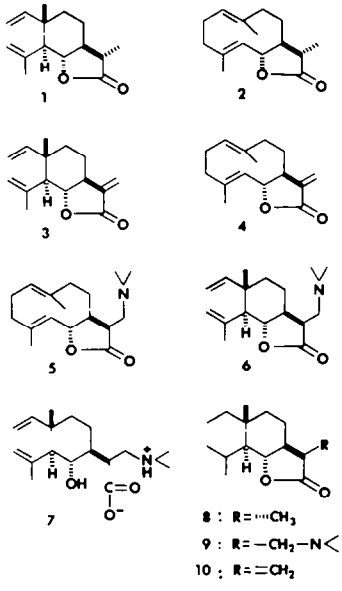
¶This was the optimum time interval for the Cope rearrangement of the adduct **5**; prolonged thermolysis led to the elimination of tertiary nitrogen yielding costunolide **4** in 0·7% yield. In fact, one could follow the course of reaction by the disappearance of $-NMe_2$ signal in the NMR spectrum of the crude thermolytic product.

$C_{17}H_{29}NO_3$ with m.p. of 170–174° which constituted about 60% of the secondary reaction product. Its IR and NMR spectra were completely devoid of γ-lactone and $-NMe_2$ units. However, bands at 3327 cm^{-1} (OH) and 1601 cm^{-1} (carboxylate ion) and a 6-proton singlet at τ 7·33 due to two methyls on a quaternary nitrogen plus the solubility of the compound in water implied that the polar material was an amino acid existing as a zwitter ion **7**. Final proof was garnered by its conversion to the adduct **6** by simple stirring in glacial acetic acid.

In order to avoid the formation of undesirable products experienced with silica gel chromatography, the product was successfully chromatographed on basic alumina column which yielded dehydrosaussurea lactone amine adduct† **6**,[8] m.p. 120–122°, whose NMR spectrum gave the 6-proton singlet at τ 7·77 ($-NMe_2$) and a one-proton quartet of lines centered at τ 4·16 representing the X part of an ABX system in a $-CH=CH_2$ unit.[9]

The methiodide salt of **6** was used to synthesize dehydrosaussurea lactone **3**. Rather than utilize the conventional Hofmann pyrolytic elimination procedure leading to extensive polymerization of the heat sensitive product, a method developed by van Tamelen[10] was employed to achieve this goal. This route took advantage of the lability of the hydrogen alpha to the lactonic carbonyl which could be easily abstracted by a mild base. The methiode salt dissolved in water was treated at room temperature with 5% $NaHCO_3$ aq to yield dehydrosaussurea lactone **3**, m.p. 84–85°, in almost quantitative yield. The synthetic specimen of dehydrosaussurea lactone **3**, $C_{15}H_{20}O_2$, exhibited as expected, an absorption maximum in its UV spectrum at 211·5 nm (*cf* UV) max of costunolide 214·5 nm). The IR spectrum displayed absorptions at 1765, 1635 and 890 cm^{-1} which were in agreement with an α,β-unsaturated methylene γ-lactone. Finally, the NMR spectrum of dehydrosaussurea lactone was compatible with the structure portrayed in **3**. The diagnostic low field doublets were found at τ 3·89 *and* 4·56 (J = 3·0 Hz, $\diagdown$C=CH$_2$ next to $\diagup$C=O). A quartet of lines appearing at τ 4·13 represented the olefinic proton at C-1. the remaining vinylic hydrogens resonated as a complex multiplet at τ 5·08. The lone C-6 hydrogen alpha to the etherial oxygen of the γ-lactone appeared as a quartet at τ 5·87. A broadened doublet (J = 1·0 Hz) at τ 8·20 and a sharp singlet at τ 8·93 represented the C-4 and C-10 methyls respectively. The proof of the stereostructure of dehydrosaussurea lactone implicit in **3** was adduced by its conversion to hexahydrodehydrosaussurea lactone **8**, m.p. 122–124°, (lit. m.p. 123–125°[3]), identical with an authentic specimen (IR, NMR and m.m.p.).

Comparison of elimination procedures. Having accomplished the synthesis of dehydrosaussurea lactone **3** by basis treatment of the methiodide salt, we compared this method with that of the conventional Hofmann procedure described in a recent communication[8] wherein no yields were reported. Comparison of efficiency and ease of preparation of the two methods was effected by preparing tetrahydrodehydrosaussurea lactone **10** from the parent amine adduct **9**. The quaternary ammonium salt of **9** prepared with methyl iodide was pyrolyzed at 140°/20 mm for 4 hr yielding the lactone **10** in 68% yield whereas treatment with 5% $NaHCO_3$ aq at room temperature gave the lactone **10** in 90% yield. Furthermore, the former method presented a great deal of difficulty in purification of the product whereas the latter only required one crystallization to furnish sharp melting crystals, m.p. 80–81·5°. This comparative study thus proves that the regeneration of an α,β-unsaturated methylene γ-lactone from its quaternary ammonium salt by simple base treatment at room temperature is undoubtedly superior to the conventional Hofmann pyrolytic procedure. Kupchan *et al.*[11] have recently reported a blocking sequence involving the use of 1-propanethiol as a blocking agent for conjugated α-methylene γ-lactones. Finally, Grieco and Miyashita have recently employed selenium[12] and sulfur[13] reagents to effectively block and deblock α-methylene-γ-butyrolactones.



EXPERIMENTAL

General. M.ps were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer Model 337 grating spectrophotometer calibrated with polystyrene film at 1601·4 cm^{-1} and 1028·0 cm^{-1}; model 700 was used for routine scans. UV spectra were obtained in abs EtOH with Unicam models S.P. 700 and S.P. 800 spectrophotometers. Mass spectra were measured with Hitachi-Perkin-Elmer R.M.U.-6E mass spectrometer at 70 eV. Specific rotations were determined in chloroform with a Perkin-Elmer Model 141 Polarimeter. NMR spectra were obtained in $CDCl_3$ with a Varian Associates HA-60 spectrometer, the chemical shift data are given in ppm (τ) from TMS. The removal of solvent under reduced pressure was accomplished with a Buchi flash evaporator at ~ 40°/25 mm of Hg. Microanalyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Demark and by Schwarzkopf Microanalytical Laboratory, New York.

Preparation of costunolide dimethylamine adduct **5**. Costunolide **4** (10 g) dissolved in MeOH (200 ml) containing an excess of dimethylamine was left for 90 hr at − 20°. The solvent was removed *in vacuo* and the crude product was crystallised from MeOH to yield needles of adduct **5**, m.p. 109–110°, $[\alpha]_D^{25}$ + 122·3° (*c*, 0·65). IR: 2840, 2820 and 2785 cm^{-1} (C-H stretch in $-NMe_2$). 1672 cm^{-1} (−C=CH), 1755 cm^{-1} (γ-lactone); Mass spectrum *m/e* (%Σ_{27}): 277 (1·50, molecular ion), 58 (46·60, base peak); NMR τ 5·03–5·44 (m, 3H, vinylic and C-6 protons), 7·74 (s, 6H, $-NMe_2$), 8·30 (singlet with finer splitting, 3H, Me on sp^2 carbon), 8·58 (d, J = 1·5 Hz, 3H, Me on sp^2 carbon). (Found: C, 73·12; H, 9·72. Calcd. for $C_{17}H_{27}O_2N$: C, 73·60; H, 9·81%).

The over-all yield of the crystallized adduct was approximately 60%.

†This name is referred to in Ref. 8 without preparing the parent lactone **3**. Furthermore, neither the physical constants nor the yields for this and related compounds are reported therein.

Thermolysis of adduct **5**

(a) *Six hours.* The adduct **5** (350 mg) in a 5 ml semi-micro flask fitted with a condenser was heated in a nitre bath at 230°under N_2 for 6 hr. The product consisted mainly of a hardened black crust which for the most part resisted dissolution into chloroform. The soluble portion was filtered through a silica gel column, and the product was assayed by IR and NMR spectra which indicated the complete absence of $-NMe_2$ unit in the thermolysate. When the thermolysis was conducted for 2, 1·5 and 1 hr similar results were obtained.

(b) *Five minutes.* The thermolysis of the adduct **5** (5 g) was carried out for 5 min at 205–210° under N_2 and the product was chromatographed over a 30-fold silica gel column. Forty-six fractions (1–43, each of 80 ml; 44–46, each of 200 ml) were collected, examined spectroscopically and combined together as shown in Table 1.

Table 1

Fraction	Solvent	Volume	Weight	ν_{max}
1–8	Benzene	640 ml	trace	-
9–11	Benzene	240 ml	14 mg	1634 cm^{-1}
12–18	Benzene	560 ml	87 mg	1666, 1634 cm^{-1}
19–23	10% $CHCl_3$/ Benzene	400 ml	86 mg	2785 cm^{-1}
24–30	$CHCl_3$/Benzene (1:1)	560 ml	261 mg	2785 cm^{-1}
31–38	$CHCl_3$	640 ml	1.24 g	2785 cm^{-1}
39–43	$CHCl_3$	400 ml	trace	-
44–46	MeOH	600 ml	3.13 g	1601 cm^{-1}

Fr. 9–11 gave dehydrosaussurea lactone **3** (*vide infra*); Fr. 12–18 consisted of mixture of **3** and **4**; Fr. 19–23 contained mixtures of **4** and **5**; Fr. 24–38 were composed of adduct **5**.

Conversion of **5** *to costunolide* **4** *by silica gel.* The adduct **5** (50 mg) dissolved in spectrograde chloroform (10 ml) was stired for 48 hr in the presence of silica gel (1·5 g). A further amount of silica gel (1·5 g) was added and stirring continued for another 12 hr. The extent of elimination was established by withdrawing a small sample every 2 hr for spectral check. After filtration and evaporation the compound was crystallised from MeOH to yield needles of **4**, m.p. 106–108°, undepressed upon admixture with natural costunolide. (Found: C, 77·43; H, 8·73. Calcd. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68%).

Polar material **7**. Fr. 44–46 (Table 1) were crystallized from acetone yielding water soluble crystals of **7**, m.p. 170–174° $[\alpha]_D^{27}$ – 51·4° (*c*, 1·19). IR 3327 cm^{-1} (–OH), 1601 cm^{-1} (carboxylate CO) 1640 and 885 cm^{-1} (terminal methylene); NMR τ 3·98–4·45 (m, 1 H, HC=CH_2), 5·02 – 5·29 (m, 4 H, HC=CH_2, –C=CH_2), 7·33 [s, 6 H, HN$(CH_3)_2$], 8·22 (s, 3 H, H_2C=C–CH_3), 9·00 (s, 3H, –C–CH_3); Mass spectrum: *m/e* 295 (molecular ion for $C_{17}H_{29}O_3N$). An accurate analysis could not be obtained due to its hydroscopic nature; however, subsequent conversion to **6** established its formula (*vide infra*).

Preparation of dehydrosaussurea lactone amine adduct **6** *from the polar material* **7**. The acid **7** (100 mg) was dissolved in glacial AcOH (5 ml) and stirred magnetically for 24 hr. Removal of solvent *in vacuo* followed by crystallization from MeOH yielded **6**, m.p. 120–122° (undepressed upon admixture with an authentic sample).

Dehydrosaussurea lactone amine adduct **6** *from* **5**. Adduct **5** (500 mg) was heated for 5 min under N_2 at 205–210°. The product was chromatographed over a 30-fold basic alumina column (grade IV). There were 17 fractions collected and each fraction of 30 ml was concentrated, examined by spectral data and combined together as shown in Table 2.

Fraction 1 gave **6**; Fr. 2–7 were mixtures of **5** and **6**; Fr. 8–11 gave **5**; Fr. 17 was composed of acid **7**. Fraction 1 (Table 2) crystallized from MeOH yielding plates of **6** (67% yield based upon NMR analysis of crude product as well as upon pure fractions isolated from the column), m.p. 120–122°, $[\alpha]_D^{32}$ + 82·9° (*c*, 1·21). IR: 2835, 2816 and 2778 cm^{-1} (C–H stretch of $-NMe_2$), 1772 cm^{-1} (γ-lactone), 1644, 1635 and 888 cm^{-1} (methylene);

Table 2

Fraction	Solvent	Volume	Weight	ν_{max}
1	Pet. ether	30 ml	146 mg	1635 cm^{-1}
2–7	Pet. ether	180 ml	120 mg	1672, 1635 cm^{-1}
8–11	Pet. ether	120 ml	67 mg	1672 cm^{-1}
12–13	Pet. ether/ Benzene (1:1)	60 ml	trace	-
14–15	Benzene	60 ml	trace	-
16	$CHCl_3$	30 ml	trace	-
17	MeOH	30 ml	63 mg	1601 cm^{-1}

NMR: τ 3·91–4·37 (q, 1 H, X part of an ABX system in –CH=CH_2 unit), 5·10 (m, 4 H, HC=CH_2, –C=CH_2), 5·84 (m, broad, 1 H, HC–O–C=O), 7·77 (s, 6 H, $-NMe_2$), 8·20 (d, J = 1·5 Hz, 3 H, H_2C=C–CH_3), 8·92 (s, 3 H, –C–CH_3). (Found: C, 74·08; H, 10·04. Calcd. for $C_{17}H_{27}O_2N$: C, 73·60; H, 9·81%).

Preparation of dehydrosaussurea lactone **3**. Adduct **6** (30 mg) dissolved in ether (5 ml) together with an excess of freshly distilled MeI was allowed to stand at room temp. for 1 hr. The precipitated methiodide salt was dissolved in water to which 5% $NaHCO_3$ aq was added and the soln was stirred for 1 hr. The basic aqueous layer was extracted with ether (3 × 10 ml); the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to yield **3** (25 mg), crystallised from pet. ether to yield plates, m.p. 84–85° $[\alpha]_D^{25}$ + 65·7° (*c*, 1·12). UV: λ_{max} 211·5 nm (ε 8630). IR: 1765 cm^{-1} (γ-lactone), 1635 and 890 cm^{-1} (terminal methylene), 1675, 972 and 907 cm^{-1} (vinyl grouping); Mass spectrum: *m/e* 232 (% Σ_{27} = 0·10; molecular ion); NMR τ 3·89, 4·56 (d, J = 3·0 Hz, 1 H each, $\diagdown$C=CH_2 next to $\diagdown$C=O), 3·91–4·38 (q, 1 H, HC=CH_2), 5·08 (m, 4 H, HC=CH_2, –C=CH_2), 5·87 (q, 1 H, C-6 proton), 8·20 (d, J = 1·0 Hz, 3 H, H_2C=C–CH_3), 8·93 (s, 3 H, tertiary Me). The IR and NMR spectra were identical with the specimen obtained earlier (Table 1) and the mixed m.p. was undepressed. (Found: C, 77·58; H, 8·72. Calcd. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68%).

Hexahydrodehydrosaussurea lactone **8**. Lactone **3** (47 mg) dissolved in AcOH (5 ml) was hydrogenated (12 hr) in the presence of PtO_2 (6 mg). The soln was filtered and the AcOH was distilled off under reduced pressure. Crystallization of the residual liquid from EtOH afforded plates of **8**, m.p. 122–124° (undepressed upon admixture with authentic sample), $[\alpha]_D^{25}$ + 39·4° (*c*, 1·02). IR spectrum superimposable with that of the authentic specimen. NMR: τ 6·02 (m, broad, HC–O–C=O), 8·75–9·17 (m, 15 H, five C-methyls of the molecule). (Found: C, 75·65; H, 10·92. Calcd. for $C_{15}H_{26}O_2$: C, 75·58; H, 11·00%).

Tetrahydrodehydrosaussurea lactone amine adduct **9**. Adduct **6** (221 mg) dissolved in AcOH (10 ml) was stirred in an atmosphere of H_2 over PtO_2 (40 mg) for 96 hr. The catalyst was filtered and the solvent removed *in vacuo*. Crystallization of the residual mass from pet. ether afforded cubes of **9**, m.p. 62·64°, $[\alpha]_D^{25}$ + 65·8° (*c*, 1·15). IR: 2873, 2826 and 2773 cm^{-1} (C–H stretch in $-NMe_2$), 1777 cm^{-1} (γ-lactone). NMR: τ 6·01 (m, broad, 1 H, HC–O–C=O), 7·77 (s, 6 H, $N-Me_2$), 8·89–9·17 (m, 12 H, four C-methyls in the molecule). (Found: C, 72·34; H, 11·10. Calcd. for $C_{17}H_{31}O_2N$: C, 72·55; H, 11·10%).

Tetrahydrodehydrosaussurea lactone **10**. To an ether soln (25 ml) of **9** (100 mg) an excess of freshly distilled MeI was added. The precipitated salt was filtered and dried, m.p. 210–215°. This material was subsequently used without further crystallization for the following experiments:

(a) The salt (50 mg) dissolved in water was treated with 5% $NaHCO_3$ aq at room temp. for 1 hr. The soln was extracted with ether (3 × 10 ml) and the ether was dried over Na_2SO_4 and evaporated to yield crude **10** which on crystallization from pet. ether gave plates (25·5 mg, 90% yield), m.p. 80–81·5°, $[\alpha]_D^{25}$ + 58·6° (*c*, 0·95). UV: λ_{max} 213 nm (ε 6300); IR: 1761 and 1672 cm^{-1} (γ-lactone and exocyclic methylene respy); NMR: τ 3·95, 4·63 (d, J = 3·0 Hz, 2 H, –C=CH_2), 6·04 (m, 1 H, HC–O–C=O), 8·85–9·15 (m, 12 H, four C-methyls). (Found: C, 76·12; H, 10·13. Calcd. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%).

(b) The methiodide salt (55 mg) was pyrolyzed at 140°/20 mm in

an atmosphere of N_2 for 4 hr and then sublimed to give the product (22 mg, 68% yield), crystallized three times from pet. ether to give **10**, m.p. 80–81°, $[\alpha]_D^{25}$ + 59·3 (*c*, 0·60). Its spectra were identical with those of the specimen obtained under (a) above.

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