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Total Synthesis of (±)-9-Pupukeanone

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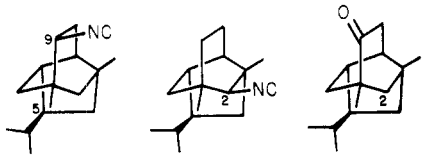
A synthesis of (±)-9-pupukeanone (**3**) is described in which the pupukeanane skeleton is assembled by means of an intramolecular Diels–Alder reaction of **20** to **21**. The vinyl ketone **20** was constructed via a sequence beginning from **8** and proceeding through diene ester **14**. Cycloadduct **21** was converted to **3** via **29** and **31**.

The nudibranch *Phyllidia varicosa* (Lamarck, 1801) secretes from its skin glands a strong smelling mucus which is lethal to predatory fish and crustaceans.[1] An investigation by Scheuer et al. of the toxic principle from this mollusk and subsequently from a sponge (*Hymeniacidon sp.*) on which the nudibranch was observed to feed led to its characterization as 9-isocyanopupukeanane (**1**).[2] An

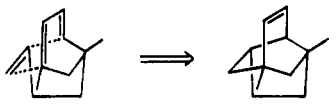


1 **2** **3**

isomeric substance, 2-isocyanopupukeanane (**2**), which can be separated only with difficulty from **1**, has also been isolated from *Phyllidia*.[3] In the course of the structural elucidation of **1**, the isocyano function was degraded to a ketone, yielding 9-pupukeanone (**3**). This substance could be obtained in pure form and was fully characterized.

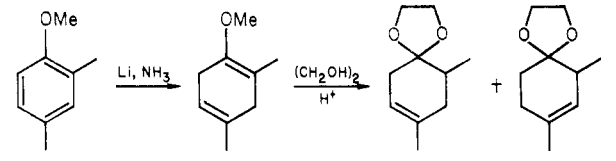
Recently, independent total syntheses of **1** by Corey[4] and Yamamoto[5] have been achieved. Both pathways proceed via **3**, the ketone function of which can be transformed to the 9-isocyano group in a highly stereoselective fashion. Since 9-pupukeanone (**3**) provides an obligatory stage at which to correlate synthetic and naturally derived materials en route to the isocyanide, our synthetic efforts were also directed toward this key substance. We now describe a synthesis of **3**, in which the focus—articulation of the pupukeanane framework—is accomplished by means of an intramolecular Diels–Alder reaction.[6]

Conceptually, an attractive formulation of the cycloaddition route to the pupukeanane skeleton is that represented in eq 1, since it readily permits the strategic



(1)

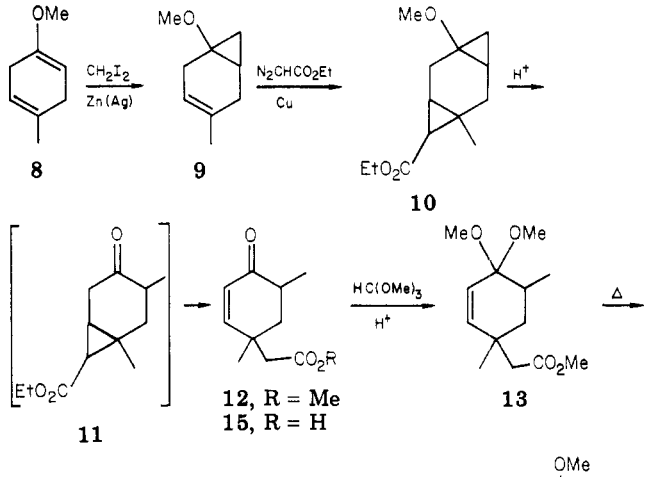
placement of functional groups for subsequent elaboration to **3**.[7] Implementation of this plan first required the preparation of a suitable cyclohexadiene. After this, our aim was to attach a dienophilic butenyl chain which would be induced to undergo the desired intramolecular cycloaddition. Our intention at the outset was to incorporate both the C-1 and C-3 methyl substituents of pupukeanone into the cyclohexadiene moiety, and a starting material which appeared particularly well-suited to this purpose was 2,4-dimethylanisole (**4**). Birch reduction of **4** afforded a



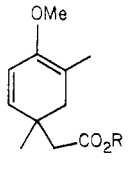
4 **5** **6** **7**

single diene **5** in 69% yield, which was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid. Unfortunately, conversion of the enol ether function of **5** to an ethylene ketal was accompanied by isomerization of the trisubstituted double bond, so that an approximately 1:1 mixture of two olefins, **6** and **7**, resulted from this process. Since the separation of these isomers, as well as subsequent products derived from them, proved difficult and particularly since no means could be found for ketalization of **5** which avoided olefin isomerization, an alternative plan was adopted which introduced the two methyl groups in sequential fashion.

For this purpose, the diene **8**, prepared by Birch re-



8 **9** **10** **11** **12**, R = Me; **15**, R = H **13**



14, R = Me; **16**, R = Li

duction of *p*-cresyl methyl ether,[8] was employed. The

(1) R. E. Johannes, *Veliger*, **5**, 104 (1963).
(2) B. J. Burreson, P. J. Scheuer, J. Finer, and J. Clardy, *J. Am. Chem. Soc.*, **97**, 4763 (1975).
(3) Private communication from Professor P. J. Scheuer. For a synthesis of **2**, see E. J. Corey and M. Ishiguro, *Tetrahedron Lett.*, 2745 (1979).
(4) E. J. Corey, M. Behforouz, and M. Ishiguro, *J. Am. Chem. Soc.*, **101**, 1608 (1979).
(5) H. Yamamoto and H. L. Sham, *J. Am. Chem. Soc.*, **101**, 1609 (1979).
(6) For a review of intramolecular cycloaddition, see W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).
(7) After completion of this phase of our work, we became aware of a similar strategy adopted by Professor Hisashi Yamamoto in his synthesis of **1**; we are grateful to Professor Yamamoto for communicating his results prior to publication.
(8) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968).

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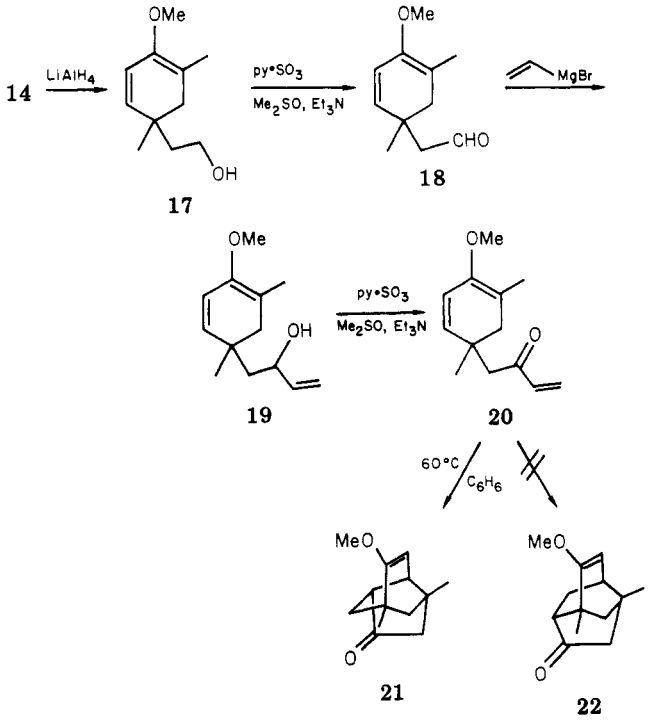
anticipated, regioselective cyclopropanation of the enol ether double bond of **8** was accomplished with the modification of the Simmons–Smith reaction developed by Conia[9] and furnished the bicyclic ether **9** in 64% yield. The residual olefinic link in **9** was then cyclopropanated with ethyl diazoacetate in the presence of copper–bronze.[10] This afforded the tricyclic ester **10** as a mixture of cis–trans and endo–exo isomers in 57% yield.

The functionality of **10** is deployed so that an acid-catalyzed, double fragmentation of the cyclopropane moieties can lead only to the desired enone ester **12** and, in the event, treatment of **10** with aqueous methanolic hydrogen chloride was found to produce **12** in 93% yield. The conversion of **10** to **12** can be readily understood in terms of an initial protonation of the more electrophilic of the two cyclopropanes which liberates an α-methyl ketone, **11**,[11] upon hydrolysis. Rupture of the carboethoxy-substituted cyclopropane is now assisted by the newly generated ketone which activates the adjacent methylene group and thereby promotes eliminative fragmentation to **12**.[12] The NMR spectrum of **12** revealed that, not unexpectedly, transesterification to a methyl ester had occurred under the conditions of this fragmentation. It was also apparent that **12** was a mixture of cis and trans isomers. However, since configuration α to the ketone was to be removed at the next step, no attempt was made to separate these stereoisomers. The conversion of **12** to diene **14** was carried out in a straightforward fashion by treatment of the enone with trimethyl orthoformate. Slow distillation of the resulting ketal **13** caused elimination of methanol to yield **14** in 79% yield.

With the requisite diene secured, we now turned to elaboration of its acetate appendage. The initial goal here was a direct chain extension of the ester to a vinyl ketone to provide the dienophilic unit. It soon became clear, however, that the dienol ether moiety of **14** was extremely susceptible to acidic hydrolysis due, probably, to the juxtaposition and enforced coplanarity of the methoxy and methyl substituents. Thus, it proved impossible to obtain the carboxylic acid corresponding to **14** from saponification and acidification, the principal product being the enone **15**. Saponification of **14** with lithium hydroxide afforded the lithio salt **16** which was stable in neutral media and could be characterized. Unfortunately, attempts to convert this lithium carboxylate to the desired vinyl ketone **20** by treatment with vinyllithium under a wide variety of conditions were unsuccessful.[13] It was therefore necessary to adopt a more conventional but less direct route to this ketone.

Reduction of **14** with lithium aluminum hydride yielded alcohol **17** cleanly and in good yield. The sensitive enol ether function of this material again proved troublesome, and oxidations of **17** with chromium(VI) reagents as well as several variants of the Moffatt oxidation afforded no useful products. The aldehyde **18** was eventually acquired in good yield by treatment of **17** with the sulfur trioxide–pyridine complex in dimethyl sulfoxide and triethylamine[14] and proved to be sufficiently stable for chromatographic purification on alumina. In practice, however, it was more convenient to directly transform crude **18** to carbinol **19** by reaction with vinylmagnesium bromide. The diastereomeric mixture of alcohols **19** was immediately oxidized,



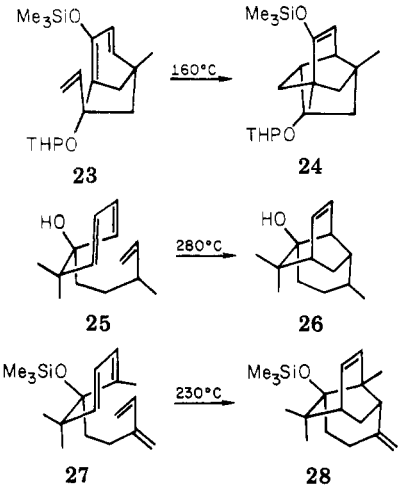
again employing the sulfur trioxide–pyridine complex in dimethyl sulfoxide–triethylamine, to the desired vinyl ketone **20**. This substance exhibited an ABX pattern of proton resonances in the δ 5.1–6.2 region of its NMR spectrum, characteristic of a vinyl ketone, as well as two vinyl proton resonances (δ 5.62 and 5.83) and a methyl group (δ 1.73) associated with the cyclohexadiene moiety. In addition, the carbonyl stretching frequency of **20** at 1685 cm^{-1} clearly defined it as an α,β-unsaturated ketone. These data provided crucial markers for assaying the Diels–Alder process which followed.

Although the contemplated transformation of **20** to the pupukeanane skeleton of **21** appeared to be feasible on both electronic and steric grounds, we were nevertheless delighted to find that this intramolecular cycloaddition occurred rapidly at 60 °C and yielded **21** in virtually quantitative yield. After rigorous purification by chromatography, **21** was obtained in 87% yield. Its structure was readily apparent from the NMR spectrum in which the vinyl proton signals described above had been replaced by a single resonance at δ 4.47, corresponding to the vinyl hydrogen of the enol ether; this proton was coupled to the adjacent bridgehead proton as expected. It was also apparent that both methyl substituents (δ 0.82 and 1.03) now resided on saturated carbons. These observations, together with other spectral data, left no doubt that the intramolecular Diels–Alder addition of **20** had occurred in the desired sense. In particular, the carbonyl frequency at 1740 cm^{-1}, which is consistent with the presence of a cyclopentanone, was clearly indicative of the framework **21** rather than the alternate twistanone **22**. The latter, by analogy with the parent ketone of this system,[15] would have been expected to show a carbonyl absorption at ca. 1718 cm^{-1}.

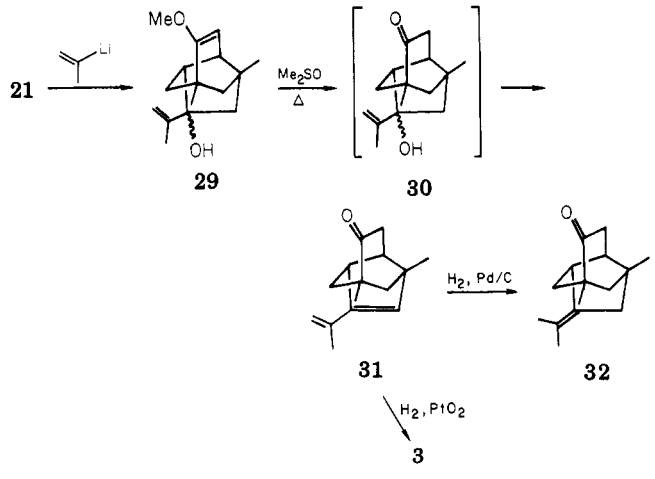
The remarkable facility with which the conversion of **20** to **21** occurs deserves a brief comment. While the substituents in the diene and dienophilic segments of **20** are arranged in a way which would give the *inter*molecular counterpart of this Diels–Alder reaction considerable impetus, it is not obvious that these substituent effects can

(9) J. M. Denis, G. Girard, and J. M. Conia, *Synthesis*, 549 (1972).
(10) V. Dane and E. W. Warnhoff, *Org. React.*, **18**, 217 (1970).
(11) E. Wenkert and D. A. Berges, *J. Am. Chem. Soc.*, **89**, 2507 (1967).
(12) R. D. Stipanovic and R. B. Turner, *J. Org. Chem.*, **33**, 3261 (1968).
(13) Cf. J. C. Floyd, *Tetrahedron Lett.*, 2877 (1974).
(14) J. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
(15) J. Gauthier and P. Deslongchamps, *Can. J. Chem.*, **45**, 297 (1967).

dominate an *intra*molecular process which requires major torsional displacements of the conjunctive entities. This is particularly true of the enone moiety, in which the carbonyl and olefinic π systems must be nearly orthogonal at the moment of cycloaddition. Yet, comparison of **20** → **21** with the intramolecular cycloaddition of **23** to **24**, carried out by Yamamoto,[5] indicates that the ketone function of **20** probably does play a role in lowering the activation energy of the addition. Moreover, when the conversion of **20** to **21** is viewed alongside related cycloadditions, **25** → **26**[16] and **27** → **28**,[17] it becomes clear that the decreased torsional strain which molecular models predict for the transition state in the latter systems does not translate into a lower activation energy. Thus, the substantial entropic advantage which must accrue through the intramolecularity of the cycloaddition **20** → **21** is apparently not significantly offset by torsional stresses.



The task of converting **21** to pupukeanone (**3**), while superficially straightforward, proved initially troublesome. Not surprisingly, the ketone function of **21** was too hindered for a Wittig reaction with isopropylidenetriphenylphosphorane; likewise, treatment of **21** with isopropyllithium and the corresponding Grignard reagent failed to give a carbonyl adduct. The problem of introduction of the C-5 isopropyl substituent was solved by the use of isopropenyllithium,[18] which furnished carbinol **29** as a single epimer after chromatography. Dehydration of **29** in dimethyl sulfoxide[19] unexpectedly led to demethylation of the enol ether moiety as well and provided dienone **31** in excellent yield. A more careful examination of this sequence revealed that demethylation of **29** *preceded* (at ca. 120 °C) the dehydration (150–160 °C) and that hydroxy ketone **30** could be isolated if desired. The cleavage of enol ethers in this fashion, presumably by nucleophilic attack of sulfoxide oxygen to yield an enolate, appears not to have been previously recognized.



The hydrogenation of **31** over palladium–charcoal disappointingly did not yield pupukeanone **3** but the product (**32**) of 1,4-addition of hydrogen. The tetrasubstituted double bond of **32** proved extremely resistant to further reduction. In contrast, hydrogenation of **31** with Adams' catalyst afforded **3** (admixed with **32**) which, after chromatographic purification, was shown to be identical, by comparison of infrared, NMR, and mass spectra, with a sample of 9-pupukeanone furnished by Professor Yamamoto. Since **3** has been previously converted to 9-isocyanopupukanane (**1**), this constitutes a formal total synthesis of the racemic toxin.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 727B spectrophotometer and ^{1}H nuclear magnetic resonance (NMR) spectra were measured on Varian EM-360A, HA-100, or FT-80A spectrometers. Peak positions are given in parts per million (δ) downfield from the internal standard Me_4Si. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. The coupling constant (J) is given in hertz. Mass spectra were determined on a Varian MAT CH-7 (low resolution) or CEC-103B (high resolution) spectrometer. The abbreviation M^+ signifies the molecular ion.

1-Methoxy-2,4-dimethylcyclohexa-1,4-diene (5). To 750 mL of liquid ammonia was added sequentially 130 mL of anhydrous *tert*-butyl alcohol, 130 mL of anhydrous tetrahydrofuran, and 40.7 g (0.3 mol) of 2,4-dimethylanisole. Lithium metal (4.2 g, 0.6 mol) was added and the solution was maintained at dry ice temperature until the blue color had discharged. An additional 4.2 g (0.6 mol) of lithium was introduced and the reaction was continued for a further 2 h. The mixture was quenched with ammonium chloride and the liquid ammonia was allowed to evaporate overnight at room temperature. The crude residue was diluted with water and extracted with ether. The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was distilled to afford 28.6 g (69%) of **5**: bp 33–35 °C (0.15 mm); ^{1}H NMR (CCl_4) δ 5.32 (1 H, m), 3.46 (3 H, s), 2.64 (4 H, m), 1.66 (3 H, s), 1.58 (3 H, s).

1,1-(Ethylenedioxy)-4,6-dimethylcyclohex-3-ene (6) and 1,1-(Ethylenedioxy)-2,4-dimethylcyclohex-3-ene (7). In a Dean–Stark apparatus, a mixture of 300 mg (2.2 mmol) of diene **5**, 1 mL of ethylene glycol, and a catalytic amount of *p*-toluenesulfonic acid in 20 mL of benzene was maintained at reflux for 3 h. The reaction mixture was made alkaline with sodium bicarbonate, extracted with ethyl ether, and washed with water and brine. The ethereal extracts were dried over magnesium sulfate, and the solvent was removed in vacuo to give 273 mg (84%) of a mixture of ketals **6** and **7**: ^{1}H NMR (CCl_4) δ 5.31 (1 H, m), 3.97 (3 H, s), 2.18 (4 H, m), 2.00 (1 H, m), 1.69 (3 H, s), 0.94 (3 H, d, J = 6 Hz); mass spectrum, m/e 168.114 (M^+; calcd for $C_{16}H_{10}O_2$ 168.115).

1-Methoxy-4-methylcyclohexa-1,4-diene (8). To 750 mL of liquid ammonia was added sequentially 150 mL of anhydrous *tert*-butyl alcohol, 150 mL of anhydrous tetrahydrofuran, and 48.8 g (51 mL, 0.4 mol) of *p*-cresol methyl ether. Lithium metal (11.5 g, 1.6 mol) was added during 40 min, and the solution was maintained at dry ice temperature for an additional 2.5 h. The excess lithium was quenched with ammonium chloride, and the ammonia was allowed to evaporate at room temperature overnight.

(16) F. Naf and G. Ohloff, *Helv. Chim. Acta*, **57**, 1868 (1974).
(17) W. Oppolzer and R. L. Snowden, *Tetrahedron Lett.*, 3505 (1978).
(18) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Am. Chem. Soc.*, **89**, 4133 (1967).
(19) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).

The crude residue was diluted with water and extracted with ethyl ether. The combined ethereal extracts were washed thoroughly with water and brine and dried over magnesium sulfate. Removal of the solvent in vacuo and distillation yielded 31.6 g (64%) of **8** as a colorless oil: bp 64–66 °C (10 mm) [lit.[20] bp 74 °C (17 mm)]; ^{1}H NMR (CCl_4) δ 5.28 (1 H, m), 4.46 (1 H, m), 3.46 (3 H, s), 2.63 (4 H, s), 1.67 (3 H, s).

1-Methoxy-4-methylbicyclo[4.1.0]hept-3-ene (9). To a solution of 100 mg of purified silver acetate in 50 mL of glacial acetic acid at 100 °C was added 8.5 g (13 mmol) of zinc dust. The mixture was stirred vigorously for 1 min and the acetic acid was removed by decantation. The residue was washed with anhydrous ether until all traces of acetic acid had been removed. The zinc–silver couple was suspended in 75 mL of anhydrous ether, and 17.4 g (65 mmol, 5.25 mL) of diiodomethane was added at such a rate as to maintain a moderate reflux. The suspension was stirred for 1 h, 6.2 g (50 mmol) of diene **8** was added, and the mixture was maintained at reflux for 2 h. An additional 8.5 g of zinc–silver couple and 5.25 mL of diiodomethane in 75 mL of ethyl ether was introduced, and the reaction was continued under reflux for 12 h. The mixture was worked up by slow dilution with a saturated aqueous sodium bicarbonate solution followed by extraction with ether. The combined ethereal extracts were washed with sodium bicarbonate and brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was distilled to give 4.4 g (64%) of **9**: bp 75–78 °C (10 mm); ^{1}H NMR (CCl_4) δ 5.16 (1 H, m), 3.19 (3 H, s), 2.49 (2 H, m), 2.31 (1 H, m), 2.09 and 1.92 (1 H, m), 1.57 (3 H, br s), 1.18 (1 H, m), 0.70 (1 H, dd, J = 5, 10 Hz), 0.31 (1 H, dd, J = 5, 6 Hz); mass spectrum, m/e 138.106 (M^+; calcd for $C_9H_{14}O$ 138.104).

4-(Carboethoxy)-1-methoxy-5-methyltricyclo[5.1.0.0^{3,5}]octane (10). A mixture of 9.59 g (69 mmol) of **9** and 250 mg of copper–bronze was heated to 140 °C under a nitrogen atmosphere. A solution (ca. 100 mL, 1 M) of ethyl diazoacetate in methylene chloride was added dropwise over 7.5 h, at which time thin-layer chromatography showed the absence of starting material. The crude reaction mixture was filtered through Celite, evaporated under reduced pressure, and distilled to give 8.86 g (57%) of **10**: bp 86–110 °C (0.25 mm); ^{1}H NMR (CCl_4) δ 4.04 (2 H, q, J = 7 Hz), 3.16 and 3.11 (3 H, s), 2.34–1.78 (3 H, m), 1.68–0.82 (4 H, m), 1.22 (3 H, t, J = 7 Hz), 1.07 and 1.04 (3 H, s), 0.57 (0.5 H, dd, J = 5, 10 Hz), 0.26 (0.5 H, dd, J = 5, 6 Hz), 0.05 (0.5 H, m); mass spectrum, m/e 224.143 (M^+; calcd for $C_{13}H_{20}O_3$ 224.141).

Methyl 1,5-Dimethyl-4-oxo-2-cyclohexenylacetate (12). In a 100-mL round-bottom flask, 8.86 g (39.6 mmol) of **10** was treated with 7% aqueous methanolic hydrochloric acid, and the mixture was maintained at reflux under a nitrogen atmosphere for 24 h. The mixture was concentrated by evaporation in vacuo, diluted with water, and extracted with ether. The organic extracts were washed with water and brine and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave 7.19 g (93%) of **12** as a mixture of two diastereomers: IR (film) 1735 and 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.72 and 6.60 (1 H, dd, J = 2, 10 Hz), 5.80 and 5.78 (1 H, d, J = 10 Hz), 3.64 (3 H, s), 2.42 (2 H, m), 2.33 (1 H, s), 1.71 (2 H, t, J = 13 Hz), 1.29 and 1.22 (3 H, s), 1.08 (3 H, d, J = 6 Hz); mass spectrum, m/e 196.112 (M^+; calcd for $C_{11}H_{16}O_3$ 196.110).

Methyl 1,5-Dimethyl-4-methoxy-2,4-cyclohexadienylacetate (14). To a solution of 4.2 g (21.4 mmol) of **12** in 30 mL of anhydrous methanol was added 3 mL of trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid. The mixture was maintained at reflux for 22 h, following which the methanol and excess trimethyl orthoformate were removed by distillation at atmospheric pressure. The bath temperature was then raised to 160–170 °C for 15 min, the reaction was allowed to cool, and the product was distilled under reduced pressure to give 3.54 g (79%) of **14** as a pale yellow oil: bp 78–82 °C (0.25 mm); IR (film) 1735 and 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.81 (1 H, d, J = 10 Hz), 5.56 (1 H, d, J = 10 Hz), 3.61 (3 H, s), 3.49 (3 H, s), 2.26 (2 H, s), 2.13 (2 H, m), 1.68 (3 H, s), 1.11 (3 H, s); mass spectrum, m/e 210.128 (M^+; calcd for $C_{12}H_{18}O_3$ 210.126).

Lithium 1,5-Dimethyl-4-methoxycyclohexa-2,4-dienylacetate (16). A solution of 2.1 g (10 mmol) of **14** and 420 mg (10 mmol) of lithium hydroxide monohydrate in 10% aqueous methanol was maintained at reflux for 7 h. The product was concentrated in vacuo and washed with anhydrous benzene. Drying the residue at 60 °C for 36 h at 0.01 mm gave 1.9 g (94%) of the lithium carboxylate **16** as a white amorphous solid: mp 98–102 °C; ^{1}H NMR (CD_3COCD_3) δ 5.90 (1 H, d, J = 10 Hz), 5.72 (1 H, d, J = 10 Hz), 3.47 (3 H, s), 2.25 (2 H, m), 2.06 (2 H, m), 1.65 (3 H, s), 1.11 (3 H, s).

2-(1,5-Dimethyl-4-methoxycyclohexa-2,4-dienyl)ethanol (17). To a solution of 840 mg (4.0 mmol) of **16** in 10 mL of anhydrous tetrahydrofuran cooled to −78 °C was added 91 mg (2.4 mmol) of lithium aluminum hydride. The reaction mixture was allowed to come to room temperature, and after 45 min it was quenched with water. The mixture was extracted from aqueous saturated sodium bicarbonate with ether, and the combined ethereal extracts were dried over magnesium sulfate. Removal of the solvent in vacuo gave 626 mg (86%) of **17**: ^{1}H NMR (CCl_4) δ 5.76 (1 H, d, J = 10 Hz), 5.45 (1 H, d, J = 10 Hz), 3.47 (3 H, s), 3.80–3.10 (3 H, m), 2.10 (2 H, m), 2.80 (2 H, m), 1.64 (3 H, s), 1.00 (3 H, s); mass spectrum, m/e 182 (M^+). This material was used without further purification.

1,5-Dimethyl-4-methoxycyclohexa-2,4-dienylacetaldehyde (18). To a solution of 450 mg (2.47 mmol) of **17** in 5 mL of anhydrous triethylamine and 5 mL of anhydrous dimethyl sulfoxide was added a solution of 1.90 g (11.9 mmol) of sulfur trioxide–pyridine complex (prepared according to Baumgarten[21]) in 7 mL of anhydrous dimethyl sulfoxide. The reaction mixture was stirred at room temperature for 2.25 h and then partitioned between water and ether. The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. The solvent was removed to give 323 mg (72%) of virtually pure **18**. Column chromatography on this material on alumina (benzene as eluant) gave a sample of pure **18**: IR (film) 1700 cm^{-1}; ^{1}H NMR (CCl_4) δ 9.63 (1 H, t, J = 3 Hz), 5.87 (1 H, d, J = 10 Hz), 5.58 (1 H, d, J = 10 Hz), 3.48 (3 H, s), 2.28 (2 H, m), 2.12 (2 H, m), 1.66 (3 H, br s), 1.14 (3 H, s); mass spectrum, m/e 180 (M^+).

(1,5-Dimethyl-4-methoxycyclohexa-2,4-dienyl)but-3-en-2-ol (19). To a 1 M solution of vinylmagnesium bromide in tetrahydrofuran (3 mL) cooled to 0 °C was added a solution of 323 mg (1.8 mmol) of **18** in 1 mL of anhydrous tetrahydrofuran. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 15 min. The mixture was extracted with ether after dilution with water, and the combined organic extracts were washed with brine and dried over magnesium sulfate. Removal of the solvent in vacuo followed by column chromatography of the residual oil on silica gel [benzene–ethyl acetate (9:1) as eluant] gave 312 mg (83%) of the unstable alcohol **19**: IR (film) 3425 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.04–5.48 (3 H, m), 5.14 (1 H, dd, J = 2, 17 Hz), 4.99 (1 H, dd, J = 2, 12 Hz), 4.26 (1 H, m), 3.48 (3 H, s), 2.14 (2 H, m), 1.56 (3 H, s), 1.06 (3 H, s); mass spectrum, m/e 208.

(1,5-Dimethyl-4-methoxycyclohexa-2,4-dienyl)but-3-en-2-one (20). To a solution of 10 mg (0.05 mmol) of **19** in 0.2 mL of anhydrous dimethyl sulfoxide and 0.2 mL of anhydrous triethylamine was added a solution of 70 mg (0.11 mmol) of sulfur trioxide–pyridine complex[21] in 0.3 mL of anhydrous dimethyl sulfoxide. After 1 h at room temperature, the reaction mixture was diluted with ether and partitioned against water. The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. Removal of the solvent in vacuo yielded 6.5 mg (66%) of **20**: ^{1}H NMR (C_6D_6) δ 6.13 (1 H, dd, J = 10, 17 Hz), 5.84 (1 H, dd, J = 3, 17 Hz), 5.83 (1 H, d, J = 10 Hz), 5.62 (1 H, d, J = 10 Hz), 5.21 (1 H, dd, J = 3, 10 Hz), 3.28 (3 H, s), 2.48 (1 H, d, J = 15 Hz), 2.20 (1 H, d, J = 15 Hz), 2.04 (2 H, m), 1.73 (3 H, br s), 1.08 (3 H, s); mass spectrum, m/e 206 (M^+).

1,3-Dimethyl-9-methoxy-5-oxotricyclo[4.3.1.0^{3,7}]dec-8-ene (21). A solution of 15 mg (0.72 mmol) of **20** in 0.3 mL of anhydrous benzene containing a trace of 2,6-di-*tert*-butyl-*p*-cresol was placed in a sealed tube and heated to 60 °C in an oil bath. The reaction was terminated after 1.5 h and the solvent was removed in vacuo. Column chromatography of the residual oil on alumina [benzene–hexane (7:3) as eluant] gave 13 mg (87%) of **21**: IR (film)

(20) A. J. Birch, *J. Chem. Soc.*, 596 (1946).

(21) P. Baumgarten, *Ber.*, **59**, 1166 (1926).

1740 and 1635 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.47 (1 H, d, J = 7 Hz), 3.18 (3 H, s), 2.29–1.40 (4 H, m), 1.34 (1 H, m), 1.20–0.94 (3 H, m), 1.03 (3 H, s), 0.82 (3 H, s); mass spectrum, m/e 206.131 (M^+; calcd for $C_{13}H_{18}O_2$ 206.130).

1,3-Dimethyl-5-isopropenyl-9-methoxytricyclo[4.3.1.0^{3,7}]-dec-8-en-5-ol (29). To a solution of isopropenyllithium[22] (1 mL, 1 M in ether) at 0 °C was added dropwise 18 mg (0.09 mmol) of **21**. The reaction mixture was maintained at 0 °C for 30 min and then was allowed to come to room temperature. After an additional 30 min, the reaction was quenched with water, and the mixture was partitioned between ether and water. The organic extract was dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was subjected to column chromatography on alumina (benzene as eluant) to give 15.3 mg (69%) of **29**: ^{1}H NMR (C_6D_6) δ 5.04 (1 H, br s), 4.95 (1 H, s), 4.79 (1 H, q, J = 2 Hz), 4.59 (1 H, d, J = 7 Hz), 3.28 (3 H, s), 2.47 (1 H, m), 2.14 (3 H, m), 1.78 (3 H, s), 1.86–0.92 (4 H, m), 1.26 (3 H, s), 0.89 (3 H, s); mass spectrum, m/e 248 (M^+).

1,3-Dimethyl-5-isopropenyltricyclo[4.3.1.0^{3,7}]dec-4-en-9-one (31). A solution of 52 mg (0.2 mmol) of **29** in 0.3 mL of dimethyl sulfoxide was heated in an oil bath at 150–160 °C. The course of the reaction was followed by NMR and after 11 h the reaction mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. Removal of the solvent in vacuo gave 43 mg (94%) of virtually pure **31**. A portion of the material which was subjected to column chromatography on alumina [benzene–hexane (9:1) as eluant] afforded a sample of **31**: IR (film) 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.80 (1 H, s), 4.94 (1 H, br d, J = 6 Hz), 2.78 (1 H, m), 2.48 (2 H, d, J = 3 Hz), 1.92 (3 H, s), 1.78–1.01 (4 H, m), 1.12 (3 H, s), and 0.88 (3 H, s); mass spectrum, m/e 216 (M^+).

1,3-Dimethyl-5-isopropyl-9-oxotricyclo[4.3.1.0^{3,7}]decan-9-one (9-Pupukeanone, 3). To a prereduced suspension of 50 mg of platinum oxide in 3 mL of methanol under a hydrogen atmosphere was added 27 mg (0.13 mmol) of **31**. After 46 h, the reaction mixture was diluted with ether and filtered through Celite to give 24 mg of a mixture of **3** and **32** in a 7:3 ratio (as determined by ^{1}H NMR). Preparative chromatography of this mixture on silver nitrate impregnated silica gel provided a sample of pure **3**: ^{1}H NMR ($CDCl_3$) δ 2.34 (2 H, d, J = 3 Hz), 1.71, 1.63, 1.56, 1.49 (br s), 1.04 (3 H, s), 0.91 (3 H, s), 0.90 (6 H, m); mass spectrum, m/e 220 (M^+).

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(22) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3333 (1956).

Macrocyclic Lactone Formation through Sulfide Contraction. Synthesis of (±)-Diplodialide A[1]

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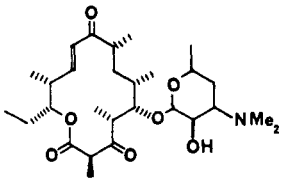
A methodology for the synthesis of macrocyclic β-keto lactones from ω-hydroxy thioamides is described. The hydroxy thioamides were esterified with chloroacetyl chloride, and the resulting chloro esters underwent Eschenmoser sulfide contraction when treated with sodium iodide, diisopropylethylamine, and triethyl phosphite in acetonitrile. The β-keto lactones were obtained in 25–58% yield. The utility of the method was demonstrated by synthesis of diplodialide A.

Recently, several procedures for macrocyclic lactone formation have appeared.[3] Although a few alternate routes have been used, most of the procedures rely on the formation of the lactone bond as the ring-forming step. Existence of natural products such as narbomycin (**1**)[4] and diplodialide A (**2**)[5] which contain the β-keto lactone system suggested that such macrocycles might be synthesized through formation of this grouping by some modification of the Claisen condensation. The Eschenmoser sulfide contraction,[6] in which thioamide **3** was converted into



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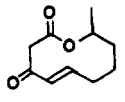

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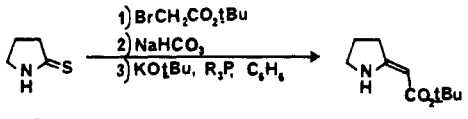

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(2) Institute fellow, 1975–76. Predoctoral fellow of the National Science Foundation, 1976–79.

(3) Ishida, T.; Wada, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 323–7, and references cited therein.

(4) Corbaz, R.; Ettlinger, L.; Gäumann, E.; Keller, W.; Kradolfer, F.; Kyburz, E.; Neipp, L.; Prelog, V.; Reusser, P.; Zähner, H. *Helv. Chim. Acta* **1955**, *38*, 935–42.

(5) Ishida, T.; Wada K. *J. Chem. Soc., Chem. Commun.* **1975**, 209–10.

0022-3263/80/1945-1868$01.00/0