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Regio- and Stereoselective Cyclopentannulation with Ketones and Propargyl Alcohol Derivatives. Synthesis of *dl*-Nootkatone and *dl*-Muscopyridine

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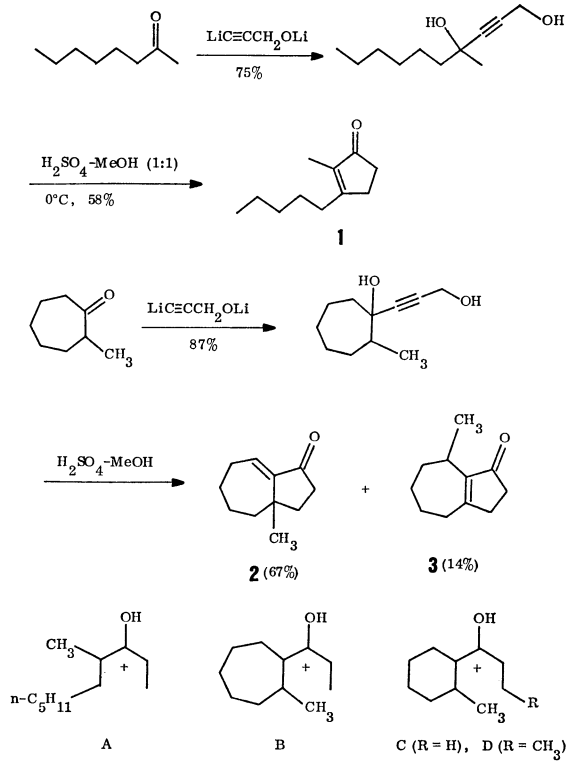
A highly regio- and stereoselective five-membered ring annulation involving the acid-treatment of propargyl alcohol dianion adducts of ketones is described. The propargyl alcohol adduct of 2-octanone was converted into 2-methyl-3-pentyl-2-cyclopentenone by treatment with sulfuric acid–methanol (1:1) at 0 °C. As the major product, 1-methylbicyclo[5.3.0]dec-6-en-8-one was produced from 2-methylcycloheptanone. Remarkable regioselective cyclopentannulation was observed in 2-methylcyclohexanone and 2,3-dimethylcyclohexanone wherein 1-methyl- and *trans*-1,2-dimethyl-substituted bicyclo[4.3.0]non-5-en-7-one (BNO) are produced, respectively. With 3-butyn-2-ol, 2-methylcyclohexanone was converted into the *cis*-1,9-dimethyl-substituted BNO. 4-Isopropyl-2-methylcyclohexanone was transformed into an 83—85:17—15 mixture of *c*-3-isopropyl-*r*-1,*c*-9-dimethyl-BNO and its 3-epimer. These results are explained in terms of the conrotatory ring-closure of thermodynamically most favorable hydroxypentadienyl cation intermediates. 3-Methoxycarbonyl-*cis*-1,9-dimethyl-BNO produced from 4-methoxycarbonyl-2-methylcyclohexanone and 3-butyn-2-ol was successfully transformed into *dl*-nootkatone by converting the methoxycarbonyl group into isopropenyl of correct stereochemistry followed by ring enlargement. Cyclopentannulation using propargyl alcohol dianion adducts of 2-cycloalkenones is discussed. Annulation takes place regioselectively to give conjugated dienones, *e.g.*, (*E*)-bicyclo[10.3.0]pentadeca-1(12),2-dien-13-one from 2-cyclododecenone. This product is led to *dl*-muscopyridine by conjugate 1,6-addition of methyl group followed by ring expansion and finally by aromatization with hydroxylamine hydrochloride.

Selective ring-forming reactions are important with respect to construction of fused carbocyclic skeletons. The regio- and stereochemistry of the annulation in particular should be controlled. The Robinson annulation has been extensively studied and is now well-established.[1] The analogous synthetic problem for five-membered ring annulation[2] still remains unsolved in spite of the development of efficient three-carbon annulation process.[3–5] In view of the stereospecificity of electrocyclic reactions, the ring-closure of pentadienyl cation intermediates was utilized.[6] Characteristic procedures have been developed for cyclopentannulation,[7,8] but though highly efficient for simple cyclic ketones, the method[7b] involving dichloroallyllithium–ketone adducts is not applicable to a moderately hindered ketone such as 2-methylcyclohexanone. Having made efforts to elaborate access to 2-substituted cycloalkanones, we have found a process noted briefly by Islam and Raphael[9a] and others[9b,c] which is effective as regards to regio- and stereoselectivity. Details are reported herein.[10]

Cyclopentannulation of 2-Methylcyclohexanones. In order to disclose the regioselectivity of the Raphael process, 2-octanone was allowed to react with the dilithium salt of propargyl alcohol, and the resulting adduct was treated with sulfuric acid–methanol (1:1) at 0 °C to give 2-methyl-3-pentyl-2-cyclopentenone (**1**) as a sole product. Starting with 2-methylcycloheptanone, we obtained **2** as the major product. Thus, the more substituted α-carbon of these ketones is preferentially incorporated into the five-membered ring. This selectivity may be attributed to the thermodynamically most stable intermediates of types A and B, respectively, showing a sharp contrast to the exclusive production of **3** from 2-methylcycloheptanone by the dichloroallyllithium method.[7b]

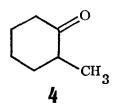
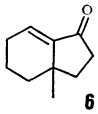
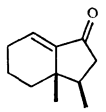
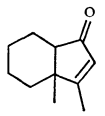
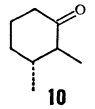
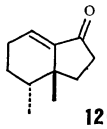
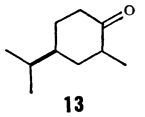
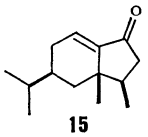
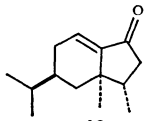
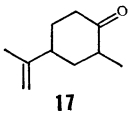
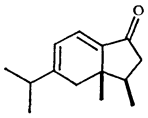
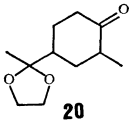
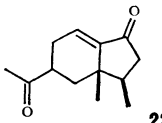
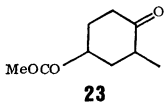
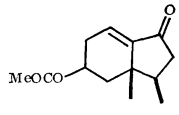
Remarkable selective annulation was observed in 2-methylcyclohexanone derivatives (Table 1). The propargyl alcohol adduct **5** of 2-methylcyclohexanone (**4**) was cyclized under acidic conditions to give the



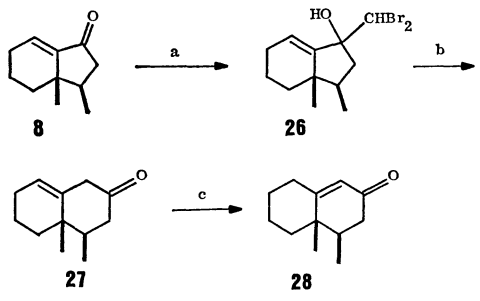
hexahydroindenone derivative **6** exclusively. The electrocyclic ring-closure of the intermediate C followed by deprotonation should be responsible for selective annulation.

When 3-butyn-2-ol was added to **4** and the adduct **7** treated with sulfuric acid and methanol, *cis*-3,3a-dimethylhexahydroindenone **8** was produced along with its isomer **9**. The stereochemistry of **8** was unambiguously established by transforming **8** into the known octalone **28** (Scheme 1). Thus, dibromomethyllithium[11] was allowed to react with **8**, and the adduct **26** was then treated with 2 mol of butyllithium to give **27**. One methylene unit is selectively insert-

TABLE 1. CYCLOPENTANNULATION OF 2-METHYLCYCLOHEXANONE DERIVATIVES

Entry	Cyclohexanone	Propargyl alcohol derivative	Adduct (% yield)	Annulated product (% yield)
1	 **4**	$CH{\equiv}CCH_2OH$	**5** (88) [a]	 **6** (70)
2		$CH{\equiv}CCHOH$ $\vert$ CH_3	**7** (84) [b]	 **8** (67)  **9** (10)
3	 **10**	$CH{\equiv}CCH_2OH$	**11** (89) [c]	 **12** (60)
4	 **13**	$CH{\equiv}CCHOH$ $\vert$ CH_3	**14** (87) [b]	 **15**  **16** (64% yield, **15**:**16** 83-85:17-15)
5	 **17**	$CH{\equiv}CCHOH$ $\vert$ CH_3	**18** (71) [b]	 **19** (55)
6	 **20**	$CH{\equiv}CCHOH$ $\vert$ CH_3	**21** (84) [d]	 **22** (34)
7	 **23**	$CH{\equiv}CCHOH$ $\vert$ CH_3	**24** (86) [e]	 **25** (60)

a) Diastereomer ratio 42:58. Although the compounds were separable, the mixture was used directly for the next annulation. b) Two of the diastereomers were separable, the mixture being used for the subsequent annulation. c) About 1:1 diastereomeric mixture. d) Based on the consumed cyclohexanone. e) Isolated as carboxylic acid.



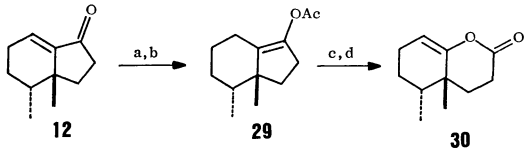
a: $LiCHBr_2$, b: n-BuLi, c: 5% H_2SO_4-THF

Scheme 1.

ed between the carbonyl and olefinic carbon of **8**. Treatment with aqueous sulfuric acid gave **28** having a ^{1}H-NMR absorption at δ 1.08 (singlet for the bridgehead methyl) consistent with the *cis* isomer **28** (*cf.* the *trans* isomer, δ 1.27).[12] The sole formation of **8** is ascribed to the conrotatory ring-closure of the intermediate D wherein the steric interaction between the two methyl groups is most reduced.

Using 2,3-dimethylcyclohexanone and propargyl alcohol, we attempted to cyclize the adduct **11** with sulfuric acid–methanol mixture as above and obtained an intractable mixture of products. The result was improved by converting the diol **11** into a monoacetate with acetic anhydride in pyridine and by employing 2,2,2-trifluoroethanol in place of methanol, a single product **12** being formed whose stereochemistry was established by transformation into the known enol lactone **30**[13] (Scheme 2). The enone moiety of **12** was reduced with lithium in anhydrous ammonia and the resulting enolate was trapped with acetic anhydride to give **29**. Ozonolysis of **29** fol-

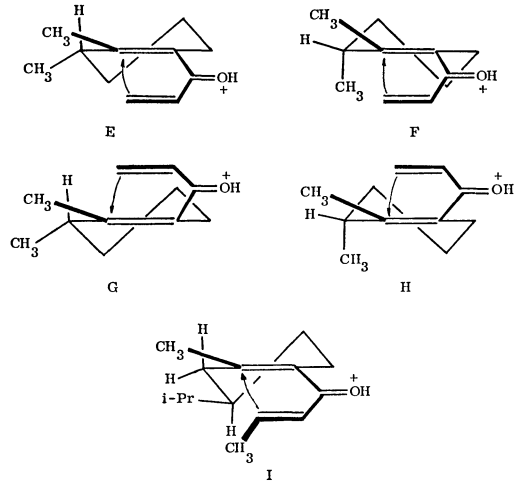
lowed by lactone formation with acetic anhydride and sodium acetate gave **30** which exhibited a ^{1}H-NMR absorption at δ 1.20 (singlet for bridgehead methyl) pertinent to the *trans* isomer (*cf.* δ 1.03 for the *cis* isomer).[13]



a: Li/NH_3, b: Ac_2O, c: O_3, Me_2S, d: Ac_2O, AcONa

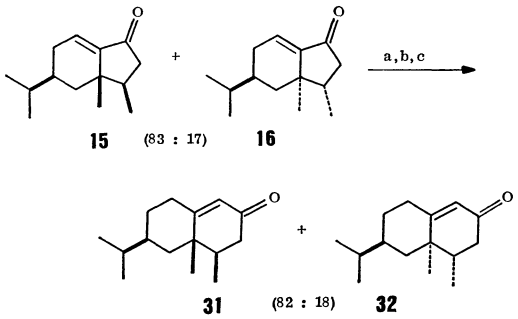
Scheme 2.

Let us consider the factors governing the transformation of **11** into **12**. *A priori*, four intermediates E—H are conceivable precursors for the five-membered ring annulation. The intermediate E or F gives **12** while G or H affords the *cis* isomer of **12**. Examination of molecular models suggests that in G or H severe interaction between the two methyl groups takes place as new C–C bond formation proceeds. However, such an interaction is not crucial in E or F since the two methyl groups are further apart during the course of C–C bond formation. Of the two favorable intermediates E and F, E seems to be the responsible one since the methyl group on the six-membered ring takes a pseudoequatorial position and C–C bond formation takes place from the antiperiplanar direction of a pseudoaxial C–H bond under orbital control.[14]



Provided that such orbital control is operative during the course of cyclization, we can take advantage of this effect by starting with 4-isopropyl-2-methylcyclohexanone (**13**) and 3-butyn-2-ol. The intermediate postulated here would be I whose isopropyl group should prefer an equatorial position; C–C bonding should occur from the antiperiplanar direction of the pseudoaxial C–H bond to produce a hexahydroindenone derivative with all *cis* substituents predominantly. This was found to be the case.

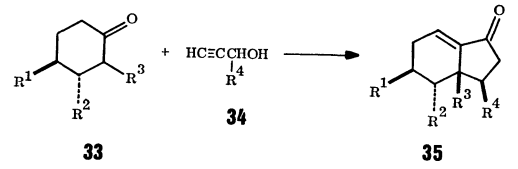
Addition of 3-butyn-2-ol to **13** gave an acetylenic diol **14** as a mixture of eight possible diastereomers. Without separation of the diastereomers, **14** was treated with sulfuric acid and methanol (1:1) at 0 °C to afford two products **15** and **16** in a ratio of 83:17 or 85:15 as revealed by ^{1}H-NMR or GLC respectively. The stereochemical outcome was secured by converting the mixture of products into an 82:18 (^{1}H-NMR) mixture of **31** and **32** by the sequence shown in Scheme 3 and by comparison of the retention time on capillary column GLC as well as ^{1}H-NMR spectra with those of each authentic sample. The authentic samples of **31** and **32** were prepared by the hydrogenation of 7-*epi*-nootkatone[15] and nootkatone,[16] respectively, with the aid of the catalyst chlorotris(triphenylphosphine)rhodium(I).



a: $LiCHBr_2$, b: n-BuLi, c: 5% H_2SO_4-THF

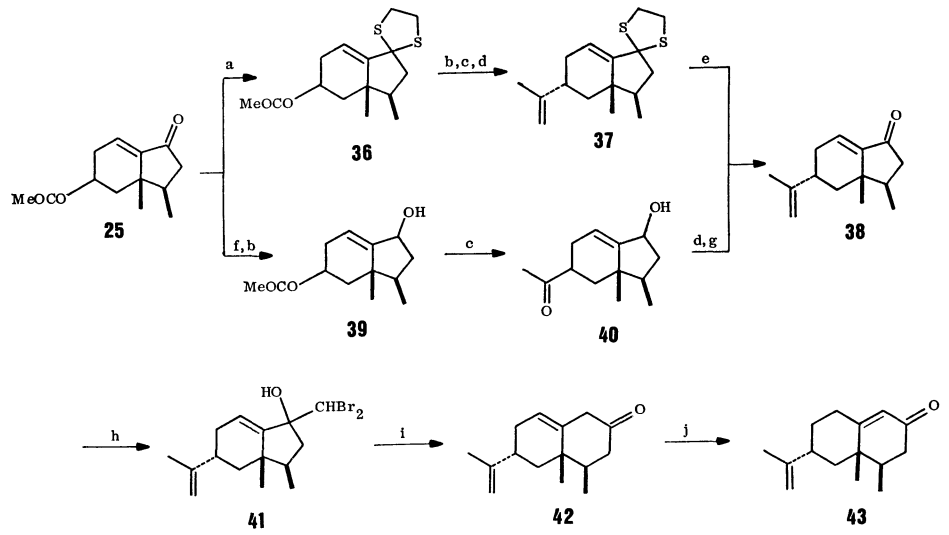
Scheme 3.

The results of entries 1—4 in Table 1 can be summarized as follows. A cyclohexanone **33** is converted by attaching a three-carbon unit of **34** into **35** in which the alkyl substituent R^3 on the bridgehead carbon comes invariably *cis* to R^4, *trans* to R^2 and selectively *cis* to R^1.



Synthesis of dl-*Nootkatone.* Scheme 3 shows that the annulation process is effective for stereoselective synthesis of an eremophilane-type sesquiterpene. We have applied this process to the synthesis of *dl*-nootkatone,[16,17] a component of the taste and flavor of grapefruit (*Citrus paradisi* Macfayden). Its carbon framework is characterized by the C(7)-epimer of eremophilane, *vis.*, valencane. An attempt using the adduct **18** of **17** and 3-butyn-2-ol resulted in the isomerization of the isopropenyl C=C bond to the conjugated one to give **19**. Taking account of the required epimerization at C(7), we started with **20** and obtained apossible precursor of nootkatone, **22**, in 34% yield. Because of the relative inefficiency of the annulation as well as the difficulty to obtain the starting material in large amount, we abandoned this route.

An ester group is found to be the appropriate functional group equivalent to isopropenyl group. The starting cyclohexanone **23**[18] was synthesized by the Diels-Alder reaction of methyl acrylate and 2-methyl-



a: $HSCH_2CH_2SH$, BF_3OEt_2, b: KOH, c: MeLi, d: $Ph_3P{=}CH_2$, DMSO, e: i-$C_5H_{11}ONO$, f: $CeCl_3$-$NaBH_4$
g: $PyHClCrO_3$, h: $LiCHBr_2$, i: BuLi, j: 5% H_2SO_4-THF

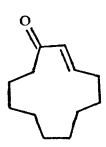
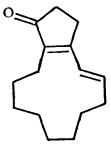
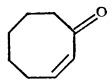
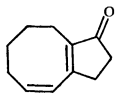
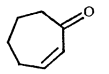
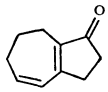
Scheme 4.

3-trimethylsilyloxybutadiene[19] followed by hydrolysis. Subsequent addition of 3-butyn-2-ol was effected with concomitant hydrolysis of the ester group to give the adduct **24** as a stereoisomeric mixture, which was then treated with sulfuric acid–methanol (1:1) at 50 °C. The annulation product **25** was found to be a 3:2 mixture of epimers as evidenced by GLC and ^{13}C-NMR. Subsequent steps toward the target **43** are illustrated in Scheme 4.

In order to convert the methoxycarbonyl group of **25** into isopropenyl moiety of the correct configuration, we first transformed **25** into the ethylene dithioacetal **36** whose methoxycarbonyl group was transformed into isopropenyl group by standard methods. The final product **37** exhibited a ^1H-NMR spectrum revealing at least 97% stereochemical purity although one of its precursors, the methyl ketone, was a *ca.* 7:3 mixture of epimers. Probably epimerization took place before the Wittig olefiniation to yield a thermodynamically favorable product and/or the thermodynamically favorable isomer reacted more rapidly. Deprotection of the dithioacetal group was accomplished with isopentyl nitrite[20] to give the desired intermediate **38**. The configuration at C(5) turned out to be the correct one (purity >97%) as evidenced by hydrogenation of **38** to **16** with chlorotris(triphenylphosphine)rhodium(I) as a catalyst[16a] and by comparison of the spectrometric and chromatographic feature of **38** with those of the authentic specimen. Although the stereochemical outcome of **38** prepared by this route is acceptable, both formation and removal of the dithioacetal group were relatively inefficient (57% and 48% yield respectively), and hence another route from **25** to **38** was explored.

The enone **25** was reduced with sodium borohydride–cerium(III) chloride[21] in methanol to give an allyl alcohol **39** which was converted into a methyl ketone **40** as above. The Wittig reaction of **40** followed by oxidation with pyridinium chlorochromate gave **38** of >88% stereochemical purity at C(5) in 78% overall yield.

Table 2. Cyclopentannulation of 2-cycloalkenones

2-Cycloalkenone	Propargyl alcohol adduct (% yield)	Annulated product (% yield)
 44	**45** (92)	 **46** (65)
 47	**48** (51[a], 76[b])	 **49** (42)
 50	**51** (65)	 **52** (49)

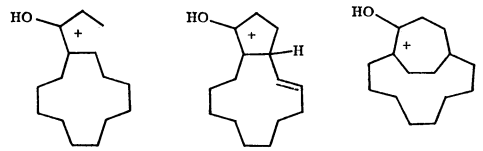
a) Cyclooctenone (30%) recovered. b) Yield based on the consumed starting enone.

Final ring-enlargement was effected by the β-oxido carbenoid procedure.[11] The hexahydroindenone **38** was allowed to react with dibromomethyllithium at −78 °C to give the adduct **41** which in turn was treated with 3 equivalents of butyllithium at −95 °C for 1.6 h to give an octalone **42**. The IR of **42** showed the presence of a cyclohexanone moiety with no contamination of a conjugated enone. Subsequently, **42** was isomerized to *dl*-nootkatone in 5% sulfuric acid–THF (1:1). The synthetic sample thus prepared was of more than 93% purity and chromatographically and spectrometrically identical with the authentic specimen.[16a]

Cyclopentannulation of 2-Cycloalkenones. Having disclosed the salient feature of the cyclopentannula-

tion using 2-methylcycloalkanones and propargyl alcohol we extended the concept to 2-functionalized cycloalkanones such as 2-phenylthiocyclohexanone, 2-chloro-2-methylcyclohexanone, and 2-propargylcyclohexanone. Although the addition of propargyl alcohol dianion occurred with no trouble, the next acid-catalyzed cyclization turned out futile. We eventually found that 2-cycloalkenones undergo regioselective annulation (Table 2).

2-Cyclododecenone (**44**) was allowed to react with propargyl alcohol and the adduct **45** was treated with a 1:2 mixture of sulfuric acid and methanol at −20 to −3 °C to give the conjugated dienone **46**. The spectral data of **46** (see Experimental) are fully consistent with the given structure. In particular, the configuration of the newly produced C=C bond was found to be (*E*) based on the ^{1}H-NMR and IR spectra. The formation of the conjugated dienone is explained in terms of the conrotatory ring-closure of a heptatrienyl cation J to a vinylcyclopentenyl cation K,[22] since the disrotatory ring-closure of J to a cycloheptadienyl cation L is sterically hindered by the octamethylene chain. It is worthy to note that the C(1) and C(2) solely of **44** are incorporated into the five-membered ring. In this sense the annulation is regioselective.

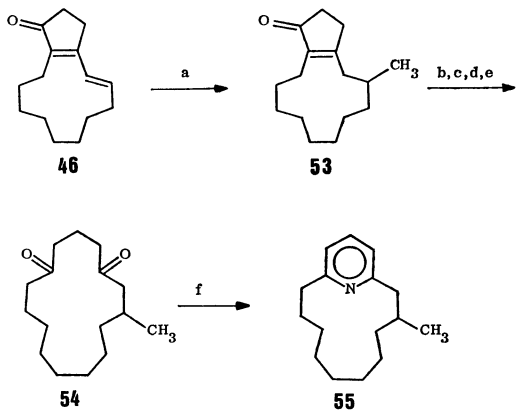


J K L

This two-step annulation was applied to lower homologs (Table 2) with less satisfactory results. The major obstacle was low efficiency in the addition of propargyl alcohol dianion to enones to induce enolization of the enones. The next cyclization is best performed by using the monoacetates of the adducts and by dissolving the monoacetates in sulfuric acid–methanol. Thus, bicyclic conjugated dienones **46**—**52** are now easily available which are otherwise hardly accessible.

Synthesis of dl-*Muscopyridine.* With the dienone **46** in hand, we planned to synthesize *dl*-muscopyridine (**55**).[23] A logical precursor of **55** should be 7-methyl-1,5-cyclopentadecanedione (**54**, Scheme 5). However, the introduction of methyl group into the parent diketone at the desired position is apparently difficult. We anticipated that diketone **54** would be derived from the bicyclic cyclopentenone **53**.

Selective 1,6-conjugated addition of the methyl group across the dienone moiety of **46** was best carried out using methylmagnesium iodide in the presence of copper(I) chloride,[24] **53** being obtained as the sole product. Dimethylcopperlithium turned out futile to give an intractable mixture of products with no trace of the desired one. Subsequent transformation into the diketone **54** was carried out according to the procedure of Gray and Dreiding.[25] Thus, **53** was reduced with sodium borohydride to an allyl alcohol which was then oxidized to an epoxy alcohol with *m*-chloroperoxybenzoic acid. Tosylation followed by solvolysis



a: CH_3MgI, CuCl, THF, b: $NaBH_4$, c: m-$ClC_6H_4CO_3H$, d: p-$CH_3C_6H_4SO_2Cl$, pyridine, e: aq dioxane, $CaCO_3$, f: NH_2OH·HCl

Scheme 5.

in aqueous dioxane gave the diketone, which was finally heated with hydroxylamine hydrochloride in ethanol at 160 °C.[26] *dl*-Muscopyridine (**55**) thus prepared exhibited correct spectra.

Experimental

Distillation was carried out by use of Kugelrohr (Büchi) and boiling points were determined by measuring the bath temperature. All temperatures are uncorrected. ^{1}H-NMR spectra (tetramethylsilane as an internal standard) were obtained on a Varian EM 390 spectrometer, chemical shifts being given in ppm unit, ^{13}C-NMR spectra on a Varian CMR-20 spectrometer, IR spectra on a Shimadzu IR-27G spectrometer in neat liquid film unless otherwise stated, MS on a Hitachi RMU-6L spectrometer, exact mass on a JEOL-JMS-D 300 spectrometer and UV on a Hitachi 124 spectrophotometer. Propargyl alcohol was distilled before use. 3-Butyn-2-ol (Tokyo Kasei-Kogyo Co. or Nakarai Chemicals Ltd., 55% aqueous solution) was used. Commercial sulfuric acid (95%) was used for cyclization. Preparative TLC plates (20 cm × 20 cm) were prepared with Merck Kiesel-gel PF_{254}. Column chromatography was carried out with silica gel (Wakogel C-100) at atmospheric pressure.

Synthesis of 2-Methyl-3-pentyl-2-cyclopentenone (1) from 2-Octanone. Under a nitrogen atmosphere at −78 °C, butyllithium (1.50 M† hexane solution, 6.0 ml, 9.0 mmol) was added dropwise to a tetrahydrofuran (THF, 15 ml) solution of propargyl alcohol (0.25 g, 4.5 mmol). After stirring for 70 min, 2-octanone (0.39 g, 3.0 mmol) in THF (5 ml) was added and the reaction mixture was warmed to room temperature and stirred for 30 min. Work-up followed by preparative TLC purification (ether, R_f 0.68—0.84) gave 4-methyl-2-decyne-1,4-diol (0.42 g, 75% yield) as a viscous oil. IR: 3324, 1038, 1000 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.7—1.8 (m, 13H), 1.43 (s, 3H, CH_3), 4.20 (s, 2H, $C\underline{H}_2OH$), 3.9—4.5 (br s, 2H, OH); MS: *m/e* (rel intensity) 169 (M^+-CH_3, 4), 99 (100, $M^+-C_6H_{13}$), 81 (24). Found: C, 71.73; H, 11.22%. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94%.

Sulfuric acid (1.5 ml) was added dropwise over a period of 20 min to a methanol solution (1.5 ml) of 4-methyl-2-

† 1 M = 1 mol dm^{-3}.

decyne-1,4-diol (172 mg, 0.93 mmol) at 0 °C. After stirring for 1.7 h, the reaction mixture was diluted with ether (10 ml) and neutralized with aqueous sodium hydrogencarbonate solution. The organic phase was separated, and the aqueous phase was extracted thoroughly with ether, the combined ethereal extracts being dried (Na_2SO_4) and concentrated *in vacuo*. Preparative TLC (hexane–ether 1:1, R_f 0.34—0.53) of the residue gave **1**[7b] (90 mg, 58% yield).

Cyclopentannulation of 2-Methylcycloheptanone. Butyllithium (1.81 M hexane solution, 8.3 ml, 15 mmol) was added at −78 °C under a nitrogen atmosphere to propargyl alcohol (0.40 g, 7.1 mmol) in THF (30 ml) in 5 min. The resulting viscous solution was stirred for 1 h and admixed with 2-methylcycloheptanone (0.60 g, 4.8 mmol) in THF (5 ml) during a period of 10 min. Stirring at −78 °C for 3 h, at room temperature for 0.5 h, followed by work-up, gave an oil (1.15 g). Purification by column chromatography (hexane–ether 1:1) gave the desired diol (TLC, hexane–ether 10:3, R_f 0.28, single spot, 0.67 g, 77% yield; 87% based on the consumed ketone) along with the recovered 2-methylcycloheptanone (68 mg, 10% recovery). The diol, mp 68.0—68.1 °C (hexane), showed the following spectra. ^{1}H-NMR (CCl_4): δ 1.08 (d, J=6.0 Hz, 3H, CH_3), 1.2—2.2 (m, 11H, methylenes and methine), 3.95 (br s, 1H, OH), 4.20 (s, 2H, $C\underline{H}_2OH$), 4.60 (br s, 1H, OH); IR: 3340, 1090 cm^{-1}; MS: *m/e* (rel intensity) 182 (M^+, 5), 164 (7), 151 (29), 111 (64), 79 (80), 55 (100). Found: C, 72.54; H, 10.09%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

Sulfuric acid (1.0 ml) was added dropwise over a period of 10 min at 0 °C to a methanol (0.1 ml) solution of the diol (17 mg, 0.093 mmol). The reaction mixture turned dark reddish purple. After 4 h the reaction was quenched by dilution with ether (10 ml) and neutralization with sodium hydrogencarbonate aqueous solution. TLC purification of the crude product (hexane–ether 2:1) gave 1-methylbicyclo[5.3.0]dec-6-en-8-one (**2**) (10.0 mg, 67% yield, R_f 0.41—0.50) and 6-methylbicyclo[5.3.0]dec-1(7)-en-8-one (**3**)[7b] (2.1 mg, 14% yield, R_f 0.22—0.26). Physical properties of **2**: bp 97—103 °C (bath temp)/0.06 Torr††. ^{1}H-NMR (CCl_4): δ 1.11 (s, 3H, CH_3), 1.3—2.8 (m, 12H, methylenes), 6.57 (dd, J=7.0, 5.0 Hz, 1H, olefinic H); IR: 1716, 1643 cm^{-1}; MS: *m/e* (rel intensity) 164 (M^+, 70), 149 (67), 122 (100), 107 (91), 93 (98), 79 (93). Found: C, 80.57; H, 10.08%. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83%.

The regioselectivity of the annulation at 0 °C was dependent on the acidic conditions. Conditions, yield(%), ratio of **2** to **3** were as follows: sulfuric acid–methanol (1:1), 61%, 77:23; sulfuric acid–methanol (1:10), 90, 40:60; sulfuric acid–acetic acid (1:1), 59, 84:16; sulfuric acid–2,2,2-trifluoroethanol (1:1), 55, 75:25; sulfuric acid only, 62, 88:12; sulfuric acid–methanol (1:1) and 1 mol of mercury(II) sulfate, 97%, 82:18.

*Cyclopentannulation of 2-Methylcyclohexanone (**4**) with Propargyl Alcohol.* Propargyl alcohol dianion solution was prepared at −78 °C under a nitrogen atmosphere by adding butyllithium hexane solution (2.0 M, 15.8 ml, 32 mmol) to propargyl alcohol (0.85 g, 15.1 mmol) in THF (40 ml), and stirring for 3 h. Addition of 2-methylcyclohexanone (1.12 g, 10.0 mmol) dissolved in THF (10 ml) followed by stirring at −78 °C for 1 h, at room temperature for 0.5 h, and then work-up gave an oil which was purified by column chromatography to give the adduct **5** (1.48 g, 88% yield) as *ca.* 3:2 diastereomeric mixture (TLC, hexane–ether 1:2, R_f 0.14 and 0.22). ^{1}H-NMR (CCl_4): δ 1.01 (d, J=5.0 Hz, 3H), 1.2—2.2 (m, 9H), 3.67 (br s, 1H), 4.19 (s, 2H), 4.50 (br s, 1H); IR: 3340, 1012, 968 cm^{-1}; MS: *m/e* 168 (M^+). Each diastereomer was separated by careful column chromatography. The less polar isomer: colorless needles, mp 36.2—37.0 °C (hexane). Found: C, 71.29; H, 9.66%. The more polar isomer: bp 126—128 °C (bath temp)/0.06 Torr; Found: C, 71.44; H, 9.71%. The mixture was used for the subsequent cyclization.

Sulfuric acid (1.5 ml) was added dropwise at 0 °C over a period of 15 min to a methanol (1.5 ml) solution of the adduct **5** (162 mg, 0.96 mmol). Stirring for 1.5 h at 0 °C, followed by extractive work-up as before and preparative TLC (dichloromethane), gave 1-methylbicyclo[4.3.0]non-5-en-7-one (**6**) (101 mg, 70% yield, R_f 0.35—0.49). GLC assay of the reaction mixture showed the presence of a trace amount (less than 5%) of the regioisomer corresponding to **3**. Physical properties of **6** are: bp 78—80 °C (bath temp)/0.04 Torr; ^{1}H-NMR (CCl_4): δ 1.08 (s, 3H, CH_3), 1.2—2.5 (m, 10H), 6.37 (t, 1H, J=3.6 Hz); IR: 1716, 1646 cm^{-1}; MS: *m/e* (rel intensity) 151 (M^++1, 8), 150 (M^+, 42), 135 (32), 122 (33), 108 (75), 93 (88), 79 (100). Found: C, 79.69; H, 9.33%. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39%.

Each diastereomer of **5** was separated by preparative TLC and subjected to cyclization under similar conditions. The more polar isomer gave **6** in 66% isolated yield, and the less polar one in 62% isolated yield.

*Annulation of 2-Methylcyclohexanone (**4**) with 3-Butyn-2-ol.* Potassium hydroxide (6.80 g, 121 mmol) was dissolved in 55% aqueous solution (5.7 g, 45 mmol) of 3-butyn-2-ol and the resulting solution was warmed at 40 °C. To this mixture was added dropwise 2-methylcyclohexanone (3.4 g, 30 mmol) over a period of 2 h, and the whole was stirred for 24 h at 40 °C, then diluted with water (10 ml) and extracted with ether (20 ml×4 times). The ethereal extracts were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography of the residue (hexane–ether 1:2) gave 1-(3-hydroxy-1-butynyl)-2-methylcyclohexanol (**7**) as a diastereomeric mixture (R_f 0.24 and 0.35 on TLC with hexane–ether 1:2) (4.6 g, 84% yield), bp 110—118 °C (bath temp)/0.08 Torr. ^{1}H-NMR (CCl_4): δ 0.91 (d, J=6.0 Hz, 3H), 1.02 (d, J=6.0 Hz, 3H), 1.1—2.1 (m, 9H), 3.5—4.3 (br s, 2H, OH), 4.3—4.7 (m, 1H, C$\underline{H}$–OH); IR: 3344, 1116, 1062, 1024 cm^{-1}; MS: *m/e* 182 (M^+). Found: C, 72.20; H, 10.15%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

Sulfuric acid (1.0 ml) was added at 0 °C over a period of 10 min to **7** (106 mg, 0.58 mmol) dissolved in methanol (1.0 ml). After 30 min the reaction was stopped by dilution with ether (10 ml) and neutralization with aqueous sodium hydrogencarbonate solution. The ethereal extracts were dried (Na_2SO_4), concentrated *in vacuo* to give an oil (107 mg). Preparative TLC purification (hexane–ether 1:1) gave 1,9-*cis*-dimethylbicyclo[4.3.0]non-5-en-7-one (**8**) (63 mg, 67% yield, R_f 0.58—0.71) and 1,9-dimethylbicyclo-[4.3.0]non-8-en-7-one (**9**) (10 mg, 10% yield, R_f 0.47—0.58). GLC assay of the crude product gave the **8**:**9** ratio to be 86:14. Physical properties of **8** were as follows. Bp 105—112 °C (bath temp)/0.07 Torr; ^{1}H-NMR (CCl_4): δ 0.95 (s, 3H, C–CH_3), 1.07 (d, J=6.0 Hz, 3H, CH–C$\underline{H}_3$), 1.5—2.3 (m, 9H), 6.37 (t, 1H, J=3.0 Hz, olefinic H); IR: 1723, 1653 cm^{-1}; MS: *m/e* (rel intensity) 164 (M^+, 50), 149 (23), 136 (15), 122 (95), 79 (100). Found: C, 80.65; H, 10.04%. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83%. Physical properties of **9**: bp 110—118 °C (bath temp)/0.09 Torr; ^{1}H-NMR (CCl_4): δ 1.23 (s, 3H), 1.0—2.3 (m+d (J=1.7 Hz) at δ 1.99, 12H), 5.70 (q, J=1.7 Hz, 1H); IR: 1700, 1619 cm^{-1}; MS: *m/e* (rel intensity) 164 (M^+, 46), 149

†† 1 Torr=133.322 Pa.

(100), 135 (22), 122 (27). Exact mass, found: *m/e* 164.1213 (M^+). Calcd for $C_{11}H_{16}O$: *m/e* 164.1201.

Transformation of ***8*** *to an Octalone* ***28***. Lithium dicyclohexylamide, prepared by addition of butyllithium (1.81 M hexane solution, 1.70 ml, 3.1 mmol) to a THF (2 ml) solution of dicyclohexylamine (0.56 g, 3.1 mmol) at 0 °C and by stirring the solution at 0 °C for 15 min, was added dropwise over a period of 2.3 h to a mixture of **8** (0.163 g, 1.0 mmol) and dibromomethane (0.37 g, 2.1 mmol) dissolved in THF (3 ml) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 40 min and quenched by adding methanol (1.0 ml) at −78 °C. The reaction mixture was then warmed to room temperature, diluted with water (10 ml) and then treated with 5% hydrochloric acid. The precipitated insoluble material was filtered and washed with ether thoroughly. The aqueous phase of the filtrate was separated from the ethereal one and extracted with ether (20 ml×4 times). The combined ethereal extracts were dried (Na_2SO_4), and concentrated under reduced pressure to give an oil (0.45 g). Preparative TLC purification (benzene) gave the adduct **26** (R_f 0.34—0.46, 0.20 g, 60% yield; 83% yield based on the consumed starting material) along with the recovered **8** (R_f 0.08—0.21, 46 mg). ^{1}H-NMR (CCl_4) of **26**: δ 0.94 (d, J=7.5 Hz, 3H), 1.00 (s, 3H), 1.0—2.7 (m, 9H), 5.63 (t, J=3.3 Hz, 1H), 5.80 (s, 1H, $CHBr_2$); IR: 3440 cm^{-1}.

The adduct **26** (168 mg, 0.50 mmol) was dissolved in THF (4 ml) under an argon atmosphere, and a butyllithium hexane solution (1.83 M, 0.60 ml, 1.1 mmol) was added dropwise over a period of 12 min to the solution cooled at −95 °C. The reaction mixture was stirred at −95 °C for 2 h, then warmed to 0 °C, stirred for 5 min, and quenched with water (10 ml). Ether extraction (20 ml×4 times) followed by drying (Na_2SO_4) and concentration gave a crude product (115 mg) which was purified by preparative TLC (benzene) to give the octalone **27** (R_f 0.32—0.43, 36 mg, 41% yield). IR: 1715 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.94 (d, J=6.0 Hz, 3H), 1.10 (s, 3H), 1.1—2.5 (m, 9H), 1.73 (d, J=15.6 Hz, 1H), 3.10 (dm, J=15.6 Hz, 1H), 5.3—5.5 (m, 1H); MS: *m/e* (rel intensity) 178 (M^+, 50), 163 (23), 150 (23), 136 (56), 108 (76), 93 (100).

The octalone **27** (15 mg, 0.08 mmol) was dissolved in THF (0.5 ml) and 5% aqueous sulfuric acid (0.5 ml) and stirred for 2 h at room temperature. Work-up and TLC purification (hexane–ether 1:1) gave the octalone **28**[12] (R_f 0.23—0.31, 11 mg, 73% yield). ^{1}H-NMR (CCl_4): δ 0.94 (d, J=6.0 Hz, 3H), 1.08 (s, 3H), 1.1—2.5 (m, 11H), 5.60 (br s, 1H); IR: 3129, 1663, 1614 cm^{-1}; MS: *m/e* (rel intensity) 178 (M^+, 44), 163 (15), 150 (12), 136 (100), 121 (56). The recorded chemical shifts (CCl_4) of **28**:[12] δ 1.08 (s, 3H), and its *trans* isomer δ 1.27 (s, 3H).

*Cyclopentannulation of 2,3-Dimethylcyclohexanone (****10****) with Propargyl Alcohol.* Propargyl alcohol dianion was prepared by adding butyllithium hexane solution (1.92 M, 7.8 ml, 15.0 mmol) to propargyl alcohol (0.39 g, 7.0 mmol) in THF (35 ml) at −78 °C and allowed to react with 2,3-dimethylcyclohexanone (0.57 g, 4.5 mmol) dissolved in THF (10 ml) at −78 °C for 2.5 h, and at room temperature for 40 min. Work-up followed by column chromatography (hexane–ether 1:2) gave 1-(3-hydroxy-1-propynyl)-2,3-dimethylcyclohexanol (**11**) (0.74 g, 89% yield). Bp 118—126 °C (bath temp)/0.06 Torr; ^{1}H-NMR ($CDCl_3$): δ 0.8—1.0 (d, 6H), 1.0—2.3 (m, 8H), 3.08 (s, 2H), 4.26 (s, 2H); IR: 3340, 1008 cm^{-1}; MS: *m/e* (rel intensity) 182 (M^+, trace), 164 (M^+-H_2O, 8), 149 (33), 135 (42), 93 (44), 55 (100). Found: C, 72.42; H, 10.11%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

The diol **11** (0.28 g, 1.5 mmol) was admixed with acetic anhydride (1 ml) and pyridine (0.1 ml) at room temperature for 50 min, all volatile material being evaporated with the aid of a vacuum pump. The residue was dissolved in 2,2,2-trifluoroethanol (1 ml). To the resulting solution was added dropwise at 0 °C a mixture of sulfuric acid (1 ml) and 2,2,2-trifluoroethanol (1 ml). The reaction mixture was stirred overnight and warmed up to room temperature. Work-up gave an oil (0.37 g) which was purified by preparative TLC (benzene–ether 10:1) to give *trans*-1,2-dimethylbicyclo[4.3.0]non-5-en-7-one (**12**) (R_f 0.40—0.52, 150 mg, 60% yield), bp 95—102 °C (bath temp)/0.06 Torr. The homogeneity of the sample was confirmed by GLC assay as well as ^{1}H-NMR assay using shift reagent, Eu(fod)$_3$. ^{1}H-NMR (CCl_4): δ 0.87 (d, J=7.2 Hz, 3H, CH–C$\underline{H}_3$), 1.19 (s, 3H, C–CH_3), 1.2—2.5 (m, 9H), 6.46 (t, J=3.6 Hz, 1H); IR: 1718, 1712, 1654, 1649 cm^{-1}; MS: *m/e* (rel intensity) 165 (M^++1, 11), 164 (M^+, 29), 149 (18), 122 (100), 107 (50), 93 (59), 79 (95). Found: C, 80.59; H, 9.93%. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83%.

Transformation of ***12*** *into* ***30***. Lithium metal (18 mg, 2.6 mmol) was dissolved at −78 °C in anhydrous liquid ammonia (distilled over sodium). To this blue solution was added dropwise the enone **12** (0.21 g, 1.29 mmol) dissolved in THF (12 ml). The blue color vanished at the completion of addition. After 4 min the cooling bath was removed and ammonia was allowed to evaporate over a period of 2 h. The residue was then treated with acetic anhydride (1 ml) in THF (6 ml) and stirred at room temperature for 45 min. Work-up followed by column chromatography (hexane–ether 15:1) gave the enol acetate **29** (178 mg, 66% yield). ^{1}H-NMR (CCl_4): δ 0.95 (d, J=7.0 Hz), 1.18 (s), 2.03 (s, $OCOCH_3$).

The dichloromethane (5 ml) solution of **29** (101 mg, 0.49 mmol) was allowed to react with ozone at −78 °C until the solution turned slightly blue. Quenching with dimethyl sulfide (0.5 ml) at −78 °C, warming to room temperature followed by concentration and purification on preparative TLC plate (hexane–ether 1:1) gave a keto carboxylic acid (R_f 0.05—0.27, 29 mg, 31% yield), IR ($CHCl_3$): 3600—2400, 1710 cm^{-1}.

The keto carboxylic acid (28 mg, 0.14 mmol) was heated with sodium acetate (30 mg, 0.37 mmol) in acetic anhydride (3 ml) at reflux temperature for 2.3 h. Work-up followed by preparative TLC (hexane–ether 1:1, R_f 0.38—0.49) gave the enol lactone **30**[13] (8 mg, 32% yield) having ^{1}H-NMR ($CDCl_3$): δ 0.95 (d, J=6.8 Hz, 3H, CHC$\underline{H}_3$), 1.20 (s, 3H, C–CH_3), 1.2—2.3 (m, 7H), 2.62 (dd, J=8.5, 6.0 Hz, 2H), 5.30 (quintet, J=3.0 Hz, 1H); IR (CCl_4): 1758, 1680, 1132 cm^{-1}; MS: *m/e* 180 (M^+). The reported chemical shift ($CDCl_3$) of **30**:[13] δ 0.96 (d, 3H, J=6.5 Hz), 1.21 (s, 3H), and its *cis* isomer: δ 0.96 (d, 3H, J=6.0 Hz), 1.03 (s, 3H).

*Cyclopentannulation of 4-Isopropyl-2-methylcyclohexanone (****13****) with 3-Butyn-2-ol.* **13** (0.33 g, 2.1 mmol) was added at 40 °C over a period of 2 h to a solution of potassium hydroxide (0.62 g, 11.0 mmol) dissolved in 55% aqueous solution of 3-butyn-2-ol (0.58 g, 4.5 mmol). After 16 h, the reaction mixture was worked up to give an oil (580 mg) which was purified by column chromatography (hexane–ether 1:1) to give 4-isopropyl-1-(3-hydroxy-1-butynyl)-2-methylcyclohexanol (**14**) as a viscous oil (0.42 g, 87% yield). TLC (hexane–ether 1:1) showed roughly two spots at R_f 0.09 and 0.14, but these were not separated. Bp 118—126 °C (bath temp)/0.08 Torr. ^{1}H-NMR (CCl_4): δ 0.87 (d, J=6.0 Hz, 6H, CH(C$\underline{H}_3$)$_2$), 1.02 (d, J=6.0 Hz, 3H, CHC$\underline{H}_3$), 1.1—2.2 (m+d (δ 1.43 J=6.0 Hz), 12H), 3.9—4.3 (br s, 2H, OH),

4.3—4.7 (m, 1H, CH(OH)); IR: 3346, 1120, 1071 cm^{-1}; MS: *m/e* (rel intensity) 224 (M^+, trace), 206 (8), 191 (15), 163 (16), 107 (24), 57 (72), 43 (100). Found: C, 75.18; H, 10.55%. Calcd for $C_{14}H_{24}O_4$: C, 74.95; H, 10.78%.

Sulfuric acid (1.5 ml) was added to a methanol (1.5 ml) solution of **14** (0.34 g, 1.5 mmol) at 0 °C over a period of 15 min and the resulting solution was stirred at 0 °C for 30 min and then worked up to give an oil (0.33 g) which was purified by preparative TLC (hexane–ether 1:1), giving a mixture of 3-isopropyl-*cis*-1,9-dimethylbicyclo[4.3.0]non-5-en-7-one (**15** and **16**) (R_f 0.60—0.71, 196 mg, 64% yield), bp 123—127 °C (bath temp)/0.05 Torr. The ratio of **15** to **16** was estimated by GLC (PEG 20 M, 10% on Celite 545, 2 m, 170 °C, N_2 carrier gas 0.8 kg/cm^2, FID detector) to be 85:15, R_t being 18.4 min and 19.7 min respectively. The ratio was alternatively estimated to be 83:17 by ^{1}H-NMR (CCl_4): δ 0.91 (s, 3H, CCH_3), 0.92 (d, J=6.2 Hz, 6H, $CH(CH_3)_2$), 1.03 (d, J=5.7 Hz, 3H, $CHCH_3$), 1.1—2.4 (m, 9H), 6.36 (t, J=3.3 Hz, 0.17 H), 6.53 (dd, J=7.7, 3.0 Hz, 0.83H). IR: 1715, 1652 cm^{-1}; MS: *m/e* (rel intensity) 206 (M^+, 31), 191 (9), 178 (6), 164 (87), 121 (100). Found: C, 81.55; H, 10.98%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

Transformation of a Mixture of ***15*** *and* ***16*** *into a Mixture of* ***31*** *and* ***32***. Lithium dicyclohexylamide generated from butyllithium hexane solution (1.79 M, 2.5 ml, 4.4 mmol) and dicyclohexylamine (0.79 g, 4.4 mmol) in THF (3 ml) at 0 °C was added dropwise at −78 °C over a period of 1.5 h to a mixture of dibromomethane (0.76 g, 4.4 mmol), **15** and **16** (0.36 g, 1.76 mmol) in THF (7 ml) under an argon atmosphere. Stirring was continued for 1.5 h, and the reaction was stopped by addition of methanol (1 ml) at −78 °C. The reaction mixture was then allowed to warm to room temperature and treated with saturated aqueous ammonium chloride solution (20 ml). The precipitated material was filtered off and the filtrate was extracted with ether (20 ml×4 times). The ethereal phase was dried with anhydrous sodium sulfate, and concentrated *in vacuo* to give an oil (1.00 g) which was purified by column chromatography (hexane–benzene 1:1) to give the adduct (R_f 0.47—0.56, 0.45 g, 67% yield; 74% yield based on the consumed starting material) along with the starting material (36 mg, 10%). ^{1}H-NMR (CCl_4) of the adduct: δ 0.91 (d, J=6.0 Hz, 6H), 0.95 (d, J=6.4 Hz, 3H), 1.00 (s, 3H, CCH_3), 1.1—2.7 (m, 9H), 5.76 (s, 1H, $CHBr_2$), 5.6—6.1 (m, 1H); IR: 3435, 1120 cm^{-1}.

Butyllithium hexane solution (1.79 M, 1.40 ml, 2.5 mmol) was added at −95 °C over a period of 20 min to the above adduct (0.39 g, 1.0 mmol) in THF (8 ml) under an argon atmosphere. The reaction mixture was stirred at −95 °C for 1.7 h, at 0 °C for 5 min and then quenched with water (10 ml). Work-up followed by preparative TLC (benzene) gave an octalone (R_f 0.24—0.36, 186 mg, 83% yield). Bp 120—125 °C (bath temp)/0.06 Torr. IR: 1721, 1661 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.90 (d, J=6.3 Hz, 6H, $CH(CH_3)_2$), 0.91 (d, J=6.3 Hz, 3H, $CHCH_3$), 1.09 (s, 3H, CCH_3), 1.1—2.3 (m, 9H), 2.69 (dm, J=15.0 Hz, 1H, one of C(7) methylene), 3.20 (dm, J=15.0 Hz, 1H, the other of C(7) methylene), 5.3—5.5 (m, 1H); MS: *m/e* (rel intensity) 220 (M^+, 30), 178 (19), 177 (29), 107 (100), 93 (49), 91 (38), 79 (35), 77 (24), 69 (30). Exact mass, found: *m/e* 220.1827 (M^+). Calcd for $C_{15}H_{24}O$: *m/e* 220.1827.

A mixture of the octalone (103 mg, 0.47 mmol), THF (1.5 ml), and 5% sulfuric acid (1.5 ml) was stirred overnight vigorously. Work-up and preparative TLC separation gave a mixture of the conjugated octalones **31** and **32** (R_f 0.55—0.67, 48 mg, 47% yield, 79% yield based on the recovered octalone) along with the starting unconjugated octalone (42 mg, 41%). The bp of **31** and **32**: 121—123 °C (bath temp)/0.06 Torr; ^{1}H-NMR (CCl_4): δ 0.87 (d, J=6.0 Hz, 6H, $CH(CH_3)_2$), 0.97 (d, J=6.0 Hz, 3H, $CHCH_3$), 1.05 (s, 3H, CCH_3), 1.1—2.6 (m, 11H), 5.59 (br s, 0.18 H), 5.65 (br s, 0.82 H); ^{1}H-NMR ($CDCl_3$): δ 5.75 (br s, 0.18H), 5.80 (br s, 0.82H). IR: 3030, 1663, 1627 cm^{-1}; MS: *m/e* (rel intensity) 220 (M^+, 22), 178 (39), 177 (24), 135 (48), 108 (28), 107 (28), 91 (24), 79 (27), 55 (22), 40 (100). Found: C, 81.49; H, 11.23%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

GLC retention times of these samples (glass capillary column, 30 m×0.3 mm, SF-96 at 180 °C) were 27.4 min and 28.0 min, respectively, identical with those of the authentic samples (*vide infra*).

*An Authentic Sample of 11,12-Dihydro-7-*epi*-nootkatone* ***(31)***. A mixture of 7-*epi*-nootkatone[15] (43 mg, 0.2 mmol) and chlorotris(triphenylphosphine)rhodium(I) (20 mg) in benzene (2 ml) was stirred under a hydrogen atmosphere at room temperature for 19 h. Concentration followed by preparative TLC (benzene–ether 5:1, R_f 0.40—0.52) gave **31** (35 mg, 81% yield). ^{1}H-NMR (CCl_4): δ 0.86 (d, J=6.3 Hz, 6H, $CH(CH_3)_2$), 0.96 (d, J=6.5 Hz, 3H, $CHCH_3$), 1.046 (s, 3H, CCH_3), 1.1—2.6 (m, 11H), 5.65 (br s, 1H); IR: 1665, 1617 cm^{-1}. A *ca.* 1:1 mixture of 7-*epi*-nootkatone and nootkatone was also hydrogenated under similar conditions to give the corresponding dihydro derivatives of *ca.* 1:1 mixture which showed ^{1}H-NMR (CCl_4) absorptions: two broad singlets at δ 5.59, 5.65, and two singlets at 1.046 and 1.066.

An Authentic Sample of 11,12-Dihydronootkatone ***(32)***[16a] exhibited ^{1}H-NMR (90 MHz) peaks at δ 5.75 (br s) and 1.066 (s) in $CDCl_3$, and 5.60 (br s) in CCl_4. GLC coinjection experiments revealed an identical R_t to that of the minor product, **32**.

Cyclopentannulation of 4-Isopropenyl-2-methylcyclohexanone ***(17)*** *with 3-Butyn-2-ol.* **17** (149 mg, 0.98 mmol) was added at 40 °C to a mixture of potassium hydroxide (0.24 g, 4.3 mmol) and 55% aqueous solution of 3-butyn-2-ol (193 mg, 1.50 mmol), and the resulting mixture was stirred at 40 °C overnight. Work-up followed by preparative TLC gave the adduct **18** (154 mg, 71% yield). ^{1}H-NMR (CCl_4): δ 1.01 (d, J=7.2 Hz, 3H), 1.44 (d, J=6.5 Hz, 3H), 1.1—2.3 (m, 8H), 1.71 (s, 3H), 4.1 (br s, 2H, OH), 4.4—4.7 (m+br s at δ 4.63, 2H); IR: 3355, 1642, 1040, 889 cm^{-1}; MS: *m/e* (rel intensity) 222 (M^+, trace), 204 (M^+-H_2O, 6), 189 (13), 107 (51), 79 (42), 55 (56), 43 (100). Exact mass, found: *m/e* 204.1500 (M^+-H_2O). Calcd for $C_{14}H_{20}O$: *m/e* 204.1512 (M^+-H_2O).

Sulfuric acid (0.5 ml) was added at 0 °C to a methanol (0.5 ml) solution of **18** (43 mg, 0.19 mmol) over a period of 15 min. After 30 min the reaction mixture was worked up and the crude product purified by preparative TLC (hexane–ether 1:1, R_f 0.66—0.76) to give 3-isopropyl-*cis*-1,9-dimethylbicyclo[4.3.0]nona-3,5-dien-7-one (**19**) (22 mg, 55% yield). ^{1}H-NMR (CCl_4): δ 0.91 (s, 3H, CH_3), 1.07 (d, J=6.6 Hz, 6H, $CH(CH_3)_2$), 1.09 (d, J=6.6 Hz, 3H, $CHCH_3$), 1.8—2.6 (m, 6H), 5.85 (dm, J=5.4 Hz, 1H), 6.53 (d, J=5.4 Hz, 1H); IR: 1702, 1644, 1574, 835 cm^{-1}; MS: *m/e* (rel intensity) 204 (M^+, 23), 161 (21), 147 (70), 119 (100), 91 (28). Exact mass, found: *m/e* 204.1493 (M^+). Calcd for $C_{14}H_{20}O$: *m/e* 204.1513.

Cyclopentannulation of 4-(2-Methyl-1,3-dioxolan-2-yl)-2-methylcyclohexanone ***(20)*** *with 3-Butyn-2-ol.* The keto acetal **20**[27] (0.60 g, 3.0 mmol) was added over a period of 2 h to a solution of potassium hydroxide (0.65 g, 11.6 mmol) in 55% aqueous 3-butyn-2-ol (0.64 g, 5.0 mmol) at 40 °C and the resulting mixture was stirred overnight. Work-up

followed by column chromatography (ether) gave the adduct **21** (0.40 g, 48% yield; 84% yield based on the consumed **20**) along with the recovered **20** (0.25 g, 42%). The adduct showed ^{1}H-NMR (CCl_4): δ 1.18 (s, 3H), 0.9—1.3 (m, 6H), 1.3—2.3 (m, 8H), 3.87 (br s, 6H), 4.4—4.7 (m, 1H); IR: 3420, 1038 cm^{-1}; MS: *m/e* (rel intensity) 253 (M^+-CH_3, 4), 87 (100). Exact mass, found: *m/e* 253.1312 (M^+-CH_3). Calcd for $C_{14}H_{21}O_4$: *m/e* 253.1332.

Sulfuric acid (1.0 ml) was added at 0 °C over a period of 15 min to **21** (92 mg, 0.34 mmol) dissolved in methanol (1.0 ml), and the reaction mixture was stirred for 30 min. Work-up followed by preparative TLC (hexane–ether, 1:1, R_f 0.21—0.35) gave 3-acetyl-*cis*-1,9-dimethylbicyclo[4.3.0]-non-5-en-7-one (**22**, 24 mg, 34% yield). Bp 120—128 °C (bath temp)/0.05 Torr. ^{1}H-NMR (CCl_4): δ 0.99 (s, 3H), 1.09 (d, J=6.5 Hz, 3H), 1.1—3.0 (m, 8H), 2.16 (s, 3H), 6.42 (t, J=3.0 Hz, 1H); IR (CH_2Cl_2): 1708, 1654, 1249, 894 cm^{-1}; MS: *m/e* (rel intensity) 206 (M^+, 1), 204 (11), 163 (100), 121 (59). Exact mass, found: *m/e* 206.1324 (M^+). Calcd for $C_{13}H_{18}O_2$: *m/e* 206.1307.

*Synthesis of Methyl 3-Methyl-4-oxocyclohexanecarboxylate (**23**).* A mixture of 2-methyl-3-trimethylsilyloxy-1,3-butadiene[19] (158 mg, 1.0 mmol) and methyl acrylate (175 mg, 2.0 mmol) dissolved in benzene (1 ml) was heated in a sealed tube at 160—180 °C for 4 h. After cooling to room temperature the volatile material was evaporated with a water-aspirator, and the residue was dissolved in 90% methanol (20 ml) containing potassium fluoride (*ca.* 0.2 g). After 4 h the reaction mixture was diluted with water (10 ml) and extracted with ether (20 ml×4 times). The ethereal extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a crude product (172 mg) which was purified by preparative TLC. The desired product **23**[18] at R_f 0.10—0.23 weighed 134 mg, 78% yield.

A large scale synthesis was carried out by using the diene (15.5 g, 0.10 mol), methyl acrylate (17.2 g, 0.20 mol) in benzene (10 ml) at 184—191 °C for 4 h and by hydrolyzing the resulting enol silyl ether with 20% acetic acid (30 ml) and methanol (30 ml) at room temperature for 1 h. The product (13.1 g, 77% yield) was collected by distillation at 140—142 °C/18 Torr. ^{1}H-NMR (CCl_4): δ 0.99 (d, J= 6.0 Hz, 3H), 1.1—2.9 (m, 8H), 3.66 (s, 3H); IR: 1735, 1710, 1195 cm^{-1}; (Found: C, 63.42; H, 8.26%).

*Synthesis of 3-Methoxycarbonyl-*cis*-1,9-dimethylbicyclo[4.3.0]non-5-en-7-one (**25**).* The keto ester **23** (0.39 g, 2.3 mmol) was added at 40 °C over a period of 1 h to potassium hydroxide (0.84 g, 14.9 mmol) dissolved in 55% aqueous solution (0.67 g, 5.3 mmol) of 3-butyn-2-ol and the mixture was allowed to react overnight. Dilution with water (10 ml), acidification with 10% hydrochloric acid, extraction with ether (20 ml×4 times), followed by drying (Na_2SO_4), and concentration gave a viscous oil (0.68 g) which was purified by column chromatography (ether) to give 4-hydroxy-4-(3-hydroxy-1-butynyl)-3-methylcyclohexanecarboxylic acid (**24**) (0.45 g, 86% yield). IR: 3650—2400, 1704 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.0—1.2 (d, 3H, CHC$\underline{H}_3$), 1.2—2.7 (m+2d (δ 1.43 and 1.47 each J=6.0 Hz), 11H), 4.4—4.9 (m, 3H, HO-C$\underline{H}$ and OH). No peak due to the carboxyl group was observable. However, treatment of **24** with diazomethane gave the methyl ester (δ 3.68, s).

A large scale experiment using **23** (7.3 g, 43 mmol), potassium hydroxide (13.5 g, 0.24 mol) and 55% aqueous solution 3-butyn-2-ol (10.4 g, 82 mmol), afforded 8.9 g of **24** (91% yield).

Sulfuric acid (0.3 ml) was added at room temperature to **24** (24 mg, 0.11 mmol) dissolved in methanol (0.3 ml). The mixture was then heated at 50 °C for 30 min. Work-up followed by preparative TLC (hexane–ether 1:1, R_f 0.27—0.41) gave 3-methoxycarbonyl-*cis*-1,9-dimethylbicyclo-[4.3.0]non-5-en-7-one (**25**) (15 mg, 60% yield), bp 139—145 °C (bath temp)/0.05 Torr. ^{1}H-NMR (CCl_4): δ 0.84 and 0.98 (2s, 3H, CCH_3), 1.07, 1.09 (2d, J=6.0 Hz, 3H), 1.1—2.9 (m, 8H), 3.83 (s, 3H, CH_3COO), 6.3—6.6 (m, 1H). ^{13}C-NMR ($CDCl_3$) showed two peaks at δ 128.72 and 129.09 ($\underline{C}H_3O\underline{C}O$), with the ratio 1.9:1. IR: 1735, 1719, 1654, 1200 cm^{-1}; MS: *m/e* (rel intensity) 222 (M^+, 23), 207 (12), 180 (14), 163 (39), 121 (100), 93 (57), 77 (24). Found: C, 70.15; H, 8.40%. Calcd for $C_{15}H_{18}O_3$: C, 70.24; H, 8.16%.

A large scale experiment using **24** (8.9 g), methanol (25 ml), sulfuric acid (25 ml) resulted in 49% yield (4.3 g) of **25**.

Synthesis of t-*3-Isopropenyl-*r-*1,*c-*9-dimethylbicyclo[4.3.0]non-5-en-7-one (**38**).* A methanol (2 ml) solution of sodium borohydride (76 mg, 2.0 mmol) was added at room temperature to a mixture of **25** (0.45 g, 2.0 mmol) and cerium-(III) chloride heptahydrate (0.30 g, 0.80 mmol) in methanol (5 ml). After 20 min the reaction mixture was worked up to give a crude allyl alcohol **39** (0.50 g), which was dissolved in methanol (5 ml), treated with potassium hydroxide (0.23 g, 4.1 mmol) in water (5 ml) at room temperature and heated at 80 °C for 30 min. The reaction mixture was acidified with 5% hydrochloric acid and then extracted with ethyl acetate. The crude product thus obtained was dissolved in ether (5 ml) and methyllithium (1.14 M ether solution, 7.9 ml, 9.0 mmol) was added at 0 °C under an argon atmosphere and allowed to react for 2 h. Work-up followed by column chromatography (hexane–ethyl acetate 2:1) gave **40** (0.20 g, 49% yield, 97% yield based on the recovered **39**) along with **39** (0.21 g, 50%). The methyl ketone **40** showed IR: 3210, 1705 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.7—1.0 (m, 6H), 1.0—2.9 (m, 8H), 2.15 (s, 3H), 3.4—3.8 (br s, 1H), 4.2—4.7 (m, 1H), 5.5—5.7 (m, 1H).

Sodium hydride (50% in oil, 0.24 g, 5.0 mmol) was added to DMSO (2 ml) under an argon atmosphere and heated at 80 °C for 30 min. The resulting solution was cooled with a water bath and admixed with a DMSO (2 ml) solution of triphenylmethylphosphonium bromide (2.7 g, 4.8 mmol). After 15 min **40** (0.25 g, 1.20 mmol) in DMSO (5 ml) was added to the resulting red solution. After 1 h the reaction mixture was worked up. The crude product was dissolved in dichloromethane (2 ml) and added to pyridinium chlorochromate (1.33 g, 5.0 mmol) in dichloromethane (5 ml) at room temperature and allowed to react for 1. 5h. Work-up and preparative TLC purification (hexane–ether 1:1) gave **38** (0.20 g, 80% yield), bp 128—135 °C (bath temp)/0.3 Torr. ^{1}H-NMR (CCl_4): δ 1.00 (s, 3H, CCH_3), 1.07, 1.10 (2d, J=6.0 Hz, 3H, CHC$\underline{H}_3$), 1.5—2.7 (m, 8H), 1.76 (s, 3H, C$\underline{H}_3$C=CH_2), 4.72 (br s, 2H, CH_2=C), 6.39 (t, J=3.6 Hz, 0.88H), 6.53 (m, 0.12 H); IR: 3086, 1718, 1654, 886 cm^{-1}; MS: *m/e* (rel intensity) 204 (M^+, 61), 189 (31), 161 (28), 147 (41), 136 (30), 133 (32), 119 (100), 105 (50), 93 (53), 91 (48), 77 (43). Found: C, 82.21; H, 9.73%. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87%.

*Alternative Route from **25** to **38**.* A mixture of **25** (0.68 g, 3.0 mmol), 1,2-ethanedithiol (0.43 g, 4.5 mmol), chloroform (10 ml) and boron trifluoride etherate (40 mg) was stirred at room temperature under an argon atmosphere. After 16 h boron trifluoride ethereate catalyst (5 drops, *ca.* 50 mg) was added and the reaction mixture was stirred for 24 h. Work-up followed by preparative TLC (hexane–ether 3:1) gave **36** (R_f 0.64—0.76, 0.51 g, 57% yield). ^{1}H-NMR (CCl_4): δ 0.8—1.1 (m, 6H), 1.1—3.0 (m, 8H), 3.0—3.5 (m, 4H, SCH_2CH_2S), 3.65 (s, 3H, CH_3OCO), 5.9—6.2

(m, 1H); IR: 1728, 1195, 1167 cm^{-1}; MS: *m/e* 298 (M^+).

A mixture of **36** (126 mg, 0.42 mmol), methanol (2 ml), potassium hydroxide (53 mg, 0.95 mmol) dissolved in water (2 ml) was heated to reflux for 1 h. The reaction mixture was extracted once with ether and acidified with 10% hydrochloric acid. Extractive work-up with ether (20 ml×4 times) gave the carboxylic acid (120 mg) which was dissolved in ether (2 ml) at 0 °C. To this solution was added methyllithium (1.66 M ether solution, 0.76 ml, 1.26 mmol) over a period of 5 min and the resulting solution was stirred at 0 °C for 4.5 h. Work-up followed by preparative TLC (hexane–ether 2:1) gave the corresponding methyl ketone (78 mg, 66% yield). IR: 1707 cm^{-1}; ^{1}H-NMR (CCl_4, * refers to the major isomer): δ 0.79, 0.97 (s, 3H, CCH_3), 0.93*, 0.97 (d, J=7.0*, 7.5 Hz respectively, 3H), 1.1—2.9 (m, 8H), 2.13*, 2.10 (s, 3H, CH_3CO), 3.0—3.5 (m, 4H, SCH_2CH_2S), 5.97 (t, J=3.0 Hz, 0.29 H), 6.06* (dd, J=6.0, 3.0 Hz, 0.71 H); MS: *m/e* 282 (M^+).

The methyl ketone (73 mg, 0.26 mmol) was allowed to react with triphenylphosphonium methylide (0.52 mmol) in DMSO (7 ml) at room temperature for 2.3 h. Work-up followed by preparative TLC (hexane–ether 5:1) gave the corresponding isopropenyl derivative **37** (69 mg, 96% yield). ^{1}H-NMR (CCl_4): δ 0.91 (d, J=6.0 Hz, 3H), 0.97 (s, 3H, CCH_3), 1.0—2.7 (m, 8H), 1.73 (s, 3H, CH_3C=), 3.0—3.5 (m, 4H, SCH_2CH_2S), 4.67 (br s, 2H, CH_2=C), 5.96 (t, J=3.6 Hz, 1H). Careful examination of the olefinic region confirmed purity >97%. IR: 3090, 1642, 887 cm^{-1}; MS: *m/e* 280 (M^+).

Hydrolysis of the dithioacetal group was carried out by mixing **37** (40 mg, 0.14 mmol) in dichloromethane (1 ml) with isopentyl nitrite (19 mg, 0.16 mmol) and 30 min after with water (9 mg, 0.5 mmol). After 1.5 h isopentyl nitrite (0.5 ml) was added to complete the reaction and the entire mixture was stirred for 14.3 h. Work-up and preparative TLC purification (hexane–ether 1:1) gave the key intermediate **38** (14 mg, 48% yield) having the correct spectra. ^{1}H-NMR (CCl_4) gave olefinic absorption at δ 6.41 (t, J=3.6 Hz, 1H) only, thus indicating the purity higher than 97%.

Synthesis of dl-*Nootkatone.* A THF (2 ml)–hexane (1.6 ml) solution of lithium dicyclohexylamide (2.6 mmol) was added dropwise at −78 °C over a period of 2 h to **38** (88% purity) (177 mg, 0.87 mmol), dibromomethane (0.31 g, 1.77 mmol) dissolved in THF (5 ml) under an argon atmosphere, and the reaction mixture was stirred for 1 h, and then quenched with methanol (1.0 ml) at −78 °C. Work-up and preparative TLC (benzene) gave the adduct **41** (198 mg, 60% yield; 84% yield based on the consumed **38**) along with the recovered **38** (50 mg, 28%). ^{1}H-NMR (CCl_4): δ 0.98 (d, J=4.5 Hz, 3H, $CHC\underline{H}_3$), 1.07 (s, 3H, CCH_3), 1.1—2.7 (m, 8H), 1.74 (s, 3H, $C\underline{H}_3$-C=), 4.69 (s, 2H, CH_2=C), 5.66 (t, J=3.6 Hz, 1H), 5.81 (s, 1H, $CHBr_2$); IR: 3450, 3085, 1643, 888 cm^{-1}; MS: *m/e* 205 (M^+-CHBr_2).

A butyllithium hexane solution (1.57 M, 0.94 ml, 1.47 mmol) was added over a period of 20 min to the adduct **41** (185 mg, 0.49 mmol) in THF (10 ml) at −95 °C under an argon atmosphere. Stirring was continued at −95 °C for 100 min, and then at room temperature for 5 min. Work-up and preparative TLC (benzene) gave *t*-8-isopropenyl-*r*-5,*c*-6-dimethylbicyclo[4.4.0]dec-10(1)-en-3-one (**42**) (89 mg, 83% yield). ^{1}H-NMR (CCl_4): δ 0.97 (d, J=6.5 Hz, 3H, CH-C$\underline{H}_3$), 1.17 (s, 3H, CCH_3), 1.1—2.5 (m+s (δ 1.75), 11H), 2.73 d, J=16.5 Hz, 1H), 3.10 (dm, J=16.5 Hz, 1H), 4.70 (br s, 2H, CH_2=C), 5.3—5.5 (m, 1H); IR: 3090, 1721, 1644, 887 cm^{-1}; MS: *m/e* 218 (M^+).

The octalone **42** (78 mg, 0.36 mmol) was stirred at room temperature in THF (3 ml) and 5% sulfuric acid (3 ml) for 4 h. Work-up followed by preparative TLC (hexane–ethyl acetate 5:1) gave *dl*-nootkatone (**43**) (45 mg, 58% yield; 74% yield based on the recovered **42** (17 mg, 22%)). The synthesized sample had IR absorptions at 3080, 1671, 1619, 887 cm^{-1}, and ^{1}H-NMR (CCl_4) at δ 0.97 (d, J=6.5 Hz, 3H), 1.13 (s, 3H), 1.1—2.6 (m, 10H), 4.67 (s, 2H), 5.61 (s, 1H) identical exactly with the spectra of the authentic specimen. Careful integration around δ 5.9—5.5 revealed that the sample has purity higher than 93%. The 7-*epi*-nootkatone should give a peak at δ 5.68.[15]

*Cyclopentannulation of 2-Cyclododecenone (**44**).* A butyllithium hexane solution (1.49 M, 8.8 ml, 13.1 mmol) was added dropwise at −78 °C to a THF (90 ml) solution of propargyl alcohol (0.37 g, 6.5 mmol) under an argon atmosphere, and the reaction mixture was stirred for 2 h. To this solution was added a THF (5 ml) solution of 2-cyclododecenone (0.78 g, 4.4 mmol) over 8 min, and the whole was stirred at −78 °C for 2 h, then allowed to warm to room temperature and stirred for 16 min. Work-up followed by column chromatography (hexane–ethyl acetate 2:1 to 1:1) gave 1-(3-hydroxy-1-propynyl)-2-cyclododecenol (**45**) (0.95 g, 92% yield) as colorless needles, mp 71.5—72.5 °C (hexane–dichloromethane, *ca.* 2:1). ^{1}H-NMR (CCl_4): δ 1.0—2.3 (m, 18H), 2.93 (br s, 2H), 4.22 (s, 2H), 5.40 (d, J=16.1 Hz, 1H), 5.80 (dt, J=16.1, 6.3 Hz, 1H); IR: 3300, 785, 760 cm^{-1}; MS: *m/e* (rel intensity): 236 (M^+, 1), 218 (30), 205 (13), 187 (11), 175 (11), 161 (16), 147 (21), 125 (47), 117 (100), 95 (100), 91 (87), 79 (63), 67 (53), 55 (89). Found: C, 76.24; H, 10.46%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

The adduct **45** (1.20 g, 5.1 mmol) was dissolved in methanol (80 ml) and cooled at −20 °C. To this solution was added sulfuric acid (40 ml) over a period of 40 min. The resulting mixture was stirred for 14 h, being allowed to warm to room temperature. The reaction mixture was diluted successively with ether (100 ml) and satd. aq sodium chloride solution (100 ml), and shaken vigorously. The ethereal layer was separated, neutralized with aq sodium hydrogencarbonate solution, dried with anhydrous sodium sulfate and concentrated. The residue purified by column chromatography (hexane–ethyl acetate 5:1) gave *trans*-bicyclo-[10.3.0]pentadeca-1(12),2-dien-13-one (**46**) (0.72 g, 65% yield) as a colorless needles, mp 87—87.5 °C (hexane–dichloromethane *ca.* 1:1). ^{1}H-NMR (CCl_4): δ 0.8—1.9 (m, 12H), 2.1—2.4 (m, 6H), 2.4—2.7 (m, 2H), 6.17 (dt, J=16.5, 4.5 Hz, 1H), 6.68 (d, J=16.5 Hz, 1H); IR (CCl_4): 1693, 1643, 1596, 972 cm^{-1}; UV (EtOH); λ_{max} 281 nm (log ε 4.3); MS: *m/e* (rel intensity) 218 (M^+, 38), 203 (4), 189 (6), 175 (8), 161 (10), 147 (17), 133 (100), 122 (35), 105 (17), 91 (33). Found: C, 82.37; H, 9.8%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

*3-Methylbicyclo[10.3.0]pentadec-1(12)-en-13-one (**53**).* A methylmagnesium iodide ether solution (4.6 ml, 3.7 mmol), THF (10 ml) and then copper(I) chloride (29 mg, 0.29 mmol) were added successively at 0 °C over a period of 11 min to a THF (5 ml) solution of the dienone **46** (0.40 g, 1.83 mmol) and copper(I) chloride (14 mg, 0.14 mmol) under an argon atmosphere. The mixture was stirred for 1.4 h, treated with ice–hydrochloric acid mixture and then extracted successively with ether and ethyl acetate. The combined organic phase was dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by preparative TLC (hexane–ethyl acetate 3:1) to give **53** (0.29 g, R_f 0.6—0.68, 68% yield; 74% yield based on the consumed **46**) along with the recovered dienone **46** (28 mg, R_f 0.55—0.60). Bp 157—159 °C (bath temp)/0.04 Torr. ^{1}H-NMR

(CCl_4): δ 0.9—3.0 (m+d (δ 1.08, J=6.6 Hz), 26H); IR: 1692, 1630 cm^{-1}; MS: *m/e* (rel intensity) 234 (M^+, 100), 219 (60), 191 (28), 177 (52), 163 (73), 149 (63), 135 (52), 121 (34), 110 (45), 79 (45), 155 (59). Found: C, 81.70; H, 11.45%. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18%.

*7-Methylcyclopentadecane-1,5-dione (**54**).* Sodium borohydride (0.56 g, 14.7 mmol) was added portionwise at 0 °C to the cyclopentenone **53** (0.29 g, 1.25 mmol) dissolved in a 5:1 mixture of methanol and water (17 ml) and the reaction mixture was stirred for 2.5 h. Work-up gave an allyl alcohol (0.32 g) which was dissolved in dichloromethane (14 ml) and treated at 0 °C with *m*-chloroperoxybenzoic acid (0.26 g, 1.5 mmol) dissolved in dichloromethane (14 ml). The reaction mixture was stirred at 0 °C for 1.2 h, quenched with satd. aq sodium sulfite solution and neutralized with aq satd. sodium hydrogencarbonate solution. Extraction with dichloromethane followed by concentration gave an epoxy alcohol (0.34 g) which was dissolved in pyridine (4 ml) and treated with *p*-toluenesulfonyl chloride (0.36 g, 1.87 mmol) at 0 °C under an argon atmosphere, and the whole was left at 0 °C for 21 h, then poured into 2 M hydrochloric acid solution, and extracted with ether. The usual work-up gave a crude epoxy tosylate (0.47 g) which was dissolved in a 3:2 mixture of dioxane–water (10 ml) and heated at reflux in the presence of calcium carbonate (185 mg, 1.85 mmol) for 24 h. Work-up followed by preparative TLC (hexane–ethyl acetate 2.5:1) afforded the desired diketone **54** (0.22 g, R_f 0.47—0.60, 71% overall yield). Bp 156—158 °C (bath temp)/0.05 Torr, ^{1}H-NMR (CCl_4): δ 0.8—2.9 (m+d (δ 0.91, J=5.7 Hz), 28H); IR: 1709 cm^{-1}; MS: *m/e* (rel intensity) 252 (M^+, 24), 195 (15), 167 (22), 128 (39), 97 (54), 69 (42), 55 (100). Found: C, 76.00; H, 11.39%. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18%.

dl-*Muscopyridine (**55**).* A mixture of the diketone (**54**) (90 mg, 0.36 mmol), ethanol (20 ml), and hydroxylamine hydrochloride (0.55 g, 0.79 mmol) was heated under an argon atmosphere at 150—160 °C in an autoclave (capacity 100 ml) for 17.6 h. After cooling the reaction mixture was taken in ether, and the ethereal solution was washed with aq satd. hydrogencarbonate solution, then dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (hexane–ethyl acetate 5:1) to give *dl*-muscopyridine (**55**) (54 mg, R_f 0.65—0.75, 65% yield). The synthetic sample exhibited the following spectra identical with those of the authentic chiral specimen. ^{1}H-NMR (CCl_4): δ 0.6—2.3 (m+d (δ 1.11, J=7.5 Hz), 18H), 2.3—3.0 (m, 4H), 6.83 (d, J=7.8 Hz, 2H), 7.42 (t, J=7.8 Hz, 1H), IR: 3065, 1589, 1575, 1453, 763, 743 cm^{-1}; MS: *m/e* (rel intensity) 231 (M^+, 88), 188 (38), 160 (41), 147 (31), 146 (41), 134 (59), 133 (34), 120 (100), 107 (97).

*Cyclopentannulation of 2-Cyclooctenone (**47**).* A butyllithium hexane solution (1.49 M, 20.1 ml, 30.0 mmol) was added to a THF (170 ml) solution of propargyl alcohol (0.84 g, 15.0 mmol) at −78 °C under an argon atmosphere, and the reaction mixture was stirred for 2.7 h. The solution was warmed to −55 °C, and to this was added a THF (6 ml) solution of 2-cyclooctenone (**47**) (1.24 g, 10.0 mmol) over a period of 10 min. The reaction mixture was stirred for 10.7 h, and warmed to 20 °C. Work-up gave an oil (2.2 g) which was purified by column chromatography to give 1-(3-hydroxy-1-propynyl)-2-cycloocten-1-ol (**48**) (0.92 g, 51% yield; 76% yield based on the consumed enone **47**) along with the recovered **47** (0.37 g, 30%). Physical properties of **48**: bp 170—173 °C (bath temp)/0.07 Torr; ^{1}H-NMR (CCl_4): δ 1.2—2.8 (m, 10H), 3.17 (br s, 2H), 4.24 (s, 2H), 5.25—5.7 (m, 2H); IR: 3350, 1063, 1035, 708 cm^{-1}; MS: *m/e* (rel intensity) 180 (M^+, 2), 106 (51), 91 (100), 77 (51), 55 (60). Found: C, 73.55; H, 8.95%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%.

The adduct **48** (68 mg, 0.38 mmol) was stirred with acetic anhydride (0.5 ml) and pyridine (0.05 ml) at room temperature for 1 h. All the volatile material was evaporated *in vacuo*. The residue was dissolved in methanol (1 ml) and to this was added sulfuric acid (1 ml) dropwise at −15 °C over a period of 10 min. The solution was stirred for 25 min, and warmed up to −5 °C. Work-up followed by preparative TLC (hexane–ethyl acetate 2:1) gave bicyclo-[6.3.0]undeca-1(8),2-dien-9-one (**49**) (26 mg, 42% yield). Bp 114—118 °C (bath temp)/0.08 Torr; ^{1}H-NMR (CCl_4): δ 1.3—1.9 (m, 4H), 1.9—2.7 (m, 8H), 5.7—6.4 (m, 2H); IR: 1693, 1620, 741 cm^{-1}; MS: *m/e* (rel intensity) 162 (M^+, 100), 133 (87), 115 (56), 91 (77). Found: C, 81.65; H, 8.98%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70%.

*Cyclopentannulation of 2-Cycloheptenone (**50**).* Butyllithium (1.49 M hexane solution, 8.4 ml, 12.5 mmol) was added dropwise to a THF (70 ml) solution of propargyl alcohol (0.35 g, 6.3 mmol) at −78 °C under an argon atmosphere and the resulting solution was stirred for 4.5 h and warmed to −25 °C. At this temperature 2-cycloheptenone (**50**) (0.46 g, 4.2 mmol) dissolved in THF (5 ml) was added in 3 min and the reaction mixture was stirred for 15 h and allowed to warm to room temperature. Work-up followed by column chromatography (hexane–ethyl acetate 1:1) gave 1-(3-hydroxy-1-propynyl)-2-cyclohepten-1-ol (**51**) (0.45 g, 65% yield); bp 169—172 °C (bath temp)/0.07 Torr; ^{1}H-NMR (CCl_4): δ 1.2—2.9 (m, 8H), 4.29 (s, 2H), 4.42 (br s, 2H), 5.7—5.9 (m, 2H); IR: 3330, 1072, 1015, 686 cm^{-1}; MS: *m/e* (rel intensity) 166 (M^+, 14), 148 (24), 119 (43), 115 (48), 98 (33), 92 (43), 91 (100), 79 (52), 78 (48), 77 (52), 47 (43), 65 (43), 55 (67). Found: C, 72.06; H, 8.78%. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%.

The diol **51** (68 mg, 0.41 mmol) was stirred with acetic anhydride (0.5 ml) and pyridine (0.05 ml) at room temperature for 1.5 h. The volatile material was evaporated off and the residue was dissolved in methanol (4 ml). To the solution was added sulfuric acid (2 ml) at −15 °C over a period of 5 min. Stirring was continued for 2.5 h and the reaction mixture was diluted with dichloromethane (5 ml), poured onto crushed ice (*ca.* 10 g), and the extracted with dichloromethane. The usual work-up followed by preparative TLC (hexane–ethyl acetate 2:1) gave bicyclo-[5.3.0]deca-1(7),2-dien-8-one (**52**) (30 mg, 49% yield); bp 124—126 °C (bath temp)/0.06 Torr; ^{1}H-NMR (CCl_4): δ 1.7—2.1 (m, 2H), 2.2—2.7 (m, 8H), 5.90 (d, J=11.6 Hz, 1H), 6.20 (dt, J=11.6, 5.0 Hz, 1H); IR: 1689, 1639, 1607, 726 cm^{-1}; MS: *m/e* (rel intensity) 148 (M^+, 65), 133 (26), 116 (58), 115 (65), 92 (35), 91 (100), 79 (25), 78 (35), 77 (25), 65 (21). Found: *m/e* 148.0876 (M^+). Calcd for $C_{10}H_{12}O$: *m/e* 148.0888.

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