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SYNTHETIC APPROACHES TO POLYHYDROXYAGAROFURANS†

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Abstract—In a synthetic approach to the polyhydroxyagarofurans found throughout the family Celastraceae, the Robinson annulation of hydroxycarvone with ethyl vinyl ketone has been repeated. In contrast to the reported results 10-epieudesma-4,11-diene-3,9-dione is the major product (43%) of the annulation and eudesma-4,11-diene-3,9-dione is a minor product (24%). The structure and stereochemistry of these isomers was determined by conversion to eudesmane derivatives of known structure and stereochemistry. The requisite isomer from the annulation, 10-epieudesma-4,11-diene-3,9-dione, was converted to 9-keto-α-agarofuran by epoxidation with *m*-chloroperoxybenzoic followed by reduction to a stereoisomeric mixture of 10-epieudesm-4-en-3,9,11-triols. Oxidation of this mixture with Jones reagent afforded the ketoagarofuran. This annulation and agarofuran synthesis has also been carried out using hydroxy-carvone and methyl vinyl ketone to afford 14-nor-9-keto-α-agarofuran.

The family Celastraceae is well known as a source of the tumor inhibitory compounds of the maytansine[1] and triptolide[2] groups; however, in addition to these substances, many of the plants of this family produce polyhydroxy sesquiterpenes based on the agarofuran ring system. These polyhydroxyagarofurans range in structural complexity from the relatively simple triol, isocelorbicol (**1**),[3] through compounds bearing nine hydroxyl groups, such as euonyminol.[4] Many of these polyols occur in nature as ester alkaloids, usually derived from nicotinic acid or substituted nicotinic acids.[5]

In an approach to the synthesis of these sesquiterpenes, we envisioned carrying out one of the established agarofuran syntheses,[6] modified to use as starting material a 9-oxygenated-10-epieudesmane derivative (e.g. 10-epieudesma-4,11-diene-3,9-dione (**2**). Based on the known stereochemical outcome of the Robinson annulation reaction,[7] dione **2** would be predicted to be the major product from the reaction of 2-methyl-5-isopropenylcyclohexane-1,3-dione (hydroxycarvone) with ethyl vinyl ketone. However, some years ago Lacoume and Zalkow reported that the alkylation of hydroxycarvone with ethyl vinyl ketone affords a triketone (**3**) which on cyclization with pyrrolidine gives ketol **4**. Dehydration of this ketol gives dione **5**, with the normal eudesmane configuration at C-10.[8] The stereochemistry of dione **5** was established by its conversion to eudesm-4-ene (**6**).[8]

Although these workers reported that the alkylation of hydroxycarvone produced exclusively triketone **3**, this seemed unlikely in view of the known stereochemistry of the alkylation of cyclohexanone enolates,[7] and a reinvestigation of Lacoume and Zalkow's annulation was undertaken. The starting material for this sequence, hydroxycarvone (2-methyl-5-isopropenyl-1,3-cyclohexanedione) was prepared many years ago by Treibs in low yield by the vigorous alkaline peroxide oxidation of carvone.[9] The procedure was modified by Lacoume and Zalkow, but the yields were still low and variable (25–40%).[10] We have further modified this preparation by isolating the epoxide formed by mild alkaline peroxide oxidation of carvone and carrying out the rearrangement to the diketone with warm base in a subsequent step. This procedure consistently affords yields of 60–70% of once recrystallized material. Alkylation of hydroxy-carvone under the reported conditions[8,10] gave material which appeared to be homogeneous (glc, tlc) and agreed in its spectral properties with those described by Lacoume.[10] Subsequent determination of the NMR spectrum under optimum conditions resolved the quaternary methyl singlet at δ 1.20 into a pair of singlets at δ 1.20 and 1.21, indicating that this material was actually a mixture. One component of this mixture is trione **3** and the other is presumably its epimer at the quaternary center (**7**). Cyclization of this mixture of triketones with pyrrolidine–acetic acid,[10] afforded in 32% yield a 3:1 mixture of ketol **4** and diketone **5**, both of which agreed in their spectral and physical properties with those of material prepared by Lacoume and Zalkow.[11]

On the assumption that the low yield of cyclized material and the failure to isolate or detect any products with the 10-epieudesmane stereochemistry was caused by a facile reverse Michael reaction of trione **7** under the weakly basic reaction conditions, the cyclization was repeated under mildly acidic conditions. Prolonged treatment of the mixture of triones with aluminum-t-butoxide in benzene[12] gave in low yield a mixture of three compounds, enone **5**, an isomer, subsequently shown to be enone **2**, and a ketol isomeric with ketol **4**. On the basis of its spectral properties and subsequent conversion to enone **2** on heating with p-toluenesulfonic acid in benzene, the isomeric ketol was assigned structure **8**. It was ultimately found possible to effect the conversion of the mixture of triketones **3** and **7** cleanly and in good yield to a mixture of enones **2** and **5** in a ratio of ca. 2:1 with *p*-toluenesulfonic acid in benzene. Although this cyclization method afforded the 10-epieudesmane derivative (**2**) as the major product, some effort was made to improve both the yield and stereoselectivity of

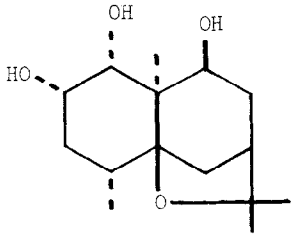
†Dedicated to the memory of Professor Robert Burns Woodward.

the initial alkylation. The use of methanolic potassium hydroxide as a catalyst increased the yield somewhat, however, neither this procedure nor the use of sodium hydride in the presence of excess hydroxycarvone caused a significant change in the ratio of stereoisomers obtained from the alkylation. As predicted, and in contrast to the published work of Lacoume and Zalkow,[8] the Robinson annulation of hydroxycarvone follows the normal stereochemical path and affords the 10-epieudesmane derivative as the major product. The earlier workers were apparently misled by the near identity of the physical and spectral properties of triones **3** and **7** combined with the failure of trione **7** to cyclize to the 10-epieudesmane (**2**) on heating with pyrrolidine–acetic acid.

Although there seemed to be no reason to question Lacoume and Zalkow's assignment of stereochemistry to dione **5**, there was some question at this stage regarding the two diones we had obtained from the acid catalyzed cyclization of the mixture of triones **3** and **7**. These diones have virtually identical IR and NMR spectra, the m.p.s of their dinitrophenylhydrazones are nearly the same and in our hands the m.p. of the monothioketal of enone **5** differs markedly from that reported.[8] In the absence of a comparison samples of enone **5** or a derivative, and prior to investigating synthetic routes to the agarofuran ring system, the stereochemical assignments of enone **2** and **5** were confirmed by their conversion to 10-epieudesm-4-ene (**9**) and eudesm-4-ene (**6**), respectively.

Enone **5** was converted to eudesm-4-en-9-one (**10**) by essentially the method described by Lacoume and Zalkow;[8] however, a number of attempts to repeat the reported desulfurization of the thioketal of ketone **10** afforded complex mixtures. Ketone **10** was, however, smoothly converted to eudesmene **6** by Wolff–Kishner reduction.

The conversion of enone **2** to 10-epieudesm-4-ene (**9**) followed essentially the same route as that used for the conversion of enone **5** to olefin **6**: selective



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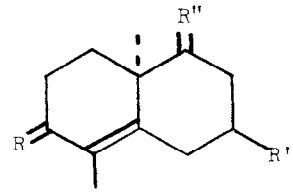
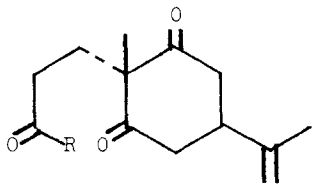
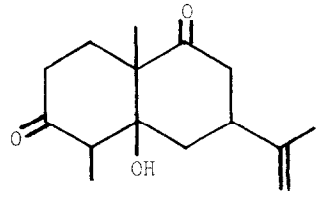


2 R,R"=O,R'=$CH_3CH{=}CH_2$
9 R,R"=H_2, R'=$(CH_3)_2CH$
11 R,R"=O, R'=$(CH_3)_2CH$
12 R=SCH_2CH_2S, R'=$(CH_3)_2CH$,R"=O
13 R=H_2,R'=$(CH_3)_2CH$, R"=O



3 R=C_2H_5
17 R=CH_3



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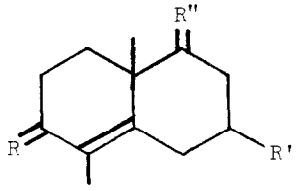
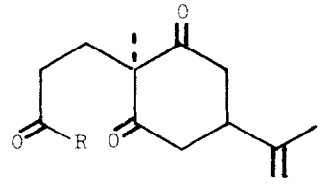
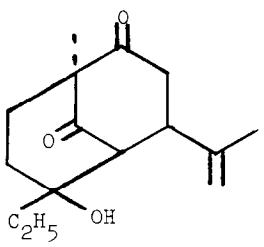


5 R,R"=O, R'=$CH_3CH{=}CH_2$
6 R,R"=H, R'=$(CH_3)_2CH$
10 R=H_2, R'=$(CH_3)_2CH$,R"=O
14 R=H, OH, R"=$(CH_3)_2COH$, R"=H_2



7 R=C_2H_5
18 R=CH_3



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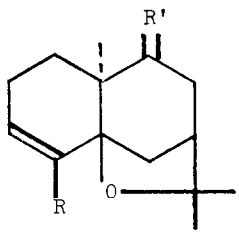
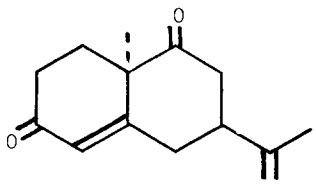


15 R=CH_3, R'=H_2
16 R=CH_3, R'=O
20 R=H, R'=O



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reduction to enone **11**, using Wilkinson's catalyst, conversion to monothioketal **12**, desulfurization of which afforded 10-epieudesm-4-en-9-one (**13**). Wolff–Kishner reduction of ketone **13** afforded 10-epieudesm-4-ene (**9**), identical to a sample prepared by an established method.[13]

Having confirmed that enone **2** has the requisite 10-epieudesmane structure, efforts to effect its conversion to an agarofuran derivative were initiated. The original synthetic design envisioned a modification of Büchi's agarofuran synthesis which leads to a 2-ketoagarofuran *via* the photooxygenation of 2,4-diene system. This route would provide the functionality necessary for the introduction of the 1α,2α-diol system characteristic of the vast majority of the polyhydroxyagarofurans isolated to date. The initial step of this proposed sequence was to be the preparation of the 2,4-diene derived from enone **2** by the lithium disiopropylamide induced decomposition of the corresponding tosylhydrazone.[14] Although this sequence was effective for the conversion of enone **5** to the corresponding 2,4-diene,[15] it failed in the case of enone **2**.

Several years ago we made the fortuitous observation that Jones oxidation of 3,11-dihydroxyeudesm-4-ene (**14**, epimers at C-3) gave α-agarofuran (**15**) in good yield.[6d] Accordingly, treatment of enone **2** with *m*-chloroperbenzoic acid afforded a mixture of epimeric 11,12-oxides, which on reduction with lithium aluminum hydride gave a mixture of stereoisomeric 3,9,11-triols. Jones oxidation of this mixture of triols proceeded smoothly to produce 9-keto-α-agarofuran (**16**) in 47% yield from enone **2** and an overall yield of 15% from hydroxycarvone.

In our synthetic design, the 4α-(axial) Me group, which is present in virtually all naturally occurring polyhydroxyagarofurans, is to be introduced by reduction of the unsaturation present in the ring-A of a suitably functionalized conversion product of agarofuran **16**. In anticipation of potential problems in obtaining stereoselectivity at this center, it was felt that as an alternative approach the addition of the 4α-Me group via a suitable organometallic reagent at some later stage in the synthesis might prove more satisfactory. Accordingly, the 14-nor analogue of 9-keto-α-agarofuran was prepared by a synthetic route essentially identical to that used for the synthesis of ketone **16**: Alkylation of hydroxycarvone with methyl vinyl ketone afforded a mixture of triones **17** and **18**, which on cyclization with *p*-toluenesulfonic acid gave a mixture of the 14-nor analogues of enones **3** and **5**. From this mixture 14-nor-10-epieudesma-4,11-diene-3,9-dione (**19**) was obtained as a crystalline solid and the stereochemistry at C-10 was tentatively assigned on the basis of the similarity of the NMR spectra of this compound to that of enone **2**. This assignment was confirmed by conversion to 14-nor-9-keto-α-agarofuran (**20**) by the route used for the preparation of ketone **16**. Although no difficulty in preparing ketone **16** was encountered, the overall yield from enone **19** was low and various modifications in this sequence have resulted in no significant improvement.

9-Keto-α-agarofuran (**16**) and its 14-nor analogue (**20**) are both reasonable substrates for the synthesis of various members of the polyhydroxyagarofuran group of sesquiterpenes. The synthetic routes described provide methods for preparing these potentially useful synthetic intermediates in sufficient quantity for their use as starting materials for the synthesis of isocelorbicol (**1**) and other representative members of this group of natural products.

EXPERIMENTAL

Microanalyses were performed by Atlantic Microlab, Atlanta, Georgia. IR Spectra were routinely measured as liquid films or as solns in CCl_4. NMR spectra were carried out in $CDCl_3$ and were recorded at 60 MHz using a Varian A60A spectrometer; signals are reported in parts per million

relative to TMS (δ). M.ps were obtained using a Kofler hot stage and are uncorrected. Mass spectra were determined at 70 eV using a Hewlett–Packard 5985B spectrometer.

2-Methyl-5-isopropenyl-1,3-cyclohexanedione (hydroxycarvone)

To a soln of 40.0 g (0.266 mol) *l*-carvone in 40 ml MeOH, previously cooled to 0° in an ice–salt bath, was added with stirring a soln of 32.0 g (0.570 mol) KOH in 40 ml water and 120 ml MeOH. To the resulting mixture at −5° was added in one portion, 30 ml 30% H_2O_2, previously cooled to −13°. The temp rose to 15° after 10 min. Another 35 ml portion of 30% H_2O_2 was added after 25 min, by which time the temp had fallen to −3°. The mixture was stirred at or slightly below 0° for 1 hr during which time an oily layer separated and 200 ml water were added. The mixture was extracted with four portions of benzene, the organic layers were combined, washed with water, and bring, dried and the solvent removed to give 43.9 g of pale yellow epoxide, which was sufficiently pure for further use; IR (CCl_4), 1708 cm^{-1}; NMR δ 1.35 (s, 3 H, CH_3), 1.68 (d, 3 H, J = 1 Hz, CH_3C=), 3.35 (dd, 1 H, J = 3 Hz, 1 Hz, –CHOC), (m, 2 H, H_2C=C). To 1 *l* of 1 N NaOH at room temp was added 43.9 g (0.264 mole) of crude epoxide and the heterogeneous mixture was heated on a steam bath and occasionally swirled until dissolution occurred (approximately 1 hr). The soln was cooled to room temp and acidified with 20% HCl aq. The resulting slurry was cooled to 0° and the ppt filtered off. The crude wet ppt was dissolved in 1.5 *l* EtOAc and the bulk of the water was removed by azeotropic distillation. On cooling there was obtained 29.3 g (60%) hydroxycarvone, m.p. 184–186° (Reported, 187–189°[10]). Concentration of the mother liquor afforded an additional 3.8 g (9%) material of similar purity; IR 1730, 1710, 1610 cm^{-1}; NMR δ 1.77 (s, 3 H, CH_3), 1.85 (d, 3 H, J = 1 Hz, CH_3C=), 2.61 (m, 5 H, CH_2–C=O, CH), 5.05 (q, 4 H, J = 1.5 Hz, H_2C=).

Alkylation of 2-methyl-5-isopropenyl-1,3-cyclohexane-dione with ethyl vinyl ketone

A. To a stirred soln of 5.00 g (0.03 mol) hydroxycarvone in 50 ml benzene containing 4 ml pyridine and maintained under N_2 was added 4.00 g (0.047 mol) ethyl vinyl ketone in 5 ml benzene. The mixture was heated at reflux for 19 hr, cooled and extracted with ether. The ethereal extracts were washed with dil HCl aq, sat $NaHCO_3$ aq and water. After drying the solvent was removed leaving a brown oil which on distillation (bp 120–150°, air bath, 0.05 mm) afforded 3.33 g (55% based on 0.023 mols hydroxycarvone consumed) of a mixture of **3** and **7**; IR, 1705, 1695 cm^{-1}; NMR δ 1.03 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.20, 1.21 (s, 3 H total, CH_3 for each isomer) 1.86 (m, 3 H, CH_3–C=), 2.96 (m, 4 H, CH_2COCH_2), 4.95 (m, 2 H, CH_2=C). Acidification of the basic extracts afforded 1.15 g of recovered hydroxycarvone.

B. To a stirred suspension of 2.76 g NaH (57% dispersion in mineral oil, washed thrice with dry hexanes) in 200 ml dry THF and maintained under N_2 was added 21.8 g (0.03 mol) hydroxycarvone and an additional 50 ml THF and the mixture stirred at ambient temp for 10 min. A soln of 5.50 g (0.065 mol) ethyl vinyl ketone in 75 ml dry THF was added dropwise. The mixture was stirred and heated at reflux for 18 hr, cooled, and 100 ml of 1.0 N HCl was added dropwise, followed by 200 ml water. The THF was removed with warming at reduced pressure and the aqueous suspension made alkaline by the cautious addition of solid KOH. The product was isolated as described in Part A to give 9.85 g (61% based on ethyl vinyl ketone) of a mixture of **3** and **7**, the spectral properties of which were identical to those described in part A.

C. To a soln of 54.4 g (0.328 mol) hydroxycarvone in 225 ml MeOH was added 25.0 g (0.290 mol) ethyl vinyl ketone and 12.5 ml of 11.7% (w/v) methanolic KOH. The mixture was stirred and heated at reflux 5.5 hr, cooled, and poured into 1000 ml water. The product was isolated as described above to give 53.6 g (74%) of a mixture of **3** and **7**, the spectral properties of which were identical to those described in part A.

Cyclization of triketones **3** *and* **7**

A. *With pyrrolidine-acetic acid.* To 1.00 g (0.004 mol) of the mixture of the epimeric triketones in 50 ml dry THF was added, with stirring and under N_2, 0.37 ml pyrrolidine, followed by the dropwise addition of 0.26 ml AcOH in 25 ml dry THF. The mixture was heated at reflux under N_2 for 4 hr, cooled, poured into ether and extracted with dil KOH aq. The organic layer was washed with successive portions of dil HCl and $NaHCO_3$, dried and the solvent removed to give 0.70 g partially crystalline material. Crystallization from hexanes afforded 0.24 g (24%) of **4**, m.p. 129–130° (lit m.p. 129–130°[8]). The IR and NMR spectra were identical to those of material prepared by Lacoume and Zalkow.[11]

The mother liquors were concentrated to dryness, the residue taken up in ether–hexanes (1:9) and chromatographed on Woelm silica gel. Elution with ether–hexanes afforded 0.070 g (8%) of **5** as a colorless oil, the IR and NMR of which were identical to those of the material prepared by Lacoume and Zalkow. The 2,4-dinitrophenyl hydrazone had m.p. 205–206° (reported: 207–208°[8]). Dehydration of **4** afforded **5** as described by Lacoume and Zalkow.[8]

B. *With aluminum t-butoxide.* A soln of 10.00 g (0.40 mol) of **3** and **7** in 250 ml dry benzene containing 12.3 g (0.050 mol) aluminum t-butoxide was heated at reflux under N_2 for 80 hr. The cooled mixture was poured into 800 ml 1 N HCl, the aqueous layer drawn off and extracted with ether. The organic extracts were combined, extracted with three portions of sat $NaHCO_3$ aq, washed with brine, dried and the solvent removed at reduced pressure to give 6.01 g brown oil which was dissolved in ether–hexanes (1:7) and chromatographed on Woelm silica gel. Elution with ether–hexanes mixtures afforded first 1.22 g (12%) of **5** followed by 1.46 g (15%) of (**2**); IR 1720, 1675, 1610 cm^{-1}; NMR δ 1.40 (s, 3 H, CH_3), 1.75 (s, 6 H, CH_3C=C), 4.56, 4.75 (m, 2 H, CH_2=C). The 2,4-dinitrophenylhydrazone formed red crystals from EtOAc cyclohexane, m.p. 200–202° (Found: C, 61.02; H, 5.92; N, 13.52. Calc. for $C_{21}H_{24}N_4O_5$: C, 61.16; H, 5.87, N, 13.58%).

The final ether–hexanes fractions afforded 0.493 (5%) bridged ketol as white crystals, m.p. 106–107° from hexanes: IR 1745, 1645 cm^{-1}; NMR δ 1.05 (s, 3 H, CH_3), 1.05 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.75 (s, 3 H, CH_3C=C), 4.75, 4.92 (m, 2 H, CH_2=C). (Found: C, 72.04, H, 8.87. Calc. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%). Acidification of the original bicarbonate extracts afforded 1.80 g of hydroxycarvone.

C. *With p-toluenesulfonic acid.* To a soln of 24.6 g (0.098 mols) of **3** and **7** in 1250 ml benzene was added 1.51 g *p*-toluenesolfonic acid. The mixture was stirred and heated at reflux under N_2 with the continuous removal of water for 72 hr. The products were isolated as described in part B, to give 6.00 g (24%) of **5** and 10.40 (43%) of **2**.

10-Epieudesma-4,11-diene-3,9-dione (**2**)

A soln of 0.83 g (0.033 mol) of bridged ketol **8** in 125 ml benzene containing 0.10 g *p*-toluenesulfonic acid was heated at reflux with the continuous removal of water for 5 hr. The mixture was cooled, washed with sat $NaHCO_3$ aq, dried and the solvent removed to give 0.77 g (100%) of **2** as a brown oil, the spectral properties of which were identical to those described above.

Eudesm-4-en-9-one (**10**)

This material was prepared from (**5**) following the method outlined by Lacoume and Zalkow.[8] The spectral data for all the intermediates and **10** agreed with those reported, as did their physical properties, with the exception of the monothioketal of eudesm-4-en-3,9-dione which in our hands has m.p. 64–65° (lit. m.p. 74–75°[8]) after repeated recrystallization from pentane.

Eudesm-4-ene (**6**)

To a soln of 0.047 g (0.00017 mol) semicarbazone of eudesm-4-en-9-one in 2 ml diethylene glycol was added

0.050 g KOH and two drops hydrazine hydrate. The mixture was heated with stirring and the solvent slowly distilled off until a vapor temp of 185 was attained, and then heated at reflux for 4.25 hr. The mixture was cooled and extracted with two portions hexanes. The hexane extracts were combined, washed with sat $NaHCO_3$ aq, dried and the solvent removed to give a brown oil which was dissolved in hexanes and chromatographed on Woelm silica gel to give 0.017 g (49%) of **6** as a colorless oil. The spectral properties agreed with those reported by Lacoume and Zalkow, and were markedly different from those of **9**.

10-Epieudesm-4-ene-3,9-dione (**11**)

To a soln of 0.814 g (0.00351 mol) of **2** in 40 ml benzene was added 0.401 g tris (triphenylphosphine) rhodium (I) chloride. The reaction flask was purged with H_2 for 20 min, sealed and stirred under H_2 for 25 hr. The mixture was filtered through a column of alumina and the solvent removed to give a yellow oil. Distillation (159–165°, air bath, 0.01 mm) gave 0.597 g (73%) of **11** as a colorless oil, IR, 1715, 1660, 1605 cm^{-1}; NMR δ 0.89 (d, J = 5.5 Hz, CH_3CH); 1.37 (s, 3 H, CH_3), 1.75 (s, 3 H, $CH_3C{=}C$). The 2,4-dinitrophenylhydrazone was obtained as red crystals from EtOAc-cyclohexane, m.p. 184–186° (Found: C, 60.90; H, 6.36; N, 13.49. Calc. for $C_{21}H_{26}N_4O_5$: C, 60.85; H, 6.32; N, 13.51%).

Monothioketal of 10-epieudesma-4-ene-3,9-dione (**12**)

To a stirred soln of 0.305 g (0.0013 mol) of **11** in 2 ml AcOH, under N_2, was added successively 0.122 g (0.0013 mol) ethanedithiol in 1 ml AcOH and 0.117 g *p*-toluenesulfonic acid in 1 ml AcOH. The mixture was stirred under N_2 for 14 hr, poured into water and extracted with three portions ether. The etheral extracts were combined, washed with 10% NaOH aq and sat $NaHCO_3$ aq, dried and the solvent removed to give a pale yellow semi-solid. This material was dissolved in ether–hexanes (1:24) and chromatographed on Woelm silica gel. Elution with ether–hexanes afforded 0.325 g (81%) crystalline thioketal, m.p. 107–108° after recrystallization from hexanes: IR 1720 cm^{-1}; NMR δ 0.90 (d, J = 5.5 Hz, 3 H, CH_3CH); 0.94 (d, J = 5.5 Hz, CH_3CH); 1.24 (s, 3 H, CH_3); 1.97 (s, 3 H, $CH_3C{=}$); 3.32 (br s, 4 H, $S(CH_2)_2S$). (Found: C, 65.79; H, 8.45. Calc. for $C_{17}H_{26}OS_2$: C, 65.76; H, 8.44%).

10-Epieudesm-4-en-9-one (**13**)

To a soln of 0.192 g (0.00062 mol) of **12** in 30 ml EtOH was added 4.0 ml (settled volume) Raney Ni suspended in 30 ml EtOH. The mixture was heated, with stirring, under N_2 for 30-hr, cooled, filtered through Celite and concentrated to afford 0.183 g yellow oil. The crude material was dissolved in ether-hexanes (1:9 and chromatographed on Woelm silica gel. Elution with the same solvent system afforded 0.106 g (78%) of **13** as a colorless oil. b.p. 70–80° (air bath, 0.025 mm); IR (CCl_4) 1715 cm^{-1}; NMR δ 0.98 (m, 6 H, $(CH_3)_2CH$); 1.22 (s, 3 H, CH_3); 1.68 (br s, 3 H, $CH_3C{=}$). (Found: C, 81.57; H, 11.00 Calc. for $C_{15}H_{24}O$: 81.76; H, 10.98%).

10-Epieudesm-4-ene (**9**)

To a soln of 0.033 g (0.00015 mol) of **13** in 3 ml triethylene glycol was added 0.493 g hydrazine hydrate and 0.125 g hydrazine hydrochloride. The mixture was heated to 130°, with stirring, and maintained at that temp for 2.5 hr. The mixture was cooled slightly, 0.184 g of solid KOH was added, and the temp increased to 210° for 2.5 hr. After cooling, 5 ml water was added and the mixture extracted with two portions water and sat $NaHCO_3$ aq, dried and the solvent removed at reduced pressure to give a pale yellow oil. This oil was taken up in hexanes and filtered through Woelm silica gel to give 0.025 g (77%) of **9**, which was identical in all respects (IR, NMR, glc) to a sample prepared by an alternative route.[13]

9-Keto-α-agarofuran (**16**)

To a stirred soln of 5.87 g (0.0253 mol) of **2** in 260 ml dry $CHCl_3$ was added 5.73 g *m*-chloroperbenzoic acid (80%). The mixture was stirred under N_2 for 30 hr, washed successively with two portions of 10% Na_2SO_3 aq, three portions of 10% NaOH aq, water and brine. After drying the solvent was removed to give 5.84 g of a mixture of epimeric epoxides which was used in the succeeding step without purification: NMR δ 1.31 (s, 3 H, $CH_3C(O)C$), 1.39 (s, 3 H, CH_3) 1.81 (s, 3 H, $CH_3C{=}C$).

To a stirred suspension of 2.66 g LAH in 200 ml dry ether at 0° under N_2 was added dropwise 5.84 g crude epoxide mixture in 100 ml dry ether. The reaction was stirred at 0° for 8 hr, warmed to room temp and stirred an additional 18 hr. After cooling to −10°, 2.7 ml water was added cautiously, followed by 2.7 ml 15% NaOH aq and 8.1 ml water. The ppt was filtered off and washed thoroughly with THF. Removal of the solvents afforded 6.0 g of a mixture of triols as a colorless glass, the IR of which showed no CO absorption. The crude mixture of triols was dissolved in 200 ml permanganate stable acetone and 11.0 ml Jones reagent was added dropwise with stirring. The mixture was stirred at ambient temp for 2.5 hr, poured into water and extracted with ether. The etheral extracts were washed with water, sat $NaHCO_3$ aq and brine, dried and the solvent removed at reduced pressure to give a yellow oil. This oil was dissolved in ether–hexanes (1:1) and chromatographed on Woelm silica gel. Elution with the same solvent pair gave 2.80 g (47%) of **16** as a nearly colorless oil, homogeneous to tlc, which crystallized on standing. A small portion was crystallized from pentane, m.p. 73–74°; IR 1750 cm^{-1}; NMR δ 1.04 (s, 3 H, CH_3), 1.19, 1.26 (s, 3 H each), $(CH_3)_2C{-}O$), 1.77 (br s, 3 H, $CH_3C{=}$); 5.55 (m, 1 H, HC=C). (Found, C, 76.84; H, 9.47. Calc. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%).

Alkylation of 2-methyl-5-isopropenyl-1,3-cyclohexanedione with methyl vinyl ketone

The alkylation of hydroxycarvone with methyl vinyl ketone was effected using methanolic KOH as described above for the preparation of **3** and **7**. From 25.4 g (0.153 mol) diketone and 9.07 g (0.129 mol) methyl vinyl ketone there was obtained 26.5 g (87%) of a mixture of **13** and **18** of sufficient purity for subsequent reactions. A small sample of the product triketones was distilled (b.p. 150°, air bath, 0.05 mm), to give a colorless oil. IR (CCl_4) 1725, 1700, 1645 cm^{-1}, NMR δ 1.20, 1.22 (s, total 3 H, CH_3 for each isomer), 1.76 (br s, 3 H, CH=), 2.07 (s, 3 H, CH_3CO), mass spectrum *m/e* (rel intensity), 236.2 (28), 179.2 (30), 178.2 (19, 125.1 (21), 123.1 (21), 110.1 (24), 109.1 (40), 95.1 (100).

14-Noreudesma-4,11-diene-3,9-dione and 14-nor-10-epieudesma-4,11-diene-3,9-dione (**19**)

Treatment of 26.50 g (0.112 mol) of **17** and **18** with *p*-toluenesulfonic acid in benzene as described above, followed by chromatography on Woelm silica gel and elution with EtOAc-cyclohexane (3:7) afforded 2.06 g (9%) 14-norcudesma-4,11-diene-3,9-dione as a colorless liquid (b.p. 150–155°, air bath, 0.05 mm); IR 1718, 1680, 1642, 1620 cm^{-1}; NMR δ 1.47 (s, 3 H, CH_3), 1.78 (br s, 3 H, $CH_3C{=}$), 4.79 (m, 2 H, $H_2C{=}$), 5.81 (br s = CHCO). (Found: C, 76.82; H, 8.35. Calc. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%).

Continued elution with EtOAc-cyclohexane afforded 8.00 g of a mixture of ketones followed by 9.50 g (39%) of **19** as crystals from hexanes, m.p. 93–95°; IR (CCl_4) 1715, 1676, 1638, 1620 cm^{-1}; NMR δ 1.48 (s, 3 H, CH_3), 1.65 (br s, 3 H, $CH_3C{=}$), 4.46, 4.68 (m, 1 H each, $H_2C{=}$), 5.67 (m, 1 H = CHCO). (Found: C, 77.03; H, 8.35. Calc. for $C_{14}H_{18}O_2$: 77.03; H, 8.31%).

14-*Nor*-9-*keto*-α-*agarofuran* (**20**)

The conversion of 14-nor-10-epieudesma-4,11-diene-3,9-dione to **20** was carried out as described for the preparation of **16**. From 5.52 g (0.025 mol) of **19**, after chromatography on Woelm silica gel and elution with ether–hexanes (1:7), there was obtained 0.835 g (15%) of **20** as crystals from pentane, m.p. 93–94°; IR 1716 cm^{-1}; NMR δ 1.04 (s, 3 H, CH_3), 1.17, 1.21 (s, 3 H, each, $(CH_3)_2CO$), 5.41 (d, J = 10 Hz, CH–C<u>H</u>=CH–), 5.81 (dd, J = 10 Hz, J = 3 Hz, CH_2C<u>H</u>=CH). (Found: C, 76.33; H, 9.16. Calc. for $C_{14}H_{20}O_2$: C, 76.33, H, 9.15%).

REFERENCES

[1]S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, C. J. Gilmore, R. C. Haltiwanger and R. F. Bryan, *J. Am. Chem. Soc.* **94,** 1354 (1972).

[2]S. M. Kupchan, W. A. Court, R. G. Dailey, C. J. Gilmore, R. F. Bryan, *Ibid.* **94,** 7194 (1972).

[3]G. R. Smith, R. W. Miller, D. Weislander, W. K. Rohwedeler, N. Eickman and J. Clardy, *J. Org. Chem.* **41,** 3264 (1976).

[4]Y. Shizuri, H. Wada, K. Sugiura, K. Yamada and Y. Hirata, *Tetrahedron* **29,** 1773 (1973) and other papers in this series.

[5]R. M. Smith, *The Alkaloids* (Edited by R. H. F. Manske), Vol. 16, pp. 215–248. Academic Press, New York (1977), has reviewed the chemistry of this group of natural products.

[6a]H. C. Barrett and G. Büchi, *J. Am. Chem. Soc.* **89,** 5665 (1967); [b]J. A. Marshall and M. T. Pike, *J. Org. Chem.* **33,** 435 (1968); [c]A. Asselin, M. Mongrain and P. Deslongchamps, *Can. J. Chem.* **46,** 2817 (1968); [d]J. W. Huffman, C. A. Miller and A. R. Pinder, *J. Org. Chem.* **41,** 3705 (1976).

[7a]F. J. McQuillin, *J. Chem. Soc.* 528 (1955); [b]J. A. Marshall and W. I. Fanta, *J. Org. Chem.* **29,** 2501 (1964); [c]D. C. Humber and A. R. Pinder, *Ibid.* **31,** 4188 (1966); [d]J. A. Marshall and R. A. Ruden, *Tetrahedron Letters* 1239 (1970); [e]A. Van Der Gen, L. M. Van Der Linde, J. W. Witteveen and H. Boelens, *Rec. Trav. Chem.* **90,** 1034, 1045 (1971) have all discussed in detail the stereochemical course of the Robinson annulation.

[8]B. Lacoume and L. H. Zalkow, *Tetrahedron Letters* 5881 (1966).

[9]W. Treibs, *Ber Dtsch Chem. Ges.* **64,** 2178 (1931); **65,** 1314 (1932).

[10]B. Lacoume, private communication to A. R. Pinder.

[11]The authors wish to thank Professor L. H. Zalkow for copies of the IR and NMR spectra of compounds **2** and **4**.

[12]W. G. Dauben, J. W. McFarland and J. B. Ragan, *J. Org. Chem.* **26,** 297 (1961).

[13]C. A. Miller, Doctoral dissertation, Clemson University, (1976).

[14]K. J. Kolonko and R. H. Shapiro, *J. Org. Chem.* **43,** 1404 (1978).

[15]G. F. Hillenbrand, unpublished work.