drolyzed by addition to a solution of $NaHCO_3$ in ice–water. The solution was extracted with six 100-mL portions of $CHCl_3$. The extracts were dried ($MgSO_4$) and concentrated to leave a residue of 16.6 g (68%) of a mixture of isomeric phospholene oxides. The mixture was distilled at 132–135 °C (0.7 mm). ^{31}P NMR signals for the mixture were recorded at δ 70.48 (**13**, major), 68.55 (**17**, minor), 65.37 (**15** or **16**, major), 65.17 (**15** or **16**, major), 62.78 (**14**, intermediate), and 61.49 (**18**, minor).

Cycloadditions of 4-*tert*-Butyl-1-vinylcyclohexene with CH_3PCl_2. Copper stearate (0.2 g), 10.5 g (0.064 mol) of diene **1b**, 6.25 mL (0.07 mol) of CH_3PCl_2, and 200 mL of hexane were combined and allowed to stand for 32 days at room temperature. The solid adduct was then collected by filtration (^{31}P signal in $CDCl_3$ at δ 106.5) and hydrolyzed with $NaHCO_3$–ice-cold water. The aqueous solution was extracted continuously with $CHCl_3$ overnight. The resulting $CHCl_3$ extract was dried ($MgSO_4$) and concentrated by rotary evaporation to yield 1.5 g (10%) of **20** and **21** as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.95 (s, $C(CH_3)_3$), 1.63 (d, $^2J_{PH}$ = 12 Hz, PCH_3); ^{31}P NMR ($CDCl_3$) δ 66.2, 66.6 (1:1).

Anal. Calcd for $C_{13}H_{23}OP$: C, 69.00; H, 10.24; P, 13.69. Found: C, 69.01; H, 10.47; P, 14.07.

In another experiment, 0.5 mL each of diene **1b**, CH_3PCl_2, and $CDCl_3$, with a trace of copper stearate, were mixed in a 5-mm NMR tube; the ^{31}P NMR spectrum was measured directly at intervals over a 240-h period. Some ^{31}P shifts observed are recorded in the text.

Registry No. **1a**, 23985-33-3; **1b**, 33800-81-6; **1b** maleic anhydride adduct (isomer 1), 82189-08-0; **1b** maleic anhydride adduct (isomer 2), 82189-09-1; **4**, 82149-59-5; **5**, 82149-60-8; **6**, 82149-61-9; **7**, 82149-62-0; **8**, 82149-63-1; **9**, 82149-64-2; **10**, 82149-65-3; **11**, 82167-35-9; **12**, 82189-51-3; **13**, 82149-66-4; **14**, 82189-10-4; **15**, 82149-67-5; **16**, 82149-68-6; **20**, 82149-69-7; **21**, 82149-70-0; SO_2, 7446-09-5; $MePCl_2$, 676-83-5; tetracyanoethylene, 670-54-2; maleic anhydride, 108-31-6.

Synthesis of Agarofurans by Cyclization of 10-Epieudesmene-3,11-diols

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The course of the direct cyclization of 10-epi- and 14-nor-10-epieudesm-4-ene-3,11-diols (**2**, **5**) to α-agarofuran (**1**) and its derivatives has been investigated in detail. The reaction of 10-epieudesm-4-ene-3α,11-diol (**9**) with Jones reagent, *p*-toluenesulfonic acid, diethyl azodicarboxylate–triphenylphosphine, or *p*-toluenesulfonyl chloride affords **1** in variable yields. The 3-epimer of diol **9** (**8**) also affords **1** under similar conditions. The 14-nor analogues of diols **8** and **9** (**12**, **13**) were prepared and have been found to afford 14-nor-α-agarofuran (**14**) with *p*-toluenesulfonic acid and to afford mixtures containing variable amounts of **14** with Jones reagent. The preparation in good yield of 14-nor-9-oxo-α-agarofuran (**4**), an intermediate in the synthesis of polyhydroxyagarofurans, is described. The stereochemistry of diols **8** and **9** has been confirmed, and a variety of minor reaction products from the cyclizations reactions have been characterized.

Following the clarification of the structure and first synthesis of α-agarofuran (**1** Chart I) by Barrett and Buchi,[1] several other syntheses have been described.[2] Among the more convenient of these is the direct conversion of a 10-epieudesm-4-ene-3,11-diol of unspecified stereochemistry (**2**) to α-agarofuran by treatment with either mild acid[2b] or Jones reagent.[2d] In recent work from this laboratory, the latter procedure was used successfully for the preparation of 9-oxo-α-agarofuran (**3**), a key intermediate in the synthesis of polyhydroxyagarofurans derived from plants of the family Celastraceae. However, the conversion of the corresponding triol to 14-nor-9-oxo-α-agarofuran (**4**), a possible intermediate in an alternative approach to the natural products, proceeded in only 15% yield.[3] On the basis of the data available there appeared to be no a priori reason for the differences in the course of the reactions leading to oxoagarofurans **3** and **4**; however, there had also been no definitive study of the stereoelectronic aspects of these cyclizations. In order to gain some insight into the course of these reactions as a function of the stereochemistry of the allylic hydroxyl group at C-3 and the substitution of C-4, we undertook an investigation of the behavior of both isomers of 10-epieudesmene-3,11-diol (**2**) and 14-nor-10-epieudesmene-3,11-diol (**5**) toward mild acid and Jones reagent. The results of this study are summarized in Table I.

Table I. Conversion of 10-Epieudesmene-3,11-diols to Agarofurans

		products (% yield[a])	
diol	reaction conditions	agarofuran	other
9	Jones reagent	**1** (34)	**10** (27)
9	HOTs, benzene	**1** (56)	**11** (28)
9	DEAD, triphenylphosphine[b]	**1** (48)	
9	TsCl, pyridine	**1** (63)	
8	Jones reagent	**1** (35)	**10** (19)
8	HOTs, benzene	**1** (75)	**11** (21)
12	Jones reagent	**14** (5)	**15** (14)
12	HOTs, benzene	**14** (60)	**16** (15)
12	DEAD, triphenylphosphine[b]	**14** (53)	
13	Jones reagent	**14** (39)	**17** (47)
13	HOTs	**14** (49)	**16** (44)

[a] Isolated yields. [b] Reference 13.

Metal hydride reducation of enone **6**, or the corresponding 11,12-epoxide, has been reported to afford mixtures of the epimeric 3-ols,[2a,b,5] one of which has been isolated and tentatively assigned 3α (quasi-equatorial) stereochemistry.[5] Precedent in similar systems would seem

(1) Barrett, H. C.; Buchi, G. *J. Am. Chem. Soc.* **1967**, *89*, 5665.

(2) (a) Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435. (b) Asselin, A.; Mongrain, M.; Deslongchamps, P. *Can. J. Chem.* **1968**, *46*, 2817. (c) Heathcock, C. H.; Kelly, T. R. *Chem. Commun.* **1968**, 267. (d) Huffman, J. W.; Miller, C. A.; Pinder, A. R. *J. Org. Chem.* **1976**, *41*, 3705. (e) Buchi, G.; Wuest, H. *Ibid.* **1979**, *44*, 546.

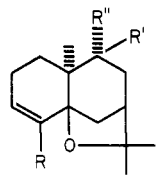
(3) Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron Suppl.* **1981**, *No. 9*, 269.

(4) Some years ago, an investigation of these reactions as a function of the stereochemistry at C-3 was said to be forthcoming;[2b] however, to the best of our knowledge, the results have not been reported.

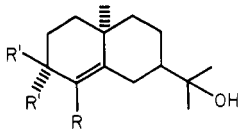
(5) Miller, C. A. Ph.D. Dissertation, Clemson University, 1976. The authors are indebted to Dr. A. R. Pinder for making available to them various samples and spectra of Dr. Miller's samples.

0022-3263/82/1947-3254$01.25/0

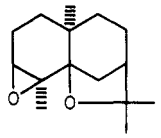
Chart I



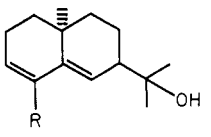
1, R = CH_3; R′ = R″ = H
3, R = CH_3; R′,R″ = O
4, R = H; R′,R″ = O
14, R = R′ = R″ = H
18, R = R′ = H; R″ = OH



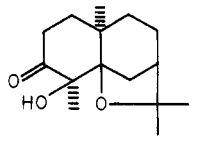
2, R = CH_3; R′,R″ = H, OH
5, R = H; R′,R″ = H, OH
6, R = CH_3; R′,R″ = O
8, R = CH_3; R′ = OH; R″ = H
9, R = CH_3; R′ = H; R″ = OH
12, R = R′ = H; R″ = OH
13, R = R″ = H; R′ = OH
17, R = H; R′, R″ = O



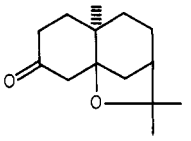
7



11, R = CH_3
16, R = H



10



15

to indicate that reduction of enone **6** by metal hydrides should afford primarily the quasi-equatorial alcohol.[6] In contrast to the reported results, we find that lithium aluminum hydride reduction of the 11,12-epoxide derived from enone **6** affords almost exclusively the crystalline diol assigned the 3α configuration;[5] however, the NMR spectrum showed the carbinol proton as a triplet at δ 4.00 (J = 6.4 Hz), indicative of a quasi-axial (3α) alcohol.[7]

The preparation of a C-3 epimer of this diol by lithium–ammonia reduction of a compound assumed to be 3β,4β-epoxydihydro-α-agarofuran (**7**) has been described;[5] however, the original assignment of stereochemistry to this epoxide was made on the basis of an incorrect structure for α-agarofuran.[8] Reaction of α-agarofuran (**1**) with *m*-chloroperbenzoic acid afforded an epoxide identical with that described by earlier workers,[5,8] the NMR spectrum of which showed H-3 as a doublet of doublets (J = 1.5 and 2.4 Hz), entirely consistent with the previously assigned stereochemistry.[9] Lithium–ammonia reduction afforded a noncrystalline and rather labile diol, the spectral properties of which agreed with those reported.[5,7] The NMR spectrum of this compound showed the carbinol proton as a broadened singlet at δ 3.86, indicating that this material was the quasi-axial (3β) isomer of diol **2** (**8**) and that the previously described crystalline diol must be the corresponding 3α-ol (**9**).[10] The ^{13}C NMR spectra of alcohols **8** and **9** confirmed this assignment, with C-3 of alcohol **9** appearing at 71.2 ppm while that of alcohol **8** was at 69.6 ppm.[11]

Treatment of crystalline diol **9** with Jones reagent afforded α-agarofuran as the major product although in a considerably lower yield (34%) than obtained in the earlier work,[2d,5] and in addition a 27% yield of a waxy, saturated hydroxy ketone was obtained. This compound gave a parent ion in the mass spectrum at m/e 252, and the ^1H NMR spectrum showed methyl singlets at δ 1.21, 1.30, and 1.35, with a fourth methyl group as a doublet (J = 0.9 Hz) at δ 1.38; the hydroxyl proton appears as a doublet (J = 0.9 Hz) at δ 3.16, the chemical shift of which is insensitive to concentration. On the addition of D_2O, not only did this signal disappear but the methyl peak at δ 1.38 also collapsed to a singlet. The ^{13}C NMR spectrum of this compound shows the presence of three quaternary carbons bonded to oxygen at δ 77.7, 83.2, and 95.2. The absence of a signal in the region of δ 74–75[11] and the presence of two very-low-field signals are consistent only with an agarofuran skeleton.[12] On the basis of these data and the observation that the hydroxyl proton is internally hydrogen bonded and W coupled to the protons of one of the methyl groups, this compound is assigned the structure 4β-hydroxy-3-oxodihydroagarofuran (**10**). Since hydroxy ketone **10** is also formed from the treatment of diol **8** with Jones reagent (see below), it probably arises by oxidation of the double bond effected by the chromate ester of the 11-hydroxyl in diols **8** and **9**. As reported by Deslongchamps, reaction of diol **9** with *p*-toluenesulfonic acid afforded a mixture of α-agarofuran and dienol **11**.[2b] In an effort to effect a more direct preparation of diol **8**, the quasi-equatorial epimer **9** was treated with diethyl azodicarboxylate–triphenylphosphine–benzoic acid.[13] Although this procedure has been reported to afford the epimeric benzoate in a similar system,[6c] diol **9** was instead converted to agarofuran **1** in 48% yield. Also, treatment of diol **9** with *p*-toluenesulfonyl chloride in pyridine afforded α-agarofuran as the only isolable product.

Although it had been reported that the quasi-axial epimer of diol **9** (**8**) did not afford α-agarofuran on treatment with mild acid,[5] in our hands this reaction gave in excellent yield a mixture of α-agarofuran (75%) and dienol **11** (21%). On treatment with Jones reagent, diol **8** gave a complex mixture of products from which α-agarofuran and hydroxy ketone **10** could be isolated in low yield.

The synthesis of 14-nor-10-epieudesm-4-ene-3α,11-diol (**12**) and its 3-epimer (**13**) were carried out in the same manner as the preparation of diols **8** and **9** (see Experimental Section). By analogy with the NMR data for diols **8** and **9**[10] and in contrast to the data for similar systems,[6c]

(6) (a) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526. (b) Dawson, D. J.; Ireland, R. E. *Tetrahedron Lett.* **1968**, 1899. (c) Ando, M.; Sayama, S.; Takuse, K. *Chem. Lett.* **1979**, 191.

(7) The coupling constants of the C-3 protons for this alcohol, its epimer, and epoxy-α-agarofuran **7** are not reported in ref 5, and the original 60-MHz spectra are not sufficiently well resolved to permit their determination.

(8) Maheswari, M. L.; Varma, K. R.; Bhattacharyya, S. C. *Tetrahedron* **1963**, *19*, 1079.

(9) Examination of models indicates that in the α-oxide H-3 should appear as a doublet of doublets ($J \approx 1$ and 8 Hz). The predicted coupling constants for the β-oxide are approximately 2 Hz. Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, 1964; pp 49–50.

(10) The observed differences in coupling constants for H-3 in diols **8** and **9** are internally consistent with the assigned structures; however, they are much less than those in very similar systems.[6c] The chemical shift differences for these protons agree with those reported in ref 6c.

(11) No effort was made to assign the upfield ^{13}C peaks in diols, and in both C-11 appears at 74.2 ppm. These peaks were assigned by the usual method of off-resonance decoupling. The ^{13}C peak due to an equatorial hydroxyl is expected to be downfield relative to that for an axial alcohol. Levy, G. C.; Lichter, R. L. Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York, 1980; p 253.

(12) It has been found that in the dihydroagarofurans and a series of hydroxyagarofurans that the chemical shift of C-11 is in the range δ 80.1–83.7, while that of C-5 is δ 87.3–92.0: Wherli, F. T.; Nishida, T. "Fortschritte der Chemie Organischer Naturstoffe"; Vol 36, Springer-Verlag: Wien and New York, 1979; Vol. 36, pp 1–229. In polyhydroxyagarofurans with a hydroxyl group at C-4, the chemical shift of C-5 is in the range δ 92.5–93.7: Baxter, R. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Braenden, O. J.; Szendrei, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2965.

(13) Mitsunobu, O. *Synthesis*, **1981**, 1 and references therein.

the coupling constants for H-3 were considerably smaller than predicted.

Reaction of 3α,11-diol **12** with Jones reagent gave a very low yield (5%) of 14-nor-α-agarofuran (**14**) and a small amount of a compound which had the spectral characteristics of a noroxoagarofuran (see Experimental Section) in addition to traces of several other compounds. 14-Nor-4-oxodihydroagarofuran is a known compound[2c,e,8] the NMR spectrum of which differs markedly from those of the reaction product. On the assumption that the facile oxidation of diol **12** is followed by cyclization, this compound is almost certainly 14-nor-3-oxodihydroagarofuran (**15**).[14] Treatment of diol **12** with *p*-toluenesulfonic acid in benzene afforded a 60% yield of 14-nor-α-agarofuran (**14**) and 15% of dienol **16**. By analogy with the reaction of diol **9**, the Mitsunobu epimerization[13] afforded only agarofuran **14**.

Reaction of the quasi-axial epimer of diol **12** (**13**) with Jones reagent gave a nearly equimolar mixture of noragarofuran **14** and the product of direct oxidation, enone **17**, while diol **13** with *p*-toluenesulfonic acid afforded a nearly 1:1 molar ratio of agarofuran **14** and dienol **16** in 93% yield.

On the basis of its method of preparation, the mixture of triols which is converted in low yield to ketone **4** has predominently the pseudoequatorial 3α configuration.[3] Diol **12** which has analogous stereochemistry and substitution at C-4 also gives a poor yield of the corresponding agarofuran (**14**) on treatment with Jones reagent; however, diol **12** gives a 60% yield of cyclized product with *p*-toluenesulfonic acid. Reaction of the 9-hydroxy analogue of diol **12** under these conditions, with tetrahydrofuran as a cosolvent, afforded in 64% yield 14-nor-9α-hydroxyagarofuran (**18**), which was oxidized to 9-oxo-14-nor-α-agarofuran (**3**)[3] in 98% yield. The stereochemistry of alcohol **18** at C-9 was assigned on the basis of standard NMR considerations (see Experimental Section).

Empirically, this investigation indicates that the *p*-toluenesulfonic acid catalyzed cyclization of either epimer of diols **2** and **5** is a viable synthetic method for the corresponding α-agarofuran. However, reaction with Jones reagent affords at best moderate yields of agarofurans from these allylic alcohols. These data are presented in Table I.

The *p*-toluenesulfonic acid catalyzed cyclizations appear to be mechanistically equivalent to S_N2' reactions, accompanied by predictable and competitive E2′ eliminations to dienols **10** and **16**.[15] It is known that in S_N2' reactions a syn relationship between the leaving group and the nucleophile is unusually favored,[15] and in agreement with this generalization, the overall yields of agarofuran and dienols from diols **8** and **13** are somewhat greater than those from the quasi-equatorial epimers (**9** and **12**).[16] The cyclization of diols **9** and **12** under Mitsunobu's conditions[13] and the very facile cyclization of diol **9** on treatment with *p*-toluenesulfonyl chloride–pyridine are almost certainly S_N2' reactions in which there is a precedented, but relatively uncommon, anti relationship between between the leaving group and the nucleophile.[15] Although intramolecular S_N2 reactions under Mitsunobu's conditions have been reported previously,[13] the formation of agarofurans **1** and **4** from diols **9** and **13** appear to be the first examples of S_N2' reactions encountered in these reactions.

The cyclizations effected by Jones reagent would appear to be mechanistically similar to those with *p*-toluenesulfonic acid. These reactions are, however, complicated by competitive oxidations which are known to be more rapid for quasi-equatorial allylic alcohols than for the corresponding quasi-axial epimer.[17] Thus, the yields of agarofurans **1** and **4** under these conditions are considerably greater from diols **8** and **13**, respectively, than from diols **9** and **12** (Table I).

Experimental Section

Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Infrared spectra were measured as liquid films or in chloroform solution. NMR spectra were carried out in deuteriochloroform at 60 mHz by using a Hitachi Perkin-Elmer R-24 spectrometer or at 90 MHz by using a JEOL FX90Q spectrometer: signals are reported in parts per million (δ) relative to tetramethylsilane. Mass spectra were determined at 70 eV by using a Hewlett-Packard 5985B spectrometer. Melting points were obtained by using a Kofler hot stage and are uncorrected.

10-Epieudesm-4-ene-3α,11-diol (9). To a solution of 0.83 g of $LiAlH_4$ in 15 mL of dry ether at 0 °C was added slowly 1.00 g of 11,12-epoxy-10-epieudesm-4-en-3-one[2a] in 10 mL of dry ether. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to ambient temperature, and stirred for 15 h. The excess hydride was decomposed by the careful addition of 1 mL of water followed by 1 mL of 15% aqueous NaOH and 3 mL of water. The precipitated solids were filtered off and washed with hot THF. Evaporation of the solvents afforded 1.11 g of a thick, colorless oil which crystallized on standing. Recrystallization from ether–hexanes gave 0.72 g (70%) of diol **9**: mp 102–103 °C (lit.[5] mp 100–101 °C); NMR δ 1.15, 1.19, 1.24 (s, 3 H each, CH_3), 1.79 (br s, 3 H, vinyl CH_3), 4.00 (t, J_{app} = 6.4 Hz, CHOH). The 3-acetate, prepared with acetic anhydride–pyridine, showed the C-3 proton at δ 5.26 (t, J_{app} = 6.9 Hz).

3β,4β-Epoxydihydro-α-agarofuran (7). This material was prepared from α-agarofuran (**1**) by oxidation with *m*-chloroperbenzoic acid following the published procedure.[8] From 0.710 g of α-agarofuran there was obtained, after recrystallization from pentane, 0.558 g (73%) of epoxide **7**: mp 88–89 °C (lit.[8] mp 88 °C); NMR δ 0.86 (s, 3 H, CH_3), 1.28 (d, 3 H, J = 0.6 Hz, CH_3 C–O–CH), 1.29, 1.36 (s, 3 H each, CH_3), 2.95 (dd, J = 1.5, 2.4 Hz, HC–O–C).

10-Epieudesm-4-ene-3β,11-diol (8). In a modification of the procedure of Miller,[5] a solution of 0.545 g of epoxide **7** was added to a solution of 0.15 g of lithium in 40 mL of distilled dry liquid ammonia. The reaction mixture was stirred at reflux for 4.5 h and quenched with ammonium chloride and the ammonia evaporated. The residue was taken up in ether and washed with water, the ethereal extracts were dried, and the solvent was removed to give a thick, colorless oil, which was taken up in dry ether and chromatographed on Woelm neutral alumina. Elution with ether afforded 0.091 g of an unidentified nonpolar material, and elution with methanol gave 0.430 g (78%) of diol **8** as a thick oil, the spectral properties of which agreed with those described by Miller:[5] NMR δ 1.06, 1.20, 1.25 (s, 3 H each, CH_3), 1.82 (d, J = 1.2 Hz, vinyl CH_3), 3.86 (br s, 1 H, CHOH).

Reactions of 10-Epieudesm-4-ene-3α,11-diol (9). (A) With Jones Reagent. Reaction of 4.12 g of diol **9** with Jones reagent as previously described[2d] afforded after distillation 1.29 g (34%)[18] of α-agarofuran [bp 110–115 °C (air bath; 1.0 mm)], the spectral

(14) In addition the NMR data agree well with those of 3-oxodihydroagarofuran.[2b]

(15) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. This author has recently reviewed the S_N2' reaction and has discussed several "intramolecular S_N2' reactions". One of the reviewers has noted that an S_N2' reaction is by definition bimolecular, and thus an intramolecular S_N2' reaction is not possible. The reactions we describe are mechanistically equivalent to the S_N2' but are unimolecular.

(16) There is a possibility that these acid-catalyzed reactions may proceed via an S_N1 mechanism; however, an S_N2' path appears to be more favorable energetically. The usually accepted mechanism for the S_N2' reaction involves the interaction of a nucleophile (either inter- or intramolecularly) with an incipient allylic cation, a process which is known to be exceedingly facile.[15]

(17) Burstein, S. H.; Ringold, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 4722.

(18) No attempt was made to optimize the yield in this preparation. It should be noted that compounds in the agarofuran series are extremely volatile, and considerable care must be exercised to avoid their loss during the evaporation of solvents and other routine laboratory operations.

properties (^{1}H NMR, IR) of which were identical with those reported.[2d] In a subsequent experiment in which the reaction products were separated by chromatography, oxidation of 0.200 g of diol **9** afforded, in addition to α-agarofuran, 0.051 g (27%) of hydroxy ketone **10** as a waxy solid: IR 3600, 1700; NMR δ 1.21, 1.30, 1.35 (s, 3 H each, CH_3), 1.38 (d, J = 0.9 Hz, CH_3COH), 3.16 (d, J = 0.9 Hz, OH); mass spectrum, m/e (relative intensity) 252 (100), 234 (5), 216 (6), 209 (16), 191 (24), 177 (11), 152 (39).

(B) With *p*-Toluenesulfonic Acid. To a solution of 1.00 g of diol **9** in 30 mL of benzene was added 0.23 g of *p*-toluenesulfonic acid, and the solution was stirred at ambient temperature for 3.5 h. The reaction mixture was washed successively with water, saturated $NaHCO_3$, water, and brine and dried, and the solvent was removed carefully at room temperature. The residue was taken up in 5% ether–hexanes and chromatographed on Woelm silica gel. Elution with ether–hexanes mixtures afforded first 0.518 g (56%) of α-agarofuran. The latter fractions gave 0.260 g (28%) of dienol **11**: mp 66–67 °C (lit.[2b] mp 67–68 °C); mass spectrum, m/e (relative intensity) 220 (1), 162 (96), 147 (100), 133 (22); NMR 0.96 (s, 3 H, CH_3), 1.24 (s, 6 H, $(CH_3)_2COH$), 1.80 (d, J = 1.5 Hz, vinyl CH_3), 5.60 (m, 2 H, vinyl H).

(C) With Diethyl Azodicarboxylate–Triphenylphosphine. To a solution of 0.500 g of diol **9** in 20 mL of benzene, containing 0.825 g of triphenylphosphine and 0.384 g of benzoic acid, was added 0.548 g of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperatures for 48 h, concentrated to a small volume at reduced pressure, and residue taken up in ether. After filtering off the precipitated solids, the ether-soluble material was chromatographed on Woelm silica gel. Elution with ether–hexane mixtures afforded 0.219 g (48%) of α-agarofuran identical in all respects with the matrial described above.

(D) With *p*-Toluenesulfonyl Chloride. To a stirred solution of 0.100 g of diol **9** in 5 mL of dry pyridine at 0 °C was added 0.131 g of *p*-toluenesulfonyl chloride. The reaction was stirred at 0 °C for 1 h and then refrigerated (−17 °C) for 16 h. TLC analysis of an aliquot indicated that little reaction had taken place, and the reaction mixture was allowed to stand at ambient temperature for 24 h. After dilution with water, the products were isolated by using ether. The ethereal extracts were washed with 5% HCl, water, and brine and dried, and the solvent was removed to give 0.058 g (63%) of nearly pure (TLC) α-agarofuran.

Reactions of 10-Epieudesm-4-ene-3β,11-diol (8). (A) With Jones Reagent. Reaction of 0.095 g of diol **8** with Jones reagent as described above afforded a mixture of 0.070 g of at least seven compounds (TLC). This mixture was dissolved in 5% ether–hexanes and chromatographed on Woelm silica gel. Elution with ether–hexanes mixtures gave 0.031 g (35%) of α-agarofuran. Further elution with the same solvent pair gave 0.019 g (19%) of epoxy ketone **10** as a colorless wax, identical with the material described above.

(B) With *p*-Toluenesulfonic Acid. A solution of 0.100 g of diol **8** in 10 mL of benzene was treated with 0.024 g of *p*-toluenesulfonic acid as described above to give after chromatography 0.069 g (75%) of α-agarofuran and 0.019 g (21%) of dienol **11**.

14-Nor-10-epiudesm-4-ene-3α,11-diol (12). To a solution of 4.00 g of 14-nor-10-epieudesm-4-en-3-one[19] in 80 mL of CH_2Cl_2 was added 5.0 g of *m*-chloroperbenzoic acid. The reaction mixture was stirred at ambient temperature for 6 h and washed successively with 10% Na_2SO_3, 10% NaOH, water, and brine. After the mixture was dried, the solvent was removed to give 4.19 g of a mixture of epimeric epoxides which was used in the subsequent step without further purification.

To a stirred suspension of 2.82 g of lithium aluminum hydride in 40 mL of dry THF at −70 °C was added a solution of 3.07 g of the mixture of epoxides in 50 mL of dry THF. The reaction mixture was stirred at −70 °C for 2 h, allowed to warm to ambient temperature, and stirred for 15 h. The excess hydride was destroyed by the cautious addition of successive portions of water, 15% NaOH, and water, the precipitated solids were filtered off, and the solvent was removed to give 3.06 g of diol **12** as a white solid. Recrystallization from ether–hexanes gave the analytical sample: mp 81–82 °C; NMR δ 1.16, 1.20, 1.24 (s, 3 H each, CH_3), 4.20 (br s, 1 H, CHOH), 5.43 (br s, vinyl H).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.97; H, 10.81.

Reactions of 14-Nor-10-epieudesm-4-ene-3α,11-diol (12). (A) With Jones Reagent. A solution of 0.500 g of diol **12** in 12 mL of acetone was treated with Jones reagent as described above to give 0.457 g of a mixture of six compounds (TLC). Chromatography on Woelm silica gel afforded 0.023 g (5%) of 14-nor-α-agarofuran (**14**) as a volatile liquid: NMR δ 0.93, 1.21, 1.34 (s, 3 H each, CH_3), 5.40 (dd, J = 2.0, 11.7 Hz, H-4), 5.82 (m, 1 H, H-3); mass spectrum, m/e (relative intensity) 206 (39), 191 (100), 173 (33), 134 (34).

The more polar fractions of the chromatogram afforded 0.070 g (14%) of 14-nor-3-oxodihydroagarofuran (**15**) as a viscous oil: IR 1704 cm^{-1}; NMR δ 1.32 (s, 6 H, 2 CH_3), 1.32 (s, 3 H, CH_3) mass spectrum, m/e (relative intensity), 222 (11), 207 (100), 164 (23), 149 (15).

(B) With *p*-Toluenesulfonic Acid. A solution of 0.500 g of diol **12** in 20 mL of benzene was treated with 0.125 g of *p*-toluenesulfonic acid at ambient temperature for 4 h. The products were isolated as described above, taken up in 5% ether–hexanes, and chromatographed on Woelm silica gel. Elution with ether–hexanes afforded 0.276 g (60%) of 14-nor-α-agarofuran (**14**) identical with that described above. The more polar fractions from the chromatogram afforded 0.068 g (15%) of 14-nor-10-epieudesma-3,5-dien-11-ol (**16**) as a colorless oil which decomposed on standing: NMR δ 0.99, 1.22, 1.23 (s, 3 H each, CH_3), 5.71 (m, 3 H, vinyl H); mass spectrum, m/e (relative intensity), 206 (2), 148 (100), 133 (96), 119 (14).

(C) With Diethyl Azodicarboxylate–Triphenylphosphine. A solution of 1.00 g of diol **12** in 20 mL of benzene was treated with 1.165 g of diethyl azodicarboxylate, 1.75 g of triphenylphosphine, and 0.81 g of benzoic acid as described above for the reaction of diol **9**. After chromatography there was obtained 0.510 g (53%) of 14-nor-α-agarofuran.

3β,4β-Epoxy-14-nordihydroagarofuran. To a solution of 0.25 g of 14-nor-α-agarofuran (**14**) in 10 mL of CH_2Cl_2 was added, with cooling, 0.25 g of *m*-chloroperbenzoic acid. The reaction mixture was allowed to stand at −17 °C for 30 h and the excess peracid destroyed with saturated Na_2SO_3. The mixture was diluted with ether and the aqueous layer drawn off. The organic phase was washed successively with 8% NaOH and brine and dried, and the solvent was removed to give 0.249 g of a mixture of epoxide and starting olefin. This mixture was dissolved in 10% ether–hexanes and chromatographed on Woelm neutral alumina (activity III) to give 0.174 g of epoxide as an oil which crystallized on standing. Recrystallization from pentane at low temperature gave crystals: mp 36–39 °C; NMR δ 0.86, 1.29, 1.36 (s, 3 H each, CH_3), 2.93, 3.20 (br s, 1 H each, HC–O–CH); mass spectrum m/e (relative intensity), 222 (6), 207 (100), 164 (22), 149 (40).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.61; H, 9.98.

14-Nor-10-epieudesm-4-ene-3β,11-diol (13). The lithium ammonia reduction of 3β,4β-epoxy-14-nordihydroagarofuran was carried out inthe same manner as the reduction of epoxide **7**. From 0.500 g of epoxide there was obtained 0.415 g (82%) of diol **13** as a colorless oil which was homogeneous to TLC: NMR δ 1.06, 1.20, 1.24 (s, 3 H each, CH_3), 4.04 (t, J = 1.4 Hz, 1 H, CHOH), 5.52 (br d, J = 2.71 Hz, vinyl H).

Reactions of 14-Nor-10-epieudesm-4-ene-3β,11-diol (13). (A) With Jones Reagent. Reaction of 0.095 g of diol **13** with Jones reagent as described above afforded after chromatography 0.34 g (39%) of 14-nor-α-agarofuran, identical in all respects with the material described above. The later fractions from the chromatogram afforded 0.044 g (47%) of 14-nor-11-hydroxy-10-epieudesm-4-en-3-one (**17**) as a viscous oil: IR 1670 cm^{-1} NMR δ 1.15, 1.20, 1.23 (s, 3 H each, CH_3), 5.66 (br s, vinyl H); mass spectrum, m/e (relative intensity) 222 (1), 204 (34), 176 (15), 164 (75), 149 (100).

(B) With *p*-Toluenesulfonic Acid. Reaction of 0.095 g of diol **13** with *p*-toluenesulfonic acid as described above afforded, after chromatography on Woelm silica gel, 0.043 g (49%) of agarofuran **14**. The more polar fractions from the chromatogram afforded 0.039 g (44%) of dienol **16** identical in all respects with that described above.

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14-Nor-9α-hydroxy-α-agarofuran (18). A solution of 0.15 g of 14-nor-10-epieudsm-4-ene-3,9,11-triol[3] was treated with 0.040 g of *p*-toluenesulfonic acid in 10 mL of benzene and 4 mL of THF, as described above. After chromatography on Woelm silica gel there was obtained 0.090 g (64%) of hydroxyagarofuran 18 as a thick oil, which slowly decomposed on standing: NMR δ 0.87, 1.21, 1.34 (s, 3 H each, CH_3), 3.94 (dd, J = 5.8, 10.5 Hz, 1 H, CHOH), 5.38, 5.87 (m, 1 H each, vinyl H).

Oxidation of 0.072 g of this with Jones reagent in the usual manner gave 0.070 g (98%) of 14-nor-9-oxo-α-agarofuran (4), identical in all respects with material obtained previously.[3]

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Registry No. 1, 5956-12-7; 4, 82309-55-5; 7, 60064-95-1; 8, 82309-56-6; 9, 82309-57-7; 10, 82246-77-3; 11, 60113-60-2; 12, 82309-58-8; 13, 82309-59-9; 14, 82246-78-4; 15, 82246-79-5; 16, 82246-80-8; 17, 82390-13-4; 18, 82246-81-9; 11,12-epoxy-10-epieudesm-4-en-3-one, 82309-60-2; diethyl azodicarbonylate, 1972-28-7; 14-nor-10-epieudesm-4-en-3-one, 66428-81-7; 3β,4β-epoxy-14-nordihydroagarofuran, 82246-83-1; 14-nor-10-epieudesm-4-en-3,9,11-triol, 82246-84-2.

Solid-Phase Synthesis of Protected Peptides on a Polymer-Bound Oxime: Preparation of Segments Comprising the Sequence of a Cytotoxic 26-Peptide Analogue

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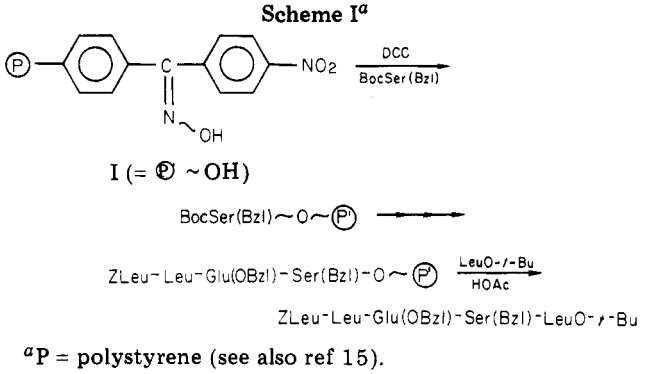
For demonstration of the utility of the *p*-nitrobenzophenone oxime polymer I, protected peptides ranging in length from three to seven amino acids were prepared. These peptides were removed from this support by carboxylic acid catalyzed aminolysis with amino acid or peptide esters. These products were obtained in yields ranging from 16% to 65% and were of high purity. The segments synthesized correspond to the sequence of a cytotoxic 26-peptide analogue of melittin.

We have recently developed the *p*-nitrobenzophenone oxime polymer I as a support for solid-phase peptide synthesis of protected peptide segments.[1] Peptides are displaced from this support with nucleophiles such as hydrazine, yielding peptide hydrazides. Peptides may also be cleaved from this support by nucleophilic displacement with amino acid esters. This reaction is rather slow, but its catalysis by carboxylic acids felicitously allowed synthesis of a number of di- and tripeptides. Furthermore, displacement of dipeptides from I appeared to occur without concomitant racemization when the reaction was catalyzed by carboxylic acids. We now report the application of this approach for the synthesis of longer protected peptides (cf. Scheme I) which might serve as useful intermediates in the segment condensation approach to peptide synthesis. We also show that not only amino acid esters but also peptide esters may be used to cleave peptides from I. This allows segment condensation of peptides assembled on I with previously purified amino compounds.

To illustrate the utility of this approach, we have prepared segments comprising the sequence of the cytotoxic peptide II, which is an analogue of melittin (Figure 1). The synthesis of this highly active cytotoxin[2,3] by the stepwise Merrifield method has been described. Peptide II was designed with little sequence homology to melittin in the amino terminal 20 residues to demonstrate that these residues serve a purely structural role and may be replaced by a sequence with a high potential to form a predominantly hydrophobic amphiphilic α helix. We would now like to prepare analogues of peptide II with replacements in the C-terminal portion of the chain. We have therefore prepared segments of II which are suitably protected for condensation from the amino toward the carboxyl terminus.[4]

Scheme I[a]



[a] P = polystyrene (see also ref 15).

Results

The C-terminal segment Z-Leu-Leu-Glu(OBzl)-Ser-(Bzl)-Leu-O-*t*-Bu (III; see ref 15 for a list of abbreviations) was prepared by starting from BocSer(Bzl)-I (Scheme I). The subsequent residues were coupled as symmetric anhydrides,[6] and the resulting tetrapeptide was displaced

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