Terpenic Acids by Cyclopentane Annulation of Exocyclic Dienes. Synthesis of Triquinane Portion of Retigeranic Acid

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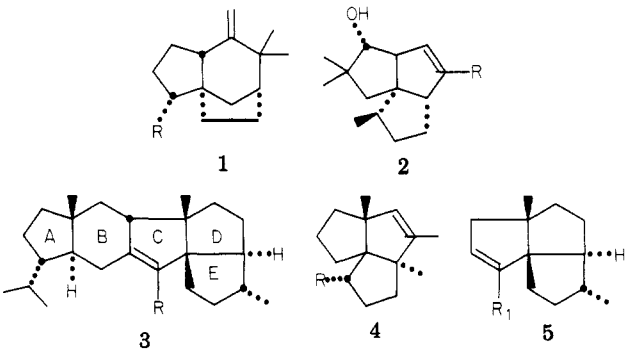
Tricyclic ester **5** has been prepared in 13 steps from (+)-pulegone. The key step in the synthesis of **5** involved the condensation of keto ester **15** with ethyl bromocrotonate under Reformatsky conditions to yield lactone **16** as one diastereomer. Either lithium diisopropylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene was used to effect the elimination to the dienic acid **17**, obtained as a mixture of diastereomers in an 80:20 ratio. Conditions were developed for the cyclopropanation of **18** in good isolated yields. The pyrolysis of **19** gave tricyclic ketone **20** in 50% yield. The ^{13}C NMR data are provided for all relevant intermediates. The deoxygenation of this ketone provided ester **5**. The structural and stereochemical assignments are based on data amassed previously on appropriate model compounds. Potential use of **5** in a convergent synthesis of retigeranic acid (**3**) is indicated. The concept of generality of this method in the context of total synthesis of other naturally occurring cyclopentene carboxylates is introduced.

Introduction

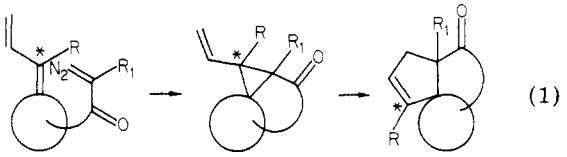
The cyclopentene annulation of simple dienes via their internal cyclopropanation and rearrangement has been successfully applied to the synthesis of carbocyclic systems including some cyclopentanoid natural products.[2] An extrapolation of this methodology to dienes possessing electronically perturbing substituents such as carboxylic acids or esters would provide direct means for the construction of various terpenic acids, among them, zizanoic acid (**1**),[3] pentalenic acid (**2**),[4] retigeranic acid (**3**),[5] and isocomenic acid (**4**).[6] The carboxylic acid functionality in these terpenes arises biogenetically via the enzymatic oxidation of the relevant methyl groups in the parent hydrocarbons. A successful method for the synthesis of these acids would lend generality to the cyclopentene annulation procedure which could be utilized to produce *either* the hydrocarbon terpenes *or* the acids without necessitating their interconversion. Although such interconversions would be more facile from the acids to the *hydrocarbons* than vice versa.

It should be noted that acid **4** which we term *isocomenic* has not to date been isolated. However, the metabolic parallel between zizaene/zizanoic acid and isocomene/isocomenic acid is obvious from biogenetic considerations. In all probability acid **4** does exist and may in time be isolated from those plant genera which produce isocomene.[6] The aforementioned conversion of acids to hydrocarbons would also allow the synthesis of various diastereomers of these terpenes in a *controlled* fashion since the cyclopentene carboxylates of type **8** can be manipulated in reductive and epimerizable manners at the α-carbon.

In general, the above acids are obtainable by the cyclopropanation and subsequent rearrangement of appropriate exocyclic vinyl acrylates of type **6** provided that these acrylates be receptive to the internal carbenoids (eq 1).



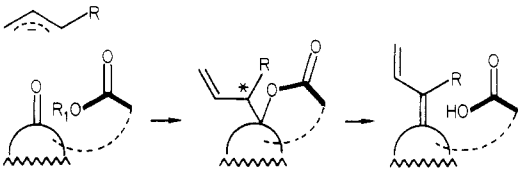
$R = CO_2H$; $R_1 = CO_2Et$



(1)

$R = CO_2Et$; $R_1 = H, CH_3$

The generation of a suitable exocyclic acrylate involves the addition of a crotonate unit to a cyclic ketone followed by the elimination of a β-acetoxy group (eq 2). Should



(2)

$R = CO_2Et$; $R_1 = CH_3$, C_2H_5, or alkyl

this group be a part of a lactone formed from an appropriately situated ester side chain during the reaction, the elimination then generates the requisite vinylacrylate while liberating a carboxylic acid functionality necessary for further elaboration to a diazo ketone. The stereochemistry of the α-carbon (marked with an asterisk) is of no consequence, since any diastereomers about this center in intermediates **9**, **10**, **6**, and **7** eventually converge in **8**.

We have committed ourselves to several programs designed for total syntheses of acids **1**-**4**. We report herein

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1983.

(2) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, 102, 6351. References 15 and 19.

(3) For recent syntheses in this area, see Vettel, P. R.; Coates, R. M. *J. Org. Chem.* **1980**, 45, 5430. Piers, E.; Banville, J.; *J. Chem. Soc., Chem. Commun.* **1979**, 1138.

(4) See, for example, Seto, H.; Sasaki, T.; Ozwaw, T.; Takeuchi, S. *Tetrahedron Lett.* **1978**, 4411.

(5) See the following: Rao, P. S.; Sarma, K. G.; Seshadri, T. R. *Curr. Sci.* **1965** *34*, 9. Rao, P. S.; Sarma, K. G.; Seshadri, T. R. *Ibid.* **1966**, *35*, 147; see also Yoshimura, I.; *J. Hattori Bot. Lab.* 1971, *34*, 231-264. Kaneda, M.; Takabashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1972**, 4609. Kaneda, M.; Iitaka, Y.; Shibata, S. *Acta. Crystallogr., Sect. B* **1974**, *30*, 358.

(6) It is likely this acid will be isolated (provided proper pH conditions are used) from the following species: *Isocoma wrightii* and *Berkheya radula*. See references to isolation work of parent hydrocarbons: Zalkow, L. H.; Harris, R. N.,III; VanDerreer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. Bohlman, R.; LeVan, N.; Pickardt, J. *Chem. Ber.* **1977**, *119*, 3777.

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on the successful construction of ester **5** employing the strategies outlined above. This ester is the key intermediate in the total synthesis of retigeranic acid **3**, currently underway in our laboratory.

Results and Discussion

The synthesis of **5** began with (+)-pulegone (**11**) after careful retrosynthetic considerations indicated that the methyl group in **11** possesses the necessary *R* configuration of the ring-E methyl in retigeranic acid. The Favorski rearrangement of pulegone dibromide[7,8] followed by ozonolysis gave the known keto ester **13**[9] in a good overall yield (Scheme I). Initially, better yields were obtained when the crude ester **12** was hydrolyzed to the corresponding acid which was easily purified and esterified[10] prior to ozonolysis. Following a new procedure for the Favorskii rearrangement,[8] we found that the crude methyl pulegonate (contaminated with unreacted pulegone) could be ozonized directly and the keto ester **13** easily separated from the oxidation products derived from pulegone by extracting these into dilute acid. In this way, overall yields of 60–65% of **13** were attained.

Alkylation with ethyl bromoacetate gave the mixed diester **14** in 86% overall yield. Selective "hydrolysis" followed by the in situ decarboxylation of the methyl ester afforded the keto ester **15** in 76% yield.

At this stage an appropriate four-carbon unit had to be selected for the eventual production of lactone **16** or its equivalent. We have attempted additions of *tert*-butyl 2-lithiocrotonate, *trans*-2-lithio-2-butene, *trans*-2-bromomagnesio-2-butene to the cyclopentanone **15** without success.

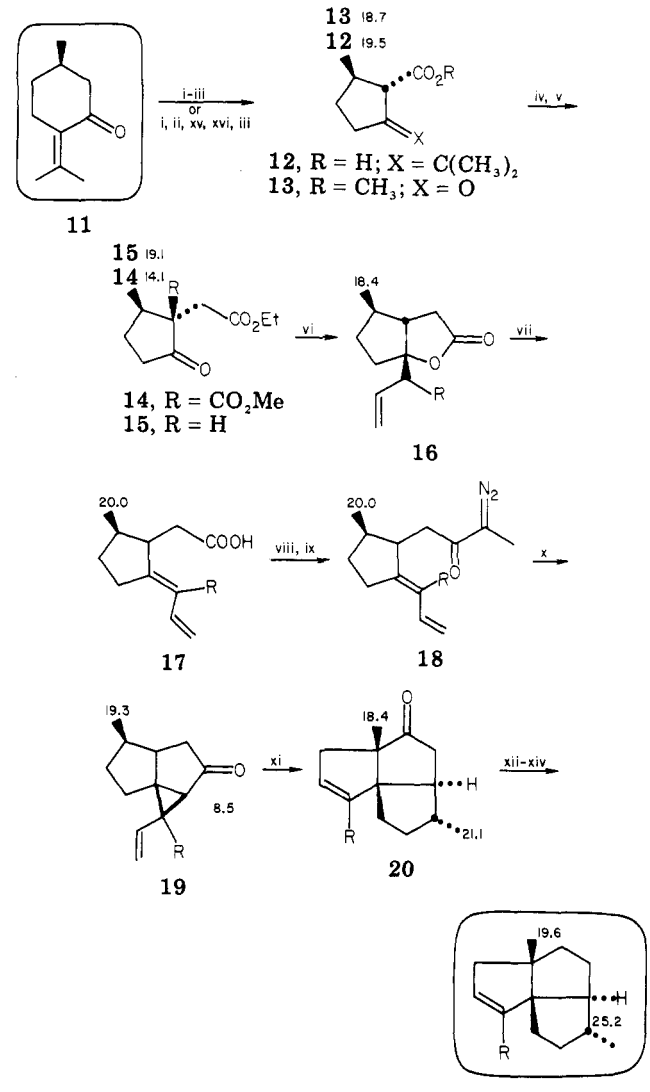
Even simple organometallics failed to add to this ketone. Eventually we found that the organozinc reagent derived from ethyl 4-bromocrotonate underwent a smooth addition to **15**, producing the lactone **16** as one diastereomer in 81% yield. This eventual optimization was due to the use of a zinc–copper couple in the preparation of the catalyst.[11] Two observations regarding the above reaction are worth noting.

First, the yields of lactone **16** were 15–20% higher with the use of the Zn–Cu couple rather than Zn dust. Second, we observed a complete regioselectivity in the normally unpredictable α and/or γ modes of addition.[12]

When the active Zn–Cu catalyst was prepared in HOAc, it was normally "rinsed" with anhydrous ethyl ether. The use of this catalyst then led to 100% α addition of the crotonate unit to a carbonyl. We have observed this behavior in other cyclopentanones as well.[13] Use of activated zinc dust or vacuum-dried Zn–Cu couple almost always produced mixtures of products contaminated with some γ isomer as evidenced from the IR absorptions due to the α,β-unsaturated ester moiety. Since the regiochemical outcome of the Reformatsky reaction of bromocrotonates is sensitive to the polarity of the medium, traces of HOAc in the catalyst may favor the α addition normally expected to take place in solvents such as THF or dioxane.

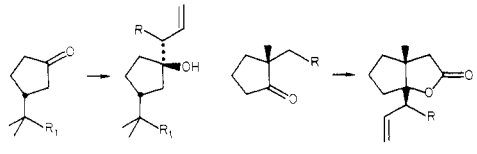
The lactone **16** was subjected to a low-temperature elimination effected by lithium diisopropylamine in THF, but the yields of acid **17** were quite low (<30%). Subsequently, we found that a 92% yield could be achieved by the use of 1 equiv of DBU in THF at room temperature. The ^{13}C NMR spectra of acids **17** obtained in the above two manners were not identical. Both showed the presence of two diastereomers but in varying proportions. We have abandoned the low-temperature method in favor of the higher yielding procedure. The dienic acid **17** was shown by ^{13}C NMR and by 300-MHz ^1H NMR to be approxi-

Scheme I[a,b]



[a] Reagents: (i) Br_2/HOAC/0 °C, (ii) NaOMe/MeOH/Δ, (iii) $O_3/CH_2Cl_2/Me_2S$, (iv) NaH/DME/$BrCH_2CO_2Et$, (v) LiI/DMF/Δ, (vi) Zn-Cu/$BrCH_2CH{=}CHCO_2Et/Et_2O$/Δ, (vii) DBU/THF/room temperature, (viii) $(COCl)_2$/benzene/room temperature, (ix) CH_3CHN_2, (x) $Cu(acac)_2/CuSO_4$/benzene/Δ, (xi) Vycor ($PbCO_3$), 550 °C (0.4 mm), (xii) $NaBH_4$/MeOH, Et_2O, (xiii) NaH/THF-CS_2-MeI, (xiv) (n-Bu)$_3$SnH, toluene/Δ, (xv) KOH, EtOH, H_2O, reflux, (xvi) NaH/THF/Me_2SO_4. [b] R = CO_2Et.

(7) Wolinsky, J.; Chan, D. *J. Org. Chem.* **1965**, *30*, 41.
(8) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602. See also Yates, P.; Jorgenson, M. J.; Singh, P. *J. Am. Chem. Soc.* **1969**, *91*, 4739.
(9) Coates, R. M.; Vettel, P. R. *J. Org. Chem.* **1980**, *45*, 5430.
(10) We found it advantageous to hydrolyze crude methyl pulegonate to the acid (which was easily purified by extraction) and then reesterify with NaH/Me_2SO_4.
(11) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.
(12) For a recent review of Reformatsky reaction, see Rathke, M. W. *Org. React.* **1975**, *22*, 423.
(13) We have performed a similar reaction on the ketones below (geared toward the synthesis of zizanoic and isocomenic acids). In these cases as well as in various model studies the use of a Zn–Cu couple produced only the α-addition products.



mately an 80:20 mixture of Z/E diastereomers. It proved impossible to separate or even unambiguously assign these diastereomers. For *convenience only* we indicate the major isomer as Z (shown in Scheme I). However, this mixture was easily carried through to the tricyclic ketone **20** at which point only one diastereomer was obtained (evidenced by both ^{13}C and high-field ^1H NMR spectra). This demonstrated that the diastereomeric inhomogeneity in **17–19** was due to the E/Z diastereomers only. The acid **17** was converted to diazo ketone **18** by a previously described method[15] and the diazo ketone subjected to cyclopropanation.

The conditions normally used to effect cyclopropanations in our laboratory[2,15,19] ($Cu(acac)_2$/benzene/reflux) gave poor yields of **19**. This was not surprising considering the diminished electron content of the acrylate double bond in **18**. We were able to improve the low yields slightly by performing the reaction in the presence of Me_2S or diphenyl sulfide. Under such conditions the keto carbenoid derived from **18** may have generated a sulfonium ylide which would then form **19** through a Michael-type addition to the acrylate followed by internal alkylation.[16] The yields were not excellent but this could be attributed to the reluctance of β,β-disubstituted acrylates to act as Michael receptors, even in an intramolecular mode.

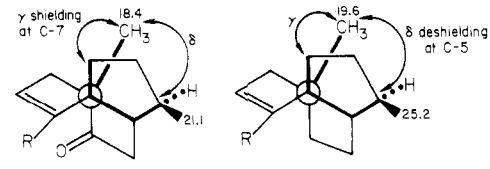
Surprisingly, however, the cyclopropanes obtained in the above two fashions were *identical* (their diastereomeric composition reflected that of acid **17** and diazo ketone **18**). We interpreted this to mean that the original low yield of **19** obtained under "true cyclopropanation" conditions was due to the nitrogen ylide-type addition rather than a carbenoid-like cyclopropanation. We, therefore, reinforced such behavior by performing the reaction in benzene under heterogeneous conditions. When **18** was slowly added to refluxing benzene containing a large excess of suspended anhydrous $CuSO_4$ together with a catalytic quantity of $Cu(acac)_2$, 70–75% yields of cyclopropane **19** were attained.[17] To our knowledge this constitutes a unique example of a high-yielding cyclopropanation of an α,β-unsaturated ester without the formation of pyrazoline.[17,18]

Flash pyrolysis of **19** over a $PbCO_3$-treated Vycor column[2,15,19] furnished the tricyclic ketone **20** in ~50% yield. This compound was shown to be one diastereomer by ^{13}C NMR as well as by 300-MHz ^1H NMR spectra. The deoxygenation was carried out with conditions developed by Barton[20] and utilized most recently by Hart.[21] Thus, $NaBH_4$ reduction of **20** gave a mixture of alcohols which were converted to the corresponding xanthates and reduced by the action of freshly prepared $(n\text{-Bu})_3SnH$.[22]

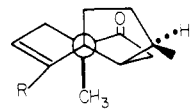
The tricyclic ester **5** was obtained in an overall yield of 50–60% from the ketone **20** and was shown to be one diastereomer only.

Stereochemical Assignments

On the basis of a rather extensive study of ^{13}C NMR shifts of various substituted bicyclic ketones,[19] we were able to deduce relative stereochemistry of **20** and **5** with a fair degree of confidence in spite of having only one diastereomer in our possesion. We assigned the relative peripheral stereochemistry of all intermediates on the basis of the chemical shifts of the secondary methyl group whose configuration remained fixed. (See chemical shift data in Scheme I.)



20 **5**



21

R = CO_2Et

In agreement with the shielding arguments (γ effects)[19,23] utilized in the assignment of model compounds, we monitored the introduction of side chains into **12** and the subsequent intermediates. We assigned the trans stereochemistry to **13** and **15** based on the absence of shielding at the secondary methyl group. The chemical shift of this methyl remained remarkably constant, indicating no serious perturbation in its spatial environment. Lactone **16** was assigned as cis fused on the basis of the known reluctance of trans lactones to form under mild conditions (35 °C, ether).[24] The final stereochemistry of **20** and **5** was deduced as follows. In simple bicyclo[3.3.0]octanones the angular methyl should resonate around 21 ppm if unshielded. A γ effect of an alkyl substituent would shield this methyl to an extent of 5 ppm, placing it around 16 ppm.[19] In ketone **20** as well as in **5** the angular methyl is *shielded* by the cis-situated methylene (C-7). However, it is also exposed to a syn-1,3-diaxial interaction with C-5. This interaction or δ effect is deshielding[23] and would place the methyl downfield. The combination of these two effects (a bit more pronounced in **5** due to a removal of sp^2-hybridized carbonyl) will produce resonances placed somewhere between the two extremes. The observed shift of 18.4 and 19.6 ppm for **20** and **5**, respectively, would support these arguments. The only other possible diastereomer which could be considered (even though impossibly strained) is the trans-fused system **21**. However,

(14) Procedure adopted from Ciufolin, M. A.; Koreeda, M. Central and Great Lakes Regional Meeting of the American Chemical Society, Dayton, OH, May 1981; American Chemical Society: Washington, DC, Abstract 272.

(15) For representative experimental, see Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.

(16) For a mechanistic discussion of ylide cyclopropanations, see Trost, B. M.; Melvin, L. S., Jr. "Sulfur Ylides", Organic Chemistry Monographs; Academic Press: New York, 1975; Vol. 31.

(17) The word "catalyst" applies only to $Cu(acac)_2$ used in 10 mol % $CuSO_4$ has been used in 2-fold excess over diazoketone. The use of $CuSO_4$ for acrylic cyclopropanation in modest yields has been reported. Becker, D.; Lowenthal, H. J. E. *Isr. J. Chem.* **1972**, *10*, 375.

(18) We believe that pyrazoline is not an intermediate since temperatures higher than refluxing benzene are required for its decomposition to cyclopropane. The amount of N_2 evolved in this reaction is stoichiometric and immediate.

(19) Hudlicky, T.; Koszyk, F. J.; Dochwat, D. M.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 2911.

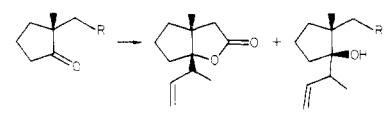
(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1975**, 1574.

(21) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367.

(22) Van Der Kerk, G. J. M.; Noltes, J. G.; Suijten, J. G. H. *J. Appl. Chem.* **1937**, *7*, 366.

(23) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: London, 1978.

(24) The formation of a trans-fused lactone did not take place under the reaction conditions used in the following instance (refluxing ether):



R = CO_2Et

Therefore, it is unlikely that lactone **16** is trans-fused.

in this compound the angular methyl should be around 21 ppm.

If the assignments of the methyl groups were switched in **20**, the secondary methyl would be ascribed 18.4 ppm which could only be possible in the presence of shielding. The examination of a model of **21** indicated no possibility of such shielding, ruling out not only the assignment of the methyl groups in this fashion but also the trans-fused ring system. A good reinforcement for the above arguments comes from the comparison of Büchi stereomodels of **20**, **21**, and **5** with models of isocomene and derivatives thereof in the context of their ^{13}C NMR spectra which are known.[25] Our assignment compares favorably with these data. An explanation of a pronounced downfield shift of the "pulegonic" methyl in **20** and in **5** compared with those in intermediates **12–19** can be formed on the basis of the proximity of this methyl to the deshielding cone of the ester carbonyl, an arrangement possible only in the sterically rigid tricyclic systems **20** and **5**. Naturally, the unambiguous confirmation of these assignments will have to await the conversion of **5** to retigeranic acid (**3**) and the comparison of natural and synthetic substances.

Conclusion

We have demonstrated the possibility of access to cyclopentene carboxylates by an extension of cyclopentene annulation to exocyclic acrylates. The difficult problem of forming cyclopropanes from these acrylates has been solved by altering the conditions and thus the possible mechanism of the reaction. The tricyclic ester **5** is a potential intermediate on its way to retigeranic acid. The union of **5** with proper fragment derived from optically active menthene is the subject of current study in our laboratory as is the synthesis of other terpenoid cyclopentene carboxylates by this method. We hope to report our progress in these domains in the near future.

Experimental Section

Melting and boiling points are uncorrected. Melting points were determined on a Mel-Temp apparatus. ^1H NMR spectra were determined at 60 MHz on a Varian T-60 spectrometer or at 300 MHz on a Nicolet 300 spectrometer. ^{13}C NMR spectra were determined on a Varian CFT-20 spectrometer. Chemical shifts are reported in parts per million relative to internal tetramethylsilane. Infrared spectra were recorded on a Pye-Unicam 3-300 or on a Perkin-Elmer Model 257 infrared spectrophotometer. Mass spectra were obtained on a Du Pont 20-491 instrument (low resolution) or on a double-focusing (high resolution) Du Pont 21-110C instrument.

Tetrahydrofuran was freshly distilled before use from potassium and benzophenone. Anhydrous ethyl ether was Mallinckrodt reagent grade and was used without further purification. All other solvents were purified by filtration through neutral alumina. Medium-pressure liquid chromatography was performed with E. Merck silica gel columns. Column chromatography was performed with Macherey Nagle and Co. silica gel 60 (70–270 mesh) or J. T. Baker 1-0540 alumina. All nonhydrolytic reactions were performed under nigrogen atmosphere.

The purity of all compounds was ascertained by chromatographic and spectral means (chiefly analytical thin-layer chromatography and ^{13}C NMR spectra) with emphasis on the latter.

2β-(Carbomethoxy)-3α-methylcyclopentanone (13). Methyl pulegonate was prepared by either of the published methods.[7,8] In the former the crude ester was hydrolyzed to the acid **12** which was easily purified by extraction (**12**): IR (neat) 3400 (br), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 7 Hz), 1.7 (br s, 6 H), 1.4–2.8 (m, 5 H), 3.0 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.5 (q), 20.9 (q), 21.8 (q), 30.1 (t), 33.5 (t), 40.6 (d), 55.3 (d), 126.3 (s), 133.6 (s), 181.6 (s).

Spectral data for the methyl ester of **12**: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (d, 3 H, J = 7 Hz), 1.6 (br s, 3 H), 1.7 (br s, 3 H), 1.8–2.4 (m, 5 H), 3.0 (br d, 1 H), 3.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 19.4 (q), 20.6 (q), 21.2 (q), 30.1 (t), 33.4 (t), 40.5 (d), 51.2 (q), 55.4 (d), 125.5 (s), 134.0 (s), 175.6 (s).

In the latter procedure[8] the crude methyl pulegonate (14.45 g, 0.08 mol) was dissolved in 100 mL of methanol and ozonized at dry ice/2-propanol temperature, using a Purification Sciences Inc. ozone generator (5–7 std ft^3 h^{-1} of O_2, 3.5 h). After the solution had been purged (N_2), 50 mL of dimethyl sulfide was added, causing the solution to reflux mildly.

Upon attaining room temperature (2.0 h), the mixture was concentrated in vacuo and partitioned between 50 mL of ethyl ether and 100 mL of dilute aqueous HCl. The aqueous phase was extracted 3 times with 50 mL of ethyl ether, and the combined organic extracts were washed with brine and dried ($MgSO_4$).

Solvent was removed in vacuo and the residue distilled through a short-path column to give 9.5 g (76%) of keto ester **13**: bp 69–70 °C (0.3 mm); overall yield from pulegone, 60–65%; IR (neat) 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 3 H, J = 7 Hz), 2.0–2.8 (m, 6 H), 3.8 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 18.7 (q), 28.8 (t), 35.9 (d), 38.8 (t), 51.7 (q), 62.4 (d); mass spectrum (70 eV), m/e (relative intensity) 156 (M) (20), 141 (22), 128 (42), 125 (30), 109 (35), 101 (48), 96 (36), 69 (B), 55 (30).

Anal. Calcd for $C_8H_{12}O_3$: 156.0786. Found: 156.0790.

2β-[(Carboethoxy)methyl]-2-(carbomethoxy)-3α-methylcyclopentanone (14). Sodium hydride (1.7 g of 60% oil dispersion, 0.0425 mol) was rinsed 3 times with 50 mL of dry dimethoxyethane, and the oil-free solid was suspended in 60 mL of the same solvent.

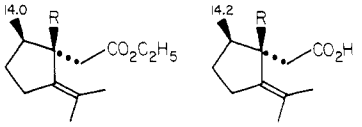
To this stirred suspension was added dropwise over a 5-min period a solution of keto ester **13** (6.0 g, 0.0385 mol) in 15 mL of dry DME. After the mixture was stirred for an additional 15 min at room temperature, ethyl bromoacetate (13 mL, 0.0778 mol) was added in one portion, and the now yellow-white mixture was warmed under reflux for 15 h.

The cooled mixture was partitioned between 50 mL of ethyl ether and 100 mL of dilute aqueous HCl. The aqueous phase was extracted 3 times with 50 mL of ethyl ether, and the combined organic extracts were washed with brine and dried ($MgSO_4$).

The solvent was removed in vacuo and the residue was distilled through a short-path column to give, after a forerun of ethyl bromoacetate, 8.0 g (86%) of diester **14**: bp 110–115 °C (0.10 mm); IR (neat) 1750, 1720 cm^{-1} (br); ^1H NMR ($CDCl_3$) δ 1.0 (d, 3 H, J = 7 Hz), 1.2 (t, 3 H, J = 7 Hz), 1.8–2.6 (m, 5 H), 2.8 (AB q, J_{AB} = 14 Hz), 3.65 (s, 3 H), 4.1 (q, 2 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 15.5 (q), 28.2 (t), 36.6 (t), 38.9 (t), 39.3 (d), 52.0 (q), 60.7 (t), 62.2 (s), 170.1 (s), 170.7 (s), 215.0 (s); mass spectrum (70 eV), m/e (relative intensity) 242 (M, 10), 210 (30), 197 (35), 155 (40), 109 (65), 99 (60), 81 (90), 55 (B).

Anal. Calcd for $C_{12}H_{18}O_5$: 242.1154. Found: 242.1159.

During the initial phases of research we also alkylated the methyl pulegonate (LDA, –78 °C, THF) and obtained the diester i. The hydrolysis of this compound (KOH, EtOH, reflux) proved troublesome, producing only monoacid ii even in the presence of ethylene glycol and after ~72 h of reflux. In view of the ease of keto ester alkylation and the subsequent steps, we have abandoned this approach. For completeness we include the spectral data for i and ii.



i ii

Diester i: IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (d, 3 H, J = 7 Hz), 1.2 (t, 3 H, J = 7 Hz), 1.6 (br s, 3 H), 1.7 (br s, 3 H), 1.8–2.4 (m, 5 H), 2.8 (AB q, 2 H, J_{AB} = 14 Hz), 3.61 (s, 3 H), 4.2 (q, 2 H, J v 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 14.0 (q), 25.8 (t), 20.4 (q), 22.2 (q), 31.7 (t), 32.2 (t), 38.8 (t), 43.8 (d), 51.4 (q), 59.8 (t), 62.2 (s); mass spectrum (70 eV), m/e (relative intensity)

(25) See, for example, ^{13}C NMR data on substances related to isocome: Zalkow, L.; Harris, R., III; Burke, N. I. *J. Nat. Prod.* **1979**, *42*, 96. Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, 103, 82. Paquette, L. A.; Han, Y. K. *Ibid.* **1981**, 193, 1835.

269 (M) (30), 210 (80), 196 (70), 181 (B), 162 (40), 135 (70), 120 (60).

Monoacid ii: IR (neat) 3400–2700, 1720, 1700 cm^{-1} (br); ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz), 1.6 (br s, 3 H), 1.7 (br s, 3 H), 1.8–2.6 (m, 5 H), 2.98 (AB q, 2 H, J_{AB} = 14 Hz), 3.7 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 20.4 (q), 22.2 (q), 31.6 (t), 32.3 (t), 39.1 (t), 43.9 (d), 51.6 (q), 56.4 (s), 125.7 (s), 137.4 (s), 175.8 (s), 176.9 (s); mass spectrum (70 eV), m/e (relative intensity) 240 (M, 60), 194 (40), 181 (65), 180 (60), 121 (B), 84 (40).

Anal. Calcd for $C_{13}H_{20}O_4$: 240.1361. Found: 240.1354.

2β-[(Carboethoxy)methyl]-3α-methylcyclopentanone (15). Lithium iodide (15 g, 0.11 mol) was dissolved in 100 mL of dimethylformamide and diester **14** (5.0 g, 0.021 mol) was added in 15 mL of the same solvent. The solution was warmed under reflux for 2.0 h, cooled to room temperature, and partitioned between 100 mL of ethyl ether and 200 mL of dilute aqueous HCl.

The aqueous phase was extracted 6 times with 50 mL of ethyl ether, and the combined organic extracts were washed 6 times with 100 mL of water and then brine and dried ($MgSO_4$).

Solvent was removed in vacuo and the residue distilled to give 2.9 g (76%) of keto ester **15** [Kugelrohr, 105–120 °C (0.75 mm)]: IR (neat) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz), 1.2 (t, 3 H, J = 7 Hz), 1.8–2.6 (m, 5 H), 2.7 (AB q, 2 H, J_{AB} = 12 Hz), 3.7 (br s, 1 H), 4.2 (q, 2 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 19.1 (q), 29.7 (t), 32.3 (t), 36.9 (d), 37.6 (t), 53.2 (d), 60.6 (t), 172.0 (s), 218.6 (s).

Ethyl 2-(2,3,3a,6a-Tetrahydro-4α-methyl-2-oxocyclopentano[*b*]furan-6α-yl)but-3-enoate (16). Granulated zinc (30 mesh, 4.1 g) was stirred at room temperature for 0.5 h in 6.75 mL of a previously prepared stock solution of copper(II) diacetate hydrate [$Cu(OAc)_2 \cdot H_2O$, 16 g] in 300 mL of acetic acid.

The acetic acid was decanted and the Zn–Cu couple was washed thoroughly with anhydrous ethyl ether and then covered with 20 mL of the same solvent. To this stirred suspension was added dropwise a solution of keto ester **15** (4.0 g, 0.022 mol) and freshly distilled ethyl 4-bromocrotonate (5.2 g, 0.027 mol) in 10 mL of ether. Addition of iodine crystals (ca. 0.1 g) was found to aid in initiation of the reaction, and the addition proceeded so as to keep the mixture at gentle reflux.

Following addition, the mixture was warmed at reflux an additional 2.0 h, cooled to room temperature, and partitioned between 50 mL of ethyl ether and 100 mL of 10% aqueous acetic acid. The aqueous phase was extracted 3 times with 50 mL of ethyl ether, and the combined organic extracts were washed with brine and dried (Na_2SO_4).

Solvent was removed in vacuo and the residue distilled through a short-path column to give 4.46 g (81%) of lactone **16**: bp 124–127 °C (0.1 mm); IR (neat) 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (d, 3 H, J = 6 Hz), 1.3 (t, 3 H, J = 7 Hz), 1.6–2.8 (m, 8 H), 3.3 (d, 1 H, J = 8 Hz), 4.2 (q, 2 H, J = 7 Hz), 5.1–6.1 (ABX m, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 18.4 (q), 32.1 (t), 35.3 (t), 35.5 (t), 41.8 (d), 48.1 (d), 57.6 (d), 60.6 (t), 95.7 (s), 120.9 (t), 130.8 (d), 170.1 (s); mass spectrum (70 eV), m/e (relative intensity) 252 (M, 20), 234 (20), 206 (20), 178 (30), 138 (80), 68 (40), 54 (B).

Anal. Calcd for $C_{14}H_{20}O_4$: 252.1361. Found: 252.1360.

[5α-Methyl-2-(vinyl(carboethoxy)methylene)cyclopentyl]acetic Acid (17). Lactone **16** (6.0 g, 0.024 mol) was dissolved in 140 mL of dry THF and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 4.0 g, 0.026 mol) in 10 mL of THF was added dropwise.

The solution was stirred for 8 h at room temperature, diluted with 100 mL of methylene chloride, was 3 times with 50 mL of dilute aqueous HCl followed by brine and dried (Na_2SO_4).

Solvent was removed in vacuo and the residue distilled through a short-path column to give 5.5 g (92%) of dienic acid **17**, bp 110–112 °C (0.01 mm), as a ca. 80/20 mixture of Z/E diastereomers. The spectral data have been obtained on this mixture, but only the absorptions corresponding to the major component are listed for ^1H and ^{13}C NMR. **17**: IR (neat) 3400–2700, 1710, 1700, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 6 Hz), 1.3 (t, 3 H, J = 7 Hz), 1.8–3.2 (m, 8 H), 4.2 (q, 2 H, J = 7 Hz), 5.1–6.6 (ABX m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 20.0 (q), 27.5 (t), 30.0 (t), 38.3 (t), 38.6 (d), 47.9 (d), 60.7 (t), 116.2 (t), 126.7 (s), 131.9 (d), 155.0 (s), 167.7 (s), 176.0 (s); mass spectrum (70 eV), m/e (relative intensity), 252 (M, 5), 206 (10), 138 (20), 90 (30), 54 (B).

Anal. Calcd for $C_{14}H_{20}O_4$: 252.1361. Found: 252.1357.

3-Diazo-1-[5α-methyl-2-(vinyl(carboethoxy)methylene)cyclopent-1-yl]butan-2-one (18). Dienic acid **17** (9.0 g, 0.036 mol) was dissolved in 120 mL of dry benzene. Freshly distilled oxalyl chloride (9.0 g, 0.071 mol) was added in one portion and the mixture stirred at room temperature for 8 h.

Solvent was removed in vacuo and the crude oil distilled to give 7.7 g (80%) of acid chloride [Kugelrohr, 120–130 °C bath (0.3 mm)]: IR (neat) 1790, 1710 cm^{-1}.

Ethereal diazoethane was prepared by the slow addition at 0 °C of 18 g of *N*-nitroso-*N*-ethylurea to a two-phase system consisting of 55 mL of 50% aqueous potassium hydroxide and 180 mL of ethyl ether. The solution was swirled as addition proceeded and after 15 min the ethereal layer was decanted onto KOH pellets for drying at 0 °C. After 0.5 h the ethereal layer was again decanted into a precooled flask and the acid chloride (9.0 g, 0.033 mol) was added dropwise (neat).

The solution was permitted to stand 0.5 h, heated briefly to dispel excess diazoethane, and concentrated in vacuo to give 9.6 g of diazo ketone **18**, essentially pure by TLC analysis. If an impure diazo ketone was obtained, it could be repidly (<1.5 h) chromatographed on silica gel/CH_2Cl_2. As in the case of acid **17**, the NMR absorptions represent the major component. **18**: IR (neat) 2075, 1720, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz), 1.22 (t, 3 H, J = 7 Hz), 1.96 (s, 3 H), 1.8–3.2 (m, 8 H), 4.2 (q, 2 H, J = 7 Hz), 4.9–6.4 (ABX m, 3 H); ^{13}C NMR ($CDCl_3$) δ 8.2 (q), 14.3 (q), 20.1 (q), 30.4 (t), 31.6 (t), 39.0 (d), 41.6 (t), 46.4 (d), 59.5 (t), 61.0 (s), 115.3 (t), 127.2 (s), 130.6 (d), 154.9 (s), 167.9 (s), 192.4 (s); mass spectrum (70 eV), m/e (relative intensity) 290 (M, 10), 178 (20), 138 (50), 96 (60), 54 (B).

Anal. Calcd for $C_{16}H_{22}O_3N_2$: 290.1630. Found: 290.1639.

(1α,6α)-9α-Methyl-4β-methyl-5α-(carboethoxy)-5β-vinyltricyclo[4.3.0.0^{4,6}]nonan-3-one (19). A solution of diazo ketone **18** (5.5 g, 0.019 mol) in 50 mL of benzene was added dropwise over a 20-min period to 600 mL of refluxing benzene containing 20 g of anhydrous cupric sulfate and 0.5 g of copper(II) acetoacetonate. The mixture was kept at reflux for 1.0 h, cooled to room temperature, and filtered through alumina, eluting with methylene chloride.

Solvent was removed in vacuo and the crude oil distilled to give 3.8 g (75%) of vinylcyclopropane **19**, bp 80–85 °C (0.01 mm). Spectral data correspond to the major diastereomer. **19**: IR (neat) 1720, 1705, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz), 1.1 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 1.4–2.8 (m, 8 H), 4.1 (q, 2 H, J = 7 Hz), 5.0–6.2 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 8.5 (q), 14.4 (q), 19.3 (q), 29.8 (t), 33.5 (t), 34.5 (s), 41.6 (s), 42.7 (t), 46.9 (d), 53.3 (s), 53.8 (s), 60.8 (t), 118.7 (t), 131.7 (d), 174.8 (s), 231.6 (s); mass spectrum (70 eV), m/e (relative intensity) 262 (M, 20), 234 (30), 216 (35), 206 (25), 178 (20), 138 (25), 96 (55), 54 (B).

Anal. Calcd for $C_{16}H_{22}O_3$: 262.1569. Found: 262.1579.

(4β,8α)-1α-Methyl-5β-methyl-9-(carboethoxy)tricyclo[6.3.0.0^{4,8}]undec-9-en-2-one (20). Vinylcyclopropane **19** (2.47 g, 0.009 mol) was vaporized [120 °C (0.1 mm)] through a horizontally situated hot tube (Vycor or Pyrex, 580–600 °C) and condensed in a liquid nitrogen cooled trap. The glass tubes were conditioned prior to use with a slurry of lead carbonate in water and dried in vacuo at ~300 °C. The *total* distillation time was approximately 10 min.

The crude condensate was chromatographed on silica gel (3:1 hexane/Et_2O) to give 1.6 g (60%) of tricyclic ketone **20**. No stereoisomeric material otherwise consistent with the structure of **20** was found at this point, indicating the convergence of the diastereomeric mixture originated with acid **17**. **20**: IR (neat) 1710, 1735, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 7 Hz), 1.05 (s, 3 H), 1.2 (t, 3 H, J = 7 Hz), 1.4–2.8 (m, 10 H), 4.1 (q, 2 H, J = 7 Hz), 6.6 (t, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 18.4 (q), 21.1 (q), 30.7 (t), 34.6 (t), 40.0 (t), 42.3 (d), 44.8 (t), 57.3 (s), 60.0 (t), 66.7 (s), 141.0 (s), 161.4 (d), 164.2 (s), 224.6 (s); mass spectrum (70 eV), m/e (relative intensity) 262 (M, 15), 244 (10), 216 (30), 188 (30), 166 (35), 146 (40), 118 (52), 104 (65), 91 (B), 76 (74), 54 (85).

Anal. Calcd for $C_{16}H_{22}O_3$: 262.1569. Found: 262.1572.

(4β,8α)-1α-Methyl-5β-methyl-9-(carboethoxy)tricyclo[6.3.0.0^{4,8}]undec-9-ene (5). To a stirred solution of tricyclic ketone **20** (1.0 g, 0.004 mol) in 50 mL of anhydrous ether was added sodium borohydride powder (0.6 g, 0.016 mol) followed by 1.0 mL of methanol. The mixture was stirred at room temperature for

6 h, after which time TLC indicated absence of starting material.

The mixture was poured slowly into 50 mL of water, carefully acidified with 50 mL of 5% aqueous HCl, and extracted 3 times with 50 mL of methylene chloride. The combined organic extracts were washed with brine and dried (Na_2SO_4).

Solvent was removed in vacuo, giving 0.94 g (93%) of crude alcohols suitable for the next step. Spectral data: IR (neat) 3400, 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8–5.9 (2 m, ca. 60:40); ^{13}C NMR ($CDCl_3$) δ 81.0 (d), 79.6 (d); mass spectrum (70 eV), *m/e* (relative intensity) 264 (M, 10), 246 (15), 218 (25), 200 (20), 167 (30), 149 (B), 105 (45), 95 (60), 91 (65), 77 (52).

Anal. Calcd for $C_{16}H_{14}O_3$: 264.1725. Found: 264.1732.

Sodium hydride (0.19 g, 60% oil dispersion, 0.005 mol) was rinsed 3 times with 50 mL of dry tetrahydrofuran, and the oil free solid was suspended in 20 mL of the same solvent. The alcohol (0.94 g, 0.004 mol) was added in 10 mL of THF followed by 20 mg of imidazole. The solution was refluxed 1.0 h followed by the addition of 3 mL carbon disulfide in one portion. The solution was refluxed 30 min followed by the addition of 3 mL of iodomethane in one portion. The mixture was refluxed 30 min, cooled to room temperature, and partitioned between 50 mL of methylene chloride and 50 mL of water. The aqueous phase was extracted twice with 50 mL of methylene chloride, and the combined organic extracts were washed with brine and dried (Na_2SO_4).

Solvent was removed in vacuo and the residue filtered through silica to give 1.0 g (82%) of xanthates suitable for the next step.

Spectral data: IR (neat) 1700, 1220, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6, 2.8 (s, 3 H), 5.8, 5.9 (m, ca. 60:40, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.8 (q), double intensity, 90.5 (d), 92.5 (d).

To 1.0 g (0.0034 mol) of tri-*n*-butyltin hydride and 5 mg of AIBN in 30 mL of dry, degassed (N_2) toluene were added the xanthates (1.0 g, 0.003 mol) in 25 mL of the same solvent over a 10-min period. The mixture was warmed to reflux during addition, refluxed an additional 6 h after addition was complete, cooled to room temperature, and concentrated in vacuo.

The pure product was isolated by preparative TLC (2:8 CH_2Cl_2/hexanes, four to six elutions). The band corresponding to R_f 0.6 gave 662 mg (70%) of tricyclic ester **5** as one diasteromer.

5: IR (neat) 1710, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, 3 H, J = 7 Hz), 1.1 (s, 3 H), 1.2 (t, 3 H, J = 7 Hz), 1.4–2.6 (m, 12 H), 4.1 (q, 2 H, J = 7 Hz), 6.6 (t, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 19.6 (q), 25.2 (q), 28.6 (t), 30.7 (t), 36.3 (t), 40.3 (t), 41.5 (d), 46.9 (t), 52.5 (s), 59.8 (d), 59.8 (t), 68.7 (s), 141.1 (d), 142.1 (s), 165.4 (s); mass spectrum (70 eV), *m/e* (relative intensity) 248 (M, 40), 202 (45), 174 (50), 118 (72), 104 (80), 90 (B), 78 (72), 54 (95).

Anal. Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1777.

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Registry No. **5**, 80781-43-7; **11**, 89-82-7; **12**, 7712-68-7; **12** methyl ester, 30165-01-6; **13**, 80796-76-5; **14**, 80781-44-8; **15**, 80781-45-9; **16**, 80781-46-0; (*E*)-**17**, 80781-47-1; (*Z*)-**17**, 80796-77-6; **17** acid chloride, 80781-48-2; **18**, 80781-49-3; **19**, 80781-50-6; **20**, 80781-51-7; **20** alcohol, 80781-52-8; **20** xanthate, 80781-53-9; i, 80781-54-0; ii, 80781-55-1; ethyl bromoacetate, 105-36-2; diazoethane, 1117-96-0.

Synthesis and Carbon-13 Nuclear Magnetic Resonance Assignments of Xenognosin

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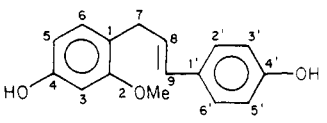
Xenognosin (**1**) is a modified flavonoid isolated from gum tragacanth, and it stands as the first natural host recognition substance for parasitic angiosperms. Xenognosin (**1**) was synthesized by converting umbelliferone (**2**) to the key aldehyde **6** which was treated with the aryllithium derived from **7**. The resulting alcohol **8** was heated in the presence of methyl sulfoxide to give **1**. In addition, a study of the ^{13}C NMR spectrum of **1** was undertaken.

Xenognosin (**1**) is a modified chalcone that was isolated[1] from gum tragacanth, and it stands as the first host recognition substance for parasitic angiosperms. Since xenognosin (**1**) was obtained in only microgram amounts, its structure elucidation was based solely on the study of its ^1H NMR and mass spectral data.



1

We herein report on an efficient synthetic scheme (Scheme I) for this biologically active compound that confirms its structure and also makes it available in sufficient amounts for further biological evaluations.

Xenognosin (**1**) was synthesized by first methoxymethylating umbelliferone (**2**) by treatment with methoxymethyl chloride in alkaline medium and in the presence of Adogen 464 as a phase-transfer catalyst.[2] The product, **3**, was hydrogenated in ethanol solution in the presence of 10% Pd/C to give the ethyl ester **4**, which was then methylated to **5** by using methyl iodide and anhydrous potassium carbonate. Diisobutylaluminum hydride reduction of **5** furnished **6** in about 75% yield. Unfortunately, the unreacted ester could not be easily separated from the product. As a result, **5** was alternatively reduced with lithium aluminum hydride to the corresponding alcohol which was then oxidized by using pyridinium chlorochromate to give the aldehyde **6** in an overall yield of 80% from **2**.

p-Bromophenol was then conveniently methoxymethylated by refluxing with dimethoxymethane[3] in the

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