An Attempted Synthesis of

Camphor-8-oic Acid Derivatives

by

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Thesis

for the

Degree of Bachelor of Science

in

Chemistry

College of Liberal Arts and Sciences

University of Illinois

Urbana, Illinois

1987

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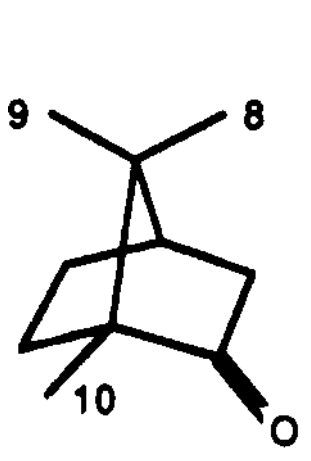
Introduction

Strict delineation of the position of functional groups is important for evaluating the interactions of groups in both transition and ground state structures. To this end derivatives of camphor, 1, have been shown to be useful for mechanistic studies.[1] We have investigated the synthesis of camphor derivatives which are substituted at carbon 8. Using a carboxyl group as the substituent as in 2, we have the ability to hold two carbonyl groups in close proximity. Changing the substituents on the carboxyl will allow investigations of a variety of different systems.



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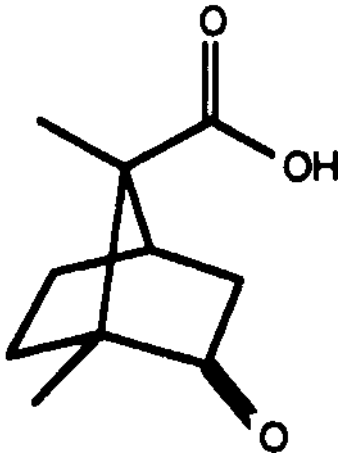
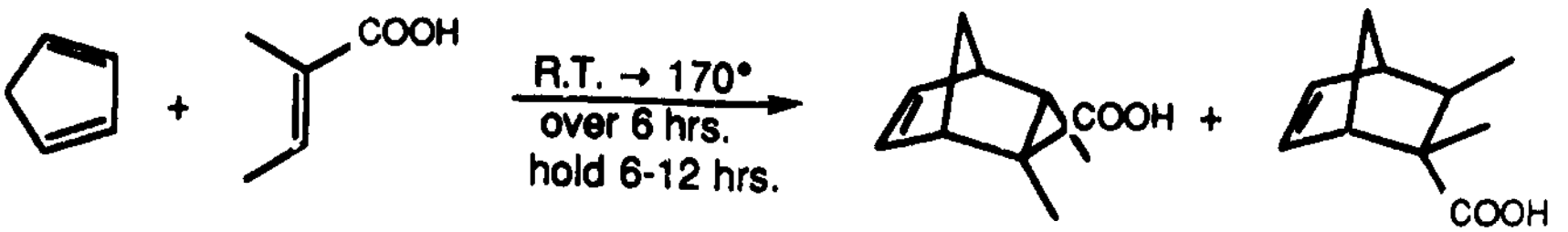


2

Historical

Our initial goal was the synthesis of camphor-8-oic acid, 2. A number of preparations for 2 or its lactone precursor, 3, have been reported. One of the earlier syntheses for the lactone was reported by Beckmann and Geiger (Scheme I).[2] They performed a Diels-Alder reaction between cyclopentadiene and tiglic acid which produced both the exo-, 4, and endo-, 5, isomers. The disadvantage of this synthesis is the exo-acid, which is the desired isomer, is the minor product from the reaction. The exo- and endo- isomers are separated through the iodolactonization of 5. This method of separating regio isomers in cyclic systems has long been in use.[3] The lactone, 3, is formed by allowing 4 to stand in 85% sulfuric acid. Beckmann and Geiger reported an overall lactone yield from tiglic acid of 5.4%[2] while Finch and Vaughan report a 9.5% yield of lactone.[4]

Scheme I



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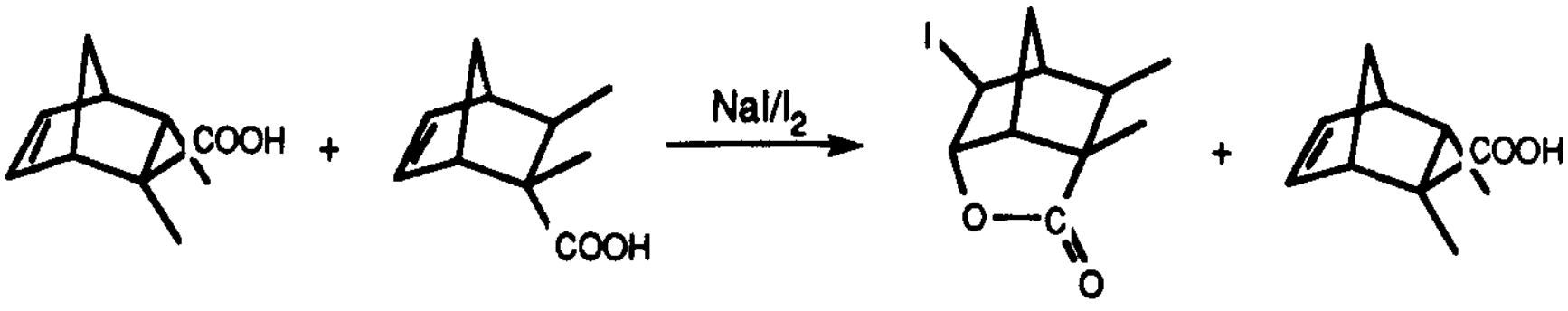
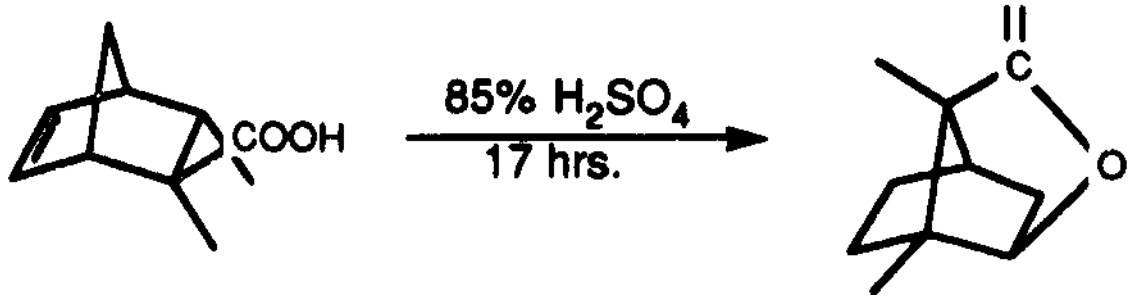


4 5 6 4



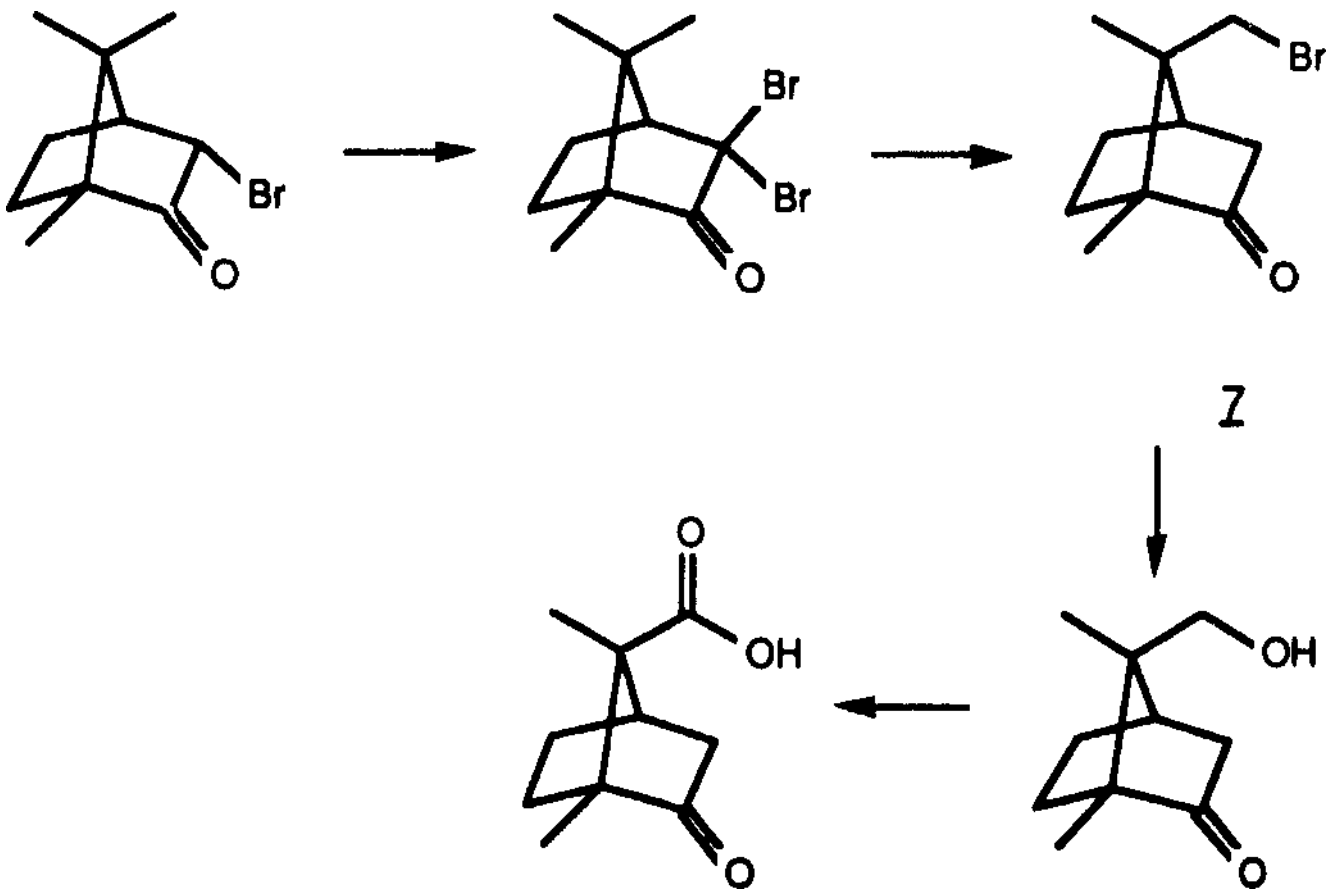
4 3

An alternative synthesis for 3 has been reported by Finch and Vaughan.[4] They conducted a Diels-Alder condensation with 2-acetoxy-1-butenonitrile and cyclopentadiene. This reaction resulted in only a 2.7% overall yield of 3 in 9 steps.

Another approach to 2 could be through (+)-8-bromocamphor, 7. The synthesis of this compound had been reported as an 11 step process which produced 7 in only about 6% yield.[5] In the 8th step of this process, 2 is produced. Money *et.al.*[6] have since reported a three step synthesis of 7 from (+)-3-bromocamphor in much higher yields than the earlier methods. In their initial communication they reported a 75% overall yield but in later communications they

report yields of approximately 40%. This synthesis does not proceed through 3, so it is conceivable (Scheme II) that Z could be hydrolized to the alcohol and the alcohol oxidized to form the acid.

Scheme II



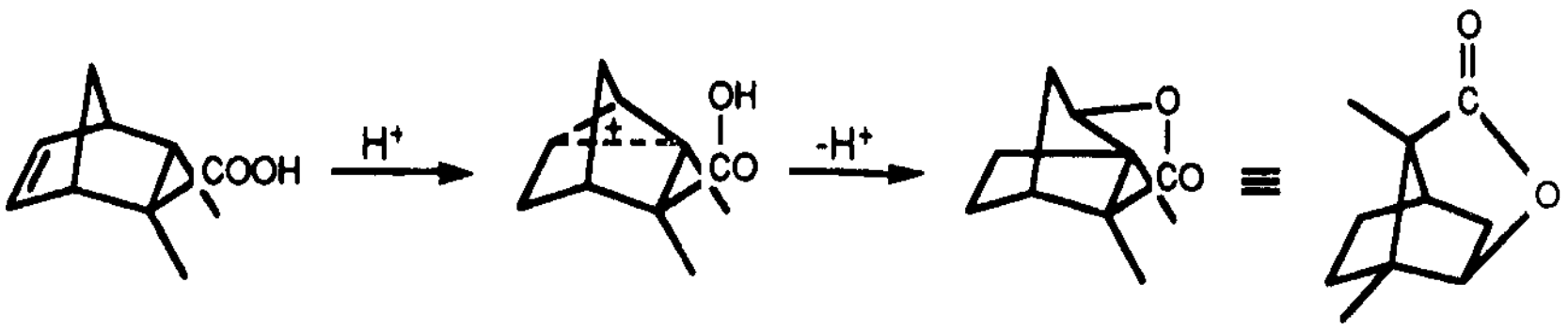
2

Results and Discussion

The synthesis that we employed to produce the lactone, 2, was based on that developed by Beckmann and Geiger.[2] Tiglic acid is reacted with freshly cracked cyclopentadiene (Scheme I) to yield the two Diels-Alder adducts 4 and 5. The minor, exo, adduct 4 is the desired isomer. The two adducts are separated by the formation of the iodolactone, 6 (Scheme I) from the endo adduct, 5. The two acids, 4 and 5, were dissolved in a sodium carbonate solution and treated with an aqueous sodium iodide/iodine solution to produce the 6. The unreacted exo-adduct, 4, remained in the basic solution while the iodolactone was extracted with ether. Other investigators reported that 6 could be removed by filtration.[2,4,7] In our experience, this procedure was ineffective.

The lactone, 3, of the exo adduct was formed by allowing 4 to stand overnight in 85% sulfuric acid. The sulfuric acid protonates the double bond causing a

Scheme III



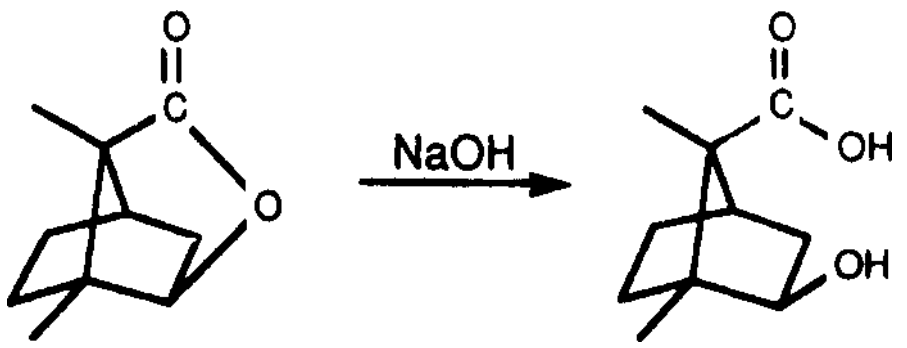
3

rearrangement through the carbonium ion to give 3 (Scheme III).

A number of different methods were attempted with 3 to obtain 2. The first

attempt was to hydrolize the lactone to give the acid-alcohol, 8, using 20% NaOH (Scheme IV). This hydrolysis was successful since no significant amount of 3 was recovered in the organic layer when the basic solution was extracted with ether prior to acidification. However, on acidification the sodium salt of 8 reverted back to the lactone. Attempts to acidify more carefully, such as using pH5 buffer as well as acidifying with 5% hydrochloric acid rather than concentrated hydrochloric acid, did not give satisfactory results.

Scheme IV

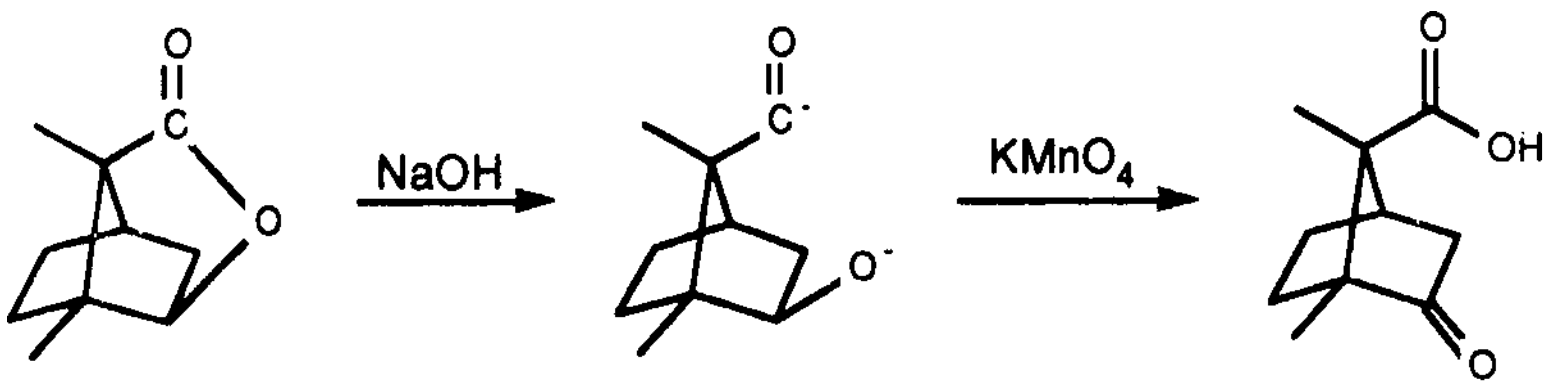


3 8

In the next attempt, 3 was hydrolized with base followed by addition of potassium permanganate directly to the basic reaction mixture to oxidize the ionic form of the open lactone, 9, to form 2 directly (Scheme V). The conditions used for this oxidation were those reported for the oxidation of manelic acid.[8] Reaction at -4°C as specified caused the reaction mixture to freeze during the 1.5 hour reaction period. A negligable amount of 2 was obtained from this reaction. The oxidation was repeated at room temperature from which a mixture of 2 and 3 was recovered. The acid 2 was obtained in less than 20% yield. The ^{1}H NMR spectrum showed no

signals indicative of starting material.

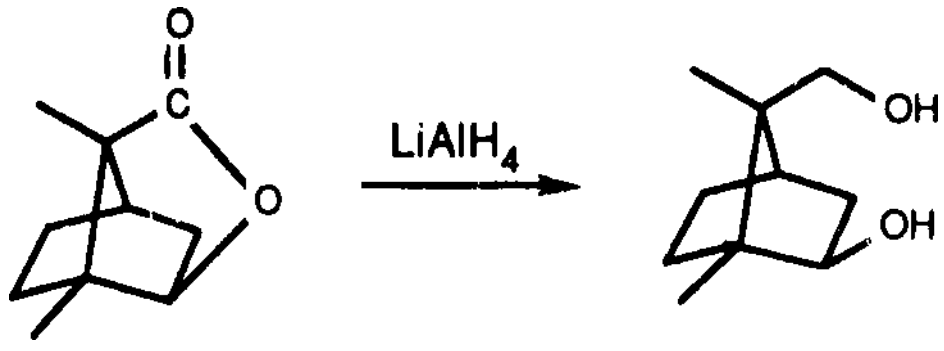
Scheme V



3 9 2

The method that produced the best results and was used in later reactions was reduction of the lactone ring with lithium aluminum hydride (Scheme VI) to form the diol, 10.[4] The reduction was carried out at room temperature for 4-6 hours. Yields were generally 50-60% and a product, of good purity as indicated by microanalysis, was obtained. The infrared spectrum of 10 indicated the loss of the lactone carbonyl at 1770 cm^{-1} and the appearance of a hydroxyl peak at 3330 cm^{-1}.

Scheme VI

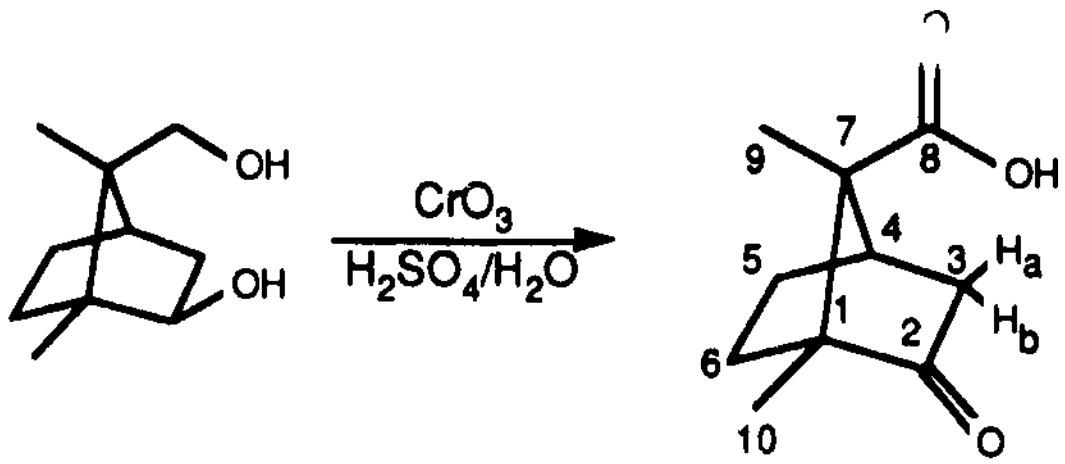


3 10

The acid, 2, was formed by oxidizing the diol, 10, with Jones' reagent. This

worked well producing 2 in good purity as indicated by the spectral properties (vide infra). Yields were relativly poor, usually 38-52%.

Scheme VII



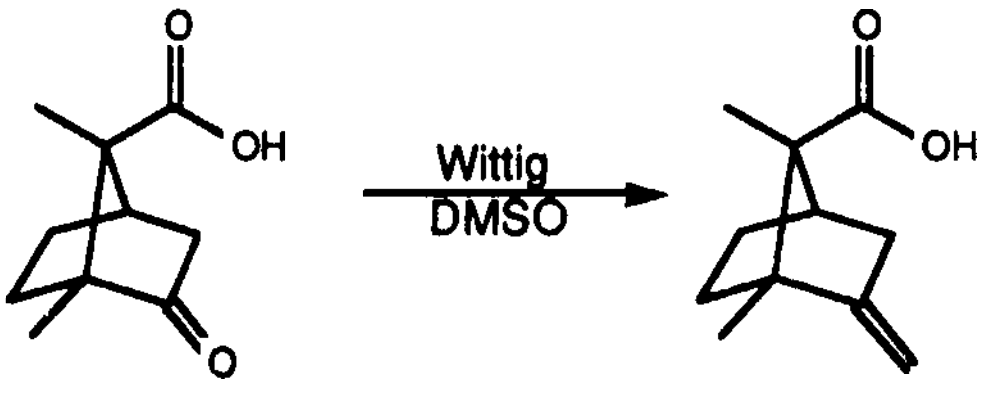
10 2

The structure of 2 was determined using ^{13}C and ^{1}H NMR as well as infrared spectroscopy. The ^{1}H NMR (figure 1) was difficult to interpret due to the large amount of coupling and the fact that most signals appear in the ∂ 0.9-2.5 ppm range. The most obvious assignments are at ∂ 10.35 ppm for the acid proton and the singlets at ∂ 1.23 ppm and ∂ 1.1 ppm for the methyl at position 10 and the methyl at position 9 respectivly. Assignments for the other protons are estimates based on expected values. The ∂ 2.5 ppm peak is due to proton a on carbon 3, ∂ 2.32 ppm is proton b on C3, ∂ 1.91 ppm is due to the protons on C5, ∂ 1.65 ppm due to the proton on C4, and ∂ 1.38 ppm for the protons on C6. The ^{13}C spectrum (fig. 2) allowed for better assignments. It was a very good match to that provided by D. Loo.[7] The

ketone carbonyl carbon, C2, is furthest downfield at ∂ 216 ppm and the acid carbonyl carbon, C8, is next at ∂ 181 ppm. The remaining assignments are: ∂ 57.8 ppm, carbon 7; ∂ 57.2 ppm, C1; ∂ 43.5 ppm, C3; ∂ 42.3 ppm, C4; ∂ 29.9 ppm, C6; ∂ 25.9 ppm, C5; ∂ 14.0 ppm, C9; ∂ 10.4 ppm, C10. The infrared spectrum displayed two seperate carbonyl stretches at 1742 and 1688 cm^{-1} for the acid and ketone carbonyl groups respectivly. The hydroxyl peak was very broad and centered around 3000 cm^{-1}.

The first reaction attempted with 2 was a Wittig reaction to change the carbonyl to a methylene group. Corey *et.al.* [9] made 2-methylenebornane, 11, from (+)-camphor, 1, using dimethyl sulfoxide as the solvent. The authors claimed that the use of dimethyl sulfoxide increased yields while decreasing reaction times. Since 2 is very simlar to 1, the conditions published were used. No products or starting material were recovered from the reaction mixture.

Scheme VIII

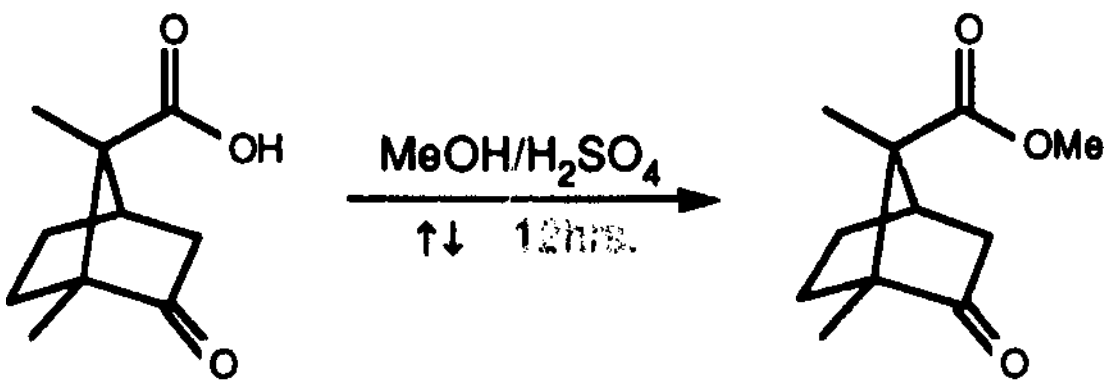


10 12

The methyl ester was synthesized next in anticipation that it would reduce any

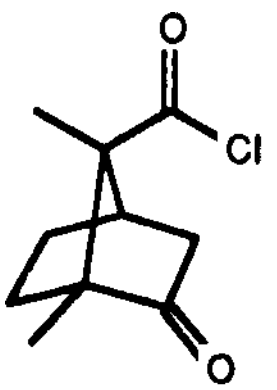
effects that the acid would have on the Wittig reaction. The keto acid, 2, was placed in methanol with a catalytic amount of concentrated sulfuric acid and allowed to reflux overnight (Scheme IX). The methyl ester, 13, was obtained in less than 20% yield. No attempt was made to recovere starting material. Formation of 13 was confirmed by ^{13}C and ^{1}H NMR spectroscopy. The ^{13}C spectrum indicated another carbon at ∂ 51.6 ppm that was not in the spectrum of 2. The ^{1}H spectrum gave a strong singlet at ∂ 3.6 ppm indicative of the presence of methoxy protons.

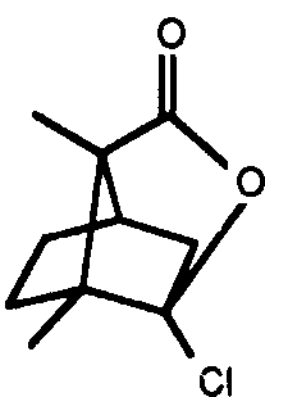
Scheme IX



2 13

The Wittig reaction was not conducted on 13, because the diisopropyl amide, 14 , was determined to be more useful in further studies. The acid chloride, 15, of 2 was necessary to perform the amidation. A variety of conditions and reagents were tried to form 15. In the first attempt, 2 was dissolved in excess thionyl chloride and allowed to reflux for 5 hours. A black residue formed during the reaction. The excess thionyl chloride was distilled off. Benzene was then added and distilled to azeotrope any remaining thionyl chloride. A black residue remained after removal of the





15 15a

thionyl chloride/benzene solution.

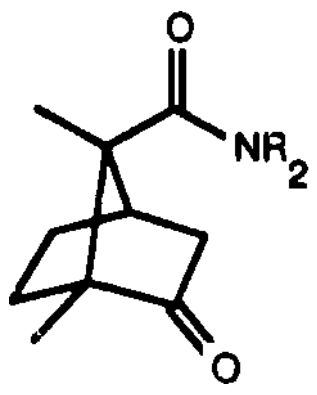
Shorter reflux time was tried in an attempt to avoid formation of the black residue. The reaction mixture was clean after the 2 hour reflux period but a black residue formed upon distillation of the thionyl chloride. Crude 15 was recovered from the black residue via kugelrohr distillation in 83% yield.

An attempt was made to form 15 under milder conditions using oxalyl chloride. The acid 2 was dissolved in distilled tetrahydrofuran and 2.3 equivalents of oxalyl chloride was added. The solution was allowed to stir at room temperature for 10 hours. This also produced a black mass upon evaporation in vacuo of the tetrahydrofuran and excess oxalyl chloride. The residue was distilled on a kugelrohr apparatus and only 2 was recovered in 73% yield.

Pure 15 was obtained by refluxing 2 in thionyl chloride for 2 hours. The excess thionyl chloride was evaporated in vacuo producing a black residue. This residue was distilled on a Kugelrohr apparatus producing 15 in 50-73% yield and in high purity as indicated by microanalysis.

The structure was determined to be 15 and not the pseudoacid chloride, 15a. This determination was made from the fact that the infrared spectrum indicated two carbonyl groups. The carbonyl that had been determined to be the acid cabonyl shifted from about 1690 cm^{-1} to 1785 cm^{-1}. The ketone carbonyl remained at about 1745 cm^{-1}.

The conversion of 15 to the diisopropyl amide, 14, was tried under a variety of conditions. The first trial was with the residue remaining from the first formation of 15. The residue was partially soluble in dichloromethane, so the reaction was carried out using this solution with the suspended solids remaining. The solution was cooled to 0°C and 2 equivalents of diisopropyl amine were added over a 5 minute period.



R = i-pr

14

After stirring for 35 minutes at 0°C, the material collected via neutral work-up and distilled on a Kugekrohr apparatus. The material recovered from the distillation did not show the expected ^1H spectrum indicative of the diisopropyl group.

The formation of the amide was then attempted by dissolving 15 in distilled

ether and cooling the solution to 0°C. The cooled solution was then treated with 3 equivalents of diisopropyl amine and the solution allowed to warm to room temperature over 5 hours. The material recovered upon neutral work-up had a carbonyl stretch at approximately 1780 cm^{-1} in the infrared spectrum which is outside the range for an amide carbonyl group.

Next, 15 was dissolved in distilled tetrahydrofuran and treated with 3 eqivalents of diisopropyl amine at room temperature. This mixture was allowed to stir for 6 hours. The recovered material once again did not conclusivly indicate formation of the amide as indicated by ^1H NMR. Starting material was recovered as the acid in 25% yield by washing the reaction mixture with base after the reaction was completed.

The next attempt was performed by dissolving 15 in tetrahydrofuran and treating with 3 equivalents of diisopropyl amine. This time the solution was heated to reflux for 3 hours. Again the amide was not present as indicated by ^1H NMR. Starting material was recovered in 66% yield as the acid.

An attempt was made to form the amide using lithium diisopropyl amine which was formed by reacting diisopropyl amine with *sec*-butyl lithium. A 2:1 excess of lithium diisopropyl amine was used to allow for any enolization of the ketone that could occur. The ^1H NMR was still inconclusive but the infrared spectrum displayed a shift of one of the carbonyl peaks to 1722 cm^{-1}, which is on the high end of the expected range for amides.

Summary

Our intended goal of the synthesis of derivatives of camphor-8-oic acid, 2, a compound that has use in both synthetic[1] and mechanistic[2] studies was achieved. The acid itself was synthesized using methods developed by Beckmann and Geiger[2] as well as modifications of their procedures as reported by Finch and Vaughan.[4] The difficulty in producing derivatives of 2, demonstrates a low reactivity of the 8-carbon of camphor.

We have shown that the methyl ester can be formed and there is enough evidence to justify pursuing the investigation of use of lithium diisopropyl amine to form the amide. The use of the 8-bromocamphor system to produce 2 would also be valuable in increasing the utility of this reagent by making it easier to produce with increased yields.

Experimental

General:

Melting points were recorded on a Buchi melting point apparatus using open capillarie tubes and are uncorrected. Infrared spectra were recorded on an IBM-32 FT-IR. NMR spectra were recorded on a Varian XL-200 FT-NMR at 200 Mhz for ^{1}H and at 50.3 Mhz for ^{13}C. Microanalyses were performed by J. Nemeth and associates in the Microanalytical Laboratory, Roger Adams Laboratory, University of Illinois, Urbana, Illinois.

Materials:

All reagents used were of reagent grade quality and used without furthur purification. The acetone used in the Jones oxidation was distilled from $KMnO_4$. Jones' reagent refers to a solution of 26.7 g of chromium trioxide in 23ml concentrated sulfuric acid diluted with 40ml of water. Dry diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone. *sec* -Butyl lithium was titered using N-benzyl benzamide[11] and determined to be 0.99M.

1,7-Dimethylnorbornane-7-carbo-2-lactone (3):

Tiglic acid (10.0 g, 0.0999 mole) was added to freshly cracked cyclopentadiene (93.5 g, 1.42 mole). The solution was heated slowly to a

temperature of 180°C (±5°C) at the end of 6 hours. The reaction was held at this temperature for 10 hours. At the end of this time, the hot reaction mixture was poured into 10% KOH (100 ml) and stirred for 3 hours. The solution was allowed to cool with stirring for 1 hour. The basic solution was then extracted with ether and acidified with conc. HCl until the pH<1. The aqueous solution was extracted with ether, the extract dried over $MgSO_4$, and the solvent removed in vacuo. The material remaining after evaporation of the solvent was distilled on a Kugelrohr apparatus yielding a white semi-solid.

The semi-solid was dissolved in 1M Na_2CO_3 with heating to promote solution. The solution was cooled to room temperature then titrated with a 1M aqueous sodium iodide/iodine solution until the reaction mixture remained dark red indicating excess iodine. The solution was allowed to stir for an additional 30 min. after which time it was extracted with ether. The aqueous portion was then acidified with conc. hydrochloric acid and extracted with ether. The etheral solution was then dried over $MgSO_4$ and the solvent removed in vacuo. The remaining material was distilled on a kugelrohr apparatus yielding a pink solid.

The pink solid was dissolved with cooling in 85% sulfuric acid and allowed to stand for 17 hours. During the reaction period, the solution turned from light red to a dark red. The acidic solution was then poured over ice and extracted with ether. The etheral solution was then washed with cold 5% KOH and cold saturated NaCl, dried

over $MgSO_4$, and evaporated in vacuo to give a white solid. This solid was recrystallized from octane to give 1.537 g 3 (9.25 mmole, 9.26%). Mp; 185-187 (lit.[2] 192-194). IR (nujol mull, cm^{-1}) 1769 (s, C=O).

8-Hydroxyisoborneol (10):

The lactone, 3, (328 mg, 1.973 mmole) was dissolved in dry ether. Lithium aluminum hydride (135 mg, 3.558 mmole) was suspended in dry ether under nitrogen. The solution of 3 was slowly transfered into the $LiAlH_4$ suspension via cannula and the flask that contained 3 was rinsed with 2 portions of dry ether. This mixture was allowed to stir for 4 hours at room temperature. The excess $LiAlH_4$ was carefully decomposed with ethyl acetate followed by water. A slurry of Na_2SO_4 in water was added to the flask. The solids were removed by vacuum filtration and the solution extracted with 10% KOH. The ether solution was dried over $MgSO_4$ and the solvent evaporated in vacuo yielding a white solid. The white solid was recrystallized from hexane / ethyl acetate (10:1) to give 193 mg 10, (1.134mmole, 57.5%) mp. 152-155 °C (dec.) (lit.[4] 275-276° C). ^1H nmr ($CDCl_3$/TMS) ∂ ppm 3.76 (d within q, 2H); 1.82 (s, 4H); 1.8 (m, 2H); 1.1, 0.96 (2s, 6H). IR (Nujol Mull, cm^{-1}) 3380 (O-H). Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H,10.60. Found: C, 70.81; H, 10.47.

Camphor-8-oic Acid (2):

The diol, 10, (150mg, 0.892mmole) was dissolved in distilled acetone. Jones reagent was added until a brown color persisted. This mixture was then allowed to stir for an additional 30 minutes. The solution was diluted with water, at which time it turned green due to dissolution of the chromium salts, and was extracted with ether. The etheral solution was extracted with 10% KOH which was acidified with 10% HCl to pH<2 and extracted with ether. The ether solution was dried over $MgSO_4$ and evaporated in vacuo to yield a white solid (77mg, 47.6%). mp. 240°C. IR (nujol mull) (cm^{-1}) 3468 (b, OH); 1742 (s, acid C=O); 1688 (s, ketone C=O). ^{13}C ($CDCl_3$/TMS) ∂ ppm (for assignments, see text) 216, 181, 57.8, 57.2, 43.5, 42.3, 29.9, 25.9, 14.0, 10.4. ^{1}H ($CDCL_3$/TMS) ∂ ppm (for assignments, see text) 10.35 (bs,1H); 2.5(t, 1H); 2.32 (d of t, 1H); 1.91 (d, 2H); 1.65 (m, 1H); 1.38 (m, 2H); 1.23 (s, 3H); 1.1 (s, 3H).

Camphor-8-oic Acid Chloride (15):

The keto-acid, 2, (107mg, 0.587 mmoles) was dissolved in thionyl chloride. The solution was heated to reflux for 2 hours. The solution was evaporated in vacuo producing a black residue. The residue was distilled on a Kugelrohr apparatus (1.3 torr/ 88° C) to give 87 mg (0.4335 mmole 73.8%) of a white sticky solid. IR (cm^{-1})

(C=O only) 1784 (acid chloride) 1746 (ketone). Anal: Calcd.; C, 59.84: H, 6.53: Cl,17.69. Found: C, 59.94: H, 6.57: Cl, 17.54.

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Figure 1

^{1}H NMR Spectrum of **2**

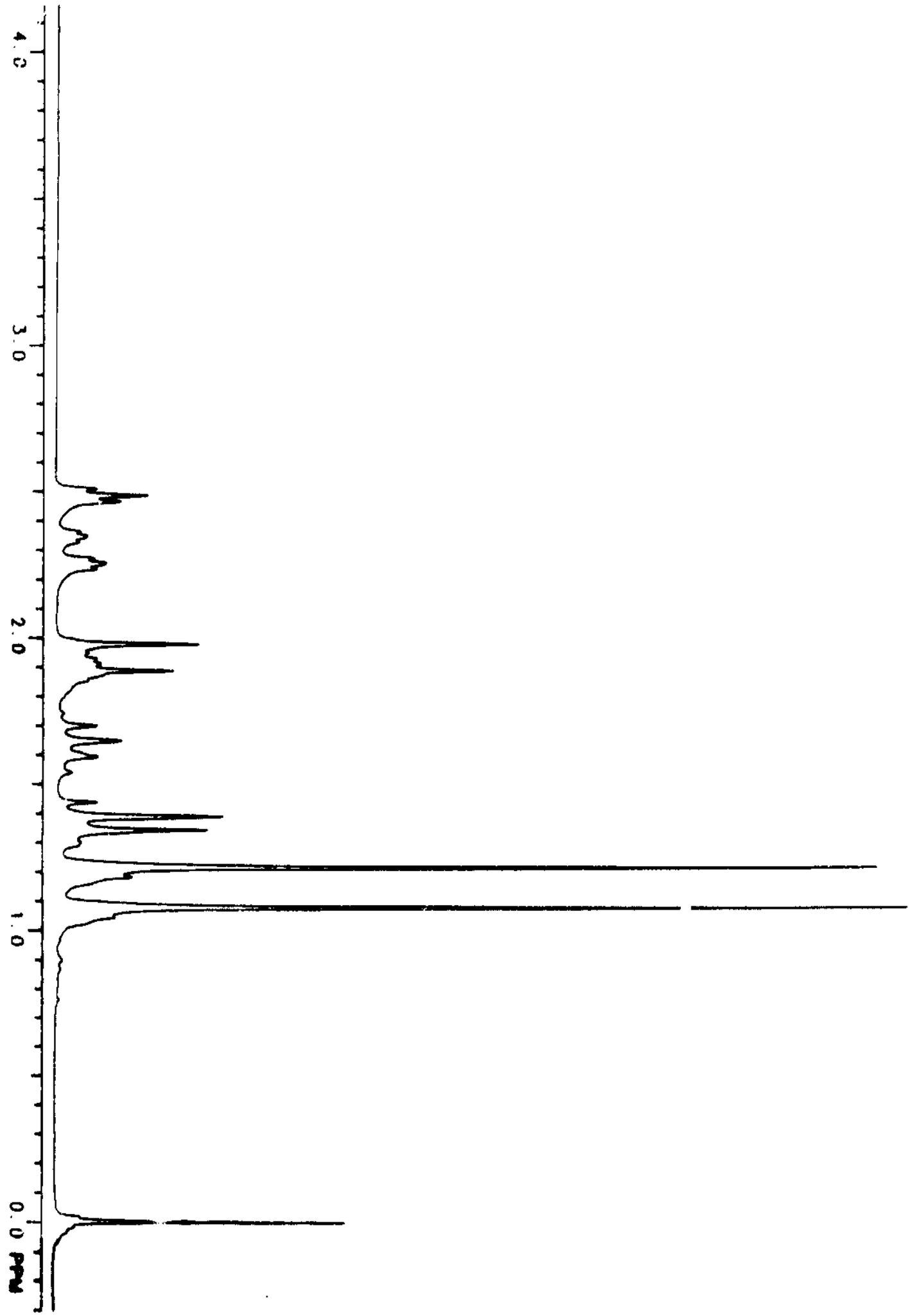

Figure 2

^{13}C Spectrum of 2