cular Dystrophy Associations of America. We thank Dr. S. N. Banerjee for help with the preparation of 8 and Mrs. Barbara Cottrell for amino acid analyses.

Registry No. DL-1, 870-93-9; L-2, 56-89-3; L-4, 6027-13-0; L-5 HCl, 52-89-1; 6, 42855-17-4; 6a, 42855-18-5; 7, 38254-63-6; 8, 42855-20-9.

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The Lewis Acid Catalysis of Ene Reactions

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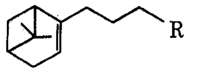
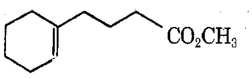
The ene reaction of olefins with highly activated enophiles has been well studied and is a synthetically useful reaction.[2] With less reactive enophiles such as methyl vinyl ketone and methyl acrylate, the ene reaction is of little value, since harsh conditions are required and yields are usually low.[2-4] Since Diels–Alder reactions often proceed in much higher yield and with greater stereospecificity in the presence of Lewis acid catalysts, it was decided to study the ene reaction of olefins with moderately reactive enophiles in the presence of these catalysts.

The reaction of (−)-β-pinene with methyl acrylate in the presence of aluminum chloride at *room temperature* gave the ene adduct 1 in 70% yield. Similarly, (−)-β-pinene with methyl vinyl ketone or acrolein in the presence of zinc bromide at *room temperature* afforded the adducts 2 and 3 in 62 and 32% yields, respectively. In the absence of Lewis acid catalysts, (−)-β-pinene reacted with acrolein at 135° for 17 hr to give a 30% yield of 3[5] and with acrylonitrile at 230° for 6 hr to give a 41% yield of 4.[4] From these data it is clear that Lewis acid catalysts greatly accelerate the ene reaction.



1, R = CO_2CH_3
2, R = $COCH_3$
3, R = CHO
4, R = CN



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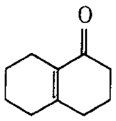

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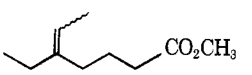
The reaction of methylenecyclohexane with methyl acrylate in the presence of aluminum chloride gave the known ester 5[6] in 70% yield. The reported conversion of 5 to the acid chloride followed by a Friedel–Crafts type acylation results in a very short and efficient synthesis of the octalone 6 (59% from 5).[6] The reaction of 2-ethyl-1-butene with methyl acrylate under similar conditions afforded a mixture from which the ene adduct 7 and the 2:1 adducts 8 and 9 were isolated in 59 and 9% yield, respectively. The 2:1 adducts are presumably obtained by ene reaction of the original adduct 7 with methyl acrylate. In support of this, it was found that, by allowing the reaction to proceed for a longer time in the presence of excess methyl acrylate, higher yields of 8 and 9 and lower yields of 7 were obtained. The 2:1 adduct mixture was identified by its mass spectra, by the doublet in the nmr spectra at δ 0.98 due to the methyl groups of 8 and 9, and by the triplet at δ 0.95 due to the second methyl group of 9. 2-Methyl-1-pentene and methyl acrylate under similar conditions gave a complex mixture of the 1:1 adducts 10 and the 2:1 adducts 11 and 12 which was not investigated further.



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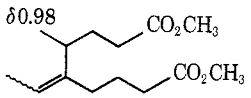

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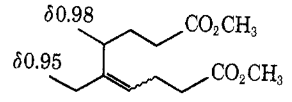

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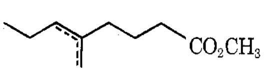

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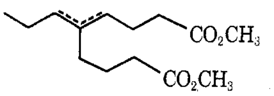

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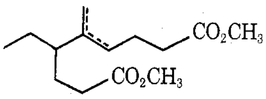

12

It has previously been observed that 1,1-disubstituted olefins give the highest yields in thermal ene reactions.[4] In this study ene reactions were obtained only with 1,1-disubstituted olefins. Preliminary experiments indicated that ene products were not obtained from methyl acrylate and allylbenzene, 1-octene, cyclohexene, or allyl bromide. It was also found that a mixture of products was obtained from (−)-β-pinene and methyl methacrylate or methyl *trans*-crotonate.

The ene reaction of olefins with dienophiles in the presence of Lewis acid catalysts provides an effective synthesis of compounds not readily available by other methods.

Experimental Section

Reaction of (−)-β-Pinene with Methyl Acrylate. To a solution of methyl acrylate (10.3 g, 0.12 mol) in 50 ml of dry benzene was added aluminum chloride (1.4 g, 0.01 mol). After the aluminum chloride had dissolved, (−)-β-pinene (13.6 g, 0.10 mol) was added. The solution was stirred for 48 hr at 25°, 25 ml of saturated sodium bicarbonate solution was added, and the solution was filtered by suction from the precipitated alumina. The organic layer was removed and the aqueous layer was extracted with 3 × 30 ml of ether. The combined organic extracts were dried over sodium sulfate and evaporated, giving 17 g of colorless liquid. Fractional distillation gave 15.38 g (70%) of **1**, bp 90° (0.5 mm). A gc retention time of 4.82 min (6 ft, 5% SE-30, 151°) showed the product to be greater than 98% pure: nmr ($\mathrm{CDCl_3}$) δ 5.19 (1 H, br, CH═), 3.76 (3 H, s, $\mathrm{OCH_3}$), 1.5-2.5 (12 H, m), 1.27 (3 H, s, $\mathrm{CH_3}$), and 0.83 (3 H, s, $\mathrm{CH_3}$); ir (neat) 2920, 1740, 1430, 1360, 1200, and 1160 $\mathrm{cm^{-1}}$.

Anal. Calcd for $\mathrm{C_{14}H_{22}O_2}$: mol wt, 222.1620. Found: mol wt, 222.1616.

Reaction of Methylenecyclohexane with Methyl Acrylate. To a solution of methyl acrylate (1.3 g, 15 mmol) in 5 ml of benzene were added aluminum chloride (0.14 g, 1 mmol) and methylenecyclohexane (1.25 g, 13 mmol). The solution was stirred for 48 hr at 25° and worked up as described above, giving 1.66 g (70%) of **5**. A gc retention time of 3.15 min (6 ft, 5% SE-30, 143°) indicated that the material was *ca.* 97% pure: nmr ($\mathrm{CDCl_3}$) δ 5.4 (1 H, m, CH═), 3.67 (3 H, s, $\mathrm{OCH_3}$), 2.26 (2 H, t, J = 6.5 Hz, $\mathrm{CH_2CO_2}$), and 1.3-2.1 (12 H, m, $\mathrm{CH_2}$); ir (neat) 2940, 2850, 1745, 1440, 1250, and 1160 $\mathrm{cm^{-1}}$.

Anal. Calcd for $\mathrm{C_{11}H_{18}O_2}$: mol wt, 182.1307. Found: mol wt, 182.1311.

Reaction of 2-Ethyl-1-butene with Methyl Acrylate. To a solution of methyl acrylate (10.3 g, 0.12 mol) in 50 ml of benzene was added aluminum chloride (1.4 g, 0.01 mol). After the aluminum chloride had dissolved, 2-ethyl-1-butene (8.4 g, 0.10 mol) was added. The solution was stirred for 72 hr at 25° and worked up as described for **1**, giving 14.2 g (83%) of yellow oil. Gc (6 ft, 5% SE-30, 115-190°) indicated this to be a mixture consisting of 83% of **7**, 13% of **8** and **9**, and 4% of two unidentified minor products. A 10-g portion of this was distilled, giving 7 g (58%) of methyl 5-ethyl-5-heptenoate (**7**), bp 78° (6 mm). Gc indicated the distillate to be greater than 95% pure. Gc indicated that the residue (1.3 g, 9%) consisted of 92% of a mixture of diadducts (**8** and **9**) and 8% of **7**.

The spectral data for **7** are ir (neat) 2960, 2870, 1740, 1435, 1245, 1200, and 1150 $\mathrm{cm^{-1}}$; nmr ($\mathrm{CDCl_3}$) δ 5.2 (1 H, q, J = 6 Hz, CH═), 3.66 (3 H, s, $\mathrm{OCH_3}$), 1.7-2.5 (8 H, m), 1.58 (3 H, d, J = 6 Hz, $\mathrm{CH_3}$), and 0.96 (3 H, t, J = 7 Hz, $\mathrm{CH_3}$); gc retention time 3.8 min (6 ft, 5% SE-30, 112°).

Anal. Calcd for $\mathrm{C_{10}H_{18}O_2}$: mol wt, 170.1303. Found: mol wt, 170.1307.

The spectral data for **8** and **9** are ir (neat) 2900, 2870, 1740, 1435, 1245, 1200, and 1168 $\mathrm{cm^{-1}}$; nmr ($\mathrm{CDCl_3}$) δ 4.9-5.5 (1 H, m, CH═), 3.63 (6 H, s, $\mathrm{OCH_3}$), 1.3-2.5 (11 or 14 H, m), 0.98 (3 H, d, J = 6.5 Hz, $\mathrm{CHCH_3}$), and 0.95 (0 or 3 H, t, J = 6 Hz, $\mathrm{CH_3}$); gc retention time 3.2 min (6 ft, 5% SE-30, 185°).

Anal. Calcd for $\mathrm{C_{14}H_{24}O_4}$: mol wt, 256.1674. Found: mol wt, 256.1668.

Reaction of 2-Methyl-1-pentene with Methyl Acrylate. To a solution of methyl acrylate (1.03 g, 12 mmol) in 5 ml of benzene was added aluminum chloride (0.28 g, 2 mmol). After dissolution of the aluminum chloride, 2-methyl-1-pentene (0.82 g, 10 mmol) was added and the solution was stirred for 96 hr at 25°. Work-up as for **1** gave 1.2 g (71%) of colorless oil. Gc (6 ft, 5% SE-30, 115-190°) indicated that a complx mixture of the various 1:1 and 2:1 adducts with methyl acrylate were present. These were not separated: ir (neat) 2960, 2870, 1745, 1440, and 1150 $\mathrm{cm^{-1}}$; nmr ($\mathrm{CDCl_3}$) δ 5.1 (t, J = 7 Hz, CH═), 4.7 (s, $\mathrm{CH_2}$═), 3.65 (s, $\mathrm{OCH_3}$), 1.58 (s, $\mathrm{CH_3C}$═), and 0.89 (t, J = 6 Hz, $\mathrm{CH_3}$). The gc characteristics follow: **10**, retention time 3.55 min (6 ft, 5% SE-30, 112°); **11** and **12**, retention times 3.40 and 3.80 min (6 ft, 5% SE-30, 185°).

Anal. Calcd for $\mathrm{C_{10}H_{18}O_2}$: mol wt, 170.1307. Found: mol wt, 170.1309.

Reaction of (−)-β-Pinene with Methyl Vinyl Ketone. To a solution of anhydrous zinc bromide (4.0 g, 0.02 mol) in 100 ml of ether were added methyl vinyl ketone (10.5 g, 0.150 mol) and (−)-β-pinene (13.6 g, 0.10 mol). The solution was stirred for 7 days at 25°. It was then poured into water and filtered by suction to remove zinc salts. The ether layer was separated and the aqueous layer was extracted with 2 × 50 ml of ether. The combined ether layers were dried and evaporated. Fractional distillation of the residue gave the ketone **2**, bp 92° (0.5 mm) (13.04 g, 0.062 mol, 62%), which was 95% pure by gc: ir (neat) 2920, 1720, 1450, 1365, and 1165 $\mathrm{cm^{-1}}$; nmr ($\mathrm{CDCl_3}$) δ 5.20 (1 H, br, CH═), 1.4-2.6 (12 H, m, $\mathrm{CH_2}$), 2.11 (3 H, s, $\mathrm{COCH_3}$), 1.28 (3 H, s, $\mathrm{CH_3}$), and 0.82 (3 H, s, $\mathrm{CH_3}$); gc retention time 4.4 min (6 ft, 5% SE-30, 151°).

Anal. Calcd for $\mathrm{C_{14}H_{22}O}$: mol wt, 206.1671. Found: mol wt, 206.1663.

Reaction of (−)-β-Pinene with Acrolein. To a solution of anhydrous zinc bromide (4.0 g, 0.02 mol) in 100 ml of ether were added acrolein (8.4 g, 0.15 mol) and (−)-β-pinene (13.6 g, 0.10 mol). The solution was stirred for 30 hr at 25° and worked up as for **2**. Fractional distillation of the residue gave the aldehyde **3**, bp 86° (0.45 mm) (6.05 g, 0.032 mol, 32%), which was 95% pure by gc: ir (neat) 2920, 2830, 2710, and 1725 $\mathrm{cm^{-1}}$; nmr ($\mathrm{CDCl_3}$) δ 9.78 (1 H, t, J = 1.9 Hz, CHO), 5.20 (1 H, m, CH═), 1.35-2.7 (12 H, m, $\mathrm{CH_2}$), 1.23 (3 H, s, $\mathrm{CH_3}$), and 0.83 (3 H, s, $\mathrm{CH_3}$); gc retention time 3.25 min (6 ft, 5% SE-30, 145°).

Anal. Calcd for $\mathrm{C_{13}H_{20}O}$: mol wt, 192.1514. Found: mol wt, 192.1513.

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Registry No. 1, 42913-51-9; **2**, 42913-52-0; **3**, 22553-58-8; **5**, 42908-43-0; **7**, 42908-44-1; **8**, 42908-45-2; **9**, 42908-46-3; (−)-β-pinene, 18172-67-3; methyl acrylate, 96-33-3; methylenecyclohexane, 1192-37-6; 2-ethylene-1-butene, 760-21-4; 2-methyl-1-pentene, 763-29-1; methyl vinyl ketone, 78-94-4; acrolein, 107-02-8.

References and Notes

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Preparation of an Optically Active Intermediate for the Synthesis of Prostaglandins

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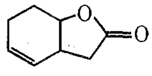
This paper describes the resolution of the (±)-cis-fused lactone **1** and unambiguous demonstration that the levo form possesses the absolute configuration shown in **1a**, which corresponds to the natural prostanoic acid stereochemistry. Since (±)-**1** has been utilized previously for the synthesis of (±)-11-deoxyprostaglandins[1] and also racemic primary prostaglandins,[2] a new route is thus established to these prostanoids in the optically active natural series.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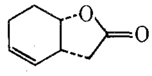
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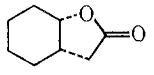
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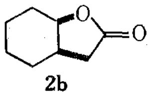
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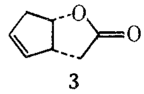
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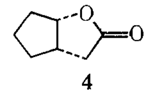
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The (±)-lactone **1** was hydrolyzed to the hydroxy acid and treated with (−)-1-(1-naphthyl)ethylamine[3] in ethyl acetate. Three recrystallizations of the resulting salt from ethyl acetate-methanol afforded a product of constant rotation, $[\alpha]^{27}\mathrm{D}$ +63°. Conversion of this salt to the dextro