J. Org. Chem. **1987**, *52*, 1984–1989

A New Synthetic Route to (±)-Strigol

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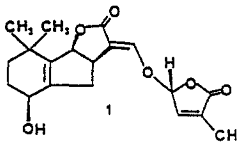
Received August 26, 1986

A new more facile synthetic route to strigol, a potent weed seed germination stimulant, utilizes as starting material ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate (**2**), obtained by the condensation of mesityl oxide and ethyl acetoacetate. Compound **2** was converted in six steps in 38% overall yield to the previously reported strigol intermediate, 1,4-dioxo-7,7-dimethyl-4,5,6,7-tetrahydro-2-indanacetic acid (**11**). The new approach is based upon inexpensive starting materials and reagents and is suitable for large-scale production. The key features of the synthesis include reduction of enone **2** to olefin **5** with triethylsilane and boron trifluoride etherate and a one-pot conversion of ethyl 2-(bromomethyl)-6,6-dimethyl-3-oxocyclohex-1-ene-1-carboxylate (**10**) to the diketo acid **11**.

(+)-Strigol is a very effective germination stimulant for the parasitic weeds in the genus *Striga* (witchweed).[1] Recently the absolute structure of natural (+)-strigol has been established as shown in **1**.[2] Natural (+)-strigol induced greater than 50% germination of witchweed [*Striga asiatica* (L.) Kuntze] seeds at a concentration of 10^{-11} M. Synthetic (±)-strigol effected comparable germination in the concentration range of 10^{-10} to 10^{-12} M.[3,4]



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The parasitic weeds of *Striga* species are thought to germinate primarily in response to a chemical signal of the host plant. Corn, rice, sugarcane, and sorghum are the major crop plants affected by *Striga*. However, the structure of the seed germination stimulant exuded from their roots remains unknown. Strigol was originally isolated in small quantities from the root exudates of cotton (a nonhost plant).[1]

Striga asiatica (L.) Kuntze, one of many species of *Striga* found commonly in the Eastern Hemisphere, was found in North and South carolina in 1956. Once established, the *Striga* derives carbohydrates, water, minerals, and some photosynthates from the infected parasitized plant, which generally appears drought-stricken and often dies if the parasitic plant is not removed. Crop losses often have approached 100% in heavily infested fields.[5-7]

Because of the lengthy periods of viability of the seeds of *Striga* and *Orobanche* in the soil, effective control of these parasitic weeds is extremely difficult. An attractive method of control would involve treatment of an infected field with a biosynthetic product (such as strigol) or a synthetic analogue to induce suicidal germination of the weed seed in the absence of a host plant. The results of field tests with ethylene[8] and synthetic strigol analogues[9] offer evidence of the utility of this method of control.

To date, probably less than 5 g of (±)-strigol has been synthesized. For extensive field studies and basic biological studies a large quantity (in excess of 100 g) will be required. Although several syntheses of strigol have been reported, the need for an economic synthesis adaptable to large-scale preparation still exists. The goal of the present study[10] was to achieve a preparation of strigol, suitable for large-scale production, based upon inexpensive starting materials and reagents and requiring a minimum of chromatographic purification.

Four total syntheses of strigol have been reported.[11-13] Several partial syntheses of strigol have been reported,[14] offering alternative approaches to intermediates in the Sih[11] synthesis. Of the literature preparations, those of Sih and Brooks[13] are the most pertinent to the approach presented herein (Scheme I). In the Sih procedure, citral is utilized as starting material, whereas α-ionone is used in Brooks' synthesis. The primary synthetic target of these investigations is 1,4-dioxo-7,7-dimethyl-4,5,6,7-tetrahydro-2-indanacetic acid (**11**, Scheme I). This material is an intermediate in the latter stages of both the Sih and Brooks strigol syntheses. In the synthesis reported herein, enone **2** converted to olefin **5** by a new method utilizing triethylsilane and boron trifluoride etherate.

Results and Discussion

Preparation of Starting Material 2. The starting material utilized in these investigations directed toward an improved synthetic route to (±)-strigol is ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate (**2**, Scheme I). This compound possesses the methyl groups and ester functionality in the appropriate positions for further ela-

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boration to strigol. Compound **2** has been prepared by the zinc chloride[15] or born trifluoride[16] catalyzed condensation of mesityl oxide with ethyl acetoacetate or by the boron trifluoride catalyzed condensation of ethyl acetoacetate with acetone.[16,17] These reactions give a product mixture of isomeric **2** and **3** with **2** as the major product. In addition, isophorone has been isolated as a product. Presumably isophorone is formed by preferential hydrolysis and decarboxylation of **3**, thus accounting for the predominance of **2** in the product mixture.

For the large-scale preparation of **2** (1–8 m), best results were obtained by using a modification of the procedure of Surmatis et al.[15] Distillation of the crude product mixture afforded material consisting of **2** and **3** in ratios ranging from 7:1 to better than 10:1 (NMR analysis) in yields in the 27–37% range. The higher yield corresponds to the lower **2**:**3** ratio. The distilled material was sufficiently pure for use in the subsequent reaction.

It was reported that **2** could be separated from **3** by selective hydrolysis of **3**, but these results were later disputed.[17] Indeed, in our hands purification of **2** by selective hydrolysis of **3** to isophorone using the literature method[15] failed. There was no observed change in the product mixture.

Conversion of Enone 2 to Olefin 5. Compound **2** was obtained in pure form by column chromatography for use in investigating direct conversion to the olefin **5** (Scheme I). Neither of the traditional methods (Clemmensen reduction or Wolff–Kishner reduction) could be employed due to the presence of the labile ester group and the potentially labile double bond.

Since initial attempts[18–22] at a direct or one-step conversion of enone **2** to olefin **5** were not fruitful, the practicality of a two-step conversion (dithioketalization–desulfurization) was investigated. Liu[17] had reported that **2** could be conveniently separated from **3** by the selective dithioketalization to **4** (Scheme I) followed by purification by column chromatography. In our hands, pure **4** (81% yield) could be obtained by treatment of a 8:1 mixture of **2** and **3** with 1,2-ethanedithiol and boron trifluoride etherate and subsequent distillation of the crude product.

Raney nickel desulfurization of **4** and **5** was accomplished in high yield (>80%) on a 10–30-g scale; however, the yields decreased substantially when the reaction was done on a larger scale (>100 g). Since the conversion of **2** to **5** by dithioketalization–desulfurization did not prove to be sufficiently adaptable to optimal scale-up, a more practical alternative was sought.

There are examples in the literature of the reduction of simple aliphatic ketones to the corresponding hydrocarbons using gaseous boron trifluoride and triethylsilane in methylene chloride.[23] However, these compounds do not possess additional functional groups such as the ester group and double bond of compound **2**. In investigating the literature method,[23] enone ester **2** was treated with 4 equiv of triethylsilane[23] and excess BF_3 gas in dichloromethane at 0 °C for 1 h. There was no observed reaction. However, treatment of **2** with 6 equiv of triethylsilane and excess BF_3 gas at room temperature (20 °C) for 6 h afforded olefin **5** in 64% yield following distillation.

Since it would be considerably easier to handle and measure, the use of boron trifluoride etherate instead of boron trifluoride gas was investigated. Under the optimal conditions established, compound **2** is cleanly reduced to olefin **5** in 1–2 h upon treatment with 2.5–4.0 M excess of triethylsilane and boron trifluoride etherate at 80–95 °C. Compound **3** does not react under these conditions. Using a 9:1 mixture of **2** and **3** as starting material, the yields of **5** were in the range of 66–74% for three experiments. The reaction also proceeds at lower temperature but requires longer reaction times and a greater excess of boron trifluoride etherate and triethylsilane.

There is no report in the literature of the reduction of a ketone to a methylene compound using boron trifluoride etherate and triethylsilane. However, it has been reported that "aldehydes and ketones are rapidly reduced at room temperature by triethylsilane in boron trifluoride etherate primarily to borate esters and symmetrical ethers".[24] The reduction of aromatic and cyclopropyl ketones to hydrocarbons by the action of silanes and trifluoroacetic acid has been reported.[25,26] When α,β-unsaturated aromatic ketones are substrates, reduction of both the carbonyl group and double bond takes place, yielding hydrocarbons. However, reduction of an aliphatic α,β-unsaturated ketone with excess organosilane/trifluoroacetic acid results in the intermediate formation of a ketone and ultimate production of an alcohol. By limiting the amount of silane, the selective reduction of the double bond takes place to provide the saturated ketone.[27] By contrast, the reaction of **2** with triethylsilane/boron trifluoride etherate is an example of the selective reduction of the carbonyl group of an aliphatic α,β-unsaturated ketone. An investigation into the generality of this selective reduction is in progress.

Synthesis of Enone 8. Treatment of olefin **5** with *m*-chloroperoxybenzoic acid afforded a mixture of approximately 75% epoxide **6** and 25% **7** (NMR analysis). Structural assignments were based upon assumed epoxidation preferentially from the less hindered side. The isomers were separated by column chromatography for characterization purposes, affording 81% **6** and 19% **7**. Large-scale epoxidations of **5** (50–100 g) with peracetic acid[27] consistently furnished the epoxides in essentially quantitative yield. Treatment of the epoxides (40–100 g) with sodium ethoxide in refluxing ethanol provided allylic alcohol **8**. Oxidation of **8** (0.50 mmol–0.50 mol) with the Jones reagent[10,28] consistently afforded enone **9** in yields of 95% or better. In large-scale conversions of **5** to **9**, the crude intermediate compounds **6**, **7**, and **8** were used directly in the subsequent reaction without further purification (distillation). Typically, for the three-step process, **9** is obtained in 95% yield, sufficiently pure for the next reaction.

Preparation of 1,4-Dioxo-7,7-dimethyl-4,5,6,7-tetrahydro-2-indanacetic Acid (11). In Sih's synthesis of strigol,[11] it was reported that reaction of keto ester **12** with a 20% excess of *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride with illumination under an incan-

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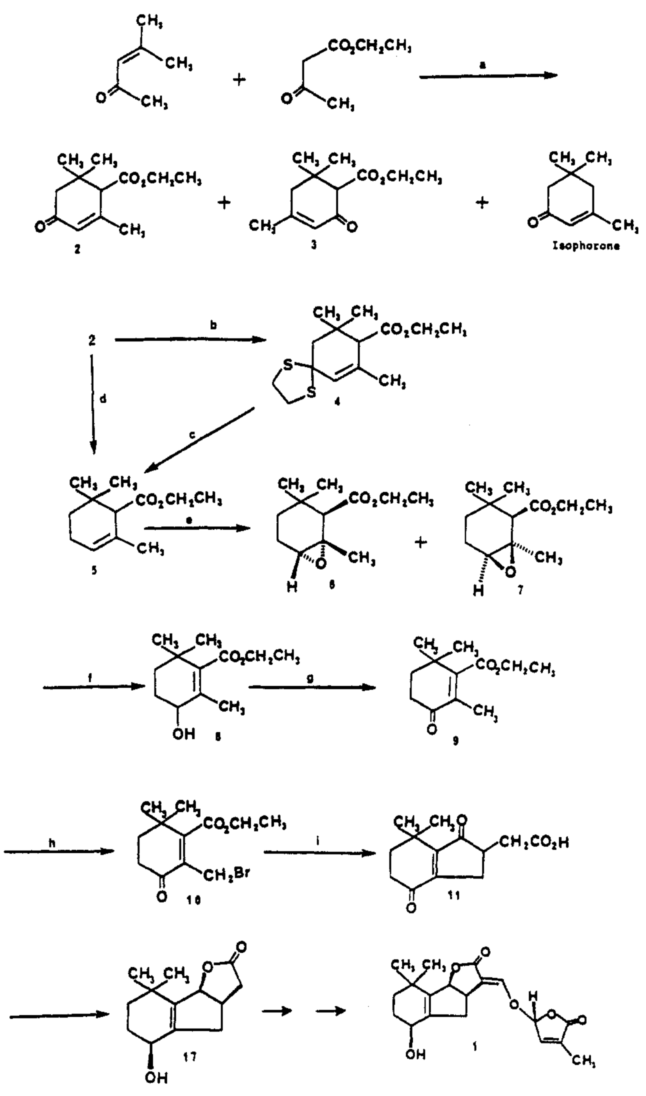
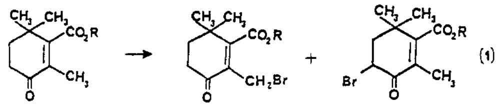
Scheme I[a]



[a] (a) $ZnCl_2$, toluene, heptane, Δ; (b) $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, 0 °C → room temperature; (c) W-2 Raney nickel, EtOH, room temperature; (d) $BF_3 \cdot Et_2O$, Et_3SiH, 80–95 °C; (e) 35% CH_3CO_3H, NaOAc, CH_2Cl_2, room temperature; (f) NaOEt, EtOH; (g) Jones reagent; (h) NBS, CCl_4, $h\nu$; (i) $CH_2(CO_2CH_3)_2$, NaH, THF, 0 °C; $BrCH_2CO_2Et$, 0 °C → room temperature; HOAc, 6 N HCl, 66–100 °C.

descent lamp provided bromo ketone **13** in quantitative yield. However, results in these laboratories indicate that a second product is formed. This side product has been assigned structure **14** (based upon comparison of the NMR spectrum of the product mixture with that of the analogous ethyl ester **15**). The amount of side product could be minimized by using an incandescent lamp as sole source of heat and by maintaining the temperature of the reaction mixture at or below 50 °C.[29]

The light-initiated bromination of ethyl ester **9** was studied extensively. Initially, the literature procedure[11] for the bromination of the methyl ester **12** was followed exactly except lower concentrations of the substrate were used. The results were highly variable. In all instances, a significant amount of bromo ketone **15** was formed in addition to the desired product **10**.[30] When less than 1 g of **9** was brominated, the product mixture consisted of 85–90% **10** and 10–15% **15** (eq 1). On larger scales (using



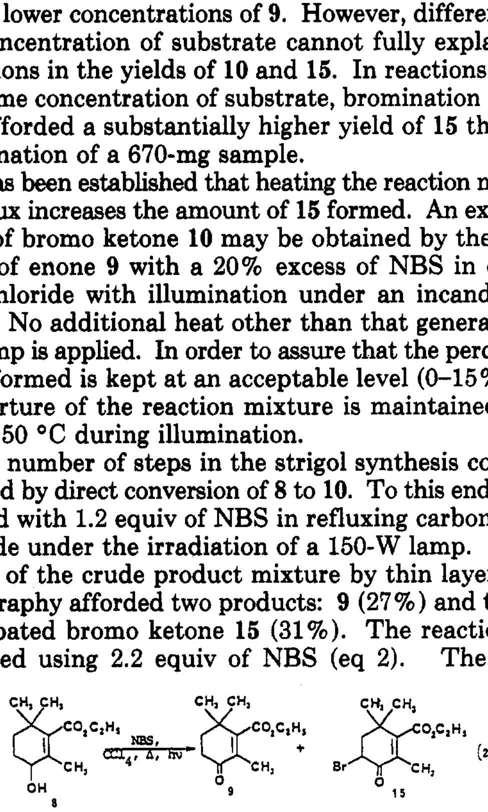
12 R = CH_3 13 R = CH_3 14 R = CH_3 (1)
9 R = CH_2CH_3 10 R = CH_2CH_3 15 R = CH_2CH_3

15 to 45 g of **9**), the percentage of **15** increased to 25–42%. On one occasion, following a 30-min induction period, the reaction became highly exothermic, resulting in expulsion of a portion of the reaction mixture from the flask. In all the reactions studied, the reaction mixture turned orange-red in color. Disappearance of the coloration indicated that the reaction was complete.

There is no clear explanation for the formation of **15**. The cause does not appear to be impurities in the NBS used. Comparable results were obtained by using a yellow sample of NBS (172–178 °C) and a pure white sample (179–181 °C). In general, the small-scale reactions were run at lower concentrations of **9**. However, differences in the concentration of substrate cannot fully explain the variations in the yields of **10** and **15**. In reactions run at the same concentration of substrate, bromination of 16 g of **9** afforded a substantially higher yield of **15** than did bromination of a 670-mg sample.

It has been established that heating the reaction mixture at reflux increases the amount of **15** formed. An excellent yield of bromo ketone **10** may be obtained by the treatment of enone **9** with a 20% excess of NBS in carbon tetrachloride with illumination under an incandescent lamp. No additional heat other than that generated by the lamp is applied. In order to assure that the percentage of **15** formed is kept at an acceptable level (0–15%), the temperture of the reaction mixture is maintained at or below 50 °C during illumination.

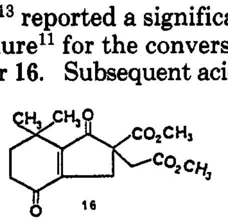
The number of steps in the strigol synthesis could be reduced by direct conversion of **8** to **10**. To this end, **8** was treated with 1.2 equiv of NBS in refluxing carbon tetrachloride under the irradiation of a 150-W lamp. Purification of the crude product mixture by thin layer chromatography afforded two products: **9** (27%) and the unanticipated bromo ketone **15** (31%). The reaction was repeated using 2.2 equiv of NBS (eq 2). The major



(2)

products were **9** and **15** with only a trace of **10** being formed. There was no significant change in product composition upon using 3.3 equiv of NBS under the same reaction conditions.

Recently, Brooks[13] reported a significant improvement over the Sih procedure[11] for the conversion of bromo ketone **13** to the diester **16**. Subsequent acid hydrolysis gives



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the diketo acid **11**. In a modification of Brooks' procedure, bromo ketone **10** may be converted directly to **11** in a one-pot synthesis in 60% yield (Scheme I).

The two literature methods for conversion of **11** to the hydroxy lactone **17** (Scheme I) were investigated: reduction with diisobutylaluminum hydride[11] and treatment with ceric chloride followed by excess sodium boro-

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[29] E. J. Blanchard, personal communication.

[30] It had been reported[10] previously that bromination of **9** on a small scale gave **10** as the only product. However, subsequent reexamination of the NMR spectrum of the crude product showed approximately 15% **15**.

hydride.[13] The latter method gave superior results. The synthesis of strigol may be completed as described in the literature.[11,13]

Conclusions. The results reported in this paper provide the basis of an attractive alternative for large-scale preparation of strigol in terms of cost and practicality. Sih's synthesis[11] using citral as starting material affords diketo acid **11** in 16% yield in eight steps. Brooks' procedure[13] using α-ionone as starting material provides **11** in 28% yield in seven steps. With ethyl 4-oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate (**2**) as starting material, **11** can be produced in 38% yield in six steps. The relative low cost of mesityl oxide and ethyl acetoacetate more than offsets the low yield of the condensation reaction producing **2**. Each step of the new synthetic route to strigol is suitable for large-scale production, on the basis of inexpensive starting materials and reagents and requiring no chromatographic purification.

The compounds synthesized in this study (**2**–**11**, **16**) have been tested as seed germination stimulants.[31] Several of the compounds have shown significant activity as germination stimulants for weeds of the genera *Orobanche* and *Striga*.

Experimental Section

General.[32] Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in a chloroform-*d* solution on a Varian EM-360L 60-MHz NMR spectrometer; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane (Me_4Si). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. Mass spectra were recorded on a Finnigan-MAT GC/MS Model 4000 mass spectrometer at an ionizing voltage of 70 eV with repetitive scanning from 33 to 450 amu every second. The samples were run in the solid probe and were heated ballistically from room temperature to 300 °C. Scanning, data acquisition, and data processing were done with a Finnigan-MAT INCOS data system. The ion source was at 250 °C. The electron multiplier voltage was 1500 V. Infrared (IR) spectra were obtained on a Beckman AccuLab 8 spectrometer and were calibrated with the 3027.9, 1601.8, and 1028.3 cm^{-1} bands of polystyrene. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. Microanalyses melting points and boiling points are uncorrected. Micoanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Raney nickel activated catalyst was supplied as a 50% slurry in water, pH 10, by Aldrich Chemical Company, Milwaukee, WI. Boron trifluoride gas (99.5%) was supplied in a lecture bottle by Matheson Gas Products. Triethylsilane was purchased from Aldrich Chemical Company, and, in larger quantities, from Petrarch Systems, Inc., Bristol, PA. Peracetic acid, 35%, was purchased from FMC Corporation, Buffalo, NY. Boron trifluoride etherate was used from a newly opened bottle and subsequently distilled, as necessary, upon darkening. Tetrahydrofuran (THF) was distilled from calcium hydride and stored over 4A molecular sieves. Sodium hydride, obtained as a 50% dispension in mineral oil, was freed of the oil by being washed with hexanes and stored under anhydrous conditions.

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} 5 cm × 10 cm × 0.25 mm plates supplied by EM Reagents. Preparative TLC was performed on silica gel 60 F_{254} 20 cm × 20 cm × 2.0 mm plates supplied by EM Reagents. Column chromatography was done on silica gel (60–200 mesh) from J. T. Baker Chemical Company.

Preparation of Ethyl 4-Oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate (2). A stirred mixture of 1020 mL (1041 g, 8.00 mol) of ethyl acetoacetate, 960 mL (824 g, 8.40 mol) of mesityl oxide, 1000 mL of heptane, 600 mL of toluene, and 175 g of zinc chloride was heated at reflux in a 5000-mL round-bottomed flask equipped with a Dean–Stark trap and drying tube. After 24 h, an additional 25 g of zinc chloride was added and refluxing was continued for 36 h. After cooling, the reaction mixture was washed with 1500 mL of water, 5% sodium bicarbonate solution (2 × 1000 mL), and 1500 mL of water. Removal of solvent yielded 979 g of crude product. Distillation provided 453.5 g of a mixture consisting of 90% **2** and 10% **3** (27.0% yield): bp 124–125 °C (3.0 Torr) [lit.[15] bp 115–117 °C (2.3 Torr)].

Ethyl 7,9,9-Trimethyl-1,4-dithiospiro[4.5]dec-6-ene-8-carboxylate (4).[17] Boron trifluoride etherate (15 mL) was added to a mixture of 90% **2** and 10% **3** (147.13 g, 0.700 mol) and 1,2-ethanedithiol (100 mL, 1.20 mol) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 16 h. The reaction mixture was poured into 1000 mL of 10% sodium hydroxide at 0–5 °C and extracted with dichloromethane (3 × 500 mL). Combined organic extracts were washed with 500-mL portions of water and brine and dried ($MgSO_4$). Removal of solvent afforded 190 g (95%) of crude **4** suitable for use in the subsequent reaction. In another large-scale preparation, 405 g (1.93 mol) of a 8:1 mixture of **2** and **3** was converted to 550 g (99.7%) of crude **4**. Distillation afforded 447.2 g (81%) of pure **4**: bp 160–162 °C (0.50–0.60 Torr). The NMR spectrum was in agreement with that reported by Liu et al.[17]

Ethyl 2,6,6-Trimethylcyclohex-2-ene-1-carboxylate (5). A solution of crude dithioketal **4** (167.5 g, 0.585 mol) in 250 mL of ethanol was added to a 3-L, two-necked flask equipped with mechanical stirrer. Raney nickel activated catalyst (Aldrich, 500 g) was washed twice with 500-mL portions of ethanol and then added to the reaction flask with the aid of 1000 mL of ethanol over a 30-min period. The reaction mixture was stirred at room temperature for 30 h. Thereupon, an additional 90 g of Raney nickel was added, and stirring was continued for 90 h. The Raney nickel was removed by filtration and washed with ethanol (2 × 250 mL). Removal of solvent gave 130 g of residue that was partitioned between 300 mL of water and dichloromethane (2 × 300 mL). The combined organic layers were washed with 300 mL of brine and dried ($MgSO_4$). Removal of solvent afforded 112.8 g of material that was distilled to give 27.4 g (23.8%) of **5**: bp 69–72 °C (1.0 Torr); IR (thin film) 2965, 2920, 2880, 1736, 1722, 1150, 1138, and 1047 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (s, 6, 2 CH_3) 1.26 (t, 3, J = 7 Hz, CH_2CH_3, 1.64 (s, 3, CH_3), 1.53–2.47 (m, 4, CH_2CH_2), 2.57 (s, 1, C-1 H), 4.12 (q, 2, J = 7 Hz, CH_2CH_3), and 5.56 (br s, 1, C-3 H); mass spectrum, m/e (rel intensity) 196 (18), 181 (3), 139 (8), 123 (55), 123 (55), 122 (61), 107 (52), 82 (37), 81 (71), 69 (34), 67 (38), 55 (33), 53 (27), 43 (56), 41 (100), 39(51).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.32; H, 10.32.

In addition to the fraction containing pure **5**, continued distillation afforded fractions containing a percentage of **5** [bp 75–135 °C (0.45–0.55 Torr), 15.2 g)] and containing unreacted **4** [32.2 g, 19.2% recovery, bp 135–160 °C (0.45–0.55 Torr)]. Column chromatography of the intermediate fractions afforded an additional 5.35 g (4.7%) of **5** and 3.03 g (1.8%) of **4**.

Direct Conversion of Ethyl 4-Oxo-2,6,6-trimethylcyclohex-2-ene-1-carboxylate (2) to Ethyl 2,6,6-Trimethylcyclohex-2-ene-1-carboxylate (5). A mixture of 100.4 g (0.478 mol) of a 9:1 mixture of **2** and **3**, 155 mL (1.26 mol) of boron trifluoride etherate, and 200 mL (1.25 mol) of triethylsilane was heated at 80–95 °C for 2 h. After cooling, the reaction mixture was partitioned between water (400 mL) and ether (3 × 300 mL). The combined organic layers were washed with 500-mL portions of 10% sodium bicarbonate solution and brine and dried ($MgSO_4$). Distillation of the crude isolated product afforded 67.8 (72.4%) of pure **5**: bp 82–85 °C (3.9–4.1 Torr).

Ethyl 2α,3α-Epoxy-2,6,6-trimethylcyclohexane-1β-carboxylate (6) and Ethyl 2β,3β-Epoxy-2,6,6-trimethylcyclohexane-1β-carboxylate (7). Sodium acetate (6.0 g) was added to 80 mL (0.419 mol) of 35% peracetic acid. The resulting mixture was added to a solution of 55.0 g (0.280 mol) of distilled **5** in 400 mL of dichloromethane at 23 °C over a 10-min period. After 5 min, the temperature rose to 38 °C. The reaction mixture was cooled to 20 °C over a 10-min period. Stirring was continued at 20–30 °C for 2 h. Following refrigeration at 0 °C overnight,

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(31) Vail, S. L.; Blanchard, E. J.; Dailey, O. D.; Riopel, J. L. *WSSA Abstracts* **1986**, *26*, 68.

(32) Mention of a trademark, proprietary product, or vendor does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture and does not imply its approval to the exclusion of other products or vendors that may also be suitable.

the reaction mixture was washed with 250 mL of water and the aqueous layer extracted with 200 mL of dichloromethane. Combined organic layers were washed with 250-mL portions of 10% sodium bicarbonate and brine and dried ($MgSO_4$). Removal of solvent gave 74.7 g of crude product (**6** and **7** in a 3:1 ratio), which was used directly in the next reaction.

In a separate experiment 4.18 g (21.3 mmol) of **5** was treated with a 50% excess of MCPBA, yielding 4.81 g of crude product. The material was chromatographed on a column containing 200 g of silica gel. Elution with 3% ether/hexanes and 4% ether/hexanes afforded 0.61 g (13.5%) of **7**. Distillation through a short-path distillation apparatus provided the analytical sample: bp 50–51 °C (0.26 Torr); IR (thin film) 2970, 2940, 2880, 1740, 1180, and 1148 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.28 (s, 3, CH_3), 1.28 (t, 3, *J* = 7 Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.48–2.38 (m, 4, CH_2CH_2), 2.60 (s, 1, C-1 H), 2.97 (t, 1, *J* = 2 Hz, C-3 H) and 4.14 (q, 2, *J* = 7 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); mass spectrum, *m/e* (rel intensity) 213 (5), 212 (M^+, 1), 197 (5) 167 (34), 156 (17), 139 (31), 86 (24), 84 (17), 83 (30), 73 (38), 68 (26), 56 (20), 53 (25), 49 (45), 45 (23), 43 (100), 39 (39).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.75; H, 9.45.

Continued elution of the column with 4%, 6%, 8%, and 10% ether/hexanes provided 2.58 g (57.1%) of **6**: bp 56–57 °C (0.16 Torr); IR (thin film) 2970, 2930, 2880, 1745, 1723, 1370, 1334, 1242, 1150, 1048, and 1033 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.28 (t, 3, *J* = 7 Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.40 (s, 3, CH_3), 1.57–2.30 (m, 4, CH_2CH_2), 2.42 (s, 1, C-1 H), 2.96 (distorted t, 1, *J* = 2 Hz, C-3 H), and 4.17 (q, 2, *J* = 7 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); mass spectrum, *m/e* (rel intensity) 213 (7), 212 (M^+, 1), 197 (5), 167 (40), 156 (21), 139 (22), 111 (22), 97 (22), 95 (20), 86 (16), 85 (18), 83 (43), 82 (18), 81 (21), 73 (25), 72 (67), 69 (20), 67 (22), 55 (36), 43 (100), 41 (51), 39 (35).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.00; H, 9.52.

Ethyl 3-Hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (8).[33] A solution of 1.59 M sodium ethoxide (195 mL, 0.310 mol), prepared from 7.30 g of sodium and 200 mL of ethanol, was added to a stirred solution of 74.7 g of crude **6** and **7** (assumed to contain 0.280 mol of pure epoxides) under argon. The solution, which turned red, was heated under reflux for 1 h. After cooling, the pH was adjusted to 6 by addition of 2.4 M HCl (130 mL). Ethanol was removed in vacuo and the residue was extracted with dichloromethane (2 × 250 mL). Combined organic layers were washed with 250 mL of brine and dried ($MgSO_4$). Removal of solvent furnished 69.35 g of crude **1**, which was used directly in the following reaction.

On a smaller scale, 1.99 g (9.37 mmol) of epoxides **6** and **7** was converted to 1.88 g (94.5%) of crude **8**. Distillation provided the analytical sample: bp 90–95 °C (0.16 Torr); IR (thin film) 3420 (br), 2975, 2940, 2880, 1721, 1705, 1460, 1450, 1365, 1297, 1250, 1226, 1067, 1055, and 1027 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.30 (t, 3, *J* = 7 Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.77 (s, 3, CH_3), 1.5–2.3 (m, 4, CH_2CH_2), 3.62 (s, 1, $\mathrm{O}\mathit{H}$), 3.73 (t, 1, *J* = 14 H_z, $\mathrm{C}\mathit{H}\mathrm{OH}$), and 4.22 (q, 2, *J* = 7 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); mass spectrum, *m/e* (rel intensity) 212 (3), 197 (4), 195 (4), 167 (7), 156 (11), 139 (17), 123 (21), 121 (13), 110 (24), 95 (16), 82 (14), 81 (13), 79 (12), 67 (15), 55 (20), 43 (100), 41 (40), 39 (24).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C 67.87; H, 9.21.

Ethyl 2,6,6-Trimethyl-3-oxocyclohex-1-ene-1-carboxylate (9). A 2.63 M chromic acid solution was prepared from 30.5 g (0.305 mol) of chromium trioxide, 90 mL of water, and 26 mL of concentrated sulfuric acid and was added dropwise over a 2-h period at 5 to 15 °C to a solution of 69.35 g of crude **8** (assumed to contain 0.280 mol of **8**) in 200 mL of acetone. The reaction mixture was allowed to stand at room temperature overnight. To assure completion of the reaction, 0.50 mL of 2.64 M chromic acid solution was added at 5 to 10 °C. 2-Propanol (5 mL) was added to destroy excess chromic acid and the bulk of the acetone was removed in vacuo. The residue was partitioned between water (200 mL) and ether (2 × 200 mL) following removal of the green solids by filtration. The ether solution was dried ($MgSO_4$) and evaporated to give 55.9 g of **9** containing no observable impurities. The overall yield for the three-step conversion of **5** to **9** was 94.9%.

In another experiment, 91.75 g (0.432 mol) of **8** was converted to 86.55 g (95.2%) of crude **9**. Distillation and preparative TLC (silica gel; 15% ether/hexanes) of a portion of the crude product afforded the analytical sample: bp 117–119 °C (1.6 Torr); IR (thin film) 2975, 2940, 2880, 1724, 1680, 1240 (br), 1062, and 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (s, 6, 2 CH_3), 1.35 (t, 3, *J* = 7 Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.73 (s, 3, CH_3), 1.8–2.7 (m, 4, CH_2CH_2), and 4.29 (q, 2, *J* = 7 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); mass spectrum, m/e, (rel intensity) 211 (57), 210 (M^+, 33), 182 (40), 165 (39), 154 (27), 149 (27), 137 (100), 109 (50), 79 (27), 67 (36), 55 (30), 53 (30), 43 (37), 41 (55), 39 (48).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.69; H, 8.98.

Ethyl 2-(Bromomethyl)-6,6-dimethyl-3-oxocyclohex-1-ene-1-carboxylate (10). A solution of enone **9** (4.67 g, 2.27 mmol) in 30 mL of carbon tetrachloride under argon was treated with 4.74 g (26.7 mmol) of NBS. The stirred reaction mixture was irradiated with a 150-W lamp for 70 min. The mixture eventually turned orange-red in color and finally became colorless with a floating white precipitate (succinimide). The mixture was filtered, and the filtrate was washed with 50-mL portions of 10% sodium sulfite solution and brine and dried. Removal of solvent afforded 5.76 g (89.7%) of bromo ketone **10**, containing negligible impurities. Distillation furnished the analytical sample: bp 129–130 °C (0.60 Torr); IR (thin film) 2980, 2945, 2910, 2880, 1738, 1723, 1690, 1250, 1220, 1160, 1035, and 620 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (s, 6, 2 CH_3), 1.57 (t, 3, *J* = 7 Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.92 (t, 2, *J* = 7 Hz, C-5 H), 2.28 (t, 2, *J* = 7 Hz, C-4 H), 4.06 (s, 2, CH_2Br), and 4.40 (q, 2, J = 7 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); mass spectrum, *m/e* (rel intensity) 291 (16), 289 (19), 245 (10), 243 (10), 209 (100), 208 (73), 181 (21), 180 (20), 165 (28), 163 (20), 137 (73), 135 (79), 109 (36), 107 (44), 93 (67), 91 (50), 79 (55), 77 (52), 55 (38), 49 (43), 43 (50), 41 (54), 39 (64).

Anal. Calcd for $C_{12}H_{17}O_3Br$: C, 49.84; H, 5.93; Br, 27.63. Found: C, 49.57; H, 5.85, Br, 27.94.

Ethyl 4-Bromo-3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (15). A solution of 114 mg (0.54 mmol) of allylic alcohol **8** in 25 mL of carbon tetrachloride was treated with 115 mg (0.64 mmol) of NBS. The mixture was heated at gentle reflux for 45 min. After cooling, the mixture was diluted with 25 mL of dichloromethane, extracted with 25-mL portions of 10% sodium sulfite solution and brine, and dried ($MgSO_4$). Removal of solvent furnished 145 mg of material that was purified by preparative TLC (SiO_2; 10% ether/hexanes, two developments; 12% ether-/hexane, four developments) to afford 30 mg (27%) of enone **9** and 48 mg (31%) of **15**: bp 123–124 °C (1.2–1.3 Torr); IR (thin film) 2980, 2950, 1723, 1690, 1307, 1246, 1230, 1197, 1053, and 1032 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (s, 3, CH_3), 1.37 (t, 3, *J* = 7 Hz, $\mathrm{CH_2C}\mathit{H}_3$), 1.46 (s, 3, CH_3), 1.80 (s, 3, CH_3), 2.47 (d, 2, *J* = 9.5 Hz, CH_2), 4.34 (q, 2, *J* = 7 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), and 5.00 (t, 1, *J* = 9.5 Hz, C-4 H); mass spectrum, *m/e* (rel intensity) 291 (M + 1, 61), 289 (M + 1, 67), 245 (19), 243 (20), 217 (23), 215 (25), 209 (100), 182 (58), 137 (72), 136 (49), 135 (53), 126 (48), 107 (48), 91 (56), 81 (53), 55 (61), 53 (54), 41 (80), 39 (78).

Anal. Calcd for $C_{12}H_{17}O_3Br$: C, 49.84; H, 5.93; Br, 27.63. Found: C, 49.78; H, 6.06; Br, 27.70.

1,4-Dioxo-7,7-dimethyl-4,5,6,7-tetrahydro-2-indanacetic Acid (11). In a modification of the literature procedure,[12] 4.3 mL (5.0 g, 37 mmol) of dimethyl malonate was added to a mixture of 1.87 g (78 mmol) of sodium hydride and 80 mL of THF under nitrogen at −7 °C to 0 °C over a 15-min period. The mixture was stirred at −8 °C for 30 min. Thereupon, a solution of 9.00 g (31.1 mmol) of bromo ketone **9** in 35 mL of the THF was added at −8 °C to 0 °C over a 30-min period via a dropping funnel. The dark yellow solution was stirred at 0 °C for 0.5 h and then at room temperature for 3.5 h. Methyl bromoacetate (4.0 mL, 42 mmol) was added via syringe over a 5-min period. After 18 h at room temperature, the reaction mixture was treated wtih 40 mL of glacial acetic acid and 40 mL of 6 N HCl. The mixture was heated at reflux (66–72 °C) for 1 h. Thereafter the mixture was heated with distillation of solvent until a temperature of 100 °C was reached (2 h). After cooling, the undistilled residue was diluted with 50 mL of water and extracted with dichloromethane (75 mL, 50 mL, 50 mL). The combined organic layers were extracted with 10% sodium bicarbonate solution (100 mL, 100 mL, 50 mL). The

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(33) The synthesis of this compound has been reported: Kaiser, R.; Lamparsky, D. *Helv. Chem. Acta* **1978**, *61*, 373.

combined aqueous layers were extracted with 100 mL of ether and then acidified with concentrated HCl and extracted with dichloromethane (3 × 75 mL). The combined organic extracts were washed with 100 mL of brine and dried ($MgSO_4$). Removal of solvent gave 4.38 g (59.6%) of **11** as a yellow solid. Recrystallization from ether yielded material with mp 136.5–137.5 °C (lit.[11] mp 136–137 °C).

Acknowledgment. The author thanks Michael G. Legendre for providing the mass spectra and Ingenue' Cobbinah, Angela Haynes, Jacki Novak, Mary P. Lovisa, Jan Ferrara, and James Philips for technical assistance.

[3 + 2]- and [5 + 2]-Cycloadditions of the Cyclohepta-2,4-dienyl Cation

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Received October 14, 1986

The cyclohepta-2,4-dienyl cation (**9**), generated in situ from 5-chloro-1,3-cycloheptadiene (**10**) and zinc chloride, undergoes a [3 + 2]-cycloaddition with 1-phenylpropyne (**11**) to give the bicyclo[4.2.1]nona-2,7-dien-9-yl cation (**18**), which is stereoselectively trapped by a chloride ion. The corresponding reaction of **10** with 1-methoxy-2-methylpropene (**13**) yields the aldehyde **14** and the bicyclo[3.2.2]nonenes **15a–c** and **16**, which are rationalized by a stepwise [5 + 2]-cycloaddition process. Configurations and conformations of the bicyclo[3.2.2]nonenes are investigated by NMR spectroscopy.

The thermally allowed [${}_{\pi}4_{s}$ + ${}_{\pi}2_{s}$]-cycloaddition reactions[1] can be realized in four different ways (eq 1–4).


(1)

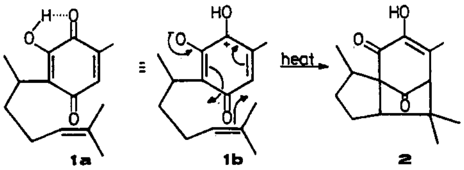

(2)


(3)


(4)

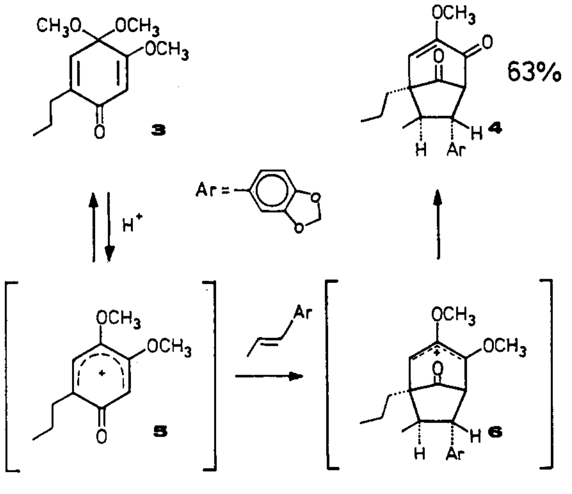
Synthetic as well as mechanistic aspects of Diels–Alder reactions (eq 1)[2,3] allyl anion,[4] azallyl anion,[4] and 1,3-dipolar cycloadditions[3,5] (eq 2) have been studied in great detail. Allyl cation cycloadditions with 1,3-dienes (eq 3) offer a synthetic access to seven-membered ring compounds, but the mechanism of these reactions is still questionable.[6] As shown in the following discussion, examples of eq 4 are rare.

Woodward and Hoffmann[1] cited the perezon pipitzole rearrangement (eq 5)[7a] as the only representative of reaction 4. Deuterium labeling studies provided arguments



(5)

for the concerted nature of this reaction[7b] and proved that the rearrangement proceeds stepwise in the presence of a Lewis acid.[7c] Intermolecular analogues of this transformation, e.g., the reaction sequence **3** → **4**,[8d] have been carried out with 2-alkoxybenzoquinone derivatives[8] and 3-hydroxy-4-pyrones.[9,10]



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