distilled, 0.142 mL, 2.2 equiv) was added via syringe to a stirring solution of **6** (208 mg, 0.71 mmol) in pyridine (1.2 mL), and the mixture was stirred for 2 h at room temperature. Methanol (10 mL) was added and sodium borohydride (300 mg) was added immediately in one portion.[22] After the exothermic reaction was complete (~5 min), saturated aqueous NH_4Cl (10 mL) was added; and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The organic layer was dried ($MgSO_4$), and solvent was removed under reduced pressure. Flash chromatography[20] (1:1 ethyl acetate–petroleum ether) of the residue afforded **8** (134 mg, 68%) as an oil. **8**: $[\alpha]^{20}_D$ +71.2° (*c* 2.67, $CHCl_3$); IR (CH_2Cl_2) 3580, 1720 cm^{-1}; ^1H NMR δ 7.28–7.36 (m, 5 H), 6.98 (br s, 1 H), 5.66 (s, 1 H), 4.49–4.60 (m, 2 H), 4.11 (br s, 1 H), 3.76 (s, 3 H), 3.19 (d, *J* = 10.4 Hz, 1 H), 3.14 (d, *J* = 16.7 Hz, 1 H), 1.94 (dm, *J* = 16.3 Hz, 1 H); ^{13}C NMR δ 166.1, 142.7, 136.1, 129.9, 128.6, 128.4, 127.1, 103.4, 77.2, 73.6, 68.1, 52.0, 26.4; MS (EI), *m/e* (relative intensity) 276 (M^+, 2.5), 275 (4), 170 (100); high-resolution mass spectrum, calcd for $C_{15}H_{16}O_5$ 276.0998, found 276.1002.

(1*R*,2*R*,6*R*,8*S*)-2-(Benzoyloxy)-4-(methoxycarbonyl)-8-phenyl-7,9-dioxabicyclo[4.3.0]non-3-ene (9). The reaction of **8** (19.6 mg, 0.071 mmol) with triphenylphosphine (36 mg, 0.137 mmol), diisopropyl diazocarboxylate (15.6 mg, 0.077 mmol), and benzoic acid (8.67 mg, 0.077 mmol) in THF was carried out according to the procedure of Mitsunobu[15] and Bose.[16] The mixture was stirred for 3 h at room temperature, and the solvent was removed under reduced pressure. Flash chromatography[20] (ethyl acetate–petroleum ether, 1:9, 1.5:3.5, then 1:1) afforded **9** (25 mg, 91%) as an oil. **9**: IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR δ 8.04 (m, 2 H), 7.55–7.61 (m, 1 H), 7.36–7.48 (m, 7 H), 7.08 (d, *J* = 3.8 Hz, 1 H), 5.83 (s, 1 H), 5.68–5.72 (m, 1 H), 4.53–4.65 (m, 2 H), 3.78 (s, 3 H), 3.07 (dd, *J* = 16.9, 5.8 Hz, 1 H), 2.76 (dm, *J* = 16.9 Hz, 1 H); ^{13}C NMR δ 165.8, 165.6, 136.4, 136.2, 133.4, 131.4, 129.8, 129.6, 128.5, 128.4, 126.9, 126.2, 103.7, 77.1, 73.4, 71.3, 52.1, 27.3; MS (EI), *m/e* (relative intensity) 380 (M^+, 15), 379 (8), 274 (86); high-resolution mass spectrum, calcd for $C_{22}H_{20}O_6$ 380.1260, found 380.1222.

(–)-Methyl 4,5-*O*-Benzylidene-4-*epi*-shikimate (2). A solution of **9** (270 mg, 0.71 mmol) and NaOMe (42.2 mg, 1.1 equiv) in MeOH (20 mL) was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried and concentrated under reduced pressure. Flash chromatography[20] (ethyl acetate–petroleum ether, 1.5:3.5, then 1:1) gave **2** (179 mg, 92%) as a colorless oil. **2**: $[\alpha]^{20}_D$ –18.0° (*c* 2.40, $CHCl_3$); the IR, ^1H NMR, and ^{13}C NMR spectra were identical with the corresponding spectra of the major acetal diastereomer of (±)-**2** prepared previously;[2] high-resolution mass spectrum, calcd for $C_{15}H_{16}O_5$ 276.0998, found 276.1012.

(–)-4-*epi*-Shikimic Acid (10). Alcohol **2** (111 mg, 0.40 mmol) was dissolved in THF (4 mL), and an aqueous solution of KOH (24.6 mg, 1.1 equiv in 1 mL of H_2O) was added. The mixture was stirred for 1 h at room temperature. A solution of aqueous acetic acid (80%, 5 mL) was added, and the mixture was stirred for 12 h at room temperature. Solvents were removed under reduced pressure. Methanol (1 mL) and excess diethylamine (1 mL) were added to the residue, and the mixture was concentrated under reduced pressure. The residue was loaded on a 10-cm ion-exchange resin column (Amberlite IR-120, H^+ form) and 50 mL of eluent were collected. Evaporation of the water under reduced pressure gave 67 mg (96%) of pure **10**. Sublimation (150–180 °C, 10^{-3} mm) gave **10** as an extremely hygroscopic, amorphous solid.[10] **10**: $[\alpha]^{22}_D$ –80.6° (*c* 1.03, H_2O) (lit.[10] $[\alpha]^{22}_D$ –93° (*c* 0.9, H_2O)); the ^1H NMR spectrum of **10** was in agreement with the literature spectral data.[10]

Acknowledgment. We are grateful to the National Institutes of Health, Grant GM 31958, for financial support.

Registry No. (–)-**2**, 94903-41-0; (–)-**3**, 77-95-2; **4** (isomer 1), 32384-44-4; **4** (isomer 2), 94903-42-1; **5**, 94843-95-5; **6**, 94843-96-6; **8**, 94903-43-2; **9**, 94843-97-7; (–)-**10**, 94903-44-3; chorismic acid, 617-12-9.

(22) In large-scale preparations enone **7** was isolated prior to borohydride reduction to **8**.

Diels–Alder Reactions of Cycloalkenones. 4. Short Syntheses of Some Cadinenes[1]

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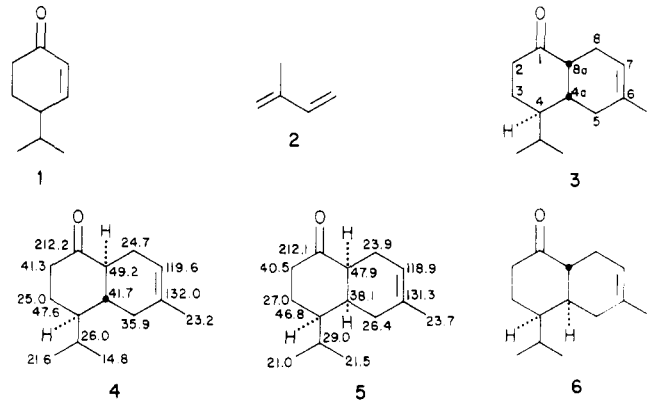
Received August 20, 1984

As part of a general study of the Lewis acid catalyzed Diels–Alder reaction of cycloalkenones with dienes, 4-isopropyl-2-cyclohexenone (**1**)[3] was allowed to react with isoprene (**2**) in toluene solution under the influence of



anhydrous aluminum chloride, leading in 75% yield to a 9:1 mixture of octalones **4** and **5** as well as a trace of isomer **3**. Whereas the latter substance was not isolated and its presence in the product mixture recognized only by GC analysis, its structure **3** is based on the observation of the compound being formed on treatment of ketone **4** with base. The equilibrium constants (by GC analysis) of the trans/cis octalone pairs **4**/**3** and **6**/**5** are ca. 200 and 10^{-2}, respectively.[1]

The structures of the Diels–Alder reaction products were determined by ^{13}C NMR spectroscopy on the basis of previously described octalone models.[1] The carbon shifts are shown on formulas **4** and **5**.[4] *cis*-Octalones **3** and **5** are the primary Diels–Alder products. However, in analogy with the behavior of other *cis*-octalones,[1] ketone **3** had undergone acid-induced isomerization into the more stable *trans*-octalone **4**. The low tendency for the isomerization of *cis*-octalone **5** into its trans isomer **6** is due presumably to the fact of the latter carrying its isopropyl group in an axial orientation. The product structures reveal that the cycloaddition leading to the *cis*-octalones had occurred by

(1) For previous papers, see: Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1979**, *9*, 391. Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056. Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802.

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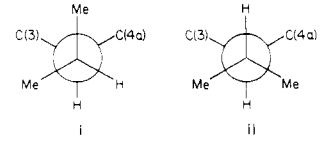
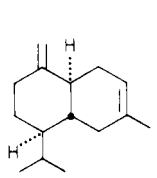
(4) The δ values of the isopropyl methyl groups of ketones **4** and **5** indicate rotamer preferences i and ii for the two compounds, respectively.



preferred diene attack on enone 1 from the side away from the isopropyl group.

Octalone 4, prepared previously in 12 steps from *p*-anisaldehyde,[5,6] has been converted into the racemate of the sesquiterpene γ_2-cadinene (7) by exposure to methylenetriphenylphosphorane.[6] The above Diels–Alder method of construction of ketone 4 thus becomes a formal, two-step, total synthesis of the sesquiterpene.



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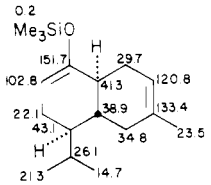

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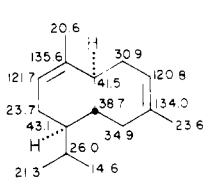

9

The ready availability of octalone 4 led to a three-step, total synthesis of the sesquiterpene β-cadinene (9). Base-induced, kinetic deprotonation of ketone 4 and enolate silylation[7] yielded silyl enol ether 8, whose treatment with methylmagnesium bromide in the presence of nickel acetylacetonate[8b] gave (±)-β-cadinene (9).[9]

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{13}C NMR spectra of $CDCl_3$ solutions were taken on a Nicolet NT-200 (wide-bore, broad-band, with an Oxford solenoid) spectrometer, operating at 50.31 MHz in the Fourier transform mode. The carbon shifts on formulas 4, 5, 8, and 9 are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm.

Octalones 4 and 5. A solution of 5.00 g (36 mmol) of ketone 1 in 30 mL of dry toluene was added slowly to a solution of 1.20 g (9 mmol) of anhydrous aluminum chloride in 200 mL of dry toluene under nitrogen at a temperature of up to 20 °C, and the mixture was then stirred at room temperature for 40 min. A solution of 36.7 g (0.54 mol) of isoprene (2) in 80 mL of dry toluene was added, and the solution was stirred at 60 °C under nitrogen for 7 h. The usual workup[1] and product distillation (at 100–110 °C (0.2 torr)) yielded 6.00 g (75%) of a 180:19:1 mixture of ketones 4, 5, and 3 (GC analysis on 2 m Carbowax 20M, 160 °C, 25 mL/min). Crystallization of the mixture from pentane at ca. −30 °C yielded 4.00 g of crystalline ketone 4. Evaporation of the mother liquor, chromatography of the residue on Silal 13, and gradient elution with 100:1 to 9:1 pentane–ether gave an additional 1.00 g of solid ketone 4: mp 33–34 °C (lit.[6] mp 35 °C); IR (CCl_4) 1720 (C=O, s) cm^{-1}; ^1H NMR δ (CCl_4) 0.78, 1.00 (d, 3 each, J = 7 Hz, i-$PrMe_2$), 1.64 (s, 3, Me), 5.37 (br s, 1, olefinic H). 2,4-Dinitrophenylhydrazone: mp 178–179 °C (EtOH). Anal. Calcd for $C_{20}H_{26}O_4N_4$: C, 62.15; H, 6.79; N, 14.50. Found: C, 61.86; H, 6.90; N, 14.11.

A later eluate gave 400 mg of solid ketone 5: mp 62–63 °C (pentane); IR (CCl_4) 1720 (C=O, s) cm^{-1}; ^1H NMR δ (CCl_4) 0.99 (d, 6, J = 5 Hz, i-$PrMe_2$), 1.60 (s, 3, Me), 5.19 (br s, 1, olefinic H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.74. Found: C, 81.35; H, 10.75. 2,4-Dinitrophenylhydrazone: mp 176–177 °C (EtOH). Anal. Calcd for $C_{20}H_{26}O_4N_4$: C, 62.15; H, 6.79; N, 14.50. Found: C, 61.77; H, 6.44; N, 14.06.

The base-catalyzed epimerizations of ketones 4 and 5 followed a previous procedure.[1]

Ether 8. Diisopropylamine, 957 mg (11.0 mmol), was added to a solution of 11.0 mmol of *n*-butyllithium and 5 mg (0.02 mmol) of triphenylmethane (as indicator) in 30 mL of anhydrous tetrahydrofuran at 0 °C over nitrogen. Octalone 4, 2.00 g (9.70 mmol), was added dropwise over a 10-min period to the stirring solution at 0 °C (until the red indicator color had nearly been discharged). A silylating solution of 1.63 g (15.0 mmol) of trimethylsilyl chloride and 0.5 mL of triethylamine in 10 mL of anhydrous tetrahydrofuran, from which precipitated triethylammonium chloride has been removed by centrifugation, was added rapidly through a cannula into the cold constantly stirred solution of the enolate of 4. After 35 min at room temperature a saturated sodium bicarbonate solution was added, and the mixture was extracted with methylene chloride. The extract was dried and evaporated under vacuum. Rapid filtration of a hexane solution of the residue through a 5-g silica gel column afforded 2.40 g (89 %) of colorless, liquid trimethylsilyl enol ether 8: IR (neat) 1665 (C=C, m) cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.20 (s, 9, $SiMe_3$), 0.75, 0.93 (d, 3 each, J = 6 Hz, i-$PrMe_2$), 1.1–2.6 (m, 10, methylenes and methines), 1.68 (s, 3, Me), 4.8–5.0 (m, 1, enol ether olefinic H), 5.4–5.6 (m, 1, olefinic H). Anal. Calcd for $C_{17}H_{30}OSi$: C, 73.31; H, 10.86. Found: C, 73.41; H, 10.86.

(±)-β-Cadinene (9). A 3.00 M ethereal solution of methylmagnesium bromide, 1.0 mL (3.0 mmol), was added dropwise to a stirring suspension of 33 mg (0.13 mmol) of $Ni(acac)_2$ in 10 mL of dry benzene under argon, and the mixture was refluxed for 15 min. A solution of 350 mg (1.3 mmol) of enol ether 8 in 2 mL of dry benzene was added, and the mixture was stirred at 80 °C for 40 h. It was then cooled, poured into 20 mL of saturated ammonium chloride solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residue (a 3:2 mixture of starting ether and diene product, by GC analysis) on 30 g of neutral alumina (activity I) and elution with hexane yielded 102 mg (39%) of colorless, liquid diene 9:[10] ^1H NMR δ ($CDCl_3$) 0.78, 0.88 (d, 3 each, J = 6 Hz, i-$PrMe_2$), 1.0–2.4 (m, 10, methylenes and methines), 1.67, 1.68 (s, 3 each, methyls), 5.3–5.5 (m, 2, olefinic Hs). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.35; H, 11.76.

Acknowledgment. F.F., F.P., and A.T. acknowledge gratefully support for the work in Perugia by the Consiglio Nazionale delle Ricerche and A.T. and E. W. are indebted to NATO (Grant No. 257.81) for grant support.

Registry No. 1, 2158-61-4; 2, 78-79-5; 3, 86391-43-7; 4, 29292-32-8; 5, 94841-67-5; 8, 94782-08-8; 9, 5951-61-1.

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(9) The replacement of a (trimethylsilyl)oxy group on a double bond by an alkyl group through the use of a nickel-catalyzed Grignard reaction was discovered in 1979[8a] and utilized bis(triphenylphosphino)nickel dichloride for catalysis. A year later[8b] there appeared a report on a study of the same reaction catalyzed by nickel species ligated by triphenylphosphine, 1,1′-bis(diphenylphosphino)ferrocene or acetylacetonate, which claimed the latter to be the ligand of choice for efficient catalysis and yield improvement. Whereas the 8 → 9 conversion could be accomplished in the presence of bis(triphenylphosphino)nickel dichloride in up to 80% yield of isolated diene 9, the reaction proved erratic and not consistently reproducible. Nickel acetylacetonate was a more dependable catalyst.
(10) In contrast to the claim[8b] of major yield improvement by the execution of the Grignard reactions in ether solution under nickel acetylacetonate catalysis the formation of β-cadinene dropped to less than 10% under these conditions (refluxing for 24 h), the remaining contents of the reaction mixture being starting material.

Synthesis of 2(*R*),5(*R*)-Bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine. A Novel Glycosidase Inhibitor†

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Received October 5, 1984

The 5-amino-5-deoxy-D-glucose antibiotics nojirimycin (1) and 1-desoxynojirimycin (2) are reportedly active

† Contribution No. 3614.

0022-3263/85/1950-0891$01.50/0