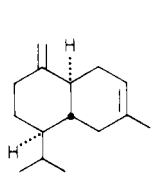
preferred diene attack on enone 1 from the side away from the isopropyl group.

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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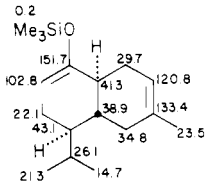

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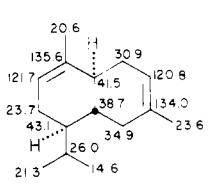

9

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†

Peter J. Card* and William D. Hitz

Central Research & Development Department, E. I. du Pont de Nemours & Co., Experimental Station, Wilmington, Delaware 19898

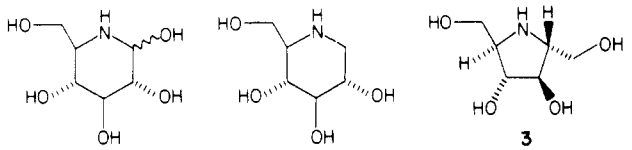
Received October 5, 1984

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

against diabetes and atherosclerosis.[1] Their biological



1 2 3

activities have been attributed to their potent inhibition of α-glucosidases where they act as apparent transition-state analogues. Because of our interest in sucrose transport and inhibitors of invertase,[2] and since invertase (β-D-fructofuranosidase) is known to act by a mechanism analogous to that of glucosidase, we synthesized the 5-aminofructose analogue 2(*R*),5(*R*)-bis(hydroxymethyl)-3-(*R*),4(*R*)-dihydroxypyrrolidine (**3**) to investigate its activity as an invertase inhibitor.

Pyrrolidine **3** with absolute configuration as indicated represents a challenging synthetic target because of its four contiguous asymmetric centers. We chose L-sorbose as our starting material because it contains the desired absolute configuration at C-3 and C-4 and the opposite configuration at C-5 that would be inverted upon substitution by a nitrogen nucleophile. Subsequent ring closure via attack of the nitrogen upon C-2 followed by reduction should afford the pyrrolidine **3**.

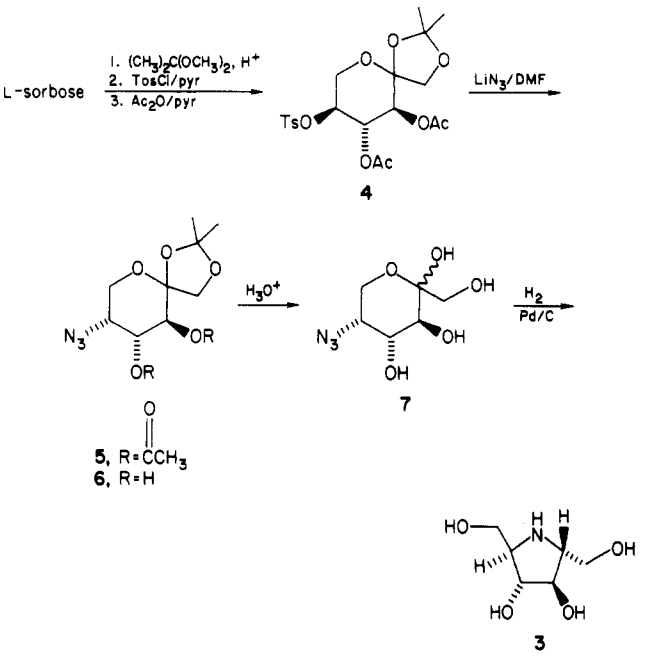
In three steps, L-sorbose is readily converted into the known 3,4-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-L-sorbose (**4**).[3] Heating **4** with lithium azide in DMF at 70 °C for 72 h afforded a 74% yield of the C-5 inverted azide **5** (Scheme I). The stereochemistry at C-5 was assigned on the basis of the small (4 Hz) coupling exhibited between H-4 and H-5, suggesting that H-5 is in an equatorial position. Hydrolysis of the acetate moieties of **5** with 4 mM NaOMe/MeOH gave the diol **6** which was hydrolyzed further with an acidic ion-exchange resin to afford 5-azido-5-deoxy-D-fructose (**7**; 93%) as a crystalline solid.

Catalytic hydrogenation of azide **7** over 10% Pd/C (EtOH) gave a quantitative yield of pyrrolidine **3** ($[\alpha]_D$ + 55.8°); no trace of the C-2 epimer was detected. The configuration at C-2 follows from the ^{13}C NMR spectrum of **3** (see Experimental Section) which exhibits only three carbon resonances and therefore requires that **3** contains a C_2 axis of symmetry.

In addition to the above structure proof, **3** is a natural product which has been isolated from the leaves of *Derris elliptica* and has been structurally characterized by X-ray diffraction.[4,5] The reported optical rotation ($[\alpha]_D$ +56.4°) and ^{13}C NMR of natural **3** are in good agreement with our preparation, and since these investigators were unable to determine the absolute configuration of natural **3** our synthesis also serves to unambiguously define its configuration.

The hydrolysis of sucrose by either invertase or α-glucosidase was strongly inhibited by **3** as was the hydrolysis of *p*-nitrophenyl α-D-glucopyranoside by α-glucosidase and of *p*-nitrophenyl β-D-glucopyranoside by β-glucosidase. Inhibition was apparently competitive in all cases and was dependent upon pH in a manner which suggests that only the nonprotonated form of **3** is active as an inhibitor. Concentrations of **3** required for 50% inhibition of hydrolysis at pHs above 6.5 were about 0.2 μM for either glucosidase and about 1.5 μM for invertase. Further characterization of the inhibition will be reported elsewhere.

Scheme I



Experimental Section

General Methods. All reactions were performed under a nitrogen atmosphere. Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Nicolet 7199 FT-IR spectrometer. Optical rotations were determined on a Perkin-Elmer 241 MC polarimeter. ^1H NMR spectra (360-MHz) were obtained on a Nicolet NT WB 360 spectrometer and are referenced to internal tetramethylsilane. ^{13}C NMR spectra were determined on a Bruker WH-90 spectrometer.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (6). A solution of tosylate **4**[3] (13.81 g, 30.1 mmol) and lithium azide (14.4 g, 300 mmol) in 200 mL of DMF was heated at 70 °C for 72 h. The DMF was removed on a rotatory evaporater and the resulting residue was partitioned between water and ether. The ether layer was dried ($MgSO_4$), and concentrated under reduced pressure, and the products were column chromatographed on silica gel (2:1 hexane/ether) to afford **5** (7.38 g, 74%) as a colorless syrup: IR (KBr) 2110, 1755, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.48 (s, 3 H), 2.13 (s, 3 H), 2.14 (s, 3 H), 3.76 (dd, H-6, $J_{6,6'}$ = 13, $J_{6,5}$ = 2 Hz), 3.94 (AB, H-1 and 1', $J_{1,1'}$ = 10 Hz), 4.04–4.15 (m, 2 H), 5.13 (dd, H-4, $J_{3,4}$ = 10, $J_{4,5}$ = 4 Hz), 5.41 (d, H-3).

The above syrup in 100 mL of ether was treated with 250 mL of 4 mM $NaOCH_3$ in CH_3OH. After stirring for 1 h at room temperature, the volatiles were removed under reduced pressure, and the residue was recrystallized from ether–hexane to give **6** (3.44 g, 63%) as a colorless solid: mp 113.5–115 °C; IR (neat) 3445, 2105, 1170, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.50 (s, 3 H), 1.88 (br, 1 H, OH), 2.68 (br, 1 H, OH), 3.70–3.82 (m, 2 H), 3.9–3.99 (m, 4 H), 4.03 ($^1/_2$ of AB, H-1, $J_{1,1'}$ = 9 Hz), 4.19 ($^1/_2$ of AB, H-1').

Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.39; H, 6.13; N, 17.16.

5-Azido-5-deoxy-D-fructose (7). A solution of diol **6** (3.44 g, 14 mmol) in EtOH (14 mL) and water (45 mL) was treated with Biol-Rad AG 50W-X8 (7 g; hydrogen form), and the mixture was heated at 45 °C for 2 h. The reaction mixture was filtered, decolorized, and then extracted with ether. The aqueous layer was partially concentrated on a rotatory evaporater to remove

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the EtOH and then lyophilized to afford **7** as a solid (2.66 g, 93%): mp 117–119 °C; IR (KBr) 3370, 2110, 1090, 1065 cm^{-1}; ^{13}C NMR (D_2O) δ 61.0, 62.7, 63.8, 67.9, 69.9, 98.3.

Anal. Calcd for $C_6H_{11}N_3O_5$: C, 35.12; H, 5.40; N, 20.48. Found: C, 35.21; H, 5.27; N, 20.60.

2(*R*),5(*R*)-Bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine (3). A solution of 5-azidofructose **7** (2.05 g, 10 mmol) in 100 mL of EtOH containing a catalytic amount of 10% Pd/C was treated with H_2 at ~25 psi. When H_2 uptake ceased, the mixture was filtered through Celite and the volatiles were removed under reduced pressure affording 1.63 g (100%) of **3** as a colorless solid: mp 115–117 °C; ^{13}C NMR (D_2O) δ 61.8, 62.2, 78.1; $[\alpha]_D$ + 55.8° (*c* 1.0, H_2O) [lit.[4] $[\alpha]_D$ +56.4° (*c* 7.0, H_2O)].

Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found: C, 44.09; H, 8.03; N, 8.40.

Glycosidase Inhibition Studies. Invertase (EC 3.2.1.26), α-glucosidase (EC 3.2.1.20), β-glucosidase (EC 3.2.1.21), *p*-nitrophenyl α-D-glucopyranosides and *p*-nitrophenyl β-D-glucopyranosides were obtained from Sigma Chemical Co. Hydrolysis of sucrose was monitored by the rate of glucose production as assayed by NAD reduction during enzymatic oxidation of glucose 6-phosphate to 6-phosphogluconate. Hydrolysis of *p*-nitrophenyl glucosides was monitored by absorbance at 405 nm after appropriate dilution of the hydrolysate with 0.1 M $NaHCO_3$. The buffer system for all pHs tested was 25 mM citrate, 25 mM *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid, and 25 mM 2-morpholinoethane sulfonic acid and all reactions were run at 30 °C.

Registry No. **3**, 59920-31-9; **4**, 53821-66-2; **5**, 94801-00-0; **6**, 94801-01-1; **7**, 94801-02-2; α-glucosidase, 9001-42-7; β-glucosidase, 9001-22-3; invertase, 9001-57-4; *p*-nitrophenyl α-D-glucopyranoside, 3767-28-0; *p*-nitrophenyl β-D-glucopyranoside, 2492-87-7; sucrose, 57-50-1; glucose, 50-99-7.

Synthesis of 4-Substituted Cycloheptatrienones by Oxidative Cheletropic Elimination of Nitrosobenzene from 6-Substituted 8-Phenyl-8-azabicyclo[3.2.1]octa-3,6-dien-1-ones

Victoria A. Roberts*

Agouron Institute, 505 Coast Blvd., La Jolla, California 92037

Michael E. Garst*[1]

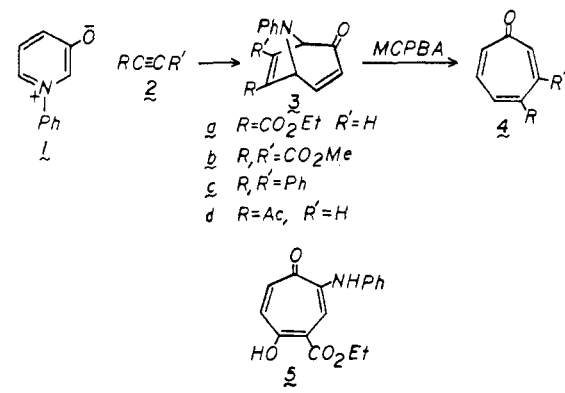
Allergan, 2525 Dupont Drive, Irvine, California 92713

Received June 18, 1984

Three recent model studies for natural product synthesis have made use of cycloheptatrienone.[2-4] Actual application of these models will require efficient preparations of substituted cycloheptatrienones. We have reported a preparation of 3- and of 4-carbethoxycycloheptatrienone in which we mentioned our attempts to remove "*N*-phenyl" from 6,*N*-diphenyl-8-azabicyclo[3.2.1]octa-3,6-dien-1-one (**3d**).[5] In this note, we describe a solution to this cheletropic elimination that yields 4-substituted cycloheptatrienones in two steps.

Katritzky, Dennis, and co-workers[6] have attempted to synthesize cycloheptatrienones starting with cycloadducts

Scheme I



obtained from the reactions of electron-deficient olefins with 3-hydroxypyridinium betaines. During Hofmann elimination, an oxidation occurred to give 2-aminocycloheptatrienones despite numerous attempts to prevent this oxidation. Our plan was to react 1-phenyl-3-hydroxypyridinium betaines with acetylenes. The resulting cycloadducts would be oxidized to amine *N*-oxides that then would be pyrolyzed to provide the desired cycloheptatrienones and nitrosobenzene.[7]

These two steps were realized with the following limitations. Betaine **1** was reacted with acetylenes **2a–d** to provide cycloadducts **3a–d**. No cycloadducts were obtained with diphenylacetylene or 1-hexyne (Scheme I). Treatment of **3a–c** with *m*-chloroperbenzoic acid provided cycloheptatrienones **4a–c** respectively. No intermediate *N*-oxides could be isolated. Two equivalents of *m*-chloroperbenzoic acid were necessary for complete reaction of the cycloadduct. A mixture of nitrosobenzene and nitrobenzene also was formed. Oxidation of **3d** provided trace amounts (<5%) of a mixture of products.[8]

Side product **5** was obtained from the oxidation of cycloadduct **3a**. Meisenheimer rearrangement of the *N*-oxide followed by cleavage of the N–O bond would provide **5**. Compound **5** exhibited a carbonyl stretch at 1668 cm^{-1} in the infrared spectrum for the ester group, which is similar to that for ethyl salicylate. The lack of a large hydroxyl stretch at 3300 cm^{-1} indicates strong intramolecular hydrogen bonding. The rest of the spectral data is consistent with structure **5**.

This cheletropic loss of nitrosobenzene from **3a–c** appears to be among the more facile examples of this reaction. Although aziridine *N*-oxides[9] and aromatic 1,4-imine N-oxides[10] fragment under comparable conditions, the former reaction relieves ring strain and the latter generates an aromatic system. The 8-azabicyclo[3.2.1]octa-3,6-dien-1-one is not strained, and the product lacks substantial resonance stabilization. We have noted that 4-carbethoxycycloheptatrienone and nitrosobenzene do not react with each other under these conditions.

We have developed a two-step synthesis of 4-substituted cycloheptatrienones. This route is limited by the cyclo-

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(8) The major compound was bright red and formed during workup. We have been unable to purify or isolate anything from this mixture. The NMR spectrum of this material showed no methyl ketone. No **3d** remained at the end of the reaction, and nitrosobenzene was formed. Therefore, cycloheptatrienone **4d** probably was formed during the reaction but was either further oxidized or decomposed during workup.
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