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A three-step synthesis of grisan (spiro[benzofuran-2(3*H*)-1'-cyclohexane]), using methoxymethoxybenzene and 1-chloromethylcyclohexene as starting materials, is described.

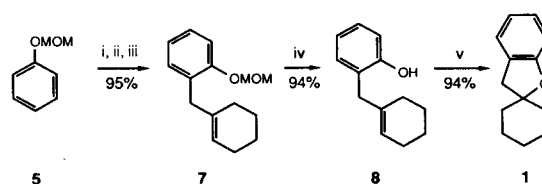
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In 1952, Grove *et al.* [1] proposed the name grisan (**1**) for the spiro[benzofuran-2(3*H*)-1'-cyclohexane] moiety of griseofulvin (**2**) [2]. Structure **1** is shared not only by griseofulvin and its analogs and derivatives, but it is also a substructure present in several natural products such as isochromazonarol (**3**) [3], and the unique complement inhibitor K-76 (**4**) [4]. In addition, biologically active BCD-ring analogs of K-76 bearing the grisan skeleton have been synthesized recently [5].

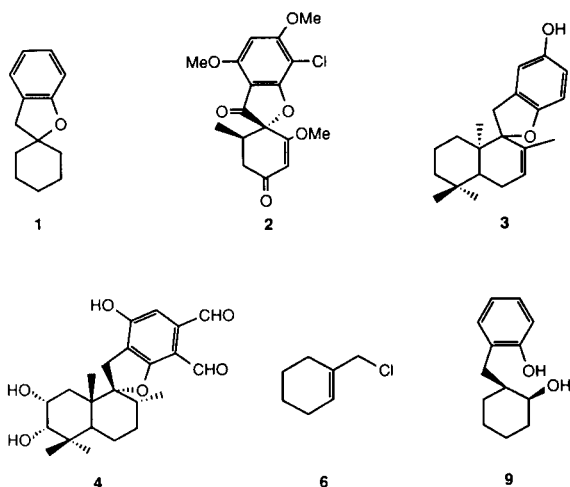
The only synthesis of grisan reported to date was achieved by Antus *et al.* [6]. The fortuitous preparation of **1** was described as occurring during the attempted synthesis of related hexahydroxanthenes. However, the use of this synthetic sequence as a preparative route to grisan suffers from many drawbacks, such as the excessive number of steps, a relatively low overall yield, and the requirement of chromatographic separation of diastereoisomers.

carbon tetrachloride couple in methylene chloride) afforded the precursor **7** in excellent yield.

Scheme



[i] *n*-BuLi-TMEDA, THF, 1.75 h 0° → RT [ii] CuI, -45°C, 1 h [iii] 1-chloromethylcyclohexene, overnight [iv] HCl, 2-propanol-H₂O [v] Amberlist-15, CH₂Cl₂.



Here we report a short, facile and efficient synthesis of grisan, using the readily available methoxymethoxybenzene (**5**) [7,8] as a starting material. Metalation of **5** (Scheme) with the *n*-butyllithium-tetramethylethylenediamine (*n*-BuLi-TMEDA) complex in tetrahydrofuran (THF), followed by copper-assisted coupling of 1-chloromethylcyclohexene (**6**) [9-11] (prepared in 91% overall yield by lithium aluminum hydride reduction of methyl 1-cyclohexene-1-carboxylate and subsequent treatment of the resulting allylic alcohol with the triphenylphosphine-

Removal of the methoxymethyl protecting group was accomplished by hydrochloric acid hydrolysis of **7** in a 2-propanol-water system. It was observed that, while a 2*N* concentration of acid resulted in a slow (2 days) deprotection process, the use of 6*N* hydrochloric acid yielded a mixture of **8** and **1**. The partial cyclization could be avoided by employing a 3*N* hydrochloric acid solution, which cleanly afforded **8**, a synthetic equivalent of the *cis* alcohol **9** employed by Antus *et al.* as the grisan precursor, in 94% yield.

Finally, transformation of **8** into grisan was accomplished in 94% yield by treatment of the phenol with an excess of acidic Amberlist 15 ion-exchange resin in methylene chloride [12]. Generation of grisan as the sole product of the cyclization of **8** was confirmed by examination of the ¹H- and ¹³C-nmr spectra of the product, which were in excellent agreement with the published data [6] and with the proposed structure. In addition, gc analysis of the cyclized material under several temperatures revealed a single peak in the chromatograms. This selectivity can be rationalized by assuming that Amberlist 15-promoted protonation of the double bond leads to the more stable, tertiary carbocation which, in turn, is attacked by the phenolic OH giving exclusively the five-member ring product.

EXPERIMENTAL

The ir spectra were obtained with a Perkin Elmer 281B spectrophotometer. The ^1H - and ^{13}C nmr spectra were recorded at 300 MHz and 75 MHz respectively, on a Varian VXR 300 instrument in deuteriochloroform, and chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ). A Hewlett Packard 5890 gas chromatograph, with a 30 m DB-5 capillary column in the isothermal mode (170°, 200° and 250°) using helium (1 ml/min) as carrier, was employed for purity analysis. Elemental analyses were performed by Atlantic Micro-lab, Inc., Norcross, GA.

All solvents and reagents were purified and dried by standard techniques. All reactions were performed under a dry nitrogen atmosphere. All chromatographic separations were performed on a Chromatotron® (Harrison Research) on 2 and 4 mm silica gel 60 PF₂₅₄ plates, employing increasing amounts of diethyl ether in hexane as the elution solvent.

1-Chloromethylcyclohexene (**6**).

To a stirred and cooled (0°) suspension of lithium aluminum hydride (509 mg, 13.39 mmoles) in ether (20 ml), methyl 1-cyclohexene-1-carboxylate (2500 mg, 17.85 mmoles) was added dropwise. After a 2 hour period, excess decahydrated sodium sulfate was added, and the solids were separated by filtration through a short plug of silica gel. The solids were washed with ethyl acetate (3 x 30 ml) and filtered; the combined filtrates were concentrated under reduced pressure giving 1-hydroxymethylcyclohexene (1960 mg, 17.5 mmoles, 98%) as an oil bp 68°/1.8 mm Hg (lit [13] bp 96°/18 mm Hg); ir (neat): 3330 (-OH), 3020-2820, 1440, and 1010 cm^{-1} ; ^1H nmr: 1.64 (m, 4H), 2.02 (m, 4H), 2.92 (broad s, exch, 1H, -OH), 3.97 (s, 2H, -CH₂O-), and 5.67 (broad s, 1H, =CH-).

Triphenylphosphine (5332 mg, 20.35 mmoles) was added to a solution of 1-hydroxymethylcyclohexene (1900 mg, 16.96 mmoles) in carbon tetrachloride (5 ml) and methylene chloride (5 ml). The reaction was refluxed overnight, then it was poured into hexane (100 ml) and the solids (triphenylphosphine oxide) were separated by filtration. After repeating this operation for three times, the collected solvent was removed under reduced pressure, and the residual oil was distilled under reduced pressure to give **6** (2055 mg, 15.75 mmoles, 93%) as an oil, bp 65°/15 mm Hg (lit [10] bp 62-64°/11 mm Hg); ir (neat): 3040-2820, 1660 (C=CH-), 1440, 1255, 1130, 920, and 675 cm^{-1} ; ^1H nmr: 1.50-1.72 (m, 4H), 2.01-2.12 (m, 4H), 3.99 (s, 2H, -CH₂Cl), and 5.81 (s, 1H, =CH-); ^{13}C nmr: 21.96, 22.41, 25.25, 25.93, 50.72, 127.50, and 134.44.

1-(2-Methoxymethoxybenzyl)cyclohexene (**7**).

To a cold (0°), stirred solution of methoxymethoxybenzene (2000 mg, 14.49 mmoles) in THF (100 ml), TMEDA (2.62 ml, 17.39 mmoles) was added, followed by *n*-butyllithium (8.69 ml, 17.39 mmoles). After 15 minutes, the ice bath was removed and the system was allowed to react at room temperature for 90 minutes, then it was cooled to -45° (acetonitrile-dry ice), and copper(I) iodide (3441 mg, 18.11 mmoles) was added. After 1 hour the allylic chloride **6** (2363 mg, 18.11 mmoles) was introduced *via* syringe, and the system was stirred overnight. Concentrated ammonium hydroxide (50 ml) was added and the organic material was extracted with ether (4 x 200 ml). After drying (magnesium sulfate), concentration *in vacuo* and chromatography of the pooled organic phases, **7** (3210 mg, 13.84 mmoles, 95%) was obtained as a clear oil (bp 107-108.5°/0.095 mm Hg, external bath); ir

(neat): 3040-2820, 1600, 1585, 1490, 1460, 1240, 1160, 1110, 1080, 1050, 1010, 925, and 755 cm^{-1} ; ^1H nmr: 1.49-1.64 (m, 4H), 1.88-2.05 (m, 4H), 3.27 (s, 2H, ar-CH₂-C), 3.46 (s, 3H, -OCH₃), 5.17 (s, 2H, -OCH₂O-), 5.39 (broad s, 1H, =CH-), and 6.89-7.18 (m, 4H, aromatic); ^{13}C nmr: 22.51, 23.05, 25.37, 28.42, 37.91, 55.95, 94.48, 114.16, 121.59, 122.45, 127.04, 129.61, 130.46, 136.70, and 155.25.

Anal. Calcd. for C₁₅H₂₀O₂: C, 77.54; H, 8.68. Found: C, 77.63; H, 8.69.

1-(2-Hydroxybenzyl)cyclohexene (**8**).

A solution of hydrochloric acid (14 ml, 84 mmoles) was added to a solution of **7** (900 mg, 3.88 mmoles) in 2-propanol (14 ml). After stirring overnight, sodium bicarbonate (6720 mg, 80 mmoles) was added in small portions, and the organic products were extracted with ether (4 x 50 ml). After drying (magnesium sulfate), concentration *in vacuo* and chromatography of the combined ethereal phases, **8** (686 mg, 3.85 mmoles, 94%) was recovered as a colorless oil; ir (neat): 3450 (-OH), 3000-2820, 1590, 1490, 1455, 1340, 1220, 1100, 1040, and 755 cm^{-1} ; ^1H nmr: 1.49-1.70 (m, 4H), 1.86-2.05 (m, 4H), 3.31 (s, 2H, ar-CH₂-C), 5.64 (broad s, 1H, =CH-), and 6.79-7.16 (m, 4H, aromatic); ^{13}C nmr: 22.24, 22.69, 25.26, 28.02, 40.37, 115.95, 120.57, 123.91, 124.86, 127.89, 130.93, 136.87, and 155.07.

Anal. Calcd. for C₁₃H₁₆O: C, 82.93; H, 8.57. Found: C, 82.83; H, 8.59.

Spiro[benzofuran-2(3*H*)-1'-cyclohexane] (grisan, **1**).

Amberlist 15 (2000 mg) was added to a solution of **8** (200 mg, 1.06 mmoles) in methylene chloride (20 ml). After stirring overnight at room temperature, the solids were decanted and washed with ethyl acetate (4 x 20 ml). Grisan (192 mg, 1.02 mmoles, 94%) was recovered after concentration *in vacuo* and chromatography of the organic phase; ir (neat): 3000-2830, 1600, 1485, 1465, 1240, 1035, 930, 880, and 750 cm^{-1} ; ^1H nmr: 1.43-1.90 (m, 8H), 2.99 (s, 2H, ar-CH₂-C), 6.74-6.85 (m, 2H, aromatic), and 7.08-7.16 (m, 2H, aromatic); ^{13}C nmr: 23.07, 25.20, 37.15, 40.98, 88.36, 109.49, 119.71, 125.14, 126.77, 127.84, and 158.85.

Anal. Calcd. for C₁₃H₁₆O: C, 82.93; H, 8.57. Found: C, 82.91; H, 8.62.

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