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Boron Trifluoride Etherate on Alumina-A Modified Lewis Acid Reagent(V) A Convenient Single-step Synthesis of Cannabinoids

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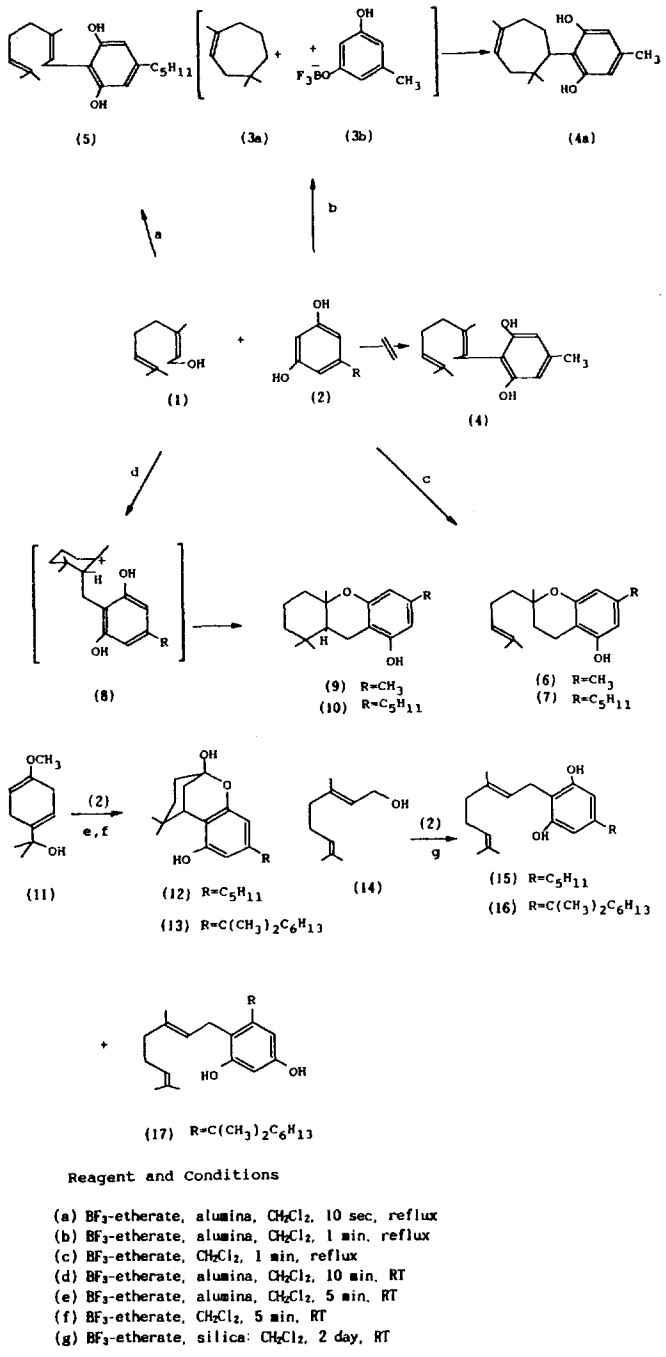
Since the early 1960s, when the structures of cannabinoid analogs were elucidated,[1] cannabinoid research has maintained sustained progress resulting in the synthesis of a large number of analogs with a varied degree of resemblance to the natural substances. Although accurate correlation between the structure and function for the several hundred cannabinoid analogs is complicated by uncertainties about the enantiomeric purity of the different analogs and by the large variability of the testing procedures, some general features associated with pharmacological activity can be identified from the existing literature.[2a]

Recently, several syntheses of delta-9-tetrahydrocannabinol (Δ^9-THC) metabolites have been reported. Tius *et al.*[2d] reported a novel syntheses of (±)-11-hydroxy-Δ^9-THC which does not address the double-bond isomerization difficulties. A new approach to 11-nor-9-carboxy-Δ^9-THC by Huffman *et al.*[2e] avoided both of these problems but gave racemic product as well as a cis/trans mixture which had to be separated. The same group solved the problem of racemization subsequently.[2f] Siegel *et al.*[2g] described in detail their efforts to circumvent these problems in the synthesis of optically active Δ^9-THC metabolites.

We have reported that when BF_3-diethyl ether on alumina was used as a condensing reagent, the reaction of (+)-*p*-mentha-2,8-dien-1-ol with olivetol on 0.8 mmole scale led to cannabidiol (CBD) as the major product in 55% yield as chromatographically pure oil or 41% yield as crystalline material.[2b] In previous paper we reported a much more efficient



Reagent and Conditions

(a) BF_3-etherate, alumina, CH_2Cl_2, 10 sec, reflux
(b) BF_3-etherate, alumina, CH_2Cl_2, 1 min, reflux
(c) BF_3-etherate, CH_2Cl_2, 1 min, reflux
(d) BF_3-etherate, alumina, CH_2Cl_2, 10 min, RT
(e) BF_3-etherate, alumina, CH_2Cl_2, 5 min, RT
(f) BF_3-etherate, CH_2Cl_2, 5 min, RT
(g) BF_3-etherate, silica: CH_2Cl_2, 2 day, RT

Scheme 1.

preparation of the desired alkylation of 5-(1,1-dimethylheptyl) resorcinol with cyclic allylic alcohol by the use of BF_3-diethyl ether on alumina as the catalyst. When 5-(1,1-dimethylheptyl) resorcinols were alkylated with cyclic allylic alcohols in the presence of BF_3-diethyl ether on alumina, no isomers were detected in any product under the reaction conditions used in the investigation. The anticonvulsant activity of 5-(1,1-dimethylheptyl)resorcinols was studied by audiogenic seizure and rotorod neurotoxicity test.[2c]

In the present study, we report a simple and convenient method for intra- and intermolecular Friedel-Crafts alkylation reaction in a simple single synthesis from cyclic allylic alcohol and 5-alkylresorcinol in the prescence of boron trifluoride-diethyl ether and basic alumina in methylene chloride at room temperature. We wish to report here another extension of this method, *viz.* the alkylation of 5-alkylresorcinol with terpenoid and 2-(4-methoxy-1,4-cyclohexadienyl)-2-propanol (**11**) in a Lewis acid medium to isomerize cannabinoid derivatives.[4]

Both inter- and intramolecular Friedel-Crafts alkylations proceeded in moderate yields. In addition, small amounts of unidentified products were also formed. The products were separated by medium pressure liquid chromatography on silica gel and preparative TLC. The alkylation of orcinol with nerol (**1**) in BF_3-diethyl ether on alumina gave a bicyclic compound (**4a**). However, cannabinerol type reaction (**4**) did not take place under the same reaction conditions. The postulated carbocation (**3a**) might be produced by treatment of nerol with Lewis acid.[5]

In the above reaction, subsequent intramolecular cyclization product,that is the addition of one hydroxyl group to a suitably placed double bond such as compound (**6**) was not observed. This is undoubtedly due to the "mildness" of BF_3-diethyl ether on alumina reagent which catalyzes a Friedel-Crafts type reaction but apparently does not attack olefins (or attacks them at a slow rate) to form a cationic center.

When the reaction was undertaken with BF_3-diethyl ether, the condensation reactions were followed by intramolecular cyclization to form **6** or **7**.[6] The condensation of nerol with orcinol and olivetol gave the *cis* tricyclic compounds **9**[7] or **10**,[6] which is in sharp contrast to the condensation obtained with BF_3-diethyl ether on alumina as the catalyst.

The observed chemical reactions may be due not to any basic mechanistic difference but to the rate of ring closure of the intermediate (**8**) at the monocyclic stage. The nucleophilic phenolic group apparently reacts with the monocyclic carbocation before the achievement of conformational equilibration or the elimination of a proton.[4]

For the preparation of hemiketals such as **12** or **13**, the diene (**11**) is a readily available starting material. It can be prepared from P-methoxyacetophenone by Grignard addition to provide 2-(4-methoxyphenyl)-2-propanol, which was followed by Birch[8] reduction to the desired diene (**11**).

The reaction of 2-(4-methoxy-1,4-cyclohexadienyl)-2-propanol (**11**) with the resorcinol (**2c**) was studied under a Lewis acid catalysis conditions. The product of the reaction showed a suprising independence on the nature of the acidic catalyst. The hemiketal (**12**) was isolated in 8% yield from the reaction of **2b** with **11** using BF_3-diethyl ether in methyene chloride at room temperature. The hemiketal (**12**) was isolated in 11% yield.[8]

Recent work from our laboratories has resulted in a facile synthesis of cannabigerols which prompted as to examine the Friedel-Crafts type reaction in the cannabigerol type cannabinoids.[2b] Various active supports were tried using BF_3-diethyl ether. In each case cannabigerol was formed (*e.g.* Alumina, Florisil, Bentonite), the complicated mixture was obtained. Better results were obtained by using boron trifluoride-diethyl ether as the condensing agent in the presence of silica (Woelm silica gel "for partition chromatography")

In these series we observed that on passing from a 5-methyl substitution of the resorcinol (*e.g.* **6** and **9**) through a 5-pentyl substitution (*e.g.* **7** and **10**) to a 5-(1,1)-dimethylhe-

ptyl (*e.g.* **13** and **16**) the yield of the product increased. The formation of alkylation products depends on the nature of the alkyl group. The structure of these compounds was established based on their molecular weight (mass spectra) and NMR spectra. It was shown that alkylation of orcinol and olivetol took place at C-2 position. All known reaction products were identified by comparison of their spectral data [4] (ms, nmr and ir) with those published or by direct comparison.[6] Several of synthetic cannabinoids described above are being tested for antitumor activity.

In summary we have developed a simple and convenient procedure for preparing cannabinoids from terpenoid and 2-(4-meyhoxy-1,4-cyclohexadienyl)-2-propanol (**11**) with 5-alkylresorcinol by the use of boron trifluoride diethyl ether as the catalyst.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 457 grating infrared spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker WH-60, WH-200 and WH-300 pulsed FT spectrometers. Chemical shifts are given in parts per million downfield from Me_4Si internal standard. Mass spectra were recorded on a Varian Mat CH-5 mass spectrometer. Analytical TLC was performed by using commercially available silica plates, (Polygram sil N-HR/UV_{254}) and the plates were visualized with fast blue phenol reagent. Medium pressure liquid chromatography was performed on an ALTEX glass column, 1 meter long, diameter 9 mm internal using an FMI pump and silica gel 60 (230-400 mesh) purchased from Merck, Fractions were collected with LKB 2070 or LKB 7000 fraction collectors at a late of 2-10 mL/min.

Preparation of 2-(2,2,5-trimethyl-1-cyclohepten-4-enyl)-5-methylbenzene-1,3-diol (4a). BF_3-diethyl ether (0.4 mL) was added under nitrogen to a stirred suspension of basic aluminium oxide (Woelm, grade I) (4.0 g) in dry dichloromethane (40 mL). The mixture was stirred for 5 min at room temperature and then boiled for 1 min. Nerol (**1**) (308 mg, 2.0 mmole) and orcinol (284 mg, 2.0 mmole) in dichloromethane (6 mL) were added to the boiling suspe nsion (40-41 ℃) *via* a syringe and the mixture was then stirred at 40-41 ℃ for 1 min. the reaction was quenched with 10% aqueous solution of sodium bicarbonate solution (10 mL). Ether (5 mL) and an additional proportion of sodium bicarbonate solution (50 mL) were added. The organic layer was washed with brine, dried and evaporated to dryness. The oil obtained was separated by medium pressure LC (230-400 mesh ASTM, Silica gel 60 for column chromatography; elution with diethyl ether to petroleum ether 5 : 95) to yield 2-(2,2,5-trimethyl-1-cyclohepten-5-enyl)-5-methylbenzene-1,3-diol (**4a**) (172 mg, 33%). MS, m/e (rel. int.), 260 (M^+, 23), 217 (6), 190 (19), 176 (15), 175 (100), 161 (6), 137 (29), 121 (4), 109 (3), 91 (7), 69 (7), 56 (9), 43 (18); IR (film), 3300, 1620, 1585, 1450 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (6H, t, J=6.35 Hz, CH_3), 1.76 (3H, s, CH_3), 2.18 (3H, s, arom. CH_3), 3.85 (1H, brd, J=7.9 Hz, benzylic H), 5.50 (1H, brs, olefinic H), 6.20 (2H, brs, arom. H).

Preparation of Cannabinerol (5). BF_3-diethyl ether (0.3 mL) was added under nitrogen to a stirred suspension of basic aluminium oxide (Woelm, grade I) (2.0 g) in dry dichloromethane (40 mL). The mixture was stirred for 15 min at room temperature and then boiled for 1 min. Nerol (**1**) (123.2 mg, 0.80 mmole) and olivetol (180 mg, 1.0 mmole) in dichloromethane (3 mL) were added to the boiling suspension (40-41 ℃) *via* a syringe and the reaction was quenched within 10 seconds with 10% aqueous solultion of sodium bicarbonate (10 mL), and was then worked up. The reaction product was separated on silica gel (2.5% ethyl acetate/petroleum ether) to give 94 mg (37% yield) of 5. Cannabinerol (**5**) obtained was identical with authentic material[4,6] (MS, NMR, IR and TLC).

Preparation of Dihydrocannabichromene methyl (6). To a mixture of nerol (**1**) (308 mg, 2.0 mmol) and orcinol (284 mg, 2.0 mmol) in dry dichloromethane (40 mL), BF3-diethyl ether (0.4 mL) was added under nitrogen to the solution *via* a syringe, and the mixture was then stirred at 40-41 ℃ for 1 min. The reaction was quenched with 10% aqueous solution of sodium bicarbonate (10 mL), and was then worked up. The reaction product was separated on silica gel (5% diethyl ether/n-hexane) to give 213 mg (42% yield) of dihydrocannabichromene methyl. MS, m/e (rel. int.), 260 (M^+, 32), 217 (6), 190 (18), 175 (100), 161 (9), 137 (40), 121 (4), 91 (5), 75 (5), 69 (4), 43 (13); IR (film), 3425, 1628, 1585, 1450 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3H, dd, J=7.7 Hz, CH_3), 1.76 (6H, s, CH_3), 2.18 (3H, s, arom. CH_3), 3.46 (2H, brd, J=7.7 Hz, benzylic H), 5.48 ((1H, brs, olefinic H), 6.09 (1H, s, arom. H), 6.23 (1H, d, J=2.3 Hz, arom. H).

Preparation of Dihydrocannabichromene (7). This compound was prepared as described above for 6 in 46% (115 mg) yield after chromatography (2% ethyl acetate/petroleum ether). Dihydrocannabichromene (**7**) that we obtained was identical with an authentic material[4,6] (MS, NMR, IR and TLC).

Preparation of 5a,9a-Cis-6,7,8,9a-tetrahydro-3,5a,9,9-tetramethyl-5aH-dibenzo[B,E]pyran-1-ol (9). BF_3-diethyl ether (0.4 mL) was added under nitrogen to a stirred suspension of basic aluminium oxide (Woelm, grade I) (4.0 g) in dry dichloromethane (40 mL). The mixture was stirred for 5 min at room temperature. Nerol (**1**) (308 mg, 2.0 mmol) and orcinol (284 mg, 2.0 mmol) in dichloromethane (6 mL) were added to the suspension *via* a syringe and the reaction was quenched with 10% aqueous solution of sodium bicarbonate (10 mL) and was then worked up. The reaction product was separated on silica gel (5% diethyl ether/n-hexane) to give 208 mg (40% yield) of 5a,9a-*cis*-6,7,8,9a-tetrahydro-3,5a,9,9-tetramethyl-5aH-dibenzo[B,E]pyran-1-ol. MS, m/e (rel. int.), 260 (M^+, 15), 217 (6), 190 (13), 175 (100), 161 (5), 137 (22), 91 (8), 79 (7), 69 (6), 59 (9), 43 (24); IR (film), 3350, 1623, 1580, 1440 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (3H, d, J=7.1 Hz, CH_3), 1.08 (3H, d, J=7.9 Hz, CH_3), 1.33 (3H, s, CH_3), 2.20 (3H, s, arom. CH_3), 3.33 (2H, d, J=2.3 Hz, benzylic H), 6.11 (1H, s, arom. H), 6.26 (1H, s, arom. H).

Preparation of 5a,9a-Cis-3-pentyl-6,7,8,9a-tetrahydro-5a,9,9-trimethyl-5aH-dibenzo[B,E]pyran-1-ol (10). This compound was prepared as described above for 9 in 68% (108 mg) yield after chromatography (3% ethyl acetate/petroleum ether). 5a,9a-Cis-3-pentyl-6,7,8,9a-tetrahydro-5a,9,9-trimetyl-5aH-dibenzo[B,E]pyran-1-ol (**10**) obtained was identical with authentic material[4,6] (MS, NMR, IR and TLC).

Preparation of (±)-9-(Pentyl)-3,4,5,6-tetrahydro-5-isopropylidene-2,8-methano-2H-1-benzoxocin-2,7-diol (12)[8]. (±)-9-(Pentyl)-3,4,5,6-tetrahydro-5-isopropyli-

dene-2,6-methano-2H-1-benzoxocin-2,7-diol (**12**) was prepared as described above for 9 in 9% (28 mg) yield after chromatography (5% ethyl acetate/petroleum ehter). MS, m/e (rel. int.), 316 (M^+, 100), 301 (75), 299 (37), 288 (20), 288 (32), 273 (54), 260 (20), 244 (15), 232 (15), 192 (29); IR (film), 3280, 1620, 1580 cm^{-1}; NMR ($CDCl_3$) δ 6.29 (1H, s, arom H), 6.13 (1H, d, J=2.0 Hz, arom H), 4.69 (1H, s, OH), 4.30 (1H, brs, C-6H), 2.43 (2H, t, benzylic H), 1.92, 1.67 (2s, 3H each, isopropylidene CH_3's), 0.87 (3H, t, CH_3).

Preparation of (±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2,6-methano-2H-1-benzoxocin-2,7-diol (13). (±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2,6-methano-2H-1-benzoxocin-2,7-diol was prepared as described above for 9 in 18% (65 mg) yield after chromatography (5% ethyl acetate/petroleum ether). (±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2,6-methano-2H-1-benzoxocin-2,7-diol thus obtained was identified by comparison of its spectral data with those published.[8]

Preparation of Cannabigerol (15)[2b]. BF_3-diethyl ether was added under nitrogen to a stirred supension of silica (230-400 mesh ASTM) (2 g) in dichloromethane (20 mL). The mixture was stirred for 15 min at room temperature. Geraniol (**14**) (232 mg, 1.75 mmol) and olivetol (**2b**) (180 mg, 1.0 mmol) in dichloromethane (5 mL) were added to the suspension by syringe. The reaction mixture was stirred for 2 days, and was then worked up. The reaction product was separated on silica gel (10% ethyl acetate/petroleum ether) to give 93 mg (29% yield) of cannabigerol. Cannabigerol (**15**) thus obtained was identified by comparison of its spectral data (MS, NMR and IR) with those published or by direct comparison.

Preparation of Cannabigerol dimethylhetyl and Isocannabigerol dimethylheptyl (16 and 17)[9]. Under the conditions of procedure (**15**) two compounds were obtained. Cannabigerol dimethylhetyl (**16**) thus obtained was identified by comparison of its spectral data with those published. The first compound eluted was cannabigerol dimethylhetyl (94 mg, 32%), an oil, UV_{max} (EtOH), 273 (ε 1260), 280 shnm (1190); MS, m/e (rel. int.), 372 (M^+, 29), 329 (6), 303 (24), 288 (45), 287 (48), 275 (5), 249 (100), 218 (6), 165 (28), 123 (23); IR (film), 3430, 1628, 1584 cm^{-1}; NMR ($CDCl_3$), δ 0.85 (3H, t, CH_3), 1.20 (6H, s, 2xCH_3), 1.59, 1.67, 1.80 (9H, s, olefinic CH_3), 3.42 (2H, d, J=8.0 Hz, C-8H), 5.04-4.94 (2H, H, m, olefinic h), 6.37 (2H, s, arom H). The second compound eluted was isocannabigerol dimethylhetyl (51 mg, 17%), an oil, UV_{max} (EtOH), 281 nm (ε 2610); MS, m/e (rel. int.), 372 (M^+, 31), 287 (78), 249 (22), 177 (33), 163 (31), 151 (67), 147 (31), 81 (28), 69 (100); IR (film), 3370, 1595 cm^{-1}; NMR (CDCl3), δ 0.85 (3H, t, CH_3), 1.20 (6H, s, 2xCH_3), 1.34, 1.68, 1.80 (9H, s, olefinic CH_3), 3.47 (2H, d, J=6.0 Hz, C-8H), 5.16-4.83 (2H, m, olefinic H), 6.30 (1H, d, J=2.0 Hz, arom H), 6.44 (1H, d, J=3.0 Hz, arom H).

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Catalytic Oxidation of Carbon Monoxide at Low Temperature over Pd-Cu Loaded Porous Supports

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The subject of CO removal at low temperature is of practical importance due to its utility in cleaning indoor air pollutants inherent from cigarettes, gas stoves and oil furnaces. To this end, Wacker catalyst (Pd-Cu) has been introduced with some success, for which alumina and carbons are mainly used as supports.[1,2] The homogeneous Wacker catalyst has been produced commercially for the industrial process of ethylene into acetaldehyde.[3]

Alternatively, Au-loaded catalysts containing TiO_2, α-Fe_2O_3 and Co_3O_4 as supports have been developed for use in low temperature oxidation of CO. However, it is difficult to dis-