

BORON TRIFLUORIDE ETHERATE ON ALUMINA - A MODIFIED LEWIS ACID REAGENT.
AN IMPROVED SYNTHESIS OF CANNABIDIOL.

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Abstract: Boron trifluoride etherate on alumina catalyses the condensation of resorcinols and monomethyl resorcinols with several monoterpenoid allylic alcohols: in contrast to parallel reactions with boron trifluoride etherate in solution the products obtained do not undergo further cyclisations.

Cannabidiol (CBD, 1a),¹ a major natural cannabinoid which does not cause psychotropic effects in either animals or man, has recently been found to have antiepileptic, anti-anxiety and antidystonia properties in man.² CBD and CBD-acid (which is easily decarboxylated to CBD) are present in large amounts in hashish (up to ca 8%). Hence for most clinical trials till now CBD from this natural source was used. As the scope of the clinical trials with CBD expanded a practical synthetic route to this drug seemed desirable.

The synthetic routes available ^{1c,d,e} are not of practical value as they lead to CBD in mediocre yields and the unnatural isomer ("abn-CBD") (2) is obtained in amounts considerably larger than those of CBD. The best route to CBD described so far is the condensation of (+)-p-mentha-diene-1-ol (3) with olivetol (4) in the presence of weak acids.^{1d} The "abn-CBD" (2) obtained in this reaction may be converted to CBD with BF₃-etherate by a retro-Friedel-Crafts reaction, followed by recombination. However with this reagent the reaction proceeds further causing cyclisation of CBD to Δ¹-THC (5) and iso-THC (6).³

We report now that when BF₃-etherate on alumina is used as condensing reagent the reaction of (3) with (4) on a 0.8 mmol scale, leads to CBD (1a) as the major product, in 55% yield as chromatographically pure oil or 41% yield as crystalline material. No cyclisations were observed and as the rest of the products were much more polar (mainly "abn-CBD", 2, 14% yield) or much less polar (mainly compound 7, 6% yield) than CBD, the last was separated with ease. On a 100 mmol scale, the yields were 46% as an oil, and 37% as crystalline material.

Numerous reagents on alumina, silica or other active supports have been described and used in various fields of synthetic chemistry;^{4a} apparently BF₃ on alumina and silica has been thus employed mostly in fuel and industrial chemistry.^{4b}

A number of related reactions with this reagent were performed. The results are presented in Table 1. The general procedure, exemplified for the synthesis of CBD, is as follows: BF₃-etherate (0.3 ml) was added under nitrogen to a stirred suspension of basic aluminum oxide (Woelm, grade I) (2 g) in dry dichloromethane (20 ml). The mixture was stirred for 15 min at room temperature and then boiled for 1 min. (+)-p-Mentha-2,8-dien-1-ol

(3) (122 mg, 0.8 mmol) and olivetol (4) (180 mg, 1.0 mmol) in dichloromethane (5 ml) were added to the boiling suspension (40-41°C) by syringe and the reaction was quenched within 10 seconds with 10% aqueous solution of sodium bicarbonate (10 ml). Ether (50 ml) and an additional proportion of the above 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 ethyl acetate to petroleum ether 2.5:97.5).

When the reactions delineated in Table I were performed in the absence of alumina the yields obtained were either low, or the desired products could not be isolated at all, due to cyclization reactions.

Some of the reactions which proceed in disappointing yields on alumina can be improved by substituting silica (Woelm silica gel "for partition chromatography") for the alumina. Thus the reaction leading to cannabigerol (8) when undertaken with BF_3 -etherate (0.2 ml), silica (2g) in dry dichloromethane (10 ml) at room temperature for 2 days leads to (8) in 29% yield. However the reactions leading to CBD or CBD methyl ether when undertaken on silica, rather than on alumina, produced the desired products in rather low yields.

All known reaction products described in the Table were identified by comparison of their physical data (m.s., n.m.r. and i.r.) with those published or by direct comparison. The physical data of the new compounds are indicated in the Notes.

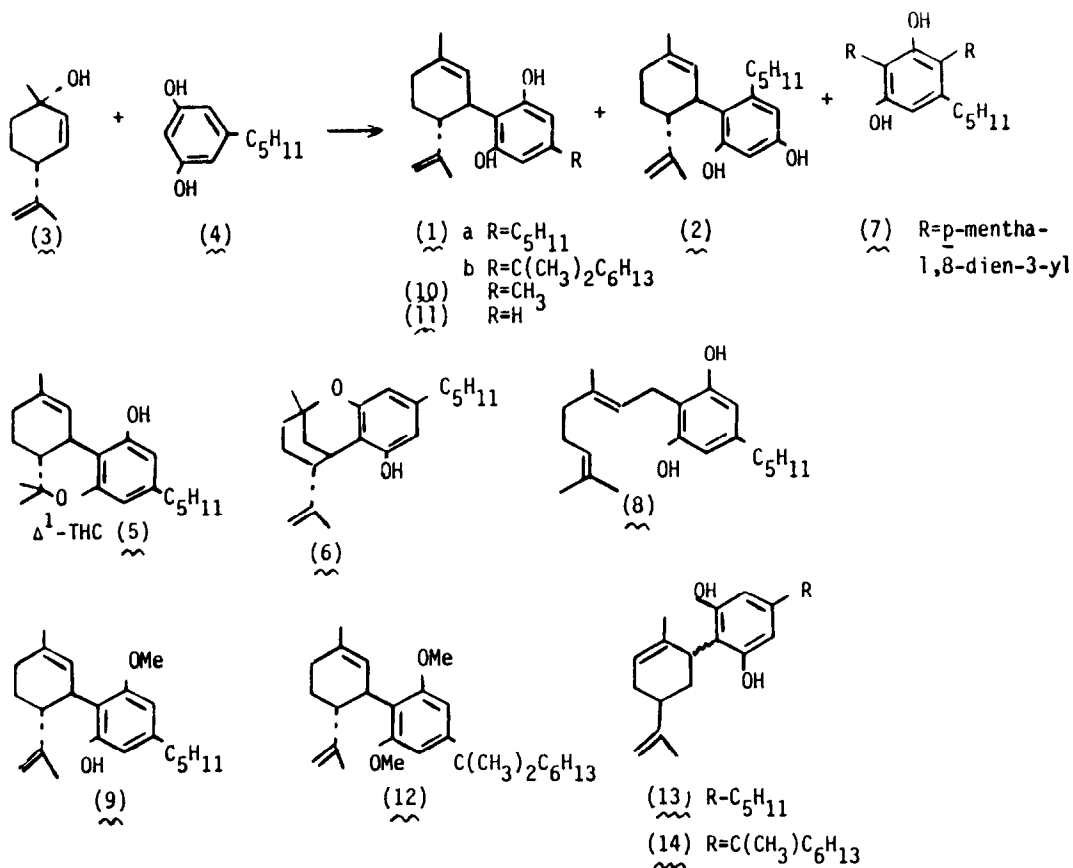
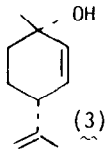
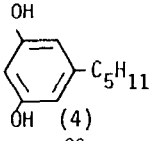
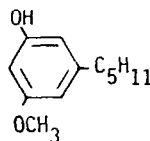
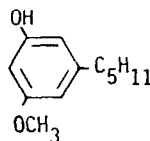
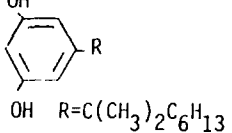
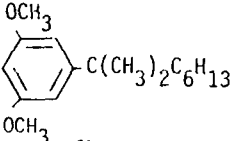
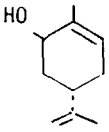
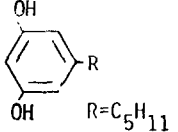
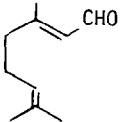
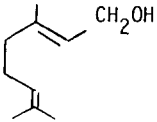


Table I

Condensations of monoterpenes with resorcinols by catalysis with BF_3 etherate on alumina^a

| Monoterpene ^b | Resorcinol ^c | Product(s) | Yield | Ref |
|--|---|--|-----------------------------|----------------------|
|  (3) |  (4) | CBD (1a); m.p. and rotation identical to natural CBD | 55% (as oil) 41% (cryst) | 1 |
| as above |  (4) | abn-CBD (2) (7) | 14% 6% | 1d,e 1d |
| as above |  (4) | (9) | 51% | 5 |
| as above |  R OH R=C(CH ₃) ₂ C ₆ H ₁₃ | (1b) | 70% | 6 |
| as above | as above; R=CH ₃ | (10) | 34% | 7 |
| as above | as above; R=H | (11) | 35% | 8 |
| as above |  OCH ₃ OCH ₃ C(CH ₃) ₂ C ₆ H ₁₃ | (12) | 24% | 9 |
|  HO |  OH OH R=C ₅ H ₁₁ | (13) | 18% | 10 |
| as above | as above; R=C(CH ₃) ₂ C ₆ H ₁₃ | (14) | 42% | 11 |
|  CHO | as above; R=C ₅ H ₁₁ | d1 - (1a) | 3.2% | 1c |
| as above | as above; R=C(CH ₃) ₂ C ₆ H ₁₃ | d1 - (1b) | 46% | cf 6 for (-)-(1b) |
|  CH ₂ OH | as above; R=C ₅ H ₁₁ | (8) | 13 ^d | 12 |

^a. For experimental conditions see text. ^b. 0.8 mmol. ^c. 1.0 mmol. ^d. For reaction on silica, see text.

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7. Physical data of compound (10): an oil, $[\alpha]_D^{25} -50^{\circ}$ (MeOH); n.m.r., δ (CDCl₃) 1.66 (3H, s, CH₃), 1.78 (3H, s, CH₃), 2.19 (3H, s, CH₃), 3.80 (1H, br d, C-3H), 4.56 (1H, br s, C-9H), 4.65 (1H, br s, C-9H), 5.54 (1H, br s, C-2H), 6.21 (2H, s, arom H); m/e 258 (M⁺, strong).
8. Physical data of compound (11): an oil, $[\alpha]_D^{25} -87^{\circ}$ (MeOH); n.m.r., δ (CDCl₃) 1.68 and 1.81 (2x3H, s, CH₃), 3.87 (1H, br, C-3H), 4.50 and 4.60 (2x1H, br s, C-9H), 5.47 (1H, br s, C-2H), 6.31, 6.45, (2H, s, arom H), 7.20 (1H, t, arom H); m/e 244 (M⁺); i.r., ν , 3395, 1615, 1585, 880cm⁻¹.
9. Physical data of compound (12): an oil, $[\alpha]_D^{25} -103^{\circ}$ (MeOH); n.m.r., δ (CDCl₃) 0.90 (3H, t, CH₃), 1.25 (6H, s, CH₃), 3.72 (6H, s, CH₃), 4.39 (2H, s, C-9H), 5.17 (1H, br s, C-2H), 6.45 (2H, s, arom H), m/e 398 (M⁺); i.r., ν 1575, 880cm⁻¹.
10. Physical data of compound (13); an oil, racemic; n.m.r., δ (CDCl₃) 0.89 (3H, t, CH₃), 1.70 1.72 (6H, 2s, CH₃), 2.46 (2H, t, benzylic), 3.67 (1H, br C-2H), 4.70 (2H s, C-9H), 5.82 (1H, br C-6H), 6.18 (2H, br s arom H); m/e 314 (M⁺); i.r. ν 3420, 1630, 1580, 885cm⁻¹.
11. Physical data for compound (14): an oil, racemic, n.m.r., δ (CDCl₃) 0.84 (3H, t, CH₃), 1.20 (6H, br s, CH₃) 3.74 (1H, br C-2H), 4.71 (2H, br s, C-9H), 5.87 (1H, br d, C-6H), 6.31 (2H, br s, arom H); m/e 370 (M⁺); i.r. ν 3430, 1629, 1580, 885cm⁻¹.
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Acknowledgement: Financial support of this research by the US National Institute of Neurological and Communicative Diseases and Stroke is gratefully acknowledged.

(Received in UK 2 January 1985)