

Expeditious preparation of various Δ^9 -6a,10a *cis* and *trans* 2-substituted tetrahydrocannabinoids

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The *one-step* preparation of various *cis* and *trans* 2-substituted tetrahydrocannabinoids (Δ^9 -THC) from aryl tertiary allylic alcohols is described. The reactions are characterized by their mild conditions, good yields and ease of work-up.

Introduction

Since the isolation of Δ^9 -tetrahydrocannabinol† (Δ^9 -THC, **1**) from *Cannabis sativa* in 1964,¹ the potent biological activity of cannabinoids such as Δ^9 -THC **1** and Δ^8 -THC **2** (Fig. 1) has

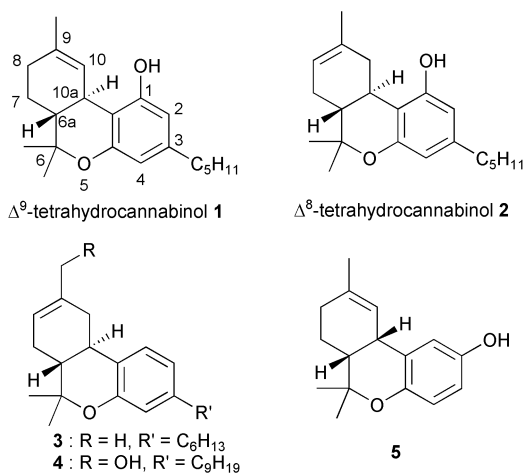


Fig. 1

stimulated the development of a large number of syntheses and pharmacological investigations.² Analgesic, antiemetic, anti-convulsant, and antiglaucoma activities have been established.³

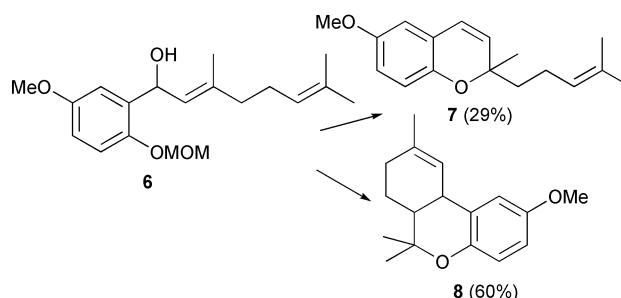
The majority of these compounds, as exemplified by Δ^9 and Δ^8 -tetrahydrocannabinols **1** and **2**, have a phenolic hydroxy at C1 and a pentyl side chain at C3. However, recent structure–activity relationship studies have shown that new cannabinoids without the phenolic hydroxy at C1 (compounds **3** and **4**) also exhibit *in vivo* pharmacological properties characteristic of cannabinoids.^{4,5} More recently a new Δ^9 -THC derivative **5** was isolated from an ascidian (*Synoicum castellatum*) which exhibits antitumor activity.⁶

Most of the reported syntheses have relied upon a small number of strategies which focused on the preparation of analogues of the Δ^8 -THC isomers rather than the Δ^9 -THC isomers because of their ease of synthesis, their considerably enhanced stability and most importantly because of the nearly identical activity of both isomers.⁷

To our knowledge, previous syntheses of Δ^9 -THC have utilised the acid-catalysed condensation of olivetol‡ with

monoterpenes, such as (+)-*p*-mentha-2,8-dien-1-ol⁸ and (+)-*trans*-2-carene oxide.⁹ These cationic condensations were promoted by Lewis acids and their regiochemical courses were found to be critically sensitive to the reaction conditions. The yields of Δ^9 -THC were only moderate and the complex mixture of by-products such as double bond isomers, open chain intermediates, 'normal' and 'abnormal' THC's and degradation products complicated the purification procedure. However, in the last decade these classical methods have been improved to give both good yields and selectivity.¹⁰

Cruz-Almanza *et al.*¹¹ described the reaction of an appropriately protected aryllithium compound with α,β -unsaturated aldehydes, which gave intermediates **6** in moderate to good yields. Subsequent deprotection and cyclization of **6** under appropriate experimental conditions, led to either chromene **7** or the Δ^9 -tetrahydrocannabinol analogue **8** in 29% and 60% yields respectively (Scheme 1).



Scheme 1

Results and discussion

In the course of our investigations into the development of new strategies for the construction of benzopyran nuclei, we recently described the preparation of the tertiary aryl allylic alcohols **9** and **10** and their thermal electrocyclic cyclization into the 2*H*-1-benzopyrans **11** and **12** (Scheme 2).¹²

In connection with this on-going study, we have turned our attention to a *one-step* protonic acid mediated, double intramolecular cyclization of the same aryl allylic alcohols **9** and **10** as a new route to the Δ^9 -THC analogues. Herein we report the successful outcome of this novel synthetic strategy, which provides a route to the syntheses of various 2-functionalized precursors for the new, more complex Δ^9 -THCs.

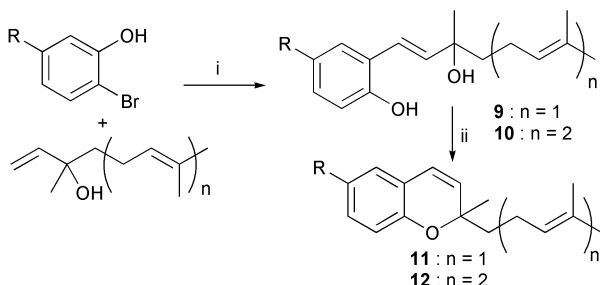
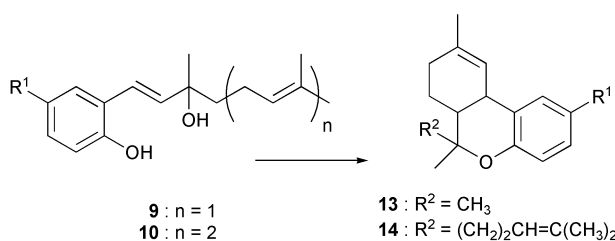
Thus, the sequence depicted in Scheme 3 is as follows: the allylic alcohols **9** and **10** were prepared according to the procedure described in a preceding paper.¹² Compounds **9** and **10**

† The IUPAC name for cannabinol is 6,6,9-trimethyl-3-pentyl-1-hydroxy-6*H*-dibenzo[*b,d*]pyran.

‡ The IUPAC name for olivetol is 5-pentylresorcinol.

Table 1 Preparation of Δ^9 -tetrahydrocannabinoids **13** and **14**

Entry	Allylic alcohols	Products	Yields (%)
1	9a : R ¹ = OBn	13a : R ² = Me	90
2	9b : R ¹ = OMe	13b : R ² = Me	87
3	9c : R ¹ = CN	13c : R ² = Me	68
4	9d : R ¹ = Me	13d : R ² = Me	88
5	10a : R ¹ = OBn	14a : R ² = C ₆ H ₁₁	72
6	10b : R ¹ = OMe	14b : R ² = C ₆ H ₁₁	79
7	10c : R ¹ = CN	14c : R ² = C ₆ H ₁₁	67
8	10d : R ¹ = Me	14d : R ² = C ₆ H ₁₁	78

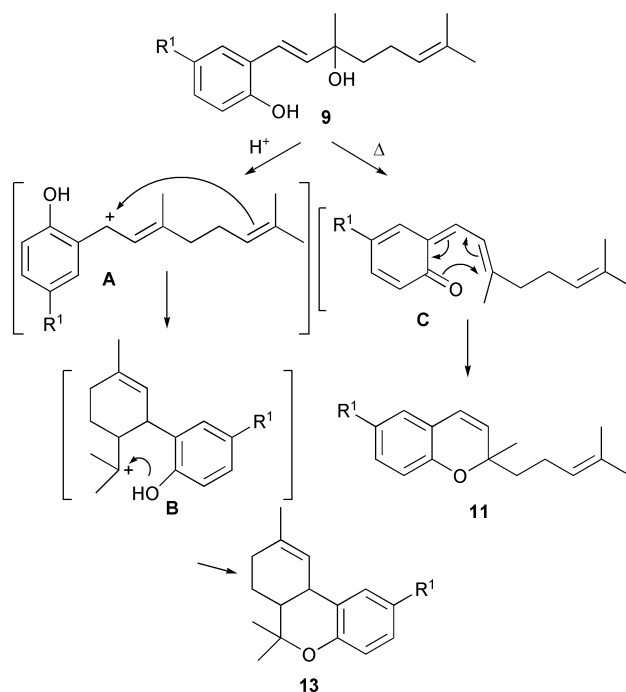
**Scheme 2** Reagents and conditions: i) Pd(OAc)₂, CH₃CN, Cs₂CO₃, 100 °C; ii) 120 °C, neat.**Scheme 3** Reagents and conditions: PTSA, DCM, 0 °C, 1 to 2 hours.

were subsequently converted into the corresponding tetrahydrocannabinoids **13** or **14** in CH₂Cl₂ at 0 °C in the presence of a catalytic amount of PTSA (Scheme 3).

No chromene nor Δ^8 -THC isomers were formed during this intramolecular cyclization. It should be noted that the Δ^9 -THCs **13** and **14** were obtained as diastereomeric mixtures (*cis-trans*: 1 : 1)¹³ and were not separated as individual isomers. The range of tetrahydrocannabinoids obtained is summarized in Table 1.

The strategy described has several advantages over the usual procedures: the synthesis is short, the yields are generally high and the desired Δ^9 -tetrahydrocannabinoids of the type **13** or **14** can be obtained in 67–90% yields with no contamination from isomeric THC-related products, a problem which is often reported in standard cannabinoid protocols.^{8,9} It is noteworthy that the reactions conducted with aryl allylic alcohols **9** and **10** in a protic medium (PTSA) favoured the exclusive formation of **13**. Whereas thermal conditions¹² favoured the exclusive formation of chromene **11** (Scheme 4). These results suggest that in a protic medium a double intramolecular cyclization occurs.

This might be explained through the formation of a very stable benzylic-allylic carbocation **A**, which as a first step, like a classical carbocation, can rearrange into **B**. Then **B** in turn can convert into the corresponding tetrahydrocannabinoid **13**. However, as expected on the basis of mechanistic considerations, electron-donating groups facilitate the reaction (Table 1, entries 1, 2, 4, 5, 6 and 8) while electron-withdrawing substituents give less satisfactory results (Table 1, entries 3 and 7). In contrast to this, thermolysis of the aryl allylic alcohols **9** and **10** result in dehydration producing the corresponding *o*-quinone methide **C**, which is rapidly converted through an intramolecular electrocyclicization to give chromene **11**.¹⁴

**Scheme 4** Proposed mechanisms for the double intramolecular cyclization and thermal electrocyclicization reactions.

Conclusion

In conclusion, we have observed that the protonic acid mediated double intramolecular cyclization of **9** or **10** provided a rapid and operationally simple method for the synthesis of new tetrahydrocannabinoids (Δ^9 -THC **13** or **14**) in good yields. This procedure complements other known methods.

Experimental

All starting materials were obtained from commercial suppliers and were used without further purification. DCM was dried by distillation from calcium hydride before use. ¹H and ¹³C NMR spectra were recorded at 200 and 50 MHz on a Bruker AC 200 spectrometer with CDCl₃ as solvent and TMS as internal standard; chemical shifts (δ) were expressed in ppm and coupling constants (*J*) in Hertz. IR spectra were recorded on a Bruker vector 22 spectrometer. Mass spectra (EI) were recorded using a Hewlett Packard 5989A (70 eV) instrument. Elemental analyses were carried out by the CNRS Analysis Laboratory, Vernaison, France.

General procedure for the cyclization of tertiary allylic alcohols to 6*H*-dibenzo[*b,d*]pyran **13** or **14**

The tertiary allylic alcohol (**9** or **10**) was diluted in CH₂Cl₂, the solution was cooled to 0 °C and then a catalytic amount of *p*-TSA was added. The reaction mixture was stirred until analysis by TLC revealed the complete disappearance of starting material (1 to 2 hours). The reaction was then diluted with 10% NaHCO₃. The organic layer was washed with brine, dried (MgSO₄), concentrated under vacuum and purified by column chromatography on silica gel, eluting with a 9 : 1 (v/v) mixture of hexane–EtOAc.

2-Benzyloxy-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b,d*]pyran (13a**).** Compound **13a** was obtained from **9a** as a colorless oil in 90% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.14 (3H, s, CH₃), 1.36–1.69 (3H, m, CH₂, CH), 1.40 (3H, s, CH₃), 1.72 (3H, br s, CH₃), 1.94–2.12 (2H, m, CH₂), 3.15 (1H, br d, *J* 11, H10a-*trans*), 3.50 (1H, br t, *J* 6.4, H10a-*cis*), 4.99 (2H, s, OCH₂), 5.85 (1H, br s, H10), 6.69–6.94 (3H, m, CHar), 7.32–7.43 (5H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 19.8, 23.5,

25.4, 27.5, 30.4, 32.5, 39.4, 70.6, 75.6, 113.5, 114.6, 117.6, 121.8, 125.6, 127.6, 127.8, 128.5, 135.3, 137.2, 146.2, 153.2; IR 2975, 2931, 1491 cm⁻¹; MS (*m/z*) 334 (M⁺, 70), 243 (100), 187 (38), 91 (87), 69 (53), 41 (40). Anal. calcd for C₂₃H₂₆O₂: C 82.60, H 7.84. Found C 82.75, H 7.92%.

2-Methoxy-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (13b). Compound 13b was obtained from 9b as a colorless oil in 87% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.14 (3H, s, CH₃), 1.39 (3H, s, CH₃), 1.39–2.11 (5H, m, 2CH₂, CH), 1.83 (3H, br s, CH₃), 3.16 (1H, br d, *J* 11, H10a-*trans*), 3.54 (1H, br t, *J* 6.4, H10a-*cis*), 3.75 (3H, s, OCH₃), 5.88 (1H, br s, H10), 6.64–6.85 (3H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 20.6, 23.5, 24.6, 25.3, 30.8, 34.3, 44.6, 55.7, 75.4, 111.0, 112.6, 117.5, 121.8, 125.5, 135.0, 143.7, 153.2; IR 2974, 2930, 2831, 1492, 1206 cm⁻¹; MS (*m/z*) 258 (M⁺, 42), 243 (19), 215 (30), 175 (100). Anal. calcd for C₁₇H₂₂O₂: C 79.03, H 8.58. Found C 79.26, H 8.42%.

2-Cyano-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (13c). Compound 13c was obtained from 9c as a pale yellow oil in 68% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.28 (3H, s, CH₃), 1.44 (3H, s, CH₃), 1.50–2.13 (5H, m, 2CH₂, CH), 1.71 (3H, s, CH₃), 3.17 (1H, br d, *J* 10.9, H10a-*trans*), 3.53 (1H, br t, *J* 6.6, H10a-*cis*), 5.87 (1H, br s, H10), 6.75–7.59 (3H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 19.8, 23.2, 26.0, 30.4, 31.6, 33.3, 38.5, 77.3, 103.0, 117.9, 120.0, 120.4, 126.0, 130.6, 133.4, 136.7, 155.8; IR 2977, 2928, 2222, 1605, 1488 cm⁻¹; MS (*m/z*) 253 (M⁺, 91), 238 (60), 210 (100), 170 (49). Anal. calcd for C₁₇H₁₉NO: C 80.60, H 7.56, N 5.53. Found C 80.50, H 7.60, N 5.44%.

2,6,6,9-Tetramethyl-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (13d). Compound 13d was obtained from 9d as a pale yellow oil in 88% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.15 (3H, s, CH₃), 1.41 (3H, s, CH₃), 1.51–2.11 (5H, m, 2CH₂, CH), 1.74 (3H, br s, CH₃), 2.28 (3H, s, ArCH₃), 3.15 (1H, br d, *J* 11, H10a-*trans*), 3.50 (1H, br t, *J* 6.6, H10a-*cis*), 5.94 (1H, br s, H10), 6.63–7.11 (3H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 20.4, 23.5, 24.6, 25.4, 28.0, 30.8, 34.0, 44.6, 77.4, 116.9, 122.0, 124.4, 125.7, 127.8, 128.5, 134.8, 151.1; IR 2968, 2924, 1489, 1247 cm⁻¹; MS (*m/z*) 242 (M⁺, 91), 227 (58), 199 (62), 159 (100). Anal. calcd for C₁₇H₂₂O: C 84.25, H 9.15. Found C 84.05, H 9.31%.

2-Benzyloxy-6,9-dimethyl-6-(4-methylpent-3-enyl)-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (14a). Compound 14a was obtained from 10a as a pale yellow oil in 72% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.37 (3H, s, CH₃), 1.36–2.21 (9H, m, 4CH₂, CH), 1.52 (3H, s, CH₃), 1.61 (3H, s, CH₃), 1.69 (3H, s, CH₃), 3.18 (1H, br d, *J* 11, H10a-*trans*), 3.47 (1H, br t, *J* 6.6, H10a-*cis*), 4.97 (2H, s, OCH₂), 5.00 (2H, s, OCH₂), 5.06 (1H, m, CH=), 5.15 (1H, m, CH=), 5.94 (1H, br s, H10), 6.69–6.93 (3H, m, CHar), 7.23–7.46 (5H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 17.5, 19.6, 22.6, 23.4, 25.7, 30.5, 31.8, 33.3, 36.7, 38.0, 79.2, 80.7, 118.3, 119.6, 121.0, 121.2, 124.2, 124.6, 126.2, 130.2, 131.1, 131.5, 131.8, 133.6, 135.9, 156.0; IR 2976, 2931, 1492 cm⁻¹; MS (*m/z*) 402 (M⁺, 6), 251 (100), 91 (51), 69 (45), 41 (45). Anal. calcd for C₂₈H₃₄O₂: C 83.54, H 8.51. Found C 83.45, H 8.60%.

2-Methoxy-6,9-dimethyl-6-(4-methylpent-3-enyl)-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (14b). Compound 14b was obtained from 10b as a colorless oil in 79% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.15 (3H, s, CH₃), 1.23–2.10 (9H, m, 4CH₂, CH), 1.38 (3H, s, CH₃), 1.61 (3H, s, CH₃), 1.70 (3H, s, CH₃), 3.18 (1H, br d, *J* 11, H10a-*trans*), 3.40 (1H, br t, *J* 6.4, H10a-*cis*), 3.76 (3H, s, OCH₃), 4.98 (1H, m, CH=), 5.15 (1H, m, CH=), 5.90 (1H, br s, H10), 6.66–6.85 (3H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 17.5, 20.1, 21.3, 23.3, 24.4, 25.5, 30.6, 33.9,

40.0, 41.5, 55.5, 78.6, 110.8, 112.5, 117.4, 121.8, 124.0, 125.6, 131.2, 134.9, 147.7, 153.2; IR 2968, 2929, 2831, 1489, 1218, 1042 cm⁻¹; MS (*m/z*) 326 (M⁺, 29), 241 (100), 175 (83), 69 (31), 41 (36). Anal. calcd for C₂₂H₃₀O₂: C 80.94, H 9.26. Found C 80.82, H 9.33%.

2-Cyano-6,9-dimethyl-6-(4-methylpent-3-enyl)-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (14c). Compound 14c was obtained from 10c as a pale yellow oil in 67% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.42 (3H, s, CH₃), 1.50–2.13 (9H, m, 4CH₂, CH), 1.53 (3H, s, CH₃), 1.63 (3H, s, CH₃), 1.72 (3H, s, CH₃), 3.20 (1H, br d, *J* 11, H10a-*trans*), 3.50 (1H, br t, *J* 6.5, H10a-*cis*), 5.01 (1H, m, CH=), 5.15 (1H, m, CH=), 5.87 (1H, br s, H10), 6.75–7.59 (3H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 17.5, 19.4, 22.2, 22.7, 23.4, 25.5, 30.3, 31.4, 36.5, 37.7, 79.4, 103.1, 118.0, 120.3, 120.7, 123.5, 125.9, 130.8, 131.2, 133.5, 135.9, 155.9; IR 2968, 2927, 2223, 1606, 1488, 1258 cm⁻¹; MS (*m/z*) 321 (M⁺, 57), 236 (100), 69 (49), 41 (77). Anal. calcd for C₂₂H₂₇NO: C 82.20, H 8.47, N 4.36. Found C 82.09, H 8.55, N 4.30%.

2,6,9-Trimethyl-6-(4-methylpent-3-enyl)-6a,7,8,10a-tetrahydro-6H-dibenzo[*b,d*]pyran (14d). Compound 14d was obtained from 10d as a colorless oil in 78% yield; ¹H NMR (200 MHz, CDCl₃): δ 1.14 (3H, s, CH₃), 1.39 (3H, s, CH₃), 1.61 (3H, s, CH₃), 1.63–2.23 (9H, m, 4CH₂, CH), 1.65 (3H, s, CH₃), 2.30 (3H, s, ArCH₃), 3.23 (1H, br d, *J* 10.9, H10a-*trans*), 3.50 (1H, br t, *J* 6.6, H10a-*cis*), 5.01 (1H, m, CH=), 5.16 (1H, m, CH=), 5.94 (1H, br s, H10), 6.62–7.09 (3H, m, CHar); ¹³C NMR (50.3 MHz, CDCl₃): δ 17.5, 20.7, 21.3, 23.5, 24.3, 25.6, 30.7, 31.9, 33.6, 40.1, 41.4, 78.9, 117.1, 122.1, 124.5, 125.5, 127.8, 128.4, 129.1, 131.5, 134.9, 150.1; IR 2967, 2924, 1494, 1249, 814 cm⁻¹; MS (*m/z*) 310 (M⁺, 100), 225 (48), 199 (75), 159 (97), 121 (82), 41 (55). Anal. calcd for C₂₂H₃₀O: C 85.11, H 9.74. Found C 84.98, H 9.85%.

Acknowledgements

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