An Expedient and Efficient Synthesis of an Optically Active Terpene Synthon for Δ^9-Cannabinoids

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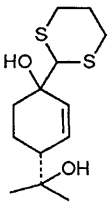
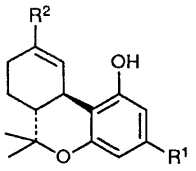
A three-step synthesis of important, enantiomeric cannabinoid terpene synthons, **1**, from (+)- and/or (−)-nopinone is described.

Δ^9-Tetrahydrocannabinol (THC) belongs to a class of compounds known as cannabinoids which are responsible for the psychoactive properties of marijuana.[1,2] The cannabinoids produce, in man and animals, a complex pattern of pharmacological effects some of which are unique to this class of compounds.[1,2] In spite of extensive pharmacological research, the mechanism(s) by which they exert their effects is not clear.[1] Structure activity relationship (SAR) studies[1,3] have pointed to a possible receptor mechanism for these drugs but the first direct evidence has come only by the recent



1a

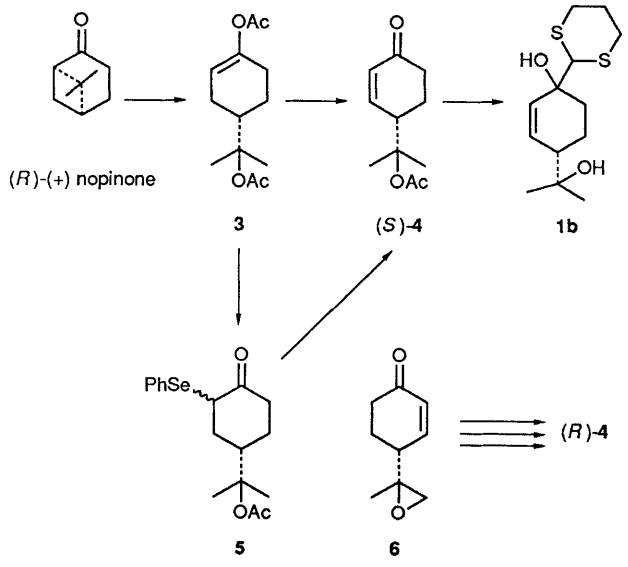


Δ^9-THC: $R^1 = C_5H_{11}$, R^2 = Me
2: $R^1 = C(Me)_2C_6H_{13}$, $R^2 = CH_2OH$

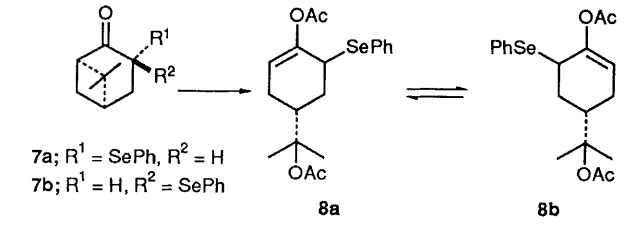
identification of a cannabinoid binding site using radiolabelled 'non-classical' cannabinoid ^{3}H-CP-55940.[4] Recently, this binding site has been further characterised by cloning experiments.[5] The structure of CP-55940 is atypical of Δ^9-THCs, and this has renewed interest in the synthesis of more typical 'Δ^9-structures' including metabolites and radiolabelled derivatives for both ligand binding and SAR studies. We recently reported the synthesis of an optically active terpene synthon **1**[6] (as a mixture of diastereoisomers) which has proved useful for the synthesis of these type of compounds (*e.g.*, metabolite analogue **2**). We report in this communication a new and shorter route (3 steps) to the synthon **1a,b** (obtained as mixtures of diastereoisomers) from optically active (+)- and/or (−)-nopinone[7] (Scheme 1).

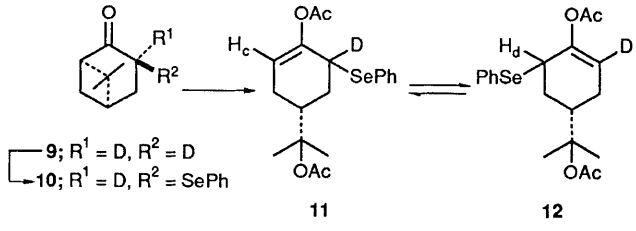
Our approach is based on the work of Yoshikoshi and coworkers[8] who recently reported the cyclobutane ring cleavage of (+)-3-methylnopinone, in high yield using $BF_3{\cdot}OEt_2$–$Zn(OAc)_2$ in acetic anhydride, with almost no loss of stereochemical integrity. Using the above conditions, (1*R*)-(+)-nopinone was converted to **3**†‡ which was isolated after flash chromatography in good yield (70–85%). Treatment of **3** with allyl ethyl carbonate catalysed by $Pd(OAc)_2$, bis(diphenylphosphino)ethane and Bu_3SnOMe[9] gave the enone (*S*)-**4**, $[\alpha]_D^{27}$ −49° (*c* 0.0615, EtOH), which was determined to be 94% optically pure by comparison with (*R*)-**4** prepared by us previously from compound **6**.[6]§ This indicated no loss of optical purity from the starting nopinone.[7] In an alternative route, the enol acetate **3** was converted to the keto phenyl selenide **5** using silver trifluoroacetate in benzene followed by treatment with phenylselenenyl bromide.[10] Following the oxidation–elimination sequence[10,11] (H_2O_2–THF, room temp.) (THF = tetrahydrofuran), compound **5** gave compound **4**.

We also attempted the ring opening of the *trans*-3-phenylseleno substituted nopinone (**7b**, Scheme 2). It was prepared along with the *cis* isomer (**7a**, 20%) by treatment of (1*R*)-(+)-nopinone with lithium diisopropylamide followed by phenylselenenyl bromide.[12] The stereochemistry of compounds **7a** and **b** was established by nuclear Overhauser effect studies. When compound **7b** was subjected to Yoshikoshi conditions,[8] the major product formed, **8** (70%), displayed a very low optical rotation value, $[\alpha]_D^{22}$ −0.96° (*c* 0.0396, MeOH).¶ Base hydrolysis of the enol acetate functionality in compound **8** (Na_2CO_3 in MeOH–H_2O, 0 °C), followed by the



Scheme 1





Scheme 2

oxidation–elimination[10,11] sequence as described above gave, *via* compound **5**, the enone **4** (40% yield, $[\alpha]_D^{22}$ 0.62° (*c* 0.0567, MeOH). This optical rotation corresponds to an enantiomeric excess of only 1% and an almost complete loss of optical purity from the starting nopinone. The loss in optical activity was demonstrated to be due to a 1,3 shift of the phenylseleno group (**8a** ⟷ **8b**) by deuterium labelling experiments. Labelled ketone **9**[13] was transformed to ketone **10** as described for **7b**. Ketone **10** under Yoshikoshi conditions[8] gave a mixture of compounds **11** and **12** in a ratio (by ^{1}H NMR integration of protons H_c and H_d) of 1.17:1, clearly demonstrating the allyl phenylseleno shift presumably *via* a 1,3 sigmatropic rearrangement. Although this kind of 1,3-shift of allylic selenides[14] and racemisation by allylic rearrangement of similarly constituted allylic esters[15] had been documented, this constitutes an interesting case of racemisation in allylic selenides.

Reaction of an excess of 2-lithio-1,3-dithiane in THF with enone **4**[6] and subsequent LAH reduction gave the desired terpene synthon **1b** (82%, 46–59% overall yield from nopinone). Similarly (1*S*)-(−)-nopinone was converted to (*R*)-**4** and to the corresponding synthon **1a**. Synthon **1b** was

† All isolated new compounds were characterised by combustion analysis and/or ^{1}H NMR spectroscopy.

‡ After the preparation of this manuscript, a communication appeared describing the conversion of (+)-nopinone to enol acetate, **3** in 68% yield [ref. 8(*b*)].

§ The intermediate epoxy enone **6**[6] was converted to enone **4** by (i) $LiAlH_4$ (LAH) reduction in Et_2O; (ii) pyridinium chlorochromate oxidation in CH_2Cl_2 and (iii) Ac_2O–dimethylaminopyridine–pyridine acetylation. Compound (*R*)-**4**, prepared by this route, displayed an $[\alpha]_D^{22}$ value of +58.76° (*c* 0.0573, MeOH).

¶ It is interesting to note that the *cis*-isomer **7a** did not react to any measurable extent under those conditions.

transformed to (+)-11-hydroxy-5-norpentyl-5-(1′,1′-dimethylheptyl) THC **2**, as previously described,[6] without any loss in optical purity from the starting nopinone.

In summary, a short and efficient route to the terpene synthons (*R*)-**1a** and (*S*)-**1b** is described which should facilitate further studies in the cannabinoid field, which will be reported in due course.

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