Communications

Synthesis of (−)-Δ^9-6a,10a-*trans*-Tetrahydrocannabinol. Boron Trifluoride Catalyzed Arylation by a Homocuprate

Summary: Boron trifluoride catalyzed arylation of (1*S*,4*R*)-*p*-mentha-2,8-dien-1-yl acetate (**3b**) with the homocuprate derived from lithiated olivetol dimethyl ether (**2b**) affords (−)-*trans*-cannabidiol dimethyl ether (**4**), which is further converted into (−)-Δ^9-6a,10a-*trans*-tetrahydrocannabinol (**1**) in 59% overall yield from the acetate **3b**.

Sir: (6a*R*,10a*R*)-Δ^9-6a,10a-*trans*-Tetrahydrocannabinol (**1**) [(−)-Δ^9-THC] is the main physiologically active constituent of *Cannabis sativa* L.[1] and has therapeutic potential in the treatment of glaucoma and as an antinauseant in patients undergoing cancer chemotherapy.[2] A number of syntheses of **1** (Chart I) from various chiral monoterpenes and olivetol (**2a**) have been reported,[2] of which the route from (1*S*,4*R*)-*p*-mentha-2,8-dien-1-ol (**3a**) or its 1*R*,4*R* diastereomer developed by Petrzilka et al.[3] and modified by Razdan et al.[2,4] offers advantages on preparative scale.[2] These cationic condensations are promoted by Lewis acids, and their regiochemical course is critically sensitive to reaction conditions.[2] The yields of (−)-Δ^9-THC (**1**) are only moderate, and the complex mixture of products formed commonly includes the thermodynamically more stable (−)-Δ^8-THC, which requires isomerization by the addition and elimination of hydrogen chloride.[2,3] We now report a carbanionoid approach to (−)-Δ^9-THC (**1**) that proceeds efficiently with high regio- and stereospecificity from olivetol dimethyl ether (**2b**) and readily available (1*S*,4*R*)-*p*-mentha-2,8-dien-1-yl acetate (**3b**).[5]

Regiospecific lithiation of olivetol dimethyl ether (**2b**) and subsequent reaction with cuprous bromide afforded a diaryl cuprate, which was insufficiently reactive to couple with the allylic acetate **3b**. However, catalysis with boron trifluoride etherate (3.5 equiv) effected smooth coupling (ether, −76 °C, 5 h) of the cuprate[6] (2 equiv) with the acetate **3b** (1 equiv) to give (−)-*trans*-cannabidiol dimethyl ether (**4**) in 78% yield after MPLC. The product showed [α^{20}_D −140° (*c* 0.015, MeOH) in agreement with literature[7] [[α]$^{28}_D$ −133° (*c* 1.07, EtOH)], and the trans-1,6 configuration was confirmed by ^{1}H (200 MHz) NMR spectroscopy [H-1 (cyclohexene numbering), δ 3.98, m, $J_{1,6}$ = 11 Hz]. The specific anti stereochemistry of the coupling reaction is that expected from a cyclohexenyl acetate which is further biased by an α-oriented isopropenyl substituent at C-4,[8] while the C-1 methyl group ensures regiospecificity. To our knowledge this is the first report of the catalysis by a Lewis acid of a formal S_N2' substitution involving a homocuprate, although such catalysis of conjugate additions of cuprates is known.[9,10]

Attempts to effect concomitant demethylation and pyran ring closure by treatment of **4** with boron tribromide gave a complex mixture containing Δ^9-THC (**1**) only in low concentration. Accordingly, in order to protect the terpenoid double bonds in **4** from the Lewis acid, and also to provide regiocontrol for the future reintroduction of the Δ^9 unsaturation, we decided to prepare the dihydrobromide of the diene **4**. Addition of hydrogen bromide occurred immediately in HBr-saturated methylene dichloride at −20 °C, affording in quantitative crude yield an apparently homogeneous, extremely unstable bisadduct (characterized by ^{1}H NMR, MS, and Br analysis), which was formulated as the axial bromo isomer **5**.[11] Surprisingly, if the reaction was left at room temperature for 5 h, the initial bisadduct **5** underwent monodemethylation and pyran ring closure, without formation of an observable intermediate, to yield quantitatively (6a*R*,9*S*,10a*R*)-9α-bromo-6a,10a-*trans*-hexahydrocannabinol methyl ether (**6a**), [α]$^{20}_D$ −48° (*c* 0.094, EtOH), with ^{1}H NMR, MS, and HRMS data in accord with this structure. Olivetol dimethyl ether (**2b**) itself is unaffected by HBr under these conditions, and we attribute this remarkable reaction to the crowding of the vicinal substituents in the dihydrobromide **5**.

Demethylation could be completed by reaction of the ether **6a** with boron tribromide[12] to afford (6a*R*,9*S*,10a*R*)-9α-bromo-6a,10a-*trans*-hexahydrocannabinol (**6b**) in 58% yield isolated by MPLC, [α]$^{19}_D$ −60° (*c* 0.13, EtOH), with identical ^{1}H NMR and MS data with (±)-**6b** reported by us elsewhere.[12] The bromide **6b** was then regiospecifically dehydrohalogenated[2,3] with potassium *tert*-butoxide as described[12] to give after purification (−)-Δ^9-THC (**1**) containing <10% (−)-Δ^8-THC.

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(2) Review: Razdan, R. K. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, pp 185–262.

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(6) Formed by reaction (ether, 0 °C) of the lithio derivative of **2b** (2 equiv) with cuprous bromide (1 equiv).

(7) Adams, R.; Hunt, M.; Clark, J. H. *J. Am. Chem. Soc.* **1940**, *62*, 196–200.

(8) (a) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854–7855. (b) Kreft, A. *Tetrahedron Lett.* **1977**, 1035–1036. (c) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318–2325. (d) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721–724. (e) Goering, H. L.; Singleton, V. D., Jr. *J. Org. Chem.* **1983**, *48*, 1531–1533.

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(10) Alkylcopper–boron trifluoride complexes (but not phenylcopper complexes) provide enhanced regioselectivity compared to the parent alkylcopper reagents in alkylation of allylic halides and acetates and permit the direct C-alkylation of allylic alcohols; see: Maruyama, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8068–8070. Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* **1978**, *156*, C9–C11. Yamamoto et al.[8c]

(11) Arising by preferred trans-diaxial addition to the cyclohexene **4**; cf. Readio, P. D.; Skell, P. S. *J. Org. Chem.* **1966**, *31*, 753–759.

(12) Moore, M.; Rickards, R. W.; Rönneberg, H. *Aust. J. Chem.*, submitted for publication.

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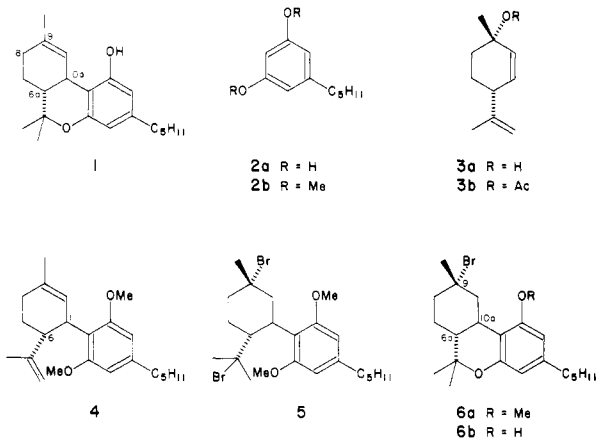
Chart I



For preparation purposes, however, it is inefficient and unnecessary to separate and purify the relatively unstable brominated intermediates **5**, **6a**, and **6b**. Instead the (−)-cannabidiol dimethyl ether (**4**) was subjected to successive hydrobromination (HBr, CH_2Cl_2, −20 °C), monodemethylation and cyclization (warmed to ambient, 5 h), and further demethylation [cooled to −76 °C, BBr_3 (9 equiv, 3.5 M in CH_2Cl_2) added, warmed to ambient, 7 h]. The resulting bromide **6b** obtained in quantitative crude yield was immediately dehydrobrominated (1.2 equiv of KOBu-*t*, benzene, 5 °C for 1 h and then 65 °C for 10 min)[12] to afford after MPLC $\Delta^{9(11)}$-THC (<5% yield) and the required (−)-Δ^9-THC (**1**) containing <10% (−)-Δ^8-THC in 75% overall yield from the diether **4**. This product had the required ^1H NMR, MS, and CH analysis and $[\alpha]^{17}_D$ −161° (*c* 0.087, EtOH) in agreement with literature[13] [$[\alpha]^{20}_D$ −156° (*c* 0.34, EtOH)].

Earlier addition of boron tribromide to the hydrobromination reaction, at the stage when only the dihydrobromide **5** was present, also gave the cyclized and fully demethylated bromide **6b** in high yield. However, the Δ^9-THC (**1**) obtained from this material was extensively racemized, showing that in order to preserve chirality the pyran ring system of the ether **6a** must be formed before treatment with Lewis acid. Presumably carbocations developed from **5** with boron tribromide are not trapped immediately by pyranyl ether formation as with hydrogen bromide alone but instead survive to cause isomerization at the two adjacent tertiary centres.

The present carbanionoid approach to (−)-Δ^9-THC (**1**) proceeds via two isolated intermediates **4** and **6b** in 59% overall yield from the menthadienyl acetate **3b** and offers advantages over the previous cationic routes[2-4] in terms of simplicity of reaction mixtures and yield of isolated product. The route is equally applicable to the synthesis of the less-studied enantiomeric (+)-Δ^9-THC (*ent*-**1**),[2] since (1*R*,4*S*)-*p*-mentha-2,8-dien-1-yl acetate (*ent*-**3b**) is readily available from (−)-(*S*)-limonene.[5]

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(13) "Dictionary of Organic Compounds"; Chapman and Hall: New York, 1982; Vol. 5, p 5178.

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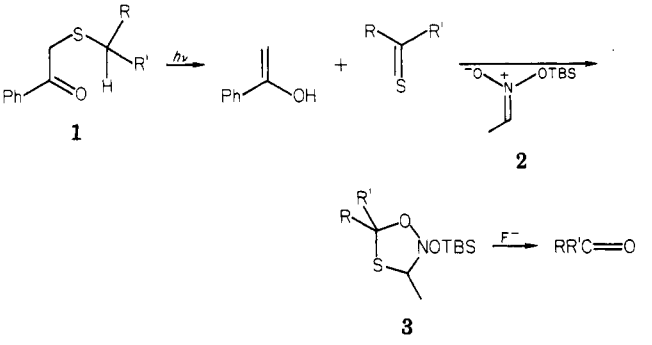
A Method for Mild Photochemical Oxidation; Conversion of Phenacyl Sulfides into Carbonyl Compounds

Summary: Sunlamp irradiation of phenacyl sulfides $PhCOCH_2SCHRR'$ affords thiocarbonyl compounds S=CRR' that can be trapped in high yield by using the nitronate $CH_3CH{=}N^+(OTBS)O^-$; the heterocycle **3** resulting from 1,3-dipolar cycloaddition is cleaved rapidly by fluoride ion to give ketones or aldehydes.

Sir: We have been interested in mild methods for oxidation α to sulfur.[1] This transformation is of general importance in syntheses using organosulfur intermediates and becomes especially significant as a tool for removal of sulfur from large ring sulfides or their transformation products.[1c,2] In this paper, we report several examples of mercaptan oxidation via the photochemical fragmentation of phenacyl sulfides **1** to thiocarbonyl compounds.[3,4] The optimum oxidation sequence involves 1,3-dipolar trapping of thiocarbonyl intermediates in situ with *tert*-butyldimethylsilyl nitronate ester **2**,[5] followed by cleavage of the intermediate heterocycle **3** with $Bu_4N^+F^-$. The starting



phenacyl sulfides are most easily prepared by treatment of mercaptans with phenacyl chloride/Et_3N in THF (method A). Michael addition of phenacyl mercaptan[6] to enones, method B (Table I; entries f and g) or alkylation of phenacyl mercaptan with alkyl halides (method C) can also be used.[4] Irradiation of a 0.05 M benzene solution of **1** and approximately 1.5 equiv of **2** using a simple sunlamp apparatus[7] affords the cycloadducts **3**. It is possible to

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