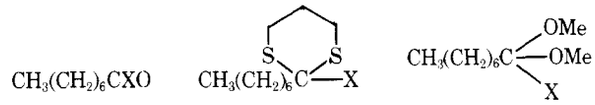
Preparative Scale Synthesis of (1*R*) [1-$^2H_1$] or [1-$^3H_1$] Primary Alcohols of High Optical Purity

Summary: A convenient and rapid procedure for the synthesis of (1*R*)[1-$^2H_1$] or [1-$^3H_1$] primary alcohols from the corresponding (1*S*) alcohols is described.

For studies of mechanisms of enzymatic reactions, we required a general procedure for the synthesis of compounds (hydrocarbons, acetic acids, propionic acids, etc.) containing chiral ("*R*" and "*S*") methyl groups.[1] The approach we chose was to prepare large amounts of (1*R*) and (1*S*) alcohols which would be converted (e.g., via tosylations and LiAl*H_4 hydrogenolyses) to the required chiral methyl groups. Finally, the chiral hydrocarbons could be oxidized (e.g., Kuhn–Roth, RuO_4) to aliphatic acids, as needed.

While the required (1*S*) alcohols[2] are more accessible, there seem to be no convenient methods for the large-scale preparation of the critically important, optically pure (1*R*) alcohols.[3] We report a general, practical procedure for the large-scale synthesis of primary (1*R*) alcohols from (1*S*) alcohols. The method is exemplified by the synthesis of (1*R*)-octanol, (1*R*)-2-phenylethanol, and (1*R*)-benzyl alcohol.

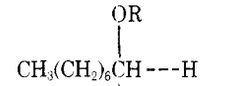
A solution of octanaldithiane (**2a,** 4 g) in dry THF was cooled to −20 °C under N_2 and then *n*-butyllithium (1 equiv)



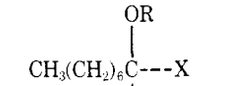
1a, X = H
b, X = D
c, X = T

2a, X = H
b, X = D
c, X = T

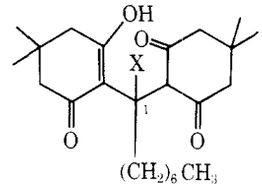
3a, X = D
b, X = T



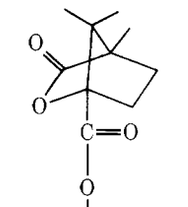
4a, X = D; R = H
b, X = T; R = H
c, X = D; R = COC_6H_5
d, X = D; R = $COC_9H_{13}O_2$



5a, X = D; R = H
b, X = T; R = H
c, X = D; R = COC_6H_5
d, X = D; R = $COC_9H_{13}O_2$



6a, X = H
b, X = D
c, X = T



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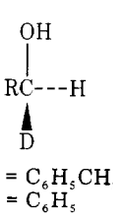
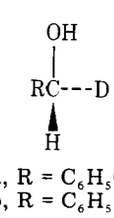


8a, R = $C_6H_5CH_2$
b, R = C_6H_5



9a, R = $C_6H_5CH_2$
b, R = C_6H_5

was added. After 2 h, excess D_2O was added and the deuterated dithiane[4] (**2b,** 4 g; d_0 9%, d_1 91%) was recovered [no triplet at 3.9 ppm for the C-1 (^1H)]. **2b** (4 g), on treatment with HgO (4.4 g) and $HgCl_2$ (11.0 g) in 90% aqueous methanol (900 ml), gave **3a,** which was hydrolyzed (dilute HCl–acetone) to [1-^2H]-octanal (**1b**) [no signal at 9.15 ppm (−CHO)].[5] The [1-^3H]-octanal (**1c**) (60 mCi) was prepared in a similar manner from **2a** (4 g), using 100 mCi of ^3H_2O.

[1-^2H]-octanal (**1b,** 700 mg), horse liver alcohol dehydrogenase (HLAD, 30 mg), NAD (180 mg) in a 0.01 M phosphate buffer (pH 6.9, 1000 ml) containing EtOH (45 ml), and dioxane (25 ml) was incubated at 30 °C for 72 h under N_2.[6] Following column chromatography of the recovered products (silica gel, hexane–ether, 6:4), (1*S*)[1-$^2H_1$]-octanol (**4a,** 690 mg) (mass spectrum d_0 8%, d_1 92%) was obtained.

The optical purity of the alcohol **4a** was determined enzymatically and by NMR spectroscopy. The (1*S*)[1-$^2H_1$]-octanol (**4a**) (30 mg) was incubated in 0.01 M phosphate buffer (pH 9.7, 65 ml) containing 5,5-dimethyl-1,3-cyclohexanedione (dimedone, 35 mg) with yeast alcohol dehydrogenase (YADH, 14 mg) and NAD (300 mg) for 40 h at 27 °C, in the air.[7] The recovered residue (40 mg) obtained following ether extraction was chromatographed (TLC) [silica gel, hexane–ethyl acetate (1:1)] and, on crystallization (EtOH), gave **6b:** mp 130–132 °C; mass spectrum d_0 10%, d_1 90%; NMR, no signal at 4.1 ppm for the C-1 (^1H). Since in the YADH–NAD oxidation of alcohols the (1-H_R) hydrogen atom is removed,[2a,8] the complete retention of ^2H in **6b** establishes the (1*S*) chirality of the alcohol **4a.**

The enantiomeric purity of **4a** was also determined by NMR, by the method of Gerlach and Zagalak.[9] The (1*RS*)-[1-$^2H_1$]-octanol-(−)-camphanic ester (**7**) was prepared and its 100-MHz NMR spectrum in the presence of Eu(dpm)$_3$[10] was recorded. The enantiotopic C-1 proton of **7a** gave two triplets (J = 6Hz) at 5.8 ppm (H_S)[9] and 5.5 ppm (H_R).[9] The 100-MHz Eu(dpm)$_3$ spectrum of the (1*S*)[1-$^2H_1$]-octanol-(−)-camphanic acid ester (**4d**) showed only *one triplet* equivalent to *one* proton at 5.5 ppm for the (1-H_R) of **4d.** For sensitivity determination, (1*RS*)[1-$^2H_1$]-octanol-(−)-camphanic acid ester (**7a**) was added in increments of 2% [corresponding to 1% (1*R*) and (1*S*) esters] to the (1*S*) ester **4d.** Following the admixture of 10% (1*RS*) ester **7a,** the signal for the (1-H_S) could be detected. Hence, the presence of a minimum of ~5% second enantiomer will be detected by this NMR method. It may, therefore, be inferred that octanol **4a** contains a minimum of 95% excess (1*S*) isomer.

A mixture of (1*S*)[1-$^2H_1$]-octanol (**4a,** 360 mg), triphenylphosphine (1.2 g), diethyl azodicarboxylate (440 μl), and benzoic acid (480 mg) in dry tetrahydrofuran (28 ml) was stirred at room temperature for 15 h under N_2.[11,12] The recovered product was fractionated by column chromatography [silica gel, hexane–ether (9:1)] to give (1*R*)[1-$^2H_1$]-benzoate **5c.** Treatment of **5c** (710 mg) with $LiAlH_4$ in ether provided (1*R*)[1-$^2H_1$]- octanol **5a** (315 mg). Oxidation of **5a** (30 mg) with YADH–NAD, as described above, gave the corresponding dimedone derivative **6a** (8 mg) (NMR triplet at 3.8 ppm for the C-1 hydrogen atom) (mass spectrum d_0 100%). Since 1-H_R is removed in the enzymatic oxidation, the absence of deuterium in **6a** establishes the (1*R*) stereochemistry of **5a.**

The 100-MHz Eu(dpm)$_3$ spectrum[10] of the (1*R*)[1-$^2H_1$]-octanol-(−)-camphanic ester (**5d**) showed a triplet at 5.8 ppm for the (1-H_S). As expected,[9] the (H_S) triplet of **5d** was at a lower field than the H_R triplet of the (1*S*)[1-$^2H_1$]-octanol (**4a**). Indeed, incremental addition of **5d** to the (1*RS*)-camphanic ester **7** resulted in an increase in intensity of the 5.8-ppm triplet. Based on the experimentally determined sensitivity of the method, it follows that the octanol **5a** contains a minimum of 95% excess (1*R*) isomer.

In an analogous sequence of reactions (1*S*)[1-$^3H_1$]-octanol (**4b**) and (1*R*)[1-$^3H_1$]-octanol (**5b**) were prepared. For the determination of their optical purities, the (1*S*)[1-$^3H_1$]-octanol (**4b**) (specific activity 1.95 × 10^7 dpm/mmol) and the (1*R*)[1-$^3H_1$]-octanol (**5b**) (specific activity 4.1 × 10^7 dpm/mmol) were oxidized enzymatically (YADH–NAD) to yield octanal **1c** (specific activity 1.90 × 10^7 dpm/mmol; counted as the dimedone derivative **6c**) and octanal **1a** (specific activity 7.8 × 10^5 dpm/mmol; counted as **6a**), respectively. Clearly the

Table I. NMR Spectra of (−)-Camphanic Acid Esters of the Indicated Alcohols. All Spectra Were Recorded at 100 MHz as CCl_4 Solutions in the Presence of 30 mol % Eu(dpm)$_3$

Esters of	^1H_R[a]	^1H_S[a]
2-Phenylethanol		
a, (1*RS*) [1-$^2H_1$]	5.2 (t, J = 6 Hz)	5.4 (t, J = 6 Hz)
b, (1*S*) [1-^{2}H]	5.2 (t, J = 6 Hz)	ND
c, (1*R*) [1-$^2H_1$]	ND[b]	5.4 (t, J = 6 Hz)
Benzyl alcohol		
a, (1*RS*) [1-$^2H_1$]	5.70 (s)	5.88 (s)
b, (1*S*) [1-$^2H_1$]	5.70 (s)	ND
c, (1*R*) [1-$^2H_1$]	ND	5.88 (s)

[a] Chemical shifts of the enantiotopic hydrogens (in ppm). [b] ND, not detectable..

oxidation of the (1*S*)-octanol **4b** to octanal **1c** proceeded with the complete retention of tritium, while the oxidation of the (1*R*)-octanol **5b** to octanal **1a** involved the loss of 98% tritium.

To test the generality of the inversion procedure, (1*S*)-[1-$^2H_1$]-2-phenylethanol (**8a**) and (1*S*)[1-$^2H_1$]-benzyl alcohol (**8b**) were prepared by HLAD–NAD reduction of the corresponding [1-^{2}H] aldehydes. The (1*S*) alcohols were treated with $(C_6H_5)_3P/C_6H_5CO_2H/EtO_2CN{=}NCO_2Et/THF$, as described above. The resulting (1*R*) benzoates were saponified (methanolic KOH) to give (1*R*)[1-$^2H_1$]-phenylethanol (**9a**) and (1*R*)[1-$^2H_1$]-benzyl alcohol (**9b**) in good yield. The 100-MHz Eu(dpm)$_3$ analyses of the (−)-camphanic acid esters of alcohols **9a** and **9b** indicated the presence of at least 95% excess (1*R*) alcohols in each case (see Table I).

The described procedure represents a facile synthesis of primary (1*R*) alcohols from the more accessible (1*S*) alcohols. In the systems investigated, the reaction proceeds in high yield with complete inversion of configuration. Aldehydes with a high C-1 tritium content can be prepared by quenching the anion derived from **2a** with tritiated water of high specific activity. It follows that by using the described methods, (1*S*) and (1*R*) [1-^{3}H] alcohols and the chiral methyls derived from these alcohols will have a high specific activity of tritium.

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References and Notes

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(10) The ^{1}H NMR spectra of the (−)-camphanic acid esters were recorded at 100 MHz in CCl_4. Optimal separation of the signals for the enantiomeric protons occurred at 30 mol % of Eu(dpm)$_3$.

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(12) The procedure can be adjusted according to the availability of the (1*S*) alcohol.

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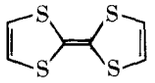
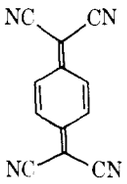
Unsymmetrical Dimethyltetrathiafulvalene[1]

Summary: A hitherto unknown unsymmetrically substituted tetrathiafulvalene (substitution on only one ring) was prepared, isolated, and purified, and its spectroscopic and physical properties are described and compared with those of other members of the family; the title compound forms highly conducting salts with TCNQ and other anions.

Sir: Organic materials whose electrical conductivity in the solid state increases with decreasing temperature belong to the theoretically interesting family of "low dimensional" or "one dimensional metals". Members of this class of substances have in common the peculiar property whereby the molecular charge carriers stack uniformly along a given axis. The solid-state packing arrangement of all known members of this family (whether organic or inorganic) consists of independent, uniform stacks of donors and/or acceptors and are subject to a theoretically predicted solid-phase transition[2a] which eventually converts them to insulators (usually at temperatures below 200 K). Within this class the most highly conducting organic materials are based on TTF (**1**) and TCNQ (**2**).

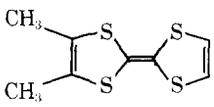


TTF (1)



TCNQ (2)

While an unsymmetrically substituted TCNQ derivative (monomethyl TCNQ), has been prepared and its electrical properties in combination with TTF have been studied,[2b] no such simple unsymmetrical TTF compounds are known. The only previously known asymmetrical TTF compound is the monomethyl dibenzotetrathiafulvalene,[3] a material which does not yield organic metals.[3] This paper is a report on the synthesis, separation, purification, and comparative spectroscopic properties of various potentially interesting methylated TTF molecules, especially the title compound (UDMTTF, **3**). The physical measurements and preparation



UDMTTF (3)

of organic conductors based on these donors will be reported separately.

Because monomethyl TTF was expected to have very similar properties to TTF and dimethyl TTF, its synthesis in