SYNTHESIS OF (+) AND (-) [10-^{14}C]-α- AND β-PINENES

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SUMMARY

[10-^{14}C]-(+) and (-)-β-Pinenes were prepared from their corresponding non-radioactive isomers by the Wittig reaction; and the [10-^{14}C]-(+) and (-)-α- isomers were obtained from the [10-^{14}C]-β-pinenes by isomerization. After purification by gas chromatography the specific activity for each of the isomers was ca. 0.025 mCimmol^{-1}, and all the isomers had high (>90%) optical purities. All four isomers were found to be chemically (>99.5%) and radiochemically (>99.5%) pure.

Key words: Pines, (+) and (-)-[10-^{14}C]-α- and β-pinenes, Wittig reaction, isomerization.

For ongoing biosynthetic studies we required samples of [10-^{14}C]-labelled (+) and (-) α- and β-pinenes of high optical purities and specific activities. These are not available commercially. Hitherto the ^{14}C-labelled pinenes that have been employed in such studies, were obtained after feeding [^{14}C]-CO_2 to Pinus pinaster or P.ponderosa followed by extraction[1]. Regretably, these labelled pinenes of unspecified chirality have very low specific activities. The specific activity of α-pinene used by Schmeers[1] in a similar study was 4.2 x 10^{-7} μCimmol^{-1}. In this paper we describe the synthesis of [10-^{14}C]-(+) and (-) α- and β-pinenes (1b, 2b, 3 and 4; Chart I) of high (>90%) optical purities and relatively high specific activities (See above). Results of the biosynthetic studies will be published elsewhere.

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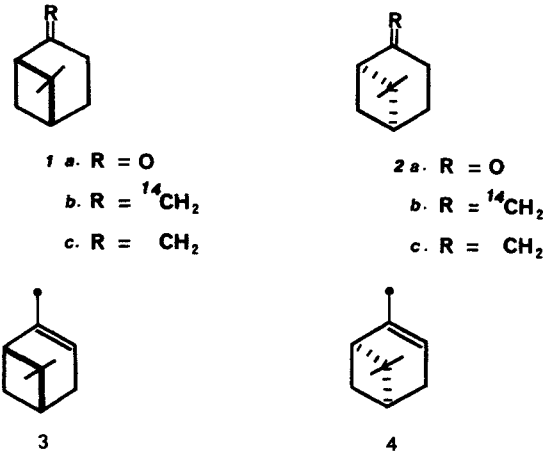
CHART I



(•) denotes ^{14}C

The [10-^{14}C]-labelled α- and β-pinenes were obtained as follows: Firstly (+) and (-)-β-pinene (1c and 2c) were converted into nopinones (1a and 2a respectively) by ozonolysis[2]. These were then converted into the desired (+) and (-) [10-^{14}C]-β-pinenes 1b and 2b respectively by a Wittig reaction with triphenyl-[^{14}C]-methylphosphonium bromide in about 30% yield. The assignment of C-10 as the carbon bearing the ^{14}C isotope rest on the proven specific replacement of a carbonyl group by a carbon-carbon double bond in the Wittig reaction[3,4]. The triphenyl-[^{14}C]-methylphosphonium bromide 7 was not prepared directly from triphenyl phosphine and [^{14}C]-methyl bromide as expected due to the high cost of the latter. Instead triphenyl-[^{14}C]-methylphosphonium iodide (5; Scheme I) was prepared ([^{14}C]-methyl iodide is readily available at low cost) and then converted via the nitrate 6 to the desired bromide 7 in excellent

SCHEME I

$$Ph_3P^{14}CH_3I \underset{5}{\rightarrow} Ph_3P^{14}CH_3NO_3 \underset{6}{\rightarrow} Ph_3P^{14}CH_3Br \underset{7}{}$$

yield. We did not use the iodide because of the difficulties encountered in its use in the Wittig reaction[5,6]. Finally (+) and (-) [10-^{14}C]-α-pinenes 3 and 4 respectively were obtained by refluxing their corresponding β-isomers 1b and 2b with benzoic acid and hydroquinone in about 75% yield.

The four pinene isomers (1b, 2b, 3 and 4) were found to be chemically (>99.5%) and radiochemically (>99.5%) pure by GLC and radiochromatographic analysis. The specific activity for each isomer was ca.0.025 mCi mmol^{-1} and their optical purities are in Table I.

Table I: Specific rotations and optical purities of [10-^{14}C]-pinenes

Pinene	$[\alpha]_D^{22}$	% Optical purity (± 1%)[b,c]
1b	+17	91
2b	-21	100
3	+47	96
4	-47	96

(a) S.D. for all compounds ± 1%.

(b) Defined of the % of the predominant enantiomer (optically pure (+)-α-pinene has $[\alpha]_D^{22}$ + 51° and the (-)-β-isomer -21°)

(c) Use of a chiral LSR - ^{1}H-nmr technique[7] gave results ± 1% in agreement with these values.

EXPERIMENTAL

GLC analyses were carried out on a Varian 1800 gas chromatograph using 10ft x 0.25 in column packed with 15% FFAP. Preparative GLC was carried out on Pye 104 series chromatograph using same column as above or on an F and M Scientific 775 prepmaster using 7.8ft x 4.0 in column packed with carbonwax 20M. Infrared spectra were taken on a

Perkin-Elmer Model 157 spectrometer. NMR spectra were taken on a Perkin-Elmer R.12. Rotations were measured on a Perkin-Elmer 141 polarimeter. Radioactivities were measured on a Packard Tricarb 3251 liquid scintillation counter and on a 2π-radiochromatograph scanner. Merck Silica gel (HF_{254}+366) was used for TLC. Melting points were taken on a Kofler hot-stage apparatus and are corrected.

Materials. (+)-α-Pinene, $[\alpha]_D^{22}$ + 46.5°, and (-)-β-pinene $[\alpha]_D^{22}$ - 21° were purchased from Aldrich Chemical Co. [^{14}C]-Methyl iodide was purchased from Amersham Chemical Co. (+)-β-Pinene is not available commercially and was prepared from (+)-α-pinene by treatment with Pd-black under hydrogen[8]. The reaction mixture contained 3% of the β-isomer and the β-compound was obtained by spinning-band distillation followed by preparative GLC on carbonwax 20M (15% chromosorb W., 7.8ft x 4.0 in, 120°C, 60 ml min^{-1} N_2); Yield 1.2%, $[\alpha]_D^{22}$ + 17°.

Nopinone (1a) from (+)-β-pinene

(+)-β-Pinene 1c (1.5g, 1.1mmol) dissolved in methanol (15ml) was cooled to -60°C and ozone was bubbled slowly through the reaction mixture for 40min. The reaction mixture still maintained at -60°C was flushed (10min) with O_2 to remove excess O_3 and dimethyl sulphide (2ml) was added. The mixture was then stirred for 3h at room temperature, diluted with water (20ml) and extracted with petroleum ether and dried. The yellow oil residue after concentration was distilled under reduced pressure to give nopinone (1a). Yield 90%, IR ν_{max} 1720cm^{-1} (C-2, C = O), 'HNMR δ 0.85 (3H, s, 8-H), 1.35 (3H, s, 9-H).

Nopinone (2a) from (-)-β-pinene

This compound was prepared as described for 1a and had identical IR and 'HNMR characteristics.

Triphenyl-[^{14}C]-methylphosphonium iodide (5)

Methyl-[^{14}C] iodide (0.82g, 0.57mmol, 0.087 mCi $mmol^{-1}$) in sodium-dried benzene (2ml) was added dropwise (30min) to a solution of triphenylphosphine (1.05g, 0.4mmol) in dry benzene (5ml) at room

temperature. The reaction vessel was sealed and left at room temperature for 15h. The white solid that formed was filtered, washed (dry benzene) and the dried (P_2O_5) in a vacuum oven at 100°C for 12h to given triphenyl-[^{14}C]-methylphosphonium iodide in quantitative yield. mp 188°C (Lit[9] 187-189°C).

Triphenyl-[^{14}C]-methylphosphonium Bromide (7)

$AgNO_3$ (0.672g; 0.4mmol) dissolved in H_2O (0.5ml) was added dropwise with constant shaking to a solution of triphenyl-[^{14}C]-methylphosphonium iodide (1.6g, 0.4mmol, 0.085mCi mmol^{-1}) in methanol (10ml). After shaking for 5 min, the AgI formed was filtered and discarded. The filtrate which contained the phosphonium nitrate was shaken with KBr (0.4712g, 0.4mmol) in H_2O (0.5ml) and the KNO_3 that formed was filtered off. The filtrate was concentrated to give crude triphenyl-[^{14}C]-methylphosphonium bromide, mp 220°C. This was purified by precipitation from ethanol (30ml) with ether (300-400ml), and dried. Yield 71% (based on the iodide). mp 232°C (lit.[9] 229-231°C).

[10-^{14}C]-(+)-β-Pinene (1b)

Sodium hydride (67.2mg, 0.14mmole, 50% dispersion previously washed with hexane) was added to dry dimethyl sulfoxide (1ml) under N_2 and stirred at 65-70°C until hydrogen evolution ceased (ca 50min). The solution was cooled to room temperature, and triphenyl-[^{14}C]-methyl-phosphonium bromide (0.5g, 0.14mmol, 0.04mCi mmol^{-1}) in dimethyl sulfoxide (DMSO)(1ml) was added. After 20min, nopinone (0.193g, 0.14mmol) in DMSO (0.5ml) was added and the reaction was maintained at 55±5°C for 4h. At the end of the reaction inactive (+)-β-pinene (0.1g) was added and the dark reaction mixture was poured onto crushed ice, extracted thoroughly with petroleum ether and dried. It was necessary to add the inactive pinene as carrier due to the inadvertent loss of the product involved in the workup process. The residue after careful concentration was purified by preparative TLC [silica gel - $AgNO_3$ (5%), hexane - Et_2O (100:1)] at 4°C and

finally by preparative GLC (FFAP 15% at 90°C) to give [10-^{14}C]-(+)-β-pinene (1b) in ca 30% yield. $[\alpha]_D^{22}$ +17°, specific activity 0.028mCi mmol^{-1} ^{1}H NMR δ0.72 (3H, s, 8-H); 1.25 (3H, s, 9-H), 4.57 (2H, m, 10-H).

[10-^{14}C]-(-)-β-Pinene (2b)

This compound was prepared from nopinone 2a derived from inactive (-)-β-pinene $[\alpha]_D^{22}$ -21° as described above for 1b and showed the following: $[\alpha]_D^{22}$ -21°, specific activity 0.026mCimmol^{-1}, ^{1}H NMR δ0.72 (3H, s, 8-H); 1.25 (3H, s, 9-H), 4.57 (2H, m, 10-H).

[10-^{14}C]-(+)-α-Pinene (3)

A mixture of [10-^{14}C]-(+)-β-pinene (0.5g, 0.37mmol, 0.03mCimmol^{-1}, $[\alpha]_D^{22}$ +17°), benzoic acid (9.6mg, 0.079mmol) and hydroquinone (0.19mg) was refluxed (under N_2) for 48h. A saturated solution of $NaHCO_3$ (10ml) was added followed by extraction with petroleum ether. The extract was washed with water, dried (Na_2SO_4) and concentrated. The resulting yellow oil was purified as described for 1b to give [10-^{14}C]-(+)-α-pinene in ca. 75% yield. $[\alpha]_D^{22}$ + 47°, specific activity 0.026mCimmol^{-1}, ^{1}H NMR δ0.84 (3H, s, 8-H), 1.26 (3H, s, 9-H), 1.65 (3H, m, 10-H), 5.2 (1H, m, 3-H).

[10-^{14}C]-(-)-α-Pinene (4)

This compound was prepared from [10-^{14}C]-(-)-β-pinene 2b as described for 3 above. Specific activity 0.028mCimmol^{-1}, $[\alpha]_D^{22}$ - 47°, ^{1}HNMR δ0.84 (3H, s, 8-H), 1.26 (3H, s, 9-H), 1.65 (3H, m, 10-H) 5.2 (1H, m, 3-H).

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