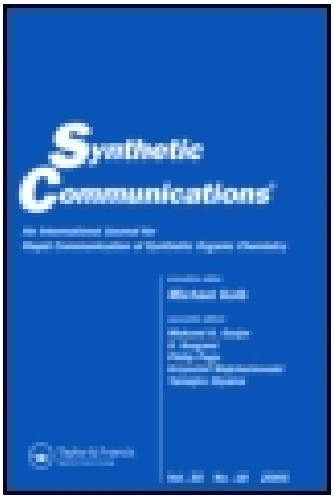

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Chiral Synthons from Monoterpenes.[1] Stereoselective Syntheses of (-)5S, 6S, 9R-6-Isopropyl-9-Methyl-2-Oxaspiro[4.4]Nonan-3-One and (-) 3aR, 6R, 7aR-3a-Methyl-6-Isopropenylhexahydrobenzofuran-2-One

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Published online: 24 Sep 2006.

SYNTHETIC COMMUNICATIONS, 22(9), 1221-1230 (1992)

CHIRAL SYNTHONS FROM MONOTERPENES.[1] STEREOSELECTIVE SYNTHESES OF (−)5S,6S,9R-6-ISOPROPYL-9-METHYL-2-OXASPIRO[4.4]NONAN-3-ONE AND (−)3aR,6R,7aR-3a-METHYL-6-ISOPROPENYLHEXAHYDROBENZOFURAN-2-ONE

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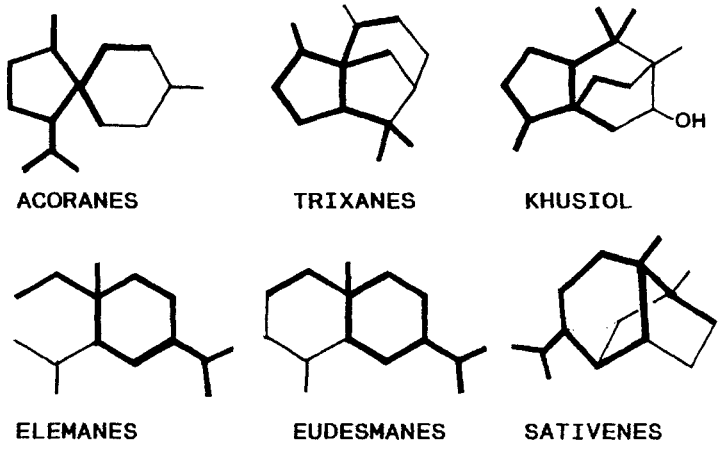
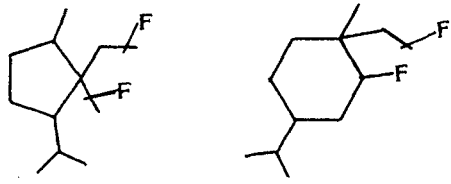
ABSTRACT: *Highly stereoselective syntheses of two C-12 chiral synthons* ***3*** *and* ***9****, mentioned in the title, starting from the monoterpenes R-limonene and R-carvone, using radical cyclisation as key reaction, are described.*

The overwhelming emphasis on carbohydrates as chiral synthons[2] for natural products synthesis, during the past decade, has some what marginalised the importance of abundantly available terpenes as building blocks for chiral synthesis.[3] This has come about despite the fact that many monoterpenes are cheap, readily available, and containing only one or two chiral centers with modest functionalisation, and thus do not require recourse to wasteful manouvers to dispense with the excess functionality. More importantly, terpenes can be restructured into cyclic and acyclic fragments that can be directly incorporated into the carbocyclic frameworks of complex target

CHART 1



F=functionality

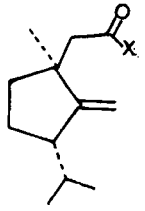


1 2

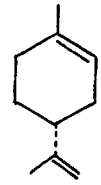
structures. Diverse terpenoids, by virtue of their common biogenesis, invariably embody common carbocyclic structural moieties. Therefore, an operationally useful strategy emerges in which such structural moieties extracted from a single, lower terpene chiron, can be evolved into a vast array of complex higher terpenes. Herein we describe the synthesis of two C-12 chiral synthons of type 1 and 2 starting from abundantly available monoterpenes R-limonene and R-carvone. In chart I are displayed basic skeletons of a few representative groups of sesquiterpenes containing the common structural core either 1 or 2.

(−)5S,6S,9R-6-ISOPROPYL-9-METHYL-2-OXASPIRO[4.4]NONAN-3-ONE (3):

The synthetic potential of the C-12 chiral synthon 4, obtained from limonene (5), via the cyclopentenylmethanol 6 by a two carbon addition at C-2 using the highly diastereoselective Claisen rearrangement, is well established.[3] We reasoned that a new C-12 chiral synthon with a two carbon addition at C-1 of 6 also will be of equal importance and a strategy based on radical cyclisation reaction[4] is developed to the spirolactone 3.



4 (X=H or OEt)



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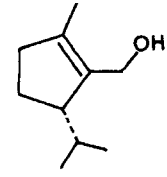

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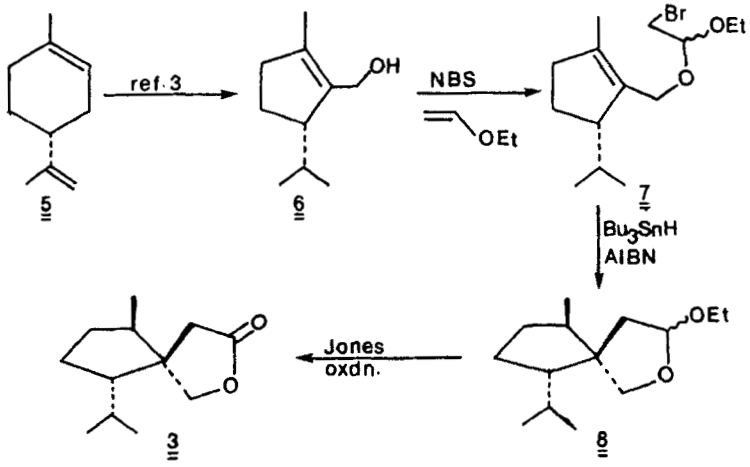
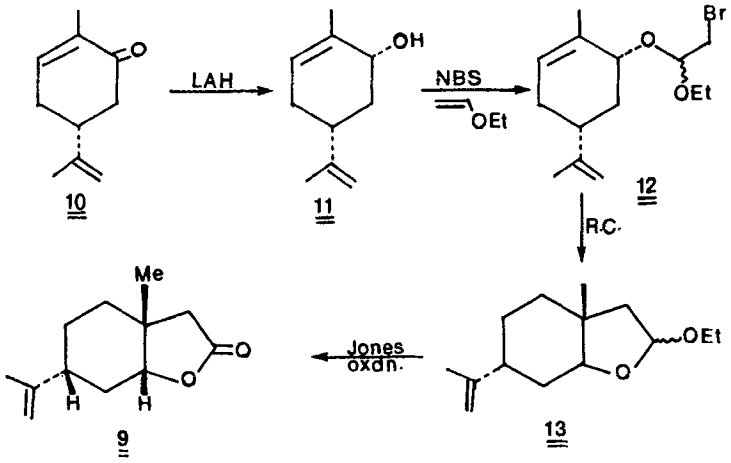
Enantiomerically pure spirolactone 3 was obtained from the readily available[3] allyl alcohol 6 as shown in the scheme 1. The key radical precursor, bromo acetal 7, was obtained, in 85% yield (mixture of diastereoisomers), by bromination of ethyl vinyl ether using N-bromosuccinimide (NBS) in the presence of the alcohol 6. Refluxing a 0.02M benzene solution of the bromo acetal 7 and tri-n-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 2 h furnished cyclised product 8, in 75% yield, with high degree of stereoselectivity.[5] Treatment of the hemiacetal 8 with Jones reagent using a ultrasonic bath[6] for 2 min furnished the spiro-

SCHEME 1



lactone 3. Structure of 3 rests secured on its spectral data, particularly the absence of olefinic methyl (^{1}H) and olefinic carbon (^{13}C) resonances and the appearance of three methyl doublets at δ 0.91, 0.95 and 1.01 (^{1}H) and singlets at 177.1 and 50.5 ppm (^{13}C) due to carbonyl carbon and spirocarbons in the NMR spectra, and the 1780 cm^{-1} band due to γ-lactone in the IR spectrum. The stereo chemical assignments at the spiro carbon and the methyl group were based on preferred approach of radical from the less hindered side of the olefin.[3,4] Having achieved the synthesis of enantiomerically pure 3, attention was turned to the extension of the same methodology to other chiral synthon of type 2.

SCHEME 2



(−)3aR,6R,7aR-3a-METHYL-6-ISOPROPENYLHEXAHYDROBENZOFURAN-2-ONE (9):

Enantiomerically pure lactone 9, an intermediate used in the first synthesis of the tricyclic sesquiterpene upial,[7] was obtained from R-carvone (10), in an overall yield of 67%, as shown in the scheme 2, by employing the radical cyclisation as the key reaction. Lithium-aluminium hydride (LAH) reduction[8] of 10 provided the requisite allyl alcohol 11. The radical precursor 12 was obtained, in 87% yield, as a mixture of diastereoisomers by a slow addition of NBS to a mixture of 11 and ethyl vinyl ether at -50 °C. The key radical cyclisation 12→13 was achieved, in 87% yield, using an in situ generated[9] catalytic tri-n-butyltin hydride ($^{n}Bu_3SnCl/NaCNBH_3/t\text{-}BuOH$)

in the presence of a catalytic amount of AIBN. Finally, Jones oxidation[6] of the hemiacetal 13 gave the lactone 9, in 94% yield. The structure of the lactone 9 rests secured from its spectral data (see experimental section) in particular the ^{1}H and ^{13}C NMR. As the LAH reduction of carvone produces the syn alcohol,[8] and the radical cyclisation[4] is known to give the cis ring junction, all the stereocentres in 9 were readily fixed.

In conclusion, we have described here the synthesis to two novel enantiomerically pure C-12 chiral synthons starting from the monoterpenes R-limonene and R-carvone. Currently, we are investigating the synthetic potential of these chiral synthons.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Hitachi 270-50 spectrophotometer. ^{1}H (60, 90 and 270 MHz) and ^{13}C (22.5 MHz) NMR spectra were recorded on Varian T-60, Jeol FX-90Q and Brucker WH-270 spectrometers, and the chemical shift (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal tetramethylsilane (^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (^{13}C). High resolution mass measurements were carried out on a Jeol JMS-DX 303 GC-MS instrument with a direct inlet mode. Sonochemical experiments were carried out using a Toshniwal SW-7.5 ultrasonic cleaning bath. Acme's silica gel (100-200 mesh) and Qualigen's neutral alumina were used for column chromatography. AIBN was crystallised from methanol and stored in dark. Methylene chloride was dried and distilled over P_2O_5. Tributyltin hydride, tributyltin chloride, sodium cyanoborohydride, NBS, LAH were

obtained from Fluka and were used as such. Jones reagent was prepared according to standard procedure.

(−)5S,6S,9R-6-ISOPROPYL-9-METHYL-2-OXASPIRO[4.4]NONAN-3-ONE (3):

To a cold (-75 °C), magnetically stirred solution of the alcohol 6 (308 mg, 2 mmol) and ethyl vinyl ether (0.8 ml, 8 mmol) in dry methylene chloride (10 ml) was added a methylene chloride solution (5 ml) of NBS (356 mg, 2 mmol) over a period of 20 min. The reaction mixture was stirred and allowed to warm up to room temperature over a period of 2 h. The reaction mixture was diluted with methylene chloride (15 ml), washed with 0.5N aqueous sodium hydroxide, water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of residue over a silica gel (10 g) column using ethyl acetate-hexane (1:50) as eluent furnished the bromo acetal 7 (1:1 mixture of diastereoisomers, 410 mg, 85%) as an oil. [^{1}H NMR (60 MHz, CCl_4): δ 0.67 (3 H, d, J=7 Hz), 0.91 (3 H, d, J=7 Hz), 1.24 (3 H, t, J=6 Hz), 1.74 (3 H, br s), 2.0-3.1 (6 H, m), 3.31 (2 H, d, J = 6 Hz), 3.64 (2 H, q, J=6 Hz), 4.0-4.35 (2 H, m), 4.5-4.9 (1 H,m)].

A solution of the bromo acetal 7 (305 mg, 1 mmol), tri-n-butyltin hydride (0.32 ml, 1.1 mmol) and AIBN (catalytic) in dry benzene (55 ml) was refluxed for 2 h. The reaction mixture was washed with 1% aqueous ammonia followed by brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of residue over a silica gel (10 g) column using ethyl acetate-hexane (1:50) as eluent furnished the cyclised compound 8 (mixture of diastereoisomers, 170 mg, 75%) as an oil. [IR (neat): ν_{max} 1173, 1113, 1050 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.8-1.1 (9 H, m), 1.2 (3 H, t, J=7.2 Hz), 1.4-2.4 (9 H, m), 3.2-3.9 (4 H, m), 5.08 (1 H, m)].

A solution of the hemiacetal 8 (150 mg, 0.6 mmol) and 1.6 M Jones reagent (1 ml, 1.6 mmol) in acetone (2

ml) was sonicated[6] for two minutes, and few drops of isopropanol was added to destroy the excess reagent. The reaction mixture was diluted with ether (10 ml), washed with saturated aqueous sodium bicarbonate followed by brine and dried (Na_2SO_4). Evaporation of the solvent and purification of residue over a silica gel (5 g) column using ethyl acetate-hexane (1:9) as eluent furnished the spiro lactone 3 (105 mg, 85%) as an oil, which was bulb to bulb distilled, b.p.120 °C (bath temperature)/1 mm. $[\alpha]_D^{26}$ −0.6° ($CHCl_3$, c 1.1). IR (neat): ν_{max} 1780, 1185, 1155, 1025 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.91 (3 H, d, J=6 Hz), 0.95 (3 H, d, J=6.5 Hz), 1.01 (3 H, d, J=6.1 Hz), 1.0-2.0 (7 H, m), 2.34 and 2.77 (2 H, AB q, J=18 Hz, 4.02 and 4.15 (2 H, AB q, J=9.6 Hz). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 13.1 (q, C_9-Me), 22.1 (t), 22.8 (q), 27 (q), 29.2 (t), 37.8 (t, $\underline{C}H_2C{=}O$), 44.6 (d), 50.5 (s, spiro C), 52.9 (d), 68.9 (t, $O{-}CH_2$), 177.1 (s, OCO). HRMS: m/e Found, 196.1456; Calcd. for $C_{12}H_{20}O_2$, 196.1463.

(−)3aR,6R,7aR-3a-METHYL-6-ISOPROPENYLHEXAHYDROBENZOFURAN-2-ONE (9):

Bromination of ethyl vinyl ether (0.5 ml, 5 mmol) with NBS (500 mg, 3 mmol) in the presence of carveol[8] (11, 278 mg, 1.8 mmol) in methylene chloride as described above followed by purification over a neutral alumina (10 g) column using ethyl acetate-hexane (1:9) as eluent gave the bromo acetal 12 (mixture of diastereoisomers, 477 mg, 87%) as an oil. [IR (neat): ν_{max} 3075, 1647, 1377, 1197, 1113, 1032, 924, 891 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 1.2 (3 H, t, J=7 Hz), 1.7 (3 H, s), 1.75 (3 H, s), 1.5-2.4 (5 H, m), 3.3 (2 H, d, J=6 Hz), 3.6 (2 H, q with st, J=7 Hz), 4.2 (1 H, m), 4.65 (3 H, br s), 5.4 (1 H, br s)].

A solution of the bromo acetal 12 (268 mg, 0.9 mmol), tri-n-butyltin chloride (0.04 ml, 0.1 mmol), $NaCNBH_3$ (95 mg, 1.5 mmol) and AIBN (catalytic) in t-butanol (10 ml) was refluxed for 1 h. t-BuOH was removed under reduced

pressure and the residue taken in ether (25 ml), washed with 1% aqueous NH_3 followed by brine and dried (Na_2SO_4). Evaporation of solvent and purification of residue over a silica gel (10 g) column using methylene chloride-hexane (2:3) as eluent furnished the cyclised product **13** (mixture of diastereoisomers, 173 mg, 87%) as an oil. [IR (neat): ν_{max} 3075, 1647, 1155, 1116, 1040, 888 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 0.8-2.4 (15 H, m), 1.7 (3 H, s), 3.0-4.0 (3 H, m), 4.66 (2 H, br s), 5.0 (1 H, m)].

Oxidation of the hemiacetal **13** (110 mg, 0.49 mmol) with 1.6M Jones reagent (1 ml, 1.6 mmol) in acetone (2 ml) as described above followed by purification over a silica gel (10 g) column using ethyl acetate-hexane (1:9) as eluent furnished the lactone **9** (90 mg, 94%) as an oil which was bulb to bulb distilled, b.p. 140 °C (bath temperature)/0.3 mm. $[\alpha]_D^{26}$ -16.6° ($CHCl_3$, c 3.3) [lit.[7] -9° ($CHCl_3$, c 47.6)]. IR (neat): ν_{max} 3075, 1780, 1695, 885 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.18 (3 H, s, C_{3a}-Me), 1.75 (3 H, s, olefinic Me), 1.0-2.4 (6 H, m), 1.98 and 2.68 (2 H, AB q, J=17 Hz), 4.18 (1 H, dd, J=10.6, 6.6 Hz, -OCH), 4.72 (2 H, brs, olefinic). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 20.8 (q, olefinic Me), 26.6 (t, C-5), 28.2 (q, C_{3a}-Me), 33.4 (t, C-7), 35.1 (t C-4), 37.8 (t, $\underline{C}H_2C{=}O$), 38.2 (s, C-3a), 41.2 (d, C-6), 84.9 (d, O-C), 109.3 (t, $=CH_2$), 147.8 (s, C=), 176.4 (s, C=O). HRMS: m/e found, 194.1315; Calcd. for $C_{12}H_{18}O_2$, 194.1307.

ACKNOWLEDGMENTS: We thank Prof. G. Mehta for his help, and the CSIR, New Delhi for the award of research fellowships to GVRS and SN.

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(Received in UK 18 November, 1991)