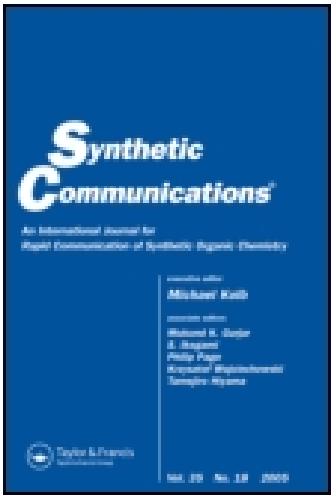

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Short New Route to the Chiral Spiro-Tetrahydrofuran Subunit Common to Some Terpenoids

Shital K. Chattopadhyay [a], Swastik Karmakar [a] & Kaushik Sarkar [a]
[a] Department of Chemistry, University of Kalyani, Kalyani, West Bengal, India
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Short New Route to the Chiral Spiro-Tetrahydrofuran Subunit Common to Some Terpenoids

Shital K. Chattopadhyay, Swastik Karmakar, and Kaushik Sarkar
Department of Chemistry, University of Kalyani, Kalyani, West Bengal, India

Abstract: Synthetic strategy based on a stereoselective iodoetherification reaction of a carvone-derived hydroxyalkene unit has been developed for the asymmetric synthesis of the key spiro-tetrahydrofuran subunit common to some naturally occurring terpenoids.

Keywords: Spirocycle, carvone, Barbier reaction, iodoetherification, terpenoid

INTRODUCTION

The spiro-tetrahydrofuran subunit embodied in the structure **1** (Fig. 1) is a common structural feature found in some norisoprenoid spiroethers that have flavoring and organoleptic properties such as theaspirone (**2**)[1] and vetispirane (**3**),[2] the principal aroma components of tea and vanilla respectively. The basic ring system is also found in the marine natural products dactyloxenes B[3] and C[4] (**3, 4**). Because of their interesting structural features and importance as flavoring and organoleptic agents, a number of synthetic efforts have been devoted[5] to the synthesis of these natural products as well as some of their analogues.[6] With a few exceptions, the great majority of these approaches have utilized α- or β-ionones as the starting

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Address correspondence to Shital K. Chattopadhyay, Department of Chemistry, University of Kalyani, Kalyani 741235, West Bengal, India. E-mail: skchatto@yahoo.com

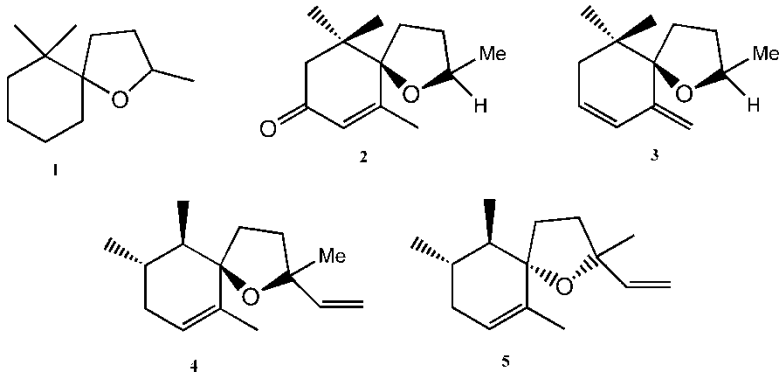


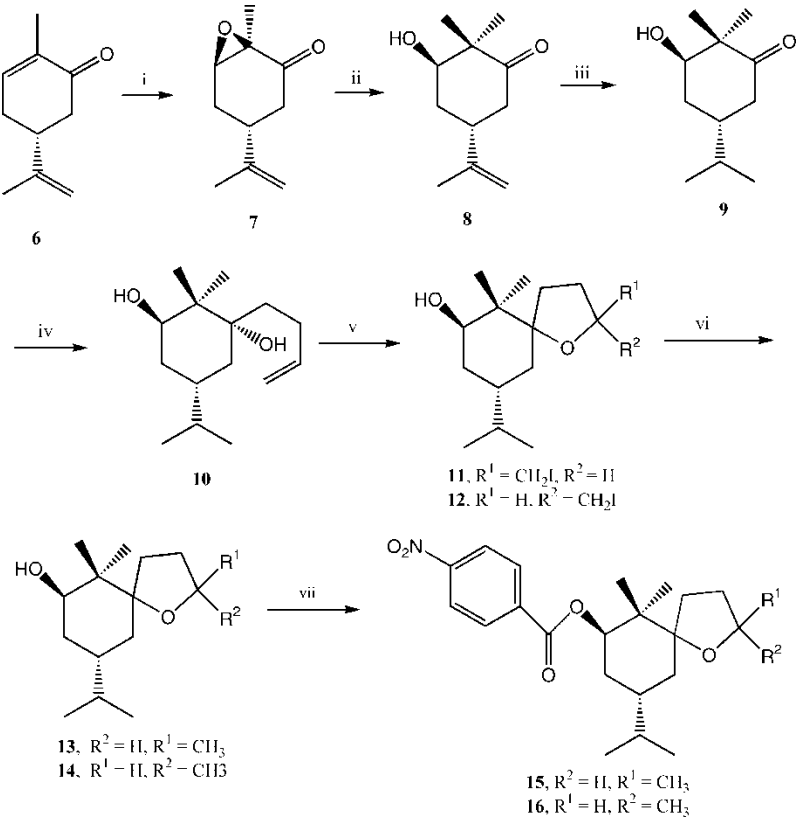
Figure 1. Natural products containing spirotetrahydrofuron subunit **1**.

material, and the spiro-tetrahydrofuran unit has been constructed by dehydration of a diol unit. A conceptually different approach[7] is Paquette's oxonium-ion-induced pinacol rearrangement of a tailored substrate as described for the synthesis of theaspirone. In continuation of our work[8] on the utility of carvone as a chiral-pool material, herein we describe our efforts toward the synthesis of the key spiro-tetrahydrofuran unit present in some of these natural products.

RESULTS AND DISCUSSION

Our synthetic approach commenced from the cheaper, more available R(−)-carvone, which was readily elaborated to the hydroxyketone **8** (Scheme 1) via a two-step sequence involving reductive methylation of the derived epoxyketone **7** as described previously.[9] Although none of the projected natural products contain the pendant isopropenyl group, the conversion of the latter to the required enone functionality through a Criegge-type rearrangement has been amply demonstrated.[10] However, for the present study, the isopropenyl group in **8** was reduced to the corresponding saturated ketone **9**. In line with our earlier observations,[8] Barbier-type addition of 4-bromo-1-butene to **9** proceeded with high diastereoselectivity, and the diol **10** was obtained in good yield after removal of the minor isomer (6%). Iodoetherification of chiral hydroxylalkenes has emerged[11] as a valuable tool for the stereoselective construction of several oxacyclic systems with various levels of 1,2-, 1,3- or 1,4-asymmetric inductions.[12] We wondered whether iodoetherification of the hydroxyalkene **10** would provide any useful level of stereoselectivity.

When the halocyclization of **10** was attempted with iodine in acetonitrile in the presence of sodium bicarbonate, the isomeric iodoethers **11, 12** formed in good yield but as an inseparable mixture (∼60 : 40). However, upon reduction[13] with tributyltin hydride in the presence of azoisobutyronitrile (AIBN), a separable



Scheme 1. (i) H_2O_2, NaOH, 0°C, 4 h, 98%; (ii) Li, NH_3, MeI, − 33°C to rt, 3 h, 61%; (iii) H_2, Pd-C (10%), ethanol, rt, 4 h, 94%; (iv) 4-bromo-1-butene, Li, THF, ultrasound, rt, 0.5 h, 61%; (v) I_2, $NaHCO_3$, CH_3CN, 0°C, 4 h, 70%; (vi) n-Bu_3SnH, AIBN, benzene, reflux, 5 h, 74%; (vii) *p*-nitrobenzoyl chloride, Et_3N, CH_2Cl_2, 4 h, 92%.

mixture of the spiro-tetrahydrofurans **13, 14** were obtained as viscous liquids in good yield. Although the gross structures of the products were easily secured from their spectroscopic properties, assignment of the stereochemistry at the newly formed stereocenter (C2) in either of these products proved to be difficult. To this end, the corresponding *p*-nitrobenzoates **15, 16** were prepared using conventional conditions. However, although the products were obtained as colorless low-melting solids, suitable crystals for examination could not be obtained.

In short, we have demonstrated that the spiro-tetrahydrofuran ring system found in some important natural products could be conveniently prepared using iodoetherification of an appropriate hydroxyalkene derived from carvone.[14] The marginal 1,4-asymmetric induction observed during the process may provide access to the proper stereoisomers as well as analogues of some of the natural products mentioned.

EXPERIMENTAL

Melting points were determined in a sulphuric-acid bath and are uncorrected. IR spectra were recorded on a Perkin Elmer 1330 apparatus purchased in a DST-FIST grant. ^{1}H NMR and ^{13}C NMR spectra were recoded on a Bruker 300-MHz instrument at the Indian Institute of Chemical Biology, Kolkata, India. Mass spectra and elemental analyses were obtained as a paid service from CDRI, Lucknow & I.I.C.B., Kolkata, India. Silica gel (60–120 mesh) was obtained from Spectrochem, India. Peteroleum ether refers to the fraction boiling in the range 60–80°C.

(3R, 5S)-3-Hydroxy-5-isopropyl-2,2-dimethylcyclohexan-1-one (9): A solution of the hydroxyketone **8** (2.00 g, 10.9 mmol) in dry ethanol (30 mL) was vigorously stirred under a hydrogen atmosphere in the presence of Pd-C (10%, 10 mg) for 24 h at room temperature. The heterogeneous mixture was then filtered through celite and the filter cake was washed with ethanol. The combined organic solution was then concentrated in vacuo to leave the crude product as a colorless liquid, which was purified by chromatography over silica gel using a mixture of petroleum ether and ethyl acetate (10 : 1) as eluent. The product was obtained as a colorless viscous liquid (1.89 g, 94%).

$[\alpha]_D$: +13.35 (c, 1.7 in $CHCl_3$). IR (neat): 3392, 2958, 1704, 1041 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.67–3.3.62$ (m, 1 H), 3.53 (brs, 1 H), 1.78–1.63 (m, 3 H), 1.52–1.38 (m, 3 H), 1.11 (s, 3 H), 0.84 (s, 3H), 0.82 (s, 3 H), 0.79 (s, 3 H). Anal. calcd. for $C_{11}H_{20}O_2$ (184.28): C, 71.70; H, 10.94. Found: C, 71.55; H, 11.08.

(1S, 3R, 5S)-1-(3-butenyl)-5-isopropyl-2,2-dimethylcyclohexane-1,3-diol (10): A heterogeneous mixture of the saturated ketone **9** (1.80 g, 9.77 mmol), 4-bromo-1-butene (3 mL, 29.4 mmol) and small pieces of lithium (411 mg, 59 mmol) in dry tetrahydrofuran (40 mL) was sonicated under nitrogen atmosphere for 30 min. The reaction mixture was then cooled to 0°C and carefully quenched by dropwise addition of methanol (1 mL) followed by saturated ammonium-chloride solution (10 mL). It was then extracted with ether (3 × 50 mL) and the combined extract was washed sequentially with water (1 × 50 mL) and brine (1 × 50 mL), and then dried (Na_2SO_4). It was filtered, and the filtrate was concentrated to leave the crude product as a pale yellow oil, which was purified by chromatography over silica gel using a mixture of petroleum ether and ethyl acetate (9 : 1) as eluent. The product was obtained as a colorless viscous liquid (1.45 g, 61%).

$[\alpha]_D$: +10 (c, 0.25 in $CHCl_3$). IR (neat): 3400, 2990, 1650, 1110 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.92–5.79$ (m, 1 H), 5.06 (d, 1 H, $J = 17.2$ Hz), 4.97 (d, 1 H, $J = 10.1$ Hz), 3.82 (dd, 1 H, $J = 11.7, 4.3$ Hz), 2.19–2.08 (m, 2 H), 1.77–1.65 (m, 3 H), 1.59–1.41 (m, 3H), 1.25–1.09 (m, 2 H), 1.11 (s, 3 H), 0.92 (d, 3H, $J = 5.9$ Hz), 0.88 (d, 3 H, $J = 5.9$ Hz),

0.83 (s, 3 H). ^{13}C NMR (75 MHz, CDCl3): $\delta = 139.5$ (d), 114.4 (t), 79.4 (d), 77.3 (s), 40.1 (s), 35.8 (t), 34.9 (t), 32.3 (d), 32.0 (d), 31.7 (t), 26.8 (t), 23.8 (q), 20.6 (q), 19.8 (q), 19.4 (q). Anal. calcd. for $C_{15}H_{28}O_2$ (240.38): C, 74.95; H, 11.74. Found: C, 75.19; H, 11.98.

(2R/S,5S,7R,9S)-2-(iodomethyl)-9-isopropyl-6,6-dimethyl-1-oxaspiro[4.5] decan-7-ol (11 and 12): Iodine (1.03 g, 8.10 mmol) and sodium bicarbonate (680 mg, 8.10 mmol) were sequentially added to a stirred solution of the hydroxyalkene **10** (650 mg, 2.71 mmol) in dry acetonitrile (15 mL) at 0°C under a nitrogen atmosphere, and stirring was continued for 4 h. The mixture was then diluted with ether (100 mL) and the ether solution was washed successively with sodium thiosulphate solution (10%, 3 × 50 mL), sodium bicarbonate solution (5%, 3 × 50 mL), and brine (1 × 50 mL). It was then dried (Na_2SO_4) and filtered, and the filtrate was concentrated to leave the crude product as a pale yellow liquid, which was purified by chromatography over silica gel using petroleum ether–ethyl acetate mixture (19 : 1) as eluent. The mixture of the diastereomers **11** and **12** was obtained as a colorless liquid (702 mg, 70.6%).

Data for the mixture: IR (KBr): 3417, 2926, 2872, 1466, 1364, 1261, 1024, 802 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.16–4.06$ (m, 1 H), 3.80–3.70 (m, 2 H), 3.35–3.19 (m, 1 H), 2.16–2.10 (m, H), 1.74–1.58 (m, H), 1.31–1.20 (m, H), 0.98 (d, 3 H, $J = 3.6$ Hz), 0.93 (s, 3 H), 0.88 (d, 3H, $J = 6.5$ Hz), 0.79 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 89.5, 79.3, 75.6, 75.3, 74.6, 43.8, 42.9, 38.6, 38.4, 37.8, 36.3, 33.7, 33.3, 32.6, 32.3, 32.2, 21.0, 19.9, 19.8, 19.6, 19.5, 16.1, 12.3, 11.5. Anal. calcd. for $C_{15}H_{27}IO_2$ (366.28): C, 49.19; H, 7.43; I, 34.65. Found: C, 49.45; H, 7.60; I, 34.96.

(2R/S,5S,7R,9S)-9-isopropyl-2,6,6-trimethyl-1-oxaspiro[4,5]decan-7-ol (13 and 14): A solution of tri-n-butyltinhydride (0.96 mL, 3.56 mmol) in dry and degassed benzene (2 mL) was added dropwise to a refluxing solution of the mixture of **11** and **12** (650 mg, 1.78 mmol) and AIBN (292 mg, 1.78 mmol) in dry and degassed benzene (5 mL), and refluxing was continued for 5 h. It was then concentrated in vacuo and the residual mass was purified by flash chromatography using a mixture of petroleum ether–EtOAc (19 : 1) as eluent.

The major product was obtained as a colorless viscous liquid (191 mg, 45%). $[\alpha]_D$: +3.5 (c, 0.4 in $CHCl_3$). IR (neat): 3400, 2960, 2880, 1450, 1400, 1380, 1080, 1010 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.02–3.93$ (m, 1 H), 3.75 (dd, 1 H, $J = 11.7$, 4.5 Hz), 2.08–1.87 (m, 2 H), 1.75–1.39 (m, 4 H), 1.36–1.18 (m, 4 H), 1.20 (d, 3 H, $J = 6.3$ Hz), 0.99 (s, 3 H), 0.88 (d, 3 H, $J = 5.2$ Hz), 0.86 (d, 3 H, $J = 4.9$ Hz), 0.79 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 88.1$ (s), 77.0 (d), 75.1 (d), 42.9 (s), 38.6 (t), 36.6 (d), 34.1 (t), 33.8 (t), 33.7 (t), 32.4 (d), 22.5 (q), 20.0 (q), 19.9 (q), 19.7 (q), 16.4 (q). m/z (EI, 70 eV): 240 (M^+),197, 179, 124, 71, 57, 43. Anal. calcd. for $C_{15}H_{28}O_2$ (240.38): C, 74.95; H, 11.74. Found: C, 75.19; H, 11.96.

The minor isomer was also obtained as a colorless viscous liquid (124 mg, 29%). $[\alpha]_D$: +8 (c, 0.1 in MeOH). IR (neat): 3412, 2965, 1445, 1230 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 4.15–3.90$ (m, 1 H), 3.45–3.25 (m, 1 H), 2.32–2.15 (m, 2 H), 1.96–1.95 (m, 2 H), 1.64–1.56 (m, 2 H), 1.28–1.10 (m, 4 H), 1.20 (d, 3 H, $J = 4.5$ Hz), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.87 (d, 3 H, $J = 1.6$ Hz), 0.85 (d, 3 H, $J = 1.6$ Hz).^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 87.6$(s), 77.4 (d), 74.5 (d), 42.1 (s), 38.4 (t), 36.9 (d), 34.7 (t), 34.0 (t), 33.5 (t), 31.8 (d), 22.8 (q), 20.1 (q), 19.7 (q), 19.5 (q), 16.3 (q). Anal. calcd. for $C_{15}H_{28}O_2$ (240.38): C, 74.95; H, 11.74. Found: C, 75.08; H, 11.88.

(2R/S,5S,7R,9S)-9-isopropyl-2,6,6-trimethyl-1-oxaspiro[4.5]dec-7-yl-4-nitro-benzoate (15 and 16): 4-Nitrobenzoyl chloride (86 mg, 0.5 mmol) was added in one portion to a stirred solution of the major alcohol **13/14** (100 mg, 0.41 mmol) and triethylamine (0.23 mL, 0.83 mmol) in dry dichloromethane (2 mL), and the resulting mixture was stirred for 4 h at room temperature. It was then diluted with dichloromethane (20 mL) and the organic extract was washed with hydrochloric acid (5%, 2 × 10 mL), sodium bicarbonate (10%, 2 × 20 mL), water (2 × 10 mL), and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated to leave the crude product as a brownish oil, which was purified by chromatography over silica gel using a mixture of petroleum ether–EtOAc (49 : 1) as eluent. The product **15/16** was obtained as a colorless solid (150 mg, 92%).

Mp 64°C. $[\alpha]_D$: +25 (c, 0.5 in $CHCl_3$). IR (neat): 2960, 1720, 1600, 1520, 1340, 1310, 1220, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.29$ (d, 2 H, $J = 8.8$ Hz), 8.21 (d, 2 H, $J = 8.8$ Hz), 5.30 (dd, 1 H, $J = 11.8$, 4.6 Hz), 4.04–3.97 (m, 1 H), 2.09–2.01 (m, 1H), 1.97–1.88 (m, 2H), 1.79–1.72 (m, 2 H), 1.53–1.47 (m, 2 H), 1.45–1.36 (m, 3 H), 1.22 (d, 3 H, $J = 7.1$ Hz), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.88 (s, 3 H, $J = 7.8$ Hz), 0.85 (d, 3 H, $J = 8.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.1$ (s), 150.4 (s), 136.4 (s), 130.6 (d), 123.5 (d), 87.5 (s), 80.2 (d), 77.4 (d), 42.2 (s), 38.2 (t), 36.1 (d), 33.7 (t), 32.2 (d), 30.1 (t), 29.7 (t), 22.2 (q), 19.9 (q), 19.7 (q), 19.4 (q), 17.7 (q). HRMS: m/z calcd. for $C_{22}H_{31}NO_5$: 389.22021, found: 389.22028.

The minor alcohol **14/13** analogously gave the p-nitrobenzoate derivative **16/15** as a colorless solid. Mp. 59°C. $[\alpha]_D$: +7.3 (c, 0.3 in $CHCl_3$). IR (neat): 2965, 1714, 1330, 1233, 1115 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.29$ (d, 2 H, $J = 8.8$ Hz), 8.20 (d, 2 H, $J = 8.9$ Hz), 4.90 (dd, 1 H, $J = 10.9$, 4.4 Hz), 4.11–4.05 (m, 1 H), 2.11–2.00 (m, 2H), 1.82–1.75 (m, 2H), 1.68–1.52 (m, 3 H), 1.48–1.34 (m, 3 H), 1.24 (d, 3 H, $J = 6.09$ Hz), 1.18 (s, 3 H), 0.95 (s, 3 H), 0.90 (d, 3 H, $J = 6.6$ Hz), 0.88 (d, 3 H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (s), 150.5 (s), 136.1 (s), 130.6 (d), 123.5 (d), 87.2 (s), 79.4 (d), 76.0 (d), 43.0 (s), 38.3 (t), 38.2 (d), 34.0 (t), 32.3 (d), 31.3 (t), 29.6 (t), 22.4 (q), 21.3 (q), 19.8 (q), 19.5 (q), 17.0 (q). m/z (EI, 70 eV): 389 (M^+, 10%), 346 (38%), 179 (100%). Anal. calcd. for $C_{22}H_{31}NO_5$ (389.49): C, 67.84; H, 8.02; N, 3.59. Found: C, 68.16; H, 8.29; N, 3.44.

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