Convenient Isoprenylation of Aldehydes and Ketones: Synthesis of (±)-Ipsdienol and (±)-Ipsenol

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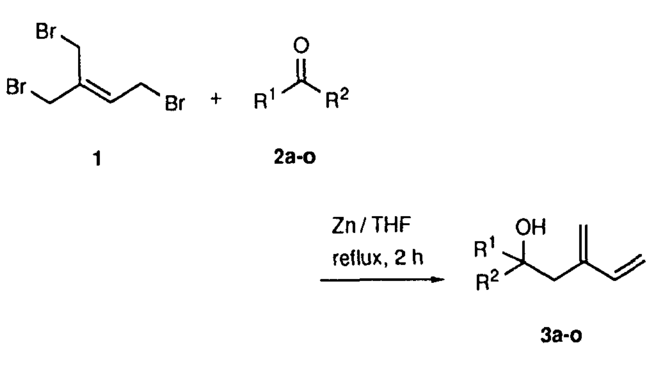
The reaction of 2-bromomethyl-1,4-dibromo-2-butene (**1**) with various aldehydes and ketones in tetrahydrofuran containing zinc powder under reflux gave the corresponding isoprenylated alcohols **3a–o** in one step in good yields. The synthesis of ipsdienol (**3e**) and ipsenol (**3c**) was achieved by the present method starting from 3-methyl-2-butenal (**2e**) and isovaleraldehyde (**2c**).

The introduction of an isoprenyl group is of importance in organic synthesis, since compounds containing an isoprene unit are useful precursors for the Diels–Alder reaction[1] and are widely distributed in nature. These compounds can be conveniently prepared by the direct isoprenylation of various electrophiles with isoprenes metalated by alkali metal,[2] zinc,[3–5] silicon,[6] tin,[7] chromium,[8] and boron metal,[9] although several other methods have also been reported.[10] However, direct isoprenylation with metalated isoprenes has a drawback, since 2-halomethyl-1,3-butadiene, a precursor for metalated isoprenes, can only be prepared in low yield by a troublesome, multistep procedure[3,11] and cannot be easily purified due to its ready polymerization.

We have now developed a simple method for the isoprenylation of aldehydes and ketones with 2-bromomethyl-1,4-dibromo-2-butene (**1**). Tribromide **1** is readily prepared by the 1,4-bromination of isoprene followed by allylic bromination,[5] and is easily purified by distillation. The reduction of **1** with metallic zinc in the presence of aldehydes or ketones gave the corresponding isoprenylated carbinols in one step in good yields. In this paper, an application of this procedure to the synthesis of ipsenol (**3c**) and ipsdienol (**3e**), principal components of the aggregation pheromones of a bark beetle, *Ips paraconfusus* Lanier,[3,12] is described. This synthesis is probably one of the simplest methods amongst many existing methods,[2b–d,3,5–9,10a–b,13] including chiral synthesis.[14]

The reaction of 2-bromomethyl-1,4-dibromo-2-butene (**1**) with 2 equivalents of isovaleric aldehyde (**2c**) in the presence of 2.5 equivalents of zinc powder in tetrahydrofuran under reflux gave the isoprenylated alcohol, ipsenol (**3c**). The results of the isoprenylation of **2c** under various conditions are summarized in Table 1. Stirring a mixture containing **1**, **2c**, and zinc powder at room temperature for 5 days gave only trace amounts of **3c** (run 1). The reaction in tetrahydrofuran under reflux (runs 2–5) and at a higher concentration of the reagents (runs 4 and 5) enhanced the yield of **3c**. The isoprenylation of various aldehydes **2a–2k** and ketones **2l–2o** under the same conditions as those of run 5 (Table 1) similarly gave the corresponding isoprenylated alcohols **3a–o** in isolated yields of 50–87%. Isolated yields and their spectral data for **3a–o** are summarized in Table 2. The functional groups, such as a carbon–carbon double bond conjugated with a carbonyl group (**2d** and **2e**) and a chloro or an alkoxycarbonyl group attached to an aromatic ring (**2g** or **2h**), were not reduced by metallic zinc under the present conditions. Isoprenylated products **3d**, **3e**, **3g**, and **3h** were obtained in good yields from the corresponding aldehydes. The isoprenylation of straight-chain aldehydes **2a** and **2b** gave the corresponding alcohols **3a** and **3b** in 55 and 87% yield, respectively, although the reaction of these aldehydes with metalated isoprene was reported to give low yields of the isoprenylation products,[2c,6] probably due to aldol condensations.



2,3	R^1	R^2	2,3	R^1	R^2
a	C_3H_7	H	**i**	4-$MeOC_6H_4$	H
b	C_9H_{19}	H	**j**	2-$MeOC_6H_4$	H
c	Me_2CHCH_2	H	**k**	2-furyl	H
d	$CH_3CH{=}CH$	H	**l**	Et	Me
e	$Me_2C{=}CH$	H	**m**	$-(CH_2)_5-$	
f	Ph	H	**n**	Ph	Me
g	4-ClC_6H_4	H	**o**	Ph	Ph
h	4-$MeO_2CC_6H_4$	H			

Table 1. Isoprenylation of **2c** under Various Conditions

Run	Concentration of **1** (M)	Reaction Time (h) reflux	Reaction Time (h) r.t.	Yield of **3c** (%)[a]
1	3.3×10^{-2}[b]	0	120	trace
2	3.3×10^{-2}[b]	1	2	30
3	3.3×10^{-2}[b]	2	2	40
4	5.0×10^{-1}[c]	0.5	2	89
5	5.0×10^{-1}[c]	2	2	93

[a] Determined by NMR using an internal standard.
[b] **1** (0.65 mmol), **2c** (1.3 mmol), Zn (1.6 mmol), THF (20 mL).
[c] **1** (3 mmol), **2c** (6 mmol), Zn (7.5 mmol), THF (6 mL).

In summary, the foregoing results indicate that 2-bromomethyl-1,4-dibromo-2-butene (**1**) can serve as a good synthetic equivalent of the isoprenyl anion.

Table 2. Isoprenylated Products 3 Prepared

Product	Yield (%)[a]	bp (°C)/Torr[b]	IR (neat) ν (cm^{-1})	^{1}H NMR (CDCl$_3$/TMS) δ, J (Hz)	MS m/z (%)
3a	55 (70)[c]	105–107/17	3382, 1635, 1596, 993, 900	0.94 (t, 3H, J = 7.0), 1.35–1.55 (m, 4H), 1.79 (br s, 1H), 2.22 (dd, 1H, J = 9.0, 13.9), 2.51 (dd, 1H, J = 3.7, 13.9), 3.76 (m, 1H), 5.09 (s, 1H), 5.11 (d, 1H, J = 10.6), 5.15 (s, 1H), 5.25 (d, 1H, J = 17.7), 6.39 (dd, 1H, J = 10.6, 17.7)	68 (56), 58 (57), 55 (37), 43 (100)
3b	87	74–79/0.6	3394, 1637, 1596, 990, 898	0.88 (t, 3H, J = 7.1), 1.27 (br s, 14H), 1.48 (br s, 1H), 1.49 (m, 2H), 2.22 (dd, 1H, J = 9.1, 13.9), 2.52 (dd, 1H, J = 3.4, 14.2), 3.74 (m, 1H), 5.09 (s, 1H), 5.11 (d, 1H, J = 10.7), 5.16 (s, 1H), 5.25 (d, 1H, J = 17.6), 6.39 (dd, 1H, J = 10.7, 17.6)	155 (15), 97 (15), 83 (26), 68 (92), 55 (55), 41 (100)
3c	74 (93)[c]	107–110/18	3370, 1630, 1595, 991, 898	0.92 (d, 3H, J = 6.8), 0.94 (d, 3H, J = 6.8), 1.27 (m, 1H), 1.46 (m, 1H), 1.63 (br s, 1H), 1.82 (m, 1H), 2.22 (dd, 1H, J = 9.1, 13.9), 2.49 (dd, 1H, J = 3.7, 13.9), 3.83 (m, 1H), 5.04 (s, 1H), 5.11 (d, 1H, J = 10.7), 5.16 (s, 1H), 5.25 (d, 1H, J = 17.6), 6.38 (dd, 1H, J = 10.7, 17.6)	85 (23), 68 (100), 57 (18), 45 (31), 43 (53)
3d	55	46–49/1.5	3374, 1674, 1635, 1595, 992, 965, 899	1.69 (s, 1H), 1.70 (d, 3H, J = 6.4), 2.37 (dd, 1H, J = 8.6, 14.2), 2.50 (dd, 1H, J = 4.4, 14.2), 4.23 (m, 1H), 5.10 (s, 1H), 5.13 (d, 1H, J = 10.7), 5.16 (s, 1H), 5.26 (d, 1H, J = 17.6), 5.52 (m, 1H), 5.70 (m, 1H), 6.39 (dd, 1H, J = 10.7, 17.6)	120 (5), 71 (100), 68 (28), 53 (24), 41 (40)
3e	68 (90)[c]	70–73/1.0	3356, 1679, 1639, 1596, 993, 901	1.64 (br s, 1H), 1.68 (s, 3H), 1.73 (s, 3H), 2.43 (dd, 1H, J = 8.3, 14.2), 2.46 (dd, 1H, J = 4.9, 14.2), 4.52 (dt, 1H, J = 4.9, 8.3), 5.09 (s, 1H), 5.12 (d, 1H, J = 10.7), 5.14 (s, 1H), 5.20 (d, 1H, J = 8.3), 5.28 (d, 1H, J = 17.6), 6.40 (dd, 1H, J = 10.7, 17.6)	85 (100), 67 (21), 55 (17), 41 (56)
3f	55 (72)[c]	60–62/1.0	3386, 1635, 1596, 1495, 994, 902, 757, 700	2.00 (br s, 1H), 2.57 (dd, 1H, J = 9.8, 14.2), 2.71 (dd, 1H, J = 4.4, 14.2), 4.85 (dd, 1H, J = 4.4, 9.3), 5.11 (s, 1H), 5.15 (d, 1H, J = 10.7), 5.18 (s, 1H), 5.33 (d, 1H, J = 17.6), 6.42 (dd, 1H, J = 10.7, 17.6), 7.3–7.4 (m, 5H)	107 (44), 79 (100), 77 (66), 68 (13), 51 (35), 41 (31)
3g	77	68–71/0.6	3380, 1635, 1596, 1493, 994, 904, 831	2.13 (br s, 1H), 2.52 (dd, 1H, J = 9.0, 14.0), 2.67 (dd, 1H, J = 4.3, 14.0), 4.82 (dd, 1H, J = 4.3, 9.0), 5.09 (s, 1H), 5.16 (d, 1H, J = 10.7), 5.18 (s, 1H), 5.31 (d, 1H, J = 17.5), 6.41 (dd, 1H, J = 10.7, 17.5), 7.32 (s, 4H)	141 (62), 113 (25), 77 (100), 68 (50), 51 (28)
3h	50	–[d]	3470, 1718, 1613, 1596, 1509, 993, 903, 758, 708	2.33 (br s, 1H), 2.54 (dd, 1H, J = 9.2, 14.2), 2.70 (dd, 1H, J = 4.3, 14.2), 3.91 (s, 3H), 4.89 (dd, 1H, J = 4.3, 9.2), 5.08 (s, 1H), 5.16 (d, 1H, J = 10.9), 5.18 (s, 1H), 5.32 (d, 1H, J = 17.8), 6.41 (dd, 1H, J = 10.9, 17.8), 7.44 (d, 2H, J = 8.3), 8.01 (d, 2H, J = 8.3)	201 (8), 165 (100), 105 (16), 77 (28), 68 (47), 59 (28)
3i	60 (81)[c]	84–86/0.3	3382, 1614, 1596, 1515, 1037, 995, 903, 833	2.06 (br s, 1H), 2.57 (dd, 1H, J = 8.6, 14.2), 2.67 (dd, 1H, J = 4.3, 14.2), 3.80 (s, 3H), 4.80 (dd, 1H, J = 4.3, 8.6), 5.09 (s, 1H), 5.14 (d, 1H, J = 10.9), 5.16 (s, 1H), 5.32 (d, 1H, J = 17.5), 6.41 (dd, 1H, J = 10.9, 17.5), 6.89 (d, 2H, J = 8.6), 7.30 (d, 2H, J = 8.6)	137 (100), 109 (27), 94 (16), 77 (19)
3j	56	–[d]	3430, 1632, 1593, 1491, 1049, 995, 906, 755, 735	2.42 (br s, 1H), 2.43 (dd, 1H, J = 9.4, 13.9), 2.87 (dd, 1H, J = 3.6, 13.9), 3.84 (s, 3H), 5.06–5.2 (m, 4H), 5.47 (d, 1H, J = 17.5), 6.43 (dd, 1H, J = 10.9, 17.8), 6.89 (d, 1H, J = 8.3), 6.98 (t, 1H, J = 7.6), 7.25 (m, 1H), 7.42 (d, 1H, J = 7.6)	137 (100), 109 (10), 107 (47), 77 (16)
3k	55	78–82/3.0	3374, 1633, 1597, 1506, 1012, 906, 811, 739	2.02 (br s, 1H), 2.71 (dd, 1H, J = 8.6, 14.2), 2.87 (dd, 1H, J = 4.6, 14.2), 4.88 (dd, 1H, J = 4.6, 8.6), 5.11 (s, 1H), 5.13 (d, 1H, J = 9.9), 5.18 (s, 1H), 5.29 (d, 1H, J = 17.8), 6.27 (d, 1H, J = 3.3), 6.33 (dd, 1H, J = 2.0, 3.3), 6.42 (dd, 1H, J = 10.6, 17.8), 7.39 (d, 1H, J = 2.0)	97 (100), 69 (10), 41 (32)
3l	24 (51)[c]	31–33/0.6	3398, 1634, 1594, 993, 902	0.95 (t, 3H), 1.13 (s, 3H), 1.53 (q, 2H), 1.60 (br s, 1H), 2.41 (s, 2H), 5.06 (s, 1H), 5.11 (d, 1H, J = 10.9), 5.25 (s, 1H), 5.32 (d, 1H, J = 17.5), 6.45 (dd, 1H, J = 10.9, 17.5)	73 (100), 68 (57), 57 (32), 55 (58), 43 (91)
3m	67 (87)[c]	45–48/1.2	3448, 1631, 1592, 989, 973, 898	1.3–1.7 (m, 11H), 2.40 (s, 2H), 5.04 (s, 1H), 5.11 (d, 1H, J = 10.6), 5.25 (s, 1H), 5.34 (d, 1H, J = 17.5), 6.44 (dd, 1H, J = 10.6, 17.5)	99 (100), 81 (81), 68 (48), 55 (39), 41 (48)
3n	74	54–57/0.2	3448, 1633, 1593, 1495, 992, 903, 767, 700	1.56 (s, 3H), 2.17 (s, 1H), 2.74 (s, 2H), 4.89 (s, 1H), 5.03 (d, 1H, J = 10.9), 5.19 (s, 1H), 5.25 (d, 1H, J = 17.5), 6.33 (dd, 1H, J = 10.9, 17.5), 7.2–7.5 (m, 5H)	121 (88), 105 (9), 77 (13), 43 (100)
3o	40 (67)[c]	–[d]	3562, 1632, 1595, 1494, 903, 755, 729, 699	2.68 (s, 1H), 3.27 (s, 2H), 4.76 (s, 1H), 4.95 (d, 1H, J = 10.9), 5.15 (s, 1H), 5.18 (d, 1H J = 17.2), 6.26 (dd, 1H, J = 10.9, 17.2), 7.2–7.6 (m, 10H)	183 (100), 105 (82), 77 (49), 71 (25), 51 (9)

[a] Yield of isolated products.

[b] Oven temperature in Kugelrohr distillation.

[c] NMR yield by an internal standard method.

[d] Not distilled due to decomposition or polymerization of the product.

Boiling points are uncorrected. The ^{1}H NMR spectra were measured with a JEOL EX-270 spectrometer (270 MHz), using TMS as an internal standard. The IR spectra were measured with a JASCO IR-810 spectrometer and the mass spectra with a JEOL JMS-D300 mass spectrometer.

2-Bromomethyl-1,4-dibromo-2-butene (1):

To a stirred solution of isoprene (68 g, 1.0 mol) in CCl_4 (120 mL) was added dropwise Br_2 (160 g, 1.0 mol) in CCl_4 (70 mL) over 8 h at 0 °C. The mixture was washed with sat. $NaHCO_3$ solution (3 × 50 mL), H_2O (3 × 50 mL), brine (60 mL), and dried ($MgSO_4$). Filtration followed by distillation gave 1,4-dibromo-2-methyl-2-butene; yield: 161 g (71 %); bp 40–42 °C/0.6 Torr.

IR (neat): ν = 1655, 1438, 1203 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.86 (d, 3 H, J = 1.3 Hz), 3.95 (s, 2 H), 3.97 (d, 2 H, J = 8.1 Hz), 5.90 (dt, 1 H, J = 1.3, 8.1 Hz).

MS (EI): m/z (%) = 230 (1.3), 228 (2.6), 226 (1.2), 149 (92), 147 (95), 82 (36), 80 (37), 68 (34), 67 (100), 53 (25), 41 (92), 40 (38), 39 (49).

A mixture of 1,4-dibromo-2-methyl-2-butene (161 g, 0.71 mol), *N*-bromosuccinimide (126 g, 0.71 mol), dibenzoyl peroxide (0.86 g, 3.6 mmol), and CCl_4 (140 mL) was heated under reflux for 2 h. After filtration, the mixture was washed with sat. $NaHCO_3$ solution (4 × 60 mL), H_2O (50 mL), and dried ($MgSO_4$). Filtration followed by distillation gave 2-bromomethyl-1,4-dibromo-2-butene (**1**); yield: 118 g (54 %); bp 74–78 °C/0.4 Torr [Lit.^{5} bp 60–95 °C/0.15 Torr]; n_D^{20} 1.6100.

IR (neat): ν = 3028, 1435, 1204 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.99 (d, 2 H, J = 8.4 Hz), 4.13 (s, 2 H), 4.17 (s, 2 H), 6.04 (t, 1 H, J = 8.4 Hz).

MS (EI): m/z (%) = 308 (2.8), 307 (2.3), 306 (2.8), 229 (54), 227 (100), 225 (57), 147 (67), 145 (63), 67 (66), 66 (53), 65 (76), 41 (49), 39 (58).

Isoprenylated Alcohols 3a–o; General Procedure:

A mixture of **1** (0.92 g, 3 mmol), aldehyde or ketone (6 mmol), and Zn powder (0.49 g, 7.5 mmol) in THF (6 mL) was refluxed for 2 h and stirred at r. t. for 2 h under an N_2 atmosphere. The mixture was dissolved in Et_2O (100 mL). The Et_2O solution was washed with sat. NH_4Cl solution (3 × 7 mL), H_2O (2 × 10 mL), brine (10 mL) and dried (Na_2SO_4). Filtration of the solution and evaporation of the solvent gave a crude product, which was subjected to either bulb-to-bulb distillation or preparative TLC (silica gel; hexane/Et_2O, 5:3) to give pure **3a–o**. The yields and spectral data of **3a–o** are summarized in Table 2.

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