Short Synthesis of (±)-Bakuchiol *via* a Geranylindium Reagent

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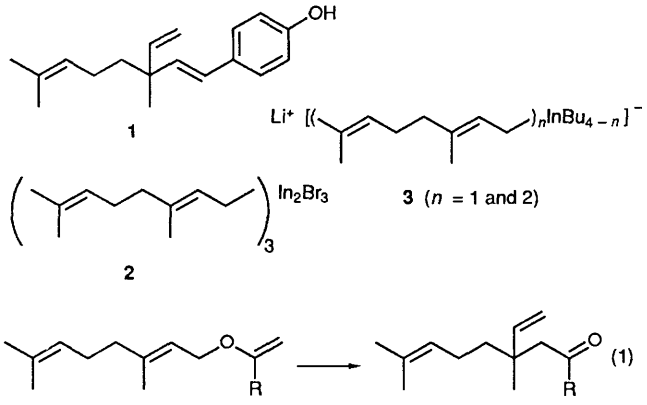
A short synthesis of (±)-bakuchiol was achieved starting with geranylindium sesquibromide and 2-(4-methoxyphenyl)acetaldehyde.

Bakuchiol **1** is a phenolic isoprenoid isolated from the seeds of the indian plant *Psoralea corylifolia* Linn.[1] Two total syntheses of this natural product have hitherto been achieved,[2,3] where the key step for the bakuchiol skeleton is the Claisen rearrangement of enol ethers of geraniol [eqn. (1)].



The coupling reaction of allylic organometallic reagents with carbonyl compounds is one of the fundamental methods for carbon–carbon bond formation. Various metals, including Li, Mg, Al, Zn and Cd, have been employed for this purpose.[4] With substituted allylic organometallic reagents, however, regioselectivity (α- *vs.* γ-coupling) often becomes a problem. Although coupling at the γ-carbon of allylic organometallics is predominant regardless of the metal, the γ-selectivity decreases with steric hindrance in the neighbourhood of the carbonyl group. Moreover, general and efficient preparative methods for allylic organometallic reagents other than simple allylic systems are lacking.

We recently reported a convenient synthesis of a variety of allylic indium reagents and their reaction with carbonyl compounds.[5] The coupling occurs at the γ-carbon of the allylic indium reagents. This high γ-selectivity allows a simple total synthesis of (±)-**1** to be undertaken starting with geranylindium sesquibromide **2**.

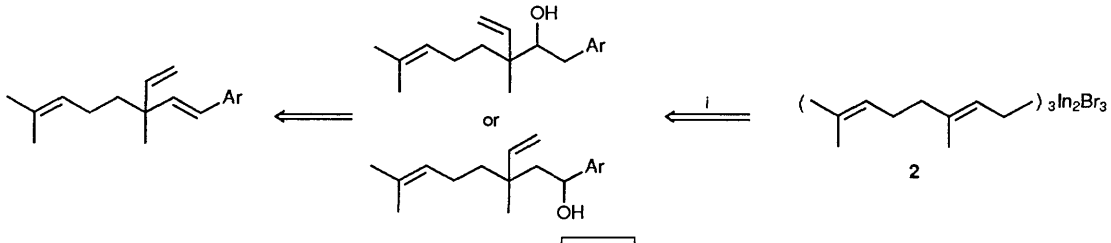
Results and Discussion

For the construction of the bakuchiol skeleton, an aryloxirane and a 2-arylacetaldehyde are considered to be appropriate electrophiles for the coupling with geranylindium reagent **2** (Scheme 1). Although allylic indium sesquihalides are known to couple with carbonyl compounds at the γ-position,[5] regioselectivity in the reactions with oxiranes is unknown. Therefore we first examined the reaction of geranylindium sesquibromide **2** with styrene oxide as a model reaction. The reaction was, however, sluggish owing to the low reactivity of styrene oxide, and after a prolonged reaction time a complex mixture of products was obtained, from which no expected products could be isolated. Even with geranylindate **3**,[6] which has a higher nucleophilicity than the sesquibromide **2**, no desired products were formed.

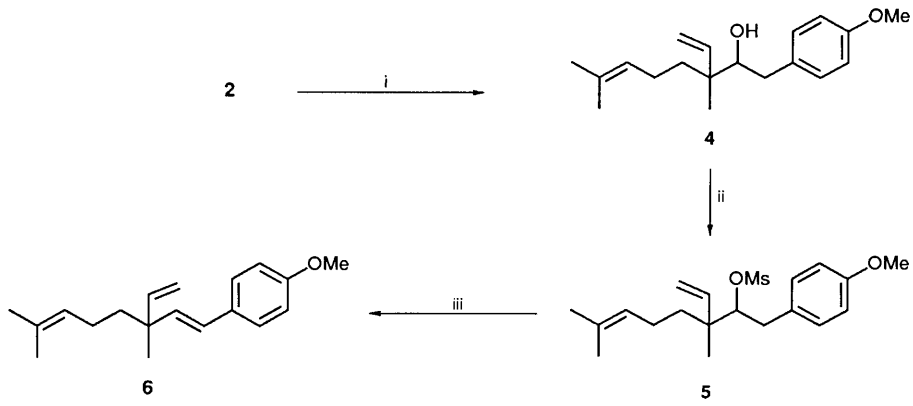
On the other hand, geranylindium reagent **2** smoothly reacted with 2-(4-methoxyphenyl)acetaldehyde to afford the alcohol **4** in 85% yield (Scheme 2). As expected, the reaction is regiospecific; the product formed by coupling at the α-carbon of reagent **2** was not formed. ^1H and ^{13}C NMR analysis showed that the product **4** was a diastereoisomeric mixture (*ca.* 8:2); presumably the major diastereoisomer is *erythro via* the chair-form transition state shown in equation (2). When substrate **4** was treated with phosphoryl trichloride in pyridine, dehydration occurred. However, an unexpected rearrangement took place during the reaction; vinyl-migration compound **8** was the major product and the expected bakuchiol methyl ether **6** was not found in the reaction mixture. Undoubtedly, compound **8** was formed *via* carbonium ion **7**. It is interesting to compare this result with the fact that bakuchiol itself is acid labile; on treatment with acid, it cyclizes to the *p*-menth-8-ene derivative **10** *via* the benzylic carbonium ion **9** (Scheme 3).[2,3]

The dehydration of the alcohol **4** to bakuchiol methyl ether **6** was eventually achieved *via* the mesyl ester **5**. Mesylation of compound **4** with mesyl chloride–pyridine gave the mesylate **5**, which is sensitive to silica gel; attempted purification by column chromatography on silica gel resulted in rearrangement to the triene **8** *via* the same intermediate **7**. However, treatment of the crude mesylate **5** with potassium *tert*-butoxide gave compound **6** in 80% yield. Thus, bakuchiol methyl ether **6** was synthesized from geranylindium sesquibromide **2** in 3 steps in 66% overall yield. Demethylation of the methyl ether **6** to bakuchiol **1** is known in the literature (methylmagnesium iodide, 93%).[2]

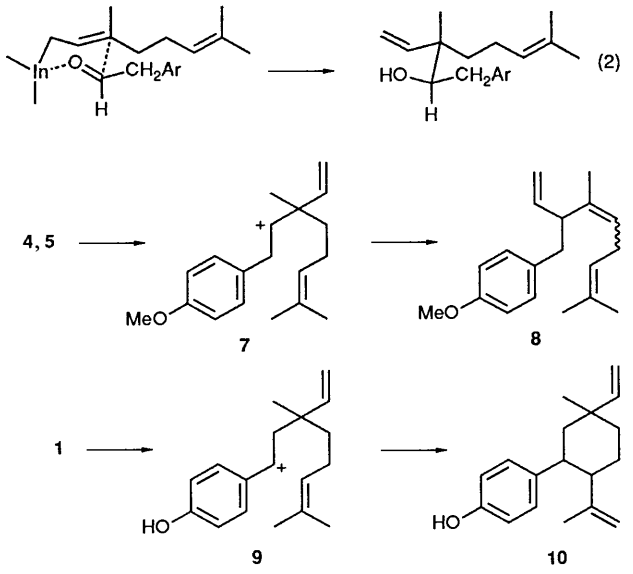
Our synthetic route is shorter and more convenient than the existing ones,[2,3] giving a higher yield of the product. This simple



Scheme 1 *Reagent:* i, $ArCHCH_2O$ or $ArCH_2CHO$



Scheme 2 *Reagents and yields:* i, 4-$MeOC_6H_4CH_2CHO$, 85%; ii, $MeSO_2Cl$, pyridine, 97%; iii, Bu^tOK, 80%



Scheme 3

synthesis of (±)-bakuchiol **1** demonstrates the usefulness of organoindium reagents in synthetic chemistry.

Experimental

IR spectra were recorded for neat oils on a JASCO A-102 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ on a Hitachi R-90 (90 MHz) and a Varian XL-200 (50 MHz) spectrometer, respectively, with Me_4Si as internal standard; *J*-values are given in Hz. Elemental analyses were performed at the Elemental Analysis Centre of Kyoto University. All reactions were carried out under argon.

1-(4-*Methoxyphenyl*)-3,7-*dimethyl*-3-*vinyloct*-6-*en*-2-*ol* **4**.—To a mixture of indium powder (127 mg, 1.1 mmol) and 2-(4-methoxyphenyl)acetaldehyde[7] (134 mg, 1 mmol) in *N*,*N*-dimethylformamide (1 cm^3) at room temperature was added geranyl bromide (358 mg, 1.65 mmol). A reaction started immediately (exothermic). The mixture was stirred at room temperature for 3 h. Dil. hydrochloric acid (1 mol dm^{-3}) was added and the product was extracted with diethyl ether. The extracts were washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel with dichloromethane as eluent to afford the *title compound* **4** (244 mg, 85%) as an oil, b.p. 180 °C/3 mmHg (bath temp.) (Found: C, 78.8; H, 9.9. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%); ν_{max}/cm^{-1} 3450, 2930, 1610, 1514, 1246, 1178 and 1038; δ_H (for major diastereoisomer) 1.04 (3 H, s, Me), 1.45 (2 H, m, CH_2), 1.54 (3 H, s, Me), 1.62 (3 H, s, Me), 1.84 (2 H, m, CH_2), 2.00 (1 H, s, OH), 2.32 (1 H, dd, *J* 14, 11, C*H*H), 2.75 (1 H, dd, *J* 14, 2, CH*H*), 3.44 [1 H, m, C*H*(OH)], 3.73 (3 H, s, OMe), 4.9–5.3 (3 H, m, olefinic), 5.76 (1 H, dd, *J* 17, 11, olefinic) and 6.93 (4 H, AA'BB', ArH); δ_C (for major diastereoisomer) 17.3 (q), 17.5 (q), 22.5 (t), 25.5 (q), 37.4 (t × 2), 44.3 (s), 55.0 (q), 78.8 (d), 113.8 (d), 114.0 (t), 124.7 (d), 130.0 (d), 131.0 (s), 131.7 (s), 143.5 (d) and 158.0 (s).

3-(4-*Methoxyphenyl*)-4,8-*dimethylnona*-1,4,7-*triene* **8**.—To a solution of the alcohol **4** (69 mg, 0.24 mmol) in pyridine (0.5 cm^3) was added phosphoryl trichloride (39 mg, 0.25 mmol), and the mixture was stirred at room temperature for 21 h. Water was added and the product was extracted with diethyl ether. The extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was distilled (b.p. 150–160 °C/3 mmHg, bath temp.) to give a mixture of triene **8** and its isomers (55 mg, 85%). The purity of compound **8** was *ca.* 80% by GLC (Found: C, 84.1; H, 9.8. $C_{19}H_{26}O$ requires C, 84.4; H, 9.7%); ν_{max}/cm^{-1} 2930, 1610, 1514, 1440, 1244, 1176, 1036, 910 and 820; δ_H 1.61 (6 H, s, Me), 1.70 (3 H, s, Me), 2.06 (1 H, m, CH), 2.6–3.0 (4 H, m, CH_2), 3.80 (3 H, s, OMe), 4.84–5.2 (4 H, m, olefinic), 5.65–5.95 (1 H, m, olefinic) and 6.94 (4 H, AA'BB', ArH); δ_C 13.9 (q), 17.7 (q), 25.6 (q), 26.9 (t), 38.2 (t), 54.5 (d), 55.1 (q), 113.3 (d), 114.4 (t), 123.1 (d), 124.8 (d), 130.0 (d), 132.7 (s), 135.7 (s), 140.7 (d), 140.8 (s) and 157.6 (s).

1-(4-*Methoxyphenyl*)-3,7-*dimethyl*-3-*vinyloct*-6-*en*-2-*yl Methanesulphonate* **5**.—To a solution of the alcohol **4** (154 mg, 0.53 mmol) in pyridine (2 cm^3) was added mesyl chloride (63 mg, 0.55 mmol) and the mixture was stirred at room temperature for 13 h. Water was added and the product was extracted with diethyl ether. The extracts were washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was almost pure mesyl ester **5** (188 mg, 97%), and was used for the next reaction without further purification; ν_{max}/cm^{-1} 2950, 1518, 1358, 1340, 1252, 1174 and 906; δ_H 1.16 (3 H, s, Me), 1.50 (2 H, m, CH_2), 1.58 (3 H, s, Me), 1.64 (3 H, s, Me), 1.90 (2 H, m, CH_2), 2.12 (3 H, s, OMs), 2.70 (1 H, dd, *J* 15, 11, C*H*H), 2.96 (1 H, dd, *J* 15, 3, CH*H*), 3.76 (3 H, s, OMe), 4.6–5.4 (3 H, m, olefinic), 4.84 (1 H, dd, *J* 11, 3, C*H*OMs), 5.80 (1 H, dd, *J* 17, 11, olefinic) and 6.98 (4 H, AA'BB', ArH).

When mesyl ester **5** was subjected to column chromatography (SiO_2; benzene–CH_2Cl_2), a mixture consisting of the triene **8** and its isomers was obtained.

Bakuchiol Methyl Ether **6**.—A mixture of mesyl ester **5** (188 mg, 0.51 mmol) and potassium *tert*-butoxide (112 mg, 1.0 mmol) was stirred in dry dimethyl sulphoxide (3 cm^3) at ~80 °C

for 2.5 h. The mixture was cooled to room temperature and poured into water. The product was extracted with diethyl ether and the extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was distilled to give the title compound **6** (110 mg, 80%) as an oil, b.p. 150 °C/3 mmHg (bath temp.); ν_{max}/cm^{-1} 2970, 1606, 1514, 1248, 1176 and 1038; δ_H 1.16 (3 H, s, Me), 1.48 (2 H, m, CH_2), 1.56 (3 H, s, Me), 1.66 (3 H, s, Me), 1.92 (2 H, m, CH_2), 3.76 (3 H, s, OMe), 4.8–5.2 (3 H, m, olefinic), 5.84 (1 H, dd, *J* 18, 10, olefinic), 6.08 (1 H, d, *J* 17, olefinic), 6.24 (1 H, d, *J* 17, olefinic) and 7.04 (4 H, AA′BB′, ArH); δ_C 17.6 (q), 23.2 (t), 23.4 (q), 25.7 (q), 41.3 (t), 42.5 (s), 55.3 (q), 111.8 (t), 113.9 (d), 124.8 (d), 126.5 (d), 127.1 (d), 130.7 (s), 131.2 (s), 135.8 (d), 146.0 (d) and 158.7 (s).

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