Regio-controlled Prenylation and Geranylation of 3-Furylmethylmagnesium Bromide. Selective Syntheses of 3-Substituted Furanoid and 2-Substituted 3-Methylfuranoid Terpenes

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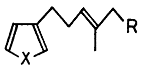
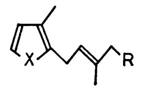
Coupling reactions of 3-furylmethylmagnesium bromide with prenyl and geranyl diethyl phosphates gave 2-substituted 3-methylfurans, rosefuran and sesquirosefuran, as the main products. When the reactions were carried out in the presence of a catalytic amount of copper(I) iodide, normal coupling occurred and 3-substituted furans, perillene and dendrolasin, were formed in good yields. The related naturally occurring 3-substituted thiophene, 3-(4-methyl-3-pentenyl)thiophene, was also synthesized from 3-thienylmethylmagnesium bromide and prenyl diethy phosphate.

3-Substituted furans and 2-substituted 3-methylfurans are widely distributed in nature.[1] Dendrolasin (**1**)[2] and sesquirosefuran (**2**),[3] and their monoterpene homologs, perillene (**3**)[4] and rosefuran (**4**),[5] are examples of such furanoid terpenes. We have previously described[6] that **1** and **2** were selectively synthesized by the regio-controlled geranylation of 3-furylmethylmagnesium bromide (**7**) with geranyl diethyl phosphate (**8**) using copper(I) iodide as a catalyst. In this article, full experimental details of the above reactions as well as the selective syntheses of **3** and **4** by the same methodology are described. A convenient synthesis of the thiophene analog (**5**), a constituent of the essential oil of hop,[7] is also reported.





1 X=O, R=$CH_2CH{=}C(CH_3)_2$
3 X=O, R=H
5 X=S, R=H

2 X=O, R=$CH_2CH{=}C(CH_3)_2$
4 X=O, R=H
6 X=S, R=H

Results and Discussion

Reaction of 3-Furylmethylmagnesium Bromide with Geranyl Diethyl Phosphate. The Grignard reagent, 3-furylmethylmagnesium bromide (**7**), was prepared in the conventional manner from the known 3-furylmethyl bromide[8] in tetrahydrofuran. Geranyl diethyl phosphate (**8**) was added to a solution of the Grignard reagent **7** at −78 °C and the mixture was left overnight at room temperature. Workup followed by vacuum distillation gave a colorless oil. GLPC analysis revealed that the oil consisted of three components (**A**, **B**, and **C**) in the ratio of 7:77:16. They were separated by preparative GLPC and the structures were assigned on the basis of the spectroscopic data. Compound **A**, having the shortest retention time, showed characteristic signals of a terminal vinyl group in addition to a methylene singlet adjacent to the furan ring in its ^{1}H NMR spectrum. This compound was assigned as 3-(2,6-dimethyl-2-vinyl-5-heptenyl)furan (**9**). IR and ^{1}H NMR data of the main product **B** and the third component **C** were in good agreement with the literature values of sesquirosefuran (**2**) and dendrolasin (**1**), respectively.

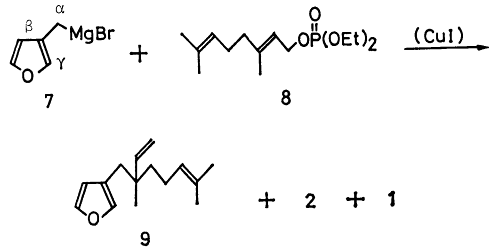


Table 1. Grignard reaction of **7** with geranyl phosphate **8** and geranyl bromide

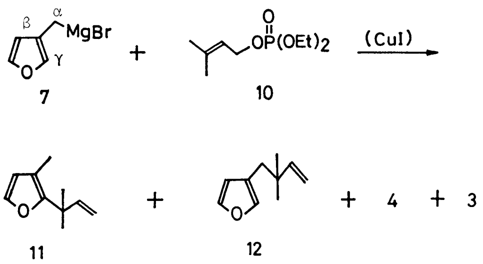
Geranyl compound	CuI	Product ratio **9** : **2** : **1**	Total yield %
Phosphate **8**	Absence	7 : 77 : 16	83
	Presence	21 : 0 : 79	81
Bromide	Absence	32 : 45 : 22	82
	Presence	25 : 6 : 68	83

The results show that the Grignard reagent **7** was electrophilically attacked mainly at the γ-position (C-2 ring carbon) by the geranyl phosphate **8**. This observation is consistent with the facts that 3-furylmethylmagnesium chloride reacts at the γ-position with hard electrophiles such as carbon dioxide and formaldehyde leading to 3-methyl-2-furoic acid and 3-methylfurfuryl alcohol, respectively.[9] When geranyl bromide, a softer electrophile than the phosphate **8**, was employed as a geranylation reagent, the γ-regioselectivity decreased from 77% to 45% (Table 1).

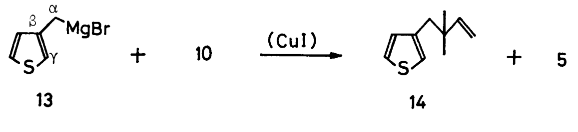
When the reaction of **7** and **8** was conducted in the presence of a catalytic amount (10 mol% of **7**) of copper(I) iodide, normal coupling at the α-position exclusively took place;[10] dendrolasin(**1**) was formed in 79% selectivity accompanied by 21% of the regioisomer **9**. In this case, reaction at the γ-position (formation of **2**) was negligible. Preference for the α-coupling was also observed in the copper(I)-catalyzed reaction of **7** with geranyl bromide, though the selectivity was lower.[11] Results are summarized in Table 1.

Reaction of 3-Furylmethylmagnesium Bromide with Prenyl Diethyl Phosphate. When prenyl diethyl phosphate (**10**) was employed in place of **8**, a mixture of prenylated 3-methylfurans was obtained in 78% combined yield. GLPC of the mixture showed four peaks (**D**,

E, **F**, and **G**) in the ratio of 2:7:72:19. Although compound **D** could not be isolated because of its small quantity, the remaining three components were isolated by preparative GLPC, and characterized. Peak **E** was a new compound and the structure was deduced to be 3-(2,2-dimethyl-3-butenyl)furan (**12**), by means of MS and ^{1}H NMR spectra. Peaks **F** and **G** were found to be identical with rosefuran **4** and perillene **3**, respectively, on the basis of IR, Mass, and ^{1}H NMR spectral comparisons with those in literatures.[4,5] Peak **D** could be, therefore, tentatively assigned as 2-(1,1-dimethyl-2-propenyl)-3-methylfuran (**11**). As expected, the copper(I)-catalyzed reaction of **7** with **10** gave **12** and **3** in the ratio of 2:98 in 83% yield. Again, in this catalytic reaction the coupling at the γ-position was not observed.



Reaction of 3-Thienylmethylmagnesium Bromide with Prenyl Diethyl Phosphate. As described, geranyl (**8**) and prenyl diethyl phosphates(**10**) attacked prefentially the harder γ-position (adjacent position to the hard oxygen atom) of 3-furylmethylmagnesium bromide **7** rather than the α-position. The γ-position of 3-thienylmethylmagnesium bromide (**13**), in which the oxygen atom of **7** is replaced by soft sulfur atom, must be softer than the α-position and therefore the phosphates should attack the α-position. This proved to be the case. The reaction of **13** with **10** gave 3-(4-methyl-3-pentenyl)thiophene (**5**) in 71% yield accompanied with a trace amount (1%) of 3-(2,2-dimethyl-3-butenyl)-thiophene (**14**). No trace of γ-substituted products such as **6** was observed in this reaction. The thiophene derivative **5** is a constituent of a hop oil,[7] and although synthesized by the photo-induced reaction between myrcene and elemental sulfur in a trace yield,[12] this is the first practical synthesis so far reported. By the addition of copper(I) iodide, the product ratio (**14**:**5**) changed from 1:99 to 18:82. γ-Substitution was not observed in this catalytic reaction.



Experimental

General. Infrared spectra were recorded on a JASCO IRA-1 spectrometer. ^{1}H NMR spectra were determined with a Hitachi R-24A (60 MHz) spectrometer, or with a JEOL JNM-FX-100 (100 MHz) spectrometer in CCl_4 or in $CDCl_3$. Chemical shifts (δ) are recorded in ppm downfield from Me_4Si. Mass spectra were measured on a Hitachi M-52 mass spectrometer, operating with an ionization energy of 20 eV. GLPC analyses and preparative GLPC were performed on a Yanaco G1800 gas chromatograph, equipped with columns (1 m, 2 m, or 3 m × 3 mm) packed with Apiezon grease L on Uniport B (15%). Elemental analyses were performed at the Elemental Analysis Center of Kyoto University. For Kugelrohr distillation, a Shibata GTO-250R glass tube oven was used.

Material. Geranyl (**8**) and prenyl diethyl phosphates (**10**) were prepared according to the method for the corresponding diphenyl phosphates.[13] 3-Furylmethyl bromide[8] and 3-thienylmethyl bromide[14] were prepared by the methods described in the literatures. Copper(I) iodide, obtained from Nakarai Chemicals, LTD., was used as received.

*Reaction of 3-Furylmethylmagnesium Bromide (**7**) with Geranyl Diethyl Phosphate (**8**).* *(a) In the Absence of Copper(I) Iodide*: 3-Furylmethyl bromide (403 mg, 2.5 mmol) in THF (4 ml) was added dropwise to magnesium turnings (120 mg, 5 mmol) in THF (1 ml) cooled in an ice-salt bath. After the addition was complete, the mixture was gradually warmed to room temperature and further stirred at that temperature for 1 h. To remove the excess magnesium, the resulting Grignard solution was transferred by a syringe to the second flask and cooled to −78 °C. To this was added a solution of geranyl diethyl phosphate (**8**) (435 mg, 1.5 mmol) in THF (3 ml), the mixture was gradually warmed to room temperature and left overnight. Saturated aqueous ammonium chloride was added and the products were extracted with ether. The extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was distilled (bp 130 °C/3 Torr, 1 Torr ≈133.322 Pa) to give a colorless oil (272 mg, 83% yield). GLPC analysis using the 1 m column (temperature 160 °C, He 90 ml/min) showed three peaks of **9** (t_R=12 min), **2** (14.5), and **1** (16.5) in the ratio of 7:77:16. They were isolated by preparative GLPC.

*3-(2,6-Dimethyl-2-vinyl-5-hepenyl)furan (**9**)*: IR (neat) 2930, 1640, 1520, 1454, 1416, 1376, 1168, 1069, 1028, 1002, 912, 872, 786, and 732 cm^{-1}; ^{1}H NMR (CCl_4) δ=7.20 (m, 1H, furan), 7.08 (s, 1H, furan), 6.13 (m, 1H, furan), 5.73 (dd, J=17, 11 Hz, 1H, $CH_2{=}C\underline{H}$–), 5.2—4.5 (m, 3H, olefin), 2.31 (s, 2H, CH_2), 2.2—1.0 (m, 4H, CH_2), 1.60 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); MS m/z (rel intensity) 218 (M$^+$; 22), 137 (22), 123 (36), 95 (59), 81 (86), and 69 (100); Found: C, 82.71; H, 10.00%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

*Sesquirosefuran (**2**)*: IR (neat) 2930, 1665, 1514, 1448, 1380, 1150, 1085, 890, and 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.21 (d, J=1.6 Hz, 1H, furan), 6.15 (d, J=1.6 Hz, 1H, furan), 5.26 (t, J=7 Hz, 1H, olefin), 5.08 (br, 1H, olefin), 3.28 (d, J=7 Hz, 2H, CH_2), 2.02 (m, 4H, CH_2), 1.96 (s, 3H, ring-CH_3), 1.70 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.59 (s, 3H, CH_3); MS m/z (rel intensity) 218 (M$^+$; 68), 175 (45), 149 (43), 131 (43), 123 (100), 95 (45), and 69 (67).

*Dendrolasin (**1**)*: IR (neat) 2930, 1670, 1562, 1505, 1444, 1382, 1164, 1064, 1025, 874, and 778 cm^{-1}; ^{1}H NMR (CCl_4) 7.19 (m, 1H, furan), 7.08 (m, 1H, furan), 6.13 (m, 1H, furan), 5.05 (m, 2H, olefin), 2.31 (m, 4H, CH_2), 1.96 (m, 4H, CH_2), 1.63 (s, 3H, CH_3), 1.55 (s, 6H, CH_3); MS m/z (rel intensity) 218 (M$^+$; 7), 203 (17), 175 (18), 136 (17), 123 (10), 95 (12), 82 (17), 81 (56), and 69 (100).

(b) In the Presence of Copper(I) Iodide: The Grignard reagent **7** prepared as above was added to a suspension of copper(I) iodide (47 mg, 0.25 mmol) in THF (1 ml) at −5 °C and stirred for 15 min. To this mixture was added the phosphate **8** (435 mg, 1.5 mmol) in THF (3 ml) at −78 °C. The mixture was treated as described. Distillation (bp 130 °C/3 Torr) gave a mixture of **9** and **1** (265 mg, 81%

yield) in the ratio of 21:79 (by GLPC).

The reactions of **7** with geranyl bromide were carried out in the same procedure. The results are summarized in Table 1.

*Reaction of 3-Furylmethylmagnesium Bromide (**7**) with Prenyl Diethyl Phosphate (**10**).* *(a) In the Absence of Copper(I) Iodide*: To the Grignard solution **7**, prepared from magnesium (240 mg, 10 mmol) and the bromide (805 mg, 5 mmol) in THF (10 ml), was added a solution of prenyl diethyl phosphate (**10**) (666 mg, 3 mmol) in THF (5 ml) at −78 °C. The mixture was treated as described. Distillation (bp 115 °C/35 Torr) afforded a colorless oil (350 mg, 78% yield). GLPC analysis using the 3 m column (temperature 135 °C, He 32 ml/min) showed four peaks of **11** ($t_R = 16$ min), **12** (18), **4** (27), and **3** (29) in the ratio of 2:7:72:19. Products **12, 4**, and **3** could be isolated by preparative GLPC.

*3-(2,2-Dimethyl-3-butenyl)furan (**12**)*: ^{1}H NMR ($CDCl_3$) $\delta = 7.31$ (m, 1H, furan), 7.18 (m, 1H, furan), 6.24 (m, 1H, furan), 5.86 (dd, $J = 18$, 10 Hz, 1H, $CH_2{=}C\underline{H}-$), 5.0—4.7 (m, 2H, $C\underline{H}_2{=}CH-$), 2.38 (s, 2H, CH_2), 1.00 (s, 6H, CH_3); MS m/z (rel intensity) 150 (M^+; 62), 135 (27), 82 (59), 81 (47), 69 (100), and 41 (24). IR and elemental analysis could not be performed because of the small quantity of this sample.

*Rosefuran (**4**)*: IR (neat) 2950, 1680, 1514, 1448, 1376, 1150, 1082, 1024, 892, and 726 cm^{-1}; ^{1}H NMR (CCl_4) $\delta = 7.03$ (d, $J = 1.6$ Hz, 1H, furan), 5.95 (d, $J = 1.6$ Hz, 1H, furan), 5.15 (t, $J = 7$ Hz, 1H, olefin), 3.10 (d, $J = 7$ Hz, 2H, CH_2), 1.83 (s, 3H, ring-CH_3), 1.63 (s, 6H, CH_3); MS m/z (rel intensity) 150 (M^+; 100), 135 (43), 111 (46), 95 (27), 71 (33), and 69 (54).

*Perillene (**3**).* IR (neat) 2950, 1680, 1508, 1446, 1380, 1168, 1068, 1030, 878, and 782 cm^{-1}; ^{1}H NMR (CCl_4) $\delta = 7.20$ (m, 1H, furan), 7.09 (m, 1H, furan), 6.13 (m, 1H, furan), 5.04 (t, $J = 7$ Hz, 1H, olefin), 2.30 (m, 4H, CH_2), 1.63 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS m/z (rel intensity) 150 (M^+; 83), 135 (27), 82 (30), 81 (47), 69 (100), and 41 (33).

(b) In the Presence of Copper(I) Iodide: The Grignard reagent **7**, prepared from magnesium (120 mg, 5 mmol) and the bromide (403 mg, 2.5 mmol) in THF (5 ml), was added to a suspension of copper(I) iodide (47 mg, 0.25 mmol) in THF (1 ml) at −5 °C and stirred for 20 min. To this mixture was added the phosphate **10** (333 mg, 1.5 mmol) in THF (3 ml) at −78 °C. The mixture was treated as described. Distillation (bp 110 °C/25 Torr) gave a mixture of **12** and **3** (187 mg, 83% yield) in the ratio of 2:98 (by GLPC).

*Reaction of 3-Thienylmethylmagnesium Bromide (**13**) with Prenyl Diethyl Phosphate (**10**).* *(a) In the Absence of Copper(I) Iodide*: 3-Thienylmethyl bromide (885 mg, 5 mmol) in THF (8 ml) was added dropwise to magnesium turnings (240 mg, 10 mmol) in THF (2 ml) cooled in an ice-salt bath. After the addition was complete, the mixture was gradually warmed to room temperature and stirred at that temperature for 1 h. The solution of the Grignard reagent thus prepared was transferred by the aid of a syringe into the second flask and cooled to −78 °C. To this was added a solution of prenyl diethyl phosphate (**10**) (666 mg, 3 mmol) in THF (5 ml) and the mixture was left overnight at room temperature. Workup followed by distillation (bp 155 °C/37 Torr) gave a colorless oil (352 mg, 71% yield). GLPC analysis using the 2 m column (tempetature 170 °C, He 76 ml/min) showed two peaks of **14** ($t_R = 11$ min) and **5** (16) in the ratio of 1:99. They were isolated by preparative GLPC.

*3-(2,2-Dimethyl-3-butenyl)thiophene (**14**)*: IR (neat) 3100, 2980, 2940, 1642, 1466, 1416, 1380, 1362, 1004, 914, 854, 836, and 784 cm^{-1}; ^{1}H NMR (CCl_4) $\delta = 7.05$ (m, 1H, thiophene), 6.77 (m, 2H, thiophene), 5.80 (dd, $J = 17$, 8 Hz, 1H, $CH_2{=}C\underline{H}-$), 5.05—4.65 (m, 2H, $C\underline{H}_2{=}CH-$), 2.55 (s, 2H, CH_2), 0.95 (s, 6H, CH_3); MS m/z (rel intensity) 166 (M^+; 38), 110 (22), 98 (41), 97 (100), and 69 (75); Found: C, 72.02; H, 8.78%. Calcd for $C_{10}H_{14}S$: C, 72.23; H, 8.49%.

*3-(4-Methyl-3-pentenyl)thiophene (**5**)*: IR (neat) 3110, 2980, 2935, 2860, 1675, 1442, 1378, 1240, 1104, 1079, 839, and 775 cm^{-1}; ^{1}H NMR (CCl_4) $\delta = 7.10$ (m, 1H, thiophene), 6.80 (m, 2H, thiophene), 5.05 (t, $J = 7$ Hz, 1H, olefin), 2.85—2.15 (m, 4H, CH_2), 1.62 (s, 3H, CH_3), 1.50 (s, 3H, CH_3); MS m/z (rel intensity) 166 (M^+; 56), 151 (16), 110 (65). 98 (38), 97 (100), and 69 (60); Found: C, 71.97; H, 8.57%. Calcd for $C_{10}H_{14}S$: C, 72.23; H, 8.49%.

(b) In the Presence of Copper(I) Iodide: The Grignard reagent **13** prepared from magnesium (240 mg, 10 mmol) and the bromide (885 mg, 5 mmol) in THF (10 ml) was added to a suspension of copper(I) iodide (94 mg, 0.5 mmol) in THF (2 ml) at −5 °C and stirred for 15 min. To the mixture was added the phosphate **10** (666 mg, 3 mmol) in THF (5 ml) and the whole was treated as described above. Distillation (bp 160 °C/40 Torr) gave an oil (387 mg, 78% yield). GLPC showed that the oil was a mixture of **14** and **5** in the ratio of 18:82.

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