STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-PEPEROMIN C

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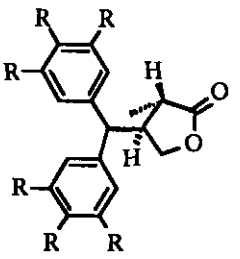
Abstract - A simple and efficient stereoselective total synthesis of (±)-peperomin C (1) was performed employing the 1,4-addition reaction of the organolithium salt (10) to the 3-methyl-2(5*H*)furanone (7) catalized by cuprous iodide as the key step. On the other hand, α-methyl-β-(diphenylmethyl)-γ-butyrolactone (4), an analogous of peperomin C, was also synthetized by the 1,4-addition reaction of the organocuprate (6) on the same 3-methyl-2(5*H*)furanone (7).

Peperomin C (1), a novel lignan having unusual *seco* structure, was recently isolated along with peperomins A and B (2 and 3) from the chinese plant *Peperomia japonica* Makino (Piperaceae).[1] The aqueous and alcoholic decoctions of the whole herb are used as a folk medicine for the treatment of malignant tumors. The structures of the peperomins (1-3) were elucidated on the bases of spectroscopic and crystallographic evidence. In view of their interesting structures and suspected antitumor activity, we decided to undertake their total synthesis. In the present work we describe a simple and efficient stereoselective total synthesis of peperomin C (1), by utilizing the 1,4-addition reaction of an organolithium salt to an α,β-unsaturated carbonyl compound catalized by cuprous iodide as key step.



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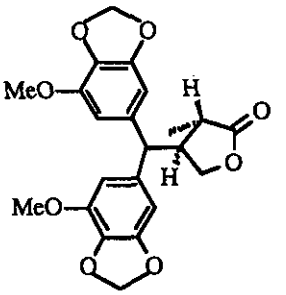
4 R= H



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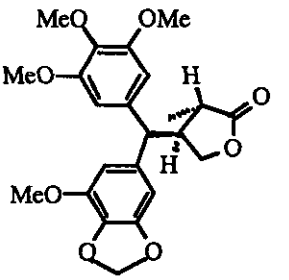

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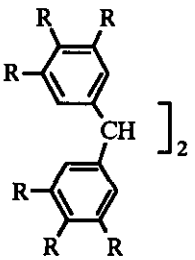
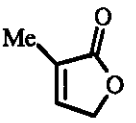


5 R= OMe

6 R= H



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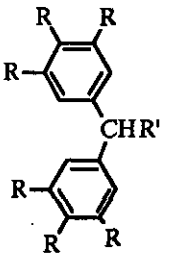
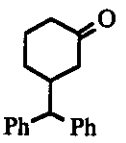


8 R= OMe, R'= H

9 R= R' = H

10 R= OMe, R'= Li



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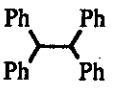

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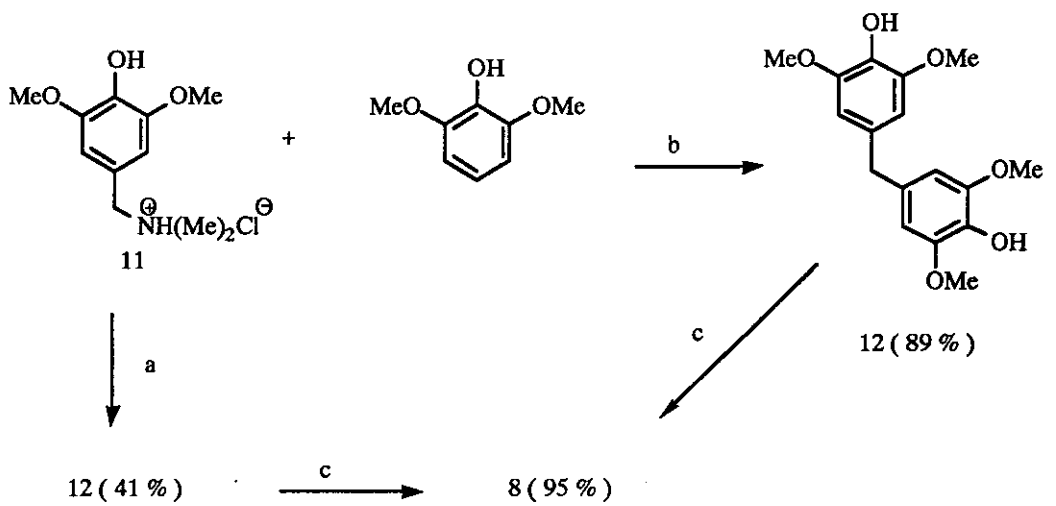
Conjugate addition reactions between cyclic α,β-unsaturated carbonyl compounds and organocopper reagents produce enolate anions which are normally protonated or trapped with a variety of electrophiles with high stereoselectivity.[2] We anticiped that the trans stereochemical relationship shown by the substituents on the lactone ring of peperomin C should thus be formed in a controlled fashion. Based on this consideration, compound (1) would be constructed by 1,4-addition of the organocuprate (5) on 3-methyl-2(5*H*)furanone (7). Thus the present synthetic route of peperomin C (1) was carried out as follows. Bis (3,4,5-trimethoxyphenyl)methane (8) was prepared as shown in Scheme 1.



a) $HOCH_2CH_2OH$, 150 °C b) $HOCH_2CH_2OH$, MeONa, 140°C
c) NaH, MeI, DMSO

Scheme 1

Compound (8) was readily prepared from 2,6-dimethoxy-4-[(*N*-*N*-dimethylamino)methyl] phenol hydrochloride (11) via two routes. First, we followed the method described by Roth *et al.*[3] which consists in heating 11 in ethylene glycol to 150°C furnishing bis(4-hydroxy-3,5-dimethoxyphenyl)metane (12) in 41% yield. In view of the low yield obtained in this reaction a modification of this method was performed. Thus compound (11) (1.1 equiv.) was heated to 140°C in the presence of 2,6-dimethoxyphenol (1.0 equiv.) and sodium methoxide under nitrogen atmosphere for 8 h to afford 12 in 89% yield. Treatment of 12 with methyl iodide in the presence of sodium hydride in anhydrous DMSO for 8 h at room temperature gave compound (8) in 95% yield. On the other hand, the synthesis of furanone (7) was achieved following a procedure recently described by us.[4]

In order to find adequate conditions to perform the key 1,4-organocopper addition reaction, a couple of model reactions were carried out. Thus, in two separate runs diphenylmethane (9) was treated with tert-butyllithium in anhydrous THF at -78°C under argon atmosphere. After two hours, cuprous iodide was correspondingly added at -60°C to each reaction and the mixtures were stirred for 1 h. Solutions of 2-cyclohexen-1-one and furanone (7) in anhydrous THF were respectively added at -78°C. After workup compound (13) (66%) and compound (4) (76%) along with the dimerization product tetraphenylethane (14) were respectively isolated. The ^{1}H-nmr spectra and gc analysis of the crude product did not show evidence for the cis isomer of 4. The virtually complete stereocontrol exhibited in this addition reaction is typical of organocopper chemistry.[5]

In order to prepare peperomin C, the same procedure described above was followed, however we were not able to prepare the desired product even under various conditions, in each case the unreacted starting materials were recovered after workup. Attempts to carry out the reaction using the hetero-organocuprate generated from the lithium salt (10) and cuprous cyanide under various conditions[6] proved futile too.

It has been described that the presence of electron donor atoms on arylcopper compounds[7] enhances the stability of the copper-carbon bond. This phenomenon has been attributed to chelation. However to the best of our knowledge no similar effects have been described for benzylic and diphenylmethane salts.

We presume that the remarkable difference in reactivity showed between the diphenylmethane cuprate (6) and the bis(trimethoxydiphenyl)methane cuprate (5) is due to the considerable

stabilization of the copper-carbon bond that is given by the presence of the methoxy groups at the aryl nucleus producing the very stable cuprate (5).

On the other hand, when the reaction between lithium salt (10) and the furanone (7) was carried out in absence of cuprous salt an untractable mixture of products was obtained.

In view of the results described above we decided to try the 1,4-addition reaction of the lithium salt (10) catalized by a cuprous salt. Indeed, the synthesis of 1 was accomplished when 10 was exposed to 0.1 equivalent of cuprous iodide at -78°C in anhydrous THF. After stirring for 5 min, a solution of furanone (7) in anhydrous THF was added and the stirring continued for 3 h more at the same temperature. After workup and column chromatography purification, peperomin C was isolated in 62% yield. The spectral properties of this compound were found to be identical with those reported[1] for the natural product.

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EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded on a Nicolet FT-5SX spectrophotometer. The ^{1}H-nmr spectra were obtained on a Varian-Gemini 200 and a Varian VXR 300S instruments with TMS as internal standard. Mass spectra were recorded with a Hewlett Packard 5985B spectrometer with gcms system, compounds were introduced through the direct insertion probe.

Bis(4-hydroxy-2,6-dimethoxyphenyl)methane (12). To a well stirred solution of 4.3 g (28 mmol) of 2,6-dimethoxyphenol and 3.25 g (60 mmol) of sodium methoxide in 30 ml of dry ethylene glycol under nitrogen atmosphere were added 7.67 g (31 mmol) of 2,6-dimethoxy-4-[(*N*,*N*-dimethylamino)methyl]phenol hydrochloride (11) and the mixture was heated to 140°C for 8 h. After this time, the reaction mixture was cooled to room temperature and glycol was removed under reduced pressure. The residual oil was treated with 5% HCl and extracted with ethyl acetate (3 x 15

ml). The combined organic layers were washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The solid residue was crystallized from ethyl acetate to give 8.10 g (89%) of 12. mp 117-119°C (lit.,[3] 108-110°C). Ir (KBr) ν_{max} 3492, 3385, 2830, 1608, 1103 cm^{-1}; ^{1}H-nmr (dmso-d_6): δ 3.74 (12H, s), 6.50 (4H, s), 7.95 (2H, br, exchangeable with D_2O); ms: m/z 320 (M^+, 39), 167 (100).

Bis(3,4,5-trimethoxyphenyl)methane (8). To a suspension of 0.47 g (19 mmol) of sodium hydride (as 50% suspension in oil) in 20 ml of anhydrous ether under nitrogen atmosphere was added via hypodermic syringe a solution of 1.13 g (3.5 mmol) of 12 in 25 ml of anhydrous DMSO and the mixture was stirred for 10 min at room temperature. After this time 9.93 g (4.36 ml, 70 mmol) of methyl iodide was added and the mixture reaction was stirred at room temperature for 8 h. The solvent was removed under reduced pressure and the product was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with a 10% cold solution of sodium hydroxide, brine, water, dried over Na_2SO_4 and solvent was evaporated. The solid residue was crystallized from ether giving 1.20 g (97%) of 8 as a white solid, mp 102-103°C. Ir (film) ν_{max} 2836, 1589, 1236, 1126 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.81 (12H, s), 3.82 (6H, s), 3.83 (2H, s), 6.37 (4H, s); ms: m/z 348 (M^+,88), 181 (100). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50, H, 6.94. Found: C, 65.69, H, 6.78.

1,4-Conjugate Addition reactions of cuprates (5) and (6). In a three-necked round bottom flask equipped with magnetic stirrer, solid addition funnel and argon atmosphere, a solution of 1.2 g (7.12 mmol) of freshly distilled diphenylmethane in 20 ml of anhydrous THF was placed and cooled to -78°C. A solution of 4.72 ml (7.14 mmol) of tert-butyllithium (1.5 M in pentane) was added dropwise through a hypodermic syringe and the mixture was stirred for 2 h at the same temperature. After this time, the temperature was allowed to rise to -60°C and 0.68 g (3.56 mmol) of dry[8] CuI was added, and the mixture was further stirred for 1 h, after this time the reaction mixture was cooled to -78°C and a solution of 0.342 g (3.56 mmol) of 2-cyclohexen-1-one and 0.348 g (3.56 mmol) of freshly distilled furanone (7) respectively in 10 ml of anhydrous THF was added dropwise and stirred for 3 h. After the addition of a saturated solution of NH_4Cl and ethyl acetate, the organic layer was separated and the aqueous layer was extracted (2 x 15 ml) with ethyl acetate. The combined organic layers were washed with brine and water, dried over Na_2SO_4 and solvent was evaporated

under reduced pressure. The residue was purified on a silica gel column using a mixture of hexane-ethyl acetate (75:25 v/v) as eluent to give

3-(diphenylmethyl)cyclohexanone (13) 0.62 g (66%), mp 93-96°C. Ir (film) ν_{max} 3025, 2949, 1708, 1493, 1450 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.70-1.95 (4H,m), 1.85 (1H,d,J=7.6 Hz), 2.30 (4H, m), 3.62 (1H,d,J=7.6 Hz), 7.25 (10H, m); ms m/z 264 (M^+, 4), 167 (100). Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.47; H, 7.55.

α-methyl-β-(diphenylmethyl)-γ-butyrolactone (4) 1.44 g (76%), mp 120-122°C. Ir (KBr): ν_{max} 3008, 2962, 2772, 2490, 1170, 1443 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 0.84 (3H,d,J=7.2 Hz), 2.34 (1H,m), 3.04 (1H,m), 3.76 (1H,dd,J=9.75 Hz,J=7.75 Hz), 3.78 (1H,d,J=11 Hz), 4.27 (1H,dd,J=9.75 Hz, J=7.75 Hz), 7.24 (10H,m); ms m/z 266 (M^+, 4), 167 (100). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17, H 6.81. Found: C, 81.32, H, 6.73.

1,1,2,2-tetraphenylethane (14), 0.075 g. mp 214-216°C, (lit.,[9] 212-213°C).

(±)-Peperomin C (1). In a round bottom flask fitted with magnetic stirrer and argon atmosphere a solution of 0.660 g (1.89 mmol) of the diphenylmethane (8) in 20 ml of anhydrous THF was placed, cooled to -78°C, and 1.73 ml (1.89 mmol) of tert-butyllithium (1.1 M in pentane) were added by hypodermic syringe and the mixture was stirred for 20 min. After this time, the temperature was allowed to rise to 0°C for 5 min and cooled down again to -78°C. Cuprous iodide (0.36 g, 0.189 mmol) was added and the stirring was continued for 5 min. To this mixture a solution of freshly distilled furanone (7) (0.186 g, 1.89 mmol) in 5 ml of anhydrous THF was added dropwise and stirred for 3 h at the same temperature. The mixture was treated with an aqueous saturated solution of NH_4Cl and extracted with ethyl acetate. The extract was washed with brine, water and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure without heating, the residue was chromatographed on a silica gel column using a mixture of dichloromethane-acetone (95:5 v/v) as eluent to afford 0.558 g (62%) of racemic peperomin C (1) as a colorless solid, mp 159-161°C. The spectral properties were found to be identical with those reported[1] for peperomin C.

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