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Synthesis and Insecticidal Activity of Novel *N*-Oxydihydropyrroles: 4-Hydroxy-3-mesityl-1-methoxymethoxy Derivatives with Various Substituents at the 5-Position

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Abstract—This paper reports the synthesis and insecticidal activity of a series of novel 4-hydroxy-3-mesityl-1-methoxymethoxy-1,5-dihydro-2*H*-pyrrol-2-one derivatives, in which the substituents at the 5-position were varied with a number of alkyl and spirocycloalkyl groups. Investigation of the structure–activity relationships revealed that small alkyl and spirocyclohexyl groups had a favorable effect on the insecticidal activity of these agents against *Myzus persicae*.

Introduction

Crop damage by insects remains a serious problem in modern agriculture. The organophosphates, carbamates, pyrethroids, and several other classes of insecticides have been used so intensively worldwide that significant insect resistance to them has emerged.[1–4] In addition, a growing social awareness of the residual agrochemicals in the environment underlines the need for the development of novel, highly potent, target-selective, and environmentally innocuous insecticides with low mammalian toxicity.[1–6]

In an upland field, hemiptera pests such as the green peach aphid (*Myzus persicae*) and cotton aphid (*Aphis gossypii*) cause serious damage to many crops, for example cucumber and cabbage. Once they pierce a plant and suck its sap, often the plant is blighted, or at the very least its market value is reduced. For a compound to be effective against these pests, it needs to have a novel mode of action because they multiple so rapidly that the chemical-resistant strains frequently emerge.[7,8] And it is also desirable for an agent to possess a systemic property, a character to be absorbed from a plant's roots or leaves and transferred to other parts of the plant, when combating these sucking pests. A systemic insecticide can spread all through a plant and kill any targeted insects that feed on it.[3]

In our previous study, we reported the synthesis and insecticidal activity of a new series of *N*-oxydihydropyrrole derivatives (**1**),[9,10] which were designed based on the insecticidal and acaricidal agents reported by Bayer's groups (Fig. 1).[11–14] Our interest focused on how the modification of the 1-position (–OR group in structure **1**) influenced the insecticidal activity against the above pests. The derived compounds demonstrated significant systemic insecticidal activity against hemiptera pests such as the brown planthopper (*Nilaparvata lugens*) and *M. persicae*. In addition, the early structure–

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activity study revealed that substituents such as small alkoxy and alkoxyalkoxyl groups exert more potent insecticidal activity than others. The affected insects died before or during ecdysis without completing molting. This symptom is unique for hemiptera pests, and the derivatives appear to provide a new mode of action. On the other hand, these derivatives also showed some phytotoxicity against rice and cucumber. While this phytotoxic damage could be alleviated by modifying the 1-position,[9] the extent of improvement was not satisfactory.

Among the derivatives studied in the previous work,[9] compound **2** controlled *M. persicae* perfectly at 0.01 ppm in systemic application, but it also exerted severe phytotoxicity against cucumber at 50 ppm in foliage application. Based on the structure (**2**) as a lead, we attempted to vary the substituents at the 5-position of the dihydropyrrole ring (R^1 and R^2 groups in **3**), substituents we had fixed to the dimethyl group in the previous study,[9] and tried to gain further insight into both the structure–activity relationships and potential for alleviating the phytotoxicity.

In this article, we report the synthesis of a series of 5,5-disubstituted-4-hydroxy- 3-mesityl-1-methoxymethoxy-1,5-dihydro-2*H*-pyrrol-2-one derivatives (**3**) and an assessment of their insecticidal activity against *M. persicae*. We also briefly refer to the phytotoxicity of the derivatives (Fig. 1).

Results and Discussion

Chemistry

Scheme 1 outlines the synthetic route to prepare 5,5-disubstituted *N*-oxydihydropyrrole derivatives (**3**). Hydroxyamino acid esters with various substituents on α-carbon (**4a–k**) were acylated into **6a–k** with mesitylacetyl chloride **5**[15] under the two-phase reaction condition developed by our group.[9,10] The desired compounds (**3a–3k**) were yielded in one pot by methoxymethylation of the hydroxy group with chloromethyl methyl ether in the presence of sodium hydride in DMF, followed by cyclization via an intramolecular Claisen condensation by treatment with potassium *tert*-butoxide (*t*-BuOK).

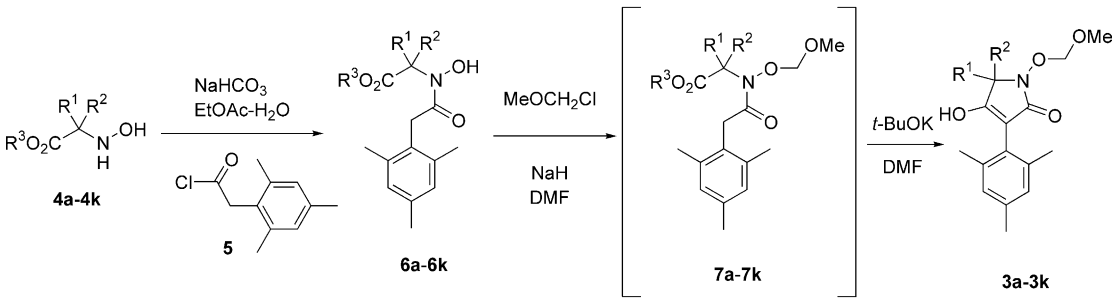
In our approaches, modification at C-5 in **3** depended on the preparation of the 2,2-disubstituted-2-hydroxy-amino acid esters (**4a–4k** in Scheme 2), a task that could be accomplished by several available synthetic methods.[16–21] Ultimately, we chose the processes[20,21] starting from amino acid esters via schiff base intermediates (**10** and **11**), as various alkyl groups could be easily introduced to the α-carbon of the intermediates. In practice, the alkyl groups can be introduced in combination with methyl or ethyl groups using a slightly modified version of the procedure in ref 20 (Route 1 in Scheme 2). Appropriate amino acid esters (**8** and **9**) were converted to schiff bases (**10** and **11**) by the condensation with 4-methoxybenzaldehyde in absolute methanol in the presence of sodium bicarbonate.[22] The α-carbons of the resultant schiff bases were variously alkylated in the presence of *t*-BuOK to give **12a–12g**, which were then oxidized with *m*-chloroperbenzoic acid (mCPBA) to give the corresponding oxaziridines. Treatment of these oxaziridines with hydroxylamine hydrochloride in methanol gave the *N*-hydroxyamino acid esters, which were taken up as salt free forms (**4a–4g**) by treatment with sodium bicarbonate.

To obtain *N*-hydroxyamino acid esters with cycloalkyl groups (**4h–4k**), we opted for a direct hydroxyamination method[10,23] (Route 2 in Scheme 2) over the above alkylation procedure since the starting materials for the former method seemed more readily accessible. This direct method was originally used for preparing 2-monosubstituted-2-hydroxyamino acid esters from corresponding esters,[23] but we conjectured that it would also be applicable to 2,2-disubstituted counterparts. Appropriate esters (**13h–13k**) were successfully converted to the desired *N*-hydroxyamino acid esters (**4h–4k**) through the following four subsequent treatments: with lithium diisopropylamide, with 1-chloro-1-nitrosocyclohexane **14**, with diluted hydrochloric acid, and with sodium bicarbonate.

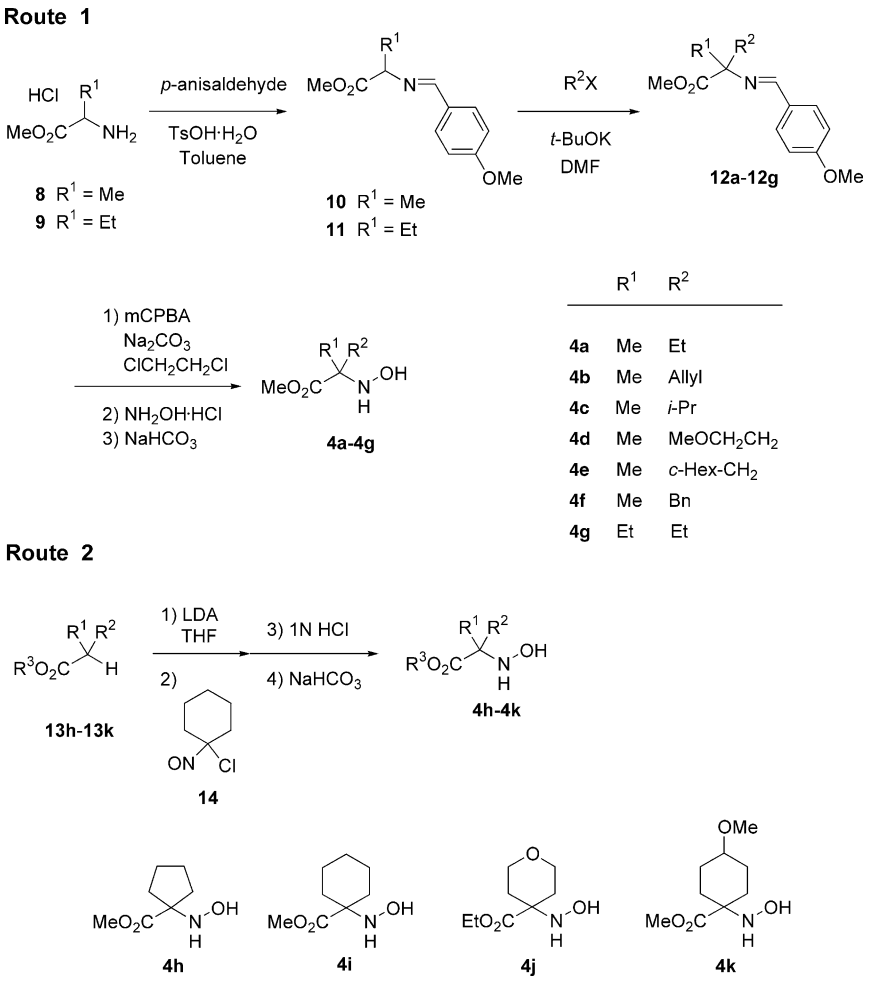
These *N*-hydroxyamino acid esters (**4a–4k**) were transformed to the desired 5,5-disubstituted-*N*-oxydihydropyrroles (**3a–3k**) by the method mentioned above (Scheme 1).

Biological evaluation

All the derivatives prepared in this work (**3a–3k**) exhibited high insecticidal activity against hemiptera pests such as *M. persicae* and *A. gossypii* at 200 ppm in contact tests. To highlight the structure–activity relationships of



Scheme 1. Synthetic route to **3a–3k**.



Scheme 2. Preparation of *N*-hydroxyamino acid esters (**4a**–**4k**).

these derivatives, Table 1 shows their insecticidal activity against *M. persicae* at lower concentrations.

Compounds with short linear alkyl (**3a** and **3b**) or alkoxy (**3d**) groups showed relatively high systemic and contact insecticidal activity, while other longer or branched alkyl substitutions tended to decrease the efficacy. It was interesting to note that the diethyl group (**3g**) decreased the efficacy, while its cyclic counterpart (**3h**) exhibited both systemic and contact activities. Spirocyclohexane derivative (**3i**) also showed moderate systemic activity. Oxygen-introduced derivative (**3j**) and methoxy-substituted derivative (**3k**) at the 4′-position of the spirocyclohexyl ring conspicuously improved the activity.

On the other hand, almost all of these derivatives exerted severe phytotoxicity against cucumber at 500 ppm. The only exception was **3e**, a derivative that had lost insecticidal activity. The derivatization presented in the study was not demonstrably effective in alleviating the phytotoxicity. Further modification of other parts of the

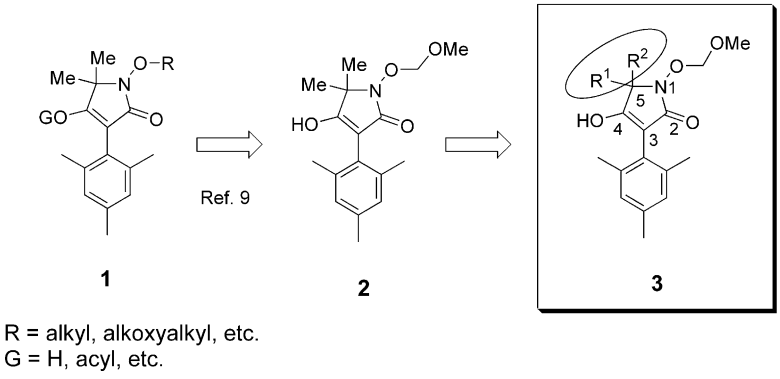
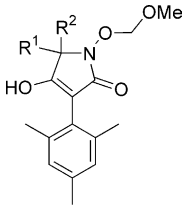
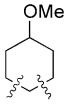


Figure 1. Structures of the lead compounds (**1**, **2**) and derivatives explored in the present work (**3**).

Table 1. Insecticidal activity and phytotoxicity of 5,5-disubstituted *N*-oxydihydropyrrole derivatives[a]



Compd	R^1	R^2	*M. persicae*				*CS*[b]
			Systemic test		Contact test		Spray test
			0.1 ppm	0.01 ppm	10 ppm	1 ppm	500 ppm
2	Me	Me	4	4	4	0	4
3a	Me	Et	4	0	3	1	3
3b	Me	Allyl	1	0	3	0	3
3c	Me	*i*-Pr	0	0	0	0	3
3d	Me	$MeOCH_2CH_2$	4	0	4	0	3
3e	Me	*c*-Hex-CH_2	0	0	0	0	0
3f	Me	Bn	0	0	0	0	3
3g	Et	Et	0	0	0	0	3
3h			2	0	2	0	2
3i			3	0	0	0	3
3j			4	4	—[c]	—	3
3k			4	0	4	0	3

[a]The insecticidal activity and phytotoxicity were each graded into five classes from 0 to 4. See text.
[b]*CS*, *Cucumis sativus* (cucumber).
[c]Not determined.

dihydropyrrole ring will clearly be necessary for separating the insecticidal potency from phytotoxicity.

Conclusion

We designed a series of novel 4-hydroxy-3-mesityl-1-methoxymethoxy-1,5-dihydro-2*H*-pyrrol-2-one derivatives (**3**) and developed general methods to synthesize them via the preparation of variously substituted *N*-hydroxyamino acid esters. Structure–activity relationships revealed that small alkyl and spirocyclohexyl groups were favorable for the insecticidal activity against *M. persicae*, while other dialkyl groups tended to decrease the activity. The derivatization did not appear to attenuate their phytotoxicity against cucumber.

Experimental

Synthetic procedure

General. All melting points (mp) are uncorrected. IR spectra were measured on a Perkin-Elmer 1600 spectrometer. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer and a VG Auto Spec M mass spectrometer. Regular silica gel (Daisogel 1001W, 63–210 mesh) was used for all column chromatography procedure except the purification of schiff bases and hydroxylamines, which was performed using a neutral silica gel (Silica gel 60, spherical, neutrality, 150 mesh, Nacalai Tesque).

Methyl 2-[(E)-(4-methoxyphenyl)methylidene]aminopropanoate (10).[22] *p*-Anisaldehyde (41.7 mL, 0.34 mol) was added to a stirred suspension of L-alanine methyl ester hydrochloride (**8**, 50.10 g, 0.36 mmol) and Na_2CO_3 (57.20 g, 0.54 mol) in methanol (300 mL) at 0 °C, and the reaction mixture was stirred at 20 °C for 2 h and then at ambient temperature for 12 h. After adding ethyl ether to the reaction mixture, the organic layer was washed with brine, dried over anhydrous magnesium sulfate ($MgSO_4$), and concentrated under reduced pressure to an oil. Treatment of this oil by neutral silica gel column chromatography (EtOAc/hexane, 1/4) yielded the com-

pound **10** (63.62 g, 80.2%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.24 (1H, s), 7.72 (2H, d, J = 8.8 Hz), 6.93 (2H, d, J = 8.8 Hz), 4.12 (1H, q, J = 6.6 Hz), 3.85 (3H, s), 3.75 (3H, s), 1.52 (3H, d, J = 6.6 Hz).

Methyl 2-[(E)-(4-methoxyphenyl)methylidene]aminobutanoate (11). This was prepared from methyl 2-aminobutanoate hydrochloride (**9**) using the same procedure. Yield: 86.2%; colorless oil; ^{1}H NMR ($CDCl_3$): 8.20 (1H, s), 7.73 (2H, d, J = 8.8 Hz), 6.93 (2H, d, J = 8.8 Hz), 3.85 (3H, s), 3.75 (3H, s), 2.08–1.81 (3H, m), 0.91 (3H, t, J = 7.3 Hz).

Methyl 2-hydroxyamino-2-methylbutanoate.[20] Potassium *tert*-butoxide (*t*-BuOK; 8.76 g, 77.8 mmol) was added to a stirred solution of **10** (17.11 g, 77.8 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6; 1.87 g, 7.8 mmol) in toluene (170 mL) at 0 °C, and then the mixture was stirred for 10 min at the same temperature. After adding ethyliodide (8 mL, 0.10 mol) and stirring for 1 h at 0 °C, the solution was mixed with a saturated aqueous solution of sodium bicarbonate, the water layer was extracted with ethyl acetate (EtOAc), and the combined organic layer was washed with brine, and dried ($MgSO_4$). Concentration of the product under reduced pressure yielded **12a** as an oil that was ready for use without further purification (crude product, 14.00 g).

Na_2CO_3 (8.33 g, 78.6 mmol) and 3-chloroperoxybenzoic acid (mCPBA; content ca. 75%, 12.60 g, ca. 62.0 mol) were added to a stirred solution of crude **12a** in 1,2-dichloroethane at 0 °C, and then the reaction mixture was stirred at the same temperature for 1 h and at ambient temperature for 2 h. After adding water and extracting the mixture with dichloromethane (CH_2Cl_2), the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the corresponding oxaziridine as an oil that was used without further purification (crude product, 13.50 g).

The hydroxylamine hydrochloride (3.50 g, 50.4 mmol) was added to a stirred solution of the crude oxaziridine in methanol (130 mL) at ambient temperature, and then the mixture was stirred at the same temperature for 12 h. After condensing the reaction mixture under reduced pressure, ethyl ether and 1 N HCl were added, the mixture was separated, and the organic layer was then extracted with 1 N HCl. The combined water layer was washed with ethyl ether and adjusted to ca. pH 8 with $NaHCO_3$. The mixture was extracted with EtOAc and the combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give a syrup. Treatment of this syrup by neutral silica gel column chromatography (EtOAc/hexane, 1/4) yielded the title compound (**4a**, 4.71 g, 41.1% in three steps) as a brownish oil. ^{1}H NMR ($CDCl_3$) δ: 4.92 (2H, br s), 3.76 (3H, s), 1.64 (2H, q, J = 7.7 Hz), 1.35 (3H, s), 0.88 (3H, t, J = 7.7 Hz); IR (neat) cm^{-1}: 3273, 2974, 1732, 1460, 1253, 1150, 1068, 1007; HRMS calcd for $C_6H_{13}NO_3$ 147.0894, found 147.0894.

Compounds **4b–4f** were synthesized by the same procedure.

Methyl 2-hydroxyamino-2-methyl-4-pentenoate (4b).[20] Yield: 38.6%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 5.85–5.64 (2H, m), 5.16 (2H, s), 5.11–5.09 (1H, m), 3.76 (3H, s), 2.53–2.30 (2H, m), 1.34 (3H, s).

Methyl 2-hydroxyamino-2,3-dimethylbutanoate (4c).[20] Yield: 58.9%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 3.75 (3H, s), 1.88 (1H, quint, J = 7.0 Hz), 1.31 (3H, s), 0.88 (6H, dd, J = 7.0, 7.7 Hz).

Methyl 2-hydroxyamino-4-methoxy-2-methylbutanoate (4d). Yield: 69.3%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 3.76 (3H, s), 3.49 (2H, t, J = 5.9 Hz), 3.33 (3H, s), 2.15–1.84 (2H, m), 1.33 (3H, s); IR (neat) cm^{-1}: 3275, 2951, 1732, 1452, 1374, 1306, 1243, 1197, 1118, 1056; HRMS(FAB) calcd for $C_7H_{15}NO_4$ 178.1079, found 178.1077.

Methyl 3-cyclohexyl-2-hydroxyamino-2-methylpropanoate (4e). Yield: 9.0%; brownish prisms; mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ: 3.74 (3H, s), 1.68–0.89 (13H, m), 1.39 (3H, s); IR (KBr) cm^{-1}: 3282, 2933, 1735, 1458, 1438, 1374, 1256, 1231, 1210, 1156, 1108, 1027; HRMS(EI) calcd for $C_{11}H_{21}NO_3$ 215.1521, found 215.1523.

Methyl 2-hydroxyamino-2-methyl-3-phenylpropanoate (4f).[20] Yield: 14.2%; colorless prisms; mp 78–80 °C; ^{1}H NMR ($CDCl_3$) δ: 7.35–7.22 (3H, m), 7.20–7.13 (2H, m), 5.10 (2H, br s), 3.73 (3H, s), 2.99 (2H, ABq, J = 14.7 Hz, Δν = 27.2 Hz), 1.33 (3H, s).

Methyl 2-ethyl-2-(hydroxyamino)butanoate (4g). This was prepared using the same procedure from (**11**) and iodoethane. Yield: 47.0%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 3.76 (3H, s), 1.82–1.58 (4H, m), 0.87 (6H, t, J = 7.5 Hz); IR (neat) cm^{-1}: 3275, 2970, 1733, 1457, 1383, 1340, 1293, 1239, 1136; HRMS(EI) calcd for $C_7H_{15}NO_3$ 161.1052, found 161.1052.

Methyl 1-(hydroxyamino)cyclohexanecarboxylate (4i). A hexane solution of *n*-BuLi (1.58 mol/L, 7 mL, 10.8 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 1.33 mL, 11.0 mmol) were added to a stirred solution of diisopropylamine (1.54 mL, 11.1 mmol) in THF (10 mL) at −78 °C, and then the reaction mixture was stirred at the same temperature for 1 h. The reaction was continued by adding methyl cyclohexanecarboxylate (**13i**, 1.42 g, 10.0 mmol) at −78 °C, stirring at the same temperature for 1 h, adding 1-chloro-1-nitrosocyclohexane (**14**, 1.62 g, 11.0 mmol) at −78 °C, stirring at the same temperature for another 1 h, and finally adding 1 N HCl (20 mL) and stirring at ambient temperature for 3 h. After the water layer was separated, the organic layer was extracted with 1 N HCl, and then the combined water layer was washed with ethyl ether, adjusted to ca. pH 9 with $NaHCO_3$, and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to a syrup. Treatment of this

syrup by neutral silica gel column chromatography (EtOAc/hexane, 1/4) yielded the title compound (**14i**, 1.02 g, 59%) as colorless prisms. Mp 39–41 °C; ^{1}H NMR ($CDCl_3$) δ: 3.76 (3H, s), 1.94–1.80 (2H, m), 1.73–1.47 (8H, m); IR (KBr) cm^{-1}: 3261, 2933, 1724, 1448, 1431, 1281, 1240, 1148, 1108, 1084, 1070, 1032; HRMS(EI) calcd for $C_8H_{15}NO_3$ 173.1052, found 173.1053.

Compounds **4h**, **4j** and **4k** were synthesized using the same procedure.

Methyl 1-(hydroxyamino)cyclopentanecarboxylate (4h).[20] Yield: 23.4%; brownish prisms; ^{1}H NMR ($CDCl_3$) δ: 3.77 (3H, s), 20.5–1.75 (8H, m).

Ethyl 4-(hydroxyamino)tetrahydro-2H-pyran-4-carboxylate (4j). Yield: 90.2%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 4.25 (2H, q, J = 7.2 Hz), 3.89–3.63 (4H, m), 2.15–2.02 (2H, m), 1.76–1.65 (2H, m), 1.31 (3H, t, J = 7.2 Hz); IR (KBr) cm^{-1}: 3391, 2964, 1730, 1470, 1445, 1391, 1304, 1256, 1205, 1148, 1106, 1016; HRMS(EI) calcd for $C_8H_{15}NO_4$ 189.1001, found 189.1002.

Methyl 1-(hydroxyamino)-4-methoxycyclohexanecarboxylate (4k). Yield: 63.5%; mp 42–45 °C; ^{1}H NMR (DMSO-d_6) δ: 4.22 (2H, q, J = 7.1 Hz), 3.38–3.31 (1H, m), 3.33 (3H, s), 2.17–2.06 (2H, m), 1.92–0.46 (6H, m), 1.29 (3H, t, J = 7.1 Hz); IR (KBr) cm^{-1}: 3260, 2944, 1731, 1452, 1371, 1257, 1224, 1189, 1090, 1030; HRMS(FAB) calcd for $C_{10}H_{19}NO_4$ 218.1392, found 218.1392.

Methyl 2-[hydroxy(mesitylacetyl)amino]-2-methylbutanoate (6a). A solution of mesitylacetyl chloride[15] (**5**, 0.98 g, 4.98 mmol) in EtOAc (10 mL) was added dropwise to a stirred two-phase solution of **4a** (0.77 g, 5.23 mmol) and $NaHCO_3$ (0.63 g, 7.5 mmol) in EtOAc (8 mL) and water (7 mL) at ca. 0 °C, and then the mixture was stirred at 0 °C for 1 h and at ambient temperature for 2 h. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to a brownish oil. Treatment of this oil by silica gel column chromatography (EtOAc/hexane, 1/4) yielded the desired title compound (**6a**, 0.60 g, 39%) as a white powder. Mp 175–176 °C; ^{1}H NMR (DMSO-d_6) δ: 9.94 (1H, s), 6.76 (2H, s), 3.66 (2H, s), 3.48 (3H, s), 2.17 (3H, s), 2.08 (6H, s), 2.01–1.65 (2H, m), 1.30 (3H, s), 0.78 (3H, t, J = 7.3 Hz); IR (KBr) cm^{-1}: 3151, 2946, 1740, 1609, 1425, 1294, 1244, 1202, 1152; HRMS(EI) calcd for $C_{17}H_{25}NO_4$ 307.1784, found 307.1783.

Compounds **6b**–**6k** were synthesized by the same procedure.

Methyl 2-[hydroxy(mesitylacetyl)amino]-2-methyl-4-pentenoate (6b). Yield: 45.1%; mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 6.13 (1H, s), 6.0–5.75 (1H, m), 5.20–5.15 (1H, m), 5.11 (1H, br.s), 3.80 (2H, s), 3.69 (3H, s), 2.95–2.82 (1H, m), 2.66–2.55 (1H, m), 2.24 (3H, s), 2.22 (6H, s), 1.54 (3H, s); IR (KBr) cm^{-1}: 3150, 2938, 1737, 1609, 1433, 1256, 1130; HRMS(EI) calcd for $C_{18}H_{25}NO_4$ 319.1784, found 319.1783.

Methyl 2-[hydroxy(mesitylacetyl)amino]-2,3-dimethylbutanoate (6c). Yield: 41.9%; mp 154–156 °C; ^{1}H NMR (DMSO-d_6) δ: 9.92 (1H, s), 6.78 (2H, s), 3.69 (2H, d, J = 4.8 Hz), 3.49 (3H, s), 2.58–2.34 (1H, m), 2.19 (3H, s), 2.10 (6H, s), 1.31 (3H, s), 0.92 (6H, dd, J = 7.0, 16.1 Hz); IR (KBr) cm^{-1}: 3137, 2948, 1742, 1597, 1432, 1377, 1257, 1203, 1191, 1114; HRMS(EI) calcd for $C_{18}H_{27}NO_4$ 321.1940, found 321.1941.

Methyl 2-[hydroxy(mesitylacetyl)amino]-4-methoxy-2-methylbutanoate (6d). Yield: 27.8%; mp 126–128 °C; ^{1}H NMR ($CDCl_3$) δ: 8.04 (1H, s), 6.83 (2H, s), 3.77 (2H, s), 3.67 (3H, s), 3.72–3.06 (2H, m), 3.37 (3H, s), 2.23 (9H, s), 2.16 (2H, t, J = 3.9 Hz), 1.51 (3H, s); IR (KBr) cm^{-1}: 3153, 2878, 1735, 1608, 1429, 1403, 1262, 1194, 1122; HRMS(EI) calcd for $C_{18}H_{27}NO_5$ 337.1889, found 337.1890.

Methyl 3-cyclohexyl-2-[hydroxy(mesitylacetyl)amino]-2-methylpropanoate (6e). Yield: 34.7%; mp 190–191 °C; ^{1}H NMR ($CDCl_3$) δ: 6.84 (2H, s), 6.23 (1H, s), 3.80 (2H, s), 3.69 (3H, s), 2.24 (3H, s), 2.22 (6H, s), 2.05–1.60 (5H, m), 1.56 (3H, s), 1.50–0.90 (8H, m); IR (KBr) cm^{-1}: 3117, 2922, 2853, 1738, 1604, 1448, 1255, 1229, 1134; HRMS(EI) calcd for $C_{22}H_{33}NO_4$ 375.2410, found 375.2411.

Methyl 2-[hydroxy(mesitylacetyl)amino]-2-methyl-3-phenylpropanoate (6f). Yield: 45.0%; mp 154–156 °C; ^{1}H NMR (DMSO-d_6) δ: 10.00 (1H, s), 7.29–7.25 (3H, m), 7.13–7.09 (2H, m), 6.80 (2H, s), 3.69 (2H, s), 3.50 (3H, s), 3.16 (2H, ABq, J = 13.2 Hz, Δν = 49.9 Hz), 2.20 (3H, s), 2.14 (6H, s), 1.23 (3H, s); IR (KBr) cm^{-1}: 3152, 2947, 1747, 1608, 1455, 1426, 1286, 1215, 1196, 1106; HRMS(EI) calcd for $C_{22}H_{27}NO_4$ 369.1940, found 369.1941.

Methyl 2-ethyl-2-[hydroxy(mesitylacetyl)amino]butanoate (6g). Yield: 9.4%; mp 192–193 °C; ^{1}H NMR ($CHCl_3$) δ: 6.85 (2H, s), 6.42 (1H, s), 3.83 (2H, s), 3.71 (3H, s), 2.24 (3H, s), 2.23 (6H, s), 2.19–1.96 (4H, m), 0.88 (6H, t, J = 7.5 Hz); IR (KBr) cm^{-1}: 3140, 2975, 1740, 1602, 1464, 1445, 1299, 1240, 1204, 1134; HRMS(EI) calcd for $C_{18}H_{27}NO_4$ 321.1940, found 321.1939.

Methyl 1-[hydroxy(mesitylacetyl)amino]cyclopentanecarboxylate (6h). Yield: 53.6%; mp 161–163 °C; ^{1}H NMR (DMSO-d_6) δ: 10.06 (1H, s), 6.76 (2H, s), 3.67 (2H, s), 3.50 (3H, s), 2.17 (3H, s), 3.08 (6H, s), 2.18–2.00 (4H, m), 1.80–1.52 (4H, m); IR (KBr) cm^{-1}: 3138, 2954, 1746, 1590, 1518, 1441, 1274, 1194, 1144, 1011; HRMS(EI) calcd for $C_{18}H_{25}NO_4$ 319.1784, found 319.1782.

Methyl 1-[hydroxy(mesitylacetyl)amino]cyclohexanecarboxylate (6i). Yield: 29.1%; mp 196–197 °C; ^{1}H NMR (DMSO-d_6) δ: 9.94 (1H, s), 6.78 (2H, s), 3.70 (2H, s), 3.52 (3H, s), 2.19 (3H, s), 2.10 (6H, s), 2.10–1.36 (10H, m); IR (KBr) cm^{-1}: 3136, 2936, 1744, 1602, 1488, 1430, 1210, 1161, 1133; HRMS(EI) calcd for $C_{19}H_{27}NO_4$ 333.1940, found 333.1939.

Ethyl 4-[hydroxy(mesitylacetyl)amino]tetrahydro-2H-pyran-4-carboxylate (6j). Yield: 12.3%; mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 6.46 (1H, s), 4.21 (2H, q, J = 7.1 Hz), 3.89 (2H, s), 3.90–3.65 (4H, m), 2.50–2.05 (4H, m), 2.23 (9H, s), 1.27 (3H, t, J = 7.1 Hz); IR (KBr) cm^{-1}: 3152, 2882, 1736, 1600, 1444, 1420, 1289, 1250, 1118, 1101; HRMS(EI) calcd for $C_{19}H_{27}NO_5$ 349.1889, found 349.1889.

Methyl 1-[hydroxy(mesitylacetyl)amino]-4-methoxycyclohexanecarboxylate (6k). Yield: 20.4%; amorphous; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 6.44 (1H, s), 4.19 (2H, q, J = 5.2 Hz), 3.89 (2H, s), 3.48–3.40 (1H, m), 3.33 (3H, s), 2.24 (3H, s), 2.23 (6H, s), 2.46–2.10 (4H, s), 1.88–1.66 (4H, m), 1.27 (3H, t, J = 5.2 Hz); IR (KBr) cm^{-1}: 3151, 2941, 1740, 1602, 1431, 1217, 1196, 1177, 1101, 1032; HRMS(EI) calcd for $C_{21}H_{31}NO_5$ 377.2202, found 377.2202.

5-Ethyl-4-hydroxy-3-mesityl-1-methoxymethoxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (3a). NaH (60% dispersion in mineral oil, 82.0 mg, 2.1 mmol) was added to a stirred solution of **6a** (0.60 g, 1.95 mmol) and chloromethyl methyl ether (0.16 mL, 2.1 mmol) in DMF (6 mL) at 0 °C, and then the reaction mixture was stirred at the same temperature for 1 h and at the ambient temperature for 12 h. Next, the reaction solution was mixed with DMF (10 mL) and *t*-BuOK (0.25 g, 2.23 mmol) at ambient temperature and stirred at the same temperature for 3 h. After pouring the mixture into water, the water layer was washed with ethyl ether, acidified to ca. pH 3 with 1 N HCl, and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to a syrup. Treatment of this syrup by silica gel column chromatography (EtOAc/hexane, 1/2) yielded the title compound (**3a**, 0.33 g, 53%) as colorless prisms; mp 157–159 °C; ^{1}H NMR ($CDCl_3$) δ: 6.91 (2H, s), 5.01 (2H, d, J = 2.9 Hz), 3.58 (3H, s), 2.28 (3H, s), 2.18 (3H, s), 2.14 (3H, s), 1.95–1.77 (2H, m), 1.51 (3H, s), 0.89 (3H, t, J = 7.3 Hz); IR (KBr) cm^{-1}: 2936, 2632, 1646, 1611, 1454, 1386, 1366, 1314, 1157, 1075; HRMS(EI) calcd for $C_{18}H_{25}NO_4$ 319.1784, found 319.1784.

Compounds **3b**–**3k** were synthesized by the same procedure.

5-Allyl-4-hydroxy-3-mesityl-1-methoxymethoxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (3b). Yield: 46.0%; mp 128–130 °C; ^{1}H NMR (DMSO-d_6) δ: 11.34 (1H, s), 6.84 (2H, s), 5.75–5.55 (1H, m), 5.16–5.04 (2H, m), 4.90 (2H, ABq, J = 7.3 Hz, Δν = 7.1 Hz), 3.47 (3H, s), 2.27 (3H, s), 2.03 (6H, s), 1.41 (3H, s); IR (KBr) cm^{-1}: 2936, 1737, 1651, 1610, 1451, 1435, 1385, 1367, 1294, 1157, 1084; HRMS(EI) calcd for $C_{19}H_{25}NO_4$ 331.1784, found 331.1784.

4-Hydroxy-5-isopropyl-3-mesityl-1-methoxymethoxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (3c). Yield: 24.7%; amorphous; ^{1}H NMR ($CDCl_3$) δ: 6.90 (2H, s), 5.02 (2H, s), 3.57 (3H, s), 2.27 (3H, s), 2.18 (3H, s), 2.12 (3H, s), 2.35–2.15 (1H, m), 1.56 (3H, s), 1.13 (3H, d, J = 7.0 Hz), 1.00 (3H, d, J = 7.0 Hz); IR (KBr) cm^{-1}: 2971, 1747, 1688, 1636, 1608, 1457, 1371, 1315, 1157, 1074; HRMS(EI) calcd for $C_{19}H_{27}NO_4$ 333.1940, found 333.1940.

4-Hydroxy-3-mesityl-5-(2-methoxyethyl)-1-methoxymethoxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (3d). Yield: 62.4%; colorless oil; ^{1}H NMR (DMSO-d_6) δ: 11.44 (1H, s), 6.86 (2H, s), 4.88 (2H, ABq, J = 7.3 Hz, Δν = 8.2 Hz), 3.50 (3H, s), 3.18 (3H, s), 2.26–1.91 (13H, m), 1.41 (3H, s); IR (KBr) cm^{-1}: 2934, 1660, 1453, 1386, 1367, 1328, 1158, 1116, 1091, 1067; HRMS(EI) calcd for $C_{19}H_{27}NO_5$ 349.1889, found 349.1889.

5-Cyclohexylmethyl-4-hydroxy-3-mesityl-1-methoxymethoxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (3e). Yield: 38.5%; amorphous; ^{1}H NMR (DMSO-d_6) δ: 11.34 (1H, s), 6.86 (2H, s), 4.87 (2H, ABq, J = 7.3 Hz, Δν = 7.0 Hz), 3.46 (3H, s), 2.24 (3H, s), 2.20–2.18 (2H, m), 2.09 (3H, s), 2.02 (3H, s), 1.81–0.80 (14H, m); IR (KBr) cm^{-1}: 2922, 1654, 1591, 1450, 1390, 1368, 1332, 1314, 1294, 1157; HRMS(EI) calcd for $C_{23}H_{33}NO_4$ 387.2410, found 387.2411.

5-Benzyl-4-hydroxy-3-mesityl-1-methoxymethoxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (3f). Yield: 49.0%; amorphous; ^{1}H NMR (DMSO-d_6) δ: 11.39 (1H, s), 7.32–7.15 (5H, m), 6.77 (1H, s), 6.65 (1H, s), 5.04 (2H, ABq, J = 7.3 Hz, Δν = 23.3 Hz), 3.56 (3H, s), 3.08 (2H, Abq, J = 13.6 Hz, Δν = 39.9 Hz), 2.16 (3H, s), 1.98 (3H, s), 1.54 (3H, s), 1.15 (3H, s); IR (KBr) cm^{-1}: 2929, 1654, 1592, 1484, 1449, 1341, 1307, 1276, 1216, 1186, 1158, 1088; HRMS(EI) calcd for $C_{23}H_{27}NO_4$ 381.1940, found 381.1941.

5,5-Diethyl-4-hydroxy-3-mesityl-1-methoxymethoxy-1,5-dihydro-2H-pyrrol-2-one (3g). Yield: 33.7%; mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ: 6.92 (2H, s), 5.01 (2H, s), 3.56 (3H, s), 2.28 (3H, s), 2.19 (6H, s), 1.95–1.77 (4H, m), 0.91 (6H, t, J = 7.4 Hz); IR (KBr) cm^{-1}: 2967, 1663, 1623, 1611, 1460, 1384, 1291, 1183, 1158, 1072; HRMS(EI) calcd for $C_{19}H_{27}NO_4$ 333.1940, found 333.1940.

4-Hydroxy-3-mesityl-1-methoxymethoxy-1-azaspiro[4.4]-non-3-en-2-one (3h). Yield: 55.0%; mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ: 6.91 (2H, s), 5.04 (2H, s), 3.58 (3H, s), 2.28 (3H, s), 2.14 (6H, s), 2.28–1.85 (8H, m); IR (KBr) cm^{-1}: 2951, 1678, 1605, 1482, 1438, 1307, 1292, 1201, 1171, 1159, 1095, 1074; HRMS(EI) calcd for $C_{19}H_{25}NO_4$ 331.1784, found 331.1784.

4-Hydroxy-3-mesityl-1-methoxymethoxy-1-azaspiro[4.5]-dec-3-en-2-one (3i). Yield: 57.6%; mp 159–161 °C; ^{1}H NMR ($CDCl_3$) δ: 6.90 (2H, s), 6.06 (1H, br s), 5.02 (2H, s), 3.60 (3H, s), 2.27 (3H, s), 2.13 (6H, s), 2.30–1.50 (10H, m); IR (KBr) cm^{-1}: 2934, 1676, 1597, 1483, 1448, 1291, 1260, 1152, 1092, 1074; HRMS(EI) calcd for $C_{20}H_{27}NO_4$ 345.1940, found 345.1940.

4-Hydroxy-3-mesityl-1-methoxymethoxy-8-oxa-1-azaspiro[4.5]dec-3-en-2-one (3j). Yield: 50.3%; mp 182–183 °C; ^{1}H NMR (DMSO-d_6) δ: 11.65 (1H, s), 6.87 (2H, s), 4.93 (2H, s), 3.95–3.85 (4H, m), 3.49 (3H, s), 2.24

(3H, s), 2.04 (6H, s), 2.21–2.05 (2H, m), 1.80–1.67 (2H, m); IR (KBr) cm^{-1}: 2958, 1683, 1625, 1608, 1440, 1352, 1336, 1247, 1153, 1090, 1070; HRMS(EI) calcd for $C_{19}H_{25}NO_5$ 347.1733, found 347.1734.

4-Hydroxy-3-mesityl-8-methoxy-1-methoxymethoxy-1-azaspiro[4.5]dec-3-en-2-one (3k). Yield: 70.4%; mp 164–165 °C; ^1H NMR (DMSO-d_6) δ: 11.43 (1H, s), 6.87 (2H, s), 4.98 (2H, s), 3.47 (3H, s), 3.35–3.18 (1H, m), 3.25 (3H, s), 2.24 (3H, s), 2.13–1.70 (14H, m); IR (KBr) cm^{-1}: 2941, 1715, 1643, 1611, 1485, 1453, 1375, 1310, 1290, 1156, 1089, 1069; HRMS(EI) calcd for $C_{21}H_{29}NO_5$ 375.2046, found 375.2046.

Biological activity tests

Insecticidal tests against *M. persicae*. Both systemic and contact tests were conducted against *M. persicae*. Each compound was formulated as an emulsifiable concentrate (EC) and then diluted with water containing a surfactant (Gramin-S; 0.01% v/v) to give the active ingredient (AI) concentration required to assess activity levels. The activity ratings were expressed by a five-point index (0, 1, 2, 3, and 4) corresponding to 0–29, 30–59, 60–89, 90–99, and 100% mortality.

Systemic test. *Brassica campestris*, a kind of Chinese cabbage, was cut at the stem and infested with five adult *M. persicae* on the leaves. After 2 days, all of the adults were removed and the number of remaining larvae was counted. The cut edge was soaked in the test solution in a flask and the whole test unit was held in the growth chamber under long-day (16L/8D) conditions at 25 °C and 60% relative humidity. Duplicate experiments were performed for each solution tested. Counts were taken of the numbers of live and dead insects after 5 days of treatment. Immobile insects were counted as dead.

Contact test. *B. campestris* was cut at the stem and infested with five adult *M. persicae* on the leaves. After 2 days, all of the adults were removed and the number of remaining larvae was counted. The leaves were sprayed with the test solution and the whole test unit was held in the growth chamber under long-day (16L/8D) conditions at 25 °C and 60% relative humidity. Duplicate experiments were performed for each solution tested. Counts were taken of the numbers of live and dead insects 5 days after treatment. Immobile insects were counted as dead.

Phytotoxicity evaluation. Compounds were formulated as EC and sprayed in a post-emergence glasshouse test for cucumber (*Cucumis sativus*) seedlings at 500 ppm. Seven days after treatment, damage to the plants was visually assessed by comparison with untreated plants using a scale of 0–4: 0, <10% growth inhibition; 1, 11–30% growth inhibition; 2, 31–60% growth inhibition; 3, 61–90% growth inhibition; 4, >91% growth inhibition.

References and Notes

1. Dent, D. *Insect Pest Management*; CABI: London, 2000; p 81.
2. Holan, G.; Winkler, D. A. In *Rational Approaches to Structure, Activity, and Ecotoxicology of Agrochemicals*; Draber, W., Fujita, T., Eds.; CRC: FL, 1992; p 123.
3. Conway, G. *In The Doubly Green Revolution—Food for All in the 21st Century*; Penguin: London, 1997; p 205.
4. Baker, D.R.; Fenyes, J. G.; Lahm, G. P.; Selby, T. P.; Stevenson, T. M. In *Synthesis and Chemistry of Agrochemicals VI (ACS Symposium Series 800)*; Baker, D. R., Fenyes, J. G., Lahm, G. P., Selby, T. P., Stevenson, T. M., Eds.; American Chemical Society (Oxford University Press): Washington, DC, 2002; p 1.
5. Halweil, B. In *State of the World*; Flavin, C., French, H., Gardner, G., Eds.; W. W. Norton & Company: London, 2002; p 51.
6. Colborn, T.; Dumanoski, D.; Myers, J. P. In *Our Stolen Future*; Abacus: London, 1997; p 122.
7. Ishaaya, I.; Horowitz, A. R. In*Insecticides with Novel Modes of Action*; Ishaaya, I., Degheele, D., Eds., Springer: Berlin, 1998, p 1.
8. Cremlyn, R. J. In *Agrochemicals*; John Wiley & Sons: Chichester, 1991; p 1.
9. Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Kinoshita, A.; Obayashi, T.; Miura, T.; Nagai, J.; Yokoi, S.; Ichinose, R.; Tanaka, K.; Kodama, K.; Iwasaki, T.; Miyake, T.; Takashio, M.; Iwabuchi, J. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2406.
10. Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Iwasaki, T.; Iwabuchi, J. *Heterocycles* **2002**, *57*, 881.
11. Fisher, R.; Bretshneider, T.; Krueger, W.; Bachmann, J.; Erdeln, C.; Wachendorff-Neumann, U.; Stantel, H. J.; Luerssen, K.; Schmidt, R. R. DE Patent 4216814, 1993; *Chem. Abstr.* **1993**, *119*, 117088b.
12. Fischer, R.; Dumas, J.; Bretschneider, T.; Erdelen, C.; Wachendorff-Neumann, U. DE Patent 4410420, 1995; *Chem. Abstr.* **1996**, *124*, 29593k.
13. Fischer, R.; Dumas, J.; Bretschneider, T.; Erdelen, C.; Wachendorff-Neumann, U.; Santel, H.-J.; Dollinger, M.; Mencke, N.; Turberg, A. DE Patent 19518962, 1996; *Chem. Abstr.* **1996**, *124*, 231916g.
14. Krauskopf, B.; Luerssen, K.; Stantel, H.-J.; Schmidt, R. R.; Wachendorff-Neumann, U.; Fisher, R.; Erdelen, C. EP Patent 456063, 1991; *Chem. Abstr.* **1992**, *116*, 106083 h.
15. Lutz, R. E.; Jordan, R. H. *J. Am. Chem. Soc.* **1950**, *72*, 4091.
16. Ozaki, S.; Sayo, H.; Masui, M. *Chem. Pharm. Bull.* **1971**, *19*, 2389.
17. Bonnet, R.; Clark, V. M.; Giddey, A.; Todd, A. *J. Chem. Soc.* **1959**, 2087.
18. Umezawa, S.; Kinoshita, M.; Yanagisawa, H. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 209.
19. Fu, Y.; Hammarström, L-G.J.; Miller, T. J.; Fronczek, F. R.; McLaughlin, M. L.; Hammer, R. P. *J. Org. Chem.* **2001**, *66*, 7118.
20. Hans-Hermann, L.; Ulrich, S. *Liebigs. Ann. Chem.* **1981**, *34*, 1378.
21. Goto, G.; Kawakita, K.; Okutani, T.; Miki, T. *Chem. Pharm. Bull.* **1986**, *34*, 3202.
22. Grigg, R.; Jordan, M.; Tangthongkum, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, *41*.
23. Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chem. Acta* **1992**, *75*, 1965.