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SYNTHESIS OF *N*-OXYDIHYDROPYRROLE DERIVATIVES

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Abstract – *N*-Oxydihydropyrrole derivatives were synthesized through an intramolecular Claisen condensation reaction. The *N*-acylation of hindered hydroxylamines played a key role in providing the useful intermediates, which could be converted to a variety of *N*-oxydihydropyrrole derivatives.

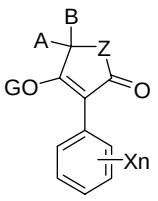
INTRODUCTION

Crop damage by insects remains a serious problem in modern agriculture. Several classes of insecticides, such as organophosphates, carbamates and pyrethroids, have been used worldwide. Because of their intense use, however, the emergence of significant insect resistance to these chemical agents has been observed. In addition, a growing social awareness of the residual agrochemicals in the environment underlines the need to develop brand-new, highly potent, target-selective, and environmentally innocuous insecticides with low mammalian toxicity. [1]

Recently Bayer's groups have reported a new series of insecticidal compounds depicted in the structure (**1**).[2] These compounds are characterized by enolated 1,3-diketone in a 5-membered ring system, and demonstrated significant insecticidal activities against pests with important economic impacts, such as

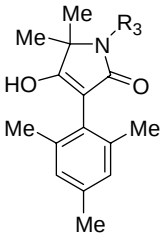
brown rice planthopper (*Nilaparvata lugens*) and cotton aphid (*Aphis gossypii*), in our preliminary experiments. These ring systems are structurally unique as an insecticide and found to have a new mode of action affecting an insect molting system. These characteristics are suitable for controlling insect pests that have already acquired resistance against the insecticides currently on the market.

The above considerations prompted us to explore new series of 5-membered heterocyclic compounds containing 1,3-diketone moiety in search of highly effective insecticides. Regarding part Z in the general structure (**1**), Bayer's groups have already established systems with Z = O,[2a] S,[2b] CR_1R_2 (R_1,R_2 = alkyl, etc)[2c] and NR_3 (R_3 = H, alkyl, etc).[2d] In our own experiments, introduction of a lipophilic substituent, such as an ethyl group, at the nitrogen atom of the dihydropyrrole ring (**2b**) resulted in a clear decrease in inseticidal activity compared to the original Z = NH derivative (**2a**). Then we turned our attention to the introduction of a hydrophilic group and focused specifically on the dihydropyrrole derivatives (**3**) with *N*-oxy substitution (-OR) at the 1-position – a series of compounds that have been scarcely explored synthetically.

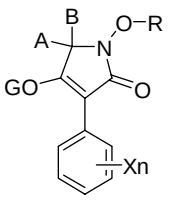


1

Z = O, S, CR_1R_2, NR_3
A,B = H, alkyl, etc
G = H, alkyl, alkoxyalkyl, acyl, sulfonyl, etc
X = H, alkyl, harogen, etc
n = 1 - 5



2a (R_3 = H)
2b (R_3 = Et)



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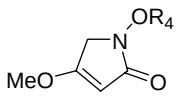

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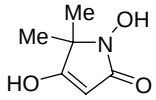
R_4 = H, *t*-Bu



5

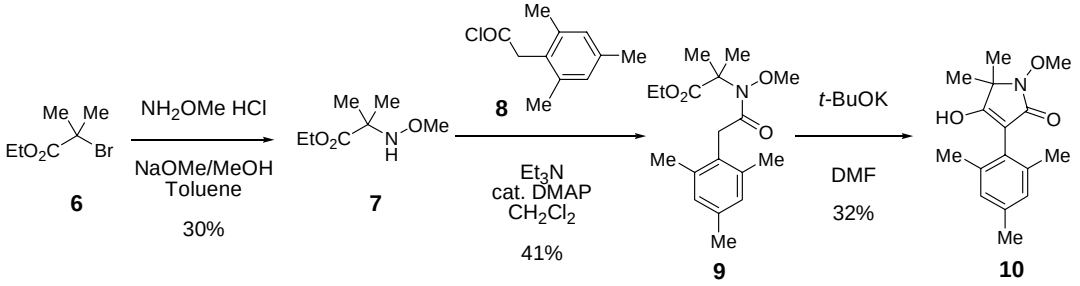
Among a few reported *N*-oxydihydropyrrole derivatives, compounds (**4**)[3] were synthesized *via* a regioselective hydride reduction of the corresponding maleic acid imides, and **5**[4] was synthesized through the cyclization of the appropriate enamino ester. However, these methods apparently lacked the ability to yield a wide variety of derivatives, and not a single dihydropyrrole compound containing a substituted

phenyl group at the 3-position like **3** has been reported. Therefore, it was a synthetically challenging task to develop versatile methods to construct the new structure (**3**).

We developed general synthetic methods for a series of *N*-oxydihydropyrrole derivatives (**3**) and wish to report four representative routes (Schemes 1–4) in this paper.

RESULTS AND DISCUSSION

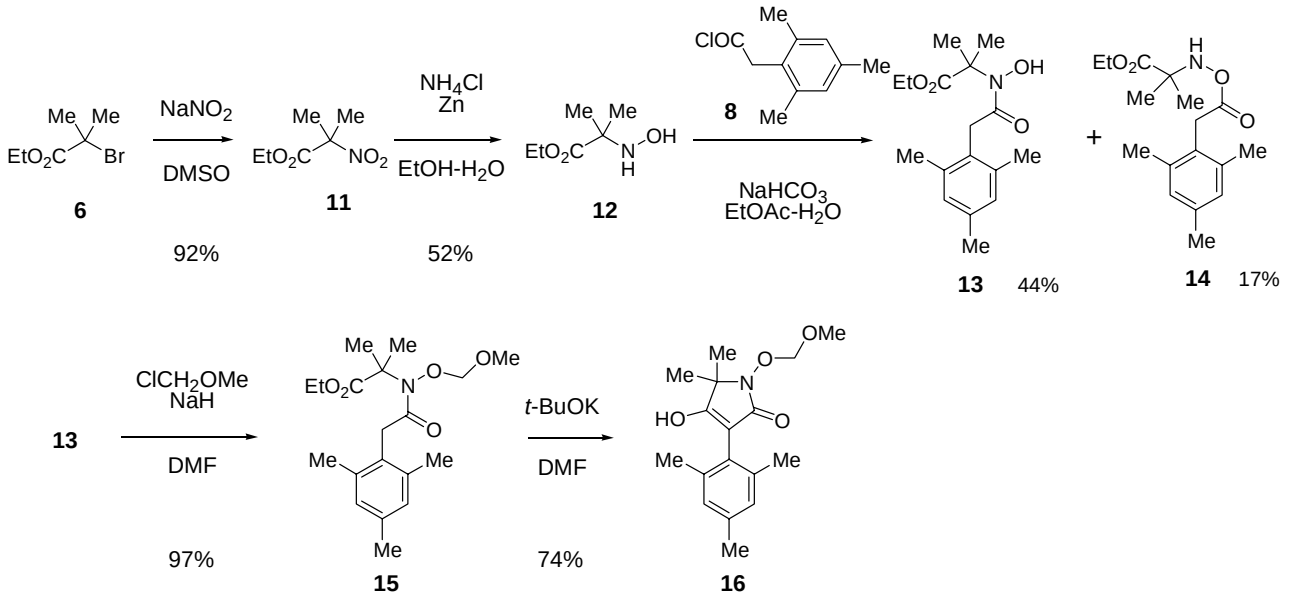
First we focused on the synthesis of the *N*-methoxy derivative (**10**) shown in Scheme 1. Ethyl 2-methoxyamino-2-methylpropionate (**7**), which was prepared from ethyl 2-bromoisobutylate (**6**) and *O*-methylhydroxylamine according to the reported method,[5] was converted to an acylated form **9** in 41% yield through a condensation reaction with mesitylacetyl chloride (**8**)[6] in the presence of triethylamine (Et_3N) and catalytic amount of 4-dimethylaminopyridine. In spite of several possible side-reactions, treatment of **9** with potassium *tert*-butoxide (*t*-BuOK) in *N*,*N*-dimethylformamide (DMF) afforded the desired cyclized compound (**10**) in 32% yield through an intramolecular Claisen condensation reaction.



Scheme 1

Although the above intramolecular Claisen condensation reaction successfully provided the *N*-methoxydihydropyrrole derivative, the reaction was somewhat limited since the substituents at the 1-position of the dihydropyrrole ring [-OR group in the structure (**3**)] utterly depend on the availability of 2-alkoxyamino-2-methylpropionate derivatives like **7**. While we examined the initial substitution reaction of **6** with a variety of *O*-alkylhydroxylamines, we found that the reaction usually required such a long time affording products in such poor yields that it could not be readily used for derivatization. Therefore we decided to develop a more versatile method for modifying the substituent at the 1-position without having to prepare individual 2-alkoxyamino-2-methylpropionate derivatives.

We surmised that the *N*-hydroxy derivative (**13**) was one of the suitable intermediates for this purpose and could be prepared as shown in Scheme 2. The substitution reaction of **6** with sodium nitrite ($NaNO_2$) by a slightly modified version of the reported procedure[7] gave a nitro derivative (**11**). Then **11** was partially reduced[8] by using zinc powder and ammonium chloride (NH_4Cl) to produce the desired ethyl 2-(*N*-hydroxyamino)-2-methylpropionate (**12**). (This two-step procedure to obtain **12** from **6** proved to be comparable to the reported method,[9] by which **12** was prepared from the corresponding amino acid derivative, in terms of facility and yield.) The first trial of *N*-acylation of **12** with mesitylacetyl chloride (**8**) in the presence of Et_3N gave only trace amount of the desired *N*-acylated adduct (**13**) with *O*-acylated hydroxylamine (**14**) as a major product. In another trial, the Mukaiyama condensation reaction[10] employed between the hydroxylamine (**12**) and mesitylacetic acid[11] by means of 2-chloro-1-methylpyridinium iodide gave only the unwanted product (**14**). Several further attempts using other base and solvent systems failed to improve the yield. Finally, we chose a two-phase reaction condition,[12] employing ethyl acetate (EtOAc) and water as solvents with sodium hydrogencarbonate ($NaHCO_3$) as a base. Under this two-phase condition, fortunately the condensation reaction of **12** with **8** successfully provided the desired adduct (**13**) predominantly (44%) over **14** (17%).

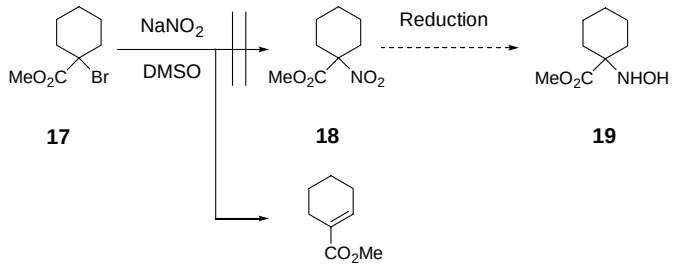


Scheme 2

With the key intermediate (**13**) in hand, we next tried an introduction of a methoxymethyl substituent into

the hydroxy group of **13** and a subsequent cyclization. The reaction of **13** with chloromethyl methyl ether (MOMCl) in the presence of sodium hydride (NaH) gave *N*-methoxymethoxy amide (**15**) in 97% yield. Next intramolecular Claisen condensation of **15** with *t*-BuOK in DMF gave cyclized compound (**16**) in 74% yield.

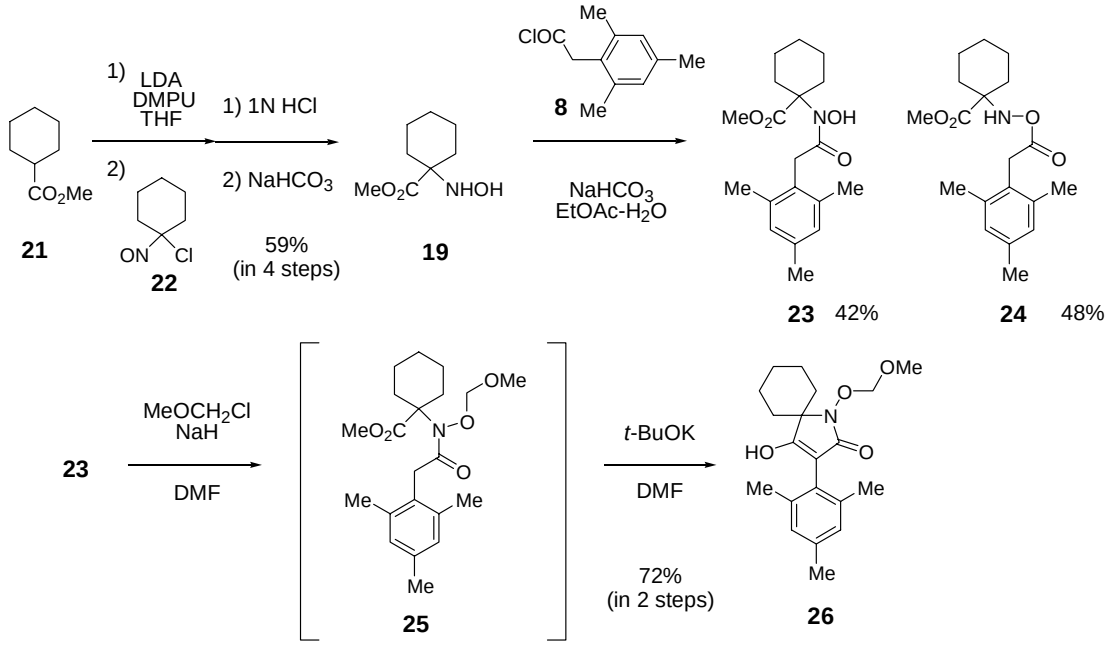
We next turned our attention to the substitution at the 5-position of the dihydropyrrole ring [A and B groups in the structure (**3**)] for further diversity. However, we found that the previous nitrite substitution method did not always successfully provide 2,2-disubstituted 2-nitroacetate, a precursor for the corresponding *N*-hydroxyamino ester. For instance, when we tried to obtain a congested *N*-hydroxyamino ester such as methyl 1-(*N*-hydoroxyamino)-1-cyclohexanecarbonate (**19**) through the same approach used to obtain **12**, the initial substitution reaction of **17** by $NaNO_2$ did not take place and we were left with only the elimination reaction yielding a methyl 1-cyclohexenecarbonate (**20**).



17 **18** **19**

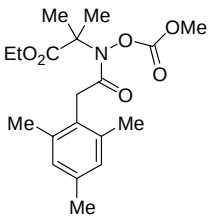
20

It was reported that the *N*-hydroxyamino ester (**19**) itself could be prepared from the corresponding amino acid derivative,[9] but we intended to seek a more general and concise method to prepare a wide variety of *N*-hydroxyamino esters. After some trial and error, we obtained **19** by applying a direct hydroxyamination method[13] to ester (**21**) using 1-chloro-1-nitrosocyclohexane (**22**), as shown in Scheme 3. It was proved that our two-phase acylation method could be applied to this hindered *N*-hydroxyamino ester (**19**), which reacted with mesitylacetyl chloride (**8**) to give both the desired *N*-acylated adduct (**23**) in 42% yield and *O*-acylated hydroxylamine (**24**) in 48% yield. The conversion of **23** into **26** was performed in one pot as follows. The reaction of **23** with MOMCl in the presence of NaH gave *N*-methoxymethoxy amide (**25**) *in situ*, which was subsequently cyclized to compound (**26**) in 72% yield by additional treatment with *t*-BuOK *via* the intramolecular Claisen condensation reaction.

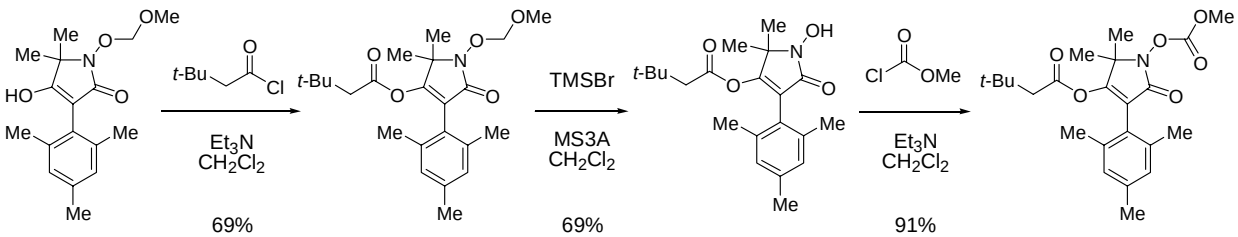


Scheme 3

Although the ring construction methods mentioned above are apparently very potent, an intermediate (**27**) did not gave any cyclized product by treatment of *t*-BuOK or several other bases, but only decomposed as expected. It was partly due to the removal of the methoxycarbonyloxy group by the basic treatments. We therefore attempted to introduce the methoxycarbonyloxy group to the 1-position after parent dihdropyrrole ring has been constructed.



27



Scheme 4

It was obvious that a *N*-hydroxy derivative such as **29** was suited for this purpose. Compound (**29**) was

prepared from **16** through acylation of its hydroxy group (**28**, 69% yield) and subsequent removal[14] of the methoxymethyl group by trimethylsilyl bromide (TMSBr) (**29**, 69% yield), as shown in Scheme 4. The intermediate (**29**) reacted with methyl chlorocarbonate in the presence of Et_3N to give **30** in 91% yield. Methoxycarbonylation is not the only serviceable method to modify the hydroxy group of the intermediate (**29**): various reactions such as acylation, alkoxycarbonylation, alkylation or sulfonylation can also be used to produce the corresponding derivatives.

CONCLUSION

We established four routes to synthesize a wide variety of new *N*-oxydihydropyrrole derivatives employing an intramolecular Claisen condensation reaction. The series of products were subjected to biological assays and exhibited high insecticidal activity, which will be discussed in detail elsewhere.

EXPERIMENTAL

General: All melting points 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. MS and HRMS spectra were obtained with a JEOL JMS-D300 mass spectrometer and a VG Auto Spec M mass spectrometer. Materials were obtained from commercial suppliers where possible. Regular silica gel (Daisogel 1001W, 63-210 mesh) was used for column chromatography except for the purification of hydroxylamines, which was performed by means of neutral silica gel (Silica gel 60. spherical. neutrality. 150 mesh, Nacalai Tesque).

Ethyl 2-(*N*-mesitylacetyl-*N*-methoxyamino)-2-methylpropanoate (9). To a stirred solution of ethyl 2-methoxyamino-2-methylpropionate[5] (**7**, 161.2 mg, 1.0 mmol), 4-dimethylaminopyridine (5 mg, 0.04 mmol) and Et_3N (0.15 mL, 10.8 mol) in CH_2Cl_2 (5 mL) was added mesitylacetyl chloride (**8**, 200.0 mg, 1.02 mmol) at 0 ^oC and the mixture was stirred at the same temperature for 1 h. Then the reaction mixture was poured into water and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried [anhydrous magnesium sulfate ($MgSO_4$)], and concentrated to an oil, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/10) to give the title

compound (**9**, 131.1 mg, 41 %) as colorless prisms; mp: 71-72 ^{o}C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 6.84 (2H, s), 4.19 (2H, q, *J*=7.0 Hz), 3.93 (3H, s), 3.54 (2H, s), 2.24 (3H, s), 2.22 (6H, s), 1.54 (6H, m), 1.19 (3H, t, *J*=7.0 Hz); IR (KBr) cm^{-1}: 2986, 1738, 1680, 1471, 1442, 1382, 1355, 1291, 1246, 1153, 1081, 1031; MS(EI) m/z: 321 (M^+); *Anal*. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.28; H, 8.44; N, 4.31.

4-Hydroxy-3-mesityl-1-methoxy-5,5-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (10). To a stirred solution of **9** (131.1 mg, 0.41 mmol) in DMF (3 mL) was added *t*-BuOK (65.0 mg, 0.58 mmol) at ambient temperature. After the resulting mixture was stirred at the same temperature for 30 min, the mixture was poured into water. And then the water layer was washed with hexane, acidified to *ca*. pH 3 with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a syrup, which was subjected to silica gel column chromatography (EtOAc/Hexane, 1/2) to give the title compound (**10**, 35.4 mg, 32%) as a white powder; mp: 204-207 ^{o}C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 6.92 (2H, s), 5.86 (1H, br s), 3.96 (3H, s), 2.28 (3H, s), 2.15 (6H, s), 1.52 (6H, s); IR (neat) cm^{-1}: 2978, 1655, 1612, 1487, 1464, 1438, 1392, 1368, 1330, 1291, 1244, 1174, 1090; MS(EI) m/z: 275 (M^+); *Anal*. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.72; H, 7.68; N, 5.06.

Ethyl 2-nitro-2-methylpropionate (11).[7] To a stirred suspension of $NaNO_2$ (52.80 g, 0.77 mol) in dimethyl sulfoxide (DMSO) (500 mL) was added ethyl 2-bromoisobutylate (**6**, 100.00 g, 0.51 mol) at ambient temperature. The mixture was stirred at 80 ^{o}C for 3 h. Then the reaction mixture was poured into ice/water and extracted with ethyl ether (Et_2O). The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a yellowish liquid, which was distilled *in vacuo* to give the title compound (**11**, 75.58 g, 92 %) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 4.27 (2H, q, *J*=7.2 Hz), 1.82 (6H, s), 1.29 (3H, t, *J*=7.2 Hz).

Ethyl 2-(*N*-hydroxyamino)-2-methyl-propionate (12).[8] To a stirred suspension of **11** (100.00 g, 0.62 mol) and NH_4Cl (132.50 g, 2.48 mol) in ethanol (EtOH) (200 mL) and water (400 mL) was added zinc powder (122.50 g, 1.87 mol) in several portions with the maintenance of a temperature under 40 ^{o}C and

the mixture was stirred at 35 ^{o}C for 5 h. Then the mixture was filtered and the filtrate was concentrated. To the resultant residue were added Et_2O and water. The water layer was separated and the organic layer was extracted with 1N HCl. The combined water layer was washed with Et_2O and its pH was adjusted to *ca*. 10 with potassium carbonate (K_2CO_3). The water layer was then extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a brownish oil, which was subjected to neutral silica gel column chromatography (EtOAc/hexane, 1/4) to give the title compound (**12**, 47.98 g, 52 %) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 4.21 (2H, q, *J*=7.2 Hz), 1.32 (6H, s), 1.29 (3H, t, *J*=7.2 Hz).

Ethyl 2-(*N*-hydroxy-*N*-mesitylacetylamino)-2-methylpropanoate (13) and **Ethyl 2-(*N*-mesitylacetyloxyamino)-2-methylpropanoate (14).** To a stirred two-phase solution of **12** (5.90 g, 40.1 mmol) and $NaHCO_3$ (3.70 g, 44.0 mmol) in EtOAc (60 mL) and water (40 mL) was added dropwise a solution of mesitylacetyl chloride (**8**, 8.70 g, 44.0 mmol) in EtOAc (40 mL) at *ca*. 0 ^{o}C. The mixture was stirred at ambient temperature for 3 h. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated to give a brownish oil, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/4) to separate the title compounds, **13** (5.46 g, 44 %) and **14** (2.09 g, 17 %). **13**: white powder; mp: 151-153 ^{o}C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 6.84 (2H, s), 6.15 (1H, br s), 4.15 (2H, q, *J*=7.4 Hz), 3.80 (2H, s), 2.24 (3H, s), 2.22 (6H, s), 1.54 (6H, s), 1.23 (3H, t, *J*=7.0 Hz); IR (KBr) cm^{-1}: 3134, 2856, 1747, 1595, 1446, 1274; HRMS(EI) Calcd for $C_{17}H_{25}NO_4$: 307.1784, Found 307.1782. **14**: colorless oil; ^{1}H NMR ($CDCl_3$) δ: 7.68 (1H, s), 6.84 (2H, s), 4.01 (2H, q, *J*=7.2 Hz), 3.64 (2H, s), 2.28 (6H, s), 2.24 (3H, s), 1.32 (6H, s), 1.16 (3H, t, *J*=7.0 Hz); IR (neat) cm^{-1}: 2985, 1737, 1614, 1446, 1382, 1279, 1241, 1154, 1025; HRMS(EI) Calcd for $C_{17}H_{25}NO_4$: 307.1784, Found 307.1782.

Ethyl 2-(*N*-mesitylacetyl-*N*-methoxymethoxyamino)-2-methylpropanoate (15). To a stirred solution of **13** (1.01 g, 3.29 mmol) in DMF (10 mL) was added NaH (60% dispersion in mineral oil, 0.15 g, 3.75 mmol) at 0^{o}C and the reaction mixture was stirred for 10 min. Then to the reaction mixture was added MOMCl (0.3 mL, 3.95 mmol) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 1 h and at ambient

temperature for 2 h. The reaction mixture was poured into brine and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a brownish oil, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/20) to give the title compound (**15**, 1.12 g, 97 %) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.84 (2H, s), 5.10 (2H ,s), 4.10 (2H, q, *J*=7.1 Hz), 3.90 (2H, s), 3.63 (3H ,s), 2.24 (3H, s), 2.21 (6H, s), 1.52 (6H,s), 1.18 (3H, t, *J*=7.1 Hz); IR (neat) cm^{-1}: 2988, 1741, 1680, 1461, 1380, 1270, 1152, 1063; HRMS(EI) Calcd for $C_{19}H_{29}NO_5$ 351.2046, Found 351.2045.

4-Hydroxy-3-mesityl-1-methoxymethoxy-5,5-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (16). To a stirred solution of **15** (351.2 mg, 1.00 mmol) in DMF (7 mL) was added *t*-BuOK (123.8 mg, 1.10 mmol) at ambient temperature and the reaction mixture was stirred at the same temperature for 2 h. The mixture was poured into water and the water layer was washed with hexane. Then the water layer was acidified to *ca*. pH 3 with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a syrup, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/2) to give the title compound (**16**, 227.1 mg, 74 %) as colorless prisms; mp: 151-153 ^{o}C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 6.91 (2H, s), 6.48 (1H, br s), 5.01 (2H, s), 3.59 (3H, s), 2.28 (3H, s), 2.14 (6H, s), 1.51 (6H, s); IR (KBr) cm^{-1}: 2985, 2938, 2574, 1630, 1466, 1393, 1368, 1340, 1286, 1156, 1082, 1062; MS(EI) m/z: 305 (M^+); *Anal*. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.89; H, 7.49; N, 4.40.

Methyl 1-(*N*-Hydroxyamino)-1-cyclohexanecarboxylate (19). To a stirred solution of diisopropylamine (1.54 mL, 11.1 mmol) in THF (10 mL) was added 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) at –78 ^{o}C, and the reaction mixture was stirred at the same temperature for 1h. To the reaction mixture, methyl cyclohexanecarboxylate (**21**, 1.42 g, 10.0 mmol) was added at –78 ^{o}C, and then the reaction mixture was stirred at the same temperature for 1 h. To the reaction mixture, 1-chloro-1-nitrosocyclohexane (**22**, 1.62 g, 11.0 mmol) was added at –78 ^{o}C, and then the reaction mixture was stirred at the same temperature for another 1 h. To the reaction mixture 1N HCl (20 mL) was added, and

the mixture was stirred at ambient temperature for 3 h. The water layer was separated and the organic layer was extracted with 1N HCl. Then the combined water layer was washed with 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 to give a syrup, which was subjected to neutral silica gel column chromatography (EtOAc/hexane, 1/4) to give the title compound (**19**, 1.02 g, 59 %) as yellowish needles; mp 39-41 ^oC; ^1H NMR (DMSO-d_6) δ: 7.32 (1H, s), 5.65 (1H, br s), 3.61 (3H, s), 1.80-1.34 (10H, m); IR (KBr) cm^{-1}: 3261, 2933, 1724, 1448, 1431, 1281, 1240, 1148, 1108, 1084, 1070, 1032; HRMS Calcd for $C_8H_{15}NO_3$ 173.1052, Found 173.1053.

Methyl 1-(*N*-hydroxy-*N*-mesitylacetylamino)-1-cyclohexanecarboxylate (23) and **Methyl 1-(*N*-mesitylacetyloxyamino)-1-cyclohexanecarboxylate (24).** Compounds (**23**) and (**24**) were prepared from **19** and mesitylacetyl chloride (**8**) by a procedure similar to that described for **13** and **14**. **23**: 42 %; white powder; mp 196-197 ^oC (from EtOAc/hexane); ^1H 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. **24**: 48 %; colorless oil; ^1H NMR ($CDCl_3$) δ: 7.70 (1H, s), 6.85 (2H, s), 3.62 (2H, s), 3.53 (3H, s), 2.27 (3H, s), 2.24 (6H, s), 1.95-1.45 (10H, m); IR (KBr) cm^{-1}: 2937, 2860, 1740, 1456, 1215, 1134; HRMS(EI) Calcd for $C_{19}H_{27}NO_4$ 333.1940, Found 333.1941.

4-Hydroxy-3-mesityl-1-methoxymethoxy-1-azaspiro[4.5]dec-3-en-2-one (26). To a stirred solution of **23** (0.62 g, 1.86 mmol) and MOMCl (0.17 mL, 2.23 mmol) in DMF (6 mL) was added NaH (60 % dispersion in mineral oil, 89.2 mg, 2.23 mmol) at 0 ^oC and the reaction mixture was stirred at the same temperature for 30 min and at ambient temperature for 2 h. Then to the stirred reaction mixture was added DMF (6 mL) and *t*-BuOK (0.31 g, 2.79 mmol) at 0 ^oC and the reaction mixture was stirred at ambient temperature for 2 h. The mixture was poured into water and the water layer was washed with Et_2O. The water layer was acidified to *ca*. pH 3 with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a syrup, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/1) to give the title compound (**26**,

72 % in 2 steps) as colorless prisms; mp 159-161 ^{o}C (from EtOAc/hexane); ^{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-Mesityl-1-methoxymethoxy-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (28). To a stirred solution of **16** (147.0 mg, 0.48 mmol) and Et_3N (0.115 mL, 0.83 mmol) in CH_2Cl_2 (2 mL) was added 3,3-dimethylbutyryl chloride (0.09 ml, 0.65 mmol) at 0^{o}C, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into water and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give an oil, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/4) to give the title compound (**28**, 133.8 mg, 69 %) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.82 (2H, s), 5.05 (2H, s), 3.61 (3H, s), 2.23 (3H, s), 2.18 (2H, s), 2.15 (6H, s), 1.49 (6H, s), 0.83 (9H, s); IR (neat) cm^{-1}: 2958, 1778, 1732, 1674, 1613, 1573, 1464, 1386, 1367, 1317, 1213, 1160, 1126, 1091, 1064; HRMS(EI) Calcd for $C_{23}H_{33}NO_5$ 403.2359, Found 403.2360.

1-Hydroxy-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (29). To a stirred solution of **28** (3.47 g, 5.60 mol) in CH_2Cl_2 (20 mL) was added TMSBr (11.4 mL, 86.4 mol) and molecular sieves 3A (*ca*. 1 g) at 0^{o}C, and the resultant mixture was stirred at the same temperature for 4 h. The reaction mixture was poured into water and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to give a solid, which was subjected to silica gel column chromatography (EtOAc/hexane, 1/3) to give the title compound (**29**, 2.12 g, 69 %) as a white powder; mp: 191-193 ^{o}C (from EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ: 9.74 (1H, s), 6.84 (2H, s), 2.24 (2H, s), 2.21 (3H, s), 2.07 (6H, s), 1.34 (6H, s), 0.75 (9H, s); IR (KBr) cm^{-1}: 2956, 2867, 1787, 1687, 1611, 1480, 1464, 1368, 1321, 1213, 1177, 1146, 1097, 1077, 1035; MS(EI) m/z: 359 (M^+); *Anal*. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.02; H, 8.01; N, 3.57.

4-Mesityl-1-methoxycarbonyloxy-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 3,3-dimethylbutanoate (30). To a stirred solution of **29** (161.0 mg, 0.45 mmol) in CH_2Cl_2 (1.5 mL) and Et_3N (0.100

mL, 0.72 mmol) was added methyl chloroformate (0.050 mL, 0.65 mmol) at 0^{o}C, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was poured into water and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a oil, which was subjected to preparative thin layer chromatography (EtOAc/hexane, 1/3) to give the title compound (**30**, 171.0 mg, 91 %) as colorless prisms; mp: 138-141 ^{o}C (from EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 6.83 (2H, s), 3.95 (3H, s), 2.24 (3H, s), 2.19 (2H, s), 2.17 (6H, s), 1.10 (6H, s), 0.83 (9H, s); IR (KBr) cm^{-1}: 2961, 1805, 1772, 1720, 1674, 1614, 1443, 1322, 1244, 1193, 1136, 1099, 1081, 1042; MS(EI) m/z: 417 (M^{+}); *Anal*. Calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N,3.35. Found: C, 66.27; H, 7.37; N, 3.12.

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