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Cyclic Dibenzoylhydrazines Reproducing the Conformation of Ecdysone Agonists, RH-5849

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Abstract—We have investigated the biologically active conformation of the non-steroidal ecdysone agonist, 1-*tert*-butyl-1,2-dibenzoylhydrazine (RH-5849) by means of design, synthesis and conformational analysis of cyclic derivatives of RH-5849. Among the synthesized compounds, a 6-membered cyclic hydrazine bearing two benzoyl groups (**5**) exists in three conformational states in solution, and the major unsymmetrical conformer of **5** is similar to that of RH-5849 on the basis of ^{1}H NMR and X-ray analyses. The 3,3-dimethyl derivative of **5** (**10**) exists as a single unsymmetrical conformer. Although there is conformational similarity of the cyclic derivatives with RH-5849, these compounds did not show any hormonal or insecticidal activity. The hydrogen bonding character of the amide N–H group of the dibenzoylhydrazine seems to play a critical role in the appearance of the biological activity.

Introduction

In 1988, 1-*tert*-butyl-1,2-dibenzoyl hydrazine (RH-5849, **1**) was reported by Wing as the first nonsteroidal ecdysone agonist.[1] Although there exists structural dissimilarity between RH-5849 and the insect molting hormone, 20-hydroxyecdysone (20-HE, **2**), RH-5849 competes with ^{3}H-ponasterone A at the binding site on *Drosophila* ecdysteroid receptor and induces a morphological change in ecdysteroid responsive cells (Kc cells) in culture.[1] Moreover, the metabolic stability of RH-5849 is superior to that of ecdysteroids and RH-5849 causes whole insects to initiate a precocious, incomplete and lethal molt.[2] Because of the unique mechanism of action and simple structure of RH-5849, a variety of dibenzoylhydrazine (DBH) derivatives were synthesized for evaluation of their insecticidal activity. In the structure–activity relationship (SAR) study, some compounds had not only strong insecticidal activity, but also neglible mammalian toxicity and high environmental safety. RH-5992 (**3**)[3] and ANS-118 (**4**)[4] were discovered and developed as new insect growth regulators (IGR) (Fig. 1). If RH-5849 does bind with the ecdysone-binding site, ecdysteroids and DBH derivatives would be expected to have some common structural character that is recognized by the receptor. Superpositional studies based on the crystalline structures of RH-5849 and 20-HE have been carried out and several different models have been proposed by various groups. For example, Nakagawa et al. analyzed SAR using comparative molecular field analysis (CoMFA) and proposed a model in which the A-ring and an oxygen atom on the carbonyl group at the B-ring of RH-5849 are superimposed on the side chain and 14α-OH of 20-HE.[5] On the other hand, Quian used the PCMODEL method and proposed a different model in which the B-ring and an oxygen atom on the carbonyl group at the B-ring of RH-5849 are superimposed on the B-ring and 14α-OH of 20-HE.[6] Recently, Wurtz et al. have constructed two homology models (ECRra and ECRvd) of the *Chironomus tentans* ECR ligand-binding domain (LBD) and suggested a novel superposition of 20-HE and RH-5849.[7] The great differences in structural and physico-chemical natures between ecdysteroids and DBH derivatives cause difficulty in identifying essential hydrogen-bonding factors and shape-recognition factors. In this paper, we describe the design, synthesis and conformational analysis of dibenzoyl derivatives having 5–7-membered cyclic hydrazines, for the purpose of conformational restriction of flexible DBH molecules.

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Results and Discussion

Molecular design

The X-ray structure of RH-5849 was elucidated in 1989 (Fig. 2).[8] It has a characteristic T-shaped conformer with the unsubstituted amide bond in *trans* conformation and the *tert*-butyl substituted amide in *cis* conformation. The dihedral angle of the two amide planes showed a gauche conformation with an angle of 71.8 or 58.1° (two molecules in the asymmetric unit) that is affected by the bulky *tert*-butyl group. The X-ray structure is assumed to be one of the lowest energy states of a molecule and may offer a clue to the active conformation. The conformational states in solution were classified into five conformational domains based on the backbone torsional angles by MACROMODEL.[9] The conformational domains can be described in terms of the geometry of the two amide bonds, where the first descriptor is for the amide bond of the unsubstituted benzamide (ring A) and the second one is for the *N*-*tert*-butyl benzamide side (ring B) of the diacylhydrazine. Among these domains, Hsu et al. suggested that two stable conformers need to be considered in developing binding models.[10] One is the *trans*/*cis* conformer in the X-ray structure and the other is the *cis*/*cis* folded conformer. These conformers were equivalent in total energy (including solvation energy) and this result indicated the existence of a possible active conformer other than the X-ray structure. Wurtz et al. conducted conformational analysis of RH-5849 by using density function theory and proposed two conformers, crystal-like and rotated, as minimum energy structures.[7] They also constructed two homology models of the *Chironomus tentans* ECR ligand-binding domain (LBD) by taking as templates the known LDB crystal structures of the retinoic acid and vitamin D receptor. A docking study of 20-HE and RH-5849 was carried out using the proposed LBD models, ECRra and ECRvd. As a result, the *tert*-butyl group was located in the hydrophobic region delineated by helices H5, H6, H7, and H11 and occupied only partially by 20-HE. Dibenzoyl derivatives of cyclic hydrazines may restrict the orientations of the two benzoyl groups and the hydrophobic cavity in the LDB models seems to be wide enough to accept the additional methylene groups of the ring. It is considered that the cyclic derivatives should be suitable for investigation of the conformational analysis of DBH derivatives. On the other hand, the introduction of a substituent group on amide–NH and replacement by another atom led to a reduction of the activity.[10] It is considered that the NH hydrogen bond contributes to the binding, though conformational change upon introduction of an *N*-substituent group could also account for the loss of activity. We have demonstrated the conformational alteration caused by *N*-methylation of aromatic amides,[11] guanidine[12] and ureas.[13] The *N*-methyl or alkyl group in these compounds exists in *cis*-orientation to the carbonyl group, both in the crystal and in solution.[14] Dibenzoyl derivatives of cyclic hydrazines, in which the orientations of the two benzoyl groups may be restricted, should be suitable for investigation of the conformational analysis of DBH derivatives. Therefore, we designed 5-, 6- and 7-membered cyclic derivatives (**5**–**9** and **10**) at the hydrazine moiety with the aim of fixing the characteristic structure of RH-5849 (Fig. 2).

Synthesis

The syntheses of the designed molecules are summarized in Scheme 1. *tert*-Butoxycarbonylhydrazine hydrochloride (**11**) was converted to 1-*tert*-butoxycarbonyl-2-carbobenzyloxyhydrazine (**12**) by treatment with carbobenzoxy chloride in CH_2Cl_2. Treatment of **12** with sodium hydride in DMF followed by reaction with 1,4-dibromobutane afforded the protected 6-membered cyclic hydrazine (**13**) (72% in two steps).[15,16] The five- (**14**) or seven-membered cyclic hydrazine (**15**) was prepared from **12** by using 1,3-dibromopropane or 1,5-dibromopentane instead of 1,4-dibromobutane (69 and 56%, respectively). Reductive deprotection of the CBZ

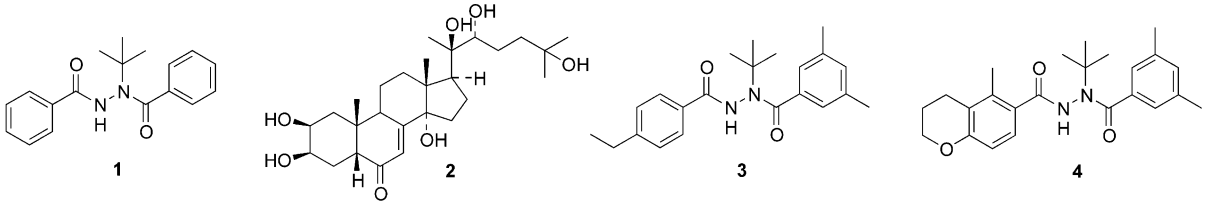


Figure 1. Structures of RH-5849 (**1**), 20-hydroxyecdysone (**2**), RH-5992 (**3**) and ANS-118 (**4**).

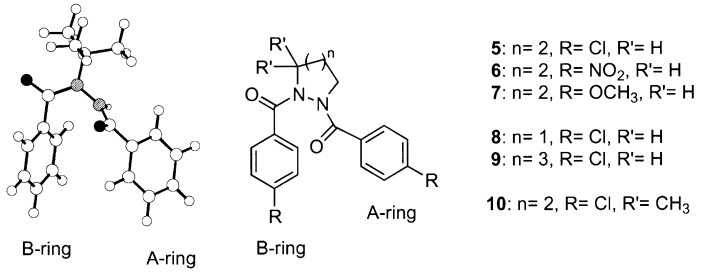
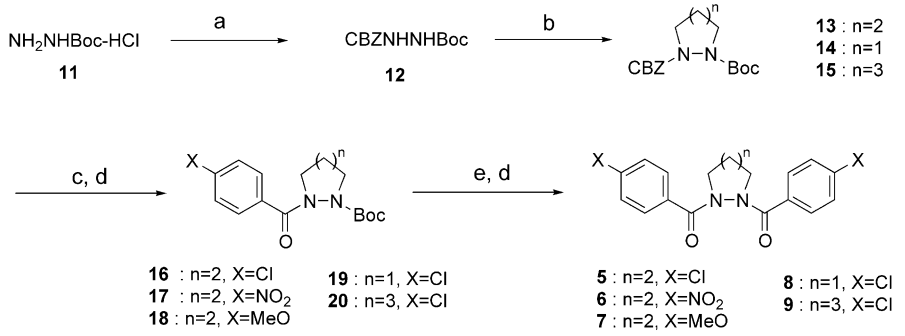


Figure 2. X-ray structure model of RH-5849 (**1**) and the designed cyclic molecules.

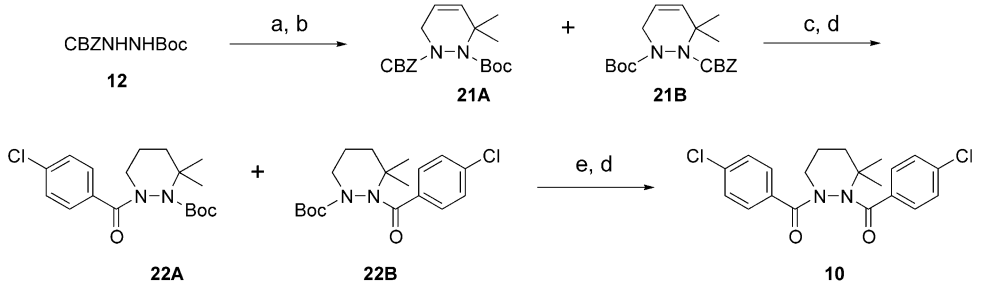
group of **13** using 10% Pd/C as a catalyst in methanol, followed by condensation with 4-chlorobenzoyl chloride, yielded the monobenzoyl compound (**16**) (90% in two steps). After deprotection of the Boc group of **16** using trifluoroacetic acid, condensation with 4-chlorobenzoyl chloride afforded the bis(4-chlorobenzoyl) derivative (**5**) (89% in two steps). The bis(4-nitrobenzoyl) (**6**) and bis(4-methoxybenzoyl) (**7**) derivatives were prepared in a manner similar to that described for **5**. The bis(4-chlorobenzoyl)hydrazines with five- (**8**) and seven-membered (**9**) structures were also prepared in a manner similar to that described for **5**. The 6-membered bis(4-chlorobenzoyl)hydrazine substituted with a dimethyl group at the 3-position (**10**), which corresponds to the *tert*-butyl group of RH-5849, was prepared as follows (Scheme 2). Oxidation of **12** using *N*-bromosuccinimide in pyridine,[17] followed by cycloaddition with 4-methyl-1,3-pentadiene in toluene, yielded a mixture of the cyclic isomers (**21A** and **21B**) (17% in two steps).[18] Catalytic hydrogenation of the mixture gave amines that were condensed with 4-chlorobenzoyl chloride to afford a mixture of monobenzoyl derivatives (**22A** and **22B**) (85% in two steps). After deprotection of the Boc group using trifluoroacetic acid, the amines were condensed with 4-chlorobenzoyl chloride to give **10** (quantitative in two steps).

Conformational Analysis in Solution and Crystalline Structure

The conformations of the cyclic derivatives were estimated in terms of three possible conformers, *trans*/*cis* (I), *cis*/*cis* (II) and *trans*/*trans* (III). These conformers correspond to T-shaped, folded and extended conformers, which were defined in the case of calculation of DBH by Hsu et al.[10] The ^{1}H NMR spectral data of the 6-membered cyclic compound (**5**) showed line-broadening at room temperature, suggesting the existence of plural conformational isomers. Then, ^{1}H NMR experiments were carried out at $-40\,^{\circ}C$ and three isomers were detected (Fig. 3 and Table 1). The ratio of these conformers was 91:7:2. Assignment of each signal was determined by examination of decoupling results and the coupling constants of all protons.



Scheme 1. Synthesis of cyclic dibenzoylhydrazine derivatives. Key: (a) ref 14; (b) $BrCH_2(CH_2)nCH_2Br$, NaH, DMF; (c) H_2, 10% Pd/C, MeOH; (d) 4-X-C_6H_4COCl, Et_3N, CH_2Cl_2; (e) TFA, CH_2Cl_2.



Scheme 2. Synthesis of **10**. Key: (a) NBS/pyridine, CH_2Cl_2; (b) 4-methyl-1, 3-pentadiene, toluene; (c) H_2, 10% Pd/C, MeOH; (d) 4-Cl-C_6H_4COCl, Et_3N, CH_2Cl_2; (e) TFA, CH_2Cl_2; (f) 4-Cl-C_6H_4COCl, Et_3N, DMAP, CH_2Cl_2.

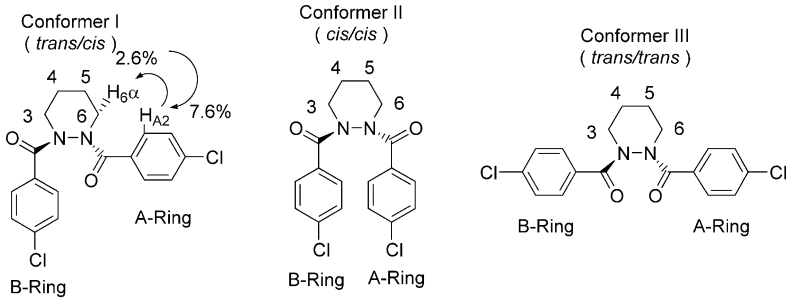


Figure 3. Conformational isomers of the six-membered cyclic derivative (**5**).

The major conformational isomer, exhibited (1) different chemical shifts in the two benzene rings (A-ring vs B-ring), and (2) different chemical shifts of four methylene protons (H3α vs H6β, H3β vs H6α) adjacent to the nitrogen atom. In addition, two characteristic phenomena were observed. One was that the signal of the benzene A-ring HA2 proton (7.11 ppm) suggested a location over the other benzene ring. In an NOE experiment, saturation of the benzene A-ring HA2 proton resulted in a 2.6% enhancement of the H6α signal and saturation of the H6α proton caused a 7.6% enhancement of the HA2 signal. These results indicate that these two protons (HA2 and H6α) are spatially close. The other was downfield shifting of the H3β proton (4.67 ppm), and high field shifting of the H6β proton (3.36 ppm). These changes were considered to be caused by the location of these protons above the benzene A-ring and the amide carbonyl, respectively. These data indicate that the *trans*/*cis* conformational isomer (I) is the major one, and is similar to the X-ray structure of RH-5849. In reference to the minor conformers, the folded conformer (II) showed downfield shifting of the H3β and H6α protons (4.90 ppm) caused by the anisotropic effect of the amide carbonyl and upper field shifting of aromatic protons (7.20 and 7.28 ppm). This conformation is similar to the folded form described by Hsu et al.[10] Moreover, the extended conformer (III) showed signals at 3.52 and 3.99 ppm due to methylene protons adjacent to the nitrogen atom and 7.47 and 7.63 ppm due to aromatic protons. The effects of functional groups (nitro and methoxy group) introduced on the benzene ring were investigated, and the ^{1}H NMR data at −40 °C are summarized in Table 1. The ^{1}H NMR spectral data of both derivatives (**6** and **7**) showed the existence of three conformers in the same way as for the 4-chloro derivative (**5**). In each conformer, all chemical shifts of methylene protons on the tetrahydropyridazine ring were similar to those of the chloride (**5**). The benzene A-ring HA2 proton was also shielded by the B-ring, and the signal was at about 1 ppm higher field than that of standard nitro or amide benzene derivatives. The conformer ratios of these derivatives were 94:4:2 and 91:8:1, respectively.

In order to investigate the effect of ring size, ^{1}H NMR spectral examination of the five- (**8**) and seven-membered ring (**9**) derivatives was performed. Sharp signals were observed at −60 °C for **8** and at −40 °C for **9** (Table 1). For both compounds, the major conformer was the unsymmetrical conformer (I). With the expansion of the ring size from five to seven, the benzene rings were brought closer together and the benzene A-ring HA2 proton (6.93 ppm) of the 7-membered ring was strongly shielded by the B-ring. The conformer ratios of the five- (**8**), and the seven-membered ring derivatives (**9**) were 81:3:16 and 81:16:3, respectively. In addition, the change of the ring size of the six-membered derivative (**5**) caused a decrease of the unsymmetrical conformer (I). The six-membered bis(4-chlorobenzoyl)hydrazine substituted with a dimethyl group at the 3-position (**10**) had a sharp ^{1}H NMR spectrum at room temperature. By substitution of the dimethyl group at the C3 carbon adjacent to amide nitrogen, the geometry of the amide

Table 1. ^{1}H NMR chemical shifts of three conformers of **5**, and the major conformer (conformer I) of **6**–**9** at −40 °C

No.	**5**			**6**	**7**	**8**[a]	**9**
Conf.	Conformer I	Conformer II	Conformer III	Conformer I	Conformer I	Conformer I	Conformer I
Solv.	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
Ring	6	6	6	6	6	5	7
H3α	3.17 (m)	n.d.[b]	3.52 (br t, J = 12.1 Hz)	3.21 (dt, J = 4.0, 12.8 Hz)	3.20 (dt, J = 3.7, 12.5 Hz)	3.63 (m)	3.61 (m)
H3β	4.67 (d, J = 13.2 Hz)	4.90 (d, J = 12.1 Hz)	3.99 (d, J = 12.8 Hz)	4.72 (d, J = 12.8 Hz)	4.66 (d, J = 12.5 Hz)	4.30 (m)	4.38 (m)
H4α	1.91 (m)	n.d.	n.d.	2.00 (m)	1.88 (m)	2.71 (m)	2.20 (m)
H4β	1.91 (m)	n.d.	n.d.	2.00 (m)	1.88 (m)	2.35 (m)	1.44–1.96 (m)
H5α	1.56 (m)	n.d.	n.d.	1.60 (m)	1.55 (m)	3.91 (br t, J = 10.0 Hz)	1.44–1.96 (m)
H5β	1.77 (br d, J = 13.6 Hz)	n.d.	n.d.	1.87 (br d, J = 14.3 Hz)	1.71 (br d, J = 12.8 Hz)	3.70 (m)	1.44–1.96 (m)
H6α	3.86 (dd, J = 2.6, 13.2 Hz)	4.90 (d, J = 12.1 Hz)	3.99 (d, J = 12.8 Hz)	3.81 (dd, J = 2.9, 13.6 Hz)	3.96 (d, J = 12.8 Hz)	—	1.44–1.96 (m)
H6β	3.36 (dt, J = 2.6, 13.2 Hz)	n.d.	3.52 (br t, J = 12.1 Hz)	3.48 (dt, J = 2.6, 13.6 Hz)	3.36 (t, J = 12.8 Hz)	—	1.44–1.96 (m)
H7α	—	—	—	—	—	—	3.54 (m)
H7β	—	—	—	—	—	—	3.15 (m)
HA2	7.11 (d, J = 8.1 Hz)	7.20 (d, J = 8.4 Hz)	7.47 (d, J = 8.4 Hz)	7.26 (d, J = 8.8 Hz)	7.23 (d, J = 8.4 Hz)	7.42 or 7.35 (d, J = 8.4 Hz)	6.93 (d, J = 8.4 Hz)
HB2	7.53 (d, J = 8.4 Hz)	7.20 (d, J = 8.4 Hz)	7.47 (d, J = 8.4 Hz)	8.27 (d, J = 8.8 Hz)	6.87 (d, J = 8.4 Hz)	7.63 (d, J = 8.4 Hz)	7.48 (d, J = 8.4 Hz)
HA3	7.37 (d, J = 8.1 Hz)	7.28 (d, J = 8.4 Hz)	7.63 (d, J = 8.4 Hz)	7.77 (d, J = 8.8 Hz)	7.58 (d, J = 8.1 Hz)	7.42 or 7.35 (d, J = 8.4 Hz)	7.36 (d, J = 8.4 Hz)
HB3	7.38 (d, J = 8.4 Hz)	7.28 (d, J = 8.4 Hz)	7.63 (d, J = 8.4 Hz)	8.32 (d, J = 8.8 Hz)	6.89 (d, J = 8.1 Hz)	7.34 (d, J = 8.4 Hz)	7.43 (d, J = 8.4 Hz)
MeO	—	—	—	—	3.83 (s)	—	—

[a]The spectral measurement of **8** was carried out at −60 °C.
[b]n.d., not detected.

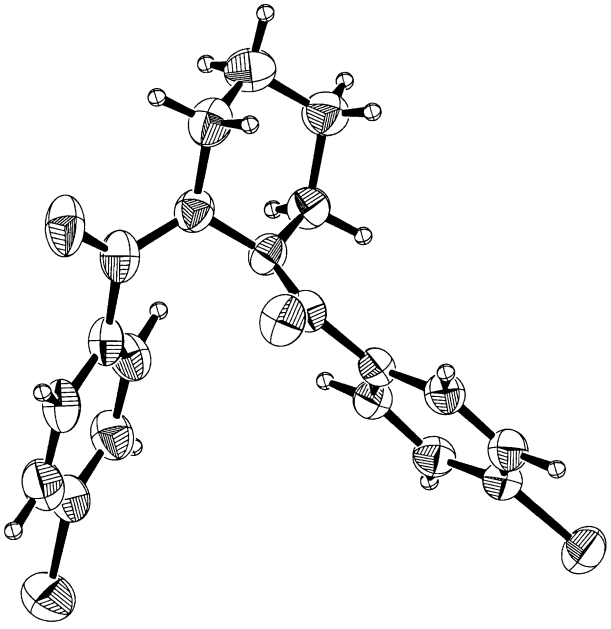


Figure 4. Crystal structure of **5** (ORTEP representation).

leading to the benzene B-ring was fixed in the *cis* conformation. The benzene A-ring HA2 proton (6.81 ppm) was strongly shielded compared with that in **5**, because the B-ring was closer to the A-ring due to the steric effect of the methyl groups.

The crystal structure of the 6-membered bis(4-chlorobenzoyl)hydrazine (**5**) is illustrated in Figure 4. The structure is a T-shaped *trans*/*cis* conformation, which is similar to the X-ray structure of RH-5849. The dihedral angle (65.5°) of the two amide planes showed a gauche conformation. In the ^{1}H NMR experiment on the major conformer (I), the highfield shielding of the A-ring HA2 proton suggested a location over the other benzene ring, and the downfield shifting of the H3β proton, and the highfield shifting of the H6β proton were consistent with the location of these protons above the benzene A-ring and the amide carbonyl. These experimental results in solution can be well explained in terms of the crystal structure.

Insecticidal activity. The insecticidal activity of the synthetic derivatives against *Spodoptera litura* (common cutworm) was evaluated. Although RH-5849 and its dichloro derivative, 1-*tert*-butyl-1,2-di-(4-chlorobenzoyl)hydrazine, caused 100% mortality owing to hyperecdysonism at 200 ppm concentration, none of the cyclic derivatives showed any significant insecticidal activity at the same concentration. Considering the LC_{50} of ANS-118 (<1 ppm), it is considered that their activity is negligible.[4]

Conclusion

In order to elucidate the biologically active conformation of 1-*tert*-butyl-1,2-dibenzoyl hydrazine derivatives, we designed and synthesized five-, six- and seven-membered cyclic derivatives, and analyzed their stereochemistry. An ^{1}H NMR study at low temperature (−40 and −60 °C) showed the existence of three different conformers in solution. The major one was considered to be the unsymmetrical conformer (I) that is similar to the X-ray structure of RH-5849, and X-ray crystallography data of **5** supported this assumption. The six-membered bis(4-chlorobenzoyl)hydrazine substituted with a dimethyl group at the 3-position (**10**) existed as a single conformer, because it was strongly fixed by the two methyl groups and the X-ray structure was well reproduced by cyclization of the hydrazine moiety. We evaluated the insecticidal activity toward *Spodoptera litura* (common cutworm); no compound had any significant hormonal or insecticidal activity on foliar application at 200 ppm concentration. Although alkylation on the amide–NH group or replacement of NH by CH_2 or O led to loss of activity, introduction of CN on the amide–NH group was exceptional.[10,19] The CN derivative showed high insecticidal activity. Because it is expected that N–CN moiety would be sensitive to acid and alkaline environments, like cyanamide, the moiety should be easily decomposed in the insect's alimentary canal, where alkaline digestive fluid is secreted,[20] thus affording the NH derivative as the active ingredient. Wurtz et al. did not mention the interaction of the amide–NH with LBD in their report, but our results suggest that hydrogen bonding of the amide–NH is necessary for interactoin with the ecdysteroid receptor to express hormonal activity.

Experimental

General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and were uncorrected. Elemental analysis was carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo and was within ±0.3% of the theoretical values. NMR spectra were recorded on a JEOL JNM-GX400 (400 MHz) spectrometer. Chemical shifts were expressed in δ relative to tetramethylsilane in $CDCl_3$.

Benzyl 2-(*tert*-butoxycarbonyl)hexahydropyridazine-1-carboxylate (13). To a stirred solution of *N*-benzyloxycarbonyl-*N*′-*tert*-butoxycarbonyl hydrazine (**12**) (3.0 g, 11.3 mmol) in DMF (60 mL), NaH (60% in oil, 947 mg, 23.7 mmol) was added at 0 °C. After stirring the reaction mixture for 30 min at room temperature, 1,4-dibromobuane (2.56 g, 11.8 mmol) was added to the mixture and stirred overnight. The solution was poured into water and extracted with AcOEt. The organic layer was washed with water, and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane–AcOEt = 4:1 to afford 3.3 g of **13** as a colorless oil (91%). ^{1}H NMR ($CDCl_3$) 1.20–1.75 (13H, m, *t*-Bu, 2×CH_2), 2.8–3.2 (2H, br, N–CH_2), 4.0–4.25 (2H, m, N–CH_2), 5.0–5.35 (2H, m, OCH_2), 7.29–7.40 (5H, m, ArH_5).

Benzyl 2-(*tert*-butoxycarbonyl)pyrazolidine-1-carboxylate (14). The procedure was the same as that used for the preparation of **13**, employing 1.0 g (3.76 mmol) of *N*-benzyloxycarbonyl-*N*′-*tert*-butoxycarbonylhydrazine (**12**) and 797 mg (3.95 mmol) of 1,3-dibromopropane to afford 1.0 g of **14** (87%) as a colorless oil. ^{1}H NMR ($CDCl_3$) 1.42 (9H, s, *t*-Bu), 1.98–2.10 (2H, m, CH_2), 3.12–3.33 (2H, br d, N–CH_2), 3.82–4.02 (2H, br s, N–CH_2), 5.0–5.33 (2H, m, OCH_2), 7.30–7.40 (5H, m, ArH_5).

Benzyl 2-(*tert*-butoxycarbonyl)hexahydro-1, 2-diazepine-1-carboxylate (15). The procedure was the same as that used for the preparation of **13**, employing 6.0 g (22.6 mmol) of *N*-benzyloxyarbonyl-*N*′-*tert*-butoxycarbonylhydrazine (**12**) and 5.45 g (23.7 mmol) of 1,3-dibromopentane to afford 5.3 g of **7** (71%) as a colorless oil. ^{1}H NMR ($CDCl_3$) 1.20–1.75 (15H, m, *t*-Bu, 3×CH_2), 2.70–3.20 (2H, m, N–CH_2), 4.0–4.25 (2H, m, N–CH_2), 5.0–5.35 (2H, m, OCH_2), 7.27–7.40 (5H, m, ArH_5).

***tert*-Butyl hexahydropyridadine-1-carboxylate.** A mixture of 3.0 g (9.38 mmol) of **13** and catalytic amount of 10% Pd/C in 60 mL of MeOH was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and filtered. The filtrate was concentrated to give 470 mg of *tert*-butyl hexahydropyridadine-1-carboxylate (98%) as a colorless oil. ^{1}H NMR ($CDCl_3$) 1.48 (9H, s, *t*-Bu), 1.52–1.60 and 1.62–1.73 (each 2H, m, 2×CH_2), 2.88 (2H, t, J = 5.5 Hz, N–CH_2), 3.52 (2H, t, J = 5.5 Hz, N–CH_2).

***tert*-Butyl 2-(4-chlorobenzoyl)hexahydropyridadine-1-carboxylate (16).** To a stirred solution of 500 mg (2.69 mmol) of *tert*-butyl hexahydropyridadine-1-carboxylate and 0.75 mL (5.38 mmol) of Et_3N in dry CH_2Cl_2 (10 mL), 4-chlorobenzoylchloride (526 mg, 3.0 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 808 mg of the benzoyl (**16**) (93%) as a white crystal: mp 92–93.5 °C: ^{1}H NMR ($CDCl_3$) 1.35 (9H, br s, *t*-Bu), 1.70 and 1.83 (each 2H, br s, 2×CH_2), 2.70–3.05 (2H, m, N–CH_2), 4.15 and 4.54 (2H, br and br d, N–CH_2), 7.32 (2H, d, J = 8.4 Hz, ArH_2), 7.49 (2H, d, J = 8.4 Hz, ArH_2).

***tert*-Butyl 2-(4-nitrobenzoyl)hexahydropyridadine-1-carboxylate (17).** The procedure was the same as that used for the preparation of chloride (**16**), employing 500 mg (2.69 mmol) of *tert*-butyl hexahydropyridadine-1-carboxylate and 484 mg (2.28 mmol) of 4-nitrobenzoylchloride to afford 781 mg of **17** (91%) as a white crystal: mp 103–104 °C: ^{1}H NMR ($CDCl_3$) 1.36 (9H, s, *t*-Bu), 1.62–1.90 (4H, m, 2×CH_2), 2.8–3.0 (2H, m, N–CH_2), 3.80–4.25 (1H, br, N–CH), 4.55 (1H, br d, J = 12.8 Hz, N–CH), 7.68 (2H, d, J = 8.8 Hz, ArH_2), 8.22 (2H, d, J = 8.8 Hz, ArH_2).

***tert*-Butyl 2-(4-methoxybenzoyl)hexahydropyridanine-1-carboxylate (18).** The procedure was the same as that used for the preparation of chloride (**16**), employing 500 mg (2.69 mmol) of *tert*-butyl hexahydropyridadine-1-carboxylate and 412 mg (2.82 mmol) of 4-methoxybenzoylchloride to afford 816 mg of **18** (95%) as a colorless oil. ^{1}H NMR ($CDCl_3$) 1.32 (9H, br, *t*-Bu), 1.70 and 1.81 (each 2H, each br, 2×CH_2), 2.75–3.10 (2H, m, N–CH_2), 4.10–4.30 (1H, br, N–CH), 4.54 (1H, br d, J = 13.2 Hz, N–CH), 6.85 (2H, d, J = 8.4 Hz, ArH_2), 7.45 (2H, d, J = 8.4 Hz, ArH_2).

1-(4-Chlorobenzoyl)hexahydropyridazine. Trifluoroacetic acid (3.0 mL) was added to a solution of 676 mg (2.08 mmol) of **16** in 5 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 30 min, and then the solvent was removed under reduced pressure. The residue was dissolved in AcOEt, and saturated $NaHCO_3$ aq was added. The organic layer was separated and the aq layer was extracted with AcOEt. The combined extract was washed with water, and brine, and dried over $MgSO_4$. Concentration afforded 420 mg (99%) of 1-(4-chlorobenzoyl)hexahydropyridazine as a white crystal: mp 105–107 °C; ^{1}H NMR ($CDCl_3$) 1.40–2.0 (4H, br, 2×CH_2), 2.97 (2H, br, N–CH_2), 3.0–3.95 (2H, br, N–CH_2), 7.30–7.70 (4H, br, ArH_4).

1-(4-Nitrobenzoyl)hexahydropyridazine. The procedure was the same as that used for the preparation of chloride, employing 668 mg (2.17 mmol) of **17** to afford 460 mg of 1-(4-chlorobenzoyl)hexahydropyridazine (100%) as a pale yellow crystal: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) 1.30–1.95 (5H, br, 2×CH_2 and NH), 2.80–3.10 (2H, br, N–CH_2), 3.35–3.60 (1H, br, N–CH), 3.80 (1H, br s, N–CH), 7.58–7.75 (2H, br, 2-ArH_2), 8.18–8.35 (2H, br, 3-ArH_2).

1-(4-Methoxybenzoyl)hexahydropyridazine. The procedure was the same as that used for the preparation of chloride, employing 693 mg (2.17 mmol) of **18** to afford 423 mg of amine (89%) as a white crystal: mp 93–95 °C; ^{1}H NMR ($CDCl_3$) 1.40–1.90 (5H, br, 2×CH_2 and NH), 2.99 (2H, br s, N–CH_2), 3.68 (2H, br s, N–CH_2), 3.83 (3H, s, OMe), 6.90 (2H, d, J = 8.8 Hz, ArH_2), 7.49 (2H, br, ArH_2).

1, 2-Bis-(4-chlorobenzoyl)hexahydropyridazine (5). To a stirred solution of 320 mg (1.43 mmol) of 1-(4-chlorobenzoyl)hexahydropyridazine and 0.397 mL (2.85 mmol) of Et_3N in dry CH_2Cl_2 (5 mL), 4-chlorobenzoylchloride (275 mg, 1.57 mmol) was added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 515 mg of **5** (99%) as a white crystal. Mp 150–152 °C; anal. calcd for $C_{18}H_{16}C_{l2}N_2O_2$: C: 59.52, H: 4.44, N: 7.71; found: C: 59.69, H: 4.28, N: 7.83: ^{1}H NMR ($CDCl_3$) (conformer I) 1.56 (1H, m H5α), 1.77 (1H, br d, J = 13.6 Hz, H5β), 1.91 (2H, m H4α, β), 3.17 (1H, m, H3α), 3.36 (1H, dt, J = 2.6 and 13.2 Hz, H6β), 3.86 (1H, dd, J = 2.6 and 13.2 Hz, H6α), 4.67 (1H, d, J = 13.2 Hz, H3β), 7.11 (2H, d, 8.1 Hz, $ArHA_2$), 7.37 (2H, d, J = 8.1 Hz, $ArHA_3$), 7.38 (2H, d, J = 8.4 Hz, $ArHB_3$), 7.53 (2H, d, J = 8.4 Hz, $ArHB_2$); (conformer II

) 4.90 (2H, d, $J=12.1$ Hz, H3β and H6α), 7.02 (4H, d, $J=8.4$ Hz, $ArHA_2$ and $ArHB_2$), 7.28 (4H, d, $J=8.4$ Hz, $ArHA_3$ and $ArHB_3$); (conformer III) 3.52 (2H, br t, $J=12.1$ Hz, H3 and H6), 3.99 (2H, d, $J=12.8$ Hz, 3H and 6H), 7.47 (4H, d, $J=8.4$ Hz, $ArHA_3$ and $ArHB_3$), 7.63 (4H, d, $J=8.4$ Hz, $ArHA_2$ and $ArHB_2$).

1, 2-Bis-(4-nitrobenzoyl)hexahydropyridazine (6). The procedure was the same as that used for the preparation of chloride (**5**), employing 360 mg (1.63 mmol) of amine and 278 mg (1.63 mmol) of 4-nitrobenzoylchloride to afford 52 mg of **6** (9%) as a white crystal: mp 242–242.5 °C; anal. calcd for $C_{18}H_{16}N_4O_6$: C: 56.25, H: 4.20, N:14.58; found: C: 56.26, H: 4.09, N: 14.68. ^{1}H NMR ($CDCl_3$) (conformer I) 1.60 (1H, m H5α), 1.87 (1H, br d, $J=14.3$ Hz, H5β), 2.00 (2H, m, H4α, β), 3.21 (1H, dt, $J=4.0$ and 12.8 Hz, H3α), 3.48 (1H, dt, $J=2.6$ and 13.6 Hz, H6β), 3.81 (1H, dd, $J=2.9$ and 13.6 Hz, H6α), 4.72 (1H, d, $J=12.8$ Hz, H3β), 7.26 (2H, d, 8.8 Hz, $ArHA_2$), 7.77 (2H, d, $J=8.8$ Hz, $ArHB_2$), 8.27 (2H, d, $J=8.8$ Hz, $ArHA_3$), 8.32 (2H, d, $J=8.8$ Hz, $ArHB_3$); (conformer II) 4.95 (2H, d, $J=12.8$ Hz, H3β and H6α), 7.24 (4H, d, $J=8.8$ Hz, $ArHA_2$ and $ArHB_2$), 7.88 (4H, d, $J=8.8$ Hz, $ArHA_3$ and $ArHB_3$); (conformer III) 3.57 (2H, br t, $J=13.2$ Hz, H3 and H6), 3.91 (2H, d, $J=13.2$ Hz, H3 and H6), 8.20 (4H, d, $J=8.8$ Hz, $ArHA_2$ and $ArHB_2$), 8.40 (4H, d, $J=8.4$ Hz, $ArHA_3$ and $ArHB_3$).

1, 2-Bis-(4-methoxybenzoyl)hexahydropyridazine (7). The procedure was the same as that used for the preparation of chloride (**5**), employing 315 mg (1.43 mmol) of amine and 244 mg (1.43 mmol) of 4-methoxybenzoylchloride to afford 501 mg of **7** (99%) as a white crystal. Mp 85–87 °C; anal. calcd for $C_{20}H_{22}N_2O_4$; C: 67.78, H: 6.26, N: 7.90; found: C: 67.69, H: 6.20, N: 14.68; ^{1}H NMR ($CDCl_3$) (conformer I) 1.55 (1H, m H5α), 1.71 (1H, br d, $J=13.6$ Hz, H5β), 1.88 (2H, m H4α, β), 3.20 (1H, dt, $J=3.7$ and 12.5 Hz, H3α), 3.36 (1H, t, $J=12.8$ Hz, H6β), 3.83 (6H, s, 2×OMe), 3.96 (1H, d, $J=12.8$ Hz, H6α), 4.66 (1H, d, $J=12.5$ Hz, H3β), 6.87 (2H, d, 8.4 Hz, $ArHA_3$), 6.89 (2H, d, $J=8.1$ Hz, $ArHB_3$), 7.23 (2H, d, $J=8.4$ Hz, $ArHA_2$), 7.58 (2H, d, $J=8.1$ Hz, $ArHB_2$); (conformer II) 3.11 (2H, t, $J=13.2$ Hz, H3α and H6β), 4.88 (2H, d, $J=13.2$ Hz, H3β and H6α), 6.77 (4H, d, $J=8.4$ Hz, $ArHA_2$ and $ArHB_2$), 7.15 (4H, d, $J=8.4$ Hz, $ArHA_3$ and $ArHB_3$); (conformer III) 3.56 (2H, t, H3 and H6), 4.11 (2H, d, H3 and H6), 6.97 (4H, d, $J=8.4$ Hz, $ArHA_3$ and $ArHB_3$), 7.67 (4H, d, $J=8.4$ Hz, $ArHA_2$ and $ArHB_2$).

***tert*-Butyl pyrazolidine-1-carboxylate.** A mixture of 1.0 g (3.27 mmol) of **14** and catalytic amount of 10% Pd/C in 20 mL of MeOH was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and filtered. The filtrate was concentrated to give 470 mg of *tert*-butyl pyrazolidine-1-carboxylate (84%) as a colorless oil. ^{1}H NMR ($CDCl_3$) 1.49 (9H, s, *t*-Bu), 2.05 (2H, quint, $J=7.0$ Hz, CH_2), 3.07 (2H, t, $J=6.6$ Hz, N–CH_2), 3.46 (2H, t, $J=7.0$ Hz, N–CH_2).

***tert*-Butyl 2-(4-chlorobenzoyl)pyrazolidine-1-carboxylate (19).** To a stirred solution of 470 mg (2.73 mmol) of *tert*-butyl pyrazolidine-1-carboxylate and 0.761 mL (5.46 mmol) of Et_3N in dry CH_2Cl_2 (10 mL), 4-chlorobenzoylchloride (526 mg, 3.0 mmol) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 820 mg of benzoyl (**19**) (97%) as a white crystal: mp 170–172 °C: ^{1}H NMR ($CDCl_3$) 1.32 (9H, s, *t*-Bu), 2.13 (2H, br, CH_2), 3.20 and 3.40 (2H, each br, N–CH_2), 4.10 (2H, br, N–CH_2), 7.45 (2H, d, $J=8.8$ Hz, ArH_2), 7.64 (2H, d, $J=8.8$ Hz, ArH_2).

1-(4-Chlorobenzoyl)pyrazolidine. Trifluoroacetic acid (1.0 mL) was added to a solution of 88 mg (0.283 mmol) of **19** in 1 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 30 min, and then the solvent was removed under pressure. The residue was dissolved in AcOEt and saturated $NaHCO_3$ aq was added. The organic layer was separated and the aq layer was extracted with AcOEt. The combined extract was washed with water and brine and dried over $MgSO_4$. Concentration afforded 40 mg of 1-(4-chlorobenzoyl)pyrazolidine (67%) as a white crystal: mp 139–140 °C. ^{1}H NMR ($CDCl_3$) 2.13 (2H, quint, $J=7.0$ Hz, CH_2), 3.05 (2H, br, N–CH_2) 3.74 (2H, br, N–CH_2), 4.0 (1H, br, NH), 7.37 (2H, d, $J=8.8$ Hz, ArH_2), 7.67 (2H, br, ArH_2).

1, 2-Bis-(4-chlorobenzoyl)pyrazolydine (8). To a stirred solution of 117 mg (0.553 mmol) of 1-(4-chlorobenzoyl)pyrazolidine and 0.154 mL (5.46 mmol) of Et_3N in dry CH_2Cl_2 (2 mL), 4-chlorobenzoylchloride (106.5 mg, 0.608 mmol) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 147 mg of **8** (76%) as a white crystal. mp: 92–93.5 °C; anal. calcd for $C_{17}H_{14}Cl_2N_2O_2$; C: 58.47, H: 4.04, N: 8.02; found: C: 58.26, H: 4.19, N: 8.31. ^{1}H NMR ($CDCl_3$) (conformer I) 2.17 (1H, m, H4α), 2.35 (1H, m, H4β), 3.63 (1H, m, H3α), 3.70 (1H, m, H5β), 3.91 (1H, br t, $J=10$ Hz, H5α), 4.30 (1H, m, H3β), 7.34 (2H, d, $J=8.4$ Hz, $ArHB_3$), 7.42 (2H, d, $J=8.4$ Hz, $ArHA_3$), 7.53 (2H, d, $J=8.4$ Hz, $ArHA_2$), 7.63 (2H, d, $J=8.4$ Hz, $ArHB_2$); (conformer II) 2.49 (2H, br, H4α, β), 4.50 (2H, br, H3β and H5α), 6.97 (4H, br, $ArHA_2$ and $ArHB_2$), 7.27 (4H, br, $ArHA_3$ and $ArHB_3$); (conformer III) 2.26 (2H, m, H4α, β), 3.84 (4H, m, H3α, β and H3α, β).

***tert*-Butyl hexahydro-1, 2-diazepine-1-carboxylate.** A mixture of 5.19 g (15.54 mmol) of **15** and catalytic amount of 10% Pd/C in 80 mL of MeOH was vigorously stirred under 1 atm of H_2 at room temperature for 3 h and filtered. The filtrate was concentrated to give 2.92 g of *tert*-butyl hexahydro-1,2-diazepine-1-carboxylate (96%) as a colorless oil. ^{1}H NMR ($CDCl_3$)

1.48 (9H, s, *t*-Bu), 1.57–1.68 and 1.69–1.80 (4H and 2H, each m, 3×CH_2), 2.93 (2H, br s, N–CH_2), 3.48 (2H, br t, J = 6.0 Hz, N–CH_2).

***tert*-Butyl 2-(4-chlorobenzoyl)hexahydro-1, 2-diazepine-1-carboxylate (20).** To a stirred solution of 930 mg (4.65 mmol) of *tert*-butyl hexahydro-1, 2-diazepine-1-carboxylate and 1.30 mL (9.30 mmol) of Et_3N in dry CH_2Cl_2 (20 mL), 4-chlorobenzoylchloride (854 mg, 4.88 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 1.20 g of benzoyl (**20**) (76%) as a white crystal: mp 120–121.5 °C. ^{1}H NMR ($CDCl_3$) 1.39 (9H, s, *t*-Bu), 1.50–2.10 (6H, m, 3×CH_2), 2.70–2.95 (1H, m, N–CH), 3.30–3.55 (1H, m, N–CH), 3.60–4.00 (1H, m, N–CH), 4.05–4.25 (1H, m, N–CH), 7.28–7.45 (4H, m, ArH_4).

1-(4-Chlorobenzoyl)hexahydro-1, 2-diazepine. Trifluoroacetic acid (4.0 mL) was added to a solution of 1.06 g (3.13 mmol) of **20** in 3 mL of CH_2Cl_2 at 0 °C with stirring. The mixture was stirred for 30 min, and then the solvent was removed under pressure. The residue was dissolved in AcOEt, and saturated $NaHCO_3$ aq was added. The organic layer was separated and the aq layer was extracted with AcOEt. The combined extract was washed with water, and brine and dried over $MgSO_4$. Concentration afforded 420 mg of 1-(4-chlorobenzoyl)hexahydro-1,2-diazepine (99%) as a white crystal. Mp 79–80 °C; ^{1}H NMR ($CDCl_3$) 1.40–1.95 (6H, m, 3×CH_2), 2.75–3.15 (2H, m, N–CH_2), 3.40–3.95 (2H, m, N–CH_2), 5.88 (1H, br s, NH), 7.30–7.70 (4H, m, ArH_4).

1, 2-Bis-(4-chlorobenzoyl)hexahydro-1, 2-diazepine (9). To a stirred solution of 388 mg (1.15 mmol) of 1-(4-chlorobenzoyl)hexahydro-1, 2-diazepine and 0.32 mL (2.85 mmol) of Et_3N in dry CH_2Cl_2 (10 mL), 4-chlorobenzoylchloride (211 mg, 1.21 mmol) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 1:1 afforded 515 mg of **9** (91%) as a white crystal: mp 174–175 °C; anal. calcd for $C_{19}H_{18}Cl_2N_2O_2$; C: 60.49, H: 4.81, N: 7.43; found; C: 60.53, H: 4.64, N: 7.60; ^{1}H NMR ($CDCl_3$) (conformer I) 1.44–1.96 (5H, m, H5α, β and H6α,β), 2.02 (1H, m H4α), 3.15 (1H, m, H7β), 3.54 (1H, m, H7α), 3.61 (1H, m, H3α), 4.38 (1H, m, H3β), 6.93 (2H, d, J = 8.4 Hz, $ArHA_2$), 7.36 (2H, d, J = 8.4 Hz, $ArHA_3$), 7.43 (2H, d, J = 8.4 Hz, $ArHB_3$), 7.48 (2H, d, J = 8.4 Hz, $ArHB_2$); (conformer II) 3.43 (2H, m, H3α and H7β), 4.33 (2H, m, H3β and H7α), 7.05 (4H, d, J = 8.4 Hz, $ArHA_2$ and $ArHB_2$), 7.31 (4H, d, J = 8.4 Hz, $ArHA_3$ and $ArHB_3$); (conformer III) 3.72 (2H, m, H3 and H7), 7.59 (4H, d, J = 8.4 Hz, $ArHA_2$ and $ArHB_2$).

Benzyl 2-(*tert*-butoxycarbonyl)-3,3-dimethyl-6H-pyridazine-1-carboxylate (21A) and benzyl 2-(*tert*-butoxycarbonyl)-6,6-dimethyl-6H-pyridazine-1-carboxylate (21B). To a solution of 3.0 g (11.3 mmol) of **12** and 0.91 mL (11.3 mmol) of pyridine in CH_2Cl_2 (30 mL), NBS (2.01 g, 11.3 mmol) was added at 0 °C and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water, and brine and dried over $MgSO_4$. Concentration afforded crude diimide and the residue was used without purification at next step. A mixture of the crude diimide and 1.3 mL (11.3 mmol) of 4-methyl-1,3-pentadiene in 30 mL of the solvent was stirred under argon at 70 °C overnight. After evaporation of the solvent, the residue was purified by chromatography on silica gel with *n*-hexane/AcOEt = 19:1 to afford 675 mg (17%) of a mixture of **21A** and **21B** (1:4) as a colorless oil. ^{1}H NMR ($CDCl_3$) (**21A**) 1.33 (3H, s, CH_3), 1.34 (9H, s, *t*-Bu), 1.43 (3H, s, CH_3), 3.75 (1H, d, J = 16.0 Hz, H6), 4.27 (1H, dd, J = 5.5 and 16.0 Hz, H6), (**21B**) 1.38 (3H, s, CH_3), 1.55 (9H, s, *t*-Bu), 1.63 (3H, s, CH_3), 3.65 (1H, d, J = 17.0 Hz, H3), 4.48 (1H, ddd, J = 1.83, 5.13 and 17.0 Hz, H3), 5.00–5.22 (2H, m, OCH_2), 5.42–5.56 and 5.62–5.75 (each 1H, m, H4 and H5), 7.28–7.52 (5H, m, ArH_5).

1-*tert*-Butyl 6,6-dimethyl-2-(4-chlorobenzoyl)hexahydropyridazine-1-carboxylate (22A) and 1-*tert*-Butyl 3,3-dimethyl-2-(4-chlorobenzoyl)hexahydropyridazine-1-carboxylate (22B). A mixture of 670 mg (1.94 mmol) of **21A** and **21B**, and catalytic amount of 10% Pd/C in 20 mL of EtOH was vigorously stirred under 1 atm of H_2 at room temperature for 4 h and filtered. The filtrate was concentrated to give 379 mg of amine (A/B, 1:4) (91%) as a white solid. ^{1}H NMR ($CDCl_3$) 1.10 (6H, s, 2 CH_3), 1.47 (9H, s, *t*-Bu), 1.45–1.73 (4H, m, 2×CH_2), 2.90 (2H, t, J = 5.9 Hz, H3 of **A**), 3.48 (2H, t, J = 5.5 Hz, H6 of **B**), 3.8–4.3 (1H, br, NH) To a stirred solution of 100 mg (0.467 mmol) of the amine and 0.13 mL (0.935 mmol) of Et_3N in dry CH_2Cl_2 (10 mL), 4-chlorobenzoyl chloride (90 mg, 0.514 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 165 mg of monobenzoyl (**22A** and **22B**, 1:4) (99%) as a white solid. ^{1}H NMR ($CDCl_3$) (**23A**) 1.22 (9H, s, *t*-Bu), 1.46 (3H, s, CH_3), 1.68 (3H, s, CH_3), 3.17 (1H, quint, J = 6.6 Hz, H3), 3.90 (1H, quint, J = 6.6 Hz, H3), (**23B**) 1.28 (9H, s, *t*-Bu), 1.48 (3H, s, CH_3), 1.66 (3H, s, CH_3), 3.17 (1H, quint, J = 6.6 Hz, H3), 4.17 (1H, quint, J = 6.6 Hz, H3), 7.43 (2H, d, J = 8.4 Hz, ArH_2), 7.31 (2H, d, J = 8.4 Hz, ArH_2).

1,2-Bis-(4-chlorobenzoyl)-3,3-dimethylhexahydropyridazine (10). Trifluoroacetic acid (0.13 mL) was added to a solution of 30 mg (0.085 mmol) of the mixture of **22A** and **22B** in 1 mL of CH_2Cl_2 at room temperature with stirring. The mixture was stirred overnight, and then the solvent was removed under pressure. The residue was dissolved in AcOEt, and saturated $NaHCO_3$ aq was

added. The organic layer was separated and the aq layer was extracted with AcOEt. The combined extract was washed with water and brine and dried over $MgSO_4$. Concentration afforded 21.5 mg of 1-(4-chlorobenzoyl)-6,6-dimethylhexahydropyridazine (100%) as a white solid. ^{1}H NMR ($CDCl_3$) 1.41 (6H, s, 2×CH_3), 1.76 and 1.93 (each 2H, br s, H4 and H5), 3.30 (2H, br s, H3), 7.38 (2H, d, J = 8.1 Hz, ArH_2), 7.44 (2H, d, J = 8.1 Hz, ArH_2), 9.12 (1H, br, NH). To a stirred solution of 60 mg (0.238 mmol) of the monocholorobenzoylhydrazine, catalytic amount of DMAP and 0.066 mL (0.475 mmol) of Et_3N in dry CH_2Cl_2 (3 mL), 4-chlorobenzoylchloride (46 mg, 0.262 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ aq, water, and brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel with *n*-hexane/AcOEt = 4:1 afforded 93 mg of **10** (100%) as a white crystal: mp 178.5–179 °C. ^{1}H NMR ($CDCl_3$) 1.54–1.86 (4H, m, H4 and H5), 1.61 and 1.75 (each 3H, s, 2×CH_3), 3.50 and 3.58 (each 1H, quint, J = 6.2 Hz, H6), 6.81 (1H, d, J = 8.4 Hz, ArH), 7.26 (1H, d, J = 8.4 Hz, ArH), 7.33 (1H, d, J = 8.4 Hz, ArH), 7.48 (1H, d, J = 8.4 Hz, ArH).

X-ray crystallography

The X-ray crystal structure analyses were performed on crystal compound (**5**). Diffraction data were obtained on a Rigaku AFC-S four-circle diffract meter and a Rigaku RAXIS-II imaging plate diffract meter with graphite-monochromated MoK_α (λ = 0.71070 Å) radiation, respectively. Generally, indexing was performed from three oscillations which were exposed for 4.0 min, and a total of 15 oscillation images within the 2θ value of 50.3 were collected in the analyses using the imaging plate area detector. The crystal data; formula: $C_{18}H_{16}N_2O_2Cl_2$, recrystn solvent: *n*-hexane/AcOEt, crystal system: monoclinic, space group: $P2_1/n$ (#14), lattice parameters: a = 9.507(3) Å, b = 18.33(2) Å, c = 10.08(2) Å, β = 103.03(3) Å, V = 1711.5500 Å^3, D_{calc}: 1.410 g/cm^3, Z value: 4, temp: 288 K, no. of reflections measured: total 2123, R: 0.068. The crystal structure was solved by the direct method, and the hydrogen atoms were located on a different electron-density map.

Evaluation of insecticidal activity. A cabbage leaf of a medium size cut from cabbage grown to decafoliate stage was dipped for 20 s in a treatment solution prepared by diluting each of the formulations with water to an effective ingredient concentration of 200 ppm. After having been air-dried, the two thus treated leaves were placed in a plastic container having a diameter of 9 cm, and five *Spodoptera litura* larvae (third inster) were transferred thereon. This was left with a covering in a temperature-controlled chamber at 25 °C. four days after the treatment, the number of live and dead insects were counted to calculate the mortality rate.

References and Notes

1. Wing, K. D. *Science* **1988**, *241*, 467.
2. Wing, K. D.; Slawecki, R. A.; Carlson, G. R. *Science* **1988**, *241*, 470.
3. Heller, J. J.; Mattioda, H.; Klein, E.; Sagenmuller, A. *Brighton Crop Protection Conference: Pests and Diseases 2-* **1992**, *5*, 59.
4. Yanagi, M.; Watanabe, T.; Masui, A.; Yokoi, S.; Tsukamoto, Y.; Ichinose, R. *Brighton Crop Protection Conference: Pests and Diseases* **2000**, *2A-2*, 27.
5. Shimizu, B.; Nakagawa, Y.; Hattori, K.; Nishimura, K. *Steroids* **1997**, *62*, 638.
6. Quian, X. *J. Agric. Food Chem.* **1996**, *44*, 1538.
7. Wurtz, J.-M.; Guillot, B.; Fagart, J.; Moras, D.; Tietjen, K.; Schindler, M. *Protein Sci.* **2000**, *9*, 1073.
8. Chan, T. H.; Ali, A.; Britten, J. F. *Can. J. Chem.* **1989**, *67*, 1178.
9. Editor, Paul, A. H.; Robert, M. H.; Edward, P. M.; Junshi, M.; Dean, G. T. ACS Symposium Series 658. American Chemical Society: Washington DC. *Phytochem. Pest Control* **1997**, 206.
10. Editor. Baker, D. R.; Fenyes, J. G.; Moberg, W. K. Hsu, A. C.-T; Fujimoto, T. T.; Dhadialla, T. S. In *Synthesis and Chemistry of Agrochemicals II*. ACS Symposium Series 443. American Chemical Society: Washington DC, 1991; 478.
11. Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649. Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083.
12. Tanatani, A.; Kagechika, H.; Azumaya, I.; Fukutomi, R.; Ito, Y.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 4425.
13. Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474.
14. Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715.
15. Maeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **1998**, *39*, 681.
16. Morley, J. S. *J. Chem. Soc., Perkin Trans. 1*, 1712.
17. Brimble, M. A.; Lee, C. K. Y. *Tetrahedron Asymmetry* **1998**, *9*, 873.
18. Lawton, G. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 877.
19. Unpublished results.
20. International Chemical Safety Cards (ICSCs). *An International Program on Chemical Safety Project* (http://www.cdc.gov/niosh/ipcs/icstart.html).