Studies in iridoid chemistry and spruce budworm (*Choristoneura fumiferana*) antifeedants

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This paper is dedicated to Professor John T. Edward

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Several compounds derived from aucubin and catalposide were prepared and tested for spruce budworm antifeeding activities. Definite biological activity was observed for compound **11**.

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On a préparé plusieurs composés dérivés de l'aucubine et du catalposide et on les a testés pour leurs activités contre la tordeuse d'épinette. On a observé une activité biologique bien définie pour le composé **11**.

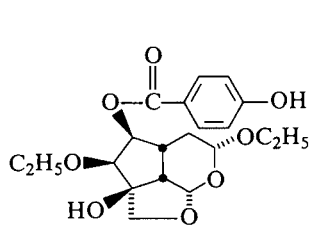
[Traduit par la revue]

Introduction

The spruce budworm, *Choristoneura fumiferana*, is a pest that infests North American fir and spruce forests. In Eastern Canada the larvae of the budworm begin to feed on the buds or the newly opened shoots of the host tree in mid-May, while they consume the greatest amount of foliage during their sixth instar in late June. During a budworm outbreak, this inflicts huge damage to the forest resource, and has devastating consequences for the pulp and paper industry. Efforts to control the spruce budworm up to now have relied on the spraying of insecticides. A strategy that has been suggested for pest control is to employ antifeedants to interfere with the feeding behaviour of insects. The term antifeedant is defined as a chemical that inhibits feeding but does not kill the insect directly, i.e., the insect remains near the treated leaves and dies through starvation (1). The approach is attractive since, in principle, it protects current year foliage while leading indirectly to budworm mortality through use of an agent that may not be generally toxic in the conventional sense. The feeding preferences of spruce budworm larvae have been studied (2). In eastern Canada, balsam fir (*Abies balsamea*) is the most favorable host species, followed by white spruce (*Picea glauca*), red spruce (*Picea rubens*), and black spruce (*Picea mariana*).

In screening programs, a number of natural products have been found to have antifeedant activity against spruce budworm (3, 4). Recently, Chang and Nakanishi reported their studies on extracts of the leaves of 40 different trees that are not attacked by the budworm (4). The extracts were assayed for antifeedant activity using budworm fed on artificial diets with or without the extract. This led to the isolation of the active component from the leaves of *Catalpa speciosa* Warder (Bignoniaceae). They named the compound specionin and proposed its structure to be **1** on the basis of its spectroscopic data (4). However, a chemical synthesis of **1** was recently reported (5) and comparison of spectral data revealed that it was not identical with the natural compound. An alternative structure, **2**, was proposed for specionin and recently synthesized (5).

A common structural feature of many antifeedants known to date, including azadirachtin (6) and clerodin (7), is that they are polyoxygenated compounds. However, there has been little study of structure–activity relationships with respect to antifeedant activity.



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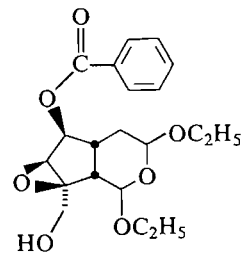

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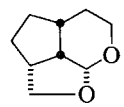

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The present study led to development of a facile method to obtain the tricyclic structure **3** and several polyoxygenated compounds thereof. At least one of these compounds was found to have definite antifeedant activity against spruce budworm larvae.

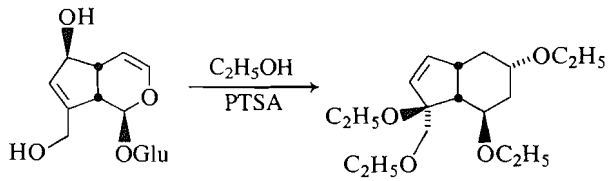
While the structures of **1** and **2** are relatively simple so that they are amenable to total synthesis (5), we feel that a totally synthetic approach is not likely to yield compounds in quantities sufficient for large-scale bioassay either in the laboratory or eventually in the field. Our strategy is to effect the syntheses of these compounds starting from iridoid natural products, which are abundant. Furthermore, since the natural antifeedant is likely to be optically active, optical resolution or asymmetric synthesis would be required in a totally synthetic approach. On the other hand, it may be possible to correlate configurationally one of the iridoid natural products with specionin.

As a starting material, we have chosen aucubin (**4**), an iridoid glycoside. It is present to the extent of ~1% of fresh plant weight in *Aucuba japonica* (8, 9) and can be extracted and purified in large quantities (9).[1] In fact, aucubin has been used as starting material for the synthesis of optically active prostaglandinoids (9, 10).

Derivatives from aucubin

The reaction of aucubin with CH_3OH–HCl has been reported

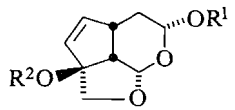
[1]We thank Professor Berkowitz for providing us with the procedure for the extraction of aucubin.



4 5

in the literature (11, 13). Normally, aucubin is degraded extensively under acidic conditions. After trying a number of reaction conditions (BF_3·etherate, HCl, H_2SO_4, etc.), we found that ethanolysis of aucubin with catalytic amounts of *p*-toluenesulfonic acid (PTSA) at room temperature for 11 days gave compound **5** in relatively good yield (~60%). The structure of **5** was based on spectroscopic evidence, in particular, 2D nmr. The absence of the glucose moiety was evident from its tlc mobility and the absence of OH absorption in its ir spectrum. The presence of four ethoxy groups was deduced by its chemical ionization mass spectrum (MH^+ = 315 and base peak at m/z = 269, M − OC_2H_5) and confirmed by the four ethoxy methylene carbons in the ^{13}C nmr spectrum (Table 1). The migration of the double bond is the result of an acid-catalysed allylic rearrangement. In normal allylic rearrangement under acidic conditions, the thermodynamically more stable allylic isomer, which usually is the more substituted double bond isomer, predominates (12). In the present as well as previous cases (11, 13), it is surprising that the less substituted double bond isomer is the only isolable product. The only (speculative) explanation that we can offer at this time is that the ethoxy group, being at C-8 instead of at C-6, can cooperate with the other ethoxy groups in the molecule to form hydrogen bonds more effectively with the solvent or with the acid.

If the ethanolysis of aucubin was carried out with boron trifluoride-etherate as the catalyst, compound **6** was also obtained in addition to **5**. Compound **6** has no hydroxy group according to its ir and ^1H nmr spectra (Table 2). It has only two ethoxy groups, evidenced by its ^{13}C nmr spectrum. The ^1H nmr spectrum of **6** is in agreement with those published for **7***a* and **7***b* (5). Compound **6** could also be prepared from the cyclization of **5**. Thus, when **5** was subjected to *p*-toluenesulfonic acid treatment in methylene chloride instead of ethanol, compound **6** was obtained in moderate yield.

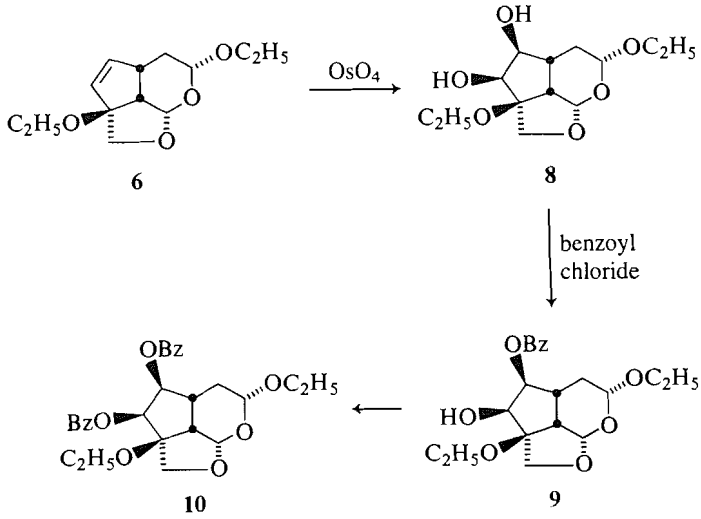


6: $R^1 = R^2 = C_2H_5$
7a: $R^1 = R^2 = H$
7b: $R^1 = C_2H_5$, $R^2 = H$

The double bond of **6** can be further functionalized by hydroxylation or epoxidation to give polyoxygenated derivatives. Oxidation of **6** with osmium tetroxide/pyridine at the less hindered *exo* face gave the diol **8**. Benzoylation of **8** gave the monobenzoate **9** first, then the dibenzoate **10**. Epoxidation of the double bond with *m*-chloroperbenzoic acid gave the epoxide **11**, again from the *exo* face. Treatment of **11** with *p*-toluenesulfonic acid monohydrate gave the tetracyclic alcohol **12**. The structure of **12** was assigned on the basis of spectroscopic data. The alternative structure **12′** was ruled out on the basis of ^1H 2D-HOMO correlation nmr spectrum which showed that H-7 coupled with the hydroxy proton (Fig. 1).

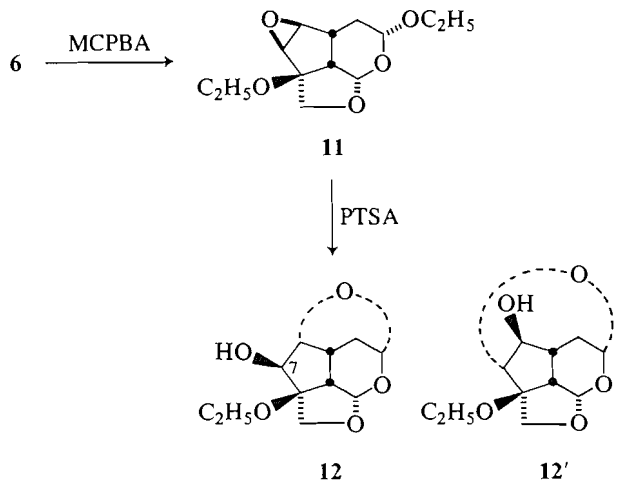
Ethanolysis of catalposide

Both **1** and **2** are structurally similar to catalposide (**13**), the major iridoid compound from the *Catalpa* species. Indeed, Chang and Nakanishi (4) have suggested that specionin could be an artifact derived from catalposide during ethanol extraction.



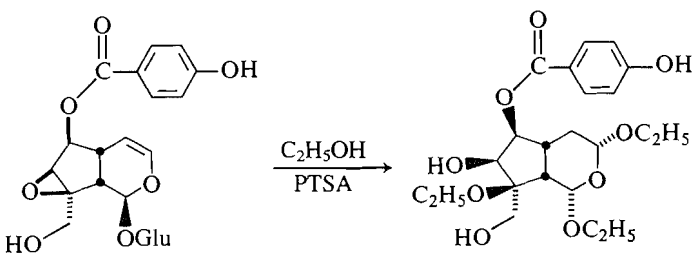
6 8 10 9

In view of the ease of ethanolysis of aucubin, we also attempted the ethanolysis of catalposide. However, in spite of repeated attempts under different conditions, catalposide either resisted ethanolysis or suffered extensive degradation. Using the mildest conditions (catalytic amount of PTSA in ethanol at room



11 12 12′

temperature for 60 days), we were able to isolate compound **14** in very poor yield. Every effort to isolate an intermediate with the epoxide moiety still intact was unsuccessful. It is interesting to note that in the opening of epoxide to give **14**, the ethanol attacked at the more hindered carbon (C-8) with resultant *cis* stereochemistry. The positions of the hydroxyl groups at C-7 and C-10 were assigned by ^1H nmr of **14** in DMSO-d_6, which



13 14

showed the appropriate coupling between the hydroxyl protons and the adjacent methine (H-7) and methylene (H-10) protons. The relative stereochemistry was determined by nuclear Overhauser effects in that irradiation of H-7 resulted in enhancement of H-6, H-10, and the OH at C-7. Presumably, under the acidic conditions used, epoxide opening proceeded via an S_N1-like

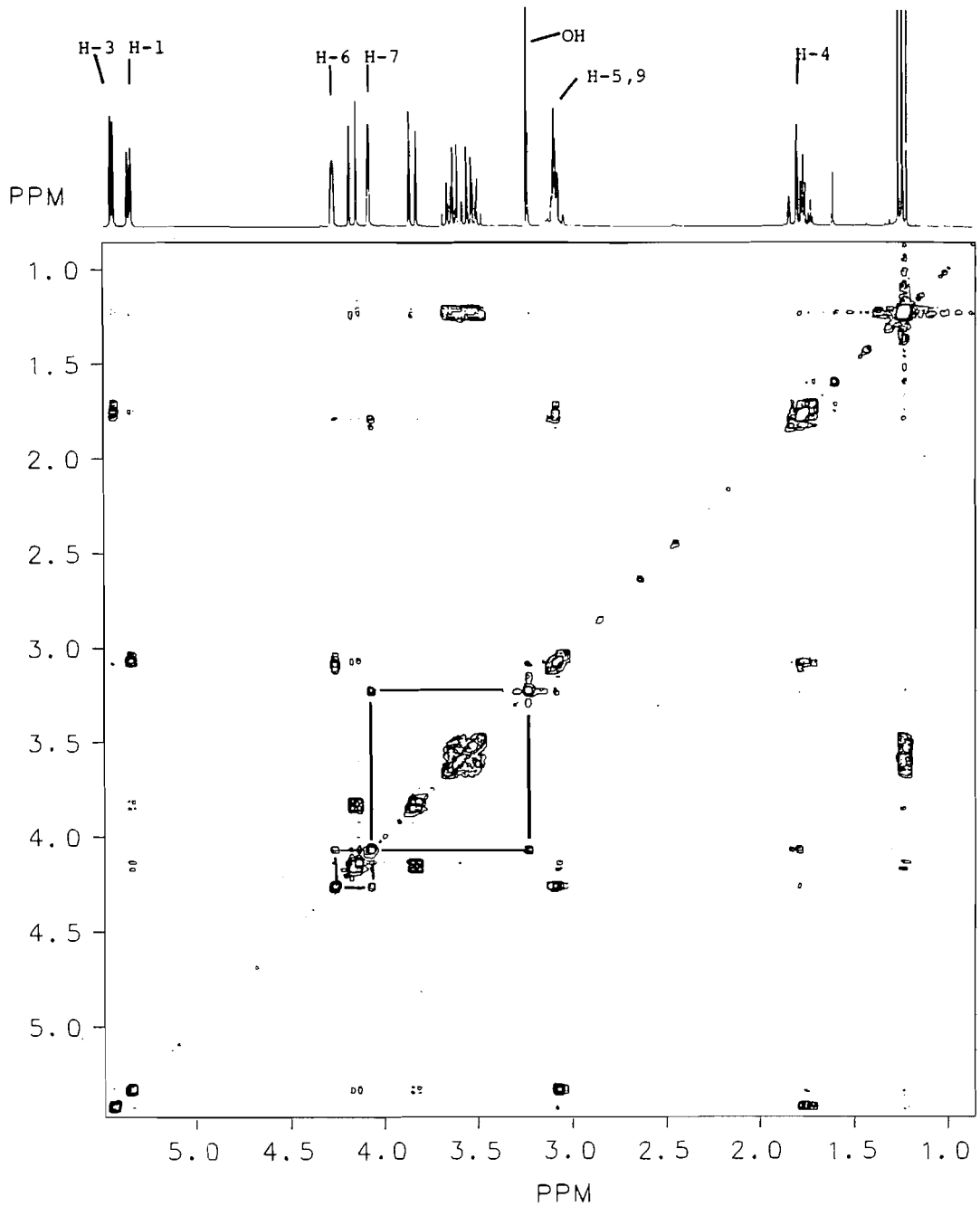


FIG. 1. 2D-HOMO correlation ^{1}H nmr spectrum of **12**. H-7 showed coupling with -OH and H-6.

TABLE 1. ^{13}C nuclear magnetic resonance data[a]

	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Others
5	105.53	102.02	34.80	42.41	131.48	139.48	98.30	53.15	73.38	15.28(3C), 15.69, 60.00, 61.08, 61.59, 62.68
6	100.66	94.66	30.43	40.06	132.73	139.84	98.59	44.99	43.95	15.12, 15.64, 59.70, 63.48
9	98.74	95.20	26.84	34.94	77.00	73.09	90.47	46.45	71.40	15.16, 15.59, 60.18, 63.76, 128.42, 129.80, 133.26, 166.36
11	99.00	94.85	27.50	30.09	59.75[b]	61.04[b]	93.96	46.35	71.34	15.12, 15.82, 61.21, 63.23
12	95.42	98.46	31.63	36.51	89.51	74.60	95.52	53.13	71.43	15.58, 60.06
14	94.74	97.62	32.24	37.67	80.85	74.69	85.32	49.06	64.57	14.84, 15.21, 16.01, 58.20, 62.52, 63.41, 115.37(2C), 121.32, 131.97(2C), 160.90, 165.98

[a]Measured in $CDCl_3$.
[b]The assignment may be reversed.

TABLE 2. ^{1}H nuclear magnetic resonance data

	H-1	H-3	H-4	H-5	H-6	H-7	H-9	H-10	Others
5	5.02 (d, 1.4)	4.58 (t, 6)	1.86 (dt, 6.3, 6.3, 13.8), 1.72 (ddd, 6, 8.8, 13.8)	3.14 (m)	5.61[a] (dd, 2.7, 5.6)	5.97[a] (dd, 1.7, 5.5)	2.61 (dd, 1.2, 8.5)	3.98, 3.82 (AB, 8.8)	1.16 (t, 7.0), 1.21 (t, 7.2), 1.22 (t, 7.1), 3.28–3.80 (m, 9H)
6 ($CDCl_3$)	5.55 (d, 6.1)	4.81 (dd, 3.6, 8.2)	1.95 (dt, 3.8, 3.8, 13.9), 1.79 (ddd, 6.4, 8.4, 1.40)	3.22 (m)	5.72 (dd, 2.8, 5.5)	5.91 (dd, 1.9, 5.5)	2.61 (dd, 6.1, 8.4)	3.95, 3.81 (AB, 9.3)	1.17 (t, 7.0), 1.20 (t, 7.2), 3.28 (m), 3.40 (m), 3.50 (m), 3.89 (m)
7[e]	5.59 (d, 6)	4.80 (dd, 3.7, 8)	1.92 (ddd, 4, 4.1), 1.77 (ddd, 14.8, 6, 5)	3.34 (m)	5.86[b] (dd, 5.5, 2)	5.77[b] (dd, 2.5, 5.5)	—	3.98, 3.78 (AB, 9.5)	1.20 (t, 7), 3.49 (m), 3.88 (m)
9 ($CDCl_3$)	5.54 (d, 5.1)	5.14 (dd, 5.1, 7.3)	2.00 (ddA, 2.9, 5.3, 14.6), 1.64 (ddB, 5.6, 7.3, 14.6)	3.00 (m)	5.25 (dd, (3.6, 10.7)	4.27 (d, 3.6)	2.70 (dd, 5.1, 10.3)	4.14, 3.79 (AB, 11.0)	1.20 (t, 7.1), 1.26 (t, 7.1), 3.55 (m, 3H), 3.90 (m), 7.45–8.11 (m, 5H)
10	5.61 (d, 5.1)	5.20 (dd, 4.8, 7.7)	2.00 (ddA, 2.9, 4.8, 14.5), 1.68 (ddB, 5.6, 7.7, 14.5)	3.08 (m)	5.54 (dd, 3.7, 11.0)	5.80 (d, 3.7)	2.83 (dd, 5.1, 10.2)	4.21 (AB, 10.8), 3.94 (AB, 10.8)	1.05 (t, 6.9), 1.22 (t, 6.8), 3.30 (m), 3.47 (m), 3.54 (m), 3.91 (m), 7.26–8.08 (m, 10H)
11 ($CDCl_3$)	5.44 (d, 5.4)	4.96 (t, 3.1)	1.82, 1.78 (m)	2.80 (dt, 9.2)	3.37[c] (d, 2.5)	3.50[c] (d, 2.5)	2.50 (dd, 5.4, 9.2)	3.89, 3.86 (AB, 10.2)	1.15 (t, 7.1), 1.20 (t, 7.0), 3.46 (m), 3.58 (m), 3.59 (m), 3.76 (m)
12 ($CDCl_3$)	5.33 (d, 4.9)	5.42 (d, 3.5)	1.81 (A, 12.1), 1.75 (Bt, 12.1, 3.5, 3.5)	3.08[d] (m)	4.26 (bs)	4.06 (bs)	3.08[d] (m)	4.15, 3.82 (AB, 10.8)	3.23 (d, 1.7), 1.23 (t, 7.0), 3.51 (m), 3.62 (m)
14 (DMSO-d_6)	5.00 (d, 7.0)	4.79 (dd, 5.3, 8.8)	2.04 (tD, 13.3, 5.3, 5.3), 1.47 (tD, 13.3, 13.3, 8.8)	1.30 (m)	4.96 (dd, 4.5, 5.3)	4.37 (dd, 5.2, 4.5)	2.19 (dd, 6.9, 10.8)	3.79–3.60 (m)	5.08 (d, 5.2, 7-OH), 4.28 (t, 5.2, 10-OH), 1.07–1.16 (m, 9H), 3.46–3.79 (m, 6H), 6.84 (d, 8.8), 7.85 d, 8.8)

[a,b,c,d]Numbers with the same superscript can be exchanged due to uncertain assignment.
[b]Data from ref. 5.

TABLE 3. Mean development stage (instar) of spruce budworm larvae after 15 days at 26°C

Diet	Mean instar[a]
Treated control	5.28
Untreated control	5.12
Compound **13**	5.32
Compound **15**	5.12
Compound **9**	4.40*
Compound **10**	5.32
Compound **11**	4.36*
Compound **12**	4.96
Compound **14**	4.60

[a]Maximum = 6.00 (i.e., all larvae 6th instars).
*Means significantly different from treated control ($P \leq 0.05$, Mann–Whitney *U*-test).

mechanism with the ethanol molecule attacking the carbonium ion from the *exo* face.

Biological assay

Compounds **9**, **10**, **11**, **12**, and **14** were tested for antifeedant activity against spruce budworm larvae. As control, catalposide **13** was also included. To exclude the possibility that specionin could be an artifact derived from catalposide during ethanol extraction, a sample of catalposide was treated with ethanol for 30 days, and then the solvent was removed. The residue, referred to as ethanol-treated catalposide (sample **15**), was also bioassayed.

Two different bioassays were conducted (see Experimental), both of which involved feeding laboratory-colony spruce budworm larvae on artificial diet (14) containing 0.2% (wet weight) of the test compounds. The first assay showed that the development of larvae reared from second instar on test diets was significantly retarded by compounds **9** and **11**, but not by the other compounds (Table 3). Recognizing that reduction in development rate could be caused by factors other than reduced feeding, a second assay was devised to provide a true reflection of the amount of food ingested by 6th (final) instar larvae. In this test it was found that only compound **11** caused significant reduction in frass produced and moth weight for both male and female insects (although **10** showed significant reductions for males alone) (Table 4).

It is interesting to note that none of the catalposide-derived samples (**13**, **14**, and **15**) showed significant antifeedant activity at the concentration tested. This suggests that specionin is not likely to be an artifact resulting from the ethanolysis of catalopside, since Nakanishi reported that specionin is active at the ca. 50–100 ppm level.

The definite biological activity observed for compound **11** (and possibly compound **10**) provides a lead for further study in the structure–activity relationship of spruce budworm antifeedants.

Experimental

Infrared spectra were obtained on thin films on NaCl plates for liquids and in solution in 0.1-mm cells for solids, using a Perkin–Elmer 297 spectrophotometer. The nmr spectra were recorded on a Varian XL-300 or XL-200 nmr spectrometer. Mass spectra were taken on a Dupont 492B or HP-5980A mass spectrometer. Column chromatography was performed on silica gel 60 (Merck). Elemental analyses were performed by the Institute of Elemento-organic Chemistry, Nankai University, Tianjin, China.

Aucubin and catalposide were isolated according to literature procedure (9).

Ethanolysis of aucubin

A solution of 200 mg of aucubin, 10 mg of *p*-toluenesulfonic acid (PTSA) monohydrate, and 20 mL of C_2H_5OH was stirred at room temperature. Thin-layer chromatography was used to follow the reaction. The colour of the reaction mixture changed from blue to green, brown, and finally yellow. After 11 days, the solution was neutralized with aqueous $NaHCO_3$, filtered, and evaporated under vacuum. Elution on SiO_2 flash chromatography with a mixture of ethyl acetate and hexane (1:2) afforded 0.1 g of compound **5**. (yield 58%); $[\alpha]_D^{22}$ 115.5° (*c* 2.1, $CHCl_3$); ms (CI) (*i*-Bu): 315 (0.3), 314 (0.2), 269 (100), 223 (13). *Anal.* calcd. for $C_{17}H_{30}O_5$: C 64.94, H 9.62; found: C 64.60, H 9.31.

*Cyclization of compound **5** to the tricyclic compound **6***

To 200 mL of CH_2Cl_2 was added 1.2 g of **5** and 0.1 g of PTSA monohydrate. The solution was stirred for 10 h at room temperature. After neutralization with $NaHCO_3$ the mixture was filtered and evaporated under vacuum. Elution of the residue on SiO_2 column flash chromatography with a mixture of ethyl acetate and hexane (1:2) gave 0.60 g of compound **6** as a colorless liquid; $[\alpha]_D^{22}$ 158.4° (*c* 1.9, $CHCl_3$); ms (CI, *i*-Bu): 241 (3), 240 (2), 239 (14), 211 (100), 195 (30). *Anal.* calcd. for $C_{13}H_{20}O_4$: C 64.98, H 8.39; found: C 64.52, H 8.11.

*Epoxidation of compound **6***

To a solution of 0.5 g of **6** in 20 mL of benzene was added 0.2 g of *m*-chloroperbenzoic acid (MCPBA). After stirring for 10 h at room temperature, another 0.2 g of MCPBA was added. Stirring was continued for 5 h at 50–60°C. Additional MCPBA (2 × 0.2 g) was added after each 5 h stirring at 50–60°C. The mixture was washed with aqueous $NaHCO_3$ and dried with $MgSO_4$. It was filtered and evaporated under vacuum. The residue was eluted on SiO_2 column flash chromatography with a mixture of ethyl acetate and hexane to give 0.23 g of **11** as a waxy low-melting white solid; $[\alpha]_D^{22}$ 126.7° (*c* 2.0, $CHCl_3$); ms (CI, *i*-Bu): 257 (14), 256 (2), 255 (14), 211 (100). *Anal.* calcd. for $C_{13}H_{20}O_5$: C 60.92, H 7.87; found: C 60.51, H 7.38.

*Hydroxylation and benzoylation of compound **6***

To 0.11 g of **6** in 10 mL of pyridine was added 0.13 g of OsO_4 in 10 mL pyridine at 5°C. The mixture was kept for 2 h, then at room temperature for 40 h. The mixture was evaporated under vacuum. The residue was eluted on SiO_2 flash chromatography with a mixture of ethyl acetate and hexane (1:1) to give 0.065 g of the diol **8**. The diol was benzoylated without further purification.

To 0.05 g of **8** and 1.0 g of pyridine in 5 mL of $CHCl_3$ was added a solution of 0.03 g benzoyl chloride in 5 mL of $CHCl_3$, dropwise at room temperature. The mixture was stirred at room temperature for 48 h. It was evaporated under vacuum and the residue was purified by silica gel flash chromatography with a mixture of ethyl acetate and hexane (1:1).

Compound **9** (0.03 g) was obtained as the monobenzoate; $[\alpha]_D^{22}$ −18.7° (*c* 1.8 $CHCl_3$); ms (CI, *i*-Bu): 378 (1), 377 (4), 333 (23), 315 (29), 211 (100). *Anal.* calcd. for $C_{20}H_{26}O_7$: C 63.48, H 6.93; found: C 63.71, H 7.23.

If benzoylation was carried out under identical conditions but with excess benzoyl chloride (0.50 g), the dibenzoate **10** was obtained. It had $[\alpha]_D^{22°C}$ −65.05° (*c* 1.5, $CHCl_3$); ms (CI, *i*-Bu): 483 (2), 481 (2), 437 (74), 315 (100). *Anal.* calcd. for $C_{27}H_{30}O_8$: C 67.20, H 6.27; found: C 67.06, H 6.05.

*Acid catalysed reaction of epoxide **11***

To 0.05 g of **11** in 15 mL of ether, 0.01 g of PTSA monohydrate was added. The solution was refluxed for 3 h, then neutralized with aqueous $NaHCO_3$. The ether solution was dried and evaporated under vacuum. The residue was purified on SiO_2 flash chromatography with a mixture of ethyl acetate and hexane to 0.035 g of compound **12**. It had $[\alpha]_D^{22}$ 39.4° (*c* 3.5, $CHCl_3$); ms (EI): 228 (8), 211 (5), 198 (33), 181 (29), 169 (48), 28 (100). *Anal.* calcd. for $C_{11}H_{16}O_5$: C 57.89, H 7.07; found: C 57.99, H 7.37.

Ethanolysis of catalposide

To a solution of 0.5 g of catalposide in 30 mL of C_2H_5OH, 0.05 g of PTSA monohydrate was added. The mixture was stirred at room

TABLE 4. Frass weights and moth weights resulting from 6th-instar spruce budworm larvae feeding on test diets

Diet	Frass[a] mg dry weight		Moth[a] mg dry weight[b]	
	Males	Females	Males	Females
Treated control	37.5 ± 5.8	50.9 ± 8.2	9.7 ± 1.4	17.7 ± 3.5
Untreated control	32.6 ± 7.4	52.3 ± 12.3	10.1 ± 2.0	18.4 ± 3.5
Compound **13**	37.0 ± 6.2	60.6 ± 12.5	9.9 ± 1.9	19.2 ± 4.6
Compound **15**	36.5 ± 7.1	54.7 ± 13.2	10.6 ± 1.9	18.5 ± 5.0
Compound **9**	35.4 ± 6.5	53.7 ± 8.5	9.8 ± 2.5	18.3 ± 3.9
Compound **10**	29.0 ± 7.0*	49.5 ± 12.6	7.6 ± 2.3*	16.0 ± 5.7
Compound **11**	31.7 ± 7.1*	38.4 ± 10.0*	7.9 ± 1.5*	14.4 ± 4.3*
Compound **12**	35.2 ± 4.6	55.2 ± 18.7	9.9 ± 0.8	21.0 ± 4.5
Compound **14**	38.1 ± 6.1	53.5 ± 22.4	9.9 ± 2.2	18.1 ± 6.9

[a]Mean ± sd.
[b]n = 15–20.
[c]Means significantly different from treated control ($P \leq 0.05$, t-test).

temperature for 60 days. Thin-layer chromatography was used to follow the reaction. The mixture was neutralized with $NaHCO_3$, filtered, and evaporated under vacuum. The residue on elution from Al_2O_3 column by flash chromatography with a mixture of ethyl acetate and hexane (1:2) gave 0.03 g of compound **14**. It had $[\alpha]_D^{22°C}$ −61.6° (c 2.75, $CHCl_3$); ms (CI, i-Bu): 439 (1), 423 (2), 395 (21), 349 (100).

Bioassays

Diet containing 0.2% (wet weight) of the test compounds was prepared by treating lyophilized diet (14) with a solution of the compound, usually in methylene chloride, and then removing the solvent completely at 30°C on a rotary vacuum evaporator. The residual powder was rehydrated to 80% water content with 0.4% aqueous potassium sorbate solution (fungicide). Control diets were treated as above with solvent alone, or were untreated. In the first assay, newly-emerged 2nd-instar larvae were reared individually at 26°C, 17-h photoperiod, 25 replicates per test compound. After 15 days, the larvae were sacrificed and their mean development stage determined (Table 3). In the second assay, newly-moulted 6th-instar larvae were reared under the same conditions. At pupation, the frass were dried (60°C) and weighed. Moths were allowed to emerge and were sacrificed after 24 h, dried, and weighed (Table 4).

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