Pergamon

Tetrahedron Letters, Vol. 38, No. 2, pp. 263-266, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02277-0

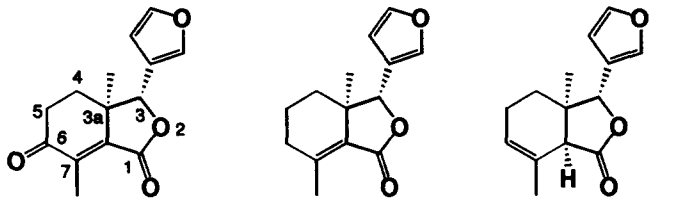
Synthesis and Biological Activities of Degraded Limonoids, (±)-Fraxinellonone and Its Related Compounds

Hiroaki Okamura,* Keiko Yamauchi, Keiji Miyawaki, Tetsuo Iwagawa, and Munehiro Nakatani*

Department of Chemistry, Faculty of Science, Kagoshima University,
1-21-35 Korimoto, Kagoshima, 890 Japan.

Abstract: The first synthesis of (±)-fraxinellonone and its short step conversion into (±)-fraxinellone and (±)-isofraxinellone is described. The synthesized compounds exhibited moderate insect-antifeeding activity against *Spodoptera exigua* H. (Boisduval) and ichthyotoxicity against killifish. Copyright © 1996 Elsevier Science Ltd

Limonoids constitute a large group of natural products. At present, more than three hundred compounds have been isolated from mainly rutaceae and meliaceae plants. Many of them display various biological activities, including antifeeding and growth regulating activities against insects,[1] and are therefore, considered as prototypes for insecticide. In connection with limonoids, some degraded limonoids are known.[2] Since they are small and rather simple compounds showing partial structures in common with limonoids, they are regarded as important intermediates for the total synthesis of limonoids, and in fact, several degraded limonoids have already been synthesised.[3] In addition to being synthetically useful, these compounds seem to be effective probes for seeking the relationship between the structures and biological activities of limonoids. Previously, however, there has been no information with regard to their biological activities. In this report, we describe the first synthesis of (±)-fraxinellonone (**1a**),[2a] and its short step conversion into (±)-fraxinellone (**2a**)[2b,3a,b] and (±)-isofraxinellone (**3a**),[2c,3a,b] along with the biological activities of all three degraded limonoids and their related compounds (Fig. 1).



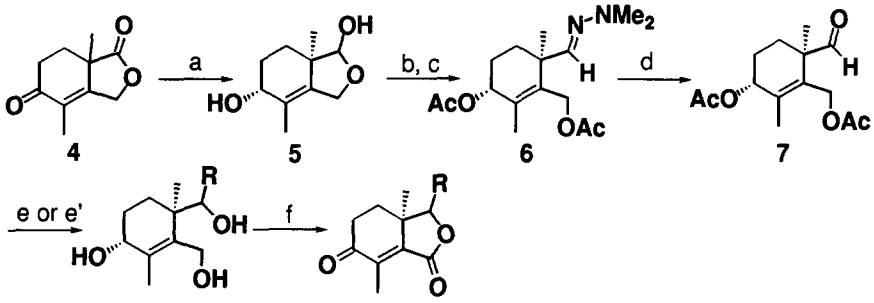
1a: fraxinellonone **2a**: fraxinellone **3a**: isofraxinellone

Fig. 1

Synthesis of degraded limonoids

Synthesis of (±)-fraxinellonone (**1a**) was started from racemic keto lactone **4** which was readily prepared by Robinson annulation[4] of ethyl vinyl ketone and 2-methyl-3-oxo-butanolide[5] (Scheme 1). Reduction of **4** with DIBAL afforded dihydroxyl compound **5** as a single isomer[6,7]. To introduce the 3'-furyl

group at the C-3 position of **5**, we initially examined the direct reaction of **5** with excess 3-lithiofuran.[8] Unfortunately, no reaction occurred at low temperature (less than -20°C), and decomposition of 3-lithiofuran occurred predominantly at the higher temperature (-20°C~rt). Thus we converted compound **5** into more reactive aldehyde **7** by the following process: i) hydrazone formation; ii) acetylation of the resulting hydroxyl groups; and iii) hydrolysis of hydrazone.[9] The reaction of **7** with 3-lithiofuran proceeded smoothly and afforded the desired isomer **8a** as a major isomer (9.6 : 1) after hydrolysis.[10] Fortunately, oxidation of 1- and 6- hydroxyl groups was immediately achieved by Ag_2CO_3-celite,[11] and afforded a good yield of an easily separable diastereomeric mixture of (±)-**1a** and its epimer (±)-**1b**. Since the ^1H and ^{13}C NMR spectra of the synthesized (±)-**1a**[12] showed good agreement with those of the naturally occurring compound,[2a] the first synthesis of (±)-fraxinellonone (**1a**) was achieved. Phenyl analogs of fraxinellonone (±)-**1c** and **1d** were also synthesized by a similar method.



a) DIBAL, 71% b) dimethylhydrazine c) Ac_2O, Et_3N, DMAP, two steps 93% d) $Cu(AcO)_2$, 85% e) 3-lithiofuran then aq. KOH, 87% **8a**:**8b** = 9.6 : 1 e') PhLi then aq. NaOH, 82% **8c**:**8d** = 15 : 1 f) Ag_2CO_3, 68% for **8a**, 65% for **8c**

Scheme 1

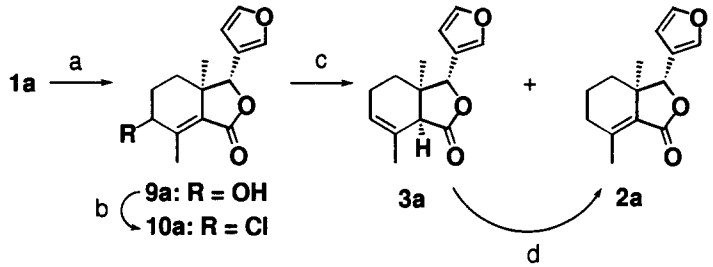
(±)-Fraxinellone (**2a**) and (±)-isofraxinellone (**3a**) were derived from (±)-**1a** in short steps (Scheme 2). DIBAL reduction of (±)-**1a** afforded 6-hydroxyfraxinellone (**9a**) which was further converted into chloride **10a** by TsCl and Et_3N treatment. Reductive dehalogenation of **10a** yielded (±)-isofraxinellone (**3a**) along with a small amount of (±)-fraxinellone (**2a**).[12] Since the conversion of **3a** into **2a** was already reported,[2b] we herein confirmed a general synthetic route of the degraded limonoids having γ-lactone ring.

In the above synthesis, total yields from compound **4** were 30% for (±)-fraxinellonone (**1a**), 14% for (±)-fraxinellone (**2a**), and 16% for (±)-isofraxinellone (**3a**).

Biological activities of degraded limonoids and their related compounds.

The biological activities of the synthesized degraded limonoids (±)-**1a~3a**, the phenyl analog (±)-**1c**, the synthetic intermediates **9a** and **10a**, and their epimers were examined with ichthyotoxicity (against killifish) and antifeeding activity (against *Spodoptera exigua* H. [Boisduval], leaf disk test[13]). The results listed in the table suggest that the type and stereochemistry of the substituent at C-6 exert a rather strong

influence on the biological activities of degraded limonoids and intermediates, whereas the substituent at C-3, the characteristic 3'-furyl substituent of the limonoid family, has only a limited influence.



a) DIBAL b) TsCl, Et_3N, DMAP, two steps 70% c) Zn, AcOH 77% for **3a** 3% for **2a** d) aq. NaOH, EtOH, 82%

Scheme 2

Table. Biological activities of synthesized compounds

compound	ichthyotoxicity[a] 50 ppm	10 ppm	antifeeding activity[b] 1000 ppm	500 ppm
1a	++	-	++	+
1b	++	-	++	+
1c	++	-	nt[c]	nt[c]
1d	++	-	nt[c]	nt[c]
2a	++	+	++	+
2b	++	+	++	+
3a	++	+	+	-
3b	++	+	+	-
9a	-	-	-	-
9b	-	-	-	-
10a	++	++	-	-
10b	++	++	-	-

a) ichthyotoxicity: ++ strong (within 12h), + moderate (within 24h), - no activity. b) antifeeding activity: ++ strong (remainder leaf disk ≥ 50 %), + moderate (< 50 %), - no activity. c) nt: not tested.

Acknowledgment: We are grateful to Prof. Takasi Tokoroyama, Osaka City University, and Prof. Tsutomu Katsuki, Kyushu University, for their helpful advice and encouragement.

References and Notes

1. As a review of the biologically active limonoids, see: D. E. Champagne, O. Koul, M. B. Isman, G. G. E. Scudder, and G. H. N. Towers, *Phytochemistry* **1992**, *31*, 377-394.
2. To our knowledge, only five naturally occurring degraded limonoids are known at present. a) fraxinellonone, J. Boustie, C. Moulis, J. Gleye, I. Fouraste, P. Servin, and M. Bon, *Phytochemistry* **1990**, *29*, 1699-1701; b) fraxinellone, M. Pailer, G. Shaden, G. Spiteller, and W. Fenzl, *Monatsh. Chem.* **1965**, *96*, 1324-1346; P. Coggon, A. T. McPhail, R. Storer, and D. W. Young, *Chem.*

Commun. **1969**, 828; c) isofraxinellone, A. J. Blaise and F. Winternitz, *Phytochemistry* **1985**, *24*, 2379-2381; d) dictamdiol, C. Hu, J. Han, J. Zhao, G. Song, Y. Li, and D. Yin, *Zhiwu Xuebao* **1989**, *31*, 453-458; J. Boustie, J. Gleye, A. Blaise, and I. Fouraste, *Planta Med.* **1992**, *58*, 228; e) calodendrolide, J. M. Cassady and C. S. Liu, *J. Chem. Soc., Chem. Commun.* **1972**, 86-87.

3. a) Y. Fukuyama, T. Tokoroyama, and T. Kubota, *Tetrahedron Lett.* **1972**, 3401-3404; b) T. Tokoroyama, Y. Fukuyama, T. Kubota, and K. Yokotani, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1557-1562; c) T. Tokoroyama, Y. Kotsuji, H. Matsuyama, T. Shimura, K. Yokotani, and Y. Fukuyama, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1745-1752. d) Y. Fukuyama, T. Tokoroyama, and T. Kubota, *Tetrahedron Lett.* **1973**, 4869-4872; e) T. Tokoroyama, Y. Fukuyama, and Y. Kotsuji, *J. Chem. Soc. Perkin Trans. 1* **1988**, 445-450; f) S. E. Drewes, P. A. Grieco, and J. C. Huffman, *J. Org. Chem.* **1985**, *50*, 1309-1311; g) D. Friedrich and L. A. Paquette, *J. Org. Chem.* **1991**, *56*, 3831-3840; h) A. F. Mateos and J. A. F. Blanco, *J. Org. Chem.* **1991**, *56*, 7084-7092; i) M. Renoud-Grappin, C. Vanucci, and G. Lhommet, *J. Org. Chem.* **1994**, *59*, 3902-3905.
4. Compound **4** was synthesized by a similar method with that employed for the preparation of Wieland-Miescher ketone derivative, see: H. J. Liu and T. Dieck-Abularach, *Heterocycles* **1987**, *25*, 245-249.
5. Preparation of 2-methyl-3-oxo-butanolide, see: *Beilstein*, **17**, 412.
6. Satisfactory spectral data were obtained for all synthetic intermediates.
7. Relative stereochemistry of **5** was determined from NOE between the signals corresponding to 6-H and pseudo axial 4β-H.
8. Y. Fukuyama, Y. Kawashima, T. Miwa, and T. Tokoroyama, *Synthesis* **1974**, 443-444.
9. E. J. Corey and S. Knapp, *Tetrahedron Lett.* **1976**, 3667-3668.
10. Orientation of 3'-furyl group was established by comparison of ^{1}H and ^{13}C NMR spectra with those of natural product after derivation to (±)-**1**.
11. M. Fetizon, M. Golfier, P. Mourgues, and J. M. Louis, "Organic Synthesis by Oxidation with Metal Compounds", ed. by W. J. Mijis and C.R.H. I. de Jonge, Plenum Press, **1986**, 503-567.
12. Synthesized (±)-**1a**, **2a**, and **3a** showed identical ^{1}H and ^{13}C NMR spectra with those of natural products. **1a**: 1H-NMR (400 MHz, CD_3OD) δ 7.60 (brs, 1H), 7.57 (dd, 1H, *J* = 1.5, 1.8 Hz), 6.48 (d, 1H, *J* = 1.1 Hz), 5.24 (s, 1H), 2.70 (ddd, 1H, *J* = 5.5, 14.3, 18.3 Hz), 2.53 (ddd, 1H, *J* = 2.2, 5.1, 18.3 Hz), 2.22 (ddd, 1H, *J* = 5.1, 13.0, 14.3 Hz), 2.09 (s, 3H), 2.02 (ddd, 1H, *J* = 2.2, 5.5, 13.0 Hz), 1.07 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.0, 168.6, 145.1, 144.0, 140.1, 139.4, 119.2, 108.3, 82.8, 43.9, 32.9, 31.9, 18.9, 10.0. **2a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (brt, 1H, *J* = 1.5 Hz), 7.44 (t, 1H, *J* = 1.8 Hz), 6.35 (brd, 1H, *J* = 0.73 Hz), 4.88 (brs, 1H), 2.28 (dd, 1H, *J* = 6.6, 19.8 Hz), 2.13 (s, 3H), 2.10-2.20 (overlap, 1H), 1.66-1.89 (m, 3H), 1.45 (dt, 1H, *J* = 2.9, 11.9 Hz), 0.86 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.8, 148.5, 143.4, 139.8, 127.4, 120.6, 108.5, 83.4, 43.0, 32.1, 31.7, 20.3, 18.4, 18.2. **3a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, 1H, *J* = 1.5, 1.8 Hz), 7.43 (dd, 1H, *J* = 0.73, 1.1 Hz), 6.37 (dd, 1H, *J* = 1.1, 1.8 Hz), 5.63-5.66 (m, 1H), 5.19 (brs, 1H), 2.73 (brs, 1H), 2.13-2.17 (m, 2H), 1.92 (q, 3H, *J* = 0.73 Hz), 1.70 (ddd, 1H, *J* = 6.6, 7.0, 13.2 Hz), 1.54 (ddd, 1H, *J* = 6.2, 7.0, 13.2 Hz), 0.89 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.6, 143.7, 139.9, 127.4, 123.6, 121.2, 108.8, 80.0, 51.2, 41.7, 28.9, 22.0, 21.8, 21.0.
13. K. Wada and K. Munakata, *J. Agr. Food. Chem.* **1968**, *17*, 471-474.

(*Received in Japan* 21 *October* 1996; *revised* 14 *November* 1996; *accepted* 15 *November* 1996)