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Concise Approach to Pupukeanane Skeleton: Synthetic Study of Chloropupukeananin

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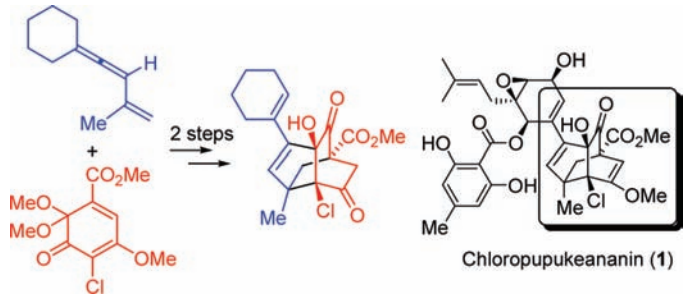
ABSTRACT



A concise synthesis of a highly functionalized chloropupukeananin (1) skeleton via a reverse electron-demand Diels−Alder reaction and intramolecular carbonyl-ene reaction sequence based on our proposed biosynthetic pathway is described.

The pupukeanane family of secondary metabolites from marine sponges[1] includes 2- and 9-isocyanopupukeanane, 2- and 9-pupukeanone, 2-thiocyanatopupukeanane, and 9-isothiocyanatopupukeanane. Pupukeananes possess a common complex tricyclic skeleton, 5-isopropyl-1,3-dimethyltricyclo[4.3.1.$0^{3,7}$]decane, which has made them attractive synthetic targets for the last three decades.[2] Recently, chloropupukeananin (**1**) was isolated from the plant endophyte fungus *Pestalotiopsis fici*, collected in the suburb of Hangzhou, China, by Che and colleagues as a new inhibitor against HIV-1 replication in C8166 cells (IC_{50} = 14.6 μM).[3a,b] Structurally, chloropupukeananin possesses a highly functionalized pupukeanane skeleton that includes an isoprenylated epoxycyclohexenol group (Figure 1). The array of functional groups in a rigid tricyclic structure of **1** has provided us with a strong motive to investigate a novel strategy for an effective construction of the pupukeanane core.

Che and colleagues also reported that iso-A82775C (**2**)[4] and pestheic acid (**3**),[5a] also known as RES-1214−2[5b] and

(1) (a) Burreson, B. J.; Scheuer, P. J.; Finer, J. S.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 4763–4764. (b) Hagadone, M. R.; Burreson, B. J.; Scheuer, P. J.; Finer, J. S.; Clardy, J. *Helv. Chim. Acta* **1979**, *62*, 2484–2494. (c) Fusetani, N.; Wolstenholme, H. J.; Matsunaga, S. *Tetrahedron Lett.* **1990**, *31*, 5623–5624. (d) He, H.; Salva, J.; Catalos, R. F.; Faulkner, D. J. *J. Org. Chem.* **1992**, *57*, 3191–3194. (e) Simpson, J. S.; Garson, M. J.; Hooper, J. N. A.; Cline, E. I.; Angerhofer, C. K. *Aust. J. Chem.* **1997**, *50*, 1123–1127.

(2) For 9-isocyanopupukeanane :(a) Corey, E. J.; Behforouz, M.; Ishiguro, M. *J. Am. Chem. Soc.* **1979**, *101*, 1608–1609. (b) Yamamoto, H.; Sham, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 1609–1611. For 2-isocyanopupukeanane: (c) Corey, E. J.; Ishiguro, M. *Tetrahedron Lett.* **1979**, *20*, 2745–2748. For 2-pupukeanone: (d) Hrater, G.; Wenger, J. *Helv. Chim. Acta* **1984**, *67*, 1702–1706. (e) Chang, N.-C.; Chang, C.-K. *J. Org. Chem.* **1996**, *61*, 4967–4970. (f) Srikrishna, A.; Vijaykumar, D.; Sharma, G. V. R. *Tetrahedron Lett.* **1997**, *38*, 2003–2004. (g) Kaliappan, K.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1997**, *38*, 2185–2186. For 9-pupukeanone: (h) Schiehser, G. A.; White, J. D. *J. Org. Chem.* **1980**, *45*, 1864–1868. (i) Piers, E.; Winter, M. *Liebigs Ann. Chem.* **1982**, *5*, 973–984. (j) Srikrishna, A.; Kumar, P. R. *Tetrahedron Lett.* **2002**, *43*, 1109–1111.

(3) (a) Liu, L.; Liu, S.; Jiang, L.; Chen, X.; Guo, L.; Che, Y. *Org. Lett.* **2008**, *10*, 1397–1400. (b) Liu, L.; Li, Y.; Liu, S.; Zheng, Z.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. *Org. Lett.* **2009**, *11*, 2836–2839. Very recently, several related compounds were isolated from the same extract with **1** and **4**. See: (c) Liu, L.; Niu, S.; Lu, X.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. *Chem. Commum.* **2010**, *46*, 460–462.

(4) An isomer of A82775C, see; Sanson, R.; Gracz, H.; Tempesta, M. S.; Fukuda, D. S.; Nakatsukasa, W. M.; Sands, T. H.; Baker, P. J.; Mynderse, J. S. *Tetrahedron* **1991**, *47*, 3633–3644.

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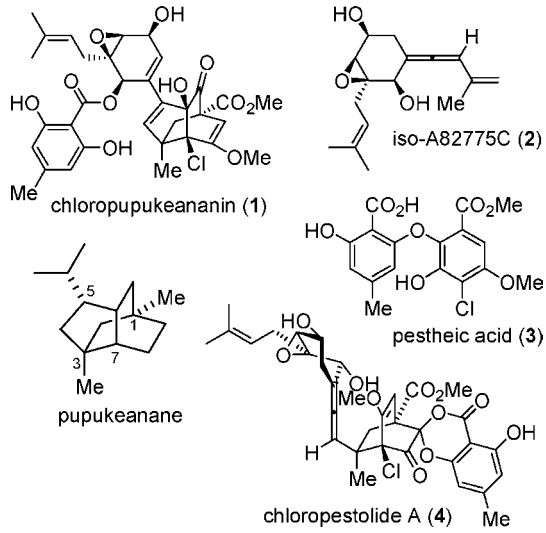


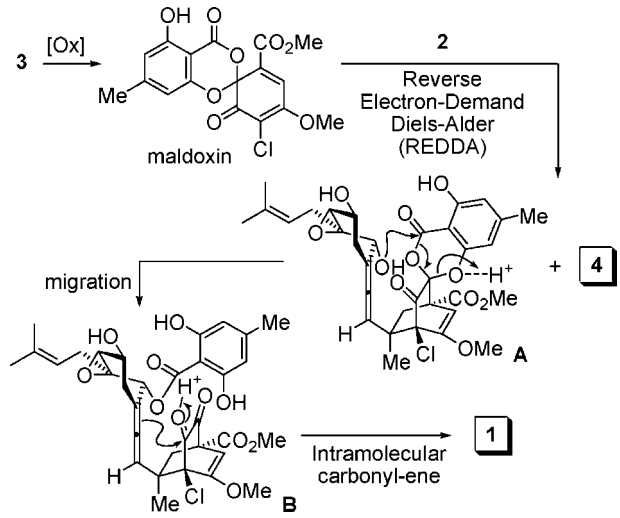
Figure 1. Chloropupukeananin (**1**) and its related compounds.

dihydromaldoxin,[5c] were concomitantly isolated and claimed that these compounds were possible biosynthetic precursors of **1**.[3a] Furthermore, they proposed a biosynthetic pathway for chloropupukeananin from **2** and **3** involving a reverse electron-demand Diels−Alder (REDDA) reaction. More recently, the same group reported the isolation of chloropestolide A (**4**),[3b] which is regarded as a stereoisomer in the proposed Diels−Alder reaction.

These findings led us to propose an alternative biosynthetic hypothesis involing maldoxin[5c] (Scheme 1). Thus, pestheic acid is first oxidized to maldoxin which possesses a reactive diene, known as a masked *o*-benzoquinone (MOB).[6] REDDA reaction of the diene of maldoxin and the terminal alkene of iso-A82775C would furnish two bicyclo[2.2.2]octanes, cycloadduct **A** and chloropestolide A. Then, an acid-mediated spiroketal opening of cycloadduct **A** and a simultaneous migration of the benzoyl group would afford 1,2-diketone **B**, which is spontaneously transformed to a tricyclic compound via an intramolecular carbonyl-ene reaction to produce chloropupukeananin.

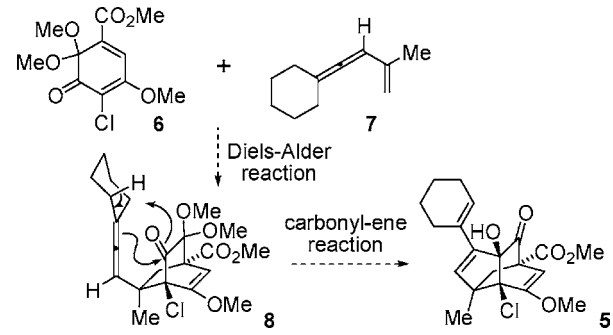
At the outset of our synthetic investigation on chloropupukeananin, we planned a synthetic study of the model core structure **5** starting from MOB **6** and vinylallene **7** based on our proposed biosynthesis (Scheme 2). Tricyclic **5** contains all the functional groups of the core moiety of chloropupukeananin. Our primary concern was to realize the construction of the tricyclo[4.3.1.0^{3,7}]decane core structure by REDDA reaction of MOB **6** and vinylallene **7**, followed by carbonyl-ene reaction. We report herein a novel biomimetic

Scheme 1. Proposed Biosynthetic Pathway Involving Maldoxin



approach to a highly functionalized pupukeanane skeleton which involves the right half of chloropupukeananin.

Scheme 2. Synthetic Strategy toward Model Compound **5**



The preparation of MOB **6** and vinylallene **7** was readily achieved (Scheme 3). Chlorination of 3-hydroxy-2,5-dimethoxybenzoic acid[7] (NaOCl aq, KOH aq, rt),[8] followed by acidic esterification, furnished benzoate **9** (40% yield over 2 steps). Oxidation of the aromatic ring with $PhI(OAc)_2$ in CH_2Cl_2/MeOH (5/1) afforded MOB **6** in 81% yield. Vinylallene **7** was prepared from the known 1- ethynylcyclohexyl acetate[9] with an isopropenyl-copper reagent (CuCN, isopropenyl-MgBr, BF_3•OEt_2, THF, −20 °C)[10] in moderate yield.

With both precursors in hand, thermal and Lewis acid promoted REDDA reaction of MOB **6** and vinylallene **7** was

(5) (a) Shimada, A.; Takahashi, I.; Kawano, T.; Kimura, Y. *Z. Naturforsch.* **2001**, *56B*, 797–803. (b) Ogawa, T.; Ando, K.; Aotani, Y.; Shinoda, K.; Tanaka, T.; Tsukuda, E.; Yoshida, M.; Matsuda, Y. *J. Antibiot.* **1995**, *48*, 1401–1406. (c) Adeboya, M. O.; Edwards, R. L.; Lassøe, T.; Maitland, D. J.; Shields, L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1419–1425.

(6) For reviews on MOBs, see: (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856–866. (b) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221–1234.

(7) Churcher, I.; Hallett, D.; Magnus, P. *J. Am. Chem. Soc.* **1998**, *120*, 10350–10358.

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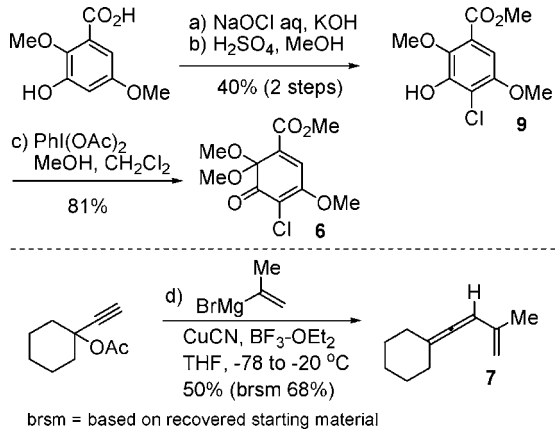
(9) Riveiros, R.; Rodríguez, D.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **2006**, *8*, 1403–1406.

(10) Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 1207–1214.

Scheme 3. Preparation of Simplified Biosynthetic Precursors



carried out (Table 1). Simply heating a mixture of two precursors in toluene (entry 1, 110 °C, 48 h) gave reverse electron-demand cycloadducts **8** and **10** (ca. 1:3 inseparable mixture) in very low yield (14%), along with a normal electron-demand cycloadduct **11**. Most of the starting materials were recovered. All attempts to perform the Lewis acid promoted Diels−Alder reaction[11] were unsuccessful. Nevertheless, intriguingly the initially formed **8** underwent an undesired carbonyl-ene reaction affording tricyclic compound **12** through a Lewis acid-promoted activation of acetal carbon. The structures of cycloadducts **8**, **10**, and **12** were determined by NMR spectroscopy (^{1}H NMR, ^{13}C NMR, DEPT, HMQC, HMBC, and NOESY). Key NOESY correlations of **8** and **10** are shown in Figure 2.

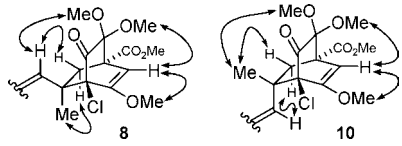
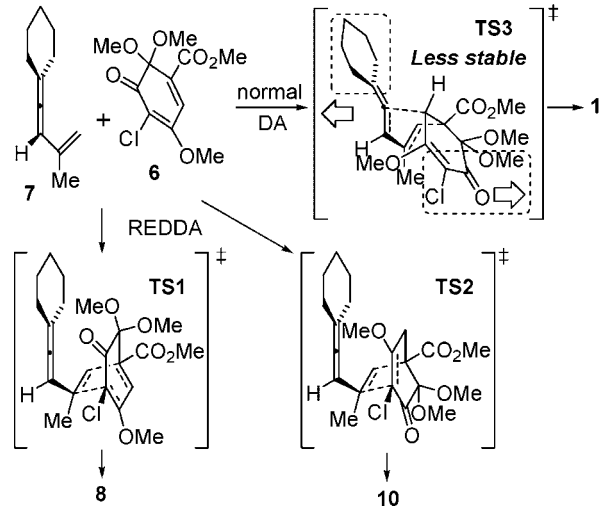


Figure 2. Key NOESY correlations of cycloadducts **8** and **10**.

These unsuccessful results under normal conditions prompted us to examine a REDDA reaction under high-pressure conditions.[12] Surprisingly, the intermolecular Diels−Alder reaction under 0.8 GPa (0.1 M in CH_2Cl_2, rt, 24 h) predominantly produced REDDA cycloadducts **8** and **10** (**8**:**10** = 1.0:1.6) in 34% yield (entry 5). Some typical results are also summarized in Table 1. Other solvents (entries 6−8) gave the cycloadducts in low yield probably due to the low solubility of MOB **6**. High concentration conditions (0.5 M in CH_2Cl_2, entry 9) improved the total yield of **8** and **10**, while prolonged reaction time (entry 10) resulted in a decrease in yield due to the competitive decomposition of the products. Finally, we found that the use of 2.0 equiv of vinylallene **7** (entry 11) afforded the cycloadducts in 70% yield. We reasoned that relatively insoluble MOB **6** precipitated under high-pressure conditions when a large excess of vinylallene **7** was employed.

Scheme 4. Proposed Transition States under High-Pressure Conditions



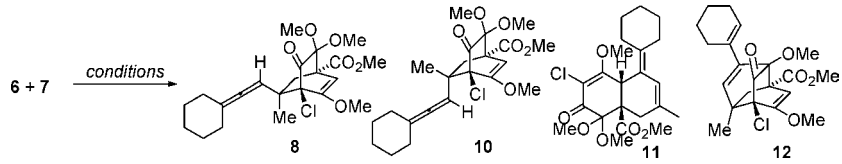
The predominant formation of the REDDA cycloadducts **8** and **10** over normal Diels−Alder cycloadduct **11** under high-pressure conditions is quite interesting. Qualitative explanation of the observed selectivity is shown in Scheme 4. Cycloadducts **8**, **10**, and **11** might be formed through the transition states **TS1**, **TS2**, and **TS3**, respectively. The reaction rate in high-pressure chemistry depends on the volume of activation ($\Delta V^{\ddagger}$).[12a−d] Among them, **TS3** has a larger volume due to the extended cyclohexylidene and α-chloroenone moiety (the arrows in Scheme 4 represent $\Delta\Delta V^{\ddagger}$). Thus, REDDA cycloadducts **8** and **10** might predominantly be produced through compact transition states **TS1** and **TS2** under high-pressure conditions. Although the diastereoselectivity of the REDDA reaction is unsatisfactory in favor of **10**, the undesired cycloadduct **10** could be regarded as a model compound for chloropestolide A.

Next, we examined the intramolecular carbonyl-ene reaction to construct the tricyclo[4.3.1.0^{3,7}]decane skeleton (Scheme 5). The Lewis acid-promoted carbonyl-ene reaction of bicyclic compounds **8** and **10** was unsuccessful, resulting in the hydrolysis of the methyl enol ether moiety. In contrast, treatment of a mixture of **8** and **10** with 80% aqueous TFA in CH_2Cl_2[13] gave the desired tricyclo[4.3.1.0^{3,7}]decane

(11) Using other Lewis acids (e.g., Me_3Al, $EtAlCl_2$, $ZnCl_2$, $TiCl_4$, etc.) resulted in no reaction or decomposition of **6**.

(12) For recent reviews on high-pressure Diels−Alder reaction, see: (a) Jenner, G. *Tetrahedron* **1997**, *53*, 2669–2695. (b) Jenner, G. *J. Phys. Org. Chem.* **2002**, *15*, 1–13. (c) Matsumoto, K.; Hamana, H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033–2234. (d) Kotsuki, H.; Kumamoto, K. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 770–779. For recent examples of high-pressure Diels−Alder reaction in natural product synthesis, see: (e) Pandey, S. K.; Orellana, A.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 5665–5668. (f) Kienzler, M. A.; Suseno, S.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 8604–8605. (g) Waalboer, D. C. J.; Schaapman, M. C.; van Delft, F. L.; Rutjes, F. P. J. T. *Angew. Chem.* **2008**, *47*, 6678−6680; *Angew. Chem., Int. Ed.* **2008**, *47*, 6576−6578. (h) Ballerini, E.; Minuti, L.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **2009**, *74*, 4311–4317.

Table 1. Reverse Electron-Demand Diels−Alder Reaction



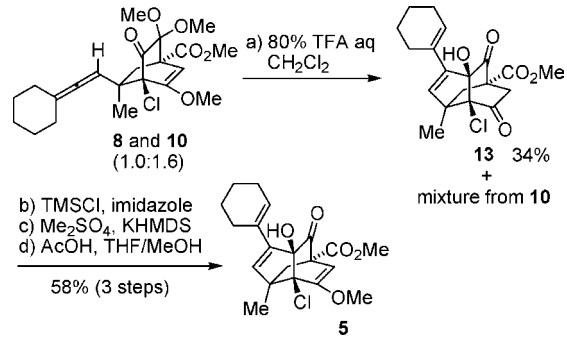
entry	**7** (equiv)	conditions	M (mol/L)	time (h)	**8** and **10** (%)	product ratio (**8:10**)	**11** (%)	recovered[a] **6** (%)
1	2.0	toluene, reflux	0.1	48	14	1.0:3.0	11	69
2	4.8	neat, 110 °C	-	48	decomposed	−	-	-
3	2.0	Me_2AlCl (1.5 equiv), CH_2Cl_2, rt	0.05	48	8	(**10** only)	7	50
4	4.0	Me_2AlCl (2.0 equiv), CH_2Cl_2, rt	0.2	48	31	(**10** only)[b]	11	0
5	2.5	0.8 GPa, CH_2Cl_2, rt	0.1	24	34	1.0:1.6	6	60
6	2.5	0.8 GPa, Et_2O, rt	0.1	24	6	1.0:1.4	trace	90
7	2.5	0.8 GPa, toluene, rt	0.1	24	12	1.0:1.6	2	75
8	2.5	0.8 GPa, MeOH/CH_2Cl_2 (10/1), rt	0.1	24	31	1.0:1.6	7	61
9	2.5	0.8 GPa, CH_2Cl_2, rt	0.5	24	48	1.0:1.6	6	47
10	2.5	0.8 GPa, CH_2Cl_2, rt	0.5	96	33	1.0:1.6	5	42
11	2.0	**0.8 GPa**, CH_2Cl_2,**rt**	**0.5**	**24**	**70**	**1.0:1.6**	**10**	**20**
12	1.5	0.8 GPa, CH_2Cl_2, rt	0.5	24	67	1.0:1.6	9	25

[a] Vinylallene **7** could not be recovered because of its volatility. [b] Tricyclic compound **12** was isolated in 11% yield.

skeleton **13** in 34% yield (88% calculated yield from **8**). HMQC, HMBC, and NOESY data for **13** confirmed the anticipated stereochemistry of the tricyclo[4.3.1.$0^{3,7}$]decane skeleton. Under this condition, dimethyl acetal of **8** might be initially hydrolyzed to 1,2-diketone, and the latter underwent a simultaneous carbonyl-ene reaction to afford **13**. The corresponding carbonyl-ene reaction of isomer **10** gave a complex mixture of products including tricyclo[4.3.1.$0^{3,7}$]decanes.[14] Finally, protection of alcohol **13** with the TMS group, enol etherification,[15] followed by removal of the TMS group afforded the model compound **5** which possesses all the requisite functional groups of the right half of chloropupukeananin. The ^{1}H and ^{13}C NMR spectral data of the model compound **5** resemble those of chloropupukeananin.

In conclusion, we were able to construct a highly functionalized chloropupukeananin core skeleton based on our proposed biosynthetic pathway. The characteristic feature of the present study is that MOB **6** and vinylallene **7** can be converted to the tricyclo[4.3.1.$0^{3,7}$]decane skeleton **13** in two steps, i.e., the REDDA reaction under high-pressure conditions followed by a TFA-promoted intramolecular carbonyl-ene reaction. Synthetic efforts toward chloropupukeananin by a tandem Diels−Alder/carbonyl-ene reaction under acidic and high-pressure conditions with pestheic acid and iso-A82775C are currently underway.

Scheme 5. Acid-Promoted Carbonyl-ene Reaction and Synthesis of Model Compound **5**



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Supporting Information Available: Detailed experimental proedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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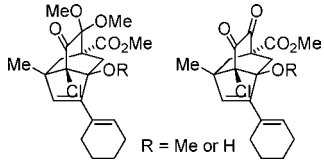
(13) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237–2239.

(14) ^{1}HNMR analysis of the crude mixture indicated the formation of following tricyclic derivatives



(15) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107–124.