Tetrahedron Letters 52 (2011) 5983–5986

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of (−)-muricatacin

Maria González [a], Zoila Gándara [a], Berta Covelo [b], Generosa Gómez [a,*], Yagamare Fall [a,*]

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Vigo, 36200 Vigo, Spain
[b] Servicio Determinación Estructural y Proteómica, CACTI, Universidad de Vigo, 36310 Vigo, Spain

ARTICLE INFO

Article history:
Received 22 June 2011
Revised 2 August 2011
Accepted 26 August 2011
Available online 5 September 2011

Keywords:
Butenolide
Singlet oxygen
Natural products
Total synthesis
γ-Lactone

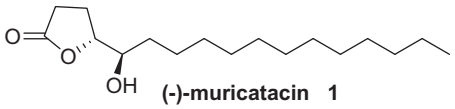
ABSTRACT

A total synthesis of (−)-muricatacin has been achieved using a commercially available starting material and our furan approach to oxacyclic systems, the proven scope of which is thus broadened.

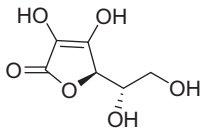
Butenolides, and the corresponding saturated γ-lactones, are found as structural subunits in a wide range of biologically active natural products,[1] some of which are depicted in Figure 1. They are often used as intermediates for the synthesis of biologically significant natural products.[2]

(−)-Muricatacin (**1**) was discovered when isolated from the seeds of the tropical evergreen *Annona muricata* L. (Annonaceae),[3] commonly known as 'sour sop' or 'guanabana'. Both the enantiomers are found in nature, and both exhibit the same potent cytotoxicity towards several human tumour cell lines.[3] This biological activity has stimulated significant interest in the synthesis of muricatacin.[4] Here, we report a new synthesis that may be efficient and flexible enough to give access to potentially interesting new analogues.

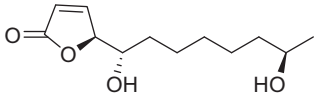
As outlined in Scheme 1, we anticipated that once the relatively inexpensive and readily available chiral reagent D-malic acid (**4**) had been transformed into chiral furan **5**, the stage would be set for the synthesis of **1** by what we call our furan approach to oxacyclic systems.[5] Accordingly, aldehyde **18**, containing the desired muricatacin side chain, hence the precursor of compound **5** was prepared as



(-)-muricatacin 1



vitamin C 3

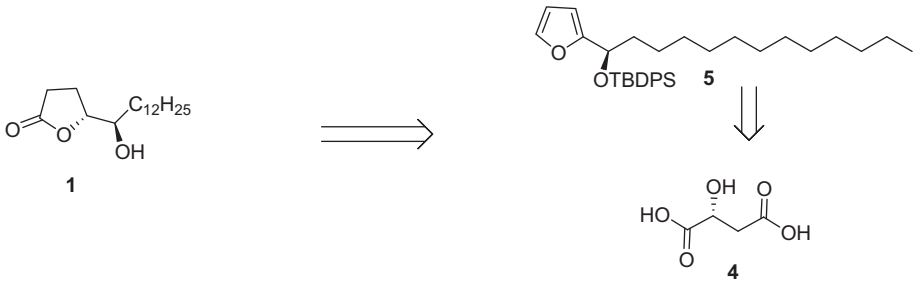


***iso*-cladospolide B 2**

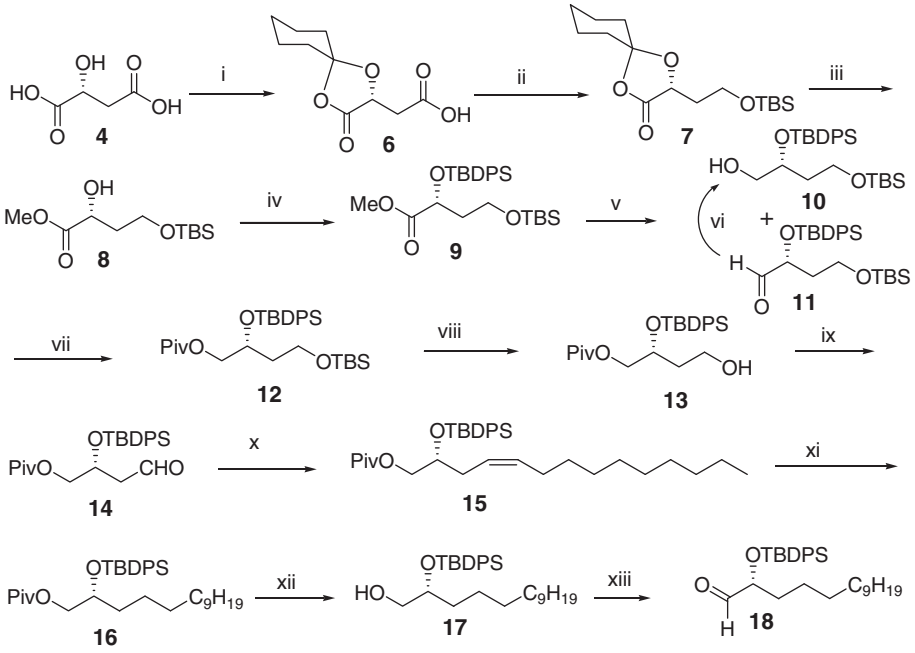
Figure 1. Some natural products containing butenolide or γ-lactone moieties.

* Corresponding authors. Fax: +34 986 81 22 62.
E-mail addresses: ggomez@uvigo.es (G. Gómez), yagamare@uvigo.es (Y. Fall).

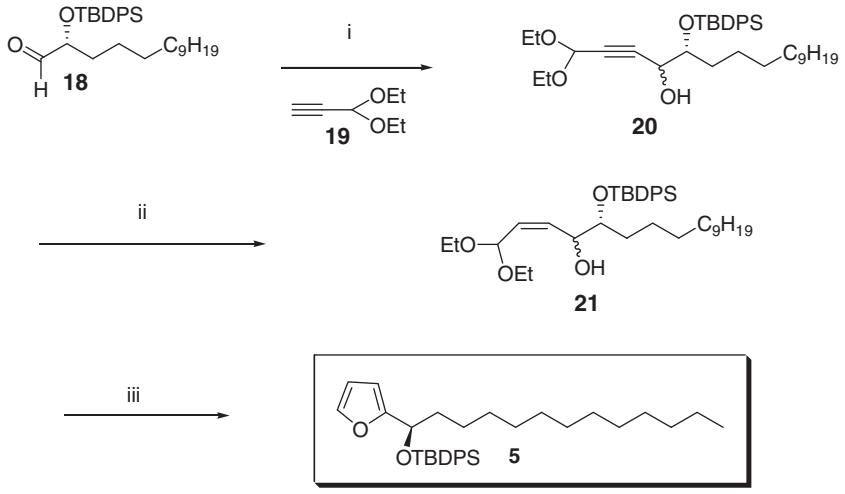
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.08.160



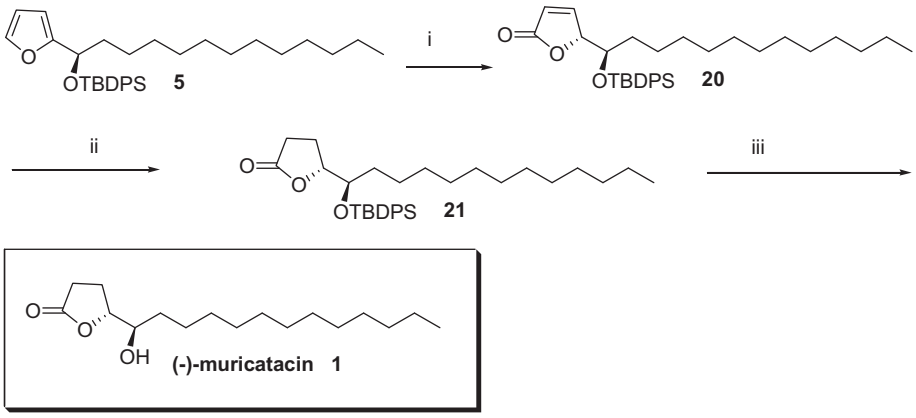
Scheme 1. Retrosynthetic analysis of (−)-muricatacin **1**.



Scheme 2. *Reagents and conditions:* (i) cyclohexanone, $BF_3{\cdot}OEt_2$, Et_2O, 0 °C to rt (93%); (ii) (a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C to rt; (b) TBSCl, Imid, DMAP, DMF, rt (57% from **4**, three steps); (iii) NaOMe, MeOH, rt (97%); (iv) TBDPSCl, Imid, DMAP, DMF, rt (71%); (v) DIBAL, CH_2Cl_2, −78 °C (**10**, 77%; **11**, 12%); (vi) $NaBH_4$, MeOH, 0 °C (87%); (vii) PivCl, DMAP, pyr (90%); (viii) HF/pyr, THF, pyr, 0 °C to rt (80%); (ix) TEMPO, BAIB, CH_2Cl_2 (97%); (x) $C_{10}H_{21}IPPh_3$, *n*-BuLi, THF, (86%); (xi) H_2, Pd/C, MeOH, rt (96%); (xii) DIBAL-H, CH_2Cl_2, −78 °C (97%); (xiii) TEMPO, BAIB, CH_2Cl_2 (97%).



Scheme 3. *Reagents and conditions:* (i) **19**, *n*-BuLi, THF, −78 to 0 °C (89%); (ii) H_2, Lindlar catalyst, hexane, rt; (iii) HCl, or PPTS (72%).



Scheme 4. *Reagents and conditions:* (i) (a) O_2, MeOH, rose Bengal, Hünig's base, *hν*; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; (c) HCl, MeOH (71%, three steps); (ii) H_2, Pd/C, MeOH, rt (99%); (iii) TBAF, THF, rt (80%).

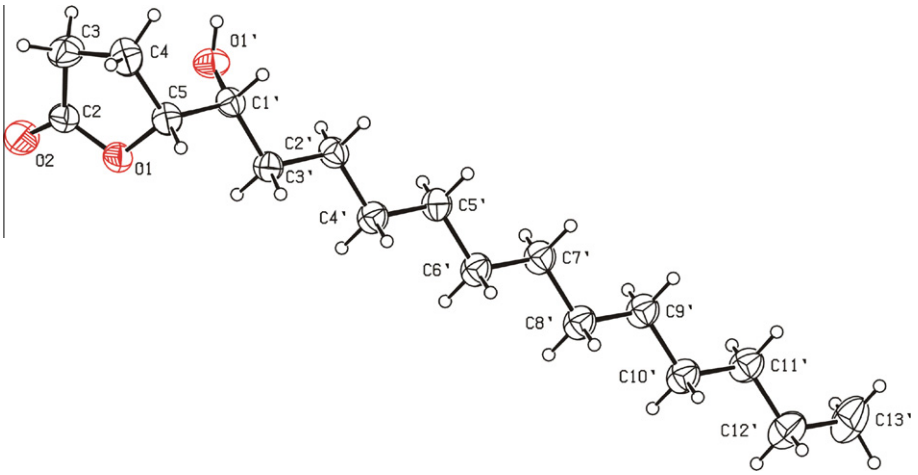


Figure 2. X-ray structure of **1**.

shown in Scheme 2. Reaction of D-malic acid (**4**) with cyclohexanone in the presence of a Lewis acid[6] gave acid **6** in 93% yield. Reduction of the latter with borane dimethyl sulphide complex[7] afforded a rather labile alcohol that without further purification was protected as *tert*-butyldimethylsilyl ether **7** (57% yield from **4**), and removal of the cyclohexylidene protecting group with NaOMe afforded hydroxyester **8** in 97% yield. Protection of the hydroxyl group of **8** afforded *tert*-butyldiphenylsilylether **9** in 71% yield, and the reaction of **9** with DIBAL-H gave the desired alcohol **10** (77%) together with an aldehyde (**11**, 12%) that was easily transformed into **10** by the reduction with sodium borohydride in methanol (87% yield). Alcohol **10** was protected as its pivaloyl ester **12** (90% yield), and the selective removal of the TBS protecting group of **12** afforded alcohol **13** (80%), which upon TEMPO oxidation gave aldehyde **14** in 97% yield. Wittig reaction of aldehyde **14** afforded 86% yield of alkene **15**, which upon catalytic hydrogenation gave **16** in 96% yield. Deprotection of the primary hydroxyl group of **16** afforded 97% yield of alcohol **17**, and TEMPO oxidation of **17** gave 94% yield of aldehyde **18**.

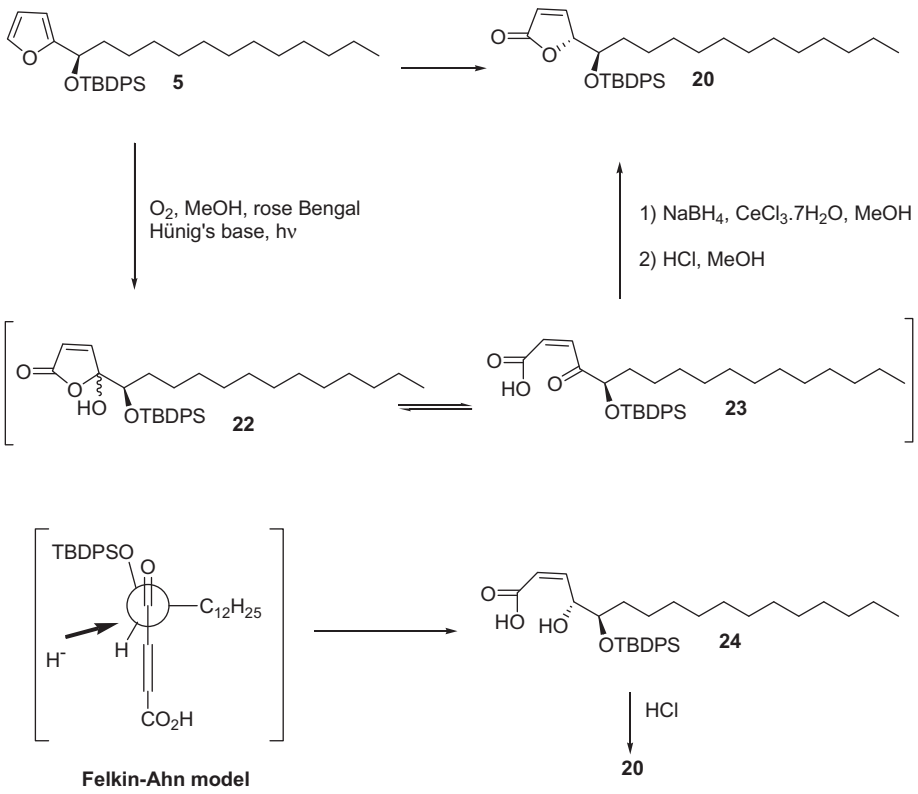
Aldehyde **18** was easily transformed into furan **5** in two steps (64% yield) as shown in Scheme 3. Treatment of **18** with the lithium derivative of alkyne **19** gave a mixture of epimeric propynyl alcohols **20** which was hydrogenated over Lindlar catalyst, providing a mixture of diastereoisomeric (*Z*)-alkenes **21** which was used in the next reaction without further purification. Treatment of allylic alcohol **21** with catalytic pyridinium toluene-*p*-sulphonate (PPTS) or HCl resulted in cyclisation with the loss of two molecules of ethanol, affording the desired furan.[8]

With furan **5** in hand, the stage was set for the crucial oxidation step using singlet oxygen (Scheme 4). Furan **5** was subjected to singlet oxygen oxidation followed by sodium borohydride reduction under Luche's conditions to give an intermediate hydroxy acid which underwent acid catalysed in situ lactonization, affording butenolide **20** in 71% overall yield (three steps). Catalytic hydrogenation of **20** gave **21** in 99% yield. Treatment of **21** with TBAF afforded target compound **1**.[9]

The structure of **1** was unambiguously confirmed as that shown in Figure 2 by X-ray crystallographic analysis of crystals obtained by recrystallization from hexane.[10]

The high diastereoselectivity observed in the conversion of **5** to **20** can be explained by assuming that the reduction of intermediate **23** takes place via a Felkin–Anh model[11] (Scheme 5).

In conclusion, we have carried out an enantioselective synthesis of (−)-muricatacin from commercially available starting material using a method developed by our research group for oxacyclic systems. Work is now in progress on the synthesis of new analogues of muricatacin with a view to their biological evaluation.



Scheme 5. Mechanistic explanation of the diastereoselectivity observed in the conversion of **5** to **20**.

Acknowledgements

This work was supported by a Grant from the Xunta de Galicia (PGIDIT04BTF301031PR). We also thank the NMR service of the CACTI, University of Vigo, for NMR studies and X-ray structure determination.

Supplementary data

Supplementary data associated (experimental procedures and spectral data) with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.160.

References and notes

1. (a) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. J. *Nat. Prod.* **1999**, *62*, 504–540; (b) Zafra-polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087–1117; (c) Koch, S. S. C.; Chamberlin, A. R. In *Enantiomerically Pure γ-Butyrolactones in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1995; pp 687–725.
2. (a) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993–1998; (b) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701–712; (c) de March, P.; Figueredo, M.; Font, J.; Raya, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 2437–2447; (d) Kang, K. H.; Cha, M. Y.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Koh, H. Y.; Chung, B. Y. *Tetrahedron Lett.* **2000**, *41*, 8137–8140; (e) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020; (f) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067–7073; (g) Kabeya, M.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1997**, *53*, 9769–9776; (h) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217–7221.
3. Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137–1140.
4. For recent synthesis of muricatacin, see the following: (a) Kumarasway, G.; Ramakrishna, D.; Santhakumar, K. *Tetrahedron: Asymmetry* **2010**, *21*, 544–548; (b) Ghosal, P.; Kumar, V.; Shaw, A. K. *Carbohydr. Res.* **2010**, *345*, 41–44; (c) Barros, M. T.; Charmier, M. A. J.; Maycock, C. D.; Michaud, T. *Tetrahedron* **2009**, *65*, 396–399; (d) Prasad, K. R.; Gandi, V. *Tetrahedron: Asymmetry* **2008**, *19*, 2616–2619; (e) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Synlett* **2007**, 2891–2893; (f) Prasad, K. R.; Anbarasan, P. *Tetrahedron: Asymmetry* **2006**, *17*, 2465–2467; (g) Ahmed, Md. M.; Cui, H.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 6686–6689; (h) Popsavin, V.; Krstić, I.; Popsavin, M.; Srećo, B.; Benedeković, G.; Kojić, V.; Bogdanović, G. *Tetrahedron* **2006**, *62*, 11044–11053; (i) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143–4145; For a recent review on the synthesis of muricatacin and related compounds, see: Csákÿ, A. G.; Moreno, A.; Navarro, C.; Murcia, M. C. *Curr. Org. Chem.* **2010**, *14*, 15–47.
5. (a) Canoa, P.; Gándara, Z.; Pérez, M.; Gago, R.; Gómez, G.; Fall, Y. *Synthesis* **2011**, *3*, 431–436; (b) Álvarez, C.; Pérez, M.; Zúñiga, A.; Gómez, G.; Fall, Y. *Synthesis* **2010**, *22*, 3883–3890; (c) Canoa, P.; Pérez, M.; Covelo, B.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2007**, *48*, 3441–3443; (d) García, I.; Gómez, G.; Teijeira, M.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2006**, *47*, 1333–1335; (e) Teijeira, M.; Suárez, P. L.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2005**, *46*, 5889–5892; (f) Alonso, D.; Pérez, M.; Gómez, G.; Covelo, B.; Fall, Y. *Tetrahedron* **2005**, *61*, 2021–2026; (g) Pérez, M.; Canoa, P.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2004**, *45*, 5207–5209; (h) Fall, Y.; Vidal, B.; Alonso, D.; Gómez, G. *Tetrahedron Lett.* **2003**, *44*, 4467–4469.
6. Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768–7781.
7. Hanessian, S.; Ugolini, A.; Dubé, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146–2147.
8. (a) Canoa, P.; Vega, N.; Pérez, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2008**, *49*, 1149–1151; (b) Kocienski, P. J.; Brown, R. C.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9–40.
9. Compound **1**: mp 70–72 °C (reported synthetic product[4e] mp 69–72 °C); $[\alpha]_D^{21}$ −19.9 (c 1.0, $CHCl_3$) (reported synthetic product[4e] $[\alpha]_D^{21}$ −19.6 (c 1.0, $CHCl_3$)); IR (neat): 3445, 2916, 2845, 1746, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (m, 1H), 3.60 (m, 1H), 2.68 (m, 2H), 2.20 (m, 2H), 1.55 (m, 2H), 1.30 (s, 20H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C=O), 82.9 (CH), 73.7 (CH), 33.0–21.1 (13 CH_2), 14.1 (CH_3); HRMS: m/z Calcd for $C_{17}H_{33}O_3$, 285.2424; found, 285.2426.
10. Crystallographic data were collected on a Bruker Smart 1000 CCD diffractometer at CACTI (Universidade de Vigo) at 20 °C using graphite monochromated Mo Kα radiation (λ = 0.71073 Å), and were corrected for Lorentz and polarisation effects. The frames were integrated with the Bruker SAINT software package and the data were corrected for absorption using the program SADABS. The structures were solved by direct methods using the program SHELXS97. All nonhydrogen atoms were refined with anisotropic thermal parameters by full-matrix least-squares calculations on F^2 using the program SHELXL97. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters. The structural data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with reference number CCDC 826375. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk)
11. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205–2208; (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–170.