Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6591–6594

A new method for the synthesis of carba-sugar enones (gabosines) using a mercury(II)-mediated opening of 4,5-cyclopropanated pyranosides as the key-step☆

Antonino Corsaro,[a,*] Venerando Pistarà,[a] Giorgio Catelani,[b] Felicia D'Andrea,[b] Roberto Adamo[a,†] and Maria Assunta Chiacchio[a]

[a]*Dipartimento di Scienze Chimiche, Università degli Studi di Catania, viale A. Doria 6, Catania 95125, Italy*
[b]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università degli Studi di Pisa, via Bonanno 33, Pisa 56126, Italy*

Received 9 June 2006; revised 6 July 2006; accepted 6 July 2006
Available online 31 July 2006

Abstract—The stereoselective transformation of the cyclopropyl derivative **2**, stereoselectively obtained with the Simmons–Smith reaction of methyl 2,6-di-*O*-benzyl-α-L-*threo*-hex-4-enopyranoside (**1**), into gabosines and deoxy-carbahexoses is described. The treatment of **2** with mercuric trifluoroacetate in dry methanol gives the organomercuric chloride **3**, which by demercuration with lithium aluminum hydride affords the 4-*C*-deoxy-4-methyl-1,5-bis-glycoside **4**. The acid hydrolysis of **4** produces a mixture of the two diastereoisomeric 2-methyl-cyclohex-2-enones **6** and **7**, catalytically reduced to carba-sugars **10** and **11**. Structures and stereochemistry of all isolated compounds were determined by 1D and 2D NMR experiments.

McCasland et al.[1a] and Ogawa and Suami[1b] introduced *pseudo-sugars* and *carba-sugars* terms, respectively, to indicate a class of carbocyclic analogues of monosaccharides containing a methylene group in the place of the pyranose ring oxygen atom and showing very important biological activities. Particularly, trihydroxylated cyclohexanone and cyclohexenone carba-sugars, named gabosines, were isolated from *Streptomyces* strains by chemical screenings in the search of new secondary metabolites from natural sources.[2] Gabosines bearing a methyl substituent, were detected, isolated and structurally characterized, but initially no biological activity could be found for them. Later, a variety of biological activities such as plant growth regulating effects,[3] and inhibition of glyoxalase-I[4] and glycosidases[5] were found. Recently, Thiericke and co-workers[6] discovered weak DNA-binding properties for A, B, F, N, and O gabosines (Fig. 1) by their so-called biomolecular screening.[7]

Because of their interesting biological activities, the synthesis of these compounds has stimulated a considerable interest from organic chemists, who have followed synthetic strategies involving the transformation of carbohydrates to carbocycles[8a–c] and chemical or enzymatic elaboration of existing carbocycles.[8d–h] Furthermore, gabosines reported in Scheme 1 could be devised as direct chemical precursors of 6-deoxy-carba-pyranose derivatives, such as carba-fucopyranose, a potential

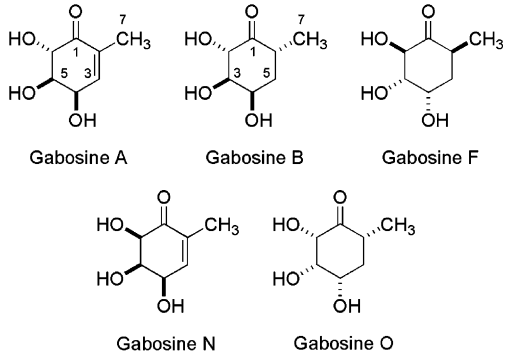


Figure 1. Structures of selected gabosines.

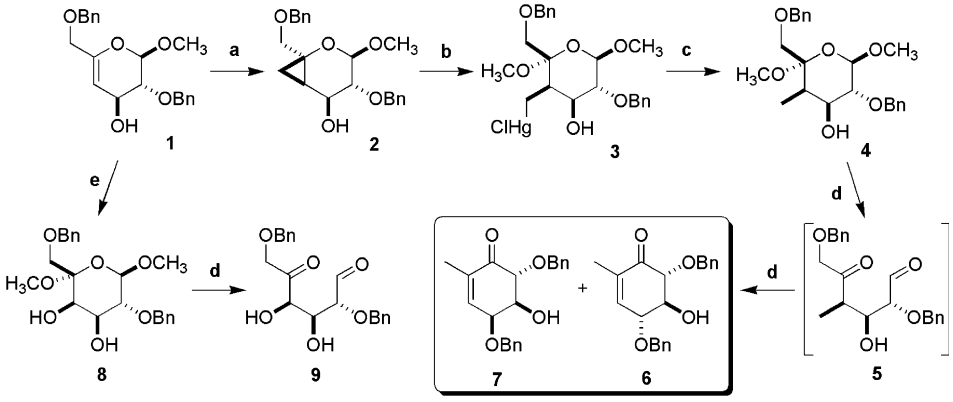
Keywords: 4,5-Cyclopropanated sugars; Intramolecular aldol condensation; Gabosines; 6-Deoxy-5a-carba-hexopyranosides.

☆ Part 21 of the series, 'Chemical Valorisation of Milk-Derived Carbohydrates'; for part 20, see Ref. 11.

* Corresponding author. Tel.: +39 095 7385017; fax: +39 095 580138; e-mail: acorsaro@unict.it

† Present address: Bijvoet Center, Department of Bio-organic Chemistry, Utrecht University Padualaan 8, 3584 CH Utrecht, The Netherlands.

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.023



Scheme 1. Reagents and conditions: (a) CH_2I_2, Et_2Zn, Et_2O; (b) $Hg(OCOCF_3)_2$, dry CH_3OH, rt then $NaCl/H_2O$; (c) $NaBH_4$, THF, rt; (d) CF_3COOH, CH_3CN/H_2O, rt and (e) MCPBA, MeOH.

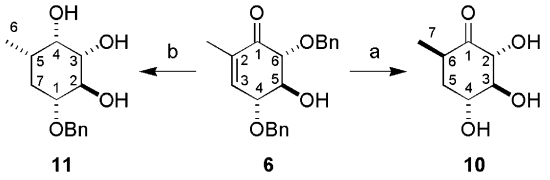
candidate for the inhibition of oligosaccharide processing enzymes.[9]

Through a project on the elaboration of unsaturated intermediated derivatives from lactose,[10] we have recently studied the cyclopropanation reactions of hex-4-enopyranosides, such as **1**, explaining the stereochemical aspect of the reaction.[11]

In this letter, we describe, for the first time, a sequence of reactions which allows the stereoselective transformation of a cyclopropyl derivative into gabosines and 6-deoxy-carbahexoses. To our best knowledge, until now, there are no examples which use a cyclopropanation reaction to transform an hexopyranose into a carba-sugar.

The cyclopropyl derivative **2** was obtained in a near quantitative yield and with a high stereoselectivity[11] in the Simmons–Smith[12] reaction of 4-hexenopyranoside **1** with diethyl zinc and diiodomethane, and was treated with mercuric trifluoroacetate in dry methanol to give, after exchange with NaCl, the organomercuric chloride **3** with high yield.[13] It is noteworthy that the cyclopropane ring-opening takes place with the same high, if not complete, regio- and stereoselectivity previously reported for the methanolysis of analogous epoxide of **1** leading to **8**[14a] (Scheme 1). The crude reaction mixture was used without purification in the reductive demercuration with lithium aluminium hydride to afford, after flash-chromatography, the 4-*C*-deoxy-4-methyl-1,5-bis-glycoside **4**[15] in 71% yield over three steps from **1**. The structure and the stereochemistry of compound **4** were deduced from its ^1H and ^{13}C NMR, COSY and NOE spectra. Particularly, in the ^1H NMR spectrum of **4**, diagnostic signals were doublet ($J_{4,Me} = 7.0$ Hz) centred at 0.98 ppm for the methyl protons in 4-position, and a double quartet for the H-4 proton at 2.44 ppm ($J_{3,4} = 5.0$ Hz).

When the bis-glycoside **4** was submitted to the same hydrolytic conditions ($CF_3COOH/H_2O/CH_3CN$ 0.1:0.5:1, rt, 12 h) as that reported for the transformation of the bis-glycoside **8** into the corresponding 1,5-dicarbonyl-hexose **9**,[14] a mixture of the two diastereoisomeric 2-methyl-cyclohex-2-enones **6**[16] and **7**,[17] was obtained, which were isolated, after flash-chromatography, in 65 and 20% yield, respectively. It could be reasonably supposed that, in the acid reaction medium, after the expected formation of the dicarbonyl compound **5**, a fast intramolecular aldol condensation takes place, affording two diastereoisomeric cyclohexanone intermediates, which subsequently loose water with high regiochemistry from 2,3-position, to give the α,β-unsaturated ketones **6** and **7**, the structure and stereochemistry of which determined by 1D and 2D (NOE, COSY and HETCOR) NMR experiments. The ^1H NMR spectrum of **6**[16] shows a double doublet centred at 6.58 ppm for the unsaturated H-3 proton which couples with methyl protons at 1.82 ppm (d, $J = 1{,}5$ Hz) and H-4 proton at 4.24 ppm ($J = 2.5$ Hz). The H-6 proton appears as a doublet at 3.85 ppm with a large $J_{ax/ax} = 11.0$ Hz because of the coupling with the adjacent H-5 proton at 4.04 ppm (dd, $J_{ax/eq} = 8.0$ Hz), which in its turn couples with the H-4 proton. NOE experiments confirmed the assigned stereochemistry, showing, in particular, an enhancement (6%) of the H-6 signal upon irradiation of the H-4 proton, and vice versa. The ^1H NMR spectrum of **7**,[17] corresponding to the 2,6-di-*O*-benzyl derivative of Gabosine A, shows a double doublet ($J = 1.5$ and 4.0 Hz) centred at 6.66 ppm for the unsaturated H-3 proton which couples with methyl protons at 1.74 ppm and H-4 proton at 4.33 ppm. A doublet with a $J_{ax/eq} = 8.0$ Hz centred at 4.06 ppm is apparent for the H-6 proton owing to the coupling with the adjacent H-5 proton which in its turn resonates as double doublet at 4.17 ppm. Also in this case, NOE experiments are in agreement with the assigned stereochemistry, the irradiation of the H-4 proton giving rise to enhancements of 4.5 and 3.6% of the H-5 and H-6 signals, respectively, and vice versa. When the hydrolysis of bis-glycoside **4** was carried out by using a catalytic amount of trifluoroacetic acid, it stops at the dicarbonyl compound **5** as pointed out by the ^1H NMR spectrum of the unprocessed reaction mixture, which does not show any evidence of condensation products, but signals for the anomeric protons in the 5.20–5.70 ppm range are characteristic of a complex mixture of tautomeric forms in solution, which will be the object of further studies.



Scheme 2. Reagents and conditions: (a) Pd/C, H_2, MeOH; and (b) Raney/Ni, H_2, EtOH.

With the aim of chemically supporting the structure of **6**, it was reduced with hydrogen and Pd/C to give, as unique product, the tri-hydroxy-methylcyclohexanone **10**,[18] a diastereoisomer of the naturally occurring Gabosines B, F and O (Scheme 2).[19] Furthermore, the catalytic hydrogenation of **6** with Ni-Raney determines the complete reduction of the conjugate system, leading with high stereoselectivity to a partially debenzylated carba-sugar isolated with 71% yield and identified (NMR) as the benzyl 5a-carba-β-L-fucopyranoside **11**[20] (Scheme 2). The position of the benzyl group was unequivocally assured with NOE experiments; in particular, the irradiation of CH_2 protons determines the enhancement of the equatorial H-7 proton (2.1%) and H-2 proton signals (1.5%), and vice versa.

In conclusion this letter describes a new route for the preparation of 6-deoxy-carbasugars from a cyclopropanated D-galactose derivative. The key steps of this synthesis are the stereocontrolled cyclopropanation of 4-hexenopyranoside, the stereoselectivity of the mercury-mediated cyclopropane ring opening and the stereoselective reduction of the carbonyl group, which allows to obtain different isomers of the title compound in a stereocontrolled manner.

Recently, this reaction route is carried out with a cyclopropanated lactose analogue to **2**;[11] preliminary results are like those reported in this letter for the monosaccharide derivative, and therefore they outline a new route for the stereoselective transformation of lactose into new and biologically interesting carba-sugars, expanding, thus, the series of applications directed towards an economical valorisation of this natural disaccharide, a by-product of the cheese-industry. The results of these studies will be the object of a next publication.

Acknowledgements

The authors are grateful to MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca, Roma) for partial financial support in the frame of the COFIN 2004 program.

References and notes

1. (a) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516–1521; (b) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21–90.
2. Bach, G.; Breiding-mack, S.; Grabley, S.; Hammann, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 241–250.
3. Grabley, S.; Wink, J.; Hammann, P.; Giani, C.; Huetter, K.; Zeeck A. (Hoechst A. G., Fed. Rep. Ger.), PCT Int. Appl., PIXXD2 WO 8912038, 1989, *Chem. Abstr.*, **1990**, *113*, 22211y.
4. (a) Takeuchi, T.; Chimura, H.; Hamada, M.; Umezawa, H. *J. Antibiot.* **1975**, *28*, 737–742; (b) Douglas, K. T.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 31–44.
5. (a) Iwasa, T.; Yamamoto, H.; Shibata, M. *J. Antibiot.* **1970**, *23*, 595–602; (b) Suami, T.; Ogawa, S.; Chida, N. *J. Antibiot.* **1980**, *33*, 98–102.
6. Grabley, S.; Thiericke, R.; Zeeck, A. In *Drug Discovery from Nature*; Grabley, S., Thiericke, R., Eds.; Springer: Berlin, 1999; pp 124–148.
7. (a) Tang, Y.-Q.; Maul, C.; Hofs, R.; Sattler, I.; Feng, S.; Zeeck, A.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, 149–153; (b) Hofs, R.; Schoppe, S.; Thiericke, R.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 1883–1887.
8. (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831; (b) Lubineau, A.; Billault, I. *J. Org. Chem.* **1998**, *63*, 5668–5671; (c) Dalko, D. I.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 773–777; (d) Shing, T. K. M.; Li, T. Y.; Kok, S. H.-L. *J. Org. Chem.* **1999**, *64*, 1941–1946; (e) Banwell, M. G.; Bray, A. M.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1351–1354; (f) Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y.; Ohfune, Y. *Synlett* **2002**, *8*, 1341–1343; (g) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049–3051; (h) Alibes, R.; Bayon, P.; De March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Org. Lett.* **2006**, *8*, 1617–1620.
9. Wilkox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102–3104.
10. Catelani, G.; Corsaro, A.; D'Andrea, F.; Mariani, M.; Pistarà, V.; Vittorino, E. *Carbohydr. Res.* **2003**, *338*, 2349–3258.
11. Corsaro, A.; Chiacchio, U.; Adamo, R.; Pistarà, V.; Rescifina, A.; Romeo, R.; Catelani, G.; D'Andrea, F.; Mariani, M.; Attolino, E. *Tetrahedron* **2004**, *60*, 3787–3795.
12. Simmons, H. E.; Cairns, T. L.; Vladuchik, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1–131.
13. *Methyl 2,6-di-O-benzyl-4-deoxy-5-C-methoxy-4-(methyl-chloromercurio)-β-D-galactopyranoside* **3**: syrup, 98% yield, $[\alpha]_D^{25}$ +110.5 (*c* 0.1, $CHCl_3$). Selected NMR data: ^1H (500 MHz, $CDCl_3$) δ: 1.29 (t, 1H, $J = 12.5$ Hz, H_{7a}), 1.54 (dd, 1H, $J = 5.5$, 12.5 Hz, H_{7b}), 2.58 (dt, 1H, $J = 5.5$, 12.5 Hz, H_4), 3.21 (dd, 1H, $J = 7.5$, 10.0 Hz, H_2), 3.23 (s, 3H, C_5OCH_3), 4.32 (dd, 1H, $J = 5.0$, 10.0 Hz, H_3), 4.45 (d, 1H, $J = 7.5$ Hz, H_1); ^{13}C (50 MHz, $CDCl_3$) δ: 20.11 (C_7), 42.65 (C_4), 48.37 (C_5–OCH_3), 56.91 (C_1–OCH_3), 65.37 (C_6), 66.97 (C_3), 78.52 (C_2), 101.07 (C_1), 102.47 (C_5).
14. (a) Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F. *Gazz. Chim. Ital.* **1992**, *122*, 135–142; (b) Pistarà, V.; Barili, P. L.; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *41*, 3253–3256.
15. *Methyl 2,6-di-O-benzyl-4-deoxy-5-C-methoxy-4-methyl-β-D-galactopyranoside* **4**: syrup, 96% yield, $[\alpha]_D^{25}$ −26.7 (*c* 0.3, $CHCl_3$). Selected NMR data: ^1H (500 MHz, $CDCl_3$) δ: 0.98 (d, 3H, $J = 7.0$ Hz CH_3), 2.44 (dq, 1H, $J = 5.0$, 7.0 Hz, H_4), 2.58 (d, 1H, $J = 2.5$ Hz, OH), 3.26 (s, 3H, C_5–OCH_3), 3.33 (dd, 1H, $J = 8.0$, 9.5 Hz, H_2), 3.53 (s, 3H, C_1–OCH_3), 4.17 (ddd, 1H, $J = 2.5$, 5.0, 9.5 Hz, H_3), 4.49 (d, 1H, $J = 8.0$ H_1); ^{13}C (125 MHz, $CDCl_3$) δ: 8.39 (CH_3), 38.74 (C_4), 47.95 (C_5–OCH_3), 56.70 (C_1–OCH_3), 65.65 (C_6), 68.92 (C_3), 79.58 (C_2), 101.01 (C_1), 101.65 (C_5).
16. *(4R,5S,6R)- and (4S,5R,6S)-4,6-bis(benzyloxy)-5-hydroxy-2-methylcyclohex-2-enone* **6**: syrup, 65% yield, $[\alpha]_D^{25}$ +7.7 (*c* 0.5, $CHCl_3$). Selected NMR data: ^1H (500 MHz, $CDCl_3$) δ: 1.82 (dd, 3H, $J = 1.5$, 2.5 Hz, CH_3), 3.85 (d, 1H, $J = 11.0$ Hz, H_6), 4.04 (dd, 1H, $J = 8.0$, 11.0 Hz, H_5), 4.24

(dq, $J = 2.5$, 8.0 Hz, H_4), 6.58 (dd, 1H, $J = 1.5$, 2.5 Hz, H_3); ^{13}C (125 MHz, $CDCl_3$) δ: 15.16 (CH_3), 29.21, 73.14 and 73.99 (CH_2), 76.55, 77.80, 82.60 (C_4, C_5 and C_6), 135.05 (C_2), 142.85 (C_3), 197.04 (C=O).

17. *(4R,5R,6R)- and (4S,5S,6S)-4,6-bis(benzyloxy)-5-hydroxy-2-methylcyclohex-2-enone* **7**: syrup, 20% yield, $[\alpha]_D^{25}$ −89.7 (*c* 0.8, CD_3CN). Selected NMR data: ^1H (500 MHz, $CDCl_3$) δ: 1.74 (t, 3H, $J = 1.5$ Hz, CH_3), 4.06 (d, 1H, $J = 8.0$ Hz, H_6), 4.17 (m, 1H, H_5), 4.33 (ddd, 1H, $J = 1.5$, 2.5, 4.0 Hz, H_4), 6.66 (dd, 1H, $J = 1.5$, 4.0 Hz, H_3); ^{13}C (125 MHz, $CDCl_3$) δ: 15.58 (CH_3), 29.68, 71.42, 72.61 (CH_2), 72.99, 73.49 (CH_2), 80.18, 136.39 (C_2), 139.02 (C_3), 196.63 (C=O).
18. *(2R,3S,4R,6R)- and (2S,3R,4S,6S)-2,3,4-trihydroxy-6-methylcyclohexanone* **10**: syrup, 92% yield, $[\alpha]_D^{25}$ −55.6 (*c* 1.1, $CHCl_3$). Selected NMR data: ^1H (500 MHz, CD_3OD) δ: 1.04 (d, 1H, $J = 6.5$ Hz, CH_3), 1.20 (ddd, 1H, $J = 5.0$, 5.5, 13.5 Hz, H_{5b}), 2.13 (ddd, 1H, $J = 5.5$, 12.5, 13.5 Hz, H_{5a}), 2.61 (ddd, 1H, $J = 5.5$, 6.5, 12.5 Hz, H_6), 3.21 (d, 1H, $J = 9.5$ Hz, H_3), 3.85 (m, 1H, $J = 9.5$ Hz, H_4), 4.03 (dd, 1H, $J = 0.9$, 9.5 Hz, H_2); ^{13}C (50 MHz, CD_3OD) δ: 13.81 (CH_3), 38.99 (CH_2), 40.13, 71.77, 79.37, 81.39, 194.6 (C=O).
19. The generally adopted numbering for carbacycles of naturally occurring derivatives or their analogues does not always follow the standard prioritisation rules. We have attributed (Scheme 2) to compounds **6** and **10** the numbering system used in the literature for Gabosine analogues (Ref. 8), and that used for carba-sugar derivatives for compound **11** (Ref. 21).
20. *Benzyl 5a-carba-β-L-fucopyranoside* **11**: syrup, 71% yield, $[\alpha]_D^{25}$ +7.70 (*c* 1.3, $CHCl_3$). Selected NMR data: ^1H (500 MHz, CD_3CN) δ: 0.95 (d, 1H, $J = 6.8$ Hz, CH_3), 1.34 (dd, 1H, $J = 11.5$, 12.6 Hz, H_{7ax}), 1.54 (m, 1H, H_5), 1.71 (dt, 1H, $J = 3.8$, 4.6, 12.6 Hz, H_{7eq}), 3.20 (ddd, 1H, $J = 4.6$, 9.5, 11.5 Hz, H_1), 3.23 (dd, 1H, $J = 3.0$, 9.5 Hz, H_3), 3.48 (t, 1H, $J = 9.5$ Hz, H_2), 3.60 (br t, 1H, $J = 3.0$ Hz, H_4); ^{13}C (50 MHz, $CDCl_3$) δ: 17.3 (CH_3), 30.9 (CH_2), 31.4, 71.1, 72.5, 74.2, 74.9, 80.1. For previous synthesis of 5a-carbafucopyranoside derivatives, see Ref. 21.
21. (a) Carpintero, M.; Jaramillo, C.; Fernandez-Mayoralas, A. *Eur. J. Org. Chem.* **2000**, 1285–1296; (b) Carpintero, M.; Bastida, A.; Garcia-Junceda, E.; Jimenez-Barbero, J.; Fernandez-Mayoralas, A. *Eur. J. Org. Chem.* **2001**, 4127–4135; (c) Calderon, F.; Carpintero, M.; Garcia-Junceda, E.; Fernandez-Mayoralas, A.; Bastida, A. *Lett. Org. Chem.* **2005**, *2*, 247–251; (d) Verduyn, R.; van Leeuwen, S. H.; van der Marel, G. A.; van Boom, J. H. *Rec. Trav. Chim. Pays-Bas* **1996**, *115*, 67–71.