Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2219–2222

L-Ascorbic acid in organic synthesis: DBU-catalysed one-pot synthesis of tetramic acid derivatives from 5,6-*O*-isopropylidene ascorbic acid☆

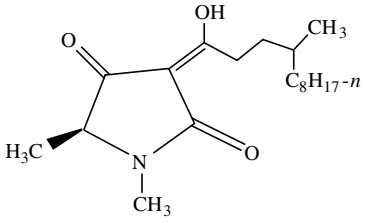
Biswajit K. Singh, Shyam S. Verma, Namrata Dwivedi and Rama P. Tripathi*

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

Received 6 October 2005; revised 10 January 2006; accepted 19 January 2006

Abstract—Reaction of 5,6-*O*-isopropylidene-2,3-bis-*O*-alkyl ascorbic acid with different amines in the presence of DBU at ambient temperature resulted in the formation of 3,4-bis-*O*-alkyl-1-alkyl-5-(2-hydroxy ethyl)-5-hydroxy-1,5-dihydropyrrol-2-ones in moderate yields.

Tetramic acid derivatives are the key structural core found in a variety of natural products including many antibiotics such as melophilin B, reutericyclin, tirandamycin, BU2313A, blasticidin A and vancoresmycin.[1–5] The wide spectrum of biological activities in this class of molecule include potent antiviral, antibiotic and antifungal properties as well as cytotoxicities and antitumour action.[6–8] These compounds have also been designed as glycine site *N*-methyl-D-asparatate (NMDA) antagonists for the treatment of neurological disorders.[6] One such prominent molecule, melophilin B, is depicted in Figure 1.



Melophilin B

Figure 1.

Recently a number of solution- and solid-phase syntheses of tetramic acids have been reported.[9–13] Ascorbic acid has been used in organic synthesis for the preparation of many intermediates and biologically active molecules. Our interest in ascorbic acid chemistry arose from our quest for new drugs against tuberculosis. Thiolactomycins and thiotetronic acid derivatives, which show antitubercular activity via mycobacterial FAS-II inhibition[14a,b] and many 5-hydroxymethyl tetronic acid analogues exhibit HIV protease inhibitory activity.[14c] We were interested in the synthesis of compounds where the ring oxygen of ascorbic acid is replaced with nitrogen and the resulting core, a tetramate, might serve as a good pharmacophore. Ascorbic acid as a synthon has been used in the synthesis of pyrano[3,4-*b*]indoles and a variety of other heterocycles by Preobrzhenskaya's group.[15] Very recently Dallacker's group[16] and Khan et al.[17] reported the reaction of liquid ammonia and amines with ascorbic acid derivatives to give lactams. Encouraged by their reports we decided to synthesise tetramic acid derivatives from a suitably protected ascorbic acid.

The reaction of 2,3-*O*-bis-allyloxy-5,6-*O*-isopropylidene ascorbic acid **2a**, prepared by the slightly modified method reported earlier,[18] with *n*-butylamine in THF at 0–40 °C did not result in any product as was evident from TLC. However, addition of DBU as catalyst led to the formation of several products (TLC) and compound **2a** was totally consumed within 10 h at ambient temperature. Column (SiO_2) chromatography of the

Keywords: Ascorbic acid; Tetramic acids; Addition reactions; Aminations; Eliminations.
☆CDRI Communication No. 8606.
* Corresponding author. Tel.: +91 522 2612412; fax: +91 522 2623405; e-mail: rpt_56@yahoo.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.098

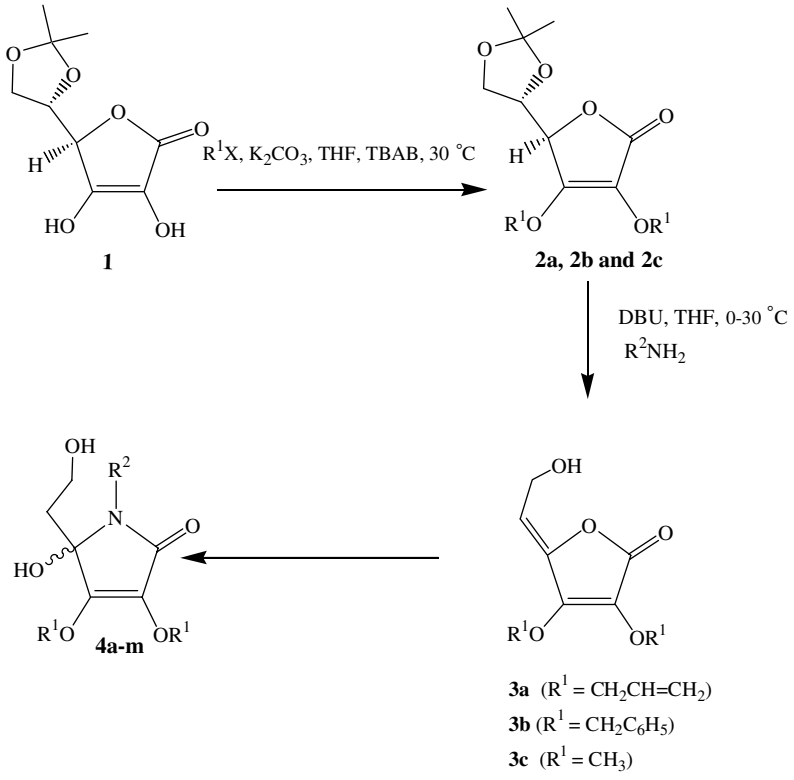
crude reaction mixture led to the isolation of only two compounds as major and minor products. Other compounds (in very minute amounts) could not be isolated in pure forms. The major compound isolated was found to be 3,4-bis-allyloxy-1-propyl-5-hydroxy-5-(2-hydroxyethyl)-1,5-dihydropyrrol-2-one **4a** in 50% yield. The structure was confirmed from spectroscopic data and analysis.[19] The minor product was characterised as 3,4-bis-allyloxy-5-(2-hydroxyethylidene)-5*H*-furan-2-one **3a** in 10% yield. The *Z* geometry of the double bond in this compound was apparent from its PMR spectrum and its structure was also evidenced on the basis of spectroscopic data. Careful monitoring of the reaction by TLC showed that **2a** was formed first and with the passage of time it was converted into **4a**. We reacted **3a** under similar conditions with *n*-butylamine to give **4b** in good yield. Similarly, reaction of 2,3-allyloxy-5,6-*O*-isopropylidene ascorbic acid with other amines in the presence of DBU at ambient temperature led to the formation of the respective 1-alkyl tetramates (**4c**–**4h**) in good yields along with the 5-hydroxyethylidene products in minor amounts (Table 1).

To see the effect of 2,3-alkoxy substitutents on this reaction we carried out the reaction of 2,3-bis-benzyloxy-5,6-*O*-isopropylidene ascorbic acid **2b** and 2,3-bis-methoxy-5,6-*O*-isopropylidene ascorbic acid **2c**, which were reacted with *n*-butylamine separately. The products obtained were the respective 1-alkyl tetramates **4j** and **4k** in moderate yields along with the intermediate ethylidene derivatives (**3b** and **3c**) in $\leqslant$15% yields. There was no major improvement in the yield of the isolated

Table 1. Synthesis of 2,3-O-substituted-1-alkyltetramates (**4a**–**m**)

Entry	R^1	R^2	Reaction time (h)	% Yield[a] of (**4a**–**m**)	% Yield[a] of (**3a**–**c**)
4a	$-CH_2CH{=}CH_2$	*n*-Propyl	15	50	10
4b	$-CH_2CH{=}CH_2$	*n*-Butyl	16	50	10
4c	$-CH_2CH{=}CH_2$	*n*-Hexyl	14	60	8
4d	$-CH_2CH{=}CH_2$	*n*-Octyl	15	60	10
4e	$-CH_2CH{=}CH_2$	*n*-Dodecyl	10	55	10
4f	$-CH_2CH{=}CH_2$	Benzyl	8	60	15
4g	$-CH_2CH{=}CH_2$	$-(CH_2)_5-$	15	45	10
4h	$-CH_2CH{=}CH_2$	Adamantyl	20	25	15
4i	$-CH_2C_6H_5$	*n*-Propyl	12	60	10
4j	$-CH_2C_6H_5$	*n*-Butyl	7	50	15
4k	$-CH_3$	*n*-Butyl	9	50	10
4l	$-CH_3$	*n*-Octyl	8	55	10
4m	$-CH_3$	Benzyl	8	35	15

[a] After column chromatography.



Scheme 1.

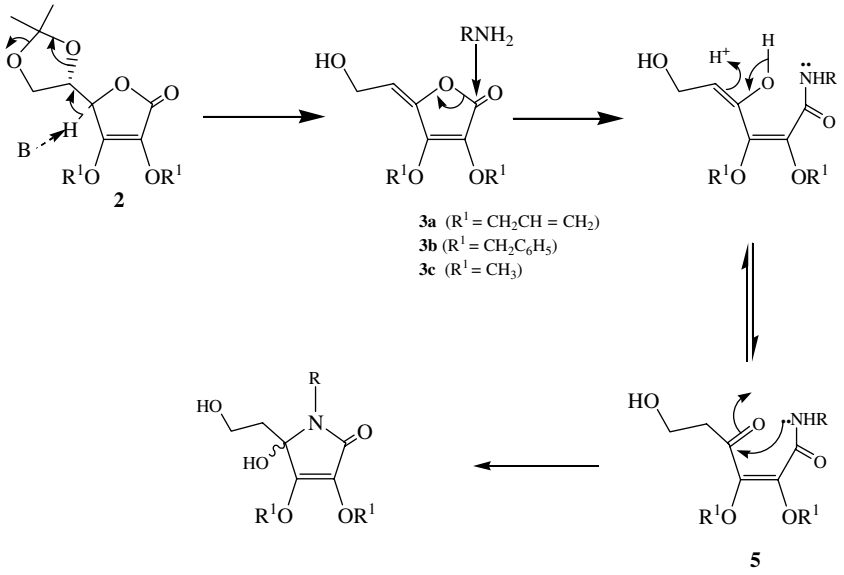


Figure 2. A plausible mechanism of reaction.

products in any of the reactions suggesting that 2,3-O-substitutents do not affect the course of the reaction. Dichloromethane, ethanol and chloroform were also used as solvents in this reaction but resulted in no improvements in the yields. 4-Dimethylaminopyridine and triethylamine, when used as bases, did not lead to any reaction (Scheme 1).

The introduction of a nitrogen atom in place of the oxygen atom in the ring of ascorbic acid leading to formation of tetramates can be explained via intermediates **3a**–**c** (Fig. 2). In fact, the formation of these intermediates was evident from TLC after just a few minutes and with the passage of time they were consumed to give the respective products. A reaction mechanism for this reaction most probably involves the abstraction of a proton from C-4 of the ascorbic acid derivatives followed by β-elimination of acetone from the 5,6-*O*-isopropylidene unit of **2** resulting in the unsaturated 5-ethylidene derivatives **3a**–**c**. Such a rearrangement has been reported by Poss et al.[20] during reaction of a 5,6-*O*-isopropylidene derivative with *t*-BuOLi in *t*-BuOH at ambient temperature. Once the unsaturated lactone **3** is formed, it would undergo a ring-opening reaction with the amines to give the enol-keto-amide **5**. The latter would undergo intramolecular ring closure to give the lactams or tetramates, (Fig. 2).

In summary, we have developed a simple, one-pot and novel method for the synthesis of tetramic acid derivatives from the reaction of a 5,6-*O*-isopropylidene ascorbic acid and amine nucleophiles in the presence of DBU.

Acknowledgements

The authors thank the Director CDRI for his keen interest in this programme and B.S., S.S.V. and N.D. thank CSIR and UGC New Delhi, for the award of JRFs.

References and notes

1. Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981–2001.
2. Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145–1174.
3. Wang, C.-Y.; Wang, B.-G.; Wiryowidagdo, S.; Wray, V.; Van Soest, R.; Steube, K. G.; Guan, H.-S.; Proksch, P.; Ebel, R. *J. Nat. Prod.* **2003**, *66*, 51–56.
4. Höltzel, A.; Gänzle, M. G.; Nicholson, G. J.; Hammes, W. P.; Jung, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2766–2768.
5. (a) Iwata, Y.; Maekawara, N.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1532–1536; (b) Elbe, T. E.; Large, C. M.; De Vries, W. H.; Crum, G. F.; Shell, J. W. *Antibiotics Annual 1955–1956, Medical Encyclopedia*. New York, 1956; p 893.
6. Meyer, C. *J. Antibiot.* **1971**, *24*, 558–560.
7. Terret, N. *Drug Discovery Today* **1998**, *3*, 299.
8. Hashidoko, Y.; Nakayama, T.; Homma, Y.; Johar, S. *Tetrahedron Lett.* **1999**, *40*, 2957–2960.
9. (a) Hamilakis, S.; Kontonassios, D.; Sandris, C. *J. Heterocycl. Chem.* **1996**, *33*, 825–833; (b) Hamilakis, S.; Kontonassios, D.; Sandris, C. *J. Heterocycl. Chem.* **1996**, *33*, 1145–1151; (c) Li, B. Q.; Franck, R. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629–2634; (d) Pei, H. Q.; Wu, T. J.; Ruan, Y. P. *Org. Lett.* **2003**, *5*, 4341–4344, and references cited therein.
10. Liu, Z.; Ruan, X.; Huang, X. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2505–2507.
11. (a) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345; (b) Chen, B. C. *Heterocycles* **1991**, *32*, 529; (c) Gaber, A. E.-A. M.; McNab, H. *Synthesis* **2001**, 2059–2074.
12. (a) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195–214; (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472; (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600; (d) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–92.
13. (a) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 4369–4372; (b) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1998**, *63*, 4808; (c) Romoff, T. T.; Ma, L.; Wang, Y. W.; Campbell, D. A. *Synlett* **1998**, 1341–1342.
14. (a) Miyakawa, S.; Suzuki, K.; Noto, T.; Harada, Y.; Okazaki, H. *J. Antibiot.* **1982**, *35*, 411–419; (b) Kremer, L.;

Douglas, J. D.; Baulard, A. R.; Morehouse, C.; Guy, M. R.; Alland, D.; Dover, L. G.; Lakey, J. H.; Jacobs, W. R., Jr.; Brennan, P. J.; Minnikin, D. E.; Besra, G. S. *J. Biol. Chem.* **2000**, *275*, 16857–16864; (c) Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H. B.; Peter, H. H.; Rossel, J. *J. Antibiot.* **1994**, *47*, 136–142.

15. (a) Larvrenov, S. N.; Turchin, K. F.; Korolev, A. M.; Anisimova, O. S.; Preobrzhenskaya, M. N. *Tetrahedron* **2005**, *61*, 6610–6613; (b) Preobrzhenskaya, M. N.; Korolev, A. M. *Russ. J. Bioorg. Chem.* **2000**, *26*, 85–97.
16. Dallacker, F.; Sanders, J. *Chem. Ztg.* **1985**, *109*, 277–280; *Chem. Abstr.* **1986**, *105*, 115308k.
17. Khan, M. A.; Adams, H. *Carbohydr. Res.* **1999**, *322*, 279–283.
18. Olabisi, A. O.; Wimalasena, K. *J. Org. Chem.* **2004**, *69*, 7026–7032.
19. Typical procedure for the synthesis of **3a** and **4a**: To a stirred solution of compound **2a** (1.7 g, 5.74 mmol) and *n*-propylamine (0.52 mL, 6.31 mmol) in THF (8 mL) at 0 °C, DBU (50 mol %) was added and stirring was continued for 10 min at this temperature. The reaction mixture was further stirred at ambient temperature until the complete disappearance of **2a** (TLC). The solvent was evaporated and the residue was partitioned between ethyl acetate (5×20 mL) and water (2×10 mL). The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure to afford a crude mass, which was chromatographed over silica gel (240–400 mesh) using a gradient of hexane–EtOAc (4:1) as eluent to give the intermediate 5-hydroxy-5-(2-hydroxyethylidene)-furanone **3a** followed by the required tetramic acid **4a**. Compounds **4b**–**m** were prepared in a similar manner. Spectroscopic and analytical data: **4a**: MS (FAB): 298 $(M+H)^+$; IR (neat): 3394, 1688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.64–1.66 (m, 3H), 2.21–2.36 (m, 2H), 2.63–2.75 (m, 2H), 3.16–3.19 (m, 1H), 3.38–3.49 (m, 2H), 3.86–4.22 (m, 4H), 5.09–5.31 (m, 4H), 5.88–6.02 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 11.9, 22.5, 35.4, 36.5, 42.3, 66.2, 66.9, 82.6, 95.5, 104.7, 116.9, 119.0, 133.6, 135.5, 171.8. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.60; H, 7.74; N, 4.71. Found: C, 60.70; H, 7.62; N, 4.76. Compound **4c**: MS (FAB) 312 $(M+H)^+$, IR (neat) 3388, 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.25–1.40 (m, 3H), 1.56–1.64 (m, 2H), 2.23–2.36 (m, 3H), 2.65–2.72 (m, 2H), 3.11–3.44 (m, 2H), 3.88–4.19 (m, 4H), 5.09–5.31 (m, 4H), 5.88–6.02 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 20.7, 30.3, 35.3, 36.5, 40.4, 66.2, 66.9, 82.6, 95.2, 104.7, 116.9, 119.0, 133.6, 135.5, 171.1. Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.73; H, 8.03; N, 4.50. Found: C, 61.75; H, 8.19; N, 4.32. Compound **4d**: MS (FAB) 368 $(M+H)^+$; IR (neat) 3372, 1714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, $J = 6.8$ Hz, 3H), 1.27 (m, 8H), 1.65 (m, 3H), 2.17–2.37 (m, 2H), 3.15–3.50 (m, 3H), 3.96–4.43 (m, 8H), 5.17–5.39 (m, 4H), 5.92–6.00 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.4, 22.9, 27.6, 29.4 (2C), 29.5 (2C), 32.1, 36.3, 40.7, 65.4, 67.2, 72.6, 77.6, 96.2, 104.4, 117.3, 119.0, 134.4, 170.4. Anal. Calcd for $C_{20}H_{33}NO_5$: C, 65.39; H, 8.99; N, 3.81. Found: C, 65.40; H, 8.74; N, 3.82. Compound **4e**: MS (FAB): 424 $(M+H)^+$; IR (neat): 3353, 1685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, $J = 7.2$ Hz,3H), 1.24 (m, 20H), 2.27–2.31 (m, 2H), 2.65–2.68 (m, 2H), 3.20–3.41 (m, 2H), 3.82 (m, 2H), 4.19–4.21 (m, 4H), 5.07–5.30 (m, 4H), 5.94–5.98 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.4, 23.0, 27.6, 29.4 (2C), 29.7 (3C), 29.8, 30.0, 32.2, 35.5, 36.6, 40.5, 66.3, 67.0, 82.4, 95.3, 104.9, 116.6, 118.9, 133.8, 135.7, 171.3. Anal. Calcd for $C_{24}H_{41}NO_5$: C, 68.08; H, 9.69; N, 3.30. Found: C, 68.10; H, 9.60; N, 3.38. Compound **4f**: MS (FAB): 346 $(M+H)^+$; IR (neat): 3339, 1699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68 (br s, 1H), 2.00–2.16 (m, 2H), 3.45 (br s, 1H), 3.68–4.00 (m, 2H), 4.18–4.39 (m, 4H), 4.53 (d, $J = 15.2$ Hz, 1H), 4.76 (d, $J = 15.2$ Hz, 1H), 5.17–5.41 (m, 4H), 5.94–6.02 (m, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): 35.8, 43.3, 65.2, 67.1, 72.7, 82.6, 96.0, 104.3, 117.2, 119.0, 127.7, 128.1 (2C), 128.7 (2C), 134.1, 134.2, 137.7, 170.8. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.08; H, 6.69; N, 4.05. Found: C, 66.10; H, 6.60; N, 4.18. Compound **4j**: MS (FAB): 412 $(M+H)^+$; IR (neat): 3748, 3389, 1676 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.25–1.39 (m, 2H), 1.57–1.64 (m, 3H), 1.90–1.98 (m, 1H), 2.18–2.22 (m, 1H), 3.13–3.18 (m, 2H), 3.36–3.54 (m, 3H), 5.06–5.28 (m, 4H), 7.21–7.40 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): 14.2, 20.9, 32.0, 37.4, 38.5, 58.4, 73.4, 74.2, 86.5, 123.8, 128.0 (2C), 128.7 (2C), 128.9 (4C), 129.5 (2C), 136.6, 136.8, 153.1, 167.9. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.07; H, 7.05; N, 3.40. Found: C, 70.10; H, 7.15; N, 3.39. Compound **4m**: MS (FAB) 294 $(M+H)^+$; IR (neat) 3677, 3391, 1688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54 (br s, 1H), 1.78–1.90 (m, 1H), 2.05–2.17 (m, 1H), 3.34–3.40 (m, 1H), 3.54–3.60 (m, 1H), 3.88 (s, 3H), 4.09 (s, 3H), 4.16 (br s, 1H), 4.37 (d, $J = 15.6$ Hz, 1H), 4.64 (d, $J = 15.6$ Hz, 1H), 7.26–7.34 (m, 5H), ^{13}C NMR (50 MHz, $CDCl_3$): 37.6, 41.6, 58.3, 59.6, 61.2, 86.6, 125.4, 127.6, 128.2, 128.4, 128.8, 128.9, 139.0, 154.3, 168.3. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48; N, 4.77. Found: C, 61.41; H, 6.45; N, 4.75.
20. Poss, A. J.; Belter, R. K.; Bensimon, C. *Tetrahedron: Asymmetry* **1993**, *4*, 169–172.