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Cyclononitols: a flexible synthetic approach towards nine-membered carbasugar analogues

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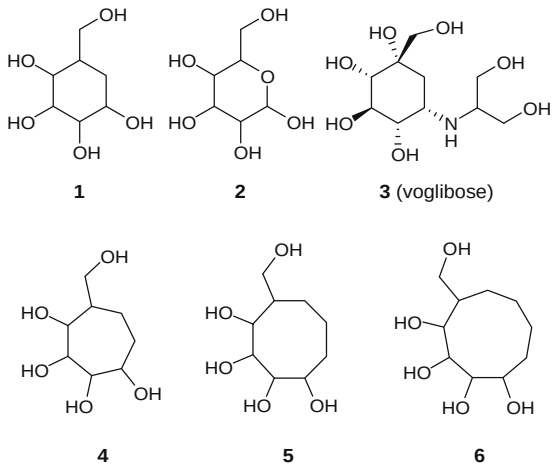
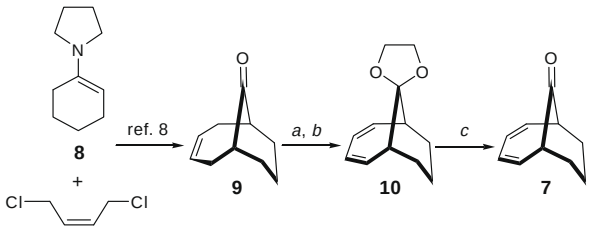
ABSTRACT

A novel, concise, stereocontrolled approach to nine-membered carbasugar analogues (cyclononitols) from a bicyclo[4.3.1]deca-2,4-dien-10-one scaffold, harbouring a 'locked' cyclononane ring and latent functionalities, is described.

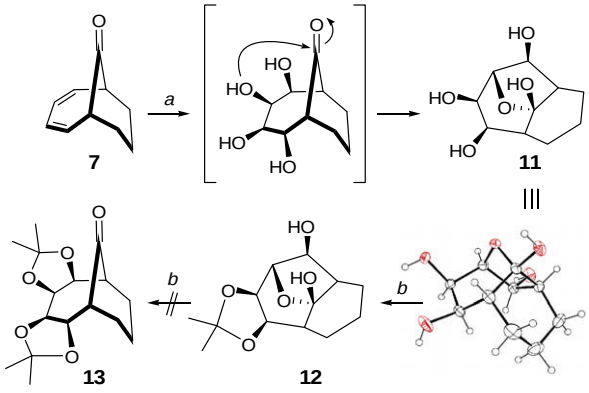
The impressive advances in the area of carbohydrate mimetics in recent years, have been largely prompted by their ability to function as glycosidase inhibitors and have led to the conception and synthesis of a wide variety of novel structures.[1] The commonly pursued approach towards the design of glycosidase inhibitors has been to generate structures that resemble monosaccharides in shape, size and functionality and to mimic the geometry and charge in the transition state of the enzyme-mediated glycoside cleavage.[2] This quest led to the intense exploration of the carbasugar motif **1**, in which a methylene group has replaced the endocyclic oxygen atom of the hexose sugar **2**, and the consequent deletion of the glycosidic linkage minimizes its vulnerability to glycosidase enzymes.[3,4] Already, some carbasugar derivatives such as voglibose **3** (Basen®) have been used for the treatment of type 2 diabetes and the search for new variants and analogues based on **1** is being pursued vigorously.





Scheme 1. Reagents and conditions: (a) Ethylene glycol, PTSA, C_6H_6, reflux, 14 h, 84%; (b) DDQ, C_6H_6, reflux 14 h, 75%; (c) 5% HCl, THF, rt, 5 h, 78%.

While the tactic of replacing the glycoside linkage with a methylene group to resist in vivo degradation by glycosidases has been rewarding, there are other conceptual variations which include fine-tuning the hydrophilic–hydrophobic balance and accessing



Scheme 2. Reagents and conditions: (a) OsO_4, NMMO, acetone/H_2O (4:1), rt, 24 h, 90%; (b) 2,2-dimethoxypropane, PPTS, rt, 95%.

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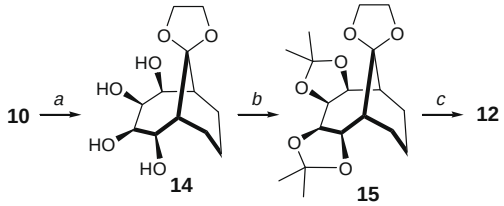
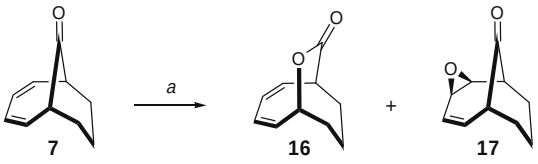
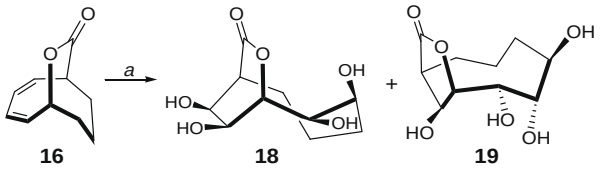


Scheme 3. Reagents and conditions: (a) OsO_4, NMMO, acetone/H_2O (4:1), rt, 24 h, 90%; (b) 2,2-dimethoxypropane, PPTS, rt, 95%; (c) Amberlyst-15, acetone, rt, 70%.



Scheme 4. Reagents and conditions: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 30 min, **16** (60%) and **17** (30%).



Scheme 5. (a) OsO_4, NMMO, acetone/H_2O (4:1), rt, 2 d, **18** (54%) and **19** (32%).

conformations other than the traditional chair, boat and skew boat of six-membered rings, which offer interesting possibilities. These considerations have led to the exploration of seven- **4** and eight-membered **5** analogues of the carbasugar scaffold **1**, in which the glycosidic oxygen is replaced with two or three methylene groups, respectively.[5–7] Crafting a carbasugar motif on a medium ring platform also offers the opportunity to amplify and relocate the distribution of the hydroxy groups to modulate the signalling and recognition capabilities. These considerations and our ongoing interest and effort on the synthesis of cyclooctitols **5** led us to prepare cyclononitols **6**, the next homologue of these interesting entities. Herein, we describe the first synthetic approach to cyclononitols (carbanonanoses) through a short and flexible approach.

In devising an approach to carbanonanoses **6**, we were conscious of the propensity of the medium rings to undergo facile transannular reactions which would render manipulations of functional groups difficult, leading to the inevitability of recourse to extensive protective group manoeuvers. To circumvent such prospects, we opted for a strategy in which the nine-membered ring was locked in a bicyclo[4.3.1]decan-10-one scaffold from which it could be tactically extracted through strategic bridge scission deploying the carbonyl bridge as the handle. In addition, the bicyclo[4.3.1]decan-10-one framework was to be endowed with sufficient latent functionality to install the contemplated network of hydroxy groups.

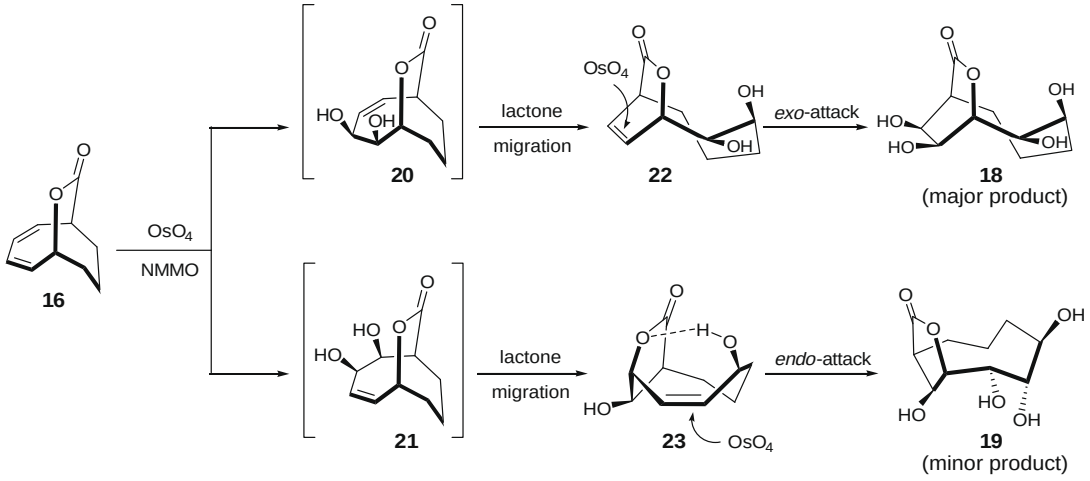
Thus, bicyclo[4.3.1]deca-2,4-dien-10-one **7** was selected as the key precursor and the first task was to have a ready access to it in multi-gram quantities. This was ensured through a modification of the literature protocol,[8] starting from cyclohexanone enamine **8** and *cis*-1,4–dichlorobutene to furnish **9**, and its further elaboration to **7** via the intermediacy of **10** as depicted in Scheme 1.

The diene moiety in **7** was subjected to OsO_4-NMMO-mediated exhaustive dihydroxylation following the Upjohn protocol to afford stereoselectively, a single tetrahydroxylated hemiacetal product **11** whose stereostructure was elucidated through single-crystal X-ray structure determination, Scheme 2.[9,10] The hemiacetal moiety in **11** proved extremely robust and efforts to convert it into the bis-acetonide **13** to reveal the C-10 carbonyl group met with repeated failure and only the monoacetonide **12** could be isolated and characterized. To circumvent this problem, ketal **10** was subjected to exhaustive dihydroxylation and the tetrahydroxy ketal **14** was realized in good yield. However, various manoeuvers on **14** to reveal either directly the C-10 carbonyl group or through conversion into bis-acetonide ketal **15** and selective deprotection led only to the hemiacetals **11** or **12** and not the desired bis-acetonide **13**, Scheme 3.

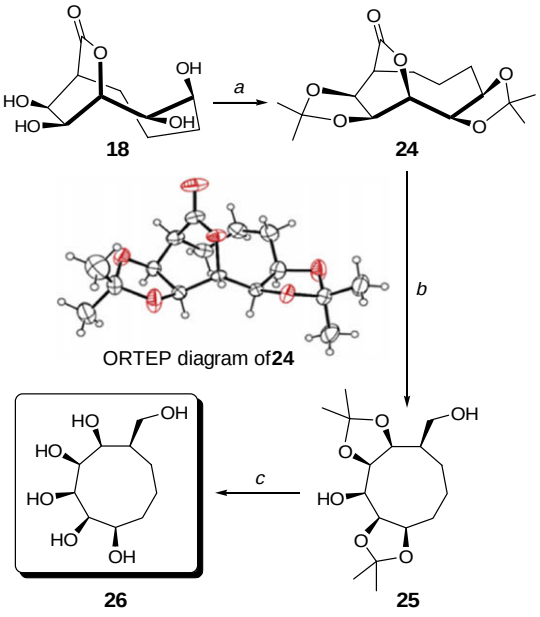
At this stage, it was decided to re-sequence our core strategy with the bridge scission tactic preceding the hydroxylation. Consequently, bicyclic dienone **7** was subjected to the Baeyer–Villiger oxidation to furnish the lactone **16** along with a minor monoepoxide product **17** (2:1), Scheme 4.

The diene-lactone **16** on prolonged exposure to OsO_4–NMMO furnished a mixture (5:3) of two rearranged tetrahydroxylated lactones **18** and **19** whose structures were unambiguously established on the basis of spectral data analyses and X-ray crystal structure determination (vide infra), Scheme 5.[9,10]

The unexpected but not unwelcome formation of **18** and **19** could be rationalized as follows. Initial dihydroxylation on either of the double bonds of the diene moiety of **16** is stereoselective and leads to the regioisomeric diols **20** and **21**. Lactone migration



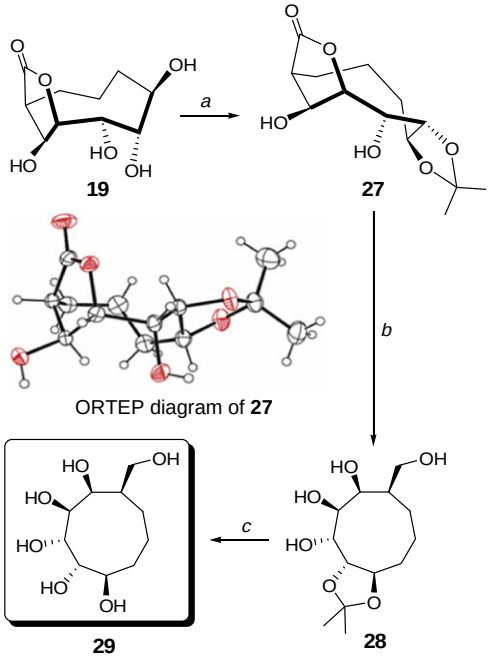
Scheme 6. Predicted mechanism for the formation of **18** and **19**.



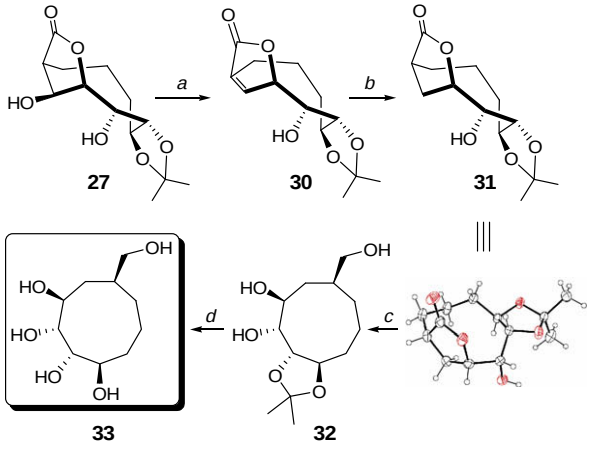
Scheme 7. Reagents and conditions: (a) Acetone, PPTS, rt, 12 h, 95%; (b) $LiAlH_4$, THF, Δ, 12 h, 90%; (c) 2 N HCl, THF, 0 °C–rt, 36 h, 88%.

in **20** and **21** leads to **22** and **23**, respectively. A second stereoselective dihydroxylation from the *exo*-face in **22** delivers the observed product **18**, Scheme 6. On the other hand, in the lactone **23**, intramolecular hydrogen bonding shields the *exo*-face and paves the way for stereoselective *endo*-dihydroxylation to afford **19**. This proposal is supported by the fact that when the exhaustive dihydroxylation of **16** was stopped before proceeding to completion, the intermediate lactone **23** could indeed be isolated. Dihydroxylation of **23** was *endo* selective and furnished **19** exclusively, Scheme 6.[11]

The major tetrol **18** was readily transformed into its bis-acetonide **24** and a single-crystal X-ray structure determination secured its formulation, Scheme 7. LAH reduction of the lactone moiety in



Scheme 8. Reagents and conditions: (a) Acetone, PPTS, rt, 12 h, 92%; (b) $LiAlH_4$, THF, Δ, 12 h, 50%; (c) 2 N HCl, THF, 0 °C–rt, 36 h, 88%.



Scheme 9. Reagents and conditions: (a) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 10 min, 90%; (b) H_2, 10% Pd/C, EtOAc, 1 h, 99%; (c) $LiBH_4$, THF, Δ, 12 h, 80%; (d) 2 N HCl, THF, 0 °C–rt, 36 h, 90%.

24 was smooth and yielded the nine-membered cyclitol derivative **25**. Aqueous acid-mediated hydrolysis of **25** delivered the first cyclononitol **26**,[9] Scheme 7. The minor tetrol **19**, on the other hand, furnished only monoacetonide **27** and its X-ray crystal structure revealed its stereochemical disposition. LAH reduction of **27** was straightforward to render the cyclononane derivative **28**. Acid-mediated deprotection of **28** led to the cyclononitol **29** with subtle variation in hydroxy group disposition, Scheme 8.[9,10]

To demonstrate further the diversity and inherent flexibility of our approach, acetonide **27** was subjected to a classical dehydration protocol to give the *anti*-Bredt alkene **30**, Scheme 9. Catalytic hydrogenation of **30** was quantitative to deliver **31**.[10] The structure of **31** was secured through X-ray crystal structure determination (vide infra). $LiBH_4$ reduction of **31** into **32** and subsequent acetonide deprotection led to the cyclononitol **33**, an interesting variant with five hydroxy groups on the cyclononane framework with an unusual 'ring-stretched' carbasugar-like architecture.

In conclusion, a short, stereocontrolled approach of general utility to cyclononane-based carbasugar analogues has been devised employing a readily available bicyclo[4.3.1]deca-2,4-dien-10-one building block. The inherent flexibility of this approach should enable access to many cyclononitol analogues with varied hydroxy group patterns and efforts along these lines are underway.

Acknowledgements

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9. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of selected compounds. **11** IR (neat) 3409 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.19 (s, 1H), 3.88–3.45 (m, 1H), 3.83–3.75 (m, 1H), 3.69–3.65 (m, 1H), 1.80–1.70 (m, 2H), 1.60–1.48 (m, 4H), 1.40–1.30 (s, 2H); ^{13}C NMR (75 MHz, D_2O) δ 102.9, 83.8, 73.1, 68.2, 65.7, 51.4, 43.9, 23.5, 22.3, 15.4; HRMS (ES) m/z calcd for $C_{10}H_{16}NaO_5$ [M+Na]$^+$: 239.0895; found: 239.0890; **18** IR (neat) 3376, 1743 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 4.68 (br s, 1H), 4.37 (t, J = 2.1 Hz, 1H), 4.09 (t, J = 2.7 Hz, 1H), 4.00 (br s, 1H), 3.82–3.78 (m, 1H), 2.80–2.70 (m, 1H), 1.95–1.79 (m, 3H), 1.63–1.54 (m, 1H), 1.45–1.20 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 184.4, 91.9, 75.0, 74.1, 70.4 (2C), 48.4, 28.4, 27.4, 21.6; HRMS (ES) m/z calcd for $C_{10}H_{16}NaO_6$ [M+Na]$^+$: 255.0845; found: 255.0840; **19** IR (neat) 3407, 1758 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 4.74 (s, 1H), 4.58 (d, J = 8.1 Hz, 1H), 4.25 (d, J = 8.1 Hz, 1H), 3.74 (t, J = 7.5 Hz, 1H), 3.60 (d, J = 7.5 Hz, 1H), 2.79 (t, J = 6.0 Hz, 1H), 2.01–1.51 (m, 5H), 1.19–1.09 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 182.8, 89.8, 73.9, 72.4, 71.1, 70.9, 50.8, 31.1, 27.4, 19.7; HRMS (ES) m/z calcd for $C_{10}H_{16}NaO_6$ [M+Na]$^+$: 255.0845; found: 255.0837; **26** IR (neat) 3392 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.93 (br s, 2H), 3.83–3.82 (m, 3H), 3.30–3.27 (m, 2H), 2.04–1.84 (m, 2H), 1.62–1.46 (m, 3H), 1.27–1.12 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 76.5, 75.6, 73.2, 72.4, 71.4, 64.2, 41.9, 30.2, 23.4, 22.8; HRMS (ES) m/z calcd for $C_{10}H_{20}NaO_6$ [M+Na]$^+$: 259.1158; found: 259.1175; **29** IR (neat) 3366 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.98 (s, 1H), 3.89–3.81 (m, 2H), 3.67–3.65 (m, 2H), 3.30–3.28 (m, 2H), 1.77–1.02 (series of m, 7H); ^{13}C NMR (75 MHz, D_2O): δ 79.1, 74.0, 72.6, 70.0, 67.6, 65.2, 44.9, 40.0, 36.5, 21.0; HRMS (ES) m/z calcd for $C_{10}H_{20}NaO_6$ [M+Na]$^+$: 259.1158; found: 259.1159; **33** IR (neat) 3440 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.97 (dd, J = 6.6, 1.2 Hz, 1H), 3.85 (dt, J = 5.1, 1.2 Hz, 1H), 3.77 (t, J = 5.7 Hz, 1H), 3.62 (dd, J = 6.9, 1.5 Hz, 1H), 3.33–3.25 (m, 2H), 1.70–1.40 (m, 7H), 1.34–1.22 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 79.1, 74.0, 72.7, 69.9, 67.6, 40.0, 36.5, 29.6, 29.4, 21.0; HRMS (ES) m/z calcd for $C_{10}H_{20}NaO_5$ [M+Na]$^+$: 243.1210; found: 243.1210.
10. X-ray data were collected at 291 K on a SMART CCD-Bruker diffractometer with graphite-monochromated MoK_α radiation (λ = 0.7107 Å). The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on F^2 using SHELXL-97. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre and assigned to the corresponding CCDC numbers. Compound **11**: $C_{10}H_{16}O_5$, MW = 213.20, crystal system: orthorhombic, space group: *Pbca*; cell parameters: a = 10.239(2) Å, b = 9.382(2) Å, c = 22.180(5) Å, V = 2130.6(8) Å^3; Z = 8, ρ_{calc} = 1.329 g cm^{-3}, F(0 0 0) = 904, μ = 0.107 mm^{-1}, number of l.s. parameters = 217, R_1 = 0.0476 for 1881 reflections with $I > 2\sigma(I)$ and 0.0529 for all 2091 data, wR_2 = 0.1142, G.O.F = 1.103 for all data, CCDC 629482. Compound **24**: $C_{16}H_{24}O_6$, MW = 208.22, crystal system: orthorhombic, space group: $Pca2_1$; cell parameters: a = 21.348(6) Å, b = 7.096(2) Å, c = 10.647(3) Å, V = 1612.9(8) Å^3; Z = 4, ρ_{calc} = 1.286 g cm^{-3}, F(0 0 0) = 672, μ = 0.098 mm^{-1}, number of l.s. parameters = 203, R_1 = 0.0542 for 2566 reflections with $I > 2\sigma(I)$ and 0.0592 for all 2830 data, wR_2 = 0.1444, G.O.F = 1.067 for all data, CCDC 629483. Compound **27**: $C_{13}H_{20}O_6$, MW = 272.29, crystal system: monoclinic, space group: *Cc*; cell parameters: a = 10.670(4) Å, b = 11.169(4) Å, c = 12.243(4) Å, β = 108.928(7)°, V = 1380.2(8) Å^3; Z = 4, ρ_{calc} = 1.310 g cm^{-3}, F(0 0 0) = 584, μ = 0.103 mm^{-1}, number of l.s. parameters = 176, R_1 = 0.0341 for 2362 reflections with $I > 2\sigma(I)$ and 0.0377 for all 2531 data, wR_2 = 0.0841, G.O.F = 1.046 for all data, CCDC 629484. Compound **31**: $C_{13}H_{20}O_5$, MW = 256.29, crystal system: monoclinic, space group: $P2_1/c$; cell parameters: a = 8.0347(18) Å, b = 15.713(4) Å, c = 10.136(2) Å, β = 94.899(4)°, V = 1275.0(5) Å^3; Z = 4, ρ_{calc} = 1.335 g cm^{-3}, F(0 0 0) = 552, μ = 0.102 mm^{-1}, number of l.s. parameters = 243, R_1 = 0.0386 for 1931 reflections with $I > 2\sigma(I)$ and 0.0468 for all 2239 data, wR_2 = 0.0905, G.O.F = 1.115 for all data, CCDC 629485.
11. We have also observed that other electrophilic additions to **23**, such as epoxidation also proceed preferentially from the *endo*-face, thus further reinforcing our proposition.