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Synthesis of tri-arylated cyclotriveratrilenes with *ortho*- and *meta*-extended functionality

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ABSTRACT

Aromatic nucleophilic substitution reaction between cyclotriguaiacylene and *ortho*- or *meta*-functionalized fluoroarenes affords a series of *ortho*- or *meta*-extended cyclotriveratrilene (CTV) cavitands. Further transformation of the functional groups into NH and/or OH moieties has been demonstrated. This enabled us to prepare an amphoteric water-soluble cavitand bearing anilino-NH_2 and phenolic-OH substituents. In addition, one molecular structure was successfully determined by crystallographic analysis, which suggests an extended/flattened structure. We propose that vase-shaped conformations with inwardly directed functional groups will soon be possible with the CTV scaffold.

Natural receptors like enzymes have functional groups oriented inwardly for molecular recognition.[1,2] Amino acid functional groups converge to create reactive sites inside the hydrophobic pockets, and part of the pockets remains open so that guests can sample the space, enter and leave. Thus they serve as well-organized chemical cavity for performing biological operations, and most assemblies operate in aqueous media.[3] Inspired by these, chemists have quested for syntheses of artificial cavitands bearing functional groups inside chemical spaces, and water-soluble cavitands.[4,5] For example, Rebek group has invented a type of inwardly functionalized resorcin[4]arene-based cavitands, and water-soluble cavitands. The former provides a reactive site which converges onto the concave surface, and the latter hydrophobic space in water.[6] Those cavitands have been employed as a tool of chemical reactions for understanding facets of bio-relevant phenomena.[7–9]

During this past decade, our group has focused on the novel synthesis of inwardly functionalized cavitands which are derived from a platform of triquinoxaline-spanned resorcin[4]arene. The template is a rigid scaffold so that functional groups of dialkylsilanes,[10] allylsilanes,[11] pyridine *N*-oxide[12] point to the cavity; hence, the functionalized cavitands enabled us to find unique supramolecular effects in terms of reactivity and encapsulation. From the viewpoint of rigid macromolecular terminals, a threefold symmetrical Cyclotriveratrilene (CTV)[13] also has intrinsically been fixed hollow like at the tapered end of resorcin[4]arenes.[14] The CTV macrocycle has been deployed as a hemicryptophane-based capsule with functional groups in its interior pocket;[15,16] for example, Makita and Ogawa prepared a Zinc(II)-induced hemicryptophane that enhanced chemical catalysis as compared to model complexes.[17] One of key features of Makita and Ogawa's capsule would exist in the shape of '*para*-extended' hemicryptophane which is derived from a reaction between *para*-fluorobenzene and cyclotriguaiacylene **1** (Scheme 1). The usage of *para*-substituted fluorobenzene extended its cavity and provided the capsule with a rigid framework. Despite such an attractive achievement as a capsule, CTV has never been developed as an inwardly functionalized cavitand. To do so, '*meta*-extended' or '*ortho*-extended' CTV architectures could be effective, because as modelling suggests the functional groups can point internally (Scheme 2). We envisioned several applications. With *ortho*- or *meta*-positioned functional groups the potential to bind a central metal could position a reactive site inside the cavity.[10–12] Alternatively, the tri-functional groups can converge inwardly to recognize a guest molecule selectively. To the best of our knowledge, few examples of such a type of CTV-cavity have been reported so far.[18] Perhaps owing to perceived steric hindrance in '*meta*-and *ortho*-extended' CTV they haven't been pursued. Indeed '*para*-extended' CTV has been reported by Pochini in 2004.[19]

We present a synthetic study to prepare '*meta*- and/or *ortho*-extended' CTV-cavitands. First, three molecules of *ortho*- and/or

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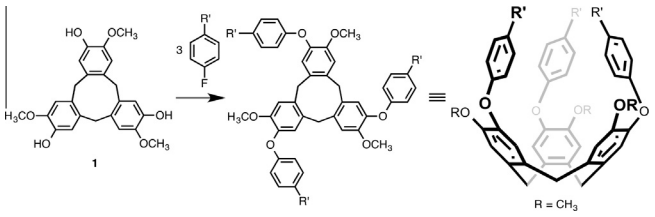
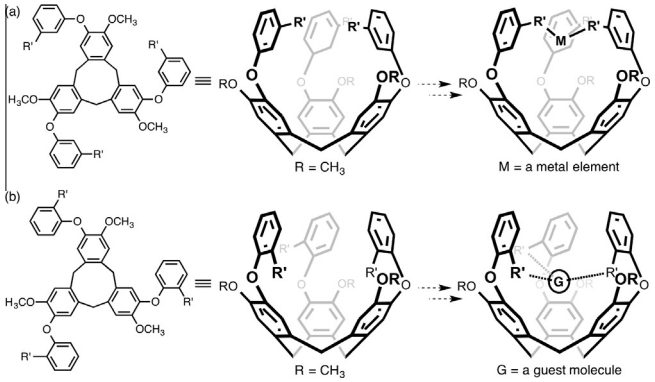


Scheme 1. Synthesis of '*para*-extended' cyclotriveratrilenes.

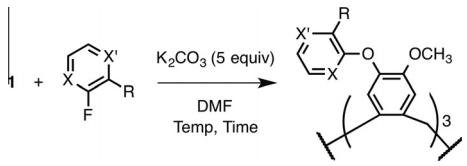


Scheme 2. Representation of (a) '*meta*-extended' or (b) '*ortho*-extended' cyclotriveratrilenes for embodiment of inwardly functionalized CTV-cavitands.

meta-substituted fluoroarenes reacted with three phenolic OH of triguaiacylene **1**; then, further transformations of the *ortho*- and/or *meta*-positioned substituents produced newly extended CTV functionalized with amino or hydroxy groups. These studies enabled us to characterize an extended solid-state structure and to provide a molecular design of novel water-soluble amino-phenol cavitand.

Nucleophilic aromatic substituent reactions (S_NAr) in DMF with K_2CO_3 were performed between **1**[20] and *ortho*-substituted fluoroarenes (Table 1). For entries 1–3, electron-withdrawing groups of NO_2, CN, and CHO facilitated the S_NAr reactions, giving CTV analogues **2**, **3**, and **4** in from 81% to 93% yield. Compared to S_NAr utilizing *para*-substituted fluorobenzenes reported by Pochini in 2004,[19] *ortho*-substituted fluorobenzenes have similar reactivity. However, for entry 4, methyl ester group that is less electron-withdrawing was not an efficient reaction partner, only yielding 19% of **5** even with prolonged heating. For entries 5 and 6, nitriles fluoropyridines reacted with **1** under a more mild heating of 90 °C, and yielded **6** in 60% and **7** in 75%. This S_NAr for *ortho*-extended CTV compounds except the preparation of **5** is readily amenable to multi gram-scale (entry 1).

Table 1
Reaction of **1** with *ortho*-substituted fluoroarenes

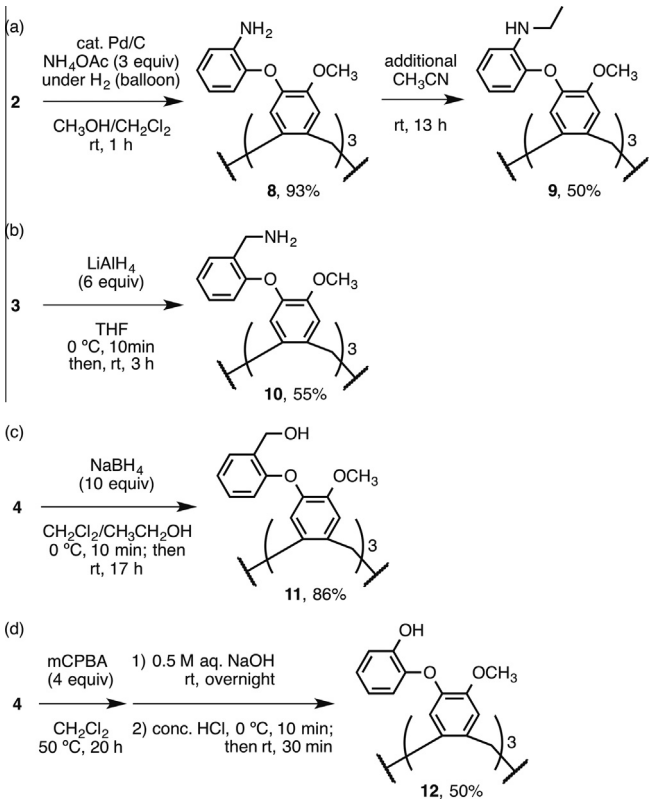


Entry	X	X′	R	Temp (°C)	Time (h)	Product	% yield[a]
1	C	C	NO_2	150	4	2	93 (2.37 g)
2	C	C	CN	150	4	3	81 (2.32 g)
3	C	C	CHO	150	2.5	4	91 (2.62 g)
4	C	C	CO_2CH_3	150	24	5	19 (461 mg)
5	N	C	CN	90	2	6	60 (1.52 g)
6	C	N	CN	90	5	7	75 (1.66 g)

[a] Actual formations in parenthesis.

The substituents at *ortho*-positions of **2**–**4** were readily converted into electron-donating groups as NH_2 and OH (Scheme 3). For the reduction of nitro **2** to aniline **8**, conventional hydrogenation utilizing NH_2NH_2[19] and/or gaseous H_2 in the presence of catalytic amount of Pd/C were tried; however, both reactions were very sluggish.[21] Finally, addition of NH_4OAc turned out to accelerate and complete the reduction within 1 h to give **8** (Scheme 3a).[22] Furthermore this conversion can provide a one-pot protocol for mono-alkylation of **8** to synthesize **9**: an appropriate amount of CH_3CN was sequentially added to the reaction mixture of **8**. Careful addition of CH_3CN and TLC monitoring readily furnished **9** in moderate 50% yield. Reduction of **3** needed with $LiAlH_4$ (6 equiv) yielded **10** in 55% Scheme 3b. For Scheme 3c, while the solvent of CH_2Cl_2/ethanol scarcely dissolved the aldehyde **4**, prolonged reaction time completed the reduction by $NaBH_4$ in 86% yield of **11** with giving colourless solution state. For Scheme 3d, Dakin oxidation of **4** proceeded as a overnight reaction, and followed by hydrolysis to afford **12** in 50% yield. The solubility of **8**–**12** in organic solvents was drastically improved compared to the parent **2**–**4**.

Crystals of benzyl alcohol **11** were obtained by slow diffusion of a solution of compounds in CH_2Cl_2/CH_3CN.[23] The X-ray crystal structure analysis shows *ortho*-positioned moieties of CH_2OH are randomly floating and doesn't form intra-molecular hydrogen bonds between OH and OCH_3 (Fig. 1a). Instead from the view point of head-to-head arrangement in crystal lattice (Fig. 1b), one molecule makes a pair with another through one hydrogen bonding between mutual two CH_2OH groups, and embraces partner's one phenyl moiety. This indicates pi-donor ability of three phenyl rings of CTV skeleton **11** attracts the counter phenyl moiety.



Scheme 3. Synthesis of *ortho*-functionalized CTV derivatives; (a) anilines **8** and **9**, (b) benzylamine **10**, (c) benzylalcohol **11**, and (d) phenol **12.**

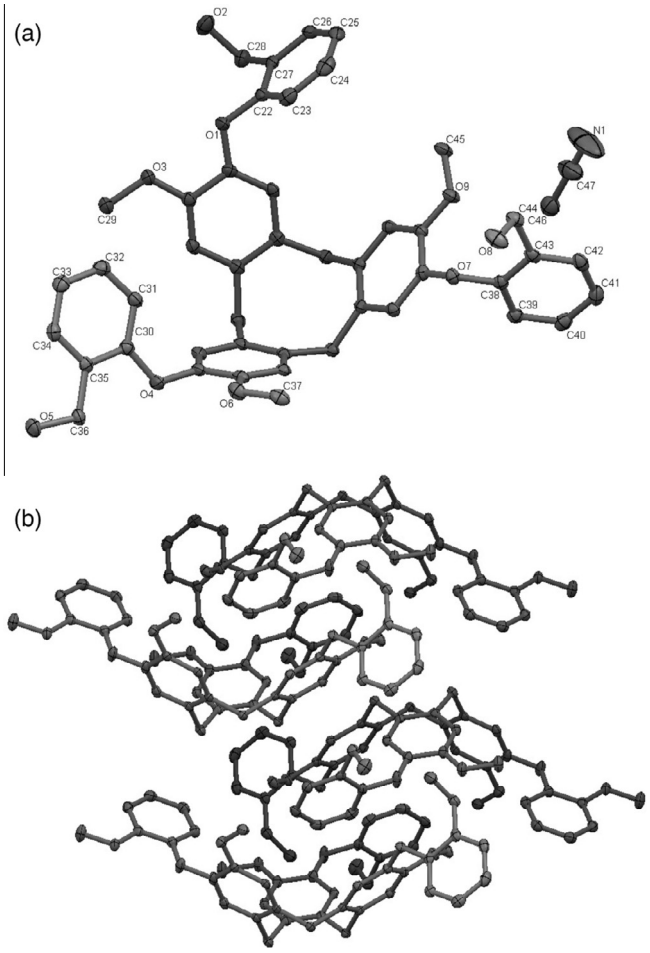
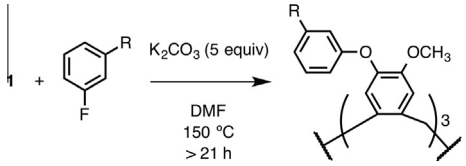


Figure 1. ORTEP drawing of **11** with thermal ellipsoids at the 50% probability level, and hydrogen atoms are omitted for clarity; (a) perspective view showing the one disordered acetonitrile molecule residing nearby a benzyl alcohol moiety, and (b) head-to-head arrangement in the crystal lattice (the acetonitrile is omitted for ease of view).

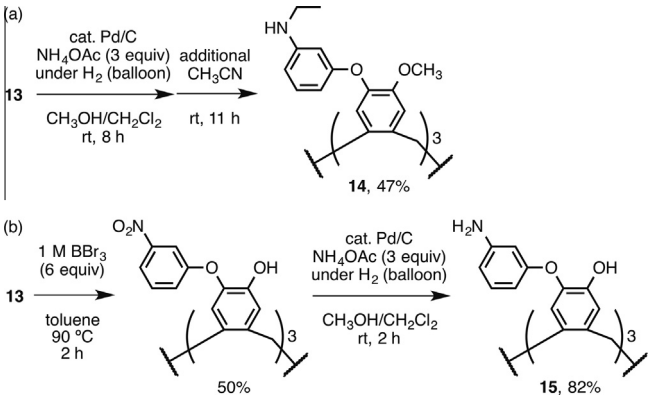
Next, S_NAr reaction of **1** with *meta*-substituted fluorobenzenes was demonstrated (Table 2). For entry 1, 1-fluoro-3-nitrobenzene needed overnight to complete the reaction, and purification of recrystallization from propionitrile yielded 1.57 g of desired nitro **13** in 51% yield. For entries 2 and 3, the starting 1-fluoro-3-cyanobenzene or 1-fluoro-3-formylbenzene disappeared on TLC monitoring; however, the crude products resulted in complicated mixtures. Further transformation of nitro **13** was attested in Scheme 4, and *mono*-alkylation procedure of *ortho*-version **2** in

Table 2
Reaction of **1** with *meta*-substituted fluorobenzene



Entry	R	Product	% yield[a]
1	NO_2	**13**	51 (1.57 g)
2	CN	—	—
3	CHO	—	—

[a] Actual formations in parentheses.



Scheme 4. Synthesis of *meta*-functionalized CTV derivatives; (a) aniline **14**, and (b) amphoteric CTV **15.**

Scheme 3a was successfully applicable to give **14** in 47% yield (Scheme 4a). Then we envisioned synthesis of water-soluble CTV **15** that possesses amphoteric substructures of $–NH_2$ and –OH. The demethylation step of **13** needed heat condition at 90 °C to give the corresponding phenol in moderate 50% yield, and the following reduction step smoothly proceeded in the presence of NH_4OAc, and purification by simple reprecipitation from EtOAc/Hexane yielded **15** in 82% (Scheme 4b).[24] Thus, the water-soluble **15** is endowed with basic NH_2 and acidic OH at the upper rim of the CTV skeleton. With these results we predict future application of **15** may provide a unique hydrophobic concave shape in aqueous media.[25]

With a viable protocol in hand for the preparation of *ortho*- and *meta*-extended CTV, we have explored possibility for binding with a transition metal like representation in Scheme 2. Not only transition metal-sources of Mo and Ti but also nonmetal precursors of Boron, Aluminium, Silicon, and Phosphorus were attempted to react with *ortho*-extended **9**–**11**, and *meta*-extended **14**: however, at this time, desired complexes were not observed while the starting CTV compounds were consumed on TLC monitoring. Some were found but not isolated successfully, owing to the thermodynamically unstable condition caused by steric hindrance.

In summary, the successful arrangement of NH and OH groups, placed at *ortho*- and/or *meta*-positions of extended aromatic rings, affords a new architecture for CTV derivatives. The new CTV archetypes are prepared with the aim of inward orientation of functional groups towards the CTV concave surface; actually crystallographic analysis shows the possibility that such functionalities converge to create reactive and interactive sites inside the hydrophobic hollow. Such an inwardly directed functional group of the CTV cavitand will be a form of synthetic receptor, which can provide a ligand to make a complex with transition metals and can serve as a host to recognize guest species. While we envisioned so, this goal has not yet materialized. Nevertheless an interesting class of compounds was made for future study. Towards the goal of synthetic receptors based on these *ortho*- and/or *meta*-extended CTV cavitands, further synthetic developments are ongoing and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.030.

References and notes

1. (a) Gerlt, J. A. *Chem. Rev.* **1987**, *87*, 1079–1105; (b) Rodnina, M. V.; Wintermeyer, W. *Curr. Opin. Struct. Biol.* **2003**, *13*, 334–340; (c) Shen, K.; Hines, A. C.; Schwarzer, D.; Pickin, K. A.; Cole, P. A. *Proteomics* **2005**, *1754*, 65–78.
2. (a) Varani, G. *Annu. Rev. Biophys. Biomol. Struct.* **1995**, *24*, 379–404; (b) DeRose, V. J. *Curr. Opin. Struct. Biol.* **2003**, *13*, 317–324; (c) Shuman, S.; Lima, C. D. *Curr. Opin. Struct. Biol.* **2004**, *14*, 757–764.
3. (a) Skerra, A. J. *J. Mol. Recognit.* **2000**, *13*, 167–187; (b) Khosla, C.; Har-bury, P. B. *Nature* **2001**, *409*, 247–252; (c) Bruice, T. C. *Acc. Chem. Res.* **2002**, *35*, 139–148.
4. (a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828; (b) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707–5714; (c) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, 1994. pp 85–130.
5. (a) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991–2005; (b) Haino, T.; Rudkevich, D. M.; Shivanyuk, A.; Rissanen, K.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 3797–3805.
6. (a) Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281–3283; (b) Zhang, K.-D.; Ajami, D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2013**, *135*, 18064–18066.
7. (a) Purse, B. W.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 14682–14683; (b) Purse, B. W.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10777–10782.
8. (a) Gissot, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 7424–7425; (b) Hooley, R. J., ; Rebek, J., Jr. *Chem. Biol.* **2009**, *16*, 255; c) Mosca, S.; Yu, Y.; Gavette, J. V.; Zhang, K. -D.; Rebek, J. Jr., *J. Am. Chem. Soc.* doi: http://dx.doi.org/10.1021/jacs.5b10028.
9. (a) Iwasawa, T.; Hooley, R. J.; Rebek, J., Jr. *Science* **2007**, *317*, 493–496; (b) Hooley, R. J.; Iwasawa, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 15330–15339; (c) Butterfield, S. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 15366–15367.
10. Iwasawa, T.; Nishimoto, Y.; Hama, K.; Kamei, T.; Nishiuchi, M.; Kawamura, Y. *Tetrahedron Lett.* **2008**, *49*, 4758–4762.
11. Ohashi, K.; Ito, K.; Iwasawa, T. *Eur. J. Org. Chem.* **2014**, 1597–1601.
12. Kanaura, M.; Ito, K.; Schramm, M. P.; Ajami, D.; Iwasawa, T. *Tetrahedron Lett.* **2015**, *56*, 4824–4828.
13. Hardie, M. *Chem. Soc. Rev.* **2010**, *39*, 516–527.
14. (a) Hardie, M. J. *Chem. Soc. Rev.* **2010**, *39*, 516; (b) Collet, A. *Tetrahedron* **1987**, *43*, 5725; (c) Ajami, D.; Iwasawa, T.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8934–8936.
15. (a) Matouzenko, G.; Veriot, G.; Dutasta, J.-P.; Collet, A. *New J. Chem.* **1995**, *19*, 881; (b) Veriot, G.; Dutasta, J.-P.; Matouzenko, G.; Collet, A. *Tetrahedron* **1995**, *51*, 389.
16. (a) Collet, A. In *Comprehensive Supramolecular Chemistry*; Vogtle, F., Ed.; Pergamon: New York, 1996; Vol. 2, p 325; (b) Gauiter, A.; Mulatier, J.-C.; Crassous, J.; Dutasta, J.-P. *Org. Lett.* **2005**, *7*, 1207; (c) Martinez, A.; Dutasta, J.-P. *J. Catal.* **2009**, *267*, 188; (d) Gosse, I.; Dutasta, J.-P.; Perrin, M.; Thozet, A. *New J. Chem.* **1999**, *23*, 545; (e) Raytchev, P. D.; Perraud, O.; Aronica, C.; Martinez, A.; Dutasta, J.-P. *J. Org. Chem.* **2010**, *75*, 2099.
17. Makita, Y.; Sugimoto, K.; Furuyoshi, K.; Ikeda, K.; Fujiwara, S.-I.; Shin-ike, T.; Ogawa, A. *Inorg. Chem.* **2010**, *49*, 7220–7222.
18. Henkelis, J. J.; Hardie, M. J. *Chem. Commun.* **2015**, 11929–11943.
19. Arduini, A.; Calzavacca, F.; Demuru, D.; Pochini, A.; Secchi, A. *J. Org. Chem.* **2004**, *69*, 1386–1388.
20. Scalable and column-free protocol for preparation of **1** was developed on the basis of procedure reported by Dutasta of Ref.[16d], which are summarized in Supporting Information.
21. Hydrazine reduction in the presence of Raney/Ni consumed all of **2** in refluxing condition; however, annoying byproducts prevented **8** from being isolated in pure form.
22. (a) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977–4980; (b) Nacario, R.; Kotakonda, S.; Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *Org. Lett.* **2005**, *7*, 471.
23. CCDC-1400888 (foe **11**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Triclinic, space group *P*-1, colourless, $a = 8.736(6)$ Å, $b = 15.859(5)$ Å, $c = 16.012(14)$ Å, $\alpha = 115°$, $\beta = 102°$, $\gamma = 94°$, $V = 1931(3)$ Å^3, $Z = 2$, $T = 93$ K, $D_{calcd} = 1.321$ g cm^{-3}, μ(Mo-Kα) = 0.742 mm^{-1}, $R_1 = 0.0434$, $wR_2 = 0.1620$, GOF = 1.107.
24. Opposite order of the transformation that is the first reduction and the second demethylation didn't work well.
25. Schmitt, A.; Robert, V.; Dutasta, J.-P.; Martinez, A. *Org. Lett.* **2014**, *16*, 2374–2377.