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A NEW ROUTE TO (–)-APHANORPHINE USING A DIOXABICYCLO[3.2.1]OCTANE CHIRAL BUILDING BLOCK†

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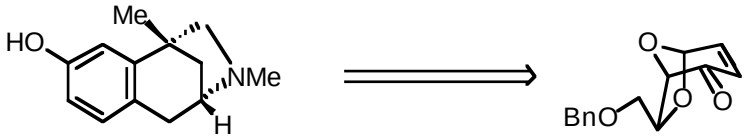
Abstract — A new stereocontrolled route to (–)-aphanorphine, isolated from the fresh-water blue-green algae *Aphanizomenon flos-aquae* has been developed by using a chiral building block having a dioxabicyclo[3.2.1]octane framework and originally designed for the construction of the aldohexose molecules.

Recently, we designed a chiral building block (**1**) having a dioxabicyclo[3.2.1]octane framework for the diastereodivergent synthesis of all of the eight possible diastereomers of aldohexoses.[1] Owing to its biased structure, (–)-**1** allowed convex-face selective modification of its enone functionality leading to all of the eight L-aldohexose diastereomers in a diastereocontrolled manner.[2] We report here another use[3] of the sugar building block for an alternative synthesis of (–)-aphanorphine[4~6] (**2**), the only naturally occurring norbenzomorphan structure isolated from the fresh-water blue-green algae *Aphanizomenon flos-aquae* on the basis of the same methodology employed in the sugar synthesis (**Scheme 1**).

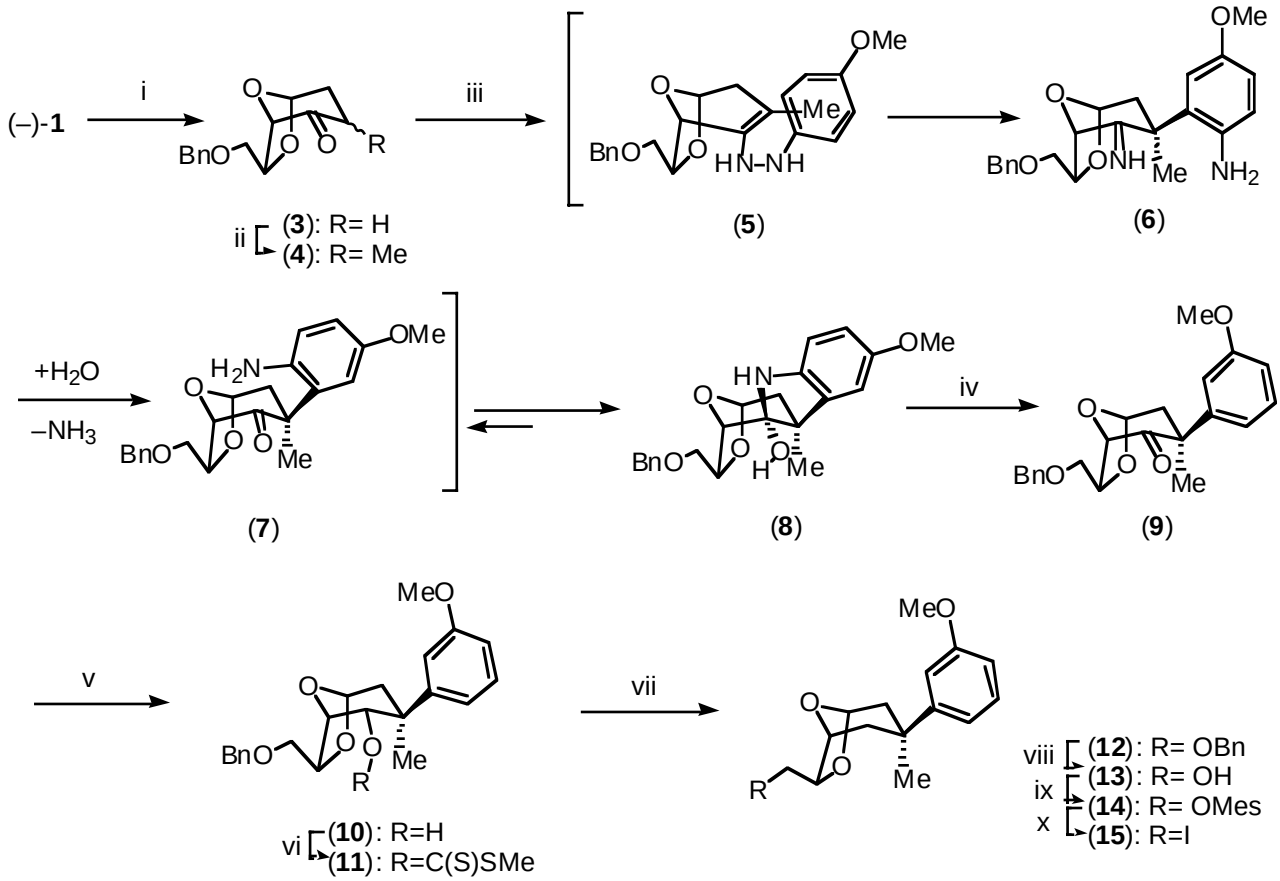


(–)-aphanorphine (**2**) (–)-sugar block (**1**)

Scheme 1

Enantiopure [(–)-**1**] was reduced with diisobutylaluminum hydride (DIBAL) in the presence of copper (I) iodide in THF containing hexamethylphosphoric triamide (HMPA) to give the ketone (**3**), $[\alpha]_D^{30}$ +37.4° (*c*1.1, $CHCl_3$). On reaction with iodomethane in the presence of lithium hexamethyldisilazide (Li-HMDS) in THF containing HMPA,[7] **3** afforded a 2.5:1 mixture of the monomethylated ketone (**4**), which was refluxed with 4-methoxyphenylhydrazine hydrochloride in 90% aqueous pyridine[3c,8] to give rise to the

†Dedicated to Prof. James P. Kutney, University of British Columbia, on the occasion of his 70th birthday.



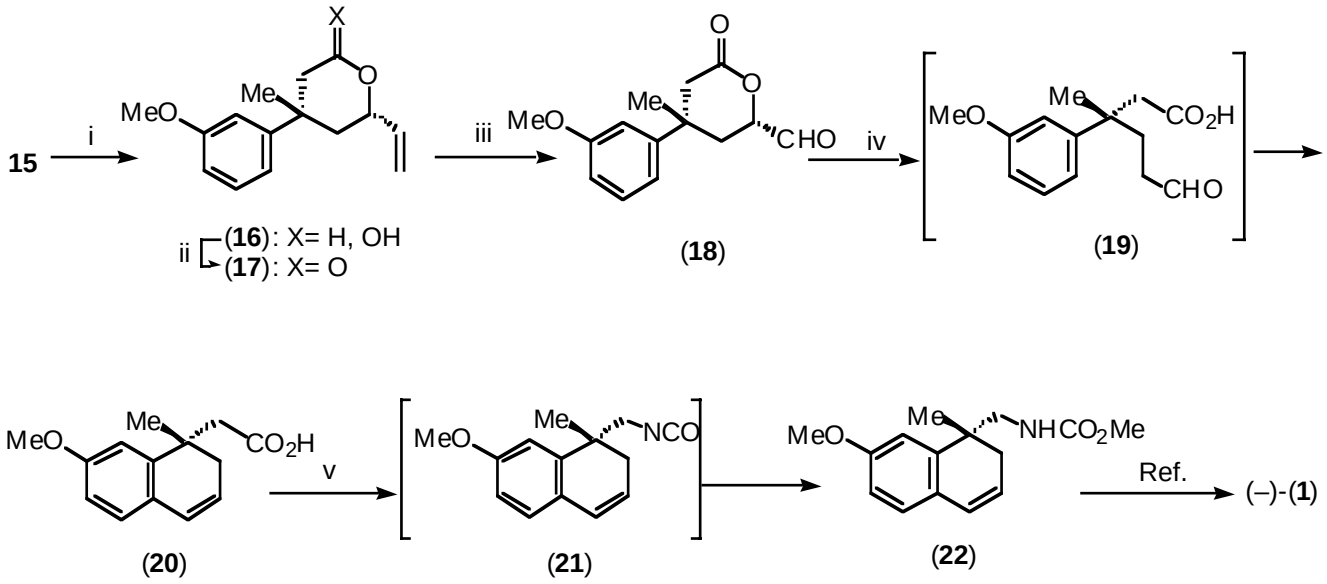
Scheme 2

Reagents and conditions: (i) DIBAL, CuI, HMPA, THF, –78℃ (89%). (ii) Li-HMDA, MeI, HMPA, THF, –78~–30℃ (72%). (iii) 4-$MeOC_6H_4NHNH_2$-HCl, 90% aq. pyridine, reflux (92%). (iv) H_3PO_2, $NaNO_2$, Et_2O, AcOH, 0℃ ~ rt. (81%). (v) $NaBH_4$, MeOH, 0℃ (100%). (vi) CS_2, MeI, NaH, THF (95%). (vii) Bu_3SnH, AIBN (cat.), benzene, reflux (95%). (viii) Raney Ni (W-2), EtOH, reflux (ix) MsCl, Et_3N, CH_2Cl_2, 0℃. (x) LiI, THF, reflux (94% from **12**).

carbinol amine (**8**), $[\alpha]_D^{29}$ –88.7°(*c* 1.0, $CHCl_3$), as a single product. Apparently, the reaction proceeded through a convex-face selective 3,3-sigmatropic pathway via a diaza-1,5-diene intermediate **5** to give a transient imine (**6**) from which **8** was resulted *via* the amino-ketone (**7**) with hydrolytic loss of an ammonia under the conditions. This indicated that convex-face selectivity prevails even in the intramolecular reaction owing to the inherent steric nature of a bicyclo[3.2.1]octane system. To eliminate the extra aromatic amine functionality, **8** was exposed to sodium nitrite and hypophosphorus acid[9,10] to initiate diazotization under reductive conditions. The expected reaction did occur to furnish the ketone (**9**), $[\alpha]_D^{28}$ –31.9° (*c* 1.0, $CHCl_3$), in good yield. Since a single-step reduction of the carbonyl functionality of **9** under Wolff-Kishner conditions failed, **9** was first reduced with sodium borohydride to give the *endo*-alcohol (**10**), $[\alpha]_D^{29}$ –7.2° (*c* 0.4, $CHCl_3$), which then was converted into the xanthate (**11**), $[\alpha]_D^{28}$ +32.1° (*c* 1.0,

$CHCl_3$). On reflux with tributylstannane in benzene in the presence of a catalytic amount of azobisisobutyronitrile (AIBN),[11] (**11**) afforded the deoxygenation product (**12**), $[\alpha]_D^{30}$ +36.2° (*c* 1.9, $CHCl_3$), excellently. To cleave the dioxolane functionality, which was found to be sturdy under standard acid-hydrolysis conditions, **12** was transformed into the iodide (**15**) through a sequential debenzylation with Raney nickel (W-2),[12] mesylation of the primary alcohol (**13**), $[\alpha]_D^{29}$ +66.3° (*c* 1.1, $CHCl_3$), obtained, followed by substitution of the resulting mesylate **14** with lithium iodide to yield the iodide **15**, $[\alpha]_D^{30}$ +2.8°(*c* 1.1, $CHCl_3$). Overall yield of **15** from the starting building block (**1**) was 41% in ten steps (**Scheme 2**).

The iodide (**15**) was then refluxed with zinc in ethanol containing acetic acid[1,2] to initiate reductive cleavage to give the hemiacetal (**16**), as an epimeric mixture, which afforded the δ-lactone (**17**), $[\alpha]_D^{30}$ +35.7° (*c* 1.2, $CHCl_3$), on oxidation with tetrapropylammonium perruthenate[13] (TPAP) in the presence of 4-methylmorphorine *N*-oxide. Cleavage of the vinyl functionality of **17** was next carried out in a two-step sequence involving catalytic dihydroxylation and periodate cleavage[14] to give the aldehyde (**18**). When **18** was refluxed with zinc in acetic acid intending to initiate cleavage of the α-oxygen bond of the formyl functionality,[15] the reaction proceeded more easily than we anticipated. Gratifyingly, the product generated



Scheme 3

Reagents and conditions: (i) Zn, AcOH-EtOH(1:10), reflux. (ii) TPAP(cat.), NMO, THF (96% from **15**). (iii) OsO_4(cat.), NMO, 50% aq. THF, then $NaIO_4$, 50% aq. THF (83%). (iv) Zn, AcOH, reflux (69%). (v) $(PhO)_2P(O)N_3$, Et_3N, benzene, sealed tube, 140°C, 1 h, then MeOH, 4 h (92%).

was found to be the dihyronaphthalene (**20**), a more advanced intermediate, though not the initially expected formyl-acid (**19**). Upon heating with diphenylphosphoryl azide[16] (DPPA) in benzene containing triethylamine in a sealed tube at 140 ℃ for one hour and for four hours at the same temperature after addition of methanol in the same sealed tube, **20** afforded the methyl carbamate[17] (**22**), $[\alpha]_D^{28}$ +6.6° (*c* 1.1, $CHCl_3$){lit.,[17] $[\alpha]_D^{30}$ +6.85° (*c* 0.9, $CHCl_3$)}, through a formation of the isocyanate intermediate (**21**). Since we have previously developed a five-step transformation[17] of [(+)-**22**] into (–)-aphanorphine (**2**), the present acquisition of (+)-**22** from the sugar building block [(–)-**1**] constitutes an alternative synthesis of the natural products in a formal sense. Overall yield of (+)-**22** from the iodide **15** was 51% in five isolated steps and, thus, 21% from the block [(–)-**1**] in 15 steps (**Scheme 3**).

In summary, we have demonstrated an alternative utilization of the chiral building block originally developed for the construction of the aldohexose molecules for a concise synthesis of (–)-aphanorphine, the only naturally occurring alkaloid known to have the norbenzomorphan framework.

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