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Asymmetric Synthesis of Epicylindrospermopsin via Intramolecular Nitrone Cycloaddition. Assignment of Absolute Configuration

James D. White* and Joshua D. Hansen

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

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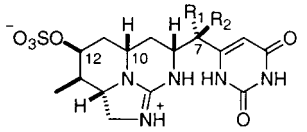
Cylindrospermopsin (**1**) and its C7 epimer **2** are potent naturally occurring environmental toxins which contain a guanidinium unit embedded in a unique tricyclic skeleton.[1] The isolation of cylindrospermopsin by Moore from the cyanobacterium *Cylindrospermopsis raciborskii* was followed by a detailed structural investigation based upon NMR evidence which concluded incorrectly that the structure of this substance was represented by **2**.[2] Subsequent isolation of cylindrospermopsin from the alga *Umezakia natans* found in Japan[3] and the isolation of both cylindrospermopsin[4] and an epimer[5] from *Aphanizomenon ovalisporum* present in a lake in Israel did not rectify this misassignment, nor did a synthesis of (±)-cylindrospermopsin by Snider,[6] which unfortunately failed to distinguish between this substance and its C7 epimer. A recent unambiguous synthesis of (±)-**2** by Weinreb has established definitively that this is the structure of 7-epicylindrospermopsin;[7] our approach, which was directed toward an asymmetric synthesis of **2** in the belief that this structure corresponded to cylindrospermopsin, thus became a prospective route to its natural C7 epimer.[8] The key feature of our route is an intramolecular nitrone cycloaddition[9] that sets configuration at C10 and C12 of **2** from a precursor assembled from the hydroxylamine **3** and aldehyde **4**.

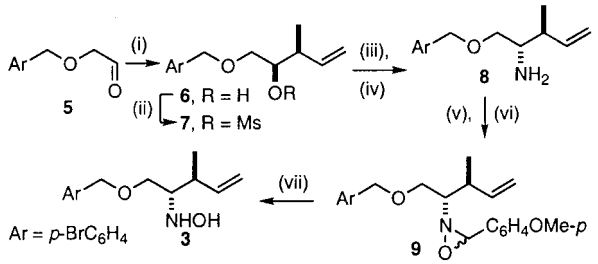


1, R_1 = H, R_2 = OH (Cylindrospermopsin)
2, R_1 = OH, R_2 = H (Epicylindrospermopsin)

Asymmetric crotylation of *p*-bromobenzyloxyacetaldehyde (**5**) with the reagent obtained from *cis*-2-butene and (+)-diisopinylcampheylmethoxyborane[10] gave the syn homoallylic alcohol **6** in 94% enantiomeric excess, as determined by NMR analysis of its Mosher ester[11] (Scheme 1). Displacement of the mesylate **7** with sodium azide, followed by reduction of the azide with triphenylphosphine, afforded the inverted primary amine **8**, which was condensed with *p*-anisaldehyde. The resulting imine was oxidized in situ with *m*-chloroperbenzoic acid to give oxaziridine **9**, and upon treatment with hydroxylamine hydrochloride this substance furnished **3**.[12]

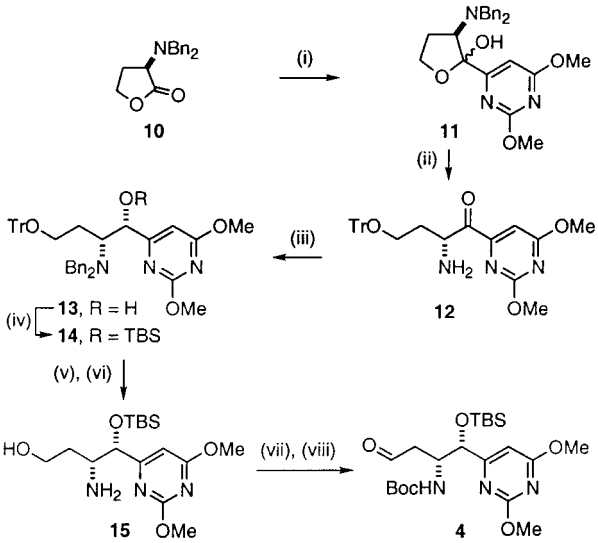
Synthesis of the aldehyde **4** commenced from (*R*)-methionine, which upon exposure to excess benzyl bromide yielded (*R*)-2-(*N*,*N*-dibenzyl)butyrolactone (**10**) (Scheme 2).[13] The latter was reacted with 4-lithio-2,6-dimethoxypyrimidine[14] in the presence of cerium trichloride to furnish a quantitative yield of lactol **11** as a mixture of stereoisomers. Treatment of **11** with triphenylmethyl chloride gave the primary trityl ether **12**, and reduction of this ketone with L-Selectride produced the syn amino alcohol **13** along with its anti isomer in the ratio 12:1. The secondary alcohol of **13** was protected as its *tert*-butyldimethylsilyl ether **14**, after which the trityl group was removed quantitatively with formic acid. The *N*,*N*-dibenzyl moiety was cleaved by hydrogenolysis to give primary amine **15**, which was then converted to its *N*-Boc derivative, and subsequent oxidation of the primary alcohol with Ley's reagent[15] produced aldehyde **4** in nine steps and 20% overall yield from (*R*)-methionine.

Scheme 1[a]



[a] Conditions: (i) *cis*-2-butene, *t*-BuOK, *n*-BuLi, (+)-MeOB(Ipc)$_2$, Et_2O−THF, 45%; (ii) Ms_2O, pyr, CH_2Cl_2, 100%; (iii) NaN_3, DMF, 85 °C; (iv) Ph_3P, THF−H_2O, 56% from **7**; (v) *p*-$MeOC_6H_4CHO$, MeOH, Na_2CO_3, 60 °C; (vi) *m*-CPBA, CH_2Cl_2, 0 °C → room temperature; (vii) $HONH_2$·HCl, MeOH, 0 °C → room temperature, 60% from **8**.

Scheme 2[a]



[a] Conditions: (i) 4-Bromo-2,6-dimethoxypyrimidine, *n*-BuLi, $CeCl_3$, Et_2O−THF, −78 °C → room temperature, 97%; (ii) Ph_3CCl, Et_3N, DMAP, CH_2Cl_2, Δ, 93%; (iii) L-Selectride, THF, 84%; (iv) TBSOTf, Et_3N, THF, 87%; (v) HCO_2H, THF, 100%; (vi) H_2, $Pd(OH)_2$/C, EtOH, 81%; (vii) Boc_2O, Et_3N, CH_2Cl_2, 68%; (viii) TPAP (cat.), NMO, mol. sieves, CH_2Cl_2, 91%.

Condensation of hydroxylamine **3** with aldehyde **4** gave (*Z*)-nitrone **16** in good yield (Scheme 3), and intramolecular cycloaddition of **16** in refluxing toluene afforded the unstable oxazabicyclo-[2.2.1]heptane derivative **17**, accompanied by two unidentified

* Corresponding author. E-mail address: james.white@orst.edu.

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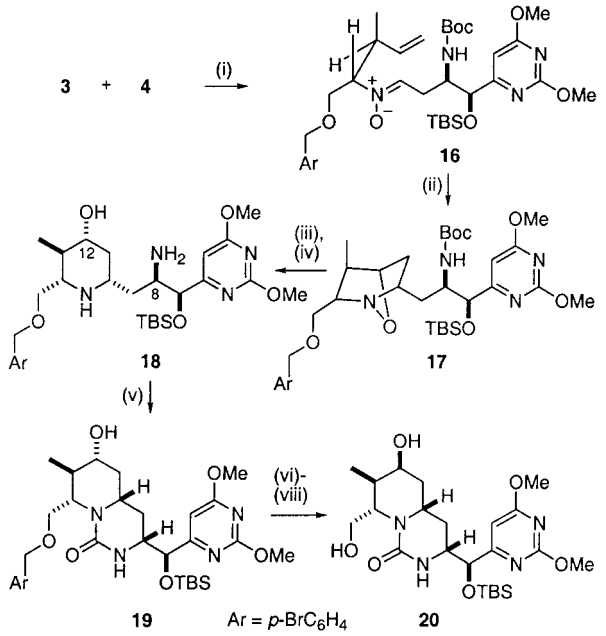
Scheme 3[a]

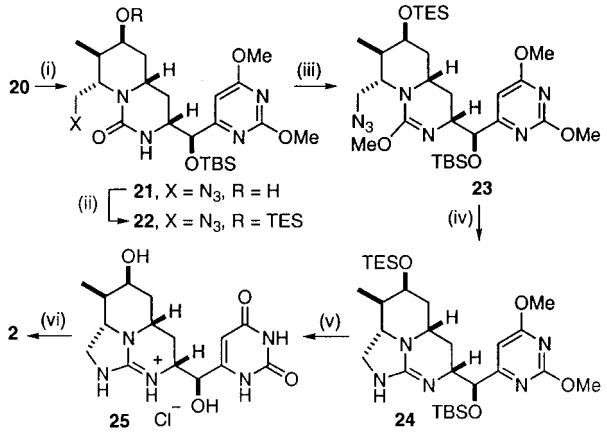


[a] Conditions: (i) MeOH mol. sieves, Δ, 60%; (ii) Toluene, mol. sieves, Δ; (iii) Zn, NH_4Cl, THF−H_2O; (iv) HCl, MeOH, 68% from **16**; (v) $CO(Im)_2$, CH_2Cl_2, then K_2CO_3, MeOH, 85%; (vi) Dess−Martin periodinane, CH_2Cl_2; (vii) L-Selectride, THF; (viii) H_2/C, $Pd(OH)_2$, EtOH, 55% from **19**.

stereoisomers in the ratio 10:5:1. As predicted from conformational analysis of **16**, the major product **17** arose from an exo cycloaddition to the *re* face of the terminal alkene in the orientation shown.[16] In situ reduction of **17** with zinc and ammonium chloride followed by acidic removal of the Boc group furnished piperidine **18** in which five of the six stereocenters correspond to those of **2**. Before inverting the C12 hydroxyl group, it was decided to bridge the piperidine nitrogen and the amino function at C8 via a urea, and for this purpose **18** was treated with carbonyldiimidazole to produce **19**. The secondary alcohol of **19** was oxidized to a ketone, and subsequent reduction of this substance with L-Selectride afforded the 12β alcohol as the major product (β:α > 15:1). Hydrogenolysis of the primary *p*-bromobenzyl ether gave the crystalline diol **20** whose relative stereostructure was confirmed by X-ray crystallographic analysis.

Diol **20** was converted to azide **21**, and the remaining secondary hydroxyl group was protected as its triethylsilyl ether **22** (Scheme 4). Exposure of **22** to trimethyloxonium tetrafluoroborate in the presence of potassium hexamethyldisilazide gave the *O*-methylated derivative **23** which was subjected to catalytic hydrogenation over palladium-on-carbon. The resultant primary amine underwent spontaneous cyclization to give guanidine **24**, and subsequent exhaustive hydrolysis in concentrated hydrochloric acid led to cleavage of silyl ethers as well as methyl ethers attached to the pyrimidine nucleus to yield **25**. This diol was shown to be identical by comparison of ^1H and ^{13}C NMR spectra with the corresponding racemic substance prepared by Weinreb,[7] and sulfation as previously described[6] gave (−)-7-epicylindrospermopsin (**2**) accompanied by the bis sulfate of **25** (ca. 2.5:1, respectively). These substances were separated by HPLC, and purified **2** was found to have spectral data in good agreement with those recorded for both natural[5] and synthetic[7] epicylindrospermopsin. The specific rotation of synthetic material establishes that the absolute configuration of natural epicylindrospermopsin is 7*S*, 8*R*, 10*S*, 12*S*, 13*R*, 14*S*, as represented by **2**.

Scheme 4[a]



[a] Conditions: (i) (a) $(Cl_3CO)_2CO$, THF; (b) NaN_3, DMF, 49%; (ii) TESOTf, Et_3N, CH_2Cl_2, 99%; (iii) KHMDS, Me_3O^+ BF_4^-, CH_2Cl_2; (iv) Pd/C, H_2, MeOH; (v) HCl (conc.) Δ, 21% from **22**; (vi) SO_3·pyr, DMF, 63%.

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Supporting Information Available: Experimental procedures and characterization data and X-ray crystallographic data for **20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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