Automated Reactivity Prediction of Complex Molecules and Its Application to Total Synthesis of AgeliferinClick to copy article link

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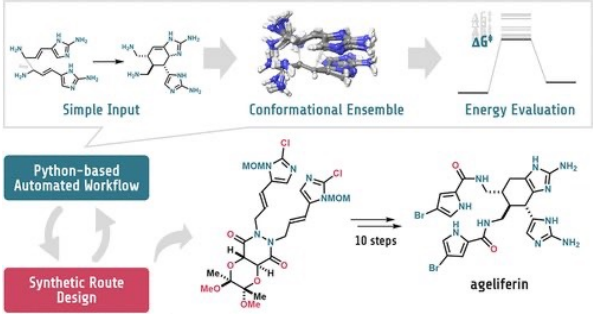
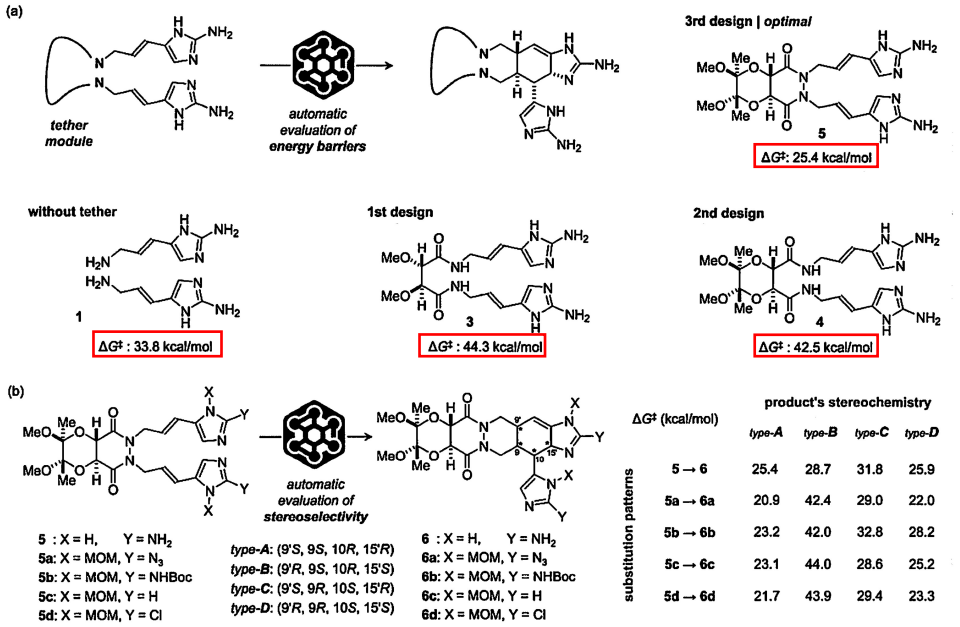
This report has demonstrated the application of Conformers, an ACCel-based program that automatically



dearomative [4 + 2] Diels-Alder-type dimerization

the high energy penalty for dearomatization of imidazole



substitution patterns	ΔG‡ (kcal/mol)	product's stereochemistry			
		type-A	type-B	type-C	type-D
5 → 6	25.4	28.7	31.8	25.9	
5a → 6a	20.9	42.4	29.0	22.0	
5b → 6b	23.2	42.0	32.8	28.2	
5c → 6c	23.1	44.0	28.6	25.2	
5d → 6d	21.7	43.9	29.4	23.3	

Figure 3. (a) Design process for the optimal tether module. (b) Evaluation of the effect of substitution patterns on stereoselectivity. Values of $\Delta G^{\ddagger}$ represent the difference between the most stable conformation of the reactant and the lowest-energy transition state in the postulated cycloaddition. Note that the conformers used for these energy evaluations are not always connected by a direct conformational pathway. Logo created by the author, reproduced with permission.

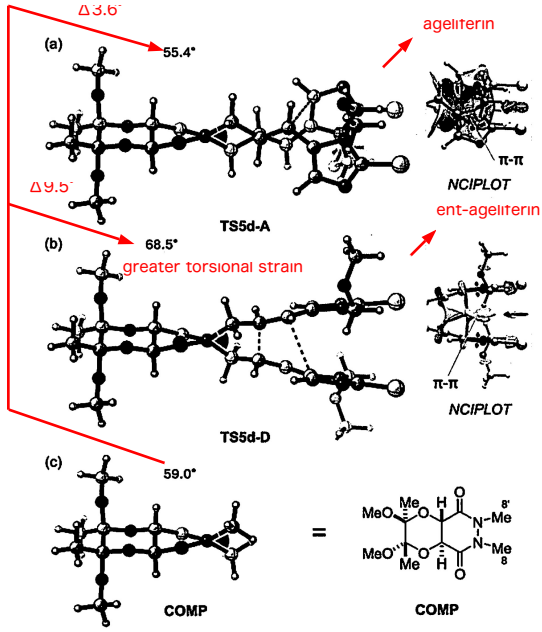
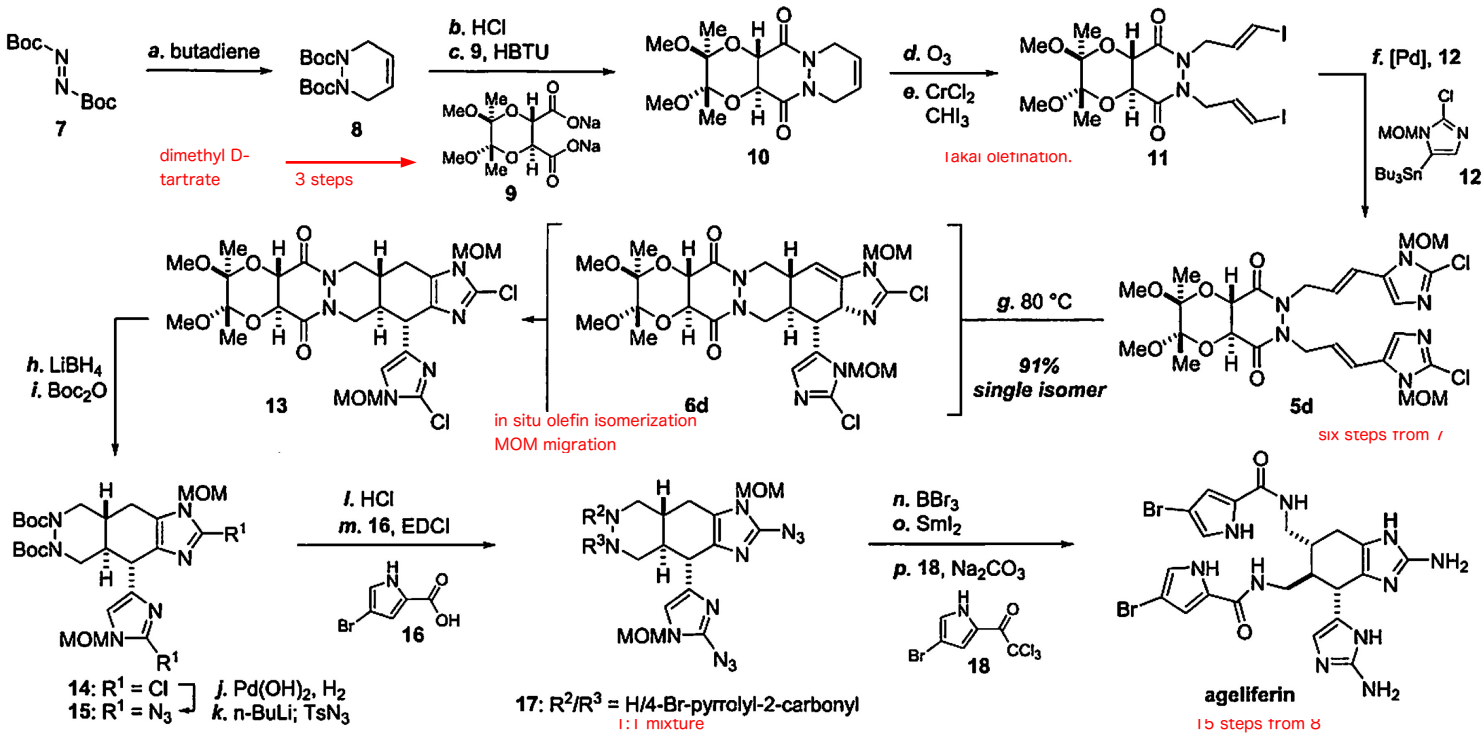


Figure 4. (a) Transition state from 5d to 6d with type-A stereochemistry (TS5d-A). (b) Transition state from 5d to 6d with type-D stereochemistry (TS5d-D). (c) Structural component analysis for the chiral auxiliary.

Scheme 1. Total Synthesis of Ageliferin[a]



[a]Reagents and conditions: (a) 1,3-butadiene, toluene, 95%; (b) HCl, 1,4-dioxane; (c) 9, HBTU, Et_3N, 1,4-dioxane, reflux, 71% (2 steps); (d) O_3, CH_2Cl_2, −78 °C; PPh_3; (e) $CrCl_3$, $LiAlH_4$, CHI_3, THF, 1,4-dioxane, 45% (2 steps); (f) 12, *t*BuXPhos Pd G3, CuI, CsF, DMF, 81%; (g) 1,2-dichloroethane, 80 °C, 91%; (h) $LiBH_4$, THF, 60 °C; (i) Boc_2O, Et_3N, H_2O, THF, 60 °C, 40% (2 steps); (j) $Pd(OH)_2$, H_2, MeOH; (k) *n*-BuLi, TMEDA, THF, −100 °C; TsN_3; LDA, 33% (2 steps); (l) HCl, 1,4-dioxane; (m) 16, EDCI, HOAt, Et_3N, MeCN, 60% (2 steps); (n) BBr_3, CH_2Cl_2, NH_4OH, 0 °C; (o) SmI_2, THF, MeOH; (p) 18, Na_2CO_3, DMF, 35 °C, 5.3% (3 steps).

reduced the azido groups to amines and removed the two MOM groups.