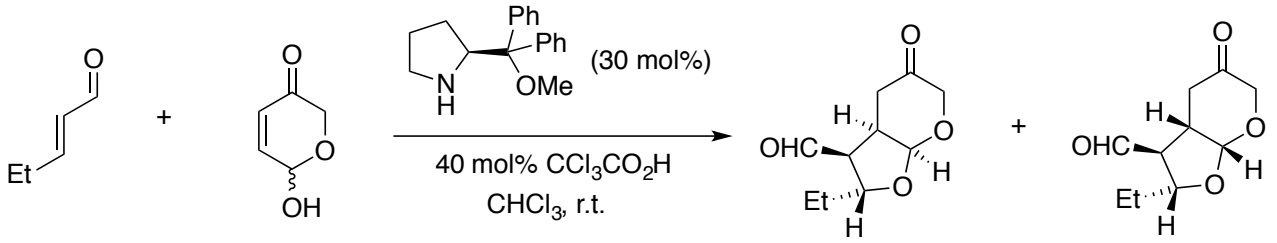
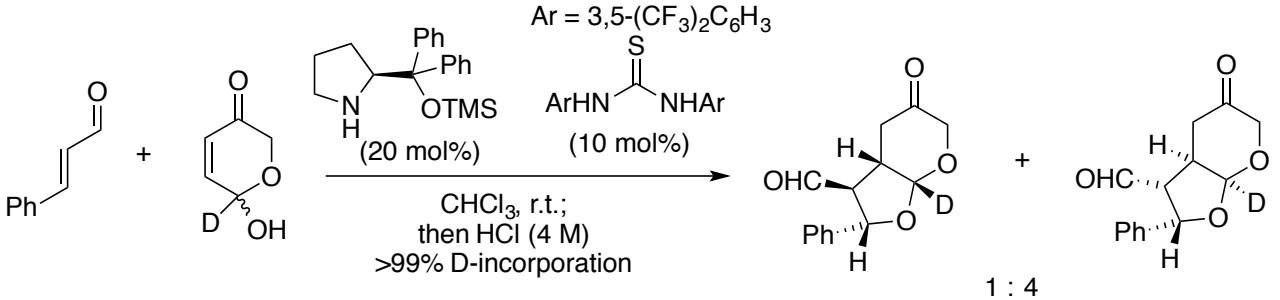
Problem set Wed 15th March

Submitted by Nicholas Tappin

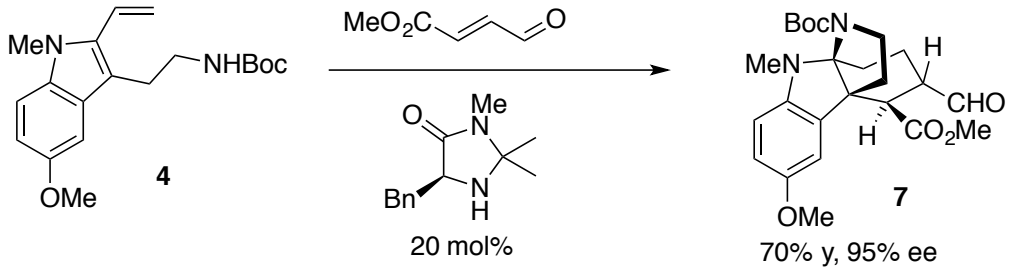
1) Propose a mechanism that could rationalize the following *enantioselective* cascade reaction between an enal and a *racemic* hydroxypyranone. You may assume that hydroxypyranone proton is acidic and this centre may epimerize through simple acid-base chemistry.
Hint: think about the nature of a reaction that begins with a racemic mixture and finishes with an enantioenriched product.



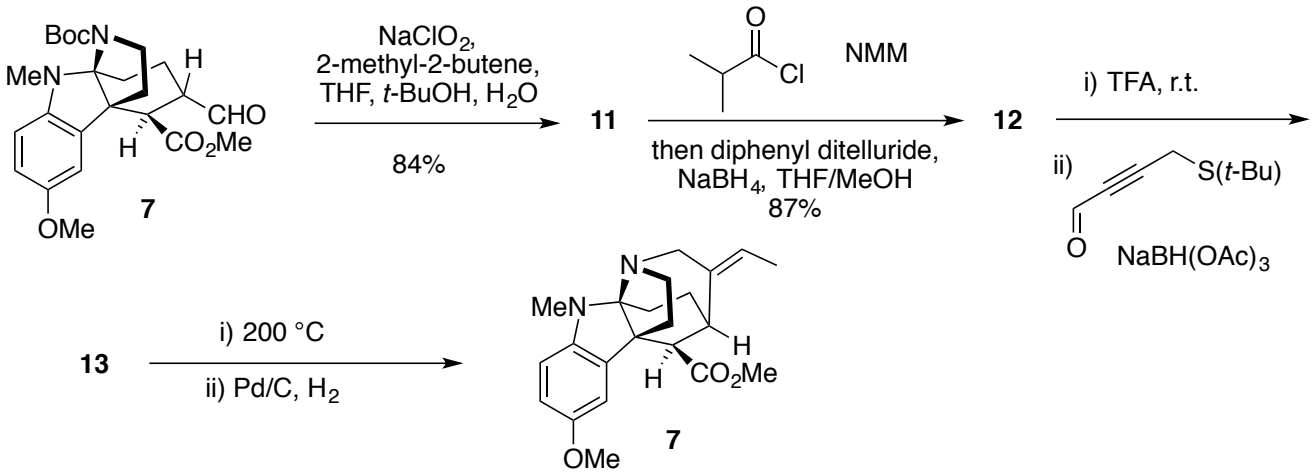
2) You may not assume that the aforementioned proton is epimerizable via a deprotonation, as seen in the following deuterium incorporation experiment. Explain how the racemic mixture can otherwise epimerize.



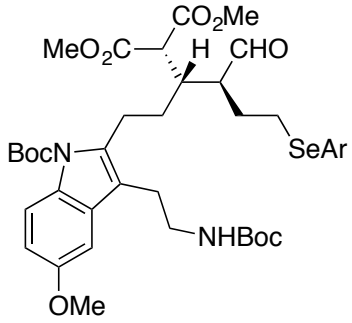
3) Propose a mechanism and transition state to rationalize the stereoselectivity of the following reaction



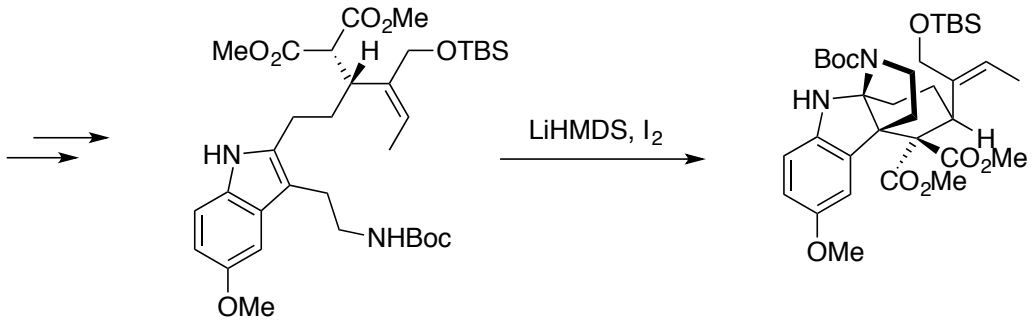
4) Complete the scheme depicted below with the missing structures and mechanisms to arrive there.



5) Considering the preceeding proline-derivative catalysis problems, suggest a disconnection and reactants/ reagents of the following aldehyde. Don't worry about stereochemistry.

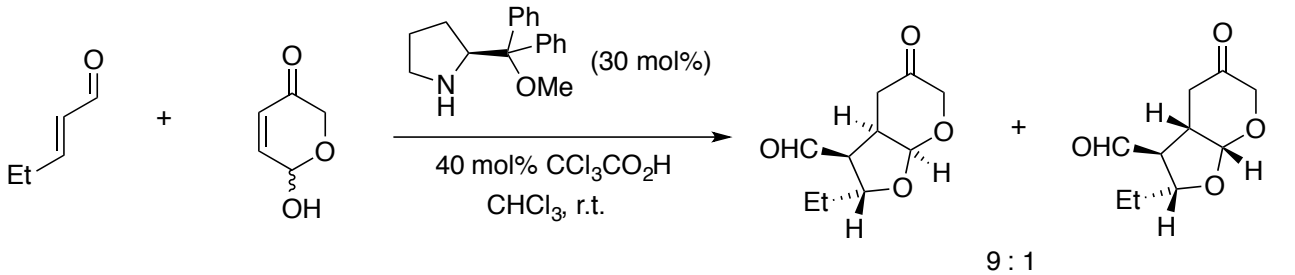


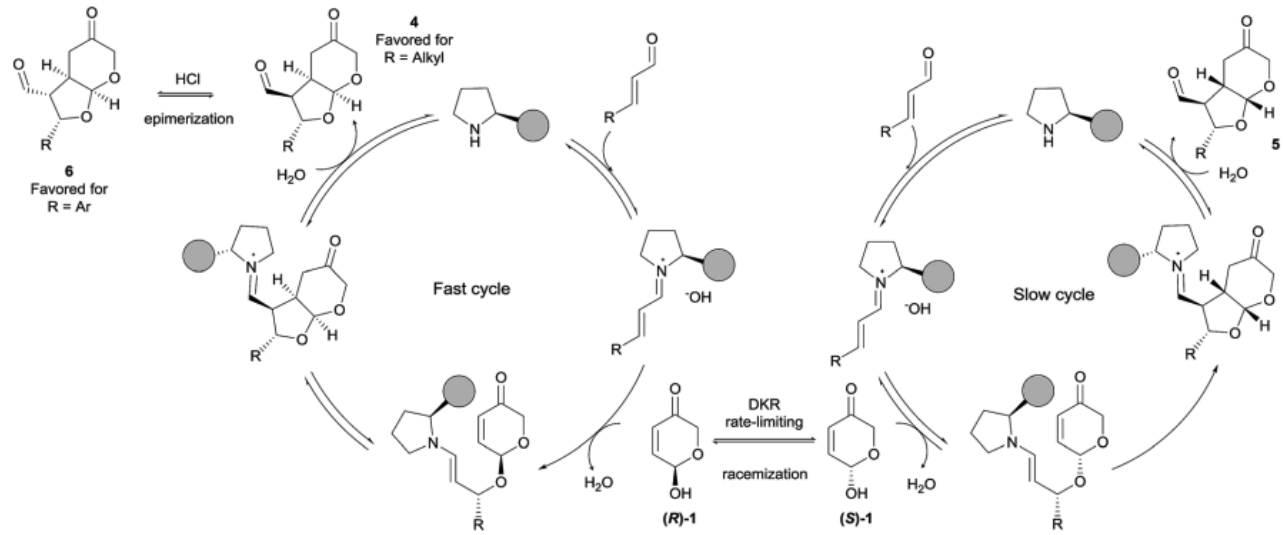
6) With the help of mechanisms, explain what happens below.



7) Think about the prevalence of these exo-ethylidene moieties in natural products and the different strategies employed to synthesize them. Can you provide one elegant and/or robust example?

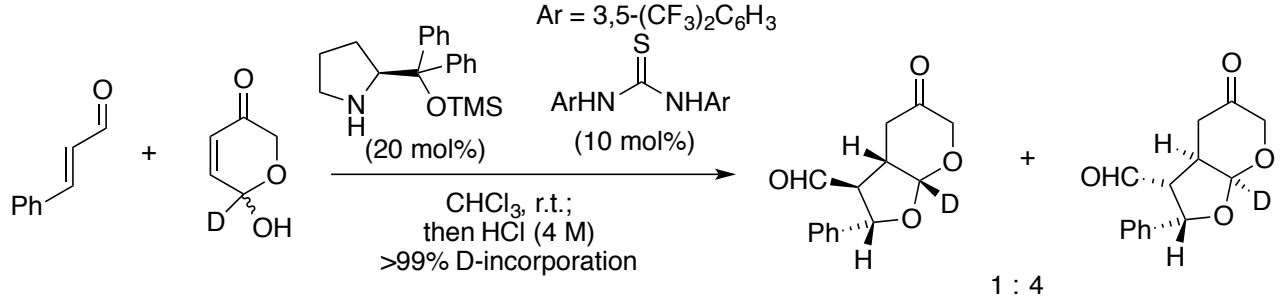
1) Propose a mechanism that could rationalize the following *enantioselective* cascade reaction between an enal and a *racemic* hydroxypyranone. Suggest a name for this cascade reaction. You may assume that hydroxypyranone proton is acidic and this centre may epimerize through simple acid-base chemistry.
Hint: think about the nature of a reaction that begins with a racemic mixture and finishes with an enantioenriched product.

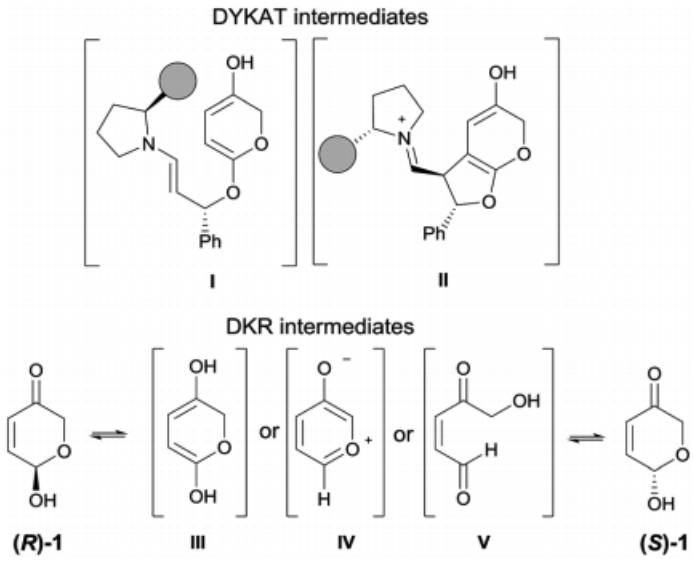




Scheme 7 Proposed catalytic cycles for DKR.

2) You may not assume that the aforementioned proton is epimerizable via a deprotonation, as seen in the following deuterium incorporation experiment. Explain.



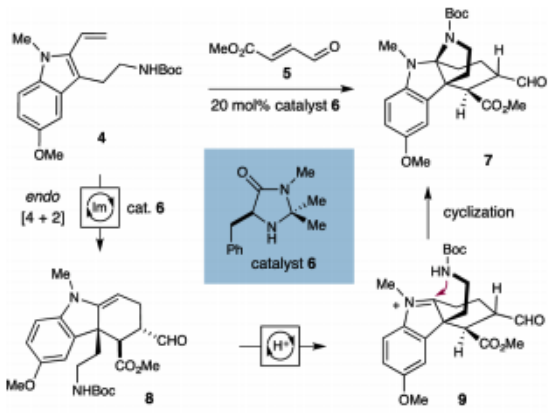


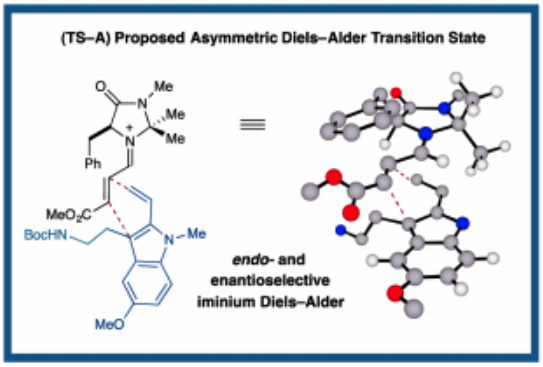
Scheme 5 Possible intermediates involved in the kinetic resolution process.

Ane Orue,a Uxue Uria,a David Roca-López,b Ignacio Delso,c Efraím Reyes,a Luisa Carrillo,a Pedro Merino*b and Jose L. Vicario*a, ***Chem. Sci.*** 2017 DOI: dy

3) Propose a mechanism and transition state to rationalize the stereoselectivity of the following reaction

Scheme 2. Enantioselective Organocatalytic Cascade Sequence





Benjamin D. Horning and David W. C. MacMillan*
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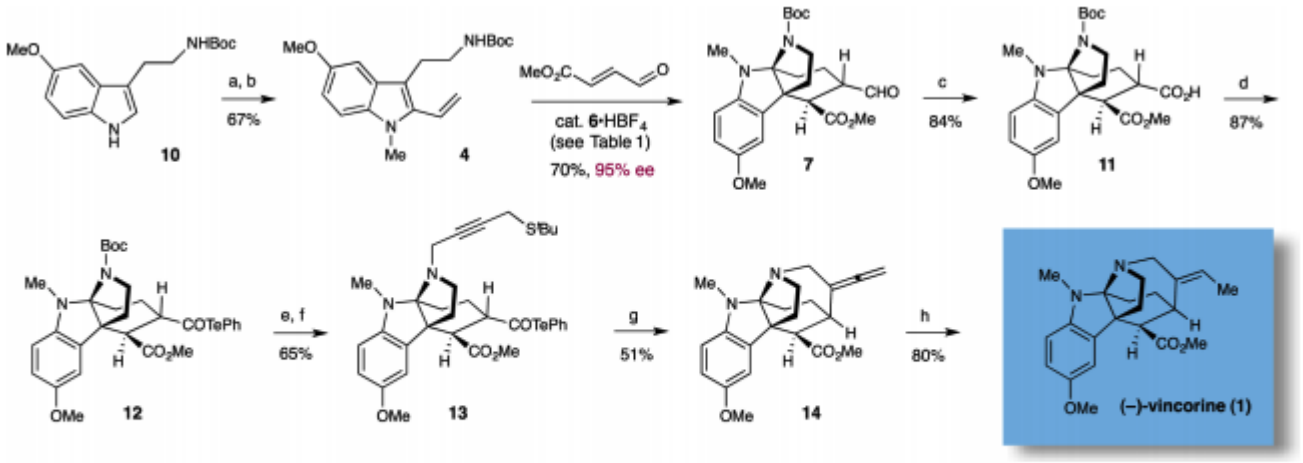
DOI: 10.1021/ja402933s

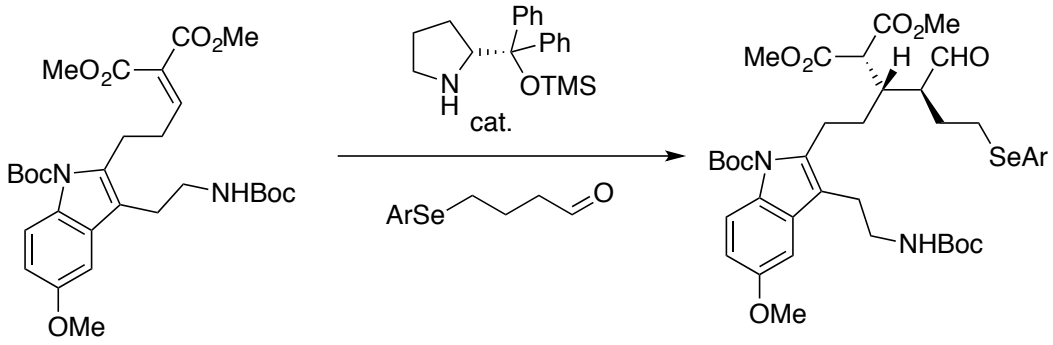
4) Complete the scheme depicted below with the missing structures and mechanisms to arrive there.

Scheme 3. Nine-Step Enantioselective Catalytic Total Synthesis of Vincorine[a]



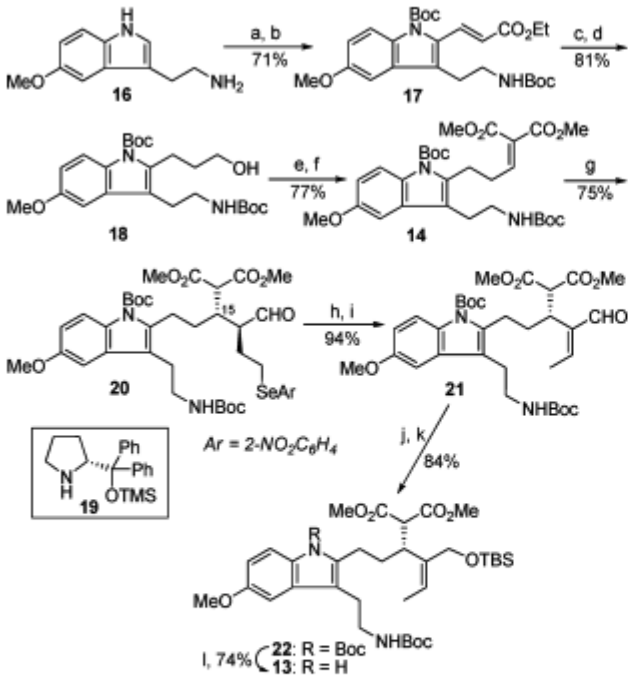
[a]Reagents and conditions: (a) NaH, DMF, 0 °C; MeI. (b) *n*-BuLi, DME, −40 °C; $ZnCl_2$, −78 °C to rt; XPhos precatalyst, vinyl iodide. (c) $NaClO_2$, 2-methyl-2-butene, THF, *tert*-butanol, H_2O, 0 °C. (d) Isobutyl chloroformate, *N*-methylmorpholine, THF; diphenyl ditelluride, $NaBH_4$, THF/MeOH, rt. (e) TFA, rt. (f) 4-(*tert*-Butylthio)but-2-ynal, $NaBH(OAc)_3$, CH_2Cl_2, rt. (g) 1,2-Dichlorobenzene, 200 °C. (h) Pd/C, H_2, THF, −15 °C.

5) Considering the preceeding proline-derivative catalysis problems, suggest a disconnection and reactants/ reagents of the following aldehyde.



6) With the help of mechanisms, explain what happens below.

Scheme 1[a]

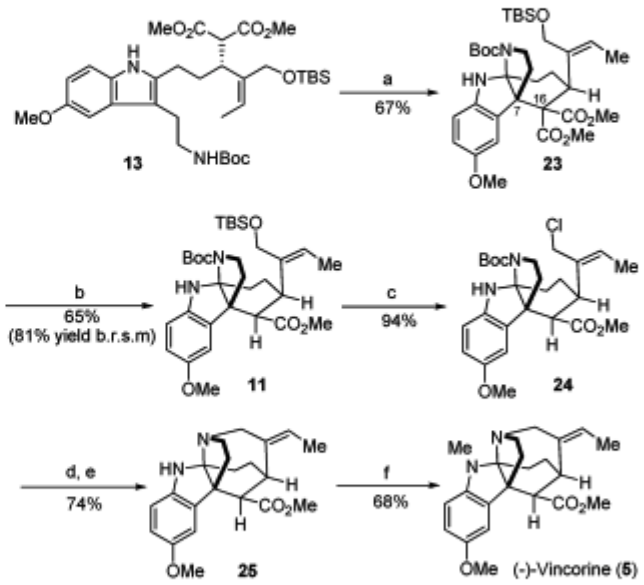


[a]Reagents and conditions: (a) $(Boc)_2O$, cat. DMAP, CH_2Cl_2; (b) $Pd(OAc)_2$, ethyl acrylate, *t*-BuO_2Bz, 1,4-dioxane/AcOH, 70 °C; (c) Pd/C, H_2 (1 atm), THF/MeOH; (d) DIBAL-H, THF, −78 to −40 °C; (e) IBX, ethyl acetate, reflux; (f) dimethyl malonate, cat. proline, DMSO, r.t.; (g) cat. **19**, **15**, CH_3CN, 0 °C, 3 days; (h) *m*-CPBA, THF, −78 °C to r.t., Et_3N workup; (i) UV light (360 nm); (j) $NaBH_4$, MeOH, −78 to 0 °C; (k) TBSCl, imidazole, DMF; (l) silica gel, 70 °C, 0.2−0.3 mmHg.

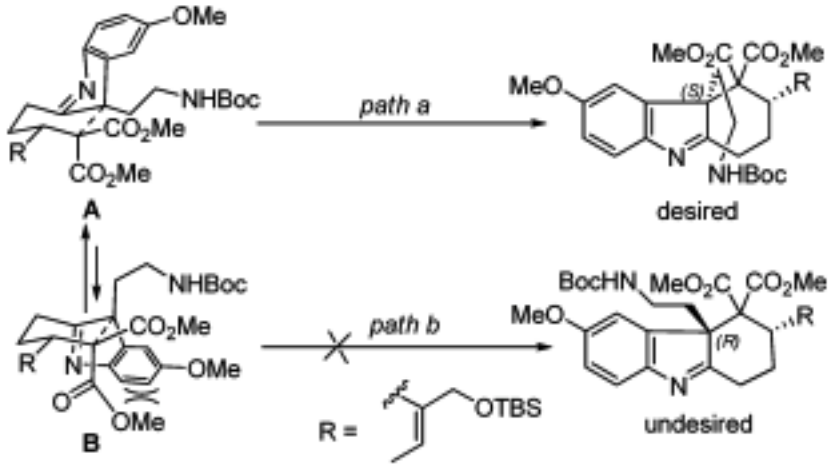
resultant alcohol delivered **22** in 84% yield. Finally, selective removal of the *tert*-butoxycarbonyl (Boc) protecting group in the indole moiety[15] was achieved by treatment with silica gel at low pressure to furnish **13** in 74% yield.

With diester **13** in hand, we attempted the crucial intramolecular oxidative coupling (Scheme 2). Deprotonation

Scheme 2[a]



[a]Reagents and conditions: (a) LiHMDS, I_2, THF, −40 °C to r.t.; (b) KCN, H_2O, DMF, 100 °C; (c) Ph_3PCl_2, CH_2Cl_2; (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; (e) K_2CO_3, KI, CH_3CN, 60 °C; (f) 37% aq. HCHO, $NaBH_3CN$, CH_3CN, AcOH.



Weiwei Zi, Weiqing Xie, and Dawei Ma*
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