Concise Enantioselective Total Synthesis of (+)-Punctaporonin U

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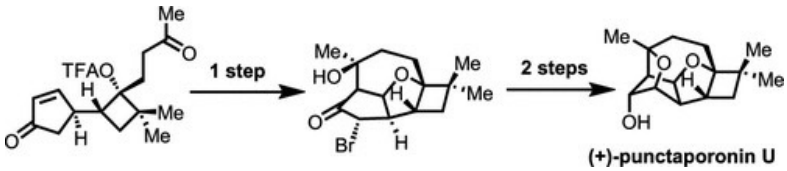
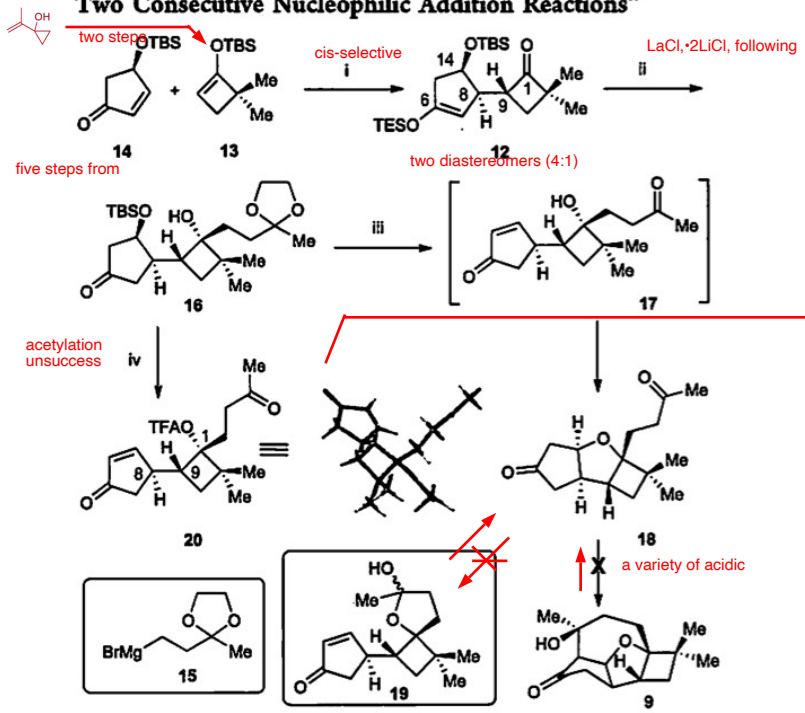
caryophyllene-type sesquiterpenes

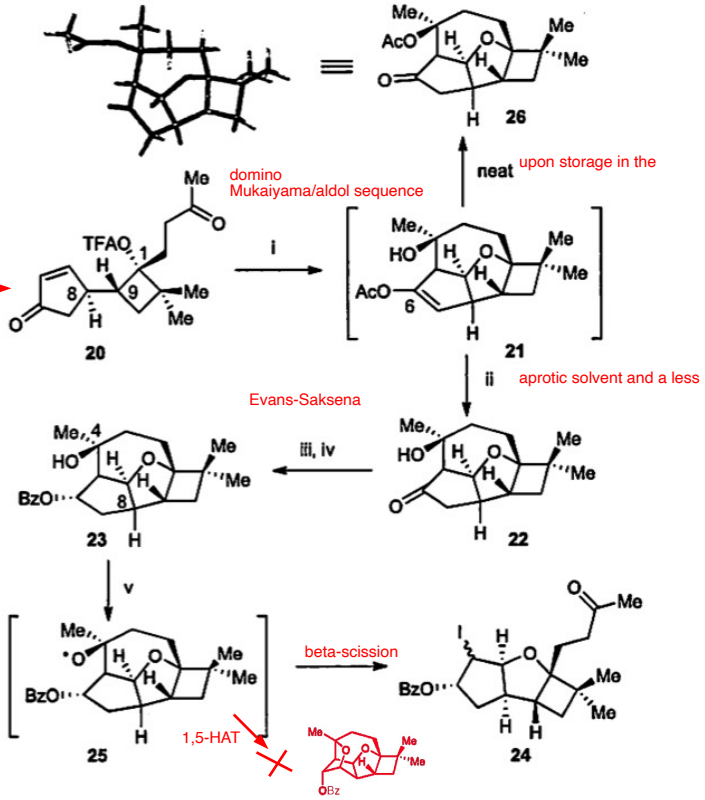


Scheme 2. Convergent Assembly of Building Blocks through Two Consecutive Nucleophilic Addition Reactions[a]



[a]Reagents and conditions: (i) 14 (23 mmol), 13 (2.0 equiv), TESOTf (2.0 equiv), 2,6-di-*tert*-butylpyridine (2.5 equiv), CH_2Cl_2, −40 °C, 6 h, 48% (dr 4:1); (ii) 12 (7.3 mmol), 15 (2.5 equiv), $LaCl_3$•2LiCl (2.5 equiv), THF, −20 °C, 5 min; (iii)TsOH•H_2O (10.0 equiv), acetone, 50 °C, 12 h, 85%; (iv) 16 (7.5 mmol), TFAA (4.0 equiv), pyridine (8.0 equiv), DCM, −15 °C then TsOH•H_2O (10.0 equiv), acetone, 50 °C, 12 h, 64% over two steps from a diastereomeric mixture of 12 (dr 4:1). TESOTf = triethylsilyl trifluoromethanesulfonate, TFAA = trifluoroacetic anhydride, TsOH = toluenesulfonic acid.

Scheme 3. Implementation of Domino Mukaiyama/aldol Sequence for the Construction of Tetracyclic Compounds[a]

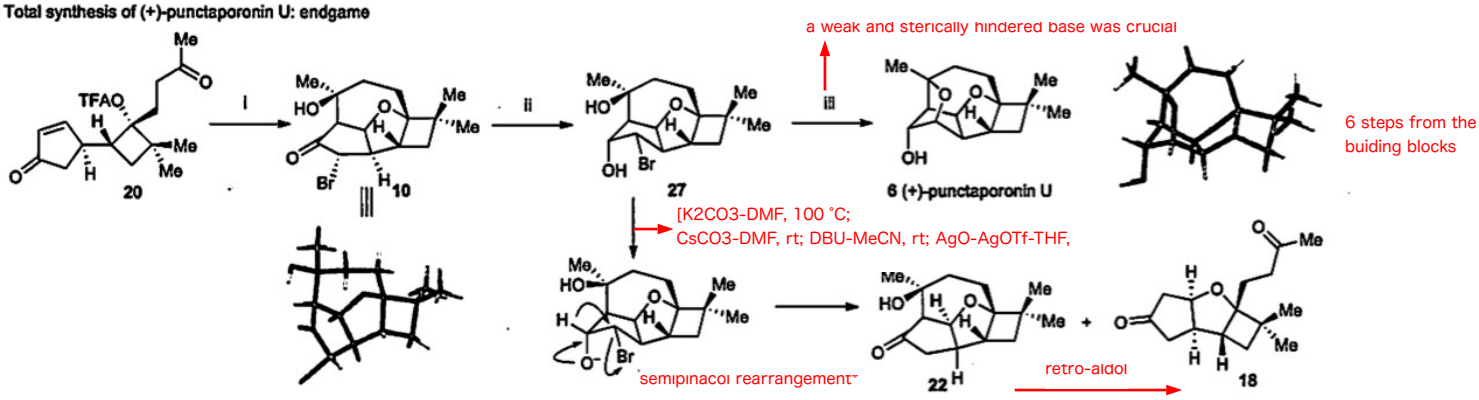


[a]Reagents and conditions: (i) NaOMe (1.5 equiv), DMF (c 0.025M), −50 °C, 1.5 h, then Ac_2O (6.0 equiv), −50 °C to rt; (ii) 4-ppy (5.0 equiv), MeCN, rt, 80%; (iii) $NMe_4BH(OAc)_3$ (5.0 equiv), MeCN/AcOH (v/v = 2:1), 0 °C, 6 h; (iv) Bz_2O (5 equiv), Et_3N (10.0 equiv), DMAP (1.0 equiv), DCM, 40 °C, 65% over two steps; (v) PIDA (2.0 equiv), I_2 (1.1 equiv), halogen lamp, DCM, 40 °C, 1 h, 86%. PIDA = phenyliodonium(III) diacetate, 4-ppy = 4-pyrrolidinylpyridine.

pKa 9.58

Scheme 4. Total Synthesis of (+)-Punctaporonin U

(a) Total synthesis of (+)-punctaporonin U: endgame



[a]Reagents and conditions. (i) MeONa (2.5 equiv), DMF, −50 °C, 2 h then iPr_2SiCl_2 (4.0 equiv), Et_3N (3.0 equiv), −50 °C to rt, 30 min then DBDMH (0.7 equiv), −50 °C, 1 h then pyridine•$(HF)_x$ (150 equiv), −50 to 0 °C, 16 h, 50%; (ii) $NMe_4BH(OAc)_3$ (5.0 equiv), MeCN/AcOH (4:1), −20 to 0 °C, 6 h; (iii) 2,6-di-*tert*-butylpyridine (5.0 equiv), DMF, 65 °C, 72 h, 60% over two steps. DBDMH = 1,3-dibromo-5,5-dimethylhydantoin.

(b) Domino oxa-Michael/aldol/bromination sequence: A possible reaction pathway