Total Synthesis of (+)-Resiniferatoxin via a Pyridinium Salt Photorearrangement

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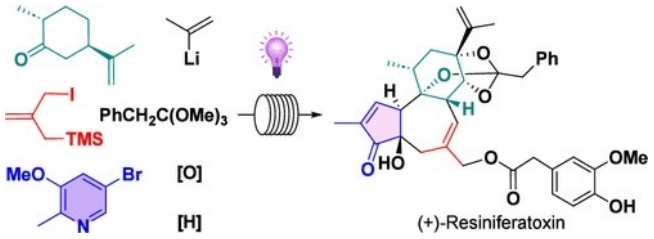
transient receptor potential vanilloid 1 (TRPV1)

TRPV1 agonist



Scheme 1. Total Synthesis of (+)-Resiniferatoxin (1)[a]

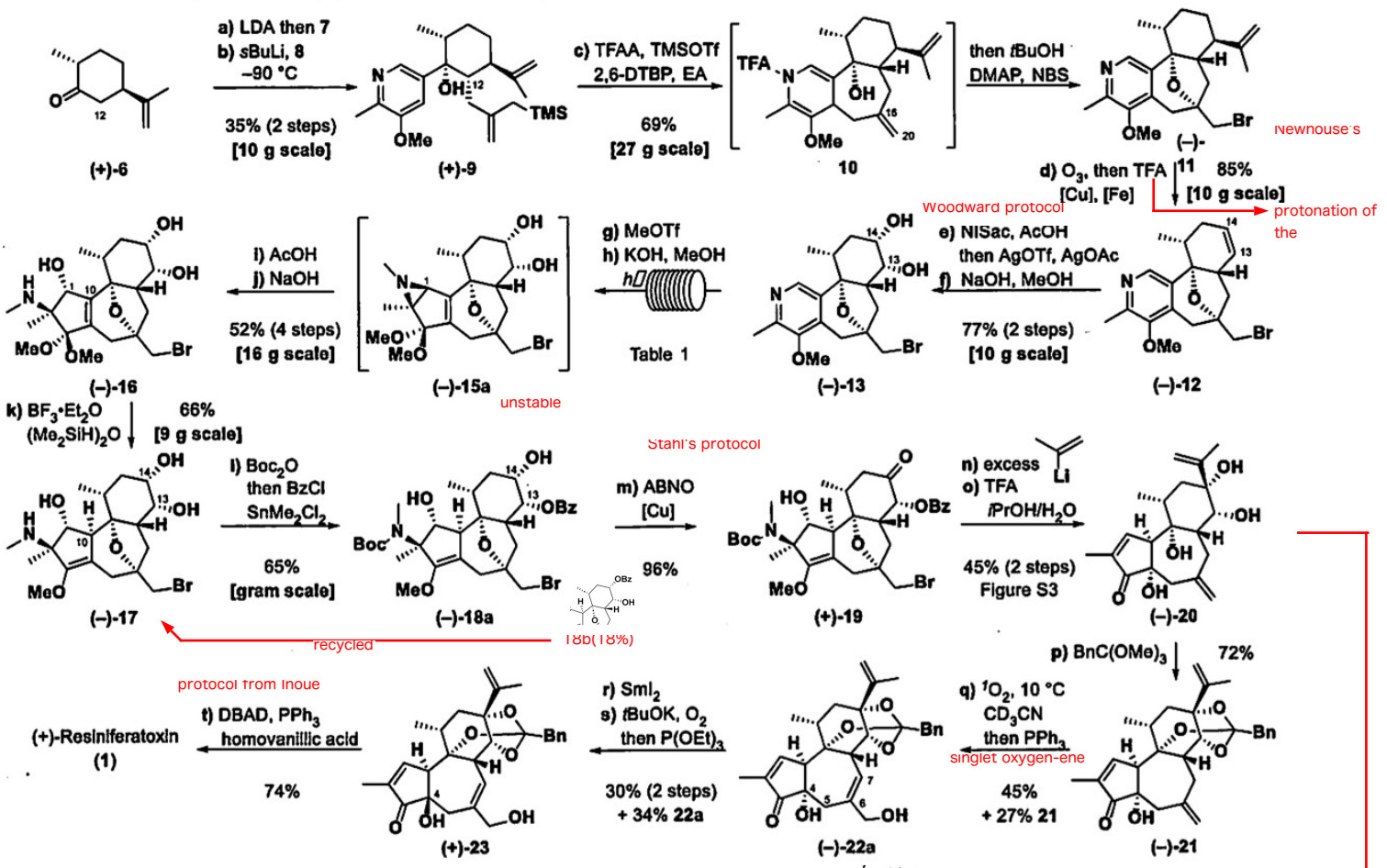
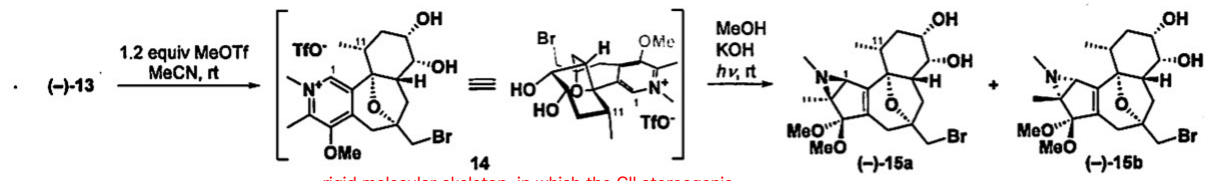


Table 1. Optimization of the Pyridinium Salt Photorearrangement[a]



rigid molecular skeleton, in which the CII stereogenic center-proximal to C1-biased the torquoselectivity

entry	wavelength (nm)	concn (mM)	equiv of KOH	time	yield, %[b] 15a	15b
1	300	24	2.25	4 h	54	11
2	300	12	2.25	2 h	53	11
3	300	6	4.5	1 h	52	12
4	254	6	4.5	10 min	47	12
5	254	12	2.25	20 min	47	11
6	254 (pyrex tube)	12	2.25	2 h		trace[c]

preparative flow processing

limited UV transmission

[a]Reaction performed on 0.06 mmol scale and set up in the 10 mL quartz test tubes. [b]NMR yield determined using 1,3,5-trimethoxybenzene as the internal standard. [c]Low conversion.

[a]Reagents and conditions: (a) LDA (1.1 equiv, 2.0 M in THF), 7 (3.0 equiv), THF/DMI (4:1), −78 to −40 °C, 1 h, then 25 °C, 30 h. (b) 8 (1.5 equiv), *s*BuLi (1.4 equiv, 1.3 M in *n*-hexane), 2-methyl-THF, −90 °C, 15 min, 35% (2 steps). (c) 2,6-DTBP (2.5 equiv), TFAA (1.6 equiv), TMSOTf (1.5 equiv), EtOAc, −78 to 25 °C, 2 h, then DMAP (5 equiv), *t*BuOH, −78 °C, 15 min, then NBS (3.0 equiv), −78 to 0 °C, 2 h, 69%. (d) O_3, MeOH, −78 °C, then TFA (1.1 equiv), $Cu(BF_4)_2{\cdot}H_2O$ (1.5 equiv), $(NH_4)_2Fe(SO_4)_2$ (1.2 equiv), −78 to 25 °C, 85%. (e) NISac (1.1 equiv), AcOH, 25 °C, 1.5 h, then H_2O (20 equiv), AgOAc (1.0 equiv), AgOTf (1.2 equiv), 90 °C, 6 h, then NaI (2.3 equiv), MeOH, 25 °C. (f) NaOH (5 equiv), MeOH, 25 °C, 10 min, 77% (2 steps). (g) MeOTf (1.1 equiv), acetonitrile, 0 °C, 15 min. (h) KOH (4.5 equiv), MeOH, 254 nm, 25 °C. (i) AcOH, DCM, 12 h. (j) NaOH, (25 equiv), MeOH, 60 °C, 1.5 h, 52% (4 steps). (k) $BF_3{\cdot}Et_2O$ (10.0 equiv), $(Me_2SiH)_2O$ (5 equiv), DCM, −78 to 25 °C, 16 h, 66%. (l) Boc_2O (1.5 equiv), Et_3N (4 equiv), DCM, 25 °C, 3 h, then BzCl (2.0 equiv), $SnMe_2Cl_2$ (0.5 equiv), 5 min, 18a, 65%; 18b, 18%. (m) ABNO (0.05 equiv), dMeObpy (0.05 equiv), $Cu(MeCN)_4OTf$ (0.05equiv), NMI (0.10 equiv), O_2, acetonitrile, 0 °C, 40 min, 96%. (n) Isopropenyl bromide (13.0 equiv), *t*BuLi (26.0 equiv), Et_2O, −78 °C, 30 min, then 19 (1.0 equiv), −78 °C, 30 min, then NH_4Cl (15.0 equiv), H_2O. (o) TFA (10.0 equiv), *i*PrOH/H_2O (3:1), 60 °C, 50 min, 45% (2 steps). (p) $BnC(OMe)_3$ (5.0 equiv), (+)−CSA (0.2 equiv), DCM, 25 °C, 1.5 h, 72%. (q) TPP (0.02 equiv), O_2, white LED, CD_3CN, 10 °C, 40 min, then PPh_3 (1.2 equiv), 22a, 45%; 22b, 14%; recovered 21, 27%. (r) SmI_2 (2.0 equiv, 0.1 M in THF), THF, 25 °C, 5 min. (s) $P(OEt)_3$ (25.0 equiv), *t*BuOK (10.0 equiv), O_2, THF/*t*BuOH (3:1), 0 °C, 5 min, 23, 30% (2 steps); 22a, 34% (2 steps). (t) DBAD (2.6 equiv), homovanillic acid (2.6 equiv), PPh_3 (2.5 equiv), 0 to 25 °C, 1.5 h. 74%.