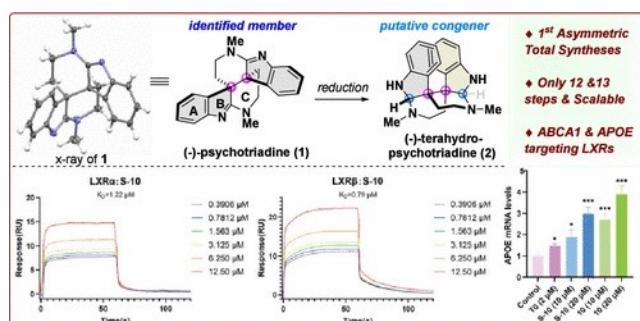


Asymmetric Total Synthesis of (–)-Psychotriadine Featuring [3,3]-Rearrangement and Stereo-Controllable Ring-Contraction

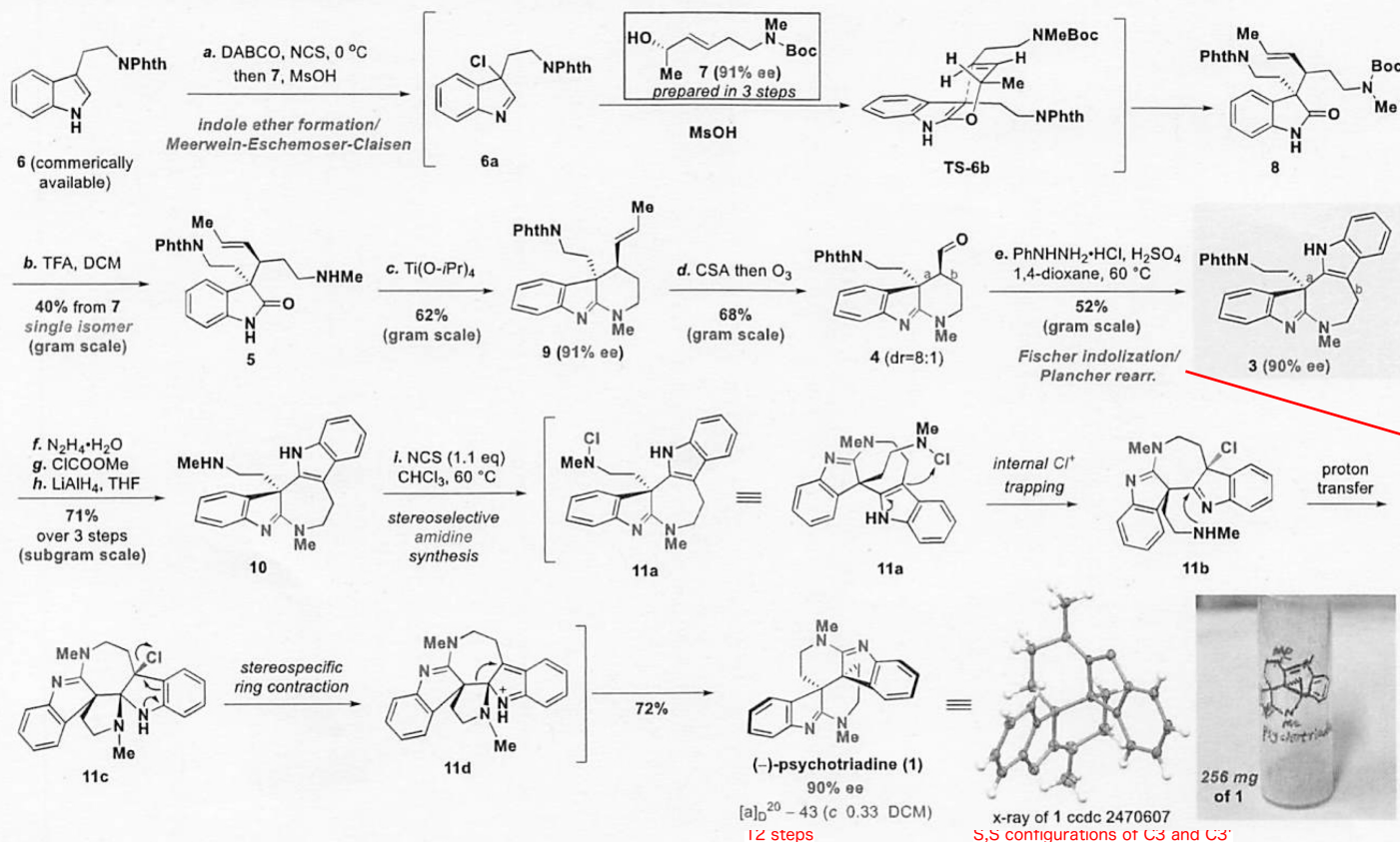
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bis(cyclooctriptyamine)

the C3-C3' connecting hydrolyzed bis-



Scheme 1. Enantioselective Total Synthesis of (–)-Psychotriadine (1)^a



^aReagents and conditions: (a) DABCO (1 equiv), NCS (1.8 equiv), DCM 0 °C, 2 h then 7 (1 equiv), MsOH (0.25 equiv), 0 to 25 °C, 24 h; (b) TFA:DCM = 1:10, 0 to 25 °C, 5 h, 40% over two steps; (c) Ti(O-*i*Pr)₄ (3.0 equiv), THF, 130 °C, 20 h, 62%; (d) CSA (2.5 equiv), DCM, –78 °C; then, O₃, 1 h, 68%; (e) PhNHNH₂·HCl (2.5 equiv), 1% H₂SO₄ in 1,4-dioxane, 60 °C, 12 h, 52%; (f) N₂H₄·H₂O (20 equiv), DCM:MeOH = 2:1, 0–25 °C, 4 h; (g) CICOOMe (1.2 equiv), DIPEA (1.5 equiv), DCM, 0 to 25 °C, 1 h; (h) LiAlH₄ (6.0 equiv), THF, 75 °C, 5 h, 71% over three steps; and (i) NCS (1.1 equiv), CHCl₃, 25 °C, 10 min, then 60 °C, 3 h, 72%.

Phth group was used in the enantioselective synthesis

Table 1. Selected Optimization Conditions for the Cascade Reaction^a

the mechanistic hypothesis

path a: interrupted Fischer indolization

path b: Fischer indolization/Plancher rearr.

only bond "a" migrated, due to the more electron-rich C3-carbon.

intermediates S-1U and 1U act as highly effective dual subtype agonists targeting

Entry	Conditions	Results ^a
1	PhNHNH ₂ ·HCl (5 eq), 1,4-dioxane, 80 °C, 2 days	13 ^b
2	PhNHNH ₂ , AcOH, 80 °C, 24 hrs	13 ^b
3	PhNHNH ₂ , eq. H ₂ SO ₄ (4% v/v); 1,4-dioxane=1:1, 80 °C	17 (14%)
4	PhNHNH ₂ , eq. H ₂ SO ₄ (4% v/v); 1,4-dioxane=1:1, 80 °C, 3 days	17 (21%) + 18 (16%)
5	PhNHNH ₂ , eq. H ₂ SO ₄ (10% v/v); 1,4-dioxane=1:1, 80 °C	17 (20%) + 18 (29%)
6	PhNHNH ₂ , eq. H ₂ SO ₄ (10% v/v); 1,4-dioxane=1:1, 80 to 100 °C	18 (29%)
7	PhNHNH ₂ , eq. H ₂ SO ₄ (2% v/v); 1,4-dioxane=1:1, 80 °C	17 (23%) + 18 (5%)
8	PhNHNH ₂ , eq. H ₂ SO ₄ (4% v/v); AcOH=1:1, 80 °C	17 (5%) + 18 (47%)
9	PhNHNH ₂ , eq. H ₂ SO ₄ (4% v/v); FIP=1:1, 80 °C	17 (12%) + 18 (15%)
10	PhNHNH ₂ , NPA-3Cy (1.0 eq), Tol, 80 °C, 2 days	18 (36%)
11	PhNHNH ₂ , HCl (3M); 1,4-dioxane=1:1, 70 to 75 °C, 24 h	18 (37%)
12	PhNHNH ₂ , BF ₃ ·OEt ₂ (10 equiv), THF, 60 °C	18 (56%)
13	PhNHNH ₂ , 1% H ₂ SO ₄ in 1,4-dioxane, 80 °C	18 (41%)

^aAll reactions were performed with compound 12 (20 mg, 0.049 mmol, 1 equiv) and PhNHNH₂ (12 μL, 0.122 mmol, 2.5 equiv) in solvent (2 mL) and acids indicated in the table entries for 20 h unless otherwise noted. ^bIsolated yield. ^cMonitored by TLC.

