Eschenmoser sulfide contraction

Biginelli reaction

Curtius rearrangement

Meerwein's salt



Total Synthesis of (±)-Saxitoxin

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A Stereospecific Total Synthesis of d,l-Saxitoxin

1. **B**, PTSA, PhMe, Δ 2. N₂H₄·H₂O, MeOH, Δ D, NaHCO₃ 3. P₄S₁₀, PhH, 80 °C CH₂Cl₂, Δ Eschenmosei sulfide contraction С KOH, MeOH, 50 °C 37% from A NH_2 1. N₂H₄·H₂O, MeOH Si(NCS)₄ 2. NOCI, CH₂CI₂, .OMe G, PhH 3. PhH, 90 °C then PhMe, 110 °C 4. NH₃, PhH 75% ŃΗ Curtius rearrangement Biginelli reaction 1. J, BF₃·OEt₂, MeCN 2. AcOH-TFA (9:1), 50 °C 1. NaHCO₃, Et₃OBF₄, CH₂Cl₂ 2. EtCO₂NH₄, 135 °C OBn 33% NH ŃΗ II S Κ L 4 steps HN CISO₂NCO НО HCO₂H̄, 5 °C ΗN 50%

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Significance: In 1977, Kishi and co-workers reported the first total synthesis of (±)-saxitoxin in 19 steps. Associated with paralytic shellfish poisoning, the potent neurotoxin was one of the most lethal non-protein substances known. The natural product features three contiguous stereocenters and a remarkably dense collection of heteroatoms with two quanidinium moieties in its tricyclic core.

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(±)-Saxitoxin

Comment: Vinylogous carbamate F was accessed in two steps from thionolactam **C** via Eschenmoser sulfide contraction. Bignelli reaction with silicon tetraisocyanate and subsequent Curtius rearrangement furnished tricyclic thiourea I. Deprotection of the thioketal and benzyl-ether in four steps from di-guanidine L gave rise to decarbamoylsaxitoxin M. Treatment with chlorosulfonyl isocyanate afforded the natural product.

ŃΗ NН

М

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