Total Synthesis of Azadirachtin: 22 Years to Harvest

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Total Synthesis

Natural-product synthesis:
• originated in the 1820’s when Friedrich Wöhler synthesized urea
• has generated serendipitous discoveries such as the first synthetic dye, mauveine, by William Perkin in 1856 while attempting to synthesize quinine

Has modern natural-products synthesis outgrown it’s usefulness?

Isolation of Azadirachtin

- *Azadirachta indica* (Neem Tree) is native to tropical and subtropical areas of India
- First isolated from the ethanolic extract of Neem seeds in 1968 by Morgan and coworkers

Biological Activity

- Initial biological studies by Morgan and coworkers found Azadiractin to completely inhibit feeding by the desert locust *Schistocerca gregaria* at 1 ng/cm².

- Further studies have revealed that azadirachtin exhibits potent antifeedant and growth-disruptant properties against a broad spectrum of insects yet low mammalian toxicity (LD₅₀ (rat) > 5 g/kg).

Structural Assignment

First complete structure of Azadirachtin by Nakanishi in 1975 using extensive NMR

Revised structure by Kraus in 1985 which proposed a C13-C14 epoxide

Structural Features

16 stereogenic centers

Hemi-acetal

Tetrasubstituted epoxide

Enol ether

7 tetrasubstituted carbon atoms
Retrosynthetic Question

Please take a few minutes to come up with a general retrosynthetic analysis.
Synthetic Endeavors


Ley’s Original Retrosynthetic Analysis

Coupling Reaction

Decalin Fragment

Pyran Fragment
Beginning – The Decalin Fragment

Synthesis of IMDA Precursor

4 possible diastereomers; please make a general prediction of the product ratio by transition state structure analysis of this simplified model.

IMDA Answer

Synthesis of Decalin Fragment

Formation of the Hemi-Acetal

Synthesis of Decalin Fragment

Coupling of Fragments

Ley’s Revised Retrosynthetic Analysis

Ley’s Revised Retrosynthetic Analysis


Formation of the Furan Ring

1. CH₂Cl₂/TFA/H₂O (20:1:1) rt, 99%
2. TBSCI, DMAP, DMF, NEt₃ rt, 90%

1. AlBN, nBu₃SnH toluene, 110 °C, 70%
2. CH₂Cl₂/TFA/H₂O (20:1:1) rt, 80%

1. O₃, CH₂Cl₂, -78 °C then PS-Ph₃, rt
2. TPAP NMO, CH₃CN, rt, 95%

1. CS₂, NaHMDS, -78 °C then Mel, -78 °C, 99%

1. SO₃ py, DMSO, iPr₂NEt CH₂Cl₂, 0 °C
2. tBuOK, Ph₃PCHBr₂Br THF, rt, 80%

Synthesis of Pyran Fragment

1. TMSBr, CH₂Cl₂, 0 °C, 82%
2. PMB TCA, La(OTf)₃, THF, rt, 90%

1. DIBAL-H, CH₂Cl₂, hexane, -78 °C
2. Amberlyst 15, MeOH, rt, 70%, 1:1 (α : β)

1. MeLi LiBr, THF, -78 - 0 °C, 80%
2. iPrMgCl, (CH₂O)ₙ, THF, 45 °C, 80%
3. Ms₂O, iPr₂NEt, CH₂Cl₂, 0 °C, 90%

Coupling of Fragments and Key Intramolecular Claisen

Radical Cyclization

1. TBS-imidazole
   DMF, 100 °C 90%

2. DDQ
   CH₂Cl₂, H₂O, rt, 85%

3. CS₂, NaHMDS
   THF, -78 °C
   then MeI, -78 °C, 60%

Bu₃SnH, AIBN
toluene [0.02], 100 °C
80%

Epoxidation / End-Game


Summary of Synthesis

- Intramolecular Diels-Alder reaction
- Intramolecular Claisen rearrangement
- Intramolecular radical cyclization
Summary and Comments

• 0.00015% Overall Yield
• 71 Synthetic Steps
• 48 Step longest linear sequence
• More than 35 co-workers
• Interesting Chemical Reactions:
  • Intramolecular (IM) Diels-Alder reaction
  • IM Claisen rearrangement
  • IM radical cyclization

Was new synthetic technology reaped over the course of the 22 year synthesis?

Do elegant syntheses have aesthetic and monetary value?

www.scripps.edu/chem/baran/html/home.html