Enantioselective Total Synthesis of Hyperforin

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Hyperforin
Polycyclic Polypropenylated Acylphloroglucinol (PPAP) Natural Products

- Bicyclo[3.3.1]nonanone core
  - Highly oxygenated
  - Dense prenyl and/or geranyl side chain substitution
- Biological activity
  - Antimicrobial
  - Antidepressant
  - Antioxidant
  - Cytotoxic
  - Anti-HIV

Isolation and Structural Confirmation

- First isolated in 1971 from St. John’s Wort (Hypericum perforatum)
- Characterized by NMR and X-ray
- Relative and absolute stereochemistry determined by an X-ray crystal structure of the 3,5-dinitrobenzoate ester

Antibiotiki 1971, 16, 510.
Biological Activity and Stability

• Constituent of St. John’s Wort responsible for antidepressant activities
  – Blocks reuptake of neurotransmitters
  – Possible MOA: selective activation of TRPC6 (classical transient receptor potential protein)
  – Possible treatment of depression and other diseases

• Therapeutic potential limited
  – Poor water solubility
  – Facile oxidation when exposed to light and air
  – Potent activation of pregnane X receptor
  – Limited ability to manipulate isolated material (semisynthetic analogs)

Biological Activity:
Komplementmed. 2009, 16, 146.
FASEB J. 2007, 21, 4101.

Stability:
Phytochemistry 1998, 49, 1305.
Structural Modification of Hyperforin

\[ R = \]
- Me, 65%
- 2,4-(NO₂)₂Ph, 58%
- (2,4,6)-(OMe)₃Ph, 81%

10-fold or greater decrease in the inhibition of neurotransmitter reuptake

\[ J. \text{Nat. Prod.} \ 2002, \text{65}, \ 433 \]
Structural Modification of Hyperforin Cont.

- Increased solubility
- Stable in solution for a week (DMSO and H₂O)
- Aristoforin: anti-tumor activity *in-vitro* and *in-vivo*

ChemBioChem 2005, 6, 171
Synthesis of ent-hyperforin

- Allylic oxidation
- RCM
- Claisen rearrangement

51 steps from propargyl bromide!!!

Bio-synthesis

Phytochemistry 2005, 66, 139.
Phytochemistry 2007, 68, 1038.
Title Paper: Retrosynthetic analysis

Hyperforin vs. title paper
Title Paper: Synthesis of Coupling Partners

\[ \text{geraniol} \xrightarrow{\text{Ti(Oi-Pr)}_4, \text{L-DET}, \text{TBHP}} \xrightarrow{\text{CH}_2\text{Cl}_2, 92\%, 91\% \text{ ee}} \xrightarrow{1. \text{MsCl, NEt}_3, \text{CH}_2\text{Cl}_2, 91\% \text{ over two steps}} \xrightarrow{2. \text{LiBr, acetone}} \xrightarrow{91\% \text{ ee}} \xrightarrow{1. \text{Hg(OAc)}_2, \text{THF, H}_2\text{O}; 3\text{M NaOH}; \text{NaBH}_4, 3\text{M NaOH}} \xrightarrow{2. \text{TESCl, imidazole, DMF}} \xrightarrow{88\% \text{ over two steps}} \text{TESO} \xrightarrow{\text{Br}} \]
Title Paper: Synthesis of Bicyclic Core

prostereogenic  diastereotopic

Lewis acid

favored
disfavored

only product observed
not
Title Paper: Functionalization of the Core

1. BrBMe₂, NEt₃, CH₂Cl₂; NEt₃, NaHCO₃, H₂O
2. LiTMP, THF
55% over two steps

1. LiTMP, TMSCl, THF
2. LiTMP, i-PrC(O)CN, THF
44% over two steps

1. LiTMP, TMSCl, THF
2. LiTMP, i-PrC(O)CN, THF

44% over two steps

p-TsOH in AcOH
μwave, Toluene
65%
Title Paper: Completion of the Synthesis

- **Enantioselective total synthesis**
  - 18 steps longest linear sequence from geraniol
  - Highly scalable: 40 mg of Hyperforin prepared at publication
  - Key step: Latent symmetry elements to set two quaternary stereocenters and access the bicyclic core

- **Modular route**
  - Diverse analog synthesis *in-progress*
  - New analogs will be tested to probe mechanism(s) of bioactivity