Total Synthesis of (−)-Calyciphylline N

Artem Shvartsbart and Amos B. Smith, III J. Am. Chem. Soc.,
DOI: 10.1021/ja411539w

(-)-Calyciphylline N (1)

Current literature
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16.01.2014
About (-)-Calyciphylline N (1)

- Isolated from the leaves and stems of *Daphniphyllum calycinum* in 2008.
- The biological activity has not been investigated.
- **Structural features:**
  - six contiguous stereogenic centers, three of which are quaternary bridgehead, a fused A ring *dihydropyrrole*, and a DEF *decahydrocyclopentazulene* ring system surrounding a central bicyclo[2.2.2]octane BC core.

Retrosynthesis

(-)-Calyciphylline N (1)

1,4-reduction

Tamao-Kumada oxidation

condensation

cyclopentenone annulation

IMDA

EtOOC

SiMe₂Ph

Retrosynthesis
Synthesis of silyl ether 10 from silyl acrylate 7

Installation of the C1 ketone

1. LAH, 94%
2. I₂, PPh₃, imidazole, 85%

1. NaCN, DMSO
2. DIBAL-H, DCM
91% for two steps

NaBH₄, EtOH 99%

m-CPBA, NaHCO₃, DCM, 70%

1. PPTS, DCM, 0 °C
2. DMP, NaHCO₃, DCM, 0 °C, 67%

Sml₂, THF/MeOH 82%

TBSCl, imidazole
DMF, 0 °C, 97%
Construction of ring D

1. LDA, MeCHO, THF, -78 °C
2. DMP, NaHCO₃, DCM, 0 °C
91% for two steps

(+)-17 → (+)-18

(+)-17 → (+)-18

OAc

NaH, Pd(PPh₃)₄

THF, 95%

(-)-19

P-TsOH, MeOH

92%

(-)-19 → (-)-20

I₂, PPh₃, imidazole, THF, 97%

(-)-19 → (-)-21

LDA, THF, -20 °C, 77%

confirmed by X-ray analysis

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(-)-19 → (-)-21

LDA, THF, -20 °C, 77%

confirmed by X-ray analysis

(+)-4

(+)-4
1. 9-BBN; then NaOH, H₂O₂ 71%
2. TBSCl, imidazole, DMF, 0 °C 94%

Phthalimide, PPh₃, DEAD
THF, 0 °C, 99%

KHMDH, PhN(Tf)₂
THF, -78 °C, 73%

Pd(PPh₃)₄, LiCl, CO
DMF, 90 °C 97%

Stille carbonylation

Nazarov cyclization and protodesilylation
(+)-27 → KF, m-CPBA, DMF, 74% → Fleming-Tamao oxidation → (+)-28

(+)-28 → TESCl, imidazole, DMF, 0 °C, 83% → (+)-29

(+)-29 → i-Pr₂NEt, MOMBr, DCE, 80 °C, 88% → (+)-30

(+)-30 → IBX, DMSO, 95% → (+)-31

(+)-31 → \( \text{O}_2\text{CHCF}_3 \), \( \text{Bn}_2\text{NH}_2 \) → PhH, 50 °C, 69% → (+)-32

(+)-32 → AcOH, NaCN, \( \text{MnO}_2 \), MeOH, 82% → (+)-2
1. N$_2$H$_4$ H$_2$O, EtOH
2. aq. NH$_4$Cl, EtOH, 70 °C, 73%

(-)-2

H$_2$ (900 psi)
[(cod)(py)(PCy$_3$)]IrBARF
DCE, 25 °C, 16 h, 84% dr =4:1

1, 4-reduction

(+)-2

(-)-33

PhthN

COOMe

MOMO

PhthN

COOMe

MOMO

(-)-34

COOMe

MOMO

Ph$_2$BBr

DCM, 79%

(-)-Calyciphylline N (1)
Summary

• The first total synthesis of a member of the calyciphylline alkaloids, (−)-calyciphylline N (1), has been achieved with a longest linear sequence of 37 steps from known alcohol (−)-8.

• Highlights of the synthesis include:
  • a Et₂AlCl-promoted, highly stereoselective, substrate-controlled intramolecular Diels–Alder reaction;
  • a transannular enolate alkylation;
  • an effective Stille carbonylation/Nazarov cyclization sequence;
  • a high-risk diastereoselective hydrogenation of a fully substituted conjugated diene ester.