Asymmetric Total Synthesis of (−)-Scabronine G via Intramolecular Double Michael Reaction and Prins Cyclization

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Current Literature
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Sarcodon scabrosus is a mushroom belonging to the family Thelephoraceae and has a strongly bitter taste. It is a widely distributed species in Europe and in North America.

Scabronine G was isolated by Ohta and co-workers in 2001 and is shown to enhance the secretion of neurotrophic factors from 1321N1 human astrocytoma cells.

Scabronine G and their methyl ester are useful drugs to clarify the mechanisms underlying the synthesis and secretion of neurotrophic factors.

(−)-Scabronine G

• Cyathane diterpene natural product
• tricyclic 5-6-7 ring system
• trans- fused 6-7 ring
• angular C-17 carboxyl group
Previous total synthesis (−)-Scabronine G

Previous total synthesis (−)-Scabronine G

Previous total synthesis (−)-Scabronine G

\[
\text{MeO}_2\text{C} \quad \text{H} \quad \text{MeO}_2\text{C} \\
i) \text{NaH, HCO}_2\text{Me, DME, 97%} \\
\text{ii) } n-\text{PrSH, TsOH, benzene, 50 °C, 93%} \\
\]

\[
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{H} \quad \text{H} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{SPr} \quad \text{SPr} \\
\text{O} \quad \text{O} \\
\text{HgCl}_2, \text{HCl/MeCN, 80 °C, 86% over two steps} \\
\]

\[
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{H} \quad \text{H} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{SPr} \quad \text{SPr} \\
\text{O} \quad \text{O} \\
\text{DBU, benzene, 75 °C, quant.} \\
\]

\[
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{H} \quad \text{H} \\
\text{MeO}_2\text{C} \quad \text{MeO}_2\text{C} \\
\text{SPr} \quad \text{SPr} \\
\text{O} \quad \text{O} \\
\text{Methyl-(−)-Scabronine G} \\
\]

\[
\text{i) } \text{TsOH, HO(CH}_2\text{)_2OH, benzene, 89%} \\
\text{ii) aq. NaOH, MeOH, 55 °C, then HCl, 87%} \\
\]

\[
\text{HO}_2\text{C} \quad \text{HO}_2\text{C} \\
\text{H} \quad \text{H} \\
\text{HO}_2\text{C} \quad \text{HO}_2\text{C} \\
\text{SPr} \quad \text{SPr} \\
\text{O} \quad \text{O} \\
\]

9.6% after 20 steps,

Total synthesis (−)-Scabronine G

N. Kanoh and co-workers *Org. Lett.* 2011, ASAP
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Summary

- (-)-Scabronine G was synthesized in 29 steps in 3.2%
- Key transformations include selective Diels-Alder cyclization and Prins cyclization