

SILYLMETHYL RADICAL CYCLIZATION IN THEOPEDERINS SYNTHESIS --- A NEW ACCESS TO PEDERIC ACID[#]

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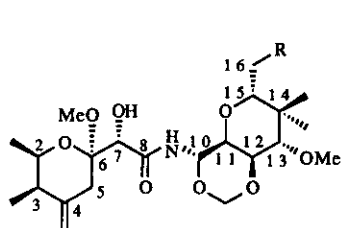
Abstract--Silylmethyl radical cyclization of the silyl ether (6) provided the 2-silatetrahydropyran derivative (7) possessing the correct C2, C3 and C7 stereochemistries of theopederins (1) and functionalities suitable for further elaboration.

Theopederins A-E (1),¹ mycalamides,² and onnamide A³ have been recently isolated from marine sponges. These compounds are very potent antiviral agents, and have been shown to have promising antitumor activity. They also show a striking structural resemblance to pederin (2),⁴ a potent insect toxin. Each contains the pederic acid as a subunit (8) which may play an important role in the origin of their biological properties.

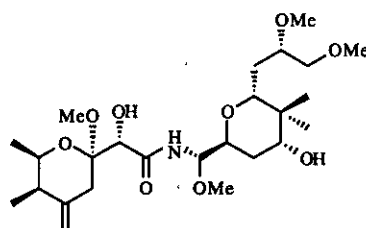
In our first contribution to this area, we describe an approach based upon a silylmethyl radical cyclization strategy.

In order to explore the feasibility of the designed synthetic strategy, the requisite silyl ether (6) for the radical cyclization was prepared as described below. The synthesis of 6 began with

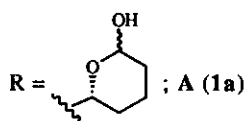
[#]Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.



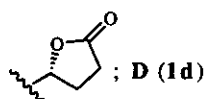
Theopederins A-E (1)



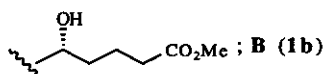
Pederin (2)



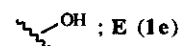
R = ; A (1a)



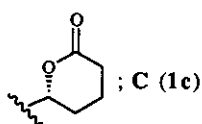
; D (1d)



; B (1b)



; E (1e)

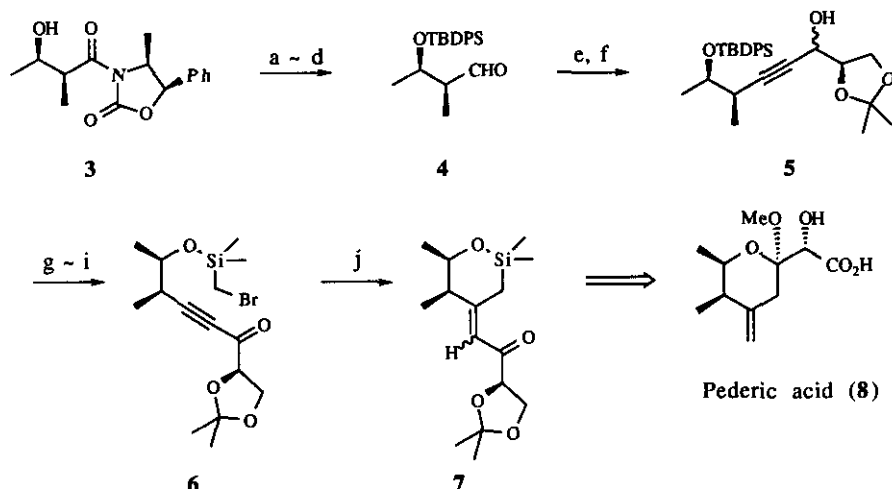


; C (1c)

protection of the Evans aldol adduct (3).^{5,6} Removal of the chiral auxiliary [1, LiOBn, THF, 0 °C; 2, DIBAH, CH₂Cl₂, -78 °C → 0 °C] and subsequent Parikh modified Moffatt oxidation⁷ of the hydroxyl group afforded the aldehyde (4),⁶ which was converted into the acetylenic alcohol (5)⁶ as a 1 : 1 diastereomeric mixture at carbinol carbon by a two-step sequence [1, CBr₄, Ph₃P, Zn dust, CH₂Cl₂; 2, ⁿBuLi (2.5 eq.), THF, -78 °C, then 2,3-*O*-isopropylidene-D-glyceraldehyde, -78 °C → 0 °C].⁸ Consecutive deprotection with ⁿBu₄N⁺F⁻, MnO₂ oxidation and silyl etherification [(bromomethyl)chlorodimethylsilane, Et₃N, CH₂Cl₂] provided 6.⁶

All systems were now ready for the all-important regioselective introduction of a carbon unit. An intramolecular radical cyclization reaction⁹ was finally performed in C₆H₆ under reflux in the presence of tris(trimethylsilyl)silane¹⁰ and AIBN to furnish the enone (7)⁶ possessing the correct C2, C3 and C7 stereochemistries of theopederins (1) and functionalities suitable for further elaboration.

Scheme



Reagents and conditions: a, TBDPSCl, imidazole, DMF, 77%, b, LiOBn, THF, 0 °C, 44%, c, DIBALH, CH₂Cl₂, -78 °C→0 °C, 80%, d, SO₃·Py, DMSO, Et₃N, 93%, e, CBr₄, Ph₃P, Zn dust, CH₂Cl₂, 87%, f, ⁿBuLi (2.5 eq.), THF, -78 °C; 2,3-*O*-isopropylidene-D-glyceraldehyde, -78 °C→0 °C, g, ⁿBu₄N⁺F⁻, THF, 53% for 2 steps, h, MnO₂, CH₂Cl₂, 78%, i, BrCH₂Si(Me)₂Cl, Et₃N, CH₂Cl₂, 42%, j, (Me₃Si)₃SiH, AIBN, C₆H₆, reflux, 36%.

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