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 A[3] 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

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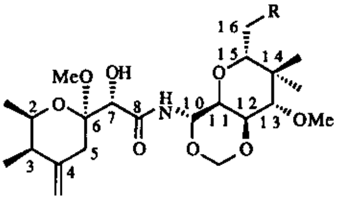
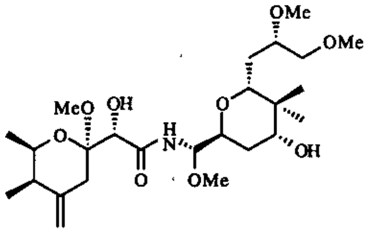
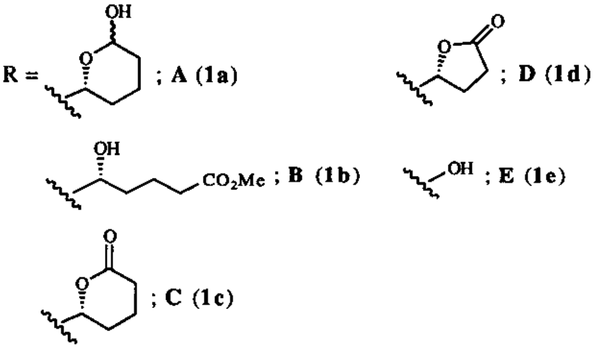
#Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.



Theopederins A~E (**1**)



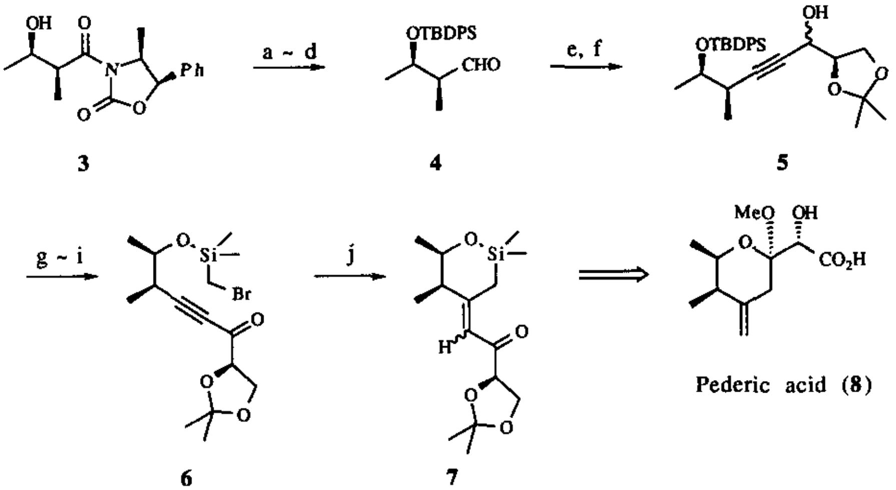
Pederin (**2**)



protection of the Evans aldol adduct (**3**).[5,6] Removal of the chiral auxiliary [1, LiOBn, THF, 0 °C; 2, DIBAH, CH_2Cl_2, -78 °C → 0 °C] and subsequent Parikh modified Moffatt oxidation[7] 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, CBr_4, Ph_3P, Zn dust, CH_2Cl_2; 2, ^nBuLi (2.5 eq.), THF, -78 °C, then 2,3-*O*-isopropylidene-D-glyceraldehyde, -78 °C → 0 °C].[8] Consecutive deprotection with $^nBu_4N^+F^-$, MnO_2 oxidation and silyl etherification [(bromomethyl)chlorodimethylsilane, Et_3N, CH_2Cl_2] provided **6**.[6]

All systems were now ready for the all-important regioselective introduction of a carbon unit. An intramolecular radical cyclization reaction[9] was finally performed in C_6H_6 under reflux in the presence of tris(trimethylsilyl)silane[10] 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, DIBAH, CH_2Cl_2, -78 °C→0 °C, 80%, d, SO_3·Py, DMSO, Et_3N, 93%, e, CBr_4, Ph_3P, Zn dust, CH_2Cl_2, 87%, f, ^nBuLi (2.5 eq.), THF, -78 °C; 2,3-*O*-isopropylidene-D-glyceraldehyde, -78 °C→0 °C, g, $^nBu_4N^+F^-$, THF, 53% for 2 steps, h, MnO_2, CH_2Cl_2, 78%, i, $BrCH_2Si(Me)_2Cl$, Et_3N, CH_2Cl_2, 42%, j, $(Me_3Si)_3SiH$, AIBN, C_6H_6, reflux, 36%.

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