Asymmetric Synthesis and Its Applications: Towards the Synthesis of Bryostatin 1

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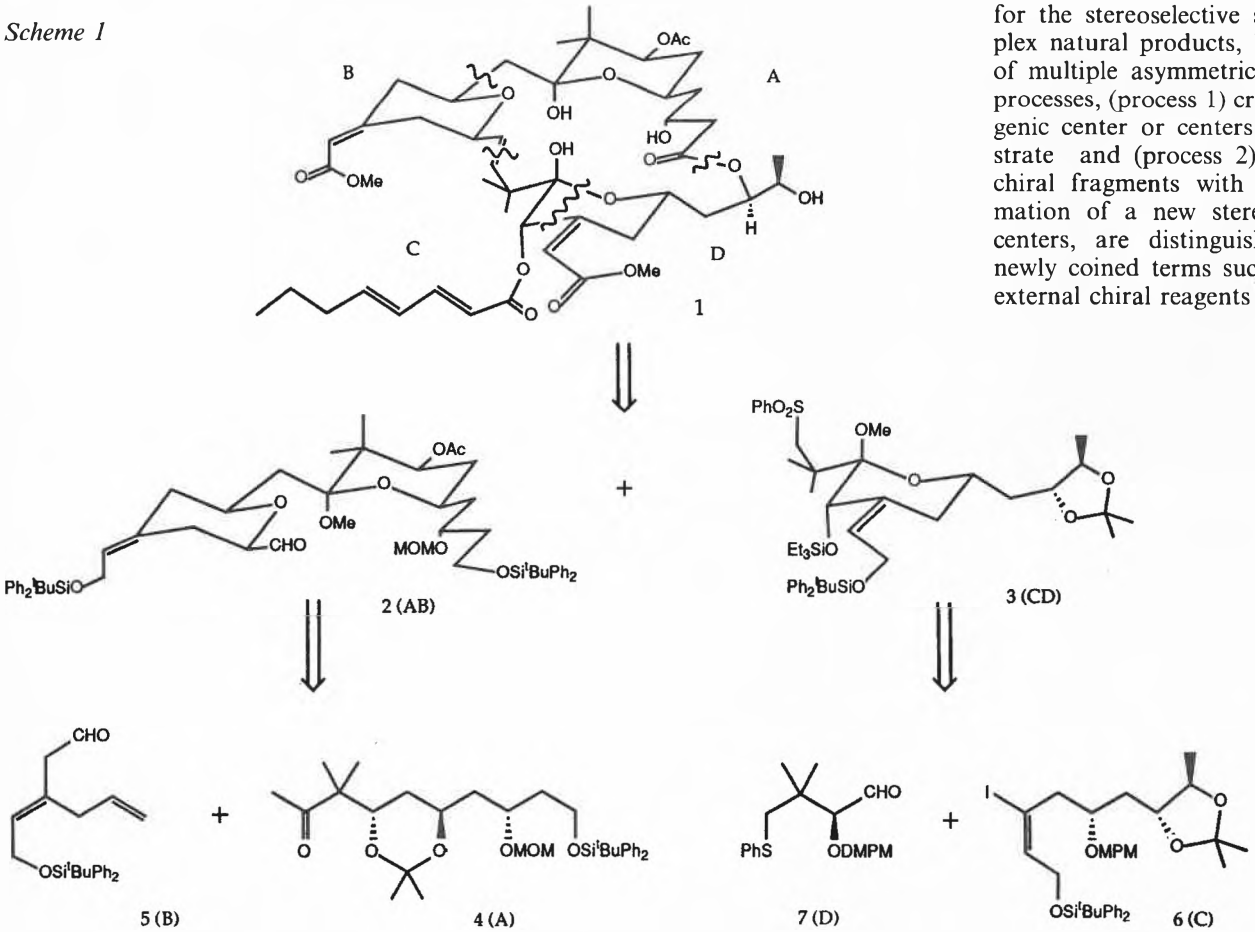
Scheme 1



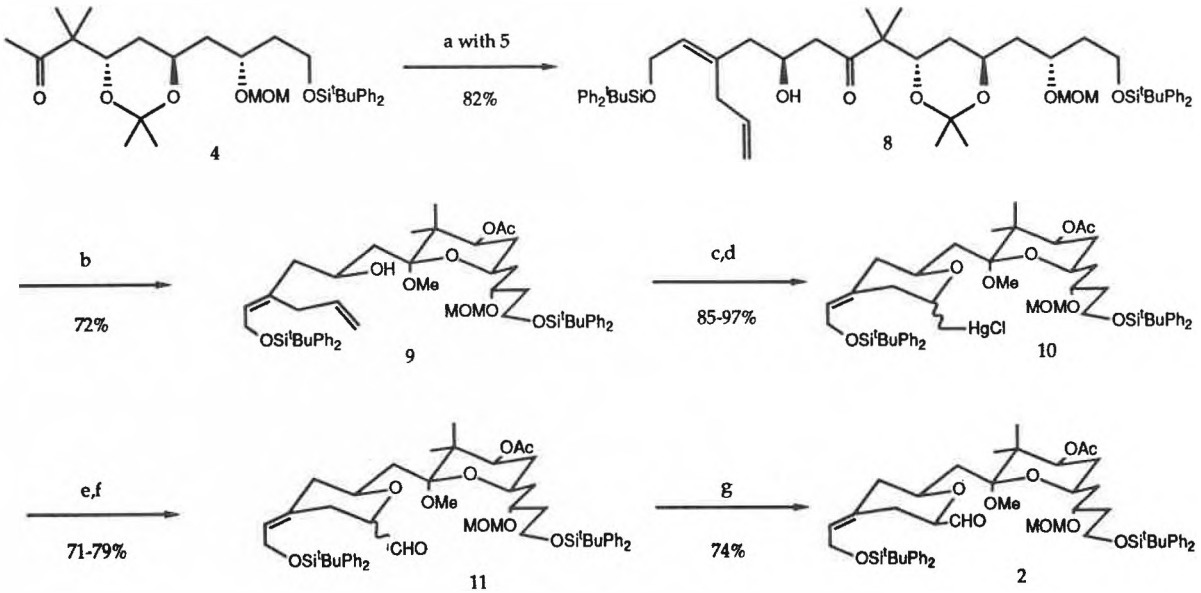
The lecture begins with a brief introduction that outlines our general strategy for the stereoselective synthesis of complex natural products, based on the rule of multiple asymmetric synthesis[1]. Two processes, (process 1) creation of a stereogenic center or centers on a chiral substrate and (process 2) coupling of two chiral fragments with concomitant formation of a new stereogenic center or centers, are distinguished, and several newly coined terms such as internal and external chiral reagents are defined. Then

follows a critical evaluation of reagents recently developed to effect asymmetric aldol reaction and allyl- and crotylboration, perhaps the two most important carbon-carbon bond forming reactions in the synthesis of polyketide-type natural products. Special emphasis will be placed on the newly discovered mechanistic and synthetic aspects of (*R*)- or (*S*)-2-trimethylsilylborolane-mediated reactions.

The latter half of the lecture concerns the application of these reactions as illustrated in the synthetic route toward bryostatin 1, (**1**) $C_{47}H_{68}O_{17}$, a marine natural product isolated in minute quantities from *Bulgula neritine* [2]. A retrosynthesis of **1** provides fragments AB (**2**) and CD (**3**), both of which are further dissected [AB → A(**4**) + B(**5**); CD → C(**6**) + D(**7**)] as shown in Scheme 1. Syntheses of fragments A, B, C, and D (mainly involving process 1) proceeded satisfactorily to meet today's standards for a stereoselectivity of > 20:1. The assembly of these fragments, however, has been a challenging task [see Scheme 2 (A + B → AB), Scheme 3 (C + D → CD), and Scheme 4 (AB + CD → ABCD → **1**)]. The stereoselectivities attained thus far for conversions **4** to **8** and **6** to **12** are of the order of 6:1 to 10:1 and new design of external chiral reagents is highly desirable for these reactions (process 2). While further efforts are being made to solve the fundamental problem of process 2, the project has now entered its final stages (Scheme 4). Hopefully, macrolactonization of the seco-acid will be achieved in time for presentation.

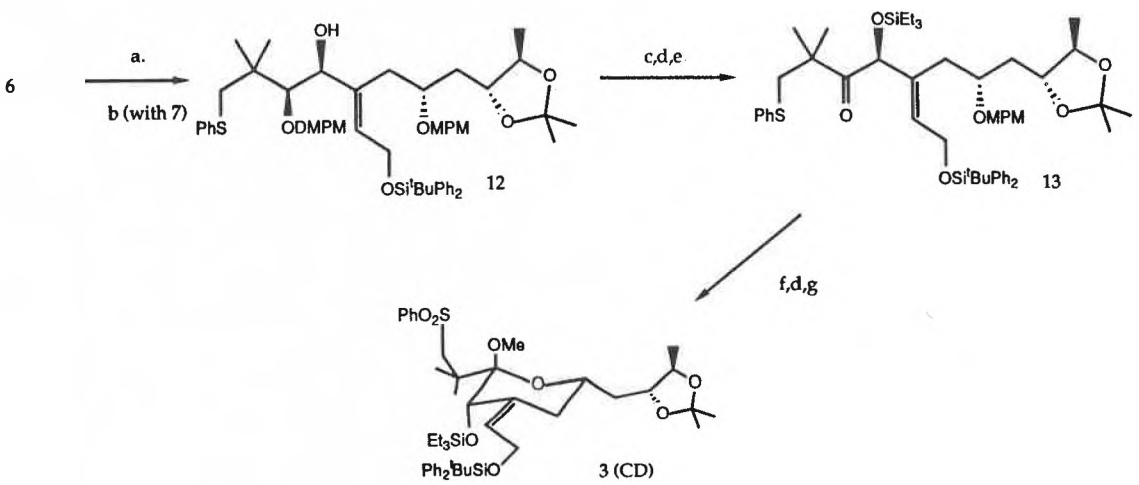
[1] S. Masamune, W. Choy, J.S. Petersen, L.R. Sita, *Angew. Chem. 97* (1985) 1; *Angew. Chem. Int. Ed. Engl. 24* (1985) 1.
[2] G.R. Pettit et al., *J. Am. Chem. Soc. 104* (1982) 6846.

Scheme 2



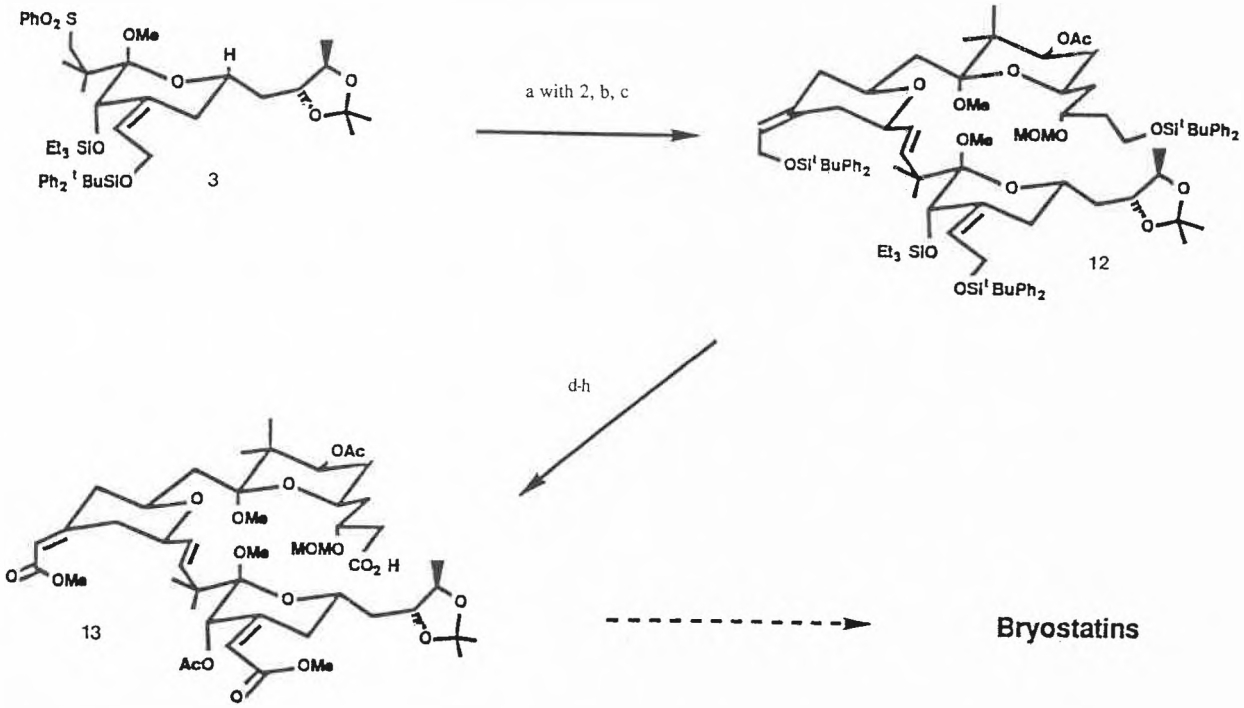
a) 2 eq. (R,R)-2,5-dimethylborolanyl trifluoromethanesulfonate, 4 eq. diisopropylethylamine, ether, -78°C; (b) $HC(OCH_3)_3$, methanol, PPTS, 25°C; (c) $Hg(OAc)_2$, THF / methanol, 25°C; 50% KCl; (d) AcCl, pyridine, 0°C; (e) $NaBH_4$, O_2, CH_2Cl_2 / DMF; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; (g) Al_2O_3, benzene, 25°C.

Scheme 3



(a) t-BuLi, CuCN, ether, -78°C; (b) 1.0 eq. 7; (c) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (d) 1.2 eq DDQ, 20:1 CH_2Cl_2 / H_2O, 0°C; (e) DMSO, Ac_2O, 25°C; (f) MoO_5•HMPA•H_2O, CH_2Cl_2; (g) TMSOTf, TMSOMe, CH_2Cl_2, -60°C.

Scheme 4



(a) PhLi, then 2; (b) Ac_2O; (c) Na(Hg); (d) Bu_4NF; (e) $ClSi^tBuPh_2$; (f) Ac_2O; (g) MnO_2, NaCN, MeOH; (h) PDC.