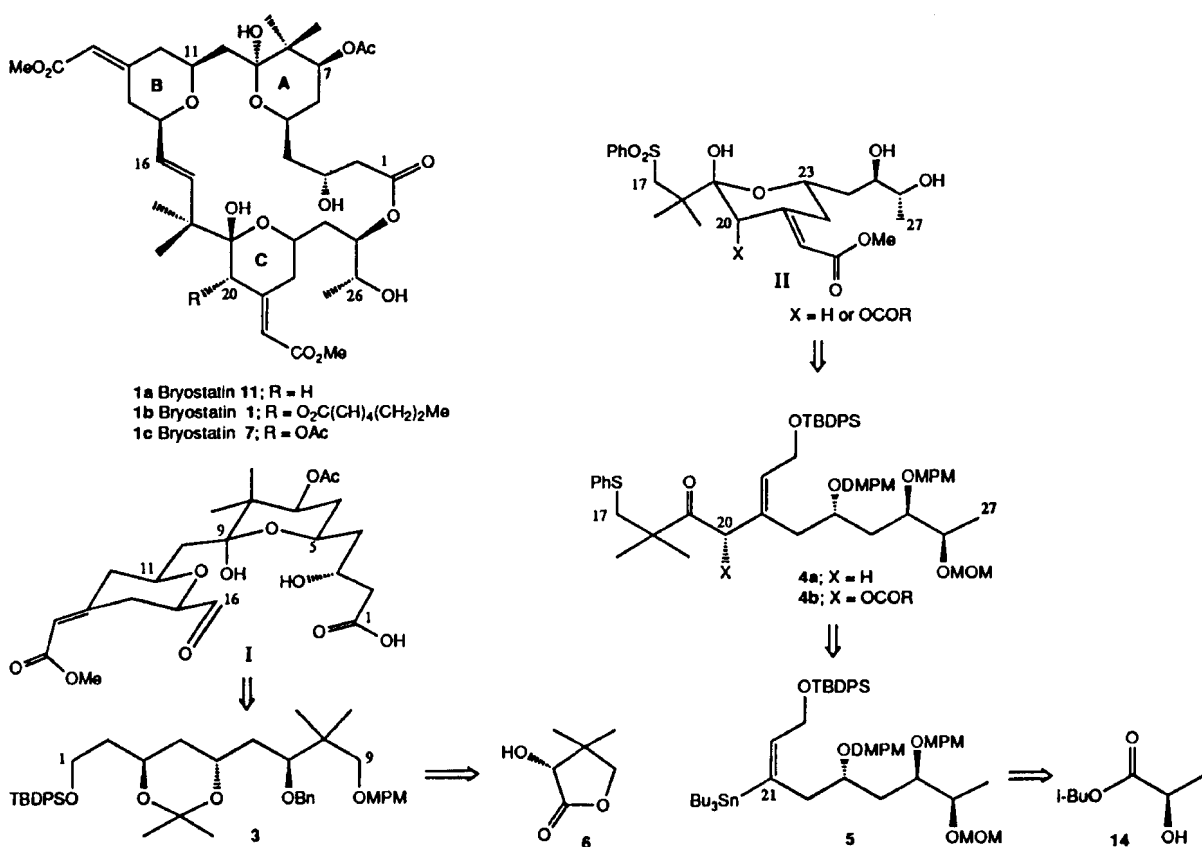# Towards the asymmetric synthesis of bryostatin 1

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Abstract : The construction of the fragments C_1-C_9 **3** and C_{17}-C_{27} **4a** of the bryostatins in a enantioselective and highly diastereoselective fashion is described. The usefulness of the "chiron" approach is illustrated with the synthesis of these fragments from respectively D-pantolactone (**6**) and D-isobutyl lactate (**14**) as chiral templates.

The bryostatins have been isolated from the marine *Bryozoan Bugula* neritina and constitute a family of some 17 related macrocyclic lactones based on a polyacetate derived backbone[1]. Except for three C_{20} deoxy analogues they differ in the nature of the ester functions at C_7 and C_{20}. Bryostatin 1 (**1b**) possesses antineoplastic activity against lymphocytic leukemia and ovarian carcinoma[2]. Next to the first completed total synthesis of **1c**, by Masamune et al.[3], other groups have described the synthesis of fragments of the basic 20-membered ring lactone[4].


Scheme 1

This paper describes out efforts towards the synthesis of the advanced intermediates **3** and **4a** of bryostatin 11 (**1a**) and illustrates the usefulness of the "chiron"[5] approach combined with the power of single asymmetric induction[6]. Our retrosynthetic analysis is outlined in Scheme 1. Disconnection of the

C_{16}-C_{17} bond gave subunits I and II; the final step for assembling the skeleton will involve double bond formation *via* a Julia-Lythgoe reaction.[3,7] We plan to construct the northern-eastern part I *via* 3 and a C_{11}-C_{16} fragment and to connect them *via* a keto-phosphonate thus providing C_{10}. We have already reported on the synthesis of the tetrahydropyran ring B (C_{11}-C_{16}) and on a model study for joining rings A and B.[6a] The strategy for the construction of the southern fragment II (C_{17}-C_{27}) centers around disconnection of the C_{20}-C_{21} bond. The formation of this bond, *via* 5 and using Pier's[8] conjugate organostannyl cuprate addition method, provides control for the E-geometry of the double bond. Furthermore this strategy carries the potential for the synthesis of both the 20-desoxy and 20-oxy series.

Synthesis of the C_1-C_9 fragment 3 (Scheme 2)

Our second and succesfull approach involves the creation of C_3 as a new stereogenic center during diastereoselective reduction of β-hydroxy ketone 12. Moreover, it was anticipated that aldol reaction involving 11 and chiral β-alkoxy-aldehyde 10, could induce chirality at C_5.

Scheme 2
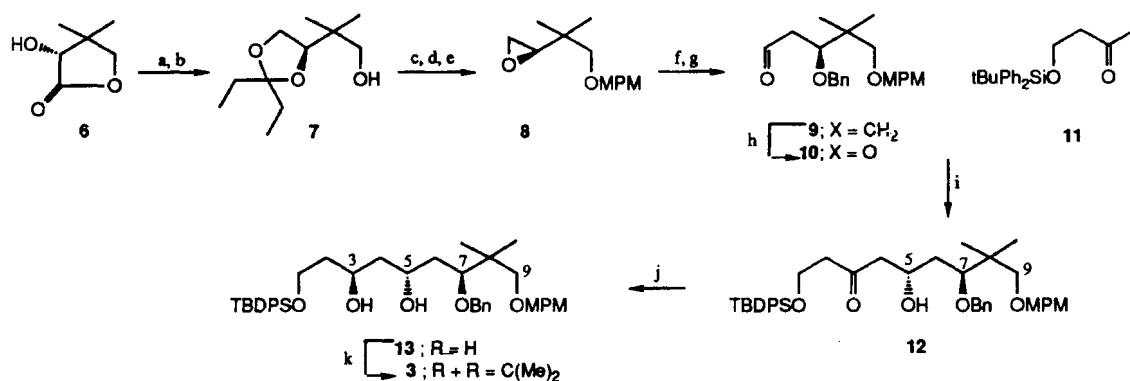
(a) LiAlH$_4$, THF, 0°C, reflux, 5 h, r.t.; (b) 3-pentanone, PTSA, THF, reflux, 5 h (81 %, two steps); (c) t-BuOK, THF, then MPMCl, r.t., 12 h (94 %); (d) 10 % HCl-THF, r.t., 5 h (92 %); (e) NaH, DMF-THF, r.t., 4 h, then tosylimidazole, r.t., 2 h (92 %); (f) (CH$_2$=CH)$_2$CuCNLi, Et$_2$O, 0°C, 30 min (84 %); (g) t-BuOK, THF, then BnBr, r.t., 12 h (96 %); (h) *i*) OsO$_4$, NMO, H$_2$O-THF, r.t., 5 h; *ii*) Pb(OAc)$_4$, toluene, pyridine, r.t., 10 min (90 %, two steps); (i) LDA, THF, -78°C, 5 min, then 18, -78°C, 5 min then 17 (77 %); (j) LiAl(Ot.Bu)$_3$H, LiI, Et$_2$O, -78°C, (90 %); (k) Me$_2$C(OMe)$_2$, Amberlyst-15, CH$_2$Cl$_2$, r.t., 30 min (94 %).

D-pantolactone (6) was selected as chiral template for the synthesis of 10 by virtue of the correct stereogenic C_7 flanked by a *gem*-dimethyl group. Aldol condensation between 10 and 11 led exclusively to the *anti*-diastereoisomer 12 as expected on the basis of a Cram-type transition state, involving β-chelation of the lithium cation with the benzyl ether oxygen atom[9].

We faced the formation of the C_3-stereogenic center with some confidence because stereoselective reduction of β-hydroxy ketones is well-documented. However, selection of an appropriate *anti*-selective β-hydroxy ketone reducing agent proved to be very troublesome. It is remarkable that reduction with the Saksena-Evans reagent[10], known to be highly *anti*-selective, showed no selectivity. Only tri-t-butoxy-aluminum hydride in the presence of lithium iodide[11], finally induced a 17.6:1 ratio in favour of 13; this only when the reaction proceeded at -78°C.

The formation of this fully identified fragment 3 in 89 % d.e. and 27 % overall yield compares favourably with other described procedures[3,4].

Synthesis of C_{17}-C_{27} fragment 4a (Schemes 3 and 4)

The strategy for the synthesis of fragment 4a, a fully protected open form of the southern hemi-acetal I, has already been outlined in Scheme 1. The starting material for 5 (C_{21}-C_{27}) is D-isobutyl lactate which is, in contrast to the ethyl or methyl ester of unnatural D lactic acid, pricewize a reasonable chiral building block[12] (Scheme 3).
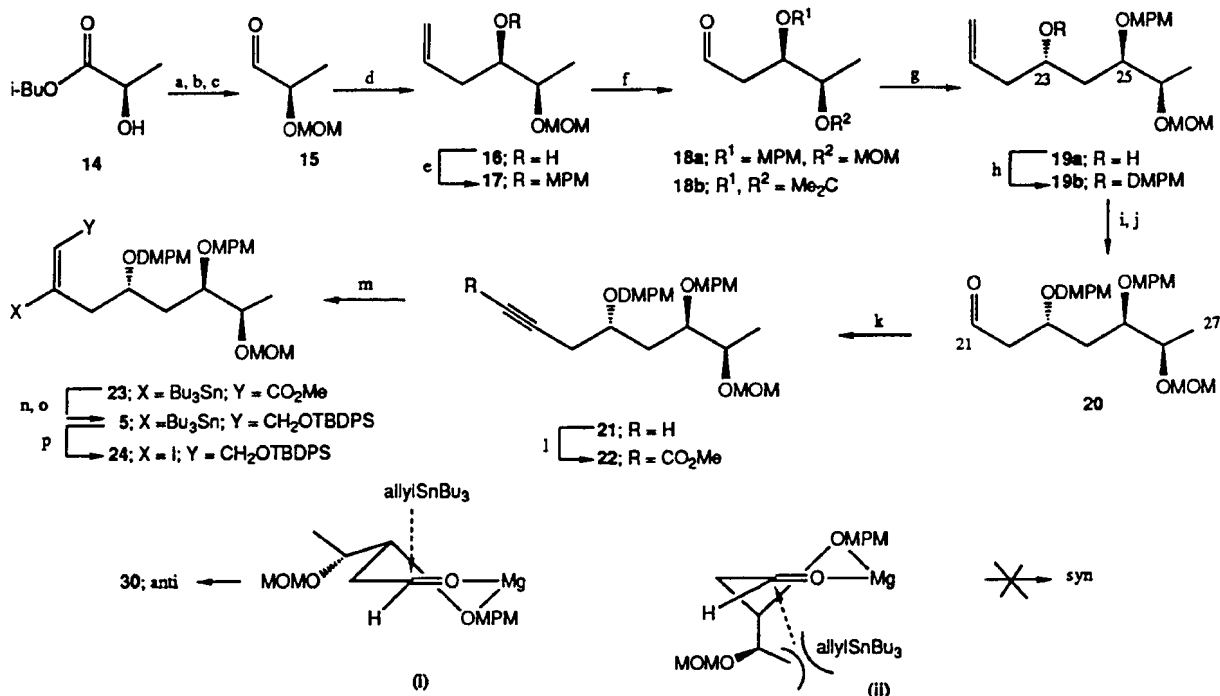
(a) MOMCl, DiPEA, CH_2Cl_2 (92 %); (b) $LiAlH_4$, THF; $Na_2SO_4.10H_2O$ (83 %); (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78°C; (d) allylSnBu$_3$, $MgBr_2.Et_2O$, CH_2Cl_2, -78°C → 0°C (60 % from 14); (e) t-BuOK, MPMCl, THF (69 %); (f) OsO_4, $NaIO_4$, THF, H_2O (70 %); (g) allylSnBu$_3$, $MgBr_2.Et_2O$, CH_2Cl_2, -78°C → 0°C (97 %); (h) t-BuOK, DMPMBr, THF (79 %); (i) OsO_4, NMO, acetone (81 %); (j) $NaIO_4$, Bu_4NBr, CH_2Cl_2, H_2O (92 %); (k) $(MeO)_2P(O)CHN_2$, t-BuOK, THF, -78°C → -20°C (quant.); (l) $ClCO_2Me$, n-BuLi, THF (95 %); (m) $Bu_3SnCu.Me_2S.LiBr$, THF, -78°C, 1.7 eq. MeOH (80 %); (n) DIBAH, Et_2O, -78°C → -0°C (95 %); (o) TBDPSCl, imidazole, DMAP, CH_2Cl_2 (95 %); (p) I_2, CH_2Cl_2 (quant.).

Scheme 3

We anticipated a diastereoselective construction of the C_{25}- and C_{23}-stereogenic centers initially induced by the lactate chirality. The intermediate aldehyde **25** could not be purified (distillation or chromatography) without decomposition and was used as such in the 1,2-chelation-controlled allylation[13] which led to the single diastereoisomer **16** in 60 % overall yield.

Oxidative cleavage of the double bond, gave aldehyde **20** which upon 1,3-chelation-controlled allylation gave exclusively in 97 % yield the 23-*anti*-epimer **19**. This complete selectivity results from the preferred stereoelectronically controlled addition on chelate (i) *versus* (ii). This result sharply contrasts with the low diastereoselectivity, under identical conditions, observed for the corresponding acetonide **29b** (*syn-anti* 2.5:1) which is probably due to the fact that each acetal oxygen atom can be involved in the chelation. The complete diastereoselective construction of the 23 and 25 stereogenic centers in this C_{21}-C_{27} fragment compares favourably with reported results[3b,4bc].

Having achieved the first goal we now faced the formation of acetylenic ester **22** from aldehyde **20**. A number of methods are described to construct this structural unit *via* homologation of an aldehyde. Extensive experimentation was needed before we finally observed that the Seyferth reagent, dimethyl diazomethyl phosphonate[14], produced **21** in quantitative yield; subsequent formation of **22** was uneventful.

Conjugate organostannyl cuprate addition[8] on **22** led to the E-isomer **23**, subsequent reduction of the carboxyl group and silyl ether formation gave the key intermediate **5**.

The C_{17}-C_{20} fragments **25** and **26** were also obtained from D-pantolactone **6**. Although the stereogenic center in **6** is destroyed, it carries the potential for diastereocontrolled formation of C_{20} in an eventual synthesis of **4b**.

Finally, the C_{20}-C_{21} bond formation was undertaken. Reaction of the mixed higher order cuprate (from iodide **24**) with epoxide **25** led, albeit in low yield, to **29**, next to a substantial amount of reduced E-alkene (cf. **24** but X=H). Although, we plan to oxidize the 19-hydroxyl group subsequently to C_{16}-C_{17} coupling, we checked whether this can be performed without concomitant double bond shift to the 20-21 position. Oxidation of **27** led quantitatively to **4a**.

25

24 | a

26

24 | c

OTBDPS

OTBDPS

27 X = OH, Y = H
4a X, Y = O

28; X = OH, Y = H
29; X = H, Y = OH
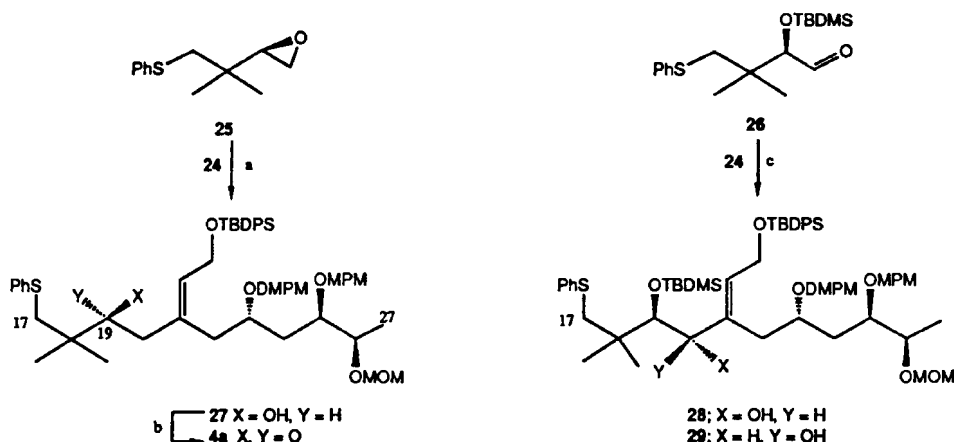
(a) **24**, t-BuLi (2 eq.), Et_2O, -78°C, 30 min; 2-thienylCuCNLi, THF, **41** (1.5 eq), BF_3·Et_2O (1.5 eq), 4 h, -78°C (29 %); (b) SO_3-pyridine, DMSO, NEt_3, CH_2Cl_2, rt (100 %); (c) **24**, t-BuLi (2 eq), THF, -78°C, 1 h; **43** (1.2 eq), 3 h (50 %).

Scheme 4

Reaction of the anion derived from **24** with **26** led to **28** and **29** (2:1 separable mixture); this result indicated that the anticipated influence of the α-stereogenic center in **26** is not operating with the expected degree of diastereoselectivity as predicted by the Anh-Eisenstein model; **29** is a precursor for **4b** and for 20-oxy-bryostatins. However better stereocontrol is needed; further work is in progress.

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