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Bryostatins : The Asymmetric Synthesis of C_1-C_9 and C_{11}-C_{16} Fragments

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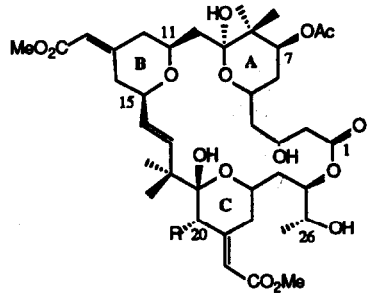
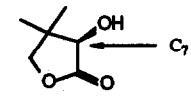
***Abstract** : The fragments C_1-C_9 **19** and C_{11}-C_{16} **26** of the bryostatins are constructed in an enantioselective and highly diastereoselective fashion from respectively D-pantolactone (**2**) and L-erythrulose (**3**) as chiral templates.*

The bryostatins[2] 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. Except for three C_{20} deoxy analogues (e.g. **1a**) 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[3]. Next to the first completed total synthesis of **1c**, described by Masamune et al.[4] other groups have described the synthesis of fragments of the basic 20-membered ring lactone[5,6].

Presently we want to report our efforts towards the total synthesis of bryostatin 1 (**1b**). Retrosynthetic analysis led us to disconnections at the C_{10}-C_{11} and C_{16}-C_{17} bonds. We decided to concentrate our initial studies on the construction of the eastern-northern part (C_1-C_{16}) *via* fragments C_1-C_9 and C_{11}-C_{16} which we planned to connect *via* a keto-phosphonate, thus providing C_{10}. Both fragments are respectively constructed from chiral templates each possessing one stereogenic center; D-pantolactone (**2**) for the C_1-C_9 fragment and L-erythrulose (**3**) for the C_{11}-C_{16} fragment.



1a Bryostatin 11; R = H
1b Bryostatin 1; R = $O_2C(CH)_4(CH_2)_2Me$
1c Bryostatin 7; R = OAc



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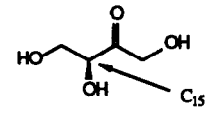

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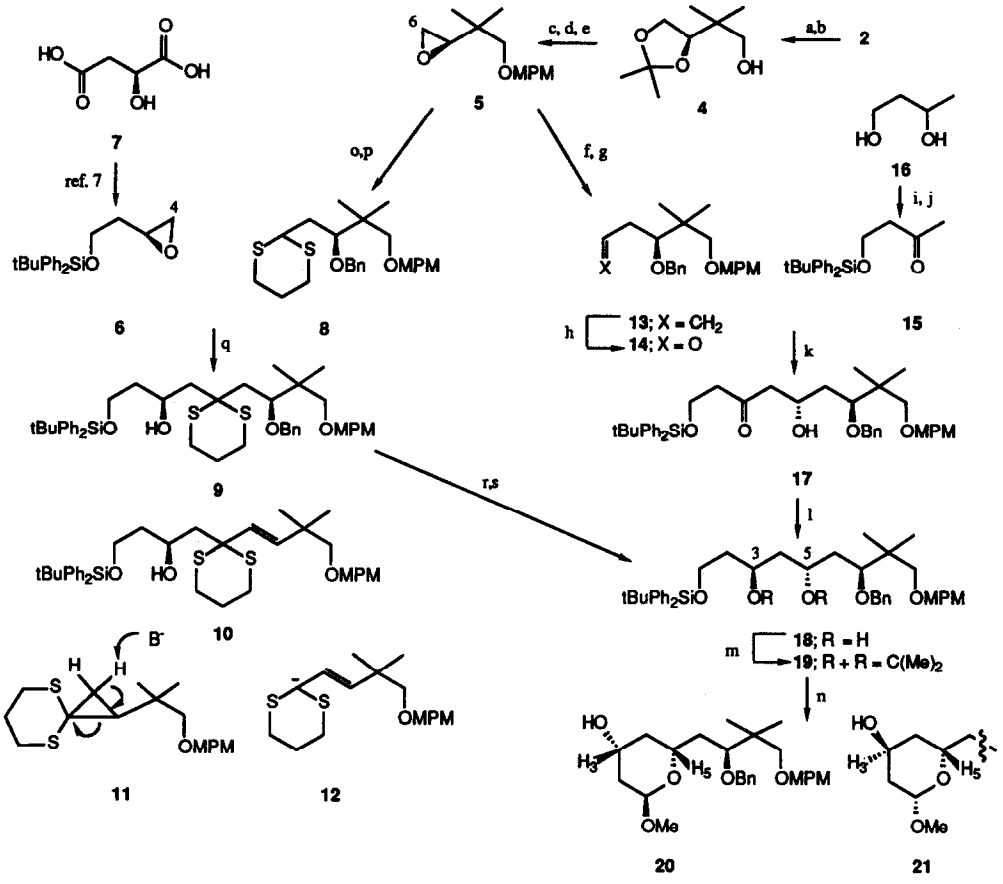
For the synthesis of the fragment C_1-C_9, D-pantolactone (**2**) was selected for the C_6-C_9 fragment by virtue of the correct stereogenic C_7 flanked by a *gem*-dimethyl group (scheme 1). **2** was transformed into epoxide **5** in a 5-step sequence *via* **4**.[7] A first attempt for the construction of the C_1-C_9 fragment centered around coupling of epoxides **5** and **6** (C_1-C_4 fragment; available from L-malic acid (**7**))[8] *via* dithiane as C_5.

Subsequent to dithiane cleavage in **9**, the resulting ketone could then be a substrate for diastereoselective reduction to the *anti*-3,5-diol **18**. Reaction of epoxide **5** with 2-lithiodithiane and protection of the alcohol function led to **8**.



(a) $LiAlH_4$, THF, 0°C, reflux, 5 h, r.t.; (b) 3-pentanone, PTSA, THF, reflux, 5 h (81 %, two steps); (c) KOt.Bu, 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) $(CH_2{=}CH)_2CuCNLi_2$, Et_2O, 0°C, 30 min (84 %); (g) KOt.Bu, THF, then BnBr, r.t., 12 h (96 %); (h) i) OsO_4, NMMO, H_2O-THF, r.t., 5 h; ii) $Pb(OAc)_4$, toluene, pyridine, r.t., 10 min (90 %, two steps); (i) TBDPS-Cl, imidazole, DMF, r.t., 2 h (91 %); (j) $CrO_3.(Py)_2$, CH_2Cl_2, r.t., 30 min (98 %); (k) LDA, THF, -78°C, 5 min, then **14**, -78°C, 5 min (77 %); (l) $LiAl(Ot.Bu)_3H$, LiI, Et_2O, -78°C (90 %); (m) $Me_2C(OMe)_2$, Amberlyst-15, CH_2Cl_2, r.t., 30 min (94 %); (n) i) TBAF, THF, r.t., 4 h; ii) Dess-Martin periodinane (ref. 18); iii) MeOH, Amberlyst-15, r.t., 15 h; (o) 1,3-dithiane, n.BuLi, THF, -10°C, 3 h (100 %); (p) KOt.Bu, THF, then BnBr, r.t., 30 min (84 %); (q) n.BuLi, TMEDA, then **6**, DMPU (13 % of **9**, 4 % of **10**); (r) $Hg(OClO_3)_2$, $CaCO_3$, THF-H_2O, r.t., 2 h (100 %); (s) $NaBH_4$, MeOH, r.t., 10 min (52 % of the two C_5-epimers).

Scheme 1

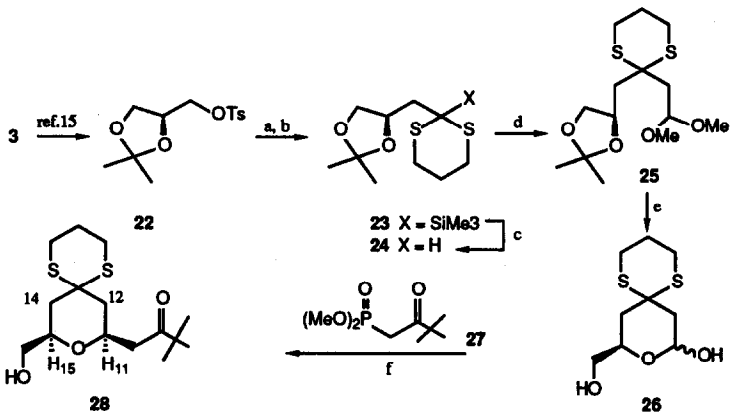
However, the lithiated anion of **8** was virtually unreactive towards epoxide **6**. When the anion of **8** (n.BuLi, THF) and epoxide **6** were kept at 0°C for 5 days, 21 % yield of **10** was obtained next to recovered **8** (76 %) and **6** (78 %). This could be explained by the intermediacy of **11**, slowly formed in an intramolecular fashion from the anion of **8**, followed by base induced cyclopropane ring opening to the more reactive anion **12**. Only

when the anion of **8** was formed in the presence of TMEDA and epoxide **6** was added mixed with 3 eq. DMPU,[9] a low yield (13 %) of the desired **9** was obtained next to **10** (4 %) and recovered starting materials.

This unexpected result led us to explore another approach which now involves the diastereoselective formation of both C_3 and C_5 stereocenters. The key-template **5** was transformed *via* olefin **13** into the aldehyde **14** as the C_5-C_9 fragment, while the C_1-C_4 fragment **15** is easily obtainable from (±)-1,3-butanetriol **16**. Aldol condensation between **15** and **16** led exclusively to one single diastereoisomer **17**. On the basis of a Cram-type transition state, involving coordination of the lithium cation with the benzyl ether oxygen atom, the *anti* isomer is expected; this assumption will be proven later (*vide infra*).[10]

Although high diastereoselective reduction of β-hydroxy-ketones is well documented,[11] formation of **18** from **17** proved to be problematic. Out of 19 different reaction conditions studied only one gave a 3,5-*anti-syn* ratio above 2:1. For instance, surprisingly, $Me_4NB(OAc)_3H$, known as a selective reducing agent[11d], gave 0 % d.e. Only lithium tri-t.butoxy-aluminum hydride in the presence of lithium iodide,[12] at -78°C, resulted in a 17.6:1 ratio in favour of **18**; however when the reaction was allowed to reach r.t. a ratio of 1.85:1 was observed. The *anti*-diol **18** could be separated from the *syn* isomer by preparative reversed phase HPLC.

The relative configuration at C_3 and C_5 in **18** was proved by the transformation of both **19** and the minor C_3-epimer to respectively **20** and **21**. The ^1H NMR spectra show for **20** axially oriented H_3 ($\Sigma J = 44$ Hz) and H_5 ($\Sigma J = 29$ Hz) while in **21**, H_3 ($\Sigma J = 16$ Hz) is equatorial with H_5 ($\Sigma J = 29$ Hz) axial.[13] This proves the 3,5-*syn* relationship in **18**. For the proof of the absolute configuration at C_3 and C_5, advantage was taken from compound **9** with the firmly established (from L-malic acid) C_3 stereogenic center. Cleavage of the dithiane group and reduction of the resulting ketone led to two C_5 epimers, one of which was found to be identical to **18** (^1H NMR, rf value on reversed phase HPLC). This fully identified acetonide **19** as a suitable protected C_1-C_9 fragment. The formation of this fragment from **2** in 89 % d.e. and 27 % overall yield compares favourably with described procedures.[4,6]



(a) NaI, acetone, reflux, 12 h, (90 %); (b) 2-TMS-1,3-dithiane, n.BuLi, THF, -60°C → r.t., 24 h (82 %); (c) TBAF, THF, r.t., 2 h (98 %); (d) n.BuLi, $BrCH_2CH(OMe)_2$, THF-HMPA, -60°C → -20°C, 36 h (80 %); (e) HCl (3 %), THF, r.t., 2 h (90 %); (f) n.BuLi, 1,2-DME, 85°C, 12 h (75 %).

Scheme 2

Next we explored the creation of C_9-C_{16} fragment (scheme 2) with the two stereogenic C_{11} and C_{15} centers and a potential C_{13}-carbonyl group allowing at a later stage the formation of the unsaturated ester via an

asymmetric Horner-Emmons reaction.[14,15] Our strategy centers around the formation of the stereogenic C_{11} via a nucleophilic addition reaction of a C_{15} hydroxyl group as the chiral inductor. Tosylate **22**, obtained from L-erythrulose (**3**),[16] was transformed into the dithiane **24** *via* **23**[17]; direct formation of **24** from **22** suffered from low yields. Reaction of the anion of **24** with 2,2-dimethoxy-1-bromo-ethane and subsequent hydrolysis afforded **26** as an anomeric mixture.

As a model for the C_9-C_{16} fragment we selected pivalic acid, in order to study the cyclization conditions. The keto-phosphonate **27** was deprotonated and reaction with **26** yielded **28** as the sole product. The axial orientation of both H_{11} and H_{15} was proven by the ^1H NMR spectrum; H_{11} and H_{15} show *trans* diaxial coupling with the corresponding proton at respectively C_{12} and C_{14} (J = 11.67 Hz and 11.65 Hz. This establishes that the configuration at C_{11} can be controlled by the C_{15} stereogenic alcohol. With this model study a viable route to the C_1-C_{16} fragment is at hand. Further studies on the total synthesis of **1b** are in progress.

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