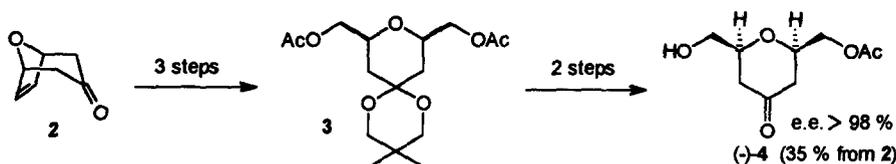




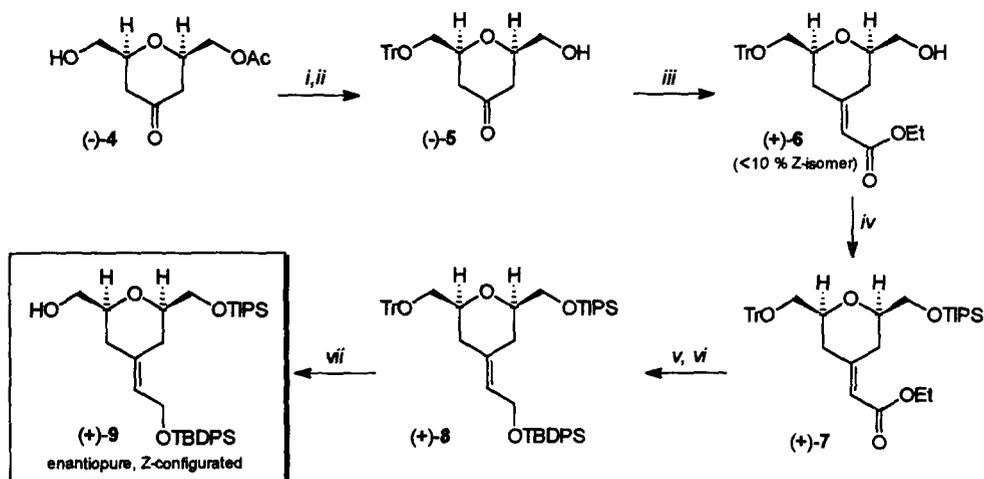
Thus, additional disconnection (b) of the C(1)-C(9) segment at the C(7)-C(8) bond gives rise to one 2-carbon and two 7-carbon atom units. Previously<sup>4</sup> we have reported an innovative and efficient asymmetric synthesis of the polyacetate derived polyketide (+)-1, a C(1)-C(9) segment precursor.<sup>2c</sup>

Scheme 2



Starting from *meso* oxabicyclic ketone **2**, we prepared C-glycoside derivative (-)-**4** as key intermediate in an asymmetric synthesis of a C(10)-C(16) segment (*via* chemoenzymatic synthesis in 5 steps and overall 35 % yield, Scheme 2).<sup>5</sup> From extensive modelling studies we assumed that a bulky protecting group at the *S*-hydroxymethyl substituent in (-)-**4** would block one side of the tetrahydropyran-4-one moiety, as in (-)-**5** (Scheme 3). Thus, efficient control of enoate geometry and stereoselective construction of the trisubstituted, exocyclic double bond at C(13) through remote 1,5-induction in the course of a Horner-Wadsworth-Emmons olefination was considered feasible.<sup>6</sup>

Scheme 3



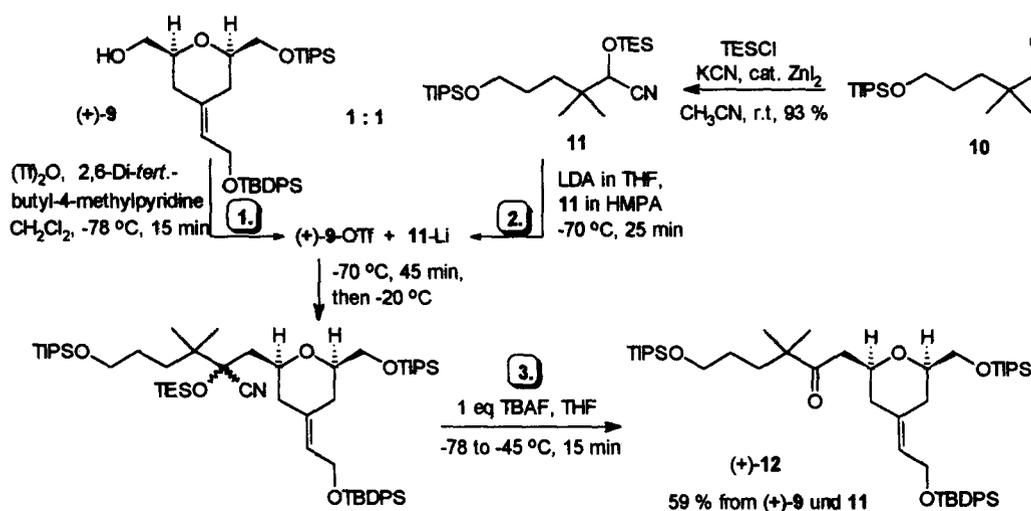
(i) Trityl chloride, Et<sub>3</sub>N, cat. 4-DMAP, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; (ii) K<sub>2</sub>CO<sub>3</sub> 5 % H<sub>2</sub>O in MeOH, 0 °C (79 %, two steps); (iii) ethyl diisopropoxyphosphonoacetate, NaH, toluene, -50 to -35 °C then -25 °C, 72 %; (iv) TIPSCl, imidazole, DMF, r.t., 97 %; (v) DIBALH, toluene, -65 °C; (vi) TBDPSCl, imidazole, DMF, r.t. (90 %, two steps); (vii) excess ZnBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (6:1), 0 °C to r.t., 83 % isolated yield of pure *Z*-isomer (+)-**9**.

The enantiopure alcohol (-)-**4** was protected as a triphenylmethyl (trityl) ether and successive deacetylation furnished *cis*-2,6-disubstituted tetrahydropyran-4-one (-)-**5** (79 % combined yield, Scheme 3). A synergistic effect in the interaction of the bulky trityl protecting as well as directing group with the sterically demanding HWE reagent ethyl diisopropoxyphosphonoacetate favoured the formation of desired *E*-isomer with

high selectivity (9:1).<sup>7</sup> Upon treatment of (-)-5 with the sodium phosphonate in toluene at low temperature unsaturated ester (+)-6 was isolated in 72 % yield, contaminated with less than 10 % Z-isomer, which could be removed at a later stage of the synthesis. The E-configuration of the predominating isomer was established by detailed <sup>1</sup>H NMR spectroscopy.<sup>8</sup> Functional group and protecting group manipulation afforded chemodifferentiated triol (+)-8 (3 steps, 87 % combined yield). Chemoselective removal of the trityl group completed the synthesis of the C(10)-C(16) segment of bryostatin 1 and was best carried out by the action of the Lewis acid ZnBr<sub>2</sub><sup>9</sup> in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and MeOH (6:1) to afford (+)-9 in stereoisomerically pure form after simple column chromatography on silica gel (83 % yield).

According to our retrosynthetic analysis, C-C bond formation between C(9) and C(10) is crucial to allow an efficient and convergent synthesis of the C(1)-C(16) segment from fully elaborated C(1)-C(9) and C(10)-C(16) building blocks. Adopting the strategy of *umpolung* triethylsilyl (TES) protected cyanohydrin 11, derived in high yield from aldehyde 10<sup>10</sup>, served among other investigated cyanohydrins<sup>11</sup> as a C(1)-C(9)-model acyl anion equivalent in S<sub>N</sub>2 reactions.

Scheme 4



The free primary hydroxyl group of the C(10)-C(16) segment (+)-9 was activated by conversion into the triflate<sup>12</sup> (99 % yield) and treated with one equivalent of deprotonated TES cyanohydrin 11 (Scheme 4). Reestablishing the keto carbonyl group in the coupling product was accomplished by chemoselective cleavage of the tertiary TES ether in the presence of three other silyl protecting groups. Upon the action of TBAF (1 eq) in THF at low temperature ketone (+)-12 was obtained in good yield (59 % from 11 and (+)-9).

In conclusion, starting from the *meso*-configured oxabicyclic 2 we have prepared a C(10)-C(16) segment of the bryostatins in 12 steps and 15 % overall yield. The synthesis of (+)-9 has been carried out on a multigram scale. With the TES cyanohydrin based coupling strategy, successfully examined on a model stage, a

viable and convergent route to the complete C(1)-C(16) segment is at hand. Further results towards a total synthesis of bryostatin 1 will be reported in due course. All compounds gave satisfactory spectroscopic and analytical data.<sup>13</sup>

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- Aldehyde **10** has been prepared from 2,2-dimethylglutaric acid in 3 steps: i. LiAlH<sub>4</sub>, Et<sub>2</sub>O, 71 %; ii. TIPSCl, imidazole, DMF, 85 %; iii. (COCCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 88 %.
- Various cyanohydrins with different protecting groups (EE, TBDMS, TES, TMS) have been investigated. The TES protected cyanohydrins performed extraordinary well with respect to: ease of formation, stability and reactivity of the corresponding anions and ease of unmasking in the presence of additional protecting groups.
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- Analytical data for selected compounds: (+)-9: colourless, highly viscous oil;  $[\alpha]_D^{22} = +2.9$  (c = 1, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>):  $\nu = 3592, 3420, 2944, 2892, 2864, 1428, 1252, 1196, 1140, 1112$  cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS):  $\delta = 7.70\text{--}7.66$  (m, 4 H), 7.44-7.35 (m, 6 H), 5.47 (t, <sup>3</sup>J = 6.5 Hz, 1 H), 4.24 (d, <sup>3</sup>J = 6.5 Hz, 2 H), 3.72 (dd, <sup>2</sup>J = 10.5, <sup>3</sup>J = 5.5 Hz, 1 H), 3.66-3.60 (m, 1 H), 3.58 (dd, <sup>2</sup>J = 10.5, <sup>3</sup>J = 5.5 Hz, 1 H), 3.55-3.42 (m, 2 H), 3.25 (m, 1 H), 2.37 (dd, <sup>2</sup>J = 14, <sup>3</sup>J = 1.5 Hz, 1 H), 2.07-1.99 (m, 3 H), 1.63 (t, <sup>23</sup>J = 13 Hz, 1 H), 1.05-1.01 (m, 30 H); <sup>13</sup>C NMR (50 MHz, APT, CDCl<sub>3</sub>):  $\delta = 135.51$  (-), 135.28 (+), 133.80 (+), 129.52 (-), 127.56 (-), 123.70 (-), 78.99 (-), 78.10 (-), 66.57 (+), 65.81 (+), 60.00 (+), 37.43 (+), 31.43 (+), 26.78 (-), 19.09 (+), 17.88 (-), 11.87 (-); HR-MS: calc. for C<sub>30</sub>H<sub>45</sub>O<sub>4</sub>Si<sub>2</sub> = (M-C<sub>4</sub>H<sub>9</sub>)<sup>+</sup>: 525.2856, found: 525.2857. (+)-12: colourless, highly viscous oil;  $[\alpha]_D^{22} = +3.1$  (c = 1, CHCl<sub>3</sub>); 2940, 2888, 2864, 1708, 1108, 1068 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS):  $\delta = 7.70\text{--}7.65$  (m, 4 H), 7.44-7.35 (m, 6 H), 5.46 (t, <sup>3</sup>J = 7 Hz, 1 H), 4.23 (d, <sup>3</sup>J = 7 Hz, 2 H), 3.85-3.77 (m, 1 H), 3.69-3.59 (m, 3 H), 3.49 (dd, <sup>2</sup>J = 10, <sup>3</sup>J = 6 Hz, 1 H), 3.21-3.27 (m, 1 H), 2.84 (dd, <sup>2</sup>J = 17, <sup>3</sup>J = 6 Hz, 1 H), 2.46 (dd, <sup>2</sup>J = 17, <sup>3</sup>J = 6 Hz, 1 H), 2.42 (d, <sup>2</sup>J = 14 Hz, 1 H), 2.20 (d, <sup>2</sup>J = 13 Hz, 1 H), 1.87 (t, <sup>23</sup>J = 13 Hz, 1 H), 1.65-1.50 (m, 3 H), 1.47-1.32 (m, 2 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 1.06-0.99 (m, 56 H); <sup>13</sup>C NMR (100 MHz, DEPT, CDCl<sub>3</sub>):  $\delta = 213.06, 135.6, 135.53, 135.52, 133.92, 133.86, 129.51, 129.47, 127.58, 127.55, 123.51, 78.04, 74.43, 66.49, 63.46, 60.06, 47.32, 43.31, 41.69, 35.89, 31.55, 28.21, 26.81, 24.21, 23.87, 19.11, 18.01, 17.92, 11.95, 11.89$ ; MS-FAB (m/z, r.t.) 850 (M<sup>+</sup>, 0.4), 807 (M-C<sub>3</sub>H<sub>7</sub>, 1.7), 285 (64), 199 (56), 135 (100).

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