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Asymmetric Synthesis of the C(10)-C(16) Segment of the Bryostatins

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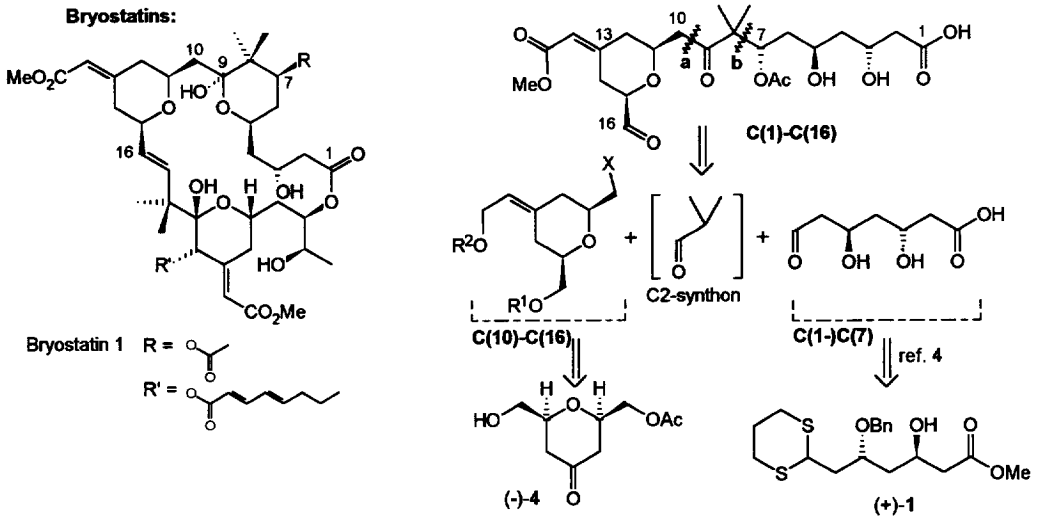
Abstract:.The C(10)-C(16) segment of the bryostatins has been synthesized (12 steps, 15 % overall yield) and a cyanohydrin based strategy was developed for coupling with a C(1)-C(9) model.

The bryostatins,[1] a class of highly oxygenated natural occurring marine macrolides with a polyacetate derived backbone, exhibit promising therapeutical antineoplastic activities and feature a variety of structural and stereochemical challenges. Although several synthetic contributions leading to fragments of the bryostatins have been reported[2], so far only Masamune and his coworkers[3] have achieved a total synthesis of bryostatin 7, leaving the need for a synthesis of bryostatin 1 and of biologically active analogues. This situation prompted us to set up a program aimed at the development of a convergent and efficient synthesis of these macrolides and especially of bryostatin 1.

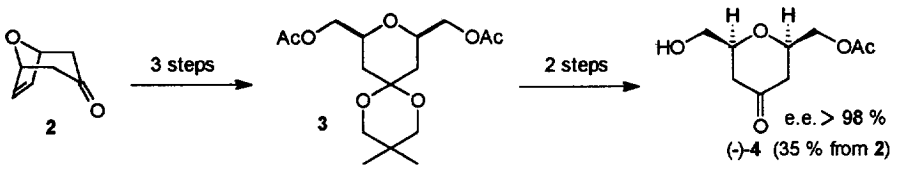
Scheme 1



Our retrosynthetic analysis as outlined in Scheme 1 leads to the key disconnection (**a**) of the C(1)-C(16) segment at the C(9)-C(10) bond providing segments of almost equal size and stereochemical complexity.

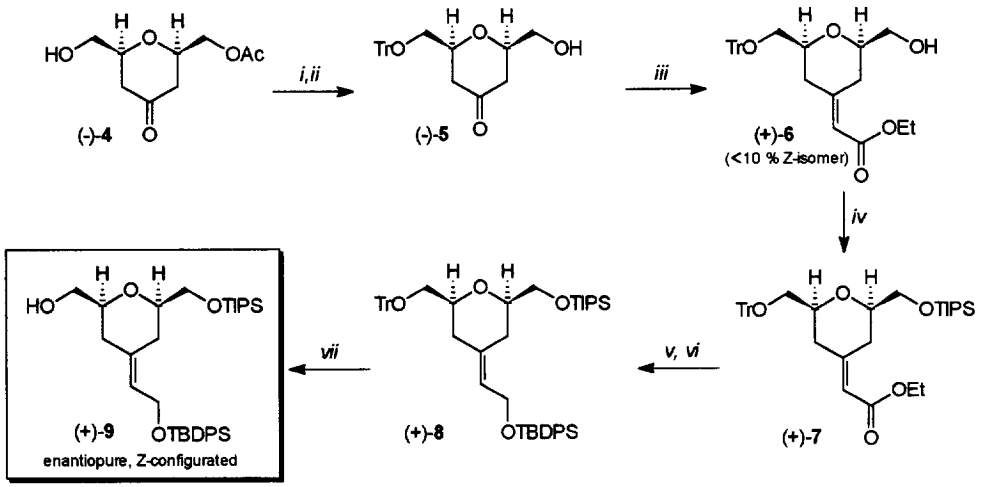
Thus, additional disconnection (**b**) of the C(1)-C(9) segment at the C(7)-C(8) bond gives rise to one 2-carbon and two 7-carbon atom units. Previously[4] we have reported an innovative and efficient asymmetric synthesis of the polyacetate derived polyketide (+)-**1**, a C(1)-C(9) segment precursor.[2c]

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).[5] 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.[6]

Scheme 3



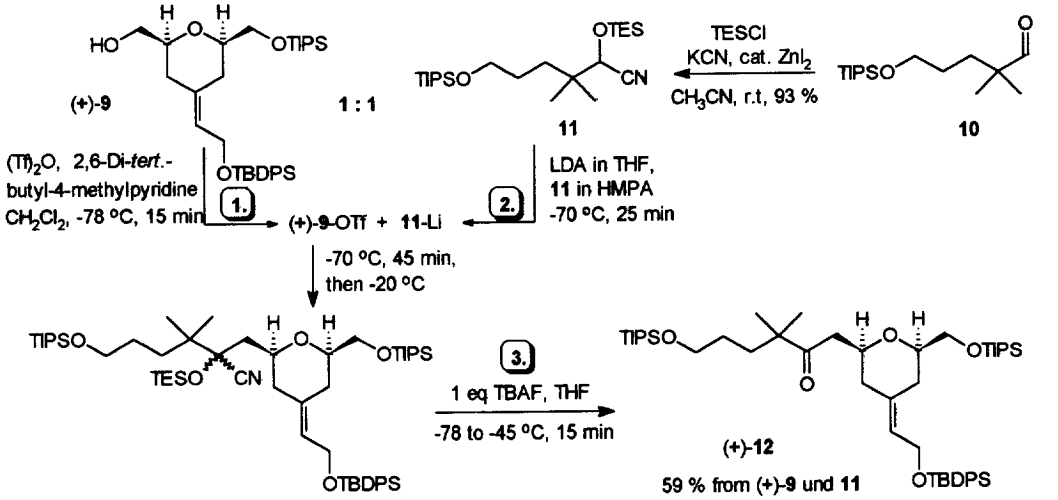
(*i*) Trityl chloride, Et_3N, cat. 4-DMAP, CH_2Cl_2, r.t.; (*ii*) K_2CO_3 5 % H_2O in MeOH, 0 °C (79 %, two steps); (*iii*) ethyl diisopropoxyphosphonoacetate, NaH, toluene, -50 to -35 °C then -25 °C, 72 %; (*iv*) TIPSCl, imidazole, DMF, r.t., 97 %; (*v*) DIBAH, toluene, -65 °C; (*vi*) TBDPSCl, imidazole, DMF, r.t. (90 %, two steps); (*vii*) excess $ZnBr_2$, CH_2Cl_2/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).[7] 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 ^{1}H NMR spectroscopy.[8] 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 $ZnBr_2$[9] in a mixture of CH_2Cl_2 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**[10], served among other investigated cyanohydrins[11] as a C(1)-C(9)-model acyl anion equivalent in S_N2 reactions.

Scheme 4



The free primary hydroxyl group of the C(10)-C(16) segment (+)-**9** was activated by conversion into the triflate[12] (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*-configurated oxabicycle **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.[13]

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References and Notes

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5. For an innovative approach to 2,4,6-trifunctionalized C-glycosides see: Lampe, T. F. J.; Hoffmann, H. M. R, Bornscheuer, U. T. *Tetrahedron: Asymmetry*, **1996**, *7*, in press.
6. An elegant solution for control of remote enoate geometry by use of a tethered HWE reagent giving a 14-membered, monounsaturated bislactone has been reported by: Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.*, **1990**, *31*, 4703.
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8. The E-configuration of the double bond was apparent from 600 MHz ^{1}H NMR and H-H-COSY spectra of a TBDMS-derivative of (+)-**6**; additional support was obtained from NOE experiments at 200 MHz.
9. Kohli, V.; Blöcker, H.; Köster, H. *Tetrahedron Lett.*, **1980**, *21*, 2683.
10. Aldehyde **10** has been prepared from 2,2-dimethylglutaric acid in 3 steps: **i**. $LiAlH_4$, Et_2O, 71 %; **ii**. TIPSCl, imidazole, DMF, 85 %; **iii**. $(COCCl)_2$, DMSO, Et_3N, CH_2Cl_2, 88 %.
11. 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.
12. Shen, Q.; Sloss, D. G.; Berkowitz, D. B. *Synth. Commun.*, **1994**, 1519.
13. Analytical data for selected compounds: (+)-**9**: colourless, highly viscous oil; $[\alpha]_D^{22}$ = +2.9 (c = 1, $CHCl_3$); IR ($CHCl_3$): ν = 3592, 3420, 2944, 2892, 2864, 1428, 1252, 1196, 1140, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.70-7.66 (m, 4 H), 7.44-7.35 (m, 6 H), 5.47 (t, ^3J = 6.5 Hz, 1 H), 4.24 (d, ^3J = 6.5 Hz, 2 H), 3.72 (dd, ^2J = 10.5, ^3J = 5.5 Hz, 1 H), 3.66-3.60 (m, 1 H), 3.58 (dd, ^2J = 10.5, ^3J = 5.5 Hz, 1 H), 3.55-3.42 (m, 2 H), 3.25 (m, 1 H), 2.37 (dd, ^2J = 14, ^3J = 1.5 Hz, 1 H), 2.07-1.99 (m, 3 H), 1.63 (t, $^{2/3}J$ = 13 Hz, 1 H), 1.05-1.01 (m, 30 H); ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 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 $C_{30}H_{45}O_4Si_2$ = $(M-C_4H_9)^+$: 525.2856, found: 525.2857. (+)-**12**: colourless, highly viscous oil; $[\alpha]_D^{22}$ = +3.1 (c = 1, $CHCl_3$); 2940, 2888, 2864, 1708, 1108, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.70-7.65 (m, 4 H), 7.44-7.35 (m, 6 H), 5.46 (t, ^3J = 7 Hz, 1 H), 4.23 (d, ^3J = 7 Hz, 2 H), 3.85-3.77 (m, 1 H), 3.69-3.59 (m, 3 H), 3.49 (dd, ^2J = 10, ^3J = 6 Hz, 1 H), 3.21-3.27 (m, 1 H), 2.84 (dd, ^2J = 17, ^3J = 6 Hz, 1 H), 2.46 (dd, ^2J = 17, ^3J = 6 Hz, 1 H), 2.42 (d, ^2J = 14 Hz, 1 H), 2.20 (d, ^2J = 13 Hz, 1 H), 1.87 (t, $^{2/3}J$ = 13 Hz, 1 H), 1.65-150 (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); ^{13}C NMR (100 MHz, DEPT, $CDCl_3$): δ = 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^+, 0.4), 807 ($M-C_3H_7$, 1.7), 285 (64), 199 (56), 135 (100).

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