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Asymmetric Synthesis of the Northern Half C1–C16 of the Bryostatins

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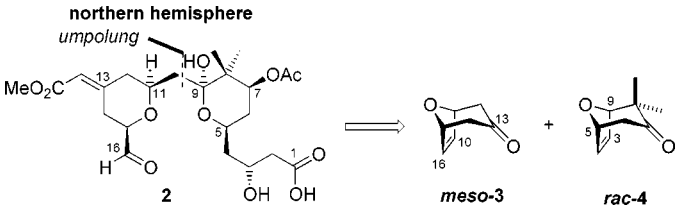
ABSTRACT



Starting from 8-oxabicyclo[3.2.1]oct-6-en-3-one and racemic 2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, the C1–C16 segment of the bryostatins has been synthesized in 30 steps and 9% overall yield (17 steps longest linear sequence). Fragment coupling by dithiane strategy and protecting group manipulations provided an advanced chemodifferentiated northern half segment.

The bryostatins,[1] first described by Pettit in 1982, are a family of 18 promising cancer chemotherapeutic candidates. They exhibit a highly oxygenated pattern with a polyacetate-derived backbone. The bryostatins bind to protein kinase C (PKC) and activate it in a fashion different from the phorbol esters: Exogenous agonists of PKC, such as the phorbol esters, usually are tumor promoters, but the bryostatins act as anticancer drugs.[2] Although the molecular mode of biological activity is unknown, the bryostatins are currently in phase II human clinical trials for treatment of non-Hodgkin's lymphoma, melanoma, and renal cancer.[3]

Since their discovery, three total syntheses of a bryostatin have been completed up to date.[4] Furthermore, several groups,[5] including our own,[6] set up a program directed toward a convergent and efficient synthesis of these challenging macrolides and especially of bryostatin 1 and some simplified bryostatin analogues,[7] which exhibit biological activity similar to that of bryostatin 1. In this study, we describe the completion of the C1−C16 segment, the northern half of the bryostatins.

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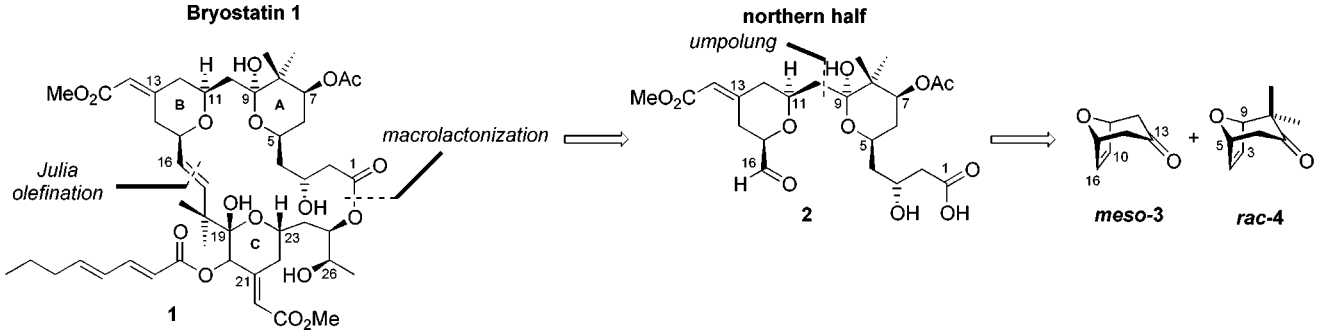
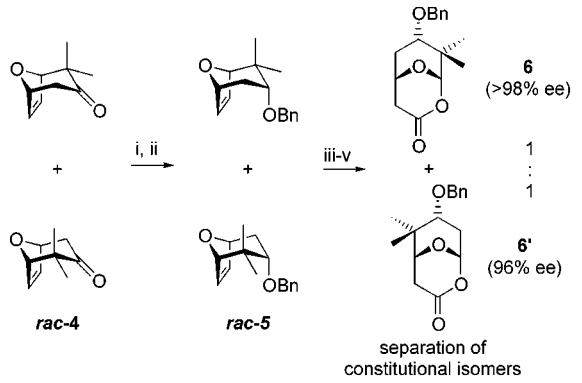
Scheme 1



Our retrosynthetic analysis (Scheme 1) involves disconnection of the C1−C25 lactone bond and the C16−C17 trans olefinic bond. Further scission at the C9−C10 glycoside bond provides two segments of comparable size, which are accessible from oxabicyclic ketone ***meso*-3** and racemic oxabicyclic ketone ***rac*-4**.

Synthesis of the C1−C9 Subunit. The starting racemic material ***rac*-4** was prepared in 40 g per batch[8] and reduced with L-Selectride, providing the axial alcohols without formation of the equatorial alcohols (Scheme 2). After

Scheme 2[a]



[a] (i) 1. L-Selectride, THF, −78 °C, 2 h; 2. NaOH, H_2O_2, rt, 1 h, 98%; (ii) BnBr, NaH, reflux, 1 h, 98%; (iii) 1. (−)-Ipc_2BH, THF, −15 °C, 3 d; 2. NaOH, H_2O_2, rt, 1 h, 92%; (iv) PCC, CH_2Cl_2, rt, 16 h, 96%; (v) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 16 h, 90%.

conversion into the protected *endo*-alcohol ***rac*-5**, reagent-induced asymmetric hydroboration[9] of the double bond with (−)-Ipc_2BH was carried out, requiring careful temperature control (−15 °C). Oxidation to the resulting alcohols using PCC and subsequent Baeyer−Villiger ringexpansion gave the lactone acetals **6** and **6′** in excellent ee. Separation by flash chromatography was feasible at this stage.[6c]

[3.3.1]Lactone acetal **6** was opened under standard basic conditions to afford acetal ester **7** as an anomeric mixture in excellent yield (Scheme 3). Further opening to the acyclic polyketide segment was critical and was accomplished by two methods: With ethanedithiol/$BF_3{\cdot}Et_2O$ to the polyketide 1,3-dithiolane (five-membered ring) in nonpolar solvent dichloromethane, but not with 1,3-propanedithiol/$BF_3{\cdot}Et_2O$ in this solvent (potential six-membered ring), even though the nondimethylated acetal could be opened.[6b] However, the 1,3-dithiane polyketide was indispensable for *umpolung*. After further experimentation it was found that *trans*-thioacetalization with 1,3-propanedithiol/$BF_3{\cdot}Et_2O$ was feasible but only in the much more polar solvent nitromethane. Thus, the desired polyketide **8** could be obtained after careful optimization of the temperature window in very good yield.[10] Claisen condensation of **8** using an excess of the enolate, prepared from *tert*-butyl acetate and lithium diisopropylamide, gave the δ-hydroxy-β-keto ester **9** (94%). Reduction with the Saksena−Evans reagent[11] provided the C3,C5-*anti* diol **10** (*anti*:*syn* = 91:9), which was then protected as its acetonide **11**. After the ester functionality had been reduced with $LiAlH_4$, the benzyl ether was cleaved using lithium di-*tert*-butylbiphenyl (LDBB) radical anion[12] to circumvent deprotonation problems during the planned segment coupling. Finally, chemodifferentiated protection of the resulting diol **12** occurred with ease, affording the target **13** in 14 steps from ***rac*-4** and 27% overall yield (50% maximum yield).

Optimized Synthesis of the C10−C16 Subunit. Our initial synthesis of this segment began with the protection of the oxabicyclic ketone ***meso*-3** with an excess of 2,2,5,5-tetramethyl-1,3-dioxane in the presence of catalytic amounts of p-TsOH at reduced pressure to afford the desired ketal ***meso*-15** (50% yield, Scheme 4) in the first step of the synthesis sequence.[13] Improvement of the yield was feasible by two modifications: Transketalization with acetal **14**, which is more labile under acid conditions, and *Kugelrohr distillation*, to remove the excess of **14** in the workup,

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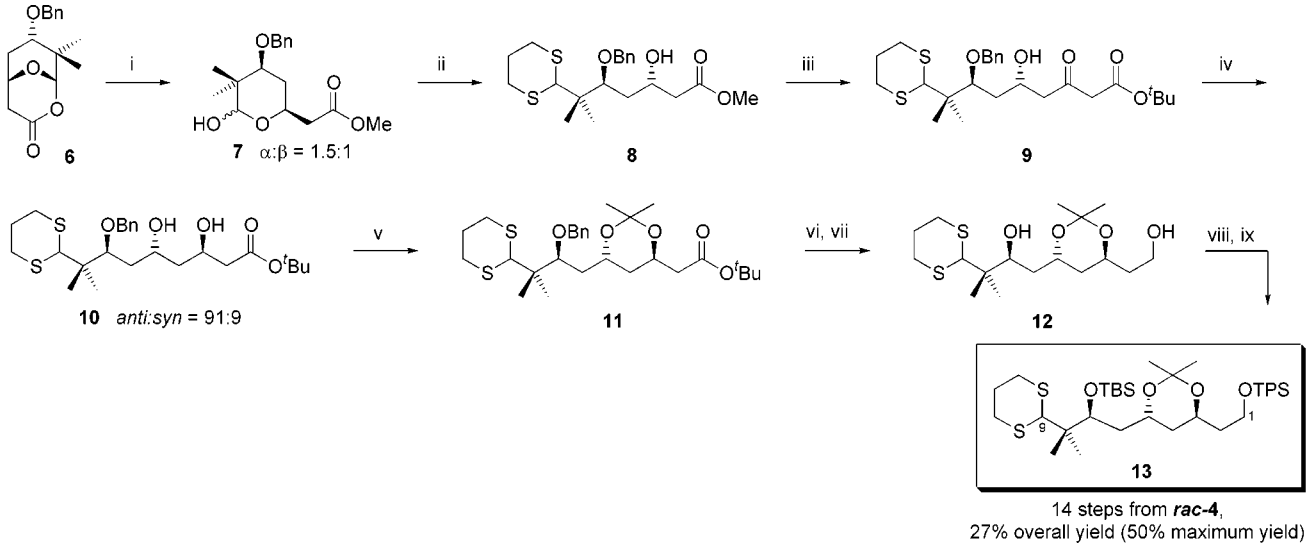
Scheme 3[a]



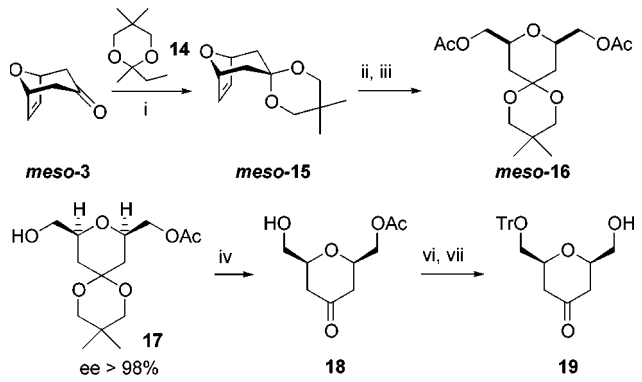
[a] (i) K_2CO_3, MeOH, rt, 6 h, 99%; (ii) 2 equiv of $HS(CH_2)_3SH$, 3 equiv of $BF_3{\cdot}Et_2O$, $MeNO_2$, −20 → −15 °C, 0.5 h, 95%; (iii) 5 equiv of $CH_3CO_2Bu^t$, LDA, −78 → 0 °C, 2 h, 94%; (iv) $Me_4NBH(OAc)_3$, MeCN/AcOH (1:1), −35 °C, 3 d, −25 °C, 24 h, 97%; (v) $(CH_3)_2C(OMe)_2$, p-TsOH (catalytic), rt, 16 h, 88%; (vi) $LiAlH_4$, THF, 0 °C → rt, 2 h, 99%; (vii) 10 equiv of LDBB, THF, −78 → −50 °C, 0.5 h, 98%; (viii) TPSCl, imidazole, CH_2Cl_2, rt, 2 h, 99%; (ix) TBSOTf, imidazole, 60 °C, 2 h, 99%.

provided ketal ***meso*-15** in 75% yield (98% based on recovered starting material). Ozonolysis of the olefinic double bond and subsequent reduction afforded a diol which was transformed into ***meso*-16**.

Differentiation of the two enantiotopic acetoxymethyl groups works best by lipase PS-mediated hydrolysis.[14] Extending the reaction time from 24 to 38 h was feasible without loss of enantiomeric purity (ee > 98%) and raised also the chemical yield. Again, prolongation of reaction time in the next two steps, regeneration of carbonyl group, and protection of the hydroxy group as a trityl ether improved the yield slightly. Standard deacetylation conditions furnished the corresponding hydroxy ketone **19**.[6a]

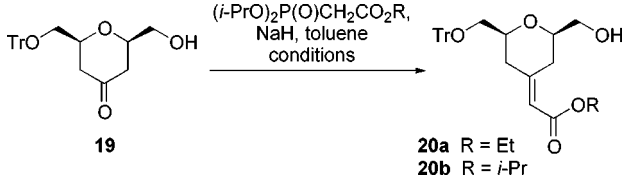
The stereoselective formation of an exocyclic α,β-unsaturated ester from cyclic ketones such as **19** is far from trivial (Scheme 5): It was found that a synergistic effect of the bulky trityl group with a sterically demanding HWE reagent phosphonoacetate favored the formation of the desired *E*-isomer in good selectivity (9:1) by remote stereoinduction (1,6 or 1,7 depending on atom counting).[15] Further experimentation provides additional insight (Table 1): In general, chemical yields increased by diluting the reaction mixture. Furthermore, the use of the sterically more demanding isopropyl diisopropoxyphosphonoacetate[16] furnished the desired unsaturated ester **20b** in high chemical yield and excellent *E*-selectivity (*E*:*Z* = 98:2), after careful optimization of the temperature window (Table 1, entry 5).

Scheme 4[a]



[a] (i) p-TsOH (6 mol %), 35−45 mmHg, rt, 7 d, 75% (98% borsm); (ii) 1. O_3, $MeOH/CH_2Cl_2$, −78 → −20 °C; 2. $NaBH_4$, −20 → 0 °C, 1 h, 98%; (iii) Ac_2O, DMAP (catalytic), py, rt, 5 h, 91%; (iv) lipase PS, toluene/phosphate buffer (1:4), pH = 7, 38 h, 96%; (v) acetone, $Pd(CH_3CN)_2Cl_2$ (catalytic), rt, 24 h, 93%; (vi) TrCl, Et_3N, DMAP (catalytic), CH_2Cl_2, rt, 24 h, 84%; (vii) K_2CO_3, H_2O/MeOH, 0 °C, 2 h, 99%.

Scheme 5



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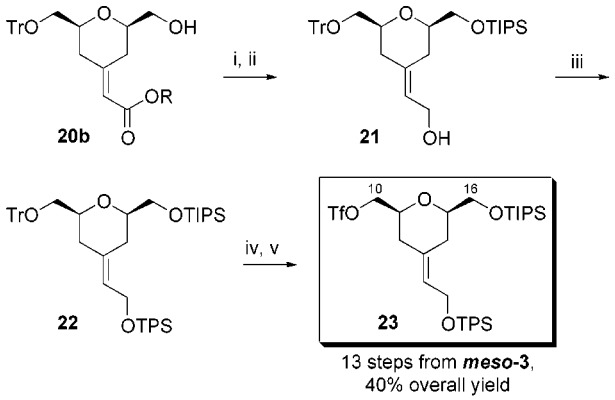
(16) Prepared in two steps: (a) $(EtO)_2P(O)H + Ti(O\text{-}i\text{-}Pr)_4 \rightarrow (i\text{-}PrO)_2P(O)H$: Froneman, M.; Modro, T. A. *Tetrahedron Lett.* **1988**, *29*, 3327. (b) $(i\text{-}PrO)_2P(O)H + ClCH_2CO_2i\text{-}Pr \rightarrow (i\text{-}PrO)_2P(O)CH_2CO_2i\text{-}Pr$: Ye, W.; Liao, X. *Synthesis* **1985**, 986.

Table 1

no.	R	*c* [M]	conditions	yield [%]	*E*:*Z*
1	Et	0.08	−50 °C → −35 °C, 1 h; −17 °C, 14 h	80	88:12
2	Et	0.048	−50 °C → −35 °C, 1 h; −25 °C, 17 h	96	90:10
3	*i*-Pr	0.048	−50 °C → −35 °C, 1 h; −25 °C, 22 h	64	>98:2
4	*i*-Pr	0.048	−50 °C → −35 °C, 1 h; −5 °C, 67 h	78	98:2
5	***i*-Pr**	**0.02**	**−50 °C → −5 °C, 1 h; −8 °C, 7 d**	**99**	**98:2**

Protection of the hydroxy group in **20b** and ester reduction were accomplished under standard conditions (Scheme 6).

Scheme 6[a]

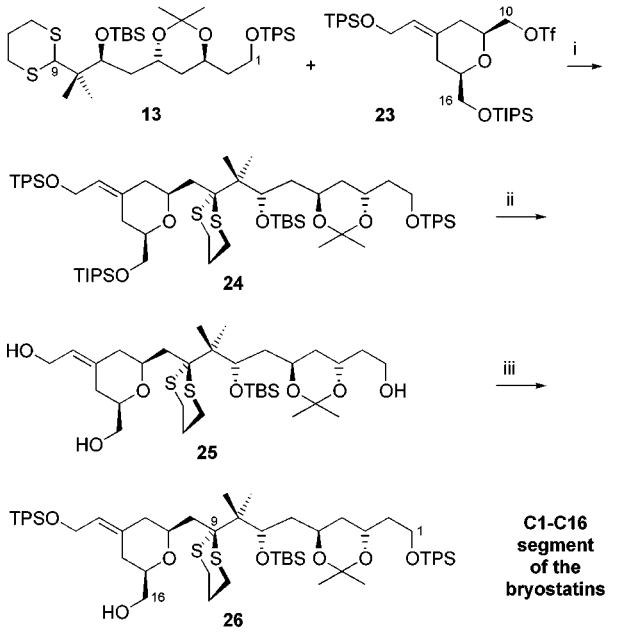


[a] (i) TIPSCl, imidazole, DMF, rt, 1 h, 98%; (ii) DIBAH, toluene, −65 → −20 °C, 1 h, 97%; (iii) TPSCl, imidazole, DMF, rt, 1.5 h, 93%; (iv) $ZnBr_2$, CH_2Cl_2/MeOH, 0 °C → rt, 1.5 h, 94%; (v) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −78 °C, 15 min, 99%.

After protection of the alcohol **21**, the trityl group was removed under Lewis acidic conditions. Impurities from the *Z*-isomer resulting from the HWE olefination were now marginal and separable at this stage. According to the synthetic plan, the alcohol was converted into its triflate **23** in 13 steps from ***meso*-4** and in 40% overall yield.

Fragment Coupling. In general, the coupling of segments in polyketides raises challenges which do not occur in segment syntheses. Our initial study on a model A−B segment coupling utilized a deprotonated TES cyanohydrin and triflate **23** and revealed that the condensation was feasible in the presence of HMPA.[6a] Due to the lability of TES cyanohydrins, complicated handling in generating a TES cyanohydrin anion and fluctuating yields in the desired coupling, we changed our strategy and used 1,3-dithianes[17] instead. In this case it was discovered that the hydroxy protecting group at C7 in **13** (TBS, TIPS, SEM, MEM) had a marked influence on coupling yield. After detailed investigation, best coupling yields were observed for the TBS group. Lithiation of the sterically encumbered dithiane **13** was best effected using *tert*-BuLi in the presence of HMPA. The addition of triflate **23** then afforded a good yield of the C1−C16 segment **24** (Scheme 7). The release of the C16-

Scheme 7[a]



[a] (i) −78 °C, THF, 1.1 equiv of *t*-BuLi, 3 equiv of HMPA, 5 min, then **23**, −78 → −50 °C, 1 h, 63%; (ii) 20 equiv of TBAF/AcOH (1:1), THF, rt., 48 h, 73%; (iii) 2.1 equiv of TPSCl, 2.5 equiv of imidazole,CH_2Cl_2, −30 → 0 °C, 2 h, 71%.

OH group was achieved in two steps. Removal of the TIPS and TPS groups in the sensitive compound **24** proceeded smoothly with TBAF buffered with HOAc[18] to give triol **25**. Selective protection of the C1-OH group and of the allylic alcohol supplied the fully resolved segment **26** containing three silyl groups ready for single-step deprotection.

In summary, our oxabicyclics are multiple aldol addition equivalents which furnish a wide variety of polyketide patterns by both novel and efficient strategy.[19] Starting from ***meso*-3** and ***rac*-4**, we have prepared a C1−C16 segment of the bryostatins (longest linear sequence 17 steps) in 9% overall yield. C1−C9 subunit **13** and C10−C16 subunit precursor of triflate **23** were obtained on a multigram scale. A further spin off of our efforts has been a facile deprotection method of SEM ethers with $MgBr_2$ in homogeneous solution (Et_2O/$MeNO_2$).[20]

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft, Volkswagen Foundation, and Fonds der Chemischen Industrie for their support and Ulrike Eggert for her help.

Supporting Information Available: Experimental procedures and spectroscopic data of the compounds **7**−**13** and **19**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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