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Enantioselective Synthesis of the C1-C9 Segment of Bryostatin by Kinetic Resolution of Racemic β-Keto Esters

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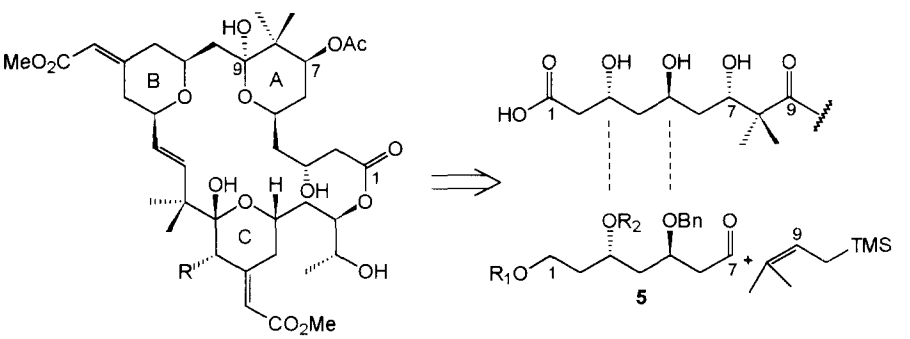
Abstract: The enantioselective synthesis of the C1-C9 segment of bryostatins is described. Racemic β-keto ester **2** was subjected to kinetic resolution. Reduction with baker's yeast establishes two of the three chiral centers. Chemical transformation of the terminal acetylene moiety generates aldehyde **5** which is transformed diastereoselectively to the corresponding alcohol **6** via Sakurai reaction.

The bryostatins are a family of 17 macrolides antibiotics isolated from the marine bryozoan *Bengula neritina* Linnaeus, which exhibit exceptional antineoplastic activity against lymphocytic leukemia and ovarian carcinoma.[1] The first total synthesis was reported by Masamune[2] in 1990 and since then various groups have made contributions to the synthesis of bryostatins.[3] We would like to thank Prof. H. M. R. Hoffmann and J. Weiß for bringing this problem to our attention.[4]



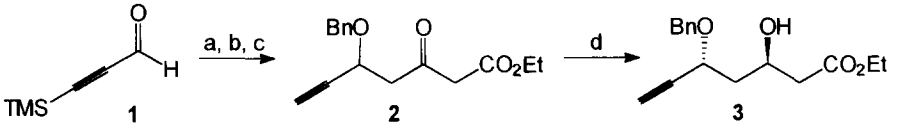
bryostatins

R=H; OAc;
$O_2C(CH)_4(CH_2)_2Me$

Scheme 1

Here we report on the synthesis of the C1-C9 segment of bryostatin utilizing the kinetic resolution of racemic β-keto ester **2** with baker's yeast. Analysis of the backbone of the C1-C9 segment identifies the product derived from baker's yeast kinetic resolution to be identical with the desired stereochemistry of the natural product (Scheme 1). Baker's yeast reduction of **2** already establishes two asymmetric centers of the C1-C9 segment and allows functionalization of the terminal acetylene moiety. The overall strategy is to generate an

aldehyde at C7 which enables a chelation-controlled Sakurai reaction. This reaction establishes the third asymmetric center and additionally the geminal dimethyl group at C8.

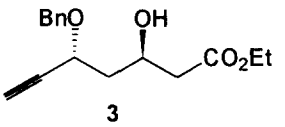


38%; de = 82 %; ee = 84 %

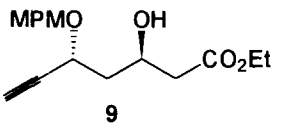
a) Ethyl acetoacetate, 1 eq. NaH, 0°C, 1 eq. LDA, -78°C, THF, then **1**, 83 %; b) $C_6H_5CH_2OC(=NH)CCl_3$, CH_2Cl_2, 77 %; c) KF, 18-crown-6, DMF, H_2O, 99 %; d) baker's yeast, H_2O, sucrose, 3 d, 38 %.

Scheme 2

Racemic β-keto ester **2** was generated by addition of ethyl acetoacetate to propargylic aldehyde **1**. Protection with benzyl trichloracetimidate and desilylation established compound **2** suitable for baker's yeast reduction. Kinetic resolution of **2** yields **3** in very good enantiomeric and diastereomeric excess (de = 82 %; ee = 84 %) (Scheme 2).[5] Even though the kinetic resolution of **2** did not yield the excellent ee values observed for the kinetic resolution of **9** (Scheme 3),[6] we decided to use **3** as the precursor due to the greater stability of the benzyl group under Sakurai conditions.



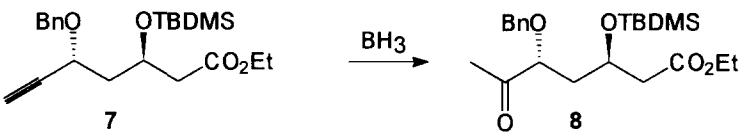
38 %; de = 82 %; ee = 84 %



40 %; de > 98 %; ee = 93 %

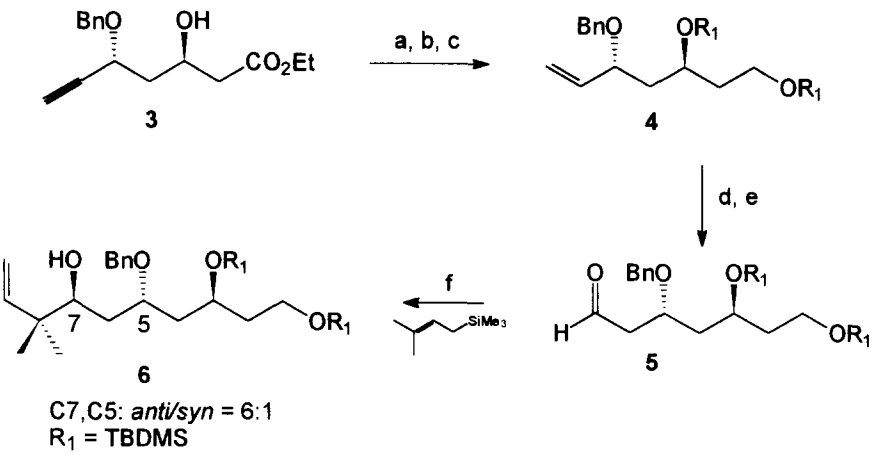
Scheme 3

The diastereomeric ratio of **3** was determined by chiral GC analysis.[7] The enantiomeric purity was established by NMR-shift experiments with $Eu(hfc)_3$ [8] as described by Meyer and Oetting.[9] However, hydroboration of the triple bond did not yield the desired aldehyde but methyl ketone **8** instead (Scheme 4).



Scheme 4

We therefore hydrogenated the acetylene moiety to the corresponding double bond with Lindlar catalyst (70 %) and reduced the ester group with $LiAlH_4$. Double protection with TBDMS triflate[10] generated the protected triol **4** in 43 yield (three steps). Hydroboration and successive oxidation with Dess-Martin periodinane[11] gave aldehyde **5**. The Sakurai reaction was performed under standard conditions[12] at -78° C in CH_2Cl_2 with $TiCl_4$ as the Lewis acid and gave tetraol **6**[13] as a 6:1 mixture of two diastereomers with the desired trans diol as the major isomer (Scheme 5).



a) Lindlar catalyst, H_2, EtOH, 70 %; b) $LiAlH_4$, Et_2O, 67 %; c) 2 eq. TBDMS-triflate, THF, 92%; d) BH_3xTHF, THF, 41 %; e) Dess-Martin periodinane, 88 %; f) $TiCl_4$, CH_2Cl_2, 1-Trimethylsilyl-3-methyl-2-butene, 82 %.

Scheme 5

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5. Sering, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175. Baker's yeast reduction of compound **2**: Baker's yeast (10 g) was suspended in 100 ml warm water (30°C) and sucrose (20 g) was added. From the time the yeast started fermentation, the mixture was stirred for an additional 45 min. Then β-keto ester **2** (0.52 g, 3.36 mmol) was added and the reaction mixture was stirred for 24 h. Another 10 g of baker's yeast were suspended in warm water containing sucrose (20 g) and added to the reaction mixture. β-Keto ester **2** (0.52 g, 3.36 mmol) was added to this slurry. The reaction was stirred gently for additional 2 days and then filtered through a plug of Celite (12 g). The aqueous layer was extracted with Et_2O (3 x 200 ml), the combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (hexane/EtOAc 3:1) to yield diol **3** (385 mg, 38%) and unchanged β-keto ester **2** (1.4 mmol, 440 mg, 43%).

3: $[\alpha]_D^{20}$ = +36.7 (c 1,0 in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, 20°C, TMS): δ 7.33 (s, 5H; CH); 4.82 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2); 4.49 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2); 4.47 - 4.28 (m, 2H; CH); 4.15 (q, ^{3}J(H,H) = 7 Hz, 2H; CH_2); 3.30 (s, br., 1H; OH); 2.52 (d, ^{4}J(H,H) = 2 Hz, 1H; CH); 2.57 - 2.40 (m, 2H; CH_2); 1.92 (dd, ^{3}J(H,H) = 7 Hz, ^{3}J(H,H) = 6 Hz, 2H; CH_2); 1.25 (tr, ^{3}J(H,H) = 7 Hz, 3H; CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$, 20°C, TMS): 172.34 (+), 137.41 (+), 128.08 (-), 127.78 (-), 82.21 (+), 74.46 (+), 70.95 (+), 65.86 (-), 64.67 (-), 60.67 (+), 42.01 (+), 41.39 (+), 14.16 (-); IR ($CHCl_3$): ν = 3520 (w), 3304 (m), 1720 (s), 1496 (m), 1452 (m), 1256 (m).

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7. The diasteromeric excess was determined by GC chromatography on a chiral GC cyclodextrin column at 175°C. (Macherey-Nagel Lipodex column: [Oktakis-(2,6-di-o-pentyl-3-O-butyryl)-γ-cyclo-dextrin]; retention time 7.5-8.2 min; 25 m). We refer to the diastereomeric excess as the ratio of *trans*-diol/*cis*-diol.
8. Eu(hfc)$_3$: tris[3-(heptafluoropropyl)hydroxymethylene)-(+)-camphorato] europium (III).
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13. **6:** $[\alpha]_D^{20}$ = - 18.0 (c 0.05 in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C, TMS): δ 7.32 (s, 5H; CH); 5.87 (dd, ^{3}J(H,H) = 17 Hz, ^{3}J(H,H) = 11 Hz, 1H; CH); 5.07-4.98 (m, 2H; CH_2); 4.58 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2); 4.50 (d, ^{2}J(H,H) = 11 Hz, 1H; CH_2); 4.22 (t, ^{3}J(H,H) = 6 Hz, 1H; CH); 4.00-3.93 (m, 1H; CH); 3.91-3.82 (m, 1H; CH); 3.67 (t, ^{3}J(H,H) = 6Hz, 1H; CH); 1.75-1.58 (m, 6H; CH_2); 1.20 (s, 3H; CH_3); 1.05 (s, 3H; CH_3); 0.88 (s, 9H; CH_3); 0.87 (s, 9H; CH_3); 0.06 (s, 6H; CH_3); 0.05 (s, 6H; CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C, TMS): 145.49 (-); 138.45 (+); 128-.79 (-); 128.45 (-); 127.75 (-); 112.51 (+); 75.37 (-); 74.43 (-); 1.09 (+); 68.16 (+); 67.12 (-); 59.44 (+); 42.11 (+); 41.53 (+); 40.97 (+); 25.94 (-); 22.80 (-); 22.65 (-); -4.20 (-); -5.32 (-); IR ($CHCl_3$): ν = 3467 (w); 1720 (m); 1260 (s).

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