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# Control of Remote Enoate Geometry in the Bryostatins with a Tethered Horner-Wadsworth-Emmons Reagent

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**Abstract:** The stereochemistry of the exocyclic unsaturated ester at $C_{13}$ of the bryostatins may be established with a tethered phosphonate reagent anchored to a proximal hydroxyl function at $C_{16}$ of an advanced intermediate en route to the total syntheses of the bryostatins.

We have been engaged in activities directed towards the total synthesis of bryostatin 1.[2] This fungal metabolite, whose structure was secured by X-ray crystallography, was isolated as a constituent of the bryozoan *Bugula neretina* and was found to possess activity against lymphocytic leukemia and ovarian carcinoma. Since the initial isolation work, eleven additional congeners have been extracted from *Bugula neritina*, and one, bryostatin 8, has been isolated from the bryozoan *Amathia convulata*.[3] Among the various stereochemical challenges posed by this class of polyacetate-derived natural products is the synthesis of the exocyclic unsaturated esters in rings B and C. In our retrosynthetic analysis, disconnection at the $C_1$-O acyl and the $C_{16}$-$C_{17}$ olefin bonds reveals two synthons of roughly equal complexity where the $C_1$-$C_{16}$ portion consists of a $C_1$-acid and a $C_{16}$-aldehyde, and the $C_{17}$-$C_{27}$ portion consists of a $C_{17}$ sulfone and a $C_{25}$ carbinol.

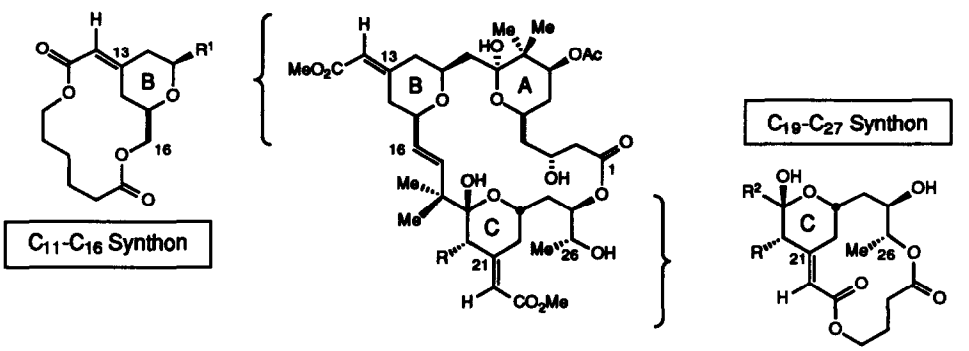
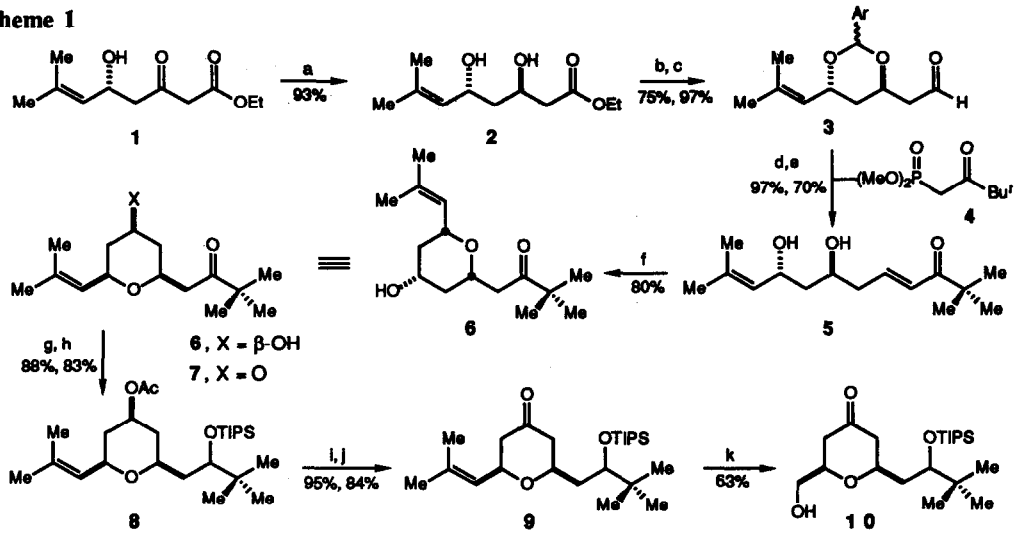



**Figure 1.** Macrocyclic Stereocontrol of Enoate Geometry in Bryostatins 1 & 11.

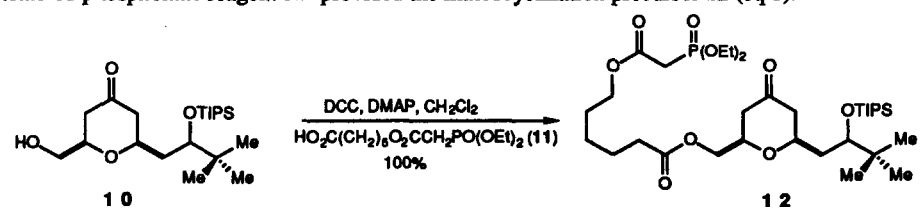
The disposition of the exocyclic ester in ring B relative to the derived oxygen function at $C_{16}$ suggests a plan where a primary alcohol at $C_{16}$ would serve as both an aldehyde precursor and anchor for a tethered phosphonate reagent. Inspection of the $C_{17}$-$C_{27}$ fragment reveals a similar spatial relationship between the $C_{21}$ enoate and the $C_{25}$ alcohol, so that an analogous strategy could be utilized to control the olefin geometry at $C_{21}$.[4] The purpose of the present Letter is to disclose the diastereoselective synthesis of the unsaturated ester at $C_{13}$ in an elaborated intermediate ($C_1$-$C_{16}$) en route to bryostatin 1.[5] The study documents the use of a tethered phosphonate reagent to effect a highly selective and efficient macroolefination reaction to control remote enoate geometry.

**Scheme 1**



(a) $Me_4NBH(OAc)_3$, $MeCO_2H$, MeCN, -40 °C; (b) *p*-$MeOC_6H_4CH_2OMe$, DDQ, $CH_2Cl_2$, 23 °C; (c) $LiAlH_4$, THF, -12 °C; $(COCl)_2$, DMSO, *i*-$Pr_2NEt$, $CH_2Cl_2$, -78 °C; (d) LiCl, *i*-$Pr_2NEt$, MeCN, 0 °C; (e) 4.5:4.5:1 THF/$H_2O$/$MeCO_2H$, 23 °C; (f) *t*-BuOK, THF, -12 °C; (g) $Ac_2O$, py, DMAP, $CH_2Cl_2$; (h) $NaBH_4$, EtOH, 0 °C; TIPSOTf, $Et_3N$; **8** produced as a 1:1-mixture of O–TIPS diastereomers; (i) $K_2CO_3$, MeOH, 23 °C; (j) PDC, pyridinium trifluoroacetate, $CH_2Cl_2$, 23 °C; (k) $O_3$, -78 °C, $CH_2Cl_2$; $Me_2S$; $LiAlH(OCEt_3)_3$, THF, -78 °C.

At the outset, we chose a model substrate that would allow us to adequately define various reaction parameters such as tether length, enolization, and cyclization conditions. Preparation of the model system is illustrated in Scheme 1. Reduction of hydroxyketo ester **1** with $Me_4NBH(OAc)_3$ (2.5 equiv, -40 °C, $MeCO_2H$, MeCN)[6] provided diol **2** (93%, 15:1 diastereoselection). Treatment of **5** with KO*t*Bu (THF, 0 °C) delivered **6** as an 86:1 diastereomeric mixture of cis/trans-substituted tetrahydropyrans **6** as determined by capillary vapor-phase chromatography. The stereochemistry of the substituted tetrahydropyran was established by n.O.e. experiments on the derived diketone **7**; irradiation of the axial $C_6$ proton (4.33 ppm) led to a 6% enhancement of the axial $C_2$ proton (4.16 ppm). The illustrated four-step transformation of ketone **6** afforded ketone **9** which as utilized in subsequent experiments as an unresolved mixture of OTIPS diasdtereomers. Treatment of **9** with a dilute stream of ozone in oxygen (-78 °C, $CH_2Cl_2$) followed by reductive workup ($Me_2S$, 0 °C) provided an unstable keto-aldehyde that was selectively reduced with $LiAlH(OCEt_3)_3$[7] to provide hydroxyketone **10**. Acylation of **10** with the tethered phosphonate reagent **11**[8] provided the macrocyclization precursor **12** (eq 1).



(1)

Several criteria were examined to determine the optimal tether length: overall thermodynamic stability of the product, stereoelectronic requirements of the two esters within the macrocycle,[9] and minimization of unfavorable transannular interactions of the tether with the bridging methylene. Dreiding models suggest that a six-carbon tether engenders a fourteen-member ring with low energy conformations which satisfy the criteria delineated for the desired enoate diastereomer. In an effort to quantify the free energy differences of the two enoates, a multiconformational search was executed with the ring-generating molecular mechanics program of Still.[10] The

lowest energy conformers found for each geometrical isomer differed in energy by ~10 kcal/mol (Figure 2). It is reassuring that the more stable diastereomer **A** bears both esters in the *s*-cis conformation (O=C-O-C equals 5.8° for the unsaturated ester and 3.5° for the saturated ester); in contrast, the less stable macrocycle **B** possesses the unsaturated ester moiety in the *s*-trans arrangement (O=C-O-C equals 173.8°) while the saturated ester is perturbed away from the *s*-cis minimum (O=C-O-C equals 25.1°). In addition, whereas enoate **A** benefits from some degree of conjugation (O=C-C=C equals 165°), the less stable counterpart **B** lacks this stabilizing feature (O=C-C=C equals 53°). To the extent that these effects are reflected in the transition structure leading to the macrocycle, the diastereoselection is expected to be high.

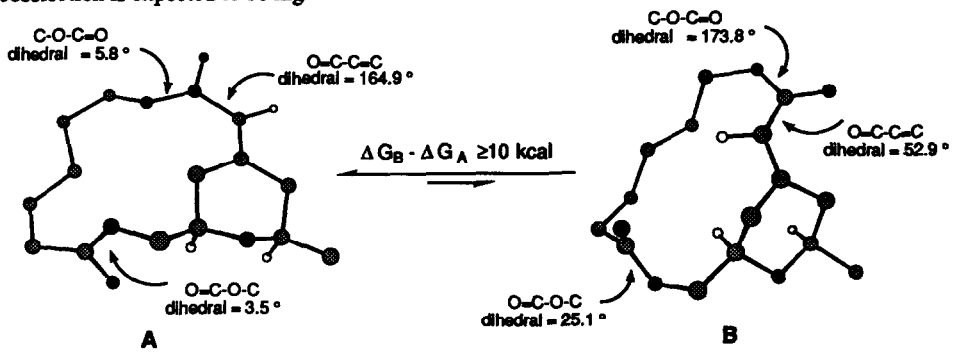
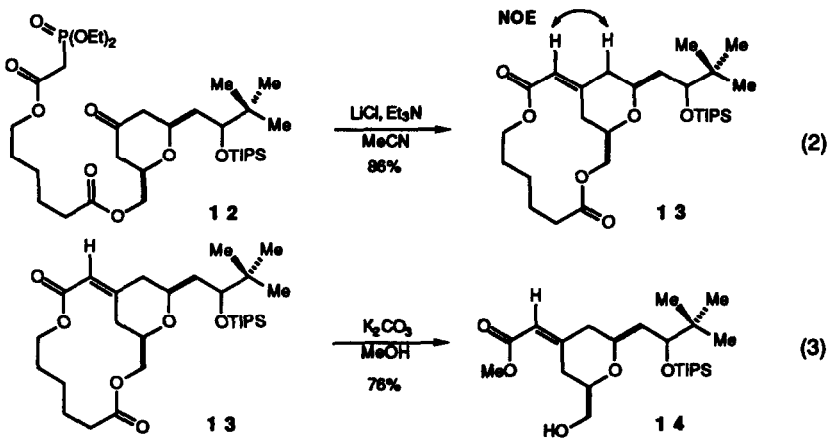


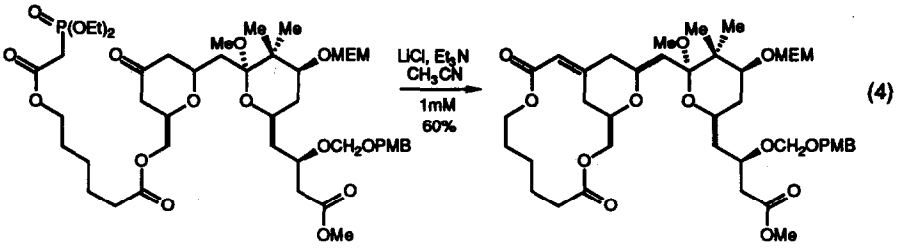

**Figure 2.** Lowest Energy Structures for Cis- and Trans-substituted Macrodilactones.

We were gratified to find that treatment of a 1 mM solution of **12** with 33 equiv of lithium chloride and 30 equiv of triethylamine for 36 h afforded the desired macrocycle **13** in 86% yield as a single olefin diastereomer by $^1$H NMR spectroscopy (eq 2). The enoate geometry is supported by n.O.e. experiments; irradiation of the vinyl proton at 5.63 ppm resulted in 5% enhancement at the proximal endocyclic methylene protons at 2.15-2.08 ppm. In addition, mass spectrometric analysis (electron impact) confirmed that the desired product, and not high-molecular weight oligomers, had been formed in this transformation. Having served its function, the tether was cleanly removed with $K_2CO_3$ in methanol (1.2 equiv, 25 °C, 36 h) to afford **14** (eq 3).




A similar cyclization was performed on an advanced intermediate in the synthesis of the $C_1$-$C_{16}$ portion of bryostatin 1 (eq 4). Cyclization of **15** under identical conditions (33 equiv LiCl, 30 equiv $Et_3N$, MeCN, 25 °C, 36 h) afforded the 14-member dilactone **16** in 60% yield as a single olefin diastereomer judged by $^1$H NMR

spectroscopy. The lower yields obtained as compared to the model system may be attributed to elimination across $C_2$-$C_3$ by competitive deprotonation of the $C_1$ ester. Moreover, methanolysis of the resulting macrocyclic dilactone ($Li_2CO_3$, MeOH) selectively transesterifies the saturated ester and provides a primary alcohol. Oxidation of the $C_{16}$ alcohol provides the $C_1$-$C_{16}$ aldehyde for subsequent coupling to the $C_{17}$-$C_{27}$ subunit.




15 16

In conclusion, we have demonstrated that the stereochemistry of the remote unsaturated ester at $C_{13}$ of the bryostatins may be controlled through a macrocyclic olefination reaction. Further studies on the total synthesis of bryostatin 1 will be reported shortly.

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## References and Notes

(1) National Science Foundation Predoctoral Fellow, 1985-1988.

(2) Pettit, G. R.; Herald, C. L.; Clardy, J.; Arnold, E.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 6846-6848.

(3) See: Pettit, G. R.; Leet, J. E.; Herald, C. L.; Kamano, Y.; Boettner, F. E.; Baczynskyj, L.; Nieman, R. A. *J. Org. Chem.* **1987**, *52*, 2854-2860 and references therein.

(4) For those members of the bryostatin family bearing a substituent at $C_{20}$, the geometry of the unsaturated ester at $C_{21}$ in fact could be expected to be controlled by minimization of $A_{1,3}$ allylic interactions in analogy to literature precedents for substituted cyclohexanones, for example, see: Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2629-2631.

(5) As an alternative method we envisioned employing modifications of the asymmetric Wittig reaction reported by Hanessian, see: Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754-5756. Since the initiation of this project a similar asymmetric olefination has been reported with (+)-8-phenylneomenthyl phosphonoacetate, see: (a) Rehwinkel, H.; Skupsch, J.; Vorbrüggen, H. *Tetrahedron Lett.* **1988**, *29*, 1775-1776. (b) Gais, H.-J.; Schmiedl, G.; Ball, W.; Bund, J.; Hellmann, G.; Erdelmeier, I. *Tetrahedron Lett.* **1988**, *29*, 1773-1774.

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(7) Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628-4629.

(8) The tethered phosphonate reagent was prepared by monosilylation of 1,6-hexanediol (NaH, THF, *t*-$BuMe_2SiCl$, 0 °C) followed by acylation with diethyl phosphonoacetic acid and two-phase Jones oxidation.

(9) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872-1874.

(10) The calculations were performed with the MM2 force field on a series of structures generated in the multiconformer mode of the MacroModel program generously provided by Professor W. Clark Still, Columbia University.

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