Soluble Polymer-Supported Chemoenzymatic Synthesis of the C_{21}−C_{27} Fragment of the Bryostatins†

José A. López-Pelegrín, Paul Wentworth, Jr.,* Frank Sieber, William A. Metz,‡ and Kim D. Janda*

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

paulw@scripps.edu

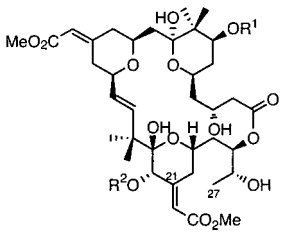
Received June 9, 2000

A chemoenzymatic synthesis of the C_{21}−C_{27} fragment of the marine macrolide family of bryostatin antibiotics is presented. The approach commences from achiral starting materials and has as its crucial step the enzymatic resolution of a racemic mixture of soluble polymer-supported alcohols (*syn*-**10** and *syn*-**11**). The immobilized lipase from *Candida antarctica* (Novozym 435) catalyzes the enantioselective acetylation of *syn*-**10** (in 40% conversion and >99% ee), allowing isolation of the key intermediate (*R*)-**14** in enantiomerically pure form following its cleavage from the poly(ethylene) glycol (PEG) scaffold. The PEG matrix is both compatible with the multipolymer enzymatic transformation and allows for rapid purification and facile NMR characterization of all intermediates throughout the synthesis.

Introduction

Extracts from the marine bryozoans *Bugula neritia* (Linnaeus) and *Amathia convoluta* exhibit potent antineoplastic activity against lymphocytic leukemia and ovarian carcinoma,[1] as well as the potential to promote protein kinase C activity.[2] The active constituents are a family of related macrocyclic lactones: the bryostatins.[3]

Two total syntheses of bryostatins have been accomplished,[4] and a tremendous amount of research has been directed toward the partial syntheses of the composite segments of these 20-membered ring lactones.[5] Recent computational and SAR studies reveal that a central pharmacophoric recognition domain within the total bryostatin structure is located around the heteroatoms at C_1, C_{19}, and C_{26}.[6] This allows intensive combinatorial and parallel synthetic efforts targeted at optimizing the biological activity of each fragment.



Bryostatin 1 $R^1 = COCH_3$, $R^2 = CO(CH{=}CH)_2nPr$
Bryostatin 2 $R^1 = H$, $R^2 = CO(CH{=}CH)_2nPr$
Bryostatin 6 $R^1 = COnPr$, $R^2 = COCH_3$
Bryostatin 7 $R^1 = COCH_3$, $R^2 = COCH_3$

Ever since the work of Merrifield,[7] it has become increasingly clear that polymer-supported chemistry offers distinct advantages over its solution-phase counterpart.[8] The synthetic strategies employed by such disciplines as high-throughput organic synthesis and combinatorial library construction are driven by the need for optimal conversion, minimal side reactions, and simplified purification procedures, features that are also essential paradigms for natural product synthesis. Therefore, there is an increasing effort to convert the synthetic chemistry associated with small molecule natural products into a polymer-supported format.[9] However, the modification of chemistry from solution- to solid-phase format can be very time-consuming and is not always successful due to the heterogeneous nature of the ensuing process. Liquid-phase organic chemistry, which utilizes soluble polymer supports, offers a unique resolution to these problems and is becoming an increasingly useful adjunct to existing solid-phase methods.[10] As part of an

* To whom correspondence should be addressed. (P.W.) Tel: (858) 784-2576. Fax: (858) 784-2590. (K.D.J.) Tel: (858) 784-2515. Fax: (858) 784-2595. E-mail: kdjanda@scripps.edu.

† This paper is dedicated to Professor Robert V. Hoffman on the occasion of his retirement.

‡ On sabbatical leave from Aventis, New Jersey.

(1) (a) Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature* **1970**, *227*, 962. (b) Pettit, G. R.; Herald, C. L.; Clardy, J.; Arnold, E.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (c) Pettit, G. R.; Kamaro, Y.; Herald, C. L.; Tozawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6768.

(2) a) Kraft, A. S.; Smith, J. B.; Berkow, R. L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1334. (b) Berkow, R. L.; Kraft, A. S. *Biochem. Biophys. Res. Commun.* **1985**, *131*, 1109. (c) Ramsdell, J. S.; Pettit, G. R.; Tashjian, A. H., Jr. *J. Biol. Chem.* **1986**, *261*, 17073.

(3) Review: Pettit, G. R. The Bryostatins. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Ed.; Springer-Verlag: New York, 1991; No. 57, pp 153−195.

(4) (a) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. G.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407. (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2354.

(5) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041 and references therein.

(6) Wender, P. A.; Lippa, B. *Tetrahedron Lett.* **2000**, *41*, 1007 and references therein.

(7) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

(8) (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (c) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817.

(9) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Glannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268.

10.1021/jo005539u CCC: $19.00
Published on Web 11/21/2000

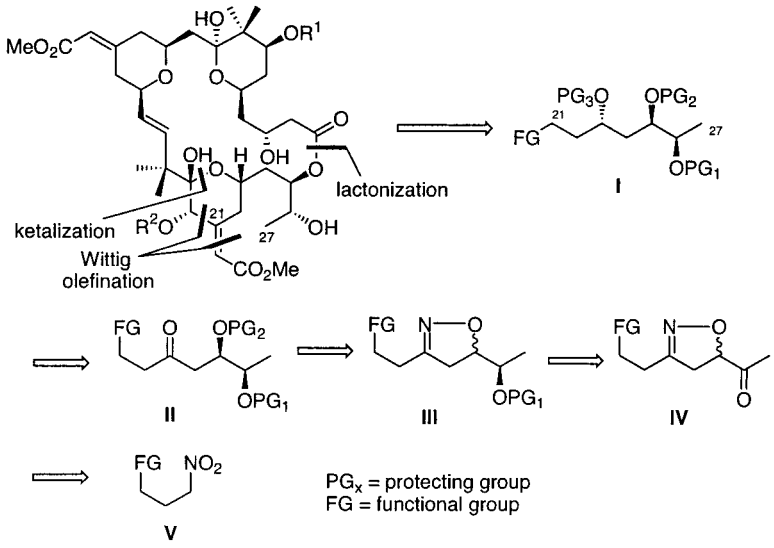


Figure 1. Retrosynthetic strategy to the orthogonally protected $C_{21}-C_{27}$ fragment **I** of the bryostatins.[13]

ongoing effort to improve and expand the utility and applicability of liquid-phase chemistry into asymmetric organic synthesis we recently reported the linear polystyrene-supported syntheses of prostaglandin E methyl ester and prostaglandin $F_{2\alpha}$.[11] Herein, we report the first polymer-supported synthetic approach to a composite fragment of the bryostatin natural products. Poly(ethylene glycol) (PEG) is explored as a matrix for a novel synthetic approach to the $C_{21}-C_{27}$ fragment of the bryostatins[12] that incorporates a stereoselective enzymatic transformation.

Results and Discussion

The retrosynthetic strategy to the target fragment **I** is shown in Figure 1. The crux of the challenge is the sequential stereoselective generation and orthogonal protection of the three secondary alcohols at C_{23}, C_{25}, and C_{26}.

The synthons **II**−**IV** are generated following a preliminary [3 + 2] dipolar cycloaddition between a nitrile oxide, generated in situ from nitroalkane **V**, and a suitable dipolarophile.[14] With no stereocontrol applied during the cycloaddition reaction, the C_{25}-stereochemistry remains undefined at this juncture. However, by exploiting one of the plethora of available enantioselective enzymatic reductions, it was envisaged that the ketone of **IV** could be reduced to give **III** as pair of diastereomers that would be separated following cleavage from the support. This then gives indirect entry to **III** as the necessary (*R*,*R*)-C_{25},C_{26} diastereomer. Reduction of the isoxazoline ring in **III** followed by in situ hydrolysis then gives **II** the ketone group of which can be reduced stereoselectively to yield the desired *anti*-diol **I**, the ultimate synthetic target.

The particular requirements of the enzymatic transformation guided the choice of PEG as a polymer support. The required matrix must be compatible with this biocatalytic transformation and resins, with a few notable exceptions,[15] are incompatible with enzymatic processes. In addition, the polymer support must be soluble under both organic and aqueous conditions as demanded by the enzymatic reaction.

Monomethoxy PEG of 5000 molecular weight (MeO−PEG_{5000}) was chosen as the specific matrix for this synthesis. While the loading associated with this particular support (0.2 mmol/g) is lower than other PEG matrixes we have utilized previously for liquid-phase chemistry, such as PEG_{3400},[16] it provides the optimal relationship between polymer recovery by precipitation and ease of NMR interpretation. Furthermore, comparison of the integral ratios of polymer-bound intermediates with the terminal methyl group allows a direct and easy measure of both loading and conversion after each synthetic step.

Of primary consideration when developing a polymer-supported synthesis is the linker strategy. It was anticipated that an acid-labile linker, while being completely stable during the synthetic process, would facilitate orthogonal cleavage of the final polymer-linked intermediate from the support. Therefore, we prepared the soluble polymer-supported dihydropyran **1**, an analogue of Ellman's linker utilized in solid-phase chemistry (Scheme 1).[11,17]

(10) (a) Gravert, D.; Janda, K. D.; *Chem. Rev.* **1996**, *97*, 489. (b) Wentworth Jr., P.; Janda, K. D. *Chem. Commun.* **1999**, 1917.

(11) (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724. (b) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943.

(12) For other approaches to the synthesis of this fragment: (a) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (b) Roy, R.; Rey, A. W.; Charron, M.; Molino, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1308. (c) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741. (d) De Brabander, J.; Vanderwalle, M. *Synthesis* **1994**, *8*, 855. (e) Hale, K. J.; Lennon, S. A.; Manaviarar, S.; Javaid, M. H. Hobbs, C. J. *Tetrahedron Lett.* **1995**, *36*, 1359. (f) Ohmori, K.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 6515.

(13) A similar approach to enantiomerically defined 1,2,4-triols has been utilized previously; see: (a) Ticozzi, C.; Zanarotti, A. *Tetrahedron Lett.* **1988**, *29*, 6167. (b) Ticozzi, C.; Zanarotti, A. *Liebigs Ann. Chem.* **1989**, *12*, 1257.

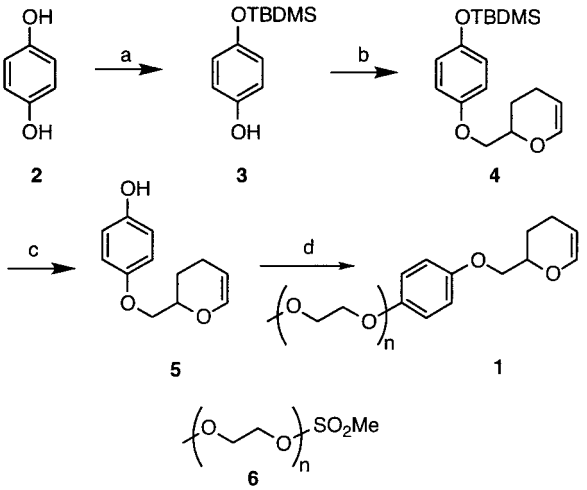
(14) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(15) (a) Rademann, J.; Grøtli, M.; Meldal, M.; Block, K. *J. Am. Chem. Soc.* **1999**, *121*, 5459.

(16) (a) Sieber, F.; Wentworth, P., Jr.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188. (b) Wentworth, P., Jr.; Vandersteen, A. M.; Janda, K. D. *Chem. Commun.* **1997**, 759. (c) Wentworth, A. D.; Mansoor, U. F.; Wentworth, P., Jr.; Janda, K. D. *Organic Lett.* **2000**, *2*, 477.

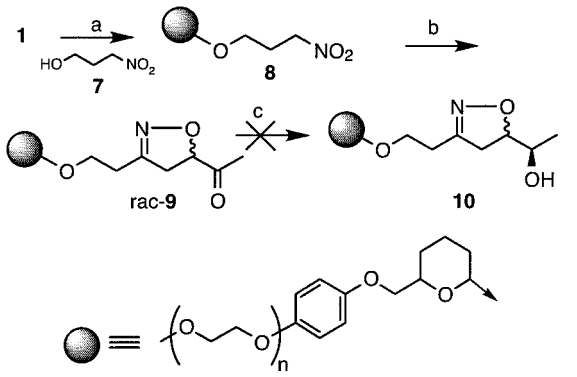
(17) (a) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333. (b) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859. (c) López-Pelegrín, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, in press.

Scheme 1[a]



[a] Reagents and conditions: (a) TBDMSCl (1.1 equiv), imidazole (2.5 equiv), CH_2Cl_2 (53%); (b) PPh_3, DIAD, 6-hydroxymethyl-3,4-dihydro-2*H*-pyran, THF (82%); (c) TBAF, THF (91%); (d) **6**, $CsCO_3$, DMF (91% PR).

Scheme 2[a]



[a] Reagents and conditions: (a) 3-nitropropan-1-ol, PPTS, CH_2Cl_2 (89% PR); (b) PhNCO, methylvinyl ketone, Et_3N (cat.), benzene (93% PR); (c) attempted enzymatic reduction.

The relative ease of formation of aryl alkyl ethers of PEG relative to dialkyl ethers meant that 6-hydroxymethyl-3,4-dihydro-2*H*-pyran was attached to PEG via the intermediacy of dihydroquinone **2**. Thus, mono silyl ether protection of **2** gave alcohol **3** in acceptable yield (53%). Mitsunobu[18] coupling of **3** with 6-hydroxymethyl-3,4-dihydro-2*H*-pyran, followed by tetrabutylammonium fluoride (TBAF)-mediated deprotection of **4**, yielded phenol **5** (75% overall yield from **3**). Reaction of **5** with PEG-mesylate **6**, prepared as previously described,[19,15a] gave the desired polymer-supported dihydropyran **1** with 91% polymer recovery (PR) and optimum loading (0.2 mmol/g).

With the linker in place, the synthetic route to the bryostatin fragment commenced (Scheme 2). 3-Nitropropan-1-ol **7**,[20] was attached to the PEG-support by reaction with the dihydropyran moiety of **1** to give the polymer-supported nitroalkane derivative **8**.

Routine ^{1}H NMR spectroscopy was used to follow this reaction, which confirmed derivatization with **7** by loss of the alkene proton resonance (δ 6.4 ppm) of **1**. Following in situ transformation of the nitro group of **8** into its respective nitrile oxide using Mukaiyama's procedure,[21] a dipolar [3 + 2] cycloaddition was performed with methylvinyl ketone as the dipolarophile. The cycloaddition proceeded smoothly, giving a racemic mixture of polymer-supported isoxazolines (*rac*-**9**) with excellent PR (>93%) following precipitation into cold diethyl ether. ^{1}H NMR of the polymer-bound isoxazoline showed the presence of only the favored 5-substituted regioisomer.

With polymer-supported *rac*-**9** in hand, the key enzymatic reduction to alcohol **10** was then attempted. Two well-characterized enantiocomplementary NADPH-dependent preparations were investigated; Baker's yeast extract (type I and II)[22] and *Lactobacillus kefir*[23] (cell extract). Baker's yeast catalyzes the transfer of the *pro-R* hydride from the cofactor to the *re* face of its carbonyl substrate that leads to the (*S*)-**10** alcohol. In constrast *L. kefir* reductase transfers the *pro*-R hydride to the *si*-face of the ketone substrate thus generating the required (*R*)-**10** alcohol. While the use of Baker's yeast installs the incorrect stereochemistry at C-26 for the naturally occurring bryostatin $C_{21}-C_{27}$ fragment, it nevertheless allows access to a homochiral epimer ideal for SAR analysis vide supra.

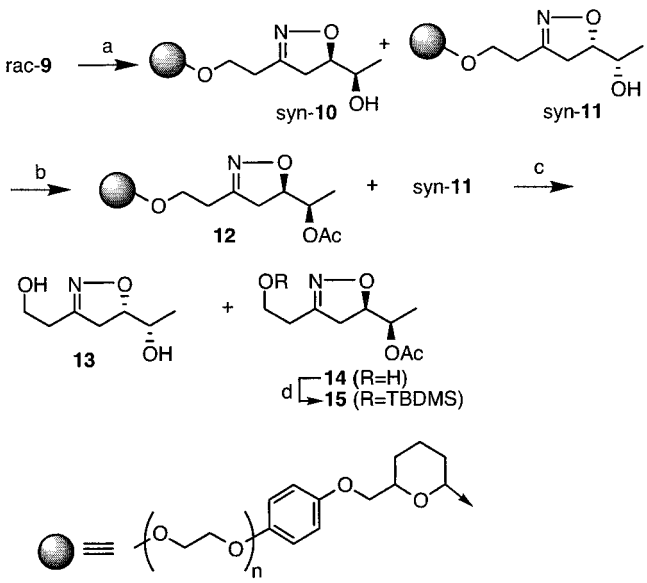
Preliminary enzyme-catalyzed reactions, undertaken in phosphate buffer, in which the PEG-ketone **9** is completely soluble were however not successful. No reduction of the ketone of *rac*-**9** could be detected. Modification of reaction conditions such as temperature, pH and *rac*-**9** concentration did not lead to significant formation of **10**. Control experiments with *rac*-**9** in solution confirmed that the 5-acetylisoxazoline group was compatible with both the baker's yeast and *L. kefir* reductions. Reduction occurred either in the presence or absence of PEG in the reaction mixture further suggesting that the PEG chain does not have a detrimental effect on the enzyme-catalyzed process. The only conclusion that can be drawn thus far is that the linker may be influencing the enzymes' activity. However maintenance of Ellman's linker was considered important within the whole synthetic strategy. Therefore, the synthetic approach was modified as outlined in Scheme 3, which while containing the same linker includes a modified enzyme step.

Selective syn reduction of *rac*-**9** using L-Selectride,[24] generated racemic alcohols (*syn*-**10** and *syn*-**11**) in almost quantitative yield, and with complete diastereoselectivity (determined by ^{1}H NMR). This then setup the prospect for a potential stereoselective enzyme-catalyzed resolution of *syn*-**10** and *syn*-**11** with a suitable lipase.

A panel of commercially available esterase/lipase enzymes were examined; including the CloneZyme library of recombinant thermophilic enzymes (ESL-001-01 to -07), Novozym 435 (immobilized *Candida antarctica* lipase) and CRL (*Candida rugosa* lipase). Vinyl acetate was used as the acyl donor and the reaction was performed in anhydrous benzene or toluene with conditions such as temperature and reaction time being

(18) Mitsunobu, O. *Synthesis* **1981**, 1.
(19) (a) Zhao, X.-Y.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433.
(20) Öhrlein, R.; Schwab, W.; Ehrler, R.; Jäger, V. *Synthesis* **1986**, 535.
(21) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(22) Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49.
(23) Hummel, W. *Appl. Microbiol. Biotechnol.* **1990**, *34*, 15.
(24) Curran, D. P.; Zang, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2613.

Scheme 3[a]



[a] Reagents and conditions: (a) L-Selectride, CH_2Cl_2 (90% PR); (b) Novozym 435, vinyl acetate, benzene (40% conversion, >99% ee, 96 % PR); (c) HF (aq), CH_3CN (54%); (d) TBDMSCl, imidazole, CH_2Cl_2 (85%).

Table 1. Enzyme Screening for the Stereoselective Acylation of PEG-Bound Alcohols *syn*-10 and *syn*-11

entry	enzyme	*T* (°C)	time (h)	% convn	% ee[a]
1	Novozym 435	20	48	48	86
2	PCL	20	48	32	n.d.
3	ESL-01 to 07	20	48	<5	n.d.
4	Novozym 435	70	6	50	92
5	Novozym 435	70	4	40	>99

[a] Measured by capillary GC on purified **14** samples. n.d. = not determined.

investigated (Table 1). In contrast to the oxidoreductase enzyme reaction vide supra, this enzyme-catalyzed acylation reaction has to be carried out in organic solvent to minimize the reverse esterase action. PEG-supported *syn*-**10** was indeed a viable substrate for Novozym 435 and CRL under these conditions. Optimization of the reaction conditions revealed that the Novozym 435 catalyzed acylation of *syn*-**10** (*R*-alcohol) can be carried to almost complete conversion in anhydrous toluene as the solvent (70 °C, 4 h, 40% conversion, entry 5 in Table 1). The reactivity of Novozym 435 with the PEG-supported alcohol **10** is of particular significance because the enzyme is itself immobilized on a macroporous poly(propylic) resin (containing ca. 1% w/w of enzyme). Therefore this biocatalytic reaction is occurring on two separate polymer supports, in a so-called multipolymer reaction.[25] This is, to our knowledge, the first such example of this phenomenon and offers a real advantage of soluble polymer-supported chemistry over its solid-phase homologue where such a polymer−polymer reaction would be unfeasible.

The enzyme-catalyzed reaction was routinely monitored by ^{1}H NMR following removal of aliquots from the reaction mixture. The downfield chemical shift of the resonance of the methine proton on C_{26} from 4.36 ($C_{26}H$-OH) to 4.93 ($C_{26}H$-OAc) ppm was a clear indication of the acylation progress. The stereoselectivity of the acylation process was excellent (>99%) as determined by chiral capillary GC of the product **14** after its cleavage from the PEG-support (aqueous HF in acetonitrile) (Figure 2).[26] The enzymatic resolution allowed ready separation of alcohol **14** and diol **13**, by silica gel chromatography, after cleavage. This separation also concomitantly solves the so-far undefined stereochemistry at C_{25}, resulting from the 1,3-dipolar cycloaddition reaction vide supra, since alcohol **14** now contains exclusively the desired (*R*)-configuration at both C_{25} and C_{26}. Diol **13** contains the (*S*)-configuration at C_{25} and C_{26} and offers an entry point into diastereomeric libraries of bryostatin analogues.

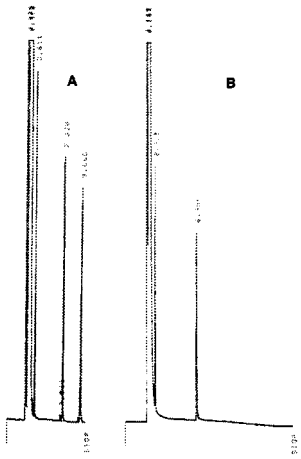
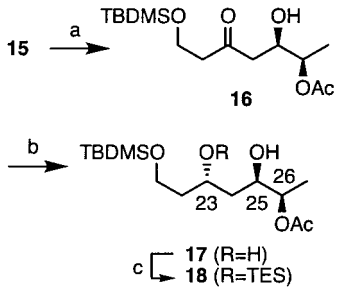


Figure 2. Capillary GC chromatograms of **14**. (A) racemic mixture of *syn*-acetates (generated by acetylation of *syn*-**10** and *syn*-**11** with acetic anhydride/pyridine). (B) purified *syn*-acetate **14** generated by Novozym 435 catalyzed resolution and HF cleavage from the polymer support.

Scheme 4[a]



[a] Reagents and conditions: (a) H_2, Raney Ni, MeOH/AcOH/H_2O; (b) $Me_4NHB(OAc)_3$, CH_3CN, AcOH (66% from 15, 89 % *de*); (c) TESCl, DMAP, CH_2Cl_2 (79%).

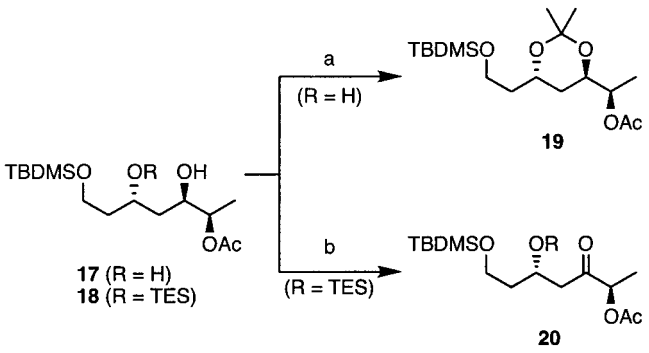
Alcohol **14** was silylated to the isoxazoline **15** in 85% yield and the heterocyclic ring was then reduced to the *β*-hydroxy ketone **16** (Scheme 4).[27] Among the different reductive conditions explored, Raney Nickel afforded the best results; *β*-keto alcohol **16** being essentially pure by NMR without the need for column chromatography.[28] A

(25) For examples of multipolymer strategies in polymer-supported chemistry, see: (a) Han, H.; Janda, K. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1731. (b) Toy, P. H.; Reger, T. S.; Janda, K. D. *Organic Lett.* **2000**, *2*, 2205.

(26) For the selectivity of Novozym 435 toward acylation of *R* alcohols see: (a) Arroyo, M.; Sinisterra, J. V. *J. Org. Chem.* **1994**, *59*, 4410. (b) Uenishi, J.; Hiraika, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 2481. (c) Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287. (d) Frykman, H.; Öhrner, N.; Norin, T.; Hult, K. *Tetrahedron Lett.* **1993**, *34*, 1367.

(27) a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

Scheme 5[a]



[a] Reagents and conditions: (a) $Me_2C(OMe)_2$, HCl (83%); (b) Dess–Martin reagent, CH_2Cl_2 (93%).

clean reduction was essential, because attempts to purify **16** by column chromatography were hampered by extensive elimination, leading to the isolation of the corresponding α,β-unsaturated ketone.

Induction of the last stereogenic center at C_{23} was accomplished following the methodology of Evans and coworkers.[29] Treatment of **16** with $Me_4NHB(OAc)_3$ at low-temperature allowed the formation of the *anti*-diol **17** via intramolecular hydride transfer, with an 89% de (as determined by ^1H NMR integration of representative signals). Both diastereoisomers were separated by silica gel chromatography and the assigned anti-configuration of the major isomer was established by a ROESY-NMR experiment performed on the respective acetal derivative **19** (Scheme 5).[30]

To selectively protect one of the two alcohol functions, diol **17** was treated with 1 equiv of triethylsilyl chloride, giving rise to the required orthogonally protected triol **18**, with exclusive silylation of the less hindered alcohol (in 79% yield).[12c] The regiochemistry of this last protection step was unequivocally determined by oxidation of the remaining alcohol to the corresponding ketone **20**.[31]

Conclusions

This paper reports a novel soluble polymer-supported synthetic approach to the $C_{21}-C_{27}$ fragment of the bryostatin macrocyclic lactone natural products. The use of the PEG support offers the classical benefits of polymer-supported chemsitry over its solution-phase counterpart of rapid purification and high yields. The unique benefit of the PEG support relative to a comparative synthesis on most resins is the facility to incorporate enzymatic transformations and especially in this case where the enzyme itself was bound onto a macroporous support. The mulitpolymer biocatalytic transformation exploited, a stereospecific acylation reaction, was critical to the strategy and incorporated most of the necessary chiral information into the poly-oxygenated fragment allowing the synthesis to commence from inexpensive achiral starting materials.[32] Furthermore, the use of enzyme-assisted chemistry within this novel route, allows access to all available diastereomers of the $C_{21}-C_{27}$ fragment, which is a valid starting point for combinatorial chemistry and SAR analysis.

Acknowledgment. This work was supported by The National Institutes of Health (GM-56154), The Scripps Research Institute, and The Skaggs Institute for Chemical Biology (K.D.J.). The authors also thank Diversa for the kind donation of the CloneZyme samples and Dr. A. Córdova for helpful suggestions during lipase selection. J.A.L.-P. thanks the Spanish Ministerio de Educación y Ciencia for a postdoctoral Fulbright fellowship.

Supporting Information Available: Full experimental details. ^1H and ^{13}C NMR spectra of compounds **14**–**20** and ROESY of compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005539U

(28) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.

(29) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(30) Even though $Me_4NHB(OAc)_3$ is known to give selective anti reductions of β-keto alcohols (see ref 29), there are examples in the literature where no selectivity is obtained from this transformation (De Brabander, J., Vandewalle, M. *Pure Appl. Chem.* **1996**, *68*, 715), therefore necessitating the ROESY experiment.

(31) The methine proton of C-26 (C*H*OAc) in **20** is only coupled with its vicinal methyl group, as determined by ^1H and COSY–NMR experiments.

(32) For other related syntheses starting from achiral materials, see ref 12c,e.