Pergamon

Tetrahedron Letters, Vol. 36, No. 36, pp. 6519-6522, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01310-5

Synthetic Studies on Bryostatins, Potent Antineoplastic Agents: Synthesis of the C_{17}-C_{27} Fragment of C_{20} Oxygenated Bryostatins

Ken Ohmori, Shigeru Nishiyama* and Shosuke Yamamura*
Department of Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi, Yokohama 223, Japan

Abstract: Synthetic process towards the bottom half portion of C_{20} oxygenated series of bryostatins is described. The stereogenic center at C_{20} position was constructed through a hydroxyl group-directed epoxidation by using mCPBA. It was found that silver (I) salt is an effective and mild reagent for regioselective ring cleavage of α-bromoepoxides into the corresponding α-hydroxyketones via oxonium ion intermediates.

Bryostatins,[1] polyether macrolides isolated from the marine bryozoans *Bugula neritina* Linnaeus and *Amathia convoluta*, possess remarkably powerful antineoplastic activities and the potential to promote kinase C activity, properties which have attached the interest of synthetic chemists.[2] In a previous paper,[3] we described the efficient synthesis of the bottom-half fragment suitable for the C_{17}-C_{27} backbone of the C_{20} deoxygenated series (bryostatins 10, 11 and 13). With this encouraging result in hand, we extended our attention to synthesis of the same part of other C_{20} oxygenated series that include a majority of the bryostatin family. We disclose herein efficient construction of the bottom-half fragment suitable for the C_{17}-C_{27} portion, according to a retrosynthetic analysis involving the bond disconnection between C_{21} and C_{22} (Figure 1).

Asymmetric synthesis of the C_{17}-C_{21} fragment (1). Scheme 1 summarizes preparation of the subject alkyne (1) whose asymmetric center was indispensable for the following stereoselective epoxidation of a secondary allyl alcohol unit. Thus, commercially available 2,2-dimethyl-1,3-propanediol was submitted to a four-step sequence consisting of monomesylation (65%), alcohol protection as a THP ether (95%), treatment with sodium thiophenoxide to introduce a phenyl sulfide substituent (82%), then removal of the THP group under acidic conditions (80%) to afford 3. Oxidation and Horner-Emmons olefination sequence effected conversion of 3 into α,β-unsaturated ester 4 in high yield. Several chiral ligands for asymmetric

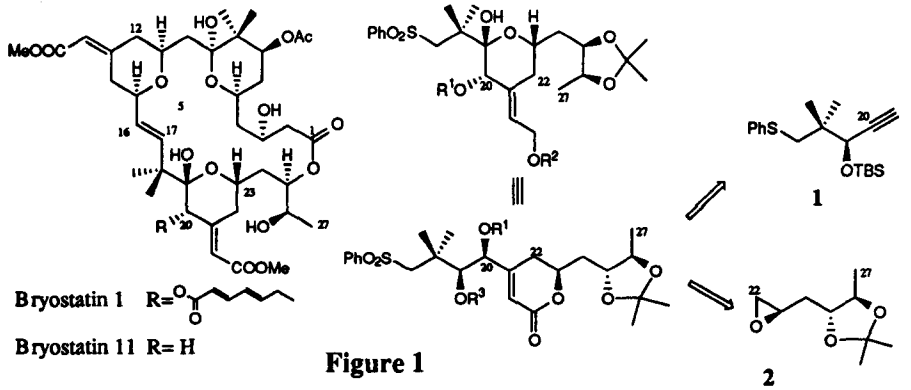
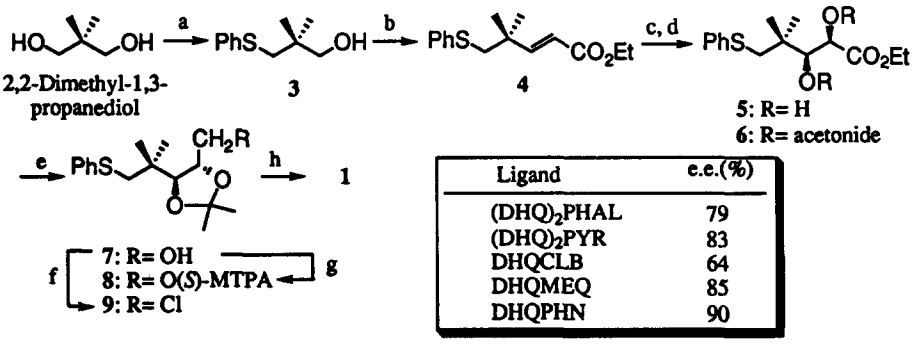


Figure 1

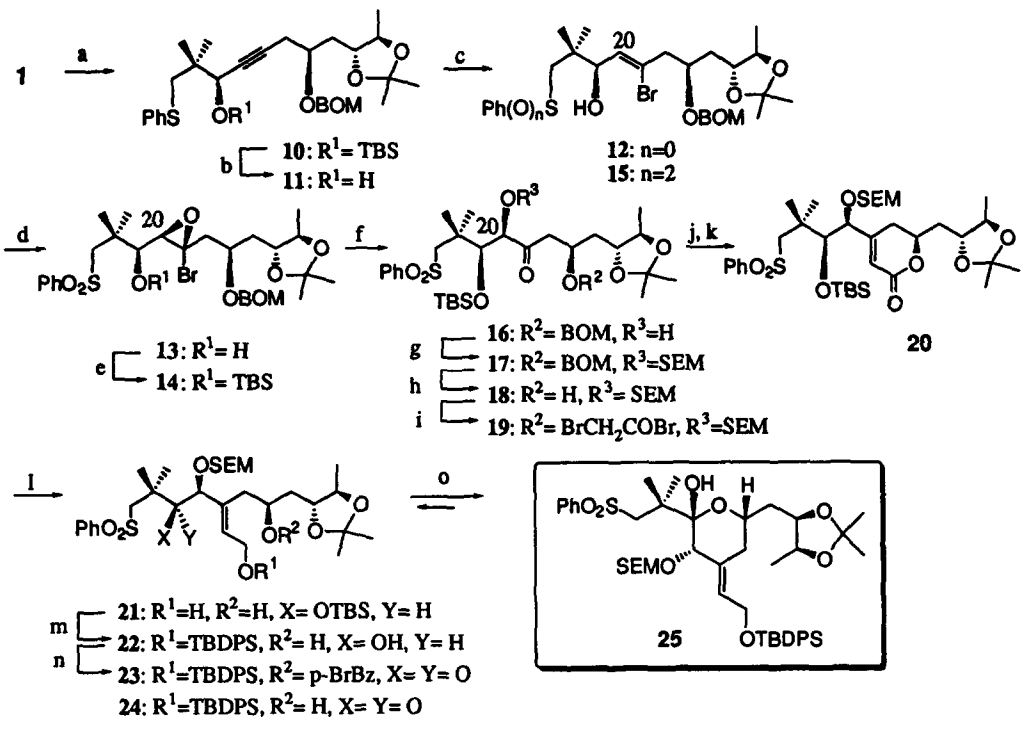


Ligand	e.e.(%)
$(DHQ)_2PHAL$	79
$(DHQ)_2PYR$	83
DHQCLB	64
DHQMEQ	85
DHQPHN	90

Scheme 1. *reagents:* a) i. MsCl, pyr/CH_2Cl_2; ii. DHP, p-TsOH/CH_2Cl_2 (62% in 2 steps); iii. PhSNa, 18-Crown-6/DMF, 90 °C (82%); iv.THF-H_2O-AcOH (4:2:1) (80%). b) i. SO_3·Pyr, Et_3N, DMSO/CH_2Cl_2 (83%); ii. $(EtO)_2P(O)CH_2CO_2Et$, NaH/toluene (quant). c) DHQPHN (2mol%), $K_2OsO_2(OH)_4$ (0.4mol%), K_3FeCN_6 (3eq.), K_2CO_3 (3eq.), $MeSO_2NH_2$ (1eq.)/tBuOH-H_2O, 0 °C, 18 h (94%, 90% ee.). d) $Me_2C(OMe)_2$, p-TsOH/CH_2Cl_2. e) $LiAlH_4$/THF. f) Ph_3P, CCl_4, reflux (93% in 3 steps). g) (*R*)-MTPACl, pyr, DMAP/CH_2Cl_2. h) i. nBuLi, HMPA; ii. TBSCl, imidazole (90% in 2 steps).

dihydroxylation according to Sharpless protocol[4] were evaluated to introduce stereogenic centers to **4**. Among them, interestingly, the dihydroquinine-based phenanthryl ether ligand (DHQ-PHN) gave the corresponding diol **5** with much higher enantioselectivity[5] than other chiral ligands. After protection of the diol moiety of **5** as an acetonide, exhaustive reduction of **6** using excess $LiAlH_4$ in THF provided primary alcohol **7**, which was then treated with Ph_3P-CCl_4 to give chloride **9**. Transformation from **9** to **1**[12] was performed by base-induced fragmentation[6] under nBuLi-HMPA conditions at -60°C, followed by protection of the resulting secondary alcohol as a TBS ether.

Construction of the bottom-half unit (25). A lithium anion of **1** generated by nBuLi at -78°C was reacted with epoxide **2**[3] in the presence of BF_3OEt_2[7] to afford a mixture of the adduct **10** (92%) and its C_{19} epimer that was easily separable by silica gel chromatography. Protection of a secondary alcohol of **10** as a BOM ether followed by desilylation using nBu_4NF provided propargyl alcohol **11** (93% in 2 steps). Regioselective hydroalumination[8] of a propargyl unit of **11** was achieved with $LiAlH_4$, and subsequent NBS work-up gave vinyl bromide **12** (80%). It was then necessary to introduce an oxygen function into the C_{20} position. Previous attempts to oxidize this position by stereoselective dihydroxylation of **12** or its C_{19} protected derivatives employing OsO_4 failed, probably due to a sterically hindered situation of the olefinic moiety. After numerous efforts, the optimal result was obtained by the C_{19} hydroxyl group-directed epoxidation by using mCPBA in the presence of Na_2HPO_4 buffer in CH_2Cl_2. The reaction proceeded slowly and accompanied oxidation of a phenyl sulfide to the corresponding sulfone, leading to α-bromoepoxide **13** as a single diastereomer (40%), along with vinyl bromide **15** (35%). During our related investigation,[9] we found that silver (I) salt is an effective and mild reagent to convert α-haloepoxides to the corresponding α-hydroxyketones via oxonium ion intermediates. Indeed, after protection as a siloxy ether, exposure of **14** to $AgBF_4$ afforded α-hydroxyketone **16** (84%) as the only detectable isomer,[10] which was labile to silica gel work-up to course a serious epimerization. This difficulty was overcome by protection of the C_{20} hydroxyl group as a SEM ether before purification procedure to give **17** and its C_{20} epimer as a 16:1 separable diastereomeric mixture. Reductive removal of a BOM group furnished aldol **18**, which upon acylation gave α-bromoacetate **19**. According to a previous paper,[3] **19** was submitted to SmI_2-mediated intramolecular Reformasky reaction[11] and



Scheme 2. *Reagents:* a) nBuLi/THF, -78°C, 30 min, then **2**, BF_3-OEt_2, -78°C, 15 min (92%). b) i. BOMCl, iPr_2NEt/CH_2Cl_2; ii. nBu_4NF/THF (93% in 2 steps). c) $LiAlH_4$ (1.5eq.)/THF, rt, 20 h, then NBS, 0 °C (80%). d) mCPBA, Na_2HPO_4, CH_2Cl_2, -30 °C then rt, 30 h (40%, and 35% recovered **15**). e) TBSOTf, 2,6-lutidine/CH_2Cl_2, 0°C (83%). f) $AgBF_4$/10% aq.THF, 0 °C, 10 min (84%). g) SEMCl, nBu_4NI, iPr_2NEt/CH_2Cl_2. h) Pd-C, H_2/EtOH (70% in 2 steps). i) $BrCH_2COBr$, pyr/CH_2Cl_2 (93%). j) SmI_2/THF, -78 °C (82%). k) Ac_2O, DMAP, pyr/PhH, reflux (97%). l) $NaBH_4$/dioxane-MeOH (10:1). (92%). m) i. nBu_4NF/THF; ii. TBDPSCl, imidazole/DMF (85% in 2 steps). n) i. p-BrBzCl, DMAP/pyr; ii. Ac_2O/DMSO (80% in 2 steps). o) K_2CO_3/MeOH then SiO_2 (36%).

subsequent β-elimination to provide the desired α,β-unsaturated lactone **20** (80% in 2 steps). Reductive cleavage of the lactone moiety of **20** to allyl alcohol **21** was accomplished by using $NaBH_4$ in high regioselectivity. Deprotection of a TBS group with $nBuN_4F$ and the following selective silylation of a primary allyl alcohol gave **22** (85% in 2 steps), which was subjected to selective protection of the less hindered hydroxyl group with p-BrC_6H_4COCl-pyr, and then the remaining secondary alcohol (C_{19}) was oxidized to ketone **23**[12] (80% in 2 steps) which is a synthetic equivalent of the bottom half of C_{20} oxygenated bryostatins. Finally, deprotection of a p-bromobenzoyl ester group, and silica gel treatment afforded an equilibrium mixture (*ca.* 12:1) of the desired hemiacetal (**25**) and the corresponding δ-hydroxyl ketone (**24**).[12]

In conclusion, we have demonstrated an approach involving an efficient chirality induction (**12**→**16**) to the bottom-half unit of C_{20} oxygenated bryostatin series involving bryostatin 1 .

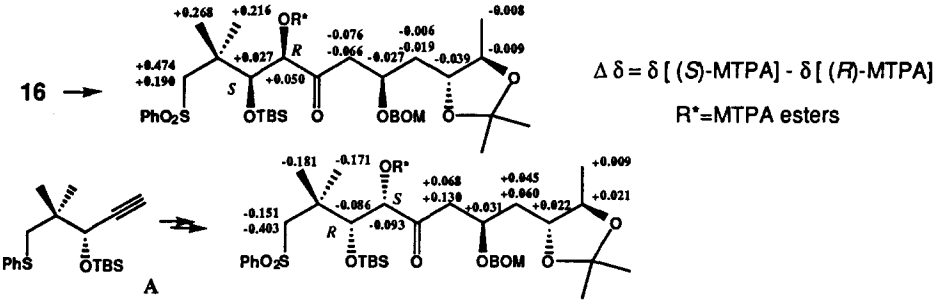
This research was financially supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, which is gratefully acknowledged. The authors also thank the Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists (to K. O.).

REFERENCES

1. *Isolation and propaties of bryostatins:* a) Pettit, G. R., Progress in the Chemistry of Organic Natural Products, Vol 57, Springer-Verlag, New York, **1991**, 153. b) Pettit, G. R.; Gao, F.; Sengupta, D.; Coll,

J. C.; Herald, C. L.; Doubek, D. L.; Schmidt, J. M.; Van Camp, J. R.; Rodloe, J. J.; Nieman, R. A. *Tetrahedron* **1991**, *47*, 3601. c) Schaufelberger, D. E.; Chmurny, G. N.; Beutler, J. A.; Koleck, M. P.; Alvarado, A. B.; Schaufelberger, B. W. ; Muschik, G. M. *J. Org. Chem.* **1991** *56*, 2895. d) Pettit, G. R.; Gao, F.; Herald, D. L.; Blumberg, P. M.; Lewin, N. E.; Nieman, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 6693. e) Chmurny, G. N.; Koleck, M. P.; Hilton, B. D. *J. Org. Chem.* **1992**, *57*, 5260.

2. *Synthetic studies on bryostatins:* a) Munt, S. P.; Thomas, E. J. *J. Chem. Soc. Chem. Commun.* **1989**, 480. b) Roy, R.; Rey, A. W.; Charron, M.; Molino, M. *J. Chem. Soc. Chem. Commun.* **1989**, 1308. c) Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703. d) Roy, R.; Rey, A. W. *Synlett* **1990**, 448. e) Evans, D. A.; G.-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741. f) De Bander, J.; Vanhessche, K.;Vandewalle, M. *Tetrahedron. Lett.* **1991**, *32*, 2821. g) Ohmori, K.; Suzuki, T.; Miyazawa, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 4981. h) De Brabander, J.; Vandewalle, M. *Synlett* **1994**, 231. i) De Brabander, J.; Vandewalle, M. *Synthesis* **1994**, 855. j) Hale, K. J.; Lennon, J. A.; Manaviazar, S.; Javaid M. H. *Tetrahedron Lett.* **1995**, 1359. k) Kageyama, M.; Tamura, T.; Nantz, M. H.; Rberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407.
3. Submitted to this journal.
4. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B.*Chem. Rev.* **1994**, *94*, 2483.
5. Enanthiomeric excess was determined by ^{1}H-NMR spectrum of (-)-MTPA ester **8** derived from **7**
6. a) Takano, S.; Samizu, K.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.*, **1989**, 1344. b) Yadav, J. S.; Despande, P. K.; Sharma, G. V. M. *Tetrahedron Lett.* **1990**, *31*, 4495. c) Yadav, J. S.; Despande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033. d) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *Synlett.*, **1994** 119.
7. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
8. Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
9. Detailed results will be published elsewhere.
10. Absolute configuration was determined by the modified Mosher method (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.) employing (*R*) and (*S*)-MTPA esters of **16.** Additionally, this result was supported by the opposite observation, upon using both MTPA esters of α-hydroxyketone derived from enantiomer A of **1.**



11. Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556.
12. **1**: IR (film) 3300, 1585, 1465, 1250 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.10 (3H, s), 0.17 (3H, s), 0.89 (9H, s), 1.05 (3H, s), 1.08 (3H, s), 2.39 (1H, d, J=2.2Hz), 3.04 (1H, d, J= 12.5Hz), 3.11 (1H, d, J= 12.5Hz), 4.30 (1H, d, J= 2.2Hz), 7.14 (1H, tt, J= 7.3, 1.5Hz), 7.23-7.28 (3H, complex), 7.33-7.36 (2H, complex). **23**: $[\alpha]_D^{19}$ +22.9° (*c* 0.15, $CHCl_3$); IR (film) 1720, 1590, 1450, 1430, 1380 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ –0.05 (9H, s), 0.81-0.89 (2H, complex), 1.00 (9H, s), 1.19 (3H, d, J= 5.9Hz), 1.23 (3H, s), 1.24 (3H, s), 1.38 (3H, s), 1.58 (3H, s), 1.45-1.80 (2H, complex), 2.35 (1H, brs), 2.37 (1H, brs), 3.40 (1H, d, J= 13.9Hz), 3.45-3.52 (2H, complex), 3.61-3.73 (2H, complex), 4.14 (1H, dd, J= 13.2, 4.8Hz), 4.43 (1H, dd, J=13.2, 8.1Hz), 4.63 (1H, d, J=7.0Hz), 4.65 (1H, d, J=7.0Hz), 5.24 (1H, s), 5.34 (1H, m), 5.94 (1H, dd, J= 7.7, 4.4Hz), 7.34-7.44 (8H, complex), 7.52-7.67 (9H, complex), 7.90-7.92 (2H, complex). **25** (contaminated with **24**): $C_{45}H_{65}O_9SSi_2$ [*m/z* 837.3881 (M^+-CH_3)]; IR (film) 3480, 1720, 1440, 1430, 1370 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$, assigned as a major tautomer) δ 0.00 (3H, s), 0.02 (6H, s), 0.85-0.92 (2H, complex), 1.03 (9H, s), 1.20 (3H, d, J= 5.5Hz), 1.25 (3H, s), 1.28 (3H, s), 1.33 (3H, s), 1.37 (3H, s), 1.40-1.70 (2H, complex), 1.80 (1H, brt, J= 13.6Hz), 2.08 (1H, dd, J= 13.6, 2.9Hz), 2.90 (1H, brs, OH), 3.38 (1H, d, J= 14.6Hz), 3.49 (1H, td, J= 10.3, 6.6Hz), 3.59-3.64 (2H, complex), 3.76 (1H, td, J= 10.3, 6.6Hz), 3.82 (1H, m), 3.95 (1H, s), 4.25 (2H, d, J= 6.2Hz), 4.48 (1H, d, J= 6.9Hz), 4.54 (1H, d, J= 6.9Hz), 5.77 (1H, td, J= 6.2, 1.5Hz), 7.36-7.42 (6H, complex), 7.52-7.55 (2H, complex), 7.59-7.66 (5H, complex), 7.90-7.92 (2H, complex).

(*Received in Japan* 24 *May* 1995; *accepted* 13 *July* 1995)