ORGANIC LETTERS

2003
Vol. 5, No. 4
503−505

New, Abridged Pathway to Masamune's "Southern Hemisphere" Intermediate for the Total Synthesis of Bryostatin 7

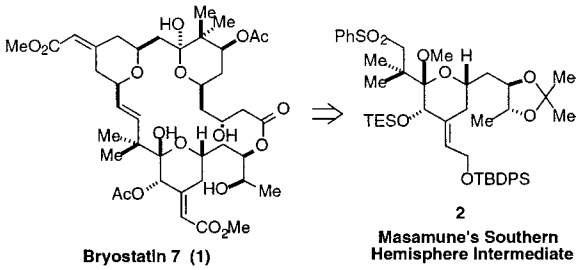
Karl J. Hale,* Mark Frigerio, and Soraya Manaviazar

The Christopher Ingold Laboratories, The Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, United Kingdom

k.j.hale@ucl.ac.uk

Received December 3, 2002

ABSTRACT



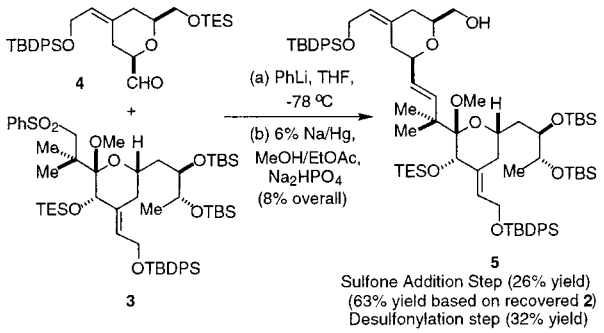
The "Southern Hemisphere" intermediate 2, used by Masamune and co-workers for their asymmetric total synthesis of bryostatin 7 (1), has been synthesized from (*E*)-1,4-hexadiene (11) by a 24-step pathway that has a longest linear sequence of only 20 steps. This is the shortest synthesis of 2 so far recorded, and moreover, it is fully stereocontrolled.

Bryostatins[1] and their simplified analogues remain at the forefront of medical and biological interest due to their powerful antitumor effects in man and their ability to selectively modulate protein kinase C (PKC) activity within cells.[2]

For some time now, we have been involved in the total synthesis of various bryostatin family members for the purpose of increasing future clinical supply and for creating novel analogues that can be used to probe PKC structure and function by biophysical and biological methods.[3]

In the accompanying communication,[4] we highlighted the difficulties that we encountered in performing a Julia olefination with the phenyl sulfone **3** and the aldehyde **4** (Scheme 1). Typically, this merger delivered the desired

Scheme 1. Julia Coupling with Phenyl Sulfone **3**



alkene **5** in a rather disappointing 8% overall yield for the two-step sequence. While this union did actually enable us to complete the synthesis of a novel BC analogue that was

(1) Pettit, G. R.; Gao, F.; Blumberg, P. M.; Herald, C. L.; Coll, J. C.; Kamano, Y.; Lewin, N. E.; Schmidt, J. M.; Chapuis, J.-C. *J. Nat. Prod.* **1996**, *59*, 286.

(2) For reviews on bryostatin chemistry and biology, see: (a) Norcross, R.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (b) Mutter, R.; Wills, M. *Biorg. Med. Chem.* **2000**, *8*, 1841. (c) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, 413.

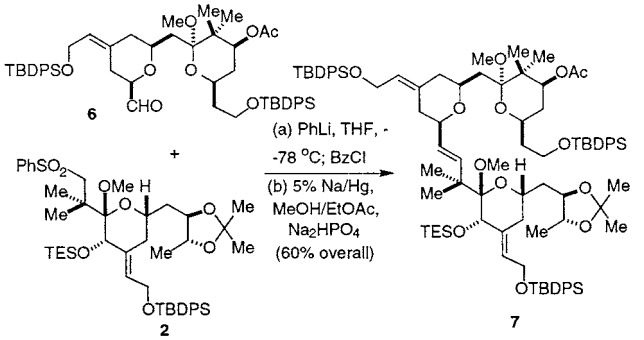
(3) For recent synthetic work from our group, see: (a) Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189. (b) Hale, K. J.; Frigerio, M.; Manaviazar, S. *Org. Lett.* **2001**, *3*, 3791. (c) Hale, K. J.; Lennon, J. A.; Manaviazar, S.; Javaid, M. H.; Hobbs, C. J. *Tetrahedron Lett.* **1995**, *35*, 2041.

10.1021/ol027393m CCC: $25.00
Published on Web 01/23/2003

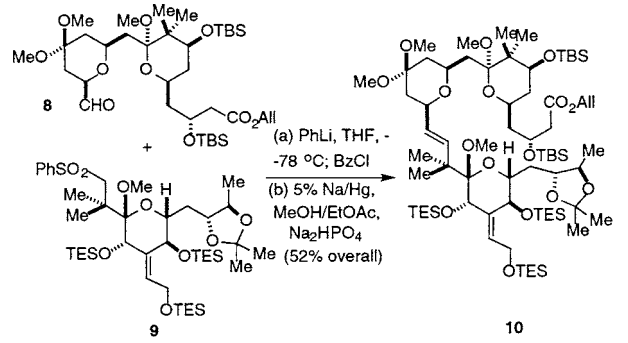
needed for NMR binding studies with the CRD2 of human PKC-α, it did highlight the problems that we would face if we employed phenyl sulfone **3** for the synthesis of various bryostatin family members and other analogues.

Our results stood in stark contrast to those reported by Masamune and co-workers[5a] for their total synthesis of bryostatin 7. They investigated the Julia coupling of phenylsulfone **2** with aldehyde **6** and obtained the desired (*E*)-alkene **7** in 60% overall yield after desulfonylation (Scheme 2).

Scheme 2. Other Julia Couplings in the Bryostatin Area



S. Masamune and coworkers (Ref 5a)

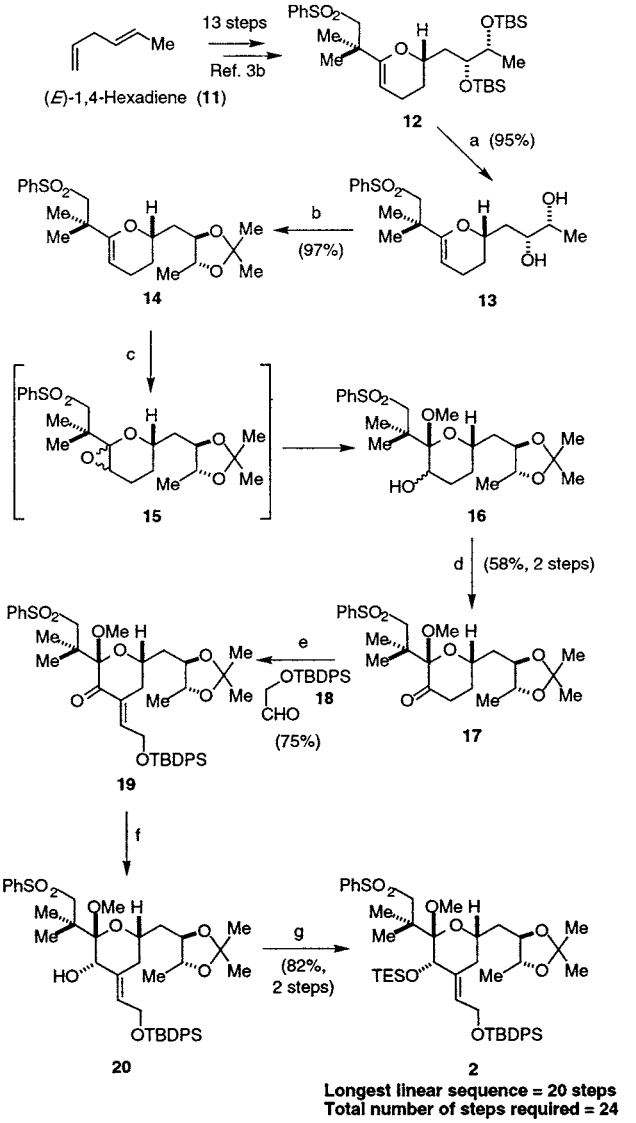


S. Nishiyama/S. Yamamura and coworkers (Ref 5b)

Likewise, Nishiyama and Yamamura recorded a 52% yield of alkene **10** when they executed a Julia coupling between **8** and **9** en route to bryostatin 3 (Scheme 2).[5b] Given the greatly improved results in bryostatin systems when the Julia olefinations are performed with O(25)/O(26)-isopropylidenated C-ring phenyl sulfones, we thought it prudent to pursue future work with the Masamune "Southern Hemisphere" intermediate **2**.[6] However, the current synthesis of **2** requires 35 synthetic operations to be performed in the laboratory, notwithstanding its longest linear sequence being only 21 steps.[6] Given that our newly developed pathway to **3** is only 22 steps overall and has a longest linear sequence of 17 steps,[3b] we thought it worthwhile to investigate whether it could be adapted to produce **2** much more expediently. Herein, we now report success in this undertaking.

The departure point for our synthesis of **2** was the glycal **12** (Scheme 3). It is readily prepared from (*E*)-1,4-hexadiene **11** by a 13-step protocol[3b,c] that employs Sharpless AD[7] and

Scheme 3. New Pathway to Masamune's Bryostatin 7 "Southern Hemisphere" (**2**)[a]



[a] Reagents and conditions: (a) *n*-Bu_4NF (2.8 equiv), THF, rt, 12 h. (b) $Me_2C(OMe)_2$ (3 equiv), PPTS (0.25 equiv), Me_2CO ([**13**] = 0.13 M), 40 °C, 15 min. (c) To **14** and 4 Å MS in MeOH: $Me_2C(OMe)_2$ ([**14**] = 0.02 M) at 0 °C was added DMDO (ca. 0.07 M solution in Me_2CO) dropwise over 2−3 min. The mixture was stirred for 12 min, and PPTS (0.01 equiv) was added; the mixture was warmed to rt and stirred for 10 min. (d) PDC (4 equiv), DMF ([**16**] = 0.1 M), rt, 20 h. (e) *n*-BuLi (2.5 M solution in hex, 2 equiv), THF, −78 °C, stirring (14 min), addition of **18** (2.5 equiv) in THF ([**18**] = 0.15 M), stirring (15 min), warming to 0 °C, stirring (10 min). (f) **19**, $CeCl_3 \cdot 7H_2O$ (10 equiv), MeOH ([**19**] = 0.07 M), −78 °C, 45 min, addition of $NaBH_4$ in three portions; stirring (20 min), then warming to rt, 15 min. (g) To **20**, CH_2Cl_2 ([**20**] = 0.06 M), and 2,6-lutidine, 0 °C, was added Et_3SiOTf (3 equiv); after 5 min, the solution was warmed to rt, 1.5 h.

(4) Hale, K. J.; Frigerio, M.; Manaviazar, S.; Hummersone, M. G.; Roberts, G. C. K.; Fillingham, I.; Gescher, A. *Org. Lett.* **2002**, *4*, 499.

(5) (a) Total synthesis of bryostatin 7: Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407. (b) Total synthesis of bryostatin 3: Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290. (c) Total synthesis of bryostatin 2: Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2354.

AE[8] reactions as key steps. The actual pathway to **2** commenced with the global O-desilylation of **12** using tetra-*n*-butylammonium fluoride in THF; this afforded the diol **13** in 95% yield. Diol **13** was then O-isopropylidenated in nearly quantitative yield (97%) by treatment with 2,2-dimethoxypropane in acetone. The epoxidation of glycal **14** was initially attempted under the conditions that we first developed for the epoxidation of **12**;[3b] that is, with doubly distilled dimethyldioxirane[9] in a mixture of methanol and acetone at −78 °C. However, when the in situ methanolysis of **15** was performed according to our original procedure (by adding 0.2 equiv of PPTS to the crude reaction mixture), we found that the *O*-isopropylidene acetal of **16** was also cleaved and extensive product decomposition quickly ensued.

After considerable effort, we eventually discovered that the glycal epoxides **15** could be ring-opened cleanly when the amount of PPTS was cut down to 0.01 equiv and when the epoxidation/epoxide ring-opening reaction was conducted in a 1:1 mixture of MeOH and 2,2-dimethoxypropane. Thereafter, **16** was isolated as a (rather unstable) mixture of C(20)-alcohol epimers as judged by TLC analysis. Presumably, the axial methyl glycoside emerges from this reaction for steric reasons, through attack of MeOH on the ring-opened tertiary oxonium ion. Since the newly introduced alcohol functionality at C(20) was now destined to be oxidized, no attempt was made to separate the individual C(20)-epimers at this stage.

In accordance with our past synthetic findings on **3**,[3b] the oxidation of **16** proceeded smoothly; ketone **17** was isolated as a single product in 58% yield for the three steps from **14** (viz. glycal epoxidation, epoxide ring-opening, and oxidation). With ketone **17** in hand, we then addressed the issue of stereospecific olefination via our previously developed aldol addition/dehydration tactic involving the Marshall aldehyde **18**.[10]

To our great delight, enolization of **17** proceeded readily when effected with *n*-butyllithium in THF at −78 °C, and as anticipated, the aldol addition and dehydration sequence took place in a simple one-pot fashion to provide **19** as a single geometrical isomer in 75% yield. The Luche reduction[11] of **19** also furnished **20** as essentially one compound in good yield. The final step in our route to **2** was the O-triethylsilylation of **20** with TESOTf and 2,6-lutidine, which was complete within 1.5 h at rt. The latter two steps proceeded in 82% yield.

In closing, we have devised a new and considerably abridged asymmetric synthesis of Masamune's "Southern Hemisphere" intermediate for bryostatin 7. Significantly, our new pathway to **2** has a longest linear sequence of only 20 steps, and now requires only 24 synthetic operations to be performed overall to arrive at the target.[12] Further applications of **2** in the synthesis of a naturally occurring bryostatin, as well as other PKC-binding analogues, will be reported in due course.

Acknowledgment. We thank the BBSRC for support through project grant 31/B09691 and for a studentship to M.F. We also thank Merck Sharp & Dohme (Harlow) and Pfizer (Sandwich) for additional financial support and the London School of Pharmacy for HRMS measurements.

Supporting Information Available: 500 MHz ^{1}H and 125 MHz ^{13}C NMR and mass spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027393M

(6) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587.
(7) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.
(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 1378.
(9) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Murray, R. W.; Jeyaraman, *J. Org. Chem.* **1985**, *50*, 2847.
(10) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1996**, *61*, 8732.
(11) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.
(12) For other bryostatin "Southern Hemisphere" synthetic studies, see: (a) Roy, R.; Rey, A. W.; Charron, M.; Molino, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1308. (b) Ohmuri, K.; Suzuki, T.; Miyazawa, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 4981. (c) Ohmuri, K.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 6515. (d) Ohmuri, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 6519. (e) Obitsu, T.; Ohmuri, K.; Ogawa, Y.; Hosomi, H.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1998**, *39*, 7349. (f) De Brabander, J.; Vandewalle, M. *Synlett* **1994**, 231. (g) De Brabander, J.; Vandewalle, M. *Synlett* **1994**, 231. (h) De Brabander, J.; Vandewalle, M. *Synthesis* **1994**, 855. (i) Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534. (j) Baxter, J.; Mata, E. G.; Thomas, E. J. *Tetrahedron* **1998**, *54*, 14359. (k) Almendros, P.; Rae, A.; Thomas, E. J. *Tetrahedron Lett.* **2000**, *41*, 9565. (l) Lopez-Pelegrin, J. A.; Wentworth, P., Jr.; Sieber, F.; Metz, W. A.; Janda, K. D. *J. Org. Chem.* **2000**, *65*, 8527.