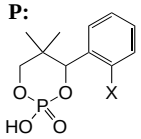
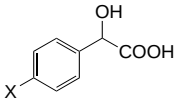
P:



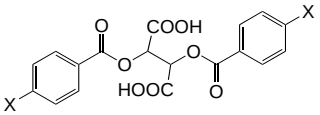
X = H, Cl, OMe

M:



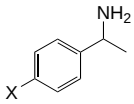
X = H, Me, Br

T:



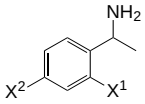
X = H, Me, OMe

Pe-I:



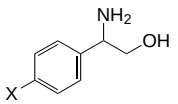
X = Cl, Br, Me

PE-II:



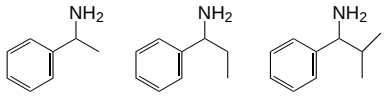
$X^1 = X^2 = H$; $X^1 = NO_2$, $X^2 = H$;
$X^1 = H$, $X^2 = NO_2$

PG:

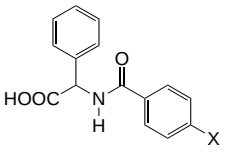


X = H, Me, OMe

PE-III:

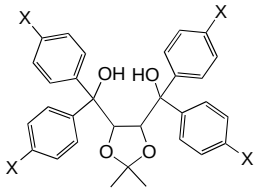


PGA:



X = H, Me, OMe

TA:



X = H, OMe

Scheme 1. Resolution of racemates with mixtures of reagents. Mixtures used: **P**: *ortho*-substituted phenylphosphoric acids; **M**: *para*-substituted mandelic acids; **T**: *para*-substituted benzoyltartrates; **PE-I**: *para*-substituted phenylethylamines; **PE-II**: nitrated phenylethylamines; **PG**: *para*-substituted 2-amino-2-phenylethanols; **PE-III**: α-alkylbenzylamines; **PGA**: *para*-substituted *N*-benzoylphenylglycines; **TA**: *para*-substituted bis(hydroxydiphenylmethyl)dioxalanes. For the preparation of the mixes, see the Experimental Section.

Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, **1962**; J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley-Interscience, New York, **1981**; E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**; the most complete description of the resolution of racemates (167 pages of chapter 7) can be found in the latter book.

[4] R. A. Sheldon, *Chirotechnology*, Marcel Dekker, New York, **1993**, chap. 6.

[5] A. D. van der Haest, H. Wynberg, *Recl. Trav. Chim. Pays-Bas* **1992** *111*, 111 – 118; A. D. van der Haest, H. Wynberg, F. J. J. Leusen, H. J. Bruins, J. H. Noordik, A. Bruggink, *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 13 – 18.

[6] R. O. Gould, M. D. Walkinshaw, *J. Am. Chem. Soc.* **1984**, *106*, 7840 – 7842; R. O. Gould, A. M. Gray, P. Taylor, M. D. Walkinshaw, *J. Am. Chem. Soc*. **1985**, *107*, 5921 – 5927. This paper specifically uses the term "a small family of related crystal structures" in discussing nonbonding interactions. To our understanding the word "family" already implies a relationship. See also R. O. Gould, R. Kelly, M. D. Walkinshaw, *J. Chem. Soc. Perkin. Trans. 2* **1985**, 847 – 852.

[7] S. P. Zingg, E. M. Arnett, A. T. McPhail, A. A. Bother-By, W. R. Gilkerson, *J. Am. Chem. Soc*. **1988**, *110*, 1565 – 1580; A. D. van der-Haest, H. Wynberg, F. J. J. Leusen, A. Bruggink, *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 523 – 528.

[8] E. Fogassi, F. Faigl, M. Acs, K. Simon, E. Kozsda, B. Podányi, M. Czugler, G. Reck, *J. Chem. Soc. Perkin Trans 2* **1988**, 1385 – 1392, and earlier papers.

[9] *Acc. Chem. Res.* **1996**, *29* (special issue; Eds.: A. W. Czarnik, J. A. Ellman).

[10] Because of the confidential nature of much of our work, less than half of the resolutions we have carried out during the past year are listed in Tables 1 and 2. Approximately half of all of the resolutions were performed on a 3-mmol scale, whereas the other half was carried out on a 5- to 500-g scale. The enantiomeric excesses was examined in all cases, but an accurate yield was determined for the larger scale resolutions only. In the latter cases this yield was consistently above 20% (50% maximum) and frequently in the range of 40 – 45%, even without complete optimization. The method has been patented: T. R. Vries, H. Wijnberg, E. van Echten, L. Hulshof and Q. B. Broxterman (DSM NV), NL 1 004 346, **1996**.

[11] W. ten Hoeve, H. Wynberg, *J. Org. Chem*. **1985**, *50*, 4508 – 4514.

[12] Exceptions to this generalization have already been found. Thus, when mixtures of amino acids are used as resolving agents, a single resolving agent was found in the diastereomeric salt. Substitution of the amino group of a single amino acid by various benzoyl chlorides led to formation of a "family" (**PGA** mix).

[13] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds,* Wiley-Interscience, New York, **1994**, pp. 329 – 343.

[14] Tartaric acid, malic acid, and lactic acid also did not constitute a family.

[15] L. Addadi, J. Van Mil, M. Lahav, *J. Am. Chem. Soc.* **1981.** *103*, 1249 – 1251.

[16] See, for example, F. Toda, *Top. Curr. Chem*. **1987**, *140*, 43 – 51.

[17] K. Mikami, S. Matsukawa, T. Volk, M. Terada, *Angew. Chem.* **1997**, *109*, 2936 – 2939; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2768 – 2771.

Asymmetric Synthesis of Bryostatin 2**

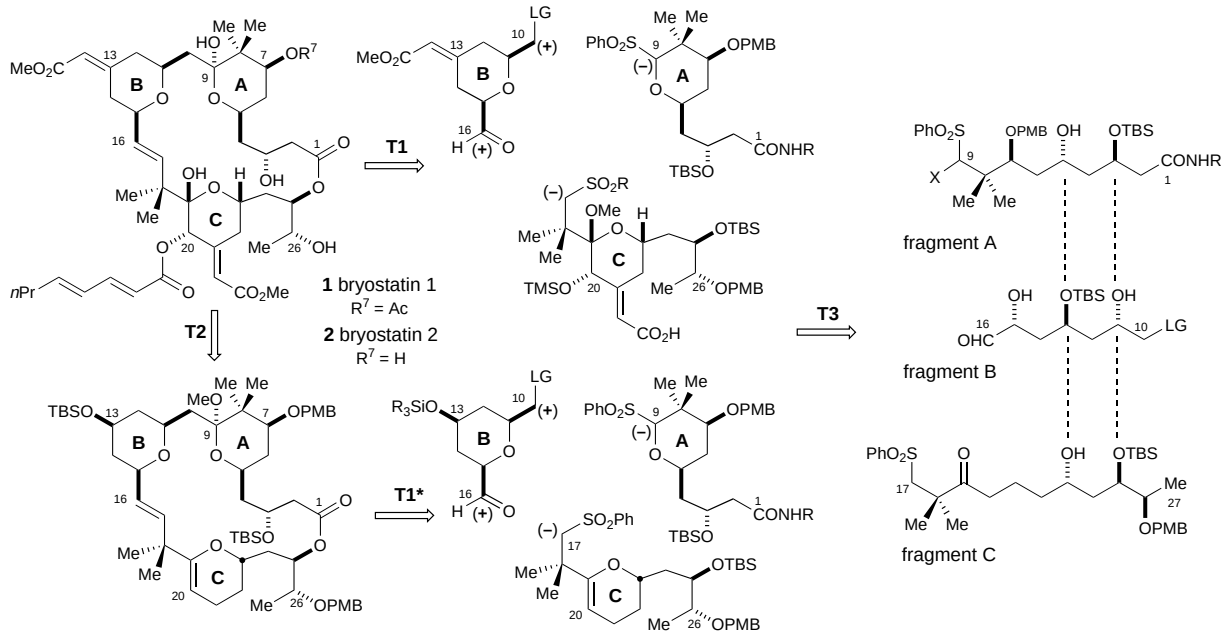
David A. Evans,* Percy H. Carter, Erick M. Carreira, Joëlle A. Prunet, André B. Charette, and Mark Lautens

Bryostatin 1 (**1**), a biologically active marine macrolide with clinical potential for the treatment of several forms of cancer,[1] was isolated and structurally characterized by Pettit et al. in 1982.[2] Since that time, Pettit and co-workers have reported the isolation of seventeen other bryostatin macrolides, most of which differ from **1** in their substitution at C7 or C20 (e.g. **2**).[3] The biological and clinical importance of bryostatin 1 has prompted a major effort towards the syn-

[*] Prof. D. A. Evans, P. H. Carter, E. M. Carreira, J. A. Prunet, A. B. Charette, M. Lautens
Department of Chemistry & Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

[**] Financial support has been provided by the National Institutes of Health. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

  1433-7851/98/3717-2354 $ 17.50+.50/0

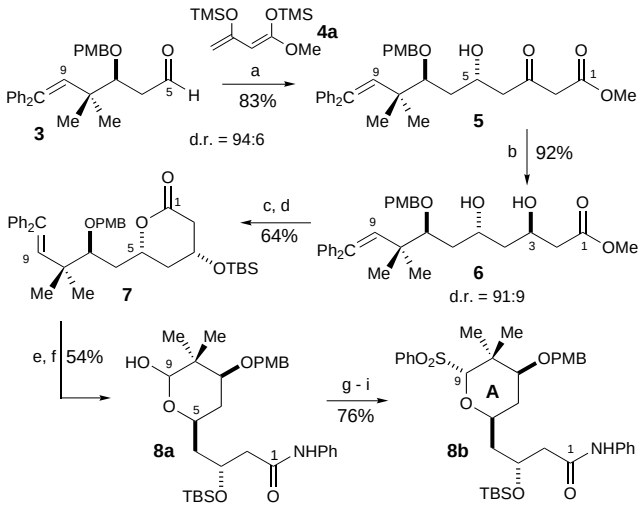


Scheme 1. Retrosynthetic analysis of bryostatins 1 and 2. See reference [7] for abbreviations.

thesis of this macrolide,[4] including one total synthesis of bryostatin 7 (OAc at C7 and C20).[5] Here we describe the first total synthesis of bryostatin 2 (**2**) by the general plan outlined in Scheme 1.[6]

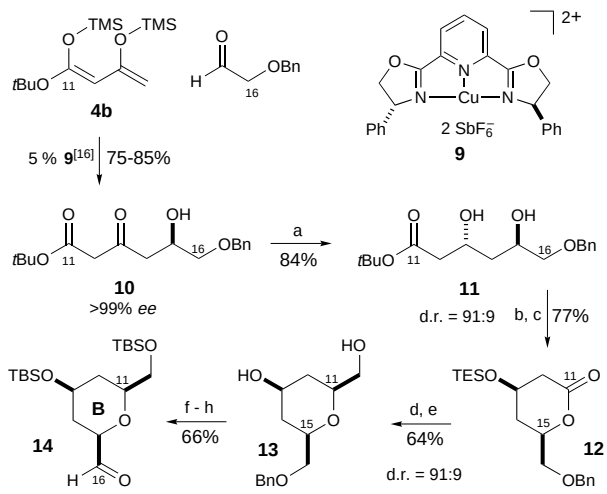
Following the retrosynthetic analysis shown, application of macrocyclization, olefination, and sulfone alkylation affords fragments **A**–**C** of comparable complexity (Scheme 1, T1). While each of the indicated subunits could be fully synthesized, sulfone-based fragment coupling could not be employed when the exocyclic enoate appendages at C13 and C21 were in place owing to unwanted proton transfer. Accordingly, the synthesis plan was modified to accommodate introduction of these moieties at a later stage (T2 → T1*). Both the elaborated and simplified versions of rings **A**–**C** were derived from the same set of acyclic precursors, each of which contains a common *anti*-1,3-diol subunit (T3). In all instances, the synthesis of this stereochemical motif can be effectively addressed by sequential aldol and reduction reactions.

Our route to the ring **A** synthon (C1–C9) began with β-alkoxyaldehyde **3** (Scheme 2), which is available in greater than 98% *ee* via a chiral imide enolate.[8] Addition of the bis(trimethylsilyl)dienol ether **4a**[9] to **3** proceeded with good 1,3-*anti* diastereoselectivity (d.r. = 94:6)[10] only when the alkoxytitanium Lewis acid $TiCl_2(OiPr)_2$ was employed. Subsequent hydroxyl-directed 1,3-*anti* reduction[11] afforded diol **6**, which was successively cyclized and monosilylated to provide the diastereomerically pure lactone **7**. Lactone **7** was then transamidated[12] to the open-chain anilide, which was cyclized to the lactol **8a** by oxidative cleavage of the C–C double bond.[13] Acylation, thiol displacement,[14] and thiol oxidation then served to convert **8a** ($\alpha:\beta = 1:1$) into the analytically pure α-sulfone **8b** (76% yield for three steps).[15] The carboxyl terminus of fragment **8b** was functionalized as an amide in order to accommodate the metalation of the C9 sulfone, an operation required for the union of rings **A** and **B**.



Scheme 2. Synthesis of the ring **A** synthon **8b** (C1–C9). a) $TiCl_2(OiPr)_2$, $PhCH_3$, −78 °C; then **4**, −78 °C; b) $Me_4NHB(OAc)_3$, AcOH/MeCN, −35 °C; c) PPTS, C_6H_6, 80 °C; d) TBSOTf, 2,6-lut, CH_2Cl_2, −10 °C; e) Me_3Al, $HCl \cdot H_2NPh$, CH_2Cl_2, 30 °C; then **7**, 0 °C; f) O_3, CH_2Cl_2/MeOH (10/1), −78 °C; then Me_2S; g) Ac_2O, pyr; h) PhSTMS, ZnI_2, nBu_4NI, CH_2Cl_2; i) *m*CPBA, $NaHCO_3$, EtOAc. See reference [7] for abbreviations.

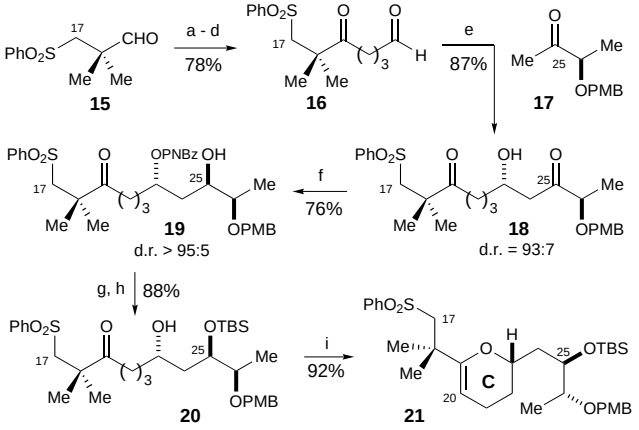
The synthesis of the ring **B** synthon (C10–C16) began with the enantioselective aldol reaction between enolsilane **4b** and α-benzyloxyacetaldehyde, catalyzed by the copper complex **9** (5 mol%), which afforded **10** in 75–85% yield and with greater than 99% *ee* (Scheme 3).[16] Subsequent hydroxyl-directed 1,3-*anti* reduction[11] provided synthon **11** in good yield.[17] Sequential lactonization and protection with chlorotriethylsilane gave lactone **12**, which was homologated by treatment with *para*-methoxybenzyloxymethyllithium.[18] Reduction ($BF_3 \cdot OEt_2$, Et_3SiH)[19] of the derived lactols afforded the deprotected β-*C*-glycoside **13** in good yield and diastereoselectivity. Silylation of the hyrdoxyl groups, hydrogenol



Scheme 3. Synthesis of the ring **B** synthon **14** (C10–C16). (a) Me_4N-$HB(OAc)_3$, AcOH/MeCN, $-35\,^{\circ}C$; b) F_3CCO_2H, CH_2Cl_2; c) TESCl, im, CH_2Cl_2, $0\,^{\circ}C$; d) $PMBOCH_2Li$, THF, $-78\rightarrow-50\,^{\circ}C$; e) $BF_3\cdot OEt_2$, Et_3SiH, CH_2Cl_2, $-20\,^{\circ}C$; f) TBSCl, im, DMAP (cat.), CH_2Cl_2; g) H_2 (1 atm), 10% Pd/C, AcOH, EtOAc; h) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, $-78\rightarrow-50\,^{\circ}C$. See reference [7] for abbreviations.

ysisof the benzyl ether, and Swern oxidation of the resultant alcohol provided the target synthon **14**.

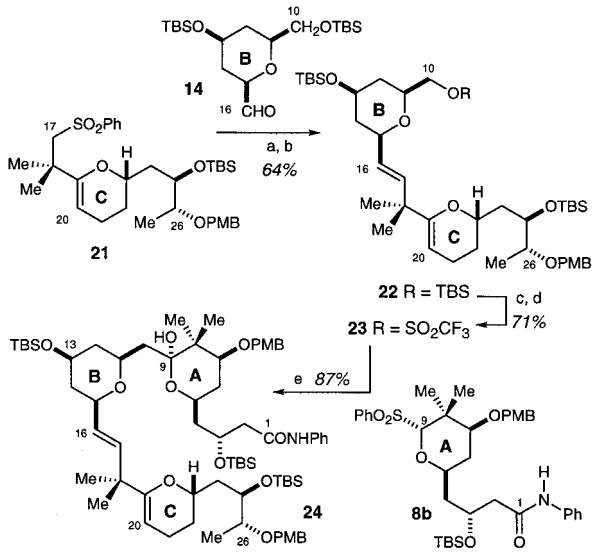
The synthesis of the ring **C** synthon (C17–C27) commenced with the homologation of aldehyde **15** (Scheme 4).[20] Thus, addition of pent-1-en-5-ylmagnesium bromide was



Scheme 4. Synthesis of the ring **C** synthon **21** (C17–C27). a) $BrMg(CH_2)_3CH{=}CH_2$, Et_2O/CH_2Cl_2 (1/1), $0\rightarrow23\,^{\circ}C$; b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, $-78\rightarrow-50\,^{\circ}C$; c) $K_2OsO_4(OH_2)_2$ (2 mol%), quinuclidine (2 mol%), $[K_3Fe(CN)_6]$, K_2CO_3, *t*BuOH/H_2O (1/1); d) $NaIO_4$, $NaHCO_3$, *t*BuOH/H_2O/THF (2/2/1); e) **17**, (−)-DIPCl, NEt_3, CH_2Cl_2, $-78\,^{\circ}C$; then **16**, $-70\,^{\circ}C$; f) SmI_2 (20 mol%), *p*-$O_2NC_6H_4CHO$, THF, $0\,^{\circ}C$; g) TBSOTf, 2,6-lut, CH_2Cl_2, $-15\,^{\circ}C$; h) LiOH, THF/MeOH/H_2O (2/2/1); i) CSA (5 mol%), C_6H_6, $80\,^{\circ}C$. See reference [7] for abbreviations.

followed by Swern oxidation, osmium-mediated dihydroxylation, and periodate cleavage to afford ketoaldehyde **16** in 78% overall yield. The aldol reaction of aldehyde **16** with ketone **17**[21] was only moderately diastereoselective under a wide variety of enolization conditions.[22] Accordingly, we used chiral boryl enolates, and found that the aldol addition could be carried out in good yield and diastereoselectivity with the isopinylboryl enolates of Paterson and Brown.[23] Subsequent samarium-promoted Tishchenko reduction[24] afforded the *p*-nitrobenzoate **19**, which was readily converted into alcohol **20** in two steps. Acid-catalyzed cyclization and dehydration of **20** (CSA, C_6H_6, $80\,^{\circ}C$) provided the target dihydropyran **21** in 92% yield.

Exploratory experiments directed at defining the optimal sequence for fragment coupling revealed the preferred order to be **C**→**CB**→**CBA**. Accordingly, union of the metalated ring **C** sulfone **21** with one equivalent of aldehyde **14** afforded the hydroxysulfone adduct, which was transformed by a modified Julia procedure[25] to *trans* olefin **22** (64% overall yield, $E{:}Z > 95{:}5$; Scheme 5). Selective removal of the TBS

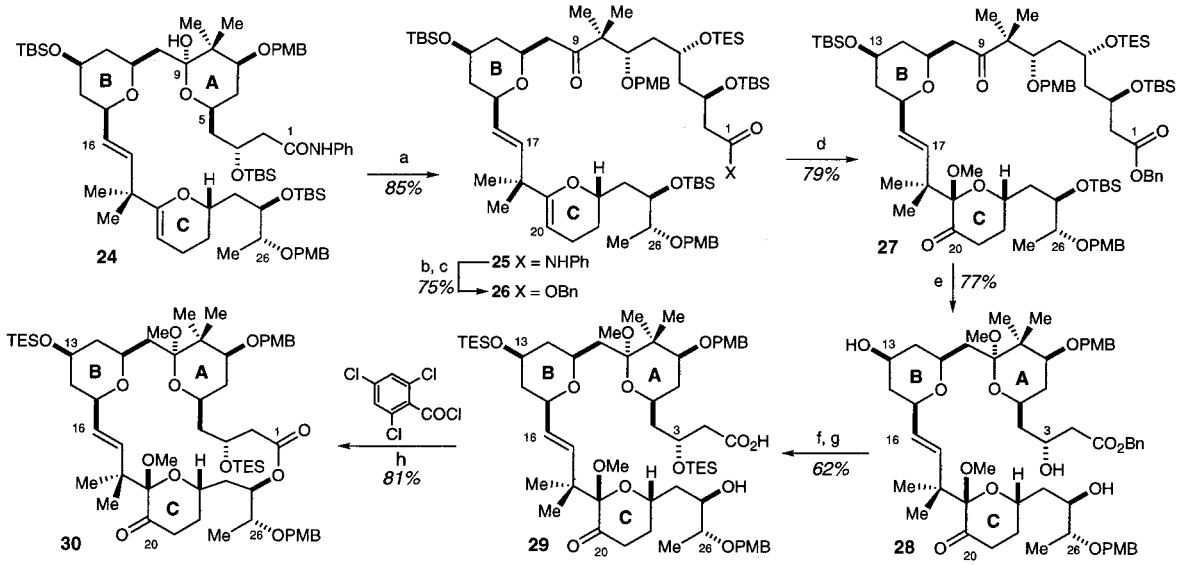


Scheme 5. Fragment assemblage. a) 1. *n*BuLi, THF, $-78\,^{\circ}C$; then **14**, $-78\rightarrow-50\,^{\circ}C$; 2. Ac_2O, DMAP, CH_2Cl_2; b) Mg, $HgCl_2$ (20 mol%), EtOH; c) TBAF, THF, $-15\,^{\circ}C$; d) Tf_2O, 2,6-lut, CH_2Cl_2, $-10\,^{\circ}C$; e) **8b**, *n*BuLi (2 equiv), THF, $-78\,^{\circ}C$; then HMPA; then **23**, $-78\,^{\circ}C$. See reference [7] for abbreviations.

group from the primary silyl ether (TBAF, $-15\,^{\circ}C$) and treatment of the derived alcohol with buffered trifluoromethanesulfonic anhydride produced the unstable triflate **23**. The triflate was purified and then immediately coupled with bis-metalated **8b** (THF/HMPA, $-78\,^{\circ}C$) in good yield (87%).[26]

Refunctionalization of **24** to the optimal macrocyclization precursor **29** is shown in Scheme 6. While the overall transformations ideally could have been implemented in several different permutations, the indicated sequence of chemical events proved to be closely constrained by reactivity considerations. In preparation for the refunctionalization of the carboxyl terminus, the lactol (C9) was silylated to provide the open-chain silyl ether **25** (85%). Conversion of anilide **25** into the benzyl ester **26** was accomplished through the action of lithium benzyloxide on the *N*-Boc-amide (THF/DMF, $-30\,^{\circ}C$, 75%).[27] With the carboxyl terminus protected as its benzyl ester, the ring **C** glycal was elaborated by a three-step sequence: 1) epoxidation/methanolysis, 2) equilibration of the C19 ketal with monochloroacetic acid (d.r. > 95:5), and 3) Dess–Martin oxidation of the hydroxyl group at C20. These reactions were executed without purification of inter-

  1433-7851/98/3717-2356 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 17

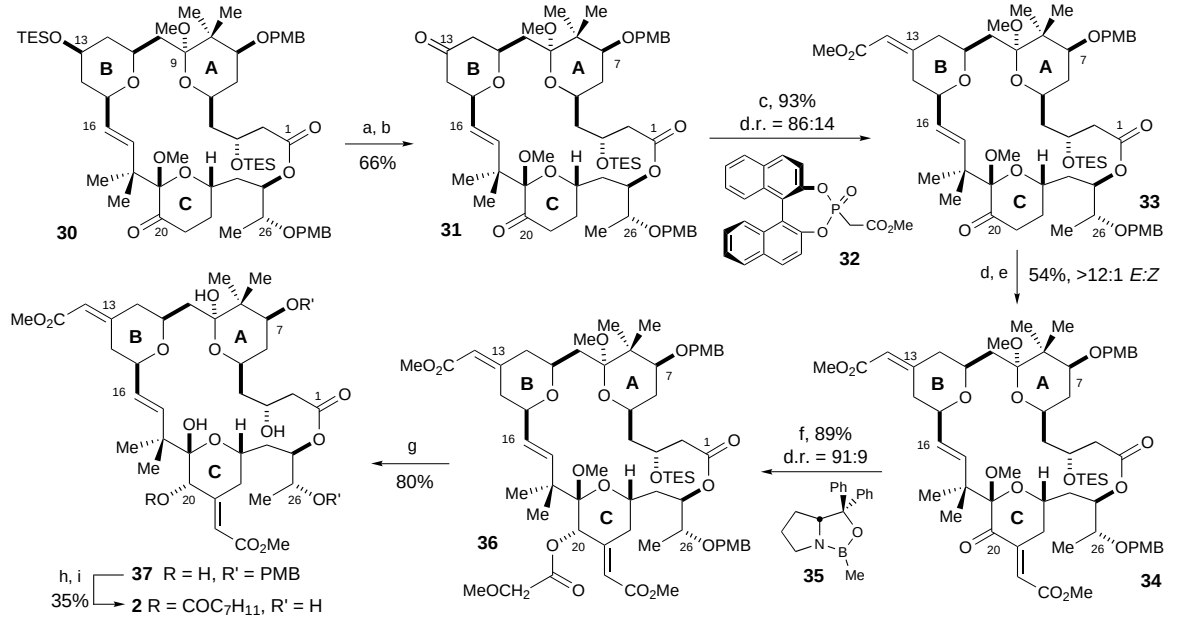


Scheme 6. Functionalization and macrocyclization of the tricycle. a) TESCl, im, MeCN; b) Boc_2O, DMAP, MeCN; c) BnOLi, THF/DMF (1/1), $-30\,^{\circ}C$; d) 1. *m*CPBA, MeOH, $-20\,^{\circ}C$; 2. $ClCH_2CO_2H$, MeOH, $0\,^{\circ}C$; 3. Dess–Martin periodinane, pyr, CH_2Cl_2; e) HF·pyr, THF/MeOH/pyr (4/4/1); f) TESCl, DMAP, CH_2Cl_2, $-10\,^{\circ}C$ (65% plus 15% each of the mono- and tris-silylether); g) 1,4-cyclohexadiene, 10% Pd/C (50 mol%), EtOAc; h) 2,4,6-trichlorobenzoyl chloride, *i*PrNEt_2, C_6H_6; then DMAP, C_6H_6 (1.0 mM). See reference [7] for abbreviations.

mediates to provide ketone **27** in 79% overall yield after chromatography on silica gel.

In preparation for macrocyclization, all silyl groups of ester **27** were removed with methanolic HF·pyridine to afford triol **28** (Scheme 6). Initial attempts to macrocyclize this triol-carboxylic acid were frustrated by the reactivity of the hydroxyl group at C3, and macrocyclization could only be accomplished in low yields (<35%) from the thiopyridyl ester. Consequently, the hydroxyl groups at C3 and C13 were selectively protected (TESCl, DMAP, $-10\,^{\circ}C$) before proceeding. Debenzylation of the ester (cyclohexadiene, 10% Pd/C) provided the monohydroxy acid **29**, which was successfully lactonized in good yield (81%) according to a modified Yamaguchi procedure.[28]

With macrocycle **30** in hand, elaboration of the ring **B** and **C** enoate moieties was undertaken. Selective deprotection of the silyl ether at C13 and Dess–Martin oxidation of the resultant hydroxyl group afforded C13,C20-diketone **31** (66%, Scheme 7). Condensation of **31** with two equivalents of Fuji's chiral phosphonate **32** as its derived sodium enolate[29] selectively transformed the C13 ketone to the C13,C30-unsaturated enoate in 93% yield and diastereoselectivity of



Scheme 7. Synthesis of bryostatin 2 (**2**). a) PPTS (20 mol%), MeOH/$(MeO)_3CH$ (2/1), CH_2Cl_2, $-30\,^{\circ}C$; b) Dess–Martin periodinane, pyr, CH_2Cl_2; c) **32**, NaHMDS, THF, $-78\,^{\circ}C$; then **31**, $-15\,^{\circ}C$; d) KHMDS, THF, $-78\,^{\circ}C$; then $OHCCO_2Me$, $-78\,^{\circ}C$; e) $Et_3NSO_2NCO_2Me$, C_6H_6; f) **35**, $BH_3\cdot SMe_2$, CH_2Cl_2; then MeOH; then $(MAc)_2O$, pyr, DMAP; g) 1. PPTS, THF/H_2O (3/1); 2. Na_2CO_3, MeOH; 3. TsOH, MeCN/H_2O (4/1); h) (*E*,*E*)-2,4-octadienoic acid, DIC, DMAP, CH_2Cl_2; i) DDQ, CH_2Cl_2/buffer (10/1, pH 7). See reference [7] for abbreviations.

  1433-7851/98/3717-2357 $ 17.50+.50/0

Z:E = 86:14 (75% yield of isolated **33**). Subsequent installation of the ring **C** enoate was best accomplished with a two-step protocol (KHMDS, $OHCCO_2Me$; then Burgess reagent). The ability of KHMDS to selectively enolize a ketone (C20) in the presence of an ester (C1) is precedented,[30] and is favored in the present system by the conformation of macrolactone **33**.[31] In contrast to its monocyclic analogue, reduction of the ring **C** enone in **34** was troublesome; however, it was eventually discovered that the CBS reagent[32] **35** stereoselectively mediated this reduction when $BH_3 \cdot Me_2S$ was utilized as the hydride source (89%, d.r. = 10:1, 55–70% yield of isolated **36**). In situ acylation of the hydroxyl group at C20 was required in order to isolate the product in good yield.

The deprotection of **36** required a careful ordering of the hydrolysis steps. A three-step sequence consisting of hydrolysis at C9 (and desilylation at C3), methanolysis of the methoxyacetate group, and hydrolysis at C19 could be reliably executed to afford **37** after only one chromatographic purification. The hydroxyl group at C20 could be selectively[33] acylated using carbodiimide chemistry ((*E*,*E*)-2,4-octadienoic acid,[34] DIC, DMAP, 23 °C, 1.5 d, 62% yield). The subsequent oxidative removal of the PMB ethers was best effected under buffered conditions (DDQ, CH_2Cl_2, pH 7) to provide pure bryostatin 2 (**2**) in 57% yield. The synthetic bryostatin 2 obtained by this procedure was identical to a natural sample[35] by several criteria: $[\alpha]_D$, R_f (TLC), reverse-phase HPLC, mass spectrometry, and ^1H NMR spectroscopy (500 MHz, $CDCl_3$ and C_6D_6, including COSY-90). Pettit et al. have previously documented the three-step conversion of bryostatin 2 (**2**) into bryostatin 1 (**1**).[6]

Received: May 14, 1998 [Z11861IE]
German version: *Angew. Chem.* **1998**, *110*, 2526–2530

Keywords: aldol reactions · antitumor agents · bryostatin · total synthesis

[1] a) A. S. Kraft, *J. Nat. Cancer Inst.* **1993**, *85*, 1790–1792; b) R. M. Stone, *Leukemia Res.* **1997**, *21*, 399–401.
[2] G. R. Pettit, C. L. Herald, D. L. Doubek, D. L. Herald, E. Arnold, J. Clardy, *J. Am. Chem. Soc.* **1982**, *104*, 6846–6847.
[3] See, for example, G. R. Pettit, F. Gao, P. M. Blumberg, C. L. Herald, J. C. Coll, Y. Kamano, N. E. Lewin, J. M. Schmidt, J.-C. Chapuis, *J. Nat. Prod.* **1996**, *59*, 286–289.
[4] Review: a) R. D. Norcross, I. Paterson, *Chem. Rev.* **1995**, *95*, 2041–2114; recent work: b) S. Kiyooka, H. Maeda, *Tetrahedron: Asymmetry* **1997**, *8*, 3371–3374; c) J. M. Weiss, H. M. R. Hoffmann, *Tetrahedron: Asymmetry* **1997**, *8*, 3913–3920.
[5] M. Kageyama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, S. Masamune, *J. Am. Chem. Soc.* **1990**, *112*, 7407–7408.
[6] For the conversion of bryostatin 2 (**2**) into bryostatin 1 (**1**), see G. R. Pettit, D. Sengupta, C. L. Herald, N. A. Sharkey, P. M. Blumberg, *Can. J. Chem.* **1991**, *69*, 856–860.
[7] Abbreviations: Bn = benzyl; Boc = *tert*-butoxycarbonyl; CSA = camphorsulfonic acid; DDQ = 2,3-dichloro-5,6-dicyanoquinone; DIBALH = diisobutylaluminum hydride; DIC = diisopropylcarbodiimide; DIPCl = *B*-chlorodiisopinocampheylborane; DMAP = 4-dimethylaminopyridine; d.r. = diastereomer ratio; HMDS = bis(trimethylsilyl)amide; im = imidazole; LG = leaving group; 2,6-lut = 2,6-lutidine; MAc = methoxyacetate; *m*CPBA = *meta*-chloroperoxybenzoic acid; PMB = *para*-methoxybenzyl; PMP = *para*-methoxyphenyl; PNBz = *para*-nitrobenzoate; PPTS = pyridinium *p*-toluenesulfonate; pyr = pyridine; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; Tf = trifluoromethanesulfonyl; TMS = trimethylsilyl; Ts = *p*-toluenesulfonyl.
[8] Aldehyde **3** was prepared in six steps (58% overall yield) from the known 2,2-dimethyl-4,4-diphenyl-3-butenal (H. E. Zimmerman, A. C. Pratt, *J. Am. Chem. Soc.* **1970**, *92*, 6259–6267): 1) (4*S*)-3-chloroacetyl-4-phenylmethyl-2-oxazolidinone, Bu_2BOTf, NEt_3, CH_2Cl_2, −78 → 0 °C (D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett.* **1987**, *28*, 39–42); 2) Zn, AcOH, THF; 3) $LiBH_4$, THF/MeOH, 0 °C; 4) $PMPCH(OMe)_2$, PPTS, CH_2Cl_2; 5) DIBALH, CH_2Cl_2, 0 °C; 6) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C.
[9] P. Brownbridge, T. H. Chan, M. A. Brook, G. J. Kang, *Can. J. Chem.* **1983**, *61*, 688–693.
[10] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.
[11] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
[12] J. I. Levin, E. Turos, S. M. Weinreb, *Synth. Comm.* **1982**, *12*, 989–993.
[13] The epoxide was also isolated in about 20% yield. This could be recycled by reduction with samarium diiodide (RT, THF, 50% yield, unoptimized).
[14] S. Hanessian, Y. Guindon, *Carbohydr. Res.* **1980**, *86*, C3.
[15] Approximately 5% of the (separable) C9 β-anomer was isolated from the thiol installation.
[16] D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815.
[17] For an earlier approach to these synthons, see D. A. Evans, J. A. Gauchet-Prunet, E. M. Carreira, A. B. Charette, *J. Org. Chem.* **1991**, *56*, 741–750.
[18] Prepared in analogous fashion to benzyloxymethyllithium; see W. C. Still, *J. Am. Chem. Soc.* **1978**, *100*, 1481–1486.
[19] M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
[20] Aldehyde **15** was prepared from 1,3-propanediol by the following four-step sequence in 76% overall yield: 1) TsCl, pyr, 0 → 23 °C; 2) PhSNa, DMF, 80 °C; 3) *m*CPBA, CH_2Cl_2; 4) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 → 0 °C.
[21] Prepared in three steps from 3-methyl-4-phenyl-buten-2-ol: 1) L-(+)-DIPT (15 mol%), $Ti(OiPr)_4$ (10 mol%), $tBuO_2H$ (0.7 equiv), CH_2Cl_2, −20 °C; 2) NaH, PMBBr, nBu_4NI (cat.), THF; 3) O_3, CH_2Cl_2/MeOH, −78 °C; then Me_2S, −78 → 23 °C. This sequence was performed without purification of the intermediates to afford the resolved ketone **17** in 25–35% overall yield and 96–99% *ee* after flash chromatography.
[22] a) For the synthesis of the undesired 1,4-*syn* diastereomer in the aldol reactions of lactate-derived methyl ketones, see: B. M. Trost, H. Urabe, *J. Org. Chem.* **1990**, *55*, 3982–3983; b) for the aldol reactions of lactate-derived ethyl ketones, see I. Paterson, D. J. Wallace, S. M. Velázquez, *Tetrahedron Lett.* **1994**, *35*, 9083–9086.
[23] a) Fortuitously, this is an example of a "matched" double diastereodifferentiating reaction. b) P. V. Ramachandran, W.-C. Xu, H. C. Brown, *Tetrahedron Lett.* **1996**, *37*, 4911–4914; c) I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663–4684.
[24] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
[25] G. H. Lee, H. K. Lee, E. B. Choi, B. T. Kim, C. S. Pak, *Tetrahedron Lett.* **1995**, *36*, 5607–5610.
[26] For a precedent for this transformation, see S. V. Ley, B. Lygo, F. Sternfeld, A. Wonnacott, *Tetrahedron* **1986**, *42*, 4333–4342, and references therein.
[27] For amide deprotection, see D. A. Evans, P. H. Carter, C. J. Dinsmore, J. C. Barrow, J. L. Katz, D. W. Kung, *Tetrahedron Lett.* **1997**, *38*, 4535–4538.
[28] a) D. A. Evans, A. S. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 11323–11324; b) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[29] a) The use of trimethyl phosphonoacetate afforded a Z:E mixture (63:37) of **33** in 100% yield. b) K. Tanaka, Y. Ohta, K. Fuji, T. Taga, *Tetrahedron Lett.* **1993**, *34*, 4071–4074; c) K. Tanaka, K. Otsubo, K. Fuji, *Tetrahedron Lett.* **1996**, *37*, 3735–3738.
[30] a) R. E. Ireland, J. L. Gleason, L. D. Gegnas, T. K. Highsmith, *J. Org. Chem.* **1996**, *61*, 6856–6872; b) R. E. Ireland, P. Wipf, J. D. Armstrong, III, *J. Org. Chem.* **1991**, *56*, 650–657.

  1433-7851/98/3717-2358 $ 17.50+.50/0

[31] The conformation of **33** in solution was determined by NOESY analysis (500 MHz, [D_6]acetone).
[32] a) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926; b) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
[33] The hydroxyl groups at C20 and C26 of bryostatin 14 may be selectively acetylated (Ac_2O, pyr) in the presence of hydroxl groups at C3, C9, and C19: G. R. Pettit, F. Gao, D. Sengupta, J. C. Coll, C. L. Herald, D. L. Doubek, J. M. Schmidt, J. R. Van Camp, J. J. Rudloe, R. A. Nieman, *Tetrahedron* **1991**, *47*, 3601–3610.
[34] Prepared in good yield from 2-hexenal according to the method of Coutrot et al.: P. Coutrot, M. Snoussi, P. Savignac, *Synthesis* **1978**, 133–134.
[35] We thank Prof. G. R. Pettit for providing us with a natural sample of bryostatin 2.

The Cluster Anion Si_9^{4-}

Hans Georg von Schnering,* Mehmet Somer, Martin Kaupp, Wilder Carrillo-Cabrera, Michael Baitinger, Andre Schmeding, and Yuri Grin

Dedicated to Professor Achim Müller on the occasion of his 60th birthday

The 40 valence electron cluster anions E_9^{4-} of the Group 14 (E14) elements Ge, Sn, and Pb have been known for many years. These anions form monocapped square antiprisms (SAPRS-9)—that is, the framework of a 22e *nido*-E_{10} Wade cluster—as shown by the investigations of Kummer et al.,[1] Corbett et al.,[2] and Fässler et al.[3] Until recently, it appeared certain that these cluster anions are only formed by the reactions of intermetallic phases with suitable solvents.[4] However, the existence of the isolated anions in these binary phases of the alkali metals M = Na, K, Rb, Cs was then established.[5, 6] Besides X-ray structure analyses, the successful stepwise thermal decomposition of the alkali metal tetrahedranides ME (M_4E_4), the quantitative analysis of the vibrational spectra, and the quantum chemical calculation of these spectra proved be essential tools in our investigations.[5] The binary compounds $M_{12}E_{17} = M_{12}[(E_4)_2E_9] = ME_{1.42}$ and $M_4E_9 = ME_{2.25}$, which contain the cluster anions E_4^{4-} and E_9^{4-}, were identified as well as clathrates of the types $M_6E_{25} = ME_{4.17}$,[7] $M_8E_{44}\square_2 = ME_{5.50}$, and M_xE_{136} ($5 \le x \le 12$) $\approx ME_{11-27}$. These results also suggested a route to the elusive Si_9^{4-}, for which no evidence for its existence was available.

The thermal decomposition of the alkali metal monosilicides MSi (M_4Si_4) by Schäfer and Klemm[8] 40 years ago only led to the clathrates $M_8Si_{44}\square_2$ in steep thermogravimetric (TG) steps, as was also observed for the germanides. We have now reinvestigated these reactions in a Knudsen cell under dynamic vacuum[9] and found the following:

1. In the thermal decomposition of NaSi, a distinct step appears for $NaSi_{2.3}$ (Na_4Si_9 ?), followed very quickly by the steps for the clathrates Na_6Si_{25} and $Na_8Si_{44}\square_2$, and then by that of Na_xSi_{136}.
2. According to DTG investigations, the thermal decomposition of KSi and RbSi passes through two steps close to KSi_2 and $RbSi_2$. However, only the later formed clathrates M_6Si_{25}, $M_8Si_{44}\square_2$, and M_xSi_{136} can be characterized unambiguously.
3. The thermal decomposition of CsSi (Cs_4Si_4) starts at 500 K and passes through three distinct steps at 630, 690, and 850 K (Figure 1). These steps represent the formation and decomposition of several phases, and these processes overlap over appreciable temperature intervals. The quantitative analysis of the DTG curves show that the mass loss at A corresponds to the formation and decomposition of the cluster phase $CsSi_{1.3}$ and the formation of the phase cluster $CsSi_{2.2}$. Before the formation of the latter is complete, its decomposition into the clathrate phases $CsSi_{4.2}$ and $CsSi_{5.5}$ commences (at B). The slightly declining TG plateau between 690 and 800 K indicates that the transformation into $CsSi_{5.5}$ needs a longer period of time. The mass loss at C corresponds to the formation of the clathrate phase Cs_xSi_{136} ($x \approx 10-12$, $CsSi_{11-14}$), which subsequently decomposes to silicon (ca. 1050 K). The phases identified here are direct analogues of the germanides and stannides of the types $M_{12}E_{17}$, M_4E_9, M_6E_{25}, $M_8E_{44}\square_2$, and M_xE_{136}.[5]

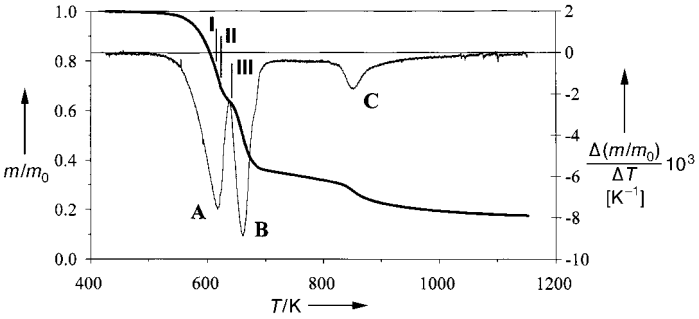


Figure 1. Thermal decomposition of Cs_4Si_4 in a Knudsen cell under dynamic vacuum (TG: bold lines; DTG: thin lines, m_0 = sample mass). See text for details of the analysis of the mass losses A–C and of products **I**–**III**.

We then tried to isolate individual phases during the decomposition. All attempts to characterize these phases by X-ray diffraction failed. Upon disappearance of the reflections of the M_4Si_4 phases, X-ray amorphous products were formed. After annealing for several weeks, these products gave sharp diagrams, but with many reflections of low intensity. We therefore applied Raman spectroscopy to the characterization of the phases close to $CsSi_2$.[10] We used three samples from region A (Figure 1), which were obtained by stopping the decomposition reaction.

The vibrations of the tetrahedranide anions E_4^{4-} (E = Si, Ge, Sn) have been described in detail by Kliche et al.[11] These

[*] Prof. Dr. H. G. von Schnering, Priv. Doz. Dr. M. Kaupp, Dr. W. Carrillo-Cabrera, Dipl.-Chem. M. Baitinger, Dipl.-Ing. A. Schmeding, Dr. Yu. Grin
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1, D-70569 Stuttgart (Germany)
Fax: (+49) 711-689-1502
Prof. Dr. M. Somer
Koç Universitesi, Cayir Cad.5 Istinye
80860 Istanbul (Turkey)

  1433-7851/98/3717-2359 $ 17.50+.50/0