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: para-substituted 2-amino-2-phenylethanols; Bis(hydroxydiphenylmethyl)dioxalanes. For the preparation of the mixes, see the Experimental Section.

Asymmetric Synthesis of Bryostatin 2**

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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-
thesis of this macrolide,[6] 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.[8]

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.[9] 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 TiCl2(OPr)2 was employed. Subsequent hydroxyl-directed 1,3-anti reduction[11] afforded diol 6, which was successively cyclized and monosilylated to provide the diasteromerically 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 (α:β = 1:1) into the synthetically 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 metatation of the C9 sulfone, an operation required for the union of rings A and B.

The synthesis of the ring B synthon (C10−C16) began with the enantioselective aldol reaction between enol silane 4b and α-benzylxoyacetaldehyde, 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 chloro triethylsilane gave lactone 12, which was homologated by treatment with para-methoxybenzylxymethylthiylmethyl.[18] Reduction (BF3·OEt2, Et3SiH)[19] of the derived lactols afforded the deprotected β-C-glycoside 13 in good yield and diastereoselectivity. Silylation of the hydroxyl groups, hydrogenol
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Scheme 3. Synthesis of the ring B synthon 14 (C10–C16). (a) Me,N-HB(OAc),, AcOH/MeCN, –35 °C; b) F3CCO2H, CH2Cl2; c) TESCl, im., DMSO, NEt3, CH2Cl2, –78 °C; d) PMBOCH2Li, THF, 0 °C; e) BF3 ·OEt2, Et3SiH, CH2Cl2, –20 °C; f) TBSCl, im., DMAP (cat.), CH2Cl2; g) TBSOTf, 2,6-lut, CH2Cl2.

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, CH2Cl2, 80 °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 metatalated 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

ysis of 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 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]

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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°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 d.r. = 86:14.

Scheme 6. Functionalization and macrocyclization of the tricycle. a) TESCl, im, MeCN; b) Boc2O, DMAP, MeCN; c) BnOLi, THF/DMF (1/1), −10°C; d) 1. mCPBA, MeOH, −20°C; 2. CH2Cl2, 0°C; 3. Dess – Martin periodinane, pyr, CH2Cl2; e) HF · pyridine, THF/MeOH/pyridine (4/4/1); f) TESCl, DMAP, CH2Cl2, −10°C (65% plus 15% each of the mono- and tris-silyl ether); g) 1,4-cyclohexadiene, 10% Pd/C (50 mol%), EtOAc; h) 2,4,6-trichlorobenzoyl chloride, iPrNEt2, C6H6; then DMAP, C6H6 (1.0 m). See reference [7] for abbreviations.

Scheme 7. Synthesis of bryostatin 2 (2). a) PPTS (20 mol%), MeOH/(MeO)3CH (2/1), CH2Cl2, −30°C; b) Dess – Martin periodinane, pyr, CH2Cl2; c) 32, NaHMDS, THF, −78°C; then 31, −15°C; d) KHMS, THF, −78°C; then OHCCO2Me, −78°C; e) Et2NSO2NCO2Me, C6H6; f) 35, BH3·SMe2, CH2Cl2; then MeOH; then (Mac)O, pyr, DMAP; g) 1. PPTS, THF/H2O (3/1); 2. Na2CO3, MeOH; 3. TsOH, MeCN/H2O (4/1); h) (E,E)-2,4-octadienoic acid, DIC, DMAP, CH2Cl2; i) DDQ, CH2Cl2/buffer (10/1, pH 7). See reference [7] for abbreviations.
hydrolysis steps. A three-step sequence consisting of hydrol-

group, and hydrolysis at C19 could be reliably acylated using carbodiimide chemistry (purification. The hydroxyl group at C20 could be selective-

effected to afford 2358 WILEY-VCH Verlag GmbH, D-69451 Weinheim, 1998 1433-7851/98/3717-2358 $ 17.50+.50/0

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14 [33] diastereomer in the aldol

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For a precedent for this transformation, see S. V. Ley, B. Lygo, F. H. O’Hare, J. Am. Chem. Soc. 1996, 118, 2864 –2871.


15 For a precedent for this transformation, see S. V. Ley, B. Lygo, F. H. O’Hare, J. Am. Chem. Soc. 1996, 118, 2864 –2871.

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[31] The conformation of 33 in solution was determined by NOESY analysis (500 MHz, D_{2}J-acetone).


[35] We thank Prof. G. R. Pettit for providing us with a natural sample of bryostatin 2.

The Cluster Anion Si_{12}^{2-}

Hans Georg von Schnering,* Mehmet Somer, Martin Battiger, Andre Schmeding, and Yuri Grin

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

The 40 valence electron cluster anions E_{x}^{y-} 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 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_{x}E_{136}), the quantitative analysis of the vibrational spectra, and the quantum chemical calculation of these spectra proved to be essential tools in our investigations.[7]

The binary compounds M_{2}E_{9} = M_{2}[(E_{14}E_{9}E_{16}] = ME_{142} and M_{2}E_{5} = ME_{225}, which contain the cluster anions E_{3}^{+} and E_{5}^{+}, were identified as well as clathrates of the types M_{x}E_{35} = ME_{43}(x \leq 12), ME_{55} = ME_{55}, and M_{x}E_{36} (5 \leq x \leq 12) = ME_{11-27}. These results also suggested a route to the elusive Si_{12}^{2-}, for which no evidence for its existence was available.

The thermal decomposition of the alkali metal monosilicides MSI (M_{x}Si_{y}) by Schäfer and Klemm[9] 40 years ago only led to the clathrates M_{x}Si_{14}E_{21} in steep thermogravimetric (TG) 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_{13}, and the formation of the phase cluster CsSi_{12}. Before the formation of the latter is complete, its decomposition into the clathrate phases CsSi_{12} and CsSi_{8} commences (at B). The slightly declining TG plateau between 690 and 800 K indicates that the transformation into CsSi_{8} needs a longer period of time. The mass loss at C corresponds to the formation of the clathrate phase CsSi_{12} (x = 10–12, CsSi_{11-13}), which subsequently decomposes to silicon (ca. 1050 K). The phases identified here are direct analogues of the germanides and stannides of the types M_{x}E_{12}Si_{2}, M_{x}E_{8}, M_{x}Si_{25}, M_{x}E_{44}Si_{2}, and M_{x}E_{36}.[8]

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_{x}Si_{y} 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_{x}^{+} (E = Si, Ge, Sn) have been described in detail by Kliehe et al.[11] These steps, as well as also observed for the germanides. We have now reinvestigated these reactions in a Knudsen cell under dynamic vacuum[8] and found the following:

1. In the thermal decomposition of NaSi, a distinct step appears for NaSi_{13} (Na_{x}Si_{13}), followed very quickly by the steps for the clathrates Na_{x}Si_{12} and Na_{x}Si_{14}, and then by that of NaSi_{13-16}.

2. According to DTG investigations, the thermal decomposition of KSi and RbSi passes through two steps close to KSi_{12} and RbSi_{12}. However, only the later formed clathrates M_{x}Si_{12}, M_{x}Si_{44}, and M_{x}Si_{136} can be characterized unambiguously.

3. The thermal decomposition of CsSi (Cs_{x}Si_{14}) starts at 500 K and passes through three distinct steps at 630, 690, and 850 K (Figure 1). These steps represent the formation and