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[15] HPLC separation (analytic): Chiralpak AD (Daicel); 4.6 mm × 250 mm; isohexane/2-propanol 97:3 (v:v); 215 nm; 1 mL min^{-1}; 25 °C; t_R (−)-(*R*)-**4a**: 15 min, t_R (+)-(*S*)-**4a**: 21.4 min. Preparative: as analytical separation but 40 mm × 250 mm and 60 mL min^{-1}.

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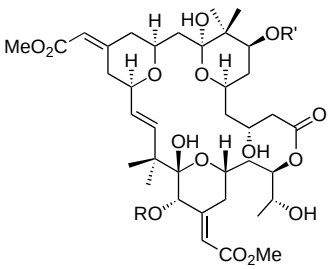
Total Synthesis of Bryostatin 3**

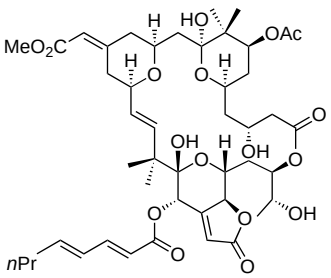
Ken Ohmori, Yasuyuki Ogawa, Tetsuo Obitsu, Yuichi Ishikawa, Shigeru Nishiyama,* and Shosuke Yamamura*

Bryostatins, 18 related macrolides isolated from the marine bryozoa *Bugula neritina Linnaeus* and *Amathia convuluta*, have been known to possess remarkably powerful antineoplastic activities against the murine P388 lymphocytic leukemia and other tumors, and have the potential to activate protein kinase C without tumor promotion, in contrast to the activities of phorbol and aplysiatoxin.[1] In particular, bryostatin 1, which is the most abundant congener in the family, is in phase II of clinical trials.

From the viewpoints of their interesting biological activity and novel macrolide structure, the bryostatins have been attracting the attention of many synthetic chemists.[2] However, only a few bryostatins have been synthesized: bryostatin 7 by Masamune et al.[3] and bryostatin 2 by Evans et al.[4] We have also carried out extensive synthetic studies on the bryostatins.[5] Bryostatin 3 (**1**), which includes the exceptional γ-lactone structure, was taken as a challenging target molecule, because it was isolated as a very minor component from natural sources (a few milligrams from each 100 kilograms of source),[6] yet it is expected to be a promising antitumor agent. We describe herein the total synthesis of bryostatin 3 (**1**).



bryostatin 1: R = COC_7H_{11}, R' = Ac
bryostatin 2: R = COC_7H_{11}, R' = H
bryostatin 7: R = Ac, R' = Ac



1: bryostatin 3

Based on the retrosynthetic analysis depicted in Scheme 1, the molecule of **1** is divided into two fragments (**I** and **II**). The C1−C16 fragment **I**, which is shared by all bryostatins, has been synthesized by a convergent synthetic methodology.[5d]

To accomplish the desired coupling reaction, the functionality of fragment **I** was required in an appropriate form, which was obtained from the intermediate **2**.[5d] As can be seen in

[*] Prof. Dr. S. Nishiyama, Prof. Dr. S. Yamamura, Dr. K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa
Department of Chemistry
Faculty of Science and Technology
Keio University, Hiyoshi, Yokohama 223-8522 (Japan)
Fax: (+81) 45-566-1697
E-mail: nisiyama@chem.keio.ac.jp, yamamura@chem.keio.ac.jp

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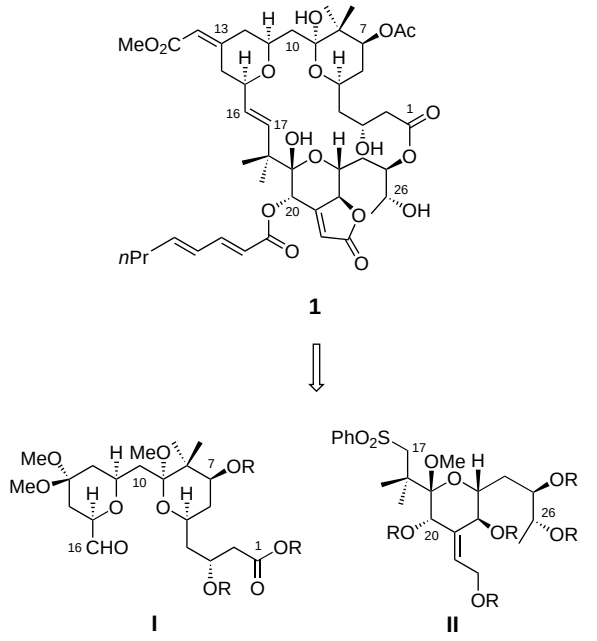
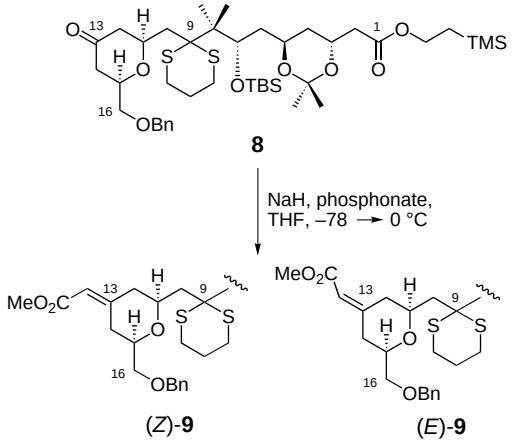


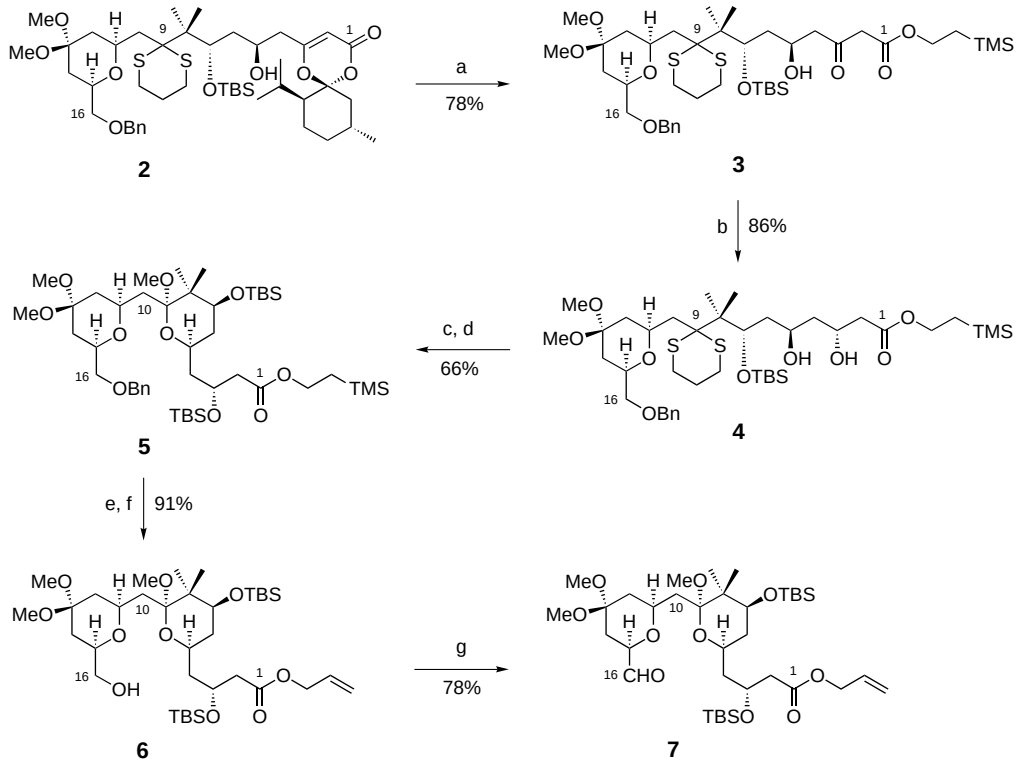
Scheme 1. Retrosynthesis of bryostatin 3 (**1**).

Scheme 2, treatment of **2** with 2-(trimethylsilyl)ethanol gave ester **3**. The resulting ketone group of **3** was selectively reduced with $Me_4NBH(OAc)_3$[7] to afford diol **4**. Subsequently, **4** was subjected to deprotection with $HgCl_2$/HgO in CH_3CN/H_2O (90/10) followed by methyl acetal formation with PPTS in MeOH, and then silylation to give the desired compound **5**, which was smoothly converted into allyl ester **6** in 3 steps. Finally, the desired C1–C16 fragment **7** was synthesized by TPAP oxidation of **6**.

Stereocontrolled introduction of a methoxycarbonylmethylene unit to the C13 position is one of the crucial steps in the bryostatin synthesis. In contrast to the syntheses by Masamune et al.[3] and Evans and co-workers,[4c] we carried out a simple Horner-Wadsworth-Emmons reaction with the known ketone **8**,[5d] as a model experiment (Scheme 3). As previously



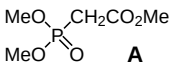
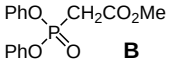
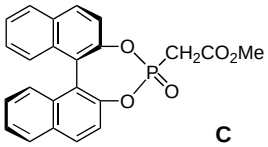
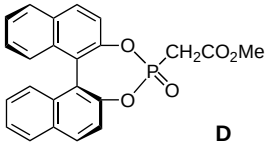
Scheme 3. Indroduction of a methoxycarbonylmethylene unit (**8** → **9**).



Scheme 2. Synthesis of the C1–C16 fragment **7**. a) $TMS(CH_2)_2OH$, toluene, reflux; b) $Me_4NBH(OAc)_3$, AcOH/CH_3CN (1/2), −20 °C; c) 1. $HgCl_2$, HgO, CH_3CN/H_2O (9/1); 2. PPTS, MeOH; d) TBSOTf, 2,6-lutidine, CH_2Cl_2; e) H_2, $Pd(OH)_2$/C, MeOH; f) 1. $LiOH \cdot H_2O$, THF/MeOH/H_2O (1/2/1); 2. CH_2=$CHCH_2Br$, $NaHCO_3$, DMF; g) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2. Bn = benzyl, NMO = *N*-methylmorpholine *N*-oxide, PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, TPAP = tetrapropylammonium perruthenate.

reported,[5d] treatment of **8** with an anion generated from $(MeO)_2P(O)CH_2CO_2Me$/NaH gave a mixture of the corresponding α,β-unsaturated esters **9** in 94% yield, with the desired ester (*Z*)-**9** obtained as a major product (*Z*:*E* = 1.6:1), which suggested a possibility for the selective construction of the methylene unit. In order to improve the selectivity, several Horner-Wadsworth-Emmons reagents were examined. The representative entries are shown in Table 1.[8] Clearly, the reagent **C**[9] is the most suitable for the formation of the desired (*Z*)-**9** (*Z*:*E* = 4:1). This result is almost the same as that of the recent Evans investigation.[4a]

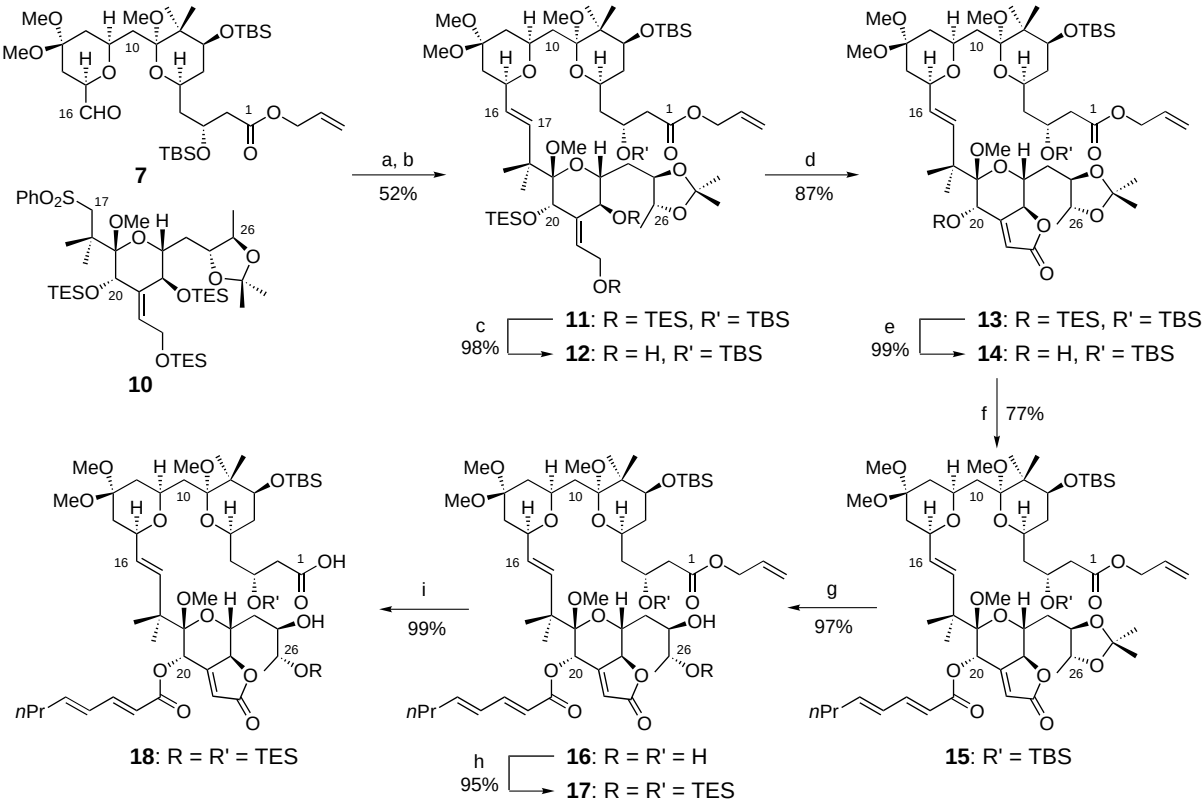
Table 1. Horner-Wadsworth-Emmons reaction of **8** with various reagents.

Phosphonate	Yield [%]	*Z*:*E* ratio of **9**
 **A**	94	1.6:1
 **B**	90	2.0:1
 **C**	92	4.0:1
 **D**	85	2.3:1

The Julia–Lythgoe olefination[10] of the previously synthesized sulfone C17-C27 fragment **10**[5a] with the aldehyde **7** was successively effected under PhLi conditions, and the following treatment with BzCl/DMAP and then 5% Na-Hg (in Na_2HPO_4) gave olefin **11** (Scheme 4), which possesses a *trans* double bond ($^3J_{H16,H17}$ = 16.1 Hz). The olefin **11** was treated with TBAF/AcOH (1/1) in THF (0 °C, 1 h) to selectively afford diol **12** in nearly quantitative yield.

Oxidation of **12** with TPAP/NMO afforded the desired α,β-unsaturated γ-lactone **13**, which on selective deprotection with TBAF/AcOH (2/1) in THF (0 °C, 5 min) gave **14**. According to the Yamaguchi protocol,[11] **14** was treated with (*E*,*E*)-2,4-octadienoic acid to afford ester **15**, which was selectively deprotected with CSA in MeOH to give triol **16**, with the protecting group of the most hindered C7 position being kept intact. Reprotection of **16** with $TESCl/Et_3N$ in DMF (−30 °C, 30 min) was carefully carried out to give the desired disiloxy ether **17** in 95% yield, which was subsequently treated with $[Pd(PPh_3)_4]$/morpholine to give seco acid **18**.

Macrolactonization of **18** was successfully accomplished by using the Yamaguchi protocol[11] to give **19** (see Scheme 5) in 93% yield, which was submitted to deprotection with 46% HF (aq.) in CH_3CN at room temperature overnight to give



Scheme 4. Synthesis of the seco acid **18**. a) **10**, PhLi, THF, −78 °C, then **7**, −78 °C, then BzCl, DMAP, −78 → 0 °C; b) 5% $Na/Hg(Na_2HPO_4)$, MeOH/EtOAc (2/1), −35 °C; c) TBAF, AcOH, THF, 0 °C; d) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2; e) TBAF, AcOH, THF, 0 °C; f) (*E*,*E*)-2,4-octadienoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then **14**, DMAP, toluene; g) CSA, MeOH; h) TESCl, Et_3N, DMF, −30 °C; i) $[Pd(PPh_3)_4]$, morpholine, THF. Bz = benzoyl, CSA = camphorsulfonic acid, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl.

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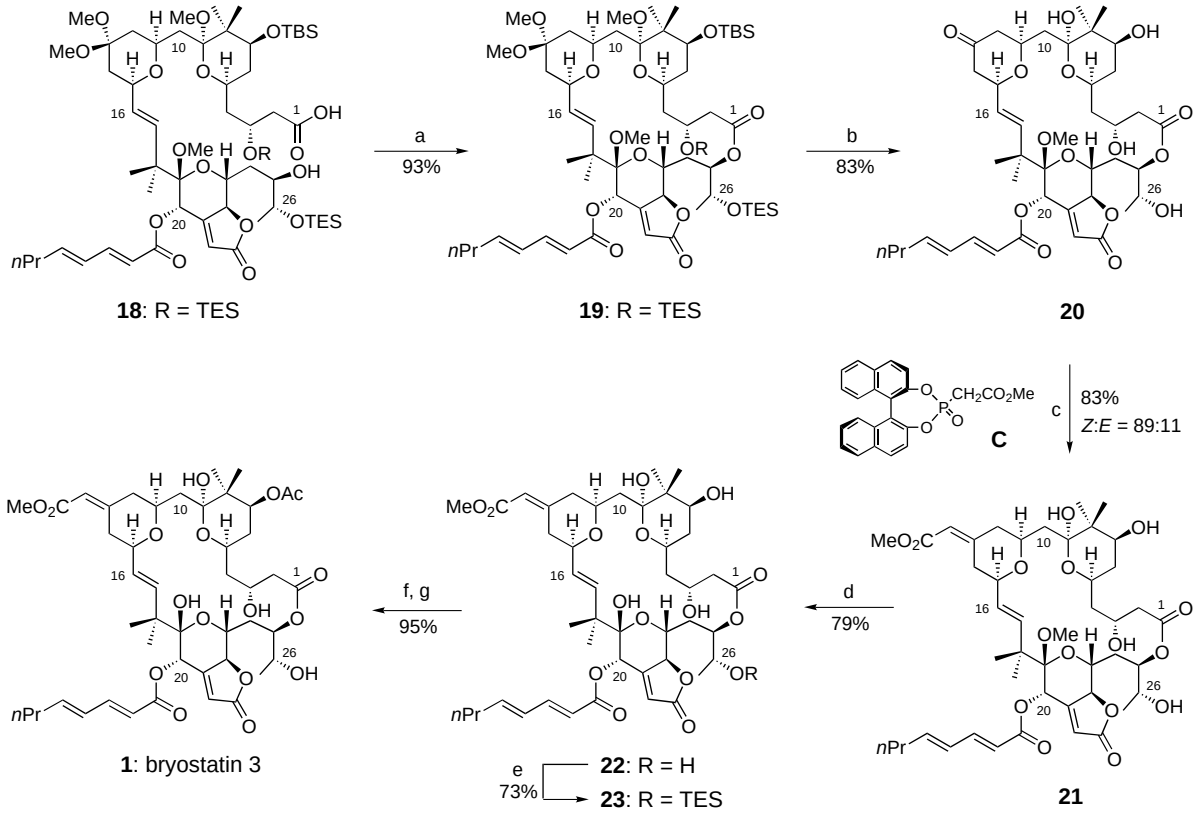

Scheme 5. Total synthesis of bryostatin 3 (**1**). a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP, toluene; b) 46% HF (aq.), CH_3CN; c) NaH, **C**, THF, 0 °C, then **20**, 50 → −10 °C; d) TFA, H_2O, CH_2Cl_2; e) TESCl, DMAP, CH_2Cl_2, −10 °C; f) Ac_2O, pyridine; g) 46% HF (aq.), CH_3CN/H_2O. TFA = trifluoroacetic acid.

ketone **20** in high yield. At this stage, we carried out the Horner-Wadsworth-Emmons reaction of **20** with an anion generated from reagent **C**/NaH in THF to give a mixture of α,β-unsaturated esters **21** ($Z:E = 89:11$)[12] in 83% yield. In the next step, any efforts made to cleave the methyl acetal at the C19 position were unsuccessful because this acetal is less reactive than that at the C9 position. However, extremely drastic conditions for hydrolysis gave rise to decomposition of the tetrahydropyrane part including the unsaturated γ-lactone. Such a property was quite different from those of other bryostatins.[3a, 4a] Ultimately, **21** was successfully hydrolyzed with TFA/H_2O (10/1) in CH_2Cl_2 (room temperature, 1 h) conditions to afford the desired compound **22** in 79% yield. Based on the ^1H and ^{13}C NMR spectra including ROESY experiments, **22** appears to adopt the same conformation as that of natural bryostatin 1,[13] which is different from that of the methyl acetal **21**, owing to the hydrogen bonding effect of the C19 hydroxyl group.[14]

Furthermore, **22** was treated with TESCl/DMAP to selectively protect the C26 hydroxyl group and form siloxy ether **23**, which on acetylation with Ac_2O/pyridine and desilylation with 46% HF (aq.) in CH_3CN provided bryostatin 3 (**1**) in almost quantitative yield. The synthetic compound is completely identical with natural bryostatin 3 in all respects of the spectral data (IR, ^1H and ^{13}C NMR (in $CDCl_3$), and UV spectroscopy and mass spectrometry). Up to now, we have been able to acquire 25 mg of synthetic bryostatin 3 (**1**), which will be used for a variety of biological tests, as well as for studying interactions with protein kinase C and other substances.

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[12] The relative ratio was determined by ^{1}H NMR spectroscopy and the configuration of the resulting olefin was confirmed by ROESY experiments.
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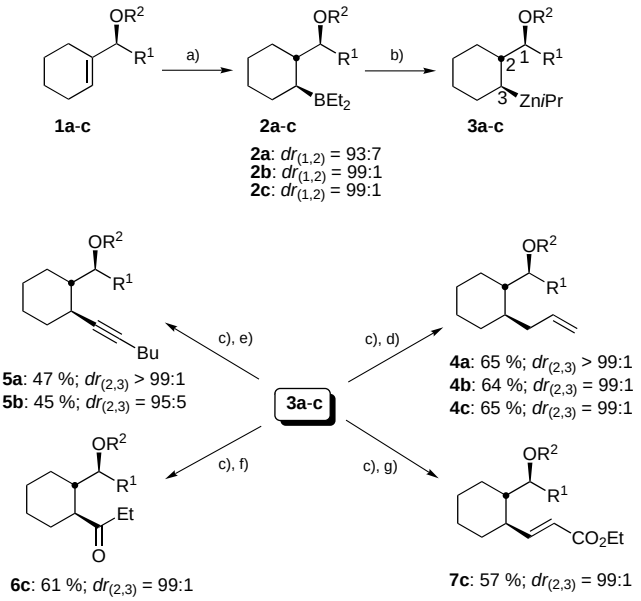
[14] The conformational difference between **21** and **22** had an influence on the stereoselectivity of methoxycarbonylmethylene introduction; the desired stereochemistry (Z:E = 8:1) was obtained by reagent **C** in the case of **21**, whereas **22** gave rise to no reaction under the same conditions. Additionally, reaction of **22** with **A** proceeded in favor of the undesired selectivity (Z:E = 1:4).

Highly Diastereoselective Synthesis of Monocyclic and Bicyclic Secondary Diorganozinc Reagents with Defined Configuration**

Andreas Boudier, Eike Hupe, and Paul Knochel*

Dedicated to Professor Bernd Giese on the occasion of his 60th birthday

The stereoselective formation of new C–C bonds is an important goal in organic synthesis. A requirement for stereoselective coupling is the availability of C(sp^3)-hybridized organometallic compounds having a defined configuration. Organolithium compounds with high configurational stability are obtained only in strained cyclic systems or for organolithium reagents bearing a chelating heteroatom in the α-position.[1, 2] Although remarkable progress has recently been made in this field,[3, 4] a more general approach would be desirable. Recently, we have shown that secondary cyclic and acyclic chiral diorganozinc reagents can be prepared in the absence of any chelating heteroatom with high diastereoselectivity, allowing the stereochemical control of two adjacent stereocenters.[5, 6, 7] Herein, we report the diastereoselective hydroboration of various monocyclic and bicyclic ring systems allowing, after subsequent boron–zinc exchange,[8] the preparation of configurationally stable secondary dialkylzinc compounds with three adjacent chiral centers. Initially, we investigated the diastereoselective hydroboration of allylic ethers[9] of type **1**, since the corresponding alcohols can be readily obtained in optically pure form.[10] Thus, the hydroboration of **1a** (R^1 = Ph; R^2 = CH_2Ph) with Et_2BH in Me_2S[11] produces the corresponding organoborane **2a** with a diastereoselectivity of 93:7 (Scheme 1). An improved stereoselectivity of 99:1 is obtained by using an ethoxymethyl (EOM) protecting group (**2b**, R^2 = EOM). The presence of this acetal function also considerably facilitates the boron–zinc exchange, yielding secondary diorganozinc compounds of type **3**. After transmetalation with CuCN · 2 LiCl,[12] a smooth C–C bond-forming reaction occurs with various electrophiles such as allyl bromide, 1-bromo-1-hexyne,[13] propionyl chloride, or ethyl propiolate furnishing various polyfunctional products of type **4**–**7** (Table 1, entries 1–7).[14] This one-pot sequence proceeds with good overall yields (45–73%) and excellent



Scheme 1. Diastereoselective hydroboration of **1a**–**c**, boron–zinc exchange and reaction with electrophiles. For compounds of type **1**–**7**: **a**: R^1 = Ph; R^2 = Bn; **b**: R^1 = Ph; R^2 = CH_2OEt; **c**: R^1 = *t*Bu; R^2 = CH_2OEt. Reaction conditions: a) Et_2BH (3 equiv) in Me_2S, 50 °C, 16 h; b) *i*Pr_2Zn (3 equiv), 25 °C, 5 h; c) CuCN · 2 LiCl (1 equiv), −78 °C, 30 min; d) allyl bromide (3 equiv), −78 °C to 25 °C, 12 h; e) 1-bromo-1-hexyne (5 equiv), −55 °C, 2 d; f) EtC(O)Cl (3 equiv, −78 °C to 25 °C, 12 h; g) ethyl propiolate (3 equiv), −78 °C to 25 °C, 12 h.

[*] Prof. Dr. P. Knochel, Dipl.-Chem A. Boudier, Dipl.-Chem. E. Hupe
Department Chemie, Ludwig-Maximilians-Universität
Butenandtstrasse 5–13 (Haus F), 81377 München (Germany)
Fax: (+49) 89-2180-7680
E-mail: Paul.Knochel@cup.uni-muenchen.de

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