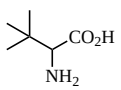
[7] A. S. K. Hashmi, *Angew. Chem.* **1995**, *107*, 1749 – 1751; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581 – 1582; A. S. K. Hashmi, T. L. Ruppert, T. Knöfel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295 – 7304.
[8] H. Sheng, S. Lin, Y. Huang, *Synthesis* **1987**, 1022 – 1023.
[9] B. Seiller, C. Bruneau, P. H. Dixneuf, *Tetrahedron* **1995**, *51*, 13089 – 13102. For a recent example, see also: B. Gabriele, G. Salerno, E. Lauria, *J. Org. Chem.* **1999**, *64*, 7687 – 7692.
[10] J. A. Marshall, C. A. Sehon, *J. Org. Chem.* **1995**, *60*, 5966 – 5968.
[11] Silver nitrate 99.9999 %.
[12] Comparable aurations have been observed in the stoichiometric coupling of nucleobases by $[AuCl_4]^-$: F. Zamora, P. Amo-Ochoa, B. Fischer, A. Schimanski, B. Lippert, *Angew. Chem.* **1999**, *111*, 2415 – 2417; *Angew. Chem. Int. Ed.* **1999**, *38*, 2274 – 2275; F. Zamora, E. Zangrando, M. Furlan, L. Randaccio, B. Lippert, *J. Organomet. Chem.* **1998**, *552*, 127 – 134. The darkening and polymerization have been discussed already: P. W. J. de Graaf, J. Boersma, G. J. M. van der Kerk, *J. Organomet. Chem.* **1976**, *105*, 399 – 406.
[13] S. Cacchi, A. Arcadi, *J. Org. Chem.* **1983**, *48*, 4236 – 4240; R. Benhaddou, S. Czernecki, G. Ville, *J. Org. Chem.* **1992**, *57*, 4612 – 4616; H. Hagiwara, Y. Eda, K. Morohashi, T. Suzuki, M. Ando, N. Ito, *Tetrahedron Lett.* **1998**, *39*, 4055 – 4058.
[14] R. T. Baker, P. Nguyen, T. B. Marder, S. A. Westcott, *Angew. Chem.* **1995**, *107*, 1451 – 1452; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1336 – 1338.
[15] Au^I, in the form of [AuCl(tetrahydrothiophene)], converted **1b** to **3b** only and no dimer **4b** was observed.

α-Trialkylsilyl-Substituted α-Amino Acids**

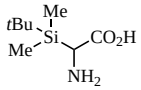
Carsten Bolm,* Andrey Kasyan, Karlheinz Drauz, Kurt Günther, and Gerhard Raabe

Dedicated to Professor Franz Effenberger on the occasion of his 70th birthday

As building blocks of peptides and proteins, α-amino acids are widespread throughout nature.[1] Various methods have been developed to gain access to them,[2] and among these catalytic processes appear particularly attractive.[2d] Among the nonproteinogenic amino acids *tert*-leucine (**1**) has emerged as an outstanding representative.[3] Bearing a hydrophobic and sterically demanding *tert*-butyl substituent, it has proved to be a valuable building block for pharmacologically effective peptide analogues[4] and has been frequently employed in syntheses of chiral auxiliaries.[5, 6] Here, we report the first synthesis of *tert*-leucine-analogous α-trialkylsilyl-substituted α-amino acids **2** and their corresponding, amino- and carboxyl-protected derivatives **4**.[7]

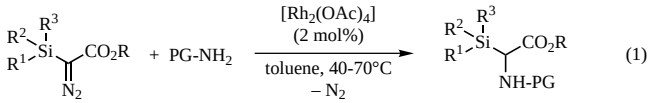


1



2

For the synthesis of **2**, fully protected α-trialkylsilyl-α-aminoacetates **4** play a pivotal role. These are prepared starting from α-trialkylsilyl-α-diazoacetates **3**,[8] which in turn are accessible through reaction of the corresponding α-diazoacetates with trialkylsilyltriflates in the presence of tertiary amine bases.[9, 10] Rhodium-catalyzed cleavage of nitrogen[11, 12] and intermolecular carbenoid-type N,H-insertion[12, 13] leads to the protected α-trialkylsilyl-α-aminoacetates **4** [Eq. (1); PG = protecting group]. The yields in these



(1)

3 **4**

insertion reactions are good (up to 86 %; Table 1). An X-ray crystal structure analysis of ester *rac*-**4a** confirmed its constitution.[14]

Table 1. Synthesis of protected α-trialkylsilyl-α-aminoacetates **4**.

R	R^1/R^2	R^3	PG[a]	Product	Yield [%]
Et	Me	*t*Bu	Tos	**4a**[b]	58
Et	Me	*t*Bu	Boc	**4b**	72
Et	Me	*t*Bu	Z	**4c**	83
Et	Me	Me	Boc	**4d**	65
Et	Me	Me	Z	**4e**	69
Et	Et	Et	Boc	**4f**	77
Et	Et	Et	Z	**4g**	86
Bn	Me	*t*Bu	Boc	**4h**	47
Bn	Me	*t*Bu	Z	**4i**	53

[a] Tos = tosyl = *p*-toluenesulfonyl, Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl. [b] From a reaction sequence as described in the Experimental Section.

The enantiomers of **4a** were separated by means of preparative HPLC using a chiral stationary phase.[15] Enantiopure **4a** is configurationally stable even upon prolonged storing. The absolute configuration of the later-eluted (+)-enantiomer of **4a** was determined to be (*S*) by a second X-ray crystal structure analysis. Figure 1 shows the molecular structure of (*S*)-**4a** in the crystal.[14]

The Si–C11 bond (1.919(5) Å) in (*S*)-**4a** is significantly longer than those between the silicon atom and C13 (1.904(6) Å), C12 (1.862(5) Å), and C17 (1.865(4) Å); the last two bond lengths fall within the range that is considered average for a bond between a four-coordinate Si atom and an

[*] Prof. Dr. C. Bolm, Dr. A. Kasyan, Priv.-Doz. Dr. G. Raabe
Institut für Organische Chemie der RWTH Aachen
Professor-Pirlet Strasse 1, 52074 Aachen (Germany)
Fax: (+49) 241-8888-391
E-mail: Carsten.Bolm@oc.RWTH-Aachen.de
Prof. Dr. K. Drauz[+]
Forschung, Entwicklung und Anwendungstechnik des Geschäftsbereichs Feinchemikalien
Degussa-Hüls AG, Postfach 1345, 63403 Hanau (Germany)
Dr. K. Günther
Analytisch Technische Services
Infracor GmbH, Postfach 1345, 63403 Hanau (Germany)

[**] This work was financially supported by the Fonds der Chemischen Industrie and Degussa-Hüls. We are grateful to Dr. P. Phansavath for preliminary studies in this field.

[+] Transformation of Amino Acids, Part 15. Part 14: A. S. Bommarius, K. Drauz, K. Günther, G. Knaup, M. Schwarm, *Tetrahedron: Asymmetry* **1997**, *8*, 3197.

  1433-7851/00/3913-2288 $ 17.50+.50/0

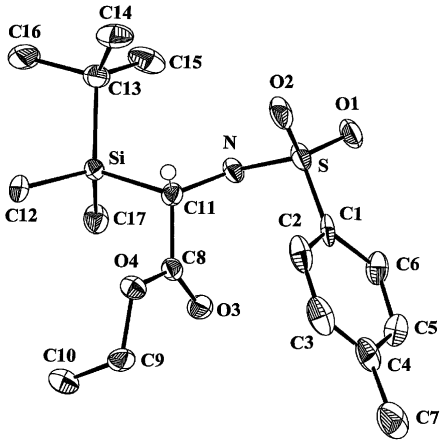
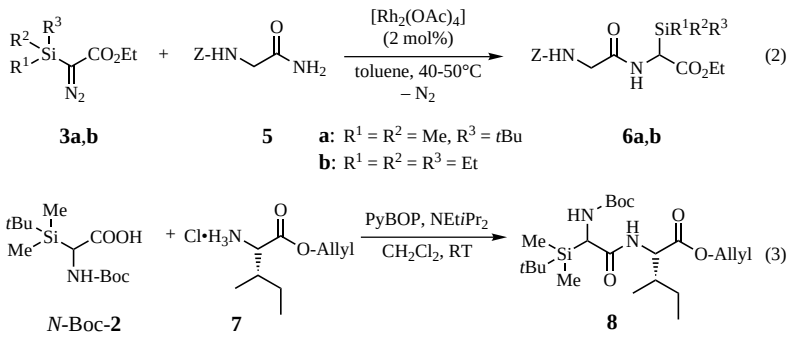


Figure 1. Molecular structure of (*S*)-**4a** in the solid state. Selected distances [Å] and angles [°]: Si-C11 1.919(5), N-C11 1.469(6), C8-C11 1.512(7), C8-O3 1.198(5), C8-O4 1.327(5); C8-C11-Si 108.7(3), N-C11-Si 110.2(3), N-S-C1 109.3(2), C13-Si-C11 110.3(2), C12-Si-C17 112.2(2), C12-Si-C13 109.8(2).



sp^3-hybridized carbon atom (1.863(24) Å).[16] A quantum-chemical calculation at the B3LYP/6-31G* level confirms this tendency. Starting from the experimentally found structure of crystalline *rac*-**4a**, a complete geometry optimization resulted in a bond length of 1.959 Å for Si–C11, while the Si–C13, Si–C12, and Si–C17 bonds of 1.922, 1.895, and 1.892 Å, respectively, are significantly shorter.

In order to allow the incorporation of α-trialkylsilyl-substituted α-amino acids into peptides, processes needed to be devised that selectively released the amino and carboxy termini of protected esters **4** and, in addition, stability of the derivatives formed had to be ensured. Therefore, *N*-Boc derivative **4b** was treated with concentrated trifluoroacetic acid (in CH_2Cl_2 2 h, ambient temperature) and subsequently with tosyl chloride and a base. The formation of tosylated product **4a** (58% yield) may be taken as evidence for the stability of the intermediate α-trialkylsilyl-substituted α-amino ester, which bears a free amino group. Hydrogenolysis of benzyl *N*-Boc-ester **4h** selectively furnished the corresponding, still *N*-protected α-trialkylsilyl-substituted α-amino acid (*N*-Boc-**2**) in 93% yield. In the same manner an entirely unprotected α-trialkylsilyl-substituted α-amino acid was synthesized for the first time. Thus, twofold debenzylation of **4i** afforded **2** in 92% yield. Consequently, starting from either enantiomer of **4i**, amino acids (*S*)-**2** and (*R*)-**2** were obtained in optically pure form.

Two methods exemplifying the synthesis of peptide-type structures were investigated. On the one hand, rhodium-catalyzed reaction of **3a** and **3b** with Z-protected glycine amide **5** gave rise to dipeptides **6a** and **6b** in 20–25% yield; that is α-trialkylsilyl α-diazoacetates **3** could react directly with amides to yield dipeptidic entities [Eq. (2)].[17] A more efficient approach, on the other hand, was the peptide coupling of *N*-Boc-**2** and the HCl salt of L-isoleucineallylester (**7**) under standard conditions involving benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), which gave dipeptide **8** in about 88% yield [Eq. (3)].[18]

Experimental Section

Synthesis of **4a**: $[Rh_2(OAc)_4]$ (18 mg, 0.04 mmol, 2 mol%) was added at room temperature to a stirred solution of **3a** (457 mg, 2 mmol) and *tert*-butylcarbamate (586 mg, 5 mmol) in dry toluene (5 mL). The reaction mixture was heated to 50 °C and stirred at this temperature for 24 h. After the mixture had been allowed to cool to ambient temperature, the solvents were removed under reduced pressure and the product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 5:1). Thus, *N*-Boc-protected ester **4b** (457 mg, 72%) was obtained as a colorless oil. For the synthesis of **4a**, trifluoroacetic acid (0.2 mL) was added dropwise to a solution of **4b** (317 mg, 1 mmol) in dry dichloromethane (3 mL) under argon. The reaction mixture was stirred for 2 h at ambient temperature before the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (5 mL) and treated sequentially with triethylamine (0.28 mL) and tosyl chloride (190 mg, 1 mmol). After 1 h of stirring the reaction was quenched with water (10 mL) and the mixture was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 3:1) to afford **4a** (216 mg; 58%) as a white solid (m.p. 127–128 °C (ethanol)). The separation of the enantiomers was performed by means of HPLC using a chiral stationary phase.[15]

Received: October 14, 1999 [Z14148]
Revised version: April 7, 2000

[1] a) H.-D. Jakubke, H. Jeschkeit, *Aminosäuren, Peptide, Proteine*, VCH, Weinheim, **1982**; b) H.-D. Jakubke, *Peptide: Chemie und Biologie*, Spektrum, Heidelberg, **1996**; c) *Peptides* (Ed.: B. Gutte), Academic Press, San Diego, **1995**; d) S. M. Hecht, *Bioorganic Chemistry: Peptides and Proteins*, Oxford University Press, New York, **1998**.

[2] a) R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, Oxford, **1989**; b) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889; c) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539; d) M. J. Burk, F. Bienewald in *Transition Metals for Organic Synthesis*, *Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, p. 13; e) M. Calmes, J. Daunis, *Amino Acids* **1999**, *16*, 215.

[3] a) A. S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher, K. Drauz, *Tetrahedron: Asymmetry* **1995**, *6*, 2851; b) K. Drauz, *Chimia* **1997**, *50*, 310.

[4] For examples, see: a) R. J. Andersen, J. E. Coleman, E. Piers, D. J. Wallace, *Tetrahedron Lett.* **1997**, *38*, 317; b) P. Ettmayer, M. Hübner, A. Billich, B. Rosenwirth, H. Gstach, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2851; c) K. Paulvannan, T. Chen, *Synlett* **1999**, 1371; d) G. Bold, A. Fässler, H.-G. Capraro, R. Cozens, T. Klimkait, J. Lazdins, J. Mestan, B. Poncioni, J. Rösel, D. Strover, M. Titelnot-Blomley, F. Acemoglu, W. Beck, E. Boss, M. Eschbach, T. Hürlimann, E. Masso, S. Roussel, K. Ucci-Stoll, D. Wyss, M. Lang, *J. Med. Chem.* **1998**, *41*, 3387; e) K. Paulvannan, T. Chen, *Synlett* **1999**, 1371.

[5] Reviews: a) A. Studer, *Synthesis* **1996**, 793; b) H. Waldmann, *Synlett* **1995**, 133; c) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835.

  1433-7851/00/3913-2289 $ 17.50+.50/0

[6] Further recent examples of successful asymmetric metal catalyses involving ligands based on *tert*-leucine: a) C. Bolm, K. Muñiz, J. P. Hildebrand, *Org. Lett.* **1999**, *1*, 491; b) C. Bolm, K. Muñiz-Fernandez, A. Seger, G. Raabe, K. Günther, *J. Org. Chem.* **1998**, *63*, 7860; c) C. Bolm, F. Bienewald, *Synlett* **1998**, 1327; d) C. Bolm, T. K. K. Luong, G. Schlingloff, *Synlett* **1997**, 1151; e) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem*. **1998**, *110*, 3047; *Angew. Chem. Int. Ed.* **1998**, *37*, 2897; f) M. Peer, J. C. de Jong, M. Kiefer, T. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese, G. Helmchen, *Tetrahedron* **1996**, *52*, 7547; g) S. Kudis, G. Helmchen, *Angew. Chem*. **1998**, *110*, 3047; *Angew. Chem. Int. Ed.* **1998**, *37*, 3047; h) D. A. Evans, T. Rovis, M. C. Kozlowski, J. S. Tedrow, *J. Am. Chem. Soc*. **1999**, *121*, 1994.

[7] A fully protected ethyl α-trimethylsilyl-α-amino ester was identified as minor isomer in a product mixture that was obtained by reaction of a lithiated aminosilane with ethyl chloroformate. S. McSieburth, J. J. Somers, H. K. O'Hare *Tetrahedron* **1996**, *52*, 5669.

[8] For the synthesis of benzyl α-diazoacetate, which—like the corresponding, commercially available ethyl ester—can be silylated, see: S. R. Angle, D. S. Bernier, N. A. El-Said, D. E. Jones, S. Z. Shaw, *Tetrahedron Lett.* **1998**, *39*, 3919.

[9] a) M. Martin, *Synth. Commun.* **1983**, *13*, 809; b) A. Fronda, F. Krebs, B. Daucher, T. Erle, G. Maas, *J. Organomet. Chem.* **1992**, *424*, 253; c) G. Maas, S. Bender, *Synthesis* **1999**, 1175; d) general overview of diazocarbonyl chemistry: T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091.

[10] Reviews on silyl-substituted diazocarbonyl compounds, α-silylcarbenes and -carbenoids: a) G. Maas in *The Chemistry of Organic Silicon Compounds, Vol. 2*, *Part 1* (Eds.: Z. Rappoport, Y. Apeloig), Wiley, Chichester, **1998**, chap. 13, p. 703; b) H. Tomioka, *Methoden Org. Chem. (Houben Weyl)*, *4th ed.*, *1952–*, *Vol. E 19b*, **1989**, p. 1410.

[11] Examples of other Rh-catalyzed reactions of α-silyl-α-diazoacetates: a) G. Maas, M. Gimmy, M. Alt, *Organometallics* **1992**, *11*, 3813; b) V. Gettwert, F. Krebs, G. Maas, *Eur. J. Org. Chem*. **1999**, 1213; c) S. N. Kablean, S. P. Marsden, A. M. Craig, *Tetrahedron Lett*. **1998**, *39*, 5109; d) S. P. Marsden, W.-K. Pang, *Tetrahedron Lett*. **1998**, *39*, 6077; e) S. P. Marsden, E.-K. Pang, *Chem. Commun.* **1999**, 1199.

[12] Simple trialkylsilylcarbenes do not react under *N,H*-insertion: a) R. L. Kreeger, H. Shechter, *Tetrahedron Lett.* **1975**, 2061; b) in ref. [10b], p. 1417.

[13] Examples of N,H-insertions in Rh-catalyzed transformations with other diazocarbonyl compounds: a) S. N. Osipov, N. Sewald, A. F. Kolomiets, A. V. Fokin, K. Burger, *Tetrahedron Lett*. **1996**, *37*, 615; b) L. Ferris, D. Haigh, C. J. Moody, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2885; c) C. J. Moody, L. Ferris, D. Haigh, E. Swann, *Chem. Commun*. **1997**, 2391; d) M. C. Bagley, R. T. Buck, S. L. Hind, C. J. Moody, A. M. Z. Slawin, *Synlett* **1996**, 825; e) G. Mloston, M. Celeda, A. Swiatek, M. Kägi, H. Heimgartner, *Pol. J. Chem.* **1998**, *72*, 1907; f) diastereoselectively (de_{max}: 13%): E. Aller, R. T. Buck, M. J. Drysdale, L. Ferris, D. Haigh, C. J. Moody, N. D. Pearson, J. B. Sanghera, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2879; g) enantioselectively (ee_{max}: 45%): C. F. García, M. A. McKervey, T. Ye, *Chem. Commun*. **1996**, 1465.

[14] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-135676 (*rac*-**4a**) and -135677 (*(S)*-**4a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[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}.

[16] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1.

[17] Reactions of the like have already been utilized to synthesize simple dipeptides; cf. ref. [13].

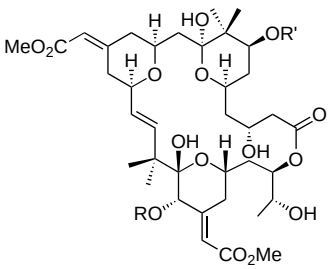
[18] This transformation was performed with racemic *N*-Boc-**2**. It is still to be investigated how enantiopure α-trialkylsilyl-α-amino acids will react.

Total Synthesis of Bryostatin 3**

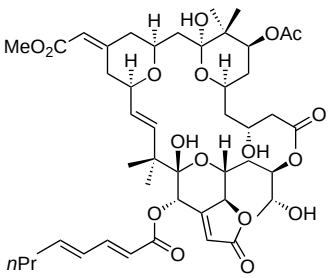
Ken Ohmori, Yasuyuki Ogawa, Tetsuo Obitsu, Yuichi Ishikawa, Shigeru Nishiyama,* and Shosuke Yamamura*

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

[**] This work was supported by the Ministry of Education, Science, Sports, and Culture (Japan). K.O. is grateful to JSPS for a predoctoral fellowship. The authors thank Dr. G. N. Chmurny (NIH) for providing them with ^{1}H and ^{13}C NMR spectra of bryostatin 3 and for helpful discussions.

  1433-7851/00/3913-2290 $ 17.50+.50/0