

Asymmetric Synthesis of the Northern
Half C1–C16 of the Bryostatins

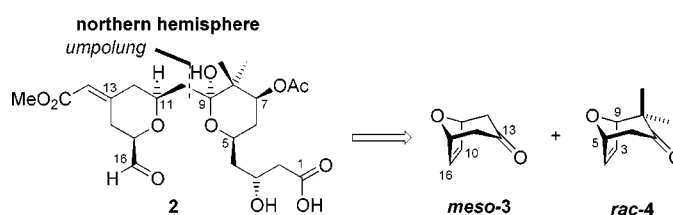
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ABSTRACT



Starting from 8-oxabicyclo[3.2.1]oct-6-en-3-one and racemic 2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, the C1–C16 segment of the bryostatins has been synthesized in 30 steps and 9% overall yield (17 steps longest linear sequence). Fragment coupling by dithiane strategy and protecting group manipulations provided an advanced chemodifferentiated northern half segment.

The bryostatins,¹ first described by Pettit in 1982, are a family of 18 promising cancer chemotherapeutic candidates. They exhibit a highly oxygenated pattern with a polyacetate-derived backbone. The bryostatins bind to protein kinase C (PKC) and activate it in a fashion different from the phorbol esters: Exogenous agonists of PKC, such as the phorbol esters, usually are tumor promoters, but the bryostatins act as anticancer drugs.² Although the molecular mode of biological activity is unknown, the bryostatins are currently in phase II human clinical trials for treatment of non-Hodgkin's lymphoma, melanoma, and renal cancer.³

Since their discovery, three total syntheses of a bryostatin have been completed up to date.⁴ Furthermore, several

groups,⁵ including our own,⁶ set up a program directed toward a convergent and efficient synthesis of these challenging macrolides and especially of bryostatin 1 and some simplified bryostatin analogues,⁷ which exhibit biological activity similar to that of bryostatin 1. In this study, we describe the completion of the C1–C16 segment, the northern half of the bryostatins.

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(3) Information on the status of bryostatin clinical trials can be found via the Internet at <http://cancernet.nci.nih.gov/prot/protscrch.shtml>.

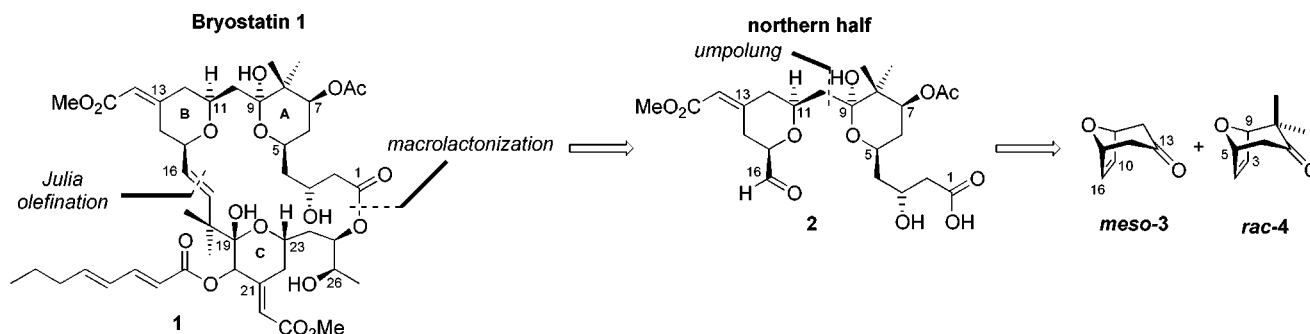
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(6) (a) Lampe, T. F. J.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1996**, 37, 7695. (b) Lampe, T. F. J.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1996**, 1931. (c) Weiss, J. M.; Hoffmann, H. M. R. *Tetrahedron: Asymmetry* **1997**, 8, 3913.

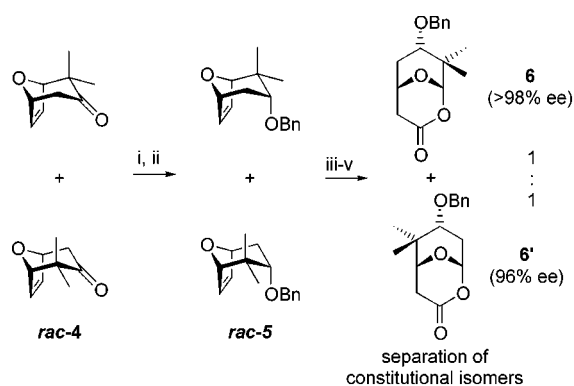
(7) (a) Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, 120, 4534. (b) Wender, P. A.; De Brabander, J.; Harran, P. G.; Hinkle, K. W.; Lippa, B.; Pettit, G. R. *Tetrahedron Lett.* **1998**, 39, 8625. (c) Wender, P. A.; Lippa, B. *Tetrahedron Lett.* **2000**, 41, 1007. (d) Wender, P. A.; Hinkle, K. W. *Tetrahedron Lett.* **2000**, 41, 6725.

Scheme 1



Our retrosynthetic analysis (Scheme 1) involves disconnection of the C1–C25 lactone bond and the C16–C17 trans olefinic bond. Further scission at the C9–C10 glycoside bond provides two segments of comparable size, which are accessible from oxabicyclic ketone **meso-3** and racemic oxabicyclic ketone **rac-4**.

Synthesis of the C1–C9 Subunit. The starting racemic material **rac-4** was prepared in 40 g per batch⁸ and reduced with L-Selectride, providing the axial alcohols without formation of the equatorial alcohols (Scheme 2). After

Scheme 2^a

^a (i) 1. L-Selectride, THF, -78°C , 2 h; 2. NaOH, H_2O_2 , rt, 1 h, 98%; (ii) BnBr, NaH, reflux, 1 h, 98%; (iii) 1. (–)-Ipc₂BH, THF, -15°C , 3 d; 2. NaOH, H_2O_2 , rt, 1 h, 92%; (iv) PCC, CH_2Cl_2 , rt, 16 h, 96%; (v) *m*-CPBA, NaHCO_3 , CH_2Cl_2 , rt, 16 h, 90%.

conversion into the protected *endo*-alcohol **rac-5**, reagent-induced asymmetric hydroboration⁹ of the double bond with (–)-Ipc₂BH was carried out, requiring careful temperature control (-15°C). Oxidation to the resulting alcohols using PCC and subsequent Baeyer–Villiger ringexpansion gave the lactone acetals **6** and **6'** in excellent ee. Separation by flash chromatography was feasible at this stage.^{6c}

(8) (a) Föhlisch, B.; Herter, R. *Synthesis* **1982**, 976. (b) Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940. Hoffmann, H. M. R.; Iqbal, M. N. *Tetrahedron Lett.* **1975**, *16*, 4487.

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[3.3.1]Lactone acetal **6** was opened under standard basic conditions to afford acetal ester **7** as an anomeric mixture in excellent yield (Scheme 3). Further opening to the acyclic polyketide segment was critical and was accomplished by two methods: With ethanedithiol/ $\text{BF}_3\cdot\text{Et}_2\text{O}$ to the polyketide 1,3-dithiolane (five-membered ring) in nonpolar solvent dichloromethane, but not with 1,3-propanedithiol/ $\text{BF}_3\cdot\text{Et}_2\text{O}$ in this solvent (potential six-membered ring), even though the nondimethylated acetal could be opened.^{6b} However, the 1,3-dithiane polyketide was indispensable for *umpolung*. After further experimentation it was found that *trans*-thioacetalization with 1,3-propanedithiol/ $\text{BF}_3\cdot\text{Et}_2\text{O}$ was feasible but only in the much more polar solvent nitromethane. Thus, the desired polyketide **8** could be obtained after careful optimization of the temperature window in very good yield.¹⁰ Claisen condensation of **8** using an excess of the enolate, prepared from *tert*-butyl acetate and lithium diisopropylamide, gave the δ -hydroxy- β -keto ester **9** (94%). Reduction with the Saksena–Evans reagent¹¹ provided the C3,C5-*anti* diol **10** (*anti:syn* = 91:9), which was then protected as its acetonide **11**. After the ester functionality had been reduced with LiAlH_4 , the benzyl ether was cleaved using lithium di-*tert*-butylbiphenyl (LDBB) radical anion¹² to circumvent deprotonation problems during the planned segment coupling. Finally, chemodifferentiated protection of the resulting diol **12** occurred with ease, affording the target **13** in 14 steps from **rac-4** and 27% overall yield (50% maximum yield).

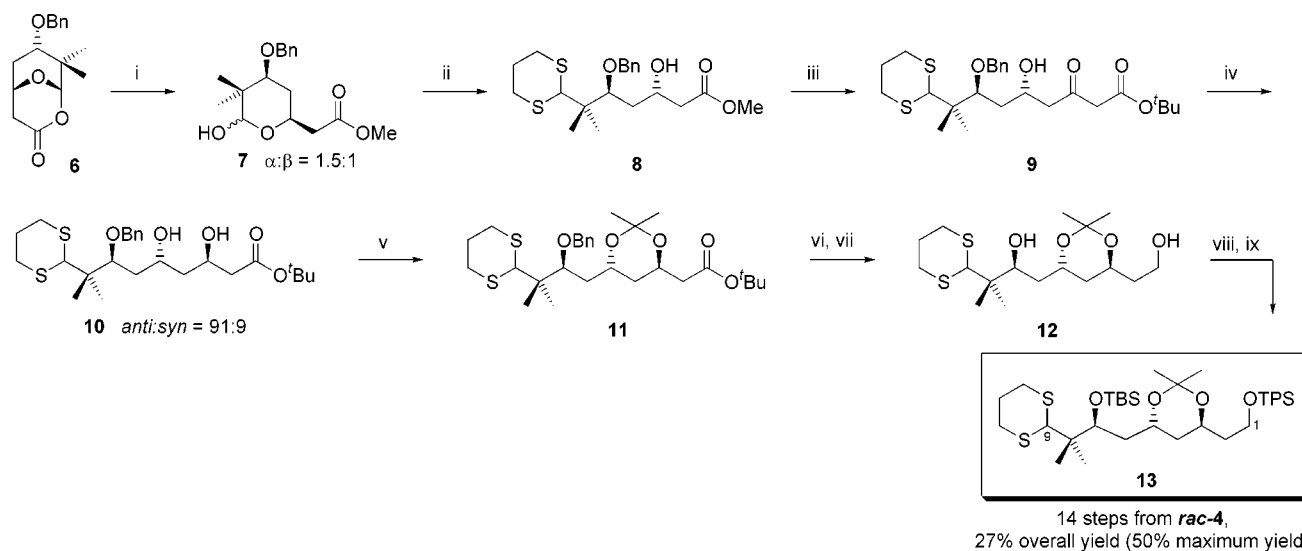
Optimized Synthesis of the C10–C16 Subunit. Our initial synthesis of this segment began with the protection of the oxabicyclic ketone **meso-3** with an excess of 2,2,5,5-tetramethyl-1,3-dioxane in the presence of catalytic amounts of *p*-TsOH at reduced pressure to afford the desired ketal **meso-15** (50% yield, Scheme 4) in the first step of the synthesis sequence.¹³ Improvement of the yield was feasible by two modifications: Transketalization with acetal **14**, which is more labile under acid conditions, and *Kugelrohr* distillation, to remove the excess of **14** in the workup,

(10) For a detailed consideration of the opening of methoxy acetals, see: Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177.

(11) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(12) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

(13) Lampe, T. F. J.; Hoffmann, H. M. R.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **1996**, *7*, 2889.

Scheme 3^a

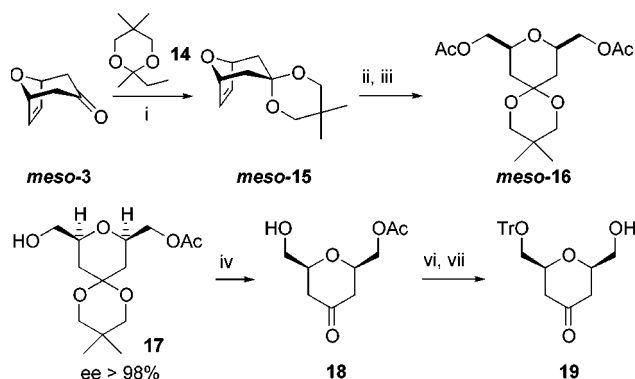
^a (i) K₂CO₃, MeOH, rt, 6 h, 99%; (ii) 2 equiv of HS(CH₂)₃SH, 3 equiv of BF₃·Et₂O, MeNO₂, -20 → -15 °C, 0.5 h, 95%; (iii) 5 equiv of CH₃CO₂Bu^t, LDA, -78 → 0 °C, 2 h, 94%; (iv) Me₄NBH(OAc)₃, MeCN/AcOH (1:1), -35 °C, 3 d, -25 °C, 24 h, 97%; (v) (CH₃)₂C(OMe)₂, p-TsOH (catalytic), rt, 16 h, 88%; (vi) LiAlH₄, THF, 0 °C → rt, 2 h, 99%; (vii) 10 equiv of LDBB, THF, -78 → -50 °C, 0.5 h, 98%; (viii) TPSCl, imidazole, CH₂Cl₂, rt, 2 h, 99%; (ix) TBSOTf, imidazole, 60 °C, 2 h, 99%.

provided ketal **meso-15** in 75% yield (98% based on recovered starting material). Ozonolysis of the olefinic double bond and subsequent reduction afforded a diol which was transformed into **meso-16**.

Differentiation of the two enantiotopic acetoxy methyl groups works best by lipase PS-mediated hydrolysis.¹⁴ Extending the reaction time from 24 to 38 h was feasible without loss of enantiomeric purity (ee > 98%) and raised also the chemical yield. Again, prolongation of reaction time in the next two steps, regeneration of carbonyl group, and protection of the hydroxy group as a trityl ether improved

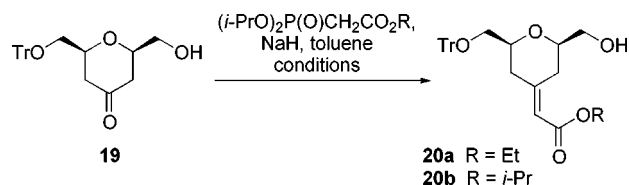
the yield slightly. Standard deacetylation conditions furnished the corresponding hydroxy ketone **19**.^{6a}

The stereoselective formation of an exocyclic α,β-unsaturated ester from cyclic ketones such as **19** is far from trivial (Scheme 5): It was found that a synergistic effect of the

Scheme 4^a

^a (i) p-TsOH (6 mol %), 35–45 mmHg, rt, 7 d, 75% (98% borsm); (ii) 1. O₃, MeOH/CH₂Cl₂, -78 → -20 °C; 2. NaBH₄, -20 → 0 °C, 1 h, 98%; (iii) Ac₂O, DMAP (catalytic), py, rt, 5 h, 91%; (iv) lipase PS, toluene/phosphate buffer (1:4), pH = 7, 38 h, 96%; (v) acetone, Pd(CH₃CN)₂Cl₂ (catalytic), rt, 24 h, 93%; (vi) TrCl, Et₃N, DMAP (catalytic), CH₂Cl₂, rt, 24 h, 84%; (vii) K₂CO₃, H₂O/MeOH, 0 °C, 2 h, 99%.

Scheme 5



bulky trityl group with a sterically demanding HWE reagent phosphonoacetate favored the formation of the desired *E*-isomer in good selectivity (9:1) by remote stereinduction (1,6 or 1,7 depending on atom counting).¹⁵ Further experimentation provides additional insight (Table 1): In general, chemical yields increased by diluting the reaction mixture. Furthermore, the use of the sterically more demanding isopropyl diisopropoxyphosphonoacetate¹⁶ furnished the desired unsaturated ester **20b** in high chemical yield and excellent *E*-selectivity (*E*:*Z* = 98:2), after careful optimization of the temperature window (Table 1, entry 5).

(14) For further enzymatic desymmetrization of related tetrahydropyrans, see: Chênevert, R.; Goupil, D.; Rose, Y. S.; Bédard, E. *Tetrahedron: Asymmetry* **1998**, 9, 4285.

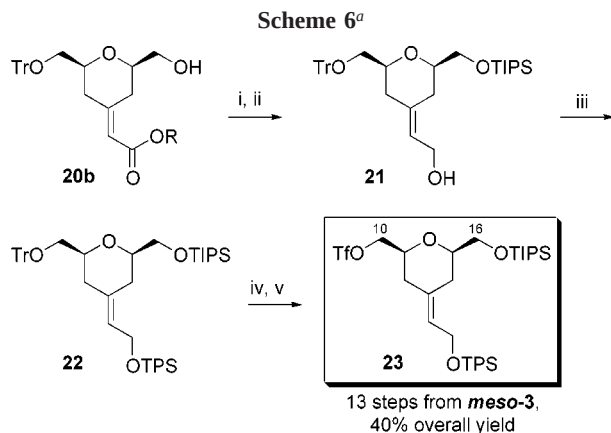
(15) Lampe, T. F. J.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1996**, 2637.

(16) Prepared in two steps: (a) (EtO)₂P(O)H + Ti(O-*i*-Pr)₄ → (*i*-PrO)₂P(O)H: Froneman, M.; Modro, T. A. *Tetrahedron Lett.* **1988**, 29, 3327. (b) (*i*-PrO)₂P(O)H + ClCH₂CO₂*i*-Pr → (*i*-PrO)₂P(O)CH₂CO₂*i*-Pr: Ye, W.; Liao, X. *Synthesis* **1985**, 986.

Table 1

no.	R	c [M]	conditions	yield [%]	E:Z
1	Et	0.08	−50 °C → −35 °C, 1 h; −17 °C, 14 h	80	88:12
2	Et	0.048	−50 °C → −35 °C, 1 h; −25 °C, 17 h	96	90:10
3	<i>i</i> -Pr	0.048	−50 °C → −35 °C, 1 h; −25 °C, 22 h	64	>98:2
4	<i>i</i> -Pr	0.048	−50 °C → −35 °C, 1 h; −5 °C, 67 h	78	98:2
5	<i>i</i> -Pr	0.02	−50 °C → −5 °C, 1 h; −8 °C, 7 d	99	98:2

Protection of the hydroxy group in **20b** and ester reduction were accomplished under standard conditions (Scheme 6).

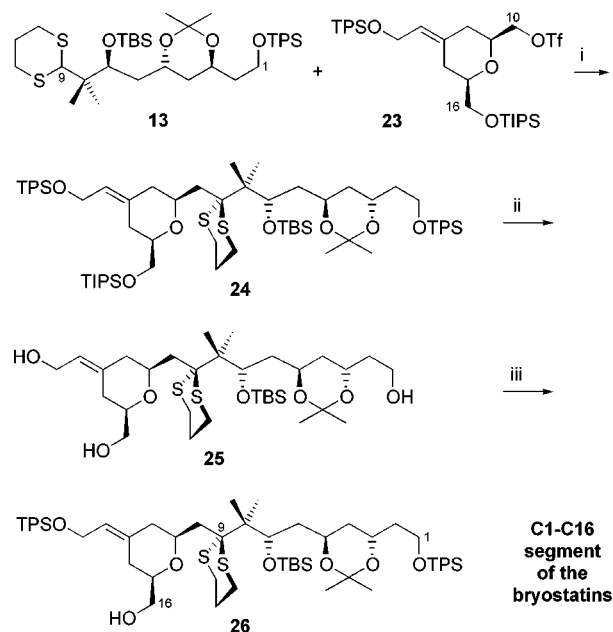


^a (i) TIPSCl, imidazole, DMF, rt, 1 h, 98%; (ii) DIBAH, toluene, −65 → −20 °C, 1 h, 97%; (iii) TPSCl, imidazole, DMF, rt, 1.5 h, 93%; (iv) ZnBr₂, CH₂Cl₂/MeOH, 0 °C → rt, 1.5 h, 94%; (v) Tf₂O, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, −78 °C, 15 min, 99%.

After protection of the alcohol **21**, the trityl group was removed under Lewis acidic conditions. Impurities from the *Z*-isomer resulting from the HWE olefination were now marginal and separable at this stage. According to the synthetic plan, the alcohol was converted into its triflate **23** in 13 steps from *meso*-4 and in 40% overall yield.

Fragment Coupling. In general, the coupling of segments in polyketides raises challenges which do not occur in segment syntheses. Our initial study on a model A–B segment coupling utilized a deprotonated TES cyanohydrin and triflate **23** and revealed that the condensation was feasible in the presence of HMPA.^{6a} Due to the lability of TES cyanohydrins, complicated handling in generating a TES cyanohydrin anion and fluctuating yields in the desired coupling, we changed our strategy and used 1,3-dithianes¹⁷ instead. In this case it was discovered that the hydroxy protecting group at C7 in **13** (TBS, TIPS, SEM, MEM) had a marked influence on coupling yield. After detailed investigation, best coupling yields were observed for the TBS group. Lithiation of the sterically encumbered dithiane **13** was best effected using *tert*-BuLi in the presence of HMPA. The addition of triflate **23** then afforded a good yield of the C1–C16 segment **24** (Scheme 7). The release of the C16-

(17) Smith, A. B.; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639.

Scheme 7^a

^a (i) −78 °C, THF, 1.1 equiv of *t*-BuLi, 3 equiv of HMPA, 5 min, then **23**, −78 → −50 °C, 1 h, 63%; (ii) 20 equiv of TBAF/AcOH (1:1), THF, rt., 48 h, 73%; (iii) 2.1 equiv of TPSCl, 2.5 equiv of imidazole, CH₂Cl₂, −30 → 0 °C, 2 h, 71%.

OH group was achieved in two steps. Removal of the TIPS and TPS groups in the sensitive compound **24** proceeded smoothly with TBAF buffered with HOAc¹⁸ to give triol **25**. Selective protection of the C1-OH group and of the allylic alcohol supplied the fully resolved segment **26** containing three silyl groups ready for single-step deprotection.

In summary, our oxabicyclics are multiple aldol addition equivalents which furnish a wide variety of polyketide patterns by both novel and efficient strategy.¹⁹ Starting from *meso*-3 and *rac*-4, we have prepared a C1–C16 segment of the bryostatins (longest linear sequence 17 steps) in 9% overall yield. C1–C9 subunit **13** and C10–C16 subunit precursor of triflate **23** were obtained on a multigram scale. A further spin off of our efforts has been a facile deprotection method of SEM ethers with MgBr₂ in homogeneous solution (Et₂O/MeNO₂).²⁰

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft, Volkswagen Foundation, and Fonds der Chemischen Industrie for their support and Ulrike Eggert for her help.

Supporting Information Available: Experimental procedures and spectroscopic data of the compounds **7–13** and **19–26**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) (a) Brief survey: Misske, A. M.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 3313 and literature therein. (b) Reference 10.

(20) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1447.