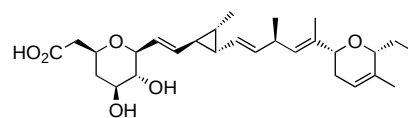


- lics **1997**, 16, 2492–2494; c) J. S. Rogers, G. C. Bazan, C. K. Sperry, *J. Am. Chem. Soc.* **1997**, 119, 9305–9306; d) R. A. Lee, R. J. Lachicotte, G. C. Bazan, *J. Am. Chem. Soc.* **1998**, 120, 6037–6046; e) J. S. Rogers, R. J. Lachicotte, G. C. Bazan, *J. Am. Chem. Soc.* **1999**, 121, 1288–1298; f) G. C. Bazan, W. D. Cotter, Z. J. A. Komon, R. A. Lee, R. J. Lachicotte, *J. Am. Chem. Soc.* **2000**, 122, 1371–1380.
- [6] For studies of cyclotrimerization reactions catalyzed by cobalt–boratabenzene complexes, see: a) H. Bönemann, W. Brijoux, R. Brinkmann, W. Meurers, *Helv. Chim. Acta* **1984**, 67, 1616–1624; b) H. Bönemann, *Angew. Chem.* **1985**, 97, 264–279; *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 248–262.
- [7] For pioneering studies of boratabenzene chemistry, see: a) G. E. Herberich, G. Greiss, H. F. Heil, *Angew. Chem.* **1970**, 82, 838–839; *Angew. Chem. Int. Ed. Engl.* **1970**, 9, 805–806; b) A. J. Ashe III, P. Shu, *J. Am. Chem. Soc.* **1971**, 93, 1084–1085.
- [8] For reviews on boratabenzene chemistry, see: a) G. E. Herberich, H. Ohst, *Adv. Organomet. Chem.* **1986**, 25, 199–236. b) G. C. Fu, *Adv. Organomet. Chem.* **2001**, 47, 101–119.
- [9] For a versatile synthesis of *B*-substituted boratabenzenes, see: S. Qiao, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1996**, 118, 6329–6330.
- [10] For an application of 1,2-azaborolyl complexes in olefin polymerization, see: S. Nagy, R. Krishnamurti, B. P. Etherton, PCT Int. Appl. WO 9634021, **1996**; [*Chem. Abstr.* **1997**, 126, 19432j].
- [11] For overviews of 1,2-azaborolyl chemistry, see: a) G. Schmid in *Comprehensive Heterocyclic Chemistry II*, Vol. 3 (Ed.: I. Shinkai), Elsevier, Oxford, **1996**, chap. 3.17; b) G. Schmid, *Comments Inorg. Chem.* **1985**, 4, 17–32.
- [12] For a recent contribution to 1,2-azaborolyl chemistry, see: A. J. Ashe III; X. Fang, *Org. Lett.* **2000**, 2, 2089–2091.
- [13] Stannacycle **1** can be synthesized in two steps from commercially available materials: D. Hänsgen, E. Odenhausen, *Chem. Ber.* **1979**, 112, 2389–2393.
- [14] For precedent with *B*-alkyl- or *B*-arylboracycles, see: a) J. Schulze, R. Boese, G. Schmid, *Chem. Ber.* **1980**, 113, 2348–2357; b) J. Schulze, G. Schmid, *J. Organomet. Chem.* **1980**, 193, 83–91.
- [15] For a review, see: A. G. Lee, *Organomet. React.* **1975**, 5, 1–99.
- [16] For certain nucleophiles (e.g., LiNMe_2 and LiAlH_4), not only the *B*–OTf complex (**5**; vide infra), but also the *B*–Cl complex (**4**), serves as a suitable substrate for displacement reactions at boron.
- [17] As Nöth has noted, boron-containing heteroaromatic compounds that bear a hydrogen substituent on boron are relatively uncommon: H. Nöth, M. Schmidt, *Angew. Chem.* **1996**, 108, 311–312; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 292–293.
- [18] a) For leading references to electrochemical studies of ferrocene complexes, see: P. Zanello in *Ferrocenes* (Eds.: A. Togni, T. Hayashi), VCH, New York, **1995**, chap. 7. b) All of the azaborolyl complexes depicted in Table 2, except for the *F*- and PPh_2 -substituted compounds, display reversible redox behavior.
- [19] a) C. Hansch, A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979; b) C. G. Swain, E. C. Lupton, Jr., *J. Am. Chem. Soc.* **1968**, 90, 4328–4337; C. G. Swain, S. H. Unger, N. R. Rosenquist, M. S. Swain, *J. Am. Chem. Soc.* **1983**, 105, 492–502.
- [20] G. C. Bazan, W. D. Cotter, Z. J. A. Komon, R. A. Lee, R. J. Lachicotte, *J. Am. Chem. Soc.* **2000**, 122, 1371–1380.
- [21] The short *B*–O bond length (1.384 Å) is consistent with a significant π interaction (sum of covalent radii: 1.47 Å).
- [22] In the case of η^6 -benzene versus η^6 -borazine complexes, substitution of *B*–N for *C*–C does not appear to significantly change the electronic character of the metal. For example, see: a) H. Werner, R. Prinz, E. Deckelmann, *Chem. Ber.* **1969**, 102, 95–103; b) G. Huttner, B. Krieg, *Angew. Chem.* **1971**, 83, 541–542; *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 512–513.

Total Synthesis of Ambruticin**

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Ambruticin (**1**) was isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum* var. *fulvum*. It is an orally active antifungal agent showing in vitro and in vivo activity against a variety of pathogenic fungi, including *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*, as well as the dermatophytic filamentous fungi.^[1] Ambruticin features unique *cis*-2,6-disubstituted tetrahydropyran and dihydropyran ring systems together with a methylcyclopropane moiety. In spite of considerable interest



1 (+)-Ambruticin

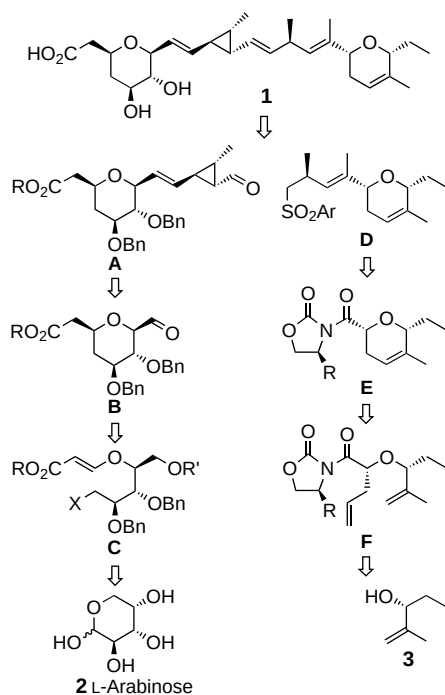
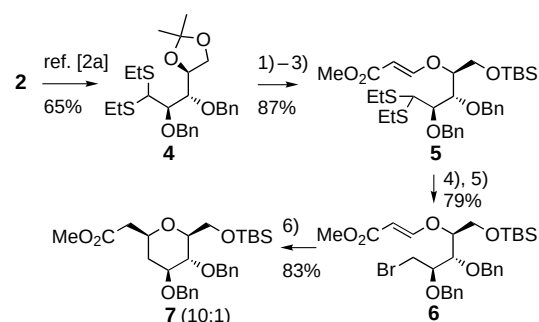
in the preparation of **1**,^[2] we found in the literature only one total synthesis, reported by Kende in 1990,^[3] and the difficulty in designing a stereoselective total synthesis is manifested in recent reports dealing with partial syntheses of the molecule.^[4] In our continuing search for new applications of stereoselective radical cyclization reactions of β -alkoxyacrylates,^[5] we examined the efficacy of these reactions in a stereocontrolled synthesis of **1**.

In our retrosynthetic analysis, the tetrahydropyran aldehyde **B** was to be prepared from a β -alkoxyacrylate precursor **C**, which may be obtained from *L*-arabinose (**2**). The dihydropyran derivative **E** was envisaged to arise from the diene **F** by olefin metathesis.^[6] Connection of the parts **A** and **D** by Julia-type olefination would then complete the construction of the carbon framework (Scheme 1).

Selective acetonide protection of the dithioacetal derivative of *L*-arabinose (**2**) and benzylation of the remaining hydroxy groups gave the acetonide **4** (Scheme 2).^[2a] The β -alkoxyacrylate **5** was obtained from **4** by acetonide deprotection, regioselective TBS protection of the primary hydroxy group, and reaction with methyl propiolate. The aldehyde group generated from the dithioacetal moiety in **5** was reduced with NaBH_4 , and bromide substitution led to the primary bromide **6**, which was then stereoselectively transformed into the

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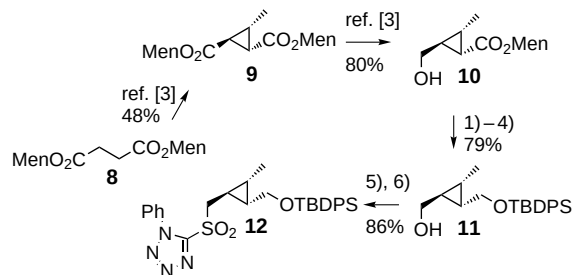
[**] The authors thank the Ministry of Science and Technology, Republic of Korea, and Korea Institute of Science and Technology Evaluation and Planning for a National Research Laboratory grant (1999). The authors also thank Professor A. S. Kende (University of Rochester) for NMR spectra of natural and synthetic ambruticin, and Professor G. Höfle (GBF) for a sample of natural ambruticin and NMR spectra.

Scheme 1. Retrosynthetic analysis of **1**.

Scheme 2. 1) Cat. HCl, MeOH, 0°C → RT, 8 h. 2) 1.05 equiv TBSCl, 2.0 equiv imidazole, CH₂Cl₂, RT, 10 min. 3) 1.1 equiv HC≡CCO₂Me, 0.2 equiv NMM, CH₂Cl₂, RT, 2 h. 4) 1.5 equiv PhI(TFA)₂, 3.0 equiv NaHCO₃, MeCN/H₂O (9:1), 0°C, 5 min; 1.0 equiv NaBH₄, 0°C, 30 min. 5) 1.5 equiv CBr₄, 1.2 equiv Ph₃P, 3.0 equiv NEt₃, CH₂Cl₂, 0°C → RT, 2 h. 6) 1.2 equiv Bu₃SnH, 0.2 equiv AIBN, benzene (0.005 M), reflux, 2 h, (syringe pump, 1 h). AIBN = azobisisobutyronitrile, NMM = *N*-methylmorpholine, TBS = *tert*-butyldimethylsilyl.

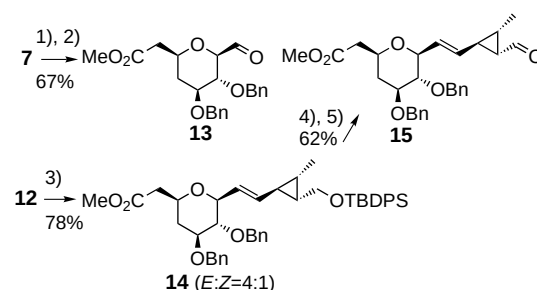
desired tetrahydropyran derivative **7** (2,6-*cis:trans* = 10:1) under the standard high-dilution radical-generating conditions in the presence of tributylstannane and AIBN.

Preparation of the primary alcohol **10** from dimethyl succinate (**8**) was achieved by following the Kende protocol,^[3] which involves stereoselective double alkylation with 1-bromo-1-chloroethane, selective hydrolysis of the sterically less hindered ester moiety of the diester **9**, and borane reduction (Scheme 3). Conversion of **10** into the TBDPS ether **11** was then effected by TBS protection, LiAlH₄ reduction, TBDPS protection, and TBS deprotection. Mitsunobu-type reaction of **11** with 1-phenyl-1*H*-tetrazole-5-thiol proceeded efficiently to provide the expected sulfide, which was converted into the sulfone **12** by oxidation with MCPBA.



Scheme 3. 1) 1.1 equiv TBSCl, 2.0 equiv imidazole, CH₂Cl₂, RT, 30 min. 2) 1.5 equiv LiAlH₄, Et₂O, 0°C, 1 h. 3) 1.1 equiv TBDPSCl, 2.0 equiv imidazole, CH₂Cl₂, RT, 1 h. 4) 0.1 equiv CSA, MeOH, 0°C, 40 min. 5) 2.0 equiv 1-phenyl-1*H*-tetrazole-5-thiol, 1.8 equiv DIAD, 1.5 equiv Ph₃P, THF, 0°C, 5 min. 6) 2.0 equiv MCPBA, CH₂Cl₂, 0°C, 30 min. DIAD = diisopropyl azodicarboxylate, MCPBA = *m*-chloroperoxybenzoic acid, Men = menthyl, TBDPS = *tert*-butyldiphenylsilyl.

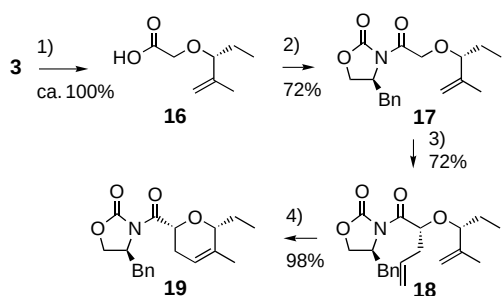
The aldehyde **13** was obtained from the TBS ether **7** by deprotection, separation of diastereomers, and Swern oxidation (Scheme 4). Construction of the *trans*-disubstituted double bond at C8–C9 was problematic. Classical Julia



Scheme 4. 1) Cat. HCl, MeOH, 0°C → RT, 30 min. 2) 2.2 equiv (COCl)₂, 4.0 equiv DMSO, CH₂Cl₂, –78°C, 1 h; 5.0 equiv NEt₃, –78°C, 7 h. 3) 2.0 equiv NaHDMS, THF/HMPA (4:1), –78°C, 5 min; 2.0 equiv **13**, –78°C → RT, 3 h. 4) Cat. HCl, MeOH, RT, 1 h. 5) 2.2 equiv (COCl)₂, 4.0 equiv DMSO, CH₂Cl₂, –78°C, 30 min; 5.0 equiv NEt₃, –78°C → RT. HMPA = hexamethylphosphoramide, NaHDMS = sodium hexamethyldisilazide.

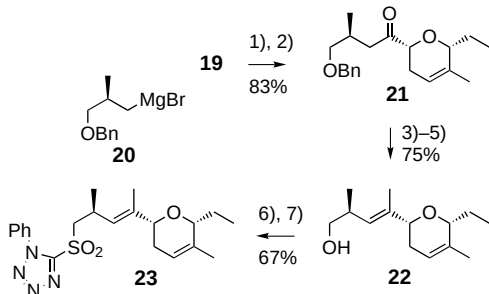
reactions employing the aldehyde **13** did not work, but after considerable experimentation, the Kocienski–Julia reaction proved fruitful.^[7] The olefin **14** (*E:Z* = 4:1) was obtained in 78% yield by deprotonation of the sulfone **12** by two equivalents of sodium hexamethyldisilazide and subsequent addition of two equivalents of the aldehyde **13** in the presence of HMPA. Use of lithium hexamethyldisilazide gave **14** with better selectivity (*E:Z* = 9:1) but lower yield (63%), and the reaction became essentially nonstereoselective when potassium hexamethyldisilazide was employed (63% yield, *E:Z* = 1:1). The required aldehyde **15** was prepared from **14** by deprotection of the TBDPS group under acidic conditions, separation of the geometric isomers, and Swern oxidation.

Synthesis of the right-hand half of ambruticin (**1**) commenced with (*R*)-3-hydroxy-2-methylpent-1-ene (**3**),^[8] which was converted to the ether **16** by reaction with sodium bromoacetate (Scheme 5). The sodium enolate of the corresponding imide **17** reacted with allyl iodide to yield the diene **18** in a stereoselective manner. Olefin metathesis of the diene **18** proceeded uneventfully with the Grubbs catalyst^[9] to give the dihydropyran imide **19** in excellent yield.



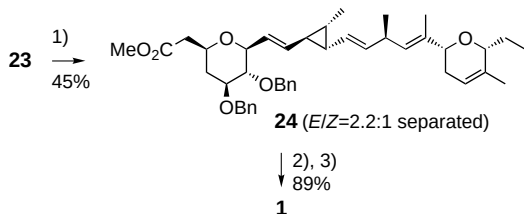
Scheme 5. 1) 1.0 equiv NaH, $\text{BrCH}_2\text{CO}_2\text{Na}$, RT, 8 h (reverse addition). 2) 1.0 equiv PivCl, 1.1 equiv NEt_3 , Et_2O , $-78 \rightarrow 0^\circ\text{C}$; 1.0 equiv $\text{X}_c\text{-Li}$, THF, -78°C , 8 h. 3) 1.2 equiv NaHDS, 5.0 equiv $\text{H}_2\text{CCHCH}_2\text{I}$, THF, $-78 \rightarrow -45^\circ\text{C}$, 5 h. 4) 0.05 equiv $[\text{RhCl}_2(\text{CHPh})(\text{PCy}_3)_2]$, CH_2Cl_2 (0.005 M), reflux, 3 h; 0.075 equiv $\text{Pb}(\text{OAc})_4$. Piv = pivaloyl.

Conversion of **19** to the corresponding Weinreb amide and subsequent reaction with the Grignard reagent **20**^[10] led to the ketone **21** (Scheme 6). The trisubstituted olefin **22** was obtained by regioselective enol triflate formation and reaction with lithium dimethylcuprate^[11] followed by lithium/ammonia debenzoylation. Mitsunobu-type reaction of **22** with 1-phenyl-1*H*-tetrazole-5-thiol and selective oxidation with ammonium heptamolybdate and hydrogen peroxide^[12] provided the sulfone **23** in reasonable yield.



Scheme 6. 1) 3.5 equiv $\text{MeNH}(\text{OMe})\cdot\text{HCl}$, 3.5 equiv Me_3Al , THF, 0°C , 3 h. 2) 3.0 equiv **20**, 40°C , THF, 8 h. 3) 1.25 equiv LiHMDs , 1.5 equiv PhNTf_2 , THF/HMPA (4:1), -78°C , 30 min. 4) 3.0 equiv Me_2CuLi , Et_2O , -78°C , 1 h. 5) 10 equiv Li ($\times 3$), $\text{NH}_3(\text{l})/\text{EtOH}$ (5:1), -78°C , 10 min. 6) 2.0 equiv 1-phenyl-1*H*-tetrazole-5-thiol, 1.8 equiv DIAD, 1.5 equiv Ph_3P , THF, 0°C , 30 min. 7) 2.0 equiv $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$, H_2O_2 , EtOH , 0°C , 3 h.

The final coupling reaction was performed by treating the sulfone **23** with sodium hexamethyldisilazide in the presence of HMPA, and then with 1.5 equivalents of the aldehyde **15** (Scheme 7). Thus, 45% of the desired (*E*)-olefin **24** was



Scheme 7. 1) 1.2 equiv NaHDS, THF/HMPA (4:1), -60°C , 30 min; 1.5 equiv **15**, $-60 \rightarrow 0^\circ\text{C}$, 3 h. 2) 0.5 N LiOH, THF/ H_2O (3:1), RT, 8 h. 3) 10 equiv Li ($\times 3$), $\text{NH}_3(\text{l})/\text{EtOH}$ (5:1), -78°C , 10 min.

obtained directly along with the (*Z*)-isomer, which was isolated in 21% yield. Use of potassium hexamethyldisilazide resulted in higher stereoselectivity (*E*:*Z* = 6:1), but the yield was low (15%). Ambruticin (**1**) was obtained from **24** by basic hydrolysis and lithium/ammonia debenzoylation.

In summary, oxacyclic building blocks were prepared by using highly stereoselective radical cyclization and olefin metathesis reactions. The convergent strategy featuring the Kocienski–Julia reaction may be easily adapted to the synthesis of ambruticin analogues for the evaluation of bioactivities.

Received: August 16, 2001 [Z17742]

- [1] a) S. M. Ringel, R. C. Greenough, S. Roemer, D. Connor, A. L. Gutt, B. Blair, G. Kantor, M. von Strandtmann, *J. Antibiot.* **1977**, *30*, 371–375; b) D. T. Connor, R. C. Greenough, M. von Strandtmann, *J. Org. Chem.* **1977**, *42*, 3664–3669; c) P. Knauth, H. Reichenbach, *J. Antibiot.* **2000**, *53*, 1182–1190.
- [2] a) G. Just, P. Potvin, *Can. J. Chem.* **1980**, *58*, 2173–2177; b) N. J. Barnes, A. H. Davidson, L. R. Hughes, G. Procter, V. Rajcoomar, *Tetrahedron Lett.* **1981**, *22*, 1751–1754; c) N. J. Barnes, A. H. Davidson, L. R. Hughes, G. Procter, *J. Chem. Soc. Chem. Commun.* **1985**, 1292–1294; d) A. H. Davidson, N. Eggleton, I. H. Wallace, *J. Chem. Soc. Chem. Commun.* **1991**, 378–380.
- [3] A. S. Kende, Y. Fujii, J. S. Mendoza, *J. Am. Chem. Soc.* **1990**, *112*, 9645–9646; b) A. S. Kende, J. S. Mendoza, Y. Fujii, *Tetrahedron* **1993**, *49*, 8015–8038.
- [4] a) I. E. Markó, D. J. Bayston, *Tetrahedron* **1994**, *50*, 7141–7156; b) I. E. Markó, D. J. Bayston, *Synthesis* **1996**, 297–304; c) L. Liu, W. A. Donaldson, *Synlett* **1996**, 103–104; d) M. Michelet, K. Adie, B. Bulic, J.-P. Genêt, G. Dujardin, S. Rossignol, E. Brown, L. Toupet, *Eur. J. Org. Chem.* **1999**, 2885–2892.
- [5] For selected examples of stereoselective radical cyclization reactions of β -alkoxyacrylates in natural product synthesis, see: a) E. Lee, C. M. Park, J. S. Yun, *J. Am. Chem. Soc.* **1995**, *117*, 8017–8018; b) E. Lee, S.-K. Yoo, Y.-S. Cho, H.-S. Cheon, Y. H. Chong, *Tetrahedron Lett.* **1997**, *38*, 7757–7758; c) E. Lee, S.-K. Yoo, H. Choo, H. Y. Song, *Tetrahedron Lett.* **1998**, *39*, 317–318; d) E. Lee, S. J. Choi, *Org. Lett.* **1999**, *1*, 1127–1128; e) E. Lee in *Radicals in Organic Synthesis*, Vol. 2 (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 303–333.
- [6] For examples of asymmetric glycolate alkylation (or aldol addition) ring-closing metathesis approach to oxacyclic natural products, see: a) M. T. Crimmins, K. A. Emmitte, *Org. Lett.* **1999**, *1*, 2029–2032; b) M. T. Crimmins, K. A. Emmitte, J. D. Katz, *Org. Lett.* **2000**, *2*, 2165–2167; c) M. T. Crimmins, A. L. Choy, *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660; d) M. T. Crimmins, E. A. Tabet, *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476.
- [7] P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28.
- [8] I. Paterson, M. V. Perkins, *Tetrahedron* **1996**, *52*, 1811–1834.
- [9] a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110; b) L. A. Paquette, J. D. Schloss, I. Efremov, F. Fabris, F. Gallou, J. Méndez-Andino, J. Yang, *Org. Lett.* **2000**, *2*, 1259–1261.
- [10] G. S. Garrett, T. J. Emge, S. C. Lee, E. M. Fischer, K. Dyehouse, J. M. McIver, *J. Org. Chem.* **1991**, *56*, 4823–4826.
- [11] A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. W. Leahy, R. E. Maleczka, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 947–961.
- [12] D. R. Williams, D. A. Brooks, M. A. Berliner, *J. Am. Chem. Soc.* **1999**, *121*, 4924–4925.